Int J Clin Exp Pathol 2019;12(3):1041-1046
www.ijcep.com /ISSN:1936-2625/IJCEP0090309

Case Report

Intraductal tubulopapillary neoplasm (ITPN) of the pancreas with invasive cancer misdiagnosed as a mesenteric cyst for 12 years: a case report and literature review

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Received December 23, 2018; Accepted January 22, 2019; Epub March 1, 2019; Published March 15, 2019

Abstract: Introduction: An intraductal tubulopapillary neoplasm (ITPN) depicts a distinct entity in the subgroup of premalignant epithelial tumors of the pancreas. Due to the rarity of ITPN, information regarding the disease is currently limited. We present herein a case of pancreatic ITPN with invasive cancer that was misdiagnosed as a mesenteric cyst during a 12-year follow-up period. Case report: A 23-year-old female initially presented with an incidental asymptomatic 4-cm retroperitoneal cystic lesion in 2005. For 12 years of surveillance, the lesion remained largely unchanged in size (4-5 cm). In 2017, the cystic lesion was found to have grown to 9 cm. The pre-operative diagnosis was highly suggestive of a benign lesion. However, after total resection of the mass was performed, the final diagnosis was pancreatic ITPN with invasive cancer. The patient recovered uneventfully and is disease-free without recurrence at the time of this report (12 months post-surgery). Conclusion: The clinicopathologic features of ITPN remain unclear due to its rarity, thus making diagnosis difficult. Clinicians should always consider the possibility of ITPN for cystic lesions located at the retroperitoneum near the tail of the pancreas. More data are needed to understand the disease's long-term outcome to identify clinical and radiological features that can be useful for its diagnosis.

Keywords: Intraductal tubulopapillary neoplasm, pancreas, mesenteric cyst

Introduction

An intraductal tubulopapillary neoplasm (ITPN) is an intraductal neoplasm of the pancreas that was first reported in 2009 by Yamaguchi et al. [1]. In 2010, the World Health Organization recognized ITPNs of the pancreas as a distinct entity included in the subgroup of premalignant epithelial tumors of the pancreas. ITPNs are defined as an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt mucin production [2]. It is a rare primary pancreatic tumor, and accounts for approximately <1% and 3% of all cases of pancreatic exocrine tumor and pancreatic intraductal neoplasm, respectively [1]. It usually appears as a solid mass obstructing the main pancreatic duct, thereby causing upstream duct dilation. Due to the rarity of ITPN, information regarding the disease is currently limited, which leads to the difficulty of accurately recognizing this disease prior to its pathologic diagnosis. In this context, we present a case of pancreatic ITPN with invasive cancer that was misdiagnosed as a mesenteric cyst over a 10-year follow-up.

Case report

A 23-year-old female initially presented with an incidental asymptomatic 4-cm retroperitoneal cystic lesion in 2005. The patient did not exhibit any significant findings on physical examination. The results of laboratory analysis including alpha fetoprotein, carcinoembryonic antigen (CEA), cancer antigen 19-9, cancer antigen 125, cancer antigen 724, cancer antigen 50, and cancer antigen 242 were within the normal ranges. Computed tomography (CT) revealed a mass in the retroperitoneal space (**Figure 1A**). At the time of diagnosis, the radiologists and

