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Case Report

Successful management of a case of systemic Epstein Barr-virus-positive T-cell lymphoma of childhood

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Abstract: Systemic EBV-positive (EBV$^+$) T-cell lymphoma of childhood (systemic EBV$^+$ TCL of childhood) is a kind of mature T lymphocyte cell and NK cell neoplasms that extremely rare but life-threatening. Efficacy of conventional chemotherapy is limited, and no recommended guidelines currently are available. Here we report a 25-year-old patient presented with persistent fever, cervical lymphadenopathy and pancytopenia. The biopsy of enlarged cervical node showed infiltration of lymphocytes, which expressed CD3, CD4, CD8, Bcl-2, MUM-1 with scattered positivity of CD20, PAX5, Bcl-6, CD30 as well as EBV-encoded RNA (EBER). IG κ-chain and TCR β-chain rearrangement were also detected. Ultimately, the diagnosis of systemic EBV$^+$ TCL of childhood coupled with pan large B-cell infiltration was rendered. He experienced CHOP-like chemotherapy but had a poor response. And then rituximab was added for high load of EBV-DNA. Interestingly, the case was successfully controlled by 4-course of R-CHOP-like regimen, which suggested that such treatment prescription may do some help to this kind of patients. It is a rare case, to the best of our knowledge, that systemic EBV$^+$ TCL of childhood was successfully treated with R-CHOP-like regimen.

Keywords: EBV, systemic, lymphoma, R-CHOP, treatment, T-cell

Introduction

The 4th edition of the WHO classification of hematopoietic and lymphoid neoplasms in 2008 classified systemic EBV-positive T-cell lymphoproliferative disorder (LPD) of childhood as a subset of mature T-cell and NK-cell neoplasms [1]. However, LPD is no longer referred to this kind of lymphoma for a fulminant clinical course, and it was renamed as systemic EBV$^+$ T-cell lymphoma of childhood (systemic EBV$^+$ TCL of childhood) in 2016 WHO update of the current 4th edition [2]. The life-threatening disease primarily occurs in children and young adults in Asia and Latin American which characterized by clonal proliferation of EBV-infected T cells with an activated cytotoxic phenotype [3]. And quite a few patients presented with prolonged fever, weight loss, hepatosplenomegaly, pancytopenia, peripheral lymphadenopathy and high LDH levels [4]. The most involved sites are liver, spleen, lymph node and bone marrow. It can occur shortly after primary acute EBV infection, or in the setting of chronic active EBV infection (CAEBV) with a median survival of only a few months despite intensive chemotherapy [5]. To note, the young adult group is associated with more aggressive process and worse prognosis than those of childhood [6].

Morphologically, pleomorphic medium- to large-sized lymphoid cells with irregular nuclei and frequent mitoses are detected in tissues. The most common typical phenotypes are CD2$^+$, CD3$^+$, CD56$^-$ and TIA$^+$ [7]. Neoplastic cells have monoclonal rearrangement of TCR genes, and are consistently positive for EBER in situ hybridization.

Although antiviral therapy, immunosuppressive agents and intensive chemotherapy may delay its progression, no effective treatment has been suggested for this kind of lymphoma [8, 9]. To the best of our knowledge, successful treatment with R-CHOP-like regimen hasn't ever been reported yet. In this report, we share the experience of diagnosis and treatment.

