

# Successful Radiofrequency Ablation Therapy for Hepatocellular Carcinoma in a Male Patient with Early Stage Primary Biliary Cirrhosis and Positive Serum Hepatitis B Core Antibody

Chien-Wei Su<sup>1,5,7</sup>, Jaw-Ching Wu<sup>2,5\*</sup>, Yi-You Chiou<sup>3</sup>, Shyh-Haw Tsay<sup>4</sup>, Teh-Ia Huo<sup>1,6</sup>,  
Yi-Hsiang Huang<sup>1,5,7</sup>, Hung-Hsu Hung<sup>1</sup>, Han-Chieh Lin<sup>1,7</sup>, Shou-Dong Lee<sup>1,7</sup>

<sup>1</sup>Division of Gastroenterology, Department of Medicine, Departments of <sup>2</sup>Medical Research and Education, <sup>3</sup>Radiology, and <sup>4</sup>Pathology and Laboratory Medicine, Taipei Veterans General Hospital; Institutes of <sup>5</sup>Clinical Medicine and <sup>6</sup>Pharmacology and <sup>7</sup>Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Hepatocellular carcinoma (HCC) occurring in a 66-year-old male patient with early stage primary biliary cirrhosis (PBC) was successfully treated by radiofrequency ablation (RFA) therapy. He was diagnosed with PBC based on the findings of pruritus, elevated serum alkaline phosphate level and positive serum antimitochondrial antibody in 2005. The serologic tests for hepatitis B surface antigen, hepatitis B surface antibody and hepatitis C virus antibody were all negative. But antibody against hepatitis B core antigen was positive. Abdominal ultrasonography and dynamic computed tomography revealed 1 hypervascular tumor, 2.6 cm in diameter, in segment V of the liver in 2007. Liver biopsy showed a moderately differentiated HCC. Non-tumorous liver was compatible with Scheuer's classification of stage II PBC. The tumor was successfully treated by RFA. This case report demonstrates that HCC can arise from precirrhotic PBC and can be successfully treated by RFA. Regular surveillance for HCC is warranted for all patients with PBC, irrespective of stage. [*J Chin Med Assoc* 2008;71(1):40–44]

**Key Words:** hepatitis B virus, hepatocellular carcinoma, primary biliary cirrhosis, radiofrequency ablation therapy

## Introduction

Primary biliary cirrhosis (PBC) is a chronic, slowly progressive, cholestatic, autoimmune disease of the liver.<sup>1,2</sup> It is characterized by fatigue, pruritus and the presence of antimitochondrial antibody (AMA).<sup>3</sup> Histologically, PBC causes portal inflammation and destruction of the small intrahepatic bile ducts through an immune-mediated mechanism.<sup>1</sup> It affects predominantly middle-aged women.<sup>1–4</sup> The ratio of women to men is around 10 to 1.<sup>1</sup> The clinical manifestations,

progression and prognosis of PBC are quite diverse.<sup>1–4</sup> Some patients remain asymptomatic decades after diagnosis, while others progress to end-stage liver disease rapidly in spite of ursodeoxycholic acid (UDCA) therapy.<sup>4,5</sup> Hepatocellular carcinoma (HCC) has been reported in some patients with PBC.<sup>6–15</sup> The tumors occurred in the late stage of PBC in the majority of cases and were seldom diagnosed in the asymptomatic stage.<sup>10–12,15</sup> Hence, except for liver transplantation, such patients rarely underwent curative therapies such as resection surgery or local ablation therapy and were



\*Correspondence to: Dr Jaw-Ching Wu, Institute of Clinical Medicine, National Yang-Ming University School of Medicine, 155, Section 2, Li-Nong Street, Taipei 112, Taiwan, R.O.C.  
E-mail: jcwu@vghtpe.gov.tw • Received: June 28, 2007 • Accepted: September 14, 2007

associated with dismal outcomes.<sup>13</sup> It may be due to poor liver reserve in the late stage of PBC when HCC was diagnosed. Herein, we report a case of successful radiofrequency ablation (RFA) therapy of HCC in a 66-year-old male patient with PBC.

## Case Report

A 66-year-old man had suffered from intermittent pruritus for 8 years. But he had not experienced yellowish discoloration of the skin or tea-colored urine in that period. He denied any history of blood transfusion, acupuncture, tattoo, herbal medicine, smoking or alcohol drinking.

