CASE REPORT

Hyperbilirubinaemia and haemolytic anaemia in acute alcoholic hepatitis: there's oil in them thar veins

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SUMMARY

A Caucasian woman in her late 30s was evaluated after a period of binge drinking and found to have hyperbilirubinaemia for which she was referred for consideration of cholecystectomy. After exclusion of other possibilities, Zieve's syndrome was diagnosed. This is a condition of hyperbilirubinaemia, Coombs' negative haemolytic anaemia and hyperlipidaemia associated with alcoholism. Abstinence from alcohol remains the only known effective treatment, and appreciation of the entity can prevent unnecessary biliary procedures. The patient improved with supportive measures and was discharged in stable condition.

BACKGROUND

First described in 1957, Zieve's syndrome includes alcoholic steatohepatitis, hyperlipidaemia and Coombs' negative haemolytic anaemia. Recovery typically occurs over several days to weeks after cessation of alcohol consumption. As Dr Zieve himself noted, the recognition of this entity is of value in that it may, as in this case, prevent an unnecessary surgery.

CASE PRESENTATION

A Caucasian woman in her late 30s, and who had been struggling with alcoholism voluntarily entered an alcohol rehabilitation programme after a period of very heavy drinking. Owing to her jaundiced appearance, the staff promptly referred her for medical evaluation at an outside hospital where her liver function tests were notable for high transaminase levels and a total bilirubin of 39.2 mg/dL. A right upper quadrant ultrasound (RUQ US) and an abdominal CT showed a thickened, distended gallbladder. Out of concern that the patient might have acute cholecystitis, she was transferred to our hospital for possible cholecystectomy or cholecystostomy tube placement.

The patient's medical history was notable for hypothyroidism, hypertension and prior alcoholic hepatitis. Her only home medication was levothyroxine.

On physical examination, the patient was afebrile with a heart rate of 92 bpm and blood pressure of 124/86 mm Hg. She exhibited marked scleral icterus ([figure 1](#)) and palatal jaundice. Abdominal examination was unremarkable; no masses, tenderness or hepatomegaly were present. Notable laboratory studies on admission are summarised in [table 1](#) and included hepatitis with hyperbilirubinaemia and a Coombs' negative haemolytic anaemia.

Figure 1 The patient was severely jaundiced and icteric.

Shortly after admission, blood drawn from the patient was noted to be milky, suggesting a high lipid content ([figure 2](#)). On hospital day 2, her serum triglyceride level was measured at 696 mg/dL. In the evaluation of her hepatitis with Coombs' negative haemolysis, assays of genetic mutations for haemochromatosis, liver biopsy copper stains and glucose-6-phosphate dehydrogenase deficiency were negative. As the appearance of a thickened gallbladder on ultrasound and CT were considered non-specific, further testing for cholecystitis was deemed necessary prior to any invasive intervention. Hepatobiliary iminodiacetic acid scan was uninterpretable due to complete lack of uptake by the liver. MR cholangiopancreatography showed findings potentially suggestive of acute acalculous cholecystitis together with mild ascites and hepatomegaly. A liver biopsy demonstrated fatty infiltration ([figure 3](#)). Given the patient's long-standing heavy alcohol use, alcoholic hepatitis, jaundice, marked hyperbilirubinaemia, haemolytic anaemia and hypertriglyceridaemia, a diagnosis of Zieve's syndrome was made.

DIFFERENTIAL DIAGNOSIS

Patients with Zieve's syndrome will often exhibit right upper quadrant pain, elevated transaminases and hyperbilirubinaemia which may prompt imaging of the gallbladder to look for acute cholecystitis or imaging of the biliary tree to look for common duct obstruction. Cholecystitis and cholangitis are maintained in the differential of patients with Zieve's syndrome, and knowledge of Zieve's syndrome may prevent clinicians from misinterpreting non-specific findings from biliary imaging. Recognition of haemolytic anaemia will distinguish Zieve's syndrome from uncomplicated acute alcoholic hepatitis.

