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CASE REPORT

An extremely rare case who underwent total remnant pancreatectomy due to recurrent pancreatic metastasis of intraductal tubulopapillary neoplasm

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Abstract
We describe a rare case of recurrent pancreatic metastasis of intraductal tubulopapillary neoplasm (ITPN). A 53-year-old woman diagnosed with an intraductal papillary mucinous neoplasm (IPMN) and a pancreatic ductal adenocarcinoma (PDAC) of the pancreatic body underwent a distal pancreatectomy. The tumor was composed of cuboidal, high-grade dysplastic cells proliferating in a tubulopapillary growth pattern without mucin production; hence, the final diagnosis was ITPN. A follow-up computed tomography scan revealed an enhanced 2 cm mass of the pancreatic head 3 years after the surgery. From workup investigations, the patient was diagnosed with PDAC or a recurrent ITPN of the remnant pancreas. A total remnant pancreatectomy was then performed. Histopathological findings revealed that the new ITPN had the same features as the prior ITPN. In IPMNs, the presence of an invasive component and high-grade dysplasia can lead to progression to a recurring IPMN and the development of PDAC. Because there have been few reports of recurrent ITPN developing into PDAC, the risk factors for ITPN have not been investigated. Because of the uncertain clinicopathological characteristics of ITPN, more data should be gathered to assess the long-term outcome and malignant potential of ITPN.

Keywords Intraductal tubulopapillary neoplasm · Pancreatic intraductal neoplasm · Tubulopapillary growth · Recurrence

Introduction

In the 2010 World Health Organization classification, intraductal neoplasms of the pancreas are divided into two subtypes: intraductal papillary mucinous neoplasms (IPMNs) and intraductal tubulopapillary neoplasms (ITPNs) [1]. IPMNs are characterized by mucin production, various grades of cellular atypia, and papillary architecture. Invasive IPMNs with lymph node metastases and positive margins of the resected specimens, especially in IPMNs involving the main duct, can recur after partial pancreatectomy procedures [2]. ITPNs are also characterized by tumor cells with no clinically evident mucin production, high-grade cellular atypia, and tubulopapillary growth [3]. However, there have been no reports about recurrent remnant pancreatic metastasis after surgical resection of ITPNs. Here, we report an extremely rare case of an ITPN of the pancreas with postoperative recurrence 3 years after distal pancreatectomy.

Case report

A 53-year-old woman presented with a 5-day history of left flank pain and vomiting. She came to our hospital complaining of worsening left flank pain and abdominal distension. Initially, her laboratory data were almost within the normal range, except that her C-reactive protein level was elevated (3.3 mg/dL), serum and urine amylase were elevated (1704 and 11,386 U/L, respectively), and other serum pancreatic enzymes—including trypsin, phospholipase-A2, elastase-1, and lipase—were highly elevated at 900 ng/mL, 5210 ng/dL, 1900 ng/dL, and 2460 U/L, respectively. Contrast-enhanced computed tomography (CT) revealed that a 2 cm, low-density mass was located in the body of the pancreas,

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and the peripheral side of the main pancreatic duct (MPD) was dilated with cystic formations (Fig. 1a). Based on these findings, the patient was primarily diagnosed with acute obstructive pancreatitis owing to any pancreatic neoplasms. We abandoned endoscopic retrograde cholangiopancreatography, intraductal ultrasonography, and endoscopic ultrasound-guided fine needle aspiration due to the symptomatic pancreatitis. However, magnetic resonance cholangiopancreatography also showed disruption of the MPD at the tumor site, dilatation of the peripheral MPD, and gigantic pancreatic cysts (Fig. 1b). Therefore, the patient was diagnosed with pancreatic ductal adenocarcinoma (PDAC) of the pancreatic body with an IPMN, and we performed a distal pancreatectomy with a radical lymphadenectomy as a curative treatment for PDAC. A gross examination of the specimen showed no mucin and a solid tumor measuring 15 × 10 mm invaginating the MPD (Fig. 2). There was dilatation of the MPD and multiple cysts with severe inflammation located in the pancreatic tail (Fig. 2). The MPD and the branches of the pancreatic ducts were replete with tumor cells (Fig. 3a). The tumor was composed of cuboidal, high-grade dysplastic cells that proliferated in a tubulopapillary growth pattern (Fig. 3b); however, there was no mucin production (Fig. 3c), vascular invasion, perineural infiltration, or lymph node metastasis. An immunohistochemical examination was performed, as described elsewhere, indicating that the tumor cells were positive for MUC1 and CK7, but negative for MUC2 and MUC5AC (Fig. 3d–g). The tumor was focally positive for MUC6 (Fig. 3h). There was dilatation of the peripheral MPD and multiple pancreatic cysts with severe inflammation. However, there was no IPMN component in the epithelia of the pancreatic cysts. These features led to the final diagnosis of ITPN with noninvasive adenocarcinoma of the pancreas, as well as cystic formation of the distal pancreatic ducts due to intraductal growth of ITPN. This phenomenon might have led to preoperative misdiagnosis of IPMN. The surgical margin of the pancreatic

