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HYPER – IgE SYNDROME: A CASE REPORT*

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A four-year-old-girl with hyper-IgE syndrome is presented. She had a coarse facial appearance, pruritic dermatitis, recurrent skin abscesses, pulmonary infection, spontaneous bone fractures, and an elevated serum IgE concentration. She has been treated with cimetidine, ascorbic acid and trimethoprim-sulfamethoxazole for the last two years and there has been no evidence of a severe infection. *Key words: hyper-IgE syndrome, bone fractures, cimetidine, vitamin C.*

The hyper-IgE syndrome (HIES) is a rare disorder characterized by pruritic dermatitis, recurrent staphylococcal skin abscesses, lung infections with pneumatocele formation, extreme elevations in serum IgE levels and generally normal or near-normal serum concentrations of the other immunoglobulins[1-3]. The coarse facial appearance, the defects in cellular and humoral immunity, and variable polymorphonuclear (PMN) leukocyte chemotactic abnormalities have also been reported in this syndrome[1].

We present a four-year-old girl who had dermatitis and recurrent superficial and deep bacterial infections in association with raised IgE levels.

Case Report

The patient (Y.T.) was first hospitalized at 18 months of age for numerous skin abscesses and fever. Her medical history revealed persistent dermatitis localized on the scalp, face and retroauricular areas, which started at 20 days of age, and also recurrent pneumonia, pustular skin lesions, diarrhea and oral candidiasis. She did not have any unusual reactions following routine immunizations and neither

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was there any clinical evidence of parasitic infestation, history of respiratory allergy or asthma. The parents were first degree cousins and healthy. Physical examination revealed a coarse facial appearance (Figs. 1, 2). Her weight was above the 15th percentile and her height was above the 25th percentile. There were numerous skin abscesses on her scalp, face and right buttock. Cultures of the abscesses yielded *Staphylococcus aureus*. The lesions responded to surgical drainage and two weeks of oral trimethoprim-sulfamethoxazole therapy. Laboratory examinations showed hypochromic anemia and a peripheral leukocyte count of 20,400 per mm^3 with 75% neutrophils. Total peripheral eosinophil count was 550 per mm^3. Serum IgE level was above 2,500 kU/lt. Other serum immunoglobulin levels were within normal limits (IgG: 1560 mg/dl; IgM: 123 mg/dl; IgA: 77.7 mg/dl). Delayed hypersensitivity skin tests were positive with PHA, Candida and PPD but negative with SKSD. The percentage of E-rosette forming cells was normal (60%). Lymphocyte blastogenic response to PHA, NBT reduction test, and total complement (CH_{50}: 47 u) were found to be normal. Serum anti-A and anti-B titers were 1/64 and 1/512, respectively. In vitro neutrophil chemotaxis value using Boyden's chamber and Zymosan activated serum (ZAS) as a chemoattractant was 57.4% of the healthy control.

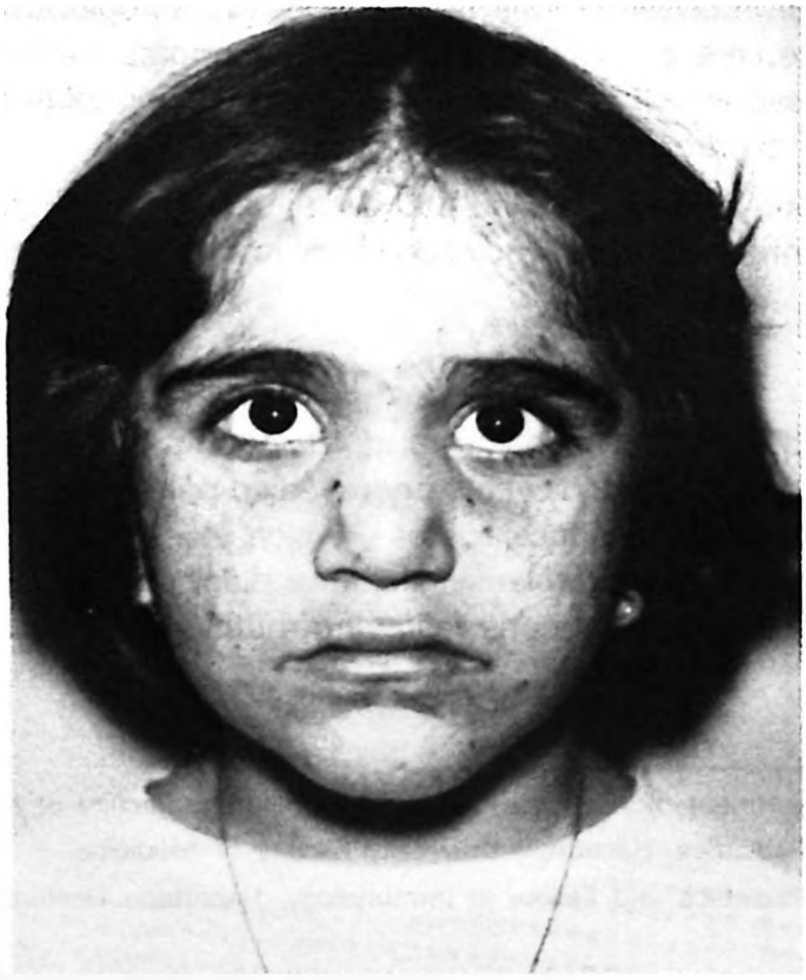

Fig. 1: Coarse facial appearance

Fig. 2: Skin infection and pruritic dermatitis

In view of the clinical picture and laboratory findings, the patient was diagnosed as having hyper-IgE syndrome. She was administered cimetidine (as a histamine-receptor blocking agent) and trimethoprim-sulfamethoxazole.

