

Epstein-Barr Virus-associated Post-Transplant Lymphoproliferative Disorders presented as Interstitial Pneumonia; Successful Recovery with Rituximab

We describe a patient that developed Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorders (PTLD), which presented as interstitial pneumonia. He had received allogeneic bone marrow transplantation for the treatment of acute myeloid leukemia 17 months before, when he developed hypoxemia requiring emergent admission. Chest computed tomography revealed pulmonary interstitial shadows, but neither hepatomegaly nor lymphadenopathy were detected. Bronchoscopy with lung biopsy revealed a lymphomatous proliferation of EBV-infected B cells. The interstitial pneumonia rapidly deteriorated, but improved dramatically after treatment with anti-CD20 monoclonal antibody (rituximab). This is the first report of a patient with lung EBV-PTLD that presented as interstitial pneumonia and was successfully treated with rituximab.

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Introduction. Pulmonary infiltrates are occasionally observed in hematopoietic stem cell transplant (SCT) recipients. The causes of the pulmonary infiltrates are heterogeneous, such as infectious pathogens, cytomegalovirus (CMV), *Aspergillus* or *Nocardia* organisms, bronchiolitis obliterans (BO), graft-versus-host disease (GVHD), drug reaction, idiopathic interstitial pneumonitis (IP), or post-transplant lymphoproliferative disease (PTLD). The rate of pulmonary complications following transplant is high. Although encouraging survival statistics are now reported after SCT, respiratory complications occur in 40% to 60% of patients after SCT and they are the major causes of morbidity and mortality.¹ Thus, prompt diagnosis of lung complications is very important. PTLD is a severe complication that arises in SCT recipients with an incidence of 1% to 20%. The median onset of the disease in SCT recipients is 70 to 90 days, but cases have been reported as early as 1 week and as late as 9 years post-transplant.² PTLD characteristically has a rapid onset, aggressive behavior, and a poor prognosis.^{2,3} Epstein-Barr virus (EBV)-PTLD can present within the central nervous system, thoracic and abdominal cavities, or extravisceral lymphoid tissue, with lymphadenopathy or extranodular masses in most cases.² We report here a patient with acute myeloid leukemia (AML) that underwent allogeneic bone marrow transplantation, and developed EBV-PTLD. He presented as severe interstitial pneumonia, and was successfully treated with rituximab.

Case Report. A 53-year-old Japanese man was diagnosed with AML with multilineage dysplasia or, according to the French-American-British classification, AML M0, by bone marrow examination in May 2003. He was treated with IDA-FLAG regimen⁴ and complete remission was achieved. Bone marrow transplantation from his human leukocyte-antigen-matched healthy brother was performed on January 29, 2004. Because of impaired renal function (serum creatinine value around 2mg/dL), a reduced-intensity conditioning regimen consisting of busulfan 4 mg/kg for 2 days, fludarabine 15 mg/m² for 5 days, and 2 Gy of total body irradiation was used before allo-SCT. The prophylaxis for GVHD was a combination of tacrolimus and methotrexate (5mg/m², day +1, +3, +6).

The bone marrow engrafted without complications, and because there was no evidence of residual AML and no symptoms of GVHD, we began to taper the tacrolimus 3 months after transplantation and ended it by 6 months. In June 2005, on day 512 after the allo-SCT, the patient presented with a 2-week history of low-grade fever and fatigue. The physical examination was unremarkable, and the laboratory data showed a slightly elevated C-reactive protein (9.1 mg/dL) and arterial hypoxemia (PaO₂ 63mmHg in room air). We performed computed tomography (CT) of the chest, which revealed bilateral interstitial shadows in the lungs. Antibacterial therapy was first initiated for the interstitial pneumonia and low-grade fever. The examination of his chimerism status using whole peripheral blood and bone marrow showed complete donor chimerism. Flowcytometric analysis using peripheral blood mononuclear cells showed that the CD4 T cell, CD8 T cell, and CD20 B cell counts were 224, 280, and 161 cells/ μ L, respectively. Polymerase chain reaction (PCR) analyses of the sputum indicated that the patient was negative for tuberculosis and *Pneumocystis carinii*. CMV DNA was not detected in the peripheral blood lymphocytes (PBL) using PCR, but quantitative PCR for EBV DNA was high (6800 copies/10⁵ cells) in the PBL. Anti-EBV anti-viral capsid antigen IgG (X 1280) and anti-early antigen IgG(X 160) titers were elevated. On day 516, transbronchial lung biopsy (TBLB) to determine the cause of the interstitial pneumonia led to the pathologic diagno-

Figure 1. Histological findings of a transbronchial lung biopsy. A, Large lymphocytes infiltrate sub-bronchial lesion (hematoxylin and eosin staining). B, Immunohistochemical staining with anti-CD20 monoclonal antibody. The infiltrated lymphocytes are CD 20 positive. C, *In situ* hybridization for Epstein-Barr virus-encoded RNA (EBER). The infiltrated lymphocytes are EBER positive.

sis of EBV-associated PTLD (CD20-positive, *in situ* hybridization for EBV-encoded RNA-positive) (Figure 1). Abdominal CT and head magnetic resonance imaging showed no evidence of PTLD, which led to the diagnosis of lung EBV-PTLD presenting as interstitial pneumonia. The interstitial shadows spread rapidly, and hypoxic respiratory failure progressed to the point that the patient required a high level of supplementary oxygen by day 526 after allo-SCT. After the administration of rituximab for lung EBV-PTLD on day 528, the interstitial shadows in the lungs disappeared bilaterally and the patient no longer required supplementary oxygen on day 538 (Figure 2, 3). He has been doing well for 1 year after developing lung EBV-PTLD.