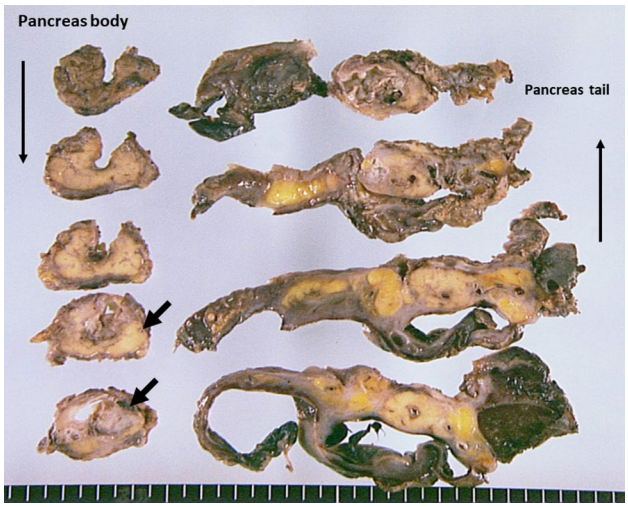

Fig. 2 Macroscopic findings of resected primary specimens. The gross examination showed no mucin and a solid tumor measuring 15 × 10 mm in size invaginating into the MPD (black arrows)

head side was negative, and there was an 8 mm MPD margin from the proximal side of the intraductal tumor spread. And there were any other independent multifocal ITPN lesions in all thin slice of the specimen. This patient was discharged from the hospital on postoperative day 12 without any complications, and she was followed up for 3 years without any adjuvant chemotherapies after the ITPN was resected. A CT scan taken 2 years after the first operation is shown as Fig. 4. We could not detect any obvious tumor lesions, except for the dilatation of the remnant MPD.

However, a follow-up CT scan 3 years after the first operation revealed an enhanced 2 cm mass of the pancreatic head (Fig. 5a). In addition, this tumor showed high intensity in magnetic resonance imaging with T2 weighted sequences (Fig. 5b). Positron emission tomography CT also revealed that the maximum standardized uptake

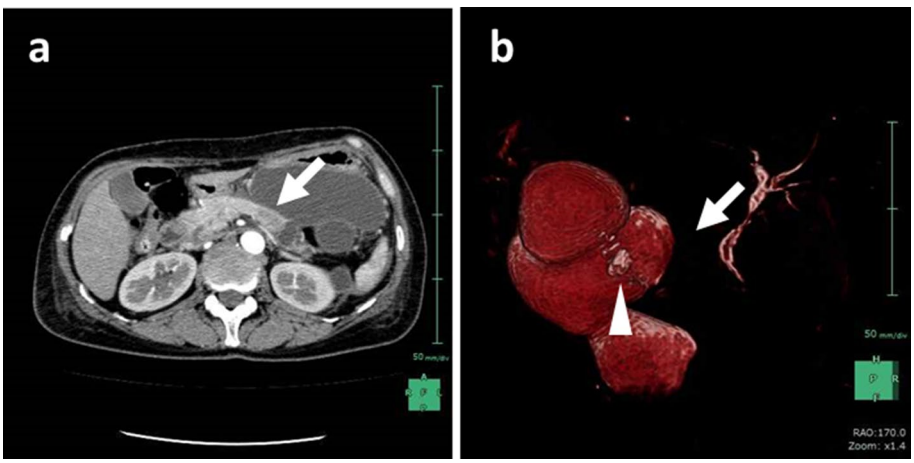

Fig. 1 Findings of abdominal CT and MCRP. **a** A contrast-enhanced computed tomography (CT) revealed the 2-cm low-density mass located at the pancreas body (white arrow). **b** A magnetic resonance cholangiography (MRCP) also showed that interruption and of the main pancreatic duct (MPD) (white arrow) and dilatation of the peripheral MPD dilatation (white triangle)

