—Case Reports—

Epstein-Barr Virus-positive T-cell Lymphoproliferative Disease Following Umbilical Cord Blood Transplantation for Acute Myeloid Leukemia

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We report a case of the extremely rare condition Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disease (LPD) which occurred after umbilical cord blood transplantation. A 25-year-old Japanese man underwent cord blood transplantation from a male human leukocyte antigen 4/6-matched donor due to acute myeloid leukemia with trisomy 8. Bone marrow examination on day 30 showed chimerism with at least 90% donor cells and complete hematological response. Chronic symptoms of graft-versus-host disease appeared only on the skin and were successfully treated with cyclosporine alone. Three years later, however, the patient experienced repeated cold-like symptoms and was hospitalized with liver dysfunction. A high fever developed and was followed by significant edema of the right side of the face. The EBV DNA copy number in whole peripheral blood was 2×10^4/mL. Liver biopsy showed invasion of EBV-infected CD8-positive T cells. Southern blotting analysis of the whole peripheral blood showed that the T-cell receptor Cβ1 rearrangement was positive. On the basis of these results, EBV-positive T-cell LPD was diagnosed and treated with prednisolone, cyclosporine, and etoposide, followed by cyclophosphamide, doxorubicin, vincristine, and prednisone. However, the patient died of cardiac function failure, pneumonia, and pulmonary hemorrhage, all of unidentified cause. Most cases of EBV-related LPD after hematopoietic stem cell transplantation consist of EBV-positive B-cell LPD, and, to our knowledge, *de novo* EBV-positive T-cell LPD subsequent to transplantation has not been previously reported. (J Nippon Med Sch 2016; 83: 35–42)

Key words: Epstein-Barr virus-positive T/natural killer-cell lymphoproliferative disease, CD8-positive T cells, infectious mononucleosis, umbilical cord blood transplantation, multiple organ failure

Introduction

Epstein-Barr virus (EBV)-positive T/natural killer (NK)-cell lymphoproliferative disease (LPD) is a systemic condition characterized by EBV infection and clonal proliferation of T/NK cells[1]. This extremely rare disease affects mostly children in Japan and is associated with persistent or recurrent infectious mononucleosis-like symptoms and the proliferation of EBV-infected cells in the peripheral blood. The condition previously referred to as chronic active EBV infection syndrome is one of its most typical forms[2]. According to the 2008 World Health Organization classification[3], systemic EBV-positive T-cell LPD of childhood and hydroa vacciniforme-like lymphoma are also included in this category of diseases, which, if occurring subsequent to transplantation, are equivalent to post-transplant lymphoproliferative disorder[4].

While rituximab is effective against EBV-positive B-cell LPD after hematopoietic stem cell transplantation (HSCT), no established therapy exists for EBV-related T/NK-cell LPD, which has a poor prognosis due to the se-

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vere symptoms arising from multiple organ infiltration.

In the present case, following umbilical cord blood transplantation (CBT) for acute myeloid leukemia, complete remission had been maintained for 3 years, until the patient presented with the untypical symptom of facial edema (right side). Symptoms first appeared similar to those of graft-versus-host disease (GVHD), and even after the diagnosis of EBV-related infection was established, the patient's condition continued to be difficult to distinguish from infectious mononucleosis. Because EBV-related T/NK-cell LPD following allogeneic HSCT has not, to our knowledge, been previously reported, we present a review of the present case, including diagnosis, clinical course, and autopsy findings.

Case Report

In 2009 a 21-year-old man with previously unremarkable family and medical histories received a diagnosis of acute myeloid leukemia M_0 (trisomy 8). Because the patient was unresponsive to induction therapies consisting of a 3/7 regimen (daunorubicin hydrochloride and arabinosylcytosine) and a regimen with ifosfamide, carboplatin, and etoposide, CBT was performed 2 months after diagnosis under nonremission status (preconditioning regimen: total body irradiation, 12 Gy; arabinosylcytosine, 4.6 g×4 days; cyclophosphamide, 3,100 mg×2 days; GVHD prophylaxis, cyclosporine, and short-term methotrexate). Bone marrow examination revealed ≥90% donor-type chimerism on day 30 after CBT, and complete remission was maintained for 3 years.

