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Author(s)	Kawakami, Hiroshi; Kuwatani, Masaki; Hirano, Satoshi; Kondo, Satoshi; Nakanishi, Yoshitsugu; Itoh, Tomoo; Asaka, Masahiro
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**Pancreatic endocrine tumors with intraductal growth into the main pancreatic duct and tumor thrombus within the portal vein: A case report and review of the literature**

Hiroshi Kawakami <sup>1</sup>, Masaki Kuwatani <sup>1</sup>, Satoshi Hirano <sup>2</sup>, Satoshi Kondo <sup>2</sup>,  
Yoshitsugu Nakanishi <sup>3</sup>, Tomoo Itoh <sup>3</sup>, and Masahiro Asaka <sup>1</sup>

<sup>1</sup> Department of Gastroenterology, Hokkaido University, Graduate School of Medicine, Sapporo, Japan \*

<sup>2</sup> Department of Surgical Oncology, Hokkaido University, Graduate School of Medicine, Sapporo, Japan †

<sup>3</sup> Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan ‡

Address correspondence to: Dr. Hiroshi Kawakami,

Department of Gastroenterology, Hokkaido University Graduate School of Medicine,  
Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

TEL: 81-11-716-1161 (Ext 5920), FAX: 81-11-706-7867

e-mail: [hiropon@med.hokudai.ac.jp](mailto:hiropon@med.hokudai.ac.jp) (H.Kawakami)

**Running Head:** Endocrine carcinoma of the pancreas

## **ABSTRACT**

Pancreatic endocrine tumors are rare tumors classified into "functioning" and "nonfunctioning" tumors. A 68-year-old man was admitted to our hospital with the chief complaint of abdominal pain. Various imaging studies demonstrated a mass in the head of the pancreas with intraductal growth into the main pancreatic duct and an intraportal mass. The patient underwent a curative surgical operation. Histopathological examination revealed that it was nonfunctioning endocrine carcinoma of the pancreas. This is the first reported case of a pancreatic endocrine tumor with intraductal growth into the main pancreatic duct and tumor thrombus within the portal vein.

**Key words:** Endocrine tumor; Endocrine carcinoma; Intraductal growth into the main pancreatic duct; Portal vein thrombus; Intraportal growth

## Introduction

Pancreatic endocrine tumors are rare, an estimated frequency being less than 1/100,000 of the population (1). Generally they are classified into "functioning" and "non-functioning" tumors. The functioning tumors generally manifest symptoms earlier and are small compared with nonfunctioning tumors, and they present a mass effect, local invasion or metastases (2). Nonfunctioning endocrine tumors are clinically important because they have a high frequency of malignancy, ranging from 60% to 92% (3, 4). Since endocrine tumors present an expansive growth, oppression and deviation of the main pancreatic duct or portal venous system are commonly seen. Intraductal growth into the main pancreatic duct and simultaneous tumor thrombus in the portal vein, as in the present case, are rare features for a nonfunctioning endocrine tumor. Here, we present a case of nonfunctioning endocrine tumor of the pancreas.

## Case report

A 68-year-old Japanese man was hospitalized because of upper abdominal pain in August 2005. He had diabetes mellitus since 1982, but had no personal or family history of pancreatic disease. The abdomen was soft; no mass was palpable. Results of laboratory tests were as follows: serum amylase, 216 IU/L (normal range: 43-131 IU/L); lipase, 122 U/mL (13-49 IU/L); trypsin, 1430 ng/mL (101-480 ng/mL); elastase-I, 571 ng/dL (<400 ng/dL); and white blood cell count, 5900/ $\mu$  L (3500-9300/ $\mu$  L). The fasting blood glucose level was 119 mg/dL (<110 mg/dL), and hemoglobin A<sub>1C</sub> was 7.4% (<5.8%). Tumor marker values were as follows: carcinoembryonic antigen, 3.6 ng/mL (1.0-6.5 ng/mL); carbohydrate-associated antigen 19-9, 53.4 U/mL (<37 U/mL);

and DUPAN-2, 75 U/mL (<150 U/mL). Pancreatic hormone was as follows: insulin, 5.4  $\mu$  U/mL (<9.9 $\mu$  U/mL); glucagon, 112 pg/mL (<180 pg/mL); gastrin, 178.23 pg/mL (<200 pg/mL).

