

## Intraductal Tubular Carcinoma of the Pancreas: Case Report with Review of Literature

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**Abstract.** A 67-year-old man presented with leg edema. Laboratory data showed elevated blood glucose and carbohydrate antigen (CA) 19-9 levels, and anemia. Further imaging studies revealed a relatively clear-margined tumor totally occupying the main pancreatic duct (MPD) from the head to the tail of the pancreas (maximum diameter 10 cm) without mucin hypersecretion. Total pancreatectomy with splenectomy and regional lymphadenectomy were performed. Intraductal tubular carcinoma (ITC) was diagnosed by immunohistochemical staining and electron microscopic examination. Previous reports showed that this tumor is characterized by slow growth, with a favorable prognosis and intraductal nodular growth occupying the MPD and no macroscopic mucus. Whether ITC should be distinguished from other types of pancreatic neoplasm is controversial, and the accumulation of more ITC cases and multi-institutional analysis are necessary to establish the diagnostic criteria and characteristics of this histological entity.

Intraductal tubular neoplasm (ITN), with tubular architecture or scant mucus production, has recently been described as a variant of intraductal neoplasm of the pancreas. This type of tumor is described in a recent Armed Forces Institute of Pathology series (1) and in the General Rules for the Study of Pancreatic Cancer published by the Japan Pancreas Society (2) but not in the World Health Organization (WHO) Classification of Tumours published by the International Agency for Research on Cancer (IARC) (3). According to the latest revised edition of the General Rules for the Study

of Pancreatic Cancer published by the Japan Pancreas Society (2), ITN is classified as a subtype of intraductal papillary-mucinous neoplasm (IPMN) (4). ITN is further classified into intraductal tubular adenoma and intraductal tubular carcinoma (ITC). To date, only fifteen cases of ITC have been reported in the clinical literature (5-14).

The Authors recently encountered a case of ITC in which it was difficult to make a decisive pathological diagnosis.

### Case Report

A 67-year-old man attended a local hospital with chief complaint of leg edema. Peripheral blood examination revealed severe anemia (Hb: 6.4 g/dl). Gastrointestinal endoscopy showed a duodenal tumor, and adenocarcinoma was confirmed histologically. He was referred to our hospital for further examinations. Physical examination revealed no findings except for leg edema. The results of hematological, general biochemical, and urinalysis tests were all within the normal ranges, except for elevated blood glucose (155 mg/dl), CA19-9 (58.3 U/ml), and anemia (Hb: 9.9 g/dl).

Gastrointestinal endoscopy showed an ulcerated tumor with sharply demarcated margins on the wall of the duodenum. The papilla of Vater was swollen (Figure 1). Enhanced computed tomography (CT) detected a low density, relatively clear-margined tumor, with maximum diameter of 10 cm in the pancreatic head. The tumor totally occupied the main pancreatic duct (MPD) from the head to the tail of the pancreas. The duodenum was definitely invaded by the tumor. The tumor was close to the portal vein (Figure 2). Even with the use of magnetic resonance (MR) imaging with MR cholangiopancreatography (MRCP) it was not possible to identify the MPD. Diffusion-weighted image showed a high intensity mass in the head of the pancreas. A high intensity tumor was also observed in the distal pancreas (Figure 3).

Based on the findings of these examinations, we made a tentative preoperative diagnosis of acinar cell carcinoma (ACC)

