Consultation for Elevated Blood Eosinophils: Clinical Presentations, High Value Diagnostic Tests, and Treatment Options

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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.

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List of Design Committee Members: Paneez Khoury, MD, MHSc, and Bruce S. Bochner, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To initiate a rational and cost-effective workup for eosinophilia based on clinical and laboratory features at presentation.

2. To formulate a differential diagnosis and initiate appropriate treatments for patients with specific causes of eosinophilia.

3. To understand how to monitor and assess treatment responses in patients with eosinophilia.

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The workup of a patient found to have eosinophilia should follow a thorough path with a detailed history and physical examination aimed at eliciting eosinophilic organ involvement, followed by histological confirmation whenever possible. The differential diagnosis of hypereosinophilia is extensive, but a rational approach beyond the history and physical examination including serologic, blood, and bone marrow cell analyses, genetic testing, and radiologic imaging can distinguish many of the causes. Often input from specialists (eg, hematology, dermatology, pulmonary, gastroenterology, and neurology) can

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Abbreviations used
AEC- Absolute eosinophil count
CBC- Complete blood cell count
CT- Computed tomography
EGPA- Eosinophilic granulomatosis with polyangiitis
FDA- Food and Drug Administration
HES- Hypereosinophilic syndrome
IV- Intravenously
LHES- Lymphoid hypereosinophilic syndrome
MRI- Magnetic resonance imaging

help narrow down the possibilities and eventually result in a specific diagnosis. An accurate diagnosis is key to choosing the optimal treatment for a particular condition, and this is certainly true for eosinophilic disorders. Myeloid neoplasms that present with eosinophilia, for example, may respond to medicines that the allergist may be less accustomed to using, such as immunosuppressive agents and kinase inhibitors. Similarly, newly approved biologics that target IL-5 and eosinophils may provide new options for management. What follows is a case-based approach that helps to underscore key features of diagnosis, management, and follow-up when faced with a patient with a potential eosinophil-related disorder. **(J Allergy Clin Immunol Pract 2018;6:1446-53)**

Key words: *Eosinophilia; Hypereosinophilic syndromes; Diagnosis; Testing; Treatment*

INITIAL CASE HISTORY

A 42-year-old woman presents for evaluation of an itchy rash and eosinophilia. She was healthy until her mid 30s when she developed arthralgias in her hands and she was diagnosed with sero-negative rheumatoid arthritis. She was treated with nonsteroidal anti-inflammatory drugs with symptomatic improvement. At age 38 years, she developed xerosis and a rash described in previous medical notes as fine, pruritic, erythematous papules involving the extremities and torso without blistering. The rash is persistent, unresponsive to high-potency topical steroids and oral antihistamines, but is improved with oral glucocorticoids. Occasionally, she gets hives on exposure to the cold, and she had a few episodes of localized angioedema. Four years ago, around the time of the development of her skin rash, she was found to have a persistently elevated absolute eosinophil count (AEC) in the 4,000 to 9,000 cells/μL range that was partially responsive to high doses of prednisone. Prior eosinophil counts are unavailable, and other blood cell count parameters have been normal. On review of systems she notes profound fatigue and frequent generalized aches and pains.

She was previously evaluated by another allergist, a rheumatologist, a dermatologist, and a hematologist before seeing you. Diagnoses that have been entertained include severe atopic dermatitis, chronic spontaneous urticaria with angioedema, cold urticaria, and hypereosinophilic syndrome (HES). She was first treated with high doses of antihistamines, then with omalizumab with minimal improvement, so these were stopped. She is currently being treated with short courses of prednisone, but skin symptoms promptly return after tapering and she is unhappy about the glucocorticoid side effects including significant weight gain. She denies foreign travel except for a cruise to Mexico and the Caribbean. Her current medications include prednisone 10 mg daily and ibuprofen 600 mg every 6 hours as needed for aches and pains.

On physical examination she has normal vital signs. Head, eyes, ears, nose, and throat, and cardiac, pulmonary, abdominal, and musculoskeletal examination results are normal. Detailed lymph node examination reveals 1-cm mobile, nontender inguinal lymph nodes bilaterally. Skin examination is significant for generalized xerosis and 2 to 5 mm erythematous papules. A faint erythematous rash is noted at the nape of her neck. Physical urticarial testing result is negative. She shows you cellphone pictures demonstrating similar, albeit more intense, diffuse erythematous papules.

Review of outside testing and labs show a recent complete blood cell count (CBC) with differential demonstrating white blood cells 15,200 cells/μL, hemoglobin 13.1 g/dL, platelets 198,000/μL, and a differential of 28% neutrophils, 16% lymphocytes, 3% monocytes, 52% eosinophils (AEC = 7,850/μL), and 1% basophils. A random serum tryptase level was 11 ng/mL, vitamin B_{12} level was 1,126 pg/mL, and serum total IgE level was 1,320 kU/L. There was no evidence of transaminitis, and glomerular filtration rate was within normal limits. Workup 4 years ago when her AEC was 5,200/μL included a skin biopsy demonstrating superficial to deep dermal perivascular lymphocytic infiltrate with scattered eosinophils, and a computed tomography (CT) scan of the chest/abdomen/pelvis was normal. A bone marrow biopsy and aspirate showed trilineage hematopoiesis with an increase in morphologically normal eosinophils, no increase in mast cell aggregates, and only few scattered spindle-shaped mast cells by tryptase immunohistochemical staining. Testing for both the *JAK2 V617F* and the *FIP1L1-PDGFRA* mutation by fluorescence *in situ* hybridization (FISH) was negative and T-cell receptor gene rearrangement by RT-PCR analysis revealed an oligoclonal pattern.

INITIAL DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hypereosinophilia is quite broad. Important historical details that are gathered in the initial workup include determination of the onset, duration, and magnitude of the eosinophilia as well as associated symptoms, taking into consideration the types and doses of medications taken when the counts were obtained. Although symptoms can occur with even mild eosinophilia in a patient with HES, for the purposes of the initial workup, characterization of marked eosinophilia (>5000/μL) as well as the duration is important because it might alter the decision to initiate treatment more urgently.[1] Other important historical factors include consideration of exposures such as recent infections or medications. An appropriate exposure history should include determination of recent or remote travel to, or history of residence in, areas with parasitic infestations as well as other exposure history that might coincide with eosinophilia. Depending on the acuity and duration of eosinophilia, as well as types of organs involved, certain parasitic infections are more commonly the cause of eosinophilia when presenting in North America. For example, *coccidiodes* species, *echinococcus*, and *fasciola* species typically present with acute eosinophilia and may be seen in clinical practice in North America. In contrast, common causes of chronic eosinophilia include *Strongyloides stercoralis, clonorchis, ospisthorchis* species,