Delayed diagnosis of hyperimmunoglobulin E syndrome with STAT3 mutation in mainland China: a case report and literature review

Jiazhui Fang ⓘ, Qiao Yang and Borui Pi

Abstract

Hyperimmunoglobulin E syndrome (HIES) is a rare immunologic disorder. Typical clinical features of HIES include recurrent bacterial pneumonia, lung cysts, characteristic facial features, and newborn dermatitis. The varied clinical presentation can lead to a delayed diagnosis. We herein present a sporadic case of HIES in a man who initially presented with a longstanding history of intractable skin abscesses.

Introduction

Hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by a remarkably high level of serum immunoglobulin (Ig) E accompanied by eczema, recurrent skin and pulmonary infections, and connective tissue and skeletal abnormalities.[1] The prototype of this disorder is autosomal dominant HIES

Department of Liver and Infectious Diseases, Sir Run Run Shaw Hospital, Hangzhou, China

Corresponding author:
Borui Pi, Department of Liver and Infectious Diseases, Sir Run Run Shaw Hospital, #3 East Qingchun Road, Hangzhou 310016, China.
Email: 3309041@zju.edu.cn

(AD-HIES), also termed Job syndrome, which is caused by heterozygous loss-of-function mutations with a dominant negative effect in signal transducer and activator of transcription 3 (STAT3).[2] However, several other genetically characterized immunodeficiency disorders have been identified during the past decade and placed under the umbrella category of HIES, including autosomal recessive mutations in the DOCK8,[3] ZNF431,[4] and PGM3[5] genes and heterozygous mutations with a dominant negative effect in the CARD11 gene.[6] We herein report a case of HIES in a man with STAT3 mutation in mainland China.

Case report

A 26-year-old man presented with a >14-year history of recurrent skin abscesses. Although the abscesses could be controlled by drainage and antibiotics, they reappeared continuously on different parts of his body, including his chest, back, buttocks, and shoulders (Figure 1). He also reported that he had undergone two lung surgeries for treatment of lung abscesses at the ages of 6 and 9 years. His medical history was significant for eczema since the newborn period and recurrent pustular and eczematoid rashes on the face and scalp in childhood.

On physical examination, the patient's vital signs were normal, and he exhibited a characteristic facial appearance with rough facial skin and exaggerated pore size (Figure 2). Scattered rash scars were present on the skin of the chest and back. Bilateral fine crackles were audible in the lower lung, and decreased breath sounds were present at the bases. Abdominal examination was unremarkable, and neurological examination was normal.

The patient denied any history of food or drug allergies. His family history was negative for any inherited genetic diseases.

Both of his parents and his younger sister were healthy.

His leukocyte count was 11.6×10^9/L (62% neutrophils, 19% lymphocytes, and 9% eosinophils), erythrocyte sedimentation rate was 87 mm/hour, and C-reactive protein level was 38.2 mg/L. Further laboratory workup included the following: serum IgA, 493 mg/dL (reference range, 82–453 mg/dL); serum IgG, 2150 mg/dL (reference range, 751–1560 mg/dL); and serum IgE, >3000 IU/mL (reference range, 0–165 IU/mL). His IgM concentration was within the reference range. His CD4/CD8 count was normal, and his CD16/56+ NK cell count was slightly decreased (5.58%; reference range, 7%–27%). An interferon-γ release assay (T-SPOT.TB) was negative.