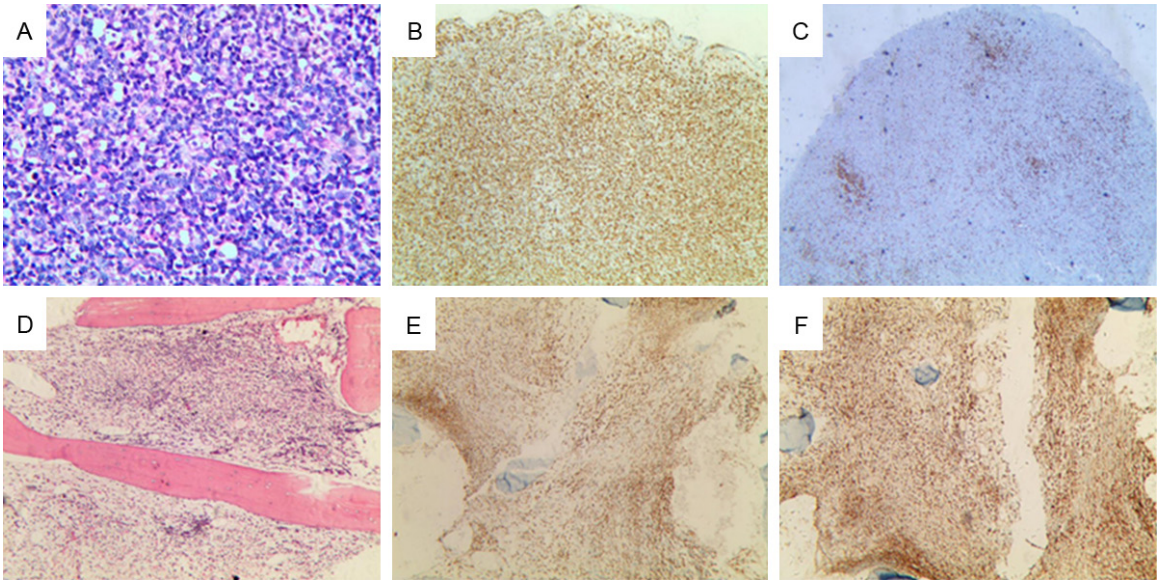

Figure 1. Histilogic features of systemic EBV+ T-cell lymphoma of Childhood. (A) The haematoxytoxylin and eosin stain (H&E) in lymph node section showed diffuse infiltration with lymphoid cells (×400). (B) Immunohistochemistry showed a strong reactivity with CD3 (original magnification, ×100) and (C) scattered activity with CD20 (×100) in lymph node section. (D) Bone marrow trephine showing infiltration with lymphoid cells (H&E stain, ×100). (E) Immunohistochemistry indicating that most lymphocytes express CD3 (×400) and (F) CD4 (×400) in bone marrow.

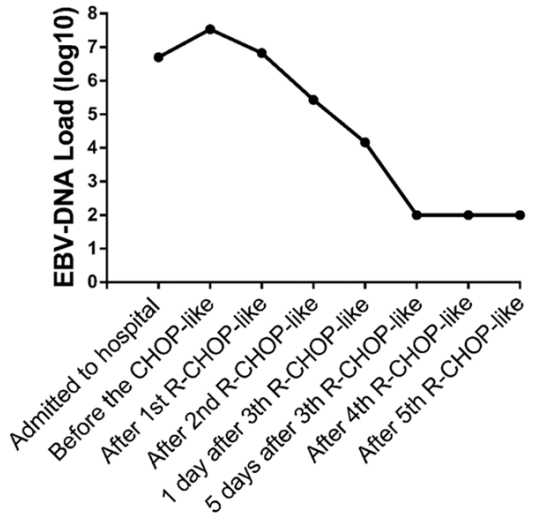

Figure 2. Logarithmic graph showed developing trend of EBV-DNA in patient's peripheral blood following treatment.

