

CASE REPORT

Hepatoid Carcinoma of the Pancreas Combined with Neuroendocrine Carcinoma

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Hepatoid carcinoma is a primary extrahepatic carcinoma whose morphology, immunohistochemistry, and behavior are similar to those of hepatocellular carcinoma. The most common sites of extrahepatic carcinoma are the stomach and ovary, but nine cases of hepatocellular differentiation of the pancreas have been reported in the literature. We report another case of hepatoid carcinoma of the pancreas that was associated with the development of a pancreatic endocrine carcinoma in a 46-year-old man. Serum alpha-fetoprotein (AFP) was elevated to 262.49 IU/mL and radiological examinations revealed a mass measuring 7.5 cm in diameter in the head of the pancreas. He underwent a conventional Whipple operation, and light microscopy showed adenocarcinoma that was immunopositive for AFP, hepatocyte antigen, cytokeratin, chromogranin, synaptophysin, and alpha-1 antichymotrypsin. Although hepatoid differentiation was not shown unequivocally histologically, other immunohistochemistry findings supported the diagnosis of hepatoid carcinoma combined with neuroendocrine carcinoma. The patient was healthy and had no evidence of recurrence at 4 months after the surgery. This report describes why hepatoid carcinoma should be considered as a differential diagnosis of a pancreatic mass, especially when serum AFP is elevated. (*Gut Liver* 2010;4:98-102)

Key Words: Hepatoid carcinoma; Pancreas; Neuroendocrine carcinoma

INTRODUCTION

Hepatoid carcinoma is a type of extrahepatic carcinoma that shows a strikingly similar morphology to hepatocellular carcinoma (HCC) with alpha-fetoprotein (AFP) production, positive immunohistochemistry staining of several liver-synthesized proteins, presence of positive periodic acid-Schiff (PAS), diastase-resistant intracytoplasmic globules, bile production, and recently, the more specific and sensitive *in situ* hybridization detection of albumin messenger RNA (mRNA).¹⁻³ Since Ishikura *et al.*¹ reported a HCC-like differentiation in a primary gastric tumor in 1985, cases of hepatoid carcinoma of the esophagus, papilla of Vater, colon, lung, gallbladder, adrenal gland, kidney, urinary bladder, ovary, uterus, vagina, and testicle have been documented.² We report a case of AFP producing hepatoid carcinoma combined with poorly differentiated neuroendocrine carcinoma arising from the pancreas.

CASE REPORT

A 46-year-old man was referred from a local clinic to our hospital because of dyspepsia and pancreatic head mass. He had complained of dyspepsia for 1 week and visited a local clinic, where an abdominal computed tomography (CT) scan was taken. He was neither a habitual drinker nor smoker and did not have any specific personal or family history of other diseases.

Physical examinations on admission were unremarkable,

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except for a palpable mass around the epigastric area of about 7 cm. Laboratory tests showed normal serum levels of carcinoembryonic antigen (CEA) (1.26 ng/mL; normal <5.0 ng/mL), carbohydrate antigen 19-9 (CA19-9) (6.8 U/mL; normal <37.0 U/mL), and vitamin K absence or antagonist II (PIVKA-II) (15 mAU/mL; normal, <40.0 mAU/mL), but elevated serum level of AFP (262.49 IU/mL; normal, <7.0 IU/mL). Blood cell counts, blood coagulation tests, liver function tests, total bilirubin, amylase, and lipase were all in normal range.

Both contrast-enhanced (CE) pancreas CT and pancreaticobiliary magnetic resonance imaging (MRI) showed possibility of gastrointestinal stromal tumor (GIST) arising from the distal gastric antrum and greater curvature side with possible adhesion to the pancreas (Fig. 1A, B). A 7.5×5.8 cm well-defined mass was seen along the pancreatic groove. The mass was abutting the second duodenal wall and compressing the anterior surface of the pancreatic neck, causing narrowing of the main pancreatic duct. However, there was no definite evidence of invasion of pancreatic parenchyma. On positron emission tomography, no other abnormal uptake in the rest of the imaged body was seen, except in the duodenum or in the pancreatic head, suggesting malignancy. Moreover, many multiple lymph node enlargements were seen on the lesser omentum (Fig. 1D).