Chest computed tomography displayed mild pulmonary infection and regional bronchiectasis (Figure 3). The bone density of the lumbar vertebrae was evaluated by a dual-energy X-ray absorptiometry scan and showed a T score of −1.9. Percutaneous skin abscess puncture and drainage was performed several times, and laboratory examination of the drained liquid revealed purulent fluid with a large number of leukocytes. Gram staining of the fluid revealed Gram-positive cocci, and further culture revealed methicillin-sensitive *Staphylococcus aureus* four times and penicillin-sensitive *Streptococcus pneumonia* once. He received a score of 44 on the National Institutes of Health HIES scoring system[7,8] (Figure 4), and he was diagnosed with AD-HIES. We also performed a skin biopsy, and the pathologic examination showed necrosis in the deep dermis with numerous neutrophilic infiltrations. Amyloid deposits of homogeneous amorphous reddish masses were seen under hematoxylin–eosin staining (Figure 5). Further Congo red staining was positive (Figure 6). We also performed serum and urine protein electrophoresis, and no monoclonal Ig or light chains were detected.

**Figure 1.** Diffuse skin discoloration and scars over the patient's body.
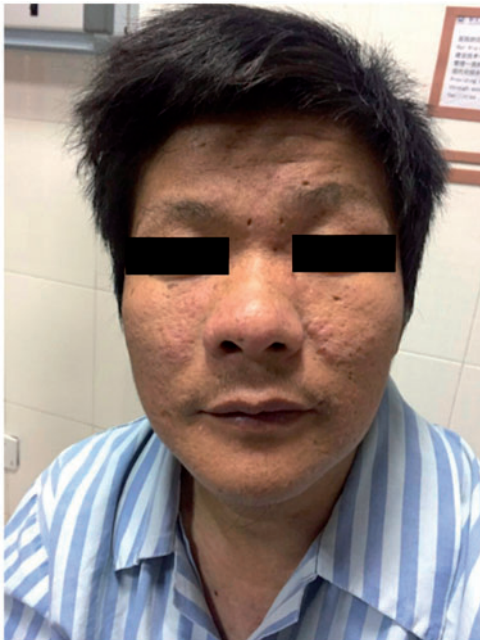
Figure 2. Characteristic facial appearance with rough skin and exaggerated pore size.

His echocardiographic and electrocardiographic examinations and liver function tests were all within the normal ranges. There was no evidence that the amyloidosis involved any other organs.

Intravenous amoxicillin/clavulanate was administered according to the drug sensitivity test results. His condition greatly improved during a 2-week hospitalization, and he was discharged with oral prophylaxis for reinfection with trimethoprim/sulfamethoxazole. He developed no further skin abscesses during the next 1.5 years.

Mutation analysis

To confirm and further clarify the diagnosis, we performed targeted next-generation sequencing to screen potential mutations, followed by confirmation by Sanger sequencing. Targeted capture next-generation sequencing revealed wild-type sequences in all targeted genes except for a
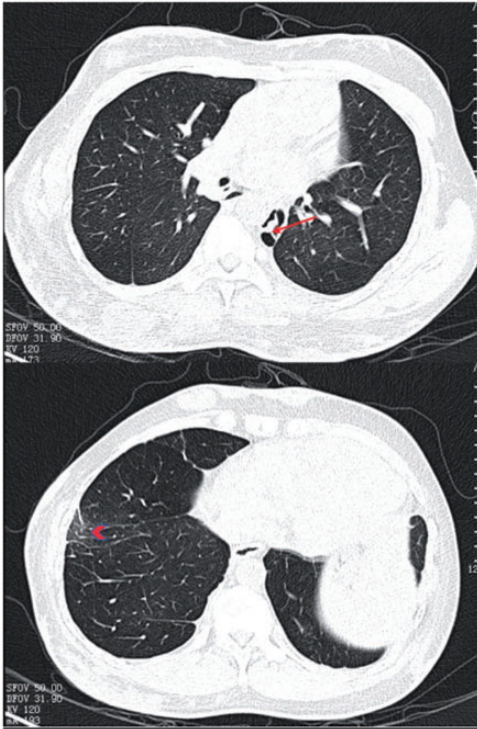
Figure 3. Chest computed tomography shows pneumatocele and mild bronchiectasis in the left lower lung (arrow) and regional fibrosis in the right lower lung (arrowhead).

heterozygous missense mutation in exon 22 of STAT3 (c.2137G>A:p.V713M) (Figure 7).

