An adult case of systemic Epstein-Barr virus-positive T-cell lymphoproliferative disorder with severe hepatic dysfunction and megalosplenia

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ABSTRACT

Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorder (EBV+T/NK-LPD) is a continuous spectrum of diseases that share a common feature observed in T cells and NK cells: Excessive lymphoid proliferation. This disease is rare in adults and predominantly affects children with high mortality. Herein, we present a case of EBV+T-LPD that occurred in an adult with clinical manifestations of hepatic dysfunction and megalosplenia. The patient received a splenectomy at a local hospital for the treatment of megalosplenia. Before surgery, she exhibited mild hepatomegaly and normal liver function. However, after the operation, abdominal computed tomography (CT) showed obvious hepatomegaly and severely damaged liver function. After a final diagnosis of EBV+T-LPD at our hospital, the patient received combination therapy with antiviral and immunosuppressive agents. At the 4-month follow-up visit, hepatic function was normal and the size of the liver decreased. Because this patient presented with hepatomegaly before the splenectomy and because hepatic dysfunction rapidly progressed after surgery, an early diagnosis of EBV+T-LPD was crucial. Splenectomy may be recommended before liver involvement to reduce negative postoperative effects on the liver.

Key words: Epstein-Barr virus. T/natural killer-cell. Lymphoproliferative disorder. Liver disease.

INTRODUCTION

The Epstein-Barr virus (EBV) is an ubiquitous virus that is associated with many malignancies that affect B lymphocytes, T lymphocytes, NK cells and epithelial cells. Epstein-Barr virus-associated lymphoproliferative disease (EBV-LPD) in non-immunocompromised hosts encompasses a heterogeneous group of clinical manifestations, pathological features, and clonal disorders that share a common feature: Excessive lymphoid proliferation, which is mainly observed in T cells and NK cells. EBV-LPD is different from LPD secondary to immunosuppression, such as LPD in AIDS patients or transplant recipients, and other immunosuppressive and immunodeficiency conditions that result from iatrogenic treatment. In addition, EBV-LPD differs from lymphoproliferative disorders that have been defined according to the 2001 World Health Organization classification, such as Hodgkin’s lymphoma, extranodal NK/T-cell lymphoma of the nasal type and Burkitt lymphoma (1). According to the 2008 WHO classification criteria, EBV-associated T/NK neoplasms include extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia and systemic childhood Epstein-Barr virus-positive T/NK-cell lymphoproliferative disease. In the 4th edition of the WHO classification of tumors that affect hematopoietic and lymphoid tissue, childhood EBV+T/NK-LPD is proposed as a distinct disease entity (2). This disease is rare in adults but is associated with high mortality. EBV+T/NK-LPD is characterized by fever, lymphadenopathy, and splenomegaly (3). In this report, we present an adult case of systemic EBV+T-LPD with severe hepatic dysfunction and megalosplenia.

CASE REPORT

A 52-year-old female was admitted to the Department of Gastroenterology at West China Hospital because of recurrent fever over the previous 3 years, fatigue and anorexia over the previous 2 months and yellow discoloration of the sclera and skin during the previous 10 days. Three years ago, she experienced a recurrent fever without chills that occurred mainly at night. Her temperature ranged from 38.5 °C to 40 °C but returned to normal early the next morning. She was admitted to a local hospital for...
fatigue and anorexia 2 months ago. Routine blood testing indicated a significant decrease in leukocyte, erythrocyte and platelet counts. Bone marrow smears revealed hypoplasia with occasional myeloblasts and promyelocytes and an increased proportion of erythroid cells. Liver function was normal. Abdominal CT revealed obvious splenomegaly (18x12x9 cm) and mild hepatomegaly. A splenectomy was subsequently performed, and a pathological examination revealed hypersplenism with congestion and expansion of splenic hilar vessels and desmoplasia of splenic tissue. After the operation, the patient’s blood cell count was restored to normal. However, she still suffered from recurrent fever with fatigue and anorexia. She developed jaundice with fatigue and aggravated anorexia 10 days before admission. She had no history of hepatitis or alcohol or drug abuse.

A physical examination at admission revealed listlessness, marasmus, and a yellow discoloration of the sclera and skin without superficial lymphadenopathy. A markedly enlarged liver was palpated at 6.0 cm below the costal margin with tenderness. Additionally, she presented with reduced red blood cell and platelet counts, severe liver dysfunction and coagulation disorders (Table I). EBV-DNA and EBV antibody tests were positive, whereas hepatitis virus and human immunodeficiency virus (HIV) tests were negative (Table I). No definitive evidence of tuberculosis was detected (Table I). In addition, the serum levels of tumor markers were normal. The Coomb’s test was positive; however, other immunological functions were normal. Chest CT revealed slight inflammation, whereas abdominal CT showed hepatomegaly with lower parenchymal density and normal intrahepatic and extrahepatic bile ducts (Fig. 1).

