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Case report

Combined hepatocellular and cholangiocellular carcinoma in a non-cirrhotic liver

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Abstract: Combined hepatocellular (HCC) and cholangiocellular carcinoma (CCC) (mixed carcinoma) is a rare subtype of primary hepatic carcinoma. We report a case of mixed carcinoma that developed in a non-cirrhotic liver, in a patient who was serologically negative for both hepatitis B and C viruses. A 65-year-old Japanese woman with a 25-year history of chronic rheumatoid arthritis had been treated with steroids and anti-inflammatory drugs, and was diagnosed by ultrasonography with an asymptomatic solitary tumor in the right lobe of the liver. On computed tomography scan and hepatic arteriography, the tumor was well enhanced by contrast medium in the early phase. Based on the findings of elevated serum alpha-feto protein (AFP, 245 ng/ml) and normal carcino-embryonic antigen (CEA, 2.6 ng/ml) levels, a preoperative diagnosis of hepatocellular carcinoma was made. Right lobectomy of the liver was performed on January 7, 1997. Histological examination showed that the resected tumor consisted of combined CCC cells and HCC cells in an intermingled form, with CCC being far more dominant than HCC. The tumor was therefore determined to be a combined carcinoma, subclassified as intermingled type. This case appears to indicate that mixed type carcinoma developed in a non-cirrhotic liver, with CCC being dominant; such a finding is extremely unusual, based on previously published reports.

Key words: hepatocellular carcinoma, cholangiocellular carcinoma, mixed carcinoma, non-cirrhotic liver

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Introduction

Combined hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCC) (mixed carcinoma) has been reported in only 1.4% of cases of primary liver cancer in a survey of primary liver cancer in Japan.[1] Allen and Lisa[2] and Haratake and Hashimoto[3] divided this mixed carcinoma into three subtypes: separate masses composed of either HCC or CCC (double cancer or separate type); contiguous masses, composed of independent elements of HCC and CCC (combined or collision type); and a mass with an intimate intermingling of HCC and CCC components (mixed or intermingled type). The intermingled (mixed) type has been reported to develop exclusively in cirrhotic liver, suggesting the involvement of hepatitis viruses in its oncogenesis.[3] In the case we report, the tumor was of intermingled type but had several unique features that did not match the findings of previous studies. We evaluated the features of this particular subtype and report a brief review of the English-language and Japanese literature.

Case report

A 65-year-old Japanese woman who had a 25-year history of chronic rheumatoid arthritis treated with steroids and anti-inflammatory drugs was diagnosed by ultrasonography with an asymptomatic hypoechoic mass (3 cm in diameter) in the right lobe of the liver. She was referred to the Department of Radiology at our hospital for further examination.

An enhanced computed tomography (CT) scan revealed a hypervascular mass in the right posterior segment of the liver. There was a central scar-like structure in this tumor, which is not a common feature of HCC (Fig. 1a). In the CT scan during arterial portography (CTAP), this mass was recognized as a defective area.

