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Drug Induced Liver Injury due to Hydralazine: A Case Report and Review of Literature

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Abstract Drug Induced Liver Injury (DILI)accounts for around 11% of all Acute Liver Failure (ALF)cases and are usually associated with over the counter supplements [1]. Hepatotoxicity due to Hydralazine is not commonly reported [2]. Often times DILI may have variable presentations and latency times, making diagnosis difficult. Here we present a 70-year-oldfemale with multiple medical problems who presented to the hospital with jaundice and abdominal pain and concluded to have hydralazine induced liver injury.

Keywords: *DILI, hydralazine, liver failure, transaminitis, liver injury*

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1. Introduction

Hydralazine is a medication often used to control blood pressure, particularly in patients with renal impairment. Hydralazine is a vasodilator and primarily works by reducing peripheral resistance by relaxing the smooth muscle cells in arterial vessels [3]. Common side effects include headache, nausea, tachycardia and dizziness [3]. Furthermore, immune phenomena such as hydralazine induced lupus erythematosus (DILE), vasculitis and glomerulonephritis are also associated with hydralazine use [3]. Hydralazine has also been noted to cause liver disturbances and can be grouped with other medications causing drug induced liver injury (DILI) [2]. DILI due to hydralazine is difficult to diagnose due to variability in presentation and often times polypharmacy of our patients. Several case reports have been written about DILI due to hydralazine, however the mechanism of action remains unclear.

2. Case Report

Patient is a 70-year-old female with past medical history of uncontrolled hypertension, diabetes, stroke with residual left sided weakness and left eye blindness, who presented to the hospital with abdominal pain and jaundice for one week. Patient described her abdominal pain as diffuse, non-radiating, 6/10 in intensity, and dull in character. She had no aggravating or alleviating factors and it was associated with postprandial vomiting. Patient also began to notice scleral icterus in both her eyes a week prior. She denied any recent travel, sick contacts, blood transfusions, new medications, or rashes. At home, patient was taking Lisinopril, Hydralazine, Novolog Insulin and Crestor; she had been on these medications for five years. Blood pressure on admission was 146/75 mm Hg, heart rate was 84 beats per minute, temperature was 97.8 degrees F, respiratory rate was 18 breaths per minute, and pulse oximetry was 98% on room air. Patients physical exam was significant for jaundice, scleral icterus, and subungual icterus; patients' abdominal exam was within normal limits.

On admission, the patient had a CT Abdomen and Pelvis with intravenous contrast which did not show any intra-or extrahepatic biliary ductal dilatation. The liver appeared to be of normal size and contour. Admitting laboratory work was significant for an elevated Alkaline Phosphatase of 349 (20to 140 IU/L), transaminitis with an aspartate aminotransferase (AST) of 796 (10-40 IU/L) and alanine aminotransferase (ALT) of 582 (7-56 IU/L). Patient also had a mixed hyperbilirubinemia, with a total bilirubin of 21.3 mg/dL (0.1-1.2 mg/dL) and a direct bilirubin level >10 (<0.3 mg/dl). Patients viral hepatitis panel was also unremarkable.

The patient mentioned to the medical team taking care of her that she had started taking hydralazine and atorvastatin about 2-3 months ago; which were both subsequently held after admission. Gastroenterology was subsequently consulted who believed the patient may be presenting with DILI from either previous hydralazine or atorvastatin use; they recommended the primary team complete a chronic liver disease work up and monitor liver function tests (LFTs) on a daily basis. Patients LFTs were monitored on a daily basis, a summary can be seen in Table 1 and Figure D. Of note, patient got a dose of intravenous hydralazine on day 4 of admission due to hypertensive urgency which coincides with a peak in both

