CASE REPORT

Unveiling Zieve's syndrome: A rare yet underdiagnosed complication of chronic alcoholic hepatitis

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Abstract

Zieve's Syndrome (ZS), also known as hyperlipidemic jaundice, is a rare and intriguing clinical entity characterized by a unique constellation of symptoms, including hemolytic anaemia, jaundice, and transient hyperlipidemia. The aetiology of ZS primarily revolves around chronic alcohol abuse, although non-alcoholic causes have been reported. Syndrome is believed to result from alcohol-induced hepatotoxicity leading to hepatic steatosis, impaired lipid metabolism, and subsequent hemolysis and jaundice. Acanthocytes, or spur cells, are a distinct feature observed in some cases of ZS, particularly in the context of hemolytic anaemia. The clinical presentation typically includes symptoms of anaemia, such as fatigue and pallor, accompanied by jaundice and possibly hepatomegaly. Laboratory investigations often reveal elevated liver enzymes, hyperbilirubinemia, and elevated lipid levels, particularly triglycerides. In this case study, we present a 46-year-old male patient with a history of chronic alcoholism, who presented with chief complaints of yellowish discoloration of the eyes, extreme fatigability, and abdominal pain. Diagnosis of alcoholic hepatitis with ZS was confirmed, and appropriate management, including thiamine supplementation, intravenous fluids, and proton pump inhibitors, was initiated. The patient exhibited notable improvement following treatment, highlighting the efficacy of comprehensive intervention in such cases.

Keywords: Zieve's Syndrome, hemolytic anaemia, jaundice, hyperlipidemia, chronic alcohol abuse, acanthocytes

Introduction

Zieve's Syndrome (ZS), a rare condition associated with chronic alcoholism, and is characterized by a triad of hemolytic anaemia, cholestatic jaundice, and transient hyperlipidemia [1]. The incidence of ZS is estimated to be one in 1,600 admissions. Non-alcoholic causes of ZS may include conditions such as severe malnutrition, metabolic disorders, liver diseases (such as hepatitis or cirrhosis), and certain medications. These cases are relatively rare compared to those associated with alcoholism as the majority of cases are linked to alcohol abuse [2]. It was first described by Dr. Leslie Zieve in 1957. It is often under recognized and can present with severe hypertriglyceridemia, requiring plasmapheresis. ZS is caused by the release of fat from the liver and the breakdown of red blood cells due to sudden cessation of excessive alcohol consumption [3]. Acanthocytes, or spur cells, are irregularly shaped red blood cells with spiky projections on their surface, often observed in the setting of hemolytic anaemia [4]. While the pathogenesis of ZS remains incompletely understood, the presence of acanthocytes in peripheral blood smears aids in diagnosis. It highlights the complex interplay between alcohol-induced liver injury and derangements in lipid metabolism. Treatment typically involves bed rest, adequate food intake, hydration, and vitamin supplementation [5].

Case Report

A 46-year-old male, with history of chronic alcohol consumption since 16 years, presented to this hospital with chief complaints of yellowish discolouration of eyes associated with extreme fatigability for 8 days and abdominal pain for 4 days. There was no history of fever, vomiting, hematemesis, melena, haematochezia, distension of the abdomen, or altered mental status.

On general examination, patient had a regular pulse rate of 106 per minute and blood pressure of 98/60 mm of Hg, along with pallor and icterus. Grade 1 clubbing was present with no lymphadenopathy or oedema. Signs of hepatocellular failure in the form of spider angiomas were present along with gynecomastia. His Body Mass Index (BMI) was 21 thus ruling out comorbidities like obesity or any other metabolic syndrome which could contribute to hyperlipidemia. On per abdomen examination, the abdomen was scaphoid, with no free fluid, and the liver was palpable 2 cm below the right costal margin, soft and tender. Other systemic examination was unremarkable. Ultrasonography (USG) of abdomen showed fatty infiltration and grade 2 fatty liver without ascites, cephalocaudal splenic length was 11.6 cm and portal vein diameter was normal thus ruling out splenomegaly and portal hypertension. Patient was also advised for Fibro scan but couldn't be done due to monetary constraints.

