TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Internal Medicine

Acute cholestatic hepatitis due to infectious mononucleosis: A case report

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ABSTRACT

Cholestatic hepatitis is a rare complication of acute Epstein-Barr virus (EBV) infection. Here, we presented a case of acute cholestatic hepatitis secondary to acute infectious mononucleosis, who presented with complaints of abdominal pain, yellowing of the eyes and body, itching, widespread body pain, fever, nausea and vomiting. It was emphasized that EBV infection should also be considered in the differential diagnosis of cholestatic hepatitis etiology.

Turk J Int Med 2024;6(2):97-101
DOI: 10.46310/tjim.1303184
Case Report

Keywords: *Cholestatic hepatitis, EBV, infectious mononucleosis*

Received: *May 29, 2023;* ***Accepted:*** *February 4, 2024;* ***Published Online:*** *April 29, 2024*

How to cite this article: *Satılmış O, Ozturk Y, Yönet F, Özer H, Keskin PB, Baloğlu İ, Asıl M, Tonbul HZ. Acute Cholestatic Hepatitis Due to Infectious Mononucleosis: A Case Report. Turk J Int Med 2024;6(2):97-101. DOI: 10.46310/tjim.1303184*

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INTRODUCTION

Epstein-Barr virus (EBV) is from the Herpetoviridea family. It is transmitted from person to person through close contact with the mouth, throat fluids, and bodily secretions. The virus infects pharyngeal epithelial cells and B lymphocytes and causes polyclonal B lymphocyte proliferation. Acute infectious mononucleosis caused by EBV is a disease characterised by lymphadenopathy, sore throat, fever, and positivity of heterophile antibodies in serology.[1] Cases with hepatic involvement are mostly asymptomatic, and in approximately 80-90% of these cases, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) values can reach two to three times the normal value. Cholestatic hepatitis, consistent with serum alkaline phosphatase (ALP) and bilirubin differences, is rare and may occur in less than 5% of cases. In cases with liver involvement, liver enzymes usually regress to normal values within [2-6] weeks. It has been reported in the literature that there are cases of fulminant hepatitis due to acute EBV infection.[2-7] Herein, a case of acute cholestatic hepatitis due to EBV is described to remind EBV infection in the differential diagnosis of cholestatic hepatitis.

CASE REPORT

A 19-year-old female patient with no known additional disease was admitted to our hospital with complaints of jaundice, itching, myalgia, abdominal pain, fever, nausea and vomiting that lasted for seven days. She applied to the gastroenterology clinic with preliminary diagnoses of acute hepatitis and cholangitis due to elevated LDH, ALP, bilirubin and liver enzymes. It was learned that she had upper respiratory tract infection complaints a week ago. There were no complaints of weight loss or night sweats. The patient's personal and family history was unremarkable. Physical examination revealed icterus in the sclera, closed traube's space, and painful lymphadenopathy with firm palpation lymphadenopathy of the right anterior cervical triangle of the neck. No pathological finding was detected in other system examinations.

In laboratory tests, she had lymphocytosis, monocytosis, increased liver disease, and hyperbilirubinemia *(Table 1).* Complete urinalysis, blood culture, and urine culture were taken from the patient with a fever of 38.8 °C. Bilirubin (2+) and leukocyte (–) were found in the requested complete urinalysis. The patient, who had a refractory high fever, was started on intravenous hydration with 0.9% isotonic sodium chloride, ursodeoxycholic acid and paracetamol treatments, and empirical ceftriaxone 2 g/day. In the abdominal ultrasonography of the patient, the spleen was approximately 14 cm in the long axis, and no dilatation was observed in the intra-extrahepatic bile ducts. In magnetic resonance cholangiopancreatography (MRCP), the gallbladder contracted, intrahepatic and extrahepatic bile ducts were normal, and the common bile duct was not dilated. No filling defect compatible with the stone was detected in the lumen of the common bile duct, and it was observed that the pancreatic duct was not dilated. The absence of pathology in the biliary tract on imaging excluded extrahepatic cholestasis causes such as choledocholithiasis in the diagnosis.

