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Double cancer — hepatocellular carcinoma and intrahepatic cholangiocarcinoma with a spindle-cell variant

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Abstract: Intrahepatic cholangiocarcinoma (ICC) with a spindle-cell variant is very rare. We report here a surgical patient who had double cancer — hepatocellular carcinoma (HCC) and ICC with a spindle-cell variant. In this 70-year-old man, who had a history of hepatic resection for HCC about 2 years previously, two large discrete masses were identified in the right lobe of the liver. A right lobectomy of the liver was performed. Pathological findings revealed that one tumor was a typical HCC, and the other was ICC with sarcomatous lesions. Immunohistochemical examinations of the sarcomatous lesions in ICC demonstrated that some of the spindle cells were positive for keratin, epithelial membrane antigen, and vimentin, but negative for S-100 protein, desmin, and actin. From these findings, we concluded that the sarcomatous lesions of ICC were not a true sarcoma, but sarcomatous transformation of cholangiocarcinoma cells, that is, a spindle-cell variant of ICC.

Key words: primary liver cancer, cholangiocarcinoma, spindle cell variant, immunohistochemistry, hepatectomy

Introduction

Hepatocellular carcinoma (HCC) with a spindle-cell component is treated as a "spindle" variant of HCC and such synonyms as "pseudosarcomatous" and "sarcomatoid" HCC[1] are used. Sarcomatoid HCCs, the incidence of which is relatively rare, have been specifically found in patients in advanced or terminal stages of the disease in relation to repeated transcatheter arterial embolization or chemotherapy.

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare form of malignant epithelial tumor of the liver, accounting for about 5% of primary liver cancers.[2] Although the development of ICC is generally not related to hepatitis B virus infection,[2,3] an involvement of hepatitis C virus infection in ICC has been suggested.[4] ICC with spindle-cell areas resembling fibrosarcoma is defined as a spindle-cell (pseudosarcomatous) variant.[1] However, there have been only a few reports of this variant.[5–7]

We report here a surgical patient with synchronous double cancer — HCC and ICC, a mass of which had a predominantly sarcomatous appearance.

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Case report

A 70-year-old Japanese man was referred and admitted to Hiroshima University Hospital on May 18, 1998 complaining of general fatigue and fever.

He had no history of jaundice, blood transfusions, high alcohol intake, or exposure to hepatotoxins. In September, 1994, liver dysfunction had been discovered during routine screening. Close examination revealed a tumor measuring 2 cm in diameter in segment VIII[8] of the liver. His serum level of alpha-fetoprotein (AFP) was 293 ng/ml (normal range, below 20 ng/ml) before treatment. He had been admitted to our hospital and received transcatheter arterial infusion chemotherapy (with cisplatin emulsified with lipiodol) through the right hepatic artery, and partial hepatic resection, performed on February 2, 1995. Postoperative pathological examination indicated that the tumor was HCC with massive necrosis, and the associated liver disease was chronic active hepatitis. No viable cancer cells were found in the resected specimen. The patient's postoperative course was uneventful. After leaving our hospital, he had been followed-up by his family doctor.

Physical examination on his second admission to our hospital showed no abnormalities except for the incisional operation scar on his abdomen from the first hepatic resection. Serum liver function test results

on the second admission were within the normal range, except for a decreased albumin level (3.1 g/dl; normal range, 3.3–4.7 g/dl), increased alkaline phosphatase level (348 IU/l; normal range, 90–340 IU/l) and increased indocyanine green retention rate at 15 min after injection (21.6%; normal range, below 10%). Serum levels of carbohydrate antigen 19-9 (CA 19-9) and prothrombin induced by vitamin K deficiency or antagonist-II were 2634 U/ml (normal range, below 37 U/ml) and 0.34 AU/ml (normal range, below 0.01 AU/ml), respectively, while carcinoembryonic antigen (CEA) and AFP levels were within the normal range. Both hepatitis B surface and hepatitis C antibodies were positive, while hepatitis B surface antigen was negative. Computed tomography showed two separate masses in the right lobe of the liver. One was a well demarcated, low-density mass measuring 5 cm in diameter with distinct capsule formation in segment VIII of the liver. The tumor was located near the previous surgical stump (Fig. 1a). The other was a poorly demarcated, low-density mass measuring 8 cm in diameter without capsule formation in segments V to VI of the liver (Fig. 1b).

Right lobectomy of the liver, the second operation, was performed under the diagnosis of recurrent HCC, on June 4, 1998. The patient's postoperative course was uneventful, and he is doing well without any evidence of recurrence in March, 1999.

