CASE REPORT

Nodular Regenerative Hyperplasia of the Liver

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Nodular regenerative hyperplasia (NRH), characterized by diffuse hepatic micronodular transformation in groups without fibrous septa between the nodules, is a rare benign liver lesion that has many synonyms in previous literature. Pathologic evaluation is the mainstay of accurate diagnosis. Treatment is focused on its underlying conditions and complications of portal hypertension. A 39-year-old man visited our hospital due to right upper quadrant pain and a palpable liver mass. Magnetic resonance examination revealed a slightly hyperintense tumor on T2-weighted images, and focal nodular hyperplasia was diagnosed by the radiologists. Atypical radiologic findings could not yield an accurate diagnosis. Surgical intervention was therefore performed. Pathologic examination of the resected liver tumor confirmed the diagnosis of NRH. We conclude that NRH should be included in the differential diagnosis of benign liver tumor. [*J Chin Med Assoc* 2008;71(10):523–527]

Key Words: benign liver tumor, diagnosis, nodular regenerative hyperplasia

Introduction

Nodular regenerative hyperplasia (NRH) is a benign proliferative lesion that has many synonyms, including nodular transformation, partial nodular transformation and noncirrhotic nodulation.[1,2] macroscopically, NRH is characterized by multiple regenerative nodules with varying sizes from 0.1 cm to 15 cm in groups.[2–4] Microscopic features are very characteristic, revealing diffuse micronodular transformation of the hepatic parenchyma without fibrous septa between the regenerative nodules.[3,5] The pathogenesis of NRH is not well known. Based on large case series, the prevalence of NRH ranges from 0.6% to 2.6%.[6,7] NRH mostly affects patients older than 60 years of age.[6] The male-to-female ratio is equal.[6] NRH has been associated with a variety of systemic diseases including collagen vascular diseases, lymphoproliferative and myeloproliferative disorders as well as some specific medications.[6,7] Clinically, NRH usually does not cause symptoms and is discovered incidentally unless it is complicated by portal hypertension and its sequelae such as hepatomegaly, splenomegaly, ascites, or esophageal varices.[6,7] Imaging findings are nonspecific.[7] In asymptomatic patients, no treatment is recommended. In patients with complications of portal hypertension, appropriate treatments such as drug therapy and endoscopic therapy are necessary.[8–10]

Case Report

A 39-year-old man visited our hospital due to intermittent right upper abdominal dull pain for 1 week. The dull pain was aggravated gradually but not associated with meal and position. The patient denied any nausea, vomiting, or changes in bowel or urinary habits, and was without obvious body weight loss. Thalassemia minor was first noted when he was a young adult. He had no hepatitis or drug abuse history. Physical examination on admission showed mild pale conjunctiva and a palpable mass with rubbery consistency about 2 finger breadths below the right costal margin. The patient's vital signs, including body temperature, pulse rate and respiratory rate, were all within normal limits. Initial laboratory data were: aspartate aminotransferase (AST) level of 21 IU/L (normal range, 5–35 IU/L), alanine aminotransferase (ALT)

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level of 45 IU/L (normal, 0–40 IU/L), total bilirubin of 0.8 mg/dL (normal, 0.2–1.6 mg/dL), alkaline phosphatase of 75 U/L (normal, 3.7–5.3 U/L), albumin of 4.9 g/dL (normal, 3.7–5.3 g/dL), normal prothrombin time, white blood cell count of 12,990 cells/mm^3 (normal, 4,000–9,900 cells/mm^3), hemoglobin of 11.7 g/dL (normal, 13.5–17.8 g/dL), and platelet count of 217,000 cells/mm^3 (normal, 150,000–450,000 cells/mm^3). Viral serology was negative for hepatitis B surface antigen and antibody to hepatitis C virus. Serum α-fetoprotein level was normal. Fecal occult blood test was negative. Renal function, electrolytes and urine analysis were normal.

