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Case Report

Mixed Ductal-Endocrine Carcinoma of the Pancreas Occurring as a Double Cancer: Report of a Case

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We present a successfully treated case of mixed ductal-endocrine carcinoma of the pancreas complicated by right renal cell carcinoma. The patient had no symptoms, and laboratory data were close to the normal range. Enhanced computed tomography demonstrated a marked enhanced tumor, which appeared to be an endocrine tumor, at the pancreas uncus. We performed pyrolus-preserving pancreaticoduodenectomy, regional lymph node resection, and right nephrectomy. Histologically and immunohistochemically, the pancreas tumor had both a ductal (exocrine) and an endocrine component. The renal tumor was a typical clear cell carcinoma. A diagnosis of synchronous double cancer was made. As demonstrated in previously published reports, this type of mixed tumor has malignant potential for invasive ductal carcinoma. We propose that mixed ductal-endocrine carcinoma of the pancreas should be treated by surgical resection with a sufficient surgical margin and regional lymph node resection to improve the patient's prognosis.

Key words: Mixed tumor – Ductal carcinoma – Endocrine tumor – Pancreatic cancer – Double cancer

The pancreas parenchyma is composed of three cell types: ductal cells, acinar cells, and endocrine cells, including islets of Langerhans. These three cell types are thought to be derived from the embryonic foregut[1]; therefore, three types of pancreatic tumors—ductal, acinar, and endocrine tu-

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mors—develop from the pancreas parenchyma. Mixed tumors including these elements, although very rare, are known to develop from the pancreas parenchyma. These tumors are mixed ductal-endocrine tumor, mixed acinar-endocrine tumor, mixed ductal-acinar tumor, and mixed ductal-acinar-endocrine tumor.

Mixed ductal-endocrine carcinoma, one of the histologic variants, is defined according to World Health Organization criteria as ''a carcinoma in which ductal and endocrine cells are intimately admixed.''[1,2] Because pancreatic ductal carcinomas frequently exhibit endocrine components, as is the case with carcinomas in other organs, the endocrine cell component must constitute more than 30% of the tumor area to meet the diagnostic criteria for mixed ductal-endocrine carcinoma.[2] We report here a case of mixed ductal-endocrine carcinoma of the pancreas complicated by renal cell carcinoma.

Case Report

In 2006, a 68-year-old man was referred to Gunma University Hospital for treatment of a pancreatic tumor and a right renal tumor detected by physical examination. He had no symptoms but had been treated for hypertension, hyperlipidemia, and hyperuric acidemia. He had undergone surgery for right lung cancer in 2004 and for rectal cancer in 1988. His blood cell counts and biological chemistry data were nearly within normal ranges. Tumor marker levels (carbohydrate antigen 19-9, carcinoembryonic antigen, and DUPAN-2) were not elevated. Based on further imaging of the lesions, we suspected that the pancreatic tumor was an endocrine tumor, even though endocrinologic laboratory findings were almost within the normal range. The gastrin level was slightly elevated (210 pg/mL), and the patient had been treated with a proton pump inhibitor. No lesion was found in the upper gastrointestinal fiber.

Enhanced computed tomography (CT) revealed a hypervascular tumor, 2 cm in diameter, at the pancreas uncus and an isodensity tumor, 1.5 cm in diameter, at the upper portion of the right kidney (Fig. 1A and 1B). Abdominal angiography with CT during arteriography (CTA) revealed that the pancreatic tumor was fed by the inferior pancreatic duodenal artery branching from the superior mesenteric artery and was partially fed by the anterior superior pancreatic duodenal artery branching from the gastroduodenal artery (Fig. 1C). The right renal tumor was fed by an upper branch of the right renal artery. The pancreatic tumor was markedly enhanced in the arterial phase and was rapidly washed out in the venous phase. Abdominal ultrasonography revealed that both the pancreatic tumor and the renal tumor were hypoechoic. Endoscopic retrograde pancreatography revealed no lesion at the main pancreatic duct. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed abnormal accumulation (maximum standard uptake value [SUV], 9.0) at the pancreas head lesion but no abnormal accumulation at the right renal lesion (Fig. 1D).