Ultrasonography (US) demonstrated a hypoechoic mass in the head of pancreas. Early-phase-enhanced computed tomography (CT) showed a heterogeneously enhanced mass of 35 × 30-mm in the head of the pancreas, and CT imaging of the portal phase revealed a filling defect within the main portal vein as well as the superior mesenteric vein (Fig. 1A). Endoscopic ultrasonography (EUS) revealed a heterogenous hypoechoic mass of about 30 mm with an irregular central echogenic area of about 5 mm in the head of the pancreas (Fig. 1B) and a hypoechoic mass within the superior mesenteric vein (Fig. 1C) and portal vein. It was unclear whether or not the pancreatic tumor was connected with the filling defects in the portal vein. On endoscopic retrograde pancreatography (ERP), interruption of the main pancreatic duct with an intraductal filling defect was noted in the pancreatic head (Fig. 1D). Although pancreatic ductal adenocarcinoma or pancreatic endocrine tumor could not be completely ruled out, subtotal stomach-preserving pancreaticoduodenectomy with segmental resection of the portal vein was performed with the preoperative diagnosis of acinar cell carcinoma with intraductal growth into the main pancreatic duct and portal vein thrombus in September 2005. Intraoperative ultrasonography revealed continuity of the mass in the head of the pancreas and thrombus in the superior mesenteric vein. Doppler examination demonstrated a flow within the filling defect in the main portal vein as well as normal venous flow around it, confirming that the mass was a viable vascularized tumor rather than thrombus within the vein. Gross appearance of the resected specimen was a white nodular mass with

cystic change, measuring  $29 \times 26$  mm. The nodular mass in the pancreas had spread into the main pancreatic duct and protruded into the portal vein (Fig. 2). Microscopically, the tumor consisted of a large amount of fibrovascular stroma, and small, relatively uniform cuboidal cells with centrally located hyperchromatic nuclei, elevating mitotic index ( $>10$  per 10 high-power fields), and eosinophilic cytoplasm (Fig. 3). Immunohistochemical staining with chromogranin-A and neuron-specific enolase was strongly positive in the tumor mass. However, the tumor was negative for anti-insulin, gastrin, glucagon, somatostatin, and pancreatic peptide antibody. According to the World Health Organization classification, a definitive diagnosis of poorly-differentiated endocrine carcinoma of the pancreas was made. As diabetes mellitus worsened postoperatively, insulin treatment was administered. Pancreatic hormone was as follows: insulin,  $3.3 \mu\text{U/mL}$  ( $<9.9 \mu\text{U/mL}$ ); glucagon,  $118 \text{ pg/mL}$  ( $<180 \text{ pg/mL}$ ); gastrin,  $131.6 \text{ pg/mL}$  ( $<200 \text{ pg/mL}$ ); the values were not significantly different from preoperative values. Since then the postoperative course was uneventful. However, at postoperative 7 months, tumor recurrence of multiple liver metastasis occurred. We performed systemic chemotherapy with streptozotocin and others, which was unsuccessful. At postoperative 11 months, the patient died from liver failure.

## Discussion

We herein described a case of a nonfunctioning endocrine tumor with intraductal growth into the main pancreatic duct and tumor thrombus in the portal vein. Endocrine tumors of the pancreas are rare pancreatic tumors, of which accurate diagnosis is achieved with imaging modalities (5). However, preoperative differentiation of benign

