Chronic Active Epstein–Barr Virus Infection Indistinguishable from Autoimmune Hepatitis: A Case Report

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ABSTRACT

Chronic active Epstein–Barr virus (CAEBV) infection is a rare disease, mainly affecting children, typically characterized by persistent infectious mononucleosis (IM)-like symptoms. We describe an adult case of CAEBV without IM-like symptoms, which was indistinguishable from autoimmune hepatitis (AIH). A 60-year-old woman with liver damage was diagnosed with AIH (International Diagnostic Score: 16 points). She had been treated with prednisolone for three years; however, her transaminases had never normalized. She was admitted for another liver biopsy due to repeated high fevers and worsening of her liver damage over two months. Her EBV-DNA copy number was 2.9×10^4 copies/μg DNA, and EBV-encoded small RNA1-positive lymphocytic infiltration was observed in both the present and previously collected (three years ago) liver tissue samples. This case implies that hepatic involvement in a CAEBV without IM-like symptoms is difficult to distinguish from AIH and may be misdiagnosed. In some steroid resistant AIH cases, evaluating for CAEBV may be valuable.

Key words autoimmune hepatitis; chronic active EBV infection; EBV-encoded small RNA1; Epstein–Barr virus

The Epstein–Barr virus (EBV) is a ubiquitous gamma herpesvirus that preferentially infects B lymphocytes, and more than 90% of adults worldwide have been infected with EBV.[1–3] Primary infection with EBV is usually asymptomatic, but a delayed primary infection can lead to symptomatic infectious mononucleosis (IM) in adolescents and young adults, particularly in affluent societies.[3] The symptoms usually resolve within two weeks of onset; however, in rare cases, patients' symptoms do not resolve.[4] In 1975, Horwitz et al. described a few patients who had chronic IM-like symptoms characterized by persistent or intermittent fever and lymphadenopathy.[5] The rare EBV-infected individuals without apparent immunodeficiency present with persistent or intermittent IM-like symptoms, including fever, persistent lymphadenopathy, splenomegaly, and hepatitis, called chronic active EBV (CAEBV) disease or infection.[4, 6, 7] This rare condition is typically characterized by persistent (over three months) IM-like symptoms, and EBV can be detected in the peripheral blood and organs.[8] In the United States, patients with CAEBV most often present with B- or T-cell involvement, while in Asia, the disease usually involves T or NK cells.[4] The rate of onset of CAEBV in Japan is 23.8/year according to the annual report of the Measures Against Intractable Diseases research group of the Ministry of Health, Labor, and Welfare of Japan.[7]

CAEBV mainly affects children; however, half of the patients were adults in the Japanese nationwide CAEBV survey, and the prognosis is reportedly worse in adult-onset patients than in childhood-onset patients.[7] Some reports have indicated that CAEBV can induce chronic hepatitis in adults.[9–17] We experienced an adult case of a persistent, three-year EBV infection without IM-like symptoms, which was initially misdiagnosed as autoimmune hepatitis (AIH).

PATIENT REPORT

A woman in her 60s was admitted to our hospital for a liver biopsy because of a persistent mild elevation of liver enzymes without fever for three years. She had a past treatment history for rheumatoid arthritis (RA), which had achieved complete remission and she stopped treatment five years before her first admission. She had undergone a cholecystectomy and appendectomy and had no history of alcohol use. The patient was 156 cm

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Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antigen; ANA, anti-nuclear antigen; AST, aspartate aminotransferase; BMI, body mass index; CAEBV, chronic active Epstein–Barr virus; CT, computed tomography; EBV, Epstein–Barr virus; EBER1–ISH, EBV-encoded small RNA1–in situ hybridization; GGT, gamma-glutamyl transpeptidase; HBs, Hepatitis B surface; HBc, Hepatitis B core; HCV, Hepatitis C virus; HSCT, hemopoietic stem cell transplantation; IM, infectious mononucleosis; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; OS, overall survival; RA, rheumatoid arthritis

