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CASE REPORT | LIVER

Late-Onset Acute Liver Injury From Azathioprine

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ABSTRACT

Azathioprine is a widely prescribed immunosuppressant. Although hepatotoxicity is rare, it commonly presents as mild asymptomatic liver enzyme elevation or acute cholestatic liver injury. We report a case of a 46-year-old woman who presented with jaundice, abdominal pain, fatigue, and elevated aminotransferases in a cholestatic pattern. Endoscopic retrograde cholangiopancreatogram demonstrated no abnormalities, and recently started medications were discontinued without improvement. Liver biopsy was performed, which was consistent with drug-induced liver injury. Despite multiple years of treatment without issue, after azathioprine was discontinued, symptoms and laboratory abnormalities resolved. This case highlights azathioprine's potential for hepatotoxicity even multiple years after initiation.

INTRODUCTION

Drug-induced liver injury (DILI) is a very common cause of acute liver injury (ALI) in the United States, with an estimated 44,000 cases annually.[1] While some drugs linked with DILI cause intrinsic, dose-dependent hepatotoxicity, others cause idiosyncratic, dose-independent liver injuries. These idiosyncratic reactions are unpredictable; are poorly understood; and can cause hepatocellular, cholestatic, or mixed liver injury. Many widely prescribed medications can cause DILI in susceptible individuals even when the patient is on the medication chronically.

Azathioprine, a widely prescribed immunosuppressant, has been associated with different forms of hepatotoxicity. Azathioprine is a purine analog that acts as an antagonist, interfering with the cell cycle subsequently inhibiting normal leukocyte function, thus performing a role as a steroid-sparing immunosuppressive agent. Mild transient and asymptomatic aminotransferase elevations can occur in the first several months of treatment and are generally benign, resolving with dose changes or cessation.[2–4] However, azathioprine can also cause an idiosyncratic cholestatic ALI, which usually presents as jaundice and fatigue within the first year of therapy and is often associated with mild alanine aminotransferase (ALT) and alkaline phosphatase elevations. Liver biopsy typically reveals intrahepatic cholestasis with focal hepatocellular necrosis and scant inflammation.[2] It typically resolves on azathioprine discontinuation. Previous studies have shown that time to onset in idiosyncratic cholestatic liver injury cases was generally within a few months and rarely exceeded 6 months of azathioprine initiation or dose increase.[3,5] We present a case with symptomatic and clinically significant cholestatic ALI multiple years after azathioprine initiation.

CASE REPORT

A 46-year-old woman with a history of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), hepatitis B virus (HBV) exposure with seroconversion (Hepatitis B Surface Antigen (HBsAg) negative, Hepatitis B Surface Antibody (HBsAb) positive, Hepatitis B Core Antigen (HBcAg) positive, and DNA−), hypertension, hyperlipidemia, diabetes, hypothyroidism, and remote cholecystectomy presented to the emergency department with acute abdominal pain, jaundice, and fatigue. Vital signs were within normal limits and physical examination only notable for mild epigastric tenderness. Initial laboratory test results revealed alkaline phosphatase 386 U/L, aspartate aminotransferase (AST) 189 U/L, ALT 95U/L, total bilirubin 4.3 mg/dL, albumin 2.8 g/dL, lipase 459U/L, and international normalized ratio 1.14. Computed tomography was notable for a 1 × 1 cm hypodense left hepatic lesion, stable from years before and an unremarkable pancreas. She had been stably on azathioprine 150 mg twice daily and prednisone 10 mg daily for CLIPPERS treatment for 32 months. Before the initiation of treatment, she had a normal thiopurine methyltransferase genotype. She was found to have HBV exposure during workup for planned transition to rituximab for CLIPPERS treatment and had been recently started on tenofovir alafenamide (TAF) for antiviral prophylaxis. She denied alcohol use or herbal supplementation.

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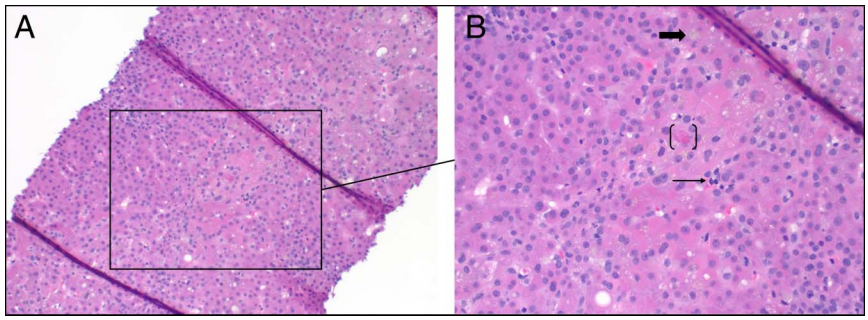

Figure 1. Hematoxylin and eosin stain of the liver biopsy. (A) Representative low-power image of the liver biopsy demonstrating acute cholestatic hepatitis without evidence of steatosis, fibrosis, or cirrhotic morphology and (B) inset image of the liver biopsy demonstrating cholestasis (➡), an acidophil body ([ ]), and lobular inflammation (⟶).

