Patient-Oriented Problem Solving (POPS) Case Report Series: PO*PS FROM THE PAST*

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Patient Oriented Problem Solving (POPS) Case Report

C1-esterase inhibitor autoantibodies in a patient with acute tongue swelling

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ABSTRACT

Angioedema occurs when there is fluid leakage into the deep dermis of the skin and underlying subcutaneous tissues. Affected individuals usually present with swelling of the face or extremities. Acquired angioedema is an uncommon but potentially life-threatening disease in the older adult population. After the individual is cleared of the initial danger period, a thorough workup for an underlying etiology must be done. We report a 62-year-old male presenting with significant tongue swelling who was diagnosed with acquired angioedema. He had autoantibodies to C1 esterase inhibitor and was subsequently diagnosed with a lymphoma. Angioedema should be recognized by clinicians as a potential presentation of a more ominous malignancy.

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Key words: Acquired angioedema, angioedema, C1-esterase inhibitor autoantibody

CASE PRESENTATION

History of Present Illness

A 62-year-old Caucasian man presented to the Allergy and Immunology Clinic with a history of sudden-onset, isolated tongue swelling. This was the first swelling episode he had ever experienced. There were no stressful preceding events or recent changes in medications. He was rushed to the emergency room because of impending airway obstruction and received a dose of intramuscular epinephrine. He received no other supportive medications. The tongue swelling gradually abated over the next few hours and he was discharged without further medical interventions. The patient presented to our clinic 1 month later for evaluation; he had not experienced any further swelling episodes aside from this isolated incident. Review of systems was unremarkable. For several years, the patient has been taking niacin for elevated serum cholesterol as well as aspirin, and he has had no adverse reactions to either medication. There is no family history of angioedema (AE).

Physical Examination

The patient was afebrile with stable vital signs. His physical examination was unremarkable with no evidence of tongue swelling or skin abnormalities.

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Laboratory and Other Diagnostic Findings

No laboratory studies, including complement testing, were done during the tongue swelling episode. Laboratory studies, although asymptomatic, showed a normal complete blood count with no eosinophilia. Sedimentation rate was elevated at 64 mm/hour (normal range, 0–10 mm/hour). Complement studies showed a C4 of <10 mg/dL (normal range, 12–34 mg/dL) and CH50 was <60 complement activity enzyme (CAE) units (normal range, above 60 CAE units). C1 esterase inhibitor (C1-INH) quantity was <4 mg/dL (normal, 11–25 mg/dL), and C1-INH function was 3% (normal, ≥68%). C1q was normal at 6.6 mg/dL. Antinuclear antibody, rheumatoid factor, and thyroid autoantibodies were negative. Urinalysis was unremarkable. Serum immune protein electrophoresis showed faint monoclonal IgM κ-protein.

Bone marrow biopsy showed atypical lymphoid aggregates but no monoclonality or evidence of lymphoma. Follow-up serum and urine immunofixation showed increased presence of monoclonal IgM κ-protein. CT scan of the chest, abdomen, and pelvis showed slightly enlarged retroperitoneal lymph nodes, and he was given a preliminary diagnosis of a very low-grade lymphoproliferative disease.

Clinical Course

The patient was diagnosed with acquired AE (AAE) and was started on danazol with close follow-up. There were no further AE attacks. His complement studies, including C1-INH quantity and function as well as C4 levels, normalized after 8 months of ther-

apy. The patient continued on danazol without complications. Approximately 18 months after the tongue swelling incident, the patient was diagnosed with a lymphoma.

QUESTIONS

What Is the Differential Diagnosis?

In order of least likely to most likely, the differential diagnosis includes:

1. Gleich syndrome
2. Allergic AE secondary to food or medications
3. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)–associated AE
4. Physical AE: pressure AE or vibratory AE
5. AE secondary to infection: bacterial, fungal, viral, or helminthic
6. Systemic illness: collagen vascular disease or malignancy
7. Chronic idiopathic AE
8. Hereditary AE (HAE)
9. AAE

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Additional laboratory data regarding autoantibody to C1-INH would be helpful in diagnosing this patient.

DISCUSSION

AE develops secondary to fluid leakage into the deep dermis and subcutaneous tissues. It was first described in 1876 by John Laws Milton as "giant urticaria."[1] Urticaria also is caused by fluid leakage but only into the superficial dermis. AE most commonly affects the extremities, lips, tongue, eyelids, and the genitalia; lesions are nonpitting. Approximately 10% of Americans develop isolated AE with no associated urticaria.

Gleich syndrome (episodic AE with eosinophils)[2] is a rare but benign condition involving recurrent AE associated with peripheral blood and/or tissue eosinophilia. Attacks vary in length and frequency and occasionally may be associated with urticaria and fever.

IgE-mediated allergic reactions to foods and drugs is the most common cause of acute urticaria and/or AE. However, our patient's clinical and laboratory histories did not suggest these possible causes of AE.

AE also can develop during ACE inhibitor therapy, even occurring months after initiating medication. Symptoms likely occur secondary to increased bradykinin and its metabolites, which are normally metabolized by ACE. Increased bradykinin leads to vasodilation and fluid extravasation into the interstitial space. There have been scattered cases of AE associated with ARB use[3]; the exact mechanism is unknown. Nevertheless, most patients who develop AE with ACE inhibitors have safely switched to ARBs with no further attacks.[4]

Patients with physical AE develop symptoms after an environmental trigger. Pressure-induced AE can develop 4–6 hours after a pressure stimulus to the affected area. Vibratory AE can be inherited in an autosomal dominant pattern[5] and symptoms occur within minutes after a vibratory stimulus. Infections including hepatitis and helminths also have been associated with AE. Our patient had no clinical history or laboratory studies suggesting a physical trigger or infection.

AE also can be an associated symptom of an underlying systemic illness such as collagen vascular disease or malignancy. Chronic idiopathic AE is diagnosed after an individual has had >6 weeks of recurrent symptoms and all other possible diagnoses have been ruled out.

Our patient's history and abnormal complement studies were more consistent with HAE or AAE. HAE is an autosomal dominant disease caused by a defective C1 esterase inhibitor enzyme (C1-INH). The prevalence of the disease is ~1 in 50,000 with no ethnic or gender predominance.[6] Affected patients usually present with AE in childhood. The frequency of AE bouts in HAE patients can be variable throughout an individual's life and does not correlate with laboratory findings. C1-INH controls activation of the complement system by limiting the autoactivation of the C1 component. The enzyme also controls contact phase activation by inhibiting kallikrein, the protease involved in bradykinin release. Approximately 85% of HAE patients have low levels of C1-INH and are considered to have type I HAE.[7] Although there is one functional gene, plasma levels of C1-INH are usually 5–30% of normal, likely because of increased catabolism of the enzyme.[8] The remaining 15% have the type II variant and have normal to high C1-INH levels, but the enzyme is dysfunctional. Patients with HAE I and II have uncontrolled complement system activation; laboratory studies show low C4, low C2, and decreased C1-INH levels and/or activity. Recently, another presentation of HAE not associated with the C1-INH mutation has been described and is believed to be estrogen dependent. These patients had normal C4 as well as normal C1-INH levels and function.[9,10] All cases have been in female patients with a dominant mode of inheritance. Our patient did not appear to have HAE because he had no family history of AE and his initial presentation occurred in adulthood.

Approximately 4.4% of patients with nonallergic AE are diagnosed with AAE.[11] Patients with AAE are clinically similar to patients with HAE, but there is no family history of AE. Initial presentation usually occurs during the fourth decade of life or later, as in our

patient. AE results from excessive catabolism of C1-INH and subsequent hyperactivation of the classic complement pathway. Therefore, patients are classically described as having not only low C1-INH and C4 levels but also decreased C1q levels. AAE often is classified into two types; type I is associated with B-cell lymphoproliferative disease and type II is rarely associated with an autoimmune disorder. Lymphoproliferative diseases include multiple myeloma,[12] Waldenstrom macroglobulinemia,[13] gastric carcinoma,[14] and B-cell lymphoma.[15] Neoplastic lymphatic tissues consume C1-INH[16] and/or classic pathway components,[17] leading to enzyme deficiency and more bradykinin release. Autoimmune processes include Churg-Strauss vasculitis[18] and systemic lupus erythematosus.[19] These patients produce autoantibodies to C1-INH,[20] enhancing immune-mediated cleavage of the enzyme and thereby inactivating it. The differentiation between the two AAE types may not be so clear, however; patients with lymphoproliferative disease and AAE also can develop C1-INH autoantibodies. Final diagnoses ranged from monoclonal gammopathy of unknown significance to B-cell lymphoma.[21]

Our patient's free C1-INH IgG autoantibody level was elevated at 70.8 (normal range, <14.3). However, his C1q was in the normal range. Cicardi *et al.* reported that 5 of 23 AAE patients who developed lymphoproliferative disease had normal C1q levels.[22] Hence, some patients with AAE associated with lymphoproliferative disease also have normal C1q.

Initial laboratory workup for AE includes a C1-INH level and function as well as a C4 level. If low, then C1q should be ordered to distinguish between hereditary or acquired C1-INH deficiency. However, C1q levels are not always depressed in AAE, so history and physical examination should help determine the final diagnosis. If autoimmune disease is suspected, then an ANA, rheumatoid factor, and sedimentation rate should be ordered. If AAE is suspected, then workup for an underlying malignancy should be pursued. This includes immunophenotyping of peripheral blood lymphocytes for circulating malignant B cells; serum protein electrophoresis and immunoelectrophoresis for underlying dysproteinemia; and CT of the chest, abdomen, and pelvis. Bone marrow biopsy is also helpful.

Treatment for acute AE of the larynx, pharynx, and tongue should be approached as life-threatening emergencies. If airway obstruction is suspected, then emergency procedures include epinephrine and intubation. However, commonly used agents for airway edema such as epinephrine as well as glucocorticoids and antihistamines have not been effective in treating C1-INH–deficient patients because the underlying pathogenesis is not histamine-mediated. More effectively, C1-INH concentrate can treat acute HAE and AAE attacks. C1-INH preparations are currently unavailable in the United States, but preliminary studies investigating its effectiveness are promising. Sixty-nine percent of attacks abated within 30 minutes of infusion, and 95% of attacks were relieved within 4 hours.[11] In AAE, higher doses of C1-INH may be required because of the rapid catabolism of C1-INH that characterizes AAE.

Fresh frozen plasma (FFP) is widely used in the United States for treatment of acute AE attacks and as short-term prophylaxis before surgery because it contains complement components.[23–25] However, there is concern that administration of additional complement proteins in FFP can also exacerbate AE attacks.[26] There is also a risk of urticaria, anaphylactic shock, hemolysis, and infectious agent transmission during an FFP infusion. For abdominal pain during attacks, spasmolytics such as butylscopolamine may be used.[11]

Long-term prophylaxis is indicated for patients who have more than one disabling attack a month.[11] These agents include attenuated androgens and antifibrinolytics. Danazol and stanozolol are attenuated androgens that increase hepatic synthesis of C1-INH. Long-term administration may be associated with weight gain, virilization in women, hemorrhagic cystitis, hepatoxicity, hepatic adenocarcinomas, and liver cell carcinomas. Hepatic studies should be followed while patients are on attenuated androgens; liver ultrasounds may be more sensitive than changes in aminotransaminase levels for early diagnosis of liver tumors.

Patients with AAE may benefit more from long-term treatment with antifibrinolytic agents, such as tranexamic acid, which act by inhibiting plasminogen activation. The production of plasmin also can facilitate the release of bradykinin. Side effects of antifibrinolytics include abdominal discomfort, diarrhea, and nausea. ε-aminocaproic acid is also used but adverse effects including postural hypotension and weakness could be more severe. There is a theoretical risk of increased thrombosis in patients taking antifibrinolytics.

Other options are being investigated for treatment of acute AAE attacks.[11] The kallikrein inhibitor DX-88 has a high affinity for kallikrein and therefore blocks the release of bradykinin from high molecular weight kininogen. Icatibant, a bradykinin antagonist, is a synthetic bradykinin-like peptide with the same affinity for bradykinin receptors. Finally, recombinant C1-INH has been developed from the milk of transgenic rabbits.

In autoantibody-mediated AAE, the underlying syndrome needs to be identified and treated for successful control of symptoms. Immunosuppressive therapy such as cyclophosphamide[27] and rituximab,[28] a chimeric monoclonal antibody that causes rapid and specific B-cell depletion in the peripheral blood,[29] have led to complete and partial remissions. Nevertheless, the

therapeutic or palliative effects of these options are still unclear.

Final Diagnosis

The final diagnosis was acquired AE (AAE) secondary to autoanti-bodies to C1-INH associated with lymphoproliferative disease.

SUMMARY

AAE is an uncommon but potentially life-threatening disease in the older adult population. After the individual is cleared of the initial danger period, a thorough workup for an underlying etiology must be done. C1-INH autoantibody–producing lymphoproliferative disease is a rare cause of AAE.

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Patient Oriented Problem Solving (POPS) Case Report

Fever of unknown origin and isolated noncaseating granuloma of the marrow: Could this be sarcoidosis?

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ABSTRACT

Fever of unknown origin (FUO) is both a clinical and a diagnostic challenge. Furthermore, an FUO case with isolated marrow noncaseating granuloma can further confound diagnosis. However, these two findings together may help narrow down the pathological possibilities. This article presents a case report of FUO and lymphopenia for 2 months. Multiple studies to evaluate infectious etiology were unremarkable. Bone marrow biopsy revealed isolated bone marrow granuloma, suggestive of sarcoid. The patient responded well to glucocorticosteroids with resolution of lymphopenia. Sarcoid should enter the differential of lymphopenia and FUO even without lymphadenopathy or abnormal chest radiography. This article provides a of review of CD4 lymphopenia, noncaseating granuloma of the marrow, and sarcoidosis.

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Key words: Bone marrow granuloma, CD4 lymphopenia, fever of known origin, noncaseating granuloma, sarcoid

Sarcoidosis is a poorly understood syndrome that is frequently found incidentally and diagnosed by both exclusion and the finding of noncaseating granulomas. The presentation of sarcoid can be varied. Historically, sarcoid presented with skin pathology, but more recently, pulmonary symptoms are the initial presentation. Despite these presentations, physicians also must be aware of the rare cases such as a patient with a fever of unknown origin (FUO) and/or isolated marrow granulomas. Awareness of such possibilities could save patients from multiple hospitalizations and expensive unnecessary diagnostic tests and treatments.

CASE PRESENTATION

Chief Complaint

Shortness of breath and daily fevers for 2 months.

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History of Present Illness

A 61-year-old man presented with shortness of breath, daily fevers up to 38.9°C (102°F), and night sweats for 2 months. He was discharged from another hospital with antibiotics for presumed pneumonia 6 weeks before coming to the emergency department for persistent symptoms.

Medical History

His medical history was significant only for hypertension. During his previous admission, he had a normal chest x ray, negative blood cultures, and negative sputum cultures. Notes indicated that he had a low CD4 level (absolute number was not available). HIV, ELISA, antinuclear antibody, tuberculin purified protein derivative, rheumatoid factor, cytomegalovirus (CMV) serology, immunofixation, and hepatitis panel were all negative. Chest CT with contrast showed small subsegmental atelectasis. Bronchoscopy was unremarkable. Bronchoalveolar fluid was negative for acid-fast bacilli, fungal or bacterial growth, and abnormal cytology. There was no report of transbronchial biopsy. His discharge diagnosis was "walking pneumonia." His social history was remarkable for being a former smoker with a 40-pack/year history. He had no recent travel history, HIV risk factors, or tuberculosis (TB) exposures. His family history was noncontributory.

Physical Exam

Vital signs were normal except for a temperature of 38.9°C (102.1°F). Exam was normal with a well-appearing man in no distress. There were no skin lesions, joint abnormalities, or lymphadenopathy. Lungs were clear to auscultation, heart sounds were normal, and abdomen was soft without hepatosplenomegaly.

Laboratory Data

Laboratory results revealed a hemoglobin of 9.3 g/dL (normal, 14–17 g/dL), hematocrit of 27.5% (normal, 39–50%), and WBC of 10,300 cells/μL (normal, 4200–10,300 cells/μL) with a differential of 75% neutrophils, 13% bands, and 4% lymphocytes. Platelet count, comprehensive metabolic panel, and chest radiograph were normal. CD4 T-cell count was 365 10^6/L (normal, 810- 3340 10^6/L), CD8 T-cell count was 179 10^6/L (220–960 10^6/L) and CD4/CD8 ratio was 2.1 (normal, 1–4.5).

QUESTION 1

What is the differential diagnosis for HIV^- $CD4^+$ lymphopenia?

a. Idiopathic $CD4^+$ lymphopenia (ICL)
b. TB
c. Viruses
d. Parasites
e. Hospitalization for acute illness
f. Sarcoidosis

Differential Diagnosis

There is a short but growing list of disease processes associated with HIV^- CD4 lymphocytopenia. These include ICL, TB, HIV^- infants of HIV^+ mothers, viruses, parasites, and hospitalization for acute illness.

ICL is an entity recently recognized and defined by the Center for Disease Control and Prevention to include HIV^- patients whose $CD4^+$ cell count is <300 cells/mm^3, or a $CD4^+$ cell count $<20\%$ of the total T cells on two occasions. Criteria also include the absence of any defined immunodeficiency or therapy associated with depressed $CD4^+$ levels.[1,2] Patients generally present with opportunistic infections and unexplained immunodeficiency.[3,4] Despite proposed but unproven theories, the cause of ICL is unclear, and many believe it to be the result of a heterogeneous pathological process.[1,2,4] For example, some authors postulate that ICL actually may be caused by diminished primitive stem cell precursors whereas other research suggests a defect in CD3-T-cell receptor stimulation.[2,5]

Pulmonary TB is another possibility to consider. Recent studies have shown that HIV^- patients with pulmonary TB have significantly lower CD4 counts as well as CD4/CD8 ratios when compared with normal blood donors.[6,7] Pilheu *et al.* found that patients with CD4 $<$ 300 cells/mm^3 have a poor prognosis and require intensive care during the 1st weeks of treatment.[7] Uppal *et al.* found that CD4 counts normalized after treatment with antitubercular medications, suggesting that TB is a reversible cause of $CD4^+$ lymphopenia.[6]

In addition, on the differential are HIV^- infants of HIV^+ mothers, although in this case, the age excludes this differential. However, for the purpose of academic interest, we provide a brief note. In this case, a recent study showed that HIV^- infants of HIV^+ mothers have low CD4 counts. The proposed theory was that this likely is caused by inhibition of progenitor cell function by the transplacental diffusion of HIV-soluble proteins *in utero*.[8,9]

Another consideration is a viral etiology. Numerous viruses are known to result in reversible CD4 lymphopenia and decreased CD4/CD8 ratios. These include, but are not limited to, human T-lymphotropic virus I and II, hepatitis B virus, CMV, group C adenoviruses, herpes simplex viruses, RSV, measles, mumps, influenza, parainfluenza, coronavirus, poliovirus, and lymphocytic choriomeningitis virus.[10–16] Although the exact cause is unknown and may be different for the various viruses in question, apoptosis of uninfected cells is one of the principal causes for the immunosuppression induced by measles virus infection.[16] The early lymphopenia and the later neutropenia in the influenza-infected patient may represent migration of these cells from the circulation to the infected respiratory tract as a consequence of infection.[17]

Sarcoidosis also is important to remember when evaluating a patient with HIV^- lymphopenia. This disease will be more thoroughly discussed in the Discussion section; however, it is important to note that patients with sarcoid may show impaired delayed cutaneous hypersensitivity reactions and low levels of T-helper cells and monocytes in the peripheral blood.[18] Sarcoid-associated lymphopenia is felt to be caused by compartmentalization of lymphocytes in the lungs and at sites of granuloma formation.[18]

In this case, the outside hospital preformed the bronchoalveolar lavage and there was more concern for resistant infectious organisms and sarcoid was not considered. This was based on the finding of no mediastinal lymphadenopathy on chest CT. Therefore, bronchoalveolar lavage fluid was sent for cytology and cultures, but transbronchial biopsy was not performed. Thus, a CD4/CD8 ratio on the fluid was unavailable also. This is unfortunate because the finding of an elevated CD4/CD8 ratio, even in the absence of radiological abnormalities and in the absence of granuloma on biopsy, may strongly suggest the diagnosis of sarcoidosis.[19] This again emphasizes the importance of considering this pathology in the differential, thus leading to the inclusion of the appropriate studies. Finally, we must always consider the idiopathic/iatro-

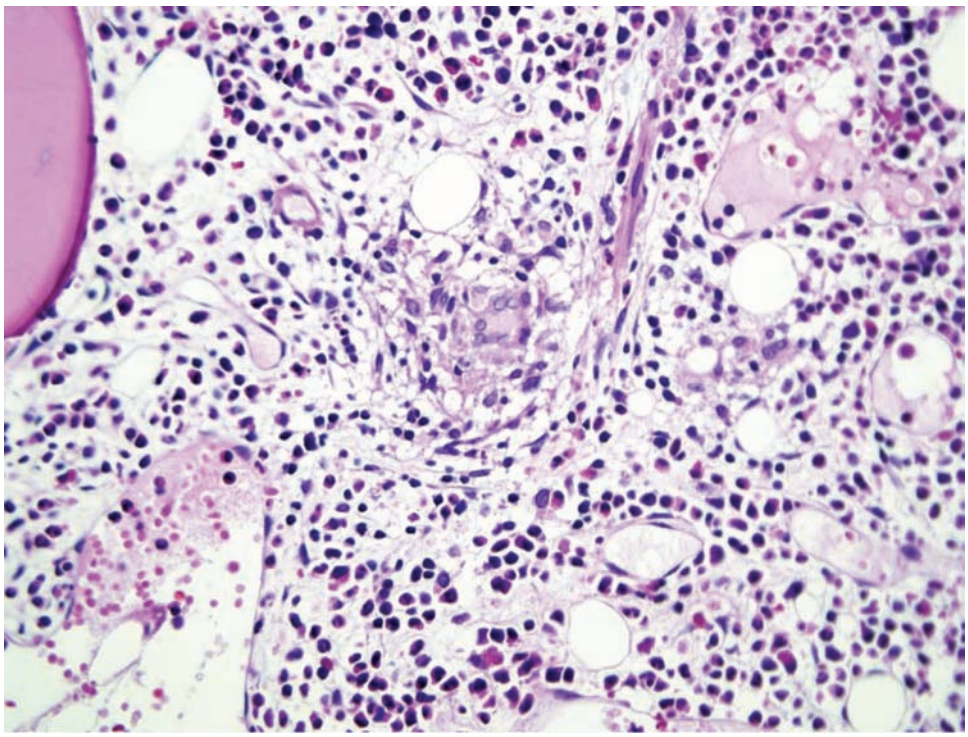

Figure 1. *Bone marrow biopsy specimen showing a noncaseating granuloma.*

genic causes. Lymphopenia associated with hospitalization is most often reversible and caused by acute illness such as sepsis, trauma, surgery, malignancy, chemotherapy, and steroid use.[10,20]

Clinical Evaluation, Laboratory Data, and Clinical Course

The patient was readmitted for evaluation of FUO and started on broad-spectrum antibiotics. A high-resolution chest CT was preformed and was unremarkable without lymphadenopathy or infiltrate. Blood cultures were negative. The angiotensin-converting enzyme level in the blood was normal at 41 U/L. Multiple studies to evaluate infectious etiology were unremarkable including *Histoplasma capsulatum* urine antigen and antibodies to Q fever, *Blastomycosis*, *Brucella*, and *Coccidiomycosis* species. A bone marrow biopsy revealed noncaseating granulomas (Fig. 1). The bone marrow biopsy was negative for acid-fast bacilli and culture for bacteria, fungi, and mycobacteria.

The patient was diagnosed with sarcoid and started on oral prednisone, 40 mg daily. Within 48 hours, the patient was afebrile and felt well. He was discharged on oral prednisone. On 2-month follow-up, the patient was asymptomatic on a gradual prednisone taper. His total CD4 T-cell count, CD8 T-cell count, and hemoglobin were now within normal range.

QUESTION 2

What is the differential diagnosis of this patient's bone marrow granuloma?

a. Malignancy
b. Infection
c. Environmental exposure
d. Drug exposure
e. Sarcoidosis
f. Idiopathic granulomatosis

Differential Diagnosis

The differential diagnosis of bone marrow granulomas is extensive including malignancy, infection, environmental exposure, drug exposure, and idiopathic granulomatosis. Clinical, radiological, and biological correlation is needed to distinguish between bone marrow granulomas caused by sarcoidosis and those resulting from Hodgkin's lymphoma. It is unusual for non-Hodgkin's lymphoma to present initially as a bone marrow granuloma, and immunophenotyping may be helpful in distinguishing the granuloma of non-Hodgkin's lymphoma from the epithelioid granuloma of sarcoid.[21]

Infectious causes of bone marrow granulomas include the noncaseating granulomas of brucellosis, typhoid fever, Q fever, CMV, Epstein-Barr virus, TB, mycobacterium avium-intracellulare, and disseminated fungal infections such as histoplasma capsulatum.[21–26] The granuloma of TB uncommonly displays the classically described caseating necrosis, and marrow patchy necrosis may be seen.[27] With typhoid fever, chronic granulomatous inflammation was the most common finding on bone marrow biopsy and was associated with hemophagocytosis.[28] Bone marrow

cultures are more sensitive than blood cultures for organism recovery.[29] Ebstein-Barr virus and CMV are the most frequently reported viruses to cause bone marrow granulomas; however, no unique or distinguishing characteristics have been described.[21] Serological testing and pathological staining can help to distinguish between infectious etiology and sarcoidosis.

Environmental and drug exposures also have been reported as causes for bone marrow granulomas. Silicosis and coal workers' pneumoconiosis have been reported in association with bone marrow granulomas.[21] In the case of coal workers, a characteristic yellow-brown pigment was found in the granuloma.[21,30] In addition, multiple case reports implicate the class III antiarrhythmic amiodarone in marrow granuloma formation.[31–33] Case reports also exist implicating procainamide and sulfonamide.[21]

Finally, sarcoidosis is one of the most frequent causes of bone marrow granuloma. However, it is rare for sarcoidosis to present as a granuloma in bone marrow, and isolated extrapulmonary sarcoidosis occurs in $<5\%$ of cases.[21] Sarcoidosis will be discussed in greater detail in the following section.

DISCUSSION

In 1877, Jonathan Hutchinson described a dermatologic disease believed today to be the multisystem disorder known as sarcoidosis; however, to this day, the etiology is not known.[33] Currently, the lifetime risk for U.S. black individuals is 2.4% and that for U.S. white individuals is 0.85%.[35,36] It is more common in the 20- to 40-year age group. Compared with other races, black patients frequently present more acutely and experience more severe disease. Furthermore, bone marrow involvement is more common in black patients.[37] White patients tend to present with asymptomatic and chronic disease.[36] Thus, awareness of both the common and the uncommon presentation of this disease is of great clinical relevance.

Progress has been made in understanding the pathogenesis of sarcoid. In the early sarcoid reaction, there is an influx of $CD4^+$ T_{H1} lymphocytes and mononuclear phagocytes into affected tissues. Macrophages fuse and differentiate into epithelioid and multinucleated giant cells. CD4 and CD8 T cells encircle the granuloma, and with time, a dense band of fibroblasts, mast cells, collagen fibers, and proteoglycans encase the granuloma. Cytokines interleukin (IL)-2, interferon (IFN) γ, and tumor necrosis factor (TNF) α play key roles in granuloma formation.[36,37]

Sarcoidosis may involve single or multiple organs at a time. Asymptomatic cases often are diagnosed when chest radiography performed for unrelated reasons reveals bilateral hilar adenopathy. Patients commonly present with constitutional symptoms such as fever, anorexia, fatigue, weight loss, and arthralgias coupled with dyspnea on exertion, cough, and retrosternal chest pain. Patients also may experience dermatologic (lupus pernio and erythema nodosum), ocular, cardiac, neurological, and musculoskeletal involvement. Diagnosis depends on clinical, radiographic, hematologic and histologic findings. Ultimately, diagnosis is that of exclusion, based on the finding of noncaseating granulomas with no identified cause.[36]

Bone involvement occurs in 3–30% of patients and normally occurs in patients with generalized and advanced disease, depending on the interest of the author and the radiological evaluation performed.[38,39] A worldwide review of 3676 patients with sarcoidosis showed osseous lesions in only 109 patients (3%).[38,40] The mortality rate is reported to be four times higher in patients who are found to have abnormalities on bone radiography.[41,42] Overall, osseous involvement is reported to portend a worse prognosis and has been thought to indicate chronic, persistent, and irreversible systemic disease. Interestingly, bone marrow involvement is more commonly associated with skin lesions in 50% of cases.[41] Pulmonary infiltration was observed in 60% of sarcoid cases and hilar adenopathy alone was present in 33% of cases.[41]

Skeletal sarcoidosis is rare in early stages, with the centrifugal skeleton being affected more commonly (phalanges, metacarpals, and metatarsals), and the axial skeleton and skull affected less commonly.[39] The long bones are rarely involved. Radiographically, bone lesions appear as variable-sized cysts in areas of expanded bone, lattice-like changes, or punched-out lesions. Generally, sarcoidosis of the bone can be visualized with bone radiography, radioisotope bone scans, or MRI. MRI has been found to be more sensitive in detecting bone involvement.[42] Conversely, MRI is not specific in determining the etiology of the lesions, so clinical correlation is important when interpreting the images.[43,44] Overall, definitive marrow involvement may be diagnosed only with a biopsy.

Sarcoidosis also may involve the bone marrow; however, isolated sarcoidosis of the marrow as an initial presentation, without radiographic abnormalities or involvement of other organ systems, is not as common.[45,46] With sarcoidosis of the marrow, peripheral blood tests may show evidence of anemia, leucopenia, or lymphopenia.[47] Patients also may exhibit an increased erythrocyte sedimentation rate, hyperglobinemia, an elevated level of angiotensin-converting enzyme, and false positive results for rheumatoid factor and antinuclear antibody testing. Abnormalities of bone and calcium metabolism also may be encountered, although hypercalcemia is seen in only 10% of patients with sarcoidosis.[39,48]

Corticosteroids are the mainstay of treatment for sarcoidosis. However, noncorticosteroid agents such as methotrexate, hydroxychloroquine, azathioprine, cyclosporine, and pentoxifylline are being used more frequently.

In conclusion, we present a rare case of isolated noncaseating marrow granuloma in a patient with a FUO. Although the possible etiologies of such lesions are numerous, a series of exclusions lead us to our ultimate diagnosis of sarcoid. To this date, it is unclear whether such isolated marrow noncaseating granulomas are, in fact, sarcoid. However, based on the exclusion of other pathologies and the response to corticosteroids, we believe that for the moment, this is the best diagnostic and therapeutic path to take. Furthermore, with the prevalence and debilitating nature of this disease, unique cases such as this are vital to further our awareness and understanding of sarcoid. Rare and unique cases will only teach us more about sarcoid and further spur both interest and future reports. Ultimately, this will give us new thoughts, theories, and studies into the etiology of sarcoid.

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Patient Oriented Problem Solving (POPS) Case Report

A case of fever, eosinophilia, and pneumonia

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ABSTRACT

There is a broad differential for patients presenting with fever, eosinophilia, and pneumonia. We present a case of a 48-year-old man who presented with recurrent fever, pleuritic chest pain, and cough. His medical history was significant for a recent trip to Arizona. A chest x ray showed a right lower lobe infiltrate and CT examination of the chest showed extensive mediastinal lymphadenopathy. Tissue culture from a biopsy specimen of the mediastinal lymph nodes revealed growth of Coccidioides immitis *and a diagnosis of coccidioidomycosis was made. He was treated with a total of a 9-month course of itraconazole and has remained disease free for >2 years. This case shows how a careful history and evaluation will direct the clinician to the correct diagnosis.*

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Key words: Coccidioides, coccidioidomycosis, diagnosis, eosinophilia, fever, pneumonia

CASE PRESENTATION

Chief Complaint

The patient is a 48-year-old man who presents with recurrent fever, pleuritic chest pain, and cough.

History of Present Illness

The patient presented to his primary care physician complaining of a fever of 101°F, shaking chills, and hives over his extremities and back. He was started on hydroxyzine with improvement of the hives, but the fever persisted and he developed pleuritic chest pain. A chest radiograph (CXR) was performed, which showed a right lower lobe infiltrate, and a 5-day course of azithromycin was started. He completed azithromycin and reported improved symptoms, but the chills and fever returned 4 days later. Inhaled albuterol was of no benefit. Twelve days after the initial presentation, a complete blood count (CBC) was obtained, which showed a white blood cell count of 24,200/mm^3 with 28% eosinophils, 51% neutrophils, 7% lymphocytes, and 10% atypical lymphocytes. He was started on prednisone at a fixed dose of 60 mg daily and his symptoms improved, but after 4 days, the fever reoccurred and he reported pleuritic chest pain, night sweats, and cough. This prompted a hospital admission.

Medical history was significant for a torn left gastrocnemius muscle (complicated by deep vein thrombosis), depression, and obstructive sleep apnea. Review of systems was negative for weight loss or gain, diarrhea, adenopathy, or hemoptysis.

Physical Examination on Hospital Admission

Vital signs included a temperature of 99.2, heart rate of 104, respiratory rate of 20, and a blood pressure of 144/90. There was no cervical adenopathy. The chest was clear to auscultation bilaterally and there were no wheezes or rales on exam. The rest of the physical examination was within normal limits.

QUESTIONS

1. What of the following are included in the differential diagnosis of a patient presenting with fever, eosinophilia, and pneumonia?
   - A. Acute eosinophilic pneumonia
   - B. Drug reaction
   - C. Churg-Strauss syndrome (CSS)
   - D. Lymphoma
   - E. Tuberculosis
   - F. Coccidioidomycosis
   - G. Loffler's syndrome (transpulmonary passage of helminth larvae)
   - H. Chronic eosinophilic pneumonia (CEP)
   - I. Allergic bronchopulmonary aspergillosis
   - J. Hypereosinophilic syndrome

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2. What additional laboratory data or investigations would be helpful in arriving at a diagnosis in this patient?
   A. Purified protein derivative placement
   B. Serum *Coccidioides* antigen and antibodies
   C. Sputum evaluation for acid fast bacilli
   D. Lymph node biopsy

Discussion of the Differential Diagnosis

An elevated peripheral blood eosinophil count can be associated with a number of reactive conditions.[1] The differential diagnosis of a patient with recurrent fever, eosinophilia, and pneumonia is listed in Table 1.

The association of eosinophilia and diffuse vasculitis can indicate the presence of CSS,[2] which usually is accompanied by severe asthma symptoms.[3] The etiology is unknown. According to Lanham's criteria there must be fulfillment of the following: the presence of asthma, peak peripheral eosinophilia >1500/mm^3, and systemic vasculitis involving two or more extrapulmonary organs.[4] Tissue vasculitis can be found on biopsy in the later stages of disease and can involve the gastrointestinal tract, heart, lungs, skin, and nervous system.[5] The average age of diagnosis is 48 years.[6]

Drug reactions occasionally may present with eosinophilia, fever, and pulmonary symptoms. The nonsteroidal anti-inflammatory drugs (NSAIDs), minocycline, nitrofurantoin, pentamidine, L-tryptophan, and phenytoin can cause pulmonary eosinophilia.[7,8] There have been reports of azithromycin-induced eosinophilia.[9,10]

Acute eosinophilic pneumonia presents with acute onset of fever and respiratory symptoms and may be a cause of respiratory failure.[7,11–13] Peripheral eosinophilia may occur but usually is absent. CEP has similar features but presents in a subacute fashion.[14] The clinical picture often is similar to that of CSS, and some feel that CEP actually might be a milder variant of CSS.

Loffler described a syndrome of pulmonary infiltrates and peripheral eosinophilia in 1956.[15] The cause was found to be *Ascaris* infection contracted from fertilizer contaminated with human night soil. As part of the lifecycle of *Ascaris lumbricoides*, larvae travel through the bloodstream, migrate into lung alveoli, travel up the airways, and, subsequently, descend the esophagus, eventually reaching the small bowel. This transpulmonary passage of the helminth larvae leads to Loffler's syndrome. *Ascaris* is known to be the most common cause, but hookworms and *Strongyloides stercoralis* have similar life cycles and can less frequently cause the syndrome.[16]

Allergic bronchopulmonary aspergillosis occurs in asthmatic patients who develop a hypersensitivity reaction to *Aspergillus*, which colonizes their airways.[8,17] Patients have pulmonary symptoms and eosinophilia and may have fever. The syndrome is characterized by a markedly elevated total IgE level, along with specific antibodies to *Aspergillus.*

The hypereosinophilic syndrome is characterized by chronic peripheral eosinophilia (>1500/mm^3) and specific organ dysfunction due to eosinophil infiltration and mediator release, which is otherwise unexplained by other medical conditions that are known to cause eosinophilia.[18] Clinical features may vary considerably from patient to patient. Organs that may be affected include the heart, spleen, gastrointestinal tract, kidneys, peripheral nerves, skin, and lungs.[19]

Tuberculosis is caused by the intracellular pathogen *Mycobacterium tuberculosis*. Primary pulmonary tuberculosis involves the lower lung lobes, while reactivation tuberculosis typically involves the upper lung lobes. Tuberculosis is diagnosed by the identification of the organism or from polymerase chain reaction–based amplification of *M. tuberculosis* DNA from sputum or infected tissues.[20]

Pulmonary and peripheral eosinophilia also can occur when lymphoma involves the lung.[7] The symptoms of lymphoma include constitutional symptoms or B symptoms including fever higher than 38°C, night sweats, and weight loss of >10% of the total body weight over 6 months.[21]

Typically, fungal infections do not cause an eosinophilia. Coccidioidomycosis, however, is an exception.[22] Pulmonary eosinophilia represents a hypersensitivity reaction to *Coccidioides immitis* and has been observed in up to 88% of patients with a primary infection.[22] In the early stages of infection, peripheral blood eosinophilia is present in 5–18% of patients and eosinophil counts as high as 20–25% of the total white blood cell count are not unusual.[22] *C. immitis* is found primarily in the southwestern United States and the San Jaoquin Valley in California. The fungi propagate in the soil and the infectious arthrospores can be spread during hot and dusty weather.[23] Spores are inhaled and deposit in alveoli or bronchioles, initiating an inflammatory response.[23] Dissemination from the primary pulmonary focus can occur weeks to months after infection. Initial clinical symptoms can include cough, sputum production, fever, night sweats, malaise, anorexia, and chest pain.[24] The severity of the illness is highly variable. Symptoms may be fairly mild, and the disease often goes undiagnosed. Within the first 2 days of illness, an erythematous exanthem that can be macular may develop. Erythema nodosum or erythema multiforme may develop 3 days to 3 weeks after the first symptoms. Disseminated disease may involve the central nervous system, kidneys, thyroid gland, pancreas, or skeletal system and with disseminated disease there may be a persistence of fever.[23,24] Infants and immunocompromised individu-

Table 1 **Differential diagnosis of recurrent fever, eosinophilia, and pneumonia**

Disease Process	Causative Organism	History	Clinical Features	Laboratory Findings	Radiographic Appearance	Treatment
Acute eosinophilic pneumonia	None known ('idiopathic')	Acute febrile illness with respiratory symptoms	Fever, cough, dyspnea, pleuritic chest pain	May have peripheral eosinophilia, although usually absent	Nonspecific: diffuse migratory bilateral interstitial opacities, pleural effusion	Oral or intravenous glucocorticoids
Drug reaction	None	History of medication use	Variable	May have eosinophilia	Variable	Removal of offending agent
CSS	None known ('idiopathic')	Asthma and rhinitis may precede the syndrome	Respiratory sxs, rhinitis, neuropathy, skin vasculitis, gastrointestinal symptoms	Eosinophilia, positive ANCA; biopsy shows eosinophilic infiltrate, granulomatous vasculitis	Variable: most commonly transient patchy opacities	Systemic corticosteroids
Lymphoma	None	May have prior history of malignancy	Fever, cough adenopathy	Pulmonary eosinophilia. Reed-Sternberg cells	May have infiltrates	Radiotherapy, chemotherapy, immunotherapy
Tuberculosis	*M. tuberculosis*	History of exposure to tuberculosis	Hemoptysis, fever, cough, weight loss	Tuberculin skin test, cultures showing acid fast bacilli	Cavitary lesions, hilar adenopathy, consolidation	Isoniazid ethambutol streptomycin rifampin
Coccidioidomycosis	*C. immitis*	Travel or residence in endemic area	Erythema nodosum, fever, chills, cough	Complement fixation and precipitin test positive, coccidioidin skin test positive	Unilateral infiltrate, hilar adenopathy	Antifungal therapy
Loffler's syndrome	*Ascaris* hookworms *Strongyloides*	Travel or residence in endemic area	Cough, fever, chest pain, dyspnea, wheezing	Sputum shows Charcot-Leyden crystals	Migratory, round or oval infiltrates	Antiparasitic agents
CEP	None known ('idiopathic')	May be preceded by asthma	Subacute: fever, cough dyspnea	Interstitial and alveolar eosinophils and histiocytes, multinucleated giant cells	Bilateral peripheral or pleural infiltrates: the "photographic negative of pulmonary edema"	Systemic corticosteroids
Allergic broncho-pulmonary aspergillosis	*Aspergillus*	Asthma	Fever, cough, malaise, wheezing, hemoptysis	Eosinophilia, elevated IgE	Central bronchiectasis	Systemic corticosteroids
Hypereosinophilic syndrome	None known ('idiopathic')	More common in male patients	Symptoms of organ damage, fatigue	Chronic eosinophilia	May be normal; variable infiltrates may be present	Corticosteroids interferon-α imatinib

ANCA = antineutrophil cytoplasmic antibody.

Table 2 **Summary of laboratory findings at the time of hospitalization**

Laboratory Test	Result	Reference Range
WBC	27,100/mm^3 (87% seg 3% band 6% lymph 1% eos)	4500–10,000 cells/mm^3
Urine eosinophils	Negative	Negative
ANCA	Negative	Negative
ESR	60 mm/hr	0–15 mm/hr
CRP	10.2 mg/dL	0–0.5 mg/dL
IgE	6743 IU/mL	0–150 IU/mL
Serum CMV titer	Negative	Negative
Monospot	Negative	Negative
Bacterial blood cultures	Negative	Negative
CT scan: head	Normal	
CSF	No red blood cells No white blood cells Protein, 24 mg/dL Glucose, 80 mg/dL Bacterial cultures: negative Fungal cultures: negative	Protein: 15–45 mg/dL
HIV test	Nonreactive	
Sputum for acid fast bacilli	Negative ×3	
Urinalysis	Normal	
Mediastinal biopsy histology	Eosinophils, microabscesses, and fungal spherules	
Fungal culture from biopsy	*C. immitis*	
Coccidioides serology	Positive for TP and F antigens	

ANCA = antineutrophil cytoplasmic antibody; CMV = cytomegalovirus; CRP = C-reactive protein; CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate; F = complement fixation; HIV = human immunodeficiency virus; TP = tube precipitating; WBC = white blood cell count.

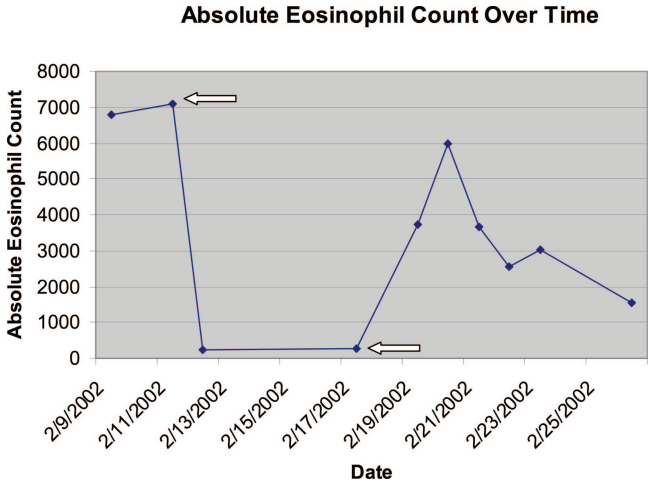

Figure 1. *Absolute eosinophil count over time. The first arrow indicates the initiation of treatment with prednisone, and the second arrow indicates the time of hospitalization, at which point the prednisone was discontinued.*

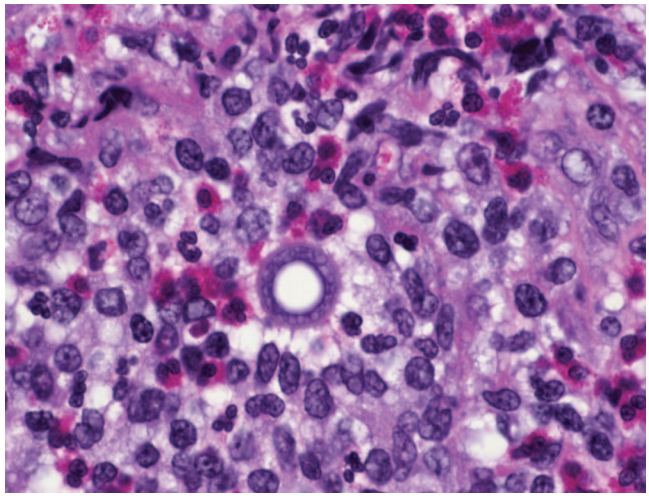

Figure 2. *Tissue histology showing a mixed inflammatory infiltrate, including eosinophils, and a spherule that is characteristic of* C. immitis *(center).*

als are most at risk for the disseminated form.[23] CXRs may show hilar adenopathy, lobar infiltrates, or pleural effusions.[24] The diagnosis of coccidioidomycosis can be made *via* direct culture of blood, tissue, sputum, or fluid samples. A positive coccidioidin skin test simply indicates past infection, and therefore is not helpful in ascertaining acute infection.[25] Immunodiffusion for antibodies to *Coccidioides* can be very helpful in confirming diagnosis. Antibodies against the tube-precipitating antigen in-

dicate recent, active infection. These are primarily IgM antibodies that appear within several days to a week after infection and revert to negative within a few months. Antibodies to the complement-fixation antigen indicate active or recent past infection (up to 1 year), usually develop within a month after infection, and remain positive throughout the clinically active disease.[26]

The treatment for coccidioidomycosis is antifungal therapy, but patients with minimal symptoms who are not immunocompromised or infants do not need treatment.[23,25] If antifungal therapy is started, ketoconazole or fluconazole, 400 mg/day, or itraconazole, 200 mg twice daily, for 3–6 months are common regimens.[25] Although systemic steroid therapy will lead to rapid improvement of eosinophilia (as seen with our patient) and may lead to temporary amelioration of some symptoms, it may increase the likelihood of disseminated infection and therefore is contraindicated. Patients diagnosed with coccidioidomycosis should be monitored with serial testing of anti-*Coccidioides* antibodies at intervals of weeks to months to ensure that progressive disease has not developed.[25]

Additional History

The patient lives in Massachusetts. Travel history was remarkable for a recent 1-week visit to Arizona. He spent the duration of the visit at a deceased parent's house, taking care of the affairs, and throughout the week was packing and unpacking boxes in the basement. He also went on a hiking excursion while there.

Laboratory and Other Diagnostic Findings

The laboratory data at the time of hospitalization is presented in Table 2. The chemistry and liver panels were normal. Electrocardiogram (EKG) was normal. A CT scan of the chest showed extensive mediastinal lymphadenopathy and bulky lower cervical lymphadenopathy. Peripheral eosinophil count over time, both before and during the hospitalization, is depicted in Fig. 1.

The patient underwent mediastinoscopy and biopsy of his mediastinal lymph nodes. The tissue histology showed mixed inflammatory cells including eosinophils, microabscesses, and spherules that are characteristic of *Coccidioides* (Fig. 2). The tissue culture from the biopsy showed *C. immitis*. Immunodiffusion for *Coccidioides* antibodies was positive for both the tube-precipitating and the complement-fixation *Coccidioides* antigens.

Final Diagnosis

The final diagnosis was coccidioidomycosis.

CONCLUSION

Our patient was diagnosed with coccidioidomycosis. His recent travel history to Arizona was a significant clue toward making the diagnosis. His biopsy was consistent with coccidioidomycosis and the tissue culture and serology was confirmatory. He was started on a prolonged course of itraconazole with good response. He has remained relapse free for >2 years.

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Patient Oriented Problem Solving (POPS) Case Report

Persistent dyspnea and leg edema

Khoi Duc Nguyen, M.D., and Marianne Frieri, M.D., Ph.D.

ABSTRACT

This case illustrates a complexity of confounding and overlapping symptoms that can masquerade as another diagnosis. A 56-year-old African American man with persistent dyspnea and leg edema was hospitalized three times in a period of 6 months. The patient was treated for asthma, chronic obstructive pulmonary disease, and congestive heart failure. Hypertension and peptic ulcer disease were treated also. Complete clinical improvement was not observed. A careful review of his last admission and current admission clinical presentation and laboratory evaluation revealed a systemic manifestation and laboratory findings consistent with atypical systemic lupus erythematosus.

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Key words: Asthma, atypical, chest pain, CHF, COPD, diagnosis, dyspnea, edema, problem solving case, SLE

CASE PRESENTATION

Chief Complaint

Persistent shortness of breath and leg swelling

History of Present Illness

A 56-year-old African American man presented with persistent dyspnea and bilateral leg edema. The symptoms first started about 6 months before this admission. The patient was admitted to another hospital with a diagnosis of asthma, peptic ulcer disease, and hypertension. He was treated and discharged home with montelukast, ipratropium bromide, felodipine, and a proton pump inhibitor. The patient was evaluated in our hospital for the first time approximately 1 month before this admission with complaints of shortness of breath, left-sided chest pain, and palpitation. He also was found to have fever, chills, cough with white sputum, reproducible chest pain, and bilateral leg edema. Laboratory evaluation on this admission was significant for small to moderate pericardial effusion, scattered bilateral patchy infiltrates, and mild thoracic adenopathy on chest CT angiography. Bilateral knee joint effusion on lower extremities CT scan was observed also. The patient was diagnosed with asthma and bronchitis and treated with Levaquin along with his home medications. His symptoms had not resolved since the last discharge, which led to this admission. He remained in the hospital for 2 weeks and was treated for congestive heart failure with diuresis and enalapril, an angiotensin-converting enzyme (ACE) inhibitor. He also continued his regular medications, and corticosteroids were added. Although the patient was able to ambulate and maintain his daily activities, he still experienced dyspnea and his legs remained edematous.

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Medical History

The patient had a history of syphilis and gonorrhea that were treated 30 years ago and a positive syphilis test in 1996. An umbilical hernia repair was preformed also 2 years ago.

Family History

His family history is significant for emphysema and cirrhosis in his father and diabetes in his mother.

Social History

He was a drug abuser, drinker, and smoker (1 pack/day for >40 years). Today, he is still smoking ~5 cigarettes a day.

Physical Examination

Examination revealed a middle aged man with puffy eyes in slight respiratory distress. Some fine crackles in the bases without wheezing were noted on lung auscultation. Heart examination revealed regular heart sounds without murmurs or pericardial rub. Jugular veins were distended with positive Kussmall's sign. Abdomen was soft and distended. Ascites was noted. Liver was palpated ~3 cm below the costal margin. Spleen was not palpable. Legs were edematous without erythema or pain.

Table 1 **Laboratory evaluation**

CBC and differential		Immunology (Cont.)	
Hemoglobin (g/dL)	9.5	Anti SSB antibodies	(−)
Hematocrit (%)	30.5	RF	(−)
WBC × 10/L	12.8	Proteinase 3 Antibody	<6
Neutrophils (%)	70.5	Myeloperoxidase Ab	9
Lymphocytes (%)	21.5	Anti-trypsin	178
Chemistry		aCL	<10
Sodium (mmol/dL)	142	RPR	Reactive
Potassium (mmol/dL)	5.2	FTA-ABS	Reactive 3+
Chloride (mmol/dL)	106	HIV	(−)
Bicarbonate (mmol/dL)	27	Cardiac enzymes	
BUN (mg/dL)	55	CK (U/L)	36
Creatinine (mg/dL)	1.9	Troponin (ng/dL)	<0.01
Glucose (mg/dL)	108	Lipid profile	
Liver function test		Cholesterol (mg/dL)	148
ALT (U/L)	7	Triglycerides (mg/dL)	118
AST (U/L)	13	HDL (mg/dL)	38.4
Alkaline phosphate (U/L)	63	LDL (mg/dL)	86
Total bilirubin (mg/dL)	0.1	Peak flow	
Total protein (g/dL)	6.1	Before nebulizer treatment (mL)	250
Albumin (g/dL)	3.0	After nebulizer treatment (mL)	650
Iron study		Urine analysis	
Iron (mg/dL)	93	Creatinine (mg/dL)	144.3
Iron saturation (%)	42	Sodium(mmol/L)	49
Ferritin (ng/dL)	92	Protein(mg/dL)	1014
TIBC (mmol/dL)	219	24-hours Creatinine (mg/day)	1681
Immunology		24-hours Protein (g/day)	10,058
C3 (mg/dL)	42.2	Epithelium cells	0–2
C4 (mg/dL)	<10	Bacterial	Few
ANA	(+); Nucleolar, 160	RBC	50–100
Anti-dsDNA	(−)	WBC	5–10
Anti-Sm antibodies	(−)	Hyaline cast	0–2
Anti-RNP antibodies	(−)		
Anti SSA antibodies	(−)		

WBC = white blood cell count; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TIBC = total iron binding capacity; ANA = antinuclear antibody; dsDNA = double strand DNA; RF = rheumatoid factor; aCL = anti-cardiolipin; RPR = rapid plasma reagin = FTA-ABS = fluorescent treponemal antibody absorbed; CK = creatine kinase; HDL = high density lipoprotein; LDL = low density lipoprotein.

Laboratory and Other Diagnostic Findings

Laboratory evaluation is summarized in Table 1. Ventilation-perfusion scan and spiral CT scan of the thorax were negative for pulmonary embolism, and lower extremities Doppler sonography negative for deep vein thrombosis. Echocardiogram revealed pericardial effusion as did the CT angiogram of the chest. The echocardiogram, left ventricle function was normal with ejection fraction of 55%. There was no segmental motion. Left atrium, mitral valve, and aortic valve were normal. There were mild concentric left ventricle hypertrophy, mild dilatation of right atrium, mild dilatation of right ventricle, and mild tricuspid regurgitation. Pulmonary hypertension was noted. Chest x ray revealed no infiltrates. Biopsy of the left kidney revealed fibrillary glomerulonephritis.

QUESTION

What is the Differential Diagnosis?

A. Asthma
B. Chronic obstructive pulmonary disease (COPD) exacerbation
C. Congestive heart failure
D. Atypical systemic lupus erythematosus (SLE)

Table 2 **ARA criteria for SLE**

Criterion	Description
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging
Photosensitivity	Skin rash as a result of usual reaction to sunlight
Oral ulcer	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Proteinuria >0.5 g/day or >3+ or cellular cast
Neurologic disorder	Seizure or psychosis without other causes
Hematologic disorder	Hemolytic anemia or leucopenia (<4000/μL) or lymphopenia (<1500 /μL) or thrombocytopenia (<100,000/μL) in the absence of offending drugs
Immunologic disorder	Anti-dsDNA, anti-Snti-am, and/or antiphospholipid
Antinuclear antibodies	An abnormal titer of ANAs by immunofluorescence or equivalent assay at any point in time in the absence of offending drugs

Source: Ref. 6.

DISCUSSION

Asthma is defined as a chronic inflammatory disease of airways characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy, and clinically by paroxysm of dyspnea, cough, and wheezing.[1] A current review on asthma pathophysiology discussed current concepts of airway inflammation with a special emphasis on the epithelium, smooth muscle dysfunction, and airway remodeling.[2] Diagnosis is made on clinical presentation, and pulmonary function test in which FEV_1 will be lower than normal and is reversible with using β-adrenergic agonists. Asthma may be difficult to recognize or treat in seniors with COPD.[3] COPD has been defined by the Global Initiative for Chronic Obstructive Lung Diseases as a diseased state characterized by airflow limitation that is not fully reversible.[4] This includes emphysema characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airway disease, a condition in which chronic small bronchioles are narrowed.[4] Smoking, air pollution, and some occupational hazards are implied in its pathophysiology. Genetics is considered in patients with α-antitrypsin deficiency. Metalloproteinase dysregulation and other enzymic imbalance also are thought to be the causes.[5] Clinical presentations of this disorder are typical of emphysema, which is called "pink puffer," and chronic bronchitis, which is called "blue bloater." However, the symptoms may vary. Congestive heart failure is classified as systolic and diastolic heart failure. Dyspnea can be at rest, orthopnea, or exertional. Usually, jugular vein distention is observed. Leg edema is a very common sign. Echocardiogram will show some evidence of heart failure such as low ejection fraction or hypokinesis.

SLE is a disorder of the immune system in which pathogenic subsets of autoantibodies and immune complexes cause damage to the tissues. Consequently, multiple organ involvement is seen in patients with SLE, such as skin and mucosal membrane, joints, heart, lungs, kidneys, and other organs. The disorder is thought to be caused by the abnormal immune responses, which include polyclonal and antigen-specific T- and B-lymphocyte hyperactivity and the inadequate regulation of that hyperactivity.[6] The interaction between susceptibility genes and the environment is implied in the etiology. There is an increased concordance for disease in monozygotic twins compared with dizygotic twins. People with homozygous deficiency in early components of complement also were found to have SLE. A review on complement-related diseases addressed basic aspects of complement biology and clinical hereditary complement deficiencies in various pathologies.[7] There also is an association with human leukocyte antigen (HLA), particularly HLA class II DR and DQ genes, and HLA class III genes encoding C'2 and C'4.[6] A new study shows that smoking is associated with SLE.[8] The criteria for diagnosing SLE by the American Rheumatism Association (ARA) are shown in Table 2. Many patients, however, do not fulfill the criteria of the ARA and are referred as incomplete SLE. A trial in Europe followed up 122 patients who did not fulfill the ARA for SLE for 3 years. The first follow-up year, 22 patients fulfilled the ARA criteria. After 3 years, among the rest of the 100 patients, 3 patients developed full SLE.[9]

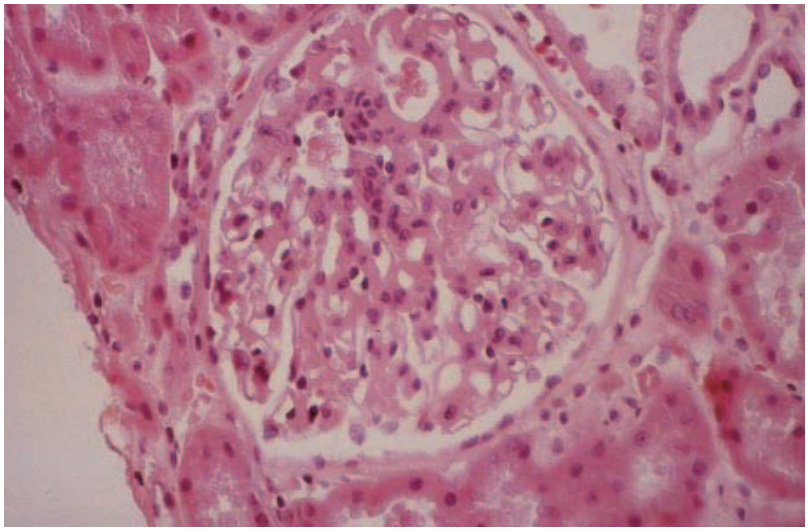

Figure 1. *Fibrillary glomerulonephritis (H & E, 250×): deposition of amorphous material in mesangium with slight segmental increase of mesangial cellularity. (Source: Frascá, GM, Canova C, Pasuinelli G et al. Institute of Nephrology, Cytopathology Service, St. Orsola-Malpighi Hospital, Bologna, Italy. Available online at www.sined.net/sin/ipr/casocl2/case2.htm. Last accessed Aug. 20, 2006.)*

Because SLE is a systemic disease, symptoms of multiple organs can be seen. Skin manifestation can be varied with malar or discoid rash or photosensitivity. A complication of SLE is toxic epidermal necrolysis, an acute rapid evolving mucocutaneous reaction with a high mortality.[10] Pleurisy, coughing, and dyspnea often are the first clues to either lung involvement or SLE itself. Musculoskeletal pain can be appreciated by patients as chest pain. It is from muscles, connective tissues, or the costochondral joints and can be reproducible. Pulmonary hypertension is not common but has been seen in SLE patients followed up for 5 years.[11] Cardiac involvement usually is pericardial effusion and can precede the clinical symptoms. Tricuspid regurgitation is seen also. Hematologic manifestation usually is hemolytic anemia as a criterion in ARA. However, many patients present with anemia of chronic inflammation. Lymphocytopenia is another symptom, but leukocytosis can occur. Renal involvements can be manifested by persistent proteinuria or established by kidney biopsy that shows the intrinsic glomerular disease. There are many types of glomerulonephritis seen in SLE. Fibrillary glomerulonephritis is a type in which there are glomerular and extraglomerular deposits of amorphous, noncongophilic material. It has been associated with chronic lymphocytic leukemia, related B-cell lymphoma, hepatitis C virus infection, cryoglobulinemia, and SLE.[12–14] A report of 10 cases in which glomerular deposits of Congo red negative amyloid-like fibrils were confirmed by electron microscopic identification. Two of these cases were from patients with SLE.[15] Representative microphotographs of fibrillary glomerulonephritis are shown in Figs. 1 and 2.

A variety of autoantibodies are found in patients with SLE. Antibodies to DNA were first described in the 1950s and are the best-recognized antibodies found in SLE patients. The antibody to single-strand DNA reacts with denatured DNA and does not cross-react with native DNA. It is less specific for SLE because it can be found in other connective tissues disorders. However, it may be of pathogenic significance for patients with proliferative lupus nephritis.[16] It does not correlate well with disease activity and therefore is not useful for management. Antibody to double-strand DNA (dsDNA), on the other hand, is more specific for disease (97%), but only ~5% patients with SLE will be positive for this disease,[17,18] as noted in this case. It reacts with native DNA and correlates well with disease activity and active glomerulonephritis. Anti-Smith antibodies and anti-RNP (ribonucleic protein) antibodies usually coexist in SLE and are found in 10–50% and 15–60%, respectively, of patients with SLE. The specificity of anti-Sm antibodies is ~55–100% for SLE.[19,20] Antiphospholipid antibodies also are found in a small portion of patients with SLE. A study on prevalence, onset, and clinical significance of this antibody in 130 patients using anticardiolipin enzyme-linked immunosorbent assay found only 24 patients (18.5%) positive before SLE diagnosis.[21] A recent study showed that anti-nucleosome antibodies have a sensitivity of 100% and a specificity of 97% in SLE patients, especially in those who had negative dsDNA antibodies. According to the study, this antibody is considered a diagnostic tool and a disease activity marker for the future.[22] Complements are found to be low in patients with SLE, especially C3 and C4, and also is correlated with lupus nephritis.[23] A study of patients with SLE over a duration of 10 years showed evidence of active disease, and the

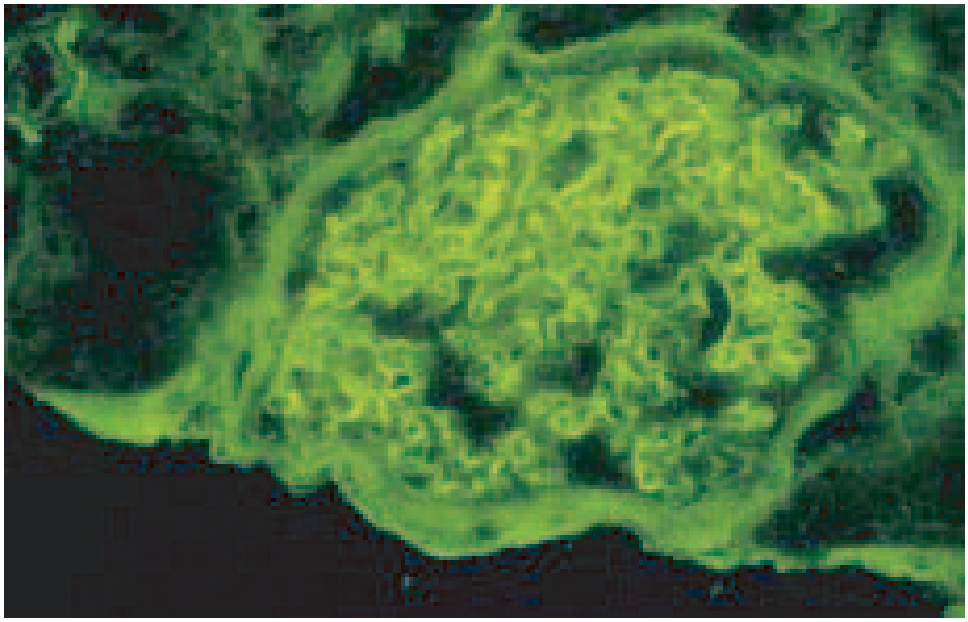

Figure 2. Fibrillary glomerulonephritis (immunofluorescence, 250×): diffuse deposits in the mesangium and along the capillary walls with a pseudolinear pattern. (Source: Frascá GM, Canova C, Pasuinelli G, et al. Institute of Nephrology, Cytopathology Service, St. Orsola-Malpighi Hospital, Bologna, Italy. Available online at www.sined.net/sin/ipr/casocl2/case2.htm. Last accessed Aug. 20, 2006.)

damage index was related to the involvement of the central nervous system, renal involvement, and the presence of hypertension[24]

FINAL DIAGNOSIS

D. Atypical SLE

This patient was first diagnosed with asthma in another hospital. Asthma can overlap with COPD and can be associated with bronchitis. Based on his clinical presentation and peak flow value, he may have a component of reactive airway disease. Asthma, however, may not have been a diagnosis in this patient. He has a family history of emphysema and is a smoker associated with COPD. The echocardiogram showed normal heart function, and treating the patient with diuresis and an ACE inhibitor did not improve much of the symptoms of his heart failure. The total clinical picture in this patient was systemic manifestations with respiratory, cardiac, hematologic, and renal involvement. On immunologic evaluation, a positive antinuclear antibody (ANA) with low complement levels seemed to correspond more with an immunologic process. Based on ARA criteria for SLE, this patient had four criteria that fulfilled the diagnosis of SLE: serositis with pericardial effusion, renal involvement with nephritic syndrome, positive ANA, and bilateral joint effusion. Although this patient did not present with arthralgia, he had bilateral joint effusion on the last admission. Anti-dsDNA, anti-Sm, anti-SSA, and anti-SSB antibodies were negative in this patient. Although anti-dsDNA and anti-Sm antibodies are specific for SLE, these antibodies are fluctuated during the course of disease, and, therefore, its negativity would not exclude the diagnosis of SLE in the presence of systemic manifestations. Atypical SLE therefore is considered in this patient. Although the pattern of ANA in this patient is not classic for SLE, it is worth considering the diversity of the pathology of this disorder. It is also worth noting that since the symptoms first started six months ago, this patient might have incomplete SLE until this admission, more ARA criteria for SLE is fulfilled. Because of the complexity of the disorder, SLE is commonly masqueraded by other diseases such as urticarial vasculitis for erythematous lesions or oral mucosal lesions for food hypersensitivity.[25] In our patient, the prominent symptoms of heart failure had masqueraded other signs of SLE. Diagnosis of SLE can be very difficult and misleading in patients who do not present all symptoms at once or who present symptoms differently from the classic manifestation.

CONCLUSIONS

The patient presented with the symptoms of congestive heart failure with dyspnea and leg edema. Clinical improvement was not observed by treating him with diuresis and ACE inhibitor. The cause of his presenting symptoms seemed to be caused by pericardial effusion and consequent pericarditis, which was a part of the systemic manifestation of SLE. Corticosteroids had somewhat improved his respiratory distress. The patient was referred to the rheumatology and nephrology service for treatment and follow-up. According to the

study of anti-nucleosome antibodies,[22] these antibodies may need to be tested in this patient. Moreover, the panel of autoantibodies, especially ds-DNA, and anti-Sm antibodies need to be repeated over a period of time.

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Patient Oriented Problem Solving (POPS) Case Report

Perioperative anaphylaxis in a 44-year-old man

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ABSTRACT

This article presents a case report of perioperative anaphylaxis in a previously nonallergic 44-year-old man undergoing cervical spine surgery. After receiving general anesthesia with midazolam, propofol, lidocaine, fentanyl, rocuronium, and sevoflurane and cefazolin for prophylaxis, the patient developed hypotension, tachycardia, bronchospasm, and generalized erythema. A serum tryptase concentration was markedly elevated 2 hours after the anaphylactic episode. Initial prick and intradermal skin tests (excluding skin testing for unavailable benzylpenicilloyl polylysine) and IgE immunoassays for penicillin and cefazolin were negative. However, repeat prick skin testing for cefazolin 6 weeks after anaphylaxis was positive. Although anaphylaxis to cephalosporins is rare, it remains a potential cause of perioperative anaphylaxis. All cases of perioperative anaphylaxis require a workup to identify the offending agent and to avoid future reactions. Skin testing regimens for several commonly implicated drugs used for general anesthesia are available and are described.

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Key words: Adverse reactions, allergy, anaphylaxis, anesthesia, cephalosporin, drug hypersensitivity, intraoperative anaphylaxis, perioperative anaphylaxis, skin test, tryptase

CASE PRESENTATION

Chief Complaint

Anaphylaxis after general anesthesia induction and cefazolin administration.

History of Present Illness

A 44-year-old man with cervical myelopathy and progressive bilateral lower extremity weakness was scheduled to undergo a C5-C6 and C6-C7 anterior cervical discectomy and fusion. Anesthesia was induced with administration of midazolam, propofol, lidocaine, fentanyl, rocuronium, and sevoflurane. He was intubated without complication. A latex Foley catheter was placed. Twenty minutes after intubation, the patient was given i.v. cefazolin for surgical prophylaxis. Within a minute, he developed hypotension, tachycardia, and decreased oxygen saturation. The patient was noted to have wheezing with increased peak inspiratory pressures and generalized erythema without urticaria or angioedema. His hypotension and tachycardia did not initially respond to aggressive fluid resuscitation or i.v. phenylephrine. He was subsequently given i.v. epinephrine boluses, diphenhydramine, and hydrocortisone to treat anaphylaxis. The surgery was aborted before a skin incision was made.

Medical History

The patient had no history of asthma, allergic rhinitis, atopic dermatitis, food allergy, stinging insect venom allergy, latex allergy, or drug allergy. He reported tolerance of unknown antibiotics in the past. In a motorcycle accident in 1992, he suffered a mandible fracture and underwent surgical repair. He underwent general anesthesia without difficulty. In the late 1990s, he had a left knee arthroscopic repair and once again tolerated general anesthesia without sequelae. The patient has had progressive bilateral lower extremity weakness over the last several years and magnetic resonance imaging of the cervical spine showed C5-C6 and C6-C7 myelopathy.

Physical Examination

During the anaphylactic reaction in the operating room, the patient had a temperature of 36.2°C, blood pressure of 32 mmHg over palpable, pulse of 112 beats/minute, and oxygen saturation of 91% on an FiO_2 of 100%. The patient was sedated and intubated. Cardiovascular exam was significant only for tachycar-

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dia with a regular rhythm and no murmurs. Auscultation of the lungs revealed bilateral wheezing. Peak inspiratory pressures were increased. Evaluation of the skin showed diffuse, full body erythema without edema or urticaria.

Initial Laboratory and Other Diagnostic Findings

The patient's complete blood count and basic metabolic panel obtained after administration of pressors and hydrocortisone were normal except for an elevated white blood cell count of 24,800 cells/μL, low serum bicarbonate of 20 mmol/L, and glucose of 176 mg/dL. There was no anion gap. An arterial blood gas had a low pH of 7.27 and a normal pCO2 (38.7) and pO2 (78.6). His magnesium, phosphorus, lactic acid, troponin, and INR were within normal limits.

QUESTIONS

What Is the Differential Diagnosis?

Perioperative anaphylaxis may be caused by a variety of agents including local anesthetics, neuromuscular blocking agents (NMBAs), opioids, induction drugs, inhaled anesthetics, antibiotics, or latex. Specifically, this patient was exposed to latex and received midazolam, propofol, lidocaine, fentanyl, rocuronium, sevoflurane, and cefazolin in the perioperative period.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Given the extensive differential diagnosis of intraoperative hypotension and bronchospasm (discussed later), a serum tryptase collected within a few hours of the reaction would help to unambiguously establish the diagnosis of anaphylaxis. To evaluate possible causes of perioperative anaphylaxis, complete skin testing with penicillin G, benzylpenicilloyl polylysine, penicillin minor determinant mix, cefazolin, midazolam, propofol, lidocaine, fentanyl, rocuronium, and sevoflurane should be performed. IgE immunoassays for latex, penicilloyl G, penicilloyl V, ampicilloyl, and cefazolin may be helpful in the setting of negative skin tests.

TREATMENT AND CLINICAL COURSE

After treatment of anaphylaxis with epinephrine, diphenhydramine, and hydrocortisone, the patient's hypotension, tachycardia, wheezing, and generalized skin erythema resolved. He was stabilized, transferred to the intensive care unit, and remained intubated and sedated with propofol and fentanyl for 10 hours. The patient recovered completely. Based on the history of anaphylaxis occurring temporally within 1 minute of i.v. cefazolin administration and 20 minutes after anesthesia induction, there was a high suspicion for a β-lactam or cephalosporin antibiotic allergy in this patient. IgE immunoassays for penicilloyl G, penicilloyl V, ampicilloyl, and cefazolin, collected before discharge from the hospital, were normal. A serum tryptase, sent within 2 hours of his reaction, was markedly elevated at 102 ng/mL. Consequently, the diagnosis of an anaphylactic reaction was confirmed.

Table 1 **Prick and ID skin testing for penicillin G, penicillin minor determinant mix,* ampicillin, and cefazolin**

	Prick	ID
Penicillin G	10,000 U/mL	10,000 U/mL
Minor determinant mix*	10 mmol/mL	10 mmol/mL
Ampicillin	1 mg/mL	1 mg/mL
Cefazolin	1 mg/mL	1 mg/mL
Benzylpenicilloyl polylysine	N/A	N/A

**Contains benzylpenicilloate, 1.164 g/100 mL, sodium penilloate, 0.978 g/100 mL, and penicillin, G 1.068 g/100 mL.17*

ID = intradermal; N/A – not currently commercially available

The patient returned to the allergy clinic 6 days after his anaphylactic reaction for prick and intradermal skin tests using penicillin G, penicillin minor determinant mix, ampicillin, and cefazolin (Table 1). Benzylpenicilloyl polylysine was not commercially available at the time. The prick and intradermal skin tests were negative except for a slight flare and a 4-mm wheal from the 1:1 intradermal skin test of cefazolin. This result was negative and as such could not be used to support the concept that cefazolin was the cause of the patient's anaphylaxis. An IgE immunoassay for latex was negative. Since the patient had his episode of anaphylaxis only 6 days before the skin testing, these tests may have been suppressed. Because skin tests may be unreliable for several weeks after an episode of anaphylaxis, he was scheduled for repeat prick and intradermal skin testing 6 weeks after his anaphylactic episode. His repeat skin-prick test for cefazolin was positive with a 12 $\times$ 10 mm wheal and flare. The penicillin G, penicillin minor determinant mix, and ampicillin prick and intradermal skin tests remained negative. A repeat tryptase was normal at 7.5 ng/mL. After sensitization to cefazolin was determined through skin testing, the patient underwent successful surgery subsequently with the avoidance of cefazolin.

DISCUSSION

The risk of perioperative anaphylaxis in patients undergoing general anesthesia ranges from 1:5000 to

1:25,000 with a mortality rate of 3.4%.[1] The cause of anaphylaxis often is difficult to determine because during general anesthesia, patients receive multiple medications and other exposures such as latex at one time. Charting of administered medications is helpful; however, not all reactions occur immediately after the culprit agent is given. To further complicate determining the specific etiology, recognizing the signs and symptoms of anaphylaxis in the operating room is not easy because patients are covered with sterile drapes that hide skin manifestations and receiving drugs that affect blood pressure and heart rate. Bronchospasm (increased lung resistance) and cardiovascular collapse frequently are the first hints of anaphylaxis. The differential diagnosis of hypotension and increased airflow resistance in the operating room includes myocardial infarction, cardiac dysrhythmia, drug overdose, pulmonary embolus, irritant-induced bronchospasm, endotracheal tube malfunction, aspiration, seizure, hypoglycemia, stroke, stress-induced anaphylaxis in patients with systemic mastocytosis, and surgical hypothermia in cold urticaria patients.[2,3] A recent survey of patients diagnosed with anaphylaxis during anesthesia found that 74.7% had cardiovascular symptoms including hypotension, collapse, cardiac arrest, or arrhythmias; 71.9% had cutaneous symptoms including erythema, angioedema, or urticaria; and 39.8% had bronchospasm.[4]

The occurrence of an anaphylactic episode can be established by measuring allergic mediators in blood or tissue samples. In anaphylaxis, plasma histamine levels rise quickly but its rapid metabolism limits its usefulness as a diagnostic test.[5] Increased serum levels of mast cell–derived tryptase can be measured within 30 minutes after the fist signs of anaphylaxis, peak a few hours after mast cell degranulation, and remain high for several hours.[5] The half-life of tryptase is 2 hours. Because a serum tryptase level correlates with mast cell activation, samples collected within hours after a suspected anaphylactic episode can be pathognomic for the diagnosis of anaphylaxis and excludes the other diagnoses in the differential.[6] In our patient, the markedly elevated serum tryptase (102 ng/mL) that was collected 2 hours after his reaction confirmed our diagnosis of intraoperative anaphylaxis. The repeat tryptase was normal, verifying that the elevated tryptase was purely anaphylaxis and not anaphylaxis superimposed on underlying mastocytosis. Cysteinyl leukotrienes, prostaglandins (especially PgD_2), and platelet-activating factors are considered important mediators of IgE- and non-IgE–mediated anaphylaxis, but laboratories that can perform validated tests for these mediators are not always available.

Once the diagnosis of anaphylaxis is established, a thorough workup to identify the causative agent must be completed. Implicated agents in perioperative anaphylaxis include local anesthetics, NMBAs, opioids, barbiturates, propofol, etomidate, ketamine, benzodiazepines, inhaled anesthetics, aprotinin, heparin, protamine, antibiotics, povidone-iodine, iodinated contrast material, chlorhexadine, latex, colloids, and isosulfan blue dye.[7] Penicillin is the most common cause of anaphylaxis in the general population and accounts for ~75% of anaphylactic deaths in the United States.[7] However, in a 2-year survey from France, antibiotics were implicated in only 15.1% of perioperative anaphylaxis cases, and NMBAs caused 58.2% of perioperative anaphylaxis.[4] NMBAs are the most common cause of perioperative anaphylaxis with an overall incidence of 1 in 6500 patients receiving NMBAs.[8] Latex has been reported to account for up to 12–20% of perioperative anaphylaxis cases,[4,9] although this is now less frequent since the advent of appropriate precautions.

Based on the patient's immediate reaction after administration of cefazolin, two previous tolerances of general anesthesia, and resolution of anaphylactic symptoms with continued use of propofol and fentanyl, we had a very high suspicion that cefazolin was the offending agent. In the general population, cepha-

Table 2 **Prick and ID skin testing for general anesthetic agents**

	Prick	ID	ID	ID
Etomidate	2 mg/mL	0.002 mg/mL	0.02 mg/mL	0.2 mg/mL
Fentanyl	50 μg/mL	0.05 μg/mL	0.5 μg/mL	5 μg/mL
Midazolam	1 mg/mL	0.005 mg/mL	0.05 mg/mL	0.5 mg/mL
Pancuronium	1 mg/mL	0.002 mg/mL	0.02 mg/mL	0.2 mg/mL
Propofol	10 mg/mL	0.01 mg/mL	0.1 mg/mL	1 mg/mL
Succinylcholine	20 mg/mL	0.001 mg/mL	0.01 mg/mL	0.1 mg/mL
Thiopental (2.5%)	2.5%	0.0025%	0.025%	0.25%
Vecuronium	1 mg/mL	0.004 mg/mL	0.04 mg/mL	0.4 mg/mL

Source: Adapted from Refs. 8 and 18.
ID = intradermal.

losporin anaphylaxis is rare with a frequency of 0.0001–0.1%.[10] In a survey of 518 cases of perioperative anaphylaxis, cephalosporins were identified as the offending agent in 31 cases.[4] A Canadian group reported four cases of cefazolin anaphylaxis over a 6-month period in patients without penicillin allergy or previous cefazolin exposure.[11] In these cases, all skin tests were negative to penicillin and positive to cefazolin. The anaphylactic reactions were attributed to cephalosporin side-chain–specific IgE development. However, as in this case, IgE immunoassays that detect side-chain–specific epitopes of cephalosporins are less sensitive than skin testing,[12] and therefore an IgE immunoassay using cefazolin may not be helpful.

Initial prick and intradermal skin tests for cefazolin performed 6 days after the anaphylactic episode were negative. This fact, coupled with subsequent positive skin-prick tests for cefazolin at 6 weeks, clearly support the recommendation that skin testing should be performed 4–6 weeks after an anaphylactic episode because of the tendency of anaphylaxis to induce a transient mast cell and basophil-mediator nonreleaser phenotype.[13] If the patient did not have a categorically positive skin-prick test to cefazolin at the time of his repeat skin testing,[14] we would have performed skin testing as described for the most commonly implicated agents. Several studies of perioperative anaphylaxis have shown that negative skin tests reliably predict subsequent benign operative courses.[15,16] Suggested concentrations for intradermal skin testing in patients with perioperative anaphylaxis have been published.[8,18] Using these suggestions, we have adapted an approach to skin testing for the most likely offending agents of perioperative anaphylaxis (Table 2). This approach should be performed in order of likelihood of causative agents and the workup should be considered complete when an unequivocal cause is identified.

Final Diagnosis

Perioperative anaphylaxis secondary to cefazolin.

CONCLUSIONS

This case illustrates the difficult nature of diagnosing perioperative anaphylaxis, the value of serum tryptase in the diagnosis of anaphylaxis, the most likely offending agents of perioperative anaphylaxis, and the importance of mast cell and basophil nonresponsiveness after an anaphylactic episode. Unfortunately, not all cases of perioperative anaphylaxis are straightforward. Complete workups including comprehensive skin testing, IgE immunoassays to causative agents, and possibly graded drug challenges. A logical approach to skin testing in patients after perioperative anaphylaxis is essential.

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Patient Oriented Problem Solving (POPS) Case Report

Rhinorrhea not responding to nasal corticosteroids

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Sami L. Bahna, M.D., Dr.P.H.*

ABSTRACT

A woman with multiple illnesses including allergic rhinitis presented for a follow-up visit at our clinic with constant rhinorrhea for 2 weeks despite regular use of nasal corticosteroids. Two weeks earlier, after alcohol drinking and doubling some of her medications for missed doses, she fell on her face. The Emergency Department records documented headache, bradycardia, hypotension, dehydration, and right infraorbital swelling. She was admitted for hydration and observation, and was discharged after two days without radiologic evaluation of the head. At our clinic, physical examination revealed pale turbinates bilaterally and clear watery discharge from the right nostril. Cerebrospinal fluid (CSF) rhinorrhea was suspected, but glucose testing was not available at our clinic. The patient was immediately admitted into the hospital. A beta-2-transferrin test confirmed CSF from the right nostril. High resolution sinus CT revealed fluid in the right sphenoid sinus, a large cyst in the left maxillary sinus, a cribriform plate dehiscence on the right side, and fluid collection adjacent to the middle turbinate. A lumbar drain was placed to release the pressure and antibiotic prophylaxis was started. Nasal endoscopy revealed CSF leak from the cribriform plate with bone dehiscence and a dural tear. A graft from nasal septal cartilage and temporalis fascia was applied using Tisseal fibrin glue. The persistent rhinorrhea resolved and on follow-up visits, the patient remained asymptomatic. Thinking of CSF rhinorrhea in the differential diagnosis of rhinitis would lead to early diagnosis and prevention of serious medical complications and potential legal liabilities.

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Key words: Cerebrospinal fluid, cribriform plate fracture, head trauma, nasal discharge, rhinitis, differential diagnosis, rhinorrhea

CASE PRESENTATION

Chief Complaint

Constant runny nose for two weeks despite regular use of nasal corticosteroids.

History of Present Illness

A 52-year-old African-American female with allergic rhinitis, asthma, and atopic dermatitis presented for a follow-up visit with constant rhinorrhea for two weeks despite regular use of nasal fluticasone propionate, two sprays in each nostril once a day. Two weeks earlier, after alcohol drinking and doubling the dose of some of her medications for missed doses, including antihypertensives, she felt dizzy and fell on her face. She was transferred to the Emergency Department at a local hospital where the records documented headache, bradycardia, hypotension (107/58 mmHg), dehydration, and right infraorbital swelling. The patient was admitted for hydration and observation and was discharged after two days apparently without significant symptoms. No radiologic evaluation of the head was done.

Her review of systems revealed numerous additional diseases, including iron deficiency anemia, gastroesophageal reflux, glaucoma, hypertension, hypercholesterolemia, diabetes, obesity, sleep apnea, and depression. Her past medical history is significant for malignant soft tissue sarcoma, necrotizing fasciitis, and leg cellulitis. She had several surgical procedures, including hemicolectomy, hysterectomy, cholecystectomy, appendectomy, hernia repair, and tubal ligation. She also had a past history suggestive of penicillin allergy.

Her medications included nasal fluticasone propionate, oral inhaled fluticasone/salmeterol, albuterol, oral inhaled ipratropium bromide, triamcinolone cream, aspirin, lansoprazole, ferrous sulfate, furosemide, potassium, glucophage, lisinopril, simvastatin,

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Table 1 **Differential diagnosis of rhinorrhea**

Allergic rhinitis
Vasomotor rhinitis
Infectious rhinitis
Nonallergic eosinophilic rhinitis
Foreign body
Neoplasm
Ruptured mucous retention cyst
Cerebrospinal fluid leak
Traumatic: accidental or iatrogenic
Nontraumatic: high intracranial pressure, neoplasm, radiation therapy, infection, meningoencephalocele
Vasculitis
Churg-Strauss syndrome
Wegener granulomatosis

and sertraline. She admitted alcohol consumption of a moderate-to-severe degree. The family history revealed asthma in a niece and a sister, and hypertension in the mother and a sister.

Physical Examination

During her visit to our clinic, her vital signs were within normal limits, with temperature of 98.3°F and blood pressure 133/70 mmHg. She was alert, oriented, and in no acute distress. Nasal examination revealed pale turbinates bilaterally and clear watery discharge from the right nostril. Chest was clear to auscultation. Spirometry was normal. The rest of the physical examination was unremarkable.

What Is the Differential Diagnosis of Her Rhinorrhea?

Although allergic rhinitis is by far the most common cause of rhinorrhea, several other causes should be considered in the differential diagnosis (Table 1). In unilateral rhinorrhea, in particular, it is important to consider ruptured mucous retention cyst or CSF.[1]

What Further Diagnostic Tests Are Needed?

In this particular patient, because of the history of a preceding facial trauma, CSF leak was the primary suspect. The nasal fluid may be tested for glucose as a screening procedure, but a confirmatory test would be β-2 transferrin content. Fiberoptic nasopharyngeal endoscopy and CT studies on the head would be necessary to identify the site of the leak.

DIAGNOSTIC FINDINGS AND CLINICAL COURSE

Glucose testing strips were not available in our clinic. The patient was immediately admitted to the hospital. Fluid from the right nostril was positive for β-2 transferrin. Complete blood count was normal, including white blood cell differential count. Initial CT scan of the head and face showed a left maxillary sinus cyst but no apparent fractures. High resolution CT with sinus cuts revealed mucosal thickening in the right ethmoid sinus, fluid in the right sphenoid sinus, a large retention cyst in the left maxillary sinus, an area of cribriform plate dehiscence on the

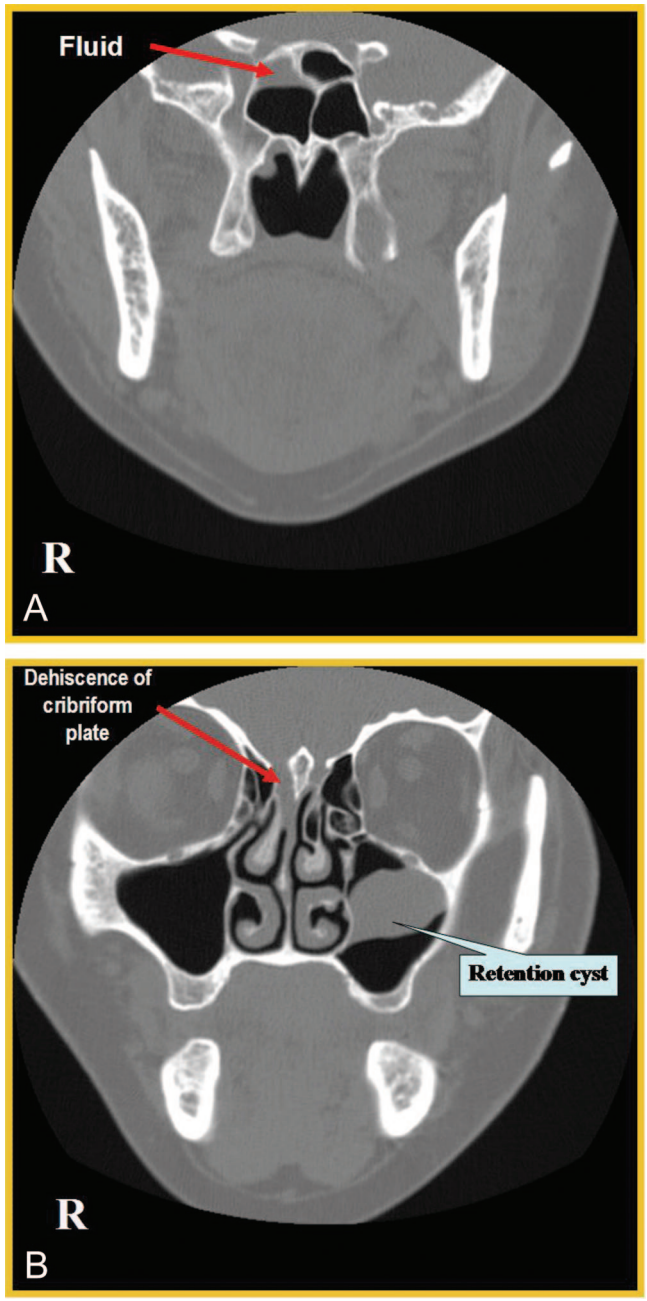

Figure 1. *High resolution sinus CT scan showing (A) fluid in the right sphenoid sinus, and (B) cribriform plate dehiscence on the right side with apparent fluid collection adjacent to the middle turbinate and retention cyst in the left maxillary sinus.*

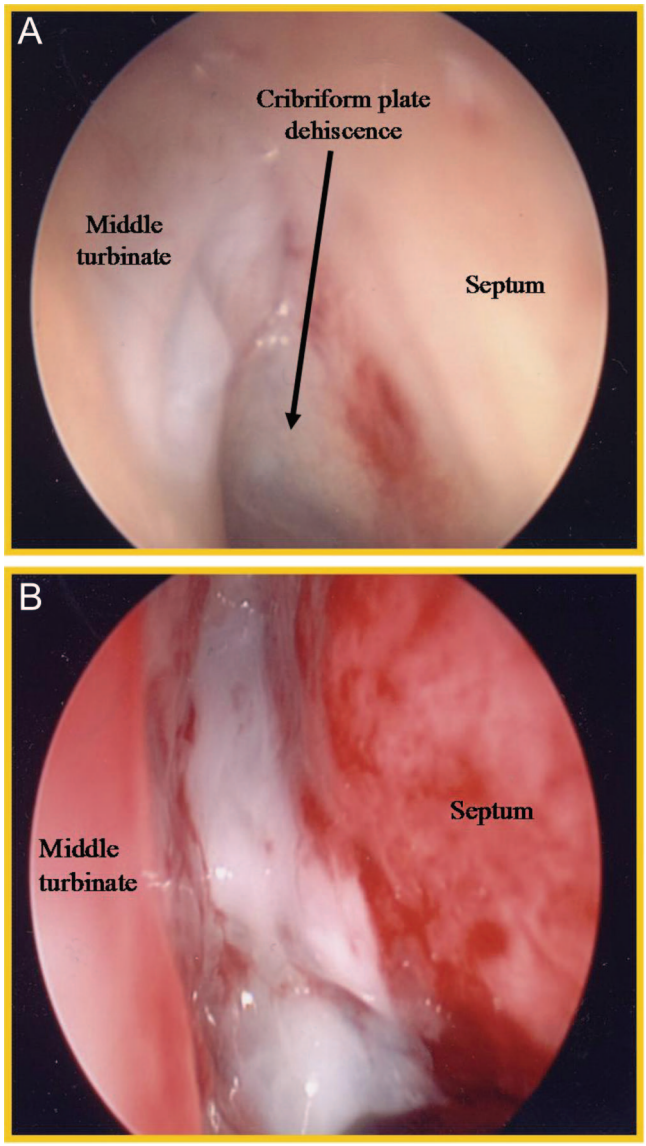

Figure 2. Nasal endoscopy. (A) Preoperative view showing cribriform plate dehiscence and dural tear. (B) Intra-operative view after a graft from nasal septal cartilage and temporalis fascia applied using Tisseal fibrin glue.

right side and apparent fluid collection adjacent to the middle turbinate (Fig. 1). A lumbar drain was placed, and antibiotic (clindamycin) prophylaxis was started. Nasal endoscopic surgical repair was arranged. At surgery, a 2 × 0.6-cm bone dehiscence and a 3-mm dural tear were noted at the cribriform plate (Fig. 2 *A*). A graft from the nasal septal cartilage and temporalis fascia was applied using Tisseal fibrin glue (Baxter International) (Fig. 2 *B*). Two days postsurgical repair, examination of CSF from the drain showed 7150 RBCs/mm^3, 39 WBCs/mm^3 (87% neutrophils, 5% lymphocytes, 7% monocytes, and 1% eosinophils), and normal levels of glucose at 77 mg/dL and protein at 33 mg/dL. A repeat CSF analysis 5 days later showed 1200 RBCs/mm^3, 7 WBCs/mm^3 (72% neutrophils, 12% lymphocytes, and 16% monocytes), and normal glucose and protein content. Gram stain and culture of the CSF were also negative. The persistent rhinorrhea resolved and, on follow-up visits, the patient remained asymptomatic.

DISCUSSION

CSF rhinorrhea may develop after head trauma or spontaneously. Trauma, including surgical, is by far more common and usually affects the cribriform plate. In our patient who had a fall, the cribriform plate was the affected site.

Nontraumatic CSF rhinorrhea may be associated with high or normal CSF pressure. High-pressure leaks are primarily due to tumor obstruction, benign intracranial hypertension, or hydrocephalus. Normal pressure leaks may be due to bony erosion by tumor, radiation therapy, arachnoid granulations, infection, or congenital defects such as fistulas, meningoceles, meningoencephaloceles, or encephaloceles.[2]

Patients who have CSF rhinorrhea may complain of headache and an unusual taste to the postnasal, usually sweet because CSF normally has about two-thirds the sugar content of blood. Nasal drainage is usually watery, clear, and continuous. It may be increased with cough, change in head position, straining effort, or Valsalva's maneuver.[2] Our patient did complain of headache and continuous drainage.

The CSF often leaves a halo sign on tissue paper or linen.[2] Glucose detection by strips is suggestive but has low specificity and sensitivity. β-2-Transferrin is highly specific and sensitive in identifying CSF and is the test of choice.[2,3] It is a protein produced via desialization of β-1 transferrin in CSF by neuraminidase activity in the brain and is found only in perilymph, vitreous humor, and CSF.[2] High mucus content of nasal discharge fluid may cause a falsely negative result.[4] To accurately localize sites of CSF leaks, high-resolution CT is the primary imaging modality of choice and may be used in conjunction with intrathecal fluorescein study.[5,6] In our patient, the nasal fluid was positive to β-2-transferrin, and the high-resolution CT scan showed cribriform plate dehiscence and fluid adjacent to the right middle nasal turbinate.

Most traumatic CSF leaks heal spontaneously within 7–10 days of conservative measures.[2] Initial management includes bed rest with head elevation, avoiding straining activity such as nose blowing, sneezing, and coughing, and the using of stool softeners.[2] Because of the risk of meningitis, surgical closure is recommended if drainage does not stop within 1–2 weeks.[2,7]

The use of antibiotic prophylaxis is controversial. In a review of medical records of 101 cases of posttrau-

matic CSF leak, the use of prophylactic antibiotics was associated with a lower incidence of meningitis (10% *versus* 21%).[8] In contrast, avoiding the use of prophylactic antibiotics would reduce the development of resistant microorganisms.[9,10]

In conclusion, rhinorrhea, particularly when unilateral or preceded by trauma, should alert for possible CSF leak. Not recognizing CSF rhinorrhea early is likely to lead to central nervous system infection with consequent high morbidity and mortality, and potential legal liability. The diagnosis can be confirmed by β-2-transferrin test. The leaking site may be identified by nasopharyngeal endoscopy or high-resolution CT scan. Surgical repair is necessary for large leaks or if drainage does not cease within 1–2 weeks of conservative measures.

FINAL DIAGNOSIS

Cerebrospinal fluid rhinorrhea; traumatic.

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Patient Oriented Problem Solving (POP) Case Report

A 15-year-old girl with recurrent pneumonia

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ABSTRACT

Hodgkin's disease (HD) represents a group of lymphomas with distinct clinical and histopathological features that account for ~5% of cancers in patients who are <15 years old and ~15% in patients who are 15–19 years old. Although the cause of HD is unknown, serologically confirmed infectious mononucleosis has been associated with an increased risk of HD, in addition to its known association with Burkitt's lymphoma. The Reed-Sternberg (RS) cell, a large and multinucleated cell with unique morphology, is the hallmark cell of HD. RS cells are clonal tumor cells that recently have been shown to be derived from B cells originating from germinal centers. Of four histological subtypes of HD, three have a good to excellent prognosis when recognized and treated early. We report a case of HD in a 15-year-old adolescent with a 14-month history of recurrent pneumonia. Open lung biopsy ultimately led to the diagnosis of HD. Although uncommon in this age group, the need to consider the possibility of neoplasm in the setting of recurrent respiratory infection is illustrated in this case. Early diagnosis and intervention may determine the prognosis of such neoplasms.

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Key words: Burkitt's lymphoma, EBV, Epstein-Barr virus, histiocyte, Hodgkin's disease, infectious mononucleosis, lymphadenopathy, lymphoma, recurrent pneumonia, Reed-Sternberg cell

CASE PRESENTATION

Chief Complaint

Recurring left lower-lobe pneumonia.

History of Present Illness

A 15-year-old Caucasian girl with a 14-month history of recurrent left lower-lobe pneumonia was admitted to the hospital with fever, chest tightness, shortness of breath, and cough productive of yellow sputum. She had been in good health until 14 months before admission when she first developed these symptoms and was diagnosed with pneumonia. Chest radiograph findings are noted in Fig. 1. Her symptoms resolved with antimicrobial treatment but recurred shortly after completion of therapy, leading to a second course of oral antibiotics. Over the ensuing months, the patient received 10 courses of antibiotics because of persistent and recurrent symptoms. She was admitted to the hospital at this time for further evaluation and placement of a peripherally inserted central catheter to facilitate antimicrobial treatment because of her recurrent symptoms and radiological findings of persistent left lower-lobe consolidation. An allergy/immunology consultation was requested on admission.

The patient reported night sweats, fevers and chills, and a weight loss of 10 lb over several months before admission. Medical history included well-controlled mild intermittent asthma since the age of 10 years and mild perennial rhinitis since the age of 7 years. She had had nonpruritic eczema localized to her feet since childhood, with associated fungal infections of the nails the previous year. Additionally, she had a pruritic rash diagnosed as atopic dermatitis localized to her antecubital fossae for the previous several months. The family history was positive for asthma and allergic rhinitis in a sibling and her father, anemia in her mother, rheumatoid arthritis in her maternal grandmother, and systemic lupus erythematosus in a paternal first cousin. There was no family history of recurrent sinopulmonary infections, candidiasis, chronic diarrhea, abscesses, serious bacterial infections, or early unexplained deaths.

Physical Examination

Vital signs included a temperature of 37.5°C, heart rate of 87 bpm, and respiratory rate of 20/minute.

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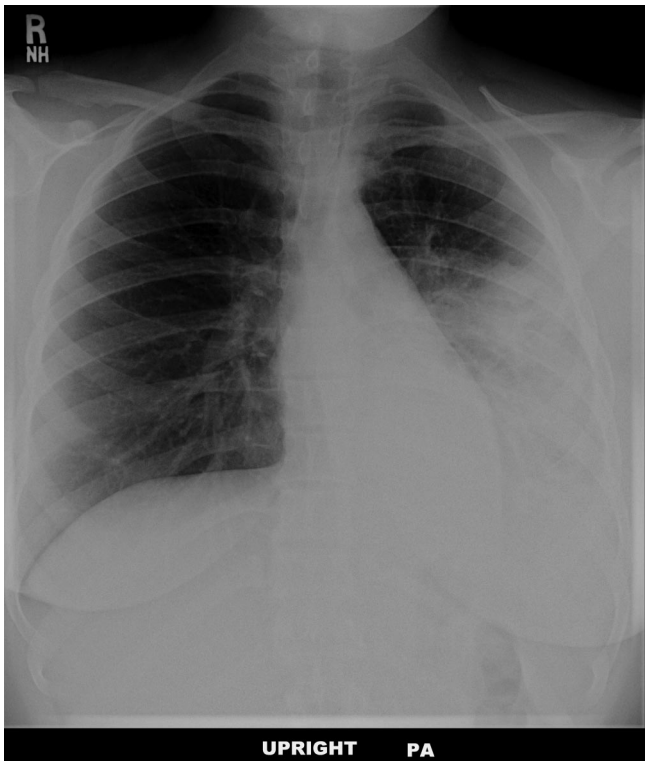

Figure 1. Chest radiograph. Chest radiograph revealed left lower-lobe consolidation with air bronchograms and a normal cardiothymic shadow.

Oxygen saturation was 96% in room air. Her weight was 89 kg (>95th percentile for her age). The patient's neck was supple with shotty lymph nodes that were symmetric and nontender to palpation. Tonsillar tissue was symmetric and normal in size and appearance. Respiratory examination revealed normal work of breathing. There were diminished breath sounds at the left base, with associated dullness to percussion. Remaining lung fields were clear to auscultation. Skin examination was notable for tinea unguium of the fourth and fifth digits of both feet. There were dry patches with scant papules and minimal excoriation localized to the antecubital fossae.

Initial Laboratory and Other Diagnostic Findings

Initial laboratory studies are shown in Table 1 with normal results except for elevated bands (3%), C-reactive protein (11.5 mg/dL; reference range, 0.0–0.9 mg/dL), and elevated erythrocyte sedimentation rate (97 mm/hour; reference range, 0–20 mm/hour). The results of a nasopharyngeal wash were negative for respiratory viruses. Purified protein derivative and sweat chloride test results were negative (Table 1). Chest radiograph on admission revealed left lower-lobe consolidation that appeared to be progressing when compared with several earlier studies (Fig. 1).

Clinical Course

Bronchoscopy with bronchial alveolar lavage was performed revealing generalized inflammation and hyperemia with increased edema of the left lung airways. Copious mucopurulent bloody secretions were recovered from the lingula and left lower lobe. All bacterial, viral, fungal, and acid-fast bacillus study results were negative.

Despite continued broad-spectrum antibiotics, fever and dyspnea persisted, and a supplemental oxygen requirement developed. Repeat chest radiograph on day 5 of hospitalization revealed progression of the left lower-lobe consolidation despite antimicrobial therapy. Computed tomography of the chest revealed enlarged mediastinal lymph nodes up to 18 mm in diameter (Fig. 2).

The patient then underwent thorascopic lung biopsy, which revealed lung tissue that was firm and nodular in appearance and with very little exudate. A decision was made to perform a left lower lobectomy. Microscopic description of resected pulmonary tissue revealed parenchyma extensively replaced by fibrosis and patchy necrosis with areas of lymphohistiocytic infiltrates, with Reed-Sternberg (RS) cells identified, establishing a diagnosis of Hodgkin's disease (HD; Fig. 3). The patient then began chemotherapeutic treatment.

QUESTIONS

What Is the Differential Diagnosis?

Diagnoses to be considered in this patient include tuberculosis, cystic fibrosis, primary immunodefi-

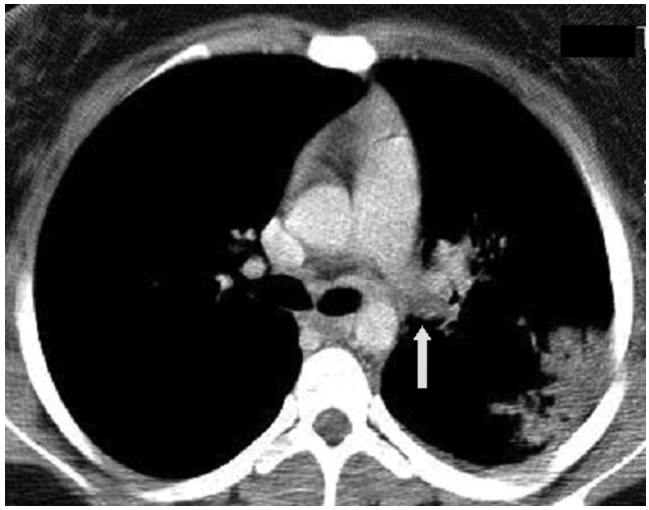

Figure 2. *Computed tomography of the chest. Chest computed tomography revealed left lower-lobe parenchymal consolidation, isolated left apex opacity, small peripheral lucencies consistent with parenchymal necrosis, and several bilateral mediastinal lymph nodes (arrow).*

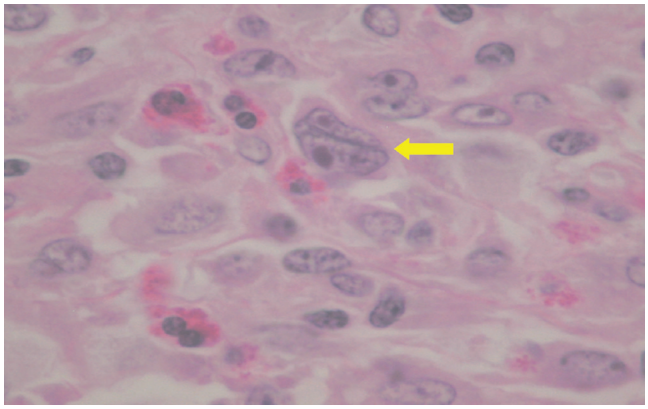

Figure 3. Microscopic description of resected pulmonary tissue (40× magnification). RS cell with characteristic large double-nucleoli (arrow) and surrounding single-nucleoli RS variants.

ciency, human immunodeficiency virus infection, other microbial infection, asthma, foreign body or recurrent aspiration, and anatomic abnormality causing endobronchial obstruction, in addition to mass or neoplasm. Asthma can cause transient subsegmental atelectasis that frequently is misdiagnosed as pneumonia. Cystic fibrosis is unlikely because it is frequently associated with malabsorption and other gastrointestinal issues that usually present before adolescence. Primary and acquired immunodeficiencies often present with recurrent infections. Patients with recurrent aspiration frequently have neurological deficits and also most often present before adolescence. An aspirated foreign body also should be considered, although there was no history supporting such an event in this patient.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis?

Quantitative immunoglobulin levels revealed low IgM levels, a normal lymphocyte enumeration panel, normal diphtheria antitoxoid antibody (tetanus not done), subprotective pneumococcal antibody titers, normal total complement level, negative human immunodeficiency virus polymerase chain reaction, and Ep-

Table 1 **Laboratory findings**

Test	Result	Reference Range
WBC*	13,900 cells/μL	4700–14,00 cells/μL
(88% neutrophils, 3% bands, 7% lymphocytes, 10% monocytes, 6% eosinophils)		
CRP*	11.5 mg/dL	0.0–0.9 mg/dL
ESR*	97 mm/hr	0–20 mm/hr
HIV PCR	Negative	
EBV-VCA*		
IgG	1.91 mg/dL	<0.90 mg/dL
IgM	Negative	
PPD	Negative	
IgG	1190 mg/dL	635–1775 mg/dL
IgA	290 mg/dL	106–668 mg/dL
IgM*	31 mg/dL	37–154 mg/dL
Diphtheria antitoxoid antibody	0.18 IU/mL	>0.01 IU/mL
Pneumococcal antibody 12 serotype*	2 of 12 protective	>2.0 μg/mL
CD3 (absolute)	588 cells/μL	800–3500 cells/μL
(%)	74%	52–78%
CD4 (absolute)	339 cells/μL	400–2100 cells/μL
(%)	43%	25–48%
CD8 (absolute)	218 cells/μL	200–1200 cells/μL
(%)	27%	9–35%
CD19 (absolute)	97 cells/μL	200–600 cells/μL
(%)	12%	8–24%
CD56 (absolute)	90 cells/μL	70–1200 cells/ μL
(%)	11%	6–27%
CH50	61 U/mL	31–66 U/mL

** = Abnormal value as compared to reference range.*
WBC = white blood cell count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HIV-PCR = human immunodeficiency virus polymerase chain reaction; EBV-VCA = Epstein-Barr virus viral capsid antigen; PPD = purified protein derivative; CH50 = total complement level.

stein-Barr virus (EBV) serology indicative only of past infection (Table 1).

Bone marrow aspiration/biopsy was performed, revealing absence of clonal B- and T-cell populations by DNA polymerase chain reaction testing. Initial microscopic examination of lung biopsy tissue revealed an atypical lymphohistiocytic lesion with marked eosinophilia and tissue fibronecrosis. Final identification of RS cells in the background of pleomorphism, plasmacytoid lymphocytes, and eosinophils with invasion of pulmonary arterioles was subsequently made and established the diagnosis of HD.

DISCUSSION

The clinical, macroscopic, and microscopic features of HD were first described >100 years ago. Initially, it was seen as a process rather than a spreading cancer, and it was noted that male children and young adults of both sexes were most commonly affected, especially those whose general health before the disease had been excellent.[1] Three clinical age-based types of HD have been identified in epidemiological studies, including a childhood form (<14 years), a young adult form (15–34 years), and an older adult form (55–74 years). Preexisting immunodeficiency increases the risk of developing the disease in all three forms, and serologically confirmed infectious mononucleosis (IM) also has been associated with an increased risk of HD, suggesting a possible causal association between IM-related EBV infection and the EBV^+ subgroup of HD in young adults.[2,3] Although the patient described in this study did not have acute IM by history, she did have serological evidence of previous EBV infection (Table 1).

The RS cell is the hallmark of HD and was found in this patient's resected lung tissue. RS cells are large, multinucleated, clonal tumor cells that are felt to be derived from B cells.[4] They are characteristically surrounded and outnumbered by lymphocytes, histiocytes, eosinophils, and plasma cells that represent the host reactive inflammatory response to the neoplastic cells. Molecular studies have established that RS cells are a clonal population of transformed B lymphocytes with somatically mutated immunoglobulin variable-region genes. The somatic mutations in these cells are induced within a germinal center and represent the distinctive feature of germinal-center B cells and their descendents.[5]

In the progression of HD, RS cells spread to adjacent lymph nodes before hematogenous dissemination to more distant sites including the liver, spleen, bone, marrow, and central nervous system. Local elevated tissue levels of interleukins-1 and -2 and tissue necrosis factor are present, which may account for systemic symptoms of fever and night sweats seen in patients with HD. The most common presenting sign of HD is painless, firm cervical or supraclavicular lymphadenopathy, or both, with anterior mediastinal mass. Airway obstruction, pleural and pericardial effusion, hepatic dysfunction, and marrow infiltration occur less commonly. The patient described in this study presented with fever, weight loss, and drenching night sweats, which have been commonly reported.[2]

Gross and microscopic findings were consistent with the nodular sclerosing subtype of HD. Subsequent imaging studies, along with the patient's presenting symptoms, classified her disease as stage IV-B (Ann Arbor Staging System), the prognosis for which is guarded.[6]

Final Diagnosis

Stage IV-B nodular sclerosing HD.

CONCLUSION

This patient was diagnosed with HD following an atypical presentation. Her response to antimicrobial therapy on multiple occasions raised the question of immunodeficiency. Equally plausible, however, was the possibility of bronchial obstruction as an etiology for her recurrent pneumonia. Preliminary laboratory tests revealed no specific immunologic abnormalities with the exception of subprotective pneumococcal titers and low IgM levels. After additional imaging and subsequent lobe resection, the diagnosis of HD was definitively made. This case illustrates the importance of prompt evaluation of persistent or recurrent unexplained illnesses. Early stages of HD carry a favorable prognosis and, thus, prompt diagnosis is essential.

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Patient Oriented Problem Solving (POPS) Case Report

A boy with fever, lymphadenopathy, hepatosplenomegaly, and lymphocytosis

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ABSTRACT

Proliferation of the lymphoid system should arouse suspicion of a potentially serious illness. We present a 4.5-year-old boy who developed fever, vomiting, diarrhea, lymphadenopathy, hepatosplenomegaly, lymphocytosis, anemia, thrombocytopenia, and increased liver enzymes. Lymph node and bone marrow biopsies showed lymphoproliferation, Epstein-Barr virus (EBV) infection, and hemophagocytosis leading to the diagnosis of hemophagocytic lymphohistiocytosis (HLH). Chemotherapy was initiated for HLH with dexamethasone, etoposide, and cyclosporine. Because of a high level of EBV viremia, rituximab was added a few days later and resulted in a remarkable drop in the EBV in the circulation but not in the cerebrospinal fluid. However, the patient succumbed to encephalitis, pneumonia, and cardiopulmonary failure. Autopsy revealed the presence of EBV in the brain, indicating the ineffectiveness of rituximab therapy in treating central nervous system infection with EBV.

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Key words: EBV, hemophagocytosis, hepatosplenomegaly, lymphadenopathy, lymphocytosis, lymphoproliferative disease, rituximab

CASE PRESENTATION

Chief Complaint

Fever, vomiting, diarrhea, and fatigue.

History of Present Illness

A 4.5-year-old African American male with no significant medical history was initially diagnosed with fever and ear infection. However, the fever persisted despite two courses of antibiotics over 2 weeks. He subsequently developed vomiting, diarrhea, cough, fatigue, decreased activity, loss of appetite, and easy bruising.

Family History

The patient's 6-year-old male cousin had died 6 months earlier with apparent sepsis and the autopsy was suggestive of lymphoproliferative disease.

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Physical Examination

His temperature on admission was 100.4°F, heart rate was 120–130 bpm, respiratory rate was 26, and blood pressure range was 110–120 mmHg/60–70 mmHg. He had periorbital edema with cervical, submandibular, and inguinal lymphadenopathy as well as hepatosplenomegaly. Auscultation of the chest revealed coarse breath sounds with crackles. The rest of his physical examination was within normal limits, except for vitiligo.

Laboratory Findings

The initial laboratory findings are presented in Table 1. Of particular importance is the white blood cell count of 14,160 cells/mm,^{3} with 92% lymphocytes and many atypical lymphocytes. In addition, he had increased liver enzymes and low fibrinogen.

QUESTIONS

What is the Differential Diagnosis?

Given the lymphadenopathy, hepatosplenomegaly, lymphocytosis, and increased liver function tests, the differential diagnosis in this patient should include malignancy, especially leukemia, EBV infection, lymphoproliferative diseases such as lymphoma or X-linked lymphoproliferative (XLP) disease, and hemophagocytic lymphohistiocytosis (HLH). Because

Table 1 **Laboratory findings**

WBC, 14,160 cells/mm^3 (nl 5–15.5); 3% N (nl 42%); 92% L (nl 50%); 4% M (nl 5%)
Hgb, 8.6 g/dL (nl 11.5–13.5); platelets, 70,000 cells/mm^3 (nl 150,000–350,000)
Sodium, 127 mmol/L (nl 136–145)
Potassium, 3.8 mmol/L (nl 3.5–5.1)
Chloride, 96 mmol/L (nl 98–107)
Bicarbonate, 19 mmol/L (nl 18–29)
BUN, 9 mg/dL (nl 8–25); creatinine, 0.7 mg/dL (nl 0.7–1.3)
Glucose, 105 mg/dL (nl 60–100)
Calcium, 6.5 mg/dL (nl 8.9–10.0)
Aspartate transaminase, 672 g/L (nl 5–24); alanine transaminase, 268 g/L (nl 5–55); alkaline phosphatase, 305 g/L (nl <500)
C3, 37 mg/dL (nl 80–170); C4, 3.8 mg/dL (14–44)
IgG, 667 mg/dL (nl 463-1236 mg/dL)
IgM, 562 mg/dL (nl 43–196 mg/dL)
IgA, 195 mg/dL (nl 25–154 mg/dL)
Triglycerides, 101 mg/dL (nl 32–116)
Fibrinogen, 155 mg/dL (nl 214–451)

Flow Cytometry	Patient	Normal Range
CD4	45.1%, 1553/mm^3	23–48%, 500–2400/mm^3
CD8	43.9%, 1512/mm^3	14–33%, 300–1600/mm^3
CD4:CD8	1.1	0.9–2.9
CD19	7.3%, 251/mm^3	14–44%, 200–2100/mm^3
CD56	5.2%, 179/mm^3	4–23%, 100–1000/mm^3

these are all serious diseases, they should be suspected and evaluated early.

Clinical Course

A chest roentogram revealed infiltrates in the hilar and perihilar regions of the lung bilaterally. Antibiotic therapy was started with azithromycin, 160 mg initially, and then 80 mg/day and ceftazidime, 800 mg, every 8 hours. He had increased difficulty breathing and a decreased oxygen saturation and, consequently, was intubated. The Hematology/Oncology and Infectious Disease Services were consulted. Because the patient's male cousin had died several months earlier with a similar presentation; XLP was considered a likely diagnosis. The hematology consultant requested measuring the immunoglobulin levels and ordered i.v. immunoglobulin, 10 g, before knowing the results. In addition, the consultants requested an Epstein-Barr virus (EBV) panel and perforin analysis. Dexamethasone, 4 mg, every 8 hours was initiated also.

The Allergy and Immunology Service was subsequently consulted, with XLP being the most likely diagnosis. Flow cytometric evaluation and the immunoglobulin levels were within normal limits (Table 1). Lymph node biopsy was consistent with XLP disease and EBV infection. Bone marrow biopsy (Fig. 1 *A*) and aspiration (Fig. 1 *B*) showed hypocellularity and hemophagocytosis. This along with the presence of EBV

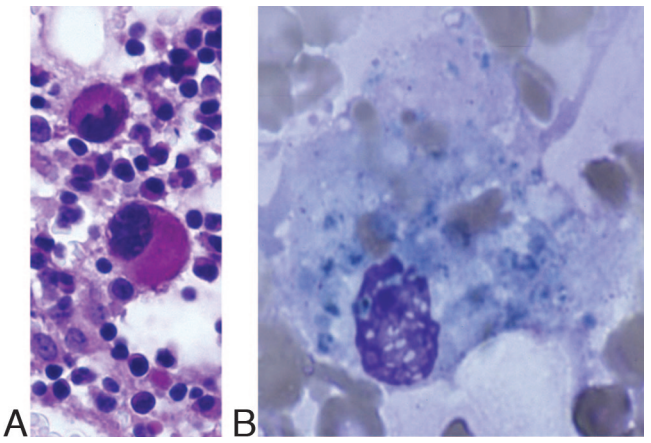

Figure 1. *(A) Bone marrow core biopsy specimen showing dysmorphic mononuclear megakaryocyte (PAS stain, ×400). (B) Bone marrow aspirate showing a macrophage with hemophagocytosis (Wright-Giemsa stain, ×1000).*

by *in situ* hybridization is consistent with XLP. The diagnosis was considered HLH secondary to XLP and EBV infection.

Cyclosporine, 100 mg, every 12 hours and etoposide (VP-16), 100 mg, biweekly were added to the steroid therapy.[1] The EBV titer 3 days after admission was 92,240 copies/mL. Because rituximab had been used previously for the treatment of XLP[2] and lymphoproliferative disorders,[3] weekly rituximab, 247 mg, was

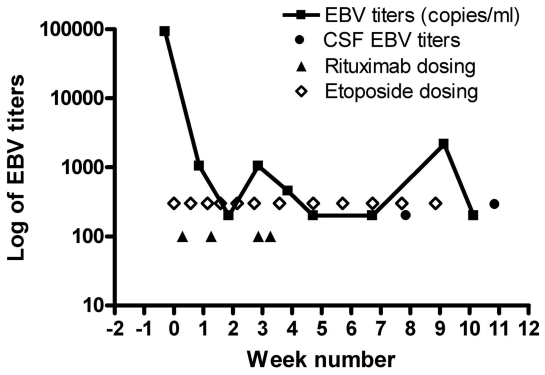

Figure 2. EBV titers in the circulation and in the cerebrospinal fluid before and during treatment with rituximab and etoposide. Dexamethasone and cyclosporine were given throughout.

added to his treatment (6 days after admission). His EBV titers decreased to 1045 copies/mL within 4 days and to <200 copies/mL on the 11th day after initiating rituximab treatment. Subsequently, the EBV titers increased to 1045 copies/mL, and then decreased again with subsequent doses of rituximab (Fig. 2). At day 14 of chemotherapy (12 days after rituximab was started), his B-cell count decreased to zero.

What Additional Tests Are Needed?

A defect in perforin should be checked as an underlying cause of familial HLH (FHL). However, the test showed increased expression of this protein, suggesting secondary HLH. Confirmation of the diagnosis of XLP requires flow cytometric analysis for the SH2D1A gene product, SAP (SLAM [signaling lymphocyte-activation molecule]–associated protein). A decreased expression of SAP was noted and genetic sequencing confirmed a mutation in the SH2D1A gene. Increased expression of perforin and granzyme B were shown also in this patient.

DEFINITIVE DIAGNOSIS

Because of a family history (male cousin) suggestive of an X-linked process, together with SAP deficiency and SH2D1A gene mutation, XLP disease was confirmed. The presence of hemophagocytosis, lymphoproliferation, and EBV infection, persistent fever, low fibrinogen, cytopenias, splenomegaly, and increased liver enzymes led to the diagnosis of HLH secondary to XLP and EBV infection.

CLINICAL COURSE PROGRESS

Respiratory distress was improving, but, he later developed seizures. During the patient's hospital course, he developed hyponatremia (118–135 mmol/L) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) and he did not improve despite treatment. MRI of the brain was then ordered

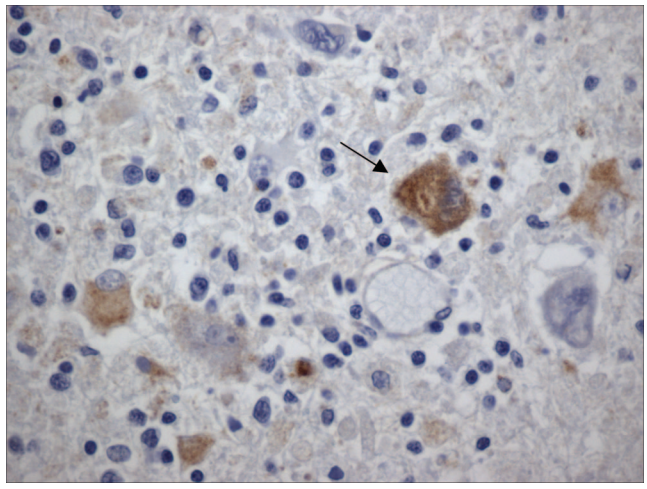

Figure 3. Brain autopsy showing gliotic chronic inflammation with positive in situ *hybridization staining for EBV. EBV staining is indicated by arrow (original magnification, ×600).*

and showed edema suggestive of encephalitis. Lumbar puncture indicated an EBV titer in the cerebrospinal fluid of 289 copies/mL. His mental status continued to decline. Intrathecal chemotherapy was initiated with two doses (5 days apart) of both methotrexate (24 mg) and hydrocortisone (12 mg). Given the declining mental status, the family elected palliative care only, particularly since a definitive cure with bone marrow transplant would not be considered at this stage. He died 90 days after admission and the autopsy revealed EBV encephalitis (Fig. 3), multifocal bacterial pneumonia, cardiorespiratory failure, and a decreased brain weight.

DISCUSSION

HLH is a reactive disorder of the mononuclear phagocyte system and usually occurs in infants and children. The manifestations include fever, hepatosplenomegaly, cytopenia, and bone marrow hemophagocytosis without signs of malignancy. There also may be symptoms of central nervous system (CNS) involvement. The onset often follows a gastrointestinal or an upper respiratory infection.[4] Biochemical abnormalities also can be seen including low fibrinogen, high triglycerides, and increased ferritin, liver enzymes, and bilirubin.

HLH can be primary or secondary. The primary or familial form of HLH is the result of perforin deficiency and can be associated with immune deficiency syndromes such as Chediak-Higashi syndrome, Griscelli's syndrome, and XLP. The familial form is fatal if not treated.[5] Fatality usually results from bacterial or fungal sepsis, pneumonias, bleeding, or cerebral dysfunction. The secondary form can be caused by certain infections, particularly EBV, rheumatic disease, malignancies, tissue damage, radical stress, metabolic prod-

ucts, or a combination of factors such as XLP and EBV infection.[1]

Diagnostic criteria for HLH as proposed by the FHL study group include familial disease/known genetic defect and five of the following eight criteria: fever for ≥7 days; splenomegaly; cytopenia of two or more cells lines (hemoglobin, <9 g/dL [<4 weeks, <10 g/dL]; platelets, $<100 \times 10^9$/L; neutrophils, $<1 \times 10^9$/L); hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides, ≥3 mmol/L; fibrinogen, <1.5 g/L); ferritin, ≥500 μg/L; sCD25, ≥2400 U/mL; decreased or absent natural killer (NK) cell activity; hemophagocytosis in bone marrow, cerebral spinal fluid, or lymph nodes.[4] Supporting evidence for this diagnosis includes cerebral symptoms, cerebrospinal fluid with moderate pleiocytosis, and/or elevated protein. Often, there are increased serum transaminases, bilirubin, and lactate dehydrogenase. Although these are specific to FHL, they also can be applied to the secondary form.[4] Our patient had fever for >7 days, cerebral symptoms, splenomegaly, cytopenia in three cell lines (red blood cells, neutrophils, and platelets), elevated liver transaminases, hypofibrinogenemia, and hemophagocytosis in the bone marrow.

Patients with HLH usually have impaired or absent function of NK cells and $CD8^+$ cytotoxic T cells.[1] The hallmark of FHL is deficiency in NK cell activity. Perforin expression, which normally mediates the cytotoxic activity of T cells and NK cells, usually is decreased or absent.[5,6] Perforin defect results in susceptibility to infection by viruses such as EBV. Low perforin level is a hallmark of FHL,[7] but some patients may have dysfunctional perforin at normal levels.[7–9] Our patient had increased perforin and granzyme B, which excluded FHL. Because he had a very high titer of EBV, his HLH was considered secondary to the combination of XLP and EBV.[1] The mechanism for the susceptibility to EBV infection in XLP is under investigation.

The gene SH2D1A encodes for SAP, an NK cell, and T-cell–specific signaling adaptor protein.[5,6] A deficiency in SAP leads to dysregulation of T- and B-cell interactions as well as NK cell functions. The surface molecule 2B4, present on NK cells, and a large subset of $CD8^+$ T cells, is involved in the recruitment of SAP, an SH2 adapter protein.[10–12] NK cell cytotoxicity is increased when 2B4 binds to CD48 or specific antibodies. Consequently, defects in 2B4 signaling through SAP may impair recognition of virally infected cells and contribute to the susceptibility to EBV infection in patients with XLP.[6,11]

The goal of HLH treatment is to stop the hyperinflammation responsible for the life-threatening symptoms. In addition to the anti-inflammatory agents, elimination of the pathogen-infected cells is necessary, which would remove the stimuli for NK and T-cell activation.[4,13] Treatment of HLH is dependent on whether the disease is primary or secondary with chemotherapy being important in both. Corticosteroids, cyclosporine A, and etoposide have been used to control inflammation. Intrathecal therapy with methotrexate ± corticosteroids has been used for treatment of recurrent CNS involvement.[4] Correction of the underlying genetic defect requires bone marrow transplantation.

In HLH cases associated with EBV infection, eradication of the virus would be of importance. In patients with EBV-driven disease, the rationale behind the use of rituximab is to destroy the EBV-infected B cells and reduce EBV synthesis. Rituximab has been used to treat EBV in patients with lymphoproliferative disorders[3] including XLP.[2] Rituximab is a chimeric murine/human monoclonal antibody directed against $CD20^+$ cells. A review of the literature showed no published reports of rituximab use in the treatment of HLH driven by EBV. In our patient, rituximab therapy was followed by a remarkable drop in the circulating EBV levels. However, the autopsy revealed the presence of EBV in the brain, which was probably the main cause of this patient's demise. This case shows the efficacy of rituximab in eradicating EBV from the circulation but not from the tissues, at least not from the CNS.

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Patient Oriented Problem Solving (POPS) Case Report

Liver enzyme elevation and normal pulmonary function in an adult with a declining forced expiratory volume in 1 second

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ABSTRACT

This article presents a case report of a 41-year-old male firefighter with cholecystitis and a history of mildly elevated alanine aminotransferase. Liver biopsy showed periodic acid Schiff–positive, diastase-resistant periportal globules. Retrospective review of clinical data revealed progressive lung function decline despite absent pulmonary symptoms and normal pulmonary function testing. The following disorders should be considered in any patient with elevated transaminases without an apparent etiology: viral hepatitides, medication toxicity, autoimmune hepatitis, alcohol-induced hepatic injury, and alpha-1-antitrypsin deficiency.

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Key words: Adult, alpha-1-antitrypsin, asymptomatic, hepatitis, liver enzymes, Mmalton, presymptomatic, pulmonary function, transaminases

CASE PRESENTATION

Chief Complaint

Right upper quadrant pain.

History of Present Illness

A 41-year-old man presented with right upper quadrant pain exacerbated by oral intake over 1 month's time. A liver ultrasound was remarkable for cholecystitis. On referral for cholecystectomy, elevated transaminases were noted on a preoperative metabolic panel. Further questioning revealed a 6-year history of elevated alanine aminotransferase (ALT) without an etiology. The patient underwent successful cholecystectomy with resolution of his abdominal pain. An intraoperative liver biopsy was performed to evaluate the longstanding liver function abnormalities.

Medical History

The patient's medical history was significant for a 6-year history of an elevated ALT, seasonal allergic rhinitis, and gastroesophageal reflux. Evaluation of medial records showed elevation of ALT with normal aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT) levels. Serology for viral hepatitides was negative. There was no history of hepatotoxic medication use, prior transfusions, i.v. drug use, excessive alcohol use, or international travel. Family history was negative for cirrhosis and lung disease. Social history was remarkable for work as a firefighter over a 27-year period.

Physical Examination

Vital signs were normal. The patient's sclera was anicteric. His cardiac and pulmonary exams were normal. The remainder of the exam was negative for stigmata of chronic liver disease in that there were no spider angiomata, jaundice, or evidence of palmar erythema, asterixis, organomegaly, or testicular atrophy.

QUESTION 1

What is the differential diagnosis of hepatocellular injury without cholestasis?

a. Viral hepatitis
b. Acetaminophen toxicity
c. Alcohol-induced injury
d. Autoimmune hepatitis
e. α-1-Antitrypsin (A1AT) deficiency

Initial Laboratory Data

Laboratory results revealed a normal complete blood count with differential, an ALT of 92 U/L (normal,

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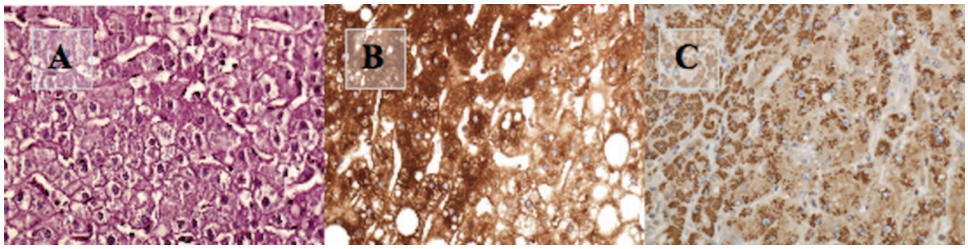

Figure 1. Liver biopsy specimens. (A) Periodic acid Schiff diastase (PAS-d) staining showing intracytoplasmic accumulation of PAS-d–resistant material; (B) immunohistochemical staining of the case patient's hepatocytes; and (C) control immunohistochemical staining of a known AlAT-deficient patient.

5–45 U/L) and AST of 52 U/L (normal, 5–45 U/L), an albumin of 4.6 g/dL (normal, 3.5–5.5 g/dL), a total bilirubin of 0.6 mg/dL (normal, 0.1–1.2 mg/dL), a GGT of 67 U/L (normal, 15–73 U/L), a c-reactive protein of 0.416 mg/dL (normal, 0–0.744 mg/dL), nonreactive hepatitis B surface antigen, hepatitis B core antibody (IgM and IgG), hepatitis A IgM and IgG, and hepatitis C antibody; antinuclear antibody testing was negative. A liver biopsy revealed periportal and intracytoplasmic periodic acid Schiff–positive, diastase-resistant globules. Macrovesicular steatosis was noted; however, trichrome staining was negative for fibrosis.

QUESTION 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis for this patient?

a. Serum α-1-antitrypsin (A1AT) level
b. A1AT genotype
c. Immunohistochemical staining of the liver biopsy specimens (for A1AT)
d. CT of the chest
e. Pulmonary function testing

Clinical Course

The patient was referred to allergy–immunology for additional workup and evaluation of suspected A1AT deficiency. His liver biopsy specimens were sent for immunohistochemical staining of A1AT and found to be positive (Fig. 1). A serum level of A1AT was found to be <30 mg/dL, below the lower limit of quantitation for the test, and genotyping of the A1AT locus revealed homozygosity for the Z allele. Review of the patient's records showed normal pulmonary function parameters (Table 1); however, evaluation of annual spirometry from his employer revealed a marked decrement in forced expiratory volume in 1 second (FEV_1) over time (Fig. 2). Review of the patient's liver function testing showed chronic elevation of the ALT over a 6-year period with otherwise normal hepatic function.

Consideration of an employment change was discussed given the job hazard of significant smoke exposure. Screening for the A1AT Z allele was performed on the patient's two children and they were heterozygous for the Z allele. Hepatitis A and B vaccines were administered to the patient, and full pulmonary function testing was performed revealing a normal diffusion limited carbon monoxide test. Monitoring with serial spirometry was initiated. The patient continued to do well clinically until he developed a left upper extremity tremor and was diagnosed with glioblastoma multiforme.

DISCUSSION

α-1-Antitrypsin deficiency, first described in 1963, arises from mutations of the *PI* gene, which is located

Table 1 **Pulmonary function testing data over time**

Date	FEV_1 (L)	FEV_1 (%)	FEV_1/FVC	FEV_1/FVC (%)	DLCO (%)
June 24, 2002	4.37	89	0.82	101	NA
June 3, 2003	4.54	94	0.79	99	NA
June 30, 2004	4.27	89	0.82	101	NA
July 12, 2005	4.17	91	0.81	101	NA
July 15, 2005	3.96	86	0.81	101	79
February 2, 2006	4.16	90	0.80	100	79
July 25, 2006	3.94	84	0.80	100	67
February 8, 2007	3.42	75	0.82	103	NA

DLCO = diffusion limited carbon monoxide.