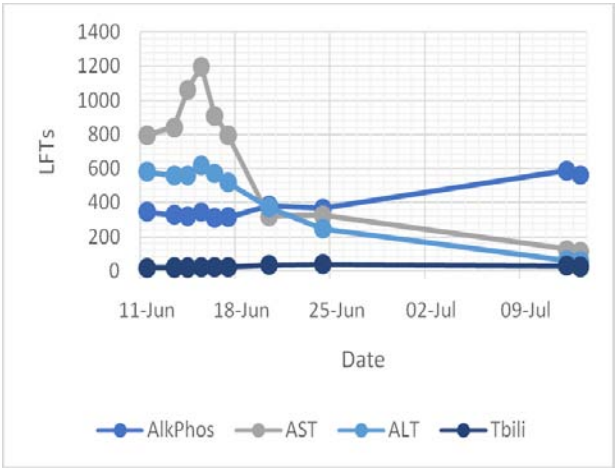
AST and ALT. Further laboratory testing including Smooth muscle Ab, mitochondrial Ab, EBV, HSV, CMV, Proteinase-3Ab, Myeloperoxidase Ab, and Liver Kidney Microsomal Ab was unremarkable.

As can be seen from Table 1, patients LFTs were persistently elevated and her abdominal pain continued to get worse; patient subsequently had an abdominal ultrasound, Magnetic resonance cholangiopancreatography (MRCP) and Cholescintigraphy/ HIDA scan to examine the hepatobiliary system with more detail. Ultrasound showed gallbladder wall thickening with adherent stones versus polyps measuring up to 4 Mm. The HIDA scan was significant for severe hepatocellular dysfunction pattern; extrahepatic biliary obstruction cannot be determined due to poor hepatic uptake and absence of tracer clearance into biliary tree. MRCP showed a contracted gallbladder and no evidence of cholelithiasis or choledocholithiasis. The liver appeared mildly heterogeneous which was consistent with hepatocellular disease.

Our patients' abdominal pain improved, and her hydralazine was successfully replaced by other anti-hypertensive medications. Patients AST and ALT began to trend down two days after her last hydralazine exposure, however her alkaline phosphatase and total bilirubin remained elevated. Patient was scheduled for an outpatient hepatology clinic visit, as well as a percutaneous liver biopsy. Liver biopsy was suggestive of portal inflammation with extensive destruction of limiting plate, ductular reaction, fibrous expansion and bridging (Figure A, B, C). There was focal ballooning of hepatocytes and apoptosis, as well as hepatocyte hyperplasia. Biopsy results were consistent with severe hepatitis with chronic and cholestatic features (Figure A, B, C). After multiple etiologies were discussed, it was determined that patient likely had DILI due to hydralazine exposure. Patient returned to the hospital a month after the above discussed hospital course with persistent jaundice, and laboratory studies can be seen in Table 1 and Graph 1. After this subsequent discharge, patient was lost to follow-up.

Table1. Laboratory Values Demonstrating trends in Liver Function Tests

Date (2019)	ALP	AST	ALT	T.Bili	D.bili
6/11	349	796	582	21.3	>10
6/13	333	842	560	22.2	
6/14	323	1062	561	22.3	
6/15	347	1199	619	23.9	>10
6/16	313	909	571	25.9	
6/17	317	797	520	26.1	
6/20	385	321	375	38.3	
6/24	369	329	248	41.9	
7/12	589	127	63	33.1	>10
7/13	564	115	59	27.1	



Graph 1. Laboratory Values Demonstrating trends in Liver Function Tests

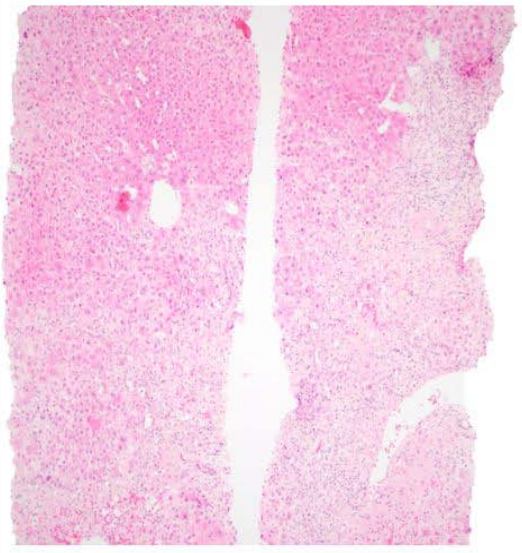


Figure A: Hematoxyline and eosin stain(100X):Portal inflammation with extensive destruction of limiting plate

