Hepatocellular Carcinoma in a Male Patient with Early Stage (Stage I) Primary Biliary Cirrhosis

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Abstract

The true incidence of hepatocellular carcinoma (HCC) in patients with primary biliary cirrhosis (PBC) remains undetermined due to limited epidemiological studies and some conflicting results. Some studies indicated that in PBC, male gender, cirrhosis, hepatitis C virus (HCV) superinfection, and history of blood transfusion are associated with the development of HCC, and the occurrence of HCC in the early stage of PBC is rare. We present herein a 75-year-old male patient with stage I PBC who developed oropharyngeal squamous cell carcinoma, followed by HCC and duodenal adenocarcinoma without hepatitis B or C virus infection. While it could be argued that the concurrence of HCC and stage I-PBC in our patient was coincidental, patients with early stage PBC should be strictly followed up as cirrhotic patients with PBC by monitoring the serum concentration of tumor markers for HCC and appropriate imaging methods.
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Key words: hepatocellular carcinoma, primary biliary cirrhosis, Scheuer's classification

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic autoimmune liver disease characterized by progressive bile duct injury caused by portal and periportal inflammation, resulting in fibrosis and eventual cirrhosis in a significant proportion of patients (1). The presence of cirrhosis, especially in patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, is a major risk factor for the development of hepatocellular carcinoma (HCC) (2). The association of PBC and HCC is not well known, but almost all reported cases with HCC had cirrhotic (stage IV) PBC (3). Like other types of cirrhosis, atypical adenomatous hyperplasia has also been seen in the periphery of some HCC in cirrhotic PBC liver, suggesting that HCC in PBC may evolve through a multi-step process (4). Thus, the development of HCC in early-stage PBC is reported to be rare. In the present report, we described a male patient with stage I-PBC who developed HCC without HBV or HCV infection.

For editorial comment, see p 169.

Case Report

A 75-year-old Japanese man was admitted to our department in November 2002 for further management of an asymptomatic liver mass. Three months earlier, the patient was diagnosed with oropharyngeal squamous cell carcinoma and underwent systemic chemotherapy including 5-fluorouracil and nedaplatin combined with radiotherapy. The combination chemo-radiotherapy induced complete tumor remission and no further viable cancer cells were histologically identified. On admission, physical examination showed mild hepatomegaly but no ascites. There was no family history of liver disease, malignancy, or autoimmune disease, and the patient had never received a blood transfusion. The patient smoked approximately 7 cigarettes per day for 55 years, and reported an average alcohol intake of 45–60 g per day for 55 years. Laboratory tests revealed anemia and an elevated serum level of protein induced by vitamin K absence or antagonist II (PIVKA-II). Anti-nuclear antibody and anti-mitochondrial antibodies (AMA) by both indirect immunofluorescence and enzyme-linked immunosorbent assay

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Table 1. Laboratory Data on Admission

Peripheral blood		ChE	95 (IU/*l*)	Tumor markers	
WBC	4,000 (/mm^3)	BUN	13 (mg/dl)	AFP	3.6 (ng/ml)
Seg	63 (%)	Cr	0.7 (mg/dl)	PIVKA-II	465 (mAU/ml)
Ly	24 (%)	TTT	14.9 (Unit)	CEA	5.6 (ng/ml)
Eo	1 (%)	ZTT	15.8 (Unit)	SCC antigen	3.1 (ng/ml)
RBC	298×10^4 (/mm^3)	AMY	33 (IU/*l*)	CYFRA	1.9 (ng/ml)
Hb	9.7 (g/dl)	T.Chol	138 (mg/dl)	Viral markers	
Ht	30.1 (%)	T.G.	127 (mg/dl)	HBsAg	(–)
PLT	18.4×10^4 (/mm^3)	Na	141 (mEq/*l*)	HBsAb	(–)
PT	101 (%)	K	4.7 (mEq/*l*)	HBeAg	(–)
Blood chemistry		Cl	108 (mEq/*l*)	HBeAb	(–)
TP	7.4 (g/dl)	ICG R15	18 (%)	HBcAb	45.9 (%)
Alb	3.9 (g/dl)	Serological tests		HBcAb (×200)	0 (%)
T-Bil	0.6 (mg/dl)	CRP	0.42 (mg/dl)	HBV-DNA (TMA)	(–)
AST	23 (IU/*l*)	IgG	1,310 (mg/dl)	HCV-Ab	(–)
ALT	10 (IU/*l*)	IgM	132 (mg/dl)	HCV-RNA (PCR)	(–)
LDH	185 (IU/*l*)	IgA	333 (mg/dl)	HGV-RNA (NCR)	(–)
ALP	376 (IU/*l*)	ANA	×160 (cytoplasmic)	TTV-DNA (PCR)	(–)
γ-GTP	42 (IU/*l*)	AMA	×320		
LAP	42 (IU/*l*)	Anti-M2	149.4 (Index)		

