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CASE REPORT

Role of Omalizumab in a Patient with Hyper-IgE Syndrome and Review Dermatologic Manifestations

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SUMMARY Hyper-IgE syndrome (HIES) is a rare idiopathic primary immunodeficiency. It is characterized by a triad of findings, including high levels of serum IgE, recurrent skin abscesses and pneumonia and leads to pneumatocele formation. The diagnosis of HIES is complicated by a diversity of clinical and immunological spectrums and a heterogeneous set of genetic defects. The National Institute of Health (NIH) developed a scoring system for HIES in which a score greater than 14 indicates a probable diagnosis. Our patient presented with recurrent multiple abscesses on her scalp, recalcitrant eczema, candida onychomycosis, alopecia universalis, and highly elevated levels of serum IgE. Using the NIH scoring system, a 30 total-point score in this patient indicated the likelihood of carrying the HIES genotype. To our knowledge, there are no specific treatments of HIES. The humanized recombinant monoclonal antibody against IgE, subcutaneous omalizumab, was successfully used in this patient.

Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency (prevalence < 1:1 million), most commonly characterized by a triad of findings, including increased serum IgE levels, recurrent skin abscesses and recurrent pneumonia, leading to pneumatocele formation. Most patients with HIES are sporadic, but some cases are inherited with autosomal dominant (AD) with variable expressivity. Skeletal and dental abnormality, such as retained primary teeth, high palate, scoliosis, fracture with minor trauma, hyperextensibility of joints, and characteristic face, are found in sporadic cases and familial cases with AD form. Recently, an autosomal recessive (AR) variant, which is characterized by no apparent abnormalities in the skeletal and dental system but induces suffering from recurrent severe infection, has been described. As a result of the heterogeneity of the clinical phenotype and polymorphic markers in the chromosome, a definite diagnosis of HIES is complicated and difficult. A scoring system for diagnosis of HIES was developed by the National Institute of Health (NIH). The index of clinical suspicions is consistent with the total-point score assessment as follows: at $\geq$ 15 points, the patient is likely to carry the HIES genotype; at 10-14 points, HIES genotype is indeterminate; and at < 10 points, the patient is unlikely to have an HIES genotype.[1]

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The purpose of this article is to report a case of HIES with omalizumab usage, noting dermatologic manifestations as a clinical clue for diagnosis.

CASE REPORT

A 32 year-old Thai woman, who was born of non-consanguineous parentage, came to our Dermatology Department due to pruritic skin lesions on her face, upper back and extremities. The symptoms had persisted for 2 years. She also had a past history of recurrent multiple abscesses on her scalp; originally occurring at the age of 8 years, each time subsided with systemic antibiotics. At the age of 19 years, she developed alopecia universalis. She had no history of atopic diseases, lung diseases, or dental or skeletal abnormalities. Physical examination revealed alopecia universalis, multiple discrete and confluent erythematous papules and plaques on the trunk, back, and all extremities. All fingernails and toenails showed onychodystrophy. Other systems were unremarkable; with normal dentition, no scoliosis, and normal facial physiognomy. Laboratory findings were as follows: hemoglobin (Hb), 15.1 g/dl, hematocrit (Hct), 45%, WBC 12,300 cells/µl (neutrophils, 37%; lymphocytes, 44.2%; monocytes, 6.2%; eosinophils, 12% (absolute eosinophils, 1,476 cells/µl) and platelets, 293,000/µl. Stool examination for parasites was negative. Nail clippings were collected for KOH examination and cultures, which revealed *Candida* spp. The skin biopsy, obtained from a skin lesion on her back, showed superficial perivascular and interstitial infiltration with lymphocytes and eosinophils. Due to the erythematous pruritic skin lesions and hypereosinophilia, our first diagnosis was hypereosinophilic syndrome. Thus, we consulted a hematologist to evaluate hypereosinophilic syndrome in this patient. The bone marrow biopsy and whole abdomen CT showed normal findings. After the 5-month follow-up, she continued developing pruritic skin lesions intermittently as well as persistent hypereosinophilia. Evaluating further, the recalcitrant eczema, hypereosinophilia and candida onychomycosis of multiple fingernails, indicated another differential diagnosis of HIES. She was referred to an immunologist for evaluation of HIES. The immunologic study demonstrated highly elevated of serum total IgE, 17,300 IU/ml (normal, < 100); IgG, 1,350 mg/dl (normal, 548-1,768); IgM, 133 mg/dl (normal, 45-153) and IgA, 370 IU/ml (normal, 78-322). Her cellular immunity was evaluated and showed CD_4 T-cells, 1,301 cells/µl (normal, 470-1,404); CD_8 T-cells, 2,342 cells/µl (normal, 360-1250) and NK cells, 393 cells/µl (normal, 100-770). T-cell functions including responsiveness to tuberculin, tetanus toxoid, streptase, and candida were normal. Chest radiography was also done to exclude pneumatocele formation and revealed normal findings. The NIH scoring system was used to diagnose HIES, and revealed a total point-score of 30 (10 points for serum IgE > 2,000 IU/ml, 6 points for eosinophil counts [> 800 cells/µl], 4 points for severe eczema, 2 points for candidiasis of fingernails and 8 points for recurrent multiple skin abscesses). Therefore, this patient is likely to carry the HIES genotype according to the NIH scoring system.

Management of HIES is crucial in treatment and prevention of infection. At first, potent topical steroid and topical tacrolimus were used to control her skin disease but she did not respond well. Fortunately, she did not have any evidence of pneumonia or any other systemic infections. Therefore, systemic corticosteroids were started at 30 mg/day for controlling her pruritic skin lesions. Her skin symptoms responded well with systemic corticosteroids and hypereosinophilia was partially regressed. However, systemic corticosteroids could not be stopped because of occasional flare up in her skin symptoms and lesions when decreasing the dosage.