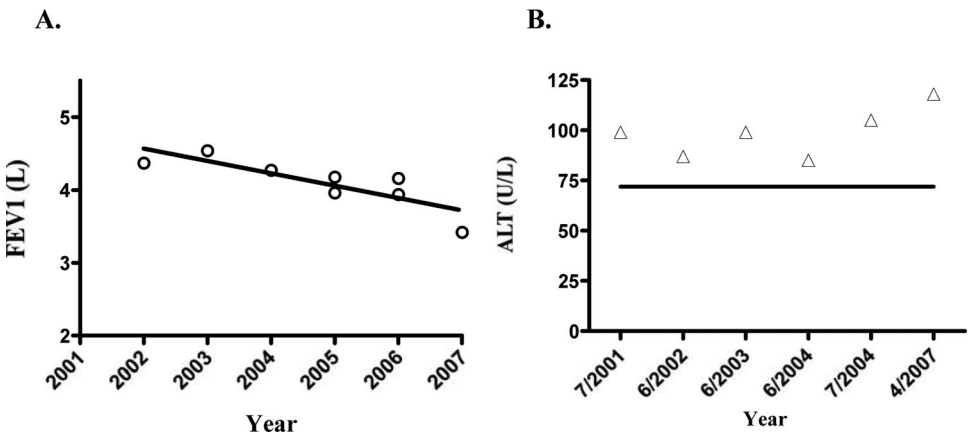

Figure 2. (A) Measurements of FEV_1 over time revealed a decline of 170 mL/year. (B) The patient's serum ALT over a 6-year period compared with the upper limit of normal for the test (72 U/L).

on chromosome region 14q31-32.3.[1–3] This disorder has been reported to affect up to 3.4 million individuals worldwide (PI*ZZ phenotype), with an estimated prevalence ranging from 1:1600 in Sweden to 1:5097 in Oregon.[4–6] Approximately 100 genetic variants of A1AT are known; their alphabetical designation (phenotype) is based on the protein's mobility in an electrophoretic field at alkaline pH.[4] The normal phenotype is MM, and the phenotype most commonly associated with lung disease is ZZ.

Diagnosis of A1AT deficiency is made by "phenotyping" or performing isoelectric focusing on serum, plasma, or on blood that has been applied to Guthrie filter paper.[4] Molecular diagnosis or "genotyping" is performed on genomic DNA extracted from circulating mononuclear blood cells.[4] Phenotyping and genotyping identify mutated A1AT proteins and DNA, respectively. Serum levels of A1AT are available and should be obtained in all patients suspected of having the disease. Individuals with A1AT levels below 20 μmol/L are considered deficient, and patients with the ZZ phenotype typically have levels of $\sim$5–6 μmol/L.[4]

The pulmonary pathophysiology of A1AT deficiency stems from an inability to degrade neutrophil elastase and other serine proteases.[4] This results in susceptibility to emphysema, which typically develops in a panacinar distribution with basilar predominance. In patients with A1AT, emphysema is the leading cause of death and FEV_1 is the most important predictor of survival.[7–9]

Liver disease in A1AT patients is thought to result from buildup of the abnormal protein within the hepatocyte endoplasmic reticulum.[10–12] The presentation of liver disease in A1AT patients is diverse, ranging from rare fulminant neonatal hepatic failure to presentation in adulthood with upper gastrointestinal bleeding, hepatosplenomegaly, ascites, chronic cirrhosis, hepatic failure, or simply elevated transaminases.[3,13–16]

The presentation of liver disease in A1AT deficiency is highly variable.[17] Patients with PI*ZZ are at risk in childhood, while patients heterozygous for a Z allele or with an S allele should not be expected to develop liver disease.[18–21] Rarely, patients may present in infancy with fulminant hepatitis; however, elevated transaminases and/or conjugated hyperbilirubinemia are commonly seen in PI*ZZ individuals.[22] Other Pi mutations such as the Mmalton allele also confer a risk for liver disease, which may not manifest in childhood. Some patients with the Mmalton allele present with fulminant hepatic failure and require liver transplantation in adulthood.[23]

Among patients with A1AT, risk factors for cirrhosis in adults are maleness, advanced age, obesity, alcohol abuse, viral hepatitis, and steatohepatitis.[24–26] Logically, avoidance of hepatotoxic medications and significant alcohol intake also would be expected to benefit patients with A1AT deficiency. In some series, liver disease is the leading cause of death among nonsmoking PI*ZZ individuals.[27]

Early diagnosis of A1AT deficiency is important for the purpose of disease outcome modification. Given that tobacco smoke accelerates the decline of lung function in patients with PI*ZZ, avoidance of smoke and other environmental toxins would be expected to attenuate the decline of lung function in patients with A1AT.[28] Additionally, augmentation therapy with A1AT concentrate slows the decline of lung function.[4]

We present a case of an asymptomatic adult with chronic elevation of ALT and normal pulmonary function but accelerated lung function decline. As suggested elsewhere, practitioners must have a high index of suspicion for occult obstructive pulmonary diseases

and consider a broad list of differential diagnoses.[29,30] This patient likely would have suffered early and advanced pulmonary disease given the rate of decline and his occupational exposure to smoke as a firefighter. Close monitoring with serial spirometry and flow volume loop analysis is indicated in such patients and allows for timely implementation of augmentation therapy.[31]

Final Diagnosis

α-1-Antitrypsin deficiency (Pi*ZZ).

SUMMARY

Cardinal manifestations of α-1-antitrypsin deficiency are early chronic obstructive lung disease and liver dysfunction. However, presentation may be subtle; therefore, practitioners should maintain a high index of suspicion for the disease in patients with evidence of pulmonary and/or hepatic disease. Early diagnosis of α-1-antitrypsin deficiency is important in reducing morbidity and for long-term disease modification.

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Patient Oriented Problem Solving (POPS) Case Report

Interleukin-2 treatment for persistent cryptococcal meningitis in a child with idiopathic CD4$^+$ T lymphocytopenia

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ABSTRACT

We report a 16-year-old male patient who presented with headache, behavior changes, and fever. His cerebral spinal fluid and blood cultures grew Cryptococcus neoformans*. His laboratory evaluation was negative for human immunodeficiency virus infection but flow cytometry revealed low CD4$^+$ count of 39 cells/mm^3 and CD4:CD8 ratio of 0.43. He was initially treated with antifungal agents with only partial clinical improvement, and he was discharged to home on oral fluconazole and prophylactic co-trimoxazole. After discharge, he continued to have persistent headache and recurrent episodes of vomiting. He was readmitted several times because of worsening of meningitis symptoms and received prolonged courses of multiple antifungal therapy, with clearance of infection from the central nervous system. He was subsequently placed on prophylactic therapy with fluconazole. His peripheral CD4$^+$ cell count remained low after resolution of his meningitis. Eight months after the initial diagnosis, recombinant IL-2 therapy was initiated and within a few months, his CD4$^+$ cell count started to increase. Treatment with rIL-2 and prophylactic antifungal therapy continued and he has been asymptomatic for almost 20 months so far. This case is the first reported pediatric idiopathic CD4$^+$ T-lymphocytopenia case with cryptococcal meningitis that was successfully treated by the addition of rIL-2 therapy to antifungal therapy.*

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Key words: CD4 lymphocytopenia, cryptococcal infection, fungal infection, immunodeficiency, interleukin-2, meningitis, T cells

CASE PRESENTATION

Chief Complaint

Fever, headache, neck pain, and change in behavior.

History of Present Illness

A 16-year-old male patient had a 2-week history of fever, headache, neck pain, weakness, intermittent episodes of vomiting, and worsening of psychotic behavior. His medical history included three hospitalizations for croup as a toddler, a motor vehicle accident with a closed head injury at 6 years of age, and schizoaffective disorder diagnosed at 9 years. His only medication was risperidone. He had four healthy siblings, a sister with type I diabetes, his mother had bipolar disorder, and a maternal aunt had schizophrenia. Because of schizoaffective disorder, he was homeschooling. He denied any use of tobacco, alcohol, illicit drugs, or sexual activity.

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Physical Examination

The patient was awake and cooperative but obviously introverted and emotionally distant from other family members, suggestive of personality disorder. His temperature was 38.3°C, other vital signs were within normal limits. His weight and height were between 50th and 75th percentiles. He exhibited meningeal irritation signs; the rest of his physical examination was normal.

His complete blood cell count showed anemia and the white blood cell count included 82% neutrophils. His cerebrospinal fluid (CSF) analysis showed leukocytosis, increased protein, an low glucose, and India ink stain revealed budding yeast cells (Table 1).

Table 1 **Laboratory findings in a child with ICL and cryptococcal meningitis**

CBC: WBC 16.3 K/mm^3; 82% N, 13% L, 3% M; Hgb 9.5 gm/dL, Hct: 27%
CSF analysis: 75 nucleated cells/HPF; 44% N, 30% L, 21% M
Protein: 175 mg/dL
Glucose: 44 mg/dL
India ink stain: budding yeast cells
Cryptococcal antigen titer: 1:1024
Culture: *Cryptococcus neoformans*
PCR for HIV-1 and -2: negative
IgG 691 mg/dL (nl 639-1339)
IgA 64 mg/dL (nl 63–484)
IgM 43 mg/dL (nl 52–242)
Hepatitis C antibody: negative
CMV-IgG: negative
CMV-IgM: negative
FISH analysis for 22q11.2 deletion: negative

Flow cytometry	Initial	9 mo of IL-2 therapy	Normal
CD4	16.2%, 158/mm^3	18.6%, 323/mm^3	27–57%, 562-2692/mm^3
CD8	37.8%, 368/mm^3	28%, 486/mm^3	14–34%, 331-1445/mm^3
CD4:CD8 ratio	1:2.3	1:1.5	1.7–0.2:1
CD19	27.2%, 265/mm^3	35.6%, 618/mm^3	9–29%, 200-1259/ mm^3
CD56	3.1%, 56/ mm^3	10.9%, 189/mm^3	3–12%, 70–120/mm^3

CBC = complete blood count; WBC = white blood cell count; HPF = high power field; PCR = polymerase chain reaction; CMV = cytomegalovirus; FISH = fluorescein in situ *hybridization.*

Working Diagnosis

The initial laboratory findings were compatible with fungal meningitis. Therapy with amphotericin B (1 mg/kg per day i.v.) and flucytosine (100 mg/kg per day orally) was initiated. Blood and CSF cultures grew *Cryptococcus neoformans.*

Differential Diagnosis

As an opportunistic infection, cryptococcal meningitis rarely affects immune competent subjects. The differential diagnosis of the underlying disorder should include primary and secondary immune deficiencies.

Human immunodeficiency virus (HIV) infection was the most suspected; however, ELISA and polymerase chain reaction testing for HIV-1 and HIV-2 were negative. Serum immunoglobulin levels were normal, except for a slightly reduced IgM level. The peripheral $CD4^+$ (T-helper lymphocytes) count was very low at 39 cells/mm^3. A detailed flow cytometric analysis (Table 1) showed normal counts of $CD19^+$ cells (B lymphocytes) and $CD8^+$ cells (T-suppressor lymphocytes) but low $CD4^+$ at 158 cells/mm^3 and a reversed CD4:CD8 ratio of 0.43. Serological testing for Epstein-Barr virus did not suggest active infection. Other viral infections such as cytomegalovirus and hepatitis C can also be associated with low $CD4^+$ counts and abnormal CD4:CD8 ratios,[1] but they were excluded by repeated testing in this patient.

Malignancies and autoimmune disorders can be associated with a low $CD4^+$ count. However, our patient did not have any physical or laboratory findings suggestive of such diseases. Medications may also be a cause, but he was receiving only risperidone and a review of the literature did not reveal any association between risperidone and low $CD4^+$ counts.

The 22q11.2 deletion syndrome comprises a low $CD4^+$ count and reversed CD4:CD8 ratio and should be considered particularly because it may have a wide spectrum of clinical presentations, including psychiatric disorders.[2] However, florescent *in situ* hybridization study for 22q11.2 deletion was negative in our patient.

Definitive Diagnosis

Our patient's low $CD4^+$ count seems to be the most probable underlying cause of cryptococcal meningitis. A low $CD4^+$ count secondary to severe infections is almost always associated with normal CD4:CD8 ratio.[3] Therefore, the laboratory findings are most compatible with "idiopathic $CD4^+$ T lymphocytopenia" (ICL).[4]

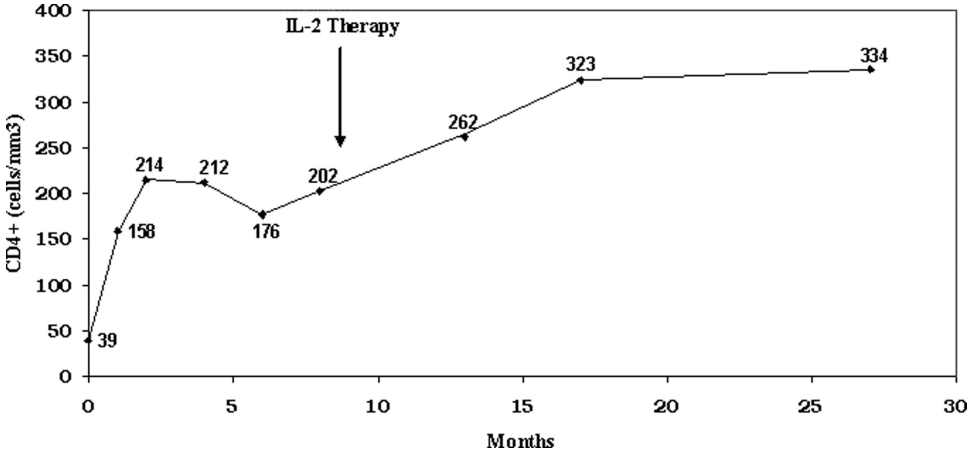

Figure 1. CD4 cell count before and during recombinant IL-2 treatment.

Clinical Course

On the 2nd week of amphotericin B therapy, the patient developed dehydration and renal toxicity with a serum creatinine level up to 4.3 mg/dL. His antifungal therapy was changed to liposomal amphotericin B (5 mg/kg per day i.v.) and fluconazole (200 mg/day orally). One week later, creatinine was stabilized around 1.5 mg/dL. During the 3rd week of treatment, the patient developed severe abdominal pain and vomiting, serum lipase was 800 U/dL, indicating pancreatitis, which resolved in 1 week. However, during the 4th week of therapy, he developed lower extremity weakness and decreased visual acuity. Lumbar puncture revealed increased intracranial pressure at 55 cmH_2O. Daily lumbar puncture for drawing CSF was instituted. Then, the patient developed a complete visual loss, which was thought to be caused by optic neuritis. His vision partially improved after initiation of i.v. corticosteroids. CT did not show hydrocephaly. Increased intracranial pressure was controlled with intermittent lumbar punctures. However, it recurred and eventually required placement of a lumboperitoneal shunt on the 42nd day of admission. He was discharged from the hospital on day 47 on oral co-trimoxazole, 160 mg, orally twice a day, 3 days/week (Monday, Wednesday, and Friday), and fluconazole at 400 mg/day orally. At that time, he had low CSF cryptococcal antigen titers and negative cultures for *C. neoformans,* but his $CD4^+$ count remained low.

One month later, he was readmitted because of vomiting and staggering gait. It was found out that he was noncompliant with the intake of his medications. A lumbar puncture showed that the CSF was positive for fungal spores by India ink stain and its antigen titer for *C. neoformans* had increased from 1:128 to 1:1024 dilution in a 6-week period. A repeat HIV antibody test and polymerase chain reaction testing for HIV-1 and HIV-2 were negative. Lymphocyte proliferation testing showed decreased responses to phytohemagglutinin, *Staphylococcal enterotoxin* B, and *Candida albicans*. Amphotericin B and flucytosine were reinstated at the previous doses, and after 3 weeks he was discharged on prophylactic fluconazole (200 mg/day orally) and co-trimoxazole (160 mg orally twice a day, 3 days/week). He came back 18 days later with persistent vomiting, weight loss of 4 kg, and hypokalemia (K 2.7 mEq/L). He received i.v. amphotericin B and flucytosine for 2 weeks and was discharged on prophylactic doses of fluconazole and co-trimoxazole under the supervision of a home health care service. The patient continued to have low $CD4^+$ cell counts and intermittent episodes of vomiting with headache.

What Else Can Be Done?

A few ICL case reports[5–7] showed promising results after treatment with recombinant IL-2. This therapy (Proleukin; Chiron Corporation, Emeryville, CA) was initiated (8 months after onset of illness) as subcutaneous injections of 50,000 U/m^2 of bovine serum albumin twice during the 1st week and then was increased to the maintenance dose of 125,000 U/m^2 of bovine serum albumin twice weekly. The $CD4^+$ count increased to 262 cells/mm^3 at 5 months and to 323 cells/mm^3 at 9 months of therapy (Fig. 1). The treatment has been maintained and is well tolerated without recurrence of meningitis symptoms.

DISCUSSION

The affliction of this teenager with fungal meningitis led to suspicion toward an underlying immune defect. His immunologic evaluation findings were compatible with the rare defect ICL. According to the Centers for Disease Control and Prevention, ICL is defined as (1) $CD4^+$ cell count of $<300/\mu L$ or $<20\%$ (of total lymphocytes) on more than one occasion, (2) no evidence of HIV infection, and (3) absence of other known immune deficiency disease or therapy-associated lym-

phocytopenia.[4] It should be distinguished from $CD4^+$ lymphocytopenias secondary to severe infections, malignancies, autoimmune disorders, and medications. Clinical presentation can vary from asymptomatic state to severe recurrent opportunistic infections,[8–12] malignancies,[13,14] or autoimmune disorders.[15,16] There have been a few reports on familial cases.[17,18] The disease can be associated with substantial morbidity and mortality.[19,20]

IL-2 is a cytokine produced by activated T helper lymphocytes and it mediates a number of biological activities that may induce T-cell proliferation and function, promote the release of secondary cytokines, induce activation of natural killer cells and T cells, and improve antigen recognition and processing. Moreover, it stimulates further expression of IL-2 receptors on T cells, B cells, and natural killer cells.[21] Recombinant IL-2 has been used in varying doses in the treatment of disorders associated with low $CD4^+$ counts such as acquired[22] and congenital[23] immunodeficiency disorders and malignancies.[24] The first ICL case[5] that was successfully treated with rIL-2 was published in 1999. It was followed by two more case reports in 2000 and 2001.[6,7] Those three cases were all adults, and the dose of rIL-2 varied from 50.000 U/week to 15 million U/week.

After multiple treatments with various antifungal agents, our patient only partially improved. Furthermore, he developed serious complications of meningitis (*i.e.*, loss of visual acuity) and side effects of medications (*i.e.*, renal toxicity from amphotericin B), and had very negative physical and psychological experiences secondary to repeated lumbar punctures and anxiety and depression due to being away from home during his multiple hospital admissions. Hence, the decision was made to try rIL-2 therapy. After 1 month of rIL-2 therapy the patient's symptoms gradually resolved, his quality of life improved, and he has been tolerating the treatment well. His most recent $CD4^+$ count at 19 months of therapy continues to be adequate (334 cells/mm^3).

This case is of particular interest because it shows that rIL-2 may be an effective and safe additional therapy in children with ICL who do not completely respond to conventional therapy. To the best of our knowledge, this is the first report of a pediatric ICL case that was treated with rIL-2 with success.

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Patient Oriented Problem Solving (POPS) Case Report

Giant cell arteritis presenting as facial swelling

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ABSTRACT

Facial swelling is commonly ascribed to angioedema and a host of other causes. Temporal arteritis (TA), a disease most often diagnosed in patients over the age of 50 years, frequently presents with nonspecific and often ignored complaints (headache, symptoms of polymyalgia rheumatica, low-grade fever, fever of unknown origin, loss of appetite, depression, joint pains, weight loss, hair loss, and even respiratory symptoms). The diagnosis of TA is highly likely in the presence of new-onset headaches, polymyalgia rheumatica, and a tender, cord-like, or swollen temporal artery. Facial swelling must be appreciated as another presentation of TA, especially when accompanied by other nonspecific symptoms. High clinical suspicion, immediate treatment, and definitive diagnosis by temporal artery biopsy are necessary to prevent the most severe vascular complications of blindness and cerebrovascular accidents. Treatment with corticosteroids is most often successful. Because this treatment is fraught with all the risks of high-dose and prolonged steroid therapy, it should only be initiated in cases of significant clinical suspicion, followed by a timely temporal artery biopsy to confirm the diagnosis. Delay in therapy increases the risk of a vascular catastrophe. Delay in obtaining a temporal artery biopsy after therapy has been initiated decreases the diagnostic sensitivity of the test. Other modalities of immunosuppressive therapy remain either unsuccessful or unproven. Concomitant low-dose aspirin therapy appears to hold promise.

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Key words: Blindness, corticosteroid treatment, facial swelling, giant cell arteritis, jaw claudication, ophthalmoplegia, polymyalgia rheumatica, temporal arteritis, temporal artery biopsy

CASE PRESENTATION

Chief Complaint

The patient is an 85-year-old white woman who presents with severe frontal headache, facial pain and swelling, and difficulty swallowing.

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History of Present Illness

The patient presented with 3 days of severe frontal headache, facial pain and swelling, and difficulty swallowing. She noted fever to 101.6°F, neck pain, myalgias, weakness, and swelling of her tongue. Swelling of her face, eyelids, and tongue steadily progressed. One day before admission, she experienced nausea and several episodes of vomiting. The patient denied any prior episodes of chronic or severe headaches or angioedema. Over the next 24 hours, there was marked improvement in the facial swelling but no improvement in facial pain, neck pain, or swallowing and worsening of tenderness over the temporal areas. The patient denied any prior episodes of chronic or severe headaches, angioedema, or drug or food hypersensitivity.

Physical Examination on Hospital Admission

Vital signs were temperature, 101.6°F; heart rate, 93/minute; respiratory rate, 18/minute; and a blood pressure of 150/80 mm Hg. Her face, eyelids and tongue were markedly swollen. The extraocular movements were intact, but the fundi could not be well visualized. Her head was tender in the temporal regions, but no cords were appreciated. Mild nuchal rigidity and ten-

derness and a thyroid goiter were noted. The remainder of the physical examination was normal.

QUESTION 1

Which of the following are included in the differential diagnosis of a patient presenting with a painful face with or without swelling?

A. Angioedema
B. Submandibular calculi
C. Infections of the submandibular gland
D. Osteomyelitis
E. Muscle contraction headaches
F. Carotidynia
G. Trigeminal neuralgia
H. Giant cell (temporal) arteritis

QUESTION 2

Which of the following are included in the differential diagnosis of giant cell (temporal) arteritis?

A. Migraine headache
B. Carotidynia
C. Polymyalgia rheumatica (PMR)
D. Rheumatoid arthritis
E. Trigeminal neuralgia
F. Temporomandibular joint disease
G. Sinusitis
H. Oral/dental pathology
I. Autoimmune thyroid disease
J. Occult malignancy
K. Causes of sudden blindness

Discussion of the Differential Diagnosis

Causes of facial swelling include angioedema (chronic idiopathic, acquired, or hereditary angioedema), malignancy, allergic angioedema secondary to food or drug allergy, submandibular calculi or infections, osteomyelitis, Gleich syndrome, malignancy, and sinusitis.[1,2] C1-esterase inhibitor autoantibodies have caused isolated tongue swelling.[3] Angina, temporomandibular joint disease, muscle contraction headaches, carotidynia, trigeminal neuralgia, PMR, and temporal arteritis (TA) (giant cell arteritis [GCA], or cranial arteritis) comprise causes of facial pain. The differential diagnosis for TA/GCA includes all of the aforementioned, multiple myeloma, myalgias from statin therapy, osteoarthritis, rheumatoid arthritis, occult malignancy, and causes of sudden blindness.[1,4,5]

TA/GCA is the most common form of idiopathic large- and medium-sized vessel vasculitis of branches of the aortic arch.[6] GCA has an incidence of 18 cases/100,000 in patients >50 years of age.[5] The disease affects all races but predominates in white people from Scandinavia, Great Britain, and the northern United States.[7] In northern Europe the ratio of women to men is 3:1, and in Spain this ratio is lower.[8,9]

TA/GCA's clinical picture includes new onset of headache (from temporal or occipital artery involvement), a tender and/or nodular temporal artery with decreased pulsation, elevated erythrocyte sedimentation rate (ESR), and a diagnostic temporal artery biopsy.[1,5,6] Rarely, physical examination has revealed cord-like pulseless and thickened facial and occipital arteries.[10] In an older study of 100 patients, the most common initial complaints were headache (60% of patients) and PMR (40–60% of patients).[7,8,11–13] Five to 40% of patients with PMR have occult TA.[14] Synovitis has been reported not infrequently, and arthralgia in the proximal joints is common.[15,16] Respiratory symptoms are infrequent but not rare (9% incidence) and may be the presenting complaint in 4% of patients.[1] Aortic regurgitation, myocardial infarction, and deafness are rare complications.[17]

It should be noted that a normal ESR is found in 5–24% of patients.[1] Biopsies are diagnostic in 80–95% of untreated patients.[1] Steroids reduce their diagnostic value to 78% after <2 weeks of therapy, 65% after 2–4 weeks of therapy, and 40% after 4 or more weeks of therapy.[18] However, most clinicians will start steroid therapy as soon as TA/GCA is suspected and quickly proceed with a temporal artery biopsy.[16,19] Unilateral biopsies have a 4–5% false-negative frequency.[7,12,14] Bilateral temporal artery biopsies are mandatory. In one study, 14% of patients were diagnosed on the innocent-appearing side.[20] Reactive bone marrows, leukocytosis, thrombocytosis, elevated liver enzymes, elevated C-reactive protein, and anemia of chronic disease are well documented in these patients.[12,14,16,21]

In typical cases, the superficial temporal artery will be readily visible, knotty, pulseless, tortuous, thickened, and tender. Hair loss and ischemic scalp ulceration have been reported. Similar findings have been reported in the contralateral upper extremity, neck, and chest arteries.[1] One-half of the patients have eye complaints. Diplopia is caused by vasculitis affecting cranial nerves III, IV, and VI. Thirteen to 50% of untreated patients develop sudden onset of permanent blindness from occlusion of the posterior ciliary artery. Blindness in both eyes is rare. This is often preceded by amaurosis fugax or ophthalmoplegia.[1,5–7]

Significant involvement of large arteries (27% of patients) includes aortic aneurysms or dissection (18%), stenosis of the superior branches of the aortic arch especially the subclavian and axillary arteries (10–15%), and, occasionally, stenosis of the lower aortic vessels (<1%). These patients have a 17-fold increased risk of thoracic aortic aneurysms and a 2.4-fold increased risk of abdominal aortic aneurysms. Symptoms related to these vessels include extremity and jaw claudication (34% of patients with TA) and diffuse mandibular, dental, and sinus pain or discomfort.[5,6,14]

Facial swelling has been infrequently reported as the initial presentation of TA/GCA.[15,22,23] Scalp necrosis, tongue necrosis, other cranial neuropathies, peripheral neuropathies, cerebrovascular accidents, transient ischemic attacks, and cotton–wool exudates secondary to retinal ischemia have been reported. TA/GCA is a well-appreciated cause of fever of unknown origin, anorexia, weight loss, wasting syndrome, depression, headache, and failure to thrive.[5,14,17]

A review of 260 consecutive patients with TA/GCA found 17 patients (6.5%) with head-and-neck swelling. These authors report that facial swelling was often the initial manifestation of disease and transient. Facial swelling was often painful, involved the orbital region and face, especially the lower part of the cheeks and maxillae. The neck was less frequently involved, and rarely the tongue, limb, or forehead. Ear, nose, throat symptoms were observed in 80% of cases (jaw claudication and frank trismus). Two patients had permanent visual impairment and one patient had sudden hearing loss. The swelling either spontaneously disappeared or regressed after steroid therapy. A small number of patients suffered recurrence of their facial swelling.[24,25] A variant of this presentation is hemifacial edema, trismus, and fever. These manifestations disappeared before more typical findings of TA/GCA led clinicians to the diagnosis.[26]

Facial swelling as a result of TA/GCA has preceded anterior ischemic optic neuropathy and is believed to be "an indicator" of anterior ischemic optic neuropathy.[15] The mere sensation of facial puffiness may be an initial manifestation of TA/GCA and a predictor of visual disturbances.[27] Another case of TA/GCA facial swelling was accompanied by glossitis and odynophagia (claudication-like symptoms of the tongue and muscles of deglutition).[12] Even more unusual is TA/GCA presenting as a submandibular mass as the result of facial artery involvement.[22]

Patients must meet three of the following five criteria to be accepted in studies for TA: age of >50 years, new onset of headache (found in 65–75% of TA patients), abnormal temporal artery by physical examination, ESR of >50 mm/hour, and diagnostic temporal artery biopsy. An ESR of <50 mm/hour significantly reduced finding TA by temporal artery biopsy.[14] These criteria distinguish TA from other forms of vasculitis described in Table 1[28–38] with 93.5% sensitivity and 91.2% specificity.[14,39] Jaw claudication alone or with either scalp tenderness or a new headache increased the chances of a positive temporal artery biopsy to >75%.[19]

Early biopsy reveals patchy segmental inflammation with infiltrated macrophages and lymphocytes limited to the elastic lamina or adventitia. This may progress to necrosis of the arterial wall with granulomas containing multinucleated histiocytes, some of foreign body type and some of Langhans' type giant cells. Thrombosis occurs and late recanalization has been noted. Bilateral and multiple sections are necessary to confirm the diagnosis.[1,6]

Standard therapy for TA is corticosteroids (equivalent of prednisone, 1 mg/kg per day, for 1 month followed by a 5–10% taper every 2–4 weeks until discontinued or the lowest tolerated dose). Prognosis is good if therapy is begun before visual loss. Visual loss has occasionally reversed.[14] Duration of therapy is usually 2–3 years. Visual loss while on therapy is rare.[5]

In a retrospective study, aspirin appears to reduce the risk of cranial ischemic complications.[39] Alternate-day steroid therapy had a higher failure rate (70%) when compared with once-daily therapy (20%).[40] Aziothioprine, dapsone, cyclophosphamide, infliximab, and methotrexate have not established efficacy.[40–42] There is a case report of the successful treatment with adalimumab of relapsed TA after high-dose steroids had to be tapered.[43]

TCA/GA appears to be a T-cell–mediated disease. The pathogenesis involves activation of the $CD4^+$ T cells, release of cytokines, activation of macrophages, and production of reactive oxygen intermediates and metalloproteinases. What factor initiates this cascade of inflammatory tissue destruction remains to be determined. The presence of dendritic cells and Toll-like receptors are one avenue of research that is being investigated.[44] Interleukin (IL)-10 promoter gene and myeloperoxidase (MPO) promotor gene polymorphisms (−592 C/A IL-10 promoter gene and −463 G/A MPO promoter gene) are associated with susceptibility to GCA.[45,46]

Additional History

The patient's medical history was significant for hypertension, hypothyroidism, chronic anxiety, goiter, and T-12 dermatomal zoster 2 months before this illness. She took no over-the-counter medications and denied recent travel, change in medications, or home environment. Her medications included metoprolol, levothyroxine, sertraline, alprazolam, amlodipine, and aspirin.

Alprazolam-induced angioedema must be included as a specific cause of drug-induced angioedema. Alprazolam has been reported to cause allergic reactions and tongue angioedema. One such report implicated the tartrazine dye used in the drug preparation. Other benzodiazepines have caused erythema multiforme and toxic epidermal necrolysis (tetrazepam).[47–51]

Laboratory and Other Diagnostic Findings

A head CT scan revealed small vessel white matter changes. The initial ESR was 60 mm/hour. Her he-

Table 1 **The vasculitides**[28-38]

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Hereditary angioedema (HAE)				
Autosomal-dominant Prevalence 1:50,000. Type 1 HAE: Low levels of active C1-INH	Subcutaneous nonpruritic swelling without accompanying urticaria; typical symptoms include voice change, respiratory stridor, or asphyxia	May present late in life after treatment with ACE inhibitor treatment	Type 1: Low C4 and C1-INH levels and normal C3, CH_{50} and C1q serum levels	Danazol (an attenuated androgen); antifibrinolytic agents ε-aminocaproic acid or tranexamic acid; C1-INH concentrate; recombinant transgenic C1-INH; DX-88 (ecallantide, a plasma kallikrein inhibitor); or, icatibant
Type 2 HAE: Normal levels of dysfunctional C1-INH		Type 2 has presented as food allergy	Type 2: Reduced C1-INH activity, normal serum antigen level	
Type 3: A recently described HAE exclusively found in women with mutations in coagulation factor XII gene		Type 3: Disease triggered by estrogen therapy, oral contraceptives, and pregnancy	Type 3: Two different missense mutations identified at the same position in the factor XII gene with normal C1-INH levels	
Acquired deficiency of C1-INH (AAE)				
Associated with lymphoproliferative or rheumatologic disorders. Type 1 AAE: Antiidiotype antibodies against B-cell surface immunoglobulins, resulting in formation of immune complexes. These immune complexes activate C1, which causes consumption of C1-INH Type 2 AAE: Immune blockade of the C1-INH molecule active site by autoantibodies producing a nonfunctional cleaved C1-INH		May present after treatment with ACE inhibitor treatment		

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
ANCA-associated primary vasculitic syndromes				
See Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis	Cutaneous manifestations: Palpable purpura or infiltrated erythema May involve the small vessels around the temporal artery and present with typical manifestations of giant cell arteritis	Nodular erythema, livedo racemosa, deep ulcers, digital gangrene		
Wegener's granulomatosis				
ANCA-associated vasculitis; small and medium vessel necrotizing vasculitis and granulomatous inflammation; giant cells present; proliferative GN (pauci-immune)	Triad of upper airway involvement (which is often indolent), lower respiratory tract involvement, and GN; abnormal CXR is very common; ocular, cutaneous and musculoskeletal manifestations are common	Central diabetes insipidus, retro-orbital mass, hearing loss, thyroid, prostate and breast involvement	Tissue biopsy of site with active disease Open lung or thoracoscopic biopsy often best Renal biopsy can be supportive but is generally not diagnostic ANCA positivity is most often c-ANCA (anti-PR3 specificity)	Nonsevere or limited disease: Methotrexate Severe or generalized disease: Initial treatment with corticosteroids and cyclophosphamide Once in remission, maintenance therapy with methotrexate or azathioprine
Microscopic polyangiitis				
ANCA-associated small vessel vasculitis; proliferative GN (pauci-immune); no giant cells	Often has a long prodromal phase RPGN is essentially universal; alveolar hemorrhage and gastrointestinal symptoms are common		GN and pulmonary involvement are absent in classic PAN; p-ANCA (anti-MPO positivity is present in 60%)	High-dose corticosteroids initially with additional immunosuppressive therapy depending on severity of disease

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Churg-Strauss syndrome ANCA-associated small vessel vasculitis; giant cells and eosinophilia present; granulomatous inflammation of the respiratory tract	Has prodromal, eosinophilic and vasculitic phases; typically, asthma precedes other symptoms by years; eosinophilia, pulmonary infiltrates, and mononeuritis multiplex are classic; sinusitis, allergic rhinitis, abdominal symptoms, cutaneous manifestations, and cardiac disease are common; cardiac disease is a leading cause of mortality in this disease	Reversible exophthalmos; skull base infiltration with granulomas	Tissue biopsy of site with active disease (*i.e.* lung, nerve); has low frequency of $ANCA^+$ tests; when positive usually p-ANCA (anti-MPO)	Primary treatment is high dose glucocorticoids; in patients with severe or refractory disease, additional agents such as cyclophosphamide or azathioprine are typically used
Takayasu's arteritis Myointimal proliferation with vessel wall thickening and luminal stenosis, or if smooth muscle cell and elastic fiber destruction predominates, aneurysm formation	Most common signs and symptoms are upper extremity claudication, asymmetric blood pressures, and vascular bruits (carotid, subclavian and aortic vessels most often) Systemic symptoms are not as common; signs and symptoms of cerebrovascular insufficiency are very common Abnormal pulmonary imaging studies are common but clinical symptoms present only ~25% of the time; hypertension is present in 40–80% of patients and may be underestimated in patients with subclavian and innominate artery stenosis	Retinopathy, vitreous hemorrhage	Diagnosis is based on clinical findings in the setting of compatible vascular imaging abnormalities	High-dose glucocorticoid therapy (1 mg/kg per day) is the standard for those patients with relapsing disease on prednisone taper or with steroid resistant disease, methotrexate or cyclophosphamide may be added Surgical interventions include bypass, PTCA, aortic root repair or replacement; overall, bypass grafting maintains better patency Disease activity is extremely difficult to assess

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Giant cell arteritis				
Large vessel vasculitis; involvement tends to be patchy and rarely affects intracranial arteries; multinucleated giant cells present in ~50% of biopsies	Age of onset ≥50 year; new onset localized headache; ESR >50, temporal artery tenderness, jaw claudication, amaurosis fugax, polymyalgia rheumatica, anemia, mononeuritis multiplex, and constitutional symptoms are common Aortic aneurysms can be seen as early or late complications	Nonproductive cough, arm claudication, tumor-like mass in the breast, SIADH, tongue infarction, hearing loss, and Charles Bonnet syndrome (visual hallucinations)	Suspect if patient is >50 years old, PMR, FUO, unexplained anemia, new headache, acute visual changes and/or elevated ESR Temporal artery biopsy If temporal artery not clinically involved may need to biopsy other arteries such as occipital or facial	High-dose glucocorticoids and low dose aspirin (81–100 mg/day)
Henoch-Schonlein purpura (IgA-associated vasculitis)				
Capillary and venule involvement. IgA containing complexes	Purpura, urticaria, abdominal pain, GI bleeding, intussusception, arthritis/arthralgias and GN are common manifestations; often self-limited; frequently recurrent	Venous thrombosis with high levels of factor VIII and homocystein		In absence of renal dysfunction, symptomatic treatment; need to periodically monitor for recurrence until complete resolution of symptoms
(Cutaneous) Leukocytoclastic angitis				
Postcapillary venules are the vessels most commonly involved Characterized by leukocytoclasis (nuclear debris from invading neutrophils)	Generally purpuric lesions that occur in crops and are more pronounced in gravity-dependent areas May have striking dependent edema		Diagnosis is made by skin biopsy	Eliminate underlying precipitant. Treatment options include NSAIDs, colchicine, pentoxyfylline, dapsone, and short-term low-dose steroids Compression stockings for edema

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Central nervous system isolated angiitis. Including (1) granulomatous angiitis of the CNS (GACNS) (2) BACNS (3) Atypical PACNS				
Granulomatous medium vessel vasculitis limited to the central nervous system Langerhans and foreign-body type multi-nucleated giant cells often present	Decreased cognition (83%), headache (56%), seizure (30%), stroke (14%), and hemorrhage (12%) are most common presentations Elevated ESR, and CSF protein are common. Three clinical subset: GACNS—male predominant, any age, with long prodromal period and classic histology on biopsy BACNS—more likely female, acute onset of headache or neurologic symptoms, classic angiogram, more often monophasic and benign course Atypical PACNS—most common presentation; does not fit the diagnostic criteria for either GACNS or BACNS		Cerebral angiography may be helpful; brain and leptomeningeal biopsy are the gold standard	GACNS: Treated with cyclophosphamide and corticosteroids (see treatment for Wegener's) BACNS: Glucocorticoids for ≤6 mo with adjunctive calcium channel blockers Atypical PACNS: Treated initially with steroids alone
Polyarteritis nodosa				
Medium-sized vessel vasculitis with segmental transmural inflammation of muscular arteries Unlike the ANCA-associated vasculitides it does not involve veins and granulomatous inflammation does not occur	Weight loss, skin nodules, livedo reticularis, hypertension, renal insufficiency, abdominal pain, blood in the stool, myalgia and weakness, neuropathy, testicular pain, and an association with hepatitis B infection are common; many of these are part of the classification criteria for this disease May involve the small vessels around the temporal artery and present with typical manifestations of giant cell arteritis	Breast and uterine involvement; rare vasculitis of the cystic or appendiceal arteries may mimic acute cholecystitis or appendicitis	There is no diagnostic lab test; tissue biopsy and arteriography	High-dose glucocorticoids are the initial mainstay Patients with critical organ involvement (renal or gastrointestinal ischemia, cardiomyopathy or dense neuropathy) usually are treated with an additional immunosuppressive agent such as cyclophosphamide or methotrexate If active hepatitis B or C infection is present, a relatively short course of steroids in conjunction with aggressive antiviral therapy is fairly standard

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Kawasaki Disease (KD)				
Medium vessel vasculitis	Mucocutaneous lymph node syndrome: Fever, conjunctivitis, mucositis, polymorphous rash, edema/erythema/desquamation of hands and feet, lymphadenopathy Complications include coronary artery aneurysms, MI, heart failure, and arrthythmias	Fusiform aneurysms of brachial arteries Incomplete KD, in which adenopathy is finding most often absent	Clinical	i.v. immune globulin therapy and aspirin
Behcet's disease				
Necrotizing leukocytoclastic obliterative perivasculitis and venous thrombosis; affects capillaries, veins and arteries of all sizes; immune complex vasculitis	More common in Middle Eastern men, and women from the Far East; recurrent, usually painful mucocutaneous ulcers (oral and urogenital) Ocular disease present in 2/3 (uveitis most common) Vascular disease present in 1/3, especially venous thromboembolic disease CNS disease present in 10–20% Pathergy test positive. Cutaneous disease is common and varies	Renal and peripheral nervous system involvement is less common	On the basis of clinical findings. ICAM-1 levels appear to correlate with disease activity	Severity of the illness usually improves over time; life expectancy is normal Major serious complication is blindness; mucous membrane involvement is treated with topical steroids and thalidomide can be used in more severe cases; colchicine and interferon α can be used Thrombophlebitis is treated with aspirin; uveitis and CNS disease require systemic high dose steroids and azathioprine Anti-TNF may be an alternative treatment for panuveitis and mucocutaneous disease
Cogan's syndrome				
	Interstitial keratitis with vestibuloauditory symptoms; may be associated with systemic vasculitis especially aortitis with aortic valve involvement			Glucocorticoids are the mainstay of treatment; treat as early as possible with onset of hearing loss; early treatment improves outcome

Table 1 **Continued**

Pathologic Entity and Pathology	Typical Presentation	Unusual Clinical Presentations	Diagnosis	Treatment
Secondary vasculitides				
Infection related; secondary cryoglobulinemic; connective tissue disease related; drug hypersensitivity-related; malignancy related hypocomplementemic urticarial vasculitis; organ transplant related; and, pseudovasculitis (antiphospholipid syndrome, atrial myxoma, endocarditis, Sneddon syndrome)	Secondary cryoglobulinemic vasculitides may involve the small vessels around the temporal artery and present with typical manifestations of giant cell arteritis			

HAE = hereditary angioedema; ANCA = antineutrophil cytoplasmic antibody; C1-INH = C1 esterase inhibitor; ACE = angiotensin-converting enzyme; GN = glomerulonephritis; PR3 = proteinase-3; GN = glomerulonephritis; CXR = chest x-ray; RPGN = rapidly progressive glomerulonephritis; MPO = myeloperoxidase; PTCA = percutaneous transluminal coronary angioplasty; ESR = erythrocyte sedimentation rate; SIADH = syndrome of inappropriate antidiuretic hormone; PMR = polymyalgia rheumatica; FUO = fever of unknown origin; GI = gastrointestinal; NSAID = nonsteroid anti-inflammatory drug; BACNS = benign angiopathy of the CNS; PACNS = primary angiitis of the CNS; MI = myocardial infarction; ICAM-1 = intercellular adhesion molecule-1; TNF = tumor necrosis factor.

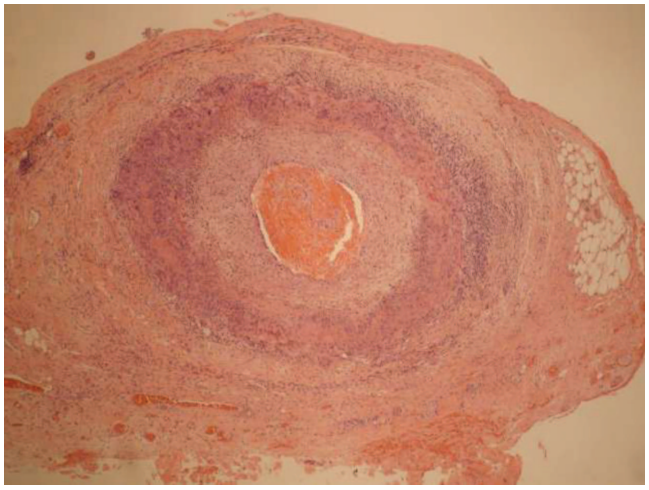

Figure 1. *Low-power view of hematoxylin and eosin–stained section of the right temporal artery. Extensive transmural inflammatory infiltrate is involving the medium-size artery wall. Multinucleated histiocytes (giant cells) are frequently present in the media and some extending to adventitia where areas of prominent inflammatory infiltrate are present. Foci of medial necrosis (homogenous acellular areas) can be identified. Marked intimal thickening with edema and early fibrosis are seen also.*

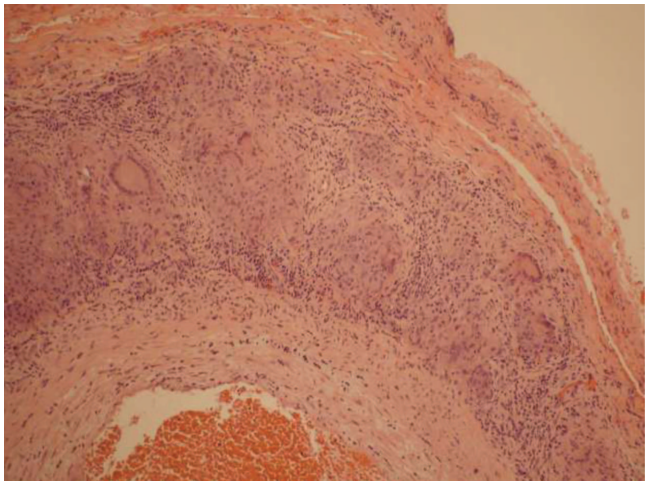

Figure 2. *Medium-power view of hematoxylin and eosin-stained section of the left temporal artery. There is marked multinucleated giant cell and epithelioid histiocyte infiltrate, forming occasionally nodular aggregates (granulomata). Some of giant cells are of Langhans' type (peripherally lined nuclei) and some others are of typical foreign body type (random location of multiple nuclei). Other inflammatory cells visible are lymphocytes, neutrophils, and eosinophils, signifying acute and chronic inflammation. Special stains were negative for acid-fast bacilli and fungal microorganisms, in the setting of appropriate controls (not shown).*

moglobin was 11.4 gm/dL, (with normochromic normocytic indices). The white blood cell count was 12,400 cells/mm^3 with no eosinophils and a normal differential count. Other laboratory tests were normal or negative (cerebral spinal fluid chemistry, culture, cytology, and bacterial antigen survey; TSH; free T_4; C_3; C_4; CH_{50}; C_1q; C_1-INH; serum IgE; C_1q binding assay; cryoglobulins; ANA; rheumatoid factor; antimicrosomal antibodies; antithyroglobulin antibodies; and, serum protein electrophoresis). Figures 1–3 show her pathological findings in bilateral temporal artery biopsy specimens.

She was treated with antibiotics, acyclovir, diphenhydramine, and methylprednisolone (40 mg i.v. b.i.d.). Bilateral temporal artery biopsy specimens showed extensive granulomatous inflammation with disruption of the wall architecture.

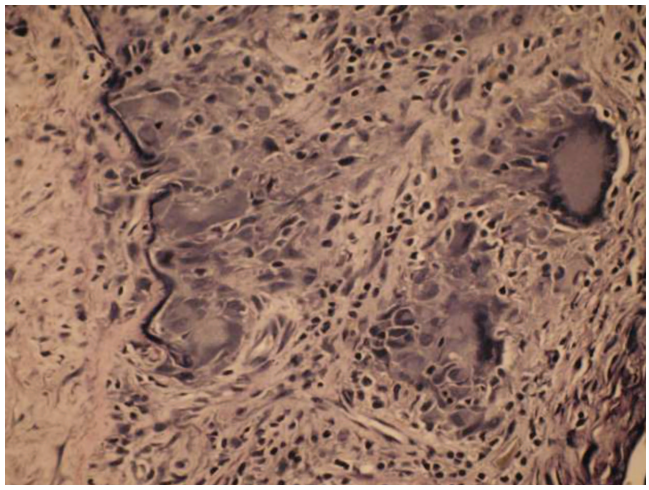

Figure 3. *High-power view of elastic-stained section of the right temporal artery. Destruction of the wall by granulomatous inflammation is present. A group of giant cells have accumulated on the medial side of intimal-medial junction, closely approaching the internal elastic lamina (dark linear stain), in the process of phagocytosis. There is a disruption of continuity and absence of internal elastic lamina in the other area that is not involved by giant cells and showing early neovascularization. Separately, a prominent giant cell of Langhans' type can be seen. Again, a mixed acute and chronic inflammatory infiltrate is noted.*

Final Diagnosis

The headache, neck, and facial pain gradually improved over the next 5 days. She was discharged on prednisone 60 mg/day. The final diagnosis was TA.

CONCLUSION

This patient's age, elevated ESR, and tenderness over the temporal areas were significant clues. The biopsy specimens and response to steroid therapy were consistent with TA.

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Patient Oriented Problem Solving (POPS) Case Report

Sinusitis and chronic progressive exercise-induced cough and dyspnea

Adam N. Williams, M.D., Ronald A. Simon, M.D., and Katharine M. Woessner, M.D.

ABSTRACT

We present the case of a 47-year-old man with exercise-induced dyspnea, cough, chest tightness, and recalcitrant chronic rhinosinusitis. Evaluation revealed IgE sensitization to grass, tree, and weed pollen, no evidence of obstruction on spirometry, and a negative methacholine challenge. Diagnostic considerations included allergic and nonallergic rhinitis, asthma, aspirin-exacerbated respiratory disease, vocal cord dysfunction, extra-esophageal manifestations of acid reflux, and vasculitits. Further evaluation with sinus imaging, laryngoscopy, ambulatory pharyngeal pH testing, upper endoscopy, and bronchoscopy led to a diagnosis. Key issues surrounding the diagnostic and therapeutic approaches to this patient's condition are reviewed.

(Allergy Asthma Proc 29:669–675, 2008; doi: 10.2500/aap.2008.29.3177)

Key words: Asthma, chronic rhinosinusitis, cough, exercise, gastroesophageal reflux disease, laryngopharyngeal reflux, laryngopharyngitis, pharyngeal pH, vocal cord dysfunction

CASE PRESENTATION

Chief Complaint

Persistent and progressive cough, chest tightness, and dyspnea with exercise.

History of Present Illness

A 47-year-old man presented with a 3-year history of progressively worsening exercise-induced dyspnea and cough. He recalls onset of chest symptoms a few weeks after the resolution of a presumed viral upper respiratory infection. An avid cyclist, he initially noted dyspnea and cough only with extremes of exertion, such as climbing hills on his bicycle. Over time, these symptoms were provoked by less intense exercise. Six months after the onset of his chest symptoms, he noted left-sided facial pain, nasal congestion, anosmia, and purulent nasal drainage. A CT scan of the sinuses revealed extensive sinus disease, prompting treatment with a course of erythromycin, moxifloxacin, and prednisone. A repeat CT scan 3 weeks later showed mild improvement but persistent left maxillary and bilateral ethmoid sinus opacification (Fig. 1). Despite treatment with oral fexofenadine, oral montelukast, inhaled albuterol/ipratropium, intranasal astemizole, and intranasal triamcinolone the patient continued to have progressive worsening of his exercise-induced chest symptoms and chronic sinusitis. Two years after presentation, he underwent functional endoscopic sinus surgery with transient improvement in his chest and nasal symptoms. Six months after surgery, however, his sinus disease relapsed and he continued to have exertional cough and dyspnea. The next 18 months of his clinical course were marked by persistent nasal congestion, hyposmia, purulent nasal drainage, globus pharyngeus, and facial pressure. His exertional cough and dyspnea continued to worsen and did not respond to inhaled or systemic corticosteroids. His exercise had become severely limited, with dyspnea and coughing attacks provoked by climbing a flight of stairs. A second sinus surgery was performed without significant improvement in his symptoms.

Medical History

The patient reported a history of severe depression that occurred while on treatment with systemic corticosteroids for treatment of a trauma-related cervical myelopathy. For the past 12 months, he had intermittent solid dysphagia, but he did not report a history of heartburn, reflux, or prior diagnosis of gastroesophageal reflux disease (GERD). He was otherwise healthy.

Social History

He was a very avid cyclist and in very good physical condition. He also enjoyed surfing and golf. He did not smoke or drink alcohol.

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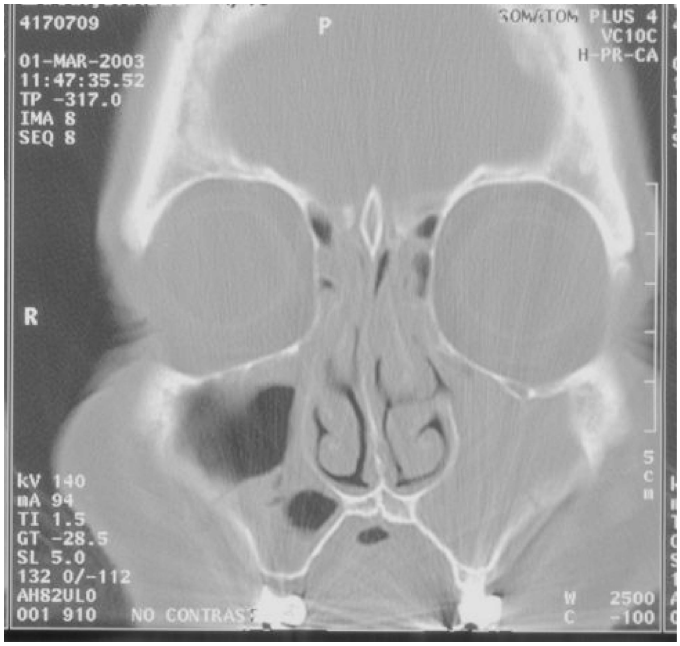

Figure 1. *CT of sinuses showing opacification of ethmoid and maxillary sinuses.*

Family History

He was not aware of any family members with a diagnosis of allergic rhinitis, asthma, or cardiovascular disease.

Physical Examination

Examination revealed a healthy appearing man breathing comfortably at rest. The nasal mucosa was erythematous and without polypoid changes or purulent drainage. The oropharynx exam was normal without evidence of tonsillar adenopathy, postnasal drainage, or other lesions. Chest auscultation revealed clear lungs. The cardiac exam revealed a normal heart rate and rhythm and no murmurs. The extremities were warm with strong, symmetric peripheral pulses and no cyanosis, edema, or purpura. The remainder of the physical examination was normal.

Laboratory and Other Diagnostic Findings

Skin-prick testing revealed IgE sensitization to grass pollen, tree pollen, and weed pollen (12-, 9-, and 10-mm wheal diameter, respectively). Spirometry was normal with a forced vital capacity of 4.58 (84% predicted) and a forced expiratory volume in 1 second of 3.44 (80% predicted). Complete blood count with differential, sedimentation rate, total IgE, and kidney and liver function tests were normal.

QUESTIONS

What is the Differential Diagnosis?

The differential diagnosis of chronic rhinosinusitis includes infectious (bacterial or fungal) rhinosinusitis, allergic rhinitis, vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome, aspirin-exacerbated respiratory disease, anatomic abnormalities (polyposis, severe septal deviation, foreign body, tumors, and turbinate deformation), vasculitis (Churg-Strauss, Wegener's granulomatosis), immunodeficiencies, and supraesophageal reflux of gastric contents.[1] Dyspnea, cough, and chest tightness provoked by exercise is suggestive of asthma, which can be exacerbated by chronic sinus disease, allergic triggers, and acid reflux. Asthma and chronic sinusitis are also features of aspirin-exacerbated respiratory disease. Other considerations for exercise-induced chest symptoms in association with sinusitis include vocal cord dysfunction (which has been associated with postnasal drainage, GERD, and psychiatric illness[2]) bronchiectasis, and vasculitis.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

If aspirin sensitivity can not be excluded by history, oral aspirin challenge should be considered.[3] Methacholine challenge would be helpful to document or exclude airways hyperresponsiveness.[4] Nasopharyngoscopy would provide a great deal of information about the anatomy of the upper airway and if performed while the patient is having chest symptoms, could be diagnostic for vocal cord dysfunction. A positive 24-hour pH monitoring study of the proximal esophagus or upper airway would provide support for a possible contribution of extraesophageal reflux (EER) of gastric contents to sinus inflammation, laryngospasm, or chest symptoms. If symptoms persist and

these studies do not provide a clear answer, bronchoscopy with biopsy should be considered to evaluate for vasculitis, chronic infection, or bronchiectasis.

CLINICAL COURSE

Because the patient takes ibuprofen regularly without adverse effects, aspirin-exacerbated respiratory disease could be excluded by history. Methacholine challenge was negative for airway hyperresponsiveness. Shortly after his initial consultation, the patient presented urgently for the evaluation of an acute exacerbation of cough and dyspnea, he was observed to have stridor and cough while attempting to perform spirometric maneuvers and blunting of the inspiratory loop of the flow-volume curve. Nasopharyngoscopy (performed while the patient was not coughing or complaining of dyspnea) revealed no signs of sinusitis and patent antral windows but did show significant edema, swelling, and inflammation of the vocal cords. Paradoxical vocal cord motion was not observed, but vocal cord dysfunction was suspected and he was referred for speech therapy. The Belafsky reflux symptom index score was 40 (normal, <14).[5] Ambulatory pharyngeal pH monitoring with the Dx-pH Measurement System (Restech, San Diego, CA) was then performed, showing a number of pharyngeal events and periods of sustained supine reflux (Fig. 2). In light of these findings, the patient was treated with immediate-release omeprazole/sodium bicarbonate, 40 mg twice daily, and referred to gastroenterology. Upper endoscopy revealed a nonobstructing distal esophageal Schatzki ring and diffuse gastric erythema. Biopsy specimens of the gastric antrum and body revealed mild chronic gastritis and were negative for *Helicobacter pylori*. Bronchoscopy revealed tracheobronchial inflammation with cobblestoning and mucosal friability. Histopathology of proximal bronchial tissue revealed benign respiratory mucosa and submucosal patchy chronic inflammation. Bronchial washings, acid-fast bacilli cultures, and fungal cultures were all negative.

After 3 months of treatment with twice-daily proton-pump inhibitors (PPIs) with the goal of sustained acid suppression, the patient had marked improvement in his upper and lower respiratory symptoms. After 6 months of twice-daily PPIs, the patient has successfully reduced the dosing frequency to once daily without recurrence of symptoms.

DISCUSSION

In this patient presenting with chronic rhinosinusitis, chronic laryngopharyngitis, and vocal cord dysfunction, the ambulatory pharyngeal pH testing results together with the laryngoscopic and endoscopic findings confirm the diagnosis of extraesophageal manifestations of reflux. Marked and sustained improvement in his symptoms with acid suppressive therapy further supports this diagnosis.

Gastroesophageal reflux has been implicated in the pathophysiology of a number of conditions affecting the upper and lower respiratory tract, including chronic cough, laryngopharyngitis, asthma, vocal cord dysfunction, chronic rhinosinusitis, and serous otitis media (Table 1).[6–8] Although there is general agreement that gastroesophageal reflux may be associated with conditions of the upper and lower airway, the degree and mechanism of causality for most conditions that relate to EER are somewhat controversial and incompletely understood. Extraesophageal manifestations of reflux may contribute to the development of airway disorders through either direct contact of acidic or nonacidic refluxate with airway mucosa or indirect stimulation of vagally mediated reflex pathways.[6]

Establishing the diagnosis of EER as a contributing factor to upper airway disorders can be challenging. Ambulatory 24-hour dual-probe esophageal pH testing is the gold standard for the diagnosis of GERD, but its utility in patients with EER is uncertain. Proximal esophageal acid exposure may not be a reliable indicator of EER and is a poor predictor of response to acid suppression therapy.[9] The role of ambulatory hypopharyngeal and pharyngeal pH testing has also been investigated, but consensus regarding diagnostic pH thresholds and ideal probe positioning is lacking. Differences between the epithelium, physiology, and tolerance of reduced pH of the esophagus and upper airway would seem to indicate that the current diagnostic pharyngeal pH threshold of 4, developed for use in patients with reflux esophagitis, may be too low for patients with EER.[10] In addition, clinical use of dual-probe with or without pharyngeal pH testing is not widely available. For these reasons, some authors advocate a therapeutic trial of once- or twice-daily PPIs and reservation of the use of ambulatory pH testing only for those patients with refractory symptoms.[11]

Laryngoscopy has also been investigated as a potential diagnostic modality in patients with laryngeal or pharyngeal symptoms in whom the diagnosis of EER is suspected. An eight-item reflux finding score has been developed and validated for use in the diagnosis of laryngopharyngeal reflux,[12] but laryngoscopic findings lack adequate specificity to be used as a sole diagnostic modality in most patients.[13]

The recognition that acid reflux may contribute to upper airway symptoms has prompted a number of investigators to evaluate the role of antireflux treatment measures to the management of these conditions. PPIs are the most widely used, but studies designed to evaluate their effectiveness in EER have had inconsistent results. In a randomized placebo-controlled trial of 22 patients with chronic idiopathic laryngitis, El-Serag *et al.* found significantly more subjects treated with

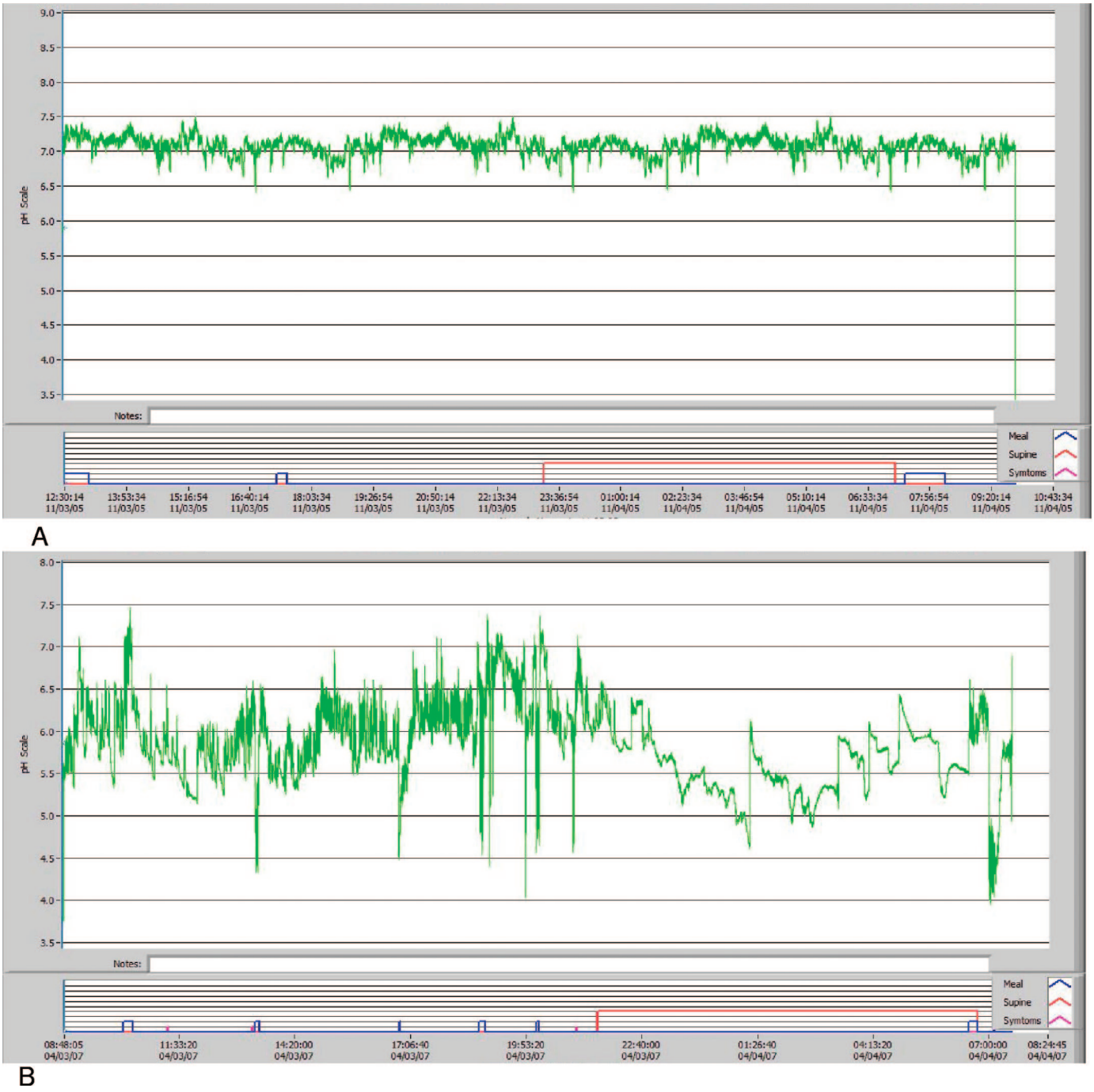

Figure 2. *Ambulatory pharyngeal pH test results in (A) a normal subject and (B) the case patient.*

twice-daily lansoprazole for 3 months had a complete symptomatic response when compared with placebo.[14] Four subsequent small studies failed to confirm a beneficial effect of PPIs over placebo on the signs or symptoms of chronic reflux laryngitis.[15–18] Other controlled and uncontrolled studies have suggested a beneficial effect of PPIs in patients with reflux laryngopharyngitis.[19,20]

In the largest study to date of 145 subjects with moderately severe symptoms of chronic posterior laryngitis and laryngoscopic findings suggestive of reflux laryngitis, Vaezi *et al.* found that treatment with esomeprazole, 40 mg twice daily, for 16 weeks failed to result in improvement in symptom scores or laryngoscopic changes when compared with placebo.[21] Because patients with typical symptoms of GERD were excluded and most subjects did not have evidence of pharyngoesophageal reflux with ambulatory pH testing, the significance of the lack of observed effect is questionable.

Table 1 **Extraesophageal airway manifestations of reflux in adults**

Laryngeal
Laryngopharyngeal reflux
Laryngospasm
Paradoxical vocal cord motion
Vocal cord neoplasms, granulomas, ulcers
Pulmonary
Asthma
Bronchiectasis
Aspiration pneumonia
Other
Chronic cough
Chronic sinusitis
Otitis media
Obstructive sleep apnea
Dental erosions

Source: Adapted from Ref. 6.

A systematic review of the published literature examining the possible association between gastroesophageal reflux and sinusitis by Weaver led to the conclusion that there is grade C evidence (evidence based on case series and extrapolations from cohort and case-control cohort studies[22]) for a positive correlation between GERD and sinusitis.[23] A number of subsequent case series and controlled studies have provided additional support for a link between GERD and chronic rhinosinusitis.[24–28] The exact pathophysiological mechanism whereby acid reflux contributes to the development of chronic sinus disease remains controversial. The possibility of direct nasopharyngeal reflux of gastric acid resulting in mucosal inflammation and impaired mucociliary clearance is suggested by a recent study showing reduced nasopharyngeal pH in patients with chronic rhinosinusitis.[27] Another study involving dual-probe pH monitoring in patients with chronic rhinosinusitis and healthy volunteers failed to establish a significant difference in reflux events, prompting the investigators to suggest a vagally mediated neuroinflammatory reflex was a more likely factor.[28] The detection of *H. pylori* in sinonasal biopsy specimens in a small number of patients with chronic sinusitis has prompted some to speculate a pathogenic role for these bacteria in the pathogenesis of chronic rhinosinusitis due to EER.[29,30] Further research will be necessary before any conclusions can be drawn regarding the relative contributions of each mechanism to the apparent association between acid reflux and chronic sinusitis.

In a report of laryngoscopic findings in nonsmoking adolescents with documented vocal cord dysfunction, Powell *et al.* found laryngoscopic abnormalities consistent with chronic reflux laryngitis in 19 of 22 subjects.[31] Other case series have suggested a possible association between laryngospasm and GERD. In a recent prospective study of 35 patients with paroxysmal laryngospasm, gastroesophageal reflux was established by upper endoscopy and pH monitoring in 94% of subjects. An open label trial of PPIs and lifestyle modification was associated with resolution of laryngospasm symptoms in all subjects.[32] Additional studies in the form of large-scale randomized placebo-controlled trials of PPIs in patients with laryngopharyngeal reflux, chronic rhinosinusitis, and vocal cord dysfunction are needed.

A limited number of studies have examined the application of other antireflux treatment measures to patients with manifestations of EER. A small number of uncontrolled prospective trials of prokinetic medications, such as metoclopramide and cisapride, have suggested a possible benefit in patients with ongoing reflux-related laryngopharyngitis, cough, or laryngospasm despite acid suppressive therapy.[33–37] The withdrawal of cisapride from the market, side effect profile of metoclopramide, and lack of high-grade evidence supporting their use in patients with EER limit the use of currently available prokinetics in this patient population.

Endoscopic procedures designed to improve the integrity of the lower esophageal sphincter such as suturing, radiofrequency thermal injury, and ethylene vinyl alcohol injection have been used with some success in patients with GERD.[38] The application of these procedures to patients with EER has not been extensively studied, but a recent uncontrolled trial of endoscopic suturing suggests some benefit.[39]

A number of studies investigating the potential role of laparoscopic antireflux surgery, such as the Nissen and Toupet fundoplications, in patients with manifestations of EER have shown significant improvement in symptom scores, laryngeal exam findings, quality of life, and PPI use.[40–49] Clear selection criteria for fundoplication have not been established, but higher success rates have been reported in patients with abnormal ambulatory pH studies and symptom improvement with PPI therapy.[50–54] Thus, in patients with a clear diagnosis of acid-related upper airway disorders who respond to treatment with PPIs, but who have an incomplete response or find the prospect of indefinite PPI therapy objectionable, fundoplication appears to be reasonable consideration.

Final Diagnosis

The final diagnosis was extraesophageal manifestations of gastroesophageal reflux, including cough, vocal cord dysfunction, laryngopharyngeal reflux, and chronic rhinosinusitis.

SUMMARY AND CONCLUSIONS

Until diagnostic approaches are standardized and higher-quality prospective therapeutic trials are avail-

able, clinicians involved in the care of patients with extraesophageal manifestations of reflux will continue to rely on the available literature and personal experience to make management decisions. In consideration of the patient presented in this article, the symptom complex, laryngoscopic and endoscopic abnormalities, ambulatory pharyngeal pH testing results, and response to PPIs provide strong evidence for the role of EER as the likely explanation for his presentation. This case illustrates that EER can be an important contributing factor to a number of upper airway conditions. Although a number of questions remain regarding the optimal diagnostic and therapeutic approach, there is evidence to suggest that the recognition and treatment of EER can improve symptoms in some patients with these conditions.

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ERRATUM

There was a editorial misinterpretation of an abbreviation in "Interleukin-2 treatment for persistent cryptococcal meningitis in a child with idiopathic CD4+ T-lymphocytopenia" by Yesim Yilmaz-Demirdag, M.D., Brian Wilson, M.D., Mary Lowery-Nordberg, Ph.D., Joseph A. Bocchini, Jr., M.D., and Sami L. Bahna, M.D., Dr.P.H. *Allergy and Asthma Proceedings* 29:421–424, 2008.

On page 423, under the heading What Else Can Be Done?, the two terms "bovine serum albumin" should be replaced by "body surface area".

ERRATUM

In "The effect of omeprazole on asthmatic adolescents with gastroesophageal reflux disease" *Allergy and Asthma Proceedings*, 29:517–520, the authors were not listed in the correct order. The correct author order should be "Enayatollah Nemat Khorasani, M.D., Gholam Hossein Fallahi, M.D., Fariba Mansouri, M.D., and Nima Rezaei. M.D."

Also, in the affiliation footnote of the same page, "Medical Sciences/ University of Tehran" should be "Tehran University of Medical Sciences".

Patient Oriented Problem Solving (POPS) Case Report

Carmine hypersensitivity masquerading as azithromycin hypersensitivity

Matthew Greenhawt, M.D., M.B.A., Marc McMorris, M.D., and James Baldwin, M.D.

ABSTRACT

Macrolide hypersensitivity is a rarely reported event. However, carmine dye has become increasingly important as a provocative agent. We present a case of a woman with documented carmine hypersensitivity, who reported anaphylaxis 90 minutes after ingestion of a generic azithromycin. Our investigations revealed that this was an allergy to the carmine dye in the tablet's coating rather than to the antibiotic. Seven extracts were prepared including carmine dye, crushed dried female cochineal insects, crushed tablets of Zithromax (Pfizer Inc.) and generic azithromycin (Teva Pharmaceuticals), and the crushed colored coatings from both tablets. These were suspended in preservative-free normal saline, and then applied as a skin-prick test and read at 30 minutes. The skin-prick skin test results were 4+ to histamine and carmine dye, but negative to cochineal insect extract, Pfizer crushed tablets, and negative control. The patient was 1+ to the Teva crushed tablet, but was 4+ to the Teva brand coating and negative to the Pfizer brand coating, which did not contain carmine. The patient subsequently ingested Pfizer Zithromax without any sequelae. To our knowledge, this is the first reported case of carmine anaphylaxis attributed to carmine-containing medication. Careful history and skin-prick testing to the appropriate agents allowed elucidation of the subtlety of the true offending agent without unnecessary avoidance of the medication class. Patients with a carmine hypersensitivity should actively check with their pharmacy or prescribing physician to verify their medications are free of this offending agent.

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Key words: Anaphylaxis, carmine, cochineal extract, cosmetic allergy, dye allergy, food allergy, macrolide allergy, natural colorant allergy, noncertified dye, red dye allergy

CASE PRESENTATION

A 47-year-old woman with history of mild persistent asthma, allergic rhinitis to pollen and dander, and oral allergy syndrome, presented to our clinic for evaluation of facial edema attributed to eating a red raspberry yogurt; swelling of the face and tongue, and respiratory distress attributed to eating red-colored tortellini; and a facial rash and swelling attributed to wearing red eye makeup. It was subsequently discovered that all 3 items contained carmine dye.

Her medications included hydrochlorothiazide, lisinopril, rabeprazole, fluticasone/salmeterol, and albuterol. Allergies included urticaria attributed to sulfa-containing antibiotics. Her past medical history included hypertension, gastroesophageal reflux, and asthma.

Her baseline spirometry was FVC 3.84 L (107% predicted), FEV_1 2.9 L (105% predicted), FEF 25–75% of 2.21 L/second (72% predicted), with normal flow loops. Epicutaneous testing to carmine liquid, read at 30 minutes, was 4+ (Wheal 11 mm, Flare 42 mm) with appropriate controls. She was diagnosed with sensitivity to carmine dye, and was counseled about avoidance of carmine-containing products, including how it is labeled on products.

Approximately 45 days later, she was prescribed azithromycin by her primary-care physician for symptoms of an upper respiratory infection. Within 90 minutes of taking the first dose of generic azithromycin (Teva Pharmaceuticals, North Wales, PA) she developed facial itching and eye swelling. She immediately took 50 mg of diphenhydramine and contacted the pharmacy to verify whether the red dye in the medication was carmine. The pharmacist verified that this brand contained carmine, but the Pfizer brand did not. She immediately had a coworker administer her EpiPen (Dey Pharmaceuticals, Napa, CA), and she was

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brought to our office within 15 minutes of her epinephrine dose. She reported previous tolerance to Zithromax (Pfizer Inc., New York, NY).

Physical Exam

Vital signs on arrival were: oxygen saturation of 97% on room air, pulse 108, respirations 14, blood pressure 138/92. Pertinent findings on exam included angioedema of her left upper eyelid, facial erythema and urticaria, but no wheezing audible on auscultation.

Clinical Course

She was given 60 mg of prednisone and observed for 2 hours before being discharged home in stable condition to continue 60 mg of prednisone daily for 3 days along with every 6-hour dosing of diphenhydramine. No symptoms returned.

DIFFERENTIAL DIAGNOSIS

In considering the acute onset of facial angioedema and pruritus in a woman taking an antibiotic, drug allergy was an immediate concern. However, evidence for macrolide hypersensitivity in the medical literature is sparse. Other foods consumed during the course of the day also needed to be considered, as well as angiotensin-converting enzyme inhibitor–induced angioedema. Contact urticaria from a makeup or facial agent was possible, but unlikely given an acute process. Based on a previous diagnosis of sensitivity to carmine, this seemed to be the most likely diagnosis to pursue, given previous tolerance to brand name Azithromycin.

Diagnostic Testing

We performed epicutaneous testing to both the brands Azithromycin (Teva Pharmaceuticals) and Zithromax (Pfizer Inc.) to establish that the reaction was attributable to carmine in the medication covering and not to Azithromycin.

Briefly, one pink-colored 250-mg tablet of each brand was separately crushed and suspended in saline for epicutaneous testing. An additional 250-mg tablet of each brand was stripped of its dye coating with a scalpel, crushed, and suspended in preservative-free saline for testing. Dried female cochineal insects were pulverized and suspended in saline as well (~10 insects in 3-mL saline diluent). These items, and commercial-grade carmine obtained from Warner Jenkinson (St. Louis, MO), histamine (ALK-Abello Laboratories, Round Rock, TX, 0.1 mg/mL), and the saline (Allergy Laboratory Inc., 0.9% saline with 0.03% serum albumin) were applied to her forearm skin. Greer Dust Mite Mix (Greer, Lenoir, NC, 1:20 wt/vol) was also applied to disprove environmental causes.

Epicutaneous testing, checked at 15, 20, and 30 minutes, revealed 4+ reactivity to the Teva coating (wheal 9 mm, flare 24 mm) and to carmine (wheal 10 mm, flare 29 mm). There was 1+ reactivity to the Teva tablet (wheal 5 mm, flare 8 mm), and no reactivity to Dust Mite Mix, cochineal insect extract, the Pfizer tablet, and the Pfizer coating (Fig. 1). Controls were appropriate. Both carmine and the Teva reactivity developed between 20 to 30 minutes, as has been typical of our experience with carmine.

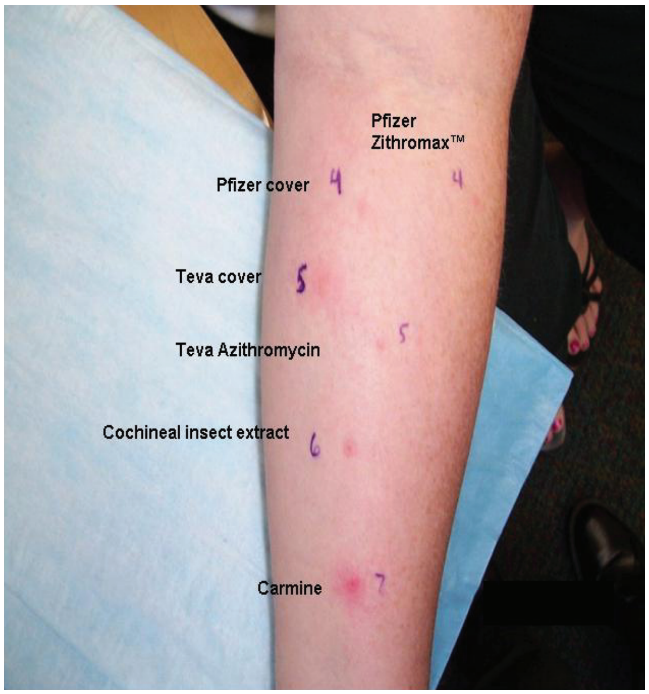

Figure 1. *Epicutaneous tests results for azithromycin and carmine.*

DISCUSSION

Macrolide hypersensitivity has been rarely reported.[1,2,3,4] However, carmine dye has become increasingly important as a provocative agent in hypersensitivity to a number of carmine-containing products.[5,6,7] Carmine is a red color derived from the *Dactylopius cocus costa* insect that grows on the prickly pear cactus. It is also referred to as cochineal extract.[5,8,9,10,11] The color is produced from the aqueous-alcohol extract of the dried, gravid female insect, and consists of 10% carminic acid, plus the residual insect body.[11] Carmine has been approved by the Food and Drug Administration (FDA) as a noncertified dye for use in foods and drugs since 1967, and in cosmetics since 1977.[12] It is the only biogenic dye allowed for use in cosmetics around the eye. As a noncertified color, carmine/cochineal extract does not have to be specifically declared on food product labels, and can be referred to generically as "color added", "artificial color added", or "carmine color".[12,13] However, its presence is required to be declared in all cosmetics except for professional-use-

Table 1. Known Cases of Carmine Hypersensitivity

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
Sarkany et al. 1961[16]	3 pts	cutaneous–lip salve	contact dermatitis		Yes	Patch test	First known report in medical literature
Burge et al. 1979[6]	M, M	inhalation	bronchospasm	factory workers		Bronchial challenge	
Park et al. 1981[17]	M	cutaneous–lip stick	anaphylaxis	soldier			
Tenabene et al. 1987[18]	F, M, M	inhalation	bronchospasm	spice/food handlers	Yes	Epicutaneous, bronchial challenge	
Quirce et al. 1994[18]	M, F, M	inhalation	bronchospasm	dye factory workers: manufacturer (M), cleaning staff (F), ex-worker(M)	Yes	Epicutaneous, *in-vitro* IgE, bronchal challenge	
Kägi et al. 1994[20]	F	ingestion–Campari-Orange	anaphylaxis		Yes	Epicutaneous, *in-vitro* IgE	First reported case from ingestion
Beaudouin et al. 1995[7]	F	ingestion–fruit flavored yogurt	anaphylaxis		Yes	Epicutaneous, basophil histamine release	
Stücker et al. 1996[21]	F	inhalation	bronchospasm	food factory worker	Yes	Epicutaneous, *in-vitro* IgE	
Wüthrich et al. 1997[22]	F, F, F, F, F	ingestion–alcoholic beverage	anaphylaxis		Yes	Epicutaneous, *in-vitro* IgE	
Baldwin et al. 1997[23]	F	ingestion–red popsicle	anaphylaxis		Yes	Epicutaneous, *in-vitro* IgE (P-K)	
Acero et al. 1998[24]	M	inhalation and ingestion	bronchospasm, rhinoconjunctivitis	spice factory packer, non-manufacturing	Yes	Epicutaneous, immunoblot, bronchial challenge	
DiCello et al. 1999[25]	F, F	ingestion–artificial crabmeat, fruit flavored yogurt	anaphylaxis		Yes	Epicutaneous	
Lizaso et al. 2000[26]	M, F, F	inhalation	bronchospasm	dye plant worker, dye plant clerical worker, dye plant chemist	Yes	Epicutaneous, immunoblot, bronchial challenge	

Table 1. Continued

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
Chung et al. 2000[115]	F, F, F	ingestion	anaphylaxis		Yes	Epicutaneous, immunoblot	No patient sera recognized the same protein bands. Sera also recognized cochineal insect.
Tabar et al. 2003[27]	F, F	inhalation	bronchospasm	dye factory clerical worker, dye factory laboratory worker	Yes	Epicutaneous, immunoblot, bronchial challenge	
Anibarro et al. 2003[28]	M, M	inhalation	bronchospasm	both butchers	Yes	Epicutaneous, immunoblot, bronchial challenge	
Ferrer et al. 2005[29]	M	inhalation	bronchospasm	spice blender	Yes	Epicutaneous, *in-vitro* IgE immunoblot, bronchial challenge	
Greenhawt et al. Present Case	F	ingestion and topical–generic azithromycin, fruit flavored yogurt, colored pasta, eye makeup	anaphylaxis, local rash and angioedema	office worker	Yes	Epicutaneous	This is the first case report of exposure from a pharmaceutical source.
FDA MedWatch[13]	F	ingestion–Tropicana Ruby Red Grapefruit Juice; topical–purple eye shadow	anaphylaxis; skin rash		Yes	Epicutaneous	Test positive to the grapefruit juice, Good and Plenty candy, eye shadow
FDA MedWatch[13]	F	ingestion–custard style strawberry banana yogurt	anaphylaxis		Yes	Epicutaneous	Test positive to the yogurt

Table 1. Continued

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
FDA MedWatch[13]	F	ingestion–SoBe fruit juice	anaphylaxis				Cochineal extract was declared on the bottle label
FDA MedWatch[13]	F	ingestion–Crab soup, yogurt, candy, Ruby Red Grapefruit Juice, pasta salad with artificial crab meat	anaphylaxis		Yes	Epicutaneous	
FDA MedWatch[13]	F	ingestion–gelatin based desert	eyelid angioedema				
FDA MedWatch[13]	F	ingestion–custard style yogurt, multiple cosmetics	anaphylaxis (to the ingestion)				
FDA MedWatch[13]	NA	NA	NA				
FDA MedWatch[13]	NA	ingestion–yogurt	anaphylaxis		Yes	Epicutaneous	
FDA MedWatch[13]	F	ingestion, topical–neither specified	NA				
FDA MedWatch[13]	F	topical–eyeliner	NA				

M = male; F = female; FDA = The United States Food and Drug Agency; NA = not available.

only products and free samples.[13] Under the FDA Modernization Act of 1997, all inactive ingredients in over-the-counter medications for oral consumption, including noncertified colors, must be declared.[13,14,15] Presently, this does not apply to prescription drugs, but the FDA is planning to formally recommend similar recommendations for the declaration of inactive ingredients, including noncertified colors.[13] The Center for Science in the Public Interest has successfully petitioned the FDA to reconsider the present labeling regulations for carmine/cochineal extract and require its declaration in all products.[13]

Since 1961, there have been ~35 known case reports in the medical literature and FDA MedWatch program of allergic reactions to carmine in food and cosmetic products[5–7,16–29] (Table 1). To our knowledge, this is the first reported case of carmine sensitivity from its use as a pharmaceutical dye. Sensitization has been thought to occur through a topical route via cosmetics, and through occupational exposure to carmine powder dust in European dye factory workers.[29]

Because there is residual biogenic contamination in commercial carmine, it has been theorized that insect protein is responsible for the clinical allergy to carmine.[5,22,24,25,29] It is unknown exactly how much insect protein contamination exists in commercial preparations of carmine used in food, cosmetic, or pharmaceutical dye. Furthermore, its use in products is elusively disclosed, creating a dangerous situation for carmine-sensitive patients. Several investigative groups have shown that carmine allergy is IgE-mediated, *via* epicutaneous tests, Prausnitz-Küstner tests, *in vitro*-specific IgE, and immunoblot/inhibition analysis. Unfortunately, there has been no universal pattern of recognition among these studies, and there remains no conclusive evidence that cochineal insect biogenic protein is the major allergen.[5,22,24,25,28,29] Though there is no conclusive evidence to this point, it is believed that the processing of cochineal to carmine creates a haptenized particle with residual insect-body protein that is presumably the source of the hypersensitivity.

At our center, in performing a workup of a patient with suspected carmine hypersensitivity, we first confirm a suspected reaction involving a red-, purple-, or pink-colored food and try to identify any commercial product involved. Epicutaneous testing to other foods and pollen agents is performed before carmine testing when appropriate. When carmine is tested, we apply liquid carmine as a standard epicutaneous test and do not read the test until 30 minutes after application. It has been our experience over the past 10 years that this antigen is associated with late-developing test results. We do not routinely test to cochineal extract.

Final Diagnosis

Carmine hypersensitivity.

CONCLUSION

Carmine/cochineal extract is a known allergen that is used as a dye in foods, drugs, and cosmetics. Because it is a noncertified color, in most situations it does not have to be explicitly labeled, creating a dangerous situation for the carmine-sensitive patient. Many patients give a history of previous intolerance to carmine-containing foods. It is widely suspected that some biogenic protein contaminant in carmine is the major antigen, though this has not been definitively proven. The protein may be altered through processing into a more allergenic form, accounting for the negative skin tests to cochineal insect themselves. Providers need to have a high index of suspicion even if carmine does not appear on the label of the suspected product. Epicutaneous tests should be observed for 30 minutes because the reactivity often develops after 20 minutes. Carmine allergy has now been reported from use in foods, cosmetics, and drugs.

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ERRATUM

In "A case of hydrocortisone desensitization in a patient with radiocontrast-induced anaphylactoid reaction and corticosteroid allergy," *Allergy and Asthma Proceedings*, 27:265–268, the correct name for the senior author is Evans R. Fernandez-Perez, M.D., M.S.

Patient Oriented Problem Solving (POPS) Case Report

Surfer's asthma

Rachel U. Lee, M.D., Katharine M. Woessner, M.D., and David A. Mathison, M.D.

ABSTRACT

Common asthma triggers during recreational activities include allergen exposure, concomitant viral infection, and exercise. We present the case of a 42-year-old man with a 2-year history of wheezing, chest tightness, and upper respiratory symptoms that were associated with surfing. He denied symptoms with other forms of exercise and had no personal history of asthma. His physical exam was unremarkable and his pre- and postbronchodilator spirometry was normal. After detailed history and keen observation on the patient's part, a diagnosis was made and he enjoyed good response to the therapy for this condition. Underrecognized asthma triggers and exposures in the recreational environment should be investigated.

(Allergy Asthma Proc 30:202–205, 2009; doi: 10.2500/aap.2009.30.3211)

Key words: Allergic, asthma, brevetoxin, environmental exposures, harmful algae, irritant asthma, recreational exposures, red tide, rhinitis, surfing

CASE PRESENTATION

Chief Complaint

Wheezing and chest tightness

History of Present Illness

A 42-year-old male university researcher and professor in San Diego presented with a complaint of wheezing and chest tightness. He has been an avid surfer from childhood; from his mid-30s, he noticed a feeling like he "caught a cold" with nasal ocular symptoms, chest tightness, and wheezing associated with days when he surfed. He had no difficulties while he surfed, however, he would note the symptoms ~2–3 hours later. This syndrome would last ~1–2 days and then self-resolve. He did not develop these symptoms after other forms of exercise.

Because he lives in close proximity to the beach, he has been able to observe the bioluminescent glow of the red tides in the evenings. Over an approximate 2-year time span, he noticed the association with symptom that would occur on days when he saw the red tide glow and less so during seasons that were not associated with red tides (Figs. 1 and 2).

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Medical History

Medical history was notable for perennial allergic rhinitis, with skin test positive to pollen, dust mites, and cockroaches. He denied history of asthma or wheezing associated with exercise or viral infections and he was a lifelong nonsmoker. He was not taking any medications. Family history was noncontributory. Social history did not reveal any exposure to sick contacts.

Physical Examination

Vital signs were normal. The patient's conjunctivae were clear, his nasal passages showed normal pink turbinates, and his ear canals showed exostosis, consistent with his many years of surfing in cold wind and water. There was no lymphadenopathy. His lungs were clear without wheezes, rales, or ronchi. The rest of his exam was unremarkable.

Diagnostic Studies

At baseline, his pulmonary function testing was normal with a forced expiratory volume at 1 second of 4.39 L, which is 102% predicted. No reversibility was seen after a bronchodilator treatment. Methacholine challenge was deferred.

QUESTION 1

What is the differential diagnosis of these respiratory complaints?

a. Exercise-induced asthma
b. Allergic asthma
c. Recurrent viral infection and asthma
d. Irritant or toxin-induced asthma

Figure 1. *Red Tide caused by Dinoflagellates off the Scripps Institution of Oceanography Pier, La Jolla, California. (Credit: Wikipedia)*

QUESTION 2

Are There Any Additional Diagnostic Studies That Would Be Helpful in Arriving at the Diagnosis?

Given his observations, exposures during surfing, and duration of symptoms, spirometry within 24 hours of surfing would be helpful. However, there was scheduling difficulty in obtaining one. Our presumptive diagnosis of red tide–associated asthma would have been validated by challenge with the toxin associated with red tides; however, the toxin is not commercially available for testing.

Clinical Course

He did not want to stop surfing but wanted to prevent the symptoms associated with the red tides. Prophylactic inhaled fluticasone/salmeterol 250/50 was prescribed, which he used twice daily starting 2 days before surfing in red tides with prevention of symptoms.

DISCUSSION

Asthma is a heterogeneous disease in which environmental factors are strongly associated with disease manifestation. Despite the increasing prevalence of asthma worldwide, recreational exposures are often overlooked. One less commonly known and recognized trigger is exposure to aerosolized brevetoxin, produced by the marine dinoflagellate *Karenia brevis*.

Red tides are harmful algal blooms of *K. brevis* and other regional dinoflagellates, which occur annually in the Gulf of Mexico and in many other parts of the world. They have gained notoriety in the media and literature in association with neurological and gastrointestinal illness from ingestion of the heat stable toxin, which causes neurotoxic shellfish poisoning; it is less commonly known for the effects on upper and lower airways.[1,2] Cases of brevetoxin associated syndromes have been described mostly in Florida where the blooms may last for months along the entire coastline. However, many coastal communities around the world have described these occurrences, including the Mediterranean coast, New Zealand, and Japan.[3,4]

In humans, exposure to aerosolized brevetoxin results in conjunctival irritation, and inhalation may cause rhinorrhea, wheezing, cough, and chest tightness; individuals with underlying airway disease, *i.e.*, asthmatic patients, are particularly susceptible, but healthy individuals may also be affected. Both allergic and nonallergic subjects react to red tide exposures.[5–7]

Brevetoxins are potent lipid-soluble polyether neurotoxins with at least nine structurally related forms isolated. They are depolarizing substances that activate voltage-sensitive sodium channels; this can cause uncontrolled sodium influx and excitability of affected cells.[1] In the lower airways, this can equate to significant bronchoconstriction; *ex vivo* human bronchial smooth muscle cells contract with exposure to brevetoxins and *in vivo* animal models also show significant bronchoconstriction. Picograms of brevetoxins have been found to be equally potent to micrograms of leukotriene D_4, which is considered one of the most potent bronchoconstrictors in asthma.[7,8]

Additional studies have shown that brevetoxin-induced bronchoconstriction may be blocked by atropine, cromolyn, topical corticosteroids, leukotriene modifying drugs, and H_1-antagonist; therefore, brevetoxin appears to be a potent toxin acting by both cholinergic and histamine (H_1)-related mechanisms (see Fig. 3). The β2-adrenergic agents will rapidly reverse the bronchoconstriction after exposure to near baseline levels (see Fig. 4). Recently, bradykinin B2-receptor antagonist (HOE-140) was also found to decrease the response to brevetoxin, suggesting that kinins are released after toxin inhalation and may be involved in this process.[9]

Fleming *et al.*[5,6] recently published a study of physician-diagnosed asthmatic patients showing statistically significant decrease in forced expiratory volume at 1 second and increased symptomatology after spending 1 hour walking on the beach during active red tides compared to when there was no active red tide. In

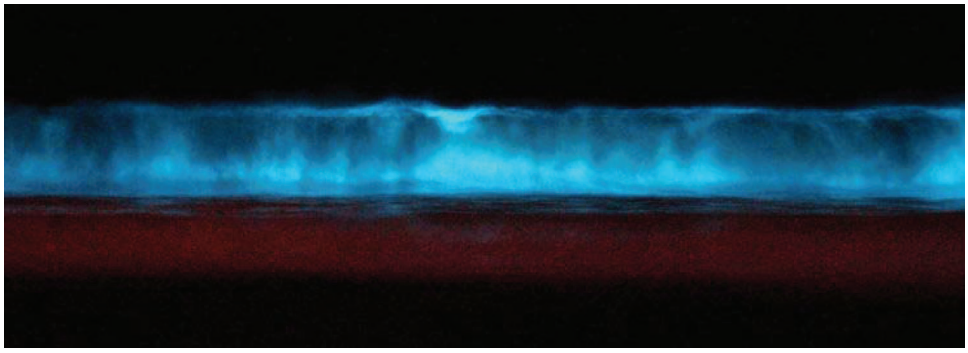

Figure 2. Image of bioluminescent red tide event of 2005 at a beach in Carlsbad, California. (Credit: Wikipedia)

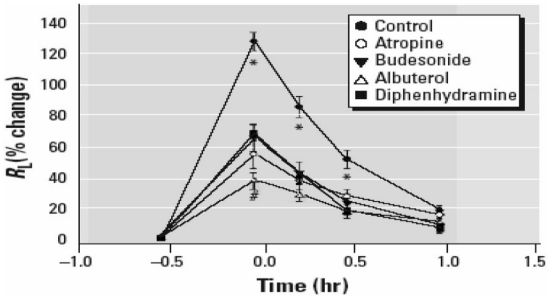

*Figure 3. Effect of pharmacologic agents on brevetoxin-induced bronchoconstriction. Crude brevetoxins produced an immediate increase in R_L, which then returned to baseline values within 1 hour. Pretreatment with atropine, budesonide, albuterol, and diphenhydramine all reduced the toxin-induced response. Values are mean ± SE for five sheep. *$p < 0.05$ versus all others; #$p < 0.05$ albuterol versus diphenhydramine. (Reproduced with permission from Ref. 9.)*

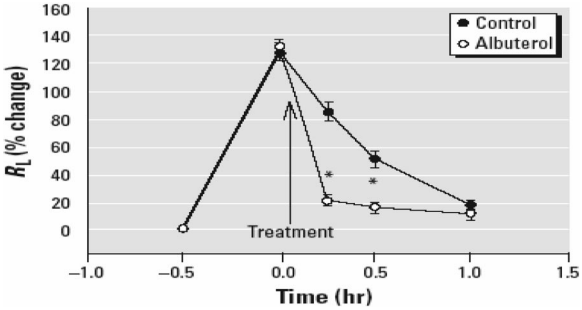

*Figure 4. Reversal of crude brevetoxin-induced bronchoconstriction with albuterol. Values are *$p < 0.05$ versus untreated. (Reproduced with permission from Ref. 9.)*

Florida, where this is an annual occurrence, there is much interest and environmental monitoring for red tides. However, in other parts of the world, where red tides may be more intermittent, such as in southern California, there is no monitoring and, therefore, less awareness of when this toxin may be affecting individuals who are coastal residents or frequent the beaches for both recreational or occupational reasons, such as lifeguards and the military (*i.e.*, navy seals, marines, etc.). Because occupational asthma comprises 9–15% of adult asthma, brevetoxin should be an etiologic consideration in exposed patients.[10] Backer examined this effect in healthy lifeguards in Florida showing increased upper respiratory symptoms and decreases in spirometry during exposed periods compared with unexposed periods after 8-hour shifts; she also evaluated and saw similar trends in recreational beachgoers.[11,12] In addition, studies show that aerosols of brevetoxins have been measured ≥1 mile inshore. A recent study also indicated an increased rate of respiratory-related complaints in the local emergency department during the red tides.[13]

Because the red tides are quite variable, morbidity may be associated with the levels of toxin, length of exposure, and preexisting respiratory disease. Given the variability and lack of knowledge on the levels of toxin in the environment and lack of readily available diagnostic testing for brevetoxin, health care professionals and the general population should be educated on this potential health risk and exposure.[1] Long-term consequences of repeated exposure are unknown. The possibility of this toxic exposure should be considered in patients who live near the beach or spend time on the beach. At this time, there is no known monitoring for red tides in San Diego and it is, therefore, difficult to assess the degree of concern for this toxin. Furthermore, the winds and waves are more powerful along the Pacific coastline, which may result in increased release and exposure further inland. More studies and awareness may be needed to better assess the health impact of brevetoxin and other harmful algal blooms.

Final Diagnosis

Red tide (brevetoxin)-associated asthma.

SUMMARY/CONCLUSION

Exposure to aerosolized brevetoxins during red tides is an underrecognized trigger for asthma. It can produce upper and lower respiratory symptoms that may be prevented and treated with standard pharmacotherapeutics for allergies and asthma.

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Patient Oriented Problem Solving (POPS) Case Report

A case of severe refractory chronic urticaria: A novel method for evaluation and treatment

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ABSTRACT

With cholinergic urticaria (ChU), the ultimate diagnosis often depends on the demonstration of characteristic urticaria by appropriate provocation. Several treatment options may be helpful but traditional options (antihistamines, leukotriene inhibitors, and immunosuppressives) may be exhausted by the refractory ChU patient. Here, we describe such a case. Demonstration of immediate hypersensitivity to autologous sweat skin testing (ASwST) may provide a rationale for use of omalizumab (Xolair, Genentech Novartis, South San Francisco, CA). Patients with severe ChU may have difficulty producing sufficient quantities of sweat for ASwST given that the very effort that produces the sample exacerbates ChU. Generation of sweat by iontophoresis with pilocarpine nitrate can be performed at many large medical centers. The procedure is simple, safe, and produces varying amounts of sweat depending on the individual. This sweat can then be used for ASwST. Our patient had a positive ASwST with appropriate positive and negative controls. Our testing methods were validated by negative ASwST, saline control, and positive histamine control in a nonatopic, nonurticarial control patient. By the patient's second injection of omalizumab, her quality of life score was significantly improved, as were her daily medication scores and exercise tolerance. We describe the first case of a patient with severe refractory ChU who had a positive ASwST by a novel collection method who has been successfully treated with omalizumab. We present a novel tool for the evaluation and demonstration of sweat-specific IgE in ChU patients who are unable to provide sweat by more traditional means.

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Key words: Autologous sweat skin test, cholinergic urticaria, omalizumab, pilocarpine iontophoresis, sweat collection, urticaria, Xolair

CASE PRESENTATION

Chief Complaint

Hives.

History of Present Illness

A 25-year-old woman initially presented in early 2007 complaining of very pruritic red raised bumps with strenuous exercise since 2000. She reported <5-mm pruritic bumps that would coalesce triggered by significant exertion and with other increases in her body temperature, such as hot showers or getting into a hot car. Over the years, her lesions had become more severe and her exercise tolerance had reduced from 45 minutes before the development of her condition to <5 minutes. By summer 2007, climbing a flight of stairs or physical labor at work would cause her to urticate to the point that she would have to stop what she was doing.

Medical History

Medical history was significant for intermittent seasonal rhinitis and dysmenorrhea.

Physical Examination

The patient rarely had lesions on the days of her clinic visits and her exam was otherwise normal. There was no evidence of dermatographism, hyper- or hypopigmentation, chronic angioedema or other rashes. She had several pictures showing generalized urticaria and facial swelling on different occasions at home, work, and after exercise.

Initial Laboratory and Other Diagnostic Findings

The patient's baseline labs in winter 2007 total serum tryptase were 2 ng/mL, total IgE was 103 IU/mL, and

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ESR was 15 mm/hour. Thyroid stimulating hormone, metabolic and hepatic panels, and CBC were all normal including a normal differential. *Helicobacter pylori* serum antibody was positive.

Clinical Course

The rash progressively worsened to the point of requiring twice-daily cetirizine, ranitidine, fexofenodine, once-daily montelukast, and as-needed hydroxyzine. She described her daily urticarial severity as 8/10 points on a subjective scale with 10/10 off medications or during light exertion. By early 2008, the patient's duties were severely limited and she could not perform her mandatory physical fitness testing. Hyoscyamine was tested twice daily without any beneficial effect, consistent with previous reports.[1] Secondary causes of chronic urticaria (CU) were evaluated as recommended in the CU practice parameter.[2] The patient received triple therapy for her positive *H. pylori* antibody without improvement in her cholinergic urticaria (ChU). With assistance from her gynecologist, different birth control medications were tested without avail. She was hesitant to test long-term steroids, danazol or immunosuppressant medications.

QUESTIONS

What Is the Differential Diagnosis?

The different diagnosis includes ChU, chronic idiopathic urticaria (CIU), exercise-induced anaphylaxis, food-induced exercise-induced anaphylaxis, mastocytosis, and idiopathic anaphylaxis.

What Additional Laboratory Data or Investigations would be Helpful in Arriving at a Diagnosis?

Additional diagnostic testing could include exercise challenge, hot water bath, intradermal skin testing with methacholine or autologous serum, and/or sweat testing.[3–5]

In spring 2007, the patient underwent exercise challenge and developed pinpoint urticaria after several minutes of exertion. Her classic pinpoint urticaria quickly coalesced and she then developed angioedema (Fig. 1) and her forced expiratory volume in 1 second dropped 12.4% from baseline. She received a nebulized albuterol treatment and two doses of epinephrine with rapid symptom resolution. The patient's tryptase after exercise testing in spring 2007 was 8 ng/mL.

The patient's response to exercise was suggestive of the diagnosis but further provocative testing was considered to allow consideration of additional therapeutic options. As such, autologous serum skin testing (ASST) and autologous sweat skin testing (ASwST) were considered. ASST was negative with positive histamine and a negative saline control. We discounted hot water immersion because we do not have access to hot water baths in our hospital and the water would wash away the sweat for collection. Given the patient's ChU severity, she was unable or unwilling to exercise sufficiently long to develop a sweat despite two additional attempts. Therefore, alternatives for sweat collection were considered.

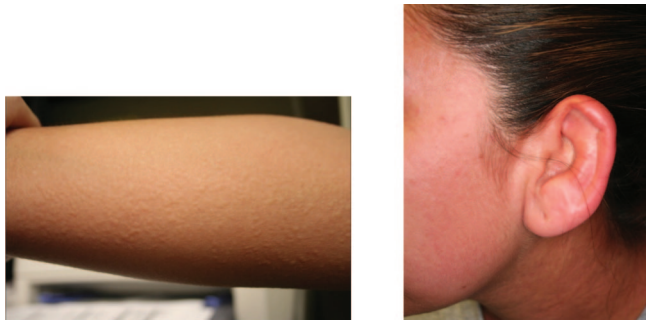

Figure 1. *Punctate urticaria, facial and ear swelling immediately after exercise challenge in April 2007.*

Pilocarpine iontophoresis (PI) is the most common diagnostic technique for cystic fibrosis. Although never attempted, for our purpose of ASwST by literature search, we performed PI for sweat collection as described elsewhere.[6] Briefly, the arm is first cleaned with sterile water. Then pilocarpine 0.5% and an inert electrolyte solution in agar gel discs (Pilogel discs by Wescor, 459 S. Main ST., Logan, UT 84321) were secured to the patient's arm and connected to a battery-powered stimulator (Macroduct sweat collection system, Model 3700-SYS; Wescor, Logan, UT). The current and time typically necessary to drive adequate pilocarpine nitrate into the skin are 1.5 mA for 5 minutes. The collecting device grossly consists of a sponge funneling into a coiled capillary tube with a small amount of dye to mark the sweat front. This device is placed over the pilocarpine-stimulated area for 30 minutes. Variable amounts of sweat are collected depending on the patient (18–135 mg).[6] Both the patient and the control (H.F.O.) had sweat collected by this method. Given the small amount of sweat collected in the patient, sweat was diluted with an equal amount of saline to make 0.01 mL and injected unfiltered. The control provided more than enough sweat by pilocarpine method and was similarly tested with autologous undiluted, unfiltered sweat. As originally described, a wheal $\geq 9 \times 9$ mm and erythema $\geq 20 \times 20$ mm was interpreted as positive at 15 minutes.[7] The patient had a positive ASwST intradermal (ID) at 12×12-mm wheal and 55×60 flare with a negative saline ID (0×0-mm wheal and flare) and positive histamine control ID of 11×12-mm wheal and 27×22 flare (Fig. 2). This supported the clinical impression of severe ChU. The control had negative results to ASwST as previously defined with appropriate negative saline and positive histamine controls. On a subsequent day, the control

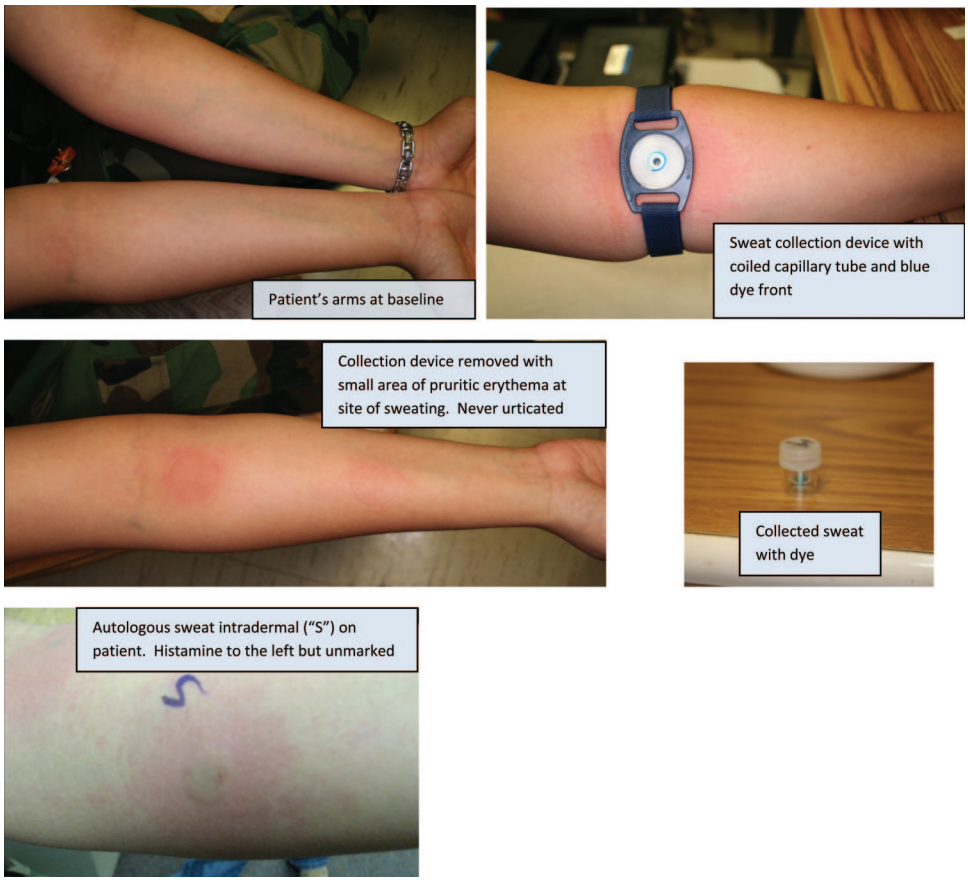

Figure 2. *Findings of sweat collection by pilocarpine iontophoresis and autologous sweat skin testing on patient.*

had an identically negative ASwST on sweat gathered after exercise.

Further Clinical Course

Once a positive ASwST was indicated, suggesting anti–sweat-specific IgE, a trial of omalizumab, 300 mg, monthly was instituted according to dosing guidelines based on weight and total IgE (Genentech Novartis, South San Francisco, CA). A validated CU quality of life questionnaire (CU-Q_2OL) was used to subjectively monitor the patient's response to treatment.[8] Before her second injection, she reported that her severity by CU-Q_2OL had been reduced 50%, from baseline of 97/115 points to 43/115, and has remained reduced (Fig. 3 *A*). Her ability to exercise without significant urticaria increased over 800%, from <5 minutes to just >40 minutes (Fig. 3 *B*). She had self-weaned her medications down from eight pills daily to once-daily cetirizine (Fig. 3 *C*).

DISCUSSION

ChU, first described in 1924, is characterized by unique clinical features: pinpoint-sized, highly pruritic wheals with surrounding erythema that occur after sweating during exercise, strong emotions, hot baths, eating hot or spicy foods, or raising the body temperature.[9] ChU is believed to account for ~5% of all CU and 30% of all physical urticaria. ChU patients predictably record the greatest disability by QOL scores and are the only urticarial group relatively restricted in sexual activities.[10] ChU typically has its onset during the second or third decade.[1,3] Overall, prognosis is generally favorable, because 31% of patients have persistence of symptoms ≥10 years with an average duration of 7.5 years (range, 3–16 years).[3,11]

Although classic ChU lesions associated with typical triggers are often enough to suggest the diagnosis, confirmatory testing can be performed. Classically, an ID injection of 0.01 mg of methacholine in 0.1 mL of saline produces a local area of hives and is diagnostic of ChU. However, because only ~1/3 of ChU patients show a positive test, it can not be used to "rule out" ChU and has fallen out of favor.[3,5] Other specific provocative challenges may include exercise or hot water bath challenge.[4,5] For hot bath testing, a patient should be submerged partially in a hot water bath at 40–44°C until the core body temperature has increased ≥0.7°C.[5,12] Under these conditions, the appearance of generalized urticaria confirms the diagnosis of ChU.[5]

The pathogenesis of ChU is unclear but is generally believed to involve an abnormal cutaneous response in the presence of cholinergic agents,[4] although certainly

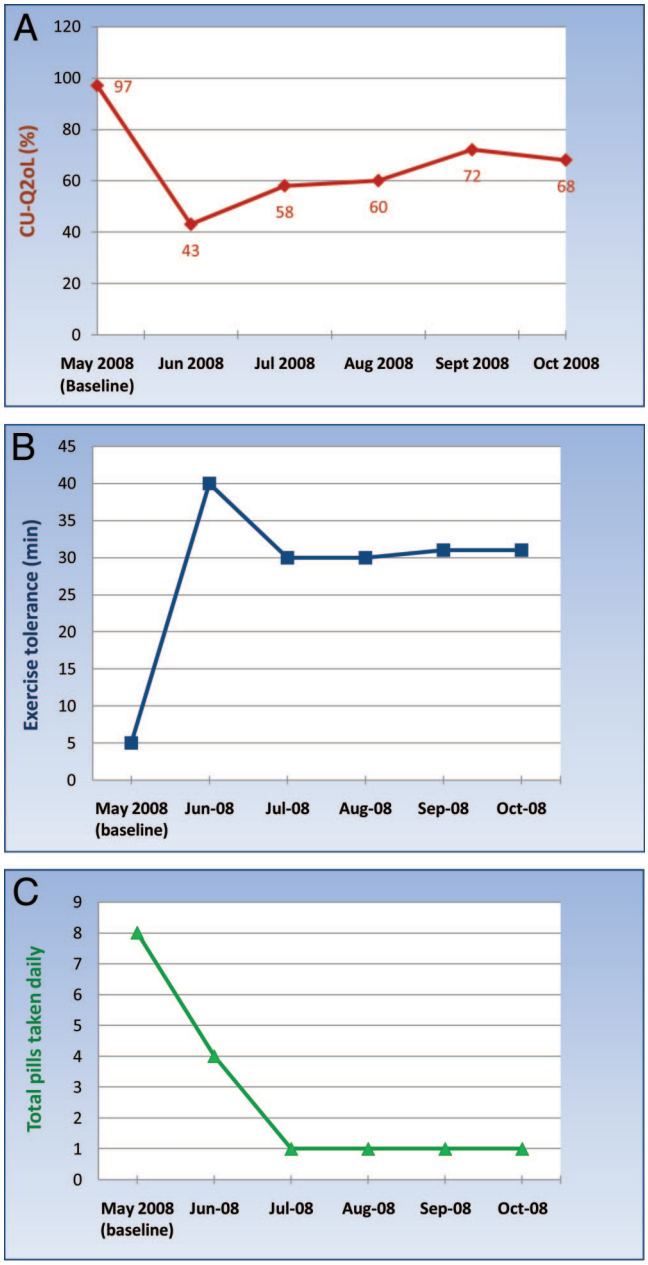

Figure 3. (A) Chronic urticaria quality of life (CU-Q_2OL) scores starting at baseline (worst possible severity is 115 points and best is 0) before her first injection. Subsequent CU-Q_2OL scores obtained at monthly omalizumab injection visits. Patient filled out the CU-Q_2OL questionnaire and reviewed exercise tolerance and the number of pills taken daily for each injection visit. (B) Self-reported exercise tolerance times. Initially, could not exercise >5 minutes before having to stop because of severe urticaria. (C) Number of pills needed for control of cholinergic urticaria. Initially, eight pills were needed and control still was not achieved.

other mediators could be involved. In patients with ChU, injection of acetylcholine into normal appearing skin produces a wheal and flare reaction, often surrounded by smaller satellite lesions.[5] Adachi and colleagues reported a group of 20 ChU patients who showed a positive ASwST as well as positive Prausnitz-Kustner tests in all 6 patients in whom the procedure was performed, compared with negative ASwST in 20 control patients.[7] They used 0.02 mL of various dilutions of sweat, and a positive response was read at 15 minutes and defined as a wheal of $>9 \times 9$ mm or erythema of $>20 \times 20$ mm. The large cutoff in size is caused by irritant effects of sweat.[7] Although a positive response to autologous skin testing does not prove or disprove the presence of antibodies, it does show histamine-releasing properties of the serum or sweat.[13] Fukunaga *et al.* showed that there may be two subgroups of ChU patients, a nonfollicular group that shows a positive ASwST and negative ASST, and a follicular ChU group that shows a weak ASwST and positive ASST. They also showed that autologous sweat was able to induce histamine release from basophils, which correlated with the size of the positive ASwST, implying the sweat itself contains factors that can induce histamine release.[14] Adachi *et al.* collected sweat as described by Boysen *et al.*,[15] who described an anaerobic method of collecting large volumes of sweat with less epidermal contamination. They heated the area with a hair dryer and constructed a sweat collector out of petroleum jelly and paraffin oil covered by polyethylene film attached to rubber tubing and a syringe.[15] Otherwise, published articles on the methods of ChU and sweat collection are lacking in further details.[14,16] Therefore, this is the first study using PI for sweat collection to perform ASwST.

Management of ChU involves avoidance of triggers. Medical therapy is predominantly oral antihistamines, either H_1- and/or H_2-blockers, often at higher doses. Hydroxyzine has been reported to be the drug of choice.[1,17] Leukotriene inhibitors are often added to standard regimens. Oral anticholinergic agents have not shown efficacy.[1] Danazol has shown effectiveness although its potential for adverse effects limits it to severe cases.[18] Cautious use of β-blocker therapy has been recommended for certain cases because of its anxiolytic effects.[17] Tanaka and colleagues report the successful treatment of a ChU patient with partially purified sweat antigen immunotherapy.[16] Moore-Robinson and Warin described two cases of a successful desensitization regimen in which patients pretreated themselves with antihistamine followed by a hot bath 3 hours later.[1]

Although the pathophysiology of ChU still is not known, with the demonstration of a positive immediate skin test response to autologous sweat, we considered omalizumab's anti-IgE mechanism as a viable treatment option. Omalizumab is a recombinant humanized anti-IgE antibody that inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils and reduces the numbers of FcεRI receptors, thus reducing circulating

levels of free IgE and has been shown to decrease tissue eosinophils, lymphocytes, and IL-4 cells and inhibit early and late-phase responses to allergen.[19,20] Omalizumab has shown promise in CIU in several recent pilot studies and case reports. In 2007, Spector and Tan reported the rapid improvement of refractory CIU in three patients treated with omalizumab.[21] In 2008, Kaplan *et al.* reported complete resolution of chronic autoimmune urticaria in 7 of 12 patients treated with omalizumab.[22] All of these patients had different serum IgE and anti-IgE receptor antibody profiles and none with ChU. Gober *et al.* reported a successful double-blind, placebo-controlled treatment of CIU with omalizumab without indicating IgE levels or immediate-type hypersensitivity to serum.[23] Metz *et al.* reported the first successful case of omalizumab used to treat ChU, similarly without noting the total IgE level or demonstrating a positive ASST or ASwST.[24] Thus, our case is the second reported use of omalizumab in ChU, and the first involving a documented positive ASwST using a novel collection method. Improvement with anti-IgE antibody (omalizumab) suggests a role for IgE in ChU.

CONCLUSIONS

In conclusion, this case shows that PI can be used for sweat collection to perform ASwST in patients with severe ChU and reports the successful use of omalizumab for severe ChU. It is important to distinguish this was not a new means of diagnosis. Because this method produces variable amounts of sweat depending on the patient, filtering and using serial dilutions are recommended for ID testing with sufficient quantities.[1,3,7,22] If the quantity of collected sweat is limited, then one could consider using undiluted, unfiltered sweat with appropriate informed patient consent. A positive ASwST could serve as rationale for clinical use of omalizumab.

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Patient Oriented Problem Solving (POPS) Case Report

Hemophagocytic lymphohistiocytosis in a patient with x-linked lymphoproliferative disease

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ABSTRACT

X-linked lymphoproliferative disease (XLP) is a primary immunodeficiency affecting ~1 to 3 per million live male births. Patients are generally healthy until facing a viral infection such as Epstein-Barr Virus and then may develop fulminant infectious mononucleosis and die. XLP patients are also at increased risk of hemophagocytic lymphohistiocytosis (HLH), which may be triggered by assorted viruses. Here we report a novel case of HLH in a patient with XLP. Significant to his presentation is a paradoxical increase in natural killer (NK) cell activity. We hypothesize that this indicates that Parvovirus B19 activates NK cells via a signaling lymphocytic activation molecule–associated protein (SAP)-independent mechanism. Our case demonstrates an important etiology to consider in the differential diagnosis of XLP patients with nonfocal findings and febrile illnesses.

(Allergy Asthma Proc 30:458–462, 2009; doi: 10.2500/aap.2009.30.3259)

CHIEF COMPLAINT

Persistent fever and recurrent otitis media.

History of Present Illness

A 24 month-old male with recurrent ear infections and persistent fever up to 104°F was evaluated by the Allergy and Immunology consult service. X-ray revealed that the child had pneumonia and was not responsive to antibiotic therapy. The patient's mother had one first-degree cousin and more than 10 second-degree male cousins with X-linked lymphoproliferative disease (XLP) with fatal infections and liver failure. No individual in this child's immediate family had been identified as affected with XLP or as a carrier. Immune evaluation revealed normal serum quantitative immunoglobulins, protective antibody titers to diphtheria and tetanus, and normal T-cell function. Epstein-Barr Virus (EBV) serology showed previous infection and undetectable virus by quantitative polymerase chain reaction (PCR) analysis (Table 1). The patient improved clinically, and cultures obtained during this illness were positive for Adenovirus. At his second presentation (six weeks later), the patient again had a febrile illness, diffuse maculopapular rash, and absolute neutropenia (ANC = 0).

Physical Examination

Vital signs on the second admission revealed a temperature of 101.4°F, heart rate of 156 bpm and respiratory rate of 30 breaths per minute. His weight was 15.6 kg (>90th percentile for age). His examination was remarkable for shotty submandibular, axillary and inguinal lymph nodes and raised erythematous plaques with irregular borders on his face, arms, diaper area, and legs. There was a lighter erythema present on the trunk and back. There was no detectable hepatosplenomegaly.

Initial Laboratory and Other Diagnostic Findings

Laboratory studies for this admission are shown in Table 1. Parvovirus B19 infection was documented by PCR (1700 DNA copies/mL). Previous analysis had revealed specific antibody present for EBV, but repeat testing showed an absence of EBV IgG and IgM, indicating loss of recall antibody. *In vitro* lymphocyte functional studies revealed absence of T-cell function. Flow cytometry did not reveal any significant deviations from normal, including normal nat-

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Table 1 **Laboratory values on first admission (adenoviral infection) and second admission (HLH and Parvovirus B19 infection)**

Test	Admission #1	Admission #2	Reference Range
WBC	12,530 cells/μL	7,120 cells/μL	5,000–14,500 cells/μL
ANC	6641 cells/μL	0 cells/μL	1,500–8,000 cells/μL
AST	57 units/L	596 units/L	20–60 units/L
ALT	61 units/L	522 units/L	5–45 units/L
Albumin	3.0 g/dL	3.8 g/dL	3.7–5.5 g/dL
Ferritin	Not performed	7,821 ng/mL	20–236 ng/mL
Triglycerides	Not performed	317 mg/dL	20–150 mg/dL
EBV IgM	1:20	undetectable	<1:10
EBV IgG	1:1280	undetectable	<1:80
EBV EA	Negative	Negative	Negative
EBV PCR		Negative	Not detected
Adenovirus PCR	Not performed (culture positive)	Negative	Not detected
Parvovirus PCR	Not performed	1,700 copies/mL	Not detected
HHV-6, HHV-8, CMV PCR	Not performed	Negative	Not detected
HHV-7 PCR	Not performed	200 DNA copies/ml	Not detected
IgG	1080 mg/dL	1070 mg/dL	442–1139 mg/dL
IgA	140 mg/dL	111 mg/dL	21–150 mg/dL
IgM	126 mg/dL	77 mg/dL	43–184 mg/dL
NK Cell Activity	Not performed	NK Lytic Units >100 Interpretation: Robust*, Abnormal	Normal >3.1
PHA stimulation	206,797 (Normal)	1,744 (severely depressed)	165,549–307,659

Flow Cytometry Phenotypes	**% Admission 1**	**% Admission 2**	**#/mm^3 Admission 1**	**#/mm^3 Admission 2**	**Normal Range**
CD3	62.4	50.4	3,923	1,657	58.0–74; 1656–3841
CD4	46.4	36.1	2,915	1,188	28–47.2; 871–2379
CD8	15.4	13.1	971	431	16.0–31.8; 518–1433
CD19	26.1	38.2	1,641	1,257	12.8–30.6; 421–1397
CD56	7.7	8.2	484	270	8.6–25.0; 142–599

WBC = white blood cell count; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; EBV = Epstein Barr Virus; HHV = Human Herpes Virus; CMV = Cytomegalovirus.
**NK cell activity performed by Chromium Release Assay at Children's Hospital Medical Center in Cincinnati, OH*

ural killer (NK) cell numbers. Immunogenetic studies revealed a mutation in the SH2D1A gene consistent with an XLP diagnosis.

Bilateral clonus developed along with persistent fever, rising ferritin (7800 μg/mL), pancytopenia (leukopenia with neutropenia, anemia, and thrombocytopenia), elevated triglycerides (317 mg/dL), splenomegaly, and elevated soluble IL-2 receptor (8198 units/mL) which led to the diagnosis of hemophagocytic lymphohistiocytosis (HLH). NK cell activity was robust.

Two bone marrow biopsies were performed throughout the hospital stay to evaluate multiple cytopenias. Bone marrow specimens showed a lack of cellular elements, with predominantly lymphocytes noted and an absence of hematopoetic elements.

Table 2 **Diagnostic Guidelines for HLH-2004**

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled.

1. A molecular diagnosis consistent with HLH (either perform gene mutations at 10q21, mutations in hMunc 13–4, or mutations associated with XLP (SAP mutations), Griscelli syndrome (linked to two genes on 15q21), RAB27a (a key effector of cytotoxic granule exocytosis), and MYO5a (involved in organelle transport machinery) . . . OR
2. Diagnostic criteria for HLH fulfilled (5/8 of the following):
   1. Fever
   2. Splenomegaly
   3. Cytopenias (affecting > = 2 or 3 lineages in the peripheral blood)
   4. Hypertriglyceridemia and/or hypofibrinogenemia
   5. Hemophagocytosis in bone marrow or spleen or lymph nodes.
   6. Low or absent NK-cell activity.
   7. Ferritin > = 500 microgram/L
   8. Soluble IL-2 receptor > = 2400 U/mL

Criteria fulfilled in this patient:

1. Molecular diagnosis–mutation in SH2D1A gene along with the following clinical criteria:
   1. Fever–up to 104 F for more than 3 weeks
   2. Splenomegaly–confirmed by ultrasound
   3. Cytopenias (neutropenia, anemia, and thrombocytopenia)
   4. Hypertriglyceridemia (>300)
   5. Ferritin > = 500 microgram/L (>500 since admission and up to >7800)
   6. Soluble IL-2 receptor > = 2400 U/ml (8198 shortly after admission)

Source: Ref. 5.

Clinical Course

Chemotherapy with etoposide, dexamethasone, and cyclosporine was initiated and resulted in resolution of fever and improvement in developed neurologic symptoms. Despite immunoglobulin replacement therapy, significant cytopenias persisted. The patient continued to have elevated ferritin (>4000) and recurrent bacteremia. Multiple reinductions with dexamethasone and etoposide were instituted without complete resolution of symptoms. Ultimately, the patient succumbed to multiorgan failure secondary to *Enterococcus* sepsis.

QUESTIONS

What is the Differential Diagnosis?

The family history suggests that this child has XLP disease that was confirmed by SH2D1A genetic analysis. Children affected with XLP are at risk for fulminant infectious mononucleosis secondary to EBV infection. This should be considered very early in the clinical presentation.

This Patient Also Had Signs of HLH

As described below, Hemophagocytic Lymphohistiocytosis (HLH) may be caused by multiple different viruses. The signs of anemia, rash, and persistent fever in our patient are consistent with Parvovirus B19 infection, which was confirmed by PCR analysis. Other viruses that may have a similar presentation and may cause HLH include EBV, cytomegalovirus or other herpes viruses, and *Leishmania*. Parvovirus B19 has not been reported to date in XLP patients with HLH.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis?

Early in the course of the first febrile illness that proved to be secondary to adenoviral infection, the diagnosis of XLP was not established. Given the family history, it would have been helpful for this child's mother to have had genetic testing for the carrier state during her pregnancy and to have established a genetic diagnosis of XLP soon after the patient's birth. This would have provided opportunities for bone marrow transplantation prior to this child's presenting illnesses and would have given the patient a better probability for long-term survival. Family history of XLP was not provided to any physician until the child's presenting illness.

DISCUSSION

Hambleton and Cottom described what is believed to be the first reported case of XLP[1] in 1969 when they reported two brothers who suffered from lymphosarcoma and hypogammaglobulinemia following infectious mononucleosis. This patient's kindred was reported in 1973 with a fatal X-linked recessive reticuloendothelial syndrome and hyperglobulinemia,[2] which is now identified as XLP by genetic analysis. XLP is caused by a defect in the SH2D1A gene, which is located on the long arm of the X chromosome at

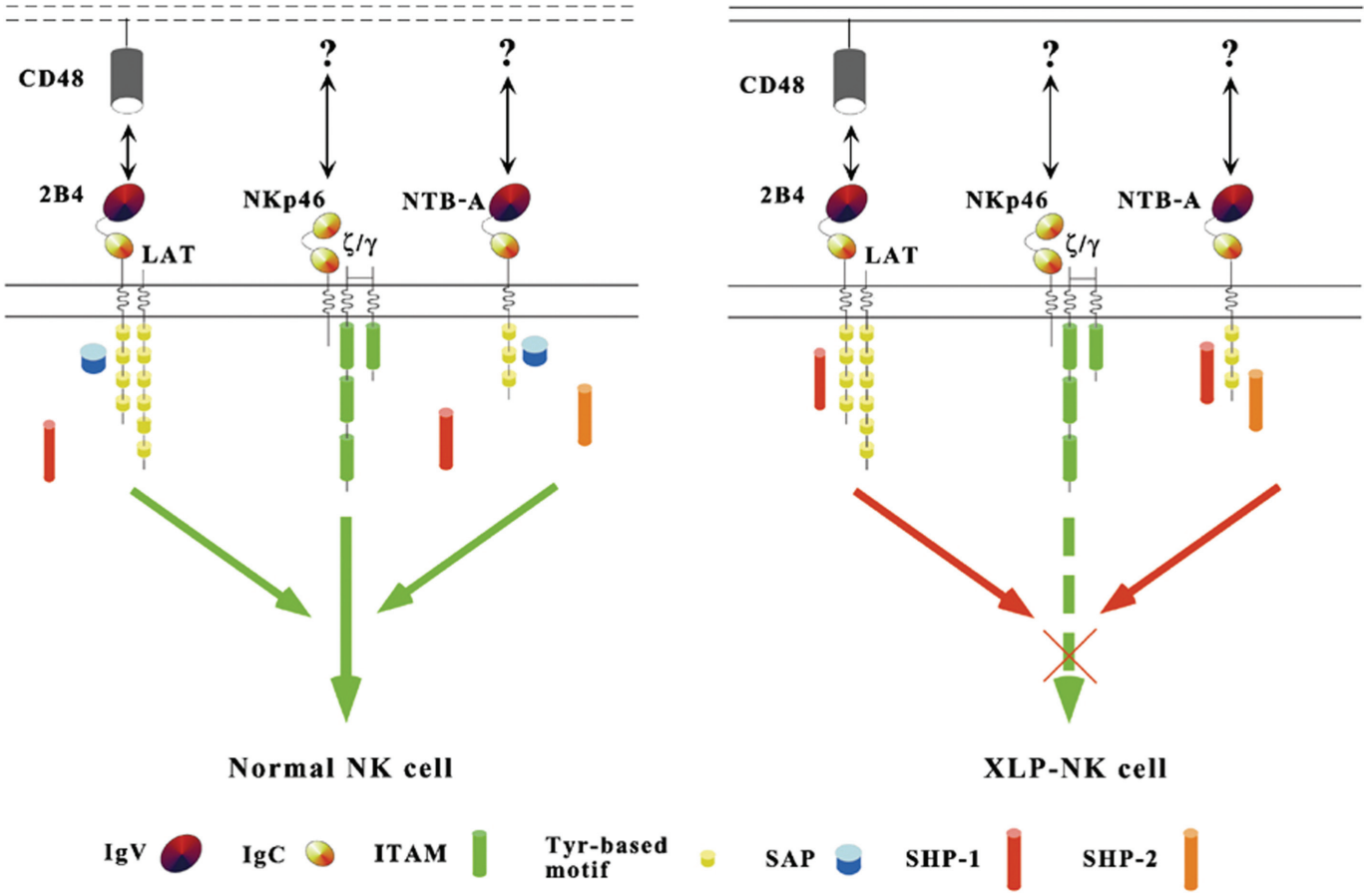

Figure 1. *EBV-infected B cells express high levels of CD48, the ligand for 2B4 and likely for NKp46 and NTBA. In the normal host (left) triggering signals delivered via NKp46 and amplified by 2B4 and NTBA lead to NK cell activation and induction of cytolysis of EBV-infected B cells (B-EBV cells). This occurs following recruitment of SAP, an intracytoplasmic polypeptide, that blocks SHP-1 production of inhibitory signals to NK cell activation. This cascade of events is impaired in XLP (right). XLP patients lack functional SAP molecules, and NK cell signaling is skewed to SHP-1 activation. NKp46 and other activator receptors are impaired, and NK cells are hampered from effective lysis of B-EBV and inability to control viral infection. In over 70% of XLP patients, the clinical outcome is fulminant infectious mononucleosis and death.*

Xq25. SH2D1A or signaling lymphocytic activation molecule (SLAM)–associated protein (SAP), important for signal transduction with primarily T, NK, and NK T cells affected.[3] In T cells, the protein binds to SLAM and in NK cells it binds to 2B4, an NK-cell-activating receptor.[4,5] Affected individuals are susceptible to overwhelming EBV infection and 50% develop fatal infectious mononucleosis. Lymphoproliferative disorders occur in one-third of affected males and dysgammaglobulinemia in one-quarter of patients, and by 10 years of age more than 70% of affected boys are dead.[6]

Approximately 58% of boys with XLP will develop fulminant infectious mononucleosis, and of those, 90% will develop HLH.[3] HLH, also known as virus-associated hemophagocytic syndrome, is characterized by the appearance of numerous highly activated histiocytes and macrophages affecting varying organs (bone marrow, liver, lymph nodes). Malignancies, infections, and rheumatoid disorders may lead to HLH. HLH diagnostic criteria, as outlined by the HLH-2004 Treatment Protocol[5] are listed in Table 2. This patient had a molecular diagnosis consistent with HLH with a mutation identified in the SH2D1A gene. He also had the following clinical criteria: (1) fever, up to 104°F for more than 3 weeks; (2) splenomegaly, confirmed by ultrasound; (3) cytopenias (neutropenia, anemia, and thrombocytopenia); (4) hypertriglyceridemia (>300); (5) ferritin ≥ 500 microgram/L (>500 since admission and up to >7800); and (6) soluble IL-2 receptor ≥ 2400 U/mL (8198 shortly after admission). The mechanism by which EBV triggers HLH in patients with XLP lies in the interaction between EBV and NK-T-B antigen (NTBA), NKp46, and 2B4, which are coreceptors located on NK cells[7] (Fig. 1). 2B4 Activates the NK cell *via* an SAP-dependent mechanism. The signal generated by the interaction of 2B4 and NTBA, amplifies the signal generated by NKp46, leading to NK cell-mediated lysis of B-cells infected with EBV. With XLP, SAP is absent or not functional. This leads to the binding

and activation of an inhibitory signal, SHP-1, which stops the activation signal triggered by NKp46. Patients with HLH induced by EBV infection, either with or without XLP, often show decreased or absent NK-cell activity.[5] In patients with XLP, this may be accounted for by the absence of functional SAP.

