Am J Transl Res 2025;17(7):5207-5213
www.ajtr.org /ISSN:1943-8141/AJTR0164131

Case Report

Treatment of chronic active EBV infection in children and management of post-transplant complications: a case report

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Received February 24, 2025; Accepted June 10, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: Chronic active Epstein-Barr virus (CAEBV) infection is a rare and fatal disease caused by persistent EBV infection. During the progressive phase of CAEBV, children are highly susceptible to life-threatening complications such as hemophagocytic syndrome, multiple organ failure (particularly liver and kidney failure), coagulation disorders, and hemangiomas, resulting in a high mortality rate. Traditional treatments such as immunotherapy or chemotherapy are limited in effectiveness, and children may succumb to the disease within a few years. Currently, allogeneic therapy (hematopoietic stem cell transplantation [HSCT]) is the only curative measure for this disease. However, this procedure may lead to a series of complications that threaten the lives of the transplanted children. Therefore, mastering the correct management approach and exploring new preventive and therapeutic measures are crucial. This paper reports a case of a child with CAEBV who developed complications after allogeneic HSCT. Through the comprehensive use of immunomodulators and personalized treatment strategies, patient's conditions was improved significantly.

Keywords: CAEBV, EBV, children, HSCT, transplantation-related complications

Introduction

EBV, classified as human gammaherpesvirus type IV, is one of the nine identified viruses that exclusively infect humans [1]. It has a latent infection rate of 95% in the population [2]. Typically, EBV targets B cells during latency, but its titer is regulated and inhibited by cytotoxic T cells and NK cells in the body. In most cases, infected individuals are asymptomatic. However, when immune dysregulation occurs, EBV enters the bloodstream, leading to serological reactions. Patients may subsequently exhibit symptoms of infectious mononucleosis (IM), such as fever, lymphadenopathy, and hepatosplenomegaly, which can be improved with antiviral and immunomodulatory treatments. Another latent target cell type is epithelial cells, and this is closely related to the occurrence of epithelial cancers [3]. EBV can exist in T cells and NK cells in a very small number of cases, leading to a decline in immune function and persistent long-term presence of EBV in the body, known as chronic active EBV infection (CAEBV) [4]. During the nonprogressive stage, CAEBV only presents with mild IM lasting more than three months.

At this stage, treatment for affected children primarily involves the use of steroids or immunosuppressants for maintenance. However, the sudden onset of lethal complications such as hemophagocytic syndrome, hemangiomas, multi-organ failure, coagulation disorders, and pancytopenia poses a significant threat to children's lives. Without HSCT, children may die within a few years from one or more of those complications [4]. Current studies have shown that EBV infection also occurs in the bone marrow hematopoietic stem cells of CAEBV patients [5] and that the EBV genes can be transmitted to their progeny cells through the proliferation and differentiation of hematopoietic stem cells, possibly because traditional treat-

https://doi.org/10.62347/FSWU8553

Table 1. Key clinical timeline of this case

Date	Key Clinical Process
2017/9	Diagnosis of EBV-associated T-cell lymphoproliferative disease
2023/12	Cervical lymphadenopathy for 4 d, fever for 3 d
2023/12	Diagnosis of CAEBV, T-cell type, grade 1-2
2023/12-2024/3	Prednisone and etoposide chemotherapy, EBV-PCR <500
2024/3/11	Peripheral blood stem cell infusion
2024/3/12	Donor lymphocyte infusion-related rash
2024/3/13	Sepsis
2024/3/25	Engraftment syndrome
2024/3/27	Grade 3 skin GVHD
2024/4/9	Hyponatremic seizures, hypertensive encephalopathy
2024/4/12	Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

