SHORT REPORT

Mercaptopurine-induced hepatoporal sclerosis in a patient with Crohn's disease

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Abstract

Thiopurines play a pivotal role in the management of inflammatory bowel disease. Azathioprine and mercaptopurine have been associated with a number of liver abnormalities, including hepatitis, veno-occlusive disease, nodular regenerative hyperplasia, and peliosis hepatitis. Patients treated with azathioprine and mercaptopurine have their liver chemistry tests routinely checked due to this potential for hepatotoxicity. Hepatoporal sclerosis is a cause of non-cirrhotic portal hypertension that is increasingly being recognized; its etiopathogenesis is not well defined. We present the first case report of mercaptopurine-induced hepatoporal sclerosis leading to non-cirrhotic portal hypertension in a patient with Crohn's disease. He had been treated with mercaptopurine for five years, and his liver chemistry tests were always within normal limits. This case underscores the potential serious liver adverse events that may arise silently and go undetected during treatment with mercaptopurine, and should alert clinicians as to the potential need to discontinue mercaptopurine in this setting.

1. Introduction

Thiopurines, such as azathioprine (AZA) and mercaptopurine (MP), are widely used in the treatment of inflammatory bowel disease (IBD). They are effective and potent medications, which can have significant toxicity, which are major obstacles to their long term use. Liver toxicity is a well-recognized phenomenon that
Physicians often rely on liver chemistry testing in order to detect hepatotoxicity. However, some of these complications may occur without prior or ongoing laboratory abnormalities. We present a case of hepatoportal sclerosis (HPS) leading to non-cirrhotic portal hypertension in a patient with Crohn’s disease who was treated with MP for many years without having alterations in liver chemistry tests. HPS is a cause of non-cirrhotic portal hypertension that is being increasingly recognized in light of its association with didanosine use in patients with HIV. This case highlights a new serious complication of MP use, and also suggests for HPS a similar etiopathogenesis as nodular regenerative hyperplasia (NRH).

2. Case report

A 23-year-old white male with a history of Crohn’s disease was transferred from an outside hospital for treatment of a partial small bowel obstruction in addition to an intra-abdominal abscess. The patient was diagnosed with Crohn’s disease at age 12 and had ileo-colonic involvement with a spontaneous perforation (that was managed conservatively with intravenous antibiotics) in the remote past. He had been previously treated with aminosalicylates and was started on MP at age 17, undergoing a prolonged period of remission. Eight months prior to the current admission, the patient developed epistaxis and was first found to have thrombocytopenia, splenomegaly and abnormal liver chemistries as follows: AP 164 μ/L, BR 0.5 mg/dL, ALT 62 μ/L, AST 14 μ/L and platelet count 141 × 10^9/μL. At that time, MP was discontinued, and the liver enzyme abnormalities gradually returned to normal within three weeks. Of note, during the 5-year period that the patient was treated with MP, he was regularly followed by his gastroenterologist and had frequent liver chemistry tests that were always normal.

Two weeks prior to the current hospitalization, he was admitted to the hospital with a partial small bowel obstruction. This episode was medically managed, and he was treated with bowel rest, steroids and antibiotics. Upon resolution of the obstruction, he received a single dose of infliximab and was discharged home. His medical course was complicated by the development of severe abdominal pain, nausea and vomiting 4 days after his hospital discharge. A CT scan of his abdomen was significant for a partial small bowel obstruction, a 7 cm anterior intra-abdominal abscess, a small retroperitoneal fluid collection, splenomegaly and ascites. He was then transferred to our hospital for further management. On admission, the patient was noted to have significant abdominal distention and tenderness, and pitting leg edema, although no cutaneous stigmata of chronic liver disease were observed on physical exam. His labs were significant for leukocytosis, microcytic anemia, and a normal platelet count. The liver chemistry tests were significant only for a low albumin (3.0 g/dL) and a slightly prolonged prothrombin time (17.2 s). The patient was treated with bowel rest and antibiotics. On hospital day 2, he underwent CT-guided drainage of the anterior abdominal abscess, which yielded 90 mL of purulent material. A diagnostic paracentesis was done as well, and analysis of the ascitic fluid was consistent with portal hypertension (serum ascites albumin gradient greater than 1.1 g/dL) and negative for spontaneous bacterial peritonitis.

