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Case report

A malignant nonfunctioning pancreatic endocrine tumor with a unique pattern of intraductal growth

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A short title: a nonfunctioning endocrine tumor

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Abstract

The intraductal growth of nonfunctioning pancreatic endocrine tumors (NFPTs) is been considered to be rare, and in our survey of the English literature only three cases have been described previously. We herein report the case of a 36-year-old male with a malignant NFPT that uniquely grew within the lumen of the main pancreatic duct (MPD) and completely obstructed the MPD by endoscopic retrograde pancreatography (ERP). Endoscopic ultrasonography clearly detected the tumor with intraductal growth. In addition, positron emission tomography using 18F-fluorodeoxyglucose (FDG) and CT by the same scanner (FDG-PET/CT) showed an enhanced uptake of FDG in the tumor. A pylorus-preserving pancreaticoduodenectomy and regional lymphadenectomy were performed under a preoperative diagnosis of a NFPT. Microscopically, positive immunoreactions for synaptophisin and vasoactive intestinal peptide indicated neuroendocrine differentiation of the tumor while in addition metastasis to a lymph node along the common hepatic artery was also observed. The patient has survived for six months after surgery without any evidence of recurrence and metastasis. Both ERP and FDG-PET/CT were thus found to be useful for predicting the malignant potential of NFPTs in the preoperative diagnosis.

Introduction

Endocrine tumors of the pancreas are relatively rare, and the majority of clinically relevant pancreatic endocrine tumors are functional (1). Nonfunctioning pancreatic endocrine tumors (NFPTs) are found in 15-35% of all surgical cases, and they are usually associated with signs of an expanding mass (1, 2). NFPTs are thus generally detected at more advanced stages with an invasion of the surrounding structures or metastases to the liver and lymph nodes. Recent advances in diagnostic imaging modalities including endoscopic ultrasonography (EUS) and endoscopic retrograde pancreatography (ERP) contributed for the diagnosis of pancreatic disorders. During ERP, stenosis and a complete obstruction of the main pancreatic duct (MPD) are occasionally observed, which are generally suggestive of pancreatic malignancy. Although these findings are often demonstrated in pancreatic cancer, they are uncommon in pancreatic endocrine tumors (3-13). In addition, the intraductal growth of NFPTs may also rarely occur and our survey of the English literature showed only three such cases to have been described (10-12). We herein present a patient demonstrating a malignant NFPT with a unique pattern of intraductal growth in the head of the pancreas and an obstruction the main pancreatic duct.

Case report

A 36-year-old man was referred to our hospital for the evaluation and treatment of a pancreatic mass. He had epigastric pain while dilatation in the body and tail of MPD was also detected by ultrasonography (US). He had no past history of any pancreatic disorders. A laboratory examination on admission showed normal serum levels of amylase, lipase and pancreatic hormones including gastrin, insulin, and glucagons. In addition, the carcinoembryonic antigen, carbohydrate antigen 19-9 and elastase-I levels showed normal ranges while DUPAN-II (220 U/ml) was slightly elevated. Abdominal CT demonstrated an enhanced mass in the head of the pancreas with a dilatation of the MPD in the body and tail (Fig. 1A). On positron emission tomography using 18F-fluorodeoxyglucose (FDG) and CT with the same scanner (FDG-PET/CT), this pancreatic lesion showed an enhanced uptake of FDG, SUV: 4.67 (Fig. 1B). EUS revealed a well-defined isoechoic mass measuring about 15 mm in size within the lumen of the MPD (Fig. 1C). On ERP, an interruption of the MPD in the head of the MPD was noted (Fig. 1D). We could not detect any malignant cells in the pancreatic juice. Magnetic resonance cholangiopancreatography (MRCP) shows a dilation of the main pancreatic duct in the body and tail (Fig. 2). On MR imaging, the lesion demonstrated a low signal intensity on the T1-weighted image and a high signal intensity on the T2-weighted image with a good contrast enhancment (Fig. 3). No tumor in the parathyroid glands or the pituitary gland was detected. Although acinar cell tumors or combined tumors could not be ruled out, a pylorus-preserving pancreaticoduodenectomy (PPPD) with a pancreaticogastrostomy and a regional lymphadenectomy were performed under a preoperative diagnosis of a NFPT. Neither extra pancreatic invasion nor metastases to the lymph nodes was observed

