

Hepatocellular Carcinoma with Fibrolamellar Pattern in a Patient with Autoimmune Cholangitis

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Abstract

A 75-year-old woman with a 15-year history of autoimmune cholangitis underwent orthotopic liver transplantation because of progressive liver decompensation. A clinically unsuspected hepatocellular carcinoma was found. A portion of the tumor showed fibrolamellar differentiation. Hepatocellular carcinoma, either with the usual pattern or with a fibrolamellar pattern, is rare in the setting of primary biliary cirrhosis, but has been seen in the setting of autoimmune hepatitis. Autoimmune cholangitis is a relatively recently recognized form of autoimmune liver disease whose association with hepatocellular carcinoma has yet to be determined.

Key Words: Autoimmune cholangitis, primary biliary cirrhosis, hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma.

Introduction

In recent years, there has been recognition of “autoimmune cholangitis” (AIC) as a new variant of autoimmune liver disease serologically indistinguishable from type 1 autoimmune hepatitis, often with high titers of antinuclear antibodies (ANA). Autoimmune cholangitis has the clinical, biochemical, and histologic features of primary biliary cirrhosis (PBC), but without demonstrable antimitochondrial antibodies (AMA) (1–3). Liver biopsies from these patients show the bile duct damage characteristic of PBC and may also show granuloma formation. Patients with this condition have previously been designated as having “atypical PBC” or “AMA-negative PBC.” Some consider that this entity is unique (4), while others believe it controversial (5). Patients with autoimmune cholangitis, like patients with autoimmune hepatitis (6), appear to be more responsive to corticosteroid therapy than patients with PBC. The response to ursodeoxycholic acid has been shown to be similar in both AMA-positive and AMA-negative PBC (7).

Primary biliary cirrhosis was first described by Addison and Gull in 1851 (8) and then by Hanot in 1892 (9), but only became well recognized as a distinct disease entity in the 1950s and 1960s (10–12). Primary biliary cirrhosis is a disease typically of middle-aged women who present with the slow onset of cholestasis (13). The diagnosis of PBC is based on the findings of elevated serum alkaline phosphatase values indicative of bile duct destruction, increased levels of immunoglobulin M (IgM), increased titers of antimitochondrial antibodies, and histological evidence of bile duct injury and associated portal inflammation (14). In its early stages, as is well known, the name “cirrhosis” is incorrect, since the development of fibrosis and regenerative changes of hepatocytes does not occur for five or more years after the onset of disease (14, 15). The development of hepatocellular carcinoma in the setting of PBC has been thought to be exceedingly rare (16–21). Recently, however, an incidence of 6% has been reported in a study of 123 patients (22). In some patients with PBC, hepatitis C virus has been implicated as a potential co-carcinogenic factor (23).

Clinical studies (1–4, 6) and response to therapies (5–7) have shown that autoimmune cholangitis is a separate entity. In addition, recent studies have shown that the T-cell lymphocyte inflammatory cell infiltration in autoimmune cholangitis is distinct from that of both the usual form of autoimmune hepatitis and of PBC (24).

We had the opportunity to study the liver from a patient with autoimmune cholangitis who underwent orthotopic liver transplantation. A clinically unsuspected hepatocellular carcinoma was found in which there was a distinctly unusual histologic pattern. To the best of our knowledge, there has not been a previously reported case of hepatocellular carcinoma arising in the setting of autoimmune cholangitis.

Case Report

A 75-year-old Hispanic woman first developed clinical evidence of liver disease in 1981, at the age of 60, when she presented with pruritus and jaundice. The patient was reported to have detectable ANAs at significant levels, no detectable AMAs, and a liver biopsy consistent with PBC. Unfortunately, these studies were not available for review. Other laboratory test results were similarly not available. Her liver disease remained stable until 1995, when she had manifestations of progressive liver decompensation, with ascites, peripheral edema, increasing jaundice, and fatigue. The serum bilirubin value was 10.9 mg/dL, and reduced synthetic function was evidenced by a serum albumin value of 2.5 g/dL. At this time the ANAs were only demonstrable at a titer of less than 1:40, and AMAs were not unequivocally demonstrable. The α -fetoprotein value was 8.5 ng/mL. There was, however, no evidence of hepatic encephalopathy, and varices were not seen endoscopically. Imaging studies confirmed the presence of cirrhosis and did not identify a tumor. The patient underwent orthotopic liver transplantation in June 1996. Her post-operative recovery and subsequent course were uneventful and she was well eight months after transplantation.

