

CASE REPORT

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Double Cancer, Cholangiocellular and Hepatocellular Carcinomas, in the Cirrhotic Liver

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A 70-year-old male patient presented with cirrhotic liver caused by hepatitis C virus and complicated with hepatocellular carcinoma. The carcinoma was effectively treated by transarterial chemoembolization, but cholangiocellular carcinoma occurred in a different segment of the liver and rapidly grew and metastasized systemically. He died 13 months after the first admission.

Double cancer of the liver is uncommon, but it must be considered in the differential diagnosis of cases of hepatocellular carcinoma associated with chronic hepatitis or cirrhosis. Failure to note the occurrence of cholangiocellular carcinoma is thought to be a diagnostic pitfall in the follow-up studies of patients with hepatocellular carcinoma.

Key words: double cancer, liver, transarterial chemoembolization

INTRODUCTION

DOUBLE CANCER of the liver, hepatocellular carcinoma and cholangiocellular carcinoma occurring in different sites in the same liver, is uncommon, and only 18 cases have been reported.¹⁻⁴ We report a case of cholangiocellular carcinoma in a patient with a cirrhotic liver who also had hepatocellular carcinoma that was being treated by transcatheter arterial chemoembolization therapy.

CASE

The patient was a 70-year-old man with about a 20-year history of hepatitis C. He was found to have a high level of serum α -fetoprotein (AFP). Ultrasonography (US) detected a mass lesion in segment 8 of the liver, and he was admitted to our hospital. At the time of admission,

he was asymptomatic. Serum examinations revealed slight liver dysfunction and high levels of serum AFP (101 ng/ml), carcinoembryonic antigen (CEA, 12.3 ng/ml), carcinoma antigen 19-9 (CA19-9, 40 U/ml), and des- γ -carboxy prothrombin (PIVKA II, 0.084 AU/ml).

On computed tomography scans (CT) during arterial portography (CT-AP), focal perfusion defects were noticed in segments 1 and 8 (Fig. 1). CT-AP images were obtained with a slice thickness of 10 mm approximately 30 seconds after intraarterial injection of contrast material via the superior mesenteric artery. On the delayed image of digital subtraction angiography (DSA), a tumor stain was seen only in the same areas of segment 1 (Fig. 2). He was diagnosed as having hepatocellular carcinoma in segments 1 and 8 based on the finding of CT-AP. Transarterial chemoembolization (TAE) using an oily emulsion of anticancer agent and iodized oil (Lipiodol Ultra-Fluide, Guerbet, Villepinte, France) and subsequent use of small pieces of gelatin sponge (Gelfoam, Pharmacia & Upjohn Ltd., Kalamazoo, MI) was performed for the anterior branch of the right hepatic artery and the branches of the caudate lobe. The emulsion consisted of 40 mg of adriamycin (Adriacin injection, Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) and 150 mg carboplatin (Paraplatin injection, Bristol-Myers Squibb Company, Princeton, NJ) in 3 ml of lipiodol. After the treatment, the serum

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Fig. 1. CT scan during arterial portography (CT-AP) on the first admission shows focal perfusion defects in segment 1 of the patient's liver (*arrow*).



Fig. 2. Delayed-phase image of the common hepatic arteriogram on the first admission shows tumor stain in the peripheral area of A1, indicating hepatocellular carcinoma (*arrow*).

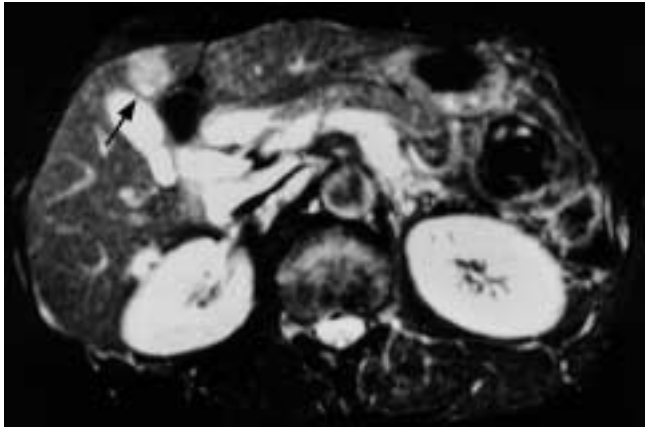


Fig. 3. T2-weighted MR image 6 months after the first TAE shows a hyperintense mass in segment 4 (*arrow*).

