

Intraductal Tubulopapillary Neoplasms of the Pancreas: Case Report and Review of the Literature

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Abstract

A 69-year-old woman was referred to our hospital after incidental identification of a pancreatic mass during follow-up for diabetes mellitus. Various imaging examinations showed a tumor in the main pancreatic duct, without apparent hypersecretion of mucin. Brush cytologic examination revealed class V disease (adenocarcinoma). Because preoperative examination suggested an intraductal neoplasm with associated invasive cancer, total pancreatectomy was performed. Histological examination, based on current World Health Organization classifications, suggested a diagnosis of intraductal tubulopapillary neoplasm. A small cystic lesion adjacent to the intraductal tubulopapillary neoplasm was incidentally diagnosed as serous cystadenoma. The patient has remained well without recurrence as of 24 months postoperatively. Computed tomography and magnetic resonance imaging of the intraductal tubulopapillary neoplasm suggested ductal cell carcinoma of the pancreas rather than intraductal papillary mucinous neoplasm. Distinguishing intraductal tubulopapillary neoplasm from ductal cell carcinoma is clinically important, as intraductal tubulopapillary neoplasm has a favorable prognosis after curative resection.

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Key words: intraductal tubulopapillary neoplasm, intraductal tubular carcinoma, serous cystic neoplasm, clinicopathological features, imaging diagnosis

Introduction

According to current World Health Organization (WHO) classifications, intraductal neoplasms of the pancreas are classified as intraductal papillary mucinous neoplasms (IPMNs) or intraductal tubulopapillary neoplasms (ITPNs)¹. ITPNs represent a new disease entity for intraductal neoplasms

encompassing intraductal tubular carcinoma (ITC) and are defined as intraductal, grossly visible, tubule-forming epithelial neoplasms with high-grade dysplasia and ductal differentiation without overt production of mucin¹. ITPN is a rare neoplasm accounting for <1% of all pancreatic exocrine neoplasms and only 3% of intraductal neoplasms of the pancreas². The clinicopathological features of ITPN remain unclear. We report a rare case of

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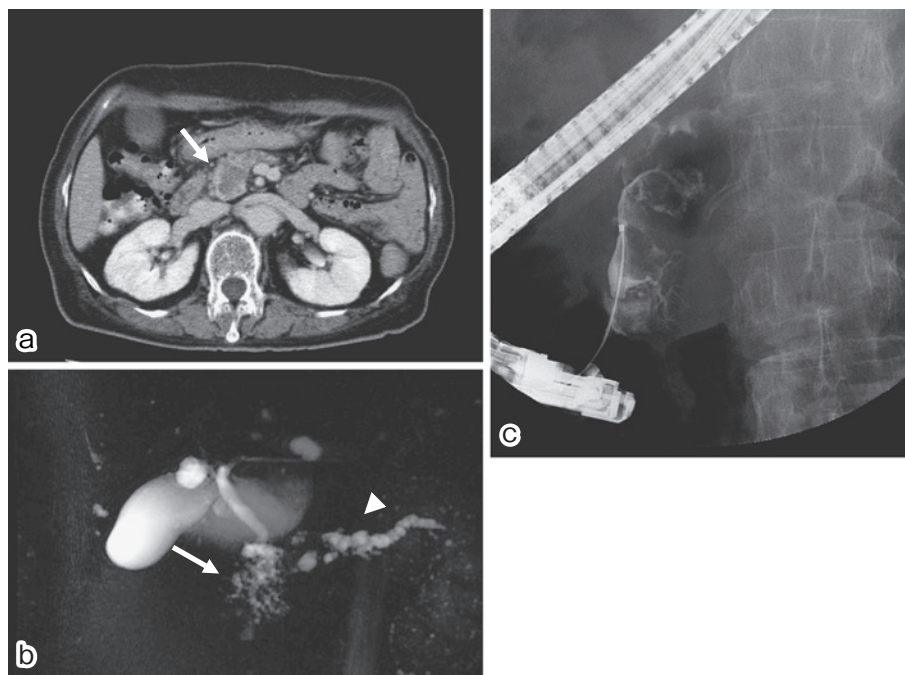


Fig. 1 CT showing a multiloculated hypovascular tumor (**arrow**) in the head of the pancreas (a). MRCP showing a multiloculated hypovascular tumor (**arrow**) in the head of the pancreas and mild dilatation of the MPD in the distal pancreas (**arrowhead**) (b). ERCP showing a large filling defect in the markedly dilated MPD of the head of the pancreas. The upstream MPD is not visualized (c).

ITPN concomitant with serous cyst adenoma (SCA) with a focus on the clinicopathological features.

