

Hypersensitivity to Mosquito Bites as a Potential Sign of Mantle Cell Lymphoma

Akane KUNITOMI, Yoshiteru KONAKA and Masato YAGITA

Abstract

Hypersensitivity to mosquito bites (HMB) is known to be an allergic reaction and also a skin symptom in some cases of natural killer cell leukemia/lymphoma associated with Epstein-Barr virus (EBV) infection. We describe a patient who had suffered from HMB for 5 years, and subsequently developed mantle cell lymphoma (MCL), which resembled chronic lymphocytic leukemia in the early phase. EBV monoclonality was not detected in lymph nodes by Southern blotting. Serum levels of interleukin-4 and IgE were increased, but they decreased and HMB disappeared when MCL was predominant. We consider that HMB may be a potential sign of MCL. (Internal Medicine 44: 1097–1099, 2005)

Key words: hypersensitivity to mosquito bites, mantle cell lymphoma, chronic lymphocytic leukemia, Epstein-Barr virus

Introduction

Hypersensitivity to mosquito bites (HMB) is characterized by necrotic skin reactions and subsequent generalized symptoms following the bites. It is seen mostly in the first two decades of life, and some cases are associated with Epstein-Barr virus (EBV) infection and natural killer (NK) cell leukemia/lymphoma (1). Shigekiyo et al reported a mantle cell lymphoma (MCL) patient with HMB, which thus suggested a relationship between EBV and MCL (2). On the other hand, Mori et al reported a patient with HMB who developed MCL, which suggested that HMB might be a pathophysiologic condition with a malignant potential (3).

MCL is characterized by CD5-positive immature B cells of the follicular mantle zone, and it accounts for 3–10% of all non-Hodgkin's lymphoma cases, and it tends to have a

poor prognosis. It is characterized by the chromosomal t(11;14)(q13;q32), juxtaposing the BCL-1 gene locus at 11q13, thus resulting in the over-expression of cyclin D1 which regulates the early phases of the cell cycle. Since MCL shares some biological features with chronic lymphocytic leukemia (CLL), it is sometime difficult to distinguish MCL from CLL (4).

We herein report a patient with HMB who subsequently developed MCL that resembled CLL in the early phase of the clinical course. We also discuss the potential of HMB as a sign of MCL or CLL.

Case Report

A 54-year-old man was admitted to our hospital because of general lymphadenopathy and skin eruptions with ulceration after suffering mosquito bites in August 1997. A physical examination revealed mild anemia and systemic lymphadenopathy. A biopsied cervical lymph node showed non-specific hyperplastic lymphadenitis. Because an examination for anemia revealed gastric cancer, he underwent a total gastrectomy. Subsequently, both the lymphadenopathy and HMB did not improve. The generalized lymphadenopathy worsened, and hepatosplenomegaly appeared in August 2002. Laboratory data showed lymphocytosis (lymphocytes $80 \times 10^2/\mu\text{l}$) and mild thrombocytopenia (platelets $10 \times 10^4/\mu\text{l}$), and the serum IgE level had increased (42,000 IU/ml). The serum cytokine levels, including interferon- γ , interleukin (IL) -2, IL-4, IL-5, and IL-10, were measured and the serum level of IL-4 was markedly elevated (2,980 pg/ml; normal range <6.0), but the other cytokine levels were not determined. Anti-viral capsid antigen (anti-VCA) IgG and anti-early antigen (anti-EA) IgG against EBV were elevated, but EBV DNA was not detected in the peripheral blood using the polymerase chain reaction. A biopsied cervical lymph node showed a monotonous proliferation of lymphocytes which were positive for CD5, CD19, CD20, bcl-2, and κ chains, weakly positive for CD23, and negative for Cyclin D1. A re-

From the Division of Hematology and Rheumatology, Department of Medicine, The Tazuke Kofukai Medical Research Institute, Osaka

Received for publication January 28, 2005; Accepted for publication June 23, 2005

Reprint requests should be addressed to Dr. Akane Kunitomi, Division of Hematology and Rheumatology, Department of Medicine, The Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480

