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Single Case

Mosquito Bite-Induced Localized NK/T-Cell Lymphoma Relapsed in a Patient with Complete Remission of Extranodal NK/T-Cell Lymphoma, Nasal Type

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Keywords

Extranodal NK/T-cell lymphoma, nasal type · Epstein-Barr virus infection · Mosquito bite · Complete response · Malignant lymphoma

Abstract

We report a rare case of localized NK/T-cell lymphoma following a mosquito bite after achieving complete response of extranodal NK/T-cell lymphoma, nasal type (ENKL). T cells and NK cells infected by Epstein-Barr virus (EBV) lead to NK/T-cell lymphoma, including ENKL. Lymphoma related to mosquito bites usually requires a prolonged treatment course, and the disease onset of hypersensitivity begins in early childhood. In the current case, the patient had no history of hypersensitivity to mosquito bites. We speculate that the latently EBV-infected NK/T cells in the blood were reactivated by mosquito gland antigens, expanded abnormally, and accumulated at the site of the mosquito bite.

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Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is a clinical entity mostly seen in Asian countries. The development of ENKL is associated with latent Epstein-Barr virus (EBV) reactivation. On the other hand, hypersensitivity to mosquitoes is also associated with chronic EBV infection. Persistent EBV infection is a risk factor for malignant lymphoma. Usually, the onset of mosquito hypersensitivity takes place in childhood, followed by ENKL associated with EBV in middle age. It is rare that relapses of NK lymphoma occur at the site of mosquito bites without a history of mosquito hypersensitivity.

Case Presentation

A 76-year-old female experienced nasal obstruction and visited her primary physician. A tumor in the nasal cavity was detected, and ENKL was diagnosed from the biopsy specimen. Accumulation of fluorodeoxyglucose (FDG) was detected only in the nasal cavity by PET-CT. In the patient's serum 1.2×10^2 copies/μg of EBV DNA (normal $<2 \times 10$ copies/μg) were detected. She received immediate chemotherapy every 3 weeks for three cycles – RT-2/3DeVIC (radiation 50 Gy and three courses of DeVIC [day 1: carboplatin 200 mg/m^2; days 1–3: etoposide 67 mg/m^2 plus ifosfamide 1.0 g/m^2 + dexamethasone 40 mg]) – and achieved complete response. She had no history of hypersensitivity to mosquito bites or chronic active EBV infection. However, 1 month after complete response, a granulomatous nodule gradually appeared on her right leg at the site of a possible mosquito bite (Fig. 1a). She had been bitten on both legs by mosquitoes within 1 month. She showed no general symptoms, including fever and fatigue. The skin biopsy from the nodule showed massive lymphocyte infiltration positive for CD3, CD56, granzyme B, TIA-1, and Epstein-Barr encoded RNA, which are the same staining patterns as for primary ENKL (Fig. 1c). Although 2.4×10^2 copies/μg of EBV DNA were detected in her serum (normal $<2 \times 10$ copies/μg), chronic active EBV infection was denied from the results of several antibodies against EBV (VCA IgA/M/G, EADR IgA/G, EBEA IgG, and EBNA IgG). FDG was detected in her nasal cavity; however, FDG accumulated more intensively on her right lower leg as shown by PET-CT (Fig. 1b). In addition, small FDG accumulations were detected on both legs, suggesting that subclinical recurrence may have been due to multiple mosquito bites. The patient underwent repeated chemotherapy every 3 weeks for six cycles: GDP chemotherapy (days 1 and 8 gemcitabine 1,000 mg/m^2, day 1 cisplatin 75 mg/m^2, days 1–4 dexamethasone 40 mg/day), and EBV DNA levels decreased to 4.1×10^1 copies/μg in her serum after six courses of GDP chemotherapy. At the time of writing, the patient is in stable condition.