Abdominal ultrasonography revealed a large heterogeneous mass in liver segment 6 without halo sign, measuring about 5.6 × 4.7 cm. Liver parenchyma appeared normal, and the spleen was not enlarged. Hemangioma or hepatocellular adenoma was initially diagnosed. Magnetic resonance (MR) of the liver, using T1- and T2-weighted imaging, demonstrated a nodular mass lesion, about 5.1 cm in size, with slight hyperintensity on T2 and isointensity on T1 images, in liver segment 6 (Figure 1). Focal nodular hyperplasia rather than hepatocellular adenoma was diagnosed by the radiologists. However, no characteristic high T2 signal scar on the T2-weighted image was disclosed.

Because of apparent right upper abdominal pain related to the liver tumor, the patient requested surgical intervention. Thus, segmentectomy of S5 was performed. The tumor was a solitary well-demarcated nodule without fibrous capsular formation, measuring about 6.3 × 6.1 × 3.5 cm (Figure 2). Neither hemorrhage nor necrosis was present. The hepatic surgical margins were free of tumor grossly.

Microscopically, the liver tissue adjacent to the large nodules was composed of vaguely multiple small nodules with hepatocyte atrophy and bile ducts but without fibrosis. In contrast, the hepatocytes were arranged in 1 or 2 cell-thick plates in the large nodules. Most hepatocytes had uniform regular nuclei, but a focal area of moderately pleomorphic cells with dysplastic nuclei (large-cell change) could be seen. Absence of portal tracts and fibrosis was found. The large