Based on the diagnosis of a pancreatic endocrine tumor with malignant potential and right renal cell carcinoma, we performed pyrolus-preserving pancreaticoduodenectomy with regional lymph node resection and right nephrectomy. A resected specimen of the pancreatic tumor was macroscopically a solid tumor with a hemorrhage lesion (Fig. 2A). The renal tumor was a round tumor with a capsule. Pathologic study revealed that the pancreatic tumor had 2 components: invasive ductal carcinoma and neuroendocrine tumor (Fig. 2B). Immunohistochemically, the lesion with ductal carcinoma had 30% stainings for the Ki-67 labeling index, and the neuroendocrine tumor had stainings of chromogranin A and synaptophysin (Fig. 2D, 2E, and 2F). Other immunohistologic findings, including those for insulin, glucagon, gastorin, and somatostatin, had no staining at the pancreatic lesion. The renal tumor was a typical renal cell carcinoma (Fig. 2C). The resected regional lymph nodes were not metastasized. We diagnosed mixed ductal-endocrine carcinoma of the pancreas complicated by renal cell carcinoma. The patient was discharged 30 days after the operation and had had no recurrence 52 months after the surgery.

Discussion

A pancreatic tumor most often is derived from the exocrine cells (ductal cells), as well as from the endocrine cells (islet cells) and the acinar cells in the pancreatic parenchyma.[3] A mixed tumor of the pancreas, which is very rare, includes these cell components. In a series of 645 pancreatic tumors reported by Cubilla *et al*, ductal cell carcinomas represented 88.8% of pancreatic tumors, while endocrine cell tumors and acinar cell carcinomas represented only 7.4% and 1.2% of tumors, respectively.[4] Mixed cell carcinomas were very rare, representing only 0.2% of all cases.[4] The Japan Pancreatic Cancer Registry Report 2007 reported

