

Case Report

A case of reduced Th17 cell numbers in a 61-year-old man with hyper IgE syndrome

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Abstract: Hyper immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency disorder characterized by eczema, recurrent skin and lung infections, and significantly elevated plasma IgE levels. Recurrent exacerbations of infection and pulmonary hemorrhage are very difficult to treat and are major causes of morbidity and mortality for these patients. As HIES presents early in life, the occurrence of the disease among middle-aged adults has been rarely reported. Here, we describe a 61-year-old Chinese man with a 30-year history of eczema, groin abscesses, and lung infections. Consistent with a diagnosis of HIES, the patient exhibited eosinophilia, defective differentiation of T helper 17 cells, and elevated plasma IgE levels. There are few reports of HIES in an individual over 60 years old. To our best known, this is the first report of defective differentiation of T helper 17 cells in an over 60-year-old man with HIES. Early diagnosis and surgical therapy are helpful in prevention of repeated infections in these patients.

Keywords: Hyper immunoglobulin E syndrome, Th17 cell, eosinophilia, abscess

Introduction

Hyper immunoglobulin E syndrome (HIES) was first described in 1966 by Davis, Wedgwood and Schaller. The authors noted the similarity of the syndrome's severe dermatitis and "cold" abscesses with the disease attributed to the prophet Job and hence designated it "Job's Syndrome" [1]. In 1972, Buckley and colleagues described two children who presented with severe chronic dermatitis, coarse faces, and a high concentration of plasma immunoglobulin E; these manifestations were termed "Buckley's Syndrome" [2]. Although the first data concerning the prevalence of HIES referred only to the Caucasian race, subsequent reports indicate that the disease occurs in Asian and African individuals as well [3, 4]. Previous reports on HIES concerned the prevalence of the disease in children [1, 2, 5, 6] and adults [7, 8]. In this case report, we highlight the importance of recognition of recurrent "cold" abscesses which contain *S. aureus* infections in a 61-year-old patient with raised IgE levels.

Case report

A 61-year-old man presented with eczema and skin lesions in both legs (**Figure 1**). The patient

had a >30-year history of eczema, recurrent skin "cold" abscesses and fever. From the age of 30, he also had recurrent bilateral groin abscesses (**Figure 2**). The patient was born and living in rural areas, and his sisters and brothers did not exhibit these pathologies. The patient had multiple hospital admissions because of the recurrent groin abscesses and fever.

At the age of 54, the patient required incision and drainage of bilateral groin abscesses, which showed lymph node eosinophilic granulomas. At the age of 58, the cold abscesses were aspirated and frank pus was drained from the subcutaneous swellings. The pus contained *Staphylococcus aureus*.

At the age of 54, the patient was found to have an abscess in his liver (CT scan, **Figure 3**). At the age of 58, the hepatic abscess was drained, which revealed granulomatous inflammation and the presence of *S. aureus*. At present, the liver was palpable three fingers below costal margin, and the spleen was just palpable, suggestive of hepatosplenomegaly. There was tenderness between the xiphoid process and right costal margin. Lung CT scans (HRCT) showed emphysema in the left lower lobe and right upper lobe (**Figure 4**).

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Figure 1. Skin lesions in both legs.



Figure 2. Cold abscesses in bilateral groin.

T-helper cell analysis

The relative numbers of plasma Th17 cells and other T-helper subsets were determined in the patient and six healthy individuals. This study was approved by the Institutional Human Research Ethics Committee (Beijing Friendship Hospital). PE-anti-IL-17A, FITC-anti-CD8, APC-anti-CD3 were purchased from eBioscience (San Diego, CA, USA). Phorbol myristate acetate (PMA), ionomycin and Brefeldin A were all pur-

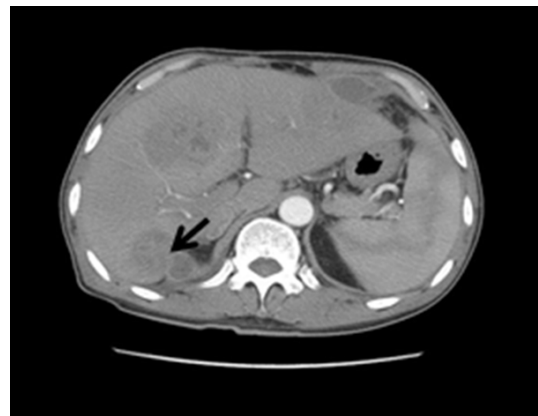


Figure 3. Liver abscess at the age of 54.

chased from Sigma-Aldrich (St Louis, MO, USA). Fixative was purchased from Invitrogen (Carlsbad, CA, USA).

