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Nodular regenerative hyperplasia of the liver: A case report

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Nodular regenerative hyperplasia of the liver is characterized by hepatocellular nodules distributed throughout the liver in the absence of fibrous septa between the nodules. In the literature, most reports have been single cases so that the prevalence and clinical significance of the disease is not exactly known. The critical lesion is obliterative portal venopathy which is obstruction to terminal radicals of hepatic arterioles and portal venules, possibly secondary to endothelial cell damage. Resultant hepatic ischemia may be responsible for induction of the nodular regenerative change. Portal hypertension which is secondary to nodular regenerative hyperplasia and is often complicated by bleeding esophageal varices. We report a rare case of nodular regarative hyperplasia of the liver, with onset of symptrom in childhood.

Key words: Nodular regenerative hyperplasia, portal hypertension, portal venopathy, hepatic failure.

Nodüler rejeneretif hiperplazi, aralarında fibroz septa olmaksızın yaygın hepatosüllüler nodülerin varlığı ile karakterizedir. Çoğu çalışma olgu sunumundan ibaret olduğundan sıklık ve klinik önemi iyi bilinmez. Kritik lezyon, endotel hasarına bağlı terminal hepatik arterial ve portal venüllerin obliteratif vaskülopatisidir. Ortaya çıkan istemi, nodüler değişikliğe yol açar. Nodüler hiperplaziye sekonder portal hipertansiyon, özofagus varis kanaması nedenidir. Bu çalışmada, çocukluk çağında başlayan bir nodüler reganeratif hiperplazi olgusu sunuyoruz.

Anahtar sözcük: Nodüler rejeneratif hiperplazi, portal hipertansiyon, portal venopati, karaciğer yetmezliği.

INTRODUCTION

Nodular regenerative hyperplasia of the liver (NRHL) is defined by hepatocellular nodules distributed throughout the liver in the absence of fibrous septa between the nodules. The critical lesion is obliterative portal venopathy, which is obstruction to terminal radicals 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 (1).

The disease occurs more often in adults than in children. It has been found to be associated a with variety of conditions, such as collagen disorders, Felty's Syndrome, congestive heart failure, hematologic abnormalities (especially myeloproliferative disorders), metabolic diseases, neoplasms and drugs. Portal hypertension which is secondary to NRHL, is often complicated by bleeding esophageal varices. The correct diagnosis of NRHL is made histologically by liver biopsy, preferably an open "wedge" biopsy (5).

CASE REPORT

A 18 year old woman from South Easthern Anatolia was admitted to our internal medicine department with a five years history of recurrent non-localized abdominal pain and fatigue. There was no history of any other associated disease, or alcohol and drug use. On physical examination, there was hepatosplenomegaly and portal type collateral formation, around the umblicus. Examination of other systems was normal and laboratory values were as follows: complete blood count and peripheral blood smear showed normochrom normocytic anemia and thrombocytopenia (hemoglobin: llgr/dl, hematocrit: 35%,

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leucocyte count: 4900/mm^3, platelets: 80000/mm^3, mean corpuscular volume: 89 qm^3, mean corpuscular hemoglobin concentration: 30.4 pgr). Other laboratory values were within normal limits: erythrocyte sedimentation rate: 15 mm/hour, urea: 29 mgr/dl, creatinine: 0.55mgr/dl, AST: 32 U/L, ALT: 39U/L, LDH:349 U/L, ALP: 251 U/L, GGT: 47 U/L, total bilirubin: 0.94 mgr/dl, direct bilirubin: 0.19mgr/dl, indirect bilirubin: 0.75 mgr/dl, albumin: 4.1gr/dl, globulin: 3.7 gr/dl, serum iron: 44 qgr/dl, total iron binding capacity: 296 qgr/dl, serum ferritin: 204 ngr/ml, activated partial thromboplastin time: 34 second, prothrombin time: 15.3 second, PTA: 72% and fibrinogen 3.31gr/d. Urinalysis was normal and serum anticardiolipin antibodies Ig M and Ig G were negative.

