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Correspondence

A systemic form chronic active Epstein–Barr virus infection diagnosed from erythema nodosum-like skin lesions

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Dear Editor,

Chronic active Epstein–Barr virus (EBV) infection (CAEBV), systemic form, is a disease associated with latent EBV infection [1, 2]. We report a case of CAEBV, systemic form, diagnosed from erythema nodosum (EN)-like skin lesions.

A 19-year-old woman was referred to our department for tender erythema on the extremities that had persisted for 1 month. Her body weight was 58 kg. Physical examination revealed several swollen erythematous lesions with tenderness on the extremities (Fig. 1a). There was no history of hypersensitivity to mosquito bites (HMB) nor of hydroa vacciniforme (HV). A skin biopsy specimen from the left lower leg showed lobular panniculitis with angiocentric infiltration in the dermis, with no apparent vasculitis (Fig. 1b and c). Laboratory examinations revealed elevated anti-viral capsid antigen (VCA) IgG antibody (x2,560 positive) and anti-EBV nuclear antigen antibody (x40 positive). Atypical lymphocytes were not detected in the patient's peripheral blood. Serum aspartate aminotransferase was 130 U/L (normal range: 13-30) and alanine aminotransferase was 94 U/L (normal range: 4-44). With oral prednisolone at 15 mg/day, the lesions gradually flattened. We tapered and ceased the prednisolone in one month. Induration of the lesions remained and sporadic swollen erythema relapsed repeatedly. Her liver dysfunction continued. Six months later, numerous swollen erythematous lesions recurred on the extremities (Fig. 1d). A skin biopsy specimen from the left lower leg showed findings similar to those of the previous biopsy (Fig. 1e). The histopathological features differed from those of the septal panniculitis that is typical of EN. The infiltrated cells were positive for CD3, but negative for CD56. They consisted of a mixture of $CD4^+$ cells, $CD8^+$ cells and Granzyme B^+ cells. *In situ* hybridization for EBV-encoded small RNA showed positive signals in infiltrating lymphocytes (Fig. 1f). The EBV-DNA load in the peripheral blood was abnormally elevated (1.0×10^5 copies/ml of whole blood). Flow cytometry analysis revealed that the rates of $sCD3^{\pm}CD4^{\pm}$, $sCD3^{\pm}CD8^{\pm}$, $sCD3^{-}CD56^{\pm}$ and $sCD3^{-}CD16^{\pm}$ cells were 2.7%, 0%, 74.2% and 57.8%, respectively, among EBV-infected cells in the patient's peripheral blood. These results revealed the EBV-infected cells to be predominantly NK cells in the

patient's peripheral blood. After the skin biopsy, the site was swollen and she had a 39°C fever. Computed tomography revealed hepatosplenomegaly, but no lymph node swelling. We diagnosed CAEBV, systemic form, with EN-like skin lesions. We treated her with oral prednisolone at 30 mg/day, and the swelling and fever promptly improved. We tapered and ceased the oral prednisolone in three weeks. One month after this cessation, skin lesions relapsed and a constant high fever appeared. She was transferred to another hospital to receive hematopoietic stem cell transplantation (HSCT).

Latent EBV infection in the peripheral blood leads to CAEBV with prolonged infectious mononucleosis (IM)-like symptoms [3]. CAEBV is a high-mortality disease with life-threatening complications, such as hemophagocytic lymphohistiocytosis and NK-cell lymphoma, and HSCT is the only effective therapy for CAEBV at present [4]. Patients with CAEBV frequently have characteristic cutaneous complications, HMB and HV [4]. Japanese patients with adult-onset CAEBV frequently show skin symptoms of IM and infrequently have a history of HV and HMB [5]. Virus-associated EN is usually self-limiting in non-immunosuppressed patients. A case of EN associated with CAEBV after liver transplantation was reported [6]. In our patient, the EN-like skin lesions had been refractory and had relapsed without an immunosuppressive condition. Moreover, the patient presented panniculitis with angiocentric lymphocytic infiltration. The affinity of EBV-infected lymphoid cells to blood vessels was reported in EBV-positive NK/T-cell lymphoma patients [7]. To our knowledge, CAEBV with EN-like skin lesions in a non-immunosuppressed patient has been rarely reported. The present case suggests that we should keep CAEBV in mind as a differential diagnosis for patients who show EN-like skin symptoms that are refractory to conventional treatments and that relapse, especially for patients with high titers of VCA IgG. Careful follow-up is essential in cases of CAEBV because their clinical features may change or overlap during the clinical course [8].

