Clinical Case Report

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Chronic active Epstein–Barr virus infection associated with hemophagocytic syndrome and extra-nodal natural killer/T-cell lymphoma in an 18-year-old girl

A case report

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Abstract

Rationale: Chronic active Epstein–Barr virus infection (CAEBV) associated with hemophagocytic syndrome (HPS) and extra-nodal natural killer (NK)/T-cell lymphoma (ENKL) is a rare life-threatening disorder. This disease is easily misdiagnosed because of its varied presentations.

Patient concerns: An 18-year-old girl was admitted to our hospital with a history of edema in the lower limbs and intermittent fever lasting for more than 1 month. At admission, she had severe liver injury of unknown etiology. Laboratory test results revealed pancytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. Results of serologic tests for EBV were positive. Results of a skin biopsy indicated EBV-positive NK/T-cell lymphoma, and bone marrow aspiration revealed focal hemophagocytosis and atypical lymphoid cells.

Diagnosis: On the basis of these findings, we diagnosed the case as extra-nodal NK/T-cell lymphoma-associated HPS (natural killer/T-cell lymphoma-associated hemophagocytic syndrome), which is commonly induced by CAEBV.

Interventions: Treatment consisted of general management of hepatitis, supplemented with albumin and empirical antibiotic therapy.

Outcomes: The patient died from massive gastrointestinal hemorrhage a week after she was discharged from the hospital.

Lessons: ENKL and HPS present with varied features and are generally fatal; therefore, clinicians should proceed with caution in suspected cases. HPS should be considered when the patient presents with fever, hepatosplenomegaly, pancytopenia, and liver failure. When HPS is suspected, clinicians should determine the underlying cause, such as severe infection, including infection with viruses such as EBV; genetic predisposition; or underlying malignancies, especially lymphoma because of its strong association with HPS.

Abbreviations: APTT = activated partial thromboplastin time, CAEBV = chronic active EBV infection, CD = cluster of differentiation, CTV = computed tomography vein, DNA = deoxyribonucleic acid, EBER = EBV-encoded early small RNA, EBV = Epstein–Barr virus, ENKL = extra-nodal NK/T-cell lymphoma, HIV = human immunodeficiency virus, HLH = hemophagocytic lymphohistiocytosis, HPS = hemophagocytic syndrome, LPD = lymphoproliferative disorder, NASH = nonalcoholic steatohepatitis, NK = natural killer, NK/T-LAHS = natural killer/T-cell lymphoma-associated hemophagocytic syndrome, TIA-1 = T-cell restricted intracellular antigen 1.

Keywords: chronic active EBV infection, Epstein–Barr virus, extra-nodal NK/T-cell lymphoma, hemophagocytic syndrome

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1. Introduction

Epstein–Barr virus (EBV) is a member of the human pathogenic herpes virus family. It is estimated that over 90% of the world's population has been infected by EBV, and the infection persists for life.[1] Primary infections occurring in childhood are usually asymptomatic. However, approximately one-third of EBV infections occurring in adolescence or adulthood often manifest as self-limiting infectious mononucleosis syndrome, with a minority of these cases evolving into chronic active EBV infection (CAEBV).[2] CAEBV is a rare disease with a high mortality rate and potential life-threatening manifestations such as hemophagocytic syndrome (HPS), liver failure, disseminated intravascular coagulopathy, malignant lymphomas, and pneumonia.

In this report, we describe a case of CAEBV associated with extra-nodal NK/T-cell lymphoma (ENKL) and HPS. The case was originally misdiagnosed as nonalcoholic steatohepatitis

(NASH) and secondary Budd–Chiari syndrome. This case could provide clinicians critical insight into the manifestation and treatment of this rare condition.

2. Case report

An 18-year-old girl was admitted to our hospital with a history of edema in the lower limbs and intermittent fever lasting for more than 1 month. She had lost 5 kg since the first appearance of symptoms and had no history of liver disease, alcohol consumption, drug abuse, or herbal medicine use. On the basis of the results of computed tomography vein (CTV) imaging of the hepatic vein and inferior vena cava (Fig. 1A), we diagnosed the case as secondary Budd–Chiari syndrome caused by NASH.

