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CASE REPORT | LIVER

Atypical Intrahepatic Cholestasis of Pregnancy: A Red Herring

Blake H. Bentley, MD[1], Alexa E. Cecil, MD, MPH[1], and William C. Lippert, MD, MPH[1]

[1]*Department of Internal Medicine. Wake Forest University School of Medicine, Winston-Salem, NC*

ABSTRACT

Intrahepatic cholestasis of pregnancy is an intrahepatic etiology of acute cholestasis commonly defined by pruritus and increased bile acids, liver transaminases, and, occasionally, bilirubin. Azathioprine is an immunosuppressive agent associated with various forms of hepatoxicity, ranging from transient rises in serum aminotransferase levels, acute cholestatic injury, and chronic hepatic injury. In this report, we present a 20-year-old pregnant woman who presented with cholestatic liver injury due to intrahepatic cholestasis of pregnancy with a clinical picture complicated by increased levels of azathioprine metabolites.

INTRODUCTION

Azathioprine is typically associated with asymptomatic elevations of serum aminotransferase levels and rare occurrences of acute, cholestatic liver injury. Owing to pregnancy-induced physiological changes, drug metabolism can be altered, increasing the likelihood of drug-related azathioprine toxicity. Intrahepatic cholestasis of pregnancy (ICP) occurs in 0.2%–2% of pregnancies and is associated with jaundice, marked pruritus, increased bile acids, increased liver transaminases, and, occasionally, hyperbilirubinemia.[1,2] It is a diagnosis of exclusion and defined as severe cholestasis with total bile acids >40 μmol/L.[3]

CASE REPORT

A 20-year-old G1P0 woman with alpha thalassemia trait and idiopathic pulmonary hemosiderosis, treated with azathioprine and hydroxychloroquine, presented at 33 weeks' gestation with new-onset nausea, myalgias, abdominal pain, and jaundice. Initial vitals were within normal limits, and physical examination disclosed conjunctival icterus, mucosal jaundice, and absence of abdominal tenderness. Serology revealed total bilirubin peaking at 11.5 mg/dL (normal 0–1.0), direct bilirubin 6.3 mg/dL (normal 0–0.2), AST 20 U/L (normal 13–39), alanine transaminase (ALT) 12 U/L (normal 7–52), and alkaline phosphatase (ALP) peaking at 148 U/L (normal 34–104). Baseline liver function tests before pregnancy included ALP 84 U/L (34–104), ALT $<$ 5 U/L (7–52), and AST 17 U/L (13–39) with unknown bile acids. INR was 1.18. R-factor was calculated at 0.3. Urinalysis was without proteinuria. Obstetrics, hematology, hepatology, and rheumatology were consulted. Azathioprine was held on admission. Hepatitis A IgM antibody was negative, and hepatitis B and C serologies were nonreactive. Antinuclear antibody was mildly elevated at 1:640. Bile acids were elevated (Table 1). Peripheral blood smear revealed no schistocytes or spherocytes. Hemolysis laboratory test results were unremarkable. Liver ultrasound demonstrated normal echogenicity; however, the common bile duct was not visualized. Magnetic resonance cholangiopancreatography revealed no intrahepatic or extrahepatic biliary dilatation (common bile duct $<$7 mm) and normal liver echogenicity. Liver Doppler and echocardiogram were both normal. On day 4 of admission, the patient had an uncomplicated spontaneous vaginal delivery, with her total bilirubin and ALP subsequently down-trending (Figure 1). She was successfully restarted on azathioprine 2 days postpartum due to gradual improvement of associated metabolites (Figure 2).

DISCUSSION

Occurring during the third trimester of pregnancy, determining the etiology of the patient's presentation posed a challenging dilemma. Pregnancy engenders profound physiologic changes influencing drug metabolism through variations in hepatic enzyme

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Correspondence: Blake H. Bentley (bbentley@wakehealth.edu).

Table 1. Additional laboratory testing of patient's liver injury workup

Laboratory Tests	Results (normal)
Bile acids	
Total ursodeoxycholic acid	0.80 μmol/L (<1.6)
Cholic acid	201 μmol/L (<2.2)
Chenodeoxycholic acid	77 μmol/L (<5.8)
Deoxycholic acid	75 μmol/L (3.3)
Total bile acids	354 μmol/L (<9.2)
Ceruloplasmin	21.3 mg/dL (19–39)
24-hour copper, urine	82 μg/24 h (3–35)
Proteinase 3 Ab	Negative
Myeloperoxidase Ab	Negative
C-ANCA	Negative
P-ANCA	Negative

activity, particularly in the cytochrome P450 system. Furthermore, expanded plasma volume and alterations in plasma protein concentrations can affect the active drug fraction.[4] Disruption of hepatic conversion of azathioprine during pregnancy may lead to heightened metabolite levels, increasing toxicity risk.[5]

Based on the acuity of presentation and an R-factor of 0.3, acute cholestatic disease processes were considered. As related to pregnancy, these can include extrahepatic (eg, biliary obstruction or pancreatitis) or intrahepatic cholestasis (eg, preeclampsia-associated liver dysfunction, acute fatty liver of pregnancy or intrahepatic cholestasis).[6,7] Based on a normal liver ultrasound and magnetic resonance cholangiopancreatography, extrahepatic causes of cholestasis were less likely. In the absence of hypertension, headache, or proteinuria, preeclampsia-associated liver dysfunction was also felt unlikely. Other pregnancy-related etiologies of hepatic impairment can include acute fatty liver of pregnancy, which is often associated with nausea, vomiting, and renal impairment as well as hemolysis, elevated liver enzymes, and low platelet syndrome, which is associated with hypertension and proteinuria.[1] Our patient's clinical presentation did not correspond with either of these conditions.

