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Hyperimmunoglobulinemia E Syndrome with Recurrent Infections

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Hyperimmunoglobulinemia E syndrome (HIES) is a rare primary immunodeficiency disorder characterized by markedly elevated serum immunoglobulin E (IgE) levels (>2000 IU/ml), recurrent pyogenic infections of the skin and the respiratory tract, chronic eczematous dermatitis, skeletal abnormalities, and peripheral eosinophilia. We describe a 29-year-old female with HIES, who suffered from chronic generalized eczema and recurrent pyogenic cutaneous infection since early childhood. Laboratory analysis revealed a persistent elevation of total serum IgE level (>8000 IU/ml). *Escherichia coli* and *Enterobacter aerogenes* were isolated from a cold abscess on the buttocks. Flow cytometry showed impairment of neutrophil phagocytotic uptake capacity of gram-negative *Klebsiella pneumoniae*. The cutaneous abscess responded to incision, drainage, and prolonged oral antibiotic therapy. Improvement of the skin condition was achieved after treatment with antihistamines, topical steroids, and prophylactic antibiotics.

Key words: hyperimmunoglobulinemia E, Job's syndrome, dermatitis, cold abscess

INTRODUCTION

Hyperimmunoglobulinemia E syndrome (HIES), also called "Job's syndrome", "Buckley's syndrome", and "hyperimmunoglobulin E (hyper-IgE) recurrent infection syndrome", is a rare idiopathic primary immunodeficiency[1]. It was first reported in 1966 by Davis *et al*., who described two girls with severe skin abscesses and infections[2]. In 1972, Buckley *et al*. described two boys with similar symptoms[3]. Since then, reports of more than 200 cases have been published. HIES is now recognized as a disorder of unknown etiology, affecting multiple organ systems including the immune system, dentition, bones, and connective tissues. It is characterized by recurrent cutaneous abscesses, respiratory tract infections (mainly, but not exclusively, with *Staphylococcus aureus* and *Candida* species), elevated serum IgE levels (>2000 IU/ml), persistent eczematous dermatitis, and eosinophilia[4]. Skeletal abnormalities include joint hyperextensibility, scoliosis, and multiple bone fractures[5]. HIES may thus be seen as a disease spectrum due to the diversity of the clinical and immunological manifestations. Here, we report a case of HIES with nonstaphylococcal infection and defective neutrophil phagocytosis.

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CASE REPORT

A 29-year-old woman with chronic eczema and recurrent pyoderma was seen for evaluation and management. She had an uneventful neonatal course, but at an age of two months was noted to have eczema on the head, face, neck, and upper trunk. A tentative diagnosis of atopic dermatitis was made at the age of two years because of generalized, atopic-like dermatitis and episodes of suspected asthma attack. She was treated with topical and systemic corticosteroids, but the eczema persisted. At 10 years of age, multiple draining abscesses of the scalp developed, requiring incision and drainage as well as systemic antibiotic therapy. Chronic recurrent episodes of pyoderma presenting as furunculosis, skin abscesses, and mucocutaneous candidiasis were noted and treated at the Veterans General Hospital in the ensuing months and years. She also experienced recurrent bronchitis and intermittent low-grade fever since early childhood. Otherwise, a review of physical systems was unremarkable. She denied a history of family members with similar findings. Physical exami-

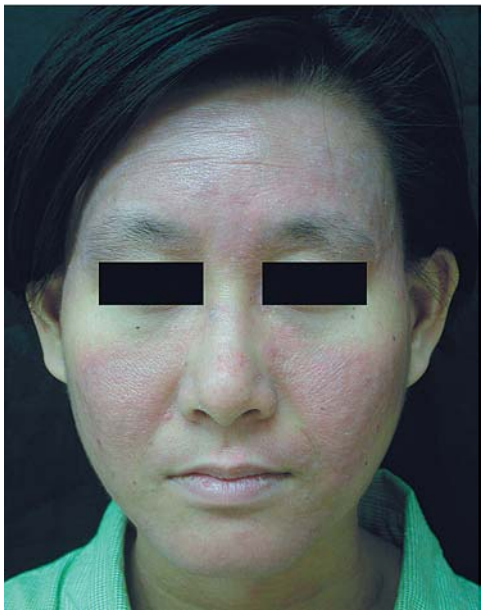

Fig. 1 The patient with HIES shows typical coarse facial features. Pruritic, erythematous, lichenoid plaques of various sizes were present on her scalp, posterior auricular areas, and neck.

