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The Rare Intraductal Tubular Carcinoma of the Pancreas with Invasive Growth outside the Duct Wall: Histopathological Subtype, Tumor Markers Expression, Microsatellite Detection, and Differential Diagnosis

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Abstract

Intraductal Tubular Carcinoma (ITC) is a very rare type of tumor with a complex tubular structure in pancreatic intraductal tumors. Till now, a total of 9 articles have been reported in the international literature. However, many surgeons, imaging doctors, and even pathologists are not familiar with this tumor yet. It is not easy to make a correct diagnosis only by imaging, and misdiagnosis easily led to excessive treatment. Here we describe a case of pancreatic intraductal tubular carcinoma at the body and tail. A 77-year-old male was found to have a mass at the body and tail of the pancreas during the physical examination. Abdominal enhanced CT and enhanced MRI considered it might be a malignant tumor that needed to be differentiated from Malignant Intraductal Papillary Neoplasm (IPMN). "Body and tail of pancreas + splenectomy" was performed. The tumor cells were obvious atypia and arranged in a tubular shape with an invasion of the outer wall of the pancreatic duct under the microscope. The histopathological classification is a neonatal subtype. CK7, CK19, CK20, and MUC1 were diffusely expressed in tumor cells. MLH1, PMS2, MSH2 and MSH6 proteins were not missing (pMMR). Through the diagnosis of ITC and differential diagnosis with pancreatic intraductal tubular adenoma, IPMN, intraductal oncocytic papillary neoplasm, and pancreatic acinar cell carcinoma, this article helps to improve the diagnosis level of pathologists and the treatment level of clinicians.

Keywords: Pancreatic intraductal tubular carcinoma; Pathological diagnosis; Differential diagnosis; Histopathological subtype; Tumor markers expression

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Introduction

Pancreatic Intraductal Tumors (ITs) are divided into Intraductal Tubular Neoplasm (ITN) and Intraductal Papillary Mucinous Neoplasm (IPMN). Intraductal Tubular Carcinoma (ITC) is an extremely rare type of tumor in pancreatic ITN. To date, only a few international reports in English can be retrieved on PubMed. No reports in China. Most surgeons, imaging doctors, and even pathologists don't have much knowledge of this disease. Therefore, there is little experience in the treatment and prognosis of the disease. Accumulating more experience in ITC diagnosis and differential diagnosis with other diseases will help improve the precise diagnosis of the disease, formulate treatment plans and predict prognosis.

Materials and Methods

The surgical specimen was fixed in 10% neutral buffered formalin and processed routinely. Then, the specimens were sectioned and stained with hematoxylin and eosin. Immunohistochemistry was carried out with EnVision method. CK17, CK19, CK20, MUC1 and MUC2 were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., China. MLH1, PMS2, MSH2 and MSH6 were come from Maijie Biotechnology Co., Ltd., China. Syn and p53 were from Leica Biosystems. CK7 and CD56 were purchased from Beijing Jinqiao Yatu Biotechnology Co., Ltd., China. CgA was from Fuzhou Maixin Biotechnology Development Co., Ltd., China.

Results

Clinical characteristics

A 77-year-old male was found to have a heterogeneous hypoechoic mass in the body and tail of

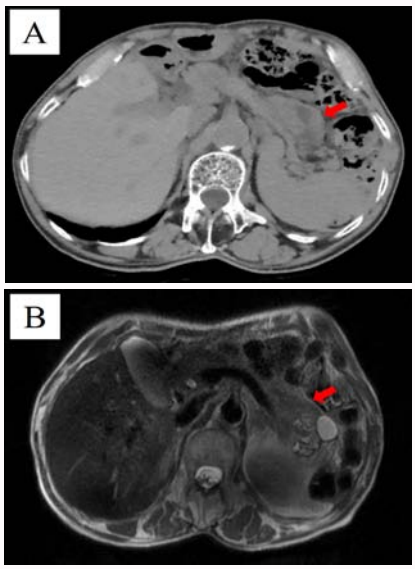

Figure 1: Imaging characteristics of ITC. (A) Computer tomography imaging of the abdomen and pelvis. Pancreatic tail swelling slightly reduced density (red arrowhead). (B) Upper abdominal MRI: The body and tail of pancreas was swollen, irregular abnormal signal shadow could be seen, and the boundary was not clear (red arrowhead).