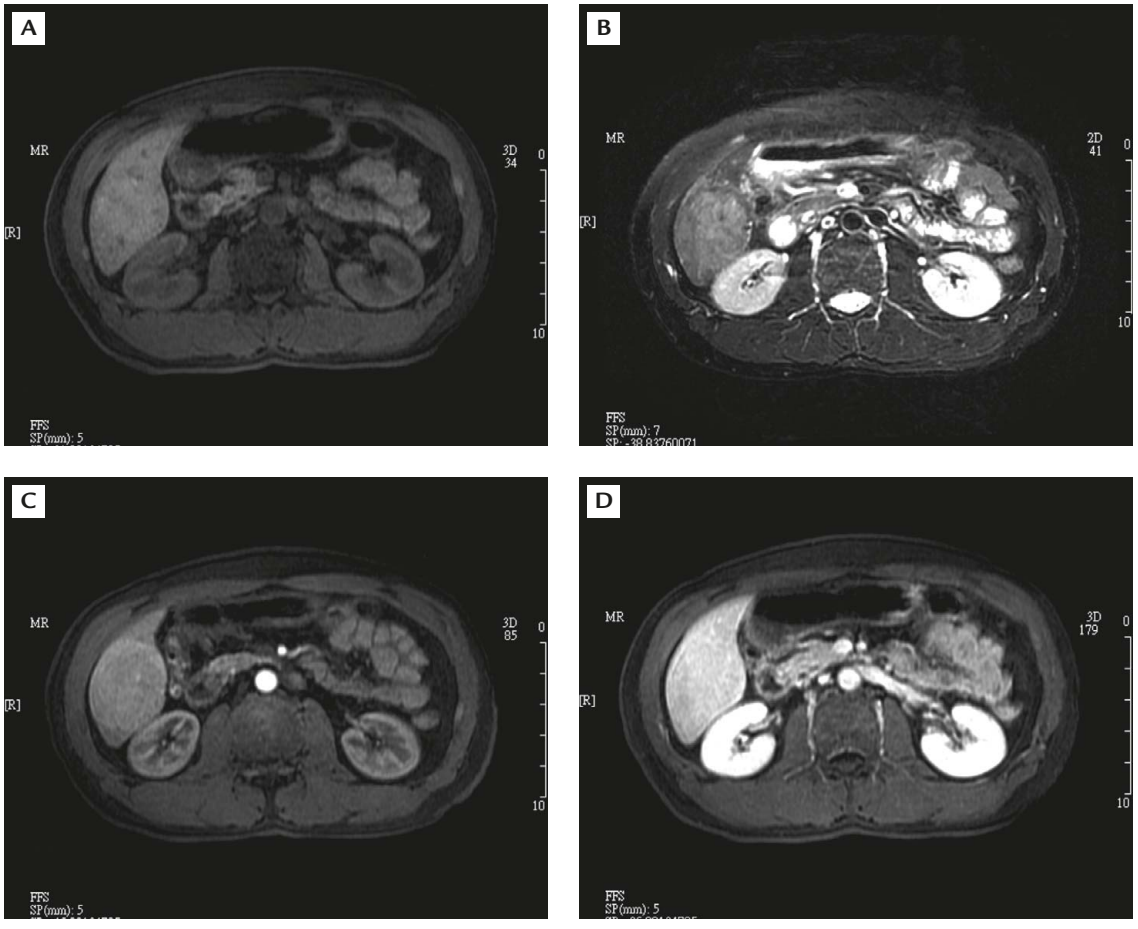

Figure 1. Liver tumor appears as: (A) an isosignal on T1-weighted image; and (B) a slightly bright homogeneous signal on T2-weighted imaging. Dynamic study shows: (C) early arterial enhancement of the tumor; and (D) iso-enhancement in the late phase.

nodules showed adenoma-like features. Furthermore, staining for collagen with Masson trichrome showed that fibrosis was absent. The overall findings were considered to be NRH of the liver (Figure 3).

The patient was discharged after 13 days of hospitalization. During the 20-month follow-up period, the patient became symptom-free and tumor-free after liver resection.

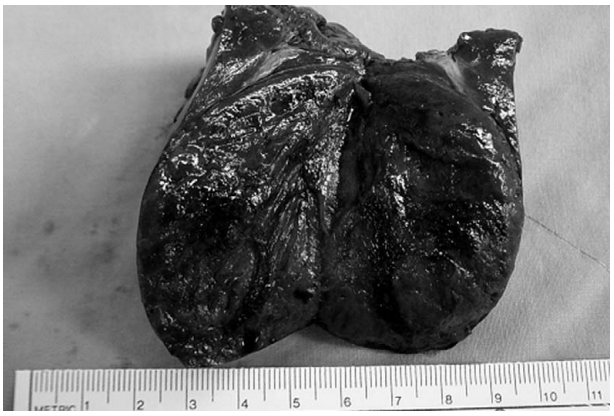

Figure 2. Segmentectomy of S5 was performed. The tumor is a solitary well-demarcated nodule without fibrous capsular formation, measuring about 6.3 × 6.1 × 3.5 cm.

Discussion

The etiology of NRH is not fully understood.[10] At present, the nodular transformation in NRH is considered to be a consequence of alterations in portal blood flow.[11] The "vascular hypothesis" presumes that the basic pathologic injury leading to NRH is obliteration and/or thrombus in the portal venous system.[12] The central atrophy, produced by decreased blood flow, is compensated for by proliferation of hepatocytes from the portal region that form regenerative nodules. Most of the hepatocyte regeneration takes place over the portal region.[13] In addition, the portal venous system shows abnormalities in NRH patients, presenting with phlebosclerosis of the portal radicles