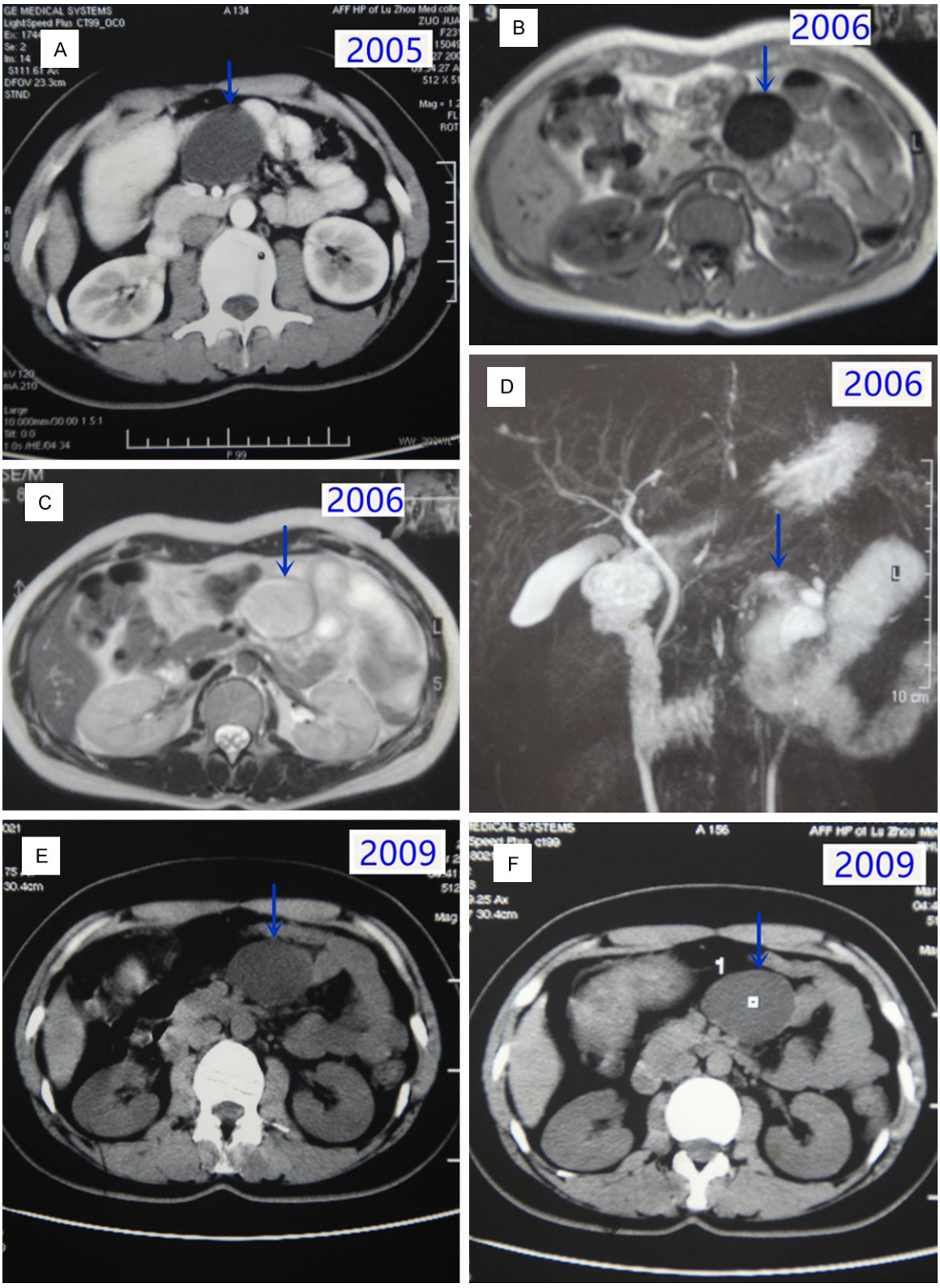

Figure 1. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 4-5 cm cystic mass in the retroperitoneum in 2005, 2006, and 2009. A. CT images in 2005. B. T1-weighted images in 2006. C. T2-weighted images in 2006. D. Magnetic resonance cholangiopancreatography (MRCP) images in 2006. E and F. CT images in 2009.