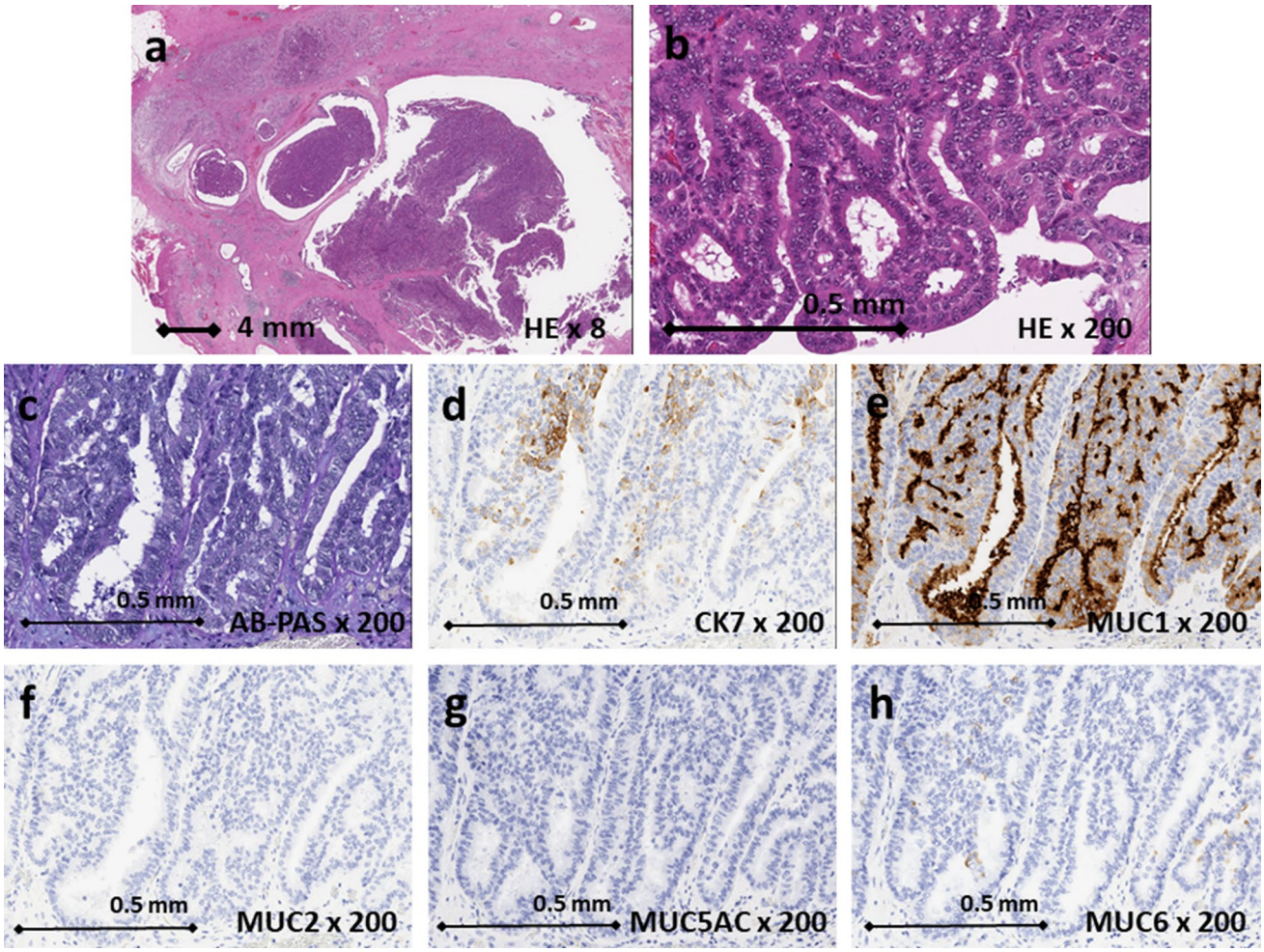

Fig. 3 Histopathological findings of resected primary specimens. **a** A low-magnification image revealed that the MPD and the branches of the pancreatic ducts were replete with tumor cells. **b** A high-magnification image revealed that the tumor was composed of solid proliferating tumor cells with tubular or papillary formation with high-grade dysplasia. **c** An AB-PAS stain showed no mucin production from tumor cells. **d** Tumor cells were positive for CK7. **e** Tumor cells were positive for MUC1. **f** Tumor cells were negative for MUC2. **g** Tumor cells were negative for MUC5AC. **h** Tumor cells were focally positive for MUC6

