

NK/T-cell Lymphoma in a Child With Hypersensitivity to Mosquito Bites

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Summary: Hypersensitivity to mosquito bite (HMB) is defined as intense skin reactive lesion after mosquito bite. However, some kind of malignant tumor is closely associated with HMB, especially natural killer (NK)/T-cell lymphoma. We described a nasal-type NK/T-cell lymphoma in a 9-year-old girl after a history of 2 years earlier of HMB. Pathologic evaluation revealed the typical histologic features of NK/T-cell lymphoma, and the dermal and subcutaneous inflammatory reaction of HMB lesions. HMB is rarely reported and should be kept in mind as a clinical sign of subsequent NK/T-cell lymphoma in Asian country where HMB is relatively frequently encountered.

Key Words: hypersensitivity to mosquito bites, NK/T-cell lymphoma (*J Pediatr Hematol Oncol* 2009;31:855–857)

Hypersensitivity to mosquito bite (HMB) is characterized by an intense skin reaction including ulceration and necrosis with systemic symptoms after mosquito bite. HMB may occur in close association with chronic Epstein-Barr virus (EBV) infection, and natural killer (NK) cell leukemia/lymphoma. In this report, we present a child patient with extranodal nasal-type NK/T-cell lymphoma after a history of 2 years earlier of HMB.

CASE REPORT

In 2003, a 9-year-old girl was referred to our hospital complaining of pharyngalgia and hyperthermia up to 40°C for 2 weeks. Anti-inflammatory therapy was ineffective in the previous hospital. On physical examination, the pharyngeal mucosa was pale with some purulent secretion on the posterior wall. The soft palate was necrotic and the uvula was absent due to extensive necrosis. On the hematologic examinations, white blood cell count $15.3 \times 10^9/L$ (reference range: 4 to $10 \times 10^9/L$) were highly increased, monocytes 0.138 (reference range: 0.03 to 0.08) and lymphocytes 0.496 (reference range: 0.2 to 0.4) were also increased, hemoglobin and platelet were within normal range but erythrocyte sedimentation rate 56 mm/h was increased. There were no abnormal findings in the bone marrow smear. Hepatosplenomegaly and other lymphadenopathy were not noted on abdominal and chest computed tomography. Extranodal nasal-type NK/T-cell lymphoma was highly suspected despite young age of the patient, and this result was confirmed by a second nasopharynx biopsy as the first biopsy was not evaluable histologically. From September 2003 to November 2004, the patient received totally 6 cycles of CHOPE chemotherapy regimens, and 3 cycles of CHOP regimens in the initial days. Radiotherapy was not performed.

Interestingly, the patient had experienced an intense skin reaction at sites of mosquito bite over a period of 2 years beginning in 2001. These skin lesions were accompanied by systemic symptoms such as fever and malaise, and presented as ovoid to round hemorrhagic erythematous zones with margins well demarcated from adjacent normal skin. These lesions evolved into erosions and ulcers, and skin induration could be found. The skin lesions could recover itself, but the symptom would be got again from the next mosquito bites. After implementation of CHOP chemotherapy for lymphoma, symptoms of HMB were obviously alleviated during the period after 2004. However, the patient experienced HMB again during the time when the patient was not receiving chemotherapy in 2007.

PATHOLOGIC FINDINGS

From nasopharynx biopsy pathology, we found that tumor cells were medium sized and characterized by ovoid nuclei with stippled or granular chromatin, and mitotic figures were easily seen (Figs. 1, 2). The tumor cells showed angiocentricity and angioinvasion. Hyaline degeneration of small vessels was found frequently around neoplastic cells. Coagulative necrosis and apoptotic bodies were readily identifiable, and there was prominent infiltration of inflammatory cells in the tissue. Immunohistochemistry showed that tumor cells were positive for CD56, perforin, GranB, and T-cell markers CD45RO and CD43. The proliferative index using Ki-67 was 90% in tumor cells. EBV in situ hybridization showed a strong positive reaction.

Skin biopsy was first performed in 2007, and it revealed dense dermal and subcutaneous infiltration of atypical lymphoid cells and smaller numbers of eosinophils around eccrine glands, blood vessels, and adipose tissue (Fig. 3). These atypical lymphocytes were CD4 positive, CD8 and CD56 negative, and showed about 60% Ki-67 positivity (Fig. 4). EBV in situ hybridization was positive in about 10% of cells. The recently second skin biopsy revealed similar morphologic changes and immunophenotype in 2008.