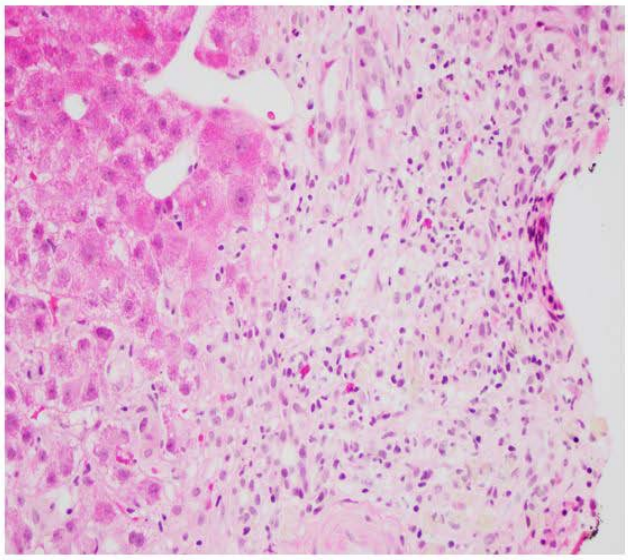


Figure B: Hematoxylin and eosin stain(400X):Portal inflammation showing mixture of eosinophils and plasma cells

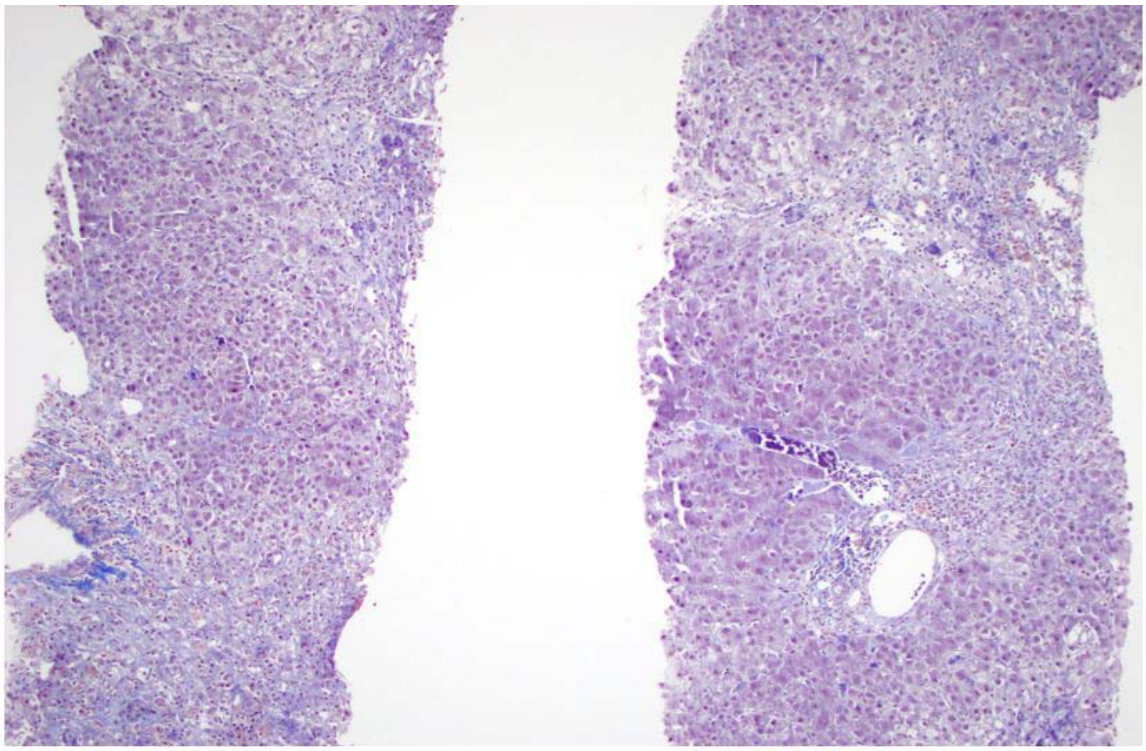


Figure C: Trichrome stain (100X): Fibrous expansion of portal areas and bridging fibrosis

