

Hypereosinophilic Disorders

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a

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List of Design Committee Members: Princess U. Ogbogu, MD, and Amy D. Klion, MD

Activity Objectives

1. To recognize the clinical presentation of myeloproliferative HES.
2. To describe the approach to treatment of *PDGFRA*-associated myeloproliferative disease.

Recognition of Commercial Support: This CME has not received external commercial support.

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The Difficult Cases Feature is based on the *Difficult Cases Course* presented at the AAAAI Annual Meeting and coordinated by the AAAAI New Allergist-Immunologist Assembly (NAIA). View the entire presentation and obtain CME by visiting the JACI: In Practice homepage www.jaci-inpractice.org.

Key words: *Eosinophil; Hypereosinophilic syndrome; FIP1L1-PDGFR*

A 36-year-old man presented to his local emergency department with complaints of acute onset vertigo and chest discomfort. He underwent evaluation that was remarkable for a normal electrocardiogram (EKG), negative serum troponin levels, and abnormal complete blood count, which revealed an absolute eosinophil count (AEC) of 12,400 (normal <500 cells/μL). He

was admitted to the hospital for evaluation of presyncope and hypereosinophilia. His hospital evaluation revealed a normal repeat EKG, echocardiogram with normal ejection fraction (65%), and mild diastolic dysfunction. A cardiac stress test was normal. Bone marrow biopsy revealed hypercellularity with marked eosinophilia, eosinophil dysplasia, and no increase in blasts. No cytogenetic abnormalities were detected, and evaluation for mutations in *PDGFRA*, *PDGFRB*, and *JAK2* were negative. Stool examinations were negative for ova and parasites. Repeat laboratory evaluation confirmed an elevated AEC of 12,000 cells/μL and did not identify any other significant abnormalities. He was discharged home with no specific therapy. He presented 3 months later with worsening chest discomfort and pressure. His AEC remained elevated at 11,380 cells/μL. His EKG now revealed T-wave inversions in the anterior leads. CT scans of the chest, abdomen, and pelvis were obtained and were remarkable for interstitial lung changes, bilateral lung nodules, mediastinal lymphadenopathy, and splenomegaly. Pulmonary function tests showed a restrictive pattern with diffusion defect, and transbronchial biopsies showed patchy interstitial fibrosis without evidence of vasculitis. Cytology was negative for malignancy. Further laboratory evaluation revealed unremarkable peripheral blood lymphocyte immunophenotyping, polyclonal

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T-cell receptor rearrangement, elevated serum vitamin B12 level 1725 (normal 180-914 ng/L), and elevated serum tryptase level 17.1 (normal <11.5 ng/mL). He was treated with high-dose steroids (1 mg/kg Solu-Medrol) and referred for further evaluation. On repeat evaluation, the AEC was 8640/ μ L. He was started empirically on imatinib 400 mg daily and a prednisone taper was initiated. Within 1 week of starting imatinib, his AEC normalized. Repeat testing for *FIP1L1-PDGFR*A returned positive. After 6 months, his imatinib dose was tapered to 100 mg daily, and the patient has remained stable since that time.

DISCUSSION

This patient presented with marked eosinophilia and cardiac complaints. His clinical manifestations (cardiac involvement, pulmonary fibrosis, and splenomegaly) coupled with his laboratory findings (elevated serum vitamin B12 and tryptase levels and a hypercellular bone marrow with dysplastic eosinophils and spindle-shaped mast cells) were most consistent with myeloproliferative variant hypereosinophilic syndrome (MHES).¹ The most common cause of MHES is an interstitial deletion in chromosome 4 that leads to the imatinib-sensitive fusion tyrosine kinase, *FIP1L1-PDGFR*A.² Although prednisone is the first-line therapy for most forms of HES, *PDGR*F A-positive disease is typically steroid refractory and should be treated with imatinib.¹⁻⁴

Because MHES with cardiac involvement is life threatening, imatinib therapy should be initiated irrespective of the results of testing for *FIP1L1-PDGFR*A if this diagnosis is strongly suspected. Concomitant steroids should be given in the setting of an elevated serum troponin or other evidence of eosinophilic myocarditis to prevent myocardial necrosis, a rare complication of imatinib therapy in patients with HES.⁵

This case and power point slide presentation can be found in this article's Online Repository at www.jaci-inpractice.org.

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