Clinical Case Reports

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CASE REPORT

Successful treatment of immediate allogeneic myeloablative hematopoietic stem cell transplantation from a HLA-mismatched sibling donor for active systemic epstein–barr virus-positive T-cell lymphoproliferative disease of childhood following primary acute epstein–barr virus infection

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Key Clinical Message

A 22-year-old female was admitted for sustained high fever and diagnosed with systemic Epstein–Barr virus-positive T-cell lymphoproliferative disease. As her clinical course was so aggressive, she immediately underwent allogeneic myeloablative bone marrow transplantation from an HLA-mismatched sibling donor on hospital day 46. The patient has remained in complete remission for 3 years.

Keywords

EBV-positive T-cell LPD, HPS, HSCT, MAC.

Introduction

Epstein–Barr virus (EBV) infection commonly occurs in early childhood. Although infants and young children with primary acute EBV infection are generally asymptomatic in which EBV infects B cells, adolescents and adults often develop infectious mononucleosis (IM). However, IM is usually self-limiting and resolves spontaneously due to immune surveillance by the polyclonal proliferation of CD8-positive cytotoxic T cells which are free of EBV [1, 2].

Systemic EBV-positive T-cell lymphoproliferative disease of childhood (systemic EBV+T-cell LPD of childhood) was first described in the 4th World Health Organization (WHO) classification of hematopoietic and lymphoid tissues [3]. The disease is a life-threatening to children and young adults characterized by a clonal proliferation of EBV-infected T cells which can occur shortly after primary acute EBV infection or in the setting of chronic active EBV infection (CAEBV). It is most prevalent in Asia, primarily in Japan and Taiwan. Although the pathogenesis is still unknown, the association with primary EBV infection and the racial predisposition suggest a genetic defect in the host immune response to EBV, resulting in a defect in T-cell-mediated immune regulation causing uncontrolled immune responses through EBV-infected T cells [4, 5].

The prognosis of patients with systemic EBV+T-cell LPD of childhood is very poor in both pediatric and adult patients. Patients with EBV+T-cell LPD shortly after primary acute EBV infection are usually resistant to multiple chemotherapies and are associated with a fulminant clinical course. These patients have a poor prognosis with death from 3 days to 3 months after diagnosis [6]. To date, immunochemotherapy with steroids, cyclosporine A (CyA), and etoposide (ETP) has been intensively investigated as treatment options [7, 8], and the efficacy is limited and complete responses are rare in most cases [9].

Currently, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been considered to be an effective way to eliminate EBV-infected cells completely and reconstitute a normal immune system for EBV [10]. Since the first case report of successful allo-HSCT for CAEBV [11], the effectiveness of allo-HSCT, using either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC), has been established [9, 12].

Here, we present the case of a patient with active systemic EBV+T-cell LPD of childhood who successfully received immediate allogeneic bone marrow transplantation (allo-BMT) from an HLA-mismatched sibling donor. To the best of our knowledge, this case is unique because of the intractable aggressive clinical course, the time to allo-BMT following hospitalization for a severe illness was only 46 days, the least amount of days compared to previous studies [9, 13], and the urgent treatment using MAC protocol and an HLA-mismatched sibling donor that was so successful for eradicating the active disease.