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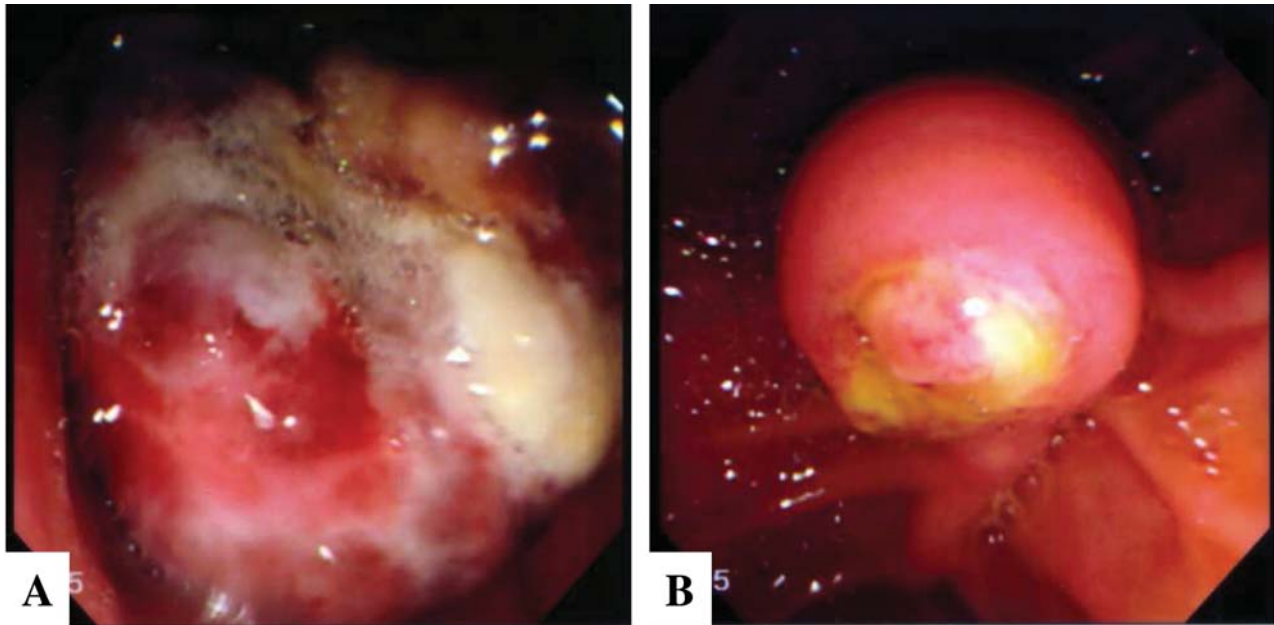


Figure 1. Gastrointestinal endoscopy showed an ulcerated tumor with sharply demarcated, raised margins in the wall of the duodenal bulb (A). The papilla of Vater was swollen (B).



Figure 2. Enhanced computed tomography detected a low density, relatively clear-margined tumor with maximum diameter of 10 cm in the pancreatic head. The tumor totally occupied the main pancreatic duct from the head to the tail of the pancreas. The duodenum was clearly invaded by tumor (A). The tumor was close to the portal vein (B).

with intraductal spread of the pancreas. Total pancreatectomy with splenectomy and regional lymphadenectomy were performed. The patient's postoperative course was uneventful, and he remains alive 3 years after the operation without any symptoms or signs of tumor recurrence.

Macroscopically, the tumor was 6.5 cm in maximum diameter. The lumen of the MPD was totally filled with solid and hemorrhagic tumor. There was no mucus hypersecretion (Figure 4). The tumor was exposed to the duodenal bulb. Microscopically, the main pancreatic duct was filled with