Physical examination revealed a pale and lean appearance with a body mass index of approximate 15 kg/m^2, upper abdominal wall varicose veins, and cutaneous nodules on her limbs and left buttock (Fig. 2). The liver, which was palpable 3 cm below the right costal margin, was firm and tender, whereas the spleen was palpable 5 cm below the left costal margin. Pitting edema was detected bilaterally on her lower limbs. Laboratory tests showed severe pancytopenia, with a white blood count of 2.2×10^9/L, red blood count of 2.75×10^{12}/L, hemoglobin level of 81 g/L, and platelet count of 135×10^9/L. Serum total protein and albumin levels were low at 58.4 g/L (normal range, 65–86 g/L) and 22.3 g/L (normal range, 40–55 g/L), respectively. The erythrocyte sedimentation rate was elevated at 46 mm/h (normal range, 0–20 mm/h) and procalcitonin level was high at 0.77 ng/ml (normal range, <0.05 ng/ml). Liver function tests revealed a total bilirubin of 37 μmol/L, conjugated bilirubin of 28 μmol/L, aspartate aminotransferase of 208.4 U/L (normal range, 13–35 U/L), alanine aminotransferase of 76.7 U/L (normal range, 7–40 U/L), alkaline phosphatase of 959.3 U/L (normal range, 45–125 U/L), and glutamyl transpeptidase of 163.2 U/L (normal range, 7–45 U/L). Serum triglyceride and ferroprotein levels were elevated at 2.24 mmol/L (normal range, 0.52–1.56 mmol/L) and 700 ng/ml (normal range, 5.5–135 ng/ml), respectively, while fibrinogen levels were low at 0.79 g/L (normal range, 2.0–4.0 g/L). Results of a thyroid function test were normal, and urine was negative for protein. A T-SPOT test for tuberculosis yielded negative results. Results of serologic tests for hepatitis A, B, and C virus were all negative. Abdominal- and pelvic-enhanced computed tomography showed decreased liver density as well as hepatosplenomegaly, intrahepatic nodules, and lymphadenectasis around the mesenteric root (Fig. 1B and C).

After admission, the patient experienced persistent fever and skin rashes that might have been caused by hypersensitivity to mosquito bites. She received treatment according to guidelines for general management of hepatitis, supplemented with albumin and empirical antibiotics. However, her symptoms and liver function did not improve. Coagulation function deteriorated rapidly from normal to markedly abnormal. Plasma prothrombin ratio and plasma fibrinogen decreased to 35.56% and 0.48 g/L (normal range, 2–4 g/L), respectively, with an activated partial thromboplastin time (APTT) of 67.20 second. We performed serologic tests for EBV and human immunodeficiency virus (HIV). No evidence of HIV infection was found; however, the test results for EBV infection were positive, and the titer of EBV-deoxyribonucleic acid (DNA) was 2.20×10^5 (normal range, $<4.0 \times 10^2$). Cutaneous nodule biopsy and ultrasound-guided liver biopsy were performed, without hepatic nodule because of the obstruction of the hepatic nodules by the ribs. The skin biopsy specimen showed diffuse lymphoid cell infiltration, combined with immunohistochemical staining of clusters of differentiated 3 (CD3)+, CD4+, CD8+, CD20−, Ki67 (60%), CD2+, CD7+, CD56+, T-cell restricted intracellular antigen 1 (TIA-1), and positive to EBV-encoded early small ribonucleic acid (EBER) (Fig. 3A–J). The liver biopsy specimen showed diffuse steatosis and sinusoidal dilatation, along with the presence of lymphocytes (Fig. 4). However, EBER and other CD were not detected in the liver biopsy specimen. A subsequent bone marrow biopsy revealed focal hemophagocytosis and atypical lymphoid cells (Fig. 5). On the basis of these findings, we diagnosed the case as NK/T-cell lymphoma and HPS and recommended chemotherapy and immunomodulating therapy; however, the patient's parents refused further treatment. On the 12th hospital day, the patient's serum albumin decreased to 20.5 g/L, but aspartate aminotransferase increased to 269.8 U/L and alanine aminotransferase to 84.4 U/L. Coagulation function worsened markedly. Plasma prothrombin ratio and plasma fibrinogen were 29.5% and <0.45 g/L, respectively, whereas APTT increased to 74.60 second. Concurrently, pancytopenia was noted with a white blood count of 1.6×10^9/L, red blood count of 2.53×10^{12}/L, hemoglobin level of 77 g/L, and platelet count of 38×10^9/L. One week after being discharged, the patient died from massive gastrointestinal hemorrhage, which was likely caused by the deteriorated coagulation function.

