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Nodular regenerative hyperplasia mimicking cirrhosis of the liver

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Abstract

Nodular regenerative hyperplasia of the liver usually presents with signs of portal hypertension with little evidence of obvious liver disease. We report a 47 year old man who presented with clinical signs of decompensated cirrhosis, recurrent encephalopathy, and tense ascites but at liver transplant was found to have nodular regenerative hyperplasia associated with a portal vein thrombosis.

Nodular regenerative hyperplasia of the liver is an unusual condition of unknown aetiology. It is characterised histologically by multiple parenchymal nodules throughout the liver, made up of hepatocytes that are hyperplastic in some areas and atrophic in others. Central veins are usually absent or atretic and there is little or no fibrosis or inflammation, which distinguishes this disorder from cirrhosis.[1]

Patients usually present with oesophageal variceal haemorrhage associated with a few or no signs of liver disease.[2-7] We describe a patient, referred for a liver transplant, who presented with recurrent bacterial peritonitis, recurrent episodes of hepatic encephalopathy, and signs of end stage liver disease. The preoperative diagnosis was decompensated cirrhosis but at operation the resected liver showed nodular regenerative hyperplasia without evidence of cirrhosis.

Patient

A 47 year old man in end stage liver failure was referred for liver transplant assessment. He had developed alopecia totalis at age 7 years and acute nephrotic syndrome at 17 years but had made a complete recovery. At 37 years (in 1978) he developed submassive hepatic necrosis, the aetiology of which was unknown. He gave no history of drug or alcohol abuse. The autoantibody screen, hepatitis A and B antibodies, cytomegalovirus, Epstein-Barr, and toxoplasmosis antibodies were all negative. The copper, iron, and α_1 antitrypsin studies were normal. On admission to hospital at this time he had hepatic encephalopathy and bacterial peritonitis. He required peritoneal dialysis for one week and suffered ototoxicity and renal toxicity secondary to oral neomycin treatment. Four months later he was discharged in good health with some residual splenomegaly but no other stigmata of liver disease, and he returned to a normal working life.

In 1986, when he was 45 years old, he developed lethargy and ascites. Hypothyroidism was diagnosed and treated but with no symptomatic improvement. He was admitted to hospital on five occasions (March, June, August, September, and October) in 1987 with episodes of hepatic encephalopathy confirmed by electroencephalography. There were no precipitating aetiologies except for a single episode of spontaneous bacterial peritonitis. He was transferred for liver transplantation assessment during November 1987.

On admission to hospital he was grossly oedematous with ascites, tender gynaecomastia, testicular atrophy, and splenomegaly 5 cm below the costal margin. He was not jaundiced and did not have spider naevi. A full blood count showed pancytopenia with a haemoglobin of 7·4 g/dl, platelet count of 55×10^9/l, and a white cell count of $2{\cdot}6\times10^9$/l. The prothrombin index was 85% and the APTT was 34 seconds. The patient's electrolyte studies were within the normal range, the serum creatinine concentration was 177 μmol/l (range 55–120 μmol/l) and creatinine clearance was 42 ml/min, with no proteinuria. The bilirubin concentration was 24 μmol/l (range 0–18), albumin 26 g/l (range 40–52), alkaline phosphatase 80 IU/l (<160), aspartate transaminase 28 IU/l (range 5–55), and gammaglutamyl transferase 27 IU/l (range 0–55). The prealbumin value was within normal range at 170 mg/ml (150–450). The patient was euthyroid. His hepatitis A and B serology was negative, antinuclear factor, antimitochondrial antibody, and smooth muscle antibody were negative, his α_1 antitrypsin value was normal, as were iron and copper studies.

An abdominal computed tomogram showed noticeable ascites, a very small nodular liver, and an appreciably enlarged spleen. There was evidence of large collateral venous channels within the abdomen. The coeliac and superior mesenteric angiograms showed a tortuous splenic vein, with no filling of the portal vein and retrograde flow down the superior mesenteric vein communicating with the inferior vena cava. Hepatic wedge venography showed an atretic portal vein but during this investigation the portal flow was towards the liver. The patient's hospital stay was marked by recurrent bouts of hepatic encephalopathy, often associated with episodes of spontaneous bacterial peritonitis. *Citrobacter freundii*, *Enterobacter cloacae*, and *Streptococcus faecalis* were grown on separate occasions from the ascitic fluid.

