Hepatocellular carcinoma arising in hepatic adenoma: diagnostic and management implications

Sandra E Fischer

Abstract

Hepatocellular adenomas (HCA) are benign neoplasms that rarely affect men. However, male subjects are more likely to develop a subset of β-catenin activated HCAs which are associated with a higher risk of malignant transformation. Moreover, glycogen storage disease is a known risk factor for the development of HCA. We report an unusual case of hepatocellular carcinoma arising in the background of multiple hepatic adenomas and glycogen storage disease type 2 in which a targeted liver biopsy failed to demonstrate the malignant component of the hepatocellular tumor. We discuss the main diagnostic criteria of HCA and its management implications.

Keywords adenoma; carcinoma; hepatocellular; liver neoplasms

Introduction

HCAs usually affect young women during their reproductive years and only rarely occur in men or children.[1] Most often patients present with an abdominal mass discovered incidentally on imaging-based exploration. Malignant transformation of HCAs into HCC is a rare complication with an overall frequency of 4.5–9%.[2–4] Patients with known glycogen storage disease, a history of androgen or anabolic steroids, male gender, and β-catenin activated HCAs have a higher risk of developing HCC.[2,5,6] We report a case of hepatocellular carcinoma arising in HCA in a patient with glycogen storage disease type 2, describe the pathological features, discuss the differential diagnoses and management implications.

Case description

A 43-year-old man with a hepatic mass discovered incidentally during insurance workup. The patient was diagnosed with glycogen storage disease type 2 at birth, and has hypercholesterolemia for which he is not on any medication. No history of significant alcohol intake. Physical examination was unremarkable and there were no stigmata of chronic liver disease. Abdomen was soft with no masses felt. Blood work did not suggest any evidence of underlying chronic liver disease and liver function was preserved. No evidence of hepatitis B or hepatitis C viral infection (hepatitis B surface antigen: negative, hepatitis B core total Ab: negative, HBV DNA: not detected, hepatitis C antibody: negative, HCV RNA PCR: not detected). An MRI abdomen/pelvis revealed a 9.5 cm tumor in the right lobe and two smaller lesions in the left lobe, 2.3 cm and 0.7 cm. An ultra-sound guided needle biopsy of the larger mass was performed. Sections of the liver biopsy are shown in Figures 1–3. The low power view of the liver biopsy shows a uniform population of hepatocytes arranged in 1–2 cells thick plates (Figure 1). Portal tracts are not seen within the lesion which also contains unpaired arteries surrounded by scant fibrous stroma. Sinusoidal dilatation is present in areas. The nucleus-to-cytoplasm ratio of the tumor cells is similar to normal hepatocytes, and mitotic figures are not present (Figure 2). Immunostaining for keratin 7 confirms the lack of ductular reaction and native bile ducts in the lesion (Figure 3). These morphological and immunohistochemical features are characteristic of HCA. Based on the results of the biopsy, the patient above underwent a liver resection (right hemi-hepatectomy). Gross examination revealed 9.8 cm tumor lesion, round and light-colored, with a central area with green discoloration, approximately 2.0 cm, in a "nodule-in-nodule" pattern. A transverse section across the tumor is shown in Figures 4–7. The low power view of the liver biopsy shows a hepatocellular lesion with a "nodule-in-nodule" pattern of grow where the central portion of lesion is separated from the outer by a thick pseudo-capsule (Figure 4). There is increased cellularity in the central part of the tumor along with an increased nucleus-to-cytoplasm ratio and irregular nuclear contours (Figure 5). The reticulin framework is also markedly decreased in the central area of the tumor (Figure 6). The outer portion of the tumor contains proliferating hepatocytes with no atypia, intact reticulin framework, unaccompanied arteries and lack of portal tracts (Figures 5 and 6). By immunohistochemistry, the atypical hepatocytes stain positive with glypican-3 antibody (Figure 7). The background liver had no evidence of cirrhosis or fibrosis. These morphological and immunohistochemical features are in keeping with malignant transformation of HCA with both components, HCA and HCC, present in the resected tumor. The patient was subsequently followed up with 6-monthly serial MRIs which have shown that he has at least ten lesions in the liver which are presumed to be hepatic adenomata. He then had an RFA to the lesion in segment 2, followed by another RFA to the lesion in segment 3. His last MRI showed stable lesions. The histopathology of the two ablated lesions was in keeping with hepatocellular adenomas.

