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Case Report

An adult case of systemic Epstein-Barr virus-positive T/natural killer-cell lymphoproliferative disorder with good outcome

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Abstract: Epstein-Barr virus-positive T/natural killer (NK)-cell lymphoproliferative disorder (EBV+T/NK LPD) encompasses a heterogeneous group of disorders that have a common feature with excessive lymphoid proliferation of mainly T cells and/or NK cells. This disease is rare, predominantly affects children and young adults, and associated with high mortality. Herein, we report a case of EBV+T/NK LPD that occurred in an old woman with good outcome. The patient presented with fever, splenomegaly, and pancytopenia. Computed tomography (CT) scan of the abdomen showed splenomegaly. The clinical impression was a malignant tumor of spleen, so splenectomy was performed. Microscopically, the architecture of the spleen was preserved. The white pulp Malpighian corpuscles were atrophied. The red pulp showed intact sinusoids and pulp cords with increased cellular infiltrate. The proliferating lymphoid cells were mostly small lymphoid cells with minimal or no nuclear atypia, mixed with rare medium-sized or large cells. Immunohistochemical study and in-situ hybridization showed that the EBER-positive lymphoid cells were positive for CD3 and CD56. They were also positive for cytotoxic molecules, such as T-cell restricted intracellular antigen (TIA1), granzyme B. The case exhibited polyclonal rearrangement of T-cell receptor gene (TCR) by polymerase chain reaction (PCR) studies. Without radiotherapy and chemotherapy, the patient is alive and well with no evidence of disease 25 months after surgery.

Keywords: Epstein-Barr virus, T/natural killer-cell, lymphoproliferative disorder

Introduction

Epstein-Barr virus (EBV) is a ubiquitous virus that can cause both acute and chronic active infections. Most persons have a chronic asymptomatic infection with EBV, but the virus has been associated with a number of malignancies and can infect B cells, T cells, NK cells, and epithelial cells [1]. Rare persons infected with EBV develop a life-threatening condition termed chronic active EBV disease (CAEBV). This disease has been defined as a systemic EBV-positive lymphoproliferative disease (EBV+LPD) characterized by fever, lymphadenopathy, and splenomegaly developing after primary virus infection in patients without known immunodeficiency [2]. Affected patients have high levels of EBV DNA in the blood, histological evidence of organ disease, and elevated levels of EBV RNA or viral proteins in affected tissues.

EBV+T/NK LPD encompass a heterogeneous group of disorders that have a common feature with excessive lymphoid proliferation of mainly T cells and/or NK cells. This disease is rare, predominantly affects children and young adults [1, 3-7], and associated with high mortality. Herein, we report an adult case of EBV+T/NK LPD with good outcome.

Clinical history

74-year-old female was admitted with a persistent fever for more than 6 months. On admission, her temperature was 39.1°C and ranged from 37.2°C~39.3°C, leukocyte count was 1,500 units (segmented neutrophils 69.7%, lymphocytes 21.5%), hemoglobin was 114 g/L, and platelet count was 40,000/μL. Physical examination revealed marked splenomegaly, and no enlarged lymph nodes was found. Blood and urine cultures did not grow any bacteria or