DISCUSSION

The incidence of extranodal NK/T-cell lymphoma is relatively low, especially in children. However, pediatric patients may exhibit HMB before malignancy in some cases of NK/T-cell lymphoma. A distinct clinical entity which presents as a triad of HMB, chronic EBV infection, and NK/T-cell lymphoma has been described as HMB-EBV-NK disease or Tokura-Ishihara disease.^{1,2} HMB is reported mainly in children in the first 2 decades of life, and was first described in the literature in 1938.³ More than 50 cases of HMB have been reported in Japan, and there have been several cases in Taiwan and Mexico. In 2001, Tokura et al¹ reviewed the most amount of 58 cases of HMB up to now, including 39 cases reported in the literature and

Received for publication October 25, 2008; accepted January 12, 2009.
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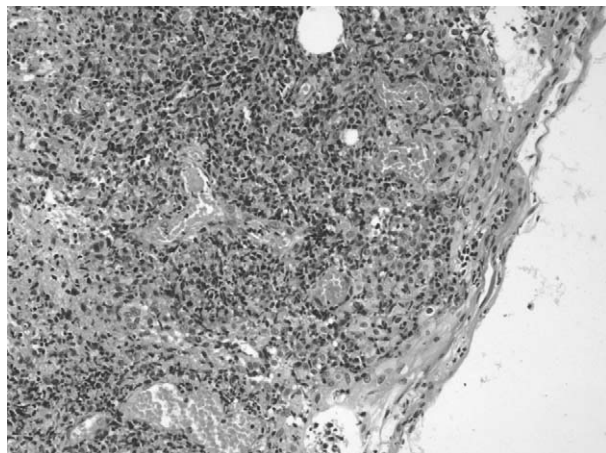


FIGURE 1. Histology of natural killer/T-cell lymphoma showing invasion of squamous epithelium of soft palate by medium-sized tumor cells (hematoxylin and eosin stain, low-power view).

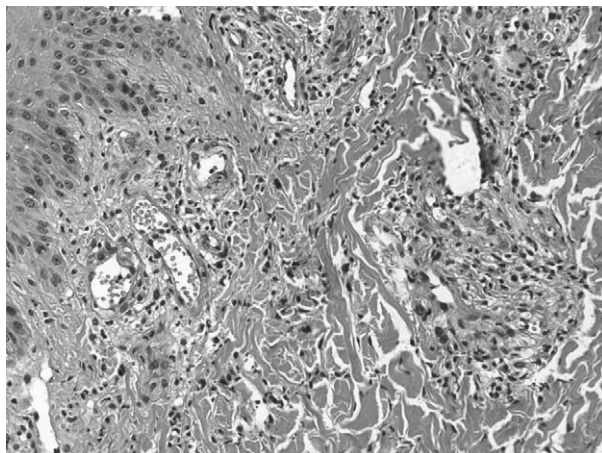


FIGURE 3. Hypersensitivity to mosquito bite lesion shows subcutaneous infiltrate of atypical lymphoid cells around vessels and eccrine glands (hematoxylin and eosin stain, low-power view).

19 cases from inquiry investigation performed by authors, the age at onset of HMB ranged from birth to 18 years [6.7 ± 5.03 y (mean $\pm$ SD)], there was no sex preponderance. More than half of patients (31 cases) died at the age of 10 to 31 years [16.3 ± 5.74 y (mean $\pm$ SD)]. Death was caused by hemophagocytic syndrome in 15 patients (52% of fatal cases) and by malignant lymphoma in 11 patients (35% of fatal cases). There was an extremely high incidence of fatality due to hemophagocytic syndromes, which often happened to patients with chronic EBV infection. It seems likely that the majority of these cases suffered from HMB-EBV-NK disease if they had been characterized according to the clinical triad presented. To the best of our knowledge, this is the first reported case of HMB fulfilling the triad of HMB-EBV-NK disease in Mainland China.

HMB is defined as an intense local skin reaction including erythema, bullae, severe ulcers, and necrosis with systemic symptoms after mosquito bite. High fever and malaise are common symptoms, and lymphadenopathy, hepatosplenomegaly, hepatic dysfunction, hematuria, and

proteinuria are occasionally seen in the clinical course. Serum titers of anti-EBV antibody and peripheral blood mononuclear cells counts are elevated in most cases. After patients recover from these symptoms, they are typically symptom free until the next mosquito bite, thus the patients usually have repeated episodes of severe symptoms induced by mosquito bites. Histologically, HMB is a non-neoplastic inflammatory lesion, showing epidermal necrosis, dermal edema, and perivascular and perieccrine infiltration of lymphoid cells with irregular nuclei. Eosinophils and neutrophils are also seen in the lesion, but there is no evidence of vascular invasion. In this case, the patient had a 2-year history of HMB with high fever and malaise before NK/T-cell lymphoma was diagnosed. Although the EBV antibody titer in peripheral blood was not evaluated, the positive results of EBV in situ hybridization in both lymphoma tissue and the HMB skin lesion indicated this patient had EBV infection. At the same time, the negative CD56 result and low-level expression of EBV in the skin lesion indicated that the skin lesions were HMB rather than

