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CASE REPORT

Two cases of pancreatic ductal adenocarcinoma with intrapancreatic metastasis

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Abstract

There are no standardized diagnostic criteria for intrapancreatic metastasis of pancreatic ductal adenocarcinoma (PDAC). Here, we report two cases of patients with PDAC who were pathologically diagnosed as harboring intrapancreatic metastasis. In both cases, the main lesions were located in the pancreatic body, and no other lesion was detected preoperatively. The patients were diagnosed with pancreatic body cancers and distal pancreatectomy was performed. Pathological findings revealed microscopic cancer nests, which had connections to neither the main lesion nor the premalignant lesion in the pancreatic tail parenchyma. In both cases, the histological type of the daughter lesion was quite similar to that of the main lesion. Hence, we diagnosed the daughter lesions as metastatic foci in the pancreas. Although intrapancreatic metastasis of PDAC has been regarded as a poor prognostic factor, few reports of intrapancreatic metastasis are available. This article reports two such cases and provides a review of the literature.

Key words: Carcinoma; Pancreatic ductal; Neoplasm micrometastasis; Recurrence; Carcinogenesis

Core tip: Although intrapancreatic metastasis (IPM) of pancreatic ductal adenocarcinoma has been regarded as a poor prognostic factor, few reports of IPM are available. Furthermore, the diagnostic criteria and the

clinicopathological significance of IPM still need to be clarified. It should be remembered that IPM is present at a constant rate, and may be located in the remnant pancreas or in resected specimens other than the main lesion. IPM could be a cause of early recurrence. Here, we have presented two cases of IPM and provided suggestions regarding the foundation of the diagnosis of IPM.

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INTRODUCTION

Despite progress in diagnosis and treatment, the prognosis of pancreatic ductal adenocarcinoma (PDAC) has remained dismal. The disease prevalence and age-adjusted death rate of pancreatic cancer are increasing yearly, and pancreatic cancer is the fourth-leading cause of cancer death in Japan[1].

Based on studies of hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and lung cancer, tumor metastasis in the primary organ is a poor prognostic factor. Furthermore, it contributes to the T factor in the Union for International Cancer Control TNM classification. In clinical practice, we occasionally encounter patients with two or more PDACs in the pancreas (preoperatively or postoperatively), a situation that bears some resemblance to tumor metastasis in the primary organ. However, there is no consensus or handling convention for multiple lesions in cases of PDAC.

There are two forms of multiple lesions in PDAC: multicentric carcinogenesis and intrapancreatic metastasis (IPM). It is difficult to discriminate between multicentric carcinogenesis and IPM because there are no diagnostic criteria for their pathological findings. Furthermore, few reports have specifically described IPM of PDAC, and its clinicopathological significance has remained unclear. On a search of the literature, we found only two prior reports about IPM of PDAC[2,3].

In this article, we have reported two further cases of IPM of PDAC that were diagnosed pathologically. We have also reviewed the prior literature and discussed the importance of IPM.

CASE REPORT

Case 1

A 30-year-old Japanese man visited his doctor with the complaint of epigastric pain. Abdominal enhanced computed tomography (CT) revealed a hypovascular tumor in his pancreatic body. He was referred to our hospital for further examination and treatment. He had no significant past medical history and no surgical history, but had a family history of pancreatic cancer (his uncle had had this disease). Although he had no history of smoking, he regularly consumed alcohol.

On examination, his abdomen was soft and flat, without any evident mass or tenderness. His laboratory data were unremarkable, except for the carbohydrate antigen 19-9 (CA-19-9) level, which was elevated to 139 U/mL. Abdominal enhanced CT revealed an 18-mm hypovascular tumor in the pancreatic body and a dilated main pancreatic duct in the tail side of this tumor (Figure 1A). The tumor was compressing the splenic vein. Endoscopic ultrasound showed a 15-mm low echoic tumor that had ill-defined borders and was located next to the splenic vein. Endoscopic retrograde pancreatography demonstrated disruption of the main pancreatic duct in the pancreatic body (Figure 1B). We diagnosed PDAC with invasion of the splenic vein and performed distal pancreatectomy, lymph node dissection, and splenectomy.

