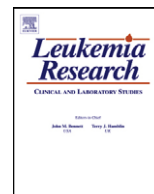




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## Case report

# Diffuse large B-cell lymphoma in a patient with hyper-IgE syndrome: Successful treatment with risk-adapted rituximab-based immunochemotherapy

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## ABSTRACT

Hyper IgE syndrome (HIES) is a rare primary immunodeficiency characterized by eczema, recurring skin and lung infections, elevated serum IgE and skeletal/connective tissue abnormalities. Increased incidence of malignancies, especially lymphomas has been previously described. Here we report a case of a 44-year-old patient with diffuse large B-cell lymphoma successfully treated with risk-adapted rituximab-based immunochemotherapy. Despite dose reductions and schedule adaptations required by severe pneumonia with sepsis occurring during the first cycle of R-CHOP immunochemotherapy, the patient achieved a long-lasting complete remission. This case reports underscores the need for multidisciplinary approach to management of malignancies in patients with HIES.

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## 1. Introduction

Hyper-immunoglobulin E (IgE) syndrome (HIES) or Job's syndrome is a rare primary immunodeficiency first described in 1966 [1] and characterized by eczema, *Staphylococcus aureus*-induced skin abscesses, recurrent pneumonias with pneumatocele formation, Candida infections, skeletal/connective tissue abnormalities and high serum level of IgE (>2000 IU/ml). To date, approximately 300 cases of HIES have been published. The prevalence of HIES is lower than 1:1,000,000. Most cases are sporadic but autosomal dominant [2] as well as autosomal recessive forms [1] have been described. The mechanism of immunodeficiency in HIES is still unknown. Diagnosis of HIES is based on combination of clinical and laboratory findings, including recently introduced molecular biology testing. Here we report a case of patient with HIES and diffuse large B-cell lymphoma who achieved a durable remission after modified immunochemotherapy.

## 2. Case report

A 44-year-old male was diagnosed with HIES in early childhood. He suffered from recurrent infections—multiple otitis media, sinusitis, bronchitis, pneumonias with pneumatocele formation

resulting in bronchiectases with perifocal fibrosis (Fig. 1), *S. aureus*-induced skin abscesses and candidiasis. His face had typical features of HIES—facial asymmetry, broad nose, deep-set eyes with a prominent forehead, rough appearance of facial skin with exaggerated pore size with asymmetry and dysmorphic signs. Severe skeletal osteoporosis lead to vertebral fractures and slight injuries to fractures of long bones. The level of serum IgE was 2000–4500 IU/ml. The patient was admitted to hematology department because of abdominal pain and enlarged inguinal lymph nodes. Diffuse large B-cell lymphoma was diagnosed from the biopsy of retroperitoneal lymph node in April 2006. Computer tomography revealed abdominal, mediastinal and inguinal lymphadenopathy. Bone marrow aspirate and biopsy was negative. The diagnosis was concluded as diffuse large B-cell lymphoma, Ann Arbor stage IIIA, age-adjusted International Prognostic Index 2 (high-intermediate risk group). After a short prephase (methylprednisolone 80 mg intravenously days 1–5, vincristine 2 mg intravenously day 1), the patient received R-CHOP immunochemotherapy in standard doses (rituximab, 375 mg/m<sup>2</sup>, cyclophosphamide, 750 mg/m<sup>2</sup>, doxorubicine 50 mg/m<sup>2</sup> and vincristine 2 mg intravenously day 1, prednisone 100 mg orally days 1–5). Primary prophylaxis of febrile neutropenia (FN) with granulocyte colony-stimulating factor (G-CSF) was started from day 6 because of expected high risk of infectious complications. Nevertheless, the patient was readmitted on day 10 of the first cycle for pneumonia with severe neutropenia (positive sputum cultures for *Pseudomonas aeruginosa* and *Aspergillus fumigatus*) and septic shock requiring volume resuscitation at

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**Fig. 1.** Computer tomography of chest showing bronchiectasis with perifocal fibrosis.

intensive care unit. After aggressive antimicrobial treatment with combination of antibiotics (piperacillin/tazobactam, amikacin) and antimycotics (voriconazole), pneumonia partially resolved. We decided to continue with 6 weekly doses of rituximab monotherapy because of life-threatening complications after the first cycle of R-CHOP. Restaging CT after this treatment showed partial remission. After complete recovery from pneumonia, further 3 cycles of dose-attenuated R-CHOP (reduction of cyclophosphamide and doxorubicine to 2/3) with primary prophylaxis of febrile neutropenia with G-CSF and antibiotic support were administered without substantial complications. The patient achieved complete remission confirmed by final CT/PET scan. Interestingly, levels of IgE decreased during immunochemotherapy to normal values, but increased again to levels >2000 IU/ml within 3 months. After cessation of immunochemotherapy, recurrent pulmonary infections caused by multiresistant *P. aeruginosa* have occurred. Dilated cardiomyopathy was diagnosed 1 year after chemotherapy with substantially decreased ejection fraction to 30%. This complication was considered to be associated with multiple infections and with the use of anthracyclins in R-CHOP regimen. The patient is currently in complete remission lasting more than 3 years. DNA sequencing detected point mutation of STAT3 (Signal Transducer and Activator of Transcription 3, lysin–threonin replacement in exon 340 of DNA-binding domain) which confirmed the diagnosis of autosomal dominant HIES (Fig. 2).