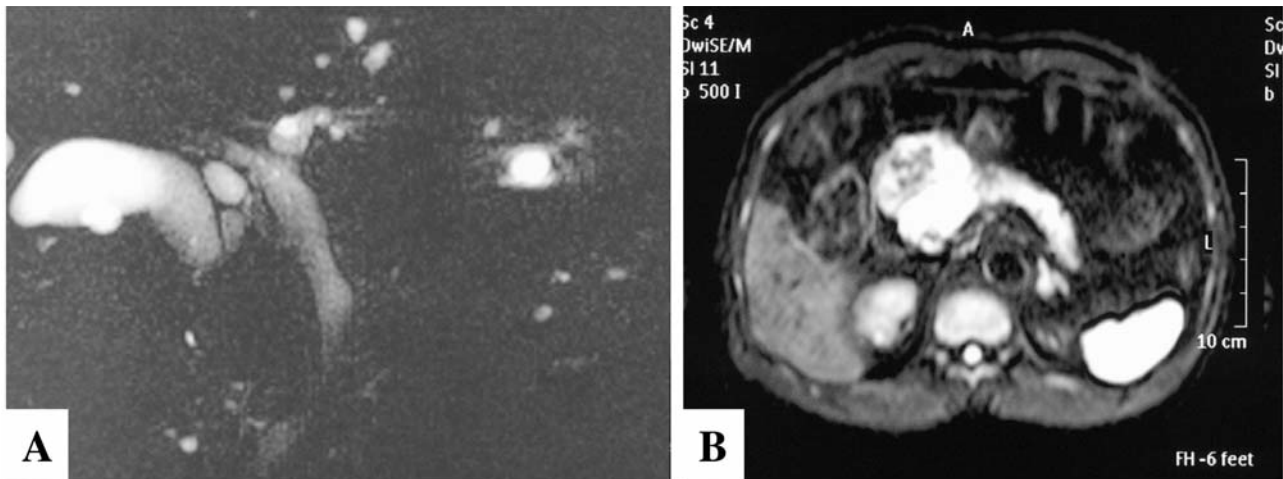


Figure 3. Even with the use of Magnetic resonance (MR) imaging with MR cholangiopancreatography, it was not possible to identify the MPD (A). Diffusion-weighted image showed a high intensity mass in the head of the pancreas. High intensity was also observed the distal pancreas (B).

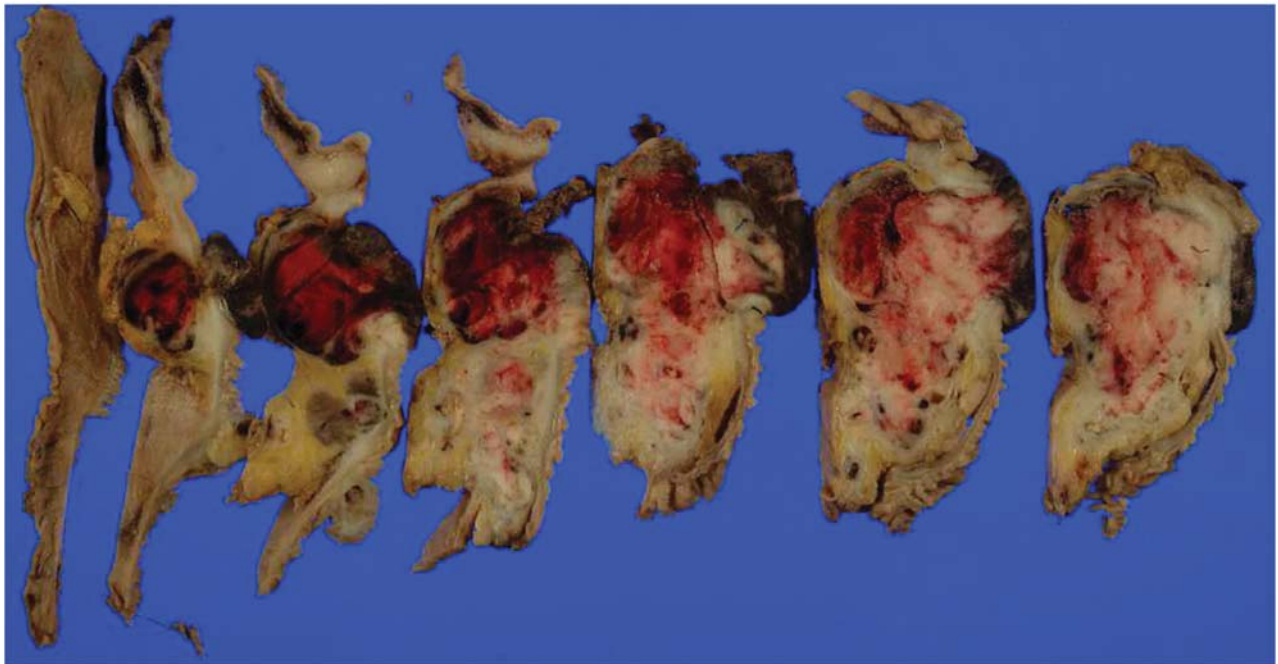


Figure 4. Macroscopically, the tumor was 6.5 cm in maximum diameter. The lumen of the MPD was totally filled with solid and hemorrhagic tumor. There was no mucus hypersecretion.

tumor cells, and the epithelium of most of the pancreatic duct contained atypical cells. The tumor showed small tubular structures, and tumor cells had granular and eosinophilic cytoplasm. Partially eosinophilic cells showed a sheet-like distribution. Most of the tumor was confined to the intraductal but with focal invasion to the duodenum. Periodic acid-Schiff (PAS) and diastase digestive PAS staining showed intracytoplasmic mucin secretion (Figure 5).