Case Report

A 22-year-old Japanese woman was referred to our hospital. On our first day of reference, the patient presented with persistent high fever, systemic joint pain, low saturation of pulse oximetry oxygen (SpO_2), and the appearance of blastic cell and low platelet count in the peripheral blood. Five days from reference, she complained of high fever (38.9°C) and the pain of several joints, she was given acetaminophen and an antibacterial agent for 3 days at a nearby clinic. She had been healthy until the onset of disease. She was the second-born child of healthy nonconsanguineous parents and had no family history of similar disorders. On admission (the day of reference), her body temperature was 37.8°C, which responded to acetaminophen, and SpO_2 was 99% under O_2 inhalation of 3 L/min. There was no systemic superficial lymphadenopathy or skin eruption. Blood examination revealed a white blood cell count of 6680/μL with 44% of atypical lymphocytes, hemoglobin was 15.2 g/dL, hematocrit was 43.5%, and the platelet count was $2.6 \times 10^4/\mu$L. In coagulation study, PT, PT-INR, APTT, Fibrinogen(Fib) and FDP were 16.9 sec, 1.59, 71.8 sec, 160.4 mg/dL, and 137.6 μg/mL, respectively. Blood chemistry showed a total protein of 5.1 g/dL, albumin of 2.8 g/dL, AST of 537 IU/L, ALT of 256 IU/L, LDH of 5574 IU/L, total bilirubin of 5.4 mg/dL with 4.7 mg/dL of direct bilirubin, ALP of 1174 IU/L, triglyceride (TG) 362 of mg/dL, BUN of 68.6 mg/dL, Cre of 2.67 mg/dL, uric acid (UA) of 13.3 mg/dL, and C-reactive protein (CRP) of 17.78 mg/dL. Serum ferritin was elevated to 23,700 ng/mL, and soluble IL-2 receptor (sIL-2R) to 35,300 U/mL. A computed tomography (CT) scan revealed bilateral pneumonia, bilateral pleural effusion (Fig. 1A), mild cardiomegaly, intra-abdominal lymph node swelling, and hepatosplenomegaly. Bone marrow (BM) examination

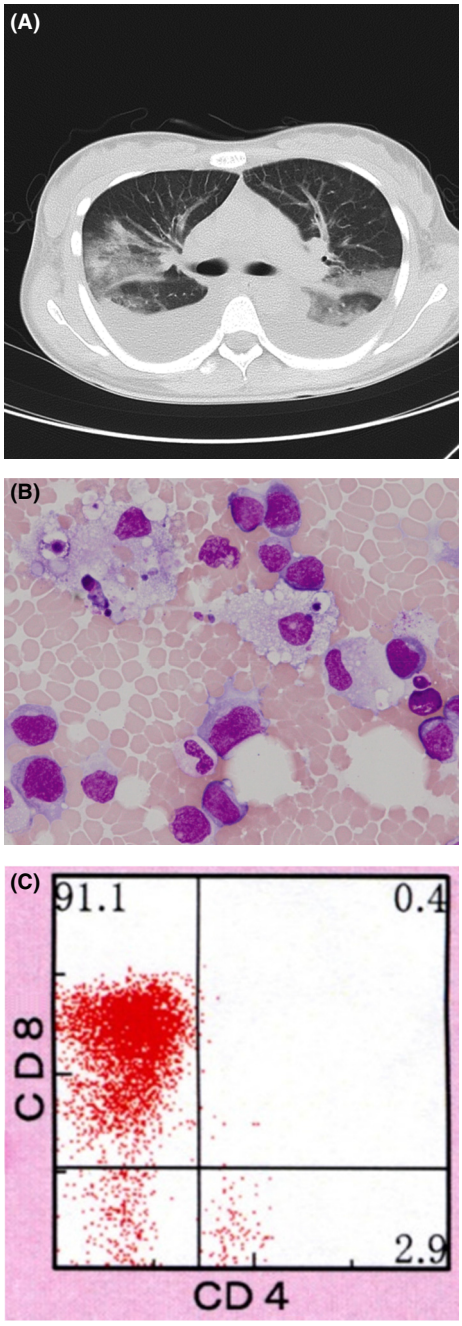

Figure 1. Radiological and hematological picture on admission. (A) CT scan showing bilateral pneumonia with ground-glass opacity and bilateral pleural effusion. (B) Bone marrow aspirate smear documenting medium-sized to large atypical lymphoid cells with irregular nuclei, prominent nucleoli, and basophilic cytoplasm and active histiocytes with prominent hemophagocytosis. (C) Flow cytometric analysis of bone marrow cells indicating a highly predominant population of CD8-positive T cells.

