Adult systemic EBV-positive T-cell lymph-proliferative disease requiring clinical and pathological as well as immunohistochemical features to confirm the diagnosis: a case report

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Abstract

Introduction: We present a rare case of adult systematic EBV-positive T-cell lymph-proliferative disease in a patient with high fever, yellow sclera, bilateral tonsils enlargement, hepatosplenomegaly, superficial lymphadenopathy, nose-pharynx neoplasm. We are reporting this case with the aim of drawing attention to a single disease with different stages of development; the Physicians need to correctly understand the development and changes of the disease.

Case presentation: A 21-years old Chinese woman in her late 20 days presented with high fever, yellow sclera, bilateral tonsils enlargement, hepatosplenomegaly, superficial lymphadenopathy, nose-pharynx neoplasm. The other routine test showed pancytopenia, serum EBVCA-IgM was positive, bone marrow smear showed heterotype lymphocytes accounting for 3.5%, lymph nodes immunophenotyping exhibited the NK/T cells hyperplasia, pathological examination of cervical lymph nodes showed atypical hyperplasia of lymph node T area, adult systematic EBV-positive T-cell lymph-proliferative disease was clinically diagnosed.

Conclusion: Adult systematic EBV-positive T-cell lymph-proliferative disease is a spectrum of disease that includes different stages of development from benign proliferation progress to malignant proliferation. The physicians and pathological physicians need to combine with clinical and laboratory findings as well as pathological and immunohistochemical features for making the correct diagnosis.

Keywords: Epstein-Barr virus; lymph-proliferative disease; NK/T cell lymphoma; infectious mononucleosis

Introduction

Systemic Epstein-Barr virus (EBV)-positive T-cell lymph-proliferative disease exists mainly in Asia and South America,[1, 2] and very rare in adults.[3, 4] the disease is associated with poor prognosis and can be life-threatening, the clinical manifestations, pathological types and cell clones show diversity and pedigree characteristics, namely a single disease has different stages of development, which is neither different from benign lesions as infectious mononucleosis (IM), nor the typical lymphoma sample lesions.[5]

Case presentation

A 21-years old Chinese woman was admitted to our hospital on Sep. 1 for a 20 days history of high fever, fatigue, yellow sclera, bilateral tonsils enlargement, hepatosplenomegaly, superficial
lymphadenopathy, nose-pharynx neoplasm. She had no any medical history. Peripheral blood examination showed pancytopenia, liver function tests: (ALT 417 U/L, AST 231 U/L, TBA 209.7 µmol/L, TB 107.6 µmol/L), serum EBVCA-IgM test was positive. The other routine tests were negative (bacterial culture, virus research by immunological or molecular methods, tumor antigen, heterophil agglutination test, etc). Imaging examination exhibited bronchitis, bilateral axillary lymph node enlargement, and obvious hepatosplenomegaly. Cytological examination of bone marrow exhibited the karyocytes hyperplasia (fig. 1), heterotype lymphocytes accounted for 3.5%, and hematophagocytes was visible. By lymph nodes immunophenotyping, it was found that CD56+ cells occupied 58.75% of karyocytes, and T-antigens such as CD2, CD3 and HLA-DR were also simultaneously expressed in some CD56+ cells which may be considered as abnormal T/NK cells. Pathological examination of cervical lymph nodes showed cells proliferated markedly, and featured the lymphoma morphologically, immunohistochemistry studies showed that infiltrated cells were EBER (+), CD3 (+), Ki67 (20% +), CD20 (+), TIA-1 (+), CD5(+) , CD8 (+), CD2 (-), CD4 (-), CD30 (-), MPO (-), CD34 (-) (fig. 2), T cells marker CD2 was lost, indicating the tumorigenesis, however, the absence of tumor-related immune markers did not favor lymphoma, atypical hyperplasia of lymph node T area was pathologically diagnosed.

On Sep. 18, neoplasma was found at patient’s pharynx nasalis, and the patient was subjected to tonsillectomy and the neoplasma biopsy. Pathological examination of the nasopharynx and bilateral tonsil showed chronic inflammation change. On Sep. 28, patient’s body temperature was still rising (highest 40°C), a plenty of pus emboli adhered to the posterior wall of nasopharynx. Nasopharynx magnetic resonance imaging did not show a malignancy of the lesions. Antigen receptor gene rearrangement test and immune globulin heavy chain (IgH) and light chain (Ig κ and Ig λ) gene rearrangement studies by PCR failed to demonstrate conclusive evidence for a clonal B or T-cell population. The conventional chromosomal study revealed normal karyotype. Given the changes in patient’s disease condition, ASEBV+T-LPD was clinically diagnosed. During hospitalization, the patient was given anti-infection treatment (cefepime, fluconazole, etc.), the body temperature was returned to the normal level, jaundice disappeared, and there was no systematic superficial lymphadenopathy or hepatosplenomegaly.

