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Author(s)	Kawakami, Hiroshi; Kuwatani, Masaki; Onodera, Manabu; Hirano, Satoshi; Kondo, Satoshi; Nakanishi, Yoshitsugu; Itoh, Tomoo; Asaka, Masahiro
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**Primary acinar cell carcinoma of the ampulla of Vater: a case report and literature review**

Hiroshi Kawakami<sup>1</sup>, Masaki Kuwatani, Manabu Onodera, Satoshi Hirano<sup>2</sup>,  
Satoshi Kondo, Yoshitsugu Nakanishi<sup>3</sup>, Tomoo Itoh 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)

**Short title:** Ampullary acinar cell carcinoma

## **Abstract**

Acinar cell carcinoma of the pancreatobiliary system is a relatively rare malignant neoplasm usually arising in the pancreatic parenchyma. We experienced a 68-year-old woman who presented with obstructive jaundice due to ampullary mass 1.0 cm in diameter, detected by the abdominal computed tomography and endoscopic examination. The patient underwent a curative surgical operation, and histopathological examination revealed that the tumor was confined to the ampulla of Vater with no continuity to the pancreatic parenchyma, and the tumor cells showed acinar or tubular arrangement with eosinophilic to basophilic granular cytoplasm, whose findings were identical to those of acinar cell carcinoma of the pancreas. Immunohistochemically, the tumor cells were positive for lipase. From these findings, it was concluded that the tumor was primary acinar cell carcinoma arising in the ampulla of Vater, probably originating from the heterotopic pancreatic tissue. This is the first reported case of primary acinar cell carcinoma in the ampulla of Vater.

**Key Words:** Ampullary neoplasms; Pancreatic neoplasms; Acinar cell carcinoma; Ampulla of Vater; Heterotopic pancreas

## **Introduction**

Acinar cell carcinoma of the pancreatobiliary system is a relatively rare neoplasm that accounts for approximately 1-2% of the exocrine pancreatic tumors in adults,<sup>1-2</sup> and usually arises in the pancreatic parenchyma, most commonly in the pancreatic head. Although the tumor has highly characteristic histologic features, the tumor cells produce pancreatic enzyme. Acinar cell carcinoma has two variant types, acinar cell cystadenocarcinoma and mixed acinar-endocrine carcinoma. Its definite diagnosis can be made on the basis of immunohistochemical and electron microscopic findings. Ectopic pancreatic tissue in the upper gastrointestinal tract is relatively a common finding, which may be found in up to 15% of individuals at autopsy; and the duodenum and stomach are the most common locations.<sup>4</sup> In most duodenal cases, the lesions are located in the portion several centimeters proximal to the ampulla of Vater, often in the submucosa beneath the minor duodenal papilla. In addition, it can present in the ampulla of Vater.<sup>5</sup> Exocrine pancreatic neoplasms and endocrine tumors are practically very rare.<sup>6,7</sup>

Herein, we present a primary case of acinar cell carcinoma of the ampulla of Vater. To our knowledge, this is the first report of an acinar cell carcinoma, except the previously reported carcinoma in the ampulla of Vater which was mixed acinar-endocrine carcinoma.<sup>8</sup>

## Case report

A 65-year-old woman was hospitalized because of fatigue persisting for about 3 months. Two months earlier, she had been diagnosed as having jaundice (serum direct bilirubin level at 15.0 to 17.4 mg/dL) by her primary physician. Percutaneous biliary drainage was performed. She also underwent endoscopic examination, which revealed a tumor in the ampulla of Vater. On admission, she showed no signs of jaundice. She had no personal or family history of pancreatic or biliary disease. The abdomen was soft; no mass was palpable. Results of laboratory tests were as follows: serum direct bilirubin, 0.8 mg/dL (normal range: <0.3 mg/dL); alkaline phosphatase, 622 IU/L (103-335 IU/L); serum amylase, 74 IU/L (43-131 IU/L); lipase, 74 U/mL (13-49 IU/L); trypsin, 403 ng/mL (101-480 ng/mL); elastase-I, 685.69 ng/dL (<400 ng/dL); and white blood cell count, 6300/ $\mu$  L (3500-9300/ $\mu$  L). The fasting blood glucose level was 107 mg/dL (<110 mg/dL). Tumor marker values were as follows: carcinoembryonic antigen, 1.5 ng/mL (1.0-6.5 ng/mL); carbohydrate-associated antigen 19-9, 11.4 U/mL (<37 U/mL); SPan-1, 6.7 U/mL (<30 U/mL); and DUPAN-2, 28 U/mL (<150 U/mL); alpha-fetoprotein, 5.3 ng/ml (<10 ng/ml).