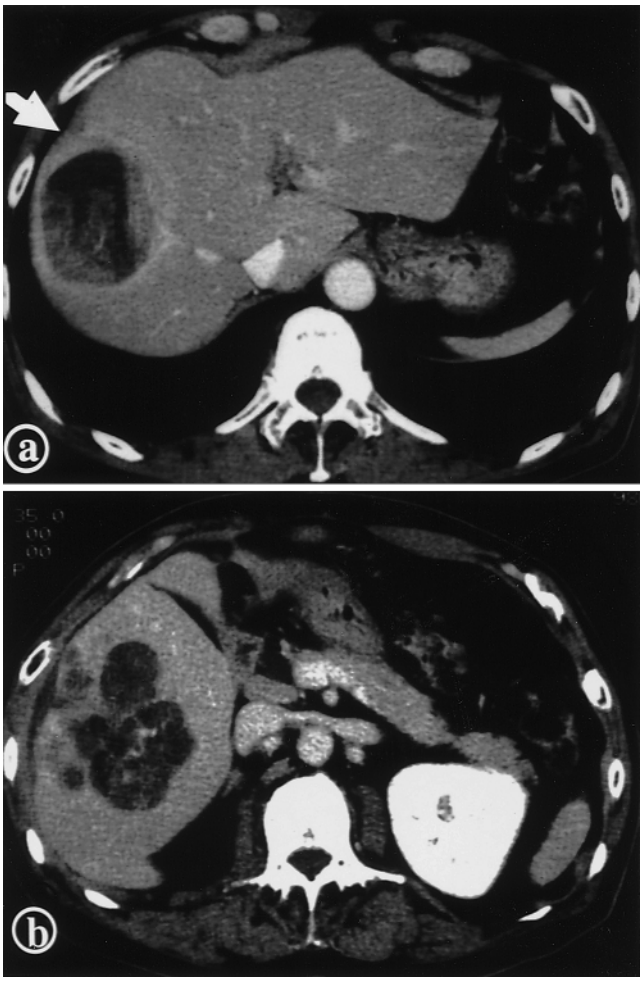

Fig. 1a,b. Computed tomography shows two separate masses in the liver; **a** a well demarcated, low-density mass, located near the previous surgical stump (*arrow*), in segment VIII and **b** a poorly demarcated, low-density mass in segments V to VI

Gross findings

The resected specimen weighed 970 g. In the specimen, there were two separate tumors, measuring 6.0 cm and 10.7 cm in diameter, respectively. The tumor in segment VIII was yellowish-white and encapsulated (Fig. 2a), and the tumor in segments V to VI was yellowish-white, focally brown, and had no capsule (Fig. 2b). There were no tumor thrombi in the portal and hepatic veins. The surrounding liver parenchyma was not cirrhotic.

Microscopic findings

The resected specimens were fixed in 10% formalin and processed for light microscopy. Paraffin-embedded blocks were sectioned. After being deparaffinized, the sections were stained with hematoxylin and eosin (H & E), and periodic acid-Schiff (PAS).

The tumor in segment VIII of the liver consisted almost entirely of a carcinomatous proliferation of moderately differentiated HCC with a thick trabecular pattern. The tumor cells exhibited large nuclei and abundant cytoplasm. The nuclear/cytoplasmic ratio was greater than that of a normal hepatocyte. This carcinoma corresponded to grade II of Edmondson's and Steiner's classification[9] (Fig. 3). No vascular invasions into the portal and hepatic veins were found.

The tumor in segments V to VI had atypical glandular structures of various sizes. Mucin production, as demonstrated by PAS, was found in the lumina of the glandular structures. The atypical glands were covered with some layers of cuboidal epithelium with prominent nucleoli. These findings corresponded to moderately differentiated tubular adenocarcinoma. In this tumor, there were no histologic elements suggestive of HCC. The interstitial areas of the cancer lesions were entirely composed of spindle cells with atypical nuclei. Transitional features from carcinomatous to sarcomatous areas were not observed. Many neutrophils and other inflammatory cells were intermingled with these sarcomatous spindle-shaped cells. There were no multinucleated giant cells in the sarcomatous areas (Fig. 4a,b).

