

The hyperimmunoglobulin E syndrome

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Hyperimmunoglobulin E syndrome is a primary immunodeficiency disease characterized by markedly high titers of serum immunoglobulin E (IgE), chronic eczema, recurrent staphylococcal infections, pneumatoceles, reduced neutrophil chemotaxis, and variable impaired T cell function. There are no clinical tools for diagnosis and definitive laboratory investigation. Variability of presentation makes it easy to confuse the diagnosis with that of severe atopy or other rare immunodeficiencies. We report a case of a 6-year-old boy with hyperimmunoglobulin E syndrome with recurrent methicillin-resistant *Staphylococcus aureus* furunculosis. Physical examination revealed a peculiar facial appearance, pruritic dermatitis, and furunculosis over the scalp, neck, and back. Laboratory investigation revealed mild leukocytosis with eosinophilia, a very high immunoglobulin E level, defective neutrophil chemotaxis, and impaired lymphocyte proliferation to anti-CD3/CD28 monoclonal antibodies. The boy was discharged without incident after 2 weeks of antibiotic therapy and debridement.

Key words: Furunculosis, hyper-IgE syndrome, methicillin resistance, *Staphylococcus aureus*

Hyperimmunoglobulin E (hyper-IgE) syndrome is a rare idiopathic primary immunodeficiency [1]. It consists of pruritic dermatitis with recurrent staphylococcal abscess formation, respiratory tract infection, eosinophilia and very high titers of serum immunoglobulin E (IgE). A coarse facial appearance, hyperextensibility of the joints, bone fractures, craniosynostosis, delayed shedding of the primary teeth, neutrophil chemotactic dysfunction, and mucocutaneous or systemic fungal disease are variable features which have been reported [2-7]. There are no clinical tools for diagnosis and definitive laboratory investigation. Therefore, the marked variability of symptoms and signs makes it easy to confuse the diagnosis with that of severe atopy or other rare immunodeficiencies [8,9]. We report here a case of a 6-year-old boy with hyper-IgE syndrome with recurrent staphylococcal furunculosis.

Case Report

A 6-year-old boy was admitted to the infectious ward because of a large carbuncle on the occipital scalp and multiple furuncles over the scalp, neck and back. In addition, cellulitis of the right upper eyelid was noted. He had been under common oral antibiotics prescribed

by local clinics for approximately 1 month, but without improvement. There was no fever during the period before admission.

Reviewing his past medical history, he began suffering from similar problems from the age of 2 years. He was admitted to Tri-Service General Hospital twice at 2 years, and once at 4 years old. He was admitted to Wan-Fang Hospital once and National Taiwan University Hospital once at 3 years old. All hospital visits were related to the recurrent carbuncle, cellulitis and lymphadenitis, mainly over the scalp, face, neck, and back. The results of cultures in previous hospitalizations all tested positive for methicillin-resistant *Staphylococcus aureus* (MRSA). After adequate antibiotic treatment and debridement, he was discharged without incident and without significant sequelae.

The patient's birth history did not reveal any significant events, and development milestones were within normal limits. He did not have any other medical diseases, including allergic respiratory diseases, such as bronchial asthma or allergic rhinitis. His parents and 3 elder sisters did not show any evidence of a similar condition.

Physical examination upon admission revealed a coarse facial appearance (Fig. 1). In addition to many old scars and granulation tissue, there were numerous furuncles and "cold" abscesses on his scalp, bilateral external ear canals, face, neck, and back. Pruritic

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Fig. 1. A coarse facial appearance, a broad nasal bridge, facial asymmetry, and hemihypertrophy in a boy with hyperimmunoglobulin E syndrome.

dermatitis was also noted in a distribution atypical for true atopic dermatitis. Laboratory data collected upon admission included mild leukocytosis ($12720/\mu\text{L}$) with eosinophilia (12%) and an elevated C-reactive protein level (2.86 mg/dL). The results of the pus culture and nasal and throat swabs all revealed MRSA. Intravenous vancomycin was subsequently administered.

Because of recurrent MRSA furunculosis throughout his medical history, a series of immunologic investigations was performed in order to rule out the possibility of immunodeficiency. The serum levels of IgG (993 mg/dL), IgA (121 mg/dL), and IgM (111 mg/dL) were within normal limits for his age, but a markedly high titer of IgE (5600 IU/mL) was found. Lymphocyte subsets produced the following: T cells 79%, B cells 16%, NK cells 5%, CD3/CD8+ 37%, CD4+ 35%, naïve cells 22%, and memory cells 13%. Lymphocyte responses to mitogens, phytohemagglutinin (PHA), concanavalin A (ConA) and pokeweed mitogen (PWM), were normal compared to the control. However, lymphocyte proliferation to anti-CD3/CD28 monoclonal antibodies was impaired [stimulation index, 2.5 (patient) vs 111.5 (control)]. As for the neutrophil function assays, the chemiluminescence test and nitroblue tetrazolium test both revealed normal results. The chemotaxis study, using a Boyden chamber assay, showed impaired chemotactic function. In view of the clinical picture and

laboratory findings, the patient was diagnosed with hyper-IgE syndrome.