the pancreas by ultrasound during the physical examination before more than one month. He was admitted to Peking University People's Hospital on January 4th, 2021. Abdominal enhanced CT (Figure 1A) showed that an irregular mass in the body and tail of the pancreas was about 9.5 cm × 2.4 cm in size, without obvious enhancement, but low-density shadows inside considering the possibility of malignancy. Further enhanced MRI of the upper abdomen (Figure 1B) prompted that it needed to be differentiated from malignant Intraductal Papillary Neoplasm (IPMN), pancreatic cancer, or other diseases. The patient was admitted to our hospital with" a malignant pancreatic tumor". Soon after, "body and tail of pancreas + splenectomy" under general anesthesia was performed.

Pathological findings

Gross findings: (Pancreas body and tail + spleen) Resection specimens, the total size is about 18 cm × 8 cm × 6 cm, nodular masses is 5 cm × 3.5 cm × 3 cm in the main pancreatic duct at the body and tail of the pancreas, and the boundary between the tumor and the surrounding tissues is clear. The mass is grayish-white and gray-yellow, with a medium texture, and the focal area is slightly hard, without mucus (Figure 2).

Microscopically: A tumor could be seen in the large pancreatic duct. The tumor cells were obvious atypia and arranged in a tubular shape. Most of the cells showed eosinophilic cytoplasm and clear nucleoli, no mitoses, no intravascular tumor thrombi, and perineural invasion. Tumor tissue invaded the focal duct epithelium to the outside of the tube wall and surrounding fibrous tissue proliferated (Figure 3A). The pancreatic ductal epithelial cells near the tumor nodule showed high-grade intraepithelial neoplasia, and there was no obvious atypia in the remaining ductal epithelial cells (Figure 3B, 3C).

Immunohistochemistry: CK7 (+) (Figure 4A), CK19 (+) (Figure 4B), CK20 (+) (Figure 4C), MUC-1 (+) (Figure 4D), CK17 (-), MUC-2 (-), CgA (-), Syn (focus +), CD56 (focus +), p53 (5% +), MLH1 (+), PMS2 (+), MSH2 (+), MSH6 (+).

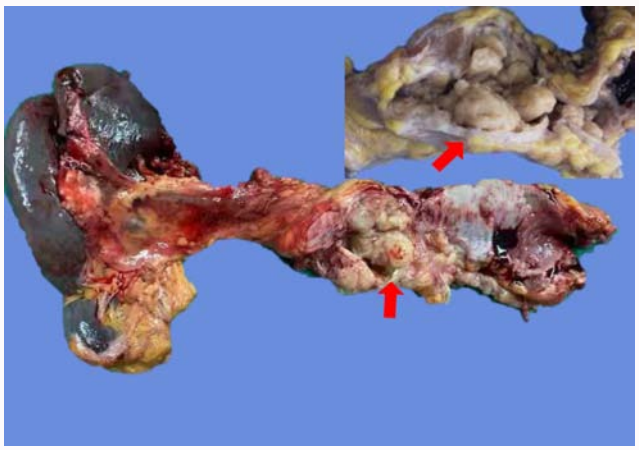

Figure 2: Cut section of the resected specimen of the ITC. (Red arrow referred to intraductal tumor, and the right upper corner was the enlarged view of tumor after 10% formalin fixation).

Pathological diagnosis: Intraductal Tubular Carcinoma (ITC) of pancreas (neonatal subtype). pMMR.