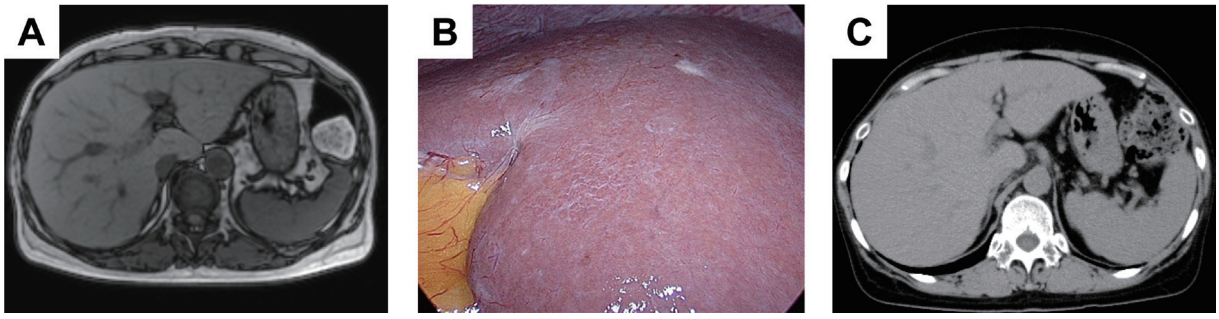

Fig. 1. Imaging of the liver. (**A**) Abdominal magnetic resonance imaging (T1 weighted imaging) at the time of the first admission showed neither hepatomegaly nor splenomegaly. (**B**) Close-up view of the right lobe by laparoscopic examination at the first admission. The liver surface is slightly rough, the edge is dull, and whitish markings are scattered, but reddish markings are not apparent. The nodule formation is not remarkable. (**C**) Abdominal computed tomography at the time of the second admission showed splenomegaly but no hepatomegaly.

tall, weighed 55.4 kg, and had a body mass index (BMI) of 22.8 kg/m^2. On physical examination, there was no lymphadenopathy, and her liver and spleen were not palpable.

At her first admission, laboratory tests revealed the following: erythrocyte count, 410 × 10^4/mm^3; hematocrit, 38.1%; hemoglobin, 12.3 g/dL; leukocyte count, 4,600/mm^3; and platelet count, 20.7 × 10^4/mm^3. Her total protein was 6.4 g/dL. In addition, the following values were obtained: albumin, 3.9 g/dL; urea nitrogen, 14.9 mg/dL; creatine, 0.54 mg/dL; total bilirubin, 0.4 mg/dL; aspartate aminotransferase (AST), 36 U/L; alanine aminotransferase (ALT), 37 U/L; alkaline phosphatase (ALP) (JCCLS), 276 U/L; gamma-glutamyl transpeptidase (GGT), 20 U/L; Na, 141 mEq/L; K, 4.2 mEq/L; Cl, 106 mEq/L; total cholesterol, 181 mg/dL; plasma glucose, 80 mg/dL; HbA1c, 5.8%; immunoglobulin (Ig) G (JCCLS), 900 mg/dL; Ig-M, 42 mg/dL; anti-nuclear antigen (ANA), 1:640; anti-mitochondrial M2 antigen (AMA-M2), negative; Hepatitis B surface (HBs) antigen, negative; HBs antibody, negative; Hepatitis B core (HBc) antibody, negative; Hepatitis C virus (HCV) antibody, negative; and HCV-RNA, negative. Abdominal magnetic resonance imaging (MRI) (T1 weighted imaging) showed neither hepatomegaly nor splenomegaly (Fig. 1A). Laparoscopic examination indicated chronic hepatitis (Fig. 1B).

A liver biopsy was performed, which showed mild portal infiltrates of lymphocytes and eosinophils focally spilling into the surrounding parenchyma, resembling mild interface hepatitis (Fig. 2A). Retrospectively, characteristic features of EBV hepatitis, such as chain-like infiltrates of lymphocytes into the sinusoids and lobular microgranulomas, were also observed (Fig. 2B), but they were overlooked at the time of diagnosis because the patient's age was outside the typical range for this disease. As a result, her histology was consistent with AIH. According to the International Scoring System, we diagnosed the patient with AIH (16 points before treatment, definite AIH[19]).

We started prednisolone at 0.6 mg/kg. The patient had been treated with prednisolone for three years; however, her transaminases had never normalized (Fig. 3). She was admitted to the hospital again for a liver biopsy due to repeated high fevers and worsening of her liver damage over two months. On physical examination, there was no lymphadenopathy, no tenderness in her abdomen, and her liver and spleen were not palpable. Laboratory tests from the second admission are shown in Table 1.