Discussion

Clinical features

HCAs develop almost exclusively in young women during their reproductive years and only rarely occur in men or children.[1] Most often patients present with an abdominal mass discovered incidentally on imaging-based exploration. Sometimes HCA is associated with abdominal pain, discomfort, or nausea. Serum liver enzymes are infrequently elevated and routine tumor markers are normal. The most common complications include rupture and hemoperitoneum. Radiographically, most HCA show an enhanced vascular pattern. Ultrasonography (US), multidetector computed tomography (CT), and magnetic resonance (MR) imaging are often used for the evaluation of HCA.[7] Contrast-enhanced MR imaging is also a valuable tool in identifying certain subtypes of HCA, specially inflammatory and

Sandra E Fischer *MD is a Consultant in Liver Pathology at Laboratory Medicine Program, University Health Network and Assistant Professor, University of Toronto, Toronto, Ontario, Canada. Conflicts of interest: none declared.*

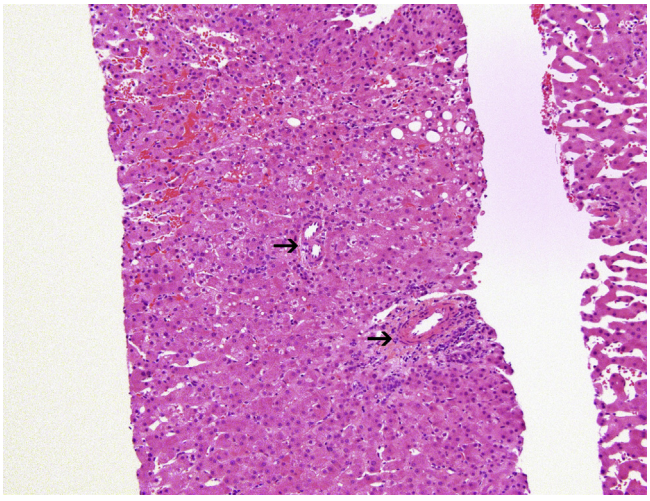

Figure 1 Ultra-sound guided liver biopsy. The image shows hepatocellular proliferation with no intervening portal tracts, with solitary arteries (arrow) surrounded by scant stroma (hematoxylin–eosin, ×100).

HNF1α-mutated HCA. Known risk factors associated with the development of HCA include exposure to estrogenic or androgenic steroids, vascular diseases (e.g. Budd–Chiari syndrome, hereditary hemorrhagic telangiectasia), genetic disorders (glycogen storage diseases type 1 and 3, tyrosinemia, familial polyposis coli, MODY3), overweight/obesity, anemia (e.g. β-thalassemia, Fanconi anemia).[7,8] HCA has a small but not negligible risk of malignant transformation into hepatocellular carcinoma (HCC).[5] Following the diagnosis of HCA, oral contraception or intake of androgen must be discontinued because regression of HCA has been described after withdrawal of hormones.[9,10] Surgical treatment is recommended for HCA that do not regress after hormone withdrawal.[1] Tumor excision may also benefit patients with large lesions (>4 cm) because of the risks for tumor growth, life-threatening hemorrhage, and development of HCC.[10,11] HCA is usually solitary, but hepatocellular adenomatosis (i.e. more than 10 HCAs) is present 10–24% of patient with HCA and presents management difficulties.[9]

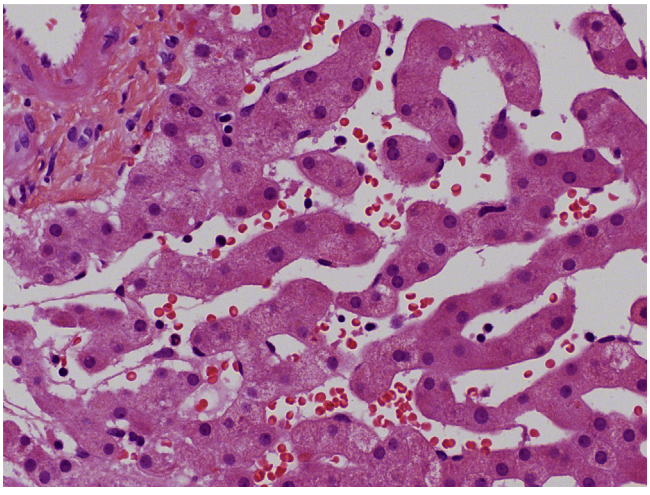

Figure 2 Ultra-sound guided liver biopsy. The hepatocyte plates are 1–2 cells thick, and they lack nuclear atypia (hematoxylin–eosin, ×200).