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Table 1 Laboratory data

	Reference range	Admission
Leucocyte count (per μL)	4500–11 000	18 800
Haemoglobin (g/dL)	11.5–15.5	10.6
Reticulocyte count (%)	0.5–1.5	8.1
Platelet count ($/\mu\text{L}$)	150 000–400 000	28 000
Haptoglobin (mg/dL)	36–195	<10
Iron ($\mu\text{g/dL}$)	60–170	139
Total iron binding capacity ($\mu\text{g/dL}$)	240–450	167
Ferritin (ng/mL)	12–150	5737
Peripheral blood smear		Left shift; no schistocytes
Total protein (g/dL)	6.0–8.5	5.2
Albumin (g/dL)	3.2–5.0	1.5
Total bilirubin (mg/dL)	0–1.3	38
Direct bilirubin (mg/dL)	0–0.3	26
Alkaline phosphatase (IU/L)	20–125	480
Aspartate aminotransferase (IU/L)	0–42	217
Alanine aminotransferase (IU/L)	0–48	63
Creatinine (mg/dL)	0.4–1.0	1.8
Creatine clearance (mL/min)	87–107	41.7
Thyroid stimulating hormone ($\mu\text{IU/mL}$)	0.4–4	13.9
Cholesterol (mg/dL)		309
Triglycerides (mg/dL)		578
High-density lipoproteins (mg/dL)		24
Low-density lipoproteins (mg/dL)		152

Patients with acute cholecystitis classically present with right upper quadrant pain, fever and a positive Murphy's sign on examination. Laboratory tests are non-specific in cholecystitis. Hyperbilirubinaemia is not uncommon, but bilirubin levels are rarely elevated to the extent seen in patients with Zieve's

Figure 2 Blood sample demonstrating lipaemia.

Figure 3 Liver biopsy demonstrating marked steatosis (H&E staining).

syndrome. Bilirubin elevation in cholecystitis reported in one large study typically range from 34 to 86 $\mu\text{mol/L}$ (2.0–5.0 mg/dL).¹ Biliary imaging through RUQ US or cholescintigraphy can be used to evaluate the clinical suspicion of cholecystitis. Findings of gallstones and pericholecystic fluid, classic for acute acalculous cholecystitis, are rarely seen in Zieve's syndrome. Non-specific findings on biliary imaging, such as gallbladder wall thickening and distension, however, offer little utility in refining a differential diagnosis in this setting.

Ascending cholangitis and choledocholithiasis are diseases that can produce right upper quadrant pain and jaundice with hyperbilirubinaemia. In Zieve's original case series, one patient underwent operative intervention evaluating for choledocholithiasis, which was not present and Dr Zieve asserted that recognition of this syndrome could prevent unnecessary invasive biliary procedures.^{2,3} The patient we present had a series of imaging studies performed with no evidence of an obstructive biliary stone. If the clinical presentation of jaundice and hyperbilirubinaemia after acute alcohol consumption is combined with findings of haemolytic anaemia and hyperlipidaemia, testing and interventions (such as endoscopic retrograde cholangiopancreatography) to assess for choledocholithiasis may be avoided.

Acute alcoholic hepatitis presents with elevated transaminases, hyperbilirubinaemia and an elevated international normalised ratio (INR) in patients with a typical history of decades of heavy alcohol consumption. Patients will have transaminase elevations that are elevated, with an aspartate aminotransferase (AST) typically less than 300 IU/mL and an AST/alanine aminotransferase ratio greater than 2.⁴ Although clinical symptoms and certain laboratory findings are similar, patients with acute alcoholic hepatitis do not have the combination of haemolytic anaemia and hyperlipidaemia characteristic of Zieve's syndrome. Furthermore, patients with acute alcoholic hepatitis will progress to liver failure and death in 40% of cases, even with the best available treatment and abstinence.⁴ Patients with Zieve's syndrome will recover by remaining abstinent from alcohol.

Patients with liver disease occasionally present with haemolytic anaemia, which results from alterations of the red blood cell (RBC) membrane and portal hypertension-induced splenic sequestration. These two mechanisms can work independently or in concert to cause haemolysis.

