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Case report

Epstein-Barr virus induced acute hepatitis with hyperferritinemia: A rare presentation

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ABSTRACT

Elevated aminotransaminases and hyperbilirubinemia are common in primary Epstein-Barr Virus (EBV) infection in the adult and pediatric population and the disease course is usually subclinical and self-limited. However, EBV-induced hepatitis is an uncommon diagnosis, accounting for less than 1% of acute hepatitis causes. Acute EBV-hepatitis usually affects immunocompromised and older populations, with nearly half of patients being aged greater than 60 years. Significantly elevated ferritin levels correlate with severe infection and have been associated with EBV complications such as infectious mononucleosis, autoimmune hemolytic anemia, and hemophagocytic lymphohistiocytosis. We present a case of isolated acute cholestatic EBV-hepatitis and hyperferritinemia in an adult immunocompetent patient.

Introduction

Epstein-Barr Virus (EBV) infects humans with a high prevalence globally. It is predominantly acquired from close contact involving the exchange of oral secretions via toys, utensils, and bottles [1]. The infection is asymptomatic in most children under the age of ten [2]. However, it can cause a constellation of symptoms in adults and teenagers, including infectious mononucleosis. Infectious mononucleosis presents as a triad of fever, pharyngitis, and lymphadenopathy. Additional symptoms of EBV infection include malaise, splenomegaly, and maculopapular skin rash [1]. Rarely, it has been associated with elevated ferritin levels which has been reported with infectious mononucleosis [3], cold-type autoimmune hemolytic anemia [4], and hemophagocytic lymphohistiocytosis [5]. Acute EBV-hepatitis is an uncommon diagnosis and accounts for less than 1% of acute and chronic hepatitis causes. Compared with infectious mononucleosis, EBV-hepatitis affects an older age group, with nearly half of patients being 60 years or greater [5].

Case Report

A 42-year-old Chinese male with no significant past medical history presented to the emergency department with chief complaints of nausea, vomiting, and low-grade fever over the last 4 days. The patient was transferred from an urgent care facility with elevated liver function tests (LFTs) due to an unknown etiology. He had been experiencing worsening flu-like symptoms with decreased appetite for 1 week. His symptoms were accompanied by a lingering non-productive cough provoked by deep inspiration post-non-hospitalized COVID-19 infection 1 month ago. The patient had a history of travel to Mexico one month prior, where he experienced an episode of diarrhea that resolved without treatment. No history of raw food consumption, hiking, or insect bites in Mexico was reported. He admitted to symptoms of fever, polyarthralgia, myalgia, intolerance to oral intake, and clay colored stool, but denied shortness of breath, chest pain, abdominal pain, diarrhea, hematochezia, and hematemesis. The patient had no previous history of smoking, alcohol, or drug use. He denied any recent exposure to sick contacts and his wife was asymptomatic. He received two hepatitis B vaccination doses in 2008 but did not receive any hepatitis A vaccination before traveling to Mexico.

Abbreviations: EBV, Epstein-Barr virus; LFT, Liver function test; COVID-19, Coronavirus disease of 2019; MRCP, Magnetic resonance cholangiopancreatography; NPO, Nothing by mouth (nil per os); D5–1/2NS, 5% dextrose and half normal saline solution (0.45% NaCl); AST, Aspartate aminotransferase; ALT, Alanine aminotransaminase; ALKP, Alkaline phosphatase; IV, Intravenous; IgM, Immunoglobulin M; IgG, Immunoglobulin G; IL-18, Interleukin-18.

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Table 1
Laboratory values on admission.

