

Nodular regenerative hyperplasia of the liver: a rare differential diagnosis of non-cirrhotic portal hypertension and occult chronic variceal hemorrhage

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Summary

We report the case of a 40-year old male with Still syndrome, unexplained non-cirrhotic portal hypertension and anemia. This patient was treated with azathioprin, methotrexate and steroids. Anemia was referred to azathioprin treatment. Except for hemoglobin laboratory examinations were within normal limits. Surprisingly, liver biopsy, undertaken to unravel the cause of portal hypertension, showed the typical characteristic histological feature of nodular regenerative hyperplasia (NRH). As a conclusion, it is mandatory to consider NRH as a cause in each and every patient with unexplained non-cirrhotic portal hypertension. Furthermore, patients presenting with NRH should undergo upper endoscopy as a standard in order to diagnose and treat varices in a timely fashion.

Introduction

Nodular regenerative hyperplasia (NRH) of the liver is an uncommon clinicopathologic condition characterized by diffuse micronodular transformation of hepatic parenchyma in absence of fibrous septa between the nodules (1). NRH was first described by Ranstorn in 1953 under the term “miliary hepatocellular hyperplasia” (2). The term nodular regenerative hyperplasia of the liver was then proposed by Steiner (3). It is distinguished histologically from liver cirrhosis by minimal or absent fibrosis, a cardinal feature of cirrhosis including the absence of hepatic necrosis (4). Progression to cirrhosis is rare. A minority of cases may end up in incomplete septal cirrhosis (5). Up to now, the exact pathogenesis could not be elucidated. It has been suggested that obliteration of portal veins may initiate the nodular transformation caused by a nonuniformity of blood supply to various parts of the liver parenchyma (6). Furthermore, it was hypothesized that atrophy occurred in poorly perfused areas followed by a secondary development regenerative nodules in well perfused areas. (6). Most patients with nodular regenerative hyperplasia are asymptomatic. The main complications are due to portal hypertension. Liver function tests may be normal. Slight increases of ALP (alkaline phosphatase) and γ -glutamyl-transferase (γ -GT) were detected in some studies (1,7,8). Nodular regenerative hyperplasia was found to be associated with autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis. Further associations are with haematological malignancies, exposure to drugs, prothrombotic disorders, connective tissue diseases (1,9,10) and familial occurrence have been described (11).

Case report

A 40-year old male with adult Still's disease was diagnosed in 1998, treated with azathioprin between 08/98-05/99 (average dose 1.5 mg/kg/day), which was stopped due to anemia development. As anemia persisted he was continuously treated with iron supplementation. Subsequently, the patient was treated with methotrexate between 05/99-12/99 (average dose 7.5 mg/week) and variable doses of prednisone between 01/02-06/02 (average dose 3 mg/day). Since 06/02, medication only consisted of 1mg prednisone/day since. Liver function tests such as prothrombin, factor V level, serum albumin showed normal values. Serum bilirubin, alkaline phosphatase, gamma-glutamyl-transpeptidase, aspartate-transaminase, alanine-transaminase and globins were within normal limits. His medical history did not exhibit any prior liver disease or alcohol abuse.

In 2003 the patient developed a steadily increasing physical weakness, which led to admission to our hospital following a now 4-year history of malaise and anemia. On admission he was afebrile with normal vital signs. Clinical examination revealed a palpable spleen extending 2 cm below the left costal margin. No signs of portal hypertension (e.g., ascites, spider naevi) were observed. No findings of chronic rheumatoid arthritis were noted. In abdominal ultrasound splenomegaly (17 x 6,8 cm in diameters) and a Cruveilhier-Baumgarten syndrome were identified. The mean diameter of the portal vein was found to be 13 mm. Doppler ultrasound examination noted a hepatopedal flux rate with 0.11 m/sec (normal value greater than 0.15 m/sec). Hemoglobin was 7.5 g/dl, erythrocytes 3.32 Mio/ μ l, platelet count $102 \times 10^3/\text{mm}^3$, MCH 22.6 pg, iron 4 μ g/dl, ferritin 0.4 ug/dl. The liver function tests, gamma-glutamyl-transpeptidase, aspartate-transaminase, alanine-transaminase, total bilirubin, globins, renal function tests, electrolytes, C-reactive protein, erythrocyte sedimentation rate, peripheral blood and bone marrow were determined normal. At the time of admission the patient's medication consisted only of 1 mg prednisone/day (since 06/02). Since 01/02 no further activity of the Still's disease was noticed. An upper endoscopy showed esophageal varices (grade II^o) with red color signs, congestive gastropathy and hematin as a sign of variceal bleeding. Further examinations including lower endoscopy and wireless capsule endoscopy revealed no other causes of bleeding.

Liver Histology

The characteristic histological feature on liver biopsy seen on sirius red and gomori stain was micronodular transformation consisting of parenchymal nodules of less than 3 mm, not surrounded by fibrosis. There was no evidence of centrilobular necrosis or veno-occlusive disease (fig.1&2).

Treatment

The treatment was directed primarily to the management of portal hypertension and consecutive chronic variceal bleeding. We banded the varices at three times within four months. Successively, the varices decreased to grade I^o. In the follow-up over 8 months hemoglobin remained within normal range (>14.0 g/dl) subsequent to an initial transfusion two erythrocyte concentrates.