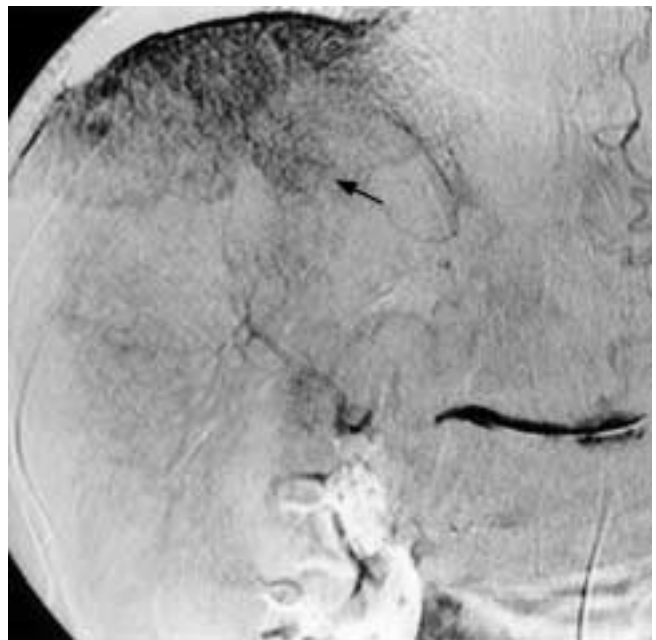


Fig. 4. A faint stain was seen in the peripheral area of A7 on a delayed-phase image of the common hepatic arteriogram during the second admission (*arrow*). No tumor stain was seen in the peripheral area of A4.

AFP and CEA levels decreased to 50.6 ng/ml and 11.3 ng/ml, respectively, and follow-up CT scans showed a dense accumulation of lipiodol in segment 1, showing a good effect of the TAE. No other tumor was detected in the liver.

Six months later, a recurrent tumor was suspected in segment 7 on US. Another recurrent tumor was suspected in segment 4 based on a T2-weighted magnetic resonance (MR) imaging (TR/1,800 msec, TE/90 msec, ETL/9, slice thickness/8 mm) (Fig. 3). The CT-AP image obtained during his second admission showed a focal perfusion defect in segment 7, and a faint stain was seen in the same area on the delayed image of the subsequently performed DSA (Fig. 4). CT-AP was performed by the above-mentioned method. TAE was performed for segment 7. No apparent tumor was detected in segment 4. The lesion in segment 4 was suspected to be a recurrence or a new lesion of

hepatocellular carcinoma. Well-differentiated hepatocellular carcinoma, whose pathogenesis is explained by multicentric carcinogenesis, was most highly suspected because of its hypovascularity. Metastatic tumor from the gastrointestinal region was included in the differential diagnosis. On repeated US and CT scans, no obvious tumor was seen in segment 4; therefore biopsy or percutaneous ethanol injection (PEI) could not be performed. Subsequently performed



Fig. 5. Parenchymal-phase image of follow-up CT scans obtained 3 months after the second TAE shows a hypodense mass in segment 4. Swelling of hepatic hilar lymph nodes (LNs) and paraaortic LNs is also visible.

colonoscopy and gastrofiberscopy showed no abnormal findings, and thus the patient was observed carefully.