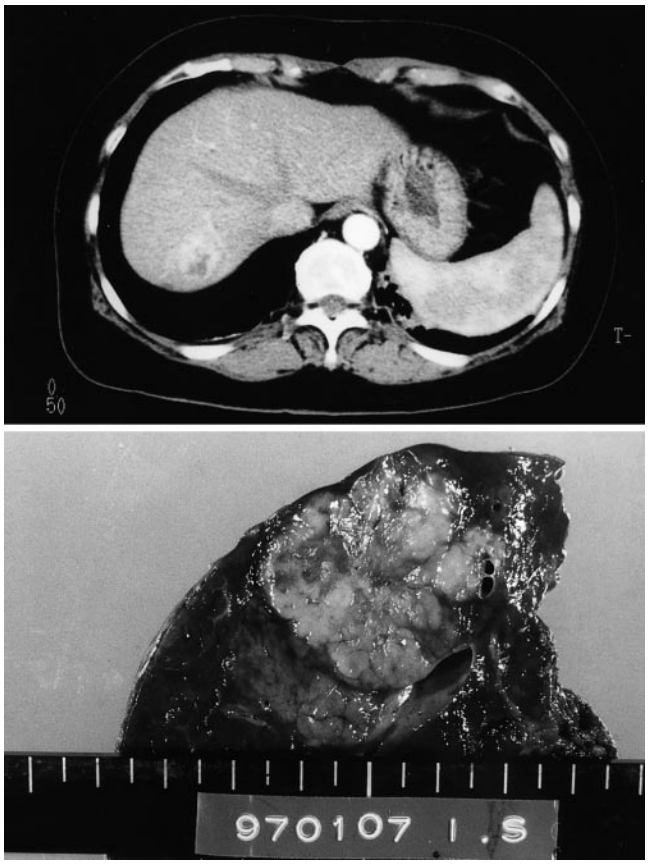

Fig. 1. a Enhanced computed tomography (CT), showing a hypervascular mass in the right posterior segment of the liver. A central scar-like structure was observed in the mass. **b** The cut surface of the resected specimen, showing a well encapsulated tumor measuring 3.5 × 3.5 cm, with adjacent right hepatic vein

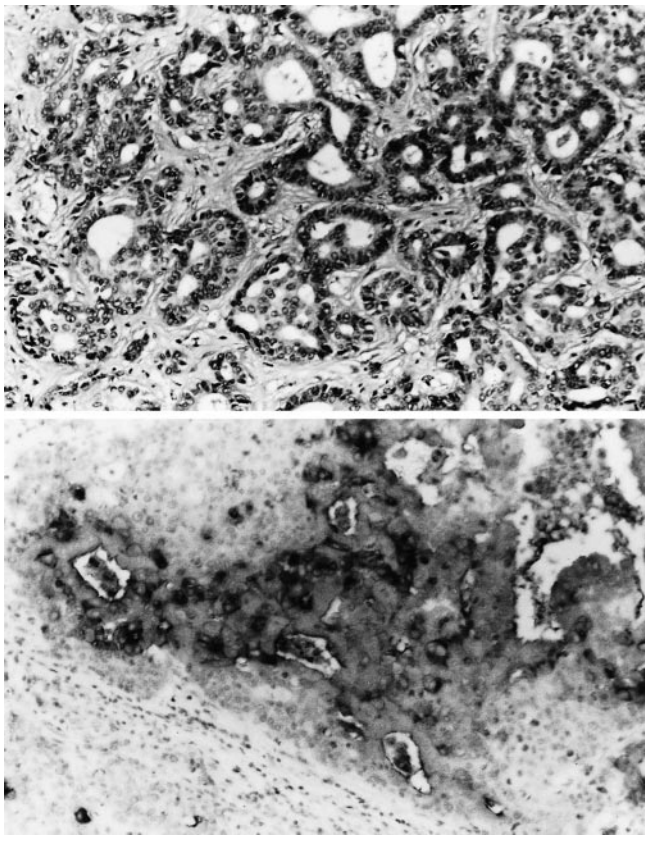

Fig. 2a,b. Photomicrographs showing well differentiated tubular adenocarcinoma. **a** H&E, ×400. **b** Immunohistochemical study demonstrating a positive reaction for carcinoembryonic antigen (CEA), ×400

Hepatic arteriography also detected a hypervascular tumor in the late arterial phase, which continued to be well stained until the venous phase. The tumor was thus diagnosed as hepatocellular carcinoma and the patient was referred to our department on December 12, 1997 to undergo surgical treatment.

On admission the patient was 153 cm tall and weighed 57.5 kg. Physical examination revealed a deformity of the right hand joint, due to rheumatoid arthritis. Routine blood analysis revealed elevated glutamate oxaloacetate transaminase (GOT, 331 IU/l) and glutamate pyruvate transaminase (GPT, 411 IU/l) levels. Serum alpha-feto protein (AFP) and CA19-9 levels also showed mild elevations (245 IU/ml and 440.4 ng/ml, respectively). Serum carcinoembryonic antigen level (CEA, 2.6 ng/ml), was within the normal range.

A laparotomy was performed on January 7, 1997. No ascites was observed and the liver was not cirrhotic. On intra-operative ultrasonography, a single nodular tumor was located in the right posterior segment of the liver, involving the right hepatic vein, and a right lobectomy was performed. Serum AFP and CA19-9 levels returned to normal by 2 weeks after surgery.

On the cut surface of the resected specimen, the tumor measured 3.5 × 3.5 × 3 cm, was grayish-white in color, well encapsulated, and lobulated with a septum (Fig. 1b). Microscopically, the tumor was predominantly composed of well differentiated tubular adenocarcinoma (Fig. 2a), and partially of well differentiated hepatocellular carcinoma in a trabecular pattern (Fig. 3a). The boundary between these two components was not demarcated, and focal transitional features from CCC to HCC were evident.

