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CASE REPORT

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An unusual case of Zieve's syndrome in a 36-year-old male with latent autoimmune diabetes of adult and disseminated intravascular coagulation

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Key Clinical Message

Zieve's syndrome, associated with chronic alcoholism, manifests as hemolytic anemia, transient hyperlipidemia, and cholestatic jaundice. Key symptoms comprise nausea, abdominal pain, and jaundice. Diagnosis relies on recognizing the triad in those with an alcohol use history. Supportive management includes blood transfusions and alcohol cessation. The exact pathophysiology remains uncertain, with hypotheses ranging from alcohol-induced liver damage to autoimmune processes. The report emphasizes diagnostic complexities, particularly when concurrent with autoimmune disorders such as latent autoimmune diabetes of adults or complicated by disseminated intravascular coagulation (DIC). A 36-year-old male with latent autoimmune diabetes of adults and an 18-year history of chronic alcoholism presented with yellowish skin discoloration, abdominal pain, and distension. Physical examination revealed signs of anemia, jaundice, pedal edema, hepatomegaly, splenomegaly, and abdominal tenderness. Over eight admissions, multiple tests revealed severe anemia, thrombocytopenia, elevated bilirubin, and positive autoantibodies. Treatment for suspected autoimmune hepatitis showed no improvement. Subsequent examinations indicated DIC, altered liver function, and cirrhosis progression. A confirmed diagnosis of Zieve's syndrome was made. Upper gastrointestinal endoscopy was done to check for esophageal varices which were banded. The patient was subsequently managed on supportive treatment with multiple blood transfusions and abstinence from alcohol. Prompt recognition of Zieve's syndrome is crucial to avoid unnecessary interventions. Alcohol cessation is the keystone of treatment, emphasizing the need to raise awareness among practitioners. This case points toward the importance of comprehensive evaluation, serial investigations, and multidisciplinary collaboration for accurate diagnosis and management. Further research is needed to enhance understanding and optimize therapeutic strategies.

KEYWORDS
cholestatic jaundice, chronic alcoholism, hemolytic anemia, latent autoimmune diabetes of adult, transient hyperlipidemia, Zieve's syndrome

1 | INTRODUCTION

Zieve's syndrome is an uncommon clinical entity characterized by a triad of hemolytic anemia, transient hyperlipidemia, and cholestatic jaundice.[1,2] This syndrome is most frequently encountered in individuals with a history of chronic alcoholism. Patients with Zieve's syndrome commonly present with symptoms such as nausea, abdominal pain, jaundice, abdominal distension, and edema. The overall incidence of this syndrome is estimated to be one case per 1600 admissions. A confirmed diagnosis of Zieve's syndrome is established by identifying the triad of hemolytic anemia, transient hyperlipidemia, and cholestatic jaundice, which develops in individuals with a history of chronic alcoholism. The recommended treatment approach is solely supportive and includes procedures like repeated blood transfusions and abstaining from alcohol.[3] The mechanism underlying the syndrome remains elusive, with proposed theories ranging from direct alcohol-induced hepatocyte damage to autoimmune mechanisms.[4] The report emphasizes the novelty and intricate diagnostic challenges associated with Zieve's syndrome, particularly when it coexists with an autoimmune disorder (LADA), and when complicated by disseminated intravascular coagulation (DIC).

2 | CASE PRESENTATION

A 36-year-old male with latent autoimmune diabetes of adults (LADA) and an 18-year history of chronic alcoholism presented with yellowish skin discoloration, abdominal pain, and distension. Physical examination revealed clinical signs of pallor, icterus, pedal edema, hepatomegaly, splenomegaly up to the umbilicus, and generalized abdominal tenderness. The patient had been admitted a total of eight times between April 8, 2022, and June 9, 2023, with similar complaints. During this period, he underwent 16 packed cell volume (PCV) transfusions, multiple ultrasounds, blood tests, one contrast-enhanced CT scan (CECT), and various antibody tests.