Discussion and literature review

Despite having been recognized for about 50 years, the prevalence of HIES remains unclear, with only about 500 cases reported worldwide to date. Until December 2018, only about 40 cases had been reported in mainland China.[9–12] Because of the clinical course of the disease, most patients are diagnosed in childhood or early adolescence; few are diagnosed in adulthood. Although some cases of familial HIES with autosomal dominant or recessive inheritance have been reported, most cases

of HIES are sporadic. There are two distinct forms of HIES: AD-HIES (OMIM 147060) and autosomal recessive HIES (OMIM 243700). They have different genetics, pathogeneses, clinical presentations, and outcomes.[13] AD-HIES is mainly caused by mutations in the STAT3 gene.[2,14] STAT3 is a transcription factor that binds to the STAT3-responsive elements in the promoters of various genes and plays a critical role in responses to many cytokines, including interleukin (IL)-6 and IL-10. In patients with HIES, the DNA-binding ability of STAT3 in these cells is greatly diminished.[2] Additionally, IL-17 produced by T-helper 17 cells is an important cytokine that is protective in the host defense against extracellular bacteria, and IL-22 stimulates cells in the skin and respiratory systems to produce β-defensins through STAT3 activation, both of which are remarkably decreased after STAT3 mutation.[15,16] STAT3 also plays an important role in the regulation of extracellular matrix metalloproteinases; as expected, patients with STAT3 deficiency have abnormal levels of matrix metalloproteinases.[17] Such defects in tissue remodeling likely explain the vascular aneurysms, poor lung healing after infection, and characteristic facial features with porous skin seen in most patients with HIES. HIES has both immunological and non-immunological manifestations. AD-HIES is characterized by eczema, recurrent staphylococcal infections in the skin and lungs, and abnormalities in the vessels, connective tissue, and skeleton. Our patient exhibited many clinical characteristics of AD-HIES, including recurrent skin abscess, pneumatoceles, and rough facial skin with exaggerated pore size. The mild clinical course and lack of advanced medical resources led to a delayed diagnosis at the age of 26 years.

STAT3 is located on human chromosome 17q21.[4] The structure of STAT3 includes three major regions: the

Scoring System with Clinical and Laboratory Tests for Individuals in Kindreds with HIES

Clinical Findings	Points[a]									
	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)[b]	<200	200–500			501–1,000				1,001–2,000	**>2,000**
Skin abscesses	None		1–2		3–4				**>4**	
Pneumonia (episodes over lifetime)	None		1		**2**		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		**Pneumatocele**	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	**<10°**		10–14°		15°–20°				>20°	
Fractures with minor trauma	**None**				1–2				>2	
Highest eosinophil count (cells/µl)[c]	<700			700–800			**>800**			
Characteristic face	Absent		Mildly present			**Present**				
Midline anomaly[d]	Absent					**Present**				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	**Mild**	Moderate		Severe					
Upper respiratory infections per year	1–2	**3**	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Present					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width[e]	<1 SD	**1–2 SD**		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2–5 years		1–2 years		≤1 year		

[a] The entry in the furthest-right column is assigned the maximum points allowed for each finding.

[b] Normal <130 IU/ml.

[c] 700/µl = 1SD, 800/µl = 2 SD above the mean value for normal individuals.

[d] For example, cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc. (see Grimbacher et al. 1999a).

[e] Compared with age- and sex-matched controls (see Farkas et al. 1994).

