Primary immunodeficiency update

Part I. Syndromes associated with eczematous dermatitis

Dominique C. Pichard, MD,[a] Alexandra F. Freeman, MD,[b] and Edward W. Cowen, MD, MHSc[a]
Bethesda, Maryland

Learning Objectives
After completing this learning activity participants should be able to differentiate the new primary immunodeficiency syndromes based on their cutaneous and systemic infection profile.

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In the past decade, the availability of powerful molecular techniques has accelerated the pace of discovery of several new primary immunodeficiencies (PIDs) and revealed the biologic basis of other established PIDs. These genetic advances, in turn, have facilitated more precise phenotyping of associated skin and systemic manifestations and provide a unique opportunity to better understand the complex human immunologic response. These continuing medical education articles will provide an update of recent advances in PIDs that may be encountered by dermatologists through their association with eczematous dermatitis, infectious, and non-infectious cutaneous manifestations. Part I will discuss new primary immunodeficiencies that have an eczematous dermatitis. Part II will focus on primary immunodeficiencies that greatly increase susceptibility to fungal infection and the noninfectious presentations of PIDs. (J Am Acad Dermatol 2015;73:355-64.)

Eczematous dermatitis is a common finding among several primary immunodeficiencies (PIDs) and may be the presenting clinical manifestation to the dermatologist. However, atopic dermatitis is also common in the general population, and the recognition of additional features of immunodeficiency can facilitate an earlier diagnosis. In a series of 75 patients with severe dermatitis with no known underlying primary immunodeficiency, Aghamohammadi et al[1] identified 5 patients with hyperimmunoglobulin E (IgE) syndrome (HIES) and 1 patient with Wiskott–Aldrich syndrome (WAS). The mean age at diagnosis was 5 years. This underscores the importance of eliciting a history of recurrent infections or family history suggestive of immunodeficiency in patients with severe atopic dermatitis. In this continuing medical education article, we provide an update on primary immunodeficiencies associated with dermatitis.

From the National Institutes of Health, National Cancer Institute[a] and the National Institute of Allergy and Infectious Disease,[b] Bethesda.
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Correspondence to: Edward W. Cowen, MD, MHSc, Senior Clinician and Head Dermatology Consultation Service, Dermatology Branch, National Cancer Institutes, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892. E-mail: cowene@mail.nih.gov.
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HYPERIMMUNOGLOBULIN E SYNDROMES

The first HIES to be described was Job's syndrome. This multisystem PID was initially described in 1966 as a disorder of recurrent cold abscesses, eczematous dermatitis, and lung disease.[2,3] Autosomal dominant HIES (AD-HIES) shares several clinical features with dedicator of cytokinesis 8 (DOCK8) deficiency, also known as autosomal recessive (AR)-HIES, but also has several key differences that result in distinct phenotypes and prognoses. In addition, there are 2 other rare autosomal recessive diseases associated with HIES. The first is caused by mutations in phosphoglucomutase-3 (*PGM3*). The second disorder, associated with a mutation in tyrosine kinase 2 (*Tyk2*), was reported in 1 patient with elevated IgE levels, eczema, and susceptibility to viral, fungal, and bacterial infections, including mycobacteria.[4,5] A subsequently reported patient with a mutation in *Tyk2* also had a susceptibility to mycobacterial infections, but did not have HIES, making the link between *Tyk2* mutation and AR-HIES uncertain.[6,7] Although elevated serum IgE levels and eczematous skin disease is a known presentation among the aforementioned HIES immunodeficiencies, WAS and Netherton syndrome may also present with similar skin and laboratory findings. Fig 1 reviews PIDs associated with eczematous dermatitis and the distinctive features of each syndrome. In this article, we review in greater detail AD-HIES and DOCK8 deficiency and discuss the recently described PGM3 deficiency.

AUTOSOMAL DOMINANT HYPERIMMUNOGLOBULIN E SYNDROME

Key points

- **Early onset dermatitis**
- **Cold abscesses and lung infections**
- **Multisystem disease with skeletal and connective tissue abnormalities**

In 2007, AD-HIES was found to be caused by dominant negative mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene, a key transcription factor that regulates a diverse number of biologic processes, including cell growth regulation and inflammation.[8,9]

A majority of patients with AD-HIES develop a neonatal papulopustular eruption (Fig 2, *A*)—often within the first week of life—that typically begins on the face and scalp, but can generalize. The rash often changes into an eczematous morphology within the first year.[10] Chronic dermatitis (Fig 2, *B*) in AD-HIES is strongly associated with *Staphylococcus aureus* skin colonization and infection. Control of *S aureus* through prophylactic systemic antimicrobials and topical antiseptics limits eczematous disease, but recurrences throughout life are common. Exacerbations of dermatitis are often caused by resistant *S aureus* strains or poor antimicrobial adherence. Dilute sodium hypochlorite baths, as used in atopic dermatitis, may be effective, but further clinical study in this population is needed.[11] The recommended therapy is a half-cup of household bleach in a full tub of water with exposure for 15 minutes for 3 days each week. For those who are not able or willing to use dilute bleach baths, chlorhexidine- or sodium hypochlorite–containing washes may be helpful.[12] In contrast to DOCK8 and patients with atopic dermatitis with high serum IgE levels, anaphylaxis is rare and food allergies are not a major concern in AD-HIES—although the latter is more prevalent in AD-HIES than in the general population.[13,14]

S aureus is also the major pathogen responsible for recurrent cold skin abscesses and sinopulmonary infections in patients with AD-HIES. Pulmonary infection results in abscess formation and pneumatocele development (Fig 3, *A*), which predisposes patients to infection with Pseudomonas, Aspergillus, and nontuberculous mycobacteria, and additional morbidity. Prophylactic antistaphylococcal antibiotics are recommended to decrease the risk of pneumonia and staphylococcal abscesses.[3] Chronic mucocutaneous candidiasis (CMC) occurs in 83% of patients, and many patients require long-term antifungal treatment.[3,10]

STAT3 is integral for the differentiation of T_H17 cells. AD-HIES patients lack T_H17 cells, thereby leading to impaired interleukin (IL)-17/IL-22 signaling and this high risk of CMC.[15] STAT3 is also important for the production of other proinflammatory cytokines and $CD8^+$ T cell memory maintenance, which likely contributes to the risk of reactivation of varicella zoster virus (VZV) and Epstein–Barr virus (EBV).[16] Memory B cell differentiation is also impaired, leading to variable specific antibody production; therefore, some patients require chronic immunoglobulin replacement in addition to prophylactic antimicrobials.[17]

As the name implies, elevated serum IgE levels are seen in all patients with AD-HIES, with peak IgE levels above 2000 IU/mL in 97% of patients and eosinophilia in 93%.[3] However, IgE levels may diminish over time and be within the normal range in adulthood. Craniofacial, musculoskeletal, and vascular abnormalities are also common and help