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Hemolytic Anemia in Alcohol-Induced Liver Disease: A Case Report on Zieve's Syndrome

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Abstract

We report a case of Zieve's syndrome in a patient with a longstanding history of alcohol abuse admitted for acute alcoholic hepatitis. Zieve's syndrome is defined as the triad of hemolytic anemia, hypertriglyceridemia, and jaundice in patients with known liver disease. It is an uncommon diagnosis, but is an important one to consider in patients with known liver disease admitted with these constellation of signs and symptoms.

Keywords

Zieve syndrome, Alcoholic hepatitis, Aemolytic anemia

Case Presentation

A 54-year old Caucasian male with a past medical history of hypertension and alcoholic cirrhosis presented with a 1-week history of right upper quadrant pain and jaundice. His only medication prior to admission was Metoprolol 25 mg twice daily. Social history was significant for consumption of 750mL of vodka daily. He reported his last alcoholic beverage to be 2 days prior to admission, and was found to have a serum ethanol level of 179 on day of admission. He complained of diarrhea and tremors but denied confusion, nausea, hematemesis, hematochezia, or melena.

Vital signs were notable for an oral temperature of 36.7 degrees Celsius, heart rate of 72 beats per minute, and blood pressure of 116/71mm Hg. On exam he appeared overtly jaundiced with scleral icterus. He had bilateral palmar erythema as well as facial and chest telangiectasias. Abdominal exam revealed no masses, organomegaly, or appreciable ascites. He did have mild right upper quadrant tenderness to palpation. He was alert and oriented to person, place, time and situation, and he exhibited no asterixis. Imaging studies included an abdominal ultrasound showing cirrhotic morphology of the liver with no focal masses and no evidence of ascites. Liver Doppler showed patent portal veins, hepatic veins, and hepatic arteries. A chest radiograph showed no acute airspace disease.

Laboratory examination on admission was notable for the following: total bilirubin, 17.3mg/dL; direct bilirubin 7.7mg/dL; albumin 4.0g/dL; aspartate aminotransferase, 293U/L; alanine aminotransferase, 74U/L; alkaline phosphatase 246U/L; gamma-glutamyl transpeptidase 1363U/L; white blood cell count, 4,500/uL; hemoglobin 13.8 g/dL; Platelet count, 38,000/uL; hematocrit, 41.1% with a mean corpuscular volume of 93.7fL and a red cell distribution width of 21.3%; prothrombin time, 21.4 sec; activated partial prothrombin time, 49 sec; international normalized ratio, 1.9. Blood and urine cultures were negative throughout admission.

Hemoglobin dropped from 13.8g/dL to 11.6g/dL on Hospital Day 3, prompting the workup for hemolysis. Labs at this time were notable for an increased LDH of 346U/L (reference range 100-190U/L) and decreased haptoglobin of <6mg/dL (reference range 20-240mg/dL). A direct antiglobulin test was positive for IgG disease. Manual differential reported occasional schistocytes, ovalocytes, and polychromasia. Triglycerides were elevated at 153mg/dL. Given the presentation of hemolytic anemia in the setting of hypertriglyceridemia and prolonged alcohol abuse with sudden cessation, the diagnosis of Zieve's syndrome was confirmed.

On hospital day 2, the patient was started 40mg/day of PO Prednisolone for acute alcoholic hepatitis. After 1 week it was discontinued due to a lack of improvement in liver function tests. The rest of his hospital course was unremarkable, and liver labs trended down. His hemoglobin leveled off at 10.5g/dL. He was eventually transferred to an inpatient rehabilitation facility.

The patient was seen in clinic 2 weeks following discharge. He had been compliant with abstinence from alcohol, and reported improvement in jaundice. His hemoglobin had recovered to 11.8g/dL, and total bilirubin and direct bilirubin had dropped to 7.0mg/dL and 3.0, respectively. His liver function tests had improved as well, with aspartate aminotransferase of 80U/L, and alanine aminotransferase of 33U/L.

Discussion

Zieve's syndrome

Zieve's syndrome was first described by Leslie Zieve in 1958 in a series of 20 cases of hemolytic anemia, jaundice, and hyperlipidemia in patients with known alcohol-related liver disease [1]. Zieve originally proposed that elevated circulating lipid levels in these patients led to alterations in erythrocyte membrane composition, leading to increased susceptibility to hemolysis. Zieve also described rapid improvement in hemolysis and hyperlipidemia upon cessation of alcohol use.

This syndrome was described in several case reports over the

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next decade; however the pathological mechanisms remained unknown. In 1968, a study of 6 patients with this constellation of symptoms demonstrated increased destruction of autologous as well as transfused donor erythrocytes during the acute phase of Zieve's syndrome [2]. The authors also found normal survival of erythrocytes in subjects during periods of remission. This led to the theory of the development of an extra corpuscular factor in the plasma during periods of acute illness, and regression of this factor during periods of remission.

In 1977, Goebel et al. [3] furthered knowledge of the disease process through a case control study of patients with alcoholic liver disease in the acute and remittent phases of Zieve's Syndrome [3]. The researchers analyzed the plasma and red cell chemistry of subjects, and found elevated levels of membrane-linked cholesterol and decreased polyunsaturated fatty acid levels in patients with Zieve's syndrome. They also found decreased levels of Vitamin E, increased pyruvate kinase instability, and increased lytic sensitivity of the erythrocytes to hydrogen peroxide in patients in the active phase of Zieve's syndrome. Patients in remission and other controls did not exhibit these changes in plasma chemistry and erythrocyte membrane composition. They proposed that hemolysis in Zieve's syndrome was the result of pyruvate kinase instability caused by alcohol-induced Vitamin E deficiency in combination with altered erythrocyte membrane lipid composition.

Goebel et al's theory of hemolysis is further supported by Melrose et al. [4] who in 1990 described a case series of 5 patients with Zieve's syndrome [4]. The erythrocytes from these patients demonstrated an acquired pyruvate kinase deficiency, low erythrocyte ATP levels and instability of pyruvate kinase upon heating hemolysate to 55°C.

Conclusion

The true incidence of Zieve's syndrome among patients with alcoholic liver disease is not known, as it is believed that this syndrome is under diagnosed. Few cases have been reported in medical literature since its initial description. It is an important consideration in patients presenting with a predominant indirect hyperbilirubinemia in the context of alcoholic liver disease. Other causes of hemolytic anemia must be considered, including autoimmune hemolytic anemia and the various forms of microangiopathic hemolytic anemia. Cholesterol and triglyceride levels may be checked in these patients to confirm the diagnosis, however we now know that hypertriglyceridemia is commonly found in patients who are large consumers of alcohol. No treatments are currently recommended for patients with transient hemolytic anemia due to Zieve's syndrome, and treatment is supportive with encouragement to abstain from drinking alcohol.

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