Heterochronous Development of Intrahepatic Cholangiocellular Carcinoma Following Hepatocellular Carcinoma in a Hepatitis B Virus Carrier

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Abstract

A 68-year-old Japanese woman was admitted to our hospital in September 1995, because of a mass detected by ultrasonography during a follow-up examination for chronic hepatitis B. Hepatocellular carcinoma (HCC) in the right liver lobe was diagnosed based on imaging studies and elevated alpha-fetoprotein (AFP). Percutaneous ethanol injection therapy (PEIT) was performed. PEIT was repeated in November 1998, because the tumor had enlarged and serum AFP was re-elevated. Follow-up ultrasonography (US) demonstrated low echoic mass in the left liver lobe in August 1999; serum AFP was normal, but serum carbohydrate antigen 19-9 (CA19-9) was elevated to 420 U/ml. In October 1999, radiofrequency interstitial tissue ablation (RITA®) was performed after tumor biopsy. Pathological findings revealed adenocarcinoma and pathological diagnosis was made as intrahepatic cholangiocellular carcinoma (ICC). Three weeks later, her serum CA19-9 was remarkably decreased (180 U/ml). The patient has been well for 5 months. Her latest AFP and CA19-9 in the serum were 2 ng/ml and 89 U/ml, respectively. The incidence of double cancer in the liver is rare. This is also the first case report to discuss ICC treated with RITA®.

Key words: radiofrequency, RITA®, PEIT, double cancer, AFP, CA19-9

Introduction

With the recent advances in imaging techniques, it has become possible to detect intrahepatic small masses of less than 2 cm in diameter. Ultrasonography (US) guided tumor biopsy allows for pathological diagnosis of very small lesions. Hepatocellular carcinoma (HCC) combined with cholangiocellular carcinoma is sometimes encountered (1), but cases of double cancers of combined HCC and intrahepatic cholangiocellular carcinoma (ICC) are very rare. We herein describe a patient with heterochronous double cancer, in whom a pathological diagnosis of ICC was made based on the tumor biopsy specimen, and a clinical diagnosis of HCC was made based on imaging findings and serum tumor marker such as alpha-fetoprotein (AFP).

Case Report

A 68-year-old Japanese woman was admitted to our hospital for evaluation in September 1995, because of a mass detected in the subsegment 7 of right liver lobe (S7) by US (Fig. 1A) during a follow-up examination for hepatitis B virus (HBV). The woman had been identified as an HBV carrier 5 years earlier. Two years prior she had undergone cholecystectomy for gallbladder stones. She had no history of jaundice, blood transfusion, alcohol abuse, or exposure to hepatotoxins.

Upon admission, laboratory data were as follows: aspartate aminotransferase (AST), 19 IU/l (normal <35 IU/l); alanine aminotransferase (ALT), 5 IU/l (normal <31); and indocyanine green 15-minute serum retention test (ICG R15) 10% (normal <10%). Hepatitis B surface antigen (HBsAg), anti-hepatitis B virus envelope antibody (HBeAb), and anti-hepatitis B virus core antibody (HBcAb) were positive; anti-hepatitis B surface antibody (HBsAb), hepatitis B virus envelope antigen (HBeAg), and anti-hepatitis C antibody (HCVAb) were negative. Her serum AFP level was 67 ng/ml (normal range, <20 ng/ml). Repeat US disclosed a hypoechoic mass in S7. Hepatic angiography disclosed faint hypervascular staining in the same area (Fig. 1B). Dynamic computed tomography (CT) also showed this lesion (Fig. 1C). Early-phase contrast CT showed a well en-
Double Cancer of Combined HCC and ICC

Figure 1A-E. A: A low echoic mass (arrow) in subsegment 7 of the liver was detected by abdominal ultrasonography, B: a fine staining (arrow) by common hepatic arterial angiography, C: a low density mass was detected by plain computed tomography, D: a mass lesion was centrally enhanced in the early phase of contrast medium infusion, E: the enhancement disappeared in the late phase of contrast medium infusion in September 1995.

Enhanced tumor in S7, 2.0×1.5 cm in diameter (Fig. 1D); late-phase contrast CT showed a low density area (Fig. 1E). Under a diagnosis of HCC, percutaneous ethanol injection therapy (PEIT) (2, 3) was carried out for the tumor in S7 in October 1995 after informed consent was obtained from her. Thereafter, PEITs were repeated twice within a week. The total injected ethanol was 15 ml. Two weeks after PEITs, her serum AFP fell to 7.8 ng/ml, when contrast CT did not show tumor enhancement (Fig. 2A–C).

