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Epstein-Barr virus–associated hemophagocytic syndrome masquerading as lymphoma: a case report

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Virus-associated hemophagocytic syndrome (VAHS) is a non-neoplastic, generalized histiocytic proliferation with prominent hemophagocytosis associated with a systemic viral infection. Although Epstein-Barr virus (EBV) is one candidate virus for this association, thorough serologic and molecular biologic studies to determine the presence of the viral infection have been lacking in many reports. Whereas elevated liver function tests are common findings in patients with VAHS, exudative ascites and abdominal lymphadenopathy are rare. We describe a case of EBV-AHS masquerading as lymphoma in which treatment with intravenous immunoglobulins was associated with complete clinical remission at 2 years and 6 months after the onset. Regardless of the exact mechanism responsible for ascites formation in VAHS, this case adds support to the possible involvement of EBV in patients with abdominal lymphadenopathy and ascites.

Key words: Abdominal lymphadenopathy, Epstein-Barr virus (EBV), intravenous immunoglobulins, virus-associated hemophagocytic syndrome (VAHS)

Hemophagocytic syndrome (HS) has been described in viral, bacterial, fungal, and protozoan infection [1]. In general, it is seldom identified as the responsible cause of HS. Nevertheless, Epstein-Barr virus-associated HS (EBV-AHS) has a relatively high mortality rate [2]. We describe a case of which a previously healthy child girl who has developed exudative ascites and abdominal lymphadenopathy during EBV-AHS. Ascitic fluid analysis showed atypical lymphocytosis.

Case Report

A 2-year-old girl was admitted to the Chang Gung Children's Hospital in January 1999 with a 3-day history of persistently high spiking fever, fatigue, and jaundice. Her body temperature was 40.6°C, blood pressure: 102/65 mm Hg, pulse rate: 95 /min, and respiration rate: 18 /min. Physical examination revealed small, palpable cervical lymph nodes. The abdomen was distended with normal bowel sounds; there was a positive fluid wave, shifting dullness, and an enlarged, very tender liver with a 10-cm span. The spleen tip was noted 4 cm below the costal margin in the mid-clavicular line. Initial laboratory investigations showed thrombocytopenia with a platelet count of 64 x 10^9 /L, hemoglobin concentration of 9.2 g/dL, and leukocyte count of 3.7 x 10^9 /L (26% neutrophils; 47% lymphocytes; 18% atypical lymphocytes). Liver function tests showed an elevated aspartate aminotransferase of 131 U/L (normal range, < 25 U/L), alanine aminotransferase of 54 U/L (normal range, < 30 U/L), total and direct bilirubin of 86 μmol/L (normal range, 2-18 μmol/L) and 54 μmol/L (normal range, 0-4 μmol/L), alkaline phosphatase of 461 U/L (normal range, 28-94 μmol/L), triglycerides of 3.44 mmol/L (normal range, < 1.8 mmol/L), total protein of 4.2 g/dL, and albumin of 2.4 g/dL. The chest X-ray showed insignificant pleural effusion. Abdominal ultrasonography revealed hepatosplenomegaly with a large amount of ascites and lymph nodes at the liver hilum. Computed tomography (CT) of the abdomen revealed soft tissue masses in the porta hepatica adjacent to the celiac trunk, as well as enlargement of paraoaortic and retrocaval lymph nodes (Fig. 1). Lymphoma was highly suspected.

On the next day, examination of a peripheral blood

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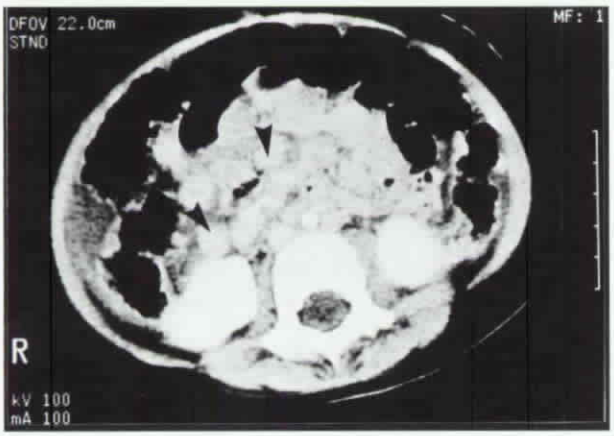

Fig. 1. EBV-AHS in a 2-year-old girl. Computed tomography demonstrates intraperitoneal and retroperitoneal lymphadenopathy (black arrowheads).