(MESACUP-2 Test Mitochondrial M2 kit, Medical & Biological Laboratories, Nagoya, Japan) were positive. There was no evidence of chronic hepatitis B, hepatitis C, hepatitis G, or TT virus infection except for a low-titer of antibody to hepatitis B core antigen (HBcAb) (Table 1). Abdominal ultrasonography showed a hypoechoic tumor in the left lobe (segment III) of the liver. Abdominal computed tomography showed a contrast-enhanced liver mass, 20 mm in diameter, in the same segment (Fig. 1). The mass appeared as an area of hyperintensity on both T1- and T2-weighted unenhanced magnetic resonance images. Hepatic arteriography demonstrated a hypervascular tumor in segment III of the liver. With a diagnosis of HCC ["liver damage" was grade A and "tumor staging" was stage I according to the Japanese classification of primary liver cancer (5)], the patient received 1 mg of mitomycin and 5 mg of epirubicin with 1ml of Lipiodol (Lipiodol Ultrafluide, Laboratoire Guerbet, Aulnay-sous-Bois, France) by infusion through the hepatic artery and transcatheter arterial embolization (TAE) was subsequently performed with gelatin-sponge (Gelfoam, Pharmacia & Upjohn, Kalamazoo, MI, USA) in December 2002. Upper gastrointestinal endoscopy showed a flat elevated lesion in the duodenal bulb. Histopathological examination of a duodenal biopsy specimen confirmed the diagnosis of a well-differentiated adenocarcinoma of the duodenum.

Because TAE did not lead to complete necrosis of HCC, partial hepatic resection and surgical mucosal resection of the duodenum were performed in February 2003. The cut surface of the resected specimen of the liver demonstrated a whitish solid tumor measuring 14×13 mm in diameter in segment III. A grayish segment, 6×5 mm in diameter, was seen in the whitish solid tumor (Fig. 2). Histopathological examination of the surgical specimen of the liver showed a moderately differentiated HCC in the grayish segment (Fig. 3), and a necrotic tissue due to TAE in the whitish part of the tumor. Histopathological examination of the surgical specimen of the duodenum demonstrated a well-differentiated adenocarcinoma within the duodenal mucosal layer. The noncancerous liver specimen showed lymphoplasmacyte infiltration and a damaged bile duct surrounded by epithelioid granuloma in the portal tract, representing stage I-PBC (3), but no histopathological evidence of alcohol or nodular regenerative hyperplasia (Fig. 4). Both hepatic and duodenal resections were curative, but the patient died of recurrent

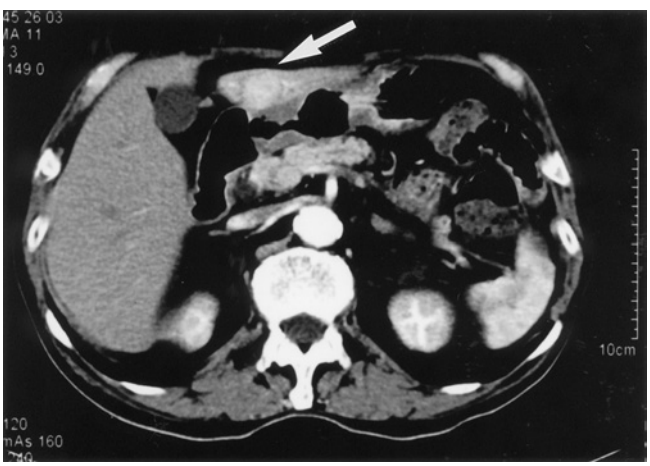

Figure 1. Abdominal computed tomography showed an enhanced liver mass, 2 cm in diameter, in the left lobe (segment III) of the liver (arrow).