The patient did well for 3 years. However, a considerable elevation in serum AFP (159 ng/ml) was noted in an outpatient visit in November 1998. Subsequent US disclosed a round mass in S7 measuring 2.5×1.7 cm and demonstrating a mosaic pattern. Contrast-enhanced early-phase CT demonstrated a central high density area (Fig. 3B); a low density area was seen at late phase (Fig. 3C). Under a diagnosis of recurrent HCC, the patient was admitted to our hospital for the second time, and PEITs were performed four times after informed consent was obtained from her. The total injected ethanol was 7.5 ml. Two weeks after PEITs, her serum AFP fell to 68.0 ng/ml, when contrast CT did not show tumor enhancement (Fig. 4A–C).

She was free from recurrence for 9 months. However, follow-up US demonstrated an irregular low echoic mass in the subsegment 3 of the left liver lobe (S3) in August 1999 (Fig. 5). She was admitted to our hospital for the third time. Physical examination upon this third admission showed no abnormality. Serum liver function tests were within normal range, except for increased carbohydrate antigen 19-9 (CA19-9) (420 U/ml; normal range, <37 U/ml). Serum hepatitis B virus markers were the same as those at the first admission. CT showed a
Figure 2A–C. Abdominal computed tomography (CT) demonstrating hepatocellular carcinoma 2 weeks after PEIT in October 1995. A: a low density area (arrow) was detected in the subsegment 7 of the liver by plain CT, B: a low density area (arrow) was not enhanced in the early phase, C: and in the late phase of contrast medium infusion.

Figure 3A–C. Abdominal computed tomography (CT) demonstrating recurrence of hepatocellular carcinoma in subsegment 7 of the liver in November 1998. A: a low density area (arrow) shown on plain CT, B: the low density area was enhanced in the early phase of contrast medium infusion, C: the enhancement disappeared in the late phase of contrast medium infusion.
Double Cancer of Combined HCC and ICC

Figure 4A-C. Abdominal computed tomography (CT) demonstrating recurrence of hepatocellular carcinoma 2 weeks after repeated PEIT in November 1998. A: a low density area (arrow) in subsegment 7 of the liver by plain CT, B: the low density area (arrow) was not enhanced in the early phase, C: and in the late phase of contrast medium infusion.

Figure 5. A new low echoic mass lesion in subsegment 3 of the liver was disclosed by abdominal ultrasonography in September 1999.

low density mass with an irregular margin in S3. Plain CT demonstrated a low density mass, 2.0×2.0 cm in diameter (Fig. 6A). Contrast CT showed centrally faint enhancement at the early phase (Fig. 6B) and a central low density area with remaining marginal enhancement at the late phase in S3 (Fig. 6C). Preoperative ultrasonic cardiography (UCG) showed moderate to severe aortic regurgitation (AR). We explained the possibility of malignant tumor in the liver and a risk in regard to the partial hepatectomy. Since we were not able to obtain her informed consent for the partial hepatectomy, the S3 mass was treated by radiofrequency interstitial tissue ablation (RITA®, 50 W, 100°C, for 10 minutes), which has a possibility of cure (4, 5), other than surgical resection, immediately after tumor biopsy in October 1999. Four weeks after RITA® her serum CA19-9 had fallen remarkably to 180 U/ml, and serum AFP was 7.0 ng/ml, when contrast CT did not show tumor enhancement (Fig. 7A–C).

The patient has remained well for 6 months. In February 2000, her serum AFP and CA19-9 levels were 2 ng/ml and 83 U/ml, respectively, when contrast CT did not show tumor enhancement (Fig. 8A–C).

Microscopic tumor biopsy specimen findings

Biopsy specimens were fixed in 10% formalin and processed for light microscopy. Paraffin-embedded tissue blocks were sectioned. After deparaffinization, the sections were stained with hematoxylin and eosin (HE stain).

The S3 tumor consisted almost entirely of lumina of the glandular structures (Fig. 7A). The tumor cells exhibited large nuclei and abundant cytoplasm. The atypical glands were covered with several layers of cuboidal epithelium with prominent nuclei. These findings were indicative of moderately differentiated tubular adenocarcinoma. No HCC was demonstrated in the tumor biopsy specimen (Fig. 9B).
Figure 6A–C. Abdominal computed tomography (CT) demonstrating the new low density area in subsegment 3 of the liver in September 1999. A: a low density area (arrow) by plain CT, B: the low density area (arrow) was faintly enhanced in the early phase of contrast medium, C: a central low density area with remaining marginal enhancement (arrow) in the late phase of contrast medium infusion.