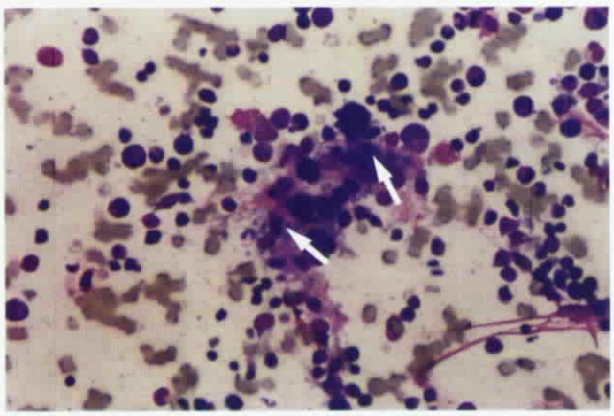

Fig. 2. Evidence of hemophagocytosis in a mature histiocyte in bone marrow showing ingested red cells (arrows) [Liu's stain, 240x].

film revealed atypical lymphocytosis up to 80%. No blast cells were seen on the blood film and a coagulation screen was normal. Bone marrow aspiration showed an increased number of mature histiocytes, many of which contained ingested red cells (Fig. 2). EBV capsid antigen (EBV VCA) IgG and IgM titers were 1:160 and positive, respectively. Elevated anti-EB nuclear antigen, VCA-IgG (1:640), and early antigen titers (1:640) were noted 1 week later, suggesting that the disease was not associated with primary EBV infection. No virus was isolated from urine, stool cultures, or marrow aspirates. Other serological tests revealed no evidence of infection with cytomegalovirus (IgM negative), human herpes virus-6 (IgM negative), or parvovirus (IgM and IgG negative).

Paracentesis was performed on day 5 of hospitalization day. About 80 mL straw-colored exudative fluid was obained, which revealed a specific gravity of 1.023 and a cell count of 1025 red blood cells /mm^3, 1% of polymorph, and 99% lymphocytes, mostly atypical. Analysis of the peritoneal fluid showed a lactate dehydrogenase level of 526 U/L, and an elevated serum lactate dehydrogenase level of 941 U/L (normal range, 50-150 U/L) at the time of paracentesis. Negative cultures and stains of the ascitic fluid ruled out bacterial peritonitis. The patient's condition met the diagnostic criteria of hemophagocytic lymphohistiocytosis (HLH), which include clinical, laboratory, and histopathological features. She remained febrile and did not respond to antibiotics on day 6. Intravenous immunoglobulin (IVIG; Gamimune N, Bayer, NC, USA) was then given 1 g/kg daily for 2 days and she responded with a reduced hepato-splenomegaly and abdominal lymphadenopathy. Normalization of peripheral full blood counts was noted 2 weeks later. She remained healthy thereafter during 2 years and 6 months of follow-up.

Discussion

The absence of confirmed familial inheritance in this patient fulfilled the diagnostic guidelines for secondary HLH, which was proposed by the Study Group of the Histiocytic Society [3]. She was found to have definite serological evidence of EBV infection, with subsequent development of secondary HLH.

EBV VCA IgM was positive on admission. Furthermore, anti-EB nuclear antigen was present early in the course of the illness, which indicates an reactivation of EBV immunity. A specific diagnosis of virus infection is made by detecting specific virus capsid IgM and IgG antibodies, and by using *in situ* hybridization and polymerase chain reaction to detect viral DNA. Although a spontaneous recovery is common in cases of VAHS, the long-term prognosis of EBV-AHS is poor [2,4-6]. Chen *et al* [7] reported the progression to EBV-containing T-cell lymphomas in three of 22 children with HS, which suggests that EBV-AHS is a potentially malignant disease. Recent studies also identified various T-cell lymphomas that were associated with EBV infection [8-10].

Lymphomas account for the majority of intraperitoneal abdominal masses that are identified as solid by CT scanning [11]. For these patients, however, CT cannot determine whether lymph nodes are enlarged because of tumor involvement or because of reactive hyperplasia. Ascites cytology may eventually enable the differentiation of benign, reactive hyperplasia caused by VAHS from malignant lymphomas.

The clinical spectrum of disease associated with

VAHS may vary from clinically benign illnesses to aggressive syndromes with features of a T-cell lymphoma. These variations suggest that the EBV-infected T-cells in EBV-AHS represent a range from preneoplastic to overtly malignant proliferation [7,12, 13]. The pathophysiology in EBV-AHS appears to be mediated by the unrestricted release of cytokines produced by the EBV-infected T-cells [14,15]. The immunomodulatory effects of IVIG were evident in the present case through the stabilization of constitutional symptoms and improvement of hematological profiles.

Differential diagnosis is difficult among familial HLH, infection-AHS and malignancy-AHS [6,14,16]. The precise incidence of childhood malignancy-AHS is not known, although Imashuku *et al* [4] reported a 20% incidence among 98 cases of pediatric HS. Viral serology and ascitic fluid studies could convey useful information about the etiology of HS. Correct diagnosis of EBV-AHS can only be achieved by careful clinical observation and a combination of thoroughly scrutinized laboratory tests for EBV.

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