

Cutaneous Manifestations of Hyper IgE Syndrome

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ABSTRACT

Hyper-IgE syndrome (HIES) is a primary immunodeficiency disorder characterized by atopic manifestations and susceptibility to infections with extracellular bacteria and fungi. Atopic manifestations include atopic dermatitis-like skin lesion and extremely high serum IgE levels. Most of the extracellular bacterial infections are caused by *Staphylococcus aureus*, which is associated with milder inflammation compared to normal. Recent studies have revealed that the most cases of the HIES are caused by dominant negative mutations in *STAT3* gene. Cutaneous manifestations of HIES includes newborn rash, eczematoid dermatitis, cold abscesses, mucocutaneous candidiasis, and coarse texture of the facial skin. Impaired Th17 cell development due to the defective IL-6 signaling in T cells and impaired induced regulatory T (iTreg) cell generation due to defective IL-10 signaling in dendritic cells may, at least in part, account for the cutaneous pathology of HIES.

KEY WORDS

atopic dermatitis, cold abscess, newborn rash, *Staphylococcus aureus*, *STAT3*

INTRODUCTION

Hyper IgE syndrome (also called Job's syndrome; #147060 and #243700 in OMIM) is a complex primary immunodeficiency, characterized by atopic dermatitis-like skin lesion associated with extremely high serum IgE levels and susceptibility to infections with extracellular bacteria and fungi.^{1,2} Non-immunological abnormalities, including a distinctive facial appearance, fracture with minor trauma, scoliosis, hyper-extensive joints, and the retention of primary teeth are also observed in most of the patients. The original description of this syndrome was made in 1966, in which the two patients had recurrent staphylococcal skin infections that lacked the typical features of inflammation including warmth, redness, and tenderness, therefore Davis and Wedgwood coined the name "cold abscesses" for the unusual skin manifestations.³ The syndrome was further investigated by Buckley and her colleagues, who identified that the recurrent staphylococcal skin infections and cold-abscess formation in HIES were associated with severe dermatitis and highly elevated serum IgE levels.⁴ Later study established the multisystem na-

ture of HIES, in which the clinical manifestations are not restricted to the immune system, but extend to skeletal and connective tissue abnormalities.⁵ In 2006, we identified that a variant form of HIES, autosomal-recessive HIES, is caused by the homozygous null mutation in tyrosine kinase 2 (*TYK2*) gene.^{6,7} Based on this finding, we identified that the most of the patients of HIES have dominant negative mutations in *STAT3*, responsible for the clinical manifestations of HIES.⁸⁻¹⁰ We now know HIES is caused by "loss-of-function" mutations in *STAT3*, but we have very limited knowledge of the molecular pathogenesis of HIES. In this article we will focus on the HIES due to the dominant negative mutations in *STAT3*.

CLINICAL FEATURES OF HIES

The patients with HIES present extremely high serum IgE levels, atopic dermatitis-like skin lesion, and recurrent bacterial and fungal infections.^{11,12} The levels of IgE in the serum are very high, which are often more than one hundred times higher than normal individuals. The atopic dermatitis-like skin lesion usually starts in the neonatal period as a newborn rash and extracellular bacterial infections generally com-

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mence in infancy or early childhood.¹³ The most common bacteria involved are *Staphylococcus aureus*, but *Streptococcus pneumoniae*, *Haemophilus influenza* and enteric gram-negative bacteria are also isolated in infectious episodes of this syndrome.

In our series, most cases of HIES are sporadic, but some familial cases of HIES have been reported, either with autosomal dominant (AD)⁵ or autosomal recessive (AR)¹⁴ mode of inheritance. Skeletal and dental abnormalities, such as characteristic facial appearance, hyper-extensibility of joints, scoliosis, fracture with minor trauma, and retained primary teeth, are observed in sporadic and AD form, but not in the AR form. Usually by the age of 16 years, almost all of the patients show distinctive facial appearance; coarse texture of facial skin, asymmetric facial appearance, prominent forehead, deep-set eyes, broad nasal bridge, and bulky nasal tip. In this type of HIES, pneumonia is frequently followed by the formation of pneumatoceles, most likely due to the impaired remodeling capability of lung tissue. The AR form is characterized by severe recurrent viral infections, extreme eosinophilia, and neurological complications.¹⁴ HIES patients with AR-inheritance suffered from severe viral infections such as chronic refractory molluscum contagiosum and herpes simplex virus infections, which were not observed in AD form. A recent study identified that HIES patients have decreased number of central memory CD4⁺ and CD8⁺ T cells and impaired ability to control varicella zoster virus and Epstein-Barr virus latency compared to healthy individuals.¹⁵ Interestingly, no pneumatoceles were found in this form of HIES unlike in the AD type HIES patients, even though the incidence of pneumonia was equivalent in both types.