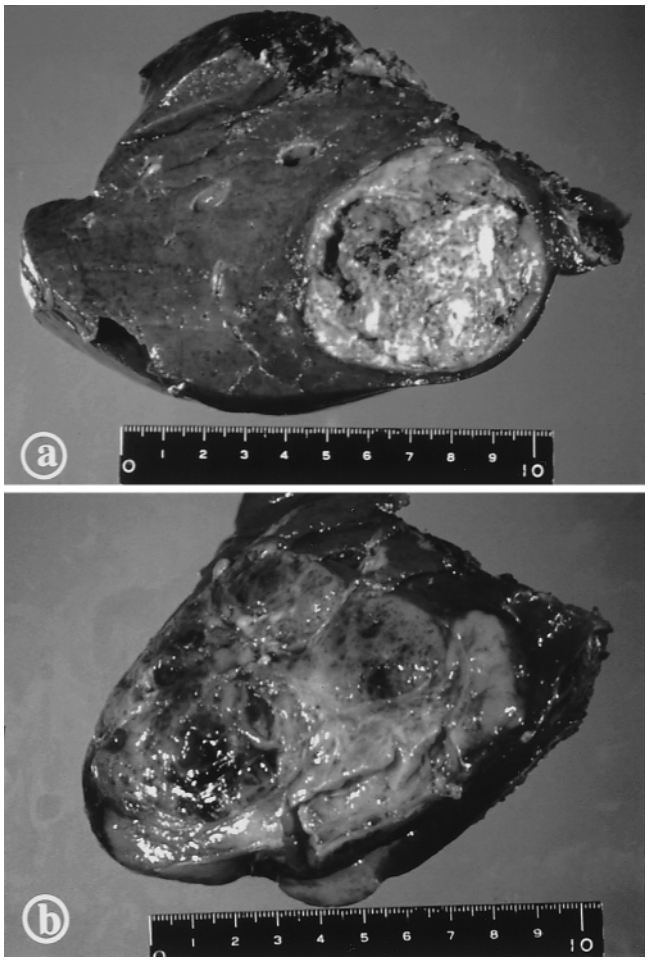

Fig. 2a,b. Macroscopic findings of the resected liver specimen, which contained two separate tumors. **a** A tumor measuring 6.0 cm in diameter with a thin capsule in segment VIII of the liver. **b** Tumor measuring 10.7 cm in diameter without capsule formation in segments V to VI of the liver

Immunohistochemistry (Table 1)

Immunohistochemical studies were performed, using the avidin-biotin complex (ABC) method according to the procedure of Hsu et al.[10] Antibodies were used for the following: AFP (Histofine; Nichirei, Tokyo, Japan), CEA (Campaign, IBL, Fujioka, Japan), CA 19-9 (NS 19-9; Centocor, Pennsylvania, USA), keratin (epithelial keratin AE1/AE3; ICN Biomedicals, Costa Mesa, CA, USA), epithelial membrane antigen (EMA; Dako, Glostrup, Denmark), vimentin (Dako), actin (Dakopatts, Glostrup, Denmark), desmin (Dako), and S-100 protein (Dakopatts). Results of the immunohistochemical examinations in the spindle-shaped sarcomatous cells which appeared in the ICC tumor were that: keratin (Fig. 5), EMA, and vimentin were focally positive in the cytoplasm, but S-100, desmin, and actin were negative.

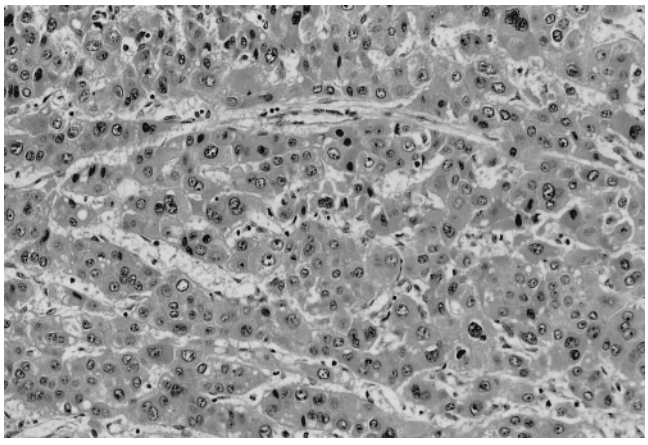

Fig. 3. Microscopic findings of the tumor in segment VIII of the liver. The tumor consisted almost entirely of a carcinomatous proliferation of moderately differentiated hepatocellular carcinoma with a thick trabecular pattern. H & E, ×400

