Eosinophilia Associated with Disorders of Immune Deficiency or Immune Dysregulation

Kelli W. Williams, MD, MPH[a], Joshua D. Milner, MD[b], Alexandra F. Freeman, MD[c,*]

KEYWORDS

• Eosinophilia • Immune • Deficiency • Dysregulation

KEY POINTS

- Eosinophilia can be seen in many disorders of immune deficiency or immune dysregulation; however, there are a few key syndromes that have eosinophilia as a consistent clinical feature.
- In these monogenic diseases of immune deficiency or immune dysregulation, peripheral and tissue eosinophil counts are variable and do not correlate with severity of disease.
- A marginal number of patients with eosinophilia have an underlying immune defect, but given the profound impact these diseases can have on morbidity and mortality, all cases of eosinophilia warrant a thorough clinical evaluation.

INTRODUCTION

Although increased peripheral eosinophilia can be found in patients with parasitic infection, significant atopic disease, drug hypersensitivity reactions, connective tissue disorders, malignancy, and rare hypereosinophilic syndromes, monogenic disorders of immune deficiency or dysregulation should be considered, particularly in the pediatric age group. Some of these syndromes include clinical manifestations of atopy,

Disclosures: the authors have nothing to disclose.
[a] Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 33 North Drive, Building 33, Room 2W10A, Bethesda, MD 20892, USA; [b] Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Building 10/CRC, Room 5-3950, Bethesda, MD 20892, USA; [c] Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Building 10/CRC, Room 12C103, Bethesda, MD 20892, USA
* Corresponding author.
E-mail address: freemaal@mail.nih.gov

Immunol Allergy Clin N Am 35 (2015) 523–544
http://dx.doi.org/10.1016/j.iac.2015.05.004 **immunology.theclinics.com**
0889-8561/15/$ – see front matter Published by Elsevier Inc.

such as atopic dermatitis or food allergy, which may contribute to the eosinophilia; however, the mechanism driving the eosinophilia is not well understood. Many of these monogenic diseases are characterized by increased production of Th2 cytokines, such as interleukin 5 (IL-5), which is an essential promoter of eosinophil differentiation, maturation, and survival.[1]

In this article, several disorders of immune deficiency or dysregulation are reviewed that have documented eosinophilia as part of the syndrome (Fig. 1). The clinical features, common infections, laboratory findings, diagnostic methods, and genetic basis of disease of each syndrome are discussed.

SYNDROMIC CAUSES OF INCREASED IGE LEVELS AND EOSINOPHILIA

Autosomal Dominant Hyper IgE Syndrome

Job's syndrome was first described in 1966 with 2 patients who had recurrent staphylococcal abscesses, similar to the boils borne by the prophet Job in the Bible.[2] This clinical syndrome, which was first characterized as a triad of recurrent staphylococcal abscesses, pulmonary infections, and an eczematous dermatitis, was later found to be associated with increased serum IgE levels, leading to the name autosomal dominant hyper IgE syndrome (AD-HIES).[3]

Clinical features, infections, and management

AD-HIES typically presents within the first few days of life as neonatal acne or erythema toxicum neonatorum secondary to the pustular rash that often encompasses the face, scalp, and upper body.[4,5] Histologically, the skin infiltration is predominantly eosinophils.[6] The rash usually evolves to resemble an eczematous dermatitis, which is papular, pruritic, lichenified, and typically driven by *Staphylococcus aureus* colonization and superinfection.[7]

Patients with AD-HIES classically have recurrent, cold *S aureus* abscesses, which have frank pus when excised despite their lack of dolor, rubor, and calor.[2] Recurrent sinopulmonary infections generally start in the first several years of life, with *S. aureus* being the most common pathogen implicated in the pneumonias. *Streptococcus pneumoniae* and *Haemophilus influenzae* also occur frequently, and the first presentation of pneumonia in infancy may be caused by *Pneumocystis jirovecii*.[8,9] As with the cold abscesses, patients with AD-HIES with pneumonia lack systemic signs of inflammation, including fever, frequently delaying diagnosis leading to parenchymal lung damage (Fig. 2). Pneumatoceles and bronchiectasis increase the patients' susceptibility to difficult to treat microbes, like *Aspergillus*, *Scedosporium*, *Pseudomonas*, and nontuberculous mycobacteria, which contribute significantly to their morbidity and mortality.[9–11]

Fungal susceptibility is apparent, with more than 80% of patients having chronic mucocutaneous candidiasis (Fig. 3).[12] Unlike patients with dedicator of cytokinesis 8 (DOCK8) deficiency, those with AD-HIES do not commonly have severe viral infections (Table 1).[13,14]

Despite the increased levels of serum IgE characteristic of these patients, allergy and asthma are not typically severe or difficult to manage in AD-HIES. Siegel and colleagues[15] reported a diminished allergic phenotype in patients with AD-HIES compared with other patients with a comparably increased IgE level and atopic dermatitis, although allergies are more frequent than those with normal IgE levels.

AD-HIES is a multisystem disease with many nonimmunologic abnormalities. A characteristic facial appearance usually emerges during adolescence, with porous skin, a prominent forehead, deep-set eyes, and a bulbous and broad nose (see Fig. 3). Most patients fail to shed their primary teeth, requiring medical removal to