

Transient Hepatocellular Injury Associated with Hypertriglyceridemia and Hemolysis in an Alcoholic Filipino Male

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Abstract

Background: Zieve's syndrome is an uncommon complication of chronic alcohol abuse, which presents with a constellation of symptoms, particularly hepatic dysfunction, hyperlipidemia and reversible hemolytic anemia.

Objective: This paper presents the first documented case of Zieve's syndrome in the Philippines.

Case History: We present a rare case of a 46-year-old Filipino male, who manifested with a two-week history of intermittent high grade fever, jaundice, crampy non-radiating epigastric pain, which were later accompanied by tea colored urine and acholic stools. The patient subsequently presented with sudden anemia on his third hospital day with no signs of bleeding or blood loss. Physical examination revealed diffuse jaundice and hepatomegaly with mild epigastric and right upper quadrant tenderness.

Laboratory findings showed significant elevation of liver transaminases, bilirubins and triglycerides. Complete blood count (CBC) revealed a drop of hemoglobin from 134 mg/dl to 64 mg/dl. Coomb's test was negative. Repeat aspartate transaminase (AST) and alanine transaminase (ALT) was decreased.

Conclusion: The patient was diagnosed with Zieve's syndrome and was given supportive management including adequate hydration and nutritional supplementation with abstinence from alcohol. Improvement in general status with a gradual resolution of jaundice and anemia were observed. Without further intervention, the patient was discharged improved after five days. Out patient follow-up noted further reduction of liver enzymes and triglycerides, and normalization of hemoglobin.

Zieve's syndrome is an uncommon condition characterized by hemolytic anemia in conjunction with secondary hyperlipidemia in patients suffering from alcohol-related toxic liver damage. This condition must be considered in the differential diagnosis of liver injury with uncertain origin, hemolysis or hemorrhage to prevent unnecessary workups and invasive interventions. Vigilance and high clinical suspicion is important in the diagnosis of the syndrome.

Keywords: Zieve's syndrome, hepatocellular injury, hypertriglyceridemia, hemolysis, hepatic dysfunction, alcoholism

Introduction

While alcohol use and its related liver damage are widely documented, Zieve's syndrome is a less recognized complication of chronic alcoholism. This syndrome presents with jaundice, hemolysis and hyperlipidemia in the setting of a chronically alcoholic individual. Following a thorough literature review, this is the first reported case of Zieve's syndrome in the country.

The syndrome was first described in 1958 by Leslie Zieve as a combination of jaundice, hyperlipidemia and hemolytic anemia in alcoholic patients. These manifestations were described in his initial case series,

documenting acute hemolytic anemia associated with alcohol abuse¹ and is a rarely recognized clinical phenomenon with roughly 200 reported cases to date.² The most recent were documented by Shukla³ and Nath⁴ in their respective case reports in 2015.

This syndrome can occur in a patient with or without pre-existent alcohol liver damage.⁵ It is often difficult to identify patients with alcoholic liver damage because of their denial of the degree of how much they drink. If the diagnosis is suspected, liver function and hematologic tests should be done to detect signs of liver injury and anemia. A complete medical history of the patient must be confirmed by family members. The CAGE questionnaire, which has been extensively validated for use in identifying alcoholism⁶, can then be used to screen patients for alcohol abuse.^{7,8} The diagnosis requires the exclusion of viral, autoimmune hepatitis and cholelithiasis.

The precise pathophysiologic mechanism for Zieve's syndrome is still unknown, but several theories have been postulated to explain the different clinical manifestations

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of this disorder. Hemolysis in Zieve's syndrome is due to alcohol-induced vitamin E deficiency, which reduces polyunsaturated fatty acid levels and causes exudation of erythrocyte glutathione, leading to enzyme instability and erythrocyte hemolysis. Abnormalities in fatty acid oxidation cause changes in cell membrane composition, which leads to injury of both erythrocytes and hepatocytes. In some patients with Zieve's syndrome, severe hypophosphatemia can reduce adenosine-5-triphosphate levels, affect erythrocyte membrane rigidity, fragmentation, reduce erythrocyte surface area and spheroidicity.⁹

This case report highlights the first reported case in the Philippines and the need of the clinician to be vigilant to the diagnosis of Zieve's syndrome and appreciate the variability in its presentation.