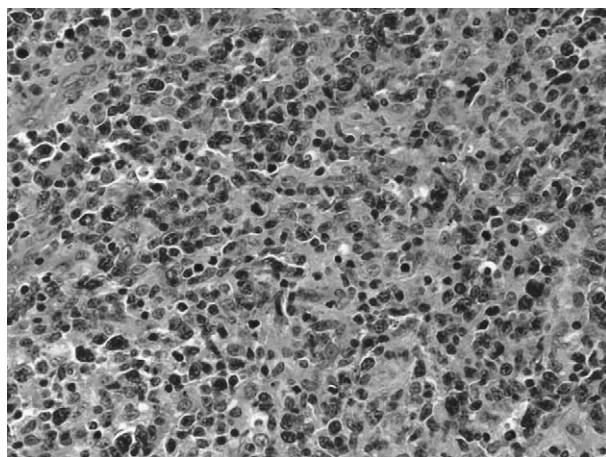


FIGURE 2. Tumor cells were medium sized and characterized by ovoid nuclei with stippled or granular chromatin (hematoxylin and eosin stain, high-power view).

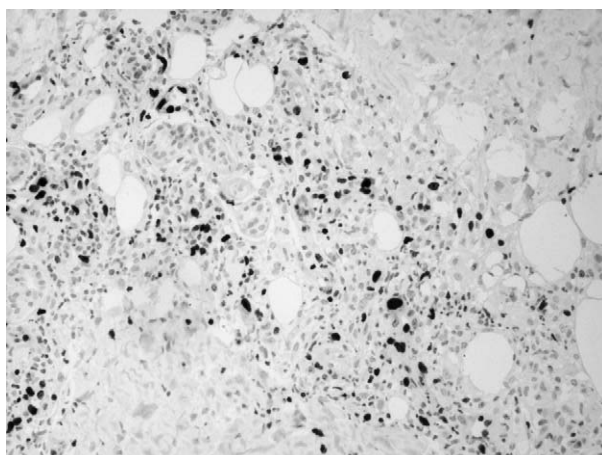


FIGURE 4. Ki67 shows strong positivity in atypical lymphoid cells (immunohistochemistry, low-power view).

involvement of skin by NK/T-cell lymphoma. In fact, the patient cannot live so long time if skin lymphoma involvement happened.

EBV plays a key role in HMB occurrence and in NK/T-cell oncogenesis irrespective of the low level of EBV, which is typically detected in HMB lesions. Both T and NK cells are target cells of EBV, whereas NK-cell-type chronic EBV infection is characterized by HMB and large granular lymphocytosis.⁴ Asada⁵ found that CD4⁺ T cells from HMB patients show a pronounced response to mosquito salivary gland extracts and subsequently induce reactivation of latent EBV infection in NK cells. EBV virus particles are released from NK cells resulting in an intense immune reaction, wherein infectious mononucleosis-like systemic symptoms such as high fever and malaise may appear. These CD4⁺ T cells do not react to EBV directly. The positive CD4, negative CD56 result and low level of EBV in the skin lesion in our case suggest that NK cells infected by EBV may not be an important factor in HMB skin lesions, and instead it is possible that immune reaction mediated by T cells plays a key role in pathogenesis of HMB.

In research into the mechanism of NK-cell malignancy developing in the context of HMB, Asada⁵ have found that CD4⁺ T cells play an important role in lymphoma oncogenesis. Mosquito salivary gland extracts -stimulated CD4⁺ T cells can induce CD56⁺ NK-cell proliferation in vitro. Ishii et al⁶ revealed the augmented expression of Fas-ligand (Fas-L) in EBV-infected NK cells and resultant increase in secreted soluble Fas-L in the sera, EBV-infected NK cells might make a counterattack against cytotoxic T lymphocyte by means of Fas-L on their cell surface and also secreted soluble Fas-L, which leads to the vulnerability of cytotoxic T lymphocyte response in HMB. In addition, high expression of Bcl-2 is responsible for the resistance of Fas-induced apoptosis of infected NK cells, and aberrant expression of CD25 contributes to the IL-2 dependent abnormal proliferation of these cells.

The phenomenon of HMB may occur in adult patients, but the HMB-EBV-NK triad has not been reported in adults. Shigekiyo et al⁷ and Mori et al⁸ reported a case of adult HMB developing into mantle cell lymphoma, respectively. Konuma et al⁹ also reported a case of an adult atypical HMB patient which did not developed into any NK/T-cell proliferative disease. It

therefore seems that not all HMB will develop into NK/T-cell lymphoma, and other lymphomas such as mantle cell lymphoma may evolve in the context of HMB. Most HMB cases in which NK/T-cell malignancies evolve occur in the setting of pediatric patients with chronic active EBV infection.

In conclusion, we present herein a case of young patient with NK/T-cell lymphoma and HMB, and investigate the pathologic features of HMB and its role in developing into NK/T-cell lymphoma. We also found that HMB was reported mostly in young patients from Asian countries. Therefore, we must distinguish HMB from other skin lesions, and it should be kept in mind as a clinical precursor sign of NK/T-cell lymphoma in the pediatric patients from prevailing countries.

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