surgeons considered it to be a mesenteric cyst. CT, MRI, or ultrasound were conducted annually in different hospitals as follow-up. For 12 years of surveillance, the lesion remained largely unchanged in size (4-5 cm) (**Figure 1**). However, at her follow-up visit in 2017, the cystic lesion was found to have grown to 9 cm. Laboratory analysis showed normal findings, except for CA-199 (106 IU/ml; normal range, <37 IU/ml). A CT scan revealed a 9-cm mass in the left upper quadrant of the abdomen near the tail of the pancreas. The mass was mainly cystic with enhanced solid tissue (**Figure 2**). The differential diagnoses based on the CT scan findings included a mesenteric cyst, a pseudocyst, or a lymphatic cyst. Contrast-enhanced ultrasound (CE-US) revealed a 9.5×9.2 cm cystic-solid mass located in the pancreatic tail, and its border with the pancreas was indistinct. The possible diagnosis with CE-US was a solid pseudopapillary neoplasm of the pancreas (**Figure 3**). Based on the aforementioned findings, the pre-operative diagnosis was still more suggestive of a benign lesion. A laparotomy was performed under general anesthesia. A well-encapsulated mass was found at the roots of the transverse mesocolon near the tail of the pancreas. The mass was supplied by the mesenteric artery. The roots of the mass infiltrated the pancreatic tail and the mesentery. A total resection of the mass was performed, and the specimen was submitted for frozen section examination. Because the result was highly suggestive of a malignancy, another distal pancreatectomy was performed (**Figure 4D**).

After surgery, a histopathological examination of the H&E-stained sections taken from most parts of the resected specimen revealed an intraductal lumen-occluding lesion with a mainly tubular growth pattern with back-to-back tubular glands. In areas with intraductal growth, a remainder of the original ductal epithelium was observed. Nodular tumor cell aggregates showing the same histomorphologic appearance were seen extraductally. Some malignant glands had invaded into the wall of the tumor (**Figure 4A**, **4B**).

Immunohistochemical staining was positive for cytokeratin (CK)7, CK19, CK20, CD10, AAT, NSE, Ki-67, and P53 and diffusely positive for CEA, while negative for MUC2, MUC5AC, CDX2, Vim, Syn, and CgA (**Figure 4C**). The final diagnosis was pancreatic ITPN with associated invasive cancer. The patient recovered uneventfully and is disease-free without recurrence at the time of this report (12 months post-surgery). Follow-up is on an outpatient basis.

Discussion

ITPN depicts a rare subgroup of intraductal epithelial neoplasms of the pancreas. Due to its rarity, information regarding the disease is currently limited; thus, the clinicopathological features of ITPN remain to be elucidated. Previous studies have shown that ITPN had no sexpredilection and is frequently diagnosed in people aged 35 to 84 years (average, 56 years) [1]. ITPN most commonly shows a morphologic appearance of a solid nodular tumor arising in the main pancreatic duct and obstructing the ducts with subsequent upstream dilatation [1]. Imaging findings are important for clinical diagnosis. ITPN is visualized as low and high signal intensities on T1-weighted and T2-weighted MR images, respectively. Dilatation of the pancreatic duct and atrophy of the pancreatic parenchyma in the tail region are frequently seen on contrast-enhanced CT [3]. However, in our case, the mass was located at the rear left of the tail of the pancreas without a dilated pancreatic duct and presented as a retroperitoneal cystic lesion. At the time of diagnosis, it was thought to be a mesenteric cyst, which are also rare. Mesenteric cysts appear as an anechoic mass with acoustic enhancement on US and as a fluid-filled mass with low signal intensity on T1-weighted images with no discernible wall and no internal septations on CT and MRI [4]. Moreover, most patients with mesenteric cysts remain asymptomatic. The similarities of the image features and clinical characteristics of this case to a mesenteric cyst may have led to the misdiagnosis.

In addition, ITPN should be differentiated from intraductal papillary mucinous neoplasm (IPMN) because of their similar characteristics. They are both intraductal and have the capability to become invasive. They also share some similar symptoms, such as epigastric pain and jaundice. However, ITPN shows a uniform high-grade atypia, while IPMN shows a more variable expression of cells with low- to high-grade atypia. One of the main differences between the neoplasms is the presence of mucin production

