Hereditary Hemochromatosis Unmasked by Drug Induced Liver Injury from Amoxicillin-Clavulanate

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INTRODUCTION

- Drug-induced liver injury from amoxicillin-clavulanate remains one of the most frequent causes of non-acetaminophen drug-induced liver injury per prospective registries across the US and Europe – such as *Liver Tox*. It is estimated the incidence is 1 case per 2,500. Patients typically present with symptoms of cholestasis – fatigue, nausea, loss of appetite and pruritis. This translates to cholestatic liver enzyme abnormalities. It is important to rule out other causes of liver injury which makes DILI – *drug induced liver injury* a difficult diagnosis.
- We present a patient with newly diagnosed hereditary hemochromatosis unmasked by drug induced liver injury secondary to amoxicillin-clavulanate use.

LEARNING OBJECTIVES

- Differentiate the two main types of drug induced liver injury -*intrinsic* and *idiosyncratic*
- Identify amoxicillin-clavulanate as a cause of drug induced liver injury
- Underlying genetic conditions (as in our patient with HH) may play a role in drug induced liver injury
- Familiarity with registries such as Liver Tox for prescription and non-prescription medications (i.e. dietary supplements)

CASE PRESENTATION

- 75-year-old female presented to her primary care provider for sinusitis and was prescribed amoxicillin-clavulanate two weeks prior to initial presentation.
- She began to experience nausea, vomiting, reflux and epigastric abdominal pain. Subsequently developed worsening pruritus, and scleral icterus. No other new medications or alcohol use were reported.
- Lab work showed an alkaline phosphatase of 574, AST 251, ALT 602, total bilirubin 4.2 and INR of 1.06. Elevated ferritin of 635 and iron saturation of 94%. Abdominal ultrasound and CT abdomen/pelvis were unremarkable.
- Extended liver work up revealed a negative acute hepatitis panel, ANA positivity however anti-actin antibody, anti-smooth muscle antibody, and anti-mitochondrial antibody were all negative. Interestingly, the patient was found to be an HFE H63D homozygote with no known family history of hemochromatosis.
- Gastroenterology follow up was arranged one week after hospital discharge with lab work at that time showing improving values ALP 571, AST 144, ALT 233, and total bilirubin of 2.7. Patient required cholestyramine, ursodiol and hydroxyzine to control the pruritus, otherwise the remainder of her symptoms were vastly improved.
- She was referred to Hematology-Oncology for further evaluation of Hemochromatosis. Fortunately this variant is often not clinically penetrant. Phlebotomy – mainstay of treatment of iron overload was held off and repeat labs were performed 3 months later which all normalized resulting in continued close observation.

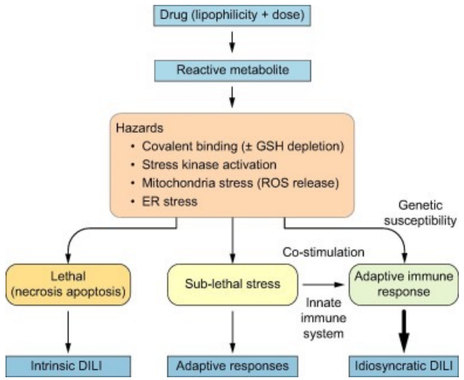

Figure 1: Demonstrates the pathway for hepatotoxic insult. Depending on the type of insult, the metabolism, pharmacokinetics and consequential reactive species formation the pathway illustrates how drug induced liver injury may be categorized into *intrinsic* and *idiosyncratic*.

DISCUSSION

- The exact mechanism of amoxicillin-clavulanate causing drug induced liver injury is unknown, but theorized to be in relation to an immune-allergic response. The onset of injury can last up to 8-10 weeks, fortunately there is rarely long-lasting injury.
- There are two generalized categories of DILI – *intrinsic* and *idiosyncratic*. Intrinsic injury, is directly toxic to the hepatocyte causing a predictable and dose-dependent injury. The most common cause of this is high doses of acetaminophen. Conversely idiosyncratic injury is not directly hepatotoxic, nor is it predictable and dose-dependent. This subset of liver injury can be further classified into hepatocellular, cholestatic or mixed based upon the R ratio.
- Drug-induced liver injury remains an important clinical disease that clinicians should be cognizant of. It is a clinical entity that is very difficult to diagnose as often times there are significant delays from the time of onset of insult to presentation, and is ultimately a diagnosis of exclusion. Idiosyncratic DILI may unmask hepatotoxic prescription drugs with environmental and genetic susceptibilities playing an underlying role.
- As in our patient, hereditary hemochromatosis (HH) was diagnosed during the diagnostic work up. H63D homozygosity is associated with a less than 10% risk of developing an iron overload state.
- It remains unclear if the patients underlying hereditary condition which is known to cause liver disease played any active role in this circumstance.

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