

A SEVERE CASE OF AZATHIOPHRINE-INDUCED LIVER INJURY OCCURRING 22 MONTHS AFTER TREATMENT START

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Introduction

Drug-induced liver injury (DILI) is the most common cause of acute liver failure in high-income countries. Most cases involve idiosyncratic, immune-mediated mechanisms which are independent of the dose used ⁽¹⁾.

In population-based studies, the incidence of DILI ranges between 13.9 and 19.1 cases per 100,000 people per year ⁽¹⁾, a figure likely flawed by systematic underreporting.

Identification of the liable drug and its prompt discontinuation are critical to achieving patient recovery.

Azathioprine is an immunosuppressive drug that works by inhibiting lymphocyte proliferation, thus limiting inflammatory and autoimmune responses. Azathioprine is a well-known cause of DILI, with an incidence of 1 case per 1103 users ⁽²⁾.

Most cases of Azathioprine-induced liver injury have been reported between the first month ⁽³⁻⁵⁾ and the first year ⁽⁶⁻¹²⁾ of treatment, and only a few cases of DILI have been described in long-term users of Azathioprine ^(13, 14).

In the present report, we describe a severe case of Azathioprine-induced liver injury, occurring after 22 months of administration.

Case presentation

The patient is a 55-year-old woman. Her previous medical history include hypertension, I grade obesity (body weight 100 kg, height 181 cm, BMI 30.5 kg/m²), Hashimoto's thyroiditis with hypothyroidism, obstructive sleep apnea syndrome (OSAS). She was on long-term treatment with Lansoprazole, Levothyroxine, Candesartan and Verapamil.

In December 2019 the patient was diagnosed myasthenia gravis and subsequently started Azathioprine treatment. The drug was titrated to a dose of 300 mg/day (3 mg/kg/day), with a favorable clinical response.

Since the beginning of Azathioprine administration, the patient regularly attended follow-up consultations with her Neurologist and underwent systematic assessment of serum transaminase, gamma-GT and bilirubin levels, with unremarkable results.

In October 2021, due to scleral icterus the patient presented to the Emergency department of another Institution. Laboratory evaluation was consistent with acute cholestatic liver injury of uncertain etiology (total bilirubin 11.6 mg/dl ; direct bilirubin 4.1 mg/dl; AST 92 U/L; ALT 37 U/L). Abdomen CT scan showed a normal sized liver with regular margins, steatosis with an otherwise homogeneous parenchyma, undilated bile ducts, no splenomegaly, and some reactive lymph nodes at the hepatic hilum.

The patient was soon referred to our Liver Unit for continuation of care.

On physical examination she presented marked scleral and cutaneous jaundice and complained of abdominal discomfort and asthenia. On laboratory tests, we found a negative viral hepatitis panel (hepatitis A, B, C and E), negative autoimmune panel (antinuclear, anti-smooth muscle, antimitochondrial, and anti-LKM antibodies), negative CMV, EBV, HIV, HSV, VZV viral assays. Wilson's disease, hemochromatosis, primary sclerosing cholangitis and primary biliary cholangitis were excluded based on both laboratory and radiological findings.

During the hospitalization, we observed a progressive and marked rise of cholestasis markers, with a peak value of total bilirubin of 35.62 mg/dl (direct bilirubin 30.79 mg/dl), and marked increases of Gamma-GT and ALP levels, with peak values of 310 U/L (ULN 58 U/L) and 189 U/L (ULN 126 U/L), respectively. Serum aminotransferase levels were mildly elevated, with a peak value of 130 U/L for AST (ULN 36 U/L) and of 40 U/L for ALT (ULN 35 U/L), respectively.

Abdominal ultrasound examination showed normal sized liver with moderate steatosis and no focal lesions, physiological portal blood flow, normal spleen, and no biliary tree alterations. Subsequent Magnetic Resonance Cholangiography again showed no evidence of morphological alterations in the intrahepatic and extrahepatic bile ducts.

During hospitalization the patient temporarily developed acute kidney failure. Serum creatinin levels rose to 3.9 mg/dl (ULN 1.2 mg/dl), probably due to renal tubular injury of prerenal origin and hyperbilirubinemia. Following intravenous fluid administration and acidosis correction, serum creatinine returned to normal levels.

We suspected Azathioprine-induced liver injury, and on day 4 from admission the drug was withdrawn in agreement with the Neurologist.

At that time, the patient also developed Azathioprine myelotoxicity, with pancytopenia (Hb 7.7 g/dl; platelet count 27000/microliter; WBC 1760/microliter; Neutrophil count 310/microliter) requiring blood transfusion and Filgrastim administration.

In order to confirm the suspect of Azathioprine-induced injury, a liver biopsy was performed. The histological examination showed cholestasis, peri-cholangitis, mild bile duct injury, interface inflammation and steatosis. These findings were indicative of toxic/drug induced liver injury (figures 1 and 2).

After dismissing Azathioprine, we observed a marked improvement of cholestasis, with progressive reduction of serum levels of total bilirubin to 18 mg/dl, Gamma-GT value to 114 U/L on day 21 from drug withdrawal (figures 3, 4 and 5).

The patient was discharged from our Unit a few days later in good clinical conditions, with full recover from acute kidney failare and pancytopenia.

In the absence of any symptoms related to myasthenia, no specific therapy was introduced. No relapse was observed at the follow-up neurological visits.

The subsequent hepatological follow-up showed complete normalization of liver function, with normal values of bilirubin and cholestasis marker (ALP, Gamma-GT) on the latest laboratory test assessment in March 2022.

Discussion

DILI is the most common cause of acute liver failure in Western countries, with Azathioprine being one of the most frequent culprits.

Azathioprine is an immunosuppressant agent that inhibits lymphocyte proliferation, through its antagonistic effect to purine metabolism. It is used in the treatment of several autoimmune-mediated diseases such as myasthenia gravis, inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis, as well as in the anti-organ rejection ⁽¹⁵⁻¹⁸⁾.

Azathioprine-induced hepatotoxicity occurs secondary to depletion of glutathione, which results in mitochondrial injury, ATP depletion and hepatocyte necrosis ⁽¹⁹⁾.

Different forms of hepatotoxicity induced by Azathioprine have been described, including mild, transient, and asymptomatic elevation of serum aminotransferase levels, acute cholestatic injury and a chronic hepatic injury associated to peliosis hepatis, veno-occlusive disease or nodular regenerative hyperplasia ⁽²⁰⁾.

Acute cholestatic injury, is uncommon but not rare, and occurs in approximately one in a thousand treated people ⁽²⁰⁾. The patients present asthenia and jaundice that usually develop 1 to 12 months after starting the medication ⁽²⁰⁾.

It is important for clinicians to suspect and identify DILI when they face cases of acute hepatic injury, since prompt discontinuation of the involved drug is central to prevent irreversible liver damage or liver failure, and allow patient recovery ^(3–5, 7–10, 12, 13).

With this report, we suggest clinicians to retain high level of suspicion toward Azathioprine as the causative agent of liver injury. The lapse of time from starting of drug administration may be longer than commonly anticipated, and potential life-threatening hepatotoxicity should be expected even more than one year since treatment onset ⁽¹⁴⁾.

Likewise, when DILI is suspected and other causes of liver injury have been excluded, it seems reasonable to withhold Azathioprine treatment even before the histological report. This may optimize the chances of hepatic recovery in view of the long-lasting immunomodulating effect of the drug, which may persist several months following its discontinuation.

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