N. Ebrahimi Daryani MD[1].
H. Ghanaati MD[2].
Y. Jahangiri Noudeh MD[3].
B. Haghpanah MD[4].
M. Bashashati MD[4].
A.A. Shadman Yazdi MD[5].
A. Sayyah MD[4].

Nodular Regenerative Hyperplasia of the Liver: Report of a Case

Nodular regenerative hyperplasia of the liver (NRHL) is characterized by hepatocellular nodules without fibrous septa between the nodules, and has been described in association with certain diseases. The NHRL should be considered in a liver mass and coexisting portal hypertension.

We described the case of a 33-year-old Iranian man with NRHL in association with essential thrombocythemia.

Keywords: nodular regenerative hyperplasia, liver, essential thrombocythemia

Introduction

Nodular regenerative hyperplasia of the liver (NRHL) is the presence of hepatocellular nodules in the absence of fibrous septa between the nodules.[1] It is a regenerative nodular lesion in a non-cirrhotic liver. One of the proposed pathophysiological mechanisms for this condition is obliterative portal venopathy, which is the obstruction to terminal radicles of hepatic arterioles and portal venules, possibly secondary to endothelial cell damage. The resultant hepatic ischemia may be responsible for induction of nodular regenerative change.[2]

This condition is a rare entity whose etiology remains unknown, and is often seen in association with other diseases such as collagen disorders, Felty's syndrome, congestive heart failure, hematological abnormalities, metabolic diseases, neoplasms or drug use. The disease occurs more often in adults than in children.[3-6] NRHL is diagnosed histologically by liver biopsy, preferably an open "wedge" biopsy.[7,8]

Herein, we report an Iranian case of NRHL in association with essential thrombocythemia.

Case report

A 33-year-old Iranian man was referred to our internal medicine department with severe epigastric pain with radiation to the back after an episode of alcohol intake. There was a history of dull paroxysmal nocturnal right upper quadrant pain of 2 weeks' duration without nausea, vomiting, fever, icterus or diarrhea, and also a history of fullness and mass sensation in the left upper quadrant since about 6 months before, along with weight loss of about 4-5 Kg. The patient's appetite had been normal during the same period. There was no history of any other associated disease or drug use. He reported drinking on social occasions. A positive family history of gastric cancer in his paternal aunt was present, the type of which was not clear.

Splenomegaly, but not hepatomegaly was present. Physical examination was otherwise normal.

1- Professor, Department of Gastroenterology and Hepatology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
2- Associate Professor, Department of Radiology, Medical Imaging Center, Imam Khomeini Hospital, Tehran University of medical sciences, Tehran, Iran.
3-Medical Students Research Committee, Iran University of Medical Sciences, Tehran, Iran
4- Department of Gastroenterology and Hepatology, Imam Khomeini Hospital, Tehran University of medical sciences, Tehran, Iran.
5- Department of Radiology, Medical Imaging Center, Imam Khomeini Hospital, Tehran University of medical sciences, Tehran, Iran.

Corresponding Author:
Naser Ebrahimi Daryani
Address:
Department of Gastroenterology and Hepatology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Tel: 009821- 88799446
Fax: 009821- 88799840
E-mail: nebrahim@sina.tums.ac.ir

Received September 11, 2005;
Accepted after revision December 7, 2005.

Autumn 2005; 3:7-10

Laboratory values revealed leukocytosis without shift (WBC:19400/mm^3, PMN:70%, Lymphocyte:21%), thrombocytosis (950000/ mm^3), an indirect hyperbillirubinemia (total billirubin:1.7 mg/dL, direct billirubin: 0.6 mg/dL), and increased values for alkaline phosphatase (487 IU/dL), LDH (745 IU/dL) and erythrocyte sedimentation rate (26 mm/first hour) and a normal amylase level (86 IU/dL). Liver enzymes and α-FP were in the normal range (ALT: 34 IU/dL, AST: 25 IU/dL, α-FP: 5 mg/L) and viral markers were negative.

Abdominal sonography revealed an echogenic focus of about 60×58 mm with ill-defined borders in the left liver lobe with some extension to the right lobe. Mesenteric vessels dilatation and a heterogeneous liver echogenecity was detected. Abdomino-pelvic spiral CT scanning with triphasic contrast media (Figure 1) demonstrated the following features:

A large hypodense mass with ill-defined borders in the hepatic hilar region involving the central regions of the right and left liver lobes was evident. The mass showed no enhancement in the arterial and portal phases. The mass seemed to encase the portal vein completely, and there were some linear hypodense regions around it that could be attributed to peripheral venous dilatation. Liver size was normal. However, spleen was to some degree larger than normal, and there were several foci of splenosis around. Collateral veins in the splenic hillum and porta hepatis were seen as tortuous vessels. Some ovoid and circular hypodense foci appeared in the splenic subcapsular region, without significantly visible enhancement in different phases.