Investigations

Peripheral blood smear examination revealed the presence of acanthocytes, characterized by irregularly spaced, spiky projections on the surface of red blood cells (Figure 1). Maddrey's Discriminant Function (MDF) was calculated to be 21.2. A final diagnosis of alcoholic hepatitis with ZS was made. The presence of jaundice confirmed ZS along with evidence of hemolysis by the presence of acanthocytes in the peripheral smear, elevated serum LDH, increased reticulocyte counts and an undetectable haptoglobin level with negative direct antiglobulin test, and lastly, altered lipid profile. Normal B12 and folate levels ruled out other causes of hemolytic anemia. The patient was treated with injection thiamine 100 mg once daily, Intra-venous (IV) fluids, IV dextrose, and IV Proton Pump Inhibitors (PPI) and was advised complete abstinence from alcohol. Seven days after treatment, the patient symptomatically improved. Repeat investigations showed improvement, and the patient was discharged (Table 1).

Interpreation of the peripheral blood smear

The slide stained with leishman stain (oil immersion 100×) showed predominantly normocytic normochromic RBCs, at places ovalocytes were seen, few schistocytes and spur cells were also seen. Platelets and total leucocytes appeared to be adequate on smear.

Table 1: Parameters on day 1 and day 7

Parameter	Result	After 1 week	Reference Range
Hemoglobin (Hb)	9.0 g/dL	9.1 g/dL	13.5-17.5 g/dL
Hematocrit (Hct)	30.2%	30.2 %	41-53%
Mean Corpuscular Volume (MCV)	90 fL	90 fL	80-100 fL
Red Blood Cell Count (RBC)	4.1 × 10^6/uL	-	4.5-5.5 × 10^6/uL
White Blood Cell Count (WBC)	7.2 × 10^3/uL	-	4.0-11.0 × 10^3/uL
Platelet Count	220 × 10^3/uL	-	150-400 × 10^3/uL
Alkaline Phosphatase (ALP)	80 U/L	76 U/L	
Aspartate Aminotransferase (AST)	250 U/L	220 U/L	10-40 U/L
Alanine Aminotransferase (ALT)	70 U/L	50 U/L	7-56 U/L
Total Bilirubin	12 mg/dL	9 mg/dl	0.2-1.2 mg/dL
Conjugated Bilirubin	5 mg/dL	3	0.1-0.3 mg/dL
Unconjugated Bilirubin	7 mg/dL	6	0.1-0.9 mg/dL
Lactate Dehydrogenase (LDH)	320 U/L	300	140-280 U/L
International Normalized Ratio (INR)	1.2	1.1	<1.5
Serum Albumin	3.9 gm/dl	-	
Serum Haptoglobin	undetectable	-	
Serum Reticulocyte	4.8%	-	0.5-2.5%
Triglyceride	206 mg/dL	200	<150 mg/dL
Total Cholesterol	322 mg/dL	322	<200 mg/dL
HbsAg	-ve	-	
IgM Anti-HAV	-ve	-	
Anti-HCV	-ve	-	
Vitamin B12	273 pg/ml	-	239 – 931 pg/ml
Folate	5 ng/ml	-	2.7 – 17 ng/ml