Clinical diagnosis of HIES is based on the criteria established by Grimbacher *et al.*, which scores clinical findings such as the number of skin abscesses (more than 4 times in a lifetime is 8 points) and pneumonia (more than 3 episodes in a lifetime is 8 points), parenchymal lung abnormalities (pneumatocele is 8 points), characteristic facial appearance (if typical, 5 points), newborn rash (if present, 4 points), hyper-extensibility (if present, 4 points) as well as laboratory findings such as high serum IgE concentrations (>2000 IU/ml; 10 points) and eosinophilia (>800/mm³; 6 points).¹⁶ We clinically diagnose HIES if the score of the patient is above 40 points, which is confirmed by molecular analysis.

CUTANEOUS MANIFESTATIONS

NEWBORN RASH

Most of HIES patients had a history of a newborn rash,¹³ which usually begins in the first month of life. Many of the patients were first diagnosed as neonatal acne. The papules and pustules often began on the face and scalp, then unlike neonatal acne, progressed to entire upper body. In many cases, the rash had a

protracted course that developed into eczema, while in some there was improvement or resolution following treatment with oral antibiotics or topical corticosteroid. The histologic evaluation shows an eosinophilic spongiotic dermatitis, eosinophilic folliculitis, and superficial and deep perivascular dermatitis with abundant eosinophils.¹⁷

The differential diagnosis of the newborn rash includes eosinophilic pustular folliculitis, erythema toxicum neonatorum, and neonatal cephalic pustulosis. The distribution, appearance, and histologic characteristics of the newborn rash in HIES are similar to those of eosinophilic pustular folliculitis. The age of onset is usually older in eosinophilic pustular folliculitis, with most cases occurring between ages 5 and 10 months rather than in the first month.¹⁸ Furthermore, eosinophilic pustular folliculitis of infancy does not improve with antibiotic treatment but does improve with topical steroid treatment.¹⁹ In contrast, newborn rash of HIES frequently responds to antibiotic treatment. Erythema toxicum neonatorum can be similar to newborn rash of HIES in appearance, age of onset, distribution, and histologic characteristics. It usually presents on the first or second day of life and resolves within 5 days. Milder recurrences may occur within 5 to 10 days after the original eruption.²⁰ Similar to newborn rash of HIES, erythema toxicum neonatorum can be seen at birth. However, the newborn rash of HIES is more severe and prolonged. Neonatal cephalic pustulosis is synonymous with neonatal acne.²¹

ATOPIC DERMATITIS-LIKE SKIN LESION

Atopic dermatitis affects approximately 15% of children in Westernized countries including Japan, which is characterized by eczematoid skin lesions, dry skin, and pruritus.^{22,23} Atopic dermatitis is a multifactorial and heterogeneous disorder caused by the interaction of environmental and genetic components. Entire molecular pathogenesis of atopic dermatitis remains unknown, but recent studies indicate that a defective skin barrier function is one of the mechanisms of this disorder. A loss-of-function mutation in the gene encoding filaggrin is identified as an important risk factor/molecular cause for atopic dermatitis.^{24,25} Filaggrin protein is located in the granular layers of the epidermis. In the differentiation of keratinocytes, the protein is dephosphorylated and cleaved into 10 to 12 almost identical 27 kDa filaggrin molecules, which aggregate in the keratin cytoskeleton to form a dense protein-lipid matrix. This structure prevents epidermal water loss and blocks the entry of innocuous allergens and infectious microorganisms.

There are some different descriptions of skin manifestations of HIES. Davis *et al.* referred as "infected eczematoid skin lesions."³ Buckley *et al.* mentioned as "a generalized dermatitis that was similar to, but atypical for atopic dermatitis."⁴ Erlewyn-Lajeunesse

also noted that the distribution of the rash in HIES was atypical for atopic dermatitis.²⁶ Anyhow, all the previous studies equivalently claim almost all the HIES patients have eczematoid, i.e. atopic dermatitis-like skin manifestations.

