Systemic Epstein-Barr virus-positive T-cell lymphoma of childhood combined with hemophagocytic lymphohistiocytosis: a case report

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Background: Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoma of childhood (STCLC) is a rare disease with few clinical reports and high mortality. By exploring the clinical manifestations of a child with STCLC in our hospital auxiliary examination and diagnostic and therapeutic process, to deepen pediatricians' understanding of this disease.

Case Description: This paper describes a 5-year-old Chinese girl who presented with acute fever and epistaxis. After admission, relevant ancillary tests indicated the presence of hemophagocytic lymphohistiocytosis (HLH) and the combination of EBV infection in this patient. Pathology of the cervical lymph node biopsy and bone marrow flow cytology examination indicated STCLC, and a diagnosis of STCLC combined with HLH was clear. Although the girl was clearly diagnosed within a few days and treated with chemotherapy and symptomatic support, she eventually died on the 6th day after admission due to progressive worsening of her disease.

Conclusions: STCLC is a rare T-cell lymphoproliferative disorder that occurs primarily in the setting of acute EBV infection, usually presenting as HLH. It is a rapidly progressive and fatal disease of children and young adults characterized by monoclonal expansions of EBV-positive T-cells with an activated cytotoxic phenotype and by malignant proliferation. The mortality rate is close to 100%.

Keywords: Epstein-Barr virus (EBV); systemic Epstein-Barr virus-positive T lymphoma of childhood (STCLC); hemophagocytic lymphohistiocytosis (HLH); pathogenesis; case report

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Introduction

Systemic Epstein-Barr virus-positive T-cell lymphoma of childhood (STCLC) is defined as fulminant, systemic T-cell lymphoma with an aggressive clinical course, usually occurring soon after Epstein-Barr virus (EBV) infection or secondary to chronic active EBV infection (CAEBV) (1). Reports on STCLC are sporadic and rare. Patients with STCLC often have hemophagocytic lymphohistiocytosis (HLH), which usually progresses rapidly to multiorgan failure, sepsis, and even death in a matter of days to weeks (2,3).

Here, we report the case of a five-year-old Chinese girl who presented with a primary complaint of fever and epistaxis but was finally diagnosed with STCLC combined with HLH. The aim of this report and our analysis is to promote recognition of STCLC. We present this case in accordance with the CARE reporting checklist (available at

Table 1 Clinical symptoms and laboratory tests

Project	Result
Clinical symptoms	Fever for 10 days and epistaxis for one day
Ultrasound of the abdomen	Splenomegaly
Hematology routine	NEU 0.32×10^9/L, Hgb 80 g/L, PC 20×10^9/L
Fibrinogen	0.3 g/L
Ferritin	14,278.00 ng/mL
Soluble CD25	Untested
Bone marrow and lymph nodes	Visible hemophagocytes
NK cell activity	Low
Interferon-γ	12,777.51 pg/mL

NEU, neutrophil; Hgb, hemoglobin; PC, platelet count; NK, natural killer.

