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Case Report

A Resected Case of Intraductal Tubulopapillary Neoplasm of the Pancreas: Report of a Case

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The patient was a 61-year-old male who was referred to our hospital after dilatation of the main pancreatic duct was detected by screening ultrasonography. Computed tomography revealed a protruding lesion measuring 15 mm in diameter within the main pancreatic duct in the head of the pancreas, and magnetic resonance cholangiopancreatography revealed interruption of the duct at the tumor site. We performed pancreaticoduodenectomy under a suspected diagnosis of invasive ductal carcinoma. Gross examination of the resected specimen showed that the tumor invaginated into the main pancreatic duct, and no mucin was found. Histological examination revealed proliferation of high-grade dysplastic cells in a tubulopapillary growth pattern. Immunohistochemically, cytokeratin 7 expression was detected, but not trypsin expression. Based on these morphological features, we diagnosed the tumor as intraductal tubulopapillary neoplasm (ITPN). We report the case with bibliographic consideration, together with a review of intraductal neoplasms of the pancreas encountered at our institution.

Key words: Intraductal tubulopapillary neoplasm (ITPN) – Intraductal neoplasms of the pancreas – Pancreaticoduodenectomy

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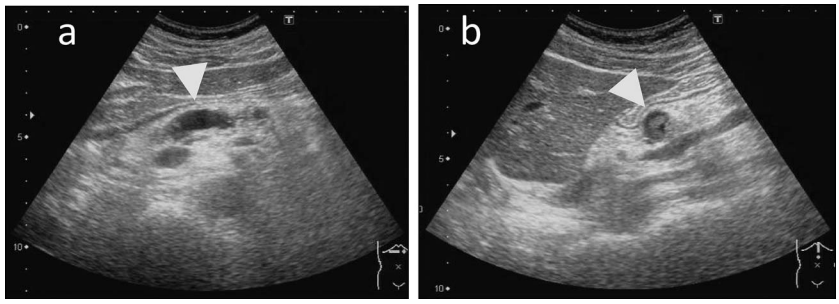

Fig. 1 Abdominal ultrasonography. (a) Dilatation of the main pancreatic duct is seen (arrowhead), ranging from the pancreas body to the pancreas tail. (b) A protruded lesion (arrowhead) measuring 16 mm in diameter is seen within the main pancreatic duct.

Intraductal tubulopapillary neoplasms (ITPN) were first reported in 2009 by Yamaguchi *et al*[1] and were adopted by the WHO classification revised in 2010, as a subclass of intraductal neoplasms of the pancreas, along with intraductal papillary mucinous neoplasm (IPMN). Intraductal tubulopapillary neoplasms are rare, accounting for less than 1% of all pancreatic exocrine neoplasms, and are considered to have a better prognosis than conventional pancreatic cancer.[1] Clinicopathologically, ITPNs have features distinct from those of other intraductal neoplasms of the pancreas. Here, we report on a case of ITPN encountered by us who was treated by resection, along with some bibliographic consideration, as well as present a comprehensive review of intraductal neoplasms of the pancreas encountered at our hospital.

Case Report

A 61-year-old man without any symptoms was detected to have an abnormality in a screening ultrasonography. His past history included hypertension, hyperlipidemia, mitral regurgitation, infective endocarditis, cerebral infarction, appendicitis, and cholecystitis. The screening ultrasonography revealed dilatation of the main pancreatic duct and the patient was referred to our hospital with suspected pancreatic carcinoma. Examination on admission showed that the abdomen was flat, with no tenderness or mass felt on palpation. Blood examination showed no significant abnormalities. Tumor markers were within normal range: CEA 1.9 ng/mL and CA 19-9 30.0 U/mL. Abdominal ultrasonography revealed dilatation of the main pancreatic duct from the body to the tail of the pancreas (Fig. 1a) and a protruded lesion within the main pancreas duct (Fig. 1b). Abdominal computed tomography (CT) revealed, in addition to the dilatation of the main pancreatic duct from the pancreatic body to the tail (Fig. 2a), a mass lesion in the head of the pancreas, which showed persistent enhancement on contrast-enhanced CT (Figs. 2b, 2c). On abdominal magnetic resonance imaging (MRI),