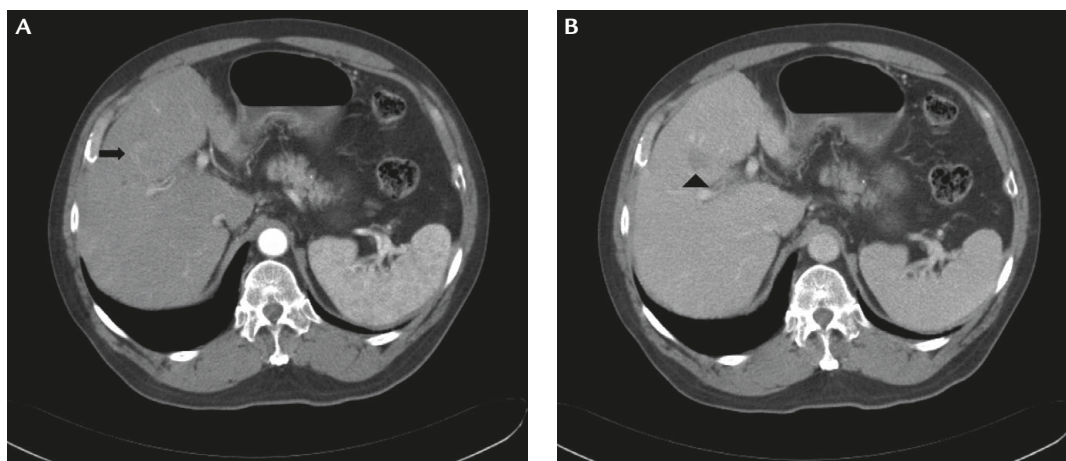
He underwent physical check-up in September 2005, and a diagnosis of PBC was established after a series of examinations. Serum biochemistry tests showed alanine aminotransferase (ALT) level of 86 U/L (normal, 0–40 U/L), aspartate aminotransferase (AST) level of 92 U/L (normal, 5–45 U/L), alkaline phosphatase (ALK-P) level of 229 U/L (normal, 10–100 U/L), total bilirubin level of 0.9 mg/dL (normal, 0.2–1.6 mg/dL),  $\gamma$ -glutamyltransferase (GGT) level of 630 U/L (normal, 8–61 U/L), albumin level of 4.5 g/dL (normal, 3.7–5.3 g/dL), immunoglobulin G (IgG) level of 2,270 mg/dL (normal, 1,188–1,800 mg/dL), IgA level of 309 mg/dL (normal, 158–358 mg/dL) and IgM level of 138 mg/dL (normal, 72–216 mg/dL).

Serologic tests for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis C virus (anti-HCV) were all negative. But antibody against hepatitis B core antigen (anti-HBc) was positive, indicating a previous or occult hepatitis B virus (HBV) infection.

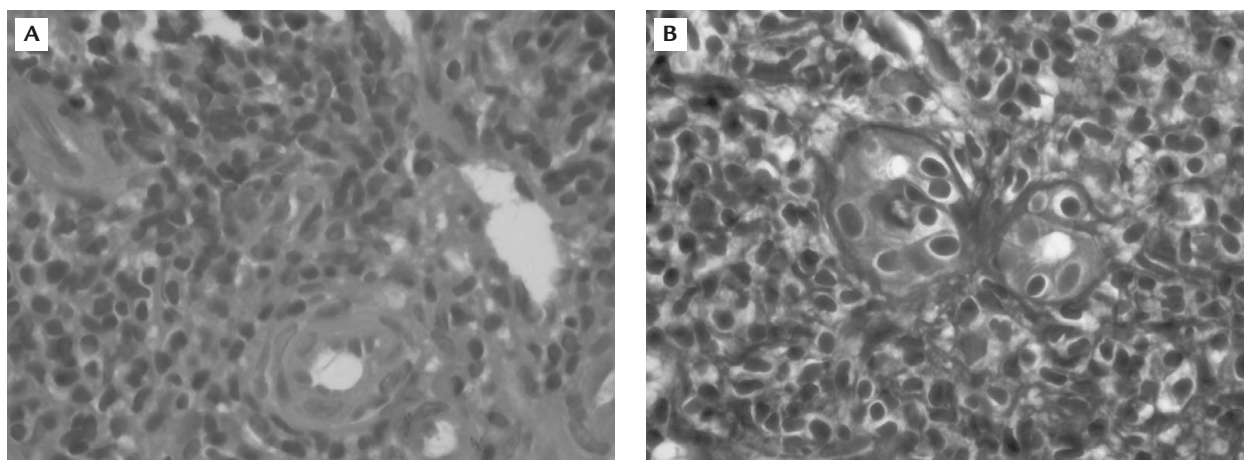
Serum HBV DNA was negative by polymerase chain reaction method. Serum autoantibodies including anti-nuclear antibody and anti-smooth muscle antibody were negative, but AMA (Fluoro-kit; Incstar, Stillwater, MN, USA) was positive. The patient refused to receive liver biopsy at that time and UDCA at a dosage of 200 mg thrice a day was prescribed based on the diagnosis of probable PBC.<sup>1</sup> Serum ALK-P level gradually declined, with levels of 118 U/L and 108 U/L after 5 months and 8 months of UDCA therapy, respectively.