Recently, a recombinant monoclonal antibody against IgE (omalizumab) has been studied in several clinical trials of moderate to severe persistent allergic asthma. Within the Pubmed Database, there was one case report of HIES that had clinical improvement with omalizumab. Thus, we decided to use omalizumab subcutaneously every 2 weeks at a dose of 300 mg. One month after initiating omalizumab treatment, her eczematous lesions were markedly improved. Systemic corticosteroids was gradually decreased and then discontinued.

DISCUSSION

Hyper-IgE syndrome (HIES) is a rare multisystem primary phagocytic disorder that affects the dentition, skeleton, connective tissue and immune system. Inherited patterns with AD, AR have been reported, but most HIES cases are sporadic. Muta-

tions in the signal transducer and activator of transcription-3 gene (STAT3) on chromosome 17q21 is a major cause of AD and sporadic HIES whereas a null mutation in tyrosine kinase 2 underlies the AR forms.[2-3] STAT3 regulates multiple cytokines that are critical to differentiation of T_H17 cells, which are important in inflammatory response to bacterial and fungal pathogens.[2] Additionally, the functions of tyrosine kinase 2 are involved in innate and adaptive human immunity.[3] Al Khatib et al. reported that both STAT3 mutation-positive and STAT3 mutation-negative HIES exhibited a profound deficit in T_H17 differentiation.[2] Therefore, defective T_H17 responses are a common attribute of HIES cases with different genetic forms and sporadic cases.[2] Our patient did not have severe viral infections or severe neurological complications which usually tend to develop in the AR variant. Her family also does not have any history of HIES. Thus, our patient may be a sporadic case.

Several of the symptoms of HIES are also features of related conditions, such as atopic dermatitis or Wiskott-Aldrich syndrome, which lead to difficulty in the diagnosis of HIES, especially in young patients with atypical, less severe cases (HIES-variants). In our patient, her dermatological findings led us to suspect HIES because hypereosinophilic syndrome and adult onset-atopic dermatitis are not related to alopecia universalis or multiple fingernail candidiasis. Therefore, further investigations for HIES were done and the diagnosis was made by the NIH scoring system. Many clinical and laboratory findings in this patient met the criteria of the NIH scoring system.

Clinical features of HIES can be classified into two categories, immunologic type and nonimmunologic type. Dermatologic manifestations, lung disease, highest serum IgE level, eosinophilia and increased incidence of lymphoma are immunologic findings. Breakdown of dermatologic manifestations indicate eczema, skin abscesses, mucocutaneous candidiasis and newborn rash are found in 100%, 87%, 83% and 81% of cases, respectively.[4-6] Results from our review show other dermatologic manifestations which have been reported are alopecia areata,[6] alopecia totalis,[7] alopecia universalis,[7] red hair,[8] urticaria,[8] erythema nodosum,[9] keloid formation,[9] cutaneous vasculitis,[10] retroauricular fissure,[11] infected dermatitis of axillae and groin,[11] pitted scarring of the face,[11] extensive xanthelasma,[12] bullous pemphigoid,[13] and gingival hyperplasia.[14] Our patient also had alopecia universalis at 19 years of age. The infected skin organisms, other than mucocutaneous candidiasis and *Staphylococcal aureus* abscesses, that have been reported, are severe herpes simplex infection,[4] recurrent varicella-zoster infections,[9-10] chronic refractory molluscum contagiosum,[9] disseminated plane warts,[9] and vulvar wart.[15] Non-immunological features of HIES have been reviewed. Characteristic face, failure or delay of shedding of primary teeth, scoliosis, joint hyperextensibility, and recurrent bone fractures occurred in 80%, 72%, 70%, 68% and 57% of the patients, respectively.[5]

Intensive care of skin lesions, prompt antibiotic and antimycotic treatment for infections, and surgical drainage of abscesses are the mainstay of HIES management. Immunoglobulin supplement agent, IFN-gamma, cyclosporine A have been reported as beneficial in a limited number of patients but they are not generally indicated for HIES.[1,16] Bone marrow transplantation has been performed but it is unlikely to be the correct method.[4]

Omalizumab, the humanized recombinant monoclonal antibody against IgE, is known to result in marked reduction in serum free IgE and down-regulation of IgE receptors on circulating basophils. Thus, it limits the release of mediators of the allergic response. Omalizumab is approved by the U.S. Food and Drug Administration for the treatment of moderate to severe persistent asthma in adults and adolescents older than 12 years of age who have a positive skin test to a perennial allergen.[17] However, it has also shown to have benefit in the treatment of allergic rhinitis, occupational latex allergy, atopic dermatitis, chronic urticaria and severe peanut allergy with recurrent anaphylaxis.[18] Several studies reported clinical improvement in patients with severe atopic eczema with high serum IgE level.[19] The immune mechanism of omalizumab demonstrated by an increase in eosinophil apoptosis and decrease in granulocyte macrophage colony stimulating factor, IL-2 and IL-13. IL-2 influences eosinophil activity.[20] Omalizumab also decreased mRNA ratio for IgE/IgG and might be a promising marker to identify patients responding to its treatment.[19] Bard *et al.*[7]

used it firstly to treat severe recalcitrant eczematous dermatitis in the setting of HIES and reported successful treatment. Due to high serum IgE level, recalcitrant eczema and prolonged usage of systemic corticosteroids, omalizumab was tried in our patient and also exhibited benefit for her skin lesions. However, prospective studies and long term follow-up are required to confirm the efficacy of omalizumab in HIES. Additionally, the drugs that target JAK-STAT cascade or T_H17 differentiation may be a potential successfully treatment in HIES cases in the future.

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