Abdominal computed tomography (CT) showed only splenomegaly (Fig. 1C). A second liver biopsy was performed, which showed mild lobular and portal infiltrates of lymphocytes and histiocytes without apparent interface hepatitis (Fig. 2C), suggesting some type of active hepatitis. Thus, because of a fever of unknown origin, CAEBV was considered. Her EBV-DNA copy number was 2.9 × 10^4 copies/μg DNA. EBV-encoded small RNA1 in situ hybridization (EBER1–ISH) was performed on the first and the second liver biopsy specimens, which showed numerous EBER1-positive cells within the parenchyma and portal areas in both specimens (Figs. 2D and E). These results revealed that the patient had a chronic EBV infection without mononucleosis-like symptoms from the beginning. We performed infected cell type determination, and diagnosed as NK-cell type CAEBV. To control symptoms, the patient received immunochemotherapy consisting of prednisolone, cyclosporine, and etoposide. Her fever subsided after the therapy, and her liver damage also improved. The patient had fludarabine, melphalan, and total body irradiation (2Gy) as conditioning. Then, she

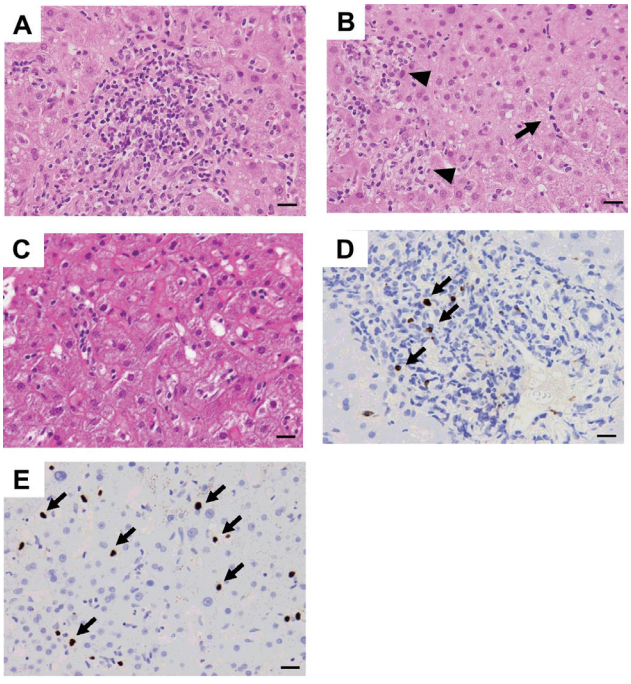

Fig. 2. Histology of the liver. (**A**) The first biopsy showing mild portal infiltrates of lymphocytes and eosinophils focally spilling into the surrounding parenchyma, resembling mild interface hepatitis. (**B**) Retrospectively, chain-like infiltrates of lymphocytes into the sinusoids (arrow) and lobular microgranulomas (arrowheads) were also recognized. (**C**) The second biopsy showing mild lobular infiltrates of lymphocytes and histiocytes. (**D**) and (**E**) EBER1–ISH reveals many EBV-positive cells (arrows) in both the initial (**D**) and the second biopsy (**E**) specimens. (**A**)–(**C**), hematoxylin and eosin; (**D**) and (**E**), EBER1–ISH. Bar = 20 μm, EBER1–ISH, EBV-encoded small RNA in-situ hybridization.

underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) and achieved remission. Her liver enzyme levels are now normal without the use of prednisolone.

DISCUSSION

We herein described an adult case of hepatic involvement in a CAEBV not demonstrating IM-like symptoms for three years. This rare disease entity was indistinguishable from AIH.

Vine et al. demonstrated that acute EBV hepatitis, a self-limiting hepatitis, affects an older age group than infectious mononucleosis[20]; however, little is known about CAEBV. There are a small number of reports of hepatic involvement in CAEBV in adults.[9–17] Four previous reports also indicated that CAEBV induces AIH-like hepatitis in adults.[10, 14, 17, 18] Kojima et al. reported the case of a 73-year-old male who had IM-like symptoms with a history of abnormal lactate dehydrogenase (LDH) noted a year prior to admission.[10] His liver biopsy demonstrated chronic hepatitis with positive ANA, and EBV-DNA and EBER1-positive lymphocytes were observed in his serum and peripheral blood mononuclear cells. Peng et al. reported that a 42-year-old female who had acute hepatits with flu-like symptoms at her first admission. She was diagnosed as EBV hepatitis by serological results and liver biopsy. Her liver enzyme decreased significantly by symptomatic management for the first month. However, her jaundice became worse again. Her anti-SMA elevated significantly after exacerbation, and diagnosed as EBV induced AIH.[18] Chiba et al. reported a case of a 22-year-old female who showed mild liver dysfunction with a low-grade fever and mild hepatosplenomegaly six years previously, and AIH was diagnosed based on an examination of the laboratory data and a liver biopsy.[14] A retrospective analysis of blood samples taken six years earlier revealed the presence of the EBV genome and high-titer anti-EBV antibodies at the time of AIH diagnosis. Yamashita et al. reported that a 50-year-old woman with systemic lupus erythematosus complicated by AIH began to suffer from acute respiratory failure and clinical symptoms.[17] EBER1-positive lymphocytes were observed in her liver and gastric mucosal tissue, and EBV-DNA was observed in her CD4-positive T cells. The latter two patients died of hepatic failure.