Ultrasonography demonstrated marked dilatation of the main pancreatic duct by about 6 mm. There was no bile ductal dilatation. Portal venous phase-enhanced computed tomography showed a heterogeneously enhanced mass of 1.2  $\times$  1.0-cm in the ampulla of Vater (Fig. 1A). No other lesion was detected in the liver or other organs. Endoscopic examination revealed a polypoid, exophytic mass in the ampulla of Vater (Fig. 1B). Endoscopic ultrasonography revealed a heterogenous hypoechoic mass of about 1.0-cm in the ampulla of Vater without evidence of infiltration into the pancreas or muscularis

propria of the duodenum, and dilatation of the main pancreatic duct (Fig. 1C, D). On percutaneous cholangiography, interruption of the bile duct was noted in the distal bile duct.

At the previous biliary drainage, the drainage tube had been placed directly in the common bile duct, instead of via transhepatic route. Thus we attempted ampullary biopsy, and transpapillary biliary drainage by rendezvous technique. However, the patient suffered from abdominal pain, likely from biliary peritonitis, during the drainage, and thus we gave priority to transpapillary biliary drainage rather than biopsy.

Subtotal stomach-preserving pancreaticoduodenectomy was performed with the preoperative diagnosis of carcinoma of the ampulla of Vater morphologically. Pancreatogram of the specimen revealed total occlusion of the main pancreatic duct in the head of the pancreas.

Gross appearance of the resected specimen was a white nodular submucosal mass, measuring  $1.2 \times 1.0$  cm at the greatest dimension in the ampulla of Vater (Fig. 2). Cut surface of the tumor showed a ill-defined whitish tumor with no continuity to the pancreatic parenchyma. Histologically, the tumor was located mainly within the ampulla of Vater (Fig. 3A). It invaded duodenal muscular layer without extending into the parenchyma of the head of the pancreas (Fig. 3B). The architectural pattern was the acinar pattern with the tumor cells arranged in small glandular units. The tumor cells were similar to the normal pancreatic acinar cells. There was no component of ductal adenocarcinoma or endocrine tumor. Moderate to severe atypias were seen in the tumor cells, e.g., the nuclei with dispersed chromatin, and central to eccentric prominent nucleoli (Fig. 3C). Moderate desmoplastic reaction in the stroma was also seen. The

mitotic activity was in the range from 0 to 2 per high-power field. Periodic acid-Schiff stain after diastase digestion showed positive granules within the eosinophilic granular cytoplasm of the tumor cells (not shown). Immunohistochemical stainings with lipase (dilution 1:2,000, Biodesign) were strongly positive in the tumor cells (Fig. 3D), and negative for amylase (dilution 1:1,000, SIGMA), trypsin (dilution 1:10, DAKO), chymotrypsin (dilution 1:100, Zymed), alpha 1-antitrypsin (dilution 1:10, DAKO), chromogranin A (dilution 1:150, DAKO), neuron-specific enolase (dilution 1:200, DAKO), synaptophysin (dilution 1:20, DAKO) and alpha-fetoprotein (dilution 1:2,000, DAKO). Based on these findings, a definitive diagnosis of acinar cell carcinoma of ampulla of Vater was made. The postoperative course was uneventful. At 19 months' follow-up, there was no clinical evidence of recurrence.

