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Case Report

Systemic Epstein-Barr virus positive T-cell lymphoproliferative disease of childhood with hemophagocytic syndrome

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Abstract: Epstein-Barr virus (EBV) associated lymphoproliferative disease (LPD) are commonly derived from B-cells, however, it is becoming more and more apparently that EBV can also infect T-lymphocytes. Systemic EBV positive T-cell LPD of childhood is rare and characterized by an extremely aggressive course and poor prognosis. Here, we report a 22-year-old female of systemic EBV positive TLPD with acute EBV infection and review the clinical features of this disorder. A 22-year-old previously healthy female without immunocompromised status presented with persisting coach and fever resistant to conventional therapies. Physical examination showed hemorrhage and hepatosplenomegaly. Laboratory examinations revealed severe pancytopenia, disseminated intra-vascular coagulopathy (DIC), and anti-EBV-IgM positivity. Peripheral blood smears and bone marrow investigation identified a number of atypical lymphocytes. Flow cytometry (FCM) did not show any significant evidence of leukemia or lymphoma. The lymph node biopsy showed apparent infiltration of lymphocytes, which expressed CD2+, CD3+, CD7+ and TIA1+. There was no CD20+ or CD56+ cells. EBV early RNA (EBER) was positive. Cytogenetic analysis showed a normal karyotype. T-cell receptor (TCR) gene rearrangement revealed a polyclonal pattern. The patient received prednisolone and IVIG therapy with a transient good condition, and then died of multiorgan failure one week after diagnosis.

Keywords: Epstein-Barr virus, lymphoproliferative disease, hemophagocytic syndrome

Introduction

Epstein-Barr virus (EBV) is implicated in the pathogenesis of lymphoproliferative disease (LPD). EBV-associated LPD are common in immunocompromised patients, especially in the post-transplant and HIV-associated LPD [1, 2]. Typically, EBV-associated-LPD is derived from B-cells, such as Hodgkin disease and Burkitt lymphoma [3]. However, it is becoming more and more apparently that EBV can also infect T-lymphocytes, which is supported by patients with chronic active EBV infection (CAEBV) or EBV positive T-cell non-Hodgkin's lymphoma [4].

Systemic EBV positive T-cell LPD (TLPD) of childhood and hyroa vacciniforme-like lymphoma are the two major types of EBV positive TLPD of childhood according to World Health Organization (WHO) classification [5]. The clinical course and prognosis are quite different between the two diseases. Systemic EBV positive TLPD of childhood is rarely seen and characterized by an extremely aggressive course and poor prognosis [6]. Here, we report a fatal case of systemic EBV positive TLPD of childhood and review the clinical features of this disorder.

Case presentation

The patient, a 22-year-old female was admitted for a persistent coach and fever for 15 days resistant to conventional therapies. She had no history of immunological abnormalities prior to experiencing these symptoms. On physical examination, she presented with hemorrhage in the bilateral conjunctiva and hepatosplenomegaly, no enlarged lymph nodes were record-