The boy was discharged without incident after 2 weeks of antibiotic therapy and debridement.

Discussion

Hyper-IgE syndrome is a multisystem disorder that affects the dentition, the skeleton, connective tissue and the immune system [2]. Before detailed immunologic and broad clinical characteristics of the syndrome were appreciated, Davis et al in 1966 assigned the term “Job’s syndrome” to this disease, in reference to the Biblical character whose body was stricken with boils [10].

There is marked variation in the constellation of symptoms and signs that constitute the diagnosis. Because there are no useful criteria for diagnosis and no definitive laboratory tools for investigation, clinical diagnosis of hyper-IgE syndrome has relied primarily on the following characteristics: elevated serum IgE levels; eczematoid rashes; and unusual, severe, recurrent infections such as skin abscesses, candidiasis, and pneumatocele-forming pneumonias, in the absence of any other underlying defect in the immune system [2]. Our patient was also diagnosed in this manner.

The clinical and laboratory hallmarks of hyper-IgE syndrome often become apparent in infancy, but the diagnosis may not be made until childhood or adulthood. In addition to the common observation of coarse facial features, chronic dermatitis, mucocutaneous fungal infection, skin infection of the head and neck regions, and peripheral blood eosinophilia (absolute eosinophil count $>700/\mu\text{L}$) are the common initial presentations. Skin manifestations include staphylococcal furuncles, cold abscesses, and cellulitis. Among them, cold abscesses are occasionally seen and are pathognomic to hyper-IgE syndrome, but not essential to the diagnosis. Cold abscesses are neither hot nor tender, and they are not associated with systemic symptoms, fever, or other signs of local or generalized inflammation. Our patient suffered from recurrent MRSA superficial infection compatible with the features of hyper-IgE syndrome.

Possible findings in later childhood and adulthood include recurrent staphylococcal pneumonia with the formation of persistent pneumatoceles; chronic and recurrent sinus, ear, and eye infection; and occasional septic arthritis and osteomyelitis. With age, osteopenia and consequent pathologic fractures may occur, leading to further debilitation [11]. It has been suggested that staphylococcal pneumonias with pneumatocele

formation are essential for diagnosis, but they are not always present in otherwise typical presentations [2]. Our patient did not develop any episode of pneumonia, probably due to his younger age or the different presentation.

The immunologic features of hyper-IgE syndrome are variable despite primary immunodeficiency. They include markedly elevated IgE levels; positive immediate wheal-and-flare responses to a variety of food, inhalant, bacterial, and fungal antigens; marked eosinophilia; impaired anamnestic (IgG) antibody responses and poor responses to neoantigen; variably depressed cell-mediated immunity with normal responses to mitogens; highly variable chemotactic abnormalities; and abnormal intrafamilial mixed leukocyte responses [12]. Our patient showed a markedly elevated IgE level, marked eosinophilia, defective neutrophil chemotaxis and impaired lymphocyte proliferation to anti-CD3/CD28 monoclonal antibodies.

The mainstay of therapy is prophylactic antibiotic therapy, primarily to prevent staphylococcal infection. During episodes of disseminated or invasive bacterial or fungal infection, aggressive parenteral antibiotics and supportive care measures are mandatory. Other therapies reported to be effective, but not prospectively studied, include high-dose intravenous gamma-globulin, cyclosporin A, and interferon [13-16]. Topical antibiotic preparations and good skin care measures may also be beneficial.

In conclusion, hyper-IgE syndrome is a rare primary immunodeficiency of unknown etiology affecting multiple systems. It has variable features, and there is no single laboratory or clinical tool for investigation that can secure diagnosis. A clinician, especially a pediatrician, dealing with a patient with a peculiar appearance and recurrent infection, should keep in mind the possibility of the disorder. Treatment is supportive, and prophylactic skin care and antibiotics are the most helpful interventions. Recent advances in the understanding of the genetics and immunology of this condition may elucidate the responsible gene, genes or chromosomal deletion responsible for this condition. This in turn will provide new hope for treatment strategies for the long term.

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