In February 2007, a relatively hypoechoic nodule, measuring 2.6 cm in diameter, with nodule-in-nodule appearance and a hypoechoic halo in segment V of the liver, was found by routine abdominal ultrasound examination. Dynamic computed tomography (CT) examinations revealed 1 hypodense nodular lesion with faint contrast enhancement in the arterial phase and rapid washout in the portal venous phase in the same segment (Figure 1). Serum  $\alpha$ -fetoprotein (AFP) level was 189 ng/mL (normal, <8.50 ng/mL).

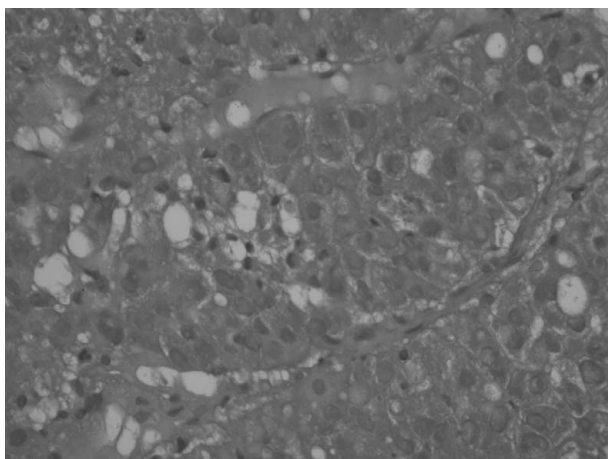
Liver biopsy was performed and 2 specimens were taken from the tumor part and non-tumor part, respectively. Non-tumorous liver revealed focal destruction of bile duct epithelium with lymphocyte infiltration, and focal absence of bile duct combined with periportal fibrosis and necrosis (Figure 2). The aforementioned findings were compatible with Scheuer's classification of stage II PBC.<sup>4</sup> Moreover, HBcAg stain and HBsAg stain were both negative. The tumor part showed a moderately differentiated HCC in a trabecular and acinar pattern (Figure 3). So the patient underwent percutaneous RFA. The course was smooth with no specific complications. One month after RFA, no viable tumor was found by CT examination (Figure 4).



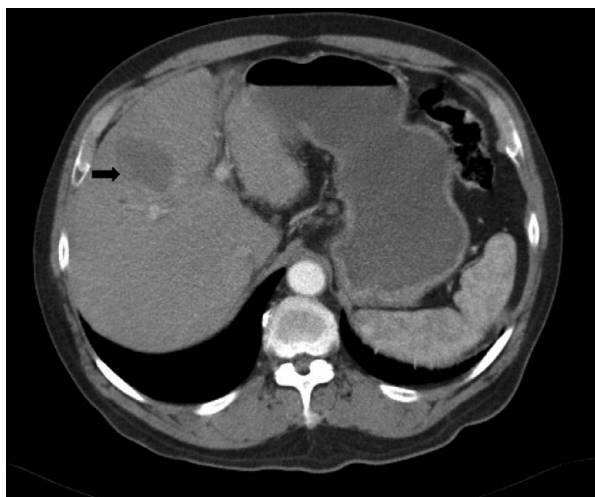
**Figure 1.** Abdominal computed tomography shows a nodular lesion, 2.6 cm in diameter, in segment V of the liver, with: (A) faint contrast enhancement in the early arterial phase (arrow); and (B) rapid washout in the portal venous phase (arrowhead).



**Figure 2.** The non-cancerous liver specimen shows focal destruction of bile duct epithelium with lymphocyte infiltration, focal absence of bile duct combined with periportal fibrosis, and necrosis: (A) hematoxylin & eosin stain (800 $\times$ ); (B) Masson stain (1,600 $\times$ ).