Upper gastrointestinal endoscopy revealed the lower third esophageal (grade II) and gastric fundal varices. Biopsy of the antrum was negative for *Helicobacter pylori*. Doppler sonography of hepatic and splenic veins was done to rule out splenic venous thrombosis and gave evidence for portal vein thrombosis and consecutive cavernous formation at the hepatic hillum (Figure 2). Thrombosis of the splenic vein with partial recanalization was clearly seen. Collaterals and varicose veins appeared in the gastric cardiac region.

No tumoral tissue was detected on ultrasound-guided biopsy of the mass, but liver tissue with irregular dilatation of sinusoids, partially thickened liver plates and some engorged central vein associated with small regions of few hepatocytic necrosis and replacement of inflammatory cells with a mild collagen and inflammatory cell increase in portal spaces were detected on pathology. This was compatible with the mass effect, but could not reveal its exact nature. Subsequently, CT-guided biopsy demonstrated a vaguely nodular, non-fibrotic pattern, proving the diagnosis of NRHL (Figure 3).

Bone marrow aspiration biopsy suggested a chronic myeloproliferative disorder, attributable to essential thrombocythemia.

Under supervision of the hematologist and with a diagnosis of essential thrombocytemia as a cause of venous thrombosis, hydroxyurea was started for the patient at a dose of 1 gr/day accompanied by warfarin.

Four months after the start of treatment, the patient no longer had any complaints about the abdominal pain. Platelet count was lowered down to 350,000. Although a control Doppler sonography showed resolution of the splenic vein thrombosis, the thrombosis in the portal vein and the splenomegaly (with no change in size) were still detected.

Discussion

NRHL was first reported in1953 and was called miliary hepatocellular adenoma. Multiple reports have been published on NRHL since then. NRHL occurs in both male and female, with a possible male predominance.[9,10]

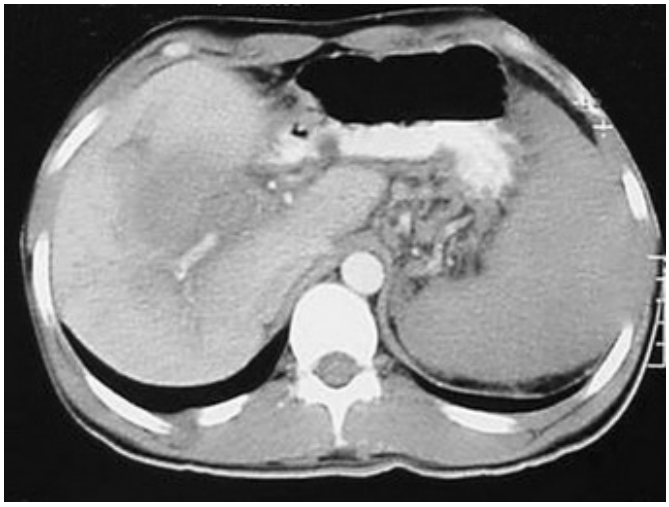

Fig 1. The large hypodense mass on abdomino-pelvic spiral CT-scanning with triphasic contrast media

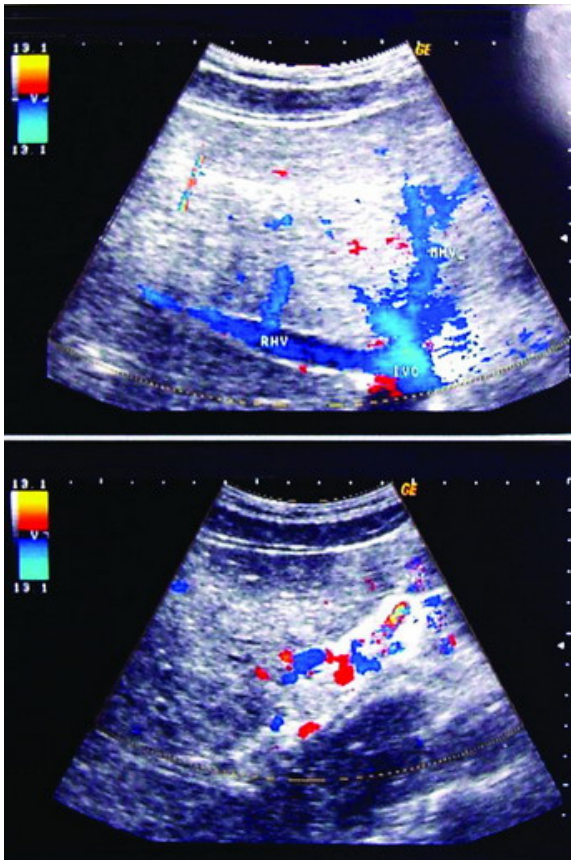

Fig 2. Splenic vein thrombosis and partial recanalization on Doppler sonography of the hepatic and splenic veins

This condition has been described in association with certain diseases (e.g. rheumatic and hematological diseases) and drugs (e.g. immunosuppressive agents**).** [3,4,11] Myeloproliferative diseases such as essential thrombocytosis, as was present in our patient, are more frequently associated with NRHL.