https://acr.amegroups.com/article/view/10.21037/acr-24-42/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents or legal guardians for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. A five-year-old Chinese girl was hospitalized with persistent fever for 10 days and epistaxis for one day. The child had night-time fever for two days, with a maximum temperature of 37.8 ℃. She then had irregular hyperthermia with a fever peak of 39.0 ℃, but without cough, headache, vomiting or limb pain, and antipyretic treatment was ineffective. Routine blood tests showed triplet reduction (hemoglobin 93 g/L; neutrophil count 0.74×10^9/L; platelet count 20×10^9/L), elevated transaminases [alanine aminotransferase (ALT) 206 U/L, aspartate aminotransferase (AST) 241.1 U/L], normal albumin (34.4 g/L), and elevated lactate dehydrogenase (650.1 U/L). She was treated with amoxicillin, glutathione, compound glycopyrrolate and methylprednisolone at another hospital, but the results were poor. No prior immunological abnormalities, recurrent respiratory infections or hepatitis were recorded. The aunt of the girl had died prematurely, and the exact cause of the disease was unknown. On physical examination, our patient presented with clear consciousness, poor mental health, bilateral cervical and inguinal lymph node enlargement, and marked hepatosplenomegaly. Combined with the clinical manifestations, laboratory tests (*Table 1*) and bone marrow routine analysis (*Figure 1*) and according to 2004-HLH diagnostic criteria (4), a diagnosis of HLH in children was clear. Bone marrow flow cytology results showed 0.2% of phenotypically abnormal T lymphocytes. Pathological findings of cervical lymph node biopsy suggested STCLC (*Figure 2*). Flow cytometry assay of cervical lymph node biopsy showed that 50.55% (of all cells) of $CD3^+/CD5^-$ cells were seen, forward scatter (FSC) and side scatter (SSC) were medium sized, expressing CD45bright, CD4, CD8, CD2, CD45RO, CD26, CD38, HLA-DR and TCRαβ, TRBC1 was seen to be restricted expression, partial expression of CD7, no expression of CD99, CD34, CD117, TdT, CD1a, CD10, CD45RA, TCRγ/δ, CD56, CD57, CD94, CD16, CD11b, CD52, CD13, CD33, CD14, and CD15, for mature T lymphocytes with abnormal phenotype. Pathogenesis examination revealed the presence of EBV infection (plasma EBV-DNA 1.42×10^5 copies/mL; Anti-EBV capsid antigen IgG antibody, Anti-EBV early antigen antibody IgG, and Anti-EBV nuclear antigen antibody IgG positivity). Results of high-resolution karyotype analysis were as follows: among the 20 mid-phase divisions analyzed, one karyotype was a tetraploid karyotype with the presence of a long arm addition of chromosome six, +mar, without clonality; the remainder were normal karyotypes. No mutations associated with hematologic neoplastic disease were detected by next generation sequencing (NGS) examination, but the patient carried

Highlight box

Key findings

- *PTPRT* may be the causative gene for systemic Epstein-Barr virus-positive T-cell lymphoma of childhood (STCLC).

What is known and what is new?

- STCLC is a rare disease, often associated with hemophagocytic lymphohistiocytosis, with rapid progression, high mortality, and unknown pathogenesis.
- We found that the JAK1/2 STAT3 pathway may be involved in the development of STCLC.

What is the implication, and what should change now?

- This means that we may explore new options for treating STCLC.

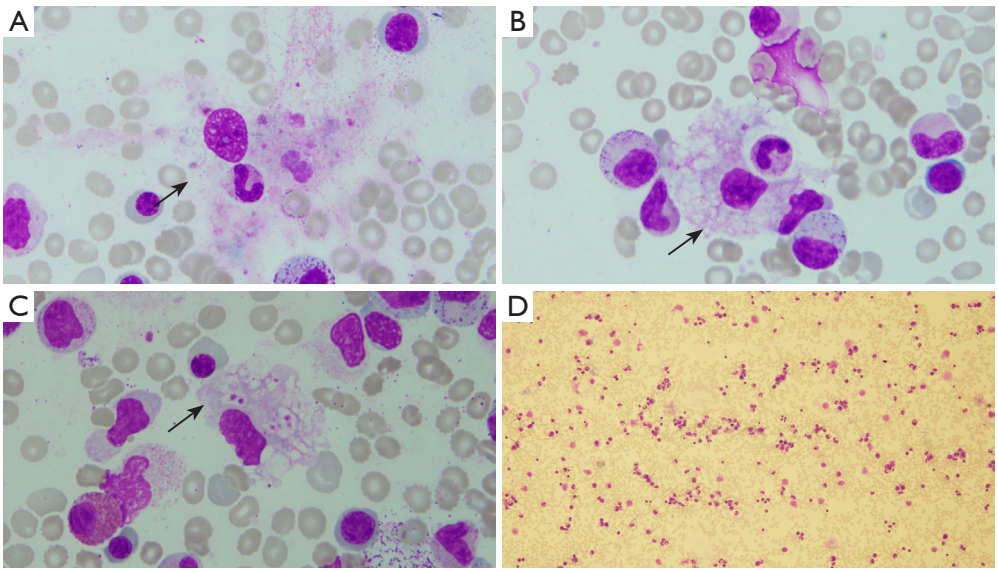

Figure 1 Results of routine bone marrow tests (Rigi staining): the cells indicated by arrows are phagocytic histiocytes (A-C, ×1,000); active bone marrow proliferation can be seen (D, ×100).