during the operation. The resected specimen of the pancreas confirmed the presence of an intraductal yellow mass which measured 16 X 15 mm in size (Fig. 4A and 4B). Microscopically, the tumor consisted of small nests and cords of uniform cuboidal cells arranged in a trabecular pattern (Fig. 4C). Immunohistochemically, the tumor was negative for insulin, gastrin, glucagons, somatostatin, and pancreatic peptide. Positive immunoreactions for synaptophisin (Fig. 4D) and vasoactive intestinal peptide (Fig. 4E) indicated the neuroendocrine differentiation of the tumor. In addition, metastasis to a lymph node along the common hepatic artery was detected. As a result, we finally diagnosed the tumor to be a malignant NFPT. The postoperative course was uneventful and the patient has survived for six months without any evidence of recurrence or metastasis.

Discussion

We herein described a patient with a malignant NFPT that uniquely grew within the lumen of the MPD and obstructed the MPD. In most NFPTs, the size of the tumor correlates well with its malignant potential, and tumors measuring less than 2 cm in size are considered to be benign (14,15). On the other hand, a rare malignant NFPT (8 mm in size) has been previously reported with no abnormalities in the pancreatic ductal system (16). To the best of our knowledge only 20 cases of NFPTs have described with ERP that were accompanied by a complete obstruction of the MPD (Table 1) (3-13). Regarding clinical symptoms, pancreatitis due to a complete obstruction of the MPD has been observed 6 cases. In addition, seventeen of 20 cases (85%) were diagnosed to be malignant. A complete obstruction of the MPD caused by NFPTs indicated a malignant behavior of the tumor rather than a mass effect. We should consider the possibility of malignancy based on preoperative imaging including ERP, even if the tumor is small. Recently, FDG-PET/CT represents a useful tool for identifying tumor malignancy and also for accurately determing the preoperative staging (17). The finding of FDG-PET/CT suggested this lesion to have a malignant potential.

The intraductal growth of NFPTs is thought to be very rare. There have only been four cases of NFPTs, including our case, which showed an intraductal growth pattern within the lumen of the MPD (Table 2). The fusion of the dorsal and ventral anlagen may thus have induced the MPD, while the multipotent stem cells of the pancreatic duct thereafter differentiated into endocrine cells. The origin of pancreatic endocrine tumors from hypothetical multipotent ductular stem cells has been suggested (18 - 21). Another possibility is that the tumor may originate from islet cells adjacent to the MPD.

Unlike typical pancreatic ductal carcinoma, the above described tumor grew slowly within the lumen of the MPD without invading the pancreatic duct epithelium.

On ERP, interruption of the MPD with an intraductal filling defect in the head of the MPD was noted (Fig. 1D). On FDG-PET/CT, this pancreatic lesion showed an enhancement of FDG (Fig. 1B). Based on these findings, even though the tumor measured less than 2 cm in size, we still performed a PPPD to completely resect the tumor with sufficient margins while also performing a regional lymphadenectomy. According to the histological findings, it was finally diagnosed to be a malignant NFPT due to detect the detection of metastasis to a lymph node along the common hepatic artery. The presence of metastases does not rule out the possibility of a prolonged survival, as the overall survival rate for patients undergoing a pancreaticoduodenectomy is 81% and 70% at 5 and 10 years, respectively (22).

In conclusion, we herein reported a rare case of a patient with a NFPT that uniquely grew within the lumen of the MPD without ductal involvement, while also completely obstructing the MPD. EUS and ERP were helpful for accurately delineating the intraductal growth of the tumor while also determining the resection line of the pancreas. Based on our avove findings, a malignant NFPT should therefore be included in the differential diagnosis when a complete obstruction of the MPD is demonstrated on ERP.

