Azathioprine Induced Severe Cholestatic Hepatitis In A Crohn's Disease Patient.

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Citation

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Abstract

Severe cholestasis with azathioprine is rare. Azathioprine induced severe cholestasis has been reported in children but not in adults. We report a 30 years old female with Crohn's disease who after a recent escalation of her maintenance dose of azathioprine presented with severe cholestasis, which improved after withholding the drug.

CASE

A 30 year-old female patient with Crohn's disease presented with deep jaundice and abnormal liver enzymes for 2 weeks of duration. She was diagnosed with Crohn's disease in 2002 and was on maintenance dose of azathioprine (AZA) 100mg daily. The patient had history of itching for the same duration. The patient denied any history of fever, rigors or chills. Four weeks before the presentation with jaundice, patient had exacerbation of the symptoms of the Crohn's disease in the form of diarrhoea 6 to 8 times per day associated with blood and mucous with the stools. Colonoscopy revealed pancolitis and was started on prednisolone, 40 mg daily, pentasa 1 gm qid, ciprofloxacin 500 mg bid. Azathioprine was increased from 100 mg to 200 mg daily. The patient's diarrhoea improved and prednisolone was tapered over a period of 8 weeks time.

Investigations showed liver function tests; AST of 65 U/L (normal, 0–37 U/L), ALT of 74 U/L (0–37 U/L), alkaline phosphatase of 180 U/L (36–110 U/L), and -feto protein of 15 g/L (0–20 g/L). The total bilirubin was 185 mol/L (0–17 umol/L); direct bilirubin, 156.3 mol/L (0–5 mol/L), albumin, 22 g/L (33–53 g/L); APTT; 66.49 seconds (27¬¬-41); PT 24.2 (11–114); INR, 2.2 (0.8–1.2); white cell count, 2,02; platelet count, 162; and hemoglobin,10.85 g/dl (12–16). ESR, 32 mm/h (0-20); CRP; 121; Ceruloplasmin, 0.603 g/L (0.2 -0.6). Viral serology, anti. HAV-total negative, HAV IgM, negative. HBsAg, negative; AntiHBs, 100 IU/L; Anti HCV, negative; Cryoglobulin levels, negative. ANA, ASMA, LKM, AMA, were negative. ASCA IgG, 83.1 (0-24); ASCA IgA, 34.4 (0-24); ANCA, Negative. Abdominal ultrasound showed the liver span measures about 15 cm, homogeneous echotexture. No focal liver lesion or biliary ductal dilatation. The gallbladder was contracted. No pericholecystic fluid. No evidence of intra or extra hepatic biliary dilatation. On color Doppler, portal vein, IVC, and hepatic veins were patent and showed normal waveform. CT scan abdomen with intravenous and oral contrast revealed liver enlarged in size measuring 20 cm in its craniocaudal dimensions with no focal liver lesion seen. The gallbladder was normal. No intra or extra hepatic biliary ductal dilatation. There was circumferential thickening of the descending colon reaching up to the proximal hepatic flexure. Also the distal third of the ileum showed circumferential wall thickening with a maximum thickness of 9.3 mm. Liver biopsy showed portal and peripotal inflammation with no evidence of primary sclerosing cholangitis (PSC).

Azathioprine was put on hold and liver function tests were monitored, the itching and jaundice improved and there was a progressive downward trend of the liver enzymes and the last liver function tests after 6 weeks showed AST of 27 U/L, ALT of 28 U/L, alkaline phosphatase of 114 U/L, total bilirubin, 16 mol/L; direct bilirubin, 10 mol/L and serum albumin, 22 g/L.

DISCUSSION

There are many causes of cholestasis in patients with Crohn's disease. PSC can occur in 5% of patients of Crohn's disease and ultrasound will show biliary dilatation and strictures. The cholestasis in PSC is progressive and will not be completely reversible even after urosodeoxycholic acid (UDCA) and biliary intervention. The biopsy in PSC will be

diagnostic.

Our patient had complete reversal of the cholestasis and her liver function tests became completely normal within 6 weeks time. Ultrasound did not show any biliary dilatation. Hepatitis serology for hepatitis virus B and virus C were negative. Autoimmune serology was negative. There was no ductopenia or features of PSC on liver biopsy.

In Crohn's disease patients, AZA treatment can induce abnormality of liver function tests in a relatively high proportion of the cases, but the development of true hepatotoxicity is rare. Most of the patients present with a slight elevation of liver function tests that improve without stopping the medication. [1]

Azathioprine can produce liver injury due to direct toxic effect that is dose dependent and can be reversed by stopping the offending agent. [2, 4] Other mechanisms by which azathioprine can induce liver injury is idiosyncratic drug reaction which is infrequent and unpredictable and is not dose dependent. [3] This reaction is associated with hypersensitivity reaction such as rash, arthragia and leucocytosis. [6] A small percentage of patients with azathioprine present with a slight elevation of liver function tests that do not have clinical implications and liver function tests return to normal values during the follow-up. [7, 8] Our patient had a dose dependent azathioprine induced cholestasis which happened after a recent increase in the dose of the offending drug and improved with stopping the azathioprine.

References

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