Ethical approval of this study was obtained by the Ethics Committee of the Xiangya Hospital of Central South University, China. Written informed consent was obtained from the patient's

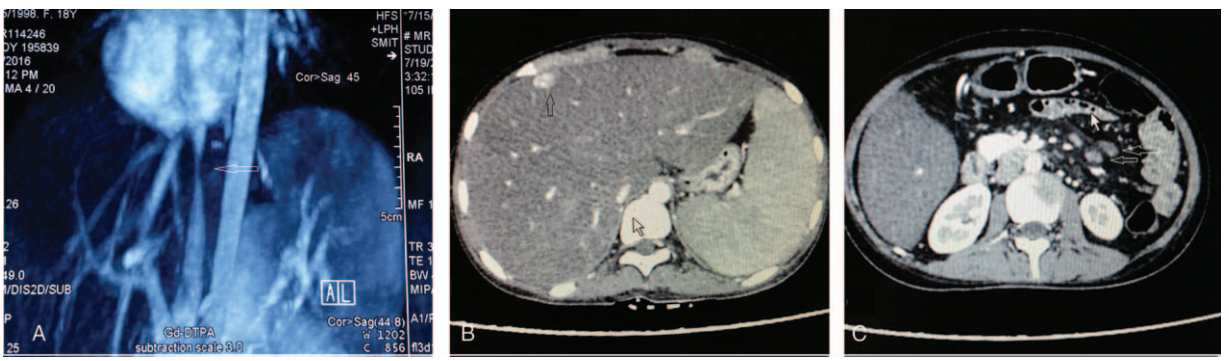

Figure 1. (A) Computed tomography vein imaging showed compressed constrictive inferior vena cava (arrow). (B) Decreased liver density and hepatosplenomegaly, strengthen intrahepatic nodules (arrows). (C) Lymphadenectasis around the mesenteric root (arrows).

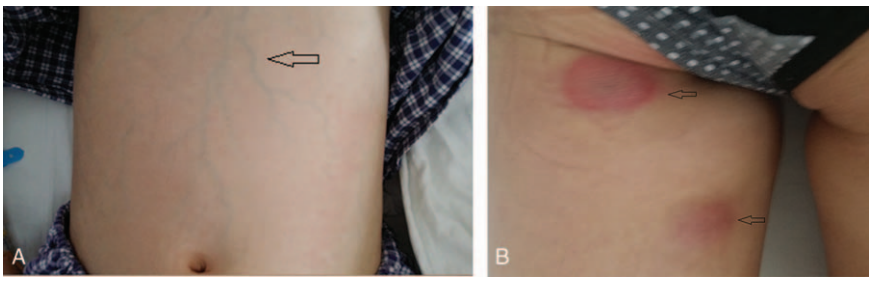

Figure 2. (A) Upper abdominal wall varicose veins (arrow). (B) The skin lesions of the patient (arrows).

parents for the publication of this case report and the accompanying images.

