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


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
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 x10^9/L, neutrophils 0.17 x10^9/L, lymphocytes 0.17 x10^9/L, platelet 48 x10^9/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/5μL (4.38 copies/5μL).

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 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

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

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.

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>
<thead>
<tr>
<th>NK/T-cell lymphoproliferative diseases (LPD)</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD56</th>
<th>EBER</th>
<th>TCR gene rearrangement</th>
<th>Other</th>
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<tbody>
<tr>
<td><strong>Systemic EBV-positive T-cell LPD of childhood</strong></td>
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<td>+</td>
<td></td>
<td>-</td>
<td>+</td>
<td>monoclonality</td>
<td>CD2+</td>
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<td>CD4+,CD8- (severe CAEBV)</td>
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<td></td>
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<td>(αβ)</td>
<td>cytotoxic molecule+ (TIA1)</td>
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<td>CD4-,CD8+ (acute IM)</td>
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<td>CD4+,CD8+ (rare)</td>
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<tr>
<td><strong>Aggressive NK leukemia</strong></td>
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<td>CD3-</td>
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<td>-</td>
<td>+</td>
<td>no monoclonality</td>
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<td>CD3E+</td>
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<td>cytotoxic molecule+ Fas ligand+</td>
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<td><strong>Hepatosplenic T-cell lymphoma</strong></td>
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<td>+</td>
<td>-</td>
<td>+/-</td>
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<td>monoclonality</td>
<td>CD6</td>
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<td>(γδ)</td>
<td>cytotoxic molecule+ (TIA1 and granzyme M)</td>
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<td>cytotoxic molecule- (granzyme B and perforin)</td>
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<td><strong>Peripheral T-cell NOS</strong></td>
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<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
<td>monoclonality</td>
<td>CD5 and CD7- (frequently)</td>
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<td>CD4+,CD8- (nodal case)</td>
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<td>(αβ)</td>
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<tr>
<td>CD4+,CD8+ (some)</td>
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<td>CD4-,CD8- (some)</td>
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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. The outcome of alloSCT depends on the status of patients and the detection of EBV-DNA by PCR before induction for transplantation. 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. 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.

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. In the future, the inhibition of molecular pathways in EBV-infected cell is the candidate for cure of this extremely aggressive disease.

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

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Abstract: Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disease of childhood is a rare disease, mostly occurring in Asia, particularly Japan and Taiwan. It is known that the genetic factor is significant in the development of the disease. However, there have never been any reports of this disease in Thailand. EBV is a herpesvirus that is known to be associated with cancer. The majority of infections are in B-cells, but for this disease, EBV is infected in T-cells leading to an increase in cells from the same origin. The unique clinical features of this disease are a rapid deterioration of the patient, with a significant decrease in all types of blood cells, and the failure of various organs which can lead to death within a few weeks of symptoms. Therefore, the significant factors are the early and accurate diagnosis of the disease and timely treatment.

Case report: A female patient aged 15 years presented with a high fever and sore throat for 2 weeks. She was found to have enlarged liver and pancytopenia. Bone marrow examination found atypical cells and positive for CD3 and CD8. EBV (EBER) and monoclonal rearrangement of T-cell receptor were positive. The patient died after diagnosis of 1 month, despite monoclonal antibody to CD52, chemotherapy, and antiviral treatment.

Key Words: Epstein-Barr virus, T-cell lymphoproliferative disease, childhood.