and malignant variants is difficult except in the cases with distant metastases or massive local invasion of adjacent organs (2). Among various imaging modalities, EUS plays a major role in the diagnosis of pancreatic diseases. It is useful in the differential diagnosis of benign and malignant endocrine tumors of the pancreas. Malignant endocrine tumor should be suspected in the cases of a hypoechoic tumor with an irregular central echogenic area (6). ERP, which was developed earlier than EUS, continues to play a role, in the diagnosis of pancreatic diseases. It is said that, if complete obstruction of the main pancreatic duct is revealed on ERP in the cases of nonfunctioning endocrine tumors, it indicates their malignancy (7). If ERP found such complete obstruction of the main pancreatic duct and EUS revealed a hypoechoic tumor with an irregular central echogenic area in the pancreas, as in the present case, these findings prove that the lesion is a malignant tumor of the pancreas. With these methods, we diagnosed the present case which characteristically had intraductal growth. Pancreatic endocrine tumor with intraductal growth is thought to be very rare. There have been only 6 cases of nonfunctioning endocrine tumors that extended into the lumen of the main pancreatic duct (8-12), and 5 of them were diagnosed as malignant tumors (Table 1). Thus, intraductal growth of nonfunctioning endocrine tumors into the main pancreatic duct is thought to indicate malignant behavior of the tumor. In particular, the present case presented a unique pattern in terms of extension of the tumor into the main pancreatic duct and intraductal growth, giving rise to increased levels of serum pancreatic enzymes. Extrinsic venous involvement is a common feature of pancreatic ductal adenocarcinoma. However, it is a rare feature for nonfunctioning endocrine tumors; few cases with venous occlusion, venous encasement, or intraportal

growth have been reported (13). There is no report of intraductal growth and tumor thrombus simultaneously caused by endocrine tumors as in the present case as far as we know based on a MEDLINE search for the period from 1983 to September 2006 of the following key words: endocrine tumor, intraductal growth, portal vein thrombus and intraportal growth.

The origin of the tumor remains controversial, and several hypotheses for this unique growth may be proposed. However, it is strongly speculated that such tumor arises from islets or ducts adjacent to the main pancreatic duct (14,15). It should be noted that the tumor in the present case expanded into the lumen of the main pancreatic duct without invading the pancreatic epithelium, unlike ductal adenocarcinoma. For such a case where intraportal growth is observed, close follow-up is needed even after radical treatment because circular recurrence can occur (particularly liver metastasis) at high frequency.

In summary, we reported a rare case of a nonfunctioning endocrine tumor of the pancreas that uniquely grew within the lumen of the main pancreatic duct with development of venous thrombus. EUS was very helpful to delineate the intraportal growth of the tumor, and ERP to delineate the intraductal growth of the tumor. These are very unusual characteristics for an endocrine tumor.



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## **Figures legends**

### **Figure 1**

(A) CT image showing a heterogeneously enhanced mass in the head of the pancreas, which was associated with tumor thrombus in the superior mesenteric vein (arrows).

(B, C) Transduodenal EUS image showing a heterogenous hypoechoic mass with an irregular central echogenic area in the head of the pancreas and tumor thrombus in the

superior mesenteric vein.

(D) Endoscopic retrograde pancreatogram showing total occlusion of the main pancreatic duct in the head of the pancreas.

### **Figure 2**

A gross photograph of a white nodular mass (arrows) spreading into the main pancreatic duct and portal veins (arrowheads).