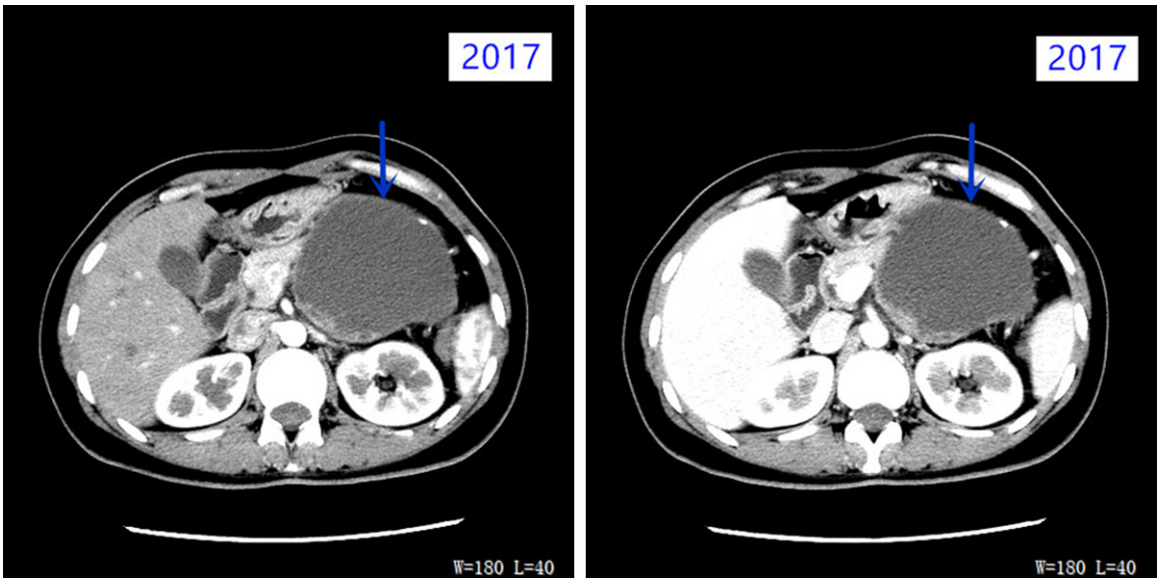

Figure 2. Contrast-enhanced computed tomography (CT) in 2017 revealed a 9-cm mass in the left upper quadrant of the abdomen near the tail of the pancreas. The mass was mainly cystic with enhanced solid tissue.