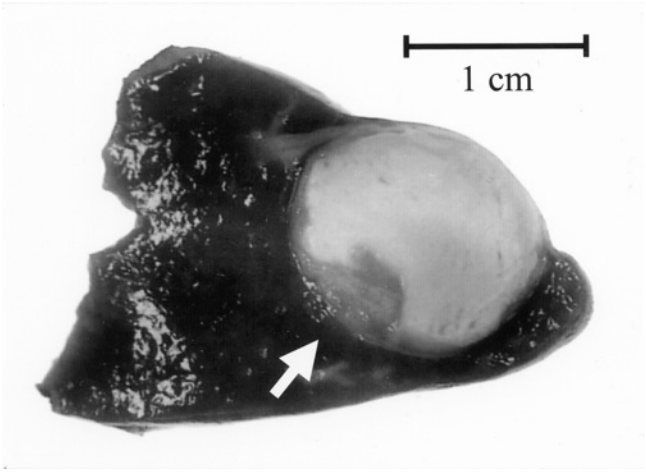

Figure 2. The cut surface of the resected specimen demonstrated a whitish solid tumor, 14×13 mm in diameter, in segment III of the liver. A grayish segment, 6×5 mm in diameter, was seen in the tumor (arrow).

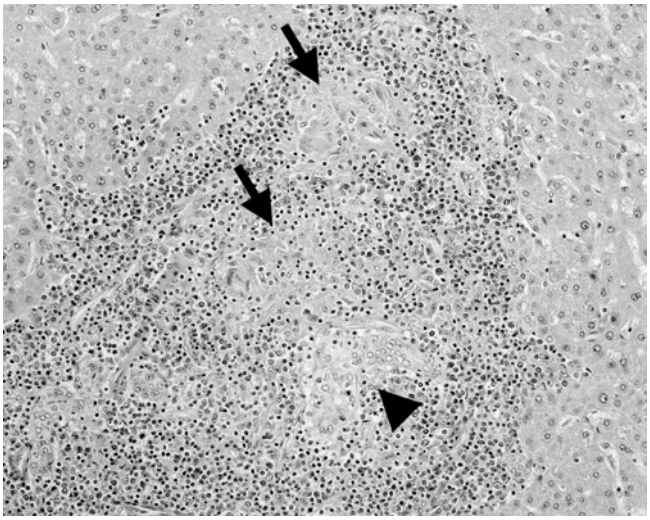

Figure 4. The non-cancerous liver specimen showed lymphoplasmacyte infiltration and damaged bile duct (arrowhead) surrounded by epithelioid granuloma (arrows) in the portal tract, representing stage I-primary biliary cirrhosis (HE stain, ×150).

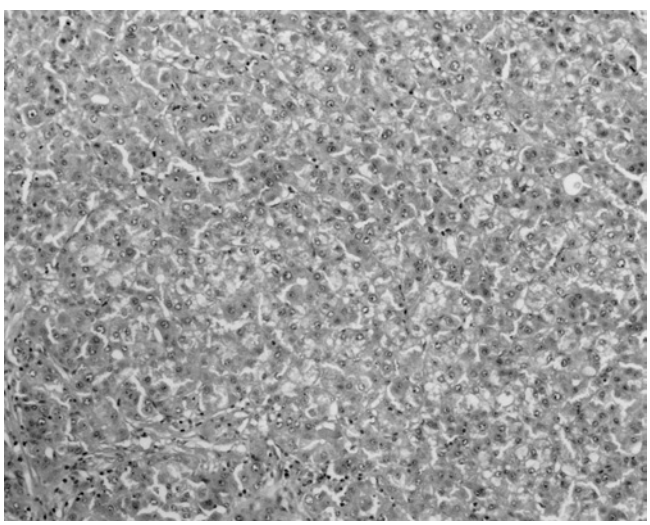

Figure 3. Histopathological examination of the surgical specimen showed a trabecular type moderately differentiated hepatocellular carcinoma (HE stain, ×100).

oropharyngeal squamous cell carcinoma in January 2004.

Discussion

Our patient developed oropharyngeal squamous cell carcinoma, followed by HCC and duodenal adenocarcinoma. It is well known that patients with squamous cell carcinoma of the head and neck are at risk of developing a second or subsequent primary tumor. Second tumors occur more likely in male patients, and the most common site being the lung, followed by the mouth, oropharynx, larynx, hypopharynx, and bowel. Most tumors are squamous cell carcinoma or adenocarcinoma, but HCC or duodenal cancer is seldom reported (6).