Immunohistochemical investigation showed the tumor cells to strongly express alpha-1-antitrypsin, cytokeratin (CK) 7, CK19, cancer antigen (CA) 19-9, and MUC1, and to weakly express amylase focally, whereas trypsin, chromogranin A, synaptophysin, cluster of differentiation (CD) 56, CK20 were not expressed (Figure 6). Electron microscopic examination did not reveal zymogen granules in the tumor cells (Figure 7). The final diagnosis was T3N1M0 stage ITC.



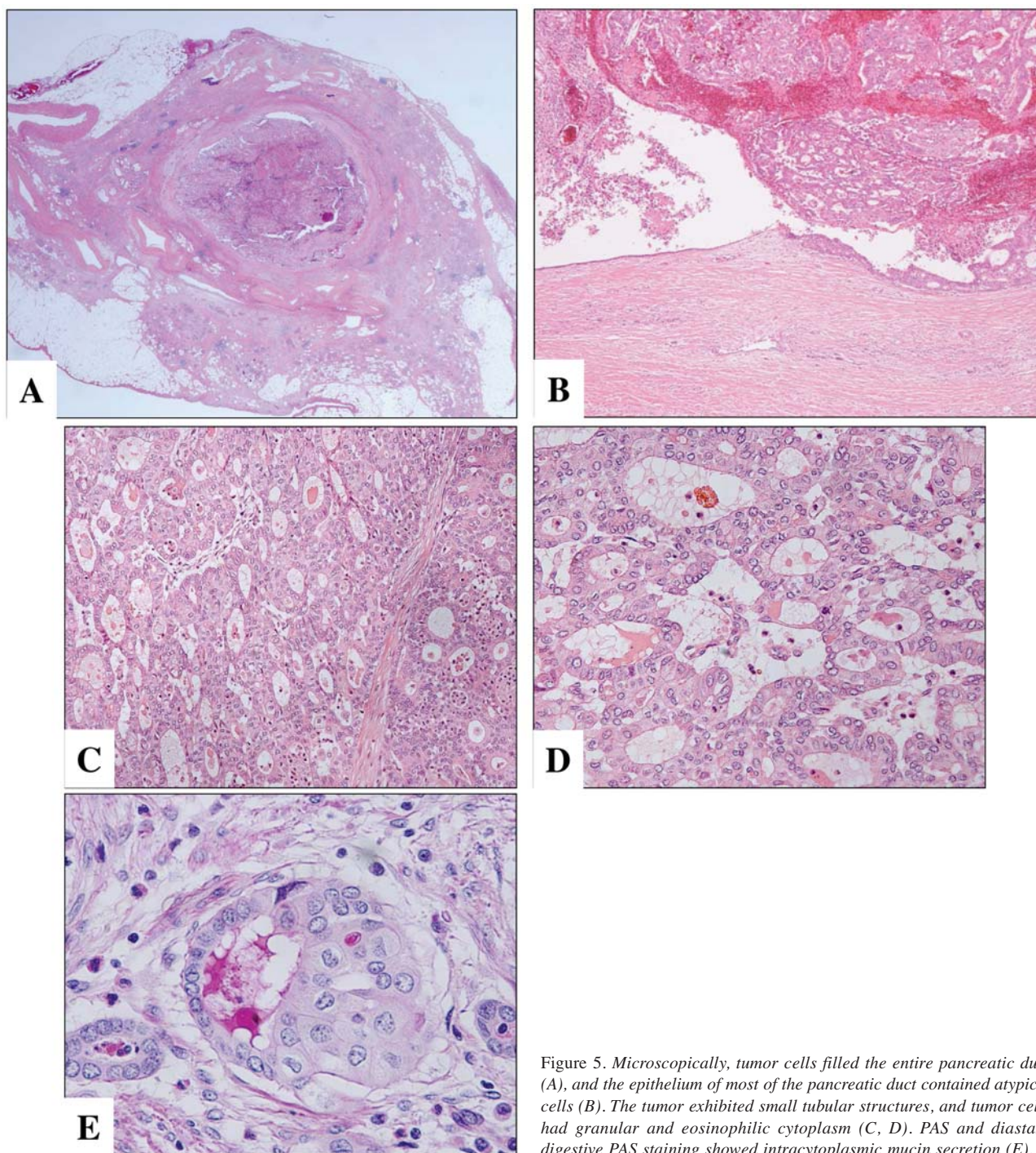


Figure 5. Microscopically, tumor cells filled the entire pancreatic duct (A), and the epithelium of most of the pancreatic duct contained atypical cells (B). The tumor exhibited small tubular structures, and tumor cells had granular and eosinophilic cytoplasm (C, D). PAS and diastase digestive PAS staining showed intracytoplasmic mucin secretion (E).

