Case Report

Acute Epstein-Barr virus hepatitis presenting clinically as ascending cholangitis in an immunocompetent patient

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ABSTRACT

Symptomatic acute Epstein-Barr virus (EBV) hepatitis, without associated infectious mononucleosis syndrome, is exceptionally rare. A 30-year-old female presented to hospital with jaundice, fevers, and right upper quadrant abdominal pain. Her blood tests demonstrated marked hyperbilirubinemia and mild global liver function test abnormalities consistent with obstructive jaundice. Preliminary imaging with ultrasound showed gallbladder wall thickening and cholelithiasis, suggestive of potential cholecystitis. Authors were concerned for potential ascending cholangitis in the setting of her hyperbilirubinemia. The diagnosis was refuted after magnetic resonance cholangiopancreatography demonstrated no choledocholithiasis. A hepatic panel was performed which revealed positive EBV IgM serology. This case highlights the importance of considering EBV hepatitis as a potential differential diagnosis in patients with right upper quadrant pain, fevers and jaundice in the absence of an obstructing cause.

Keywords: Cholestatic jaundice, Epstein-Barr virus, Hepatitis, Jaundice

INTRODUCTION

Epstein-Barr virus (EBV) is a herpesvirus and one of the most common viruses in the world, with a seroprevalence between 90% and 95%.[1] Infection is usually acquired in childhood, typically via spread of oral secretions, and is asymptomatic.[2] If infection is acquired during adolescence, it usually presents as infectious mononucleosis syndrome with the triad of pharyngitis, lymphadenopathy and fevers. The peripheral blood smear typically shows at least 50% mononuclear cells and 10% atypical lymphocytes.[2]

The liver is affected in greater than 90% of cases of EBV-related mononucleosis, but is usually subclinical and manifests as transient and mild transaminitis.[1] Jaundice has been reported in less than 5% of patients.[3] In adults, acute EBV infection is rare and can present with unusual signs and symptoms, making diagnosis challenging.[2]

CASE REPORT

A 30-year-old female presented to our hospital after 5 days of a nonspecific febrile illness, that initially began as sinusitis and rhinorrhea. She was commenced on oral clarithromycin twice daily by her local doctor on day 5 of symptoms.

Shortly after attending her local doctor, she began to notice upper abdominal pain, dyspnoea, pruritus, scleral icterus, and darkening of her urine and presented to the emergency department. On arrival, she was febrile to 39.7°C, tachycardic to 145 beats per minute and mildly tachypneic to 22 breaths per minute but all other vital signs were within the normal range.
Examination revealed an unremarkable cardiorespiratory examination, with no cervical lymphadenopathy or pharyngitis identified. Her abdomen was soft, but tender in the right upper quadrant and epigastrium with a negative Murphy’s sign.

Her past medical and surgical history was significant only for 2 previous pregnancies and deliveries, with gestational diabetes mellitus, and previous wisdom teeth extraction. Her body mass index was 38.1 kg/m². Her only regular medication was the combined oral contraceptive pill. She was a non-smoker, did not consume alcohol and had no risk factors for blood borne diseases (such as intravenous drug use, previous blood transfusions or tattoos).

Initial laboratory evaluation demonstrated the following: full blood count: normal haemoglobin 133 g/l (115-160 g/l), normal white cell count 10 x 10⁹ cells/l (4-11 x 10⁹ cells/l) and low platelets 101 x 10⁹ cells/l (140-400 x 10⁹ cells/l); deranged liver function tests: total bilirubin 77 umol/l (<20 umol/l), conjugated bilirubin 50 umol/l (<4 umol/l), Alkaline Phosphatase (ALP) 215 U/l (30-110 U/l), Gamma-Glutamyl Transferase (GGT) 291 U/l (<60 U/l), alanine transaminase (ALT) 166 U/l (<34 U/l), aspartate transaminase (AST) 140 U/l (<31 U/l); normal albumin 35 g/l (35-50 g/l); elevated C-Reactive Protein (CRP) 77 mg/l (<3 mg/l); normal lipase 47 U/l (<60 U/l) and largely unremarkable coagulation profile international normalized ratio (INR) 1.0 (0.9-1.2), prothrombin time (PT) 11s (9-13s), activated partial thromboplastin time (APTT) 43s (24-39s).

An ultrasound of her abdomen was performed, revealing a contracted gallbladder containing several small mobile calculi and had normal calibre and free of calculi on the views obtained.

In hospital, the patient was commenced on broad spectrum antibiotics with ceftriaxone and metronidazole to treat empirically for either ascending cholangitis or cholecystitis. She was provided with analgesia and antiemetics as required.

