Primary Hepatocellular Carcinoma and Hepatoid Adenocarcinoma of the Stomach with Liver Metastasis: An Unusual Association

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Alpha-fetoprotein (AFP)-producing hepatoid adenocarcinoma of the stomach is a rare and recently discovered entity. We report an unusual combination of hepatocellular carcinoma and hepatoid adenocarcinoma of the stomach with multiple liver metastases. The patient, a 62-year-old Japanese man, was clinically diagnosed as having hepatocellular carcinoma because of the presence of liver tumors, a markedly elevated serum AFP level, and a positive hepatitis C virus (HCV) antibody titer. Autopsy revealed multiple tumors in the liver; one was a primary hepatocellular carcinoma without metastasis, and the others were metastases from latent hepatoid adenocarcinoma of the stomach. In the hepatocellular carcinoma, bile production was observed although the tumor was immunohistochemically negative for AFP. On the other hand, both the primary gastric and metastatic liver hepatoid adenocarcinomas were positive for AFP. Therefore, hepatoid adenocarcinoma of the stomach was responsible for the excessive production of AFP and was the cause of death.

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Key words: Hepatoid adenocarcinoma—Stomach—Alpha-fetoprotein—Hepatocellular carcinoma—Liver

Introduction

Alpha-fetoprotein (AFP) is the most thoroughly characterized oncofetal protein and its usefulness in the diagnosis of hepatocellular carcinoma and yolk sac tumors of gonadal and extragonadal origin is well established. Recently, elevation of the serum AFP level in patients with gastric cancers has been reported.[1–3]

Hepatoid adenocarcinoma is the term recently proposed for a special type of primary gastric carcinoma characterized by histologic resemblance to hepatocellular carcinoma and excessive production of AFP.[4–6] It frequently occurs together with liver metastasis, and has a poor prognosis. The combination of a high serum AFP level, a liver mass, and histologic features resembling hepatocellular carcinoma does not always indicate the presence of primary hepatocellular carcinoma. Consequently, there have been difficulties in diagnosing this condition.

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Chronic hepatitis C virus (HCV) infection is a well-known risk factor for hepatocellular carcinoma.[7, 8] Therefore, if a patient presents with HCV infection as well as a high serum AFP level and a liver mass, the physician usually suspects hepatocellular carcinoma and does not consider another malignancy. We describe an unusual case in which HCV seropositivity was detected in addition to a high serum AFP level and liver masses, and autopsy revealed the coexistence of primary hepatocellular carcinoma and hepatoid adenocarcinoma of the stomach with multiple liver metastases. The latter was the main source of excessive AFP production and was responsible for the patient's death.

Case Report

On November 30, 1994, a 62-year-old Japanese man was admitted because of weight loss of 11 kg during the previous 6 months, abdominal distension, and a 3-month history of abdominal tumors. Physical examination revealed anemia, accumulation of ascitic fluid and hard tumors without tenderness in the upper abdomen. Superficial lymph nodes were not palpable. Laboratory data included RBC $356 \times 10^4/mm^3$, Hb 9.1 g/dl, Ht 30.1%, erythrocyte sedimentation rate 67 mm/h, CRP 5.3 mg/dl, GOT

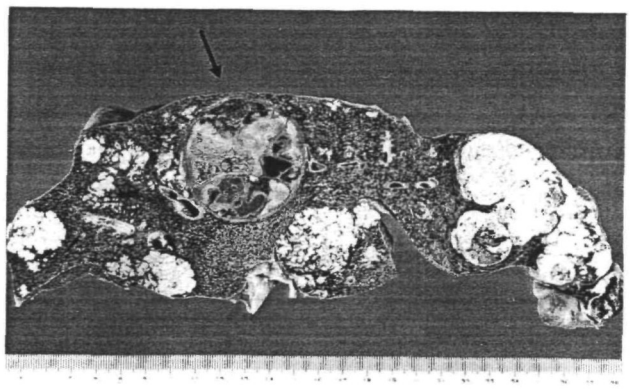

Fig. 1. Cut surface of the liver containing two types of tumor, an encapsulated necrotic tumor (arrow, hepatocellular carcinoma) and multiple whitish tumors (metastatic hepatoid adenocarcinoma).