NK cell activity in EBV-associated HLH and XLP has been extensively described in contrast to Parvovirus B19-associated HLH. Parvovirus B19 primarily infects erythroid progenitor cells.[8] The immune response is primarily humoral. A cellular immune response is difficult to detect but must be present for a functional humoral response. Studies have shown that healthy individuals mount a Th1 response to the virus[9] with capsid proteins presented to CD4 T cells through class II molecules. NK cell activity is increased during viral infections along with IFN-γ, an NK-cell derived cytokine. In our patient NK cell activity was increased, and we hypothesize that NK cell activation may have occurred *via* an SAP-independent mechanism. SAP-independent mechanisms of NK-cell activation include through *C*D2-like *r*eceptor *a*ctivating *c*ytotoxic *c*ells (CRACC).[10] CRACC is functional in SAP-deficient XLP patients, and it may be crucial in host responses against viruses other than EBV.

CONCLUSION

Parvovirus is the most likely cause of HLH in our patient with documented XLP. An unusual immunologic finding was increased NK cell activity. We hypothesize that this occurred secondary to Parvovirus B19 stimulation of NK cells *via* an SAP-independent mechanism. Early diagnosis of XLP is critical and can be easily accomplished through commercially available genetic analyses. Bone marrow transplantation as an early intervention in patients with XLP is the only curative treatment. In patients with concomitant XLP and HLH, optimal timing for transplantation/engraftment should occur following HLH control with chemoimmunotherapy. Our case demonstrates the importance of early diagnosis of XLP. Additionally, Parvovirus B19 should be considered in XLP patients with nonfocal findings, febrile illnesses, and cytopenias.

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ERRATUM

In the Letters to the Editor in the March–April issue, Vol. 30, No. 2, page 211, the title of the letter by Drs. Rafael Martínez-Girón and Hugo van Woerden was inadvertently left out. The title of the letter should be, "Inhaled Protozoa Associated with Dust Mites as a Trigger of Respiratory Allergy?"

Patient Oriented Problem Solving (POPS) Case Report

Twenty-one year old woman with severe eosinophilia and left bundle branch block

Anupama Padi, M.D., Bernard Silverman, M.D., and Arlene Schneider, M.D.

ABSTRACT

Peripheral and tissue eosinophilia can occur in a wide variety of disease processes that include infectious, allergic, and primary hematologic disorders, and other more rare diseases such as hypereosinophilic syndromes (HES). We describe a case of a patient with severe eosinophilia and left bundle branch block. A 21-year-old woman with asthma and allergic rhinitis presented with neck pain and cough for >6 months with no other complaints. Physical exam was normal except for fever and minimal expiratory wheezes. Chest CT revealed diffuse airway inflammation with bronchiectasis. Admission electrocardiogram (EKG) was normal. Initial laboratory tests showed an absolute eosinophil count of 30,000 cells/mL. A thorough workup for eosinophilia was initiated, but the patient subsequently left against medical advice. The next day, in the outpatient pulmonary clinic, she was found to be tachycardic and an EKG showed sinus tachycardia with a new left bundle branch block. Laboratory tests revealed an eosinophil count of 33,200 cells/mL and elevated troponins. She was started on i.v. Solu-Medrol (Pfizer, Inc.). The next day, her EKG returned to normal. Three days later her absolute eosinophil count normalized. Identifying the cause of marked, persistent eosinophilia is a challenging problem. Excluding the more common causes of severe eosinophilia is required before making a diagnosis of HES and early therapeutic intervention can prevent morbidity from the disease.

(Allergy Asthma Proc 30:558–562, 2009; doi: 10.2500/aap.2009.30.3274)

Key words: Differential diagnosis, electrocardiogram, eosinophilic myocarditis, glucocorticoids, hypereosinophilic syndrome, left bundle branch block, severe eosinophilia

CASE PRESENTATION

Chief Complaint

Dry cough and neck pain.

History of Present Illness

A 21-year-old nonsmoking, African-American woman with a history of bronchial asthma and allergic rhinitis presented to the hospital with worsening neck pain for 1 week and a dry cough for >6 months. She reported a personal history of intermittent asthma since childhood, which is well controlled with albuterol as needed (≤2×/month). She denied any previous hospitalizations or intubations. She was recently given several short courses of prednisone for asthma exacerbations, which improved her cough. Her family history was significant for asthma and atopy. She denied any food or drug allergies or recent travel. A review of systems did not reveal fatigue, joint pains, or paresthesias.

Physical Examination

Her physical exam was significant for a temperature of 101°F and minimal expiratory wheezes. Her cardiac exam was normal S1 and split S2 without any murmurs. She had no skin rashes, organomegaly, or lymphadenopathy.

Laboratory and Other Diagnostic Findings and Clinical Course

Laboratory tests revealed a white blood cell count of 39,000 with 78% eosinophils. The absolute eosinophil count was >30,000/μL. Chest x ray revealed a left lower lobe consolidation and small nodular densities bilaterally. Her electrocardiogram (EKG) was normal sinus rhythm. The patient was admitted for the treatment of pneumonia and asthma exacerbation based on the presence of cough, fever, and chest x-ray findings.

The workup for eosinophilia included negative blood and stool cultures, an elevated erythrocyte sedimentation rate, C-reactive protein (CRP), and rheumatoid factor. A negative antinuclear antibody, negative

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Table 1 **Summary of laboratory findings**

Laboratory Tests	Initial Admission	Re-admission	Posttreatment
White blood cells (K/μL)	39.1	40.1	14.5
Hemoglobin (g/dL)	13.6	13.1	12.5
Hematocrit (%)	38.3	38.0	36.2
Platelet (K/μL)	381	424	410
Neutrophils %	7.5	10	81.9
Lymphocytes (%)	15	6	10
Monocytes (%)	0	6	6.2
Eosinophils (%)	78	83	1.7
Basophils (%)	0	6	0
C-reactive protein (mg/dL)	2.1		
Erythrocyte sedimentation rate (mm/hr)	100		
Sodium (mmoL/L)	144	137	138
Potassium (mmoL/L)	3.6	4.0	4.3
Chloride (mmoL/L)	105	101	104
Bicarbonate (mmoL/L)	26	25	24
Urea nitrogen (mg/dL)	7	9	16
Creatinine (mg/dL)	1.0	0.9	0.9
Glucose (mg/dL)	84	76	84
Calcium (mg/dL)	9.3	8.7	9.1
Albumin (g/dL)	3.6	3.4	3.3
Alkaline phosphatase (U/L)	117	103	92
Aspartate aminotransferase (U/L)	22	28	15
Alanine aminotransferase (U/L)	26	26	25
Antinuclear antibody	Negative		
Rheumatoid factor (IU/mL)	14,300		21,900
IgE (IU/mL)	2390		
A. fumigatus titer	Negative		
C-/P-Antineutrophil cytoplasmic antibody		Negative	
Troponin I (ng/mL)		0.81	0
Creatine kinase (U/L)		81	

antineutrophil cytoplasmic antibodys (ANCAs), and elevated IgE with a negative *Aspergillus* titer (Table 1). High-resolution chest CT showed diffuse airway inflammation with mild bronchiectasis in the right lower lobe (Fig. 1). Pulmonary function testing showed a severe obstructive lung defect with a mild bronchodilator response and a moderate restrictive lung defect (forced expiratory volume in 1 second [FEV_1], 47%; forced vital capacity [FVC], 37%; FEV_1/FVC, 63%; diffusing capacity of the lung for carbon monoxide, 48%). Bronchoalveolar lavage showed 46% eosinophils without any malignant cells and negative respiratory/acid-fast bacteria/fungal cultures. Echocardiogram showed normal chamber size and wall motion with an ejection fraction of 68%. Hematology workup for malignancy was ruled out with normal flow cytometry (CD3, CD4, CD5, CD7, CD8, CD14, CD16/56, CD19, CD25, CD45, and CD64) and cytogenetics (fluorescent *in situ* hybrid-

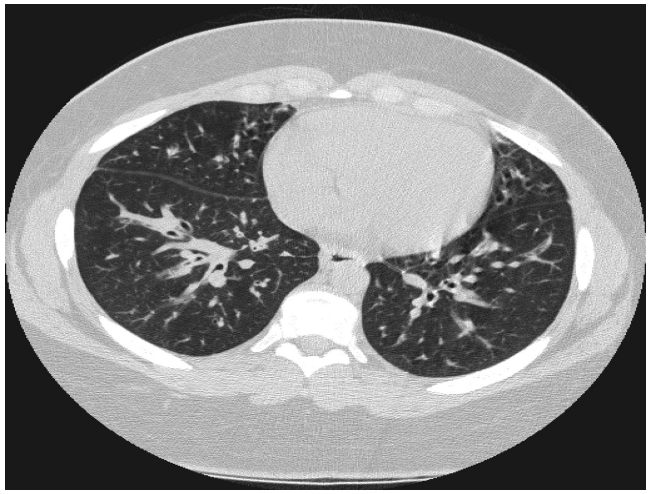

Figure 1. *Chest CT with diffuse airway inflammation and mild bronchiectasis in right lower lobe.*

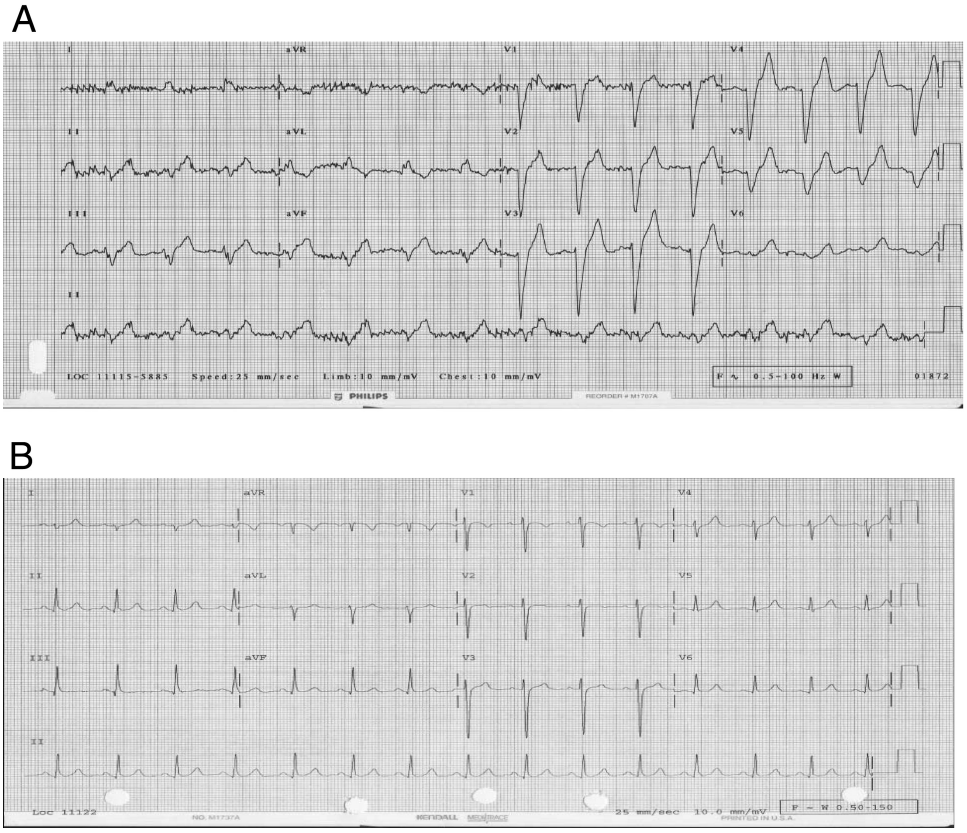

Figure **2.** *(A) Electrocardiogram showing new left bundle branch block with a widened QRS, negative QRS in lead V1, and upright QRS in V6. (B) Repeat electrocardiogram after glucocorticoids showing normal sinus rhythm.*

ization), but a bone marrow biopsy was not performed because of patient refusal. The patient subsequently left against medical advice.

She was seen the next day in the outpatient pulmonary clinic where she was found to be tachycardic. The patient denied any new complaints but the EKG showed sinus tachycardia with a new left bundle branch block (Fig. 2 *A*). She was sent to the Emergency Department for further management. Her laboratory tests were significant for an eosinophil count of 33, 200/μL, and elevated cardiac enzymes. The patient was started on i.v. Solu-Medrol (Pfizer, Inc.) and a repeat EKG performed the next day reverted back to normal sinus rhythm (Fig. 2 *B*). A repeat echocardiogram remained unchanged. After 3 days on steroids, the absolute eosinophil count normalized to 247 cells/ μL and the patient was discharged on prednisone, 60 mg daily.

QUESTIONS

What is the Differential Diagnosis?

A. Allergy/asthma.
B. Parasitic infections.
C. Drug hypersensitivity.
D. Connective tissue diseases.
E. Churg-Strauss syndrome.
F. Eosinophilic leukemia.
G. Eosinophilic pneumonia.
H. Hypereosinophilic syndrome (HES).

What Additional Laboratory Data or Investigations Would be Helpful in Arriving at a Diagnosis in This Patient?

Evaluating a patient with persistent, marked eosinophilia should include a careful history and physical exam directed at the nature of symptoms and disorders known to be associated with eosinophilia. The initial approach should assess general health status and whether there is underlying organ dysfunction. The eosinophilia must be confirmed with an estimation of the absolute eosinophil count. Studies to assess hematologic status (CBC, platelet, and prothrombin time/partial prothrombin time), organ function (liver function tests, renal function tests, urinalysis, chest x ray, and EKG), inflammation (CRP/erythrocyte sedimentation rate), and immune status (quantitative immunoglobulins and IgE) should be performed routinely. Further diagnostic evaluation based on the initial studies or localizing symptoms is usually required to distinguish among the many disorders underlying hypereosinophilia. A tissue examination is often necessary in patients with evidence of organ dysfunction and an endomyocardial biopsy would have been helpful in our patient to evaluate for early cardiac damage. Also, bone marrow aspirates and biopsy specimens for flow cytometry and cytogenetic studies would have been preferred to definitively rule out a hematologic malignancy such as leukemia. Additional dis-

ease defining tests may be necessary to exclude particular diagnoses such as serologies for parasitic infections and serum tryptase/cKIT mutations for systemic mastocytosis.

DISCUSSION

A systematic approach is necessary in identifying the cause of severe eosinophilia. Although asthma and allergic diseases are known causes of mild to moderate eosinophilia, they could not explain the severe eosinophilia seen in our patient. A thorough history also did not reveal any drug hypersensitivities and the patient denied taking any new medications. Parasitic causes were ruled out. Connective tissue diseases such as Churg-Strauss syndrome was a strong consideration because it is the major vasculitis associated with eosinophilia and may affect the same organ systems seen in HES; however, the absence of clinically evident vasculitis, renal disease, and negative ANCAs likely excluded this condition. Chronic eosinophilic pneumonia was also considered in light of the patient's history of asthma and considerable eosinophilia on bronchoalveolar lavage but would not account for the severe peripheral eosinophilia and presence of cardiac involvement. Eosinophilic leukemia can also be distinguished from HES. HES is a diagnosis of exclusion, but should be considered early on in a patient with severe eosinophilia. (Table 2)[1–6]

HESs are disorders marked by a sustained overproduction of eosinophils, peripheral eosinophilia, and tissue infiltration.[7–10] The diseases are characterized clinically by damage to multiple organs caused by eosinophilic infiltration and mediator release rather than by the level of absolute blood eosinophil count.[1,4] HES commonly affects the heart, lungs, skin, and central and peripheral nervous systems causing impaired organ function.[7,11]

The diagnostic criteria of HES includes a blood eosinophil count of >1500/μL for >6 months, exclusion of other etiologies for eosinophilia, and signs and symptoms of end-organ dysfunction.[12] HES occurs more commonly in men than women (9:1) and tends to occur between the ages of 20 and 50 years, although a few cases have been reported in children.[14–16]HES patients usually present with fatigue, cough, breathlessness, muscle pains, angioedema, rash, fever, and retinal lesions. Cardiac disease is the major cause of morbidity and mortality in HES, occurring in 48–75% of HES cases.

Eosinophilic myocarditis involves increased eosinophils in conjunction with other stimuli that recruit and/or activate eosinophils within the heart. The cardiac disease is associated with extracellular deposition of eosinophil granule proteins and evidence of eosinophil activation at sites of myocardial injury.[7,12,17] In-

Table 2 **Diseases with severe, marked eosinophilia diagnostic criteria**

Chronic eosinophilic pneumonia
1. Presence of pulmonary infiltrates on chest radiographs
2. Eosinophilic infiltration in lung parenchyma
3. Progressive respiratory symptoms present for >3 wk at initial evaluation, with course of disease lasting >1 mo
4. Careful exclusion of other causes of eosinophilia (*e.g.* asthma, drugs, and parasites

Acute eosinophilic pneumonia
1. Acute febrile illness of <5 days duration
2. Hypoxemia
3. Diffuse alveolar or mixed alveolar-interstitial infiltrates on chest radiographs
4. Infection
5. Prompt and complete response to corticosteroids
6. Failure to relapse after discontinuation of corticosteroids

Churg-Strauss syndrome (At least 4 of the 6 criteria)
1. Asthma
2. Eosinophilia of >10% white blood cell count
3. Neuropathy
4. Migratory or transient pulmonary opacities
5. Paranasal sinus abnormalities
6. Extravascular eosinophils revealed at biopsy

Allergic bronchopulmonary aspergillosis
1. Asthma
2. Peripheral blood eosinophilia
3. Immediate (+) skin test for *Aspergillus* antigens
4. Increased serum IgE levels
5. Pulmonary infiltrates on chest radiographs

Eosinophilic leukemia
1. Marked increase in the number of immature eosinophils in the blood and/or bone marrow
2. Greater than 10% blasts in the marrow, infiltration of tissues with immature eosinophil forms
3. Clinical course similar to other acute leukemias (anemia, thrombocytopenia, etc.)

Hypereosinophilic syndrome
1. Persistent eosinophilia of >1500/μL for more than 6 mo
2. Absence of parasitic, allergic, or other known causes of eosinophilia
3. Evidence of organ involvement and multiorgan system dysfunction

Source: The diagnostic criteria are based on criteria from Refs. 1–6, 10, and 13.

terleukin (IL)-5 produced by eosinophils at these sites may participate in local eosinophil activation.[18]

The development of cardiac disease in HES is not predictable. Some patients with sustained eosinophilia never develop cardiac involvement, and the severity of cardiac injury does not clearly correlate with the degree of peripheral eosinophilia.[7] Eosinophil-mediated heart damage evolves through three stages: (1) an acute necrotic stage, (2) an intermediate phase characterized by thrombus formation along the damaged endocardium, and (3) a fibrotic stage.[7,19]

The acute necrotic stage occurs approximately 5–6 weeks after the onset of illness and is characterized by endocardial damage, myocardial infiltration with eosinophils, eosinophil degranulation, and myocardial necrosis. The disease is usually clinically silent at this phase and physical examination is generally normal. Echocardiography can be normal, and an endomyocardial biopsy may be required to make the diagnosis in patients with signs or symptoms of cardiac disease.

The second stage of heart disease involves thrombus formation along areas of damaged endocardium, which can detach and cause a peripheral embolism. In the third, fibrotic stage, progressive scarring causes endomyocardial fibrosis, producing a restrictive cardiomyopathy and/or mitral or tricuspid valve regurgitation due to entrapment of the chordae tendineae. Patients usually present clinically during this stage with signs of left and/or right heart failure.

First-line therapy for the management of HES with eosinophilic myocarditis is glucocorticoids. The initial therapy consists of a 1- to 5-day trial of prednisone at doses of 1 mg/kg per day or 60 mg/day in adults to determine whether the blood eosinophilia is suppressible by glucocorticoids. This is performed even in asymptomatic patients, as this information is useful if the patient develops rapidly progressive organ involvement necessitating therapy later on, and also provides prognostic information, as a response to glucocorticoids is generally associated with a better prognosis. If blood eosinophilia is suppressed, doses may slowly be tapered and changed to alternate-day therapy.[7]

Final Diagnosis

HES.

CONCLUSION

HES should be suspected early in patients with persistent eosinophilia due to insidious organ damage. Patients with severe eosinophilia on at least two occasions should be evaluated for possible HES. Cardiac involvement carries significant morbidity and mortality and cardiac conduction abnormalities as a manifestation of HES should be sought. Early identification and treatment of HES could prevent complications from the disease.

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Patient Oriented Problem Solving (POPS) Case Report

A 6-year-old boy with fever and eosinophilia

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ABSTRACT

Tissue and blood eosinophilia can be associated with a variety of infectious, allergic, and systemic diseases. Eosinophilia can range from mild and clinically inconsequential levels to high-grade eosinophilia with severe and potentially fatal consequences. Because of its ability to degranulate and produce cytotoxic mediators such as major basic protein and eosinophil peroxidase the eosinophil has the potential to cause considerable tissue damage, including potentially fatal conditions such as endomyocardial fibrosis. The most common infectious cause of eosinophilia worldwide is the parasitic helminth; fungal infection as a cause of eosinophilia is rarer, but must also be considered in the differential diagnosis. In this article we describe a unique case of reactive eosinophilia.

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Key words: Amphotericin B, *Candida parapsilosis*, caspofungin, eosinopenia, eosinophil, eosinophilia, fever, fungal infection, IgE, IL-5

CASE PRESENTATION

Chief Complaint

Fever and abdominal pain.

History of Present Illness

The patient was a 6-year-old boy with multiple medical problems who was admitted to our Children's Medical Center presenting with 2 days of fever, nausea, abdominal pain, and projectile vomiting. His history was remarkable for prune belly syndrome with dysplastic kidneys requiring bilateral nephrectomy and regular dialysis. Surgical history was notable for prior gastrostomy tube placement, Nissen fundoplication, and bladder augmentation 2 weeks before admission, which was done in preparation for renal transplantation. He had no history of allergic disease. The patient had been relatively symptom free after the recent surgery, but in the last few days complained of worsening midepigastric pain and intolerance of his feeds. His vomiting was bilious and nonbloody. Volume and frequency of bowel movements had decreased.

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Physical Examination

Vital signs included a temperature of 102°F, blood pressure of 101/58, heart rate of 140 beats/minute, and respiratory rate of 23/minute. The child was in mild distress and uncooperative. His lungs were clear to auscultation, heart rate was regular rhythm but tachycardic, and his abdomen was soft and nondistended. He had a gastrostomy-jejunostomy tube to gravity and a midline surgical incision that was clean and intact. The rest of his physical examination was unremarkable.

Initial Laboratory and Diagnostic Findings

Laboratory analysis revealed a hemoglobin of 8.6 g/dL (normal, 14–17 g/dL), hematocrit of 26.9% (normal, 39–50%), and platelets of $504 \times 10^3/mm^3$ (normal, $130–400 \times 10^3/mm^3$). The patient initially had a leukocytosis with a white blood cell count of $17{,}700/mm^3$ (normal, $4200–10{,}300/mm^3$) with a differential of 68% neutrophils, 16% lymphocytes, 6% monocytes, 0% eosinophils, and 10% bands. His creatinine was 4.6 mg/dL (normal, 0.6–1.2 mg/dL) and blood urea nitrogen was 23 mg/dL (normal, 6–23 mg/dL). C-reactive protein and erythrocyte sedimentation rate were not evaluated. Basic metabolic panel and liver function tests were within normal limits.

A computed tomography (CT) scan of the abdomen showed free air and an intraabdominal abscess in the left lower quadrant thought to be a complication of his recent bladder augmentation surgery. Empiric antimicrobial therapy was initiated with vancomycin (10 mg/kg i.v. q12 hours), ticarcillin/clavulanate (2 gm i.v.

Table 1 **Laboratory findings on selected hospital days**

Hospital Day	WBC (/mm^3)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Bands (%)	AEC (/mm^3)
1	17,700	68	16	6	0	10	0
12	30,600	45	24	8	13	6	3978
23	42,800	12	18	4	66	0	28,248
27	19,100	13	20	5	61	0	11,651
48	8800	51	35	12.3	1.1	0	97

WBC = white blood cell count; AEC = absolute eosinophil count.

q12 hours), and metronidazole (500 mg i.v. q6 hours). An exploratory laparotomy was performed soon after admission (hospital day 1) and an abscess found in the left lower quadrant behind the bladder was drained. Cultures from this abdominal abscess grew Gram-negative rods and rare yeast, but a specific organism was not identified. Fungal cultures were not obtained from the abscess fluid. The ticarcillin/clavulanate and metronidazole were stopped and meropenem (500 mg i.v. q12 hours) was started.

On hospital day 4, the patient's eosinophil count began to rise. By hospital day 12, he had a leukocytosis of 30,600/mm^3 (normal, 4200–10,300/mm^3) and an absolute eosinophil count (AEC) of 3978/mm^3 (normal, <350/mm^3). His C-reactive protein was 22.5 mg/dL (normal, 0.0–0.9 mg/dL) and erythrocyte sedimentation rate was 66 mm/hour (normal, 0–20 mm/hour). As his eosinophilia worsened over the next several days, potential pharmacologic culprits such as nonsteroidal anti-inflammatory drugs and methadone were discontinued; however, his eosinophilia continued to increase. On hospital day 12, amphotericin B (100 mg i.v. q24 hours) was added to his antimicrobial regimen for the rare yeast in the abdominal abscess culture. His clinical status and leukocytosis slightly improved over the next few days, but the eosinophilia kept rising. At this point in time, the allergy and immunology service was consulted.

Further review of the patient's chronic medications led to mild suspicion that oxcarbazepine (used for seizure prophylaxis) and lansoprazole (for gastroesophageal reflux) were possible contributors to the eosinophilia; however, this was deemed unlikely to have actuated the sudden intrahospital rise in his peripheral blood eosinophils since he had been on each medication for over a year. The patient's AEC peaked on hospital day 23 at 28,248/mm^3 (normal, <350/mm^3) despite broad-spectrum antimicrobials including amphotericin B. In the following sections are selected laboratory values, including those from hospital day 23 (Table 1).

QUESTIONS

What Is the Differential Diagnosis of the Patient's Eosinophilia?

Eosinophilia can be associated with a multitude of causes. Allergic disorders such as allergic rhinitis, asthma, and allergic bronchopulmonary aspergillosis are associated with eosinophilia. Medication hypersensitivity reactions must also be in the differential diagnosis as well; removal of the drug often leads to resolution of the eosinophilia.[1] The most common infectious cause worldwide is helminthic infections,[1] but other parasitic infections can be implicated. In rare cases, fungal infections such as aspergillosis and coccidioidomycosis can cause eosinophilia. Bacterial infections are even rarer causes of eosinophilia, because most of the time, they are likely to decrease the eosinophilic count.[2] Hematologic and neoplastic disorders may be culprits, examples being reactive eosinophilia to carcinomas and lymphomas, as well as primary disorders such as acute eosinophilic leukemia. Even adrenal insufficiency for any reason can be a cause of eosinophilia because glucocorticoids normally exert eosinopenic effects, partly by stimulating eosinophil apoptosis.[3] Some other associated conditions with eosinophilia are listed later in text (Table 2). In our patient, because of his fevers, multiple comorbidities that could lead to unique infections, and worsening leukocytosis, the most likely diagnosis was thought to be infectious even though initial studies could not identify an infectious trigger for his eosinophilia.

What Diagnostic Studies Should Be Performed?

A thorough history should be taken for allergic symptoms, international travel, and recent medication changes. In addition to complete blood count with differential, peripheral blood smear looking for abnormal or immature eosinophils should be performed to evaluate for eosinophilic leukemia. Urine sediment on urinalysis may indicate a medication reaction or evidence of parasites. The stool should be sent for serial ova and parasite studies. Serological testing for infec-

Table 2 **Disorders associated with eosinophilia**

Allergic or hypersensitivity diseases
Asthma
Rhinitis
Bronchopulmonary aspergillosis
Medication related reactions
Atopic dermatitis
Infectious diseases
Parasitic infections, mostly helminths
Specific fungal infections
Other infections including nonparasitic (cocci, HIV, or scarlet fever)
Diseases with specific organ involvement
Skin and subcutaneous (*e.g.*, atopic dermatitis, episodic angioedema, and eosinophilic cellulitis)
Pulmonary (*e.g.*, eosinophilic pneumonia, hypersensitivity pneumonitis, and Churg-Strauss)
Gastrointestinal (*e.g.*, eosinophilic gastroenteritis, Churg-Strauss, and inflammatory bowel disease)
Neurological (*e.g.*, eosinophilic meningitis and Churg-Strauss)
Rheumatologic (*e.g.*, Churg-Strauss and eosinophilia-myalgia syndrome)
Cardiac (*e.g.*, hypersensitivity myocarditis and Churg-Strauss)
Renal (*e.g.*, eosinophilic cystitis and drug-induced interstitial nephritis)
Hematologic and neoplastic disease
Hypereosinophilic syndrome
Eosinophilic leukemia
Lymphoma (*e.g.*, Hodgkin's, non-Hodgkin's, and T-cell lymphoma)
Solid tumors
Mastocytosis
Immunodeficiency states
Hyper-IgE syndrome
Omenn syndrome
Wiscott-Aldrich syndrome
Selective IgA deficiency
Endocrine
Adrenal insufficiency

HIV = human immunodeficiency virus.

tious causes like *Strongyloides* and antibody titers for *Coccidioides* can also be done. Bacterial cultures and fungal cultures should be sent from blood and urine, as well as from any abscess specimens. For more severe eosinophilia, bone marrow (for hematologic cancer) and tissue biopsies can be performed, particularly if there is organ involvement suspected. Interleukin-5 (IL-5), the principal eosinophil growth factor cytokine,[4] can show elevation in eosinophilia, and can be checked, although most texts make no specific recommendations for routine screening.

When Is Eosinophilia Just an Incidental Finding?

An abnormally high number of eosinophils are important for several reasons. First, it alerts the physician to the likelihood that there is either a foreign organism in the body that needs to be treated or a possible malignancy that is still undiagnosed. It may also indicate that some adverse drug or allergic reaction is taking place. Peripheral blood eosinophilia can be dangerous because of the potential for organ and tissue damage[5] if present long term. Unfortunately, there is no evidence-based consensus on what constitutes a critical or clinically dangerous level of eosinophilia. However, patients with hypereosinophilic syndrome who by definition have an AEC of $>1500/mm^3$ are clearly at risk for eosinophil-related tissue damage.[6] Eosinophils can infiltrate any organ and cause damage thought to be secondary to expulsion of their destructive intracellular granule contents.[5] Diseases such as acute and chronic eosinophilic pneumonia, endomyocardial fibrosis, eosinophilic myocarditis, and eosinophilic gastroenteritis are a few of the known consequences of prolonged eosinophilia. Therefore, baseline and periodic echocardiograms should be obtained to detect eosinophil-mediated cardiac damage particularly in patients with eosinophilia of $>1500/mm^3$.

Clinical Course

Subsequent evaluation for his eosinophilia included ova and parasite stool studies, serum *Coccidioides* antibody titers, IgE, and echocardiogram, which were all negative or normal. IL-5 level was elevated at 26 pg/mL (normal, <10 pg/mL). A bone marrow biopsy was performed that showed normocellular marrow with no evidence of malignancy.

Three weeks after the initial surgery, on hospital day 21, the patient underwent repeat laparotomy because of continued abdominal pain, persistent leukocytosis, and evidence on CT scan of bowel perforation. Anastomosis leakage repair of past surgeries was performed and intraabdominal fluid was again cultured, this time with both bacterial and fungal cultures. On this occasion *Candida parapsilosis* grew out of the abdominal fluid culture. Caspofungin (50 mg i.v. q24 hours) was added to amphotericin B on hospital day 24 to give more tailored antifungal coverage against the newly cultured yeast.

Within 2 days of initiating caspofungin, the patient's eosinophil count began to decline. Rapid clinical improvement was noted as well; abdominal pain decreased, he was soon able to tolerate feeds, and his fever defervesced. After >3 weeks of treatment with caspofungin and amphotericin B, his AEC had de-

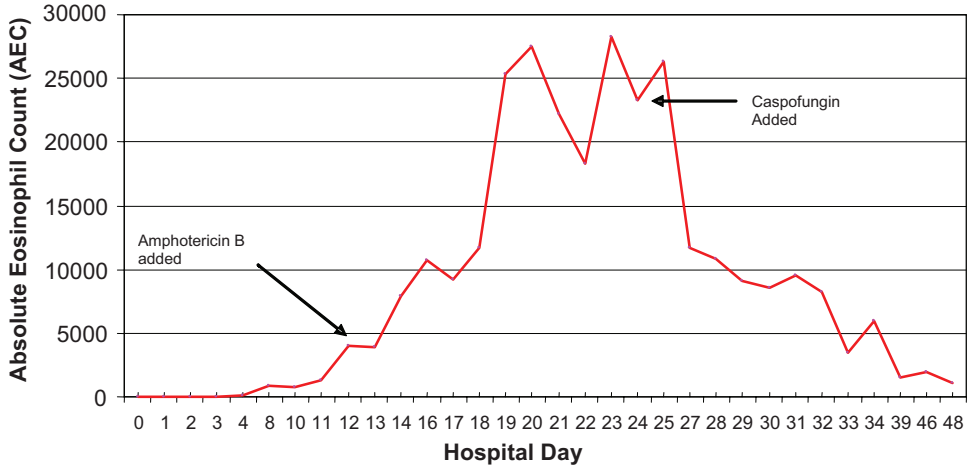

Figure 1. *Eosinophil levels in response to antifungal agents.*

Table 3 **Severity of eosinophilia**	
Mild eosinophilia	351–1500/mm^3
Moderate eosinophilia	>1500–5000/mm^3
Severe eosinophilia	>5000/mm^3

clined to 97/mm^3 (normal, <350/mm^3) on hospital day 48 (Fig. 1).

Our patient was discharged from the hospital 48 days after initial hospitalization, with continued antifungal treatment for another 3 weeks at home. At the conclusion of a total of 6 weeks of treatment with caspofungin and amphotericin B, his repeat fungal blood cultures were negative and his AEC was 83/mm^3 (normal, <350/mm^3).

How Would We Classify the Severity of the Patient's Eosinophilia?

Eosinophilia has been arbitrarily classified in most texts on a scale from mild to severe (Table 3). In this case, *C. parapsilosis* caused quite a heightened systemic response. The AEC peaked at >28,000/mm^3 (normal, <350/mm^3), making the degree of eosinophilia far higher than the typical threshold for severe eosinophilia.

DISCUSSION

Eosinophilia may be caused by a large variety of allergic, infectious, and neoplastic diseases. Many times, however, the cause is idiopathic. Although parasites and fungi are the most common infectious causes for elevated AEC, acute bacterial and viral infections characteristically cause a decrease in eosinophils, presumably because of increased endogenous corticosteroid production during illness.[7] Therefore, in a clinically ill, febrile patient with eosinophilia, the clinician must have a high clinical suspicion for fungal and parasitic etiologies, as was the case in the patient presented.

Previous reports that have linked peripheral blood eosinophilia to *Candida* spp. have been reported with *Candida albicans*[8,9] and *Candida guilliermondii*,[10] but not *C. parapsilosis*. Importantly, in our case, discontinuation of potential eosinophilia-causing medications did not cause a decline in the AEC in our patient. Additionally, laboratory investigation and bone marrow biopsy evaluating for conditions associated with eosinophilia was unrevealing. Drainage of abdominal fluid (in his initial exploratory laparotomy) did not affect eosinophilia, as the eosinophilia actually started after the drainage. The patient's improvement only after targeted antifungal treatment against *C. parapsilosis* led to the conclusion that his eosinophilia was a result of infection with this specific fungus, and that improvement was the direct result of treatment with caspofungin. To our knowledge, this is the first report of an association between eosinophilia and *C. parapsilosis* infection.

Candida species are the fourth most common cause of hospital-related bloodstream infection, and although *C. albicans* is still the most commonly isolated yeast in fungal culture specimens, *C. parapsilosis* is being cultured in increasing frequency, especially in intensive care units.[11] This yeast is especially virulent because of its affinity for foreign materials, such as central venous catheters used for dialysis and total parenteral nutrition,[12] both of which were necessary in our patient. The increased surface adherence capacity of *C. parapsilosis* and its ability to form biofilms allows it to sustain growth and makes it more resistant to antifungal agents.[13] These properties have made it an increasingly prominent cause of nosocomial infections, and in one study the predominant *Candida* species was found to be *C. parapsilosis*, not *C. albicans*.[14]

In many cases, including the one presented, the finding of peripheral blood eosinophilia is an epiphenom-

enon, and the patient's clinical condition can be better attributed to the primary disease process.[15] However, consequences of peripheral eosinophilia regardless of etiology may include tissue and organ damage[16]; therefore, effective treatment addressing the underlying cause is crucial. In our patient, eosinophil counts were followed over time and used as a marker of clinical improvement; effectively treating the infection correlated with a decreasing AEC. Obtaining a baseline echocardiogram is important in chronic eosinophilia in the event the patient develops endomyocardial fibrosis. IL-5, which is the only known eosinophilopoietin,[5] was appropriately elevated in our patient, although the mechanistic association of *C. parapsilosis* infection and elevated IL-5 level remains unclear.

CONCLUSION

We report to our knowledge, the first known case of reactive eosinophilia to *C. parapsilosis* infection. Our patient's eosinophilia cleared when the infection was discovered and treated. When confronted with a febrile patient with an elevated AEC, it is important to consider infectious causes in the differential diagnosis. Specific investigation for fungal causes of peripheral blood eosinophilia such as *Candida* spp. should be undertaken, especially if examination of other infectious causes is unrevealing. Discovery of the correct etiology of eosinophilia will lead to appropriately tailored treatment and will reduce the consequences of the underlying disease process as well as the eosinophilia itself.

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Patient Oriented Problem Solving (POPS) Case Report

Small bowel intussusception: An unusual presentation of angioedema

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ABSTRACT

This article presents a case report of a 13-year-old boy who presented to the Emergency Department with abdominal pain and vomiting. He had a known history of recurrent swelling but no previous abdominal episodes. A computed tomography scan revealed small bowel intussusception and he was scheduled for surgery. The patient had a history of multiple episodes of swelling of extremities, face, and genitalia. The Allergy Consult Service was consulted for perioperative management of his angioedema.

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Key words: Angioedema, bowel swelling, C1-INH, HAE, hereditary angioedema, intussusception, small bowel intussusception

CASE PRESENTATION

Chief Complaint

Abdominal pain and vomiting.

History of Present Illness

A 13-year-old African American boy presented with complaints of abdominal pain occurring off and on for 1 week. On the day of presentation he had noted exacerbation of the abdominal pain along with development of severe vomiting. He presented to a peripheral hospital where a computed tomography (CT) scan of his abdomen was obtained revealing small bowel intussusception involving the ileum. He was transferred to Pediatric Surgery at our hospital for possible surgical intervention. Given his medical history of recurrent swelling, the Allergy Service was consulted for perioperative management. He was passing flatus and had a bowel movement that morning.

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Medical History

The patient had a reported history of multiple episodes of swelling of extremities, face, and genitalia. No previous abdominal or airway involvement was documented by history. He also had allergic rhinitis and asthma for which he was on allergen immunotherapy, mometasone nasal spray, and albuterol inhaler. He had bipolar disorder and was taking aripiprazole and benztropine mesylate. His review of systems was negative for fever, trauma, diarrhea, or illness in the family. The patient was living with foster parents.

Physical Examination

He was lying in bed and seemed in minimal distress. His vitals were stable with a temperature of 37.3°C, respiratory rate of 16/minute, heart rate of 76 bpm, and blood pressure of 127/59 mmHg. Some cervical lymph nodes were palpable but were <1 cm, discrete, and nontender. Abdominal exam revealed mild guarding and tenderness in the epigastric area, no rebound tenderness, and active bowel sounds. The remainder of the physical examination was within normal limits.

Laboratory and Radiological Findings

The initial and subsequent laboratory findings are presented in Table 1. Of note is the initial white blood cell count of 13.8 k/μL with 73% neutrophils and increase in absolute neutrophil count. His initial CT scan of abdomen is presented in Fig. 1.

Table 1 **Laboratory results**

Results	Day 1	Day 2	Reference Range
WBC	13.8	10.1	4.8–12 k/μL
Hgb	14.3	11.6	14–18 g/dL
Hct	42	35.5	39–50%
Plts	378	343	140–340k/μL
Neutrophil (%)	73	61	35–71%
Lymphocyte (%)	19	27	25–45%
Monocyte (%)	7	9	0–10%
Basophil (%)	0	0	0–2%
Eosinophil (%)	1	3	0–6%
Neutrophil, absolute	10	6.1	1.7–8.5 k/μL
Lymphocyte, absolute	2.7	2.7	1.2–5.4 k/μL
Monocyte, absolute	1	1	0–1.2 k/μL
Basophil, absolute	0	0	0–0.2 k/μL
Eosinophil, absolute	0.1	0.3	0–0.7 k/μL

Hct = hematocrit; Hgb = hemoglobin; Plts = platelets; WBC = white blood cell count.

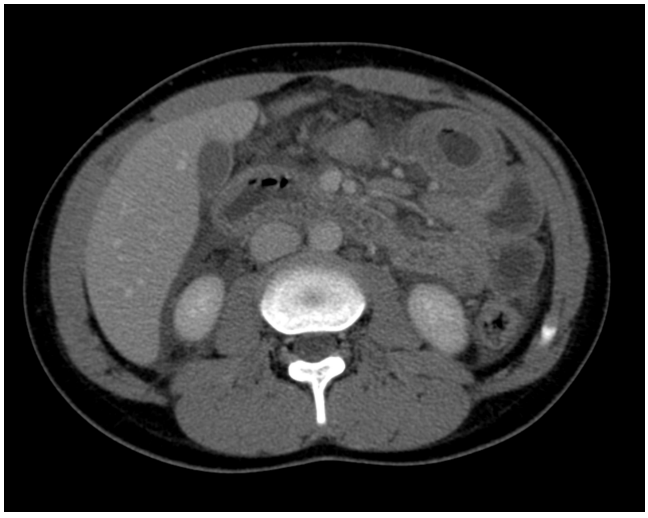

Figure 1. *Computed tomography scan showing bowel wall edema.*

QUESTIONS

What Is the Differential Diagnosis?

a. Abdominal lymphadenopathy resulting in intussusception
b. Acute appendicitis
c. Hereditary angioedema (HAE) with abdominal exacerbation
d. Viral gastroenteritis

Viral gastroenteritis is a common cause of abdominal pain and vomiting in children. However, our patient already had a CT scan of the abdomen suggesting another cause for his presentation. His white blood cell count was elevated on presentation with neutrophil predominance, which along with abdominal pain and vomiting puts acute appendicitis in the differential. However, white blood cell count elevation in this case was presumably caused by stress/dehydration because it reverted to normal the next day. Elevated white blood cell count can be seen in HAE abdominal exacerbations. The CT scan showed small bowel intussusception but failed to identify a cause for it.

Table 2 **Complement studies**

Test	Results	Reference Range
Serum C4	<8	14–44mg/dL
C1-INH	3	11–26mg/dL

C1-INH = C1 esterase inhibitor.

What Additional Laboratory Data Would Be Helpful in Arriving at a Diagnosis for This Patient?

a. Serum C1
b. C3
c. C4
d. CH50

The single best screening test for diagnosis of HAE is serum C4. Because of the history of recurrent swelling, the Pediatric Surgery Service was concerned with the possibility of exacerbation of angioedema with surgery and wanted an allergy consult for perioperative management. After the Allergy Service was consulted, we considered that HAE can cause bowel wall edema. Theoretically, this edema can serve as a lead point for intussusception that would explain the patient's presentation. In light of this, we ordered serum C4, which confirmed the diagnosis (Table 2). In HAE C1 is not affected. C3 is often abnormal in systemic lupus erythematosus and other diseases with excessive immune complex formation but is usually normal in HAE. CH50 is also unlikely to be affected in HAE and is used as a screening for complement deficiency.

We reviewed the literature to see if small bowel or other types of intestinal intussusception had been previously reported in association with HAE. A literature search was conducted using PubMed search engine and keywords, HAE, hereditary angioedema, and intussusception. Three reports of colocolic intussusception and one report of colorectal intussusception are reported in patients with HAE. No previous report of small bowel intussusception was found in association with HAE. Because intussusceptions can result from a pathological lead point, a repeat CT scan was considered to rule out any other pathology for the current episode of intussusception.

TREATMENT AND CLINICAL COURSE

Surgery was deferred on the recommendations of the allergy consult team. The patient received ondansetron

intramuscular injection and his vomiting improved. He was put on bowel rest and given i.v. fluids. Two units of fresh frozen plasma were transfused. On the subsequent day, his symptoms resolved, his diet was advanced, and he was later discharged home. A follow-up outpatient CT scan of the abdomen was obtained, which was normal. On contacting his primary allergist it was found that he had been worked up for HAE and a low serum C4 level had been documented at some point in the past. At that point, no therapy was offered to him because due to his prepubertal age he was not a candidate for prophylactic androgen therapy. Unfortunately, this history was not forthcoming from his foster parents during his hospital stay. He remained asymptomatic at follow-up and was subsequently started on prophylactic therapy with danazol.

DISCUSSION

HAE is characterized by recurrent, unpredictable episodes of swelling affecting the extremities, face, abdomen, urogenital tract, or upper airway. It is mostly inherited in an autosomal dominant fashion but can also result from spontaneous mutations (20–25% of cases). The gene mutation is located on chromosome 11. Two main types are identified. Type 1 occurs in 80–85% and is caused by quantitative deficiency of C1 esterase inhibitor (C1-INH). Type 2 occurs in 15–20% and is caused by normal or elevated levels of C1-INH protein that is functionally abnormal. C1-INH plays an important role in inhibition of the complement, fibrinolytic, and contact systems. Deficiency of C1-INH leads to activation of these systems thereby leading to overproduction of bradykinin. This bradykinin leads to vasogenic edema resulting in the classic symptoms of the disease. Involvement of gastrointestinal mucosa/submucosa can result in symptoms such as abdominal pain, vomiting, and diarrhea. This presentation can mimic acute surgical conditions leading to unnecessary abdominal surgeries.[1]

Diagnosis is based on thorough personal and family history as well as low serum levels of C4. As noted previously, up to 25% of patients may not have a family history and are due to spontaneous mutations resulting in HAE. Type 1 HAE will be expected to have low levels of C1-INH and low function, but type 2 has normal and at times high levels of the protein, but the protein functions poorly and thus the C1-INH functional level is low. The combination of low serum C4 and low C1-INH function is 98% specific for C1-INH deficiency; however, in the United States the functional assay is not sensitive or specific.[2] Genetic testing is also available at some research laboratories. Similar to cystic fibrosis, the failure to document a preexisting mutation does not eliminate the diagnosis of HAE.

Acute management includes supportive care including pain management and fluid replacement. There is no Food and Drug Administration–approved drug for acute treatment in the United States. Fresh frozen plasma replaces C1-INH and has been used with good results and without significant adverse events despite previous concerns regarding possible worsening of acute exacerbations.[3] C1-INH human concentrate (Cinryze; ViroPharma, Exton, PA) has recently been approved for prophylactic treatment. It is available for treatment of acute exacerbations *via* research protocols at sites involved in clinical trials and can be used off label for acute exacerbations if available. Ecallantide (Dyax, Cambridge, MA) is undergoing review by the Food and Drug Administration for the treatment of acute attacks of HAE. Danazol, an attenuated androgen, has been the conventional agent for prophylaxis and has been used at high doses for acute exacerbations, but the activity is dependent on up-regulation of proteins and thus the benefit is delayed making it unlikely to benefit acute exacerbations.[4] Other drugs under investigation for therapy of acute exacerbations include icatibant (Shire, Wayne, PA), and C1-INH (Viropharma, Exton, PA; CSL Behring, King of Prussia, PA; and Pharming, Leiden, The Netherlands).[5]

Our literature search identified four previous reports of large bowel intussusception in association with HAE. A case report in the French literature describes a 15-year-old girl with HAE and colocolic intussusception.[6] One adult patient with HAE had colocolic intussusception affecting the transverse colon and required surgery, during which he received C1-INH infusion.[7] Another 13-year-old girl with HAE had recurrent colocolic intussusception and was treated with air reduction enemas with each of her four episodes of colocolic intussusception.[8] Lastly, a 21-year-old man with HAE had protracted abdominal pain that failed to respond to C1-INH infusion. A CT scan was subsequently done, which revealed extensive colorectal intussusception. He ultimately required surgical intervention. The intraoperative examination suggested initiation of intussusception by local mucosal edema in the transverse colon.[9]

Intussusception of the colon has been described as a rare complication of HAE.[10] However, small bowel intussusception has not been previously described in association with HAE. Small bowel intussusception is seen mainly in young children, usually <6 years of age. The majority of the cases in young children are idiopathic or related to enteric viral infections. Pathological lead points, which can be identified in approximately one-fourth of cases, include Meckel diverticulum, polyps, small bowel lymphoma, duplication cysts, vascular malformations, inverted appendiceal stumps, parasites (*e.g.*, ascaris lumbricoides), Henoch-Schönlein purpura, cystic fibrosis, and hemolytic-uremic syndrome. Rare causes include inflammatory fibroid polyps of ileum, gastrointestinal stromal tumors, intestinal lipoma, eosinophilic enteritis, and blunt abdominal

trauma. Treatment modalities include pneumatic reduction and surgical intervention.

Final Diagnosis

Small bowel intussusception caused by HAE.

CONCLUSIONS

This case illustrates the varied presentation and difficult nature of diagnosing HAE. To the best of our knowledge, this is the first report of a case of small bowel intussusception caused by HAE. In previous case reports of patients with colocolic intussusception, most have been treated with pneumatic reduction or surgical intervention without a trial of HAE therapy. We found only one case where treatment with C1-INH was tried, and we suspect that it was not successful because of the extensive area of involvement. Our patient responded very well to fresh frozen plasma. Now that C1-INH is available in the United States, it appears to be the intervention of choice in patients with HAE and intestinal intussusception before more invasive procedures.

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Patient Oriented Problem Solving (POPS) Case Report

Recurrent stridor in a 9-year-old child after a choking and aspiration event

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ABSTRACT

This is a case report of a 9-year-old boy with new onset stridor 5 days after a choking event. Symptoms would last 5–45 minutes. His stridor was unresponsive to nebulized epinephrine but improved when he relaxed. Otlaryngology examination noted laryngeal irritation that was suggestive of gastroesophageal reflux (GER). Episodic stridor continued, despite treatment for GER, prompting hospitalization. On admission, barium swallow indicated hyperinflation of the left lung and bronchoscopy confirmed the aspiration of food. Within 12 hours of bronchoscopy, his stridor recurred. The recurrence of stridor after bronchoscopy resulted in further evaluation of his upper airway disorder. The true diagnosis was revealed during methacholine challenge. This case illustrates a unique presentation of a common upper respiratory disorder, the need for a high index of suspicion to make the diagnosis, and the importance of the multispecialty approach needed to treat patients with this disorder.

(Allergy Asthma Proc 31:154–157, 2010; doi: 10.2500/aap.2010.30.3271)

Key words: Allergic rhinitis, aspiration, asthma, choking, gastroesophageal reflux (GER), stridor, vocal cord dysfunction (VCD)

CASE PRESENTATION

Chief Complaint

Two-week history of recurrent stridor.

History of Present Illness

A 9-year-old boy was admitted for 2 weeks of intermittent stridor. Symptoms started 5 days after choking on macaroni. The Heimlich maneuver was used to dislodge the food. Episodes would start suddenly and last 5–45 minutes. His mother reported cyanosis during one of the events. On two occasions he received racemic epinephrine and corticosteroid treatment in the emergency room with minimal response. His stridor improved with relaxation. Rhinolaryngoscopy showed laryngeal irritation and the patient was empirically treated for gastroesophageal reflux (GER). Subsequent episodes of stridor, despite treatment with lansoprazole, prompted hospital admission for further evaluation. Medical history included five episodes of wheezing before the age of 3 years, eczema, pressure equilization tubes, and seasonal rhinitis. He lived at home with his parents and four siblings. He was an A/B student with no reported social stressors. Family history included maternal anxiety, asthma, and allergic rhinitis. His older brother had asthma and attention deficit hyperactivity disorder.

Physical Exam

On physical exam he was a polite and cooperative 9-year-old boy. Vital signs were normal. Examination of his nares showed pale, enlarged nasal turbinates and clear nasal discharge. Otherwise, his exam was unremarkable.

QUESTIONS

What Is the Differential Diagnosis for Recurrent Stridor?

Upper airway dysfunction secondary to trauma would be the most likely diagnosis; however, there was no laryngeal trauma noted by laryngoscopy (see Table 1).

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The local Institutional Review Board approved this study for exempt status under 45CFR46.102(d); IRB number 5379
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Table 1. **Differential diagnosis of stridor**

Trauma	Angioneurotic edema
Laryngomalacia	Vocal cord dysfunction
Tracheomalacia	Laryngeal webs
Infections (viral croup, epiglottis, bacterial tracheitis)	Head and neck cancers
Papillomas	Compressive injuries to the spine or brain
Inflammatory diseases—*i.e.*, Wegener's granulomatosis.	Foreign body or inhalation injury
Vocal cord paralysis	Hemangiomas
Myasthenia gravis	Vascular ring
Arnold-Chiari malformation	Aspiration secondary to GERD

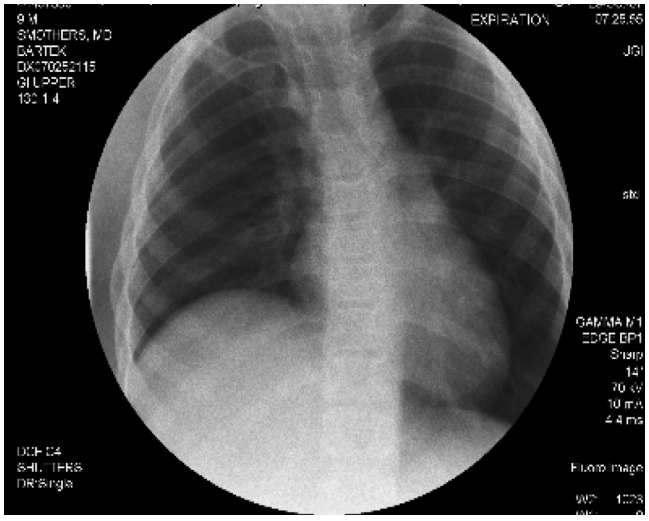

Figure 1. *Hyperinflation of the left lung noted during upper gastrointestinal esophagram.*

What Additional Diagnostic Tests Are Needed?

Complete blood count and chemistry should be considered if infection or metabolic derangements are suspected. Visual inspection of the upper and lower airway would exclude intrinsic and extrinsic anatomic abnormalities. If vocal cord dysfunction (VCD) is suspected, provocative testing may be helpful in making a diagnosis. Upper gastrointestinal esophogram would further characterize his esophageal reflux and evaluate for structural abnormalities that may contribute to symptoms. Neurological imaging should be done if history or physical are suggestive of central nervous system disease.

Clinical Course

On admission a barium esophagram revealed esophageal reflux and hyperinflation of the left lung (Fig. 1). The patient denied "heart burn" but his mother did note frequent burping and hiccups after meals. His admission pulmonary function test showed the ratio of FEV_1/FVC as 76% predicted and the $FEF_{25–75\%}$ as 70% predicted.

Bronchoscopy was performed twice and the repeat procedure revealed left lower lobe debris consistent with aspiration. Twelve hours after both bronchoscopies the patient developed stridor and chest pain. He received nebulized epinephrine with minimal improvement. Symptoms resolved with calming. Spirometry and laryngoscopy were unavailable during both episodes. Provocative testing with methacholine was recommended because of suspected VCD and marginal PFT results on admission. Bronchial challenge with escalating doses of Provocholine (0.001–10 mg/mL; Methapharm, Inc., Coral Springs, FL) was performed. His baseline PFT was improved from admission to normal. Chest tightness and throat discomfort were noted at 1.25 mg/mL of Provocholine without a decrease in FEV_1 or oxygen saturation. At 5 mg/mL, FEV_1 decreased by 10% and he complained of chest and throat tightness. Provocholine at 10 mg/mL concentration provoked stridor and accessory muscle use. Rhinolaryngoscopy confirmed paradoxical vocal cord adduction on inspiration. His vocal cords were symmetric with near complete adduction on inspiration. Both expiratory and inspiratory flow loops were affected (Fig. 2). His FEV_1 decreased by 57% but his oxygen saturation was >95%. A single dose of nebulized epinephrine was given but his symptoms resolved with calming. Abdominal breathing exercises were demonstrated before discharge. His instructions were to practice abdominal breathing two to three times daily and to use the maneuver if his stridor recurred. Speech therapy and psychological counseling were recommended.

Lansoprazole was continued because of his upper gastrointestinal esophagram findings and suggestive clinical symptoms. Allergy skin puncture tests were positive to grasses, consistent with his complaints of spring and summer rhinitis symptoms. Treatment with nasal steroids was initiated. His symptoms continued despite speech therapy and medical therapy for upper airway irritation. His parents were resistant to psychological evaluation until his symptoms became so frequent that he had to be removed from school. He was subsequently diagnosed with obsessive compulsive disorder and generalized anxiety disorder. Brain MRI was normal. Symptoms of VCD resolved when treatment for anxiety and obsessive compulsive disorder was added to the treatment plan.

DISCUSSION

VCD is a disorder characterized by paradoxical movement of the vocal cords, most commonly on in-

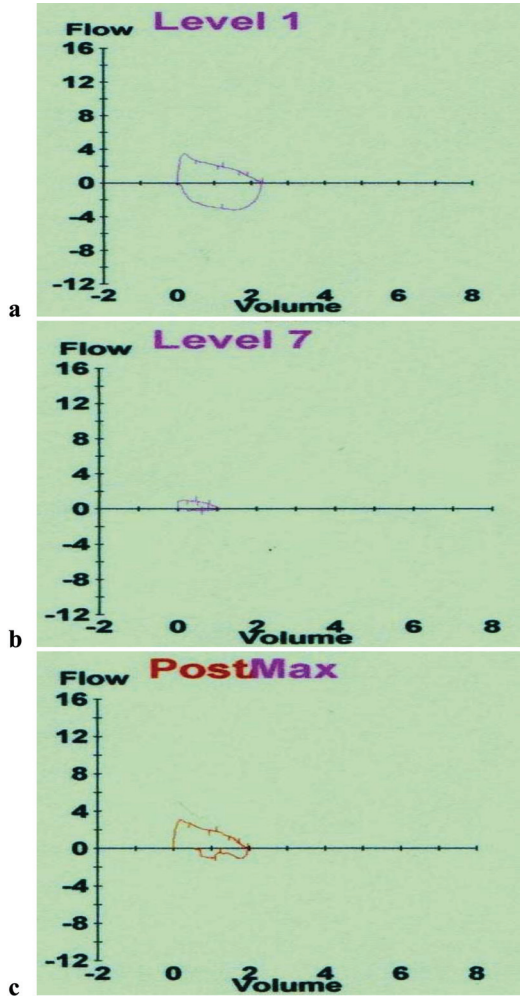

Figure 2. *(a) Normal flow volume loop (FVL) after 0.001 mg/mL of Provocholine. (b) Flattening of both inspiratory and expiratory FVL after 10 mg/mL of Provocholine. Inspiratory and expiratory stridor present. (c) Repeat FVL during the patient's recovery from the acute stridor event. There is persistent truncation of the inspiratory flow loop.*

spiration.[1] This disorder often presents as poorly controlled asthma or recurrent stridor. There are two clinical subtypes, exercise induced VCD (EIVCD) and spontaneous VCD (SVCD). EIVCD occurs in high-performance athletes during exercise. Patients with SVCD are frequently high-achieving adolescent or adult female patients.[2] Children with VCD will often have an above average IQ and are driven to perform well in academics or in competitive sports.[3] Risk factors for VCD include female gender, GER, rhinitis, sinusitis, asthma, airway trauma (intubation), psychological stressors, psychiatric disease, and medical training.[2,4–8]

The overall prevalence of VCD is unknown.[9] VCD is often misdiagnosed as asthma, but asthma coexists in 56% of patients with VCD.[9] Patients with VCD often present with a history of recurrent wheezing or poorly controlled asthma.[6] A history of recurrent stridor should prompt the appropriate evaluation. Stridor history is often absent in patients with VCD. Dysphonia during or after "wheezing" episodes, rapid resolution of respiratory distress with calming, complaints of tightness in the throat or upper chest, and costochondritis are all suggestive of VCD.[1] Having a high index of suspicion is necessary to identify possible VCD patients.

The aforementioned case presentation of a 9-year-old boy with a choking and aspiration event who subsequently developed recurrent stridor 1 week after the event is a unique presentation for VCD. An extensive search of the literature did not reveal any other reports of VCD after a choking or aspiration events.

The patient described in this report did not have a history of stridor but he did have evidence of both allergic rhinitis and GER, which may have contributed to upper airway inflammation but were unlikely causal in this patient's VCD. The airway trauma from his choking event triggered his VCD. There are reports in the literature of VCD after intubation and other forms of upper airway trauma.[8] Weinberger *et al.*[10] described a case of a 15-year-old girl who developed both EIVCD and SVCD after two episodes of allergen-induced laryngeal edema. This case was similar to ours in that recurrent VCD was incited by a traumatic upper airway event. It is reasonable to infer that a combination of esophageal reflux, rhinitis, and an underlying psychiatric disorder may have perpetuated our patient's symptoms.

The diagnosis of VCD was considered in this patient because of the episodic nature of the symptoms, lack of anatomic abnormalities on bronchoscopy, and improvement of symptoms with calming and relaxation. Visualization of paradoxical adduction of the vocal cords during inspiration by rhinolaryngoscopy confirmed VCD in this patient.[9] In VCD, adduction of the cords occurs usually during inspiration, but may occur on expiration. Classically, there is anterior closure of the cords and a posterior diamond-shaped "chink" opening; however, closure of the cords can be complete, including the overlap of the false cords. This type of cord closure has been described in younger patients and is more consistent with the cord movement described in our patient.[3,11] The diagnostic dilemma of VCD is that often rhinolaryngoscopy may be normal between episodes of stridor. Provocation testing with methacholine, histamine, or exercise may be useful to reproduce symptoms and allow confirmation of VCD by laryngoscopy.[12–14] A negative response to provocative testing does not rule out the diagnosis of VCD. Perkins *et al.*[12] showed that methacholine challenge had a high specificity but low sensitivity when used to diagnose VCD. PFT findings acutely, if laryngoscopy is not available, may be suggestive of the diagnosis. A

ratio of the FIF_{50}/FEF_{50} of ≥1 or a truncation of the inspiratory flow loop supports the diagnosis of VCD.[2] However, recently, Watson *et al.*[15] recently evaluated the use of spirometry for the diagnosis of VCD and found that none of spirometric variables were predictive. The study was limited because spirometry was not performed when the patients were acutely symptomatic. Fluoroscopy has also been used to make the diagnosis of VCD.[16] Videostroboscopic laryngoscopy, often used by speech pathology, can be used to diagnose VCD in the absence of acute symptoms.[3] Finally, Davis *et al.*[17] showed the use of parental videography in the diagnosis of VCD. This approach would be a very inexpensive way to collect clinical information considering the unpredictable nature of VCD. Patients with suspected VCD should have laryngoscopy to rule out structural abnormalities or unilateral vocal cord paralysis, which may suggest the presence of a more serious systemic disease.

Acute treatment of VCD may include calming through diaphragmatic breathing or sedation. Heliox has been used to relieve acute symptoms. In extreme cases, patients have been treated with intubation or tracheostomy. Unilateral paralysis of a vocal cord, with surgery or botulinum toxin injections, has also been used to treat severe cases.[18] Long-term treatment for VCD is multifaceted. Patients should be instructed to practice abdominal breathing exercises daily and to use the technique during acute episodes.[3,6,8] Treatment of possible triggers, such as upper and lower respiratory tract infections, GER, allergic rhinitis, and asthma, is essential to controlling VCD symptoms. Referrals to speech therapy and psychology are also critical. Speech therapists can help the patient recognize the onset of symptoms and show techniques to extinguish acute events.[3] Psychological stressors, anxiety and depression, are frequently associated with VCD and, if left untreated, VCD symptoms are likely to continue.[13] Ipratropium inhalation treatments may be useful for preexercise prophylaxis of EIVCD.[2] Barriers to successful treatment include poor acceptance of the diagnosis, failure to treat comorbid illnesses, and failure to follow-up with recommendations.

Final Diagnosis

The final diagnosis was VCD.

CONCLUSION

This is the first case report of a choking episode precipitating VCD. This case also shows the utility of provocation testing for the diagnosis of VCD and outlines the importance of the multispecialty approach needed to successfully treat patients with VCD. Our patient's initial treatment failure was secondary to the family's partial acceptance of the diagnosis and reluctance to persue psychological evaluation. Poor acceptance of the diagnosis is a common challenge when treating patients with VCD; however, patience and continued education can help to overcome these challenges.

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Patient-Oriented Problem Solving (POPS) Case Report

Seventy-four-year-old woman with myelodysplastic syndrome and splenomegaly

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ABSTRACT

We present a 74-year-old woman with a recent diagnosis of myelodysplastic syndrome who presented with left upper quadrant abdominal pain and fatigue with significant splenomegaly, anemia, and thrombocytopenia. She underwent splenectomy and bone marrow biopsy. Pathology of both spleen and bone marrow revealed an unusual diagnosis. A review of the differential diagnosis, laboratory tests, nature of the underlying disease, and treatment are provided.

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Key words: D816V, hematologic non–mast cell lineage disease, hypersplenism, mast cells, mastocytosis, myelodysplastic syndrome, splenomegaly, systemic mastocytosis with associated clonal, urticaria pigmentosa

CASE PRESENTATION

Chief Complaint

Left upper quadrant abdominal pain.

History of Present Illness

A 74-year-old woman with gastroesophageal reflux disorder, hypothyroidism, osteoporosis, history of breast cancer currently in remission, and recent diagnosis of myelodysplastic syndrome (MDS) presented with progressively worsening left upper quadrant abdominal pain for 4 months. The patient was diagnosed with refractory cytopenia with multilineage dysplasia, a category of MDS, just over a year before presentation. Report of a bone marrow biopsy done at the time showed dysplastic changes in the megakaryocytes and in the myeloid precursors and a cytogenetic analysis showed a 20q deletion. She had received erythropoietin injections for her anemia at an outside facility but this was refractory to treatment and she required several transfusions.

The patient first developed the left upper quadrant abdominal pain 4 months before presentation. She described it as a chronic "tight" discomfort with acute episodes of sharp pain. She also noted a fullness and then a bulge in the area. Eventually, she was able to feel a mass in her upper abdomen that was painful and very tender to touch. The pain did not radiate and was worsened by movement, cough, and deep breathing. She denied any nausea/vomiting, hematochezia, or melena as well as any skin complaints. At the same time these symptoms developed, the patient noted that she would tire easily. She was found to be anemic, and it became necessary to give her red blood cell transfusions. Serial transfusions were necessary and increased in frequency from every 3 weeks to every 2 weeks. A CT scan at the time revealed a splenic hematoma. There was no history of trauma to her abdomen. She was transfused at that time without surgical intervention.

Her abdominal pain continued to increase in frequency and severity. Repeat CT scan done 1 month before presentation showed increased spleen size of 13.5 cm in anteroposterior diameter with subcapsular splenic hemorrhage without active bleeding. She was seen by her primary care physician and was found to be profoundly anemic with a hemoglobin of 6.6 g/dL in the clinic and was admitted to the hospital for further workup.

The patient's medical history is positive for hypothyroidism, currently euthyroid, osteoporosis, gastroesophageal reflux disorder stable on esomeprazole, MDS, and history of breast cancer over 15 years ago s/p modified radical mastectomy with cancer in remission. Her medications include sucralfate, esomeprazole, and triamterene-hydrochlorothiazide as well as thyroid replacement. Her family history is significant for a brother who died at age 18 years from Hodgkin's lymphoma and a sister who also has MDS. Her mother

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is deceased and had diabetes mellitus and breast cancer. Her father is also deceased because of heart problems. Her social history is significant for a remote history of smoking (quit in 1967).

She is a social drinker. Current review of systems is notable for fatigue, left upper quadrant (LUQ) abdominal pain, daily night sweats, and mild dyspnea on exertion. She denied any cardiac, skin, or neurological problems.

Physical Examination

Vital signs included a temperature of 38°C, a respiratory rate of 20, and elevated blood pressure of 132/70 with tachycardia to 105. Oxygen saturation on room air was 96%. General examination revealed an age appropriate woman, alert and oriented in mild distress.

Head, eyes, ears, nose, and throat examination was significant for mild scleral icterus and pale conjunctivae, and neck exam showed no significant lymphadenopathy or jugular venous distention. Examination of the chest showed clear lung fields and the right breast was reconstructed with a well-healed scar. Cardiac examination was positive for tachycardia but without murmurs. Abdominal exam elicited tenderness in the LUQ with palpable splenic margin. Liver span was normal. Neurological exam was normal and the skin showed no rashes or lesions.

Laboratory and Imaging

Initial admission laboratory values are outlined in Table 1. Notable values include hemoglobin and hematocrit of 7.0 g/dL and 24.2%, respectively, with a normal mean corpuscular volume. Platelets were also low at $57 \times 10^3/\mu L$. Chemistry labs were most significant for a lipase of 324 U/L and bilirubin of 2.4 mg/dL with conjugated bilirubin 0 and direct Coombs negative. Further workup showed an elevated lactate dehydrogenase (LDH) of 1236, normal haptoglobin, and hepatitis A antibody positive; however, hepatitis B and C studies were negative. CT of the abdomen showed increasing size of the spleen to 17.1 cm in greatest anteroposterior dimension (Fig. 1), previously measuring 15.3 cm 1 month prior. The spleen appeared heterogeneous with a hyperdense rim, suggestive of recent hemorrhage. There was also a right lower pulmonary nodule that was stable and a new nodule in the right middle lobe, as well as interim development of bilateral pleural effusion. Lymph nodes were not enlarged.

Clinical Course

The patient continued to require significant transfusions; thus, splenectomy was performed. The spleen weighed 1440 g, which is approximately 7–10 times larger than normal. She tolerated the procedure well and her postoperative course was uneventful. Pneumococcal, meningococcal, and *Haemophilus influenza*

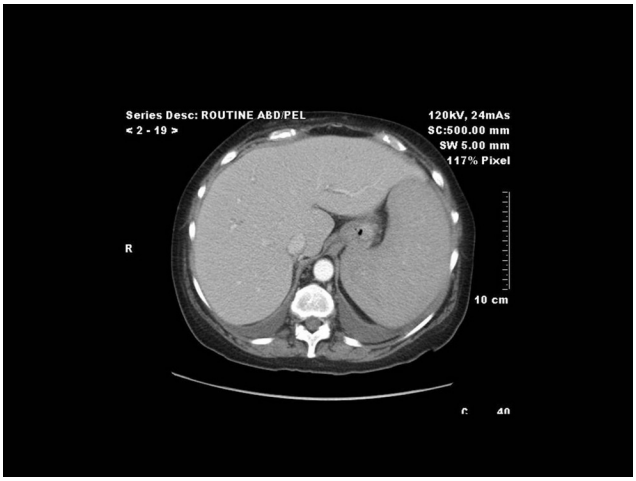

Figure 1. *CT scan of the abdomen shows enlargement of the spleen, measuring 17.1 cm in greatest anteroposterior dimension. The spleen in heterogeneous with a hyperdense rim suggestive of new blood.*

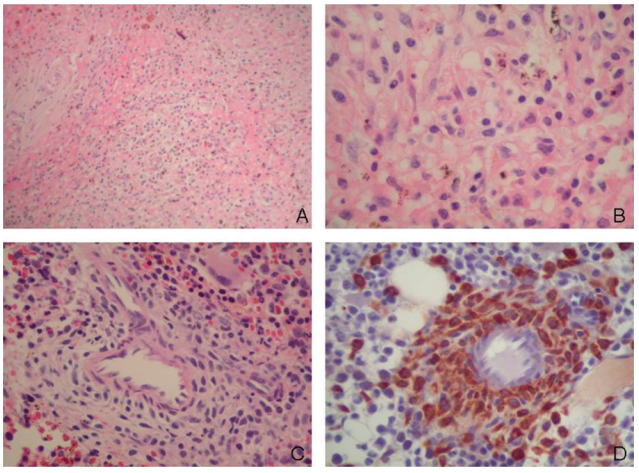

Figure 2. *(A) (Spleen hematoxylin and eosin (H&E) stain 100×) Loss of normal architecture of the spleen. (B) (Spleen H&E 500×) Infiltration of the spleen by >15 cells with abundant cytoplasm in aggregates. (C) (Bone marrow H&E 500×) Cells with clear cytoplasm surrounding blood vessels and trabeculae. (D) (Bone marrow tryptase 500×): The cells stain positive for tryptase indicating mast cells.*

immunizations were administered before discharge from the hospital. The need for red blood cell transfusions ceased immediately after the surgery, and the platelet count very quickly returned to normal. Hemoglobin was stable at 10.8 g/dL, and platelets were $510 \times 10^3/\mu L$. Pathology reports of the spleen revealed significant mast cell infiltration, extramedullary hematopoesis, and hemorrhage (Fig. 2). The spleen was stained for CD117 and the vast majority of cells stained positive. Bone marrow examination showed morphological evidence of trilineage dysplasia in >10% of erythroid, granulocytic, and megakaryocytic cell lines with <5% blasts. These findings confirmed the pre-

Table 1 **Initial laboratory data**

Laboratory	Value (Reference Range)
White blood cell $\times 10^3$	8.4 (4.0–10.0/mm^3)
Red blood cell$\times 10^6$	2.64 L (3.90–5.30/mm^3)
Hemoglobin	7.8 L (11.5–15.5 g/dL)
Hematocrit	24.2 L (34.0–45.0%)
Mean corpuscular volume	91.7 (80.0–96.0 fL)
Mean corpuscular hemoglobin	29.5 (27.0–32.0 pg)
Mean corpuscular hemoglobin concentration	32.2 (31.0–37.0%)
Red blood cell distribution width	19.0 H (11.6–14.0%)
Platelets $\times 10^3$	57 L (150–400/mm^3)
Mean platelet volume	11.1 (8.0–12.0 fL)
Nucleated red blood cells/100 white blood cells	Occasional
Peripheral Smear	Polychromasia 2+ Elliptocytes/ovalocytes 2+ Schistocytes 1+ Basophilic stippling present
Gran (%)	58.1 (40.0–73.0%)
Lymph (%)	28.3 (18.0–53.0%)
Mono (%)	13.2 H (4.0–12.0%)
Reticulocyte (%) and absolute	Reticulocyte % 6.43 H Reticulocyte absolute 0.284 $\times$ 106/μL H (0.03–0.09)
Direct antiglobulin test	Negative
Prothrombin time/Activated partial thromboplastin time	Within normal limits
Chem 7	Normal except for glucose 201 H (70–110 mg/dL)
Calcium	8.0 L (8.6–10.6 mg/dL)
Magnesium	1.7 (1.7–2.4 mg/dL)
Total bilirubin	2.4 H (0.1–1.1 mg/dL)
Conjugated bilirubin	0
Unconjugated bilirubin	2.4 H (0.1–1.1 mg/dL)
Hepatitis A Ab	Positive
Hepatitis B surface Ag and Ab	Negative
Hepatitis C Ab	Negative
T Protein	6.5 (6.3–8.2 g/dL)
Albumin	3.4 L (3.5–5.0 g/dL)
Alk Phosph	133 H (34–122 U/L)
Alanine transaminase (serum glutamic pyruvic transaminase)	21 (9–51 U/L)
Aspartate transaminase (serum glutamic oxaloacetic transaminase)	43 H (13–40 U/L)
Lipase	324 H (0–220 U/L)

vious diagnosis of refractory cytopenia with multilineage dysplasia. In addition, the bone marrow biopsy showed >15 perivascular mast cell aggregates with >25% spindling (Fig. 2). Tryptase level was subsequently ordered and found to be markedly elevated at 302 μg/L (reference range, 0.4–10.9 μg/L).

QUESTIONS

What Is the Differential Diagnosis?

Splenomegaly has numerous etiologies, including infectious (*e.g.*, viral hepatitis, Epstein–Barr virus, and tuberculosis), inflammatory disorders (*e.g.*, Felty's syndrome and systemic lupus erythematosus), congestive splenomegaly usually caused by liver cirrhosis, hematologic disorders (*e.g.*, hemolysis and malignancy, particularly, myeloproliferative disorders), storage diseases, and miscellaneous causes such as amyloidosis, cysts, and mastocytosis.[1] Hypersplenism is characterized by splenomegaly, cytopenia, and normal or hyperplastic cellularity of bone marrow, with evidence of increased cell turnover such as reticulocytosis.[1] The cytopenia resolves with splenectomy. Hypersplenism

Table 2 **World Health Organization criteria for the diagnosis of systemic mastocytosis**

Major	Multifocal dense infiltrates of mast cells in (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)*
Minor	a. Mast cells in bone marrow or other extracutaneous organs show an abnormal (spindling) morphology (>25%)*
	b. c-kit mutation D816V or other activating mutation of codon 816 in extracutaneous organs*
	c. Mast cells in the bone marrow or extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers*
	d. Serum tryptase >20 ng/mL (does not count in patients who have an associated clonal myeloid disorder)

**Fulfillment of criterion by patient.*
Diagnosis criteria fulfilled if one major and one minor or three minor criteria were met.[3]

can be primary or secondary. Common secondary causes are infectious, inflammatory processes such as systemic lupus erythematosus, congestive splenomegaly, storage disorders, malignancy, chronic hemolytic disorders, myeloproliferative disorders, and splenic malformations. Hypersplenism is not a typical feature of MDS and thus its presence arose suspicion of another pathological process underlying the splenomegaly.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

In a patient presenting with MDS, splenic hemorrhage, splenomegaly, and cytopenia, additional studies should include hepatitis A, B, and C serologies and antinuclear antibody as well as workup for hemolysis, such as a peripheral blood smear, LDH, Coombs, and haptoglobin. The peripheral smear showed polychromasia, elliptocytes, and ovalocytes and basophilic stippling as well as rare schistocytes. The polychromasia was a reflection of the increased reticulocyte count. Reticulocytes appear as polychromatophilic cells on the routine blood smear. The elevated reticulocyte count resulted from the extensive hemorrhage into the spleen. Basophic stippling is sometimes seen in the presence of massive bleeding into tissues. The presence of ovalocytes or schistocytes may possibly be explained by some red cells that might have been fragmented while passing through the spleen engorged with massive numbers of red cells. LDH was elevated; however, Coombs was negative and haptoglobin was normal; thus, an immunologic hemolytic process was less likely. Our patient's hepatitis A serology was positive, likely indicating vaccination or prior infection. Her hepatitis B and C serology and antinuclear antibody were negative. Ultimately, the final diagnosis was made with the pathological examination of the splenectomy and bone marrow specimens that revealed aggregates of mast cells, consistent with the diagnosis of systemic mastocytosis (SM).

DISCUSSION

Mastocytosis is a heterogeneous entity characterized by the abnormal growth and accumulation of mast cells in one or more organ systems. The clinical manifestations of mastocytosis typically include skin symptoms such as flushing and pruritus, gastrointestinal (GI) symptoms, syncope, anaphylaxis, osteoporosis, organomegaly, and/or cytopenia.[2] The most common skin lesions are those of urticaria pigmentosa, which typically present with fixed red–brown maculopapular lesions that intensify with rubbing, the so-called "Darier's sign." Our patient had no cutaneous symptoms although she did have some GI complaints along with the splenomegaly and cytopenia. She also had osteoporosis, which would not be unexpected given her age. It is estimated that ~80% of all mastocytosis patients have skin involvement; however, in SM, skin lesions occur in ~50% and more often are observed in those with an indolent course.[3] As a general rule, in the evaluation of patients with SM, the lack of skin lesions should arouse suspicion for an aggressive mast cell disorder, although there are certainly subvariants without skin lesions that are more benign.[4]

The World Health Organization has devised diagnostic criteria for mastocytosis (Table 2).[3] The diagnosis is established if one major plus one minor or three minor criteria are met. The major criterion involves identification of at least 15 aggregating mast cells (MC) in biopsy from the bone marrow or other extracutaneous sites.

Mediators such as tryptase may be measured in the serum as surrogate markers, which may aid in the diagnosis of mastocytosis. A serum tryptase of >20 ng/mL is a minor criterion for diagnosis, although this does not apply in patients with systemic disease with associated clonal hematologic non-MC lineage disease. Elevated tryptase levels may also be observed in MDS, hypereosinophilic syndrome, and myeloid malignancies, as well as renal failure.[5] CD25 and CD2 are markers of aberrant mast cells found commonly in SM and also qualify as a minor criterion. Other minor criteria

include atypical morphology of mast cells as well as demonstration of mutation at codon 816 of c-kit.[3]

The World Health Organization has also devised a classification schema for mastocytosis to include variants and subvariants: (1) cutaneous mastocytosis (CM), which includes urticaria pigmentosa, diffuse CM, mastocytoma of skin, and telangiectasia macularis eruptiva perstans; (2) indolent SM, which includes smoldering SM and isolated bone marrow mastocytosis; (3) SM with an associated clonal hematologic non-MC lineage disease (SM-AHNMD); (4) aggressive mastocytosis, which includes lymphadenopathic mastocytosis with eosinophilia; (5) mast cell leukemia; (6) mast cell sarcoma; and (7) extracutaneous mastocytoma.[3] CM limited to the skin is often diagnosed in children but is uncommon in adults, who tend to have more systemic disease.[4] Thus, children with isolated urticaria pigmentosa without hepatosplenomegaly, lymphadenopathy, or cytopenia need not undergo bone marrow biopsy, although it is recommended that adults with skin lesions should undergo bone marrow evaluation.[5] The bone marrow is the most commonly involved extracutaneous site but the GI tract, lymph nodes, liver, and spleen may also be affected.[6] Our patient had a concurrent hematologic disease (*i.e.*, MDS) which places her into the category of SM-AHNMD. The more common hematologic disorders associated with mastocytosis include chronic myelomonocytic leukemia, acute myelogenous leukemia, and myeloproliferative disease as well as MDS.[7,8] Mast cell leukemia is defined by the presence of >20% mast cells in bone marrow as well as ≥10% of mast cells in the peripheral white blood differential and is associated with a poor prognosis.[4,6,9]

Systemic mastocytosis may be further classified based on the presence of B and C findings. B findings suggest a high MC burden but without organ dysfunction. These include (1) infiltration of MC in bone marrow of >30% on histology and/or tryptase of >200 ng/mL; (2) hypercellular bone marrow with dysmyelopoesis without cytopenias, MDS, or acute myeloproliferative disorders; and (3) organomegaly such as palpable hepatomegaly, splenomegaly, or lymphadenopathy without impaired organ function. C findings, on the other hand, characterize aggressive mastocytosis and indicate impaired organ function: (1) cytopenia; (2) hepatomegaly with impaired liver function, ascites, and/or portal hypertension; 3) osteolyses and/or severe osteoporosis causing pathological fractures; (4) palpable splenomegaly with hypersplenism; and (5) malabsorption with weight loss.[3] B findings without C findings are suggestive of indolent SM; however, the presence of C findings indicate aggressive mastocytosis.[10]

In most patients with SM, the mutation is in the c-kit gene. The c-kit proto-oncogene encodes the tyrosine kinase–type receptor, which interacts with the cytokine stem cell factor to promote proliferation and differentiation of mast cells from progenitors.[11,12] The most common mutation identified in 95% or more of adults with SM is a substitution of valine for aspartic acid (D816V), which is a gain of function mutation.[3,11] Interestingly, most patients with the mutation have indolent disease; thus, it has been suggested that the mutation by itself is insufficient to cause oncogenic transformation.[13] Patients with SM-AHNMD may also have other genetic defects, such as RUNX1-RUNX1T fusion gene in SM associated with acute myelogenous leukemia, and JAK2 V617F in SM associated with myeloproliferative neoplasms.[3]

Patients with clinical manifestations of mastocytosis with eosinophilia, which this patient did not have, may have mutations in the platelet-derived growth factor receptor α (FIP1L1-PDGFRα).[5] This was not pursued as this mutation without eosinophilia is highly unlikely (Todd Wilson, D.O., Staff Clinician, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, personal communication). It has been shown that the D816V SM with eosinophilia is a clinically distinct entity from FIP1L1-PDGFRα hypereosinophilic syndrome[13] and these latter patients should be classified as having a myeloid neoplasm with eosinophilia and rearrangement of PDGFRα.[3]

There are currently no curative treatments for mastocytosis; thus, management consists of alleviation of symptoms caused by mediator release. Commonly used strategies use H_1- and H_2-histamine receptor blockers, leukotriene antagonists, cromolyn sodium, topical as well as systemic steroids, treatment of osteoporosis including bisphosphonates, and epinephrine for anaphylaxis.[9] Avoidance of triggering stimuli that may lead to mediator release of mast cells and subsequent anaphylaxis should be emphasized, which may include temperature extremes, heat, physical and emotional stress, alcohol, insect venoms, and certain medications such as nonsteroidal anti-inflammatory drugs and opioids as well as contrast dyes.[5,8] Methoxypsoralen and ultraviolet A may be helpful in those with skin lesions.[5] The D816V mutation is resistant to imatinib, in contrast to the FIP1L1-PDGFRα mutation, which tends to be responsive.[3,11] This is thought to be caused by the inability of imatinib to bind the activation loop of KIT, which is the structure that is altered in the mutation of the former.[5] Patients who are negative for the D816V mutation, however, may show benefit from imatinib.[14] SM with an associated hematologic disorder is treated separately as two issues, *i.e.*, treat the hematologic disorder as if the mastocytosis was not present, and treat the mastocytosis as if the hematologic disorder was not present.[12]

In patients with aggressive forms of mastocytosis, cytoreductive medications such as interferon α and cladribine (2-CdA) are first-line and second-line treatment options.[3,5,8] Interferon α has had equivocal results and is currently recommended in patients with slowly progressing aggressive SM or smoldering SM with a high mast cell burden.[6] It has been most helpful in decreasing mast

cell burden in the bone marrow, cytopenias, and osteoporosis and alleviating ascites.[8] Its use is limited by its side effects such as fatigue, bone pain, anorexia, and depression.[6] Cladribine is a nucleoside analog that has been found to be an effective treatment; however, response has been transient and incomplete.[5,6,15] Bone marrow transplantation has been performed in patients with aggressive disease with variable results.[5,6] Second-generation tyrosine kinase inhibitors such as PKC412 have had variable results,[5] although another tyrosine kinase inhibitor dasatinib was recently found to have efficacy along with chemotherapy in a case report of a patient with SM and acute myeloid leukemia.[16] Finally, splenectomy is occasionally required in aggressive mastocytosis and SM-AHNMD, particularly if there is massive splenomegaly associated with hypersplenism or portal hypertension.[6]

Prognosis is considerably variable. Children with CM have a favorable outcome and their disease may regress spontaneously before or during puberty.[3] Cutaneous lesions in adults, however, do not tend to regress. Patients with indolent disease may have a normal life expectancy, but patients with aggressive disease may survive only a few months to years. Indicators of a poorer prognosis include late onset of symptoms, absence of cutaneous lesions, cytopenia, hepatosplenomegaly, bone marrow hypercellularity, and elevated LDH and alkaline phosphatase.[3] The clinical course of patients with an associated hematologic malignancy is typically dictated by the hematologic malignancy.

The patient has continued to feel well postoperatively. Her cell counts have been stable and there have been no mast cells detected in her peripheral blood. She was subsequently evaluated at the National Institutes of Health and underwent repeat bone marrow biopsy, which showed >50% of the marrow replaced by CD2-, CD25-, and CD117-positive mast cells. Mutational analysis was negative for the D816V c-kit mutation; however, it was positive for the D816A KIT mutation.

Repeat tryptase was increased to 762 ng/mL (reference range, <11.5 ng/mL). She also showed increased numbers of monocytes in the peripheral blood (3.22×10^3 μL) and bone marrow, and this finding along with increased bone marrow blasts were suggestive of progression to chronic myelomonocytic leukemia. The bone marrow cytogenetic study also reconfirmed a 20q deletion in 10–20 metaphases, with an extra copy of chromosome X noted in two of the metaphases. BCR-ABL was negative. Because her cell counts are otherwise stable, she will be closely monitored for progression of her MDS to chronic myelomonocytic leukemia. She is also being managed with symptomatic treatment for her mastocytosis. Because the D816A mutation is also resistant to imatinib, this is not a viable option for her.

Final Diagnosis:

Systemic Mastocytosis with Associated Clonal Hematological Non-Mast Cell Lineage Disease [SM-AHNMD]

CONCLUSION

SM-AHNMD may present with hypersplenism without significant cutaneous or GI symptoms. There should be a high index of suspicion of aggressive disease in those patients without skin lesions.

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Patient Oriented Problem Solving (POPS) Case Report

A 41-year-old male with cough, wheeze, and dyspnea poorly responsive to asthma therapy

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ABSTRACT

Reactive airway disease is often triggered by an upper respiratory viral infection and readily responds to anti-inflammatory and bronchodilator therapy. The differential diagnosis for unresponsive disease includes poorly controlled asthma, noncompliance with medical regimen, vocal cord dysfunction, rhinosinusitis, gastroesophageal reflux disease or recurrent aspiration, foreign body aspiration, allergic bronchopulmonary aspergillosis, Churg-Strauss vasculitis, cardiac disorders such as congestive heart failure or mitral stenosis, or other pulmonary disorders such as chronic obstructive pulmonary disease, α-1 antitrypsin deficiency, interstitial lung disease, bronchiectasis, sarcoidosis, hypersensitivity pneumonitis, pulmonary embolism, cystic fibrosis, airway neoplasms, or laryngotracheomalacia. As is often the case, a meticulous history can expeditiously direct the clinician to the diagnosis, especially in a patient without a smoking, asthmatic, or atopic history.

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Key words: Aspiration, asthma, bronchoscopy, computerized tomography, cough, double-blind, dyspnea, hemoptysis, nodularity, placebo-controlled, randomized, sputum, viral infection

CASE PRESENTATION

Chief Complaint

The patient is a 41-year-old man who presents with respiratory symptoms over a 4-month period.

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History of Present Illness

The patient complained of wheezing, productive cough, chest tightness, and dyspnea, which started after an upper respiratory infection. He had three emergency room visits, was treated with nebulized bronchodilators and oral corticosteroids and two separate unremarkable chest radiographs. He had no previous respiratory complaints. An allergist performed allergy skin testing that was all negative. The patient was noted to have "asthma" on pulmonary function testing. Rhinopharyngoscopy showed no evidence of sinusitis or polyps. Computerized tomography (CT) of the sinuses was unremarkable. Endoscopy revealed no gastroesophageal reflux. He received five courses of oral corticosteroids. Treatment with a proton pump inhibitor for 2 months did not change his symptoms. The patient reported daily nocturnal shortness of breath and was using his rescue inhaler four to five times per day. He continued having difficulty working as a carpenter's aide.

His current medications included fluticasone/salmeterol inhalation discus, 500/50 1 puff b.i.d.; tiotropium, 1 puff daily; montelukast, 10 mg daily; esomeprazole, 40 mg daily; and albuterol, 2 puffs p.r.n. He denied any use of sedative or hypnotic drugs. He was a casual

smoker of 1–2 cigarettes/month and denied illicit drug use or excessive alcohol intake. Although his mother, sister, and brother were asthmatic, he denied any history of allergic disease.

Physical Examination

Vital signs were temperature of 98°F; heart rate, 59/minute; respiratory rate, 18/minute; O_2 saturation, 98%; and blood pressure, 122/76 mmHg. His ear, nose, and throat examination was normal. The neck was supple with no bruits or thyroid enlargement. The lungs revealed diffuse inspiratory and expiratory ronchi and wheezes. The heart revealed no S3, S4, or murmur. The remainder of the physical examination was normal.

QUESTION 1

Which of the following are included in the differential diagnosis of a patient with wheezing and no clinical response to maximal therapy for asthma?

A. Left ventricular failure, mitral stenosis
B. Bronchiectasis, cystic fibrosis
C. Vocal cord dysfunction
D. Gastroesophageal reflux disease, recurrent aspiration
E. Chronic obstructive pulmonary disease, α-1 antitrypsin deficiency
F. Interstitial lung disease, hypersensitivity pneumonitis, sarcoidosis
G. Allergic bronchopulmonary aspergillosis (ABPA)
H. Pulmonary embolism
I. Laryngotracheomalacia
J. Airway neoplasm, foreign body (FB)
K. Rhinosinusitis
L. Churg-Strauss vasculitis

QUESTION 2

What further studies would one consider at this point?

A. Pulmonary function testing
B. Complete cell count
C. IgE level
D. α-1 antitrypsin level
E. CT of chest
F. Fiberoptic bronchoscopy

Discussion of the Differential Diagnosis

The patient had no evidence of congestive heart failure and no heart murmur to suggest significant mitral stenosis. The patient had a normal chest radiograph, and CT of the chest revealed no parenchymal lung disease or airway wall abnormalities. This would make bronchiectasis, cystic fibrosis, interstitial lung disease, ABPA, sarcoidosis, hypersensitivity pneumonitis, and laryngotracheomalacia less likely to be responsible for his symptoms. The patient had minimal tobacco exposure that would make chronic obstructive pulmonary disease less likely. A normal chest radiograph with the absence of a family history for emphysema would make α-1 antitrypsin deficiency unlikely. The wheezing was not stridorous, there was no vocal cord dysfunction noted during rhinolaryngoscopy, and the CT of the sinuses was normal, excluding significant rhinosinusitis. The patient had a normal upper endoscopy and a lack of clinical improvement with a proton pump inhibitor made gastroesophageal reflux an unlikely cause of his symptoms.

The patient had no sinus symptoms, a lack of longstanding asthma, and no mononeuritis multiplex, making Churg-Strauss vasculitis unlikely. Recurrent aspiration was unlikely because the patient had no history of seizure disorder, cerebrovascular disease, parkinsonism, or other neurological or neuromuscular conditions that could lead to swallowing dysfunction.

Additional History

The patient reported having chicken soup for the upper respiratory infection. While sipping the soup, he felt as though something was inhaled into his lung. He subsequently developed violent coughing productive of brown sputum and several episodes of scant hemoptysis over the next 2 weeks.

Laboratory and Other Diagnostic Findings

A pulmonary function test revealed a mild obstructive ventilatory disorder with no bronchodilator response. The lung volumes and diffusion capacity were both within normal limits. The forced expiratory volume in 1 second/forced vital capacity was 67% of predicted and the forced expiratory volume in 1 second was 3.72 l/minute (91% of predicted). An α-1 antitrypsin level was 157 mg/dL.

The normal α-1 antitrypsin level and the normal diffusion capacity and lung volumes made α-1 antitrypsin deficiency and emphysema unlikely. The complete blood cell count revealed a white blood cell count of 5700 cells/mm^3 with 4% eosinophils. The IgE level was 30 IU/mL, making Churg-Strauss vasculitis and ABPA unlikely. The CT scan of the chest revealed a calcified density in the bronchus intermedius, near the right middle lobe and right lower lobe orifices (Fig. 1).

Bronchoscopy revealed a hard whitish lesion at the area noted on the CT scan. There was marked nodularity and inflammation in the area of the lesion (Fig. 2). With the use of forceps, a 1.5-cm chicken bone was removed (Fig. 3). Biopsies of the surrounding tissue revealed inflamed granulation tissue with severe acute and chronic bronchitis.

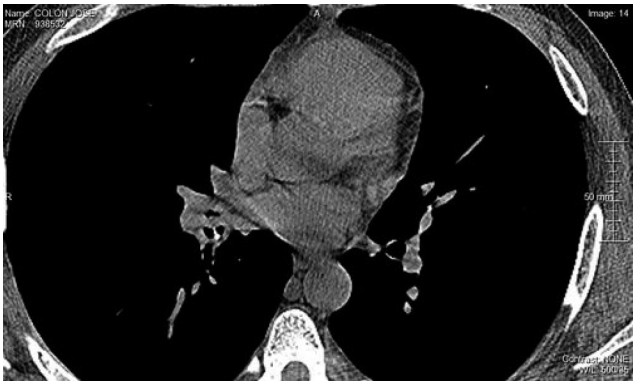

Figure 1. CT scan revealing small mass near bifurcation of the right middle and right lower lobe bronchi.

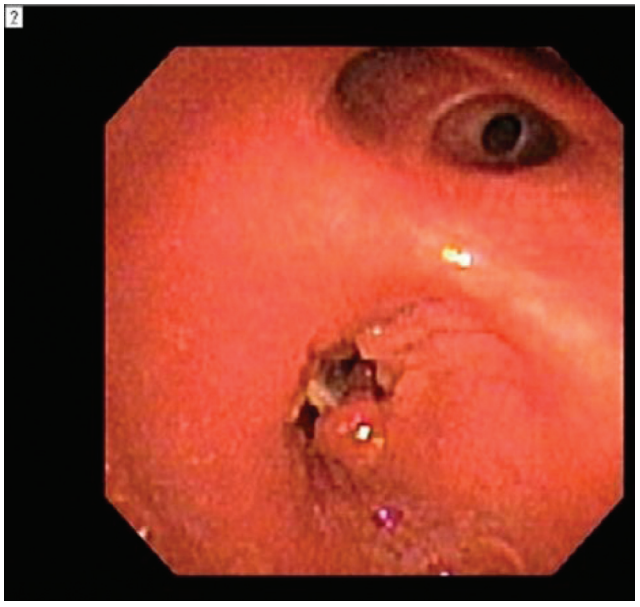

Figure 2. Endobronchial visualization of bone with nodularity of the mucosa.

DISCUSSION OF THE DIAGNOSIS

FB aspiration is more common in children than in adults. Approximately 75–85% of all FB aspiration occurs in children <15 years old, with most occurring in children <3 years of age.[1] In adults, FB aspiration is usually caused by the failure of airway protective mechanisms. This is most commonly seen in the sixth or seventh decade of life.[2] Factors that predispose to FB aspiration are (1) alcohol intoxication, (2) sedative or hypnotic drug use, (3) poor dentition, (4) dementia, (5) impaired swallowing from neuromuscular or neurological conditions, (6) seizures, (7) mental retardation, (8) trauma with loss of consciousness, and (9) general anesthesia.[3]

The presentation may be quite variable depending on the size of the aspirated material. It may be associated with severe asphyxial features or insidious and vague symptoms that are difficult to diagnose correctly. Many cases of FB aspiration are initially treated as asthma or pneumonia. The diagnosis is only correctly made in the first 24 hours in 50% of cases.[4] One study reported that symptoms of FB aspiration often respond, at least partially, to standard asthma therapy: 7 of 10 patients obtained relief in the uninvolved lung, while 2 of 10 patients obtained relief in both lungs following standard asthma therapy.[5]

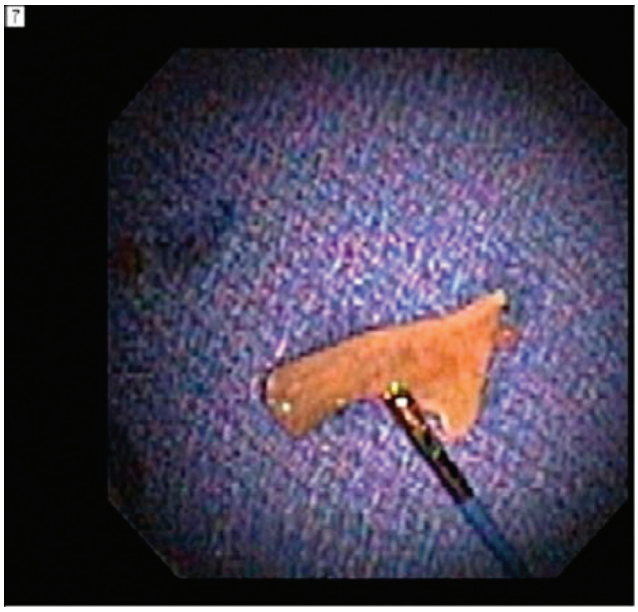

Figure 3. 1.5 cm chicken bone after removal.

The presenting symptoms are similar in children and adults. The symptoms include choking, dyspnea, hemoptysis, fever, intractable cough, fever, chest pain, wheezing, and, rarely, 1% are asymptomatic.[6] The penetration syndrome is commonly seen regardless of age and consists of the sudden onset of choking and intractable cough with or without vomiting.[7] Because of the nonspecificity of symptoms, adult airway FBs often are misdiagnosed. Diagnosis often is delayed leading to complications such as recurrent pneumonia, obstructive emphysema, bronchial stenosis, bronchiectasis, irreversible damage to the obstructed lobe, pneumothorax, pneumomediastinum, recurrent hemoptysis, chronic lung disease, bronchopleural and bronchocutaneous fistulas, pleural effusion, emphysema, or osteomyelitis of the rib.[8]

Although the nature of the FBs reported in various studies differs according to lifestyle and eating habits, nuts, in general, and peanuts, in particular, remain the most commonly found FBs in children.[9–12] In adults, the most commonly aspirated FBs are vegetables, peanuts, and bones. Inorganic substances such as dental appliances, tracheostomy tube segments, endotracheal tube appliances, and a plastic earring clasp have been reported.[6,13]

In up to 40% of patients with suspected airway FBs, the chest radiograph is normal.[14] The sensitivity and

specificity of conventional radiographic studies in the diagnosis of airway FBs range from 45 to 73%.[15,16] The radiographic abnormalities may include atelectasis, infiltrates, obstructive emphysema, mediastinal shift, hyperinflation, and, less commonly, pneumomediastinum.[17] Bones and metal objects may be evident on chest radiography, but most aspirated objects, especially food, are radiolucent and not visible.[18,19] Spiral CT may be helpful in identifying plastic aspirated FBs.[20]

Aspiration of the FB into the right bronchial tree is more commonly seen in adults secondary to the more direct pathway of the right main stem bronchus, whereas in children, there is an equal distribution between the right and left bronchial trees.[21] In children, FBs are more commonly lodged in the central airways because of their small diameters.

Many airway FBs may be expectorated before the patient comes to clinical attention. Most FBs, however, require retrieval from the airway. The four methods of extracting an FB from the tracheobroncial tree include flexible bronchoscopy, rigid bronchoscopy, laryngoscopy, and thoracotomy.[22]

Rigid bronchoscopy has been the traditional procedure of choice for the removal of tracheobronchial FBs.[23] One of the advantages using rigid bronchoscopy to remove a FB is the working channel is longer than with flexible bronchoscopy making extraction easier. A disadvantage of the rigid bronchoscope is that it requires a significant degree of training and skill and it may not be available at all medical centers.

In several medical centers, the flexible bronchoscope has replaced the rigid bronchoscope for removal of most FBs. The Mayo Clinic reported 100% extraction of airway FBs in 26 children and 89% of FBs in 61 adults with the use of the flexible bronchoscope.[24,25] The major advantages of the flexible bronchoscope are that it is widely available, relatively safe, only requires local anesthesia and conscious sedation, and is excellent for peripheral lesions. The major disadvantage is the inability to control the airway.

Final Diagnosis

After removal of the FB from the right bronchus intermedius, the patient immediately improved. The asthma medications were discontinued, and the patient has remained asymptomatic. The final diagnosis was aspiration of a chicken bone mimicking poorly controlled severe persistent asthma.

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Patient Oriented Problem Solving (POPS) Case Report

Acquired angioedema: Autoantibody associations and C1q utility as a diagnostic tool

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ABSTRACT

Acquired Angioedema (AAE) is a rare condition classified into two subtypes: Type I, which is associated with lymphoproliferative disorders, and Type II, which is linked with autoantibodies against C1-esterase inhibitor (C1-INH). Unlike Type I AAE, Type II has no correlation with lymphoproliferative disorders. We report the evaluation of angioedema that was associated with an underlying lymphoproliferative disorder for the purpose of discussing the relationship between C1q and a diagnosis of AAE. A literature review was completed for the purpose of assessing the diagnostic value of C1q when used in the workup of AAE. A PubMed/Web of Science search (1976–2010) produced 78 references (yielding 167 individual cases of AAE) using terminology "AAE." The case described a patient with a depressed C1q (<3.5 mg/dL), decreased C4 (<3 mg/dL), decreased C1-inhibitor (1 mg/dL), decreased functional C1-INH (12%), and decreased total complement (<10 U/mL). Autoantibodies against C1-INH (free and bound respectively) were normal (12.4% and 10.1% of the standard of deviation). Using the above figures and data collected from the literature search, we tabulated 168 individual cases of AAE. Of the 168 cases, C1q was drawn in 104 cases, and 64 cases have no information regarding C1q. There are 10 cases where the C1q was documented as normal. With these values, a correlation between C1q and a diagnosis of AAE was assessed: A decreased C1q correlated with a diagnosis of AAE approximately 56%–94% of the time. C1q is a useful tool when working up a case of AAE.

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CASE PRESENTATION

Chief Complaint

A 75-year-old man is referred for evaluation of recurrent angioedema.

History of Present Illness

A 75-year-old man with a medical/surgical history significant for diabetes mellitus type II, hypertension, osteoarthritis, and benign prostatic hyperplasia was referred for recurrent angioedema that began 4 years ago. He denied exposure to toxic inhalants, chemicals, or radiation. Although he denied any allergic reaction to foods/insects, he admitted using lisinopril in the past, which had been discontinued by a physician because of suspicion that it may have caused angioedema. He denied any reactions to other medications.

There was no family history of angioedema. His parents both died from cancer. A brother has coronary artery disease, and his son and daughter were reportedly healthy.

Medications taken at home included the following: tamsulosin hydrochloride, meloxicam, simvastatin/niacin extended release, losartan, potassium-hydrochlorothiazide, oxybutynin, glimepiride, metformin, folic acid, multivitamins, omega-3 fatty acid, and aspirin.

The initial episode of angioedema occurred approximately 4 years ago, described by a swelling of his foot that progressed over 1 day, which later advanced to involve the tongue and throat. The patient went to the emergency department, was admitted for observation, and was treated with i.v. corticosteroids and diphenhydramine. He had been taking lisinopril, which was discontinued on the hospital admission.

QUESTION 1

Looking at the aforementioned medication list, are there any other medications that you would discontinue, given the patient's symptoms of angioedema?

Answer

See Review Questions section for answers. Since his discharge, he continued to have recurrent episodes of

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angioedema, occurring every 4 months, which involved his extremities and oropharynx. He also mentioned multiple bouts of abdominal pain that typically last for 1 day and resolve spontaneously, although they have never occurred concurrently with airway/extremity swelling. He denied hospitalizations for small bowel obstruction.

When the symptoms appear, he often proceeds to obtain emergency room care and is usually treated with i.v. corticosteroids and diphenhydramine. He was uncertain if these treatments are contributing to his symptomatic improvement, because he had noticed angioedema episodes that have resolved spontaneously in the absence of intervention. The patient stated that these episodes will completely resolve after 2 days regardless of intervention, and many times improvement will occur within several hours. His last episode occurred 1 month before his first visit in our office, while in recovery after a cardiac catheterization. This episode followed a similar course as the prior events.

The patient had been referred to hematology/oncology and allergy/immunology offices for an extensive diagnostic workup 4 months before coming to our office.

QUESTION 2

How would you begin the diagnostic workup? What laboratory tests would you order to facilitate making a diagnosis?

Answer

See Laboratory and Other Diagnostic Data and Clinical Course sections. Also, see angioedema algorithm (Fig. 1) and angioedema subtypes review (Table 1).

Physical Examination

Vital signs obtained in our office showed the following: temperature of 98.8°F, pulse rate of 110 beats/minute, blood pressure of 162/90 mmHg, and oxygen saturation of 94% on room air. He was a healthy-appearing elderly man and measured 175 cm tall. The remainder of the exam was unremarkable. An inspection of the skin and oral mucous membranes revealed no signs of angioedema. There was a scar over chest wall/sternum from previous open heart surgery.

Laboratory and Other Diagnostic Data

Laboratory data before the referral to our office had revealed the presence of hypogammaglobulinemia: total IgG count of 446 (lower limit of normal is 650). A repeat total IgG of 382 confirmed the diagnosis. Liver function tests and complete blood counts had been unremarkable. Previous comprehensive metabolic profiles had also shown values within normal limits. A lymphoma/leukemia panel was drawn, showing an elevated percentage of CD19 (26%) and CD20 (29%). This documented elevation of B-cell markers was suspicious for chronic B-cell leukemia among other malignancies, prompting further investigation.

Serum protein electrophoresis with immunofixation additionally showed a faint IgM-κ monoclonal spike as well as faint bands in IgG and -λ against a dense polyclonal background. Peripheral blood flow cytometry/lymphoma panel conveyed a small monoclonal B-cell population that was consistent with atypical B-cell chronic lymphocytic leukemia or non-Hodgkin's lymphoma.

The aforementioned laboratory data were collected from 2 years ago until 4 months before the patient's initial visit in our office.

Clinical Course

The patient had been appropriately referred to a hematologist/oncologist for a bone marrow biopsy 4 months before our first office encounter, which recently returned negative for malignancy. He was subsequently seen in our office. Flow cytometry was repeated, yielding similar findings as those documented 2 years ago, regarding the likelihood of chronic B-cell leukemia. Serum electrophoresis was additionally repeated, showing a κ-spike.

QUESTION 3

What is the possible significance of the κ-spike that is shown in the serum protein electrophoresis?

Answer

In monoclonal gammopathy of undetermined significance or in multiple myeloma, plasma cells typically produce more light chains than are required to create a whole immunoglobulin. The excess light chains enter the blood stream as free light chains (unattached to the heavy chains). Normal levels of free light chains in serum have recently been reported, along with the normal ratio of κ-free light chains to λ-free light chains. A high κ-light chain in conjunction with a normal λ-light chain supports the diagnosis of a monoclonal gammopathy and thus requires a bone marrow biopsy. The fact that the levels of the κ- and λ-light chains are high and normal, respectively, suggests that if a monoclonal gammopathy does indeed exist, there is no bone marrow suppression. If either the λ- or κ-levels had been low, then that would suggest possible bone marrow suppression.

Laboratory data attained by our office recently revealed a low C1q at <3.5 mg/dL (reference, 5.0–8.6 mg/dL), a decreased C4 at <3 mg/dL (reference, 16–47 mg/dL), a decreased C1-esterase inhibitor level (C1-INH) at 1 mg/dL (reference, 11–26 mg/dL), decreased functional C1-INH at 12% (reference, ≥68%),

Table 1 **Acquired Angioedema Subtypes Review**

Subtype	Overview	Symptoms	Complement System Assessment	Treatment
AAE type I[13,50]	Illustrated by the presence of a C1 inhibitor deficiency and a strong association with lymphoproliferative diseases, usually affecting the B-cell line, or other malignant diseases	Largely similar to HAE type I. fatal laryngeal edema can also occur in AAE; symptoms most commonly begin after 40 years; no family history is noted	Decreased C4 level Decreased C1q level Decreased or normal C1-INH level Anti-C1-INH antibody is **absent**	Treatment of the underlying lymphoproliferative disease will often remedy the angioedema Antifibrinolytics such as tranexamic acid and ε-aminocaproic acid for possible prevention Androgens, such as danazol or stanozolol, may be useful in AAE type I; prostate cancer and pregnancy preclude the use of androgens
AAE type II[14]	Defined by the presence of autoantibodies against C1-INH, and thereby leading to the unopposed activation of the complement cascade, without a correlation with lymphoproliferative diseases	Same symptoms as in AAE type I	Decreased C4 level Decreased C1q level Decreased or normal C1-INH level Anti-C1-INH antibody is **present**	As in HAE, C1-INH concentrates or, if unavailable, fresh-frozen plasma may be used Androgens have not shown to be beneficial in AAE-II Antifibrinolytics, such as those mentioned above in the AAE type I section, have been found to be effective for long-term prophylaxis in those with AAE

AAE = acquired angioedema; C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema.

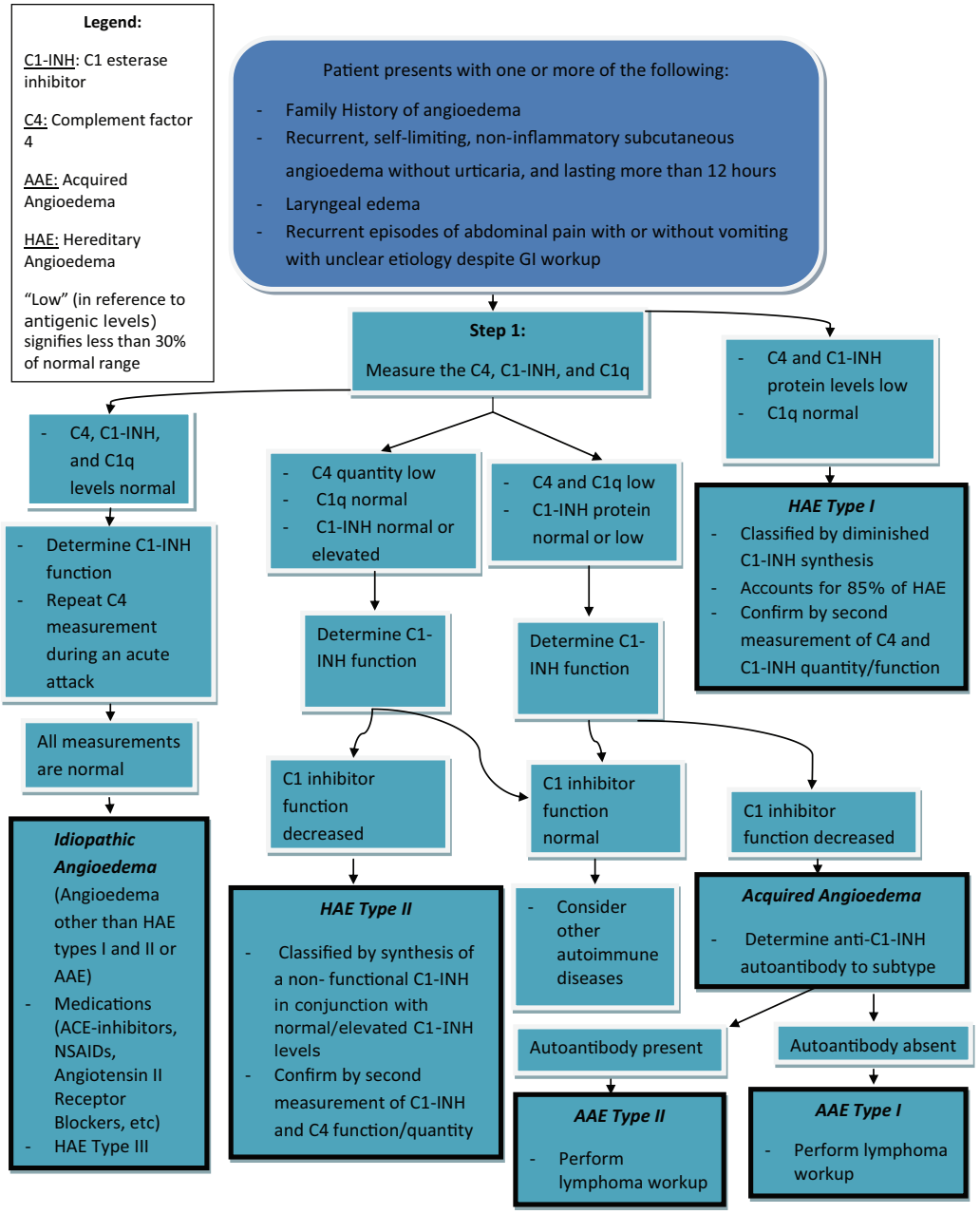

Figure 1. *Angioedema Algorithm: Diagnosis of angioedema (Source: Refs. 6, 49, and with permission from the authors of Ref. 48).*

and a decreased total complement at <10 U/mL (reference, 31–66 U/mL). C1-INH autoantibody levels were obtained 6 months after the patient's initial office visit: the free IgG autoantibody was within the normal range at 12.4% of the SD (reference, 0.89–36.1%), and the bound IgG autoantibody was also within the normal range at 10.1% of the SD (reference, 0.3–46.3%).

REVIEW QUESTIONS

1. What is the Differential Diagnosis?

The differential diagnosis includes acquired angioedema (AAE) type I, AAE type II, hereditary angioedema (type I, II, or III), medication-induced angioedema, pressure or vibratory angioedema, episodic angioedema with eosinophilia (a.k.a. Gleich's syndrome), or idiopathic angioedema.

AAE type I should be ranked the highest on the differential diagnosis, given the laboratory suggestion of a lymphoproliferative disorder. Medication-induced angioedema still remains a possibility, despite the discontinuation of the lisinopril. Gleich's syndrome should be ranked low on a differential, because there was no eosinophilia seen on a complete blood count. AAE type II was ruled out, given the normal levels of autoantibody against C1-INH. Hereditary angioedema was ruled out given the lack of a family history of angioedema and low C1q. (For the diagnostic criteria of hereditary angioedema and AAE types I and II, please see Fig. 1.)

2. What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

No additional tests are required to determine the diagnosis (see angioedema algorithm for review of laboratory testing). Medications commonly known for causing angioedema should be discontinued immediately. The angiotensin-converting enzyme inhibitor was stopped, but the patient was taking nonsteroidal anti-inflammatory drugs, specifically meloxicam, and an angiotensin receptor blocker (ARB), specifically losartan. Nonsteroidal anti-inflammatory drugs are well known for causing angiodema[1] and should be ceased entirely to thoroughly exclude medication-induced angioedema from the differential diagnosis. Although ARBs cause angioedema less commonly than angiotensin-converting enzyme inhibitors,[2] the possibility still exists that the ARB may be the cause of the patients angioedema, and thus it should be stopped as well.

DISCUSSION

AAE is a rare condition characterized by the recurrent bouts of nonpitting mucocutaneous edema involving subcutaneous tissues, the larynx,[3] or the gastrointestinal tract[4,5] in patients who have no family history of similar occurrences. Episodes of the angioedema most commonly will present after 50 years.[6] When the subcutaneous tissues are involved, the swelling is classically nonpruitic and painless. This swelling, especially when affecting the larynx and tongue, can be fatal without proper intervention.[7] It is important to distinguish this condition from the hereditary form, which is much more common in comparison.[8] There are two known forms of AAE, denoted as type I and type II.

AAE type I illustrates a C1 inhibitor deficiency and a strong association with lymphoproliferative diseases[9] (mainly affecting B cells) or other malignant diseases, such as multiple myeloma, chronic lymphocytic leukemia, myelofibrosis, Waldenström macroglobulinemia, or non-Hodgkin's lymphoma.[10] In fact, non-Hodgkin's lymphoma is found in 20% of these patients and monoclonal gammopathy is observed in 35%.[11] This relationship between AAE type I is so strong that some researchers have advised a full workup for acquired angioedema, including C1q, in anyone with presumed B-cell lymphoma. In addition, often, the presenting clinical sign of a lymphoproliferative disorder of B lymphocytes may be angioedema.[12,13]

Although a thorough diagnostic workup for AAE is indicated in all patients diagnosed with B-cell lymphoma, the converse is also true, and anyone diagnosed with AAE should have a full hematologic workup for lymphoma, because the association between the two is so clear. AAE's coexistence with a true B-cell malignancy, nonmalignant B-cell proliferation, or pathogenic autoimmune responses suggests that a large percentage of AAE patients are affected by altered B-cell proliferation control, although clinical outcomes may vary.[13] Our patient was appropriately referred to a hematology/oncology office for a comprehensive diagnostic workup.

The prognosis for AAE is variable and often depends on controlling the underlying disorder (usually a lymphoproliferative disorder/malignancy in AAE type I). AAE type II is linked to the presence of autoantibodies against C1-INH, thereby leading to the unopposed activation of the complement cascade.[14] Contrary to AAE type I, AAE type II typically does not have a correlation with lymphoproliferative diseases. However, the presence of coexisting AAE types I and II[15–18] indicates that the discrimination of the two forms of AAE may be ill defined.

AAE is an extremely rare disease, with >140 cases worldwide.[11,19] The association of AAE type II disease occurring simultaneously with AAE type I is even more extraordinary, with only eight reported cases.[15–18]

An attempt has been made to assess the correlation of C1q and a diagnosis AAE. A Pubmed literature search using the keywords "acquired angioedema" (looking at all case reports, clinical trials, and review articles with full text) yielded 167 individual cases of AAE. If we add our aforementioned case to the literature, there is a total yield of 168 AAE cases. Of those 168 cases, C1q has been drawn 104 times. The remaining 64 cases have no information regarding C1q, and the diagnosis of AAE in those cases is made by a lack of family history of angioedema in conjunction with a low C4 and/or low C1-INH or low C1-INH function. Further review of the 168 cases of AAE shows that the C1q value is reportedly normal in 10 cases[6,15,18,20] and diminished in 94 cases.[6,10,17,18,21–47] Thus, we can determine the correlation of C1q and a diagnosis of AAE in a range: a decreased C1q correlates with a diagnosis of AAE ~56–94% of the time. (This range of percentages has been calculated by looking at the two extremes: the first extreme assumes that the 64 cases with no information regarding C1q have a normal C1q value, and the second extreme assumes that all 64 cases with no information about C1q have a diminished C1q value.)

With the use of C1q in conjunction with a diagnosis of AAE established previously, we believe that C1q remains a valuable tool in the workup of angioedema. (For information regarding the diagnosis and treatment of angioedema, see Fig. 1.)

FINAL DIAGNOSIS

The final diagnosis was AAE type I.

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Patient Oriented Problem Solving (POPS) Case Report

A solitary mastocytoma presenting with urticaria and angioedema in a 14-year-old boy

Karthik R. Krishnan, M.D., and Dennis R. Ownby, M.D.

ABSTRACT

Urticaria with angioedema is a common clinical presentation that often poses a challenge for allergists. The differential diagnosis for urticaria is broad, making the evaluation and pinpointing the underlying cause difficult and frustrating for both families and physicians. Certain causes of urticaria such as infections or medications are more common and easier to identify whereas less frequently seen conditions are often overlooked because of their rarity. One such condition is mastocytosis. Mastocytosis is a rare disease that very seldom presents with urticaria but may be associated with significant morbidity and mortality if not recognized in a timely manner. We are presenting a case of a 14-year-old boy who presented with urticaria and angioedema possibly caused by a solitary mastocytoma. The learning points from this case are that mastocytosis should be considered in the differential diagnosis of urticaria and solitary mastocytomas may remain active into adolescence, raising concern for systemic progression.

(Allergy Asthma Proc 31:520–523, 2010; doi: 10.2500/aap.2010.31.3368)

CASE PRESENTATION

Chief Complaint

Urticaria with angioedema.

History of Present Illness

A 14-year-old white boy presented with a 4-week history of urticaria with angioedema. Urticarial lesions were appearing daily diffusely over his body before fading within 30–45 minutes without leaving any hyperpigmentation. The lesions were extremely pruritic. He also experienced several episodes of lip swelling each week (Fig. 1). The lip swelling would last ~24 hours before resolving and was not associated with breathing difficulties or other symptoms. He took 25 mg of diphenhydramine every 4–6 hours as needed for pruritus. He could not identify a specific pattern or an obvious trigger for his urticaria and angioedema. He had no other systemic symptoms. He did not take any other medications. His medical history was unremarkable. The family history was negative for autoimmune disorders and angioedema. His review of systems was normal.

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Physical Examination

On physical exam, his vital signs were normal. His height and weight were both in the 75th–90th percentile. His physical exam was remarkable for a 4 × 6-cm oval-shaped, dusky red–colored, blanchable macule on his inner right thigh (Fig. 2). Stroking the lesion did not elicit a Darier's sign. There were no other similar skin lesions. According to his mother, this lesion has been present since infancy. His pediatrician told his mother that the lesion was a "nonpigmented birthmark." The remainder of his physical exam was normal.

Initial Laboratory and Diagnostic Findings

His initial laboratory screen for an underlying cause for his urticaria and angioedema included a complete blood count with differential, metabolic profile with liver enzymes, and sedimentation rate, all of which were normal. No further laboratory or diagnostic testing was performed at this time.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Urticaria and Angioedema?

The differential diagnosis for urticaria with angioedema is extensive (Table 1), often making the evaluation difficult. The evaluation begins with a thorough history and physical to provide clues to help identify an underlying cause of urticaria. Laboratory evaluation (screening and/or specific tests) and diagnostic testing may be helpful in detecting an underlying etiology,

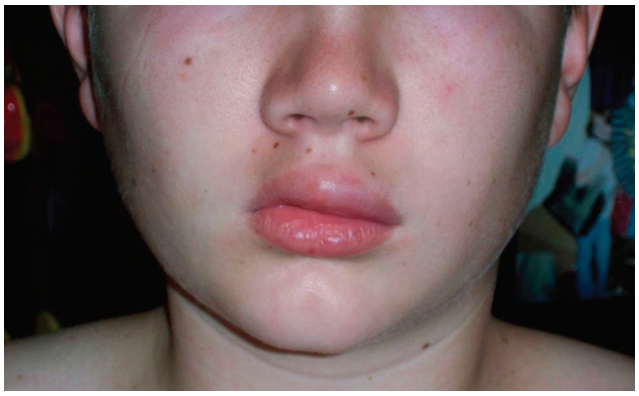

Figure 1. *Edema of upper lip that frequently occurred during the patient's episodes of urticaria.*

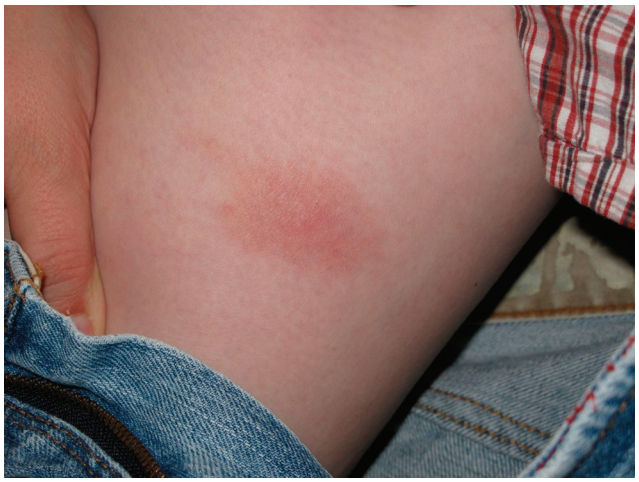

Figure 2. *Appearance of the patient's skin lesion on right inner thigh during an asymptomatic period.*

Table 1 **Causes of urticaria and angioedema**

Foods or food additives
Drug reactions
Inhalation, ingestion of, or contact with antigens
Transfusion reactions
Infection (viral, bacterial, fungal, and parasitic)
Stinging insects
Collagen vascular diseases
Thyroid disease
Malignancy
Physical urticarias
Mastocytosis
Chronic autoimmune urticaria and angioedema
Chronic idiopathic urticaria and angioedema

particularly if a cause can not be discerned from the history.

Certain causes of urticaria are much more common than others. Typical causes of urticaria include food and/or food additives, drug reactions, infections, physical urticarias, thyroid disease, and autoimmune urticaria. Food and/or food additives can be identified by use of food diaries. Drug reactions involve eliminating the putative medication(s) and monitoring response. If an underlying infection is suspected, a detailed evaluation to document the organism should be performed. Physical urticarias (*i.e.*, vibratory, pressure, and cold) can be elicited from the history in conjunction with simple procedures to reproduce symptoms. Thyroid disease secondary to thyroid autoantibodies has been reported to cause urticaria. Autoimmune urticaria can be identified by the presence of the anti–Fcε-receptor autoantibody.

Rare causes of urticaria include collagen vascular diseases, malignancy, and mastocytosis. These conditions often present with atypical urticaria (*i.e.*, persist for $>$24 hours or leave a hyperpigmented mark on remitting) in conjunction with systemic symptoms such as arthralgia, weight loss, diarrhea, or unexplained fever. If the aforementioned causes have been excluded, a diagnosis of chronic idiopathic urticaria is assigned until the urticaria spontaneously remits or a cause is discovered.

What Additional Investigations Would Be Helpful in This Patient?

Because both the history and the initial laboratory screen did not provide clues to an underlying cause for his urticaria. A trial of symptomatic treatment with an antihistamine was started and close follow-up was arranged. Although a more thorough laboratory evaluation may be conducted at the initial encounter, it is not practical or cost-effective and often does not yield additional information given the low pretest probability. If he does not respond to antihistamine therapy or the interim history and/or physical exam provides new insight into an underlying cause, further evaluation is certainly warranted.

CLINICAL COURSE

The initial history and laboratory evaluation did not provide an underlying cause for his urticaria and angioedema. He was started on 25 mg of hydroxyzine nightly. He was instructed to keep a food diary to potentially identify a trigger for his urticaria. He was to follow-up in 2 months or sooner if he had any problems. His urticaria was controlled with hydroxyzine over the next 2 months so his mother discontinued the hydroxyzine. He did not have problems with urticaria or angioedema for 10 months. Unfortunately, the urticaria and angioedema reoccurred but this time his mother reported that the so-called "birthmark" on his right inner thigh would turn bright red, swell, itch, and develop small hives around it minutes before the appearance of new urticarial lesions elsewhere on his

body. This history made us suspicious that the lesion was a solitary mastocytoma. A serum tryptase level obtained when diffuse urticaria were not present was normal. Plasma histamine and urine prostaglandin D_2 levels were not drawn when the urticaria was present. A skin punch biopsy of the lesion was positive for c-kit and mast cell tryptase on immunohistochemical staining, consistent with a mastocytoma. We speculated that the solitary mastocytoma was presumably the most likely underlying cause of his urticaria. Unfortunately, there is no practical approach to definitively prove his urticaria and angioedema were caused by activity of the solitary mastocytoma. However, based on the history provided by his mother that the mastocytoma would swell, itch, and develop small hives around it a few minutes before the appearance of new urticaria elsewhere provides the best evidence to suggest the relationship between his urticaria and the mastocytoma.

His urticaria and angioedema have been controlled with 10 mg of hydroxyzine nightly. He was also instructed to do occlusive dressings with a high potency topical steroid for 2 weeks by his dermatologist in an attempt to shrink the mastocytoma. More importantly, we will need to continue to follow this patient closely to monitor for signs and symptoms such as generalized flushing, diarrhea, or hepatosplenomegaly, and serum tryptase, which may suggest systemic involvement.

DISCUSSION

Urticaria with angioedema is a common presentation with a broad differential diagnosis. The history is critical in identifying the etiology as depicted in this case. When his mother provided the history that the lesion on his right inner thigh would swell within minutes of the appearance of new urticaria, we became highly suspicious that the lesion was a solitary mastocytoma, which was confirmed by a skin punch biopsy by the presence of positive staining for c-kit and mast cell tryptase. Although rare, mastocytomas can present with urticaria and should be considered in the differential diagnosis for urticaria.

Mastocytosis is a heterogeneous group of rare disorders characterized by abnormal proliferation and accumulation of mast cells, involving either only the skin (cutaneous mastocytosis) or the bone marrow and other extracutaneous organs (systemic mastocytosis). The majority of cases of mastocytosis in children are limited to the skin.[1] Cutaneous mastocytosis is further divided into four clinical variants (Table 2): urticaria pigmentosa, solitary mastocytoma, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans.[2] The pathogenesis of cutaneous mastocytosis is not well understood. A transient dysregulation of stem cell factor, a growth factor necessary for mast cell differentiation and growth, has been implicated as the underlying defect in cutaneous mastocytosis.[3]

Table 2 **Forms of cutaneous mastocytosis in children**

Urticaria pigmentosa
Solitary mastocytoma
Diffuse cutaneous mastocyotosis
Telangiectasia macularis eruptiva perstans

Solitary mastocytomas account for 10–15% of all pediatric cutaneous mastocytosis.[4] The majority of mastocytomas present during infancy, typically by 3 months of age, as a single indurated, red–brown macule, papule, or plaque on the trunk, extremities, head, or neck.[1,4,5] Only 10% of mastocytomas appear beyond 2 years of age.[6] Symptoms associated with solitary mastocytomas are secondary to the release of mast cell mediators (*e.g.*, histamine). Symptoms may be localized to include pruritus or blistering of the lesion or generalized with flushing and rarely, urticaria. A Darier's sign may be elicited in only ~50% of patients. Hence, the absence of a Darier's sign does not exclude the diagnosis of a mastocytoma. Mast cell degranulation within solitary mastocytomas may be triggered by a variety of factors including physical stimuli (*e.g.*, heat, cold, friction, and pressure), emotional factors, certain medications (*e.g.*, nonsteroidal anti-inflammatory drugs, opioids, dextromethorphan, vancomycin, and general anesthetics), and radiocontrast media.[6,7]

The diagnosis of a solitary mastocytoma is suspected by the presence of a characteristic skin lesion and confirmed by skin punch biopsy consisting of >15 mast cells/cluster and/or tryptase-positive mast cells on immunohistochemical staining.[8] Laboratory evaluation is rarely needed unless lesions fail to regress over time or systemic symptoms are present. The initial laboratory evaluation includes a complete blood count with differential, comprehensive metabolic profile and a serum tryptase level. A bone marrow biopsy is not necessary in infants and children unless extracutaneous organ involvement is suspected.

The goal of management of a solitary mastocytoma is to prevent mast cell mediator release and alleviate symptoms associated with mediator release, particularly pruritus. The mainstay of therapy involves avoidance of potential triggers and oral antihistamines (H_1-blockers). Other therapeutic options include psoralen-UV-A, short-term application of a topical steroid under an occlusive dressing, or targeted laser therapy.[9] Surgical excision can be curative if unresponsive to other therapies. In addition, families should be edu-

cated on the natural history of solitary mastocytomas. Fortunately, the vast majority of children with solitary mastocytomas have a good prognosis with reduction or complete resolution of symptoms by adolescence. Solitary mastocytomas rarely remain symptomatic in older children; as in this case, only 10–15% of children have symptoms that persist into adulthood.[3,10] These children may have a higher likelihood of having systemic mastocytosis.

CONCLUSION

This case illustrates several valuable learning points. First, solitary mastocytomas seldom cause urticaria but should always be considered in the differential diagnosis for urticaria. The second point and, probably, more important is that most mastocytomas regress by adolescence while a small percentage remain active beyond adolescence, raising concern for progression to systemic mastocytosis. A skin lesion suspicious for a solitary mastocytoma should prompt a diagnostic evaluation with participation of the appropriate specialist. It is important to recognize mastocytomas early to monitor progression of the lesion.

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Errata

Angioedema in a child with a liver transplant, intussusception, and normal c4 levels

Anthony M. Szema, M.D.

On page e63 of the July–August 2010 issue, there are two errors in the Abstract.

The seventh sentence of the Abstract should begin: "Serial C1 esterase inhibitor levels . . .".

The ninth sentence should read: "Although 95% of cases of hereditary angioedema (HAE) have low C4 levels, . . ."

Patient Oriented Problem Solving (POPS) Case Report

Identical twin Hispanic male infants with nonbilious nonbloody vomiting and diarrhea

Tracy R. Prematta, M.D., and Tracy B. Fausnight, M.D.

ABSTRACT

We present a case of twin Hispanic male infants fed with cow's milk formula who presented at 3 weeks of life with nonbilious, nonbloody vomiting and diarrhea. Laboratory evaluation revealed leukocytosis, acidosis, and methemoglobinemia. Sepsis evaluation was negative. Although they recovered quickly with i.v. fluids, symptoms recurred again with ingestion of soy formula. An underlying diagnosis was sought that could explain their symptoms.