revealed medium to large-sized atypical lymphoid cells with irregular nuclei, prominent nucleoli, and basophilic cytoplasm of 68.6% out of a nucleated cell count of $4.7 \times 10^4/\mu L$, and active histiocytes with prominent hemophagocytosis (Fig. 1B). Flow cytometric analysis showed a highly predominant population of CD8-positive T-cells (Fig. 1C). At this point, we considered an existing clonal T-cell lymphoproliferative disease, particularly EBV-associated disease, causing hemophagocytosis, multiorgan damages, and coagulopathy. Therefore, we promptly administered methylprednisolone (mPSL) pulse therapy (3-day schedule) on the day of admission and chemotherapy with CHOPE [cyclophosphamide (CY), doxorubicin (DXR), vincristine (VCR), PSL, and ETP] on hospital day 2. We examined EBV titers and EBV-DNA viral load in her blood, which revealed VCA IgG ×40, VCA IgM ×10, VCA IgA <×10, EA-DR IgG <×10, EA-DR IgA <×10, EBNA <×10, based on folic acid assay, and EBV-DNA viral load of 4.3×10^6 copies/10^6 cells using the quantitative polymerase chain reaction (PCR) method. This profile of antibodies to EBV was consistent with a primary acute EBV infection, although she had no documented IM. Furthermore, Southern blotting analysis demonstrated a monoclonal pattern both in the EBV-terminal repeat (Fig. 2A) and in the T-cell receptor (TCR) beta gene rearrangement (Fig. 2B) in the peripheral blood mononuclear cells. On the basis of these results mentioned above, we concluded that her diagnosis was systemic EBV+T-cell LPD of childhood following primary acute EBV infection [3]. The treatment performed with mPSL pulse and CHOPE, along with antibiotics for gram-positive cocci (GPC) and gram-negative rods (GNR) detected in her blood culture, only transiently abated the fever. On hospital day 12, she was treated with another cycle of chemotherapy with CHASE (CY, high-dose cytosine arabinoside [AraC], ETP, and PSL) because of flare-ups of a high fever and pneumonia with low partial pressure of oxygen in arterial blood (PaO_2) of 55 mmHg under O_2 inhalation of 10 L/min through a mask. She was moved to the intensive care unit (ICU) to help her respiratory distress with continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). However, CHASE regimen yielded only transient effects. On hospital day 24, with bone marrow suppression caused by the previous chemotherapy even while using rhG-CSF, she had to be treated with a third cycle of chemotherapy treatment with high-dose methotrexate (MTX) and AraC concurrently with an mPSL pulse because of reappearance of a high fever and exacerbation of pneumonia. However, a satisfactory outcome was not achieved. Allo-HSCT was immediately required to eradicate the clonally proliferative EBV-infected T-cells and to achieve remission because her EBV+T-cell LPD was so refractory and aggressive. Fortunately, her older brother was eligible as an allo-BMT donor according to the HLA profile showing only a *HLA-DRB1* allele mismatch, in which the HLA disparity could be due to somatic recombination from the parent's HLA profile. The brother was 25 years old and his serological EBV titers indicated no past infection. On hospital day 36, MAC was started, although there were only 12-day intervals from the last immunochemotherapy and her disease status was thought to be still uncontrollably active, based on several abnormal levels of clinical findings. These included an ALT of 64 IU/L, LDH of 355 IU/L, sustained low-grade fever, and the remaining fine infiltrative shadows of the lung on the chest X-ray. The conditioning regimen consisted of ETP (15 mg/kg×2 days), CY (60 mg/kg×2 days), and total body irradiation (TBI) of 12 Gy in six fractions. On hospital day 46 (= at day 0), she was transplanted with BM cells (3.25×10^8/kg nucleated cells) from the sibling donor. The prophylaxis for graft-versus-host disease (GVHD) consisted of FK506 plus short-term MTX. Engraftment was achieved at day 18, which was confirmed by Y-chromosome of 99.3% by FISH analysis on peripheral blood examination. At day 28 she developed acute grade II GVHD of the skin, which was controlled with local treatment. No other complications including veno-occlusive disease (VOD), thrombotic microangiopathy (TMA), or severe documented infections occurred during the hematological recovery phase. At day 78, just after continuous infusion of FK506 was switched to oral