Macroscopic findings of the resected specimen showed a 35 mm × 18 mm tumor in the pancreatic body and no other lesion (Figure 2). Pathological findings revealed a moderately differentiated tubular adenocarcinoma with invasion of neutrophil in the main lesion (Figure 3A). The tumor had infiltrated the tunica externa of the splenic vein. At a 20-mm distance to the tail side from the main lesion, there was a 0.6-mm cancer nest, which was a moderately differentiated adenocarcinoma with invasion of neutrophil (in resemblance with the main lesion) (Figure 3B). There was no connection to the main lesion, and we diagnosed this small lesion as intrapancreatic micrometastasis of PDAC. The patient was administered 5-fluorouracil and heparin-based infusion chemotherapy combined with cisplatin and mitomycin C (PI4W) as perioperative chemotherapy[4], and was discharged without any complications. He was administered S-1 (tegafur, gimeracil, and oteracil potassium combination) for 6 mo as adjuvant chemotherapy. However, he developed a recurrence in the liver 6 mo after surgery and underwent FOLFIRINOX therapy following GEM and nab-PTX therapy. Nonetheless, he died 25 mo after surgery.

Case 2

The physician of a 70-year-old Japanese woman noted the carbohydrate antigen 19-9 (CA-19-9) level, which was elevated to 112 U/mL, and CT revealed a tumor in the pancreatic body. She was referred to our hospital for further examination and treatment. She had diabetes mellitus and no family history of cancer. She had no smoking history or alcohol consumption.

On examination, her abdomen was soft and flat without any apparent mass or tenderness. Blood tests

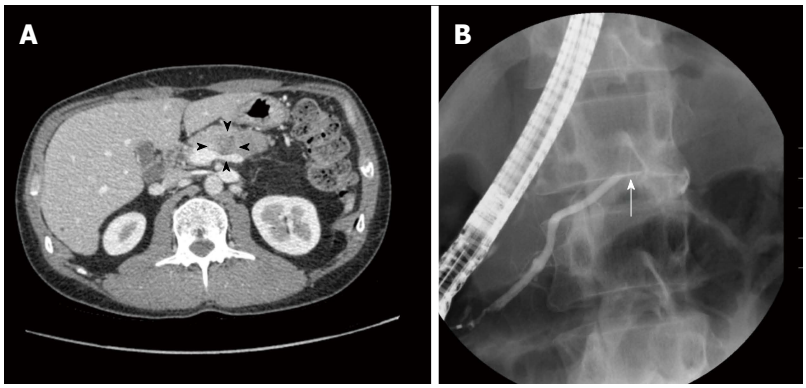

Figure 1 Enhanced abdominal computed tomography scan (A) and endoscopic retrograde cholangiopancreatography image (B) of case 1. A: The hypovascular tumor in the pancreatic body (arrowheads); B: Disruption of the main pancreatic duct (arrow).

Figure 2 Image of the resected pancreas from case 1. The resected specimen showed a 35 mm × 18 mm tumor in the pancreatic body (arrows). Pathological findings revealed a small lesion at a 20-mm distant to the tail side from the main lesion (arrowhead).

demonstrated elevated tumor markers (CA-19-9, 112 U/mL; Span-1, 41 U/mL). Abdominal enhanced CT revealed an 18-mm hypovascular tumor in the pancreatic body and a dilated main pancreatic duct in the tail side of this tumor (Figure 4A). The tumor was located next to the splenic vein. There was a 7-mm cystic lesion without a nodule in the pancreatic head. Endoscopic ultrasound showed an 18.5-mm low echoic heterogeneous tumor in the pancreatic body and a 10-mm branch duct intraductal papillary mucinous neoplasm (IPMN) in the uncinate process of the pancreas. The main pancreatic duct was narrowed at the pancreatic body and dilated in the tail side in endoscopic retrograde pancreatography (Figure 4B). We diagnosed PDAC in the pancreatic duct with a branch duct type IPMN in the pancreatic uncus and performed distal pancreatectomy, splenectomy, and lymph node dissection.