Bone marrow smears suggested that the granulocytic lineage was hyperplastic, and no abnormal cells were found. Bone marrow biopsy indicated active hyperplasia of three lines of hematopoietic cells with focal piecemeal necrosis. Small- to medium-sized lymphocytes that infiltrated into the marrow were positive for cluster of differentiation (CD3) (Fig. 2). Acid-fast staining of the bone marrow was negative. The spleen biopsy revealed enlarged red pulp, narrowed white pulp, focal necrosis and infiltrating small- and medium-sized lymphocytes in the sinus. Immunochem-

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**Table I. Patient laboratory data**

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>At admission</th>
<th>After 4 months of treatment</th>
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<tbody>
<tr>
<td>Blood cell analysis</td>
<td>RBC: 3.0x10¹²/L, WBC: 2.61x10⁹/L, PLT: 76x10⁹/L</td>
<td>RBC: 2.8x10¹²/L, WBC: 5.7x10⁹/L, PLT: 200x10⁹/L</td>
</tr>
<tr>
<td>Coagulation function</td>
<td>PT: &gt; 120 s, APTT: &gt; 180 s</td>
<td>PT: 14 s, APTT: 46 s</td>
</tr>
<tr>
<td>Virological and serological examination</td>
<td>EBV-DNA: 8.32E+03 copies/mL, EBV VCA-IgA/EA-IgG: Positive, hepatitis A, B, C, E and human immunodeficiency virus: Negative</td>
<td>EBV-DNA: 6.67E+03 copies/mL</td>
</tr>
<tr>
<td>Tuberculosis examination</td>
<td>PPD skin test and T-SPOT: negative</td>
<td>ND</td>
</tr>
</tbody>
</table>

PT: Prothrombin; APTT: Activated partial thromboplastin time; TB: Total bilirubin; DB: Direct bilirubin; IB: Indirect bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; TG: Transglutaminase; ND: Not done.

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Fig. 1. CT imaging. A. Hepatomegaly with decreased hepatic parenchymal density at admission. B. A smaller liver with increased parenchymal density after treatment.
istry suggested that the lymphocytes in the spleen were positive for CD3, cytotoxic T cell intracellular antigen 1 and granzyme B. The ratio of Ki-67-positive cells was estimated to be 40%. T-cell receptor \( \gamma \) gene PCR of the spleen did not demonstrate gene rearrangement. In addition, \textit{in situ} hybridization indicated that the CD3-positive cells in the marrow and spleen were positive for EBV encoded RNA (EBER)1/2 \textit{in situ} hybridization (Fig. 2). According to the clinical and histological findings, the patient was diagnosed with systemic EBV+T-LPD. She was administered foscarnet sodium, interferon alpha 2b and urbason for 4 months. After treatment, her energy level and appetite improved thereafter. Routine blood testing and liver function tests were normal, with no changes in the levels of EBV-DNA (Table I). Abdominal CT revealed that the size of the liver had decreased, whereas the density had increased compared with the abdominal CT results before treatment (Fig. 1).

**DISCUSSION**

Hepatic dysfunction and megalosplenia were the main clinical manifestations in this patient. She was negative for markers of viral hepatitis and autoimmune liver diseases and had no history of alcohol or drug use. Furthermore, cirrhosis and portal hypertension were excluded based on abdominal CT angiographic and gastroscopic findings. In patients with fever and marasmus, the differential diagnosis may include tuberculosis, leishmaniasis and other hematological malignancies. However, no space-occupying lesions were found on thoracic and abdominal CT imaging, and the PPD skin and the T-SPOT test for tuberculosis were negative. In addition, leishmania for leishmaniasis was not detected in the bone marrow or spleen biopsy. The biopsies revealed the typical pathological characteristics of EBV+T-LPD. The infiltrating lymphocytes in tissues were positive for CD3, cytotoxic molecules, cytotoxic T cell intracellular antigen-1, telomerase B, and EBV (EBER+). Additionally, T-cell receptor \( \gamma \) gene PCR of the spleen did not indicate gene rearrangement. In contrast, hepatosplenic T cell lymphoma usually has infiltrating lymphocytes that are negative for telomerase and EBER, and T-cell receptor \( \gamma \) gene PCR of the spleen suggests gene rearrangement (4). In chronic myelogenous leukemia, an increased number of immature granulocytes may be detected in the peripheral blood and bone marrow.
Therefore, hepatosplenic T cell lymphoma and chronic myelogenous leukemia were excluded in this patient. In addition, the patient had a 3-year history of recurrent fever and relatively slow clinical progress before the splenectomy. These clinical features, the lack of large granular lymphocytes, which is a characteristic of NK cell types, and the obvious nucleolus in the proliferative cells that expressed CD56 suggest that the liver and spleen damage in this case differed from that caused by aggressive NK-cell leukemia (5).