Case Presentation

Our case is a 46-year-old Filipino male with a significant history of alcohol abuse, averaging seven bottles of beer a day for 20 years, who was admitted because of a two-week history of intermittent high grade fever, jaundice, and crampy, non-radiating epigastric pain, which were later accompanied by tea colored urine and acholic stools. The patient denies smoking and illicit drug use.

Physical examination revealed diffuse jaundice. Abdominal examination revealed an enlarged liver (16 cm length) with mild epigastric and right upper quadrant tenderness. No splenomegaly nor ascites was noted. There was no asterixis and the patient had no abnormal neurologic signs.

Laboratory workup showed a normal complete blood count (CBC) and significant elevation of liver enzymes. The initial AST was 2,064 U/L and ALT was 3,462.2 U/L. Bilirubin levels were also elevated (Total bilirubin 1,269.92 $\mu\text{mol/L}$; indirect bilirubin 356.27 $\mu\text{mol/L}$; and direct bilirubin 913.65 $\mu\text{mol/L}$). At these levels, differentiation between unconjugated and conjugated bilirubins is unreliable. Lipid profile showed elevated triglycerides at 7.45 mmol/L (N 0.4-2.15). Ultrasound of the abdomen revealed hepatomegaly, reactive cholecystitis and non-dilated biliary tree.

Acute Viral Hepatitis was initially considered due to a reactive Anti-HAV IgM. However, a repeat CBC revealed a sudden fall in hemoglobin from 134g/L to 64 g/L with no evident signs of hemorrhage.

At this time, Zieve's syndrome was considered and the patient was referred to a hematologist and gastroenterologist. Leukocytosis at $34.5 \times 10^9/\text{L}$ is not compatible with a typical hepatitis A and thrombocytosis at $833 \times 10^9/\text{L}$ is considered reactive. Mean Corpuscular Volume (MCV) was at 10°FL , compatible with a hemolytic cause. Serial CBC results are shown in Table I. Coomb's test was unremarkable. Repeat AST and ALT were done showing gradual decrease at 203.9 U/L and 776.8 U/L respectively. The patient received a transfusion of 1.0 unit of packed red blood cells. The succeeding hospital days were unremarkable and patient was discharged improved after five days.

The patient was closely followed at the out patient department and was noted to have resolution of jaundice and anemia after the second and third week post discharge, respectively.

Table I: Summary of CBC results

CBC	five days prior to admission	three days prior to admission	third hospital day	third hospital day	4th hospital day
Hemoglobin (g/L)	137	134	64	60	87
Hematocrit (L)	42	40	20	19	25
White Blood Cells ($\times 10^9/\text{L}$)	6.1	6.8	34.5	30	13.7
Segmenters	60	47	78	76	75
Stabs	5	6	4	5	7
Lymphocytes	32	46	13	15	13
Monocytes	1	1	4	4	4
Eosinophils	1	-	1	-	1
Basophils	1	-	-	-	-
Platelet Count ($\times 10^9/\text{L}$)	224	234	833	754	729
Indices					
Mean corpuscular volume (FL)	102	98	109	110	103
Mean corpuscular hemoglobin (P)	33	33	33.9	34.8	34.4
Mean corpuscular hemoglobin concentration (g/dL)	32.6	33.6	31.2	31.6	33.4
Red cell distribution width (%)	11.3	13	13	12.7	13.2
		With atypical lymphocytes	22 nucleated RBC/100 WBC	22 nucleated RBC/100 WBC	13 nucleated RBC/100 WBC

Discussion

Alcohol abuse is defined as chronic consumption of more than 80 grams of alcohol per day, which is approximately 250mL of hard liquor, more than 500mL fortified wine, one bottle (750mL) of table wine, or 1.5 liters of beer which is equal to four 12-ounce cans or bottles.¹⁰ The World Health Organization (WHO) in its Guide to Mental Health in Primary Care¹¹ defines a hazardous level of alcohol consumption to be seven or more units per day or over 50 units per week for men (one unit is defined as the equivalent of 8.0g of ethanol), and over five units per day and over 35 units per week for women. The reason for this is due to the difference in the ability to metabolize alcohol between men and women. Hence, consuming even the same amounts of alcohol may lead to quite different outcomes in women than in men.¹²⁻¹⁴ The WHO estimated that alcohol affects approximately 140 million people worldwide. Patients are frequently admitted to the hospital for reasons unrelated to alcoholism.