Case

A 69-year-old woman presented to a local clinic complaining of excessive thirst. Hyperglucosemia was identified, and a pancreatic mass was found on abdominal ultrasonography (US). She was therefore admitted to our hospital for further investigation and treatment. The patient had no notable past history except for diabetes mellitus, and findings on physical examination were unremarkable. Laboratory data, including levels of tumor markers, were within normal limits, with the exceptions of serum glucose (241 mg/dL; normal, 70–109 mg/dL) and hemoglobin A1c (8.2%; normal, <5.8%). Both computed tomography (CT) and magnetic resonance imaging (MRI) showed a multiloculated, hypovascular tumor of the head of the pancreas and mild dilatation of the upstream main pancreatic duct (MPD) in the distal pancreas (**Fig. 1a, b**). Endoscopic US (EUS) showed an isoechoic and hypoechoic tumor

approximately 3 cm in diameter in the head of the pancreas, in addition to the proliferation of low papillary lesions along the dilated MPD in the distal pancreas. The lesion seemed to extend to the tail of the pancreas along the MPD. Endoscopic retrograde cholangiopancreatography (ERCP) revealed no enlargement of the orifice of the papilla of Vater or secretion of mucus. Pancreatography showed a large filling defect in the markedly dilated MPD of the head of the pancreas, and the upstream MPD was not visualized (**Fig. 1c**). The location of the tumor within the MPD or the parenchyma of the pancreas was unclear from the findings of CT and MRI but was strongly suggested by the findings of ERCP and EUS. Brush cytologic examination revealed class V disease (adenocarcinoma). The preoperative clinical diagnosis was intraductal neoplasm with associated invasive cancer. Total pancreatectomy was performed because the findings of intraoperative ultrasonography were identical to those of EUS, namely, papillary lesions along the MPD in the tail of the pancreas. Macroscopic examination showed that a white nodular mass (2 × 2 × 12 cm) had filled the

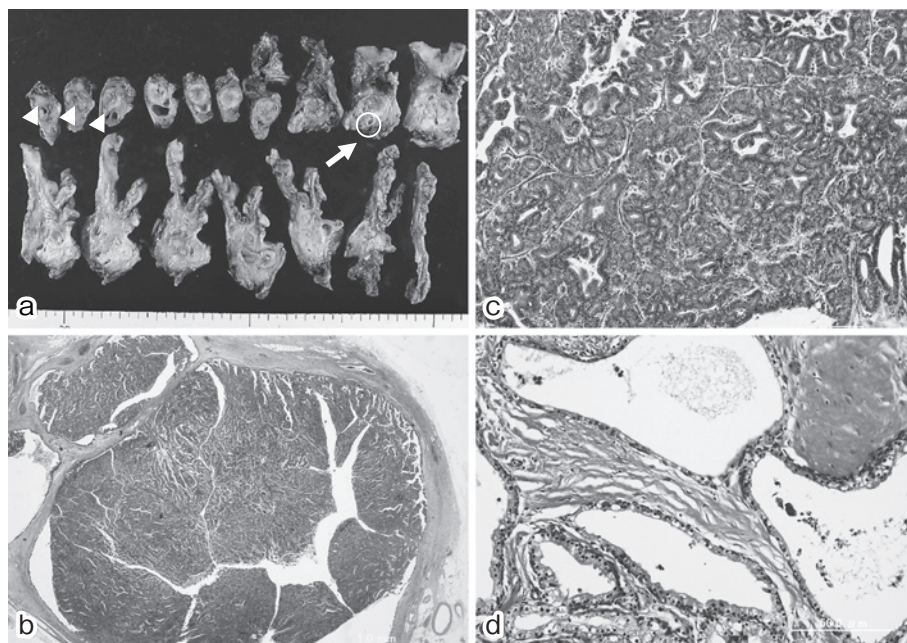


Fig. 2 Macroscopic examination showed a white nodular mass ($2 \times 2 \times 12$ cm) filling the dilated MPD without overproduction of mucin being visible on cross-sections. The mass extended to the tail of the pancreas along the MPD (**arrow heads**). A small cystic lesion (0.3×0.4 cm) adjacent to the white mass was also observed (**circle and arrow**) (a). Basophilic cuboidal cells with tubulopapillary formation closely were packed in the dilated MPD (loupe view, hematoxylin and eosin [HE] stain) (b). The tumor comprises tubular glands of various size with a back-to-back arrangement and was morphologically consistent with carcinoma (low-power view, HE stain) (c). A small cystic lesion consisted of tubular glands of various size with cystic formation and was histologically diagnosed as a serous cystic neoplasm, microcystic SCA (d).