(Allergy Asthma Proc 31:e111–e115, 2010; doi: 10.2500/aap.2010.31.3398)

CASE PRESENTATION

History of Present Illness

Identical twin 3-week-old Hispanic male infants presented to an emergency department with a 2-day history of nonbilious nonbloody vomiting and diarrhea. They were born at 38 weeks gestation with an unremarkable pre- and postnatal history. They had been doing well, taking cow's milk formula every 2–3 hours until they became acutely ill. They had no history of fevers, rash, or trauma. Laboratory test results were obtained and they received saline boluses, ampicillin, and gentamicin.

Physical Examination

Twin A was noted to be afebrile with a weight of 2.9 kg (<5th percentile; birth weight, 2.7 kg), heart rate of 150, respiratory rate of 56, blood pressure of 98/57, and oxygen saturation of 95% on room air. He was irritable but awake, crying, gray in color, and wasted in appearance. Head, eyes, ears, nose, and throat (HEENT) exam was remarkable for dry mucous membranes and a sunken anterior fontanelle. His lungs were clear and abdomen was distended but soft without organomegaly. Cardiovascular exam revealed a soft 1/6 systolic ejection murmur, 2+ pulses but delayed capillary refill. Skin exam was negative for rashes, bruises, or petechiae. Neurological exam revealed normal tone, suck, and deep tendon reflexes.

Twin B was also afebrile with a weight of 2.5 kg (<5th percentile; birth weight, 2.52 kg), heart rate of 170, respiratory rate of 63, blood pressure of 93/64, and oxygen saturation of 100% on room air. He was lethargic, gray, and wasted in appearance. HEENT exam revealed a sunken anterior fontanelle and dry mucous membranes. His lungs were clear and abdomen was soft, nondistended without organomegaly. He was tachycardic, but no murmurs were appreciated. Although his pulses were 2+, he had a delayed capillary refill and decreased skin turgor. Skin exam was otherwise unremarkable. On neurological exam, he was hypotonic with decreased cry and suck, but normal deep tendon reflexes.

Laboratory and Other Diagnostic Findings

Blood, urine, and cerebrospinal fluid cultures were obtained before antibiotics. Both boys had leukocytosis with a neutrophil predominance, nonanion gap metabolic acidosis, and evidence of prerenal failure (Table 1). Additionally, both had elevated methemoglobin levels of 9% (normal, <1.5%). Ammonia levels, liver function tests, chest radiographs, and newborn screens were normal. Stool was negative for occult blood.

QUESTIONS

What Is the Differential Diagnosis?

The differential diagnosis is extensive and includes metabolic disorders such as galactosemia, organic acidopathy, urea cycle defect, or storage disease; however, the normal newborn screen, glucose, anion gap, ammonia level, and lack of organomegaly make these diagnoses less likely. Trauma and toxic inges-

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Table 1 **Laboratory results on presentation**

Results	Twin A	Twin B	Reference Range
White blood cell count	25.3	24.4	6–17.5 ($\times 10^3/mm^3$)
Hemoglobin	14.2	13	10–13 (g/dL)
Hematocrit	42.3	36	29–42%
Platelets	373	300	300–700 ($\times 10^3/mm^3$)
Neutrophil	26	8	13–33%
Bands	37	41	4–12%
Lymphocyte	28	33	41–71%
Monocyte	7	16	4–7%
Basophil	0	0	0–1%
Eosinophil	2	2	0–3%
Sodium	138	126	133–146 (mEq/L)
Potassium	4.9	4.7	4.1–5.3 (mEq/L)
Chloride	115	112	98–113 (mEq/L)
Bicarbonate	12.5	5.4	17–24 (mEq/L)
Glucose	83	81	50–80 (mg/dL)
Anion gap	10.5	8.6	Normal <12
Blood urea nitrogen	16	25	5–18 (mg/dL)
Creatinine	0.5	1.0	0.2–0.4 (mg/dL)

tion should be entertained although the history did not support these diagnoses. Bacteremia, meningitis, and urinary tract infection must always be considered in acutely ill infants and the culture results would determine if infection were the cause. Necrotizing enterocolitis (NEC) is lower on the differential because the twins were previously healthy term infants, had relatively benign abdominal exams, and heme-negative stools. Finally, milk sensitivity, such as food protein–induced enterocolitis (FPIES), should be considered.

What Additional Laboratory Data or Investigations would be Helpful in Arriving at a Diagnosis in These Patients?

Initial laboratory results made a metabolic syndrome unlikely; however, serum amino acids and urine organic acids could be obtained. Negative culture results would make an infectious etiology less likely. There are no definitive laboratory evaluations for FPIES, although leukocytosis, elevated methemoglobin levels, and metabolic acidosis are commonly seen. IgE testing for food sensitivity is often negative in FPIES, but if positive, it may indicate increased likelihood of persistent sensitivity.

CLINICAL COURSE

Vomiting and diarrhea resolved within a few hours of i.v. fluid resuscitation and laboratory tests improved by the next morning. Cultures remained negative, so antibiotics were discontinued after 48 hours. The twins were then transitioned to oral feeds with an electrolyte solution and continued to do well. Approximately 5 days after admission, they were transitioned to soy formula.

Within 2 days of starting soy formula, they again had the acute onset of nonbilious, nonbloody vomiting and diarrhea. This time, stool was positive for occult blood. They also had the acute onset of abdominal distention; abdominal radiographs were obtained and worrisome for NEC (Figs. 1 and 2). Serum amino acids and urine organic acids were normal. Repeat blood and urine cultures were negative. The twins were made *nil per os* and again responded quickly to i.v. fluids. They were placed on total parenteral nutrition and treated with ampicillin, metronidazole, and gentamicin for presumed NEC.

However, it was felt that NEC was an unlikely primary diagnosis because of the reasons listed previously. Additionally, acidosis in NEC typically indicates necrotic bowel or sepsis; it would have been unlikely for the symptoms and laboratory test results to have improved so quickly with i.v. fluids and not recur with oral electrolyte solution feeds if NEC were the primary diagnosis. It was, at this point, that FPIES was suspected. Their clinical symptoms and laboratory test abnormalities (metabolic acidosis, leukocytosis, and methemoglobinemia) were consistent. Additionally, the rapid recurrence of symptoms and development of heme-positive stools with soy formula also supported this. On further discussion, their father revealed that he also had milk protein

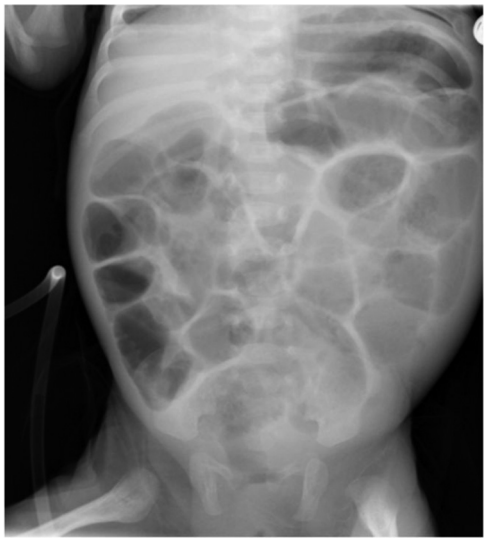

Figure 1. Twin A shows marked increase in gaseous distention of multiple bowel loops.

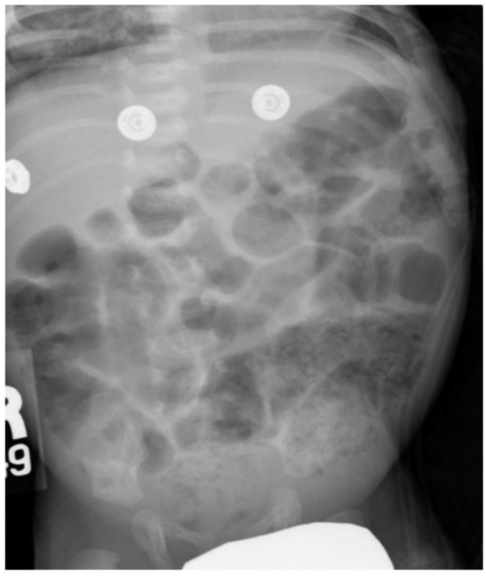

Figure 2. Twin B shows abdominal distention with bubbly lucency involving entire left colon; worrisome for necrotizing enterocolitis.

intolerance with severe illness as an infant, but was able to tolerate it as a toddler.

After completing a 14-day course of antibiotics and total parenteral nutrition, they were placed on an elemental formula and did not have recurrence of vomiting or diarrhea. Food challenge was not performed at that time because FPIES can be diagnosed on clinical grounds if typical symptoms occur without other explanation, especially if it happens more than once.[1] They were discharged home, after a 21-day hospital stay, in stable condition, gaining weight well on an elemental formula. Unfortunately, the family missed their allergy follow-up, but did follow with a gastroenterologist as outpatients. They reported normal weight gain and no symptoms with other foods. Around 2 years of age, milk was reintroduced into their diet at home (although home challenge is not recommended for FPIES) and they tolerated it without recurrence of symptoms.

DISCUSSION

FPIES is one of the non–IgE-mediated food allergies that can affect infants. It appears to be a T-cell–mediated process and research continues looking at the role of different cytokines and other cells in the pathogenesis of this disease.[2,3] Although there does seem to be an increased incidence of personal and family history of atopic disease in patients with FPIES,[1,4,5] to date, there is no specific research on genetic susceptibility.

FPIES typically presents within the first 6 months of life.[6] Cow's milk, soy, and rice are the most frequently implicated causal foods. Some studies indicate that as many as 50% of children who react to milk will also react to soy.[5] A number of other causal foods including fish, oats, vegetables, and poultry have also been described.[4,6–8] Vomiting and diarrhea are the most common presenting symptoms, although irritability, lethargy, hypothermia, and abdominal distention are also often described.[1,4,6] Hypotension and shock can ensue[9]; thus, FPIES should be considered a potentially life-threatening condition. Case reports have also described infants with clinical pictures that are consistent with NEC, some with pneumatosis on radiographs.[10] Symptoms typically begin within a few hours of ingestion of the causal protein, although some infants may have a subacute presentation with failure to thrive and hypoalbuminemia if they are ingesting the protein on a regular basis.[1,6,9] Additionally, some children with FPIES induced by cow's milk, who also react to soy, may have a delay in symptoms when they first ingest soy.[10,11]

A number of laboratory abnormalities can be seen in patients with FPIES. These include metabolic acidosis, thrombocytosis, and leukocytosis with a neutrophil predominance.[4,5,11] Methemoglobinemia and heme-positive stools have also been described.[5,11–13] Generally, testing for IgE-mediated allergy is not helpful, because the majority of infants with FPIES have negative results.[5] However, if there is evidence of IgE-mediated allergy, this may increase the risk of maintaining their sensitivity or possibly having anaphylaxis on challenge.[1,5,9] More recent evidence suggests that atopy patch testing may have a useful role in the diagnosis of FPIES.[14] Unfortunately, even endoscopy yields nonspecific results; reported biopsy findings can include diffuse inflammatory infiltrates including eosinophils and plasma cells.[6,15–19]

Table 2 **Powell criteria for oral challenge for food protein–induced enterocolitis (FPIES)**

Before Challenge the Following should be Performed	Challenge Criteria for Diagnosis	Challenge Interpretation
Verify normal weight gain and lack of symptoms while avoiding causal protein	Clinical symptoms (vomiting/diarrhea)	Positive challenge ≥3 challenge criteria met
Obtain baseline stool samples	Fecal blood	Equivocal 2 challenge criteria met
Obtain baseline peripheral blood PMN count	Fecal leukocytes	Negative 0–1 challenge criteria met
Ensure emergency therapies are in place	Fecal eosinophils	
Consider i.v. access*	Rise in PMN count (>3500 cells/mm^3)	

**Some authors advocate that i.v. access must be obtained on all patients with suspected FPIES undergoing oral challenge. PMN = polymorphonuclear neutrophil.*

Given that there is no single test that can reliably diagnose FPIES, clinical criteria must be used. Specific diagnostic criteria were developed by Powell in 1986 and involve proving that symptoms resolve when the causal protein is removed and recur when it is reintroduced[20] (Table 2). Unfortunately, these criteria have not been validated. Some authors advocate that other symptoms, such as hypotension, should be included and that within the existing criteria some elements may be more important than others. Finally, as with our patients, oral food challenge is not always needed if typical symptoms have occurred after ingestion and no other explanation exists for the patient's symptoms, especially if this happened more than once.[1]

Avoidance is currently the only therapeutic option. For children with cow's milk–induced FPIES, a hydrolyzed or amino acid–based formula should be used. The majority of children will outgrow milk-induced FPIES by 3 years of age.[4] When reintroduction is considered, it should be done in a monitored setting with appropriate emergency equipment available.

Final Diagnosis

FPIES.

CONCLUSIONS

FPIES is a non—IgE-mediated food sensitivity for which there is well-known clinical symptoms but limited diagnostic and management options. Little is known about the genetic and environmental factors that predispose individuals to this condition. This is the first case of twins with FPIES described in the literature; the fact that their father also had a history of milk protein intolerance suggests that a genetic component may have contributed to their susceptibility. Better understanding of the potential hereditary nature of this condition could lead to quicker diagnosis in certain patients.

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Patient Oriented Problem Solving (POPS) Case Report

Cardiopulmonary arrest in a patient with delayed diagnosis of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

Louanne M. Tourangeau, M.D., and Taylor A. Doherty, M.D.

ABSTRACT

We present the case of a 21-year-old male patient with a history of autoimmune nephritis, peripheral eosinophilia, eosinophilic esophagitis, and enteropathy who developed subacute worsening cardiomyopathy with systolic dysfunction. Diagnostic studies revealed a one-codon deletion in the FoxP3 gene, which led to the diagnosis of immune dysregulation polyendocrinopathy, enteropathy X-linked syndrome. Unfortunately, this patient suffered from cardiopulmonary arrest with resulting anoxic encephalopathy before diagnosis confirmation. Here, we discuss the key issues surrounding the diagnostic and therapeutic approaches to this patient's condition.

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CASE PRESENTATION

Reason for Consult

New-onset cardiomyopathy in a patient with an undefined autoimmune disorder and long-standing peripheral eosinophilia.

History of Present Illness

We report a 21-year-old white male patient with a 3-month history of progressive dyspnea, ascites, and chest discomfort who presented to the University of California, San Diego, Medical Center. Transthoracic echocardiogram revealed an ejection fraction of 33% with left ventricular dilation, moderate decreased systolic function, and global left ventricular hypokinesis. chest radiograph showed pulmonary edema and cardiac catheterization revealed normal coronary arteries. The Department of Allergy and Immunology was consulted because of long-standing eosinophilia and history of previously undiagnosed autoimmune disease.

Medical History

The patient was reportedly healthy until 6 months of age, when he developed lymphadenopathy and eczema followed by cellulitis and sinusitis at 9 months. At 2 years of age, he was evaluated for Fanconi syndrome and a renal biopsy revealed interstitial nephritis with lymphocytic infiltration and fibrosis; a diagnosis of autoimmune nephritis was made. At the age of 3 years, he developed Coombs positive autoimmune hemolytic anemia. At the age of 4 years, he suffered from chronic diarrhea; jejunal biopsy specimens revealed severe villous atrophy.

Renal transplant was performed at the age of 4 years for progressively worsening renal insufficiency. After transplant, he was started on cyclosporine. Five months after transplant his diarrhea improved and a repeat jejunal biopsy was normal.

At the age of 18 years, he experienced acute rejection of his transplanted kidney resulting in transplant nephrectomy. At the age of 19 years, he underwent a second renal transplant only to experience rejection <2 years later. At the age of 21 years, he underwent transplant nephrectomy and was taken off immunosuppression and placed on hemodialysis. This was 4 months before the patient's presentation at University of California, San Diego. Of note, he had no previous history of lung disease or recurrent pneumonias.

Social History

Previously, he was a nationally ranked competitive gymnast in good physical condition. He had no history of alcohol, tobacco, or drug use.

Family History

There was no family history of autoimmunity, recurrent infections, atopy, or consanguinity. There were no early deaths in the family. This patient has one sister

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Table 1 **Differential diagnosis**

Immunodeficiencies with Elevated IgE	Disorders with Elevated IgE and Peripheral Eosinophilia	Disorders with Autoimmunity and Elevated IgE	Other Considerations
Wiskott-Aldrich syndrome	Allergic conditions	CVID	Malignancy
Omenn syndrome	ABPA	HES with autoimmunity	Myelodysplastic syndrome
Atypical complete DiGeorge syndrome	Strongyloides	Wiskott-Aldrich syndrome	Parasitic disease
Comel-Netherson	HES	IPEX	Mastocytosis
Hyper-IgE syndrome	IPEX		Medications

HES = hypereosinophilic syndrome; WAS = Wiskott-Aldrich syndrome; ABPA = allergic bronchopulmonary aspergillosis; CVID = common variable immunodeficiency; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

who is healthy and nulliparous, one maternal uncle who is healthy and without children, and one maternal aunt who has three children including a boy who is healthy. Biological father is assumed to be healthy but he is no longer involved with the patient and his family pedigree is unknown.

Physical Examination

Examination revealed a man with short stature. Oropharyngeal exam was normal without retention of primary teeth. Chest auscultation revealed bibasilar crackles. Cardiac exam revealed a normal heart rate rhythm and no murmurs. Abdominal exam was remarkable for moderate abdominal distension, ascites, and well-healed abdominal scars. There were hyperpigmented macules scattered on bilateral lower extremities.

Laboratory and Other Diagnostic Findings

Laboratory studies revealed a white blood cell count of 10,900/mm^3 (reference range, 4000–11,000 mm^3) with 25% eosinophils (reference range, 1–3%), hemoglobin of 9.4 (reference range, 14–17 gm/dL), and platelet count of 343,000/mm^3 (reference range, 130,000–400,000/mm^3).

Total IgE was 11,444 IU/m (reference, <100 IU/mL), tryptase was 25.6 μg/L (reference range, 0.4–10.9 μg/L), and brain natriuretic peptide was >5000 pg/mL (<100 pg/mL). Thyroid stimulating hormone was 13.5 IU/mL and T4 was 0.078 IU/mL (reference range, 0.93–1.70 ng/dL) (previously undiagnosed hypothyroidism). The serum protein electrophoresis showed low albumin. Parietal cell antibody, anticardiolipin antibody, antimitochondrial antibody, antinuclear cytoplasmic antibody, and antinuclear antibody, were negative. Antismooth muscle antibody was positive with a titer of 1:160 (reference, <1:40 titer). Creatine kinase (CPK) was normal. Stool for ova and parasites was negative ×3. Blood cultures were negative ×3. T cell subsets were normal. Glucose level was 88 mg/dL (reference range, 65–110 mg/dL).

Right thigh biopsy specimen showed irregular acanthosis and parakeratosis with minimal inflammation, superficial parakeratosis, and scattered eosinophils. Chest CT showed diffuse ground glass opacities with bibasilar edema consistent with congestive heart failure exacerbation. CT of the abdomen and pelvis revealed ascites with retromesenteric lymphadenopathy and splenomegaly.

QUESTIONS

What is the Differential Diagnosis?

The differential diagnosis for cardiomyopathy with hypereosinophilia and history of autoimmunity includes hypereosinophilic syndrome as a highly likely consideration. Additional considerations include immune deficiencies with elevated IgE levels, disorders causing elevated IgE and peripheral eosinophilia, and disorders with autoimmunity and elevated IgE such as immune dysregulation polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome and hyper-IgE syndrome. A more complete differential diagnosis is summarized in Table 1.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Hypereosinophilic syndrome causes end-organ damage and is associated with a restrictive or, less commonly, a dilated cardiomyopathy, caused by eosinophil invasion of the myocardium.[1–3] To investigate this possibility, a myocardial biopsy or a cardiac MRI is necessary. Recent developments in cardiac MRI modalities provide superior detection of eosinophilic endomyocardial disease and may be preferred over right ventricular biopsy.[4,5] Additionally, a bone marrow bi-

opsy should be undertaken to evaluate the presence of FIP1L1-PDGFRA fusion gene and clonal lymphocytic populations. The FIP1L1-PDGFRA mutation has therapeutic implications because it indicates responsiveness to Imatanib.[6] Bone marrow biopsy is also obligatory to investigate malignancy, mastocytosis, and myelodysplastic syndrome.

In terms of hyper-IgE syndrome, it is imperative to assess the presence of eczema-like rashes, recurrent staphylococcal infections, and pneumatoceles.[7] Our patient had an elevated total IgE level and the presence of atopic dermatitis. We, however, failed to identify retention of primary teeth, pneumatoceles, or staphylococcal infections. Because the patient had a significant history of autoimmunity, IPEX syndrome was a consideration, requiring assays for FoxP3 mutational analysis and protein expression.

Clinical Course

The patient underwent a cardiac MRI, which did not show infiltrative disease or endomyocardial disease. Bone marrow biopsy revealed 20% eosinophils with a normal karyotype, cytogenetics, immunostaining, and mast cells. FIP1L1-PDGFRA fusion gene analysis was negative.

To investigate the possibility of IPEX, FoxP3 mutational analysis and FoxP3 protein expression was performed. He was subsequently discharged but suffered a cardiopulmonary arrest within 24 hours. Despite successful resuscitation, he suffered from anoxic encephalopathy and is currently in a persistent vegetative state.

Two weeks later, FoxP3 studies returned revealing a one-codon deletion in the leucine zipper domain of FoxP3. The deletion was located at 748_750 del AAG (K250 del; Fig. 1) and is associated with IPEX syndrome in the hemizygous state.[8–10] FoxP3 protein expression was only modestly decreased at 80% (reference range, 84–95). Flow cytometry of peripheral $CD4^+$ cells is shown in Fig. 2.

DISCUSSION

In this patient with a history of autoimmune nephritis, enteropathy, hemolytic anemia, hypothyroidism, elevated total IgE, and peripheral eosinophilia, the FoxP3 mutational analysis confirms the diagnosis of IPEX syndrome. IPEX syndrome is a rare entity that causes life-threatening systemic autoimmunity from underlying immune dysregulation. This condition was first described in 1982 in one Northern European family where 17 male infants died in the 1st years of life.[11] Interestingly, the gene itself was not mapped until 18 years later when it was found on the short (p) arm of the X chromosome at position 11.23.[12] Several studies have found that FoxP3 is expressed at high levels in thymic-derived naturally occurring Treg cells (nTreg) and $CD4^+CD25^{hi}$ adaptive Treg (aTreg) cells. Recent work suggests that cells identified as $CD4^+CD25+CD127^{lo}$ correlate well with the $CD4^+CD25+FoxP3+$ population.[13]

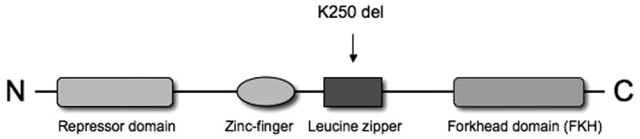

Figure 1. Organization of FoxP3 protein. K250 deletion in leucine zipper shown (arrow) and it is known to impair oligerimization.

Studies using the FoxP3-deficient scurfy mouse have provided insight into the pathogenesis of this syndrome. The scurfy mouse resembles IPEX syndrome because it shows X-linked inheritance of scaly skin, runting, hematologic abnormalities, lymphadenopathy, diarrhea, and death by 3–4 weeks of age. The mutated gene in scurfy mice was obtained by positional cloning and named "FoxP3." Mutated FoxP3 results in a complete lack of $CD4^+CD25^+$ regulatory T cells.[3] After identifying the FoxP3 mutation in murine models, the human FoxP3 was sequenced in several IPEX families and found to be mutated.[14–16]

Structurally, FoxP3 protein encodes a forkhead DNA-binding domain, a N-terminus domain that regulates transcription, a zinc-finger domain that functions in protein–DNA interactions and a leucine zipper domain that functions in dimerization.[17] The leucine zipper domain was the affected portion of the protein in the patient presented here (Fig. 1). The K250 deletion in IPEX syndrome is known to eliminate FoxP3 homooligomerization.[18]

In regard to clinical studies, the largest study to date investigated 105 IPEX syndrome and IPEX-like syndrome patients. They found that genotypes do not necessarily correspond to the expressed phenotype and that FoxP3 mutations may not always result in protein abrogation.[19,20] This is consistent with the case presented, because the FoxP3 expression was only modestly reduced compared with IPEX phenotypes where almost no FoxP3 protein is detected.

In our patient's case, he was treated with cyclosporine and prednisone from the age of 4 years as part of his antirejection regimen after renal transplant. Of interest, our patient worsened after his second transplant nephrectomy, when his immunosuppression was discontinued. It is likely that his immunosuppressive transplant regimen was inadvertently treating his undiagnosed IPEX syndrome and cessation of therapy worsened his condition. Therapeutic options for IPEX syndrome include immunosuppression with corticosteroids, calcineurin inhibitors, and, possibly, bone marrow transplantation.

It is unclear what relationship IPEX syndrome had in the pathogenesis of this patient's cardiomyopathy and

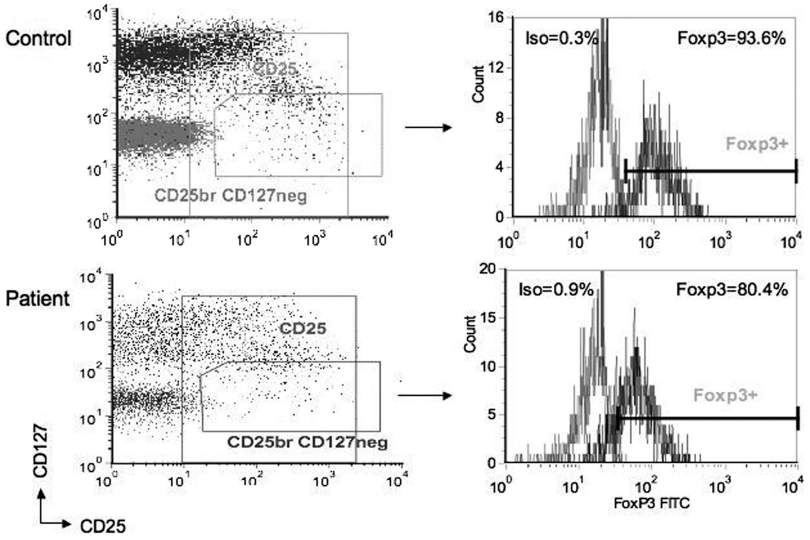

Figure 2. Flow cytometry to evaluate Foxp3 protein expression. $CD4^+CD25^+CD127-$ cells (left) were evaluated for Foxp3 expression (right). Control sample run the same day (top row) as well as the patient's sample (bottom row) are shown.

cardiac arrest, especially given the MRI without evidence of an infiltrative process. Although the symptoms reported for IPEX syndrome are diverse, we do not find any report of cardiomyopathy or cardiac arrest in IPEX syndrome patients. It is difficult to predict if ongoing immunosuppression would have led to a better outcome, especially given the severity of his cardiac dysfunction at the time of consultation.

Final Diagnosis

Final diagnosis was IPEX syndrome.

SUMMARY AND CONCLUSIONS

IPEX syndrome should be considered in any male patient with diarrhea, failure to thrive, eczema, and the presence of autoimmune disease or endocrine abnormalities. Clinicians should be aware that phenotypic expression varies greatly; as a result, a high degree of suspicion is necessary to make the diagnosis of IPEX syndrome. When establishing the diagnosis, investigation should include FoxP3 mutational analysis, as well as, FoxP3 protein expression. If diagnosed, genetic testing is recommended to identify if the condition is caused by an X-linked inherited mutation or a *de novo* mutation. If it is found to be X-linked, genetic counseling should be provided for all carriers. This case illustrates the heterogeneous nature of IPEX syndrome and the need for awareness of this disease.

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Patient-Oriented Problem Solving (POPS) Case Report

A sixty-five-year-old man with rash, fever, and generalized weakness

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ABSTRACT

Diffuse erythematous rash accompanied by high-grade fever, eosinophilia, and facial edema can be caused by a variety of infective, allergic, or systemic etiologies. We present a case of 65-year-old man with septic arthritis, who had a vancomycin antibiotic spacer placed in his infected knee and was also started on intravenous (i.v.) vancomycin. After 2 weeks he presented with sudden onset of fever and generalized weakness. Physical examination was significant for tachycardia and hypotension, facial edema, diffuse erythematous rash, and bilateral wheezing. Laboratory values indicated acute renal insufficiency associated with eosinophiluria and significant peripheral eosinophilia. Septic shock was highly suspected and he was treated with i.v. fluids and broad-spectrum antibiotics. Despite aggressive management his condition rapidly deteriorated with persistent of shock state, increase in facial edema, and rash. Other suspected etiologies included hypersensitivity reactions to i.v. antibiotics (piperacillin/tazobactam) or vancomycin, systemic vasculitis, or idiosyncratic reactions to medications such as Stevens-Johnson syndrome. The patient was started on high-dose i.v. steroids, which led to improvement of his clinical condition. Clinical presentation of adverse drug reactions is highly variable and may present as potentially life-threatening multiorgan failure. Early recognition of the etiology and removing the offending agent is important to improve the outcome.

(Allergy Asthma Proc 32:e1–e3, 2011; doi: 10.2500/aap.2011.32.3392)

CASE PRESENTATION

Chief Complaint

Sixty-five-year-old man with rash, fever, and generalized weakness.

History of Present Illness

A 65-year-old gentleman with history of bilateral total knee arthroplasties was diagnosed with septic arthritis of the left knee. Subsequently, a surgical removal of the arthroplasty was performed along with the placement of an antibiotic spacer containing vancomycin. Also, he was started on intravenous (i.v.) vancomycin infusions through a peripherally inserted central catheter line. Two weeks later he presented with a diffuse erythematous rash all over his body, fever, and facial swelling. His medical history included diabetes mellitus type 2, hypertension, and hypercholesterolemia. His other home medications included metformin, amlodipine, aspirin, and warfarin. He did not smoke or drink and had no history of drug allergies.

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Physical Examination

Vital signs included a blood pressure of 125/85 mmHg, heart rate of 130/minute, respiratory rate of 22/minute, and temperature of 102.5°F. In general, he looked uncomfortable, tachypneic, and confused. He had dark red macules and patches involving his face, trunk, and extremities along with facial edema. There was no palpable peripheral lymphadenopathy. Lung auscultation revealed diffuse wheezing. Cardiac exam revealed a rapid rate, with regular rhythm. His abdomen was distended and spleen was palpable 2 cm below the costal margin.

Laboratory Results and Initial Clinical Course

Laboratory analysis revealed a white blood cell count of 24,000 cells/μL with an absolute neutrophil count of 12,000 cells/μL, lymphocyte count of 2000 cells/μL, and an eosinophil count of 6000 cells/μL. His hemoglobin was 9.1 g/dL and he had 406,000 platelets/μL. His blood urea nitrogen was 108 mg/dL and serum creatinine was 10.17 mg/dL. The C reactive protein level was elevated at 16.75 mg/dL. Blood cultures were negative.

Initially, he was treated for suspected sepsis with i.v. piperacillin/tazobactam and ciprofloxacin. His vancomycin was discontinued because of concern for a hypersensitivity reaction. Within hours, his dyspnea and facial swelling increased and he became hypotensive (blood pressure, 82/40 mmHg). He was intubated and was started on i.v. norepinephrine. It was thought that the worsening of his facial edema with hypotension could be a type I hypersensitivity reaction to either piperacillin or ciprofloxacin, so they were discontinued. At that point, 50 mg of i.v. diphenhydramine and i.v. hydrocortisone at 100 mg every 8 hours were administered.

QUESTIONS

What Are the Differential Diagnoses?

1. Septic shock.
2. Syndrome of drug rash with eosinophilia and systemic symptoms (DRESS).
3. Anaphylactic reaction to piperacilin/tazobactam or ciprofloxacin.
4. Red man syndrome.
5. Vasculitis (*i.e.*, Churg-Strauss syndrome).
6. Stevens-Johnson syndrome.
7. Toxic epidermal necrolysis.

His initial symptoms of fever, tachycardia, hypotension, and respiratory failure were suggestive of septic shock; however, because his blood cultures were negative and he had no response to antibiotics, other diagnoses were sought. The time course of events with developing rash, fever, and systemic symptoms including pulmonary and renal failure, along with severe eosinophilia suggested a severe drug hypersensitivity syndrome (DRESS). Vancomycin was highly suspected as the causative agent because of the fact that he developed symptoms while receiving this drug i.v., in addition to its presence in the antibiotic spacer.

Type I hypersensitivity reaction to piperacillin/tazobactam or ciprofloxacin was also a possibility because he did decompensate after getting those medicines; however, most of his symptoms had started before receiving those antibiotics. Red man syndrome, caused by vancomycin, could explain the erythematous nature of his rash, but not the accompanying systemic symptoms. Churg-Strauss syndrome could explain his respiratory failure and eosinophilia, but lack of a previous asthma history and the acute presentation made this a less likely diagnosis. Stevens-Johnson syndrome or toxic epidermal necrolysis could also account for some of his symptoms, but this was less likely given the nature of the rash. He had no evidence of vesicles, bulla, skin necrosis, or mucous membrane involvement.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis?

Blood cultures were negative making sepsis less likely. His eosinophilia, eosinophiluria, and lymphocytosis along with clinical picture point toward DRESS due to vancomycin. Unfortunately, no other laboratory tests are confirmatory for the diagnosis of DRESS.

MANAGEMENT PLAN AND HOSPITAL COURSE

The patient continued to remain hemodynamically unstable despite maximal vasopressor support. Because of his declining status, methylprednisolone, 1 g i.v., was started every 12 hours, to which he responded well and his blood pressure stabilized. His rash started improving 24 hours after the start of high-dose i.v. steroids. After 2 days, when methylprednisolone dose was decreased to 125 mg i.v. every 6 hours, he became hypotensive again. The dose was reescalated to 1 g every 12 hours, which led to clinical improvement. His steroid dose was tapered much more slowly over the next few weeks. Subsequently, his steroid dose was changed from i.v. to oral and slowly tapered over the next 2 months. He required several dialysis treatments while in the intensive care unit. Later, his creatinine stabilized at 2.0 mg/dL and he no longer needed dialysis. The final recovery happened only after the antibiotic spacer was removed. His total hospital stay was 23 days long. While recovering, he still required antibiotic therapy for septic arthritis and tolerated penicillins and quinolones with no reactions, which further supported the suspected role of vancomycin as the cause of DRESS.

DISCUSSION

DRESS is a severe, acute, idiosyncratic drug reaction, defined by the presence of fever, cutaneous eruption, and systemic findings.[1] The systemic manifestations include enlarged lymph nodes, hepatitis, renal impairment, pneumonitis, myocarditis, myositis, and hematologic abnormalities, which mainly include eosinophilia and/or lymphocytosis.[2] This type of reaction was initially reported with aromatic anticonvulsants[3]; hence, the term "anticonvulsant hypersensitivity syndrome" was first used in 1988.[4] This syndrome is also known as drug-induced hypersensitivity syndrome, because it is not always associated with peripheral eosinophilia. The clinical manifestations typically occur within 2–6 weeks after the initiation of drug therapy and will not resolve unless the offending drug is discontinued.[2,4]

Various mechanisms have been proposed to explain DRESS. Abnormal detoxification of reactive arene oxide metabolites of aromatic anticonvulsants is thought to be the cause in anticonvulsant-related cases.[4] Some studies have suggested the role of reactivation of a latent human herpesvirus 6 infection.[5] Other studies have found significant association between hypogammaglobenimia and

drug hypersensitivity reaction.[6] The exact etiology is still not completely clear, but more recent studies suggest a T-cell–mediated process.[7,8] One group recently established the presence of cytotoxic $CD8^+$ T lymphocytes in the liver of a patient with DRESS and also showed the presence of granzyme-B and Fas ligand. This group postulated that certain drugs can stimulate massive expansion of drug-specific cytotoxic T cells causing cell death *via* granzyme-B and Fas ligand.[8]

Aromatic anticonvulsants are the most commonly reported drugs causing DRESS.[9] Other drugs include allopurinol, minocycline, abacavir, antidepressants, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and β-blockers.[9,10] Although vancomycin has not been a common cause, in recent years, more cases have been reported.[8,11–13]

The severity of presentation and clinical course varies significantly. In a recent case review, 15 cases with severe DRESS manifestations were described. Among them, 14 had to be admitted in an intensive care unit and 3 died.[10] Severe reactions to vancomycin have been reported including pneumonitis, severe hepatitis,[8] renal insufficiency,[12,13] myocarditis,[14] and shock.[11]

Management of mild disease primarily involves removal of the offending agent, supportive care including warming the environmental temperature, local antiseptics, and topical corticosteroids. The use of high-dose steroids in severe cases has been controversial because there have been no controlled studies. Several authors have reported improvement in symptoms with steroids in severe cases with hemodynamic instability and multisystem involvement.[15–17] There has been some concern that high-dose steroids may cause worsening of an underlying viral etiology.[16] Duration of treatment may be prolonged and if steroids are decreased rapidly, the disease may flare.[10] We faced a similar situation as we tried to decrease the dose of methylprednisolone. Removing the offending agent is most crucial to early recovery. A recent study has reported improvement in symptoms with cyclophosphamide in steroid-resistant cases.[17] Cyclosporine has also been used along with corticosteroids for the treatment of DRESS.[12] Other studies have described the role of immunoglobulins (i.v. immunoglobulin) in complicated cases.[18]

CONCLUSION

DRESS syndrome can present as a severe, life-threatening emergency, mimicking various clinical conditions including septic shock. It is a rare, but possible complication of vancomycin use. Early recognition, removal of the offending agent, and, in severe cases, high dose i.v. steroids are the mainstays of therapy. More case-controlled and randomized trials are required to establish treatment guidelines.

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Patient Oriented Problem Solving (POPS) Case Report

Lymphadenopathy, productive cough, eosinophilia, and a new-onset acquired immunodeficiency syndrome

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ABSTRACT

We present a complicated case of a human immunodeficiency virus (HIV)–infected male patient with a complexity of confounding and overlapping symptoms that can masquerade as another diagnosis. This is the case of a patient with multiple secondary sexually transmitted infectious diseases, lymphadenopathy, B-cell lymphoma, a productive cough, a clinical picture suggestive of pulmonary tuberculosis, eosinophilia, and a new-onset acquired immunodeficiency syndrome. Our presentation highlights those deteriorations seen in our patient as well as various underlying immunologic changes in the content of HIV infection. This case may not be unique, but less severe cases occur and can be underdiagnosed, indicating the need of timely screening, close evaluation, and monitoring of HIV-infected patients as well as those with high risk of acquiring HIV.

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CASE PRESENTATION

Chief Complaint

Productive cough and shortness of breath.

History of Present Illness

A 30-year old Hispanic man was referred to the Infectious Diseases Clinic of our hospital for productive cough and shortness of breath. Cough and fatigue were present for the last 4 months.

He denied fever, chills, or night sweats. Two weeks earlier, the patient had presented with left neck and inguinal masses and was diagnosed with non-Hodgkin's lymphoma (NHL)—diffuse large B-cell lymphoma (Fig. 1). Medical history was remarkable for hepatitis C, cytomegalovirus infection, and syphilis as well as history of Epstein-Barr virus and gonorrheal and chlamydial infections. Social history revealed no recent travel but did reveal bisexual orientation and multiple sexual partners. There was no known history of allergies.

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Physical Examination

Vital signs showed weight of 56 kg, height of 5 ft 2 in., respiratory rate of 16/minute, blood pressure of 130/82, pulse of 104/minute, and temperature of 97.1°F. Examination revealed a young well-developed man in slight respiratory distress. Skin examination was remarkable for hyperpigmented spots representing a resolved older rash. Lymph node palpation was significant for left neck and right inguinal lymphadenopathy. No crackles or wheezing were noted on lung auscultation. Heart examination revealed regular heart sounds without murmurs, gallop, or pericardial rub. Abdomen was soft without tenderness, rebound, palpable masses, or organomegaly. Neurological examination was without focal or sensory abnormalities.

Laboratory and Other Diagnostic Findings

Initial laboratory evaluation is summarized in Table 1. Chest x ray was remarkable for an increased density in the midaspect of the right lobe posteriorly. Chest, abdomen and pelvic computed tomography (CT) scan showed scattered right lobe infiltrates with bilateral pulmonary nodules, supraclavicular and axillary adenopathy, and diffuse abdominopelvic adenopathy with no evidence of solid organ pathology. CT of the soft tissues of the neck revealed a large area of matted lymphadenopathy involving the left neck with conglomerate necrotic nodal mass and diffuse lymphadenopathy as well as compression of the left internal jugular vein but patent airway. Analysis of bronchoalveolar lavage obtained after bronchoscopy did not reveal malignant cells, *Pneumocystis carinii* pneumonia, fungi, or viral isolates. A

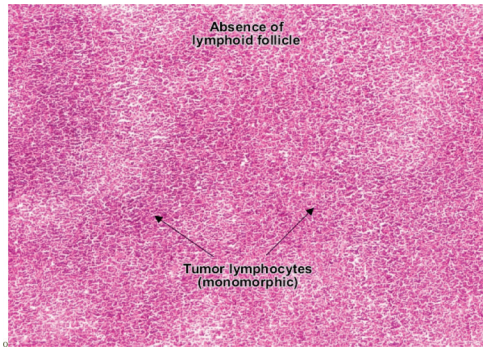

Figure 1. Diffuse lymphocytic non-Hodgkin's lymphoma. Lymph node architecture is replaced by tumor proliferated lymphocytes. Lymphoid follicles are absent. Tumor lymphocytes resemble normal lymphocytes (small, monomorphic, round hyperchromatic homogenous nuclei, and educed cytoplasm) but are immature, monoclonal, and nonfunctional. Lymph node capsule is infiltrated by tumor cells. In most of the cases, these tumor cells have a B-cell origin (H&E, ×10). Source: Ref. 31.

sputum acid fast bacilli smear was negative but the culture was positive for tuberculosis. Lymphocyte phenotypes and viral serology are shown in Table 2.

QUESTIONS

What Is the Differential Diagnosis?

Lymphanadenopathy can be associated with many causes as listed in Table 3. In addition, productive cough and eosinophilia may be a part of clinical and laboratory manifestations of a variety of disease entities as shown in Tables 4 and 5.

Clinical Course

The patient was admitted to the medicine floor of our hospital and placed on respiratory isolation for active tuberculosis. The patient was started on treatment with isoniazid, rifampin, ethambutol, pyrazinamide, and pyridoxine. Sputum samples induced on three separate days after 18 days of therapy were negative for acid fast bacilli. During the hospital stay, the patient suffered odynophagia and dysphagia. The clinical diagnosis of *Candida* esophagitis was made and the patient received a 14-day course of caspofungin with significant clinical response. The serum human immunodeficiency virus (HIV) viral load was ~500,000 RNA copies/mL. Serum fluorescent treponemal antibody was positive with titer of 1:4 and positive fluorescent treponemal antibody. The patient was treated with benzathine penicillin, 2.4 million U i.m. once a week for 3 weeks. Hepatitis C virus quantitation by branched DNA testing was 5993 RNA copies/mL. Serum cryptococcus antigen test was negative, and analysis of cerebrospinal fluid obtained after lumbar puncture did not reveal any abnormalities.

Table 1 **Laboratory evaluation**

		Reference Range
Complete blood count		
WBC	5.0	4.5–11.0 K/mm^3
RBC	3.95 L	4.60–6.20 M/mm^3
HGB	10.6 L	13.5–18.0 g/dL
HCT	31.5 L	40.0–54.0%
MCV	79.8 L	80.0–96.0 fL
MCH	26.8 L	27.0–31.0 pg
MCHC	33.6	32.0–36.0 g/dL
RDW	16.7 H	12.7–15.2%
MPV	10.4 H	7.0–9.0 fL
Manual platelets	130 L	150–450 K/mm^3
Differential		
Neutrophils	53.1	38.9–75.1%
Lymphocyte	16.9	12.8–43.9%
Monocyte	15.7 H	4.0–10.6%
Eosinophil	13.6 H	0–5.8%
Basophil	0.7	0–1.2%
Neutrophil*	2.7	1.8–7.0 K/mm^3
Lymphocytes*	0.8 L	1.5–4.0 K/mm^3
Monocyte*	0.8	0–0.8 K/mm^3
Eosinophil*	0.7 H	0–0.5 K/mm^3
Basophil*	0.0	0–0.1 K/mm^3
Chemistry		
Sodium	137	133–145 mM/L
Potassium	3.8	3.3–5.1 mM/L
Chloride	101	96–108 mM/L
Bicarbonate	27	22–29 mM/L
Glucose (random)	150 H	70–105 mg/dL
Urea nitrogen	19	6–20 mg/dL
Creatinine	0.7	0.5–1.2 mg/dL
Calcium	8.9	8.4–10.4 mg/dL
ALT	75 H	0–41 U/L
AST	54 H	0–38 U/L
Alkaline phosphatase	218 H	39–117 U/L
Total bilirubin	0.2	0.0–1.0 mg/dL
Total protein	9.4 H	6.0–8.3 g/dL
Albumin	3.8	3.4–4.8 g/dL

Source: Ref. 28.
**Absolute number of cells.*
WBC = white blood cell count; RBC = red blood cells; HGB = hemoglobin; HCT = hematocrit; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; RDW = RBC distribution width; MPV = mean platelet volume; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

While receiving two rounds of chemotherapy with a cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), and prednisone/prednisolone

Table 2 **Lymphocyte profile and viral serology**

Total T-helper/supressor subsets		
Lymphocyte	845 L	860–2760/mm^3
CD3	75	60–81%
ACC CD3	637	600–2110/mm^3
CD3/CD8	67 H	13–36%
ACC CD3/CD8	566	180–700/mm^3
CD3/CD4	6 L	34–61%
ACC CD3/CD4	51 L	390–1460/mm^3
T-helper/suppressor ratio		
CD3CD4/CD3CD8	0.09 L	1.4–4.2 Ratio
HIV viral quantitation real time PCR		
HIV viral load	244848	RNA copies/mL
HCV RNA confirmatory test		
HCV RNA	Negative	Negative
Epstein-Barr virus Ab panel		
EB VCA IgG Ab	>7.00 P	0.00–0.90
EB VCA IgM Ab	0.05 n	0.00–0.90
EBNA Ab (IgG)	0.38 n	0.00–0.90

Source: Ref. 29.
CD = cluster of differentiation; HCV = hepatitis C virus; ACC = absolute cell count; VCA = viral cuspid antigen; EBNA = Epstein-Barr nuclear antigen; PCR = polymerase chain reaction.

Table 3 **Diseases causing lymphadenopathy**

Acute infections (bacterial, viral, and fungal)
Cat-scratch fever
Cytomegalovirus inclusion disease
Brucellosis
Infectious mononucleosis
Drug reaction
Collagen diseases, lupus erythematosus or rheumatoid arthritis
Leukemia
Malignant lymphoma
Metastatic epithelial neoplasms
Tuberculosis
Sarcoidosis
Serum sickness

Source: Ref. 28, modified from Ref. 29.

Table 4 **Conditions associated with a productive cough**

Allergic rhinitis with postnasal drip
Cough-variant asthma
Bronchiectasis
Eosinophilic bronchitis
Chronic obstructive pulmony disease
Pertussis
Mycoplasma pneumoniae
Pulmonary interstitial fibrosis
Lung abscess
Pleural empyema
Mycobacterium avium-intracellulare complex
Chronic sinusitis
Chest tumor
Mycobacterial granuloma
Pulmonary tuberculosis
Pulmonary nocardiosis
Invasive pulmonary aspergillosis
Sarcoidosis
Wegener's granulomatosis
Bronchiolealveolar carcinoma
Pulmonary malignant lymphoma
Pneumoconiosis

Source: Modified from Ref. 30.

regimen for lymphoma, it was decided to hold starting the patient on highly active antiretroviral therapy medications until the viral genotype was obtained. The patient was cleared for discharge by infectious diseases and put in close contact with his case manager with thorough information about medications and subsequent follow-ups in clinic.

DISCUSSION

HIV Viral Activity and Immunity

This case is important in considering with some immediacy the diagnosis of HIV infection/acquired immunodeficiency syndrome (AIDS) in any sexually active individual with multiple sexually transmitted diseases regardless of a concomitant diagnosis of lym-

Table 5 **Conditions associated with eosinophilia**

Asthma
Rhinitis
Bronchopulmonary aspergillosis
Infectious diseases
Parasitic infections, mostly helminths
Specific fungal infections
Human immunodeficiency virus
Atopic dermatitis
Eosinophilic pneumonia
Hypersensitivity pneumonitis
Churg-Strauss
Eosinophilic gastroenteritis
Hypersensitivity myocarditis
Hematologic and neoplastic disease
Hypereosinophilic syndrome
Eosinophilic leukemia
Lymphoma (*e.g.*, Hodgkin's, non-Hodgkin's, and T-cell lymphoma)
Solid tumors
Mastocytosis
Immunodeficiency states
Hyper-IgE syndrome
Endocrine
Adrenal insufficiency

Source: Modified form Ref. 20.

phoma or mycobacterial infection and its appreciable worldwide incidence.

There is considerable variability in viral load and immune responses among HIV-infected persons. The first indications of HIV-specific immune responses are increased levels of HIV-specific cluster of differentiation $(CD)8^+$ and $(CD)4^+$ T cells. A unique feature of HIV is that a pool of latently infected resting $(CD)4^+$ T cells is established very early during primary infection. The HIV reservoir is not eradicated even after extended antiretroviral therapy that reduces viremia to undetectable levels as <50 RNA copies/mL.[1] HIV infection in a majority of untreated individuals leads to persistent viral replication and progressive $(CD)4^+$ T-cell lymphopenia. Persistent HIV replication is associated with increased immune activation that manifests itself in the B-cell compartment as well as hypergammaglobulinemia, polyclonal B-cell activation, induction of terminal differentiation of B cells, increased levels of autoantibodies, and increased frequency of B-cell malignancies. There are also concerns that rates of cancer, including those of B-cell origin, remain high in the HIV-infected population, indicating the need for a better understanding of pathways of immune surveillance and regulation in HIV disease.[2]

Many features of B-cell dysregulation in HIV disease suggest a prominent role for aberrant immune activation. HIV-induced immune activation of B cells is thought to be a contributing factor to the increased frequency of B-cell malignancies observed in HIV-infected individuals.

Disseminated Lymphadenopathy

The lymph node structure in early HIV infection shows destruction of dendritic cells with some structural disruption. Late-stage disease in the lymph node shows extensive damage, tissue necrosis, and loss of follicular dendritic cells and germinal centers with inability to support activation of T and B cells. Many clinical manifestations of HIV infection such as lymphadenopathy are closely linked to viral replication. Tissue pathology often correlates with viral gene expression in tissue macrophages, providing strong support for a central role of macrophages in progressive HIV infection and its clinical manifestations. Large numbers of HIV-infected macrophages are found in lymph nodes.[3]

The differential diagnosis in patients with disseminated lymphadenopathy has to include both benign and malignant causes, including sarcoidosis, metastatic disease, and lymphoma. The cervical lymph nodes are most frequently involved, followed by the mediastinal lymph nodes and the axillary lymph nodes. Disseminated lymphadenopathy represents a challenge to a majority of clinicians and may be caused by a vast array of diseases, including mycobacterial infection. Lymphadenitis is the most common extrapulmonary presentation of tuberculosis. The nodes in patients with mycobacterial lymphadenopathy are discrete, firm, and nontender. In time, a firm mass of matted nodes becomes visible. Hard, fixed nodes can be found in cancers and firm, rubbery nodes can be found in lymphomas.[4] The lymphocytic hypereosinophilic syndrome variant is associated with T-cell clones producing interleukin-5 (IL-5) and can evolve into lymphoma.[5]

AIDS-Related Lymphoma (ARL)

The primary difference between lymphoma in non-HIV–infected individuals and those with ARL is that ARL is consistently high grade and metastatic. Macrophage reservoirs recruit additional immune cells, including monocytes/macrophages, through the release of chemoattractants. Additionally, tumor-associated macrophages are known to promote tumor progression for most cancer types, including lymphomas.[6] Most cancers that are associated with HIV infection are driven by oncogenic viruses such as Epstein-Barr virus, human herpesvirus 8, and human papillomavirus. Systemic NHL appears to be declining in incidence as well, but to a lesser degree than Kaposi's sarcoma and primary central nervous system lymphoma.[7,8] NHL

occurs at greatly increased rates in people with HIV compared with the general population and generally has a poor prognosis.[9] The introduction of highly active antiretroviral therapy in the mid-1990s has led to marked declines in the incidence of most AIDS-associated illnesses.[10–13] ARL is now the second-most common AIDS-associated malignancy and is the AIDS-defining diagnosis in ~3% of HIV^+ patients, although it is uncertain what percentage of patients already diagnosed with AIDS develop lymphoma. Historically, patients with NHL and AIDS have been more likely to present with extranodal NHL and high-grade histological findings.[13,14] They have been less likely to respond to chemotherapy, with shorter overall survival. Reported predictors of poor survival included low (CD)4 count at diagnosis, having a prior AIDS defining illness, central nervous system presentation, other extranodal presentation, advanced stage of NHL, high serum lactate dehydrogenase levels, and older age.[15] Salemi *et al.* sequenced HIV-1 envelope glycoprotein 120 (gp120) clones obtained postmortem from several tumor and nontumor tissues of two patients who died with ARL-NHL. A 100-fold increase in the effective HIV population size in tumor versus nontumor tissues was associated with the emergence of lymphadenopathy and aggressive metastatic ARL. The different population dynamics between the viruses found in tumors versus the nontumor-associated viruses suggest that there is a significant relationship between HIV evolution and lymphoma pathogenesis.[16]

Cough in HIV Infection

Research into the physiology of coughing has established that interactions amid C-fibers and rapidly activating receptors in humans have the most significant effect on stimulation of coughing.[17] Acute cough is very common in persons with HIV infection and AIDS, and in most can be attributed to the same disorders that cause cough in the immunocompetent population.[18]

In a retrospective analysis of 26 predominantly homosexual men with AIDS and chronic cough, a diagnosis was established in 81%. Seventeen had a lower respiratory infection, 5 had Kaposi's sarcoma, and 3 had sinusitis. In a prospective multicenter investigation of a cohort of persons with HIV infection who did not have AIDS at the time of study enrollment, the most common respiratory disorders diagnosed in the first 18 months were upper respiratory infection (33.4%), acute bronchitis (16%), and acute sinusitis (5.3%). Only 4.8% of patients had bacterial pneumonia and 3.9% had *Pneumocystis* pneumonia. In HIV-infected persons, the incidence of specific pulmonary disorders correlates with threshold levels of $(CD)4^+$ lymphocytes, which is a good surrogate marker for immune function.[19] Patients with (CD)4 lymphocyte counts of >200 cells/μL and who appear well are very unlikely to have *Pneumocystis* pneumonia and other opportunistic infections, and chronic cough in these patients is far more likely to be caused by the same disorders as in the general population.[18] HIV-infected patients with $(CD)4^+$ lymphocyte counts of <200 cells/μL or those patients with counts of >200 cells/μL with unexplained fever, weight loss, or thrush who have unexplained cough should be suspected of having *Pneumocystis* pneumonia, tuberculosis, and other opportunistic infections, and should be evaluated accordingly.[18]

Eosinophilia in HIV Infection

Under certain disease conditions such as infection and inflammation, inflammatory cell recruitment along with eosinophils occurs. Neoplastic and hematologic disorders such as eosinophilic or lymphoblastic leukemias, lymphoma, mastocytosis, and hypereosinophilia can all manifest with a high eosinophil count (Table 5). Those disorders may be culprits, examples being reactive eosinophilia to carcinomas and lymphomas, as well as primary disorders such as acute eosinophilic leukemia.[20] Bacterial and viral infections usually do not cause eosinophilia, but high eosinophil counts can be seen with some fungal infections (allergic bronchopulmonary aspergillosis and coccidioidomycosis), HIV, but more commonly with parasitic infections associated with eosinophilia and Th2 lymphocyte cytokine (IL-4 and IL-5) profiles.[21] Eosinophils, or potent granulocytes are complete with their reactive oxygen species, growth factors, and inflammatory mediators. Eosinophil migration and degranulation will be the consequence, with the release of eosinophil-derived neurotoxin (EDN), IL-4 and IL-18.[22] On further stimulation, EDN primes the dendritic cell to process the antigen and lymphocyte ensuing in Th2 type of cytokine response with release of IL-4, IL-5, and IL-13.[23] These cytokines are the major products that stimulate the eosinophils resulting in eosinophil chemotaxis and inflammation.[22] Eosinophils then release their contents, including major basic protein, eosinophilic cationic protein, transforming growth factor β, and EDN (and regulating cytokines) with subsequent intense inflammatory response. IL-5, IL-13, and eotaxin play a central role in eosinophilic migration and inflammation in both tissues and blood.[24,25]

CONCLUSION

In HIV infection, the combination of innate and adaptive immunity can fail to eliminate the infectious agent, which persists in the system as a chronic infection.[26] In the case of HIV, the persistence of the infection is likely a result of both intrinsic characteristics of the virus and ineffective immune response including the ability of the virus to integrate into the host's cellular

genome, hypervariability of HIV, which escapes immune recognition and impairment of cell-mediated responses intrinsic to the disease.[26,27] Complexity of immune system deterioration seen in HIV with subsequent profound changes in structures and functions of various cells and pathways responsible for proper functioning of the major defenses of the human body ranks HIV infection as one of the imperative and vital topics in medicine.

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Patient-Oriented Problem Solving (POPS) Case Report

Fever, urticaria, lymphadenopathy, and protracted arthralgia and myalgia resistant to corticosteroid therapy

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ABSTRACT

Allergen immunotherapy is commonly incorporated in the management of allergic rhinoconjunctivitis, allergic asthma, and insect sting hypersensitivity. It is generally safe, but systemic reactions occasionally occur, mainly of the immediate type and rarely of the delayed type. We report a case of a 50-year-old man with allergic rhinoconjunctivitis on immunotherapy for 3 years and then received an injection from another patient's extract. The latter contained a higher concentration of house-dust mite and pollens of grasses, trees, and weeds. It also contained molds that the patient's correct extract did not have. Within half an hour, he developed a systemic reaction that resolved with symptomatic treatment. Two weeks later, he received one-half of his usual immunotherapy dose. Within a week, he developed urticaria, arthralgia, myalgia, fever, and lymphadenopathy. Laboratory abnormalities included leukocytosis, elevated erythrocyte sedimentation rate, hematuria, and elevated liver enzymes. Oral corticosteroid therapy for 3 weeks was ineffective. He developed significant myalgia and apparent mood changes, attributable to corticosteroid intake. After a single plasmapheresis, he felt remarkable improvement within <24 hours. Corticosteroid therapy was gradually withdrawn over 10 weeks without relapse of symptoms. This is a rare case of probable serum sickness after the administration of a wrong allergy immunotherapy extract. However, a causal relationship could not be proven. The response was poor to prolonged corticosteroid therapy but was remarkable to one plasmapheresis.

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CASE PRESENTATION

Chief Complaint

Fever, rash, joint pains, and muscle aches.

History of Present Illness

A 50-year-old man with allergic rhinoconjunctivitis has been receiving immunotherapy with an extract mixture of house-dust mite and pollens of weeds, grasses, and trees for 3 years. After an immunotherapy subcutaneous injection and returning home, his physician discovered that he received the extract mixture of another patient with a similar name. That extract contained a higher concentration of house-dust mite and pollens of grasses, trees, and weeds. It also contained molds that the patient was not originally receiving.

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The physician called the patient who reported a large local reaction and was asked to return to the office immediately. On arrival, he had generalized urticaria and facial edema but no respiratory distress. His blood pressure was 120/70 mmHg, pulse rate 92/min, respiratory rate 24/min. He was given diphenhydramine, 25 mg, and triamcinolone, 30 mg, intramuscularly. His symptoms improved during a 3-hour observation and he was discharged to continue diphenhydramine, 25 mg, orally every 4–6 hours.

He continued to have recurrent mild episodes of urticaria and facial edema for a week. After another week, he was given one-half the maintenance dose of his regular immunotherapy extract without any immediate reaction. A few days later, there was recurrence of generalized urticaria and facial edema, accompanied by enlarged cervical lymphnodes, fever, muscle aches, and stiff painful joints, particularly of the shoulders and hands. Immunotherapy was discontinued altogether.

He was started on prednisone, 20 mg, twice a day and after a few days was increased to 20 mg four times a day and then gradually reduced. Laboratory tests (Table 1) revealed leukocytosis, high erythrocyte sedimentation rate (ESR), elevated liver enzymes, and hematuria without proteinuria. Because of persistence of

Table 1 **Laboratory findings in a man with fever, urticaria, lymphadenopathy, and arthralgia after a wrong allergy immunotherapy extract injection**

Initial findings
- WBC, 17.3 K/mm^3 (neutrophil, 85.4%; lymphocyte, 9.4%; monocytes, 5.2%); Hgb, 15.7 g/dL (nl, 13.0–17.8); and platelets, 262 K/mm^3 (nl, 140–440)
- **Erythrocyte sedimentation rate, 35 mm/hr** (nl, 0–15)
- Sodium, 141 mmol/L; potassium, 3.8 mmol/L; chloride, 104 mmol/L; bicarbonate, 28 mmol/L; glucose, 81 mg/dL; BUN, 13 mg/dL; creatinine, 0.89 mg/dL; and calcium, 8.7 mg/dL
- **Alkaline phosphatase, 359 U/L; SGOT, 115 U/L; and SGPT, 123 U/L**
- **Urinalysis**: WBC, 0–1/hpf; **RBC, 15–20/hpf**; and negative casts, crystals, epithelial cells
- IgG and IgM antibody indices to *Borrelia burgdorferi*, <0.90 (negative)
- Acute hepatitis panel (hepatitis A IgM, hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core IgM), nonreactive

Subsequent findings
- Parvovirus B19 DNA PCR not detected; IgM antibody index, <0.1 (negative); and IgG antibody index, 5.3 (positive)
- IgG and IgM antibodies to CMV, negative
- ANA, <1:40; rheumatoid factor, <12 IU/mL (nl, <12)

Abnormal values are typed in bold.

symptoms, he was referred to our clinic for further management.

Physical Examination

Patient appeared fatigued, with a temperature of 98.5°F, pulse rate of 55/min, respiratory rate of 20/min, and blood pressure of 150/90 mmHg. His submandibular lymph nodes were slightly enlarged, firm, and mobile, but not tender. Chest was clear to auscultation and heart sounds were normal. There was no significant rash. Muscles of both upper and lower extremities were slightly weak. There was no hypo- or hyperreflexia. The shoulders and wrists were slightly tender but without swelling. The rest of the examination was within normal limits.

Current Medications

At this point, the patient was taking prednisone, 40 mg/day; cetirizine, 10 mg, twice a day; ibuprofen, 600 mg, every 6 hours; and hydrocodone, 10 mg, every 4 hours. He was also taking ropinirole, 1 mg, for restless leg syndrome; venlafaxine, 75 mg, once a day for depression; and zolpidem, 12.5 mg, at bedtime.

QUESTIONS

What Is the Differential Diagnosis?

The clinical picture (urticaria, arthralgia, fever, and lymphadenopathy) together with the laboratory findings (leukocytosis, high ESR, elevated liver enzymes, and hematuria) were compatible with serum sickness.[1] However, the patient's symptom complex could be the result of other illnesses, such as parvovirus B19 infection, Lyme disease, and hepatitis. Less likely causes are other viral infections (Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus) and rheumatoid arthritis (RA).

Human parvovirus B19 (HPV B19) infection has a varied clinical expression in affected individuals.[2] Most infected patients are children who may remain asymptomatic or may develop a nonspecific febrile illness. It causes erythema infectiosum, transient aplastic crisis, hydrops fetalis, and arthropathies that may persist for months or years.[3] It usually involves the hands, wrists, knees, and ankles. In a series of 22 cases,[4] elevated liver transaminases were noted in almost one-third, and elevated lactate dehydrogenase in more than one-half. In our patient, IgM anti–parvovirus B19 IgM titer index was <0.1 (negative) and IgG antibody titer index was 5.3 (>1.1 is positive), indicating a past infection. Also, his parvovirus DNA polymerase chain reaction was negative.

Lyme disease, a tick-borne illness caused by *Borrelia burgdorferi*, is commonly manifested as erythema migrans that may be associated with arthralgia, myalgia, and headache, with or without fever.[5] Our patient lived in a nonendemic area and had no recent travels or tick bites, his rash did not resemble erythema migrans, and he had negative IgM and IgG antibodies to *B. burgdorferi.*

Viral hepatitis infections may present with a serum sickness-like picture. An "arthritis-dermatitis" prodrome has been reported in ~10–30% of patients.[6] It is characterized by sudden transient polyarthritis or arthralgia of the wrists, hands, knees, and ankles. The joint symptoms precede the jaundice by days or weeks.[7] Associated skin lesions can include urticaria, maculopapular rash, and petechial rash. Our patient's acute hepatitis serological tests (hepatitis A, B, and C) were all negative.

RA presents with symmetric joint swelling, pain, and morning stiffness, accompanied by symptoms of myalgia and fatigue.[8] The classic synovitis in RA involves the metacarpophalangeal and proximal interphalangeal joints, but may also affect the wrists, knees, shoulders, ankles, and spine. The onset is usually gradual and symptoms must be present for at least 6 weeks for

diagnosis. Eighty percent of patients have positive rheumatoid factor. Our patient's acute presentation, noninvolvement of small joints, and a negative rheumatoid factor did not support the diagnosis of RA.

What Would Be the Further Management?

Serum sickness remained as the most likely diagnosis. The symptoms improved within 1 week of prednisone therapy and we began to slowly reduce the dose from 40 mg/day by 5-mg decrements every other day. However, within a week, his condition deteriorated. Prednisone was increased to 60 mg/day, without significant improvement for 1 week. Because of significant myalgia and mood changes, we became concerned about continuing corticosteroid therapy that seemingly had failed. We considered plasmapheresis based on a report of good response in a case of serum sickness secondary to wasp venom immunotherapy.[9] The premise would be the removal of circulating immune complexes. However, the result of testing for circulating immune complexes was negative and the C3 and C4 levels were normal (Table 2), which might be caused by the 6-week lapse since the onset of illness.

Initially, we considered a trial of up to three plasma exchanges. A 1-volume plasma exchange was performed using 5% human albumin for replacement, which amounted to 2.5 L. The following day, the patient reported a dramatic response with considerable decrease in joint and muscle pains and improvement in the patient's general well-being. A week later, the laboratory abnormalities resolved and prednisone was gradually tapered over 10 weeks without relapse.

The patient was living in another state and did not show up for his appointment at our clinic twice during 3 months after plasmapheresis. By telephone, he reportedly had no recurrence of fever, rash, or joint symptoms.

Final Diagnosis

Protracted serum sickness, resistant to corticosteroid therapy, with remarkable response to plasmapheresis.

DISCUSSION

Serum sickness[10] results from the deposition of circulating immune complexes (antigen–antibody–complement) in the postcapillary venules. An inflammatory reaction occurs in the blood vessel wall and surrounding tissue, with the release of proteolytic enzymes and subsequent tissue damage. The symptoms typically occur 1–3 weeks after exposure to the offending antigen, but may occur earlier within days in individuals who had previously been sensitized. The manifestations include fever, malaise, lymphadenopathy, arthralgia, and cutaneous eruption—usually urticaria. Arthralgia or arthritis occurs in 10–50% of cases, usually involving multiple, large joints. Some patients may present with nephritis, generalized vasculitis, neuropathy, and cardiopulmonary complications. Laboratory findings may include leukopenia or leukocytosis, with or without eosinophilia; elevated ESR; circulating immune complexes; variable levels of serum complement; hematuria and/or proteinuria; and hypergammaglobulinemia.

Table 2 **Levels of serum complement and circulating immune complexes 6 wk after the onset of serum sickness reaction after a wrong allergy immunotherapy extract injection**

Laboratory Test	Patient's Result	Normal Level
C3, mg/dL	136	83–239
C4, mg/dL	29	10–63
PEG IgG, mg/dL	<3.5	<3.5
C1q binding assay, μg/mL	<4	<4
Raji cell assay, μg/mL	<20	<20

Our patient presented with symptoms and signs compatible with serum sickness, with renal and hepatic involvement. Our laboratory evaluation was relatively late in the course, which explains the normal complement levels and lack of increased circulating immune complexes.

Serum sickness is most commonly caused by drugs, infectious agents, vaccines, and blood products. In some series, cefaclor was the most common antibiotic causing serum sickness in children.[11,12] In the past, animal antisera were common causes but their use has been markedly reduced. The literature contains only a few reports on serum sickness related to immunotherapy. After receiving the wrong high-dose immunotherapy extract, our patient developed an acute hypersensitivity reaction that resolved over 1 week. A week later, one-half of his usual immunotherapy extract dose caused no immediate reaction, but after a few days symptoms of serum sickness began. It is likely that because of the higher antigen concentration in the wrong extract, and possibly its mold content, immune complexes were formed during the following 3 weeks. Whether the subsequent immunotherapy injection of the patient's usual extract contributed to the reaction is unclear. If it had any role, it might be explained by the similarity of some antigens in both extracts.

Serum sickness to insect venom is more commonly caused by an insect sting[13,14] than to insect venom immunotherapy.[9] Apparently, it is very rarely caused by immunotherapy with aeroallergen extracts. Anaphylaxis and serum sickness occurred in an 8-year-old boy after his maintenance dose of immunotherapy with an extract containing house-dust mite, mold, and pollens.[15] His serum C3 and C4 levels were normal and

circulating immune complexes were not detectable. In another report,[16] serum sickness developed in two patients undergoing rush immunotherapy. One patient had four episodes of generalized urticaria during immunotherapy with house-dust mite and grass pollen, which was stopped on day 4. That same day, the patient developed joint pains and fever. The other patient's extract was a mixture of wasp and yellow-jacket venoms and he developed urticaria, fever, and arthralgia 3 days after a 4-day rush immunotherapy. In both patients, C3 and C4 levels were normal. Another report was on a 69-year-old man who developed serum sickness while on maintenance immunotherapy with wasp venom for 7 months.[9] Although immunotherapy was discontinued, he had two relapses at 6 and 11 weeks after the initial episode. The level of circulating immune complexes was slightly elevated during the first episode but normal on the subsequent two.

Most cases of serum sickness are mild and resolve within a few days to weeks.[10] In addition to discontinuation of any causative agent, symptomatic treatment may be in the form of antihistamines and nonsteroidal anti-inflammatory agents. In moderate to severe cases, corticosteroids are often needed. Our patient's symptoms persisted despite 3 weeks of corticosteroid therapy. In a patient with serum sickness to wasp venom immunotherapy, dramatic improvement occurred after plasma exchange therapy on three occasions.[9] Our patient had remarkable decrease in joint pains and muscle aches within <24 hours after plasma exchange. Plasmapheresis has been reported to be also successful in renal transplant patients who developed polyclonal antibody–induced serum sickness that did not respond adequately to systemic corticosteroids.[17]

CONCLUSION

Although a cause-and-effect relationship could not be proven, the development of serum sickness may be related to the administration of a wrong extract mixture or an erroneous high dose. If corticosteroid therapy fails, a trial of plasmapheresis is worth considering.

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Patient Oriented Problem Solving (POPS) Case Report

Recurrent diarrhea in a 26-year-old man

Troy W. Baker, D.O., Shayne Stokes, M.D., Jacob Clawson, M.D., Todd Garrett, M.D., Josh J. Sacha, D.O., and Erika Gonzalez-Reyes, M.D.

ABSTRACT

This is a case report of a 26-year-old healthy man with chronic diarrhea for 2 years. He was initially believed to have irritable bowel syndrome by his primary care physician after all stool studies yielded negative results. His symptoms persisted, which prompted a referral to a gastroenterology specialist. The patient's esophagogastroduodenoscopy revealed variable villous blunting and a paucity of CD 138 plasma cells, which helped reveal the final diagnosis. This cases illustrates a unique presentation of a common primary immunodeficiency that allergy/immunology specialists, along with primary care specialists, will likely encounter.

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CASE PRESTENTATION

Chief Complaint

Chronic diarrhea for 2 years.

History of Present Illness

A 26 year-old white male military aviator presented with a 2-year history of progressively worsening, nonbloody diarrhea. He denied any nausea, vomiting, abdominal pain, fever, chills, sweats, fatigue, or weight loss and had not traveled outside the United States in the previous year. His initial workup by his primary care physician included stool studies (bacterial culture, intestinal parasites, and occult blood), a complete metabolic panel, and a complete blood count. All initial studies were normal with the exception of a mildly decreased serum total protein level. The patient was subsequently given a diagnosis of irritable bowel syndrome. On follow-up, he continued to be symptomatic and was referred to a gastroenterology specialist for additional evaluation.

Medical History

The patient had a history of recurrent otitis media in childhood that required bilateral myringotomy with pressure equalization tube placement. He also had a history of recurrent pharyngitis resulting in tonsillectomy but denied any history of additional upper or lower respiratory tract infections. He denied any medication use and all age-appropriate vaccinations were up to date and verified by shot records. His family history was negative for any primary immunodeficiencies, unexplained early deaths, or consanguinity.

Physical Examination

This patient was a well-nourished, normal appearing adult man in no acute distress with normal vital signs. Head, eyes, nose, throat, and lymph nodes were unremarkable. Bilateral tympanosclerosis was noted. His cardiac and pulmonary exams were normal. His abdominal exam revealed no organomegaly, masses, or tenderness to palpation. Skin exam was normal.

QUESTION 1

Based on the history, what is the differential diagnosis for this patient with chronic diarrhea?

a. Irritable bowel syndrome
b. Inflammatory bowel disease (*i.e.*, Crohn's disease or ulcerative colitis)
c. Malabsorption syndrome (*i.e.*, celiac disease or chronic pancreatitis)
d. Chronic bacterial or parasitic infections (*i.e.*, *Campylobacter*, *Giardia*, or *Cryptosporidium*)
e. Primary or secondary immunodeficiency

Laboratory and Other Diagnostic Findings

A limited vitamin evaluation was performed that revealed normal vitamin B12 and folate levels. Screening antibodies for celiac disease to include antien-

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Table 1 **Laboratory results**

	Result	Reference Range
Complete blood count		
WBC	6.1	4.8–12 k/μL
Hgb	14.7	14–18 g/dL
Hct	43.9	39–50%
Plts	201	140–340 k/μL
Neutrophil (%)	62.5	35–71%
Lymphocyte (%)	28.6	25–45%
Monocyte (%)	7.5	0–10%
Eosinophil (%)	1.1	0–6%
Neutrophil, absolute	3.8	1.8–7.0 k/μL
Lymphocyte, absolute	1.7	1–4.8 k/μL
Eosinophil, absolute	0.1	0–0.5 k/μL
Quantitative immunoglobulins		
IgG	124	649–1634 mg/dL
IgA	<5	73–358 mg/dL
IgM	7	53–2512 mg/dL
Flow cytometry		
WBC	6.1	4.8–12 k/μL
Lymphocytes (%)	28.6	17–44%
Total lymphocytes	1.74	1.0–4.8 k/μL
$CD3^+$ (%)	80.5	55–82%
Total $CD3^+$	1.40	0.70–2.10 k/μL
$CD4^+$ (%)	18.3	28–57%
Total $CD4^+$	0.32	0.56–2.70 k/μL
$CD8^+$ (%)	59.4	12–35%
Total $CD8^+$	1.04	0.10–0.44 k/μL
CD4/CD8	0.31	0.9–3.9
$CD19^+$ (%)	9.9	9–29%
Total $CD19^+$	0.17	0.10–0.50 k/μL
$CD56^+$	8.8	5–22%

Hct = hematocrit; Hgb = hemoglobin; Plts = platelets; WBC = white blood cell count.

domysial IgA and antitissue transglutaminase IgA were negative (Table 1). Amylase and lipase levels were normal. Serum protein electrophoresis was ordered and revealed low serum total protein, albumin, and γ-globulin levels. Quantitative immunoglobulins were subsequently obtained and showed low IgG and IgM levels with an undetectable IgA level. A 24-hour urine protein level was normal but the patient was found to have an elevated stool α-1-antitrypsin level.

Further review of the patient's medical record revealed that on accession into the military and before the patient's initial presentation, routine vaccine titers had been performed. At that time, his titers were protective for rubeola but negative for rubella, varicella, hepatitis B, and mumps, despite confirmed prior vaccination and/or natural disease. Additional vaccine titers were subsequently drawn and showed undetectable levels against tetanus and *Streptococcus pneumoniae* (patient had no prior history of pneumococcal vaccination). Antidiphtheria IgG levels were obtained and found to be protective.

Concurrent with the aforementioned laboratory evaluation, esophagogastroduodenoscopy was performed and showed prominent duodenal nodularity with histopathological examination showing marked villous blunting, increased intraepithelial lymphocytosis, scattered active inflammation, and a paucity of plasma cells. A colonoscopy was also performed and showed scattered nodularity with histopathological examination showing reactive lymphoid hyperplasia and a paucity of plasma cells. Repeat stool and biopsy studies were negative for infectious organisms.

QUESTION 2

Based on the information obtained from additional laboratory and endoscopy evaluation, what is the differential diagnosis for this patient with chronic diarrhea, diffuse intestinal nodularity, marked villous blunting, a paucity of plasma cells, and hypogammaglobulinemia?

a. Malabsorption syndromes (*i.e.*, celiac disease and chronic pancreatitis)
b. Primary or secondary immunodeficiency
c. Gastrointestinal lymphoma
d. Protein losing enteropathy

QUESTION 3

What additional laboratory data or investigations would be helpful in obtaining the diagnosis?

a. Repeat endoscopy with biopsy after a gluten-free diet
b. Small bowel biopsies looking for malignancy
c. Human immunodeficiency virus (HIV) DNA polymerase chain reaction
d. Specific antibody production after vaccine challenge

Additional Diagnostic Evaluation

An initial diagnosis of celiac disease was considered given this patient's presentation with chronic diarrhea. After the initial endoscopy, he was placed on a gluten-free diet for 6 weeks after which he was reevaluated by esophagogastroduodenoscopy and colonoscopy. Additionally, antitissue transglutaminase IgG was performed and found to be negative. His repeat endoscopic exam and histopathological findings remained unchanged, making the diagnosis of celiac disease unlikely (see Figs. 1 and 2). Repeat histopathological evaluation was also negative for malignancy and infectious organisms, further helping to narrow the differential diagnosis. Initial evaluation of celiac disease generally begins with serological evaluation for antitissue trans-

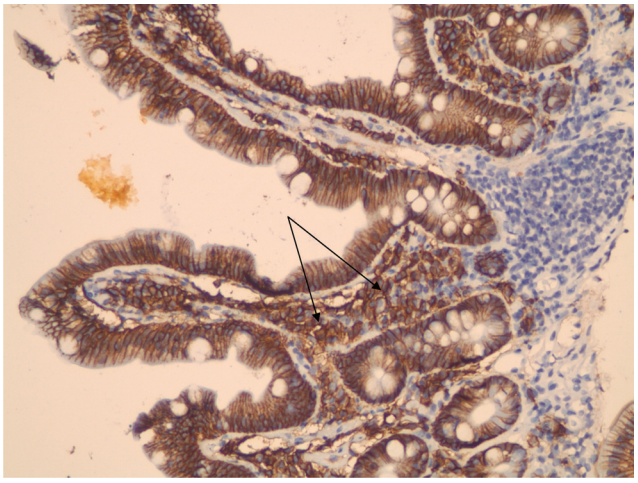

Figure 1. Photomicrograph of representative normal small intestine mucosa with normal villi and lamina propria. Membranes of the plasma cells stain brown (black arrows).

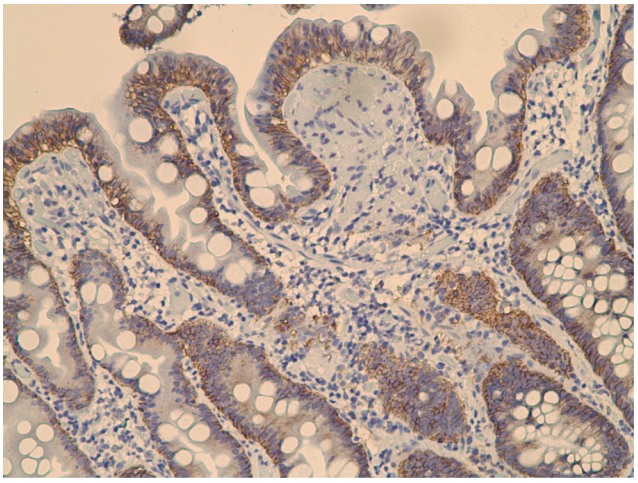

Figure 2. Photomicrograph of the subject case at 200× magnification showing variable villous blunting and lack of plasma cells in lamina propria (no brown staining). Staining materials are the same as mentioned in Fig. 1.

glutaminase IgA and antiendomysial IgA antibodies. These assays each have sensitivities and specificities exceeding 90%.[1] However, patients with concomitant celiac disease and IgA deficiency can be missed using IgA-specific tests. In such patients, testing for antitissue transglutaminase IgG antibodies, antiendomysial IgG antibodies, and/or antigliadin IgG antibodies should be performed and if positive, confirmed with small bowel biopsies.

HIV infection was also considered as an etiology of this patient's symptoms. The patient is an active duty military member where periodic HIV screening is required. Before symptom onset, he had two negative HIV screening tests using enzyme immunoassay. Although symptomatic, a third HIV enzyme immunoassay was obtained and was negative. Given his profound hypogammaglobulinemia, HIV DNA polymerase chain reaction was subsequently ordered and was likewise negative.

The patient was also given Pneumovax (Merck Sharp and Dohme Corp., Whitehouse Station, NJ) to assess his polysaccharide antigen responsiveness. Postvaccination titers obtained 4 weeks after vaccination showed undetectable titers to all serotypes tested. Serum isohemagglutinin studies would be noncontributory because of the patient's AB blood type.

Immunization with bacteriophage phiX174 was not performed but has also been used as a tool to both diagnose and monitor various primary and secondary immunodeficiencies. Patients with T-cell or T/B-cell interaction deficiencies (*i.e.*, adenosine deaminase deficiency and HIV disease) characteristically have diminished or absent amplification of antibody titers and limited antibody isotype switching from IgM to IgG after repeated immunizations with bacteriophage phiX174.[2] Computed tomography scans of his sinuses and chest were normal, and he continued to have no evidence of infection during his workup. Pulmonary function tests were normal.

Final Diagnosis

The patient's clinical presentation of chronic diarrhea with associated low total serum protein; hypogammaglobulinemia; impaired production of specific antibodies; and gastrointestinal findings of diffuse nodularity, marked villous blunting, increased intraepithelial lymphocytosis, reactive lymphoid hyperplasia, and paucity of plasma cells supports the diagnosis of common variable immune deficiency (CVID).

Clinical Course

The patient was started on monthly i.v. immunoglobulin (IVIG) replacement. Despite proper IVIG dosing, his serum total IgG trough level remained very low. In addition, a repeat stool α-1-antitrypsin level continued to be elevated. Although his hypogammaglobulinemia persisted, his diarrhea fully resolved and he remained infection free and otherwise completely asymptomatic. Quantitative immunoglobulins drawn 2 weeks after an IVIG infusion were found to be protective. Ongoing loss of immunoglobulins was assumed to be a function of CVID enteropathy. Current consultation with a gastroenterology specialist for consideration of treatment options for CVID-associated protein losing enteropathy is ongoing. In addition, the options of IVIG replacement every 2 weeks or a trial of subcutaneous immunoglobulin replacement were considered. The patient was recently started on weekly subcutaneous immunoglobulin replacement with planned follow-up of his IgG levels to monitor efficacy.

DISCUSSION

CVID, first described by Janeway and collegues,[3] is the most common symptomatic primary antibody deficiency that physicians will encounter. CVID is a heterogeneous disorder of atypical B-cell maturation and occasionally T-helper lymphocyte dysfunction, resulting in impaired plasma cell differentiation and antibody production. Because of its variable (and sometimes subclinical) manifestation, the true incidence of CVID is unknown but is estimated to affect between 1/25,000 to 1/50,000 white subjects.[4] It is most often diagnosed between the ages of 20 and 40 years but can be found in all age groups.[5]

Immunologic evaluation characteristically shows low serum IgG with low IgA and/or IgM.[6,7] Confirmation of impaired antibody production showed by poor responses to protein and/or polysaccharide vaccine challenges is also an essential part of the diagnosis.[4] Protein vaccine responses are usually assessed with tetanus or diphtheria toxoids; haemophilus conjugate; and/or measles, mumps, and rubella vaccines while polysaccharide response can be assessed with the administration of either pneumococcal polysaccharide vaccine or meningococcal polysaccharide vaccine.

Several rare, recessive gene mutations have been implicated in a handful of patients with CVID including inducible costimulator,[8] CD19,[9] the receptor of B-cell activation factor,[10] and CD20 and CD81 mutations.[11,12] Interestingly, mutations in the gene encoding TACI,[13] a transmembrane activator and calcium-modulating ligand interactor (TNFRSF13B) expressed on mature B cells, have been found in ~8–10% of patients.[14]

Up to 10% of CVID patients have no history of serious or recurrent infections[5] with ~20% manifesting gastrointestinal symptoms without an infectious cause.[15] The main gastrointestinal manifestation of CVID is transient or persistent diarrhea, which can be found in up to 57% of patients.[4] Symptoms of CVID enteropathy include diarrhea, malabsorption, and weight loss with some patients presenting with frequent watery stools without any other systemic effects.

Villous blunting in the small intestine is a common manifestation of CVID and appears to be an immune-mediated/inflammatory phenomenon resembling what is seen in celiac disease. The villous blunting can lead to diarrhea, protein losing enteropathy, and weight loss. Several features can help distinguish the villous blunting seen in celiac disease from that seen in CVID. Plasma cells are absent or decreased in patients with CVID whereas in classic celiac disease they are typically increased. In addition, removal of gluten from the diet typically causes no clinical or histopathological improvement if the underlying cause is CVID. Inflammation of the small and large intestine can also be seen in up to 13% of patients with CVID. The management of inflammatory bowel disease occurring in patients with CVID is generally the same as for immunocompetent patients, although gastrointestinal inflammation in patients with CVID can be more difficult to control.[16]

CONCLUSIONS

This case illustrates one of the varied and less common presentations of CVID. Although patients with CVID frequently report a history of recurrent sinopulmonary infections, physicians should also consider CVID in individuals presenting with isolated gastrointestinal manifestations and hypogammaglobulinemia, in particular in patients who have findings consistent with celiac disease who do not respond to a gluten-free diet and have biopsy findings showing a paucity of plasma cells.

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Patient Oriented Problem Solving (POPS) Case Report

A 71-year-old man with anaphylaxis after eating grits

Jonathon Posthumus, M.D., and Larry Borish, M.D.

ABSTRACT

The allergist is frequently called on to evaluate patients after episodes of anaphylaxis to determine the cause and implement preventive measures that will reduce the patient's risk from future episodes. The etiology of anaphylaxis can be the result of numerous causes that may go undiagnosed if a thorough evaluation is not performed. We present a 71-year-old man with no history of food allergy or atopy who presented to the emergency room and then our allergy clinic for evaluation after suffering anaphylaxis after a meal of grits and shrimp. The underlying diagnosis, which was subsequently determined, requires a high index of suspicion and should be included in the differential diagnosis of any patient presenting with unexplained anaphylaxis.

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CASE PRESENTATION

Chief Complaint

Food-induced anaphylaxis.

History of Present Illness

A 71-year-old man with a history of hypertension, gastroesophageal reflux, and dyslipidemia presented to our clinic after an allergic reaction. His allergic reaction occurred within 1 hour of his evening meal, which consisted of shrimp with grits and bacon. The reaction started with his eyes becoming itchy and watery, followed by nasal congestion and clear rhinorrhea. His tongue and lip then became swollen and he had excessive drooling. He developed an itchy rash on his arms and full body flushing. Next, he experienced shortness of breath, which prompted him to seek emergency medical care. He denied nausea, diarrhea, abdominal cramps, light headedness, or syncope. After evaluation in the emergency room, he was treated with methylprednisolone, diphenhydramine, and nebulized epinephrine. He was admitted for observation but had no further symptoms and was discharged home with an epinephrine autoinjector device and a prednisone taper and told to avoid seafood.

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He presented to our clinic the next day. He had no similar prior episodes. He denied any history of atopic disease. He had eaten shrimp from the same bag and not had similar reactions. His wife consumed the same meal that he did and did not have similar symptoms. His review of systems was unremarkable. His medications had not changed recently. He had no known drug allergies and specifically no history of reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

Physical Examination

His vital signs were normal. He was a well-appearing man, in no distress, with clear conjunctivae. Nasal, oropharyngeal, and respiratory exam were normal. Skin examination was normal with no signs of eczema, urticaria, or other rash.

Initial Laboratory and Diagnostic Findings

His complete blood count with differential and basic metabolic panel were unremarkable. His total IgE drawn 2 days after his episode was 747 IU/mL and specific IgE to the components of the meal including corn, shrimp, milk, pork, and tomato were all <0.35 kU/L. Skin testing was not performed because of the proximity to the anaphylactic episode and recent use of antihistamines.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Food-Induced Anaphylaxis?

In 2006, a panel of experts in allergy and immunology developed a definition of anaphylaxis as that of clinical scenarios that include a combination of the acute onset of reactions that involve the skin, mucosal

Table 1 **Differential diagnosis of immunologic and nonimmunologic mimics of food allergy**

Masquerading Food	Actual Trigger	Diagnosis
Fruits and vegetables	Birch, mugwort, ragweed, and profilin[5]	Oral allergy syndrome*
Corn, wheat, and flour	*Der p* 1	Oral mite anaphylaxis*
Avocado, banana, kiwi, and others	Latex (hevein,1,3β-glucanase)[6,7]	Latex-fruit syndrome*
Wheat, celery, shellfish, cabbage, peaches, grapes, apples, and others	Exercise[8]	Food dependent, exercise-induced anaphylaxis*
Mammalian meat	Galactose-α-1,3-galactose	Delayed meat anaphylaxis*
Dairy, eggs, and meats	Enterotoxin	*Staphylococcus aureus* food poisoning
Dairy	Lactose	Lactase deficiency
Pork	Cat albumin	Pork-cat syndrome[9]*
Soy sauce, tomatoes, meat, parmesan cheese, and mushrooms	Monosodium glutamate[10]	Preservative intolerance
Cheese, smoked meats, alcohol, and chocolate	Tyramine	Pheochromocytoma crisis and carcinoid syndrome[11,12]
Salad bars, dehydrated fruits, wine, and others	Metabisulfites and other sulfites[13]	Preservative intolerance
Fish and cheese	Scombroid[14] and ciguatera toxin	Scombroid and ciguatera poisoning

**IgE-mediated reaction.*

tissue, or both and respiratory or vascular compromise.[1] Anaphylactic reactions can occur as a result of IgE-mediated and non–IgE-mediated pathways.[2] The patient in our case developed symptoms within 2 hours of a meal, which prompted a thorough evaluation for a food allergen as the cause of his reaction. His serum did not contain specific IgE to any of the components of the meal and therefore we considered alternative diagnoses. Other ingested food-associated antigens and toxins mimic anaphylaxis. For example, cross-reactivity of aeroallergens and profilin contained within fruits and vegetables can cause oral allergy syndrome.[3–5] Latex allergy is also associated with cross-reactivity to fruits, which has recently been linked to 1,3β-glucanase.[6] Many other immunologic and nonimmunologic mimics of food allergy have been described (Table 1).

Figure 1. *Mite obtained from grits at 100× magnification.*

What Additional Investigations Would Be Helpful in This Patient?

Given that his reaction occurred immediately before our first visit, we had the patient return after 6 weeks for skin-prick testing. His total IgE was repeated and was 416 IU/mL. Skin testing was performed with the grits and frozen shrimp (freshly thawed) used in the original meal by making a protein extract in normal saline. Positive control with histamine resulted in a 10-mm wheal with flare and there was no reaction to saline. The protein extract made from his grits produced an 11-mm wheal with flare. Skin testing after heating the grit extract in a microwave oven for 3 minutes on high power continued to induce a 10-mm wheal with flare. The shrimp mixture produced no reaction. A new bag of grits was obtained and the skin testing protocol was repeated with negative results. Gross inspection of the grits revealed no abnormalities. Light microscopic examination of the grits, however, revealed numerous mites consistent with the appearance of *Dermatophagoides farinae*[15] (Figs. 1 and 2). Subsequently, specific IgE to various mite species was obtained and *D. farinae* was shown to be 92.30 kU/L. In addition, the patient showed sensitivity to *Dermatophagoides pteronyssinus* (33.50 kU/L), *Tyrophagus putrescen-*

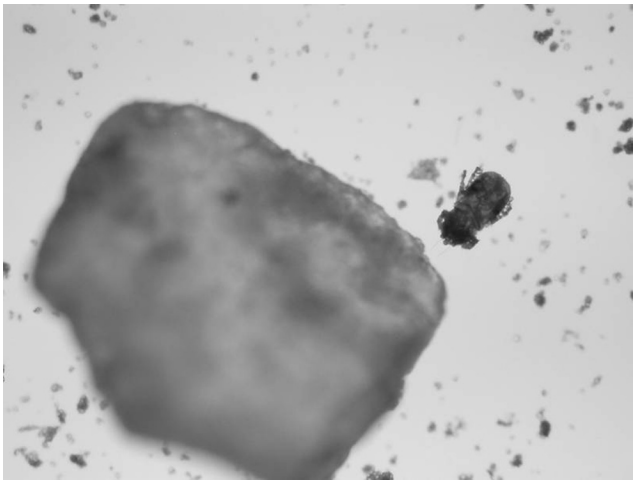

Figure 2. *Mite adjacent to grit at 40× magnification.*

tiae (3.65 kU/L), *Acarus siro* (4.12 kU/L), and *Lepidoglyphus destructor* (5.07 kU/L).

Clinical Course

On further questioning, the patient and his wife reported that the grits they had used in the meal the evening of the reaction had been in their pantry for over a year in a cloth sack. They had obtained the grits while on vacation in South Carolina and this was the first time they used them for a meal. The results of his evaluation indicated that his reaction likely occurred because of ingestion of large quantities of mites to which he was sensitized. We advised him that he could safely add back shrimp, tomato, milk, and corn to his diet. We asked him to discard the grits mixture. He was instructed on a food allergy action plan and on avoidance measures for the mites. These included appropriate bedding covers and to store his grains and cereals in airtight containers in the refrigerator because this hinders mite reproduction and to continue to carry an epinephrine injector because newly purchased grain products can occasionally contain mites.[16] He has experienced no further reactions in the last 4 months following our recommendations for avoidance.

DISCUSSION

The lifetime prevalence of anaphylaxis is estimated at 0.05–2%.[17] The most common causes of anaphylaxis are foods, followed by medications and then venom. Other rare causes of anaphylaxis are exposure to semen, latex, or exercise, although many cases of anaphylaxis are deemed idiopathic when no identifiable cause is established.[18] According to prior case series, ~32–37% of cases of anaphylaxis are left undetermined and are labeled as idiopathic.[19,20]

Oral mite anaphylaxis (OMA) involves the ingestion of wheat, flour, or grains infested with mites, either dust or storage, and their associated allergens by a patient with underlying sensitization and clinically presents with the signs and symptoms of a systemic IgE-mediated hypersensitivity reaction. OMA been commonly referred to as "pancake syndrome" given its frequency after ingestion of contaminated pancakes.[21] OMA was first reported by Erben *et al.* in 1993 after an episode of anaphylaxis that occurred in a mite-allergic patient after ingestion of *D. farinae*–contaminated *beignets* from New Orleans.[22] The word *farinae* is derived from the Latin word farina, for "flour," or a meal made from cereal grains, reflecting the recognized tendency of these insects to infest flour stores. The incidence of OMA is unknown. OMA has been mainly reported in areas of increased humidity such as the tropical/subtropical climates, although it has been seen outside the tropics, *e.g.*, in Philadelphia, Detroit, and Massachusetts.[23,24] Prior cases have typically occurred in patients known to have allergic rhinitis and/or asthma, who are sensitized to dust or storage mites, and episodes occurred when they ingested food such as wheat, flour, or other grains infested with the mites.

Our patient was unusual in that he had no history of allergic rhinitis or sensitivity to dust mites as an inhalant allergen. His total IgE was markedly elevated and >10% of this was specific for *D. farinae*. This striking elevation of total IgE, with much of the total comprised of specific IgE targeting a single antigen, is similar to the recently reported syndrome of adult-onset food anaphylaxis to mammalian meats associated with IgE to galactose-α-1,3-galactose.[25] OMA can occur regardless of whether or not the grain is cooked because the relevant allergens appear to be thermoresistant both clinically and by skin testing, as shown previously by Sánchez-Borges *et al.*[16] Although not present in our case, there has been an association between OMA and NSAID hypersensitivity, which is thought to reflect the presence of components in dust-mite extracts capable of inhibiting cyclooxygenase pathways.[21,26] There has also been a presentation of the OMA associated with exercise.[27]

Criteria for the diagnosis of OMA include (1) compatible symptoms occurring after the intake of foods prepared with wheat flour; (2) previous history of rhinitis, asthma, atopic dermatitis, and/or food allergy; (3) *in vivo* or *in vitro* demonstration of IgE-mediated sensitization to mite allergens; (4) positive immediate-type skin test with extract of the suspected flour; (5) negative skin tests to wheat and to uncontaminated flour extract; (6) clinical tolerance to foods made with uncontaminated wheat flour; (7) microscopic identification of mites in the suspected flour; (8) presence of mite allergens in the flour; and (9) hypersensitivity to NSAIDs.[21]

Final Diagnosis

Oral mite anaphylaxis.

CONCLUSION

Many cases of food-related anaphylaxis presenting to the emergency room or to an allergy clinic may be erroneously regarded as idiopathic when testing to seemingly relevant food ingredients are negative because they may contain hidden allergens.[28,29] This case reinforces that food-induced anaphylaxis can be caused by many IgE-mediated and non—IgE-mediated mechanisms. Among the IgE-mediated reactions, OMA should be a consideration in patients presenting with food-induced allergic reactions.

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Patient-Oriented Problem Solving (POPS) Case Report

A 44-year-old man with bilateral eyelid swelling

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ABSTRACT

Swollen eyelids are commonly ascribed to allergic conjunctivitis, contact dermatitis, eczema, angioedema, or acute sinusitis. The differential diagnosis extends to thyroid eye disease; blepharitis; Sjögren's syndrome; Churg-Strauss vasculitis; Wegener's granulomatosis; Gleich syndrome; orbital and ocular lymphoid hyperplasia or adnexal lymphoma; idiopathic orbital inflammatory disease/idiopathic sclerosing orbital inflammation; rarely, orbital parasitosis; and IgG4-related diseases. The likely diagnosis proceeds from the more to the less common in patients without a history of allergy or infection. Both ocular lymphoid hyperplasia and ocular adnexal lymphoma must be considered in the differential diagnosis of persistent disease, and neither of these entities can be recognized or differentiated from one another clinically or radiologically. Early diagnosis is essential because therapy may consist of frequent follow-up and/or active intervention. Outcomes in patients treated early and appropriately are often favorable.

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CASE PRESENTATION

Chief Complaint

The patient is a 44-year-old man who presents with a 4-month history of intermittent swelling of the eyelids.

History of Present Illness

The patient complained of intermittent swelling of the eyelids for 4 months with no associated ocular pain, visual disturbance, erythema, increased lacrimation, or pruritus. He denied any history of trauma, foreign body, toxic or smoke exposures, other facial swelling, or throat involvement and denied any associated facial eczema or urticaria. The swelling would completely resolve when corticosteroids were administered, but, subsequently, the swelling would slowly reappear. The patient reported a history of persistent allergic rhinitis but denied any prior eye symptoms. His history included nasal polyps status postnasal polypectomy, recurrent sinusitis, moderate persistent asthma, bicuspid aortic valve, history of eczema, chronic prostatitis, bilateral spontaneous pneumothoraces status postbilateral pleurectomy, and hyperlipidemia.

His medications included amlodipine besylate at 5 mg daily, rosuvastatin calcium at 10 mg daily, mometasone furoate monohydrate nasal spray at 50 μg 2 sprays daily, fluticasone/salmeterol at 100/50 μg 1 puff b.i.d., and montelukast sodium at 10 mg daily. The patient denied the use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, herbal therapies, or over-the-counter medications. There was a family history of allergic rhinitis but no history of angioedema or urticaria.

Physical Examination

Vital signs were temperature of 98°F; heart rate of 73/min; respiratory rate of 17/min; blood pressure of 105/79 mmHg, and O_2 saturation of 98%. Bilateral eyelid edema was noted (Fig. 1), which was boggy, not erythematous, and nontender to palpation. No proptosis was noted and the extraocular muscles were intact. The funduscopic examination was unremarkable and there was no lymphadenopathy. The lungs were clear and the heart revealed a 2/6 systolic murmur in the aortic area. The remainder of the physical examination was normal.

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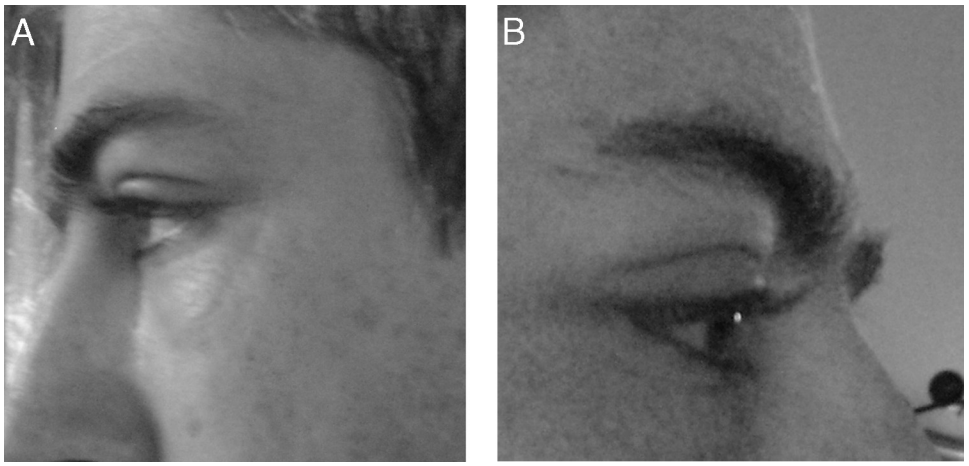

Figure 1. (A and B) Left and right eyelid edema, respectively.

QUESTION 1

Which of the following are included in the differential diagnosis of a patient with eyelid swelling?

A. Angioedema
B. Allergic conjunctivitis
C. Thyroid dysfunction
D. Contact dermatitis, eczema
E. Blepharitis
F. Sjögren's syndrome
G. Churg-Strauss vasculitis
H. Erdheim-Chester syndrome
I. Tolosa-Hunt syndrome
J. Wegener's granulomatosis
K. Sarcoidosis
L. Gleich syndrome
M. Acute sinusitis
N. Ocular lymphoid hyperplasia
O. Ocular adnexal lymphoma
P. Idiopathic orbital inflammation (IOI)/orbital pseudotumor/idiopathic orbital inflammatory disease/idiopathic sclerosing orbital inflammation
Q. Orbital parasitosis
R. IgG4-related diseases (IgG4-related systemic disease, systemic IgG4 disease, hyper-IgG4 disease, or systemic IgG4-related plasmacytic syndrome)

QUESTION 2

What further studies would one consider at this point?

A. Complete cell count
B. Thyroid-stimulating hormone, free T_4
C. cANCA, pANCA
D. Erythrocyte sedimentation rate
E. ANA, SS-A, and SS-B antibodies
F. C_3, C_4, C_H50, and IgE
G. ACE
H. Allergy skin testing
I. CT of sinuses and orbits
J. Total serum IgG and IgG4
K. Lacrimal gland biopsy with IgG4 staining

Discussion of the Differential Diagnosis

Angioedema (chronic, idiopathic, acquired, or hereditary angioedema, allergic angioedema secondary to food, or drug allergy) was unlikely in view of no history or family history of angioedema, normal complement levels, and no recent medication alterations or use of nonsteroidal anti-inflammatory drugs or ACE inhibitors. The patient had no ocular itching, tearing, or conjunctival changes to suggest allergic conjunctivitis. In addition, all allergy skin tests were negative, further excluding this diagnosis. The free T_4 and thyroid-stimulating hormone were normal, thus, excluding thyroid dysfunction. The eyelids had no erythematous, ulcerated, or eczematoid reaction and no crusted debris were noted on the eyelid excluding eyelid eczema, contact dermatitis, or blepharitis. The patient denied decreased tearing, redness, or photosensitivity. The SS-A, SS-B, and ANA were negative, making Sjögren's syndrome unlikely.

The patient denied headache, facial pain, and the sedimentation rate was normal, excluding temporal arteritis. The cANCA, pANCA, ACE, and IgE levels were all normal, making Churg-Strauss vasculitis, Wegener's granulomatosis, and sarcoidosis unlikely. The complete cell count had a total eosinophil count of 240 cells/mm^3, making Gleich syndrome unlikely. A CT of the sinuses revealed mild mucoperiosteal thickening of the maxillary and ethmoid sinuses without associated bone changes to suggest any orbital infection.

Tolosa-Hunt syndrome was unlikely because there was no involvement of the cavernous sinus on CT scan, no painful ophthalmoplegia, cranial nerve involvement, optic neuropathy, facial paralysis, or involvement of the mandibular or maxillary branches of the trigeminal nerve. The sclerosing variant of orbital inflammation is uncommon and unlikely in this case because it is characterized by proptosis, mild external inflammation, restricted motility, diplopia, and dull chronic pain.

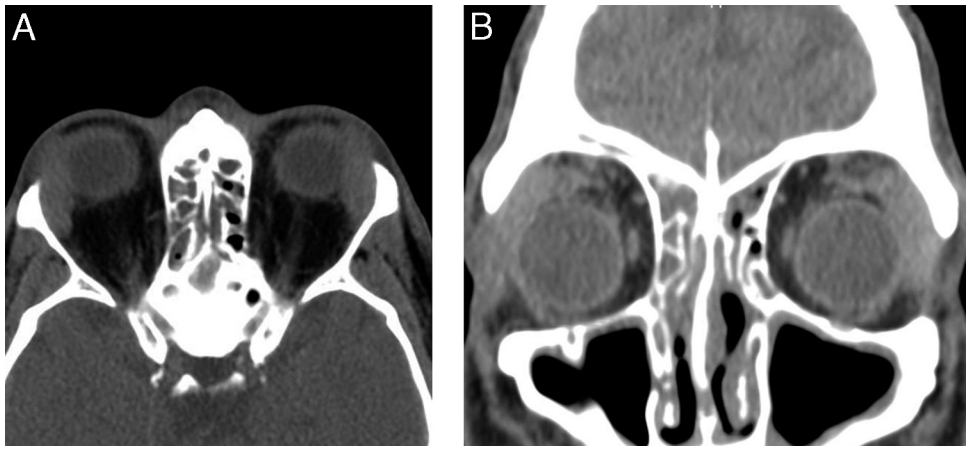

Figure 2. (A and B) Axial and coronal CT of orbits, respectively, showing bilateral lacrimal gland enlargement with the right gland appearing more prominent.

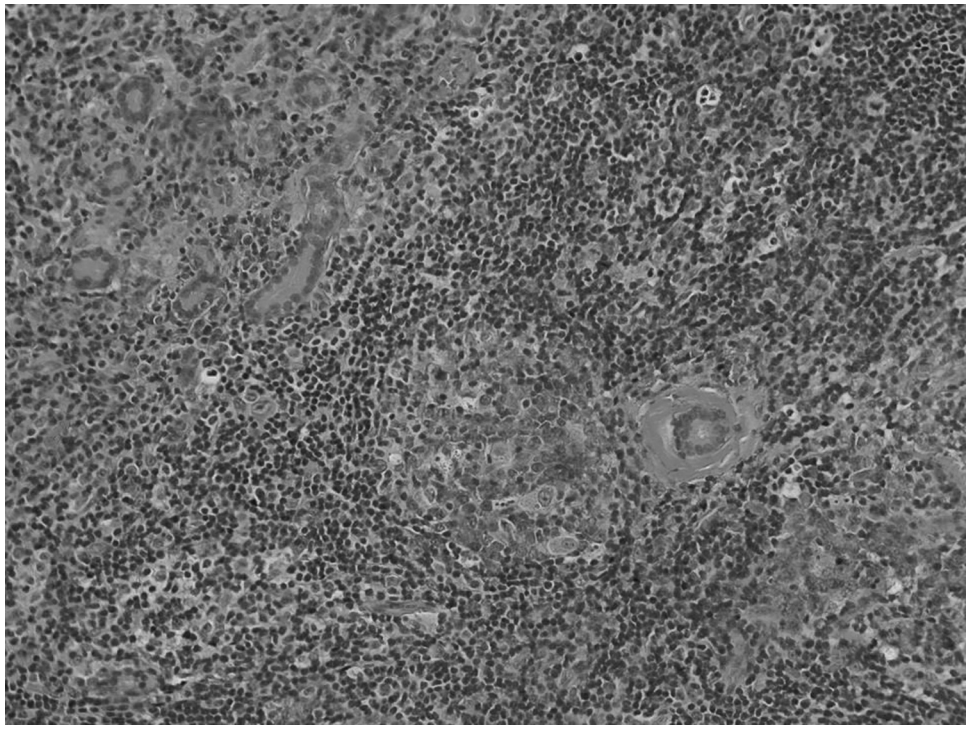

Figure 3. Right lacrimal gland biopsy showing follicular lymphoid hyperplasia with mild eosinophilia (H & E: ×200).

Erdheim-Chester syndrome may present with mild impairment to loss of vision from a mass effect. This is also unlikely because patients often have systemic involvement (brain, heart, lung, liver, kidney, retroperitoneal space, and musculoskeletal system).[1]

Additional Diagnostic Findings

The total serum IgG and IgG4 levels were elevated (IgG total, 1277 mg/dL; IgG4, 268 mg/dL). CT of the orbits (Fig 2) revealed no evidence of any obvious eyelid lesion or thickening. Both left and right lacrimal glands were enlarged, but the right lacrimal gland was more prominent. A right lacrimal gland biopsy (Fig 3) revealed severe atrophy of the parenchyma. The inflammatory infiltrate was nongranulomatous and included sheets of small well-differentiated lymphocytes and germinal centers. Flow cytometry showed a predominance of $CD5^+$ T cells and polytypic CD_5^-, CD_{10}^-, CD_{19}^-, and CD_{20}^+ B cells with a kappa-to-lambda ratio of 2.1:1. The biopsy was consistent with lymphoid hyperplasia with extensive acinar atrophy and mild fibrosis and no ocular adnexa lymphoma or orbital parasitosis. IgG4 stain (Fig 4) did show a significant number of IgG4 plasma cells at least 50/high-power field and comprising 30% of the total.

DISCUSSION OF THE DIAGNOSIS

Although the orbit is devoid of lymphatics, it is a common location for lymphoid lesions. The lymphoid lesions that are most frequently seen are idiopathic inflammation, lymphoid hyperplasia, and lymphomas.[2,3] IOI (orbital pseudotumor or idiopathic orbital inflammatory disease) is both an adult and pediatric disease characterized by a benign nonspecific inflam-

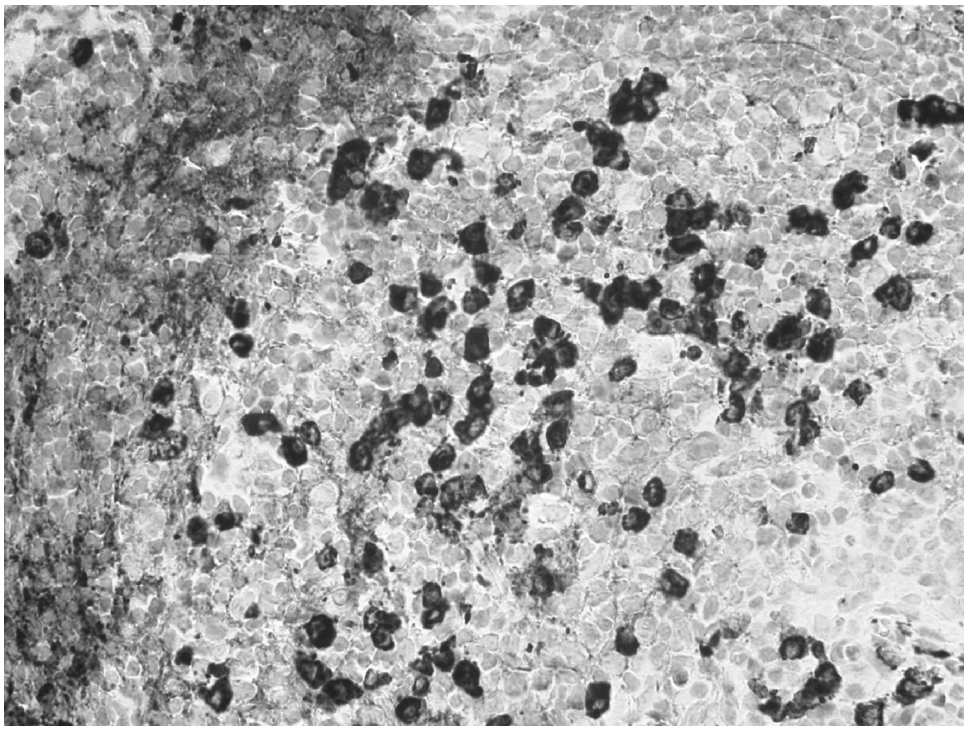

Figure 4. *Immunohistochemical stain for IgG4 showing increased $IgG4^+$ plasma cells within follicular lymphoid hyperplasia (IgG4 stain: ×400).*

matory process with a polymorphous lymphocytic infiltrate and fibrosis.[4,5] It accounts for 5–8% of all orbital masses and has involved the extraocular muscles, fat, sclera, optic nerve sheath, and/or the lacrimal gland.[4] It is a frequent cause for orbital biopsy.[1]

The differential diagnosis for IOI includes the following: sclerosing variant of orbital inflammation; autoimmune thyroid disease (endocrine exophthalmos); sarcoidosis; Wegener's granulomatosis; Crohn's disease; systemic lupus erythematosus; Churg-Strauss syndrome; Erdheim-Chester syndrome (systemic non-Langerhans histiocytic xanthogranulomatous inflammatory disease); Tolosa-Hunt syndrome; idiopathic fibrosclerotic disorders; periarteritis nodosa; scleroderma; sclerosing cholangitis; histiocytosis X; giant cell arteritis; neoplasms (lymphoma, lymphoproliferative disorders, rhabdomyosarcoma, choroidal malignant melanoma with extra sclera spread, and metastatic diseases); infectious diseases; congenital mass lesions (dermoid cyst and lymphangioma); and occult or distant trauma.[1,4] Localized anterior IOI may be caused by a retained foreign body with local granuloma.[1] Idiopathic inflammation may be diagnosed clinically, but lymphoid hyperplasia and lymphomas have a similar clinical and radiological presentation, making the differential diagnosis extremely difficult.

Treatment of IOI has included triamcinolone injection, cyclosporine A, corticosteroids, methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, anti–TNF-α, and interferon α.[1,4,5]

Ocular adnexal lymphoma (OAL) comprises lymphoma that affects the orbit, lid, lacrimal gland, and conjunctiva. These tumors can be solitary, multicentric, unilateral, or bilateral. They can invade bone, sinuses, nasopharynx, and the cranial cavity. Dissemination can occur to ipsilateral and/or contralateral regional lymph nodes as well as to more distant nodes centrally and peripherally (*e.g.*, para-aortic and popliteal nodes). OALs are mostly extranodal non-Hodgkin's lymphomas (NHLs), with the most common subtype being the extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type,[6,7] according to the latest World Health Organization lymphoma classification.[8] The other four types of OAL are follicular cell, mantle cell, diffuse large B cell, and lymphoplasmacytic lymphoma. They are all B cell, NHL, the subtype derived from various stages of B-cell maturation. The new classification of lymphoma is dependent on histological, immunophenotypic, and molecular genetic analysis.[9] Hodgkin's lymphoma does not affect the ocular adnexal structures unless there is widespread systemic involvement or a history of previous systemic Hodgkin's lymphoma.

OALs often have characteristic appearances in many patients.[10] Conjunctival lymphoid tumors tend to form mobile, salmon-colored masses that may conform to the globe. Subcutaneous tumors may present as masses with ulceration of the overlying skin.[11] Orbital tumors may produce typical signs of proptosis and extraocular muscle dysfunction.[12] The superior orbit is a frequent location of lymphoid tumors and the lacrimal gland is the site of origin for ~30% of orbital lymphoma.[13] The extraocular muscles themselves may also be the origin for orbital lymphoid tumors, with the superior rectus

and levator muscles most commonly affected.[14] Generally, nonconjunctival OALs are more often associated with systemic disease, whereas conjunctival lymphomas are most often localized with no systemic disease present.[15] The most widely used staging system for malignant lymphomas is the Ann Arbor staging system, which was first used for Hodgkin's disease in 1971.[16] Although its usefulness for the staging of other lymphomas has been challenged, the modified Ann Arbor system[17] remains the primary means for determining clinical stage of patients with both nodal and extranodal NHL. Lymphoma confined to the orbit is designated as stage I; involvement of adjacent structures (sinuses, tonsil, and nose) is stage II; stage III is nodal disease below the diaphragm; and stage IV, by definition, refers to disseminated involvement of one or more extranodal sites (*e.g.*, liver and bone). "E" is used when there is a local extranodal extent (*e.g.*, IE, IIE, IIIE, and IVE). Approximately 20% of the patients will have stage III or IV disseminated involvement.[18]

Lymphoid hyperplasia and lymphoma have similar clinical, radiological, and histopathologic features. Immunophenotypic studies of T- and B-cell composition and immunoglobulin light-chain production are very helpful features to differentiate lymphoid hyperplasia from malignant lymphoma lesions that could not otherwise be diagnosed based on morphology alone. In lymphoid hyperplasia, one usually sees a mixture of B cells (usually ≤60% of lymphocytes) and T cells, with a slight predominance of the former and polyclonal expression of immunoglobulin light chains. Lymphoma is characterized by a striking predominance of B cells and monoclonal expression of immunoglobulin light chains with kappa-chains usually more commonly expressed than lambda-chains.[9]

In 2001, the first description of systemic IgG4 disease included patients with lymphocytic (or lymphocytoplasmic) sclerosing pancreatitis (LSP) with retroperitoneal fibrosis and other sclerosing lesions.[19,20] LSP and retroperitoneal fibrosis are the most widely recognized manifestations. Orbital necrobiotic xanthogranuloma with LSP and other sclerosing lesions appear to be part of the spectrum of this disease.[19] IgG4-related diseases most often include autoimmune sclerosing pancreatitis, retroperitoneal fibrosis, and sclerosing cholangitis. Less frequently, tubulointerstitial nephritis, pulmonary plasma cell granuloma and other lung lesions, constrictive pericarditis, prostatitis, inflammatory aortic aneurysm, mastitis, pachymeningitis, thyroid lesions, hepatitis, lymphadenopathy, retroperitoneal and mediastinal fibrosis, skin, sclerosing mesenteritis, paravertebral and hypophysis lesions, hypocomplementemic urticarial vasculitis, and multiorgan involvement have been reported.[19–28] Recently reported are cases of pleural effusion with predominant lymphocytes and pleural effusion with chronic bilateral lymphoplasmacytic pleuritis on one side and neutrophil predominance on the other, complicated by acute bacterial pleuritis.[29,30] An association with sarcoidosis and Rosai-Dorfman disease has also been described.[31,32]

In Japanese patients with IgG4 autoimmune pancreatitis, the salivary gland is the third most common site of involvement after sclerosing cholangitis and lymphadenopathy. Chronic sclerosing sialadenitis (Kuttner tumor) along with Mikulicz disease and orbital pseudotumor are all associated with elevated serum and tissue levels of IgG4 and rapidly respond to immunosuppressive therapy. Geyer and Deshpande propose that IgG4-associated sialadenitis be used to describe salivary gland involvement and IgG4 dacryoadenitis be used to describe orbital involvement.[33] Obliterative phlebitis is often identified in sclerosing pancreatitis and sclerosing sialadenitis but not seen in ocular adnexal disease.[20]

A case of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma arising from IgG4-related tissue was reported by Sato *et al.*[34] MALT lymphoma is associated with a history of chronic inflammatory autoimmune disorders including *Helicobacter pylori* chronic gastritis, Sjögren syndrome, and Hashimoto thyroiditis. Sato *et al.* consider patients with ocular adnexal IgG4-related disease at increased risk for developing ocular adnexal MALT lymphomas.[20] Other authors have reported patients with IgG4-related disease developing B-cell MALT lymphoma.[20] Salivary duct carcinoma has been reported in a patient with IgG4-related disease of the parotid.[35]

Treatments include observation, corticosteroids, rituximab, bortezomib, or radiotherapy, and sequential corticosteroids and tamoxifen.[36–39]

Patients with lymphoid hyperplasia must be followed closely because it is now recognized that orbital lymphoid hyperplasia and lymphoma are a spectrum and that hyperplasia may undergo malignant transformation with time.[40,41] Irrespective of the pathology found, a staging investigation at the time of diagnosis is indicated to assess the extent of the disease and plan therapy.

Treatment options for lymphoid hyperplasia include a wait-and-watch approach or specific therapy. Often, specific treatment is recommended because of the location of hyperplasia or concern regarding the development of lymphoma. Specific treatment options include steroids, local radiotherapy, rituximab, infliximab, or chemotherapy if there is clear evidence of lymphoma.[5,36,37,40–44]

Oral corticosteroids usually result in an initial response but with time, the condition usually becomes refractory to therapy. The dosage of corticosteroids required to control the swelling usually results in significant side effects.

Radiotherapy has been the mainstay of therapy for OAL and also is efficacious when used for lymphoid hyperplasia. The dose of radiation is tapered according to the grade of lymphoma. Five-year local control rates

for low-grade lymphoma are near 100%. However, high rates of delayed systemic recurrence suggesting long-term follow-up studies are required to assess the true benefit of radiotherapy.[45] Complications of radiotherapy such as dry eyes and cataracts are frequently reported in patients that have long-term follow-up.[46]

Intralesional interferon α was used in five patients with OAL using an intensive protocol.[47] An initial complete response was seen in patients with stage I OAL, but long-term follow-up studies are required to assess the value of this treatment.

Rituximab is a monoclonal antibody that targets B cells bearing the CD_{20} surface marker and causes complement-dependent and antibody-dependent cellular cytotoxicity and apoptosis.[48,49] Rituximab may be used as an alternative first-line treatment for localized CD^{+}_{20} OAL to avoid the ocular complications of radiotherapy.[50] Rituximab has also shown high response rates in the treatment of lymphoid hyperplasia.[51,52]

Chemotherapy is reserved for treatment of OAL when there is systemic involvement, except for high-grade diffuse large B-cell lymphoma when systemic chemotherapy is first-line treatment even for stage I disease. The standard regimen is cyclophosphamide, doxorubicin, vincristine, and prednisolone.

Final Diagnosis: IgG4-Related Dacryoadenitis

After the biopsy revealed lymphoid hyperplasia, the patient had a baseline metastatic evaluation. Immunostaining of the biopsy specimen revealed >30% $IgG4^{+}$ plasma cells. There was no evidence of parasitic infestation.[53] The CT of the chest and abdomen were both unremarkable and a PET scan revealed no abnormal uptake. The final diagnosis was IgG4-related dacryoadenitis. The treatment options were discussed at length with the patient. He elected to hold off on any treatment at this time and undergo a repeat metastatic survey and MRI of the orbits in 6 months.

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Patient Oriented Problem Solving (POPS) Case Report

Prolonged urticaria and fever in a toddler

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ABSTRACT

We describe a 14-month-old girl who initially presented with 8 days of fever, conjunctival injection, rash, and irritability, admitted with a presumptive diagnosis of Kawasaki disease. Further history revealed intermittent urticarial-like rash since 3 months of age and pathological evaluation showed a perivascular infiltrate of neutrophils and lymphocytes. Here, we discuss the key points surrounding her diagnostic workup and our therapeutic approach.

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CASE PRESENTATION

Chief Complaint

Persistent urticaria and fever in a previously healthy child.

History of Present Illness

Our patient is a 14-month old girl, product of a full-term, fraternal twin gestation, who was initially hospitalized for 8 days with fever and rash with a presumptive diagnosis of Kawasaki disease. Evaluation revealed significantly elevated levels of acute-phase reactants and serum inflammatory markers without evidence of underlying infection. She received i.v. immunoglobulin (IVIG; 2 g/kg) initially, followed by a second dose of IVIG and subsequently infliximab (5 mg/kg), with only temporary resolution of fever, conjunctival injection, and rash. The allergy and immunology service was consulted for evaluation of persistent urticaria and fever.

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Medical History

Review of our patient's history revealed that she had experienced an intermittent rash since 3 months of age, which was initially treated as dermatographism. Two months before her presentation, her parents noted recurrence of the rash with associated conjunctivitis. The rash was associated with fever and was unique in that it appeared to worsen during the day and have near complete resolution overnight. It was described as nonpruritic and nondistressing to the patient and was accentuated in exposed areas of skin with some sparing of areas covered by clothing (Fig. 1, *A* and *B*). Antibiotics and antihistamines had no impact on either the fever or the dermatologic symptoms.

There was no history of significant infections or prolonged illness. She met her developmental milestones appropriately but was generally noted to be smaller in size than her fraternal twin. She tolerated routine vaccinations without incident.

Family History

There is no family history of urticaria, immunodeficiency, autoimmune disease, or recurrent fevers. Her parents, as well as her fraternal twin, are healthy.

Physical Examination

She initially presented as an irritable child, with weight at the 43rd percentile for age and height at 70th percentile for age. At our initial evaluation, her temperature was 40.1°C (104.1°F), and she was tachycardic. Physical exam was notable for cervical and inguinal lymphadenopathy, mild hepatosplenomegaly and multiple erythematous, blanchable macules, and patches of an urticarial nature, mostly coalescing on the upper and lower extremities, face, and torso, with minimal involvement of the palms and soles (Fig. 1, *A*

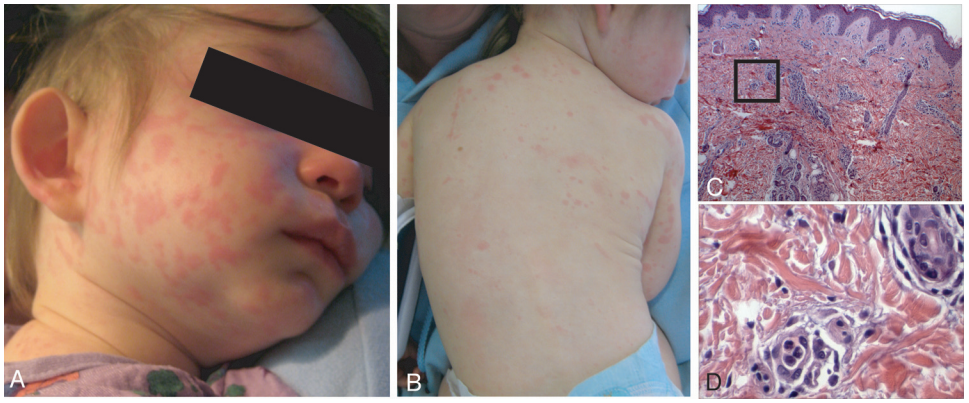

Figure 1. Urticarial-like rash. (A and B) Photographs were taken at the peak of rash development, before initiation of any therapies. (C and D) Histological examination of skin with perivascular inflammatory infiltrate.

Table 1 **Laboratory evaluation**

Laboratory	Result (normal range)	Infectious Disease Evaluation—Negative Studies	
WBC	21.9 × $10^3/\mu$L (6–14 × $10^3/\mu$L)	Pre-IVIG serologies	Cultures
Platelets	697,000/μL (140–440 × $10^3/\mu$l)	Epstein-Barr virus	Blood
CRP	22 mg/L (0–3 mg/L)	Coccidioides	Urine
ESR	43 mm/hr (0–20 mm/hr)	Toxoplasma	
D-dimer	>5000 ng/mL (<400 ng/mL)	Bartonella	ELISA
Fibrinogen	163 mg/dL (160–425 mg/dL)	Enterovirus	Mycoplasma
LDH	1901 IU/L (500–950 IU/L)		
ANA	<1:40 (<1:40)	Direct fluorescent antibody	
C3	121 mg/dL (74–127 mg/dL)	Influenzae A and B	
C4	16 mg/dL (18–47 mg/dL)	Respiratory syncytial virus	
CH50	>60 U/mL (30–75 U/mL)	Parainfluenzae 1, 2, and 3	
Urinalysis	Normal	Adenovirus	

ANA = antinuclear antibody; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; IVIG = i.v. immunoglobulin; LDH = lactate dehydrogenase; WBC = white blood cell.

and *B*). There was no evidence of skin excoriation, oral findings, or skin peeling of the fingers.

Laboratory and Other Diagnostic Findings

Laboratory evaluation revealed elevated levels of acute-phase reactants and serum inflammatory markers, including C-reactive protein at 22 mg/L (reference range, 0–3 mg/L), erythrocyte sedimentation rate of 43 mm/hour (reference range, 0–20 mm/hour), and platelets of 697,000/μL (reference range, 140–440 × $10^3/\mu$L). Cultures and diagnostic tests were negative for an infectious etiology (Table 1). Multiple echocardiograms documented normal coronary artery internal dimensions.

QUESTIONS

What Is the Differential Diagnosis?

The differential diagnosis for fever and urticaria in a child is extensive, and includes infectious causes, medication reactions (especially antibiotics), autoimmune diseases, vasculitides, and autoinflammatory disorders including the cyropyrin-associated periodic syndromes (CAPS).[1,2] The length of fever (>5 days), history of conjunctivitis, and presence of cervical lymphadenopathy is also concerning for Kawasaki disease, as initially diagnosed in this patient, although she did not meet the other criteria. For a diagnosis of classic Kawasaki disease, she would require at least two additional symptoms such as oral mucosal changes, polymorphous rather than urticarial rash, erythema/edema of palms/soles, or desquamation of fingertips/toes.[3] Table 2 summarizes a more complete list of differential diagnoses.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in this Patient?

Complex urticaria, as suggested by lack of responsiveness to antihistamines, association with fever, or other indications of a systemic process, should be biopsied.

Table 2 **Differential diagnosis of fever and urticaria**

Immunologic/Autoimmune		Infectious	Autoinflammatory	Other Considerations
Urticarial vasculitis	Macrophage activation syndrome	Respiratory virus	CAPS	Kawasaki disease
SCLE/SLE	HLH	HIV	Familial Mediterranean fever	Malignancy
Systemic onset juvenile idiopathic arthritis	Schnitzler syndrome	Parasitic infection		Medications (penicillin and other β-lactam antibiotics)

CAPS = cryopyrin-associated periodic syndromes; HIV = human immunodeficiency virus; HLH = hemophagocytic lymphohistiocytosis; SCLE = subacute cutaneous lupus; SLE = systemic lupus erythematosus; URI = upper respiratory infection.

Evaluation of the inflammatory infiltrate may identify rare but serious syndromes marked by urticaria, including the vasculitides and CAPS. Immunohistochemical identification of specific cell types, such as regulatory T cells (observed in cases of chronic urticaria), can guide diagnosis and management decisions.[4] Additional histological studies such as immunofluorescent antibody staining of the tissue may provide further information regarding antibody deposition as seen in subacute cutaneous lupus.[5]

Clinical Course

Treatment with IVIG at 2 g/kg led to only a temporary improvement in the fevers and inflammatory markers, but minimal impact on her rash. Subsequent treatment with infliximab at 5 mg/kg as well as a second course of IVIG (2 g/kg), gave similar results.

Given the failure of sustained improvement in her inflammatory symptoms and persistence of the urticarial rash, a skin biopsy of affected skin was performed, which showed a perivascular inflammatory infiltrate comprised of lymphocytes, neutrophils, and rare eosinophils without evidence of leukocytoclastic vasculitis. Some of the mixed inflammatory infiltrate also surrounded a few adnexal structures, suggestive of CAPS[6,7] (Fig. 1, *C* and *D*).

A therapeutic trial with subcutaneous anakinra (2 mg/kg per day) resulted in partial resolution of symptoms, and increasing the dose to 4 mg/kg per day led to complete resolution of her physical symptoms as well as normalization of inflammatory markers (Fig. 2). There was no evidence of papilledema, such as blurred optic margins or hemorrhage near the optic disk on ophthalmologic exam, and laboratory studies have consistently indicated normal renal function. Additional workup revealed normal bone studies, but minimal leptomeningeal enhancement on MRI as observed in neonatal-onset multisystem inflammatory disorder.[8] Her dose requirement and clinical findings characterize her as a more severe phenotype on the spectrum of CAPS. Sequencing of all *NLRP3* coding exons failed to show a mutation.

She continues to be asymptomatic on anakinra at 4 mg/kg per day, with serum inflammatory markers at the lower limits of detection: C-reactive protein at 0.02 mg/L (reference range, 0–3 mg/L) and erythrocyte sedimentation rate at 1 mm/hour (reference range, 0–20 mm/hour). Attempts at reducing her dose to every other day administration have resulted in return of clinical symptoms. She has met developmental milestones appropriately, and her growth has improved with height and weight now surpassing those of her fraternal twin sister. Therapy with anakinra has been well tolerated and she has not experienced any injection site reactions or serious infections.

DISCUSSION

The pattern of symptoms and clinical findings, as well as response to anakinra, was consistent with a diagnosis of CAPS. CAPS are a spectrum of autosomal dominant disorders, characterized by intermittent or continuous symptoms of fever, rash, conjunctivitis, and musculoskeletal pain.[9,10] The mildest form, familial cold autoinflammatory syndrome, uniquely displays episodes of inflammation after mild generalized cold exposure.[11] Muckle-Wells syndrome is similarly characterized by inflammatory episodes, which occur more frequently but without a defined inciting factor. Chronic inflammation in Muckle-Wells syndrome leads to the development of progressive sensorineural hearing loss and systemic amyloidosis in a subset of patients.[12] In the most severe phenotype, neonatal-onset multisystem inflammatory disorder, patients present early with chronic inflammation including an urticarial rash and fever. Later, they develop signs of central nervous system inflammation (increased intracranial pressure, chronic aseptic meningitis, seizures, and uveitis) as well as sensorineural hearing loss and progressive arthropathy.[8] Although classified as dis-

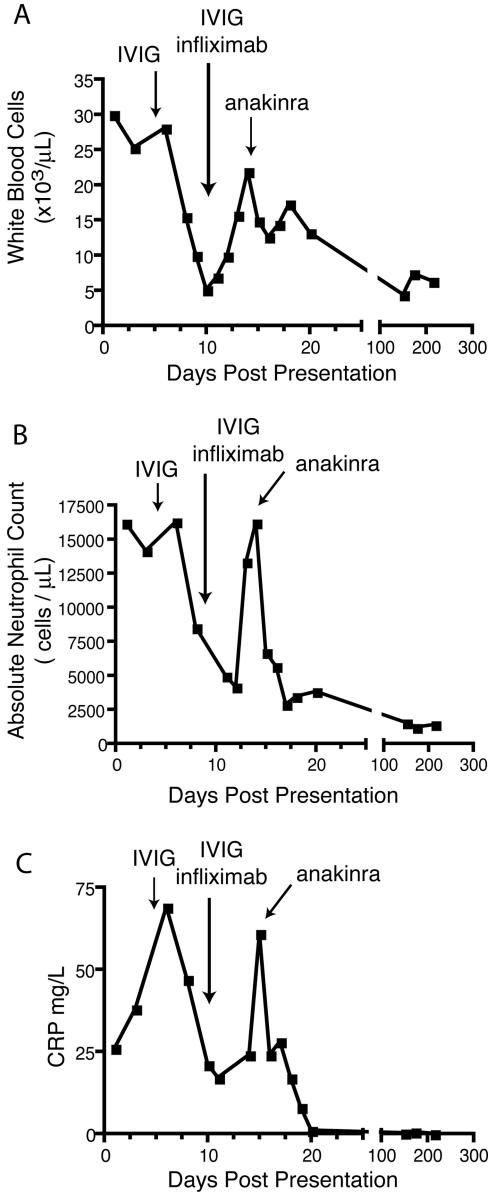

Figure 2. Select laboratory markers and response to therapy. (A) Total white blood cell count. (B) Absolute neutrophil count. (C) C-reactive protein (CRP). IVIG, i.v. immunoglobulin.

