Case Report

Diagnostic dilemmas in Epstein-Barr virus hepatitis mimicking autoimmune hepatitis: A case report

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Abstract

We report a case of 55-year-old female with chief complaints of fever and deranged liver function tests, diagnosed as autoimmune hepatitis (AIH) and under immunosuppressive therapy for two years. Following the failure in clinical improvement, she was started on anti-tubercular therapy (ATT). While investigating the underlying etiology, virological markers for Hepatitis A to E were found to be negative with plasma Epstein-Barr virus (EBV) viral load of 5 $\log_{10}$ copies/ml. Additional investigation of the liver biopsy showed Hodgkin's lymphoma (HL). The patient was initiated on chemotherapy but eventually succumbed to the illness. This case report underlines the dilemma in the initial diagnosis of AIH and the importance of considering hepatic involvement of EBV as one of the differential diagnosis among clinically suspected AIH cases not responding to immunosuppressive medications.

Keywords: Chronic active EBV, Hodgkin's lymphoma, Immunosuppressive medications

Introduction

Epstein-Barr virus (EBV) belongs to *Herpesviridae* family and is transmitted from person to person by infected salivary secretions. Primary infection may vary from asymptomatic in children to symptomatic infectious mononucleosis (IM) in adolescents and adults. The virus undergoes latency in the B lymphocytes and can reactivate asymptomatically in immunocompetent individuals. In immunosuppressed individuals, reactivation may progress to lymphoma or lymphoproliferative disorders.[1] EBV is also known to cause chronic active EBV infection (CAEBV) associated with a poor prognosis.[2,3] EBV has been reported to further induce the development of various autoimmune liver diseases like autoimmune hepatitis (AIH), primary biliary cirrhosis and primary sclerosing cholangitis. The suggested mechanism behind EBV triggering autoimmune diseases is molecular mimicry, with most of the theories still under research.[4] Here we report a case of EBV hepatitis with the complication of Hodgkin's Lymphoma (HL) who was probably misdiagnosed and treated as AIH in the index presentation.

Case History

A 55-year-old female, normotensive and non-diabetic presented 3 years back with complaints of fever, generalized weakness, and deranged liver function tests to a private practitioner. Based on laboratory markers [Anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), serum IgG – positivity], liver biopsy findings of bridging fibrosis with mild ductular changes, negative history of alcoholism and native medicine intake, no previous history of blood transfusions or intravenous drug abuse, was diagnosed to be a case of AIH. The patient was treated with azathioprine and prednisolone for 2 years. Following the failure to respond clinically, she was initiated on empirical anti-tubercular therapy (ATT). As no clinical improvement was observed, she was finally referred to our institute. On examination, the patient

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was febrile, pale with generalized lymphadenopathy, and spleen was palpable 2 cm below the left costochondral margin. The laboratory investigations revealed serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin to be 69 IU/L [normal range (NR): 5–40 IU/ml), 44 IU/ml (NR: 7–35 IU/ml] and 6.7 mg/dl (NR: 0.3–1.2 mg/dl), respectively. Alkaline phosphatase (ALP) levels were 299 IU/L (NR: 32–92 IU/L), serum albumin levels were 2.0 g/dl (NR: 3.5–5.2 g/dl), prothrombin time was 11.5 seconds and the international normalized ratio was 0.96. The autoimmune markers were retested, ANA and ASMA were found to be negative, serum IgG was 9.12 g/dl (NR: 6.39–13.49 g/dl).The complete hemogram showed anemia with pancytopenia: Hb: 8.8(NR: 12–15 g/dl), total leucocyte count (TLC) –2,700 (NR: 4,000–11,000 cells/cu mm), neutrophil: 87% (NR: 40–75%), lymphocytes: 4% (NR: 20–45%), monocytes: 7% (NR: 2–10%), platelet: 50,000 (NR: 1,50,000–4,00,000 cells/mm). Virological markers for Hepatitis A to E and human immunodeficiency viruses (HIV) were nonreactive. Dengue IgM, Widal, malaria antigen, IgM Leptospira, sputum for acid-fast bacilli, blood and urine cultures were negative. To rule out the non-hepatotropic causes, IgM antibody for cytomegalovirus (CMV), EBV, herpes simplex virus (HSV 1 and 2) were also performed and found to be negative. In view of the history of immunosuppressive medications, the viral load quantitation for CMV, EBV, and HSV 1 and 2 were done. The patient had a negative viral load for CMV and HSV 1 and 2 but 5 $\log_{10}$ copies/ml for EBV. Further, ultrasonography (USG) abdomen findings were suggestive of parenchymal liver disease with splenomegaly. Intrahepatic biliary radicles (IHBRs) were not dilated and there was no evidence of focal lesion. Multiple subcentimetric lymph nodes were noted in the aortocaval and mesenteric region. Based on the above findings, the case was provisionally diagnosed as EBV-related IM with hepatitis and splenomegaly. EBV specific treatment (valgancyclovir 900 mg BD) was started for a week and EBV viral load was retested. Following persistent EBV viral load of 5 $\log_{10}$ copies/ml on repeat sampling with no clinical improvement, further investigations were done. Magnetic resonance imaging (MRI) abdomen with magnetic resonance cholangiopancreatography (MRCP) showed enlarged liver and spleen with heterogeneous signal intensity, with multiple tiny T1 and T2 hypointense variable-sized lesions and no evidence of IHBR dilatation. Multiple variable-sized enlarged peripancreatic, portocaval, gastrohepatic ligament, mesenteric and retroperitoneal lymph nodes were seen. Also, liver biopsy showed infiltration by a lymphoproliferative disorder–HL (depicted in Figure 1) with CD30+ and CD15+ in large Reed–Sternberg (RS) cells (membranous and Golgi positivity noted); CD 3+ and CD 20+ in scattered T lymphoid cells around the RS cells and reactive B lymphoid cells. After oncology consultation, the patient was started on chemotherapy but eventually succumbed to the illness.