There are also three controversial cases. Wada et al. reported a 61-year-old male case with probable AIH (12 points before treatment) without IM-like symptoms.[21] His blood was positive for EBV DNA, but his liver was negative for EBER. Ramachandran et al. reported a case of a 55-year-old woman with fever and abnormal liver function tests; she was diagnosed with AIH and underwent immunosuppressive therapy for two years, but no clinical improvement was observed.[22] This case could not be accurately diagnosed as CAEBV or EBV reactivation. Koay et al. reported a 66-year-old woman who presented with severe acute hepatic dysfunction.[23] The authors concluded this case was an EBV superinfection of AIH with early liver cirrhosis.

The diagnostic criteria for CAEBV include persistent IM-like symptoms, increased EBV DNA (> 102.5 copies/μg DNA) in the peripheral blood, histological evidence of organ disease, and the presence of EBV RNA or viral proteins in affected tissues in patients without known immunodeficiency, malignancy, or autoimmune disorders.[7] Regarding our case, the patient had no IM-like symptoms on her first admission; therefore, she did not meet the CAEBV criteria. The serological test demonstrated past infection with EBV. Moreover, her liver histopathology and scoring system were compatible with AIH.

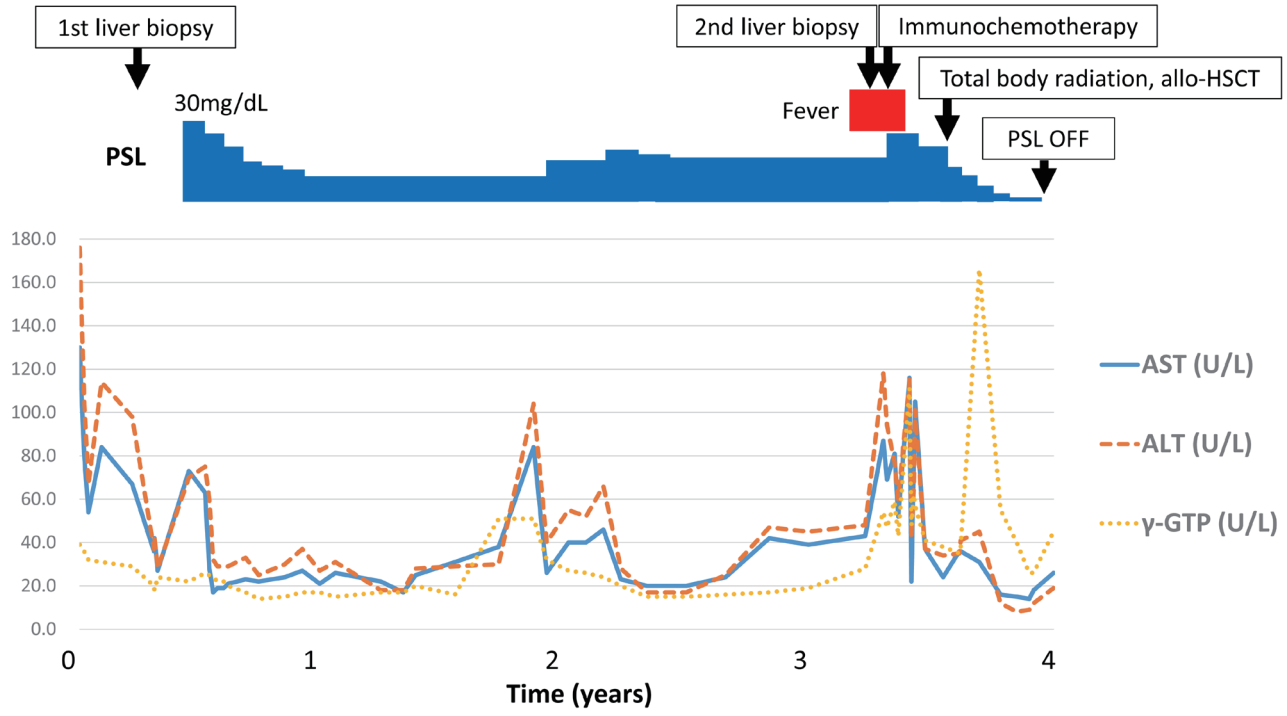

Fig. 3. Clinical course. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; PSL, Prednisolone.