3. Discussion

In the present case, the initial distinctive symptom was edema in the lower limbs. Enhanced CTV imaging revealed compression and narrowing of the inferior vena cava in the hepatic segment. We first considered the possibility of secondary Budd–Chiari syndrome induced by hepatomegaly, which would explain the appearance of upper abdominal wall varicose veins, edema, and splenomegaly. However, it did not explain the other clinical features such as fever, cutaneous nodules, and pancytopenia. Her liver biopsy results suggested NASH and liver failure, but those conditions still did not explain the cutaneous rashes. Another possibility was severe steatosis associated with a drug or poison. However, the patient had no history of drug abuse. She had experienced significant body weight loss in a short time. Therefore, we considered the possibility of a tumor, especially lymphoma, which would explain all of her clinical manifestations. Immunohistochemical testing of the skin nodule biopsy specimen revealed that it was positive for CD3+, CD4+, CD8+, CD20−, Ki67 (60%), CD2+, CD7+, CD56+, and TIA-1, which suggested the presence of NK/T-cell lymphoma. In addition, the result of an EBER in situ hybridization test was positive, and the serum EBV-DNA level was markedly elevated. On the basis of these findings, we arrived at a diagnosis of NK/T-cell lymphoma. However, the patient experienced severe steatosis and liver failure, which were unlikely to be caused by lymphoma alone. Therefore, we considered the possibility of HPS on the basis of the bone marrow findings of focal hemophagocytosis and atypical lymphoid cells. Ultimately, the final diagnosis was ENKL-associated HPS (NK/T-LAHS), which is strongly associated with CAEBV.

CAEBV is characterized by persistent infectious mononucleosis-like syndrome, with symptoms such as fever, hepatosplenomegaly, hepatitis, and pancytopenia.[3] Generally, during the viral infection, EBV-specific cytotoxic T cells suppress the proliferation of EBV-infected B cells, and the virus persists latently in B cells after resolution of the primary infection for the remainder of the patient's life. However, in some uncommon