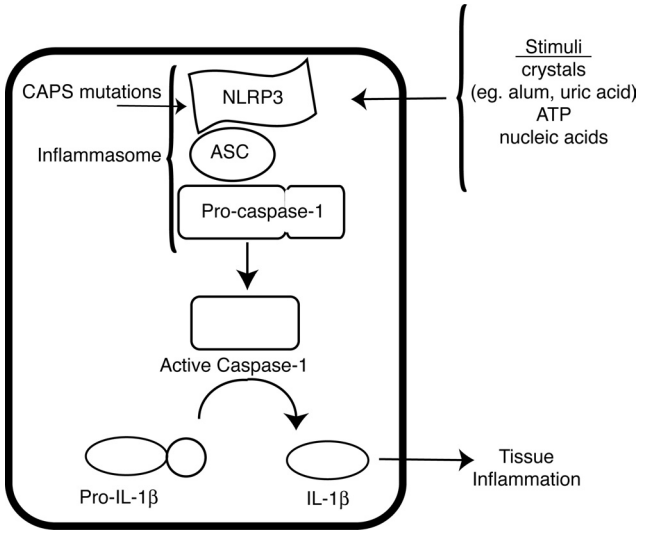

Figure 3. NLRP3 Inflammasome. Cyropyrin-associated periodic syndrome (CAPS)–associated mutations in NLRP3 lead to inflammasome hyperactivity, independent of known clinically relevant sterile inflammatory stimuli. Inflammasome activation results in pro–caspase-1 cleavage, caspase-1 activation, and IL-1β production leading to inflammation.

tinct disorders, many patients display overlapping symptoms, as we observed in our patient.

The majority of CAPS patients present within the first few weeks to months of life, consistent with the inherited nature of this systemic innate immune inflammatory disorder. However, there are several cases in which significant symptoms are not observed until after the neonatal period as was seen in our patient. This is also true for several of the other hereditary fever disorders, suggesting a role for an environmental trigger, such as microbial exposure. These autoinflammatory disorders are characterized by dysregulation of innate immunity or aberrant pattern recognition sensing, with a predominance of activated neutrophils and monocytes, rather than the antigen-specific T cells and high-titer autoantibodies observed in autoimmune diseases.

Most but not all CAPS patients have a mutation in *NLRP3* which encodes cryopyrin.[13] The identification of mutation-negative patients with a classic CAPS phenotype suggests the involvement of additional genes in the same or related pathways. Additionally, considerable evidence now exists for the presence of somatic mosaicism in *NLRP3* in many CAPS patients initially thought to be mutant negative,[14,15] but this still has not been evaluated in our patient. Cryopyrin associates with apoptosis-associated speck-like protein containing a caspase recruitment domain and procaspase-1 to form the NLPR3 inflammasome driving IL-1β and IL-18 production. Persistent activation of the inflammasome in CAPS leads to up-regulation of IL-1β and the symptoms observed in CAPS (Fig. 3).[16]

Therapies for CAPS primarily target IL-1 and include anakinra (recombinant IL-1 receptor antagonist),[17,18] rilonacept (fusion protein of IL-1 receptor and IL-1 receptor accessory protein),[19,20] and canakinumab (humanized monoclonal antibody to IL-1β).[21] Studies with IL-1 blockers have consistently shown reduction of symptomatic periods and inflammatory markers in patients with CAPS, similar to the results observed in our patient. Additionally, anti–IL-1 therapy has often shown substantial improvement of progressive and long-term complications of CAPS, including hearing loss and renal disease due to amyloidosis, as well as improvement in quality-of-life measurements.[22–24] The success of IL-1–targeted therapy in CAPS and other neutrophilic skin disorders such as Sweet syndrome[25] and Schnitzler syndrome[26]

suggest that it may have a role in the therapy of chronic urticaria with neutrophilic pathology.

Currently, rilonacept and canakinumab are Food and Drug Administration approved for CAPS, whereas anakinra is only approved for the treatment of rheumatoid arthritis. All three drugs are injectable and have established life-changing results for these patients but primarily differ in their recommended frequency of administration. IL-1–targeted therapy may be associated with increased risk of nonopportunistic infection, and patients should be monitored appropriately and treated accordingly.

Final Diagnosis

Final diagnosis was cryopyrin-associated periodic syndrome.

SUMMARY AND CONCLUSIONS

This patient with mutation-negative CAPS emphasizes the broad differential diagnosis of fever and rash in a young child and the variable clinical presentation of the CAPS spectrum. This case also illustrates the usefulness of biopsy for urticarial-like lesions that are minimally responsive to conventional therapy. It also suggests that there is a role for a therapeutic trial of anakinra in the diagnostic workup of CAPS as well as long-term maintenance therapy.

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Patient Oriented Problem Solving (POPS) Case Report

Allergy consult for eosinophilia in an infant

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ABSTRACT

Specialists in allergy/immunology are often asked to evaluate patients with eosinophilia, with the general assumption of an underlying allergic or immunologic disease. We present a case of an infant referred for marked eosinophilia. Although atopic disease may be in the differential diagnosis, it is rarely associated with hypereosinophilia, and other conditions need to be investigated. Until the underlying cause is identified, systemic corticosteroid therapy may be initiated, mainly in severe cases.

(Allergy Asthma Proc 33:370–373, 2012; doi: 10.2500/aap.2012.33.3582)

CASE PRESENTATION

Chief Complaint

Markedly elevated eosinophil count.

History of Present Illness

A 17-month-old white boy was referred to the allergy/immunology service because of hypereosinophilia. He was initially seen by a pediatrician for a 2-day history of cough, wheezing, nasal congestion, and fever up to 100.9° F. His complete blood count showed a hemoglobin of 12.1 g/dL; white blood cell count (WBC) of 33.0 $\times$ $10^3/\mu$L with 50% eosinophils (absolute eosinophil count [AEC], 17,500/μL), 31% lymphocytes, 12% neutrophils, and 1% basophils; and platelet count of 476,000/μL. Because of suspected systemic infection, he was admitted to the hospital for antibiotic therapy (ceftriaxone and then switched to vancomycin and cefotaxime) without significant improvement in his WBC (36.64 $\times$ $10^3/\mu$L) or eosinophilia (48%; AEC 17,587/μL). Wheezing continued despite aerosolized albuterol; therefore, methylprednisolone (2 mg/kg per day i.v. in four divided doses) was administered from his third hospital day for 2 days. After this treatment, his WBC decreased to 16.23 $\times$ $10^3/\mu$L with only 4% eosinophils (AEC, 649/μL), and his fever and wheezing resolved.

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The authors have no conflicts of interest to declare pertaining to this article

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A peripheral blood smear showed scattered lymphocytes in a background of red blood cells but no malignant cells. He had negative anti–Epstein-Barr virus titers (EBV-VCA IgM and IgG) and three negative stool analyses for ova and parasites, but very high serum total IgE of 1821 IU/mL (normal, <20 IU/mL). A chest roentgenogram was normal. He was discharged after 4 days on oral azithromycin for 5 days and prednisolone 5 mg/day for 5 days and then 2.5 mg/day for 5 days.

At a clinic follow-up visit by the pediatrician 18 days after hospital discharge (8 days after oral prednisolone was discontinued), the patient was asymptomatic, afebrile, and no abnormal physical findings were recorded. His WBC increased to 32.13 $\times$ $10^3/\mu$L with 43% eosinophils (AEC, 13,816/μL; Table 1). He was then referred for allergy/immunology evaluation.

Family History

The mother had allergic rhinitis and asthma, the brother had allergic rhinitis, and the sister had eczema and allergic rhinitis. The family lives in a rural area with multiple cats and dogs indoors and outdoors. They have city water and had no recent travel outside of the United States.

Physical Examination

At the initial evaluation at our Allergy/Immunologic Clinic, the patient was completely asymptomatic. He had normal vital signs; slight clear nasal discharge; and the skin, heart sounds, lung auscultation, and extremities appeared normal. However, the liver was enlarged 3 cm below the right costal margin and the spleen was enlarged 8 cm below the left costal margin. With such hepatosplenomegaly, remarkable eosinophilia, and elevated IgE level, our differential diagnosis was directed toward searching for the underlying cause.

Table 1 **Sequential eosinophil count and serum total IgE level in a 17-mo-old child with *Toxocara* infestation**

Day	WBC ($10^3/\mu L$)	Eosinophils		IgE (IU/mL)	Anti-*Toxocara* IgG (OD)
		%	Count/μL		
1	33.0	50	17,500	—	—
4*	16.23	4	649	1821	—
22	32.13	43	13,816	1770	—
38	25.29	28	7081	—	3.5
59	33.66	27	9088	2103	3.5
80	28.46	47	13,377	2585	3.8
157	19.94	41	8176	1825	—

**Received methylprednisolone on days 3 and 4; hospital discharge was on day 4. Initial allergy/immunology consult was on day 38. OD = optic density; WBC = white blood cell count.*

Table 2 **Differential diagnosis of eosinophilia**

Atopic Disease	Infections	Hematologic	Other
Eczema, asthma, and allergic rhinitis	Parasitic	Myeloproliferative	Familial
Drug reaction	Fungal (coccidioidomycosis)	FIP1L1/PDGFRA mutation	Idiopathic
Allergic bronchopulmonary mycosis	Viral (HIV and HTLV-1)	Chronic eosinophilic leukemia	
Churg-Strauss syndrome		Etiology unknown	
		Lymphocytic	

HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus type 1; FIP1L1/PDGFRA = fip1-like1-platelet-derived growth factor receptor-α.

What Tests Need to be Done?

Repeat WBC showed a reduction to $25.29 \times 10^3/\mu L$ with 28% eosinophils (AEC, $7081/\mu L$; Table 1). His blood chemistry profile and cardiac enzyme levels were normal. The chest roentgenogram showed clear lung fields with normal cardiac silhouette and thymic shadow.

What is the Differential Diagnosis?

Increased circulating eosinophils can be present in a wide variety of diseases (Table 2). *Atopic diseases* are generally associated with mild-to-moderate eosinophilia that tends to correlate with disease severity.[1–3] They are often associated with elevated serum total IgE level that can be very high in atopic eczema or allergic bronchopulmonary mycosis.

Churg-Strauss syndrome, a small- and medium-sized vasculitis, is also associated with eosinophilia, asthma, and granulomatous inflammation.[4]

Helminthic infestations are the most common cause of eosinophilia worldwide, although less prominent in the United States and other developed countries.[5] Eosinophilia secondary to parasites can be transient during the larval tissue invasion stage or persistent in the case of tissue-infesting parasites. Stool analysis for ova and parasites is the general screening test but it has poor sensitivity for *Strongyloides*, *Toxocara*, and *Trichinella*.[6] Therefore, serologic testing is often used. *Toxocara* is transmitted *via* ingestion of infective eggs of the parasite from canine (*Toxocara canis*) or feline (*Toxocara cati*) hosts that are common household pets. However, direct contact with the infested animals is not necessary to transmit *Toxocara*.[7] The commercially available test for anti–*Toxocara* IgG antibody is for both species of the parasite. Some nonparasitic infections may be associated with elevated eosinophil counts, particularly coccidioidomycosis, human immunodeficiency virus, and human T-lymphotropic virus type 1 (HTLV-1).[8]

Drug reactions are commonly associated with eosinophilia, and in some cases it may be the only finding. Drug rash with eosinophilia and systemic symptoms, DRESS syndrome, should be of particular concern. DRESS typically presents with fever, rash, lymphadenopathy, leukocytosis with eosinophilia, and liver dysfunction.[9] Given the long latency period of some drug reactions, it would be prudent to obtain a detailed history on medications, nutritional supplements, and herbal remedies for many weeks or months preceding the discovery of eosinophilia. Other clinical manifestations of drug hypersensitivity may include eosinophilic dermatitis, pulmonary infiltrate, interstitial nephritis, and hepatitis.[6]

Hypereosinophilic syndromes may be considered when no primary cause is discovered. The early definition included peripheral eosinophilia of >1500/μL for >6 months, lack of known secondary cause, and presumptive signs of end-organ involvement.[10] A more recent definition excluded the persistence of eosinophilia for 6 months, because this may lead to a delay in diagnosis or treatment.[11] Lymphocytic hypereosinophilic syndrome occurs through the generation of increased IL-3 and/or IL-5 by T lymphocytes.[12] A myeloproliferative form of hypereosinophilia could be considered if there is clinical (hepatomegaly and/or splenomegaly), laboratory (circulating myeloid precursors, increased serum vitamin B12, elevated tryptase, anemia, and/or thrombocytopenia), hematologic (myeloid fibrosis and/or left shift in maturation of myeloid precursors), and/or other cytogenic abnormalities.[11] Other myeloproliferative variants include chronic eosinophilic leukemia and hypereosinophilic syndrome associated with fip1-like1-platelet-derived growth factor receptor-α (FIP1L1-PDGFRA) mutation. Screening for the FIP1L1-PDGFRA rearrangement in the peripheral smear has important treatment implications. If this particular mutation is present, treatment with imatinib (tyrosine kinase inhibitor) may be started.[13]

Familial eosinophilia is a rare autosomal dominant disorder. Such patients often have marked eosinophilia from infancy and rarely develop clinical manifestations, which may be caused by the relative lack of eosinophil activation.[6] A linkage analysis of one kindred with familial eosinophilia pointed to gene defects in chromosome 5q31-33.[14] This region contains the cytokine gene cluster and includes genes for IL-3, IL-5, and granulocyte/macrophage colony-stimulating factor.

Idiopathic hypereosinophilia would be considered only after all the aforementioned conditions are ruled out.

What Additional Laboratory Tests Would Be Helpful in this Patient?

Parasitic infestation is generally the most common cause of eosinophilia and should be considered. Our patient is closely exposed to multiple dogs and cats, and it would be prudent to request antibody titer to *Toxocara* and other tissue-invading parasites. If the tests are negative, a hematology/oncology consultation would be warranted to perform FIP1L1-PDGFRA mutation analysis and possible bone marrow biopsy.

Our patient was reported to have wheezing during his initial acute febrile illness, which might be caused by an intercurrent upper respiratory infection. Given the very young age of our patient, the lack of asthma, and normal chest roentgenogram, neither allergic bronchopulmonary mycosis nor Churg-Strauss syndrome were contemplated at this stage. Neither were any of other organ-specific eosinophilic diseases such as eosinophilic pneumonia, eosinophilic gastroenteritides, nor skin diseases that are often associated with peripheral eosinophilia.[15] Our patient did not have symptoms related to these organs.

Final Diagnosis

Toxocara antibodies were found to be markedly elevated at 3.5 OD (normal, <0.3), and treatment with mebendazole at 100 mg orally twice a day for 5 days was prescribed.

Clinical Course

Three weeks later (day 59), the child was seen in a follow-up visit. He was completely asymptomatic and neither the liver nor the spleen was palpable. The laboratory tests revealed WBC of $33.66 \times 10^3/\mu L$ with 27% eosinophils (AEC, 9088/μL), IgE of 2103 IU/mL, and *Toxocara* antibodies titer remained the same (3.5 OD). The increase in eosinophilia and IgE level may suggest the release of antigen from the killed parasite population, with subsequent enhanced cytokine stimulation.

At the next visit 3 weeks later (day 80), the mother reported the child had been happy and normally active. On physical examination he was playful and appeared healthy, with normal vital signs and no abnormal physical findings. His WBC was $28.46 \times 10^3/\mu L$ with 47% eosinophils (AEC, 13,377/μL), IgE was 2585 IU/mL, and anti–*Toxocara* titer was 3.8 OD, probably secondary to continued immune stimulation by further release of antigen from the killed parasite.

Because the child continues to be asymptomatic after antihelminthic treatment, no further therapy was considered. He continues to be followed in our clinic until his laboratory findings become normal and to ensure no development of end-organ injury. His latest WBC (16 weeks postmebendazole treatment) was $19.9 \times 10^3/\mu L$ with 41% eosinophils (AEC, 8176/μL) and his total IgE level was 1825 IU/mL. A somewhat similar case was reported in a 3-year-old child with combined *Trichinella* and *Toxocara* infestation whose laboratory abnormalities slowly improved over a 2-year period.[16] Although our patient responded well to mebendazole, as indicated with the rapid resolution of hepatosplenomegaly, albendazole is considered a more effective antihelminthic, but it is not approved for children <4 years of age.[7]

DISCUSSION

In normal healthy individuals, circulating eosinophil count varies between 0 and 500/μL, with higher levels in children than in adults.[17] Eosinophilia is often classified into mild (500–1500/μL), moderate (1500–5000/

μL), and marked (>5000/μL).[17] Hypereosinophilia is generally considered at >1500/μL. Most cases of eosinophilia are acquired and can be classified into secondary, clonal, and idiopathic.[5] Secondary eosinophilia is considered a cytokine-driven reactive phenomenon and can occur in association with a large variety of conditions: atopic disease, parasitic infestation, drug reaction, autoimmunity, malignancy, infection (particularly certain fungal and viral infections), and endocrinopathies (*e.g.*, Addison's disease). Critical for bone marrow production of eosinophils are granulocyte/macrophage colony-stimulating factor, IL-3, and IL-5. The latter is a key cytokine in terminal differentiation of eosinophils.[17]

End-organ damage is a concern in patients with severe eosinophilia. According to a review of 105 cases from 3 studies, comorbid conditions of hypereosinophilic syndrome were hematologic (100%), cardiovascular (58%), dermatologic (56%), neurological (54%), pulmonary (49%), splenic (43%), liver/gall bladder (30%), ocular (23%), and gastrointestinal (23%).[18]

In most cases, eosinophilia is usually a marker of any of the diseases outlined previously, and the treatment is directed to the primary disease. However, asymptomatic cases of idiopathic hypereosinophilia may be monitored closely with no specific treatment. If organ involvement is present, treatment with corticosteroids at a dose of 1 mg/kg per day up to 60 mg/day is indicated. Trials in steroid-dependent adult cases showed that adjunctive medications such as hydroxyurea or interferon α were effective as steroid-sparing agents.[8]

More recently, mepolizumab, a humanized anti–IL-5 monoclonal IgG1, has been used in the treatment of hypereosinophilia syndrome. In a trial of 85 subjects with hypereosinophilic syndrome requiring 20–60 mg of prednisone per day, mepolizumab was effective in decreasing eosinophil counts to <600/μL in 95% of subjects and decreasing prednisone dose to ≤10 mg per day in 84%.[19] In a trial of patients with chronic eosinophilic leukemia, treatment with alemtuzumab, a humanized anti-CD52 monoclonal antibody, resulted in normalization in eosinophil counts in 10 of 11 patients.[20]

CONCLUSION

When specialists in allergy/immunology are asked to evaluate patients with eosinophilia, the differential diagnosis should go beyond allergic disorders as guided by a detailed history taking, including the patient's environment. In addition to physical findings, selected laboratory tests might settle the diagnosis and, consequently, the appropriate treatment. Worldwide, parasitic infestation is the most common cause of marked eosinophilia. Such patients should be followed up until all laboratory findings become normal.

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Patient Oriented Problem Solving (POPS) Case Report

Recurrent septic shock in a 34-year-old woman

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ABSTRACT

A 34-year-old woman presented to the Emergency Room (ER) with an acute presentation of septic shock that required fluid and pressor support in the Intensive Care Unit. History revealed this was her third episode of such a presentation with asymptomatic periods in between. She responded well to medical interventions but reported persistent joint pain. Immunologic workup revealed her diagnosis.

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CASE PRESENTATION

Chief Complaint

A 34-year-old woman presents to the Emergency Room with a 4-day history of joint pains and vaginal bleeding before becoming hypotensive, tachycardic, lethargic, and pale in what is her third lifetime episode of septic shock.

History of Present Illness

Initial laboratory evaluation revealed an elevated white blood cell count and thrombocytopenia. Her clinical status deteriorated requiring Intensive Care Unit management of septic shock. She was intubated for airway protection and required fluids and pressors. Broad-spectrum antibiotics were initiated and were later switched to ceftriaxone based on culture and sensitivity.

Based on the Aforementioned Clinical Presentation, What Initial Laboratory Evaluation Should Be Performed?

1. CH50
2. Full complement panel
3. IgG
4. IgM
5. IgA

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Answer: CH50, Quantitative Immunoglobulin Levels (IgG, IgM, and IgA). Based on her severe recurrent infections initial laboratory evaluation included a complement screen as well as immunoglobulin levels. Results revealed a low CH50, total IgG, IgG1, and IgG2. (Table 1) The CH50 encompasses the entire complement pathway and helps determine the functionality of the innate immune system.[1] CH50 serves as the best screening test for patients who manifest with recurrent infections suspicious for a complement deficiency. A reduction in any of the complements shows an abnormally low CH50. This necessitates a full complement panel, which ultimately helped confirm this patient's diagnosis of complement C2 deficiency. After initiating appropriate antibiotics she responded well to medical interventions; however, she reported persistent joint pain and fatigue.

Based on Her Deficiency of C2, What Organism Would Most Likely Be Isolated from Her Blood?

1. *Streptococcus pneumoniae*
2. *Pseudomonas aeruginosa*
3. *Aspergillus*
4. Pneumocystis jiroveci
5. Group B *Streptococcus*
6. *Candida*

Answer: ***S. pneumoniae*** *Would Be Expected because It Is the Most Commonly Isolated Organism in Patients with C2 Deficiency.*[2] Group B *Streptococcus*, an unlikely organism in C2 deficiency, was isolated from this patient's serum. Immunoglobulin deficiency is more likely to predispose a patient to encapsulated organisms such as *S. pneumoniae*. Our literature search revealed only one other case report of a patient with C2 deficiency who grew group B *Streptococcus*-positive blood cultures.[3] *S. pneumoniae* was isolated from our patient's serum during her previous episode of sepsis (Table 2).

Table 1 **Laboratory results**

Laboratory	Result	Normal Range
IgG	470 mg/dL	700–1600
IgM	89 mg/dL	40–230
IgA	125 mg/dL	70–400
IgG1	257 mg/dL	382–929
IgG2	164 mg/dL	241–700
IgG3	72 mg/dL	22–178
IgG4	7.2 mg /dL	4.0–86.0
CH50	<10 L	31–60
C2	Undetectable	1.6–3.5
C3	173 H	88–165
C4	22	14–44
ANA	<1:40	<1:40
RF	37 H	<12
Anti-CCP	<16	<20
CRP	11.66 H	<1.0
ESR	59 H	0–20

Table 2 **Complement deficiency manifestations**

Deficiency	Clinical Findings
C1q	SLE or SLE-like conditions most common, as well as bacterial infections
C1r	
C1s	
C4	
C2	Bacterial infections most common, with some patients presenting with SLE or SLE-like conditions
C3	Bacterial infections
C5	Recurrent *Neisseria* infections, with the most common being meningococcal
C6	
C7	
C8	
C9	
C1 inhibitor	Hereditary angioedema; some patients found to have secondary C2 deficiencies

SLE = systemic lupus erythematosus.

What Additional Testing Would You Order to Determine the Cause of Her Arthralgias?

1. Rheumatoid factor
2. Anti-CCP
3. ANA
4. Anti-ds DNA

Answer: All of the Above. Joint culture was negative for a septic joint and a rheumatologic panel that included ANA, Anti-ds DNA, and Anti-CCP were all within normal limits. Rheumatoid factor was positive but not thought to be of clinical significance to the case.

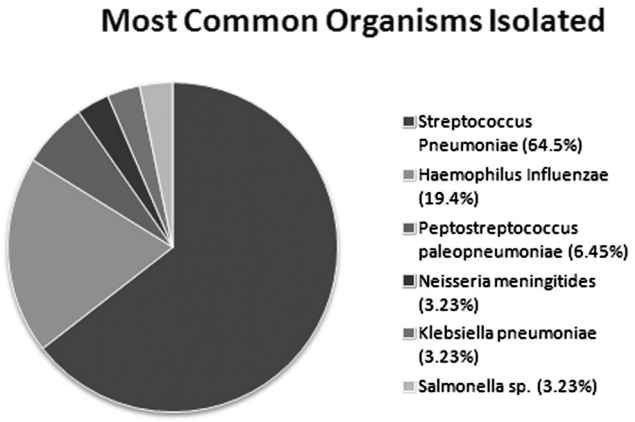

Figure 1. *The percentages for the different organisms that cause infections in patients with complement deficiencies.*

The frequency of rheumatic diseases associated with complement deficiency is believed to be secondary to complement's removal of immune complexes from the blood.[4–6] For this reason, patients with complement deficiency are predisposed to systemic lupus erythematosus (SLE)–like disease.[7] It is quite possible that her joint pains could be attributed to a rheumatologic manifestation of her complement deficiency.

On Follow-Up after Discharge, What Further Steps Would You Take?

1. *S. pneumoniae* vaccination
2. Amoxicillin prophylaxis
3. *Neisseria meningitidis* vaccination
4. *Haemophilus influenzae* vaccination
5. Ceftriaxone prophylaxis
6. Moxifloxacin prophylaxis
7. Complement testing of family members

Answer: ***S. pneumoniae****,* ***N. meningitidis****, and* ***H. influenzae*** *vaccinations and amoxicillin prophylaxis, as well as complement testing of family members.* One month later she was back to her baseline health and energy level. Vaccinations for encapsulated organisms were administered based on current recommendations for *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*.[8,9] She was started on amoxicillin prophylaxis because of her frequent severe infections and instructed to begin taking Augmentin at the first sign of a fever or illness.

The majority of complement disorders are inherited in an autosomal recessive pattern.[10,11] After her diagnosis was made we recommended the patient's children be screened with a CH50.

DISCUSSION AND LITERATURE REVIEW

It is well known that a defect in the complement system inhibits the ability of antibodies to destroy pathogens *via* inducing inflammation, opsonization, and cell lysis.[12] Different components of the complement system are responsi-

Table 3 **Associated diseases with complement level laboratory abnormalities**

Disease	C3	C4	Other Labs
Cryoglobulinemia	↓ or Normal	↓	
Hereditary angioedema	Normal	↓	Decreased or poorly functioning C1-INH; C2 during attack
Hypocomplementemia vasculitis	↓ or Normal	↓	Decreased C1q
Inflammation	↑	↑	
Poststreptococcal glomerulonephritis	Normal	↓	
SLE	↓	↓ or Normal	Associated with primary complement defects

C1-INH = C1-inhibitor; SLE = systemic lupus erythematosus.

ble for aiding the recognition and clearing of specific organisms. C2 deficiency is the most common homozygous complement deficiency, especially among white sujects, at a frequency of ~1:20,000.[13] Manifestations of C2 deficiency are diverse, and not all patients may present with recurrent infections and septic shock. When infections are seen in patients with C2 deficiency, they often involve the upper respiratory tract and are caused by encapsulated bacteria such as *S. pneumoniae*.[14] Fasano *et al.* showed that *S. Pneumoniae* was the most common organism isolated among 31 C2 complement–deficient individuals[2] (Fig. 1).

When complement deficiency is suspected, a hemolytic assay CH50 and AH50 is indicated as a screening test to determine the functionality of the classic and alternative pathways. A CH50 level below the lower limit of normal is suggestive of a complement deficiency.[1] In our case, the level was found to be <10. To confirm a specific deficiency, individual complement levels should be assayed. Because C2 deficiency is the most common homozygous deficiency, it may be cost-effective to obtain this assay first.[15] Each complement component is inherited *via* two functioning production genes. It is worth noting that several medical conditions such as cryoglobulinemia, SLE, and other inflammatory states may lead to complement level abnormalities. Some of these conditions are included in Table 3.

Of note, our patient was also found to have low IgG1 and IgG2. IgG1 deficiency has been associated with a predisposition to pyogenic infections.[16] In a study by Lacombe *et al.*, selective IgG1 deficiency was found in 119 patients of 3005 who sustained frequent infections.[17] Because IgG2 is primarily responsible for an individual's antibody response to polysaccharide capsular antigens, deficiency states predispose the body to infections from *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis*.[18] A deficiency of IgG1, IgG2, and complement C2 was unexpected in this patient; however, her response to pneumococcal and tetanus vaccines suggests that the main deficiency that predisposed her to infections was complement deficiency.

Because defects in the complement system inhibit the body's ability to remove immune complexes from circulation, it predisposes individuals to autoimmune manifestations such as SLE.[13] Our patient had suffered from various joint pains through the years before her hospitalization. After her infection seemed to clear, her chief complaint became severe right shoulder pain, for which no clear etiology could be found despite multiple studies. We could not confirm lupus in our patient; however, we suspect a positive rheumatoid factor to be associated with her recent infection. Although patients with C2 deficiency may develop a lupus-like syndrome, there are many differences between the two conditions. Lupus-like syndromes associated with complement deficiency rarely have central nervous system or renal impairment.[19,20] Cutaneous involvement is common in patients with C2 deficiency; however, this was not seen in our patient. Laboratory testing also has different results because they often do not have positive anti-dsDNA and ANA.[19]

One of the largest cohorts of C2-deficient patients was published by Jonsson *et al.* out of Sweden. Data from 40 years covering 40 patients with C2 deficiency were reviewed. Their data confirmed the well-known association between C2 deficiency and recurrent pneumonias, as well as SLE. Twenty-three of these 40 patients had a history of invasive infections, such as septicemia and meningitis, which was caused primarily by *S. pneumonia*. Twelve of these patients suffered from repeated infections of this type. Of the 40 patients, 29 patients were diagnosed with pneumonia and 10 of these cases were recurrent. SLE was found in 10 of the 40 patients. Seven additional patients were found to have undifferentiated connective tissue disease.[15]

FINAL DIAGNOSIS

Complement C2 deficiency.

CONCLUSION

Recurrent episodes of septic shock in otherwise young and healthy individuals should lead to a suspicion of an

underlying immunodeficiency. Despite having three episodes of septic shock, our patient did not have a formal immunologic workup until age 34 years. Although complement deficiencies are rare disorders, C2 deficiency is the most common of these. In patients with severe infections or recurrent meningitis, complement deficiency should be considered. Improved clinician awareness of immunodeficiencies will lead to an earlier consultation, appropriate assessment, treatment, and hopeful reduction in morbidity and mortality.

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Patient Oriented Problem Solving (POPS) Case Report

A 55-year-old man with severe persistent asthma poorly responsive to asthma therapy

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ABSTRACT

Asthma is often triggered by allergic and nonallergic factors in atopic individuals and readily responds to anti-inflammatory and bronchodilator therapy. The differential diagnosis for poorly responsive disease includes severe persistent asthma with associated allergic rhinitis, cardiac disorders such as left ventricular failure or mitral stenosis, vocal cord dysfunction, gastroesophageal reflux disease, recurrent aspiration, chronic obstructive pulmonary disease, emphysema, alpha-1-antitrypsin deficiency, sarcoidosis, hypersensitivity pneumonitis, bronchiectasis, allergic bronchopulmonary aspergillosis, airway neoplasm, and Churg-Strauss vasculitis. A careful history and physical in conjunction with appropriate screening of laboratory information will usually direct the clinician to the correct diagnosis.

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CASE PRESENTATION

Chief Complaint

The patient is a 55-year old man who presents with increased asthma symptoms over several months.

History of Present Illness

The patient reported a history of asthma for over 30 years. His symptoms were commonly provoked by both allergic and nonallergic triggers. He reported seasonal rhinitis in the spring and fall and he experienced increased cough, wheeze, and dyspnea during these times of the year. He denied nasal polyps, chronic sinusitis, or aspirin sensitivity. He denied any history of gastroesophageal reflux symptoms and denied any choking episodes or throat tightness. He denied any history of pneumonia, pleurisy, tuberculosis, or thromboembolic disease and his chest radiograph 2 years ago was reportedly normal. Despite fluticasone/salmeterol discus 500/50, 1 puff b.i.d.; tiotropium at 18 μg, 1 puff daily; montelukast at 10 mg daily; theophylline SR 3at 00 mg b.i.d.; and albuterol HFA, 2 puffs p.r.n., the patient was experiencing severe restriction in his activity and was overusing the rescue inhaler. He reported difficulty in performing his duties as a correctional officer.

He smoked 12 packs/years quitting 26 years ago secondary to cough and dyspnea. He drank 2–3 beers daily and denied illicit drug use. He denied any family history of atopy, asthma, emphysema, or other respiratory disorders. His medical history revealed hypertension and hyperlipidemia, which was treated with lisinopril and atorvastatin.

Physical Examination

Vital signs were blood pressure, 118/82; heart rate, 84/min; respiratory rate, 18/min; and O_2 saturation, 98%. There was no edema, cyanosis, clubbing, or jaundice. His ear, nose, and throat examinations were normal. The neck was supple with no bruits or thyroid enlargement. The lungs revealed hyperresonance to percussion, markedly decreased breath sounds, and expiratory wheezing at both bases. The heart revealed no S_3, S_4, or murmur. The remainder of the physical examination was normal.

QUESTION 1

Which of the following are included in the differential diagnosis of a patient with wheezing and a poor clinical response to maximal therapy for asthma?

A. Left ventricular failure and mitral stenosis

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Table 1 **Spirometry showing very severe obstructive ventilator disorder with no significant BD response**

Index	Pre-BD Measurement	Predicted Measurement	% Predicted	Post-BD Measurement	% Predicted	% Change
FVC (L)	2.21	5.87	38	2.10	36	−5.0
FEV_1 (L)	1.19	4.72	25	1.09	23	−8.4
FEV_1/FVC (%)	53.8	80.9	67	51.9	64	−3.5
$FEF_{25–75}$ (L/S)	0.8	4.7	17	0.6	13	−25
PEF (L/S)	4.4	9.7	45	4.7	49	+6.8

BD = bronchodilator; L = liters; $FEF_{25–75}$ = forced expiratory flow at 25–75%; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; PEV = peak expiratory flow; S = second.

B. Vocal cord dysfunction
C. Gastroesophageal reflux disease and recurrent aspiration
D. Chronic obstructive pulmonary disease (COPD) and α1-antitrypsin deficiency (AATD)
E. Sarcoidosis, hypersensitivity pneumonitis, and bronchiectasis
F. Allergic bronchopulmonary aspergillosis (ABPA)
G. Airway neoplasm
H. Churg-Strauss vasculitis

QUESTION 2

What further studies would one consider at this point?

A. Allergy skin testing
B. Spirometry and pulmonary function testing
C. Complete cell count and differential
D. Serum IgE level
E. Chest x ray
F. CT of chest
G. α1-Antitrypsin level

Discussion of the Differential Diagnosis

The patient had no evidence of congestive heart failure and no heart murmur to suggest significant mitral stenosis. The patient reportedly had a normal chest radiograph, which would make sarcoidosis, hypersensitivity pneumonitis, bronchiectasis, and ABPA less likely. A normal chest radiograph with absence of a family history of emphysema would make α1-antitrypsin unlikely. There was no history of throat tightness or stridorous breathing to suggest vocal cord dysfunction. The patient had no symptoms of gastroesophageal reflux and recurrent aspiration was unlikely because the patient had no history of seizure disorder, cerebrovascular disease, parkinsonism, or other neurological or neuromuscular condition that could lead to swallowing dysfunction.

Laboratory and Other Diagnostic Findings

Allergy skin testing revealed reactions to grass and ragweed. A spirometry revealed a very severe obstructive ventilatory disorder with no significant bronchodilator response (Table 1). A complete blood cell count revealed a white blood cell count of 5300 cells/mm^3 with 3% eosinophils, and the IgE level was 18 IU/mL, making Churg-Strauss vasculitis and ABPA unlikely. In view of the severe airflow obstruction noted on spirometry, a full pulmonary function study was obtained that revealed a very severe obstructive ventilatory disorder with a severe reduction in diffusion (Table 2). A chest radiograph revealed marked hyperinflation, flattening of the diaphragms, and prominence of the retrosternal airspace (Fig. 1). A CT scan of the chest revealed pulmonary hyperinflation with pulmonary emphysema and traction bronchiectasis noted (Fig. 2, *A* and *B*). In view of the chest radiograph, CT scan, and pulmonary function test findings, an α1-antitrypsin level was obtained and revealed a level of 22 mg/dL with two copies of the Z allele.

DISCUSSION OF THE DIAGNOSIS

AATD was first reported in 1963 by Carl-Bertil Laurell and Sten Eriksson who noted a link between low plasma serum levels of α1-antitrypsin and symptoms of pulmonary emphysema.[1] Since these first cases were described, an understanding of the biochemical mechanisms and genetic abnormalities has developed, and today the incidence of AATD in white newborns is similar to that of cystic fibrosis.[2] Although considered a rare condition by some, there are ~20 million individuals in the United States who carry at least one abnormal antitrypsin gene[3] and the prevalence of homozygous AATD is at least 100,000 in the U.S. population.[4] Only a fraction of those with AATD have been identified at this time, and although up to 3% of patients diagnosed with COPD have AATD,[5] most of these remain undiagnosed. Rahaghi *et al.* recently noted an AATD prevalence of 0.63% in patients with fixed airway obstruction found on pulmonary function tests, emphasizing the need for targeted testing of patients for this disease.[6]

Recent guidelines have been established to help recognize AATD patients before extensive airflow ob-

Table 2 **Full pulmonary function study showing very severe obstructive ventilatory disorder with a severe reduction in diffusion**

	Pre-BD Measurement	Predicted Measurement	% Predicted	Post-BD Measurement	% Predicted	% Change	Predrug Reported	Drug Reported	Predicted Range
Spirometry									
FVC	3.17	>4.58	56<	3.41	61	7			
FEV_1	0.95	>3.42	22<	1.05	24	11			
FEF_{25-75}	0.27	>1.82	7<	0.30	8	12			
FEF_{max}	3.85	>7.90	37<	3.68	35	−4			
FEV_1/FVC	29.80	>67.03	39<	30.76	40	3			
MVV	39.67<	127.80	31<						
Lung volumes									
TLC					77<		6.14<		6.79–9.09
FRC					119		4.54		2.82–4.79
RV					147>		3.60		1.77–3.12
Diffusion									
DCOHb					<42			14.05<	26.59–40.44
D/VAsbHb					<44			2.17	4.89

BD = bronchodialator; FEF_{25-75} = forced expiratory flow at 25–75%; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; MVV = maximal voluntary ventilation; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; DCOHb = diffusion of carbon monoxide corrected for hemoglobin; D/VAsbHb = diffusion of carbon monoxide corrected for alveolar volume and hemoglobin.

Figure 1. *Chest radiograph showing marked hyperinflation, flattening of the diaphragms, and prominence of the retrosternal airspace.*

struction has occurred.[7] Features that should prompt the physician to suspect AATD are listed in Table 3.

AATD is caused by mutations in the SERPINA 1 gene, which encodes the AAT protease inhibitor (Pi). There are three common testing strategies used to diagnose AAT deficiency: (1) measurement of serum or plasma AAT protein level, (2) AAT protein phenotyping, and (3) AAT genotyping. Although the protective threshold in serum levels has been identified as 11 μmol/L, a level of $<$20 μmol/L (113 mg/dL) will detect MZ, SZ, MS, and SS with 92% sensitivity and 90% specificity.[8] The normal Pi protein phenotype is PiM, which is most often associated with a normal MM genotype. The most common deficiency alleles are S and Z. Other Pi phenotypes include null alleles (which produce no AAT protein) and dysfunctional alleles (F), which produce normal protein levels but abnormal protein function. Genotyping may be accomplished by amplification of particular alleles extracted from circulating mononuclear cells.[9] Most commercial tests probe for S and Z genotypes and a non-S non-Z result is presumed to be MM. Because rarely it may signify another dysfunctional allele, such as F, null, or other rate mutations, one should interpret the results of genotyping in light of quantitative and other qualitative testing.

Clinically, the suggestive features of AATD manifest in the fourth and fifth decade but earlier in smokers. The emphysema is usually panacinar and usually present at the lung bases instead of the more apical distribution seen in COPD.[10] However, in a series of 165 plain radiographs from AATD patients, Gisher and colleagues observed that 15% of the films were normal

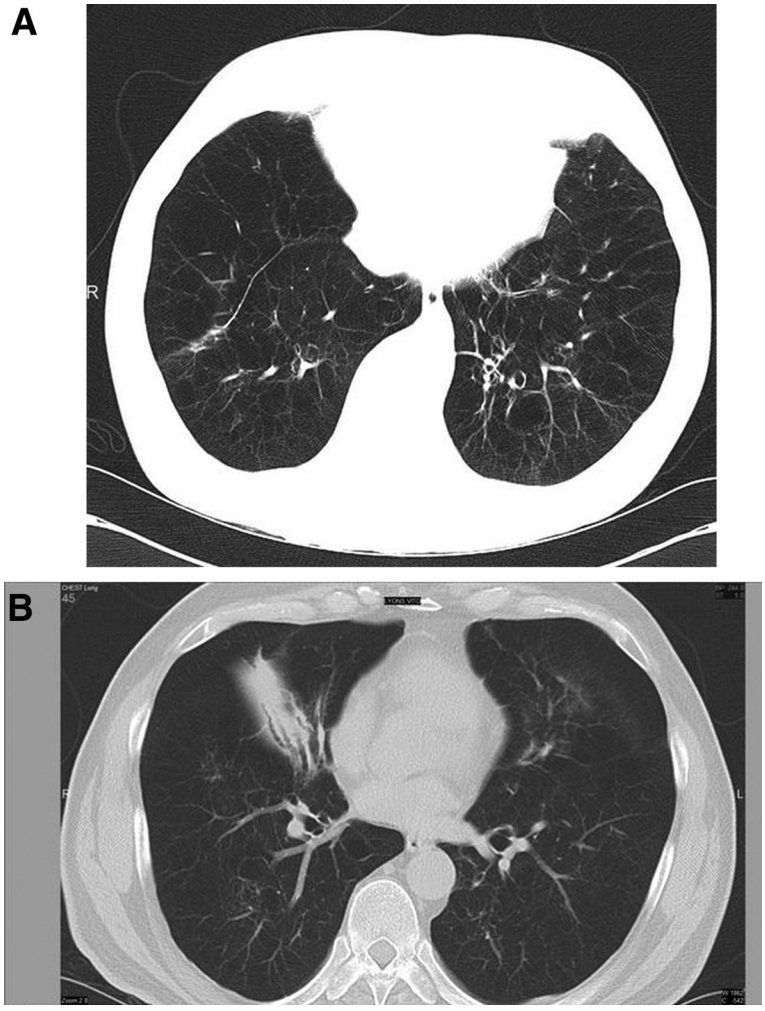

Figure 2. *(A and B) CT scan of the chest showing pulmonary hyperinflation with pulmonary emphysema and traction bronchiectasis.*

and that only 20% showed the distinctive pattern of emphysema.[11] In addition, in 102 AATD patients with evidence of emphysema on CT, Parr and colleagues reported that 64% had basal-predominant emphysema but that 36% had predominantly apical emphysema.[12] Bronchiectasis is usually present in the majority of

Table 3 **Clinical features that should prompt testing for AATD**

Early onset emphysema or emphysema in the absence of a recognized risk factor
Emphysema with a prominent basal distribution
Otherwise unexplained liver disease
Necrotizing panniculitis
Anti–proteinase 3–positive vasculitis
Family history of emphysema, bronchiectasis, liver disease, or panniculitis
Bronchiectasis without evident cause
Adults with symptomatic emphysema or COPD
Symptomatic adults with asthma that is incompletely reversible, despite aggressive treatment with bronchodilators
Asymptomatic adults with persistent airflow obstruction on pulmonary function tests with smoking or occupational exposure
Adults with necrotizing panniculitis
Siblings of affected individuals
Individuals (including neonates, children, and adults) with liver disease of an unknown origin)

AATD = α1-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease.

patients and may be clinically significant in 25% of patients with AATD.[13]

In the National Heart, Lung, and Blood Institute registry of individuals with severe deficiency of AAT, the most common symptoms seen in patients were dyspnea (84%), usual phlegm (46%), productive cough (42%), and wheezing with respiratory infections (76%).[14] Asthma is the most common respiratory diagnosis in patients with AATD before the diagnosis of AATD.[15] In a British Thoracic Society survey, asthma was considered present in 11% of AATD patients.[11] Piitulainen and colleagues reported a mean bronchodilator response of 400 mL (6%) in 41% of a group of 225 never-smoking subjects with severe AATD.[16] In a case series of 52 patients with AATD, Silverman reported asthma in 25% of these patients with a forced expiratory volume in 1 second (FEV_1) of <65% predicted.[17] Eden and colleagues indicated a 21% prevalence of asthma in a cohort of 1052 AATD patients from the National Heart, Lung, and Blood Institute registry.[18]

Atopy is a common feature in patients with AATD. Eden *et al.*[19] reported positive skin reactions to common aeroallergens in 48% of AATD patients and an increased incidence of allergic rhinitis in this cohort. They also noted an increase in IgE in patients who were atopic. In a review of patients from the α1-Foundation Registry, Eden *et al.*[20] reported a physician diagnosis of allergy and asthma in 49% of patients with AATD. Twenty-seven percent of patients were taking allergy medications to control their symptoms and 14% of patients had received immunotherapy for their disease. They also noted a high prevalence of self-reported wheezing with both allergen and irritant exposures. In view of the difficulty in distinguishing asthma from COPD in patients with established airflow obstruction and potential impact of asthma on FEV_1 loss, the evaluation of the wheezy patient with AATD should include an allergy evaluation to identify potential allergens that may contribute to bronchial hyperresponsiveness.

Treatment for patients with COPD due to AATD should include the usual therapy for COPD (smoking cessation, short- and long-acting bronchodilators, inhaled corticosteroids, rehabilitation, influenza and pneumococcal vaccines, and supplemental O_2 when indicated) with the exception of lung volume reduction surgery. In the small available series examining AATD patients, lung volume reduction surgery has generally conferred shorter-lived benefits[21,22] when compared with individuals with AATD patients treated with augmentation therapy.[23]

Beyond the usual treatment of COPD, specific treatment of AATD is available and consists of the infusion of purified pooled human plasma α-antitrypsin, known as i.v. augmentation therapy. The goal of augmentation therapy (60 mg/kg q. weekly i.v.) is to raise and maintain serum α-antitrypsin levels above the protective threshold of 11 μM over the entire dosing interval. Although therapy with α-antitrypsin augmentation does not show definitive data, the 2003 International Task Force[7] recommends augmentation therapy for patients with established airflow obstruction from AATD. Evidence that augmentation therapy slows the rate of FEV_1 decline and decreases mortality is stronger for individuals with FEV_1 of 35–60% predicted. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in patients with FEV_1 < 35% or >60% are less clear. Augmentation therapy is not recommended for PIMZ heterozygotes that may have COPD based on the absence of supportive evidence of efficacy for heterozygotes and the fact that the target nadir serum levels of augmentation therapy for PIZZ homozygotes is below the usual α-antitrypsin serum levels for PIMZ patients.[24] Augmentation therapy should also be considered for patients who have defective phenotypes of AAT such as SS, SZ, null, Z, null null, and FF, especially if the patient has emphysema on CT of the chest, borderline serum levels of AAT, and airflow obstruction on pulmonary function testing.[25]

Future treatment prospects for AATD include gene therapy by injecting adeno-associated virus carrying the human AAT gene, preparation of recombinant AAT,[26] inhibiting intrahepatic polymerization of AAT,[27] inhibiting neutrophil elastase by small molecule inhibitors,[28] using pegylation to prolong the serum half-life of AAT,[29] delivering AAT by inhalation, and using dose-ranging studies of i.v. augmentation therapy.

Final Diagnosis

After the α1-antitrypsin level was obtained, the patient was started on α1-antitrypsin replacement therapy, 60 mg/kg q. weekly i.v. The patient was referred for a baseline transplant evaluation and it was recommended that other family members be screened for this disease. The final diagnosis was AATD mistakenly treated as severe persistent allergic asthma for several years.

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Patient Oriented Problem Solving (POPS) Case Report

A 9-year-old boy with chronic urticaria and progressive spondyloarthritis

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ABSTRACT

A 9-year-old African American boy presented with chronic urticaria and progressive spondyloarthritis. Laboratory tests were abnormal for persistently positive antinuclear antibodies and undetectable total hemolytic complement (CH50) despite normal levels of complement C2, C3, and C4. Ultimately, further testing revealed an underlying deficiency in the immune system that may be associated with autoimmune disease and thus have a bearing on the patient's urticaria and spondyloarthritis. This is a unique presentation of a rare disease and underscores the importance of evaluating for systemic disease in the workup of chronic urticaria.

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CASE PRESENTATION

Chief Complaint

Chronic urticaria.

History of Present Illness

In 2008, a 9-year-old African American boy was referred for a 1-year history of urticaria. He would break out in hives on his trunk and extremities, at its worst about every week, each episode lasting a few days at a time. Hives were pruritic, not associated with pain or bruising, and individual lesions lasted <24 hours. There was no associated angioedema. Medical history was significant for premature dizygotic twin birth at 28 weeks gestation, allergic rhinitis, and mild persistent asthma. The allergies and asthma were adequately controlled on triamcinolone nasal spray and inhaled fluticasone. His fraternal twin brother also had allergic rhinitis and persistent asthma, but family history was otherwise unremarkable.

About 6 months after his initial allergy evaluation in 2008, he started to develop pain and morning stiffness in his peripheral joints and back and was seen by the university rheumatology clinic. Informed consent was obtained and the reporting of this case was approved by the Institutional Review Board at the University of Tennessee Health Science Center.

Physical Examination

He was a well-appearing child. He maintained a normal weight and height. Skin exam over multiple visits from 2008 to 2012 showed a few isolated small 5- to 8-mm wheals with large erythematous flares, variably located on the back, abdomen, chest, legs, and arms. There was no purpura, hyperpigmentation, or dermatographism. On their initial exam, the rheumatologists noted limited forward and lateral flexion of the lower back. He also had tenderness without active synovitis at all the joints, especially the hips.

Laboratory and Other Diagnostic Findings

Allergy skin-prick tests performed for the patient's respiratory allergies showed sensitization to tree, grass, and weed pollens; molds; and dust mites (a positive skin-prick test response was defined as a mean wheal diameter >3 mm than the negative control using standard techniques.) Intradermal methacholine testing to evaluate for cholinergic urticaria resulted in a large 10-mm wheal and 20-mm flare with multiple 6- to 8-mm satellite lesions. Total IgE was 87 IU/mL (normal, 0–200 IU/mL), thyroid autoantibodies were negative, and anti-IgE receptor I (FcεRI) antibody, as measured by increased CD203c surface expression on donor basophils when incubated with serum from the patient, was elevated (5.4%; normal, 0–5%; Advanced

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His rheumatologic workup revealed a persistently positive antinuclear antibody (ANA; 1:320 titer) and a low titer positive anti–Sjögren's syndrome-A. His blood count, metabolic profile, erythrocyte sedimentation rate, and C-reactive protein were normal. Human leukocyte antigen subtype B27, rheumatoid factor, and antibodies to dsDNA, Smith, ribonucleoprotein, and Sjögren's syndrome-B were negative. He had an undetectable hemolytic complement (CH50) despite normal levels of C2, C3, and C4, a finding that was confirmed over the follow-up period of 2008–2012.

Clinical Course

The patient was diagnosed with multifactorial chronic urticaria (allergic, cholinergic, and autoimmune urticaria) and largely responded to treatment with scheduled fexofenadine. However, as his arthritis pain increased, he was put on higher doses of nonsteroidal anti-inflammatory drugs, which exacerbated his hives.

The patient's arthritis was considered to be a seronegative spondyloarthritis initially treated with naproxen and physical therapy, but in 2011–2012 his symptoms progressed. His most recent physical exam was notable for a 25% loss of range of motion (flexion, extension, and rotation) in the lumbar spine with an abnormal Schober's test of 14 cm, limited abduction of both shoulders, bilateral enthesitis of the tarsal joint, and tenderness over the sacroiliac, first metatarsophalangeal, and temporomandibular joints. Radiographs of the pelvis, hips, and temporomandibular joints were normal. He has not had problems with uveitis or inflammatory bowel disease. Diclofenac was added to his treatment regimen and then hydroxychloroquine, which may also have therapeutic benefit for his urticaria.

QUESTIONS

What Is the Differential Diagnosis?

There are a number of possible etiologies for his chronic urticaria. His hives were often triggered by strong emotion and he had a positive intradermal methacholine test, features consistent with cholinergic urticaria. In addition, he had allergies to aeroallergens and was frequently on nonsteroidal anti-inflammatory drugs, factors that contributed to exacerbations but probably were not the primary cause. He also had evidence for autoimmune urticaria as indicated by the presence of functional antibodies to FcεRI. Antibodies to FcεRI can be found in a subset of patients with chronic urticaria, although the relationship between the presence of the autoantibodies and the urticaria is not clear.[1] The significance of a mildly elevated level, such as in our patient, is not known. Other considerations, in light of his abnormal complement levels, positive ANA, and arthritis, were systemic lupus erythematosus (SLE) and inflammatory arthritides. Hypocomplementemic urticarial vasculitis syndrome would not be likely with a normal C2, C3, and C4.

What Additional Investigations Would Be Helpful at Arriving at a Diagnosis in This Patient?

The patient's CH50 was persistently undetectable, which is an unusual finding; even in active rheumatologic disease, the CH50 can be low but is usually not undetectable, especially in the setting of repeatedly normal levels of C2, C3, and C4. This led us to examine levels of the other components of the complement system. Protein quantitation of C1q, C5, C6, C7, C8, and C9 by radial immunodiffusion was normal except for C8, which was undetectable (<0.2 mg/dL; normal, 10.7–24.9 mg/dL).

Subsequent DNA analysis revealed a compound heterozygote mutation in the gene encoding the C8 subunit known as C8α as the genetic basis for this patient's C8 deficiency. The first mutation leads to a splicing defect. The second mutation has been described previously by Kojima *et al.*[2] and is a C to T transition in exon 9 that creates a premature stop codon. He was given the tetravalent conjugate meningococcal vaccine and started on prophylactic penicillin V; to date, he has not had a serious bacterial infection. The remainder of his immunologic workup included normal quantitative immunoglobulins and tetanus titers. Titers to *Haemophilus influenzae B* and *Streptococcus pneumoniae* were initially low but responded appropriately to boosters with the conjugate vaccines. The patient's fraternal twin brother had normal levels of serum CH50 (23 U/mL; normal, 22–60 U/mL).

FINAL DIAGNOSIS

C8α-γ Deficiency

C8 is the eighth component of the complement system, which is composed of a series of plasma proteins that play a critical role in host defense and inflammation. Activation of C8 along with the other late complement components, C5 (in the form of C5b), C6, C7, and C9, results in the assembly of the membrane attack complex and direct lysis of cells. Deficiencies in the late complement components are rare and predominantly manifest as a predisposition to meningococcemia, meningococcal meningitis, and disseminated gonococcal disease.[3,4]

The structure of the C8 protein is unique from the other complement proteins in that it is composed of three polypeptide chains (α, β, and γ), each encoded by distinct genes. Two types of inherited C8 deficiency exist, C8β and C8α-γ deficiency, and both result in loss of total hemolytic complement activity. C8β deficiency

Table 1 **Cases of late complement component deficiencies and autoimmune disease**

Deficiency	Age (yr)	Race/Ethnicity	Sex	Clinical Features	Severe Infections	Reference No.
C5	20	African American	F	SLE, nephritis	Ear, skin, and vaginal infections	12
C5	27	Japanese	F	ANA^+ polyarthritis	No	13
C5	29	—	F	Discoid lupus erythematosus	Gonococcal arthritis	14
C5	28	Moroccan	F	Sjogren's	No	15
C6	46	Italian	F	SLE-like (polyarthritis, Raynaud's, pleurisy, and autoantibodies)	No	16
C6	60	African American	F	Episcleritis, recurrent fever, adenopathy, hepatosplenomegaly,and arthritis	Psoas abscess with *Staphylococcus albus*	17
C6	50	—	F	ANA^+ arthritis	No	18
C6	55	Black	M	SLE, nephritis, Sjogren's, hyperthyroidism	No	19
C6	—	Cameroon	—	SLE	No	20
C6, C2	8	Tunisian	F	Discoid lupus erythematosus	—	21
C7	42	French English	F	Possible scleroderma (Raynaud's, sclerodactyly, and telangiectasias)	No	22
C7	44	French Canadian	F	Ankylosing spondylitis	No	23
C7	27	Mexican	F	SLE	*Escherichia coli* sepsis	24
C7	59	White	M	Rheumatoid arthritis	No	25
C7	42	Japanese	F	SLE	No	26
C7, C4B	32	Spanish	F	SLE, nephritis, and epilepsy	No	27
C8α-γ	56	African American	F	SLE and nephrotic syndrome	No	8 and 9
C8β	38	White	F	SLE and nephritis	No	9
C8β	12	White	M	SLE-like illness, autoantibody, and immune complexes	No	10
C8β	13	White	M	Juvenile arthritis	No	6
C8β, C1q	49	White	F	Autoimmune hepatitis, hypothyroidism, and SLE-like illness (oral ulcers and autoantibodies)	Recurrent bacterial meningitis	11
C8α-γ	9	African American	M	Spondyloarthritis, ANA^+, and chronic urticaria	No	
C9	72	Japanese	M	Rheumatoid arthritis	No	28
C9	48	Japanese	F	Possible Sjogren's (sicca symptoms)	No	29
C9	35	Japanese	F	SLE	No	30
C9	51	Japanese	F	SLE	Recurrent urinary tract infections	31
C9	28	Japanese	F	Dermatomyositis	No	32

ANA = antinuclear antibody; SLE = systemic lupus erythematosus.

is more common in white subjects and C8α-γ deficiency is more common in nonwhite subjects.[3] There are a few case reports of autoimmune disease in C8 deficiency, but the association is not as robust as that seen with autoimmune disease and early complement deficiencies.[4,5]

One other case describes a 13-year-old white male patient with C8β deficiency who presented with fevers,

rash, fatigue, and mild arthritis in multiple peripheral joints.[6] Skin biopsy showed a mild, nonspecific vasculitis and he was diagnosed with juvenile chronic arthritis. Unlike our patient, he had a negative ANA, his arthritis was mild and limited to the peripheral joints, and enthesitis was not a prominent feature. The occurrence of two patients with juvenile chronic arthritis out of 150 reported cases of C8 deficiency (based on a comprehensive review of cases[4,5] plus a recent MEDLINE and EMBASE search covering the years since the review) suggests an increased prevalence of this disease in C8-deficient patients because the prevalence of juvenile chronic arthritis in the general population is estimated at 2–400 per 100,000, depending on the geographic region.[7]

Looking more broadly, we find four articles that describe patients with C8 deficiency and SLE or SLE-like illnesses and a total of 27 reported cases of autoimmune disease across all late complement component deficiencies (Table 1).[8–32] These numbers are best compared with prevalence data in the general population, but prevalence rates vary from region to region and are not widely available outside a few ethnically and geographically defined cohorts. What is known is that C5, C7, and C8 deficiency are relatively rare. Data from over 145,000 healthy blood donors in Japan showed an incidence of as 0.0014, 0.0041, and 0.0027%, respectively,[33] and case reports number in the low hundreds for C5, C7, and C8 deficiencies combined. C9 deficiency in East Asians[34] and C6 deficiency in individuals with African ancestry[35,36] are relatively more common.

CONCLUSION

There are sporadic cases of autoimmune disease reported in late complement component deficiencies, but it is not clear whether an association exists. Here, we describe a novel case of a 9-year old African American boy with spondyloarthritis and chronic urticaria found to have C8α-γ deficiency. His case adds to the number of reports suggesting a link between late complement deficiency and autoimmune disease. Although most allergists will not encounter late complement deficiency routinely, this case underscores the importance of a systemic evaluation in the workup of chronic urticaria.

Final Diagnosis

Complement C8α-γ deficiency.

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Erratum

Assessment of fractionated exhaled nitric oxide as a biomarker for the treatment of eosinophilic esophagitis

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On p 519 of the November-December 2012 issue, the Abstract printed incorrectly. The following is the correct version of the Abstract:

Diagnosis of eosinophilic esophagitis (EoE) and determination of response to therapy is based on histological assessment of the esophagus, which requires upper endoscopy. In children, in whom a dietary approach is commonly used, multiple endoscopies are needed, because foods are eliminated and then gradually reintroduced. Ideally, noninvasive methods could supplement or replace upper endoscopy to facilitate management. Fractionated exhaled nitric oxide (FeNO) has been proposed as a useful measure for monitoring disease activity in studies of patients with eosinophil-predominant asthma and in other atopic disorders. Thus, we evaluated whether FeNO levels could be a useful biomarker to assess the response to therapy in EoE patients. This study was designed to determine whether there is a change in FeNO levels during treatment with topical corticosteroids and whether changes correlated with clinical response. This was a prospective, multicenter study that enrolled nonasthmatic patients with established EoE. FeNO levels and symptom scores were measured at baseline, biweekly during 6-week swallowed fluticasone treatment, and 4 weeks posttreatment. Twelve patients completed the trial. We found a statistically significant difference between median pre- and posttreatment FeNO levels [20.3 ppb (16.0 -29.0 ppb) vs 17.6 ppb (11.7 -27.3 ppb), p=0.009]. However, neither the pretreatment FeNO level, a change of FeNO level after 2 weeks of treatment, nor the FeNO level at the end of treatment confidently predicted a clinical or histological response. Although our findings suggest nitric oxide possibly has a physiological role in EoE, our observations do not support a role of FeNo determination for management of EoE.

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Patient Oriented Problem Solving (POPS) Case Report

A 50-year old woman with nasal congestion, cough, and dyspnea

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ABSTRACT

We present a 50-year-old woman with progressive dyspnea, cough, and nasal congestion. Evaluation revealed positive skin tests (IgE) to trees and dust mites, early glottic closure on spirometry, and sinus opacities on CT. Diagnostic considerations included allergic and nonallergic rhinitis, asthma, aspirin-exacerbated respiratory disease, vocal cord dysfunction, chronic sinusitis secondary to gastroesophageal reflux disease, and systemic inflammatory and immunologic diseases, including vasculitis. Progresson of her symptoms prompted further investigation, and a biopsy yielded an unexpected diagnosis.

(Allergy Asthma Proc 34:188–192, 2013; doi: 10.2500/aap.2013.34.3637)

CASE PRESENTATION

History of Present Illness

A 50-year-old African American woman presented with 2 months of nasal congestion, worsening cough, and dyspnea. She had been unsuccessfully treated with a 14-day and a subsequent 21-day course of antibiotics for presumed sinusitis. Her history was remarkable for gastroesophageal reflux disease (GERD) responsive to proton pump inhibitor (PPI) therapy and asthma, formerly managed with an intermittent short-acting bronchodilator, now poorly controlled on fluticasone/salmeterol 250/50 mg. She had required two oral corticosteroid courses and several emergency room visits during the previous year. She reported "as-needed" dosing of fluticasone/salmeterol and self-discontinuation of reflux medication. Nasal congestion was unresponsive to nasal saline rinses or intranasal corticosteroids. Additional complaints included snoring, sleep apnea, epistaxis, dry cough, ocular irritation, ear fullness, heartburn, belching, and facial pain, treated with ibuprofen.

Other Medical History

She reported seasonal allergies. Family history included only seasonal allergies. She was a married bank teller, without occupational exposures. There were no pet, tobacco smoke, or mold exposures within the home.

Physical Examination

She had a weight of 205 lb; height, 70 in., blood pressure, 167/70; pulse 130; respirations, 18, temperature, 98.3, and peak expiratory flow rate, 270 L/min. She was uncomfortable with frequent coughing. Tympanic membranes were slightly dull bilaterally. Eyes were clear. Nasopharynx was erythematous mucosa with large inferior turbinates, with crusting. Mouth was erythema of the posterior oropharynx. Neck was supple, shotty adenopathy. Chest was clear to auscultation, equal breath sounds. Cardiovascular symptoms included tachycardic, normal heart sounds, without murmur. Extremities showed no cyanosis or clubbing. Her skin was normal.

Initial Laboratory and Diagnostic Findings

Aeroallergen skin-prick testing revealed sensitivities to late trees (3+), dust mites (2+), and appropriate controls. Spirometry showed overall decrease in inspiratory and expiratory flow rates, early glottic closure, and improvement postbronchodilator secondary to decreased anxiety and better inspiratory flow (Fig 1.). Sinus CT (unavailable for visual review) reported as showing bilateral opacities, right greater than left. Otolaryngology consultation was pending at time of initial visit.

QUESTION 1

Which of the following should be included in the initial differential diagnosis for this patient?

a. Extraesophageal manifestations of GERD

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	Pre-Bronch			Post-Bronch		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----						
FVC (L)	2.88	3.60	80	3.43	95	19
FEV1 (L)	2.50	2.89	87	2.92	101	17
FEV1/FVC (%)	87	81	107	85	105	-2
FEF 25% (L/sec)	4.40	5.85	75	7.52	129	71
FEF 75% (L/sec)	1.33	1.44	93	2.71	188	103
FEF 25-75% (L/sec)	3.18	2.90	110	4.17	144	31
FEF Max (L/sec)	5.32	7.21	74	8.01	111	50
FIVC (L)	1.19			3.03		156
FIF Max (L/sec)	2.06			5.12		148

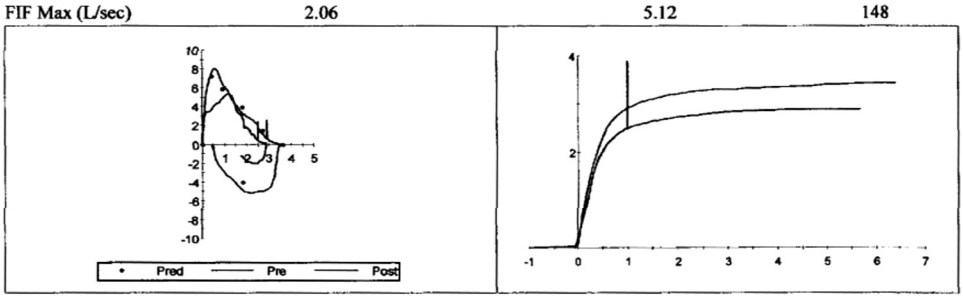

Figure 1. *Spirometry at baseline evaluation.*

b. Severe allergic rhinitis
c. Vocal cord dysfunction (VCD)
d. Aspirin-exacerbated respiratory disease (AERD)
e. Inadequately treated asthma
f. Mechanical obstruction.

The differential diagnosis of chronic rhinosinusitis is extensive (Table 1).[1] Extraesophageal manifestations of GERD include asthma, laryngitis, chronic cough, and recurrent episodes of rhinosinusitis.[2–4] "Reflux-asthma syndrome" has been implicated in bronchial hyperreactivity.[3] VCD could contribute to her dyspnea and "asthma exacerbations," suggested by limitation on inspiration and early glottic closure on spirometry.[5–7] Allergic rhinitis was suggested by positive skin tests to trees and dust mites, and presentation during tree pollen season. AERD was suggested by ibuprofen use, asthma, nasal congestion, and recurrent sinusitis[8,9]; however, spirometric changes were more consistent with anxiety than pulmonary obstruction, making AERD less likely. Mechanical obstruction should be considered with persistent sinus opacities on CT exam.[10]

Clinical Course

Undertreated GERD was plausible, and she was instructed to restart PPI therapy, in addition to regular use of fluticasone/salmeterol, breathing exercises for VCD, allergen avoidance, nasal saline rinses, and azelastine nasal spray. Otolaryngologic evaluation suggested allergic etiology; no rhinolaryngoscopy was performed.

Her asthma, cough, and heartburn initially improved; however, she experienced continued facial discomfort, epistaxis, and nasal obstruction, requiring an upright sleeping position. She was now outside tree pollen season with continued symptomatology. A prescribed prednisone taper yielded improvement.

Additional Considerations

A broader differential should be considered in patients refractory to standard treatment or whose clinical picture does not fit classic symptomatology. Systemic vasculitic diseases and sarcoidosis were contemplated in this patient's presentation, but diagnostic tests were initially deferred because of the greater probability of other causes.

QUESTION 2

What additional studies would be helpful in arriving at a diagnosis?

a. pH probe
b. Chest x-ray
c. Anti-neutrophil cytoplasmic antibodies (ANCA)
d. Methacholine challenge
e. Aspirin challenge
f. Repeat sinus CT.

Our patient responded well to PPI therapy. In those with failure of therapy, a positive 24-hour pH monitoring study of the proximal esophagus may support extraesophageal reflux causing sinusitis, laryngospasm, or chest symptoms. Methacholine challenge may document or exclude airway hyperresponsiveness in those with a questionable asthma history, and if AERD is suspected, aspirin challenge should be considered. These were not obtained, because the patient's previous spirometry did not strongly suggest asthma. A normal chest x-ray reduced the likelihood of sarcoidosis or Churg-Strauss. Vasculitis screening with serum ANCAs was negative. A repeat sinus CT scan was obtained to evaluate therapeutic effects or progression

Table 1 **Differential diagnosis of rhinosinusitis**

Allergic rhinitis
Occupational
Perennial
Seasonal
Nonallergic rhinitis
Atrophic
Chemical or irritant induced
Drug-induced/rhinitis medicamentosa
Emotional
Exercise induced
Gustatory
Hormone induced
Infectious
Acute
Chronic
Nonallergic rhinitis with eosinophilia syndrome
Occupational (irritant)
Vasomotor
Primary ciliary dyskinesia
Reflux-induced rhinitis or gastroesophageal reflux disease
Conditions that may mimic symptoms of rhinitis
Cerebrospinal fluid rhinorrhea
Inflammatory or immunologic conditions
Midline granuloma
Nasal polyposis
Sarcoidosis
Systemic lupus erythematosus
Wegener's granulomatosis
Relapsing polychondritis
Structural or mechanical
Choanal atresia
Deviated septum
Foreign bodies
Hypertrophic turbinates
Nasal tumors

(Fig. 2, *A* and *B*). When compared with her previous study, the second scan showed interval worsening of circumferential mucosal thickening in both maxillary sinuses, right greater than left, with obstruction of the right ostiomeatal unit.

Further Clinical Course

The patient's symptoms flared after prednisone taper, with daily headaches, eye pain, nighttime cough, and significant decline in forced expiratory volume in 1 second and forced expiratory flow at 25–75%. Sinus CT findings and symptomatology warranted a second otolaryngologic opinion. Nasal endoscopy was completed by the otolaryngologist and interpreted as suggestive of allergic disease, without evidence of sarcoidosis or granulomatous vasculitis. Multiple prominent vessels were observed and cauterized. She was instructed to begin amitriptyline for VCD and was referred to speech pathology.

Three months after initial presentation, she developed right upper eyelid swelling and supraorbital pain. She underwent ophthalmologic evaluation and was given tobramycin/dexamethasone and cyclopentolate ophthalmic drops for possible uveitis. Progressive periorbital swelling and new resistance to retropulsion on exam necessitated an orbital CT scan, which showed enlargement and inflammation of the right lacrimal gland, compatible with dacryoadenitis. A primary mass lesion could not be excluded.

Biopsy of the lacrimal gland and adjacent soft tissue (Fig. 3, *A* and *B*) showed "chronic granulomatous inflammation, acute inflammation with microabscess formation in association with vasculitis, showing focal necrosis within muscular vessel walls, and scarring of soft tissues." A subsequent high-resolution chest CT, urinalysis, and serum creatinine were normal. These findings and her negative tests for ANCA, anti-myeloperoxidase, and anti–peroxidase-3 were consistent with a limited form of granulomatosis with polyangiitis (Wegener's granulomatosis).

Prednisone at 0.5 mg/kg was began with a gradual taper to 10 mg/day over several months, and methotrexate, folic acid, and trimethoprim-sulfamethoxizole were added. After 3 months her cough subsided entirely and after 6 months all symptoms had resolved. She has since experienced two periorbital vasculitic flares requiring prednisone therapy, but no evidence of additional systemic involvement. Cough has flared occasionally, unrelated to vasculitis flares.

DISCUSSION

Granulomatosis with polyangiitis (GPA; Wegener's granulomatosis)[11] is a systemic necrotizing, granulomatous vasculitis of unknown etiology. In its severe form there can be multiple organ involvement with necrotizing vasculitis and granuloma formation, sufficiently severe to be life-threatening or produce failure of a major organ. Organ systems typically affected are the respiratory tract (upper and lower) and the kidneys; periorbital structures, the skin, joints, eyes, and the nervous system may also be affected.[12] Severe GPA may present as pulmonary hemorrhage, focal necrotizing glomerulonephritis, pulmonary-renal syndrome, or widespread paucimmune vasculitis affecting additional organs including the nervous system and gastrointestinal tract.[13] These manifestations are often catastrophic in onset and require prompt treatment as described later. Features of limited disease, including destructive lesions of the oropharynx, trachea, and bronchial tree; granulomatous inflammation of periorbital structures and the middle ear; and

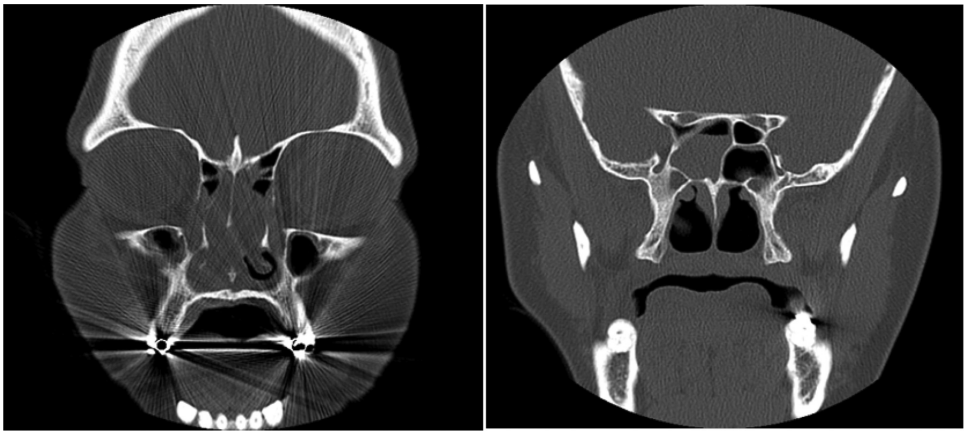

Figure 2. (A and B) CT sinus showing nasal septal deviation, polypoid opacities, soft tissue opacification obstructing ostiomeatal channel, and moderate mucosal thickening of maxillary sinuses with moderate fluid level in right posterior sphenoid sinus.

destruction of nasal cartilage are typically more insidious in onset.[14,15] The differential diagnosis of solitary periorbital swelling is broad and includes thyroid disease, Sjögren's syndrome, Churg-Strauss vasculitis, GPA, ocular lymphoid hyperplasia, orbital inflammatory disease, and a newly recognized IgG4-related disease, necessitating a thorough history, physical exam, and pathology to elicit evidence supporting a final diagnosis.[15]

Although a positive c-ANCA (usually anti–proteinase-3 antibodies) and, less frequently, p-ANCA (often antimyeloperoxidase antibodies) are significant in confirming clinical suspicion of GPA, ANCA may be absent, particularly in the limited variety. In a study of patients with active limited disease, the sensitivity of c-ANCA for GPA was only 67% by immunofluorescence and 60% by ELISA.[16]

The etiology of GPA remains largely unknown. The presence of ANCA suggests a role for autoantibodies in the pathogenesis; however, as mentioned previously, GPA can occur with negative ANCA and elevated titers may be present during remission.[17–19] $CD4^+$ T lymphocytes, Th17 lymphocytes, monocytes, and neutrophils have all been documented as significant contributors to the vasculitic process, suggesting both cellular and mononuclear immune responses may be responsible for acute and late-phase inflammatory changes.[20]

Treatment of GPA has until recently consisted of prompt administration of high doses of corticosteroids, including bolus methylprednisolone in severe disease, together with an immunosuppressive agent, typically cyclophosphamide in severe disease and either methotrexate or azathioprine for limited disease. For severe disease sequential treatment with 3–6 months of daily or monthly i.v. cyclophosphamide induction followed by transition to azathioprine or methotrexate maintenance therapy has replaced long-term cyclophosphamide therapy. Recently, B-cell directed therapy with rituximab plus prednisone, with or without concomitant cyclophosphamide, has shown beneficial effects.[21] This agent is now Food and Drug Administration approved for paucimmune vasculitis, including severe GPA.[22–24] This agent will likely supplant cyclophosphamide in many cases of severe disease because of its more acceptable toxicity profile.

Experts differ in the duration of treatment, with some attempting taper of immunosuppression after 1year and others continuing for ≥2 years. Limited disease, particularly of the nasopharynx and periorbital tissues, is especially prone to relapse and often requires longer periods of immunosuppression than pauciimmune vasculitis affecting the kidney and/or lungs. Current therapies have greatly improved morbidity and mortality, but relapse is common on tapering of treatment. Additionally, the patient may expe-

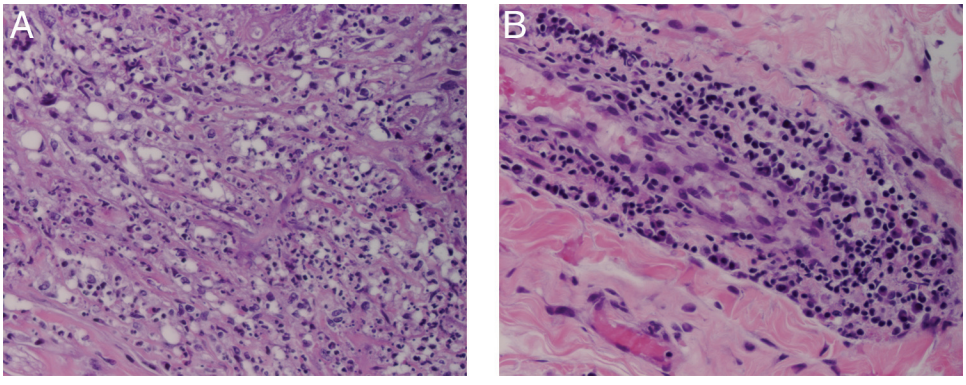

Figure 3. (A and B) Triad of histopathological findings diagnostic of Wegener's granulomatosis. (A) Granulomatous inflammation, microabscesses, and widespread necrosis, and (B) vasculitis with fibrinoid necrosis of arterial wall.

rience nasal congestion and respiratory symptoms for a variety of other reasons, such as medication toxicities and infection related to structural damage to the respiratory tract, which can represent both a diagnostic dilemma and a significant cause of debility and mortality within this population if not fully explored and treated promptly.[25]

Final Diagnosis

ANCA negative limited form of GPA (Wegener's granulomatosis).

CONCLUSION

Vasculitis syndromes may be encountered by allergists/immunologists because of nasal involvement, mimicking allergic or nonallergic rhinitis, or lung involvement suggesting asthma. It is important for the allergist to include GPA and other vasculitides in the differential of patients who fail to respond to standard treatment and to recognize the difficulties in diagnosis because of inconsistent laboratory findings.

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Patient Oriented Problem Solving (POPS) Case Report

Anosmia and an uncommon nonsteroidal anti-inflammatory drug reaction in a 38-year-old man

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ABSTRACT

Anosmia with asthma and nasal polyposis raises suspicion for aspirin-exacerbated respiratory disease (AERD). Guidelines for desensitization of patients with AERD to prevent recurrent nasal polyposis and improve upper and lower respiratory symptoms are well established. We present a patient with an uncommon reaction to acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs who required deviation from the standard ASA desensitization approach.

(Allergy Asthma Proc 34:292–296, 2013; doi: 10.2500/aap.2013.34.3650)

CASE PRESENTATION

Chief Complaint

Anosmia.

History of Present Illness

A 38-year-old man with anosmia and allergic rhinitis presented to an allergy clinic with a 2-year history of asthma. Nasal polypectomy 1 year earlier provided initial improvement in anosmia; however, anosmia and polyps recurred within 3 months. His medications included loratadine at 10 mg daily, montelukast at 10 mg daily, fluticasone/salmeterol at 250/50 q.h.s., olopatadine at 65 μg b.i.d., mometasone furoate at 50 μg b.i.d., albuterol 2 puffs q4 hours, p.r.n., and amlodipine at 10 mg daily.

Medical history included hypertension and hypercholesterolemia. He was a lifetime nonsmoker. Family history was positive for allergic rhinitis and asthma.

Physical Examination

He was a comfortable-appearing man, afebrile with age-appropriate vital signs. Sclera was mildly injected without any discharge. Nasal mucosa was boggy with evidence of nasal polyps bilaterally. Neck was supple without lymphadenopathy or thyromegaly. Cardiac exam revealed a regular rate with no murmurs. Lungs were clear to auscultation bilaterally. The remainder of the physical examination was unremarkable.

Diagnostic Findings

Initial laboratories revealed normal electrolytes, renal function, liver function, serum tryptase and complete blood count with an elevated absolute eosinophil count on the differential (Table 1). Initial spirometry revealed minimal obstructive airways disease with a reduced forced expiratory volume at 1 second (FEV_1)/forced vital capacity ratio and reduced forced expiratory flow at 25–75% (Table 2). Bronchodilator therapy was administered followed by repeat spirometric testing, revealing a significantly increased FEV_1 (Table 3).

QUESTION 1

What is the differential diagnosis of bilateral nasal polyps?

a. Cystic fibrosis
b. Allergic rhinitis
c. Fungal sinusitis
d. Chronic rhinosinusitis
e. Aspirin-exacerbated respiratory disease (AERD)
f. Churg-Strauss syndrome
g. Nonallergic rhinitis with eosinophilia syndrome

QUESTION 2

What additional investigations might be helpful?

a. Sweat chloride testing
b. Fasting blood glucose test
c. Cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA)
d. Sinus CT
e. Allergy skin testing

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Table 1 **Initial CBC with differential**

Cell Type	Value	Reference Range	Units
WBC	6.1	3.3–11.5	K/mol
HGB	15.8	12.7–17.8	g/dL
HCT	46.0	39.0–50.0	%
Platelet count	215	150–450	K/mol
Absolute neutrophil count	3.1	1.5–6.6	K/mol
Absolute lymphocyte count	1.8	1.5–3.5	K/mol
Absolute monocyte count	0.5	0.1–0.9	K/mol
Absolute eosinophil count	0.7	0.0–0.6	K/mol
Absolute basophil count	0.0	0.0–0.1	K/mol

CBC = complete blood count; WBC = white blood cell count; HGB = hemoglobin; HCT = hematocrit.

Table 2 **Initial spirometry**

Lung Mechanics		Actual	Predicted	% Predicted
FVC	L	6.68	5.89	113
FEV_1	L	4.71	4.62	98
$FEF_{25–75}$	L/s	2.98	4.46	67
FEV_1/FVC	L	69%	81%	86

FEV_1 = forced expiratory volume in 1 s; $FEF_{25–75}$ = forced expiratory flow at 25–75%; FVC = forced vital capacity.

Table 3 **Postbronchodilator spirometry**

Lung Mechanics		Actual	% Predicted	% Change
FVC	liters	7.01	119	5
FEV_1	liters	5.28	112	14
$FEF_{25–75}$	l/second	4.39	98	48
FEV_1/FVC	Liters	75%	93	9

FEV_1 = forced expiratory volume in 1 s; $FEF_{25–75}$ = forced expiratory flow at 25–75%; FVC = forced vital capacity.

f. Spirometry post–acetylsalicylic acid (ASA) challenge

Discussion of the Differential Diagnosis

The patient had no fever, headache/facial pain, or thick nasal discharge and his sinus CT scan confirmed nasal polyps but no sinus disease. He was not diabetic or immune compromised, making fungal sinusitis unlikely. Cystic fibrosis was unlikely because he had no history of pneumonia or recurrent respiratory infections and no family history of cystic fibrosis. He did not have a long-standing history of asthma or vasculitis, making Churg-Strauss syndrome unlikely. Poorly controlled allergic rhinitis, AERD, and nonallergic rhinitis with eosinophilia syndrome remained in the differential.[1,2]

Additional History

On three occasions, the patient reported upper respiratory symptoms, asthma exacerbation, and lip swelling hours after consumption of aspirin-containing products. All three events resolved spontaneously within 5 hours.

CLINICAL COURSE

Given his asthma, nasal polyps, and ASA history, aspirin desensitization according to standard practice paper approach for AERD[3] was initiated 3 weeks after repeat nasal polypectomy. All of his home medications were continued for the ASA desensitization.

On challenge day 1, he received and tolerated 20 mg of ASA. Three hours later, he received and tolerated 40 mg of ASA, remaining asymptomatic for 3 hours.

On challenge day 2, he received 81 mg of ASA. Three hours post-ASA administration, he experienced a 15% decrease in FEV_1, urticaria on his chest and upper extremities, throat itching, and chest tightness. He required two albuterol treatments, 10 mg of montelukast and 25 mg of diphenhydramine, after which spirometry, urticaria, and pruritus improved.

QUESTION 3

What is the differential diagnosis now?

a. ASA/nonsteroid anti-inflammatory drug (NSAID)-induced asthma and rhinitis in an asthmatic patient (AERD/triad asthma)
b. ASA/NSAID-induced urticaria/angioedema in a patient with chronic urticaria
c. ASA/NSAID-induced urticaria/angioedema in an otherwise normal patient
d. "Blended" reaction, choice a + choice b and/or choice c
e. Single NSAID-induced urticaria/angioedema in an otherwise normal subject

Given his 15% decrease in FEV_1 and urticarial reaction with exposure to ASA, he met the definition of a "blended" reaction (choice d). AERD with single NSAID-induced urticaria/angioedema (choices a + e) remained in the differential.

CLINICAL COURSE CONTINUED

On challenge day 3, 3 hours after receiving 81 mg of ASA, he developed urticaria on his legs, hands, and feet. Spirometry remained stable. He received 25 mg of diphenhydramine and 10 mg of cetirizine and symptoms subsequently improved.

On challenge day 4, to rule out single NSAID-induced urticaria/angioedema, the patient received 50 mg of ibuprofen. Three hours after administration of

Table 4 **Mechanisms responsible for aspirin/NSAID allergy syndromes**

COX-1 Inhibition	IgE-Like
Cross-reactive	Single agent
Time course >30 min	Time course <60 min
First dose	Requires previous doses

COX-1 = cyclooxygenase 1.

ibuprofen, he developed urticaria on his trunk and legs. He denied any respiratory symptoms and spirometry remained unchanged, thus displaying respiratory component tolerance, but continued cutaneous symptoms.

DISCUSSION

Eight types of pseudoallergic and allergic reactions to ASA and other NSAIDs have been identified.[4] AERD is characterized by inflammation of the respiratory tract with progressive nasal polyposis and asthma in response to ASA/NSAID-containing products, whereas the "blended" type ASA sensitivity reaction is characterized by AERD in combination with ASA/NSAID-induced urticaria/angioedema, in this case in a patient without chronic urticaria. There are no sensitive and specific *in vitro* tests to identify AERD patients. ASA oral challenges[5] (and in some cases intranasal aspirin–lysine or NSAID challenges)[6–8] have therefore been developed to differentiate patients with AERD from patients with similar presentations. During ASA challenges, AERD patients experience respiratory reactions ranging from naso-ocular symptoms to bronchospasm or any combination.[9,10]

The mechanisms responsible for the various allergic and pseudoallergic ASA/NSAID sensitivity reactions include cyclooxygenase (COX) 1 inhibition and "IgE-like" reactions (Table 4). In reactions secondary to COX-1 inhibition, cross-reactions are present, whereas in IgE-like reactions, patients characteristically react to a single NSAID or ASA alone. In addition, reactions mediated by COX-1 inhibition take at least 30 minutes to occur, whereas IgE-like reactions often occur within minutes of the ingestion. Reactions mediated by COX-1 inhibition can occur on first exposure, whereas IgE-like reactions usually require previous exposures.[4,11] Although pure AERD can be attributed to COX-1 inhibition, the mechanism responsible for blended reactions is poorly described.

Although the pathogenesis of AERD is still unclear, abnormalities in arachidonic acid metabolism have been implicated.[9,12,13] COX-1 and COX-2 inhibition is common to ASA and all classic NSAIDs.[14]

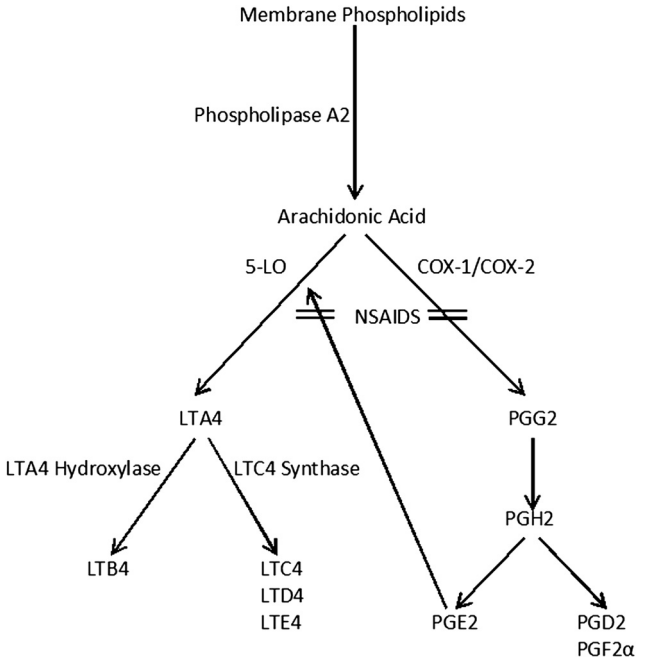

Figure 1. *Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase (COX) pathway and subsequently divert arachidonic acid metabolites to the lipoxygenase (LO) pathway. NSAIDS also decrease levels of prostaglandin E_2 (PGE_2) allowing unfettered 5-LO activation. Leukotriene C_4 (LTC_4) synthase overexpression in aspirin-exacerbated respiratory disease (AERD) patients further increases the number of cysteinyl leukotrienes resulting in a proinflammatory response.*

This mechanism is responsible for aspirin's antiplatelet effects. As a secondary effect, arachidonic acid is shunted toward the 5-lipoxygenase (5-LO) pathway increasing the production of cysteinyl leukotriene (CysLT) mediators.[12] In addition, ASA/NSAIDs suppress prostaglandin E_2 (PGE_2) and PGD_2 production.[12,15] PGE_2 normally inhibits 5-LO and, therefore, loss of PGE_2 leads to increased synthesis of leukotrienes (Fig. 1).[16] Leukotrienes induce powerful and prolonged bronchospasm, vasodilation, mucous secretion, and recruitment of additional eosinophils in bronchial smooth muscles.[17] These mediators are partly responsible for the smooth muscle constriction that leads to typical asthma symptoms of wheezing, cough, and dyspnea in sensitive individuals.[18] In addition to causing respiratory symptoms, CysLTs cause vasopermeability that could augment urticaria.[14] Although COX-1 inhibitors cause AERD symptoms in sensitive individuals, COX-2 inhibitors are a safe alternative in patients with AERD.[12,19]

The cytokine IL-4 also plays an important pathogenic role in AERD. Increased IL-4 leads to overproduction of CysLTs by up-regulating leukotriene C4 synthase and the CysLT receptors (CysLT1 and -2). IL-4 also leads to decreased secretion of PGE_2, which in turn, causes increased secretion of CysLTs. ASA is

known to directly inhibit T-cell IL-4 expression and thus may be another mechanism providing therapeutic benefit in the treatment of AERD.[20]

PGE_2 and PGD_2 also have protective effects on mast cells. Loss of these PGs leads to destabilization of cutaneous mast cells and ultimate discharge of histamine and tryptase into the skin and soft tissues. This destabilization of mast cells is the likely mechanism responsible for the cutaneous component of the blended type reaction.[4]

In the late 1990s, leukotriene modifier drugs (LTMDs) were introduced in the Unites States. There are currently two mechanisms by which LTMDs act: antagonism of the CysLT receptor (montelukast and zafirlukast) or inhibition of the 5-LO enzyme (zileuton).[21] Several studies have shown that for patients with pure AERD reactions, treatment with LTMDs provides some protection from significant aspirin-induced bronchospasm during oral aspirin challenge.[9,21,22] The effectiveness of LTMDs for the treatment of urticarial reactions is less well known.[17]

CLINICAL COURSE CONTINUED

Given that our patient continued to have urticaria, despite respiratory tolerance, the decision was made to add zileuton CR at 1200 mg b.i.d. to the medication regimen.

On day 5, he received 50 mg and then 100 mg of ibuprofen without any reactions. On day 6, he received 200 mg of ibuprofen and had no cutaneous or respiratory symptoms. After 6 hours of monitoring, he was discharged on ibuprofen at 200 mg b.i.d. and was instructed to keep zileuton CR at 1200 mg b.i.d. in his medication regimen.

In follow-up at 1, 3, and 6 months, he had no polyp regrowth, respiratory or cutaneous symptoms. Transaminases and spirometry remained normal. At 6-month follow-up, he requested stopping zileuton. Two days after discontinuing zileuton, urticaria, but not respiratory symptoms, recurred. Zileuton was subsequently restarted, which led to resolution of the cutaneous symptoms. At 1-year follow-up, he reported that he was doing "great." He denied any respiratory or cutaneous symptoms and there was no regrowth of polyps.

Final Diagnosis

Blended-type ASA/NSAID sensitivity reaction with induction of tolerance dependent on zileuton.

SUMMARY AND CONCLUSIONS

Controversy exists regarding classification of the blended ASA reaction and therefore desensitization for these patients arguably poses an even greater challenge for clinicians. Our patient experienced a 15% decrease in FEV_1 and an urticarial reaction during challenge/desensitization, meeting the definition of a blended reaction. He experienced both cutaneous and respiratory symptoms 2–3 hours after exposure to both aspirin and ibuprofen, suggesting that COX inhibition is the shared mechanism for both the cutaneous and the respiratory components of the blended ASA sensitivity reaction. Cutaneous tolerance was achieved and maintained only after introducing zileuton. Cutaneous tolerance but not respiratory tolerance was lost when zileuton was discontinued. For patients with blended reactions to ASA/NSAIDS, augmentation with the 5-LO inhibitor zileuton may be necessary for successful cutaneous induction of tolerance to occur.

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Patient Oriented Problem Solving (POPS) Case Report

Recurrent perioperative anaphylaxis in a 54-year-old man

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ABSTRACT

Reports suggest that perioperative anaphylaxis in patients undergoing general anesthesia range from 1 in 5000 to 1 in 20,000 with mortality rates as high as 9%. Because of the variety of medications that are used for general anesthesia and the rapid succession in which they are administered, it is often difficult to determine the etiology of a severe allergic episode in this setting. Antibiotics and anesthetics are notorious for precipitating allergic reactions and are often implicated. Other perioperative exposures and patient risk factors must also be considered. In this article, we describe the case of a patient who exhibited recurrent anaphylaxis episodes while trying to undergo a vital cardiac surgery.

(Allergy Asthma Proc 34:383–386, 2013; doi: 10.2500/aap.2013.34.3667)

CASE PRESENTATION

Chief Complaint

Perioperative anaphylaxis

History of Present illness

A 54-year-old dentist was taken to the operating room (OR) for repair of an ascending aortic aneurysm. During the induction of anesthesia, acute hypotension and bradycardia developed. He was initially treated with epinephrine, phenylephrine, calcium gluconate, vasopressin, and i.v. fluids. His skin was diffusely erythematous (Fig. 1) with scattered urticaria and an allergic reaction was suspected. His anesthetics and antibiotics were stopped and diphenhydramine, ranitidine, and hydrocortisone were administered. His clinical status stabilized but his procedure was aborted. He was diagnosed with anaphylaxis, admitted to the hospital for observation, and discharged the following day.

Approximately 6 weeks later, he was referred to the allergy clinic for testing to evaluate the cause of his anaphylaxis episode. The anesthesiologist provided a list of medications that were given before symptom onset including midazolam, vancomycin, lidocaine, fentanyl, propofol, and vecuronium.

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The patient denied history of allergic rhinitis, asthma, stinging insect allergy, or food allergy but described intermittent urticaria. He stated that he had episodes of urticaria precipitated by exposure to heat. He said submersion in a hot tub caused diffuse urticaria, and he also noted hives on his legs when his warm laptop computer rested there. He said the lesions resolve within hours of removing the stimulus.

The patient works as a dentist and admitted to frequent latex exposure. He had never had an adverse reaction as a result of latex exposure and wore latex gloves with no issue. The patient denied any history of pruritus, flushing, abdominal pain, diarrhea, or syncope.

Physical Examination

In the allergy clinic, the patient had normal vital signs and was asymptomatic. He had a normal exam including the absence of any organomegaly or skin findings.

Laboratory and Other Diagnostic Findings

Within 1 hour of symptom onset in the OR, a serum tryptase level was obtained showing a value of 154 ng/mL. This elevated result confirmed the presence of anaphylaxis (positive predictive value, 92.6%).[1,2] Suspecting medication allergy as the trigger, we elected to conduct skin testing to the agents that were given in the perioperative period. Using published recommendations for nonirritating concentrations of common perioperative medications, we conducted skin testing to the eight agents that were administered during his induction.[3] He showed positive results for cisatracurium, midazolam, vecuronium, and vancomycin (Table 1). In

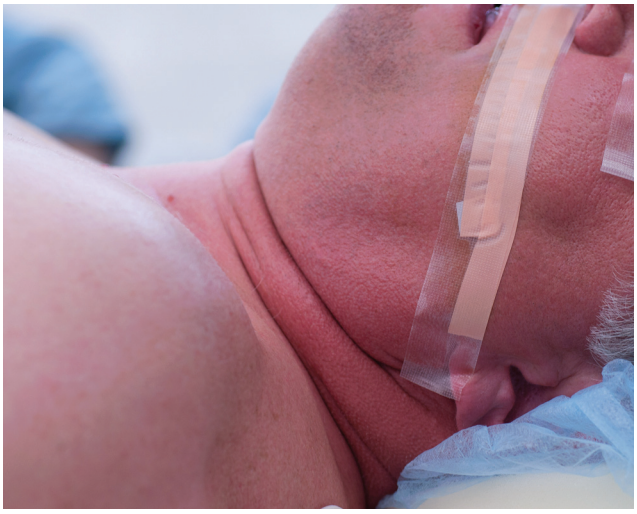

Figure 1. *Patient developed diffuse erythema with associated hypotension after induction of anesthesia.*

addition, a repeat baseline tryptase was obtained showing a level of 9.1 ng/mL.

Clinical Course

Based on the skin test results, we recommended avoidance of cisatracurium, midazolam, vecuronium, and vancomycin. Approximately 3 weeks later, the patient returned to the OR to reattempt his aortic aneurysm repair. During the induction phase of anesthesia, the patient once again developed anaphylaxis (acute hypotension, flushing, and urticaria) despite appropriate avoidance of the previously implicated medications. New agents included dexmedetomidine, sufentanil, and linezolid. He received epinephrine and required crystalloid, norepinephrine, and vasopressin before hemodynamic stability was achieved. The procedure was aborted again. A tryptase level obtained 45 minutes after symptoms developed was elevated (56.2 ng/mL).

QUESTIONS

What Is the Differential Diagnosis?

Perioperative anaphylaxis can be attributed to a number of causes. A variety of antibiotics, neuromuscular blocking agents (NMBAs), opioids, hypnotics, and volume expanders as well as exposures to surgical supplies containing latex have been implicated. Patient comorbidities must also be considered.

Drug Allergy. NMBAs, antibiotics, and opioids are among the most common medications to cause allergic reactions in the perioperative period.[3] Our patient was exposed to several of these agents within minutes of symptom onset. NMBAs and opioids can produce anaphylaxis *via* direct mast cell (MC) activation or an IgE-mediated mechanism.[3,4] Antibiotics including penicillins and cephalosporins have been implicated in up to 15% of perioperative reactions and are IgE mediated.[3,4] Vancomycin can produce histamine release from basophils and MCs directly.[5]

Latex Allergy. Our patient was at risk for latex sensitization from his frequent exposure to latex gloves at work. A sensitized patient could develop anaphylaxis if latex surgical supplies were used in the OR. Natural rubber latex is an important cause of perioperative anaphylaxis with several studies ranking it second only to NMBAs.[3,4,6,7] Diagnosis is made by skin-prick testing or measurement of Latex-specific IgE.[3,7,8] Avoidance is the only effective treatment.[3]

Physical Urticaria. Our patient reported a history of urticaria induced by heat. Cholinergic urticaria is composed of hives that are precipitated by an increase in core body temperature, often evident after exercise or bathing in hot water.[9] Heat-induced urticaria can be generalized but are typically local, with symptoms occurring specifically at the site where a warm stimulus contacts the skin.

Mastocytosis. A patient history of underlying systemic mastocytosis raises the risk of anaphylaxis during general anesthesia.[10–12] Patients typically describe history of urticaria, flushing, abdominal pain, or diarrhea. They may exhibit urticaria pigmentosa and they generally have elevated baseline tryptase levels, although an isolated history of an elevated tryptase level is not diagnostic of mastocytosis.[2,13]

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Further allergy testing for linezolid, sufentanil, and dexmedetomidine was negative. Serum-specific IgE for latex was also negative (<0.35 kU/L).

Although the patient had normal baseline tryptase levels and no clinical history of urticaria pigmentosa, pruritus, abdominal pain, or diarrhea, his presentation with recurrent perioperative anaphylaxis was concerning for mastocytosis. After ruling out extrinsic triggers for anaphylaxis, bone marrow (BM) biopsy was conducted to evaluate for an intrinsic cause for his recurrent episodes.

The BM biopsy specimen was immunohistochemically stained for tryptase and showed multiple focal dense aggregates of >15 MCs, some associated with small lymphocytes. MCs were present in the aspirate smears and frequently showed spindled morphology. Flow cytometry indicated MCs with aberrant expression of CD2 and CD25, and molecular marker analysis detected a c-kit D816V mutation in the aspirate.

Table 1 **Allergy skin testing results**

Agent	Skin-Prick Testing Concentration	Skin-Prick Testing Wheal (mm)/Flare (mm)	Intradermal Concentration	Intradermal Wheal (mm)/ Flare (mm)
Cisatracurium	**2 mg/mL**	**0/0**	**0.2 mg/mL**	**11/13**
Midazolam	**5 mg/mL**	**0/0**	**0.5 mg/mL**	**9/14**
Propofol	10 mg/mL	0/0	0.1 mg/mL	7/0
Fentanyl	0.05 mg/mL	0/0	0.005 mg/mL	9/0
Lidocaine	10 mg/mL	0/0	1 mg/mL	9/0
Vecuronium	**4 mg/mL**	**0/0**	**0.4 mg/mL**	**9/9**
Succinylcholine	10 mg/mL	0/0	1 mg/mL	9/0
Vancomycin	**0.001 mg/mL**	**0/0**	**0.0001 mg/mL**	**9/15**
Saline*		0/0		7/0
Histamine#		5/20		n/a

Positive tests are in bold type.
**Negative control.*
#Positive control.

DISCUSSION

Mastocytosis is characterized by the presence of excessive MCs in one or more tissues. The diagnosis refers to a heterogeneous group of disorders including systemic mastocytosis, cutaneous mastocytosis (urticaria pigmentosa), and mastocytoma. Systemic mastocytosis often involves multiple organs including the skin, gastrointestinal mucosa, liver, spleen, and BM. Clinical symptoms result from excessive MC mediator release, especially histamine, and may include flushing, pruritus, headache, diarrhea, abdominal pain, and hypotension. Classically, cutaneous mastocytosis involves small reddish-brown macular skin lesions (urticaria pigmentosa) that produce a characteristic wheal and flare response to skin stroking (Darier sign).[10,13]

The pathophysiological cause for mastocytosis involves constitutive proliferation of MCs because of a mutation of c-kit.[13] MC growth, differentiation, and survival are dependent on stem cell factor, which acts *via* the receptor tyrosine kinase c-kit (CD117) on the surface of MCs. The KIT gene encodes for the c-kit protein and a gain of function mutation of KIT causes overactivity that produces constitutive proliferation of MCs. The most common gene mutation producing mastocytosis is D816V (valine is substituted for aspartate at codon 816).[13]

Often, an elevated baseline tryptase level over 20 ng/mL will suggest systemic mastocytosis, but this alone is not diagnostic. Rather, BM (or extracutaneous organ) biopsy is imperative to make the diagnosis.[13] The World Health Organization has outlined major and minor criteria for the diagnosis of mastocytosis (Table 2). The major criteria for diagnosis is a BM biopsy (or biopsy of another extracutaneous organ) showing multifocal, dense infiltrates of MCs numbering 15 or more in an aggregate. The pathological diagnosis is confirmed by tryptase immunohistochemistry. Several other minor criteria have been established as well. These include (1) >25% spindle-shaped MCs on BM biopsy; (2) detection of KIT mutation in BM, blood, or other extracutaneous organ; (3) MCs that coexpress CD117 with CD2 and/or CD25; (4) a serum tryptase level persistently >20 ng/mL.[13] The diagnosis of systemic mastocytosis can be made if one major and one minor criterion are present, or if three minor criteria are met.[13]

Table 2 **World Health Organization criteria for systemic mastocytosis**

Major criterion
The presence of multifocal dense aggregates of >15 MCs as detected with tryptase or other special stains in BM or other extracutaneous organs
Minor criteria
Atypical morphology or spindle shapes in >25% of the MCs in BM sections, BM aspirate, or other extracutaneous tissues
Mutational analysis of KIT showing a codon 816 mutation (*e.g.*, Asp816Val) in BM, blood, or extracutaneous organs
BM or other extracutaneous MCs expressing the surface markers CD2, CD25, or both
Baseline serum tryptase levels of >20 ng/mL

BM = bone marrow; MC = mast cell.

Treatment for systemic mastocytosis is generally symptomatic. H_1- and H_2-antihistamines are effective in reducing pruritus, flushing, and tachycardia.[10] Oral disodium cromolyn can reduce gastrointestinal symptoms in patients with abdominal pain and diarrhea.[10]

In the event of anaphylaxis, self-injectable epinephrine remains the first-line treatment.[10]

General anesthesia poses special risks for the patient with mastocytosis. Several case reports describe intraoperative anaphylaxis in patients with underlying systemic mastocytosis and this remains a high-risk procedure.[10,14] The rate of complications during general anesthesia in mastocytosis is not known. Many agents used during surgery are direct MC stimulators increasing the risk of perioperative anaphylaxis.[10,11] Patients are often premedicated with H_1- and H_2-antihistamines and glucocorticoids. Prospective studies are lacking, but several case series and observations offer recommendations. Chaar *et al.* reported that premedication with corticosteroids and H_1- and H_2-antihistamines successfully reduces adverse events during surgery.[11] Carter *et al.* advocate the incremental administration of drugs known to activate MCs, rather than single boluses, in pediatric patients with mastocytosis.[12] Additional studies regarding optimal preoperative management of patients with systemic mastocytosis are warranted. Ultimately, our patient was premedicated with prednisone at 50 mg, diphenhydramine at 50 mg, ranitidine at 150 mg, and montelukast at 10 mg (12 hours and 1 hour before his surgery) and successfully tolerated his aortic aneurysm repair without adverse event.

Final Diagnosis

Recurrent perioperative anaphylaxis secondary to underlying systemic mastocytosis.

CONCLUSIONS

Systemic mastocytosis must be ruled out in patients with recurrent perioperative anaphylaxis, regardless of normal baseline tryptase levels and absence of suggestive clinical symptoms.

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Patient Oriented Problem Solving (POPS) Case Report

Recurrent fevers and failure to thrive in an infant

David R. Scott, M.D.,[1] Sarah Chan,[2] Johanna Chang, M.D.,[3,4] Lori Broderick, M.D., Ph.D.,[3] and Hal M. Hoffman, M.D.[3,4,5]

ABSTRACT

We describe a 2-year old boy with consanguineous parents who recently emigrated from India and presented with oral ulcers and lymphadenopathy. He also had a history of recurrent fevers, polyarticular arthritis, chronic diarrhea, failure to thrive, and developmental delay. Infectious workup revealed herpes simplex virus 1 viremia and radiological evaluation revealed osteopenia and erosions involving multiple joints. We describe the immunologic and genetic evaluation of this patient and discuss the diagnostic and therapeutic approach to an infant with recurrent fevers.

(Allergy Asthma Proc 34:473–479, 2013; doi: 10.2500/aap.2013.34.3672)

CASE PRESENTATION

S. Chan and D.R. Scott contributed equally to this work.

Chief Complaint

Recurrent fevers in a patient with oral ulcers, chronic diarrhea, and failure to thrive.

History of Present Illness

Our patient is a 2-year old Indian boy who presented with 5 days of aphthous ulcers and generalized lymphadenopathy. History revealed chronic recurrent fevers, diarrhea, polyarticular arthritis, global developmental delays, and failure to thrive. He had debilitating deformities of the elbows, wrists, and knees and was unable to crawl, stand, or walk. Laboratory analysis revealed a leukocytosis, microcytic anemia, thrombocytopenia, and elevated acute-phase reactants. The allergy and immunology service was consulted for evaluation of his unexplained recurrent fevers.

Medical History

The patient was born in India at full term by C-section complicated by NICU admission for meconium aspiration. At 44 days of life he developed intermittent fevers and diarrhea without an identified etiology. At 2 months of age he was admitted to a hospital in India with fever, diarrhea, and progressive swelling of multiple joints, including bilateral elbows, wrists, ankles, and proximal interphalangeal joints of the fingers. Ultrasound suggested multifocal osteomyelitis involving the upper and lower extremities. Bone biopsy revealed sterile pyogenic osteomyelitis. All synovial fluid and bone cultures remained negative and no infectious etiology was identified. He was discharged with an extended course of empiric broad-spectrum antibiotics with minimal improvement.

At 9 months of age, he began to manifest recurrent fevers to 103°F, initially occurring every 6 hours, but subsequently decreasing in frequency to every 3 days, which persisted until the time of his presentation. Fevers occurred without associated symptoms other than irritability and decreased energy. No diagnosis was identified and he was treated symptomatically with paracetamol.

The patient received his routine childhood vaccinations according to the Indian vaccination schedule, including a bacille Calmette-Guérin vaccine with no abnormal immunization reactions. He had no history of recurrent infections, including no previous pneumonia or sinusitis.

Social History

The patient was born and raised in southern India and moved to San Diego, CA, with his parents 2 months before presentation. He had no other siblings.

Family History

There was no family history of recurrent fevers, immunodeficiency, early childhood deaths, or develop-

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HM Hoffman has a financial conflict of interest with SOBI, the manufacturer of anakinra. The remaining authors have no conflicts of interest to declare pertaining to this article

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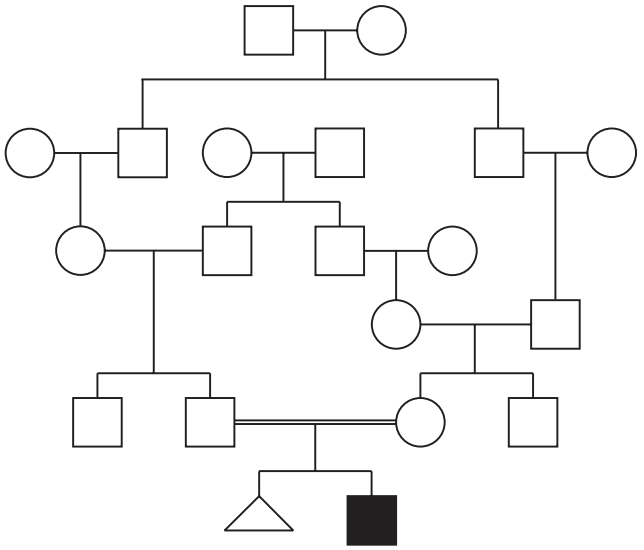

Figure 1. Family pedigree revealing multiple levels of parental consanguinity. No other family members were affected, but there was a history of prior miscarriage, indicated by triangle. Shaded box designates our patient. Double connecting line indicates consanguinity.

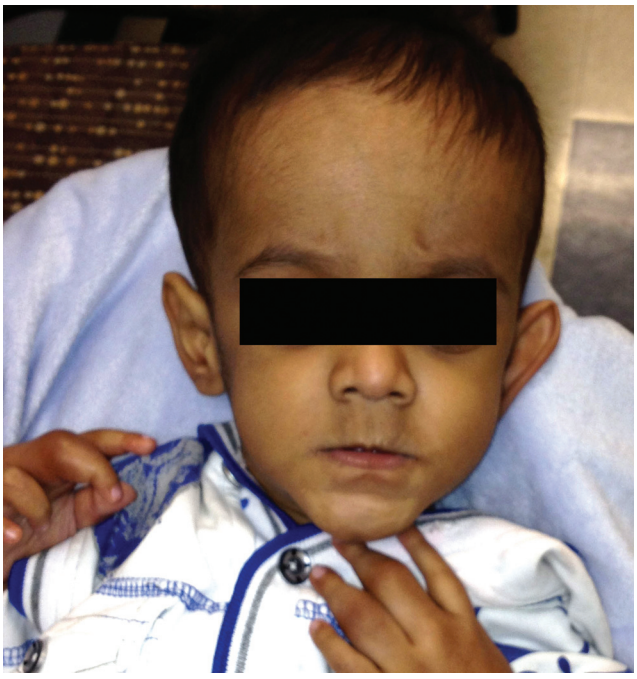

Figure 2. Facial structure of the patient showing frontal bossing characteristic of mevalonate kinase deficiency (M).

mental delays. His parents were both healthy without any medical problems. However, family history was notable for consanguinity over multiple generations and one prior miscarriage (Fig. 1). His mother's maternal grandfather and father's father are brothers and his mother's paternal grandfather and father's maternal grandfather are also brothers.

Physical Examination

On initial evaluation, he was irritable but consolable by his mother, with weight at the 0.1 percentile for age. On physical exam, he appeared thin and small with frontal bossing (Fig. 2). His exam was notable for an open anterior fontanelle, submandibular and cervical lymphadenopathy, and palpable hepatosplenomegaly. His oropharynx showed multiple ulcerative lesions. His extremities revealed hypotonia; rocker bottom feet; and swelling of the ankles, elbows, and proximal interphalangeal joints of some fingers (Fig. 3).

Laboratory and Other Diagnostic Findings

The initial laboratory and diagnostic evaluation is summarized in Table 1. Skeletal survey indicated an Erlenmeyer flask appearance of the long bones and a pointed appearance of the proximal metacarpals (Fig. 4).

QUESTIONS

What Is the Differential Diagnosis?

The differential diagnosis for chronic relapsing fevers in an infant is broad, including immunodeficiency, chronic infection, autoimmune diseases, autoinflammatory disease, and malignancy (Table 2). The presence of systemic multitissue inflammation with previous negative infectious workup was most suggestive of an autoinflammatory illness. Furthermore, his early onset multisystem involvement and severe developmental delay pointed toward an inherited syndrome.

What Additional Laboratory Data or Investigations Would Be Most Helpful in Arriving at a Diagnosis in This Patient?

a. Bone marrow biopsy
b. T-cell function studies
c. *NLRP3* gene mutational analysis
d. Serum IgD level
e. *Mevalonate kinase* (*MVK*) gene mutational analysis

Genetic testing for *MVK* gene mutations would be confirmatory for mevalonate kinase deficiency (MKD). Serum IgD levels may be measured, but lack sensitivity and, unless extremely elevated, are not specific for MKD.[1–3] Workup to help rule out other inborn errors of metabolism would include plasma and urine amino acid levels, urine organic acids, and plasma acylcarnitine profile. Lymph node biopsy and bone marrow biopsy would be appropriate to exclude malignancy or myelodysplastic syndrome, although these would be less likely in this patient.

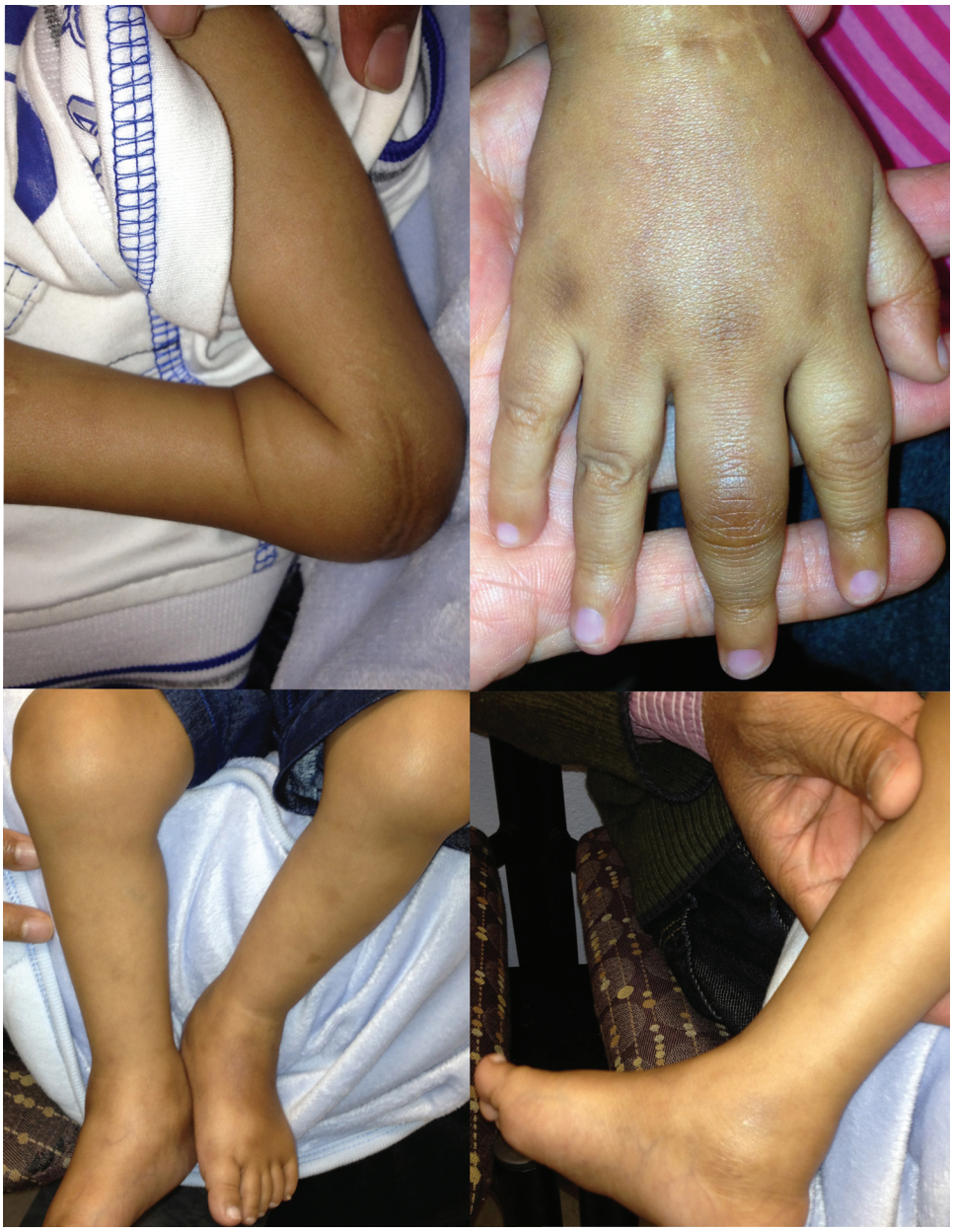

Figure 3. Photographs of the patient revealing swelling of elbows and proximal interphalangeal joints of some fingers, as well as rocker bottom feet and swelling of the ankles. Scars from previous surgical incisions can also be seen.

Clinical Course

The patient was diagnosed with acute primary herpes simplex virus (HSV) 1 infection by peripheral blood polymerase chain reaction and was treated with acyclovir. His infectious workup remained otherwise unremarkable and no immunodeficiency was identified. It was concluded that his HSV-1 infection was unrelated to his underlying chronic illness.

Bone marrow biopsy showed a normal karyotype with no cytogenetic abnormalities, marrow failure, storage disease, or malignancy. Flow cytometry did not reveal any immunophenotypic abnormalities suggestive of a cellular immunodeficiency.

Quantitative immunoglobulins revealed elevated IgG, IgA, and IgM. However, serum IgD levels were normal at 21 mg/L (reference range, <179 mg/L). Urine organic acids obtained while he was symptomatic showed an elevation in mevalonic acid to 10 mmol/mol creatinine (reference range, 0–2).

The patient was started on anakinra at 3-mg/kg injections daily for suspected hyper-IgD syndrome (HIDS) or MVA with resolution of fevers within 24 hours and decreased joint swelling within 4 days. Genetic analysis confirmed a homozygous mutation of the *MVK* gene at position 1162 C>T within exon 10, resulting in a stop codon (C → T) at amino acid position 388.

With 10 months of anakinra, he has experienced marked clinical improvement, including increased weight gain, resolution of diarrhea, improved appetite,

Table 1 **Laboratory evaluation and studies**

Laboratory	Result (normal range)	Other Diagnostic Evaluation	
Immunoglobulins		Infectious Disease Evaluation	
IgG	2100 mg/dL (413–1112)	Hepatitis B Surface Ag	Negative
IgA	300 mg/dL (21–117)	Hepatitis B Core IgM	Negative
IgM	253 mg/dL (30–146)	Hepatitis C IgG Ab	Negative
IgD	21 mg/dL (0–179)	HIV-1/HIV-2 Ab	Negative
IgE	524 kU/L (0–12.0)	CMV IgG	Positive
Urine organic acids		CMV IgM	Negative
Mevalonic acid	10 (0–2)	EBV IgG/IgM	Negative
Suberic acid	15 (0–7)	Peripheral blood HSV PCR	Positive, type 1
Hematologic		Blood bacterial culture	Negative
WBC	14 K/uL (4.0–12.0)	Blood fungal culture	Negative
Neutrophils	6.05 K/uL (1.5–5.5)		
Lymphocytes	6.7 K/uL (2.0–5.8)	Pathology	
Hemoglobin	5.5 GM/dL (11.5–14.5)	Axillary lymph node	Reactive follicular lymphoid hyperplasia with sinus histiocytosis
MCV	68.2 fL (76.0–90.0)		
Platelets	80 K/uL (140–440)		
Inflammatory markers			
ESR	>140 millimeter (0–15)	Imaging	
CRP	84 mg/L (0.0–09.9)	MRI Brain	Moderate diffuse cerebral, cerebellar and brainstem volume loss with ventriculomegaly
Chemistry			
Alk phosphatase	381 U/L (145–320)		
Total Protein	9.0 g/dL (5.9–7.0)		
AST	832 U/L (20–60)	CT neck/abdomen and pelvis	Hepatosplenomegaly and lymphadenopathy of the neck, pelvic sidewalls and inguinal area
ALT	913 U/L (5–45)		
Total bilirubin	0.6 mg/dL (0.1–1.0)		
Complement			
C3	270 mg/dL (58–119)	Skeletal survey	Osteopenia, flaring of metaphyses with inflammatory changes in the periosteum and joint destruction
C4	39 mg/dL (17–48)		

WBC = white blood cell count; MCV = ; ESR = ; CRP = ; MRI = magnetic resonance imaging; HIV = ; CMV = ; EBV = ; HSV = herpes simplex virus; PCR = polymerase chain reaction; CT = computed tomography.

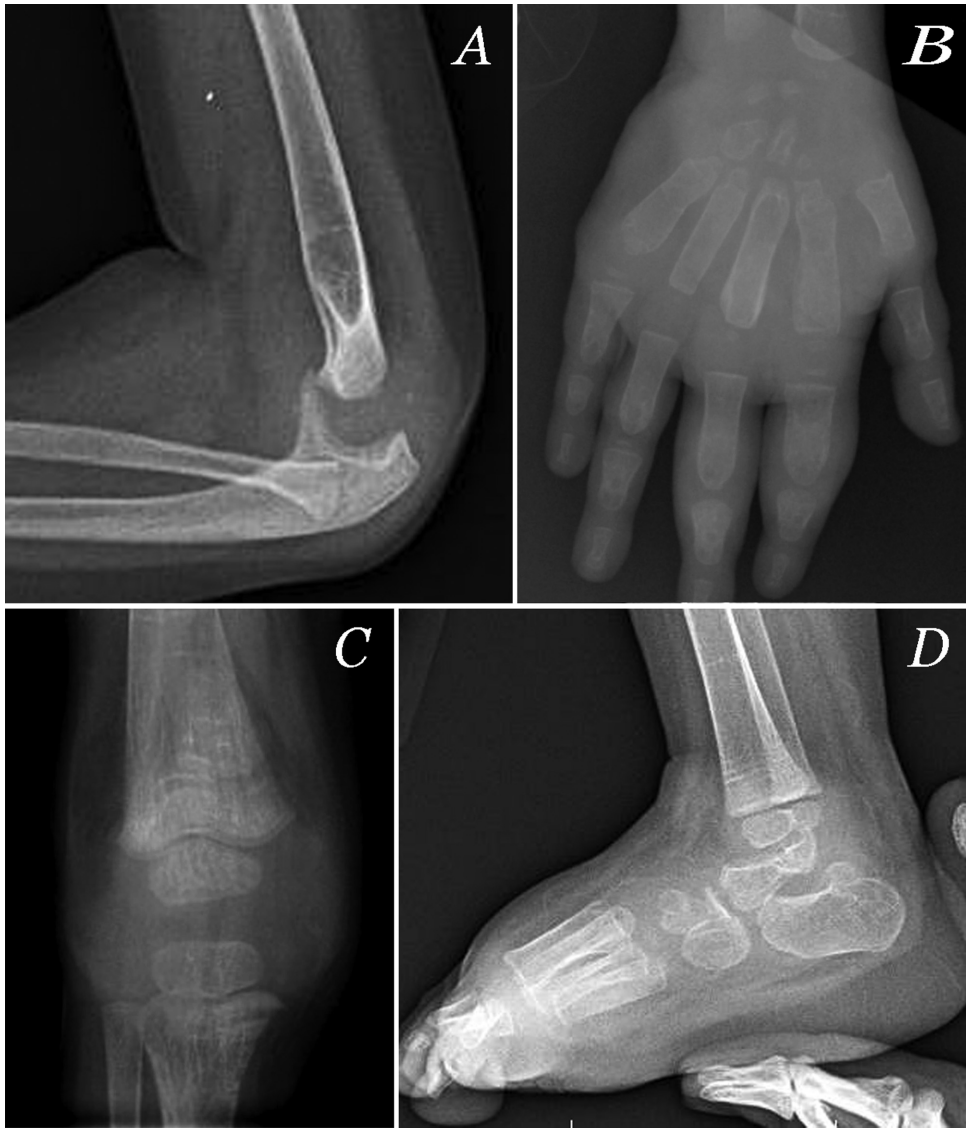

Figure 4. Skeletal survey indicating diffuse osteopenia with an Erlenmeyer flask appearance of the long bones of the (A) arm, forearm and (C) femur. (B) The distal margin of the ulna is eroded and the radial head is dislocated. (B) The hands reveal expansion of the medullary cavity of the metacarpals and phalanges and a pointed appearance of the proximal metacarpals. (D) The feet and ankles reveal osteopenia and loss of volume of the talus with associated soft tissue swelling.

and improved functional status. However, despite his clear clinical response to anakinra, he continues to have intermittent low-grade fevers and persistent elevation in his white blood cell count, CRP, ESR, and ferritin.

DISCUSSION

The constellation of findings including recurrent fevers, diarrhea, hepatosplenomegaly, developmental delay, arthritis, and failure to thrive was consistent with MKD and the presence of *MVK* mutations confirmed this diagnosis. MKD is a rare autosomal recessive disorder characterized by mutation of the *MVK* gene resulting in impaired activity of the enzyme MVK.[4–6] MVK catalyzes the conversion of mevalonic acid to 5-phosphomevalonate in the HMG-CoA reductase pathway, which results in the synthesis of isoprenoids, including non–sterol isoprenoids and sterols, such as cholesterol.[7] HIDS and MVA both result from *MVK* mutations and are distinguished based on residual enzyme activity, with HIDS typically associated with between 1 and 7% and MVA associated with <1% residual enzyme activity.[8–10] Although febrile attacks in MKD are often precipitated by immunizations, this was not observed in our patient.[2]

The pathophysiologic link between MVK dysfunction and observed clinical findings remains poorly defined.[6] It is thought that the dysregulation of the isoprenoid pathway may play a role by increasing proinflammatory cytokine, IL-1β secretion, although the precise mechanism is unclear. One postulated mechanism is that a shortage of non–sterol isoprenoid end products causes increased IL-1β secretion by peripheral blood mononuclear cells.[11]

Our patient's *MVK* mutation (R388X) is predicted to result in a truncated protein missing the last nine amino acids. This is the first case of documented homozygous R388X mutation. There are three previously

Table 2 **Defining characteristics of periodic fever syndromes considered in the differential diagnosis**

Condition	Fevers	Arthralgias	Destructive Arthritis	FTT	Developmental Delay	Dysmorphic	LAD	HSM	Cytopenias	↑ WBC	Autosomal Recessive
CAPS											
FCAS	◆	◆								◆	
MWS	◆	◆								◆	
NOMID	◆	◆	◆	◆	◆	◆	◆	◆		◆	
Other periodic fever syndromes											
TRAPS	◆	◆	◆							◆	
FMF	◆	◆					◆			◆	◆
MVA	◆	◆	±	◆	◆	◆	◆	◆		◆	◆
HIDS	◆	◆		±		±	◆	◆		◆	◆
PAPA	◆	◆	◆								
PFAPA	◆										
Other											
Malignancy	◆	◆		◆			◆	◆	◆	◆	
Myelodysplastic syndrome				◆			◆	◆	◆		
Chronic infection											
Bacterial	◆	◆		◆			◆	◆	◆	◆	
Tuberculosis	◆	◆		◆			◆	◆		◆	
Other fungal	◆	◆		◆			◆			◆	

CAPS = Cryopyrin-associated periodic syndromes; FTT = failure to thrive; LAD = lymphadenopathy; HSM = hepatosplenomegaly; FCAS = familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; NOMID = neonatal onset multisystem inflammatory disease; TRAPS = tumor necrosis factor receptor 1–associated periodic syndrome; FMF = familial Mediterranean fever; MVA = mevalonic aciduria; HIDS = hyper-IgD syndrome; PAPA = syndrome of pyogenic arthritis, pyoderma gangrenosum acne; PFAPA = periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome.

published cases of heterozygous *MVK* mutations containing the R388X mutant allele.[7,6,12] One of these patients expressed a milder (V377I) mutation on the corresponding allele and had 4% residual MVK activity and a clinical phenotype consistent with HIDS.[7,6] The other two reported patients expressed more severe mutations on their corresponding alleles, I268T and G309S, with corresponding residual MVK activity of 0.7 and 0%, respectively.[12] Although we were unable to quantify residual MVK enzyme activity in this patient, one would anticipate it to be near undetectable.

Autoinflammatory disorders with some overlap in clinical presentation with our patient include neonatal onset multisystem inflammatory disorder or tumor necrosis factor receptor 1–associated periodic syndrome. To investigate the presence of either syndrome we performed sequencing of exon 3 of the *NLRP3* gene and exons 4 and 5 of the tumor necrosis factor receptor superfamily member 1A gene that did not reveal a mutation in either region.

Therapy for MKD remains poorly defined and is largely based on case reports. Reduction in the number of febrile crises has been shown with various immunomodulatory medications, including prednisone, etanercept (a tumor necrosis factor α inhibitor) and anakinra (an IL-1 receptor antagonist).[13–16] Bone marrow transplant has also been used.[17] Our patient showed improvement in joint swelling and mobility on anakinra, in addition to weight gain and fewer and milder febrile episodes.

Final Diagnosis

Mevalonate kinase deficiency (MKD).

SUMMARY AND CONCLUSIONS

Our patient with severe MKD represents the first case of a documented homozygous recessive R388X mutation. This case highlights the systemic inflammatory nature of this disease. MKD should be considered in any pediatric patient presenting with recurrent fevers, diarrhea, lymphadenopathy, polyarthralgia, and splenomegaly. Diagnostic investigation should include urinary organic acid levels and genetic testing for *MVK* mutations. This case also illustrates the importance of a thorough family history and serves as a reminder that parental consanguinity can be commonplace in some cultures. This patient's dramatic improvement with anakinra is also noteworthy and provides additional insight into the treatment of this rare condition.

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Patient Oriented Problem Solving (POPS) Case Report

Chronic bilateral pruritic arm dermatitis in a 61-year-old woman

Kathryn D. Convers, M.D., Jacquelyn M. Sturm, M.D., and Raymond G. Slavin, M.D., M.S.

ABSTRACT

A 61-year-old woman presented to our Allergy/Immunology clinic for pruritic dermatitis of both arms since 2006. Initial symptoms included pruritus and burning dysesthesias of the upper extremities without a rash. Months later an excoriated, papular rash developed along the upper extremities. Cold compresses provided some relief, whereas sun exposure worsened symptoms. Over the years consultations with multiple dermatologists did not elicit a diagnosis, and symptoms did not improve after numerous trials of topical corticosteroids and systemic antihistamines. The differential diagnosis of pruritic rash is extensive; however, in the case of chronic pruritus without a primary rash other diagnoses should come to mind. Although pruritus is a hallmark of many atopic conditions, as allergists–immunologists it is important to remember that not all pruritus is atopic in nature. Prompt recognition and treatment of an occult process presenting primarily with pruritus will likely result in improved outcomes for the patient.

(Allergy Asthma Proc 34:558–561, 2013; doi: 10.2500/aap.2013.34.3691)

CASE PRESENTATION

Chief Complaint

Chronic pruritic dermatitis of the arms.

History of Present Illness

A 61-year-old woman presented to our Allergy/Immunology clinic for pruritic dermatitis involving both arms since 2006. Initial symptoms included pruritus and burning dysesthesias of the upper extremities without a rash. Months later, an intensely pruritic, excoriated, papular rash appeared along the upper extremities. Cold compresses, such as ice packs, provided some relief, but sun exposure worsened symptoms.

Consultations with multiple dermatologists and extensive evaluations including two skin biopsies did not elicit a diagnosis. Skin biopsy specimens revealed epidermal necrosis, suggestive of excoriation, and superficial perivascular lymphocytic infiltrate with eosinophils. These findings were initially attributed to a hypersensitivity reaction; however, symptoms did not respond to numerous trials of topical corticosteroid preparations and systemic antihistamines. A trial of empiric valacyclovir for presumed zoster sine herpete was also of no benefit.

Current Medications

Clobetasol 0.05% ointment topically b.i.d., duloxetine at 60 mg daily, cetirizine at 10 mg daily, and hydroxyzine at 25 mg every 8 hours as needed.

Review of Systems

Notable for mild neck pain and subjective muscle aches/weakness of the bilateral upper extremities.

Physical Examination

Tenderness to palpation was elicited along the spinous processes of C4–C7. The neck had good functional range of motion. She had 5/5 muscular strength of the biceps and triceps, with slightly diminished muscle strength of the brachioradialis muscles, bilaterally. Excoriated papules at the posterior base of the neck, extending to the shoulders, were noted. Numerous excoriated papules and plaques in various stages of healing were scattered along the extensor surfaces of her arms. These cutaneous markings corresponded to the C5 and C6 dermatomes of the arms and posterior neck and upper back (Fig. 1). Sensory deficits were not appreciated. The remainder of the exam was normal.

