Nodular regenerative hyperplasia of the liver and Hodgkin's disease : a case report

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Abstract

Nodular regenerative hyperplasia (NRH) of the liver is a rare entity characterized by the presence of nodules in the hepatic parenchyma, not surrounded by fibrous septa. The pathogenesis and etiology are unknown but an association with different diseases including some hematological disorders has been described. Its association with Hodgkin's disease is infrequent. We report the case of a 63 years old man who presented symptoms and signs of portal hypertension, hepatocellular failure with progressive deterioration and death. Postmortem examination disclosed Hodgkin's disease with hepatosplenic involvement and NRH of the liver. The association of these entities could be explained by the presence of portal infiltration contributing to portal venous obliteration and leading to portal hypertension and formation of the parenchymal nodules characteristic of this entity. Other mechanisms that could cause or influence this association can not be ruled out. (Acta gastroenterol. belg., **2004**, 67, **358-360**).

Key words : nodular regenerative hyperplasia, portal hipertensión, Hodgkin's disease.

Introduction

Nodular regenerative hyperplasia (NRH) of the liver is a rare entity described by Ranström in 1953 as hepatocellular miliary adenomatosis (1). The pathologic lesion is characterized by the presence of liver parenchymal nodules without fibrous septa. The macroscopic appearance shows a wavy, irregular to micronodular surface but at microscopic examination the nodules correspond to hepatocellular hyperplasia. These are surrounded by areas of atrophic and compressed hepatocytes, but without fibrous septa, which is the main difference with cirrosis (2,3). The etiology and pathogenesis are unknown. NRH has been described in association with the use of several cytotoxic and immunosupressive drugs (2,4), oral contraceptives and anabolic steroids ; exposure to thorotrast, vinyl chloride monomer and arsenic (3,4). It has also been described in patients with neoplastic lesions, following kidney, liver, heart and bone marrow transplantation (2,3), as well as in patients with autoimmune diseases like systemic lupus, polyarteritis nodosa or Felty syndrome (2,4), toxic oil syndrome (5,6), in different members of the same family (7) and in association with hematological diseases (2,4,8,10,14-17,19). Hodgkin's lymphoma has been described in association with NRH in very few cases and the pathophysiology of this association is still unclear.

Case report

We report the case of a 63 year old man whose past medical history included untreated chronic bronchitis, untreated hypertension, appendectomy 12 years prior to admission, moderate alcohol consumption (about 20 grams per day), and tobacco use. He presented an increase in his abdominal perimeter, oedema of the lower limbs, oliguria, asthenia, anorexia and weight loss during the last two months. Physical examination revealed a temperature of 37ºC, heart rate 88 bpm and blood pressure of 100/60 mm Hg. He had conjunctival jaundice without any other cutaneous sign of chronic liver disease. Ascites was present. The respiratory, cardiovascular and neurologic examination were unremarkable. Initial laboratory testing revealed normal blood cell count, an erythrocyte sedimentation rate of 2 mm in the first hour, a prothrombin index of 42% and activated partial thromboplastin time of 37 seconds. Functional liver tests were abnormal with mild cytolysis (AST 75 U/l, ALT 83 U/l normal ranges : 5-45 U/l), and cholestasis (GGT 85 U/l normal range : 3-52 U/l, alkaline phosphatase 1417 U/l normal range : 98-295 U/l, total bilirubin 6,25 mg/dl normal range : 0,2-1 mg/dl), total serum proteins were 5,40 g/dl (normal range : 6,3-8 g/dl), total cholesterol was 127 mg% (normal range : 150-200 mg%), total sodium was 133 mEq/l (normal range : 135-149 mEq/l) and total potassium was 5,5 mEq/l (normal range : 3,5-5 mEq/l). The urine analysis showed presence of nitrates and bacteria with negative culture. An electrocardiogram showed sinus tachycardia and complete right bundle branch block.

