

Clinical practice

A novel case of Hyper IgE syndrome combined with natural killer cell deficiency

Zhang Xiaolei, Liu Yangang, Liu Yan and Dai Huaping

Keywords: hyper IgE Syndrome; natural killer cell deficiency; infection

The Hyper IgE syndrome (HIES) is a rare, complex primary immunodeficiency. Here we report a case of HIES combined with natural killer cell deficiency, which has not been previously documented in the literature. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

A 20-year-old male patient was admitted to hospital with cough, dyspnea and low-grade fever. He had suffered from oral thrush at birth and scalp boils during childhood (staphylococcus aureus was isolated several times from scalp abscess). He had a long history of refractory eczema, as well as recurrent pneumonia that required prolonged intravenous antibiotics. Six months ago, he was discharged from another hospital with the diagnosis of *Pneumocystis carinii* pneumonia (PCP) which was diagnosed by bronchoscopy biopsy. At eight years old, enlarged lymph nodes were detected in his neck, armpits and groin areas. Anti-tuberculosis medication was given for 18 months after lymph node tuberculosis was confirmed by lymph node biopsy. The lower permanent teeth did not come in until ten years old, and two upper primary teeth were extracted six months ago. He was found to be infected with hepatitis B virus and hepatitis C virus eight years ago, and began EntikaweiPian (0.5 QD) treatment six months ago. His parents were not consanguineous, and there was no family history of relevant allergic or immunologic diseases. His brother is healthy.

Physical examination revealed a facial asymmetry (Figure 1), bilaterally reduced breath sounds and clubbing fingers.

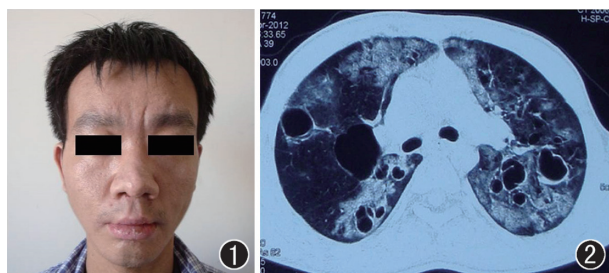


Figure 1. Photograph of the patient's face showing the characteristic coarse features in the physiognomy with a predominant forehead, a wide alar base to the nose and a wide outer canthal distance.

Figure 2. Chest CT showed diffused patchy shadows, ground glass appearance and multiple pneumatocoeles.

Complete blood panels revealed leukocytosis with marked eosinophils (8%–26%). Immunological investigations revealed grossly elevated serum immunoglobulin (Ig) E levels of more than 5 000 U/L (normal range 0 to 100 U/L), but normal IgA, IgG, IgM and complement C3 and C4 levels. Lymphocytes and respective subsets were enumerated by flow cytometry using a standard panel of monoclonal antibodies. Repeated analyses revealed a marked reduction of natural killer (NK) cells to 0.7%–1.1% (19–37/ μ l). Preceding studies with different CD56 antibodies suggested normal C56 surface antigen expression of NK cells. By negative selection of CD3, CD4, and CD14 cells through immunomagnetic beads, the NK cells could be enriched up to 10%, confirming the existence of NK cells. The co-expression pattern was normal (Table 1). Assays of NK cell function showed that the positive percentage of cells with both perforin (85.6%, normal range >84%) and granzyme B (87.9%, normal range >78%) were normal. Thus, the patient demonstrated a significant reduction of NK cells which were phenotypically and functionally normal. Analysis of serum markers of virus hepatitis showed positive results for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody IgM (HBcAb IgM), Hepatitis B e antigen (HBeAg) and Hepatitis C antibody, and negative results for Hepatitis B surface antibody (HBsAb), and Hepatitis e antibody (HBeAb). Hepatitis viral load measurements showed that the HBV DNA level was 1.1×10^8 copies/ml and HCV DNA level was 1.94×10^5 copies/ml. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were slightly elevated. Autoimmune antibody, anti-neutrophilic cytoplasmic antibody, and anti-nuclear antibody were negative. *Pseudomonas aeruginosa* was isolated from the sputum several times. Computed tomography revealed diffused patchy shadows, ground glass appearance and multiple pneumatocoeles (Figure 2).