Alterations in erythrocyte cell membrane composition in cirrhosis and liver disease can cause conformational changes that

result in various degrees of haemolysis. These changes take place due to changes in the plasma membrane concentration of cholesterol to phospholipids.⁵ A number of phenotypic RBC alterations occur in liver disease, which include acanthocytes (spur cells), stomatocytes, codocytes (target cells) and echinocytes (burr cells). Acanthocytes are typically associated with the most marked haemolysis, partly due to cell membrane changes and also due to splenic destruction of RBCs.⁶ Other cell types, such as codocytes, echinocytes and stomatocytes, have different conformational changes that lead to variable levels of haemolysis.^{5 7}

High portal pressure in chronic liver disease causes hypersplenism. The spleen can sequester and destroy RBCs, resulting in anaemia and varying levels of haemolysis.⁸ The amount of sequestration and destruction has been shown to be related to the size of the spleen.⁹

None of these scenarios of high cell turnover or spleen sequestration occur with evidence of acute, reversible hyperbilirubinaemia and hyperlipidaemia. This differentiates Zieve's syndrome from other forms of liver-induced haemolytic anaemia.

TREATMENT

Specific treatment does not exist for Zieve's syndrome. Supportive care, including treatment for the accompanying alcoholic hepatitis and abstinence from alcohol, remains the standard therapy. Prompt recognition of the syndrome prevents unnecessary treatments targeting the gallbladder and biliary tract.

OUTCOME AND FOLLOW-UP

On hospital day 5, a lipid panel revealed an elevated total cholesterol level of 309 mg/dL; however, her triglycerides were noted to have dropped from 696 to 578 mg/dL. High-density lipoprotein was low at 24 mg/dL and low-density lipoprotein was elevated at 152 mg/dL. Total bilirubin also showed a drop from 33.6 to 24.5 mg/dL and alkaline phosphatase from 381 to 299 U/L. With conservative, supportive therapy her condition improved and she was discharged home.

A year and a half after presentation, the patient was contacted and reported that she was still sober and that she was 'in perfect health' without residual liver or lipid problems.

DISCUSSION

In 1958, Leslie Zieve published a retrospective analysis of 20 chronic alcoholic men with hepatic dysfunction seen over an 8-year period at the Minneapolis Veteran's Hospital. He described a syndrome characterised by hyperlipidaemia, haemolytic anaemia and cholestatic jaundice that predictably resolved following alcohol abstinence.³ Initially, his findings were met with scepticism²; however, with the publication of a cohort of six similar cases 4 years later from the State Veterans' Hospital in Rocky Hill, Connecticut,¹⁰ the pattern gained credibility and became known as Zieve's syndrome.

Similar cases^{11 12} continued to emerge along with frequent observation of porphyrinuria,¹³ increased plasma viscosity with severe myalgias¹⁴ and retinal injury,¹⁵ all of which proved reversible with alcohol abstinence. Hyperlipidaemia was implicated as a potential causal factor of intracranial haemorrhage in a few instances of Zieve's.¹⁶

Zieve's syndrome follows excessive alcohol consumption and improves in 4–6 weeks once consumption stops. Haemolytic anaemia and jaundice typically last for 4–6 weeks, while hyperlipidaemia starts improving as early as 10 days and completely subsides in approximately 6 weeks. The syndrome's transient nature may explain, to some degree, why establishing a

diagnosis is relatively difficult.¹⁷ The clinical triad of hyperlipidaemia, haemolytic anaemia and cholestatic jaundice is typically found in conjunction with abdominal pain, low-grade fever and acute hepatitis-induced liver tenderness. These findings contribute to the diagnostic confusion with acute cholecystitis. Because its components are frequently observed independently in liver disease, Zieve's syndrome often goes undiagnosed, and the incidence is difficult to estimate.¹⁸