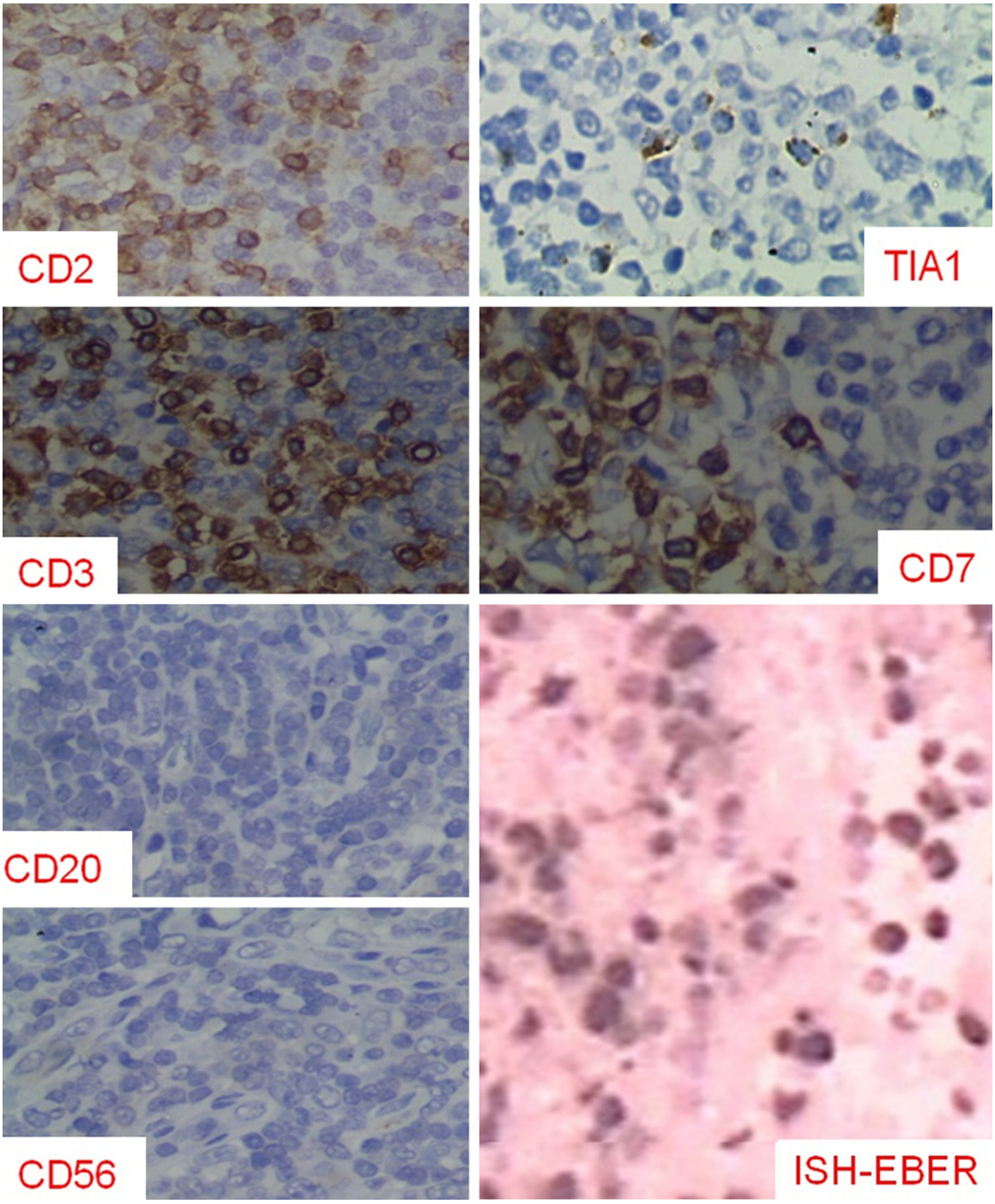

Figure 1. Pathological findings on lymph node biopsy. CD2, CD3, CD7, CD20, CD56, TIA1 immunostains and Epstein-Barr encoded RNA (EBER) in situ hybridization are shown.

ed. Laboratory examinations revealed severe pancytopenia (hemoglobin 9.3 g/dL, white blood cells 2.2×10^9 cells/L, neutrophils 0.4×10^9 cells/L, lymphocytes 1.57×10^9 cells/L, platelets 93×10^9 cells/L), a number of atypical lymphocytes in the peripheral blood smear, increased live function and LDH, signs of disseminated intra-vascular coagulopathy (DIC), and anti-EBV-IgM positivity, and normal renal function. EBV-DNA was 2.8×10^6/copies. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) were in normal