The patient underwent orthotopic liver transplantation on 16 January 1988. At the time of transplantation he was in grade IV hepatic coma. At surgery the portal vein was found to have an irregular lumen, indicating previous thrombosis and recanalisation. Macroscopically the liver had an irregular nodular appearance, with nodules ranging from 1 to 0·1 cm in diameter (Fig 1). The liver weighed 973 g. Under light microscopy the liver looked diffusely nodular. The overall archi-

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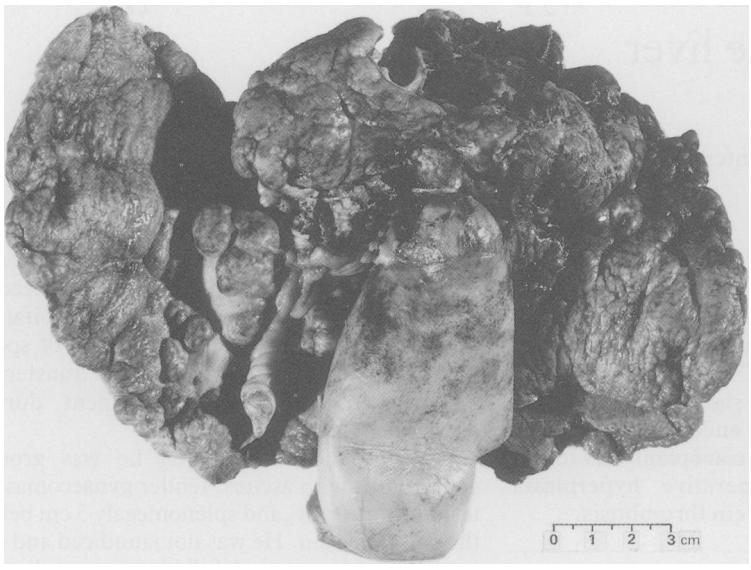

Figure 1: The macroscopic liver.

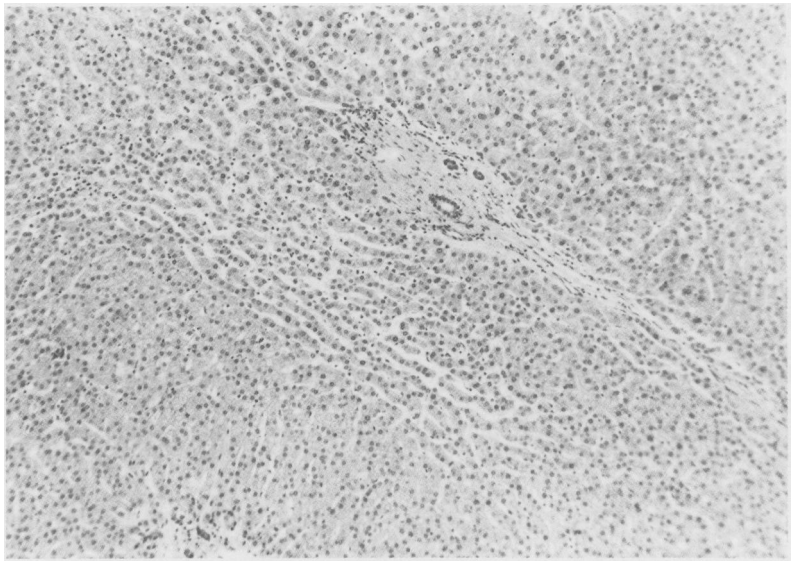

Figure 2: Reversed lobulation. Note 'central' portal tract, circumferentially aligned thin liver cell cords, and sinusoidal dilatation.

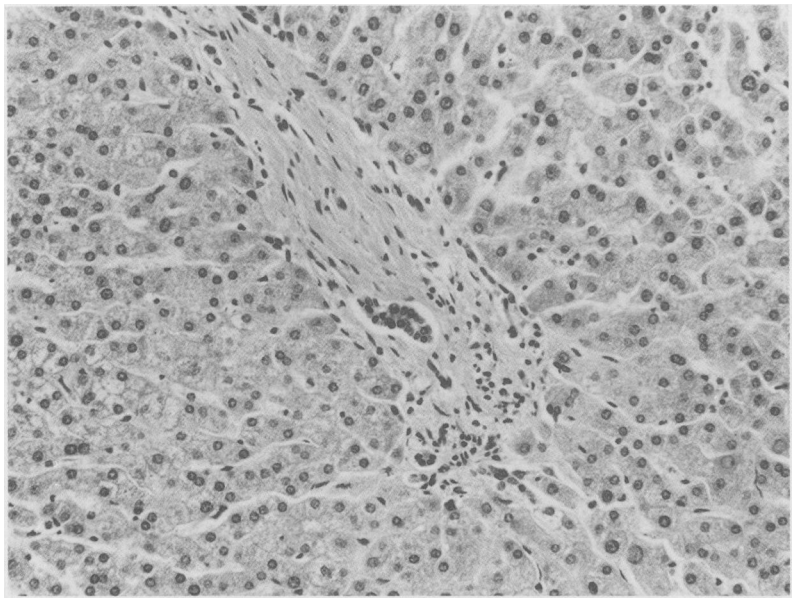

Figure 3: Portal tract devoid of portal vein radicles.