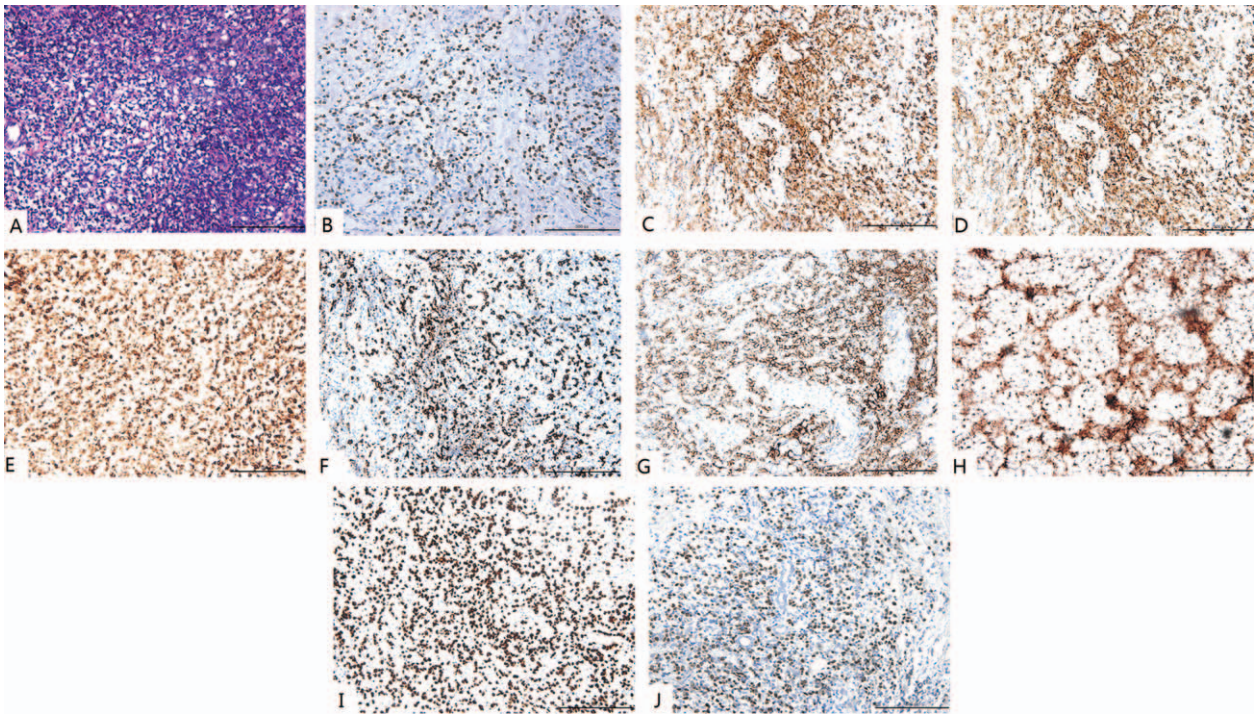

Figure 3. (A) Hematoxylin and eosin staining result of the skin biopsy with lymphocytic infiltration (H&E × 200). (B–J) Immunohistochemical stainings of cluster of differentiation 2 (CD2), CD3, CD4, CD7, CD8, CD56, Ki-67, T-cell restricted intracellular antigen 1, and Epstein–Barr virus-encoded early small RNA in cutaneous nodules were positive (×200).

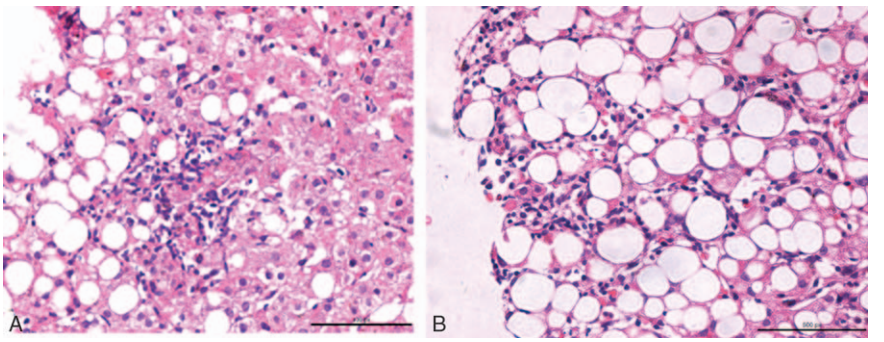

Figure 4. (A) Diffuse steatosis, sinusoidal dilatation with lymphocytic infiltration (H&E × 200). (B) Liver steatosis (H&E × 400).

instances, when T or NK cells are infected by EBV, EBV-specific cytotoxic T cells are not generated, resulting in the occurrence of CAEBV.[4,5] CAEBV associated with various lymphoproliferative diseases (LPD) of B-, T-, or NK-cell lineages and hemophagocytic lymphohistiocytosis (HLH) has a poor prognosis. According to the 2008 World Health Organization classification, EBV+ NK/T neoplasms involve ENKL, aggressive NK-cell leukemia, and EBV + childhood T-cell LPD. Moreover, EBV+ NK/T neoplasms are more prevalent in Asian and Latin American countries.[4] ENKL induced by CAEBV is rare and its incidence in adults begins to increase in the third decade of life.[4,6] However, a few cases of patients presenting with ENKL in their teens have been reported.[7] HPS or HLH, which is classified into hereditary and acquired forms, is a second predictive factor of poor prognosis in patients with CAEBV. Therefore, if bone marrow aspiration reveals focal hemophagocytosis and atypical lymphoid cells, HPS should be considered. Acquired HPS is a hyperinflammatory syndrome associated with a variety of underlying conditions such as severe infectious diseases, autoimmune diseases, malignancies, and acquired immune deficiency syndrome.[8] The prognosis of adult patients with HPS is very poor. The median overall survival of patients with tumor-associated HPS was 1.4 months compared with 22.8 months for patients with nontumor-associated HPS. Malignant tumors and hypoalbuminemia were significant predictors of inferior survival in patients with HPS.[9] Five of the following 8 criteria need to be satisfied for an HPS diagnosis: fever; hepatosplenomegaly; cytopenias affecting 2 or 3 lineages in the peripheral blood; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; hyperferritinemia, low or absent NK-cell activity; and high levels of soluble interleukin (IL)-2 receptors.[10] In the present case, the patient fulfilled 6 of these 8 criteria, resulting in a final diagnosis of NK/T-LAHS, which is commonly induced by CAEBV.