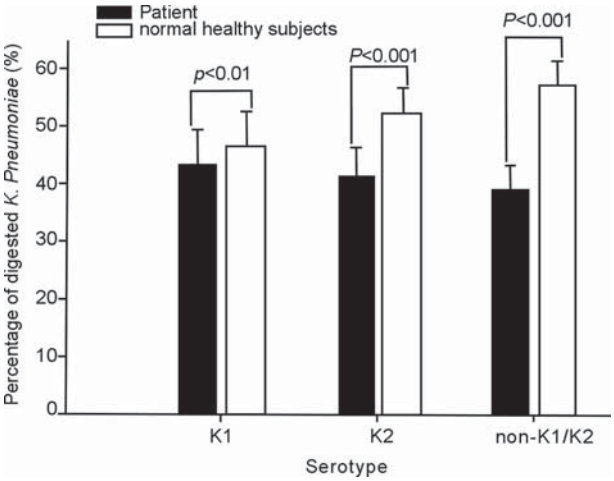

Fig. 2 *In vitro* phagocytic capacity of neutrophils. Impaired phagocytic capacity of neutrophils against different serotypes of *K. pneumoniae* was demonstrated by comparison between cells of the HIES patient and cells of normal healthy subjects ($P < 0.01$).

nation showed widespread pruritic, erythematous, and lichenoid plaques of various sizes over her scalp, face, posterior auricular areas, neck, upper back, bilateral axilla, groin region, and extremities. Her facial skin was pitted, thickened, and had a doughy consistency (Fig. 1). She had distinctive facial features with a prominent forehead, deep-set eyes, a broad nasal bridge, and a wide base of the nose. Hyperextensible joints were noted and scoliosis was revealed by X-ray. A few skin ulcers and cutaneous cold abscesses were found on the buttocks and extremities. Lymph nodes were palpable in the cervical, axillary, and inguinal regions, but were not grossly enlarged or tender. A culture of pus from a buttock abscess grew *Escherichia coli* and *Enterobacter aerogenes* with susceptibility to cephalexin. Remarkable elevations in IgE levels were noted in a series of IgE blood tests (the highest level was 17110 IU/ml and the lowest level was 8246 IU/ml; the normal range is 0-130 IU/ml). The eosinophil count was within normal limits. Serum IgG, IgM, and IgA levels were within normal ranges. A multiple antigen simultaneous test was performed, and no significant elevation of allergen-specific IgE antibodies could be detected. Stool culture showed no parasite infection. A chest X-ray revealed increased lung marking, but no pneumonia or lung abscess was noted.

A skin biopsy of facial skin showed hyperkeratosis, parakeratosis, acanthosis, spongiosis, exocytosis, and superficial perivascular and interstitial inflammatory cell infiltrations. The infiltrate was composed of lymphocytes, histiocytes, and a few eosinophils. Based on the evidence of gram-negative bacterial infection, the phagocytotic capacity of neutrophils against gram-negative *Klebsiella pneumoniae* was studied. Twenty strains of capsular serotype K. *pneumoniae* isolated from patients allowed serotypes K1, K2, and non-K1/K2 to be included in the capsular swelling test. Impaired phagocytic capacity of neutrophils toward different serotypes of K. *pneumoniae* was demonstrated by comparison between the HIES patient and matched normal healthy subjects ($P<0.01$) (Fig. 2). The cutaneous abscesses responded to incision, drainage, and cephalexin as oral antibiotic therapy. After being treated with topical and systemic steroids, systemic antihistamines, mast cell stabilizers, and oral cephalexin as a prophylactic antibiotic, the disease activity was brought under control with gradual resolution of the eczematous dermatitis and the pyogenic skin infections, despite persistent elevation in IgE levels.

DISCUSSION

HIES is a rare primary immunodeficiency with multisystem involvement including the dentition, the skeleton, connective tissue, and the immune system. The syndrome was named Job's syndrome after the biblical prophet who suffered from boils over his whole body[2]. HIES has been reported in multiple racial groups from different countries,

but the exact incidence cannot be determined because of the rarity of the disease. HIES affects males and females equally. The genetic basis of HIES is complex. Some cases are consistent with dominant inheritance with variable penetrance, but most cases are sporadic.

