Atypical Case Presentation of Zieve’s Syndrome

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The aim of this case is to make the primary care physician and hospitalist aware of the clinical presentation and treatment protocol for Zieve’s syndrome. Zieve’s syndrome is relatively rare yet serious and treatable sequela of alcohol abuse. Clinical presentation includes the constellation of symptoms of hemolytic anemia, hyperlipidemia, abdominal pain and jaundice in the context of known alcohol abuse. The exact pathophysiologic mechanism is unknown but, as reviewed in the article, has been postulated to be secondary to alcohol induced hyperlipidemia that in turn predisposes red cell membranes to lysis. The current case demonstrates a variant on the theme of Zieve’s syndrome in that the patient’s lipid panel was essentially normal suggesting that the exact mechanism of hemolysis is still uncertain. The addition of Zieve’s syndrome to the hospitalist differential of an alcoholic patient presenting with hemolysis will allow earlier diagnosis, intervention and better patient outcomes.

CASE

A 51 year-old female with a history of alcohol abuse presented to the gastroenterology service with a four-week history of early satiety, loose stools, jaundice, bilateral lower extremity swelling and abdominal distention.

Five months prior she was treated for community acquired pneumonia with incidental findings of an elevated aspartate aminotransferase (AST) (120 U/L) and alkaline phosphatase (163 U/L). Her alanine aminotransferase (ALT) was normal (66 U/L) as was her total bilirubin (0.4 mg/dL), alpha fetal protein (2.8 ng/dL) and carcinoembryonic antigen (CEA) was 2.06. Six weeks later her laboratory examinations were repeated demonstrating an interval improvement in AST (51 U/L) and alkaline phosphatase (89 U/L) while ALT remained normal (36 U/L). Her prior hepatic enzyme elevations were attributed to her alcohol intake and she was advised to decrease her consumption.

Over the following several months, the patient reported decreased alcohol consumption from “half a wine box every day” to two 8 oz glasses of wine daily. However, despite her reported reduction in alcohol intake, the patient developed the above noted symptoms of early satiety, jaundice, abdominal distention, loose stools and lower extremity swelling. On the afternoon of admission she noted sudden onset epigastric pain and sought further medical attention.

Upon admission vital signs revealed a sinus tachycardia (105 beats per minute). Her respiratory rate was 16 breaths per minute and her oxygen saturation was 96% on room air. She was afebrile (37.6 degree Celsius). Physical examination noted diffuse jaundice from the distal extremities to the forehead with associated scleral icterus and sublingual jaundice. Remainder of the dermatologic examination noted spider angiomas. Abdominal examination revealed
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a distended abdomen with an associated fluid wave and splenomegaly. Cardiac auscultation demonstrated a regular tachycardia with grade III/VI holosystolic ejection murmur at the right and left upper sternal border. Asterixis was absent and the patient had no apparent neurologic deficits.

Initial laboratory results revealed a severe macrocytic anemia [5.6 g/dL with MCV (mean corpuscular volume) 119.9 fL], elevated reticulocyte count (5.61 percent), thrombocytopenia (107 x 10^9 g/L), neutrophilic predominant leukocytosis (14.7 x 10^9 g/L), mixed hyperbilirubinemia (total 6.9 mg/dL, direct 2.9 mg/dL), elevated AST 96 (U/L) with normal ALT and alkaline phosphatase. LDH was elevated (272 U/L) as was lactate (3.1 mmol/L); haptoglobin was diminished (<14 mg/dL). The sedimentation rate (152 mm/Lh) and CRP (21.1 mg/dL) were both elevated as was her INR (2.0). Total protein was 7.8 (g/dL) and albumin was low (2.3 g/dL). A peripheral blood smear noted macrocytes with target cells (Figure 1). Total serum ethanol was elevated (160 mg/dL). Lipid panel was generally unremarkable (total cholesterol 178 mg/dL, LDL 104 mg/dL and triglycerides 104 mg/dL).

An abdominal ultrasound demonstrated a moderate amount of ascites, splenomegaly (14 cm), portal hypertension (reversed flow noted in left portal vein) and patent abdominal vasculature.

