Mod Rheumatol (2005) 15:435–439
DOI 10.1007/s10165-005-0432-8

CASE REPORT

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A case of Epstein–Barr virus-associated natural killer/T-cell lymphoma presenting as dermatomyositis: extranodal relapse after 7 years in remission

Received: July 29, 2005 / Accepted: September 13, 2005

Abstract A 56-year-old Japanese man was admitted to our hospital due to a fever of unknown origin. He had had a history of extranodal natural killer (NK)/T-cell lymphoma, nasal type, and had been in complete remission for 7 years until June 2003, when he developed high fever, eyelid swelling, and muscular weakness. Serum creatine kinase levels were elevated. Histopathological examination of skin and muscle biopsy specimens revealed subcutaneous infiltration of lymphoid cells positive for CD3, CD56, and Epstein–Barr virus-encoded small nuclear RNA-1. We report this unique case of Epstein–Barr virus-associated lymphoma mimicking dermatomyositis.

Key words Dermatomyositis · Epstein–Barr virus (EBV) · Natural killer (NK)/T-cell lymphoma

Introduction

An association of polymyositis–dermatomyositis (PM/DM) with internal malignancy has been reported in many studies.[1,2] Lymphoproliferative disorders such as Hodgkin's and non-Hodgkin's lymphomas are relatively rare malignant conditions associated with PM/DM, and the causal relationship between the two diseases remains to be elucidated.

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Epstein–Barr virus (EBV) infections have been implicated in various lymphoproliferative diseases, including cutaneous T- or natural killer (NK)-cell lymphoma.[3] The virus is integrated into the host genome and is highly oncogenic in animals. Extranodal NK/T-cell lymphomas, nasal type, are common among Oriental populations and show an aggressive clinical course.[4,5] Most cases of nasal NK/T-cell lymphoma show an EB^+ $CD56^+$ cytotoxic phenotype, suggesting a strong association with EBV infection. Here, we report a case of EBV-associated NK/T-cell lymphoma with eyelid swelling and intramuscular infiltration mimicking dermatomyositis after 7 years of complete remission from initial treatment of the extranodal NK/T-cell lymphoma, nasal type.

Case report

A 56-year-old man was referred to our hospital due to high fever, skin rash, muscular weakness, and eosinophilia in October 2003. He had been diagnosed as having extranodal NK/T-cell lymphoma, nasal type, on the basis of clinical features, including nasal obstruction and histological findings 7 years previously. He had been treated with three cycles of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) chemotherapy followed by irradiation, and complete remission had been achieved. He had been healthy until June 2003, when he developed high fever, muscular weakness, and skin rash with eosinophilia. In the previous hospital, bone marrow aspiration, Ga scintigraphic scanning, and computed tomographic scanning had disclosed no evidence of recurrence of NK/T-cell lymphoma. Although [^{18}F]fluorodeoxyglucose positron emission tomography had revealed slight uptake in the left axillary region, the finding was not of diagnostic value. He was thus referred to our hospital with the diagnosis of fever of unknown origin and eosinophilia.

Physical examination on admission revealed an alert, oriented man in no acute distress. Blood pressure was 124/82 mmHg, and his pulse was regular at 76 beats/min. Body

temperature was 37.2°C. Bilateral eyelid swelling was noted. Erythemas varying from 2 to 3 cm in diameter were observed over the trunk and upper extremities. Swollen left neck and left axillary lymph nodes less than 2 cm in size were palpable without tenderness. Neurological examination showed proximal muscle weakness with grasping pain.