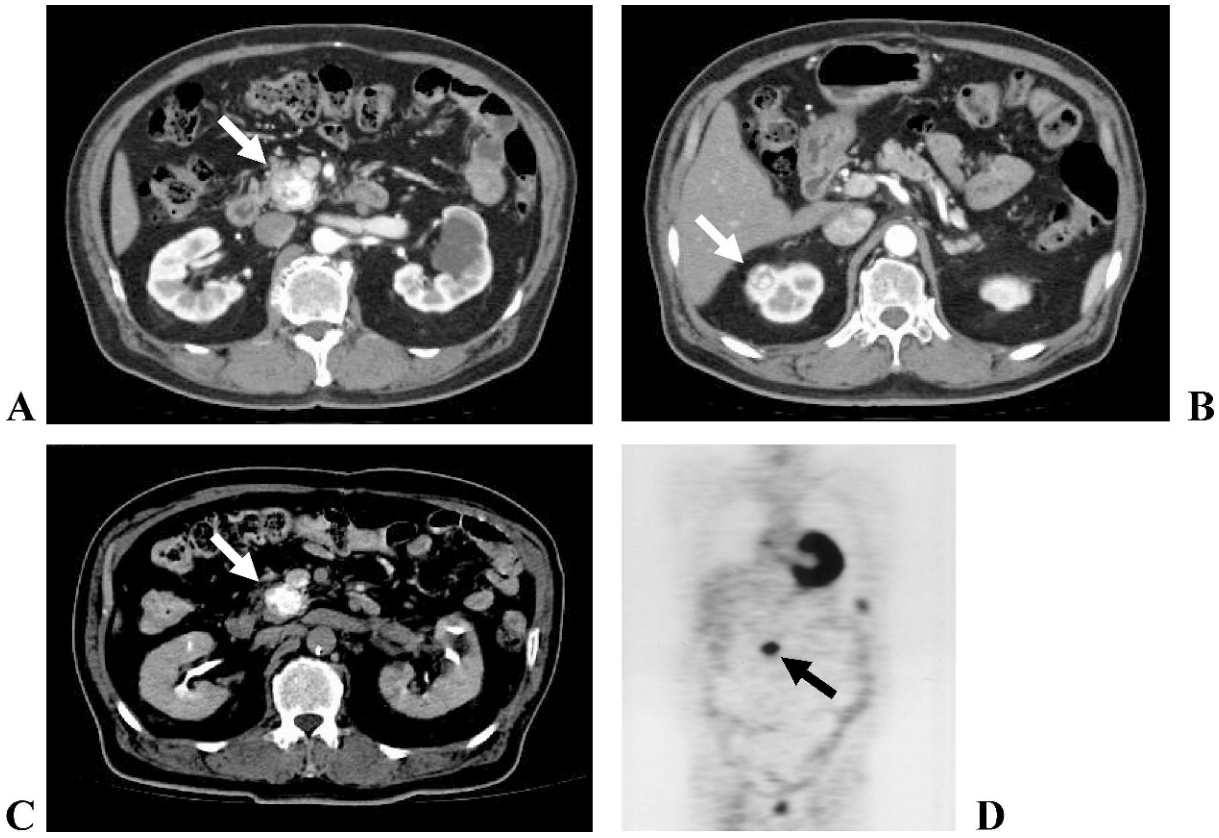

Fig. 1 Clinical images. (A) CT images. A pancreatic tumor at the pancreatic uncus (white arrow) is markedly enhanced in the arterial phase. The enhancement is a heterogeneous pattern. (B) A right renal tumor at the upper portion of the right kidney (white arrow). (C) CT during superior mesenteric arteriography. The pancreatic tumor was fed mainly by the inferior pancreatic duodenal artery branching from the superior mesenteric artery. This image also shows a heterogeneous pattern (white arrow). (D) ^{18}F-fluorodeoxyglucose positron emission tomography. An abnormal accumulation (arrow) was detected at the pancreas head lesion (maximum SUV, 9.0) but not at the right renal lesion.

10,851 cases of ductal cell carcinoma (72.8%) and only 9 cases of mixed tumor (0.06%), out of a total of 14,904 cases of pancreatic cancer histologically diagnosed in Japan from 2001 to 2004.[5] A mixed tumor of the pancreas includes 4 types of tumors: ductal-endocrine tumor, acinar-endocrine tumor, ductal-acinar tumor, and ductal-acinar-endocrine tumor. We herein report the successful treatment of mixed ductal-endocrine carcinoma of the pancreas occurring as a double cancer—a complication of right renal carcinoma.

The pancreatic tumor of the present case appeared hypervascular, indicating an endocrine tumor. A resected specimen was used for the diagnosis of mixed ductal-endocrine carcinoma of the pancreas. Seventeen case reports of pancreatic mixed ductal-endocrine tumor have been published in English language journals,[6–21] as shown in Table 1. A literature review with a case report by Iwamuro M *et al* showed 34 mixed-tumor cases in Japanese reports.[22] As shown in a review of 17 reports (Table 1), mixed ductal-endocrine carcinoma of the pancreas seems to have high malignant potential. Six patients (33%) died 6 to 24 months after diagnosis, and 8 patients (44%) were alive without evidence of disease 3 to 72 months after diagnosis, except for Terada's case, which is delay-complicated by ductal-endocrine carcinoma.[14] Follow-up information on 3 cases was not available. The median survival time is 13 ± 11 months (n = 14). Hepatic metastases were present at initial presentation or during follow-up in 39% (7 cases) of cases. The outcomes of these reports and of the present case suggest that mixed ductal-endocrine carcinoma does not present the same prognosis as invasive ductal carcinoma but has high malignant potential.

The present case was diagnosed as a double cancer. The patient had undergone 2 surgeries for lung cancer and rectal cancer. Other reported cases