Esophagogastroduodenoscopy showed extrinsic compression of the gastric antrum and second portion of the duodenum but pathologic results showed no specific find-

ings, except chronic superficial gastritis with intestinal metaplasia (Fig. 1C). Therefore, endoscopic ultrasonography-guided fine-needle aspiration biopsy was done on the primary mass revealing poorly differentiated adenocarcinoma.

The patient underwent conventional Whipple operation (radical pancreaticoduodenectomy) with dissection of lymph nodes around the para-aorta, hepatoduodenal ligament, and celiac axis.

The external serosal surface of the mass was ragged and partly retracted, and its size was 8×9 cm including the necrotic center. The gastric mucosa showed ill-defined elevated lesion with central ulceration in greater curvature of the antrum measuring about 2×2 cm. On sections after fixation, the large necrotic solid portion was noted in the pancreas area with focal calcification (Fig. 2A). No metastasis was seen on the gallbladder, common bile duct and regional lymph nodes. However, prominent peri-tumoral lymphovascular permeation of tumor cells was seen. Microscopic examination revealed poorly differentiated carcinoma showing variable architecture. The tumor was composed of polygonal cells forming glands, papillae, and sheets. Tumor cells also showed vesicular nuclei and prominent nucleoli with abundant cytoplasm (Fig. 2B, C). Immunohistochemical stainings were performed using primary antibodies of the following antigens: cytokeratin (Fig. 3A), AFP (Fig. 3B), hepatocyte antigen (Fig. 3C), chromogranin (Fig. 3D), synaptophysin (Fig. 3E), and alpha-1 antichymotrypsin (ACT) (Fig. 3F).

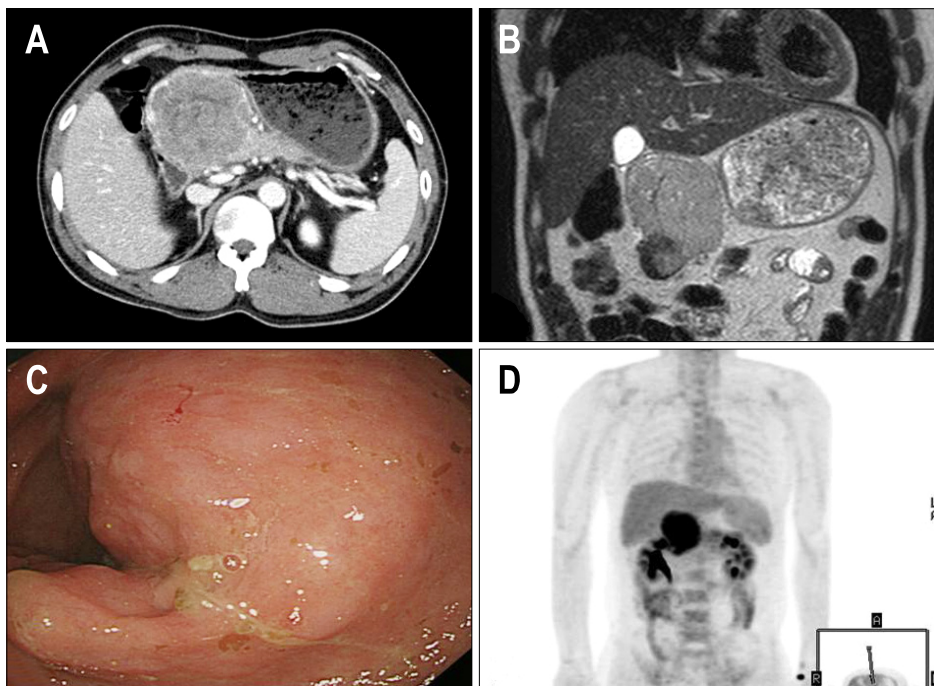


Fig. 1. Imaging studies of the patients. (A) Pancreas computed tomography and (B) pancreaticobiliary magnetic resonance imaging showed possibility of submucosal tumor arising from distal gastric antrum and greater curvature side with possible adhesion to the pancreas. (C) Esophagogastroduodenoscopy showed extrinsic compression of gastric antrum and duodenum second portion. (D) Positron emission tomography showed abnormal uptake only in duodenum or pancreatic head suggesting malignancy.