Figure 4. Hyperimmunoglobulin E syndrome/Grimbacher scale: our patient's score is highlighted (total score: 44) (all patient details have been removed from figures).
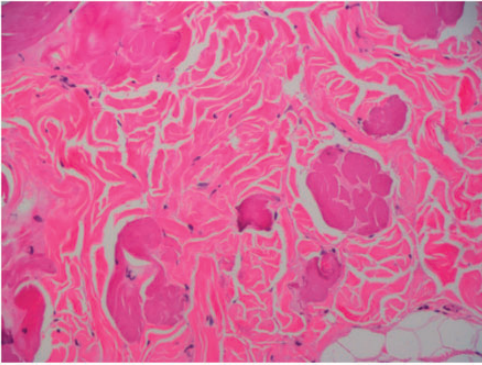
Figure 5. Skin biopsy shows homogeneous amorphous reddish mass under hematoxylin–eosin staining (arrow) (200×).
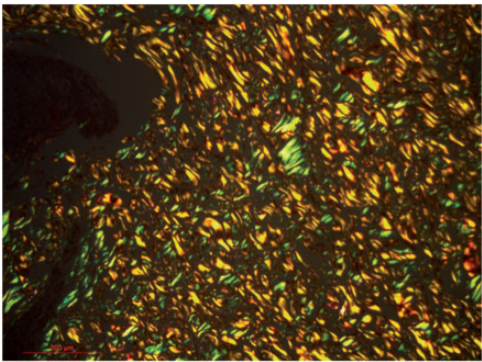
Figure 6. Congo red stain appears apple-green with polarized light (100×).

N-terminal region (1–355), the central region (355–555), and the C-terminal region (555–770).[18] The central region is the DNA-binding domain, and the C-terminal region is the Src homology 2 (SH2) domain. Large numbers of missense and some in-frame insertion/deletion mutations in STAT3 have been identified, all exerting a dominant negative effect. These mutations are mostly confined to the DNA-binding and SH2 domains of the STAT3 gene.[19] Previously reported mutational hotspots are R382W, R382Q, V463del, and V637M in the DNA-binding domain and SH2 domain. This is consistent with previous studies among the Chinese population, in which R382W/Q is the most commonly reported mutation and V637M is the hotspot mutation of SH2 mutations.[9] The present report describes the first reported patient with V713M mutation in mainland China. A previously described patient with V713M also had non-Hodgkin lymphoma.[20] Although our patient had no evidence of lymphoma, he requires close follow-up.

Chandesris et al.[20] performed a large cohort study in the form of a French national survey involving 60 patients. All patients had skin infections and more than 90% had a characteristic face, recurrent pneumonia, and eczema. In a recently
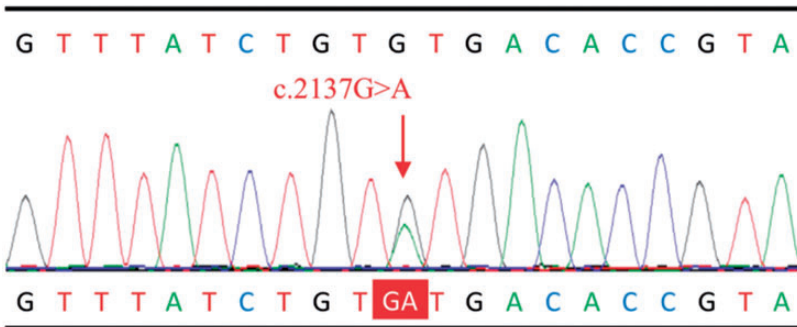
Figure 7. Missense mutation (c.2137G>A, p.V713M) in exon 13 of STAT3 was identified as a heterogeneous mutation.

published report of a United States cohort, the complications included skin abscesses (74.4%), eczema (57.7%), retained primary teeth (41.4%), fractures (39.0%), scoliosis (34.1%), and cancer (7.0%).[21] In a Chinese cohort,[10] 17 of 17 patients had a characteristic face, recurrent pneumonia, and eczema. Most of the patients had retained primary teeth, which were not found in our patient. According to that study, the prevalence of chronic otitis media and bronchiectasis is lower in China than in other countries.[10] Our patient had no history of otitis media, but he did have bronchiectasis. He also had scoliosis, which is not common among Chinese patients with AD-HIES. Decreased bone density is also a characteristic of AD-HIES and tends to deteriorate over time.[22]

