Epstein-Barr virus induced sickle hepatopathy

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Abstract

Sickle hepatopathy comprises a spectrum of disorders that vary in severity. Intravascular sickling and sinusoidal occlusion are the principal drivers of sickle hepatopathy, but infection or autoimmunity may act as triggers. We describe two cases of acute sickle hepatopathy initiated by primary Epstein-Barr virus (EBV) infection, a previously unreported association. The first case entailed a 14-year-old girl with hemoglobin SC (HbSC) disease who developed hepatic sequestration crisis that responded to a simple transfusion of erythrocytes. The second case was that of a 16-year-old boy with HbSC disease who experienced life-threatening intrahepatic cholestasis with multi-organ failure.

Introduction

Sickle hepatopathy of childhood encompasses a group of disorders ranging in severity from mild liver pain to multi-organ failure (Table 1).[1-6] These diverse clinical manifestations are thought to reflect varying degrees of erythrocyte sickling, Kupffer cell hyperplasia, sinusoidal obstruction, hepatocyte ischemia, and intracanalicular cholestasis.[2, 5, 7] Sickle hepatopathy can arise spontaneously or may be triggered by infection or autoimmune diseases.[1, 5, 8, 9] Here, we describe two cases of acute sickle cell hepatopathy caused by Epstein-Barr virus (EBV), a novel association.

Results

Patient 1

A 14-year-old girl with hemoglobin SC (HbSC) disease and a history of two to three hospitalizations per year for vaso-occlusive episodes presented with fever and pain in her back, chest, and legs. There was no lymphadenopathy, pharyngitis, or hepatomegaly. White blood cell (WBC) count was 12 x 10^3/μL, with numerous atypical lymphocytes (1.2 x 10^3/μL), and Hb was slightly lower than her baseline of 10-10.5 g/dL. Nasopharyngeal viral nucleic acid swab and blood culture were negative, and chest x-ray showed no infiltrates. Ceftriaxone and pain medications were administered, and she was hospitalized.

Following admission, she had nausea, persistent fever, right upper quadrant (RUQ) pain, and developed dark urine. By day 3, her liver edge was tender and palpable 2-3 cm below the right costal margin, and progressive anemia (Hb 8.9 g/dL) and thrombocytopenia (platelet count 67 x 10^9/L) were evident (Fig 1). Hepatic ultrasound showed moderate hepatomegaly with an echogenic liver but no thrombosis. Laboratory testing showed elevated serum levels of γ-glutamyltransferase (γGT, 155 U/L), total bilirubin (11.8 mg/dL), conjugated bilirubin (6.8 mg/dL), alanine transaminase (ALT, 781 U/L), and aspartate transaminase (AST, 1360 U/L). Plasma fibrinogen and activated partial thromboplastin time (aPTT) were normal. Her prothrombin time/international normalized ratio (INR) was borderline elevated. Laboratory testing for hepatitis A/B/C infection was negative. Parvovirus polymerase chain reaction (PCR) and adenovirus PCR were negative. Cytomegalovirus IgG was positive but IgM was negative. Quantitative blood PCR assay for EBV DNA showed significant elevation at 7020 IU/mL.

The clinical picture was most consistent with hepatic sequestration triggered by EBV. To avoid the phenomenon of reverse sequestration,[10] she received a simple transfusion of one unit of packed red blood cells with prompt and sustained improvement in her Hb level. Tests of liver function normalized by one week after hospital discharge.

Patient 2

A 16-year-old boy with HbSC disease, who had undergone splenectomy splenectomy at age 4 years after splenic sequestration, presented with fever, sore throat, fatigue, headache, and chest pain. There was no lymphadenopathy. WBC count was 13 x 10^3/μL, with increased atypical lymphocytes (1.1 x 10^3/μL), Hb was 12.9 g/dL, and platelet count was 409 x 10^9/L. Creatinine was elevated at 1.4 mg/dL, possibly reflecting dehydration, but electrolytes were within normal limits. Liver function tests were not performed at that time. Nasopharyngeal viral nucleic acid swab and blood culture were negative, and chest x-ray showed clear lungs. He received ceftriaxone and intravenous fluids. His pain was controlled with oral analgesics, so he was discharged home.