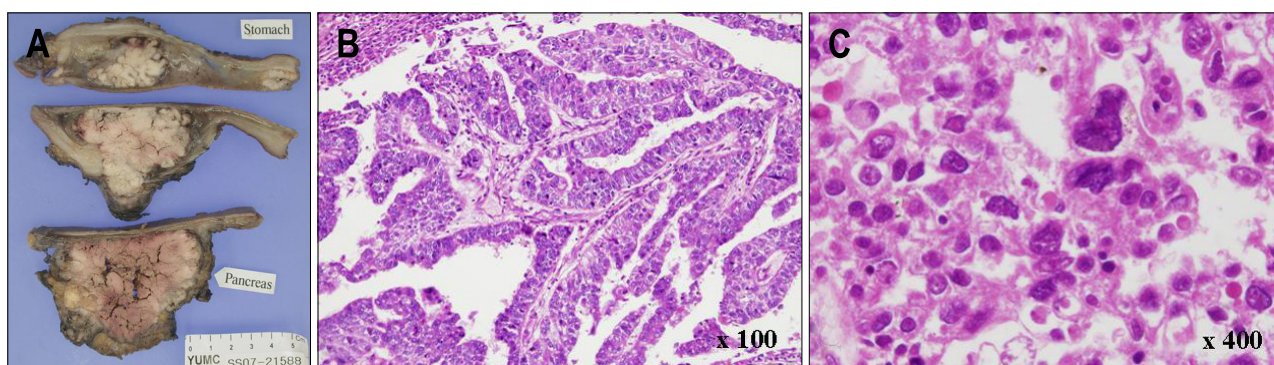


Fig. 2. (A) Cross-section of the pancreas after 24 hours formalin fixation. (B) Hematoxylin-eosin staining of carcinoma (original magnification, $\times 100$). (C) Hematoxylin-eosin staining of carcinoma ($\times 400$).