range. Antinuclear antibody test and human immunodeficiency virus antibody test were negative. Blood and urine cultures did not grow any bacteria or fungi. Computed tomography (CT) scan of chest-abdomen showed diffuse pulmonary infiltrates and splenomegaly. Bone marrow aspiration revealed marked proliferation of small-sized lymphocytes with irregular-shaped nuclei with lobated and moderately coarse chromatin, inconspicuous nucleoli and hemophagocytosis. Results of bone marrow biopsy showed it was infiltrated with numerous atypical lymphoid cells and mild hemophagocytes. Flow cytometry (FCM) of bone marrow mononuclear cells did not show any significant evidence of leukemia or lymphoma. Empirical antibiotic treatment of high dose Piperacillin-Tazobactam and Fluconazole were prescribed. Three weeks later, the patient's symptoms progressed. Although coagulation parameters were partially corrected, the fever and severe peripheral blood cytopenia persisted, enlarged lymph nodes were recorded. Positron emission tomography-CT (PET-CT) scan showed diffuse multiorgan infiltrates in the liver, spleen, gastrointestinal, pancreas, kidney, womb, ovary, mediastinum, lymph nodes and bone marrow. The second bone marrow aspiration and biopsy were performed; however, the finds were similar to those previously observed. The lymph node biopsy showed apparent infiltration of lymphocytes. Immunohistochemistry (IHC) investigation showed these lymphocytes were CD2+, CD3+, CD7+ and TIA1+ (**Figure 1**). There was no CD20+ or CD56+ cells. In situ hybridization (ISH) for EBV early RNA (EBER) was positive in the majority of lymphoid cells. Cytogenetic analysis showed a normal karyotype. Analysis for T-cell receptor (TCR) gene rearrangement revealed a polyclonal pattern. Based on the above evidences, an ultimate diagnosis of systemic EBV positive T-cell LPD of childhood was conformed. Our patient underwent persisting fever, pancytopenia and DIC, and was initially treated with prednisolone and intravenous immunoglobulin (IVIG) therapy. After a short time of relative good condition, the patient developed a respiratory and heart failure, and then succumbed to multiorgan failure one week after diagnosis.

Discussion

Systemic EBV positive TLPD is rare in western [5, 7]; the majority of records previous reported are in Eastern Asia, especially in Japan and Taiwan, mostly in children and young adults [7, 8]. Immune surveillance defect is central to this disorder [2]. In this study, we reviewed the clinical features of the disease. On reviewing all the described cases, we found that clinical, morphological, immunohistochemical and molecular biological analyses were conducted to perform a right diagnosis. We revealed clonal proliferation EBV-infected T cells express an activated cytotoxic phenotype CD4+ and/or CD8+. The most typical phenotype of the atypical lymphocytes is CD2+, CD3+, CD8+, CD20-, CD56-, and TIA+ [9]. The neoplastic cells conserved polyclonally/oligoclonally/monoclonally TCR gene and EBER positive. Most of the cases have an aggressive clinical course and high mortality [8, 10, 11]. The main clinical symptoms are high fever, skin rash, jaundice, diaeehea, pancytopenia, hepatosplenomegaly, hemophagocytic syndrome and coagulopathy. The common involved cites are the liver, spleen, lymph nodes and bone marrow, rarely involved the skin, heart sand lungs. In our patient, the clinicopathological features and course are similar to those that have been described. However, it is interesting the pathological finds are quite different between bone marrow and lymph nodes, indicating that might something underlying need to investigate it.

At present, there is no specific treatment; EBV cell-based immunotherapy was most widely applied. Modulation of the immunosuppressive treatment is recommended as a first-line approach [6]. Chemotherapy and monoclonal antibodies are the optional choices offered to those who fail the in immunosuppression [6]. The use of rituximab has significantly changed the therapeutic results, but is only indicated in B-cell post-transplant lymphoproliferative disorder (PTLD). Chemotherapy still remains the only approach to Systemic EBV positive TLPD. CHOP-like regimens are currently recommended option reduce the morbidity and mortality while also related with a high relapse rate [6, 8, 10]. Adoptive transfer of donor-derived or autologous EBV-specific CTLs (EBV-CTLs) has been successful used as a cellular immunotherapy to prophylaxis and treat the patients with of EBV-related PTLDs receiving allogeneic stem cell transplantation [12]. Maybe allogeneic hematopoietic stem cell transplantation is a cure for T-cell PLD following an acute EBV infec-

tion. In the present case, we advised usage of chemotherapy to treat this patient but it was refused. The patient received prednisolone and IVIG therapy with a transient improvement and die in one week after diagnosis.

In conclusion, we reported an uncommon case of Systemic EBV positive T cell PLD of childhood following acute EBV infection. The neoplastic lymphocytes expressed a cytotoxic T-cell phonotype. The patient has an extremely aggressive clinical course and resulted in mortality. Further researches are required to explore an accurate early diagnosis and improve the therapeutic strategies for this disease.

Disclosure of conflict of interest

None.

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