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Department of Pulmonary and Critical Care, Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China (Zhang XL, Liu Y and Dai HP)

Department of Respiratory Diseases, Hebei Qinhuangdao Third Hospital, Qinhuangdao, Hebei 066001, China (Liu YG)

Correspondence to: Dr. Dai Huaping, Department of Pulmonary and Critical Care, Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China (Email: yutian629@gmail.com)

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Table 1. Lymphocyte count and lymphocyte subsets analysis

Date	Lymphocytes absolute (/μl)			Lymphocyte subsets (%)				
	T cells (1185–1901)	B cells (180–324)	NK cells (175–567)	CD3 ⁺ (62.6–76.8)	CD4 ⁺ (30.0–46.0)	CD8 ⁺ (19.2–33.6)	CD19 ⁺ (8.5–14.6)	CD16 ⁺ CD56 ⁺ (9.5–23.5)
March 3, 2012	2149	348	35	84.8	44.6	32.4	13.2	1.1
June 14, 2012	2216	394	19	84.3	48.9	29.2	14.8	0.7
October 25, 2012	2059	284	37	86.5	27.0	28.3	11.9	1.3

According to National Institutes of Health (NIH) scoring system for HIES, the disease score for the patient was 60 points. Genetic analysis found a known STAT3 mutation (R382W) affecting the DNA-binding domain. The patient was diagnosed with STAT3-deficient HIES combined with NK cell deficiency. Cefoprazone/Sulbactam was given and led to clinical improvement of the pulmonary infection.

HIES is a rare, complex primary immunodeficiency characterized clinically by atopic dermatitis, extremely high serum IgE levels and susceptibility to infections. HIE has diverse clinical manifestations and heterogeneous genetic origins, and two distinct entities have been identified. Mutations in the signal transducer and the activator of transcription 3 (STAT3) gene result in the classical multi-systemic, autosomal dominant form of HIES. The non-immunological multi-systemic abnormalities observed in most autosomal dominant patients, include a distinctive facial appearance and skeletal/connective tissue abnormalities (pathological fracture, retention of deciduous teeth, scoliosis, and hyper extensibility). Whereas, a null mutation in the tyrosine kinase 2 (TYK2) gene causes an autosomal recessive entity associated with severe viral infections, central nervous system involvement, and intracellular bacterial infections, but absent of skeletal/connective tissue abnormalities.¹ HIES is diagnosed on the basis of a NIH scoring system which uses a combination of clinical manifestations and laboratory markers. With the advances in molecular immunology, genetic analysis may help confirm the clinical diagnosis. However, the association of genotype and phenotype of HIES needs to be further investigated. The immunologic phenotype of STAT3-deficient HIES is characterized by high serum IgE levels, eosinophilia, impaired neutrophil chemotaxis, and Th17 lymphopenia. Typically, patients with HIES have normal levels of NK cells. Chandesris et al² documented the molecular, cellular, and clinical features of 60 patients with heterozygous STAT3 mutations from 47 kindreds followed in France. They found that NK cells were present in normal numbers in 43 patients and only five patients showed low NK cell counts.

NK cells lack surface expression of T cell receptors and immunoglobulin and comprise 5%–15% of human peripheral blood lymphocytes. NK cell deficiency is defined as a consistent and significant reduction in NK cell numbers, or absence of NK cell activity. Human NK cell deficiencies are divided into four broad categories: (1) isolated NK cell deficiency associated with an identified genetic defect; (2) isolated NK cell deficiency without a known genetic defect, and not associated with a known disease; (3) NK cell deficiency associated with a disease

due to a known genetic defect that also causes another immune deficiency; and (4) NK cell deficiency associated with a known disease without a known genetic etiology. The most common forms of NK deficiency are associated with several forms of severe combined immunodeficiency (SCID).³ To our knowledge, the coexistence of HIES and NK cell deficiency has not been previously reported in the literature.

A major role for NK cells is defense against infection, viral infection in particular. NK cells play a central role in the crosstalk between innate and adaptive immune responses. The function of NK cells in the setting of viral infection most likely involves the regulation of adaptive immunity as well as the control of viral replication. NK cells have been long considered minor players in the pathogenesis of acute and chronic hepatitis B and hepatitis C. However, some recent evidence suggests that NK cell dysfunction is associated with continuous low level liver necroinflammation and a concomitant inability to eradicate the virus.⁴ In our patient, the HBV and HCV infection persists with a high level of replication in spite of aggressive antiviral therapy. Although we do not know whether the NK cell defect preceded the HBV and HCV infections, we assume that the reduction in NK cells may be a cause of his immunological susceptibility. In addition, our patient also has a history of tuberculosis and PCP, neither of which is frequently seen in isolated HIE.

In conclusion, we present a case of HIES, combined with a markedly reduced NK cell population. This case may highlight the need of NK cell evaluation whenever an autoimmunity, immunoincompetency, or immunodeficiency investigation is undertaken. Moreover, NK cells are a challenging topic and deserve further investigation, since the exact role of NK cells in human immune-relevant disease has not yet been established.

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