The pathogenesis of Zieve's syndrome remains obscure. Hyperlipidaemia, the most prominent manifestation, is transient, often precedes the onset of haemolysis, and resolves without therapy. Suggested mechanisms include an episode of massive mobilisation of fat to or from the fatty liver,³ dysregulated blood lipids due to damaged pancreatic α cells,¹⁹ an enhanced peripheral mobilisation versus decreased hepatic lipid metabolism,²⁰ a diminution of normal plasma lipids clearing factors such as heparin and albumin, potentiated by an associated pancreatitis,^{19 21} yet most cases show normal amylase levels, or a pancreatohepatic syndrome seen with severe malnutrition and hepatic lesions preceding the lesion in the pancreas.²²

Jaundice and hyperbilirubinaemia result from haemolysis and intrahepatic cholestasis.¹⁰ The hyperbilirubinaemia is higher than otherwise observed in uncomplicated alcoholic hepatitis and most often is found to be a conjugated bilirubinaemia. Furthermore, signs of haemolysis may peak despite declining bilirubin levels,¹² suggesting that haemolysis is not the predominant cause of jaundice.

Haemolytic anaemia, the *sine qua non* of the syndrome, differentiates it from alcoholic hepatitis. The 'triggering factor' could be markedly elevated haemolysins in the plasma²³ such as lysolecithin³ and lysocephalin, or an extracorporeal factor²³ that increases erythrocyte destruction of host RBCs and transfused compatible donor cells during an acute illness. In vitro incubation of remission stage erythrocytes with plasma preserved from the acute illness did not hasten erythrocyte destruction, suggesting that the inciting factor does not circulate in plasma but instead may work synergistically with an additional intracellular defect. Erythrocytes of patients with Zieve's syndrome have been shown to have low ATP levels, high 2,3-diphosphoglycerate levels and decreased glucose utilisation.²⁴ Quantitative analysis failed to detect an enzyme deficiency; however, qualitative analysis suggested defective or decreased pyruvate kinase activity with marked thermal instability and altered kinetics.²⁵ Acetaldehyde, a highly reactive metabolite of ethanol, has also been shown to inhibit activity of some erythrocyte enzymes.

The exact relationship between hyperlipidaemia and haemolysis remains unclear. Onset of haemolysis can precede a rapid fall in the high plasma lipid levels,²⁵ raising the alternate possibility that hyperlipidaemia protects the RBC against a circulating extracorporeal haemolysin.^{26 27} Cholesterol inhibits lysolecithin activity,²⁸ which further suggests that haemolysin acts when the circulating lipid concentration falls and that the metabolically depleted state of the Zieve's syndrome erythrocyte potentiates its activity. Hyperlipidaemia has been associated with an increase in erythrocyte lipids, especially the cholesterol and lecithin fractions, and a shortened RBC lifespan²⁸; however, shortened RBC lifespan was regularly accompanied by increase in RBC lipids but not in plasma lipids. This suggests that increased RBC lipids may thus be a more important association for haemolysis than increased plasma lipid.²⁸ Another striking observation is a decrease in membrane-bound polyunsaturated fatty acids (PUFA) concentrations when correlated with the concurrently decreased serum and membrane

tocopherol levels.²⁹ Vitamin E is located primarily within the phospholipid bilayer of cell membranes and is particularly effective in preventing lipid peroxidation—a series of reactions involving the oxidative deterioration of PUFAs. Alcohol-induced vitamin E deficiency of erythrocytes, which produces a decrease in PUFA levels, may oxidise reduced RBC glutathione and destabilise pyruvate kinase.²⁹

Although the aforementioned possibilities attempt to formulate a pathological basis for the syndrome, quantitative rather than qualitative differences separate patients with Zieve's syndrome from other patients with alcoholic liver disease. Nevertheless, knowledge of Zieve's syndrome is essential to avoid unnecessary treatments for hyperlipidaemia and haemolysis, as well as potentially hazardous biliary interventions in these severely ill patients.^{26 30}

Learning points

- ▶ Zieve's syndrome constitutes the combination of alcoholic hepatitis, haemolytic anaemia and hyperlipidaemia.
- ▶ Zieve's syndrome may present similarly to acute cholecystitis.
- ▶ The manifestations of Zieve's syndrome should resolve in approximately 6 weeks following alcohol cessation.

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