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Research Article

Cholestatic Hepatitis with Pancreatitis as Presenting Features of Epstein-Barr Virus Infection

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Abstract

In children with Epstein-Barr virus (EBV) infection biochemical evidence of liver involvement is frequent. However cholestasis and pancreatitis are rare. We report a child where this association, usually suggestive of biliary tract obstruction, was instead secondary to EBV infection without the typical clinical and hematological features of infectious mononucleosis (IM).

Keywords: acalculous Cholecystitis; Cholestasis; Pancreatitis; Epstein-Barr Virus.

Introduction

Hepatitis occurs frequently in children with Epstein-Barr virus (EBV) infection as reported by Crum (2006) and Massei (2001). However EBV infection is rarely associated with either cholestasis or pancreatitis and only three children have been reported by Lifschitz (1981), Koutras (1983) and Kang (2013) to have both cholestasis and pancreatitis in association with EBV infection.

When pancreatitis occurs with cholestasis, biliary tract obstruction is usually suspected as the primary cause, especially in the absence of another obvious etiology. We report a child where this association was secondary to EBV infection without

the suggestive clinical and hematological features of infectious mononucleosis (IM).

Case Presentation

A previously healthy and fully immunized 8-year-old boy presented with a 3-day history of intermittent, generalized abdominal pain, non-bloody non-bilious vomiting, dark urine, light-colored stools and one day history of fever reaching a maximum 38.6°C. There was no underlying hemoglobinopathy, history of abdominal trauma, toxin exposure, recent travel nor any medication intake. The family history was unremarkable.

On physical examination, vital signs were normal, there was scleral icterus, pharyngeal erythema without exudates and

moderate left submandibular lymphadenopathy. The abdomen was soft, non tender with a liver palpable 2 cm below the costal margin. A fine non pruritic sand-paper rash was noted on the trunk and extremities. The rest of the examination was normal.

Blood white count was $8.4 \times 10^9/L$ (75 % neutrophils, 20% lymphocytes), hemoglobin 12.2 g/dL, platelet count $233 \times 10^9/L$. No atypical lymphocytes were seen on the peripheral blood smear. Serum bilirubin was 5.7 mg/dL (normal 0.1-1.0), direct bilirubin 3.0 mg/dL (normal <0.3), total protein 7.1 mg/dL (normal 6.0-7.8), albumin 4.3 mg/dL (normal 3.5-5.5), alanine aminotransferase (ALT) 182 IU/L (normal 8-20), aspartate aminotransferase (AST) 163 IU/L (normal 8-20) and alkaline phosphatase (ALP) 250 IU/L (normal 250-750 IU/L). Serum lipase was 1,000 IU/L (normal 30-210) with normal amylase

levels at 80 IU/L (normal 25-125) and coagulation profile. Ultrasonography of the abdomen revealed a thick-walled gallbladder with minimal pericholecystic fluid but no lithiasis. Magnetic resonance cholangiopancreatography revealed absence of intra or extrahepatic dilation of the biliary tree, no lithiasis, but the pancreas was not perfectly visualized. Serologic tests for hepatitis A, B and C (HBsAg, HBsAb, HbcIgM, HCV Ab, HCV RNA, HAV IgM Ab and HCV Ab), antibodies for cytomegalovirus, coxsackie A and B, antistreptolysin-O, Listeria and antinuclear antibodies were all negative. IgM for EBV viral capsid antigen (EBV VCA) was positive and EBV nuclear antigen (EBNA) IgG was negative, confirming acute primary EBV infection.

A diagnosis of pancreatitis with acute primary EBV infection was made, enteral rest and intravenous fluids were instituted. Over

the next few days temperature rose to 39.5°C, the child looked ill, had conjunctival injection, “strawberry tongue” and worsening of the rash. Blood pressure, heart rate and peripheral perfusion remained stable. Urine and blood cultures showed no growth. Serum lipase level increased to 1,189 IU/L before decreasing to 827 IU/L, while ALT and AST levels decreased significantly to 105 and 51 IU/L respectively. Computed tomography of the abdomen, with both intravenous and oral contrast, showed no abscesses or fluid collection. Abdominal X-ray and sonogram showed no evidence of obstruction or pancreatic cyst formation. All symptoms and the jaundice resolved spontaneously over the next few days, liver function tests progressively normalized and serum lipase levels steadily decreased. He was discharged on day 10 and has remained well on follow up visits over a period of several months.

Discussion

Although the association of cholestatic jaundice with pancreatitis most commonly suggests biliary tract obstruction, this was excluded by several imaging procedures. Despite the absence of the full typical clinical and hematological features of infectious mononucleosis (IM), the diagnosis of acute primary EBV infection was confirmed by elevated serum IgM antibodies to EBV VCA as defined by Klutts (2009).

EBV infection causes asymptomatic self-resolving moderately increased serum aminotransferase levels in 80 to 90% of cases, with of lymphocytic infiltration in sinusoids and portal areas, focal necrosis and intrahepatic cholestasis as described by Crum (2006) and Massei (2001). Rarely, an

autoimmune hepatitis, with moderate necroinflammatory activity and fibrosis, may follow. Fatal chronic active EBV infection mimicking autoimmune hepatitis and caused by virus-associated haemophagocytosis, or by a severe systemic autoimmune disease with autoimmune hemolytic anemia, thrombocytopenia has also been reported. EBV superinfection on pre-existing autoimmune hepatitis may also occur and EBV has been implicated in several autoimmune disorders, but the exact mechanism remains unknown. Despite negative antinuclear autoantibodies and although we did not measure other autoantibodies nor performed an unwarranted liver biopsy, we do not believe that an autoimmune hepatitis occurred in our patient as his liver function quickly normalized within a few days.

Cholestatic hepatitis with EBV infection in a child has been reported by Kang (2013). However, cholestatic manifestations, such as jaundice or pruritus, are rare except in adults and elderly and may occur even in the absence of clinical signs of IM as described by Shaukat (2005) and by Massei (2001) These may sometimes clinically manifest as cholecystitis or be associated with gallbladder dilatation with wall thickening, as in our patient, called acute acalculous cholecystitis as described by Yang (2010).

EBV associated pancreatitis is very rare in children with only three reported cases by Lifschitz (1981), Koutras (1983) and Kang (2013). Although elevated serum or urine amylase levels are helpful for the diagnosis, normal levels may exist in 10-15% of patients. Elevated serum amylase is not specific for pancreatitis as it also occurs in small intestinal obstruction,

mesenteric ischemia, tubo-ovarian disease and renal insufficiency. With its short half-life, levels return to normal within a few days. Serum lipase, with its slightly longer half-life, is more specific for acute pancreatitis. Typically, lipase levels remain elevated 8-14 days longer than amylase levels and may therefore remain elevated after normalization of serum amylase level. The pancreatic enzymes levels do not correlate with the severity of pancreatic injury. EBV infection may also be involved in the development of pancreatitis in the context of drug-induced hypersensitivity syndrome as mentioned by Descamps (2003).

This case highlights the fact that, although the association of cholestatic jaundice with pancreatitis most commonly suggests biliary tract obstruction, EBV infection should always be

considered even in the absence of the full typical clinical and hematological features of IM.

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