**Figure 3.** Histopathologic examination of the tumor shows a trabecular and acinar pattern, with the diagnosis of moderately differentiated hepatocellular carcinoma (hematoxylin & eosin, 1,600 $\times$ ).



**Figure 4.** One month after radiofrequency ablation therapy, computed tomography shows a hypoattenuating ablation zone without enhancing portion in the early arterial phase (arrow).

## Discussion

The diagnosis of PBC is established based on the following 3 criteria: elevation of serum ALK-P, the presence of detectable AMA in serum, and characteristic histologic findings including asymmetric destruction of the bile ducts within the portal triads.<sup>1</sup> A probable diagnosis requires that 2 of the 3 criteria are met, and a definite diagnosis requires that all 3 criteria are met.<sup>1</sup> This patient responded well to UDCA and serum ALK-P level declined gradually after therapy. Although the patient did not receive liver biopsy at the time of diagnosis, the clinical findings and clinical course, response to UDCA therapy and the subsequent liver biopsy all support a definite diagnosis of PBC.

The relationship between PBC and HCC was obscure until recently. In earlier years, patients with PBC were considered to be at relatively low risk for HCC in comparison to cirrhosis from other etiologies.<sup>9,10</sup> It was assumed that the dominance of the female population and some patients being enrolled while in the early stage of PBC may explain this phenomenon.<sup>10</sup> HCC usually occurs in the late stage of PBC, so patients cannot undergo curative therapy due to the deterioration of liver reserve, which in turn leads to a dismal prognosis.<sup>8,12</sup> As more frequent screening of AMA in suspected cases occurs, patients with PBC are now more likely to be diagnosed when asymptomatic or when in an earlier stage than in the past.<sup>1</sup> The majority of patients with PBC are treated with UDCA, and excellent long-term survival was observed in those with good biochemical response to UDCA.<sup>5</sup> Moreover, these patients receive more strict tumor surveillance in the present era. All of these efforts have led to the discovery of more cases of HCC arising from PBC. In addition, several studies have evaluated

the risk factors that are associated with HCC in PBC patients.<sup>10,12,15</sup> Older age, male sex, a history of cigarette smoking or blood transfusion, superimposition of hepatitis C virus infection and advanced PBC stage were significant risk factors.

This patient had positive anti-HBc in serum, indicating past or ongoing occult HBV infection. Classically, the seroclearance of HBsAg was considered to be associated with favorable outcomes. Nevertheless, our previous study demonstrated that HBV viremia was detected in 20% of patients who had seroclearance of HBsAg and the conversion of anti-HBs.<sup>16</sup> Moreover, some patients with HBsAg seroclearance may develop serious complications, including HCC.<sup>16</sup> For this patient, past exposure to HBV might also have played a role in hepatocarcinogenesis in addition to the underlying PBC.<sup>17</sup>

Surgical intervention was regarded as the only curative modality for patients with HCC in the past. Nowadays, several percutaneous local ablation therapies, including ethanol injection (PEIT) and RFA, have also been applied for the treatment of small HCC. They both lead to promising outcomes in survival, complete tumor necrosis and reduction of local tumor recurrence.<sup>18-21</sup> Notably, the long-term survival of patients who underwent local ablation therapy was comparable to that of patients who underwent surgical resection.<sup>20,21</sup> Consequently, local ablation therapy and surgery are both considered first-line options for small HCC, especially for those less than 3 cm in diameter.<sup>22</sup> Compared to surgical resection, local ablation therapies are safe, effective, less invasive and less expensive. RFA seemed to result in a higher rate of total tumor necrosis than PEIT.<sup>18,23</sup> Hence, RFA has been applied in a substantial number of patients with HCC in recent years. However, the patients enrolled in previous studies chiefly had HCC secondary to viral hepatitis; experience with radiofrequency therapy for HCC arising from PBC is very limited worldwide. As there is ongoing improvement of diagnostic tools, both for use in PBC and HCC, we believe that the number of patients with HCC arising from PBC who are suitable for curative therapy will soon increase. This report demonstrates that RFA can successfully treat HCC in such patients, although large-scale studies may be needed for confirmation.

Based on previous studies and our case report, HCC can occur at any stage of PBC. All patients with PBC, irrespective of stage, should receive regular surveillance for HCC, including serum AFP and abdominal ultrasound examination, during their lifetime. If small HCC is detected at an early PBC stage when there is still good liver reserve, then curative therapy

modalities including surgical resection and local ablation therapy can be performed and long-term survival expected.

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