

## CASE REPORT

# Successful low-dose chemotherapy for refractory Epstein-Barr virus—related post-transplant lymphoproliferative disorder following hematopoietic stem cell transplantation in a child with Wiskott-Aldrich syndrome

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## Abstract

We report the first case of a 12-year-old boy with Wiskott-Aldrich syndrome who developed CD20-weakly expressed and CD30-highly expressed Epstein-Barr virus-related post-transplant lymphoproliferative disorder refractory to rituximab treatment. The patient was effectively and safely treated with personalized low-dose chemotherapy and subsequently remained in complete remission for 1 year.

## KEYWORDS

Epstein-Barr virus, hematopoietic stem cell transplantation, low-dose chemotherapy, pediatric, post-transplant lymphoproliferative disorder, rituximab, Wiskott-Aldrich syndrome

## 1 | INTRODUCTION

Wiskott-Aldrich syndrome (WAS) is a rare X-linked recessive inherited immunodeficiency characterized by thrombocytopenia, eczema, recurrent infections, and abnormal hemorrhage. The best treatment of choice is hematopoietic stem cell transplantation (HSCT).<sup>1</sup> Although conditioning

regimens for children with WAS include antithymocyte globulin (ATG) prophylaxis, acute grade II graft-vs-host disease (GVHD) still occurs, unfortunately. Both ATG use and acute GVHD are independent<sup>2</sup> factors for developing Epstein-Barr virus-related post-transplant lymphoproliferative disorder (EBV-PTLD) following HSCT. Approximately 44%-79% of patients respond to rituximab therapy with a reduction in

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immunosuppression, with complete remission (CR) rates of 20%-55%.<sup>2,3</sup> Although the role of treatment regimens, such as low-dose chemotherapy, has been studied in adult patients, this approach has rarely been reported for pediatric HSCT recipients. Here, we report the first case of refractory EBV-PTLD in a 12-year-old boy with Wiskott-Aldrich syndrome that resolved with personalized low-dose chemotherapy.