The acute GVHD consisted of only stage 2 (Glucksberg grade) skin involvement, which was controlled with cyclosporine; the chronic GVHD was limited to recurring bilateral periorbital rash and rash of the trunk, which were treated with oral cyclosporine (50 mg/day) and then monitored. From approximately 2 years after CBT, repeated observations were made of transient fevers, upper respiratory tract symptoms, and impaired liver function. In September 2012, 3 years after CBT and when the patient was 25 years old, severe edema developed on the right side of the face. Because chronic GVHD was suspected to have aggravation, the cyclosporine was increased in dosage but failed to improve the symptoms. Liver function became impaired, and a liver biopsy in October 2012 revealed infiltration of Epstein-Barr early region (EBER)-positive CD8-positive T cells throughout the portal region. In November 2012, the patient was hospitalized for intensive examination and treatment of EBV infection.

Symptoms on Admission

Clinical characteristics were as follows: blood pressure, 110/82 mm Hg; pulse, 125/min (regular); body temperature, 36.7℃; saturation pulse oximetry, 99% (room air); and conscious. Symptoms of the head and neck region included swelling spanning the right side of the forehead, right eyelid, right cheek, right parotid region, and right side of the neck and accompanied by slight reddening and tenderness. The abdominal region was soft and flat with normal peristaltic sound, but hepatosplenomegaly was observed. Superficial lymph nodes were impalpable. There were no other remarkable physical findings.

Laboratory Findings on Admission

Peripheral white blood cell counts revealed 45.1% lymphocytes, 0.5% atypical lymphocytes, and a decreased platelet count (**Table 1**). Biochemical examination revealed impaired liver function and increased biliary enzymes, with high levels of ferritin (4,239 ng/mL), triglycerides (151 mg/dL), and soluble interleukin 2 receptor (5,580 U/mL), but results were negative for hepatitis A, B, and C virus markers and cytomegalovirus antigen. The EBV markers were as follows: anti-viral capsid antigen-immunoglobulin G antibodies, 2,560-fold; and anti-early antigen-immunoglobulin G antibodies, 160-fold. The concentration of EBV DNA in total peripheral blood was high at 2×10^4 copies/mL (**Table 2**).

The EBV-terminal repeat Southern blot analysis of peripheral blood revealed monoclonal proliferation (**Fig. 1 A**), whereas T-cell receptor cβ1 Southern blot analysis showed a rearranged band (**Fig. 1B**). When EBV-infected cells were examined with the polymerase chain reaction after each lymphocyte subtype was isolated with flow cytometry, they were found to be mainly CD8-positive T cells (**Fig. 1D**). Liver biopsy revealed infiltration of lymphocytes mostly consisting of EBV-infected CD8-positive T cells, confirmed by *in situ* hybridization analysis of EBER (**Fig. 1D**). Histologic examination of bone marrow revealed no apparent hemophagocytosis or increase in atypical cells but did show an increase in CD8-positive T cells (CD4, 15.1%; CD8, 65.1%) as in peripheral blood. Chimerism analysis of bone marrow showed ≥90% donor-type cells, suggesting that the EBV-infected T cells in the peripheral blood were donor-derived.

Progression during Hospitalization

The above findings indicated that CD8 type EBV-T-LPD was the most likely diagnosis, but as infectious mononucleosis affecting CD8-positive T cells could not be excluded, treatment with intravenous cyclosporine

Table 1 Laboratory findings on admission

WBC	4,600 /uL	GOT	74 IU/L	Ferritin	4,239 ng/mL
Neutrophil	44.50 %	GPT	113 IU/L	TG	151 mg/dL
Eosinophil	0.40 %	LDH	452 IU/L	sIL2-R	5,580 U/mL
Basophil	2.60 %	ALP	442 IU/L		
Monocyte	7.40 %	r-GTP	124 IU/L	PT-INR	1.19
Lymphocyte	45.10 %	T-Bil	1.5 mg/dL	PT	77 %
RBC	463 /uL			APTT	50.7 sec
Hb	14.2 g/dL			FDP	4.1 μg/dL
Ht	41 %	UA	5.8 mg/dL		
Plt	7.7 /uL	BUN	24.1 mg/dL	IgG	1,396 mg/dL
Ret	22 ‰	Cr	1.22 mg/dL	IgA	252 mg/dL
		TP	6.4 g/dL	IgM	62 mg/dL
Na	130 mEq/L	Alb	3.2 g/dL		
K	4.8 mEq/L	CRP	0.64 mg/dL		
Cl	99 mEq/L				

