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Case Report

Two Case Reports of Resectable Cancer in the Remnant Pancreas after Pancreatectomy for Invasive Ductal Carcinoma of the Pancreas

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Pancreatic cancer has an extremely poor prognosis. There are several reports on resectable cancer in the remnant pancreas after pancreatectomy; however, few have compared K-ras mutation patterns to clarify recurrent or second primary cancers. Here, we report on 2 cases of cancer in the remnant pancreas after total pancreatectomy for invasive ductal carcinoma. Case 1 is a 56-year-old man who underwent pancreaticoduodenectomy for cancer of the pancreatic head. However, serum carbohydrate antigen (CA19-9) was again elevated 23 months later. A tumor in the pancreatic tail was detected on abdominal computed tomography (CT), and total pancreatectomy was performed. Histologic examination of the tumors from both operations revealed moderately differentiated adenocarcinoma, and the surgical margins of both resected specimens were free of cancerous cells. The K-ras gene mutation was detected at codon 12V of exon 1 in both cancers. Case 2 is a 72-year-old woman who underwent distal pancreatectomy for cancer of the pancreatic body. However, serum CA19-9 was again elevated 4 years postoperatively. A tumor of the pancreatic head was detected on abdominal CT, and total pancreatectomy was performed. Histologic examination of the first and second tumors revealed poorly and moderately differentiated adenocarcinomas, respectively. The surgical margins of both resected specimens were free of cancerous cells. The K-ras gene mutation was detected at codon 12D of exon 1 in both cancers. These patients with rare pancreatic cancers both had metachronous carcinogenesis in the remnant pancreas.

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The prognosis for pancreatic cancer is extremely poor, with an overall 5-year survival rate of approximately 10%.[1] There are various forms of recurrent pancreatic cancer, which are rarely resectable. Here, we report on 2 cases of resectable cancer in the remnant pancreas after total pancreatectomy for invasive ductal carcinoma and compare the K-ras mutation patterns of the original and second cancers.

Case Presentations

Case 1

A 56-year-old man with a past history of chronic subdural hematoma and duodenal ulcer was brought to our hospital with abdominal pain after a meal. His serum carbohydrate antigen (CA19-9) and amylase levels were elevated, at 311.9 U/mL and 203 IU/L, respectively. Abdominal computed tomography (CT) showed a low-density mass (22 mm in diameter) in the pancreatic head (Fig. 1). He received a diagnosis of adenocarcinoma of the pancreatic head on endoscopic ultrasound with fine-needle aspiration, and he underwent pancreaticoduodenectomy in January 2014. The histopathologic diagnosis was moderately differentiated tubular adenocarcinoma without regional lymph node metastasis (p-stage IB, T2N0M0, R0, according to the International Union Against Cancer). No cancerous invasion of the pancreatic stump was detected (Fig. 2), and adjuvant chemotherapy was not administered. The serum CA19-9 was again elevated at 59.2 U/mL 23 months postoperatively. A tumor in the tail of the pancreas (14 mm in diameter) was detected on abdominal CT (Fig. 3); however, no distant metastasis was observed. Therefore, total pancreatectomy was performed in December 2015. The histopathologic diagnosis was moderately differentiated tubular adenocarcinoma without regional lymph node invasion (p-stage IA, T1N0M0, R0). No cancerous invasion of the pancreatic stump was detected (Fig. 4). This cancer in the remnant pancreas 23 months postoperatively was considered to be recurrence of the original cancer because the histologic types were the same and the interval between diagnoses was relatively short. Genetic studies showed a K-ras mutation at codon 12V of exon 1 in both cancers. The mutation patterns of the 2 cancers were identical. The patient's postoperative course was uneventful.

