

Atypical presentation of Churg-Strauss syndrome or an undescribed hypereosinophilic disease?

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Key words: Churg-Strauss syndrome, hypereosinophilic syndrome, asthma, allergy, thrombosis, Budd-Chiari syndrome

A previously healthy 69-year-old Italian man presented with ascites and abdominal pain. He had no history of allergy, drug use, smoking, or ethanol abuse. Two months earlier, he was hospitalized for bilateral deep vein thrombosis of the lower limbs with pulmonary embolism. Laboratory tests revealed 23.2×10^9 white blood cells/L, peripheral blood eosinophilia (PBE; 11.3×10^9 /L), and 75×10^9 platelets/L. He had no risk factors for congenital prothrombosis and no history of travel to geographic areas where helminthic infections are endemic. Cultures of stool for parasites and results from serum analyses for anti-*Schistosoma* and anti-*Toxoplasma* species antibodies or *Aspergillus* species or cryptococcal antigens were negative. The patient was treated with warfarin and discharged, and hematologic analyses were performed.

Four weeks later, he complained of abdominal enlargement and pain in the left hypochondrium. Physical examination revealed moderate-volume ascites, hepatomegaly without splenomegaly, and enlarged right axillary lymph nodes. Counts of blood cells revealed 8.2×10^9 eosinophils/L (49% white blood cells) and 12.1 g/dL hemoglobin; peripheral blood smear analysis produced normal results. Serum levels of creatinine and results from urinalysis and urinary sediment analysis were normal. Levels of alanine and aspartate aminotransferase, alkaline phosphatase, and γ -glutamyltransferase were 127 U/L (normal, 6-55 U/L), 98 U/L (normal, 5-41 U/L), 329 U/L (normal, 56-199 U/L), and 262 U/L (normal, 11-50 U/L), respectively, whereas serum levels of troponin and tryptase were normal. The erythrocyte sedimentation rate was 24 mm/h (normal, 0-15 mm/h); the level of C-reactive protein was 38 mg/L (normal, 0-6 mg/L), and that of lactate dehydrogenase was 262 U/L (normal, 125-220 U/L). Serum levels of vitamins, IgA, IgM, IgG, and IgG subclasses were normal, whereas the total level of IgE was 151 IU/mL (normal, 1-100 IU/mL). The international normalized ratio was 4.95 on oral anticoagulant therapy. Repeated cultures of blood, urine, and stool

specimens were negative for bacterial and parasitic infections, as well as serologic samples for toxocariasis, HIV, and hepatitis viruses B and C. Moreover, the patient denied having asthma or rhinitis; results from respiratory function and skin prick tests and assays for serum-specific IgE for the more common inhalant, food, and mite allergens were negative.

Serum levels of β_2 -microglobulin, IL-3, IL-4, IL-5, IL-13, and GM-CSF were normal, and aberrant T-cell subsets on peripheral blood lymphocyte immunophenotyping were absent. In particular, no CD3⁺CD4⁺, CD3⁺CD4⁺CD8⁺, or CD4⁺CD7⁺ T cells were identified.

Ten days after admission, the patient experienced acute pain and muscle soreness along the right median nerve distribution, electrophysiological studies revealed axonal motor mononeuropathy, and gabapentin was administered.

Autoimmune serologic studies were then performed. The patient did not have positive results for lupus anticoagulant, antinuclear autoantibodies, or antineutrophil cytoplasmic autoantibodies. Levels of IgG anticardiolipin and IgG anti- β_2 -glycoprotein I were 25.2 IgG phospholipid units (GPL) and 27.4 U/mL, respectively (normal, 0-20).

RADIOLOGIC FINDINGS

Transthoracic echocardiography showed no abnormalities. High-resolution computed tomography of the chest revealed a normal lung parenchyma (Fig 1, A) and pathologic right axillary lymphadenopathy (Fig 1, B, arrowhead). Abdominal sequences displayed features consistent with a Budd-Chiari syndrome accompanied by arterial thrombosis of the celiac trunk at its root (Fig 1, E, arrowhead), with revascularization of downstream arteries through collaterals. These findings were confirmed by means of abdominal magnetic resonance imaging, which showed multiple areas of splenic infarction (Fig 1, C and D, asterisks), thrombotic occlusion of the main right portal tributary vein (Fig 1, C, arrowhead), and low attenuation of the right lobe because of portal perfusion defects and obstruction on the right suprahepatic vein (Fig 1, D, arrowhead). High-resolution computed tomography of the head and neck identified a thickening of the right nasal mucosa and filling of ethmoidal cells with inflammatory material (Fig 1, F, arrowheads); these findings are consistent with an asymptomatic ongoing inflammatory process.