In an immunohistochemical study, the CCC components were strongly immunoreactive for CEA (Fig. 2b), while HCC components revealed weak immunoreactivity for AFP (Fig. 3b). Focal transitional zones were also seen between these two components (HCC and CCC)

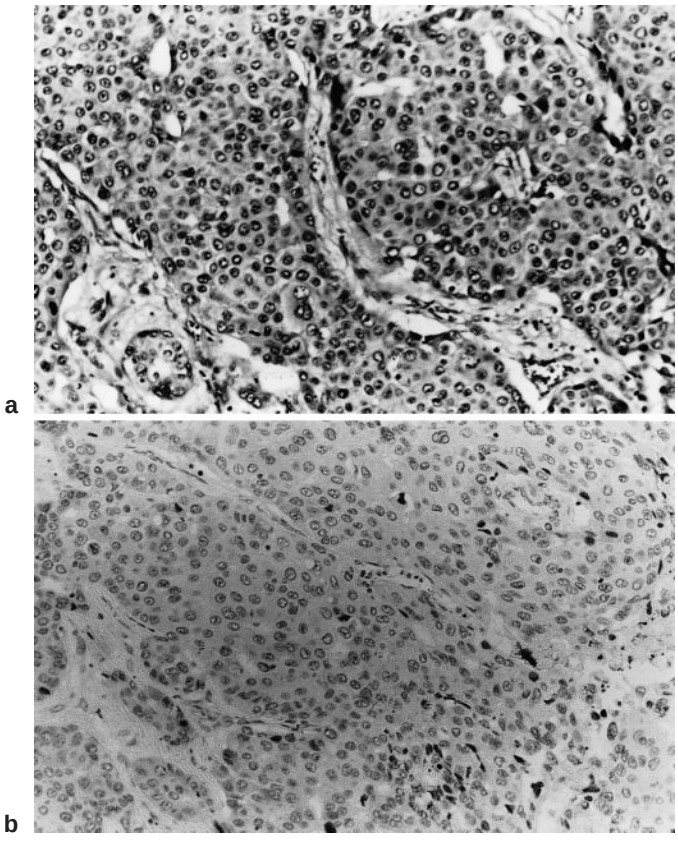

Fig. 3a,b. Photomicrographs showing well differentiated hepatocellular carcinoma in a trabecular pattern. **a** H&E, ×400. **b** Immunohistochemical study demonstrating positive reaction for alpha-fetoprotein. ×400

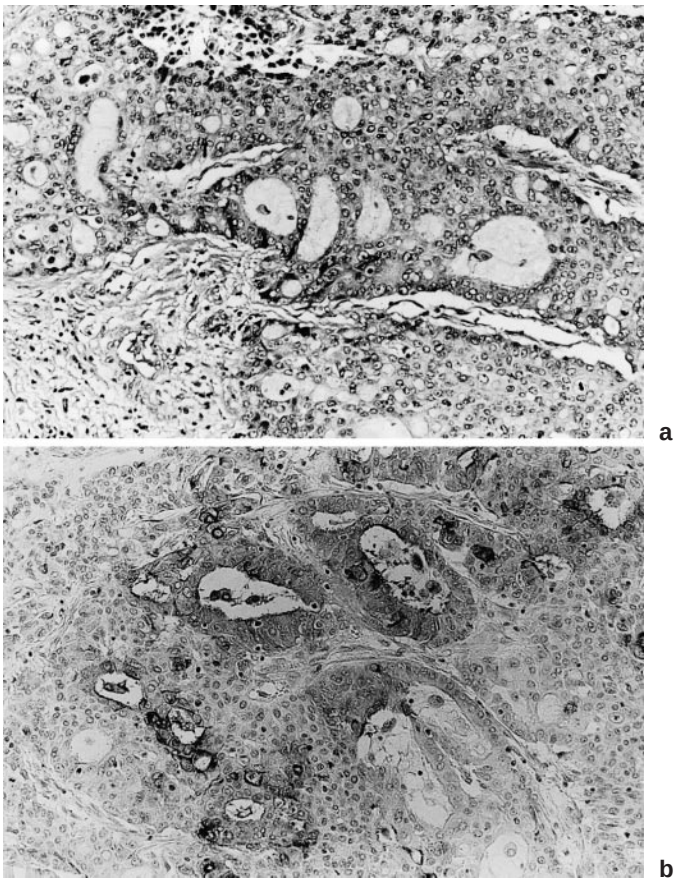

Fig. 4a,b. Photomicrographs showing the intermingled part of the hepatocellular carcinoma and cholangiocellular carcinoma (CCC). **a** H&E, ×400. **b** Immunohistochemical study demonstrating positive reaction for CEA in the CCC component. ×400

in an intermingled form (Fig. 4a), with the CCC component showing positive immunoreactivity for CEA (Fig. 4b). Based on these histological and immunohistochemical findings, the tumor was diagnosed as combined (mixed) CCC and HCC. The CCC components invaded both the surrounding liver tissue and the right hepatic vein.

