Frank elevation of bronchoalveolar lavage fluid IgE level in hyperimmunoglobulin E syndrome

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Abstract

Hyperimmunoglobulin E syndrome (HIES) is a rare hereditary immunodeficiency disorder characterized mainly by an elevated serum immunoglobulin E (IgE) level. However, the IgE level in bronchoalveolar lavage fluid (BALF) of HIES patients has not been addressed before. The case of a 24-year-old non-smoking Caucasian male HIES patient with classical eczematoid rashes and recurrent postural skin infections of staphylococcal aetiology manifested since 3 months of age on his face, scalp and limbs. From the age of 5, the patient had severe recurrent bilateral staphylococcal pneumonias, although milder respiratory tract infections such as purulent otitis media were reported already as early as 1.5 years of age. The patient also had other findings characteristic of HIES. These included slightly hyperextensible joints, clubbed fingers and characteristic facial appearance with exaggerated skin pores, but no significant scoliosis, bone fractures from minimal trauma, or abnormalities associated with primary teeth. His National Institutes of Health (NIH) HIES score was 57. There has been no HIES cases diagnosed in his family. The patient has received continuous prophylactic treatment with trimethoprim/sulfamethoxazole and has experienced an active infection. Nevertheless, he had radiographically visible pneumatoceles (Figure 1A, 1B) and sequelae of pneumonias in the form of multiple scarring, slightly reduced lung volumes (forced vital capacity, FVC and forced expiratory volume in one second, FEV1 71% and 68%, respectively) and a decline in diffusion capacity of the lung (D_{LCO}, 66% predicted). No mutations in the signal transducer and activator of transcription 3 (STAT3) gene were detected in this patient. After obtaining informed consent, fiberoptic bronchoscopy was performed out of clinical exacerbation to check for signs of infection and bacterial aetiology and to assess disease markers in BALF (Figure 1C). Bronchoalveolar lavage was performed by instilling a total of 200 mL saline, divided into 20-mL aliquots, into the 4th segment in the right middle lobe, free of radiographically detectable opacities. The total IgE content was measured by chemiluminescence immunoassay method (CLIA) using an Immulite® 2000 analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), whereas the levels of total IgA, total IgG and total IgM appeared from the centrifuged BALF. An aspirated fluid recovery of 80% (160 mL) was obtained. No ciliated bronchial epithelial cells and no eosinophils were detectable in BALF displaying 95% alveolar macrophages. A very limited number of eosinophils (2 cells on average per low power field) were detected only when the sections of cell blocks created from the centrifuged BALF pellet was analysed. The proportions of neutrophils and lymphocytes in BALF were 1% and 4%, respectively, with the CD4/CD8 T-lymphocyte ratio of 0.29. Analysis revealed an elevated IgE level in BALF of 15.10 ng/mL (6.24 IU/mL), whereas the levels of total IgA, total IgG and total IgM appeared at 9.0 mg/L, 110.0 mg/L and <15 mg/L, respectively. The level of IgE in serum was 130,583 mg/L (53,960 IU/mL), while the serum levels of IgA, IgG and IgM were 2.34 mg/mL, 22.0 mg/mL and 1.71 mg/mL, respectively. To standardise the immunoglobulin levels, as well as to assess the possible transudation of the immunoglobulins, with use of BALF and serum albumin concentrations (100.6 mg/L and 39 g/L, respectively), the relative coefficients of excretion (RCE) were calculated according to the formula RCE = ([Ig BALF]/[Ig serum])/ ([albumin BALF]/[albumin serum]). For IgE, IgA, IgG and IgM, the RCE values were 0.0448, 1.49, 1.94 and <3.40, respectively. The patient had peripheral eosinophilia of 1.10×10^9/L (23% of the total leukocyte count of 4.77×10^9/L), normal lymphocyte count (33%) and decreased neutrophil count (34%).
Discussion

The IgE level in the current patient with HIES should be deemed as frank heightenings since it appeared at a concentration, which is usually detected in the serum from normal individuals and exceeds the range reported in the BALF of healthy individuals (0.06-0.3)\(^5\) at least 50-fold. As is the case in a healthy person,\(^6\) the BALF of healthy individuals (0.06-0.3)\(^5\) at least 50-fold. As is the case in a healthy person, the IgE levels were normal in both BALF and serum, whereas those of IgE were elevated at least 5.4 fold in BALF and slightly in serum. Elevated BALF IgE has also been reported in atopic asthmatics with a further increase in both total and allergen-specific IgE after segmental allergen challenge.\(^2\) However, the fact that asthmatics present with RCE values for the total IgE as high as 29.1 suggests a selective local generation of IgE antibodies within the lung, characteristic of pulmonary atopy, and, on the other hand, further supports the diffusion if IgE from circulation in HIES. The molecular mechanisms underlying the heightened serum IgE levels in HIES still remain unresolved.\(^10\) However, recent studies\(^11,12\) identified dominant-negative mutations in the STAT3 gene as a major molecular etiology of the specific immunodeficiency mechanisms in the classical or type 1 HIES.\(^10\) Rather than associated with primary neutrophil chemotactic defects,\(^13\) the pulmonary and cutaneous staphylococcal infections in HIES are most likely due to defects in differentiation of Th17 cells\(^14-17\) resulting in significantly decreased Th17 cell counts following mutations in the STAT3 gene.\(^18,19\) This leads to deficiency of Th17 cytokines and, as a result, the lack of neutrophil-recruiting chemokines and antimicrobial \(\beta\)-defensins crucial in protecting against Staphylococcus aureus, especially in the epithelial cells of the lung and skin.\(^20\) The decreased CD4/CD8 T-lymphocyte ratio in the BALF in HIES, as shown in the current report, is novel, but its significance remains to be elusive. A possibility of inhibition of neutrophil chemotaxis by CD8 cells\(^21\) and switch to the Th2-type secretion profile\(^22\) that may lead to general IgE overproduction cannot be excluded.

Although lacking mutations in the STAT3 gene, based on the clinical and radiographic findings, the patient is most likely to have the type 1 HIES regardless of the negative family history, as such a possibility has been formerly described.\(^12,13\) As the Th17 cells are involved in the immunity of the peripheral lung by antimicrobial peptide secretion, looking at the levels of Th17 cells, as well as \(\beta\)-defensins in the BAL fluid would be of major importance.

This case study not only demonstrates a markedly elevated BALF IgE level in HIES that can be used to support the diagnosis but also raises provocative BALF-related aspects in HIES including a putative link of heightened IgE with the immunologic lesions in HIES, which need to be addressed in further BALF-based studies.

Figure 1. Images from a 24-year-old male patient with hyperimmunoglobulin E syndrome (HIES). (A) A chest computed tomography scan during a clinical exacerbation showing a thin-walled pneumatocele visible in the right upper lobe along with patchy consolidations characteristic of Staphylococcus aureus pneumonia. (B) A computed tomography scan depicting the same region during a clinical remission. (C) A bronchoscopic view of the main bronchi out of clinical exacerbation.

References

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