Case presentation

A 25-year-old man firstly presented with persisting fever and cervical lymphadenopathy for 2 weeks in local hospital in Oct. 2013. There was no evidence of underlying immunodeficiency. Laboratory results showed decreased levels of hemoglobin (75 g/L) and platelets (58*10^9/L), while serum ferritin was 1629.01 ng/ml. He was empirically treated with antivirus therapy, however, it did not work and hemoglobin and platelets continued descending. Then he was transferred to our center. Laboratory examinations showed pancytopenia (hemoglobin 77 g/L, white blood cell 2.65×10^9 cells/L and platelet 56×10^9 cells/L), high level of LDH (436.1 u/L; range, 100-225), and elevated β2-MG (5.89 ml/L; range, 0.00-2.16). Heterophil agglutination (Paul-Bunnell) test was negative. The load of EBV-DNA in the peripheral blood was 5*10^6 copies/ml. Physical examination indicated that multiple sites of lymphadenopathy on bilateral cervical and groin together with hepatosplenomegaly. And the findings were further confirmed by radiological analysis. ^{18}F-FDG Positron Emission Tomography-CT (PET-CT) scan also revealed intensive multi-organic infiltrations in liver, spleen, retroperitoneum as well as mediastinum together with the maximum SUV (standardized uptake value) of 10.1. A month later, enlarged bilateral carotid, peritoneal cavity, mediastinum and bilateral axilla nodes were observed on contrast-enhanced CT scan.

Pathological analysis

Biopsy of left cervical lymph node revealed that the majority of atypical lymphocytes expressed

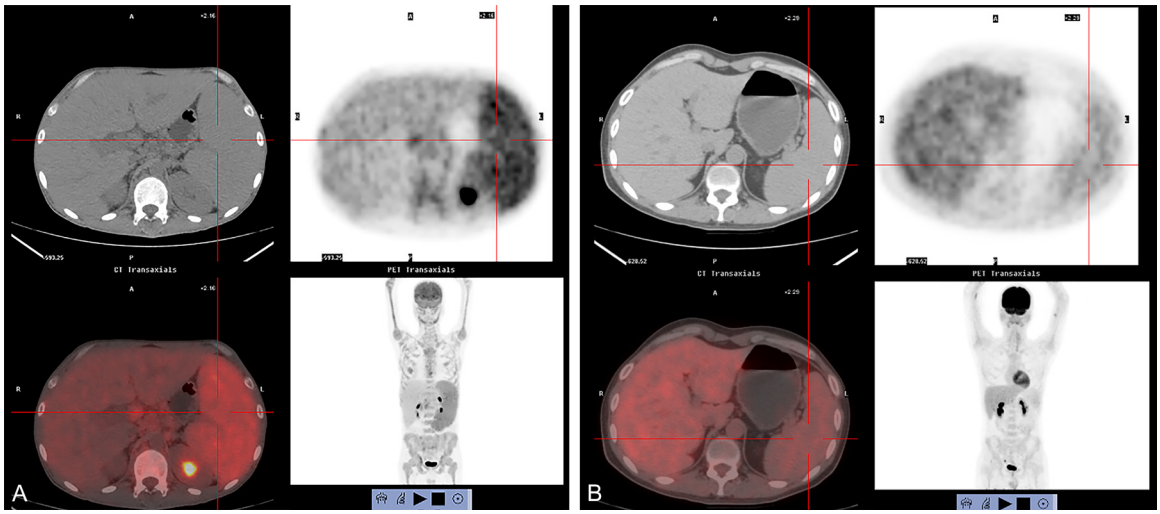

Figure 3. Comparisonof metabolism in liver and spleen with PET-CT. A. Prior to treatment with R-CHOP. B. After 4-course treatment with R-CHOP regimen.

CD3, CD4, CD8, Bcl-2, MUM-1 with scattered positive CD20, PAX5, Bcl-6 as well as CD30. FDC expressed CD21, and some plasma cells were positive for κ and λ. Ki-67 rate was about 80% (**Figure 1A-C**). EBER was positive in situ hybridization. Cytogenetic analysis showed Ig κ and TCR β gene rearrangement, which revealed a monoclonal pattern. The diagnosis of systemic EBV+ TCL of childhood coupled with pan large B-cell infiltration was taken into consideration. Moreover, characteristics of aspiration from bone marrow were consistent with cervical lymph node, suggesting that bone marrow had been involved (**Figure 1D-F**).