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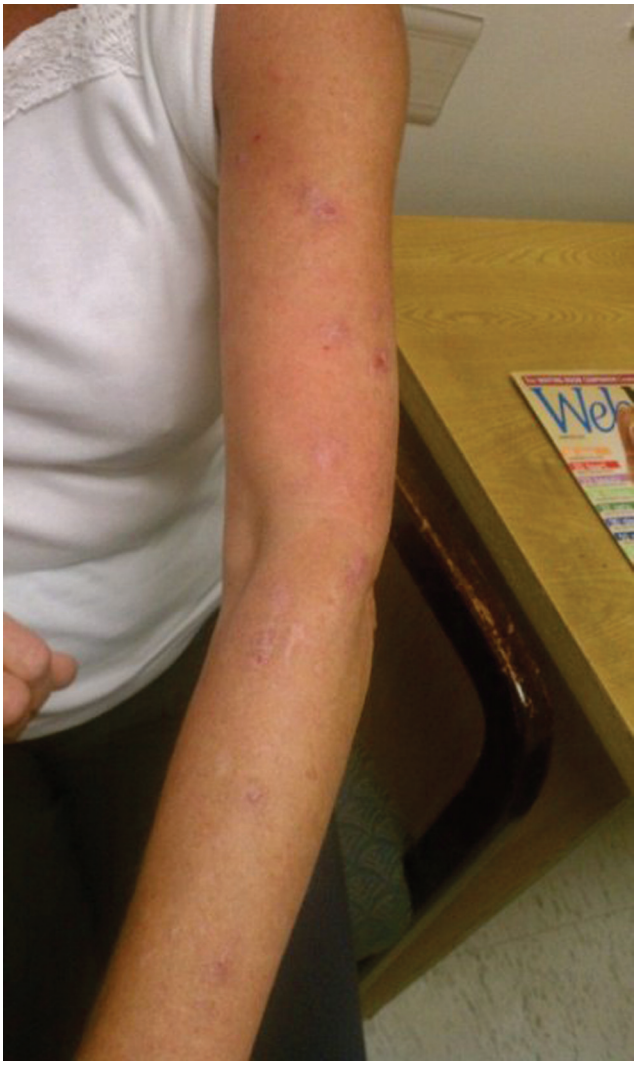

Figure 1. Our patient's dermatitis at initial visit.

Laboratory and other Diagnostic Findings

A CBC with differential, CMP, TSH, CPK, CRP, and a chest x ray were all within normal limits.

QUESTION 1

What is the differential diagnosis? The differential diagnosis of pruritic rash is extensive; however, chronic pruritus without a primary rash should prompt one to think of nonatopic diagnoses, such as poorly controlled diabetes mellitus; liver, kidney, or thyroid disease; polycythemia; lymphoma; lichen simplex chronicus; neurological abnormalities such as notalgia paresthetica; and factitial dermatitis.[1–4] (Table 1).

QUESTION 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis in this patient? A cervical spine x ray revealed anterolisthesis of C6 on C7, and spondylosis of C5–C7 with osteophytes. A cervical spine magnetic resonance imaging (MRI) revealed a herniated disk at C5–C6, centrally, with severe stenosis of the foramen.

Table 1 **Common nonatopic conditions causing chronic pruritus without a primary rash**

Systemic
Chronic kidney disease
Cholestatic liver disease
Hyper- or hypothyroidism
Diabetes mellitus
Polycythemia
Iron-deficient anemia
Lymphoma
Myelodysplastic syndrome
Human immunodeficiency virus
Medication effect
Dermatologic
Xerosis
Lichen simplex chronicus
Neuropathic
Brachioradial pruritus
Notalgia paresthetica
Postherpetic pruritus
Psychogenic
Factitial dermatitis
Depression
Obsessive–compulsive disorder

Clinical Course

Treatment with gabapentin was initiated. Over a few months the dose was titrated up to 300 mg q.i.d., at which point her symptoms were much improved. Additional increases in dosing failed to provide further benefit, at which point our patient was referred to an orthopedic–spine surgeon. Injections of epidural steroids resulted in complete resolution of pruritus, with subsequent improvement of the excoriated dermatitis. Presently, our patient remains improved; if symptoms recur in the future, a diskectomy may be potentially curative.

Final Diagnosis

Brachioradial pruritus (BRP) syndrome.

DISCUSSION

Although pruritus is a hallmark of many atopic conditions, as allergists–immunologists it is important to remember that not all pruritus is atopic.[1] This case is a good example of chronic pruritus mistaken for an allergic disorder, despite failure to respond to appropriate antihypersensitivity medications.

The diagnostic evaluation ruled out occult liver, kidney, or thyroid disease as etiologies of her pruritus. A normal CBC with differential eliminated polycythemia

and in the setting of a negative chest radiograph and normal physical exam, lymphoma could be excluded. Her type II diabetes mellitus was well controlled. The appearance of her skin was not consistent with lichen simplex chronicus, leaving either a neurological abnormality versus factitial dermatitis as the likely culprit. The distribution of pruritus was not consistent with notalgia paresthetica, which characteristically involves the back (T2–T6 dermatomes).[5] The MRI finding of a centrally herniated disk at C5–C6 with severe stenosis of the foramen, in the setting of chronic, symmetric pruritus of the arms, was most consistent with a diagnosis of BRP.

BRP is a well-described clinical entity characterized by localized pruritus of the dorsolateral aspect of the upper extremities, overlying the proximal head of the brachioradialis muscle. Involvement of the upper arms and shoulders is common.[6–8] In most cases, underlying cervical spine disease has been implicated; therefore, BRP is considered a variant of cervical radiculopathy, presenting with pruritus rather than pain.[7–9] A number of cervical spine pathologies, including nerve root compression, tumor, and cervical rib, have been found to anatomically correspond to affected dermatomes in BRP cases.[8,9]

Incidence

BRP typically affects middle-aged women living in warm climates; however, it has been also been recognized in both men and women living in temperate climates.[6] The true prevalence is unknown. Although fair-skinned patients (Fitzpatrick skin types I–III) appear to be most affected, BRP has been described in darker-skinned patients, suggesting melanin is not a protective factor.[10–12]

Presumed Pathophysiology

First described in 1968 by Waisman, BRP is thought to be primarily a neuropathic disorder, because abnormalities in cutaneous innervation have been reported.[12,13] However, whether BRP is actually a solar pruritus rather than primarily neuropathic remains controversial, because it occurs with greater frequency in tropical and subtropical climates, and sun exposure is commonly reported as an aggravating factor.[6,8,11,13] Wallengren and Sundler investigated this further and concluded BRP is histologically associated with a decreased number of epidermal and dermal nerve fibers. They also showed normalization of cutaneous innervation in affected patients during symptom-free periods.[11,13] Given the frequency of spinal pathology corresponding with involvement of the C5–C7 dermatomes in BRP patients, it appears cervical spine disease is a predisposing factor for BRP; however, symptoms can be elicited by exposure to sunlight or heat.[13,14]

Clinical Characteristics

The presenting complaint is commonly a tingling, burning, and/or pruritic sensation, which may be unilateral or symmetric.[6,11,12,15] Physical findings are typically sparse but may include atrophic skin changes or signs of sun damage. Occasionally, prurigo papules and excoriations may be noted.[7,12] Given the association of cervical spine disease as either a causative or predisposing factor of BRP, a thorough musculoskeletal exam may provide diagnostic clues. Radicular symptoms may be exacerbated or relieved by provocative testing.[14] Spurling's maneuver elicits discogenic pain by neck extension and rotation toward the more symptomatic side, as a result of increasing nerve root compression in a compromised neuroforamen.[14] Increased pain may also occur with Valsalva activities and with axial compression.[14] Upper limb tension testing, also known as Elvey's test, can characterize whether a cervical radiculopathy is affecting the median, radial, and/or ulnar nerve(s), based on a patient's ability to tolerate external rotation of a passively depressed shoulder girdle.[14] Tinel's sign reproduces radicular pain by direct palpation or tapping over the affected nerve root area.[16] Symptom relief by shoulder abduction also points to radiculopathy from soft disk herniation.[16]

Patients with BRP often report that cold compresses, such as ice packs, provide temporary relief. This is frequently referred to as the "ice pack sign," and some consider it to be pathognomonic for BRP.[8,17,18]

Diagnostic Tools

Diagnostic studies provide limited benefit in confirming BRP. Radiographs of the cervical spine may be helpful in diagnosing cervical radiculopathy, occult spinal tumor, or cervical rib. MRI of the cervical spine is the preferred modality for further characterizing cervical radiculopathy.[8,9] Electromyography and nerve conduction studies of the median and ulnar nerves have shown F-response latencies in patients with BRP but are normal in most cases.[19] Skin biopsy specimens may show atrophy and reduced number of dermal and epidermal nerve fibers during symptomatic periods.[6,7,11]

Treatments

Treatment of BRP can be a challenge, because medical management offers limited benefit. Review of the literature reveals variable success reported with a number of oral medications, such as gabapentin, lamotrigine, amitriptyline, and oxcarbemazepine.[2–4,6–8,15,20] Some success with topical preparations has also been reported, specifically with capsaicin cream (0.025–0.05%), doxepin 5%, and topical lidocaine.[2–4,7,8,15,21-,23] Additionally, it is recommended that patients with BRP avoid sun exposure. The use of sunscreen and protective clothing may help reduce exacerbations.[6,7,15,17]

Adjunct treatments may also improve outcomes in patients with BRP. A number of case reports describe improvement after acupuncture, physical therapy, and cervical spine manipulation.[6–8,15,24] Cervical nerve blocks were initially considered futile in BRP; however, more recent reports indicate potential benefit. DeRidder and colleagues described a case of BRP secondary to cervical neuroforaminal stenosis at C5–C6. Using quantitative sensory testing, they objectively determined this led to selective C-fiber dysfunction within the C6 and C8 dermatomes.[25] They showed improved C-fiber functionality and symptom resolution after intralaminar epidural steroid injections at C6–C7.[25]

CONCLUSIONS

Pruritus, in the absence of skin disease, may be a consequence of a nonatopic condition. When an "itch that rashes" is localized, an underlying neuropathic condition should be considered in the differential. Prompt recognition and treatment of an occult process presenting primarily with pruritus, will likely result in improved outcomes for the patient.

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Erratum

In the article *Interleukin-2 levels in exhaled breath condensates, asthma severity, and asthma control in nonallergic asthma*. Allergy Asthma Proc 34:e35–e41, 2013; doi: 10.2500/aap.2013.34.3680, it is noted that S. Boonpiyathad and P. Pornsuriyasak contributed equally to this work.

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Patient Oriented Problem Solving (POPS) Case Report

High-grade fever and pancytopenia in an adult patient with common variable immune deficiency

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ABSTRACT

Fever of unknown origin in patients with common variable immune deficiency (CVID) can be caused by variety of infectious, autoimmune, or malignancy-related etiologies. We present a 52-year-old man with history of CVID, who presented with 3 weeks of persistent high-grade fevers. During admission, he developed severe pancytopenia with shock and multiorgan failure. An extensive workup was performed for typical and atypical infections, autoimmune pathologies, and malignancy. His peripheral blood smear showed marked anisocytosis and poikilocytosis with elevated atypical lymphocytes. Flow cytometry showed markedly elevated CD8 counts, with abnormal CD4/CD8 ratio. Monospot test was negative but real-time polymerase chain reaction showed high Epstein–Barr virus load. Initial clinical suspicion was high for bacterial infections including pneumonia and acute sinusitis complicated by bacteremia and sepsis. Hematologic malignancy was also high on the differentials because of presence of rapidly progressive pancytopenia. The final diagnosis in this case illustrates a rare but potentially fatal disease that can present in CVID patients with persistent fevers and pancytopenia and can be refractory to standard treatment regimen. Because allergy and immunology physicians commonly treat CVID patients, they should be aware of this disease condition including pathophysiology, clinical presentation, laboratory workup, and treatment options.

(Allergy Asthma Proc 35:78–82, 2014; doi: 10.2500/aap.2014.35.3704)

CASE PRESENTATION

Chief Complaint

The patient is a 52-year male subject with history of common variable immune deficiency (CVID) who presented with persistent high-grade fevers for 3–4 weeks.

History of Present Illness

The patient developed sudden onset of high-grade fevers, accompanied by increased sinus congestion and nonproductive cough. He was treated on an outpatient basis with oral moxifloxacin (400 mg once daily for 2 weeks), but his symptoms persisted. He was diagnosed with CVID 8 years ago and was on subcutaneous IgG (SCIgG) replacement. Other medical problems included bronchiectasis and chronic rhinosinusitis, which were also well controlled. He was in a monogamous relationship with a male partner for many years. His daily medications included fluticasone/salmeterol inhaled and SCIgG. Review of systems was otherwise unremarkable.

Physical Examination

Vital signs included a blood pressure of 104/61 mmHg, heart rate of 113/min, respiratory rate of 18/min, and temperature of 100.5°F. Eye and ear exams were normal and oropharyngeal examination did not show any signs of thrush. No cervical lymphadenopathy was evident and lung auscultation revealed diffuse bilateral expiratory rhonchi without wheezing. Abdomen was mildly distended, but otherwise soft without any organ enlargement. The rest of clinical examination was normal.

Laboratory Results and Initial Clinical Course

On admission (Table 1), white blood cell count was of 5320 cells/μL, hemoglobin (Hgb) was 9.8 g/dL, and platelet count was 32,000 platelets/μL. Peripheral blood smear was notable for marked anisocytosis and moderate poikilocytosis and dominance of large and

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Table 1 **Laboratory results**

	Results	Reference Range
WBC	7.96	4.8–12 k/μL
Hgb	9.8	13–17 g/dL
Hct	28.3	39–48%
Plts	47	150–350 k/μL
Neutrophils	660	2.0–7.7 K/μL
CD3	6415	690–2300 cells/mm^3
CD4	802	450–1500 cells/mm^3
CD8	5778	120–895 cells/mm^3
CD4/CD8	0.14	0.9–1.9
IgG	641	700–1600 mg/dL
IgA	66	70–400 mg/dL
IgM	55	40–230 mg/dL
ALT	98	7–56 U/L
AST	227	7–21 U/L
T bili	1.9	0.2–1.3 mg/dL
Alkaline phosphatase	267	38–126 U/L
PT	20.7	12.3–14.9 s
INR	1.71	0.88–1.12
Albumin	2.4	3.5–5.0 gm/dL
Protein	4.6	6.3–8.2 gm/dL
Fibrinogen	143	208–435 mg/dL
Ferritin	3990	18–250 ng/mL
TGL	319	<200 mg/dL
LDH	3709	313–618 U/L
C3	70	88–165 mg/dL
C4	35	14–44 mg/dL
ANA	<1:40	<1:40
HIV PCR	<20	<20 Copies/mL
EBV PCR	15.5×10^5 copies/mL	
Mycoplasma *Pneumoniae* PCR in BAL	Negative	
Mycobacterial complex rRNA in BAL	Negative	
Chlamydia pneumonia by PCR in BAL	Negative	
Pneumocystis jiroveci by PCR in BAL	Negative	

Hgb = hemoglobin; Hct = hematocrit; Plts = platelets; WBC = white blood cell count; BAL = bronchoalveolar lavage; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; EBV = Epstein–Barr virus; TGL = triglycerides; LDH = lactate dehydrogenase; PT = prothrombin time; ANA = antinuclear antibody; INR = international normalized ratio; T bili = total bilirubin.

medium granular atypical lymphocytes. Flow cytometer showed markedly elevated CD8 counts with abnormal CD4/CD8 ratio. Over the course of 3 weeks, he developed progressive pancytopenia, with significant depletion in all cell lines (white blood cell count, 0.04 cells/μL; hemoglobin, 5.6 g/dL; platelets, 16/μL). Other labs showed elevated transaminases and low serum protein and albumin. Quantitative immunoglobulin levels of IgG, IgM, and IgA were normal. Although monospot test was negative, polymerase chain reaction (PCR)–based studies showed an elevated Epstein–Barr virus (EBV) copy number. The rest of the infectious workup including serologic and PCR-based studies and cultures from body fluids were negative for typical and atypical infections. QuantiFERON test (Qiagen Inc, Valencia, CA) for *Mycobacterium tuberculosis* was negative. Abdominal ultrasound showed splenomegaly and hepatomegaly, but the remaining imaging studies including computed tomography scan of paranasal sinuses, chest, abdomen, and pelvis were nonrevealing.

Despite treatment with piperacillin/tazobactam and azithromycin, he continued to be febrile. He later developed hypotension and other signs of systemic inflammatory response syndrome and was transferred to the intensive care unit.

QUESTION 1

What is the differential diagnosis?

1. Infection
   a. Bacterial infections
   b. Viral infections
   c. Other atypical infections (Lyme disease, rickettsia infection, and fungal infections)
2. Autoimmune diseases (sarcoidosis and systemic lupus erythematosus)
3. Malignancy (lymphoma and leukemia)
4. Drug fever
5. Immune dysregulation syndrome (hemophagocytic lymphohistiocytosis [HLH])

Discussion on Differential Diagnosis

With the background of CVID, his initial presentation of persistent fever was suggestive of an infective etiology but blood and urine cultures and PCR-based studies for common and atypical organisms were nonrevealing, except for high EBV load detected by PCR. The possibility of connective tissue diseases was less likely because his antinuclear antibody titers were within normal range and he had no other systemic symptoms such as joint swelling, rash, and mucosal ulcers. Hematologic malignancy was high on the differentials because of presence of rapidly progressive pancytopenia but peripheral blood smear did not show any findings of leukemia and imaging studies did not show any evidence of lymphadenopathy or solid organ malignancy. Drug fever was unlikely because he had not been started on any new medications. Primary human immunodeficiency (HIV) infection can account for many of the symptoms and disproportionately elevated CD8 counts, but viral load was negative for HIV. Persistent fever, rapidly progressive pancytopenia, splenomegaly, elevated transaminases, and shock can develop in HLH, which is an immune dysregulation syndrome caused by aberrant release of cytokines.

QUESTION 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis in this patient?

1. Bone marrow biopsy
2. Fasting triglycerides
3. Serum ferritin levels
4. Soluble CD25

Remaining Clinical Course

The remaining laboratory work showed elevated levels of serum ferritin, serum triglycerides, and low serum fibrinogen levels. Bone marrow biopsy (Fig. 1) showed hypercellular bone marrow with histiocytes engulfing red blood cells (hemophagocytosis) and numerous EBV-infected lymphocytes were shown by *in situ* hybridization for EBV early RNAs (Fig. 2). Based on the result of these studies, the diagnosis of EBV-associated HLH (EBV-HLH) was established. The patient was started on high-dose Solu-Medrol, antithymocyte globulin, and cyclosporine. His clinical condition progressively deteriorated and he developed severe coagulopathy with multiorgan failure and subsequently died.

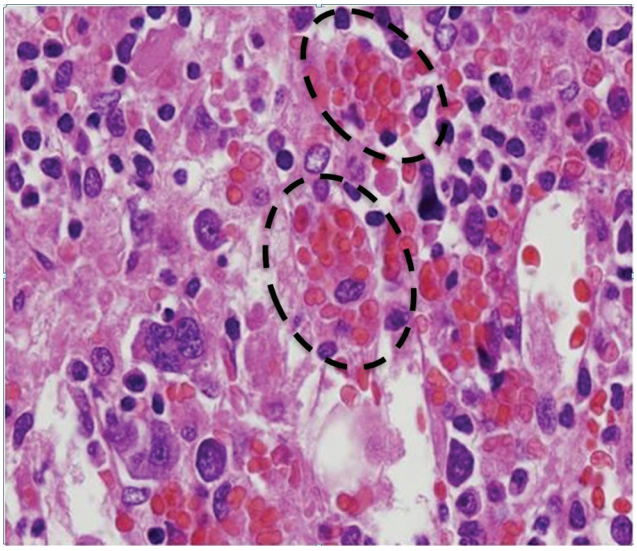

Figure 1. *Bone marrow core biopsy with histocytes containing red blood cells (hematoxylin and eosin, ×400).*

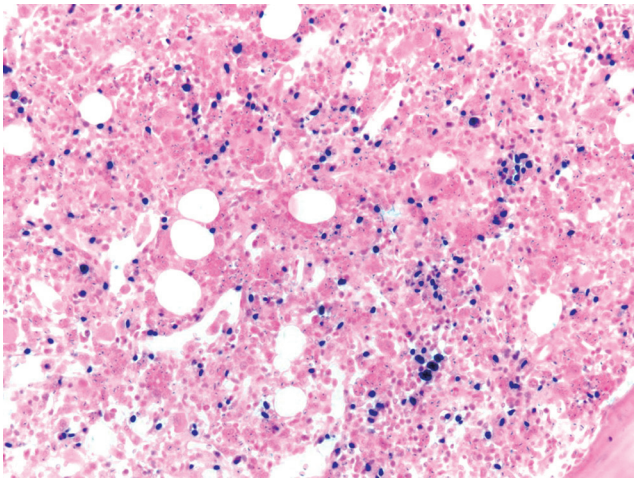

Figure 2. In situ *hybridization for Epstein–Barr virus early RNA showing numerous positive lymphocyte nuclei (blue) in a background of a hypercellular marrow (pink; original magnification, ×200).*

DISCUSSION

HLH is a potentially life-threatening syndrome characterized by dysregulation of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), which causes aberrant cytokine release. This results in activation of

histiocytes leading to hemophagocytosis and other systemic manifestations including fever, pancytopenia, and multiorgan failure.[1] Primary forms of the disease are caused by genetic mutations in perforin and other genes that control the exocytosis of cytotoxic granules from NK cells and CTLs[2] and are usually present in infancy and early childhood. Secondary or acquired forms of disease have been associated with infection,[3] malignancy,[4] and autoimmune diseases[5] and can present in both pediatric and adult age groups. Although the exact incidence of HLH is difficult to estimate because this disease is highly underdiagnosed, a recent study reported an incidence of 1 in 800,000 in the Japanese population with EBV-HLH being the most common subtype.[6]

In immune-competent individuals, viral and intracellular bacterial infections are cleared by granule-dependent cytotoxic pathways of NK cells and CTLs. This process involves generation and maturation of cytotoxic granules, which fuse with the cell membrane and release its contents into the target cell leading to its destruction.[7] Genetic defects in granule-dependent pathway leads to inability to kill infected cells and persistent stimulation by infected cells leads to hypersecretion of proinflammatory cytokines (interferon γ, TNF-α, IL-1, IL-6, IL-8, IL-10, IL-16, IL-18, IL-2, and macrophage colony-stimulating factor).[2] A recent study has reported that granzyme B may be useful as a marker of immune activation of CTLs and NK cells in HLH patients.[8] The role of EBV in causing HLH has been explained by ectopic EBV infection in T lymphocytes, mainly CD8 cells[9,10] that result in massive release of proinflammatory cytokines.[11]

Clinically, HLH presents with persistent high-grade fevers, hepatosplenomegaly, and pancytopenia.[12] Other common findings include elevated transaminases, coagulopathy,[13] and lymphadenopathy.[14] The diagnosis is often delayed because the presenting symptoms are nonspecific and commonly mimic other infectious or inflammatory disorders.

In 2004, the Histiocytic Society published updated diagnostic guidelines that proposed eight clinical and laboratory criteria, out of which five were required for diagnosing HLH (Table 2).[14] Patients with molecular diagnosis consistent with genetic forms of HLH do not need to fulfill these diagnostic criteria. The guidelines also emphasized that presence of hemophagocytic activity is not necessary for diagnosis of HLH, if other criteria are met. In EBV-HLH, the viral load of EBV are usually higher than EBV-related infectious mononucleosis[15] and can be useful in determining prognosis and response to therapy.[16] Additionally, in patients receiving pooled immunoglobulin replacement, the serologic testing is generally nonreliable. PCR-based diagnostic evaluation or cytokine assays such as interferon gamma release assays for diagnosis of *Mycobacterium tuberculosis*[17] can be useful in these situations. We also showed the presence of EBV in patient's bone marrow, further confirming this diagnosis. It is important to rule out other rare EBV-related pathologies such as lymphoma[18] because the pathophysiology and management differs from EBV-HLH.

Table 2 **Diagnostic guidelines for HLH (Histiocytic Society 2004)**

The diagnosis HLH can be established if one of either 1 or 2 is fulfilled:
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (five of the eight criteria):
1. Fever
2. Splenomegaly
3. Cytopenias (affecting >2 of 3 lineages in the peripheral blood): hemoglobin, <90 g/L (in infants <4 wk: hemoglobin <100 g/L), platelets, <100 × 109/L; neutrophils, <1.0 × 109/L
4. Hypertriglyceridemia and/or fasting triglycerides ≥3.0 mmol/L (*i.e.*, ≥265 mg/dL) or low fibrinogen levels (fibrinogen ≤1.5 g/L)
5. Hemophagocytosis in bone marrow or spleen or lymph nodes without evidence of malignancy
6. Ferritin ≥500 mg/L
7. Low or absent NK cell activity
8. Soluble CD25 (*i.e.*, soluble IL-2 receptor) ≥2400 U/mL

HLH = hemophagocytic lymphohistiocytosis; NK = natural killer.

The primary treatment goal in HLH is to suppress the severe inflammation that is responsible for life-threatening consequences. The HLH-94 Histiocytic Society study group proposed initiating treatment with high-dose dexamethasone and etoposide in these patients, followed by starting cyclosporine A after 8 weeks.[19] The updated 2004 guidelines made recommendations on starting cyclosporine A at the onset of treatment to prevent reactivation of HLH.[14] Another study reported rapid resolution of symptoms and comparable survival rate with using antithymocyte globulin, followed by hematopoietic stem cell transplantation.[20] In EBV-HLH patients, it is important to start the treatment within 4 weeks of diagnosis in severe forms of disease.[21] The role of antiviral therapy in treatment of EBV-HLH has not been established but use of novel agents that target the mature B cell population such as rituximab have been reported to improve the treatment efficacy.[21]

To our knowledge, there have been no previous case reports of HLH in adults secondary to EBV described

in CVID patients. One case of recurrent HLH in a child with CVID has been reported but was later diagnosed to have X-linked lymphoproliferative disease.[22] We speculate that the presence of immunodeficiency can predispose to severe forms of EBV infection, which can trigger HLH. In fact, HLH may be the first manifestation in other immunodeficiency states such as HIV, often triggered by an viral infection[23] or immune reconstitution syndrome[24] and can take a particularly aggressive course.[25]

Final Diagnosis

EBV-HLH.

CONCLUSIONS

This case indicates that HLH should be considered as one of the important differential diagnoses in CVID and other immunocompromised patients who present with fever of unknown origin, pancytopenia, and multisystem involvement. Although precise underlying mechanisms are not clear, these patients may be predisposed to more severe and atypical forms of EBV infection and related complications such as EBV-HLH. Early diagnosis and treatment administration is important to improve patient outcomes.

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Patient Oriented Problem solving (POPS) Case Report

A 2-year-old girl with a recurrent vesicular rash

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ABSTRACT

Rashes related to viral infection are a relatively common occurrence in pediatrics. We present the unusual case of a 2-year-old girl referred for evaluation of recurrent rashes thought to be caused by Varicella zoster. *She had no systemic symptoms of* Varicella *infection and otherwise had a benign immune history. The rashes were responsive to treatment with acyclovir. However, she did not have detectable IgG antibody to* Varicella zoster. *Relevant immunology labs were sent, which led to the diagnosis. The patient was started on prophylactic acyclovir and has since been doing well with only one minor recurrence of the rash. This case illustrates the importance of a detailed immune assessment in the evaluation of unusually severe, recurrent, or atypical pediatric exanthems.*

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CASE PRESENTATION

Chief Complaint

Recurrent rash.

History of Present Illness

A 2-year-old girl presented to the emergency room at the age of 9 months for a rash on her left shoulder, upper back, and chest. She was diagnosed with shingles. However, her pediatrician attributed the rash to a primary *Varicella zoster* virus (VZV) infection because she had not been previously vaccinated. The rash was described as macular and vesicular in various stages of healing. No treatment was given and the rash resolved after 3 weeks. At 15 months of age she developed another rash in the same area, which again resolved spontaneously. Three months later, she developed another erythematous vesicular rash near the left axilla, was diagnosed with *V. zoster* and treated with acyclovir. The rash recurred at 22 and 23 months of age and she was again treated with acyclovir. No family members had a similar rash; however, her mother had a history of cold sores. Her infection history is otherwise notable only for recurrent otitis media. There is no family history of immunodeficiency. *Varicella* IgG levels and a viral culture from an unroofed vesicle were obtained.

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Physical Examination

Vital signs were normal. Her conjunctivae were clear. She had congested nares with clear rhinorrhea bilaterally and pale, enlarged turbinates. She had normal tonsils and cervical lymph nodes. Lungs were clear and cardiac exam was normal. Skin exam showed a cluster of small (<5 mm) hypopigmented macules near her left axilla, otherwise, no lesions were seen.

Diagnostic Studies

V. zoster IgG was 0.3 (<0.9 was considered negative). IgG was 865 mg/dL, IgA was <31 mg/dL, and IgM was 145 mg/dL.

QUESTION

What is the differential diagnosis?

a. Functional natural killer (NK) cell deficiency
b. Classic NK cell deficiency
c. Molluscum contagiosum
d. Nonspecific viral exanthem

Additional Studies

What additional diagnostic studies would be helpful in establishing the diagnosis?

Laboratory studies to consider: mitogen stimulation, flow cytometry, Toll-like receptor function, vaccine titers, and NK cell function.

Clinical Course

Flow cytometry revealed low NK cell numbers (49 cells/μL; normal, 130–720 cells/μL) and NK cell

Table 1 **Flow cytometry shows reduced numbers and percentage of CD16$^+$56 cells on initial evaluation**

Flow Cytometry	9/13	10/13*
CD45	2770	4245
CD3%	61%	43%
CD3	1698	1687
CD19%	35%	52% H
CD19	982	2115
CD16$^+$ 56%	2% L (4%)	4%
CD16$^+$ 56	49 L (130)	168
CD4%	43%	25% (28%)
CD4	1177	964
CD8%	15%	16%
CD8	416 L (490)	595
H/S	2.8	1.62

**Repeat testing performed 1 mo later showed improved cell numbers.*
H = high; L = low; H/S = helper/suppressor ratio.

cytotoxicity assay showed decreased to absent NK cell function (Tables 1 and 2). Our patient was started on long-term prophylaxis with acyclovir for prevention of severe infection. Viral culture from an earlier lesion was positive for enterovirus. Her pneumococcal antibody response was suboptimal. T- and B-cell mitogen stimulation, Toll-like receptor functional assay, and tetanus and diphtheria titers were normal. At 1 month follow-up, she was doing well except for a vesicular rash on her feet that resolved within 1 week. She received Pneumovax (Merck, Summit, NJ) and had a good response. Repeat flow cytometry revealed normal NK cell numbers (168 cells/μL; normal, 130–720 cells/μL), but NK cytotoxicity assay again showed decreased NK cell function (Tables 1 and 2). *Herpes simplex* virus (HSV) 1 IgG was positive (IgM was not), but titers for cytomegalovirus (CMV) and Epstein–Barr virus (EBV) were negative. A third NK cell cytotoxicity assay again showed decreased NK cell function (Table 2). A fourth assay from another lab showed decreased NK lytic units and slightly decreased NK cells compared with control (Table 2). She remains on acyclovir prophylaxis and was doing well at her 4-month follow-up.

DISCUSSION

NK cells are large granular lymphocytes that play an essential role in innate immunity.[1] They do not require sensitization to be activated and their function is tightly integrated with other cells in the innate and adaptive immune systems.[2,3] NK cells lyse target cells and secrete immunoregulatory cytokines.[4] Their primary roles are defense against viral infections and tumor cell surveillance; however, they also participate in immunoregulation and modulation of autoreactivity.[5] NK cells are found in cord blood, peripheral blood, bone marrow, and the spleen.[6] Mature peripheral blood NK cells express low levels of CD56 as well as FcγRIIIA (CD16). NK cells that express high levels of CD56 without CD16 are a developmentally immature but functional NK cell subset.[5]

Recurrent herpesvirus infections may indicate an underlying immunodeficiency.[7] In humans, NK cells are an intricate part of the host defense against herpesviruses and human papilloma virus (HPV).[8] Once activated, NK cells mediate contact-dependent killing of target cells through mobilization of lytic granules. After a killing program is triggered in an NK cell, lytic granules, particularly perforin and granzymes, are sent to the interface formed with the target cell and their contents are dispersed. This cytotoxicity function can be antibody independent or occur through recognition of IgG-opsonized cells by CD16 to enable antibody-dependent cell-mediated cytotoxicity. NK cells thus play a role in adaptive immunity.[5]

Another function of NK cells is production of cytokines or chemokines that play a role in immune regulation, particularly type I interferons (IFNs), IL-12, IL-15, and IL-18.[5] These cytokines are also produced by infected cells, activated dendritic cells, and macrophages. Type 1 IFNs directly activate NK cells to enhance cell-mediated cytotoxicity. They also induce secretion of IL-15, a cytokine capable of inducing NK cell proliferation. IL-12 activates NK cells to increase the production of IFN-γ, which recruits and activates cytotoxic T lymphocytes and CD4$^+$ T-helper 1 cells. IL-18 induces IFN-γ production by NK cells, both independently and synergistically with IL-12. Both IL-12 and IL-18 are critical in priming the NK cell response to viral infection.[8]

The third function of NK cells is promotion of immunity through contact-dependent costimulatory and regulatory mechanisms. Activated NK cells express many important costimulatory and regulatory ligands and can home to key immunoregulatory sites, particularly secondary lymphoid tissues.[5]

NK cell deficiency represents a small but important subset of primary immunodeficiencies that increases susceptibility to viral pathogens, particularly HSV, CMV, VZV, and HPV.[1,5] In 1989, Biron *et al.* first reported the case of a young girl who lacked functional NK cells and experienced recurrent herpesvirus infections during childhood and adolescence.[9] More recently in 2005, Etzioni *et al.* described a 2-year-old girl with fatal *Varicella* and isolated NK cell deficiency found on autopsy.[10] Several subsequent studies have evaluated other immunodeficiency syndromes, such as NEMO deficiency, Hermansky–Pudliak syndrome,

Table 2 **NK cell cytotoxicity assays performed on three separate occasions consistently show decreased NK cell function**

NK cell Cytotoxicity/Functional Assays	9/17/13	10/30/13	12/30/13	1/24/14*
NK % cytotoxicity at 50:1 (≥20)	3 L	7 L	5 L	
NK % cytotoxicity at 25:1 (≥10)	1 L	4 L	2 L	
NK % cytotoxicity at 12:1 (≥5)	1 L	1 L	1 L	
NK % cytotoxicity at 6:1 (≥1)	1	0 L	0 L	
NK Lytic Units (≥2.6)	0 L	0.6 L	0.2 L	
% $CD16^+CD56$ (NK Cells) (3–16%)	2 L	5	2 L	
Patient PBMC % NK cells				4.2 L (5–16%)
Patient LU20 NK				189.8 L (>316.2)
Control PBMC % NK cells				12.1 (5–16%)
Control LU20 NK				590.1 (>316.2)
Interpretation	Decreased to absent NK cell function	Decreased NK cell function	Decreased NK cell function	Decreased LU20 compared with control

**Functional NK assay showed decreased LU20 in the patient compared with control.*
NK = natural killer; PBMC = peripheral blood mononuclear cell; L = low.

and mutations in FcγRIIIa that all cause varying degrees of NK cell impairment, resulting in increased susceptibility to viral infections.[1,5]

A diagnosis of exclusion, NK cell deficiency, requires the impact on NK cells to be the major immunologic abnormality present. Although many diseases, infections, physiological states, and drugs can affect NK cell numbers and/or function, NK cell deficiency refers to abnormalities that are fixed over time and primary in nature.[5] Classic NK cell deficiency (CNKD) is characterized by the absence of $CD3^-CD56^+$ NK cells and function. Functional NK cell deficiency (FNKD) is defined by normal numbers of NK cells with abnormal cytotoxicity. Functional analysis of NK cell activity should be performed using reliable and validated assays on at least three occasions a month apart.[5]

After Biron *et al.* published the original case of CNKD,[9] the causative gene defect was identified in GATA2 and the disease was redesignated as CNKD1. At least 18 additional patients have been described. Within this group, 53% (10/19) had recurrent herpesvirus infections. VZV was the most common infection seen, followed by CMV, EBV, and HSV. Twenty-one percent developed malignancies, including HPV-related cancers, leukemia, and an EBV-associated smooth muscle tumor.[5]

A familial form of CNKD was discovered in 2006 among members of a large consanguineous Irish cohort with NK cell deficiency and susceptibility to viral infections. These patients also had adrenal insufficiency, growth retardation, and microcephaly. One patient developed an EBV-driven lymphoproliferative disorder, and two others developed severe viral respiratory illnesses.[11] The cohort was evaluated genetically and the clinical phenotype was linked to the minichromosome maintenance 4 (*MCM4*) gene on chromosome 8 with an autosomal recessive inheritance. Two additional Irish families with similar phenotypes were found to have the same mutations in *MCM4*, leading to speculation that *MCM4* is required for immune function homeostasis. This familial form of NK cell deficiency has been designated CNKD2 and should be suspected in patients with decreased NK cell cytotoxicity, endocrine abnormalities, and/or growth abnormalities.[5]

Ornstein *et al.* evaluated patients with severe, recurrent herpesvirus infections and identified five patients with functional NK cell abnormalities.[12] The most common herpesvirus implicated was HSV1. Infections involving VZV, HPV, EBV, and respiratory viruses were also described.[5] Only one gene defect has been identified to cause FNKD—a mutation in the *FCGR3A* gene encoding CD16. This rare mutation causing FNKD1 is autosomal recessive and prevents CD16 from being used as a costimulatory receptor when CD2 is ligated during spontaneous NK cell cytotoxicity.[5]

The role of antiviral agents in treatment is limited to anecdotal reports using prophylactic acyclovir or ganciclovir to decrease susceptibility to herpesvirus infections. Given the risk for HPV infection, all patients with NK cell deficiency should receive recombinant HPV vaccination. Other novel therapeutic trials in CNKD1 include the use of IFN-α and hematopoietic stem cell transplant.[5]

Final Diagnosis

The final diagnosis was functional NK cell deficiency.

CONCLUSION

Patients with recurrent and/or severe viral infections should be evaluated for NK cell deficiency. CNKD presents with abnormal NK cell numbers and FNKD presents with normal numbers but reduced cytotoxicity function. Further research is needed to determine if there is a role for prophylactic antiviral agents in the treatment of NK cell deficiency.

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Patient Oriented Problem Solving (POPS) Case Report

Fifty-five-year-old man with chronic yeast infections

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ABSTRACT

As immunologists, we are frequently asked to evaluate patients with recurrent infections. These infections can provide us with clues regarding what pathways might be aberrant in a given patient, e.g., *specific pyogenic bacteria with Toll-like receptor problems, atypical mycobacteria with interferon gamma receptor autoantibodies, and* Candida*/staphylococcal infections with cellular immune abnormalities. We present a 55-year-old man who presented to our immunology clinic with onychodystrophy of the toenails and fingernails and recurrent oral–esophageal candidiasis. The differential diagnosis for recurrent yeast infections is complex and includes usual suspects as well as some that are not as straightforward.*

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CASE PRESENTATION

Chief Complaint

Onychomycosis and recurrent oral–esophageal candidiasis.

History of Present Illness

A 55-year-old man was referred to the University of Virginia Immunology Clinic for onychodystrophy of his fingernails and toenails and recurrent oral–esophageal candidiasis. He had the problem with his toenails since childhood, but this had subsequently spread to involve his fingernails ~4–5 years ago. Six months previously, he was diagnosed with oral candidiasis and was successfully treated with nystatin. He had no history of antibiotic or corticosteroid usage. One week later, he again developed thrush, and this pattern continued over the next months. Concomitantly, he was evaluated by the Dermatology Department for the onychodystrophy. Fingernail cultures were positive for *Candida* and his toenails grew dematiaceous mold. He was treated with fluconazole or itraconazole at various times over the past year and noted improvement with these treatments. Again, once the medications were removed, his symptoms returned. His last course of antifungal medication was completed 2 weeks before presenting to our clinic.

During our evaluation, he reported early dysphagia, especially while eating bread. He also described symptoms of gastroesophageal reflux and cough that were persistent and exacerbated after both eating and exercising. The cough would resolve with his ongoing antiyeast treatments. He denied constitutional symptoms as well as sinopulmonary, gastrointestinal, blood, bone, central nervous system, or kidney infections. He denied recurrent herpes, varicella, or human papilloma virus infections. Most importantly, he denied infections with *Staphylococcus aureus* including furunculosis. He had no history of autoimmune disease such as thyroiditis, autoimmune hemolytic anemia, or idiopathic thrombocytopenic purpura, although he did report transverse myelitis that developed temporally to receiving the tetanus and influenza vaccinations, ~17 years before presenting to our clinic. He had no human immunodeficiency virus (HIV) risk factors.

Physical Examination

On physical examination his oropharynx was without evidence of oral candidiasis. He had no lymphadenopathy and his respiratory exam was normal. Skin examination did not show atopic dermatitis or furunculosis; however, he had significant onychodystrophy of his fingernails and toenails.

Laboratory and Other Diagnostic Findings

Our initial immunologic evaluation showed absent delayed-type hypersensitivity testing to *Candida* and

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Table 1 **Patient characteristics from our initial immune workup**

	Patient Values	Normal Range
CBC with differential		
WBC	9.20 k/μL	4.0–11.0 k/μL
Neutrophils percent (Abs)	62.7% (5.77 k/μL)	47.0–82.0% (150–450 k/μL)
Lymphocytes percent (Abs)	25.2% (2.32 k/μL)	15.0–45.0% (1.00–5.00 k/μL)
Monocytes percent (Abs)	12.1% (1.11 k/μL)	2.0–12.0% (0.00–1.00 k/μL)
Eosinophils percent (Abs)	0.0% (0 k/μL)	0.0–6.0% (0.00–0.60 k/μL)
Basophils percent (Abs)	0.0% (0 k/μL)	0.0–2.0% (0.00–0.20 k/μL)
Immunoglobulins		
IgA	140.0 mg/dL	68–378 mg/dL
IgG	897.0 mg/dL	694–1618 mg/dL
IgE	8.0 IU/mL (L)	10–180 IU/mL
IgM	151.0 mg/dL	60–263 mg/dL
Flow cytometry		
CD19% (Abs)	0% (L; 0 k/μL)	5–24% (0.07–0.46 k/μL)
CD20% (Abs)	0% (L; 0 k/μL)	5–24% (0.06–0.53 k/μL)
CD3% (Abs)	88% (H; 2.04 k/μL)	57–84% (0.54–1.78 k/μL)
CD4% (Abs)	25% (L; 0.580 k/μL)	30–61% (0.31–1.14 k/μL)
CD8% (Abs)	61% (H; 1.42 k/μL)	12–37% (0.14–0.82 k/μL)
CD4/CD8 Ratio	0.41% (L)	0.9–4.6%
CD16% (Abs)	11% (0.255 k/μL)	2–22% (0.08–0.43 k/μL)
Antibody response, viral load		
Tetanus antitoxoid IgG	0.83 IU/mL	Minimum protective level, 0.01–0.15 IU/mL
Diphtheria antitoxoid IgG	0.090 IU/mL	Minimum protective level, 0.01–0.1 IU/mL
HIV copies/mL	None detected	None detected

Abs = absolute; H = high; L = low; HIV = human immunodeficiency virus; CBC = complete blood count; WBC = white blood cell count.

Trichophyton, at 48 hours. He was diagnosed with chronic mucocutaneous candidiasis (CMC). His complete blood count revealed normal numbers of neutrophils, lymphocytes, and monocytes, but, interestingly, he had no eosinophils or basophils (Table 1). Flow cytometry (Table 1) showed a low CD4:CD8 ratio with low–normal absolute CD4 T-cell numbers (585/μL) but was very surprising for the complete absence of CD19 B cells. The absence of B cells was subsequently confirmed with enumeration of CD20 cells, which were also absent. Because of the absence of B cells, quantitative immunoglobulins were measured and, along with specific antibody testing, these were surprisingly unremarkable (Table 1).

Clinical Course

A chest computed tomography scan showed the presence of a large anterior mediastinal mass. He was referred to thoracic surgery for video-assisted thoracoscopy with thymectomy. Pathology showed a noninvasive type B1 thymoma with a lymphocytic predominance but no spindle cells. A repeat computed tomography chest scan at 6 months follow-up did not reveal recurrence of his anterior mass. Interestingly, IgG levels have remained normal postthymectomy and IgG level at 6-month follow-up was 921 mg/dL.

QUESTION 1

What Is the Differential Diagnosis of CMC?

CMC is the result of the failure of T lymphocytes to mount a cellular immune response to *Candida*, leading to chronic *Candida* infections that are typically limited to mucosal surfaces, skin, and nails. CMC can present as a manifestation of a wide number of underlying conditions. Most commonly, CMC is a component of the myriad of infections associated with the comprehensive loss of T-cell function that occurs, *e.g.*, in severe combined immune deficiency, DiGeorge syndrome, HIV, *etc.* Any patient with CMC should be HIV tested. In addition to negative viral load, our patient had normal numbers of CD4 T cells (Table 1), which, along with his age, eliminated severe combined immune deficiency or other acquired or idiopathic CD4 lymphopenias as a mechanism for his disease.

The immune response to *Candida* requires complex interactions between immune cells and the yeast for

adequate recognition, engagement of innate and adaptive immune responses, phagocytosis, and killing. Innate immunity includes a combination of monocytes, macrophages, neutrophils, dendritic cells, and others that together maintain homeostasis with this usual commensal organism, using Toll-like receptors (TLR2 and 4), complement receptors (CR3), and numerous pattern recognition receptors, such as the C-type lectin receptors (CLR; macrophage mannose receptor, Dectin-1, DC-sign, *etc*.) that are necessary for recognition of mannans and mannoproteins within the cell walls of *Candida albicans*.[1] For the development of adaptive, largely Th17-mediated immunity, binding of Dectin-1 on the surface of dendritic cells signals the CARD9 complex, ultimately activating the production of cytokines including transforming growth factor (TGF) β, IL-6, and IL-23.[2] These cytokines provide "signal 3" for the adjacent T cells, which are simultaneously having *Candida* antigen presented by the dendritic cells. In the context of cellular differentiation, signal 1 refers to major histocompatibility complex/T-helper cell interactions, and signal 2 refers to costimulatory molecules CD80/86 integrating with their respective ligands. Signal 3 represents the cytokine milieu that supports T-cell activation and promotes T-helper immune deviation. In the generation of Th17 cells, the cytokine milieu required includes TGF-β, IL-6, and IL-23. These cytokines signal through tyrosine kinase 2 (Tyk2) to activate the nuclear transcription factor STAT3. These signaling molecules and, especially, STAT3, lead to the production of IL-17 and the differentiation of Th17 cells.[3,4] Mutations in genes encoding these proteins and others can lead to Th17 deficiencies and the diagnosis of CMC (Table 2; Fig. 1).

STAT3-deficient (hyper-IgE syndrome) patients are defined by their markedly elevated IgE levels and, in further contrast to this patient, are generally hypereosinophilic and show susceptibility to skin and respiratory *Staphylococcus* infections (along with the candidiasis).[5] Mutations in dedicator of cytokinesis 8 (Dock8) and Tyk2 are also characterized by elevated serum IgE levels, eosinophilia, sinopulmonary staph infections, and lymphopenia along with the CMC. These are autosomal recessive (AR) conditions that are largely distinguished from autosomal dominant hyper-IgE syndrome by the presence of frequent cutaneous viral infections and defects in humoral immunity (*e.g.*, low IgM).[6–10]

IL-17F deficiency is an autosomal dominant condition in which the host displays impaired (but not abolished) activity against *Candida*, possibly reflecting the continuing presence of IL-17A. In contrast, IL-17RA deficiency is an AR condition that completely abolishes cellular responses to both IL-17A and IL-17F[11] and thereby produces a much more severe defect in anti-*Candida* immunity. Complete STAT1 deficiency leads to diminished STAT1-dependent cellular responses to both interferon (IFN) α/β as well as IFN-γ. Patients with this disease suffer from both severe viral infections (herpes viruses), as well as intracellular pathogens (*Salmonella*, BCG, and nontuberculous mycobacteria).[12] Interestingly, gain of function autosomal dominant STAT1 mutations can develop infections similar to those with loss of function mutations but can also develop infections with dimorphic molds (Samplaio *et al.*[13]) as well as CMC and autoimmunity (Uzel *et al.*[14]). Although these patients have increased expression of cytokines that promote Th17 immune deviation (IL-6 and IL-21), ultimately, the stronger cellular responses to the STAT-1 activating cytokines IFN-α/β, IFN-γ, and IL-27 prevail, and their Th1 immune deviating influences supersede and hinder the development of Th17 cells.[15] STK4 deficiency was described in a cohort with T and B lymphopenia and histories of multiple bacterial and viral infections (especially cutaneous human papilloma virus), along with CMC[16] (Table 2; Fig. 1).

CARD9 is an important part of the pathway engaged by the pattern recognition receptor Dectin-1, which is responsible for initiating many innate immune responses to fungal elements, including, ultimately, the development of Th17 cells as discussed previously.[17] Consistent with its essential role as a "danger signal" capable of recognizing *Candida*-derived fungal elements AR mutations in Dectin-1 and CARD9 have also been associated with the CMC phenotype. However, CARD9 defects are associated less with CMC but instead with severe invasive *Candida* infections, including meningitis[18] (Table 2; Fig. 1).

Finally, autoimmune polyendocrinopathy ectodermal dystrophy results from AR mutations of the autoimmune regulator gene, which in contrast to our patient, is typically characterized by autoimmune hypoparathyroidism and adrenal insufficiency, along with CMC.[19] CMC in this population has been linked to presence of autoantibodies against IL-17A, IL-17F, and IL-22,[20,21] although diminished intrinsic Th17 responses have also been established.[20]

QUESTION 2

How Does the Finding of Absent B Cells Affect This Differential?

Absence of B lymphocytes can be seen in numerous conditions and in association with use of rituximab (anti-CD20 antibodies; Table 3). After we discovered our patient had no B cells, we broadened our differential diagnosis to include adult onset X-linked agammaglobulinemia caused by *forme fruste* mutations in the BTK gene. However, these B-cell deficiencies are not typically associated with CMC, and he lacked any of the typical presenting features suggestive of a humoral immune deficiency. As such, the most likely etiology of his acquired B-cell deficiency is Good's

Table 2 **Differential diagnosis for CMC**

Differential Diagnosis of CMC	Clinical Characteristics	Genetic Mutations	Laboratory Abnormalities
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	Recurrent *Candida* infections, hypoparathyroidism, Addison's disease; variable autoimmune endocrine associations	(Autoimmune regulator gene	Autoantibodies against adrenal cortex, pancreatic β cells, and/or thyroid Hypoparathyroidism Hypocalcemia, hyperphosphatemia Abundant autoantibodies including anti-IL-17A, IL-17F, IL-22, or others important for Th17 development or function
Hyper-IgE syndrome	Dermatitis, facial abnormalities, failure of primary dental deciduousness, pneumonia, and lung cysts	Loss of function in STAT3 gene	Elevated serum IgE of >2,000 IU/mL Hypereosinophilia Diminished Th17 cells
STAT1	Recurrent *Candida* infections	Gain of function in STAT1 gene	Low proportions of circulating IL-17A and IL-22–producing T cells
Gain of function mutations	Aneurysms		Cytokine responses such as IFN-α/β, IFN-γ, and IL-17 prevail to inhibit Th17 differentiation
STAT1 deficiency	Recurrent *Candida* infections; mycobacterial infections	Loss of function in STAT1 gene	Diminished Th17 cells
IL-17 F Mutations	Recurrent *Candida* infections	Autosomal dominant	Diminished function of Th17 cells; may be partial, because this disease only affects IL-17F leaving IL-17A functioning properly
IL-17 receptor mutations	Recurrent *Candida* infections	AR	Complete loss of responsiveness to both IL-17A and IL-17F
STK4 deficiency	Recurrent bacterial infections, viral infections, mucocutaneous candidiasis, cutaneous warts, and skin abscesses, and atrial septal defects	Homozygous premature termination mutation in the gene STK4	T- and B-cell lymphopenia and intermittent neutropenia
Dectin-1 deficiency	Recurrent *Candida* and pneumocystis jirovecii infections	Early stop-codon mutation Tyr238X	Absent *Candida*-specific Th17 cells
CARD9	Recurrent fungal, viral and bacterial infections, particularly invasive *Candida* infections including meningitis		Diminished Th17 cells

Table 2 **Continued**

Differential Diagnosis of CMC	Clinical Characteristics	Genetic Mutations	Laboratory Abnormalities
Good's syndrome	Recurrent bacterial or opportunistic (viral, fungal) infections, and thymoma; variable autoimmune associations (myasthenia gravis, pure red cell aplasia, *etc.*)		Hypogammaglobulinemia, $CD4^+$ T-cell lymphopenia, low or absent B cells, ± eosinopenia abundant variable autoantibodies including anti-IFN-α, IFN-ω, IL-12, IL-17, IL-22, and others important for Th17 development or function

AR = autosomal recessive; CMC = chronic mucocutaneous candidiasis; IFN = interferon.

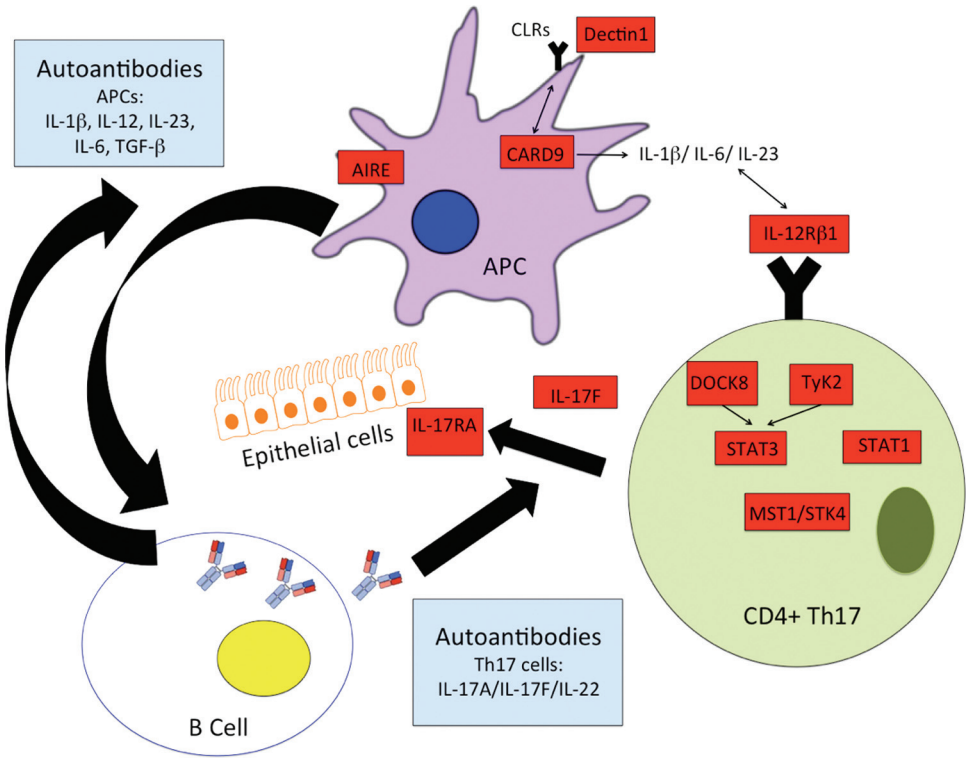

Figure 1. *Genetic- and autoantibody-associated mechanisms of chronic mucocutaneous candidiasis (CMC). See text for details. Red boxes designate potential genetic mutations associated with CMC, and blue boxes represent putative autoantibodies.*

syndrome. Good's syndrome is a rare, adult-onset primary immunodeficiency, characterized by low or absent B cells, hypogammaglobulinemia, and multiple autoimmune diseases in the setting of an underlying thymoma. As with our patient, Good's syndrome patients usually exhibit relative CD4 T-cell lymphopenia (low–normal in our patient), absent eosinophils and basophils, and present in the 4–5th decade of life.[22,23] Additionally, our patient presented with symptoms concerning for a mediastinal process (difficulty swallowing). However, Good's syndrome requires deficient IgG antibodies, and, at the time of evaluation, our patient's immunoglobulins were normal, which is inconsistent with this diagnosis (see discussion later in text).

QUESTION 3

What Additional Investigations Would Be Helpful in This Patient to Determine How His Thymoma Produced CMC?

After informed consent, blood samples were taken from the patient. Flow cytometry was performed in the research laboratory at the National Institutes of Health to measure $CD4^+$ T cells expressing intracellular IL-17A, identification markers for Th17 cells. Our patient showed absent Th17 cells compared with the control (3.12%; Fig. 2 *A*). Because patients with thymoma develop numerous autoantibodies that produce a myriad of autoimmune diseases (Table 4)[20,24–26] presumably

Table 3 **Differential diagnosis for absent B cells**

Humoral immunodeficiency	Good's syndrome	Adult-onset primary immunodeficiency, frequent opportunistic infections, and thymoma
	X-linked agammaglobulinemia (Bruton's agammaglobulinemia): mutation in the gene coding for Bruton tyrosine kinase (BTK)	Female carriers have no clinical manifestations; accounts for 85% of agammaglobulinemia; recurrent otitis, sinusitis, and pneumonia; enterovirus
	μ (IgM) heavy chain deletion/mutation	Most common cause of AR agammaglobulinemia; recurrent otitis, sinusitis, and pneumonia; arrest occurs at the pro–B-cell level
	B-cell linker protein (BLNK)- defect in adaptor protein necessary for receptor signaling	Opportunistic infections, pre-B acute lymphoblastic leukemia
	Igα and Igβ	Mutations result in arrest of maturation at the pro B-cell level
	Surrogate light chain and λ5 deletion/mutation	Recurrent otitis, sinusitis, and pneumonia (similar to μ heavy chain mutations)
Malignancy	Nijmegen breakage syndrome (NBS): AR disorder and NBS1 gene mutation	Microcephaly, growth retardation, severe combined immunodeficiency, and a high incidence of lymphoid B cell carcinoma
	Malignant thymoma: normal $CD4^+/CD8^+$ ratio and the absence of peripheral B cells	Recurrent infections, thymoma, and superior vena cava syndrome
Medications	Rituximab- anti-CD20 monoclonal	Rare side effect—absent $CD19^+$ and $CD20^+$ B cells

AR = autosomal recessive.

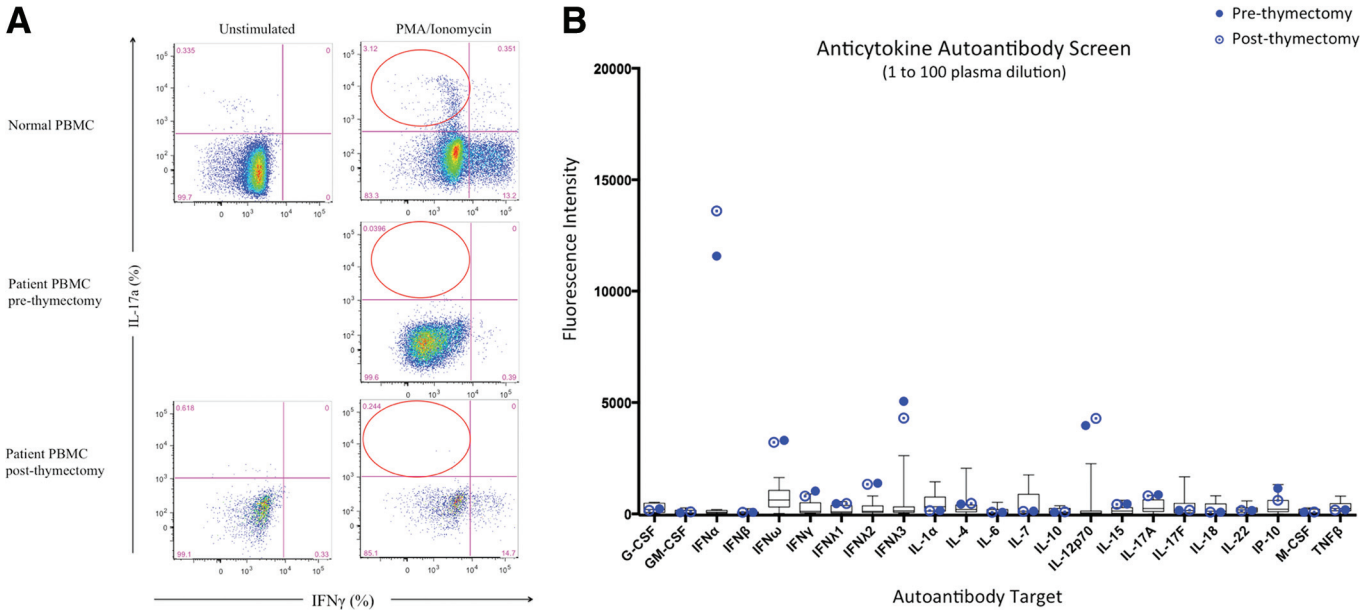

Figure 2. *Evidence of Th17 deficiency by flow cytometry and autoantibodies. (A) IL-17a production (%) in $CD4^+$ memory T cells (red circles) for normal (top panels) and patient peripheral blood mononuclear cells pre- and postthymectomy (middle and lower panels, respectively). Unstimulated (left panels) or stimulated with phorbol 12-myristate 13-acetate/ionomycin (right panels) conditions. (Right side of each panel shows interferon [IFN] γ–producing $CD4^+$ memory T cells.) Unstimulated condition not available for prethymectomy sample because of lymphopenia. B) Anticytokine autoantibodies before and after thymectomy. Plasma was mixed with the cognate beads, washed, and tested against human IgG.*

Table 4 **Anti-cytokine antibodies and their associated diseases**

Autoantibody to Cytokine	Associated Disease(s)
IFN-α	Thymoma, myasthenia gravis, SLE, and viral infections
IFN-ω	Thymoma and myasthenia gravis
IL-12	Thymoma, myasthenia gravis, CMC, and other opportunistic infections
IL-22	CMC in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and thymoma
IL-17F	CMC in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and thymoma
GM-CSF	Pulmonary alveolar proteinosis, and cryptococcal meningitis
G-CSF	Felty's syndrome (neutropenia)
Erythropoietin	Pure red cell aplasia
IFN-γ	Opportunistic infections, especially nontuberculous mycobacterial infections
Osteoprotegerin	Osteoporosis in celiac disease

IFN = interferon; CMC = chronic mucocutaneous candidiases; G-CSF = granulocyte–colony-stimulating factor; GM-CSF = granulocyte cacrophage–colony-stimulating factor; SLE = systemic lupus erythematosus.

reflecting the role of the thymus in negative selection of autoreactive cells, we hypothesized that our patient would have autoantibodies to IL-17. We worked with our partners at the National Institutes of Health to evaluate for anticytokine autoantibodies. These studies showed autoantibodies to IFN-α, IFN-ω, IFN-λ3, and IL-12p70 but not to IL-17 (including A and F) or IL-22 (Fig. 2 *B*). Further testing revealed no evidence of autoantibodies to granulocyte–colony-stimulating factor, granulocyte macrophage–colony-stimulating factor, IFN-β, IFN-γ, TNF-β, IFN-γ-inducible protein (CXCL10; IP-10), IL-4, IL-6, or IL-15.

Autoantibodies to IL-17 are thought to be one cause of CMC associated with thymoma, reflecting the subsequent loss of the ability of Th17 cells to carry out their anticandidal (and antibacterial) immune functions.[20,25] However, the absence of Th17 cells in our patient could be a reflection of defective T-cell development secondary to thymic dysfunction or could also be ascribed to autoantibodies to cytokines essential for Th17 immune development. Although IL-6 and TGF-β are the most important cytokines necessary for the generation of Th17 cells, other cytokines including IL-23 contribute. IL-23 is a heterodimer consisting of a unique IL-23α chain and the p40 chain of IL-12.[27] Thus, autoantibodies to anti–IL-12 are capable of also targeting IL-23. We hypothesize that this could explain our patient's depressed Th17 immunity (Fig. 3). Although we recognize that anti–IL-12p40 autoantibodies are prevalent in thymoma, without necessarily resulting in CMC,[28] it is also likely that anticytokine autoantibodies can manifest differently,[29] possibly depending on host and environmental factors, as well as differences intrinsic to the autoantibodies themselves.

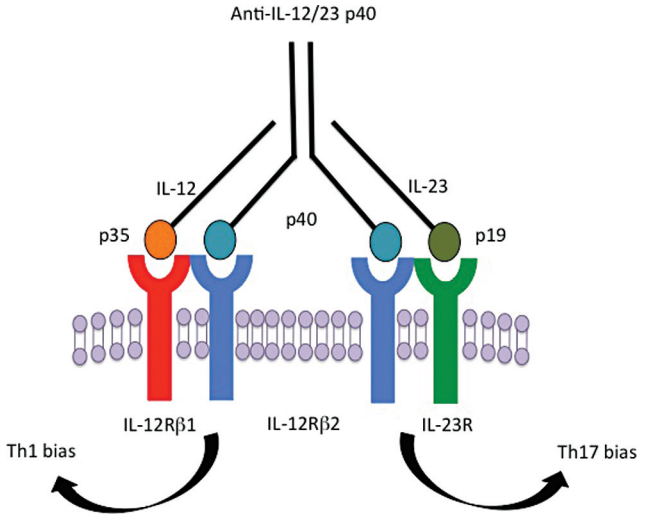

Figure 3. *The role of autoantibodies to IL-12 in the development of chronic mucocutaneous candidiasis (CMC). The shared subunit p40 allows for antibody blockade of both Th1 responses* via *IL-12 and Th17 responses* via *IL-23. See text for details.*

DISCUSSION

We speculated that as with other autoimmune syndromes associated with thymoma (*e.g.*, myasthenia gravis), thymectomy might be associated with loss of his autoantibodies and restoration of his Th17 compartment. Because it is unknown if or even whether this could occur, we decided to start the patient on continuous fluconazole as prophylaxis. However, 1 year after thymectomy, we repeated anticytokine autoantibody testing, and it appears that the autoantibodies persisted against IFN-α IFN-ω, IFN-λ3, and IL-12p70 (Fig. 2 *B*). At this time, he remains on antifungal prophylaxis to manage his infections.

Surprisingly, despite his absence of B cells, our patient had normal immunoglobulins, reflecting the ongoing presence of long-lived plasma cells. The life expectancy of human plasma cells is presently not known. However, we can expect that at some time in the future he will become the "typical" Good's syndrome patient and develop humoral immune failure. Furthermore, on biopsy, our patient did not have the typical histological finding in the thymus of spindle cells that are associated with Good's syndrome. However, spindle cells are not required for the diagnosis of Good's syndrome, and other cell types within the thymoma have been described, including epithelial cell tumors and/or mixed epithelial/lymphoid tumors.[22]

The absence of B cells in this disease is thought to also reflect an autoimmune process but, once the B-cell compartment is destroyed, this can never be restored even if these autoantibodies also resolve, presumably reflecting the absence of B lymphocyte stem cells. Although the timing of his humoral immune failure remains unclear, our patient will be monitored closely for infections and will have yearly quantitative antibody titers because we expect him to ultimately need to start replacement immunoglobulin therapy.

Final Diagnosis

This patient has a thymoma associated with autoantibodies to IFN-α and IL-12p70 and CMC. It is possible that his illness may progress in the future to be Good's syndrome.

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Patient Oriented Problem Solving (POPS) Case Report

A 68-year old woman with asymptomatic hypereosinophilia

Jessica P. Rajan, M.D., and Andrew A. White, M.D.

ABSTRACT

Eosinophilia is known to have a wide variety of etiologies including atopic diseases, infections, endocrine abnormalities, hematologic/neoplastic causes, and certain immunodeficiency disorders. In contrast, hypereosinophilic syndromes refer to a group of heterogeneous disorders with persistent eosinophilia and organ involvement. The treatment of eosinophilia varies widely based on its etiology and therefore should be evaluated thoroughly at onset. We present the case of a 68-year-old woman with isolated asymptomatic hypereosinophilia.

(Allergy Asthma Proc 35:495–497, 2014; doi: 10.2500/aap.2014.35.3775)

CASE PRESENTATION

Chief Complaint

Hypereosinophilia noted on complete blood count.

History of Present Illness

A 68-year-old woman was seen and evaluated for new-onset hypereosinophilia. The patient had a history of anemia of chronic kidney disease with stage 2 chronic renal failure. She had monthly complete blood counts drawn for routine monitoring of her anemia and was told that her two most recent evaluations were significant for hypereosinophilia. She denied any history of allergic rhinitis, asthma, food allergies, or eczema. She also denied any new symptoms of rhinorrhea, nasal congestion, conjunctival erythema, or epiphora. She denied any recent international travel. She had recently developed constipation and had started a natural supplement to treat this symptom. None of her prior medications had changed in color or size to suspect a change in manufacturer. On review of systems she denied any joint pains, skin changes, fevers, night sweats, shortness of breath, orthopnea, chest pain, edema of the extremities, weight loss, or lymphadenopathy.

Physical Examination

Vital signs were within normal limits. The patient was a healthy-appearing woman with clear conjunctivae and nasal passages with normal pink turbinates. Her lungs were clear without wheezes, rales, or rhonchi. There was no lymphadenopathy or hepatosplenomegaly. Cardiac exam revealed regular rate and normal rhythm. Skin examination did not show any urticaria, dermatitis, or angioedema.

Laboratory Findings

Regular blood counts showed a progressive eosinophilia beginning with an absolute eosinophil count of 497 rising steadily over several weeks to its peak of 6413 cells/μL (Fig. 1). Hemoglobin was 10.2 g/dL and hematocrit was 29.8%. Serum creatinine was found to be 1.3 mg/dL. In addition, fluorescence in situ hybridization analysis of serum was performed with 0% deletion for CHIC2.

QUESTION 1

What is the differential diagnosis of these symptoms?

a. Atopic disease
b. Parasitic infection
c. Hypereosinophilic syndrome
d. Drug hypersensitivity
e. Hematologic disorders

QUESTION 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis in this patient?

Given the patient's denial of constitutional symptoms, organomegaly, and otherwise normal complete blood count and metabolic panel, further investigation of all current medications should be sought, prescription as well as nonprescription. In addition, studies to assess organ function should be performed including liver function tests, renal function tests, urinalysis, and

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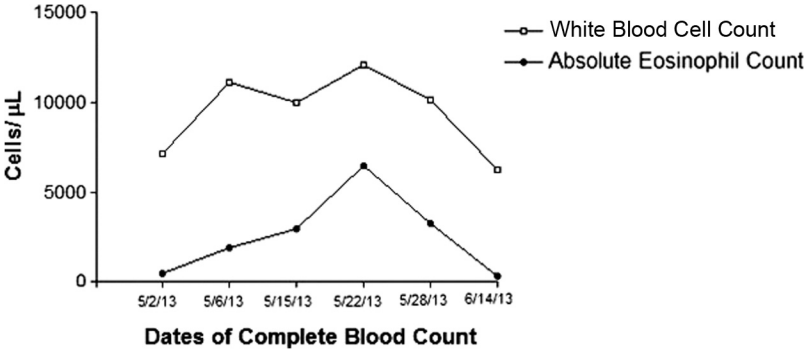

Figure 1.

chest radiograph. If no other cause for eosinophilia can be determined, bone marrow aspirate and biopsy may need to be performed to fully assess the underlying etiology. Analysis should also be performed for FIP1L1-PDGFRA fusion transcript to assess for chronic eosinophilic leukemia, which is highly responsive to tyrosine kinase inhibitors.[1]

Clinical Course

During the course of the initial patient interview, she disclosed that she felt that the newest formulation of the supplement "was different." Although she had been on this supplement for a few months, on starting a new bottle, it began to cause diarrhea rather than normal bowel movements. Therefore, the patient was advised to stop using the natural supplement "Gentle Senna," (Health Concerns, Oakland, CA) which she had used to treat her constipation. "Gentle Senna" is a product made by Health Concerns and is advertised as being helpful for constipation and digestion. Serial blood counts showed a prompt reduction in eosinophilia, which ultimately returned to the normal range.

The patient's anemia remained present and appeared to be unrelated to her eosinophilia.

DISCUSSION

Complementary and alternative medicine (CAM) includes multiple categories of which herbal supplements are a subset.[2] The use of CAM has increased in recent years and it is estimated that ~42% of adults use some form of CAM. Considering that the majority of CAM is paid out-of-pocket, annual spending for CAM is estimated at >$30 billion.[3] Herbal supplements specifically are being used for a myriad of ailments ranging from osteoarthritis to side effects from chemotherapy.

Per the Dietary Supplement Health and Education Act of 1994, herbs are classified as dietary supplements and therefore can be marketed and sold without first establishing safety and efficacy. An analysis of 25 commercially available ginseng products found significant variation in the concentration of two ingredients thought to be biologically active.[4] When DNA barcoding was used to verify the presence of active ingredients in dietary supplements, it was found that only 2 of 12 companies had products without any substitution or fillers and that most products contained additional ingredients not listed on the label.[5] A much more concerning report looked at contamination with heavy metals and pesticides in samples of Chinese herbal medicines. This study found that pesticides were detectable in 36.7% of samples and at least one metal was found in all samples.[6] The poorly regulated nature of this industry makes it likely that alternative treatments could contribute to otherwise unexplained eosinophilia. A prior study had found that up to 70% of patients who use unconventional therapies did not inform their medical doctor, which reinforces the need to take a thorough history when evaluating patient eosinophilia.[7] If there is suspicion for an adverse event that occurs as the result of a contaminated dietary supplement, a voluntary report should be filed with the U.S. Food and Drug Administration through their online website.

Eosinophilia is defined as >450 eosinophils/μL measured in peripheral blood. Eosinophils are found predominantly in peripheral tissues with a mucosal–environmental interface, such as those seen in the respiratory, gastrointestinal, and lower genitourinary tracts. Worldwide, the most common cause of eosinophilia is helminthic infection, followed by drug hypersensitivity and atopic diseases.[8] It is known that there are instances of eosinophilic syndrome occurring with supplements or their contaminants. Examples of these include L-tryptophan, which led to eosinophilia–myalgia syndrome as well as Spanish toxic oil syndrome.[9] There have also been reports of eosinophilia (without evidence of end organ damage) with use of echinacea.[10] More recently, there have been two case reports of eosinophilia with mononeuritis multiplex and necrotizing vasculitis in association with use of nonprescription probiotics.[11]

It is crucial in eosinophilia to immediately evaluate the presence of end-organ involvement, the most serious consequence of hypereosinophilic syndrome.[12] If suspected, the patient needs rapid multidisciplinary evaluation and initial treatment with systemic steroids. If there is concern about strongyloidiasis, which is

endemic in the southeastern United States, then an empiric single dose of ivermectin should also be considered because Strongyloides hyperinfection caused by systemic steroids can be fatal.

To our knowledge, this is the first reported case of eosinophilia occurring with the combined herbal supplement, sold under the name "Gentle Senna." It is unknown which herbal component led to the eosinophilia or whether a contaminant in the product was the culprit. This case exemplifies the importance of taking a thorough history when evaluating cases of isolated eosinophilia and educating patients on potential adverse effects of nonregulated herbal supplementation.

Final Diagnosis

Hypereosinophilia is associated with an herbal supplement.

SUMMARY

Seemingly harmless health supplements can be the rare cause of eosinophilia and should be fully evaluated for when approaching a patient with new-onset, isolated eosinophilia.

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Patient Oriented Problem Solving (POPS) Case Report

A 15-year old girl with asthma and lower lobe bronchiectasis

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ABSTRACT

Wet cough, wheeze, and sputum in an adolescent with evidence for bronchiectasis is an uncommon presentation. The differential diagnosis includes cystic fibrosis (CF), immunodeficiency disorders, complement deficiency, allergic bronchopulmonary aspergillosis, alpha-1 antitrypsin disease, repeated aspiration pneumonia, foreign body, bronchial carcinoid, unresolved right middle lobe pneumonia, and primary ciliary dyskinesia (PCD). The likely diagnosis proceeds from the more to less common in patients with these symptoms. The location of disease on computed tomography scanning, nasal and bronchial exhaled nitric oxide, identification of ultrastructural defects on electron microscopy, and specific genetic mutation help separate CF and PCD. Although differentiating these conditions is vital, the chronic management of the bronchiectasis usually includes clearance mechanisms, bronchodilators, regular exercise, appropriate vaccinations, and judicious antibiotics for airway infections.

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CASE PRESENTATION

Chief Complaint

The patient is a 15-year old Caucasian female subject who presented with wheezing, cough, and sputum of several years duration.

History of Present Illness

The patient had respiratory problems dating back to infancy with several episodes of otitis media, pneumatic tube placement seven times with hearing impairment, and episodes of sinusitis with flares of her asthma, which were described as a wet cough, wheeze, productive sputum, and dyspnea. She recently had a computed tomography (CT) scan of the sinuses that revealed changes of acute and chronic sinusitis. The child was hospitalized for pneumonia at the age of 3 years. Treatment with inhaled bronchodilators, inhaled steroids, leukotriene receptor antagonists, intranasal steroids, and antihistamine decongestants did not adequately control her symptoms. There was no history of other systemic infections, esophageal reflux or choking with meals. There was no family history of allergy, asthma, cystic fibrosis (CF), or immunodeficiency. The chest radiograph had an abnormal density and a CT of the chest revealed bilateral lower lobe bronchiectasis with airspace consolidation in the right middle lobe (Fig. 1).

Physical Examination

Vital signs were temperature of 98°F, heart rate of 81/min, respiratory rate of 18/min, blood pressure of 110/64 mmHg, and oxygen saturation of 98%. The child was well developed with a height of 66 in., weight of 60 kg, and body mass index of 21.5 kg/m^2. The nasal membranes were boggy without nasal polyps. There were bilateral wheezes, rhonchi, and crackles, but no clubbing or cyanosis, and cardiac auscultation was normal. The heart revealed a regular rate and rhythm and no murmur.

QUESTION 1

Which of the following are included in the differential diagnosis of wheezing, repeated infections, and bronchiectasis?

A. CF
B. Immunodeficiency disorder

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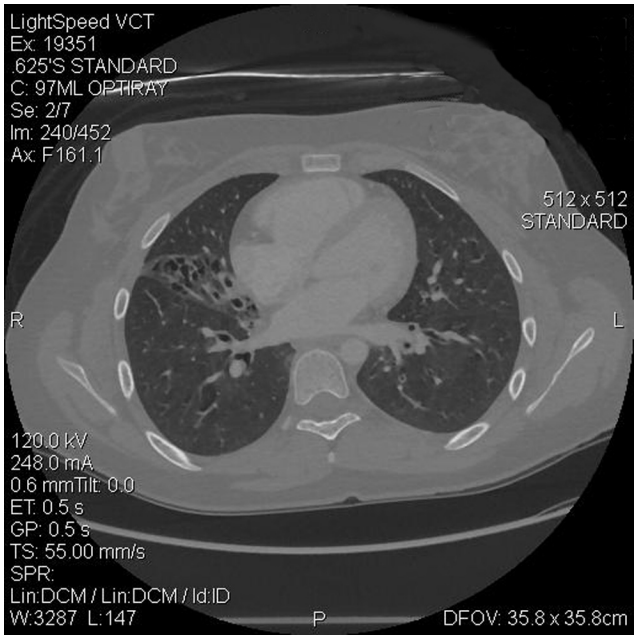

Figure 1. *Computed tomography (CT) chest scan revealing extensive bronchiectasis in the right middle lobe.*

C. Complement deficiency
D. Allergic bronchopulmonary aspergillosis (ABPA)
E. α-1 Antitrypsin deficiency
F. Repeated aspiration pneumonia
G. Foreign body
H. Airway carcinoid tumor
I. Unresolved right middle lobe pneumonia
J. Poorly controlled asthma
K. Primary ciliary dyskinesia (PCD)

QUESTION 2

What further studies would one consider at this point

A. Sweat test
B. CF gene analysis
C. Quantitative immunoglobulins
D. Pre- and post-IgG titers for pneumococcal antigens and tetanus toxoid
E. Complement levels
F. Complete cell count
G. Complete lymphocyte profile
H. Pulmonary function testing
I. α-1 Antitrypsin level
J. Allergy skin testing
K. Barium swallow
L. Nuclear medicine gastric emptying scan
M. Fiberoptic bronchoscopy
N. Ciliary structure evaluation and/or genetic testing

DISCUSSION OF THE DIFFERENTIAL DIAGNOSIS

CF was unlikely in this patient in view of the two normal sweat chloride studies and a negative DNA analysis for CF gene mutation. The immunoglobulins and IgG subclasses, complement levels, stimulation studies with pneumococcal and tetanus vaccines, the lymphocyte profile, and complete cell count were normal. ABPA was ruled out because skin testing revealed negative skin reactions to all tested allergens, the serum IgE level was normal, the complete blood count did not reveal eosinophilia, and the pulmonary function test was normal. Although ABPA may at times be associated with CF, this patient lacked evidence for either diagnosis. The normal α-1 antitrypsin level also ruled out α-1 antitrypsin disease. Fiberoptic bronchoscopy revealed no endobronchial lesions, food particles, or airway granuloma to suggest carcinoid, recurrent aspiration, or a foreign body. Copious airway secretions in both lower lobes revealed normal flora and *Moraxella catarrhalis*. The barium swallow and a nuclear medicine gastric emptying scan were normal.

ADDITIONAL DIAGNOSTIC FINDINGS

Gene analysis revealed a C.48 + 2dupT mutation of DNA/1. Exhaled nitric oxide was performed and noted to be <5 ppb.

DISCUSSION OF THE DIAGNOSIS

PCD is an autosomal recessive disorder, however, with occasional X-linked transmission.[1,2] This was first recognized in 1933 as Kartagener syndrome (chronic sinusitis, bronchiectasis, and *situs inversus*).[3] In 1976, Afzelius[4] reported "immotile" cilia and defective ciliary ultrastructure. Subsequent studies showed that most patients had cilia with stiff, uncoordinated, and/or ineffective ciliary beat. "Primary" was adopted for the term PCD for this heterogenous disorder, distinguishing it from secondary (acquired) ciliary defects associated with infection and inflammation.

PCD has an incidence of 1 per 10,000–20,000 births, based on surveys of *situs inversus* and bronchiectasis in Norway and Japan.[5,6] The prevalence of PCD in the United States is difficult to determine, because of inadequacies of diagnostic methods.[7] There are <1000 patients in the United States with a diagnosis of PCD, because of the lack of appreciation of the signs and symptoms.

PCD is characterized by congenital impairment of mucociliary clearance. There is variability in the presentation depending on the age of the patient (Table 1). Many patients present in the neonatal period with respiratory distress characterized by chest congestion, coughing, tachypnea, and hypoxia. In some patients, respiratory failure may occur and is attributed to neonatal pneumonia or transient tachypnea of the newborn.[8,9] A constantly runny nose and year-round nasal congestion may be noted in early childhood. Nasal polyposis is frequently present and most patients de-

Table 1 **Distinguishing symptoms and features of PCD by age group**

Neonates and infants
Neonatal respiratory distress, especially in term infants, with no obvious cause (tachypnea and "wet lung" atelectasis)
Rhinitis-neonatal onset, persistent ("born with a cold")
Situs inversus totalis
Heterotaxy syndromes including congenital heart disease
Infants and other children
Chronic wet cough, usually with sputum production
Middle lobe atelectasis and bronchiectasis
Chronic secretory otitis media
Persistent otorrhea after tympanostomy tube insertion
Conductive hearing loss
Chronic pansinusitis
Nasal polyposis
Older children and adults
Non-CF or "idiopathic" bronchiectasis
Chronic mucopurulent sputum production
Presence of lower airway *Pseudomonas aeruginosa* or nontuberculous mycobacteria
Male infertility due to spermatozoa immobility
Ectopic pregnancy and decreased fertility in female patients
Chronic pansinusitis

CF = cystic fibrosis; PCD = primary ciliary dyskinesia.

Table 2 **Common observations in patients with primary ciliary dyskinesia**

Neurological
Hydrocephalus
Respiratory
Low levels of NO production
Increased sputum production during the day
Moderate hyperinflation
Haemophilus influenza, Streptococcus pneumoniae, Staphylococcus aureus, and *Moraxella catarrhalis*
Cardiac
Situs inversus in 50%
Complex congenital heart disease in 12.5%
Gastrointestinal
Tracheo-esophageal fistula
Esophageal stricture
Gastroesophageal reflux
Midgut volvulus
Biliary atresia
Urogenital/renal
Polycystic kidneys
Renal failure
Sperm immobility
Hematological
Abnormal leukocyte function
Rheumatological
Rheumatoid arthritis

Source: Ref. 34.
PCD = primary ciliary dyskinesia; NO = nitric oxide.

velop chronic sinusitis of the maxillary, ethmoidal, and frontal sinuses and chronic serous otitis media[10,11] Despite myringotomy tubes, these children may develop chronic otorrhea and associated conductive hearing loss with chronic middle ear effusion and recurrent otitis media.[12]

Symptoms that comprise a strong clinical phenotype in PCD in young children include (1) neonatal respiratory distress; (2) chronic, persistent lower respiratory symptoms (early onset and persistent wet cough); (3) chronic, persistent upper respiratory (nasal congestion and otitis media); and/or (4) a lateral defect (*situs inversus* or ambiguous). Any two of these four features provide a strong clinical phenotype for PCD, assuming that CF has been excluded.[13]

CF is common in older children and adults. Some patients may have underlying nasal polyps. Lower respiratory symptoms include a wet, productive cough, usually with sputum production, recurrent bronchitis, and pneumonia. PCD may eventually lead to a loss of lung function and widespread bronchiectasis. A variety of associations have been described in different organ systems (Table 2).

Lung function tests may initially be normal but airflow obstruction may occur with increased age.[14,15] Limited data on PCD reveal that lung function remains stable in a significant percentage of individuals and may decline over time, but not to the same degree as CF.[16,17]

PCD radiographic abnormalities include peribronchial thickening, atelectasis, and air trapping leading to bronchiectasis.[18] The middle and lower lobes are affected,but usually not the upper lobes as in CF. Middle lobe densely opacified segmental or lobar atelectasis with associated bronchiectasis seems to be a common occurrence in childhood.[19]

Infection of the airway begins in early childhood and is a leading cause of morbidity and mortality in PCD with nontypeable *Haemophilus influenza*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *M. catarrhalis*. Older individuals with more advanced lung disease have a higher incidence of infection with *Pseudomonas aeruginosa* and nontuberculous mycobacteria.[20]

The diagnosis of PCD is based on the typical clinical phenotype combined with identification of ciliary dys-

motility or a specific gene mutation. Because the specialized techniques required to establish a diagnosis are not readily available, patients suspected of having PCD usually require referral to a tertiary diagnostic center.[21,22]

Screening tests for PCD include exhaled nasal nitric oxide (nNO) and saccharin testing. Exhaled nNO is usually low in PCD in contrast to other lung diseases. Exhaled NO from the lower airway is also usually low and may be a useful screening test as normal or high levels will exclude PCD.[23] In patients with PCD, a low nNO may be caused by reduced levels of NO synthetase.[24] A low nNO is not diagnostic of PCD because conditions with overlapping features of PCD may result in similar levels. Confirmation of the diagnosis of PCD by ciliary ultrastructure or genetic analysis is required.

The saccharin test is used to evaluate mucociliary function. Saccharin transport time from the inferior turbinate to oropharynx will be >60 minutes in patients with PCD. Saccharin testing is a difficult test to perform in children and has been abandoned by most research centers.

Ultrastructural defects, the traditional "gold standard" for diagnosis, can no longer be used alone because up to 30% of PCD patients may have normal ultrastructure.[25,26] The most common ultrastructural defect is absent or shortened outer dynein arms. Other identified abnormalities include absent or shortened inner dynein arms, combined defects of both the outer and inner dynein arms, central apparatus abnormalities (loss of radial spokes or transpositions), combined defects of the inner dynein arms and central apparatus, and complete absence of cilia.[27–29]

Because cilia structure in PCD may be normal, genetic testing may be helpful for diagnosis. However, PCD is a very heterogenous condition, and only a few mutations are recognized with certainty. The most known genes are localized in dynein, axonemal, intermediate chain 1 (DNA I 1) and 2 (DNA I 2), heavy chain 5 (DNA H 5) and 11 (DNA H 11), and thioredoxin domain containing protein 3 (TXNOC 3). Other genes are external to axoneme but important for cytoplasmic preassembly of axonemal dyneins (chromosome 14 open reading frame 104 (KTU) and central microtubular pair (radial spoke head 9 homolog and radial spoke head 4 homolog A (RSPH 4/A).[30]

In contrast to targeted therapies in ABPA and CF, PCD defects are not treatable with drugs and no specific treatment exists to correct ciliary dysfunction. Although treatment of PCD mirrors that of CF, patients with PCD have different microbial colonization and the bronchiectasis that is seen in the lower and middle lobe and not upper lobe as seen in CF.[31] In PCD, therapy is devoted to improving mucus clearance, treating infections, improving or stabilizing lung function, and preventing chronic lung damage. In addition to airway clearance techniques, regular exercise is also advised. Human DNase and hypertonic saline may be considered to improve airway clearance.[32] Recommended vaccinations for influenza and streptococcal pneumonias should be continued. Inhaled bronchodilators and inhaled corticosteroids should be used for airflow obstruction. The use of anti-inflammatory macrolides such as azithromycin might represent a therapeutic option.[33]

Final Diagnosis

The final diagnosis was primary ciliary dyskinesia (PCD)

CONCLUSION

After the gene study revealed a DNA I 1 mutation, the patient was placed on a mucociliary clearance regimen, inhaled bronchodilators, and inhaled corticosteroids. The patient was started on nebulized human DNase and she was recommended to engage in a regular exercise program. She was advised to receive her recommended vaccination for influenza and *S. pneumoniae*.

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Patient Oriented Problem Solving (POPS) Case Report

A 31-year-old pregnant woman with angioedema

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ABSTRACT

Angioedema is swelling of the deep layers of the dermis and subcutaneous tissue due to an increase in vascular permeability. Angioedema sometimes occurs concomitantly with urticaria and represents an allergic disease. In other cases, angioedema is not associated with an allergic condition. We present the case of a 31-year-old woman with new-onset angioedema in the setting of her first pregnancy. After detailed history, physical examination, and laboratory evaluation, a cause for her angioedema was found that had not been considered previously and had significant implications for future management, particularly in light of her current pregnancy. Because allergists are commonly called on to evaluate and treat angioedema, we should be aware of the many disease processes that can present with this symptom and be well-versed in the workup of new-onset angioedema.

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CASE PRESENTATION

Chief Complaint

Swelling and difficulty breathing.

History of Present Illness

A 31-year-old G1P0 law student with a history of intermittent asthma, allergic rhinitis, and hyperemesis gravidarum was admitted with new-onset angioedema at 12 weeks gestation. She was in her usual state of health on the day of admission until developing bottom lip and tongue swelling, throat tightness, chest pressure, shortness of breath, and wheezing. She denied urticaria, pruritus, increased nausea, vomiting, or diarrhea. En route to the emergency department (ED) she developed fatigue, lightheadedness, and blurred vision. In the ED oral angioedema was noted. She was treated with intravenous diphenhydramine, famotidine, methylprednisolone, and nebulized albuterol. Symptoms resolved within 15 minutes.

Two hours before the event, she consumed pumpkin pie for the first time but had no other food exposure within 2 hours of the event. She noted that 40 minutes before the episode, she used an "old and dirty" polyester blanket.

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The allergy service was consulted to evaluate the cause of the patient's angioedema.

Medical History

Her medical history was notable for perennial allergic rhinitis sensitive to grass, mold, dust mite, and cat and well-controlled, intermittent asthma since childhood (albuterol required approximately once every 3 months). She had developed hyperemesis gravidarum, managed with ondansetron as needed. She denied history of food allergy. Other medications included a daily prenatal vitamin and albuterol as needed. Family history was notable for allergic rhinitis in both parents and "arthritis" in her father. There was no family history of angioedema. She was married, was a lifelong nonsmoker, and denied alcohol or drug use.

Review of Systems

She denied prior oral angioedema but endorsed previous bilateral peripheral edema in her hands and feet for the past 2 weeks, accompanied by arthralgia and angioedema in her fingers, wrists, knees, ankles, and elbows (all attributed to pregnancy). She also reported experiencing 1 week of "painful hives" at the beginning of her pregnancy that self-resolved. There was a distant history of frequent bilateral knee pain and a history of an erythematous, nonpruritic facial rash with sun exposure as a child.

Physical Examination

In the ED vital signs were normal. She appeared fatigued, with notable lower lip swelling, but with-

out posterior oropharyngeal edema. Deep breaths triggered cough and increased work of breathing with intercostal muscle usage without adventitious sounds. The remainder of her exam was within normal limits.

The allergy service was consulted for evaluation of angioedema and possible pumpkin allergy, ~12 hours after treatment. We noted minimal swelling of her bottom lip and normal work of breathing. Her right hand showed diffuse nonpitting edema and joint swelling at the proximal interphalanged and metacarpophalangeal joints. There was no rash, other peripheral edema, or other joint swelling. The rest of her exam was unremarkable.

QUESTION 1

What is the differential diagnosis for this patient's angioedema?

a. Autoimmune disease
b. Nephrotic syndrome
c. Acquired angioedema
d. Idiopathic angioedema
e. Allergic angioedema
f. Allergen-induced anaphylaxis
g. Idiopathic anaphylactic episode
h. Hereditary angioedema (HAE)

QUESTION 2

Are there any diagnostic studies that would be helpful in arriving at a diagnosis in this patient?

a. Tryptase level
b. C4 complement level
c. C3 complement level
d. Serum protein level
e. Urinalysis
f. Total immunoglobulin E (IgE) level
g. Pumpkin IgE level
h. Antinuclear antibody

Discussion of the Differential Diagnosis

HAE presents as recurrent, episodic angioedema hallmarked by abdominal attacks that onset typically in childhood or early adulthood.[1] Attacks typically last 72–96 hours and do not improve with antihistamines or corticosteroids.[1] HAE is inherited in an autosomal dominant fashion, with a positive family history in 75% of cases.[1] Given a lack of family history and resolution of symptoms with diphenhydramine and methylprednisolone, the likelihood of HAE seemed very low.

Allergen-induced angioedema was also low on the differential. Although foods are a source of angioedema, there was no likely antecedent food trigger. Pumpkin seed allergy has been reported[2] but is rare, and the timing of symptoms were at the limit for a likely IgE-mediated process. Furthermore, she consumed canned pumpkin, which lacks the major pumpkin seed allergen. Despite multiple aeroallergen sensitivities, inhaled aeroallergen exposure is unlikely to produce systemic symptoms. An idiopathic anaphylactic episode remained a possibility, which generally responds to antihistamines and corticosteroids.[1,3]

Table 1 **Laboratory results**

Test	Results	Reference Range
Total protein	**4.9**	6.0–8.3 g/dL
Albumin	**2.6**	3.5–4.9 g/dL
Total IgE	**460**	0–160 kU/L
Pumpkin IgE	<0.35	<0.35 kU/L
Tryptase	2.4	<11.5 ng/mL
C2	**<10**	25–47 U/mL
C3	**39**	83–240 mg/dL
C4	**6**	13–60 mg/dL
C1q	**9**	12–22 mg/dL
CI-INH level	42	19–37 mg/dL
CI-INH function	>90	>67%
Antinuclear antibody	**Positive**	Negative
Antinuclear antibody titer	**More than 1:2560**	Negative
Anti-dsDNA	**Positive**	Negative
Ds-DNA antibody	**2545.3**	0.0–7.0 IU/mL
Anti-Smith	**Positive**	Negative
Anti–phospholipid antibody	Negative	Negative
Urine protein	**100**	1–29 mg/dL
Urine blood	**150**	Negative U/L

Abnormal results are set in boldface.
C1-INH = C1 Inhibitor; dsDNA = double-stranded DNA.

The chief concern was for an autoimmune condition, particularly systemic lupus erythematosus (SLE). This was based on intermittent joint pain throughout her life, a recurring facial rash with sun exposure as a child, and recent arthralgia/swelling and painful hives at the beginning of her pregnancy—all are potentially characteristic of an autoimmune process. SLE is known to flare during pregnancy because of increased serum estrogen levels along with intrinsically dysfunctional T-regulatory cells.[4] Another concern was angioedema secondary to nephrotic syndrome, particularly given intermittent peripheral edema recently.

Laboratory Results and Clinical Course

Serological workup revealed anemia, low total protein, hypoalbuminemia, proteinuria, hematuria, and hypocomplementemia. C1 inhibitor (C1-INH) level and function were both normal. Antinuclear

Table 2 **Classification Criteria for Systemic Lupus Erythematosus**

Item	Definition
Malar rash	Erythematous, butterfly-shaped rash across the cheeks and nose, sparing the nasolabial folds
Discoid rash	Raised, erythematous, disk-shaped patches
Photosensitivity	Appearance or worsening of a skin rash due to sunlight exposure
Oral ulcers	Mouth or nasal sores, often painless
Arthritis	Joint pain, swelling, and/or effusion in two or more joints, without bone or joint destruction
Serositis	Pericarditis—inflammation of the lining around the heart and/or Pleuritis—inflammation of the lining around the lungs
Renal disorder	Excessive and sustained proteinuria or cellular casts in the urine
Neurologic disorder	Seizures and/or psychosis
Hematologic disorder	Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
Immunologic disorder	Antibodies to ds-DNA, Sm, or existence of antiphospholipid antibodies
ANA	A positive test at any time point without drugs known to be associated with it

Source: Ref. 5.
If a patient has 4 of 11 criteria, SLE can be diagnosed with ~95% specificity and ~85% sensitivity. If fewer than 4 criteria are present, the diagnosis of SLE depends on clinical judgment.
SLE = systemic lupus erythematosus; ds-DNA = double-stranded DNA; Sm = antibodies to Smith; ANA = antinuclear antibodies.

antibody was positive and she had anti–double-stranded DNA and anti-Smith extractable nuclear antibodies present. Table 1 details pertinent laboratory workup.

Given proteinuria and low complement, SLE with nephritis was suspected. Rheumatology was consulted because she met criteria for SLE (Table 2).[5,6] She was started on hydroxychloroquine at 400 mg daily and prednisone at 60 mg daily and referred to nephrology because of possible lupus nephritis. Renal biopsy was recommended, which revealed focal proliferative lupus nephritis, World Health Organization class III[7] (Fig. 1). She was started on pulse intravenous methylprednisolone for 3 days and mycophenolate as a maintenance therapy. Her pregnancy was electively terminated before starting therapy because mycophenolate is teratogenic and because of the increased risk for poor pregnancy outcomes associated with active SLE.[4,8] Subsequent C4 level was normal and C3 level had improved to 69 mg/dL (normal, 83–240 mg/dL).

DISCUSSION

Angioedema can be categorized as either mast cell mediated or kinin mediated.[9] Mast cell–mediated angioedema is more common and typically associated with urticaria and an antigen-specific trigger. In contrast, kinin-mediated angioedema is characterized by angioedema without urticaria and often occurs in the absence of an identifiable trigger.

The best described kinin-mediated angioedema is HAE, caused by a deficiency of the inhibitor of the C1 component of complement (C1-INH). C1-INH is a serine protease inhibitor (serpin) required for termination of classic complement pathway activation (Fig. 2). HAE presents as unprovoked angioedema, although minor trauma, pregnancy, and infections may trigger events.[10] C1-INH deficiency causes complement activation, which stimulates vascular permeability *via* the kallikrein-bradykinin pathway.[1] Traditionally, two types of HAE have been described: a quantitative deficiency of C1-INH and a functional deficiency.[1] A third form of HAE, predominantly affecting women, exists and appears to be unrelated to CI-INH abnormalities.[11] Although this form of HAE is familial, both C1-INH level and function are normal. However, some patients have a gain-of-function mutation in the factor XII gene, leading to enhanced production of bradykinin.[1]

Acquired angioedema (AAE) is another type of kinin-mediated angioedema.[1,9,12–14] Unlike HAE, CI-INH synthesis is normal, and AAE likely results from increased catabolism of CI-INH. AAE is associated with increased catabolism of C1-INH (paraneoplastic type) or the presence of autoantibodies against CI-INH (autoimmune type).[12] Onset in adulthood, lack of a family history, and low levels of C1q help to differentiate AAE from HAE.

The association of SLE and angioedema has been reported.[14–16] Early complement components, includ-

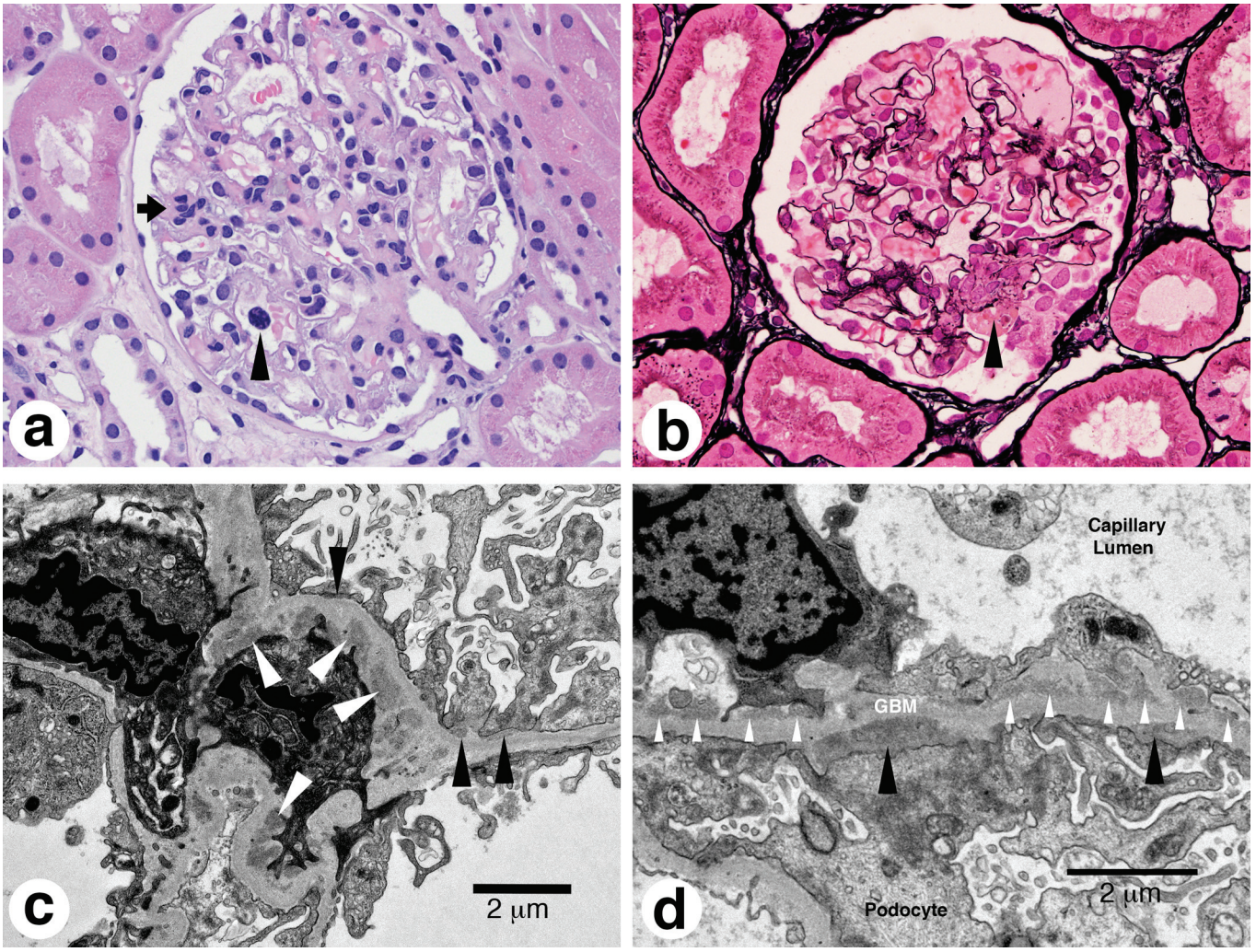

Figure 1. *Light and electron micrographs from the renal biopsy specimen. (a) Renal glomerulus and adjacent tubules from an H&E stained tissue section. The glomerulus has segmental mesangial hypercellularity (small arrow). An LE cell, evident in the capillary lumen (arrowhead), represents phagocytosis of apoptotic nuclear debris, thought specific for systemic lupus erythematosus. (b) Methenamine silver-stained glomerulus with segmental destruction of the glomerular basement membrane (arrowhead) with fibrin exudation and incipient crescent formation. (c) Electron micrograph of the glomerular mesangium with prominent mesangial electron dense deposits (white arrowheads) and occasional subepithelial electron dense deposits (black arrowheads). (d) Electron micrograph of a glomerular capillary loop showing subendothelial (white arrowheads) and subepithelial (black arrowheads) electron dense deposits. Direct immunofluorescence studies (not shown) indicated "full house" staining with granular capillary loop and mesangial deposits of IgG, IgA, IgM, C1q, C4 and C3. Together these pathogical findings are consistent with focal proliferative lupus nephritis.*

ing C1q, C2, and C4, bind apoptotic cells and participate in the removal of apoptotic debris. Congenital deficiency of these early complement components can lead to persistence of apoptotic debris, development of autoantibodies, and subsequent development of SLE.[17] SLE occurs in ~2% of patients with HAE because the congenital CI-INH deficiency leads to persistence of apoptotic debris and the development of autoantibodies.[9,18] Patients with congenital early complement deficiency can also present with recurrent bacterial infections including sinopulmonary disease, sepsis, and meningitis due to compromised opsonization and impaired B cell costimulation.[17] Because she had no history of recurrent infections, a congenital complement deficiency is unlikely in our patient.

SLE occurring in AAE has also been reported.[9,14,18] The mechanism associating AAE and SLE is not well understood but SLE may influence spontaneous consumption of C2 and C4.[14] An SLE-related autoantibody directed against CI-INH is also possible leading to C1-INH inactivation and subsequent unregulated complement consumption.[13] In such cases CI-INH function is usually, but not always, low and therefore our patient's normal CI-INH function does not exclude AAE.[10,19] Testing for the presence of anti–CI-INH antibodies was not performed. Acute angioedema or

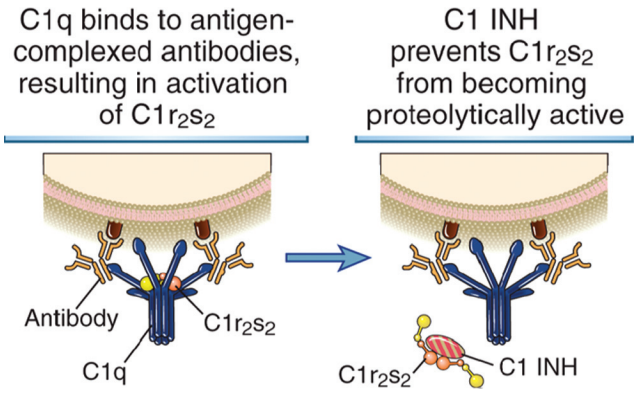

Figure 2. Regulation of C1 activity by C1 INH. C1 INH displaces C1r2s2 from C1q and terminates classical pathway activation. Souce: With permission from reference 24.

HAE is associated with depletion of C4. C4 is less abundant than other complement proteins and can be easily depleted. However, C3 is, in particular, abundant, and depletion of C3 generally rules in a renal source of complement and other protein loss, with high suspicion for a rheumatologic cause.[20]

Finally, it is possible that her edema was secondary to hypoproteinemia from lupus nephritis. In addition to new-onset facial edema, she experienced 2 weeks of peripheral edema attributed to her pregnancy. Although peripheral edema occurs in 80% of normal pregnancies, it is rare in the first trimester.[21] It is most likely that her edema was caused by reduced oncotic pressure secondary to renal protein loss.

Making the diagnosis of SLE was critical, given her pregnancy. SLE increases the risk of multiple maternal and fetal complications during pregnancy, including hypertension, preeclampsia, prematurity, intrauterine growth restriction, fetal loss, low birth weight, and neonatal lupus.[4,22,23] Pregnancy outcomes in SLE are better if conception is delayed until the disease has been inactive for at least 6 months, and the medication regimen has been adjusted in advance.[4,8] Active lupus nephritis at the time of conception poses the greatest risk for disease flares and poor obstetric outcomes.[4]

Final Diagnosis

The final diagnosis was SLE with lupus nephritis.

CONCLUSIONS

Allergists are frequently consulted for evaluation and management of angioedema. History and laboratory findings can help differentiate a primary cause of angioedema from a secondary cause, such as autoimmune disease. Our patient presented with oral angioedema, but also with recent onset of arthralgia, joint swelling, and nonpitting peripheral edema. Although the initial workup before consultation was directed at anaphylaxis, anaphylaxis was quickly ruled out and angioedema secondary to an autoimmune condition considered, with SLE and lupus nephritis ultimately diagnosed. It is important that autoimmune causes of angioedema be considered because they can a have profound impact on patients, particularly during pregnancy. Both the baby and the mother would have unknowingly been at increased risk for a poor outcome.

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Patient Oriented Problem Solving (POPS) Case Report

A 60-year-old woman with recurrent episodes of flushing, urticaria, and angioedema

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ABSTRACT

Recurrent episodes of flushing, urticaria, and angioedema raise suspicion for many conditions with a wide differential diagnosis. The diagnostic approach involves consideration of allergic, cardiovascular, gastrointestinal, endocrine, infectious, neurologic, dermatologic, and drug-related causes. We describe a unique case of recurrent episodes of flushing, urticaria, and angioedema that has gone into remission after a novel therapeutic intervention.

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A 60 year-old woman with recurrent episodes of flushing, urticaria, and angioedema presented to the allergy clinic for follow-up after an emergency department (ED) visit for "total body flushing" about an hour after eating wheat crackers, cheddar cheese, and decaffeinated tea. She had previously presented to a local ED with "flushing" involving her arms, legs, torso, neck, and face. She denied gastrointestinal symptoms at that time, but she reported previous similar episodes that were associated with abdominal discomfort and diarrhea. In the ED, she was treated with epinephrine, diphenhydramine, and steroids with resolution of her symptoms.

Her medical history included asthma, fibromyalgia, osteoarthritis, migraine headaches, hypothyroidism, and hyperlipidemia. Her medications included albuterol as needed, sumatriptan, fexofenadine, levothyroxine, and fluoxetine. Her allergy history included hives when exposed to tetracycline, gastrointestinal upset, and a syncopal episode when exposed to smells of eggs and popcorn and local swelling to stinging insects.

PHYSICAL EXAMINATION

She was a comfortable-appearing woman. Her vital signs were temperature 36.7°C, heart rate 68 beats per minute, blood pressure 120/72 mm Hg, and respiratory rate 16 breaths per minute. Head, eyes, ears, nose, and throat exam was unremarkable. Lungs were clear to auscultation bilaterally. Cardiac exam revealed a regular rate with no murmurs. Skin exam revealed no flushing, urticaria, angioedema, eczema rashes, dermatographism, or urticaria pigmentosa lesions. The remainder of the physical examination was unremarkable.

INITIAL LABORATORY FINDINGS

Laboratory studies had shown normal complete blood count and differential, mildly elevated transaminases attributed to hepatic steatosis, and normal thyroid stimulating hormone. Immunoglobulin E (IgE) Radioallergosorbent testing of suspected allergens included egg white, egg yolk, ovalbumin, ovomucoid, honey bee venom, yellow jacket wasp venom, paper wasp venom, white face hornet venom, yellow face hornet venom, and corn were less than 0.35 kU/L (reference range, less than 0.70 kU/L). Total IgE level was 54 kU/L (reference range, 0–150 kU/L).

QUESTION 1

What is the differential diagnosis of this patient's episodes of flushing, urticaria, and angioedema?

1) IgE-mediated allergies to foods, drugs, and a variety of other allergens
2) Hereditary angioedema
3) Mastocytosis
4) Monoclonal mast cell activation syndrome (MCAS)
5) Idiopathic MCAS
6) Idiopathic chronic urticaria, angioedema, or anaphylaxis
7) Carcinoid syndrome
8) Pheochromocytoma

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Table 1. **Two recently proposed criteria for the diagnosis of mast call activation**

First criterion
1) Typical clinical symptoms: flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, hypotension, or diarrhea
2) Increase in serum total tryptase by at least 20% above baseline plus 2 ng/mL during or within four hours after a symptomatic period
3) Response of clinical symptoms to histamine receptor blockers or mast cell targeting agents, *e.g.*, cromolyn

Second criterion

Major criteria
1) Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (*e.g.*, gastrointestinal tract biopsies; CD 117, tryptase, and CD25 stained)
2) Unique constellation of clinical complaints as a result of pathologically increased mast cell activity (mast cell mediator syndrome)

Minor criteria
1) Mast cells in bone marrow or other extracutaneous organ(s) showing an abnormal morphology (>25%) in bone marrow smears or histologies
2) Mast cells in bone marrow express CD2 and/or CD25
3) Detection of genetic changes in mast cells from blood, bone marrow, or extracutaneous organs, for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved
4) Evidence of a pathologically increased release of mast cell mediators by determination of the content of
   1) Tryptase in blood
   2) N-methylhistamine in urine
   3) Heparin in blood
   4) Chromogranin A in blood
   5) Other mast cell-specific mediators (*e.g.*, leukotrienes, prostaglandin D_2)

Source for first criterion, Ref. 2; source for second criterion, Ref. 8. The diagnosis of mast cell activation syndrome is made if both major criteria or the second criterion and at least one minor criterion are fulfilled.

QUESTION 2

What additional investigations might be useful?
1) Skin-prick testing to suspected allergens
2) Food challenges of suspected allergens
3) Tryptase during an episode
4) Baseline tryptase
5) Bone marrow biopsy
6) Complement component 4 (C4) and C1 inhibitor levels
7) Urine 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin
8) Urine vanillylmandelic acid/metanephrines
9) Platelet activating factor
10) C-kit D816V mutation, which is the resulting substitution of aspartate (D) to valine (V) at position 816 in the kinase domain that leads to autoactivation of the KIT receptor tyrosine kinase.
11) Twenty-four-hour urine collection for N-methylhistamine or prostaglandin-D2 or its metabolite 11β-prostaglandin F2α

DISCUSSION OF THE DIFFERENTIAL DIAGNOSIS

She then underwent skin testing to corn, egg, stinging insects, and annatto, which was negative with appropriate controls. She had denied graded food challenges, but she reported challenging herself with eggs without incident. Baseline serum tryptase level was 20.6 ng/mL (reference range, less than 11.5 ng/mL). Repeat tryptase level one month later was 17.9 ng/mL.

Additional diagnoses, such as carcinoid syndrome, pheochromocytoma, and hereditary angioedema, were less likely with negative urine 5-HIAA level, negative urinary catecholamines, and negative C4 and C1 inhibitor functional assays respectively. Due to her symptoms in the setting of elevated serum tryptase at the time of the events, she was referred for bone marrow biopsy for work-up of mastocytosis. The bone marrow biopsy showed 0.001% mast cells that were negative for cluster of differentiation 2 (CD2)/CD25 coexpression or the KIT D816V mutation. MCAS was favored as the diagnosis.

CLINICAL COURSE CONTINUED

Our patient was treated with cetirizine 10 mg nightly and given an epinephrine autoinjector with an anaphylaxis action plan. She was instructed to avoid mast cell activators and any substances that disagreed with her. She continued to have similar episodes approximately two to three times per year. She had an episode at work after preparing her usual tea and granola without any

other previous ingestions or exposure to smells. Within minutes, she experienced abdominal discomfort, diarrhea, flushing, hives, and swelling of her hands, neck, lips, cheeks, and ankles. She felt like she was going to lose consciousness but did not. She was given epinephrine and diphenydramine at work and was taken to the ED by emergency medical services. Her vital signs on presentation were unremarkable. She ultimately received three doses of epinephrine, prednisone, and ranitidine. Tryptase level was not drawn at that time. She was discharged on a prednisone taper and ranitidine 150 mg two times daily. Her cetirizine dose was then increased to 20 mg nightly. She again had similar episodes concerning for anaphylaxis, which required similar management in the ED, with tryptase up to 38.3 ng/mL after an episode. These episodes had occurred approximately 12–24 hours after her nightly cetirizine doses. She had also reported periods of constant flushing of her skin and three to five loose bowel movements daily. Montelukast 10 mg daily was then added. Ketotifen or cromolyn were not added. Between episodes her tryptase level remained elevated between 13.2 and 20.9 ng/mL (reference range, less than 11.5 ng/mL). Histamine skin test was also performed and showed a blunting of histamine response on cetirizine. The addition of montelukast had not significantly changed the frequency of her episodes.

Subsequent outpatient work-up also revealed severe vitamin D deficiency with vitamin D,25-hydroxy level of 6 ng/mL (reference range, 25–100 ng/mL). She was treated with ergocalciferol 50,000 IU weekly with repeat vitamin D,25-hydroxy level 47 ng/mL approximately 12 weeks later. She was then decreased to ergocalciferol 50,000 IU every other week. Over the next year, she had not had any episodes of flushing, angioedema, or anaphylactic reactions. At that time, she reported only intermittent erythematous blanching lesions and intermittent self-limited flushing, but she otherwise reported improved diarrhea and no epinephrine use for over a year.

DISCUSSION

Our patient had clinical findings that appeared due to mast cell activation not associated with mastocytosis or an allergic or inflammatory reaction. Symptoms can be mild with headache, fatigue, nausea, or insomnia to symptoms of an immediate type allergic reaction, including urticaria, flushing, abdominal cramping, and diarrhea. More severe cases may present with respiratory symptoms, hypotension, and anaphylaxis.[1]

Mast cell activation disorders are classified into three broad categories, primary, secondary, and idiopathic MCAS. Primary MCASs are due to monoclonal mast cell disorders and include systemic mastocytosis (SM) and monoclonal mast cell activation disorder (only one or two minor World Health Organization criteria for SM fulfilled).[2] When working up primary disorders, recent research has shown many patients with MCAS harbor mutations in KIT other than D816V, which has important implications because current clinically avail-

Table 2. **Differential diagnosis in patients with suspected MCAS**

Cardiovascular
Myocardial infarction
Endocarditis/endomyocarditis
Aortic stenosis with syncope
Pulmonary infarction
Endocrinologic
Acute hypothyroidism
Acute hypoglycemia
Adrenal insufficiency
Hypopituitarism
Gastrointestinal disorders (with diarrhea + dehydration)
Acute inflammatory bowel disease
VIP-secreting tumor (VIPoma)
Acute episodes of Morbus Crohn or colitis ulcerosa
Food intoxication
Infectious diseases
Severe bacterial or viral infections ± septic shock
Acute gastrointestinal infection with dehydration
Acute encephalitis/meningitis
Acute parasitic diseases (*e.g.*, acute Chagas disease)
Neurologic/CNS disorders
Epilepsy
CNS tumors
Other CNS diseases
Intoxication
Psychiatric conditions
Skin diseases
Hereditary or acquired angioedema
Pemphigus vulgaris
Acute lupus erythematodes
Acute toxic dermatoses
Hematologic malignancies
Acute leukemia
Myelodysplastic and myeloproliferative disorders
Myeloma
Hodgkin and non-Hodgkin lymphomas
Hematologic, acute anemia ± hypovolemic shock
Acute gastrointestinal bleeding
Massive hypermenorrhea
Drug-induced side effects
Drug-induced hypoglycemia
Drug-induced hypotension
Drug-induced diarrhea
Drug-induced CNS damage

MCAS = mast cell activation syndrome; CNS = central nervous system. Source Refs. 1 and 12.

able testing for mast cell clonality related to KIT alterations is limited to probing by polymerase chain reaction for only the specific KIT-D816V mutation.[3] In mastocytosis, mast cell aggregates may be distributed in a patchy fashion, and a single bone marrow biopsy may fail to show findings of SM in about one-sixth of cases.[4]

Secondary MCASs are due to conditions that produce the symptoms and signs of mast cell activation and include allergic disorders, physical urticarias, and chronic autoimmune urticaria.[5] When investigation for primary or secondary MCAS does not reveal an underlying cause of suspected MCAS, the diagnosis of idiopathic MCAS is made.[2,5] Idiopathic urticaria, angioedema and anaphylaxis are associated variants of mast cell activation disease and must be supported by objective physical findings and tryptase levels for idiopathic anaphylaxis when possible.[6] Idiopathic MCAS is diagnosed per specific criteria when criteria for idiopathic anaphylaxis are not met. Two recently proposed criteria for MCAS are presented in Table 1. When idiopathic MCAS is suspected, it is important to consider a broad differential diagnosis that may cause similar symptoms as presented in Table 2.

Treatment options are directed toward mast cell mediators. Options include histamine I and II blockers (*i.e.*, diphenhydramine, cetirizine, loratadine, and ranitidine), leukotriene receptor antagonists (*i.e.*, montelukast), and mast cell membrane-stabilizing medications (*i.e.*, cromolyn sodium) and avoiding triggers.[7,8] The general approach involves adding medications sequentially. Signs of improvement in symptoms with any specific therapy may be seen within four weeks.[8] Specifically with respect to our case, it is possible that more frequent dosing of histamine type 1 (H1) blockers, combined H1/H2 receptor blockade, or more frequent dosing of montelukast could have led to improved control of her symptoms.

In patients with suboptimal responses to standard therapies, it is important to consider additional factors. Recent literature has shown that vitamin D and its metabolites may affect mast cell activation. Yip *et al.* performed studies that showed vitamin D3 metabolites suppressed IgE-induced mast cell mediators *in vitro* and reduced IgE-mediated passive cutaneous anaphylaxis reactions *in vivo*.[9] Studies in chronic urticaria patients have shown trends toward lower urticaria symptom severity scores when high dose vitamin D3 was used as add-on therapy to antihistamines and leukotriene receptor antagonists.[10] Additionally, studies in children from birth to age four years old showed higher epinephrine prescription rates and anaphylaxis admissions in southern Australia compared with Northern Australia implicating the potential role of less sunlight exposure and vitamin D deficiency as contributors to anaphylaxis.[11]

FINAL DIAGNOSIS

Monoclonal mast cell activation syndrome (MCAS) exacerbated by vitamin D deficiency.

CONCLUSION

Idiopathic MCAS is becoming an increasingly recognized condition. One must consider a broad differential and exclude primary or secondary causes of mast cell activation disorders before the diagnosis is made. Recent studies have suggested vitamin D may play a role in suppression of mast cell activation and have an immunomodulatory effect. With MCAS, one may consider vitamin D deficiency when patients' symptoms continue despite traditional therapies targeting mast cell mediator release.

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Patient Oriented Problem Solving (POPS) Case Report

A 15-year-old boy with severe combined immunodeficiency, fungal infection, and weight gain

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) outcomes in X-linked severe combined immune deficiency are most effective when performed with patients <3 months of age and without coexisting morbidity, and with donor cells from a matched sibling. Even under such favorable circumstances, outcomes can be suboptimal, and full cellular engraftment may not be complete, which results in poor B or natural killer cell function. Protein losing enteropathies can accompany persistent immune deficiency disorders with resultant low serum globulins (immunoglobulin A [IgA], IgG, IgM) and lymphopenia. Patients with immune disorders acquire infections that can be predicted by their immune dysfunction. Fungal infections are typically noted in neutropenic (congenital or acquired) and T-cell deficient individuals. Coexisting fungal infections are rare, even in hosts who are immunocompromised, and they require careful evaluation. Antifungal treatment may result in drug-drug interactions with significant complications.

(Allergy Asthma Proc 36:407–411, 2015; doi: 10.2500/aap.2015.36.3876)

Chief Complaint

A 15-year-old boy with a history of severe combined immune deficiency (SCID) presented with increased weight gain, cough, and headache. He received hematopoietic stem cell transplantation (HSCT) on the 22nd day of life.

History of Present Illness

The patient had cough, headache, and weight gain over 3 weeks. He had been hospitalized for 8 weeks with disseminated histoplasmosis that involved his lungs, maxillary sinuses, and right optic disk. At presentation, therapy included itraconazole (400 mg/day) and outpatient medications for bronchiectasis, protein-losing enteropathy (PLE), and hypogammaglobulinemia. He reported facial swelling, rapid weight gain, and cough with discolored sputum. A review of systems was otherwise normal. Results of a history revealed SCID diagnosis (interleukin 2 common gamma chain receptor defect) at birth and HSCT in infancy, with good T cell but poor B- and natural killer (NK) cell engraftment. Chimerism studies showed T cells 100% donor in origin but B cells 100% host. Despite intravenous immunoglobulin replacement, he had recurrent pulmonary infections, which resulted in bronchiectasis, and he received inhaled fluticasone-salmeterol. Intestinal biopsy documented PLE associated with leukopenia, poor growth, and hypogammaglobulinemia. At 10 years of age, he was begun on low-dose oral budesonide (highest dose, 6 mg on alternate days) and subcutaneous immunoglobulin replacement with improvement of trough immunoglobulin G (IgG) levels at >700 mg/dL (Fig. 1).

Physical Examination

Vital signs were blood pressure, 111/72 mm Hg; heart rate, 96 beats per minute; respiratory rate, 24 breaths per minute; temperature, 99.4°F. Weight was 51.8 kg (23rd percentile), with a 7-kg increase over 8 weeks. Positive physical findings included hairline flat warts and new thoracic and extremity lesions. Lung auscultation revealed bilateral basal rales without wheezing.

Laboratory Results and Clinical Course

The white blood cell count was 7500 cells/mm^3, hemoglobin level was 13.9 g/dL, and the platelet count was 168,000 cells/mm^3. His lymphocyte and neutrophil counts were 1100 and 5700 cells/mm^3, respectively. Lymphocyte phenotyping studies showed de-

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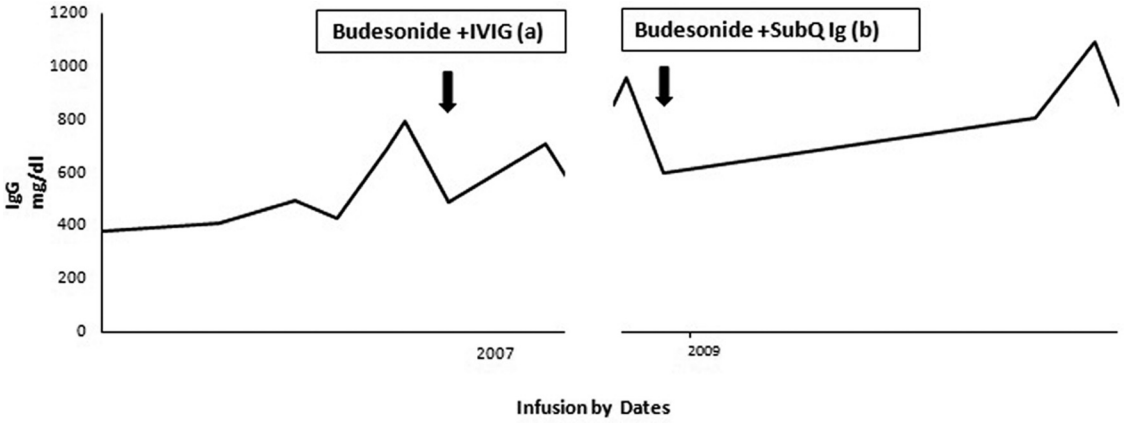

Figure 1. *Trough IgG levels after PLE treatment with budesonide and intravenous immunoglobulin (a) and then budesonide and subcutaneous immunoglobulin (SubQ Ig) (b).*

pressed CD4 count and absent NK cells (Table 1). There was no evidence of serum protein loss or of hepatic or renal dysfunction. The trough IgG level was 1010 mg/dL, and the serum cortisol level was consistent with adrenal suppression. Computed tomography of the chest showed new multiple tree-in-bud opacities in the bilateral lower lobes and no change in sinus disease (Fig. 2*A*). Sputum culture was negative for bacteria, mycobacteria, viruses, and other pathogens but positive for septated hyphae.

Question 1

What is the differential diagnosis for fungal lung disease in primary immunodeficiency disorders (PIDD)?

(a) *Histoplasma capsulatum*
(b) *Candida* species
(c) *Aspergillus fumigatus*
(d) *Cryptococcus neoformans*
(e) Other

Differential Diagnosis

Sputum microscopy with fungal elements and elevated serum fungitell levels were consistent with *H. capsulatum* recurrence (Fig. 2 *B*). Examinations of urine and blood for histoplasma antigen, blood culture, and results of repeated ocular examinations were negative. Serum galactomannan and serum cryptococcal antigen results were also negative. A new pathogen, *Hormographiella aspergillata,* was isolated from sputum (Fig. 2 *C*).

Question 2

What further studies would one consider at this point?

(a) Total protein, albumin level
(b) Alanine transaminase, Aspartate aminotransferase level
(c) Free Thyroxine, Thyroid stimulating hormone level
(d) Brain imaging (magnetic resonance imaging)
(e) Serum cortisol level
(f) Serum synthetic cortisol level

The patient was below the 10th percentile for weight before admission and had received budesonide for 5 years. He developed increased weight gain after *H. capsulatum* treatment. Excess fat accumulates with weight gain when total energy intake exceeds expenditure. There was no evidence of dietary or activity change to suggest energy imbalance. Our patient, with known PIDD mutation, had no findings to indicate another genetic disorder (*e.g.,* Prader Willi syndrome, Down syndrome). No clinical evidence of ascites, hepatic disease, or renal insufficiency was noted, and liver function and renal function studies were normal (Table 1). There was no evidence of hypothyroidism, growth hormone deficiency, hypothalamic, or pituitary lesion (data not shown: normal glucose, free Thyroxine, thyroid stimulating hormone, magnetic resonance imaging of the brain, normal height). Low serum cortisol level excluded the primary adrenal hypercortisolism as a cause of Cushing syndrome. Budesonide dosing was unchanged, but adrenocorticotropic hormone stimulation test showed depressed adrenal response.

DISCUSSION

SCID-causing genetic defects disrupt numerous cellular processes, including (a) signaling pathways; (b) DNA repair mechanisms crucial for V(D)J recombination, which results in impaired T- and B-cell development; and (c) metabolic pathways that cause lymphocyte apoptosis.[1,2] In our patient, the SCID diagnosis was made at birth with a family history of affected male family members. Despite early HSCT, neither NK nor B-cell reconstitution was achieved. He demonstrated good T-cell reconstitution but later developed

Table 1 **Clinical laboratory results**

Laboratory Study	Results	Reference Range
WBC	7.5×10^3/UL	$4.5–13.5 \times 10^3$/UL
Hgb	13.9 g/dL	12.6–17.7 g/dL
Hct	43.6%	37.5–51.0%
Platelet	168×10^3/UL	$150–450 \times 10^3$/UL
Neutrophils (ANC)	5.7×10^3/UL	$1.4–7.0 \times 10^3$/UL
Lymphocytes (ALC)	1.1×10^3/UL	$0.7–3.1 \times 10^3$/UL
Eosinophils (AEC)	0 cells/mm^3	$0.0–0.4 \times 10^3$/UL
CD 3^+	611 cells/mm^3	1014–2557 cells/mm^3
CD 4^+	208 cells/mm^3	538–1569 cells/mm^3
CD 8^+	410 cells/mm^3	371–936 cells/mm^3
CD 3^- - CD $16^+/56^+$	0 cells/mm^3	152–595 cells/mm^3
CD 20^+	162 cells/mm^3	59–457 cells/mm^3
CD 19^+	155 cells/mm^3	204–703 cells/mm^3
Total protein	6.7 g/dL	6–8 g/dL
Albumin	4.2 g/dL	3.5–5.5 g/dL
BUN	18 mg/dL	5–18 mg/dL
Creatinine	0.56 mg/dL	0.12–1.06 mg/dL
ALT	63 IU/L	0–30 IU/L
AST	57 IU/L	0–40 IU/L
IgG	1010 mg/dL	641–1353 mg/dL
Serum cortisol level	0.1 μg/dL	2.3–19.4 μg/dL
Sputum culture for bacteria	Negative	
Sputum culture for mycobacteria	Negative	
Sputum viral PCR (EBV, CMV, adenovirus, RSV)	Negative	
Sputum culture for fungus	Septate hyphae (+)	
Aspergillus galactomannan	Negative	
Serum cryptococcal antigen	Negative	
Urine histoplasma antigen	Negative	
Fungitell	>500 pg/mL	<60 pg/mL
CRP	3.7 mg/L	0.0–4.9 mg/L

AEC = absolute eosinophil count; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; CRP = C-reactive protein; EBV = Epstein-Barr virus; Hct = hematocrit; Hgb = hemoglobin; PCR = polymerase chain reaction; RSV = human respiratory syncytial virus.

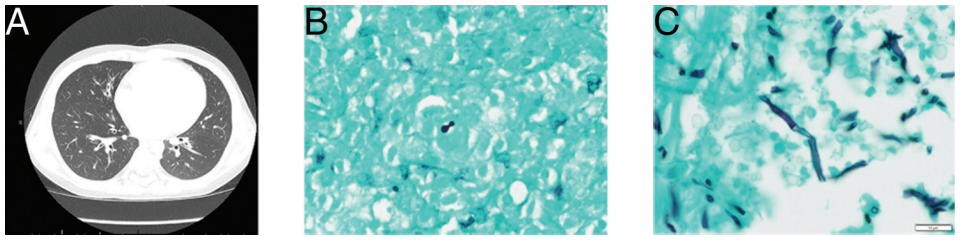

Figure 2. *Computed tomography of the chest. (A) "Tree-in-bud" findings with fungal infection and photomicrographs of H. capsulatum (with Silver methenamine stains [×60]) (B), and septated hyphae as could be seen in H. aspergillata (with GMS [Gomori methenamine silver] stain [×1000]) (C).*

PLE, which resulted in reduced serum concentrations of albumin, serum globulins (IgA, IgG, IgM), lymphopenia, and chronic sinopulmonary disease.

At 8 years of age, he developed human papillomavirus-associated flat warts on his face and trunk. Host defense against HPV relies on intact and functioning cellular immunity, including T- and NK-cell cytotoxicity. Our patient did not have other infections, such as Epstein-Barr virus, Herpes simplex virus, or cytomegalovirus, associated with his NK-cell deficiency.[3,4] Infection susceptibility in PIDD is often predicted by the nature of the immune defect.[5] Pulmonary infections

Table 2 **Drug interactions with steroids**

Drugs	Mechanism of Action	Adverse Effect
Amphotericin B	Steroids increase the hypokalemic effect of amphotericin B	Hypokalemia
CYP3A4 inhibitors		
Azoles: itraconazole, ketoconazole, posaconazole, voriconazole; clarithromycin, ritonavir, telaprevir, chloramphenicol	Inhibition of steroid metabolism	Increased steroid effect, Cushing syndrome
CYP3A4 inducers		
Carbamazepine, fosphenytoin, nevirapine, rifampin)	Increase in steroid metabolism	Decreased steroid effect

CYP3A4 = Cytochrome P450 3A4.
Glucocorticoids undergo metabolism in the liver and other tissues by CYP3A4 and other transformations; medications that strongly inhibit or induce CYP3A4 may significantly alter the glucocorticoid serum concentration.

with pyogenic bacteria occur frequently in antibody deficiency disorders. After switching to subcutaneous immunoglobulin replacement, serum immunoglobulin levels stabilized but the frequency of sinus infections persisted, likely due to his absent serum IgA. Fungal infections are more commonly seen in T-cell and neutrophil defects. Our patient's risks for fungal infection included hypogammaglobulinemia and lymphopenia but not neutropenia.

Invasive aspergillosis is the most common cause of mortality due to major invasive mycoses. *A. fumigatus* is the most frequently isolated pathogen in pulmonary disease with reports in chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion deficiencies, idiopathic CD4 lymphocytopenia, and Good syndrome.[5–7] Histopathology demonstrated narrow septated hyphae with dichotomous acute angle branching. A definitive diagnosis requires organism isolation (blood or tissue). A positive serum galactomannan can predict invasive disease with 90% sensitivity and 98% specificity.