Bone morrow biopsy was performed for investigation of bicytopenia which was normocellular. In abdominal ultrasonography (USG), liver contours were lobular and irregular. The parenchyma was heterogenous. There was evidence of the formation of many nodules, which were approximately 6 cm in diameter (macronodular) and the intrahepatic vascular structure was compressed by these nodules. There was also portal hypertension, which was characterized by splenomegaly and collateral vascular formation (figure 1). In abdominal computerized tomography (CT), there was evidence of hepatosplenomegaly and vascular collateral formation around the umblicus and left kidney, while there were isodense, multiple regeneration nodules (macronodular) in the liver, which measured 0.5cm to 7 cm in diameter. There was also caudate lobe hypertrophy. These findings were concordant with macronodular cirrhosis. Investigations for other chronic liver diseases which might be associated with portal hypertension (viral markers HbsAg, antiHBs, antiHCV and HCV-RNA) were negative. The cornea slit lamb examination and fundoscopic examination of the eyes were normal, ruling out lipid storage disease and Wilson Disease while serum seruloplasmin level and urinary excretion of copper in 24 hours were also within normal limits. To rule out primary biliary cirrhosis, alpha 1 antityripsin deficiency disease and hemochromatosis, antimitochondrial antibody, antismooth muscle antibody, alpha 1 antityripsin level, serum iron and serum ferritin level were measured and found to be within normal limits. During the initial admission period, abdominal pain was observed to be recurrent in nature. It was therefore decided to evaluate serum fibrinogen levels to rule out familial mediterranean fever, which were within normal limits. Finally, USG guided liver biopsy was performed. According to the pathologic findings of biopsy material, one half of the tissue specimen had a normal portal area, lobular structure and sinusoidal dilatation. In the other part of the biopsy specimen there were small foci of connective tissue and a proliferation of hepatocytes.

According to clinical, radiological and histological findings the diagnosis of nodular regenerative hyperplasia (figure 2) was made. Upper gastrointestinal endoscopy for a definitive diagnosis showmed grade 2 esophagel varices and antral gastritis. The patient was advised to attend for annual follow-up and was discharged.

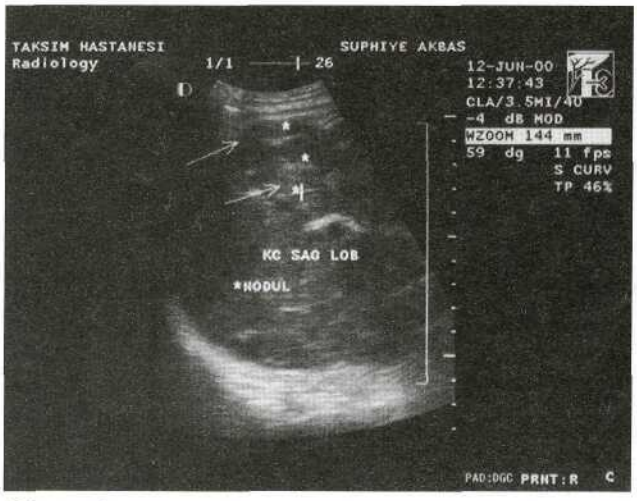

Figure 1. Nodule formation in nodular regenerative hyperplasia of the liver

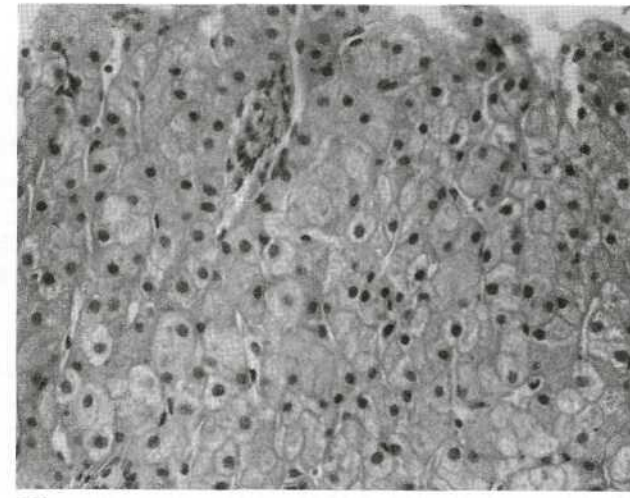

Figure 2. Proliferated hepatocytes, dilated sinusoid vessels and small foci of connective tissue area (H.E.x 125)

DISCUSSION

Nodular regenerative hyperplasia is infrequent and generally appears in association with many other diseases (3,5,6). It has been reported to occur with the same frequency in both sexes and can be observed in all ages and races. However, it is uncommon in younger age groups. Our case, with a five years history of complaints, suggests padiatric onset, which is unusual.