Table 2 EBV markers until a diagnosis

	2009/9/26 pretransplantation	2011/4/13	2012/10/18	2012/10/26	2012/10/29	2012/11/9
EBV anti-VCA-IgG (<10-fold)	80	320	2,560		2,560	2,560
EBV anti-VCA-IgM (<10-fold)		<10	<10		<10	<10
EBV anti-EA-IgG (<10-fold)						160
EBV anti-EA-IgA (<10-fold)						<10
EBV anti-EBNA antibody (<10-fold)	160	80	40			40
EBV DNA in total peripheral blood ($<2\times10^2$ copy/mL)				2×10^4		2×10^4

VCA; viral capsid antigen, EBNA; EB virus nuclear antigen, EA; early antigen

was started on day 14 of hospitalization. However, because the facial edema worsened rapidly and caused airway constriction, EBV-positive T-cell LPD was diagnosed and treatment was started on the same day with prednisolone (50 mg/day), cyclosporine (150 mg/day), and etoposide (230 mg/week). The facial edema responded to treatment, and treatment with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen was started after 2 rounds of etoposide. Thereafter, however, pneumonia of unidentified cause, alveolar hemorrhage (**Fig. 2A**), and cardiac dysfunction (ejection fraction, 38%) developed, possibly because of infiltration of EBV-infected T cells into the lung and the heart. Although the patient's condition, with the exception of the cardiac dysfunction, responded to treatment with antibiotics and artificial respiration, the swelling of the right side of the forehead and the edema of the right eyelid appeared again on day 60 of hospitalization. Because EBV DNA levels continued to increase, etoposide was administered to counter a suspected aggravation of the pathologic changes of EBV-T-LPD (**Fig. 2B**). Although the right-sided facial edema improved somewhat, pneumonia and alveolar hemorrhage developed again and necessitated the patient being reconnected to the artificial respirator. Subsequently, despite an initial amelioration, the pneumonia and alveolar hemorrhage again aggravated and liver function also gradually deteriorated. In addition, a coagulation disorder appeared with gastrointestinal bleeding. To control the patient's condition, low-dose arabinosylcytosine was administered from day 91 of hospitalization but had no effect. Multiple organs failed, with systemic convulsions causing circulatory breakdown, and the patient's death on day 96 of hospitalization (**Fig. 2B**). With the consent of the patient's family, an