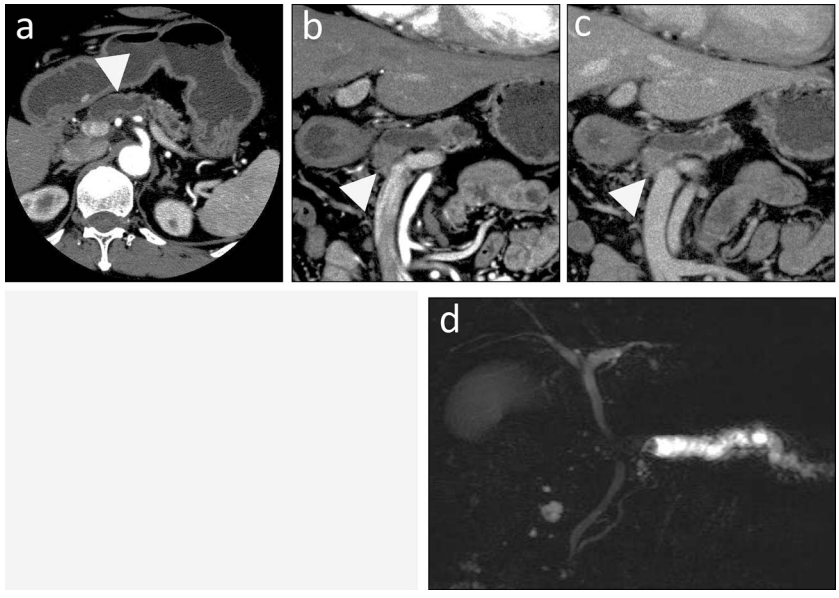

Fig. 2 Abdominal CT and MRCP. (a) CT revealed dilatation of the main pancreatic duct in the region of the body and tail of the pancreas (arrowhead). (b, c) A mass lesion (arrowhead) is seen in the head, which showed persistent enhancement after administration of contrast material. (d) MRCP revealed interruption of the main pancreatic duct at the tumor site, and beaded dilatation of the duct in the region of the body and tail of the pancreas.

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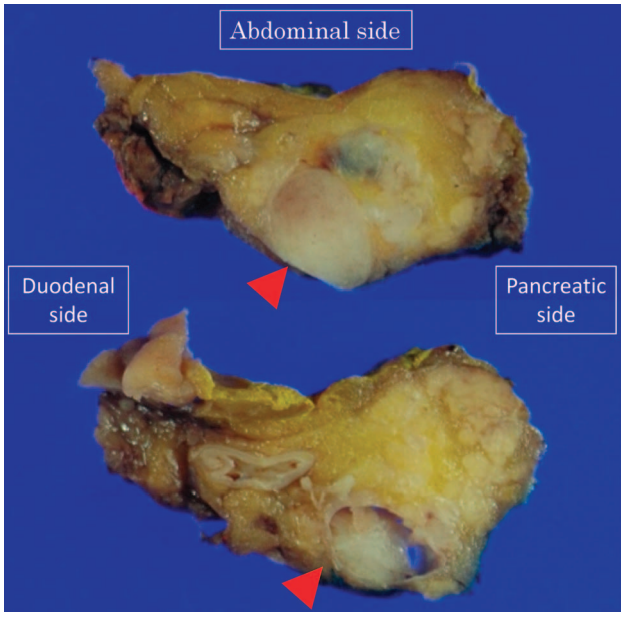

Fig. 3 Gross examination of the resected specimen showed absence of mucin and a solid tumor (arrowhead), measuring 12 × 9 mm, invaginating into the main pancreatic duct.

the mass in the pancreas head was visualized as a low signal intensity on T1-weighted images and a slightly high signal intensity on T2-weighted images. In addition, magnetic resonance cholangiopancreatography (MRCP) revealed interruption of the main pancreatic duct at the tumor site, and beaded dilatation of the duct in the body and tail of the pancreas (Fig. 2d).

Based on the above examination results, we performed subtotal stomach-preserving pancreaticoduodenectomy under the preoperative diagnosis of invasive ductal carcinoma of the pancreas.