REFERENCES

1. Cohen JI, Iwatsuki K, Ko YH, *et al.* Epstein-Barr virus NK and T cell lymphoproliferative disease: report of a 2018 international meeting. Leuk Lymphoma. 2019; 13: 1-12.

2. Iwatsuki K, Miyake T, Hirai Y, Yamamoto T. Hydroa vacciniforme: a distinctive form of Epstein-Barr virus-associated T-cell lymphoproliferative disorders. Eur J Dermatol. 2019; 29: 21-8.

3. Guissa VR, Aragao PA, Marques HH, Jacob CM, Silva CA. Chronic active Epstein-Barr virus infection mimicking Henoch-Schonlein purpura. *Acta Reumatol Port*. 2010; 35: 513-7.

4. Fujiwara S, Kimura H, Imadome K, *et al.* Current research on chronic active Epstein-Barr virus infection in Japan. *Pediatr Int*. 2014; 56: 159-66.

5. Kawamoto K, Miyoshi H, Seto M, Kimura H, Ohshima K. Clinical features of adult-onset chronic active Epstein-Barr virus infection. *Japanese J Clin Hematol*. 2019; 60: 944-52 (in Japanese).

6. Yokoyama S, Kasahara M, Fukuda A, Sato S, Koda F, Nakagawa A. Epstein-Barr virus-associated erythema nodosum after living-donor liver transplantation: a case report. *Liver Transpl*. 2009; 15: 446-8.

7. Takeshita M, Yamamoto M, Kikuchi M, *et al.* Angiodestruction and tissue necrosis of skin-involving CD56+ NK/T-cell lymphoma are influenced by expression of cell adhesion molecules and cytotoxic granule and apoptosis-related proteins. *Am J Clin Pathol*. 2000; 113: 201-11.

8. Nitta Y, Iwatsuki K, Kimura H, *et al.* Fatal natural killer cell lymphoma arising in a patient with a crop of Epstein-Barr virus-associated disorders. Eur J Dermatol. 2005; 15: 503-6.

Figure legend

Figure 1. Clinical and histopathological features of the present case.

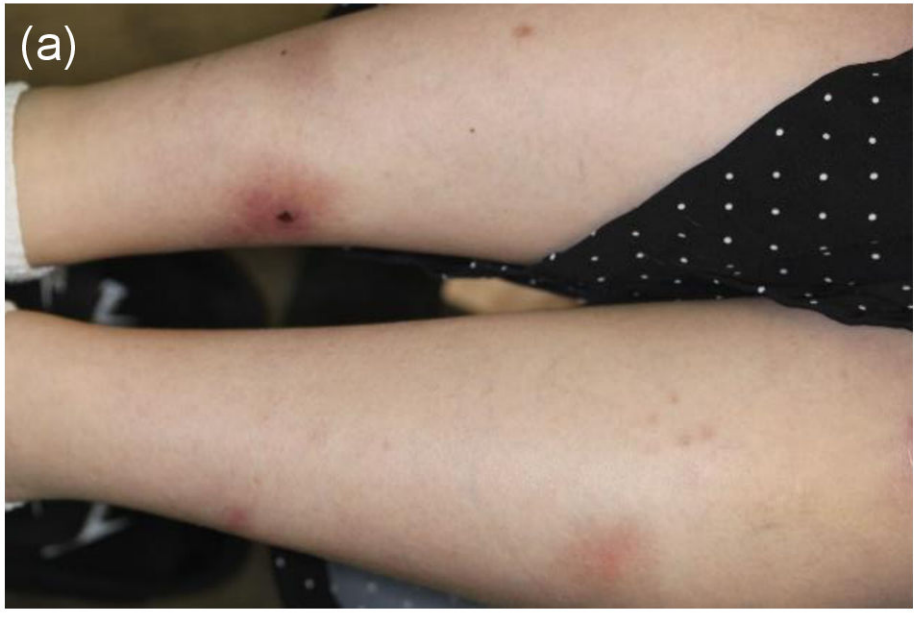
(a) Multiple swollen erythematous lesions with tenderness on the lower legs.

(b, c) A skin biopsy specimen from a lesion on the left lower leg shows lobular panniculitis with angiocentric lymphocytic infiltration, but no apparent vasculitis is observed (hematoxylin-eosin, original magnification b: x40 and c: x200).

(d) Multiple tender, swollen erythematous lesions relapsed on the lower legs 6 months after the cessation of the initial oral PSL treatment.