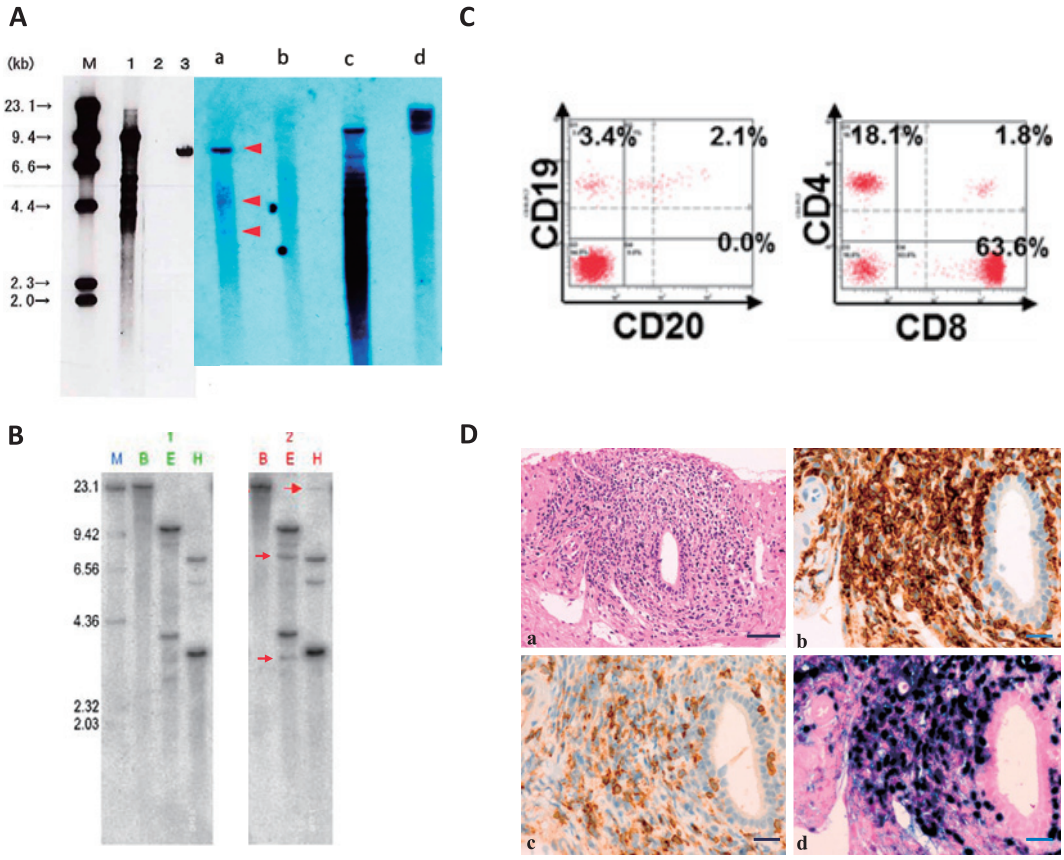


Fig. 1 Molecular biologic and pathological diagnosis of EBV-T-LPD

A) Peripheral blood EBV-terminal repeat Southern blot analysis

Left: Day 4 of hospitalization. Monoclonal EBV proliferation confirmed. M: size marker; 1: positive control; 2: negative control; 3: patient sample.

Right: Day 7 of hospitalization. Oligoclonal band detected. a: patient; b: negative control; c: positive control, B95-8; d: positive control, Raji. In flow cytometry of peripheral blood, B cells and T cells infected with EBV were present, indicating oligoclonality. The darkest band likely represents EBV that has infected T cells. Because EBV-infected cells ultimately form tumors through monoclonal proliferation, these cells appear to be at one stage earlier. Differences between the left and right may reflect differences in clonality depending on the type of probe used.

B) Peripheral blood T-cell receptor cβ1 Southern blot analysis

Day 8 of hospitalization. Peripheral blood T-cell receptor cβ1 Southern blot analysis revealed a rearranged band, confirming the monoclonal proliferation of T cells. M: size marker; 1: normal control; 2: patient sample. B: BamH I, E: EcoR I, H: Hind Ⅲ.

C) Analysis of EBV surface markers and identification of infected cells by fluorescence-activated cell sorter analysis

When EBV-infected cells were examined with the polymerase chain reaction after each lymphocyte subtype was isolated with flow cytometry, the infected cells were mainly CD8-positive T cells. Whole blood (blood cell components): 3.6×10E5 copies/μg DNA. CD19+ (B cells): 8.0×10E5 copies/μg DNA. CD4+ (T cells): undetectable. CD8+ (T cells): 1.7×10E6 copies/μg DNA. CD56+ (NK cells): undetectable. CD14+ (monocytes): undetectable. Others: undetectable.

D) Identification of EBV-infected T cell infiltration by liver biopsy

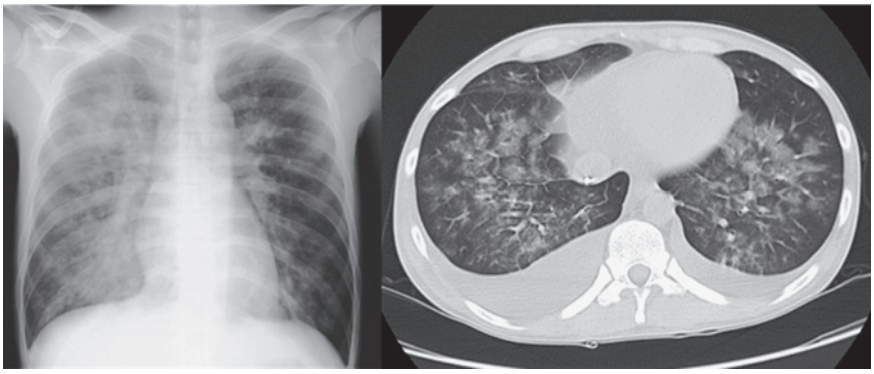
The small mononuclear cell count was increased, mainly in the portal tract regions. Immunohistochemical examination revealed these to be mainly CD3- and CD8-positive T cells, most of which were found by *in situ* hybridization analysis to be EBER-positive. a. Hematoxylin and eosin stain; b. CD8; c. CD4; d. EBER. Original magnification ×200 (a), ×400 (b, c, d). Scale bars=50 μm (a), 20 μm (b, c, d).

autopsy was performed to evaluate the relationship between the multiple organ failure and EBV-T-LPD and to clarify the etiology leading to death.

