Transpl Int (1994) 7: 309–313
Springer-Verlag 1994

BRIEF REPORT

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Nodular regenerative hyperplasia: a controversial indication for orthotopic liver transplantation

Received: 19 January 1993
Received after revision: 8 February 1994
Accepted: 18 February 1994

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Abstract Nodular regenerative hyperplasia of the liver is an uncommon cause of portal hypertension. Patients with nodular regenerative hyperplasia have signs and symptoms of portal hypertension, without evidence of hepatocellular failure or encephalopathy. We report the case of a 44-year-old woman with recurrent esophageal bleeding and refractory ascites who had a history of hemosiderosis, hepatitis C, and chronic renal allograft rejection. Our preoperative diagnosis was cirrhotic end-stage liver disease and end-stage renal disease for which the patient underwent combined hepatic and renal transplantation. Her portal hypertension symptoms resolved, and her renal function has been normal for 18 months of follow-up. Histologic examination of the liver revealed nodular regenerative hyperplasia, and a review of the literature regarding the surgical management of patients with nodular regenerative hyperplasia revealed that various shunting procedures are generally recommended. After the failure of medical management in patients with nodular regenerative hyperplasia, portosystemic shunting may be indicated before proceeding to hepatic transplantation.

Key words Nodular regenerative hyperplasia, liver transplantation
Liver transplantation, nodular regenerative hyperplasia

Introduction

Recent series from the Netherlands indicate that nodular regenerative hyperplasia (NRH) of the liver is the second most common histologic diagnosis seen in noncirrhotic portal hypertension (NCPH), comprising 27 % of NCPH cases [15]. In two autopsy series from Canada [27] and Japan [16], NRH was found in 2.6 % and 2.1 % of livers, respectively.

Clinical features of NRH include portal hypertension, ascites, bleeding esophageal varices, and anemia, and the most accurate diagnosis is made with open-wedge biopsy. The characteristic histologic features include diffuse nodulation throughout the liver parenchyma and elimination of the normal perpendicular arrangement of hepatic plates with respect to central veins. The nodules of NRH are usually 0.5 cm or less in diameter and give the appearance of "waves of regeneration", which are most clearly delineated with the reticulin stain. Thick fibrous septa dividing regenerative nodules must be absent for the diagnosis of NRH to be made [27].

Idiopathic portal hypertension (IPH) is another form of NCPH that is of particular relevance to the discussion of NRH because the clinical features, hemodynamics, and treatment of IPH have been more extensively studied than those of NRH and because parallels can be drawn between IPH and NRH. The Japan IPH Research Committee has published a list of clinicopathologic and hemodynamic criteria for diagnosing IPH [20]. No such criteria have been established for patients with NRH; however, NRH patients generally meet the same criteria detailed for IPH except that fibrosis of portal venous radicles on light microscopy is absent in NRH. The patho-

