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CASE REPORT

Hepatitis of an Unknown Etiology with Concomitant ITP

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Abstract

Alcoholic hepatitis (AH) usually presents after decades of alcohol consumption and can even manifest with recent abstinence. The clinical presentation may be compounded by underlying liver cirrhosis and liver function enzymes are not a reliable means of diagnosing AH due to poor sensitivity and specificity. One feature of alcoholic hepatitis is thrombocytopenia; however, patients may also have thrombocytopenia due to another underlying condition, such as Immune Thrombocytopenic Purpura (ITP). ITP is an autoimmune disease caused by autoantibodies against platelet glycoproteins. ITP is a diagnosis of exclusion and secondary causes of thrombocytopenia must be ruled out with persistent thrombocytopenia that is refractory to treatment for AH. Although there is limited data demonstrating a correlation between AH and ITP, both conditions respond to steroids. We present a case of a 42 YO M with an unknown cause of hepatitis and concomitant ITP who responded well to steroids.

Keywords: Hepatitis, Hyperbilirubinemia, Immune thrombocytopenia, Prednisolone

1. Introduction

Alcoholic hepatitis (AH) is a manifestation of alcoholic liver disease and occurs most commonly in men aged 40–60 years old.[1] AH presents at varying stages of liver disease however is usually after decades of significant alcohol consumption.[1,2] The exact incidence is unknown due to the prevalence of misdiagnosis; however, studies have estimated a prevalence of 20% in the general population.[2] Clinical presentation includes jaundice, proximal muscle wasting, ascites, hepatomegaly, right upper quadrant abdominal pain, fever, and encephalopathy.[3] Laboratory studies typically show a high ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), with aspartate aminotransferase (AST) twice the upper limit of normal, but generally less than 300 international units per milliliter.[4] Additionally, patients can have abnormal coagulation studies, including an elevated INR and hyperbilirubinemia with total bilirubin greater than 5 mg/dL.[3] When evaluating a patient with suspected AH, it is important to consider alternative diagnoses such as decompensated hepatocellular carcinoma, autoimmune hepatitis, pyogenic abscess, ascending cholangitis, viral hepatitis, drug-related injury to the liver, non-alcoholic steatohepatitis (NASH), Wilson's disease, alpha-1 antitrypsin deficiency.[3] Treatment with prednisolone has been recommended for patients with severe AH, based on encephalopathy and/or per Maddrey-Discriminatory Function Score, which is a severity score based on the patient's bilirubin and coagulation abnormalities.[5]

Alcoholic hepatitis may present with thrombocytopenia. In addition, these patients may have alternative causes of thrombocytopenia, such as Immune Thrombocytopenic Purpura (ITP). ITP is an autoimmune disease caused by autoantibodies against platelet glycoproteins, such as glycoprotein IIb/IIIa.[6,7] ITP is commonly seen in women ranging from 18 to 40 years old.[8] ITP has an incidence of approximately 100 cases per 1 million individuals with 50% of cases being pediatric patients.[6,9,10]

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Clinical presentation depends on the severity of thrombocytopenia, and can range from purpura, petechiae, mucocutaneous hemorrhaging, or internal hemorrhage such as bleeding in the central nervous system.[6,11] ITP is a diagnosis of exclusion and secondary causes of thrombocytopenia must be ruled out[6] For example, various autoimmune disorders, such as systemic lupus erythematosus or antiphospholipid syndrome can cause thrombocytopenia, as well as immunodeficiencies, viruses, lymphomas/leukemias, or medications.[6] A peripheral blood smear is useful in investigating alternate etiologies or pseudo-thrombocytopenia.[6] Treatment with high-dose steroids will increase platelet counts significantly, but studies have shown that steroid use does not impact overall mortality or morbidity.[12]

Herein, we present a case of a 42-year-old male with an unknown cause of hepatitis and concomitant ITP who responded well to steroids.

2. Case presentation

A 42-year-old Hispanic male with a past medical history of alcohol use disorder (in remission for three months), presented to the Emergency Department (ED) with sudden onset of bilateral lower extremity swelling with associated diffuse petechiae and ecchymoses that began two days prior to presentation. He also endorsed a change in the coloration of his skin that began a few days prior to presentation along with a 15-pound weight gain over a ten-day period. The patient denied decreased sensation, paresthesia, or pain when applying pressure to his lower extremities or with ambulation. On arrival, his blood pressure was 111/55 mmHg, heart rate was 70 beats per minute, respiratory rate was 18 breaths per minute, and temperature was 36.8 °C. He was saturating 100% on room air. On examination, the patient was diffusely jaundiced with scleral icterus, scattered ecchymoses throughout his extremities, and flank, with petechiae most prominent from his bilateral shins to ankles. His abdomen was soft, non-tender, non-distended, with normoactive bowel sounds and a negative fluid wave or shifting dullness. The remainder of his exam was notable for 2+ pitting edema bilaterally, extending up to his knees. Laboratory studies were remarkable for anemia with a hemoglobin level of 11.5 g/dL, thrombocytopenia with a platelet count of 87 K/mm^3, hyponatremia with a sodium level of 132 mEq/L, hypokalemia with a potassium level of 3.1 mEq/L, alkaline phosphatase of 226 U/L, aspartate transaminase of 156 U/L, alanine transaminase of 86 U/L, and conjugated hyperbilirubinemia with a total bilirubin of 55.2 mg/dL, and a direct component measuring 31.8 mg/dL. Maddrey-discriminatory function (MDF) was 84.6. An extensive workup for hepatitis was performed without significant findings.