## Discussion

Intraductal neoplasms of the pancreas include IPMN (4), pancreatic intraepithelial neoplasia (PanIN) (15), ITN and an intraductal variant of ACC (16-18). In this case, it was difficult to make a decisive pathological diagnosis. This case was different

from ordinary IPMN or PanIN because there was a predominantly tubular neoplasm and an absence of mucus hypersecretion. Macroscopic intraductal tumors without mucus hypersecretion such as in this case, which include ACC (16-18), endocrine tumor (19, 20), and ITN, have been recently reported. This case resembled ACC in macroscopic and microscopic



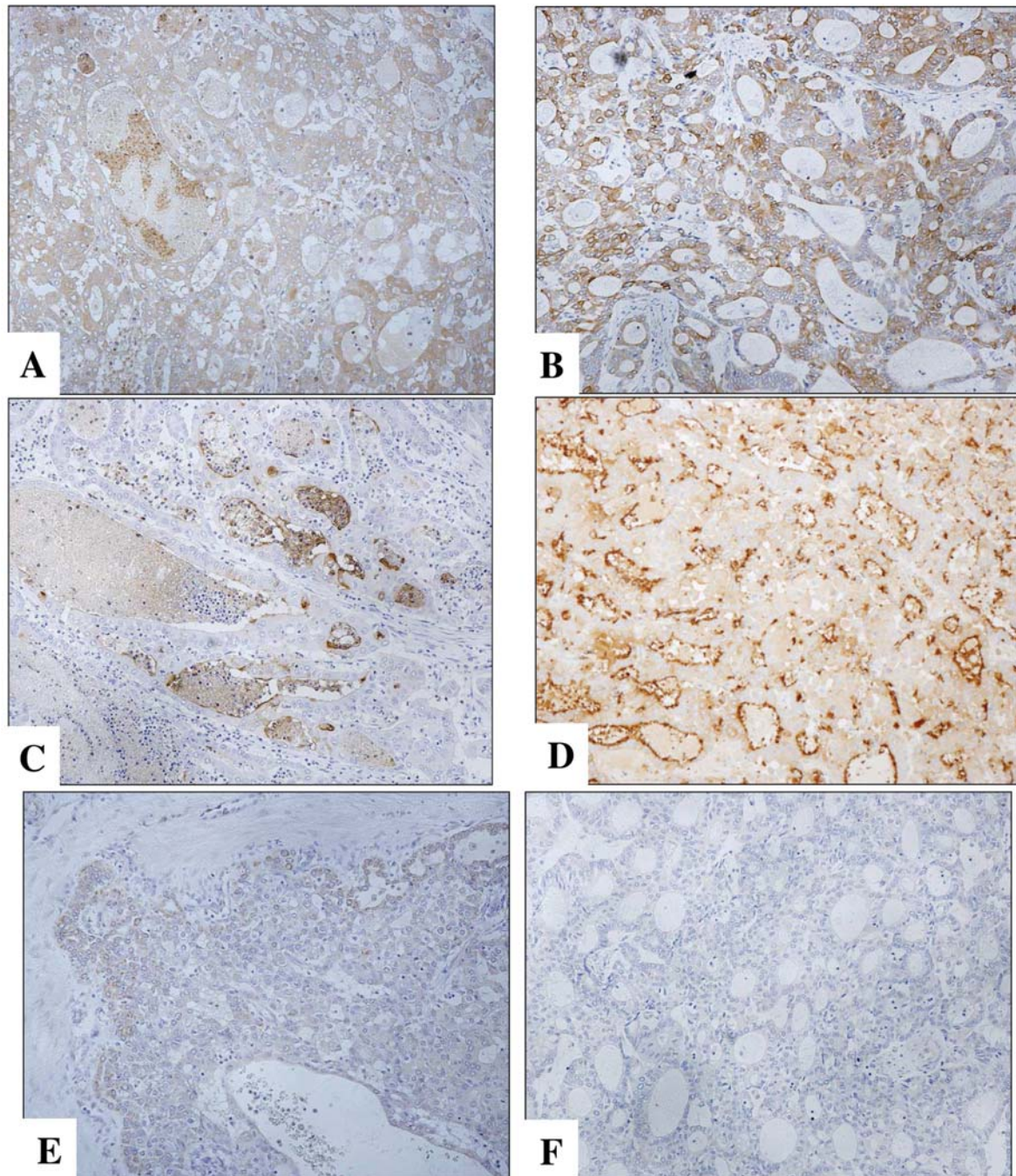


Figure 6. Immunohistochemical investigation showed the tumor cells strongly expressed alpha-1-antitrypsin (A), CK7 (B), CA19-9 (C), and MUC1 (D), and had weak focal expression of amylase (E), whereas trypsin (F) was not expressed.

appearance, and thus it was very difficult to differentiate it from ACC. In view of the ductal structure with intracytoplasmic mucin histologically, the expression of ductal markers CK7, CK19, and CA19-9 immunohistochemically, and the predominant intraductal spread of MUC1-positive cells, this case was diagnosed as ITC. Weak, focal expression of amylase was

seen immunohistochemically. However, electron microscopic examination did not reveal zymogen granules in the tumor cells. So this case was ultimately diagnosed as ITC.

ITC is an extremely rare pancreatic tumor that exhibits a nodular or polypoid gross appearance with a monotonous tubular growth pattern and no papillary projections or mucin