Laboratory data on admission were as follows. White blood cell count was 4200/mm^3 (34.0% segmented neutrophils, 20.0% lymphocytes, 36.0% eosinophils), a hemoglobin level of 10.9 g/dl, and platelets 21.2 × 10^4/μl. C-reactive protein was 1.1 mg/dl. Blood chemistry showed elevated aspartate aminotransferase 57 IU/l, alanine aminotransferase 106 IU/l, lactate dehydrogenase 1028 IU/l, aldolase 40 IU/l, and creatine kinase 2213 IU/l, respectively. Renal function was normal. Serological tests revealed negative antinuclear antibodies and negative anti-Jo-1 antibodies, Serum immunoglobulin G (IgG) levels of 1334 mg/dl, IgA 645 mg/dl, IgM 94 mg/dl, and IgE 318 IU/ml. Serum ferritin was 91.5 ng/ml. An elevated level of soluble interleukin-2 receptor (3038 U/ml) was observed. Antibody titer tests against EBV revealed an antiviral capsid antigen IgG titer of 1:640, IgM titer of less than 1:10, an anti-early antigen IgG titer of 1:80, IgM titer of less than 1:10, and Epstein–Barr nuclear antigen (EBNA) titer of 1:80.

Biopsy specimen of the right axillary skin showed infiltration of lymphoid cells in the dermis and perivascular

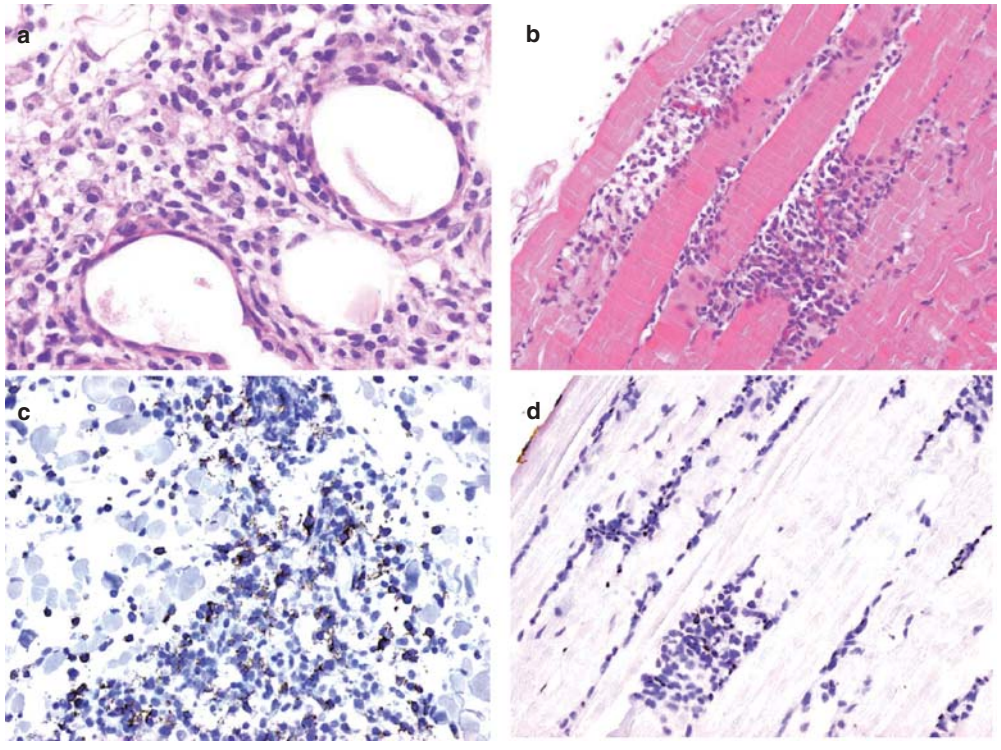

Fig. 1a,b. Microphotographs of biopsy specimens showing subcutaneous infiltration of lymphoid cells (hematoxylin–eosin staining, ×200). **a** Tissue obtained from the skin. **b** Tissue obtained from the muscle. **c,d** Infiltration of CD56-positive cells (immunohistochemical staining, ×100). **c** Tissue obtained from the skin. The majority of the infiltrates expressed CD56. **d** Tissue obtained from the muscle. CD56-positive cells were fewer than those observed in the skin specimen