A peritoneal paracentesis resulted in a sterile transudate ruling out spontaneous bacterial peritonitis. Intradermal tuberculin reaction (Mantoux test) was negative. A chest X-ray showed bilateral pleural effusions ; an abdominal X-ray showed calcifications in iliac arteries and pelvic branches. An abdominal ultrasound showed a normal liver size with increased echogenicity consistent with chronic liver disease, and ascites. Serum iron, copper and ceruloplasmin, serum 1-antitrypsin, antinuclear antibodies, anti smooth muscle antibodies,

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antimitochondriales antibodies, anti-LKM antibodies, serology for hepatitis B (HBc-Ab), and anti-HCV antibodies, urine delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), were all negative or normal. An X-ray esophago gastro duodenal study showed a hiatal hernia and nodularity of the esophageal wall consistent with the presence of small esophageal varices. An abdominal CT showed bilateral free pleural effusions with partial atelectasia of the posterior segment of the inferior lobe of the right lung, liver with parenchymal heterogeneity and nodular edges, morphology consistent with chronic liver disease. There was a huge amount of free intraperitoneal ascites, esogastric junction enlargement, multiple nodules in the retroperitoneal space, probably in relation with portosystemic collateral circulation in this area, and a mild splenomegaly. A 99mTc-colloidal liver scan suggested advanced hepatic disease compatible with hepatic cirrhosis. A liver biopsy was not performed because of the presence of ascites and a coagulation impairment that did not improve with vitamin K supplementation. Ciprofloxacin was started for the urinary tract infection ; despite diuretics (furosemide 120 mg/day and spironolactone 200 mg/day) and plasma volume expanders, there was no satisfactory response, without good diuretic response nor weight loss. Mild volume (3 litres) paracentesis with intravenous albumin infusion was performed twice. The patient developed a II-III grade hepatic encephalopathy that was resolved with oral, intrarectal lactulose and paramomycin. He had progressive deterioration of the liver function (progressive cholestasis with marked increase of bilirrubin and deterioration of prothrombin index) and developed fever with cough and copious sputum production so we prescribed intravenous ceftriaxone. Chest X-ray didn't show any sign of parenchymal consolidation. Blood cultures were positive for Clostridium perfringens and the antibiotic therapy was switched to penicillin and clindamycin. The patient had an acute deterioration of the level of consciousness along with sweating, paleness, increased respiratory effort and undetectable arterial pressure resulting in death. Partial necropsy limited to the abdominal cavity was performed with the following findings :

The macroscopic examination showed 6 litres of yellow ascites. The liver weighed 1300 grams with smooth surface without nodular transformation. In the surface, as well as on the cut surface we saw a diffuse dissemination of well delineated, white, round, indurated nodules 0,1 to 0,5 cm in diameter. The spleen weighted 170 grams and was infiltrated with nodules similar to those in the liver, without any other anomalies. Paraortic lymph nodes had an increased size and consistence reaching 3 cm in diameter with a nodular surface. The entire gastrointestinal tract was full of blood from the stomach to the colon ; the mucosa was normal at all levels, except for the smalls erosions in the stomach. The aorta and iliac arteries showed atheromatous plaques with no relevant reduction of the lumen.

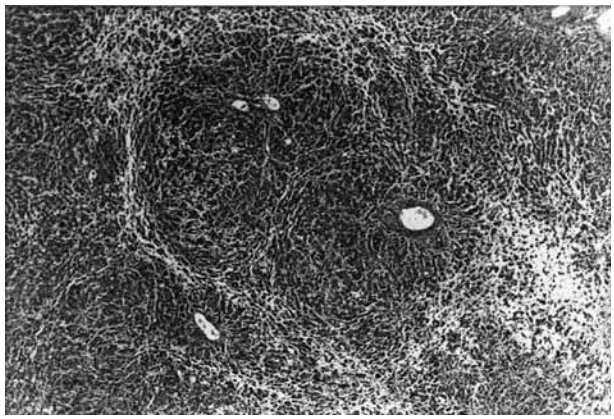

Fig. 1. — Liver with nodular transformation. Note the absence of fibrosis and nodules centered by portal tracts. HE × 40.

Histological examination showed that lymph node architecture was completely effaced and replaced by multiple, collagen surrounded nodules. These nodules showed a polymorphic infiltrate comprising lymphocytes, plasma cell and eosinophils with scattered large cells with amphophilic cytoplasm and multilobate nucleus with prominent eosinophilic nucleoli consistent with Reed-Sternberg cells. These elements were CD15 and CD30 positive. Epstein-Barr virus was not detected, neither by LMP-1 inmunostaining or in situ hybridation.