(e) A skin biopsy specimen from an erythematous lesion on the left lower leg showed lobular panniculitis and dense lymphocytic infiltration in all layers of the dermis, without any apparent vasculitis. (hematoxylin-eosin, original magnification x100). (hematoxylin-eosin, original magnification x100).

(f) *In situ* hybridization for EBV-encoded small RNA shows positive signals in infiltrating lymphocytes (original magnification x100).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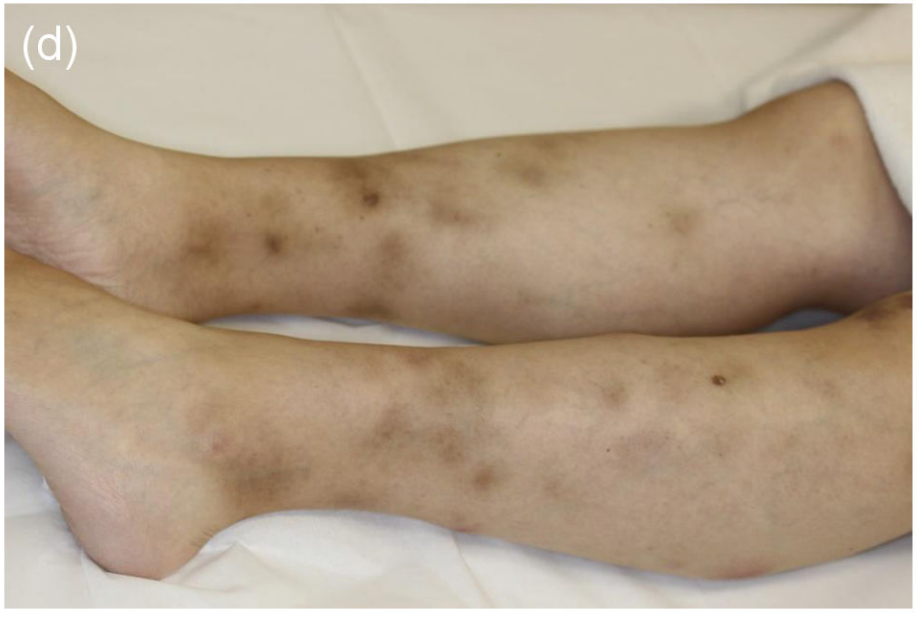
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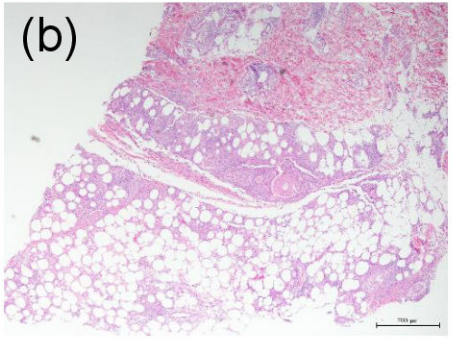
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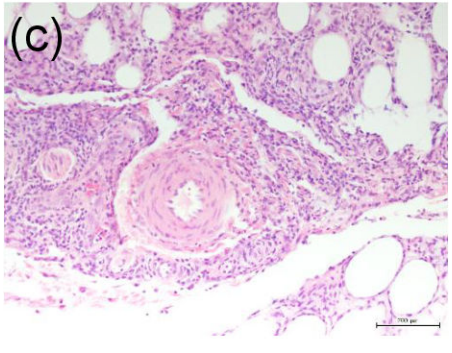
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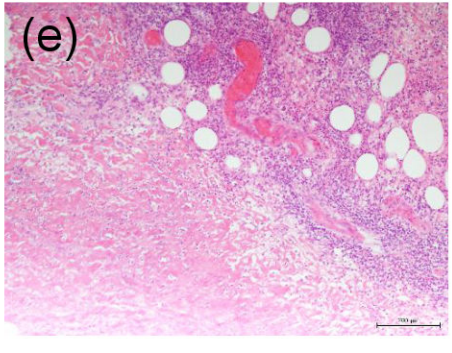
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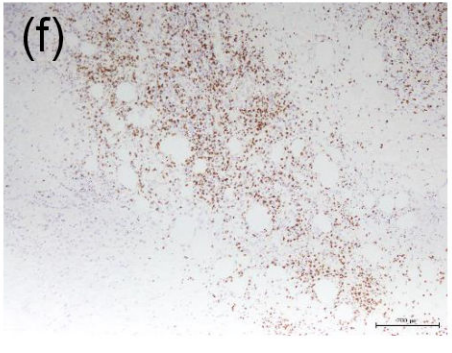
(f)