Chemotherapy and follow-up

According to the clinical symptoms and pathological results, final diagnosis of systemic EBV+ T-cell lymphoma of childhood was confirmed. The patients initially received CHOP-like regimen which consisted of cyclophosphamide (750 mg/m^2 d1), doxorubicin (60 mg/m^2 d1), vindesine (4 mg d1) and prednisone (40 mg d1-5). Effect was limited and symptoms progressed, then rituximab, a CD20 positive monoclonal antibody, (375 mg/m^2 qd*d1) was proposed for EBV. After the first cycle R-CHOP-like regimen, clinical symptoms were remarkably alleviated. Furthermore, the viral load was decreased to 1*10^6/ml. After 3 cycles of R-CHOP-like regimen, the load of EBV-DNA turned negative (<10^2 copies/ml). **Figure 2** is a semi-logarithmic graph of fluctuation of EBV-DNA in his peripheral blood following treatment. Re-evaluation after 4 cycles of the R-CHOP-like regimen revealed a complete remission, with no evidence of disease by imaging studies and flow cytometry bone marrow analysis IHC negative. Furthermore, the metabolism of liver and spleen decreased to normal level when therapeutic cycles were finished as illustrated with PET-CT (**Figure 3**). He is still free of lymphoma at the latest follow up on December 1, 2016.

Discussion

Systemic EBV+ TCL of childhood in non-immunocompromised patients is rarely encountered in clinical practice. Almost all cases have an aggressive course, which result in high mortality. At present, there is no specific treatment. According to previously reported cases, the disease showed poor response to EBV-specific cytotoxic T-lymphocyte therapy or chemotherapy [8, 10-12]. Majority of patients succumbed to multiple organ failure even though they received CHOP or CHOP-like chemotherapy. Recently, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has begun to be an alternative choice to this aggressive lymphoma and reconstitute a normal immune system [13, 14]. In spite of improving prognosis, high treatment-related mortality often accompanies with allo-HSCT. In our case, the patient also received CHOP-like regimen with no signs of improvement, but administering rituximab alleviated the poor condition. The young patient has been

in durable remission since last consolidation therapy, rituximab may play an important role in efficacy.

As we can get from the immunohistochemistry prior to treatment with rituximab, though scattered, there are atypical lymphocytes expressed CD20. This partly large B-cells infiltration in lymph nodes and peripheral organs were effectively depleted by rituximab and these EBV gene products may activate weak cytotoxic T-lymphocyte activity [15]. Three different mechanisms have been proposed for the elimination of B cells by rituximab including complement dependent cytotoxicity, antibody-dependent cellular cytotoxicity and stimulation of the apoptotic pathway [16]. Concurrently, a small population of T cells co-expressing CD20 was observed in all individuals [17]. In addition to B cells, $CD20^+$ T-cells were also completely eliminated after application of rituximab [18].

Studies on oncogenesis revealed that LMP-1 has been postulated to prohibit apoptosis by upregulating protein bcl-2 and mediating the activation of NF-κB signaling pathway among EBV-associated LPD [4]. Rituximab inhibits the constitutive NF-κB activity and down-regulates the expression of Bcl-2, which results in the sensitization of tumor cells to both chemotherapy and Fas-induced apoptosis [19].

Our patient presented with persistent fever, weight loss. A variety of potent cytokines including IL-10 and IL-2 as well as IFN-γ are induced by EBV-infected lymphoid cells [4]. Findings on patients after treatment with rituximab showed that rituximab resulted in a significant decrease in T-cell activation markers, inflammatory cytokine production as well as proliferative capacity [20]. With the B symptoms controlled by declining the production of cytokine, the condition of the patients got better. Whereas the therapy of this lymphoma is complex, at this point, we have not yet found out the exact pathogeny.

Conclusion

With many issues left to be resolved, finding ways to diagnose and treatment of systemic EBV^+ TCL of childhood remains a major clinical endeavor. In our case, the patient was timely diagnosed and effectively treated with R-CHOP regimen, indicating R-CHOP-like regimen may be a reasonable choice for those who express CD20 lymphocytes in tissue.

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Disclosure of conflict of interest

None.

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