Five ml of peripheral blood was obtained from each of the patients and healthy individuals in a fasting state. Peripheral blood mononuclear cells (PBMCs) were prepared immediately from whole blood by density centrifugation using Ficoll-Paque (1.077 g/ml, GE Healthcare BioScience AB, Uppsala, Sweden). The mononuclear cells were washed twice in phosphate-buffered saline (PBS) and cell viability was determined to exceed 95% by Trypan blue exclusion. The PBMCs were suspended at 1×10^6 cells/ml in X-VIVO15 medium (Lonza, Basel, Switzerland) and combined with PMA (50 ng/ml), ionomycin (1 μ g/ml), and Brefeldin A (1 μ g/ml), and then incubated at 37°C in a 5% CO₂ incubator for 4 h. The cells were transferred to 1.5 ml tubes and centrifuged at 300 g for 6 min. The cells were suspended and washed twice with PBS, then incubated with APC anti-CD3 and FITC

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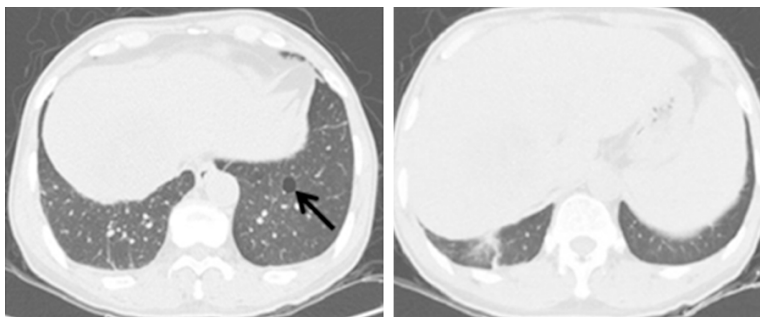


Figure 4. Pulmonary emphysema.

anti-CD8 at room temperature for 30 min. After washing the cells twice with PBS, fixative was added and the tubes were incubated in the dark at 4°C for 15 min. The cells were then centrifuged, washed twice with PBS, and divided into two tubes. PE anti-IL-17A was added to one tube and the isotype control PE IgG1 was added to the other. After 30 min at room temperature, the cells were washed twice in PBS, suspended in PBS and analyzed using a flow cytometer. CellQuest software was used for data analysis.

Th17 cell numbers were markedly decreased (0.463% of cultured CD4⁺ T cells) in the patient compared with the healthy controls (1.10-1.66% of cultured CD4⁺ T cells) (**Figure 5**).

Blood analytes and treatment

The patient exhibited leukocytosis with marked eosinophilia (5%-11%). Plasma IgE levels exceeded 5000 U/L, but other Igs were normal. Blood and urine from the patient were cultured for microbial detection (including virus, fungus, *Bacillus burgeri*, spirochetes), but no microbes were detected. Alanine aminotransferase, aspartate aminotransferase, creatinine and BUN levels were normal, indicating that the patient had proper liver and kidney function. After further deterioration, a lung CT scan revealed emphysema in the left lower lobe and right superior lobe.

Raised IgE levels, eosinophilia, decreased Th17 cell numbers, eczema, recurrent skin infections with cold abscesses and a liver abscess-both of which contained *S. aureus*-confirm the diagnosis of HIES in the patient.

The patient was for two weeks with intravenous vancomycin (1.6 g) and cefmetazon (4 g) bid. The patient responded to treatment: the liver

abscess became minimal (**Figure 6**), body temperature returned to normal, and no groin abscesses were present.

Discussion

In our study, a 61 years old man was evaluated for primary immune deficiency syndrome which revealed: elevated plasma IgE levels, eosinophilia, and a history of recurrent skin infections with cold abscesses. Moreover, the abscesses were found to contain *S. aureus* infections. Other HIES-associated clinical features, such as facial changes (frontal bossing, broad nose, prominent lower lip) were not observed. There was no significant family history.

HIES is a primary immune deficiency characterized by an abnormal susceptibility to a narrow spectrum of infectious agents, most commonly the bacterium *Staphylococcus aureus* and the fungus *Candida albicans*. Patients with HIES often suffer from mucocutaneous candidiasis, whereas local and invasive *S. aureus* infections lead to persistent eczematoid eruptions with recurrent skin and joint abscesses. In addition to recurrent tissue-destructive infections, the HIES phenotype includes coarse skin formation after relatively minor trauma. Previous studies have demonstrated that the differentiation of Th17 cells is defective in patients with HIES [9, 10]. Th17 cells play a key role in immune responses to extracellular bacteria and fungi. Mice that produce neither IL-17A nor IL-17F are susceptible to skin infection by *Staphylococcus aureus*. Administration of anti-IL-17A neutralizing antibodies to wild-type mice impairs both intra-abdominal abscess formation in response to *Bacteroides fragilis* and *Escherichia coli* and host defense against systemic infection by *Candida albicans* [11]. These results indicate that Th17 cells play a key role in immune responses to extracellular bacteria and fungi in mice.