DISCUSSION

The incidence of NRH in large autopsy series was found to be 2.6 % with equal sex distribution (1). The average age for first manifestation of NRH is 50 years (1,4). It is likely that the incidence of NRH is underestimated because the disease is asymptomatic in the first phase. The diagnosis was confirmed by percutaneous liver biopsy. Magnetic resonance imaging may be useful as a non-invasive examination for presence and follow-up (14,15). The possibility of NRH of the liver should be considered always in cases with unexplained non-cirrhotic portal hypertension or cholestatic syndrome. The incidence of esophageal varices in NRH as referred to published studies differs because not all patient underwent upper endoscopy at an asymptomatic stage. In one study 12 out of 14 patients with NRH underwent an upper endoscopy, esophageal varices were detected in 10 of 12 cases. Like in other entities of portal hypertension, bleeding risk correlates with the grade of the varices which are the main source of mortality (1,4). As a consequence, upper endoscopy is mandatory as a standard in every patient with NRH. There are no data regarding the efficacy of beta-blockers to prevent recurrence of variceal bleeding in NRH. Beta-blockers have been shown to be effective in preventing bleeding in presinusoidal portal hypertension due to other non-cirrhotic portal hypertension like schistosomiasis (12). Sclerotherapy and transjugular intrahepatic portosystemic shunt (TIPS) were noted with satisfactory results (4). NRH with cholestasis may be improved by treatment with ursodexoycholic acid (13). Patients developing ascites should be treated with diuretics (including spironolactone). In our case there is an association of NRH with Still's disease which constitutes a well-known immunological disorder. The presence of hepatic arteriitis may cause obliteration of the small arteries and their adjacent portal veins (16). Interestingly, some studies pointed out a correlation between NRH and azathioprin intake (17,18,19). Consequently, azathioprin-induced vascular toxicity has been assumed to be one cause for NRH development (18). Also an association between the intake of steroids and NRH induction has been postulated (18). Taken together, azathioprin, steroids and Still's disease could be considered as cofactors of NRH pathogenesis in our patient. Hepatic damage related to methotrexate includes elevation of aminotransferases, portal fibrosis and cirrhosis. Data on methotrexate toxicity show small risk of serious liver disease in rheumatoid arthritis patients (20). In few publications and our case relationship between the low-dose intake of methotrexate and NRH were not described. A putative predisposition of NRH for development of hepatocellular carcinomas (HCC) was not examined in prospective studies yet. A possible relationship may exist in view of the high incidence of hepatocellular dysplasia in NRH, which constitutes a putative premalignant lesion (21).

In conclusion patients with unexplained non-cirrhotic portal hypertension and normal liver function tests stringently should be examined by percutaneous liver biopsy. Furthermore, patients presenting with NRH and anemia should undergo upper endoscopy as a standard in order to diagnose and treat varices in a timely fashion. Studies would be useful to prove the effect of beta-blockers in this entity.

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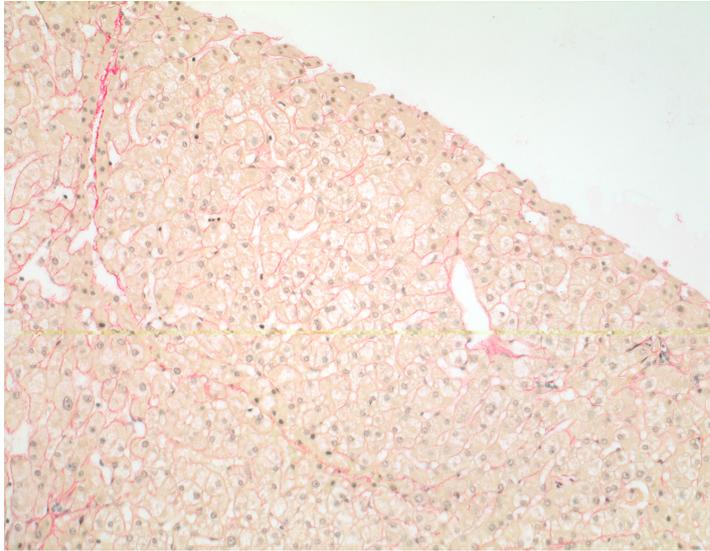


Figure 1. Micronodular transformation seen on sirius red stain (x100) with compression of the adjoining hepatocytes.

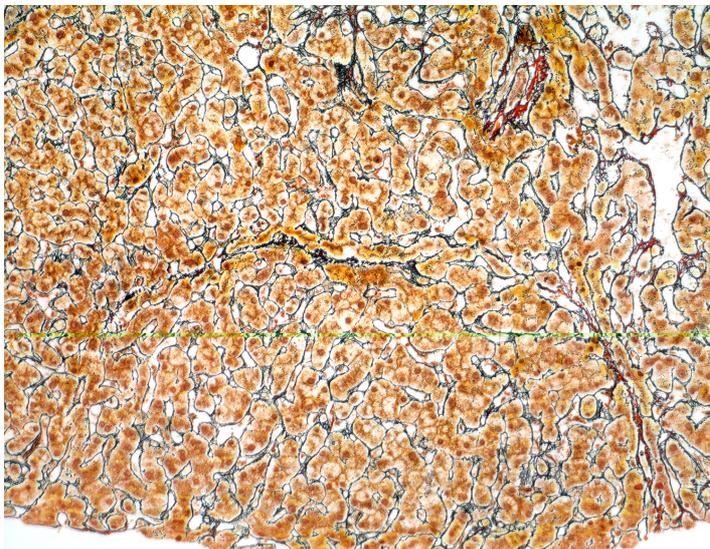


Figure 2. Gomori stain (x100) demonstrated small nodules with focal sinusoidal dilatation.