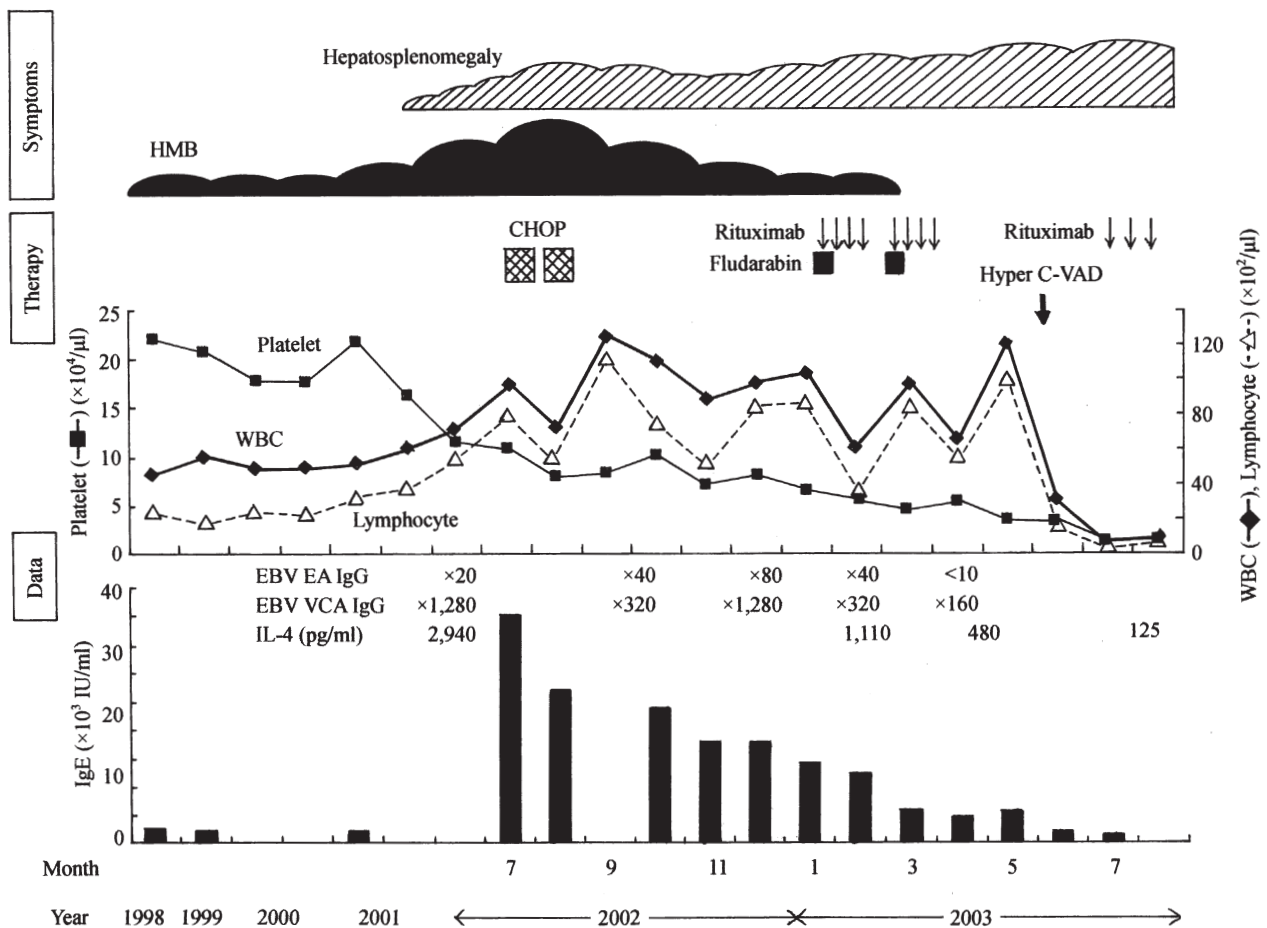


Figure 1. Clinical course of a patient with hypersensitivity to mosquito bites (HMB) who subsequently developed mantle cell lymphoma (MCL). Black arrows and boxes indicate intravenous infusion of rituximab, and fludarabine, respectively. Gray boxes and bar indicate chemotherapy of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), and hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone), respectively. EBV indicates Epstein-Barr virus; EBV EA IgG: anti-early antigen IgG against EBV, EBV VCA IgG: anti-viral capsid antigen IgG against EBV, WBC: white blood cell, IL-4: interleukin-4.

arrangement of IgJH was detected, but no monoclonal proliferation of EBV was detected by Southern blotting. A cytogenetic examination of a lymph node cell suspension showed a normal karyotype. The surface markers of peripheral blood mononuclear cells were the same as those of lymph node cells. The patient was diagnosed to have CLL, and received CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) due to marked hepatosplenomegaly, but his clinical symptoms and laboratory data did not improve.