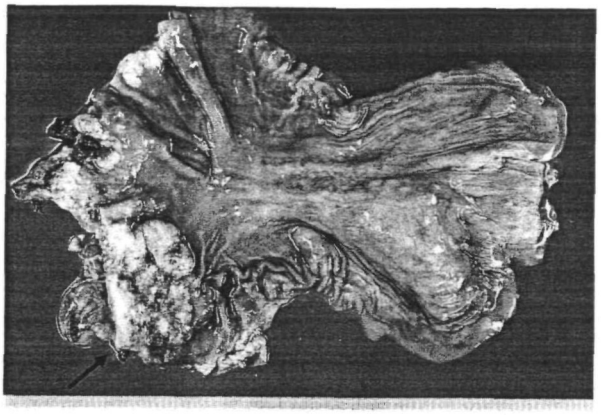

Fig. 2. Mucosal surface of the stomach showing an advanced carcinoma in the antrum (arrow).

165 IU/l, GPT 60 IU/l, LDH 1233 IU/l, alkaline phosphatase 574 IU/l, LAP 102 IU/l, albumin 2.8 g/dl, AFP 506,700 ng/ml and CEA 5.2 ng/ml. Serum anti-HCV antibody was positive. Abdominal CT revealed multiple liver tumors in addition to several abdominal tumors and ascites. Ultrasound examination of the abdomen also revealed multiple liver masses, liver cirrhosis, and swelling of the abdominal lymph nodes. Cytologic examination of the ascitic fluid yielded no tumor cells. Endoscopic examination was not performed because of the patient's poor general condition. Based on these clinical findings, especially the markedly elevated level of AFP, liver tumors, and HCV seropositivity, a tentative clinical diagnosis of hepatocellular carcinoma with metastasis to the abdominal lymph nodes was made. Because the radiological features of the multiple liver masses were not typical of hepatocellular carcinoma, a testicular germ cell tumor with liver metastasis was also considered. However, no tumor was found in the bilateral testes. The patient was treated conservatively, and repeated drainage of ascitic fluid was necessary. Gradually jaundice and renal dysfunction developed, the patient's condition deteriorated, and he died on January 7, 1995, 38 days after admission. The last determined total bilirubin level was 14.7 mg/dl and the serum AFP level 793,700 ng/ml.

The patient's medical history was not remarkable except for a moderate degree of smoking and alcohol intake. He had no history of blood transfusion.

Pathological Findings

Gross Findings

Autopsy revealed 4500 ml of ascitic fluid, massive tumors in the omentum (8.0 × 7.5 × 6.0 cm) and peripancreatic lymph nodes (13.8 × 15.0 × 6.0 cm), multiple liver tumors, and a latent gastric tumor. The liver, which weighed 1810 g, had multiple tumors in both lobes. One of these tumors was distinctly globular in shape and completely encapsulated, located in the posterior superior segment (S7) of the right lobe, and measured 5.0 × 5.0 × 4.0 cm. On sectioning, the tumor was found to be necrotic and focally greenish in color (Fig. 1). The remaining multiple liver tumors were irregular in shape and size, up to 8 cm in diameter, white, and had no capsule. Unexpectedly, a Borrmann type 2 tumor, measuring 7.2 × 4.5 cm, and penetrating the muscularis propria, was found in the greater curvature of the gastric antrum (Fig. 2). Vascular invasion was extensive, and grossly visible tumor thrombi were noted in the stomach wall as well as the duodenum (Fig. 3). Continuous tumor thrombi from the portal truncus to the intrahepatic portal trees were observed (Fig. 4).