Figure legends

Figure 1. (A) Abdominal computed tomography demonstrated an enhanced mass (arrows) in the head of the pancreas with a dilatation of the main pancreatic duct in the body and the tail of the pancreas. (B) On FDG-PET/CT, this pancreatic lesion (arrows) showed an enhanced uptake of FDG. (C) Endoscopic ultrasonography revealed a well-defined homogenous isoechoic intraductal mass (arrows) within the lumen of the main pancreatic duct. (D) Endoscopic retrograde pancreatography showed an interruption of the main pancreatic duct in the head of the pancreas.

Figure 2. MRCP shows a dilation of the main pancreatic duct in the body and tail.

Figure 3. On MR imaging, the lesion (arrows) demonstrated low signal intensity on T1-weighted image (A) and high signal intensity on T2-weighted image (B). (C-E) Dynamic MRI showed early enhanced tumor in the head of the pancreas.

Figure 4. (A) The macroscopic findings showed a resected specimen of the pancreas to confirm the presence of an intraductal yellow mass (arrows) in the main pancreatic duct. An Arrow in Figure 4 (B) showed the position of the main pancreatic duct. (C) The microscopic findings showed the tumor to consist of small nests and cords of uniform cuboidal cells arranged in a trabecular pattern. The tumor showed positive immunoreactions for synaptophisin (D) and vasoactive intestinal peptide (E).

