

Atopic dermatitis or hyper-IgE syndrome?

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ABSTRACT

A case of atopic dermatitis (AD), recurrent infections, and elevated immunoglobulin E (IgE) level is presented. Clinical characteristics, pathophysiology, diagnosis, and management in this patient are reviewed. Clinical pearls and pitfalls include the following: (1) deep-seeded *Staphylococcus aureus* infections occur rarely in AD and should raise the possibility of immunodeficiency syndromes such as hyper-IgE syndrome (HIES); (2) HIES is characterized by a clinical triad consisting of elevated serum IgE levels, recurrent staphylococcal skin abscesses, and pneumonia with pneumatocele formation; (3) although serum IgE levels in AD have been noted to be as high as 10,000 IU/mL, severe cases of AD such as that presented here can exceed this range; (4) the efficacy of anti-IgE therapy in AD or HIES is unknown and may be limited by dosing requirements.

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Question:

A 12-year-old male boy with a lifelong history of asthma, eczema, and allergic rhinitis presented to the clinic because of difficulties controlling his eczema with interest in omalizumab therapy. Previously, he has used topical steroids, emollients, and topical tacrolimus with only partial relief. He also has a history of recurrent staphylococcal skin infections that are slow to heal and require four to five courses of antibiotics annually. He has a history of hyperextensible joints and retained primary teeth. He denies any history of skin abscesses or pneumonias.

Skin exam reveals diffuse eczematous lesions with dry, flaky skin over the scalp, nose, mouth, eyes, and across the anterior aspect of neck and erythematous, thickened skin over flexural areas with excoriations on the trunk. His left nipple is draining purulent material. Lungs are clear to auscultation except for bilateral expiratory wheezes on forced exhalation. Tonsils are present.

CBC count—8960 cells/mm³; 47% neutrophils, 29% lymphocytes, 7% monocytes, and 16% eosinophils (eosinophil count of 1470). Hemoglobin, 14.4; hematocrit, 42.1; platelets, 259,000.

Culture—Nipple culture reveals *Staphylococcus aureus*.

Serologic—IgG, 9.75 gm/L (normal: 6.97–15.93 gm/L); IgM, 1.15 gm/L (normal: 0.47–3.11); IgA, 0.95 gm/L

(normal: 0.52–1.92); and IgE, 41,004 ng/mL (equivalent to 17,085 IU/mL), which is 5.9 SDs from age-dependent mean level of 48.5 ng/mL.

Spirometry—Baseline FVC = 2.20L; FEV₁ = 1.38 L (with 16% improvement postbronchodilator); FEV₁/FVC = 0.63.

Chest x ray—Shows minimal increase in interstitial markings bilaterally without evidence of focal infiltrate or pneumonia.

Which of the following statements regarding his diagnosis and management is correct?

- A. This patient has hyperimmunoglobulin E (hyper-IgE) syndrome (HIES).
- B. This patient has atopic dermatitis (AD).
- C. Omalizumab has been shown to be effective in the treatment of HIES.
- D. Omalizumab is indicated for the treatment of AD.

The differential diagnosis in a patient with eczema, altered immunoglobulin levels, and a history of recurrent infections is broad. However, the main diagnoses for this patient are AD and the much rarer condition of HIES. The constellation of historical features, physical findings, and laboratory data in this patient poses a diagnostic dilemma between AD and HIES. Therefore, it is important to differentiate between these two clinical diagnoses.

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

AD is a common chronic or relapsing eczematous dermatitis characterized by intense pruritus and occurs primarily in infants and children. Approximately 70% of AD cases start before the age 5 years.¹ The lesions

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are classically located on the face, scalp, and extensor surfaces of extremities in infancy. Acute eczematous lesions can show intense pruritic, erythematous papules with excoriation, vesicles, and serous exudates. Chronic lesions are characterized by lichenification and fibrotic papules. Associated features include IgE reactivity (increased serum IgE, RAST, or prick test positive). These patients are susceptible to *S. aureus* cutaneous infections and a high percentage of patients are colonized with *S. aureus* without overt infections.² Deep-seeded *S. aureus* infections occur rarely in AD and should raise the possibility of immunodeficiency syndromes such as HIES.

