Case Report

Acute Epstein-Barr virus Encephalitis and hepatitis without mononucleosis syndrome: a case report
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Abstract

Background: Epstein-Barr virus (EBV) mononucleosis is rarely associated with central nervous system (CNS) abnormalities, which usually appear later in the course of the illness. Neurological disorders caused by EBV infectious mononucleosis include optic neuritis, transverse myelitis, meningoencephalitis, cranial nerve (CN) palsies, and Guillain-Barré syndrome. Primary EBV infection often leads to elevated liver enzymes and infectious mononucleosis syndrome, but acute symptomatic hepatitis without typical EBV presentations is relatively uncommon. We present the case of a 12-year-old male who presented with fever, lethargy, and unusual behavior for one day, and fever for five days. The physical examination results were normal. Changes in EBV specific antibodies and EBV PCR were used to diagnose EBV encephalitis when normal examinations revealed symptoms of acute hepatitis.

Introduction

Children often contract primary Epstein-Barr virus (EBV) infections, which are often asymptomatic. EBV can cause central nervous system (CNS) disorders such as acute disseminated encephalomyelitis (ADEM), transverse myelitis, and radiculopathy 1. Mental decline is the most common clinical symptom of EBV encephalitis, leading to hospital admission for many patients. 2, 3. Rare cases of acute symptomatic hepatitis without infectious mononucleosis syndrome also occur in association with this condition. However, the majority of abnormal liver function tests in primary infections resolve on their own 4, 5. In this article, we describe a case of EBV encephalitis and hepatitis detected by EBV-specific antibody and EBV-PCR.

Case Report

A 12-year-old male was admitted to our hospital with a 5-day history of fever and sore throat. He received symptomatic treatment including paracetamol and azithromycin. Upon admission, he appeared lethargic and was found to have a tachycardia of 110 beats per minute, with an oral temperature of 38.5 degrees Celsius. There was found to have a tachycardia of 110 beats per minute, with fever, lethargy, and unusual behavior for one day, and fever for five days. The physical examination results were normal. Changes in EBV specific antibodies and EBV PCR were used to diagnose EBV encephalitis when normal examinations revealed symptoms of acute hepatitis.

During neurological examinations, he was drowsy and unresponsive to verbal commands, with normal-sized and reactive pupils. Other examinations were unremarkable, except for an unsteady gait and neck stiffness.

The laboratory findings were as follows: leukocyte count of 9,800/µL (segmental neutrophil 85.3%, lymphocyte 10.5%, and monocyte 4.2%), hemoglobin 12.5 g/dL, platelet count 115,000/µL, serum potassium 5.1 mEq/dL, sodium 133 mEq/dL, total calcium 9.5 mg/dL, urea 51.4 mg/dL, creatinine 0.7 mg/dL, glucose 103 mg/dL, INR: 1.09, PTT: 86.0, AST: 492 IU/L, ALT: 750 IU/L, Alk Ph: 694 IU/L, bilirubin (total): 2.0 mg/dL, bilirubin (direct): 1.0 mg/dL, albumin: 3.0 g/dL, amylase: 19 IU/L (normal), uric acid: 3.6 mg/dL, CRP: 133. Cerebrospinal fluid (CSF) analysis revealed white blood cell count less than 5/mm³, protein 24 mg/dL, and sugar 69 mg/dL, PT: 13.6.

The patient was suspected to have a non-hematotropic virus causing cerebral and hepatic manifestations. We conducted CMV-IgM (negative) and viral capsid antigen (VCA) for EBV (IgM) tests, which resulted in a negative value of 7.84. Based on these serologic results, an EBV-PCR was requested, which indicated a positive result with a viral load of 151,000 IU/mL.

On the radiological examination, abdominal ultrasonography indicated that the liver was mildly enlarged, measuring about 15 cm, with increased echogenicity (grade 2 fatty liver). The spleen was enlarged, measuring 145 mm in length, and the portal vein diameter was 10 mm with normal flow. The suprahepatic inferior vena cava was normal, and the gallbladder and biliary tree showed no signs of cholestasis. There were no ascites present in the abdominal cavity. A brain CT scan revealed nonspecific evidence of brain oedema.

The patient was suspected to have a non-hematotropic virus causing cerebral and hepatic manifestations. We conducted CMV-IgM (negative) and viral capsid antigen (VCA) for EBV (IgM) tests, which resulted in a negative value of 0.11. The EBV (IgG) test yielded a positive value of 7.84. Based on these serologic results, an EBV-PCR was requested, which indicated a positive result with a viral load of 151,000 IU/mL.

Additionally, blood culture, urine culture, and CSF culture all returned negative results, as did a PPD test. The serologic testing was consistent with acute EBV infection, showing a positive result for viral capsid antigen (VCA) IgG and a negative result for VCA IgM. The CMV PCR was positive, indicating cerebral and hepatic infections.