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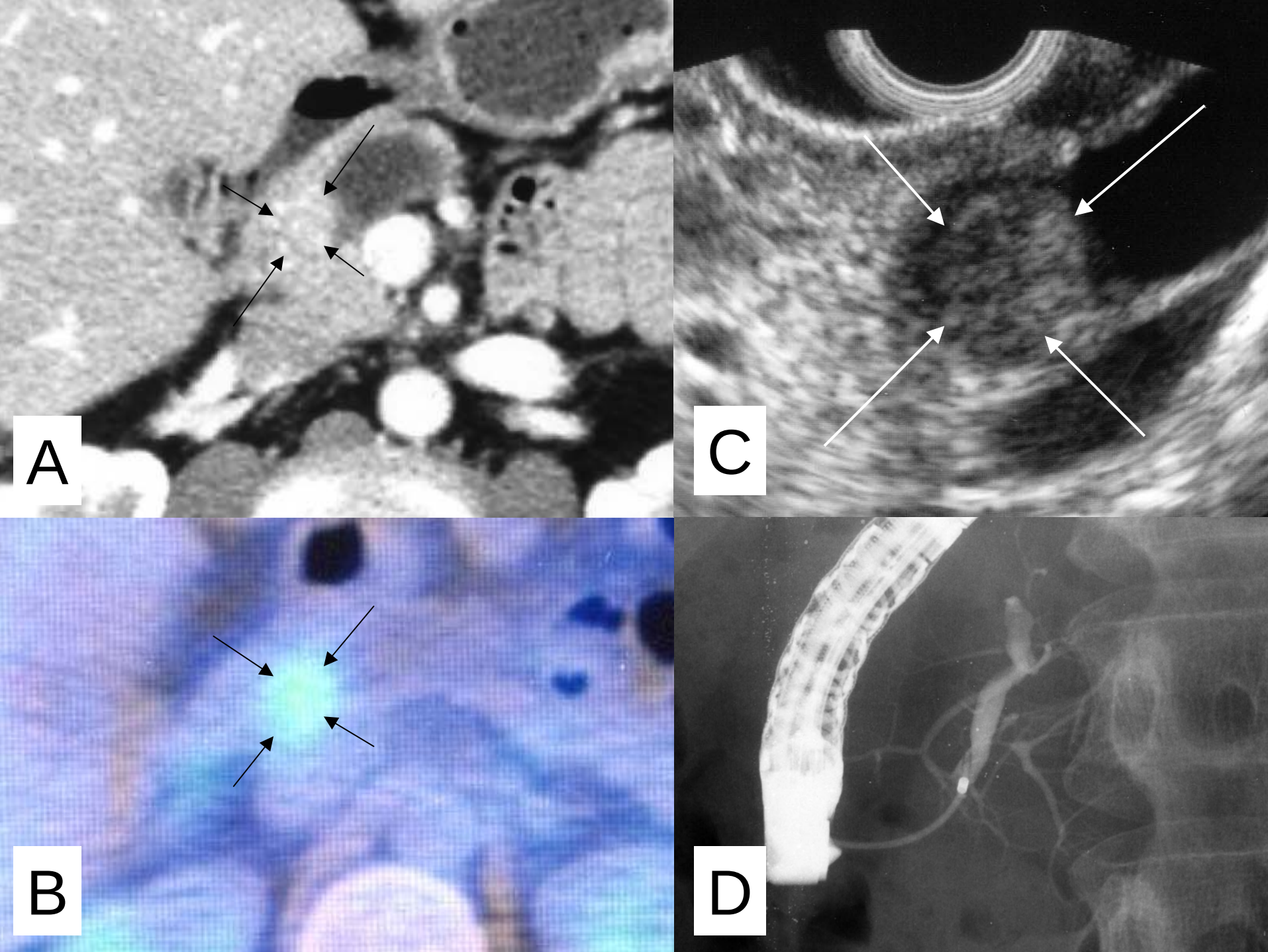
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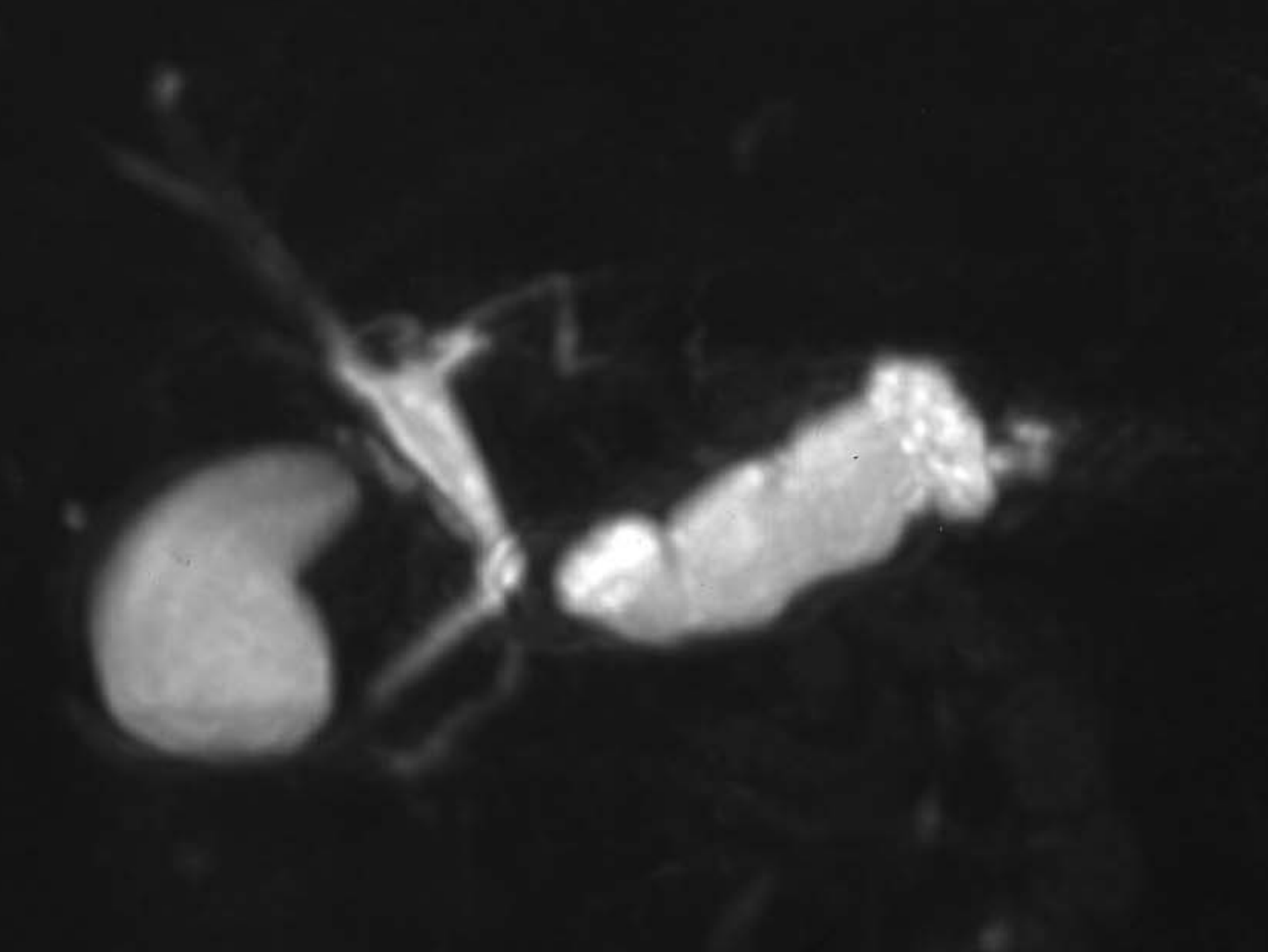

