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Case Reports

A Young Man with Unusually Severe Eczema Since Childhood

JSY ***KWOK***, BM ***JONES***, TL ***LEE***, YS ***YAU***, YL ***LAU***

Abstract A rare case of immunodeficient syndrome with a common presentation in childhood was presented. Clinical presentation, genetic inheritance and management of this rare syndrome are discussed and reviewed.

Key words Abscess; Cytokine; Eczema; Hyper IgE syndrome

Case Report

A 22-year-old gentleman presented with severe eczema and recurrent boils since early childhood. In, 1997, he was referred to the Department of Paediatrics and Adolescent Medicine of Queen Mary Hospital at 16 years of age. At that time, he has history of primary teeth retention requiring dental extraction and multiple skin abscesses requiring surgical drainage. He has broad nasal bridge, wide-fleshy nasal tip, ocular hypertelorism and coarse facial features (Figure 1). Diffuse eczematous skin involvement with furunculosis was noted. Multiple (more than 10) surgical scars were noted. Investigations showed markedly elevated immunoglobulin E level (peak ≥10000 IU/ml) and eosinophilia (peak = 2.6 x 10^9/l). He was diagnosed as Job's syndrome or hyperimmunoglobulin E syndrome (HIES). Other immunologic work-up showed that there was mild defect in *Candida* killing whilst phagocytic index, chemotactic response (to ZAS and FMLP) and leucocyte adhesion glycoprotein (CD11b) were normal. The nitrozolium blue test was normal. His lymphocyte subpopulation profile and lymphocyte proliferation response to mitogens were normal. The immunoglobulin G, G subclasses, A and M levels were all normal. His cytokine profile as determined by in vitro ELISPOT assay of cultured peripheral blood mononuclear cells showed raised unstimulated IL10, IL6 and TNFα. IL2, IL10 and TNFα production after polyclonal stimulation was increased, whereas IL12 production was distinctly depressed. IFNγ production was at the low end of the normal adult range. IL4 was however normal. Deficient production of IL12 and increased production of IL10 would likely be associated with impaired cell-mediated immunity. In the follow-up period, despite trial of antibiotic prophylaxis like flucloxacillin, septrin or clindamycin as well as interferon-gamma, he continued to have frequent cold skin abscesses (Figure 2) which required surgical incisions resulting in multiple scars (Figure 3). He had an episode of large cold intra-muscular abscess of the right vasta lateralis muscle, from which 350 ml pus was aspirated. One year later, he presented with a left pinna cold abscess which presented as cauliflower mass (Figure 4). Methicillin sensitive *Staphylococcus aureus* (MSSA) was obtained from the abscesses. No skeletal abnormality has been detected so far.

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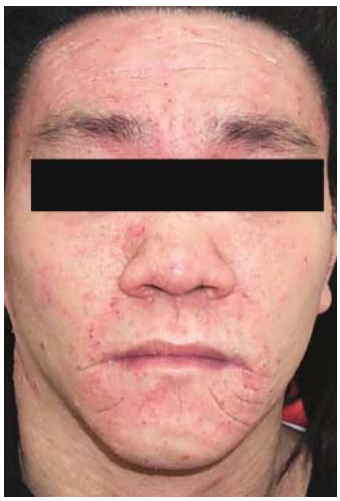

Figure 1 Facial features of a young man with hyper-IgE syndrome.

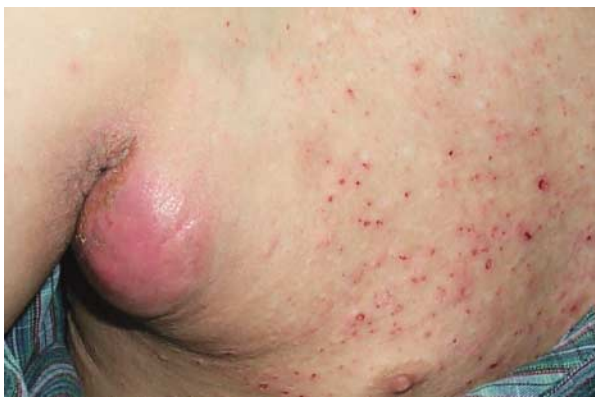

Figure 2 An episode of right axillary cold abscess with diffuse folliculitis requiring surgical intervention.

