Nodular regenerative hyperplasia of the liver secondary to azathioprine in a patient with inflammatory bowel disease

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Abstract

A case of dramatic portal hypertension with massive ascites and splenomegaly is described in a patient with inflammatory bowel disease receiving azathioprine therapy. Liver biopsy confirmed the subtle changes of nodular regenerative hyperplasia and the patient recovered following withdrawal of the azathioprine and commencement of spironolactone. Thrombocytopenia is an early clue to azathioprine-induced nodular regenerative hyperplasia of the liver.

Case report

The patient, a 54-year-old Caucasian male, was initially diagnosed with ulcerative colitis in 1983. He subsequently failed medical therapy and underwent a panproctocolectomy and ileal pouch anal anastomosis in 1988. Thereafter he developed anal stenosis and perianal disease leading to a change in diagnosis to Crohn’s disease with small bowel disease later being confirmed by capsule endoscopy in 2006.

Azathioprine was commenced at this time and due to ongoing symptoms the dose was increased eventually to 3.5 mg/kg over 18 months. The patient subsequently presented in September 2007 with abdominal swelling and a CT scan (Figure 1) revealed ascites and splenomegaly. In retrospect, he had been mildly thrombocytopenic for 2 months prior to the onset of his symptoms.

Figure 1. Coronal CT scan of the abdomen showing marked ascites and splenomegaly
A trans-jugular liver biopsy was performed. A reticulin stain (Figure 2, 100× magnification) revealing a subtle nodular pattern with some double hepatocyte plates but without fibrosis; all in keeping with a diagnosis of NRH due to azathioprine therapy. No vascular thrombi or portal tract changes were identified. The intervening parenchyma showed focal sinusoidal dilatation and some hepatocyte atrophy suggesting uneven perfusion.

**Figure 2.** Reticulin stain of transjugular liver biopsy (100× magnification) showing a subtle nodular pattern with some double hepatocyte plates but without fibrosis

The patient was managed with large volume paracentesis, spironolactone and cessation of the azathioprine and his ascites and thrombocytopenia resolved.

**Discussion**

The inflammatory bowel diseases (IBD)—Crohn’s disease (CD) and ulcerative colitis (UC)—are chronic relapsing-remitting inflammatory diseases of the gastrointestinal tract. Their incidence is rising rapidly in New Zealand for unknown reasons,1,2 and treatment (particularly medical maintenance of remission) is challenging.
The thiopurines azathioprine and 6-mercaptopurine are frequently used to maintain remission in IBD. Thiopurine therapy\textsuperscript{3} and IBD\textsuperscript{4} are both associated with hepatic pathology, including nodular regenerative hyperplasia (NRH) of the liver.

It has been estimated that the cumulative risk of developing NRH when receiving a thiopurine for 5 years is approximately 0.5\%.\textsuperscript{5} NRH is defined as a diffuse distribution of hepatocellular nodules in the absence of fibrous septae.

NRH has been documented as occurring in association with a wide variety of hepatic and systemic diseases.\textsuperscript{6} Many of these conditions have a disturbed hepatic blood flow in common and it seems that NRH is a non-specific tissue adaptation to a heterogenous distribution of blood flow.

The clinical features are variable and symptoms, if present, are mainly associated with the complications of portal hypertension such as splenomegalgy, ascites and oesophageal varices. This will often lead to delayed diagnosis but thrombocytopenia will almost always be observed on routine full blood counts which should be performed 3-monthly for patients taking long-term thiopurine therapy.

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**References:**