value of this tumor was 3.6 (Fig. 5c). From these workup investigations, the patient was diagnosed with PDAC or a recurrent pancreatic metastasis of ITPN of the remnant pancreas without any lymph node or distant metastasis; therefore, we performed a total remnant pancreatectomy. The gross examination of the specimen showed no mucin and a solid tumor measuring 20 × 15 mm (Fig. 6). The tumor was also composed of cuboidal, high-grade dysplastic cells proliferating in a tubulopapillary growth pattern without mucin production, as was the case with the earlier tumor (Fig. 7a–c). The tumor did not spread to extraductal tissue, and there was a 6 mm MPD margin from the pancreatic stump. The immunohistochemical results of the tumor cells showed that they were positive for MUC1 and CK7 but negative for MUC2 and MUC5AC, the same as the previous ITPN (Fig. 7d–g). The recurrent tumor was scatteredly positive for MUC6, and the positive result was stronger than that of the primary tumor (Fig. 7h); therefore, these features also led to the final diagnosis of a recurrent pancreatic metastasis of ITPN without an invasive component. And there were also any other independent multifocal ITPN lesions, as well as the earlier tumor.

To compare the molecular characteristics of these two ITPNs, we performed a laser micro-dissection using formalin-fixed paraffin embedded specimens, and molecular analyses were conducted to determine whether there were any somatic mutations in the *TP53, PIK3CA, KRAS, BRAF*, or *GNAS* genes, but there were no mutations found in either tumor. This patient received regular follow-ups after a total remnant pancreatectomy without local or distant recurrences for 4 years.

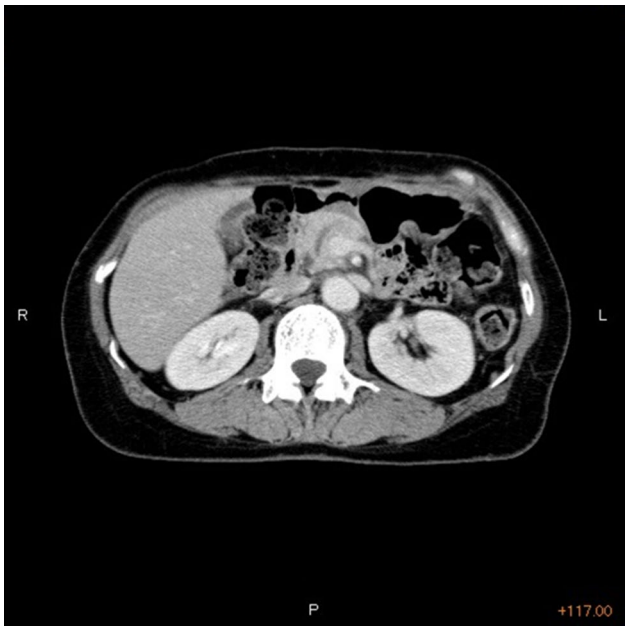

Fig. 4 A contrasted CT findings at 2 years after first operation. A CT scan revealed the dilatation of the remnant MPD, but there was no obvious tumor

Discussion

An ITPN is an intraductal neoplasm of the pancreas and was first reported by Yamaguchi et al. [3] in 2009. ITPNs are defined as intraductal, grossly visible, tubule-forming, epithelial neoplasms with high-grade dysplasia and ductal differentiation and without overt production of mucin [1, 4]. ITPNs are rare, accounting for less than 1% of all pancreatic exocrine neoplasms and approximately 3% of all intraductal neoplasms of the pancreas [5]. Regarding their immunohistochemical characteristics, ITPN tumor cells are positive for MUC1, CK7, and/or CK19, but negative for MUC2 and MUC5AC [1, 6]. The present case demonstrated all of the important histopathological characteristics of an ITPN. According to the molecular features of ITPNs, some cases harbor somatic mutations in the *PIK3CA* and *BRAF* genes [7, 8]; however, neither the incipient nor recurrent specimens in this case harbored any somatic mutations in *TP53, PIK3CA, KRAS, BRAF*, or *GNAS*. Using a histopathological comparison, we could not detect whether these tumors had the same biological origin, although they had very similar histopathological characteristics. In a recent study, Basturk et al. [9] reported that loss of CDKN2A, mutations of certain chromatin remodeling genes and genes associated