Discussion

Intraductal Tubular Neoplasm (ITN) is a very rare type in pancreatic Intraductal Tumors (ITs). If the tumor tissue in ITN with a complex tubular structure shows obvious cellular atypia, it is defined as Intraductal Tubular Carcinoma (ITC). A total of 9 articles have been reported in the international literature [1-9]. To sum up these articles, all cases were Asian patients including eight Japanese articles (8/9) and one Korean (1/9). The male to female ratio was 8:7. The age ranged from 35 years old to 84 years old. Most of the patients (7/9) reported were more than 45 years old, we speculated that the onset of ITC is concentrated more on the middle-aged and elderly. It is very interesting that among all the 9 English case reports on PubMed, 8 are from Japan and 1 is from South Korea. This case is the first report from China. After searching carefully again, we found a report from French [10], but due to the unavailability of the original text and language, we are not sure whether it is the ITC. Does this rare disease only occur in the Asian race? Or is the Asian race a vulnerable group? This may require more case reports to be further clarified. The tumor was all located in the main pancreatic duct, 53% (8/15) in the head of the pancreas, 27% (4/15) in the body of the pancreas, 13% (2/15) located at the main duct of the pancreas ranging from the head to the tail of the pancreas, only one case in the pancreatic tail. The clinical symptoms have no obvious specificity. About 33% (5/15) cases had epigastralgia; a few of patients had diarrhea, back pain, obstructive jaundice, fever, or lower extremity edema [1-9]. In this case, imaging examination showed the body and tail of the pancreatic main duct were occupied, and the clinical symptoms were not obvious. Preliminary clinical diagnosis was "pancreatic malignant tumor", and "pancreatic body and tail + splenectomy" under general anesthesia was performed.

The main differential diagnosis is pancreatic Intraductal Tubular Adenoma (ITA) or pyloric gland type adenoma. Most mucus can be seen in ITA, while almost no mucus can be seen in ITC. Microscopically, ITA shows mucous cell proliferation and pylorus gland metaplasia, tumor cells have no atypia [5]. The expression of *MUC2*, *MUC5AC*, and *MUC6* in ITA is positive, while *MUC1* is negative. Whereas, the expression of MUC1 in ITC is positive,

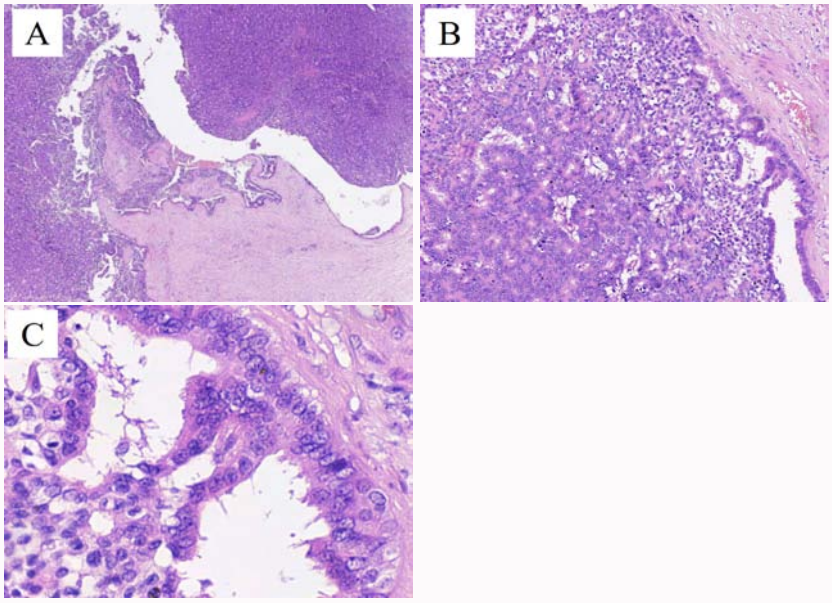

Figure 3: Microscopic examination of ITC. (A) Tumor tissue invaded the focal duct epithelium to the outside of the tube wall. (B) The tumor destroyed the pancreatic duct and infiltrated the outside of the pancreatic duct wall. HE 10x. (C) High-grade intraepithelial neoplasia of pancreatic duct epithelial cells around the tumor. HE 20x.