## **Discussion**

Heterotopic (ectopic, or aberrant) pancreatic tissue is found in 2% to 15% of all autopsies.<sup>4</sup> The most frequent sites of heterotopic pancreas are gastric antrum (30%), duodenum (30%), jejunum (20%), and Meckel's diverticulum (5%). Recently 9 cases of ectopic pancreas located in the major duodenal papilla have been reported; among their summarized clinical features, the interesting were that 5 of them developed jaundice and the 6 patients underwent excisions, including one who underwent pancreaticoduodenectomy.

Their lesions are thought to have developed during rotation of the foregut when fragments of pancreas became separated, or from pancreatic metaplasia of endodermal tissues.<sup>6</sup> Moreover, malignant change in heterotopic pancreas is very rare, and acinar

cell carcinoma in heterotopic pancreas is thought to be even rare. Makhoul et al.<sup>6</sup> reported that, of 109 cases of heterotopic pancreas in the gastrointestinal tract, 67 was in the stomach (62%) and 42 in the small intestine (38%).

According to their report, only 2 of them were carcinoma arising from heterotopic pancreas, both occurring in the jejunum; one of them was ductal adenocarcinoma and the other an acinar cell carcinoma. Recently, 2 cases of acinar cell carcinoma arising in heterotopic pancreatic tissue have been documented.<sup>8,9</sup> One of these four cases and our case had the lesion in the ampulla of Vater (Table 1). The mean age was 75 years (range, 65-86 years). There was no sex difference. The mean tumor size was 30-mm (range, 12-50 mm). The median survival time was 11 months (range, 2-19 months).

For a carcinoma to be recognized as arising from heterotopic pancreatic tissue, three criteria have been proposed<sup>10</sup> : (i) the tumor must be found within, or close to, the ectopic pancreatic tissue; (ii) transition between pancreatic structures and carcinoma must be observed (i.e., duct-cell dysplasia and/or carcinoma *in situ*); and (iii) the non-neoplastic pancreatic tissue must comprise at least fully developed acini and duct structures.

The lesion in the present case had no pancreatic tissues at the site in ampulla of Vater. However, the pancreatic remnant tissue might have been totally replaced by the tumor.

In conclusion, we have described the case of primary acinar cell carcinoma arising in the ampulla of Vater, possibly originating from a heterotopic pancreatic tissue.



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## **Figures legends**

### **Figure1**

**a**, Computed tomography image showing a heterogeneously enhanced mass of 12×10-mm in the ampulla of Vater (arrows).

**b**, Endoscopic examination showing a polypoid, exophytic mass of the ampulla of Vater.

**c** and **d**, Transduodenal endoscopic ultrasonography showing a heterogenous hypoechoic mass of about 10-mm in the ampulla of Vater, without infiltration into the pancreas or musculus propria of the duodenum (arrows). CBD, common bile duct; MPD, main pancreatic duct.

### **Figure2**

A gross appearance of the resected specimen. The tumor was a white nodular mass (arrows).