ment methods cannot cure CAEBV. Therefore, HSCT should be the most critical step in the treatment of CAEBV, aligning with the "three-step method" for treating CAEBV first proposed by Sawada and others [4]. To minimize complications and improve survival rates, CAEBV patients should undergo three-step therapy as early as possible. After the first two steps of treatment (using immunosuppressants and a combination of various chemotherapy drugs), the EBV-DNA titer in patients should be controlled below 10^3 to create conditions for transplantation. If there is no significant decrease or even an increase in the EBV virus after chemotherapy or if severe complications have occurred, hematopoietic stem cell transplantation should be performed directly without delay [6]. Allogeneic HSCT significantly affects survival rates (the 15-year survival rate is 60.6%, whereas it is 25.7% for those who did not undergo HSCT) [7]. However, CAEBV patients may experience a series of transplant-related complications after preconditioning and hematopoietic stem cell infusion, such as sepsis, which easily occurs after preconditioning; engraftment syndrome; graft-versus-host disease; thrombotic microangiopathy after cell engraftment [8]; and transplant-related lymphoproliferative disorders caused by the long-term use of immunosuppressants [9]. Therefore, exploring more effective treatment strategies and individualized management plans has become a focal point of clinical research. This study aims to provide new insight and treatment approaches in this field through an in-depth analysis of a child with chronic active EBV infection who developed several post-transplant complications after HSCT.

Case description

The patient, an 8-year-old girl, was admitted on December 11, 2023, with cervical lymphadenopathy for four d and fever for three d. Her body temperature peaked at 38.7°C, accompanied by cough, nasal congestion, and yellow nasal discharge, without other symptoms such as respiratory distress, chest tightness, palpitations, dizziness, headache, nausea, vomiting, abdominal pain, or diarrhea. Physical examination revealed multiple enlarged cervical lymph nodes, the largest measuring 2.5 cm × 2.5 cm, with hepatomegaly and splenomegaly. Upon further inquiry into her medical history, she was diagnosed with "EBV-associated T-cell lymphoproliferative disease" at Beijing Children's Hospital at the age of 1 year and 11 months. She subsequently received intermittent oral "traditional Chinese medicine" and hormonal therapy at Anyang Hospital of Traditional Chinese Medicine in Henan Province. The key clinical processes are summarized in **Table 1**.

After admission, laboratory tests revealed leukopenia (white blood cells, WBC 2.21×10^9/L), mild anemia (hemoglobin, HGB 109 g/L), and thrombocytopaenia (platelets, PLT 126×10^9/L). Imaging indicated bilateral pneumonia and mediastinal and cervical lymphadenopathy. EBV serology was positive for EBV-VCA-IgG antibodies, positive for EBV-EA-IgG, and weakly positive for EBV-NA1-IgG. The peripheral blood EBV-DNA load was positive (2.72×10^5 copies/ml). We used magnetic bead sorting combined with real-time quantitative PCR technology to detect and analyze EBV DNA. The results revealed that the EBV load was 7.9×10^2 cop-

