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A teenager with a rash and complicated recurrent *pneumoniae*

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ABSTRACT

This new section of the journal features case studies with an immunological interest, accompanied by a brief discussion on pathophysiology, treatment and prognosis. Here, we discuss a teenage girl with a long history of complicated respiratory infections and recalcitrant eczematous rash, who was sent to our hospital and diagnosed with the Hyperimmunoglobulin E syndrome.

Key words: Primary immunodeficiency, Hyperimmunoglobulin E syndrome, bronchiectasis, respiratory infections, recurrent *pneumoniae*, rash, eczema, pneumatoceles.

RESUMEN

Esta nueva sección de la revista muestra casos de interés con énfasis en la inmunología, con una breve discusión sobre fisiopatología, tratamiento y pronóstico. Se presentó una adolescente con historia de varios años de infecciones respiratorias de repetición, complicadas, y eccema recalcitrante, vista en nuestro Instituto y diagnosticada con el síndrome de Hiperinmunoglobulinemia E.

Palabras clave: Inmunodeficiencia primaria, Síndrome de hiperinmunoglobulinemia E, bronquiectasias, infecciones respiratorias, neumonía recurrente, rash, eccema, neumatoceles.

The patient

A twelve-year-old teenage girl from rural Hidalgo, a state in Mexico, lives in a hut with her family, in crowded unsanitary conditions. Two of her brothers died from infections before their first birthday; one of them with extensive cutaneous lesions at the time of his death. She had a long history of repetitive airway infections, which started shortly after birth; at age 4 and again at 7, she was hospitalized with pneumonia. At 9 she developed painless abscesses in her armpits and groins, as well as an eczematous rash with erythematous papules and small vesicules that covered her chest, neck, axillary, retroauricular and perioral regions. She was referred to our institute when she was 11; at ages 11 and 12, she had *pneumoniae* again, this time complicated with pneumatoceles that resolved.

Aside from the described cutaneous lesions (Figure 1), she had bilateral rales and crackles on auscultation, as well as axillary and inguinal adenopathies; she was hospitalized after a chest X-ray was taken (Figure 2) and started on intravenous antibiotics and fluids.

The diagnostic workup

Laboratory studies showed leukocytosis (19,600/mm^3) with neutropenia (3%) and eosinophilia (82% eosinophils, 16,070/mm^3 absolute). Serum IgE was 4,864 IU/

mL at the time of her first visit, but climbed up to 10,000 IU/mL later on. A nitro-blue tetrazolium test was negative. Bronchial, skin and lymph node biopsies showed chronic granulomatous inflammation with eosinophilic infiltration, as well as changes suggestive of fungal infection. Lymphocyte subpopulations by flow cytometry were normal; interferon gamma (IFN-γ) production in response to phytohemagglutinin (PHA) and other stimulants, was impaired. Interleukin 12 receptor (IL-12R) beta-1 levels were undetectable by flow cytometry, a finding awaiting confirmation.

Based on the Hyper-Immunoglobulin E syndome (HIES) criteria proposed by Grimbacher *et al,*[1] she had a clinical score of 53. A diagnosis of HIES was established.

The disease

The Hyper-immunoglobulin E syndrome is also known as Job Syndrome and Buckley's Syndrome.

This rare primary immunodeficiency manifests itself in early childhood with recurrent infections of the skin, lungs, lymph nodes and bones, caused by S*taphylococcus aureus* and *Candida* species. Typical presentation includes complicated *pneumoniae* with pneumatocele formation, eczematous (chronic allergic) dermatitis, mucocutaneous candidiasis, and very high levels of IgE. Retained primary dentition, bone abnormalities like scoliosis and osteopenia with multiple fractures, hyperextensible joints and dysmorphic features (coarse facies) are also common,[2] as well as peripheral eosinophilia.

Impaired IFNγ production by mononuclear cells has been reported as one of the hallmark features in HIES, resulting in a defect in neutrophil activation and chemotaxis. This IFNγ deficit, with an impaired Th1 response, is also probably the reason for the marked elevation in serum IgE, as Interleukin 4 (IL-4) is unopposed in its induction of IgE production by B cells.[3]

Recently, a heterozygous mutation in STAT3 was described,[4] which affects this transcription