### **Figure3**

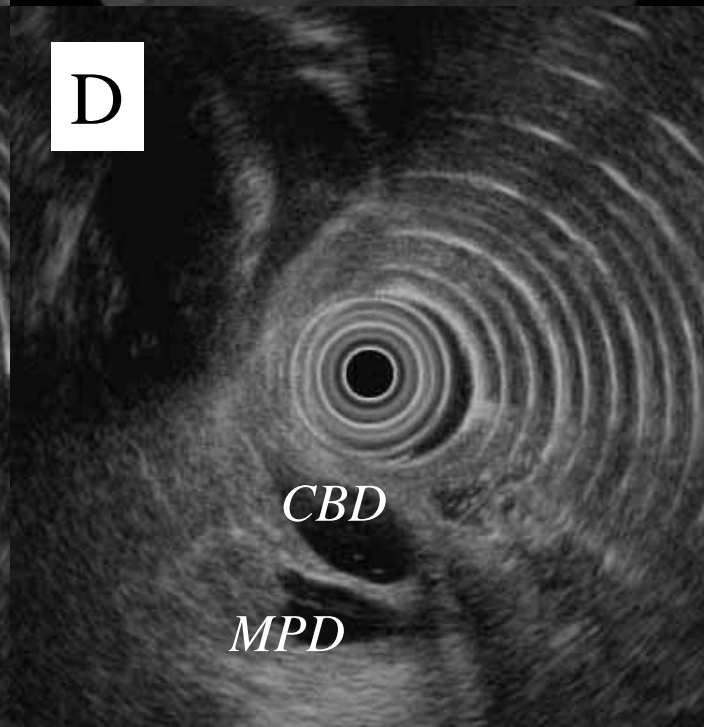
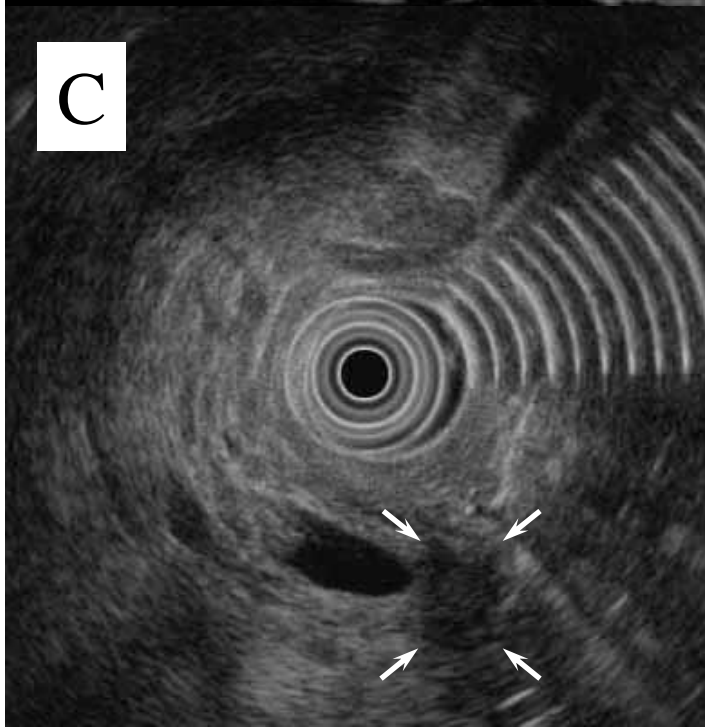
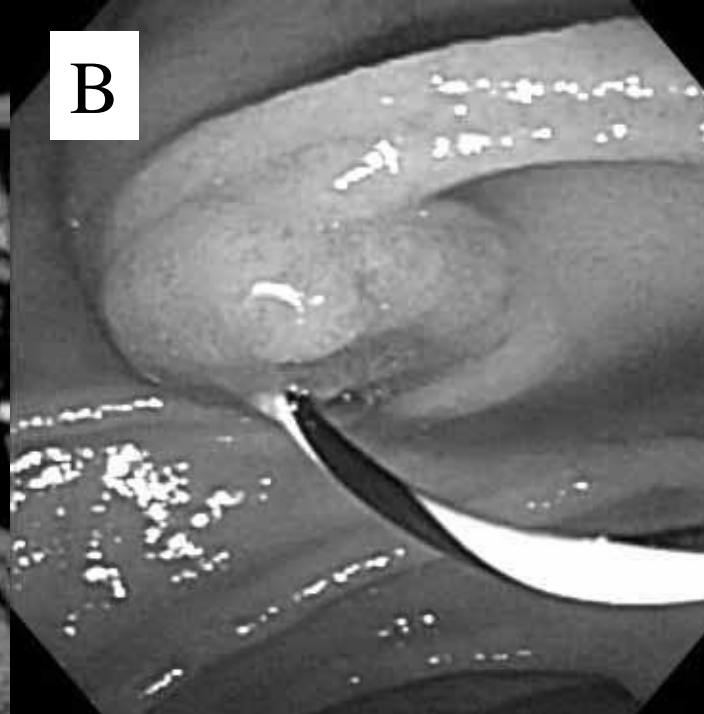
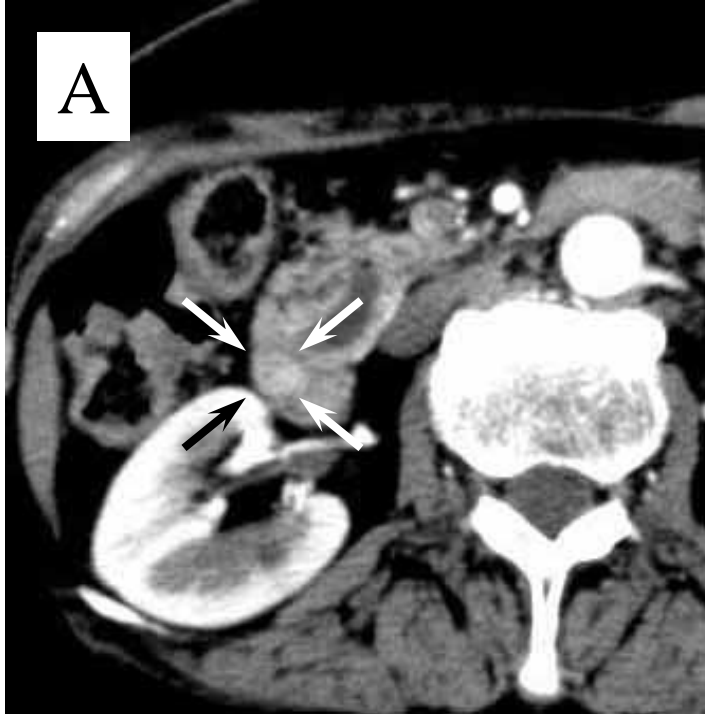
**a**, Photomicrograph of the resected specimen showing that the tumor was located in the ampulla of Vater (H&E, original magnification × 12.5).