Operation

The results of peritoneal washing cytology showed no evidence of malignancy. There was no overt finding of dissemination or hepatic metastasis. Intraoperative ultrasonography showed obstruction of the pancreatic duct by neoplasm. The pancreatic parenchyma was hard in consistency. After checking the pancreatic stump for absence of malignancy by intraoperative rapid diagnosis, we performed subtotal stomach-preserving pancreaticoduodenectomy involving dissection of the regional lymph nodes, in accordance with the operation for conventional pancreatic cancers. Reconstruction was performed by the modified Child procedure.

Resected specimen

Gross examination of the resected specimen showed no mucin and a solid tumor measuring 12 × 9 mm in size invaginating into the main pancreatic duct (Fig. 3). The specimen before formalin fixation contained a dull red elastic-hard tumor, differing in appearance from conventional pancreatic cancers.

Histopathological findings

The tumor was composed of cuboidal uniformly high-grade dysplastic cells proliferating in a tubulopapillary growth pattern (Fig. 4a). Only a small part of the tumor showed interstitial infiltration (Fig. 4b), but there was no vascular invasion, perineural infiltration, or lymph mode metastasis. Immunohistochemically, the tumor cells were positive for cytokeratin (CK)7, and negative for trypsin (Figs. 4c, 4d). Based on these findings, the tumor was suspected as an intraductal neoplasm showing ductal epithelial differentiation. Since the present case showed a predominantly tubular morphology, without any overt production of mucin, we made the final diagnosis of ITPN with an associated invasive carcinoma, on the basis of the WHO classification.

Postoperative course

After the operation, the patient made favorable progress, without complications. He was discharged on the 13th postoperative day. During the 22 months after the surgery, no evidence of recurrence or metastasis was detected.

Discussion

Intraductal tubulopapillary neoplasm is an intraductal neoplasm of the pancreas first reported in 2009 by Yamaguchi *et al*.[1] Intraductal tubulopapillary neoplasm is defined as an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation, without overt production of mucin.[1,2] The neoplasms are rare, accounting for less than 1% of all pancreatic exocrine neoplasms and for approximately 3% of all intraductal neoplasms of the pancreas. Intraductal tubulopapillary neoplasms show no sexual predilection, and are frequently diagnosed in people aged 35 to 84 years (on average, 56 years).[1] The main characteristics of ITPN are as follows: appearance of a solid nodular tumor obstructing

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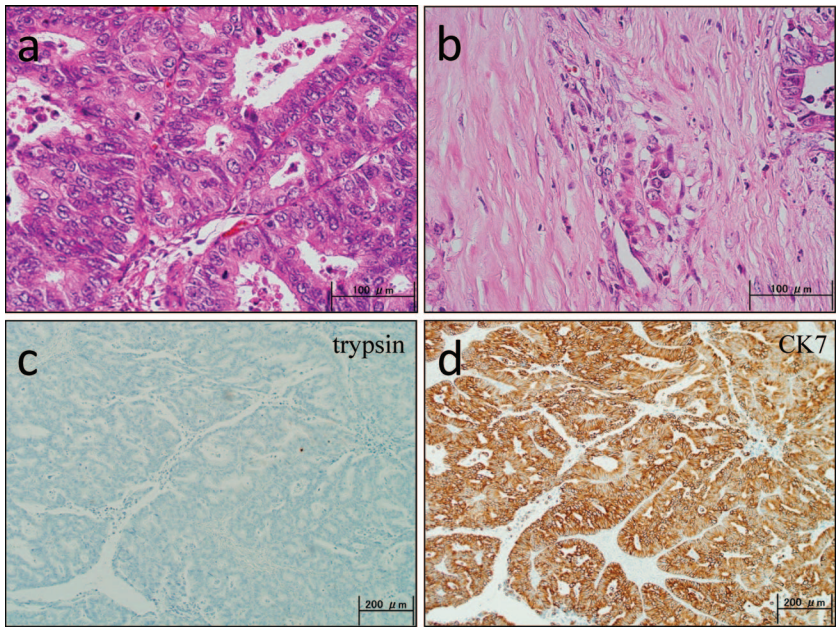