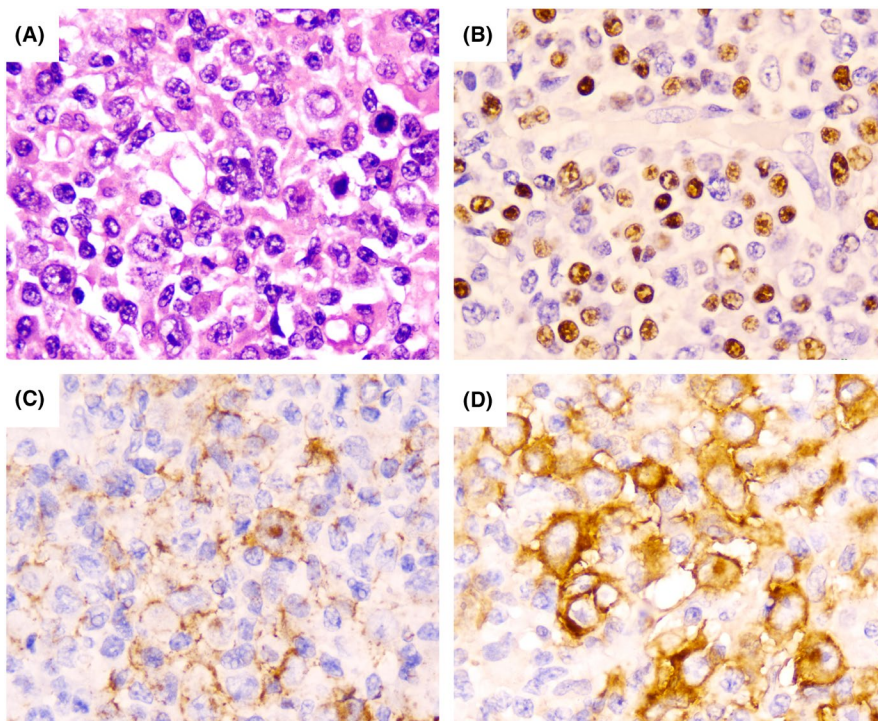
## 2 | CASE PRESENTATION

A 12-year-old boy with WAS had a hemizygote mutation (c.961C>T), inherited from his mother, which was identified by WAS gene sequencing. He had undergone allogeneic HSCT (allo-HSCT) from a human leukocyte antigen (HLA)-10/10-matched unrelated donor in 2019. The conditioning regimen before transplantation comprised the following: busulfan (Bu) 0.8 mg/kg/dose, q6h, day -9 to day -6; cyclophosphamide 50 mg/kg/dose, qd, day -5 to day -2; and ATG 2.5 mg/kg/dose, qd, day -4 to day -2. A donor graft containing  $5.1 \times 10^6$  CD34+ cells/kg was infused on day 0. The protocol for GVHD prevention included the administration of cyclosporine A (6 mg/kg/d, beginning on day -1 and daily thereafter) and methotrexate (15 mg/m<sup>2</sup>/d on day +1 [1 day after transplantation] and 10 mg/m<sup>2</sup>/d on day +3 and day +6). The dose of cyclosporine A was adjusted such that the blood serum concentrations were between 150 and 250 ng/mL. On day 12 after transplantation (day +12), successful engraftment of the donor neutrophils was observed. On day +14, the engraftment of donor platelets was achieved, and the proportion of donor chimera was 99.4% on day +16.

On day +21, the recipient developed grade II acute GVHD, characterized by vomiting, abdominal pain, and diarrhea. On day +31, the symptoms of acute GVHD disappeared after treatment with 1 mg/kg/d of methylprednisolone and 30 mg/kg/d of mycophenolate mofetil.

On day +33, asymptomatic EBV viremia was detected by quantitative reverse transcription-polymerase chain reaction; the EBV-DNA level was  $6.46 \times 10^4$  copies/mL (cps/mL). Pre-emptive antiviral therapy and immunosuppression reduction were initiated. However, because of the persistent positive blood test results for EBV, we added one dose of rituximab (375 mg/m<sup>2</sup>) to the regimen for further treatment on day +43. Despite these pre-emptive treatments, he developed cervical lymph node enlargement on day +46, with the largest node showing a size of approximately 23 × 15 mm. He exhibited no other clinical symptoms, and the second dose of rituximab was administered on day +47.

Lymph node biopsy was subsequently performed, and immunofluorescence staining revealed diffuse large B-cell lymphoma with a plasma cell phenotype. Furthermore, the samples tested positive for EBV-encoded RNA, consistent with monomorphic EBV-PTLD (Figure 1). Immunohistochemistry showed the following results: CD20(+), CD30(+), CD19(+), PAX5(-), CD79a(+), CD138(+), MPO(-), κ(-), and λ(+). Moreover, the proportion of Ki67-positive cells was approximately 60%. Whole-body [<sup>18</sup>F]-fluorodeoxyglucose positron emission tomography/computed tomography (CT) showed several nodules with high metabolism in the right neck, which was considered to represent lymphoma invasion. After immunosuppression reduction combined with four doses of rituximab, the re-examination of blood EBV-DNA levels revealed



**FIGURE 1** Hematoxylin and eosin staining and immunohistochemistry of lymph node biopsy specimens (magnification ×400). A, HE (LN) ×400. B, EREB (LN) ×400; 52% positive expression. C, CD20 (LN) ×400; 29% positive expression. D, CD30 (LN) ×400; 53% positive expression. Abbreviations: HE, hematoxylin and eosin staining; EREB, Epstein-Barr virus-encoded RNA; LN, lymph node

a reduced viral load of <500 cps/mL on day +69; the patient's EBV-DNA level subsequently reduced to undetectable levels.