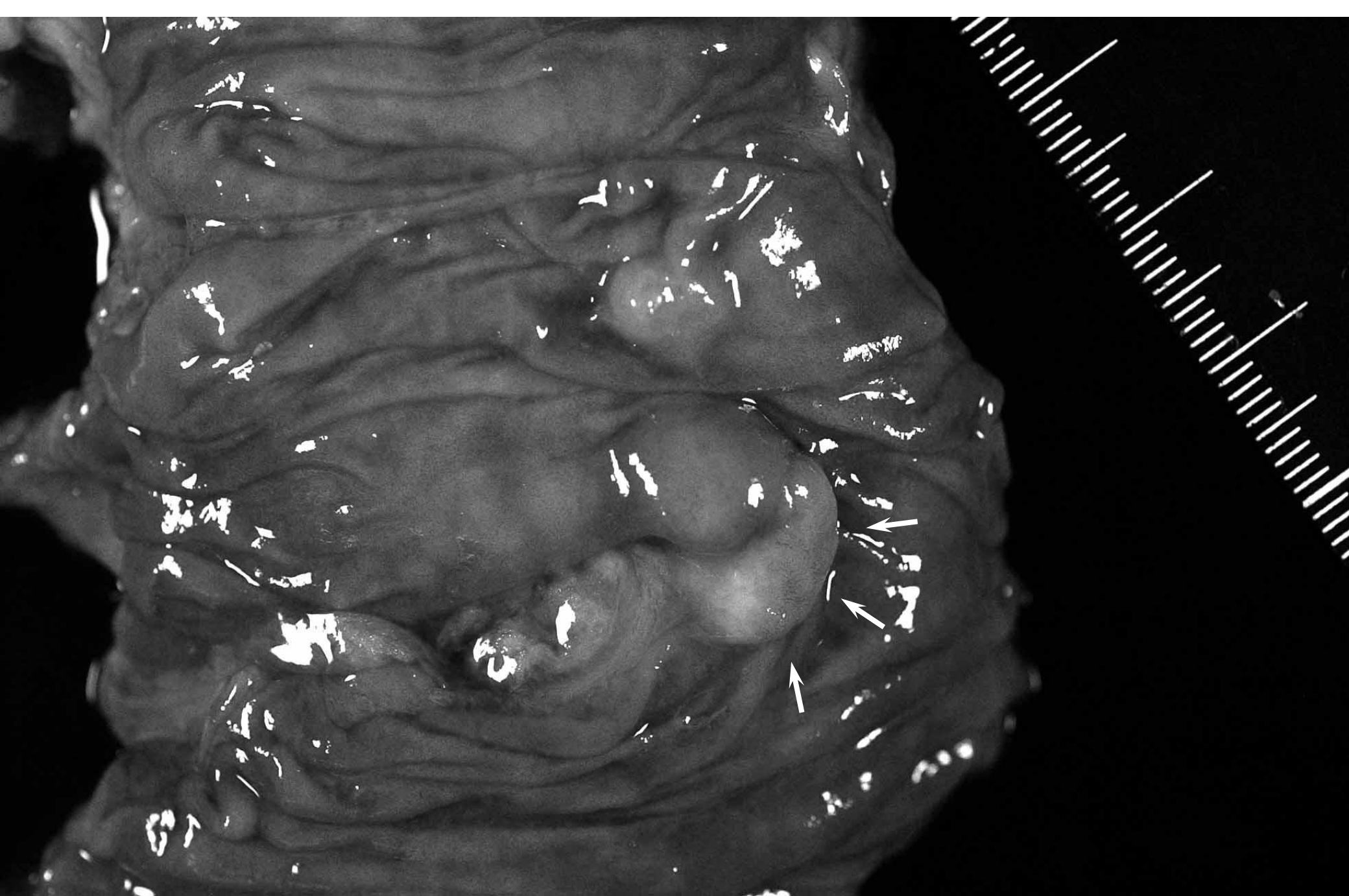
**b**, Photomicrograph of the resected specimen showing that the tumor invaded the musculus propria of the duodenum (arrows) without parenchymal invasion (H&E, original magnification × 40).

