CASE REPORT

Available from: http://www.jgld.ro/wp/archive/y2015/n3/a17
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.243.cho

Nodular Regenerative Hyperplasia after Liver Transplantation Complicated with Inferior Vena Cava Stenosis: a Clue for Etiopathogenesis?

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Received: 21.05.2015
Accepted: 21.07.2015

ABSTRACT

Nodular regenerative hyperplasia is a histopathological diagnosis characterized by the diffuse transformation of the liver parenchyma into regenerative nodules associated with rheumatologic and hematologic disorders, azathioprine immunosuppression or vascular injuries. The authors report the case of a 60-year-old female patient with a diagnosis of familial systemic paramyloidosis submitted to liver transplantation complicated by a hepatic artery thrombosis. A second liver transplant was performed and after 6 months she developed ascites and peripheral edema. The abdominal computed tomography (CT) showed an inferior vena cava stenosis. She underwent balloon angioplasty and an endovascular prosthesis was placed. The patient remained asymptomatic under immunosuppression with tacrolymus for 4 years, when she complained of peripheral edema and ascites. Laboratory work-up showed anemia and hypoalbuminemia with liver chemistry within the normal range. The ascites fluid analysis revealed a serum ascites albumin gradient superior to 1.1 g/L. Abdominal Doppler ultrasound and abdominopelvic CT angiogram confirmed endovascular prosthesis permeability. A percutaneous hepatic biopsy specimen was taken and histologic analysis showed, with reticulin stain, focal regenerative nodules of hyperplastic hepatocytes and internodular hepatocyte atrophy, compatible with the diagnosis of nodular regenerative hyperplasia. The case described is of particular interest as the nodular regenerative hyperplasia occurred after liver transplantation complicated with inferior vena cava stenosis, which might have contributed in a crucial way to liver parenchyma transformation.

Key words: nodular regenerative hyperplasia – liver transplantation – liver biopsy – non-cirrhotic portal hypertension.

Abbreviations: CT: computed tomography; IVC: inferior vena cava; LT: liver transplantation; NRH: nodular regenerative hyperplasia.

INTRODUCTION

The diagnosis of nodular regenerative hyperplasia (NRH) is based on the histopathological features, characterized by the diffuse transformation of the normal liver parenchyma into regenerative nodules [1, 2]. The underlying pathogenetic mechanism of NRH seems to be a vascular injury caused by several systemic diseases, drugs (mainly thiopurines, chemotherapeutic and antiretroviral agents) and other conditions that have an impact on the liver vasculature [1, 3-5]. When NRH occurs after liver transplantation (LT), it is traditionally associated with azathioprine immunosuppression. However, a vascular cause is described in some cases as an important etiology due to the abnormalities of portal hepatic blood flow which can contribute to the "atrophy-hypertrophy complex" [4]. Clinical manifestations of NRH range from asymptomatic to portal hypertension signs with variceal bleeding and ascites [4, 6-8].

Herein, we report a case of a patient in whom a NRH occurred 4 years after LT complicated with inferior vena cava (IVC) stenosis. The patient was immunosuppressed with tacrolimus and never used azathioprine. This case seems to support the idea that vascular abnormalities are important etiopathogenic factors for nodular parenchyma transformation in patients with NRH diagnosis.

CASE REPORT

A 60-year-old Caucasian female patient with a diagnosis of familial systemic paramyloidosis was submitted to LT. Three

days after LT, a hepatic artery thrombosis was diagnosed and a second LT was performed. After 6 months, she developed ascites and peripheral edema and an abdominal computed tomography (CT) showed an inferior vena cava (IVC) thrombosis. She underwent balloon angioplasty and an endovascular prosthesis was placed followed by symptoms resolution.

The patient remained asymptomatic for 4 years under immunosuppression with tacrolymus (1.5 mg per day). Four years later, she was admitted for peripheral edema and ascites refractory to diuretics. Laboratory work-up showed anemia (hemoglobin 10.6 g/dL, mean corpuscular volume 82 fL) with normal leukocyte and platelet counts, hypoalbuminemia (19.2 g/L) and renal function impairment with estimating glomerular filtration rate of 33.7 mL/min. Serum alanine and aspartate aminotransferase, total bilirubin and INR value were within the normal range. The ascites fluid analysis revealed a serum ascites albumin gradient superior to 1.1 g/L. Abdominal Doppler ultrasound excluded portal vein thrombosis. Abdominopelvic CT angiography was performed confirming the permeability of endovascular prosthesis (Fig. 1). Esophagogastroduodenoscopy showed small esophageal varices. A percutaneous hepatic biopsy specimen was taken and histologic analysis showed focal nodularity due to regenerative nodules arranged in double cell plate around a central portal supply and internodular hepatocyte atrophy, compatible with the diagnosis of NRH (Fig. 2).

Fig. 1. Abdominopelvic CT angiography confirming the permeability of endovascular prosthesis (axial view).

DISCUSSION

Amyloid polyneuropathy or hereditary amyloidosis is an autosomal dominant disease characterized by multisystemic deposition of amyloid variant of a mutant transthyretin protein [9, 10]. The major clinical manifestations are neurologic, such as sensory, motor and autonomic polyneuropathy. Liver transplant is the only proven effective therapy that stabilizes the neuropathy [9-11].