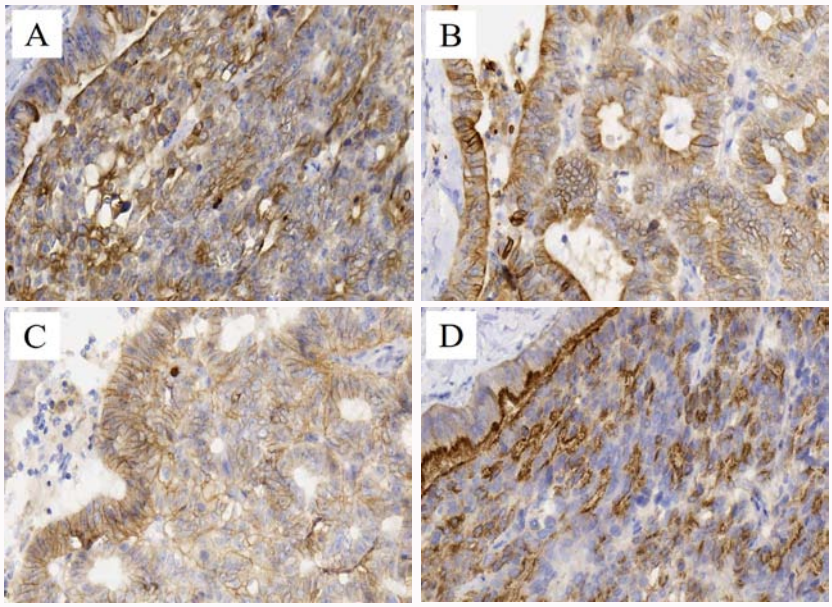

Figure 4: Immunohistochemical characteristics of ITC. The tumor cells showed a diffusely positive expression of CK7(A), CK19(B), CK20(C) and MUC1(D) En Vision 20x.

and the expression of *MUC2* and *MUC5AC* are usually negative. There is no clear mucus component, and the tumor cells have obviously atypia. In addition, *MUC1* is positive in this case. So, ITC is diagnosed. The Japanese Pancreatic Society divides pancreatic ITs into Intraductal Tubular Neoplasm (ITN) and IPMN [11-13]. IPMN is divided into different epithelial subtypes: Gastric type, intestinal type and pancreaticobiliary type [11]. Gastric IPMN tumors are usually located in the branch pancreatic duct, whereas intestinal and pancreaticobiliary IPMN tumors are located in the main pancreatic duct. The tumor in this case is located in the main pancreatic duct, so it should be differentiated from intestinal type and pancreaticobiliary type IPMN. Intestinal IPMN tumor tissue is characterized by intestinal epithelium forming villous papillae, tumor cells are tall columnar, the cytoplasm is basophilic, and mucus can be seen in the cells. Pancreaticobiliary duct type IPMN tumor tissue is arranged in a dendritic pattern, showing the papillary structure. Tumor cells are atypia, and mucus can be seen in the cells, and some areas are accompanied by metaplasia. The tumor cells are atypia, and the cytoplasm is rich in mucus. Metaplastic changes can be seen in some areas, such as ossification. The expressions of tumor markers *MUC1* and *MUC5AC* are positive, and *MUC2* is negative [11]. A case of misdiagnosis was reported in the literature. The preoperative imaging examination was misdiagnosed as IPMN, and "Whipple surgery + local lymph node dissection" was performed. The final pathological

diagnosis was ITC, and no lymph node metastasis was found. There was no tumor recurrence in the follow-up for 23 months [4]. In this case, the tumor cells are in the same shape, arranged in small tubes, no mucus, and the tissue morphology was not consistent with IPMN, so rule out the diagnosis of IPMN.

The differentiation between ITC and Intraductal Oncocytic Papillary Neoplasm (IOPN). Adsay et al. [14,15] reported that goblet cells were seen in IOPN, and the tumor cell cytoplasm is rich in eosinophilic granules. The immunohistochemical staining of IOPN is positive for *MUC2*, *MUC6*, and *MUC8*, and the expression of *MUC2* of ITC is negative. In this case, there were no obvious goblet cells in the tumor tissue, no eosinophils in the tumor cells cytoplasm, and the tumor marker *MUC2* was negatively expressed, so the diagnosis of IOPN diagnosis was excluded.