On follow-up CT scans 3 months after the second TAE, no residual tumor was seen in segment 7, but an obvious mass lesion was observed in segment 4; swelling of hepatic hilar lymph nodes (LNs), paraaortic LNs, and ascites were also seen (Fig. 5). Although his serum AFP and PIVKA II levels remained low, the recurrence and LN metastases of hepatocellular carcinoma were strongly suspected. Radiation therapy for LN metastases was performed. Subsequently, lung metastases appeared. Serum CEA and CA19-9 levels increased to 32.3 ng/ml and 177 U/ml, respectively. His general condition rapidly worsened, and he died 13 months after the first admission.

An autopsy was performed. No cancer cells or necrosed cancer tissue were found in the post-TAI and -TAE lesions in segments 1, 7, and 8 of the liver. There was a small white nodular lesion with a defined margin and a diameter of 5 mm in the central area of the right lobe that was pathologically diagnosed as moderately differentiated hepatocellular carcinoma (Fig. 6a). In addition, there was a large white tumor with an undefined margin in segment 4 that spread to the hepatic hilum. This tumor was pathologically diagnosed as poorly differentiated cholangiocellular carcinoma (Fig. 6b). Metastases were found in paraaortic LNs, peripancreatic LNs, renal hilar LNs, pulmonary hilar LNs, and both lungs. All were pathologically diagnosed as cholangiocellular carcinoma. No cholangiocellular component was found in the lesion in the right lobe diagnosed as hepatocellular carcinoma. It was thought that cholangiocellular carcinoma occurred in a different site of the liver independent of hepatocellular carcinoma, and these lesions were finally diagnosed as double cancer of the liver. Noncancerous liver parenchyma showed a cirrhotic state.

DISCUSSION

Raymond *et al.* investigated cases of hepatocellular carcinoma and cholangiocellular carcinoma occurring in the same liver and classified them into three types: hepatocellular carcinoma and cholangiocellular carcinoma a) occurring as separate nodules at different sites (double cancer), b) occurring at adjacent sites and intermingling (combined type), and c) originating from the same focus (mixed type).⁵

Double cancer is the least common of these three types. Takayasu *et al.* described only two cases in their

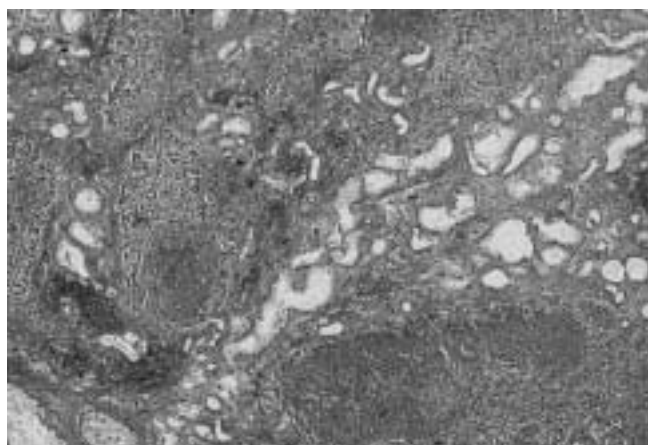
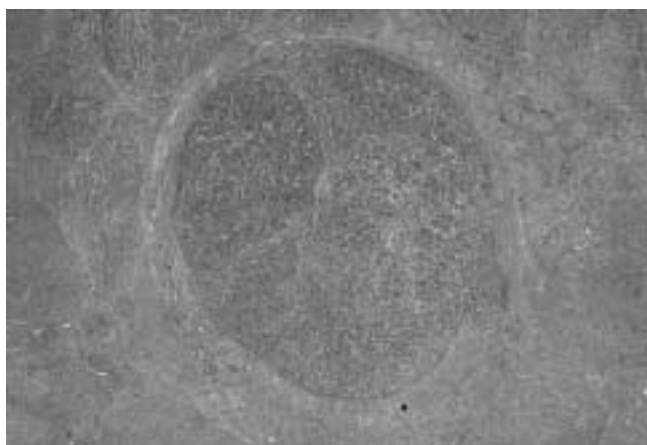


Fig. 6. a: Photomicrograph of the small tumor with diameter of 5 mm in the central area of the right lobe shows moderately differentiated hepatocellular carcinoma.
b: Photomicrograph of the large white tumor in segment 4 shows poorly differentiated cholangiocellular carcinoma.

a | b

review of 367 cases of primary liver cancer, and Kojiro *et al.* described only one case in a review of their 393 cases of primary liver cancer.^{1,2} Our case was classified as double cancer.