Fig. 4 Histopathological findings. (a) The tumor was composed of cuboidal uniformly high-grade dysplastic cells proliferating in a tubulopapillary growth pattern. (b) Only a small part of the tumor showed interstitial infiltration. (c, d) The tumor cells were positive for CK7, and negative for trypsin.

dilated ducts on macroscopic examination; no visible secreted mucin; tubulopapillary growth; uniform high-grade atypia throughout the neoplasm; easily recognizable necrotic foci; ductal differentiation, as indicated by CK7 and/or CK19 expression; absence of acinar differentiation, as indicated by the absence of trypsin; absence of MUC2, MUC5AC, and fascine; absence of KRAS and/or BRAF mutations.[1]

Molecularly and pathologically, besides the 9 characteristics mentioned above, ITPNs also feature activating mutations of phosphatidylinositol 3-kinase, catalytic, alpha polypeptide (PIK3CA); PIK3CA is a gene encoding the p110α protein of phosphatidylinositol3-kinase (PI3K). Some previous reports show that it is frequently mutated in breast cancer and colon cancer, but rarely mutated in ductal carcinoma, and that only a small number of mutations of this gene are found in IPMN.[3] This evidence suggests that ITPNs are entirely distinct neoplasms from IPMN and ductal carcinoma. For practical purposes, to differentiate ITPNs from IPMNs, which are intraductal pancreatic tumors, we could say that IPMNs feature visibly secreted mucin, MUC5AC expression, and frequent mutations in KRAS. Meanwhile, as for the differential diagnosis, pancreatic intraepithelial neoplasias are different from ITPN in showing papillary growth and, as in the case of IPMNs, featuring MUC5AC expression and mutations in KRAS.[4–7] In the current case, although we did not carry out MUC immunostaining or laboratory studies on KRAS mutations, we arrived at the diagnosis of ITPN mainly based on the macroscopic findings and morphological features.

In clinical diagnosis, imaging findings are important. As for the imaging findings of ITPN, these tumors are visualized as low signal intensities on T1-weighted and as high signal intensities on T2-weighted MR images; dilatation of the pancreatic duct and atrophy of the pancreatic parenchyma in the tail region are frequently seen on contrast-enhanced CT; cork of wine bottle-like tumors protruding into the main pancreatic duct are seen at a high frequency, according to previous reports.[8] Furthermore, with respect to pancreatic tumors showing predominant intraductal growth, tumors such as acinar cell carcinoma[9] and pancreatic endocrine tumor[10] have been reported. However, these tumors can be differentiated from ITPNs by means of immunostaining for CK7 and trypsin. The findings in the present case were not compatible with any of these cases mentioned above.

Furthermore, a case report has recently been found that a diagnosis of ITPN was made by means of endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) biopsy. Furuhata *et al*[11] reported that the large cribriform and tubular clusters with luminal spaces containing wispy mucin were considered to be diagnostic clues for the cytologic diagnosis of ITPN by EUS-FNA. Immunohistochemistry of MUC1, MUC6, and MUC5AC for cell-block preparation appears to be a useful adjunctive tool to confirm the diagnosis.

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Table 1 Clinicopathological features of the cases of ITPN encountered at our institution

Case	Age, y	Sex	Symptom	Location	Operation	Tumor size, mm	Invasion	LN metastasis	Prognosis
1	61	M	Free	H	SSPPD	12	Yes	No	Alive (22 mo)
2	75	F	Free	B	DP	100	Yes	No	Alive (51 mo)
3	67	M	Anemia	HBT	TP	65	Yes	Yes	Alive (84 mo)

B, body; DP, distal pancreatectomy; F, female; H, head; HBT, head, body, and tail; M, male; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; TP, total pancreatectomy.