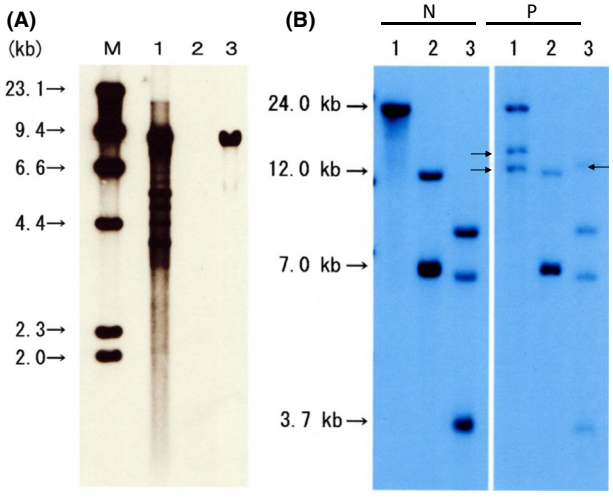

Figure 2. Analysis for clonality of peripheral blood mononuclear cells. (A) Southern blot analysis for EBV-terminal repeat. M, molecular marker; 1, positive control; 2, negative control; 3, the patient's sample. (B) T-cell receptor beta gene rearrangement. The *arrows* indicate the clonal peaks. Prepared genomic DNA was digested with *BamH*I (lane 1), *EcoR*V (lane 2), and *Hind*III(lane 3). N, negative control; P, the patient's sample.

administration, skin GVHD flared to grade III; and thus, PSL was commenced at a dose of 1 mg/kg, which cleared the skin GVHD. Laboratory data examined around day 100 from allo-BMT were as follows: AST 19 IU/L, ALT 34 IU/L, LDH 273 IU/L, ferritin 2078.3 ng/mL, sIL-2R 331 U/mL, and EBV-DNA viral load $<2.0 \times 10^1$ copies/10^6 cells. Moreover, Southern blotting analysis for EBV-DNA showed no clonality. CT scan revealed no intra-abdominal lymph node swelling or hepatosplenomegaly. She was discharged from the hospital at day 144 from allo-BMT without any symptoms. PSL and FK506 were slowly tapered and stopped at days 360 and 508, respectively, though serum trough levels of FK506 had not been detectable since around day 360 from allo-BMT. She has been in complete remission (CR) and doing well for 3 years since the allo-BMT. Blood examination after 3 years revealed normal laboratory data including LDH and ferritin, and no detection of EBV-DNA viral load with the serological change in EBV titers as follows: VCA IgG $\times$640, VCA IgM $<\times$10, VCA IgA $\times$10, EA-DR IgG $\times$80, EA-DR IgA $<\times$10, EBNA $\times$80.

Discussion

Here, we report a case of a young adult female with systemic EBV+T-cell LPD of childhood after primary acute EBV infection. She had a very aggressive and refractory disease against several immunochemotherapies; thus, immediate intervention with allo-BMT was required to stop deterioration. The allo-BMT was performed on hospital day 46 using the MAC protocol and an HLA-mismatched sibling donor. The therapeutic approach was so successful that she has been in CR for 3 years with no detectable EBV-DNA viral load. At present, she shows relatively high titers of EBV-VCA IgG and EBNA despite an EBV seronegative donor, and the finding suggests that she reconstituted a normal immunity for EBV infection which can be considered endogenous transmission or exogenous re-infection after allo-BMT [9]. However, the timing of the seroconversion is not exactly determined because no serial EBV-DNA viral load or EBV antibody titer was monitored.

On admission day, the patient already had severe complications of liver injury, pneumonia, coagulopathy, sepsis, hemophagocytosis, and leukemic transformation, all of which were not usually observed in systemic EBV+ T-cell LPD of childhood [3]. In addition, the severity and the refractoriness, particularly those of respiratory failure, against several immunochemotherapies were striking in this patient. Although we were not able to confirm the cause of these organ injuries through histological examination because of repeated respiratory distress and severe coagulopathy, the most likely explanation is that these organ injuries were attributed to the clonal expansion and infiltration into tissues of EBV+ T cells which produce inflammatory cytokines that induce the activation of macrophages and hemophagocytosis [6, 14, 15].