However, after these first-line therapies, ultrasound imaging of the neck showed that the enlarged lymph nodes had only slightly regressed, indicating rituximab-resistant PTLD. Subsequently, two cycles of reduced-intensity chemotherapy were administered, comprising one dose of rituximab (375 mg/m<sup>2</sup>), reduced-dose cyclophosphamide (600 mg/m<sup>2</sup>/d, 1 day), and methylprednisolone (0.8 mg/kg/dose, q12h, 5 days). Treatment cycles were repeated every 21 days. Follow-up CT and ultrasound showed that the lymphoma had disappeared, and EBV-DNA remained undetectable in the blood (Figure 2). Finally, the third to sixth cycles of low-dose chemotherapy without rituximab were administered according to the protocol (cyclophosphamide, 600 mg/m<sup>2</sup>; methylprednisolone, 0.8 mg/kg/dose, q12h, 5 days). After this treatment, the re-examination of EBV-DNA levels revealed a reduced viral load of <500 cps/mL, and repeated CT showed no lesion. Currently, the patient has been in CR for 1 year without any abnormalities on physical examination or further laboratory testing.

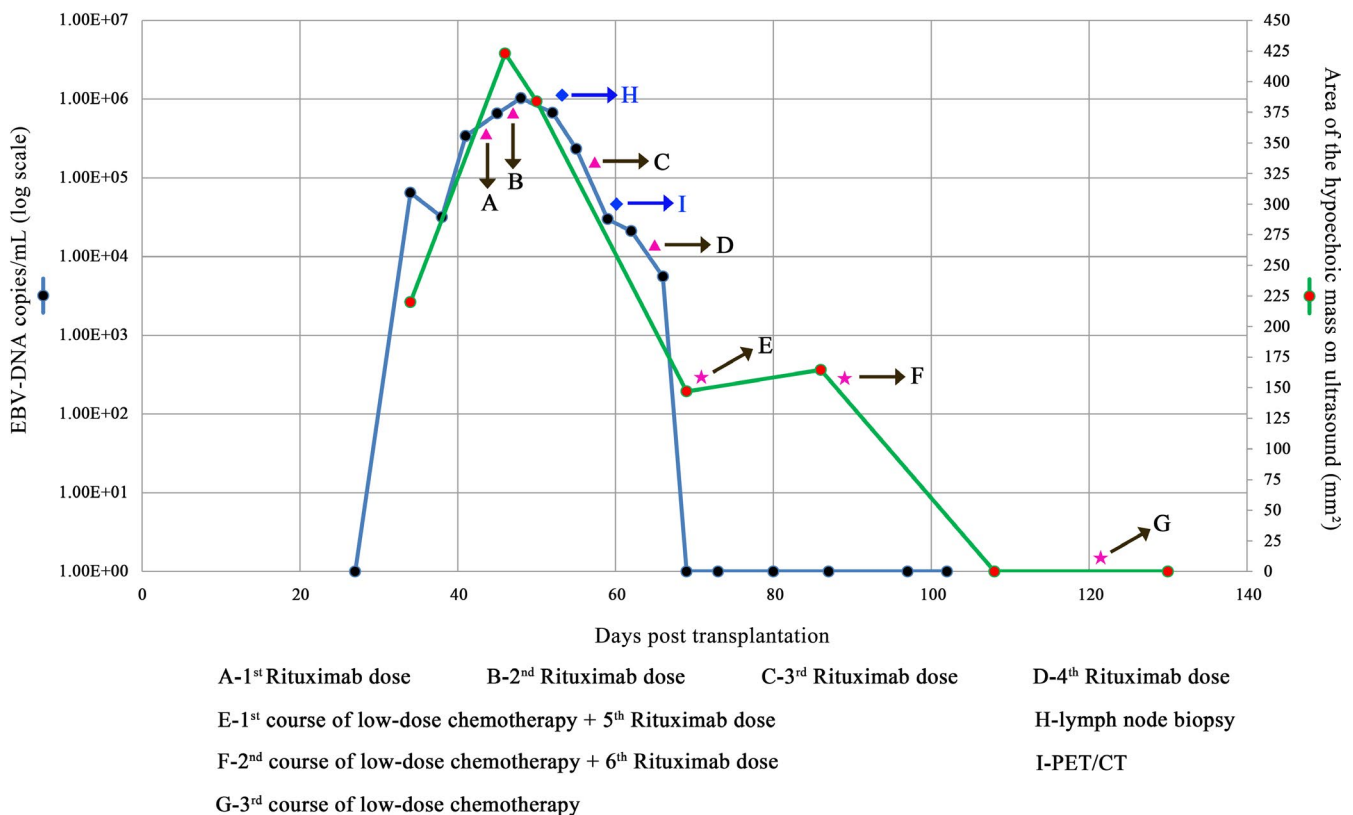
### 3 | DISCUSSION

Epstein-Barr virus-related post-transplant lymphoproliferative disorder is one of the most life-threatening complications

