Hyperimmunoglobulin E Syndrome-like Symptoms in a Hemodialysis Patient who Developed Multiple Subcutaneous *Staphylococcus aureus* Abscesses

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Abstract

Hyperimmunoglobulin E syndrome (HIES) is sporadically triggered by *de novo* genetic mutations of the signal transducer and activator of transcription 3 (STAT3). Dialysis patients frequently exhibit HIES-like symptoms including elevated IgE levels and recurrent bacterial infections. We herein report the case of a 74-year-old man on hemodialysis (HD) who developed marked IgE elevation and multiple subcutaneous cold *Staphylococcus aureus* abscesses. We are the first to report that a dialysis patient presented with HIES-like symptoms without the characteristic facies or bone and connective tissue abnormalities. A STAT3 gene analysis was conducted as part of the differential diagnosis.

Key words: hyperimmunoglobulin E syndrome (HIES), signal transducer and activator of transcription 3 (STAT3), dialysis patients

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Introduction

Hyperimmunoglobulin E syndrome (HIES) is a primary immunodeficiency that manifests with recurrent infections, particularly by *Staphylococcus aureus*, and is characterized by distinctive facies, joint hyperextensibility, multiple bone fractures, scoliosis and delayed shedding of the primary teeth. It was recently reported that HIES is sporadically triggered by *de novo* genetic mutations of signal transducer and activator of transcription 3 [STAT3 (1)]. Dialysis patients also frequently exhibit elevated IgE levels for various reasons and suffer from recurrent bacterial infections. In medical examinations of dialysis patients, clinicians often encounter cases that include the differential diagnosis of HIES.

We herein report a case in which a hemodialysis (HD) patient developed HIES-like symptoms including marked elevation of the IgE levels and multiple *Staphylococcus aureus* subcutaneous abscesses, although a STAT3 gene analysis ruled out HIES.

Case Report

In May 2011, a 74-year-old Japanese man was admitted to our hospital with fatigue and 4- to 5-cm cold abscesses on his left elbow (Fig. 1A) and the back of his head. He had previously been treated for atopic dermatitis with a steroid ointment. HD had been initiated for diabetic renal failure in March 2011. On admission, the laboratory results were as follows: white blood cell (WBC): 10,850/ μ L (eosinophil count: 173/ μ L), C-reactive protein (CRP): 8.08 mg/dL and IgE: 25,747 IU/mL (Table). By the following day, the cold abscesses had spread to the anterior surface of the patient's neck (Fig. 1B) and right lower abdomen (Fig. 1C). The blood cultures and parasitological examinations were negative (Table). The patient was treated with a course of antibiotics, and all of the abscesses were drained. The fluid from the abscesses was cultured, and the causative bacterium was identified as *Staphylococcus aureus*, which exhibited sensitivity to all the antibiotics tested. By day 33 after admission, the patient's inflammatory response had improved to a WBC count of 5,250/ μ L (eosinophil count:

Table. Results of Laboratory Tests of the Patient

Peripheral blood count		Blood biochemistry	
WBC	10850 / μ L	TP	5.9 g/dL
Neutrophil	84.8 %	Alb	3.1 g/dL
Eosinophil	1.6 %	AST	28 IU/L
(eosinophil count	173 /mm ³)	ALT	19 IU/L
Lymphocyte	8.2 %	BUN	56.8 mg/dL
Monocyte	5.1 %	Cre	8.73 mg/dL
RBC	256 $\times$ 10 ⁴ / μ L	UA	10.7 mg/dL
Hb	7.7 g/dL	Na	133 mEq/L
Ht	23.4 %	K	5.59 mEq/L
Plt	36.7 $\times$ 10 ⁴ / μ L	Cl	93 mEq/L
		Ca	8.1 mg/dL
		P	4.3 mg/dL
Immunologic blood tests		PPG	511 mg/dL
C-reactive protein	8.08 mg/dL	GA	33.3 %
IgG	1523 mg/dL	T-Chol	126 mg/dL
IgA	480 mg/dL	HDL-Chol	36.8 mg/dL
IgM	52 mg/dL	TG	115 mg/dL
IgE	25747 IU/mL	LDL-Chol	68 mg/dL
β -D-glucan	5.06 pg/mL		
<i>Candida albicans</i> antigen	(-)		
Parasite IgG antibody screening test			
Canine filariasis	(-)	Paragonimus westermani	(-)
Toxocara canis	(-)	Fasciola hepatica	(-)
Anisaxis	(-)	Liver fluke	(-)
Gnathostoma	(-)	Sparganosis mansoni	(-)
Strongyloides stercoralis	(-)	Cysticercosis cellulosae	(-)

PPG: postprandial plasma glucose, GA: glycoalbumin

Figure 1. The patient was admitted to our hospital with fatigue and 4 to 5 cm cold abscesses on his left elbow (A) and the back of his head. By the following day, the cold abscesses had spread to the anterior surface of the patient's neck (B) and right lower abdomen (C).

1,995/ μ L) and a CRP level of 0.18 mg/dL, and all of the abscesses had resolved (Fig. 2). However, the IgE value remained high (18,535 IU/mL).

