

Case report

Systemic Epstein-Barr Virus-positive T-cell Lymphoproliferative Disease of Childhood

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Abstract: Systemic Epstein-Barr virus-positive (EBV+) T-cell lymphoproliferative disease of childhood is a very rare lymphoma subtype. The majority of patients were reported from Asian countries, especially Japan and Taiwan, strongly suggesting the racial predisposition, while there has been no reported case from Thailand. EBV is a well-known oncogenic herpesvirus, mostly targeting B cells. However, T cells are also the main target of EBV-associated monoclonal T-cell proliferation, which is the distinct characteristic of this fatal entity. Its clinical course demonstrates a rapid progression with severe pancytopenia, fulminant multi-organ failure, and subsequent death, usually within days to weeks. Consequently, prompt diagnosis and treatment is crucial. **Case report:** A 15-year-old girl presented with high-grade fever and sore throat for 2 weeks. She had marked hepatosplenomegaly and pancytopenia. Bone marrow study was performed and revealed abnormal lymphoid cells expressing CD3, CD8, EBV-encoded RNA (EBER), and monoclonal rearrangement of T-cell receptor (TCR) genes. Unfortunately, she did not respond to multi-modality treatment comprising monoclonal antibody to CD52, chemotherapy, and antiviral drugs, and subsequently died 1 month after diagnosis.

Key Words : ● Epstein-Barr virus ● T-cell lymphoproliferative disease ● Adolescence

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Introduction

Epstein-Barr virus (EBV) is a member of herpesvirus family, which infects more than 90% of people worldwide. Most infected children are asymptomatic, while affected adolescents may present with acute infectious mononucleosis and recover spontaneously within a few weeks. The minority of EBV-infected patients may manifest as chronic active EBV infection (CAEBV), characterized by the presence of these following features: persistent severe illness more than six months; evidence of organ involvement such as pneumonitis, hepatitis or bone marrow hypoplasia; and detection of EBV antigens or

DNA in tissue.^{1,2} Generally, EBV infects B-cells using CD21 and major-histocompatibility-complex (MHC) class II on B-cell surface as a receptor and a cofactor, respectively. In most cases, EBV-infected B-cells are mainly eliminated by cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells, while remaining infected B-cells persist in the resting stage.^{1,3} The virus, however, can infect T-cells, NK-cells or epithelial cells. Therefore, it plays an important role in development of several malignancies, including nasopharyngeal carcinoma as well as lymphoproliferative diseases (LPDs), such as Burkitt's lymphoma, Hodgkin's disease and NK/T-cell lymphoma.

Case report

A 15-year-old previously healthy girl had protracted high-grade fever and sore throat for 2 weeks. She had been

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admitted and received broad-spectrum antibiotics. However, she developed pancytopenia with rapidly deteriorating clinical symptoms. She was subsequently referred to King Chulalongkorn Memorial Hospital. The patient denied previous hematologic abnormalities and medical history suggesting immunodeficient status. Physical examination showed injected pharynx, enlarged tonsils, oral candidiasis, hepatosplenomegaly and small multiple lymph nodes ranging from 0.8-1 cm at right cervical region. Initial laboratory tests demonstrated pancytopenia and abnormal liver function tests: Hb 9.9 g/dL, WBC $0.47 \times 10^9/L$, neutrophils $0.17 \times 10^9/L$, lymphocytes $0.17 \times 10^9/L$, platelet $48 \times 10^9/L$, PT 18.1 seconds (10.2-14.2 seconds), INR 1.47, APTT 39.3 seconds (22.8-31.2 seconds), total bilirubin 7.7 mg/dL, direct bilirubin 7.03 mg/dL, AST 684 U/L, ALT 272 U/L, ALP 555 U/L (38-126 U/L), albumin 3 g/dL, globulin 2.2 g/dL, triglyceride 586 mg/dL and LDH 4,335 U/L (105-490 U/L). Her EBV blood tests were consistent with reactivated EBV infection due to positive IgG of 52.732 U/mL (<11 U/mL), negative IgM of 2.546 U/mL (<11 U/mL) and EBV viral load of 24,200 copies/5 μ L (4.38 copies/5 μ L).

Computer tomographic (CT) scan of abdomen showed hepatosplenomegaly without space-taking lesions and subcentimeter lymph nodes at gastrohepatic and paraaortic areas. CT scan of chest showed multiple small ground glass nodules in both lower lungs.

Bone marrow study was performed and revealed hypercellular trilineage marrow with prominent histiocytes with increased erythrophagocytosis (Figure 1). Immunohistochemistry study demonstrated abnormal T-cells that were positive for CD3, CD8, TIA1, Granzyme B and BF1, but negative for CD5, CD56, CD30 and CD20. In situ hybridization (ISH) using oligonucleotide probe complementary to EBV-encoded RNA (EBER) yielded the positive result. The *TCR* gene detected by polymerase chain reaction (PCR) analysis demonstrated monoclonal rearrangement, consistent with the diagnosis of systemic EBV-positive T-cell lymphoproliferative disease of childhood.