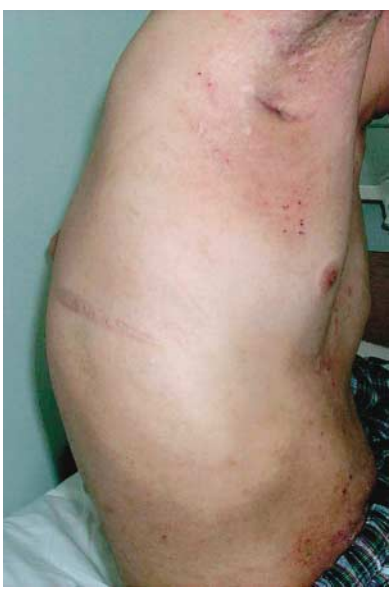

Figure 3 Multiple surgical scars after incisions for recurrent skin abscesses.

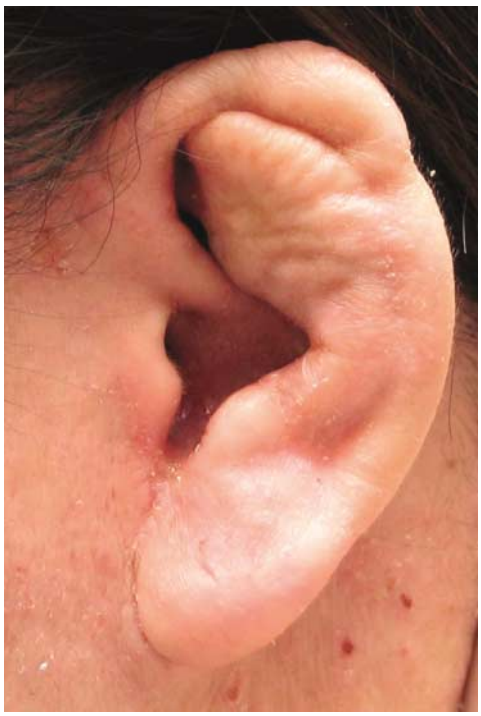

Figure 4 Left pinna cold abscess which presented as cauliflower mass.

Discussion

Hyper IgE Syndrome

HIES is a multisystem disorder characterised by recurrent bacterial skin abscesses and sinopulmonary tract infections since infancy or early childhood and later pneumonia with pneumatocele formation and extreme elevation of serum IgE levels that are ≥10 times the normal value (i.e. >2000 IU/mL).[1] Reports of more than 200 cases have been published.[1-3] Studies have focused on the immune system; they detected eosinophilia in blood, sputum, and abscesses;[1-3] defective granulocyte chemotaxis;[4-7] abnormalities in T-lymphocyte subgroups;[2,8] defective antibody production;[9-11] and decreased production of or responsiveness to cytokines such as interleukin-4 and interferon-γ.[12,13] However, no specific defect in the immune system has been found in all patients.

Genetic Basis

Although the genetic basis is not known and the central immunologic defect is largely undefined, a genetic linkage was detected between Hyper-IgE and chromosome 4q. Most cases are sporadic. It can be transmitted as an autosomal dominant trait with variable expression.[14] Variants of autosomal recessive inheritance were recently reported in

13 patients from six consanguineous families.[3,15] The presenting case is likely to be hyper-IgE syndrome, which in nonfamilial cases is diagnosed on the basis of skin abscesses, pneumonia with formation of pneumatoceles, and recurrent eczematoid rashes, as well as extreme elevations in serum IgE levels.

Immunologic Features and Infections

Eczema, abscesses, candidiasis, pneumonia, eosinophilia, and elevated serum levels of IgE were the most common manifestations of immune dysfunction in patients with the hyper-IgE syndrome. Moderate-to-severe eczematoid rashes were universal in early life, but boils and pneumonia occurred less frequently in youth, particularly in children maintained on antibiotic prophylaxis. As is characteristic of hyper-IgE syndrome,[16] pneumonia led to the formation of pneumatoceles in 77 percent of the patients.