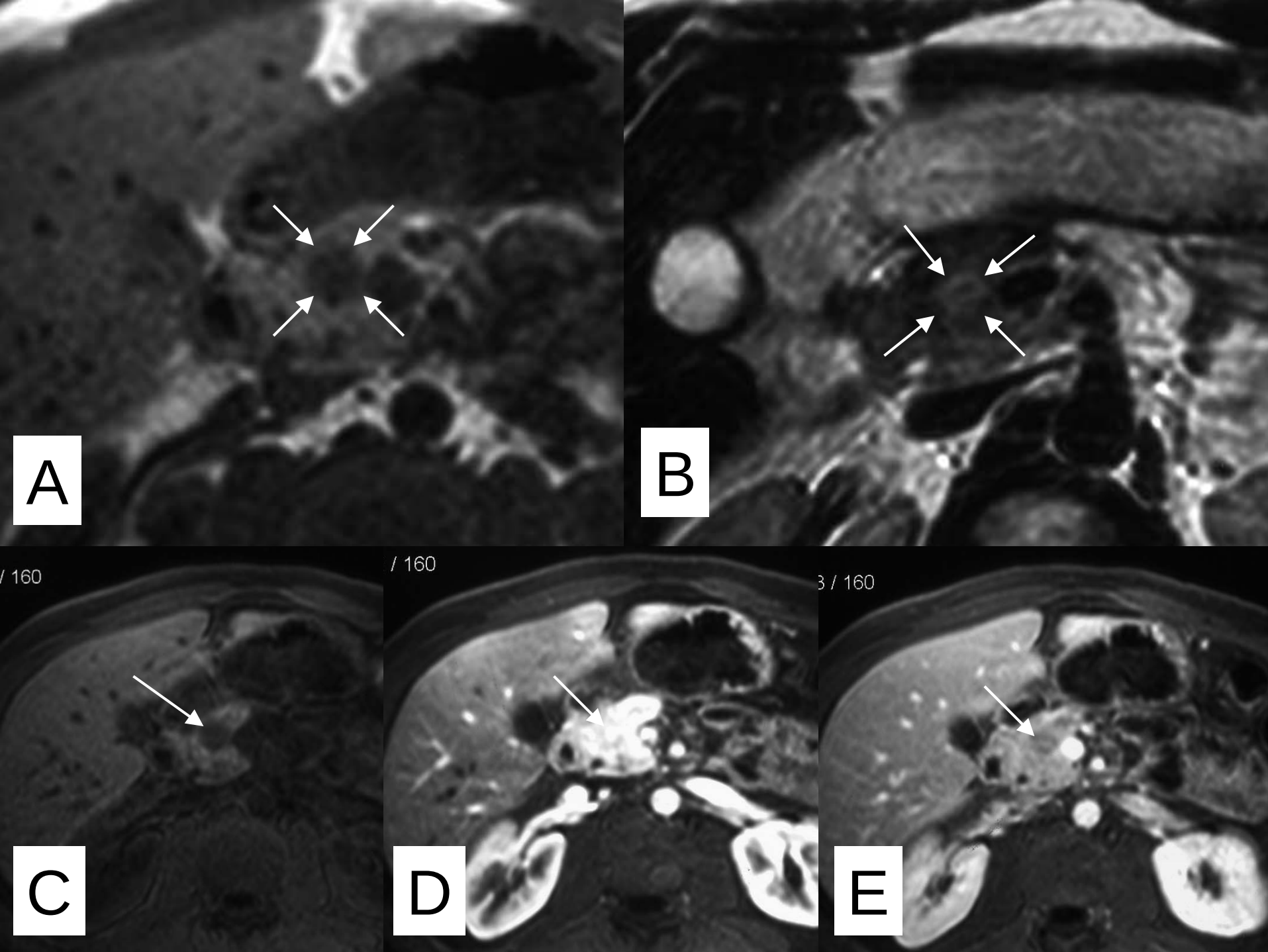
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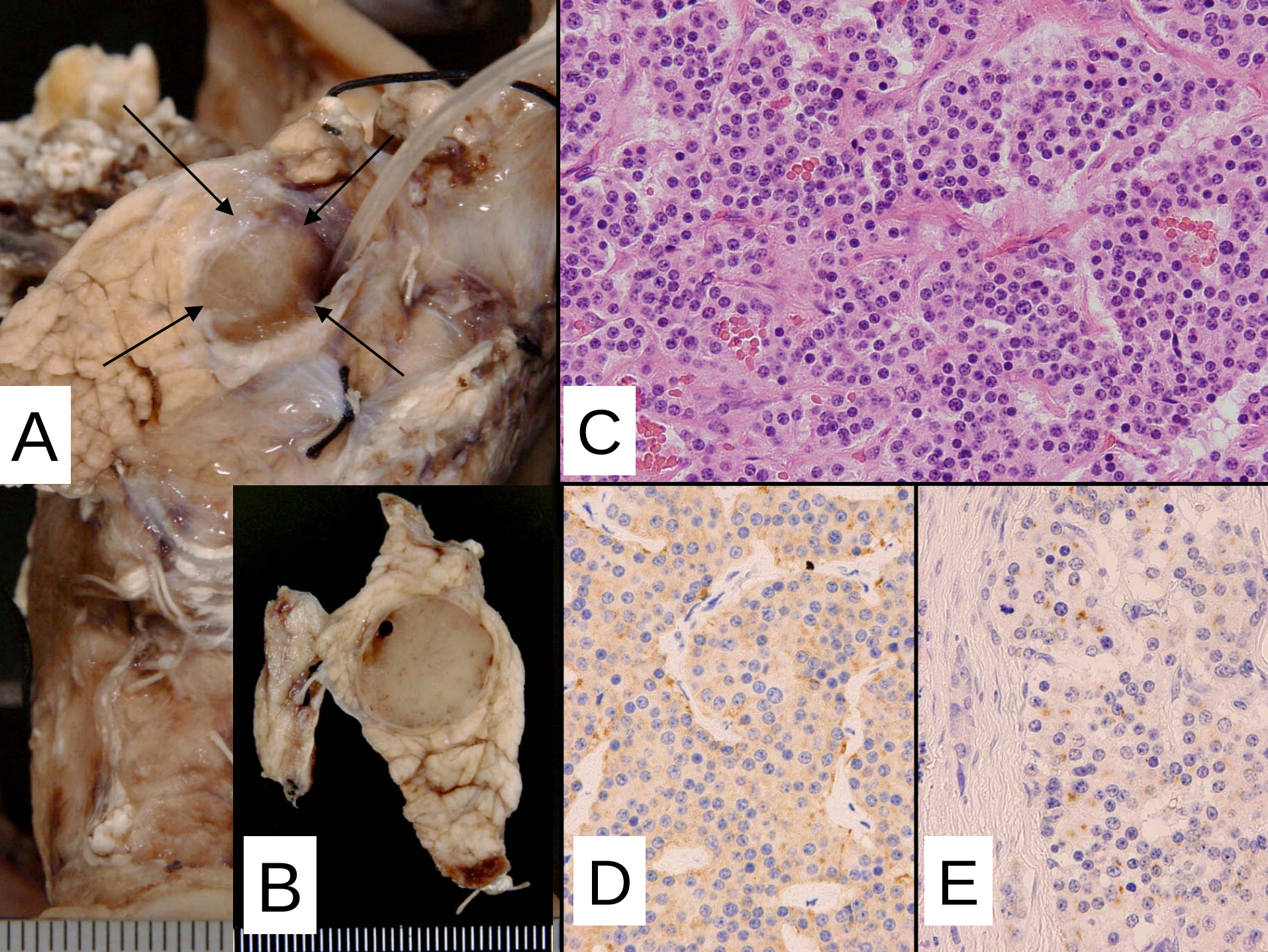
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Table 1 Reported cases of nonfunctioning pancreatic endocrine tumors that showed complete obstruction of the main pancreatic duct on endoscopic retrograde cholangiopancreatography