Abdominal ultrasound (US) was significant for a liver span of 19.8 cm with heterogeneous echogenic features, as well as nodularity concerning for cirrhosis. The US was also notable for distended gallbladder with sludge and stones with gallbladder thickening, with consideration for acute or chronic cholecystitis, and negative sonographic Murphy's sign. Computerized Tomography (CT) of the abdomen and pelvis was significant for a cirrhotic steatotic liver with evidence for portal hypertension and splenomegaly, as well as a somewhat thick-walled appearance of the gallbladder possibly indicating gallbladder inflammation or the result of hepatic disease (Fig. 1). He was admitted for suspected alcoholic hepatitis and underwent Magnetic Resonance Cholangiopancreatography (MRCP), which was notable for cholelithiasis with cholecystitis and cirrhosis with portal hypertension and trace ascites. Surgery was consulted and recommended medical management. He was subsequently treated with a 7-day course of prednisolone 40 mg (mg) as he met Maddrey criteria. He was seen by Hematology for his thrombocytopenia and further workup revealed hemosiderinuria, low haptoglobin, and positive IIb/IIIa antibodies, concerning for Immune Thrombocytopenic Purpura (ITP). Although prednisolone 40 mg daily is not an optimal dose for treatment of ITP, both the patient's labs (bilirubin and platelets) and symptoms improved significantly and he was discharged home on hospital day 5 to complete the 7 day course of steroids. Labs were repeated at one month following discharge and he was continued on steroids for a total of 48 days with taper. He was seen in office with resolution of his ITP and presumed alcoholic hepatitis, with a total bilirubin of 1.9 mg/dL.

3. Discussion

AH develops in patients with heavy alcohol use, defined as at least 30–50 g of alcohol per day for 5 years or more.[13] Interestingly, many people consume over 100 g per day in the US.[13] Heavy alcohol use can also be defined as heavy drinking for more than 6 consecutive months, and at least 2 months prior to diagnosis.[13] In the presence of abstinence for weeks prior to presentation, individuals can still develop AH[3]; however if greater than 3 months prior to presentation, then their liver disease is unlikely caused by AH.[14] The cardinal sign of diagnosis is rapid systemic jaundice,

