Case Report

Nodular Regenerative Hyperplasia of Liver Mimicking Cirrhosis: a Case Report

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A 34-year-old man with no history of any abdominal pain or fatigue was admitted to our hospital in June 2008 due to the cirrhosis found incidentally during a physical examination. Laboratory examination, electrocardiograph, abdominal ultrasonography and magnetic resonance imaging were carried out during his hospitalization. However, according to the results of the above measures, the diagnosis of nodular regenerative hyperplasia of the liver (NRHL) could not be made. The result of electrocardiograph showed there was no sinus bradycardia. The abdominal ultrasonography showed evidence of hepatosplenomegaly, and magnetic resonance imaging showed multiple non-enhancing hepatic nodules. Histologic confirmation was available by means of liver biopsy and the definitive diagnosis of NRHL was confirmed histologically by liver biopsy. NRHL always presents with signs of portal hypertension with little evidence of obvious liver disease, NRHL may mimic the cirrhosis of liver and be easily confused with cirrhosis of the liver nodules, so liver biopsy should be recommended for correct diagnosis. We here report the clinical, radiological and pathologic features of this case with NRHL in order to familiarize the physicians with its clinical manifestations.

Key words: Nodular regenerative hyperplasia of the liver; Cirrhosis; Case report

Nodular regenerative hyperplasia of the liver (NRHL) is known as hepatocellular nodules distributed throughout the liver without fibrous rim between the nodules and is a rarely clinical liver disease characterized by the micronodular transformation of normal hepatic parenchyma without fibrosis. NRHL may mimic the cirrhosis of liver and be easily confused with cirrhosis of the liver nodules and its etiology remains unknown.¹ Here we report the clinical, radiological and pathologic features of one case with NRHL in order to familiarize the physicians with its clinical manifestations.

CASE PRESENTATION

A 34-year-old male was admitted to our hospital in June 2008 due to cirrhosis found incidentally during a physical examination. There was no history of any abdominal pain, fatigue and exclusion disease included co-infection with HIV or HCV, and alcohol consumption 30 g/day, drug use, other causes of chronic liver disease were ruled out. On admission to our hospital, there was hepatosplenomegaly and

portal type collateral formation around the umbilicus. Complete blood count results were as follows: white cell count 7.5×10^9 /L, red cell count 5.22×10^{12} /L, haemoglobin 164 g/L, and platelet count 85×10^9 /L. His serum biochemistry was normal apart from a mild elevation of liver enzymes: total bilirubin (TBil) 19.64 μ mol/L (reference interval, 1.7 - 17.1 μ mol/L), alanine aminotransferase (ALT) 47.7 U/L (reference range, 10 - 40 U/L), alkaline phosphatase (ALP) 165 U/L (reference range, 40 - 110 U/L), γ -glutamyltransferase (GGT) 358.6 U/L (reference range, < 30 U/L). Other biochemical laboratory investigations were within normal limits: glucose (GLU) 4.84 mmol/L, albumin (ALB) 47.6 g/L, globulin (GLB) 38.5 g/L, aspartate aminotransferase (AST) 27.4 U/L, erythrocyte sedimentation rate (ESR) 7 mm/hour, α -fetoprotein (AFP) 4.8 μ g/L, prothrombin time (PT) 13.1 s, α 1-antitrypsin (AAT) 1.31 g/L, haptoglobin (HPT) 1 g/L, α 1-acid glycoprotein (AAG) 0.88 g/L, ceruloplasmin (CER) 0.2 g/L, antistreptolysin (ASO) 64.2 IU/ml, rheumatoid factor (RF) 5.26 IU/ml, C-reactive protein (CRP) 2.36 mg/L. Blood examination for ANA, anti-dsDNA antibody, ENA, liver kidney microsomal antibody type 1 (LKM-1), soluble liver antigen/liver pancreas autoantigen antibodies against liver cytosolic antigen type 1 (LC-1), anti-mitochondrial

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antibodies (AMAs) of M2 type (AMA-M2) were all negative. Results of detection for hepatitis B virus surface antigen (HBsAg), HAVAg, HCVAg, HDVAg and HBV DNA were all negative. The investigations on thyroid function were: human thyrotropin (hTSH) 34.078 μ IU/ml, FT40.50 ng/dl, T44.47 μ g/dl. Electrocardiograph showed there was no sinus bradycardia. Abdominal ultrasonography (USG) presented there was evidence of hepatosplenomegaly (Figure 1), and magnetic resonance imaging (MRI) results for liver showed multiple non-enhancing hepatic nodules that were isointense or hypointense on T1-weighted images and a central hyperintense area on T2-weighted images (Figures 2A, 2B). A transcutaneous needle liver biopsy was performed to investigate a possible non-cirrhotic cause of portal hypertension. When examined microscopically, the

hepatic parenchyma showed a diffuse nodule. There were no fibrosis separating nodules - each nodule presses directly against its neighbor. Between each nodule, hepatocytes are small and atrophic, and hepatocytes are pressed together into thin, parallel plates (Figures 3A, 3B). The correct diagnosis of NRHL is made histologically by liver biopsy.