In January 2003, although no typical chromosomal translocation of t(11;14)(q13;q32) in cytogenetic examination of bone marrow cells was detected, we further evaluated the same sample by fluorescence in situ hybridization (FISH) in order to detect IgH/BCL1 gene fusion, and fusion signals were observed in 70% of cells. In the spring of 2003, when MCL was predominant, the HMB disappeared, and the

serum levels of IgE, IL-4, anti-VCA IgG and EA-IgG against EBV decreased. At the same time, typical chromosomal translocation of t(11;14)(q13;q32) was revealed, since the cytogenetic examination of bone marrow cells showed chromosomal translocation, 44,XY,add(1)(p36), del(4)(q?), ?p, add(8)(p11), -9, add(10)(p11), der(11)t(11;14)(q13;q32), add(13)(q22), -14, add(14)(q24), add(21)(q22). We again examined the immunohistochemical staining of lymph node specimens, which were positive for cyclin D1. Under a diagnosis of MCL, he was treated with rituximab, fludarabine, hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, and dexamethasone), and a combination of vincristine and prednisolone, but his disease progressed and he eventually died in June 2004. The clinical course is illustrated in Figure 1.

Discussion

We had difficulty in diagnosing MCL in this case because of the normal karyotype revealed using a G-banding chromosomal analysis. It is important to distinguish MCL from other B cell lymphomas and lymphoproliferative disorders because of its poor prognosis, but this is sometimes difficult because it shares many morphologic and phenotypic features with other lymphomas. In our patient, the diagnosis of MCL was confirmed by FISH, despite the absence of a chromosomal translocation of t(11;14)(q13;q32). We therefore consider that FISH is useful for the detection of a cryptic rearrangement in the diagnosis of MCL and other hematological malignancies.

The serum level of IL-4 was high until MCL progressed in our patient. IL-4 synthesis in normal hematopoietic cells can be classified into two categories: namely, mature lymphoid cells, e.g. T helper type 2 (Th2) CD4⁺ T cells, cytotoxic CD8⁺ T cells, NK1 and γ/δ T cells, and myeloid lineage cells. IL-4 affects numerous aspects of the immune response, and in particular it plays a major role in B and T cell growth, activates macrophages, promotes both IgG1 and IgE isotype switching, and provides host-derived antitumor responses. These findings demonstrated that IL-4 inhibited the IL-2-induced growth of B-CLL as the antitumor function (5, 6). There are two possibilities regarding the mechanism of the increased the IL-4 level in the present patient: one is that MCL cells produced IL-4, and the other is that Th2 T cells produced IL-4 as an immune response to MCL. Because IL-4 decreased when MCL progressed, the latter possibility thus seems to be more likely.

The relationship between HMB and clonal proliferation of EBV DNA-positive NK cells has been reported (1). It was recently reported that HMB could occur before a diagnosis of lymphoproliferative disorders without an EBV infection, such as MCL or CLL (7, 8). The pathogenesis of HMB associated with hematological malignancy without EBV infection is still poorly understood. A cytokine imbalance with an excessive amount of IL-4 and IL-5 has been suggested to lead to a proliferation of malignant B cells while also alter-

ing the immune response (7–9). In the present patient, HMB was present when gastric cancer was found, and after a gastrectomy, HMB continued until MCL progressed. The correlation between gastric cancer and HMB is unknown, but we speculated that HMB was one of the manifestations of the patient's immune response to MCL. Although the titers of anti-VCA IgG and EA-IgG against EBV were high, the patient did not demonstrate a chronic active EBV infection because EBV DNA was not detected in the peripheral blood. HMB is rare in adults, but it may be useful as a sign of MCL or CLL, irrespective of whether EBV is associated or not. In summary, we reported a patient with MCL who presented with HMB before the diagnosis could be made. We consider that HMB may therefore be a potentially useful diagnostic sign of MCL.

References

- 1) Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. 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.
- 2) Shigekiyo T, Ohmori H, Chohraku M, et al. Unusual skin reaction after mosquito bites and Epstein-Barr virus reactivation in a patient with mantle cell lymphoma. *Intern Med* **43**: 986–989, 2004.
- 3) Mori T, Okamoto S, Kuramochi S, Ikeda Y. An adult patient with hypersensitivity to mosquito bites developing mantle cell lymphoma. *Int J Hematol* **71**: 259–262, 2000.
- 4) Schlette E, Fu K, Medeiros LJ. CD23 expression in mantle cell lymphoma: clinicopathologic features of 18 cases. *Am J Clin Pathol* **120**: 760–766, 2003.
- 5) Kay NE, Pittner BT. IL-4 biology: impact on normal and leukemic CLL B cells. *Leuk Lymphoma* **44**: 897–903, 2003.
- 6) Puri RK, Siegel JP. Interleukin-4 and cancer therapy. *Cancer Invest* **11**: 473–486, 1993.
- 7) 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.
- 8) Dodiuk-Gad RP, Dann EJ, Bergman R. Insect bite-like reaction associated with mantle cell lymphoma: a report of two cases and review of the literature. *Int J Dermatol* **43**: 754–758, 2004.
- 9) Weller PF. Human eosinophils. *J Allergy Clin Immunol* **100**: 283–287, 1997.