Discussion. Many of the pulmonary complications of allo-SCT have a nonspecific radiographic appearance. The most crucial information for the proper interpretation of chest radiographs is the chronologic onset of radiographic abnormalities after transplantation. The onset of nodular opacities after engraftment might be due to a number of disorders, such as opportunistic infection, BO, and PTLD. Thoracic presentation of EBV-PTLD occurs as mediastinal lymphadenopathy in 45% of patients, and pulmonary parenchymal lesions in 55% of patients. All patients with pulmonary parenchymal EBV-PTLD present with pulmonary masses or nodules.^{5,6} In pediatric cases, patients with PTLD have masses as well as alveolar and interstitial pulmonary lymphoma,^{7,8} but in our patient the CT scan showed only interstitial shadows. Therefore, this is the first report of an adult patient with lung EBV-PTLD that presented with severe interstitial pneumonia. In the present case, the rapid and progressive hypoxia and interstitial pneumonia were caused by EBV-PTLD, which was revealed by histology of the

TBLB specimen. Thus, the lung biopsy is very important for a definitive diagnosis and appropriate therapy in patients with lung complications after allo-SCT.

The development of impending EBV-PTLD in these patients can be predicted quantitatively by monitoring the viral load in the plasma at regular intervals during the first 6 months after allo-SCT.³ In the present case, we examined quantitative PCR of EBV DNA to determine the cause of persistent low-grade fever of unexplained origin and progressing interstitial pneumonia. Then, the examination revealed high levels of EBV DNA in the PBL, therefore, we suspected that the patient suffered from EBV-PTLD that presented with interstitial pneumonia. Our experience suggests that in transplant recipients with persistent fever of unexplained origin, quantitative EBV DNA load should be examined, as a positive finding might lead to the early diagnosis and treatment of EBV-PTLD.

Some investigators have demonstrated that EBV reactivation is common after allo-SCT, particularly in cases transplanted with unrelated donor SCT, or in cases in which T cell-depleted allo-grafts or ATG are used.^{2,3} Other investigators reported that lymphopenia after SCT might reflect an impaired immune reconstitution, and a blood profile of T lymphopenia is likely associated with a high incidence of EBV-PTLD in pediatric patients receiving allo-SCT.⁹ The exact cause of the disease in our patient is not clear, because he was not at high risk for EBV-PTLD after allo-SCT, but the mild lymphopenia might have indicated his impaired immune status. Furthermore, it is reported that EBV viremia and PTLD are significantly more common in children following SCT with a reduced intensity conditioning regimen.¹⁰ We have no information regarding the correlation between