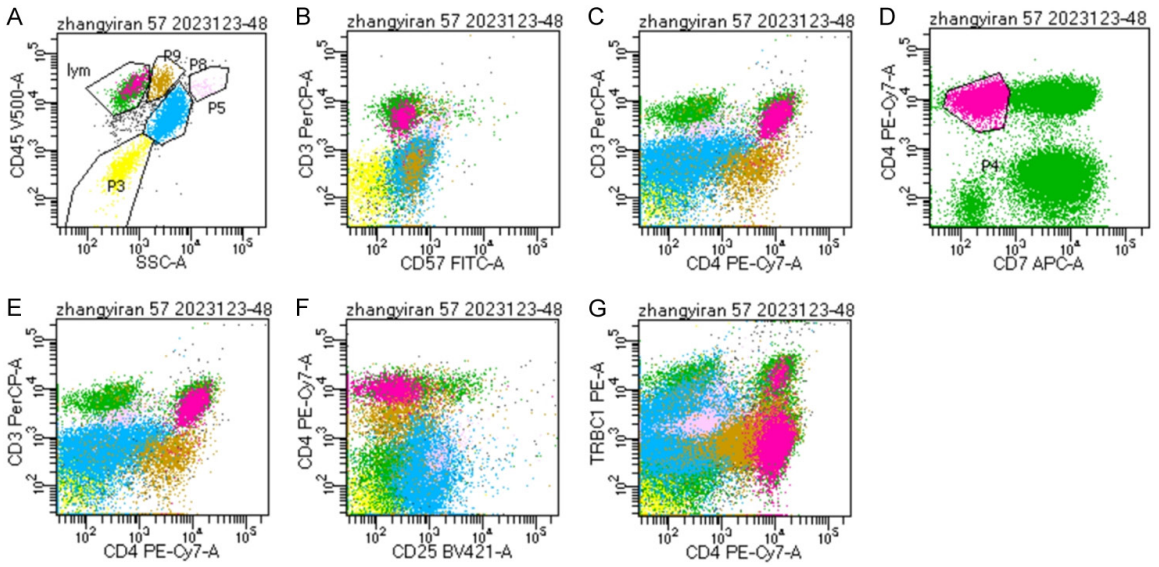

Figure 1. Flow cytometry analysis. A. In the bone marrow sample, mature lymphocytes accounted for 12.70% of the nucleated cells, with T cells comprising 81.2% of the lymphocytes. B-G. These cells expressed CD4, CD3, CD5, CD2, and CD7dim; partially expressed CD56; and slightly expressed TRBC1 (5.4%).

ies/1×10^6 cells in CD3-CD19+ cells, 2.2×10^5 copies/1×10^6 cells in CD56+ cells, 5×10^4 copies/1×10^6 cells in CD3+CD4+ cells, and 4.7×10^3 copies/1×10^6 cells in CD3+CD8+ cells. This finding indicates that in this case, both T/NK and B cells were affected, with a predominance of T and NK cells. Cytokine analysis revealed elevated interleukin-6, interleukin-8 and gamma-interferon levels. Lymphocyte subset analysis revealed that the number of abnormal CD3+ and CD4+ cells increased. Ultrasound revealed multiple enlarged lymph nodes and splenomegaly.

Further diagnostic examination involved bone marrow aspiration and biopsy. A bone marrow smear revealed active hematopoiesis, with 49% granulocytes (G), 27% erythroid (E) cells and a G/E ratio of 1.81/1. The megakaryocyte count was 148, with few platelets and phagocytosis. The diagnosis was trilineage hyperplasia, which required clinical correlation. Biopsy revealed normal marrow hyperplasia (70-80%), with a reduced granulocyte/erythroid ratio and increased lymphocyte proportion (20%), predominantly mature T cells, with mild atypia. The combination of the patient's clinical history and lymph node biopsy results was consistent with systemic CAEBV (T-cell type) involving the bone marrow.

Bone marrow immunophenotyping revealed that mature lymphocytes accounted for 12.70% of the nucleated cells, with T cells constituting 81.2% of the lymphocytes and a CD4/CD8 ratio of 1.8. Among these, 2.31% of the cells (accounting for 18.16% of the lymphocytes and nucleated cells) expressed CD4, CD3, CD5, CD2, and CD7dim; partially expressed CD56; and a small fraction expressed TRBC1 (5.4%). These cells do not express CD117, CD8, CD57, or CD25 and are suspected to be abnormal CD4+ T cells, as shown in **Figure 1**. Immunohistochemical markers revealed the expression of CD34, CD117, MPO, CD61, E-Cad, CD3, PAX-5, and TdT, among others. The detection of EBV-encoded small RNA (EBER) is considered the best marker for EBV infection in tissues and is the gold standard for diagnosing whether a tumor is associated with EBV [3]. In situ hybridization revealed EBER positivity, as depicted in **Figure 2**.

Lymph node biopsy from our pathology department revealed systemic CAEBV (T-cell type, grade 1-2), which was consistent with CAEBV (NK/T-cell type) [1].

Treatment process

On March 5, 2024, the peripheral blood EBV-DNA load was positive (1.21×10^4 copies/ml).

