

Cholestatic hepatitis: atypical presentation of Epstein-Barr virus infection

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Abstract

Epstein-Barr virus (EBV) primary infection frequently leads to a mild and self-limited increase in liver enzymes. However, clinical manifestations of hepatitis including jaundice are very rare in children. We report a case of an 11-year-old female with fever, vomiting, abdominal pain, jaundice and choluria. The physical examination showed jaundice, cervical adenopathy and mild hepatomegaly. She later developed tonsillitis and a rash. Laboratorial evaluation revealed atypical lymphocytosis (19.3%), increased aspartate aminotransferase 371 IU/L, alanine aminotransferase 373 IU/L and γ -glutamyl transpeptidase 110 IU/L, hyperbilirubinaemia (total bilirubin 14.83 mg/dL, direct bilirubin 11.39 mg/dL), bilirubinuria and hypoalbuminaemia (minimum 2.4 g/dL). The anti-EBV viral capsid antibodies IgM and IgG were positive. Other viral serologies were negative and the abdominal ultrasound was normal. EBV first infection should be considered in the differential diagnosis of cholestatic hepatitis in children.

Keywords

Hepatitis, cholestasis, Epstein-Barr virus.

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Background

Cholestasis in children is rare beyond the neonatal period. The differential diagnosis includes the most common acute viral hepatitis or drug-induced

hepatitis, but also obstructive causes, autoimmune or metabolic diseases [1, 2]. Diagnostic process can be complex.

Epstein-Barr virus (EBV) infection is very frequent worldwide, affecting over 95% of adults and results in a lifelong infection [3, 4]. The primary infection occurs more frequently in children and is usually asymptomatic. Adolescents and young adults may present the classic mononucleosis syndrome of fever, pharyngotonsillitis and lymphadenopathy, a mostly benign and self-limited disease [3].

Although hepatic involvement is common in EBV acute infection, it usually manifests as a transitory elevation of transaminases in up to 80% to 90% of patients [5, 6] Mostly the increase in liver enzymes is mild, lower than in typical acute viral hepatitis, and clinical manifestations of hepatitis are uncommon [7].

Case presentation

A previously healthy 11-year-old female was admitted with a 4-day course of high fever, epigastric and right upper quadrant (RUQ) abdominal pain, asthenia and vomiting. Jaundice and dark-coloured urine were noticed since the previous day. For symptom relief she was on paracetamol in therapeutic dose and denied other medication including over-the-counter or herbal supplements. On admission she presented with jaundice of the skin and mucous membranes, an anterior cervical adenopathy (> 1 cm, soft, painless) with no other palpable peripheral lymphadenopathy; on the abdominal exam: pain at the palpation of the RUQ with the liver edge palpable 1 cm below the right costal margin, without splenomegaly. The oropharynx was normal. On the 4th day of hospitalization the patient showed tonsillar hypertrophy with hyperaemia and bilateral exudate and on the 6th day a generalised maculopapular rash involving the palms appeared.

The initial laboratorial evaluation showed a complete blood count with 9,400 leucocytes/mcL, 42.9% lymphocytes, 19.3% atypical lymphocytes, both haemoglobin 11 g/dL and platelet count 152,000/mcL at the lower limit of normal; elevated enzymes: aspartate aminotransferase (AST) 371 IU/L (> 10 times normal value), alanine aminotransferase (ALT) 373 IU/L (> 6 times normal value), γ -glutamyl transpeptidase (γ -GT) 110 IU/L (2 times normal value), alkaline phosphatase

(ALP) 219 IU/L, lactate dehydrogenase (LDH) 941 IU/L; hyperbilirubinaemia (total bilirubin 14.83 mg/dL, direct bilirubin 11.39 mg/dL), bilirubinuria and hypoalbuminaemia (minimum 2.4 g/dL). The prothrombin time and the C-reactive protein were normal.

Serological studies for viral hepatitis A, B and C were negative and CMV, Herpes simplex 1, Parvovirus B19, Coxsackie virus (A9, A16 and B) and Echovirus were not consistent with acute infection. The anti-EBV viral capsid antibodies (VCA) IgM and IgG were positive and the anti-EBV nuclear antigen (EBNA) IgG antibody was negative. Antigen search for Group A *Streptococcus* in the oropharynx was negative. An abdominal ultrasound showed liver and spleen within the normal limits, a normal gallbladder and non-dilated extrahepatic bile ducts.

This child presented with clinical symptoms and laboratorial evidence of a cholestatic hepatitis associated with EBV infection. Although more typical manifestations of EBV acute infection, namely tonsillitis and rash, appeared only later in the course of the disease, this pathogen was initially suspected due to the presence of atypical lymphocytes.

