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LETTER TO THE EDITOR

Resolution of chronic active EBV infection and coexisting pulmonary arterial hypertension after cord blood transplantation

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Chronic active Epstein–Barr virus (EBV) infection (CAEBV) is characterised by clonal proliferation of EBV-infected T or natural killer (NK) cells and inflammation.[1–4] Cardiovascular complications, such as arteritis and coronary artery aneurysm, are observed in about 20–60% of patients with CAEBV.[1,5] The coexistence of pulmonary arterial hypertension (PAH) with CAEBV, which involves the very small arteries, is less common.[1,6] PAH is a rarely curable disease despite recent advances in treatment.[7] Here, we describe a patient with PAH in whom the disease developed after diagnosis of chronic active EBV infection (CAEBV) and resolved after cord blood transplantation (CBT).

The patient was a 36-year-old woman who had a 1-month history of fatigue, fever and skin rash. Laboratory studies showed an abnormal pattern of anti-EBV antibodies: antiviral capsid antigens IgG (5120×), anti-early antigen IgG (2560×) and anti-EB nuclear antigen (80×). Quantitative PCR showed an elevated copy number of EBV-DNA: 1.5×10^5 and 2.8×10^4 copies per microgram of DNA in fractionated peripheral blood $CD4^+$ T cells and $CD19^+$ B cells, respectively. EBV-DNA was not detected in $CD8^+$ T cells or $CD56^+$ NK cells. The $CD4^+/CD8^+$ T-cell ratio was elevated (6.3, normal 0.4–2.3). The clonality of EBV-infected $CD4^+$ T cells was determined by southern blotting using EBV terminal repeats and the T-cell receptor gene. The Ig heavy-chain gene was determined to have the germline pattern. A diagnosis of $CD4^+$ T cell-type CAEBV was made. Although allogeneic SCT (allo-HSCT) is the only curative therapy for CAEBV, we chose watchful waiting because of the lack of HLA-matched related or unrelated donors.

Eight months later, the patient developed symptoms of heart failure of New York Heart Association (NYHA) functional class IV. Chest X-ray and CT showed marked cardiomegaly and pericardial effusion. Brain natriuretic peptide (BNP) was elevated (731 pg/mL, normal <18.4 pg/mL). A diagnosis of PAH was made based on findings of echocardiography (tricuspid regurgitation pressure gradient (TRPG) 88 mm Hg) and right heart catheterisation (RHC) (pulmonary artery pressure (PAP) 90/54 mm Hg, mean PAP 65 mm Hg, pulmonary capillary wedge pressure 12 mm Hg, pulmonary vascular resistance (PVR) 1525 dyne s/cm^5, cardiac index (CI) 1.86 L/min/m^2). She was admitted to the cardiac care unit, and epoprostenol was started. Continuous intravenous administration of epoprostenol is the only treatment shown to improve survival in idiopathic PAH.[7] At the same time, we began administering corticosteroids because of worsening symptoms associated with CAEBV. Her symptoms gradually improved to NYHA II with increasing epoprostenol dose to 20 ng/kg/min. TRPG decreased to 60 mm Hg and BNP to 15.3 pg/mL. RHC showed partial improvement: mPAP 37 mm Hg, PVR 441 dyne s/cm^5, CI 2.71 L/min/m^2.

However, due to progression of CAEBV, platelet counts decreased to 4.3×10^4/μL, lactate dehydrogenase increased to 1416 IU/L (normal 106–220 IU/L), and she had haemosputum from lung involvement of CAEBV. We performed CBT against CAEBV using epoprostenol. The conditioning regimen consisted of fludarabine (125 mg/m^2), melphalan (80 mg/m^2) and low-dose total-body irradiation (4 Gy). A single unit of HLA two-loci-mismatched cord blood was transfused and $CD34^+$ cell counts were $0{\cdot}85\times10^5$/kg. Tacrolimus and short-term MTX were used as GVHD prophylaxis. Neutrophil (⩾500/μL) and platelet ($\geqslant2\times10^4$/μL) engraftment were achieved on days 18 and 44, respectively. Lung nodules disappeared and EBV-DNA load became very low or undetectable (Figure 1). Complete donor chimerism was confirmed by fluorescence *in situ* hybridisation of the X and Y chromosomes. Moreover, her symptoms of PAH were substantially improved, which was sustained even after tapering epoprostenol. Continuous infusion of epoprostenol was stopped 15 months after CBT. She developed chronic GVHD of the skin and liver, but this was not severe, and tacrolimus was discontinued 19 months after CBT. RHC (Figure 1), chest X-ray and echocardiography (Figure 2) after discontinuation of epoprostenol and tacrolimus showed normal findings: mPAP 15 mm Hg, PVR 149 dyne s/cm^5, CI 2.55 L/min/m^2.