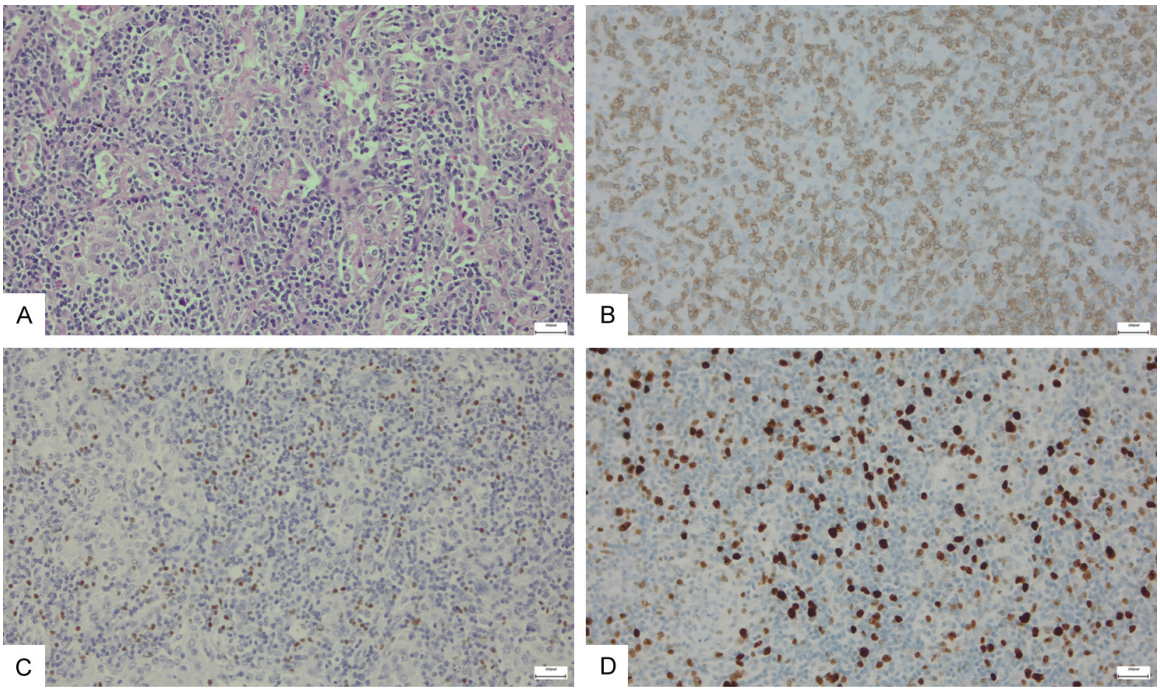

Figure 2. A. Hematoxylin and eosin staining showing a diffuse lymphocyte composition in the cervical lymph node (magnification ×200). B. Immunohistochemistry image showing that CD3+ cells are positive (magnification ×200). C. *In situ* hybridization revealed Epstein-Barr virus (EBV)-positive cells (magnification ×200). D. Immunohistochemistry image showing Ki-67 (approximately 40-50% positive in the germinal center) (magnification ×200).

Previous repeated tests of peripheral blood EBV-PCR were also positive, revealing a decreasing trend in the EBV nucleic acid concentration. However, on February 28, 2024, the peripheral blood EBV-DNA load was positive (1.54×10^5 copies/ml). On March 10, 2024, the patient received a third-party B-type Rh-positive umbilical cord blood infusion of 32.4 ml. The next d, peripheral blood stem cells from the donor (father to daughter, HLA 5/10 matched, blood type B+) were infused at 19:10 on March 11, 2020, with a volume of 250 ml. Our hospital's test revealed a peripheral blood stem cell CD34+ count of 0.47%, total nucleated cells (TNCs) of 30.33×10^8/kg, mononuclear cells (MNCs) of 18.47×10^8/kg, and CD34+ cells of 13.94×10^6/kg. External testing at Hebei Medical University Second Hospital revealed a CD34+ count of 0.3%, with 8.88×10^6 CD34+ cells/kg. The peripheral blood EBV-DNA load was less than 500 copies/ml. The 27 subsequent tests of peripheral blood for EBV-DNA were all negative. By +14 d, the patient's granulocytes were successfully engrafted; by +15 d, peripheral blood T/B-cell chimerism showed complete donor chimerism; and by +16 d, platelet engraftment was successful.

Complications and Management: On d +1, the child developed a rash on the face. Agranulocytosis (granulocyte count at the zero phase) was suspected to be related to donor lymphocyte infusion. Post-infusion cyclophosphamide was administered to suppress donor lymphocyte activation, along with oral mycophenolate mofetil and cyclosporine to inhibit lymphocyte proliferation. On d +2, the child developed a fever with a peak temperature of 39.9°C. Given the persistent agranulocytosis, sepsis was suspected. Meropenem was initiated empirically. After the blood culture results were obtained, norvancomycin was added to the target cocci. However, the patient continued to experience intermittent fever, so a fungal infection could not be ruled out. Consequently, caspofungin was added as antifungal therapy. Following this treatment, the child's body temperature returned to normal after seven d, with CRP levels also normalizing.

