CASE REPORT

Azathioprine-induced hepatitis and cholestasis occurring 1 year after treatment

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SUMMARY

Azathioprine is an immunosuppressive medication used in the management of many autoimmune conditions. Commonly reported adverse effects from azathioprine therapy are nausea and bone marrow suppression, while less common side effects include hepatotoxicity. We present the case of a 47-year-old man with a history of myasthenia gravis on azathioprine for 1 year, who presented to our institution with painless jaundice. On initial laboratory evaluation, the level of aspartate aminotransferase, alanine aminotransferase and total bilirubin were markedly elevated. Owing to the potential diagnosis of acute liver failure secondary to azathioprine toxicity, this medication was discontinued. A liver biopsy demonstrating drug-induced liver injury, along with high serum levels of 6-methylmercaptopurine nucleotide confirmed the diagnosis of azathioprine-induced hepatotoxicity. Upon discontinuation of the medication, the patient's transaminases and bilirubin levels improved steadily over the four-day hospital course. This case emphasises azathioprine's potential for hepatotoxicity, even 1 year after the initiation of its use.

BACKGROUND

Azathioprine, a mercaptopurine prodrug that inhibits lymphocyte proliferation, was initially introduced in the 1960's as an antirejection medication, and continues to be used in the management of many autoimmune conditions such as myasthenia gravis. Common reported adverse effects are nausea, rash and bone marrow suppression, while less common side effects include hepatotoxicity, both acute and chronic.¹⁻⁷ Our case presents a man with acute liver failure secondary to azathioprine-induced hepatotoxicity 1 year after initiation of therapy, and confirmed by liver biopsy and metabolic evaluation.

CASE PRESENTATION

A 47-year-old Caucasian man with a medical history of myasthenia gravis, previously on azathioprine and prednisone, presented to the emergency department with jaundice, dark urine and pale stools. One day prior to admission, the patient contacted his neurologist regarding his symptoms and was advised to discontinue azathioprine (200 mg orally daily), which he had been taking for about 1 year as treatment for myasthenia gravis. His vital signs on presentation were unremarkable and stable. His physical examination was remarkable for scleral icterus, diffuse jaundice and no hepatosplenomegaly.

INVESTIGATIONS

Laboratory evaluation was significant for elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 165 and 102 U/L, total bilirubin 16.1 mg/dL, direct bilirubin 11.6 mg/dL, a negative viral hepatitis panel (hepatitis A, B, C and E), autoimmune panel (antinuclear antibody, antismooth muscle antibody, antimitochondrial antibody), negative cytomegalovirus and Epstein-Barr viral assays and a normal iron panel. The complete blood picture was unremarkable without peripheral eosinophilia and urea and electrolytes was within normal limits. In addition, an infectious evaluation with blood and urine cultures was negative. Abdominal ultrasound showed mild cholelithiasis without common bile duct obstruction. MR cholangiopancreatography failed to show intra or extrahepatic duct dilation. An esophagogastroduodenoscopy did not reveal any malignancies, or other abnormalities. A liver biopsy was obtained which demonstrated cholestasis, pericholangitis, mild bile duct injury, and lobular apoptotic hepatocytes consistent with toxic/drug-induced injury (figures 1 and 2).

DIFFERENTIAL DIAGNOSIS

The differential diagnoses in this case involve other causes of acute hepatitis and painless cholestasis that includes viral hepatitis, autoimmune hepatitis, congestive hepatopathy, toxin-induced hepatitis and common bile duct obstruction secondary to malignancy or stones.

TREATMENT

During the hospital admission, azathioprine was not restarted. Over the course of this four-day hospitalisation the patient's symptoms of urine and stool

Figure 1 Liver biopsy with high power (×400) demonstrating cholestasis with bile plugging (blue arrow).

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Figure 2 Liver biopsy with high power (×400) showing portal triad (red arrow) with pericholangitis (neutrophils as seen near blue arrow) and cholestasis (green arrow).

discolouration improved, and his laboratory evaluation showed modest improvements in AST/ALT (86 U/L/83 U/L), total bilirubin (14.2 mg/dL), direct bilirubin (10.2 mg/dL). To confirm the diagnosis of azathioprine-induced liver toxicity, measurement of azathioprine metabolites were obtained prior to discharge. Serum level of 6-methylmercaptopurine nucleotide (6-MMPN) was 20 202 pmole/ 8×10^8 red blood cell (RBC; normal <5700 pmole/ 8×10^8 RBC) which confirmed the diagnosis of azathioprine-induced liver toxicity. Of note, the serum level of 6-thioguanine (6-TGN) was within normal range.

