

CLINICAL VIGNETTE

Zieve's Syndrome: Acute Extrinsic Hemolytic Anemia in an Alcoholic

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Introduction

Zieve's syndrome, acute extrinsic hemolytic anemia seen in alcoholics primarily after a period of binge drinking, is an uncommon condition with a debated pathophysiology. First described by Leslie Zieve in 1958 as a combination of transient hemolytic anemia, hyperlipidemia and jaundice in patients with alcoholic liver disease, the condition is rare.¹ Although the true incidence of the disease is unknown, it is assumed to be underdiagnosed² given its non-specific presentation, self-limiting nature and lack of unique pathognomonic signs or symptoms.³ In an alcoholic patient with anemia, jaundice, hyperlipidemia, and right upper quadrant abdominal pain, Zieve's Syndrome should be considered early to prevent invasive interventions and further diagnostic workup.^{4,5} In addition, laboratory evidence specifically of acute extrinsic hemolytic anemia can help aid in the diagnosis.⁶

Patient Presentation

A 54-year-old male, recently diagnosed with alcoholic hepatitis and refractory ascites was admitted to the hospital for evaluation for 1 month of recurrent abdominal distension, shortness of breath, and lower extremity swelling. The patient reported drinking three cups of vodka and three beers daily since he was ten years old. He had been discharged twice from an outside hospital within the two weeks prior to presentation where they had performed several paracenteses and transfused him five units of packed red blood cells. He denied bright red blood per rectum though he reported having intermittent dark stools for several months. Though he initially denied recent alcohol intake, he later admitted drinking just prior to presenting to the hospital. He denied any nonsteroidal anti-inflammatory drug use and had never undergone endoscopic evaluation. On physical examination, patient was chronically ill-appearing with bitemporal wasting and scleral icterus. Heart was regular rate and rhythm without murmurs and lungs were clear to auscultation bilaterally. Abdominal exam was significant for distension with flank bulging. The liver was tender to palpation and percussed 3 cm below the costal margin with a bruit heard over the liver. Murphy's sign was negative. A fluid wave was appreciated, and lower extremities had 2+ edema to the mid-calf bilaterally. Laboratory studies were significant for: total bilirubin 10.2 mg/dL, conjugated bilirubin 2.7 mg/dL, ALT 17 U/L, AST 45 U/L, alkaline phosphatase 118 U/L, hemoglobin 8.2 g/dL, hematocrit 25.1%, mean corpuscular volume 106.4 fL, platelet 98x10E3/uL, ferritin 1137 ng/mL, vitamin B12 1517 pg/mL, folate 10.2 ng/mL, reticulocyte

count 6.82%, lactate dehydrogenase 697 U/L, haptoglobin <8mg/dL, direct antiglobulin test negative, cold agglutinin screen positive (Titer 1:2), total cholesterol 197 mg/dL, LDL 117 mg/dL, HDL 61mg/dL, triglycerides 95 mg/dL, vitamin A 0.1mg/dL, vitamin B1 33 nmol/L, vitamin B6 54.1nmol/L, 25-hydroxy vitamin D 18 ng/mL, vitamin E 15.2 mg/L, zinc 37 MCG/ML, and copper 54 MCG/DL. Hemoglobin downtrended to 6.6 mg/dl. Abdominal ultrasound revealed hepatosplenomegaly, a lobulated liver surface suggesting cirrhosis, and ascites. Endoscopy and colonoscopy did not reveal an obvious source of bleeding and demonstrated moderately severe portal hypertensive gastropathy and three diminutive sessile polyps. Peripheral smear demonstrated red blood cells of various size and shape with majority of them being acantocytes, remarkable for presence of spikes on their membranes. Zieve's Syndrome was suspected, and hematology was consulted who agreed with the clinical impression. The patient required two units of packed red blood cells during his hospitalization and his hemoglobin stabilized.

Discussion

Although first defined decades ago, the pathophysiology of Zieve's syndrome remains controversial. In 1958, Zieve proposed a mechanism involving alterations in erythrocyte lipid cell membrane composition leading to increased hemolysis.¹ Decades later, Melrose et al discussed an acquired deficiency in erythrocyte pyruvate kinase leading to instability and increased auto-hemolysis.⁷ Other theories include vitamin E deficiency and hypophosphatemia leading to decreased adenosine triphosphate levels in erythrocytes, both of which lead to auto-hemolysis.⁸ The actual cause of disease is still not well understood or agreed upon.

An equally challenging aspect of this disease is recognizing it amongst numerous more common diagnoses. In particular, right upper quadrant pain and anemia are both nonspecific findings. Acute right upper quadrant abdominal pain with anemia specifically in alcoholics has a broad differential (Table 1). Cholecystitis, alcoholic hepatitis and pancreatitis are all diagnoses that are concerning in this patient population. Other etiologies of abdominal pain such as gastric disease, any small or large intestinal pathology or appendicitis remain possibilities. Misdiagnosis can lead to unnecessary and potentially harmful invasive procedures.⁴⁻⁶