dilated MPD, without overproduction of mucin being visible on cross-sections. The mass extended to the tail of the pancreas along the MPD (**Fig. 2a**). A small cystic lesion was also identified adjacent to the white mass (**Fig. 2a**). Basophilic cuboidal cells with tubulopapillary formations were closely packed in the dilated MPD. The lesion comprised tubular glands of various size with a back-to-back arrangement and was morphologically consistent with carcinoma (**Fig. 2b, c**). Mucous and immunohistochemical examinations revealed positive results for MUC-1, MUC-6, cytokeratin (CK)-7, CK-19, CAM-5.2, carcinoembryonic antigen, and carbohydrate antigen 19-9 but negative results for periodic acid-Schiff, MUC-5AC, CK-20, and trypsin (**Fig. 3a, b, c**). Furthermore, proliferative activity, as determined with the Ki-67 index, was 20% to 30%, with no mutations in exons 12 or 13 of the K-RAS gene². Because results were negative for both MUC-

5AC and trypsin but positive for both MUC-1 and MUC-6 and no K-RAS mutations were detected, the final histological diagnosis based on the current WHO classification system was ITPN with high-grade dysplasia (carcinoma in situ). The small cystic lesion adjacent to the ITPN was histologically diagnosed as a serous cystic neoplasm, microcystic SCA of the pancreas (**Fig. 2d**). Immunohistochemical and mucous results for the SCA revealed sensitivity to diastase-periodic acid-Schiff staining, positive results for MUC-1, MUC-6, CAM-5.2, carbohydrate antigen 19-9, and neuron-specific enolase, and negative results for MUC-5AC and carcinoembryonic antigen. The postoperative course was uneventful. The patient has remained well without any symptoms or recurrence as of 24 months postoperatively.

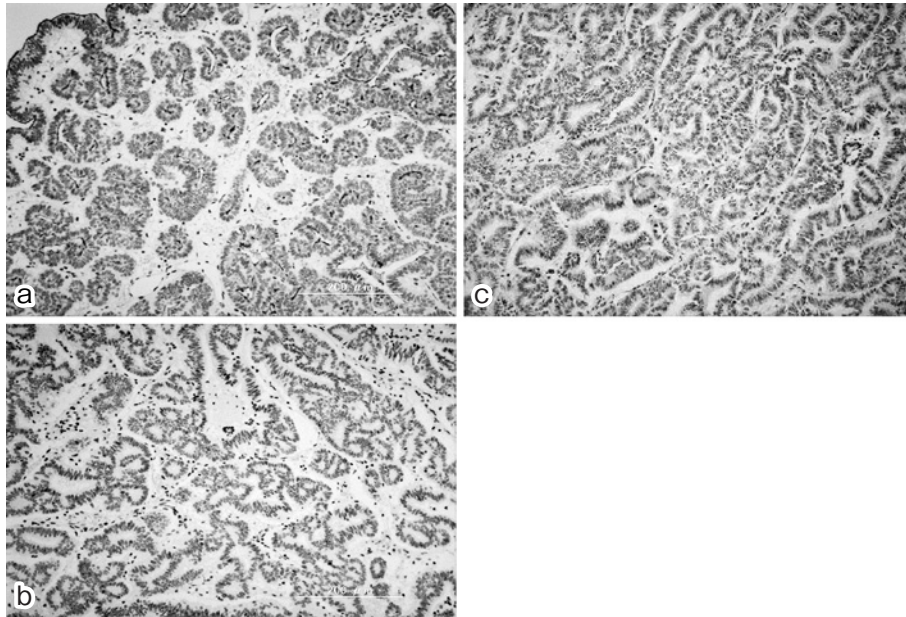


Fig. 3 Immunohistochemical studies of ITPN
 Partial positive results for MUC-1 staining (a).
 Negative results for MUC-5AC staining (b).
 Negative results for trypsin staining (c).

Discussion

The second edition of the Japanese General Rules for the Study of Pancreatic Cancer classifies intraductal tubular neoplasms (ITNs) as intraductal tubular adenomas (ITAs) showing low- or intermediate-grade dysplasia and intraductal tubular adenocarcinomas (ITCs) with high-grade dysplasia³. ITNs with high-grade dysplasia have been reported as ITCs, according to this classification. Several cases with tubulopapillary growth patterns have also been included as ITCs^{4,6}. Esposito et al. have reported an unusual pancreatic tumor with microcystic and tubulopapillary features, named microcystic tubulopapillary carcinoma⁷. On the basis of detailed histopathological and molecular analyses, they suggested that the tumor represented a new disease entity. Königsrainer et al. have also reported an unusual case of intraductal and cystic tubulopapillary adenocarcinoma of the pancreas as a possible variant of ITC⁸. Yamaguchi et al. subsequently reported 10 cases of intraductal neoplasm showing a predominantly tubular growth pattern with a papillary component and advocated