Systemic EBV+T-cell LPD of childhood in nonimmunocompromised patients is very rare. Almost all reported cases were of Asian origin, primarily in Japan, Korea, and Taiwan [16]. According to the nationwide survey from 1998 to 2010 for EBV+T- or natural killer (NK)-cell LPDs in non-immunocompromised hosts of 108 cases (91% of these were children and young adults) in Japan [17], the disease comprised 80 cases of CAEBV, 15 of hemophagocytic lymphohistiocytosis (HLH) of T/NK-cell type, nine of severe mosquito bite allergy, and four of hydroa vacciniforme. In this analysis, EBV-infected CD8-positive T-cell associated HLH (usually described as EBV-HLH), which is historically considered equivalent to systemic EBV+T-cell LPD after primary acute EBV infection [18], comprised only five patients of 15 of HLH of T/NK-cell type among 108 cases.

The clinical behavior of systemic EBV+T-cell LPD of childhood after primary acute EBV infection is aggressive and usually does not respond to immunochemotherapy [17, 19]. Even when the immunochemotherapy is effective in some patients, the effect is usually transient and fails to induce sustained CR [19]. Although a standard treatment approach has not been established, allo-HSCT following sequential immunochemotherapy and combination chemotherapy has been reported to be promising to achieve long-term remission. Allo-HSCT appears to effectively eliminate EBV-infected cells and reconstitute normal immunity for EBV [9–12]. Therefore, today allo-HSCT is recommended for patients with recurrent, persistent, or refractory severe disease status of systemic EBV+T-cell LPD of childhood [13, 17]. According to an international study analyzed by Arico et al. [20], allo-HSCT recipients with this disease have a significantly superior outcome compared with nontransplanted patients with a 66% versus 10.1% 5-year survival rate. In addition, factors associated with a good outcome have been analyzed [17], and three factors, the onset age of <15 years, no liver dysfunction, and inactive disease status at allo-HSCT, were linked to a significantly higher overall survival (OS) rate. Severe liver dysfunction is a serious complication in both pediatric and adult patients, being linked not only to elevated EBV viremia, but also to preponderant infection with CD8-positive T cells infiltrating the liver [21]. However, in the present case, the patient had three disadvantages for a preferable outcome: older age at the onset of disease, severe liver dysfunction, and uncontrollable active disease status at allo-HSCT. On the other hand, although allo-HSCT is the only way to induce CR for patients with recurrent, persistent, or refractory severe disease, the appropriate timing and criteria for making the decision regarding HSCT in the treatment strategy remains to be determined. Imashuku et al.

[13] reported that 12 out of 78 EBV-HLH patients received allo-HSCT, and they were all in partial remission at the time of allo-HSCT and eight of these patients received treatment within 12 months of diagnosis, whereas the remaining four patients received treatment between 14 and 33 months after diagnosis. In a nationwide survey in Japan [12], eight of 10 patients with EBV-HLH received allo-HSCT within 1 year from onset. In addition, EBV-HLH patients with a time of <30 months from onset to HSCT showed significantly higher OS rate [17]. Taken together, it appears to be crucial that a patient with systemic EBV+T-cell LPD of childhood whose clinical behavior was so aggressive and refractory should promptly receive allo-HSCT before developing into an intractable fulminant clinical course. In the present case, the immediate intervention with myeloablative allo-BMT was performed on only hospital day 46 due to the uncontrollable disease status, the days calculated from diagnosis would be less than 46 days, resulting in a long-term CR. Fortunately, she had a suitable sibling donor who had a *HLA-DRB1* allele mismatch. In case a patient has no available sibling or related donors, alternative stem cell sources, including unrelated cord blood, should be considered as a treatment modality considering past studies have demonstrated excellent outcomes in patients using this method [21–24].