Magnetic resonance cholangiopancreatography (MRCP) was performed to exclude gallstone disease, which revealed no ductal dilation or evidence of stones. TAF was initially held given temporal relation. HBV-DNA, Hepatitis A Immunoglobulin M (IgM), cytomegalovirus-IgM, Epstein-Barr virus-IgM, and human immunodeficiency virus were negative. Over several days, the patient's symptoms improved; Liver chemistries stabilized without significant improvement; and the patient was discharged with follow-up. The following week, however, the patient noted that her symptoms had intensified, and her laboratory test results had worsened to AST 251 U/L, ALT 127 U/L, alkaline phosphatase 89 U/L, bilirubin 8.8 mg/dL, and international normalized ratio 1.5, which led to holding her azathioprine and arranging liver biopsy to assess etiology of the injury. Subsequently, the patient's symptoms improved with stabilization of aminotransferases and bilirubin. 6-methylmercaptopurine (6-MMP) and 6-thioguanine nucleotide (6-TG) levels were 73,543 pmoL/8 × 10^8 right blood cell (RBC) (reference <5,700 pmol/8 × 10^8 RBC) and 359 pmol/8 × 10^8 RBC (reference 235-400 pmol/8 × 10^8 RBC), respectively. Biopsy revealed moderate-to-severe lobular cholestasis with lobular hepatitis suggesting DILI without evidence of steatosis, fibrosis, cirrhotic morphology, iron, copper, A1At globules, HBcAg, or HBsAg (Figures 1 and 2). Within 2 weeks, her AST improved to 98 U/L, ALT to 71 U/L, and bilirubin to 4.4 mg/dL, and all returned to normal limits within a month. TAF was resumed before rituximab, and liver chemistries remained within normal limits without return of symptoms.

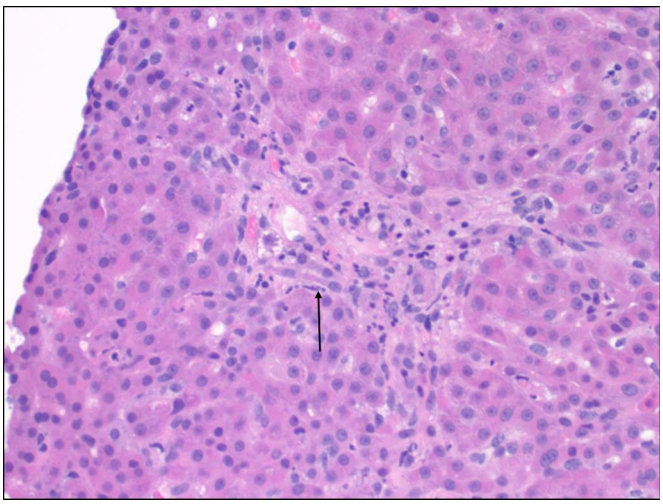

Figure 2. Hematoxylin and eosin stain of the liver biopsy demonstrating a portal tract with ductular reaction.

DISCUSSION

Azathioprine is a commonly prescribed immunosuppressant associated with hepatotoxicity. Our patient had been on a stable dose of azathioprine for 32 months, yet still developed ALI that resolved on azathioprine discontinuation. The mechanism of injury is uncertain but may demonstrate that DILI from azathioprine can occur at any time in the treatment course despite a stable regimen. An acute symptomatic azathioprine-induced liver injury has not been previously documented so many months after initiation.

Azathioprine is a prodrug that is metabolized to 6-MP and then further metabolized to 6-TGs and 6-MMP.[6,7] Through a poorly understood mechanism, some patients preferentially produce 6-MMP over 6-TG, which has been termed "metabolic shunting," and are more likely to develop hepatotoxicity.[7–9] A New Zealand database on thiopurines for inflammatory bowel disease found that 15% of patients developed preferential 6-MMP production. Of this group, 29 patients developed late-onset shunting, 11 of whom had elevated aminotransferases. The time from starting therapy to shunting was 5 months to 10 years, with a median of 21 months.

Another study examined 22 patients with thiopurine hepatotoxicity, of whom 12 were prescribed azathioprine with documented hepatotoxicity. The median time to onset of injury with azathioprine was 41 days, and the time from last dose increase was 31 days. Most patients presented with fatigue, abdominal pain, and jaundice. The authors also noted that they found wide variation in time to onset, and some patients had even been on thiopurines for years before injury. However, they found that all those patients had a recent dose increase. Prognosis was generally favorable, and only 1 patient had evidence of chronic liver injury on follow-up.[3] Rarely, cholestasis from drugs including azathioprine can persist for months and result in vanishing bile duct syndrome with the

loss of small intrahepatic bile ducts, known as ductopenia. Liver chemistries may normalize despite persistent ductopenia, which increases morbidity and mortality.[2,10–12] Our patient's biopsy did not demonstrate ductopenia.

Before azathioprine initiation, our patient had normal thiopurine methyltransferase levels. After presentation, 6-MMP levels were significantly elevated. It is possible our patient underwent metabolic shunting to high production of 6-MMP, leading to symptomatic ALI. There may also have been a correlation between the degree of 6-MMP elevation and her ALI severity because previous studies have shown a positive relationship between average 6-MP metabolite levels and aminotransferase levels.[13] Our patient had been on high-dose azathioprine, which may have increased the likelihood of injury.

This case highlights azathioprine's potential for hepatotoxicity even multiple years after initiation of treatment reminding clinicians that DILI should be considered in any patient who presents with ALI.

DISCLOSURES

Author contributions: N. Reau participated in direct patient care. B. Schwartz and N. Reau analyzed the patient's clinical course, performed literature review, and wrote and edited the manuscript. R. Al-Sabti analyzed and interpreted histology slides and assisted with manuscript writing and preparation. B. Schwartz is the guarantor of the article.

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