EBV infection may lead to the excessive proliferation of T and NK cells in lymphoid tissue and ultimately EBV+T/NK-LPD. Lymphoproliferative diseases that are marked by fever, lymphadenopathy, and splenomegaly after primary EBV infection without known immunodeficiency are defined as systemic EBV+T/NK-LPD (6). This disease mainly affects people of Asian origin (5). In studies of 128 cases of EBV+T/NK-LPD by Japanese and Chinese scholars (3,7), EBV+T/NK-LPD was more common in children; however, the adult cases had poorer prognoses and shorter survival times. In 2008, based on pathological and molecular data, Oshima (8) divided EBV+T/NK-LPD into A and B categories. Category A (A1-A3) is equivalent to chronic active Epstein-Barr virus infection, whereas category B is equivalent to explosive EBV+LPD in children (8). The symptoms in patients with a category A infection were relatively mild, and the patients could survive for several years. In contrast, the symptoms in patients with a category B infection were more serious and rapidly progressed. The survival times for the patients with category B ranged from days to weeks (8). According to those criteria (8), our case should be diagnosed with systemic EBV+T-LPD category A1, which is associated with relatively low malignancy and a comparatively good prognosis.

It remains unclear how EBV+T-LPD results in liver damage. However, it has been suggested that this damage may be related to clonal lymphoid proliferation and the release of cytokines and cytotoxic molecules (3,7,11). Studies have demonstrated that perforin gene mutations and the ectopic expression of CD40 (9,10) may lead to the clonal proliferation of EBV-infected lymphocytes, most likely because host immune abnormalities that are caused by genetic defects result in poor host immune responses to EBV. Furthermore, the infiltration of numerous proliferating cells in the hepatic portal area may contribute to hepatocyte injury by reducing blood perfusion of liver parenchyma and by facilitating intrahepatic cholestasis. Kimura (7) confirmed this hypothesis by identifying numerous infiltrating lymphocytes in the portal area, the sinus and the visible necrotic region in the hepatic lobe in EBV+T-LPD patients. In addition, activated T cells that are infected by EBV release various cytokines (11), such as tumor necrosis factor-alpha and interferon-γ-inducible protein-10, and cytotoxic molecules (3,7) such as perforin and granzymes, which may directly or indirectly lead to hepatocyte damage and necrosis.

No recommended guidelines are currently available regarding the treatment of EBV+T-LPD. Conventional chemotherapy may work for certain patients but with a limited duration of response (7). In addition, the effect of antiviral agents used alone remains controversial, and immunosuppressive drugs only temporarily relieve symptoms (7). Rafailidis (12) found that the combination of antiviral and immunosuppressive agents may be effective to a certain extent. Previous studies have indicated that hematopoietic stem cell transplantation is associated with the highest remission rate in patients with EBV+T-LPD (13). However, it was inappropriate for our patient to receive chemotherapy because of severe hepatic dysfunction, and hematopoietic stem cell transplantation could not be performed within a short period of time. The patient was given a combination of antiviral and immunosuppressive agents. After treatment, her temperature and hepatic function returned to normal and her liver was smaller in size. These results indicated that this treatment strategy may be effective; however, a long follow-up period was needed. Splenectomy has previously been considered effective in alleviating hypersplenism in EBV+T-LPD patients, and this surgical procedure creates favorable conditions for future chemotherapy even after transplantation (13). Zhang (14) reported a case of EBV+T-LPD involving fever and splenomegaly. After splenectomy, the patient’s temperature returned to normal after a 2-year follow-up period, and no new clinical manifestations were found. In this previous case, the period of time from the onset of symptoms to the splenectomy was relatively short (approximately 6 months), and no evidence for the involvement of the liver or other organs was found. Therefore, these findings suggest that splenectomy may have a therapeutic effect on EBV+T-LPD when only the spleen is involved. In our case, the period of time from the onset of symptoms to the splenectomy was 3 years. In addition, preoperative examinations revealed that the hepatomegaly and liver damage worsened after the splenectomy. This finding may have been due to the long-term proliferation of abnormal lymphocytes in both the liver and the spleen before surgery. The splenectomy resulted in a sharp increase in atypical lymphocytes that proliferated in the liver over a short period of time, which may have made the liver injury worse. Therefore, the early diagnosis of EBV+T-LPD is vital, and splenectomy before liver involvement may be recommended.

CONCLUSION

Differential diagnosis of EBV+T-LPD with hepatic dysfunction is of great importance in clinical setting for the easy misdiagnosis. Liver damage in patients with EBV+T-LPD is mainly related to the active proliferation of EBV-infected cells and the release of cytokines and cytotoxic molecules. No standard treatment is currently available for EBV+T-LPD; however, splenectomy for patients
with splenomegaly and hypersplenism may be beneficial before liver involvement, and combination drug therapy should be considered in patients with liver involvement. However, future clinical trials are needed to confirm these findings.

REFERENCES