

Although the activation of eosinophils by cytokines has been reported^{8,9} and several authors have found increased lymphocyte proliferation to food antigens in patients with food allergy,¹⁰ these data have not yet been reported in patients with pulmonary hemosiderosis. We propose that in this case a specific activation mechanism in sensitized T cells may have taken place and these cells may have released cytokines that activate eosinophils, basophils, and/or mast cells. Therefore in patients with IPH in whom milk allergy may trigger or aggravate pulmonary damage, controlled administration of milk proteins with quantitation of different inflammatory mediators may help to establish a causal relationship.

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Previously undiagnosed hyper-IgE syndrome in an adult with multiple systemic fungal infections

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First described in 1966 in two red-haired girls with recurrent "cold" staphylococcal abscesses,¹ hyper-IgE (Job's) syndrome is a rare, complex immunoregulatory disorder characterized by elevated serum IgE levels,² eczematoid dermatitis, and recurrent bacterial infections.^{3,4} The infections begin early in life and consist of recurrent skin infections, otitis media, sinusitis, and pneumonia. The major bacterial pathogen is *Staphylococcus aureus*, and less commonly *Haemophilus influenzae*, streptococci, or enteric bacteria. Nonbacterial infections, particularly

mucocutaneous candidiasis, also occur; but systemic fungal infections are unusual.⁵

Most patients with hyper-IgE syndrome are diagnosed in childhood. We describe a patient with hyper-IgE syndrome who, despite all the classical features, remained undiagnosed until adulthood when he was first seen with multiple systemic fungal infections.

CASE REPORT

A 38-year-old man was referred to Baylor College of Medicine for evaluation of multiple systemic fungal infections. The patient had a history of eczematous skin rashes from the age of 3 weeks, severe ear infections starting at 3 months, severe acne from the age of 1 year, recurrent sinusitis beginning at 12 years (status after 2 Caldwell-Luc operations with bilateral ethmoidectomies), septic arthritis of the right hip as a result of staphylococcus at 16, and multiple episodes of pneumo-

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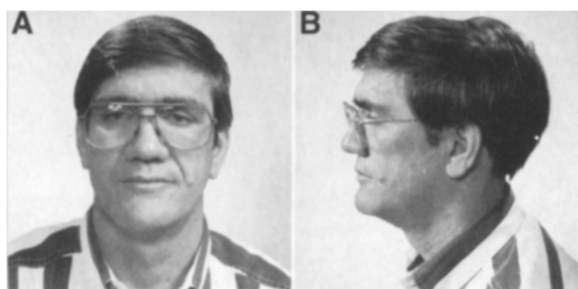


FIG. 1. Front (A) and side (B) view of patient.

nia starting at age 19. He had recurrent perioral and nasal herpes simplex infections and a single episode of shingles at the age of 36. The patient also had a history of recurrent superficial fungal infections, starting at 4 years of age with multiple episodes of thrush and onychomycosis.

At the age of 33, he had a tongue ulcer, which, on examination of a biopsy specimen, was found to contain budding yeast. At that time, cultures from an infiltrate in the middle lobe of the right lung were positive for *Histoplasma capsulatum*. No serum antibodies to *Histoplasma* species were detected. Treatment with ketoconazole was successful; however, a right middle lobectomy was required because of bronchiectasis. At the age of 37, the patient had cryptococcal meningitis, which was successfully treated with intravenous amphotericin B, followed by oral fluconazole. There was no family history of immunodeficiency.

Physical examination at the time of referral was significant for the presence of multiple skin lesions showing depigmentation and onychomycosis of the left first toenail. His facial features were coarse, with a broad nasal bridge and a prominent nose (Fig. 1), as frequently seen in patients with hyper-IgE syndrome.³ The patient had a serum IgE level of 9500 IU/ml. Other immunoglobulin levels were normal (IgG, 1540 mg/dl; IgA, 298 mg/dl; IgM, 169 mg/dl), as were IgG subclass levels. Despite previous vaccination, pneumococcal and tetanus antibody levels remained low. Total hemolytic complement was normal.

Results of delayed hypersensitivity skin tests with *Candida* species, *Trichophyton* species, tetanus toxoid, and purified protein derivative were negative. Results of tests for HIV by ELISA and Western immunoblot were negative on several occasions. The total white blood cell count was $4.5 \times 10^6/\text{ml}$ with 64% neutrophils, 28% lymphocytes, 5% monocytes, and 2% eosinophils. Immunophenotyping of the patient's peripheral blood mononuclear cells demonstrated normal levels of B cells and CD4⁺ and CD8⁺ T cells. Results of a nitroblue tetrazolium dye reduction assay were normal, as were results of assays for neutrophil chemotaxis.

DISCUSSION

We report a patient with the hyper-IgE syndrome who remained undiagnosed until adulthood. Notably, this patient had essentially all the classical laboratory features of the hyper-IgE syndrome. These included high levels of serum IgE (≥ 2000 IU/ml) with normal immunoglobulin levels of other classes, decreased ability to produce antigen-specific antibodies after immunization, normal total white blood cell and T and B lymphocyte counts, normal complement levels, and normal nitroblue tetrazolium assay results. Like most patients with this syndrome, he demonstrated diminished delayed-type hypersensitivity. The only feature that he lacked was eosinophilia. Nonetheless, he remained undiagnosed until the age of 38.

This is the first reported case of a patient with hyper-IgE syndrome who has had multiple systemic fungal infections. Although patients with hyper-IgE syndrome are prone to superficial fungal infections of the skin and mucous membranes, systemic fungal infections have been noted infrequently. A few patients have been reported with isolated cryptococcal infections of the esophagus, colon, or meninges; or *Histoplasma* infections of the ileocecum or colon.⁵ The patient in this report had both disseminated histoplasmosis and cryptococcal meningitis. Although patients with allergic diseases can have fungal infections of the respiratory tract (e.g., fungal sinusitis or allergic bronchopulmonary aspergillosis), sometimes associated with high serum IgE levels, the diagnosis of hyper-IgE syndrome should be considered in evaluation of adult patients with high IgE levels and a history of recurrent or multiple systemic fungal infections.

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