Discussion

We report the rare phenomenon of a patient developing localized NK/T-cell lymphoma following mosquito bites after complete response of lymphoma. Recurrent lymphoma occurring within the wound has also be known to occur; however, this case was believed to be associated with mosquito bites due to the elevation of EBV DNA levels after the appearance of NK/T-cell lymphoma on the patient's leg. ENKL, which is a rare type of malignant lymphoma, accounts for <3% of malignant lymphomas in Japan [1]. T cells and NK cells infected by EBV lead to NK/T-cell lymphoma, including ENKL [2, 3]. Lymphoma related to mosquito bites

usually requires a prolonged course, and the onset of hypersensitivity generally occurs in early childhood [3]. The skin lesions at mosquito bite sites result in bullae that develop into necrosis. The patients sometimes have a high fever and splenomegaly, which continue through their life after every mosquito bite [4]. Mosquito bite-stimulated CD4+ T cells are associated with the development of one main oncogenic protein, the latent membrane protein 1 (LMP1) of EBV. EBV infection of T cells and/or NK cells can lead to malignant lymphoma [5]. In our case, the patient had no history of hypersensitivity to mosquito bites. We speculated that the latently EBV-infected NK/T cells in the blood, which were reactivated by mosquito gland antigen, expanded abnormally and accumulated at the site of the mosquito bite.

In conclusion, this is a rare case of relapsed NK/T-cell lymphoma by mosquito bites in a patient in complete remission of ENKL.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that no competing interests exist.

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Author Contributions

M. Kondo and M. Mizutani took care of the patient. M. Kondo and K. Yamanaka wrote the manuscript.

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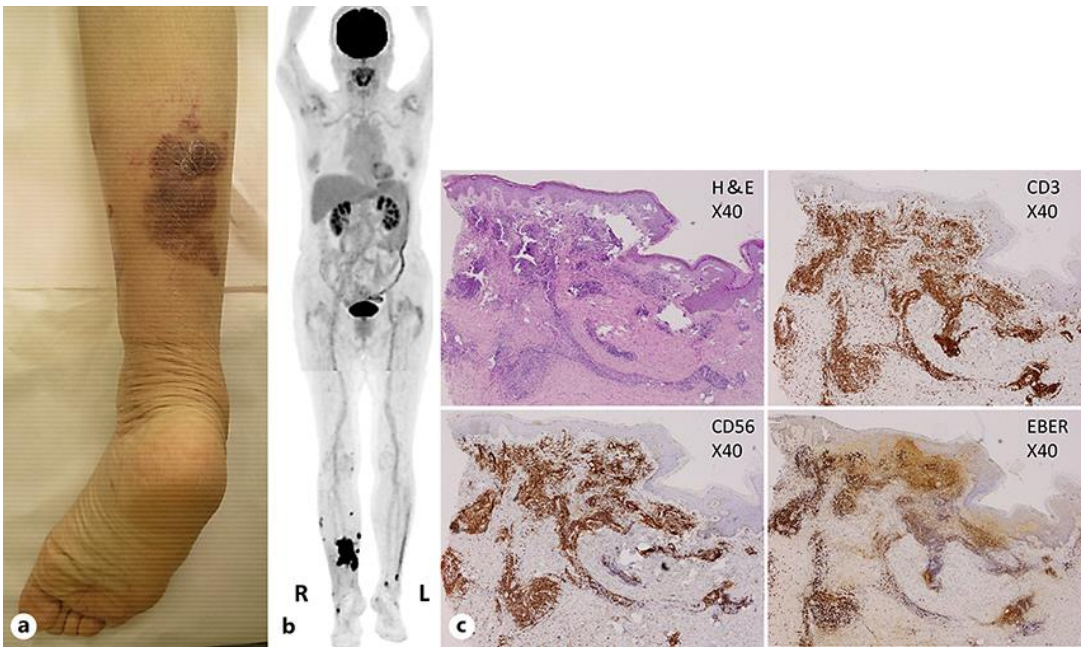

Fig. 1. **a** The granulomatous nodules which appeared on the right leg. **b** PET-CT image when the granulomatous nodules appeared on the leg following a mosquito bite. **c** Pathological images of the leg nodule at 40-fold magnification (hematoxylin-eosin, CD3, CD56, and Epstein-Barr encoded RNA).