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CLINICAL VIGNETTE

Atypical Cause of Viral Hepatitis: Epstein-Barr Virus

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Case

A 52-year-old woman with dyslipidemia on a statin was referred to the emergency department (ED) by her primary care physician (PCP) with markedly elevated transaminases 10-20 times the upper limit of normal. She reported one-month of upper abdominal pain along with fatigue, chills, nausea, dyspepsia, and bloating. She also had dark urine and generalized pruritis without significant rash. Her pain was transient and sharp in the epigastric area following any significant oral intake. She also had subjective fever mostly in the evenings with associated diaphoresis and a 3-4 lb. weight loss over that last month due to reduced intake. She did not have any bowel changes and used acetaminophen infrequently for pain, taking 500 mg every 2-3 days. She had she had initially presented to another Emergency Department for these symptoms. Labs revealed transaminase elevation to the 500-700s with a slight increase in bilirubin/alkaline phosphatase (ALP), and abdominal US showed hepatic steatosis and gallbladder wall thickening without the presence of stones. There was a concern for a possible intraabdominal infection, and she received parenteral antibiotics with recommendation for hospitalization. She declined and was discharged home on oral amoxicillin to follow up with her primary care physician.

Repeat outpatient labs showed worsening transaminase elevation to 900s, negative acute hepatitis panel for Hepatitis A, B and C, but did not include Hep A IgG. CBC, CK and other tests including lipase, WBC, TSH, acetaminophen level (<10.0 mcg/ml), CK, and electrolytes were all within normal limits. Prior iron studies suggested iron deficiency with an iron level of 39 mcg/dl, iron saturation of 10.7%, and low ferritin level of 49 ng/ml. Urinalysis was normal. Because of her worsening LFTs, she was advised to go to the ED urgently for additional evaluation and admission.

Travel history was clarified in the Emergency Department. She had recently visited Pakistan visiting with her family for one month and returned to the US a month before her initial ED presentation. She reports onset of symptoms during her return flight to the United States. She denied eating anything unusual in Pakistan, but noted that family members developed diarrhea after returning to the US. Their diarrhea lasted for 2-3 weeks before resolving. She also denied any herbal or supplement use and had been on a stable dose of daily Pravastatin 20 mg for more than a year without myalgias or LFT elevations. She has never used tobacco, alcohol or recreational drugs.

Vital signs in the ED were within normal limits except for pain related transient tachycardia to the 110s. Physical exam was notable for scleral icterus, RUQ/epigastric tenderness to palpation without Murphy's sign, and scattered excoriations on bilateral lower extremities with lichenoid hyperpigmented patches on her shins from scratching. She was admitted for further evaluation. Abdominal ultrasound revealed a smooth liver with mild steatosis, normal portal vasculature, no intra/extrahepatic biliary dilatation, and no hepatosplenomegaly. However, the gall bladder was edematous with crescentic areas of fluid in the thickened (1cm) wall, along with non-obstructive mobile stones near the neck. Other labs included positive Hepatitis A IgG and negative ceruloplasmin level. Ferritin was elevated at 1673 ng/ml.

The patient's statin was held to avoid exacerbating liver injury, and pruritis was treated with calamine lotion. General surgery had low suspicion for cholecystitis given normal vital signs and mild exam findings. Stool culture and *H. pylori* antigen were obtained given the patient's history of dyspepsia and family members' diarrheal illness after travel.

The following day transaminases increased to the 1000s with a predominantly direct bilirubin level of 3-4 mg/dl, with improving ALP and low albumin of 2.8. Her platelets decreased to 130k with INR within normal limits. Stool studies revealed the presence of Enteraggregative *Escherichia coli* (EAEC). There was a concern for potential progression to liver failure, and a multiphase hepatic CT revealed only mild diffuse periportal edema and cholelithiasis with concentric gallbladder wall thickening secondary to possible non-biliary etiology. No liver lesions were seen, and incidental myomatous urine and non-obstructing renal calculi were noted. Gastroenterology recommended MRCP to definitively rule-out biliary pathology. This revealed the previously seen periportal edema concerning for non-biliary causes of inflammation such as acute hepatitis. No hepatic or biliary pathology was noted, except for a small incidental pancreatic tail cyst.

Over the next two days, transaminases and bilirubin continued to increase, while the platelet count dropped (see Table 1). The patient reported improvement in her epigastric pain and other symptoms, and her vital signs remained normal. A liver biopsy was considered until the EBV serologies returned positive for EBV Viral Capsid Antigen (VCA) IgM (151 U/ml) and IgG (40.4 U/ml) as well as EBV Nuclear Ag Ab IgG (72 U/ml).

Other pertinent labs resulted negative, including ANA, and a weakly positive anti-smooth muscle antibody (ASMA) titer of 1:40. The patient was received supportive care for EBV hepatitis and concurrent EAEC travelers' diarrhea. Her labs were monitored until her aminotransferases and bilirubin showed definite improvement and platelets normalized. She was then discharged with close outpatient follow-up of her LFTs, as well as long term monitoring of ANA and ASMA titers. One week after discharge, LFTs improved to near-normal values. One month after discharge her symptoms had totally resolved and LFTs had completely normalized, but her ASMA titer increased to 1:80 despite a negative ANA.