Skin manifestations of HIES and atopic dermatitis both are associated with eosinophilia and high serum IgE levels. The rash in HIES is typically papular and pruritic. Lichenification is frequently observed, in which epidermis becomes hypertrophied resulting in thickening of the skin and exaggeration of the skin markings. The rash observed in HIES is very similar to atopic dermatitis clinically and histopathologically, but the distribution of the rash is reportedly slightly different. The atopic dermatitis typically involves the flexural surfaces of the body. The skin involvement in HIES is located in their face and extensor surfaces. However, the location of atopic dermatitis changes with age, thus it is not clear the previously reported difference is associated with an essential difference between the two. Atopic dermatitis is also often associated with a history of other allergic disorders such as food allergy, asthma, and allergic rhinitis, which is lacking in HIES. Staphylococcal infections in atopic dermatitis is usually superficial whereas HIES patients develop deep-seated abscesses. Mucocutaneous candidiasis is also a frequent complications of HIES, but not in atopic dermatitis. Skin lesions of atopic dermatitis usually has its onset after two to four months of age, whereas HIES have symptoms before one month of age.²⁷

Skin abnormalities in HIES are not confined to atopic dermatitis-like skin lesion, but the dermatitis is invariably colonized with *Staphylococcus aureus* and becomes infected, thus leading to the condition for more severe dermatitis. These acute episodes can be cured, but recurrences are not rare if patients fail to take prophylactic antibiotics such as trimethoprim-sulfamethoxazole. Coarse texture of the facial skin in HIES patients is frequently observed. Older subjects with HIES, despite having no history of severe acne, show distinctive thick and doughy texture of the facial skin. This might be related to the impaired remodeling in facial skin, but exact nature of this cutaneous manifestation remains to be elucidated.

COLD ABSCESSSES

Cold abscesses are a part of the original clinical description defining triad of HIES. An originally-reported patient had 6 cm × 10 cm mass in the anterior neck, but was afebrile. The mass was only slightly tender but not warm. A surgeon thought that it was an enlarged but not infected thyroglossal duct cyst, but it turned out to contain 200 ml of pus. Cold abscess is defined as an abscess with little or no evidence of inflammatory response, which can present in any part of the body, fluctuant, non-tender, and non-erythematous masses that may be mistaken for

cysts or benign tumors. The abscess may be large and the infectious agent is almost always *Staphylococcus aureus*. Recently, the incidence of cold abscesses was significantly decreased probably due to early administration of antibiotics against any signs of infections and prophylactic anti-staphylococcal antibiotics to the HIES patients.

Acute-phase responses, such as increased serum C-reactive protein levels during infections, were diminished in the HIES patients. STAT3 was originally identified as a protein binding to the IL-6 responsive element in the genes encoding hepatic acute phase proteins.²⁸ Thus, the apparent lack of classical inflammatory responses in HIES patients could be attributed to defective signaling of IL-6, but exact molecular mechanism remains unknown.

MUCOCUTANEOUS CANDIDIASIS

Approximate 60% of the HIES patients present with chronic mucocutaneous candidiasis.²⁹ Oral candidiasis starts very early in life and chronic paronychia of several fingers was found in about half of the patients. This symptom is effectively managed with a combination of oral and topical anti-fungal agents.

Recent studies have demonstrated that Th17 cell development and function is impaired in HIES.^{10,30-33} Th17 cytokines play a crucial role in protecting against mucocutaneous candidiasis.^{34,35} Furthermore autosomal recessive IL-17RA deficiency and autosomal dominant IL-17F deficiency result in chronic mucocutaneous candidiasis. These results indicate that IL-17A and IL-17F are essential for mucocutaneous immunity against *Candida albicans* in humans. Recent studies also demonstrated that most of the patients with chronic mucocutaneous candidiasis have constitutive activating mutations in *STAT1* gene,^{36,37} leading to defective Th17 cell responses. These findings strongly indicate that mucocutaneous candidiasis in HIES is resulted from defective Th17 cell development and function.

MOLECULAR MECHANISMS OF HIES

Th17 CELLS AND SKIN STAPHYLOCOCCAL AND FUNGAL INFECTIONS

STAT3 plays a critical role in signal transduction for many cytokines and growth factors, including those of the γ c family, the gp130 family, the IL-10 family, and receptor-type tyrosine kinases. STAT3 also functions as a transcription factor, binding to promoter regions and initiating transcription of its target genes. STAT3 is crucial for Th17 cell development in humans and mice.^{10,30-33} Th17 cells—a subset of helper T cells producing cytokines including IL-17A, IL-17F and IL-22—, have been extensively studied as an inducer of autoimmune disorders.³⁸⁻⁴² Th17 cells also play a key role in host defense against extracellular bacteria and fungi.^{43,44} Most of the staphylococcal and candida infections occurring in patients with