### **Figure 3**

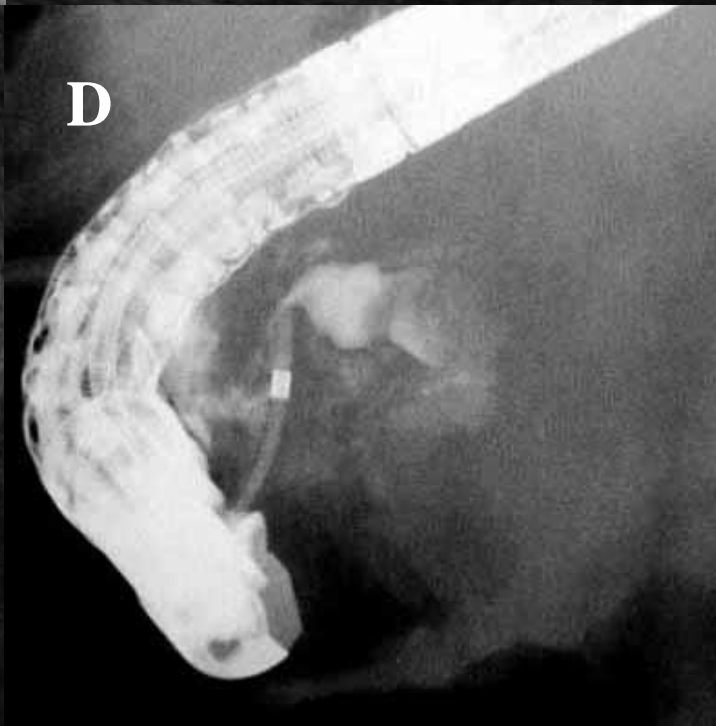
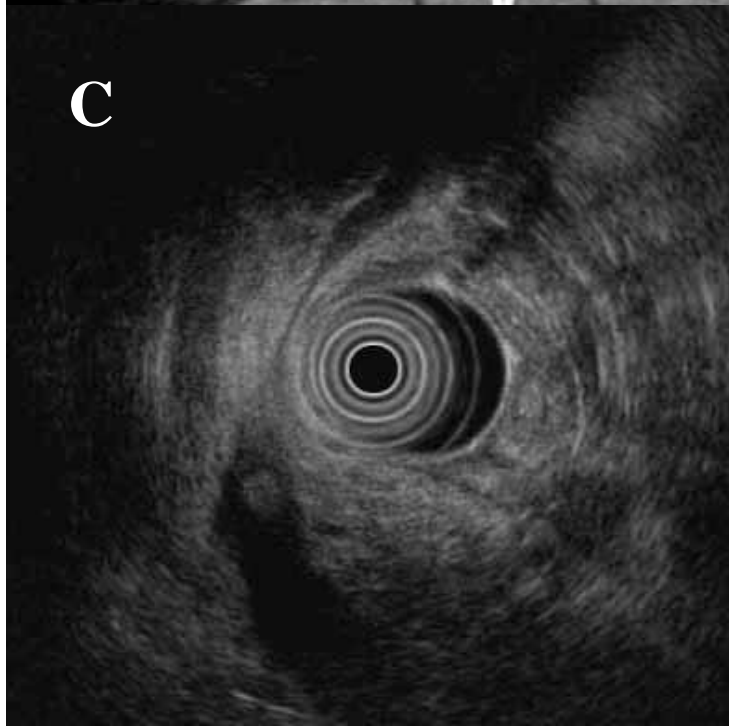
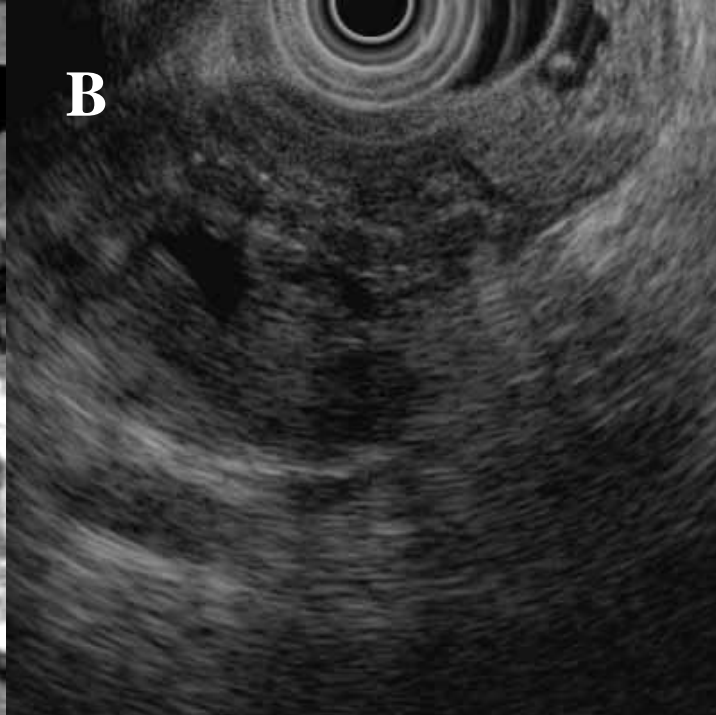
(A, B) Photomicrograph of the resected specimen showing that the tumor invaded the main pancreatic duct (arrows) without parenchymal invasion (H&E, original magnification  $\times 12.5$ ).