Macroscopic findings of the resected specimen showed a 32 mm × 20 mm tumor in the pancreatic body and a small lesion in the pancreatic tail, 15 mm away from the main tumor (Figure 5). Pathological findings revealed a poorly differentiated tubular adenocarcinoma with invasion of the splenic vein at the main tumor (Figure 6A). Carcinoma *in situ* continued in the main pancreatic duct, in the range of 15 mm from the invasive cancer. A 1-mm poorly differentiated tubular adenocarcinoma was present in the pancreatic tail parenchyma, 20 mm away from the main invasive cancer (Figure 6B). There was no continuity between this small lesion and the main tumor or carcinoma *in situ*, and we diagnosed the small lesion as an intrapancreatic micrometastasis of PDAC. We administered PI4W as perioperative chemotherapy[4] and discharged the patient without any complications. She was administered gemcitabine for 6 mo as adjuvant chemotherapy. However, she developed a recurrence in the liver at 16 mo after surgery, and underwent gemcitabine and TS-1 therapy. Nonetheless, she died 35 mo after surgery.

DISCUSSION

In each of the cases described in this report, we found a small lesion separated from the main tumor in the resected specimens, and diagnosed IPM of PDAC pathologically. The current cases and a previously reported case are compared in Table 1. Although there are no guidelines or diagnostic criteria for IPM, we reached the diagnosis of IPM in our cases for several specific reasons. First, although the small lesions had no connection to the main tumors, the small lesions and main tumors showed similar histological findings. The small lesions were separated from the main tumors by 10 mm or more, and a few sections of the intermediate regions included no invasive cancer. Second, there were no premalignant lesions in or around the small lesions. Third, the histological type of the small lesions was monotonous. PDAC essentially consists of various differentiated carcinomas, reflecting its multistep carcinogenesis[5-7]. Although there is a possibility of *de novo* carcinogenesis for such small and poorly differentiated carcinomas, it seems to be a rare occurrence.

In a report of 21 cases of IPM, Oguro *et al*[3] sug-

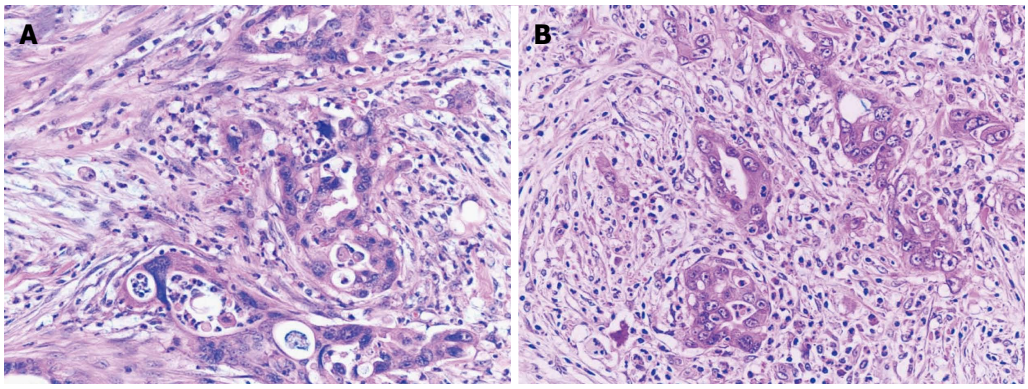

Figure 3 Microscopic findings of the main lesion (A) and the daughter lesion (B) of case 1. A: Tumor cells form irregular glands with marked infiltration of neutrophils. Hematoxylin and eosin staining. Objective magnification, × 40; B: The microscopic lesion of the pancreatic tail demonstrated similar morphology to the main lesion. Hematoxylin and eosin staining. Objective magnification, × 40.