tecture was maintained but the lobular architecture was disturbed, with reversed lobulation in some areas. Hepatocytes were hypertrophic in some areas and atrophic in others. The atrophic hepatocytes were often arranged circumferentially around nodules and accompanied by sinusoidal dilatation (Fig 2). No inflammatory infiltrate could be seen. Portal vein radicles were absent from many portal tracts (Fig 3) and hilar branches of the portal vein showed old (recanalised) thrombosis. There was no fibrosis. Overall, the appearances were characteristic of nodular regenerative hyperplasia. The patient regained consciousness and had good graft function. His recovery was complicated, however, by recurrent episodes of sepsis due to opportunistic organisms. He died four months after the transplant with herpes zoster encephalitis.

Discussion

Obvious signs of liver disease such as ascites and hepatic encephalopathy are an uncommon presentation in patients with nodular regenerative hyperplasia. A small proportion of patients, however, go on to develop hepatic decompensation after long term follow up,[2-4] particularly after portosystemic shunt surgery.[8] The usual presentation is with variceal bleeding but with relatively normal liver synthetic function, thus mimicking extrahepatic portal hypertension.[2-7] Splenomegaly with only a slightly raised serum alkaline phosphatase value are the usual findings.

This patient had histological evidence of nodular regenerative hyperplasia but the clinical findings were those of decompensated cirrhosis. The severity of the clinical picture may, however, have been contributed to by the presence of an old portal vein thrombosis. In addition, hepatofugal flow was found during coeliac and superior mesenteric angiography. This may also have contributed to uncontrollable hepatic encephalopathy. Rector[9] reported hepatofugal portal flow in five patients with cirrhosis, all with hepatic encephalopathy and ascites and no history of gastrointestinal bleeding. Similar findings were also reported in a patient with non-cirrhotic portal hypertension presenting with chronic encephalopathy.[10] Despite this, the finding of encephalopathy in non-cirrhotic portal hypertension is very uncommon, although it should be recognised that it may be precipitated by portosystemic shunt surgery.[8]

The pathology findings in this patient suggest the diagnosis of nodular regenerative hyperplasia. The nodules present were small and diffuse in nature; there was no portal fibrosis. These conclusions are supported by Dr Kamal Ishak (personal communication). The associated portal vein thrombosis, however, raises the possibility of partial nodular transformation of the liver. Portal vein thrombosis is seen infrequently in nodular regenerative hyperplasia but is common in partial nodular hyperplasia.[10,11] Partial nodular hyperplasia, however, is characterised by irregular sized nodules that are particularly prominent in the perihilar region,

associated with atrophy of the remaining liver.[11] These features were not present in this patient. Wanless *et al*[12] have suggested that nodular regenerative hyperplasia is secondary to small portal vein tributary thrombosis, with atrophy of nearby hepatocytes and regeneration of other hepatocytes. The difficulty in finding small portal vein tributaries in the portal tracts in our patient would be consistent with this hypothesis. Many authors have reported this liver problem in association with longstanding congestive cardiac failure,[1] myeloproliferative disorders,[4 12] Raynaud's syndrome,[5] CRST syndrome (calcinosis cutis, Raynaud's phenomenon, sclerodactyly, telangiectasia),[3] Walderstrom's macroglobulinaemia,[13] bacterial endocarditis,[14] miliary tuberculosis,[6] and Felty's syndrome.[15] However, it may occur de novo.[2 7]

The connection between the previous submassive hepatic necrosis and nodular regenerative hyperplasia is unclear. Although it is well established that inactive cirrhosis may be the end result of submassive necrosis of the liver,[16] this patient raised the possibility that abnormal regeneration of the liver may occasionally lead to nodular regenerative hyperplasia. Alternatively, the finding of an old portal vein thrombosis with loss of small intrahepatic venous channels raises the possibility that this disorder may be the result of portal venous obliteration after peritoneal dialysis 10 years previously, rather than submassive massive necrosis.

In conclusion, this report shows that nodular regenerative hyperplasia can present with end stage liver failure, and is a reminder that a clinical diagnosis without histological investigations can be misleading.

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