BONE MARROW PATHOLOGIC FINDINGS

On the basis of microscopic analysis, bone marrow samples were hypercellular with moderate eosinophilia (Fig 1, G) and no signs of overt dyshematopoiesis, indicating a myeloproliferative disorder. No clonal markers were detected by means of cytogenetic or karyotype analyses or by means of fluorescence *in situ* hybridization with probes specific for the flanking regions of

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication February 4, 2011; revised July 10, 2011; accepted for publication July 14, 2011.

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J Allergy Clin Immunol 2011;■■■:■■■-■■■.
0091-6749/\$36.00

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doi:10.1016/j.jaci.2011.07.052

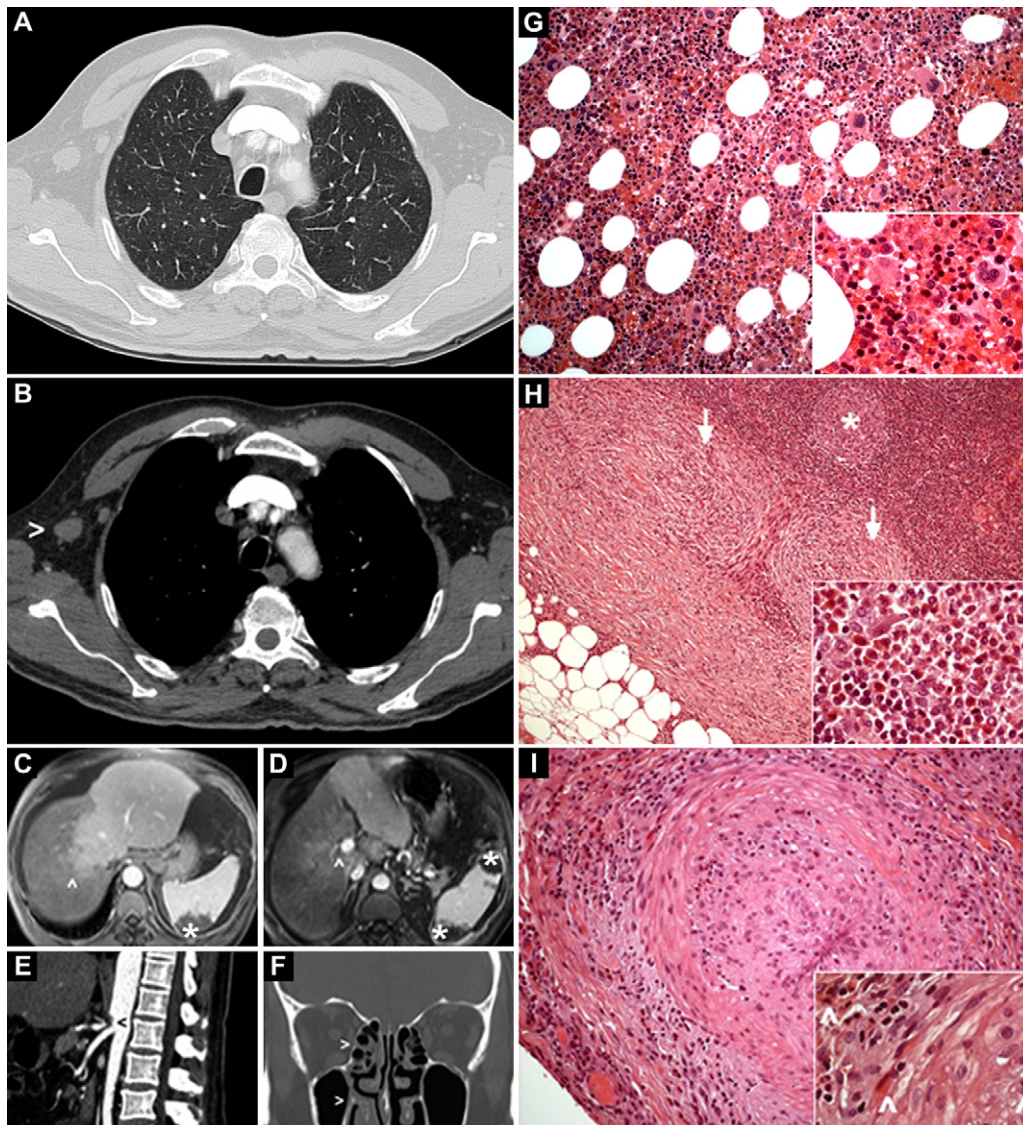


FIG 1. Axial thoracic high-resolution computed tomography (HRCT) with iodinate contrast medium. **A** and **B**, Lung (**Fig 1, A**) and soft-tissue (**Fig 1, B**) windowing. **C** and **D**, Gadolinium-enhanced, T1, fat-saturated abdominal magnetic resonance imaging. **E**, Sagittal abdominal HRCT with iodinate contrast medium. **F**, Coronal HRCT of the paranasal sinuses with bone windowing. **G-I**, Hematoxylin and eosin-stained biopsy samples of bone marrow (**Fig 1, G**; magnification $\times 200$, insert $\times 400$) and lymph nodes (**Fig 1, H** and **I**; magnification $\times 100$ and $\times 200$, inserts $\times 400$).