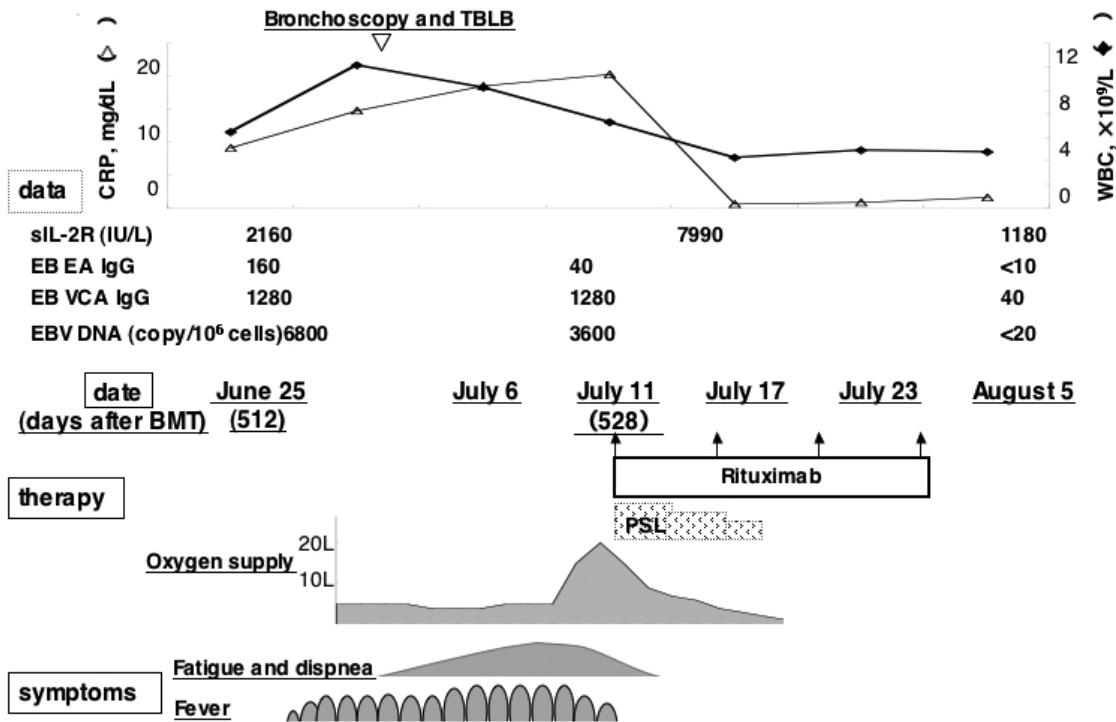


Figure 2. Summary of the main laboratory data and therapeutic interventions during the entire period of monitoring. Black arrows indicate intravenous infusion of rituximab. EBV indicates Epstein-Barr virus; EBV EA IgG, anti-early antigen IgG against EBV; EBV VCA IgG, anti-viral capsid antigen IgG against EBV; WBC, white blood cell; CRP, C-reactive protein; PSL, prednisone; TBLB, transbronchial lung biopsy; BMT, bone marrow transplantation.

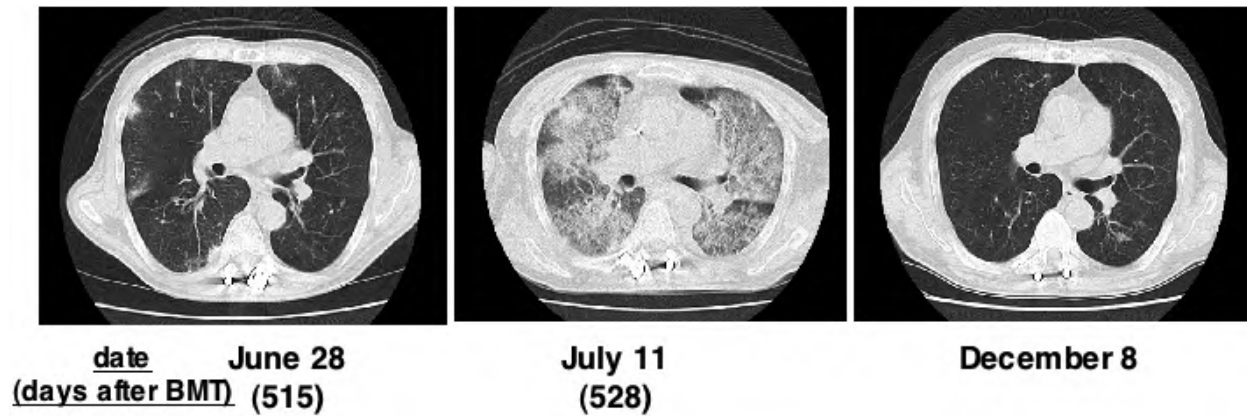


Figure 3. Computed tomography (CT) scans on day 515, on day 528 after bone marrow transplantation, and after rituximab therapy (on December 8, 2005). CT on day 515 shows interstitial shadows in the lungs bilaterally. CT on day 528 shows the interstitial shadows spread severely. CT on December 8 shows almost normal lungs. BMT indicates bone marrow transplantation.

the incidence of EBV-PTLD and a reduced intensity conditioning regimen in adult patients receiving allo-SCT. Thus, the accumulation and analysis of more adult patients with EBV-PTLD are needed.

Treatment for EBV-PTLD is controversial.¹¹ Antiviral therapy (acyclovir, ganciclovir) is not proven to be therapeutically effective. Chemotherapy is sometimes of limited value, especially if the patient is too debilitated to tolerate aggressive therapies. In EBV-PTLD occurring after allo-SCT, infusion of donor T lymphocytes is efficacious.¹² Monoclonal antibodies are also effective in B cell lymphoma as single agents or in combination with chemotherapy. Rituximab was subsequently introduced for the management of PTLD. Many studies indicate that rituximab is efficacious and safe for the treatment of EBV-PTLD.¹³⁻¹⁶ Furthermore, quantitative monitoring of EBV-DNA levels from the start of and during therapy for EBV-PTLD rapidly and accurately predicts the response to therapy.¹⁷ These findings and our experience suggest that the most effective way to minimize morbidity and mortality due to EBV-PTLD is to perform a clinical assessment by measuring EBV DNA to determine whether to start the treatment with rituximab and for evaluation of the therapeutic efficacy.

In conclusion, this is the first reported case of EBV-PTLD that presented as interstitial pneumonia and was successfully treated with rituximab. Furthermore, in the present case, quantitative PCR revealed high levels of EBV DNA in the PBL, which also directed us to the correct diagnosis following TBLB. As EBV-PTLD can be successfully managed with rituximab, the diagnosis should be kept in mind when allo-SCT recipients develop rapidly progressive interstitial pneumonia.

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