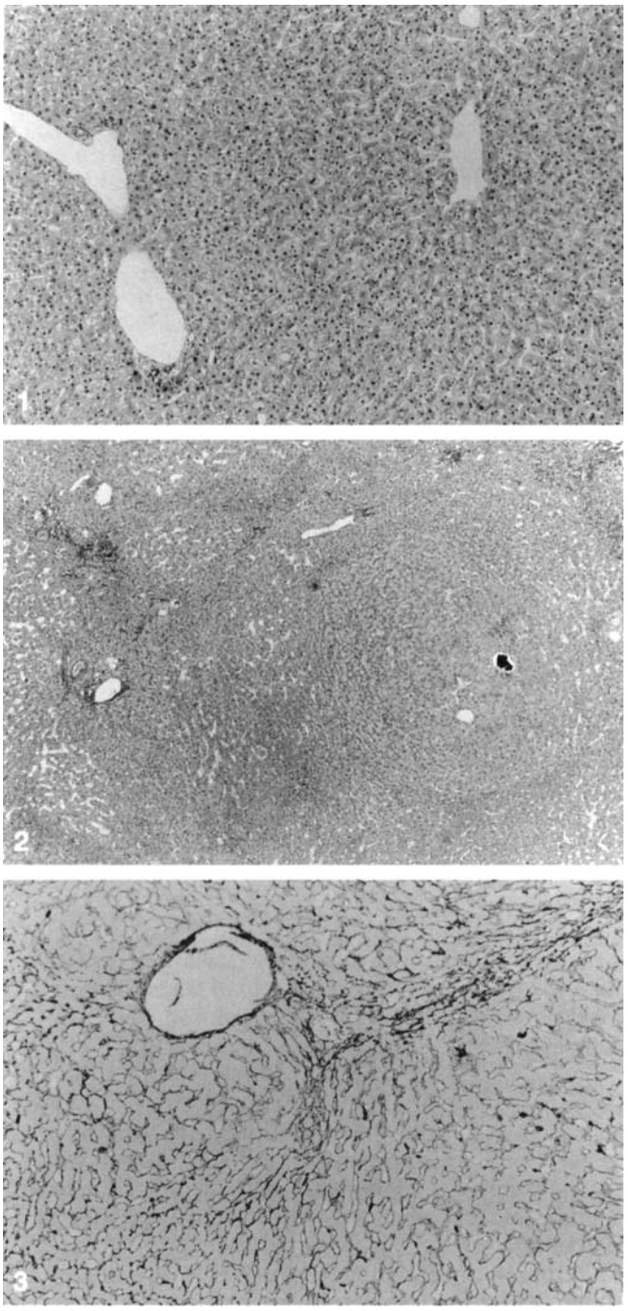

Fig. 1 H&E stain of normal hepatic lobule with peripheral portal triads and a central vein (H&E, ×50)

Fig. 2 A nodule of regenerative hyperplasia (H&E, ×50)

Fig. 3 Reticulin-stained section of an area of irregular reticulin fiber architecture secondary to regenerative hyperplasia (Reticulin stain, ×100)

genesis, diagnosis, and therapy of NRH are further addressed in the discussion.

Case report

A 44-year-old woman was referred for evaluation for liver transplantation in January of 1990. She had end-stage renal disease secondary to chronic pyelonephritis and had undergone hemodialysis for 3 years after bilateral nephrectomy for indolent pyelonephritis in 1977. In 1980 she received a cadaveric renal allograft and was noted to have persistent hepatosplenomegaly and moderate elevation in liver function tests postoperatively. A liver biopsy in 1981, at an outside institution, was said to reveal pronounced hemosiderosis with associated mild fatty change and mild portal fibrosis without evidence of cirrhosis. The patient was subsequently treated with multiple phlebotomies.

In December of 1987 the patient presented with her first episode of upper gastrointestinal bleeding. Hepatic synthetic function and bilirubin, however, remained normal (albumin 3.6, bilirubin 0.6, and normal prothrombin time/partial thromboplastin time). Despite this, she subsequently developed recurrent episodes of esophageal variceal bleeding managed with sclerotherapy, and refractory ascites managed with intermittent abdominal paracentesis. Hepatitis C virus antibody (by ELISA) was positive. Based on a history of hemosiderosis, hepatitis C virus positivity, mildly elevated liver function tests (serum glutamic-oxaloacetic transaminase 37, serum glutamic pyruvic transaminase 67, alkaline phosphatase 606), moderately low albumin, and with the clinical picture of variceal bleeding and refractory ascites, our impression was that of end-stage liver disease. Her renal function deteriorated concomitantly, due to chronic renal allograft rejection, and she underwent combined orthotopic liver and cadaveric renal transplantation. The postoperative course was uneventful, and the patient is doing well after 2 years of follow-up.

The explanted liver weighed 1850 g. The surface was irregular with ill-defined nodules separated by shallow valleys, partially filled with cream-colored connective tissue. Much of the surface of the liver had the appearance of being porcelainized. No dominant nodules were identified. The cut surface of the liver revealed a generalized bulging micronodularity. The vascular supply to the liver was normal.

The histopathology of the liver revealed no evidence of chronic active hepatitis or cirrhosis. There was no fatty change and no indication of chronic hepatitis C. The hemosiderosis reported on the earlier biopsy had totally resolved. No excess iron was identified in the liver. Irregular nodules of regeneration were sometimes the size of liver lobules and at other times were significantly larger but never occupied more than a lower power field on the microscope (Figs. 1, 2). The nodules were created by alternating waves of regenerative change in the hepatic parenchyma that altered the hepatic plate architecture, as well as the sinus arrangement between portal triads and central veins. In many areas the portal plates were virtually at right angles to the portal triads.

Sinusoidal dilatation at the periphery of the regenerating nodules and irregular placement of central and collecting veins were further features of this regenerative hyperplasia. The reticulin stain dramatically demonstrated the nodularity of the liver (Fig. 3) [25].

Recovery of hepatitis C viral DNA from the liver tissue was not attempted.

Discussion

Pathogenesis

The association of azathioprine therapy with the development of NRH is well documented in patients who have undergone renal transplantation [2, 9] and in patients who are receiving azathioprine for other conditions, including multiple sclerosis [12] and myasthenia gravis [3]. Clinical symptoms appear 8 months to 3 years after renal transplantation or after the onset of immunosuppressive therapy [2, 15]. Furthermore, NRH has also been associated with renal disease in the absence of transplantation [6]. The combination of chronic pyelonephritis compounded later by renal transplantation and azathioprine therapy may have contributed to the development of NRH in our patient.