It still remains unclear which conditioning regimens, MAC or RIC, should be selected for allo-HSCT to treat a patient with urgent life-threatening clinical complications of this disease, as in the present case. Kawa et al. [9] reported the excellent outcome of allo-HSCT with RIC for the treatment of active status in CAEBV. In this study, the 3-year event-free survival (EFS) rate was 54.5% for the MAC group and 85.0% for the RIC group, and the 3-year OS rate was 54.5% for the MAC group and 95.0% for the RIC group ($P = 0.016$). This inferior outcome in the MAC group was probably due to a higher incidence of treatment-related mortality (TRM): 45% in the MAC group versus 5.65% in the RIC group. On the other hand, Gotoh et al. [25] reported a relatively higher relapse rate in the RIC group: 30% in the RIC group versus 10% in the MAC group. Thus, in allo-HSCT using RIC one must be concerned regarding the insufficient removal of EBV-infected cells by the conditioning regimen [26]. It is also suggested that the RIC protocol provides a better outcome only to patients in a stable condition at allo-HSCT [12]. Given that the RIC protocol has been designed with the aim of reducing toxicity while exploiting the graft-versus-tumor effect [27], these findings mentioned above suggest that there should be a graft-versus-EBV-LPD effect. In fact, Okamura et al. [28] monitored the EBV-DNA viral load in patients with EBV-LPD before and after allo-HSCT, and reported a case in which a patient was positive before and within 3 months after allo-HSCT, and then became negative in 10 months, indicating that alloimmunity, that is graft-versus-EBV-LPD effect, could eradicate EBV. In the present case, because we did not monitor the serial EBV-DNA viral loads immediately before and after allo-BMT, it was uncertain whether there was truly graft-versus-EBV-LPD effect or not under the MAC protocol. Considering that her illness was so aggressive and refractory, it appeared to be appropriate that she urgently received allo-BMT with MAC, not RIC, to immediately stop her deteriorating clinical condition.

In conclusion, although the therapeutic options should be carefully considered, prompt intervention with allo-HSCT using MAC is a promising option for patients whose clinical course is fatally aggressive and refractory to immunochemotherapy. In addition, caution regarding long-term complications of HSCT, such as sterility and second malignancy, must be considered in the present case of young female adult.

To clarify the criteria for the optimal timing, conditioning regimens, and stem cell sources for allo-HSCT for young patients with EBV+LPD of childhood, it will be important to further evaluate these points in more EBV+LPD patients. In addition, a genotyping study of these patients will lead to the identification of new pathways involved in the pathogenesis of the disease.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Straus, S. E., J. I. Cohen, G. Tosato, and J. Meier. 1993. Epstein-Barr virus infections: biology, pathogenesis and management. Ann. Int. Med. 118:45–58.
2. Auwaerter, P. G. 2006. Recent advances in the understanding of infectious mononucleosis: are prospects improved for treatment or control? Expert Rev. Anti. Infect. Ther. 4:1039–1049.
3. Quintanilla-Martinez, L., H. Kimura, and E. S. Jaffe. 2008. EBV-positive T-cell lymphoproliferative disorders of childhood. World health organization classification of tumors pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon. Pp. 278–280.
4. Okano, M., and T. G. Gross. 1996. Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. Am. J. Hematol. 53:111–115.
5. Maia, D. M., and A. L. Peace-Brewer. 2000. Chronic, active Epstein-Barr virus infection. Curr. Opin. Hematol. 7: 59–63.
6. Young, K. H., D. Zhang, J. T. Malik, and E. C. Williams. 2008. Fulminant EBV-driven CD8 T-cell lymphoproliferative disorder following primary acute EBV