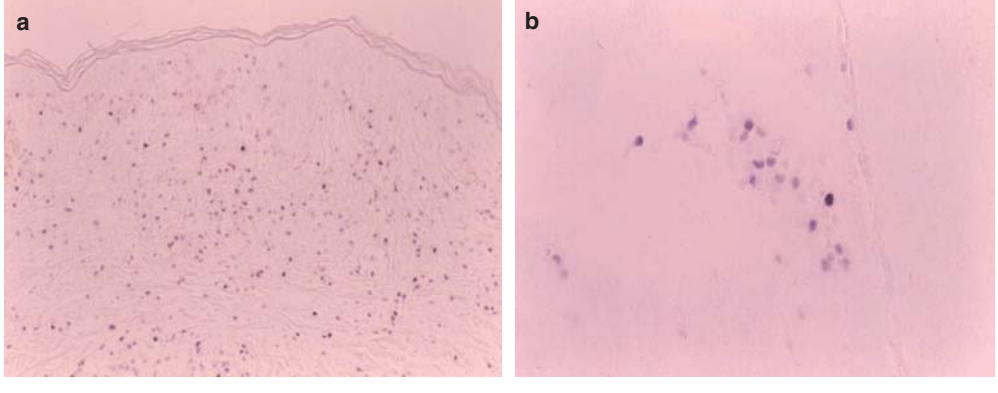

Fig. 2a,b. Epstein–Barr virus-encoded small nuclear RNA-1 (EBER) in situ hybridization. **a** Biopsy of axillary skin showing infiltration of atypical cells positive for EBER. **b** A lower number of EBER-positive cells is observed in the biopsy specimen of the quadriceps muscle (**a** ×100; **b** ×200)

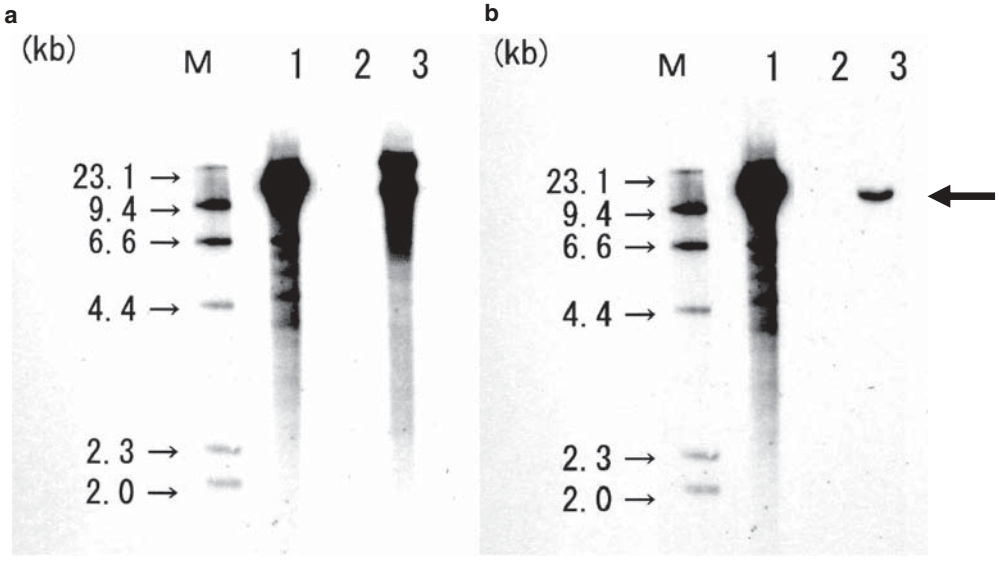

Fig. 3a,b. Southern blot analysis for Epstein–Barr virus (EBV) DNA. **a** An oligoclonal band was detected in the skin. **b** A single band of EBV genome was detected in the peripheral blood cells (*arrow*). *Lane 1*, standard positive control for EBV-DNA; *lane 2*, negative control; *M*, size markers (γDNA/*Hin*dIII), indicated on the *left margin*; *lane 3*, sample from the patient