Microscopic Findings

The encapsulated liver tumor was composed of ordinary well differentiated hepatocellular carcinoma. Because of extensive necrosis, viable tumor cells were present only in limited areas. The tumor cells were cuboidal with abundant eosinophilic granular cytoplasm and displayed an acinar pattern with obvious bile production (Fig. 5). Extracapsular

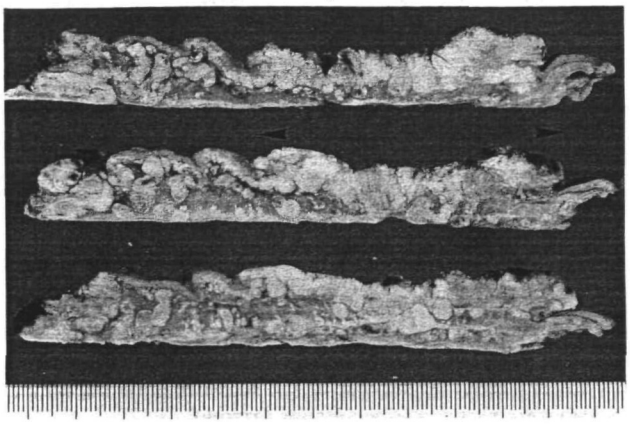

Fig. 3. Cut surface of the gastric tumor with extensive vascular invasion. Arrowheads show the extent of the primary tumor.

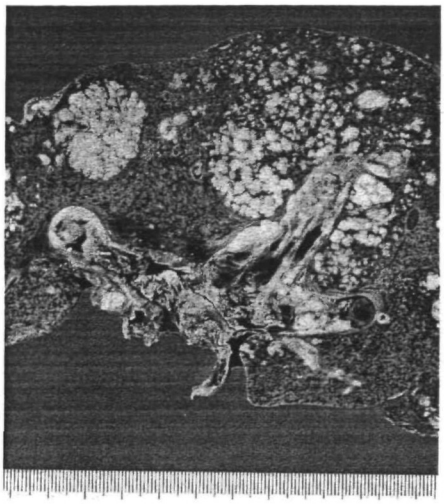

Fig. 4. Cut surface of the liver hilus showing tumor emboli in the portal veins.

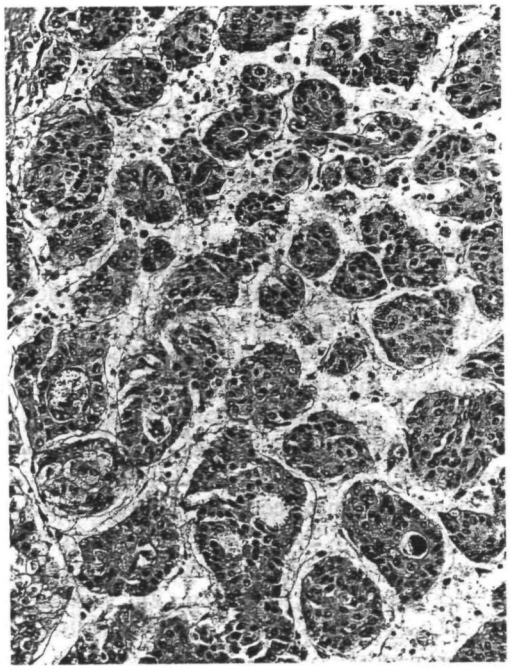

Fig. 5. Photomicrograph of the encapsulated liver tumor showing hepatocellular carcinoma with bile production.

