CASE REPORT

Epstein-Barr virus-associated cholestatic hepatitis

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SUMMARY

Epstein-Barr virus infection is common in children, usually presenting as infectious mononucleosis, including fever, tonsillitis and lymphadenopathy associated with self-resolving increase in transaminases. Cholestasis is rare in children with only a few cases reported but it was described in up to 55% of the adult population affected. We present a case of a 6-year-old boy with fever, vomiting and choluria. The physical examination showed hepatomegaly and jaundice and was otherwise unremarkable. The laboratory studies revealed increased transaminases (aspartate aminotransferase 97 U/L, alanine aminotransferase 166 U/L), hyperbilirubinaemia (total bilirubin 3.2 mg/dL, direct bilirubin 2.89 mg/dL) and increased γ-glutamyl transpeptidase (114 mg/dL). Urine urobilinogen was increased. The abdominal ultrasound showed hepatomegaly. Epstein-Barr viral capsid antibody IgM was positive and IgG was negative. Serological studies for other viruses were negative. We underline the need to consider Epstein-Barr virus in the cholestatic hepatitis differential diagnosis, in order to avoid unnecessary investigations.

BACKGROUND

Epstein-Barr virus (EBV) infections are subclinical in 80–90% of cases, particularly among children, causing asymptomatic increases in hepatic transaminases.[1 2] They can also be associated with infectious mononucleosis in adolescents and young adults (30–50%), presenting with fever, pharyngotonsillitis, lymphadenopathy and fatigue, often associated with self-limited increase in transaminase values.[3–5] Cholestatic EBV hepatitis is a rare presentation and severe cholestasis is seen in 5% of cases.[3 4]

CASE PRESENTATION

A 6-year old previously healthy boy presented at the emergency department with fever (axillar temperature of 39.8°C every 4 h), vomiting, fatigue and choluria from past 3 days. He had been medicated with paracetamol 15 mg/kg/dose to a maximum of four times/day during the previous 3 days. No other medication had been carried out.

On admission he was slightly pale, with jaundiced sclerae and had hepatomegaly (2 cm below the right costal margin). No significant lymphadenopathy or splenomegaly was palpable and the oropharynx had a normal appearance.

INVESTIGATIONS

Laboratory studies revealed: 14 200/μL leucocytes (4500–11 000/μL), 63% lymphocytes, haemoglobin 11.8 g/dL (11–13.5 g/dL), platelet count 268 000/μL (150 000–400 000/μL), aspartate aminotransferase 97 U/L (8–20 U/L), alanine aminotransferase 166 U/L (8–20 U/L), total bilirubin 3.2 mg/dL (0.1–1 mg/dL), direct bilirubin 2.89 mg/dL (0–0.3 mg/dL), γ-glutamyl transpeptidase 114 mg/dL (11–50 U/L) and increased urine urobilinogen.

The abdominal ultrasound showed hepatomegaly and was otherwise normal.

Epstein-Barr viral capsid antibody IgM was positive and IgG was negative. Serological studies for cytomegalovirus, hepatitis A, B and C virus, HIV, parvovirus B19, *Brucella*, *Mycoplasma pneumoniae*, *Leptospira* and *Legionella pneumophila* were not compatible with acute infection.

DIFFERENTIAL DIAGNOSIS

The patient presented with confirmed clinical and laboratory cholestatic hepatitis associated to an acute EBV infection. Other serological studies for common pathogens involved in such presentations were negative. The patient was medicated with paracetamol, which could cause drug-induced hepatitis, although this hypothesis was remote, since the duration of treatment was short, the dosage was correct and the outcome was favourable.

OUTCOME AND FOLLOW-UP

The patient evolved favourably, remaining afebrile from the third day of admission and showing complete clinical and analytical remission 2 months after presentation.

DISCUSSION

EBV is a very common infectious agent during childhood, affecting 345–671/100 000 people aged 15–19 years/year, with decreasing incidence in older ages (2–4/100 000/year in the population over 34 years of age).[6] It is usually associated with mild and self-limited hepatitis but there are reports of incidence as high as 55% of severe cholestatic hepatitis in adults.[7]

Atypical manifestations have been increasingly recognised. EBV infection should be considered when facing increased transaminase values and a self-limited cholestatic pattern, even in the absence of other typical symptomatology.[7 8]

Jaundice during EBV infections can be caused by autoimmune haemolytic anaemia or cholestasis (due to acalculous cholecystitis, biliary duct obstruction due to abdominal lymphadenopathy and cholestatic hepatitis).[9–16] Jaundice is more frequent in people aged 35 or older (30%) than in people aged less than 35 years (3%).[12] Increased bilirubin levels have been reported in up to 35% of patients with infectious mononucleosis but is rarely described without splenomegaly, exanthema or tonsillitis.[13]

The severity of the symptomatology is related to the immunological response, which explains why

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EBV infection is frequently subclinical during childhood and frankly symptomatic in adults.[14]

Our patient presented with a pattern of cholestatic hepatitis, with increased direct bilirubin and γ-glutamyl transpeptidase. The abdominal ultrasound showed the absence of cholecystitis or biliary obstruction. Serological results were suggestive of acute EBV infection and the other frequent infectious causes were excluded. No significant medication was carried out that would cause acute drug-induced hepatitis, since acetaminophen toxicity is a predictable intrinsic reaction and our patient had been medicated with a correct dosage.[15]

The mechanism of liver cell damage that leads to cholestasis has not been cleared yet, given the fact that EBV does not cause direct cytotoxic effects on hepatocytes. Cholestasis is possibly related to lipid peroxidation and consequent free radical production, which can explain our patient's clinical presentation.[16]

Although cholestatic hepatitis has been reported mainly in adults,[17] there are reports of atypical presentation of EBV infection associated with cholestasis among children.[11] This case illustrates the importance of considering EBV as an aetiological agent, also in children.[11–13]

Learning points

- Atypical presentations of Epstein-Barr virus (EBV) infection are more common with increasing age but can also be seen in young children.
- Jaundice may be caused by haemolytic anaemia or cholestasis, which makes laboratory studies and ultrasound valuable tools to identify its origin.
- Cholestatic hepatitis, although more commonly caused by pathogens such as hepatitis A, must elicit the hypothesis of infection by EBV.
- Considering EBV is important to avoid unnecessary investigations.

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