HIES (also called Job's syndrome) is characterized by a clinical triad consisting of elevated serum IgE levels (>2000 IU/mL), recurrent staphylococcal skin abscesses, and pneumonia with pneumatocele formation.³ They are rare primary immunodeficiencies (estimated incidence <10⁻⁶)³ with most cases occurring sporadically; however, two distinct entities—classic HIES, which is inherited in an autosomal dominant pattern,⁴ and autosomal recessive HIES⁵—have been described.

Clinical features of classic HIES were described by Grimbacher and colleagues⁴ who studied 30 patients with HIES and their relatives. They established that HIES was a multisystem disease involving the immune system, connective tissue, skeleton, and dental development. The classic triad of abscesses, pneumonia, and elevated IgE level was identified in 77% of all patients and in 85% of those >8 years old. Pneumonias are mainly caused by *S. aureus*, *Staphylococcus pneumoniae*, and *Haemophilus influenzae*. Other common features reported were eczema (occurring in all patients), pneumatocele formation, mucocutaneous candidiasis, and eosinophilia (at least 2 SD above normal occurring in 93% of patients). The pneumatoceles are infected frequently by *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Nonimmunologic features were present in all patients >8 years old. The previously unrecognized feature of failure or delay of shedding of primary teeth was observed in 72% of patients. Skeletal abnormalities identified include recurrent fractures from minor trauma (in 57% of patients), hyperextensible joints (in 68%), and scoliosis (in 76% of patients ≥16 years). Autosomal dominant HIES patients also have been noted to have distinct facial features with facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge, wide and fleshy nasal tip, and mild prognathism. Some ophthalmologic pathologies such as extensive xanthelasma, giant chalazia, eye lid tumors, and strabismus, as well as malignancies such as lymphomas and pulmonary adenocarcinoma, also have been reported in HIES patients.³

Clinical features in the autosomal recessive form of HIES include recurrent or severe infections with *S.*

aureus, *P. aeruginosa*, *H. influenzae*, *Proteus mirabilis*, and *Cryptococcus*.⁵ Severe chronic refractory *Molluscum contagiosum* infections and recurrent aphthoid herpes simplex infections were reported also. Recurrent varicella zoster infections were reported in one patient. Other rare findings reported in autosomal recessive HIES include autoimmune hemolytic anemia and pericardial effusion. Neurological symptoms observed varied from partial facial paralysis to hemiplegia.

Although the incidence of pneumonia in autosomal recessive HIES was the same, no pneumatoceles occurred in the patients studied. Of note, patients with autosomal recessive HIES did not have skeletal abnormalities, fractures, dental abnormalities, or the facial features described in autosomal dominant HIES. Serum IgE levels of patients with autosomal recessive HIES were comparable with those observed in the autosomal dominant form; however, patients with autosomal recessive HIES also had elevated levels of other immunoglobulin isotypes and they had more severe eosinophilia.

The etiology of HIES remains unresolved. The syndrome is found in diverse ethnic backgrounds and is not more common in any specific population. Grimbacher *et al.*⁶ confirmed that the proximal chromosome 4q region contains a disease locus for HIES. Previous research points to a T helper 1 cell (Th1)/Th2 cytokine and other chemokine imbalance.³ In a small study by Tanaka *et al.*,⁷ the investigators suggest that up-regulation of RGC32 (a CD14⁺ T-cell gene) decreased expression levels of *IL-17* and *CXC11* genes in peripheral blood mononuclear cells, and up-regulation of multiple immunoglobulin-related genes may play a role in the pathogenesis and pathophysiology of HIES. Thus, they support Grimbacher and colleagues' suggestion that HIES is caused by a molecule that affects various biological functions rather than only by a Th1/Th2-related molecule.^{3,8} Tanaka's findings support the multisystem involvement of HIES in which phagocyte and T-cell abnormalities would account for susceptibilities to bacterial and fungal infections, whereas bone and dental abnormalities would suggest defects in monocyte-lineage cells such as osteoclasts and osteoblasts.

