Case Study

Small Bowel Perforation Caused by Epstein-Barr Virus-Associated B Cell Lymphoma in a Patient with Angioimmunoblastic T-Cell Lymphoma

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On rare occasions, secondary Epstein-Barr virus (EBV)-associated B cell lymphoma can develop in a patient with angioimmunoblastic T-cell lymphoma (AITL). We report a case of a 66-year-old Japanese woman who developed diffuse large B-cell lymphoma (DLBCL) in her small intestine after chemotherapy for AITL. She was found to have peritonitis due to perforation of the small intestine. Partial ileectomy specimen showed DLBCL cells infiltrating into the intestinal wall. In situ hybridization for EBV-encoded RNA revealed positivity in the lymphoma cells. The lymph nodes diagnosed as AITL were negative for EBV infection and there was no coexistence of B cell neoplasms in them. We thought small bowel perforation in this case was caused by EBV-associated B cell lymphoma secondary to AITL. Our case showed a remarkable deficiency of cellular immunity after chemotherapy, which we postulate was related to the cause of occurrence of B-cell lymphoma.

Keywords: angioimmunoblastic T-cell lymphoma, small bowel perforation, Epstein-Barr virus, secondary B cell lymphoma

INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is one of the nodal peripheral T-cell lymphomas described in the WHO classification that accounts for 4-6% and 5% of all lymphomas in Western countries1-3 and in Japan,4 respectively. AITL typically presents with advanced stage disease, and is manifested by generalized lymphadenopathy, hepatosplenomegaly, and other systemic symptoms. Patients exhibit immunodeficiency secondary to the neoplastic process.1-3 In the majority of cases, expansion of B-cells positive for Epstein-Barr virus (EBV) is seen, which is thought to be a consequence of underlying immune dysfunction.5,6

It has been reported that supervening EBV-associated B cell lymphoma can occur in AITL. However, relatively few cases of EBV-associated B cell lymphomas in AITL have been fully described so far.7-15 In a previous large study, only three cases out of more than 170 cases with AITL developed EBV-associated secondary B cell lymphomas.10

We report here a rare case of AITL, in which small bowel perforation was thought to be caused by EBV-associated B cell lymphoma after combination chemotherapy and high dose corticosteroid treatment, and discuss the etiology of the secondary B cell lymphoma with a review of the literature.

CASE REPORT

In February 2005, a 66-year-old woman was admitted to our hospital due to continuous fever and loss of body weight. Clinical examination revealed general lymphadenopathy, hepatosplenomegaly, and purpura. Laboratory findings showed increase of the white blood cell count, serum lactate dehydrogenase, serum C-reactive protein and hypoalbuminemia. Eosinophilia and hyper-g-globulinemia were not observed. Tests for viral capsid antigen (VCA)-IgG and EBV-associated antigen were positive but VCA-IgM was negative. Anti-human immunodeficiency virus antibody and anti-human T-cell lymphotropic virus-I antibody were negative. Computed tomography (CT) showed multiple lymph node swellings, bilateral pleural effusion, pericardial effusion and hepatosplenomegaly. An evaluation of bone marrow aspirate showed no infiltration of atypical cells. No EBV-
infected cells were found by small EBV-encoded RNA in situ hybridization (EBER-ISH) in bone marrow. The patient then underwent biopsy of the left inguinal lymph node. Hematoxylin-eosin stained sections showed an effacement of normal nodal architecture by polymorphic cellular infiltrate, which was seen beyond the capsule of the lymph node. Diffuse infiltration was composed of small to medium-sized or large lymphoid cells admixed with plasma cells and eosinophils. Some of the large immunoblast-like lymphoid cells had a clear cytoplasm. There was also a proliferation of high-endothelial venules. Immunohistochemical staining revealed that the large immunoblast-like lymphoid cells were predominantly positive for CD3, CD10 and CXCL13. Southern blot analysis detected clonal rearrangement of the T-cell receptor (TCR) Cβ gene, but clonal rearrangement of the immunoglobulin heavy chain (IgH) gene was not demonstrated. These findings were compatible with AITL. EBER-ISH showed negativity in the lymphoma cells as well as in the reactive small lymphocytes (Fig. 1).

The patient received one cycle of THPCOP16 (cyclophosphamide, pirarubicin, vincristine and prednisolone), but her symptoms did not improve. She received CHASE17 (cyclophosphamide, cytarabine, etoposide and dexamethasone) as a salvage therapy. Her symptoms improved after two cycles of CHASE, but pancytopenia persisted. She could not continue to receive further chemotherapy. Bone marrow aspiration revealed hypocellularity and gelatinous change of the stroma. There was no neoplastic cell infiltration, hemophagocytosis, or EBV-infected cells. She was followed-up without any further treatment for one year. During this follow-up period, pancytopenia and suppression of cellular immunity was observed (Mean absolute count of CD3 positive lymphocytes was 238/μL, CD4 positive lymphocytes was 114/μL, CD8 positive lymphocytes was 131/μL). A slight increase in cytomegalovirus (CMV) antigenemia was observed without clinical symptoms.

In September 2006, the patient developed disseminated varicella-zoster followed by high grade fever, generalized lymphadenopathy and splenomegaly. A biopsy of axillary lymph node revealed a relapse of AITL. At this point, EBV positive B immunoblasts did not coexist. Since pancytopenia had persisted, she received high-dose dexamethasone therapy. Lymph node swellings completely disappeared, but pancytopenia was worsening. Neoplastic cell infiltration and EBV-infected cells into bone marrow was not observed. She was afebrile and doing well during the following two months.