We conducted a retrospective review of the resected cases of intraductal pancreatic tumors at our institution; there were a total of 116 cases from 2000 to 2012. For intraductal papillary mucinous carcinomas (IPMCs) of the pancreatobiliary type and oncocytic type, these tumors are reported to be characterized by a nodular growth pattern seen within the main pancreatic duct.[12] Differential diagnosis using a combination of both macroscopic and histological findings led to the diagnosis of ITPN in 3 cases, including the current case. Cases of ITPN accounted for 2.6% of all the cases of intraductal pancreatic tumors, which is in close agreement with the incidence mentioned above. Table 1 shows the clinicopathological features of the 3 ITPN cases that we encountered at our institution. We shall make a brief mention about the 2 cases other than the current case. One patient was a 75-year-old woman with a tumor obstructing the main pancreatic duct on macroscopic examination of a surgically resected specimen. The tumor cells showed uniform high-grade dysplasia and tubulopapillary growth. Immunostaining showed a negative result for MUC5AC expression, based on which we made the diagnosis of ITPN. At present, 4 years after the surgery, she remains alive without any signs of recurrence. The other patient was a 67-year-old man; this was a case of intraductal tubular carcinoma (ITC) previously reported by us.[13] At present, 7 years after the surgery, this patient also remains alive without any signs of recurrence. According to the Japanese General Rules for the Study of Pancreatic Cancer, ITC is classified as an intraductal tubular neoplasm of the pancreas, but is considered to be a tubular component-dominant variant of ITPN in WHO classification.

Regarding the prognosis of ITPN, according to Yamaguchi *et al*, out of the 10 ITPN cases in their series, 3 had invasive cancer and 7 had noninvasive cancer. Nine of the 10 cases survived for more than 7 months after surgery. As a result, Yamaguchi *et al* reported that patients with ITPNs have a better prognosis than patients with invasive pancreatic cancers.[1] The remaining case involved a 15-cm large tumor occupying the whole pancreas, and total pancreatectomy was performed. Seven months after the surgery, the patient died of multiple hepatic metastases.[1] In regard to the 3 ITPN cases that we encountered at our hospital, all the patients remain alive without any signs of recurrence. Of these cases, one case has shown a long survival of more than 3 years.

According to the recent reports on ITPNs, Kasugai *et al* studied 30 cases previously reported as diagnoses of ITPNs or ITCs, including their own cases. As a result, they reported that the mean age at diagnosis was 56, the male-to-female ratio was 16:14, the tumors tend to be predominantly localized in pancreatic heads, and that the most frequent symptoms were abdominal pain and abdominal discomfort. Of the 30 cases reported, 14 cases involved noninvasive cancer, 5 cases showed minute parenchymal invasion, and 7 cases had invaded the duodenum or bile duct. In 4 cases (3 invasive cancers, 1 minute invasive cancer), metastases to regional lymph nodes were found.[14]

Many other reports showed clinicopathologically characteristic cases. As clinically characteristic cases, Kasugai *et al* reported a case with concomitant serious cyst adenoma (SCN), and asserted that with only 3 cases involved concomitant SCA and IPMN in the previous reports, little evidence is available for determining whether concomitant SCA and IPMN represents an incidental event or are tumors with a common basis, and that further investigations are needed.[14] Furthermore, Bhuva *et al* reported on ITPN—which, after radiotherapy for Hodgkin's lymphoma, developed in the irradiated fields—and asserted that long-term follow-up is important as second malignancies are increasingly a risk as survival rates following curative therapy for Hodgkin's disease improve.[15] Meanwhile, as a case showing pathological characteristics, Jokoji *et al*[16] reported on ITPN with stromal osseous and cartilaginous metaplasia, and mentioned the possibility that there is some connection between the formation of metaplastic osseous and cartilaginous stroma, tumor invasion, and intraductal tumor growth. Ahls

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et al[17] reported on ITPN with clear cell morphology for the first time. As described above, regarding ITPN, cases with a variety of clinicopathological features have been reported so far. It is essential to accumulate further cases and study them with a focus on clinicopathological features and prognosis.

Conclusion

We reported a case of ITPN that was treated by resection, together with a review of the intraductal pancreatic tumors encountered at our hospital. As underlined in the current case, for a tumor that is apparently adherent to the pancreatic duct, we should bear in mind the possibility of ITPN while making a preoperative diagnosis. It is essential to accumulate further cases, clarify the clinicopathological features, and then examine the options for treatment.