observed post-HSCT in children. Multiple risk factors<sup>4,5</sup> have been associated with the onset of EBV-PTLD, such as reduced-intensity conditioning, alternative donors, use of ATG, GVHD, cytomegalovirus reactivation, umbilical cord blood transplantation, T-cell depletion, EBV-DNA load, alemtuzumab use, essential disease, total body irradiation, and splenectomy. The treatment of EBV-PTLD is rather problematic because there is no global standard of treatment, and the major setback is the lack of randomized trials.

A retrospective study<sup>6</sup> portrayed the limited efficacy of chemotherapy for EBV-PTLD after adult solid organ transplantation or allo-HSCT. EBV-specific cytotoxic T-lymphocyte (CTL) therapy has been proven to be effective and safe even against refractory or relapsed PTLT; however, obtaining donor EBV-specific CTLs or third-party HLA-matched EBV-specific CTLs is extremely time-consuming. Additionally, there is a concern about CTLs inducing GVHD. Presently, the best treatment for children with refractory or recurrent PTLT remains unclear. In one case report, a 9-year-old girl with acute lymphocytic anemia in the third remission presented with a very late-onset relapse of EBV-PTLD with large intra-abdominal lymph node masses 9 years after the first episode of PTLT.<sup>7</sup> The relapse was successfully treated with low-dose chemotherapy, and her disease was in CR for 5 years.

Here, we report the case of a 12-year-old boy with Wiskott-Aldrich syndrome who developed CD20-weakly expressed and CD30-highly expressed EBV-PTLD following



**FIGURE 2** Timeline of EBV-DNA test results, ultrasound scanning, and clinical findings. Abbreviations: EBV, Epstein-Barr virus

allogeneic HSCT that was refractory to rituximab treatment. Similar to other types of malignant lymphoma,<sup>8</sup> diminished expression of CD20 or high expression of CD30 is the most important mechanism underlying the ineffectiveness of rituximab in treating malignant lymphomas. Similarly, our case report shows that CD20-weakly expressed and CD30-highly expressed refractory EBV-PTLD can be successfully treated with reduced-intensity chemotherapy. Compared to traditional standard chemotherapy (R-CHOP, CHOP), donor lymphocyte infusion (DLI), and radiation, favorable toxicity profile makes reduced-intensity chemotherapy an attractive treatment option for rituximab refractory EBV-PTLD. Thus, reduced-intensity chemotherapy may emerge as an effective and safe option for pediatric patients with refractory EBV-PTLD. This treatment regimen can lead to a better quality of life with fewer side effects, which is especially important for children with refractory or recurrent PTLD after transplantation. Additionally, our case report may also help other physicians in the management of similar pediatric cases with poor health. Interestingly, more novel tools or agents, such as “off-the-shelf” CTLs and brentuximab vedotin combined with rituximab, which may result in better results and fewer side effects, for the treatment of refractory EBV-PTLD, are being investigated in clinical trials.

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#### CONFLICT OF INTEREST

The authors have disclosed that they have received no funding from, have relationships with, or have financial interest in any commercial companies pertaining to this article.

#### AUTHOR CONTRIBUTIONS

BX and CZ: involved in patient management. BX: collected data, suggested the diagnosis, facilitated the molecular analysis of samples, and reviewed and edited the manuscript. BX and YZ: contributed to reference citation and medical writing.

#### ETHICAL APPROVAL

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The study was performed in accordance with the Declaration of Helsinki, and written informed consent for the study and the publication of this report were obtained from the patient and his parents.

#### DATA AVAILABILITY STATEMENT

The authors declare that all the data supporting the findings of this study are available within the paper and its supplementary information files.

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