platelet-derived growth factor receptor A (*PDGFRA*), *PDGFRB*, and fibroblast growth factor receptor 1 (*FGFR1*). Chromosomal and RT-PCR analyses did not identify the fusions *FIP1L1-PDGFRA*, breakpoint cluster region (*BCR*)–*PDGFRA*, *ETV6-PDGFRA*, or *BCR-ABL*; mutations in Janus kinase 2 (*JAK2*), *PDGFRB*, or *FGFR1*; or chromosome rearrangements associated with myeloproliferative hypereosinophilic syndrome (M-HES).

Finally, we collected and analyzed biopsy samples from the enlarged right axillary lymph node.

DIFFERENTIAL DIAGNOSIS

Eosinophilia

Eosinophilia, defined as a blood eosinophil count of greater than $0.5 \times 10^9/L$, was the most prominent feature of this patient's

illness. Several common conditions are associated with hypereosinophilia.

Helminths elicit IL-5–mediated eosinophil expansion, particularly during parasitic migration through tissues; numbers of eosinophils in peripheral blood can be constant or fluctuate, depending on the developmental phase of the parasite. However, the patient did not report pulmonary or gastrointestinal symptoms or travel in geographic areas endemic for helminthic infections. Moreover, serologic evaluation and sequential examination of stool samples excluded the common parasitic infections.

The patient did not have rhinitis, symptoms of asthma, or cutaneous manifestations associated with atopic dermatitis, and therefore allergic diseases received weak consideration; furthermore, PBE of greater than $1.5 \times 10^9/L$ is rarely seen in these conditions, and normal respiratory function, skin prick test responses,

and serum levels of allergen-specific IgE excluded an allergic reaction.

Drug-induced PBE can develop without overt clinical manifestations, but an adverse drug reaction was excluded because the patient was not receiving medical therapy when his symptoms developed.

In addition to these common causes of PBE, extended examination eliminated paraneoplastic eosinophilia (particularly that associated with adenocarcinoma), Hodgkin disease, peripheral T-cell lymphoma, and mastocytosis. Moreover, the patient did not experience weight loss or profuse sweating, and his serum levels of β_2 -microglobulin and tryptase were normal.

Despite a thorough evaluation, the PBE of this patient was unexplained, prompting the exclusion of a hypereosinophilic syndrome (HES).

HESs

As proposed by Simon et al,¹ HESs include uncommon conditions of persistent eosinophilia with potentially lethal multisystemic involvement; target organ damage is not required for diagnosis. The variants M-HES and lymphocytic HES (L-HES) must be excluded. M-HES is characterized by clonal expansion of eosinophils caused by molecularly defined rearrangements. However, the patient did not have the typical features of this variant, which include splenomegaly, anemia, circulating myeloid precursors, and increased levels of vitamin B12 and tryptase. The patient's hepatomegaly might have resulted from Budd-Chiari syndrome, and the mild thrombocytopenia with normal bone marrow megakaryocyte maturation observed might have resulted from the consequent functional hypersplenism. Bone marrow biopsy analysis ruled out myeloproliferative disorders because there were no detectable markers of clonal hypereosinophilia.

L-HES is characterized by expansion of polyclonal eosinophils in response to overproduction of IL-5 by T cells with abnormal phenotypes, which are prone to malignant transformation. However, this patient had no evidence of T-cell defects, increase in serum levels of IgE, or the typical predominant cutaneous manifestations of L-HES. Taken together, these findings indicate that the patient did not have M-HES or L-HES.

Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is a rare, systemic, small-vessel, necrotizing vasculitis recently integrated into the HES classification. The American College of Rheumatology requires 4 of 6 of the following criteria for its diagnosis: greater than 10% eosinophils on differential blood leukocyte counts, asthma, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, abnormalities of the paranasal sinuses, and evidence of extravascular eosinophils in pathologic analysis.² The disease usually progresses through 3 phases. It begins with a prodromic phase that has asthma and allergic manifestations followed by eosinophilic infiltration of tissues and then, years after the onset of asthma, a systemic phase, with necrotizing vasculitis.³ Therefore a history of asthma is an important diagnostic factor for the syndrome, along with pulmonary involvement. However, even though asthma has been reported to develop even years after the onset of vasculitis in patients with CSS, all reports of adult patients included pulmonary involvement.⁴ Therefore in the absence of these 2 features, CSS resembles M-HES or L-HES,

particularly during the second prevasculitic phase of the disease.⁵ Because this patient had no hematologic abnormalities or mutations associated with hematologic malignancy, an atypical form of CSS was considered, although overlap with some of these entities could not be excluded.

