Zieve Syndrome: A Clinical Triad, or Perchance a Quartet?

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Abstract
Zieve syndrome presents with a triad of hemolytic anemia, unexplained jaundice, and hyperlipidemia secondary to alcohol use/alcohol-induced liver injury, highlighting hemolytic anemia as the hallmark feature. Zieve syndrome is more common than originally perceived as its incidence is estimated to be 1 in 1600 admissions, but its mechanism is still poorly understood. This is a case of a 29-year-old man who developed Zieve syndrome shortly after admission for pancreatitis secondary to alcohol use disorder. Early diagnosis is important to reduce unnecessary tests and interventions. Further studies should be considered to evaluate the association between Zieve syndrome and pancreatitis.

Keywords
diagnostic testing, hospital medicine, gastroenterology, other

Introduction
Since its first description in 1957 by Dr. Leslie Zieve, there have been over 200 published case reports with most cases being misdiagnosed at first presentation, reflecting that this is an under-reported and underdiagnosed syndrome.\textsuperscript{1,1} The syndrome appears to be more common than previously thought with an estimated incidence of around 1 in 1600 admissions in general wards based on extrapolation of data from a large tertiary care center in Germany.\textsuperscript{4}

Case
A 29-year-old male with no active medical problems other than heavy alcohol use presented with acute epigastric abdominal pain radiating to his back associated with nausea and vomiting. The patient’s social history was significant for heavy alcohol use but negative for smoking and illicit drug use. His vital signs on admission were heart rate of 110 bpm, blood pressure 134/78 mmHg, respiratory rate 24, oxygen saturation of 98% on room air, and temperature of 98.5°F. A physical exam uncovered jaundice, scleral icterus, and epigastric tenderness. Laboratory findings were significant for an elevated lipase to 2145 U/L (reference range 13-60 U/L), elevated transaminase enzymes aspartate aminotransferase (AST) 163 U/L (reference 5-40 U/L), alanine aminotransferase (ALT) 209 U/L (reference 0-41 U/L), total bilirubin 1.1 mg/dL (reference 0.0-1.2 mg/dL) and direct bilirubin 0.3 (0.0-0.3 mg/dL), HIV negative, ethanol level <10, IgG4 28.3 (within normal limits), triglycerides 62 mg/dL (<150 mg/dL), HbG 15.8 gm/dL (13.5-17.5 gm/dL), Hct 47.8% (41.0%-53.0%), and red cell distribution width (RDW) 15.6% (11.5-14.5%). Abdominal ultrasound was negative for gallstones. Contrast-enhanced computed tomography (CT) of the abdomen/pelvis in the axial plane demonstrates diffuse peripancreatic fat stranding, consistent with acute pancreatitis. Additionally, limited views of the chest demonstrate bilateral small pleural effusions. His acute pancreatitis was managed with in vitro fertilization (IVF) and pain control. Notably, his Bedside Index of Severity in Acute Pancreatitis (BISAP) Score was 1.

On the day after admission, his Hgb dropped from 15.8 to 11.3, without evidence of overt gastrointestinal (GI) bleed; however, an unconjugated bilirubinemia was then appreciated. Labs are noted in Table 1. Total bilirubin increased from 1.1 to 3.2 mg/dL (reference 0.0-1.2 mg/dL) direct bilirubin 1.4 (0.0-0.3 mg/dL) and indirect bilirubin increased from 0.8 to 2.2 mg/dL. Hemolysis labs were significant for lactate dehydrogenase

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Table 1. Liver Function Test During Hospital Admission.

| Component       | Latest reference range and units | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|-----------------|----------------------------------|-------|-------|-------|-------|-------|-------|-------|
| Albumin         | 3.5-5.2 g/dL                     | 4.9   | 3.8   | 3.7   | 3.3   | 3.1   | 3.1   | 3.2   |
| Total protein   | 6.6-8.7 g/dL                     | 7.3   | 6.2   | 5.8   | 5.6   | 5.3   | 5.4   | 5.6   |
| Total bilirubin | 0.0-1.2 mg/dL                    | 1.1   | 1.4   | 2.8   | 3.2   | 3.1   | 2.4   | 2.1   |
| Direct bilirubin| 0.0-0.3 mg/dL                    | 0.3   | 0.3   | 0.9   | 1.0   | 1.4   | 1.0   | 1.0   |
| ALK PHOS        | 40-129 U/L                       | 129   | 100   | 77    | 72    | 84    | 109   | 156   |
| ALT (SGPT)      | 0-41 U/L                         | 209   | 130   | 81    | 54    | 43    | 45    | 65    |
| AST (SGOT)      | 5-40 U/L                         | 163   | 88    | 56    | 49    | 49    | 37    | 39    | 56    |

Abbreviations: ALK PHOS, Alkaline phosphatase; ALT, Alanine transaminase; SGPT, Serum glutamate pyruvate transaminase; AST, Aspartate aminotransferase; SGOT, Serum glutamic-oxaloacetic transaminase.