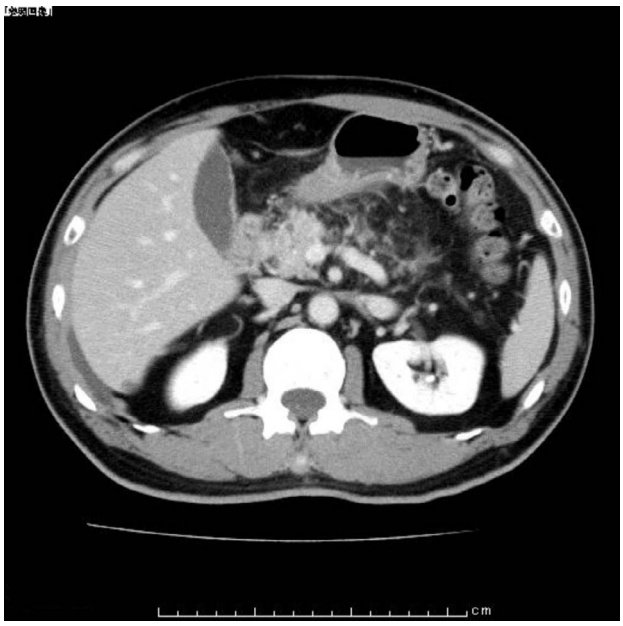

Fig. 1 Abdominal CT showing a low-density mass in the head of the pancreas in case 1.

Case 2

A 72-year-old woman with a past history of hyperlipidemia presented to our hospital with a pancreatic mass detected on abdominal ultrasonography. Pancreatic fluid cytology obtained on endoscopic retrograde cholangiopancreatography

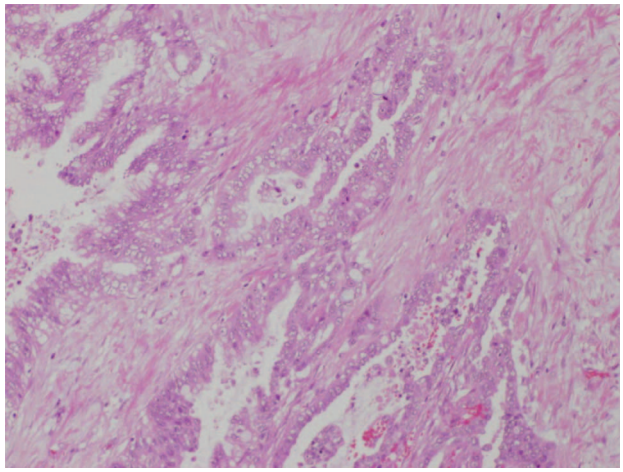

Fig. 2 Histologic findings of the first pancreatic carcinoma in case 1. This tumor consists of moderately differentiated tubular adenocarcinoma (H&E, ×100).

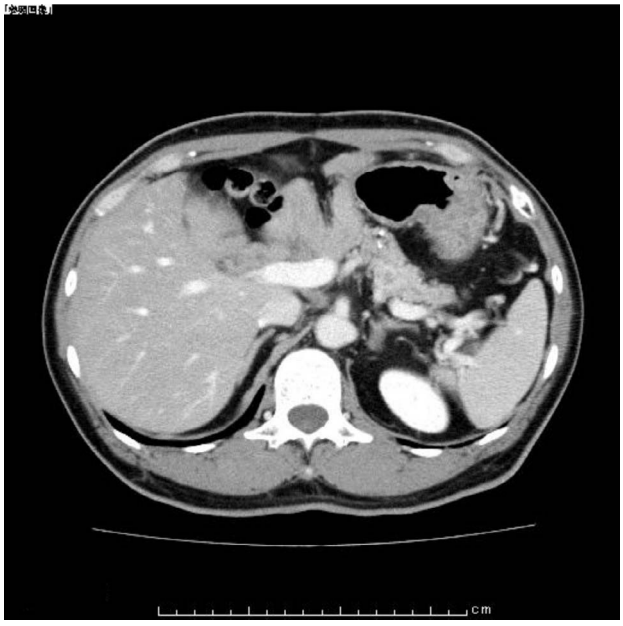

Fig. 3 CT showing a low-density mass in the tail of the pancreas in case 1.