Pathological Findings at Autopsy

Gross examination of the lungs showed extensive and severe alveolar hemorrhage, particularly involving the

A



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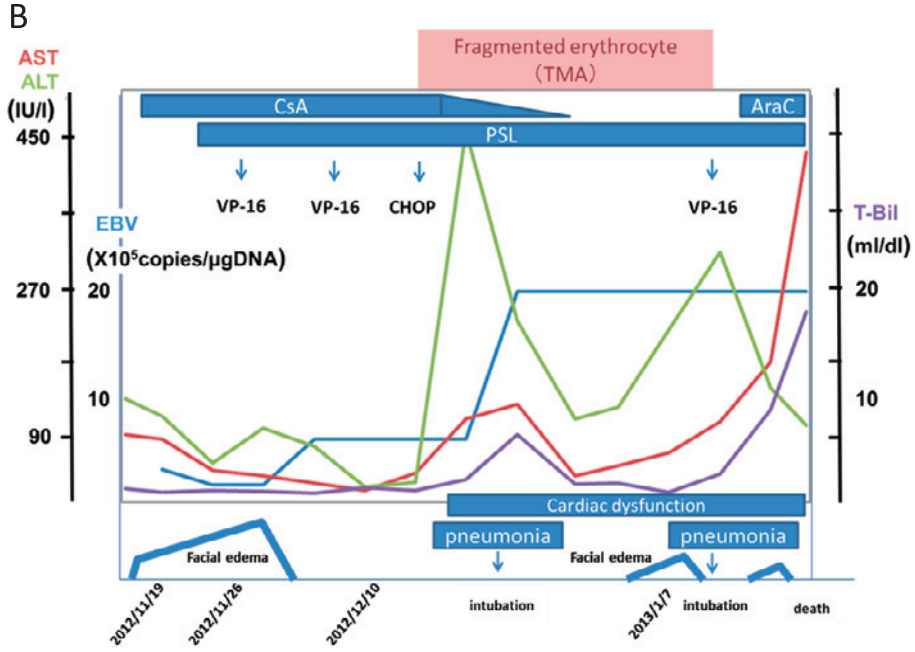

	2012/11/16	2012/12/10	2012/12/28	2013/1/5	2013/1/26	2013/2/15
Ferritin (ng/ml)	4239	2354	23452	121606	5244	66312
Plt (×10⁴/μl)	7.5	6	4.8	4.2	2.3	1.7
PT-INR	1.19	0.84	1.04	1.1	0.95	1.43
APTT (sec)	50.7	21.8	29.6	29.7	28.1	57.6
Fibrinogen (mg/dl)	97	129	318	100	173	76
D-dimer (μg/ml)			7.7	14.9	1.8	1.9

Fig. 2 Clinical course after hospitalization

A) Pneumonia imaging on day 42 of hospitalization

Chest radiography revealed interstitial pneumonia, predominantly in the right lung. Computed tomography of the chest revealed granular shadows and macular ground-glass shadows in the peripheral areas of both lung fields and centered around the bronchovascular bundles in the right lung. Bilateral pleural effusion was also observed.

B) Clinical course

On day 39 of hospitalization, fragmented erythrocytes were observed in the peripheral blood, suggesting the possibility of thrombotic microangiopathy due to increased blood levels of cyclosporine, which was therefore given in tapered doses before being discontinuated on day 42 of hospitalization. CyA: cyclosporine, 3 mg/kg/day; PSL: prednisolone, 1 mg/kg/day; AraC: cytarabine, 20 mg/m^2/day; VP-16: etoposide, 150 mg/m^2 weekly.