variants of the following seven genes: *CNTNAP5*, *NCOR2*, *MYH9*, *PTPRT*, *TET1*, *MUTYH*, and *BRCA2*. Combining her symptoms and examination results, a diagnosis of STCLC combined with HLH was considered, and she was diagnosed on the fifth day after admission. After hospitalization in the pediatric hematology department, the girl was given symptomatic supportive treatment with meropenem for anti-infection, ganciclovir as an antiviral, human immunoglobulin to suppress the immune response, liver protection, biliary support, correction of electrolyte disturbances, blood transfusion, and supplementation of coagulation factors. The girl still had recurrent high fever, and on the fifth day after hospitalization, she developed poor mental health, drowsiness, poor response to the outside world, eyelid edema, progressive increase in skin yellowing, progressive respiratory distress, abdominal bulge, progressive hepatosplenomegaly, and edema of both lower limbs. On the fifth day after admission, the girl was diagnosed with STCLC combined with HLH and was immediately given chemotherapy with a CEP regimen (etoposide, cyclophosphamide and methylprednisolone). However, her condition continued to deteriorate to multiorgan failure (respiratory, circulatory, renal, coagulation), hepatic encephalopathy, disseminated intravascular coagulation (DIC) and shock, and she was transferred to the pediatric intensive care unit (PICU). The girl was treated with ventilator-assisted ventilation and vasoactive drugs to maintain blood pressure in the PICU. One day later, the patient died due to a progressive drop in blood pressure and respiratory and cardiac arrest; resuscitation was ineffective.

Discussion

STCLC is considered a malignant form of EBV-associated T-lymphoproliferative disease in children with a fulminant, aggressive clinical course characterized by EBV infection and clonal proliferation of T-lymphocytes with an activated cytotoxic phenotype (5). Data show that HLH occurs in 26.7% to 47.8% of lymphoma patients during disease progression or treatment. Some studies have reported that patients with STCLC have a higher likelihood of developing HLH. The median survival of patients with untreated STCLC is only 30 to 60 days (5). The pathogenesis of the disease is still unclear, and definitive diagnosis takes a long time and is easily missed; there is also no effective and standard treatment method (6). The disease usually does not respond to the HLH treatment plan, and its malignant course ends in death (5). Two recently reported children with STCLC (7) started with fever combined with gastrointestinal perforation and fever alone, respectively, and were diagnosed and treated with chemotherapy, achieving partial remission after 3 and 4 months, respectively. Chemotherapy regimens and pretreatment are

