Epstein-Barr virus-related infectious mononucleosis presenting as cholestatic hepatitis

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Abstract

A 17-year-old female was admitted to the emergency room for fever, cervical lymphadenopathy and jaundice. Initial inpatient laboratory tests showed elevated transaminases and conjugated hyperbilirubinemia, along with a hepatobiliary ultrasound showing mild splenomegaly with no bile duct obstruction. Epstein-Barr virus capsid antibodies were also detected, confirming the diagnosis of acute cholestatic hepatitis secondary to a primary Epstein-Barr virus infection.

The objective of this case report is to present an atypical clinical manifestation of the disease, highlighting the importance of maintaining high clinical suspicion, beginning with the diagnostic approach, and appropriately ruling out other diseases that may have similar symptoms. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.4677).**

Keywords: *Epstein-Barr virus (EBV), infectious mononucleosis, cholestatic hepatitis*.

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Introduction

Epstein-Barr virus (EBV) belongs to the herpesvirus family and is one of the most prevalent pathogens among humans. It is mainly transmitted through oral secretions, with close contact, like kissing, being a common pathway of infection. Primary EBV infection may be asymptomatic, especially in children, or manifest as infectious mononucleosis (IMN), of which EBV is the main etiological agent in more than 90% of cases (1, 2).

Infectious mononucleosis is characterized by fever, adenopathy, splenomegaly and tonsillitis, along with an increased number of atypical lymphocytes in peripheral blood. While most EBV infections present mild, self-limited hepatic abnormalities, it has been documented that less than 5% of patients may develop acute cholestatic hepatitis, a rare form that is distinguished by a significant increase in alkaline phosphatase and direct bilirubin, indicating bile duct obstruction. The diagnosis is usually confirmed with blood tests, which can detect heterophile antibodies or anti-viral capsid antigen IgM (2).

Clinical case

A female adolescent patient consulted in the emergency room with a complaint of five days of odynophagia, fever of 39.2 degrees Celsius (°C), a feeling of a mass in the neck, jaundice, asthenia, diffuse abdominal pain, acholia and choluria.

On physical exam, she had generalized jaundice and cervical lymphadenopathy that was painful to palpation, with neck edema, whitish plaques on her tonsils and right upper quadrant pain.

The patient´s admission labs included a complete blood count with normal hemoglobin, no thrombocytopenia, and mild, predominantly lymphocytic (mononuclear), leukocytosis. Her liver panel showed elevated transaminases, direct hyperbilirubinemia, and elevated alkaline phosphatase and gamma-glutamyl transferase, constituting a cholestatic pattern (with an R factor of 1.8). The rest of her laboratory tests were within normal limits (Table 1).

Imaging studies were done due to cervical lymph node enlargement, with ultrasound showing bilateral inflammation of level I-B lymph nodes, bilaterally, and a total abdominal ultrasound showing mild hepatosplenomegaly. Magnetic resonance cholangiopancreatography showed no evidence of bile duct obstruction, ruling out obstruction as the etiology of the clinical picture. She had negative serum tests for hepatitis A, B, and C, as well as cytomegalovirus. Finally, anti-EBV capsid antigen IgM antibodies were positive (Table 2).

After evaluating the clinical picture and paraclinical findings, she was diagnosed with a primary EBV infection associated with IMN, which presented atypically with acute cholestatic hepatitis (3). She began supportive therapy, and on the fourth day, had resolved hyperbilirubinemia, lower

Table 1. *Admission laboratory tests.*

Laboratory test	Value
Complete blood count	Leukocytes: 10,530 per microliter (mcL) Neutrophils: 27.2% Lymphocytes 48% Hemoglobin 12.40 g/dL Platelets: 198,000 per microliter (mcL)
Peripheral blood smear	No atypical lymphocytes
Transaminases (NV: ALT < 40 IU/L, AST < 40 IU/L)	ALT: 256.50 U/L AST: 188.7 U/L
Bilirubin (NV: BT < 1.2 mg/dL)	BT: 5.23 mg/dL BD: 4.94 mg/dL BI: 0.29 mg/dL
Alkaline phosphatase (NV: 40-130 IU/L)	428 IU/L
Lactate dehydrogenase (NV: 135- 225 IU/L)	484 IU/L
Ferritin (NV: 20-300 ng/mL)	188 ng/mL
Gamma-glutamyl transferase (NV: 5-36 IU/L)	225 IU/L
Creatinine	0.56 mg/dL
Blood urea nitrogen	7.7 mg/dL
Coagulation times	INR: 1.04 - Normal

NV: normal value. ALT: alanine aminotransferase, AST: aspartate aminotransferase, PT: prothrombin time, PTT: partial thromboplastin time, INR: international normalized ratio.