As the patient presented with nausea, jaundice, and notably without pruritus, azathioprine toxicity was considered. Azathioprine is a purine analog and mercaptopurine prodrug that inhibits lymphocyte function by inhibition of T-cell maturation thus blocking delayed hypersensitivity reactions. It undergoes extensive hepatic metabolism to 6-mercaptopurine and thereafter to other thiopurines, including 6-methylmercaptopurine (6-MMPN) and 6-thioguanine nucleotide. 6-MMPN levels are associated with hepatoxicity and myelotoxicity while 6-thioguanine nucleotide levels correlate with therapeutic efficacy.[8] Common side effects include nausea, abdominal upset, aphthous ulcers, rash, dose-related bone marrow suppression, and increased risk of malignancy with long-term use. Furthermore, it is associated with various forms of hepatotoxicity, ranging from transient rises in serum aminotransferase levels, acute cholestatic injury, and chronic hepatic injury.[9]

Acute cholestatic injury due to azathioprine commonly presents with jaundice, fatigue, and mildly elevated serum aminotransferase levels and ALP, often in a mixed cholestatic-hepatocellular pattern. Our patient's presentation fit the criteria

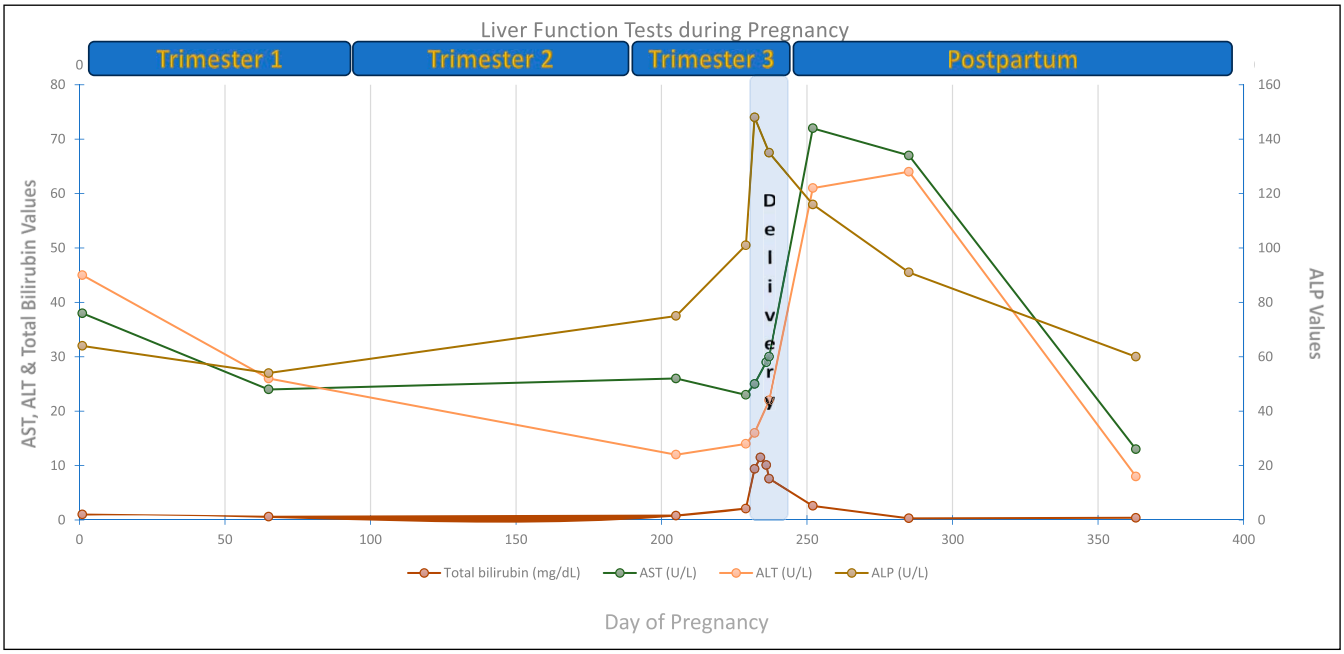

Figure 1. Time series curve on the relation of patient's liver function tests throughout pregnancy. ALP, alkaline phosphatase.