The patient was given empirical intravenous antibiotics and Acyclovir. They showed improvement on the second day and were discharged after 7 days. One week after

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discharge, follow-up tests showed the following laboratory parameters: AST: 56 IU/L, ALT: 128 IU/L, alk ph: 277 IU/L, bilirubin (total): 0.8 mg/dL, bilirubin (direct): 0.3 mg/dL, albumin: 4.0 g/dL, leukocyte count: 6,400/µL (segmental neutrophil 64.5%, lymphocyte 22.2%, and monocyte 13.3%), hemoglobin: 13.5 gr/dl, platelet count: 165,000. Three weeks after discharge, the follow-up tests showed the following laboratory parameters: AST: 39 IU/L, ALT: 44 IU/L, Alk. ph: 210 IU/L, bilirubin (total): 0.8 mg/dL, bilirubin (direct): 0.3 mg/dL, albumin: 4.3 g/dL. Over the course of six months of follow-up, all hematologic and liver function tests remained normal, and the EBV viral load became negative.

Discussion

Epstein-Barr virus (EBV) infection is widespread, with a prevalence of over 90% 5. It is often asymptomatic in children but can cause mild liver involvement in adults. Symptoms in adults typically include sore throat, fever, enlarged lymph nodes, and mild liver inflammation 5. Most cases of EBV-related liver involvement are self-limiting and can be managed with supportive care 7.

In a study by Koffertidis et al, transaminase levels increased in the first week, peaked in the second week, and returned to normal in the third week after the infection began 8. Our patient's transaminase levels rapidly increased, reaching their peak within 72 hours of admission, followed by a gradual decline and complete normalization by the end of the second week. In over 90% of cases of EBV-related mononucleosis, liver involvement is present, but it is often either subclinical and self-limited or manageable with supportive treatment alone 9. The causes and immune mechanisms of these abnormalities are not well understood, and there are no standard diagnostic criteria or management recommendations available. The severity of the condition varies, from asymptomatic hepatitis to rare cases of acute liver injury. Patients with hepatitis due to primary EBV infection may develop cholestatic features, and adults are more likely to present with jaundice than children. Jaundice in infectious mononucleosis may be caused by hemolysis or cholestasis. The condition typically resolves on its own within a few weeks 10.

The cause of EBV-hepatitis is still not fully understood. Infection of liver cells with primary hepatotropic viruses like hepatitis B or C does not directly damage the cells. Instead, symptoms of liver injury occur as a result of the immune system's response to viral antigens presented by infected liver cells 11, 12. Hepatocytes, biliary, and sinusoidal epithelium are not targeted by EBV 13. The liver tissue and bile transport systems may be affected by EBV infection through the virus's impact on the synthesis of pro-inflammatory cytokines. EBV-infected CD8+ T cells in the liver can release inflammatory mediators, including tumor necrosis factor α, interferon-γ, and Fas ligand. Additionally, the production of autoantibodies may inhibit antioxidant mechanisms 14. EBV infections can cause symptoms such as meningoencephalitis, encephalitis, seizures, peripheral neuritis, Guillain-Barre Syndrome, Bell's palsy, and cerebellar ataxia, either alone or alongside infectious mononucleosis 15,16. Laboratories use EBV-specific antibody detection to diagnose EBV infection and differentiate it from other causes of viral hepatitis. The EBV genome encodes various structural and nonstructural genes, with the most important for serodiagnosis being the genes for VCAs, EAs, and EBNAs. In immunocompetent individuals, only three serological parameters are necessary for qualitative detection of EBV-specific antibodies: VCA IgG, VCA IgM, and EBNA-1 IgG. VCA IgG and EBNA IgG indicate past or latent EBV infection, while VCA IgM helps identify acute infection 17.

Immunofluorescence (IF) is considered the "gold standard" for detecting antibodies, but enzyme immunoassays (EIAs) have also shown good sensitivity and specificity. Today, most laboratories use EIA for diagnosing EBV infection. IgM responses against VCA appear early and disappear within 4-6 weeks of infection. The original serological test for IM, the Paul-Bunnell test for detecting heterophile antibodies by agglutination of sheep or horse red blood cells, is less sensitive and specific 18. The serological picture in some patients may be complex due to extensive antigenic cross-reactivity within the herpes group of viruses 19.

Confirmatory diagnosis of acute EBV infection with atypical clinical features is done using quantitative real-time PCR on blood, plasma, or tissue samples. Immunocompetent patients with EBV infections typically have viral loads higher than 1,000 copies/ml of whole blood during the first 7-10 days of illness. After this period, the viral load declines and becomes non-detectable during the latency phase of the illness 20.

Compared to adults, EBV-IM is more harmful in children. Antiviral drugs are widely used for treatment, but the best choice is still debated. Acyclovir and ganciclovir are broad-spectrum antiviral drugs, with acyclovir mainly used for herpes virus infections like herpes zoster and chickenpox21-23. Ganciclovir is commonly used to treat cytomegalovirus infection in AIDS patients and those undergoing cancer chemotherapy 24. Acyclovir and ganciclovir are used to treat diseases associated with EB virus infection, with acyclovir being more common and effective. After ruling out common viral agents, EBV should be considered as a potential cause of acute hepatitis. In conclusion, EBV infection is a common identifiable cause of acute childhood encephalitis, and asymptomatic hepatitis may be discovered during investigation.

References