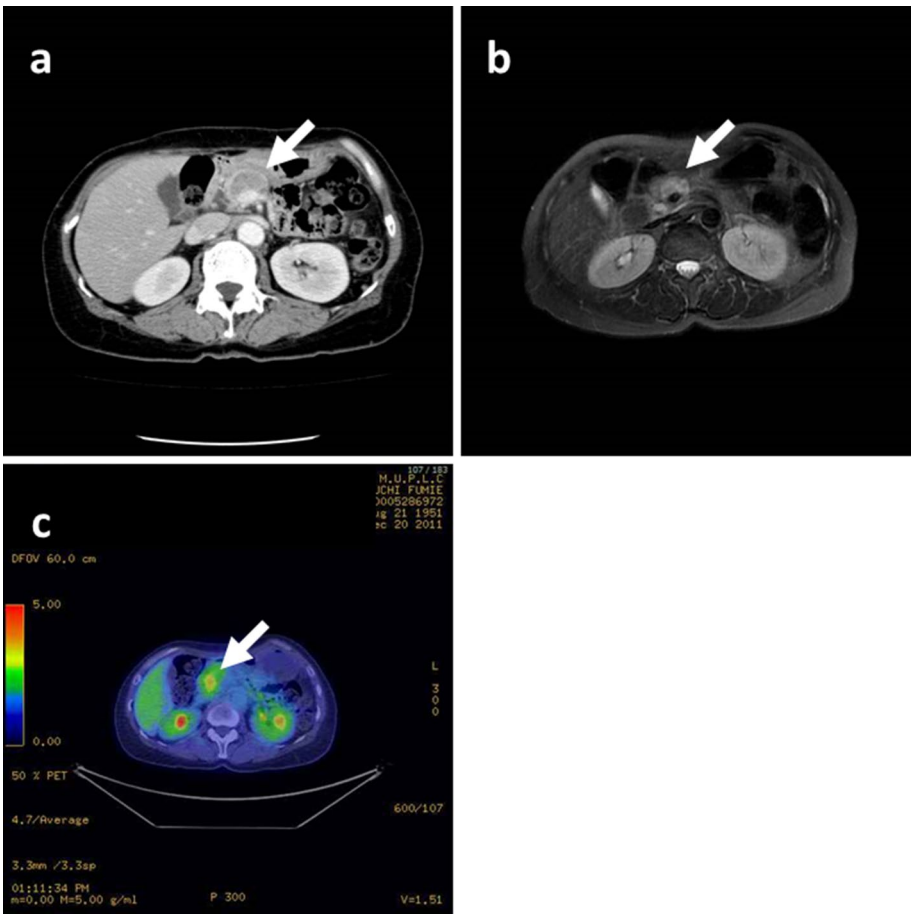

Fig. 5 Image findings at recurrence of ITPN. **a** A contrast-enhanced CT scan revealed an enhanced 2 cm mass of the pancreatic head (white arrow). **b** The tumor showed high intensity in magnetic resonance imaging with T2 weighted sequences (white arrow). **c** A positron emission tomography CT also revealed that the maximum standardized uptake value of this tumor was 3.6 (white arrow)