DISCUSSION

Nodular regenerative hyperplasia of liver is infrequent and can be described as a multi-acinar regenerative nodular lesion without fibrous septa between the nodules,² it is probably under-diagnosed because the entity is difficult to recognize. In the literature, most reports have been single cases because the prevalence and clinical significance of NRHL is not exactly

Figure 1. Abdominal ultrasonography.

Notes: The left lobe of liver volume increased, the right lobe of liver volume decreased, the echo of hepatic parenchyma increased and thickened, splenomegaly.

Figure 2. Magnetic resonance imaging of NRHL.

Notes: The liver smaller, the edge of the liver changed wavy, existing multiple small nodules in the liver, the volume of spleen increased, portal veins thickened.

Figure 3A. Pathological section of liver biopsy.

Notes: Arrangement of hepatic plates crowded, lobular spotty necrosis, hepatocyte swelling and degeneration, and central venous sinus congestion expansion (hematoxylin-eosin; original magnification, 100 $\times$).

Figure 3B. Pathological section of hepatic parenchyma.

Notes: The hepatic parenchyma showed a diffuse nodules, there is no brosis separating nodules, the hepatocytes are small and atrophic and are pressed together into thin, parallel plates (Masson trichrome; original magnification, 100 $\times$).

known. The critical lesion is the obliterative portal venopathy, presenting with obstruction to terminal radicals of hepatic arterioles, and portal venules. So the induction of nodular regenerative change may be caused by the resultant hepatic ischemia.³ According to the pathologic findings of liver biopsy material, the morbidity of patients with idiopathic portal or non-cirrhotic portal hypertension is increasing,⁴ but it is difficult to diagnose NRHL without liver biopsy and easy to confuse NRHL with cirrhosis. According to this case, NRHL of the correct diagnosis should be based on clinical, radiological and histological results. NRHL remains of unknown aetiology and mechanism, it has been found to be associated with varieties of conditions, such as collagen disorders, Felty's Syndrome, congestive heart failure, hematologic abnormalities, metabolic diseases, neoplasms and drugs.⁵ So resultant hepatic ischemia may be responsible for induction of the nodular regenerative change too.⁶ Many patients may remain asymptomatic, especially in the early stages of the disease, so NRHL is probably under-diagnosed. Clinical presentations include portal hypertension, esophageal varices and hepatomegaly in later stages of this disease. There were histories of abdominal discomfort, distension and fatigue, etc., in some patients. There is no specific biochemical changes, but the elevated liver enzymes in the majority of these patients. Elevated levels of ALP, GGT and ALT are common particularly.⁶ This case highlights elevated liver enzymes particularly ALP and GGT. Wanless⁷ proposed a classification system, provided histological criteria for the diagnosis of NRHL. These included the presence of hepatocellular nodules less than 3 mm in diameter that were not surrounded by fibrosis. Portal areas may be trapped within the nodules. No significant fibrosis is found either in or around the nodules, which is an important feature distinguishing NRHL from cirrhosis and from focal nodular hyperplasia of the liver. Besides, central veins are usually absent or atretic and there is little or no fibrosis or inflammation, which distinguishes this disorder from cirrhosis.⁸ Hepatosplenomegaly in the absence of any clinical symptom, any history of drug therapy and with no other associated disease in our case. Elevated levels of ALP and GGT were found and the routine blood tests presented a little lower of PLT. USG and MRI showed a liver with a coarse echotexture and nodular outline. However, histological evaluation is the only way to make a definitive diagnosis of

