

A 62-Year-Old Woman With Persistent Severe Asthma, Skin Rash, and Eosinophilia

Abdel Rahman Lataifeh, MD; Steven Deas, MD; Sara C. Shalin, MD, PhD; and Khaled R. Khasawneh, MD, FCCP

A 62-year-old white woman was admitted with shortness of breath, wheezing, and cough. While in the hospital a generalized pruritic skin rash developed on her trunk and upper and lower extremities. She did not have any fevers, chills, or night sweats. The patient was known to have chronic, difficult-to-control asthma despite being compliant with a treatment regimen consisting of inhaled albuterol, high-dose inhaled steroids, salmeterol, and montelukast. Her medical history was significant for hypertension and gout. She had no family history of asthma. The patient was a life-long nonsmoker and did not drink alcohol. During this hospitalization, she was started on prednisone 40 mg/d po in addition to her home medications.

CHEST 2014; 146(2):e52-e55

Physical Examination

On examination, the patient was a well-developed white woman with conversational dyspnea. Vital signs were as follows: temperature, 37°C; heart rate, 96 beats/min; BP, 146/78 mm Hg; respiratory rate, 26 breaths/min; and oxygen saturation by pulse oximetry, 94% while on 5 L/min oxygen.

Significant physical examination findings were cushingoid facies, bilateral decreased breath sounds with diffuse wheezing, and regular heart sounds with no murmurs. The patient had a generalized maculopapular, non-blanching skin rash on her arms, back, and lower limbs with no associated edema or warmth.

Diagnostic Studies

Pertinent findings were a WBC count of 12,000/ μ L (52% eosinophils); hemoglobin level, 9.6 g/dL; and platelet count, 237,000/ μ L. Her erythrocyte sedimentation rate was 32 mm/h and IgE level normal. Serum anti-*Aspergillus* antibody, antinuclear antibodies, and antineutrophil cytoplasmic antibody (ANCA) findings were all negative. Renal function and liver enzymes were within normal limits. Chest CT scan did not reveal any significant parenchymal lung disease. Pulmonary function tests revealed severe obstruction and an FEV₁ of 41% predicted. Skin biopsy was performed (Fig 1).

Manuscript received February 10, 2014; revision accepted February 18, 2014.

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Lataifeh, Deas, and Khasawneh) and Department of Pathology (Dr Shalin), University of Arkansas for Medical Sciences, Little Rock, AR.

CORRESPONDENCE TO: Khaled R. Khasawneh, MD, FCCP, Division of Pulmonary and Critical Care Medicine, University of Arkansas

for Medical Sciences, 4301 W Markham St, Slot 555, Little Rock, AR 72205; e-mail: krkhasawneh@uams.edu

© 2014 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-0347

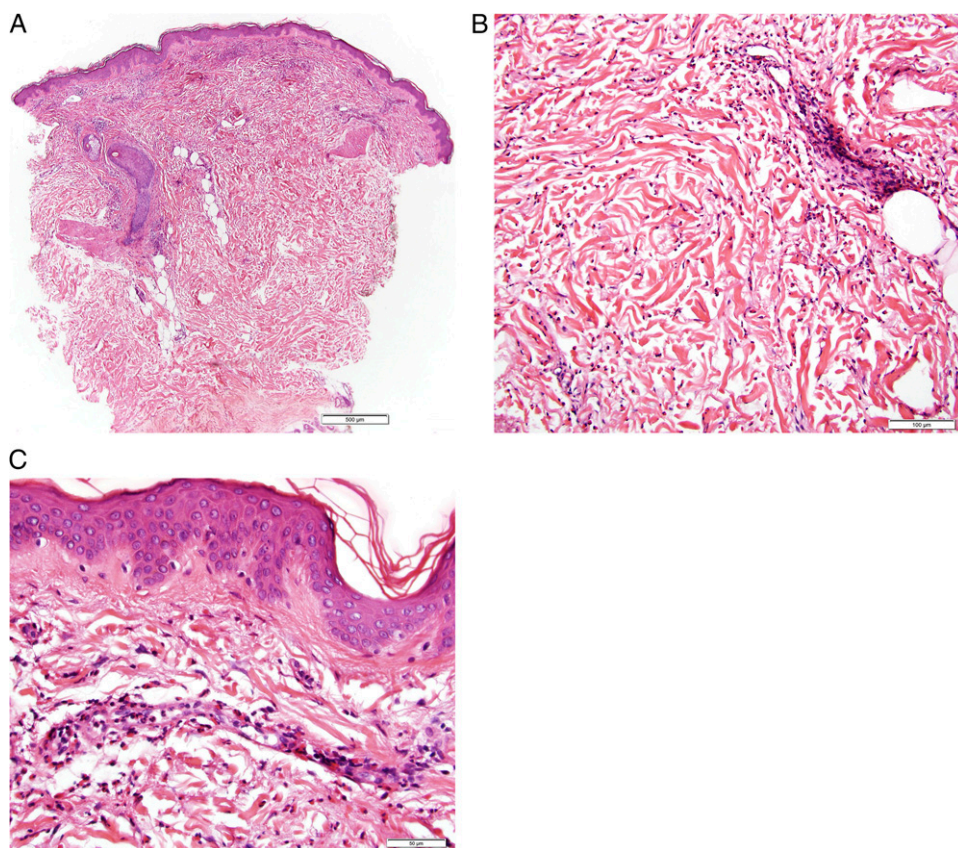


Figure 1 – A, Low-power magnification shows a punch biopsy sample of skin with a perivascular and interstitial inflammatory infiltrate. Extravascular granulomas are not present. B, An interstitial and perivascular infiltrate almost exclusively comprises eosinophils, recognizable by their granular eosinophilic cytoplasm. C, On high-power magnification of the perivascular eosinophils, endothelial cells appear swollen and slightly damaged by the eosinophils traversing the vascular walls; however, well-developed vasculitis with fibrinoid necrosis is not identified. All stains are hematoxylin and eosin.