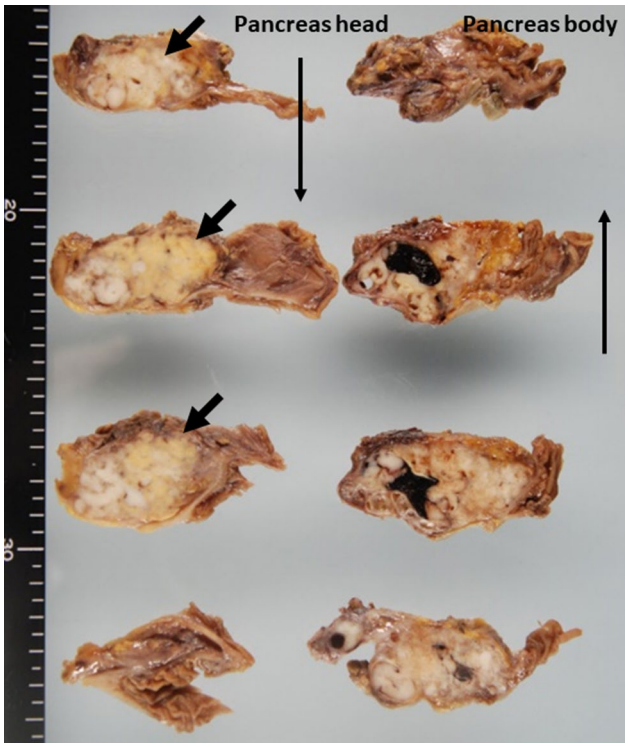

Fig. 6 Macroscopic findings of the recurrent tumor. The gross examination of the specimen showed no mucin and a solid tumor measuring 20×15 mm in size (black arrows)

with the phosphatidylinositol 3-kinase pathway (including PIK3CA), and FGFR2 fusions have been newly discovered as genetic characteristics of ITPN. Because some of these mutated genes are detectable, functional studies are warranted to clarify the roles and consequences of these gene alterations in ITPN.

IPMNs are often compared to ITPNs. They are both intraductal and have the ability to become invasive. In terms of their intraductal epithelial characteristics, ITPNs show uniform, high-grade atypia, whereas IPMNs have a more variable expression of cells with low- to high-grade atypia [1, 3]. Considering the malignant potential of high-grade atypia, one would think that ITPNs would tend to recur after surgery, but there are no reports of recurrent ITPNs of the remnant pancreas after surgery. In IPMNs, neoplasms with an invasive component become recurrent and develop into PDAC and noninvasive IPMNs with high-grade dysplasia [2]. There is ongoing debate concerning whether it is necessary to achieve a negative surgical margin during the excision of an ITPN. Because there have been few reports of recurrent ITPNs developing into PDAC, the risk factors for this phenomenon have not been investigated [10]. Kölby et al. [11] found that the Ki-67 labeling index and size of the tumor could be used as predictive factors for invasiveness; however, invasiveness has not been found to be an independent risk factor for recurrence in ITPNs. Because of the uncertain clinical behaviors and pathological characteristics of ITPNs, more data will be needed in the near future to assess the long-term outcome of ITPNs and to develop appropriate therapeutic strategies.

For metachronous pancreatic disease following surgical resection of ITPN, 4 distinct mechanisms are conceivable: a tumor-cell positive transected section, intraparenchymal spread, independent multifocal lesions, and intrapancreatic micrometastasis [12, 13]. In this case, both the original tumor and the recurrent tumor had very similar clinical features, such as dilatation of the MPD and hypovascular lesions revealed by enhanced CT. In addition, the original tumor and the recurrent tumor had almost identical histopathological and genetic characteristics, except in terms of MUC6 staining. Because all surgical margins were histopathologically negative and there were no independent multifocal ITPN lesions in either tumor, we suggested that intrapancreatic micrometastasis had already occurred before the first operation and that the micrometastasis grew slowly over several years.

To the best of our knowledge, there are no consensus or inclusion criteria concerning adjuvant chemotherapy after radical resection for IPTN. Date et al. [6] reported an overall 5-year survival rate of 81.5% in patients with an invasive component; therefore, even when ITPNs have an invasive component, they are potentially curable by radical surgical resection [6]. No concise review has been published providing statistics on the results of the prognostic factors of ITPNs, such as tumor diameter, the existence of an invasive component, or lymph node metastasis. Because no extraductal invasive component of tumor cells was observed in this patient, we did not administer adjuvant chemotherapy because a long prognosis was expected.

In conclusion, this is a rare case of an ITPN of the pancreas with postoperative recurrence 3 years after a distal pancreatectomy. Recurrent pancreatic metastasis of an ITPN is very rare. We could not detect whether the tumors had the same biological origin or heterochronous and individual origins. In the newest investigation, *FGFR2, BAP1*, and *BRCA2* will be potential target genetic alterations in the development of ITPNs [9]; hence, further analyses of these genetic alterations in biologically distinct pathways will likely shed new light on the mechanisms of ITPN formation, its development into PDAC, and new therapeutic targets for patients with ITPN [3, 6].

