Thinking Outside the Box in Liver Tox

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Introduction

There are a myriad of etiologies for patients presenting with acute hepatitis. Nearly 10% of these cases are due to drug-induced liver injury (DILI).[1] While identifying the offending agent can be difficult, there are known offenders that can be elucidated with an accurate history from the patient. However, in the non-native patient or frequent international traveler, this can become a much more challenging task given the medications, supplements and host of items used as alternative medicines in other countries and cultures that may not be available in the United States. While DILI is the most common cause of acute liver failure in the United States, it is important to consider that the agent at play may not be common to the United States.[2] We aim to highlight the importance of using a "global mindset" when treating international and frequent traveling patients, but also demonstrate the severe hepatotoxic risks associated with Nimesulide.

Case Presentation

We present a case of a 43 year-old female with comorbidities including iron deficiency anemia, hyperlipidemia, and uterine leiomyomas that initially presented to an outside hospital with chief complaint of abdominal pain. In addition, she endorsed fevers, chills, arthralgias which progressed to also include dyspnea on exertion, fatigue, dizziness, and non-bloody diarrhea. Her presenting labs revealed significant liver injury (figures 1-3). Initial imaging with RUQ US showed gallbladder wall thickening, hepatomegaly with diffuse fatty liver infiltrate. Subsequent CT A/P w/o contrast showed similar findings, with concern for acute cholecystitis. General surgery was consulted. HIDA scan was performed which did not show evidence of acute cholecystitis. Her liver enzymes continued to worsen and thus MRI abdomen w/wo contrast was ordered (fig. 4). The patient was transferred to Largo Medical Center for further hepatology evaluation and the availability of interventional endoscopic capabilities if warranted. On presentation to LMC, her pain was improving though she felt her abdominal distention was worsening. During her initial interview at LMC, she denied newly prescribed medications, OTC medications, or use of herbal supplements. She reported she traveled to the Dominican Republic where she spent 4 days and returned to the U.S. approximately 15 days prior to initial presentation. The patient's husband did have nausea, vomiting, and diarrhea for a few days while on vacation, but it resolved spontaneously. Due to concerns for infectious etiology, patient was treated with Zosyn and Doxycycline. She continued to have MEG/RUQ abdominal pain, loose stool and nausea. Labs continued to worsen. Extensive hereditary, autoimmune, vascular, inflammatory, infectious liver serologies were completed which were unrevealing. Due to the unexplainable etiology of liver injury, decision was made to proceed with liver biopsy. On the morning of her liver biopsy, patient's husband was present in the room during morning interview and on further discussion with the couple, patient reported being given medication for a headache while in the Dominican Republic. This medication was discovered to be Nimesulide, of which she completed a pack of fifteen 100mg tabs over the course of the proceeding week. Liver biopsy completed showing histology c/w drug induced hepatitis (fig. 5). She was treated with supportive care and conservative management and was able to be discharged with improvement in her symptoms. On a follow-up visit 8 months later, she had complete normalization in her liver enzymes and overall liver function.