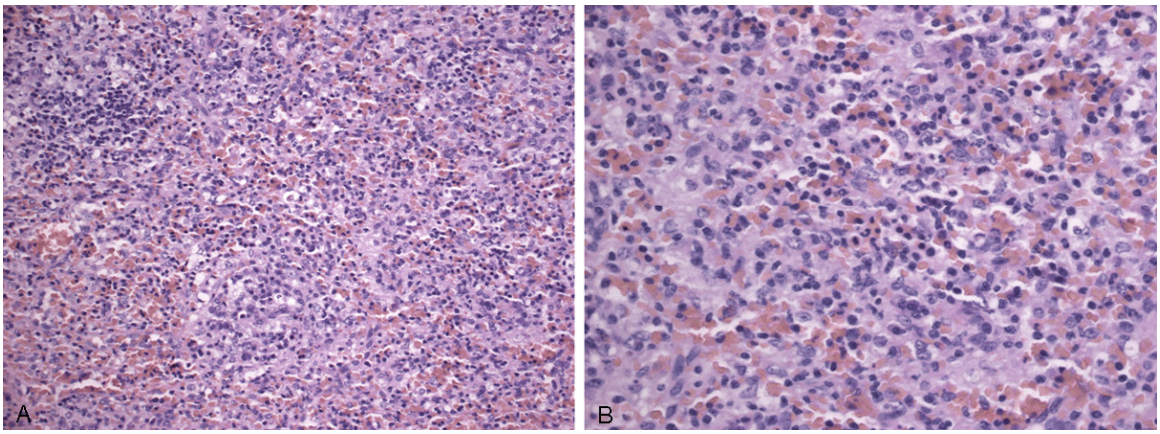

Figure 1. Histologic findings. The spleen shows depletion of white pulp and prominent sinusoidal small lymphoid infiltrate (A, hematoxylin and eosin, x200). B: The lymphocytes lack significant cytologic atypia (right, hematoxylin and eosin, x400).

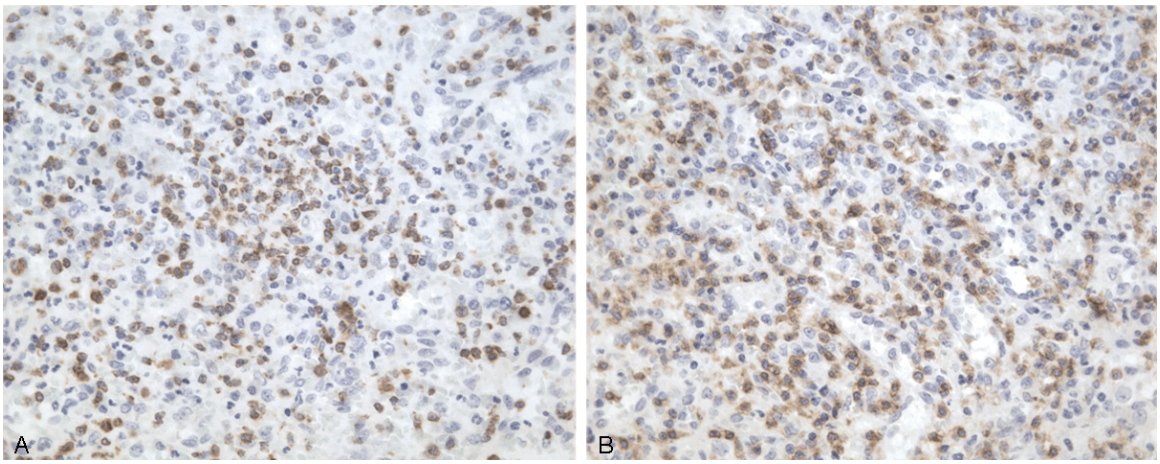

Figure 2. Immunophenotypic findings. The infiltrated lymphocytes of spleen are predominantly CD3+ (A, immunohistochemistry, x400) and some lymphocytes are also positive for CD56 (B, immunohistochemistry, x400).

fungi. Computed tomography (CT) scan of the abdomen showed splenomegaly. Antibiotic treatment had no effect for two weeks. The clinical impression was a malignant tumor of spleen, so splenectomy was performed. After surgery, the serologic tests for EBV were investigated retrospectively and showed EBV viral capsid antigen (VCA)-IgG (+), EBV VCA-IgM (–), EBV- early antigen (EA) (+). Seven days after surgery, her symptoms and signs had resolved without any other special therapies and she was discharged from the hospital. She was followed for 25 months and remained well clinically over the entire follow-up period.

Pathological findings

Grossly, the spleen was marked enlarged with measuring 18*15*10 cm and 435 g. There were no mass on cut surface. Microscopically, the architecture of the spleen was preserved. The white pulp Malpighian corpuscles were atrophied, whereas the red pulp showed intact sinusoids and pulp cords with prominent lymphoid infiltration (**Figure 1A**). The infiltrating lymphocytes were mostly small lymphoid cells with minimal or no nuclear atypia (**Figure 1B**), mixed with rare medium-sized or large lymphoid cells. Immunoblasts and plasma cells were not prominent. Bone marrow biopsy was available and showed no abnormality.