Alcohol has direct toxic effects on hematopoietic cells, causing an abnormality in membrane phospholipid and interferes with folic acid utilization. The pathogenesis of alcohol ingestion associated liver disorder is incompletely understood. Patients who chronically abuse alcohol develop liver disease primarily because the majority of the ingested ethanol is metabolized in the liver and causes hepatic injury to occur.¹⁵

In the local setting, results of a survey conducted by Department of Health (DOH) and the University of The Philippines in 2001 shows that the prevalence of regular alcohol intake among Filipinos was 11.1 percent (13% among males and 5.9% among females). The survey also revealed that 38.9% of Filipinos are occasional alcohol drinkers and 4.8% are heavy drinkers (6.6% among males and 1.3 percent among females).¹⁶ Likewise, the prevalence of alcohol use among Filipino youth is 39% with males (66.5%) twice more likely than females (33.5%) to drink alcohol. Seven out of ten youth drinkers are light drinkers (70%), almost three out of ten are moderate drinkers, and only four percent are heavy drinkers.¹⁷ Among the usual alcoholic drinks consumed are beer (78.5%), liquor-rum, gin, whisky, lambanog (coconut wine) (70.6%), wine, tuba (sugar cane wine), sangria and sherry (42.4%).¹⁸

Zieve's syndrome is rarely recognized. Based on a review of literature, there are 200 cases reported up to the present.² To date, there are no published reports of this condition in the Philippines. It usually affects males, since males more frequently abuse alcohol. The patient consumed up to seven bottles of beer a day for the past 20 years. The probable reason for the relatively small number of reported cases of Zieve's syndrome could be the lack of pathognomonic symptoms, rapid reduction of hyperlipidemic serum

levels, alcohol withdrawal and patient's denial of drinking.

Zieve's syndrome usually presents with jaundice, hemolysis and hyperlipidemia, specifically hypertriglyceridemia in the setting of a chronically alcoholic individual.¹ The patient had a significant history of alcohol abuse, presented with jaundice, elevated triglycerides and during confinement, developed sudden anemia without any signs of apparent bleeding, consistent with the diagnosis of Zieve's syndrome. This clinical presentation with negative findings for an obstructive type of jaundice on ultrasound, a negative autoimmune workup (Coomb's Test) and rapid improvement of liver enzymes (which can not be explained by acute viral hepatitis), further strengthens the diagnosis of Zieve's syndrome.

The occurrence of sudden anemia in a patient with alcoholic liver damage and hyperlipidemia is incompletely understood. Kitagawa et al., speculated that the possible cause could result from the incorporation of lysolecithin, a lysophosphatic acid into red cell membranes, which decreases its effectiveness as a barrier to glucose, resulting in more osmotically fragile membranes.¹⁹ This correlates with hemolytic activity and cell membrane instability.

In Zieve's case-series, he studied 20 male patients with an average age of 39 years and alcohol use in all cases. Laboratory examinations among these subjects were consistent with acute hemolytic anemia as well as hyperlipidemia. Of the 20 patients, 16 underwent hepatic biopsy with 14 (88%) demonstrating fatty infiltration and 15 (94%) revealing portal hypertension. Hepatic biopsy, however, was not considered in our patient because of the patient's rapid improvement. Upon follow up, Zieve noted resolution of jaundice in approximately three weeks from presentation, anemia in five weeks and hypercholesterolemia in six weeks. This pattern was also observed in our case, with rapid resolution of symptoms and normalization of laboratory parameters after three weeks at an out-patient follow up visit.

There is no specific diagnostic test for the diagnosis of this condition. A good history and physical examination is key. It also has no specific treatment. Alcohol abstinence is essential. Since many of these patients have a long history of heavy alcohol abuse, prevention and treatment of alcohol withdrawal is also important.

Other supportive measures include ensuring appropriate hydration and nutritional support. Poor oral intake may result in dehydration requiring adequate fluid resuscitation. However, overhydration should be avoided, particularly in patients with stigmata of chronic liver disease suggestive of liver cirrhosis, since it may increase the degree of ascites if present, lower plasma sodium concentration and occasionally precipitate

gastrointestinal hemorrhage.²⁰

The patient received mainly supportive treatment with hydration and nutritional support. The patient was advised to abstain from alcohol with close outpatient follow up after the discharge.

