Severe mixed cholestatic-hepatocellular damage and myelotoxicity after administration of azathioprine to a patient with systemic lupus erythematosus

In this case, exclusion of other possible etiologic factors, and the observation of clinical and biochemical improvement after withdrawal of the drug strongly support the diagnosis of a reaction to AZA alone.

CASE REPORT

A 46-year old woman was hospitalized with overt jaundice, discoloration of the feces and hyperpigmentation of the urine. SLE had been diagnosed about one year earlier and she had been treated with methylprednisolone 20 mg/day per os and acenocumarol (because of a recent history of two mild ischemic strokes and a high titer of anticardiolipin antibodies), alendronate, vitamin D and calcium. Despite the supportive medical treatment the patient developed an osteoporotic fracture of the L2 vertebra a few months after the initiation of treatment with methylprednisolone. At that time the medication was modified, with the addition of low doses of AZA (50 mg/day, orally) and tapering of methylprednisolone. A week after the initiation of treatment with AZA, full blood count, serum electrolyte levels, coagulation studies and liver and renal function tests were within the expected ranges and AZA was increased to 100 mg/day, orally, while the dose of methylprednisolone was further reduced. Three weeks later the patient developed jaundice and was admitted in our department.

Physical examination showed obvious scleral and skin jaundice, but normal vital signs without new focal central neurological deficits. Chest X-ray and ECG showed no evidence of pulmonary or cardiac disease. The abdomen was soft and nontender and extended 3 cm below the right costal margin, the spleen was not palpable and there was no evidence of ascites.

The results of blood analysis were: wBC 1.8×10^9/L (38% neutrophils, 31% lymphocytes and 23% monocytes), Hct 32.2%, Hb 10.4 g/dL, PLT 398×10^9/L, erythrocyte sedimentation rate (ESR) 45, C-reactive protein (CRP) 64 mg/L (normal 0–5). The renal and thyroid function tests were normal, but liver function tests were as follows: ALT 521 Iu/L, AST 318 Iu/L, ALP 2792 Iu/L (normal 64–280), γ-GT 632 UI/L, bilirubin 35.79 mg/dL (direct 23.8 mg/dL) (normal 0.3–1.2), LDH 713 U/L (normal 200–460), cholesterol 689 mg/dL, direct Coombs test (−). The serological enzyme-linked immunosorbent assay (ELISA) was negative for HIV. Serological studies were also negative for HBV and HCV but detected IgG antibodies to CMV, EBV and HSV 1+2. Coagulation studies revealed an increased international normalized ratio (INR 5.9), which led to the withdrawal of acenocumarol and its replacement 4 days later with heparin of low molecular weight.
During hospitalization the levels of bilirubin and ALP increased further, reaching 42.41 mg/dL (direct 25.53 mg/dL) and 4252 IU/L, respectively, while the aminotransferases reached highs of ALT 709 IU/L and AST 253 IU/L, and the cholesterol rose as high as 936 mg/dL. At the same time the WBC count fell to a minimum of 800 (2.4% neutrophils, 72.6% lymphocytes and 20.2% monocytes). The patient’s autoimmune profile showed: ANA 1/80 (diffuse pattern), antiRo (+), C3 163, C4 89, RF 45, IgM ACL 39 MPLU/mL, and the rest within the normal range. Abdominal ultrasonogram (US) showed no clear evidence of intra- or extra-hepatic duct dilatation, gallstones, ascites or pancreatic disease. The portal cava-splenic system triplex revealed intact portal and hepatic veins with no evidence of stenosis or thrombosis. Computed tomography (CT) of the liver was normal as was the magnetic resonance cholangiopancreatography which was performed 2 days later. Bone marrow aspiration was performed which revealed no specific changes other than the elective absence of granulocytes.

Treatment with AZA was stopped immediately, and the patient started receiving prednisolone in a dose of 1 mg/kg/day iv. Her clinical and laboratory state improved progressively, with gradual decrease in ALT and AST, followed by decrease in the levels of ALP, γ-GT, bilirubin and cholesterol and a rise in the WBC count to the normal range. The patient refused to undergo liver biopsy and she was discharged approximately one month later. The following 12 months she remained asymptomatic and her biochemical profile returned to normal.

