

HYPER-IGE SYNDROME WITH EPSTEIN-BARR VIRUS ASSOCIATED EXTRANODAL NK/T CELL LYMPHOMA OF SKIN

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Hyper-IgE syndrome, also known as Job's syndrome, is a rare primary immunodeficiency that was first described in 1966. This syndrome is associated with an increased risk for malignancies. Here, we report an 18-year-old woman who was frequently hospitalized since childhood because of recurrent pneumonia and urinary tract infection. Multiple erythematous papules and nodules with ulceration were found on her face and right forearm. A skin biopsy showed angiocentric and angiodestructive atypical lymphoid infiltration. *In situ* hybridization revealed latent Epstein-Barr virus-infected lymphoid cells. Accordingly, this indicates that Epstein-Barr virus infection may have induced the extranodal natural killer/T cell lymphoma in this patient with hyper-IgE syndrome.

Key Words: Epstein-Barr virus, extranodal NK/T-cell lymphoma, Hyper-IgE syndrome, Job's syndrome
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Hyper-IgE syndromes (HIES) are rare primary immunodeficient diseases. Autosomal dominant forms of HIES [1] and autosomal recessive forms [2] have been described and are characterized by recurrent skin and pulmonary infection and high serum levels of IgE. However, the exact immunologic defect responsible for the recurrent infection is unknown. An increased risk of malignancies, including Hodgkin's and non-Hodgkin's lymphoma, has also been described [3,4]. Most of the lymphoid malignancies are usually of B cell origin; few originate from T cells. Here, we present a case of HIES in a young woman with Epstein-Barr virus (EBV) infection-induced extranodal natural killer (NK)/T-cell lymphoma.

CASE PRESENTATION

An 18-year-old woman was admitted in December 2008 because of swelling and redness of her left eye persisting for 4 days even though topical eye drop antibiotics were used. On admission, she was afebrile and her vital signs were stable. Laboratory data showed anemia, pyuria, increased C-reactive protein, and hyperproteinemia (9.1 g/dL; normal 6.4–8.3 g/dL). Her renal function and liver enzymes were within normal limits.

A dermatologist was consulted because of multiple ulcerations on the patient's face. The lesion first appeared 1 month ago as a small erythematous papule over her left temporal area, which grew to a size of 6×6 cm (Figure 1). Only mild tenderness was noted and the lesion responded poorly to topical antibiotics. Multiple painless papules subsequently developed on her face and were ulcerated and encrusted. These features responded poorly to topical retinoid because of suspected folliculitis that was initially noticed by her family. A painless, central necrotic crust with an



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erythematous border nodule of fixed/rubbery consistency was noted on her right forearm on admission (Figure 1).

A skin biopsy was done on her right arm after consultation with the dermatologist. Histopathology of the skin biopsy showed marked perivascular lymphoid tumor cell infiltration and focal angiodestruction by the lymphoid tumor cells covering the dermis and subcutaneous tissue (Figure 2). Coagulative necrosis was found around the adjacent skin tissue. Immunohistochemical analysis showed the infiltrating CD3-positive lymphoid cells (Figure 3A), and the scattered

reactive lymphocytes were positive for CD20. Staining for CD56, a marker for NK cells, was negative (data not shown). However, *in situ* hybridization revealed a positive reaction for EBV-encoded small nuclear RNA covering the atypical lymphoid cells (Figure 3B). Serological tests with an enzyme-linked immunosorbent assay for EBV confirmed the presence of IgG antibodies to viral capsid antigen (antibody titer value of 11.5) and Epstein Barr nuclear antigen (antibody titer value of 2.0).

The patient's medical history included recurrent skin abscess that required drainage and systemic



Figure 1. A central ulcerated nodule was noticed over the patient's left temporal area, and a central necrotic crust, erythematous border nodule was found on the right forearm (inset).