Discussion

We describe an uncommon case of isolated EBV hepatitis with possible mono-like prodrome, but without splenomegaly or lymphadenopathy. There is an extremely wide differential diagnoses for hepatobiliary pathology that can be narrowed by LFT patterns. In patients like ours with disproportionate transaminase elevations to the 1000s and only a small, corresponding rise in ALP/bilirubin, a primary hepatitis picture was more likely than a cholestatic picture. Infectious, drug-induced liver injury (DILI), and ischemic etiologies were also near the top of the differential. Imaging was helpful to definitively rule-out other pathology, such as the MRCP ruling-out biliary obstruction and the multiphase hepatic CT ruling-out malignancy and thrombosis. The nonspecific periportal edema seen across all imaging modalities could be found in acute hepatitis, congestion, hepatic trauma, cholangitis, and primary biliary cirrhosis. Though less likely, autoimmune hepatitis/cirrhosis and other rheumatologic diseases were evaluated with ANA screen, ASMA, anti-mitochondrial Ab, rheumatoid factor (RF), and IgG4 subclass panel. Hemochromatosis was unlikely given low iron prior to admission as well as lack of other systemic symptoms. Additionally, our patient had no history of hemodynamic instability, shock or heart failure that would result in congestive hepatopathy. Therefore, only primary liver infection or DILI remained as the most likely etiologies.

A thorough history of substance ingestion, including alcohol, should be taken in patients with suspected primary hepatitis. DILI from patient's acetaminophen and statin use was unlikely given negative acetaminophen/CK levels with only intermittent acetaminophen use, as well as stable statin use for a year prior to injury. Other ingestion-induced injuries were possible, but less likely given that she denied any supplement or substance use.

Evaluation for acute viral hepatitis should extend beyond the usual hepatitis viral panel if suspicion exists. Although our patient had negative acute hepatitis panel, transient Hepatitis A infection was still considered due to her elevated IgG level and travel history with other family members with diarrhea. The continued worsening liver enzymes was atypical. Additionally, the patient was EAEC positive, which usually causes mild diarrheal illness and explained the transient illness of her family. Our evaluation then expanded to other causes of viral hepatitis, including hepatitis E, Parvovirus B19, CMV, VZV, EBV, and HSV titers. Influenza and SARS-CoV-2 viruses were considered given the current ongoing outbreak, but the absence of other symptoms lowered the likelihood of these infections. Other less likely viral causes of hepatitis such as filoviruses (Ebola, Marburg), echoviruses, flaviviruses (dengue, yellow fever), reoviruses (Colorado tick fever), bunyaviruses, arenaviruses, adenoviruses, and other herpesviruses (HHV6, 7, 8) were not pursued given lack of immunocompromised state and/or history suggestive of these infections. However, if the expanded viral screen was negative, additional viral etiologies would have been pursued, as well as liver biopsy. .

Though complicated by concurrent EAEC infection, our patient likely had acute symptomatic EBV hepatitis following a mononucleosis prodrome. This diagnosis can be established with an elevated IgM titer against EBV VCA and negative tests for other viruses that could cause similar symptoms in the context of febrile illness. Though rare, EBV hepatitis can cause transaminase elevations greater than 5 times the upper limit of normal in 30-40% of patients by the second week of infection.¹ Most cases have modest elevations in the 300-500s range, but very rarely patients can have severe transaminase elevation above 1000, which we observed. Thrombocytopenia can also be present.^{2,3} Additionally, several case series reported EBV antigen cross reactivity can lead to the autoantibodies elevation such as ASMA, which increased in our patient from a titer of 1:40 to 1:80 one month later. Occasionally, EBV can also trigger autoimmune hepatitis up to six months later, which can also occur concurrently with infection.⁴ Biopsy is usually required to differentiate the two, but in our patient the ANA screen was negative with only a weakly positive ASMA, thus concurrent autoimmune disease was less likely. However, ANA and ASMA titers should be followed to monitor development of autoimmune hepatitis. This case highlights the complexity of viral hepatitis and the potential complications that can develop. If a specific etiology can be identified, treatment and ongoing monitoring may be impacted.

	Normal range	>3 months PTA	1 week PTA	Admission date- 3/10/2020	3/11/20	3/12/20	3/13/20	3/14/20	3/15/20	3/16/20	3/23/20	4/17/20
<i>ALP (u/L)</i>	38-126	88	173	139	129	125	118	122	136	115	108	71
<i>AST (u/L)</i>	15-41	19	593	1105	982	1240	1378	1266	854	450	51	21
<i>ALT (u/L)</i>	14-54	19	770	1059	946	1138	1294	1371	1166	880	124	18
<i>Btotal (mg/dL)</i>	0.1-1.2	0.3	1.4	3.7	3.2	4.8	5.9	6.4	5.6	4.2	1.5	0.8
<i>Bdirect (mg/dl)</i>	0.1-0.4	-	0.8	2.5	2.3	3.2	3.8	4.4	3.7	2.5	0.7	0.2
<i>Albumin (g/dL)</i>	3.5-4.8	3.9	3.5	3.3	2.6	2.8	2.6	2.7	2.7	2.7	3.2	3.7
<i>Plt (K/cumm)</i>	160-360	325	176	136	116	135	145	176	196	213	-	325
<i>INR</i>	0.87-1.13	-	-	1.01	1.01	1.02	1.06	1.05	1.02	0.99	-	-

TABLE 1. Liver test trends fom prior to admission to post-discharge. Shaded boxes indicate either normal values defined by specific laboratory normal range or a non-result (-).

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