**c**, Photomicrograph of the resected specimen showing that the tumor was hypercellular, consisting of cytologically uniform cells with cords, and granular eosinophilic apical

cytoplasm. (H&E, original magnification  $\times 200$ ).

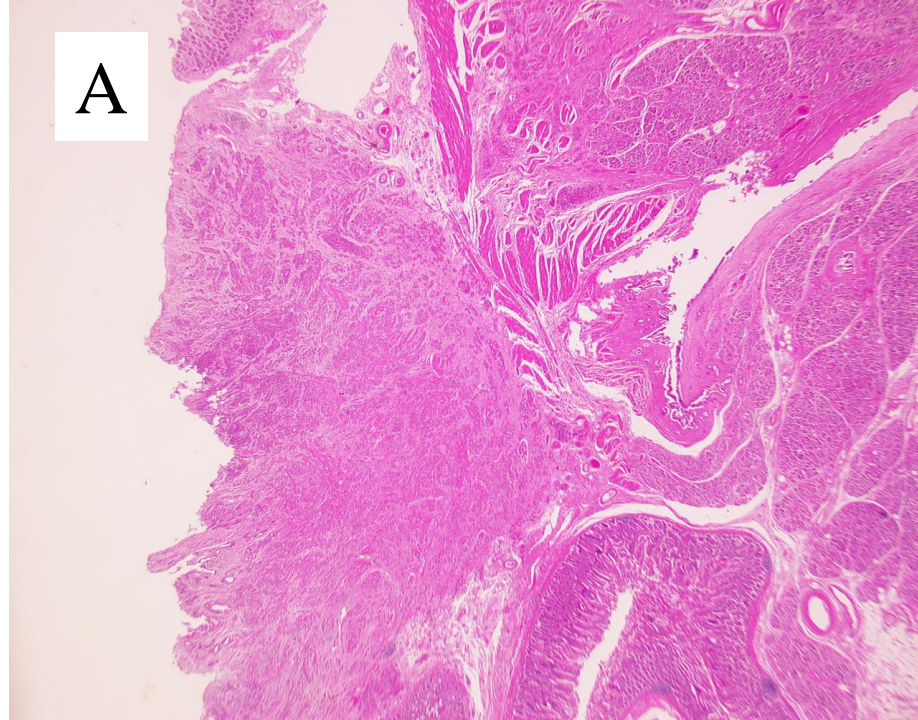
**d,** Photomicrograph of the resected specimen showing positive cytoplasmic immunoreactivity for the anti-lipase antibody (H&E, original magnification  $\times 100$ ).