He returned 2 days later with persistent fever and progressive lower back, chest, and upper abdominal pain. His WBC had increased to 26.3 x 10^3/μL with a persistent atypical lymphocytosis. Hb was 10.8 g/dL and platelet count was 297 x 10^9/L. Serum chemistries were notable for elevated bilirubin (4.5 mg/dL), ALT (366 U/L), AST (375 U/L), and γGT (74 U/L). Creatinine was slightly lower than his previous visit at 1.04 mg/dL. Plasma lipase and amylase were normal. His chest x-ray remained clear, and abdominal ultrasound showed a normal gallbladder. He was admitted for intravenous analgesia and monitoring.

Over the next 12 hours, his pain intensified and his abdomen became distended. Hepatic ultrasound demonstrated hepatomegaly with low hepatic arterial velocity and resistive index, suggestive of sequestration. He developed hypoxemic respiratory failure and was intubated. Chest x-ray showed interval development of right hilar consolidation and basilar opacities. Serial laboratory tests demonstrated a progressive leukocytosis and marked increase in ALT and total bilirubin (Fig 1) consistent with acute hepatitis. Plasma ammonia was normal.

He underwent an automated red cell exchange on the first hospital day with goal Hb 10 g/dl and Hb S <30%. Shortly thereafter, he developed hypotension requiring vasopressors. He had hypocalcemia likely caused by inability to hepatically metabolize the citrate anticoagulation utilized in the erythrocytapheresis procedure. He developed laboratory evidence of coagulopathy (aPTT = 52 s, INR = 2.3) on day 3, without clinical bleeding, that resolved over the ensuing week. He required continuous renal replacement therapy for acute kidney injury with creatinine > 5 mg/dL and circulatory overload. He received additional erythrocyte transfusions to maintain his Hb >8 g/dL.

His clinical course was consistent with intrahepatic cholestasis, a severe form of hepatopathy marked by liver synthetic dysfunction, coagulopathy and often multi-organ failure.[1, 5] He gradually improved and was extubated on day 9 but was persistently febrile, so he underwent an evaluation for infection. Cytomegalovirus IgM and IgG were negative. EBV viral capsid antigen (VCA) IgM and IgG were positive on day 10, suggesting that acute EBV infection incited his critical illness. Reinforcing this premise, a convalescent EBV VCA IgM drawn 5 months later was negative. A 6-month regimen of chronic transfusion therapy was administered to facilitate organ healing.

Discussion

The clinical entities represented under the rubric of sickle hepatopathy (Table 1) encompass a disease spectrum; clinical manifestations vary depending on the relative degrees of cell trapping, ischemia, and intracanalicular cholestasis.[1-6] There is overlap among these entities, so precise classification is often challenging. Patient 1 had a clinical course best classified as hepatic sequestration, whereas Patient 2 experienced intrahepatic cholestasis with multi-organ failure. Although illness severity differed between the two patients, there were several common features: 1) both individuals were teenagers with HbSC disease and primary EBV infection, as evidenced by atypical lymphocytosis and positive EBV IgM or PCR, 2) symptoms were

initially attributed to sickle cell-related pain rather than infectious mononucleosis, 3) hepatomegaly, anemia, and thrombocytopenia progressed rapidly, 4) erythrocyte transfusions were required, 5) there was marked elevation of serum transaminases and bilirubin, and 6) a reactive thrombocytosis was noted during the recovery phase (Fig 1).

We surmise that EBV infection triggered sickle hepatopathy in these two cases. EBV-induced sickle hepatopathy has not been reported previously. EBV is known to cause acute hepatitis, although the degree of elevation of serum ALT or bilirubin is typically mild.[11-13]Occasionally EBV results in overt cholestatic hepatitis,[14-20] and there is one noteworthy report of a 15-year-old with HbSC disease who developed EBV-induced cholestatic hepatitis without sickle hepatopathy (maximum serum ALT and total bilirubin of 770 U/L and 12.5 mg/dL, respectively).[21]We posit that the marked serum ALT elevation seen in Patient 1, which is not typical of hepatic sequestration crisis (Table 1), partly reflected EBV-induced hepatitis.

Conflict of Interest

The authors have no conflicts of interest to declare.

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TABLE 1. Spectrum of acute sickle cell hepatopathy in childhood

[1]Adapted from Shah *et al.* , Banerjee *et al.,* and Buchanan & Glader. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; RUQ, right upper quadrant.

FIGURE 1. Laboratory values versus time since hospital admission for two patients with EBV-induced sickle hepatopathy. Abbreviations: ALT, serum alanine transaminase; CR, serum creatinine; CRRT, continuous renal replacement therapy; Hb, hemoglobin; PLT, platelet count; T. BILI, serum total bilirubin; Txn, transfusion (erythrocytes).

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