

Hodgkin's Lymphoma Arising in a Patient With Hypersensitivity to Mosquito Bites: A Case Report

A 10-year-old male presented to the Department of Dermatology complaining of intense skin reactions at mosquito bite sites in September 2002. He exhibited multiple scattered, punctated ulcerations on bilateral lower extremities. In addition to the marked cutaneous reaction, he also experienced systemic symptoms including fever after mosquito bites throughout his childhood. A skin biopsy was performed, and local treatment for the lesion was administered without further systemic evaluation. In October 2008, the patient, then age 16 years, presented with a palpable mass located on the left neck of approximately 2 to 3 weeks' duration. On physical examination, a conglomerate of large lymph nodes was present in the left neck, the largest of which measured approximately 7×5 cm. Because of his history of hypersensitivity to mosquito bite (HMB), careful inspection of his legs was performed, revealing multiple shallow ulcers with healing scars (Fig 1). Computed tomography and positron emission tomography scans showed multiple poorly enhancing and variable-sized homogeneous lymph nodes involving the left cervical region and bilateral inguinal areas (Fig 2). In addition, there were multifocal lesions demonstrating increased fluorodeoxyglucose uptake in the skin and subcutaneous layer of bilateral cheeks and buttocks. On hematologic examination, blood cell counts and lactate dehydrogenase level were within normal limits. Antiviral capsid antigen immunoglobulin (Ig) G, anti-early antigen, and anti-EBNA IgG against Epstein-Barr virus (EBV) were positive, and antiviral capsid antigen IgM was negative. The EBV DNA copy number was 2,649 copies/5 μ L whole blood (normal range, < 10 copies). Lymph node biopsy revealed widening of the paracortex with infiltration of heterogeneous

inflammatory cells including small lymphocytes, histiocytes, and many eosinophils. The inflammatory infiltrates were punctuated by scattered large mononuclear or multinuclear Reed-Sternberg (RS)-like atypical cells that had large eosinophilic nucleoli and a thick nuclear membrane (Fig 3A). By immunohistochemical study, the RS-like cells demonstrated a strong membranous stain for CD30 and perinuclear staining for CD15 and were positive for PAX-5 and LMP-1 but negative for CD20, CD3, and EBNA-2. Atypical mononuclear and multinuclear RS-like cells showed a positive signal by EBV-encoded RNA (EBER) in situ hybridization. Aside from the RS-like cells, many small lymphocytes scattered in the background were also positive for EBER in situ hybridization (Fig 3B). No abnormal findings were noted in the bone marrow biopsy except for a few EBV-positive small lymphocytes (< 10 lymphocytes). The skin biopsy from the region of HMB in 2002 was retrospectively reviewed, revealing severe necrosis of the epidermis and upper dermis (Fig 4A). There was infiltration of small lymphocytes, histiocytes, and many eosinophils around the blood vessels and hair follicles, and the blood vessel lumens were often obliterated by RBCs and fibrin. Immunohistochemical analysis revealed that the infiltrating cells were heterogeneous in their lineage; some were helper or cytotoxic T cells and positive for CD3, CD4, or CD8 whereas others were natural killer (NK) cells positive for CD56. Many EBV-positive cells were documented by EBER in situ hybridization (Fig 4B). The patient was subsequently diagnosed with stage IV Hodgkin's lymphoma (HL) associated with HMB, and chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was initiated in November 2008. The patient completed the sixth cycle of chemotherapy in May 2009, and active disease was no longer detectable on follow-up computed tomography and positron emission tomography scans. The EBV DNA copy number was reduced to 135.79 copies/5 μ L whole blood in June 2009.