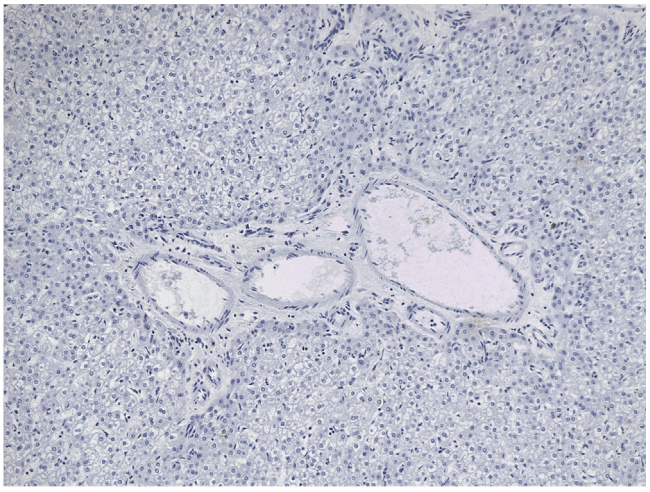

Figure 3 Hepatocellular adenoma. The image shows negative staining with keratin 7 antibody, indicating absence of bile ductules (immunohistochemistry, ×100).

Gross findings and histopathology

Macroscopically, HCA is round and soft, typically lighter in color than the surrounding liver parenchyma.[9,12] Necrosis or hemorrhage may be present. Fibrosis or nodularity is uncommon, and lesions are typically non-encapsulated. On histological examination, HCA consist of a uniform population of hepatocytes arranged in 1–2 cells in width. The tumor cells may have an eosinophilic or clear (glycogen-rich) cytoplasm, or may contain fat droplets or lipofuscin pigment.[8,12] HCA typically lacks significant nuclear atypia, and the nucleus-to-cytoplasm ration of the tumor cells is similar to normal hepatocytes. Mitotic figures are absent or rarely present. The reticulin framework in HCA is intact or only focally decreased on reticulin stains. Portal tracts are normally absent within the lesion which is typically supplied by isolated arteries unaccompanied by bile ducts. The transition between HCA and the adjacent non-lesional liver parenchyma is smooth. A pseudoglandular pattern of growth may be present

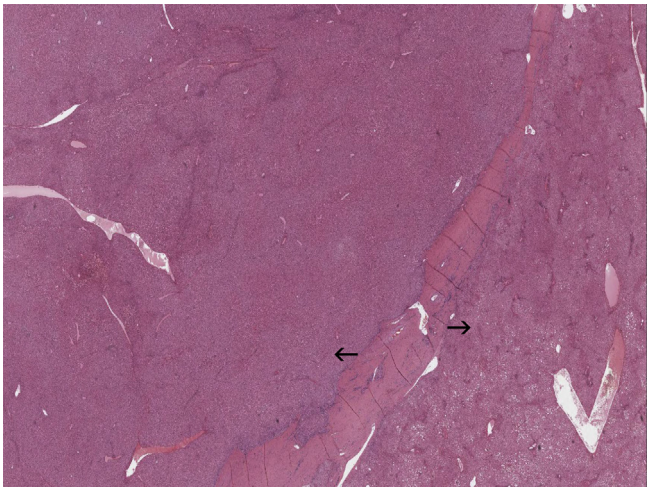

Figure 4 Section of right lobe of liver showing a tumor with "nodule-in-nodule" pattern of growth with a central hypercellular area (left arrow) surrounded by a pseudo-capsule. Right arrow points towards the less cellular peripheral portion of the mass (hematoxylin–eosin, ×25).