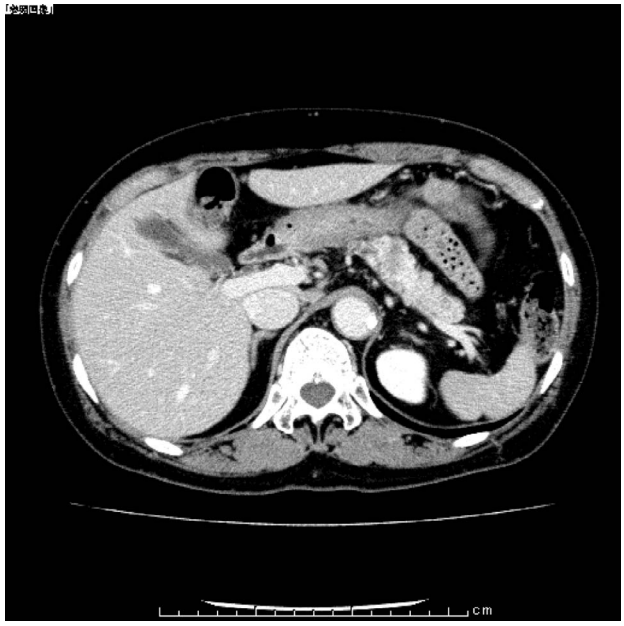

Fig. 5 CT showed a low-density mass in the body of the pancreas in case 2

showed adenocarcinoma, and she received a diagnosis of cancer of the pancreatic body without jaundice. Serum CA19-9, carcinoembryonic antigen, and amylase levels were elevated at 187.1 U/mL, 10.4 ng/mL, and 123 IU/L, respectively. Abdominal CT scan showed a low-density mass (18 mm in diameter) in the body of the pancreas (Fig. 5) without distant metastasis. Therefore, distal pancreatectomy and splenectomy were performed in January 2012. The histopathologic diagnosis was poorly differentiated tubular adenocarcinoma with regional lymph node invasion and splenic vein infiltration (p-stage IIB, T4N1M0, R0). No cancerous invasion of the pancreatic stump was detected (Fig. 6). She received gemcitabine for 6 months as adjuvant chemotherapy. Four years after surgery, serum CA19-9 level was again elevated at 141.9 U/mL, and rose further to 841.9 U/mL in the following month. Abdominal CT showed a low-density mass in the head of the pancreas with obstruction (Fig. 7);

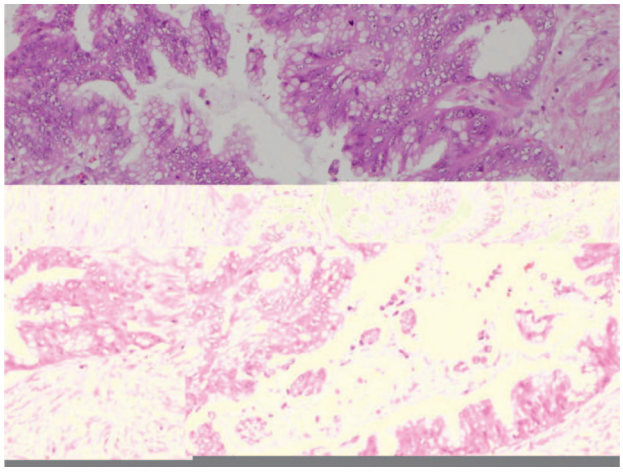

Fig. 4 Histologic findings of the second pancreatic cancer in case 1. Histologic findings are the same as those of the first pancreatic carcinoma (H&E, ×100)

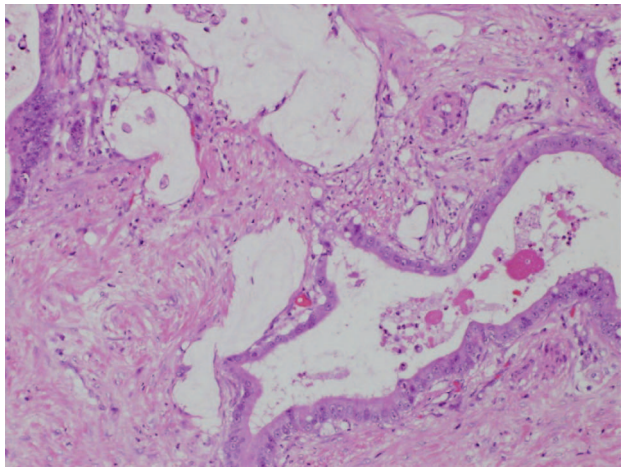

Fig. 6 Histologic findings of the first pancreatic cancer in case 2. This tumor consists of poorly differentiated tubular adenocarcinoma (H&E, ×100).