A relationship between some systemic autoimmune diseases and EBV has been noted, and EBV evidently plays an important role in the etiology of RA.[24] Our patient previously had RA, and we speculate that her RA might be induced by EBV. Furthermore, some reports have also indicated the role of EBV as a trigger of "true" AIH in both children and adults.[25–27] Nakajima et al. reported the case of a 10-year-old girl with AIH triggered by acute EBV infection.[25] In this case, her blood was positive for EBV DNA, but in situ hybridization of the liver tissue was negative. Aceti et al. reported a 23-year-old woman who developed AIH followed by EBV infection.[26] In this case, in situ hybridization of the liver tissue was negative. Cabibi et al. also reported a case of a 30-year-old man who presented with AIH about six months after IM due to EBV infection.[27] In this case, there was no EBV DNA detected in the blood, and EBER1-ISH of the liver tissue was negative. The proposed mechanism for the association is molecular mimicry between EBV antibodies and normal cellular constituents.[28]

According to these reports, there may be two types of EBV-associated AIH: (i) AIH initiated by acute EBV infection (B-cell infections) and (ii) CAEBV hepatitis (mimics AIH) (mainly T- or NK-cell infections). In addition, the case reported by Wada et al.[21] and our case suggest that there is a subset of CAEBV hepatitis that mimics AIH without IM-like symptoms. This subset is outside of the present criteria for CAEBV.

CAEBV is refractory to antiviral, interferon, and intravenous immunoglobulin therapies and conventional chemotherapy; thus, it has a poor prognosis.[4] At present, the only effective treatment strategy for eradicating EBV-infected T or NK cells is allo-HSCT.[7] Our patient achieved remission after allo-HSCT. Fifteen-year overall survival (OS) from onset among patients treated with allo-HSCT is 60.6%, whereas OS without allo-HSCT is 25.7%.[29]

Hepatic involvement of CAEBV should be a differential diagnosis in cases of liver dysfunction with IM-like symptoms or cases of steroid-resistant AIH. There are no available etiological data of CAEBV associated AIH without IM-like symptoms. Further investigation of CAEBV associated with AIH is warranted.

In conclusion, we diagnosed a rare case of CAEBV hepatitis that mimics AIH without IM-like symptoms at the first admission. This case implies that hepatic involvement in a CAEBV without IM-like symptoms is difficult to distinguish from AIH. In some steroid resistant AIH cases, evaluating for CAEBV may be valuable.

The authors declare no conflict of interest.

Table 1. Laboratory data on the second admission

CBC			Serology		
WBC	5600	/μL	anti-EBV VCA IgG	1:160	
Neut	86	%	anti-EBV VCA IgM	< 1:10	
Lymph	12	%	anti-EBV VCA IgA	< 1:10	
Mon	2	%	anti-EBV EBNA IgG	1:40	
Eos	0	%	anti-EBV EA IgG	< 1:10	
Bas	0	%	anti-EBV EA IgA	< 1:10	
RBC			anti-CMV IgG	31.4	(–)
Hb	13.6	g/dL	anti-CMV IgM	0.32	(–)
Hct	40.6	%	CMV antigenemia	Negative	
Platelet	19.3×10^4	/μL	HBs Ag	(–)	
Biochemistry			HBs Ab	(–)	
Total protein	6.3	g/dL	HCV Ab	(–)	
Albumin	4.0	g/dL	IgM-HA Ab	< 1:40	
Total bilirubin	0.7	mg/dL			
Direct bilirubin	0.2	mg/dL	Ig G	650	mg/dL
AST	81	U/L	Ig M	59	mg/dL
ALT	77	U/L	Ig A	137	mg/dL
ALP	119	U/L			
GGT	59	U/L			
LDH	416	U/L	ANA	1:40	
CRP	2.23	mg/dL	AMA-M2	1.7	index
Coagulation					
PT (%)	88.6	%			
PT (INR)	1.07				

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AMA, anti-mitochondrial antigen; ANA, anti-nuclear antigen; AST, aspartate aminotransferase; Baso, basophil; BUN, blood urea nitrogen; CBC, complete blood count; CRP, c-reactive protein; CMV, cytomegalovirus; EA, early antigen; Eo, eosinophil; EBV, Epstein Barr virus; EBNA, Epstein Barr virus nuclear antigen; GGT, gamma -glutamyl transpeptidase; Hct, hematocrit; HbA1c, hemoglobin A1c; Ig, immunoglobulin; INR, international normalized ratio; LDH, lactate dehydrogenase; Lymph, lymphocyte; Mon, monocyte; Neuto, neutrophil; PT, prothrombin time; TP, total protein; VCA, virus capsid antigen; WBC, white blood cell.

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