Figures A, B, and C

3. Discussion

In a prospective study conducted by Reuben et al., among 1198 patients noted to have acute liver failure, 133 cases were attributed to 61 various medications; hydralazine was implicated in only one case [4]. In the United States, DILI accounts for 10% of all cases of acute hepatitis [5]. The annual incidence has been estimated at 20/100,000 in developed countries [6]. DILI has been cited to be the major reason for withdrawal of a medication from the pharmaceutical marketplace [7]. Most commonly, DILI can be attributed to the use of anti- infective medications, herbal and dietary drugs, and nonsteroidal anti-inflammatory drugs [8]. Hydralazine is not commonly implicated in the development and pathophysiology of DILI

DILI is a clinical problem with an unpredictable nature and no specific diagnosis criteria which ultimately can lead to a delay in diagnosis and removal of the offending agent. Typically, DILI has three types of clinical patterns including cholestatic, hepatocellular and mixed cholestatic and hepatocellular injury [9,10]. The R factor, which is the ratio of ALT/upper limit of normal ALT to alkaline phosphatase/ upper limit of normal alkaline phosphatase, can be used to separate DILI into the mentioned three patterns. Cholestatic injury had an R <2, mixed injury with 2 <R <5 and hepatocellular injury with an R>5 [11]. Those patients with cholestatic injury alone generally have better outcomes [9,10,11]. Our patients' calculated R factor was >5 and therefore was primarily hepatocellular injury.

Multiple case reports have been written about hydralazine induced liver injury, and have described different latency periods. Some case reports described a short latency period of 3 weeks [11] while others describe periods of 2 months to 1 year [12]. In our patient, she had only been taking hydralazine for 2-3 months prior to developing acute liver injury.

Due to the persistently elevated alkaline phosphatase our patient experienced, and lack of evidence of obstruction on several diagnostic imaging modalities, a liver biopsy was warranted to determine the etiology of liver injury. A liver biopsy is not required to diagnose DILI; however, it can be helpful in confirming a clinicians' suspicion for DILI. Ultimately, DILI is a diagnosis of exclusion and biopsy results are often used to identify a non-DILI explanation for injury [13]. There are many ways to classify DILI, three common types of classifications include clinical laboratory, mechanism of hepatotoxicity and histologic findings [14]. Common histologic findings include cellular necrosis, cholestasis, steatosis (micro and macrovesicular), fibrosis, phospholipidosis, and sinusoidal obstruction (15-16). Our patient displayed "Portal inflammation with extensive destruction of limiting plate with a mixture of eosinophils and plasma cells (Figure A (100X) and Figure B 400X). Periportal ductular reaction, fibrous expansion and bridging Figure C (40x). Focal ballooning of hepatocytes and apoptosis were noted. There was an evidence of minimal bile in portal areas and ballooned hepatocytes. The overall histologic findings on her liver biopsy were consistent with DILI.

4. Conclusions

The hydralazine induced cholestatic liver injury seemingly improved once hydralazine was discontinued, however longer follow-up of the patient would have been

ideal. DILI is an extremely challenging pathology and can be difficult for clinicians to diagnose with certainty due to many confounding medications and symptoms. There have been over 350 drugs implicated in their risk to the liver, with very specific characteristics and mechanism for their respective hepatocyte injury [14]. Patients who present with liver failure secondary to DILI have a 20% chance of surviving with supportive care, which highlights the importance of early diagnosis and removal of the offending drug [14]. Medical professionals must be careful when administering new medications to patients and monitor liver function carefully. Furthermore, we should be aware of drugs that are commonly implicated in DILI in efforts to discontinue them if DILI is a clinical suspicion.

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