HPS is a rare life-threatening disorder characterized by immune dysregulation, inflammation, and immune system overactivation.[11] HPS sometimes presents with features mimicking liver failure, including severe coagulopathy, low serum albumin, and high levels of alkaline phosphatase and γ-glutamyl transpeptidase. The pathophysiological mechanism of these features that mimic liver failure is related to macrophages activated by high levels of cytokines, which are secreted by proliferating T lymphocytes. Levels of cytokines, such as interferon-γ, tumor necrosis factor-α, IL-6, IL-10, IL-12, and IL-18, are usually highly elevated in patients with HPS.[8,12,13] The activated macrophages and released cytokines might partially explain the systemic and hepatic manifestations of HPS. HPS-induced liver failure is difficult to diagnose, especially in the early stage of HPS. Many of the manifestations of HPS can be missed as they are also commonly observed in hepatic dysfunction alone, and this can lead to substantial delays in generating an accurate diagnosis. Another reason for the difficulty in diagnosing HPS is the lack of specific laboratory tests for this disorder, which makes it difficult to differentiate HPS-induced liver failure from liver failure caused by viruses, drugs, or autoimmune conditions. Moreover, the disease is rare and very few cases of liver failure secondary to HPS have been described in the literature. In one retrospective study, Parikh et al[9] reported that 49% of patients with HPS were initially misdiagnosed. Consistent with this finding, a diagnosis of HPS was significantly delayed in the present case because of the clinical presentation. Sinusoidal dilatation and Küpffer cell hyperplasia is

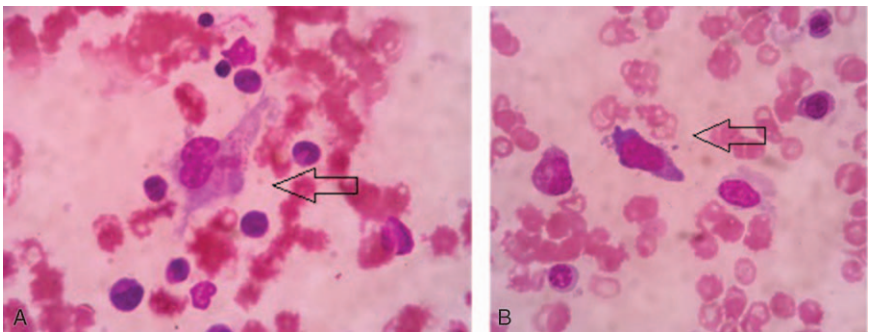

Figure 5. (A) Bone marrow aspiration showed evidence of hemophagocytosis. Arrow showing a macrophage with phagocytosed red blood cells and platelets (arrow) (×400). (B) Atypical lymphocytes (arrow) in bone marrow (×400).

found in most, but not all, liver biopsy specimens from HPS patients.[14,15] Wahbia et al[16] reported the detection of steatosis via liver biopsy in a patient with HPS. In another study, Caroline et al[17] detected steatosis in 14 of 25 patients with HPS. These findings indicate that although steatosis occurs in a minority of patients with HPS, it does occur in HPS patients with hepatic dysfunction. The mechanisms of liver injury caused by HPS remain unknown. It is reported that EBV does not directly infect hepatocytes or the biliary and vascular endothelium.[18] In the present case, we found no cholestasis in the liver biopsy specimen, and the EBER test results were also negative. Probable causes of hepatic dysfunction and severe steatosis include dysregulation of the levels of cytokines secreted by activated macrophages and proliferating T lymphocytes.[18–22]

In summary, we described the case of a young female patient with EBV-positive NK/T-cell lymphoma-associated HPS, which was misdiagnosed as secondary Budd–Chiari syndrome because of the prominent manifestation of edema. Our findings indicate that HPS should be considered when the patient presents with fever, hepatosplenomegaly, pancytopenia, and liver failure. When HPS is suspected, an underlying cause must be identified, such as severe infection, including infections with viruses such as EBV, genetic predisposition, or underlying malignancies, especially NK/T-cell lymphoma because of its strong association with HPS.

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