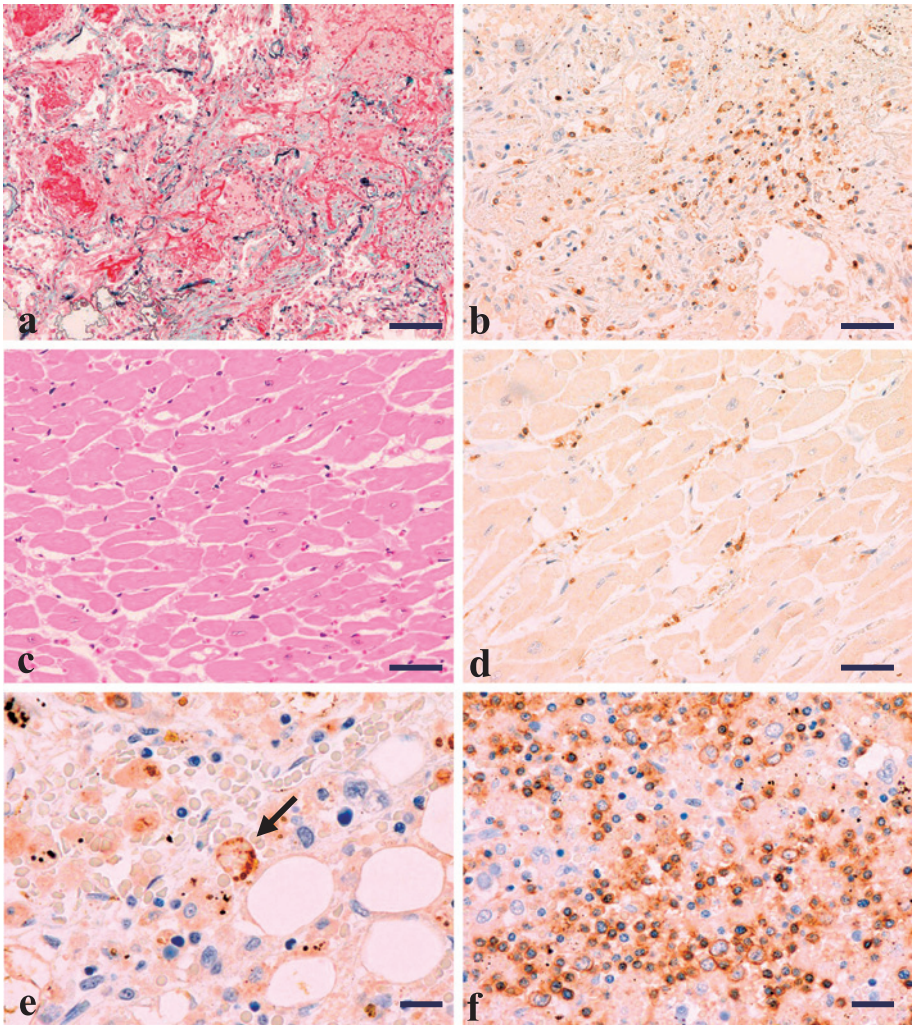

Fig. 3 Pathological findings on autopsy
In both lungs, there was diffuse alveolar damage in the exudative phase represented by hyaline membrane formation (a) associated with the infiltration of CD8-positive T cells (b). There were no histological findings in the bilateral cardiac ventricles indicative of myocardial damage, such as necrosis, fibrosis, or degenerative change (c). The small number of CD8 cells was diffused within the myocardium of the left ventricle (d). In the bone marrow, hemophagocytosis of erythrocytes by macrophages was occasionally observed (e, **arrow**). Diffuse infiltration of CD8-positive T cells was noted (e). Elastica Masson Goldner stain (a), CD8 (b, d, f), hematoxylin and eosin stain (c), CD68 (e). Original magnification ×100 (a), ×200 (b, c, d). ×400 (e, f). Scale bars=100 μm (a), 50 μm (b, c, d), 20 μm (e, f).

lower lobes. Because infiltration of CD-8-positive and EBER-positive atypical lymphocytes was observed accompanying alveolar damage and hemorrhage, the progressive respiratory failure was suspected to be related to EBV-T-LPD (**Fig. 3a, b**). Although the patient had clinical signs of pneumonia, in no areas of the lung parenchyma did histological findings suggest bacterial, fungal, or viral infection. In the heart, mild dilation of the bilateral cardiac ventricles was observed grossly, but there were no histological findings indicative of myocardial damage, such as necrosis, fibrosis, or degenerative change (**Fig. 3c**), and the infiltration of CD8-positive cells was mild and focal, involving certain regions of the left ventricle (**Fig. 3d**). In the bone marrow, there was histological evidence of hemophagocytosis and infiltration of atypical CD8-positive lymphocytes (**Fig. 3e, f**). The presence of CD8-positive and EBER-positive atypical lymphocytes was also confirmed in other organs, such as the spleen, gastrointestinal tract, adrenal glands, pancreas, and kidneys. Examination of the cerebrospinal fluid showed 2×10^3 copies/mL of EBV DNA.