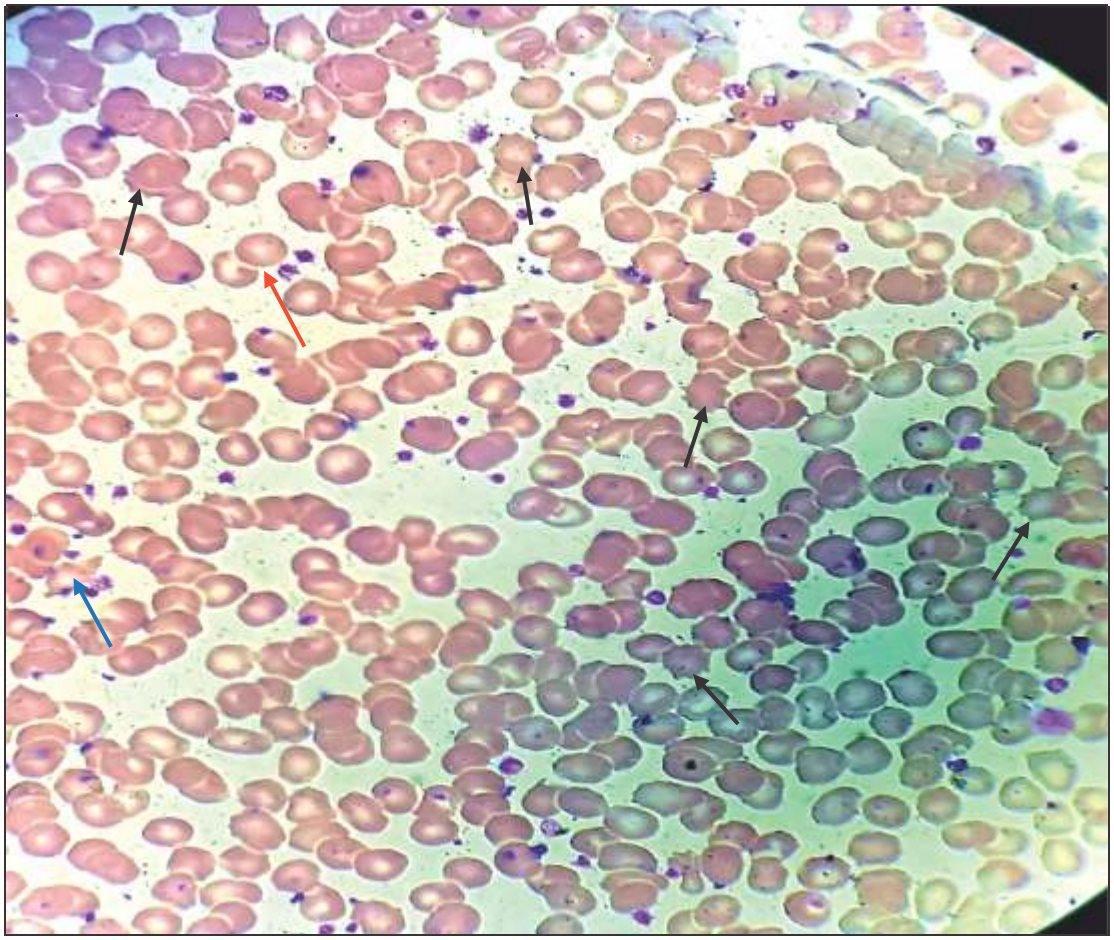

Figure 1: Black arrows depicting the presence of acanthocytes (spur cells) in peripheral smear, red arrow – ovalocytes and blue arrow – schistocytes

Discussion

ZS, a rare clinical entity, presents with a characteristic triad of jaundice, hyperlipidemia, and hemolytic anaemia, predominantly observed in individuals with chronic alcohol abuse [6]. The pathogenesis of ZS remains incompletely understood, with hepatocyte injury and hemolysis contributing significantly to the profound hyperbilirubinemia observed. The hyperlipidemia seen in ZS may be transient, potentially resulting from mechanisms such as massive fat mobilization from the liver or dysregulated lipid metabolism due to alcohol-induced pancreatic damage. Suspected mechanisms of hemolysis in ZS include abnormal lipid species, possibly lysolecithin, and alcohol-induced Vitamin E deficiency, leading to erythrocyte instability and subsequent hemolysis [7]. Notably, the absence of a positive Coombs test suggests a non-autoimmune aetiology for hemolytic anaemia, distinguishing ZS from other forms of hemolysis. Diagnosis of ZS relies on clinical observation, laboratory investigations, and the exclusion of alternative etiologies. Liver biopsy findings often demonstrate features consistent with alcoholic liver disease, such as hepatocellular steatosis and peri-sinusoidal fibrosis. The presence of acanthocytes in peripheral blood smears is a distinctive feature of ZS, reflecting underlying alcohol-induced liver injury and hemolysis. Chronic alcohol abuse disrupts erythrocyte membrane integrity, leading to the formation of acanthocytes [8].