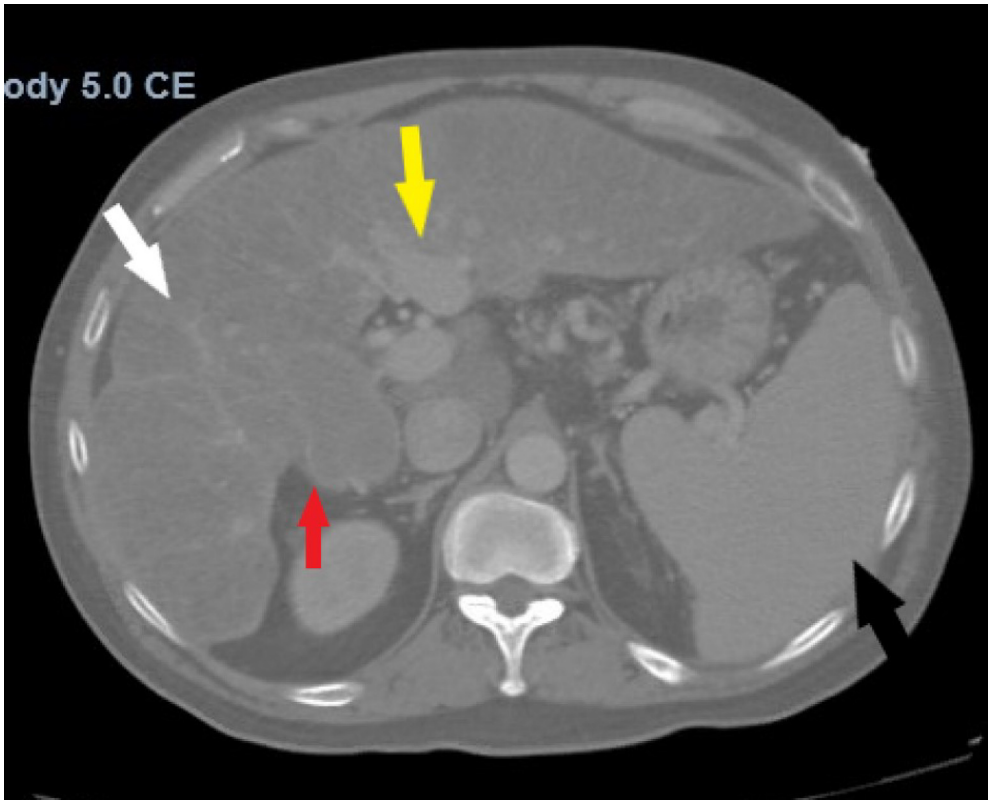

Fig. 1. ***Computerized tomography (CT) of the Abdomen and Pelvis with intravenous (IV) Contrast.*** *Sagittal views of the abdomen demonstrating extensive liver nodularity (white) indicative of cirrhotic disease, enlarged portal veins (yellow) and splenomegaly (black). Gallbladder is thickened with outer wall haziness (red) possibly indicative of inflammation or adjacent hepatic disease.*

however other signs include fever, ascites, proximal muscle loss, temporal wasting and/or encephalopathy.[15] This can compound the diagnosis of chronic cirrhosis.[15] Laboratory studies may not be a reliable means of diagnosis, as both transaminases are found in hepatocytes, as well as skeletal and myocardial muscle, and thus it may be difficult to differentiate elevated liver enzymes from non-alcoholic etiologies due to poor sensitivity and specificity.[15,16] However, since alcohol depletes pyridoxal-5′-phosphate (vitamin B6), which is required predominately for ALT production, patients suffering from alcohol use disorder tend to have lower ALT counts, causing the AST:ALT ratio to be greater than one.[17] Additionally, alcohol dehydrogenase acts in the mitochondria, increasing the AST count.[17] The best test is gamma -glutamyltransferase (GGT), which has a sensitivity of 69–73% and a specificity of 65–80% for excessive alcohol consumption.[5] As our patient was abstinent from alcohol for approximately 3 months prior to admission, the exact cause of his thrombocytopenia is unknown.

Hepatitis is only one of the major causes of abnormal platelet activation ultimately causing thrombocytopenia.[18] Further workup for thrombocytopenia should be investigated if the patient has persistent thrombocytopenia despite adequate treatment for AH. There is limited data demonstrating a correlation between AH and ITP. In our case, there may have been an association with impaired production of the glycoprotein hormone thrombopoietin (TPO), which is made in the liver parenchymal cells and ultimately stimulates platelet production.[19] There is an association between anti-platelet autoantibodies and the continuous stimulation of the TPO receptor and therefore, possible treatment may involve a TPO receptor agonist.[20] Thrombocytopenia often goes unexplored clinically; however, with minimal improvements in the context of AH, further workup is warranted. Although the treatment for both conditions remain steroids, the dosage for both conditions vary, and may relapse with any infectious causes or insults.[20]

The treatment for AH with either hepatic encephalopathy or a calculated discriminatory function greater than 32 is with steroids; however, the efficacy of this treatment has not been studied in patients with AH and a concomitant infection, such as pancreatitis, or those with internal bleeding, and/

or kidney failure.[5] Studies have demonstrated that the utilization of corticosteroids in AH patients with hepatic encephalopathy and in the absence of GI bleeding have short-term mortality benefits.[21] The mechanism behind this is a decrease in inflammation through inhibition of TNF-alpha and interleukin-8, adhesion molecules on the membrane of hepatocytes, and adhesion molecules in the hepatic venous system.[22,23]

ITP treatment is typically recommended for individuals with platelet counts of less than 50 K/mm^3 with appreciable mucosal hemorrhage, or with a platelet count of less than 20–30 K/mm^3 regardless of mucosal involvement.[12,24] Corticosteroids are utilized in ITP to increase the production of platelets and decrease their clearance.[24,25] For patients newly diagnosed with ITP who meet criteria for treatment, current guidelines recommend initiation of either dexamethasone 40 mg daily for a duration of 4 days, with repeated treatment up to 3 times (total of 12 days) as needed, or prednisone/prednisolone with a dose of 1 mg/kg and a maximum dose of 80 mg for 2–3 weeks.[24] Dexamethasone is noninferior to prednisone or prednisolone, when comparing the improvement in platelet count; however, dexamethasone confers more rapid elevations in platelet counts with fewer adverse effects.[24]

4. Conclusion

Our patient was treated for ITP and concomitant AH with prednisolone, although a definitive diagnosis could not be made. His bilirubin and platelets improved with this treatment at a dosing of 1 mg/kg, which is the regimen for ITP, albeit at one-half of the suggested duration. Due to the complexity of his presentation, determining the optimal management for this patient was difficult. It is important for clinicians to remember the broad differentials of thrombocytopenia and recognize that there may be overlapping etiologies of deranged liver enzymes.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Conflict of interest

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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