Immunohistochemical (IHC) studies showed the infiltrated lymphocytes of spleen was composed predominantly of T-cell lineage, with CD3+ (**Figure 2A**) and CD20-. CD20 stained attenuated residual B-cell areas in the spleen.

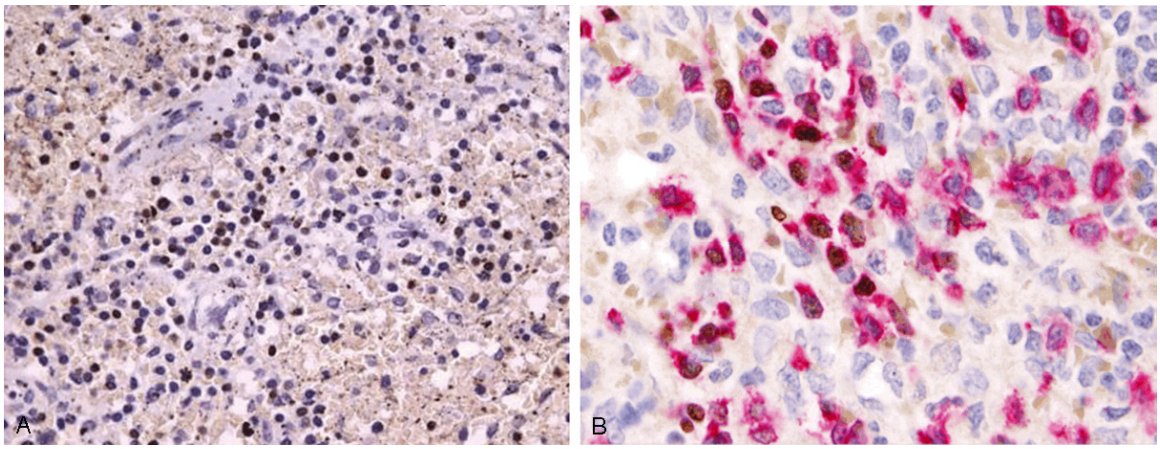

Figure 3. Some small lymphocytes are positive for EBER (A, in situ hybridization, x400). Double staining for CD3/EBER and CD20/EBER shows that the CD3+ population harbors the EBV (B, stained in Queen Elizabeth Hospital, Hong Kong, Courtesy of Dr. John K C Chan, x600).

A few infiltrated cells was CD56+. Staining for CD4 and CD8 showed that the infiltrate was CD4- and CD8-. The infiltrated lymphocytes expressed cytotoxic molecules, such as TIA1, granzyme B (**Figure 2B**). The ratio of Ki-67-positive cells was estimated with lower than 30%.

In situ hybridization(ISH) for EBV using the EBV-encoded RNA-1 (EBER1) probe (DAKO) showed up moderate number of positive cells (**Figure 3A**). These EBER+ cells were mostly small, and were scattered instead of forming clusters. Double-label ISH-IHC for EBER1 and CD20 or CD3 showed that most EBER+ cells were CD3+ (**Figure 3B**).

Analysis of paraffin-embedded tissue from the spleen by PCR showed polyclonal rearrangements of the TCR-γ genes.

Discussion

In our case, the patient presented with fever, splenomegaly, and pancytopenia for more than 6 months with no evidence of previous immunological abnormalities or other recent infections. The serologic tests showed EBV VCA-IgG (+), EBV-EA (+). Histological examination revealed the infiltrated lymphocytes of spleen were composed predominantly of CD3+, CD56+T/NK-cells and these cells were positive for EBER. Based on the clinical and histological findings, we consider this case as a rare adult EBV+T/NK LPD category A1.

EBV+T/NK LPD was first incorporated into the 4th World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, in which systemic EBV+ T-cell LPD of childhood and hydroa vacciniforme–like lymphoma are proposed as distinct entities [8]. In 2008, an international meeting was organized at the National Institute of Health to better define the pathogenesis, classification, and treatment of EBV-associated LPDs in nonimmunocompromised hosts [1]. At that meeting, acute and chronic EBV syndromes of T cells and NK cells were clarified to have a broad spectrum, in which hydroa vacciniforme (HV), HV–like lymphoma, severe mosquito bite allergy, and systemic EBV+T-LPD of childhood were listed as EBV+T/NK-LPDs under an umbrella term of CAEBV of T/NK-cell type.