On d +15, the child presented with a red rash on the face, chest, and back, but no other symptoms were observed. We suspected engraftment syndrome and initiated an empirical trial of oral ruxolitinib. On d +16, the child pre-

sented an increase in rashes, with dense red maculopapular rashes visible all over the body. We considered it acute GVHD grade II (skin grade 3) and immediately administered 2 mg/kg methylprednisolone sodium succinate by infusion. We monitored the blood counts closely and actively provided the child with red blood cell and platelet transfusions to maintain the Hb level above 100 g/L. By the next d, the rashes had subsided compared with before. The steroid dosage was subsequently gradually reduced, and the rashes did not recur. On d +21, the patient experienced a sudden seizure accompanied by loss of consciousness, a fixed gaze, tonic-clonic movements of the limbs, clenched teeth, and drooling from the mouth. Electrolyte tests revealed hyponatremia with a sodium level of 123.3 mmol/L (other ions were essentially normal), and her blood pressure was 119/88 mmHg. The patient was also diagnosed with hyponatremia and hypertensive encephalopathy. We promptly performed electrocardiogram monitoring, oxygen therapy, mannitol for intracranial pressure reduction, and slow sodium ion infusion as part of the treatment measures. The patient's vital signs were closely monitored. Luckily, the child regained consciousness. After a 24-hour urine sodium test and other auxiliary examinations of blood electrolytes, the condition was diagnosed as syndrome of inappropriate antidiuretic hormone secretion (SIADH), possibly related to the use of immunosuppressive drugs post-transplant [10]. The symptoms improved after oral administration of tolvaptan and sodium supplementation. Owing to the use of extensive immunosuppressants and post-cyclophosphamide inhibition, CAEBV patients are more susceptible to infection; thus, it is necessary to receive a 10 g intravenous immunoglobulin infusion weekly to increase infection resistance. On d +25, the patient exhibited signs of bladder irritation, including urinary frequency, urgency, and dysuria. Urinalysis revealed elevated levels of white and red blood cells, whereas bladder ultrasound revealed a thickened and irregular bladder wall. All of these findings support the diagnosis of Grade I hemorrhagic cystitis accompanied by a urinary tract infection. We administered levofloxacin for anti-infective therapy along with plenty of hydration and alkalization treatments, which ultimately led to an improvement in symptoms.

After stabilization, the patient was discharged and followed up for more than 12 months. EBV-PCR remained negative, and no other post-transplant complications were observed.

Discussion

In 2016, the World Health Organization (WHO) reclassified CAEBV as an EBV-associated T/NK-cell lymphoproliferative disorder, with diagnostic criteria including (1) persistent or recurrent IM-like symptoms for more than three months; (2) elevated EBV-DNA levels in peripheral blood or tissue lesions; (3) EBV infection in T or NK cells in tissue or peripheral blood; and (4) exclusion of other potential diagnoses, such as primary Epstein-Barr virus (EBV) infection (IM), autoimmune diseases, congenital immunodeficiencies, HIV infection, or other conditions requiring immunosuppressive treatment [6]. In the new version of the diagnostic criteria, the requirement for EBV antibodies has been removed. However, EBV-DNA PCR plays a crucial role in diagnosis and treatment. After the use of a combination of immunosuppressants and various chemotherapy drugs, the child's peripheral blood EBV nucleic acid concentration generally tends to decrease. However, in this case, the EBV levels did not significantly decrease and even increased during treatment. We proceeded with a hematopoietic stem cell transplant for the child according to the "three-step therapy" of chemotherapy combined with transplantation proposed by the Japanese EBV Collaborative Group [14]. In this case, the patient had a history of EBV-related disease and positive EBV serology, and the increased proportion of lymphocytes with mild atypia in the bone marrow suggested that the EBV infection affected the bone marrow. The lymph node biopsy results also revealed EBV-positive NK/T-cell proliferation. These findings are consistent with the manifestations of chronic active EBV disease. These pathologic and immunological findings provide crucial evidence for CAEBV diagnosis, highlighting the importance of multidisciplinary collaboration in complex case diagnosis.

