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Non-cirrhotic portal hypertension due to 6-mercaptopurine use for Crohn's disease

Suresh Pola, MD^{1,*}, Brigid S. Boland, MD^{1,*}, Grace Y. Lin, MD, PhD³, Alexander Kuo, MD², and William J Sandborn, MD¹

¹Inflammatory Bowel Disease Center, University of California San Diego and UC San Diego Health System, La Jolla, California, USA

²Section of Hepatology, Division of Gastroenterology, University of California San Diego and UC San Diego Health System, La Jolla, California, USA

³Department of Pathology, University of California San Diego and UC San Diego Health System, La Jolla, California, USA

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To the Editor

A 12-year-old boy was diagnosed with Crohn's disease (CD) of the colon and was given 50 milligrams (1.3 mg/kg) of 6-mercaptopurine (6-MP) daily. His TPMT enzyme activity was normal. His dose was subsequently increased to 1.9 mg/kg for persistent symptoms. One year later, a 6-thioguanine (6-TGN) concentration was elevated at 434 pmol/8x10⁸ RBCs (normal range 230–400) and a 6-methyl-mercaptopurine concentration was 4699 pmol/8x10⁸ RBCs. Three years after starting 6-MP, his leukocyte count dropped to 3.8 x 1000/mm³ with platelet count of 118 x 1000/mm³ with normal liver aminotransferases. 6-MP was discontinued, but his platelet and leukocyte count remained low. A bone marrow biopsy was normal. Since he was asymptomatic, he was monitored off medications.

Two years later, he developed abdominal pain and weight loss.

Esophagogastroduodenoscopy revealed esophageal varices and portal hypertensive gastropathy. Colonoscopy revealed severe CD with deep ulcers throughout the colon. Pathology showed severely active chronic colitis with granulomas but negative CMV immunostaining. Magnetic resonance cholangiopancreatography showed no biliary dilatation. A transjugular liver biopsy revealed features of nodular regenerative hyperplasia with portal fibrosis.

Corresponding Author: William J. Sandborn, M.D., Division of Gastroenterology, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093-0956, Telephone (858) 657-5284, Fax (858) 657-5022, wsandborn@ucsd.edu.

*These authors contributed equally

Discussion

The low power impression of nodularity and early bridging fibrosis suggest non-cirrhotic portal hypertension (NCPH). The differential diagnosis of NCPH includes nodular regenerative hyperplasia (NRH), hepatoportal sclerosis, and incomplete septal cirrhosis; however, these entities are heterogeneous with considerable overlap[1].

The typical diffuse micronodules in NRH formed by alternating atrophic and hyperplastic areas of hepatic parenchyma are not well developed in this biopsy, and the presence of fibrosis typically excludes NRH[2]. While his biopsy shows fibrous expansion suggesting hepatoportal sclerosis, definitive portal vein sclerosis is not present. To date, there has been a single case report of hepatoportal sclerosis in a patient with CD treated with 6-MP[3], and another case attributed to azathioprine therapy following renal transplantation[4]. Incomplete septal cirrhosis is characterized by subtle nodules with hypoplastic portal tracts and hyperplastic hepatocytes with thin septal fibrosis that may be consistent with this biopsy [5].

Thiopurines such as 6-MP and azathioprine are widely used in patients with CD, and thiopurine related toxicities include bone marrow suppression and drug induced hepatitis. While bone marrow suppression is typically dose-dependent, hepatotoxicity can be idiosyncratic in the setting of hypersensitivity and may present with either cholestatic or hepatocellular patterns of injury. In patients treated with thioguanine, a closely related thiopurine, a high proportion showed signs of NRH[6]. Azathioprine is now recognized as a risk factor for development of nodular regenerative hyperplasia with a risk of 0.5% at 5 years[7].

The present case represents an instance of NCPH with overlap features of both NRH and hepatoportal sclerosis. The hepatotoxicity with leukopenia was not reversible with the cessation of 6-MP. The safety of increasing the dose of 6-mercaptopurine above a maximum of 1–1.5 mg/kg or of azathioprine above a maximum of 2–3 mg/kg has not been established, and dose reduction should be undertaken if 6-TGN concentrations are elevated. Clinicians must carefully monitor patients' liver chemistries and complete blood counts in patients receiving thiopurines for signs of liver disease, including evidence of portal hypertension in the setting of preserved hepatic synthetic function.

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