Ceftriaxone was discontinued, and empiric piperacillin-tazobactam intravenous treatment of 4.5 g 4 times a day was started on the third day of the patient's hospitalisation, whose refractory fever continued on the third day of his treatment and whose clinical symptoms did not improve. Liver kidney microsomal antibody (LKM), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and anti-nuclear antibody (ANA) results of autoantibody tests were negative. Downey cells were seen in the peripheral smear of the patient whose serological examinations showed Brucella immunocapture (–), Salmonella TO (–), EBV VCA IgM (+), CMV IgM (+) *(Figure 1).* Anti-HAV IgM (0.08 S/CO; 0.8-1.2), anti-HBc IgM (0.15 S/CO; 0-1), HBsAg (0.05 S/CO; 0-1), anti-HIV (0.01 S /CO; 0-1) and anti-HCV (0.04 S/CO; 0.02-0.07) were negative. Beta-HCG was 1 mIU/mL (0-5).

The CMV DNA requested from the CMV IgM-positive patient resulted in negative. The patient's peripheral smear showed no schistocyte, and the Coombs test was negative. There was no growth in blood, urine, and stool cultures. On the seventh day of piperacillin-tazobactam treatment, macular eruptions were observed all over the body, which faded with pressure. Bacterial infections were excluded, and piperacillin-tazobactam was discontinued on the eighth day in the patient with no growth in 3 sets of blood cultures. It was observed that the rashes regressed and disappeared in the follow-up after the antibiotic treatment was discontinued.

The patient's clinical complaints were seen

Table 1. Patient's initial, highest and discharge values

Laboratory tests	Initial values	Highest values	Discharge values
Haemoglobin (g/dL) (12.1-17.2)	8.7		11.8
Lymphocyte (10^3/µL) (0.8-5.5)	5.83	6.42	4.19
Thrombocyte (10^3/µL) (150-400)	181		361
Monocytes (10^3/µL) (0.2-0.9)	0.98	1.78	0.48
LDH (U/L) (135-214)	711	825	257
ALP (U/L) (45-87)	213	434	138
Total bilirubin (mg/dL) (0.2-1.2)	12.39	18.39	2.12
Direct bilirubin (mg/dL) (0-0.3)	10.86	16.9	1.77
AST (U/L) (0-33)	120	208	36.3
ALT (U/L) (0-32)	183.2	201	67.2
CRP (mg/L) (0-5)	41.84	58.64	2.33
GGT (U/L) (0- 40)	173	179	36
INR (0.8-1.2)	1.2		0,98
Calcium (mg/dL) (8.4-10.2)	9.06		9,31
Sedimentation rate (mm/h) (0-20)	10	19	10

after an upper respiratory tract infection; she had lymphadenopathy and she had a rash with beta-lactam antibiotics. Considering the presence of lymphocytosis and monocytosis in the complete blood test, the appearance of Downey cells in the peripheral blood smear, and the positivity of EBV VCA IgM, the patient was diagnosed with cholestatic hepatitis due to acute EBV infection.

The patient continued to be followed up with intravenous hydration with 0.9% isotonic sodium chloride, ursodeoxycholic acid and paracetamol treatments. On the 10th day of the patient's follow-up and treatment, complaints of fever, jaundice, nausea, itching, and abdominal pain regressed. Decreases in liver enzyme and bilirubin levels were reported in control examinations. ALP 138 U/L (45-87), LDH 257 U/L (135-214), total bilirubin 2.12 mg/dL (0.2-1.2), direct bilirubin 1.77 mg/dL (0-0.3), C-reactive protein the patient's blood pressure level was 2.33 mg/dL (0-5), and the patient was discharged as the patient had no active complaints.

DISCUSSION

Studies on EBV show that 90-95% of adults have encountered the virus at some point in their lifetime.[2,3] It is known that the virus, which remains in the B lymphocytes and tonsil crypt epithelial cells of seropositive individuals for life, is transmitted to seronegative people through the infected person's secretions.[4,5] The most common symptoms in patients are nonspecific complaints such as fatigue, loss of appetite, muscle pain and headache. The classic symptoms of infectious mononucleosis are fever, sore throat, and lymphadenopathy.[2,8] Hepatomegaly and splenomegaly may also be seen in physical examination.[9,10]

In 80-90% of infectious mononucleosis cases, liver enzymes usually increase twice or three times the normal level. Hyperbilirubinemia can be seen in 45% of patients and jaundice in 5%.[11] Cholestatic hepatitis due to EBV is a rarely reported picture. The pathogenesis of cholestasis due to EBV infection is still not fully elucidated. There are opinions that inflammation in the bile ducts is caused by the accumulation of EBV-infected activated T lymphocytes in the liver or by activating autoantibody-mediated free radicals and directly damaging hepatic cells.[12-14]

