Churg-Strauss Syndrome Associated with HIV Infection

Hien Nguyen, MD, Kevin Ferentz, MD, Alkesh Patel, MD, and Connie Le, MD,

A 28-year-old woman with a history of asthma and recent deep venous thrombosis presented with fever, chest pain, and peripheral eosinophilia. The patient was subsequently diagnosed with Churg-Strauss syndrome and HIV infection, representing to our knowledge only the second case of this association. Rheumatologic manifestations of HIV may precede clinical signs of infection. This is significant because steroidal and cytotoxic therapy may potentially worsen HIV infection. As the prevalence of HIV infection rises, there may be atypical presentations of various rheumatologic syndromes. The following case demonstrates a patient whose initial presentation for HIV infection was Churg-Strauss syndrome. (J Am Board Fam Pract 2005;18:140–2.)

CASE REPORT

A 28-year-old woman with history of moderate persistent asthma, recurrent sinusitis, and a recently diagnosed deep venous thrombosis presented to her physician for follow-up of anticoagulation on enoxaparin and warfarin. A month before presentation, the patient had been diagnosed with deep venous thrombosis of her right leg; a Doppler sonogram was used to make the diagnosis. She had a hypercoagulable workup, including normal levels of protein C, protein S, and antithrombin 3 levels. She had no clinical risk factors, including trauma, immobility, pregnancy, obesity, or medications associated with thrombosis.

At this follow-up, she complained of a 5-day history of fever, pleuritic chest pain, dyspnea, and malaise accompanied by nausea, emesis, anorexia, and loose stools. She denied any recent travels or contacts with ill persons. Complete blood count revealed a leukocytosis of 50,000 cells/mm^3 with 65% eosinophils.

Enoxaparin was discontinued because of the possibility of drug allergy. Two days later, a complete blood cell count revealed worsening leukocytosis and hypereosinophilia. The patient was admitted. She had been hospitalized 1 month previously for an asthma exacerbation and had been discharged from the hospital on triamcinolone inhaler, albuterol inhaler, and a 60-mg prednisone taper over 2 weeks. She was subsequently readmitted to the hospital 2 weeks later for acute deep venous thrombosis, and discharged from the hospital in stable condition on enoxaparin and warfarin.

Vital signs at admission were: temperature, 102.6°F; respiratory rate, 20 breaths/min; blood pressure, 110/60 mm Hg; pulse, 110 beats/min; and pulse oximetry of 98% on room air. Pertinent physical findings on physical examination include generalized cervical lymphadenopathy and faint expiratory wheezing on lung auscultation. Abdominal examination revealed mild diffuse tenderness, and rectal examination revealed heme-negative brown stool. Extremity examination was consistent with a resolving deep venous thrombosis.

Leukocyte count at admission was 52,800 with 67% eosinophils. Platelet count was 122,000, and hematocrit was 0.248 with mean corpuscular volume of 69.2. Results of a metabolic panel were normal. Urinalysis revealed 3+ blood, 1+ protein, negative nitrite, and leukocyte esterase, no casts, and 18% eosinophils. Chest radiograph revealed increased interstitial markings, and abdominal radiographs revealed non-specific bowel gas pattern without evidence of obstruction or free air. Electrocardiogram revealed sinus tachycardia.

A hematology-oncology consultation was obtained. Laboratory tests were requested for HIV, IgE, stool ova and parasites, blood cultures, antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibodies. HIV testing was positive, with a CD4 count of 682 and 1004 RNA copies/mL. IgE was 1005 mg/dL, and anti-nuclear

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From the University of Maryland School of Medicine, Baltimore. Address correspondence to Dr. Nguyen Hien, 3808 Daniel's Run Court, Fairfax, VA 22030 (e-mail: htnguyen@gwu.edu).

antibody titer was 1:640 with homogeneous pattern. Erythrocyte sedimentation rate was 65. Results of all other laboratory tests were normal, including stool cultures for parasitic infection. A bone marrow biopsy was performed, demonstrating hypercellularity without malignancy. Echocardiography ruled out eosinophilic infiltration of the heart. Spiral computed tomography of the chest with contrast was consistent with eosinophilic pneumoniae and ruled out pulmonary embolus. Immunophenotyping was negative for T cell rearrangement.

The patient was prescribed oral prednisone, 60 mg daily over 2 weeks, and was discharged from the hospital in stable condition. At 2- and 4-week clinic follow-up, the patient's symptoms and hypereosinophilia had resolved completely. At 1-year follow-up, she had experienced no recurrence of the hypereosinophilia and had started antiretroviral therapy.