Discussion

Many reports have been published from Taiwan and Japan of EBV-T-LPD, a high proportion of which involve EBV infection of CD8-positive T cells, as in the present case. Also published has been a single report of EBV infection of T/NK cells in the peripheral blood and tonsillar tissue of patients with infectious mononucleosis[5], a condition that may thus be difficult to differentiate from EBV-T-LPD. The EBV infection and the proliferation of infected T/NK cells are thought to possibly arise from functional deficiencies in the T/NK cells themselves, although the pathogenic mechanism remains unclear[6]. There are some reports of EBV-T-LPD recurring after bone marrow is transplanted to treat it[7,8]. In these cases, the EBV genotype after transplantation differs from that before transplantation, leading to the theory that the main factor in EBV-T-LPD onset is not EBV but host immune function, in particular, that of host T/NK cells[7]. In the present case, EBV-T-LPD developed after umbilical cord blood was transplanted to treat acute myeloid leukemia. Although it was not tested for EBV antibodies before being transplanted in the present case, umbilical cord blood is typically considered EBV-negative. We therefore assume that the donor' s CD8-positive T cells were first infected with EBV after the transplantation. The EBV-T-LPD is thought to have been triggered by 1 of 3 possible factors: (1) deficiency in the immune function of the recipient himself, (2) abnormality in the donor lymphocytes, and (3) immunosuppression by the cyclosporine used to control chronic GVHD.

In many cases, EBV-related T/NK-cell LPD progresses rapidly to involve multiple organs and cause severe symptoms. Although EBV-infected cells often infiltrate the liver, spleen, lymph nodes, and bone marrow, they may also infrequently invade muscular tissue, such as the digestive tract and myocardium, leading, as in the present case, to gastrointestinal bleeding or perforation and heart complications[9,10]. Factors previously reported to be associated with poor prognosis include onset when the patient is 8 years or older, impaired liver function, gastrointestinal bleeding or perforation, and heart complications[1]. Hypercytokinemia resulting from EBV-related T/NK-cell LPD may also aggravate these forms of organ damage[11–13].

In the present case, progressive heart failure worsened after CHOP chemotherapy. We suspect that a possible cause was myocarditis associated with EBV infection[14,15]. The bilateral ventricular walls were thoroughly examined, but the EBER-positive lymphocytes seemed to have infiltrated too focally and mildly to trigger significant heart failure. Therefore, a definite link between the heart failure and the EBV infection could not be established. An alternative possibility is myocardiac toxicity related to CHOP therapy, but again, degeneration, necrosis, or other cardiomyocyte damage supporting this hypothesis could not be identified. More detailed morphological changes might have been revealed with further electron microscopic examinations, which we were not able to perform. Thus, the cause of heart failure in the present case remains uncertain.

When EBV-related T/NK-cell LPD is suspected, the amount of EBV DNA in peripheral blood should be measured soon and organs suspected to have been infiltrated should be biopsied so that treatment can be started where proliferation of tissues by EBV-infected T/NK cells has been shown. Regarding the treatment itself, many reports have suggested that nonmyeloablative HSCT is effective after the patient's condition has been stabilization with various chemotherapy options[16]. However, because some patients, such as the present patient, are resistant to chemotherapy and progress to multiple organ failure, several reports have recommend that HSCT be performing immediately after diagnosis[7]. Because *de novo* EBV-T-LPD onset after HSCT has not been previously reported and because the possibility of infectious mononucleosis involving T cells due to immunodeficiency after CBT could not be excluded, before planning HSCT we stabilized the patient's condition with chemotherapy. In hindsight, however, the patient might have been saved if HSCT had been prepared after diagnosis and had been performed immediately after the disease was controlled with prednisolone, cyclophosphamide, and etoposide therapy.

Conflict of Interest: None of the authors has a financial interest in the conduct or reporting of the study.

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