HIES is characterized by recurrent cutaneous abscesses, airway infections, and an elevated serum IgE level <2000 IU/ml[1]. Skin infections are frequent and start in infancy or early childhood. They include furuncles, deep-seated cold abscesses, cellulitis, and even pyomyositis. Among them, "cold" abscesses are pathognomic to HIES. The abscesses occur most commonly on the head, neck, and intertriginous areas. Fungal infections including chronic mucocutaneous candidiasis are common. Chronic sinusitis, chronic bronchitis, and lung abscesses are common sinopulmonary findings and may result in pneumococeles. The most common pathogens are *S. aureus* and *Haemophilus influenza*, while *Streptococcus pneumoniae* and enteric gram-negative rods are found in some cases[6].

Eczematous dermatitis in patients with HIES is typically severe and begins early in childhood, often within the first few weeks of life. The rash is typically pruritic and often lichenified, and is often misdiagnosed as severe atopic dermatitis. The eczematous dermatitis in patients with HIES does not, however, present with the distribution typical of atopic dermatitis. In HIES patients, the lesions are typically behind the ears and in the axillae, groin, and umbilicus[7]. Also, in patients with atopic dermatitis, while serum IgE is often increased it is almost always <1000 IU/ml. HIES patients, on the other hand, are characterized by grossly elevated serum IgE levels of >2000 IU/ml. Common histopathologic findings in patients with HIES are eosinophilic spongiotic dermatitis, superficial and deep perivascular dermatitis with abundant eosinophils, and eosinophilic folliculitis[8]. Our patient had an extremely elevated serum IgE level, recurrent cold abscess formation, and cutaneous infection with gram-negative bacilli, in addition to eczematous dermatitis since early childhood. These features are all compatible with a diagnosis of HIES.

In1998, Borges et al. defined the distinctive facial features of patients with HIES[9]. These include a prominent forehead, deep-set eyes, a broad nasal bridge, a wide fleshy nasal tip, and mild prognathism. The patient's facial skin is rough with prominent pores[5]. Midline facial anomalies such as cleft lip and palatal abnormalities may be present, and some patients reportedly fail to shed their primary teeth[10]. Hyperextensibile joints or scoliosis have been found in as many as 68%-76% of patients with HIES[11]. With age, osteopenia and consequent pathologic fractures may occur. The osteopenia may be associated with increased bone absorption caused by activated monocytes of patients with HIES. These cells release abnormally high levels of prostaglandin E2[12]. Moreover, the cytokine profile in patients with HIES suggests that bone reabsorption may be similar to that seen in postmenopausal women[13]. Our patient had distinctive facial features, hyperextensible joints, and scoliosis, all of which are consistent with HIES. However, she did not have retention of the primary teeth, nor osteopenia, nor any pathologic fracture.

Despite rigorous work over 35 years, the pathogenesis of HIES is still unclear. Defective neutrophil chemotaxis has been described in some patients with HIES, and this was suggested to account for the high susceptibility to infection[14-17]. Additional changes in HIES patients include a deficiency of neutrophil receptors for C3b, an important chemotactic factor and a mediator of neutrophil phagocytosis[18]. Phagocytosis is considered to be the main cellular process involved in the elimination of damaged cells and microorganisms[19]. Defects in phagocytosis and the bacterial killing of S. pneumoniae by neutrophils have been reported in a Japanese man with HIES[20]. Our case revealed impaired phagocytic capacity of neutrophils against different serotypes of *K. pneumoniae*, a gram-negative bacillus. We suggest that the defects in neutrophil phagocytosis might have significantly affected our patient's susceptibility to infection by gram-negative bacteria. To our knowledge, a relationship between impaired phagocytosis of gram-negative bacteria and HIES has not been previously demonstrated.

Prophylactic antibiotics, prompt treatment of infections, and surgical drainage of abscesses constitute the most important management tools for HIES. Dermatitis requires topical therapy with potent steroids and moisturizing creams. In addition, antihistamines to control pruritus are often needed. Jeppson et al. found that interferon- γ improves neutrophil chemotaxis in HIES[21]. High-dose intravenous γ-globulin was shown to decrease IgE levels and improve severe eczema in patients with HIES[22]. In previous reports, the most common prophylactic antibiotics used for HIES patients are antistaphylococcal antibiotics (e.g., oxacillin and vancomycin). We used cephalexin, however, as this was indicated by antibiotic susceptibility testing. As a result, our patient had marked clinical improvement.

In conclusion, our experience with this patient highlights the fact that HIES should be considered in patients with chronic generalized eczema associated with nonstaphylococcal infections and impaired neutrophil phagocytosis. It is important to be aware of the distinctive features of HIES, because such knowledge aids early

diagnosis and results in improvements in the prognosis and quality of life of affected patients. Also, prophylactic antibiotic therapy should be employed.

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