Common pathways in the pathogenesis of IPH and NRH do seem to exist. In 1979 Nataf et al. [18] reported a case of IPH (perisinusoidal fibrosis) after renal transplantation. Although the generalized venous vasculopathy and portal sclerosis seen in IPH are not as marked in NRH, these features are sometimes seen. Terao et al. [26] reported a case of IPH with characteristics of NRH present in the same liver. Wanless et al. [28] observed that in NRH, portal radicles of up to 0.2 mm in diameter were almost uniformly involved in obliterative portal venopathy (a characteristic feature of IPH). Haboubi et al. [5] reported endothelial cell damage as a common denominator in a range of histologic findings among livers of azathioprine-treated male patients after renal transplantation. Histology included veno-occlusive disease, perisinusoidal fibrosis, and NRH. By correlating the findings of Wanless and Haboubi, the pathogenesis of NRH may be proposed to involve (1) azathioprine or autoimmune-mediated endothelial cell damage, leading to occlusion of portal radicles by microemboli or platelet aggregates; (2) atrophy of hepatocytes supplied by each occluded radicle; and (3) subsequent regeneration, leading to diffuse nodularity.

Diagnosis

Diagnosis of NRH rests heavily on the adequacy of the biopsy specimen. Needle biopsy is often inadequate, and an open-wedge biopsy provides a confident pathologic diagnosis [22]. However, immunohistochemistry against alpha-1-antitrypsin may ultimately improve the value of needle biopsy specimens in making this diagnosis as Nakhleh and Snover [17] have shown that the regenerating compartment of the liver in NRH has increased alpha-1-antitrypsin expression. NRH may be suspected in a patient who presents with clinical symptoms of worsening portal hypertension, marginally elevated liver function tests, mildly decreased albumin, and near-normal ammonium levels. Patients may present with variceal bleeding, splenomegaly, ascites, or anemia. The incidence of NRH is higher in patients on immunosuppressive or cytotoxic chemotherapy and in patients with rheumatologic disease; patients presenting with portal hypertension in these populations should be evaluated carefully to rule out NRH.

Treatment

Several series have reviewed the efficacy of various therapeutic procedures for IPH. However, most reports on NRH are autopsy case studies, and no retrospective or prospective study with long-term follow-up has compared the efficacy of various treatment options for NRH [21]. Since NRH and IPH share similar physiology (portal hypertension with near-normal hepatocellular function), current therapeutic recommendations for NRH may have to be based on studies of IPH. Acute variceal bleeding in patients with NCPH is managed the same may as in those with cirrhosis except that there is no reluctance to perform an emergent shunt in patients with NCPH because they are much more resilient than patients with cirrhosis [7]. In New Delhi the mortality for IPH patients with acute variceal hemorrhage undergoing emergent proximal splenorenal shunt was 0/22 patients [19]. For IPH patients, the Sugiura procedure for esophageal varices yields survival rates of 80 %, 99 %, and 92 % for emergent, prophylactic, and elective cases, respectively [4]. The side-to-side splenorenal shunt without splenectomy and the left-gastric-to-caval shunt have shown 100 % actuarial survival at 10 years in IPH patients, with a low incidence of rebleeding or encephalopathy [10, 13]. On the other hand, central portocaval shunting is associated with a postoperative encephalopathy rate of 23 % in IPH patients [1]. Postoperative encephalopathy can be resolved by conversion to distal splenorenal shunt [14]. Finally, hepatorenal syndrome has been reported as a late complication of proximal splenorenal shunting in three cases among a series of 71 patients with IPH [19]. Based on his and other series, Isomatsu concluded that distal splenorenal shunt is the best operation for portal decompression in IPH [8].

Samuel et al. [23] reported two cases of patients with NRH who underwent portal decompression via interposition mesocaval shunt and subsequently developed chronic encephalopathy that resolved after occlusion of the shunt in both cases. On the contrary, Somerville et al. [24] reported a case of an elderly patient with life-threatening variceal hemorrhage secondary to NRH who was successfully treated with an emergent portocaval shunt and had no encephalopathy over a 5-year follow-up period.

The indications for liver transplantation in patients with NCPH have not been fully evaluated. Orthotopic liver transplantation in a patient with NRH (suspected to have had cirrhotic liver disease preoperatively) was reported by McDonald et al. [11]. That patient was in grade IV hepatic coma before transplantation, had a complicated postoperative course, and died 4 months post-transplantation. Our patient was referred to us for evaluation for transplantation with the diagnosis of cirrhotic end-stage liver disease. Transplantation was planned and not emergent as in the case reported by McDonald et al. [11]. Had the diagnosis of NRH been secured preoperatively in our patient, certainly we would have considered a shunting procedure as an option. Our initial approach would have been mesocaval shunting as splenorenal shunting is not a good option for refractory ascites, and portocaval shunting would decrease the feasibility of orthotopic liver transplantation if needed at a later time. Because of the risk of encephalopathy with central shunts for NCPH, hepatic transplantation may be the therapeutic option of choice in selected cases. Alternatively, it may be justifiable to attempt a feasible shunting procedure initially and then proceed to hepatic transplantation only after failure of shunting due to encephalopathy.

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