Based on the presence of atopic dermatitis, multiple *Staphylococcus aureus* abscesses (possibly recurrent), marked IgE elevation and lack of a family history, a differ-

ential diagnosis of sporadic type 1 HIES caused by *de novo* genetic mutations in STAT3 was made. After obtaining approval from the ethics committee of Takasago Municipal Hospital and informed consent from the patient, we performed a genetic analysis. Polymerase chain reaction (PCR) amplification of the patient's DNA was carried out using STAT3-specific primers, and a single-nucleotide polymorphism (SNP) analysis was conducted with a direct sequence using the PCR product as a template. Although exon 12 was not analyzed due to poor sequence quality, no mutations were found in the other STAT3 exons.

Discussion

Compared to the general population, dialysis patients more frequently suffer from eosinophilia and elevated IgE levels (2); however, the etiology of this phenomenon is unclear. Most physicians associate eosinophilia and elevated IgE levels with allergies or infection by parasites and fungal organisms. Bodner et al. suggested that eosinophilia in dialysis patients occurs due to the release of eosinophilotactic substances induced by the dialysis procedure itself (3). Some investigators have reported that eosinophilia may be induced in dialysis patients, not by renal disease, medications or the type of dialyzer or access, but by uremia or an allergic reaction to the dialysis equipment (4, 5).

In the present case, we initially hypothesized that the patient's eosinophilia and elevated IgE levels were due to

Figure 2. The patient was admitted to our hospital with fatigue and 4 to 5 cm cold abscesses on his left elbow and the back of his head. On admission, the laboratory results were as follows: WBC: 10,850/ μ L (eosinophil count: 173/ μ L) and CRP: 8.08 mg/dL. On the following day, the cold abscesses had spread to the anterior surface of the patient's neck and right lower abdomen. He was treated with a course of antibiotics, and all of the abscesses were drained. On day 33 after admission, the patient's inflammatory reaction had improved to a WBC count of 5,250/ μ L (eosinophil count: 1,995/ μ L) and a CRP level of 0.18 mg/dL, and all of the abscesses had resolved.

atopic dermatitis that was worsened by uremia or an allergic reaction to the dialysis equipment on admission. However, we conducted a differential diagnosis because we observed the presence of multiple staphylococcal cold abscesses, which are characteristic of HIES. The blood cultures were negative in this case; however, methicillin-sensitive *Staphylococcus aureus* (MSSA) was identified in all of the subcutaneous abscesses. In HD patients, *Staphylococcus aureus* infection MSSA and even methicillin-resistant *Staphylococcus aureus* (MRSA) colonization are important clinical features (6). *Staphylococcus aureus* is the most common cause of dialysis-associated bacteremia and accounts for 25% of the bacteremia isolates obtained from such patients (7). In addition, *Staphylococcus aureus* infection can lead to various complications, such as infective endocarditis, osteomyelitis, abscess formation and septic arthritis (8). However, to the best of our knowledge, there are no reports in the literature of multiple subcutaneous cold abscesses occurring in a dialysis patient. Therefore, we sought to clinically distinguish this condition from HIES.

Patients with Type 1 HIES exhibit characteristic facies (including left-right facial asymmetry, a prominent forehead, depressed orbits, a wide nose bridge and an enlarged nose tip), joint hyperextensibility, multiple bone fractures, scoliosis and delayed shedding of the primary teeth; however, our patient exhibited no apparent abnormalities. A STAT3 gene analysis was required to precisely differentiate HIES in this

case because some cases of HIES in patients without characteristic facies or bone and connective tissue abnormalities have been reported. In addition, eosinopenia has recently been reported to be a marker of sepsis (9), leading us to suspect that the current patient's low eosinophil count on admission may have been caused by a sepsis-like condition.

STAT3 mutations in HIES individuals preclude T-cell production of interleukin (IL)-17, which leads to impaired T-helper (Th) 17 cell differentiation (10). IL-17 production is required to protect against fungal infections and extracellular bacteria, as observed in mice with a targeted IL-17 mutation. Multiple HIES-like *Staphylococcus aureus* abscesses developed in this case; however, there were no apparent changes in the IL-17 levels due to the STAT3 mutations (the IL-17 levels were not measured). In this case, the results may be attributed to the patient's status as a compromised host, as he suffered from diabetes and was undergoing HD.

The genetic etiology of HIES was recently determined. While HIES was previously diagnosed based on clinical presentation, it can now be diagnosed at an early stage using gene analyses. STAT3 gene mutations have been identified in 70% of HIES individuals, and more than 90% of these STAT3 mutations are sporadic *de novo* mutations. However, the genetic basis for this condition in many HIES individuals remains to be completely elucidated. Additionally, in this case, a diagnosis of HIES could not be completely excluded because exon 12 was not analyzed due to poor sequence

quality. Future research is needed to identify other genetic causes of HIES to increase the accuracy of gene analyses.

Eosinophilia and elevated IgE levels are commonly observed in dialysis patients. In addition, HIES-like *Staphylococcus aureus* infections develop easily in dialysis patients because the patients are compromised hosts. Therefore, dialysis patients may present with symptoms similar to those of HIES individuals. However, this is the first report in which a diagnosis of HIES was specifically excluded in a dialysis patient based on a STAT3 gene analysis. We are the first to report a STAT3 genetic analysis of a dialysis patient with HIES-like symptoms who lacked the characteristic facies and bone or connective tissues abnormalities. Naturally, a genetic analysis of STAT3 cannot be performed in all cases of elevated IgE levels and *Staphylococcus aureus* infections because HIES is a rare disease. Fortunately, we had the opportunity to conduct a STAT3 gene analysis and present the results of this case report.

The authors state that they have no Conflict of Interest (COI).

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