Patient no.	Age (yr)/Sex	Author (yr)	Symptom	Site	Size (mm)	Diagnosis
1	50/M	Simpson (1988)	Pancreatitis	Head	ND	Malignant
2	63/F	Simpson (1988)	Pancreatitis	Head	40 X 50	ND
3	51/M	Ogawa (1990)	ND	Body	ND	Malignant
4	69/M	Gondo (1992)	ND	Head-body	40 X 40 X 40	Malignant
5	62//F	Gondo (1992)	ND	Head	47 X 45 X 35	Malignant
6	ND/F	Mao (1996)	Pancreatitis	Tail	40	Malignant
7	ND/F	Mao (1996)	Pancreatitis	Tail	ND	Malignant
8	46/M	Obara (2000)	Epigastric pain	Body	45	Malignant
9	41/M	Obara (2000)	Epigastric pain	Body	20	Malignant
10	57/M	Kitami (2000)	Pancreatitis	Tail	15 X 15	Malignant
11	62/F	Seki (2001)	ND	Head	47	Malignant
12	ND	Seki (2001)	Epigastric pain	Head	45	Malignant
13	ND	Seki (2001)	Epigastric pain	Head	33	Malignant
14	ND	Seki (2001)	Back pain	Head	30	Malignant
15	ND	Seki (2001)	Back pain	Body	13	Malignant
16	48/M	Seki (2001)	ND	Head	8	Borderline malignant
17	75/F	Sugiyama (2002)	Pancreatitis	Body	28	Malignant
18	43/F	Akatsu (2004)	None	Body	25 X 8 X 12	Malignant
19	64/F	Terada (2004)	None	Body	6 X 5	ND
20	36/M	present case	Epigastric pain	Head	16 X 15	Malignant

yr, year; ND, not described

Table 2 Reported cases of intraductal growth of nonfunctioning pancreatic endocrine tumors

Patient no.	Age (yr)/Sex	Author (yr)	Symptom	Site	Size (mm)	Diagnosis
1	53/F	Amano (1994)	Itching	Head-tail	70 X 50	Malignant
2	44/F	Shimizu (1998)	Steatorrhea and epigastric pain	Head-tail	ND	Low-grade malignant
3	43/M	Akatsu (2004)	None	Body	25 X 8 X 12	Malignant
4	36/M	present case	None	Head	16 X 15	Malignant

yr, year; ND, not described