HMB is characterized by intense local cutaneous symptoms including erythema, bullae, ulcers, and scar formation and by systemic symptoms such as fever, lymphadenopathy, and liver dysfunction after mosquito bites.^{1,2} Most patients are in the first two decades of life, with a median age of 6.7 years.³ The disease has a strong racial predisposition, and most cases have been reported from Japan,^{1,4-7} with a few cases each from Taiwan,^{8,9} Korea,^{10,11} and Mexico,¹² although the first case was documented in the United States in Florida in 1938.¹³ HMB was initially thought to be a simple allergic reaction to mosquito bites; however, it showed several features distinct from common mosquito bite allergies. In patients with HMB, the cutaneous reaction is much more severe compared with the general skin lesion induced by mosquito bites and is further associated with systemic symptoms. In addition, HMB has been reported in patients with lymphoproliferative disease. Tokura et al³ demonstrated that the majority of patients with HMB suffered from chronic EBV infection and NK cell leukemia/lymphoma. As cases accumulated, it became apparent that HMB is associated with chronic EBV infection syndrome, although exceptions exist in cases of chronic lymphocytic leukemia and mantle-cell lymphoma that occurred without evidence of EBV

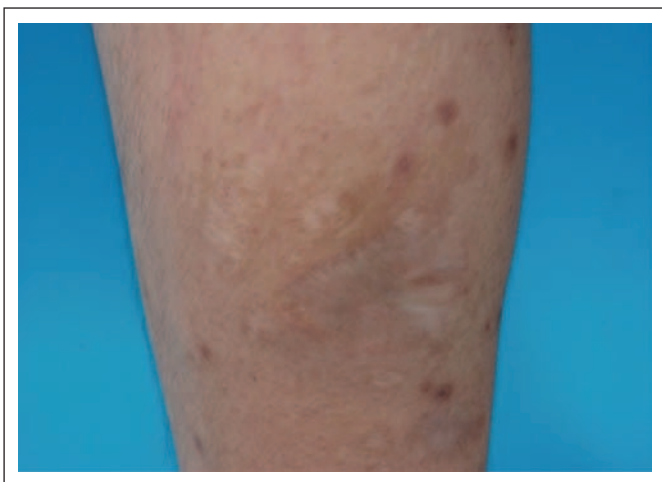


Fig 1.

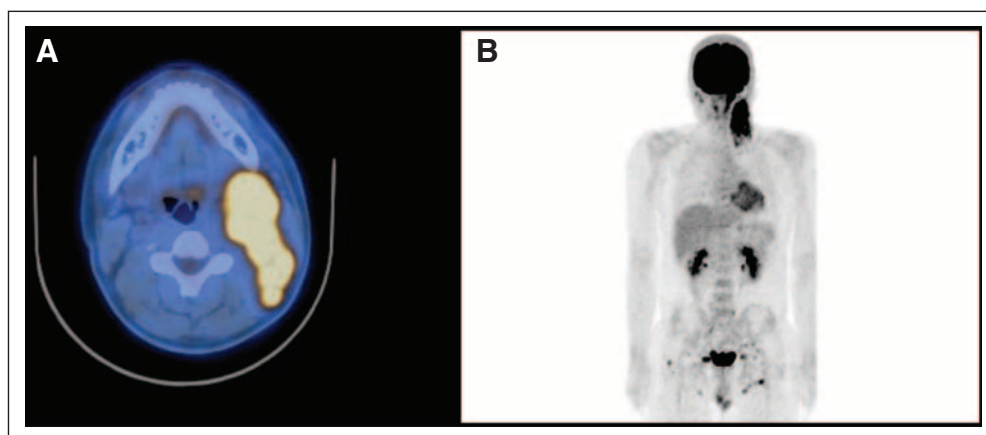


Fig 2.

infection.^{14,15} The bite site reveals a perivascular mononuclear cell infiltration with an increased number of NK and CD4⁺ T cells, a considerable proportion of which are positive for EBV.^{13,16} In the peripheral blood, an NK cell lymphocytosis is frequently observed, and some of the NK cells carry the EBV genome.^{17,18} Patients

diagnosed with chronic active EBV infection (CAEBV) or NK cell lymphoid malignancy occasionally have a history of HMB.^{3,16} Sometimes, HMB is the first manifestation of clonal EBV-positive NK cell malignancy.⁵ Consequently, researchers investigated the pathogenic