Candida species are another important cause of fungal infection in patients who are immunocompromised. *Candida* species predominantly presents with yeast morphology. Most species produce pseudohyphae but *Candida albicans* and *Candida dubliniensis* can produce true hyphae. The most-frequent invasive presentation is fungemia but pulmonary and cardiac infections are reported after hematogenous dissemination or showering of septic thrombi. *Candida* infections are reported in hyper-IgE syndrome, SCID, major histocompatibility complex II deficiency, X-linked ectodermal dysplasia, myeloperoxidase deficiency, and severe congenital neutropenia.[5,6]

Cryptococcus neoformans is a round, encapsulated basidiomycete. The most common clinical presentation of cryptococcal infection is meningoencephalitis, followed in incidence by pulmonary infection. Sputum culture has low sensitivity, and definitive diagnosis requires tissue examination and culture. Serum cryptococcal antigen is typically nondetectable in isolated organ disease. Cryptococcal infections are reported in idiopathic CD4 lymphocytopenia, hyper-IgE syndrome, and Good syndrome with associated white cell aplasia.[5–8]

In our patient, sputum culture revealed septated hyphae and a new pathogen *H. aspergillata* was isolated. The genus *Hormographiella*, first described by Guarro *et al.*,[9] is a member of the basidiomycete genus. Microscopically septated hyaline conodiophores bearing conidiogenous hyphae may be observed.[10] This fungus grows at 37°C, mostly occurring in compost and sewage. It is an uncommon human pathogen (13 reported cases), mostly found in patients with hematologic malignancies and after HSCT, with or without neutropenia.[11,12] Lungs are the primary infection site, followed by skin, eye, and brain. Coinfections of *H. aspergillata* with *Rhizomucor variabilis*[13] and *Aspergillus flavus*[14] are reported. However, coinfection of *H. capsulatum and H. aspergillata* has not been reported. The history of environmental exposure to wet, malodorous, blackened flooring during home remodelling explains exposure risk for this youngster's isolated pathogens.

Weight gain with fungal disease is uncommon. Endocrine causes of obesity and/or weight gain are infrequently identified in children and include growth hormone deficiency, hypothyroidism, pseudohypoparathyroidism, cortisol excess, and acquired hypothalamic lesions. Very low serum cortisol level (Table 1) eliminated adrenal hyperfunction as a cause of weight gain in this patient.

The most common cause of iatrogenic CS in nonendocrine diseases is prescribed oral steroids but injected, topical, and inhaled glucocorticoids have also been associated. Glucocorticoid clearance can be af-

fected by medications (Table 2), with varying clinical effects, and iatrogenic adrenal insufficiency related to azole and budesonide is reported.[15] Azoles are strong inhibitors of cytochrome-P450–dependent CYP3A4, which is involved in budesonide metabolism. In our patient, it is likely that budesonide metabolism was reduced secondary to combined budesonide-itraconazole therapy, which caused iatrogenic CS. Analysis of the data indicates that increased synthetic glucocorticoid levels resulted in further immune suppression and *H. aspergillata* growth and weight gain. Adrenocorticotropic hormone stimulation testing was performed to evaluate adrenal function and supported the diagnosis of iatrogenic CS. Oral budesonide was weaned, with absent synthetic glucocorticoid levels documented. Continued oral azole and inhaled amphotericin B improved his fungal infection. He required a marked increase in subcutaneous immunoglobulin dosing for worsening PLE.

Final Diagnosis

The final diagnosis was azole-budesonide–induced iatrogenic CS with *H. aspergillata* pulmonary infection.

CONCLUSION

Numerous medications have been shown to impact steroid metabolism (Table 2). In PIDD, azole therapy is commonly used as prophylaxis or acute treatment of fungal infections. Initiation of azole therapy in patients who are immune deficient should prompt review of all forms of steroid use. Drug-drug interactions that alter glucocorticoid metabolism can cause iatrogenic CS and significant morbidity. In our patient with interleukin 2 common gamma chain receptor defect SCID and lymphopenia, interactions of azoles with glucocorticoids (oral, topical, inhaled) affected the disease course and response to treatment. Our patient, to date, has survived an almost universally fatal fungal pathogen, *H. aspergillata.*

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POPS Case Report

A 17-month-old patient with severe anemia and respiratory distress

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ABSTRACT

Anemia can be caused by, or be associated with, many clinical conditions, including pulmonary diseases, some of which are rare and can be misdiagnosed. Nontraumatic pulmonary bleeding may be caused by a variety of conditions and results in anemia and pulmonary hemosiderosis, even when it is subtle. The differential diagnosis in such cases is extensive. We present the case of a diagnostic dilemma in a 17-month-old child hospitalized for severe anemia and respiratory distress in which the diagnosis was settled through an allergy/immunology consultation.

(Allergy Asthma Proc 36:506–511, 2015; doi: 10.2500/aap.2015.36.3888)

CASE PRESENTATION

The chief complaint was weakness and reduced activity for 10 days.

History of Present Illness

A 17-month-old African American boy had episodes of emesis and fever, with a temperature to 101°F, with decreased oral intake and decreased urine output. He was initially diagnosed as having viral gastroenteritis and was treated with fluids and acetaminophen. Within a few days, he started to show difficulty in breathing and progressively decreased activity for 10 days. Initial evaluation at a local hospital emergency department revealed severe anemia (hemoglobin level, 2 g/dL; hematocrit value, 6%); and metabolic acidosis (pH 7.23). Immediate management consisted of intravenous (IV) normal saline solution 10 mL/kg bolus, IV ceftriaxone 50 mg/kg after obtaining blood cultures, and he was transferred to our hospital's pediatric intensive care unit.

Results of a physical examination on the patient's arrival showed a weight of 10.5 kg (22nd percentile), height of 80 cm (35th percentile); temperature, 98.3°F; O_2 saturation of 86–88% on room air, respiratory rate of 40 breaths per minute, heart rate of 131 beats per minute, and blood pressure at 86/52 mm Hg. He was very pale, tachypneic, with nasal flaring and intercostal, subcostal, and suprasternal retractions. Chest auscultation revealed bilateral coarse breath sounds and diffuse crepitations on the left side. There was no lymphadenopathy, organomegaly, or skin lesions. No abnormal neurologic findings were noted. His initial arterial blood gases revealed pH of 6.96, carbon dioxide pressure of 34 mm Hg, oxygen pressure of 27 mm Hg, with a base deficit −22.2 mEq/L, and lactate level of 12.6 mmol/L. His white blood cell count was elevated to 19,020 cells/μL with 60% neutrophils and 38% lymphocyte (Table 1). Urinalysis was normal, and his stools showed no visible or occult blood. Chest radiograph showed significant alveolar airspace consolidation and infiltrates throughout the left lung, with an interstitial infiltrate in the right perihilar region (Fig. 1*A*).

Because of impending respiratory failure, assisted ventilation was initiated. Bronchoalveolar lavage (BAL) was blood-tinged, and Prussian blue staining revealed abundant hemosiderin-laden macrophages and fresh red blood cells (Fig. 2). A central line was placed, and the patient received 100 mL of PlasmaLyte bolus and 2 units of packed red blood cells, and ceftriaxone was continued at 500 mg every 24 hours. Iron IV therapy 5 mg/kg every 24 hours was also started. The patient remained afebrile, and assisted ventilation was gradually weaned over 4 days while methylprednisolone IV 4 mg every 6 hours was administered to reduce the laryngeal edema and to facilitate extubation.

Past Medical History

The patient was born full-term by uncomplicated normal vaginal delivery. He was fed cow's milk (CM)

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Table 1 **Sequential hematologic findings in the child**

Finding (reference range)	At First Admission	1 Month Later	At Second Admission	2 Months Later
WBC count, K/mm^3 (6–17 K/mm^3)	19	12.4	7.9	5.23
Hemoglobin level, g/dL (10.5–13.5 g/dL)	2	12.4	6.1	9.3
Hematocrit value, % (33–39%)	6	37.1	19.6	30.3
No. platelets, K/mm^3 (150–350 K/mm^3)	351	345	400	465
No. lymphocytes, K/mm^3 (4–10.5 K/mm^3)	7.2	4.7	3.1	1.7
Lymphocytes, % (35–91.5%)	38	37.6	39.2	32
Neutrophils K/mm^3 (1.5–8.5 K/mm^3)	11.4	5.9	3.8	3.5
Neutrophils, % (13–75%)	60	47.6	48.0	67
RBC, M/mm^3 (3.7–5.3 M/mm^3)	0.9	4.4	2.8	4.8
MCV, fL (70–86 fL)	62.9	85.3	71.4	73.5
MCH, pg (23–31 pg)	16.3	28.4	22.2	19.4
MCHC, g/dL (30–36 g/dL)	25.9	33.3	31.1	30.6
RDW, % (12.3–17.0%)	25.5	16.1	17.2	19.3
Reticulocytes, % (0.2–1.8%)	8	—	5.1	1.3

WBC = white blood cells; RBC = red blood cells; M, millions; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; RDW = red cell distribution width.

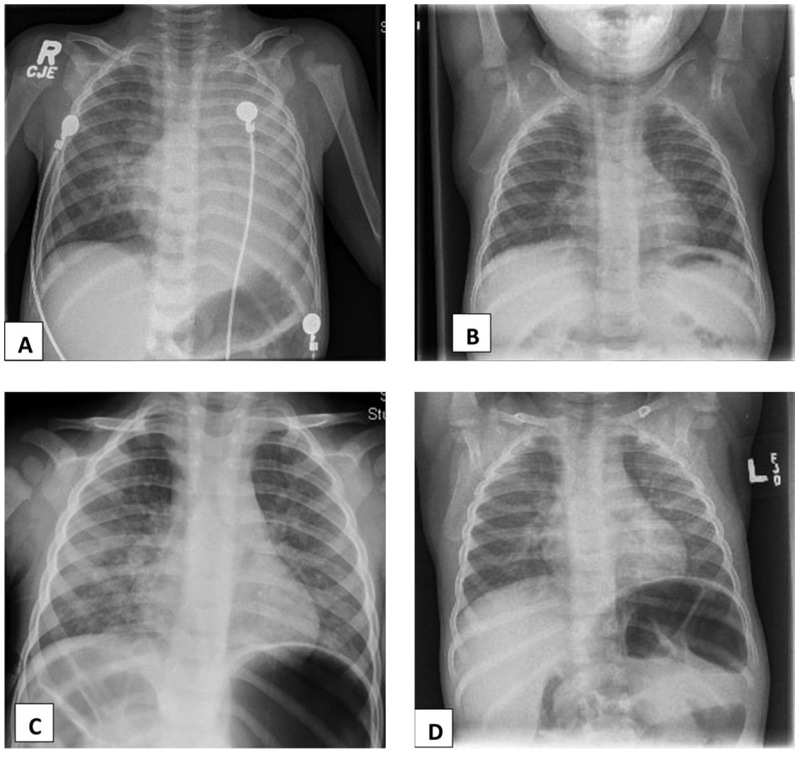

Figure 1. *Sequential chest roentgenographs in relation to cow's milk avoidance. Upper panel, showing alveolar consolidation of the entire left lung with right perihilar infiltrates on initial presentation (A), and a month later while on strict milk elimination, showing significant improvement, with slight perihilar congestion (B). Lower panel, showing bilateral reticular infiltrates after poor compliance with milk elimination for a few weeks (C) and 2 months later, showing significant improvement while on strict milk elimination (D).*

formula from birth, and pasteurized milk was introduced at approximately 12 months of age. He had no significant previous illnesses, including infections or allergies.

Family History and Social History

There is a history of allergy in the mother and two siblings. There was no exposure to tuberculosis. The family lives in a rural area with multiple indoor and outdoor cats and dogs. They have city water, and there was no recent travel outside the United States.

WHAT IS THE DIFFERENTIAL DIAGNOSIS?

Our patient presented with generalized weakness after a brief episode of gastroenteritis. He showed no focal neurologic deficit, and his weakness was attributed to severe anemia. He had no gastrointestinal or urinary blood loss. The blood-tinged bronchial secre-

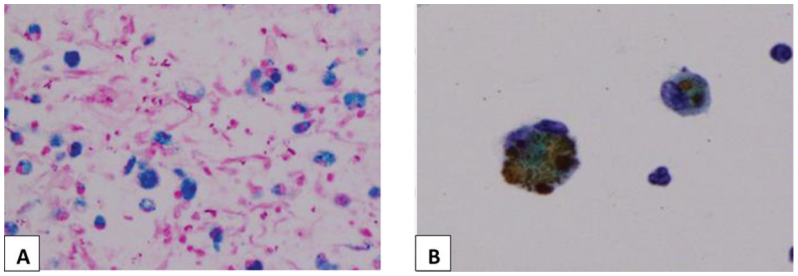

Figure 2. Prussian Blue stain of BAL, demonstrating abundance of fresh red blood cells and iron-laden macrophages (100×) (A), with magnification (B)

Table 2 **Classification of diffuse alveolar hemorrhage syndromes***

Disorders with pulmonary capillaritis
Idiopathic pulmonary capillaritis
Wegener granulomatosis#
Microscopic polyangiitis
Systemic lupus erythematosus
Goodpasture syndrome
Antiphospholipid antibody syndrome
Henoch-Schonlein purpura
IgA nephropathy
Polyarteritis nodosa
Behçet syndrome
Cryoglobulinemia
Drug-induced capillaritis
Idiopathic pulmonary–renal syndrome
Disorders without pulmonary capillaritis
Noncardiovascular causes
Idiopathic pulmonary hemosiderosis
Heiner syndrome
Acute idiopathic pulmonary hemorrhage of infancy
Bone marrow transplantation
Immunodeficiency
Coagulation disorders
Celiac disease
Infanticide
Cardiovascular causes
Mitral stenosis
Pulmonary venoocclusive disease
Arteriovenous malformations
Pulmonary lymphangioleiomyomatosis
Pulmonary hypertension
Pulmonary capillary hemangiomatosis
Chronic heart failure
Vascular thrombosis with infarction

**From Ref. 1. Reproduced with permission from the publisher Wolters Kluwer Health, Inc.*
#Currently known as "granulomatosis with polyangiitis."

tions pointed to a pulmonary origin that was not attributed to the trauma of intubation because of the preexisting pallor and the demonstration of iron-laden macrophages in the BAL. Therefore, our working diagnosis was pulmonary hemosiderosis (PH), which can have a variety of causes (Table 2).

PH is a diffuse alveolar hemorrhage process, which has recently been classified based on the presence or absence of pulmonary capillaritis.[1] Pathologically, it is characterized by an inflammatory disruption of the alveolar interstitium, including the capillary network. Its classic clinical triad consists of pulmonary hemorrhage, anemia, and pulmonary infiltrates. However, not all patients present with all three findings, thus the clinician should maintain a high index of suspicion. Most cases of PH are secondary and can be due to any of diverse underlying conditions (Table 2). In this situation, the clinician should consider the primary disease in the differential diagnosis and evaluate the patient accordingly.

FURTHER EVALUATION

Results of a detailed workup for infectious etiology was negative. His echocardiogram showed only slight tricuspid regurgitation. Results of an autoimmune and inflammatory workup showed normal results for sedimentation rate, C-reactive protein, procalcitonin, rheumatoid factor, antinuclear antibody, double-stranded deoxyribonucleic acid, antistreptolysin O, complement, coagulation tests, phospholipids antibody, antineutrophil cytoplasmic antibody, antiglomerular basement membrane, and celiac disease panel. His immunology evaluation, however, showed low T- and natural killer cell numbers, with a normal B-cell count and no evidence of leukemia or lymphoma (Table 3). The patient was continued on IV methylprednisolone 4 mg every 6 hours for PH. His repeated chest radiographs showed continuous improvement of the central pulmonary vascular congestion and perihilar pulmonary edema and infiltrates.

Because the pulmonary hemorrhage was not due to hematologic, infectious, anatomic, rheumatologic, vasculitic, cardiovascular, or neoplastic disease, primary PH was our principal diagnosis. Primary PH is rare and encompasses Goodpasture syndrome, Heiner syndrome (HS), and idiopathic PH. Goodpasture syndrome is the most common of these entities and is pathologically characterized by antibody to the basement membrane of the alveolus and the glom-

Table 3 **Result of immunodeficiency evaluation of the infant**

Finding	Reference Range	First Admission	1 Month Later
CD19 B cell, count/mm^3	720–2600	1195	1840
CD19 B cell, %	16–35	44.5	43.3
CD3 total T cell, count/mm^3	2100–620	1377	2227
CD3 total T cell, %	53–75	51.3	52.4
CD4 helper T cell, count/mm^3	1300–3400	851	1228
CD4 helper T cell, %	32–51	31.7	28.9
CD8 suppressor T cell, count/mm^3	620–2000	419	778
CD8 suppressor T cell, %	14–30	15.6	18.3
CD4:CD8 ratio	>0.9	2.0:1	1.6:1
CD16/CD56 NK cell, count/mm^3	180–920	56	94
CD16/CD56 NK cell, %	3–15	2.1	2.2
Dihydrorhodamine assay		—	Normal
Serum IgG, mg/dL	700–1600	—	694
Serum IgM, mg/dL	40–230	—	70
Serum IgA, mg/dL	8–220	—	135
Serum IgE, IU/mL	<60.0	—	217.0
Tetanus antitoxin antibody	≥0.1	—	0.24
Pneumococcal antibody titers	≥50% of serotypes protective	—	Protective

NK = natural killer.

Table 4 **Milk-induced chronic pulmonary disease (Heiner syndrome)***

Chronic or recurrent lower respiratory symptoms
Lungs, abnormal radiologic findings: patchy infiltrate, localized atelectasis, consolidation, peribronchial infiltrate, hilar adenopathy, pleural thickening, or reticular density
High titers of IgG antibodies to milk proteins
Complete blood cell count may show eosinophilia or iron deficiency anemia
Pulmonary hemosiderosis in severe cases
Improvement of symptoms within days on cow's milk-free diet, and radiologic clearing of lungs within weeks

**Modified from Ref. 4.*

erulus. It was excluded in our patient by the absence of renal involvement as evidenced by his normal blood pressure, urinalysis, and serum creatinine levels as well as a negative antiglomerular basement membrane. Idiopathic PH is a rare disorder of unknown etiology, with an estimated incidence of 0.24–1.23 cases per million in some selected populations.[2,3] It is essentially a diagnosis of exclusion. Therefore, HS (Table 4)[4] was particularly considered because the infant was fed CM formula from birth and had been ingesting pasteurized whole milk for ~5 months before his illness.

What Should Be the Further Management?

Our patient had an acute presentation of pulmonary hemorrhage and PH, with abnormal T- and natural killer cell counts, which suggested a concomitant immunologic defect.[5] To explore the diagnosis of HS, we recommended a trial of strict avoidance of all CM products. In the meantime, we ordered testing for serum immunoglobulins levels and specific immunoglobulin G (IgG) and IgE antibodies to various CM proteins. We planned to recheck the flow cytometry when the child gets better and is in good clinical condition.

Follow-up

In a follow-up clinic visit 1 month after hospital discharge, the mother reported that the child was doing well without any symptoms. Results of a physical examination was essentially normal. Specifically, he gained weight (350 g), and the lungs were clear to auscultation. A chest radiograph showed normal findings, with complete resolution of the pulmonary infiltrate (Fig. 1 *B*), and complete blood cell count a revealed normalized hemoglobin level of 12.4 g/dL and hematocrit value of 37.1% (Table 1).

Although the total IgE level was elevated (217 IU/mL), his specific IgE level to CM was only slightly elevated (1.42 IU/mL). However, IgG antibody levels to CM proteins were markedly elevated; casein value of 103.0 μg/mL (reference value, <2.0 μg/mL), α-lactalbumin value of 13.9 μg/mL (reference value, <2.0 μg/mL), β-lactalbumin level of 10.5 μg/mL (reference

value, <2.0 μg/mL), and whey level of 50 μg/mL (reference value, <2.0 μg/mL), but normal to bovine gelatin. Immunodeficiency evaluation showed age-appropriate levels of serum IgG, IgM, and IgA, and protective antibody levels against tetanus and pneumococcus. Also, the flow cytometry findings have normalized (Table 3).

The mother was advised to continue strict avoidance of CM products, and an appointment for a follow-up in 1 month was given, but they did not show up. Three months later, the patient became ill, with decreased activity and a poor appetite. His pediatrician discovered recurrence of the anemia, with an hemoglobin level that dropped to 7 g/dL (Table 1). The child was readmitted to our hospital, again with pulmonary infiltrates (Fig. 1 *C*). We found out that, although CM itself was avoided, CM products were reintroduced during the preceding few weeks. We reemphasized the importance of strict avoidance of CM products and regular follow-up in our clinic. After a few days, the patient was discharged in a good general condition. Two months later, the mother reported maintaining strict milk elimination, and the child remained asymptomatic, with normal physical examination, complete blood cell count and chest radiographic findings (Table 1, Fig. 1 *D*).

FINAL DIAGNOSIS

Heiner syndrome with pulmonary hemosiderosis.

DISCUSSION

Milk-induced chronic pulmonary disease was first described by Heiner and Sears[6] in seven children, 6 weeks to 17 months old, who were on CM and who had recurrent pulmonary infiltrates associated with chronic cough, fever, tachypnea, wheezing, rales, failure to thrive, and a family history of allergy. Chest roentgenograms showed shifting patchy infiltrates, frequently associated with areas of atelectasis, consolidation, reticular densities, pleural thickening, or hilar lymphadenopathy. By using the Ouchterlony double-immunodiffusion technique, Heiner and Sears[6] showed that the sera of all seven patients had multiple precipitin lines to CM proteins. Other findings may include chronic rhinitis, recurrent otitis media, gastrointestinal symptoms, and eosinophilia. Four patients had hemoptysis and anemia, in which PH was verified by the demonstration of iron-laden macrophages by using Prussian Blue staining of bronchial aspirates or morning gastric washes. Most symptoms strikingly decreased after a few days or weeks of CM elimination. Unlike patients with IgE-mediated CM allergy, symptoms of HS may not occur until after several days to weeks of CM consumption. Furthermore, the symptoms may last for a long period even after the withdrawal of CM. In addition, in a series by Boat *et al.*,[7] some patients also had lymphoid hypertrophy in the form of hepatosplenomegaly or hypertrophied tonsils or adenoids, and occasionally cardiomegaly or cor pulmonale.

In our previously published series of eight children,[4] the diagnosis was made at 4–29 months of age, but their chronic respiratory symptoms began at age 1–9 months. In addition to high titers of precipitating antibodies to CM proteins, milk elimination resulted in remarkable improvement in symptoms within days and clearing of the pulmonary infiltrate within weeks. Parents consented to milk challenge in only three cases, all of whom developed recurrence of symptoms. PH was confirmed in one patient by demonstrating iron-laden macrophages in the BAL, gastric washing, and open lung biopsy. In our current patient, the finding in the BAL of iron-laden macrophages as well as fresh red blood cells indicated the presence of chronic and ongoing pulmonary bleeding.

Because of the high risk, we did not intentionally challenge our patient to confirm the diagnosis after improvement on milk elimination. However, over time, his parents' vigilance grew lax, and he began consuming milk products again, which triggered recurrence of symptoms. Although HS is more likely to be induced by homogenized CM, the disease also may occur in some infants fed CM-derived formula or other food proteins in older children, *e.g.*, soy, egg, pork, wheat, and peanut (D.C. Heiner, M.D., personal verbal communication, May 2015). Although, the immunologic mechanism that underlies milk-induced pulmonary disease is not clear, it probably involves the formation of immune complexes (Arthus type or Gell and Coombs type III reaction).[8,9] Cell-mediated reaction (Gell and Coombs type IV) may also have a role.[7,10] Often, more than one immunologic mechanism is involved, and perhaps all four types of reactions are involved in certain patients.[8] Characteristically, the patient has high titers of IgG antibodies against bovine milk proteins as determined by the Ouchterlony technique or, more conveniently, enzyme-linked immunosorbent assay. However, the presence of milk-specific IgG antibodies is not pathognomonic of the disease and can be present in low titers in sera of normal subjects who ingest milk and present in high titers in several diseases, such as celiac disease, chronic diarrhea, and cystic fibrosis.[11,12]

Treatment of HS is basically strict avoidance of the causative food. Symptomatic medications may be needed initially and may include corticosteroids. Milk substitutes can be soy-based formula, extensively hydrolyzed protein formula, or synthesized free amino acid formula. The prognosis is generally good, and most patients tolerate the offending food within a few years.

CONCLUSION

HS should be considered in young children with an unexplained chronic lower respiratory symptoms and pulmonary infiltrate, and elevated levels of IgG antibodies to bovine milk proteins in the serum. The presence of hemoptysis or anemia suggests PH. Noting clinical and radiologic improvements after strict milk (or another suspected food) avoidance further supports the diagnosis. The risk of verification by oral challenge should be weighed against the benefit; in some patients, pulmonary bleeding can be severe. Undiagnosed cases are often associated with pulmonary fibrosis and cor pulmonale. Although this syndrome is rare in the general pediatric population, it should be specially suspected in pediatric pulmonary and allergy practices. Insufficient awareness about the disease is probably a major factor in its missed diagnosis, with consequent morbidity and financial burden.

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Erratum

In the article *Analysis of characteristics associated with reinjection of icatibant: Results from the Icatibant Outcome Survey*, Allergy Asthma Proc 36, 399–406, 2015; doi: 10.2500/aap.2015.36.3892, the author corrections were not included. The correct and approved version is online.

The printer regrets the error.

doi: 10.2500/aap.2015.36.1014

Patient Oriented Problem Solving (POPS) Case Report

A 73-year-old woman with persistent diarrhea and onychomycosis

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ABSTRACT

We present a case of a 73-year-old woman who presented with chronic watery diarrhea, weight loss, and frequent sinus and nail fungal infections. Her previous workup with a gastroenterologist failed to reveal any causative agent for her symptoms. She considered herself healthy until a thymic tumor was discovered and removed years ago. Subsequently, she developed multiple sinus infections refractory to treatment. Relevant immunology laboratory tests were conducted, which led to the diagnosis. This case illustrated the need for a detailed history and thorough immunologic assessment, and the requirement to maintain a broad differential diagnosis.

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CASE PRESENTATION

A 73-year-old woman was referred to our clinic for the evaluation of her persistent diarrhea, weight loss, and frequent sinus infections. She considered herself healthy until 1991, when a benign thymus gland tumor was identified and removed. Our patient was later diagnosed with common variable immunodeficiency (CVID), in September of 2005, but she declined treatment with intravenous immunoglobulin. Her infection history was significant for frequent sinus infections treated with ciprofloxacin for 1 year previous to our evaluation, without improvement. The patient underwent two sinus surgeries, in 1995 and 2013. She reported one episode of pneumonia and recurrent nail fungal infections but denied having overwhelming systemic infections or gastrointestinal complications until recently.

Over the past 9 months, our patient began having watery, nonbloody diarrhea associated with a 20-lb (9.1 kg) weight loss but normal appetite and no vomiting or abdominal pain. She was referred to a gastroenterologist but had a negative evaluation for celiac disease. She was treated empirically with ciprofloxacin for 5 days and with fluconazole for 5 days, which initially improved her diarrhea. However, it recurred, and she was started on a second course of ciprofloxacin. She subsequently was referred to our clinic for clarification and management of her CVID. She did not have symptoms of rhinitis at the time of her visit. Apart from CVID, her medical history was significant for postsurgical hypothyroidism and persistent nail fungal infections. Her immunizations were up to date, and she denied any adverse events to her vaccines. She had no family history of immune deficiencies or autoimmune conditions.

Physical Examination

On examination, her vital signs were normal. Her height was 61 inches and weight was 111.4 lb. General evaluation revealed a thin female in no acute distress. She had no oral thrush or lymphadenopathy. Results of a nasal and sinus examination were normal. Results of a neck examination revealed a transverse postthyroidectomy scar. Results of a chest examination revealed an old vertical scar in the mid-chest, previous thymus removal. She had no hepatosplenomegaly. Results of a nail examination were significant for distal subungual onychomycosis of her fingers and toes bilaterally (Figs. 1 and 2). Results of the rest of her examination were unremarkable.

Question 1: What Initial Laboratory Studies Should be Obtained?

Laboratory studies were obtained, and the results are recorded in Tables 1 and 2. Her absolute lymphocyte

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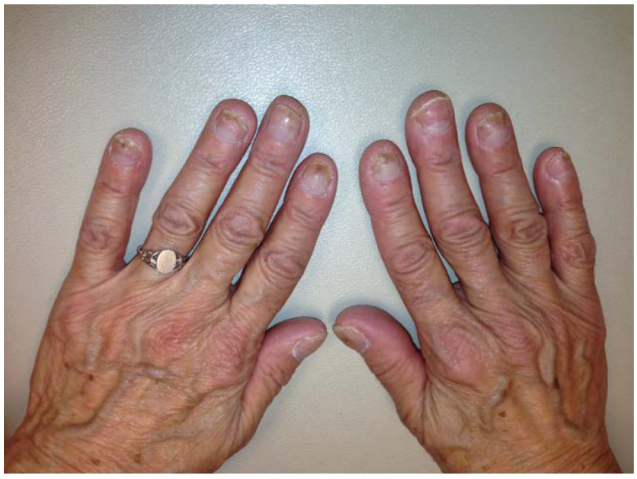

Figure 1. *Distal subungual onychomycosis.*

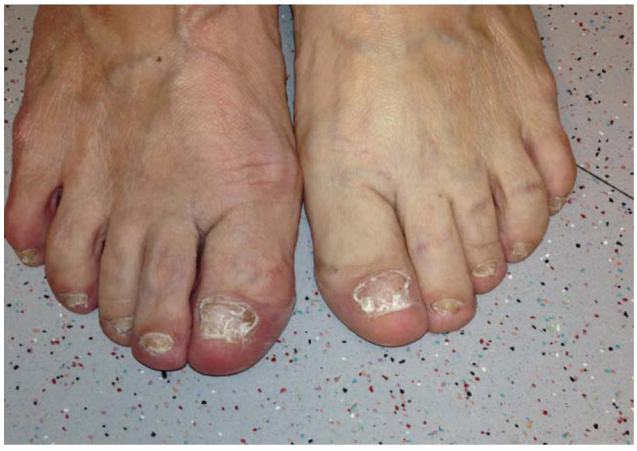

Figure 2. *Distal subungual onychomycosis.*

count was decreased, at 0.6 cells/μL Immunoglobulin (Ig) levels were IgA, <33 mg/dL; IgG, <6.7 mg/dL, and IgM, <4.2 mg/dL. Her CD19 was <1 cells/mm^3 (reference range, 5–20) and absolute B-cell count was <1 cells/mm^3 (reference range, 15–495 cells/mm^3). The absolute T-cell count was 159 cells/mm^3 (reference range, 603-2990 cells/mm^3), absolute T-helper cell count was 58 cells/mm^3 (reference range, 45–1500 cells/mm^3), absolute T cytotoxic cell count 99 cells/mm^3 (reference range, 120–895 cells/mm^3), and CD4/CD8 ratio was 0.59 (reference range, 1–3). Her CD57 was 98 cells/mm^3 (reference range, 95–640 cells/mm^3). Albumin level was normal. Responses to pneumococcal, tetanus, and diphtheria vaccinations were abnormal in the past, and we did not repeat them.

Question 2: What Is the Differential Diagnosis?

a. CVID
b. Good syndrome (GS)
c. Human immunodeficiency virus
d. Secondary immunodeficiency due to diarrhea
e. Severe combined immunodeficiency (SCID)

Question 3: What Additional Diagnostic Studies Would be Helpful in Clarifying the Diagnosis?

The following laboratory studies should be considered: human immunodeficiency virus polymerase chain reaction (PCR), genetic analysis testing, PRC-based testing for celiac disease, *Clostridium difficile* PCR assay, stool for ova and parasite, PCR for *Cryptosporidium, Microsporidium, Isospora, Giardia, Entameba histolytica,* and biopsy of intestinal mucosa. T-and B-cell proliferation studies should also be considered.

Clinical Course

Our patient's immune system evaluation showed normal eosinophil, monocyte, and neutrophil counts; lymphopenia; low absolute counts of B and T cells, with normal natural killer cells; and panhypoimmunoglobulinemia (low IgA, IgG, and IgM levels). The absolute CD4 count was 159 cells/mm^3 (Tables 1 and 2). IgA anti-transglutaminase was negative, but, in light of the IgA level, this was anticipated. Biopsy results were consistent with celiac disease. She improved with a gluten-free diet. Genetic analysis revealed a signal transducer and activator of transcription 3 (*STAT3*) mutation. The patient was started on 20% immunoglobulin therapy, 6 g subcutaneous replacement therapy weekly, and received eight injections. Due to a sulfa drug allergy, she was placed on atovaquone 1500 mg oral daily for *Pneumocystis jiroveci* pneumonia prophylaxis.

DISCUSSION

The differential diagnosis for our case includes CVID, GS, human immunodeficiency virus, SCID, and secondary immune deficiencies. CVID and GS present similarly because patients are at an increased risk for infections.[1] Diarrhea is a common symptom associated with these conditions.[2] It is unlikely for patients with SCID without bone marrow transplantation to survive into their seventies and have years without any significant infections. Our patient did not have any other causes of secondary immune deficiencies, such as HIV or other immunosuppressive states but did have severe diarrhea, which can cause immunodeficiency. Evidence against this is that she had a normal albumin level. The patient was previously diagnosed with CVID, based on her agammaglobulinemia before she was recognized to have a T-cell deficiency and a history of thymoma.

Patients with significant T-cell deficiency have an increased susceptibility toward encapsulated bacterial, viral, and fungal infections.[1,3] Prophylactic antibiotics, depending on the patient's T-cell level and CD4 count, should be initiated to prevent opportunistic infections.[4,5] Before presentation at our facility, our patient's T-cell function was not monitored. Her absolute CD4

Table 1 **Complete blood cell count with differential results of the initial and follow-up evaluations**

Variable	December 2013	September 2013
	Value (reference range)	Value (reference range)
Mature neutrophil, %	80.9 (40–80)	78 (40–80)
Absolute neutrophil count	4.97 (1.7–7.8)	4.26 (1.7–7.8)
Absolute eosinophil count	0.0 (0.0–0.45)	0.0 (0.0–0.45)
Absolute lymphocyte count	0.6 (1.0–4.8)*	0.25 (1.0–4.8)*
Absolute basophil count	0.0 (0.0–0.2)	0.0 (0.0–0.2)
Absolute monocyte count	0.56 (0.0–1.0)	0.89 (0.0–1.0)
Monocyte, %	9.1 (2–10)	16 (2–10)
Eosinophil, %	0.0 (1–6)	0.0 (1–6)
Lymphocyte, %	9.8 (20–40)*	5 (20–40)*
Basophil, %	0.0 (<1–2)	0.0 (<1–2)

**Low.*

Table 2 **Immunoglobulin levels and flow cytometry results at the initial and follow-up evaluations**

Variable	August 2013	2001
	Value (reference range)	Value (reference range)
IgA, mg/dL	<33 (61–356)	19 (61–356)
IgG, mg/dL	<6.7 (767–1590)	251 (767–1590)
IgM, mg/dL	<4.2 (37–286)	<3 (37–286)
CD19	<1 (7–27)	
B cells, absolute count	<1 (107–698)	
CD3	59 (49–84)	
T cells, absolute count	159 (603–2990)	
CD4	22 (28–63)	
T helper, absolute count	58 (441–2156)	
CD8	37 (10–40)	
T cytotoxic, absolute count	99 (125–1312)	
CD4/CD8	0.59 (1.0–3.0)	
CD 57	98 (95–640)	
Natural killer cells, absolute count	37 (4–25)	

count was 154 cells/mm^3 at the initial evaluation, which prompted the need for *P. jiroveci* pneumonia prophylaxis with atovaquone.

The combination of T- and B-cell deficiencies in combination with thymoma is consistent with GS. GS is characterized by the triad of adult-onset immunodeficiency, hypogammaglobulinemia, and thymic hyperplasia. The main findings are hypogammaglobulinemia, low or absent B cells, and variable defects in cell mediated immunity, such as CD4$^+$ T-cell lymphopenia and reduced T-cell mitogen proliferative responses.[3,4]

Thymomas are the most common anterior mediastinal tumor. Symptoms are not specific and include cough, chest pain, dysphagia, dyspnea, and hoarseness. Superior vena cava syndrome and Horner syndrome are possible consequences.[2] GS only occurs in ~10% of patients with a thymoma. The condition typically presents in the fourth or fifth decade of life, and the mean age of recognition of thymoma and hypogammaglobulinemia is 62 years.[6,7] The pathogenesis of GS remains unclear.[8] Recurrent infections are a frequent presentation of GS.[9] Chronic diarrhea has been reported in up to 50% of patients with GS.[9,10] Common findings include anemia (50%), low white blood cell count (55%), thrombocytopenia (20%), neutropenia (18%), and eosinopenia in the blood and bone marrow, and monoclonal gammopathies.[2]

Unique to our patient was the signal transducer and activator of transcription 3 (STAT3) mutation. TACI (transmembrane activator and calcium-modulator and cytophilin ligand interactor) and B-cell activating factor receptor mutations are the most common genetic mutations that have been described in association with GS.[11,12] In addition to the findings discussed above,

our patient had severe onychomycosis. There is an interesting association between onychomycosis infections and *STAT3* mutation. *STAT3* is a transcription factor essential for the differentiation of TH17 helper T cells. Mutation of the *STAT3* gene has been described in association with hyper-IgM syndrome and a variety of autoimmune diseases. Th17 cells produce a series of cytokines, among them interleukin 17 (IL-17) and IL-22, which are thought to play a role in preventing fungal infections.[13] Mucocutaneous candidiasis has been observed associated with anti-IL-17 and anti-IL-22 autoantibodies.[4] There have been positive and negative effects attributed to IL-17 during fungal infections. It has been suggested that, in early stages of infection, IL17 exerts antifungal resistance, but, in later stages, IL17 leads to infection with chronic inflammation.[14] Our patient had a *STAT3* mutation and persistent onychomycosis infections, secondary to the down-regulation of Th17; however, we did not measure her Th17 cell counts and cannot definitively confirm our hypothesis.

In addition to predisposition to infections, patients with GS have evidence of autoimmunity, including myasthenia gravis, pernicious anemia, diabetes mellitus, and thyroid disease.[3] Thymoma resection often alleviates these conditions but does not correct the immunodeficiency.[9,15] Our patient had confirmation of autoimmunity presented as hyperthyroidism. In addition, our patient initially presented with recurrent diarrhea and was diagnosed with celiac disease. Although the initial evaluation was negative, her IgA level was low, which made an IgA evaluation nondiagnostic. Relying on serology and not on PCR-based analysis in patients with hypogammaglobulinemia is a common mistake. Mucosal biopsy confirmed the diagnosis of celiac disease.

There is a variable prognosis for patients with GS. The prognosis in GS is worse compared with CVID. The GS survival rates at 5 and 10 years are 70% and 33%, respectively. By comparison, those with CVID have a 5-year survival rate of ~100% and a 10-year survival rate of ~95%.[2,9] Therefore, clinicians must have a high level of suspicion for combined immunodeficiency in patients who present with thymoma and persistent infections.

Final Diagnosis

The final diagnosis was thymoma with combined immunodeficiency or Good syndrome (GS).

CONCLUSION

Patients who present with a history of thymoma must receive a thorough evaluation of the immune system, including both B-cell and T-cell counts and function. Patients with GS have an increased mortality rate compared with CVID. Therefore, when evaluating a patient, clinicians must consider combined immunodeficiency in patients who present with a history of thymoma and recurrent infections. Serology-based testing in patients with hypogammaglobulinemia might result in a missed diagnosis, therefore, PCR-based tests for autoimmunity and viral infections are recommended. Our finding of *STAT3* mutation was unexpected but can explain why our patient was predisposed to onychomycosis. This case demonstrated the variability of phenotypic response to *STAT3* mutations and is the first report of a patient with GS associated with a *STAT3* mutation.

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Patient Oriented Problem Solving (POPS) Case Report

Chronic pruritic dermatitis and peripheral eosinophilia in a 42-year-old man

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ABSTRACT

Chronic pruritic dermatitis with or without accompanying peripheral eosinophilia can be caused by a vast array of underlying disorders broadly classified as allergic/immunologic, infectious, or neoplastic. An organized and thorough work up is crucial in order to arrive at a definitive diagnosis enabling appropriate treatment. We present the case of a 42-year-old man with a history of chronic pruritic dermatitis and peripheral eosinophilia in a patient-oriented, problem-solving format including the clinical presentation, physical findings, results of pertinent lab/radiologic studies, differential diagnosis, and final diagnosis with discussion.

(Allergy Asthma Proc 37:171–174, 2016; doi: 10.2500/aap.2016.37.3898)

CHIEF CONCERN: ITCHY RASH

History of Present Illness

A 42-year-old white man who presented with a medical history of gout, hypertension, and depression was admitted for a severe flare and evaluation of chronic pruritic dermatitis of ~5 years of duration. The rash initially presented on both arms and quickly progressed to his thighs and back, and spared his face, palms, soles, and mucus membranes. Previous treatments with prednisone provided temporary relief; however, the rash returned with worsening pruritus when the treatment was discontinued. Intermittent topical steroid therapy only provided temporary relief. Recently, mycophenolate mofetil was initiated with only temporary improvement.

Previous skin biopsy specimens had yielded nonspecific findings, including epidermal spongiosis and some nonspecific perivascular chronic inflammation with some eosinophils. Stains for fungal organisms produced negative results. Hypereosinophilia was first noted 2 months before admission, although, apparently, the eosinophil counts had previously been within normal limits. There had been no travel outside of the country or sick contacts. Medications at the time of admission included cephalexin (for presumed bacterial skin superinfection), citalopram, febuxostat, hydroxyzine, hydrochlorothiazide, lisinopril, mycophenolate 1500 mg twice a day, prednisone 30 mg daily, and topical triamcinolone.

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The authors have no conflicts of interest to declare pertaining to this article

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Physical Examination

Vital signs and physical examination results were within normal limits, except that ~1-cm palpable lymph nodes were noted in the right inguinal area, bilaterally in the axilla, and in the supraclavicular region. Results of the skin examination revealed diffuse erythroderma, with multiple punctate crusted papules and thin plaques distributed over the upper and lower extremities. Violaceous papules on the dorsum of the hands and mild scaling of the scalp were present. Crusted excoriations were diffusely distributed on all extremities and trunk. No pustules, vesicles, or bullae were observed.

Laboratory and Other Diagnostic Findings

Laboratory analysis revealed a normal hemoglobin level, hematocrit value, and platelet count, and a total white blood cell count of 10.7 cells/μL. Initial differential revealed 80.3% neutrophils, 4.2% lymphocytes, 9.0% monocytes, 1.8% basophils, and 3.5% eosinophils (absolute eosinophil count, 0.38 cells/μL). Results of a complete metabolic profile were within normal limits. A punch biopsy specimen of the skin revealed epidermal acanthosis and spongiosis, along with some over-

lying compact orthokeratosis. There was a dermal perivascular lymphohistiocytic infiltrate, with sparse eosinophils.

Clinical Course

After admission, all medications were discontinued except prednisone (30 mg daily), citalopram, and hydroxyzine. Computed tomography of the chest, abdomen, and pelvis confirmed mild lymphadenopathy within the axilla and pelvic sidewalls as well as in the right external iliac and right femoral distribution. After admission, the eosinophil count rose acutely to 3.38 cells/μL. Four days later, at discharge, this subsequently dropped to 1.98 cells/μL. Results of pertinent laboratory tests data included negative stool ova and parasites, urine culture, herpes simplex virus 6 (HSV6), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV); elevated immunoglobulin E level (571 IU/mL), and normal tryptase, thyrotropin, and creatine kinase values. The patient was discharged with several laboratory results pending.

Questions

- 1. What is the differential diagnosis in a middle-aged man with chronic pruritic rash and hypereosinophilia?

  a. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome
  b. Parasitic infection
  c. Viral infection (EBV, HIV, HSV6)
  d. Hypereosinophilic syndrome (HES)
  e. Sézary syndrome (SS)
  f. Atopic dermatitis

- 2. What additional laboratory data would be helpful in narrowing this differential diagnosis?

  Additional skin biopsies, peripheral blood smears, bone marrow biopsy, flow cytometry, and T-cell gene rearrangement studies as well as Fip1-like-1 fused with platelet derived growth factor receptor (FIP1L1-PDGFR) analysis.

DISCUSSION

The differential diagnosis in this case included multiple entities classified as infectious, allergic and/or immunologic, or neoplastic.

Infectious etiologies, particularly parasitic disease should always be considered in the setting of hypereosinophilia. Because the patient had a prolonged course; no foreign travel; no gastrointestinal symptomatology; and had a negative results for stool ova and/or parasites, EBV, HIV and HSV6 serologies, an infectious etiology was thought to be unlikely. Due to age at presentation, distribution of skin lesions, lack of family history, and other associated atopic symptomatology, atopic dermatitis was excluded.

DRESS syndrome is a distinct severe drug reaction, with a prolonged latency period characterized by fever, rash, lymphadenopathy, eosinophilia, abnormal liver function tests, skin manifestations (diffuse erythroderma plus edema), and a wide range of other systemic manifestations with an appropriate medication history.[1] Drugs commonly implicated in DRESS syndrome include, anticonvulsants, phenobarbital, allopurinol, minocycline, and sulfonamides,[2] although any drug could be a trigger. The pathogenesis of DRESS syndrome is not well understood but seems to have genetic associations and, in some instances, proposed virus-drug interactions (human herpesvirus 6, human herpesvirus 7, EBV, and cytomegalovirus).[3] Although the patient had numerous medications since the onset of his rash, DRESS syndrome is less likely due to the prolonged nature of his symptoms and lack of organ involvement other than the skin, and his medications had been discontinued or changed over the 5 years since the onset of his eruption.

HES is the other major entity in the differential diagnosis to be considered. Although not a specific diagnosis, HES is a syndrome complex characterized by the presence of hypereosinophilia (absolute eosinophil count of $>1500/\mu$L) on at least two occasions and the presence of end organ damage. HES is a heterogeneous group of disease entities, some of which can be excluded based on a lack of specific evidence of end organ damage (other than skin). A myeloid variant of HES is also unlikely with the negative result for a FIP1L1-PDGFR fusion, normal tryptase, and normal B_{12} levels.

Other neoplastic disorders that are associated with eosinophilia and cutaneous manifestations include chronic eosinophilic leukemia, mastocytosis, and cutaneous T-cell leukemia/lymphoma. It is important to differentiate between diseases by a neoplastic proliferation of eosinophils versus those in which eosinophils are a reactive component to a noneosinophilic neoplasm. The negative tryptase virtually excludes mastocytosis. Additional laboratory tests data after discharge revealed a T-cell gene rearrangement detectable in the peripheral blood as well as the presence of Sézary cells (SC) (3%) noted on flow cytometry, with a CD4 to CD8 ratio of 7:1. These findings are indicative of a peripheral cutaneous T-cell leukemia/lymphoma, specifically, SS. A bone marrow biopsy specimen revealed hypercellular marrow, with eosinophilic and megakaryocytic hyperplasia. Normal neutrophilic and erythroid maturation was noted. There was no overt lymphocytosis of the marrow or lymphoid aggregates, which indicated that the flow cytometry results on the peripheral blood may represent peripheral blood con-

tamination of the marrow sample or minimal marrow involvement.

Further support for this diagnosis was achieved when results of additional studies, including two skin biopsies, at an outside hospital, showed atypical dermal-epidermal T-cell infiltration. Repeated T-cell gene rearrangement studies that show matching T-cell clonality in peripheral blood and skin were obtained. Flow cytometry again showed a lymphoid population (52% lymphocytes), with an aberrant $CD4^+$-$CD26^-$ phenotype and a lymphoid population (44% lymphocytes) of $CD4^+$-$CD7^-$. Flow cytometry also revealed a CD4 to CD8 ratio of 13.2:1. These findings fulfill criteria for a diagnosis of SS and cutaneous T-cell lymphoma stage T4N1M0B2.

This case illustrated that cutaneous T-cell lymphoma can remain indolent for some time, with nonspecific clinical findings, which contributed to a delayed diagnosis. Skin lesions, even with a biopsy specimen, can be nonspecific, particularly in the absence of a high index of suspicion for cutaneous T-cell lymphoma. SCs in the peripheral blood early on can be at very low levels and easily missed in the absence of high clinical suspicion. Hypereosinophilia, although a common accompaniment, is also nonspecific.

SS is a rare leukemic variant of cutaneous T-cell lymphoma, characterized by the triad of circulating neoplastic T cells, and erythroderma with or without lymphadenopathy predominantly affects men >60 years old.[4,5] The incidence of cutaneous T-cell leukemia/lymphoma has risen in the United States since 1973, with an annual age-adjusted incidence of 6.4–9.6 cases per million people with SS, which represents only a small percentage of such cases (3%).[5–7] Circulating SCs can be detected and quantified by morphologic evaluation of peripheral blood smears (Fig. 1); however, this has largely been replaced by flow cytometry.

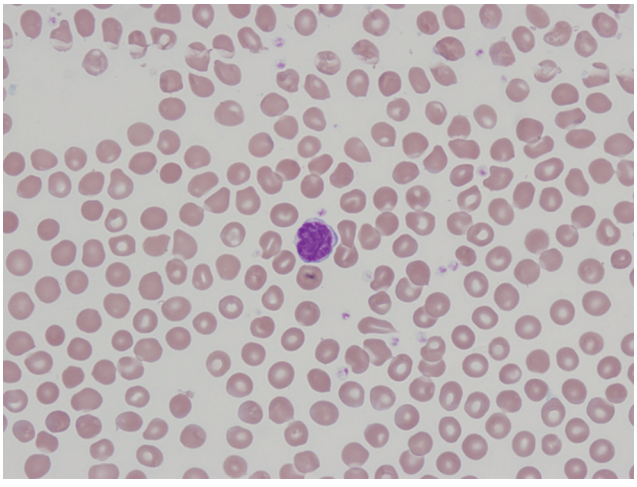

Figure 1. *A picture of Sézary cells: note the cerebriform-appearing nucleus.*

The typical immunophenotype of SCs is $CD4^+$ T cells with aberrant loss of CD26 and/or CD7.[5] More specifically, circulating SCs display a postthymic T helper cell with central memory phenotype ($CD3^+$, $CD5^+$, $CD28^+$, $TCR\alpha\beta^+$, $CD4^+$, $CD8^-$ $CD45RO^+$, $CCR7^+$, $CD27^+$)[8] phenotype with a skin-homing tendency secondary to their expression of the cutaneous lymphocyte antigen[9] and chemokine receptors CCR4 and CCR10.[10] Recent work showed that, although a lack of CD26 is one of the most common aberrancies, a lack of CD38 is also quite characteristic, and, although the phenotype of the SCs in most patients remains stable over time, in a minority of patients, the phenotype may change and potentially impact prognosis (expression of CD26 associated with survival advantage).[11] Demonstration of monoclonality by T-cell receptor gene rearrangement (PCR) strengthens the diagnosis, particularly when identical rearrangements are found in T cells from multiple sites.

Many genetic alterations in SS have been identified over the past few decades, with the most frequent being monosomy 10, losses of 10q and 17p, and gains of 8q24 and 17q, and overall chromosomal instability is characteristic, which likely contributes to the generally poor prognosis.[12] The molecular mechanisms of pathogenesis are beginning to be unraveled. Diagnosis can be difficult. In this case, the long duration and variability in the intensity of this patient's rash and its questionable relation to the time course of numerous medications complicated arriving at a definitive diagnosis. Although an unequivocal diagnosis of SS was established in this patient, it was still difficult to exclude underlying allergic reactions to various medications at various times during his course that may have exacerbated his dermatologic symptoms and contributed to the hypereosinophilia.[13]

Treatment of SS is guided by accurate staging[14] and typically involves multimodality immunomodulatory combination therapy, including skin-directed treatment (either nitrogen mustard ointment, phototherapy, or total skin electron beam RT), plus interferon alfa 2b, plus bexarotene, and monthly extracorporeal photopheresis. Response is expected to take 3–18 months. If slower, romidepsin IV and/or low-dose subcutaneous alemtuzumab[15] are next-line treatments. Quantifying the number of SCs circulating in the peripheral blood is important for proper staging at the time of diagnosis and is also useful in following up treatment response. SS carries a poor prognosis, with an estimated survival of 5 years from diagnosis.

Final Diagnosis

SS.

SUMMARY

The differential diagnosis for pruritic erythrodermic dermatitis in combination with eosinophilia is extensive. As demonstrated in this case, SS may be difficult to diagnose even with skin biopsies. A high degree of clinical suspicion with the support of appropriate laboratory testing (flow cytometry, T-cell gene rearrangement studies) is crucial to making the diagnosis.

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Patient Oriented Problem Solving (POPS) Case Report

A 45-year-old man with shortness of breath and eosinophilia

Haru Yamamoto, M.D., and David A. Khan, M.D.

ABSTRACT

A 45-year-old man who presented with dyspnea and chest tightness was found to have obstructive lung disease and eosinophilia of 10,300 eosinophils/μL. The differential diagnosis encompassed causes of primary eosinophilia and secondary eosinophilia associated with pulmonary disease, including asthma, environmental allergic reaction, eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis, acute eosinophilic pneumonia, chronic eosinophilic pneumonia, parasitic infections, tuberculosis, fungal infection, sarcoidosis, mastocytosis, drug reaction with eosinophilia and systemic symptoms, lymphoproliferative hypereosinophilic syndrome, and myeloproliferative hypereosinophilic syndrome. Infectious workup, fiberoptic bronchoscopy with biopsy, and tests for myeloproliferative mutations help differentiate among these causes. Identifying the underlying cause of eosinophilia is imperative in guiding treatment.

(Allergy Asthma Proc 37:259–262, 2016; doi: 10.2500/aap.2016.37.3902)

CASE PRESENTATION

Chief Concern

The patient was a 45-year-old man who presented with dyspnea and chest tightness of 6 months' duration.

History of Present Illness

The patient had intermittent episodes of shortness of breath for the past 6 months. He had one episode that was severe enough that he required hospital admission. He was treated with antibiotics, steroids, and nebulizers for 5 days, with gradual improvement of his symptoms. His shortness of breath episodes seem to be triggered by heat and be resolved with rest. The patient was not currently or recently using medications. He had no recent travel. His medical history was significant for hypertension and dermatographism since age 10 years. His social history was significant for a 25 pack-year history of tobacco use, and he quit using tobacco ~6 months before presentation. His family history was significant for hypertension.

Physical Examination

Vital signs were temperature of 98.6°F (37°C), heart rate of 65 beats per minute, respiratory rate of 17 breaths per minute, blood pressure of 119/83 mm Hg, and oxygen saturation of 97% on room air. The nasal mucosa was noted to be pale and boggy bilaterally. The lungs had symmetric excursion and expansion, and positive prolonged expiration without wheezes, rhonchi, or crackles. His heart had a regular rate and rhythm; normal S1 and S2; and no murmurs, rubs, or gallops. His extremities were without cyanosis, clubbing, or edema. There were no neurologic deficits. The abdomen was soft and without hepatosplenomegaly. There were no rashes or skin lesions.

Laboratory and Other Diagnostic Findings

A chest radiograph was unremarkable. Computed tomography of the chest showed innumerable centrilobular densities and scattered areas of scarring and emphysema (Fig. 1). Spirometry revealed moderate-to-severe obstruction with a forced expiratory volume in 1 second of 43% predicted and a 25% improvement in forced expiratory volume in 1 second after inhaled bronchodilator. A complete blood cell count was significant for a total white blood cell count of 14.9×10^9/L (reference range, $4–11 \times 10^9$/L) with 69% eosinophils, and an absolute eosinophil count of 10,300 eosinophils/μL (reference range, <500 eosinophils/μL). Chemistries and liver function test results were within normal limits.

QUESTIONS

1. What is in the differential diagnosis for shortness of breath, obstructive lung disease and eosinophilia?
   a. Asthma
   b. Environmental allergic reaction
   c. Eosinophilic granulomatosis with polyangiitis (also called Churg-Strauss syndrome)
   d. Strongyloidiasis
   e. Ascariasis
   f. Tuberculosis

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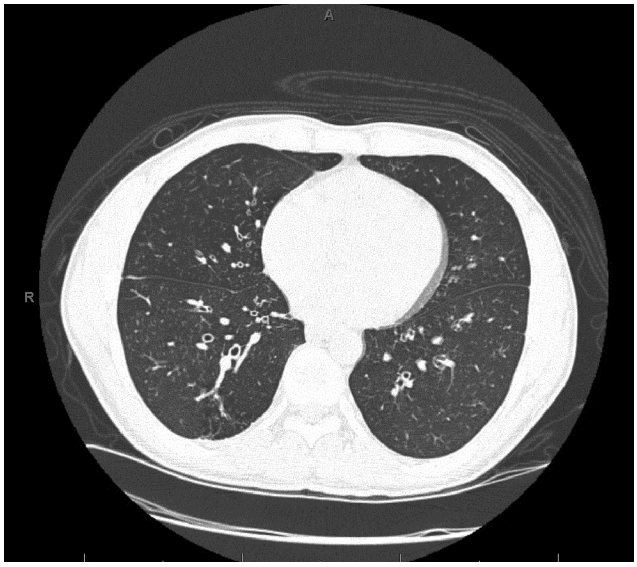

Figure 1. Computed tomography of the chest, revealing centrilobular densities.

g. Fungal infection
h. Sarcoidosis
i. Mastocytosis
j. Allergic bronchopulmonary aspergillosis
k. Acute eosinophilic pneumonia
l. Chronic eosinophilic pneumonia
m. Drug reaction with eosinophilia and systemic symptoms syndrome
n. Lymphoproliferative hypereosinophilic syndrome
o. Myeloproliferative hypereosinophilic syndrome (HES)

2. What additional laboratory data or investigations would be helpful in arriving at a diagnosis for this patient?
   a. Infectious workup for parasites and fungi
   b. *Aspergillus* antibodies
   c. Serum immunoglobulin E (IgE) level
   d. Serum B_{12} level
   e. Serum tryptase level
   f. Fiberoptic bronchoscopy with biopsy
   g. Antineutrophil cytoplasmic antibody
   h. Myeloperoxidase antibody
   i. Janus Kinase 2 (*JAK2*) mutation
   j. *Bcr-Abl* fusion protein
   k. *FIP1L1-PDGFRA* fusion protein
   l. Bone marrow biopsy

CLINICAL COURSE

The patient was treated for asthma and initiated on fluticasone-salmeterol (250/50 mcg) with albuterol as needed, with little improvement in his symptoms. A bronchoscopy with biopsy was performed and revealed bronchial wall thickening, increased mucosal eosinophilia, and nonspecific chronic inflammation. Serology test results and culture results for parasites and fungi were negative (Table 1). A nuclear medicine cardiac scan was normal.

Table 1 **Infection workup performed for eosinophilia**

AFB blood culture	No AFB isolated at 7 wk
Ascaris IgE antibody	Negative
Aspergillus fumigatus, IgE	Negative
Aspergillus fumigatus, IgG	Negative
Aspergillus galactomannan antigen	Negative
Blastomyces antibody complement fixation	Negative
Blastomyces by immunodiffusion	Negative
CMV antigenemia	Negative
CMV IgG titer	1:10 (indicates previous exposure)
CMV IgM titer	Negative
Coccidioides antibody complement fixation	Negative
Coccidioides antigen, urine	Negative
Coccidioides IgG antibody by immunodiffusion	Negative
Coccidioides IgM antibody by immunodiffusion	Negative
Cryptococcal antigen	Negative
Cysticercus IgG antibody	Negative
Filaria IgG4 antibody	Negative
Fungal blood culture	No fungus isolated at 4 wk
Histoplasma antibody	Negative
Histoplasma antigen, urine	Negative
HIV 1 and 2 antibody	Negative
HTLV I/II antibody	Negative
Ova and parasite examination, stool	No ova or parasites observed on concentrate or trichome
QuantiFERON-TB gold*	Negative
Rapid plasma reagin	Negative
Schistosoma IgG antibody	Negative
Strongyloides antibody IgG	Negative
Toxocara canis antibody	Negative
Trichinella antibody	Negative

**Cellestis, a QIAGEN company, Valencia, CA*
AFB = Acid-fast bacilli; IgE = immunoglobulin E; IgG = immunoglobulin G; CVM = cytomegalovirus; IgM = immunoglobulin M; HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus; TB = tuberculosis.

A review of previous laboratory tests from the past 7 years revealed eosinophilia, with eosinophils that ranged from 3980 to 10,300/μL. A peripheral blood test result was negative for perinuclear antineutrophil cytoplasmic

Table 2 **Recommended surveillance studies in patients with HES**

Tests	Interval of Testing
Complete blood cell count with eosinophil count	Monthly for the first 6 mo, then every 3–12 mo or sooner with therapeutic interventions
Serum chemistries, liver enzymes, serum troponins, pulmonary function tests, and echocardiogram	Every 6–12 mo
Molecular testing for *FIP1L1-PDGFRA* fusion protein*	Every 6–12 mo in the absence of clinical signs

HES = hypereosinophilic syndrome.
**In patients with known myeloproliferative HES who were positive for FIP1L1-PDGFRA fusion protein.*

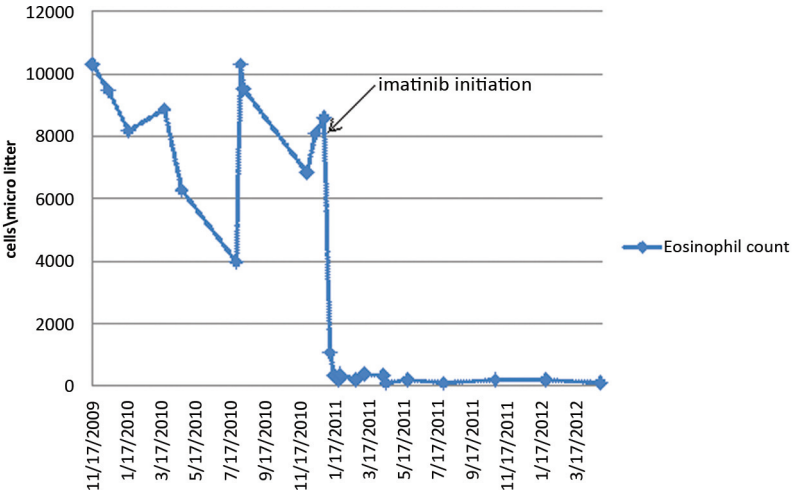

Figure 2. *Absolute eosinophil count before and after imatinib initiation.*

antibodies, myeloperoxidase antibody, *JAK2* kinase mutation, *Bcr-Abl* fusion protein, and *FIP1L1-PDGFRA* fusion transcript by using fluorescence in situ hybridization (FISH) technique. Further studies revealed a total IgE level of 36.3 kU/L, tryptase level of 9.24 ng/mL, elevated interleukin 5 level of 27.2 pg/mL, and elevated B_{12} level of 1805 pg/mL. A bone marrow biopsy showed atypical mast cells in a hypocellular bone marrow with trilineage hematopoiesis. *FIP1L1-PDGFRA* fusion gene was negative by FISH analysis. The patient was initiated on prednisone 60 mg daily, with no significant improvement in peripheral eosinophilia or respiratory symptoms. A repeated bone marrow biopsy was performed, which revealed atypical mast cells in a hypercellular marrow (>90%), with moderate-to-severe fibrosis and normal hematopoiesis, with dominance of eosinophils. FISH analysis revealed low positivity of the *FIP1L1-PDGFRA* fusion gene in 2.5% of cells, and the patient was diagnosed with myeloproliferative HES.

DISCUSSION OF THE DIAGNOSIS

Several diseases are in the differential diagnosis of a patient with dyspnea, eosinophilia, and partially reversible obstruction. Asthma would be unlikely based on the high level of eosinophilia because eosinophil counts in patients with asthma are typically <1500 cells/μL.[1] Allergy testing was not performed to diagnose environmental allergies, given the low suspicion for environmental allergies as a cause for the patient's marked hypereosinophilia. Allergic bronchopulmonary aspergillosis would be possible, but the low IgE would be very unusual.[2] With all of the patient's clinical features, eosinophilic granulomatosis with polyangiitis could present, and as many as 50% of patient are negative for perinuclear antineutrophil cytoplasmic antibodies. However, the lack of systemic symptoms, lack of response to prednisone, and the elevated B_{12} level would be atypical.[3] His presentation with chronic symptoms is not consistent with acute eosinophilic pneumonia, and his lack of response to prednisone would be atypical for chronic eosinophilic pneumonia. He did not have other clinical features suggestive of drug reaction with eosinophilia and systemic symptoms syndrome nor any recent drug history. Thus, other causes needed to be excluded.

HES is defined as an eosinophil count of >1500 eosinophils/μL sustained over more than 1 month, with evidence of organ damage.[4] Myeloproliferative HES is a variant of HES with clonal proliferation of eosinophils.[5] Myeloproliferative HES is a rare disorder, seen most commonly in male patients between the ages of 20 and 40 years. Presentation is variable and is usually a manifestation of end organ damage, including splenomegaly,

endomyocardial fibrosis, restrictive pulmonary disease, myelofibrosis, and skin findings (*e.g.*, lymphomatoid papulosis, mucosal ulcerations).[5] Common laboratory findings include anemia, thrombocytopenia, elevated B_{12} level, elevated tryptase level, and variable IgE levels.

FIP1L1-PDGFRA is the most common mutation to be seen in myeloproliferative HES.[5] This fusion mutation causes constitutive activation of a tyrosine kinase, which drives clonal eosinophilia.[4] A diagnosis can be made with reverse transcription polymerase chain reaction (RT-PCR) or FISH analysis for the presence of fusion gene in the bone marrow or peripheral blood.[5] Although some cases of myeloproliferative HES identify the presence of *FIP1L1-PDGFRA* fusion transcript, other cases lack an identifiable genetic cause.

Once the diagnosis has been established, the standard of treatment is low-dose daily imatinib therapy. Improvement is generally seen in 2–5 weeks, with molecular remission in 3–6 months.[5] Structural damage is usually permanent. Currently, no cure exists, and long-term imatinib at varying doses is required to maintain a "molecular remission."

The clinical presentation of this case was atypical, given that the patient's presentation mimicked refractory asthma, in contrast to the expected presentation of restrictive lung disease.[5] One other case report of HES in a patient who presented with severe obstructive lung disease was identified in the literature.[6] Furthermore, identifying the diagnosis was elusive, given the initial negative test result for the fusion transcript. Repeated bone marrow biopsy with FISH analysis for the fusion transcript was performed because of the high suspicion for myeloproliferative HES, with subsequent positive results. These findings indicated the poor sensitivity of the test, possible sampling error, or the absence of the gene at the initial time of biopsy. Detection of the fusion gene by RT-PCR or FISH analysis is thought to be equivalent, although a formal comparison trial has not been performed.[7] FISH may lack sensitivity for detecting the fusion transcript, given the inherent background fluorescence of eosinophils, especially in peripheral blood where the percentage of cells involved is lower than in bone marrow.[8] RT-PCR may also miss detection of fusion transcript because multiple break points exist within FIP1L1. Given the findings in this case as well as the potential for sampling error, repeated sampling may be warranted in patients with a high suspicion for myeloproliferative HES. Further research is needed to determine the validity of this approach.

The low positivity of fusion transcript seen in the diagnostic bone marrow is another anomaly. Previous descriptions of myeloproliferative HES with *FIP1L1-PDFGRA* fusion gene have shown much higher percentages of cells expressing fusion transcript (41.5–91% of cells).[7] We speculated that the low percentage of involved cells may have contributed to the initial failed detection of the fusion gene.

Imatinib is the standard of treatment for patients with known *FIP1L1-PDGFRA* fusion gene. Patients without the *FIP1L1-PDGFRA* fusion gene have also been shown to respond to imatinib, some of these cases have been identified to have different fusion products with PDGFRA.[9,10] Given the initial negative findings in this case, the lack of detection of the fusion protein may be another possible explanation of imatinib responsiveness in patients negative for *FIP1L1-PDGFRA* fusion gene. In conclusion, the allergist/immunologist needs to be aware that patients with HES can present as refractory asthma and have negative testing for the *FIP1L1-PDGFRA* fusion gene and may benefit from imatinib therapy.

After diagnosis and initiation of treatment, additional surveillance studies for HES can be followed up periodically to monitor remission (Table 2).[5]

FINAL DIAGNOSIS

The final diagnosis was myeloproliferative hypereosinophilic syndrome (HES)

CASE EPILOGUE

The patient was initiated on imatinib 100 mg daily for myeloproliferative HES. The eosinophil count decreased to a normal count within 2 weeks of initiating imatinib with maintained remission (Fig. 2). The patient experienced symptomatic improvement in his dyspnea. The patient was subsequently lost to follow up ~13 months after imatinib therapy.

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Patient Oriented Problem Solving (POPS) Case Report

A 47-year-old man with tongue swelling

Maristely Rodríguez-Roa, M.D., Sylvette Nazario, M.D., and Cristina Ramos, M.D.

ABSTRACT

Intermittent tongue angioedema can be the initial presentation of several disorders including angiotensin-converting-enzyme inhibitor induced angioedema and hereditary angioedema. Persistent angioedema on the other hand, can be associated with amyloidosis, tumors, thyroid disorders and acromegaly. We present a case of intermittent episodes of tongue swelling progressing to macroglossia.

(Allergy Asthma Proc 37:340–342, 2016; doi: 10.2500/aap.2016.37.3956)

CHIEF CONCERN

The chief concern was recurrent angioedema of the tongue and uvula.

HISTORY OF PRESENT ILLNESS

A 47-year-old male patient with a history of thyroid nodules, bilateral carpal tunnel syndrome, and gastroesophageal reflux disease presented to the outpatient allergy clinic with recurrent swelling of the left side of the tongue and uvula for ~10 months before evaluation. The patient did not have associated shortness of breath, throat tightness, difficulty swallowing, hives, peripheral edema, or abdominal pain, or use nonsteroidal anti-inflammatory drugs or angiotensin converting enzyme inhibitors.

PHYSICAL EXAMINATION

The patient was noted to have mild tongue enlargement; with superficial yellowish discoloration; coarse facial features, with a prominent forehead; and coarse or enlarged hands; results of the rest of the examination were normal.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Results of the laboratory workup for angioedema were negative for inherited or acquired deficiencies in complement components and regulators. The laboratories however demonstrated impaired fasting glucose, hematuria, and anemia (Table 1). We had serum and urine protein electrophoresis performed to rule out a monoclonal protein disorder and referred the patient to an ear, nose, and throat specialist for amyloidosis evaluation. No abnormalities were found.

CLINICAL COURSE

The patient continued with episodes of tongue swelling, which were noted to be persistent on subsequent follow-up examinations.

QUESTIONS

WHAT IS THE DIFFERENTIAL DIAGNOSIS?

The differential diagnosis for tongue swelling is broad, and several conditions need to be taken into account (Table 2).

Mast-Cell Mediated Angioedema

Angioedema that involves the face, lips, tongue, extremities, or genitalia may occur in conjunction with hives or as a separate entity, and usually resolves within 24 hours.[1] It is the most common form of angioedema, often accompanied by urticaria. The patient did not indicate any itching of the skin or the presence of hives; swelling of the tongue became persistent over time.

Non–Mast-Cell Mediated Angioedema

Non–mast-cell mediated angioedema can manifest clinically with bouts of asymmetric nondependent, nonpruritic swelling that involves cutaneous or mucosal surfaces.[1] Angioedema without urticaria should prompt an investigation for underlying hereditary angioedema or for drug-induced angioedema. The patient's laboratory results were negative for comple-

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Table 1 **Laboratory Workup**

Laboratory Test	Value	Result
C4 value	31.39 mg/dL	Normal
C1 INH esterase antigen level	26 mg/dL	Normal
C1 INH esterase function value	88%	Normal
TSH level	1.155 IU/mL	Normal
Hgb level	13.4 g/dL	Decreased
Hct value	41.4%	Mildly decreased
Fasting glucose value	106 mg/dL	Increased
Alkaline phosphatase level	146 IU/L	Increased
ACTH value	25.3 pg/mL	Normal
IGF-1 level	933 ng/mL	Elevated (reference range, 94–252 ng/mL)
Prolactin level	61.18 ng/mL	Elevated (reference range, 3.46–19.4 ng/mL)
Growth hormone level (random)	10.11 ng/mL	Elevated (reference range, 0.014–1.406 ng/mL)

C1 INH = C1-inhibitor; TSH = thyroid stimulating hormone; Hgb = hemoglobin; Hct = hematocrit; ACTH = adrenocorticotropic hormone; IGF-1 = insulin-like growth factor-1

Table 2 **Causes of tongue swelling**

Persistent Swelling	Transient Swelling
Acromegaly	Glossitis
Hypothyroidism	Stomatitis
Multiple myeloma	Angioneurotic edema
Amyloidosis	Tumor (*e.g.*, hemangioma, neurofibroma)
Sarcoidosis	Infection (actinomycosis, tuberculosis, histoplasmosis, syphilis)
Superior vena cava syndrome	
Down syndrome	

ment deficiencies or C1 inhibitor esterase deficiency or dysfunction, and he was not on an angiotensin converting enzyme inhibitor or angiotensin II receptor blockers.

Infiltrative Causes

Our patient presented with mild anemia, bilateral carpal tunnel syndrome, and, later, persistent swelling of the tongue suggestive of an infiltrative process, *e.g.*, amyloidosis. At the medical interview, there was no dysphagia or dysphonia. Results of a laboratory workup were unremarkable for liver, cardiac, or kidney dysfunction. Results of serum protein electrophoresis, and urine protein electrophoresis were normal, which excluded a monoclonal gammopathy.[2]

Acromegaly

Acromegaly can present with the typical clinical features of growth hormone (GH) excess, which include enlargement during adulthood of the jaw (macrognathia), hands, and feet as well as manifestations of soft-tissue overgrowth, including macroglossia, deepening of the voice, and paresthesias of the hands (*e.g.*, carpal tunnel syndrome is present in ~20% of patients). Our patient presented with some of the typical physical characteristics, *e.g.*, coarse facial appearance, bilateral carpal tunnel, impaired fasting glucose on results of laboratory tests, and, later, unremitting swelling of the tongue.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Laboratory tests were ordered, including prolactin, GH, and somatomedin C levels, all of which were elevated (Table 1). In view of these results, magnetic resonance imaging of the sella turcica revealed a pituitary adenoma (Fig. 1). The patient was evaluated at Mayo Clinic's endocrinology and neurosurgery department. After discussing the surgical and medical options available, a transsphenoidal microscopic gross total resection of the patient's tumor was performed. No intra- or postoperative complications were reported. Surgical pathology results confirmed a pituitary adenoma, focally positive for GH and prolactin by immunohistochemistry.

DISCUSSION

Acromegaly results from persistent hypersecretion of GH. Excess GH stimulates hepatic secretion of insulin-like growth factor 1, which causes most of the clinical manifestations of acromegaly.[3,4] The diagnosis should be suspected in individuals who present with the typical clinical features of GH excess, including macrognathia, coarse facial features (*e.g.*, enlargement of the nose and frontal bones), and enlargement of the

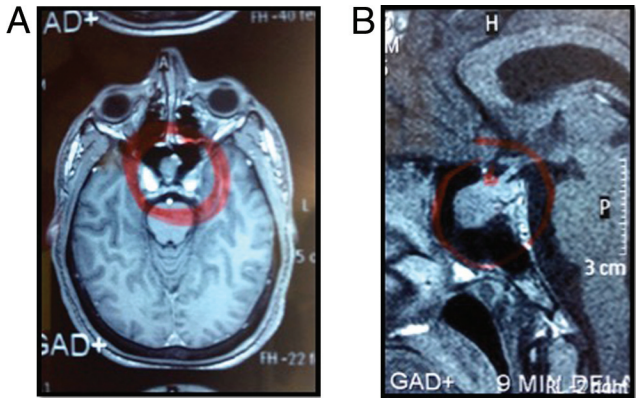

Figure 1. Pituitary adenoma. (A) Soft tissue mass arising from the anterior lobe of the pituitary gland. (B) Pituitary mass showing heterogenous contrast enhancement and extension into the sphenoid sinus which may represent a macroadenoma.

hands and feet as well as manifestations of soft-tissue overgrowth, including macroglossia, deepening of the voice, and paresthesia of the hands (*e.g.*, carpal tunnel syndrome). Despite the prominence of these findings at physician encounter, the rate of change is so slow that few patients seek care because of a change in their appearance.[5]

Complications of GH excess can include development of diabetes mellitus, hypertension, cardiovascular and pulmonary disease, sleep apnea, arthritis, and colon cancer.[6] These complications may reduce a lifespan by 10 to 15 years. The mortality rate of patients with acromegaly is two to three times the rate in the general population, mostly due to cardiovascular disease and cancer. The best single test for the diagnosis of acromegaly is measurement of the serum insulin-like growth factor 1 level, which is elevated in almost all patients with acromegaly.[1] Failure to suppress serum GH levels to <2 ng/mL after taking 100 g of oral glucose is considered conclusive (seen in >85% of patients with acromegaly). Some patients may be asymptomatic despite raised GH and insulin-like growth factor 1 levels.[5] Magnetic resonance imaging of the pituitary can detect a somatotroph adenoma of the pituitary, which is by far the most common cause of acromegaly. Seventy-five to 80% of somatotroph adenomas are macroadenomas at the time of diagnosis. The percentage of patients with visual defects at presentation is now estimated to be ~6%, down from 15–25% in 1975.[3] Selective transsphenoidal surgical resection is the treatment of choice for patients with somatotroph adenomas that are small, large but still resectable, or large and cause visual impairment.[3,6]

Final Diagnosis?

The final diagnosis was macroglossia in a patient with acromegaly.

CONCLUSION

This case illustrated the importance of considering endocrinopathies, including acromegaly, in the differential diagnosis of angioedema of the tongue.

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Patient Oriented Problem Solving (POPS) Case Report

A 30-year-old woman with chronic hives, intermittent fevers, and joint pain

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ABSTRACT

Chronic urticaria with concomitant systemic symptoms may be seen in several rheumatologic and autoinflammatory conditions. Although most of these conditions tend to improve with corticosteroids, symptoms often recur with dose tapering. The appearance of the rash in addition to the symptom pattern and laboratory data must be considered to differentiate potential causes. We presented a unique case of chronic urticaria with fevers and arthralgias. A diagnosis was made, and the patient had rapid improvement with targeted therapy.

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CHIEF COMPLAINT

Chronic hives, fevers, and joint pain.

HISTORY OF PRESENT ILLNESS

A 30-year-old woman presented with a chief complaint of chronic hives, intermittent fevers, and joint pain over the past 2 years. Rash occurred daily, which appeared as erythematous nonpruritic macules and slightly raised plaques on her trunk and extremities. Individual lesions lasted for 1–2 days before resolving without scarring or hyperpigmentation. She had tried high-dose antihistamines without relief. She began to experience diffuse arthralgias in addition to her rash. Thus, she was started on prednisone with temporary improvement in symptoms. As the prednisone was tapered, she experienced acute worsening of her urticarial rash, accompanied by fevers, with a temperature up to 39.7°C, and severe pain in her shoulders, elbows, knees, ankles, and hips on weight bearing. She was hospitalized twice, with a negative workup result for infectious etiologies. Her prednisone was again increased with improvement in symptoms and resolution of fever. When prednisone was tapered to <10 mg daily, she noted the return of her rash and onset of palpable joint swelling of her knees.

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PHYSICAL EXAMINATION

The patient's vital signs were normal. Results of the patient's head and neck examination were unremarkable. There was no lymphadenopathy. Her lungs were clear, without wheezes, rales, or rhonchi. Her heart was regular rate and rhythm without murmurs or rubs. Her abdomen was soft and nontender, without appreciable organomegaly. Widespread erythematous blanching urticarial macules and plaques were present, which covered much of her back, trunk, arms, and hands (Fig. 1). Bilateral knee pain was elicited, with passive range of motion. Bilateral knee fullness was appreciated, with palpable effusions, left greater than right. The remainder of the examination was unremarkable.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Notable findings during a recent hospitalization included leukocytosis, >18,000/μL, with 93% neutrophils and ferritin level of >2000 ng/mL. Erythrocyte sedimentation rate and C-reactive protein values were 84 mm/hour and 123.8 mg/L, respectively. Results of a battery of autoantibody serologies (rheumatoid factor, antinuclear antibody, antidouble stranded DNA, anti-smith, anti-Sjögren's syndrome-related antigen A, anti-Sjögren's syndrome-related antigen B, anti-ribonucleoprotein, anticardiolipin, antineutrophil cytoplasmic antibody), quantitative immunoglobulins, hepatitis viral serologies, and complement levels all were normal. A computed tomography of her abdomen to assess for abscess or malignancy showed only mild splenomegaly. A skin biopsy of her rash was performed, which revealed the unique finding of neutrophilic urticaria, with "low density, interstitial and

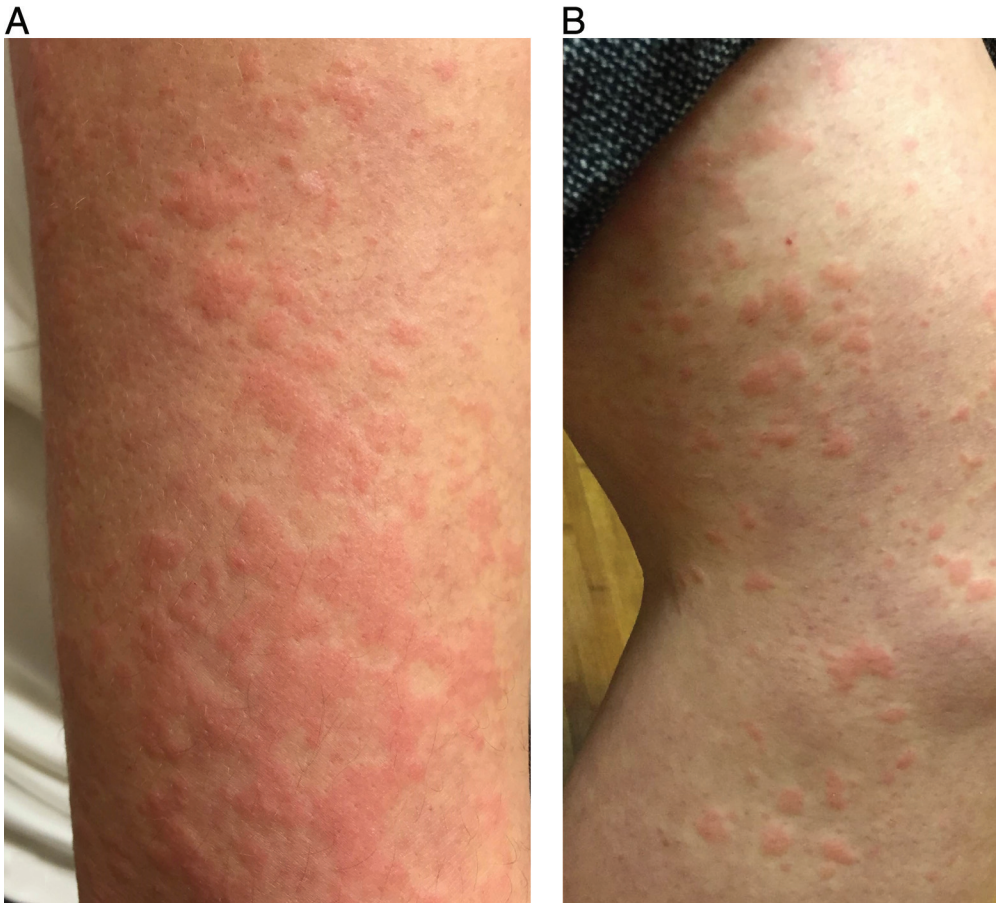

Figure 1. Erythematous macules and slightly raised plaques on the case patient's arms (A) and legs (B).

perivascular inflammatory infiltrate dominated by neutrophils" (Fig. 2). No evidence of vasculitis was found, with a reported absence of leukocytoclasis, perivascular fibrin exudate, and extravasation of red cells.

CLINICAL COURSE QUESTIONS

Question 1

What is the differential diagnosis?
(a) Systemic lupus erythematosus
(b) Schnitzler syndrome
(c) Adult-onset Still disease (AOSD)
(d) Sweet syndrome

Question 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis for this patient?

Her history was notably suggestive of Schnitzler syndrome, although serum and urine electrophoreses had not yet been ordered to assess for the presence of a monoclonal M spike. Both were obtained, and the results were negative for monoclonal immunoglobulins by immunofixation electrophoresis. Repeated testing during a mild flare in symptoms showed a polyclonal increase in immunoglobulins consistent with acute inflammation but was still otherwise normal.

DISCUSSION

Schnitzler syndrome is a rare disorder characterized by persistent urticarial rash, fevers, arthralgia and/or arthritis, bone pain, and lymphadenopathy.[1–3] Proposed diagnostic criteria require both urticarial rash and a laboratory finding of monoclonal immunoglobulin M to establish the diagnosis (Table 1).[2] The term Schnitzler-like syndrome has been used to describe a constellation of symptoms, which is otherwise characteristic but lacks one of the two major diagnostic criteria.[1] There are very few case reports that describe a Schnitzler-like syndrome without monoclonal immunoglobulin M.[4–6] Although Schnitzler-like syndrome provides a descriptive label, it has not been established as a unique diagnosis. Here we presented a case of a Schnitzler-like syndrome and discussed whether this may represent a variant of Schnitzler syndrome, an atypical presentation of AOSD, systemic lupus erythematous, or Sweet syndrome.

Perhaps the most striking and potentially diagnostic feature of this case is the neutrophilic urticaria described on histopathology. The term neutrophilic urti-

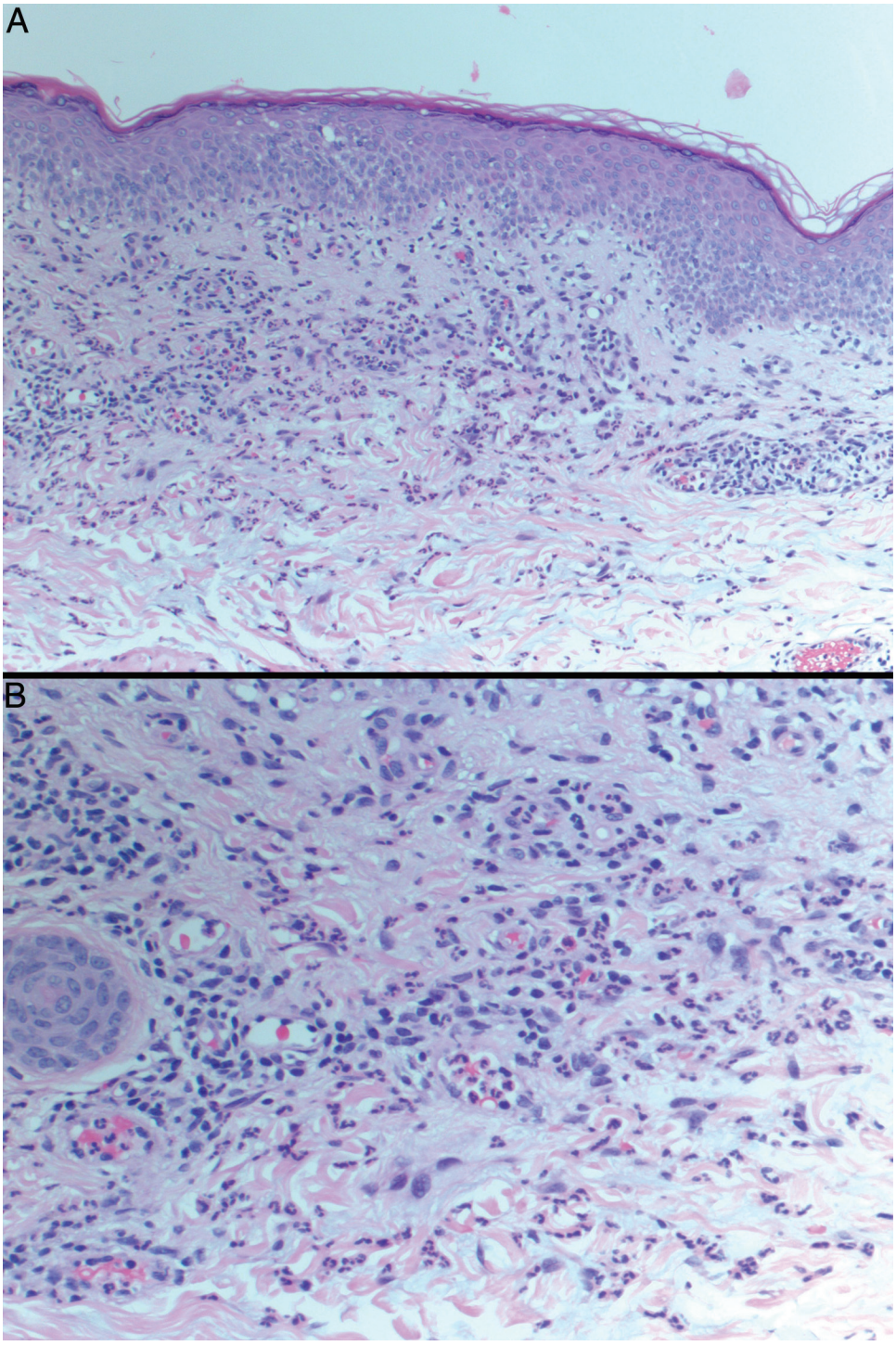

Figure 2. *Representative histopathologic findings of a skin biopsy are depicted at mid-power (A) and high-power (B); inflammatory infiltrate in the dermis is dominated by neutrophils.*

carial dermatosis has been used to categorize this rare finding and the diseases associated with it.[7] Schnitzler syndrome, AOSD, and, less often, systemic lupus erythematosus have been associated with neutrophilic urticarial dermatosis.[1,3,7,8] These syndromes are sometimes easily distinguished based on the appearance and frequency of rashes as well as by serology and multisystem involvement in the case of systemic lupus erythematosus. Neutrophilic dermatosis is also observed with Sweet syndrome, although lesions are not generally urticarial and are described as brightly erythematous or violaceous. Schnitzler syndrome presents with chronic, sometime daily urticaria, which is moderately erythematous in appearance,[1,2] whereas the rash of AOSD is classically salmon colored, maculopapular, and evanescent, often appearing and disappearing in correlation with quotidian fevers.[8,9] Urticaria is a rare manifestation of AOSD, although at least

Table 1 **Diagnostic criteria for Schnitzler syndrome and AOSD**

	Schnitzler Syndrome Criteria*#	Case Patient	AOSD Criteria§¶	Case Patient
Major criteria				
	Chronic urticarial rash	×	Fever, temperature of ≥39°C for ≥1 wk	×
	Monoclonal IgM		Arthralgia, ≥2 wk	×
			Rash (macular or maculopapular nonpruritic salmon-pink eruption, usually with fever)	
			Leukocytosis (≥10,000/mm^3) with >80% granulocytes	×
Minor criteria				
	Intermittent fever	×		
	Arthralgia or arthritis	×		
	Bone pain		Sore throat	
	Lymphadenopathy		Lymphadenopathy	
	Hepatomegaly, splenomegaly	×	Splenomegaly	×
	Elevated ESR level	×	Liver dysfunction	
	Leukocytosis	×	Negative RF and ANA	×
	Bone abnormalities			
Criteria met?		No		Yes

AOSD = Adult-onset Still disease; IgM = immunoglobulin M; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ANA = antinuclear antibody.
**From Ref. 2.*
#The diagnosis of Schnitzler syndrome requires both major criteria plus two or more minor criteria as well as exclusion of other possible causes.
§From Ref. 9.
¶The diagnosis of AOSD requires five or more criteria, including two or more major criteria with exclusion of other possible causes.

28 cases have been previously reported with urticarial lesions.[8,10]

Analysis of the epidemiologic data also reveals striking differences between Schnitzler syndrome and AOSD. Schnitzler syndrome has a male predominance, with mean age of onset of 51 years, rarely occurring before age 35 years.[1] In contrast, AOSD is more common in female patients and tends to present between 16 and 35 years of age.[8] Analysis of the epidemiologic data favors AOSD over Schnitzler syndrome. Because Schnitzler syndrome and AOSD exhibit an assortment of overlapping features (Table 1), abnormal laboratory data may aid in differentiating the two. Specifically, urticaria with monoclonal immunoglobulin M is virtually pathognomonic for Schnitzler syndrome,[1–3] whereas marked elevation of the ferritin level is more suggestive of AOSD.[1] In fact, a case series of 16 patients with Schnitzler syndrome noted normal ferritin values in all of their patients.[3] Our patient had a ferritin level of >2000 ng/mL, with normal immunofixation electrophoresis on two separate occasions.

In summary, although our patient had a daily urticarial rash suggestive of Schnitzler syndrome, analysis of epidemiologic and laboratory data strongly favored an atypical presentation of AOSD. Although pathophysiology of these diseases is not well understood, both are thought to involve dysregulation of the inflammasome, which leads to increased interleukin-1 production.[1] Anakinra, an interleukin-1 receptor antagonist, has been used therapeutically for both diseases as well as other autoinflammatory disorders, with rapid resolution of symptoms and normalization of inflammatory markers.[1,3,5,7] Given the potent efficacy of anakinra in treating both diseases, the necessity of a definitive diagnosis may be questioned. However, prognosis and disease course differ dramatically between the two diseases, with AOSD generally remitting, whereas Schnitzler syndrome leads to chronic persistent symptoms.[1] Schnitzler syndrome has also been associated with lymphoproliferative disorders in ~20% of patients, which warrants ongoing monitoring for malignancy.[1] These distinctions highlight the utility in identifying a definitive diagnosis. Ultimately, we treated our patient

with anakinra subcutaneous daily injections. She experienced rapid improvement in her arthralgias and urticarial rash, with corresponding normalization of inflammatory markers. Her rapid and complete response confirmed that she has an interleukin-1–mediated disease. Although the appearance and chronicity of her rash was certainly Schnitzler-like, epidemiologic and laboratory data support the diagnosis of AOSD.

FINAL DIAGNOSIS

AOSD.

CONCLUSION

Chronic urticaria accompanied by fevers and arthralgias warrants a thorough evaluation for rheumatologic and autoinflammatory conditions. Although the clinical presentation may guide an initial workup, skin biopsy may prove invaluable. A histologic finding of neutrophilic urticaria should prompt narrowing of the differential diagnosis, with epidemiologic and laboratory data weighed to determine the final diagnosis. AOSD can present with a broad range of cutaneous manifestations[8] and may clinically appear as a Schnitzler-like syndrome. Note that anakinra is not approved by the U.S. Food and Drug Administration for AOSD or Schnitzler syndrome.

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Patient Oriented Problem Solving (POPS) Case Report

A 28-year-old woman with fever, rash, and pancytopenia

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ABSTRACT

A 28-year-old Hispanic woman was admitted to the hospital with fever, sore throat, arthralgia, and a generalized rash of 2 weeks' duration. Her medical history was significant for various food and medication allergies. Multiple antibiotics were given for suspected infection, and she subsequently developed a new skin rash, acute liver injury, eosinophilia, and pancytopenia. Additional studies showed hypertriglyceridemia; elevated interleukin-2 receptor levels; absent natural killer cell activity; and hemophagocytosis in skin, liver, and bone marrow biopsy specimens. Treatment with intravenous immunoglobulin and steroids resulted in complete remission.

(Allergy Asthma Proc 38:322–327, 2017; doi: 10.2500/aap.2017.38.4042)

CHIEF CONCERN

The chief concerns were fever, arthralgia, and rash.

HISTORY OF PRESENT ILLNESS

A 28-year-old woman was admitted with fever, sore throat, arthralgia, and a generalized rash of 2 weeks' duration. Her initial symptoms were fever and chills, and she subsequently developed a generalized, nonpruritic rash distributed over her chest, face, and arms, as well as a sore throat and arthralgia of the wrists and ankles. A thorough review of symptoms did not reveal any additional concerns.

MEDICAL HISTORY

The patient was previously healthy, and her only medications were levofloxacin and prednisone, as a 5-day course, prescribed by her primary care physician, with no improvement in her symptoms. Two days before the onset of symptoms, she was exposed to her infant niece, who was sick and with fever and rash. The patient had recently been camping in rural southern Virginia but did not remember any insect bites. She reported multiple food allergies and a skin reaction to "some antibiotic" given for acne during adolescence. There was no illicit drug, alcohol, or tobacco use. She had not been sexually active for the past year or elicited a history of any previous sexually transmitted diseases. Her family history was unremarkable.

PHYSICAL EXAMINATION

Results of a physical examination revealed a temperature of 39.8°C, tachycardia, an erythematous morbilliform rash distributed primarily over the distal aspects of the lower extremities without palmar or mucosal involvement, and bilateral redness, swelling, and tenderness of her ankles and wrists. Head, neck, cardiopulmonary, abdominal, musculoskeletal and lymphatic examination did not reveal any additional abnormalities.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Shown in Table 1 are the results of initial laboratory findings. These revealed elevated acute-phase reactants with leukocytosis. She was extensively evaluated for viral and tickborne illnesses, which failed to reveal an infectious cause. Antinuclear antibodies and rheumatoid factor test results were negative.

CLINICAL COURSE

Ceftriaxone and doxycycline were initiated while awaiting additional test results. Ten days into the patient's hospital course, the initial rash and joint pains resolved but fever worsened, to 41°C. The patient's clinical condition deteriorated with devel-

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Table 1 **Results of pertinent initial and subsequent laboratory findings**

	Initial	Subsequent
Laboratory findings		
Hb level, × g/dL	12.5	6.7
WBC count, no./mm^3	24,600	34,000
Neutrophils, %	80	55
Bands, %	10	19
Lymphocytes, %	9	9
Eosinophils, %	0.50	3.50
Eosinophils (absolute no./mm^3)	120	1200
Platelet count, no./mm^3	160,000	79,000
AST level, U/L	50	4066
ALT level, U/L	53	2319
Ferritin level, ng/mL		10,481
Initial negative infectious and autoimmune workup		
ASO		
Parvovirus B12		
Coxsackie (A2, A4, A7, A9, A10, A16), hepatitis B		
HIV		
HSV1 and 2		
EBV		
CMV		
RPR		
Rickettsia rickettsii		
Ehrlichia		
ANA		
RF		

Hb = Hemoglobin; WBC = white blood cells; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ASO = antistreptolysin O; HIV = human immunodeficiency virus; HSV = herpes simplex virus; EBV = Epstein-Barr virus; CMV = cytomegalovirus; RPR = rapid plasma reagin; ANA = antinuclear antibodies; RF = rheumatoid factor.

opment of marked jaundice and a new rash characterized by a dark red, violaceous variably blanching morbilliform maculopapular eruption that involved her trunk and proximal extremities, accompanied by facial and acral swelling. She also developed new-onset shortness of breath, hemoptysis, and tender left cervical lymphadenopathy. Results of a subsequent set of laboratory tests revealed transaminitis (Table 1). A computed tomography of the chest showed bilateral upper-lobe airspace opacities, and a computed tomography of the abdomen showed hepatomegaly with perihepatic inflammation and no splenomegaly. Her condition continued to worsen, with hypotension as low as 80/40 mm Hg, which required transfer to the intensive care unit, where fluid resuscitation, vasopressors, and broad-spectrum antibiotics (vancomycin, meropenem, and doxycycline) were started. Results of repeated laboratory testing after restarting antibiotics demonstrated a drop in her hemoglobin and platelet levels, eosinophilia, and worsening liver function tests (LFT) results (Table 1).

QUESTION 1

What is the Differential Diagnosis?

The patient clearly had two distinct phases in her clinical presentation. The initial symptoms suggested an infectious (viral, tick-borne illness) or autoimmune condition. Her clinical deterioration and development of a new rash with shock and multiorgan dysfunction suggested several other possibilities (Table 2).

QUESTION 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis in this patient?

A battery of additional tests were performed, and results are shown in Table 3. Results of a bone marrow biopsy showed hypercellular marrow with hemophagocytosis and no evidence of malignancy. Skin and liver biopsy specimens were also obtained (Fig. 1).

Table 2 **Differential diagnosis**

Hemophagocytic lymphohistiocytosis
Adult-onset Still disease
Fulminant hepatitis
Disseminated histoplasmosis
Autoimmune hepatitis
Leukemia
Worsening infection by atypical pathogens
Drug reaction with eosinophilia and systemic symptoms syndrome

Table 3 **Final laboratory results (normal ranges)**

Triglyceride levels, mg/dL	226 (0–199)
Soluble IL-2 receptor, μ/mL	19,788 (upper limit, 1105)
Fibrinogen levels, mg/dL	85 (222–475)
NK cell activity	0 (>20)
Hepatitis E	Nonreactive
Histoplasma U. antigen	Negative
Anaplasma PCR	Negative
AMA	Negative
ASMA	Negative

IL = Interleukin; NK = natural killer; PCR = polymerase chain reaction; AMA = anti-mitochondrial antibody; ASMA = anti-smooth muscle antibody.

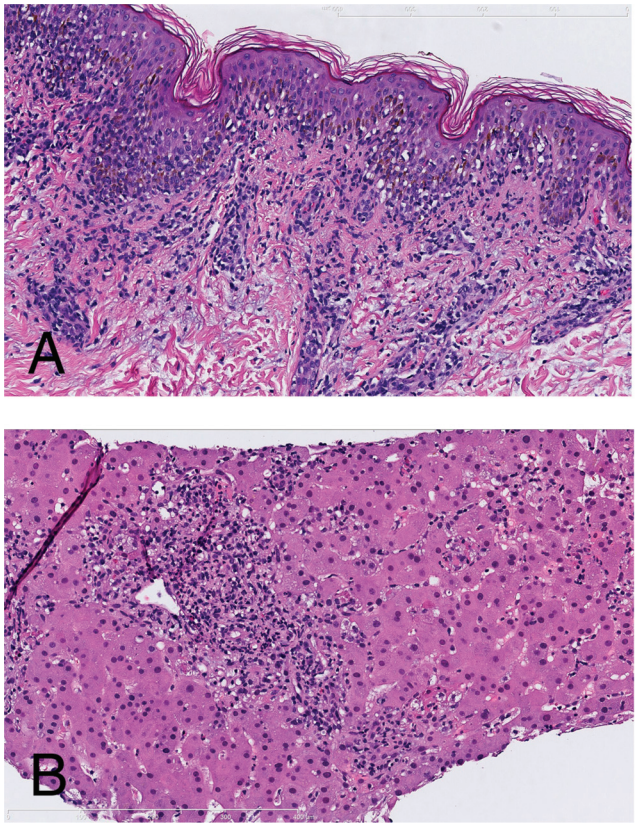

Figure 1. *Photomicrographs of skin and liver biopsies (H&E ×200). (A) Skin biopsy specimen, showing necrotic keratinocytes and perivascular lymphohistiocytic infiltrate with rare neutrophils and eosinophils. (B) Liver biopsy specimen, showing severe acute hepatitis with scattered hemophagocytic histiocytes; portal tracts show numerous polymorphonuclear leukocytes and eosinophils.*

FINAL DIAGNOSIS

The finding of abnormally elevated soluble interleukin-2 receptor levels, low fibrinogen, absent natural killer (NK) cell activity, and hemophagocytosis in multiple tissues strongly suggested a diagnosis of hemophagocytic lymphohistiocytosis (HLH). Eosinophilia, characteristic rash, fever, and organ involvement after exposure to multiple antibiotics suggested drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. A diagnosis of DRESS syndrome and secondary HLH was confirmed.

CLINICAL OUTCOME

All antibiotics were stopped, and the patient was started on pulse-dose steroids and intravenous immunoglobulin (IVIG) 1 mg/kg/day for 3 days. Clinical recovery and improvement in her LFT results, hemoglobin level, and platelet counts were observed within 48 hours. The rash, complete blood count, and LFT abnormalities completely resolved over the course of 2 weeks. She was discharged, with a slow steroid taper over the next 7 months.

CLINICAL AND LABORATORY FEATURES OF THE DISORDER

HLH is a life-threatening immunologically mediated disorder characterized by excessive macrophage activation, which results in hemophagocytosis and tissue damage. HLH is classified either as primary (familial HLH [FLH]) or secondary (sporadic HLH) and is caused by a failure of NK and cytotoxic T lymphocytes to eliminate activated macrophages due to impaired toxic granule exocytosis and perforin release, which leads to uncontrolled and massive systemic inflammation. Homozygous deficiencies in genes involved in T lymphocyte granule exocytosis or content (*e.g.*, PRF1, UNC13D, STX11, STXBP2) usually result in primary HLH (or FLH), and patients commonly present during infancy. Individuals with secondary HLH have been increasingly found to have heterozygous or partial deficiencies in the same pathways and usually present in adulthood. Common triggers for both FLH and secondary HLH are infections and autoimmune diseases. Diagnosis is made by using the 2004 HLH criteria (Table 4).[1]

DRESS syndrome should always be suspected in patients with recent high-risk drug exposure (*e.g.*, drugs commonly involved in hypersensitivity reac-

Table 4 **Diagnostic criteria for HLH**

Five of eight of the following findings
- Fever: ≥38.5°C
- Cytopenias (≥2): ANC level of <1000/μL; Hb level of <9 g/day; platelets < 100,000/μL
- Pathology evidence of hemophagocytosis: Bone marrow, spleen, lymph node, or liver
- Elevated ferritin level: >500 ng/mL
- Elevated soluble CD25 (soluble IL-2R) level: >2 SD above the limit of normal
- Hypofibrinogenemia: <150 mg/dL
- Low/absent NK cell activity
- Splenomegaly

Or
- Molecular identification of HLH-associated gene mutation with clinical findings of HLH
  - *PRF1;* perforin
  - *UNC13D; cytolytic granule maturation*
  - *STX11; cytolytic granule exocytosis*
  - *STXBP2; cytolytic granule exocytosis*
  - *Rab27A; GTP binding protein*
  - *SH2D1A; NK and CTL activator*
  - *BIRC4; apoptosis*

HLH = Hemophagocytic lymphohistiocytosis ; ANC = ; Hb = ; IL = interleukin; SD = ; NK = natural killer; PRF1 = ; UNC13D = cytolytic granule maturation; STX11 = cytolytic granule exocytosis; STXBP2 = cytolytic granule exocytosis; Rab27A = GTP binding protein; CTL = cytotoxic T lymphocyte; SH2D1A = NK and CTL activator; BIRC4 = apoptosis. Cytopenias = no. of 3 major blood lines affected (e.g. RBC, WBC, platelets).

tions), characteristic skin rash, eosinophilia, and systemic organ involvement (usually the liver or lungs), which resolve after discontinuation of the offending agent. The regiSCAR criteria are validated for the diagnosis of DRESS syndrome (Table 5).[2] We presented a patient who developed a severe systemic drug reaction (DRESS syndrome) to antibiotics, with secondary HLH. The diagnosis was established by the treating physician, with subsequent retrospective confirmation by using the previously described validated criteria. The patient scored 7 of 8 for HLH criteria (all features of HLH were met except for splenomegaly) and 7 of 9 for regiSCAR criteria, which indicated a diagnosis of definite DRESS syndrome. The patient's early onset of symptoms (10 days rather than the usual 2–6 weeks after causative drug exposure) is unusual for this disorder. This may be related to previous administration of the culprit antibiotic.

HLH SECONDARY TO SEVERE DRUG REACTIONS

There have been few case reports of HLH secondary to severe drug reactions.[3–8] Not all studies used standard criteria to diagnose HLH or to clearly establish drug causality, but, in most cases, the patient presented with a recent drug exposure, high fever, acute-onset cytopenias, biopsy-proven hemophagocytosis, and complete resolution after treatment with immune suppressants and discontinuation of the offending agent. Interestingly, all the cases were of young to middle-age female patients. Implicated drugs were those usually involved in hypersensitivity reactions (penicillins, cephalosporins, glycopeptides, sulfa drugs, phenobarbital, and allopurinol). Most patients were severely ill and required an intensive care unit level of care. Nearly all the cases had significant LFT elevations, thrombocytopenia, hypofibrinogenemia, eosinophilia, and hemophagocytosis in a bone marrow biopsy specimen. Treatment was variable and included IVIG monotherapy or steroid monotherapy, IVIG with steroids, and a combination of immunosuppressant agents (etoposide, cyclosporine with IVIG and/or steroids). Dosing and duration of high-dose steroids and IVIG were not always reported, but treatment was usually for a short duration (2–3 days). Responses were universally favorable, with relatively fast resolution of hemodynamic instability (usually 48 hours), and protracted resolution of rash and laboratory abnormalities (2 weeks to 2 months) with a long-term steroid taper. No long-term sequelae were reported.

The immunologic basis for HLH secondary to severe drug reactions has not been elucidated. In one report, a patient who developed HLH and DRESS from ceftazidime underwent a lymphocyte proliferation test 1 year after the acute event. After exposing the patient's cytotoxic T lymphocytes to different antibiotics *in vitro,* marked proliferation was observed with ceftazidime and, to a lesser degree, with ceftriaxone and vancomy-

Table 5 **RegiSCAR criteria for DRESS syndrome**

	Score			
	−1	**0**	**1**	**2**
Fever ≥ 38.5°C, enlarged lymph nodes	No/U	Yes		
		No/U	Yes	
Eosinophilia				
Eosinophilia, units × 10^9/L			0.7–1.499	≥1.5
Eosinophils, if leukocytes <4.0, %			10–19.9	≥20
Atypical lymphocytosis		No/U	Yes	
Skin involvement				
Skin rash extent, % body surface area		No/U	>50	
Skin rash that suggests DRESS		U	Yes	
Biopsy specimen that suggests DRESS	No	Yes/U		
Organ involvement*			1	≥2
Liver				
Kidney				
Lung				
Muscle and/or heart				
Pancreas				
Organ other				
Resolution >15 days	No/U	Yes		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV or HBV or HCV				
Chlamydia or mycoplasma				
If none positive and ≥3 above negative	Yes			
Total score (maximum 9)				

RegiSCAR = ; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; U = unknown or unclassifiable; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.
**After exclusion of other explanations: 1, one organ; 2, two or more organs.*
Final score 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score >5, definite case.

cin. Cephalosporins also induced secretion of INFγ, CCL2, CCL4, CXCL8, interleukin 5, GM-CSF, and G-CSF. Although currently experimental and not yet well studied for clinical use, in the future, this test may potentially be useful diagnostically in cases in which patients were exposed to multiple antibiotics, and they would have to be otherwise deemed allergic to several antibiotic classes if the specific culprit drug was not identified. In addition, cytokine and chemokine profiling can help characterize the immune mechanisms behind the overlap between severe drug hypersensitivity and HLH. Unfortunately, no studies reported genetic testing, and whether patients had known genetic mutations for HLH, or HLA haplotypes prone to DRESS (*i.e.*, HLA-B*58:01, HLA-A*31:01) remains unknown.

CONCLUSION

HLH secondary to DRESS syndrome is a rare entity, with few reported cases in the literature. There is evidence that indicates a female predominance, and treatment regimens are widely variable, albeit with rapid and favorable responses. Further studies are needed to determine the optimal treatment strategy, define the role of lymphocyte proliferation testing, and explore the immunologic mechanisms that underlie HLH secondary to severe drug-induced hypersensitivity.

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Patient Oriented Problem Solving (POPS) Case Report

A 69-year-old woman with periodic fever, facial swelling, and neck pain

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ABSTRACT

We presented a case of a 69-year-old woman who experienced monthly episodes of facial swelling and nonpruritic, erythematous rash on her face, accompanied by high fever, nausea, headache, and neck pain over 1 year. Her symptoms started with myalgia, arthralgia, fever and neck stiffness, and headache, and then angioedema occurred, which was painful to touch. She underwent multiple iatrogenic diagnostic and therapeutic procedures that did not lead to the correct diagnosis. Subsequently, relevant immunology laboratory tests were conducted after a careful history and physical examination, which led to the diagnosis. This case illustrated the need for a detailed history and thorough immunologic assessment, and the requirement to maintain a broad differential diagnosis.

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CHIEF CONCERN

Periodic fever, facial swelling, and neck pain.

HISTORY OF PRESENTING ILLNESS

We described a 69-year-old woman who experienced monthly episodes of facial swelling and nonpruritic, erythematous rash on her face, accompanied by high fever, nausea, headache, and neck pain over 1 year. Her symptoms started with myalgia, arthralgia, fever and neck stiffness, and headache, and then angioedema occurred, which was painful to touch. The episodes occurred every 3–4 weeks for almost a year. When the symptoms had initially started, she was referred to a dentist to evaluate the facial swelling and was further referred to an orthodontist and an endodontist, and the results of all workups were negative. She was then referred to an Ear, Nose and Throat specialist for evaluation of chronic sinusitis, polyps, and cyst, which were also ruled out.

Subsequently, she was referred to an oral surgeon for possible infection in her dental implants, which was also excluded. Because the patient continued to have episodes, she was then seen in an emergency department of a tertiary care center where there was concern for possible meningitis due to her symptoms of fever, neck pain, and right lip paralysis due to severe facial swelling. Results of her workup in the emergency department were negative for meningitis and computed tomography showed an infected sinus. She was then referred for sinus surgery; however, 1 week after surgery, she again developed an episode. She was then treated with intravenous (IV) antibiotics for 6 weeks. Subsequently, she had dental implant surgery due to suspicion of infection that was not detected during surgery. She again developed an episode in 1 week.

With her next episode, she was admitted to the hospital for possible *Clostridium difficile* colitis and was treated with vancomycin and solumedrol, and discharged on vancomycin. She continued to have her monthly episodes, and she was admitted again for another episode, and, at that time, a computed tomography showed retropharyngeal edema and neck muscle edema, and she was treated with intravenous steroids, intravenous antihistamines, and intravenous antibiotics. She was then started on loratadine four times a day, which did not help with her symptoms, and she continued to have attacks. The patient noted some temporary improvement in symptoms with prednisone. She was then referred to us for further evaluation in our allergy and immunology clinic. Her medical history was significant for breast cancer status-post bilateral mastectomy and uterine cancer status-post hysterectomy, Hashimoto thyroiditis, gastrointestinal bleed, and rheumatoid arthritis.

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PHYSICAL EXAMINATION

The patient's vital signs included blood pressure of 140/60 mm Hg, heart rate of 74 beats per minute, and respiratory rate of 18 breaths per minute. She was afebrile and not in any apparent distress. No facial swelling was present, and her neck was supple. Her lungs were clear to auscultation, her heart rate had regular rhythm and rate, and no murmurs were heard; her abdomen was soft and nontender, and nondistended. Results of the rest of her physical examination were unremarkable.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Periodic Fever, Rash, Myalgia, and Angioedema?

Because of the periodic nature of fever and other symptoms, we had a very high suspicion for systemic autoinflammatory diseases. These diseases are usually hereditary in nature, although nonhereditary autoinflammatory diseases have been described. They result from a mutant gene that is involved in the regulation of inflammation, which results in different clinical phenotypes associated with that genetic mutation. Diagnosing these diseases can be challenging due to overlap in their clinical presentation. In a significant number of patients with these autoinflammatory diseases, the genetic variant is not found, and a high index of clinical suspicion is the key to the diagnosis. Most of these diseases have an onset in early infancy and childhood, although some of them can present in adulthood as well.

Based on the later age of onset of symptoms for our patient, we had a high suspicion for Schnitzler syndrome, in which symptoms start in adulthood, and, often, intermittent fever is associated with a rash. Fatigue and headache are common with this condition. Fewer than 20% of patients present with lymphoma, immunoglobulin M (IgM) myeloma or Waldenstorms macroglobulinemia. More than 45% have enlarged lymph nodes. Most people have muscle and joint and/or bone pain. Other systemic autoinflammatory diseases, which can present in adulthood, include Bechet disease and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome; both of these diseases are associated with mouth ulcers. Adult onset Still disease presents with recurrent fever at least once a week, which is associated with maculopapular rash and arthralgia. Some of the pyogenic diseases, such as deficiency of interleukin (IL) 36 receptor antagonist and familial psoriasis can also present in adulthood but are associated with pustules and not angioedema. Hyper-IgD syndrome can present with fever, headache, and arthralgia; however, >90% of cases have an onset in infancy but was considered for our differential. (Table 1).

Table 1 **Differential diagnoses for systemic autoinflammatory diseases**

Familial Mediterranean fever
Tumor necrosis factor receptor-1 associated periodic syndrome
Hyperimmunoglobulin D syndrome
Mevalonic aciduria
Cryopyrin-associated periodic syndromes
Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis
Bechet disease
Schnitzler syndrome
Deficiency of the interleukin-1 receptor antagonist
Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) syndrome
Blau syndrome
NLRP12/Familial cold autoinflammatory syndrome-2 (FCAS2)
Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature
Deficiency of the interleukin-36 receptor antagonist
Familial psoriasis
Chronic recurrent multifocal osteomyelitis
STING-associated vasculopathy with onset in infancy
NLRC4-activating mutations
LUBAC deficiency
PLCG2-associated antibody deficiency and immune dysregulation
Systemic onset juvenile idiopathic arthritis
Adult-onset Still disease
Primary familial hemophagocytic lymphohistiocytosis
ADA2 deficiency
SLC29A3 Spectrum disorder

Based on the Differential Diagnosis, What Laboratory Tests Would You Obtain?

Multiple laboratory reports were reviewed from the patient's previous episodes; these reports demonstrated high white blood cell counts along with high neutrophils, high monocytes, and high eosinophil counts (up to 817 cells/μL). She also had high erythrocyte sedimentation rate and C-reactive protein (CRP) values during the episodes. In between attacks, she had a normal white blood cell count and differential but a high CRP level. Her CRP level was 256 mg/dL during one of the attacks. Her complement C2 and C4 levels were slightly low. The patient had normal immunoglobulin levels. Her rheumatoid factor was elevated (20 IU/mL). A skin biopsy was done, and no specific cells were identified. C1-esterase

inhibitor, complement C1-Q levels, and tryptase levels were normal. Anti-SSA and anti-SSB, anti-smith, double-stranded DNA, mitochondrial, and actin antibodies were negative.

What Additional Diagnostic Testing Should Be Performed?

To evaluate the diagnosis further, we recommended obtaining immunofixation in blood and urine because Schnitzler syndrome can present with monoclonal gammopathy. We also ordered an IgD level during an attack to help exclude hyper-IgD syndrome. We also recommended the following assessments during an attack: a complete blood cell count with differential; IL-1, IL-2, IL-5, IL-6 levels; and the tumor necrosis factor (TNF) α value.

How Would You Treat This Patient?

Subsequent laboratory test results during the attacks showed normal IL-2, TNF-α, and IL-1β levels but an isolated elevated IL-6 level of 30.08 pg/mL, which remained elevated (60.45 pg/mL) on repeated testing even between attacks (reference range, 0.31–5.00 pg/mL). Because the patient had mild eosinophilia during attacks, her IL-5 level was assessed during an attack and was found to be normal. The patient also had a monoclonal IgM component on immunofixation. Because of isolated high IL-6 values, she was started on tocilizumab, and her symptoms of fatigue and arthralgia resolved within days of starting the therapy, and her episodes of fever and angioedema also resolved with the therapy. Genetic testing for common autoinflammatory diseases was done but did not show any variant.

DISCUSSION

Schnitzler syndrome is an autoinflammatory disease characterized by chronic nonpruritic urticaria and monoclonal gammopathy (mainly IgM). The first case of Schnitzler syndrome was diagnosed in 1972, and, since then, 300 cases have been described in the literature.[1] By 2014, 281 cases of Schnitzler syndrome had been reported. It is more common in male patients. There usually is an average diagnosis delay of 5 years.[2] de Koning *et al.*[3] reviewed 94 cases of patients with Schnitzler syndrome and found that the mean ± standard deviation age of onset was 51 ± 12 years. Schnitzler syndrome is often associated with a variety of manifestations, including leukocytosis, elevated erythrocyte sedimentation rate, hepatosplenomegaly, and lymphadenopathy. The recurrent fever, associated weight loss, anemia, arthralgia, myalgia, and bony pains significantly affect the quality of life of individuals who are affected.[4,5]

The exact etiology of Schnitzler syndrome remains unknown. One hypothesis is that the deposition of monoclonal antibodies (IgM) in the basement membranes of blood vessels and dermis mediates complement activation, which, subsequently, causes skin damage and urticarial lesion. IL-1 has been described as the major cytokine involved in Schnitzler syndrome[6] Kurian *et al.*[7] reported the presence of polyclonal antibodies directed against IL-1 α in six of nine patients and the anti–IL-1α antibody could play a role in prolonging the half-life, affect tissue distribution, and increase the activity of IL-1α. Other cytokines involved in the pathophysiology include IL-6, which could cause the systemic features. The effect on IL-6 levels on B-cell differentiation could explain the development of monoclonal gammopathy.[3]

CONCLUSION

Our case was unique secondary to the late age of onset (69 years of age), atypical symptoms (mainly neck and head), rash (mainly angioedema and not urticaria), and elevated IL-6 level (compared with the usually elevated IL-1 level). Also, her complete resolution of symptoms with tocilizumab made this case rather rare. Our final diagnosis was Schnitzler syndrome with monoclonal IgM and elevated IL-6 levels. Several case reports have been described in literature.[8] A review of the literature for reported cases with isolated IL-6 shows that the latest presenting age was 65 years.[9]

In patients with confirmed Schnitzler syndrome, a decision to treat is usually based on significant alterations in quality of life or on the persistent elevations of inflammatory markers. Several treatments, including colchicine, dapsone, thalidomide, interferon, IV immunoglobulin, immunosuppressive drugs (including methotrexate and cyclosporine), rituximab, psoralen and ultraviolet A (PUVA), and anti–TNF-α, have been explored, with inconsistent results. IL-1 neutralizing agents, *e.g.*, anakinra, are recommended as first-line treatment. Longer-acting IL-1 antagonists, *e.g.*, canakinumab, have been successfully used but also are more expensive. A failure of anakinra should prompt reconsideration of the diagnosis but may also be managed by increasing the dosage of anakinra and possibly by the addition of colchicine or pefloxacin, or, alternatively, treatment with tocilizumab (IL-6 inhibitor) may be considered.

Krause *et al.*[9] described three patients who had complete resolution of symptoms with tocilizumab despite having tried other treatments, which failed. Tocilizumab has been shown to alleviate urticaria, fever, and muscle and bone pain, and also to reduce CRP levels and serum amyloid A levels. The recurrence of symptoms after stopping the treatment confirmed the effec-

tiveness of tocilizumab in patients with isolated IL-6 elevation.[9] The patient we described also responded well to treatment with tocilizumab. Clinical trials aimed at exploring the safety and efficacy of tocilizumab in patients with active Schnitzler syndrome are currently in progress in Germany. Our case report added to a growing body of evidence that tocilizumab is likely an efficacious treatment in Schnitzler syndrome.

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Patient Oriented Problem Solving (POPS) Case Report

A 45-year-old man with elevated levels of immunoglobulin A

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ABSTRACT

Quantitative immunoglobulin tests are often ordered as part of the initial evaluation for suspected immune deficiency. Although alterations in immunoglobulin levels can explain recurrent infections, in a patient without symptoms, there are a variety of other factors that can alter immunoglobulin levels. Common causes for elevated immunoglobulin A levels include malignancy and hepatic impairment in addition to a variety of infiltrative, infectious, and inflammatory diseases. We present a case of a 45-year-old man with a history of recurrent sinopulmonary symptoms without bacterial infection found to have an isolated elevated level of immunoglobulin A.

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CHIEF CONCERN

Elevated immunoglobulin A (IgA) level.

HISTORY OF PRESENT ILLNESS

A 45-year-old man with a history of hypertension, dyslipidemia, and irritable bowel syndrome presented for an immunology consultation for elevated IgA obtained as part of an evaluation for recurrent sinopulmonary symptoms. The patient reported 10 sinopulmonary "infections" in the past 10 months, with frequent episodes of rhinorrhea that alternated with nasal congestion, sinus pressure, sore throat, and coughing. He had no history of nasal symptoms, polyps, or major infections. He never required antibiotic treatment because the symptoms self-resolved within 2 weeks. In the past month, his symptoms became more persistent, and he received a 10-day course of amoxicillin-clavulanate for suspected sinusitis, after which symptoms completely resolved. He did not have documented abnormal cultures or imaging. A review of systems was otherwise unremarkable. He did not have fevers, chills, night sweats, weight loss, jaundice, nausea, abdominal pain, joint pain, skin changes, lymphadenopathy, or changes to bowel or bladder patterns.

He was not taking any prescription medications but started acupuncture 6 months earlier. He reported taking multiple herbal supplements and currently was taking Bone Broth Protein Turmeric (Ancient Nutrition LLC, North Palm Beach, FL), Garden of Life Super Seed (Certified B Corporations, Palm Beach Gardens, FL), Raw One Multivitamin (Certified B Corporations, Palm Beach Gardens, FL), Carlson Super Omega 3 (Carlson Laboratories Inc, Arlington Heights, IL), Syntol AMD probiotic (Arthur Andrew Medical, Scottsdale, AZ), Ecliptex (Health Concerns, Oakland, CA), and Ease 2 Chai Hu Gui Zhi Tang (Health Concerns, Oakland, CA). These supplements were frequently changed by his acupuncturist, depending on his symptoms. His family history was significant for myocardial infarction in his maternal grandmother at age 52 years old. He otherwise had no known family history of immunodeficiencies or autoimmune disease.

PHYSICAL EXAMINATION

Vital signs were within normal limits. He was well appearing and not obese. Results of his examination were remarkable only for bilateral inferior turbinate hypertrophy with boggy pale mucosa and clear mucous. Posterior oropharynx was clear without cobblestoning. Results of a cardiac examination revealed a regular rate and rhythm, and the absence of murmurs. The lungs were clear bilaterally. The abdomen was soft and nontender, with normoactive bowel sounds. There was no lymphadenopathy or significant hepatosplenomegaly. The extremities were not edematous.

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LABORATORY FINDINGS

The patient had completed recent blood work as part of his annual physical examination. A complete blood cell count revealed no neutropenia (white blood count, 5530/μL), although he had a new mild anemia (hemoglobin, 11.8 g/dL) and thrombocytopenia (118,000/μL). His basic metabolic panel was normal, with a creatinine level of 0.66 mg/dL. He had hyperbilirubinemia (total bilirubin level, 2.3 mg/dL), with elevated transaminases (aspartate transaminase level, 175 U/L; alanine transaminase level, 87 U/L; alkaline phosphatase, 212 U/L). A fasting lipid panel revealed marked dyslipidemia (total cholesterol level, 1128 mg/dL; low density lipoprotein level, 827 mg/dL; high density lipoprotein level, 50 mg/dL; triglycerides, 395 mg/dL). He had an isolated elevated IgA level of 750 mg/dL (reference range, 87–426 mg/dL), with normal IgG (1220 mg/dL), IgM (265 mg/dL), and IgE (59 mg/dL) values. Previous laboratory studies (complete blood cell count, basic metabolic panel, and liver function tests) had been normal 7 months earlier. Three years ago, he had a normal IgA level of 368 mg/dL, obtained as part of the workup for celiac disease. At that time, he had normal laboratory study results, including liver function tests, although a fasting lipid panel showed mild dyslipidemia (total cholesterol level, 284 mg/dL; low density lipoprotein level, 174 mg/dL; high density lipoprotein level, 59 mg/dL; triglyceride level, 421 mg/day).

CLINICAL COURSE AND ADDITIONAL WORKUP

To address his history of primarily sinopulmonary symptoms, we initiated an empiric regimen of daily saline solution sinus rinses, followed by an intranasal corticosteroid spray. Sinus imaging was not obtained because the patient was asymptomatic at the time of evaluation. We discussed the role of testing for environmental sensitizations, but this was deferred because testing was unlikely to change acute management of his sinus disease. In assessing the patient's risk factors for hepatic disease, we learned he had a >20-year history of heavy alcohol use. In the past month, he had cut down from 27 drinks per week (3 glasses of wine daily, 6 drinks on the weekends) to ~10 drinks per week. He endorsed that he had been drinking heavily around the time of his physical examination and laboratory tests. He stated that he had no history of illicit or intravenous drug use or blood transfusions, although he had a homemade tattoo placed on his arm during his teenage years that had subsequently been removed.

Further laboratory studies showed that the patient did not have human immunodeficiency virus and total complement was normal. B-cell, T-cell, and natural-killer cell enumerations were normal. Serum protein electrophoresis and serum immunofixation did not show a monoclonal pattern. Results of a hepatitis panel were negative. Iron studies were not consistent with hemochromatosis. Dyslipidemia was confirmed by multiple assays, and, after consultation with a lipid specialist, the patient was diagnosed with familial hypercholesterolemia. To further characterize the liver pathology, abdominal ultrasound was obtained, which showed mild hepatomegaly with hepatic steatosis.

To evaluate for fibrosis, magnetic resonance imaging with elastography was obtained of the liver, which showed steatosis without evidence of fibrosis. After 2 weeks of abstaining from alcohol and discontinuing all herbal supplements, along with medical management of his dyslipidemia, results of the patient's liver function tests quickly normalized. Due to the patient's normal liver function tests 7 months earlier, the acute change in the setting of recent antibiotics and timing of starting herbal supplements, the patient was thought to have drug-induced liver inflammation on a background of hepatic steatosis from long-term alcohol use and metabolic syndrome. No further hepatic workup, therefore, was pursued. At his follow-up visit 2 months later, the patient had not experienced any interim major infections. His sinus symptoms were well controlled. We planned to recheck his IgA level; however, we learned that he had experienced several interim relapses of alcohol use and his liver transaminase levels were elevated again. He, unfortunately, was lost to immunology follow up thereafter.

DISCUSSION

Immunoglobulins function to combine with and facilitate removal of foreign antigens from the body. Human IgA is one of these antibodies, predominantly found in its monomeric form in the serum and polymeric form in secretions.[1] IgA is known to be important in neutralizing bacteria and viruses by interfering with epithelial adhesion and removing antigens at sites with mucosal linings (mouth, digestive tract, and respiratory tract). Typically, recurrent sinopulmonary infections are associated with immunoglobulin deficiency, although numerous abnormalities of immunoglobulin production can occur. There can be either congenital or acquired deficiencies of one or all of the immunoglobulins, and, conversely, there can also be an overproduction of any immunoglobulin.[2] When considering if a level is abnormal, one should interpret the result by using reference ranges based on age-matched controls. Immunoglobulin levels change with age, with minor differences detected based on sex and race. Total serum IgA has been shown to be positively associated with increased age, male sex, heavy alcohol use, and the presence of metabolic syndrome.[3] The incidence of an isolated elevated IgA level is unknown.

Table 1 **Differential diagnoses of elevated immunoglobulin A (IgA) levels**

Monoclonal IgA
Systemic amyloidosis
Multiple myeloma
Monoclonal gammopathy of undetermined significance
Solitary plasmacytoma
Polyclonal IgA
Infection
IgA nephropathy
Wiskott Aldrich syndrome
Intestinal inflammatory disease
Connective tissue disease
Rheumatoid arthritis
Systemic lupus erythematosus
Mixed connective tissue disorder
Vasculitis
Liver disease
Cirrhosis
Hepatitis
Biliary disease
Steatosis

Increased serum immunoglobulin levels can be either monoclonal or polyclonal (Table 1). If our patient had a high IgA level with monoclonal gammopathy, then the differential diagnosis would include multiple myeloma, monoclonal gammopathy of undetermined significance, and primary systemic amyloidosis. Our patient had a polyclonal elevation of IgA, which is usually associated with underlying infectious or inflammatory processes.[4] The most common etiology for polyclonal gammopathy is liver disease, but also includes intestinal inflammatory disease, connective tissue disease, and acute and chronic infections.[5] Given the role of IgA, it is often elevated with infections that cause mucosal antigenic stimulation,[1] with one case report of an elevated IgA value in a young patient with chronic salmonellosis.[6] Gammopathies can also cause tissue deposition, such as IgA nephropathy.[1]

Very high concentrations of total IgA have especially been found in patients with chronic liver disease.[1] High levels of IgA are found in patients with hepatitis and cirrhosis, independent of alcoholic or nonalcoholic etiologies. Patients with milder disease, such as steatosis and fibrosis from alcohol use, had much higher IgA concentrations compared with those with nonalcoholic liver disease.[7] It has also been proposed that increased bacterial overgrowth and gut translocation in patients with chronic liver disease, especially those with cirrhosis, cause B cells to activate and overproduce immunoglobulins, *e.g.*, IgA.[8,9] In addition, patients with chronic liver disease have alterations in IgA receptors, which reduce IgA clearance and catabolism.[1,10]

FINAL DIAGNOSIS

Elevated IgA levels that corresponded with acute liver inflammation from multifactorial drug–induced liver injury.

CONCLUSION

Our patient had recurrent sinopulmonary symptoms that did not require antibiotic treatment, without documented culture or imaging suggestive of infection. We had a higher suspicion for untreated chronic rhinitis causing recurrent sinopulmonary symptoms rather than true immune deficiency. With empiric treatment, the patient's symptoms were well controlled. The incidental finding of an elevated IgA level, however, highlighted an interesting differential diagnosis in a patient who had multiple risk factors known to be correlated with an elevated IgA level. Interestingly, none of these risk factors corresponded with an elevated IgA level just 3 years earlier. The newly elevated IgA level seemed to correspond with acute hepatic inflammation as shown by elevated liver transaminase levels, which were thought to be due to a combination of herbal supplements, antibiotics and alcohol causing multifactorial drug–induced liver injury. Ultimately, we would have liked to repeat an IgA level assessment at the time of normal liver function tests to see if the IgA level correspondingly normalized; however, we were unable to do so due to interim alcohol relapses and the loss to follow up.

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Patient Oriented Problem Solving (POPS) Case Report

Generalized rash and pruritus in a 58-year-old woman

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ABSTRACT

Although allergists often evaluate rashes associated with allergic, IgE mediated etiologies, it is important to consider a wide range of differential diagnoses that includes inflammatory, infectious, and autoimmune etiologies. The case of a 58-year-old woman with a 1-year history of progressive pruritic rash that did not improve with topical creams and steroids is presented. The patient did not state any other symptoms, and a physical examination was notable for a widespread rash. After a detailed evaluation of the rash, a differential diagnosis was made, and results of a skin biopsy confirmed a specific diagnosis. Even in the context of a medical history of atopy, one must consider nonallergic causes of rash, including abnormal presentations of systemic conditions. It is important to determine the specific etiology of the rash because this will dictate treatment and prognosis and/or complications of the disease associated with the skin manifestations.

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CHIEF CONCERN

The patient complained of itchy rash.

HISTORY OF PRESENT ILLNESS

A 58-year-old woman presented with a 1-year history of an erythematous, pruritic rash. It started on her hips and spread to her arms, scalp, face, chest, back, and, most recently, her bilateral thighs. She reported prominent scalp itch. She did not have other physical concerns. The patient did not use any new laundry detergents, perfumes, cosmetics, nail polish, or hair products, and did not have variations in her diet.

MEDICAL HISTORY

The patient's medical history was remarkable for asthma, allergic rhinitis, Grave disease, celiac disease, and atopic dermatitis (AD). There was a family history of AD and multiple sclerosis.

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PHYSICAL EXAMINATION

The patient's vital signs were normal. She exhibited pink macules on her face in a malar distribution and diffuse erythema over her chest in a V-neck distribution as well as the upper back, shoulders, and neck. There were pink papules on the bilateral hips and forearms, and crusting, scaly red plaques on the bilateral anterior thighs. She had scaly, violaceous plaques over the knuckles, with pitting and/or ridging of fingernails (Fig. 1). Muscle strength and the remainder of her examination was normal.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

The patient had a normal complete blood cell count, and comprehensive metabolic panel was normal. Results of antinuclear antibody, anti-histone antibody, and anti-Mi-2 antibody were positive (Table 1).

CLINICAL COURSE

The rash persisted over the past year and did not improve, despite multiple courses of prednisone and trials of high-potency topical corticosteroids. She was seen by an allergist, who thought that the rash could be secondary to medication, but symptoms did not improve after stopping the medication. She was treated with topical permethrin and oral ivermectin for the possibility of scabies and a parasitic infection, but there was no symptomatic improvement.