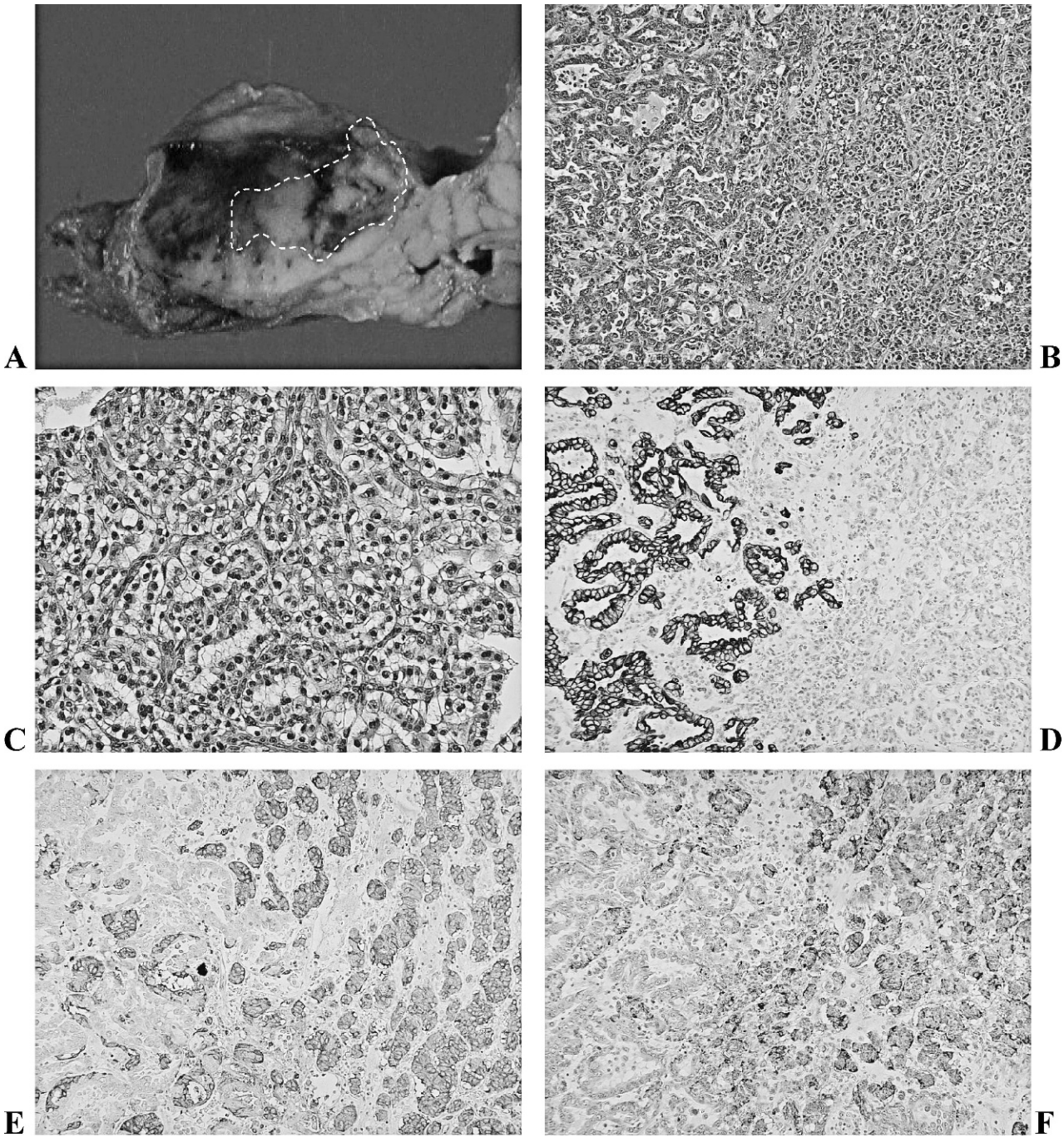

Fig. 2 Resected specimen and histologic stainings. (A) Pancreatic tumor cleavage. The tumor, 2 cm in diameter, was a solid tumor and had a partially hemorrhaged section. Histologically, the ductal component is inside the dotted line. (B) Hematoxylin and eosin stainings. The pancreatic tumor had 2 components. The first (right portion) consisted of endocrine-type tumor cells that had foamy or eosinophilic granular cytoplasm with nuclei of various sizes; the second (left portion) was made up of exocrine (ductal)-type tumor cells that proliferated, forming irregular ducts (×100). (C) The renal tumor was a clear cell carcinoma (×200). (D) Immunohistochemical staining for Ki-67. The labeling index was 30% in ductal carcinoma components and 2.93% in endocrine tumor components (×100). (E) Immunohistochemical staining for synaptophysin. The endocrine tumor cells were positive, and the ductal carcinoma cells were negative (×100). (F) Immunohistochemical staining for chromogranin A. The endocrine tumor cells were positive, and the ductal carcinoma cells were negative (×100).