NRHL and rule out conditions such as hepatocellular carcinoma and cirrhosis. Our case, with the absence of any history of drug therapy and with no other associated disease, suggests patients with NRHL may be asymptomatic or present with portal hypertension with hepatosplenomegaly, radiologically and by means of MRI. As far as reported, imaging findings of NRHL are not specific. MRI imaging and sonography usually show normal hepatic parenchyma. In some cases, sonography can depict multiple nodules, whereas CT and MRI examination show normal findings. Usually the nodules do not enhance after IV, but hyperenhancing nodules with arteriportal shunting have been reported. In one case, the findings that some nodules with peripheral rim of enhancement has been observed, which is similar to findings observed in malignant tumor or encapsulated tumor.⁹ Even though sensitive imaging modalities such as contrast-enhanced computed tomography and MRI can help characterize various nodular liver lesions. But radiologically, nodular appearance in liver may look like neoplasia. So we conclude that the diagnosis of NRHL should be made by liver biopsy. In our case, the USG presented that the volume of the left lobe increased, the volume of the right lobe decreased, the echo of hepatic parenchyma increased and thickened, splenomegaly (Figure 1). The MRI presented that the liver became smaller, the edge of the liver changed wavy, existing multiple small nodules in the liver, the volume of spleen increased, portal veins thickened (Figures 2A, B). Most importantly, liver biopsy showed that arrangement of hepatic plates crowded, lobular spotty necrosis, hepatocyte swelling and degeneration, and central venous sinus congestion expansion (Figure 3A), and the hepatic parenchyma showed a diffuse nodules, there is no fibrosis separating nodules, the hepatocytes are small and atrophic and are pressed together into thin, parallel plates (Figure 3B). From the diagnosis of our case, we wish to emphasize the importance of liver biopsy to establish early diagnosis, histological evaluation is the best way to make a definitive diagnosis of NRHL and rule out conditions such as hepatic adenoma, focal nodular hyperplasia, partial nodular transformation, large regenerative nodule, incomplete cirrhosis, and cirrhosis. The patient with NRHL was advised to attend for annual follow-up. Portal hypertension which is secondary to NRHL, is often complicated by bleeding esophageal varices, ascites or splenomegaly. Early treatment is important in the prevention of

the development of complications. It is essential to differentiate between causes of portal hypertension that are or are not associated with cirrhosis, because prognosis and treatment options are vastly different. Correct diagnosis is important because the prognosis in patients with NRHL and portal hypertension is better than that in patients with portal hypertension due to cirrhosis. The initial treatment should be directed at identifying an etiologic agent and removing it. The best choice of treatment at end stage NRHL with hepatic failure should be necessitate orthotopic liver transplantation.

CONCLUSIONS

In conclusion, our case shows that NRHL may mimic cirrhosis of the liver, the clinical diagnosis of NRHL can be made based on clinical and imaging, but the accurate diagnosis of NRHL should be made by liver biopsy. It is essential to emphasize the importance of liver biopsy to establish early diagnosis, histological evaluation can make a definitive diagnosis of NRHL.

REFERENCES

1. Reshamwala PA, Kleiner DE, Heller T. Nodular regenerative hyperplasia: not all nodules are created equal. *Hepatology* 2006;44(1):7-14.
2. Ames JT, Federle MP, Chopra K. Distinguishing clinical and imaging features of nodular regenerative hyperplasia and large regenerative nodules of the liver. *Clin Radiol* 2009;64(12):1190-1195.
3. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. *Hepatology* 1990;11(5):787-797.
4. Zheng RD, Chen XW, Lang ZW. A case of inactive HBsAg carriers and idiopathic portal hypertension. *Zhonghua Gan Zang Bing Za Zhi (Chin)* 2010; 18(4):311.
5. González-Huezo MS, Villela LM, Zepeda-Florencio Mdel C, Carrillo-Ponce CS, Mondragón-Sánchez RJ. Nodular regenerative hyperplasia associated to aplastic anemia: a case report and literature review. *Ann Hepatol* 2006;5(3):166-169.
6. Trenchel GM, Schubert A, Dries V, Benz-Bohm G. Nodular regenerative hyperplasia of the liver: case report of a 13-year-old girl and review of the literature. *Pediatr Radiol* 2000;30(1):64-68.
7. Wanless IR. Nodular regenerative hyperplasia, dysplasia, and hepatocellular carcinoma. *Am J Gastroenterol* 1996;91(5):836-837.
8. McDonald JA, Painter DM, Gallagher ND, McCaughan GW. Nodular regenerative hyperplasia mimicking cirrhosis of the liver. *Gut* 1990;31(6):725-727.
9. Clouet M, Boulay I, Boudiaf M, Soyer P, Nemeth J, Kisman R, et al. Imaging features of nodular regenerative hyperplasia of the liver mimicking hepatic metastases. *Imaging* 1999;24(3):258-261.