**DISCUSSION**

SLE is a chronic autoimmune disease characterised by multisystem involvement and diverse clinical and serological manifestations. Clinically significant hepatic disease is generally regarded as unusual in SLE, although patients with SLE have a 25–50% chance of developing abnormal liver tests in their lifetime. Treatment with potentially hepatotoxic drugs (non-steroidal anti-inflammatory medication, aspirin, AZA) or viral hepatitis have usually been implicated as the main causes of liver disease in patients with SLE, although portal and periportal hepatitis reflecting SLE activity is also a possibility. Hepatitis resulting from SLE is most likely to be insidious in onset and varying in severity, and is frequently associated with specific autoantibodies such as anti-double-stranded DNA and anti-ribosomal P antibodies, and with features of autoimmunity such as polyarthralgia, hypergammaglobulinemia and positive anti-nuclear antibodies (ANA).

Liver disease in SLE can also be related to antiphospholipid antibodies, which are associated with the Budd-Chiari syndrome, veno-occlusive disease, nodular regenerative hyperplasia, liver infarction and transient elevation of hepatic enzymes resulting from multiple fibrin thrombi. Other liver abnormalities associated with SLE are perihepatitis, primary biliary cirrhosis, granulomatous hepatitis, lupoid hepatitis (a form of chronic active hepatitis often associated with anti-mitochondrial and anti-smooth muscle antibodies), Cryptococcus infection of the liver, chronic hepatitis with IgA or IgD deficiency, arteritis, porphyria or idiopathic portal hypertension. Jaundice in SLE is mainly due to hemolytic anemia and viral hepatitis; cirrhosis and obstructive jaundice from a biliary or pancreatic tumor are responsible for the remainder of cases.

Hematological changes, including anemia, leucopenia and thrombocytopenia, occur in more than one half of patients with SLE. Anemia of various types constitutes the most common hematological abnormality seen in SLE, including the anemia of chronic disease, auto-immune hemolytic anemia and hypoplastic anemia. Leucopenia affects both granulocytic and lymphocytic lines and may be caused by autoantibodies. The influence of drugs, hypersplenism and bone marrow suppression are also possible. Thrombocytopenia occurs frequently and is generally autoimmune in origin.

AZA is an orally administered purine analogue commonly used in the setting of various autoimmune diseases, and inflammatory bowel disease and organ transplantation. Toxic side effects of AZA include myelosuppression, increased susceptibility to infection, gastrointestinal intolerance, stomatitis, hepatotoxicity and increased risk of lymphoproliferative disorders. Hepatotoxicity is a rare but serious complication of its use. The cases reported can be etiologically grouped into three categories: hypersensitivity, idiosyncratic cholestatic reaction, and presumed endothelial cell injury with resultant raised portal pressures, veno-occlusive disease or peliosis hepatic.

AZA undergoes rapid non-enzymatic conversion in the liver, yielding 6-mercaptopurine (6-MP), its active metabolite. Following intracellular uptake, 6-MP is metabolized by three enzymes, namely xanthine oxidase, thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyltransferase, and is transformed into the pharmacologically active 6-TGs. Several of these metabolites have been held responsible for induction of adverse events. TPMT plays a key role in the bioavailability of 6-TG. In addition, TPMT activity is affected by genetic polymorphism with 90% of the population having high and 10% intermediate or low activity of the enzyme. Patients with low TPMT activity are at risk for sudden onset of severe myelosuppression, occurring between 4 and 10 weeks after starting AZA. However, myelotoxicity can also occur in the presence of normal TPMT activity. Patients with intermediate activity...
have more frequent adverse gastrointestinal system side effects.\textsuperscript{13,14}

The patient described here developed severe mixed cholestatic and hepatocellular damage, along with leucopenia, in the setting of SLE under treatment with AZA. The severity of the hepatic reaction was indicated by the very high titers of the enzymes that reflect both hepatocellular and cholestatic involvement. Of great interest is that ALP was as high as 4252 uI/L and bibirubin 42.41 mg/dL (direct 25.53 mg/dl) which, to our knowledge, has never been reported before in similar cases. Clinical and laboratory evaluation excluded sepsis, viral hepatitis, hemolysis, extrahepatic bile duct obstruction or the simultaneous administration of another known hepatotoxic drug. In addition no evidence of stenosis or thrombosis of the portal or hepatic veins was found. On the other hand the patient did not have fever, polyarthralgia, rash, elevated titers of anti-double-stranded DNA or hypocomplementemia, findings that are characteristic of lupus flare, before the onset of leucopenia and liver abnormalities. Measurement of TPMT activity was not possible in any laboratory in our country at that time. Although the diagnosis was not supported by biopsy findings, due to refusal of the patient, the exclusion of other possible etiologic factors, together with clinical and biochemical improvement observed after withdrawal of the drug, strongly support a severe idiosyncratic reaction to AZA alone as the cause of the hepatocellular damage and leucopenia. It is proposed that physicians should in similar cases of otherwise unexplained clinical or biochemical disorder consider the possibility of a severe drug reaction to AZA.

References


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