2.1 | Investigations and findings

Laboratory investigations unveiled severe anemia, thrombocytopenia, an elevated bilirubin profile (direct 3.2, indirect 6.2, and total 9.4 mg/dL), 7.5% HbA1c, and positive autoantibodies including ANA, Jo-1, AMA M2, and Ro 52. Patient also had hyperlipidemia during his initial admission which later normalized on subsequent admissions. Hepatomegaly with a fatty liver Stage 1 and splenomegaly (18 cm) were confirmed through imaging. Additional findings included multiple collaterals in the pancreas and spleen, gall bladder stones (13 mm × 13 mm), and renal calculi two in the right kidney and three in the left kidney. Based on the ANA reports and hemolytic anemia, the patient was initially treated for suspected autoimmune hepatitis with prednisolone 20 mg OD for 7 days, but no improvement was noted. Peripheral smear examination depicted anisopoikilocytosis, many fragmented RBCs, acanthocytes, microcytes, and occasional target cells are seen. Other causes of anemia were ruled out as there were negative DCT, ICT with normocytic anemia and RBCs having MCV within normal range in peripheral blood. There wasn't any history of recent blood transfusion; so, there was no role of delayed hemolytic transfusion reactions. Therefore, most probable cause of hemolytic anemia was due to associated hypersplenism. Commenting on WBC series, total counts were within normal limits with neutrophils showing toxic granules. Decreased platelet count was also an important finding of examination.

2.2 | Diagnostic challenges and interventions

Repeat blood tests (Table 1) at a subsequent hospitalization showed persistent anemia, slightly decreased platelet counts, elevated HDL count, and elevated PT-INR and aPTT. It was found out later that above mentioned platelet count found earlier was due to automated cell counter as it was counting fragmented RBCs as platelets leading to falsely increased count of platelets. The actual platelet counts were in the range of 20,000–30,000/μL. On subsequent admissions D-dimer and FDP were found to be raised. Therefore, the triad of thrombocytopenia, raised PT-INR, elevated D-dimer, and FDP (factors depicting fibrinolysis) led to the diagnosis of DIC. Reports of routine LFTs (liver function tests) which revealed altered AST/ALT Ratio, A/G ratio, hypoalbuminemia, and hyperbilirubinemia (Table 1).

TABLE 1 Routine blood investigations during the admission period of the patient.

Parameters	8th July 2023	10th July 2023	12th July 2023	13th July 2023	14th July 2023	17th July 2023
Hb	4.9	6.9	6.9	7.2	6.9	5.9
RBC	1.86	2.54	2.53	2.73	2.57	2.16
Hematocrit	16	21.9	21.6	22.9	22	18.6
TLC	4.3	6.9	7.2	10	11.7	9.4
Plt.	1,04,000	90,000	1,21,000	−/−	−/−	−/−
PT	−/−	35.1	33.1	35.4	−/−	−/−
INR	−/−	3	2.81	3	−/−	−/−
ALT	−/−	41	74	−/−	−/−	−/−
AST	−/−	54	97	−/−	−/−	−/−
ALP	−/−	169	213	−/−	−/−	−/−
T. bilirubin	−/−	8.5	7.5	−/−	−/−	−/−
D. bilirubin	−/−	2.8	2.3	−/−	−/−	−/−
I. bilirubin	−/−	5.7	5.0.2	−/−	−/−	−/−
Albumin	−/−	2.1	2.1	−/−	−/−	−/−
Globulin	−/−	4.1	4.2	−/−	−/−	−/−
A/G ratio	−/−	0.51	0.5	−/−	−/−	−/−

Abbreviations: A/G ratio, albumin/globulin ratio; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; D. bilirubin, direct bilirubin; Hb, hemoglobin; I. bilirubin, indirect bilirubin; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cells; T. bilirubin, total bilirubin; TLC, total leukocyte counts.

A repeat USG revealed surface irregularities which suggested the progression of the stage to cirrhosis. In an attempt to uncover the underlying cause, investigations including alpha-fetoprotein (AFP) testing and occult blood tests were conducted to rule out hepatocellular carcinoma (HCC) and upper gastrointestinal (GI) bleeding, respectively. However, these tests were negative. Later, he was referred to a Gastroenterology hospital, where an upper GI endoscopy was then performed, revealing the presence of three large columns of esophageal varices, which were subsequently banded.

