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CASE REPORT | LIVER

Drug-Induced Autoimmune Hepatitis From Hydralazine Leading to Acute Liver Failure and Liver Transplantation

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ABSTRACT

We describe a woman with no previous liver disease who developed drug-induced autoimmune hepatitis from hydralazine prescribed to her for hypertension. Despite the discontinuation of the medication, she developed acute liver failure and subsequently underwent successful liver transplantation. She survived and had a good clinical outcome.

INTRODUCTION

Drug-induced liver injury (DILI) is a significant cause of morbidity and mortality, accounting for at least 13% of acute liver failure cases in the United States.[1] It is the leading cause of acute liver failure among patients referred for liver transplantation and the most common reason that drugs in development do not obtain the Food and Drug Administration approval. The incidence of DILI has been reported to be 1:10,000 to 1:100,000 patients; however, the actual incidence is probably higher in part because of the difficulty in diagnosis.[2] Liver damage can range from benign elevations in the liver enzymes that resolve after the discontinuation of the offending agent, all the way to liver failure and even death. This case highlights a rare but important cause of drug-induced autoimmune liver injury, ultimately leading to acute liver failure and requiring liver transplantation.

CASE REPORT

A 51-year-old woman with a history of hypertension, diabetes, coronary artery disease requiring stent placement, and cerebrovascular accident with left-sided residual weakness presented to the hospital for 2 months of generalized fatigue, malaise, poor appetite, nausea, and worsening altered mental status. In the last 2 weeks, her symptoms had progressively worsened and were subsequently brought into the hospital by her family.

The patient had no known drug allergies. Three months before admission, the patient was started on hydralazine 10 mg per oral (PO), 3 times per day because of difficulty in controlling high blood pressure. She had no other new medications but was also taking the following at home: amlodipine 10 mg PO daily, carvedilol 6.25 mg PO 2 times per day, lisinopril 5 mg PO daily, and aspirin 325 mg PO daily. Owing to the patient's altered mental status, a thorough social history was obtained from the family. They reported that the patient did not engage in any high-risk behaviors that would put her at risk for viral hepatitis, alcoholic hepatitis, or nonprescription DILI.

Vitals signs were within the normal range, and physical examination findings were consistent with scleral icterus, dry mucous membranes, and no rashes on the skin including the face. Her chest was without spider angiomas, abdomen with no hepatosplenomegaly, no shifting dullness, no surgical scar, normoactive bowel sounds, extremities without palmar erythema, and no pitting edema. The neurological examination noted that the patient opens her eyes to noxious stimuli (sternal rub) but otherwise does not respond to verbal commands. Asterixis were present; Table 1 lists all pertinent laboratory findings.

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Table 1. Laboratory studies

Basic metabolic panel:	Viral hepatitis:	Autoimmune and metabolic workup:
Na: 132, K: 4.1, Cl: 102, CO2: 24, BUN: 23, Cr: 1.3	Hepatitis A total Ab: detected	ANA: 1:320
Liver Chemistries:	Hepatitis A IgM: Nondetectable	ASMA: 1:40
TB: 18.9, AST: 576, ALT: 374, albumin 4.2, total protein: 7.8, alkaline phosphatase: 187, gamma-glutamyl transferase (GGT): 278	HBsAg: Nonreactive	IgG serum levels: 1,290
CBC:	HBcAb: Nonreactive	AMA: < 1:20
WBC: 8.7, H/H: 13.7/38, PLT: 75	HCVAb: Nonreactive	Anti-LKM: Nondetectable
INR: 3.3	Hepatitis E IgG and IgM: Nondetectable	A1AT: Normal
Urine drug screen: All negative	HIV: Nonreactive	Ceruloplasmin, ferritin, iron, and TIBC: Within normal limits
	CMV, HSV, HBV, HCV, and HIV PCR: Nondetectable	

A1AT, alpha-one antitrypsin; Ab, antibody; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibodies; Anti-LKM, anti-liver-kidney microsomal antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cl, chloride; CO2, carbon dioxide; Cr, creatinine; H/H, hemoglobin/hematocrit; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCVabva, hepatitis C antibody; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; K, potassium; Na, sodium; PCR, polymerase chain reaction; PLT, platelets; TB, total bilirubin; TIBC, total iron binding capacity; WBC, white blood cell.