Discussion

Zieve syndrome presents as an alcohol-related triad of cholestatic jaundice, transient hemolytic anemia, and hyperlipidemia. Patients usually present with anemia in the setting of alcohol use and liver disease. Most cases are associated with right upper quadrant pain and transaminitis or acute pancreatitis. Some authors report pancreatitis as an essential feature of this syndrome. Other non-specific symptoms include right upper quadrant abdominal pain, nausea, vomiting, malaise, weakness, and low-grade fever. Hyperlipidemia is usually transient and usually subsides within 1 to 2 weeks after initial insult, although atypical presentations are seen in patients where lipids are within normal limits.

Although different theories have been proposed to explain hyperlipidemia and hemolysis in this syndrome, the exact pathogenesis is obscure. Biochemical studies show changes in membrane composition, notably Vitamin E deficiency with a decrease in polyunsaturated fatty acids (PUFAs) results in oxidation of glutathione in RBCs which in turn results in instability of pyruvate kinase enzyme. Additionally, acetaldehyde, a metabolite of alcohol, binds, and inhibits RBC enzymes. The resultant RBC is more susceptible to metabolic injury to circulating hemolysins. Previous studies demonstrate hemolysis of autologous and transfused RBCs suggestive role of extracorporeal hemolytic factors. Furthermore, high levels of circulating lipids, lysolecithin, and lysocephalin act as circulating hemolysins resulting in additional insult to susceptible RBCs. It has been postulated that deficiency of lipoprotein lipase due to damaged pancreatic alpha cells and massive mobilization of lipids in the liver leads to transient hyperlipidemia and subsequent hemolysis and pancreatitis. Hyperbilirubinemia is usually cholestatic secondary to impaired liver metabolism due to alcohol intake.

Diagnosis is usually established by a history of alcohol abuse, clinical triad, and pertinent biochemical tests. Elevation of direct bilirubin, alkaline phosphatase and gamma-glutamyl transferase more than aspartate aminotransferase/alanine aminotransferase can be clues to this diagnosis. Hematolopy labs reveal anemia, with elevated reticulocytes with an increase in lactate dehydrogenase. Coombs's test is typically negative in Zieve Syndrome. Extensive workup of hemolytic anemia including genetic and biochemical studies is negative. Bone marrow biopsy if performed should demonstrate active marrow proliferation. Follow-up after resolution of the acute phase and complete abstinence demonstrating improvement in hematocrit and hyperlipidemia supports the diagnosis of Zieve syndrome.

Treatment involves supportive care and complete abstinence from alcohol use. Most documented cases recover completely within 4 to 6 weeks of alcohol abstinence. It is postulated that alcohol cessation leads to lipid mobilization from plasma to the liver and adipose tissue as lipases are re-activated leading to a slow decrease in plasma triglycerides and metabolic changes in the RBC membrane reducing susceptibility for hemolysis. Plasmapheresis should be considered in patients at high risk of intracerebral hemorrhage and a history of pancreatitis as these patients may be susceptible to acute cerebrovascular events from downstream effects of hyperlipidemia.

Conclusion

In Zieve’s original report, pancreatitis was frequently suspected but rarely established as CT scans did not yet exist at the time and amylase had poor specificity and sensitivity for acute pancreatitis. Timely recognition of this syndrome may help prevent unnecessary diagnostic or therapeutic interventions. Many cases of Zeives are documented in non-English literature and that’s why this syndrome is under-recognized and untreated, therefore there is a real need to increase reporting and awareness that will aid in treating the disease.
appropriately. Zieve syndrome and its association with pancreatitis should be suspected in patients with hemolytic anemia in the setting of acute alcohol intake without signs of gastrointestinal bleeding. Future studies should be considered to evaluate the association between Zieve syndrome and pancreatitis.

Authors’ Note
This case report was presented virtually as an abstract: “Zieve syndrome: A Clinical Triad, or Perchance a Quartet?” at the American College of Gastroenterology national conference in October 2020

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