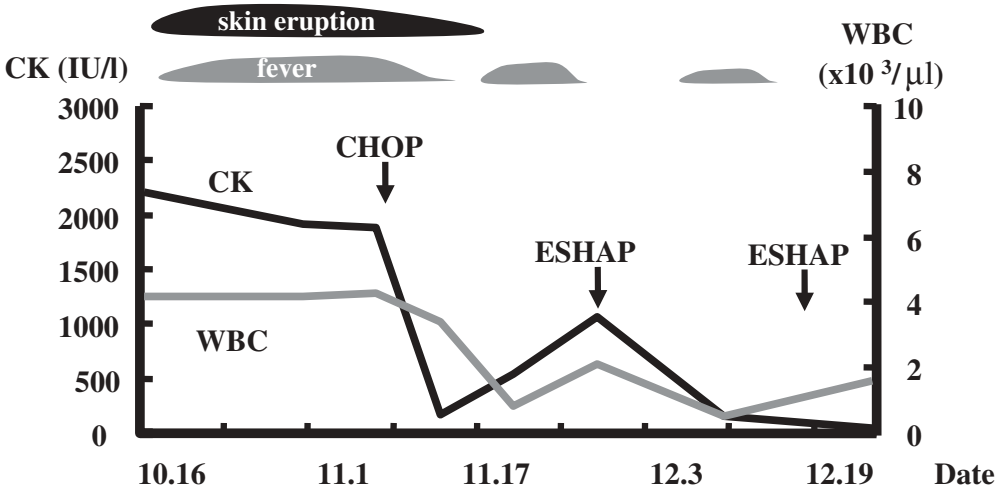

Fig. 4. Clinical course of our patient with nasal natural killer (NK)/T-cell lymphoma resembling dermatomyositis. Conventional *CHOP* (cyclophosphamide, adriamycin, vincristine, and prednisolone) chemotherapy followed by two cycles of *ESHAP* (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) chemotherapy led to partial remission, and serum creatine kinase levels were normalized. *CK*, creatine kinase; *WBC*, white blood cell count

regions resembling dermatomyositis (Fig. 1a). A biopsy specimen of the right quadriceps showed a massive infiltrate of lymphoid cells in the muscle and degenerative change of the muscle fibers (Fig. 1b). Immunohistochemical staining disclosed the lymphoid cells were positive for CD3, CD56, TIA-1, and Epstein–Barr virus-encoded small nuclear RNA-1 (EBER), suggesting that those infiltrates corresponded to NK/T lymphoma cells (Fig. 1c,d). In situ hybridization (ISH) demonstrated that most of the atypical lymphocytes contained EBER in the skin (Fig. 2a), whereas a relatively lower number of cells were positive for EBER in the muscle (Fig. 2b). Southern blot analysis using an EBV terminal region probe revealed oligoclonal bands in the skin (Fig. 3a). Furthermore, a single band of EBV DNA was detected in peripheral blood cells (Fig. 3b). Atypical lymphocytes expressing CD3 and CD56 were also found in the biopsy specimen of the axillary lymph node (figure not shown), indicating a relapse of extranodal NK/T-cell lymphoma, nasal type. No involvement of the bone marrow or other internal organs was detected. Combination chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) led to partial remission. However, the patient developed high fever and elevation of CK on day 18. We changed the regimen to ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) chemotherapy as a salvage treatment. After two cycles of ESHAP chemotherapy, his symptoms ameliorated and serum CK level normalized (Fig. 4, clinical course). The patient was transferred to a local cancer center for hematopoietic stem cell transplantation on January 7, 2004. Although he was subjected to autogenic peripheral blood stem cell transplantation (PBSCT) in June 2004, he suffered a relapse and died of multiple organ failure 2 months after PBSCT.

Discussion

It has been reported that malignancies frequently associated with PM/DM are similar to those of the general population, such as tumors of the breast, lungs, female genitalia, and digestive system.[2] There has been a limited number of reports on PM/DM associated with hematopoietic malignancies including Hodgkin's and non-Hodgkin's lymphomas.[6,7] Although the causal relationship has not been established, the two conditions may influence each other, because both diseases often overlap during their course.