Comorbidity of PAH is a very serious problem when undergoing allo-HSCT. Treatment of PAH with epoprostenol and adoption of reduced-intensity conditioning (RIC) facilitated allo-HSCT in this case. This is the first reported case in which the patient received allo-HSCT using continuous epoprostenol for coexisting PAH. Kawa *et al.*[8] showed a superior outcome for patients who received allo-HSCT (including 8 CBT) with RIC compared to the myeloablative conditioning group. However, in their retrospective study, two patients experienced graft failure after CBT with RIC, and received successfully a second or third CBT. CBT is a promising

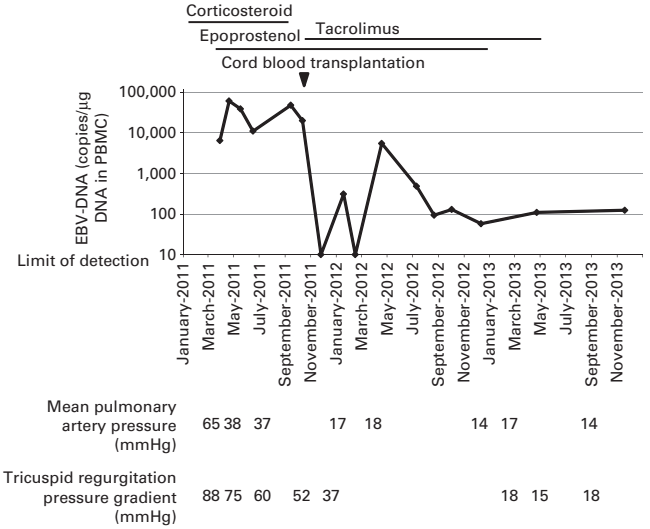

Figure 1. EBV-DNA load in PBMCs decreased to very low or undetectable levels, and haemodynamic parameters of pulmonary arterial hypertension became normal after cord blood transplantation.

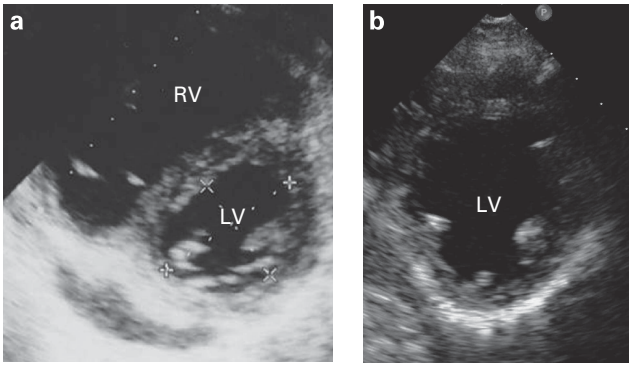

Figure 2. Short-axis image of echocardiography before transplantation showed enlargement of the right ventricle (RV) and D-shaped left ventricle (LV) (**a**), and these findings resolved after transplantation (**b**).

treatment option for CAEBV patients without HLA-matched donors, but further studies are needed to find effective RIC regimens to decrease the incidence of graft failure after CBT.[9]

Muneuchi *et al.*[5] reported two paediatric cases of CAEBV in whom coronary artery lesions regressed after CBT. It was speculated that EBV-infected T and NK cells had a central role in the development of cardiovasculopathy. Meanwhile, in their cohort, the regression of artery lesions was observed only in patients receiving CBT. Recently, we reported a case in which Takayasu arteritis was improved after CBT.[10] Cord blood as the stem cell source may have influenced these improvements of vasculopathy.

It is usually difficult to discontinue treatment with epoprostenol once it has been started in patients with severe PAH. PAH has a multifactorial pathobiology and develops in a different clinical setting depending on associated diseases.[7] Although the pathophysiological basis of the association between PAH and CAEBV is unclear, eradication of EBV-infected clonal $CD4^+$ T cells after CBT may have contributed to the improvement of PAH in our case. This case indicates that PAH is not an absolute contraindication to allo-HSCT, and curative treatment of coexisting associated disease may result in resolution of PAH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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