Figure 7A–C. Abdominal computed tomography (CT) demonstrating intrahepatic cholangiocellular carcinoma (ICC) in subsegment 3 of the liver 20 weeks after radiofrequency interstitial tissue ablation (RITA®) in February 2000. A: a low density area (arrow) by plain CT, B: the low density area (arrow) was not enhanced in the early phase, C: and in the late phase of contrast medium infusion.
Double Cancer of Combined HCC and ICC

Figure 8A-C. Abdominal computed tomography (CT) demonstrating intrahepatic cholangiocellular carcinoma (ICC) in subsegment 3 of the liver 4 weeks after radiofrequency interstitial tissue ablation (RITA®) in October 1999. A: a low density area (arrow) by plain CT, B: the low density area (arrow) was not enhanced in the early phase, C: and in the late phase of contrast medium infusion.

Figure 9A-B. Microscopic findings of tumor biopsy specimen stained with hematoxylin and eosin (HE stain) demonstrating A: almost the entire lumina of the glandular structures (HE stain, ×100). B: The tumor cells exhibited large nuclei and abundant cytoplasm. The atypical glands were covered with some layers of cuboidal epithelium with prominent nucleoli (HE stain, ×200).

Immunohistochemistry tumor biopsy specimen findings

For immunohistochemical studies, the avidin-biotin complex (ABC) method was used. Antibodies were used for the following: AFP (Histofine; Nichirei, Tokyo), CEA (Campaign, IBL, Fujioka, Japan), CA19-9 (NS19-9; Centocor, PA, USA). On immunohistochemical examination, ICC tumor showed CEA and CA19-9 to be positive, but AFP was negative.

Discussion

Combined HCC and ICC has been described in the following three categories: 1) separate masses composed of either HCC or ICC, 2) contiguous masses composed of independent
HCC and ICC elements, and 3) a mass with intermingling HCC and ICC components (1). In Japan, these three types are known as double cancer, combined-type HCC and ICC, and mixed-type HCC and ICC, respectively (6). The present case fits the double cancer category. The HCC and ICC were located in different lobes (S7 and S3) and were identified heterochronously (4-year interval). Therefore, HCC and ICC have been recognized as the double cancer type as mentioned by Raymond and James, although ICC was pathologically diagnosed and HCC was not. The incidence of double cancer in the liver is much lower than that of combined cancer, which is also rare (7). There are reports that only two cases of double cancer (0.5%) among a total of 367 adult patients with HCC and/or ICC who were surgically resected during 14.5 years (8), and that only one of five combined cases was double cancer, and that only one case was double cancer of HCC and ICC in an atrophied cirrhotic liver among their 393 consecutive autopsy cases (9). We found only two reports on heterochronous double cancer of HCC and ICC (1, 10).

HCC is known to be closely associated with chronic HBV or HCV infection (11). The development of ICC was generally unrelated to hepatitis viral infection. Recently, infection with HCV or HBV has been suggested to be involved in the pathogenesis of ICC (12, 13). In the Japanese literature (14, 15), some patients with nodular ICC were included, and all of them were positive for HCV Ab or HBsAg and were diagnosed as HCC. Since the tumor biopsy specimen came from within a part of the tumor (obtained by needle biopsy), mixed-type HCC and ICC could not be completely ruled out in the present case. However, serum CA19-9 levels are generally reported to be high in patients with ICC but not in patients with mixed-type HCC and ICC (16), and serum CA19-9 levels were increased in our patient despite the tumor’s small size. Therefore, the S3 mass was thought to be an ICC. It is thought that patients with intrahepatic gallstone have a risk for development of ICC (17). In our case, intrahepatic gallstone was not detected by several examinations, although she suffered from gallbladder stones 6 years prior to the occurrence of ICC. In our case, the development of ICC might be related to HBV infection.

US was most useful in detecting the small mass; late enhanced CT (15) played an important role in the differential diagnosis of HCC and ICC, and angiography was also helpful in making a diagnosis of HCC. US guided tumor biopsy is possible to obtain a pathological diagnosis that is definitive. With improved imaging, double liver cancer may be diagnosed with increasing frequency.

It is thought that the best therapy for ICC is surgical resection. There is one report in which ICC was treated with PEIT, and the patient has remained well (10). We performed RITA® immediately after tumor biopsy because we thought the S3 mass was a mixed-type HCC and ICC. It was only later that we recognized this lesion as an ICC. We advised her to receive partial hepatectomy after pathological diagnosis revealed ICC. However, we were not able to obtain her informed consent because she had moderate to severe AR and partial hepatectomy was a risk, as explained by the anesthesiologist. Therefore, we are following-up this patient very carefully. She continues to do well. RITA® might be a useful strategy for small ICC, but a careful and long-term observation is imperative.

References