Discussion

Combined HCC and CCC (mixed carcinoma) is a rare form of primary liver carcinoma.[1] Mixed carcinoma can be divided into three subtypes: double cancers (separate type), combined (collision type), and mixed (intermingled type).[2,3] According to Haratake and Hashimoto's[3] classification, our case could be classified as intermingled type, because the two components, HCC and CCC, coexisted in a single tumor. In this subtype, the tumor is thought to originate from a single site, but with two possible endpoints of differentiation, with HCC being far more dominant than CCC in most patients.[4] Edmondson and Craig[5] suggested that most combined carcinomas, except for the "separate" subtype, were derived from HCC and thus demonstrated a process of transition from HCC to CCC. However, in our patient, CCC was far more dominant, and scattered HCC was distributed in the prevailing area of CCC. Moreover, focal transitional zones were also seen between these two components of HCC and CCC. These findings contradict those of Edmondson and Craig.[5] We believe that this type of combined carcinoma may originate from stem cells and subsequently maintain two different differentiation potentials during tumor growth, eventually developing as either HCC or CCC.

In combined carcinomas reported in Japan, only 3% were diagnosed clinically or preoperatively, in clear

contrast to the relatively high accuracy of diagnosis for non-combined HCC or CCC (99% for HCC and 84% for CCC).[6] The abdominal ultrasonography and angiography findings for our patient's tumor were compatible with HCC. In a CT scan, the tumor was well enhanced with contrast medium in an early phase and it was then washed out at the portal phase with both of these findings being compatible with HCC. However, a central scar-like structure was also observed in the tumor, which is not typical in HCC. The various types of diagnostic imaging thus could not help to establish a diagnosis of combined carcinoma preoperatively in our patient. Nakahara[4] reported that a combination of elevated CEA and slightly elevated AFP may indicate a clinical diagnosis of combined carcinoma. In our patient, however, AFP was slightly elevated while CEA was within the normal range. Such laboratory findings were, again, not helpful in establishing the diagnosis.

Haratake and Hashimoto[3] reported that the collision type and intermingled of type tumors originated mainly from cirrhotic livers, thus suggesting a possible involvement of hepatitis virus in the development of this subtype. However, in our patient, the tumor originated from a non-cirrhotic liver, and the patient had no positive serological test for either hepatitis B or C. Thus, there may be another etiology besides cirrhosis. Since oral contraceptive steroids are reported to be involved in HCC in the non-cirrhotic liver,[7] the long-term use of steroids in our patient may have played a role in the occurrence of the combined carcinoma.[7]

In conclusion, we have reported a rare form of combined carcinoma of the liver, subclassified as intermingled type. This case indicates that combined carcinoma can originate from non-cirrhotic livers, with CCC being predominant.

References

1. The Liver Cancer Study Group. Primary liver cancer in Japan. Sixth report. Cancer 1987;60:1400–1411.
2. Allen RA, Lisa JR. Combined liver cell and bile duct carcinoma. Am J Pathol 1949;25:647–655.
3. Haratake J, Hashimoto H. An immunohistochemical analysis of 13 cases with combined hepatocellular and cholangiocellular carcinoma. Liver 1995;15:9–15.
4. Nakahara T. Clinicopathological study of combined hepatocellular and cholangiocarcinoma (in Japanese with English abstract). Kanzo 1986;27:1431–1438.
5. Edmondson HA, Craig JR. Neoplasms of the Liver. In: Schiff L, Schiff ER (eds) Diseases of the liver. 6th ed. Philadelphia: JB Lippincott, 1982;1090–1158.
6. The Liver Cancer Study Group of Japan. Survey and follow-up study of primary liver cancer in Japan. 11th Report (in Japanese with English abstract). Kanzo 1995;36:208–218.
7. Kew MC, Song E, Mohammed A, et al. Contraceptive steroids as a risk factor for hepatocellular carcinoma: A case/control study in South African black women. Hepatology 1990;11:298–302.