

Exaggerated Cutaneous Response to Mosquito Bites in a Patient with Chronic Lymphocytic Leukemia

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Received February 10, 2004; received in revised form April 15, 2004; accepted April 16, 2004

Abstract

Although various cutaneous manifestations can occur in patients with chronic lymphocytic leukemia (CLL), bullous lesions due to mosquito bites are rare. We describe a patient with a typical case of CLL complicated by exaggerated cutaneous response to mosquito bites. The symptoms of this patient were self-limited and not severe, but it has been reported that the treatment of such symptoms is sometimes difficult. Because exaggerated cutaneous hypersensitivity to mosquito bites can be observed even before the diagnosis of hematological malignancies such as CLL, careful examinations are recommended to find underlying diseases in cases in which this type of cutaneous reaction occurs.

Int J Hematol. 2004;80:59-61. doi: 10.1532/IJH97.04021

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Key words: Exaggerated cutaneous response; Mosquito bite; Chronic lymphocytic leukemia

1. Introduction

Although chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, it is much rarer in Japan. It is known that various cutaneous manifestations can occur in patients with CLL, and such skin lesions have been classified as "specific" and "nonspecific" [1]. Specific lesions, occurring in approximately 8.3% of patients with CLL, represent leukemic infiltrates and manifest as purple or red-brown papules and nodules [2]. Nonspecific lesions, occurring in 45% of patients with CLL, present as petechiae, purpura, ecchymoses, exfoliative erythroderma, herpes simplex and zoster, erythema multiforme, or urticaria [3]. In addition to these symptoms, in 1965 Weed reported exaggerated delayed hypersensitivity to mosquito bites in CLL patients [4]. This manifestation is very rare in CLL, and to the best of our knowledge, less than 40 other cases of CLL patients with this symptom have been reported since 1965 [5]. In this case report, we described a patient with CLL complicated by a typical exaggerated cutaneous response to mosquito bites, and we review the literature pertaining to this case.

2. Case Report

CLL was diagnosed in a 46-year-old woman in May 1990. Her white blood cell count was $1.4 \times 10^9/L$ (mature lymphocytes, 68%), but her hemoglobin level and platelet count were normal. The proliferating lymphocytes were monoclonal and CD5^{dim+}, CD19⁺, CD20⁺, and DR⁺. No adenopathy or organomegaly was observed; the patient was therefore considered to have clinical stage A (0) disease according to Binet (Rai) staging [6,7]. During the course of observation without therapy, superficial lymphadenopathy appeared in 1995. Because the size and number of palpable lymph nodes increased gradually, chemotherapy with vincristine, cyclophosphamide, and prednisolone was started in November 1996. Disease status stabilized with only intermittent chemotherapy.

The patient, however, noticed in 1999 that mosquito bite lesions on her extremities progressed to pruritic, blistering, erythematous lesions in 24 to 48 hours (Figure 1). These lesions gradually subsided in a week without therapy. IgE antibodies to insects, especially mosquitoes, were undetectable by radioallergosorbent tests (RAST). Antibody titer to immunoglobulin (Ig)G Epstein-Barr Virus (EBV) viral capsid antigen (VCA) was 1:160, IgM EBV-VCA was negative, and the titer to anti-EBV-specific nuclear antigen (EBNA) was 1:40. Titers to both early antigen (EA) IgG and IgA were also undetectable. The exaggerated cutaneous response to mosquito bites in this patient has continued in the same manner. Because chemotherapy with oral cyclophosphamide and prednisolone is administered intermittently, the disease activity of CLL is also stable.

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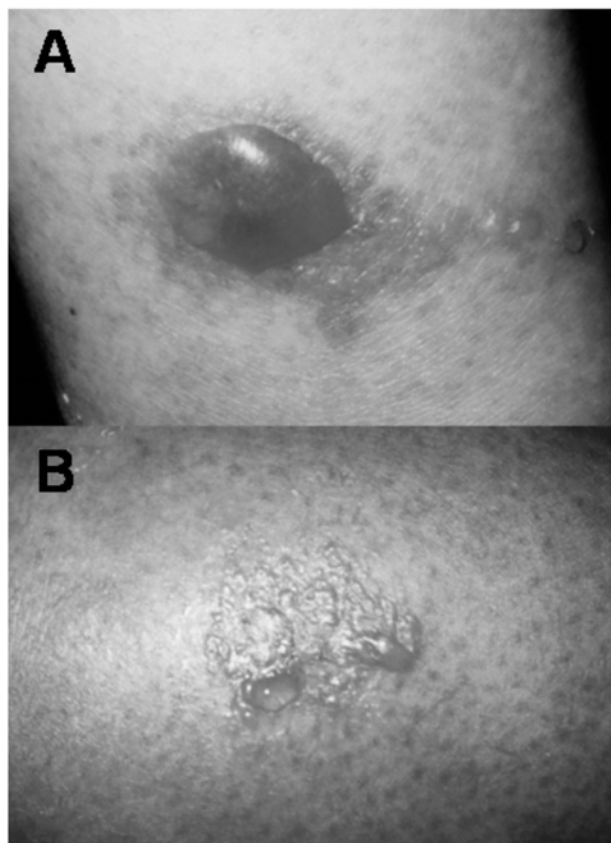


Figure 1. Cutaneous lesions in the patient with chronic lymphocytic leukemia. A, The patient's ankle, bitten by a mosquito. Forty-eight hours after the bite, a blistering, erythematous lesion appeared. B, The patient's arm, bitten by a mosquito.