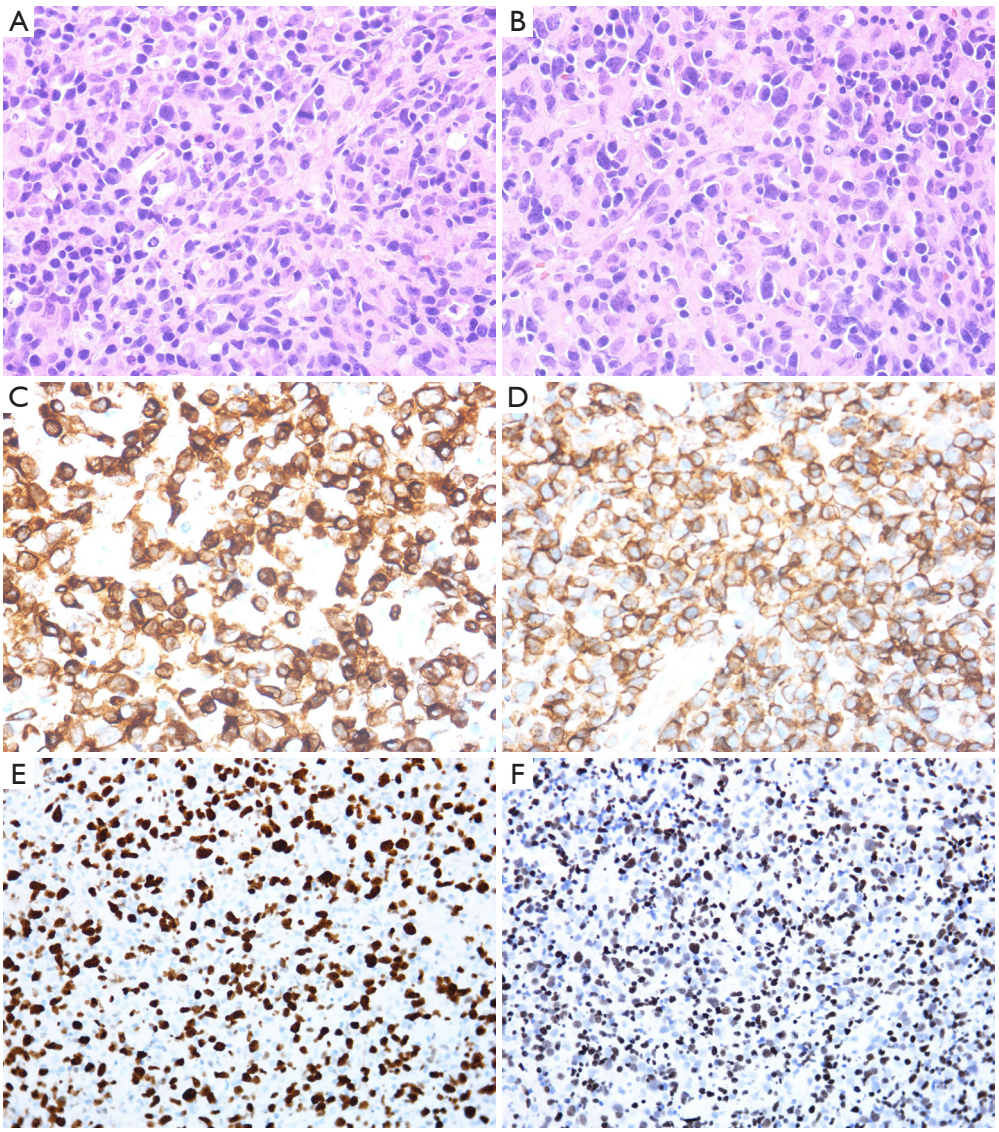

Figure 2 Hematoxylin and eosin stain of lymph node biopsy: no normal structure of lymph nodes; background histiocyte-free hyperplasia evident and phagocytosis visible (A: ×200, B: ×200); CD3 (C: ×400), CD8 (D: ×400), KI-67 (E: ×200) and Epstein-Barr virus-encoded RNA (F: ×100) are seen.

described in the Appendix 1. Subsequently, the children were pretreated and underwent allogeneic hematopoietic stem cell transplantation and survived without relapse at 11 and 22 months of follow-up fashion, respectively.

Ohshima *et al.* (8) classified and graded systemic EBV-positive T/NK lymphoid tissue proliferative disease in children according to the cellular morphology and clonality of EBV infection, including types A and B. Type A is divided into 3 classes: A1, polymorphic, polyclonal hyperplasia; A2, polymorphic, polyclonal or oligoclonal hyperplasia; and A3, monomorphic, monoclonal hyperplasia. Type B is monomorphic, monoclonal hyperplasia. Among them, STCLC is type A3 or type B (9).

In STCLC patients, infected cells are classified as $CD4^+$, $CD8^+$, and γδ T cells. Primary STCLC usually involves a cytotoxic $CD8^+$ phenotype, and most STCLC cases occurring after CAEBV are $CD4^+$. Double positivity occurs in a few cases, and patients infected with $CD4^+$ T lymphocytes have worse prognosis (10). The current patient presented with $CD8^+$ and CD4 (partial weak +).