We have described a case of extranodal recurrence of NK/T-cell lymphoma, nasal type, with subcutaneous infiltration. Ohtsuka et al.[3,8] and Shirasaki et al.[9] have reported similar cases with erythematous swelling of the eyelids and intramuscular infiltration mimicking DM that was associated with chronic active EBV infection. The initial clinical manifestations in our patient were also suggestive of DM; namely, bilateral eyelid swelling, erythematous rash over the extremities, and muscular weakness. Gottron's sign was not noted in our patient. An abnormal pattern of anti-EBV antibodies indicative of chronic activation of EBV[10] led us to examine the existence of EBV genome in the muscle and skin biopsy specimens by in situ hybridization.[11] Findings of EBER-positive abnormal lymphocytes and oligoclonal expansion of the EBV genome in these organs by Southern blot analysis[12] confirmed the diagnosis of relapse of EBV-associated NK/T-cell lymphoma. The presence of a single band of EBV genome with the peripheral blood suggested an expansion of selected clone during tumor progression. Oligoclonal expansion of EBV genome in the skin might be due to simultaneous infection of tumor cells with EBV or contamination of lytically infected nontumoral cells with the virus. Markedly fewer EBER-positive lymphoid cells were detected in the muscle compared with the skin specimen. The majority of lymphocytes that infiltrated the muscle were negative for EBER and they expressed $CD4^+$ or $CD8^+$ T-cell markers. Ohga et al.[13] studied cytokine profiles of EBV-infected T cells and showed that activated T cells in chronic active EBV (CAEBV) infection expressed high levels of Th1 and Th2 cytokines including interferon (IFN)-γ, interleukin (IL)-2, and IL-10. In our patient, cytokines produced by tumor cells may have contributed to the recruitment of $CD4^+$ or $CD8^+$ T lymphocytes. However, it is difficult to clearly distinguish malignancies associated with inflammatory muscle diseases from muscular infiltration of NK/T lymphoma cells. Although precise mechanisms for the association of malignancy and myositis are not clear, cross-reaction between antigenic epitope in the muscle and tumor antigens is believed to have a role in the pathogenesis of inflammatory myopathy. Autoimmune response against muscle may be involved in the pathological differences between skin and muscle in this patient. Peripheral eosinophilia associated with lymphomas has been reported in the literature. Production of Th2 cytokines by EBV-infected T cells might have increased eosinophil differentiation in bone marrow. However, infiltration of eosinophils was not observed in the organs of this patient (Fig. 1a,b).

The mechanism by which latent EBV infection leads to tumor development has been discussed elsewhere. Latent EBV infection plays an essential role in the induction of malignant phenotypes and transformation of virus-infected cells.[14] LMP-1 is a major oncogene involved in tumorigenesis of B cells, as well as of T and NK/T-type cells.[15] NK/T-cell lymphoma is almost constantly associated with EBV, indicating the pathogenic role of the virus. Nasal-type NK/T-cell lymphoma occurring outside the nasal cavity is highly aggressive, with short survival times and poor response to therapy. Resistance to conventional chemotherapy is thought to be due to multidrug-resistant gene expression[3] and hemophagocytic syndrome.[16] In our patient, conventional chemotherapy followed by ESHAP salvage therapy led to partial remission; however, he died of multiple organ failure after PBSCT. There are some reports of CAEBV with lymphoproliferation successfully treated with blood stem-cell transplantation followed by donor lymphocyte infusion.[17] Furthermore, adoptive immune transfer of EBV-specific cytotoxic T cells after allogenic stem-cell transplantation[18,19] is one of the promising therapies for EBV-associated lymphoproliferative disease.

Acknowledgments We thank Dr. Jun-ichi Tamaru, Department of Pathology, Saitama Medical Center, Saitama Medical School, for assistance with in situ hybridization and pathological diagnosis of this patient. We also thank Dr. Kimihiro Kawakami, Department of Hematology and Stem Cell Transplantation, Shizuoka Cancer Center, for the PBSCT treatment.

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