



CASE REPORT

Epstein-Barr virus infected natural killer cell lymphoma in a patient with hypersensitivity to mosquito bite: A case report

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KEYWORDS

Hypersensitivity to mosquito bite;
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Summary Hypersensitivity to mosquito bite (HMB) can occur in association with chronic Epstein-Barr virus (EBV) infection and natural killer (NK) cell leukaemia/lymphoma, which was named 'Tokura-Ishihara disease'. This disease is very rare and most previous reports have been documented in Japan. We present a patient who suffered from of pustules on skin, high fever, myalgia and multiple lymph node enlargements after mosquito bite from childhood. Recently, multiple lymph nodes were palpable on his both inguinal area. Peripheral blood smear (PBS) revealed many large granular lymphocytes and the skin lesion showed a dense dermal and subcutaneous infiltrate of lymphocytes. The lymph nodes and perinodal adipose tissue were infiltrated by atypical lymphoid cells in which EBER-positive signals were identified by in situ hybridization using EBV encoded RNA-1 probe. He was diagnosed as having Tokura-Ishihara disease and receives chemotherapy now. Here, we report a case of this disease with a precise pathological description on the lymph node biopsy.
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Introduction

HMB is defined as intense local skin reaction including erythema, bulla, severe ulcers and

residual scarring with general symptoms such as high fever, malaise, cramp, bloody stool, hematuria and proteinuria following mosquito bites.¹ Accumulated clinical studies have revealed that HMB can occur in association with chronic Epstein-Barr virus (EBV) infection and natural killer (NK) cell leukaemia/lymphoma, which was named 'Tokura-Ishihara disease'.² In most cases reported previously, this

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Figure 1 Multiple old ulcers with healing scar in the leg.

disease has been diagnosed through peripheral blood study and skin biopsy without pathological examination of the lymph node.³⁻⁶ Here, we report a case of HMB-associated natural killer cell lymphoma infected by EBV with a precise pathological description on the lymph node biopsy.

Case report

A 20-year-old man was referred to our hospital for the evaluation of the fever for 5 months and palpable mass on the both inguinal area. He had a history of pustules on skin, high fever, myalgia and multiple lymph node enlargements, which developed several hours after mosquito bite from his early childhood. He lost his weight about 3 kg in a month recently. On the physical examination, there were multiple skin lesions on the whole body including erythema, bulla, ulcer, pustule and healing scar, especially anterior surface of

the lower leg (Fig. 1). And multiple, conglomerated large lymph nodes were palpable on the both inguinal area. On the hematologic examinations, white blood cell count 8900/ μL , hemoglobin 12.2 g/dl and platelet 208 000/ μL were within normal range but lactate dehydrogenase (LDH, 463 IU/l) and C-reactive protein (CRP, 2.8 mg/dl) was increased. Peripheral blood smear (PBS) revealed many large granular lymphocytes. However, no atypical lymphocyte was found in PBS. There were no abnormal findings in the bone marrow biopsy. Hepatosplenomegaly and other lymphadenopathy were not noted on abdominal CT. Biopsies from the mosquito bite-skin lesion on the shin, and right inguinal lymph node was done. The skin showed a subepidermal bulla beneath the necrotic epidermis and a dense dermal and subcutaneous infiltrate of lymphocytes and fewer numbers of eosinophils and neutrophils. Multifocal atypical lymphoid cell proliferations with scattered epithelioid cells were noted as well (Fig. 2(A)). The lymph nodes were three in number and measured up to 3.5×2.0 cm. The cut surface was slightly friable. Histologically, normal lymphoid structure was almost effaced with easily identifiable atypical lymphoid cells showing large-sized atypical nuclei, irregular nuclear membrane, many mitoses, and high nuclear-cytoplasmic ratio (Fig. 2(B)). Perinodal adipose tissue was infiltrated by atypical lymphoid cells. These atypical lymphocytes expressed cytoplasmic CD3 (DAKO, Glostrup, Denmark) and CD56 (DAKO, Glostrup, Denmark). CD4, CD8, CD10, CD19, and EBV latent membrane protein 1 was negative (DAKO, Glostrup, Denmark). EBV-positive signals were identified in the nuclei of numerous atypical cells by in situ hybridization using EBV encoded RNA-1 probe (DAKO, Glostrup, Denmark) (Fig. 3). EBV was negative in bone marrow biopsy. The patient was diagnosed as having a NK cell (large granular lymphocyte) lymphoma

