Case Report

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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, aseptic meningitis, encephalitis, 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 were no signs of lymphadenopathy or hepatosplenomegaly. 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.

Serologic tests for viral hepatitis showed that HBsAg, anti HCV Ab, HCV-RNA (RT-PCR), HAV IgM, and HAV IgG were all negative. Additionally, tests for anti-HIV, ANA, ASMA, and anti LKM Ab were also negative.

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-hepatotropic 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 [6]. Most cases of EBV-related liver involvement are self-limiting and can be managed with supportive care [7].

In a study by Kofteridis 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 chicken pox[21-23].

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

1. Fujimoto, H., Asaoka, K., Imaizumi, T. (2003). Epstein-Barr virus infections of the central nervous system. Internal medicine, 42(1), 33-40.
2. Francisci, D., Sensini, A., Fratini, D. (2004). Acute fatal necrotizing hemorrhagic encephalitis caused by Epstein-Barr virus in a young adult immunocompetent

man. Journal of neurovirology, 10(6), 414-417.
3. Kim, J. H., Joo, B. E., and Koh, S. B. (2007). Serial diffusion-weighted MR imaging findings in a patient with Epstein-Barr virus encephalitis. Journal of neurology, 254(11), 1616-1618.
4. Odumade, O. A., Hogquist, K. A., & Balfour Jr, H. H. (2011). Progress and problems in understanding and managing primary Epstein-Barr virus infections. Clinical microbiology reviews, 24(1), 193-209.
5. Abbott, R. J., Pachnio, A., Pedroza-Pacheco, I., Leese, A. M., Begum, J., Long, H. M., ... & Bell, A. I. (2017). Asymptomatic primary infection with Epstein-Barr virus: observations on young adult cases. Journal of Virology, 91(21), 10-1128.
6. Heldman, M. R., Edlefsen, K. L. (2022). Combined assessment of Epstein–Barr virus viral capsid antigen and Epstein–Barr virus nuclear antigen-1 serology for post-transplant lymphoproliferative disorder risk stratification in adult solid organ transplant recipients. Transplant Infectious Disease, 24(6), e13933.
7. Vouloumanou, E. K., Rafailidis, P. I., and Falagas, M. E. (2012). Current diagnosis and management of infectious mononucleosis. Current opinion in hematology, 19(1), 14-20.
8. Kofteridis, D. P., Koulentaki, M., Valachis. (2011). Epstein Barr virus hepatitis. European Journal of Internal Medicine, 22(1), 73-76.
9. Crum, N. F. (2006). Epstein Barr virus hepatitis: case series and review. Southern Medical Journal, 99(5), 544-548.
10. Yang, S. I., Geong, J. H., and Kim, J. Y. (2014). Clinical characteristics of primary Epstein Barr virus hepatitis with elevation of alkaline phosphatase and γ-glutamyltransferase in children. Yonsei medical journal, 55(1), 107-112.
11. Chang, J. J., and Lewin, S. R. (2007). Immunopathogenesis of hepatitis B virus infection. Immunology and cell biology, 85(1), 16-23.
12. Rosen, H. R. (2003). Hepatitis C pathogenesis: mechanisms of viral clearance and liver injury. Liver transplantation, 9(11), S35-S43.
13. Kimura, H., Nagasaka, T., Hoshino, Y. (2001). Severe hepatitis caused by Epstein-Barr virus without infection of hepatocytes. Human pathology, 32(7), 757-762.
14. Tănăsescu, C. (2004). Correlation between cholestasis and infection. Romanian journal of gastroenterology, 13(1), 23-27.
15. Kalita, J., Maurya, P. K., Kumar, B. (2011). Epstein Barr virus encephalitis: clinical diversity and radiological similarity. Neurology India, 59(4), 605.
16. Weinberg, A., Li, S., Palmer, M. (2002). Quantitative CSF PCR in Epstein–Barr virus infections of the central nervous system. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 52(5), 543-548.
17. Hess, R. D. (2004). Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. Journal of Clinical Microbiology, 42(8), 3381-3387.
18. Fleisher, G. R., Collins, M., and Fager, S. (1983). Limitations of available tests for diagnosis of infectious mononucleosis. Journal of Clinical Microbiology, 17(4), 619-624.
19. Lang, D., Vornhagen, R., Rothe, M. (2001). Cross-reactivity of Epstein-Barr virus-specific immunoglobulin M antibodies with cytomegalovirus antigens containing glycine homopolymers. Clinical Diagnostic Laboratory Immunology, 8(4), 747-756.
20. Pitetti, R. D., Laus, S., and Wadowsky, R. M. (2003). Clinical evaluation of a quantitative real-time polymerase chain reaction assay for diagnosis of primary Epstein-Barr virus infection in children. The Pediatric Infectious Disease Journal, 22(8), 736-739.
21. Zhang, S., Zhu, Y., Jin, Y. (2021). Difference between acyclovir and ganciclovir in the treatment of children with Epstein–Barr Virus-associated infectious mononucleosis. Evidence-Based Complementary and Alternative Medicine, 2021, 1-6.
22. Wadé, N. B., Chang, C. M., Conti, D. (2020). Infectious mononucleosis, immune genotypes, and non-Hodgkin lymphoma (NHL): an InterLymph Consortium study. Cancer Causes & Control, 31, 451-462.
23. Kłysik, K., Pietraszek, A., Karewicz, A. (2020). Acyclovir in the treatment of herpes viruses–a review. Current medicinal chemistry, 27(24), 4118-4137.
24. Krens, S. D., Hodiamont, C. J., Juffermans, N. (2020). Population pharmacokinetics of ganciclovir in critically ill patients. Therapeutic Drug Monitoring, 42(2), 295-301.