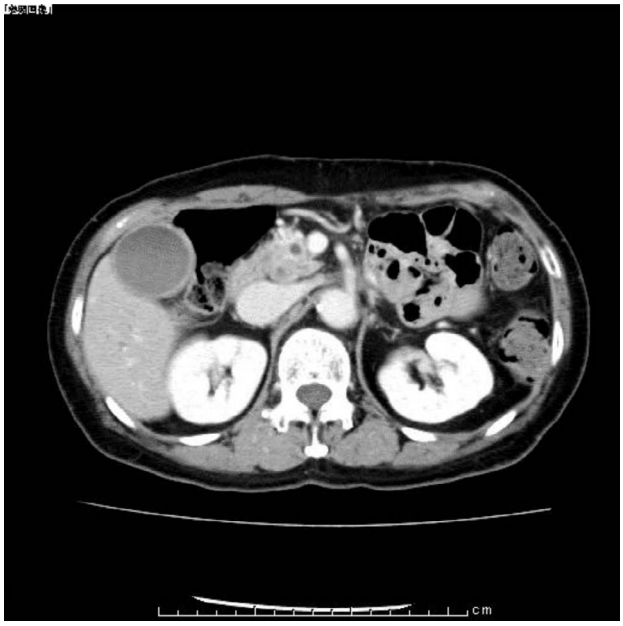

Fig. 7 CT showing a low-density mass in the head of the pancreas in case 2.

however, distant metastases were not observed. Therefore, a total pancreatectomy was performed in January 2016. The histopathologic diagnosis was moderately differentiated tubular adenocarcinoma with regional lymph node invasion (p-stage IIB, T2N1M0, R0) but without cancerous invasion of the pancreatic stump (Fig. 8). This cancer in the remnant pancreas 4 years postoperatively was considered to be a second primary cancer because the histologic types of both tumors were different, and the interval between diagnoses was relatively long. However, the mutation patterns of the 2 cancers were identical, and the K-ras gene mutation was detected at codon 12D of exon 1 in both. The patient's postoperative course was uneventful. She subsequently received another course of adjuvant gemcitabine during the course of 6 months.

Discussion

The prognosis for pancreatic cancer is extremely poor. After surgical resection, more than 50% of patients experience a relapse within 2 years, with an overall 5-year survival rate of approximately 10%.[1] Recurrence can occur at various sites, such as the pancreatic bed and peritoneum, or as distant metastases. Despite a few reports of remission by removal of the site of recurrence,[2] complete surgical resection remains the only chance for cure. Review

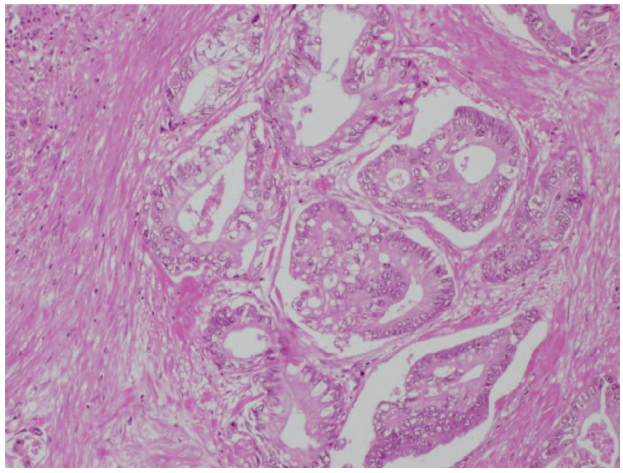

Fig. 8 Histologic findings of the second pancreatic cancer in case 2. This tumor consists of moderately differentiated tubular adenocarcinoma (H&E, ×100).

of the current literature revealed 19 cases, including the 2 present cases, of resectable cancer without low-grade intraductal papillary mucinous neoplasia in the remnant pancreas after pancreatectomy[3–15] (Table 1). A total of 10 cases were given a diagnosis of local recurrence, 6 had a diagnosis of second primary cancer, and 3 were undetermined. The critical issue is the model of development, that is, whether the second tumor is local recurrence or second primary cancer. Obvious indicators that are used to differentiate between local recurrence and second primary cancer include (1) difference in tissue type, (2) interval from the initial surgery, and (3) comparison of K-ras mutation patterns of the primary and second cancers.

