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Mesalamine induced hepatotoxicity. Is mesalamine safe?

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Dear Editor:

Mesalamine is used widely in the treatment of patients with ulcerative colitis (UC). Although this drug is considered safe, it is not without adverse effects; hepatotoxicity has been reported with an incidence of 0-4%. The clinical picture we present includes laboratory, imaging, and histological findings on a patient with hepatotoxicity due to mesalamine.

Case report

A 79-year-old woman presented with a history of total thyroidectomy for thyroid cancer. In the context of chronic diarrhea, a left-sided UC was suspected, and oral mesalamine 4 g per day, and mesalamine suppositories were initiated. Before starting treatment, she had normal liver test results. After a period of three months, she presented with headache,

fatigue, and intermittent low fever. Her laboratory tests showed a normal blood count, a liver profile with a cholestatic pattern (Fig. 1A), and elevation of inflammatory parameters. Mesalamine was suspended, and an extensive study was performed with serology for hepatitis A, B, C, and E, Cytomegalovirus, and Epstein Barr viruses. Antinuclear, antimitochondrial, and antismooth muscle antibody test results were all negative, with normal immunoglobulin count and subclasses. Magnetic Resonance Imaging (MRI) reported intra and extrahepatic bile duct dilation without obstruction, and thickening of the intrahepatic bile duct (Fig. 1B-C). She progressed with worsening of the liver profile without signs of liver failure. A liver biopsy was performed (Fig. 1D-F), which showed non-suppurative cholangitis with granulomas and focal concentric fibrosis related to medium-caliber bile ducts, and IgG4 stain was negative. QuantiFERON®-TB-Gold was negative, and angiotensin-converting enzyme activity in the normal range. We initiated ursodeoxycholic acid with good initial response, but after a 13-week period the patient presented with a new slight elevation of liver enzymes, so a short course of prednisone was administered. MRI changes disappeared, systemic symptoms subsided, but cholestasis regression was slow, so bezafibrate was added to therapy. In follow-up, no diarrhea, fecal calprotectine was normal, and colonoscopy ruled out UC. The patient presented improvement of her liver profile to a near-normal degree at 50 weeks after drug withdrawal.

Discussion

Although mesalamine induced hepatotoxicity has low incidence, it should be suspected in a patient receiving this drug with sudden liver profile alteration. Since patient had normal liver tests prior to starting mesalamine, a negative autoimmune serology and non-compatible MRI and liver biopsy findings, Primary Sclerosing Cholangitis was ruled out. Among histopathological findings reported in the literature, the presence of non-caseating granulomas is a frequent finding.

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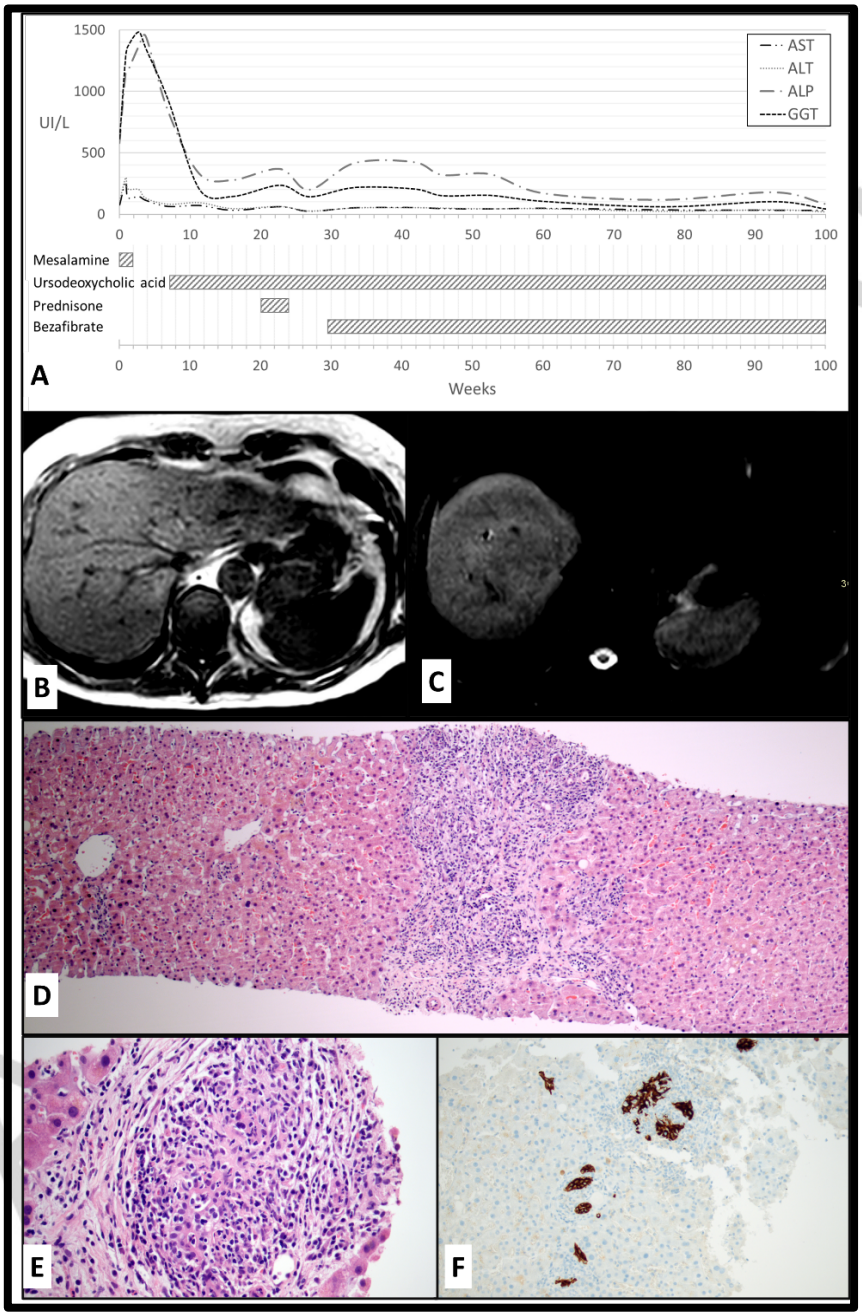

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Figure 1

Fig. 1. A. Evolution of liver tests during follow-up. (A-Top) Shows a predominantly cholestatic pattern. (A-Bottom) Shows relevant medication received by the patient: bars show the time-period the patient received each medication. B. GRE axial T1-wheighted MRI showing intrahepatic bile duct dilation. C. Axial T2-wheighted MRI showing intrahepatic bile duct diffuse hyperintensity and dilation. D. Wide portal spaces secondary to predominantly mononuclear infiltrate. E. Portal space with mononuclear infiltrate with granulomatous reaction in relation to the bile duct. F. Portal spaces with evident ductal damage. AST: aspartate aminotransferase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, GRE: Gradient Recalled Echo, MRI: Magnetic Resonance Imaging.