Conclusion

The case presented was that of a 46-year-old Filipino male who manifested with jaundice, fever, epigastric pain, tea-colored urine and acholic stools with an enlarged liver in physical examination. His work-up showed markedly elevated transaminases, elevated triglycerides and evidence of hemolysis. With these findings in the background of chronic alcoholism, Zieve's syndrome was established. The patient's treatment was mainly to ensure adequate hydration and nutritional support with abstinence from alcohol. He was discharged improved with further resolution of symptoms upon outpatient follow-up.

Recommendations

The clinical manifestations of the syndrome have no pathognomonic signs or symptoms therefore, vigilance and high clinical suspicion is necessary. Delay in the recognition of Zieve's syndrome significantly delays the diagnosis of the disease. Zieve's syndrome must always be included in the differential diagnosis of uncertain origin liver injury, hemolysis, or coagulopathy, especially in a patient with strong alcoholic history.

References

1. Zieve L. Jaundice, hyperlipemia, and hemolytic anemia: a heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. *Ann Intern Med*, 1958; 48: 471-496
2. Piccini J, Satarsi H, Jefferson B. Cases from the Osler Medical Service at John Hopkins University. Zieve Syndrome. *Am J Med*, 2003 Dec 15; 115(9):729-31
3. Shukla S. Hemolysis in Acute Alcoholic Hepatitis: Zieve Syndrome. *ACG Case Rep J* 2015; 2(4):250-251
4. Nath S, Peck JR. (2015). Hemolytic anemia in alcohol-induced liver disease: a Case Report on Zieve's Syndrome. *Int J Blood Res Disord* 2015, 2:01
5. Weiler G. Morphological findings in Zieve's syndrome. *Z Rechtsmed*. 1975;76(4):335-41
6. Kitchens JM (1994). Does this patient have an alcohol problem?" *JAMA* 272(22): 1782-7. Doi:10.1001/jama.272.22.1782. PMID 7966928
7. Goebel KM, Goebel FD, Schbotz R, Schneider J. Hemolytic implications of alcoholism in liver disease. *J Lab Clin Med*. 1979; 94:123-32.
8. Kessel L. Acute transient hyperlipemia due to hepatopancreatic damage in chronic alcoholics (Zieve's syndrome). *Am J Med*. 1962; 32; 747-57
9. Girard DE, Kumar KL, McAfee JH. Hematologic effects of acute and chronic alcohol abuse. *Hematol Oncol Clin North Am* 1987;1:321-34
10. Savage D, Lindenbaum J. Anemia in alcoholics. *Medicine (Baltimore)* 1986;65:322.
11. Andrews G, Jenkins R. (eds) (1999). *Management of Mental Disorders (UK Edition)*. London: World Health Organization Collaborating Centre for Mental Health and Substance Abuse; Goldberg, D. et al. (2000).
12. Camargo CA. (1999). Gender differences in the health effects of moderate alcohol consumption.
13. Peele S, Grant M (Eds.) *Alcohol and Pleasure: A Health Perspective*, pp. 157-170. Philadelphia: Brunner/Mazel; Mumenthaler, M. et al. (1999). Gender differences in moderate drinking effects. *Alcohol Research and Health*, 23(1), 55-64
14. Thadhani R, et al. (2002). Perspective study of moderate alcohol consumption and risk of hypertension in young women. *Archives of Internal Medicine*, 162(5), 569-574
15. Lieber CS. Metabolism and metabolic effects of alcohol. *Semin Hematol* 1980; 17:85.
16. Tiglaio TV, Baltazar JC, Baquilod MM. Baseline behavioral risk factor survey Philippines. Department of Health, Manila 2001. In: WHO Global NCD Info Base. Geneva, World Health Organization.
17. Baquilod MM. Health behaviors and practices of Filipino youth on alcohol substance abuse. Department of Health 2001.
18. Victa Labajo M. The Filipino as the quintessential drinker: a study of alcohol drinking patterns among Filipinos. Retrieved from http://www.ihra.net/files/2010/05/02/Presentation_23rd_M10_Labajo.pdf
19. Kitagawa T, Inoue K, Nojima S. Properties of liposomal membranes containing lysolecithin. *Journal of Biochemistry* 1976; Vol 79, No.6: 1123-1133
20. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; 368:1