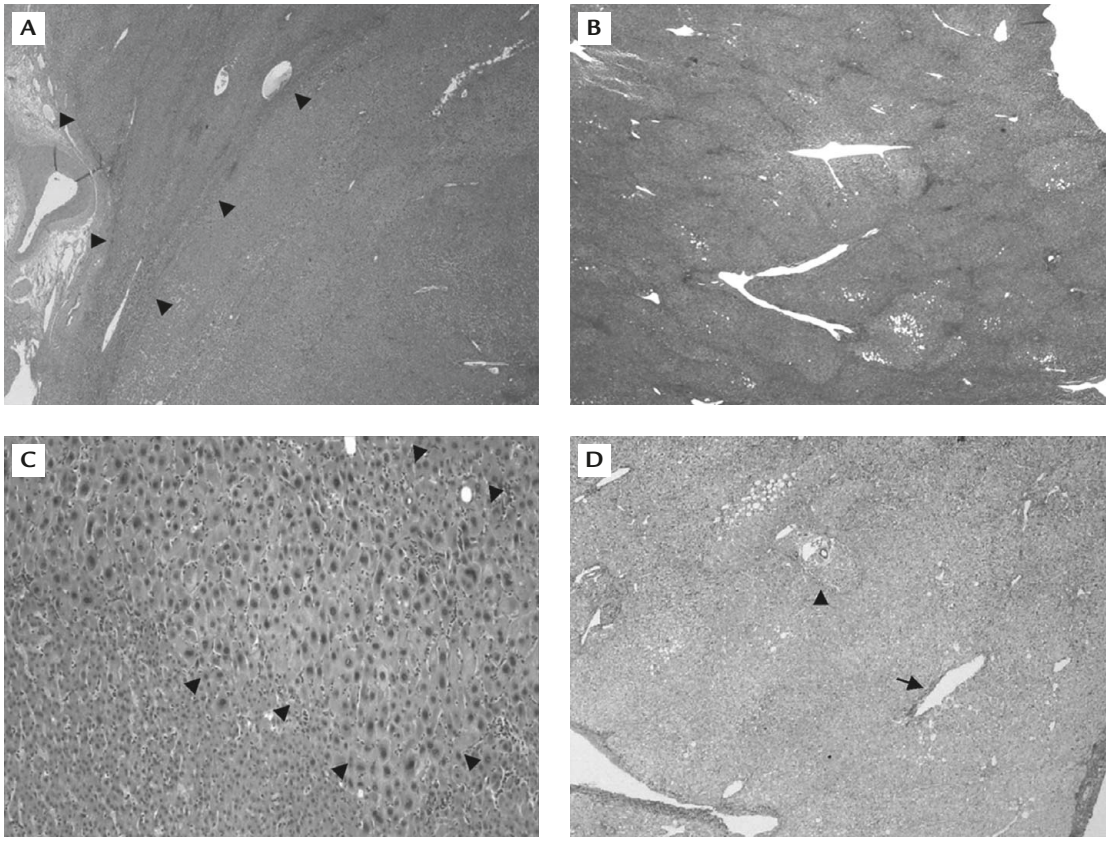

Figure 3. (A) Gross photograph of nodularity shows biphasic pattern. The liver tissue adjacent to the large nodule shows vaguely multiple small nodules (arrowheads) without fibrosis and preservation of hepatic architecture (hematoxylin & eosin, 40×). (B) More details of typical nodularity in small nodules (hematoxylin & eosin, 100×). (C) In the large nodule, most hepatocytes are arranged in 2 cell-thick plates, but a focal area of moderately pleomorphic cells with dysplastic nuclei (large cell change) can be seen (arrowheads) (hematoxylin & eosin, 400×). (D) Masson trichrome stain protocol for collagen fibers shows absence of fibrosis and presence of portal tracts (arrowhead) and central veins (arrow) (100×).

Table 1. Differential diagnosis of nodular regenerative hyperplasia of the liver—common radiologic features

	NRH	FNH	HA
Ultrasound	Rare detection (iso- to hypoechoic)	Homogeneously isoechoic Central scar: hypoechoic	Complex heterogeneous
CT scan (NECT/CECT)	NECT: isodense CECT: iso- or hypodense in both phases	NECT: iso- or hypodense CECT: arterial phase is hyperdense; venous phase is iso- or hypodense Central scar: hyperdense	NECT: iso- to hypodense CECT: arterial phase is heterogeneous hyperdense; venous phase is variable
MR image (T1/T2-weighted)	T1: hyperintense T2: iso- or hypointense	T1: iso- to hypointense Scar: hypointense T2: iso- to hyperintense Scar: hyperintense	T1 & T2: heterogeneous signal intensity (due to fat or hemorrhage)

NRH = nodular regenerative hyperplasia; FNH = focal nodular hyperplasia; HA = hepatic adenoma; CT = computed tomography; MR = magnetic resonance; NECT = non-contrast enhanced CT; CECT = contrast-enhanced CT.