Discussion
The incidence of EBV infection in the crowd is 90%, and EBV is the common pathogenic factor of many diseases, including infectious mononucleosis (IM), Burkitt lymphoma, NK/T cell lymphoma, etc. In addition, EBV is closely related to some lymphoproliferative disorders (EBV+LPD) that are between tumor and non-cancer. WHO made a classification of EBV lymphatic proliferating disease in 2008, and put forward “systemic Epstein-Barr virus-positive T-cell lymphoproliferative disease of childhood (CSEBV+T-LPD)” that exists mainly in children. AEBV+T-LPD is very rare, and characterized by EB virus-infected T-cell proliferation with cytotoxic phenotype. Some scholars propose that in the early stage of CSEBV+T-LPD, EB virus-infected cells showed polyclonal or oligoclonal proliferation, and in the later often progressed to monoclonal proliferation, meaning that CSEBV+T-LPD essentially is a spectrum of disease that includes different stages of development from benign proliferation progress to malignant proliferation. The patient reported in this paper is clinically characterized by subacute onset, moderate to severe fever, systemic lymphadenopathy, hepatosplenomegaly, swollen tonsils, bronchitis, jaundice, pancytopenia, EB virus infection, proliferative bone marrow. Pathological examination of lymph nodes revealed expansion of the interfollicular area which was diffusely infiltrated by a polymorphous infiltrate of small-to-medium-sized lymphocytes, plasma cells and immunoblasts. Immunohistochemically, infiltrated cells had strong, diffuse positivity for CD3, CD8, CD5, TIA, EBER, and CD20 stained some rare admixed normal-appearing B-lymphocytes. The infiltrated cells were negative for CD2, CD4, CD30, CD34. Overall, the pathology and immunohistochemistry studies of cervical lymph nodes present early stage of the disease, which is coincidence with A1 types of the classification of EBV+T/NK-LPD proposed by Ohshima.

In our case, the patient showed bilateral tonsil enlargement, bone marrow smear showed heterotype lymphocytes accounted for 3.5%, and lymph nodes immunophenotyping demonstrated that T/NK cells proliferation. With the disease progress, nose-pharynx neoplasm presented, and the diagnosis of NK/T cell lymphoma may be incorrectly achieved according to clinical features and immunohistochemical analysis. NK/T cell lymphoma characteristically arises in the nasal cavity or surrounding structure and presents as a destructive midline facial lesion, the tumor cells express CD2, CD56, cytotoxic granule proteins, cytoplasmic CD3, TIA-1, but CD3 (-). As infiltrated cells are small-to-medium-sized lymphocytes among them scattered large cells with
different degrees atypia, mainly express CD8, Ki67 (<30%), and the cells positive for CD3 are not crowded, we should be on guard against the possibility of progression to NK/T cell lymphoma.\textsuperscript{[8]}

The differential diagnosis of ASEBV+T-LPD vs infectious mononucleosis (IM) is raised because of the atypical pathology of cervical lymph nodes. Chen\textsuperscript{[11]} and Zhou\textsuperscript{[12]} reported the clinical and pathological diagnosis of IM, and its characteristic pathologic changes include expansion of the paracortical area, mottled morphologically and B cell differentiation spectrum change (lymphoblasts, immunoblasts, plasmacytoid cells, mature plasma cells). In the lesion, CD3 is positive, and CD20 and CD30 show the signals to varying degrees and distributed scatteredly. However in our case the pathological examination of lymph nodes did not demonstrate the typical pathological changes of IM, namely B cell differentiation spectrum change.

**Conclusion**

To avoid overdiagnosis and under-diagnosis, we need to believe that a single disease has different stages of development, and the combination of clinical and laboratory findings as well as pathological and immunohistochemical features is beneficial for the correct diagnosis.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**

The authors declare that they have no competing interests

**Authors' contributions**

YouPing Wang collected specimens, analyzed results and wrote the manuscript; XinYue Liu designed this study and reviewed the manuscript; XiaoMei She performed experiments; Lin Sun collected pathological picture

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**Figure legends**

Fig. 1 Cytological examination of bone marrow A: Ingestion of an erythrocyte into a macrophage in the aspirated bone marrow smear; B: Morphological changes of heterotype lymphocytes in bone marrow.

Fig. 2 Biopsies of cervical lymph nodes revealed that the paracortical area was diffusely infiltrated by a polymorphous infiltrate of small-to-medium-large-sized (transformed) lymphocytes, immunoblasts, and mature plasma cells. These cells were chromatin-rich, increased in size and had enlarged nucleus. The infiltrated cells stained positive for EBV latent membrane protein antigen by in situ hybridization, CD3, Ki67, CD20, respectively, and negative for CD2.