She was initially treated with infusions of acyclovir

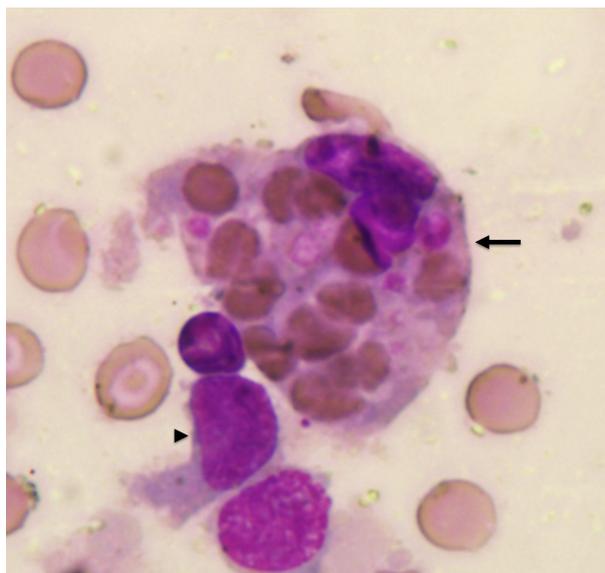


Figure 1 Phagocytosis of red cells and platelets (arrow) by an activated histiocyte and an atypical large lymphoid cell (arrow head).

and steroid. After diagnosis of systemic EBV+ T-cell LPD of childhood, the infusional regimen of EPOCH [vincristine 0.4 mg/m^2 (D1-D4), doxorubicin 10 mg/m^2 (D1-D4), etoposide 50 mg/m^2 (D1-D4), cyclophosphamide 750 mg (D5) and prednisolone 60 mg (D1-D6)] was initiated. Several broad-spectrum antibiotics and antifungal drugs were concurrently administered because of persistent neutropenic fever and radiographic findings suspecting for pulmonary infections. However, her symptoms had been deteriorating rapidly. Monoclonal antibody to CD52 (alemtuzumab) was started and resulted in transient clinical response with recovery of pancytopenia and reduced hepatosplenomegaly. Although allogeneic stem cell transplantation (alloSCT) was planned for the disease elimination, her disease became fulminant exacerbating before alloSCT was done. Intravenous immunoglobulin (IVIG) and the second course of EPOCH were prescribed, but she did not show any response and died ten days later.

Discussion

Systemic EBV-positive T-cell LPD of childhood affects several major organs and mainly occurs in children or young adults. It has a strong racial predisposition as

nearly all patients were Asian and Native American, while this entity was rarely found in western ethnic origin. Although some genetic defects in CTLs were proposed, no candidate genes have been identified.^{2,4} Its clinical course is extremely aggressive, with a median survival of less than 1 year. Patients usually develop hepatosplenomegaly and liver failure within a period of weeks and rapidly progress to multi-organ failure, coagulopathy, sepsis and death. Laboratory tests usually demonstrate profound pancytopenia and abnormal liver function tests. Rare patients manifest a subacute course of several months to a year progression.²

The histologic examination usually demonstrates infiltrating small lymphoid cells without significant cytologic atypia. However, cases with pleomorphic medium to large-sized lymphoid cells with striking morphologic atypia have been reported. Pathological findings of liver and spleen demonstrate mild to marked sinusoidal infiltration of lymphoid cells, accompanying by striking hemophagocytosis. The splenic white pulp

is usually depleted. The liver has prominent portal and sinusoidal infiltration, cholestasis, steatosis and necrosis. The architecture of lymph nodes is usually preserved with variable degree of histiocytosis and erythrophagocytosis. Bone marrow biopsy shows histiocytic hyperplasia with prominent erythrophagocytosis. The most typical phenotype of the neoplastic cells by immunohistochemistry technique is CD2+, CD3+, CD56- and TIA1+. The CD8 is usually positive in cases secondary to acute primary EBV infection, while CD4 is positive in the setting of severe CAEBV. Rare cases show double positive of CD4 and CD8. EBER is mandatorily positive, and *TCR* gene rearrangement shows monoclonality.⁵

Importantly, the diagnosis must be differentiated from other NK/T-cell LPDs, which may present with hepatosplenic lymphoma, accompanying by hemophagocytosis and rapid multi-organ failure. The immunophenotypic and genetic features for differential diagnosis are summarized in table 1.

There has been no established standard treatment

Table 1 The immunophenotypic and genetic features for differential diagnosis of systemic EBV-positive T-cell lymphoproliferative disease of childhood.