During his hospital course, the patient underwent three large volume paracenteses and was started on diuretics for persistent ascites. An extensive work up to establish the etiology of the portal hypertension was initiated. The patient had no prior history or family history of liver disease. He denied the intake of alcohol or the use of recreational, over the counter or herbal drugs. An abdominal ultrasound with Doppler flow was negative for portal/hepatic/splenic vein thrombosis but showed portal hypertension and liver nodularity suggestive of cirrhosis. Subsequent testing for viral hepatitis, Wilson’s disease, alpha-1 antitrypsin deficiency, hemochromatosis, and autoimmune hepatitis was unrevealing. An MRCP to evaluate for sclerosing cholangitis showed normal bile ducts, a heterogeneous hepatic parenchyma and nodularity.

A trans-jugular liver biopsy was performed, and portal pressure measurements were consistent with portal hypertension. The biopsy showed HPS, with thickened, herniated portal venules and capillarization of sinusoids (Fig. 1), with no evidence of cirrhosis, biliary obstruction or drug-induced liver injury. The patient underwent a surveillance upper endoscopy for varices and was found to have grade 1–2 distal esophageal varices as well as gastric varices; he was started on nadolol. Sixteen months after the patient’s discharge from the hospital his Crohn’s disease has remained in remission and his liver chemistry tests have been normal with the ascites well controlled with diuretics.

3. Discussion

Thiopurines are immunomodulators that have been widely used in transplant medicine, cancer chemotherapy, and are currently an integral part in the treatment of IBD. AZA/MP are nucleotide metabolites incorporated into cellular nucleic acids leading to inhibition of de novo purine synthesis, which explains their cytotoxic and immunosuppressive properties.

**Figure 1** Needle liver biopsy. Photomicrograph of a representative portal tract and the surrounding periporal area. Note the abnormally dilated vascular structures (asterisks) in the periporal spaces representing either herniation of the portal vein branches or some probably representing markedly dilated sinusoids. The area where the portal vein should be normally located is obliterated by fibrous tissue (arrow). (H&E, original magnification 40×.)
They have been shown to induce and maintain remission in IBD patients in whom corticosteroids cannot be tapered or discontinued. These drugs are recognized steroid-sparing agents, as they allow the withdrawal of steroids, thus preventing the long term side effects of chronic steroid use. However, there are many caveats to their use since patients tend to be treated for a prolonged period of time, as the risk of recurrence increases once treatment is discontinued and, the optimal duration of therapy has not been determined. A major drawback in using these drugs is related to their significant toxicity profile.

In most clinical trials, as many as 15% of patients had their treatment discontinued as a result of both the short term and long term toxicities of AZA/MP. The adverse events can be divided into those that are dose independent and those that are dose-dependent. The drug-independent effects usually develop within 2–4 weeks of treatment, and can present as allergic reactions, or idiosyncratic phenomena such as drug-induced pancreatitis. These toxicities cannot be reliably predicted by monitoring blood counts or measuring metabolite concentrations. Among the dose-dependent toxicities, the most recognized and potentially lethal toxicity is myelosuppression. Drug-induced hepatitis can result from either a hypersensitivity phenomena or a dose-dependent effect. The use of 6-TGN in IBD patients is being increasingly explored for its presumed hepatotoxic profile, as it has been linked to the development of NRH and non-cirrhotic portal hypertension.

The incidence of hepatotoxicity was initially reported to be as low as 0.3% by Present et al. In a more recent systematic review of the literature, Gisbert et al. estimated the incidence of hepatotoxicity in IBD patients given AZA/MP to be approximately 1% per patient per year of treatment. Most of these cases occurred during the first 6 months of treatment. However, there is significant variability among case series, which probably results from the lack of standardized definitions, and difficulties in diagnosis given the absence of specific markers or tests. Furthermore, these calculated rates are estimated from retrospective studies with relatively low numbers of patients and limited follow up.

A number of liver abnormalities have been described in patients taking AZA/MP. These range from mild and transient derangements of liver chemistry tests that resolve upon reduction or discontinuation of therapy, to more severe forms with variable prognoses. They can be divided into dose-independent hypersensitivity reactions such as acute hepatitis and idiosyncratic cholestatic hepatitis, which are usually associated with biochemical abnormalities of liver chemistry tests, and dose-dependent endothelial cell injury such as NRH, veno-occlusive disease, and peliosis hepatitis. HPS has previously been noted in patients taking AZA but not MP. The main clinical manifestation of these vascular lesions is portal hypertension. The diagnosis of thiopurine-induced liver toxicity is usually made in the setting of liver chemistry abnormalities that arise with treatment and that resolve upon drug withdrawal, and with relapse upon re-introduction of the offending agent. However, these dose-dependent adverse events may occasionally present without prior liver enzyme abnormalities, making its diagnosis more difficult.