Discussion

EBV has a multifaceted role in the causation of liver diseases. The classical form of primary EBV infection in the immunocompetent individuals is IM, which can either subside spontaneously or might lead to transient transaminitis. Severe hepatitis is rare in immunocompetent individuals, yet some chronic conditions like AIH and CAEBV are known to be triggered by EBV resulting in complications like lymphomas and lymphoproliferative disorders.[5]

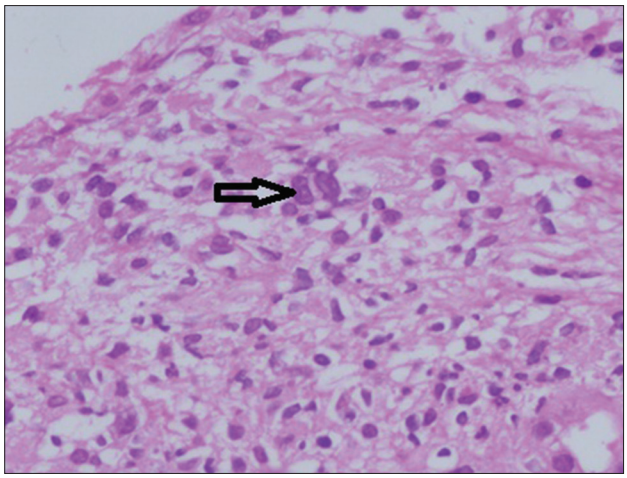

Figure 1: Liver biopsy with hematoxylin and eosin stain showing Reed–Sternberg cells in the background of reactive inflammatory infiltration (40×)

This case highlights the dilemma of the initial diagnosis of AIH and raises certain possible scenarios for the same. The first scenario maybe the patient would have been a case of EBV infection which could have triggered AIH due to autoantibody production.[4] This etiology can be ruled out because immunosuppressive treatment usually improves the outcome, unlike in our case. A study conducted by Vento *et al*. suggested that in a subset of genetically predisposed susceptible individuals, a defect lies in suppressor–inducer T lymphocytes. These lymphocytes control immune responses to the asialoglycoprotein receptor (an antigen expressed on the hepatocyte surface). Hence, autoantibodies to this self-antigen develop and result in AIH after about 4 months of EBV infection.[6] Also, Cabibi *et al*. and Peng *et al*. reported cases of AIH following EBV infection who were successfully treated with immunosuppressive therapy.[7,8]

EBV reactivation following immunosuppressive therapy for AIH can be a second scenario, which usually improves following the withdrawal of immunosuppression. Reversal of EBV associated HL within a month following azathioprine withdrawal in an AIH patient was reported by Munz *et al*., unlike the present case.[9]

The likely possibility of CAEBV presenting like AIH in the index presentation may be the third scenario, which on immunosuppression eventually led to HL. CAEBV is a chronic illness lasting for at least 6 months after a primary EBV infection or reactivation with persistent EBV DNA in blood and infiltration of organs by EBV positive lymphocytes. The initial findings are usually fever, lymphadenopathy,

splenomegaly, hepatitis, and pancytopenia ultimately ending into hemophagocytosis or EBV positive lymphomas.[10] Similar case reports of CAEBV mimicking AIH developing several complications like hemophagocytosis and lymphoma following immunosuppression have also been previously reported.[11-13] CAEBV is associated with a poor prognosis due to refractoriness to various antivirals, interferons, intravenous immunoglobulins, and conventional chemotherapy with hematopoietic stem cell transplantation being the only cure.[3,10]

Taking the above-stated scenarios into consideration, we narrow down to the probable diagnosis of CAEBV culminating in a fatal HL. Though there is a lack of pathological evidence favoring CAEBV during illness, the presence of EBV viremia cannot be surpassed. Thus, this case emphasizes the importance of considering CAEBV hepatitis in the differential diagnosis among clinically suspected cases of AIH especially those not responding to immunosuppressives. Additionally, the performance of viral load testing using blood or liver biopsy at the earliest plays a pivotal role in establishing the underlying etiology.[14] To conclude, EBV infection has a varied spectrum of clinical presentation from mild self-limiting IM to complications like CAEBV, AIH, chronic hepatitis, and lymphoproliferative disorders. Hence, this varied clinical scenario should always be borne in mind of treating physicians especially among cases with IM symptoms persisting beyond 3 months.[15]

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Conflicts of interest

There are no conflicts of interest.

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