The clinical manifestations of STCLC are high fever, hepatosplenomegaly, complete hematocrit, coagulation dysfunction, abnormal liver function, and monoclonal proliferation of EBV-positive T cells in tissues or peripheral blood, often combined with HLH at the beginning of the disease. There is a fulminant clinical course of rapid progression to multiorgan failure, sepsis, and even death within a few days to a few weeks. This case began with fever and epistaxis, and the onset of the disease was rapid. By quickly completing relevant auxiliary tests, a diagnosis was made on the fifth day after admission. Regrettably, the child's disease progressed rapidly, and she eventually died.

The disease needs to be differentiated from CAEBV. CAEBV originates from chronic or persistent EBV viral infection and has a wide variety of clinical manifestations, mainly fever, hepatomegaly, splenomegaly, abnormal liver function, thrombocytopenia, anemia, and enlarged lymph nodes, and serious complications can occur during the course of the disease, such as HLH, DIC, lymphoma, and leukemia. CAEBV shares many of the same clinical manifestations as STCLC, and its differentiation is mostly dependent on pathology and flow cytology.

The pathogenesis of STCLC is not fully understood. The present child had a high EBV load. At high viral loads, EBV can infect T cells (6), which then gradually develop into tumor cells. EBV may contribute not only to promoting cell survival but also to genetic mutations in EBV-infected cells (11). The gradual progression of T lymphocytes from polyclonal to monoclonal until the formation of T-cell lymphoma is a continuous process of the disease. In the process of its development, the anti-apoptotic regime of lymphocytes is gradually activated, and T lymphocytes become immortalized and begin to form oligoclonal or monoclonal proliferations, with gradual progression to T-cell lymphoma. Based on a review of the relevant literature, the pathogenesis of STCLC may involve cytokines, pathways and gene mutations.

EBV infection may act as an initiating factor to activate important transcriptional regulators of NF-κB, thereby affecting expression of downstream gene proteins that play a role in cell proliferation and tumorigenesis development through different pathways (12). CD40 and CD137 are upstream cytokines of NF-κB and play important roles in EBV infection of T cells. Takada *et al.* demonstrated that CD40 on EBV-infected T cells activates CD40 L-mediated signaling pathways in an autocrine or paracrine manner and inhibits their apoptosis (13). In addition, CD137 may contribute to promoting the survival of EBV-infected T cells (11).

A recent retrospective study of 169 EBV T/NK-LPD (including 34 STCLC) cases that utilized targeted NGS found mutations in 88.2% of STCLC cases, with *KMT2D* being the most commonly mutated gene (17.6%), followed by *MFHAS1* (14.7%), *STAT3* (14.7%), *EP300* (11.8%), *ITPKB* (8.8%), *DDX3X* (8.8%), *NOTCH1* (8.8%) and *NOTCH2* (8.8%) (14). STAT3 is an oncogenic transcription factor whose aberrant activation can lead to a variety of diseases, especially malignant ones. The LMP1 gene is the only proven EBV malignant transforming factor. It plays a critical role in the induction of malignant transformation of cells and in the replication cycle of the virus. STAT3 is activated in EBV-positive T cells and plays a role in the development of STCLC. EBV infection induces NF-κB activation through LMP1 (13), subsequently, STAT3 is activated downstream of LMP1. Moreover, Onozawa *et al.* (15) found that inhibition of the tyrosine kinase JAK1/2 suppresses EBV-positive T-cell lines, suggesting that the JAK1/2 STAT3 pathway is involved in the development of EBV-positive T-cell lymphoma. *PTPRT* is an endogenous STAT3 inhibitor, and *PTPRT* dysfunction is a potential mechanism for the STAT3 overactivation observed in malignancies (16). The NGS results for this child revealed the presence of a mutation in *PTPRT*, which in turn confirmed the relevance of STAT3 to the pathogenesis of STCLC.

Conclusions

In conclusion, we report a rare case of STCLC combined with HLH, which will deepen pediatricians' understanding of the disease and help in accurate diagnosis and treatment in the future.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-42/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-42/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents or legal guardians for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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