Table 1 Mixed ductal-endocrine carcinoma of the pancreas, review of literature

No.	Author (Year)	Age, y/Sex	Clinical findings	Size, mm	Location	Treatment	Follow-up (months)
1.	Eusebi (1981)	65/M	Jaundice	60	Head	PD	Died (24)
2.	Reid (1982)	29/F	Abdominal pain, weight loss, jaundice	NA	Head	PD	Alive (24)
3.	Reid (1982)	50/M	Abdominal pain, weight loss	NA	Head	DP	Alive (8)
4.	Ordonez (1988)	62/F	Diarrhea, Verner-Morrison syndrome	40	Head	Chemo	Died (13)
5.	Nonomura (1989)	76/M	Jaundice, abdominal distention	10	Tail	None	Died (6)
6.	Kashiwabara (1991)	48/M	None	19	Head	PD	NA
7.	Laine (1992)	59/M	Abdominal pain, jaundice	60	Head	PD	Alive (24)
8.	Hassan (1993)	50/M	Abdominal pain, weight loss	190	Tail	DP	Died (10)
9.	Morikane (1997)	54/F	None	10	Body	DP	Alive (36)
10.	Terada (1999)	62/M	Zollinger-Ellison syndrome	100	Body	Chemo	Died (22 y)
11.	Leteurtre (2000)	74/M	Jaundice, weight loss	30	Head	PD	NA
12.	Chatelain (2002)	72/F	None	100	Tail	DP	Alive (4)
13.	Terada (2002)	34/M	Abdominal pain	5	Body	DP	NA
14.	Ballas (2005)	65/F	Abdominal pain, nausea	12	Tail	DP	Alive (18)
15.	Hashimoto (2005)	75/M	Jaundice	35	Head	PD	Died (6)
16.	Carter (2008)	58/F	Jaundice, intractable itching	20	Head	PD	Alive (3)
17.	Brandi (2008)	68/M	Abdominal pain	10	Body	DP	Died (12)
18.	Present case	68/M	None	20	Head	PD	Alive (52)

Chemo, chemotherapy; DP, distal pancreatectomy; NA, not available; PD, pancreaticoduodenectomy.

were complicated by malignancy in other organs. Terada *et al* reported an autopsy case of mixed ductal-endocrine carcinoma presenting as gastrinoma with Zollinger-Ellison syndrome. During the follow-up period, the case was complicated by gallbladder mucosal adenocarcinoma.[14] Chatelain *et al* reported mixed ductal-endocrine carcinoma complicated by squamous cell carcinoma of the gingiva.[16] Carter *et al* reported mixed ductal-endocrine carcinoma complicated by papillary carcinoma *in situ* of the common bile duct.[20] Thus, this tumor tends to complicate synchronous or asynchronous double cancer in other organs, and patients with this type of tumor should undergo long-term monitoring for cancer of other organs.

In the present case, we initially diagnosed this tumor as a pancreatic endocrine tumor because of rapid enhancement in the arterial phase and washing out in the venous phase, as shown by CTA and angiography. Despite the histologic diagnosis in this case, CTA images revealed heterogeneous enhancement, but the lesions were very small. Iwamuro *et al* reported that, in a case diagnosed before surgery as a nontumor lesion similar to fibrosis, CT images revealed a low-density area surrounding the hypervascular tumor. Other reports have indicated difficulty with the presurgical and histologic diagnosis of this type of tumor. Thus, in cases of a hypervascular lesion with heterogeneous enhancement shown by enhanced CT or CTA, a low-density area surrounding the tumor in CT, or abnormal accumulation in FDG-PET, we propose that, if there is any doubt, surgical resection with a sufficient resection margin and regional lymph node resection should be performed.

In conclusion, we report a case of mixed ductal-endocrine carcinoma of the pancreas complicated by right renal cell carcinoma. The patient should receive careful, long-term monitoring because of the potential for recurrence of this carcinoma and carcinogenesis in other organs. This tumor is very difficult to diagnose before surgical resection and histologic examination. Therefore, when there is doubt, surgical resection with a sufficient resection margin and regional lymph node resection should be performed to improve the patient's prognosis.

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