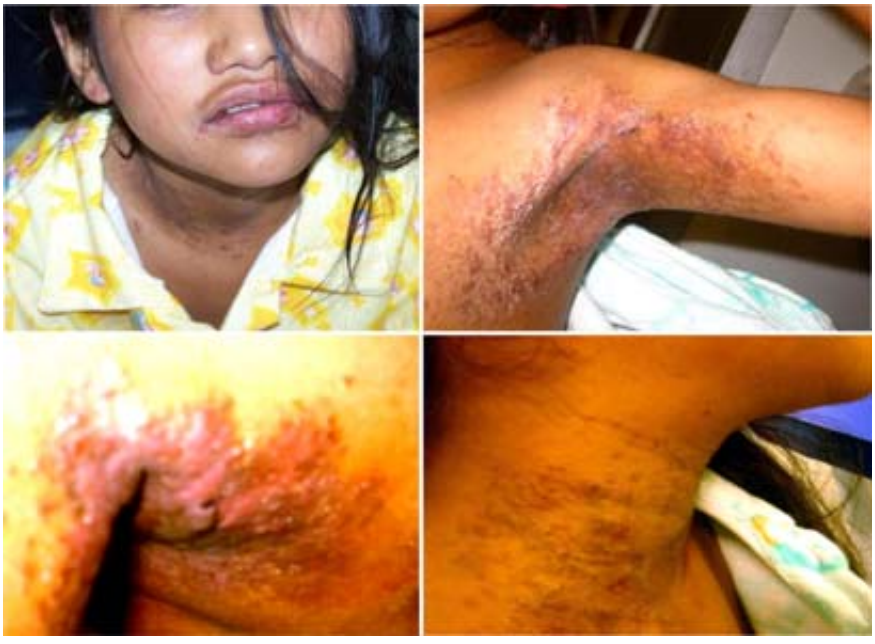

Figure 1. Eczematous cutaneous lesions affecting retroauricular, perioral, axillary and cervical regions.

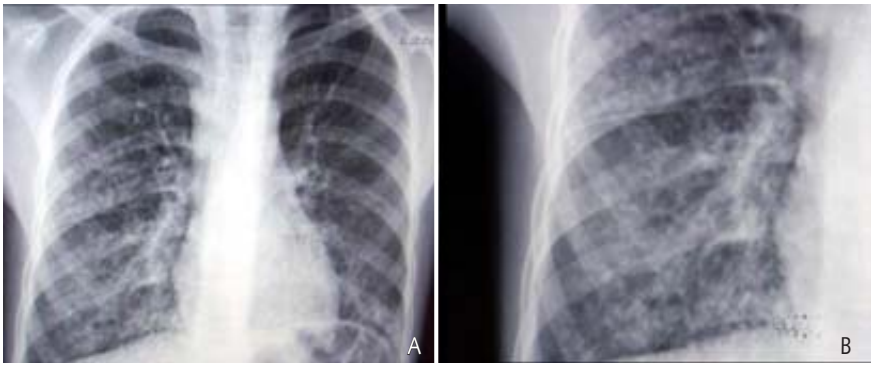

Figure 2. A) Chest roentgenogram showing diffuse, bilateral, heterogenous opacities and radio-lucid images, tubular-like, consistent with bronchiectasis; **B)** Close-up of the right chest.

factor's ability to bind DNA, thus impairing the cellular response to IL-6 and IL-10, and undermining the production and secretion of β-defensins in the skin and lung, with the resultant increased susceptibility to infections. A low serum IgA specific to *Staphylococcus* has also been reported as a probable contributing cause for the recurrent infections.

As for its genetic occurrence, most cases are sporadic. When a familial presentation can be traced, its pattern of inheritance is autosomal dominant; our patient probably belongs to this category. Autosomal recessive HIES (AR-HIES) is considered a distinct, less common entity; patients with AR-HIES do not develop pneumatoceles, usually present with severe neurological complications, and they lack skeletal or dental involvement.[5] A defect in the Jak protein TYK2 was reported in a family with recessive inheritance.[6]

— *Category:* Primary immunodeficiency, phagocytic disorder.
— *Incidence:* Very rare. A few more than 250 cases reported since 1966, when it was first described. No predilection for sex or race.
— *Heritability:* Autosomal dominant, most common; autosomal recessive also. Most cases are sporadic.
— *Defect:* STAT3 heterozygous mutation, with a dominant negative effect. Complement receptor (CR1) in neutrophils. Homozygous TYK2 mutation in autosomal recessive form.
— *Invading pathogens: Staphylococcus aureus, Streptococcus sp., Haemophilus influenzae, Candida sp., Aspergillus.*
— *Key features:* Severe cutaneous and pulmonary disease, serum IgE > 2000 IU/mL.

Prognosis and follow-up

Our patient visited many hospitals before a diagnosis of primary immunodeficiency was finally suspected. Although these patients' symptoms begin in infancy, the diagnosis is often delayed until late childhood.

At our institute she was started on endovenous gammaglobulin (iv Ig) and prophylactic oral antibiotics, with good response. Interferon gamma is also commonly used in the treatment of phagocytic disorders like this one. Antibiotic prophylaxis, with daily trimethoprim-sulfamethoxazole and/or low-dose fluconazole,[2] can be given for long periods when an appropriate response has not been attained.

Two years after diagnosis, she has not had any other respiratory infection and is practically devoid of cutaneous lesions. She still comes every month to get her iv Ig treatment, with no major adverse side effects.

The reported deficit in IL-12 beta-1 receptor is not considered a component of the syndrome and was an unexpected finding in this case; however, other abnormalities in the IL-12/IFN-γ occurring in these patients have been reported before,[7] and thus the patient and her parents are currently under evaluation to corroborate that fact.

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