Because of the normal appearance of the bile duct on ultrasound and clinical concern for ascending cholangitis, Magnetic Resonance Cholangiopancreatography (MRCP) was performed the following day to exclude choledocholithiasis and found an oedematous gallbladder with wall thickness up to 15mm containing several gallstones (Figure 2). The common bile duct was free of calculi and had normal calibre and tapering. The liver parenchyma itself showed mild reduction of signal suggesting fatty change.

At the patient’s initial presentation to hospital, a viral serological panel was sent to test for viral hepatitis. Cytomegalovirus, hepatitis A, hepatitis B and hepatitis C viral serology returned negative. However, EBV serology IgM was reactive, with IgG non-reactive, suggestive of acute EBV infection. When the diagnosis of EBV hepatitis was made, antibiotic treatment was discontinued. She remained in hospital for observation and serial blood tests until her hyperbilirubinemia began to improve. Her hyperbilirubinemia peaked on day 3 of her admission with a total bilirubin of 126 umol/l (<20 umol/l) and a conjugated bilirubin of 87 umol/l (<4 umol/l), before improving gradually.

**DISCUSSION**

Diagnosis of EBV infection can be challenging. This case demonstrates the investigative approach undertaken for a patient with a clinical diagnosis of ascending cholangitis due to the presence of Charcot’s triad (fevers, right upper
Liver function derangement during EBV infection usually occurs during the second week of infection, and resolves within 2-6 weeks. Typically, the transaminases (ALT and AST) are affected and will rise up to five times the limit of normal. Elevation of ALP and GGT is also common but is generally not associated with bilirubin rise. Liver synthetic function (as reflected by serum albumin and coagulation parameters) is generally preserved, although can be affected leading to liver failure in rare cases.

The hyperbilirubinemia associated with EBV infection is suggested to be due to intrahepatic cholestasis rather than significant hepatocellular necrosis. The virus affects both systemic and intrahepatic production of pro-inflammatory cytokines, interfering with the activity of sinusoidal and canalicular bile transporting systems. Associated acalculous cholecystitis and biliary duct obstruction from abdominal lymphadenopathy have also been reported as causes for hyperbilirubinemia in EBV infection. There have been several case reports and case series of patients with acute EBV induced hepatitis, with severity ranging from mild to severe. Severe cases, and even fatality, is more common in immunocompromised patients. EBV hepatitis can become chronic in a minority of cases, or even trigger autoimmune hepatitis and resulting chronic liver disease.

Investigation of liver function test derangement, when suggestive of an obstructive pattern, relies heavily upon imaging studies. Ultrasonography is the first line technique and can assess for cholecystitis (sensitivity 81%, specificity 83%) and choledocholithiasis (sensitivity 73%, specificity 91%). MRCP is a more powerful, expensive tool reserved for inconclusive cases of choledocholithiasis (sensitivity 90%, specificity 95%). It should be noted that acute cholangitis can occur without imaging evidence of biliary tree dilation, even in the presence of common bile duct stones. Gallbladder wall thickening is commonly observed on ultrasonographic examination in patients with active viral hepatitis, and wall thickness exceeding 3 mm has been proposed as a marker of severity of infectious mononucleosis syndrome. Studies of pediatric cases of EBV hepatitis revealed gallbladder wall thickening in 45-50%. From authors review of the literature, the majority of patients presenting with acute symptomatic EBV hepatitis, without infectious mononucleosis syndrome, have normal biliary tree imaging without dilatation. In one case report, a patient had a mildly dilated common bile duct at 9 mm and underwent ERCP to exclude biliary obstruction, which revealed no abnormality. Differentiation of EBV infection from intrabdominal infection is important to avoid side-effects associated with misplaced antibiotic treatment. Patients was covered empirically with broad spectrum antibiotics while awaiting test results. It is well known that some antibiotics, notably amoxicillin and ampicillin, can lead to severe generalized rashes in patients with EBV infection. This was not observed in this case.

Treatment of EBV hepatitis is usually supportive, with most cases resolving spontaneously as in this case. Corticosteroids, antiviral medications, and orthotopic liver transplantation have been proposed as therapeutic options in cases of severe EBV hepatitis. In one report, ganciclovir administration resulted in rapid clinical response and improvement in liver enzymes in two patients with severe EBV hepatitis. Corticosteroids have been used to treat adenopathy and splenomegaly in patients with EBV infection, although the benefits in hepatitis are difficult to ascertain. Ursodeoxycholic acid to improve bile flow has also been proposed as a therapeutic option in cases of severe and persistent cholestasis.

In summary, although rare, adult acute EBV infection is possible and can present with atypical signs and symptoms. EBV hepatitis can cause a cholestatic picture of liver function test derangement. Clinicians should be aware that EBV hepatitis is a differential diagnosis in the patient with right upper quadrant abdominal pain, jaundice and fevers, as early detection of EBV hepatitis could mitigate the need for invasive investigations such as ERCP.

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REFERENCES