The disease can be described as broad hepatocellular nodule formation without fibrous septa between the nodules (1-3,5-8). If the nodules are restricted to the portal area, this variant type of NRHL is then called 'partial nodular transformation' (7) although there is controversy, about the use of this term.

Nodular regenerative hyperplasia may mimic hepatic cirrhosis and benign or malignant neoplasms of the liver (4). The possible complications of the disease include hepatic failure, rupture of the liver and malignant transformation (8).

Clinical presentations include recurrent abdominal pain, nonspecific systemic symptoms, underlying systemic disease, hepatorenal syndrome, signs of hypersplenism (splenomegaly or hematologic abnormalities) and signs of portal hypertension such as ascites, bleeding esophageal varices or splenomegaly (2,6). Collagen diseases (rheumatoid arthritis, Felty syndrome, progressive systemic sclerosis, systemic lupus erythematosus, polymyalgia rheumatica, polyarteritis nodosa), hematologic diseases (myeloproliferative disorders, lymphoproliferative disorders, idiopathic thrombocytopenic purpura), glomerulonephritis, metabolic diseases, endocrine disorders (lymphocytic thyroiditis, diabetes mellitus) and lymphomas may occur alongside NRHL (3,5,6). Wanless, in a study of 64 cases, recently suggested that NHRL is a secondary and nonspecific tissue adaptation to heterogeneous distribution of blood flow and does not represent a specific entity (3). According to Cesar et al., patients with NRHL can be divided into three groups: (a) those presenting with hepatomegaly or splenomegaly; (b) those with a history of drug therapy and (c) those in whom NRHL appears to have no clear cause (5). Our patient presented with hepatosplenomegaly in the absence of any history of drug therapy and with no other associated disease.

Dachman et al. stated that NRHL, also known as nodular transformation, is characterized histologically by diffuse involvement of the liver with hyperplastic nodules, composed of cells resembling normal hepatocytes. The nodules range in size from smaller than a hepatic acinus to conglomerate nodules forming large masses. 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 NHRL from cirrhosis and from focal nodular hyperplasia of the liver. Large nodules, viewed out of context of the diffuse nodularity, can mimic hepatocellular adenoma histologically. Thus, limited sampling by needle biopsy may yield a false diagnosis of hepatocellular adenoma or normal liver. The radiologic features of NRHL reflect its composition of cells resembling normal hepatocytes and Kupffer cells (presenting within or between the nodules), the tendency for large nodules to bleed and the presence of portal hypertention (6). Patients with NRHL may be asymtomatic or may present with idiopathic portal hypertension with varices, splenomegaly, or ascites which is evident radiologically (4,6). In our patient's abdominal CT and gastroduodenoscopy, we also found hepatomegaly, which had developed due to nodules (macronodular), splenomegaly and esophageal varices (findings of portal hypertension).

As with other forms of noncirrhotic hypertension, the prognosis is usually better than that of patients with portal hypertension due to cirrhosis. Portal diversion is useful in relieving the symptoms of portal hypertension in NRHL (6), while liver transplantation is another choice of treatment at end stage NRHL.

In conclusion, the diagnosis of NRHL can be made during physical examination, radiologically, or while investigating other diseases. In the literature, NRHL has been rarely reported in the pediatric age group. If there is hepatic dysfunction with or without portal hypertension, or a history of drug therapy in children with liver masses, then NRHL should be considered in the differential diagnosis. Early treatment is important in the prevention of the development of complications. In cases with compatible findings, multiple needle biopsies, a laparoscopically guided needle biopsy or preferably an open wedge biopsy should be taken in order to arrive at an accurate diagnosis (5, 6).

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