In January 2007, she presented with high fever again. We suspected the second relapse of AITL and employed treatment by prednisolone. However, a significant increase in CMV antigenemia was demonstrated and CT showed neither lymph node swellings nor splenomegaly, although an increase in the intestinal gas, a thickening of the intestinal wall and an appearance of ascites were noticed. She was diagnosed as having CMV colitis and the intravenous administration of ganciclovir was started. Twelve days later, she suddenly complained of severe abdominal pain because of intestinal perforation. Partial resection of the ileum and colostomy were performed urgently. Macroscopically, the resected terminal ileum showed a short segment of prominent hemorrhagic necrosis. The mucosa was dark and granular in appearance with three pinhole perforation sites. Microscopic examination showed a diffuse infiltration of atypical large lymphoid cells in the whole thickness of the intestinal wall with hemorrhagic and necrotic changes. Immunohistochemical staining revealed that the large atypical cells were positive for CD20 and CD79a, but negative for CD3 and CD45RO. PCR analysis showed monoclonal rearrangement of the IgH gene, but no clonal rearrangement of the TCR-γ gene was detected. A diagnosis of diffuse large B cell lymphoma was made. Some lymphoma cells were positive for latent membrane protein-1, but EBV-associated antigen-2 was not expressed in both of the lymphoma cells and reactive small lymphocytes. EBER-ISH showed positivity in both cells (Fig. 2). Operative findings and pathological examination revealed no evidence of vascular occlusion. We considered the perforation to have been caused by lymphoma cell infiltration. After the surgery, high grade fever continued and CT revealed persistent retenion of ascites and multiple space-occupying lesions in the liver. Needle biopsy of the liver did not show infiltrating neoplastic cells but it did reveal a fraction of necrotic tissue. Simultaneously, the patient complained of visual disturbance, and tumor involvement of the fundus was suspected based on an ophthalmological examination.

In March 2007, she died of respiratory failure caused by severe pneumonia. The family refused an autopsy.

DISCUSSION

The lymphoma cells present in the intestinal wall in our case were thought to be derived from EBV-infected B cells because of the positivity for ISH-EBER and positive immunohistochemical reaction for latent membrane protein-1. It is well known that most cases of AITL are frequently complicated with EBV infections. It has been reported that EBV genomes are found in most of the AITL cases and almost all of the cells infected by EBV are B cells showing normal histological findings. In the majority of cases, EBV-positive cells were scattered, but there were sheets of EBV-positive cells in some cases. In spite of such a background, the complication of B cell lymphomas in AITL has been reported to be rare. Zettl et al. investigated more than 600 cases of nodal T-cell lymphoma including more than 170 cases of AITL. They found 17 cases with transformed large EBV-positive B cells and only three of these cases were secondary EBV-associated B cell lymphoma in AITL. To the best of our knowledge, eighteen cases of AITL with secon-
EBV-associated B cell lymphoma have been previously reported.\textsuperscript{7-15}

It is commonly considered that EBV-associated secondary B cell lymphomas in AITL develop from EBV-infected B cells in lymph nodes. However, EBV-infected B cells were not detected by EBER-ISH before development of secondary lymphoma in our case. This fact drove us to review the literature, and we found that in five out of nine cases investigated by EBER-ISH at initial presentation of AITL, EBV-infected cells were not detected.\textsuperscript{7,11,13} Furthermore, these cases as well as ours presented extranodal organ involvement by secondary B-cell lymphomas. We thus conclude that secondary lymphomas could occur from anywhere other than a lymph node of AITL.

This immunosuppression is thought to be related to occurrence of EBV-associated disease conditions such as post-transplant lymphoproliferative disorders,\textsuperscript{20} lymphomas associated with human immunodeficiency virus infection,\textsuperscript{31} or age-
related EBV-associated lymphoproliferative disorders.22 It is well known that patients with AITL tend to be severely immunodeficient. Moreover, a recent study has revealed that an increase in EBV load in lymph nodes is associated with histological progression of AITL.23 However, because the occurrence of secondary EBV-associated B cell lymphoma is rare, it is considered that secondary lymphomas are induced not only by immunodeficiency of AITL, but also by additional factors such as treatment and patient’s background. Recently, Weisel et al.15 reported a case where EBV-associated secondary B cell lymphoma developed after chemotherapy composed of alemtuzumab and fludarabine. Their case showed remarkable a deficiency of cellular immunity, as was seen in our case. Our case showed persistent pancytopenia after chemotherapy, deficiency of cellular immunity and reactivation of CMV and varicella zoster virus, which indicated a deeply immunodeficient state. We consider the immunodeficiency to probably be related to lymphomagenesis in our case. However, the reason for remarkable immunodeficiency after chemotherapy in our case is not exactly clear. In the previous reports, the information about treatment was described in twelve cases.7,11,13-15 In these reports, four cases underwent autologous stem cell transplantation and on the other hand, two cases developed secondary lymphoma after observation alone. Therefore, it is still unclear whether treatment is related to lymphomagenesis.

In conclusion, we observed an unexpected bowel perforation that was caused by EBV-associated secondary B cell lymphoma in AITL. Clinicians should keep in mind that there is a possibility of this phenomenon, particularly when a deep cellular immunosuppressive state is observed. It is critical that further investigations, together with the accumulation of such cases be conducted, so that we can better understand the clinicopathological features of patients with this kind of complicated lymphoma.

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REFERENCES