2.3 | Management and outcome

The Gastroenterologist suspected the diagnosis of Zieve's syndrome, given the characteristic association with chronic alcohol abuse and positive findings of hemolytic anemia and cholestatic jaundice. Management included conservative measures with insulin (actrapid and NPH), antibiotics, and carvedilol for esophageal varices. Despite these interventions, the patient and his family opted for discharge against medical advice (DAMA) and declined further management.

(Figure 1) It highlights the timeline of a complete comprehensive case scenario of the patient throughout the admission course.

3 | DISCUSSION

This case underscores the diagnostic challenges associated with Zieve's syndrome due to its rarity and overlapping clinical features with other conditions. Being a rare clinical occurrence, just 205 cases has been documented in medical literature since its first description. However, due to the prevalent and persistent excessive alcohol consumption, it's believed that the actual occurrence of this condition might be higher than reported. Some estimates suggest an incidence rate as notable as 1 in 1600 admissions.[5,6]

In this scenario, the patient's coexisting autoimmune disorder, hemolytic anemia, hepatobiliary dysfunction, chronic alcoholism, and esophageal varices collectively supported the diagnosis of Zieve's syndrome. Also, as in our case the stool occult blood testing were negative, another case report stated that medical professionals should maintain a strong clinical suspicion for Zieve syndrome when dealing with individuals who have a confirmed record of excessive alcohol consumption and exhibit symptoms like hemolytic normocytic anemia and hyperbilirubinemia and no evidence of upper GI bleeding.[7,8]

The presence of autoimmune DM (LADA) is an unusual finding associated with the case of Zieve's syndrome. This may be the first case reporting the co-occurrence of