3. Discussion

Although patients with CLL can present with various cutaneous manifestations, bullous skin lesions due to exaggerated reaction to insect bites are rare. Skin lesions usually appear months to years after the diagnosis of CLL and have no correlation to laboratory findings, disease course, or therapy. Reaction to insect bites is characterized by pruritus, erythema, edema, and bulla formation. Reaction to the bites peaks in 12 to 24 hours and spontaneously resolves in 2 to 14 days. In 1965, Weed first documented a hypersensitivity reaction to insect bites in CLL patients [4]. He found that 8 of 97 CLL patients (8.3%) demonstrated an exaggerated cutaneous response to insect bites, but other groups have reported that the incidence of this response is only 0% to 2.7% [4].

Weed has suggested that this hypersensitivity reaction to insect bites is due to an altered immune response. A sudden exaggerated cutaneous response to insect bites seems to indicate a loss or modification of acquired desensitization. Several mechanisms have been proposed, including (1) cytokine imbalance with excess of interleukin-4 and -5, which leads to proliferation of malignant B-cells and altered immune response characterized by eosinophilic infiltrate [8], and (2) an impaired response of B-cells to B-cell mitogens and to B-

cell growth factors [9]. T-cell function is also impaired in B-cell CLL and worsens as the disease progresses [10].

Most patients cannot recall their history of insect bites; the diagnosis of an exaggerated insect bite reaction is based on histological criteria. Our patient, however, reported that she had been bitten by mosquitoes; we accordingly diagnosed her cutaneous lesion without pathological examination as an exaggerated reaction to insect bites. Although the detection of IgE antibodies to mosquito bites using RAST failed, it has been reported that RAST and immunohistochemical techniques to detect IgE antimosquito antibodies have usually failed [11]. New diagnostic tests should therefore be applied; for example, Simons et al have recently described new recombinant mosquito salivary antigens that can facilitate the diagnosis of mosquito allergy [12].

Recently, the relationship between mosquito allergy and clonal proliferation to EBV DNA-positive natural killer (NK) cells has been reported [13]. Hypersensitivity occurring in association with chronic active EBV infection and NK cell leukemia/lymphoma has recently been called Tokura-Ishihara disease or hypersensitivity to mosquito bites (HMB)-EBV-NK disease [14]. Serum samples of patients with this disease show the same pattern as chronic active EBV infection: VCA-IgG positive, early antigen (EA)-IgG positive, and EBNA positive or negative. More recently, a case of EBV-associated T/NK-cell lymphoproliferative disease preceding the onset of mosquito allergy has been reported [15]. The patient in this report was asymptomatic, and the pattern of EBV antibody titers suggested that this case was solely EBV seropositive. Therefore, we suppose that the hypersensitivity to mosquito bites in this patient was not related to EBV infection.

Davis et al have reported a diagnosis of CLL in a patient after a 10-year history of exaggerated response to insect bites [9]. Adults usually have minimal or absent delayed hypersensitivity reaction to insect bites because of acquired desensitization; we should therefore remain aware of the fact that this symptom might precede the diagnosis of CLL.

Barzilai et al have described 8 patients with various hematologic disorders who developed insect bite-like reactions [16]. CLL was diagnosed in 3 of the 8 patients, and they seemed to have an accelerated disease course. Larger studies are necessary to establish that an exaggerated cutaneous reaction has prognostic implications for CLL patients.

Many cases of exaggerated cutaneous reaction to insect bites resolve spontaneously, but some patients show severe symptoms. There is no specific treatment; treatment with topical antipruritic agents, topical corticosteroids, and systemic antihistamines are almost always ineffective. Systemic corticosteroids have been found to be effective for suppressing the eruptions [9]; however, the lesions often recur when the dose of corticosteroids is tapered down. It has also been reported that intravenous immunoglobulin was effective in treating one patient [9]. On the other hand, Blum et al reported that their patients responded to oral dapsone at 50 to 150 mg per day [5].

In summary, we have reported herein a patient with CLL who presented with an exaggerated cutaneous reaction to mosquito bites. We should recognize that this cutaneous reaction can be present even before the diagnosis of CLL, and

treatment is sometimes difficult. Further studies are needed to confirm the prognostic implications of this symptom.

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