With no previous history of chronic liver disease, international normalized ratio above 1.5, and worsening altered mental status, the patient was deemed to be in acute liver failure meeting King's College criteria for nonacetaminophen-induced acute liver failure.[3] After extensive negative workup, the etiology was determined to be secondary to DILI in an autoimmune fashion, likely because of hydralazine. The remainder of the patient's medications were reviewed on the National Institute of Health LiverTox website showing no association with drug-induced autoimmune hepatitis (DI-AIH), in particular, carvedilol and lisinopril.[4] The patient required a liver transplantation and explant pathology confirmed the diagnosis (Figure 1). A liver biopsy was not obtained before transplantation because of the patient's continued coagulopathy and high risk of bleeding. Furthermore, the patient had no contraindications to liver transplantation. Therefore, a liver biopsy would not have changed the management. Post-transplant, the patient recovered well and was discharged home after 10 days of postoperative hospitalization. The patient presented to the liver transplant clinic at a follow-up and was back to functional baseline having normal graft function without evidence of graft rejection in the first-year post-transplant.

The gross examination of the 833 g total hepatectomy specimen, and the attached gallbladder showed a smooth pink liver capsule with cut sections, demonstrating a tan-brown homogeneous surface with focal hemorrhage. No masses, lesions, or dominant nodules were identified within the liver parenchyma, grossly. The hepatic and portal veins were patent without evidence of thrombi. The gallbladder was unremarkable. Histologic sections of the liver demonstrated diffuse hepatocyte necrosis and interface hepatitis, consistent with fulminant autoimmune hepatitis.

DISCUSSION

Hydralazine is a commonly used antihypertensive drug which acts by direct relaxation of arteriolar smooth muscle, probably by alteration in intracellular calcium signaling.[1] The mechanism for liver injury is thought to be because of its metabolism to an immunologic adduct that can result in immunoallergic hepatitis or delayed lupus-like and/or autoimmune hepatitis-like syndrome.[1] Hydralazine, similar to isoniazid, is metabolized by N-acetyltransferase, and hepatic injury may be more frequent with specific genetic variants in N-acetyltransferase activity.[1] Liver injury secondary to hydralazine can range from a mild immunologic reaction that self-resolves after discontinuation of the drug to liver failure requiring liver transplantation.

This case highlights the findings in DI-AIH and persistence of liver failure requiring transplantation despite discontinuation of the offending agent. We noted antinuclear antibodies and anti-smooth muscle positivity on serology suggestive of AIH, which were negative in the past in our patient. Workup, including urine and blood drug screens, resulted negative. Liver biopsy described scarce plasma cells and interphase hepatitis further supporting the diagnosis of AIH. The temporal relationship of hydralazine use, the absence of a previous history of liver disease, and compatible histology are highly suggestive of hydralazine as the culprit cause. Furthermore, the liver biopsy did not show any evidence of steatosis or steatohepatitis. Our patient met several