OUTCOME AND FOLLOW-UP

Complete recovery of all laboratory values to patient's baseline at 1-month, 2-month and 3-month follow-up visits.

DISCUSSION

Azathioprine is an immunosuppressant widely used for antiorgan rejection, and in the treatment of numerous autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus and inflammatory bowel disease.^{6 8 9} The mean annual azathioprine-induced liver injury rate is estimated to be about 1.4%.⁶ Hepatotoxicity from azathioprine occurs secondary to depletion of glutathione resulting in mitochondrial injury, ATP depletion and hepatocyte necrosis.^{6 9}

Our case emphasises crucial points that clinicians should be aware of regarding azathioprine-induced liver failure. First, our patient's initial presentation occurred 1 year after start of azathioprine use, with no reports of toxicity prior to an abrupt onset of cholestatic jaundice. Similar and dissimilar symptom latencies have been reported in the literature, with azathioprine-induced liver injury typically occurring in distinct time frames after initiation of use. For example, Pol *et al*² investigated 21 patients with azathioprine-induced hepatitis and showed a mean time to presentation of 41 months and a range of 4–143 months. Davis *et al*¹⁰ reported a case of azathioprine-induced hepatitis in a 55-year-old woman that presented 4 weeks after the initiation of azathioprine, while Eisenbach *et al*¹¹ described acute cholestatic hepatitis in a 67-year-old man taking azathioprine for 21 days. Muszkat⁴ reported azathioprine-induced cholestasis 24 years after azathioprine was started in a 57-year-old woman treated for myasthenia gravis. These temporally distinct presentations have been described as three separate syndromes: hypersensitivity, idiosyncratic cholestatic reaction and endothelial cell injury (causing portal hypertension and veno-occlusive disease due to dose-dependent toxicity to murine sinusoidal endothelial cells and hepatocytes).^{6 12} Next, our

case shows that azathioprine-induced liver failure can be demonstrated by three different methods of evaluation. The steady improvement in transaminases and bilirubin levels after discontinuation of azathioprine favours the hypothesis that our patient's liver failure was secondary to azathioprine toxicity. Similar to our patient's presentation, other authors have described recovery of liver function tests and hepatic function after discontinuation of azathioprine.^{1-4 11-13} Furthermore, we obtained a liver biopsy that showed findings suggestive of drug-induced injury, similar to biopsy findings reported by other investigators.^{1-4 7 8 10 12 14 15} Finally, we were able to support the diagnosis of azathioprine-induced hepatotoxicity by obtaining markedly elevated 6-MMPN serum levels. Azathioprine, a prodrug of 6-mercaptopurine, is metabolised to 6-MMPN and 6-TGN.^{4 11 14 16} In our patient 6-TGN, the metabolite responsible for therapeutic efficacy, was shown to be within normal range, while the serum level of 6-MMPN, the metabolite implicated in hepatotoxicity, was greater than 3.5 times the upper limit of normal, similar to levels previously associated with cholestatic hepatocellular injury.^{4 12 13} In summary, our patient's acute liver failure can be attributed to azathioprine-induced toxicity due to the improvement of liver function tests after cessation of the medication, findings suggestive of drug-induced hepatocellular injury on liver biopsy and elevated levels of the proven hepatotoxin, 6-MMPN, on laboratory evaluation.

This case emphasises important points regarding azathioprine's potential for hepatotoxicity. Most importantly, it emphasises that clinicians should suspect azathioprine as the culprit for any patient's liver failure, regardless of when azathioprine therapy was initiated. Clinical vigilance and awareness of this rare, but potentially life-threatening hepatotoxicity, can lead to cessation of azathioprine therapy so that hepatic recovery can begin.

Learning points

- ▶ Azathioprine can cause life-threatening hepatotoxicity.
- ▶ Hepatotoxicity from azathioprine can occur years after initiation of use.
- ▶ Patterns of liver injury from azathioprine include hepatitis, cholestasis or a mixed (hepatitis and cholestasis) pattern.
- ▶ Levels of 6-methylmercaptopurine nucleotide, a hepatotoxic metabolite of azathioprine, can be measured to support drug-induced liver injury.
- ▶ Clinical recovery typically occurs with discontinuation of azathioprine and supportive treatment.

Competing interests None.

Patient consent Obtained.

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