Two theories are stated about the pathogenesis of NRHL: the first and the most acceptable theory is obliteration of the small portal branches with atrophy of downstream lobules and compensatory hyperplasia in the adjacent lobules that have an intact portal venular supply. The second one is the preneoplastic process. [4]

Our case had presented as a typical acute pancreatitis, but with normal serum amylase level. Yet, with further evaluation we could not confirm nor rule out a diagnosis of pancreatitis. NRHL has variable clinical presentations, most of which are asymptomatic.[2] The abdominal pain of our patient might have resulted from an undiagnosed pancreatitis. Or it could have been related to portal thrombosis. Also, liver masses may manifest with abdominal pain. However, we could not diagnose the exact cause of abdominal pain in our case.

Portal hypertension seen in this case has been reported in about 50 percent of NRHL patients, which manifests itslelf as splenomegaly and gastroesophageal varices. [4,11] Structural obstruction of the portal venules due to recurrent embolization of the portal vein radicles by platelet aggregates, as well as larger thrombi generated in the portal venous system or the spleen are the principal causes of portal hypertension.[2,4]

Liver function tests are generally normal in such cases. However, serum alkaline phosphatase level is raised. Serum billirubin levels should be near the upper normal limits. [2] Our laboratory data were in accordance with the previously reported conditions.

Imaging studies such as ultrasonography and CT scanning are nonspecific and should be used as adjunctive diagnostic techniques. The lesions are often hyperechoic on ultrasonography but may be iso- or hypoechoic, or even undetectable. CT generally shows hypodense nodules with respect to the adjacent liver parenchyma and without significant enhancement after injection of intravenous contrast medium, or even be normal. [4,8] The other point found in imaging studies of this case was the presence of multiple accessory spleens.

The gold standard of diagnosis of NRHL is the histopathological study, which reveals the diffuse infiltration of the liver parenchyma by small nodules composed of regenerative hepatocytes with no or minimal fibrosis. The absence of fibrosis is the principal feature distinguishing hepatic cirrhosis from

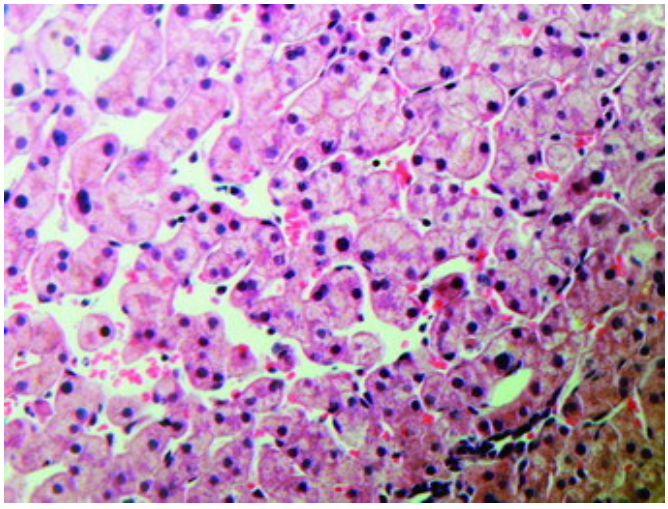

Fig 3. Vaguely nodular, non-fibrotic pattern, proving the diagnosis of nodular regenerative hyperplasia of the liver (hematoxylin and eosin)

nodular regenerative hyperplasia. [1, 2, 4]

The main differential diagnosis is focal nodular hyperplasia (FNH); but hepatocellular adenoma, metastasis, hepatocellular carcinoma and hepatoblastoma must also be considered. Radiological signs are not very specific, and the histological examination is necessary to establish the diagnosis. [10]

The prognosis of NRHL and the related portal hypertension is better than portal hypertension and cirrhosis. Nevertheless, the prognosis depends on the presence of portal hypertension, associated diseases, and the risk of rupture in larger lesions.

It is important to bear in mind the possibility of the coexistent NHRL with a liver mass and portal hypertension, especially in a background of hematological disorders.

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