DIAGNOSIS

The diagnosis of AD is based on clinical features, although negative skin or RAST tests for foods and environmental allergens may assess the contribution of allergies to disease expression in children with severe disease.¹ Positive food tests are less useful as the positive predictive value is 40% whereas the negative predictive value is above 95%. Laboratory abnormalities in AD include elevated serum IgE levels and eosinophilia. The serum IgE level in persons with AD usually is around 1000 IU/mL but may be as high as 10,000

IU/mL.⁸ Our patient has several findings consistent with AD.

HIES remains a syndrome that lacks specific diagnostic criteria, apart from elevated serum IgE levels and eosinophilia. There are no specific immunologic or molecular markers to help make the diagnosis. Thus, clinicians must depend on recognizing multisystem symptoms and clinical features, which develop over years, to make the diagnosis. In addition, clinicians must consider related conditions that may account for the features in question; thereby making the diagnosis of HIES difficult. Our patient has some findings seen in HIES.

MANAGEMENT

Topical corticosteroids are the mainstay of treatment for patients of all ages with moderate-to-severe AD.¹ Emollients are used also to reduce symptoms from dry skin. Topical tacrolimus and pimecrolimus are recommended in patients unresponsive to or intolerant of topical corticosteroids. However, it is important to note that there is a potential concern between topical pimecrolimus and tacrolimus and cancer (mainly lymphoma and skin cancer). Other agents that have been used for treating AD that have less supporting evidence include oral antihistamines, refined coal tar cream, topical doxepin, and oral corticosteroids. Secondary infections are treated usually with short courses of antibiotics.¹

Treatment of HIES is directed mainly toward prevention and management of infections. Systemic antibiotics and antifungals are used both for prophylactic and symptomatic treatment in conjunction with topical therapy for eczema and surgical drainage of abscess where indicated. Prophylactic use of antistaphylococcal antibiotics significantly reduces the incidence of skin abscesses and staphylococcal pneumonias.³ Other treatment modalities including interferons, immunoglobulin supplementation, and low-dose cyclosporine A have been reported to benefit selected patients; however, they generally are not indicated.³ Because these patients also develop noninfectious problems, it is wise to evaluate for fractures even after minor trauma, monitor for scoliosis, and have primary teeth removed.

Recently, a monoclonal anti-IgE (omalizumab) has been studied in several large-scale clinical trials in subjects with allergic asthma and rhinitis and was found to produce dose-related declines in serum-free IgE levels, which correlate with symptom improvement.^{9,10} The dosing of omalizumab is based on a patient's baseline IgE level, and in prior studies, IgE levels were much lower (generally, <1000 IU/mL) than that of our patient.^{9,10} Given that our patient's IgE level is much higher and studies of IgE reduction therapy in AD are not available, it is unknown whether he

would respond successfully to anti-IgE therapy, even though he would be a candidate based on his history of allergic asthma. Likewise, given our limited understanding of HIES, the role of IgE reduction has not been established. Therefore, this patient was continued on topical tacrolimus, steroids, and emollients for AD.

Answer: B

Pearls

- Serum IgE levels in AD may be as high as 10,000 IU/mL.
- Deep-seeded *S. aureus* infections occur rarely in AD and should raise the possibility of immunodeficiency syndromes such as HIES.
- HIES is characterized by a clinical triad consisting of elevated serum IgE levels (>2000 IU/mL), recurrent staphylococcal skin abscesses, and pneumonia with pneumatocele formation.

Pitfalls

- Making the diagnosis of HIES is challenging and requires compiling a spectrum of clinical features over several years.
- Although serum IgE levels in AD have been noted to be as high as 10,000 IU/mL, severe cases of AD such as that presented here can exceed this range.
- The efficacy of anti-IgE therapy in AD or HIES is unknown and may be limited by dosing requirements.

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