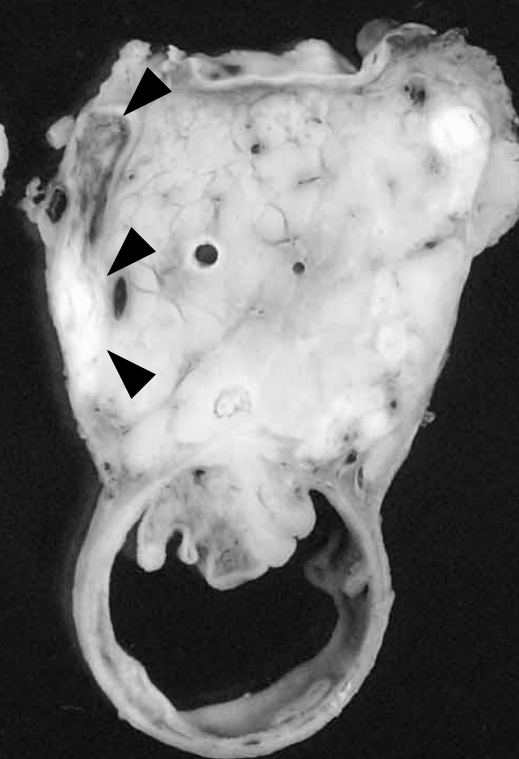
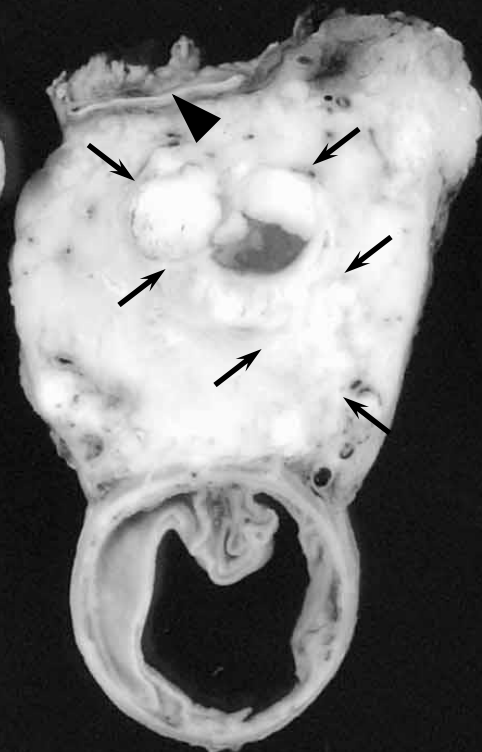
(C) Photomicrograph of the resected specimen showing that the tumor grew within the lumen of the portal vein (arrows) (Elastica-Masson, original magnification  $\times 12.5$ ).