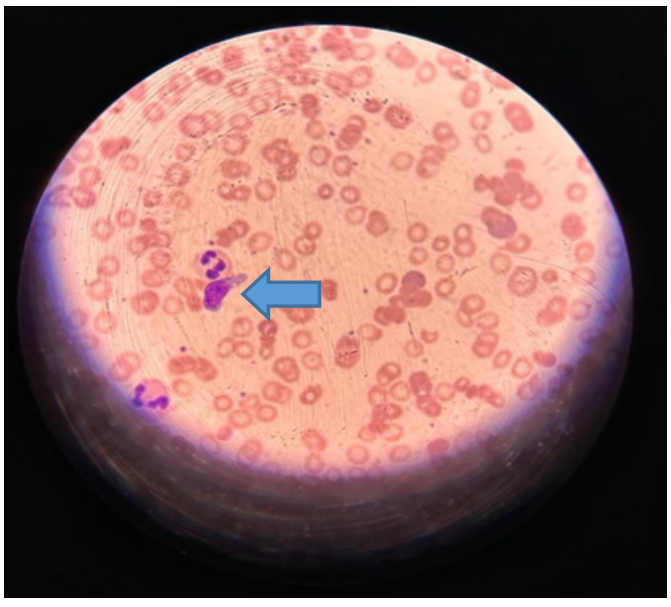

Figure 1. Downey cell seen in the patient's peripheral blood smear

The disease diagnosis is usually made by laboratory findings, clinical, heterophile antibodies, and antibodies specific to EBV.[15] When cholestatic hepatitis is considered, the causes of intrahepatic cholestasis should be investigated after excluding causes of biliary obstruction such as choledocholithiasis. Hepatocellular diseases characterised by hyperbilirubinemia and cholestasis generally develop in viral infections, paraneoplastic syndromes, alcoholic hepatitis, and after using drugs such as phenytoin, erythromycin, and estrogen. Apart from primary biliary cirrhosis and gestational cholestasis, infiltrative disorders such as lymphoma, sarcoidosis, and amyloidosis are causes of intrahepatic cholestasis. In addition to hepatitis A, B, C, and E, it is known that EBV, CMV, Herpes, and rubella are also involved in the viral aetiology of intrahepatic cholestasis.[16-19]

As in our patient, anaemia and thrombocytopenia can be seen in complete blood count in infectious mononucleosis cases; however, lymphocytosis and monocytosis are frequently seen in the blood picture.[3] In addition, lymphocytes known as "Downey cells" can be seen in the peripheral blood smear, with blue cytoplasms, large, and adhered around the erythrocytes.

In our case, the absence of risk factors such as alcohol use, pregnancy, medication for cholestasis, negative results of viral hepatitis etiological tests, lack of pathological appearance in the bile ducts related to stones, and obstruction in abdominal ultrasonography and MRCP directed us to further investigations and other causes. Cholestatic hepatitis due to acute EBV infection in a patient with a clinical picture compatible with infectious mononucleosis, anaemia, monocytosis, and lymphocytosis in complete blood examination, elevated liver enzymes, elevated ALP, LDH, and bilirubin, Downey cells in peripheral blood smear, EBV VCA IgM (+) diagnosis was made.

Cholestatic hepatitis due to EBV is generally a self-limiting disease with no specific treatment. In our case, after bacterial infections were excluded, antibiotic therapy was discontinued, and follow-up was continued with intravenous 0.9% isotonic sodium chloride hydration, ursodeoxycholic acid, and paracetamol symptomatic treatments. The laboratory values of the patient, who was followed up without any specific treatment other than symptomatic treatment, decreased, and her symptoms disappeared.

CONCLUSIONS

One of the causes of cholestasis is EBV infection. Therefore, if there is an increase in liver enzyme levels, ALP, LDH and bilirubin levels in a patient with fever, CMV and EBV infections should be considered in the differential diagnosis.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: HZT, OS; Study Design: YÖ, FY, PBK; Literature Review: PBK, MA; Critical Review: MA, OS; Data Collection and/or Processing: OS, YÖ,; Analysis and/or Data Interpretation: FY, İB; Manuscript preparing: YÖ, OS, HÖ.

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