Differential diagnosis of ZS include autoimmune hepatitis, hemolytic anemia, and drug-induced liver injury. Management of ZS primarily involves abstinence from alcohol, which typically leads to the resolution of symptoms within 4 to 6 weeks. Supportive care may include addressing complications such as anaemia and hyperlipidemia. It is essential to avoid overtreatment with glucocorticoids, as they may exacerbate complications and do not target the underlying pathophysiology of ZS [9]. Early recognition of ZS is paramount to prevent unnecessary invasive procedures and ensure appropriate management, ultimately improving patient outcomes. Continued research efforts are necessary to elucidate the underlying mechanisms and optimize treatment strategies for this intriguing clinical entity [10].

Conclusion

ZS remains a diagnostic challenge due to its rarity and nonspecific clinical presentation. Clinicians must maintain a high index of suspicion, especially in individuals with a history of chronic alcohol abuse presenting with hemolytic anaemia and jaundice. Management primarily revolves around addressing the underlying alcohol abuse and providing supportive care to mitigate complications. Long-term follow-up is essential to monitor disease progression and prevent recurrence. Since ZS is often associated with alcoholism, efforts to reduce alcohol abuse can indirectly decrease its incidence. Further research is warranted to elucidate the pathophysiological mechanisms and refine treatment strategies for this intriguing syndrome.

References

1. Abughanimeh O, Kaur A, Numan L, Bahaj W, Madhusudhana S. Zieve's Syndrome: An Under-reported Cause of Anemia in Alcoholics. *Cureus* 2019; 11(2):e4121.
2. Srikar M, Shaikh MA. Mean platelet volume in patients with non-alcoholic fatty liver disease. *J Krishna Inst Med Sci Univ* 2021; 10(3):1-10.
3. Choudhry F, Kathawa J, Kerton K, Farshadsefat S, Piper M. Zieve's Syndrome presenting with severe hyper-triglyceridemia. *ACG Case Rep J* 2019; 6(7):e00133.
4. Fung A, Mittal A. Hemolytic anemia in alcohol use disorder: a case of Zieve Syndrome. *Chest* 2022; 162(4): A1002.
5. Gosal K, Singh P, Westbrook K, Carter MK. Underrecognized Zieve's syndrome, A case report. *Ann Med Surg (Lond)* 2021; 66:102464.
6. Liu MX, Wen XY, Leung YK, Zheng YJ, Jin MS, Jin QL, *et al*. Hemolytic anemia in alcoholic liver disease: Zieve syndrome. *Medicine (Baltimore)* 2017;96(47):e8742.
7. Reyes JVM, Ahmad S, Majeed H, Kandoth E, Lieber JJ. Zieve Syndrome: A clinical triad, or perchance a quartet? *J Investig Med High Impact Case Rep* 2022; 10:23247096221121393.
8. Sams LE, Krappe J, Czihal M, Hoppe JM. Zieve syndrome presenting with lipaemia and treated by plasmapheresis. *BMJ Case Rep* 2022; 15(4):e245257.
9. Vedire A, Imburgio S, Sanekommu H, Patel R, Johnson H, Taj S, *et al*. Unique variant of Zieve Syndrome with a normal reticulocyte count. *J Med Cases* 2023;14(6): 185-190.
10. Zalavadiya R, Bhatt JH, Nagori I, Kagathara N, Neupane S. An unusual case of Zieve's syndrome in a 36-year-old male with latent autoimmune diabetes of adult and disseminated intravascular coagulation. *Clin Case Rep* 2024; 12(2):e8445.

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