Pathology

The explanted liver weighed 1440 grams and showed a deeply cholestatic macronodular cirrhosis (**Fig. 1**) with a few regenerative nodules greater than 1 cm in diameter (macroregenerative nodules [MRNs]) (**Fig. 2**).

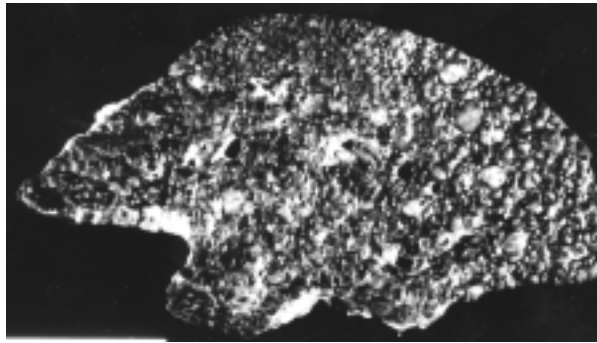


Fig. 1. Photograph of explanted liver showing macronodular cirrhosis with multiple macroregenerative (“dysplastic”) nodules.

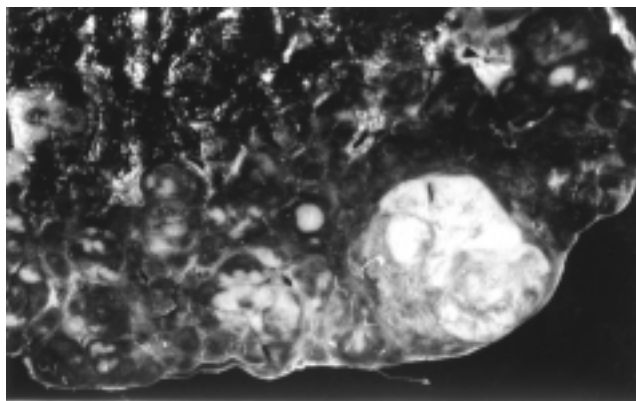


Fig. 2. Photograph of macroregenerative nodule which contained hepatocellular carcinoma.

The typical histologic features of the cirrhotic stage of PBC were seen, with marked paucity of bile ducts and without the early lesions characteristic of PBC (10). Regenerative nodules of varying size and shape were separated by broad fibrous septa in which there was marked chronic inflammation, as evidenced by infiltration of mostly lymphocytes and some plasma cells. The paraseptal rim of hepatocytes showed hydropic change of the cytoplasm with distinct bile stasis (i.e., “cholate stasis” or “feathery degeneration”). One of the 1.2 cm macroregenerative nodules consisted almost entirely of well- to moderately well-differentiated hepatocellular carcinoma (**Fig. 3a**). The most peripheral portion of the tumor showed the pattern of fibrolamellar hepatocellular carcinoma (**Fig. 3b**), with large, polygonal, slightly granular, eosinophilic malignant hepatocytes having large