Differentiating between local recurrence and a second primary cancer is easy if the tissue types are completely dissimilar; however, if there are differences in the degree of differentiation, determination may change according to the pathologist. In addition, it is possible that tissue types are altered by adjuvant chemotherapy. Furthermore, the idea of multicentricity of pancreatic cancer is well known.[16] The concept of so-called pancreatic intraepithelial neoplasia (PanIn) has been introduced to classify pancreatic duct lesions from normal to pancreatic cancer.[17] PanIn is an atypical epithelial lesion of the columnar epithelium that occurs in the pancreatic duct and cannot be recognized on macroscopic examination or preoperative diagnosis. There remains the possibility of remnant cancer even when all visible cancer tissues have been surgically resected. If a second cancer occurs metachronously

Table 1 19 cases of respectable cancer without lowgrade intraductal papillary mucinous neoplasia in the remnant pancreas after pancreatectomy in the current literature

Source, y	No.	Age, y/Sex	Time to recurrence, mo	Operation, first/second	Stage, first/second	Site of recurrence, primary or local
Hruban *et al*,[17] 2000	1	52/F	94	DP/TP	IIA/IIB	Primary
Tryka and Brooks,[16] 1979	2	58/F	38	PPPD/TP	IIB/IA	Local
Akabori *et al*,[15] 2014	3	58/F	68	PD/TP	IIB/NR	Primary
Kobayashi *et al*,[14] 2012	4	56/M	37	PPPD/TP	IIB/IA	Local
Kinoshita *et al*,[13] 2011	5	63/F	71	PPPD/TP	IIB/IB	Local
Ogino *et al*,[12] 2010	6	67/M	25	DP/TP	IA/IIB	Local
Koizumi *et al*,[11] 2010	7	65/M	85	PPPD/TP	IA/IIB	Local
Tajima *et al*,[10] 2008	8	58/M	34	PPPD/TP	IB/IB	Local
Miura *et al*,[9] 2007	9	72/F	29	PPPD/TP	IIA/IV	Local
Dalla Valle *et al*,[8] 2006	10	63/M	12	PD/TP	IIA/IIA	Local
Takamatsu *et al*,[7] 2005	11	63/M	43	PD/TP	IIA/IIA	Primary
Doi *et al*,[6] 2003	12	60/M	26	DP/TP	IIA/IB	Primary
D'Amano *et al*,[5] 2002	13	44/M	40	PPPD/TP	IIB/NR	NR
	14	75/F	7	PD/TP	IIB/NR	NR
	15	54/F	32	PPPD/TP	IIB/NR	NR
Wada *et al*,[4] 2001	16	52/F	22	PPPD/TP	IIB/NR	Local
Eriguchi *et al*,[3] 2000	17	67/F	88	DP/TP	IA/IIB	Primary
Our case	18	56/M	23	PD/TP	IB/IA	Local
Our case	19	72/F	48	DP/TP	IIB/IIB	Primary

DP, distal pancreatectomy; NR, not reported; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; TP, total pancreatectomy.

with PanIn, it is difficult to determine whether it should be considered as secondary carcinogenesis. In addition, there are individual differences in the time to invasive cancer from the state of PanIn.

The average interval from initial surgery to diagnosis of a second tumor was 43.3 months (range, 7–94 months). The intervals for recurrent and second primary cancer were 36.4 months and 61.2 months, respectively, the latter having a longer trend but without significant difference. Although the interval from initial surgery was relatively long, we found a case that had been diagnosed with recurrent cancer 85 months after the initial surgery.[17]

For pancreatic cancer cases in which genetic investigations have been performed, the rate of K-ras mutations appears to be $\geq$90%,[18] and these cases are known to have poor prognosis.[19] Among patients with K-ras mutations, those with the G12V mutation had a significantly longer overall survival than those with the G12D or G12R mutations.[20] In our 2 cases, although we measured the K-ras mutation patterns of the pancreatic cancers, we were unable to distinguish which case had recurrent or second cancers. If further gene studies, such as TP53, had been carried out, we may have been able to obtain a clearer distinction; however, this was not done for financial reasons. However, considering the K-ras mutation patterns, a search suggested that the prognosis of case 1 was better than that of case 2.

Nevertheless, it is important to diagnose pancreatic cancer recurrence in patients as soon as possible. Follow-up of patients, with monitoring of tumor marker levels and in-depth diagnostic imaging up to 60 months, which is the average time for occurrence of second carcinogenesis, should at least be performed.

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