Table 2. *Complementary serological tests.*

Laboratory test	Value
HAV IgM antibody	0.24 (NR)
HBV surface antigen	0.27 (NR)
HBV core antibody	0.22 (NR)
CMV IgG and IgM antibodies	0.04 (NR)
CMV IgG and IgM antibodies	0.30 (NR)
IgM antibodies to EBV capsid antigen	> 160 (Positive)

NR: non-reactive, HBV: hepatitis B virus, HAV: hepatitis A virus, HCV: hepatitis C virus, CMV: cytomegalovirus, EBV: Epstein-Barr virus

transaminases, no fever and overall improvement of her symptoms, and was therefore discharged.

Discussion

Epstein-Barr virus (EBV) belongs to the human herpesvirus family, classified as type 4, made up of double-helix deoxyribonucleic acid (DNA), surrounded by a protein capsid and lipid envelope (4).

It is responsible for up to 90% of infectious mononucleosis (IMN) cases in children and adolescents, is transmitted through oral secretions, invades the oropharyngeal mucosa, and activates a T-lymphocyte-mediated cytotoxic response (4). Most patients with EBV infections are exposed early in life; therefore, acute infection is not often diagnosed in adulthood. Most of these infections are benign and have a good prognosis, as they tend to be self-limited (5, 6).

Liver damage is common in EBV infections. Approximately 75% of patients have elevated transaminases. A Colombian study characterizing patients with EBV infections found that this percentage was only 49.1 and 54.2% (7). However, there was a less than 5% incidence of cholestatic hepatitis, which was considered an atypical manifestation of the disease (8, 9).

Epstein-Barr virus has little tropism for hepatocytes or bile duct epithelial cells. However, the inflammatory response is thought to possibly be mediated by estrogen-dependent eicosanoids, as well as by lipid peroxidation and free radical production, as mechanisms of hepatocyte injury. As far as the cholestatic pattern, its etiology has not been determined, but it could be explained by superoxide dismutase inhibition or direct viral infection of the bile duct epithelium (although this is less likely due to the virus's tropism) (8-10).

Typical histological findings in EBV infections include an elevated number of lymphocytes in the hepatic sinusoids, often arranged in single file, as well as degenerative changes in the hepatocytes. These changes can include acidophilic bodies and moderate hepatocellular necrosis. However, it is important to note that the characteristic viral inclusions are not often found in these cases (8).

The diagnosis is based on clinical suspicion. A descriptive Colombian study found a fever in more than 90% of the patients, enlarged lymph nodes in 64.8%, pharyngitis in 58.2%, hepatosplenomegaly in 27%, and lymphocytosis in 28.6%, but the most interesting part of the study was monocytosis in 90.1%. In addition, elevated alkaline phosphatase (ALP) at two times the normal limit, elevated bilirubin, and three times the upper limit of gamma glutamyl transferase (GGT), with an alanine aminotransferase ratio (ALT/ALP) of less than two have been reported (8). The diagnosis is subsequently complemented with blood tests, including heterophile antibodies (Paul-Bunnell test), which is a non-specific method. On the other hand, anti-viral capsid IgM antibodies are more specific (9, 11).

According to case series findings, the liver impairment associated with EBV is benign and does not require treatment. However, a retrospective cohort of 166 adult patients proposed the use of glucocorticoids, considering cholestatic hepatitis to be a serious manifestation of EBV infection. Transaminase levels decreased during the first week of treatment, with persistent markers of cholestasis (bilirubin and GGT). There was no evidence of benefits in hard outcomes like mortality or fulminating liver failure, and therefore glucocorticoids are not routinely used (12, 13).

In our clinical case, other etiologies of cholestatic hepatitis were ruled out, mainly hepatotropic viral infections

like hepatitis A, B and C. Despite having a classic IMN presentation and positive blood tests for EBV, given the low prevalence of cholestatic involvement, other possible causes (infections and bile duct obstruction) were ruled out first. Supportive measures were provided, and the fever, lymphadenopathy and hepatitis resolved within 72 hours.

Conclusion

Ebstein-Barr virus is highly prevalent in young adults and adolescents and is characterized by a varied presentation which may range from an asymptomatic infection to IMN, with fever, lymphadenopathy, pharyngitis and an inverted blood differential. It can also debut with elevated transaminases in a high percentage of people, and less frequently, it presents with a cholestatic pattern, which is considered an atypical manifestation.

It is extremely important to be aware of these types of presentations, as this helps provide a differential diagnosis when dealing with a patient with fever and acute cholestatic hepatitis. We emphasize the ease of serological diagnosis for healthcare staff, as there are tests available with high sensitivity and specificity, such as anti-capsid antibody tests, that enable proper patient diagnosis in patients in whom other hepatotropic viruses have been ruled out. Finally, we would like to point out that, in most reviews, this disease is reported as benign, and therefore more studies are needed on the use of corticosteroids, if they are to be considered as a treatment option.

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