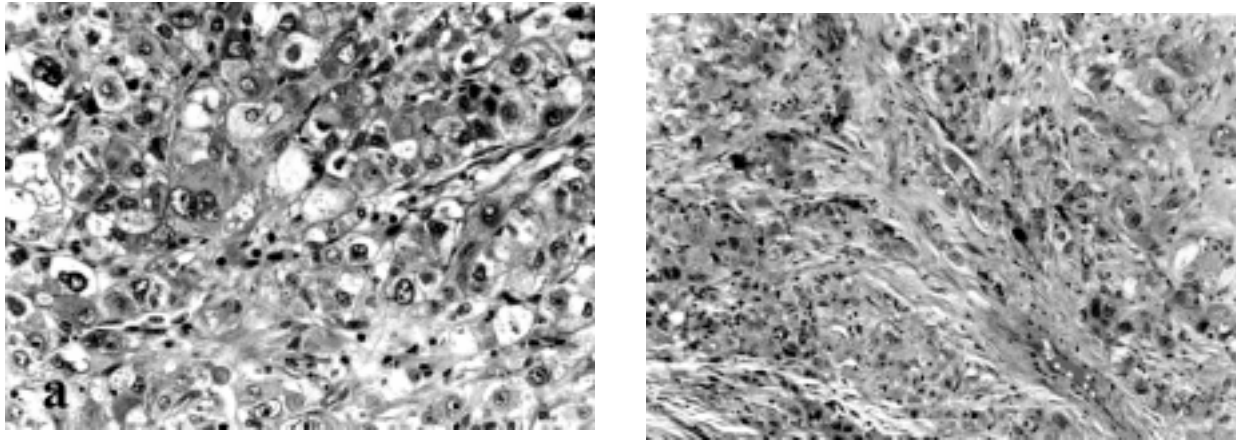


Fig. 3. a. Photomicrograph showing typical hepatocellular carcinoma arising in a macroregenerative nodule (Hematoxylin-eosin, x200). b. Photomicrograph of subcapsular portion of hepatocellular carcinoma showing features of fibrolamellar carcinoma (Hematoxylin-eosin, x100).

nuclei with prominent nucleoli. Tumor cells in this area were arranged in trabecula and separated by lamellar strands of relatively thin collagen fibers. Tumor cells reacted with antibody to α -1-antitrypsin and α -1-antichymotrypsin, but not to α -fetoprotein. There was neither vein invasion nor evidence of metastasis.

Discussion

Hepatocellular carcinoma is a well-known complication of cirrhosis (16, 21). It is prevalent in patients with cirrhosis due to hepatitis B (16, 25–29) and C (27–31), but is also well known to occur in the setting of hemochromatosis (16, 21, 32), α -1-antitrypsin deficiency (33), tyrosinemia (34), as well as other conditions (16, 21). Alcoholic liver disease is often complicated by the development of hepatocellular carcinoma, but in many patients the direct etiology may be unclear (16, 21, 35). In addition, hepatocellular carcinoma has been reported in patients with autoimmune hepatitis (36, 37), although it has recently been suggested that hepatitis C might be a contributing factor for at least some of these patients, since antibodies to hepatitis C can be found in some patients with autoimmune hepatitis (38).

Although the concept of the macroregenerative nodule, also known as “adenomatous hyperplasia,” has only recently been widely accepted (39–43), the concept of hepatocellular carcinoma arising in the setting of the larger nodules of a macronodular cirrhosis is well known (44). Progression of the regenerative nodule in cirrhosis may lead to the formation of macroregenerative nodules, or alternatively, macroregenerative nodules may arise *de novo* as “dysplastic nodules” (45). Macroregenerative nodules are commonly seen in the cirrhotic stage of PBC (46), and are more likely to be sites of liver cell dysplasia and early changes of hepatocellular carcinoma (40–42). In our patient, there were multiple macroregenerative nodules, one of which had unequivocal

hepatocellular carcinoma.

Fibrolamellar carcinoma is a variant of hepatocellular carcinoma, with distinctive histological and clinical features (47), including large eosinophilic cells arranged in trabecula that may be thin or thick and that are separated by fibrous bands imparting a lamellated appearance. Ordinary hepatocellular carcinoma can have significant fibrosis and can resemble fibrolamellar carcinoma (48), but in the usual case, the tumor cells of hepatocellular carcinoma do not have as much cytoplasm and there is generally considerable variation in nuclear and nucleolar size. In our case, the area of the tumor illustrated in **Fig. 3b** is indistinguishable from a typical case of fibrolamellar carcinoma, with large tumor cells separated by laminated collagen. In our experience, this pattern of hepatocellular carcinoma is quite unusual and is distinct from that of sclerosing hepatocellular carcinoma. The area with the fibrolamellar pattern did not represent the infiltrative edge of a usual hepatocellular carcinoma, where considerable reactive sclerosis might be seen, since it was entirely contained within the macroregenerative nodule.

The frequency of occurrence of hepatocellular carcinoma in the setting of autoimmune cholangitis is unknown. Autoimmune cholangitis is a relatively recently recognized disorder, the nature of which is still somewhat controversial. In the patient with long-standing autoimmune hepatitis, the incidence of hepatocellular carcinoma may be relatively high (36). In contrast, hepatocellular carcinoma is uncommon in PBC (16–22).

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