CAEBV treatment is challenging and requires a combination of antiviral drugs, immunomodulators and symptomatic support [4]. This paper discusses potential treatment options and their clinical application. The bone marrow and

lymph node pathology results further support the CAEBV diagnosis, particularly its T-cell and NK/T-cell characteristics [1]. The treatment of EBV should be strategized on the basis of the type of infected cells and the stage of the disease. For B-cell diseases, rituximab and chemotherapy are primarily used [15]. Since this case involved T/NK-cell CAEBV, we utilized mainly hematopoietic stem cell transplantation for treatment. Research shows that different EBV-infected cell types indicate different prognoses, with T-cell infections associated with hemophagocytic syndrome and high IgG titers, whereas NK-cell infections are related to mosquito bite hypersensitivity and high IgE levels [7]. However, T-cell CAEBV has a poor prognosis, with high complication rates and mortality [1]. In this case, a T-cell CAEBV conditioner made thorough preparations for HSCT after anti-EBV treatment, immunoglobulin infusion, interferon infusion, prednisone, and four etoposide infusions, and the patient achieved EBV-PCR negativity. However, posttransplant complications such as engraftment syndrome, skin rejection, SIADH, and hemorrhagic cystitis highlight the risks of electrolyte imbalances and secondary infection.

In the early stages of hematopoietic stem cell engraftment, the child developed red rashes on the face, chest, and back without other symptoms, which raised suspicion of engraftment syndrome. Engraftment syndrome is a potential complication following hematopoietic stem cell transplantation and is typically characterized by rash, noninfectious fever, liver and kidney dysfunction, and weight gain [11]. However, in this case, the child presented with only red rashes covering more than 25% of the body area, without other symptoms. Despite this, treatment with oral ruxolitinib was initiated. The next d, the child's rashes worsened, developing into dense red maculopapular eruptions all over the body, leading to a consideration of acute grade II GVHD (skin grade 3). To halt the progression of the rejection reaction, 2 mg/kg methylprednisolone sodium succinate was administered. Methylprednisolone is a potent glucocorticoid commonly used to control the inflammatory response in acute GVHD. Owing to poor immune reconstruction and low immunity, a 10 g intravenous immunoglobulin infusion was administered weekly to prevent infection. SIADH, possibly related to immunosuppressants, often manifests as hyponatremia, increased urine osmolality, and sodium excretion. Thus, timely diagnosis and treatment are needed to prevent cerebral edema, hyponatremic seizures, arrhythmias, and muscle weakness, which increase post-transplant mortality [10]. After symptomatic treatment and gradual reduction in the use of immunosuppressive drugs, the child's SIADH improved. Hemorrhagic cystitis is a common complication following HSCT and is caused mainly by viral infections and immune rejection, resulting in symptoms such as hematuria and bladder irritation [12]. Management requires a combination of anti-infective and supportive therapies. New treatment options now include hyperbaric oxygen therapy and mesenchymal stem cell infusions to promote mucosal and immune recovery [13]. In this case, the hemorrhagic cystitis was mild; thus, the condition disappeared quickly after hydration and alkalinization treatment and levofloxacin against infection.

Conclusion

This case of an 8-year-old girl with CAEBV emphasizes the importance of early recognition and diagnosis. By analyzing clinical presentations and laboratory findings comprehensively, clinicians can better manage such complex cases. The patient was diagnosed with CAEBV (T-cell type) on the basis of clinical, laboratory, imaging, and pathologic results, highlighting the importance of early recognition and multidisciplinary collaboration for timely and effective treatment. The patient not only successfully underwent peripheral blood stem cell transplantation and overcame posttransplant complications but also remained negative for 12 months without other newly identified posttransplant complications. This case highlights the importance of meticulous monitoring and effective management of complications during transplantation, as well as the critical role of multidisciplinary teamwork in addressing complex clinical scenarios.

Acknowledgements

We are grateful to all the members of the Departments of Hematology and Pathology at Hebei Children's Hospital. The work was supported by the Medical Science Research Project of Hebei 2021 (Grant No.: 20210749).

Informed consent was obtained from all participants. The patient's parents provided informed consent for the publication of any potentially identifiable images or data included in this article.

Disclosure of conflict of interest

None.

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