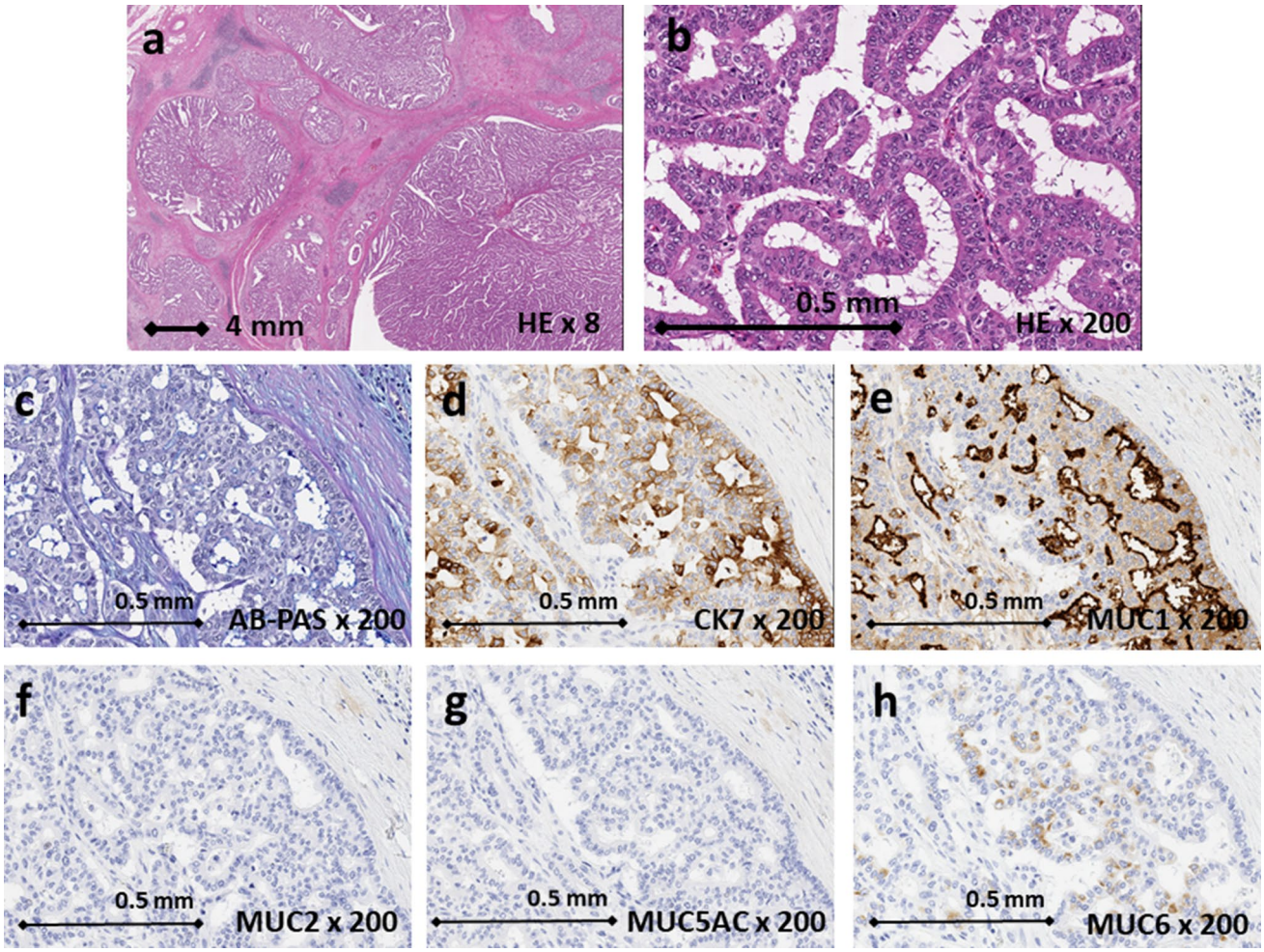

Fig. 7 Histopathological findings of the recurrent tumor. **a** The tumor was composed of cuboidal, high-grade dysplastic cells proliferating in a tubulopapillary growth pattern without mucin production. **b** A high-magnification image revealed that the tumor was composed of solid proliferating tumor cells with tubular or papillary formation with high-grade dysplasia

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Compliance with ethical standards

Conflict of interest Akira Umemura and all the co-authors have no conflict of interest.

Human/animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed consent Informed consent was obtained from the patient for being included in the study.

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