ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Takotsubo Cardiomyopathy Causing Induced Acute Liver Failure

Kevin B. Harris, MD[1], Mohannad Abou Saleh, MD[2], Carol Rouphael, MD[2], C. Roberto Simons-Linares, MD, MSc[2], and Christina C. Lindenmeyer, MD[2]

[1]*Department of Internal Medicine, Cleveland Clinic, Cleveland, OH*
[2]*Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, Cleveland, OH*

ABSTRACT

Hypoxic hepatitis is a common cause of abnormal liver biochemistries in hospitalized patients. It is important clinicians maintain a high index of suspicion for diagnosis so that appropriate supportive therapies may be implemented in a timely manner. We present a rare case of takotsubo cardiomyopathy-induced hypoxic hepatitis and resultant acute liver failure in a patient after an intentional drug overdose. Once competing etiologies of acute liver failure were excluded and the diagnosis of hypoxic hepatitis was established, therapy was focused on the patient's cardiomyopathy in an effort to simultaneously improve her liver function.

INTRODUCTION

The differential diagnosis for acute liver failure (ALF) includes autoimmune, infectious, metabolic, drug-induced, and ischemic etiologies. Clinical history and analysis of the pattern of liver biochemical abnormalities are crucial for discerning the underlying cause of ALF. Hypoxic hepatitis or "shock liver" is characterized by substantial elevations of aminotransferases (classically $>$ 1,000 U/L) because of decreased oxygenation of hepatocytes.[1] The most common causes include cardiac/circulatory failure, toxic shock states, and respiratory failure.[1] The 3 diagnostic criteria for hypoxic hepatitis are (i) a clinical setting of cardiac, respiratory, or circulatory failure; (ii) a significant increase in serum aminotransferases; and (iii) exclusion of other causes of hepatocyte necrosis.[1]

CASE REPORT

A 51-year-old woman with no significant medical history presented to the emergency department after an intentional drug overdose. She had an argument with her husband and subsequently ingested unknown amounts of tizanidine, hydrocodone, prednisone, enalapril, and the sleeping aide Alteril (a combination pill containing tryptophan, melatonin, glycine, valerian root, and gamma-aminobutyric acid). A few minutes after ingestion, she contacted emergency medical services and was transported to a large quaternary care center emergency department. On presentation approximately 1 hour after ingestion, she was minimally responsive with a Glasgow Coma Scale of 12 and subsequently experienced a generalized tonic-clonic seizure. Postictally, she was lethargic with fixed, dilated pupils, and her left pupil was slightly larger than her right. A computed tomography of the brain was negative for any acute intracranial process. Initial laboratory test results revealed normal liver biochemistries and renal function. Acetaminophen, salicylate, and ethanol levels were undetectable. The following morning, she developed a wide complex ventricular tachycardia with associated hypotension and a second seizure. She was intubated and initiated on pharmacologic hemodynamic support. Repeat liver biochemistries on day 2 were notable for alanine aminotransferase of 3,116 U/L, aspartate aminotransferase of 2,710 U/L, alkaline phosphatase of 48 U/L, total bilirubin of 3.7 mg/dL, and international normalized ratio of 2.0. Owing to the concern for ALF related to her intentional drug overdose, she was administered intravenous N-acetylcysteine and vitamin K. The patient's family denied any history of drug or alcohol abuse. Her urine toxicology screen was positive for phencyclidine (PCP). Human immunodeficiency virus, hepatitis, and autoimmune serologies were negative. Her liver ultrasound revealed normal liver parenchyma, patent vasculature, and no cholelithiasis or biliary ductal dilation. Her creatinine kinase was found to be elevated at 1,562 U/L, consistent with rhabdomyolysis. Her liver function continued to decline, and she developed acute tubular necrosis, acidosis, and oliguria requiring initiation of continuous renal replacement therapy. Clinical prognosticative scoring systems for

ACG Case Rep J 2020;7:e00413. doi:10.14309/crj.0000000000000413. Published online: June 24, 2020

Correspondence: Christina C. Lindenmeyer, MD (lindenc@ccf.org).

ALF predicted a poor transplant-free survival rate. She underwent an expedited evaluation for liver transplantation, initiated on hospital day 2. An echocardiogram revealed a severely decreased ejection fraction of 19% with severe wall motion abnormalities. The midanterior and distal anterior septum, entire apex, midinferior and distal inferior wall, and midinferoseptal segment were akinetic. Given her clinical history, these findings suggested a catecholamine-induced cardiomyopathy such as takotsubo.