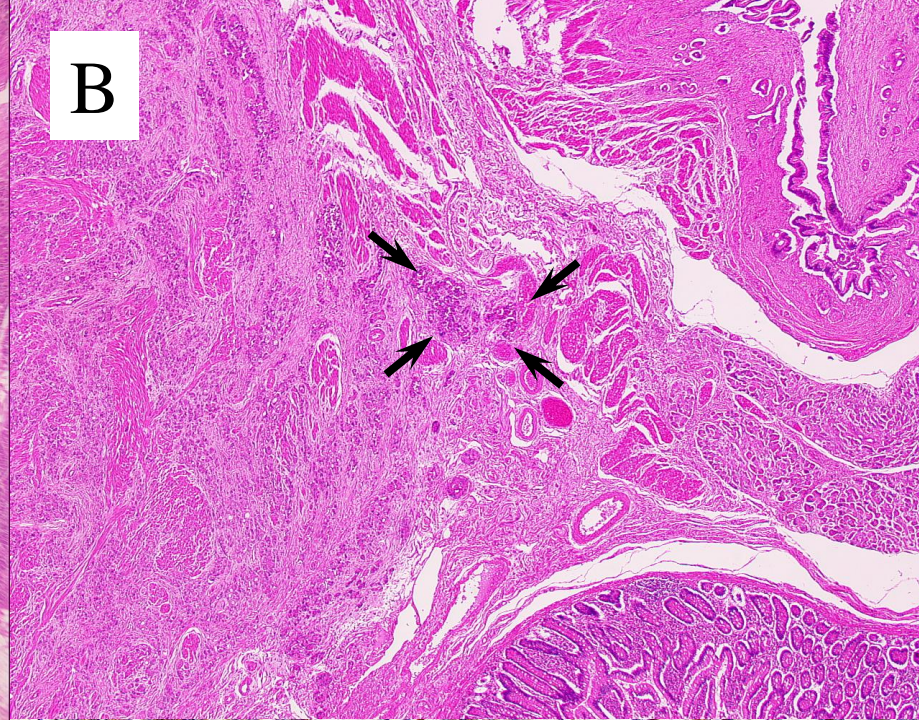




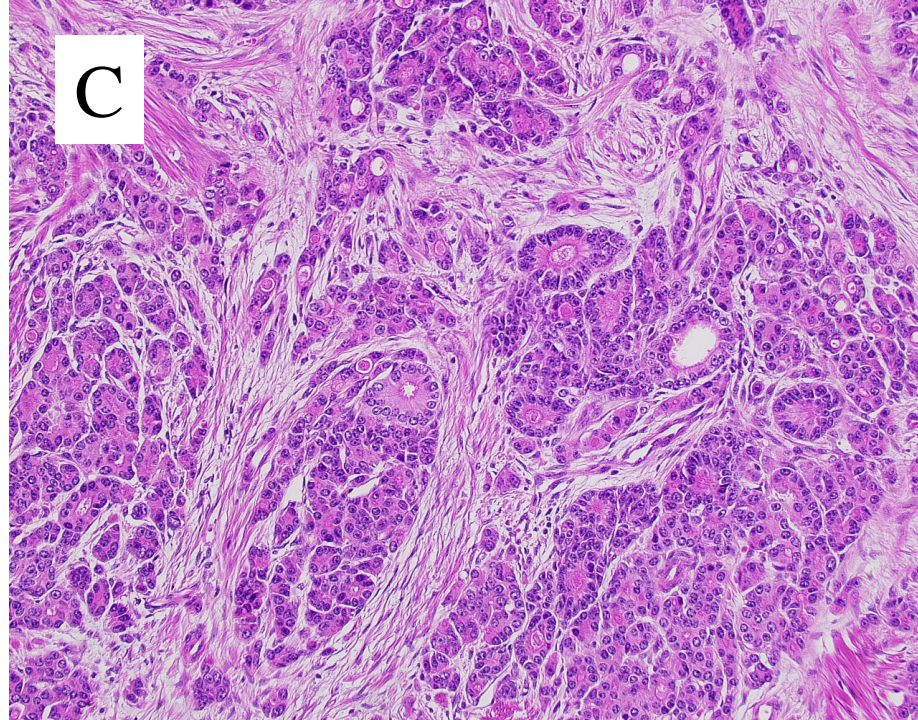
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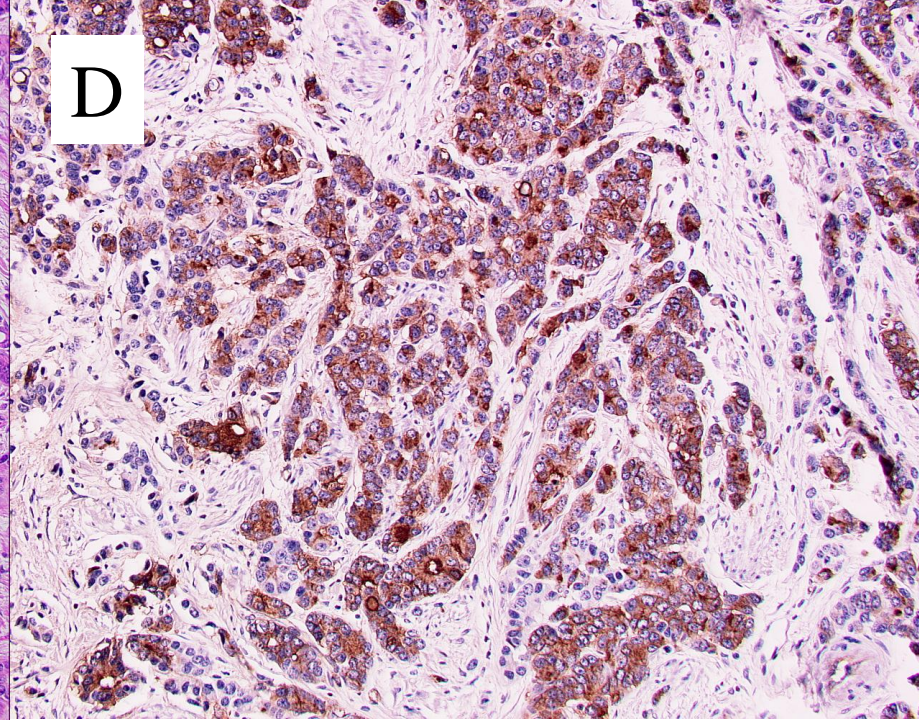
B



C



D





**Table 1. Reported cases of acinar cell carcinoma originating from the heterotopic pancreas**

Author	Age (y)	Gender	Symptoms	Location	Size (mm)	Operation	Outcome	Length of Follow-up
Makhlouf HR et al.	71	M	None	J	35	SR	DOD, LM	12 mo
Moncur JT et al.	78	M	Lower back pain	A	23	None*	Dead	2 mo
Sun Y et al.	86	F	None	S	50	PG	?	?
Present case	65	F	Jaundice	A	12	SSPPD	Alive, NED	19 mo

*M*, Male; *F*, Female; *J*, Jejunum; *A*, Ampulla of Vater; *S*, Stomach; *SR*, Segmental resection; *PG*, Partial gastrectomy with Billroth II reconstruction; *SSPPD*, Subtotal stomach-preserving pancreaticoduodenectomy; *DOD*, Dead of disease; *LM*, Liver metastases; *NED*, No evidence of disease; \*An autopsy was performed.