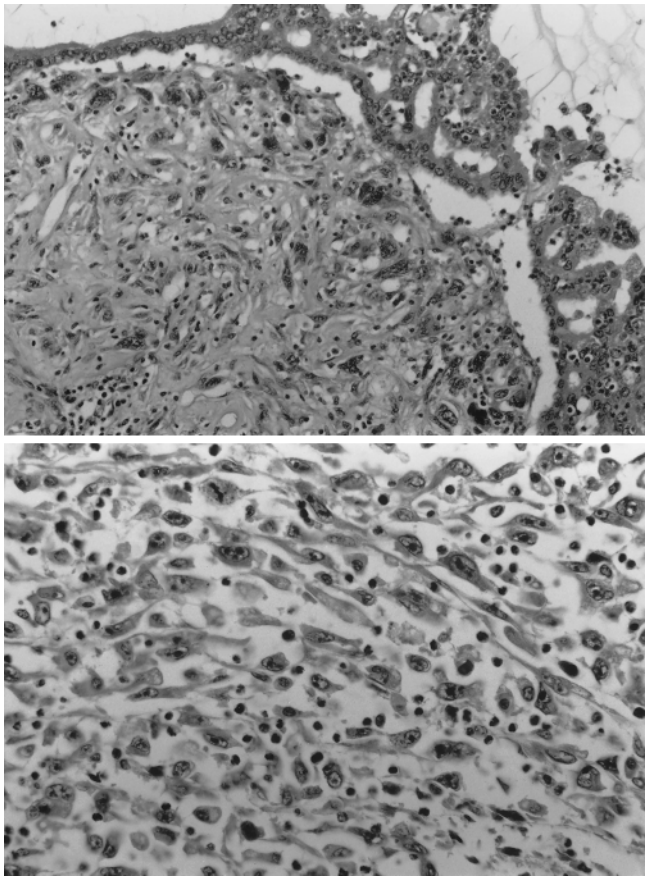

Fig. 4a,b. Microscopic findings of the tumor in segments V to VI of the liver. **a** The tumor consisted of atypical glands with mucin production, corresponding to moderately differentiated tubular adenocarcinoma. **b** The interstitial areas of the cancer lesions were entirely composed of spindle cells with atypical nuclei. **a** H & E, ×200; **b** H & E, ×400

Table 1. Summary of immunohistochemical findings

	Immunohistochemical staining								
	AFP	CEA	CA 19-9	Keratin	EMA	Vimentin	Actin	Desmin	S-100
HCC	−	−	−	++	−	−	−	−	−
ICC									
Cancer lesion	−	−	++	++	++	−	−	−	−
Sarcomatous lesion	−	−	−	+	+	+	−	−	−

−, negative; +, focally positive; ++, diffusely positive; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; EMA, epithelial membrane antigen

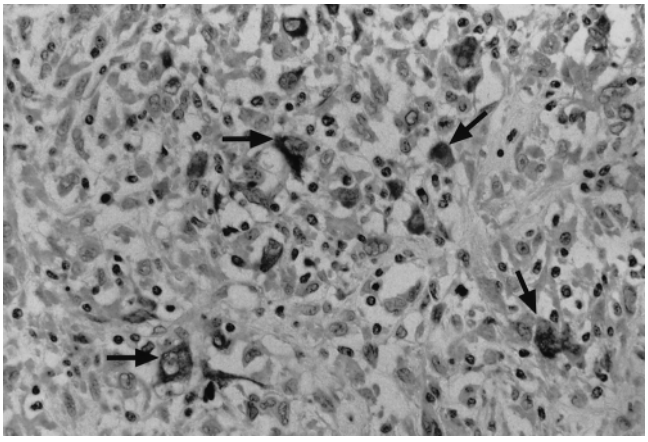

Fig. 5. Immunohistochemical demonstration of keratin in the sarcomatous lesion. Some spindle cells showed weak positivity for keratin in their cytoplasm (*arrows*). ×400

Discussion

Combined hepatocellular-cholangiocarcinoma is a relatively rare form of primary liver cancer. Allen and Lisa[11] defined three types of tumors: (1) separate masses consisting of either HCC or ICC; (2) contiguous but independent masses of HCC and ICC; and (3) an intimate intermingling of hepatocellular and glandular elements. In the recent definition;[1] however, HCC and ICC arising separately in the liver are distinguished from combined hepatocellular and cholangiocarcinoma, regardless of whether the two types of tumors are widely separated or close to each other ("collision tumor"). In our patient, there were two large nodules in the resected right lobe of the liver, and microscopic investigations revealed that one was HCC, and the other, ICC. These two large nodules were entirely discrete, that is, they were synchronous double cancers. Moreover, sarcomatous lesions were predominant in the ICC tumor, while there were no sarcomatous lessons in the HCC tumor. The interstitial areas of the cancer lesions were entirely replaced with spindle cells.