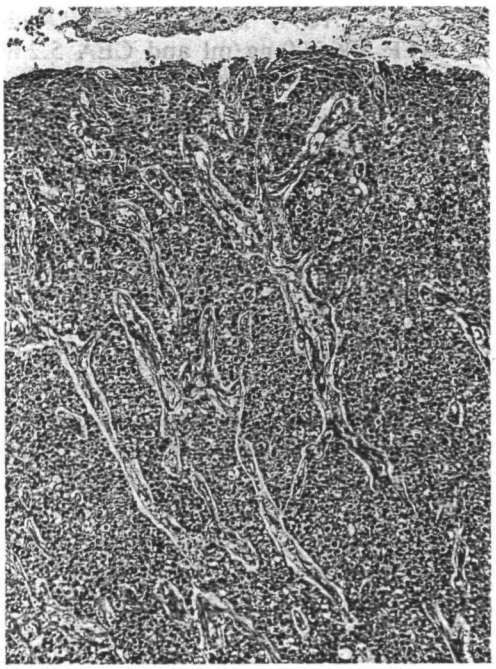

Fig. 6. Low-power view of the stomach tumor.

invasion was not observed. On the other hand, multiple whitish liver tumors showed histologic features identical to those of the gastric tumor described below.

The tumor in the stomach showed unusual histologic features, in which cuboidal or polygonal tumor cells with rather clear cytoplasm were arranged in large, thick trabeculae with a delicate stroma composed of sinusoid-like capillaries, closely resembling moderately differentiated hepatocellular carcinoma (Figs. 6, 7). Formation of microacini was seen in the trabeculae, but bile production was

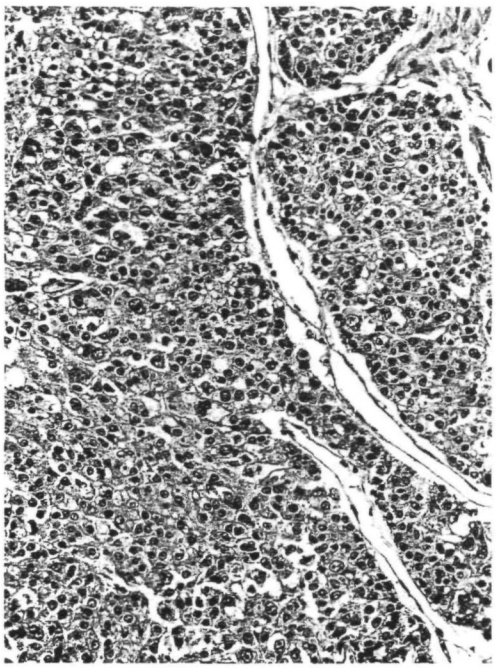

Fig. 7. Photomicrograph of the stomach tumor showing hepatoid adenocarcinoma.

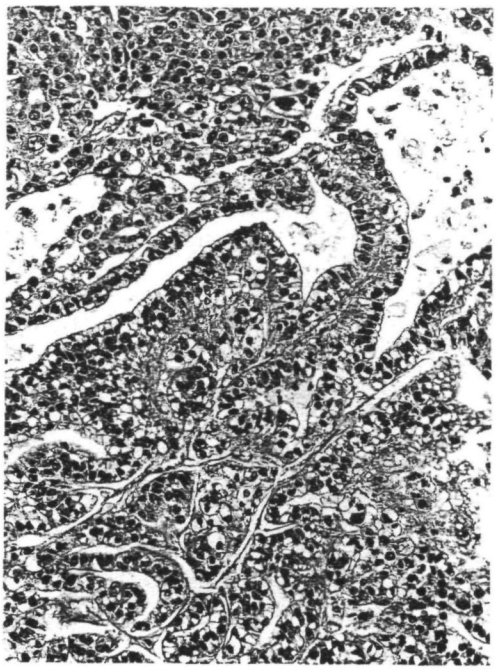

Fig. 8. Part of the stomach tumor showing papillotubular adenocarcinoma of the immature endodermal type.

not observed. Occasionally, columnar epithelial cells with clear or vacuolated cytoplasm showed papillotubule formation (Fig. 8). Glycogen was detected in the tumor cells, but mucin was not revealed by the periodic acid-Schiff reaction or alcian blue staining. The same histology as that in the stomach tumor was found in the portal tract emboli, multiple whitish liver tumors, omentum and lymph node tumors (Fig. 9).