Parameter	Result	Reference values	Parameter	Result	Reference values
Complete Blood Count with Differential			**Dipstick Urine Analysis**		
RBC	4.74	4.50–5.90 Mill/mcL	PH	5	5.0–8.0
Hgb	13.9	13.5–17.5 g/dL	Specific gravity	1.029	1.005–1.030
Hct	42.3	41.0–51.0%	Glucose	Negative	Negative mg/dL
MCV	89.2	83.0–98.0 fL	Ketones	20 (1 +) (A)	Negative mg/dL
MCH	29.3	25.0–35.0 pg/cell	Hgb	Negative	Negative mg/dL
MCHC	32.9	30.0–35.0 g/dL	Protein	100 (2 +) (A)	Negative mg/dL
RDW	12.5	11.5–16.0%	Nitrite	Negative	Negative
Platelets	127 (L)	130–400 × 1000/mcL	Leukoesterase	Negative	Negative
WBC	10.3	4.0–11.0 × 1000/mcL	Urobilinogen	4.0 (2 +) (A)	Negative mg/dL
Neutrophils	1.60 (L)	1.80–7.70 × 1000/mcL	Bilirubin	4.0 (2 +) (A)	Negative mg/dL
Lymphocytes	7.82 (H)	1.00–3.60 × 1000/mcL	**Urine Microscopy**		
Monocytes	0.69	0.10–1.00 × 1000/mcL	WBC	6–10 (A)	0–5 /HPF
Eosinophils	0.02	0.00–0.70 × 1000/mcL	RBC	0–3	0–3 /HPF
Basophils	0.08	0.00–0.20 × 1000/mcL	Bacteria	None	None /HPF
Immature granulocytes	0.04	0.01–0.09 × 1000/mcL	Squamous epithelial cells	Few	/HPF
Nucleated RBCs	0	≤ 0%	Mucous	Present	/HPF
Blood Smear			**Hepatitis A Virus Serology**		
Blood smear	Atypical lymphocytes		HAV IgM	Nonreactive	Nonreactive
Chemistry-7 Panel			HAV IgG	Nonreactive	Nonreactive
Sodium	136	135–145 mEq/L	**Hepatitis B Virus Serology**		
Potassium	4.1	3.5–5.0 mEq/L	HBV core antibody	Nonreactive	Nonreactive
Chloride	100 (L)	101–111 mEq/L	HBV surface antigen	Nonreactive	Nonreactive
Carbon dioxide	29	21–31 mEq/L	**Epstein-Barr Virus Serology**		
Blood urea nitrogen	15	≤ 18 mg/dL	EBV viral capsid antigen IgM	Positive	Negative
Creatinine	1.16	≤ 1.30 mg/dL	EBV viral capsid antigen IgG	Negative	Negative
Glucose	100	70–140 mg/dL	EBV nuclear antigen IgG	Negative	Negative
Liver Function Tests			**Additional Labs and Cultures**		
AST	344 (H)	≤ 34 U/L	Ferritin	1901 (H)	25–336 ng/mL
ALT	544 (H)	≤ 63 U/L	C-reactive protein	9.8	< 10 mg/L
ALKP	333 (H)	≤ 125 U/L	Lipase	39	≤ 58 U/L
Total bilirubin	3.6 (H)	≤ 1.0 mg/dL	Blood (2/2) culture	no growth	no growth
Direct bilirubin	2.0 (H)	≤ 0.3 mg/dL	MRSA surveillance culture	no growth	no growth

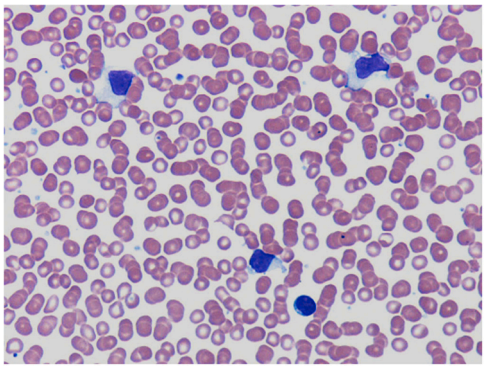

Fig. 1. Three atypical lymphocytes and one normal lymphocyte are shown on a blood smear film. These WBCs are "atypical" because they appear larger (more cytoplasm) and have nucleoli in their nuclei compared to a normal lymphocyte. Their cytoplasm tends to be indented by surrounding red blood cells. Such atypical lymphocytes are often associated with infectious mononucleosis from Epstein-Barr virus (EBV) infection. Slide courtesy of Edward C. Klatt MD, professor of pathology.

His blood pressure was 137/99 mmHg with a pulse of 88, respiratory rate of 18, oxygen saturation of 99%, and a temperature of 100.7° F. He appeared to be in no acute distress, with mild scleral icterus. Cervical lymphadenopathy, exudative tonsillitis, buccal mucosa exanthem were not observed. His cardiac examination was unremarkable. He had tussive spasms with deep inspiration, but his lungs were otherwise clear to auscultation bilaterally. His abdomen was nondistended, nontender with deep palpation, and with normal bowel sounds. There was no evidence of hepatomegaly or splenomegaly. A resolving erythematous patch was noted over the left lateral torso in addition to a slightly raised erythematous patch over his left distal arm. He did not have joint warmth, effusion, or erythema. He was alert and oriented without asterixis. His neurological examination was intact.

Table 1. A summary of laboratory values collected. RBC: Red blood cell, Hgb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALKP: Alkaline phosphatase, HAV: Hepatitis A virus, HBV: Hepatitis B virus, IgM: Immunoglobulin M, IgG: Immunoglobulin G, Blood culture (2/2): two blood samples were collected from two different intravenous sites and cultured separately, MRSA: Methicillin-resistant Staphylococcus aureus. (L): Low, (H): High, (A): Abnormal.

Hepatitis A and B serology were both nonreactive and EBV serology revealed acute infection. Liver laboratories (Table 1) revealed elevated AST (344 U/L), ALT (544 U/L), ALK (333 U/L), total bilirubin (3.6 mg/dL), direct bilirubin (2.0 mg/dL), and ferritin (1901 ng/mL). Blood smear shows atypical lymphocytes as seen in Fig. 1. Computed tomography imaging of abdomen and pelvis (with IV contrast and without oral contrast) showed no acute findings. Given the cholestatic pattern of presenting LFTs, magnetic resonance cholangiopancreatography (MRCP) was obtained and confirmed patent biliary ducts.