Recently some cases of cholangiocellular carcinoma have been reported to occur in patients with chronic hepatitis or cirrhosis, especially in cases where the hepatitis or cirrhosis was caused by hepatitis C virus.^{3,4} The occurrence of cholangiocellular carcinoma has been reported to be associated with cirrhosis in 9.7-22.2% of autopsy cases in Japan, significantly higher than that in autopsies of cases of other diseases.⁶⁻⁹ Although the mechanism has not been explained, cholangiocellular carcinoma appears to be related to viral hepatitis or cirrhosis.¹⁰ The frequency with which this type of tumor is detected in follow-up examinations of patients with hepatocellular carcinoma associated with chronic hepatitis or cirrhosis appears to be increasing because the survival time of the patients has been prolonged by improved medical care in the past several decades.

It is known that hepatocellular carcinomas become resistant to transcatheter therapies after several sessions of transcatheter chemoembolization and rapidly grow at a certain point in the clinical course. This change is thought to be caused by a change in the nature of the tumor, for example, a sarcomatous change or development of resistance to the ischemic change or chemotherapeutic agents. However, the occurrence of cholangiocellular carcinoma may be one of the causes of this resistance to therapies.

In conclusion, when treating hepatocellular carcinoma in patients with chronic hepatitis or cirrhosis, especially in cases of chronic hepatitis or cirrhosis caused by hepatitis C virus, the occurrence of cholangiocellular carcinoma must be considered in the differential diagnosis in addition to considering residual or recurrent hepatocellular carcinoma. Failure to do so is thought to

be a diagnostic pitfall in the follow-up studies of patients with hepatocellular carcinoma.

REFERENCES

- 1) Takayasu K, Muramatsu Y, Moriyama N, *et al.* Hepatocellular and cholangiocellular carcinoma, double cancer of the liver: report of two cases resected synchronously and metachronously. *Am J Gastroenterol*, 84: 544-547, 1989.
- 2) Kojiro M, Nakashima T. Pathology of hepatocellular carcinoma. In *Neoplasms of the Liver* (Okuda K, Ishak KG eds.; Springer-Verlag, Tokyo), pp. 101-102, 1987.
- 3) Nomura Y, Matsuda Y, Yabuuchi I, *et al.* A resected case of intrahepatic cholangiocellular carcinoma detected as a small liver tumor. *Acta Hepatol Jpn*, 38: 381-385, 1997.
- 4) Yokoyama T, Yahata N, Ootani H, Asahara T, Dohi K, Yamamoto M. A case of small cholangiocellular carcinoma occurring 12 years after resection of hepatocellular carcinoma associated with B viral cirrhosis. *Acta Hepatol Jpn*, 34: 753-757, 1993.
- 5) Raymond AA, James RL. Combined liver cell and bile duct carcinoma. *Am J Pathol*, 84: 647-655, 1949.
- 6) Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan -Report 8-. *Acta Hepatol Jpn*, 29: 1619-1626, 1988.
- 7) Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan -Report 9-. *Acta Hepatol Jpn*, 32: 1138-1147, 1991.
- 8) Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan -Report 10-. *Acta Hepatol Jpn*, 34: 805-813, 1993.
- 9) Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan -Report 11-. *Acta Hepatol Jpn*, 36: 208-218, 1995.
- 10) Yamamoto M, Takasaki K, Nakao M, Saito A. Minute intrahepatic cholangiocarcinoma. *Cancer*, 82: 2145-2149, 1998.