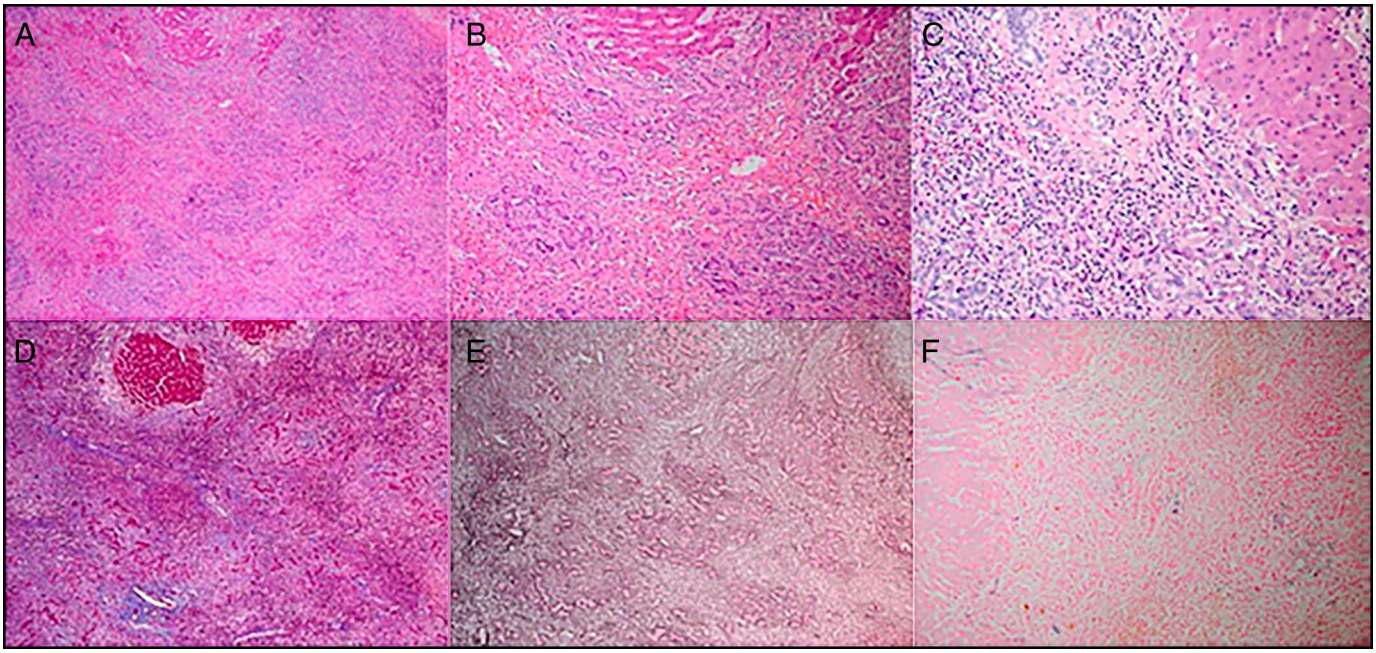

Figure 1. Histologic hematoxylin and eosin stained sections of explant pathology at (A) magnification 4×, (B) magnification 10×, and (C) magnification 20×, showing diffuse panlobular hepatocyte necrosis and focal areas of centrilobular zone III necrosis and small areas of intact tissue. There was extensive hepatocellular dropout with stromal collapse and replacement by mixed inflammatory cell infiltrates composed predominantly of lymphocytes and ductular reaction. Minimal hepatocellular cholestasis was seen. The native bile ducts appeared unremarkable. (D) Trichrome and (E) reticulin stain showing similar findings with no fibrosis (magnification 10×). An iron stain shows (F) focal hemosiderin deposition within viable hepatocytes (magnification 10×).

diagnostic criteria for AIH as established in the AASLD guidelines for AIH, with previously described compatible liver histology, positive AIH serum biomarkers, immunochemistries, and autoantibodies, along with negative viral markers and other potential etiological factors for her fulminant hepatitis. Her pretreatment aggregate score for AIH was > 15, which correlated with a "definitive diagnosis."[5] Physical examination findings included the absence of spider angiomas, palmar erythema, and ascites; therefore, there was no suggestion of chronic liver disease on history and physical examination to indicate previous nonalcoholic steatohepatitis of episodes or multiple episodes of AIH flares. A computed tomography scan of the abdomen also did not show any findings suggestive of sequela of portal hypertension such as splenomegaly or formation of collaterals. This was a new insult to the liver causing acute liver failure with very low likelihood of acute on chronic liver injury.

Autoimmune hepatitis and DI-AIH can mimic each other serologically, and on liver biopsy, a high clinical suspicion must be present.[6] On pathology, both idiopathic AIH and DI-AIH cases will have interface hepatitis, focal necrosis, and portal inflammation, but these findings tend to be more severe in idiopathic AIH rather than DI-AIH. Our patient had some hepatocellular cholestasis which can help distinguish idiopathic AIH from DI-AIH. However, we did not see portal neutrophils which tend to be more prevalent in DI-AIH.[7] In our case, the temporal relationship with hydralazine administration, lack of evidence for chronic liver disease, and negative AIH serologies in the past were key in diagnosing DI-AIH. Our patient was instructed not to receive hydralazine in the future as the liver damage can recur. Hydralazine has been implicated in DI-AIH in the past with a similar pattern of DI-AIH liver injury.[8–10] The previously reported case studies suggest that a lupus-like syndrome can be present at times.[10] Our patient did not have any rashes to suggest a lupus-like syndrome.

In conclusion, DI-AIH is a rare but serious event that can often be difficult to diagnose.[1,2,11] A high degree of clinical suspicion is required for the diagnosis of DI-AIH. This diagnosis should be suspected in patients who develop liver injury and an immunoallergic reaction while taking a drug implicated in this type of liver injury. Complete recovery of liver injury is most often seen with DI-AIH; however, cases of prolonged injury may occur, requiring treatment with immunosuppressive therapy, and cases such as ours requiring liver transplantation have been described. This type of liver injury should be documented in the medical record to avoid rechallenge with the drug in the future.

DISCLOSURES

Author contributions: J. Grewal analyzed and interpreted the data and drafted and revised the manuscript. A. Doan and AS Hong wrote and revised the manuscript. A. Amin acquired the data and wrote and revised the manuscript. JV Scapa acquired the data. R. Hanna wrote the manuscript. F. Durazo analyzed the data and revised the manuscript. B. Yanny acquired the data, wrote and revised the manuscript, and is the article guarantor.

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