EBV+T/NK LPD include polyclonal, oligoclonal, and monoclonal proliferation of T and/or NK cells. Based on pathological evaluation and molecular data, K. Oshima proposed a categorization system of EBV+T/NK LPD in 2008 [9]. They divided these cases into four categories: A1 (polymorphic and polyclonal), A2 (polymorphic and generally monoclonal), A3 (monomorphic and monoclonal proliferation of T-cell or NK cell origin), and B (monomorphic and monoclonal T-cell LPD with fulminant clinical course). Categories A1, A2, and A3 possibly constitute a continuous spectrum and together are equivalent to CAEBV. Group B was defined as equivalent to fulminant EBV+LPD of childhood. Patients with CAEBV infections usually show

clonal proliferation, although non-clonal cases do exist [1, 4]. In a national survey conducted in Japan, clonality of EBV-infected cells was analyzed in 54 patients, of whom 41 (76%) had monoclonal, seven (13%) had oligoclonal, and six (11%) had polyclonal [4]. In our case, the patient showed polyclonal proliferation of T lymphocytes. According to the above categorization criteria of EBV+T/NK LPD, our case should be diagnosed as CAEBV category A1. Recently Kimura et al. also found that most systemic EBV+T/NK LPDs are monoclonal [10]. In their study, most of the 108 patients with EBV+T/NK-LPDs had clonality of EBV-infected cells and eventually developed overt leukemia and lymphoma. They postulated that there should be a prodromal phase of expansion of EBV+T/NK-cells with variable clonality that may or may not progress to EBV+T/NK LPD.

Most cases of previously reported EBV+T/NK LPD were Asians or Native Americans [4, 5, 11-13], and were mainly children or young adults. Elderly patients were seldom reported in the literature. The phenotypes of proliferating cells vary from case to case and include CD4+T cells, CD8+T cells, γδ T-cell, NK cells, and a mixture of these types [4, 14-17]. Notably, in addition to the phenotypic diversity, all cases examined were positive for cytotoxic molecules, such as TIA1, granzyme B, and perforin, indicating their derivation from cytotoxic T cells [11, 15]. Kimura et al. demonstrated that patients with CD4+ T-cell infection had shorter survival rates than those with NK infection [10]. But it is not clear whether the EBV-infected populations in CAEBV are correlated with survival rates at present, which need to be further study on the basis of more cases.

Although with characteristic clinical features and pathological findings, differential diagnosis with extranodal NK/T-cell lymphoma, nasal type is requisite before making a definite EBV+T/NK LPD. They have some common characteristics, such as prevalent in Asians or Native Americans, EBV presence, cytotoxic phenotype, and aggressive behavior. NK/T-cell lymphoma is characterized by expression of CD2+, cytoplasmic CD3ε+, cytotoxic molecules, EBER, and CD56 may be positive or negative. These immunophenotypic features are similar with our case. Nevertheless, geographical necrosis and vasculitis characterized by NK/T-cell lymphoma were absent, and the architecture of the spleen was preserved with intact sinusoids and pulp cords in our case. Thus, we considered that overall clinicopathologic features of this elderly patient were fully consistent with those of EBV+T/NK LPD.

In conclusion, EBV+T/NK LPD encompasses a continuous spectrum of diseases from benign to malignant that is always associated with poor clinical outcome and can be life-threatening. A recent report demonstrated that adult patients with CAEBV had progressive and more aggressive courses than those of childhood [18]. The patients often die of malignant lymphoma/leukemia of T or NK-cell type, hemophagocytic syndrome and multiple organ failure. Though our patient has a relatively good outcome to date, the behavior of this disorder requires long-term follow up.

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Disclosure of conflict of interest

The authors have disclosed that they have no significant relationships with any commercial companies pertaining to this article.

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