What is the diagnosis?

Diagnosis: Eosinophilic (prevasculitis) phase of Churg-Strauss syndrome, also known as allergic granulomatous angiitis

Discussion

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a rare ANCA-associated vasculitis characterized by eosinophil-rich and granulomatous necrotizing vasculitis of the small- to medium-sized arteries. Affected patients usually have a prolonged history of allergic syndromes, including rhinosinusitis, nasal polyposis, and persistent, difficult-to-control asthma.

The disease usually progresses through three sequential phases, which are sometimes difficult to distinguish separately. The first phase is a prodromal period with many years of allergic rhinitis, nasal polyposis, and asthma. The second, eosinophilic phase is marked with blood eosinophilia and eosinophilic infiltration of different organs, including the lung (eosinophilic pneumonitis), skin (eosinophilic cellulitis), heart (infiltrative cardiomyopathy), and GI tract (eosinophilic enteritis). The third phase is the most disabling and life-threatening with necrotizing, granulomatous, multisystem, small- to medium-sized vasculitis. The disease manifestations usually start in adolescence and progress over 10 to 20 years, with vasculitis usually seen in the third and fourth decades.

The pathophysiology of EGPA is not well understood, but its association with ANCA, rheumatoid factor, hypergammaglobulinemia, and elevated IgE levels suggests autoimmunity. Multiple previous case reports suggested an association between treatment with leukotriene receptor antagonists and the development of EGPA. Some authors suggested that starting patients on leukotriene receptor antagonists leads to withdrawal of systemic steroids, which results in exacerbation of the disease manifestations.

ANCAs are present in about 40% of patients with EGPA, with a perinuclear ANCA pattern (antimyeloperoxidase) found in most patients with ANCA-positive findings. ANCA positivity has been shown in many studies to be associated with more glomerulonephritis, alveolar capillaritis, and neuropathy. Patients with ANCA-negative findings have been shown to have more cardiac involvement. The importance of this association between ANCAs and EGPA was outlined at the 2012 Revised

International Chapel Hill Consensus Conference, where EGPA was classified in a new category of ANCA-associated vasculitis.

The diagnosis of EGPA can be made with a sensitivity of 85% and specificity of 99.7% if the patient has four or more of the following American College of Rheumatology criteria: (1) asthma, (2) eosinophilia > 10%, (3) neuropathy, (4) pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) a biopsy specimen showing eosinophils accumulating in extravascular areas. Despite using such criteria, diagnosing EGPA continues to be a challenge and needs a high index of suspicion for multiple reasons, including (1) prolonged course of disease progression over 10 to 20 years; (2) the transient nature of some features, like eosinophilia and pulmonary infiltrates; and (3) concomitant use of steroid therapy for asthma that may mask the manifestations of vasculitis.

Therapy with corticosteroids alone or in combination with cyclophosphamide in severe cases is the main treatment for EGPA. Patients usually are started on prednisone 0.5 to 1.5 mg/kg/d, depending on the disease severity. The majority of patients achieve remission with corticosteroids, and most require a prolonged taper of corticosteroids. Patients with very severe disease and multiorgan involvement require combination therapy with high-dose IV corticosteroids and cyclophosphamide. Patients should receive *Pneumocystis* prophylaxis while on corticosteroid therapy. In these patients, special attention must be paid to osteoporosis prevention.

Clinical Course

After establishing the diagnosis, montelukast was discontinued, and the patient was started on IV methylprednisolone and antihistamines. A 12-lead ECG and echocardiogram were not indicative of cardiac involvement.

The patient's respiratory symptoms and skin rash started to improve after 1 week. Eosinophilia resolved after 10 days, and she was discharged home on oral prednisone and sulfamethoxazole/trimethoprim for *Pneumocystis* prophylaxis. Two months after discharge, her respiratory symptoms improved significantly and her FEV₁ increased from 41% to 78%. The skin rash has almost disappeared. The patient is currently undergoing a slow taper of corticosteroid therapy with monitoring of eosinophil count and pulmonary function testing.

Clinical Pearls

1. *EGPA is a rare, ANCA-associated multisystem disease that usually progresses through three phases over many years: prodromal, eosinophilic, and active multisystem small-vessel vasculitis.*
2. *Diagnosis is based on a history of prolonged asthma, peripheral eosinophilia, pulmonary infiltrates, neuropathy, and a tissue biopsy specimen showing granulomatous necrotizing vasculitis and perivascular eosinophils.*
3. *When positive, perinuclear ANCA is not only helpful in the diagnosis of EGPA but also indicative of an increased likelihood of glomerulonephritis, alveolar capillaritis, and neuropathy.*
4. *Patients with ANCA-negative findings are at increased risk for cardiac involvement.*
5. *The primary therapy for EGPA is systemic glucocorticoids. Patients with advanced or refractory*

disease may need an additional immunosuppressive agent.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

Suggested Readings

Eustace JA, Nadasdy T, Choi M. Disease of the month. The Churg Strauss syndrome. *J Am Soc Nephrol*. 1999;10(9):2048-2055.

Katzenstein AL. Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung. A review. *Am J Clin Pathol*. 2000;114(5):767-772.

Pagnoux C, Guillevin L. Churg-Strauss syndrome: evidence for disease subtypes? *Curr Opin Rheumatol*. 2010;22(1):21-28.

Comarmond C, Pagnoux C, Khellaf M, et al; French Vasculitis Study Group. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum*. 2013;65(1):270-281.