An immunoperoxidase study was performed on paraffin-embedded material by the avidin-biotin-peroxidase complex method. Sections were stained with antibodies against AFP (rabbit polyclonal antibody, DAKO, Copenhagen, Denmark) and carcinoembryonic antigen (CEA, mouse monoclonal antibody, Mochida Pharmaceutical Co. Ltd., Tokyo). The gastric and whitish liver tumors were positive for AFP (Fig. 10). CEA was also present, but only focally, in the papillotubules of the gastric tumor. However, the encapsulated hepatocellular carcinoma was negative for both AFP and CEA.

The non-tumorous liver tissue showed chronic active hepatitis and marked bile stasis, but no cirrhosis was detected. Sections of the kidney revealed cholemic nephrosis. No tumors were present in the bilateral testes.

On the basis of these histologic and immunohistochemical findings, the pathologic diagnosis was double primary carcinoma consisting of 1) encapsulated hepatocellular carcinoma without metastasis and 2) AFP-producing hepatoid adenocarcinoma of the stomach with multiple metastases in the liver, omentum, and peripancreatic lymph nodes.

Discussion

The incidence of AFP-producing gastric carcinomas reported in the literature has ranged from 1.3–15% of all gastric tumors.[6, 9] Recognition of AFP-producing gastric carcinoma is clinically important because of its striking biologic behavior.[9–12] Many authors have reported that the prognosis of AFP-producing gastric carcinoma is very poor, with a significantly higher incidence of venous invasion than that of non-AFP-producing carcinoma.[12] Portal venous tumor thrombosis associated with gastric carcinoma has been reported.[10] Most cases, even at the early stage, have synchronous and metachronous metastasis to the liver.[9–12] In a series reported by Chang *et al.*, most of the patients, including three who underwent radical surgery for early gastric cancer, died of liver metastasis within 2 years.[9, 12]

From a histologic viewpoint, AFP-producing gastric carcinoma is also distinctive. Kodama *et al.* have reported that medullary or papillotubular arrangements with marked nuclear atypia and eosinophilic granular or clear cytoplasm are

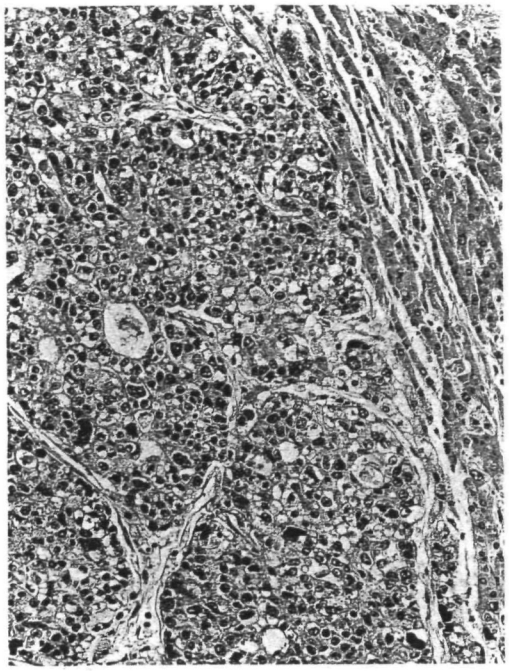

Fig. 9. Photomicrograph of the whitish liver tumor showing metastatic hepatoid adenocarcinoma.