The incidence of sarcomatoid HCC is 3.9%–9.4%[12,13] in autopsy cases of HCCs and 1.8%[14] in surgical patients with HCC. Among surgically resected HCCs less than 2 cm in diameter, there has been no case with a sarcomatous change. Kojiro et al.[12] have clarified that the incidence of sarcomatoid HCC is significantly higher in HCC patients with repeated transcatheter arterial chemoembolization therapy compared with nontreated patients. Accordingly, they suggested that the sarcomatoid changes of HCC were caused by phenotypic changes of cancer cells due to factors including anticancer chemotherapy.

Only a few reports of ICC with sarcomatous change have appeared in the English-language literature. Sasaki et al.[5] reported an autopsy case of ICC that consisted of sarcomatous transformation of cholangiocarcinoma. Nakajima et al.[7] reported seven patients with ICC with sarcomatous change, including two surgical patients and five autopsy cases. All but one had tumors greater than 7 cm in diameter. In only three of the seven patients, the sarcomatous component predominated in the tumor. Haratake et al.[6] reported a patient with ICC containing spindle cells with giant cell tumor-like elements associated with systemic cholelithiasis. They also reported an autopsy case of multiple sarcomatoid ICC with two discrete HCC nodules without sarcomatous elements in the liver, as found in the patient we have reported here. In our patient, there were no lesions that resembled HCC, and AFP was negative in the ICC tumor, while CA 19-9 was positive, so that the derivation of the sarcomatous cells from HCC was excluded.

In order to discriminate between sarcomatoid lesions and true sarcomas complicated with primary liver cancer, when sarcomatous lesions are intermingled with the cancer lesion, immunohistochemical examinations should be performed, although sarcomas of the liver are very rare. There are a few reports of the immunohistochemical properties of sarcomatoid HCC. Kakizoe et al.[13] reported that sarcomatoid HCC lesions showed positive staining for keratin in 7 of 11 patients, and for vimentin in 7 of 11 patients. Maeda et al.[14] reported that

the spindle cell components of sarcomatoid HCC, which they termed spindle-cell HCC, were positive for vimentin in 8 of 13 patients (62%) and were positive for both vimentin and cytokeratin in 6 of 13 patients (46%), while mesenchymal markers such as alpha-smooth muscle actin, desmin, and S-100 were also positive in some patients. They speculated that the expression of such mesenchymal markers in spindle-cell HCC lesions may be related to the sarcomatous differentiation of these tumors. With respect to immunohistochemical staining for sarcomatoid ICC, Nakajima et al.[7] demonstrated that sarcomatous components of ICC showed positive staining for both keratin and EMA in five of seven patients, but staining for actin, desmin, and S-100 was negative in all patients. Sasaki et al.[5] reported an autopsy case of ICC in an adult, with sarcomatous change, and they demonstrated that sarcomatous cells were weakly positive for keratin, EMA, and vimentin. In contrast, Leger-Ravet et al.[15] reported a patient with carcinosarcoma of the liver with mesenchymal differentiation in whom immunohistochemical examination demonstrated that the sarcoma components showed negative staining for keratin, and positive staining for S-100, which is a marker of nerve and cartilagious cells. In our patient, the focally positive staining for keratin and EMA in the sarcomatous lesions suggests epithelial characteristics of the spindle cells,[16] and is a possible sign of cellular transformation from carcinoma to sarcomatous lesion.[13,17] Similarly, the expression of vimentin, which is considered to be a consequence of sarcomatous transformation, was focally positive, and it has been suggested that its detection was limited to sarcomatous cells.[13,18] Moreover, in our patient, the expression of mesenchymal markers, such as S-100, desmin, and actin, was negative. From these findings, it can be presumed that the sarcomatous tumor was not a true sarcoma but a sarcomatous transformation of cholangiocarcinoma cells, that is, a spindle-cell variant of ICC.

The prognosis of patients with the spindle-cell variant of ICC is not known, as to the best of our knowledge, only three surgical patients including our patient, have been reported to date. However, considering that most of the cases with the spindle-cell variant of ICC were found on autopsy, it seems that this variant appears in advanced or terminal stages of the disease, as was the case with the spindle-cell HCCs. Our surgical patient should be carefully observed for recurrences.

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