References

1. Yamaguchi H, Shimizu M, Ban S, Koyama I, Hatori T, Fujita I, Yamamoto M *et al*. Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2008;**33**(8):1164–1172
2. Tajiri T, Tate G, Inagaki T, Kunimura T, Inoue K, Mitsuya T *et al*. Intraductal tubular neoplasms of the pancreas: histogenesis and differentiation. *Pancreas* 2005;**30**(2):115–121
3. Yamaguchi H, Kuboki Y, Hatori T, Yamamoto M, Shiratori K, Kawamura S *et al*. Somatic mutations in PIK3CA and activation of AKT in intraductal tubulopapillary neoplasms of the pancreas. *Am J Surg Pathol* 2011;**35**(12):1812–1817
4. Recavarren C, Labow DM, Liang J, Zhang L, Wong M, Zhu H *et al*. Histologic characteristics of pancreatic intraepithelial neoplasia associated with different pancreatic lesions. *Hum Pathol* 2011;**42**(1);18–24
5. Matsuyama M, Kondo F, Ishihara T, Yamaguchi T, Ito R, Tsuyuguchi T *et al*. Evaluation of pancreatic intraepithelial neoplasia and mucin expression in normal pancreata. *J Hepatobiliary Pancreat Sci* 2012;**19**(3):242–248
6. Tanaka M, Chari S, Adsay V, Castillo FC, Falconi M, Shimizu M *et al*. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 2006;**6**(1–2): 17–32
7. Yanagisawa A, Ohtake K, Ohashi K, Hori M, Kitagawa T, Sugano H *et al*. Frequent c-Ki-ras oncogene activation in mucous cell hyperplasias of pancreas suffering from chronic inflammation. *Cancer Res* 1993;**53**(5):953–956
8. Motosugi U, Yamaguchi H, Furukawa T, Ichikawa T, Hatori T, Fujita I *et al*. Imaging studies of intraductal tubulopapillary neoplasms of the pancreas: 2-tone duct sign and cork-of-wine-bottle sign as indicators of intraductal tumor growth. *J Comput Assist Tomogr* 2012;**36**(6):710–717
9. Imamura M, Kimura Y, Ito H, Nobuoka T, Koito K, Sasaki A *et al*. Acinar cell carcinoma of the pancreas with intraductal growth: report a case. *Surg Today* 2009;**39**(11):1006–1009
10. Yazawa N, Imaizumi T, Okada K, Matsuyama M, Dowaki S, Tobita K *et al*. Nonfunctioning pancreatic endocrine tumor with extension into the main pancreatic duct: report a case. *Surg Today* 2011;**41**(5):737–740
11. Furuhata A, Minamiguchi S, Mikami Y, Kodama Y, Sumiyoshi S, Adachi S *et al*. Intraductal tubulopapillary neoplasm with expansile invasive carcinoma of the pancreas diagnosed by endoscopic ultrasonography-guided fine needle aspiration: a case report. *Diagn Cytopathol* 2014;**42**(4):314–320
12. Sanada Y, Kunita S, Yoshida K. Comparison of histologic subtype and growth pattern in intraductal papillary-mucinous carcinoma of the pancreas. *Oncol Rep* 2008;**19**(6):1435–1443
13. Hioki M, Nakagohri T, Ikumoto T, Gotohda N, Takahashi S, Konishi M *et al*. Intraductal tubular carcinoma of the pancreas: case report with review of literature. *Anticancer Res* 2010; **30**(11):4435–4442
14. Kasugai H, Tajiri T, Takehara Y, Mukai S, Tanaka J, Kudo SE. Intraductal tubulopapillary neoplasms of the pancreas: case report and review of the literature. *J Nippon Med Sch* 2013; **80**(3):224–229
15. Bhuva N, Wasan H, Spalding D, Stamp G, Harrison M. Intraductal tubulopapillary neoplasm of the pancreas as a radiation induced malignancy. *BMJ Case Rep* 2011;2011
16. Jokoji R, Tsuji H, Tsujimoto M, Shinno N, Tori M. Intraductal tubulopapillary neoplasm of pancreas with stromal osseous and cartilaginous metaplasia; a case report. *Pathol Int* 2012; **62**(5):339–343
17. Ahls MG, Niedergethmann M, Dinter D, Sauer C, Lüttges J, Post S *et al*. Case report: intraductal tubulopapillary neoplasm of the pancreas with unique clear cell phenotype. *Diagn Pathol* 2014;**9**:11

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