All sections examined from the liver, both hilar and peripheral, demonstrated a transformation into nodules one to three times the diameter of a normal liver acinus. Single nodules were centred by 2-3 cell thick radial trabeculae of hypertrophic hepatocytes which were circled by a few compressed cords of small hepatocytes ; no fibrosis was detected (Fig. 1). The nodules described on gross examination corresponded to a polymorphic reactive infiltrate with scattered large atypical Reed-Sternberg cells. Sometimes nodules were detected in a portal tract (Fig. 2).

The nodules of the spleen demonstrated also infiltration by atypical Reed-Sternberg cells immersed in a reactive polymorphic infiltrate. The rest of the parenchyma showed no relevant features ; no signs of passive congestion were seen.

The pathological diagnosis was Hodgkin's disease, nodular sclerosis type, with paraortic lymph nodes, spleen and liver involvement, nodular regenerative hyperplasia of the liver and upper gastrointestinal hemorrhage.

Discussion

Nodular regenerative hyperplasia of the liver is often a postmortem diagnosis in patients with several systemic diseases (8-11). The pathogenesis is not clear and several mechanism have been described. Among these, the common factor is the heterogeneity in blood supply with portal venous obliteration that leads to atrophy of normal hepatocyte trabeculae with regenerative

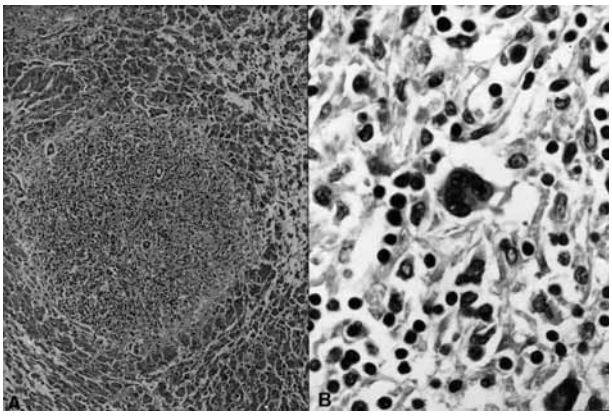

Fig. 2. — A : Detail of portal tract. Note the inflammatory infiltration and the obliteration of portal veins. HE × 40. B : Detail of a portal tract with a large multinucleated atypical cell. These cells were CD30 positive. HE × 400.

rearrangement in nodular acini whose biliary drainage is preserved (11-14).

The association with Hodgkin's lymphoma has not frequently been reported, at least six cases in the literature. Two reported cases with a diagnosis of Hodgkin's disease received chemotherapy and radiation therapy in one of them (2,3). The other four cases, like ours, had been diagnosed at necropsy (3,8,16), one of these having received anticonvulsivant therapy for epilepsy (3), but none having received chemotherapy.

Different pathogenic hypotheses have been proposed for the association of NRH with haematological diseases. One is the presence of portal lymphomatous infiltration leading to portal venous obliteration with portal hypertension (8,15,18). This would explain NRH presence in patients with untreated Hodgkin's disease as our patient. Another possibility is that NRH might be caused by miscellaneous causes such as chemotherapeutic agents (3,8). Arterial lesions, like hepatic arteritis causing obliteration of the small arteries and their adjacent portal veins, could have taken part in this association, and age related arteriosclerosis may act in concert with portal vein lesions and could explain the presence of portal venous lesions in the same acinus (8,19). Some authors have suggested that the vascular lesions are due to recurrent embolic events in small portal branches caused by platelets aggregation or thrombus from the portal system or spleen (11,21-23). Another theory for the unclear patients, is the presence of impaired arterial and portal blood flow by vascular anomaly (12,7).

In the present case, the patient did not receive any chemotherapy ; therefore the most likely mechanism of NRH was the presence of portal lymphomatous infiltration with portal vein obliteration. Aged related arteriosclerosis could have also taken part, although the atheromatous plaques were not very noticeable with no appreciable lumen reduction. We did not find any thrombus in the portal system or spleen nor any vascular anomaly.

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