Table I. Reported Cases of ITC.

Authors	Age (years)	Gender	Pancreatic site	Intraductal site	Tumor size (mm)	Macroscopic mucus	Adjacent ducts	Invasion	Prognosis
Suda <i>et al.</i> (5)	55	M	Head	MPD	70	-	NA	Duodenum <sup>+</sup>	Alive, 7 years
Suda <i>et al.</i> (5)	47	M	Head	MPD	30	-	NA	Choledochus <sup>+</sup>	Dead, 5 years
Suda <i>et al.</i> (5)	75	F	Head	MPD	40	-	NA	Periductal <sup>+</sup>	Alive, 4 years
Suda <i>et al.</i> (5)	78	F	Head	MPD	30	-	NA	Periductal	NA
Ito <i>et al.</i> (7)	51	M	Head	MPD, Ac, Br	55×33	-	NA	-	Alive, 1 year 5 months
Tajiri <i>et al.</i> (8)	65	M	Head	MPD	55×16×15	-	Normal	-	Dead, 1.5 years
Tajiri <i>et al.</i> (8)	36	F	Body	MPD	20×10×10	-	Normal	-	Alive, 4 years
Tajiri <i>et al.</i> (8)	48	F	Head	MPD	26×22×30	-	Normal	-	Alive, 6 years
Tajiri <i>et al.</i> (8)	67	M	Tail	MPD	30×25	-	Normal	-	Dead, 2 years
Itatsu <i>et al.</i> (9)	50	F	Head	MPD	8×8	-	ITA	-	Alive, 23 months
Thirot-Bidault <i>et al.</i> (10)	67	M	Tail	MPD	30	-	Normal	-	NA
Hisa <i>et al.</i> (11)	84	M	Body	MPD	10×7×28	-	Normal	-	Dead, 15 months <sup>++</sup>
Oh <i>et al.</i> (12)	63	F	Body	MPD	25	-	Normal	-	NA
Furukawa <i>et al.</i> (13)	35	F	Body	MPD, Br	NA	-	NA	-	Alive, 3 years
Terada <i>et al.</i> (14)	67	M	Total	MPD	NA	-	ITA	-	Alive, 4 years
Present case	67	M	Total	MPD	132×65×54	-	Normal	Duodenum	Alive, 3 years

<sup>+</sup>Metastasis in lymph node; <sup>++</sup>death due to other illness; ITC, intraductal tubular carcinoma; ITA, intraductal tubular adenoma; MPD, main pancreatic duct; Ac, accessory pancreatic duct; Br, branch pancreatic duct; NA: not available.