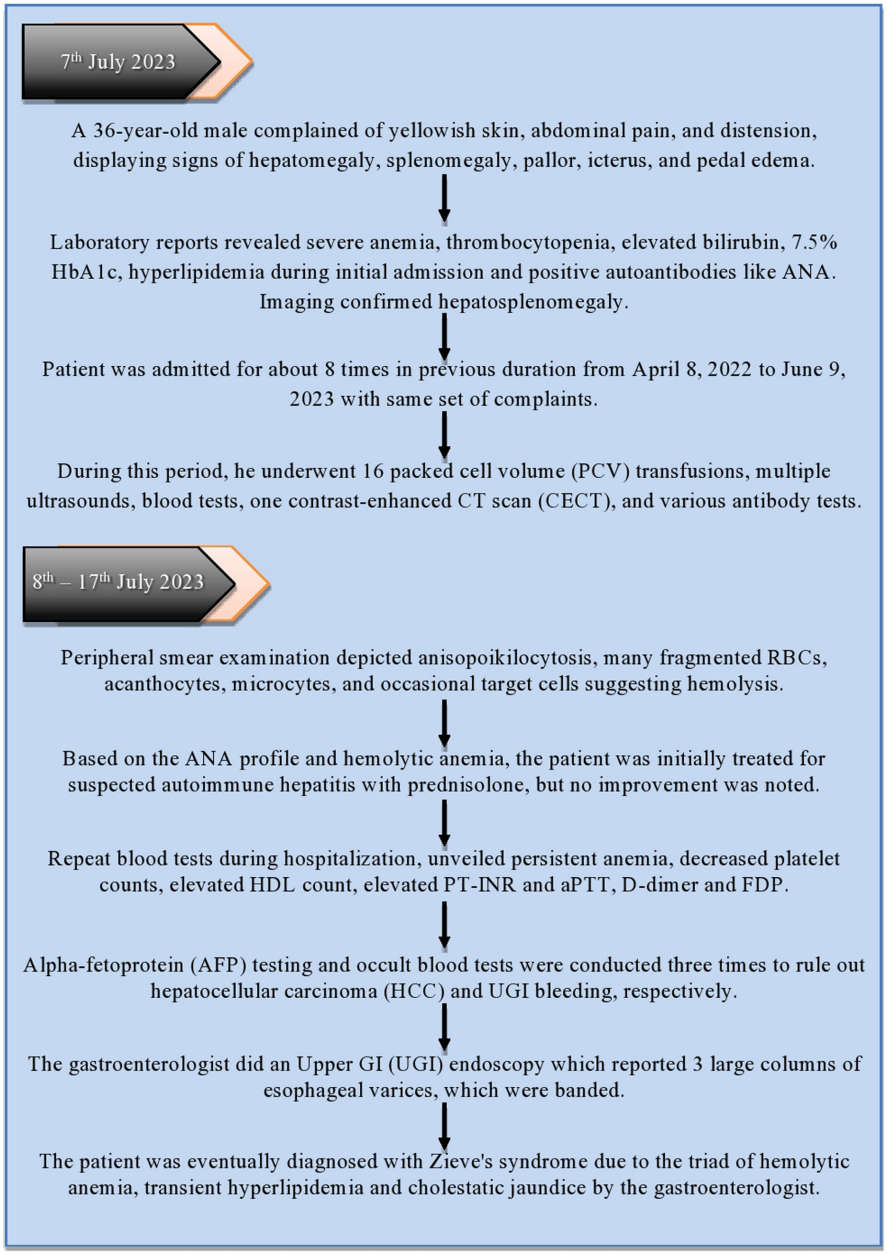

FIGURE 1 Timeline of the complete case scenario of the patient.

Zieve's syndrome and autoimmune DM (LADA). Since the patient has a strongly positive ANA profile and other associated autoantibodies (Jo-1, Ro-52, and AMA-M2) this could be the reason for the coexistence of LADA with Zieve's syndrome.[9]

The bone marrow of individuals within this particular patient group can suffer from the consequences of excessive drinking. This can lead to harmful effects on hematopoietic stem cells, suppressing their function and resulting in impaired generation of the three main types of blood cells—white blood cells, red blood cells, and platelets. Consequently, the levels of these crucial blood components are reduced.[7] This may support the findings of persistent anemia and thrombocytopenia in this case of Zieve's syndrome.

Hyperlipidaemia often goes unnoticed because of the variable levels that tend to normalize within 1–2 weeks after an acute episode.[3] A study stated that out of five patients whom they had studied, hyperlipidaemia subsided before the onset of haemolysis in two patients.[10] An unusual manifestation of Zieve's syndrome has also been observed where patients exhibit lipid levels within the normal range.[3] In our case raised HDL level was another uncommon finding in Zieve's syndrome. According to a study, patients of LADA showed lower triglycerides and higher HDL cholesterol level as compared to Type 2 Diabetes mellitus.[11] Lastly, DIC seen in this case can be attributed to the previous history of multiple blood transfusions done in the last 1 year.

Recognizing Zieve's syndrome promptly is crucial to prevent unwarranted and potentially detrimental

interventions.[5,12] With alcohol cessation being the cornerstone of Zieve's syndrome treatment, raising awareness among practitioners about its clinical features, and management becomes paramount. Early identification can spare patients from ineffective or potentially harmful therapies, focusing instead on the most effective approach—abstinence from alcohol.

We conclude that Zieve's syndrome, though rare, should be considered in individuals with chronic alcoholism, hemolytic anemia, and hepatobiliary dysfunction. This case highlights the importance of a comprehensive evaluation, serial investigations, and multidisciplinary collaboration to reach an accurate diagnosis and provide appropriate management. Further research is warranted to enhance understanding of this syndrome and optimize therapeutic strategies.

AUTHOR CONTRIBUTIONS

Rushit Zalavadiya: Conceptualization; data curation; writing – original draft. **Jugal Hiren Bhatt:** Conceptualization; data curation; writing – original draft. **Irfan Nagori:** Supervision; writing – review and editing. **Nency Kagathara:** Conceptualization; writing – original draft. **Srijana Neupane:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report and accompanying images in accordance with the journal's patient consent policy. A copy of written consent is available for review by the Editor-in-Chief of this journal on request.

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