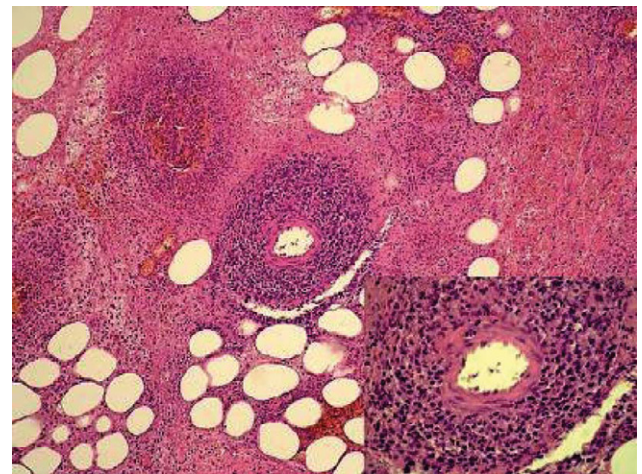


Figure 2. Histochemical staining showing dense atypical lymphocyte infiltration in the dermis, subcutis, and around the blood vessels (hematoxylin & eosin; original magnification, 100×) and focal angiodestruction induced by the atypical lymphoid cells covering the dermis (inset; original magnification, 400×).

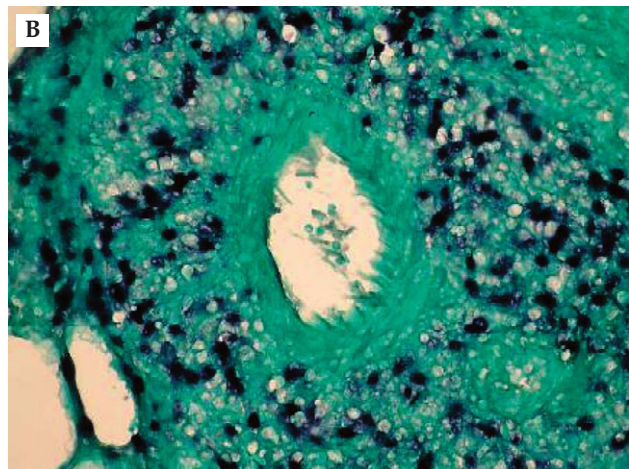
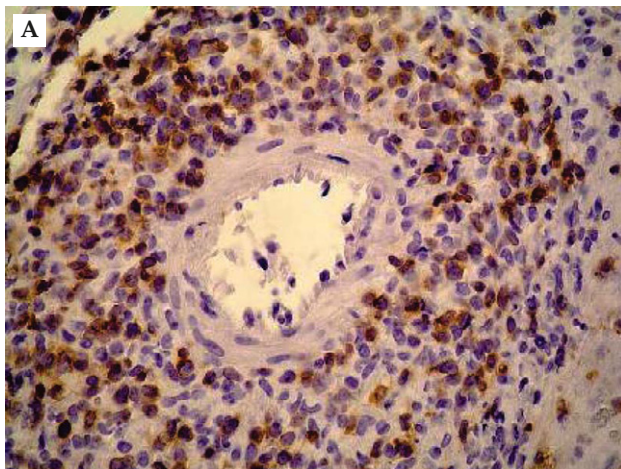


Figure 3. (A) Immunohistochemical stain showing CD3 positivity over the lymphoid tumor cells (3-amino-9-ethylcarbazole; original magnification, 400×). (B) Chromagenic *in situ* hybridization showed the expression of Epstein-Barr virus-encoded small nuclear RNA in the infiltrating atypical lymphoid cells (original magnification, 400×).

antibiotics, frequent hospitalization because of recurrent pneumonia and urinary tract infection, development delay with short stature (<3rd percentile of normal range), and hypersensitivity to mosquito bites and eczematous change with oozing since childhood. Recurrent tonic-clonic seizures were noticed since the age of 11. A high serum IgE concentration of 11,421 IU/mL was noted for the first time at the age of 8 years and remained high (>5,000 IU/mL) for several years. No family history of HIES or malignancy was mentioned. Her underlying disease was diagnosed as HIES.

A fluorodeoxyglucose-positron emission tomography scan was performed and a mild glucose hypermetabolic lesion in the left temporal subcutaneous region was consistent with lymphoma with skin involvement. Bone marrow biopsy showed hypercellular marrow (about 70% cellularity) with a decreased myeloid-erythroid ratio but without lymphoma involvement. Staging by fluorodeoxyglucose-positron emission tomography showed Ann Arbor stage IE. The CHOP (cyclophosphamide, 450 mg; liposomal doxorubicin, 30 mg; vincristine, 0.8 mg; and prednisone 40 mg per treatment course) chemotherapy protocol was used and the skin lesions had disappeared by the fifth session of chemotherapy in May 2009.