The treatment was supportive. The patient presented a favourable clinical outcome, with resolution of fever on the 9th day of admission and gradual improvement of jaundice and choluria as well as regression of exanthema and tonsillitis. She was discharged after 11 days. Considering laboratory values, the bilirubin, γ -GT and albumin were normal by the 7th week, although the transaminases remained elevated (AST 76 IU/L, ALT 141 IU/L). There was complete resolution of symptoms and normalization of liver enzymes in the next few months.

Discussion

Elevated liver enzymes are common in the setting of acute EBV infection, although usually mild and asymptomatic. Transaminases increase in the 1st or 2nd week after the onset of disease and normalize in 2 to 6 weeks [6, 8].

Studies have shown that in EBV-associated hepatitis, as defined by an increase in ALT, a cholestatic pattern with elevated γ -GT and ALP is common, in up to 40% of children [5, 9] and 60% in young adults [6]. In these patients with biochemical evidence of cholestasis, the serum ALT level is more significantly elevated and

takes longer to normalize [5, 10, 11], although the course of the disease usually remains benign. Also, in regard to the diagnostic value of liver enzymes, γ -GT elevation seems to be of greater increase in EBV infection comparing to other herpesviruses infection for instance [12, 13].

Although an increase in γ -GT and ALP is common, direct hyperbilirubinaemia and jaundice are very rare. In the review of 36 children with primary EBV hepatitis, Yang et al. [5] reported jaundice in only 5%, similar to previous studies in adults [6].

Our patient presented with symptoms of cholestatic hepatitis, with fever, vomiting, abdominal pain, jaundice and choluria, symptoms also described in other reports of severe hepatitis with EBV infection [14, 15]. In some of these cases the presence of associated acute acalculous cholecystitis (AAC), detected by abdominal ultrasound, has been reported [14, 16, 17]. AAC is rare in children, and was classically described in critically ill patients, however it has been found in the context of acute viral infections, namely EBV infection [17]. The clinical presentation of AAC is unspecific, with similar symptoms from the hepatitis findings. Once primary EBV infection is confirmed, the treatment can be conservative, as viral AAC has a good prognosis usually without complications.

A compromise in liver synthetic function may be found in some cases of EBV hepatitis, with altered coagulation parameters [14, 15]. Our patient presented with low albumin, a finding generally absent in other reported cases of EBV hepatitis [5, 6, 8]. Hypoalbuminaemia is uncommon in acute viral hepatitis and usually reflects a chronic hepatic impairment [18]. The prothrombin time remained normal and there was complete remission of symptoms and laboratory anomalies, reinforcing the benign character of this case.

The progression to liver failure in EBV hepatitis is very rare but has been reported and is associated with a high mortality rate [19, 20].

At presentation, EBV hepatitis may be clinically indistinguishable from other causes of hepatitis because only a minority of patients, 12% to 29%, have the classic mononucleosis syndrome [10, 11]. Some may develop typical symptoms after the onset of jaundice, as in our case.

In reviews of cases of children and adults with EBV-induced cholestatic hepatitis, the prevalence of symptoms are variable: cervical/general lymphadenopathy ranged from 13% to

73%, pharyngitis/tonsillitis 30% to 62% and splenomegaly 53% to 86% [10, 21]. An EBV-infection associated rash is more frequent after the use of antibiotics, and is seldom reported in patients with hepatitis [6].

Laboratory data reveals that most patients presented with atypical lymphocytosis ($\geq 10\%$), which could prompt the diagnosis of EBV infection in the absence of typical clinical manifestations [8, 10].

Unlike other hepatitis virus, EBV does not directly infect hepatocytes and it seems that the host immune response causes indirect liver cell damage [15, 22]. Liver biopsies showed minimal hepatocellular damage [21, 23]. The exact mechanism of cholestasis remains unclear since there is no obstruction of bile flow or stasis, but some authors have suggested the role of inflammatory cytokine-induced disruption, oxidative damage and centrilobular cholestasis [10].

In a study with an adult population, only 0.85% of all patients presenting with jaundice had EBV infection [11], and in a study of Turkish children beyond the newborn period with elevated transaminases, 5% had EBV infection [24].

We found no data regarding the incidence of EBV infection in children with cholestatic hepatitis in developed countries but it may be somewhat significant since there have been some cases published [25].

The diagnosis of EBV associated cholestatic hepatitis requires a combination of clinical and laboratory features and serological findings indicative of a recent EBV infection. We suggest that EBV infection should be suspected and tested in cases of jaundice regardless of the age group, as it has been recognised as a relevant cause of cholestatic hepatitis. Its early identification in suspected cases may prevent unnecessary diagnostic workup.

Typical symptoms are usually absent, but atypical lymphocytosis may be a clue in suspecting EBV infection.

Declaration of interest

The Authors declare that there are no conflicts of interest and no funding to this manuscript.

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