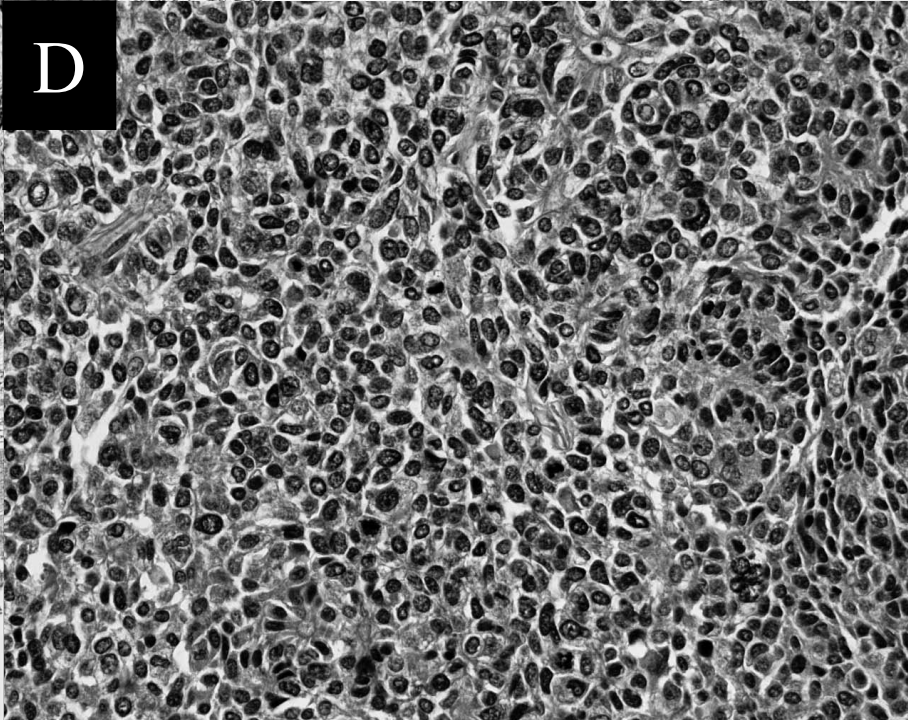
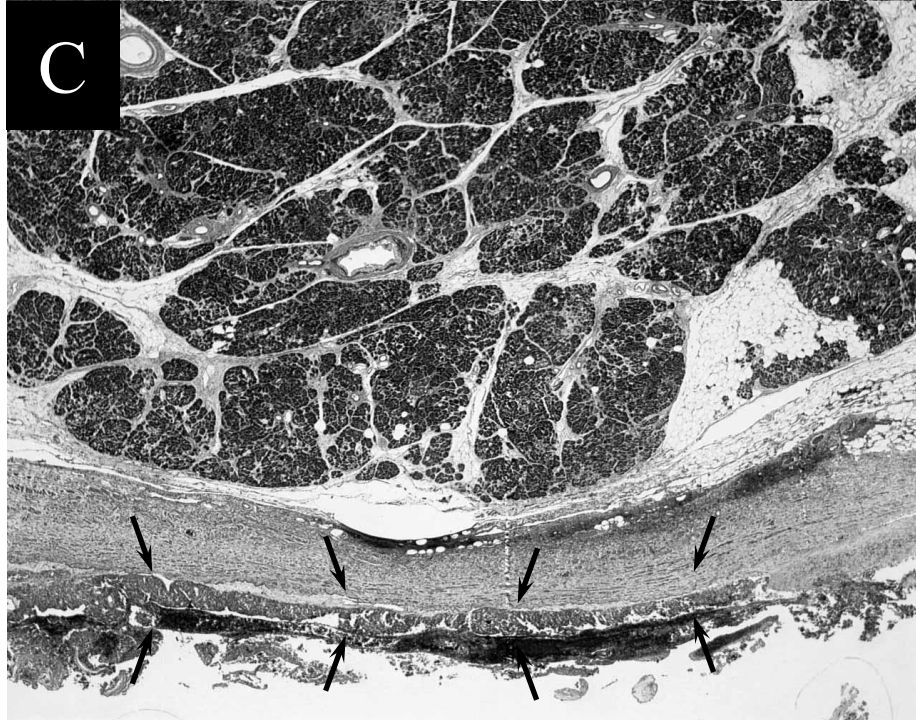
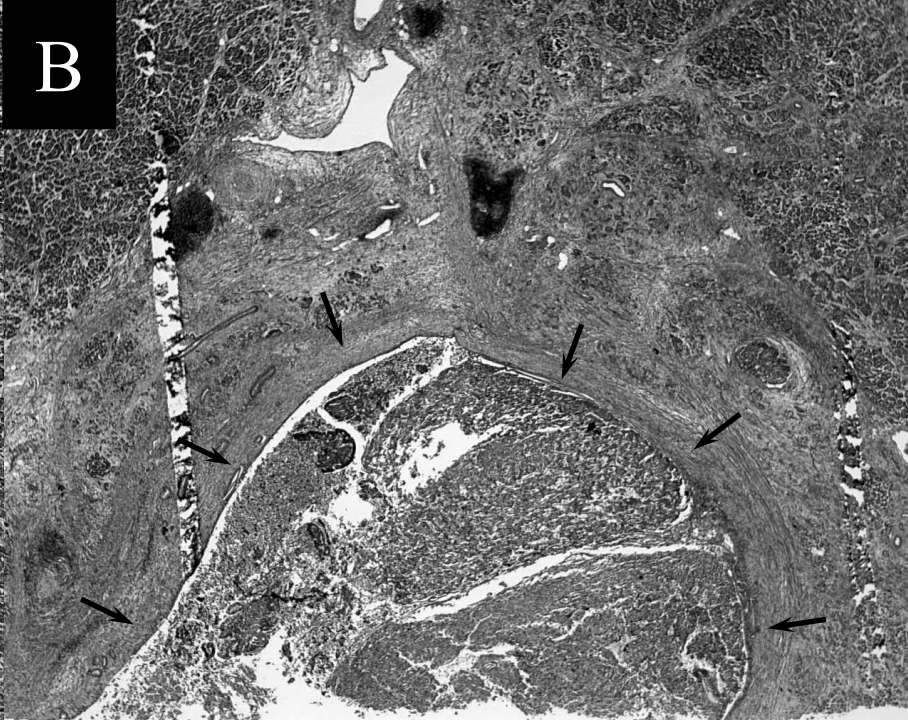
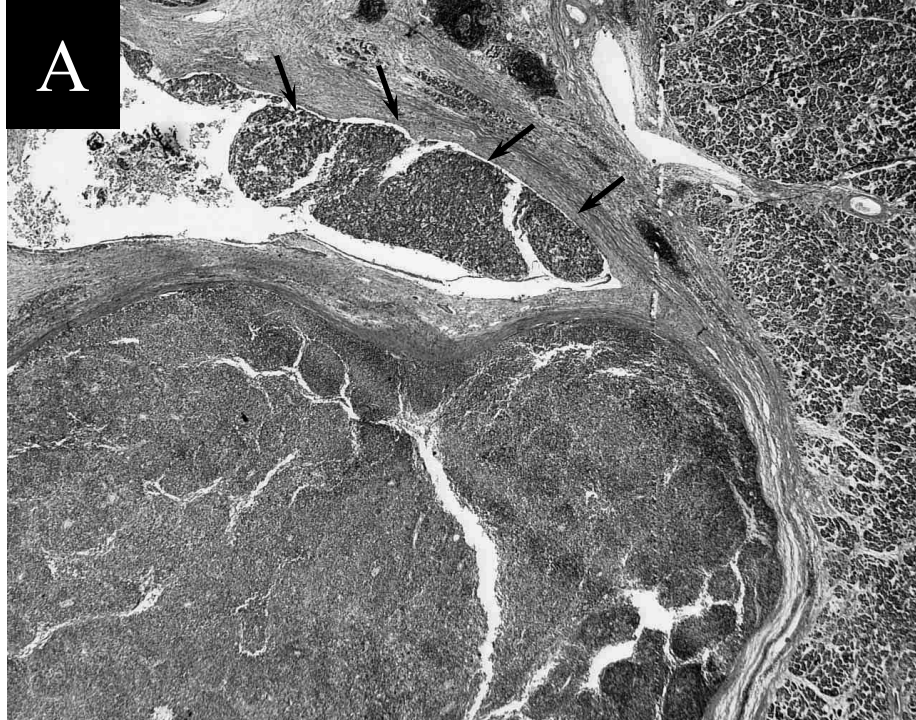
(D) Photomicrograph of the resected specimen showing that the tumor consisted of small nests and cords of uniform cuboidal cells arranged in a trabecular or ribbon-like pattern (H&E, original magnification  $\times 400$ ).