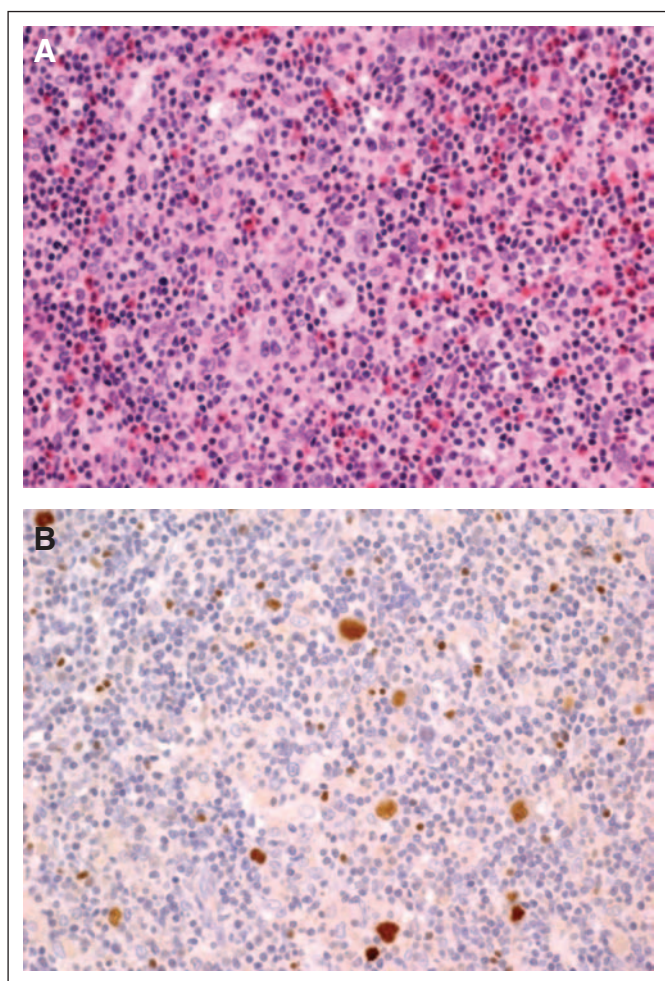


Fig 3.

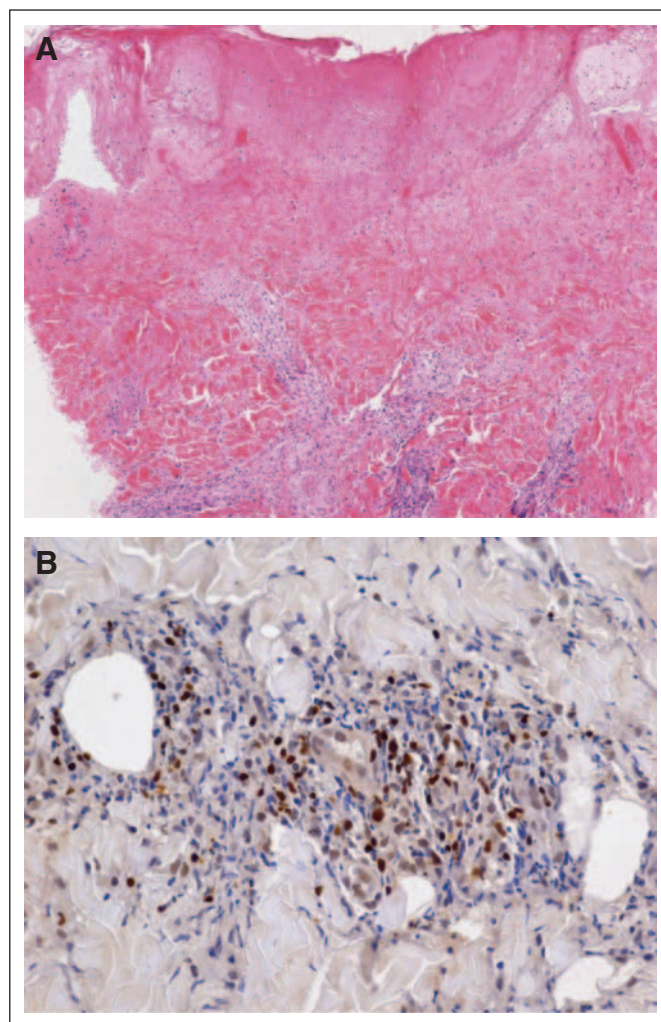


Fig 4.