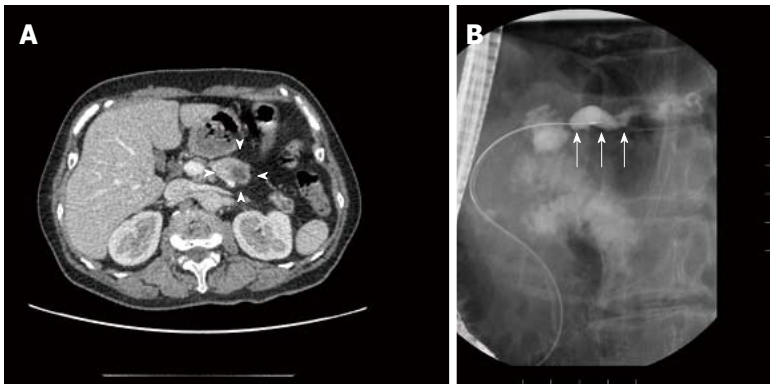

Figure 4 Enhanced abdominal computed tomography scan (A) and endoscopic retrograde cholangiopancreatography image (B) of case 2. A: The hypovascular tumor in the pancreatic body (arrowheads); B: Dilation and disruption of the main pancreatic duct (arrows).

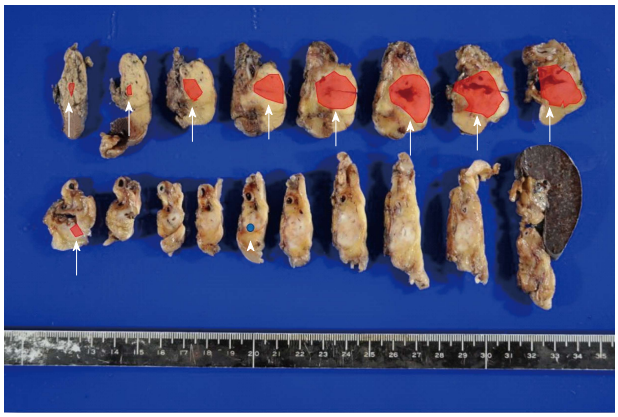

Figure 5 Image of the resected pancreas from case 2. The resected specimen showed a 32 mm × 20 mm tumor in the pancreatic body (arrows) and a small lesion at a 15 mm distance at the tail side from the main lesion (arrowhead).

gested the following diagnostic criteria: (1) located within the pancreatic parenchyma and separated from the dominant, primary tumor by a distance of 5 mm or more; (2) showing a histologic appearance identical to that of the dominant, primary tumor; (3) differentiated to the same degree as or less than the dominant, primary tumor; and (4) unaccompanied by premalignant lesions of PDAC, such as pancreatic intraepithelial neoplasia (PanIN) and IPMN. Oguro *et al*[3] also commented that IPM is an invasive lesion that is separated by a distance of 5 mm or more from PanIN-3 or noninvasive IPMN with high-grade dysplasia. Each of our two cases was consistent with first three criteria of them. With regard to premalignant lesions, there was an IPMN in the pancreatic head and an intraepithelial lesion connected to main tumor in case 2, but no connections existed between the IPM and these lesions.

There are some commonalities between our two cases. Both patients had lymph node metastasis and splenic vein invasion, both patients developed early recurrence in the liver, and both IPMs were located in the tail of pancreas. In addition, the lymphatic and venous invasions in the area of the IPM were ly1, v1 in case 1 and ly0, v1 in case 2. Oguro *et al*[3] observed no significant relationship between IPMs and tumor location, lymph node status, portal vein invasion, or other pathological factors. However, IPM was an independent poor prognostic factor, and lymphatic and venous invasion in the area of the IPM were observed for 35% and 62% of IPMs.