Please note that there is a spelling change necessary in Table 1 footnote:

differentiated → differentiated









**Table 1. Reported cases of intraductal growth of nonfunctioning pancreatic endocrine tumors**

Author	Age (y)	Gender	Symptoms	Intraductal tumor		Extraductal tumor		Operation	Histology	Prognosis
				Site	Size (mm)	Site	Size (mm)			
Amano et al.	53	F	Itching	H-T	—	H	70 × 50	TP	?	?
Shimizu et al.	44	F	Steatorrhea and epigastric pain	H-T	—	H	—	TP	Benign	—
Kitami et al.	57	M	Epigastric pain	T	—	T	15 × 15	DP	Poorly	2 y, A
Kanno et al.	62	M	Abdominal discomfort	B	10	B	—	DP	?	?
Kanno et al.	59	M	Epigastric pain	H	10	H	—	PD	?	?
Akatsu et al.	43	M	None	B	4 × 3 × 3	B	25 × 8 × 8	DP	Well	1 y, A
Present case	68	M	Epigastric pain	B	10	H	29 × 26	SSPPD	Poorly	11 mo, D

*H*, Head; *B*, Body; *T*, Tail; *TP*: Total pancreatectomy; *DP*: Distal pancreateomy;  
*PD*, Pancreaticoduodenectomy; *SSPPD*, Subtotal stomach-preserving pancreaticoduodenectomy;  
*Benign*, Benign behavior; *Poorly*, Poorly differentiated carcinoma; *Well*, Well differentiated carcinoma; *A*, Alive; *D*, Dead