QUESTION 1

What is the differential diagnosis?

a. AD

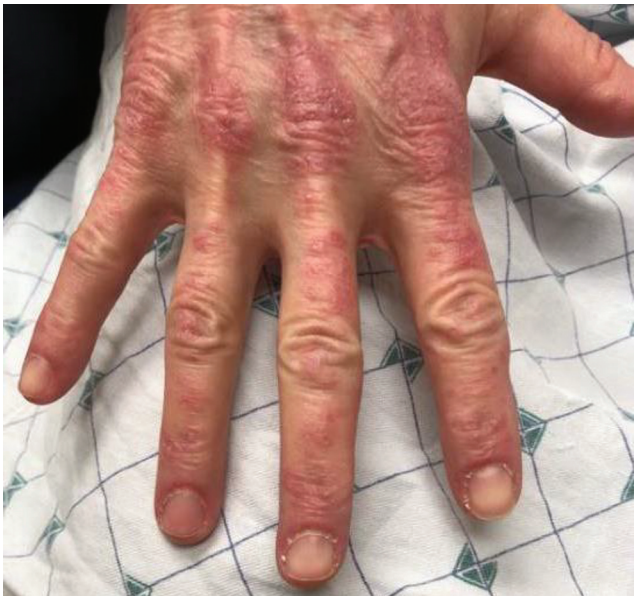

Figure 1. *Photograph of the patient's hand, demonstrating rash over the knuckles and periungual and nail bed changes.*

b. Contact dermatitis (CD)
c. Subacute cutaneous lupus erythematous (SCLE)
d. Polymorphous light eruption (PLE)
e. Dermatomyositis (DM)

QUESTION 2

What diagnostic studies should be performed?

A skin biopsy is the next logical step. A shave biopsy of the right hand and a punch biopsy of the left lateral hip were performed. Results of the shave biopsy demonstrated hyperkeratosis and mild epidermal atrophy. An interface dermatitis was noted, with scattered dyskeratotic keratinocytes seen. A mild lymphocytic inflammatory infiltrate was noted in the superficial dermis with dermal mucin deposition (Fig. 2). She was scheduled for a follow-up appointment in the rheumatologic dermatology specialty clinic, with additional workup to rule out comorbid medical conditions.

Table 1 **Laboratory results**

	Results	Reference Range
White blood cell count, k/μL	5.52	4–10.4
Hemoglobin level, g/dL	12.8	11.7–15
Hematocrit, %	38.2	35–44
Platelets, k/μL	301	150–350
Absolute neutrophils, k/μL	2.73	2–7.7
Absolute lymphocytes, k/μL	2.14	1–3.4
Absolute eosinophils, k/μL	0.10	0–0.5
ALT level, U/L	9	0–33
AST level, U/L	17	0–32
Alkaline phosphatase level, U/L	67	35–115
Total bilirubin level, mg/dL	0.2	0–1.2
CPK level, U/L	59	26–192
ANA	1:640 speckled H	<1:40
Anti–double-stranded DNA, IU/mL	10.29	<30
Anti-Smith, U/mL	5.7	<20
Anti-RNP, U/mL	5.26	<20
Anti-SSA, U/mL	3.33	<20
Anti-SSB, U/mL	3.33	<20
Anti-centromere B, U/mL	12.15	<20
Anti-SCL70, U/mL	4.58	<20
Anti-histone, U/mL	2.17 H	<1
Anti-JO1, U/mL	3.86	<20
Anti-SRP	None detected	None detected
Anti-Mi-2	None detected	None detected
CRP level, mg/dL	0.13	<0.5

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; ANA = antinuclear antibody; RNP = ribonucleoprotein; SSA = Sjögren's-syndrome-related antigen A; SSB = Anti-Sjögren's-syndrome-related antigen B; SRP = signal recognition particle; CRP = C-reactive protein.

DISCUSSION

Pruritic rashes are very common and have a broad differential diagnosis, including diseases with allergic, genetic, infectious, and autoimmune etiologies. Although rashes are commonly associated with allergic etiologies, there may be more complex etiologies with severe complications that require prompt diagnosis and more aggressive treatments.[1] Therefore, in a patient with widespread skin findings and a significant history of autoimmune conditions, the provider must have a high suspicion for uncommon variants of more complex conditions.

AD and CD are both characterized by intense pruritus. Acute AD is associated with erythematous papules, plaques, and vesicles, usually localized to flexural surfaces in adults, whereas chronic AD is dry and/or scaly patches often with excoriation or lichenification.[2] CD, which is typically localized, can also be acute or chronic, with the acute phase characterized by erythematous papules and/or plaques. Chronic CD presents with dry, scaly, thickened skin. Symptoms resolve with topical steroids and, in the case of CD, with

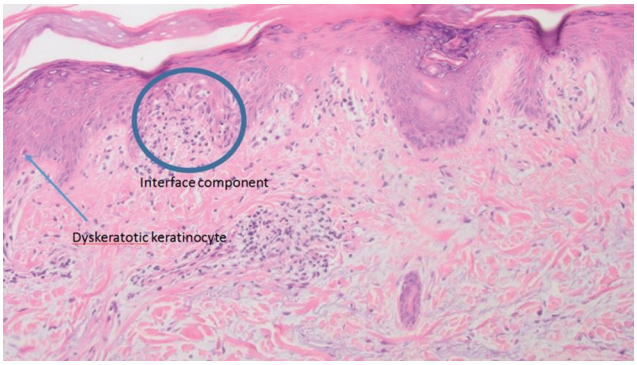

Figure 2. Shave biopsy of the right hand, showing an interface dermatitis with scattered dyskeratotic keratinocytes.

removal of the offending agent. Scalp itch is not pronounced in AD or CD as it is in other skin conditions unless the allergen is being applied directly to the scalp. Due to the widespread rash and lack of response to topical and oral steroids, AD and CD were excluded.[3]

SCLE most commonly presents as the "psoriasiform/papulosquamous" and the "annular-polycyclic" variant. The primary lesion is usually an erythematous papule or plaque covered with fine scales that either expand or merge into retiform arrays of papulosquamous lesions or develop central clearing and produce annular lesions that merge into polycyclic arrays. These lesions normally occur in sun-exposed areas and are associated with significant light sensitivity, musculoskeletal symptoms, and systemic symptoms.[4] SCLE typically responds to systemic steroids, which makes this a less likely cause of rash in our patient.

PLE is characterized by pruritic skin lesions, including papules, plaques, vesicles, and targetoid macules, that occur on sun-exposed areas during spring or early summer. These lesions occur hours to days after exposure to sunlight and resolve after a few days if sunlight is avoided. These lesions are often indistinguishable from cutaneous lupus, and the antinuclear antibody level can be elevated in both PLE and cutaneous lupus. Lesions are prevented by avoiding sun exposure, and lesions are treated with topical oral steroids, depending on severity.[5] The distribution of the patient's rash and the elevated antinuclear antibody level could be consistent with PLE, but the persistent nature of the rash and the lack of improvement with steroids make the diagnosis less likely.

DM is an idiopathic inflammatory myopathy (IIM). In addition to the features of proximal muscle weakness and muscle inflammation, DM also has specific cutaneous manifestations associated with the disease: Gottron's papules (pink to violaceous papules that symmetrically involve the dorsal aspects of the metacarpophalangeal and interphalangeal joints); Gottron's sign (pink to violaceous macules, patches, or papules that involve extensor surfaces of other joints); heliotrope rash; facial erythema; generalized erythroderma; photograph-distributed poikiloderma (including the V-neck and shawl sign in photo-exposed areas to upper chest and/or upper back); Holster sign (poikiloderma on the lateral aspects of the thighs); and periungual abnormalities, including dilated nail bed capillary loops, periungual erythema, and ragged cuticles (Samitz sign).[6]

A less well-recognized subtype of DM found in ~20% of cases,[7] amyopathic dermatomyositis (ADM) is associated with the characteristic skin manifestations of DM, without skeletal muscle weakness or diagnostic findings of muscular inflammation.[8] However, skin findings of DM may precede the onset of muscle weakness,[9] which indicates that a patient with solitary cutaneous findings may be early on in the disease process of classic DM.[6]

Historically, the diagnosis of DM was made by using the Bohan and Peter criteria,[10,11] which relied on the presence of muscular involvement on examination, laboratory and electromyography studies, and typical muscle biopsy findings, including "necrosis, phagocytosis, regeneration, and inflammation."[10,11] Dermatologic features of DM were also part of the criteria.[10,11] Newer criteria, proposed by Sontheimer[12] for ADM dropped the requirement of muscle biopsy, abnormal laboratories, and electromyographies, and, instead, relied on the presence of classic skin manifestations of DM for >6 months in the absence of muscle involvement (on examination or laboratory evaluation), with a skin biopsy result consistent with DM.[12]

Of patients with classic DM, 95% will have an elevation in serum aldolase and creatine kinase (CK), which indicates muscular involvement.[6] The CK value may be elevated by 50 times the normal level in patients with DM but is a nonspecific enzyme marker.[9] Other studies that can be performed to demonstrate muscular inflammation include lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase.[6] Antihistone antibodies may also be present in inflammatory myopathies.[13]

Autoantibodies are important for confirming the diagnosis of DM and can be identified in >80% of patients with autoimmune myositis, but they are not required for diagnosis. Myositis-specific antibodies, including anti-aminoacyl-tRNA (transfer RNA) synthetase, anti-Mi-2, anti-SRP, and several novel antibodies, including anti-TIF1-gamma, have a specificity of greater than 90% for autoimmune myositis when present.[14] Further confirmatory testing can include muscle biopsy and skin biopsy. If there is skin involvement characteristic of DM, associated with other typical clinical features of DM, then a muscle biopsy can be avoided. Skin biopsy would reveal atrophy of epidermis, associated with vacuoles in the basal keratinocyte

layer and with perivascular and lichenoid interface lymphocytic infiltrate.[7]

In addition to the typical cutaneous and muscular involvement, DM is often associated with involvement with other organs. Interstitial lung disease (ILD) is often associated with the IIMs and is seen in ~5 to 40% of patients with DM.[6] The most common patterns of myositis-associated ILD histology in lung biopsy include nonspecific interstitial pneumonia, general interstitial pneumonia, organizing pneumonia, diffuse alveolar damage, and lymphocytic interstitial pneumonia. The presence of ILD indicates a worse prognosis and requirement of more aggressive therapy for the patient.[15] Patients with DM have an ~25% chance of developing a malignancy, particularly adenocarcinoma of the breast, lung, gastrointestinal tract, and ovaries.[6] The increased risk for malignancy lasts for 3 years after initial onset of the symptoms; the risk returns to baseline by year 5.[16]

Treatment and management of DM vary with the specific presentation of the patient. Immunosuppressants are the criterion standard for treating dermatomyositis, and systemic prednisone is the most commonly used.[6] Muscle inflammation is much more responsive to prednisone than the skin manifestations.[6] If symptoms do not resolve or if the patient relapses, then a second-line immunosuppressant can be added, such as methotrexate or intravenous immunoglobulin.[9] In patients with ADM that is refractory to prednisone, the medical literature demonstrates improvement with topical corticosteroids or tacrolimus, and avoidance of sunlight, but most cases require systemic therapy.[6] The prognosis of DM is variable, depending on the timing of the diagnosis and the presence of extramuscular manifestations, including ILD and malignancy.[6] Severe forms of ILD can worsen the prognosis, *e.g.*, rapidly progressive ILD that can be associated with ADM.[17]

FINAL DIAGNOSIS

ADM.

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Patient Oriented Problem Solving (POPS) Case Report

An 82-year-old man with recurrent angioedema

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ABSTRACT

Angioedema is a potentially life-threatening swelling condition that can occur either in isolation or in the context of other syndromes, e.g., *anaphylaxis. Angioedema is typically asymmetric, lasts for hours to days, is not gravity dependent, and is often nonpitting. Recurrent angioedema is typically associated with histaminergic and bradykinin-mediated causes, some of which can indicate underlying etiologies with high morbidity or mortality. The differential diagnosis for acute angioedema can include anaphylaxis, chronic urticaria with angioedema, medications such as angiotensin-converting-enzyme inhibitors, hereditary C1 esterase inhibitor defects, and acquired defects; however, the cause is often idiopathic, and effective therapy can be elusive. In this article, we described a unique etiology of a case of isolated recurrent angioedema that improved when the possible underlying cause was successfully treated.*

(Allergy Asthma Proc 40:350–353, 2019; doi: 10.2500/aap.2019.40.4242)

CHIEF CONCERN

Swelling

HISTORY OF PRESENT ILLNESS

The patient was an 82-year-old man with a history of treated prostate cancer, hypertension, and hyperlipidemia who was admitted to our critical care medical unit with oropharyngeal swelling and difficulty handling secretions. There was no concurrent pruritus, urticaria, cough, nausea, vomiting, diarrhea, abdominal pain, chest pain, lightheadedness, or loss of consciousness. He had no fevers, chills, night sweats, or weight loss. He would take occasional nonsteroidal anti-inflammatory drugs for gout, although not recently. Home medications included amlodipine, aspirin, metoprolol, and simvastatin. He experienced one episode of facial angioedema with angiotensin-converting enzyme inhibitor use 20 years earlier, which resolved with medication cessation. Four weeks before presentation, the patient had isolated lip angioedema attributed to chlorthalidone; the medication was stopped and the swelling resolved. He had no other history of swelling, abdominal pain, or urticaria.

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The authors have no conflicts of interest to declare pertaining to this article

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PHYSICAL EXAMINATION

The patient's vital signs included a temperature of 36.4 °C, blood pressure 110/61 mm hg, heart rate 51 beats/minute, and respiratory rate 12 breaths/minute. There was nonpitting angioedema of the lips, face, and tongue (Fig. 1). The lungs were clear to auscultation, without wheezing; heart rate was bradycardic but regular; and the abdomen was without masses or hepatosplenomegaly. There was no urticaria on skin examination. The rest of the examination was unremarkable.

INITIAL LABORATORY AND DIAGNOSTIC FINDINGS

Laboratory analysis demonstrated a hemoglobin of 16.5 g/dL (normal range, 13.5–17 g/dL), platelets were 222,000/mm^3 (normal range, 150,000–400,000/mm^3), and white blood cell count was 7700/mm^3 (4000–10,000/mm^3). The differential included neutrophils, 4100/mm^3; lymphocytes, 2600/mm^3; monocytes, 500 cells/mm^3; and eosinophils, 400 cells/mm^3 (all normal). Results of the patient's chemistries showed a creatinine level of 0.93 mg/dL (normal range, 0.7–1.3 mg/dL), blood urea nitrogen level of 13 mg/dL (normal range, 8–20 mg/dL), and albumin level of 3.4 g/dL (normal range, 3.43–4.84 g/dL).

The patient received epinephrine, antihistamines, and intravenous glucocorticoids without effect. A fiberoptic laryngoscopy showed sparing of the larynx, with unremarkable glottic and supraglottic structures. Due to significant oropharyngeal swelling, the patient underwent intubation. A further laboratory workup was performed. Complement component 4 (C4) was 25 mg/dL (normal range, 13–60 mg/dL), complement

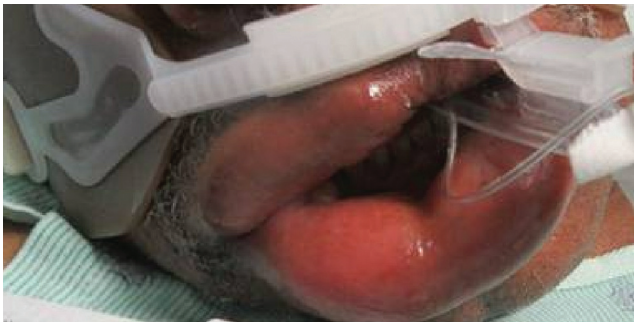

Figure 1. An example of the patient's lip swelling.

component 1q (C1q) was 20 mg/dL (normal range, 12–22 mg/dL), C1 esterase inhibitor function was >90% of normal, and C1 esterase inhibitor antigen was 36 mg/dL (normal range, 13–37 mg/dL). His immunoglobulin G (IgG) level was 1080 mg/dL (normal range, 620-1520 mg/dL), IgA level of 274 mg/dL (normal range, 40–350 mg/dL), and IgM level of 109 mg/dL (normal range, 50–370 mg/dL). The tryptase level was 3.9 ng/mL (normal value, < 11.4 ng/mL). A serum protein electrophoresis with immunofixation showed no M-protein. The prostate specific antigen was 4.2 ng/mL (normal range, 0–6.5 ng/mL), consistent with the patient's known biochemical recurrence and stable over the years. The patient's swelling improved over 2 days, and he was successfully extubated. It was requested that unnecessary medications be stopped; simvastatin and aspirin were discontinued. He was discharged on cetirizine 10 mg daily.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Angioedema?

Angioedema denotes self-limited swelling that occurs from extravasation of fluids.[1,2] Angioedema occurs during anaphylaxis, with acute and/or chronic urticaria, or in isolation. Angioedema is typically asymmetric, with onset of minutes to hours and resolution of hours to days; is not gravity dependent (usually affecting the face, larynx, upper extremities, bowels, and genitals); and is nonpitting.[2]

The differential diagnosis includes histamine- and bradykinin-related angioedema.[2,3] Anaphylaxis may occur due to foods, medications, insect stings, mastocytosis, or other causes; anaphylaxis is typically associated with additional symptoms and has a rapid onset and resolution.[2,3] Chronic urticaria is often idiopathic or related to autoimmune thyroid and rheumatologic diseases.[3] Bradykinin-related angioedema typically does not include other symptoms; causes include hereditary angioedema (HAE), acquired angioedema (often associated with neoplasms, including lymphoma), and medication-related (such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs).[3] Many cases of isolated angioedema are idiopathic, although these often respond to oral antihistamines and thus may be histamine related.[2,3] Unusual presentations of hypereosinophilic syndrome or urticarial vasculitis may be considered.[4] Gleich syndrome is a rare disorder that involves episodic angioedema and eosinophilia with an elevated IgM level, followed by increased urine production.[5] Venous thrombosis, such as superior vena cava syndrome, can be mistaken for angioedema, although clotting typically produces durable swelling that does not meet the definition of angioedema.[6]

What Additional Laboratory Data or Investigations Should Be Performed?

A thorough history should evaluate for allergic symptoms, urticaria, pruritus, previous episodes of swelling, drug exposures, insect stings, foods, autoimmune problems, thyroid derangements, and blood clots. Laboratory evaluation should include a sedimentation rate, C-reactive protein, antinuclear antibodies, and thyroid stimulating hormone (TSH) with free T3 and T4. Screening for infectious etiologies, including hepatitis A, B, and C, can be considered. Imaging of the cervical and cerebral vasculature could be pursued to rule out venous thrombosis. With future angioedema episodes, a diagnostic trial of the bradykinin receptor antagonist icatibant would be reasonable to avert intubation; case reports have shown the effects in idiopathic angioedema when given promptly.[7,8]

CLINICAL COURSE

The patient experienced four more episodes of angioedema over the subsequent months; the first required intubation for airway control, and he was extubated after 3 days. A trial of icatibant was unhelpful. The three later episodes were monitored without intubation. Episodes had an onset of several hours and took approximately 3 days to resolve. Angioedema occurred in the absence of other symptoms, such as urticaria, itching, abdominal symptoms, chest pain, dyspnea, or cough. He did not respond to discontinuing amlodipine, increasing cetirizine up to 20 mg twice daily, or adding oral glucocorticoids.

A further imaging and laboratory investigation was undertaken. Diagnostic vascular ultrasound and computed tomography venogram of the head and neck showed no evidence of venous thrombosis. Total hemolytic complement was 74 units/mL (normal range, 41–95 units/mL). Repeated studies, including complete blood cell count, comprehensive metabolic panel, complement component 4 (C4), complement component 1q (C1q), C1 esterase inhibitor antigen and function, remained unchanged. An erythrocyte sedimenta-

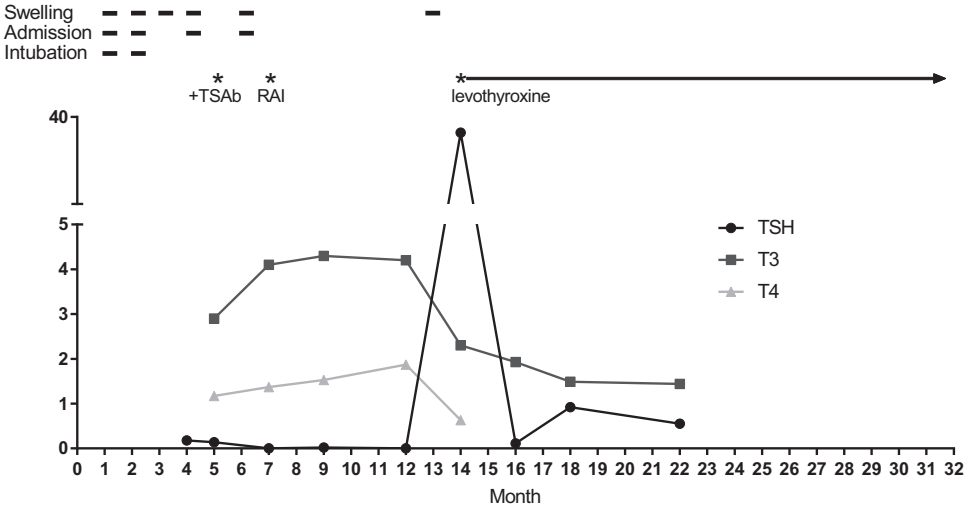

Figure 2. *A timeline of the patient's episodes, interventions, and laboratory test results. Thyroid stimulating hormone (TSH) units are mIU/L, free T3 units are pg/mL, and free T4 units are ng/mL. RAI = radioactive iodine ablation; TSAb = thyroid stimulating antibodies.*

tion rate was 24 mm (normal range, 0–15 mm). C-reactive protein was 0.6 mg/dL (normal range, 0.0–0.6 mg/dL). Results of an antinuclear antibody screening were negative. Results of hepatitis A IgM, hepatitis B surface antigen, and core IgM, and hepatitis C antibodies were all negative.

A TSH level was 0.18 mIU/L (normal range, 0.3–5.5 mIU/L) and was 0.14 mIU/L on repeated assessment. The free T3 level was 2.9 pg/mL (normal range, 1.9–3.9 pg/mL), and the free T4 level was 1.17 ng/dL (0.76–1.70 ng/dL). Subsequent TSH levels were undetectable; the patient's free T3 level rose to a peak of 4.3 pg/mL, and his free T4 level rose to a peak of 1.87 ng/dL. A thyroid stimulating immunoglobulin index was twice elevated, at 1.9 and 2.0 (normal value, <1.3).

Results of a thyroid iodine uptake scan revealed diffuse uptake throughout the thyroid. The patient was diagnosed with Graves' disease and underwent radioiodine thyroid ablation. He had one additional swelling episode after the ablation before achieving biochemical remission of his Graves' disease. After biochemical remission, the patient was started on levothyroxine replacement. In the subsequent 18 months, he did not experience further angioedema episodes. He restarted his discontinued medications without swelling. He is doing well and living independently. A detailed visual timeline is included in Fig. 2.

DISCUSSION

Isolated, recurrent angioedema is often categorized as histamine or bradykinin related, but frequently is idiopathic.[2,3] Patients who do not fit into a category or respond to therapy may have major consequences, such as airway compromise and intubation.[9] Therefore, an astute clinician must consider uncommon etiologies. Autoimmune thyroid disease has been associated with chronic urticaria and angioedema. Increased levels of antithyroid antibodies are reported in 6.5–57% of patients with chronic urticaria, and the rate may be rising.[10] Whether this represents a causative effect whereby antithyroid antibodies cause urticaria and angioedema, or correlative, whereby such antibodies serve as a marker for another process, is not known.[11]

Graves' disease occurs when auto-antibodies against the TSH receptor lead to inappropriate activation of the thyroid gland and clinical hyperthyroidism.[12] Graves' disease has long been associated with chronic urticaria and angioedema.[13] The rate of Graves' disease in patients with chronic urticaria and angioedema is 0.5–2%.[11] Graves' disease, to our knowledge, has not been associated with isolated angioedema in the absence of urticaria in this manner. One patient has been described with coincidental Graves' disease and HAE but seemed to have two separate processes, which required treatment for both HAE and Graves' disease separately.[14] In our patient's case, HAE was not the likely cause of angioedema, a key difference.

Our patient's case was notable in that his angioedema correlated with the onset and treatment of Graves' disease. This was supported by his initially detectable TSH level, which decreased while the free T3 and T4 levels rose, which co-occurred with his angioedema episodes. The TSH receptors, the main auto-antigen in Graves' disease, are primarily located on thyroid gland cells but are also distributed throughout the body.[12,15] TSH receptor antibodies may spike after radioiodine ablation, which could be related to the patient's episode of angioedema after ablation.[16,17] After radioiodine ablation in Graves' disease, the thyroid stimulating antibodies disappear in the majority of patients.[16] We suspect that, in this case, these antibodies had an off-target effect on nonthyroid tissues, which stimulated his episodes of angioedema and which ceased after biochemical remission, although this point was not provable with the current data. A correlation between Graves' disease and angioedema is

not commonly reported in the literature. This case did not establish causation between these processes but did describe a possible correlation.

CONCLUSION

We reported, to our knowledge, the first case of isolated angioedema directly related to Graves' disease, which ceased after biochemical remission of the Graves' disease. When the clinician encounters isolated angioedema not explained by typical etiologies or responsive to therapy, thyroid screening may be warranted. This case suggests that Graves' disease may coincide with isolated angioedema and that the treatment of the thyroid process may be correlated with cessation of angioedema episodes.

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Patient Oriented Problem Solving (POPS) Case Report

A 72-year-old woman with periorbital swelling

Laura J. West, M.D., Andrej A. Petrov, M.D., and Merritt L. Fajt, M.D.

ABSTRACT

As allergists, we are frequently consulted to evaluate patients with swelling presumed to be angioedema. Patients with presumed angioedema can have multiple possible underlying triggers. We present the case of a hospitalized 72-year-old woman with a history of hypertension and metastatic chordoma who developed marked periorbital swelling that precluded eye opening 2 days after a neurosurgical operation (chordoma resection and T10-11 hardware repair). After a detailed evaluation of her swelling, a broad differential diagnosis was made; she did not respond to high-dose antihistamines, systemic steroids, icatibant and angiotensin-converting enzyme inhibitor cessation. Ultimately, computed tomography imaging confirmed a specific diagnosis. The differential diagnosis for swelling is complex, and this case illustrated the importance of considering alternative causes of swelling when evaluating cases of possible angioedema.

(Allergy Asthma Proc 41:e33–e36, 2020; doi: 10.2500/aap.2020.41.190004)

CHIEF CONCERN

Postoperative periorbital swelling.

History of Present Illness

A 72-year-old woman with a history of hypertension (on enalapril for multiple years) and metastatic chordoma that involved the spine, chest wall, and tibia was admitted to the neurosurgical service for chordoma resection and T10-11 hardware repair. Before surgery, she was treated with dexamethasone (4 mg intravenous every 8 hours), which was continued in the postoperative period. Her postoperative pain was managed with scheduled oxycodone and as-needed hydromorphone. Due to perioperative blood loss and decline in hemoglobin (12.0 g/dL on admission, to a nadir of 8.5 g/dL 2 days after surgery), she received a transfusion of 5 units of packed red blood cells. Thirty minutes after initiation of the blood transfusion, the patient became hypotensive (90/64 mm Hg), which resolved within 30 minutes without intervention. However, 4 hours after completion of the blood transfusion, she developed mild periorbital swelling. Over the next 48 hours, her facial swelling progressed to severe periorbital swelling, without rash, that precluded eye opening.

The patient's primary service contacted the Allergy/Immunology consult service for evaluation of ongoing facial swelling. The patient had no history of blood transfusion reactions, facial angioedema, or anaphylaxis. The patient's chronic antihypertensive medications included atenolol and enalapril, with hydralazine added 1 month before presentation. On review of systems, the patient stated no tongue or lip swelling, dyspnea, dysphagia, pruritus, rash, wheezing, abdominal pain, vomiting, or diarrhea. She stated that she had no family history of angioedema.

Physical Examination

Vital signs were within normal limits. Examination was only remarkable for severe bilateral periorbital swelling precluding eye opening (Fig. 1). The oral mucosa was moist, without evidence of lip, tongue, or uvular swelling, or of oral lesions. Results of a cardiac examination revealed a normal rate, regular rhythm, and no murmurs. The lungs were clear bilaterally. The abdomen was soft and nontender. The extremities were not edematous. There was no rash on skin examination.

Laboratory Findings

Results of a laboratory evaluation, including C4 complement level, C1 esterase inhibitor quantity and function, C1q level, and immunoglobulin A level, were normal (Table 1).

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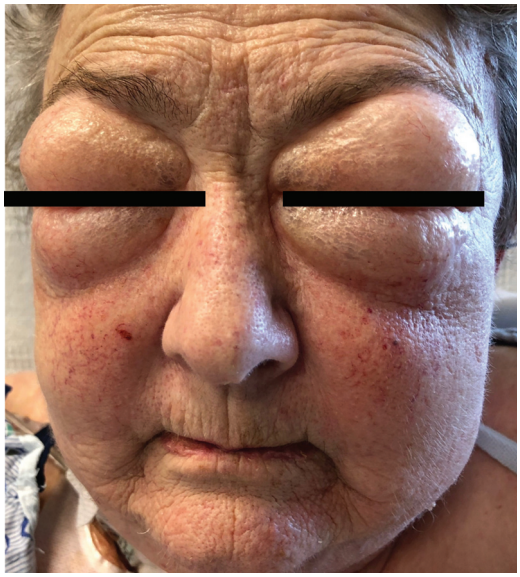

Figure 1. Photograph of the patient, demonstrating marked bilateral periorbital swelling that precluded eye opening.

Table 1 **Laboratory results**

	Results	Reference Range
C4, mg/dL	33	16–38
C1 esterase inhibitor, mg/dL	51	21–39
C1 esterase inhibitor activity, %	>100	>68
C1q, mg/dL	6.3	5–8.6
Immunoglobulin A, mg/dL	117	82–453

Clinical Course

The patient's enalapril was discontinued. Given the progressive nature of her facial swelling, empiric icatibant (30 mg subcutaneous) was administered. She was also initiated on cetirizine 10 mg and famotidine 20 mg, both twice daily, and montelukast 10 mg nightly. She was transitioned from intravenous dexamethasone to oral prednisone 40 mg twice daily. The patient did not demonstrate significant improvement in her swelling after icatibant administration. She was continued on prednisone, histamine H1 and H2 receptor antagonists (H1/H2 blockers), and montelukast without improvement over the following 4 days. Her periorbital swelling persisted, and she remained unable to open her eyes. She also developed waxing and waning bilateral swelling of the hands that intermittently improved when she was in the upright position. Because she did not show clinical improvement with these therapies, the Allergy/Immunology consult team recommended discontinuation of H1/H2 blockers and montelukast, and initiation of prednisone taper over 72 hours. Given a concern for volume overload causing dependent edema, she was administered 2 doses of furosemide without improvement. An ophthalmologist was consulted and noted normal bilateral visual acuity and had no further recommendations. Seven days after surgery, in addition to continued periorbital swelling, the Allergy/Immunology consult team noted crepitus of the bilateral upper extremities on examination.

QUESTIONS

1. What Is the Differential Diagnosis?

a. Angiotensin-converting enzyme (ACE) inhibitor induced angioedema
b. Opiate-associated angioedema
c. Angioedema secondary to a transfusion reaction (symptom onset in close temporal proximity to blood transfusion and hypotension during transfusion)
d. Acquired angioedema (active diagnosis of metastatic chordoma)
e. Idiopathic angioedema

2. What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Given the presence of bilateral upper-extremity crepitus on examination in a postsurgical patient and persistent periorbital swelling, computed tomography (CT) of the chest, head, and neck was the next logical step. CT imaging was obtained and was notable for extensive pneumomediastinum and subcutaneous emphysema throughout the entirety of the anterior and posterior chest wall and throughout the soft-tissue planes of the neck and extending into the periorbital region (Fig. 2*A*). The Cardiothoracic Surgery team was consulted for management of pneumomediastinum and subcutaneous emphysema. Angiocatheters were placed in the bilateral eyelids and bilateral anterior chest. The patient demonstrated marked improvement in periorbital swelling immediately after this intervention at the bedside, and she was able to open both eyes within hours of catheter placement (Fig. 2*B*). Angiocatheters were kept in place for 3 days and were then removed without complication.

DISCUSSION

Angioedema is defined as a "vascular reaction of deep dermal/subcutaneous tissues or mucosal/submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling."[1] Angioedema can be mediated by mast cell-mediators (allergic and idiopathic angioedema) and/or bradykinin (hereditary, acquired, or ACE-inhibitor–induced forms). For suspected bradykinin-induced

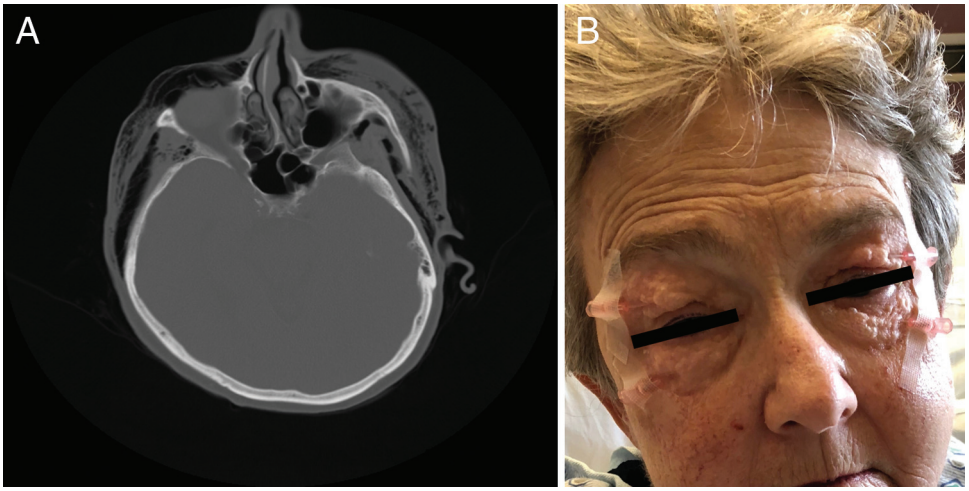

Figure 2 (A) Computed tomography of the head, demonstrating extensive subcutaneous emphysema in the bilateral periorbital regions. (B) Photograph of the patient, demonstrating marked improvement in periorbital swelling after placement of angiocatheters in bilateral eyelids.

angioedema, laboratory evaluation includes a C4 level and C1-esterase inhibitor level and function.[1] A C1q is obtained for possible acquired angioedema, which should be considered in patients ≥40 years of age, with a negative family history for swelling and/or patients with swelling in the setting of underlying conditions, such as monoclonal gammopathy and lymphoma.[1]

Mast cell–mediated angioedema is often treated with antihistamines, leukotriene-receptor antagonists, corticosteroids, and epinephrine. Bradykinin-mediated swelling can be treated acutely with C1-inhibitor concentrate or bradykinin-inhibitors, such as ecallantide or icatibant. Mast cell–mediated angioedema is more common than bradykinin-mediated angioedema. Therefore, in patients with acute onset swelling in whom the underlying diagnosis is undetermined, it is appropriate to treat these patients with antihistamines, leukotriene receptor antagonists, and corticosteroids while the diagnostic workup is underway.[1] In cases of presumed ACE-inhibitor–induced angioedema, the ACE inhibitor is discontinued and icatibant has been used acutely.[2]

In this case, the failure of the above treatments and development of subcutaneous crepitus of the upper extremities in this postoperative patient prompted further radiologic evaluation, which revealed subcutaneous emphysema as the cause of periorbital swelling. Her periorbital swelling was thought to be due to initial pulmonary barotrauma and subsequent tracking subcutaneous emphysema in the setting of her recent neurosurgical procedure.

Periorbital subcutaneous emphysema has been reported as a complication of invasive procedures. There are literature reports of this complication after dental procedures and upper-gastrointestinal endoscopy.[3,4] Moreover, there is a case report of subcutaneous periorbital and facial emphysema mistaken for angioedema after a dental procedure.[5] A review of 78 cases of patients with orbital subcutaneous emphysema from 1900 to 1994 found that the majority (49 cases) were due to blunt trauma, 7 cases were post-surgical, and 6 were due to pulmonary barotrauma.[6] This literature review indicated that subcutaneous emphysema is a recognized, albeit uncommon, complication of surgical procedures. Timely recognition of this phenomenon can lead to improved patient outcomes, targeted therapeutic intervention, and minimization of unnecessary testing and treatments.

Final Diagnosis

Periorbital subcutaneous emphysema as a postoperative complication.

CONCLUSION

The onset of periorbital or facial swelling in the patient who is hospitalized should prompt allergists to formulate a broad differential diagnosis and consider alternative causes of swelling beyond allergic and bradykinin-mediated angioedema. Normal laboratory evaluation for different causes of angioedema and the lack of response to bradykinin inhibition, steroids, antihistamines, and leukotriene receptor antagonists suggest that the appearance of swelling is not consistent with angioedema.

In this case, the establishment of a broad differential diagnosis and thorough physical examination allowed for consideration of alternative causes of swelling. Ultimately, the finding of crepitus on physical examination led to CT imaging, which demonstrated subcutaneous emphysema as a postoperative complication that caused periorbital swelling. In the evaluation of patients with presumed angioedema, the presence of crepitus in association with postoperative swelling warrants timely radio-

logic imaging for evaluation of possible subcutaneous emphysema.

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Patient-Oriented Problem Solving Case Report

A late preterm infant with lymphopenia

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ABSTRACT

The newborn screen for severe combined immunodeficiency (SCID) uses real-time quantitative polymerase chain reaction for T-cell receptor excision circles and is highly sensitive for SCID. However, T-cell lymphopenia from other primary and secondary causes, such as DiGeorge syndrome, prematurity, thymic involution from stress, and thymectomy during cardiac surgery, is also detected. We present a newborn girl with T-cell lymphopenia of unknown etiology detected via *abnormal newborn screen.*

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CHIEF CONCERN

Abnormal newborn screen.

HISTORY OF PRESENT ILLNESS

The patient was born at 34 weeks by cesarean section for fetal decelerations. The pregnancy reportedly was uncomplicated. Maternal antenatal betamethasone was administered for lung development, and the postnatal course was unremarkable. Birth weight was 2325 g. Newborn screens obtained at 1 and 10 days of life resulted with very low T-cell receptor excision circles (TRECs). The patient was referred to the immunology clinic. Her pediatrician was contacted immediately, and bloodwork was sent. On evaluation, the patient was formula-feeding well and had not developed infections, rash, or diarrhea. The family history was negative for primary immunodeficiency, consanguinity, and unexplained deaths.

PHYSICAL EXAMINATION

The patient appeared well, with no thrush, midline defects, pathologic heart murmurs, abnormal facial features, hypotonia, or other abnormalities. Her weight was appropriate for age. Flow cytometry at 2 weeks of age showed severe pan-lymphopenia, with an absolute lymphocyte count of 551 cells/μL, $CD3^+$ 429 cells/μL, $CD3^+$ $CD4^+$ 342 cells/μL, $CD3^+$ $CD8^+$ 68 cells/μL, $CD3^-$ $CD19^+$ 2 cells/μL, and $CD3^-$ $CD16/56^+$ 104 cells/μL. Naive T-cell percentages were normal, with 73% naive $CD4^+$ cells and 93% naive $CD8^+$ cells. No other hematologic abnormalities were detected. Proliferation to phytohemagglutinin was low-normal.

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QUESTIONS

Question 1: What is the Differential Diagnosis?

Primary causes of low TRECs include classic and "leaky" severe combined immunodeficiency (SCID), Omenn syndrome, complete or partial DiGeorge syndrome, CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome, and ataxia telangiectasia. Secondary causes include prematurity, surgical thymectomy, neonatal leukemia, gastroschisis, and human immunodeficiency virus. Although the patient did not meet diagnostic criteria for classic SCID, there was concern for leaky SCID. Given T-, B-, and natural killer (NK)-cell lymphopenia, adenosine deaminase (ADA), and purine nucleotide phosphorylase (PNP) deficiencies were considered.

Question 2: What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

ADA and PNP enzymatic activity can be assessed with rapid turnaround. Genetic analysis for combined immunodeficiencies and 22q11.2 deletion should be strongly considered. Human immunodeficiency virus testing is also warranted.

ADDITIONAL MEDICAL HISTORY

The mother revealed that she had undergone a kidney transplantation for lupus nephritis 3 years earlier

Table 1 **Trend of patient's immunologic studies**

Immunologic Study	Reference Range	Age		
		2 Wk	1 Mo	4 Mo
Lymphocytes, cells/μL				
Absolute lymphocyte count	3400–7600	551	1979	7107
$CD3^+$	2500–5500	429	776	3895
$CD3^+$ $CD4^+$	1600–4000	342 (73% naive)	587 (86% naive)	3042 (89% naive)
$CD3^+$ $CD8^+$	560–1700	68 (93% naive)	166 (94% naive)	832 (96% naive)
$CD3^-$ $CD19^+$	300–2000	2	975	2497
$CD3^-$ $CD16/56^+$	170–1100	104	170	571
Immunoglobulin, mg/dL				
A	7.0–48.0	<7.8	—	<7.8
G	310.0–650.0	570	—	554
M	4.0–60.0	<5.3	—	39.3
E	0.0–12.0	21.5	—	4.4

and had taken hydroxychloroquine, tacrolimus, azathioprine, and prednisone throughout her pregnancy.

ADDITIONAL LABORATORY STUDIES

TRECs rechecked at 2 weeks of age had normalized at 8852 per 1,000,000 $CD3^+$ T cells (reference value >6794). Flow cytometry repeated at 4 weeks showed absolute lymphocytes of 1980 cells/μL, $CD3^+$ 776 cells/μL, $CD3^+$ $CD4^+$ 587 cells/μL (86% naive), $CD3^+$ $CD8^+$ 166 cells/μL (94% naive), $CD3^-$ $CD19^+$ 975 cells/μL, and $CD3^-$ $CD16/56^+$ 170 cells/μL (Table 1). ADA and PNP enzymatic activities were normal.

CLINICAL COURSE

As TRECs normalized, proliferation to phytohemagglutinin was normal for age, and B- and T-cell lymphopenia improved by 1 month of age, a watchful waiting approach was adopted. Trimethoprim-sulfamethoxazole and other antimicrobial prophylaxis were held. The mother did not wish to breast-feed; she was advised to avoid public places and people with known illnesses, and to boil water for infant formula. Live viral vaccines were held. All lymphocyte subsets normalized by age 4 months and immunoglobulin G (likely reflective of maternal levels) remained stable at 554 mg/dL. At age 10 months, the patient had protective titers to tetanus, diphtheria, *Haemophilus influenzae* B, and 7 of 13 Prevnar (Wyeth Pharmaceuticals Inc., Philadelphia, PA) vaccine serotypes. She was cleared for live viral vaccines, which she tolerated well.

DISCUSSION

Previous studies showed that maternal immunosuppressive medications during pregnancy can cause transient neonatal lymphopenia and abnormal newborn screening test results for SCID. Kuo *et al.*[1] published information about two infants with low TRECs and severe T-cell lymphopenia, with prenatal exposure to azathioprine and mercaptopurine. A predominance of naive T cells, normal proliferation to mitogens, and the presence of thymic shadow on a chest radiograph were reassuring.[1] Both infants received infectious prophylaxis and/or supplemental immunoglobulin, and T-cell counts normalized by age 5 to 6 months.[1] Singla *et al.*[2] reported an infant with prenatal exposure to azathioprine who presented with abnormal TRECs, severe lymphopenia, and decreased naive T-cell percentages. Primary immunodeficiency genetic testing was negative, and lymphocyte counts spontaneously improved.[2]

Thomas *et al.*[3] reported about an infant with undetectable TRECs and with B-, T-, and NK-cell lymphopenia, whose mother was on azathioprine. The infant received infectious prophylaxis, and laboratory abnormal results improved by 3 months.[3] Conversely, a study by de Felipe *et al.*[4] described two full-term neonates with normal TRECs but low kappa-deleting recombination excision circles (KRECs), which suggests B-cell lymphopenia. Abnormal values were attributed to maternal azathioprine during pregnancy. KRECs in one infant remained low at 1 month but normalized after breast-feeding cessation.[4] Another 2-year study, by Barbaro *et al.*,[5] identified 13 infants with transiently low KRECs whose mothers were on azathioprine, mercaptopurine, and/or tacrolimus during pregnancy. Again, values normalized without intervention.[5] These studies demonstrate that use of maternal immunosuppressive medications during pregnancy can affect both B- and T-cell lines in the neonate (Table 2).

Azathioprine causes immunosuppression partially by interfering with nucleic acid synthesis in rapidly dividing cells, including lymphocytes. Although there may be associations with prematurity and low birth weight, azathioprine is considered relatively safe during pregnancy.[6] *In vitro* studies showed increased sensitivity of B cells over T cells to drug-induced apoptosis,[7]

Table 2 **Summary of cases that attributed low TRECs or KRECs in patients to maternal immunosuppressive medications**

Study	Laboratory Test Result Abnormalities	Medication	Interventions	Time to Marked Improvement or Normalization of Flow Cytometry
Kuo *et al.*[1]	↓ TREC	Azathioprine (n = 1), mercaptopurine (n = 1)	Infectious prophylaxis and/or supplemental immunoglobulin	5–6 mo
Singla *et al.*[2]	↓ TREC	Azathioprine (n = 1)	None	3 wk
Thomas *et al.*[3]	↓ TREC	Azathioprine (n = 1)	Infectious prophylaxis	3 mo
de Felipe *et al.*[4]	↓ KREC	Azathioprine (n = 1)	None	After breast-feeding cessation
Barbaro *et al.*[5]	↓ KREC	Azathioprine (n = 9), mercaptopurine (n = 1), azathioprine and tacrolimus (n = 3)	None	2–10 wk

↓ = *low; TREC = T-cell receptor excision circles; KREC = kappa-deleting recombination excision circles.*

which may explain why KRECs were preferentially affected in the European studies described.[4,5] A dose-dependent effect of maternal azathioprine on neonatal lymphopenia may also influence which, if any, neonatal cell lines are affected.[8]

Final Diagnosis

Transient neonatal lymphopenia from maternal immunosuppressive medications.

CONCLUSION

We presented an infant girl with very low TRECs, found to have severe lymphopenia, who spontaneously recovered by age 4 months. This case highlighted the importance of a thorough medical history because the mother's condition was not divulged without probing. Lymphopenia was probably multifactorial, from maternal immunosuppressive medications (particularly azathioprine), antenatal steroids, perinatal stress, and prematurity. Maternal immunosuppression, therefore, should be considered in the differential diagnosis of a neonate with lymphopenia. In general, the long-term effects of maternal immunosuppressive medications on neonatal immune function are not well established, but spontaneous normalization in all of the above cases suggested that the effects were transient.

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Patient Oriented Problem Solving (POPS) Case Report

A 27-year-old man with recurrent sinopulmonary and cutaneous infections

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ABSTRACT

The increasing availability of genetic testing for modern immunologists in the evaluation of immune diseases could provide a definite diagnosis in elusive cases. A 27-year-old white male patient presented to the clinic with recurrent sinopulmonary and cutaneous infections since childhood. The patient's mother had seronegative polyarthritis, and one of two sisters of the patient had chronic sinopulmonary infections. Serum immunoglobulins, immunoglobulin G (IgG) subclasses, lymphocyte subset markers, mannose-binding lectin, mitogen and antigen stimulation, bacteriophage study, and Streptococcus pneumoniae titers to 23 serotypes were all normal. B-cell phenotyping revealed a decrease in both nonswitched memory B cells ($CD19^+CD27^+IgD^+$) and switched memory B-cells ($CD19^+CD27^+IgD^-$). Genetic testing and the improvement of clinical symptoms after IgG replacement led to the final diagnosis.

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CHIEF CONCERN

A 27-year-old white male had recurrent sinusitis, bronchitis, cellulitis, and abscesses.

HISTORY OF PRESENT ILLNESS

The patient presented with a history of recurrent sinopulmonary and cutaneous infections since childhood. He was born to non-consanguineous parents, with an unremarkable birth. He had been hospitalized for pneumonia, mastoiditis, *Serratia marcescens* and methicillin-sensitive *Staphylococcus aureus* cellulitis, and abscesses. He had recurrent otitis media, despite myringotomy tubes; viral meningitis; and infectious mononucleosis in his teens. Each sinopulmonary infection required a prolonged course of antibiotics or a switch to a different class due to a lack of improvement. Prophylactic sulfamethoxazole-trimethoprim also failed for this patient.

MEDICAL, SURGICAL, FAMILY HISTORY

The patient's medical history was significant for retention of two primary teeth, which were extracted as an adult. His surgical history included incision and drainage of several abscesses. The patient's mother had seronegative polyarthritis on methotrexate and hydroxychloroquine sulfate. The patient had two sisters, one of whom had chronic sinopulmonary infections.

PHYSICAL EXAMINATION

On examination, an absence of cervical, supra, and infraclavicular, and axillary lymphadenopathy was noted. Tonsillar tissue was unremarkable, and no splenomegaly was detected on abdominal examination.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Results of his hepatitis panel and human immunodeficiency virus enzyme-linked immunosorbent assay were negative, and the alpha-1-antitrypsin level was within normal limits. Immunologic studies revealed normal complement, age-adjusted quantitative serum immunoglobulins (immunoglobulin G [IgG], IgA, IgM) including IgG subclasses, total IgE level, and mannose binding lectin levels (Table 1). The patient demonstrated an appropriate antibody response to protein (tetanus and diphtheria toxoids), polysaccharide (23-valent pneumococcal vaccine), and protein-conjugated antigens (13-valent pneumo-coccal conjugate vaccine, Table 1). Mitogen and antigen stimulation showed a normal response to phytohemagglutinin, concanavalin A, and pokeweed, in addition to candida and tetanus, respectively. The natural killer cell function assay and signal transducer

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Table 1 **Absolute neutrophil count, B-cell phenotyping profile, serum immunoglobulins, and pneumococcal and tetanus titers between the patient and the patient's mother**

	Laboratory Test Results		
	Patient	**Mother**	**Reference Range**
Absolute neutrophil count, $\times 10^9$/L	4.72	3.52	1.20–7.70
B-cell phenotyping			
CD19, %	17	11	6–19
CD19 absolute, $\times 10^9$/L	0.223	0.186	0.070–0.910
$CD19^+CD27^-IgD^+$, %	85.5 (H)	59.8	58.0–72.1
$CD19^+CD27^+IgD^+$, %	3.6 (L)	26.1 (H)	13.4–21.4
$CD19^+CD27^+IgD^-$, %	6.0 (L)	11.7	9.2–18.9
$CD19^+CD24^{++}CD38^{++}$, %	6.1 (H)	4.7 (H)	1.0–3.6
$CD19^+CD24^-CD38^{++}$, %	2.7 (H)	0.5 (L)	0.6–1.6
Serum immunoglobulins			
IgG, mg/dL	1140	939	700–1600
IgA, mg/dL	167	266	70–400
IgM, mg/dL	98	77	40–230
IgE, IU/mL	<2	Not available	0–150
Antibodies (response after pneumococcal polysaccharide)			
Pneumococcal*	11/14 protective serotype	14/14 protective serotype	Protective serotype >1.3
Tetanus, IU/mL	3.88	1.73	<0.10

H = high; L = low.

**Concentration >1.3 mg/mL for >70% of types with a 2-fold increase for >70% of serotypes is considered having an intact response to pneumococcal capsular polysaccharides in individuals >6 years of age. Adapted from Refernce 8.*

and activator of transcription 3 functional testing and gene sequencing were normal.

CLINICAL COURSE

What is the differential diagnosis of this patient with recurrent sinopulmonary and skin infections?

We narrowed differential diagnoses to primary immune deficiencies (PID), which encompass >250 disorders, which can be divided into disorders of the innate and adaptive systems.[1,2] The innate system defects included leukocyte adhesive defect, Chediak Higashi syndrome, and chronic granulomatous disease.[2] Our patient did not have delayed shedding of the umbilical cord at birth or a history of cellulitis with the absence of abscesses or pus, which thereby excluded leukocyte adhesive defect. Chediak Higashi syndrome was an unlikely diagnosis because our patient remained asymptomatic for easy bleeding or bruising, and did not exhibit hypopigmentation of the hair, eye, or skin.[2] Our patient demonstrated recurrent cutaneous infections with catalase positive bacteria, which prompted evaluation of chronic granulomatous disease, which is clinically characterized by recurrent and severe bacterial infections, dysregulated inflammation, and autoimmunity with individuals at increased risk of infections with catalase-positive bacteria.[2–4]

These adaptive cellular immune defects are linked to high morbidity and mortality: severe combined immune deficiency, DiGeorge syndrome, ataxia-telangiectasia, and Wiskott-Aldrich syndrome.[1,2,5,6] Our patient's isolated viral meningitis episode, with an unremarkable physical examination and laboratory findings gives evidence for the absence of an adaptive cellular defect.[1] Humoral cell defects result in variations of immunoglobulin production due to either a decrease or absence of B-cell populations, decreased or absent levels in immunoglobulin isotypes or all immunoglobulin lines, poor response to specific antigens, and a likely clinical history of severe and persistent bacterial infections.[1] Despite normal immunoglobulin levels and adequate responses to pneumococcal vaccines, our patient exhibited the clinical phenotype of individuals with underlying antibody defects (X-linked agammaglobulinemia, common variable immunodeficiency [CVID], hyper-IgM syndrome, specific antibody deficiency).[1,2,5,7]

WHAT ADDITIONAL LABORATORY DATA OR INVESTIGATIONS WOULD BE HELPFUL IN ARRIVING AT A DIAGNOSIS IN THIS PATIENT?

A neutrophil oxidase burst assay, flow cytometry for cell identification and counting, and B-cell

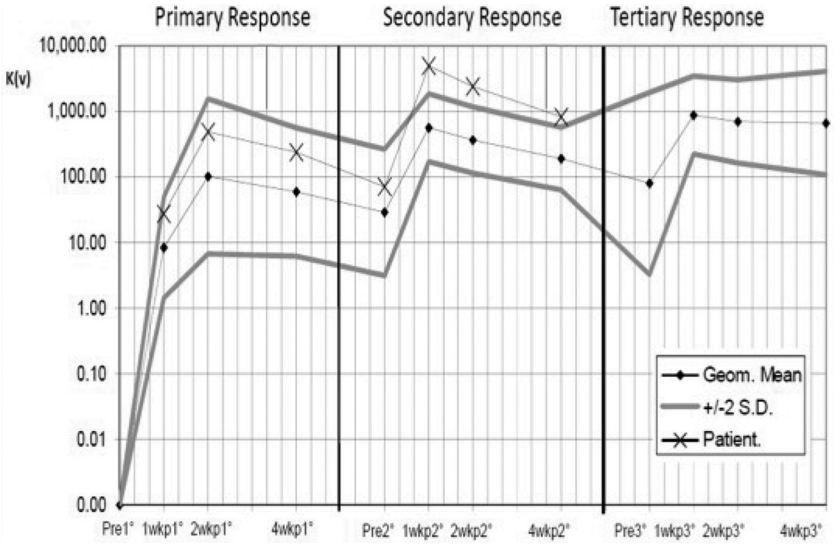

Figure 1. *Patient's immune response to bacteriophage.*

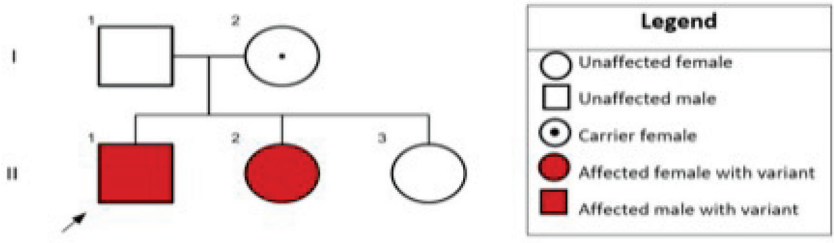

Figure 2. *Family pedigree, displaying individuals affected with the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) variant, c.542C>A (p.Ala181Glu).*

phenotyping to identify blocks in B-cell development were conducted. Flow cytometry exhibited intact neutrophil oxidation and normal ranges of $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, and natural killer cells. B-cell phenotyping showed an increase in naive B cells ($CD19^+CD27^-IgD^+$) and a decrease in both nonswitched memory B cells ($CD19^+CD27^+IGD^+$) and switched memory B cells ($CD19^+CD27^+IgD^-$) with appropriate transitional B cells ($CD19^+CD24^+CD38^+$) and plasmablasts ($CD19^+CD24^-CD38^+$, Table 1).

The patient was challenged with the neoantigen bacteriophage phi X 174 to evaluate functional production of IgG antibodies. The results showed a robust response after primary and secondary immunization to phi X 174 (Fig. 1). Genetic analysis with next-generation sequencing to a panel of 207 genes (Invitae Corporation, San Francisco, California) associated with PI resulted in a heterozygous transmembrane activator and calcium-modulator and cyclophilin ligand interactor (*TACI*) variant, encoded by the tumor necrosis factor (TNF) receptor superfamily member 13B or *TNFRSF13B*, on exon 4. c.542C>A (p.Ala181Glu).

The patient's mother and sister, who were asymptomatic, with the history of chronic sinopulmonary infections exhibited the same *TACI* variant (Fig. 2). A decrease in *TACI* expression to half of the control with intact B cell-activating factor-receptor (BAFF-R) expression on B cells were identified *via* flow cytometry for both the patient and the patient's mother (Fig. 3). The results of the surface expression of TACI proteins were conducted by Mayo Clinic Laboratories. The peripheral blood mononuclear cells were isolated and stained with CD19, *TACI*, and *BAFF-R*, each conjugated to a fluorochrome. After staining with specific antibody, the cells are washed, fixed with paraformaldehyde, and analyzed by flow cytometry on a BD FACSCanto (Becton, Dickinson and Company Biosciences, San Jose, CA) instrument. The cell-surface expression is expressed as the percentage of $CD19^+$ B cells expressing *TACI* and *BAFF-R* (unpublished Mayo method, https://www2.mayocliniclabs.com/test-catalog/Performance/87993).

DISCUSSION

A comprehensive PID workup is essential in patients who present with recurrent, severe infections. Genetic testing may narrow the diagnosis in obscure clinical cases.[7] PID display phenotypical and genetic heterogeneity; recognizing this diversity is integral to treating the patient.[7] CVID displays clinical heterogeneity and is characterized by recurrent

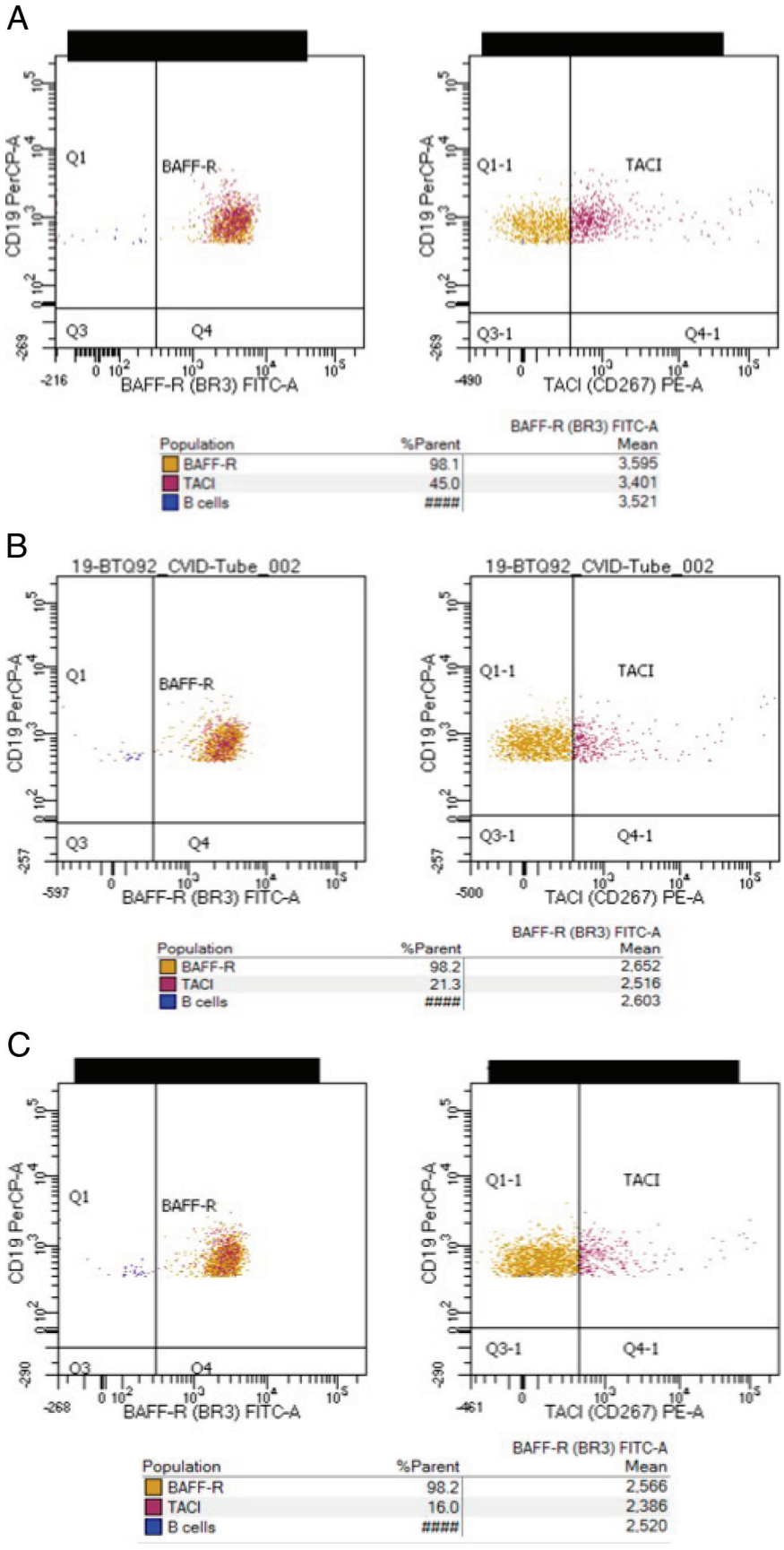

Figure 3. *(A) Four-quadrant scattered plot, indicating normal expression of transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) (control). (B) Four-quadrant scattered plot, indicating decreased expression of TACI (patient). (C) Four-quadrant scattered plot, indicating decreased expression of TACI (mother).*

sinopulmonary infections, hypogammaglobulinemia with low levels of IgA and/or IgM, and impaired or absent antibody responses to immunizations and infections.[5,7] The majority of CVID cases occur sporadically, primarily in white populations, with variable ages of onset; 5–25% of patients exhibit a positive family history for CVID. Peak incidences of disease occur in childhood and in the second and third decade of life.[7] Its association with autoimmune disorders, granulomatous disease, and malignancy is recognized.[1,7]

The hallmark immune defect of CVID is the B-cell maturation and differentiation process into memory B cells.[1] Impaired T-cell functions, including T-regulatory cells and T-cell receptor excision circles, are exhibited in a subset of patients with CVID.[7] Decreased T-cell proliferation to mitogens and antigens are demonstrated in 40% of patients with CVID.[7] Our patient's overall B-cell number was normal, with a decreased number of switched memory B cells.[1,9] Many genes have been implicated in monogenic CVID, including *TNFRSF13C* (*BAFF-R*) and *TNFRSF13B* (*TACI*).[7] *TACI* is expressed on the $CD27^+$ marginal zone and $CD27^+$ memory B cells, plasma cells, and activated $CD4^+$ T cells.[10] *TACI* regulates B-cell homeostasis in the early stages of B-cell development by navigating central B-cell tolerance and in the late stages by contributing to immunoglobulin class-switching, differentiation, and survival of plasma cells.[9–11]

BAFF and a proliferation-inducing ligand, or *APRIL*, are two ligands that cause oligomerization necessary for downstream signaling on engaging with *TACI*.[11] This pathway leads to activation of the transcription factors, nuclear factor of activated T cells and nuclear factor-κB, and expression of activation-induced cytidine deaminase (AID) messenger RNA, which results in isotype switch.[7,11,12] Deficient B-cell expression and missense mutations of *TACI* may lead to impaired B-cell function.[10] A common *TACI* variant in CVID is A181E, located within the transmembrane domain on exon 4, which leads to severely impaired signaling by affecting receptor oligomerization.[7,13] A heterozygous *TACI* variant is found in 2–5% of patients with CVID. This variant exists in 0.5–0.1% of healthy individuals; it alone cannot explain the clinical phenotype of patients with CVID.[13]

Patients with CVID and with this variant present with similar phenotypes as those with other etiologies of CVID, including recurrent sinopulmonary and/or gastrointestinal infections and autoimmune disorders. Specifically, cases reported clinical manifestations of pneumonia, sinusitis, granulomatous skin lesions, immune thrombocytopenia, autoimmune hemolytic anemia, ulcerative colitis, and anticardiolipin syndrome.[9,13] To date, no report of lymphoproliferative or recurrent cutaneous infections has been associated with this specific variant.

Our patient with a *TACI* variant associated with the clinical phenotype of CVID was started on immunoglobulin replacement therapy. Clinical improvement with immunoglobulin therapy indicates a dysregulation in the patient's B-cell differentiation and proliferation process into memory B cells. Isotype class switching defects are also commonly found in patients with CVID who are positive for *TACI*. Our patient's immunoglobulin levels and vaccine responses were appropriate. This was the first case, to our knowledge, with the *A181E TACI* variant associated with recurrent skin abscesses. Other antibody production deficiencies need to be confirmed *in vitro* to completely define our patient's cutaneous clinical phenotype.

FINAL DIAGNOSIS

The patient was diagnosed with *TACI*-associated CVID-like immunodeficiency.

CONCLUSION

CVID is a heterogeneous disease associated with genetic defects, notably *TACI* mutation variants, which results in B-cell dysfunction and hypogammaglobulinemia.[7,11] Our patient displayed a heterozygous *TNFRSF13B* variant with the clinical manifestations of patients with CVID, despite not aligning with *in vitro* diagnostic criteria of CVID. We hypothesize that indeterminate antibody mechanisms may exist.[8–10] Patients positive for the *TACI* variant who present with recurrent infections and normal laboratory findings consistent with CVID-like disease may benefit from immunoglobulin replacement therapy.[5]

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Patient Oriented Problem Solving (POPS) Case Report

POPS case: A 30-year-old Filipino woman with fevers, lymphadenopathy, painful scalp lesions, and a neck mass

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ABSTRACT

We described a case of a 30-year-old Filipino woman who presented with fevers, night sweats, left hip pain, painful scalp lesions, and a neck mass. Symptoms began 6 months earlier, with nasal drainage, fever, cough, and occasional hemoptysis, which did not resolve with outpatient antibiotics. A further workup revealed lymphadenopathy and several lytic bone lesions. Her hospital course was later further complicated by the development of a tracheoesophageal fistula secondary to an esophageal mass and, then later, aseptic meningitis. Extensive diagnostic workup and immunologic tests were performed and finally led to the diagnosis. Here, we discussed the diagnostic workup and pathophysiology of the underlying condition. This case illustrated the importance of appropriate immunologic workup to make the diagnosis of a rare condition that proves to be clinically significant and presents challenges in management.

(Allergy Asthma Proc 41:305–308, 2020; doi: 10.2500/aap.2020.41.200012)

CHIEF CONCERN

Fever, night sweats, hip pain, painful scalp lesions, and a neck mass of 6 months' duration.

HISTORY OF PRESENT ILLNESS

A 30-year-old Filipino woman presented with fevers, night sweats, hip pain, painful scalp lesions, and a neck mass. She was in good health until her symptoms began 6 months before admission, with nasal drainage, fever, cough, and hemoptysis, which did not resolve with antibiotics. She had no significant medical history. The patient was born in the Philippines and immigrated to central Pennsylvania in 2015. In the evaluation of her respiratory symptoms, a computerized tomography (CT) of the sinuses revealed an infiltrative mass in the right suboccipital region. Due to concerns of possible intracranial extension, she was referred to a neurosurgeon. Magnetic resonance imaging of the brain demonstrated a contrast-enhancing 30×20-mm mass within the right suboccipital muscles and an enhancing lesion in the left postauricular region, with invasion of the bone. An outpatient biopsy was scheduled but not performed due to the patient developing progressive fevers and palpitations, which prompted her to come to the emergency department for immediate evaluation.

PHYSICAL EXAMINATION

Results of a physical examination revealed a well-nourished, acutely ill woman, with a fluctuant mass over the right suboccipital region and tender submandibular and preauricular lymphadenopathy.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Laboratory results included hemoglobin level of 9.5 g/dL (normal range, 11.7–15 g/dL), white blood cell count of 29.4 K/μL (normal range, 4–10.4 K/μL), platelet count of 768 K/μL (normal range, 150–350 K/μL), erythrocyte sedimentation rate of 79 mm/hr (normal range, 0–20 mm/hr), a C-reactive protein level of 13 mg/dL (normal value, <0.5 mg/dL), human immunodeficiency virus (HIV) antigen/antibody non-reactive result, and a CD4 count of 538 cells/mm^3 (normal range, 450–1500 cells/mm^3) (36%). CT imaging of the chest, abdomen, and pelvis revealed a 31×18-mm subcarinal mass, adjacent to the esophagus, with near obliteration of the esophageal lumen, enlarged lymph nodes throughout the thorax and abdomen, and multiple lytic lesions in the iliac wings and ribs

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(see Figure 1). A 33 × 63-mm soft-tissue mass abutted the left iliac wing.

Three sputum samples were sent for acid-fast bacillus (AFB) stain and cultures; two of the three results were positive. Sputum *Mycobacterium tuberculosis* polymerase chain reaction and interferon (IFN) γ release assay (T-SPOT, Oxford Immunotec., Abingdon, UK) results were negative. Fine needle aspirate and core biopsy of the right skull base showed acute inflammation. Acid-fast stain was initially negative, but the AFB culture subsequently became positive. A DNA probe of the AFB from sputum and tissue samples was positive for *Mycobacterium avium–intracellulare* complex (MAC).

CLINICAL COURSE

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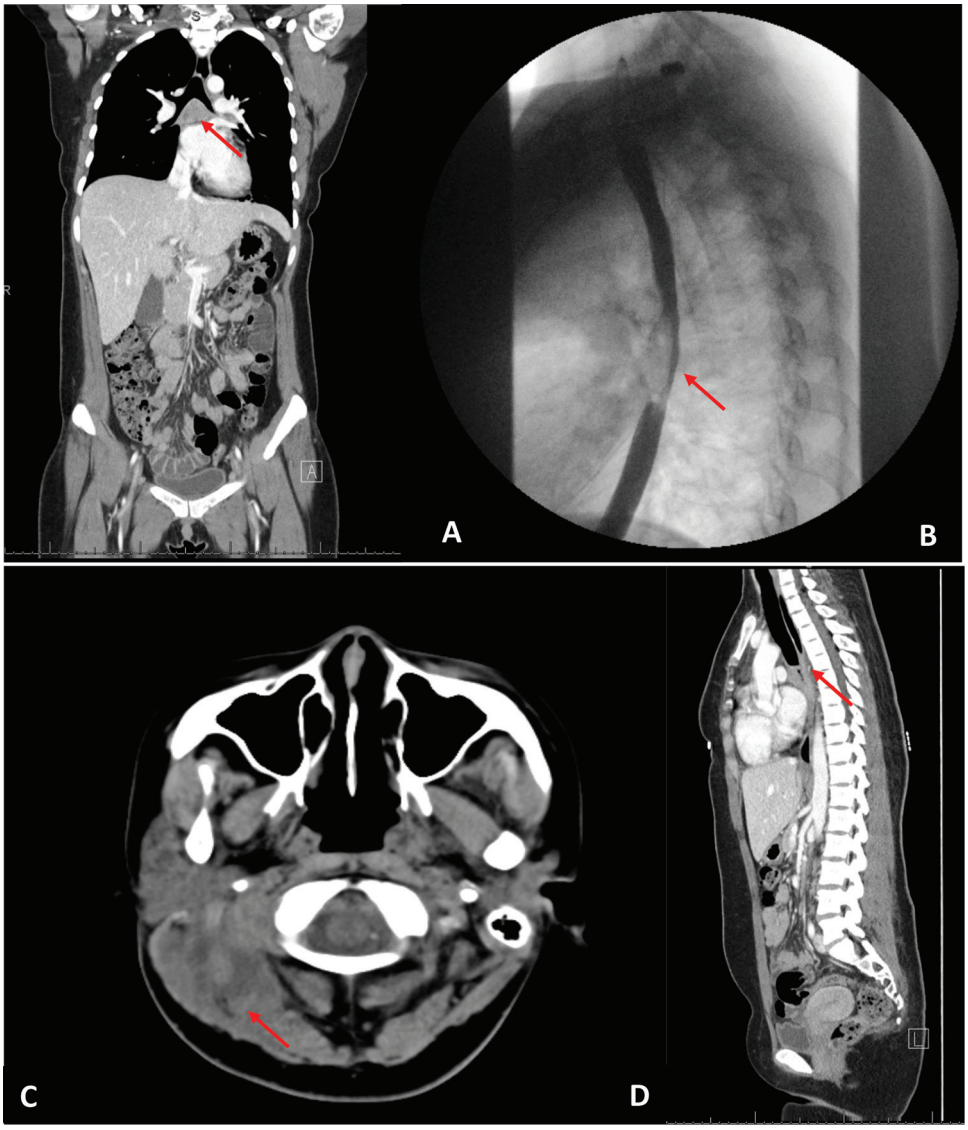

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CONCLUSION

This complex patient with an unusual presentation of esophageal involvement and meningitis highlights the importance of considering anti–IFN-γ autoantibodies as a potential cause of disseminated MAC infection, particularly in patients of Asian origin with otherwise intact immune function who are refractory to standard therapy.

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Patient Oriented Problem Solving (POPS) Case Report

POPS case: A 30-year-old Filipino woman with fevers, lymphadenopathy, painful scalp lesions, and a neck mass

Aparna S. Daley, M.B.Ch.B.,[1] Gillian R. Naro,[2] Timothy J. Craig, D.O.,[1] Rezhan H.A. Hussein, M.D.,[3] Rashmi Banjade, M.D.,[3] Jennifer B. Jacobs, M.D., M.P.H.,[4] and Ian R. Ross, M.D.[4]

ABSTRACT

We described a case of a 30-year-old Filipino woman who presented with fevers, night sweats, left hip pain, painful scalp lesions, and a neck mass. Symptoms began 6 months earlier, with nasal drainage, fever, cough, and occasional hemoptysis, which did not resolve with outpatient antibiotics. A further workup revealed lymphadenopathy and several lytic bone lesions. Her hospital course was later further complicated by the development of a tracheoesophageal fistula secondary to an esophageal mass and, then later, aseptic meningitis. Extensive diagnostic workup and immunologic tests were performed and finally led to the diagnosis. Here, we discussed the diagnostic workup and pathophysiology of the underlying condition. This case illustrated the importance of appropriate immunologic workup to make the diagnosis of a rare condition that proves to be clinically significant and presents challenges in management.

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CHIEF CONCERN

Fever, night sweats, hip pain, painful scalp lesions, and a neck mass of 6 months' duration.

HISTORY OF PRESENT ILLNESS

A 30-year-old Filipino woman presented with fevers, night sweats, hip pain, painful scalp lesions, and a neck mass. She was in good health until her symptoms began 6 months before admission, with nasal drainage, fever, cough, and hemoptysis, which did not resolve with antibiotics. She had no significant medical history. The patient was born in the Philippines and immigrated to central Pennsylvania in 2015. In the evaluation of her respiratory symptoms, a computerized tomography (CT) of the sinuses revealed an infiltrative mass in the right suboccipital region. Due to concerns of possible intracranial extension, she was referred to a neurosurgeon. Magnetic resonance imaging of the brain demonstrated a contrast-enhancing 30×20-mm mass within the right suboccipital muscles and an enhancing lesion in the left postauricular region, with invasion of the bone. An outpatient biopsy was scheduled but not performed due to the patient developing progressive fevers and palpitations, which prompted her to come to the emergency department for immediate evaluation.

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PHYSICAL EXAMINATION

Results of a physical examination revealed a well-nourished, acutely ill woman, with a fluctuant mass over the right suboccipital region and tender submandibular and preauricular lymphadenopathy.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Laboratory results included hemoglobin level of 9.5 g/dL (normal range, 11.7–15 g/dL), white blood cell count of 29.4 K/μL (normal range, 4–10.4 K/μL), platelet count of 768 K/μL (normal range, 150–350 K/μL), erythrocyte sedimentation rate of 79 mm/hr (normal range, 0–20 mm/hr), a C-reactive protein level of 13 mg/dL (normal value, <0.5 mg/dL), human immunodeficiency virus (HIV) antigen/antibody non-reactive result, and a CD4 count of 538 cells/mm^3 (normal range, 450–1500 cells/mm^3) (36%). CT imaging of the chest, abdomen, and pelvis revealed a 31×18-mm subcarinal mass, adjacent to the esophagus, with near obliteration of the esophageal lumen, enlarged lymph nodes throughout the thorax and abdomen, and multiple lytic lesions in the iliac wings and ribs

(see Figure 1). A 33 × 63-mm soft-tissue mass abutted the left iliac wing.

Three sputum samples were sent for acid-fast bacillus (AFB) stain and cultures; two of the three results were positive. Sputum *Mycobacterium tuberculosis* polymerase chain reaction and interferon (IFN) γ release assay (T-SPOT, Oxford Immunotec., Abingdon, UK) results were negative. Fine needle aspirate and core biopsy of the right skull base showed acute inflammation. Acid-fast stain was initially negative, but the AFB culture subsequently became positive. A DNA probe of the AFB from sputum and tissue samples was positive for *Mycobacterium avium–intracellulare* complex (MAC).

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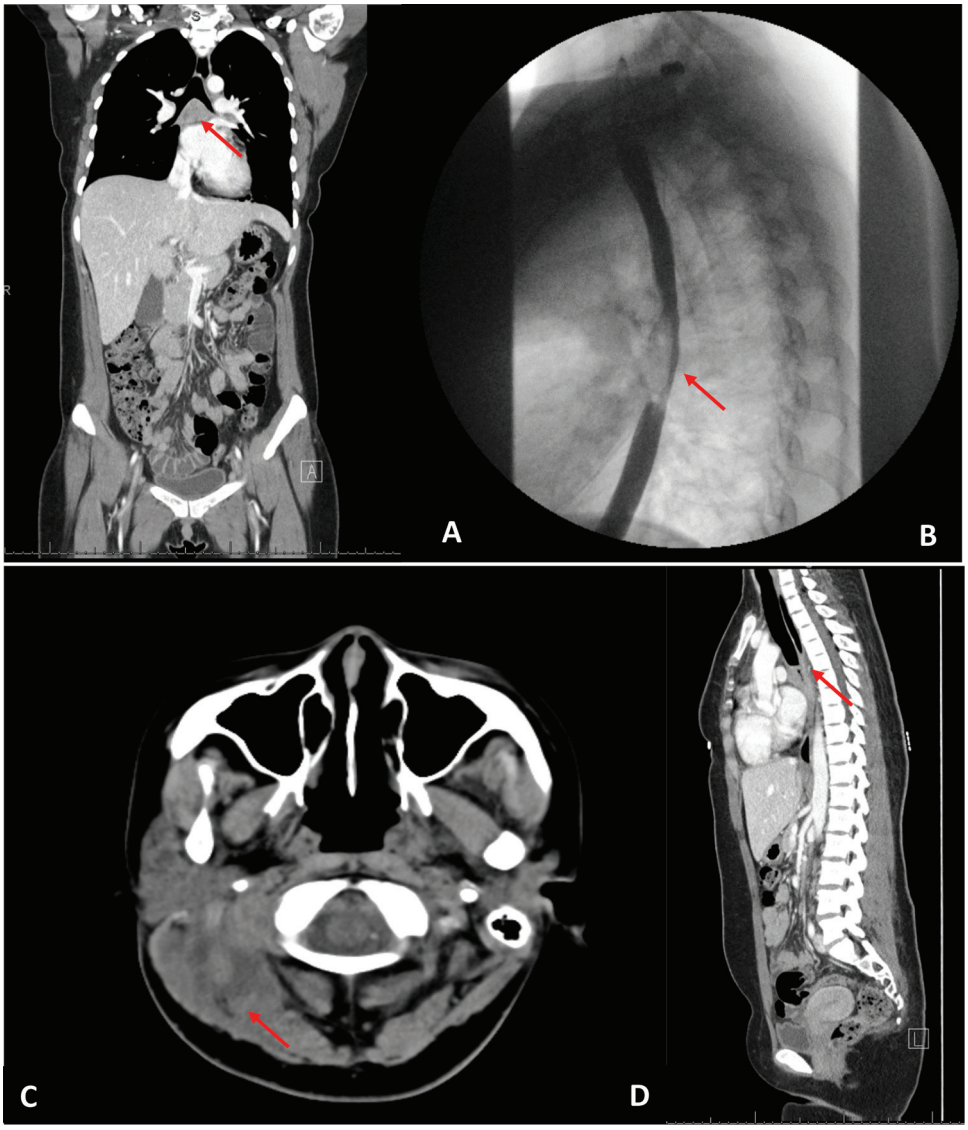

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Patient Oriented Problem Solving (POPS) Case Report

A 62-year-old man with new-onset bullae

August J. Generoso, M.D., Jordana A. Goldman, M.D., and Alan H. Wolff, M.D.

ABSTRACT

Cutaneous blisters and/or bullae can occur in autoimmune disorders, infections, genetic diseases, and drug hypersensitivity. We present the case of a 62-year-old man with two autoimmune conditions who was admitted for antibiotic treatment of a lower extremity infection and suddenly developed a bullous rash. His physical examination was significant for tense, bullous lesions that involved his chin, palms, and inner thighs. Narrowing the differential diagnosis for patients with blistering skin lesions is imperative for timely and appropriate management.

(Allergy Asthma Proc 42:175–179, 2021; doi: 10.2500/aap.2021.42.200055)

CASE PRESENTATION

Chief Concern

New-onset bullous rash.

History of Present Illness

A 62-year-old man with psoriasis and progressive multiple sclerosis that resulted in paraplegia was admitted for a gangrenous left lower leg, which, 1 week later, resulted in left knee disarticulation. He received piperacillin-tazobactam for 1 week and vancomycin for 2 days. Ten days after the first dose of these antibiotics, he again received vancomycin as a premedication for a cystoscopy scheduled the following day. Three hours later, he developed perioral tingling, lip swelling, and an erythematous rash, which then progressed to painful lesions on his palms and blisters in his mouth. The following day, the Allergy and Immunology Service was consulted. On evaluation, the patient had blisters on his face and inner thighs. He also reported pain in his mouth and odynophagia.

Medical History

The patient's medical history was significant for multiple sclerosis, psoriasis, type II diabetes mellitus, hypertension, peripheral vascular disease, and neurogenic bladder. He was taking baclofen, lisinopril, simvastatin, furosemide, and vitamin D at home, all of which he had been on for several years. He had no family history of skin problems or autoimmune conditions. He did not use intravenous or recreational drugs. He had no recent travel or sick contacts.

Physical Examination

The patient was afebrile, and all other vital signs were within normal limits. Significant findings included mild bilateral conjunctival injections, buccal mucosa ulcerations, lower lip swelling with desquamation, and multiple tense intact bullae on the chin below the lip. In addition, he had multiple tense intact bullae on the inner thighs bilaterally, tender nodular lesions on his palms (Fig. 1), and erythematous papular lesions on his lower arms bilaterally. Furthermore, there were small crusted blisters on his glans penis. There was no appreciable cervical, axillary, or inguinal lymphadenopathy. Hepatosplenomegaly was absent. The remainder of his physical examination was unremarkable.

Diagnostic Studies

Laboratory analysis revealed a white blood cell count of 5900/mm^3, a hemoglobin value of 11.3 g/dL, a hematocrit value of 33.1%, platelets of 293,000/mm^3, an absolute eosinophil count of 0, blood urea nitrogen level of 16 mg/dL, creatinine level of 0.7 mg/dL, aspartate aminotransferase value of 20 units/L, and alanine aminotransferase value of 37 units/L. On urinalysis, there was no protein or blood found. No abnormalities were noted on subsequent complete blood cell counts with differential, complete metabolic panels or urinalyses. The infectious workup was

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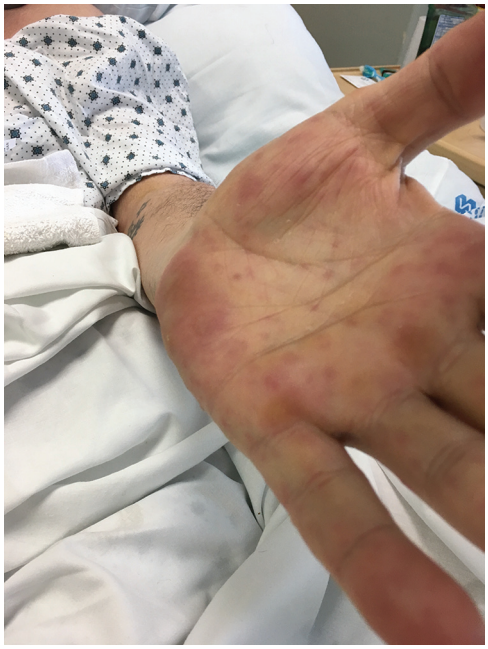

Figure 1. *Tender nodular lesions on the palms.*

unremarkable, including studies for hepatitis (A, B, and C), mycoplasma, and herpes simplex virus (1 and 2).

QUESTION 1

What is the differential diagnosis for bullous skin lesions?

QUESTION 2

Are there any additional diagnostic studies that would be helpful in arriving at the diagnosis?

DISCUSSION

The differential diagnosis for bullous skin disease includes viral infections, bullous impetigo, bullous pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, linear immunoglobulin A (IgA) bullous dermatoses (LABD), diffuse fixed drug eruption, paraneoplastic pemphigus, pemphigus vulgaris, erythema multiforme, friction blisters, bullous diabeticorum, T-cell mediated contact dermatitis, or non–Severe Cutaneous Adverse Reaction (SCAR) T-cell mediated systemic drug eruptions (Table 1).

Given that the patient was not toxic appearing and was hemodynamically stable, there was low concern for infectious etiology. As such, blood cultures were deemed to be unnecessary. As described above, the primary team performed some infectious workups, results of which were negative. There is no specific laboratory workup available to diagnose SJS/TEN, although renal and/or hepatic involvement may be seen. However, as noted, this was not the case for our patient. Moreover, by using the Registry of Severe Cutaneous Adverse Reactions scoring system, our patient's score was <2 (including no eosinophilia and no signs of end-organ involvement on laboratory tests), excluding DRESS syndrome as the diagnosis. Skin biopsy is the criterion standard for the diagnosis of most forms of bullous skin disease.

Subsequently, the patient underwent punch biopsy; the specimen was significant for subepidermal bulla with fibrin, mild superficial perivascular chronic inflammation without epidermal necrosis, and linear IgA deposition along the dermoepidermal junction under direct immunofluorescence (DIF) (Fig. 2). At this time, a diagnosis of vancomycin-induced LABD was made. In addition to discontinuing the offending agent, the patient was treated with a 10-day prednisone taper, along with topical triamcinolone. He exhibited improvement of his existing lesions within 2 days of initiation of treatment, and no interval development of new lesions.

Vancomycin is a frequently used antibiotic that has been associated with a number of adverse effects, including nephrotoxicity, ototoxicity, neutropenia, thrombocytopenia, red man syndrome, and vasculitis. Hypersensitivity reactions have also been reported, including anaphylaxis, fixed drug eruptions, SJS, and DRESS syndrome.[1,2] Another form of drug hypersensitivity reaction is LABD. LABD is a rare autoimmune skin blistering disease in which autoantibodies bind to antigens in the skin and mucous membrane. It is characterized by linear deposition of IgA at the dermoepidermal junction.[3,4] This can be both drug-induced or idiopathic.[3,5–7] LABD has an incidence of 0.2 to 2.3 cases per million individuals per year, and occurs in both adults (generally ages > 60 years) and children (onset ~4.5 years old).[3,8] The inciting factor is usually unknown, but drug exposure has been identified as a precipitating factor, with vancomycin most frequently reported.

Other medications that have been implicated in LABD include other antibiotics, nonsteroidal anti-inflammatory drugs, lithium, amiodarone, furosemide, and captopril.[9] Of note, piperacillin-tazobactam has also been implicated in LABD.[10] Although our patient also received piperacillin-tazobactam, this was ultimately believed to be the less likely culprit agent, given the temporal relationship between the second administration of vancomycin and the subsequent development of symptoms. Thus, he was deemed vancomycin-allergic only, as to not limit his potential antibiotic options in the future. Although LABD can occur within 24 hours of vancomycin administration and unrelated to trough levels,[11,12] we postulated that he likely had circulating antigen specific IgA already, which resulted in the expedited reaction on re-exposure to

Table 1 **Differential diagnosis for bullous skin disease**

Disease	Characteristic Features	Mucosal Involvement
Bullous impetigo[29]	Superficial skin infection caused by *Staphylococcus aureus;* presents with vesicles that enlarge rapidly to form bullae that burst and become covered with honey-colored crust	May occur
Bullous pemphigoid[30]	Chronic autoimmune disorder with urticarial plaques and tense bullae on the trunk and flexural and intertriginous areas	Rare
Epidermolysis bullosa acquisita[31]	Rare, acquired, chronic condition with subepidermal blistering over the extensor aspects of the elbows and dorsal aspects of the hands and feet	May occur
Dermatitis herpetiformis[32]	Intensely pruritic, chronic, autoimmune, papulovesicular cutaneous eruption associated with celiac disease; presents with clusters of erythematous, urticarial lesions, vesicles, papules, and bullae; usually symmetric distribution on extensor surfaces	Rare to none
SJS/TEN[33]	Severe cutaneous hypersensitivity reactions with macules that spread quickly and coalesce, and lead to epidermal blistering, necrosis, and sloughing; often medication induced (sulfa drugs, antiepileptics, and antibiotics most common); SJS < 10% body surface area involved, and TEN > 30% body surface area involved	Very common (90% of cases)
Linear IgA bullous dermatosis[8,14–16]	Rare, autoimmune, skin blistering disease manifesting as cutaneous or mucosal lesions described as tense bullae; can involve the trunk, face, genitalia, perineum, lower abdomen, extensor extremities, hands, feet, and inner thighs	Common
Diffuse fixed drug eruption[34]	Type IV hypersensitivity reaction with recurrent lesions at identical sites on each exposure to an offending medication; characterized by well-demarcated red or brown patches, edematous plaques with or without bullae and post–inflammatory hyperpigmentation	Can be involved
Paraneoplastic pemphigus[35]	Rare autoimmune blistering disease associated with various malignancies, such as leukemias	Common
Pemphigus vulgaris[36]	Uncommon, potentially fatal, autoimmune disorder with intraepidermal flaccid blisters and/or bullae, and widespread, extensive erosion	Usually involved
Erythema multiforme[37]	Inflammatory reaction with target skin lesions on the distal extremities (often the palms and soles) as well as the face and trunk	May occur
Friction blisters[38]	Intraepidermal blisters that occur after prolonged exercise, resulting in trauma-induced separation within the epidermis, often over the feet	None
Bullous diabeticorum[39]	Rare, spontaneous, noninflammatory, blistering condition of unknown etiology in the setting of diabetes mellitus, usually involving the acral areas and lower extremities	None
T-cell mediated contact dermatitis[40]	Acute skin inflammation caused by irritants or allergens; the main symptom is pruritus, with skin changes, including erythema, blistering, and ulceration, usually on or near the hands but can occur on any exposed skin surface	Minimum to none

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

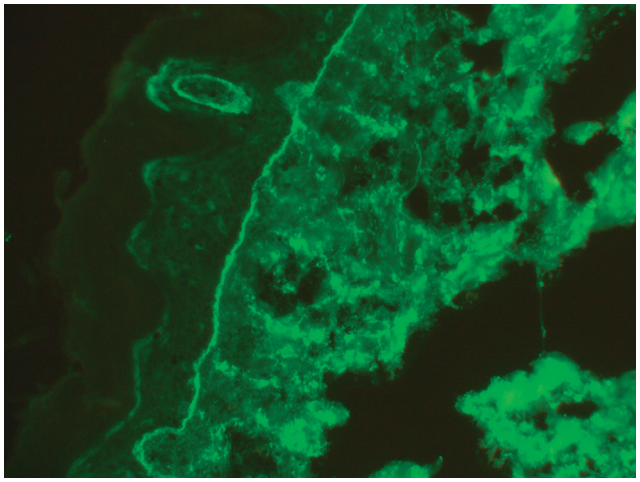

Figure 2. *Linear IgA deposition along the dermoepidermal junction under DIF.*

vancomycin. The pathogenesis of LABD is characterized by acquisition of IgA antibodies, which target basement membrane zone antigens involved in epidermal-dermal adhesion.[13] In drug-induced LABD, implicated drugs may cause an autoimmune response *via* cross-reaction with target epitopes, altering the conformation of epitopes, or exposing previously sequestered antigens to the immune system.[3]

Clinically, this disease manifests as cutaneous lesions, mucosal lesions, or both.[8,14–16] The cutaneous lesions develop acutely as tense bullae, typical of subepidermal blister formation. New blister formation occurs at the periphery of resolving lesions and results in an annular appearance, described as a "string of pearls." Lesions tend to be widespread and can involve the trunk, face (particularly the perioral area), genitalia, perineum, lower abdomen, extensor extremities, hands, feet, and inner thighs. Mucosal lesions can present as erosions or ulcers, which occur in up to 80% of adults and 3–64% of children. Involvement of the oral and ocular mucosa is most commonly seen, but involvement of the nose, genitalia, pharynx, larynx, anus, and esophagus have also been reported. Patients commonly experience pruritus, which may be severe.[17]

The lesions of drug-induced LABD resemble those of drug eruptions, *e.g.*, SJS/TEN, with large erosions and a positive Nikolsky sign (lateral pressure to the skin results in dislodgement of epidermis and extension of the blister).[18,19] Symptoms begin within 1 month of drug initiation, with resolution several weeks upon cessation of the offending agent.[8,20] Re-exposure to the offending agent may result in rapid recurrence of blisters. Demonstration of linear deposits of IgA along the basement membrane zone via DIF remains the criterion standard of diagnosis. However, serologic assays (IgA [or IgG] autoantibodies to basement membrane zone antigens Ladinin-1, Bullous Pemphigoid 180-non-collagenous16A and Bullous Pemphigoid 230) could support the diagnosis when a biopsy is not feasible or DIF results are negative.[21]

Data on treatment are limited. The mainstay of management in cases of drug-induced LABD is to discontinue the offending agent. As for idiopathic LABD, medical therapy with dapsone, an immunomodulatory sulfone, is considered first-line therapy.[14] Sulfonamides, *e.g.*, sulfapyridine, are considered second-line therapy. Other therapies include topical corticosteroids (may be sufficient in mild or localized LABD) as well as colchicine.[22,23] For severe or refractory disease, systemic glucocorticoids, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin, systemic antibiotics, or tetracycline and nicotinamide may be used.[22,24,25] Treatment for idiopathic LABD is usually tapered off after several weeks of complete remission, whereas drug-induced LABD generally subsides with cessation of the offending agent. Idiopathic LABD can persist for months to years before spontaneous resolution; it can also recur but resolves in most children before puberty. With drug-induced LABD, new lesion formation ceases within 3 days of drug removal, with complete resolution within several weeks.[19,26–28]

Final Diagnosis

Vancomycin-induced LABD.

CONCLUSION

Given the timing of symptom development, our case highlights that LABD can occur either within just a few hours of vancomycin administration or that re-exposure to the drug results in a very accelerated reaction. We suspect the latter for our patient. In addition, our case also provides further support to the speculation that comorbidities and/or infection can serve as cofactors in the pathogenesis of drug-induced LABD.[3] Ultimately, it is crucial to identify this potentially life-threatening hypersensitivity reaction to enable both timely and appropriate management and/or treatment.

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Patient Oriented Problem Solving (POPS) Case Report

A 48-year-old female with perioperative anaphylaxis

Nicholas C. Kolinsky, D.O.[1] and Richard F. Lockey, M.D.[2]

ABSTRACT

Identifying the culprit medication in cases of perioperative anaphylaxis can be extremely challenging. A detailed and accurate history, coupled with the appropriate testing, plays a key role in discovering the etiology of perioperative anaphylaxis. We present the case of a 48-year-old woman with a cranial meningioma who was scheduled for surgery. Chlorhexidine, midazolam, lidocaine, propofol, fentanyl, rocuronium, and furosemide were administered during the perioperative period. She developed hypotension, urticaria, bronchospasm, and other symptoms of anaphylaxis soon after general anesthesia. The serum tryptase level obtained during anaphylaxis was 119 ng/mL (normal, <11.4 ng/mL). Epinephrine was administered, and the surgery was canceled, with no cause identified. For the next surgical attempt, she was pretreated with diphenhydramine and ranitidine, and the neuromuscular blocker was withheld. Again, she developed hypotension consistent with anaphylaxis, and epinephrine was administered. She was referred for consultation. A detailed and accurate history was obtained. The baseline serum tryptase level was 6.4 ng/mL. Skin-prick puncture tests were completed, and a diagnosis was made. The surgical team was instructed to avoid the culprit medication, and the cranial surgery was successful. Although difficult, cases of perioperative anaphylaxis can be solved with a detailed history, keen detective work, and appropriate testing.

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CHIEF CONCERN

Anaphylaxis.

History of Present Illness

A 48-year-old woman was seen in the clinic with a chief concern of "anaphylaxis" before surgery for a cranial meningioma. Anaphylaxis, *i.e.*, generalized urticaria, wheezing, and/or hypotension occurred during two surgical attempts, 3 weeks apart, immediately after induction and before surgery. A further history was obtained; however, the patient was unable to provide any details about the specific events because she was under sedation during each episode of anaphylaxis. Her medical, social, and family histories, and a review of symptoms were unremarkable or noncontributory. She had no history of drug, food, or insect allergy, had no atopic diseases, and was not on any medications. She was seen 4 days after her second anaphylactic reaction. The exact etiology of her anaphylaxis was unknown after the initial history and physical examination. Once again, during the same initial visit, the attending physician went through a step-by-step narrative of these reactions and what she did in the 24 hours leading up to the first event. This in-depth historical investigation revealed that the night before her first surgical attempt, she used chlorhexidine to cleanse her body. Immediately thereafter, she developed generalized urticaria, pruritus, and erythema, which resolved before her surgical appointment (Figure 1).

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Physical Examination

The patient was a well-nourished woman, oriented to time, place, and person, with normal vital signs. Her body mass index was 31 kg/m^2. At the time of examination, she had mild erythema and lichenification of the skin on both wrists and the skin of the right neck, all sites of previous peripheral and central line insertions, areas that itched and she scratched for days. Pelvic, breast, and rectal examination were not done. The rest of the physical examination was normal.

Laboratory and Other Diagnostic Findings

The serum tryptase level obtained during the first episode of anaphylaxis was 119 ng/mL (normal, <11.4 ng/mL). Baseline serum tryptase level 4 weeks after initial anaphylaxis was 6.4 ng/mL. Prick-puncture test results to latex and lidocaine were negative compared with histamine and saline solution controls. The prick-puncture test to chlorhexidine resulted in a 8 × 6-mm wheal and a 12 × 10-mm

flare within 15 minutes (Figure 2). Serum specific immunoglobulin E (IgE) tests were not completed.

Clinical Course

The anesthesiologist for the case was contacted, and a further history was obtained. It was discovered that, during her first preoperative period, central and peripheral insertion sites were cleansed with a chlorhexidine scrub. The patient also received the following medications: midazolam, lidocaine, propofol, fentanyl, dexamethasone, rocuronium, sevoflurane anesthesia, mannitol, and furosemide. Twenty minutes after induction, she experienced tachycardia, hypotension, tongue swelling, diffuse urticaria, and bronchospasm. She was treated with epinephrine, famotidine, and methylprednisolone, and stabilized.

Three weeks later, the patient was in a preoperative period for a second surgical attempt. Once again, central and peripheral insertion sites were cleansed with a chlorhexidine scrub. For this surgical attempt, she was pretreated with diphenhydramine and ranitidine, and the neuromuscular blocker was withheld. She was also given the following medications: midazolam, lidocaine, propofol, fentanyl, sevoflurane anesthesia, and furosemide. Fifteen minutes after induction, she developed severe hypotension, without any other signs or symptoms of anaphylaxis. She was treated with epinephrine, methylprednisolone, and phenylephrine, and fluids, and recovered.

Questions

1. What Is the Differential Diagnosis?

For the first surgery, central and peripheral insertion sites were cleansed with a chlorhexidine scrub. The patient also received the following medications: midazolam, lidocaine, propofol, fentanyl, dexamethasone, rocuronium, sevoflurane anesthesia, mannitol, and furosemide. For the second surgical attempt, once again, peripheral insertion sites were cleansed with a chlorhexidine scrub. She was pretreated with diphenhydramine and ranitidine, and the neuromuscular blocker was withheld. She was also given the following medications: midazolam, lidocaine, propofol, fentanyl, sevoflurane anesthesia, and furosemide. Any of the above medications could potentially cause anaphylaxis, which is why an accurate history and appropriate testing is so important.

2. What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in this Patient?

Many medications were administered in close conjunction with each other, which made the diagnosis more difficult. It would have been helpful to know the exact timing of medication administration and the exact order in which they were given. Medications such as midazolam, propofol, and fentanyl are rarely used in an outpatient setting. However, it also may have been useful to perform skin-prick puncture test to these medications to aid in the diagnosis. Serum specific IgE to latex, lidocaine, and chlorhexidine also may have been useful to confirm the diagnosis. However, serum specific IgE may not be as sensitive as a skin-prick puncture test.

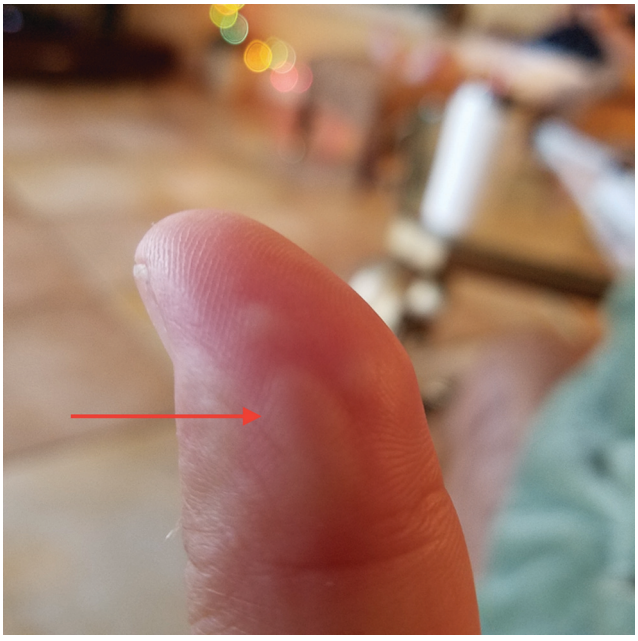

Figure 1. *The patient's urticaria after using chlorhexidine body wash.*

DISCUSSION

Antibiotics and neuromuscular blockers are the two most common causes of perioperative anaphylaxis.[1] An antibiotic was never prescribed, and she was not given a neuromuscular blocking agent for the second surgical attempt. Latex is a common cause of perioperative anaphylaxis. Caine drugs and their preservatives are rarely associated with systemic allergic reactions. A prick-puncture test helped to rule out suspect medications and to identify the culprit.

The patient's history of a generalized cutaneous allergic reaction after exposure to chlorhexidine body wash was missed by the anesthesiologist and neurosurgeon, and by the attending physician during the first of two interviews on the same day. Before surgery, the patient had central and peripheral line insertion sites cleansed with a chlorhexidine scrub and this made possible the probable introduction of chlorhexidine by the venous route.

Anaphylaxis was confirmed. The serum tryptase level during anaphylaxis was 119 ng/mL and, 4 weeks later, was <11.4 ng/mL, at baseline, which suggested acute mast cell degranulation and eliminated mastocytosis as a possible diagnosis. These findings, along with a positive percutaneous skin test and in-depth history, led to a definitive diagnosis as to which medication caused anaphylaxis.

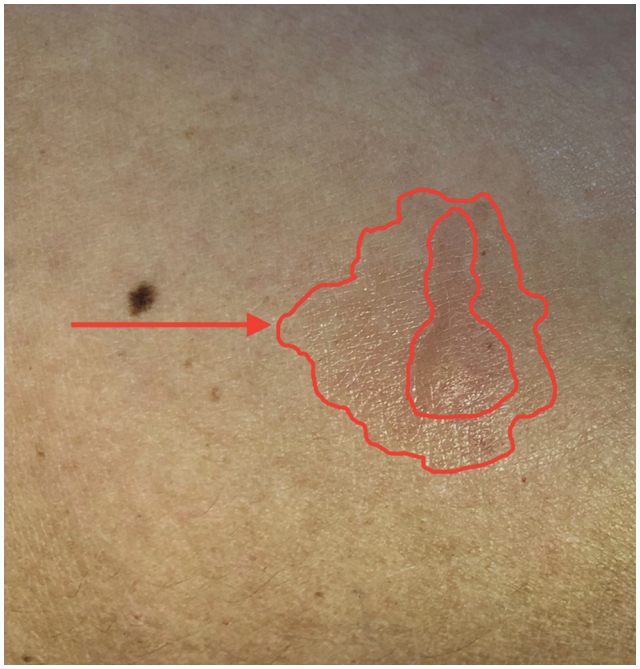

Figure 2. *Wheal and flare from chlorhexidine prick-puncture test.*

Final Diagnosis

Chlorhexidine allergy was suggested by the history and confirmed by a skin-prick puncture test. The patient experienced anaphylaxis after the probable introduction of chlorhexidine by the venous route (peripheral and central line insertions).

CONCLUSION

The patient and surgical team were instructed to avoid chlorhexidine and chlorhexidine impregnated medical equipment before surgery. They were also instructed to avoid all unnecessary medications, especially those associated with perioperative anaphylaxis, *i.e.,* antibiotics and neuromuscular blocking agents, and to be prepared to treat a potential systemic allergic reaction. Chlorhexidine was avoided, and the cranial surgery to remove the patient's meningioma was successful. The patient was discharged home shortly thereafter and is currently doing well.

Chlorhexidine is an antiseptic and disinfectant used in surgical and nonsurgical settings and is a rare cause of perioperative anaphylaxis.[2] Many types of medical equipment are impregnated with chlorhexidine and the likelihood of a reaction increases if chlorhexidine is applied to a site with direct vascular access.[3] More reactions occur with alcohol-based chlorhexidine solutions compared with other solvents, and, in this case, isopropyl alcohol was used, which increased the likelihood of a reaction. The true prevalence of chlorhexidine allergy is unknown; however, the awareness and prevalence of chlorhexidine allergy has been increasing. The 6th Annual National Audit Project of the Royal College of Anesthetists conducted a large multicentered European survey and identified chlorhexidine as the culprit of perioperative anaphylaxis in as high as 9.3% of cases in Denmark.[4] The incidence of chlorhexidine-induced anaphylaxis varies, depending on geographic location, and is significantly less prevalent in areas, *e.g.,* France, where it still reported as a rare cause of perioperative anaphylaxis.[5] This may be due to decreased awareness, increased testing, and overall use, depending on clinical and surgical practices; however, the reason is likely multifactorial.

Chlorhexidine sensitization most likely occurs in a variety of health care and community settings, and methods of exposure should be further explored. The The 6th Annual National Audit Project of the Royal College of Anesthetists Allergy Survey[6] identified chlorhexidine exposure during the perioperative period by at least one route in as high as 73.5% of all cases. Chlorhexidine is also used in a wide variety of cosmetic products and sensitization *via* topical application may commonly be overlooked.[7] Unnecessary sensitization and, ultimately, anaphylaxis may be avoided with clear product labeling, appropriate use of alternatives, physician and patient education, improved history taking, and appropriate testing when indicated.

The safest management approach for a patient with this history is the definitive identification and complete avoidance of the causative agent. Physicians should be aware that chlorhexidine is a rare and often unappreciated cause of perioperative anaphylaxis. A detailed and accurate history, coupled with appropriate skin-prick-puncture test, played a key role in discovering the etiology of this patient's anaphylaxis.

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Patient Oriented Problem Solving (POPS) Case Report

Persistent urticarial rash in a newborn

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ABSTRACT

We presented the case of a 1-month-old girl with diffuse urticarial-like rash since birth. The initial evaluation showed elevated inflammatory markers. The response to treatment helped to narrow the diagnosis. In this case, we explored the differential diagnosis of rashes in this age group and the role of a therapeutic trial of medication as a diagnostic modality.

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CHIEF CONCERN

Urticarial-like rash

HISTORY OF PRESENT ILLNESS

A 1-month old white girl was referred to the allergy/immunology clinic due to a diffuse urticarial-like rash, which started within a few hours of birth and persisted thereafter. Individual lesions lasted several hours to several days and never disappeared completely. The infant did not have any other symptoms. There were no known sick contacts. The infant was exclusively breast-fed. She was born at full term *via* a repeat caesarean section. Prenatal laboratory test results were negative. Her mother had no infections during pregnancy or at the time of the infant's birth. The family history was negative for autoimmune disease, immunodeficiency disorders, and consanguinity.

PHYSICAL EXAMINATION

At initial presentation, she weighed 3.8 kg (25th percentile). Her weight gain had been stable since birth. Her temperature was 36.6°C, heart rate was 140 beats/minute, and the respiratory rate was 54 breaths/minute. The physical examination was significant for diffuse, blanching, erythematous patches, and plaques, most prominent on the face and scalp but sparing her soles (Fig. 1, *A* and *B*).

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QUESTION 1

What Is the Differential Diagnosis?

Maculopapular and macular rashes that first appear in the newborn period can have various noninfectious and infectious etiologies (Table 1). The appearance of the rash may be atypical or vary throughout its course; thus, the rash should be evaluated in the context of the clinical presentation while keeping a broad differential diagnosis in mind. Benign noninfectious conditions include erythema toxicum neonatorum, transient neonatal pustular melanosis, neonatal cephalic pustulosis, and neonatal acne. These rashes usually have a pustular appearance, although can present as papules, especially at the onset.[1] At birth, our patient's rash was thought to be erythema toxicum neonatorum. Infections should be considered. The differential diagnosis of viral exanthems that present as maculopapular or macular rashes is broad.[2] Staphylococcal scalded skin syndrome, an exfoliative disease caused by *Staphylococcus aureus,* is a bacterial infection that may present with macular erythema early in its course.[3] Although the incidence of congenital syphilis has been on the rise, this disorder mostly presents in infants born to women with a lack of prenatal care.[4]

Clinical stability and the absence of fever, despite persistence of rash, made infection less likely in our patient. Cutaneous manifestations frequently occur with food allergy, *e.g.,* cow's milk allergy.[5] However, the patient was exclusively breast-fed, which made this diagnosis unlikely. A drug-induced rash was also unlikely because the only medication she had been on was cholecalciferol, which was started after the appearance of the rash. An etiology to consider was neonatal lupus. In neonatal lupus, congenital heart block, cutaneous annular lesions, and cytopenia are the most common clinical manifestations.[6,7] Other rare causes in the neonatal period may include cryopyrin-associated periodic syndrome (CAPS), urticaria pigmentosa, hemo-

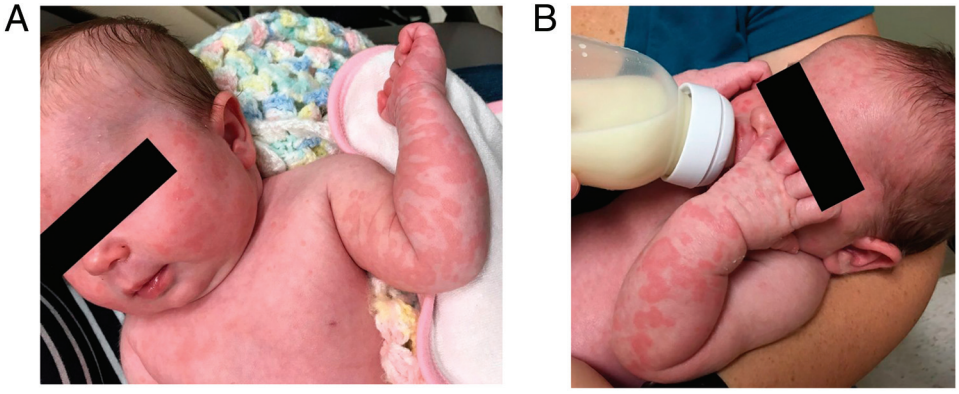

Figure 1. (A and B) Photographs, showing urticarial-like rash, taken at 1 month of age, before initiation of therapy.

Table 1 **Differential diagnosis of maculopapular and macular rashes in newborns**

Benign
Erythema toxicum neonatorum
Transient neonatal pustular melanosis
Neonatal cephalic pustulosis
Neonatal acne
Infectious
Viral exanthems
Neonatal syphilis
Staphylococcal scalded skin syndrome
Food allergy
Cow's milk allergy
Drug eruption
Malignancy
Langerhans cell histiocytosis
Other
Neonatal lupus
Cryopyrin-associated periodic syndrome
Urticaria pigmentosa
Hemophagocytic lymphohistiocytosis

Table 2 **Laboratory results**

Test	Results (reference range)
WBC count, K/μL	11.60 (5.0–21.0)
Platelets, K/μL	382 (158–470)
ALT level, units/L	15 (0–33)
Total bilirubin value, mg/dL	0.2 (0.0–1.2)
ESR, mm/hr	58 (0–10)
CRP level, mg/dL	4.79 (<0.50)
ANA	<1:80 (<1:40)
Anti-RNP antibodies, units/mL	2.3 (<20)
Anti-SSA antibodies, units/mL	3.15 (<20)
Anti-SSB antibodies, units/mL	1.87 (<20)
CMV PCR result	Negative
Blood culture result	Negative
Ferritin level, ng/mL	622.4 (13.0–150.0)

WBC = White blood cell; ALT = alanine transaminase; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA= antinuclear antibody; Anti-RNP = anti-ribonucleoprotein; Anti-SSA = anti–Sjögren's-syndrome-related antigen A; Anti-SSB = anti–Sjögren's-syndrome-related antigen B; CMV = cytomegalovirus; PCR = polymerase chain reaction.

phagocytic lymphohistiocytosis (HLH), and malignancies, *e.g.*, Langerhans cell histiocytosis.[8–11]

Initial Laboratory and Diagnostic Findings

Laboratory results showed an elevated erythrocyte sedimentation rate of 58 mm/hour (reference range, 0–10 mm/hour), and elevated C-reactive protein level of 4.79 mg/dL (reference range, <0.50 mg/dL). A complete blood cell count with differential was normal (Table 2).

QUESTION 2

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis?

In the setting of laboratory evidence of systemic inflammation, infection should be considered. Along with serologic testing, the workup usually involves ophthalmologic evaluation and imaging of the brain *via* a cranial ultrasound. Antinuclear antibody and anti-Sjögren's-syndrome-related antigen A and anti-Sjögren's-syndrome-related antigen B antibodies are valuable in evaluating for neonatal lupus. A ferritin level and liver function tests should be obtained if HLH is high on the differential diagnosis.[12] A tryptase level may be obtained if urticaria pigmentosa is suspected.[10] A skin biopsy may be needed if the diagnosis is not arrived at by less-invasive diagnostic measures.

CLINICAL COURSE

Additional studies included antinuclear antibody, which was negative. Levels of anti-ribonucleoprotein, anti–Sjögren's-syndrome-related antigen A, and anti–Sjögren's-syndrome-related antigen B antibodies were normal. Blood culture and cytomegalovirus polymerase chain reaction results were negative. The ferritin level was elevated, at 622.4 ng/mL (reference range, 13.0–150.0 ng/mL) (Table 2). However, the patient did not have splenomegaly, fever, cytopenia, or liver function abnormalities, which are common features of HLH.[11,12] Elevated inflammatory markers, a lack of other laboratory findings, and a persistent urticarial-like rash made us suspect an autoinflammatory disorder, *e.g.*, CAPS.

Radiographs of the extremities did not demonstrate periarticular soft-tissue swelling or abnormalities of the epiphyses. A cranial ultrasound showed normal parenchyma, without calcifications, ventriculomegaly, or hemorrhage. Audiologic and ophthalmologic evaluations were normal. Due to the high clinical suspicion for CAPS, anakinra was trialed at a starting dose of 2 mg/kg/day. The patient responded to the treatment; the rash resolved completely with the first dose. Subsequently, the rash reappeared but responded on increasing the dose of anakinra to 4 mg/kg/day. Several weeks later, inflammatory markers returned to normal: C-reactive protein of 0.27 mg/dL (reference range, <0.50 mg/dL), and erythrocyte sedimentation rate of 9 mm/hour (reference range, 0–10 mm/hour). An autoinflammatory syndromes genetic panel revealed a heterozygous mutation in the NLR family pyrin domain containing 3 (*NLRP3*) gene: c.911T>G.

DISCUSSION

Our patient's presentation was most consistent with CAPS. CAPS is a rare disorder characterized by episodic or chronic noninfectious systemic inflammation. It consists of three overlapping phenotypes, ranging from mild to severe: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID).[13] The most common features among these phenotypes are recurrent fever, rash, arthralgias, and conjunctivitis. Patients typically present by 6 months of age, but some cases are not recognized until later in childhood or even adulthood.[14–16] In FCAS, exposure to systemic cold precipitates symptoms. Complications such as renal disease and hearing loss are rare in FCAS.[17,18] Patients with Muckle-Wells syndrome are more likely to develop sensorineural hearing loss and amyloidosis-induced renal disease after long-term disease.[19] The most severe phenotype is NOMID, also known as chronic infantile neurological cutaneous and articular (CINCA) syndrome. Patients with NOMID frequently experience central nervous, audiologic, ophthalmic, and skeletal involvement. Neurologic manifestations include chronic meningitis, cerebral atrophy, and, sometimes, mental retardation. Arthropathy that results from epiphyseal overgrowth of the long bones can be disabling.[20,21] Some patients have features of all three phenotypes.[22] Our patient's presentation did not fit into one category.

Mutations in the *NLRP3* gene, which are dominantly inherited or *de novo* gain-of-function mutations are now known to be the cause of CAPS.[23] The *NLRP3* gene, which is also known as cold-induced autoinflammatory syndrome-1-gene, encodes cryopyrin. Cryopyrin is involved in the formation of the *NLRP3* inflammasome, which leads to the activation of caspase-1 and release of interleukin (IL) 1β.[24,25] The majority of patients with CAPS have germline mutations in the *NLRP3* gene, detected either by Sanger sequencing or next-generation sequencing. Up to 70% of patients with "genotype negative" CAPS have evidence of somatic mosaicism, which may require more-advanced techniques, which complicates the process of diagnosis.[15,26]

Our patient has a heterozygous mutation in the *NLRP3* gene: c.911T>G, which has not been reported in CAPS. The mutation is located on exon 3, which is the most common site for mutations in the *NLRP3* gene in association with CAPS.[23] This mutation may represent a pathogenic variant. Both parents had genetic testing performed, and neither carries this mutation, which suggests it is likely a *de novo* mutation. In this patient's case, a skin biopsy was not needed for a diagnosis, but a biopsy may be valuable in many cases. The rash associated with CAPS is migratory and urticarial-like, but it differs from urticaria histologically. The CAPS rash characteristically involves a perivascular neutrophilic infiltrate, without the evidence of vasculitis, which varies from the predominantly lymphocytic infiltrate of typical urticaria.[27,28]

The severity of the disease and the complications are related to the specific mutation identified. In the setting of a novel mutation, close clinical monitoring is required to detect any evidence of persistent inflammation or development of hearing loss, uveitis, or arthropathy. The main treatment for CAPS is IL-1 blockade. Anakinra is a recombinant IL-1 receptor antagonist, which is administered daily as a subcutaneous injection. Results of studies have shown that anakinra can improve daily symptoms, decrease laboratory markers of inflammation, and decrease or even prevent the risk of long-term complications such as hearing loss, vision loss, and renal disease.[14,29,30] Our patient had a quick response to anakinra. Although anakinra is considered safe, monitoring for adverse events, including surveillance for neutropenia and

thrombocytopenia, is an important part of clinical management.[31–33] An increased risk of infection may be present, and patients should be carefully monitored.[33] Other treatments include rilonacept, a fusion protein of the IL-1 receptor, and canakinumab, a fully human anti–IL-1β antibody.[34,35] Anakinra has excellent central nervous system penetration and is thus favored over rilonacept and canakinumab for patients with evidence of central nervous system involvement.[36]

Final Diagnosis

The final diagnosis was cryopyrin-associated periodic syndrome.

SUMMARY AND CONCLUSION

Urticarial-like rashes in pediatric patients can pose a diagnostic dilemma. When evidence of systemic involvement is present, a rare but serious cause, cryopyrin-associated periodic syndrome, should be considered. Early diagnosis and treatment are critical and may prevent serious sequelae. A therapeutic trial of medication can be a time-saving diagnostic modality, especially when clinical findings are few, and confirmation with genetic studies is not prompt or not entirely conclusive.

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Patient Oriented Problem Solving (POPS) Case Report

A 33-year-old man with a history of recurrent pneumonia presenting with hypoxemic respiratory failure

Taylor Eddens, M.D., Ph.D., Sara Van Meerbeke, M.D., Michael Zhang, M.D., Ph.D., Andrej Petrov, M.D., and Merritt L. Fajt, M.D.

ABSTRACT

The patient was a 33-year-old man with a history of recurrent pneumonia, autism, bipolar disorder, hypothyroidism, intermittent asthma, and nonischemic cardiomyopathy attributed to cocaine use who was admitted with hypoxemic respiratory distress with bilateral infiltrates seen on a chest radiograph. He was treated for community-acquired pneumonia but progressed to respiratory failure that required intubation and broad-spectrum antibiotic therapy. His medical history was notable for short stature, abnormal facial features, and, since childhood, at least two pneumonias per year that required antibiotics. The initial evaluation for an underlying primary immunodeficiency found that the patient had normal quantitative immunoglobulin levels, with absent CD19$^+$ B cells. This case highlighted the evaluation of the humoral immune system for hospitalized adult patients with recurrent infections as well as the use of genetic testing to diagnose rare immunodeficiency syndromes.

(Allergy Asthma Proc 42:439–442, 2021; doi: 10.2500/aap.2021.42.210032)

CASE REPORT

Chief Concern

Hypoxemic respiratory failure in the setting of recurrent pneumonia

History of Present Illness

The patient was a 33-year-old man with a history of recurrent pneumonia, attention deficit hyperactivity disorder, autism, bipolar disorder, hypothyroidism, asthma, and nonischemic cardiomyopathy attributed to cocaine use who presented with shortness of breath. The patient was found to be hypoxemic, with an O_2 saturation of 87% on room air. A chest radiograph demonstrated bilateral infiltrates that were concerning for pneumonia. He was hospitalized and initially started on ampicillin-sulbactam and azithromycin for community-acquired pneumonia. Two days later, he developed progressive respiratory failure that required intubation. During this time, he had severe hypotensive episodes that required multiple vasoactive medications and his antibiotics were broadened to vancomycin and meropenem. He also had worsening heart failure (ejection fraction of 15–20% on transthoracic echocardiogram) as well as kidney failure, which required continuous renal replacement therapy. A computed tomography (CT) of the chest at that time was also notable for bilateral lower lobe consolidations and multifocal ground-glass opacities and cardiomegaly (Fig. 1 *a*). After completion of a 10-day course of antimicrobials and aggressive dialysis, he was subsequently extubated.

Five days after extubation, the patient again developed respiratory distress. A repeated chest CT showed patchy bilateral upper lobe airspace disease that was concerning for a multifocal pneumonia (Fig. 1 *b*). He was empirically started on cefepime and vancomycin. A sputum culture demonstrated *Pseudomonas aeruginosa* infection with resistance to meropenem. He was treated with intravenous antibiotics in addition to inhaled tobramycin for a 14-day course. The patient remained hospitalized for an interim period of 3 weeks due to his tenuous cardiac and renal status. During this time, he was noted to have worsening leukocytosis, with findings on a repeated CT of the chest consistent with widespread airspace opacities. Bronchoscopic evaluation revealed grossly scant mucoid secretions, with negative viral and fungal studies, and unremarkable bronchoalveolar lavage cell counts. He was again broadly treated with ceftolozane-tazobactam and metronidazole for a total of 10 days with improvement. During this antibiotic course, an allergy/immunology specialist was consulted for evaluation of possible immunodeficiency.

In terms of infection history, the patient had had at least two pneumonias yearly that required antibiotic

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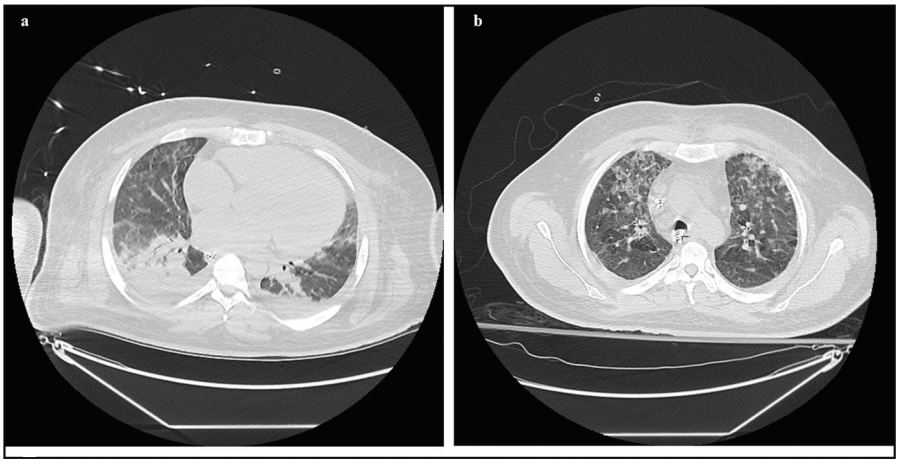

Figure 1. Computed tomographies (CT) of the chest. (a) Bilateral lower lobe consolidation, multifocal ground-glass opacities, pleural effusions, and cardiomegaly obtained during the initial episode of hypoxemic respiratory failure. (b) Bilateral upper lobe airspace disease and interstitial thickening obtained 20 days into hospitalization during the patient's second episode of respiratory distress.

therapy, which started at age 2–3 years of life. Over the past 10 years, he reported that he had had ~20 pneumonias, all of which were diagnosed radiographically. He had been hospitalized at least five times in his life for pneumonia. The patient also had several ear infections as a small child but never required tympanostomy tube placement. He denied any skin and/or soft-tissue infections or sinus infections. The family history was negative for recurrent infections or autoimmune disease.

Physical Examination

The physical examination was notable for a 5′4′ man on 2 L of supplemental oxygen who was in no acute distress. He had abnormal facies, characterized by a long philtrum and a thin upper lip. His respiratory examination was notable for a normal respiratory rate without accessory muscle use and good aeration bilaterally, with diffuse crackles and without wheeze. Results of his cardiovascular, abdominal, and skin examinations were within normal limits.

Question 1: What Initial Laboratory Studies Would Be Helpful to Assess This Patient's Immune System?

Initial Laboratory Findings. A complete blood cell count was obtained and notable for leukocytosis, with a left shift, normocytic anemia, and thrombocytopenia. To assess the patient's humoral immune system, quantitative immunoglobulin levels were obtained and were normal (Table 1). The patient had normal numbers of T-cell subsets but had no detectable $CD19^+$ B cells and low $CD16/56^+$ natural killer cells (Table 1). He had absent pneumococcal titers to 13 serotypes but protective tetanus and diphtheria titers. Human immunodeficiency virus testing results were negative.

Question 2: What Is the Differential Diagnosis?

When considering the differential diagnosis for this patient, he had several features that were concerning for a primary immunodeficiency. He had a clear history of recurrent pulmonary infections as well as syndromic features on examination. His initial laboratory assessment was notable for B-cell lymphopenia, normal immunoglobulin levels, with absent pneumococcal titers despite being fully immunized. Therefore, the differential diagnosis focused on humoral immunity, including X-linked agammaglobulinemia (XLA). XLA classically presents in infancy, after waning of maternal antibodies, with recurrent sinopulmonary infections.[1] However, there are documented cases of "leaky" XLA, in which patients have some degree of antibody production and vaccine seroconversion.[2] There are other intrinsic B-cell defects that can lead to the absence of circulating B cells, including genetic mutations in the immunoglobulin genes and PI3 kinase-related diseases.[3] However, these conditions are usually associated with decreased or absent immunoglobulin levels. Several combined immunodeficiency syndromes, such as deficiency of dedicator of cytokinesis 8 (DOCK8), interleukin 21, and induced costimulatory ligand (ICOSL) can present with low B cell levels.[3–6] However, this patient was less likely to have a combined defect because he did not have any opportunistic infections and had normal T-cell numbers. Certain hyper–immunoglobulin E (IgE) related syndromes can be associated with respiratory infections and decreased B-cell numbers, such as deficiency in caspase recruitment domain-containing protein 11 (CARD11) or phosphoglucomutase 3 (PGM3).[7] Another consideration included cystic fibrosis, given the recurrent pneumonia, short stature, and *Pseudomonas*-positive sputum culture. Hematologic malignancy was also on the differential diagnosis given his pancytopenia.

Question 3: What Additional Diagnostic Studies Were Obtained to Evaluate the Above Differential Diagnosis?

The patient's IgE level was significantly elevated (1706 kU/L [reference range, <114 kU/L]). Serum protein

Table 1 **Our patient's laboratory values at the time of initial immunologic evaluation**

Laboratory Test	Patient's Result	Reference Range
White blood cell count, $\times 10^9$ cells	12.5	3.8–10.6
Neutrophils, $\times 10^9$ cells	7.2	2.24–7.68
Lymphocytes, $\times 10^9$ cells	1.2	0.80–3.65
Bands, immature myeloid cells, $\times 10^9$ cells	4.2	0
Eosinophils, $\times 10^9$ cells	0.9	0.0–0.4
Monocytes, $\times 10^9$ cells	0.6	0.3–0.9
Hemoglobin, g/dL	8.7	12.9–16.9
Platelets, $\times 10^9$ cells	118	156–369
Immunoglobulin G, mg/dL	903	751–1560
Immunoglobulin M, mg/dL	62	40–274
Immunoglobulin A, mg/dL	138	82–453
CD3, cells/mm^3	1017	856–2669
CD4, cells/mm^3	506	491–1734
CD8, cells/mm^3	506	162–1074
CD19, cells/mm^3	0	73–562
CD16/56, cells/mm^3	21	108–680

electrophoresis demonstrated the possibility of an IgG κ monoclonal gammopathy, whereas serum light chains and urine protein electrophoresis results were normal. Results of a bone marrow biopsy were notable for mildly hypercellular marrow, with myeloid predominant trilineage hematopoiesis and no increased blasts. A neutrophil oxidative burst assay and a T-cell mitogen proliferation assay were both within normal limits. A cystic fibrosis genetic screen result was also negative. Given the abnormalities of his laboratory studies, a genetic test that consisted of 407 genes associated with primary immunodeficiency (Invitae, San Francisco, CA) was sent. This ultimately led to the final diagnosis.

Clinical Course

While awaiting the genetic study results, the patient continued to have improvement from a respiratory perspective. He returned to his baseline respiratory status after the course of ceftolozane-tazobactam and metronidazole. After these interventions, he remained hospitalized for 6 additional weeks for optimization of fluid balance and O_2 requirements in the setting of heart failure and chronic renal insufficiency. After 80 days, the patient was discharged home. Three days after discharge, the genetic panel returned with two variants (n.8C>T and n.37C>A) in the small nuclear RNA U4atac (*RNU4ATAC*) gene.

The two genetic variants isolated in this patient were individually identified in two separate patients with Roifman syndrome, otherwise known as spondyloepiphyseal dysplasia, retinal dystrophy, and antibody deficiency.[8] Whole genome sequencing of six patients with Roifman syndrome revealed that each patient had two mutations in *RNU4ATAC*, with one mutation in the stem II region (3–19 bp) and a second in the 5′ stem-loop region (20–58 bp), similar to this patient.[8] These analyzed individuals were found to have mutations in *trans* chromosomal alignment, consistent with compound heterozygous inheritance. *RNU4ATAC* encodes a small nuclear RNA involved in the minor spliceosome complex, which affects the processing of >800 genes, with ramifications in multiple organ systems.[8]

Roifman syndrome was originally described in a case of four boys, ages 4–19 years, who presented with a constellation of signs and symptoms, including B-cell lymphopenia with normal quantitative immunoglobulin levels, spondyloepiphyseal chondro-osseous dysplasia, retinal dystrophy, poor growth, cognitive delay, and facial dysmorphism.[8–11] Interestingly, the immunoglobulins produced by patients with Roifman syndrome often have poor specificity due to abnormal B-cell development. Despite the normal level of circulating antibodies, these patients are susceptible to recurrent infections due to poor immunoglobulin function.[8,10] One mechanistic study demonstrated that patients with Roifman syndrome had abnormal differentiation of B cells due to disrupted B-cell activating factor signaling, which leads to increased transitional B cells but decreased naive mature B cells and mature B cells.[9] Platelet development is also disrupted in patients with Roifman syndrome, as seen with this patient's persistent thrombocytopenia.[9]

As a result of this genetic diagnosis, the patient was started on intravenous immunoglobulin replacement (0.4 g/kg). His first infusion was administered in an intensive care unit setting because the patient had been readmitted for worsening renal failure and was receiving daily hemodialysis. Due to the large fluid volume of immunoglobulin replacement and his underlying cardiac and renal dysfunction, this infusion was administered at a renally adjusted rate. Given the other comorbidities associated with Roifman syndrome, he was advised to obtain a skeletal survey, a complete ophthalmologic assessment, and a neurodevelopmental assessment.

Two months after initiation of immunoglobulin replacement, the patient died of decompensated cardiac and renal failure. He did not develop any further identifiable infections while on immunoglobulin replacement. However, his end-organ damage was likely a sequela of his presentation with pneumonia and respiratory failure because these features have not been described as part of the natural history of Roifman syndrome. Like the patient in this case, the majority of patients with primary immunodeficiency are diagnosed in adulthood.[12] However, one population-based study demonstrated that older age at the time of primary immunodeficiency

diagnosis was associated with increased mortality.[13] Over the past 10 years, the widespread utilization of genetic testing, in part due to decreased costs, has led to a rapid increase in the number of inborn errors of immunity being diagnosed.[3] This case highlights the need to pursue and obtain genetic diagnoses when clinical concern arises for primary immunodeficiency.

Final Diagnosis

Roifman syndrome.

CONCLUSION

We reported a case of a patient with a rare primary immunodeficiency with manifestations of recurrent pneumonia in the setting of normal immunoglobulin levels, absent pneumococcal titers, and absent $CD19^+$ B cells. This patient had a compelling infection history, dysmorphism on physical examination, and conflicting immunologic laboratory values. Our patient demonstrated the workup of a presumed humoral immune defect while highlighting a clinical scenario in which quantitative immunoglobulin levels were normal with poor function. In addition, the B-cell quantity may not have been routinely assessed in the setting of "normal" immunoglobulins and a normal lymphocyte count. A teaching point of this case is to caution clinicians on being falsely reassured by normal quantitative immunoglobulins levels. Ultimately, genetic testing was used to make the final diagnosis and helped the patient and his family understand the reason for his recurrent pneumonia.

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