CHOLESTATIC HEPATITIS AS A PRESENTATION OF EPSTEIN-BARR VIRUS INFECTION

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ABSTRACT: Epstein-Barr virus (EBV) infection in children and adolescents clinically presents as infectious mononucleosis. Usually, it leads to limited self-elevation of liver enzymes, but cholestatic hepatitis with jaundice is rare. We present a 16-year-old female with fever, fatigue, vomiting, choluria and jaundice. Physical examination showed a painful abdomen, and the remaining examination was unremarkable. Laboratory tests results revealed leucocytosis and activated lymphocytes, normal haemoglobin level, the elevation of transaminases more than 7 times the upper limit, cholestasis and hypoalbuminemia. The abdominal ultrasound showed mild hepatosplenomegaly. Viral serologies revealed positive EBV viral capsid antibody IgM and negative IgG and were negative for other viral agents. Later she developed haemolytic anaemia. She received support treatment and fully recovered. We emphasize that EBV infection should be considered in patients with cholestatic hepatitis with jaundice.

KEYWORDS Epstein-Barr virus, cholestasis, hepatitis, hyperbilirubinemia, jaundice

Background

Epstein-Barr virus (EBV) infection is common in paediatric age. About 50% of the population have contact with this virus until the age of 5 years old, resulting in seropositivity over 95% in adults [1, 2]. The primary EBV infection is usually asymptomatic, but it can present as infectious mononucleosis (IM), more often in adolescents and young adults [1, 3]. A mild and self-limited elevation of liver enzymes is frequent, occurring in up to 80-90% [4-6]. Mild cholestasis can also occur, but jaundice is rare and reported in less than 5% of cases [4-6]. Acute liver failure is rarely reported [7, 8].

Case report

A 16-year-old female with a family and personal history of asthma and food allergies was admitted to the paediatric emergency department with a 6-day history of fever and fatigue and a 2-day history of vomiting, jaundice and choluria, without acholia. Earlier on the 4th day of fever, bilateral periorbital oedema was noticed, resolved in 24 hours. She had no family or personal past history of jaundice, and she was not under any medication for the past 6 months. On examination, the patient had normal vital signs and jaundice of the skin and scleras. The oropharynx examination was unremarkable, with no palpable lymphadenopathy in the head and neck examination. The abdominal palpation was painful in the epigastric region without signs of peritoneal irritation and palpable organomegaly or masses. The remaining examination was unremarkable.

Blood tests showed haemoglobin of 12.6 g/dL, leucocytosis (12300/uL) with lymphocytosis (61%) and activated lymphocytes in the peripheral blood smear, and normal platelet count (139000/uL). The liver and biliary investigation showed elevated aspartate transaminase (AST) and alanine transaminase (ALT) more than 7 times the reference upper limit (253 U/L and 267 U/L, respectively), elevated gamma-glutamyl transferase (GGT) of 158 U/L (12-43 U/L), alkaline phosphatase (ALKP) of 165 U/L (45-116 U/L) and lactate dehydrogenase of 1867 U/L (313-618 U/L), hypoalbuminemia of 2.7 g/dL (3.5-5.0), normal prothrombin time (12.4 seconds), hyperbilirubinemia with total bilirubin of 9.5 mg/dL (0.2-1.3 mg/dL) and direct bilirubin of 7.51 mg/dL (0.0-1.1 mg/dL) and bilirubinuria. The ferritin level was slightly increased (152 ng/mL, normal 6-137 ng/mL). The abdominal ultrasound revealed normal liver texture, mild and homogeneous hepatomegaly and splenomegaly; the gallbladder was empty without bile duct dilation. Serologic investigation for hepatitis A, B and C were negative, while serologies for EBV revealed positive EBV viral capsid antibody IgM (VCA IgM) and negative VCA IgG.

The adolescent was admitted to the paediatric ward with support treatment with intravenous fluid therapy and oral antipyretic as needed. On day 10 of the disease, pharyngotonsil-

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litis with exudate appeared, and infracentimetric cervical lymphadenopathies were palpable. Clinically the patient remained with a low-grade fever for a total of 15 days, and jaundice persisted during the hospital stay. Choluria and nausea gradually disappeared. Analytically the patient developed autoimmune haemolytic anaemia in the first week after admission with minimum haemoglobin of 9 g/dL on day 15 of disease, with subsequent gradual increase, positive direct Coombs test, low haptoglobin level (<20 mg/dL) and a reticulocyte count that remained above 100,000/μL. The patient was discharged on day 15 of the disease. During the next 4 weeks after discharge, the symptoms gradually resolved, jaundice disappeared, and the hepatic enzymes completely normalized. At 3 months follow up, the serum ferritin level also returned to normal.

Discussion

The primary EBV infection usually develops with mild, asymptomatic and self-limited hepatitis in 80 to 90% of cases [4-6]. In EBV infection, the hepatocyte injury is thought to occur indirectly by the host immune response [9]. Typically the elevation of ALT and AST is less than 3 times the normal upper limits [4, 10]. In our patient, the liver aminotransferases elevation was more than 7 times the upper limit of normal, higher than what is seen in typical EBV infection, but similar to other EBV induced cholestatic hepatitis reports [4, 10, 11, 12]. Cholestatic hepatitis with mild elevation of bilirubin can be found more frequently in the adult population, but jaundice was reported in less than 5% of cases [4-6, 10]. In a study including 41 adult and adolescent patients with EBV hepatitis, GGT and ALKP elevations were found in more than half of the patients, but jaundice was rare [5]. There are as few as 20 reported cases of cholestatic hepatitis with jaundice induced by EBV infection [10, 11, 13].