HPS has been documented in patients treated with azathioprine following renal transplantation. The current case is the first reported of HPS induced by MP in a patient with IBD. HPS is a clinico-pathologic entity associated with non-cirrhotic portal hypertension. It was first described by Mikkelsen in 1965, and is also known as idiopathic portal hypertension in Japan, and non-cirrhotic portal fibrosis in India. The primary lesion consists of fibrotic, sclerosed, and obliterated portal vein branches (phlebosclerosis), which are found in portal tracts, and are associated with marked dilatation of sinusoids (megasinusoids). The diagnosis is based on the presence of portal hypertension with normal or near normal liver chemistry tests, a non-cirrhotic liver, and portal fibrosis without diffuse nodule formation on liver biopsy. Portal vein thrombosis can be seen in some patients. Often the histological changes of HPS can be very subtle and the liver biopsy may be read as being normal, especially in the absence of an adequately-sized specimen. It is crucial for the clinician to communicate with the pathologist the clinical suspicion of portal hypertension. Early changes described in patients with HPS include lymphoid cell infiltration of the portal tracts and sub-endothelial regions of portal vein branches. Portal veins may be thickened to an extent that they start resembling the adjoining hepatic arterioles of the corresponding portal tract. Patients usually present with complications of portal hypertension such as ascites, variceal bleeding, and splenomegaly with or without hypersplenism; treatment is symptomatic. However, recent reports have shown that a subset of these patients may develop hepatic synthetic compromise in addition to portal hypertension, necessitating liver transplantation. All patients in these series were felt to have other etiologies for their decompensated liver disease; HPS was unrecognized prior to transplantation. None of these cases of HPS was directly ascribable to MP use.

This case highlights the potential severe and irreversible adverse events that can result from prolonged treatment with AZA/MP. In the renal transplant literature, most of the cases of dose-dependent hepatotoxicity induced by azathioprine occurred after many years of treatment (4–6 years), which reinforces a probable dose- and time-dependent effect. However, as mentioned above, most of the literature in the IBD population is based on retrospective studies with very short follow up. There has been one prospective study assessing the rate and risk factors associated with thiopurine-induced liver injury in IBD patients. This study followed a cohort of 161 IBD patients with median follow up of 271 days, and found that liver chemistry abnormalities were present in 13% of patients, and hepatotoxicity defined by elevation of liver enzymes above pre-determined parameters, was present in 10% of their cohort, necessitating treatment withdrawal in 75% of them. A percentage of patients were able to continue optimal doses of AZA/MP after dose adjustment and monitoring of liver chemistries. However, this strategy may be problematic and risky, as the long term cumulative effect of these drugs has not been well defined, especially in patients who present with liver chemistry abnormalities, suggesting an underlying susceptibility to the toxic effects of AZA/MP.

The current case also raises the question of how to best predict and prevent liver damage in patients treated with AZA/MP. It is recommended to check liver enzymes regularly during the treatment course, and to either decrease or discontinue these medications if abnormalities arise. This common practice allows for early detection of dose-independent hypersensitivity reactions. However, as demonstrated by this case report, dose-
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dependent toxicities such as HPS may develop silently without abnormalities in liver chemistries, highlighting the importance of determining better methods for early detection of these potential severe and irreversible toxicities. It is yet to be determined if genetic testing or monitoring drug levels will have an impact on these type of events. It is also important to determine when and in which circumstances these patients should undergo liver biopsy. There are no guidelines for surveillance of the development of portal hypertension in patients receiving long-term MP use. Periodic Doppler ultrasonography will detect established portal hypertension but may miss the gradual development of elevated portal pressures. Detection of portal vein thrombosis or increasing spleen size may be helpful for early detection. When available, serial transient elastography measurements (Fibroscan) might detect the interval development of fibrosis suggestive of HPS or NRH.

This is the first case report of MP induced HPS leading to portal hypertension in an IBD patient. It thus seems that HPS may have a similar etiopathogenesis as NRH, which is also a cause of drug-induced liver injury due to a hepatic vascular endothelial insult. Both can be seen concurrently within the same liver biopsy and both have been associated with didanosine use in patients with HIV. A recent report of a patient developing HPS in paired liver biopsies showing portal venule endothelitis and central venuliitis that progressed to well established portal venopathy despite resolution of the acute endothelial injury, suggests that in some cases HPS may not be reversible.

Conflict of interest

None of the authors have a conflict of interest with the production of this manuscript.

All the authors contributed in caring for the patients and in writing and reviewing this manuscript.

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