There are several clearly identified risk factors associated with HCC, including HBV, HCV, alcohol, cirrhosis, older age, and male gender (7). The present patient had no evidence of HBV or HCV infection, and also had no histopathological evidence of alcoholic liver injury or cirrhosis. The association of PBC and HCC is not known to date because epidemiological studies on this issue are limited and sometimes with conflicting results. Some studies have described that PBC does not increase the risk of developing HCC (8), but others showed that the incidence of HCC was high in patients with PBC (9–11). The latter studies indicated that male gender, advanced-stage PBC, HCV superinfection, and a history of blood transfusion were associated with the development of HCC. Indeed, most cases of HCC were reported in patients with histopathological stage IV (3) of PBC. To our knowledge, during the period between 1990 and 2003, 56 patients (37 women and 19 men with a mean age of 70.1 years) with HCC arising in PBC who were seronegative for both hepatitis B surface antigen (HBsAg) and anti-HCV antibody were reported. Of these, 50 (89%) were considered to have histopathologically-confirmed stage IV, and none was at stage I. Gluskin et al (12) reported a case of HCC associated with stage I-PBC in 1985, but anti-HCV antibody was not investigated. Thus, as far as we are aware, the present patient is the first reported case of HCC in stage I-PBC without serological evidence of HBV and HCV superinfection.

The etiology of HCC arising in non-cirrhotic PBC remains unknown. Like some other autoimmune diseases, e.g.,

sicca syndrome (13), scleroderma (14), and rheumatoid arthritis (15), early reports indicated an increased risk of hepatic or extrahepatic cancers such as breast cancer in PBC patients, but the evidence from later studies has been conflicting with the exception of hepatobiliary malignancies (16–18). One possible explanation is that there may be some mitogenic factors in the bile of PBC patients (16). Another possibility is the notion of "molecular mimicry" by microbial antigens such as *Escherichia coli*, *Helicobacter* sp, *retroviruses, and Chlamydia pneumoniae*, which has been proposed as an underlying mechanism for PBC (1). PBC is considered to be an autoimmune liver disease characterized by antibodies and T cells reactive to host proteins. However, the causative factor for the autoimmunity is unknown. One hypothesis is the "molecular mimicry", which suggests that an acute or chronic infection caused by a virus or bacterium carrying antigen homologous to a host protein may elicit B and T cell responses that cross-react with the autoantigen (19). If future studies identify an infection involved in the pathogenesis of PBC, the role of the same infecting pathogen in the development of HCC will certainly need to be explored (7). It should also be noted that the present patient had a low serum titer of HBcAb with negative HBsAg, suggesting past exposure to HBV. De Mitri et al (20) analyzed liver tissues and serum samples from 19 patients who were negative for HBsAg, and demonstrated that 7 (37%) patients were HBV-DNA positive by polymerase chain reaction (PCR) in liver tissue. Ghisetti et al (21) also reported that 4 (80%) of 5 HBsAg-negative HBcAb-positive liver transplantation recipients were positive for intrahepatic HBV-DNA by PCR. Since no PCR assay was conducted to detect HBV-DNA in the resected liver tissue in our patient, occult HBV infection and subsequent development of HCC cannot be excluded completely.

In the present patient, nodular regenerative hyperplasia (NRH) should also be considered because this nodule is common in the early histological stages of PBC (22). In this condition, multiple hyperplastic parenchymal nodules with thickened liver-cell plates are seen but fibrosis is absent or slight (23). Usually, abdominal ultrasonography shows hypoechoic or isoechoic masses, and computed tomography shows a hypodense pattern with no enhancement on contrast (24). Although the pathogenesis of NRH associated with the early stages of PBC is uncertain, it may be responsible for the sinusoidal component of portal hypertension (25). Regarding the pathogenesis of NRH, two major theories, preneoplastic and vascular, have been proposed (26). However, evidence for an association between NRH and neoplasia in humans is weak. Nzeako et al (26) reported that HCC could develop within the dysplastic foci that occur in livers with NRH, and also raised the possibility that NRH in some cases was caused by tumor-related venous obliteration. In this context, Wanless (27) further suggested that the reverse hypothesis, that vascular obliteration might lead to hepatocellular neoplasm, could be reasonable. Anyway, the clinical data showed that HCC was highly suspected, and histopathological examination showed no evidence of NRH in tumorous and non-tumorous liver specimens in our patient.

While the development of HCC and stage I-PBC in our patient could have been coincidental, it should be stressed that the number of reported cases of HCC development in early-stage or precirrhotic PBC has increased in the last 10 years (28–31). Therefore, patients with early-stage PBC should also be strictly followed up as high-risk patients for HCC by monitoring the serum concentration of tumor markers and appropriate imaging methods.

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