

Nodular Regenerative Hyperplasia: A Rare Complication of Treatment with Thiopurines in Patients with Crohn's Disease

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Abstract

A 25-year-old male with ileal pre-anastomotic recurrence of Crohn's disease (CD) experienced nodular regenerative hyperplasia (NRH) secondary to treatment with azathioprine (AZA). The subject showed increase in cholestasis indices and a reduction in platelets. The diagnosis of NRH was established by liver biopsy; outcome was favourable after treatment discontinuation, with complete normalization of liver function tests within less than one year.

Keywords: Nodular regenerative hyperplasia; Crohn's disease; Thiopurines; Hepatotoxicity

Introduction

Nodular regenerative hyperplasia (NRH) is a relatively rare benign lesion of the liver characterized by diffuse nodular transformation of the liver parenchyma, without significant fibrosis [1]. Although it is a benign condition, it could be a cause of portal hypertension, and in rare cases of liver failure [2]. The pathogenesis of NRH has not been fully elucidated. It is believed to be a hyperproliferative response to an altered perfusion of the hepatic parenchyma and an obstructive portal venopathy [3], however a direct damage of endothelial sinusoidal cells has been also postulated [4]. The diagnosis of NRH can be very challenging. There are no specific diagnostic features of NRH on imaging studies. The diagnosis is made usually by liver biopsy. Histologically, the liver parenchyma is diffusely nodular, with small regenerative nodules compressing the surrounding parenchyma that shows atrophic cell plates and dilated sinusoids. Portal tracts are usually unremarkable, and no bile duct injury or significant inflammation are present [5,6] NRH may have a prolonged silent clinical course. When symptomatic, patients develop cholestasis with elevated alkaline phosphatases and/or signs of portal hypertension that may dominate the presentation and course of disease.

NRH is associated with a number of underlying conditions, including rheumatoid arthritis, systemic lupus erythematosus, primary hypogammaglobulinemia, hematologic disorders (including aplastic anemia, polycythemia vera, and idiopathic thrombocytopenic purpura), primary biliary diseases and treatment with thiopurines for inflammatory bowel disease (treatment with azathioprine [AZA], 6-mercaptopurine [6-MP] or 6-thioguanine [6-TG]) [1,7-9].

Thiopurines are immunomodulators with potent immunosuppressive and cytostatic effect, administered in patients with Crohn's disease (CD) and ulcerative colitis (UC). Side effects of these drugs are common and may be cause of treatment discontinuation up to 20% of patients. Currently, they are classified in allergic or

idiosyncratic and dose-dependent adverse effects [10]. Hepatotoxicity is observed up to 3.5% of patients treated with thiopurines and it is usually classified into three major syndromes: hypersensitivity syndrome, cholestatic idiosyncratic reaction and dose-dependent hepatotoxicity, secondary to endothelial injury, which includes nodular regenerative hyperplasia [11].

Case Report

We present the case of a 25-years-old patient with a diagnosis of multidistrict (jejunum, ileum and colon) CD made in 2006. He received cyclic steroid therapy with reappearance of symptoms after discontinuation. On May 2009 he attended our IBD Unit and, because of severity and extensive disease, he was treated with adalimumab with good clinical and biochemical response. After 6 months of treatment, the patient gradually started to lose response to adalimumab, so in December 2009 the drug was discontinued. On February 2010 the subject started infliximab, suspended at tenth infusion because of serious allergic adverse reaction (bronchospasm, tachycardia). Therefore, because of the worsening of symptoms, on February 2011 he underwent to ileo-caecal resection. On June 2011 the subject performed an endoscopic and imaging evaluation, with the evidence of colonic and jejunal activity of disease. For this reason he started therapy with adalimumab, discontinued on March 2012 because of serious adverse reaction (flushing and dyspnea). Thus, he started therapy with AZA (150 mg/day, weight: 63 Kg). During the period of therapy with thiopurines he showed clinical benefit and weight gain. On April 2014, after two years of treatment, during periodic laboratory controls, we observed unexpected thrombocytopenia (79.000/ml) and leukopenia (2950/ml), and mild jaundice. As a consequence, he stopped AZA and was hospitalized. At admission he underwent serological examinations:

- Complete blood count: leukopenia (2800/ml), thrombocytopenia (77.000/ml)
- Liver tests: AST 61 U/L (normal value <35 U/L), ALT 62 U/L (normal value <35 U/L), ALP 172 U/L (normal range 35-104 U/L),

GGT 69 U/L (normal range 0-36 U/L), total bilirubin 5.4 mg/dL, direct bilirubin 0.72 mg/dL.

- Abdominal ultrasound: Liver with regular surface and profile, with inhomogeneous parenchyma, without focal lesions. Absence of dilatation of the biliary tract. Mild splenomegaly (Lateral diameter: 145 mm).
- Serology for hepatitis B and C virus: negative.
- Serology for Cytomegalovirus, Herpes virus and Epstein-Barr virus active infections: negative
- Serology for Leishmania Infantum active infection: positive (1:160). This report induced us to perform bone marrow aspirate.
- Bone marrow aspirate: absence of Leishmania; absence of malignant cells (Figures 1 and 2).

tissue septa were not observed. Reticulin staining with silver impregnation showed areas with more abundant and swollen cytoplasm alternating with areas of atrophic liver cell plates and sinusoidal dilatation, compressing the previous areas, thus conferring a clear "nodular" pattern to liver parenchyma. Such histology was compatible with nodular regenerative hyperplasia.

In the first months after AZA discontinuation the laboratory tests started to improve. On January 2015 we observed complete normalization of hemochrome parameters and liver tests.