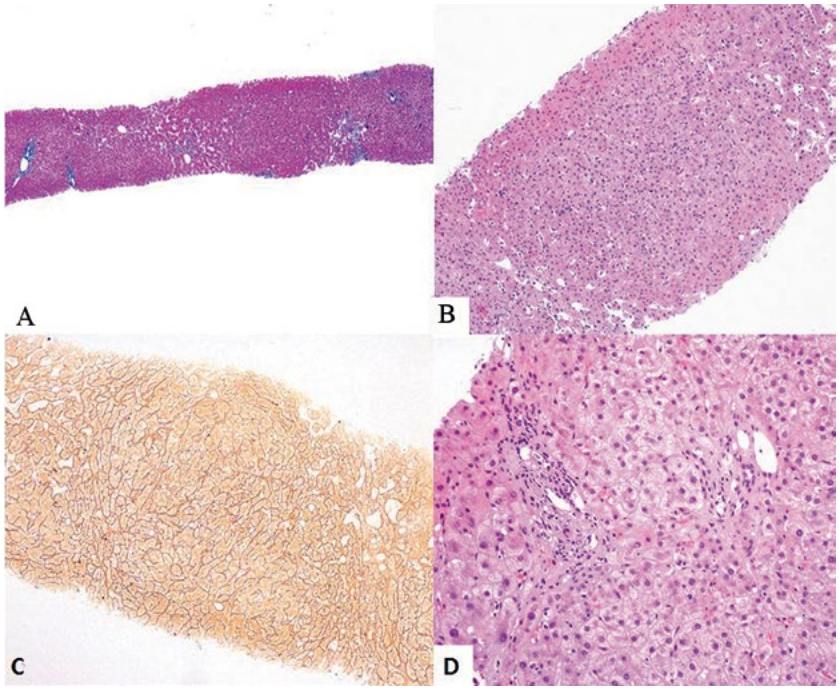

Fig. 2. Nodular regenerative hyperplasia. Liver parenchyma with focal nodularity. A) chromotrope-aniline blue (CAB) x40; B) H&E x100; C) reticulin x100. Mild lymphocytic inflammatory infiltrate in the portal tract; D) H&E x200.

To the best of our knowledge this is the first case reported in the literature of a NRH in a LT patient occurring after IVC thrombosis. The prevalence of NRH in liver transplants is about 1% [2, 8]. Devarbhavi et al. [2] classified NRH as early and later onset after LT, considering the period of four years as a landmark that distinguishes the two groups. Patients that developed NRH in the first 4 years after LT (early onset) were usually symptomatic (ascites and/or variceal bleeding) and had evidence of vascular abnormalities by ultrasound [2].

The case that we described can be classified as an early pattern as it occurred 4 years after LT and presented with ascites. In fact, this finding is in accordance with the previously reported cases of patients with recent diagnosis of NRH after LT that were usually symptomatic with portal hypertension features. Despite these concordant facts, it is important to underline that in our case no changes in the hepatic blood flow were shown. Contrary to previously published cases, the abdominal Doppler ultrasound and abdominopelvic CT angiography performed at the time of NRH diagnosis were normal. Two cases with NRH reviewed by Devarbhavi et al. [2] evidenced reversal in the hepatic histopathology, one after balloon angioplasty of the strictured hepatic vein and the other one after central splenorenal shunt. This data strongly supports a vascular etiology for NRH and highlights the possible reversibility of the process in early phases.

Despite the fact that we did not identify an abnormal hepatic blood flow at the time of the NRH diagnosis, we believe that the IVC stenosis that occurred 6 months after the second LT was a crucial event. In fact, as the patient was not under azathioprine, a commonly recognized cause of NRH in LT patients, her previous vascular event becomes even more relevant in this process.

Our patient was submitted to balloon angioplasty and an endovascular stent was placed, solving IVC stenosis. However, it seems that the adaptive hyperplastic reaction of the hepatocytes responsible for NRH after a vascular injury was permanent and evident 4 years after the thrombotic event.

In patients with LT, and mainly in cases of previous thrombotic or vascular events, physicians should have a high index of suspicion for NRH in the presence of portal hypertension manifestations. This fact is even more relevant in an acute phase of a thrombotic vascular event, when it seems to be a reversible process.

In previous clinical series of NRH patients with portal hypertension signs it was not possible to clarify whether the complications of ascites and variceal bleeding were related to the vascular abnormalities or to the NRH process. The case that we described can offer an important clue as our patient had a stent located in the IVC and a normal hepatic blood flow, which raised the hypothesis that portal hypertension signs could be a consequence of the hepatic parenchyma transformation.

CONCLUSION

This case highlights the existence of NRH after LT complicated with IVC stenosis. This diagnosis must be taken into account with a low index of suspicion in patients that have suffered from previous thrombotic and/or stenotic events in the absence of altered blood flow at the time of the disease manifestation.

Conflicts of interest: No conflict to declare.

Authors' contribution: R.C. and S.R.: drafting of the manuscript; R.S. and J.L.: histopathological image analysis; E.R.-P. and G.M.: critical revision of the manuscript.

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