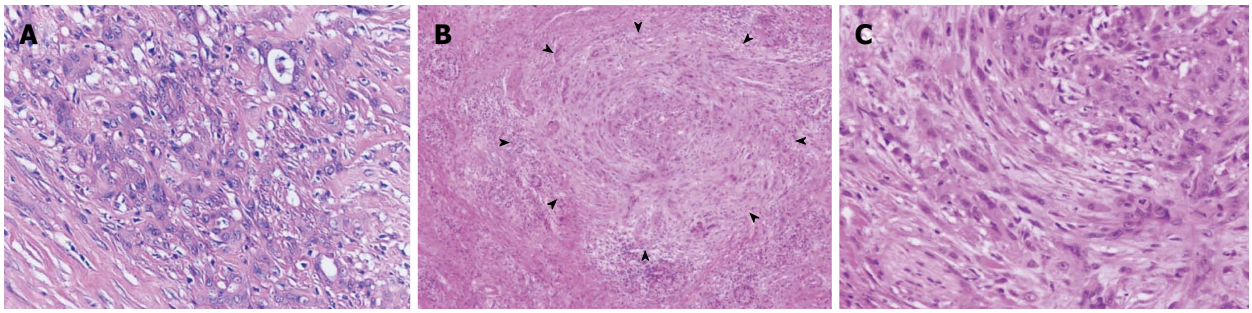

Figure 6 Microscopic findings of the main lesion (A) and the daughter lesion (B, C) of case 2. A: Carcinoma cells form trabecular or ill-defined structure with fibrosis. Hematoxylin and eosin staining. Objective magnification, × 40; B, C: A tiny cancer nest was observed in the pancreatic tail without distinct spatial connection with the main tumor. Hematoxylin and eosin staining. Objective magnification, × 10 (B) and × 40 (C).

Table 1 Intrapancreatic metastasis of pancreatic ductal adenocarcinoma

	Main tumor				Stage (UICC)	Metastatic tumor				
	Location	Size (mm)	Tumor differentiation	Major vascular invasion		Location	Distance from main tumor	Size (mm)	Tumor differentiation	Postoperative course
Ogawa (2011)	Body	15 × 12	Moderate	Unknown	Unknown	Body	2 mm	3 × 2	Unknown	12 mo NED
Case 1	Body	35 × 18	Moderate	PVsp	IIB	Tail	25 mm	0.6	Moderate	6 mo REC (liver)
Case 2	Body	32 × 20	Poor	PVsp	IIB	Tail	20 mm	1	Poor	16 mo REC (liver)

NED: No evidence of disease; PVsp: Portal vein (splenic vein); REC: Recurrence; UICC: Union for International Cancer Control.

Between January 2012 and March 2014, 48 patients with PDAC underwent initial surgical resection at our institution. All specimens were cut into serial slices of 5-mm thickness and were examined by a pathologist. Among the 48 patients, 2 (4.2%) had IPM, whereas Oguro *et al*[3] reported an IPM incidence of about 5%. However, our results may underestimate the rate of incidence for two reasons. First, most IPMs are too small to detect preoperatively using imaging tests such as CT and magnetic resonance imaging. Furthermore, our cases were less than 2 mm in size, like micrometastasis in breast cancer or melanoma. We were able to find the small lesions only after the specimens had been cut into serial slices of 5-mm thickness and all sections had been examined in detail by the pathologist. If a micrometastasis happens to occur between the slices, then we cannot identify it. Second, because we generally perform pancreatoduodenectomy or distal pancreatectomy, we cannot examine the remnant pancreas pathologically. Therefore, we think that some cases of early recurrence in the remnant pancreas of PDAC may include IPM that is overlooked at the time of first surgery. For example, Kleeff *et al*[8] reported the cases of 22 patients who underwent pancreatic surgery for recurrence of PDAC in the remnant pancreas. Among the 22 cases, there were 13 cases of recurrence within 12 mo and 2 cases of recurrence within 6 mo. It was too early to diagnose these cases as recurrence of PDAC, and it is possible that IPM was present at the time of first surgery. It should be remembered that IPM is present in a certain proportion of cases, and that the pancreas on the opposite side of the main tumor should be checked to the extent that is possible.