Acute pneumonia was caused most frequently by *Staphylococcus aureus* or *Haemophilus influenzae*; in contrast, superinfections of pneumatoceles were associated with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. Fifteen patients required thoracotomy for removal or drainage of infected pneumatoceles.

Other systemic infections could be recurrent bacterial arthritis and staphylococcal osteomyelitis at fracture sites.

Chronic candidiasis of mucosal sites and nail beds affected 83 percent of the patients with the hyper-IgE syndrome, including children who had not yet had pneumonia or skin abscesses. Some patients had median rhomboid glossitis, which is a chronic form of candidiasis,[17] and two had *Pneumocystis carinii* pneumonia. Tissue-invasive fungal infections also occurred. Patient might have a pulmonary cyst chronically colonized with aspergillus and die of a mycotic (*A. fumigatus*) aneurysm of the brain or have osteomyelitis of the femoral neck caused by yeast; or have lymphatic and visceral candidiasis; or even have invasive esophageal *Cryptococcus neoformans* infection.[17]

Cytokine Dysfunction

It has been hypothesized that hyper-IgE is associated with a Th1/Th2 imbalance. In a study by Netea et al, severe imbalance towards a Th2 phenotype was found, with 10- to 30-fold reduction in the IFNgamma/IL-10 ratios in the hyper-IgE syndrome patients.[18] It was supported by the article by Borges et al showed that the lymphocytes of 10 patients with hyper-IgE syndrome have an impaired response to IL-12, resulting in decreased IFN-γ production.[19] The study by Chehimi et al found that nine patients with hyper-IgE syndrome express more IL-12.[20] Paganelli et al[21] have also reported in vitro deficiency of IFN-γ production; indeed, IFN-γ has been used therapeutically in a few patients with hyper-IgE syndrome with suggestive clinical benefit.[22] These reported observations must be tempered by the fact that the in vitro defects, although statistically significant, were not striking or correlated with clinical severity or levels of IgE. Further, Vercelli et al[11] found that IgE synthesis by B lymphocytes of patients with hyper-IgE syndrome was relatively insensitive to suppression by IL-4 or IFN-γ which was supported by Rodriguez et al.[23] Garraud et al,[24] however, were able to suppress IgE synthesis with a monoclonal antibody to the IL-4 receptor in these patients. These finding seems to be present in the patient reported except the normal IL-4 level. Despite these caveats, the cytokine defects observed in hyper-IgE syndrome may provide a clue both to its pathogenesis and rational treatment. Further therapeutic studies with IFN-γ and other regulatory cytokines are indicated.

Clinical Phenotype

The phenotypic abnormalities are multisystemic, including dental, facial, skeletal structures and immunologic defects. The major facial and dental clinical features include: deep-set eyes, coarse facies, prominent forehead (frontal bossing), broad nasal bridge, wide and fleshy nasal tip, mild prognathism, ocular hypertelorism, primary teeth retention, double rows of teeth (primary and permanent). Common skeletal features are scoliosis, bone fragility and hyper-extensible joints. The immunologic defects include chemotactic defects, CD8-cell dysfunction, abnormal delayed hypersensitivity, and abnormal antibody production, but no single abnormality seems to occur in all patients with the syndrome. Recently, the hypothesis that cytokine dysregulation results in the predominance of type II cytokine response has gained support from several studies.[3]

Treatment

Infectious complications of HIES start early in life. Upper respiratory infections are common; *Staphylococcus* is the most frequently infecting organism. There is wide spectrum of other bacterial infections with mainly encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Fungal infections including

oral moniliasis are common. *Aspergillus* and *cryptococcal* infection have also been reported.[14] Severe eczema is quite common, as are skin infections, including furunculosis, cold abscesses, cellulitis, and superficial mycotic infections. Prolonged antibiotic therapy combined with thorough and early drainage are usually necessary to eradicate abscesses. More studies are needed to determine the role of antibiotic prophylaxis, intravenous immunoglobulin, interferon-γ and interferon-α.

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