In our patient, the abdominal ultrasound revealed mild splenomegaly and hepatomegaly, which are common findings in EBV infected patients [4, 10]. The gallbladder was unremarkable compared to gallbladder wall thickening found in other similar reported cases [10]. Usually, nobiliary stasis or obstruction are found in imaging of these patients, and the mechanism of cholestasis induced by EBV infection is not well understood [4, 10]. Several explanations have been suggested, including cytokines mediated mechanisms, oxidative damage, infection of biliary epithelial cells and centrilobular cholestasis [5, 10, 11].

Hypoalbuminaemia present in our case is uncommon and rarely reported in EBV hepatitis cases [4-6]. Low albumin was recently reported in two cases of an adolescent and an infant with EBV infection [11, 14].

Autoimmune haemolytic anaemia reported in our patient is a rare finding in EBV infection, described in up to 3% of infectious mononucleosis cases [3]. Like in our case, other authors underline the importance of conservative treatment in EBV related anaemia [15]. However, transfusion support could be necessary in severe cases of haemolytic anaemia in the context of EBV infection [14].

Elevated serum ferritin has been described as an important biomarker associated with the severity of viral disease [15]. In our case, it was only slightly increased and returned to normal after the acute infection. In our case, the typical manifestations of IM, with pharyngotonsillitis and cervical lymphadenopathies, appeared only 10 days after the first signs and symptoms. In a paediatric case series, only 30% of adolescents developed the classical manifestations of EBV acute infection at some stage of disease [10].

Conclusion

We report a case of an atypical presentation of EBV acute infection in an adolescent with cholestatic hepatitis and jaundice preceding the classical signs and symptoms of IM. Thus this infectious aetiology should be considered and investigated in patients with cholestatic hepatitis with jaundice even without typical features of EBV infection.

Disclosures

The authors have no funding or conflicts of interest to disclose.

Authors' Contributions

MN contributed to the conception of the work and data acquisition and wrote the initial draft of the manuscript. JG and SG contributed to the interpretation of data and critically revised the manuscript. All authors were involved in the care of the patient. All authors read and approved the final manuscript.

References

1. Luzuriaga K, Sullivan JL. Infectious mononucleosis. N Engl J Med. 2010;362:1993-2000.

2. Jenson HB. Epstein-Barr virus. Pediatr Rev 2011;32:375-83.

3. Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. Curr Opin Pediatr. 2000;12:263-8.

4. Crum NF. Epstein Barr virus hepatitis: case series and review. South Med. J 2006;99(5):544-7.

5. Kofteridis DP, Koulentaki M, Valachis A, Christofaki M, Mazokopakis E, Papazoglou G, et al. Epstein Barr vírus hepatitis. Eur J Intern Med. 2011;22:73-76.

6. Yang SI, Geong JH, Kim JY. Clinical Characteristics of Primary Epstein Barr Virus Hepatitis with Elevation of Alkaline Phosphatase and γ-Glutamyltransferase in Children. Yonsei Med J. 2014;55:107-112.

7. Shaw NJ, Evans JH. Liver failure and Epstein-Barr virus infection. Arch Dis Child. 1988;63:432-3.

8. Feranchak AP, Tyson RW, Narkewicz MR, Karrer FM, Sokol RJ. Fulminant Epstein-Barr viral hepatitis: orthotopic liver transplantation and review of the literature. Liver Transpl Surg. 1998;4:469-76.

9. Kimura H, Nagasaka T, Hoshino Y, Hayashi N, Tanaka N, Xu JL, et al. Severe hepatitis caused by Epstein-Barr virus without infection of hepatocytes. Hum Pathol. 2001;32(7):757-762.

10. Shkalim-Zemer V, Shahar-Nissan K, Ashkenazi-Hoffnung L, Amir J, Bilavsky E. Cholestatic Hepatitis Induced by Epstein-Barr Virus in a Pediatric Population. Clin Pediatr (Phila). 2015;54(12):1153-1157.

11. Guimarães C, Garrido R, Chaves M, Martins S. Cholestatic hepatitis: atypical presentation of Epstein-Barr virus infection. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2018;7(1):e070118.

12. Salva I, Silva IV, Cunha F. Epstein-Barr virus-associated cholestatic hepatitis. BMJ Case Rep. 2013;2013:bcr2013202213.

13. Tan ZH, Phua KB, Ong C, Kader A. Prolonged hepatitis and jaundice: a rare complication of paediatric Epstein-Barr virus infection. Singapore Med J. 2015;56(7):e112-e115.

14. Amer A, Kaidar M, Tasher D, Lotan A, Dalal I. Epstein-Barr virus infection was associated with nephrotic syndrome, severe thrombocytopenia and coombs-positive haemolytic anaemia. Acta Paediatr. 2018;107(11):2030-2031.