Lymphoid Neoplasms Associated with Mosquito Bites

Key words: mosquito bite, natural killer cell, lymphoid neoplasms, mantle cell lymphoma, Epstein-Barr virus infection

Hypersensitivity to mosquito bites (HMB) is a rare disorder characterized by intense skin reactions at bite sites accompanied by general symptoms. The initial skin lesion is typically a clear or hemorrhagic blister that subsequently develops into necrosis or an ulcer. The general symptoms include high grade fever, general malaise, cramps, lymphadenopathy, hepatosplenomegaly, bleeding tendency and renal failure. Although HMB has been reported almost exclusively from Japan, it is equivocal whether HMB occurs in people in other countries especially in east Asia.

In 1982, Hidano et al analyzed 21 HMB cases in Japan and reported that patients with severe HMB have a poor prognosis and most of them die with “malignant histiocytosis” which was renamed as hemophagocytic syndrome (1). In 1990, Tokura et al found that natural killer (NK) cell lymphocytosis is observed in patients with severe HMB (2). NK cells in most cases are large granular lymphocytes, express surface markers of normal activated NK cells including CD2, CD11b, CD16, CD38, CD56 and HLA-DR, and exhibit cytotoxicity against NK-sensitive target cells and antibody-dependent cell-mediated cytotoxicity (2, 3). One case report showed a low level of CD56 expression in NK cells in an HMB patient, but pathophysiological implication of this atypical subpopulation of NK cells remain unelucidated (4).

Apart from the reports mentioned above, Ishihara et al have pointed out that clonal proliferation of large granular lymphocytes following chronic active Epstein-Barr virus (EBV) infection is often seen in the patients with HMB (5). They also disclosed that EBV-infected clonal NK cells infiltrate into peripheral blood using Southern blot hybridization and polymerase chain reaction analysis (6).

NK cell proliferative disorders associated with HMB are characterized by the following features: 1) HMB 2) chronic active EB virus infection 3) NK cell lymphocytosis (7). According to the analysis of 58 patients with HMB (7), there were no sex differences and the mean age at the diagnosis was 6.7 years. Thirty-one patients died at the mean age of 16.3 years. The main cause of death was hemophagocytic syndrome (52%) and large granular lymphocytosis/lymphomas (35%).

NK cells which appear in HMB have the following features: 1) they have monoclonal or oligoclonal EBV infection, 2) the type of NK cells is NK1 which produces interferon-gamma and interleukin-10, and 3) they express a high level of CD94 lectin-like dimers (8). The high level expression of CD94 was found to be functional in transducing inhibitory signals because their cytotoxicity and proliferation were inhibited by anti-CD94 monoclonal antibody (8). It has been speculated that this abnormal expression of inhibitory receptor have some pathognomonic implications. Although the definite mechanism of HMB-associated NK cell proliferative disorders is yet to be determined, it is also suggested that CD4-positive T cells activated by mosquito bite accelerate EBV reactivation in NK cells (9).

Recently mantle cell lymphoma arising from HMB has been reported (10). As is seen in HMB-associated NK cell proliferative disorders, EBV was detected in the tumor cells with CD5 expression. A marked increase in serum IL-10 was observed suggesting T-helper cell 2 (Th2) dominant T cell balance (10). The case was quite different from other HMB cases, because the patient was a 61-year-old adult. In the last issue of Internal Medicine, Kunitomi et al reported a case of mantle cell lymphoma presented in a patient who had a five-year history of HMB (11).

The patient did not demonstrate a chronic active EBV infection because DNA of EBV was not detected in the peripheral blood by polymerase chain reaction. But serological tests suggested the existence of the virus. To date, EBV is thought to be associated with lymphoproliferative disorders such as mononucleosis syndrome, Burkitt’s lymphoma, pyothorax-associated B-cell lymphoma and others but it has not been established that it is associated with mantle cell lymphoma. It is uncertain whether or not mantle cell lymphoma occurs with the etiology resembling HMB-associated NK cell proliferative disorders. The mechanism of the presence of mantle cell lymphoma in HMB patients remains to be clarified.

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References
3) Mizuki M, Ueda S, Tagawa S, et al. Natural killer cel-derived large