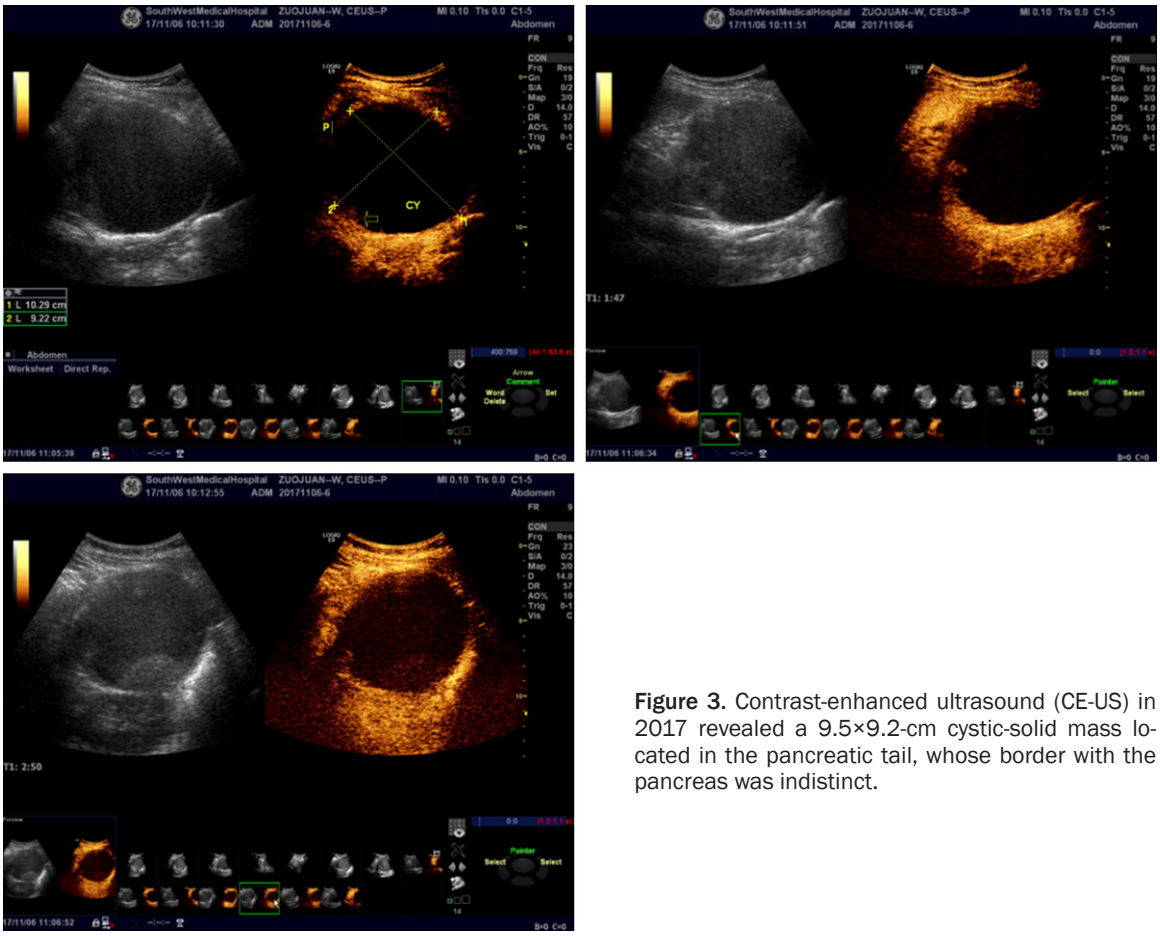

Figure 3. Contrast-enhanced ultrasound (CE-US) in 2017 revealed a 9.5×9.2-cm cystic-solid mass located in the pancreatic tail, whose border with the pancreas was indistinct.

in IPMN, while ITPN does not secrete mucin. Another difference is the tubule-forming epithelium only observed in ITPN [5]. Immunohistochemical properties and genetic muta-