ITPN as a new disease entity for intraductal neoplasms². With this new concept, intraductal neoplasms have been classified as IPMNs and ITPNs in the current WHO classification¹. ITPNs are defined as intraductal, grossly visible, tubule-forming epithelial neoplasms with high-grade dysplasia and ductal differentiation without overt production of mucin¹². Immunohistochemical stains are helpful for diagnosing ITPNs. Although both MUC-1 and MUC-6 are usually expressed, MUC-5AC is a consistent marker of IPMN that is not expressed^{2,9,10}. These patterns of mucus staining represent the characteristic findings for ITPNs and are key points for distinguishing them from IPMNs and ITAs^{9,10}. Molecular analysis of ITPNs has not detected K-RAS mutations². Almost all pathological features of ITPNs are similar to those of ITCs, except for the tubulopapillary growth pattern. ITPN can be considered to represent a new disease entity encompassing ITCs².

A PubMed search of the English-language literature from 1950 to 2011 yielded 19 cases of ITC^{4-9,11-17} and 10 cases of ITPN². The clinical characteristics of these 30 cases (including the present case) of ITC or ITPN were as follows. Mean

age at the time of diagnosis was 56 years (range, 26–84 years), and the male-to-female ratio was 16 : 14. Tumors were in the head of the pancreas in 14 cases, the body in 8, the tail in 2, the head and body in 2, and the whole pancreas in 4 and show a tendency toward greater frequency in the head. Mean tumor size was 5.2 cm (range, 0.8–15 cm) and was relatively large compared with IPMNs and ITAs. Sixteen of the 22 cases produced symptoms, while the remaining 6 cases were asymptomatic and were only incidentally identified. Abdominal pain and discomfort were the most frequent symptoms (11 cases), possibly because ITPNs easily occlude the MPD. All cases but one, which was incidentally diagnosed at autopsy, were treated with surgery (pancreaticoduodenectomy, n=15; distal pancreatectomy, n=10; total pancreatectomy, n=4). Fourteen cases involved noninvasive cancer, 5 cases showed minute parenchymal invasion, and 7 cases had invaded the duodenum or bile duct; no data were available for the remaining 4 cases. In 4 cases (3 invasive cancers, 1 minute invasive cancer), metastases to regional lymph nodes were found. Three patients (2 with invasive cancers, 1 for whom no data were available) died of progression of the ITPN. Because ITPN has often been reported to be a slow-growing tumor^{4,5,9,11,15,17}, its prognosis after surgical resection seems as favorable as that of IPMN.

On the other hand, many authors have reported that preoperative diagnosis is difficult^{12–15,17}. ITN was suspected preoperatively in only 7 cases. In 8 cases, the provisional preoperative diagnosis was IPMN. Although few articles have discussed imaging findings for ITPN, Oh et al.¹⁴ and Ishigami et al.¹⁵ have emphasized upstream dilatation of the MPD as the only important finding differentiating ITPN from IPMN. Downstream dilatation of the MPD generally suggests IPMN caused by hypersecretion of mucin. Regarding CT and MRI findings, Ishigami et al. have reported that ITNs are hypovascular tumors without delayed enhancement¹⁵. Our imaging findings for the present case were compatible with these findings. However, the findings of obstructive upstream dilation of the MPD due to a hypovascular tumor were similar to those of common ductal cell

carcinoma (DCC). Determining with CT and MRI whether the main tumor was within the MPD was difficult in the present case. Therefore, we used ERCP and EUS to confirm the tumor was in the MPD. Because brush cytologic examination revealed adenocarcinoma, we strongly suspected ITPN. Some authors have also reported that EUS and ERCP are useful for detecting intraductal tumors^{12–14}. Ito et al. have reported a case of ITC of the pancreas that was diagnosed preoperatively with transpapillary biopsy¹². Transpapillary biopsy or brush cytologic examination of ITPN may be useful for detecting tumors of the MPD. We believe that ERCP is extremely useful, not only for detecting the tumor, but also for obtaining histological diagnosis.

Another unusual feature of the present case was the presence of both SCA and ITPN, because synchronous SCA and pancreatic neoplasms are rarely reported. Only 4 cases (including the present case) involving intraductal neoplasms have been reported. The 3 cases other than the present case involved concomitant SCA and IPMN^{18–20}. Go et al. have suggested the possibility that similar molecular risk factors are involved in the development of both neoplasms¹⁸. Currently, little evidence is available for determining whether concomitant SCA and IPMN represents an incidental event or are tumors with a common basis, and further investigations are needed¹⁸.

In conclusion, preoperative diagnosis of ITPN can be difficult. Findings of ITPN on CT and MRI sometimes resemble those of DCC rather than those of IPMN. Distinguishing ITPN from both IPMN and DCC is clinically important, because ITPN shows a more favorable prognosis than does DCC after curative resection.

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