Accordingly, the patient's ALF was attributed to hypoxic hepatitis in the setting of cardiogenic shock. The liver transplant evaluation was suspended, pending observation of her clinical trajectory. She was treated with isosorbide dinitrate and hydralazine for afterload reduction. Her lactate, liver biochemistries, and mental status improved. On day 4 of hospitalization, she was weaned off vasopressors and extubated. A repeat echocardiogram performed on hospital day 13 showed a normal ejection fraction of 68% with no wall motion abnormalities. Her liver biochemistries normalized, and 16 days after initial presentation, she was discharged in stable condition to an inpatient psychiatric facility. Her last day of dialysis was 6 days after discharge, and her creatinine normalized within 1 month of discharge.

DISCUSSION

We present a rare case of ALF associated with stress-induced cardiomyopathy after an intentional drug overdose. Factors believed to contribute to the patient's ALF include polysubstance overdose and hypoxic/congestive hepatitis in the setting of acute heart failure and cardiogenic shock. Of note, the patient's urine toxicology screen was positive for PCP. As described in the literature, PCP-induced ALF is typically accompanied by seizures, followed by hyperthermia and acute renal failure.[2] It has been proposed that PCP toxicity-related seizures may lead to malignant hyperthermia and resultant hepatic necrosis, detected by markedly elevated aminotransferases within 24 to 48 hours of ingestion.[2,3] This patient's clinical course including seizures, creatinine kinase elevation, and trajectory of her liver biochemistries could be consistent with PCP-induced ALF. However, there was no observed hyperthermia with a maximum documented temperature of 99.4°F. In addition, the patient denied any history of illicit drug abuse. Interestingly, tizanidine has been reported to cause false positive toxicology results for PCP on urine assays.[4] A definitive diagnosis of PCP-induced hepatocyte necrosis is established via liver biopsy, with compatible histopathology including severe centrilobular necrosis with mild inflammation.[5] In this case, liver biopsy was not pursued in the setting of hemodynamic instability, coagulopathy, and relatively rapid clinical improvement. Given the patient's mixed clinical presentation, it is likely that other clinical factors contributed to her ALF.

In addition to polysubstance overdose, the patient was found to have an acute stress-induced cardiomyopathy, likely related to a combination of drug toxicity and recent emotional stressors. In keeping with this observation, the patient's aminotransferases peaked after an episode of wide complex tachycardia and hypotension. Our patient's psychosocial history, troponinemia, and findings on echocardiography are consistent with the typical presentation of takotsubo cardiomyopathy.[6] We suspect that the patient's stress-induced cardiomyopathy resulted in cardiogenic shock and hypoxic hepatitis. The rapid downtrend in her aminotransferases in parallel with the improvement in her cardiac function is also consistent with recovering hypoxic hepatitis in the setting of cardiogenic shock.[1]

Combining a thorough clinical history with the pattern and trajectory of liver biochemistries is crucial for developing a differential diagnosis in patients with ALF. This report highlights a classic presentation of ALF precipitated by cardiogenic shock and hypoxic hepatitis. Hypoxic hepatitis is characterized by a marked increase in aminotransferases because of decreased oxygenation of hepatocytes and resultant hepatocyte necrosis. Early diagnosis of hypoxic hepatitis may prevent unnecessary testing and facilitates directed therapy aimed at improving the hypoxic state driving liver injury. Liver transplantation is not indicated for ALF related to "shock liver."

DISCLOSURES

Author contributions: KB Harris wrote the manuscript. M. Abou Saleh, C. Rouphael, CR Simons-Linares, and CC Lindenmeyer edited the manuscript. CC Lindenmeyer is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received February 5, 2020; Accepted May 8, 2020

REFERENCES

1. Waseem N, Chen PH. Hypoxic hepatitis: A review and clinical update. *J Clin Translational Hepatol* 2016;4:263–8.
2. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2012. Phencyclidine. [Updated 2016 Apr 11].
3. Armen R, Kanel G, Reynolds T. Phencyclidine-induced malignant hyperthermia causing submassive liver necrosis. *Am J Med* 1984;77:167–72.
4. 8 common false positives on instant drug tests. Keystone Lab Website (http://drugtestsample.com/wp-content/uploads/2016/12/Cross-ReactivityGuide.pdf). Accessed December 17, 2019.
5. Riordan S, Williams R. Liver disease due to illicit substance use. *Addict Biol* 1998;3:47–53.
6. Dawson DK. Acute stress induced (takotsubo) cardiomyopathy. *Heart* 2018;104:96–102.