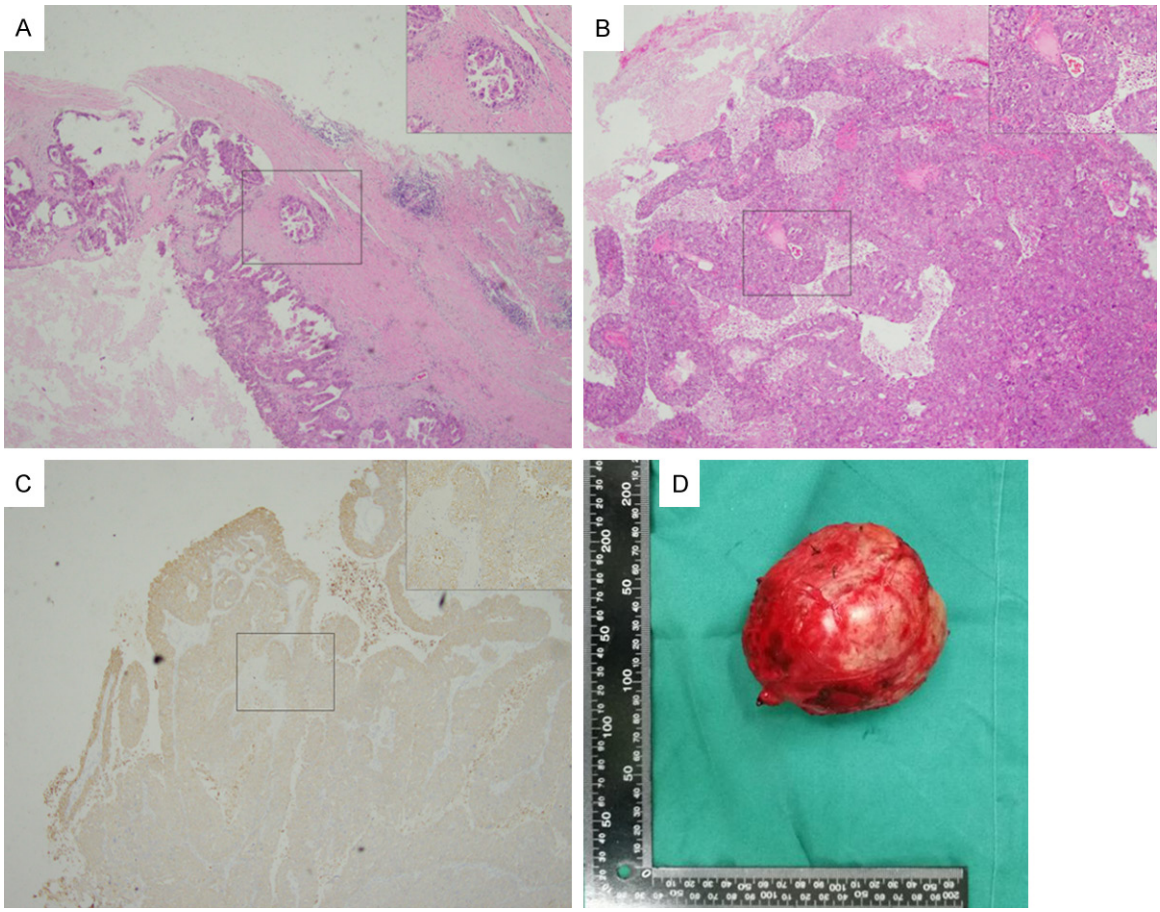

Figure 4. A, B. Histopathologic examination of H&E-stained sections revealed an intraductal lumen-occluding lesion with a mainly tubular growth pattern with back-to-back tubular glands. Some malignant glands infiltrated into the wall of tumor. C. Immunohistochemical staining of the tumor was positive for CK-7. D. A gross image of the surgical specimen showed a well-encapsulated cystic lesion with yellow serous substance.

tions help to distinguish between the two diseases. IPMN is usually positive for MUC-5AC and MUC2, while these are negative in ITPN. Additionally, recent studies investigating ITPN showed that its characteristic immunomorphologic phenotype is the expression of CK7 and CK19 [6, 7]. In the current case, immunohistochemical staining was positive for CK7 and CK19, but negative for MUC2 and MUC5AC, supporting the diagnosis of ITPN.

A significant proportion of ITPN cases may become invasive. However, the current case did not show invasive potential radiologically or morphologically in both the pre- and postoperative period. It has been reported that the invasive components of ITPN are similar in morphology to intraductal components or highly invasive, similar to conventional ductal carcinomas. Ductal cancers, like invasive tumors, are easily recognized; however, tumors showing a papillary pattern of tubules are difficult to identify. The infiltrating part of ITPN forms a circular aggregate, which is very similar to the growth area in the catheter. Invasiveness can only be determined by carefully examining the boundaries of aggregates, which may be slightly irregular. In addition, invasive areas always lack residual ductal cells, which are usually found in the ductal growth of tumors. Finally, the distribution of aggregates observed in areas without catheters is helpful in diagnosing invasiveness [8]. In our case, the tumor was located at the tail of pancreas, and only a small part of the mass invaded the tail of pancreas. This explains the radiologic and US findings.

Follow-up data on ITPN remain limited. Basturk et al. reported a follow-up study that included data from 22 patients. In these patients, the 5-year survival rate was 100% in those without an invasive component and 71% in those with

an invasive tumor [7]. Another study by Kölby reported 30 cases of ITPN; of these, 21 survived. Fifteen patients were alive and disease-free at the last follow-up that ranged from 7 months to 6 six years post-surgery. One patient died of liver metastases after 7 months and another patient died of another disease after 19 months. Four patients had recurrences after 12, 18, 24, and 34 months [5]. Our patient was alive and free of disease at the last follow-up 12 months after the operation. Close clinical follow-up is needed.

In conclusion, we report a case of ITPN misdiagnosed as a mesenteric cyst. Due to its rarity, the clinicopathologic features of ITPN remain unclear. Thus, ITPN should always be considered in the preoperative diagnosis of a cystic lesion located at the retroperitoneum near the tail of the pancreas. Further studies are needed to assess the long-term outcome and identify clinical and radiological features that can be useful for the diagnosis.

Disclosure of conflict of interest

None.

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