The inflammation of the paranasal sinuses observed on computed tomographic imaging caused controversy. Although it did not cause symptoms and was not investigated by means of biopsy specimen analysis, sinus inflammation should not be ignored in this particular context; the American College of Rheumatology classification criteria for CSS considers paranasal sinus abnormalities to be upper respiratory tract manifestations of the disorder until proved otherwise. However, further analysis of the enlarged axillary lymph nodes is required to exclude malignant lymphoproliferative disorders.

Lymph node pathologic findings

Examination of the right axillary lymph node (Fig 1, *H* and *I*) revealed a thickened capsule accompanied by vessels with thickened walls (Fig 1, *H* and *I*, arrows), reactive germinal centers (Fig 1, *H* and *I*, asterisk), and an expanded paracortex with a moderate degree of tissue eosinophilia (Fig 1, *H*, insert $\times 400$). Perivascular eosinophils were detected in perinodal, thrombotic, medium-sized vessels and permeating blood vessel walls that did not have fibrinoid necrosis deposition (Fig 1, *I*, insert $\times 400$, arrowheads). Moreover, plasma cells did not stain positive for IgG₄.

Eosinophilia in lymph nodes, based on histologic analysis, might indicate Hodgkin disease, peripheral T-cell lymphoma, leukemia, eosinophilic granuloma, mast cell disease, Kimura disease, IgG₄-related disease, or HES. CSS, in particular, is characterized by tissue eosinophilia and granulomatous reactions; patients with IgG₄-related disease usually also present with fibrosis that is associated with IgG₄-positive infiltrates of plasma cells, and neoplastic disorders rarely have features of eosinophilic vasculitis.⁶ The histologic findings of this patient were consistent with those of the perivascular, inflammatory, eosinophilic infiltrate of medium-sized vessels, and therefore even in the absence of granulomatous angiitis, an early, prevasculitic, eosinophil infiltration phase of CSS can be considered the most suggestive diagnosis.

Another intriguing aspect of this case was the ongoing thrombophilic diathesis despite adequate oral anticoagulant therapy. In the absence of underlying prothrombotic conditions, many thrombotic events can be attributed to PBE.⁷ Ames et al⁸ proposed that eosinophils are most likely to be thrombogenic when they migrate to tissues, and therefore patients are more likely to experience thrombotic events during the infiltrative phase of CSS. Intriguingly, for unknown reasons, antineutrophil cytoplasmic autoantibody-negative patients with CSS are at greater risk for thrombosis than antineutrophil cytoplasmic autoantibody-positive patients.⁸

CLINICAL MANAGEMENT

An operative diagnosis of atypical CSS was made based on the American College of Rheumatology classification criteria. The patient was discharged with a prescription for 50 mg/d prednisone, 20 mg/wk methotrexate, and oral warfarin. One month later, numbers of eosinophils in peripheral blood were

within the normal range. Two months later, the patient reported clinical improvement and had normal number of platelets, liver function test results, erythrocyte sedimentation rate, and levels of C-reactive protein, IgG anticardiolipin, and IgG anti- β_2 -glycoprotein I, and therefore the dosage of prednisone was reduced. Fifteen months later, the patient remains in remission.

Given the patient's complete response to treatment, it is not clear whether this was an atypical case of rare vasculitis or a case of an undescribed hypereosinophilic disease. Patients with PBE usually respond to prednisone and methotrexate; however, neoplastic disorders, particularly lymphomas, have usually progressed by the 15-month follow-up examination. Alternatively, CSS can present with pleiotropic manifestations, particularly during the prevasculitic phase of the disease.

We performed extensive analyses to exclude common and uncommon causes of PBE, according to guidelines.⁹ The patient's prompt response to treatment and persistent remission support the diagnosis of a benign condition rather than an infectious or neoplastic disease. Nevertheless, a definitive diagnosis was a challenge, and we continue to monitor the patient for a malignant disorder.

SUMMARY

In patients with PBE, it is important to promptly distinguish between a primary clonal expansion of eosinophil progenitors caused by genetic mutations (intrinsic eosinophilic disorders) and a response to overexpression of hematopoietins (extrinsic eosinophilic disorders).

Once treatable conditions, such as parasitic infections and allergic or adverse drug reactions, are excluded, patients with hypereosinophilic disorders and additional features should be treated quickly to prevent organ damage from eosinophilic infiltration.

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