infection: a unique spectrum of T-cell malignancy. Int. J. Clin. Exp. Pathol. 1:185–197.
7. Imashuku, S., S. Hibi, T. Ohara, A. Iwai, M. Sako, M. Kato, et al. 1999. Effective control of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis with immunochemotherapy. Blood 93:1869–1874.
8. Imashuku, S., K. Kuriyama, T. Teramura, E. Ishii, N. Kinugawa, M. Kato, et al. 2001. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J. Clin. Oncol. 19:2665–2673.
9. Kawa, K., A. Sawada, M. Sato, T. Okamura, N. Sakata, O. Kondo, et al. 2011. Excellent outcome of allogeneic hematopoietic SCT with reduced-intensity conditioning for the treatment of chronic active EBV infection. Bone Marrow Transplant. 46:77–83.
10. Imashuku, S., S. Hibi, S. Todo, M. Sako, M. Inoue, K. Kawa, et al. 1999. Allogeneic hematopoietic stem cell transplantation for patients with hemophagocytic syndrome (HPS) in Japan. Bone Marrow Transplant. 23:569–572.
11. Okumura, T., Y. Hatsukawa, H. Arai, M. Inoue, and K. Kawa. 2000. Blood stem-cell transplantation for chronic active Epstein-Barr virus with lymphoproliferation. Lancet 356:223–224.
12. Sato, E., S. Ohga, H. Kuroda, F. Yoshiba, M. Nishimura, M. Nagasawa, et al. 2008. Allogeneic hematopoietic stem cell transplantation for Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disease in Japan. Am. J. Hematol. 83:721–727.
13. Imashuku, S., T. Teramura, H. Tauchi, Y. Ishida, Y. Otoh, M. Sawada, et al. 2004. Longitudinal follow-up of patients with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Haematologica 89:183–188.
14. Maakaroun, N. R., A. Moanna, J. T. Jacob, and H. Albrecht. 2010. Viral infections associated with haemophagocytic syndrome. Rev. Med. Virol. 20:93–105.
15. Kitazawa, Y., F. Saito, S. Nomura, K. Ishii, and E. Kadota. 2007. A case of hemophagocytic lymphohistiocytosis after the primary Epstein-Barr virus infection. Clin. Appl. Thromb. Hemost. 13:323–328.
16. Cohen, J. I., H. Kimura, S. Nakamura, Y. H. Ko, and E. S. Jaffe. 2009. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. Ann. Oncol. 20:1472–1482.
17. Kimura, H., Y. Ito, S. Kawabe, K. Gotoh, Y. Takahashi, S. Kojima, et al. 2012. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood 119:673–686.
18. Quintanilla-Martinez, L., S. Kumar, F. Fend, E. Reyes, J. Teruya-Feldstein, D. W. Kingma, et al. 2000. Fulminant EBV(+)T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood 96:443–451.
19. Ishii, E., S. Ohga, S. Imashuku, M. Yasukawa, H. Tsuda, I. Miura, et al. 2007. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int. J. Hematol. 86:58–65.
20. Arico, M., G. Janka, A. Fisher, J. I. Henter, S. Blanche, G. Elinder, et al. 1996. Hemophagocytic lymphohistiocytosis. Report of 122 children from the international registry. Leukemia 10:197–203.
21. Kunitomi, A., H. Kimura, Y. Ito, K. Naitoh, N. Noda, H. Iida, et al. 2011. Unrelated bone marrow transplantation induced long-term remission in a patient with life-threatening Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J. Clin. Exp. Hematopathol. 51:57–61.
22. Minegishi, M., Y. Ohashi, S. Kumaki, Y. Sasahara, T. Hayashi, H. Asada, et al. 2001. Successful umbilical cord blood transfusion from an unrelated donor for a patient with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Bone Marrow Transplant. 27:883–886.
23. Yagita, M., H. Iwakura, T. Kishimoto, T. Okamura, A. Kunitomi, R. Tabata, et al. 2001. Successful allogeneic stem cell transplantation from an unrelated donor for aggressive Epstein-Barr virus-associated clonal T-cell proliferation with hemophagocytosis. Int. J. Hematol. 74:451–454.
24. Toubo, T., N. Suga, S. Ohga, A. Nomura, Y. Onoe, H. Takada, et al. 2004. Successful unrelated cord blood transplantation for Epstein-Barr virus-associated lymphoproliferative disease with hemophagocytic syndrome. Int. J. Hematol. 80:458–462.
25. Gotoh, K., Y. Ito, Y. Shibata-Watanabe, J. Kawada, Y. Takahashi, H. Yagasaki, et al. 2008. Clinical and virological characteristics of 15 patients with chronic active Epstein-Barr virus infection treated with hematopoietic stem cell transplantation. Clin. Infect. Dis. 46:1525–1534.
26. Ishimura, M., S. Ohga, A. Nomura, T. Toubo, E. Morihara, Y. Saito, et al. 2005. Successful umbilical cord blood transplantation for severe chronic active Epstein-Barr virus infection after the double failure of hematopoietic stem cell transplantation. Am. J. Hematol. 80:207–212.
27. Slavin, S., A. Nagler, E. Naparstek, Y. Kapelushnik, M. Aker, G. Cividalli, et al. 1998. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 91:756–763.
28. Okamura, T., T. Kishimoto, M. Inoue, M. Honda, N. Yamashita, H. Wakiguchi, et al. 2003. Unrelated bone marrow transplantation for Epstein-Barr virus-associated T/NK-cell lymphoproliferative disease. Bone Marrow Transplant. 31:105–111.