NK/T-cell lymphoproliferative diseases (LPD)	CD 3	CD4	CD8	CD56	EBER	TCR gene rearrangement	Other
Systemic EBV-positive T-cell LPD of childhood	+	CD4+,CD8- (severe CAEBV) CD4-,CD8+ (acute IM) CD4+,CD8+ (rare)		-	+	monoclonality ($\alpha\beta$)	CD2+ cytotoxic molecule+ (TIA1)
Aggressive NK leukemia	CD3- CD3E+	-	-	+	+	no monoclonality	CD2+ CD57- cytotoxic molecule+ Fas ligand+
Hepatosplenic T-cell lymphoma	+	-	-/+	+/-	-	monoclonality ($\gamma\delta$)	CD5- cytotoxic molecule+ (TIA1 and granzyme M) cytotoxic molecule- (granzyme B and perforin)
Peripheral T-cell NOS	+	CD4+,CD8- (nodal case) CD4+,CD8+ (some) CD4-,CD8- (some)		-/+	-	monoclonality ($\alpha\beta$)	CD5 and CD7- (frequently)

EBV = Epstein Barr virus; CAEBV = chronic active EBV infection; IM = infectious mononucleosis

for this rare entity. Treatment of systemic EBV+ T-cell LPD of childhood includes antiviral therapy (acyclovir or ganciclovir), immunomodulators (interferon- γ), chemotherapy (etoposide and dexamethasone) and alloSCT. Antiviral therapy, which mainly inhibits the replication of linear EBV DNA, and the immuno-chemotherapy do not demonstrate satisfactory response. Thus, most patients require alloSCT for elimination of disease.^{2,6} The outcome of alloSCT depends on the status of patients and the detection of EBV-DNA by PCR before induction for transplantation.² Some alternative immunotherapies have been used for EBV-associated LPDs. The rationale is EBV-seropositive persons have immunity against EBV. Haque T, et al. demonstrated that the response rate of EBV-positive post-transplantation lymphoproliferative disease (PTLD) treated with EBV-specific CTLs generated from EBV-seropositive blood was encouraging.⁸ However, the major obstacle to this therapy is graft-versus-host disease (GVHD) due to HLA incompatibility between donors and patients. Wang, et al. reported that using maternal lymphocytes could lower GVHD due to fetomaternal microchimerism leading to immunologic tolerance. They reported that 5 patients with systemic EBV+ T-cell LPD of childhood who received mother's lymphocyte infusion had significantly improved outcome without GVHD.⁹

Novel therapies are being developed to target EBV proteins. The expressed EBV antigens, which have roles in development and potentiation of lymphoproliferation, particularly latent membrane protein 1 (LMP1), LMP2 and Epstein-Barr virus nuclear antigen 1 (EBNA-1), might be the effective immunotherapeutic targets.¹⁰ In the future, the inhibition of molecular pathways in EBV-infected cell is the candidate for cure of this extremely aggressive disease.²

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รายงานผู้ป่วย

Systemic Epstein-Barr Virus-positive T-cell Lymphoproliferative Disease of Childhoodศรัณญา บุพพจารย์ธรรม, จินดารัตน์ ทองแถม¹ และ นพชาญ เอื้อประเสริฐ¹ภาควิชาสูติศาสตร์, ¹ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ: Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disease of childhood เป็นมะเร็งต่อมน้ำเหลืองที่พบน้อยมาก รายงานผู้ป่วยส่วนใหญ่มาจากประเทศในเอเชียโดยเฉพาะญี่ปุ่นและไต้หวันแสดงให้เห็นว่าปัจจัยด้านเชื้อชาติมีความสำคัญมากต่อการเกิดโรค อย่างไรก็ตามยังไม่เคยมีรายงานผู้ป่วยโรคนี้ในประเทศไทยมาก่อน EBV เป็นไวรัสในกลุ่ม herpesvirus ซึ่งทราบกันดีว่าสามารถก่อให้เกิดมะเร็งได้ โดยส่วนใหญ่การติดเชื้อมักจะเกิดกับ B-cell แต่สำหรับโรคนี้จะเกิดการติดเชื้อไวรัส EBV ใน T-cell นำไปสู่การเพิ่มจำนวนเซลล์ซึ่งมาจากต้นกำเนิดเดียวกัน ลักษณะทางคลินิกที่จำเพาะของโรคนี้ คืออาการทรุดลงอย่างรวดเร็วโดยจะมีเม็ดเลือดทุกชนิดต่ำลงอย่างมาก และการทำงานของระบบอวัยวะต่างๆอาจล้มเหลวนำไปสู่การเสียชีวิตภายในช่วงเวลาไม่กี่สัปดาห์หลังมีอาการ ดังนั้นปัจจัยสำคัญคือ การตรวจวินิจฉัยโรคอย่างถูกต้อง รวดเร็ว และการรักษาที่ทันเวลาที่ **รายงานผู้ป่วย** ผู้ป่วยหญิงอายุ 15 ปี มาด้วยอาการไข้สูงและเจ็บคอมา 2 สัปดาห์ ตรวจพบตับม้ามโต และภาวะ pancytopenia ผลการตรวจไขกระดูกพบเซลล์ผิดปกติซึ่งมีการแสดงออกของ CD3 และ CD8 ตรวจพบ RNA ของ EBV (EBER) และ monoclonal rearrangement ของยีน T-cell receptor ผู้ป่วยเสียชีวิตหลังจากวินิจฉัยประมาณ 1 เดือน แม้ได้รับการรักษาด้วย monoclonal antibody ต่อ CD52 ยาเคมีบำบัด และยาต้านไวรัส

Key Words : ● ไวรัส Epstein Barr ● มะเร็งต่อมน้ำเหลืองชนิด T cell ● วัยรุ่น

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