To try to detect small lesion of IPM, we suggest two methods of imaging: endoscopic ultrasound (EUS) and intraoperative ultrasound (IOUS). Ogawa *et al*[2] reported that they could diagnose IPM (2 mm) preoperatively by EUS. EUS has higher sensitivity than other imaging modalities for the detection of pancreatic small lesions, in particular solid lesions[9,10]. IOUS in which the transducer is in direct contact with the pancreas can provide higher resolution images than extracorporeal ultrasound because the pancreas is located deep in the body cavity. Marcal *et al*[11] reported that IOUS provides high spatial and contrast resolutions alongside its real-time imaging capabilities, and this imaging method has enabled us to detect additional lesions, which were not identified on preoperative imaging. Furthermore, the procedures of IOUS are easier than those of EUS. If IPM is recognized preoperatively or intraoperatively, the physician should begin to consider management methods for this lesion, for example including diagnosis by ultrasound-guided needle biopsy; a change to the operative method, such as additional resection or total pancreatectomy; or close observation after the operation. Although it may be difficult to detect micrometastasis, it is worth making the attempt.

Regarding the pathogenesis of PDAC, it is known that

multicentric carcinogenesis is derived from premalignant lesions, PanIN, or IPMN[6,12]. We discriminate IPM from multicentric carcinogenesis pathologically on the basis of discontinuity with the premalignant lesion. Premalignant lesions like IPMN have heterogeneity in the base sequence of the same gene mutation, and multicentric cancers from the same IPMN may have different base sequences in the gene mutation[13-15]. On the other hand, a metastatic lesion and its primary lesion may have the same base sequence in the gene mutation. This means that IPM and multicentric carcinogenesis can be discriminated by analyzing and comparing the base sequences of gene mutations in the two lesions. It is important that future investigations clarify the mechanisms behind the occurrence of IPM and multicentric carcinogenesis.

In conclusion, we have documented two cases of IPM of PDAC. It should be remembered that IPM is present at a constant rate, and may be located in the remnant pancreas or in resected specimens other than main lesion. Although the diagnostic criteria for IPM and the clinicopathological significance of IPM still need to be clarified, we have only encountered a small number of subjects. Therefore, further accumulation of cases is necessary.

COMMENTS

Case characteristics

The patient in case 1 was a 30-year-old man with the complaint of epigastric pain, and the patient in case 2 was a 70-year-old woman with an elevated carbohydrate antigen 19-9 level.

Clinical diagnosis

The pancreatic ductal adenocarcinoma (PDAC) lesions were diagnosed as intrapancreatic metastasis.

Differential diagnosis

The differential diagnosis of the multiple PDAC lesions was multicentric carcinogenesis.

Laboratory diagnosis

No abnormal laboratory test results were observed, except for an elevated carbohydrate antigen 19-9 level.

Pathological diagnosis

Pathology revealed small monotonous lesions that were separated from the main tumors by ⩾ 10 mm, with no premalignant lesions in or around it.

Treatment

Both patients underwent distal pancreatectomy and adjuvant chemotherapy.

Related reports

Oguro *et al* reported 21 cases of PDAC with intrapancreatic metastasis in 2013.

Term explanation

Intrapancreatic metastasis of PDAC is one type of lesion associated with PDAC.

Experiences and lessons

Intrapancreatic metastasis of PDAC is present at a constant rate, and may be located in the remnant pancreas or in resected specimens other than the main lesion; although it is difficult to identify multicentric carcinogenesis, pathological diagnostic criteria of intrapancreatic metastasis of PDAC have been suggested in this report.

Peer-review

There have been only a few reports of intrapancreatic metastasis of PDAC. This study introduces the clinicopathological characteristics and follow-up information of intrapancreatic metastasis of PDAC.

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