Patient was admitted to the hospital and was under observation for possible fulminant hepatitis. Supportive treatment included nothing my mouth (NPO), 5% dextrose in half amount of normal saline solution intravenous fluids (D5–1/2NS IV fluids), as well as medications for cough and fever. On day 1 of admission, the patient passed an oral challenge test, and his diet was advanced to clear liquid. He complained of mild nausea with his diet but denied emesis. His skin rashes resolved. No significant changes were noted in platelets, AST, ALT, ALKP or total bilirubin values. On day 2, soft diet was not tolerated, and a clear liquid diet was continued. The patient was asymptotic, LFTs improved (AST: 171, ALT: 526, ALKP: 261, total bilirubin: 2.7) and platelets were stable at 127,000. On day 3, full liquid diet was tolerated, no symptoms were

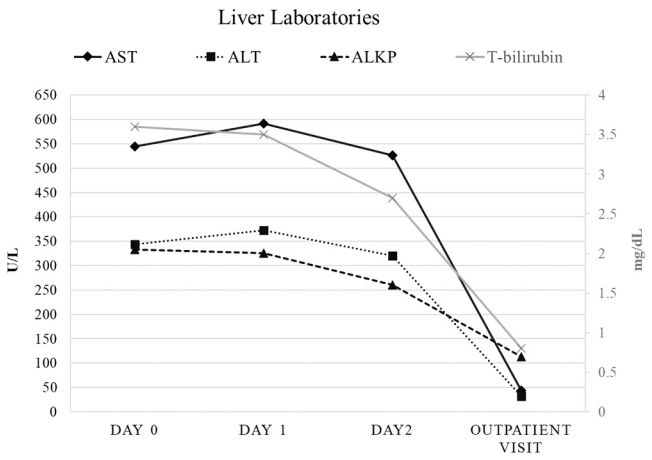

Fig. 2. AST, ALT and ALKP values over the course of hospitalization starting from admission (day 0) to discharge (day 2). Laboratory values were also collected during an outpatient visit one week post discharge.

noted, and patient was discharged home. He was recommended to follow-up in an outpatient clinic. One week later, patient was asymptomatic and his EBV viral capsid antigen IgM and IgG were both positive. His hematological, ferritin, and LFT values were all within normal range (Fig. 2).

Discussion

The acute presentation of this patient's nausea and vomiting with cholestatic liver injury guided the workup towards acute illnesses such as common viral infections and obstructive cholangitis. Given this patient's travel history to Mexico one month ago and the incubation period of hepatitis A virus to be about 28 days, the suspicion of hepatitis A infection was very high. However, lab findings suggested no evidence of hepatitis A or B infections. MRCP was then obtained, and obstructive cholangitis was ruled out. The predominance of lymphocytes on differential complete blood count and the presence of atypical lymphocytes on blood smear as seen in Fig. 1 raised the suspicion for EBV infection. EBV antibodies were ordered and revealed acute infection. Given this patient presentation with hyperferritinemia and hepatitis, hemophagocytic lymphohistiocytosis (HLH) was suspected. However, the patient did not meet diagnostic criteria for HLH [5]. Further workup was discontinued, and treatment focused on supportive management.

Hyperferritinemia is a key acute-phase reactant used by clinicians to predict the level of inflammation in various pathologies including trauma, viral and bacterial infections, autoimmune diseases, and neoplasms [6] and is associated with higher mortality [7]. Significantly elevated ferritin level in EBV infections is exceptionally rare and has been reported with complicated infectious mononucleosis [3], cold-type autoimmune hemolytic anemia [4], and hemophagocytic lymphohistiocytosis [5]. To our knowledge, there has been no report of hyperferritinemia in isolated acute cholestatic EBV-hepatitis in an adult immunocompetent patient. Elevated ferritin level has been studied as an acute phase reactant during acute EBV infection and it correlates with diseases severity [12].

Asymptomatic elevated transaminases and hyperbilirubinemia are common in primary infection in the adult and pediatric population and can be accompanied by cholestasis, but symptomatic hepatitis is rare [3]. A limited number of EBV-induced cholestatic hepatitis cases have been reported in medical literature [8,9]. Because most cases of EBV-hepatitis are uncommon and do not present with infectious mononucleosis [8,9], they can be easily missed. This diagnosis should be considered in the differential of hepatitis in people of all ages to avoid any unnecessary work up and resources including a liver biopsy [10,11].

Chronic EBV infection has been linked to autoimmune liver disease, suggested to be a triggering agent for autoimmune hepatitis [13,14]. As a result, chronic liver disease with frequent reactivations and persistent moderate or low viral load may be a sign of chronic EBV infection. Given this patient's Asian race and the high susceptibility of nasopharyngeal carcinoma in Southeast Asia and South China populations [15], additional research should investigate the susceptibility of EBV complications in these populations.

Treatment for EBV infection is often supportive. However, Gershburg et al. highlight a potential treatment for EBV infections and related malignancies. Novel anti-EBV compounds, such as maribavir, can be useful for the treatment of acute EBV infections. There has been some limitation to the use of maribavir in vivo, but researchers are working to overcoming these barriers [16].

Declaration

Ethical approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration. Informed consent was obtained from the patient for being included in the study.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

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Competing interests

Authors declare no conflict of interest.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors' contributions

All authors reviewed the literature, evaluated the discussion, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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