### 3. Discussion

The hyper IgE syndrome is a multisystem disease. Recently published data discovered causal heterozygous signal transducer and activator of transcription 3 (STAT3) mutation in autosomal-dominant HIES patients. Most STAT3 mutations were found in DNA-binding domain or Src Homology 2 (SH2) domain. Mutation leads to disruption of STAT3-dependent pathways which are crucial for signaling of many cytokines (interleukin-6, 10, 21, 22) [3,4]. T(H)17 cells are absent or low [4]. Decreased level of IL-17 has been observed in ex vivo experiments leading to failed inflammation response [5]. Association between HIES and various types of cancer is well known; lymphomas are the most frequently reported types. Due to rarity of HIES, the association between lymphoma and HIES is unlikely to be coincidental. Leonard et al. estimated that patients with HIES have 259-fold increased relative risk of lymphoma development compared to general population [6]. To the best of our knowledge, there have been only five cases of patients with diffuse large B-cell lymphoma and HIES published so far; this is the first case report of patient with HIES and lymphoma with confirmed

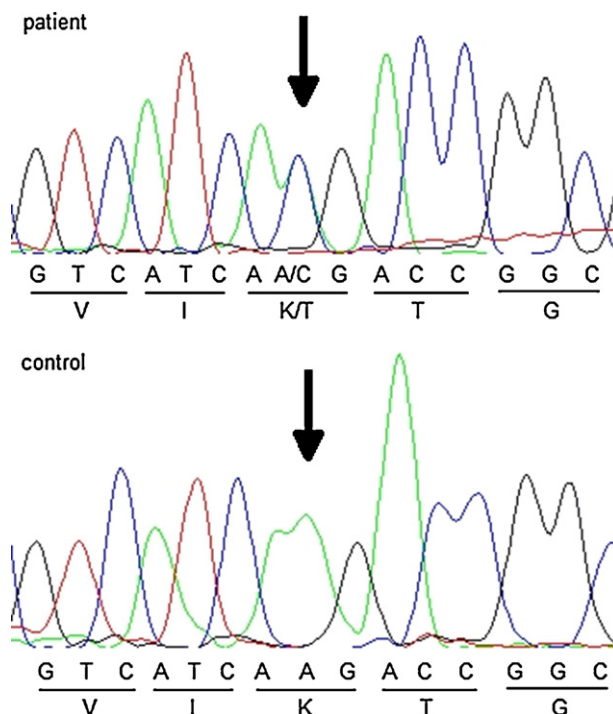


**Fig. 2.** Heterozygous point mutation (c.1259A>C) in exon 340 of the DNA-binding domain of STAT3 in the patient with hyper-IgE syndrome. Normal sequence in a healthy control.

STAT3 mutation. Other presented cases of lymphoma patients with HIES included peripheral T-cell lymphoma [7], Burkitt's lymphoma [8,9], mantle cell lymphoma [9], and Hodgkin's lymphoma [10,11]. There does not appear to be an association between HIES and any histological type of lymphoma. The true mechanism of lymphomagenesis in HIES remains obscure.

Clinically, there is no causal treatment of HIES. There is one only report of allogeneic stem cell transplantation for HIES in a 46-year-old male with aggressive B-cell lymphoma who was transplanted from HLA-identical sister. Posttransplant serum IgE decreased to normal; however, the patient died 6 months after transplant due to an interstitial pneumonia [6].

In published case reports of patients with DLBCL, one of them was successfully treated with dose-adjusted-EPOCH chemotherapy [6], others with other anthracycline-based chemotherapy [12–15]. One out of 5 presented patients died for severe infectious complication after allogeneic stem cell transplantation [6]. The fundamental problem in the treatment of HIES patients with lymphoma is profound immunodeficiency, history of multiple pulmonary and skin infections and colonization by multiresistant microbi (*P. aeruginosa*, *A. fumigatus* etc.). It is extremely difficult to administer planned dose and schedule of chemotherapy because of high risk of severe infectious complications. Therefore, intensive supportive care is necessary. Our patient has been treated with standard first-line treatment for DLBCL: R-CHOP, with primary FN prophylaxis with G-CSF. Life-threatening complications after first cycle of R-CHOP required the change of therapeutic approach to 6 doses of rituximab monotherapy in weekly intervals to bridge the period to complete recovery after severe septic shock and pneumonia. After this, we continued with other 3 cycles of R-CHOP in reduced doses. This case demonstrates the importance of tailored therapy and necessity of intensive supportive care in management of patients with HIES and aggressive lymphoma. There is no standard treatment schedule for this cohort of patients: each patient should be treated individually, on a “step-by-step” principle, with maximal caution. Dose-intensive treatment is not recommended for these patients

because of high risk of severe infectious complications. The effect of rituximab for HIES has been already described in literature [16]. The level of IgE decreased in our patient to normal value after therapy but it is hard to distinguish whether this was the effect of rituximab or other immunosuppressive drugs. Clinically, we did not see any improvement in the frequency of pulmonary infections. There is no standardized approach to HIES patients yet. Prophylactic antibiotic/antimycotic treatment is recommended. Support by intravenous immunoglobulins was successfully used in some cases. Effects of omalizumab or ranitidine for HIES is explored in several clinical trials. Finally, the system of care for patients with HIES has to be multidisciplinary: specialists in hematology, dermatology, immunology and pulmonary medicine should be involved in order to achieve optimal treatment results.

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