A paracentesis was performed which revealed 146 total cells (per mcL) comprised of 3 percent neutrophils, 22 percent lymphocytes and 68 percent monocytes/macrophages. Total protein was 1.6 (g/dL) and albumin was 0.576 (g/dL) with total SAAG (serum-ascites albumin gradient) of 1.7 (g/dL).

The patient underwent routine laboratory screening during her hospitalization with her AST reaching its zenith at 99 (U/L) and total bilirubin ascending as high as 9.6 (mg/dL) with a direct bilirubin component of 3.1 (mg/dL).

The patient was treated with pentoxifylline 100 mg three times daily, spironolactone 100 mg daily and furosemide 40 mg daily. She underwent addiction counseling during her hospitalization and has continued addiction psychiatry outpatient counseling coupled with gastroenterology follow-up.

At a seven-week follow-up, her anemia had improved but not resolved (9.9 g/dL). Her bilirubin remained elevated (total bilirubin 7.8 mg/dL, direct 1.9 mg/dL). It was noted that she had not been compliant with alcoholic anonymous counseling.

The patient’s constellation of symptoms of hemolytic anemia, abdominal pain and jaundice in the context of known alcohol abuse is consistent with the diagnosis of Zieve’s syndrome.

Discussion

Zieve’s syndrome remains a rarely documented clinical phenomenon with roughly 200 reported cases the last of which known to the current reviewers was 2003. Dr. Leslie Zieve published the initial case series documenting acute hemolytic anemia associated with alcohol intake. Zieve’s study was comprised of 20 males with an average age of thirty-nine. History of alcohol use was present in all cases with notable minimization by the patient. Symptomology consisted of diarrhea abdominal pain, jaundice, low-grade fever and ascites. Averaged laboratory examinations among these twenty patients were consistent with acute hemolytic anemia (average hemoglobin 10.3 g/dL, MCV 105 fL, reticulocyte 9.0 percent total, bilirubin 10.1 mg/dL) as well as hypercholesterolemia (total cholesterol 353 mg/dL). Ultimately sixteen patients in Zieve’s case series underwent hepatic biopsy with fourteen specimens (88 percent) demonstrating fatty infiltration and fifteen (94 percent) revealing portal cirrhosis. Follow-up noted resolution of jaundice in approximately three weeks from presentation, anemia in five weeks and hypercholesterolemia in six weeks. Zieve postulated that hyperlipidemia, particularly lipid lysocomithin, predisposed erythrocytes to hemolysis.

Ten years after Zieve’s study, Balcerzak and colleagues examined six patients with Zieve’s
syndrome and demonstrated that 1) both native and donor erythrocytes demonstrated hemolysis during the acute syndrome and 2) in vitro mixing of patient erythrocytes obtained after acute illness with stored plasma from same patient collected during acute illness did not induce hemolysis. The ultimate conclusion was that an extracorporeal abnormality played a critical role in the process but was not identified.

Further biochemical studies have supported Zieve’s original hypothesis of lipid induced membranes instability concluding “further support to the hypothesis that the putative role of the red-cell metabolic injury in the origin of hemolysis in Zieve’s Syndrome cannot be envisaged without introducing membrane-linked and extracellular cofactors”.

In the current case, the patient demonstrates several factors consistent with Zieve’s syndrome notably history of alcohol use and hemolytic anemia. However, she did not demonstrate hypercholesteremia. Zieve’s study offers several explanations as to why this may be the case. First, while the average total cholesterol levels in the original study was 535 mg/dL there was a rage of value with the low value 250 mg/dL. Second, Zieve noted that “a delay of only one to two weeks alters blood findings significantly” and moreover the “rise in cholesterol… is less extensive the more chronic the hepatic disease.” It is likely that four- week delay to presentation in the current case allowed time for cholesterol levels to normalize.

This current case demonstrates the need of the clinician to be vigilant to the diagnosis of Zieve’s syndrome and appreciate its variability in its presentation. Moreover, it is the first reported case, which we are aware of, that involves a female patient.

References