At 19 months of age, the infant was hospitalized for the second time, and the diagnosis of pneumonia was established. She had a fracture of the third metatarsal bone with no history of trauma. We learned that after she had been discharged from the hospital, she had not been receiving trimethoprim-sulfamethoxazole and cimetidine on a regular basis.

Pneumatocele formation with air-fluid levels were noted on the chest roentgenogram. Despite the administration of anti-staphylococcal antibiotic therapy, a massive pleural effusion developed and tube drainage was performed. Cultures of the pleural fluid grew *Staphylococcus aureus.* Intravenous antistaphylococcal therapy was continued for 3 weeks. Pleural effusion disappeared but the pneumatocele persisted. She was discharged and ascorbic acid was prescribed in addition to the cimetidine and trimethoprim-sulfamethoxazole. She did well for the next 8 months. At 2 1/2 years of age, she was hospitalized again because of a fracture of the left radius-ulna bone, resulting from a relatively slight trauma. A chest x-ray revealed that the pneumatocele had disappeared.

Repeated scalp abscesses and recurrent middle ear infections, although less severe and less frequent, developed during the follow-up period. The in vitro neutrophil chemotaxis value was 91 percent of the healthy control when evaluated during ascorbic acid treatment.

The patient had no major skin or lung infection but a chronic middle ear infection was present.

Discussion

This patient, who had dermatitis in the newborn period, numerous superficial and deep skin abscesses located especially on the scalp, face and neck, multiple bouts of staphylococcic pneumonia complicated with empyema and pneumatocele formation and a marked elevation of the serum IgE level, was diagnosed as having HIES.

Since Buckley's[2] first description of two patients with HIES in 1972, several cases have been reported[3-6]. Pruritic (not atopic) dermatitis, skin infections, especially on the scalp and face, recurrent episodes of pneumonia complicated by empyema, lung abscesses, pneumatocele formation, and a coarse facial appearance are the major clinical features seen in this syndrome. Infections of the ears, eyes, oral mucosa, sinuses and joints can also be present in HIES. Most patients do not have histories of allergic rhinitis or asthma.

Kirchner[7] emphasized recurrent bone fractures in some of the patients with HIES. Our patient had a bone fracture twice during the follow-up period. Leung et al[8] suggested that the monocytes from HIES patients cause osteopenia. The spontaneous release of prostaglandin E_2 (PGE_2) may induce the monocytes to resorb bone. The familial nature of HIES has been documented[9,10]. Both sexes are said to be affected. IgE levels are reported to be normal in non-affected family members[10].

The major immunologic feature of HIES is a marked elevation of serum IgE levels. An elevated concentration of IgD has been found in most patients[1]. It has been reported that IgA antibodies to *Staphylococcus aureus* are deficient in some patients[11]. High levels of IgE antibodies to staphylococcus aureus antigen were found by Buckley[1] and Dreskin[11]. Berger et al[12] and Scmitt et al[13] observed high titers of IgE antibodies to tetanus toxoid and Candida antigens. They concluded that there might be an abnormal IgE immunoregulation.

Buckley[1] et al observed negative delayed hypersensitivity skin reactions to Candida and SKSD in half of their patients. Our patient had a positive delayed hypersensitivity skin reaction to three out of four antigens tested. In Buckley's series, the lymphocytes from most of the patients with HIES had a normal proliferative response to mitogens but no, or a very low response to Candida antigen and tetanus toxoid[1].

Impaired neutrophil chemotaxis has been noted by several authors[1,3,4,6,9,14]. It has been suggested that high levels of histamine cause cyclic GMP elevation in the neutrophils from patients with HIES. A chemotactic inhibitor factor might also be responsible for the defective neutrophil chemotaxis[4,15]. Our patient's neutrophil chemotaxis was 57.4 percent of the healthy control. Hill et al[16] studied the effects of the H_2-receptor blocking agent to PMN leukocyte chemotaxis in vitro. They observed an improvement in neutrophil chemotaxis from HIES exposed in vitro to burimamide (H_2-receptor blocking agent). Defective neutrophil chemotaxis is not consistent and may vary even in the same patient. Our patient's in vitro neutrophil chemotaxis was normal during the follow-up period. This might be related to the ascorbic acid treatment or a spontaneous alteration that is seen in HIES. Buckley[1] emphasized that chemotactic abnormalities were more suggestive of atopic dermatitis than HIES. PMN leukocyte phagocytosis, killing and nitroblue tetrazolium dye-reduction were found to be normal in their patients.

Job's syndrome (JS), characterized by recurrent "cold" staphylococcal abscesses and pulmonary infections was described in 1966[3,17]. A high serum concentration of IgE was demonstrated later. There are some clinical similarities between JS and HIES. While some authors consider JS to be within the spectrum of HIES, others say it is an entirely different entity. At present, the relationship between JS and HIES is not clear.

The primary defect in HIES is unknown, therefore, definitive therapy is not possible. Several investigators have studied the effects of normal plasma transfusions, histamine-2-receptor blocking agents, transfer factor, levamisole and interferon-alpha in the treatment of HIES[3-5,9,14,18,19].

Although treatment using transfer factor or levamisole has not resulted in any significant improvement in clinical or laboratory findings, normal plasma transfusions, cimetidine and ascorbic acid are said to improve the chemotactic abnormalities of neutrophils in these patients. Mawhinney et al[18] did not observe any severe infections in their patient during the administration of cimetidine. Souillet et al[19] reported that the administration of interferon-alpha for four weeks resulted in the reduction of the serum IgE level and eczema in a HIES patient.

Lifelong antibiotic therapy seems to be useful in preventing infections in these patients, and a favorable therapeutic response to trimethoprim-sulfamethoxazole has been reported[1-5].

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