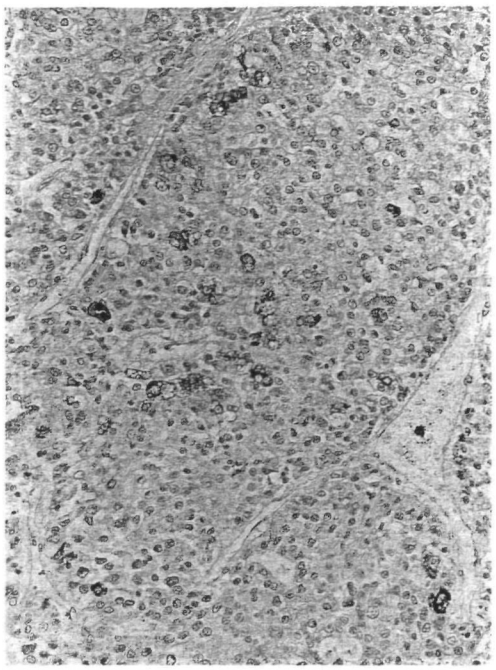

Fig. 10. Immunoperoxidase localization of AFP in hepatoid adenocarcinoma of the stomach.

characteristic.[3] They also pointed out that some tumors with a medullary pattern resembled liver cell carcinoma. Ishikura *et al.* have proposed the term hepatoid adenocarcinoma as a special type of AFP-producing gastric carcinoma.[4,5] Even in the hepatoid type, however, definite hepatic differentiation with evidence of bile production in the tumor cells is rare.[5] The papillotubular carcinoma component composed of clear cells seen in AFP-producing carcinoma has been considered to represent enteroblastic or fetal gastrointestinal differentiation.[13,14] Moreover, although extremely rare, yolk sac tumors of the stomach have also been reported.[14] Overall, however, it is generally accepted that two distinct tumor morphologies, hepatoid and clear cell, are correlated with AFP production.[13,14] These two patterns of carcinoma often show mixed growth in the same tumor. In all the cases of hepatoid adenocarcinoma described by Nagai *et al.*, small areas of well differentiated papillary or tubular structures were detected.[6]

The presence of hepatoid, enteroblastic and/or yolk sac differentiation and production of AFP in gastric cancer is reasonable considering the embryologic similarity existing among the liver, gastrointestinal tract and yolk sac. The stomach and liver are derived from the foregut, which is thought to be in direct continuity with the yolk sac at primitive stages of development. Therefore, some gastric carcinomas may share common morphologic features and antigens with hepatocellular carcinoma and yolk sac tumors.

Because of its morphological resemblance to hepatocellular carcinoma, there is a question as to whether or not stomach involvement is secondary to a primary tumor of the liver.[5] In general, hematogenous metastasis of hepatocellular carcinoma to the stomach is not common, although perigastric lymph node metastasis, peritoneal dissemination or direct invasion involving the stomach can occur rarely.[15] In fact, several cases of gastric metastasis of hepatocellular carcinoma have been reported.[16–18] In those cases, however, the alternative possibility that liver involvement was secondary to a primary hepatoid adenocarcinoma of the stomach was not considered.

Double primary carcinoma consisting of a combination of hepatocellular carcinoma and gastric carcinoma is not very unusual in Japan.[19] However, hepatoid adenocarcinoma of the stomach is so rare that, to our knowledge, its association with hepatocellular carcinoma has not been reported, although a case of AFP-producing early gastric cancer associated with liver cirrhosis has been reported.[20] The etiology of hepatoid adenocarcinoma remains to be settled, whereas chronic HCV

infection is known to be a risk factor for hepatocellular carcinoma, irrespective of the presence or absence of liver cirrhosis.[7, 8] In the present case, the combination of the two distinctive types of tumor could have been merely accidental. As for the extremely high level of serum AFP, however, it is considered that the hepatoid adenocarcinoma component was chiefly responsible, because the hepatocellular carcinoma component was extensively necrotic and the remaining viable tumor cells were immunohistochemically negative for AFP.

Even if multiple liver tumors and an elevated serum AFP level are detected clinically, not only hepatocellular carcinoma and metastatic yolk sac tumor, but also the possible presence of metastatic hepatoid adenocarcinoma should be considered. Especially for the pathologist, if a liver tumor shows hepatic differentiation microscopically, the possibility of metastatic hepatoid adenocarcinoma in addition to primary hepatocellular carcinoma should always be borne in mind.

Acknowledgments

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