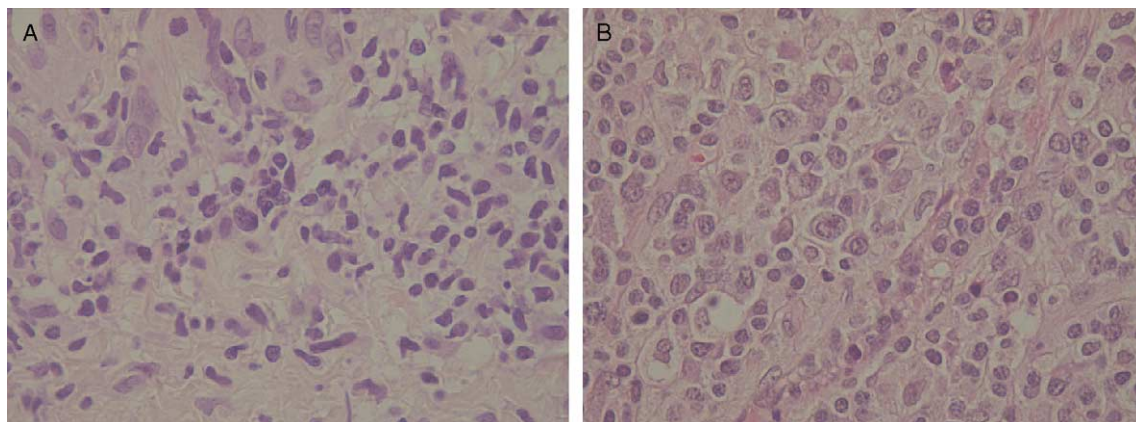


Figure 2 (A) Atypical lymphocytes in the dermis of leg skin. (B) Biopsy of a cervical lymph node showed a proliferation of medium to large-sized atypical lymphocytes with slightly irregular nuclei.

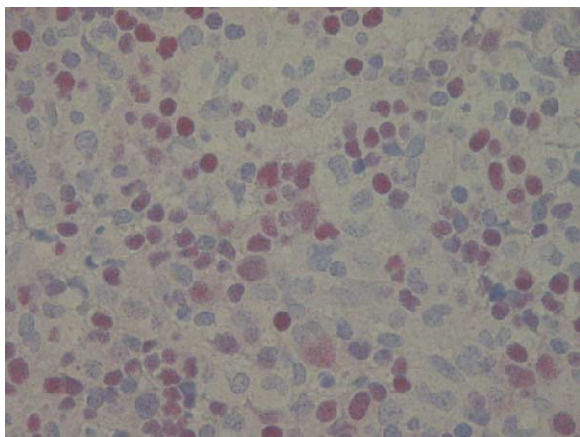


Figure 3 These large atypical lymphocytes were positive in the EBER in situ hybridization.

associated with HMB and reactivated EBV infection. He is now receiving fourth cycle of chemotherapy with IMEP (ifosfamide, methotrexate, etoposide, and prednisone) regimen.

Discussion

The majority of patient with HMB suffered from chronic Epstein-Barr virus (EBV) infection and natural killer (NK) cell leukaemia/lymphoma.² Association of HMB with NK cell lymphoproliferative disease was firstly described by Tokura et al. in 1990 and a few years later the causative role of EBV in this clinical entity was clarified by Ishihara et al.^{7,8} This disease is very uncommon and most previous reports have been documented in Japan.^{1,2,4-11} Only one case with large granular lymphocytosis has been reported in Korea so far.³ Generally, patients experience HMB at mean age of 6.7 years.² They show several exaggerated reactions to mosquito bite including skin eruption and various general symptoms. Serum titres of anti-EBV antibody are elevated in most cases. More than half of patients died at the age of 10-31 years due to a variety of hematologic malignancy including NK cell leukaemia/lymphoma.²

According to the REAL classification, lymphoproliferative lesion in this disease is classified as large granular lymphocyte leukaemia, NK-cell type while there are at least four differences in the clinical features between indolent NK-cell large granular lymphoproliferative disorders and Tokura-Ishihara disease.^{2,9} First, the median onset age of the former is approximately 60 years, whereas that of the latter is 6.6 years. Second, the vast majority of patients with the indolent type are not associated with EBV. Third, the clinical course of

Tokura-Ishihara disease is not indolent but aggressive, especially at its end stage. Finally, there has been no report of complication of HMB in patients with indolent NK-cell large granular lymphoproliferative disorders. Thus Tokura-Ishihara disease is likely to be different clinical entities from indolent NK-cell large granular lymphoproliferative disorders.²

The most reliable theory on the underlying pathophysiological mechanism is that NK cells are the targets of EBV infection and the infected NK cells activate, proliferate and release cytokines probably induced by some mosquito constituent.^{2,10,11} All these actions provoke cytotoxic mechanism which would lead to tissue damage, namely HMB.^{10,11} The repeated HMB might induce malignant clonal expansion of EBV infected NK cell.¹¹

Common and crucial pathological finding in this disease is the proliferation of clonal EBV DNA-containing NK cell. Serum viral capsid and early antigen IgG are positive.² Peripheral blood mononuclear cells contain typically 30-70% of NK cells.² For diagnosis, peripheral blood study and skin biopsy from the mosquito-bite site are useful. In our case, we documented the proliferation of clonal EBV DNA-containing NK cell in the lymph node as well as in the skin.

In conclusion, we present a case of Tokura-Ishihara disease. In patients with NK lymphoproliferative disease, careful history taking for HMB is very important to diagnose this rare disease.

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