The finding of anemia in alcoholics is concerning for bleeding though this was ruled out in our patient. Additionally, alcohol abuse can cause anemia by directly and indirectly affecting red blood cell production. A directly toxic, dose dependent effect of alcohol on bone marrow leads to suppression of blood cell production. Often simultaneously, alcohol can directly contribute to the formation of structurally abnormal red blood cell precursors. Large intracellular vacuoles and ringed sideroblasts are seen in alcoholics, the latter of which causing a decreased number of functional, mature red blood cells.⁹ Indirectly, alcohol abuse causes multiple nutritional deficiencies impacting red blood cell production and structure, including folate, B12 and iron deficiency.⁹

The unique feature of Zieve's syndrome among all of these previous diagnoses is the presence of an acute onset, extrinsic, non-immune hemolytic anemia.³ As in our patient, acanthocytes are typically found on peripheral blood smear.¹⁰ A negative Direct Antiglobulin Test, elevated Lactate Dehydrogenase, Unconjugated Bilirubin, and Reticulocyte Count, and decreased Haptoglobin further support the presence of non-immune hemolysis and were all observed with our patient. Obtaining a peripheral blood smear early in a patient's clinical course and further laboratory testing looking for evidence of hemolytic anemia will aid in narrowing the differential.

Zieve's syndrome has also been characterized in association with vitamin E deficiency and hyperlipidemia. However, neither were present in our patient. Other reports have also acknowledged that hyperlipidemia is not always seen on presentation, as it is transient and can decrease before anemia presents.⁷ Interestingly, our patient presented with vitamin A, vitamin B1, zinc and copper deficiency, with normal levels of lipids and vitamin E. To our best knowledge, these laboratory results have yet to be described in association with Zieve's syndrome in any publication to date.

Diagnosing Zieve's syndrome early can avoid invasive tests and interventions along with unnecessary workups.^{3,4} In addition, these patients are thought to be at higher risk for other complications such as myalgias, acute renal failure and intracranial hemorrhages.^{3,5,11} Once the condition is diagnosed, these other consequences can be better anticipated and treated if necessary. Supportive therapy, such as blood transfusions, fluids and nutritional supplementation, and alcohol cessation are the only known treatments for this transient anemia. In our case, hospitalization with alcohol cessation and repletion of blood products led to stabilization of the patient's hemoglobin. Nutritional supplementation was stressed, and social work was involved to help facilitate the patient's alcohol abstinence efforts. Emphasis should be placed on sustained alcohol abstinence as this disease can recur with continued alcohol use.¹¹

Conclusion

Zieve's syndrome is a rare, transient hemolytic anemia characterized by RUQ pain, anemia, and hyperlipidemia in an

alcoholic patient. We report a patient with RUQ abdominal pain, hemolytic anemia, and chronic alcohol abuse, who was found to have this syndrome. Given its non-specific presentation, accurate identification of hemolytic anemia can be helpful when working with these patients.

REFERENCES

1. **Zieve L.** Jaundice, hyperlipemia and hemolytic anemia: a heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. *Ann Intern Med.* 1958 Mar;48(3):471-96. PubMed PMID: 13521581.
2. **Nath S, Peck JR.** Hemolytic Anemia in Alcohol-Induced Liver Disease: A Case Report on Zieve's Syndrome. *Int J Blood Res Disord.* 2015, 2:1.
3. **Shukla S, Sitrin M.** Hemolysis in Acute Alcoholic Hepatitis: Zieve's Syndrome. *ACG Case Rep J.* 2015 Jul 9;2(4):250-1. doi: 10.14309/crj.2015.75. eCollection 2015 Jul. PubMed PMID: 26203455; PubMed Central PMCID: PMC4508957.
4. **Pickens S.** Fatality after hepatic angiography in Zieve's syndrome. *Postgrad Med J.* 1979 Dec;55(654):903-4. PubMed PMID: 548954; PubMed Central PMCID: PMC2425700.
5. **Pilcher CR, Underwood RG, Smith HR.** Zieve's syndrome a potential surgical pitfall? *J R Army Med Corps.* 1996 Jun;142(2):84. PubMed PMID: 8819039.
6. **Senatore FJ, McDonald K.** Pitfalls of Treating Alcoholic Hepatitis: Recognizing Hemolytic Anemia in Zieve's Syndrome. *Am J Gastroenterol.* 2016 Apr;111(4):577-9. doi: 10.1038/ajg.2016.25. PubMed PMID: 27125716.
7. **Melrose WD, Bell PA, Jupe DM, Baikie MJ.** Alcohol-associated haemolysis in Zieve's syndrome: a clinical and laboratory study of five cases. *Clin Lab Haematol.* 1990;12(2):159-67. PubMed PMID: 2208946.
8. **Acosta, Jr. DDC, Parungao D, Mirasol M, Valenzuela R.** Transient hepatocellular injury associated with hypertriglyceridemia and hemolysis in an alcoholic Filipino male. *Phillippine Journal of Internal Medicine.* 2015; 53.
9. **Ballard HS.** The hematological complications of alcoholism. *Alcohol Health Res World.* 1997;21(1):42-52. Review. PubMed PMID: 15706762.
10. **Shinton NK.** Desk Reference for Hematology, Second Edition. CRC Press, 2007. Pg 565.
11. **Kondrackiene J, Beinraviciene I, Gelman S, Kupcinskas L.** Zieve's syndrome presenting with coagulopathy, skin and subcutaneous haemorrhage. *Acta Medica Lituanica* 2012; 19(4):403-7.