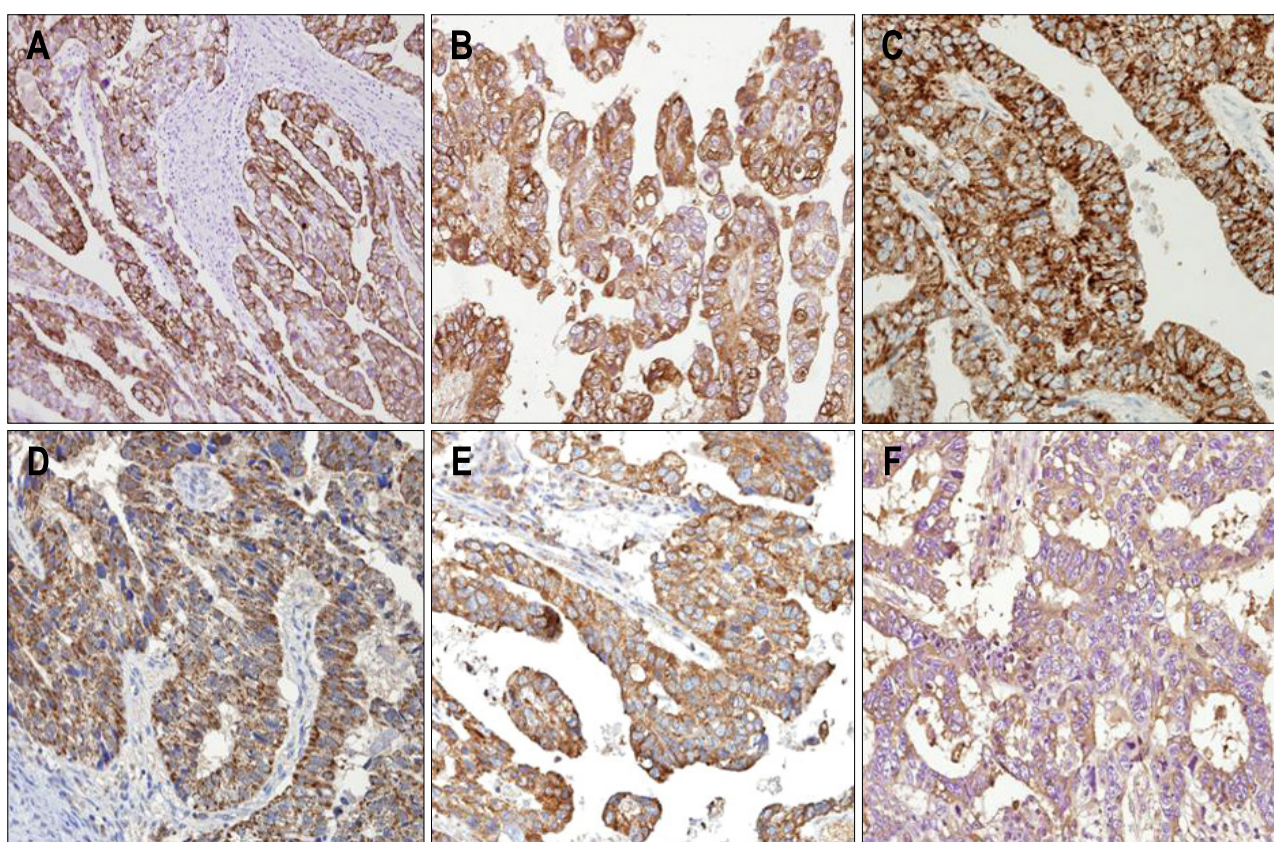


Fig. 3. Immunohistochemical analysis for (A) cytokeratin, (B) AFP, (C) hepatocyte antigen, (D) chromogranin, (E) synaptophysin, and (F) alpha-1 antichymotrypsin ($\times 400$).

Cytoplasmic positive reaction of carcinoma cells was strongly expressed for AFP, hepatocyte antigen, cytokeratin, and ACT, suggesting the hepatoid carcinoma and also for chromogranin and synaptophysin, suggesting neuroendocrine carcinoma. Therefore, final diagnosis was hepatoid carcinoma combined with poorly differentiated neuroendocrine carcinoma arising from the pancreas and extending to the stomach and duodenum.

DISCUSSION

The first hepatoid carcinoma of the pancreas was reported in 1987 by Hruban *et al.* It was a case of peri-acinar cell neoplasm with a solitary focus of hepatocellular differentiation. The clinical course of this patient demonstrated very aggressive progress including both liver and lymph nodes metastasis with an overall survival of only 2.75 months.⁴

AFP, a well-recognized oncofetal protein that appears in patients with malignant tumors such as HCC, germ-cell tumors, or some gastrointestinal tumors, has been found to be a sensitive serum marker in other extrahepatic hepatoid type tumors.^{5,6} In AFP-producing pancreatic tumors, serum AFP level is a useful marker for diagnosis and evaluation of therapeutic response and recurrence.⁷ Immunohistochemical stains can be used for detection of hepatoid carcinoma. The more frequent positive proteins include keratin/cytokeratin cell adhesion molecule 5.2/AE, albumin, ACT, prealbumin, alpha-1-antitrypsin (AAT) protease inhibitor, and transferrin.² In our case, strong expression of AFP and positive immunoreactivity for CEA and hepatocyte antigen strongly suggested the diagnosis of hepatoid tumor.

Microscopically, diagnosis of hepatoid carcinoma was based on the following 2 criteria: (i) a mixture of tubular or papillary adenocarcinoma with sheet-like or trabecular proliferation of neoplastic cells within an AFP-producing carcinoma and (ii) the presence of cells with abundant eosinophilic cytoplasm and centrally located nuclei in the sheet-like or trabecular portions.⁸ However, our case showed cells of polygonal shape with glands, papillae, sheets, and abundant cytoplasm, which confused hepatoid carcinoma with poorly differentiated adenocarcinoma.