DISCUSSION

HIES, also known as Job's syndrome, is a rare primary immunodeficiency and was first described by Davis et al in 1966 [5]. It manifests with chronic recurrent systemic infection and increased serum IgE levels. Abnormal development of connective tissue and bone may also be found. Central nervous system abnormalities have been reported. Our patient had a long history of recurrent pneumonia and urinary tract infection and persistently high serum IgE levels. Hypersensitivity to mosquito bites and eczematous changes were noted since childhood. In addition, the patient's developmental delay with a short stature may have resulted from abnormal development of connective tissue and skeleton. Therefore, HIES was diagnosed.

HIES has been reported with an unusual association of Hodgkin's and non-Hodgkin's lymphoma and most cases reported to date were B cell lymphoid malignancies [3,4]. However, extranodal NK/T-cell

lymphoma has not yet been reported in association with HIES. Immunodeficiency diseases may contribute to the increased risk of development of malignant lymphoma. Chronic stimulation with antigenic (e.g. industrial chemicals, metals, and herbicides/pesticides) or infectious agents may promote the development of cutaneous lymphoma. In our patient, the histopathological findings of the skin revealed a polymorphic infiltrate of atypical lymphocytes (CD20- and CD56-negative; CD3-positive) with an angiocentric and angiodestructive infiltration in the dermis and subcutis. Several studies have reported that the frequency of CD56 expression in extranodal NK/T-cell lymphoma ranges from 50% to 80% [6–8]. CD56 expression was negative in our patient, but *in situ* hybridization indicated latent EBV-infected lymphoid cells and the histologic features of our patient were indistinguishable from CD56-positive cases. Thus, the diagnosis was made in the presence of EBV positivity. This indicates that EBV infection induced the extranodal NK/T-cell lymphoma in a patient with HIES.

EBV, a member of the γ herpes family of viruses, is very prevalent in Asian countries. Primary infection usually causes a mild, self-limited illness, or infectious mononucleosis, and less frequently induces virus-associated hemophagocytic syndrome [9–11]. EB virus can infect B, T, and NK cells, and persistent infection has been reported. Nasal-type extranodal NK/T cell lymphomas are strongly associated with latent EBV infection (>80%) and show a very aggressive clinical course with early dissemination despite chemotherapy [12,13]. In HIV-infected individuals, the incidence of lymphomas is considerably increased, and EBV is present in 75% of these lymphomas [14,15].

Defective immunosurveillance may contribute to the development of lymphoma, such as in our case. Moreover, our patient also had hypersensitivity to mosquito bites characterized by intense local skin reactions and systemic symptoms such as high fever and lymphadenopathy. Such observations have been seen in many patients affected by hypersensitivity to mosquito bites who also have chronic active EBV infection and often develop and die due to lymphoproliferative diseases, such as hemophagocytic syndrome and NK cell lymphoproliferative disease [16]. In addition to EBV-encoded small nuclear RNA, the *in situ* hybridization assay localized the EBV to biopsy tissue and the

serological test for EBV showed IgG antibodies to VCA and EBNA. This may document prior EBV infection and reactivation. Undoubtedly, EBV infection had a pivotal role in this patient. A higher rate of reactivation of EBV infection may lead to uncontrolled lymphoproliferation. Clearly, the host immune system in patients with HIES is impaired and the immune response to EBV may be insufficient for appropriate immune control. Chronic persistent infection may trigger an abnormal transformation to malignancy.

In summary, HIES is associated with an increased frequency of lymphoma. However, most of the reported cases were B cells lymphoid malignancies. To our knowledge, we present the first case in a young adult of HIES developing unusual extranodal NK/T-cell lymphoma. Careful evaluation and the accompanying clinical findings should aid early diagnosis and treatment.

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IgE 過高症候群合併 EB 病毒有關 皮膚 NK/T 淋巴瘤

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於 1966 年，Davis 第一個描述有關 IgE 過高症候群，稱為 Job 氏症候群。有報告指出這會增加惡性腫瘤的機率。我們提出一位 18 歲年輕女性，在臉及右前臂上出現數顆紅色丘疹和有潰爛的結節。病患從童年起就因反覆性肺炎和泌尿道感染而需入院治療。皮膚切片顯示非典型的淋巴球浸潤於血管周圍並且造成破壞。利用原位雜交方式發現 EB 病毒感染的淋巴球細胞。這表示 IgE 過高症候群合併 EB 病毒感染引發皮膚 NK/T 淋巴瘤。

關鍵詞：Epstein-Barr 病毒，NK/T 淋巴瘤，IgE 過高症候，Job 氏症候群
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