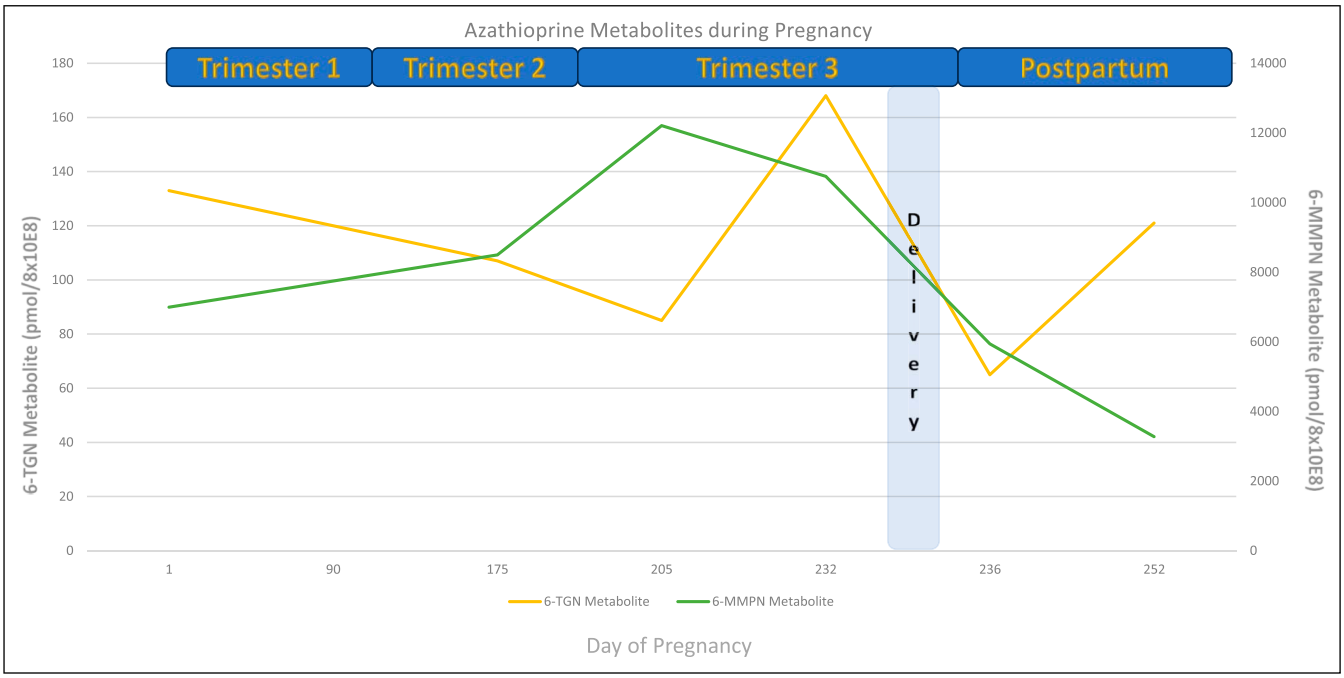

Figure 2. Time series curve on the relation of patient's 6-TGN and 6-MMPN levels over time. 6-MMPN, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotide.

of cholestatic liver injury with an initially elevated bilirubin and normal ALP and alanine transaminase. Reviewing the pattern of laboratory abnormalities in Figure 1, one will see an initial rise in total bilirubin followed by ALP and then transaminases. This is an expected pattern in which elevated bile acid levels can directly damage hepatocytes and cholangiocytes, activating an inflammatory response by stellate and Kupffer cells, ultimately impairing bile acid transport and metabolism.[10] The pattern of resolution follows the same order where transaminases are the last to return to baseline. In addition, she had been taking the offending agent far longer than the typical 4 to 24 weeks[11] following initiation of therapy, and the onset of her symptoms was quicker than would be expected. As such, ICP was considered. Our patient's breakdown of bile acid predominance of cholic acid is typical of ICP compared with normal pregnancies in which chenodeoxycholic acid is equal or in higher concentrations than cholic acid.[12]

Our patient's jaundice without pruritus and severely elevated bile acid levels were notable. Although pruritus is conventionally thought of as a core feature of ICP, some small studies have shown pruritus is not always observed.[13] Up to 27.8% of patients with laboratory-confirmed ICP may lack pruritus despite having similar clinical patterns and pregnancy outcomes,[14] suggesting that asymptomatic ICP is a clinical variant that still requires treatment. Moreover, our patient's spontaneous vaginal delivery occurred before initiation of ursodiol, and hepatic function enzymes gradually improved despite restarting azathioprine. This supported the diagnosis of ICP rather than azathioprine toxicity. Although the patient's 6-MMPN metabolite levels were higher than expected, they were starting to decline at the time of presentation and rapidly returned to a normal range. We propose this was a result of alterations of metabolism in pregnancy rather than azathioprine toxicity.

In conclusion, this case report demonstrates an atypical presentation of ICP, notably lacking one of the hallmark features of pruritus, with a clinical picture confounded by a potential hepatotoxic medication, azathioprine. It walks through the diagnostic process of differentiating between acute cholestatic etiologies while highlighting what was ultimately a red herring.

DISCLOSURES

Author contributions: B. Bentley: drafted manuscript, created figures; A. Cecil: drafted manuscript; W. Lippert: reviewed and approved manuscript.

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Informed consent was obtained for this case report.

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