Discussion

Hypereosinophilia

Hypereosinophilia is a frequently encountered clinical problem that has primary and secondary causes. Primary hypereosinophilic syndromes include Loeffler syndrome, eosinophilic leukemia, eosinophilia myalgia syndrome, and idiopathic hypereosinophilic syndrome.[2] Secondary causes of hypereosinophilia include allergic disorders, parasitic infection, malignancy, and an array of collagen vascular diseases, which include eosinophilic fasciitis and Churg-Strauss syndrome (CSS).[1]

Evaluation of Hypereosinophilia

Drug and travel histories should be obtained, along with a thorough review of systems. The focus should be on the cardiac, pulmonary, and gastrointestinal systems, because eosinophilic manifestations occur more commonly in these organ systems. Laboratory examination includes: complete blood cell count to evaluate for infection and myeloproliferative disorders; erythrocyte sedimentation rate to screen for inflammation; stool ova and parasites to exclude parasitic infection, especially *Strongyloides* spp. (contraindication for steroidal therapy); IgE; anti-neutrophilic cytoplasmic antibody; and radioallergosorbent testing to evaluate for atopy.[3] Other testing, depending on clinical organ involvement, includes endoscopy with bowel biopsy, muscle biopsy, renal biopsy, and bone marrow biopsy.[3]

Peripheral eosinophilia is defined as more than 500 eosinophils/mm^3. Manual differential should be performed because automated differentials may count hypogranular eosinophils as neutrophils. Eosinophil counts of 300 to 1000/mm^3 are associated with atopic disease, whereas counts of 1000 to 5000/mm^3 are typically observed with allergic drug reactions, Churg-Strauss syndrome, and parasitic infections. Idiopathic hypereosinophilic syndrome is associated with eosinophil levels greater than 30,000/mm^3. Eosinophils are not normally found in urine or cerebrospinal fluid.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a systemic vasculitis and allergic granulomatosis that was first described in 1951.[5] The syndrome is characterized by three distinct and progressive phases. The initial features are asthma and allergic rhinitis, which may precede systemic disease by many years. The second phase is heralded by fever, weight loss, peripheral eosinophilia, and eosinophilic infiltration of the lungs, upper respiratory tract, and gut. The third phase is manifested by systemic vasculitis, leading to cardiac failure, myocardial infarction, cutaneous disease, peripheral neuropathy, hypertension, renal diseases, and arthralgias.[6]

The American College of Rheumatology criteria for Churg Straus include (1) moderate to severe asthma, (2) peripheral eosinophilia >10%, (3) neuropathy, (4) pulmonary infiltrates, (5) para-sinus abnormality, and (6) extravascular eosinophils.[3] There are serious diagnostic challenges in patients such as ours who meet 4 of 6 classification criteria (asthma, eosinophilia, pulmonary infiltrates, and sinus abnormality) but who do not yet have clinical or bioptic evidence of systemic vasculitis. We postulate that our patient was in the second phase of Churg-Strauss syndrome, where steroidal therapy rapidly reversed the clinical syndrome. The phase in which Churg-Strauss syndrome is diagnosed may have relevant prognostic and therapeutic ramifications, and further studies need to be performed to address these issues.

Link between HIV Infection, Hypereosinophilia, and Churg-Strauss Syndrome

HIV infection has been associated with a number of rheumatologic disorders, including Reiter syn-

drome, psoriatic arthritis, septic arthritis, Sjogren syndrome, myopathy, and vasculitis.[3] Our patient's presentation represents only the second case reported of Churg-Strauss syndrome and HIV infection. Peripheral eosinophilia is a common finding in patients infected with HIV and may be due to the primary infection or to disorders unrelated to HIV.[3]

HIV glycoprotein 120 binds to CD4 receptors on eosinophils and lymphocytes, causing infection. CD4 lymphocytes are intimately involved with the function and development of eosinophils in the bone marrow to peripheral migration. HIV progression is postulated to cause a shift in cytokine pattern form TH1 to TH2, leading to increased levels of interleukin-4 and -5, which subsequently increase IgE and eosinophil levels, respectively.[3,7] These are the postulated mechanisms by which primary HIV infection is believed to cause peripheral hypereosinophilia. In our patient with preexisting asthma and allergic rhinitis, we believe that the superimposed HIV infection triggered a hypereosinophilic response that unmasked the development of Churg-Strauss syndrome. This is consistent with theories suggesting a role for th2 cytokines in the pathogenesis of Churg-Strauss syndrome. Antigen stimuli and a th2-mediated pathogenesis seem to underlie the syndrome; interleukin 5 and tumor necrosis factor-α levels are elevated in serum and bronchoalveolar lavage fluid of patients with CSS.[8] Furthermore, a cytokine analysis of patients with CSS suggests evidence for a type 2 cytokine production pattern that predominates in CSS compared with patients with Wegner granulomatosis and healthy control subjects.

Conclusion

This case demonstrates the diagnostic complexities in evaluating hypereosinophilia. In a prior case report, a patient with known advance HIV was subsequently diagnosed with Churg-Strauss syndrome. We postulate that acute HIV infection triggered a hypereosinophilic response in our patient with preexisting asthma and allergic rhinitis. Systemic and local corticosteroids for her atopic disease may have delayed the onset of Churg-Strauss syndrome. The reverse phenomenon has been noted in case reports of leukotriene inhibitors associated with Churg-Strauss syndrome. These authors postulate that Churg-Strauss syndrome developed in these patients as a result of disinhibition of hypereosinophilia, arising from cessation of systemic and pulmonary corticosteroids and initiation of leukotriene inhibitors.[10] In conclusion, this case demonstrates that Churg-Strauss syndrome may be the initial manifestation of HIV disease. Recognizing the possible associations between varying rheumatologic syndromes and HIV is important because corticosteroid and cytotoxic therapy may potentially worsen HIV infection.

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