mechanism linking EBV infection, HMB, and NK cell lymphoproliferation, in which the CD4⁺ T cell plays a major role. Mosquito salivary gland extract-stimulated CD4⁺ T cells were found to induce EBV reactivation in latently infected NK cells. EBV oncogenes, such as *LMP-1*, expressed in NK cells induce proliferation of NK cells, leading to NK cell neoplasm.¹³ In contrast to the strong association with T or NK lymphoproliferative disease,^{3,7,19} B-lineage lymphoma is rare in HMB,^{20,21} and HL has not been reported so far. HMB and CAEBV are included in the same spectrum of EBV-associated T and NK lymphoproliferative diseases with overlapping clinical features. HMB is commonly complicated by CAEBV, and up to 33% of patients with CAEBV show cutaneous HMB.²² In CAEBV, the predominant cell types infected by EBV are $\alpha\beta$ T, $\gamma\delta$ T, CD4⁺ T, CD8⁺ T, NK, and rarely, B cells.^{23,24} Although malignant neoplasms in patients with CAEBV are usually of the T- or NK-cell type, there was a previous report of HL arising in a patient with CAEBV.²⁵ The development of HL in CAEBV suggests that the rare EBV-infected B cells are a source of B-cell neoplasm and undergo neoplastic transformation under the influences of oncogenic EBV-latent genes. Likewise, HL in HMB seems to develop from such rare EBV-infected B cells, although NK cells are the main target of neoplastic transformation. In summary, we report a case of HL in a patient with known HMB. In chronic EBV-associated T or NK lymphoproliferative disease, T or NK cells are the predominant cell type, but rare EBV-infected B cells may lead to development of B-cell neoplasm.

**Silvia Park, Sunha Bahng, Eun Kyoung Kim,
Sung Bum Park, Young Kyung Sung, Suk Jin Kim,
and Won Seog Kim**

Division of Hemato-Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Young Hyeh Ko

Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Tokura Y, Tamura Y, Takigawa M, et al: Severe hypersensitivity to mosquito bites associated with natural killer cell lymphocytosis. *Arch Dermatol* 126:362-368, 1990
2. Kawa K, Okamura T, Yagi K, et al: Mosquito allergy and Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disease. *Blood* 98:3173-3174, 2001
3. Tokura Y, Ishihara S, Tagawa S, et al: Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol* 45:569-578, 2001
4. Hidano A, Kawakami M, Yago A: Hypersensitivity to mosquito bite and malignant histiocytosis. *Jpn J Exp Med* 52:303-306, 1982
5. Ishihara S, Ohshima K, Tokura Y, et al: Hypersensitivity to mosquito bites conceals clonal lymphoproliferation of Epstein-Barr viral DNA-positive natural killer cells. *Jpn J Cancer Res* 88:82-87, 1997