The two most frequent infections in patients with AD-HIES are localized skin abscesses and pneumonia.[18] The most common causative agent is *Staphylococcus aureus*. These are so-called "cold" abscesses because of the lack of characteristic features of inflammation (pain, heat, redness, and swelling). The lack of these features is partly due to the defective immune response in patients with AD-HIES. Recent research has demonstrated that STAT3 dysfunction is associated with overproduction of tumor necrosis factor-α and that aberrant epithelial responses to *Staphylococcus aureus* are caused by defective epithelial-to-mesenchymal transition rather than a failure of bacterial killing.[23] Other commonly reported infectious organisms include *Candida albicans*, *Aspergillus fumigatus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumonia*.

Amyloidosis is a group of systemic diseases in which abnormal proteins known as amyloid fibrils build up within tissue. Symptoms depend on the type of amyloidosis and are often variable. The principal types of amyloidosis are primary amyloidosis (AL amyloidosis) and secondary amyloidosis (AA amyloidosis). AL amyloidosis is caused by plasma cell dyscrasia induced by deposition of protein derived from Ig light chain fragments. In contrast, AA amyloidosis is a potential complication of chronic diseases in which there is ongoing or recurring inflammation that results in the production of serum amyloid A protein, an acute-phase reactant, which can form amyloid deposits. Genetic factors can play an important role in the pathogenesis of amyloidosis. Some diseases, such as early-onset Alzheimer's disease, are directly caused by mutations in the gene for amyloid precursor protein. AA amyloid also complicates genetic diseases; this is most often seen in autoinflammatory diseases, with varying frequencies of >60% in untreated familial Mediterranean fever, 25% in tumor necrosis factor receptor-1-associated periodic syndrome and cryopyrin-associated periodic syndrome, and <5% in mevalonate kinase deficiency.[24] The relationship between HIES and amyloidosis has not been fully clarified, and only one case has been reported.[25] Though the skin pathology of our patient showed amyloidosis, no other organs were involved. The amyloidosis of the skin was probably caused by longstanding inflammation, which led to deposition of the AA protein.

There is no definite treatment for AD-HIES. Prophylactic anti-staphylococcal and antimycotic agents represent the mainstay of therapy. Because patients with AD-HIES do not display classic inflammatory signs, vigilance and early administration of antimicrobials for skin and pulmonary infections are key measures. Our patient developed recurrent skin and lung infections early in his disease course and received prophylactic trimethoprim/sulfamethoxazole, and he has since developed no further infections. Despite the possible efficacy of intravenous Ig in reducing the frequency of pneumonia,[26,27] guidelines specifying which

patients with AD-HIES will benefit from Ig replacement therapy have not been established. The role of hematopoietic stem cell transplantation has been controversial for a long time, but recent experiences have been more successful.[28,29]

Conclusion

Though AD-HIES has many characteristic features, including recurrent skin and pulmonary infections accompanied by eczema, connective tissue and skeletal abnormalities, and a high serum level of IgE, patients' presentations can vary dramatically. Patients may present to various departments, including dermatology, infectious, respiratory, and other departments. Careful history-taking, including a thorough family history, and a detailed physical examination are extremely important in general practice to establish the final diagnosis. Physicians should consider all of the above findings as a whole picture and make connections with the underlying immunodeficiency, also taking the patient's genetic background into consideration. Mutational analysis can aid in the diagnosis of many primary immunodeficiencies with a genetic background. Prophylactic antibiotics can prevent recurrent infections and complications and improve patients' quality of life.

Ethics

This case report was written according to the Equator network guideline (https://www.equator-network.org/reporting-guidelines/care/). All patient details have been de-identified. The patient provide verbal informed consent. The requirement for ethics approval was waived because the patient was treated according to the latest guideline (i.e., non-interventional study).

ORCID iD

Jiazhui Fang 🆔 https://orcid.org/0000-0003-0603-2823

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