The patient refused a second liver biopsy.

Discussion

NRH is a very rare but potentially severe complication of thiopurines treatment. It is a dose-dependent liver injury characterized by damage to endothelial cells of liver sinusoids and venules, resulting in non-thrombotic vessel occlusion and subsequent development of portal hypertension [12]. It usually occurs between 3 months and 3 years of treatment with thiopurines, but the exact pathogenesis in CD is unknown and seems to be multifactorial [13,14]. In CD patients we can find high tumour necrosis factor alpha (TNF- α) levels that might induce NRH by promoting thrombogenesis and obliterative portal venopathy (OPV) [15,16].

Moreover, extensive small bowel involvement or resection, as in our case, might promote OPV by causing malabsorption of vitamins B12, B6 and folic acid, with consequent hyperhomocysteinemia, which can promote thrombosis in the portal vessels. In addition, thiopurines therapy can act synergistically with these factors in causing NRH, probably mediated by high 6-TGN levels, in genetically predisposed individuals [17,18]. In particular, AZA has been postulated to damage hepatic sinusoidal endothelial cells and small hepatic and portal venules [3].

Many Authors identified several risk factors that might predispose CD patients to NRH [11,12]. The published case reports on NRH associated with AZA/6-MP involved predominantly male (87%), CD patients (78% with CD, 22% with UC), as in our case report. In literature we have found onset of NHR in subject with a median age of 44 years (range 23 to 66), while our patient was younger. The majority of subjects had a phenotype suggestive of severe or progressive CD (terminal ileal location, stricturing/penetrating disease, perianal disease, extensive bowel resections, or steroid dependency). Some data indicate that genetic factors may also play a role in the pathogenesis of NRH.

de Boer et al. [17,19,20] suggested that NRH might only develop in patients treated with thiopurines carrying inactivating thiopurine S-methyltransferase (TPMT) single nucleotide polymorphisms (SNPs), resulting in high 6-TGN levels. Other Authors showed no association with inactivating TPMT SNPs or TPMT enzyme levels in patients with inflammatory bowel disease [21-23]. In our case we did evaluate neither the genetic profile, nor 6-TGN levels, but we would like to underline an interesting aspect of the patient's history: he shows familiarity for IBD: his mother is affected by multidistrict steroid-dependent CD, not responder to anti-TNF alpha, but in remission with AZA since more than ten years, without side effects.

The evolution of NRH after discontinuation of thiopurines is generally good, with laboratory normalization and regression of signs of portal hypertension [24,25], even if this disorder could be

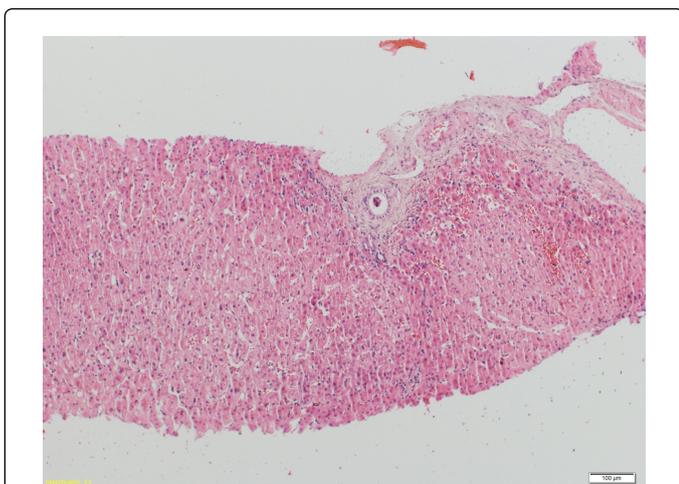


Figure 1: Liver biopsy was characterized by nodularity as well as the presence of regenerating liver cell plates.

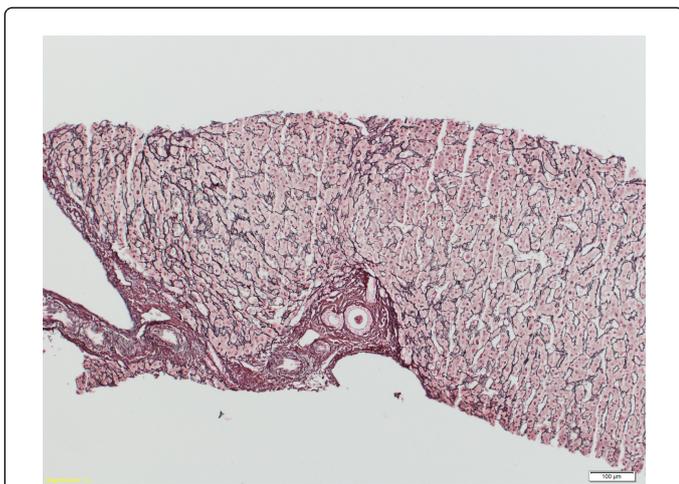


Figure 2: Reticulin staining highlighted the nodular aspect of liver parenchyma (Novotny stain, 100X).

Because of persistent cholestasis and thrombocytopenia, the subject underwent liver biopsy, which showed preservation of lobular architecture but a clear-cut nodular aspect of liver parenchyma. Some portal tracts were slightly widened with mild fibrosis, but connective

potentially cause of liver failure. According to literature, our patient showed normalization of blood tests after stopping AZA.

In our experience, NHR is a very rare disease: in our IBD Unit we have treated about 600 patients with thiopurines, with evidence of a single case of NHR. For this reason, clinicians experienced in IBD should be aware of the possibility of NHR occurrence in patients treated with thiopurines in order to get an early identification of such a condition.

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