HIES are confined to the epithelium. Previous reports indicated that the levels of production of Th17 cytokines including IL-17A, IL-17F, and IL-22 by activated T cells from HIES patients are much lower than those from control subjects, whereas the production of other proinflammatory cytokines, including IFN γ , IL-1 β and TNF α is equivalent. Primary keratinocytes and bronchial epithelial cells do not produce sufficient amounts of neutrophil-recruiting chemokines and β -defensins in response to the supernatants of activated HIES T cells. The neutralization of Th17 cytokines in the supernatants of activated control T cells decreases the production of the chemokines and defensins. By contrast, primary dermal fibroblasts and endothelial cells respond equally well to the supernatants from patients and controls. Furthermore, primary keratinocytes and bronchial epithelial cells do not produce sufficient amounts of neutrophil-recruiting chemokines and β -defensins in response to Th17 cytokines, but produce sufficient amounts of neutrophil-recruiting chemokines and β -defensins in response to Th17 cytokines and proinflammatory cytokines. Collectively, these results indicate that keratinocytes and bronchial epithelial cells respond differently from other types of cells to Th17 cytokines, with Th17 cytokines playing a more important role in the production of the chemokines and β -defensins in epithelial cells. This observation suggested that Th17 cytokines play a crucial role in human host defense against *Staphylococcus aureus* and *Candida albicans*, particularly at the surface barriers of the body. These findings underscore the physiological role of Th17 cytokines in the protection against extracellular pathogens in humans.

Topical application of Th17 cytokines or downstream products of Th17 cytokines might be beneficial for the management of staphylococcal and candida infections, if conventional therapy is not sufficient to control this disorder.

INDUCED TREG (iTreg) CELLS AND ATOPIC DERMATITIS

Effector Th2 cells are the major cell type responding to allergens and produce Th2 cytokines including IL-4, IL-5, IL-9 and IL-13. These Th2 cytokines induce changes in blood vessels, upregulating adhesion molecules and eosinophil recruiting chemokines. Th2 cytokines also induce class switching to IgE.⁴⁵ Recently identified cytokines including IL-25, IL-31, and IL-33, also participate in Th2 cell-mediated allergic diseases.⁴⁶⁻⁴⁸ Th1 cytokines also play a role in the pathogenesis of atopic dermatitis contributing at a later time-point in epithelial cells.⁴⁹

The dendritic cells play a crucial role for induction and suppression of immune responses. We found that DCs of HIES patients display defective IL-10 signaling, resulting in impairment of the suppression of cytokine production and T cell proliferation.⁵⁰ The gen-

eration of Foxp3⁺ iTreg cells educated by IL-10 treated dendritic cells was also impaired in HIES. IL-10 upregulates the expression of PD-L1 and ILT-4 on the surface of dendritic cells, and both of the molecules play a critical role for the induction of Foxp3⁺ iTreg cells. IL-10 treated dendritic cells induce iTreg cells as efficiently as TGF- β and the combination of IL-10 treated dendritic cells and TGF- β synergistically upregulates the induction of iTreg cells. These results suggest that IL-10 signaling in dendritic cells may be crucial for the generation of iTreg cells *in vivo*, to maintain an appropriate Th2-Treg cell balance. FOXP3⁺ Treg cells mediate peripheral tolerance and play a central role in determining several immune diseases, including autoimmunity, chronic infections, tumors, and allergies.⁵¹ FOXP3⁺ Treg cells is involved in protecting humans against allergic diseases, because patients with immunodeficiency, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome suffer from allergic symptoms. PBMCs from atopic patients proliferate more extensively and produce more Th2 cytokines in response to allergen than do PBMCs from non-atopic healthy individuals.⁵²

CONCLUSION AND PERSPECTIVE

The identification of a molecular cause of HIES leads to the elucidation of the molecular mechanisms of cutaneous manifestations of HIES, which revealed the critical function of STAT3 in the signal transduction of multiple cytokines involved in the epithelial immunity in humans. The investigation of dominant negative mutations in *STAT3* resulting in atopic dermatitis and the susceptibility to staphylococcal and candida infections highlight the multiple and critical roles of STAT3 for its effector and regulating functions *in vivo*. Furthermore, the identification of molecular mechanisms of cutaneous manifestations of HIES may bring about an improvement in controlling atopic dermatitis and staphylococcal and candida infections for the future.

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