Based on the patient's clinical features, decreased Th17 cell levels and the histopathology findings, the diagnosis of HIES was confirmed. Moreover, a *S. aureus*-containing hepatic abscess was prominent in this case. Chronic granulomatous disease, hyper IgE, and complement

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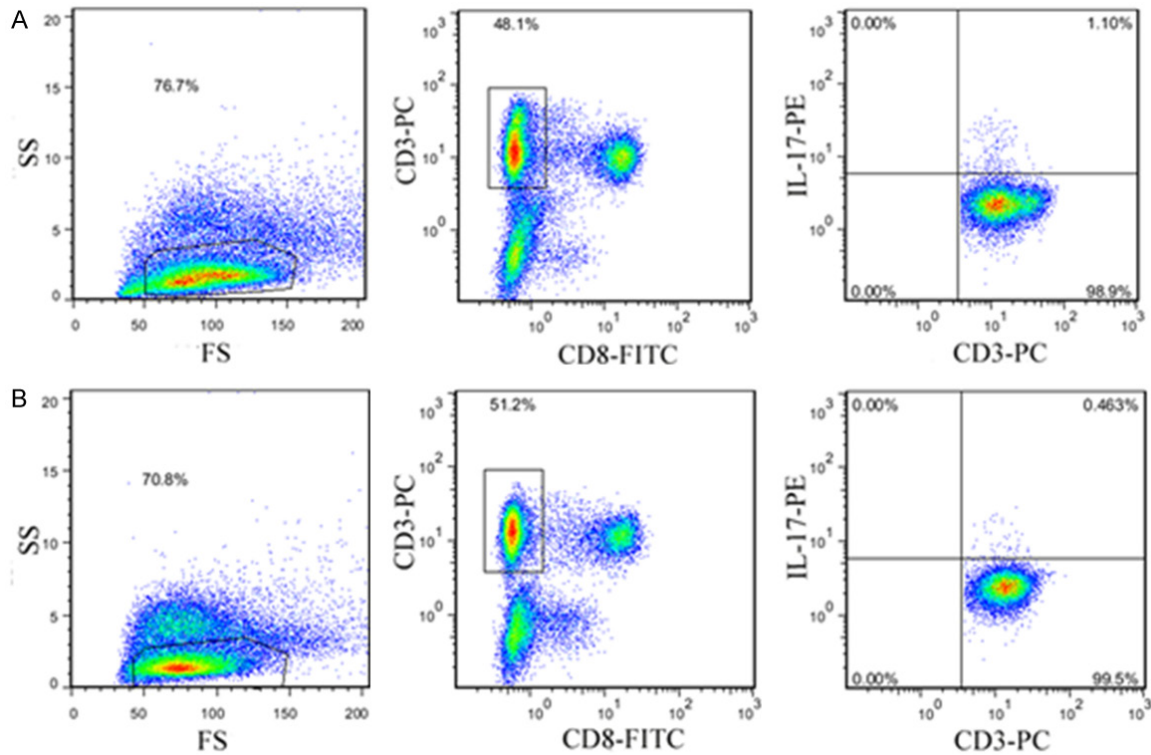


Figure 5. Decreased Th17 cells in the patient. A: Representative healthy individual; B: The patient. Left panels: gating on low-side scatter (mononuclear) cells. Middle panels: gating on CD3⁺CD8⁺ (T-helper) cells. Right panels: Fewer IL-17⁺ cells (upper right quadrant) were observed for the patient than the healthy individual.

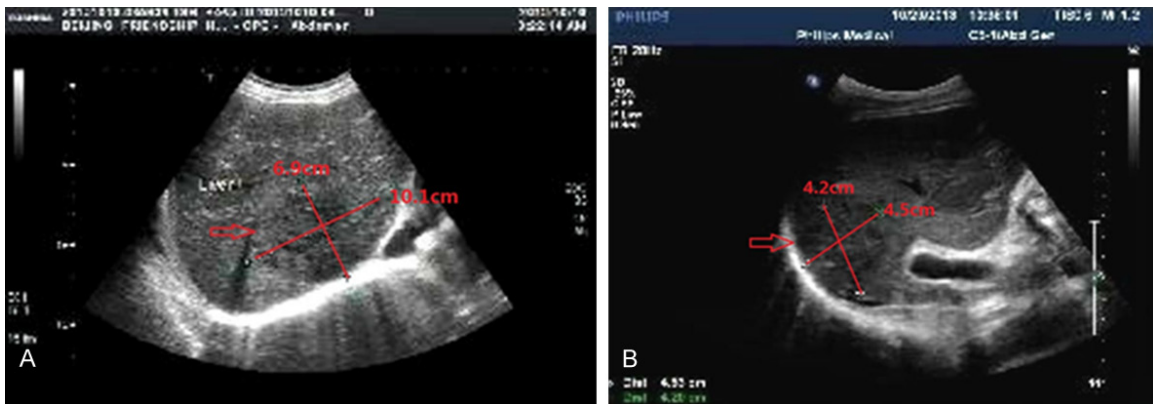


Figure 6. Liver abscess before and after treatment. A: Liver abscess before treatment. B: Liver abscess after treatment.

deficiencies are immunopathologies known to be associated with liver abscesses [12]. The patient was treated with antibiotics to shrink the abscess. Improvement was noted at week four post-treatment and the treatment was well-tolerated.

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Disclosure of conflict of interest

None.

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