Hepatocyte induction from the pancreas has been performed in various animal models. Rao *et al.*⁹ induced hepatocytes from the pancreas of rats maintained on a copper-deficient diet and followed by copper repletion. Therefore, a common progenitor cell in the pancreas from which hepatocytes and pancreatic cells could differentiate may exist. On the other hand, regenerating acinar cells or other differentiated cell types can transdifferentiate. Scarpelli *et al.*¹⁰ suggested that hepatocytes in the hamster pancreas were derived from acinar cells since transformation had been apparently triggered by the carcinogen bis(oxopropyl) nitrosamine administered at the peak of pancreatic regeneration when the majority of acinar cells were in S-phase. Makino *et al.*¹¹ documented that pancreatic ductular epithelium in the hamster is the cell of origin. In addition, the fact that cells with features of both acinar/islet cells and hepatocytes were found in the pancreas of rats treated with hypolipidemic drugs could make the presumption that acinar/intermediate cells were precursor cells for hepatocytes.⁹ Paner *et al.*¹² reviewed 5 cases of hepatoid carcinoma of the pancreas. Three showed ductal cell carcinoma, 1 showed acinar cell carcinoma, and 1 malignant glucagonoma. Therefore, hepatic differentiation could arise from any of the 3 main pancreatic cells (acinar, ductal, and islet cells). In our case, the tumor cells expressed both hepatoid and endocrine tumor

cell features, suggesting islet cell origin. However, pancreatic cells might possess liver-specific genes normally in the repressed state that may be activated during the process of carcinogenesis, expressing cells with a hepatic phenotype. This is supported by the close proximity and common embryonic origin (foregut endoderm) of the liver and pancreas.^{6,12} However, since hepatoid carcinoma can be developed in other germ-layer origins of organs, cellular transdifferentiation is a more primordial explanation.

The prognosis of hepatoid carcinoma of the pancreas could not be established due to the lack of cases. After a thorough review of the literature, only 9 cases of hepatoid carcinoma primarily arising from the pancreas have been reported to date. Although hepatoid carcinoma of the gastrointestinal tract generally shows poor prognosis, 4 out of 9 cases did not have poor outcome; that is, after the initial diagnosis, 1 survived for 14 months, 1 for 48 months, and the other 2 for 8.5 years and 28 months.^{6,12-14} However, their biologic aggressiveness can be predicted through massive lymphatic and venous invasion at the time of diagnosis, resulting in liver and lymph nodes metastasis. Moreover, florid proliferation within local veins mimics the behavior of HCC.¹⁴ The reason for poor prognosis of gastrointestinal tract-originated hepatoid carcinomas is not clearly understood. Nagai *et al.*¹⁵ reported that hepatoid carcinoma of the stomach had poorer prognosis regardless of producing AFP or not than AFP-producing nonhepatoid carcinoma. One possibility is that hepatoid carcinoma produces AAT and/or ACT as well as AFP. AAT and ACT have immunosuppressive and protease-inhibitory properties that enhance invasiveness.⁸ AFP also has suppressive effects on lymphocyte transformation.¹⁶ In addition, Koide *et al.*¹⁷ have reported that AFP-producing gastric cancer has high proliferative activity, weak apoptosis, and rich neovascularization.

Hepatoid carcinoma is known to be resistant to chemotherapy. There was only 1 patient who was given chemotherapy with gemcitabine for 26 months because of newly developed liver metastasis at 12 months after operation. However, she underwent right lobectomy of the liver 39 months after the initial operation because of increase in tumor size.¹³

In summary, we present a case of hepatoid carcinoma of the pancreas combined with neuroendocrine tumor. In reported examples in the literature, hepatoid carcinomas are often associated with early liver metastasis and short median survival although those arising as a component of endocrine tumors might fare slightly better. Therefore, it is important that hepatoid carcinoma should be considered as a possible malignant tumor of the pancreas.

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