hypersecretion in the pancreatic ducts. Based on a MEDLINE search from 1980 through 2009, fifteen cases of ITC have been reported (5-14) (Table I). All fifteen ITC cases showed characteristics of intraductal nodular growth, occupying the MPD without macroscopic mucus hypersecretion. Suda *et al.* reported four cases of ITC with relatively longer survival despite invasion and metastasis to lymph nodes (5). Despite tumor invasion to the duodenum and metastasis to lymph nodes, our patient has survived for more than 28 months without any sign of recurrence. These results suggest that ITC is a slow-growing tumor with a favorable prognosis.

In summary, we had difficulty diagnosing this case precisely from morphologic findings alone. The results of immunohistochemical staining in reported cases were also not consistent (Table II). We diagnosed this case as ITC ultimately because of the findings of immunohistochemical staining and electron microscopic examination. Previous reports have suggested that this tumor is characterized by slow growth with intraductal nodular growth occupying the MPD and no macroscopic mucus, with a favorable outcome in the majority of cases. Whether ITN should be distinguished from other types of pancreatic neoplasm is controversial, and the accumulation of more ITN cases and multi-institutional analysis are necessary to establish the diagnostic criteria and characteristics of this histological entity.

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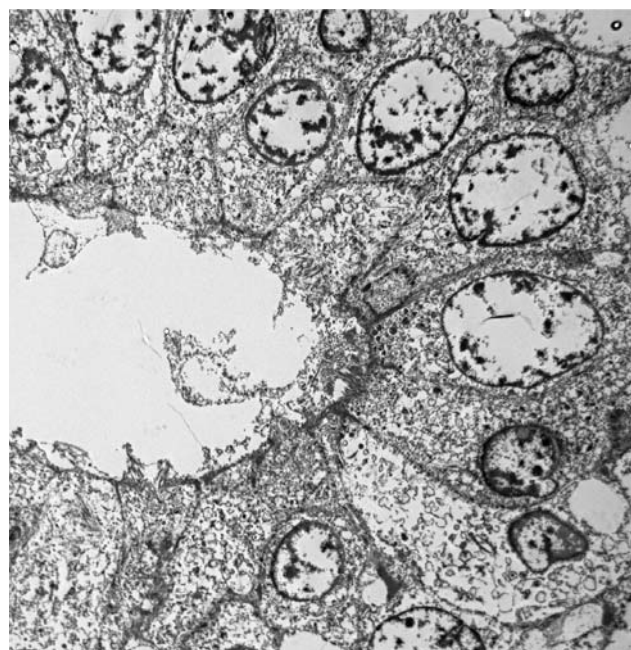


Figure 7. Electron microscopic examination did not reveal zymogen granules in the tumor cells.

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Table II. Immunohistochemical data of ITC.

Authors	PAS-AB	MUC-1	MUC-2	MUC-5AC	MUC-6	CA19-9	CEA	Dupan-2	P53	Chromo-granin	Synapto-physin	Trypsin	Chymo-trypsin	Amylase	Lipase
Ito <i>et al.</i> (7)									+						
Tajiri <i>et al.</i> (8)	–	+	–	–		++	–	+	–	–					
Tajiri <i>et al.</i> (8)	–	+	–	–		+	–	+	–	–					
Tajiri <i>et al.</i> (8)	–	++	–	–		–	–	+	–	–					
Tajiri <i>et al.</i> (8)	–	–	–	–		–	–	–	–	–					
Itatsu <i>et al.</i> (9)		+	–	–					+		–		–		
Thirot-Bidault <i>et al.</i> (10)		+	–	–						–	–	–	–	–	
Hisa <i>et al.</i> (11)		+	–	–	+	+	+		–						–
Oh <i>et al.</i> (12)		+	–	–					+						
Furukawa <i>et al.</i> (13)		–	–	–	+						–	–			–
Terada <i>et al.</i> (14)	–	–	+	++	++	+			+++	+	+	–		–	–
Present case	+	++				+				–	–	–		+	

ITC, Intraductal tubular carcinoma; PAS, periodic acid-Schiff staining; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; –, negative; +, <30% or partially positive; ++, >30%.

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