and portal venule obliteration, the so-called "portal obliterative venopathy". Another theory is that NRH is a primary generalized proliferative disorder of the liver. Some investigators have advocated that NRH is a premalignant lesion that may increase the incidence of hepatocyte dysplasia and hepatocellular carcinoma.[14] The pathogenesis of portal hypertension in this condition may result from the compression of the intrahepatic portal radicles by the regenerating nodules or due to the thrombosis of portal veins and venules.[15]

Clinical manifestations associated with NRH may be nonspecific, including fatigue, general malaise or abdominal pain. Long-term sequelae of NRH include ascites, splenomegaly, hepatomegaly, portal hypertension, esophageal varices, cirrhosis, hepatic failure, and hepatic rupture. The most common sequelae are cirrhosis and portal hypertension, with estimated frequency of 30–50%. However, if the lesion is solitary, as in this case, it may not induce any significant complication. The clinical findings and laboratory tests are variable and must be interpreted in view of the possibility of primary systemic illness. Liver function tests are usually normal or slightly elevated.[15] There was mild elevation of ALT in our patient. A number of systemic diseases and drugs, such as myeloproliferative syndromes, lymphoproliferative syndromes, rheumatoid arthritis, Felty's syndrome, polyarteritis nodosa, scleroderma, antiphospholipid syndrome, lupus erythematosus, and the use of antineoplastic medication, have been reported in association with NRH.[16–21] However, these conditions could not be traced in our patient.

NRH of the liver does not have characteristic radiologic findings.[7] At present, the best imaging tools are non-contrast/contrast computed tomography (CT) or MR. The important differential diagnoses of NRH should include focal nodular hyperplasia and hepatic adenoma (Table 1). Ultrasonography in most cases shows normal hepatic parenchyma or well-delineated hypoechoic or isoechoic nodules.[3] Hyperechoic nodules have been reported in very rare cases.[2] Sometimes, a diffusely heterogeneous hepatic parenchyma can be seen. Our case, manifesting as a solitary heterogeneous mass, is very different from the previous reports. NRH, on enhanced CT, showed normal parenchyma or hypoattenuating nodules. Hemorrhage or arterioportal shunting are present in hyperattenuating sections.[7,22] MR examination may find hyperintensity on T1-weighted images and iso- or hypointense to normal liver on T2-weighted images.[23,24] It is no wonder that our case, slightly hyperintense on T2 and isointense on T1 images, was misdiagnosed as focal nodular hyperplasia rather than hepatocellular adenoma.[25] Furthermore, most scintigraphic findings, such as liver scan, demonstrated that the hyperplastic nodules of NRH took up technetium sulfur colloid but might not have a characteristic appearance.[26,27]

However, clinical and radiologic signs are not very specific, and pathologic confirmation via needle biopsy or operation is necessary to establish the diagnosis. Many authors suggest open wedge biopsy because tissue obtained by needle biopsy is seldom sufficient.[2,3] Most hepatocytes are clustered into nodules that vary in size from 0.1 cm to 1 cm, although a few nodules measuring more than 10 cm have been reported.[2–4,6] Histologically, the characteristics are pure liver cell nodularity, abnormal hepatocyte plate arrangement by 2 or more cells thick, and proliferating and distorting acini and lobules. Vascular derangement of liver due to portovenous or hepatovenous flow may also be present.[6,17] In the past, many cases of liver adenomatosis

were confused with NRH of the liver, and sometimes the terms were used synonymously. Differentiating NRH from liver adenomatosis is a very important reason for sampling the tissue that surrounds the large nodules. NRH can be easily distinguished from micronodular cirrhosis, regenerative nodule and focal nodule hyperplasia by the absence of fibrous septa between the nodules. However, NRH is not clearly distinguishable from hepatic adenoma by only similarly abnormal cell plates based on a single-needle biopsy. Among benign lesions, NRH can mimic hepatocellular adenoma histologically, being composed of similar liver cells arranged in sheets and cords without acinar architecture, especially in small biopsies.

In conclusion, our case shows that NRH should be included in the differential diagnosis of a benign liver nodule. Clinical presentations and radiologic images are not sufficiently specific to enable an accurate diagnosis in practice. Liver biopsy with a large tissue sample is mandatory for diagnosis.

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