6. Ohsawa T, Morimura T, Hagari Y, et al: A case of exaggerated mosquito-bite hypersensitivity with Epstein-Barr virus-positive inflammatory cells in the bite lesion. *Acta Derm Venereol* 81:360-363, 2001
7. Ishihara S, Okada S, Wakiguchi H, et al: Chronic active Epstein-Barr virus infection in children in Japan. *Acta Paediatr* 84:1271-1275, 1995
8. Tsai WC, Luo SF, Liaw SJ, et al: Mosquito bite allergies terminating as hemophagocytic histiocytosis: Report of a case. *Taiwan Yi Xue Hui Za Zhi* 88:639-642, 1989
9. Fan PC, Chang HN: Hypersensitivity to mosquito bite: A case report. *Gaoxiong Yi Xue Ke Xue Za Zhi* 11:420-424, 1995
10. Chung JS, Shin HJ, Lee EY, et al: Hypersensitivity to mosquito bites associated with natural killer cell-derived large granular lymphocyte lymphocytosis: A case report in Korea. *Korean J Intern Med* 18:50-52, 2003
11. Cho JH, Kim HS, Ko YH, et al: Epstein-Barr virus infected natural killer cell lymphoma in a patient with hypersensitivity to mosquito bite. *J Infect* 52:e173-e176, 2006
12. Ruiz-Maldonado R, Parrilla FM, Orozco-Covarrubias ML, et al: Edematous, scarring vasculitic panniculitis: A new multisystemic disease with malignant potential. *J Am Acad Dermatol* 32:37-44, 1995
13. Asada H: Hypersensitivity to mosquito bites: A unique pathogenic mechanism linking Epstein-Barr virus infection, allergy and oncogenesis. *J Dermatol Sci* 45:153-160, 2007
14. Kunitomi A, Konaka Y, Yagita M: Hypersensitivity to mosquito bites as a potential sign of mantle cell lymphoma. *Intern Med* 44:1097-1099, 2005
15. Asakura K, Kizaki M, Ikeda Y: Exaggerated cutaneous response to mosquito bites in a patient with chronic lymphocytic leukemia. *Int J Hematol* 80:59-61, 2004
16. Kanno H, Onodera H, Endo M, et al: Vascular lesion in a patient of chronic active Epstein-Barr virus infection with hypersensitivity to mosquito bites: Vasculitis induced by mosquito bite with the infiltration of nonneoplastic Epstein-Barr virus-positive cells and subsequent development of natural killer/T-cell lymphoma with angiodestruction. *Hum Pathol* 36:212-218, 2005
17. Ohshima S, Ishii M, Asada H, et al: A possible mechanism of NK cell-lineage granular lymphocyte proliferative disorder (NK-GLPD) in a patient with chronic active Epstein-Barr virus infection (CAEBV) and severe hypersensitivity to mosquito bites (SHMB). *Intern Med* 41:651-656, 2002
18. Ishihara S, Okada S, Wakiguchi H, et al: Clonal lymphoproliferation following chronic active Epstein-Barr virus infection and hypersensitivity to mosquito bites. *Am J Hematol* 54:276-281, 1997
19. Kase S, Adachi H, Osaki M, et al: Epstein-Barr virus-infected malignant T/NK-cell lymphoma in a patient with hypersensitivity to mosquito bites. *Int J Surg Pathol* 12:265-272, 2004
20. Shigekiyo T, Ohmori H, Chohraku M, et al: Unusual skin reactions after mosquito bites and Epstein-Barr virus reactivation in a patient with mantle cell lymphoma. *Intern Med* 43:986-989, 2004
21. Mori T, Okamoto S, Kuramochi S, et al: An adult patient with hypersensitivity to mosquito bites developing mantle cell lymphoma. *Int J Hematol* 71:259-262, 2000
22. Cohen JL, Kimura H, Nakamura S, et al: Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: A status report and summary of an international meeting, 8-9 September 2008. *Ann Oncol* 20:1472-1482, 2009
23. Ohshima K, Kimura H, Yoshino T, et al: Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: Overlap with chronic active EBV infection and infantile fulminant EBV T-LPD. *Pathol Int* 58:209-217, 2008
24. Kimura H, Hoshino Y, Hara S, et al: Differences between T cell-type and natural killer cell-type chronic active Epstein-Barr virus infection. *J Infect Dis* 191:531-539, 2005
25. Tamayose K, Egashira M, Sugimoto K, et al: Epstein-Barr virus-positive Hodgkin's lymphoma in a patient with chronic active Epstein-Barr virus infection. *Int J Hematol* 80:199-200, 2004

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