Imaging & Laboratory Findings

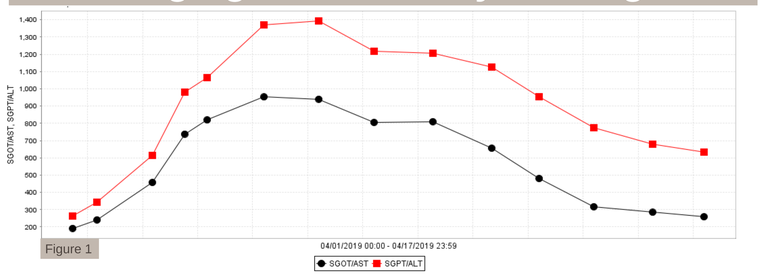

Figure 1

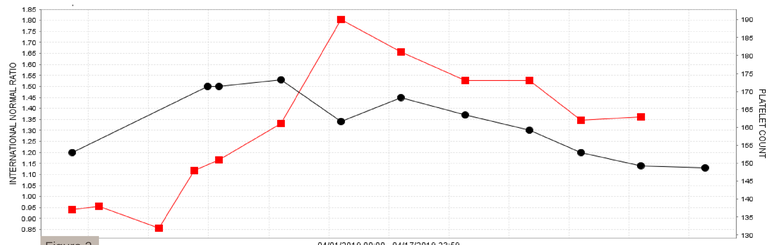

Figure 2

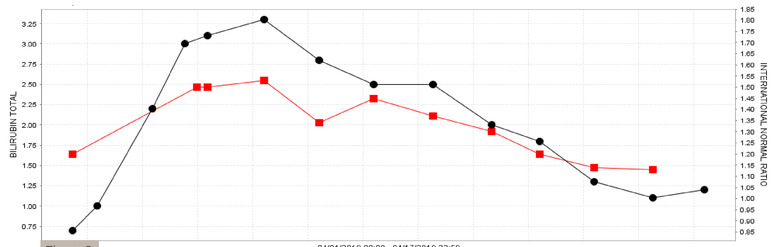

Figure 3

MRI w/wo contrast: Mild hepatomegaly. Findings compatible with hepatocellular disease. Questionable gallbladder sludge and tiny stones. No significant inflammatory change around the gallbladder. No biliary dilatation.

Figure 4

Histology

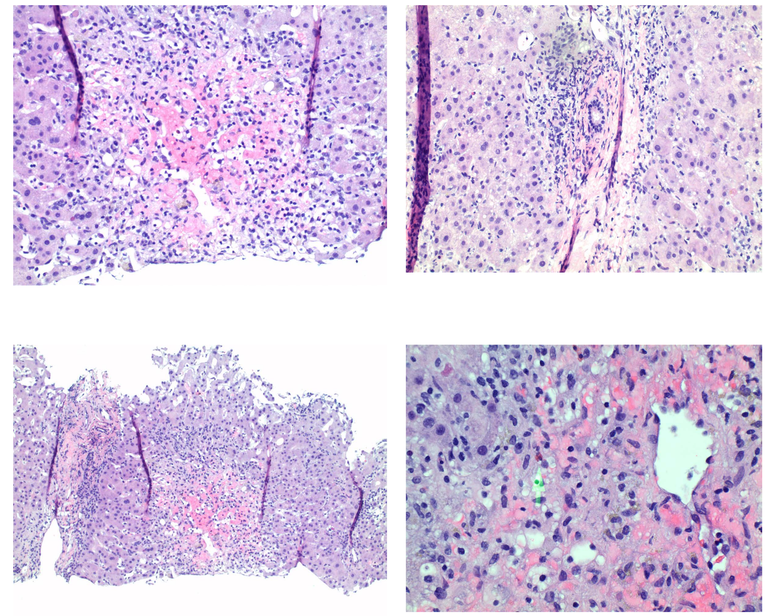

Figure 5

Microscopic description: mild to moderate perivenular hepatocyte degeneration and congestion associated with lymphocytes and eosinophils, and intracellular cholestasis. Portal tracts show lymphocyte and eosinophil infiltrates, and intracellular cholestasis. Portal tracts show lymphocyte and eosinophil infiltrates.

Conclusion

Our patient experienced drug-induced hepatocellular liver injury attributed to Nimesulide. Hepatocellular injury is the most common pattern of liver enzyme elevation seen with Nimesulide, though cholestatic elevations have also been demonstrated.[4] Nimesulide is predominantly a COX-2 inhibitor.[4] There is no evidence that patients sustaining DILI from Nimesulide will experience similar response to other non-steroidal anti-inflammatory drugs.[4] NSAIDs as a class do carry a risk of hepatotoxicity and this appears to be highest with Nimesulide.[3] Cases of fulminant liver failure requiring liver transplantation and other cases ending in death related to Nimesulide have been reported in the literature.[4] Even more exist demonstrating transient, but significant, liver injury.[4] This case demonstrates the need for U.S. physician and patient awareness of the hepatotoxic risks associated with Nimesulide.

References

1. Zimmerman HJ. *Drug-induced liver disease.* Clin Liver Dis. 2000 Feb;4(1):73-96, vi. doi: 10.1016/s1089-3261(05)70097-0. Review. PubMed PMID: 11232192.
2. Ostapowicz G, et al. *Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States.* Ann Intern Med. 2002 Dec 17;137(12):947-54. doi: 10.7326/0003-4819-137-12-200212170-00007. PubMed PMID: 12484709.
3. Donati M, et al. *Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case-control study in Italy.* Br J Clin Pharmacol. 2016 Jul;82(1):238-48. doi: 10.1111/ bcp.12938. Epub 2016 Apr 27. PubMed PMID: 26991794; PubMed Central PMCID: PMC4917796.
4. Nimesulide. 2012;. Review. PubMed PMID: 31643281.

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