ITC also needs to be differentiated from carcinomas that invade the pancreatic parenchyma. There was one misdiagnosed case reported in the literature [9]. The preoperative imaging data was misdiagnosed as pancreatic Acinar Cell Carcinoma (ACC). After "total pancreatectomy + splenectomy + local lymph node dissection", the pathological diagnosis of ITC was confirmed without lymph node metastasis. There was no tumor recurrence after a 3-years follow-up. ACC is a malignant epithelial tumor of the pancreas characterized by differentiation of acinar cells, with clear borders, and the cut section is grayish pink, grayish brown, and medium in texture. Microscopically, the tumor mainly invades pancreatic parenchyma. The tumor cells are arranged in acinar, adenoid, and trabecular shapes. The acinar structure is similar to the normal pancreatic acinar morphology, with a small lumen, a single layer of tumor cells, and the nucleus is located at the basement. The survival rate of ACC patients is very low. The median survival time is about 19 months, and the 5-year survival rate is 25% [11]. Pancreatic Ductal Adenocarcinoma (PDAC) is an aggressive epithelial tumor with adenoid distribution, which invades the pancreatic parenchyma. Most PDAC are well moderately differentiated, with tubular and adenoid distribution, with obvious fibrous stromal reaction, and visible lumen and intracellular mucus [11]. The average survival time of PDAC without treatment is 3 to 5 months, the average survival period after surgical resection is 10 to 20 months, and only 10% to 20% of patients can be treated with surgery when they are diagnosed [11].

ITC is very rare. It is very important to avoid misdiagnosis. Compared with other ITs of the pancreas and pancreatic cancer, it is more difficult for ITC to make a clear diagnosis through clinical and imaging examination before an operation, and the final diagnosis depends on pathology. Reviewing the literature, ITC is mainly treated by “Whipple surgery” or “distal pancreatectomy” (6/9), only one case is “distal pancreas + splenectomy”, “a subtotal pancreatectomy” and “pancreas + splenectomy and lymph node dissection”. The disease progresses slowly, lymphatic metastasis rare, and the prognosis is good. The prognosis is very different from other pancreatic malignancies. No death reports based on this disease have been found. However, the disease is easily misdiagnosed. If it can be diagnosed early and is treated with surgery in time, the wide-ranging “Whipple operation and lymph node dissection” can be avoided. Therefore, the correct diagnosis is of great significance for the selection of clinical treatment and prognosis evaluation.

We found that the immunohistochemical expression profile of this tumor was different from that of pancreatic ductal adenocarcinoma, and it was double positive for CK7 and CK20. According to our experience, only gastric adenocarcinomas of the upper gastrointestinal tract can show double-positive CK7 and CK20 at the same time, but they are not diffusely positive. It is often one of the markers that is focal expression. Mixed subtypes of ampullary carcinoma can have the simultaneous expression of CK7 and CK20 [16]. The expression of ITC tumor markers may be related to its mechanism and prognosis, and further research is needed. There are few studies on the molecular pathology of ITC in the world, and the pathogenesis is still unclear. Furukawa [7] found that no KRAS or BRAF mutations were detected in ITC, any *SMAD4* expression loss, *TP53* overexpression, and abnormal expression of β-Catenin. However, PDAC is often accompanied by KRAS mutation, and PDAC without KRAS mutation may be accompanied by BRAF mutation. Reviewing the literature [1-9], P53 (+) ITC cases accounted for about 44% (4/9), and in our case, 5% positive expression of P53 can be seen. Overexpression of *TP53* is an alternative marker for missense mutation of *TP53*, which is common in PDAC [11]. However, the molecular pathological characteristics and related mechanisms of ITC need to be summarized in more cases for further exploration and research. Itatsu proposed that ITC may be divided into two subtypes: Neonatal subtype and adenoma-carcinoma sequence subtype, and it also reported a case of both the main pancreatic duct intraductal tubular adenoma and ITC. This provides direct histological evidence of adenoma-carcinoma sequence [4]. Tajiri proposed that the de novo subtype is a homogeneous tumor without multi-step progress [2]. In this case, high grade intraepithelial neoplasia was observed in the pancreatic duct epithelial cells around the tumor tissue under the microscope. The occurrence of ITC in this case may belong to the neonatal subtype, and the tumor is derived from the pancreatic duct epithelial cells.

Through the diagnosis and differential diagnosis research and literature summary, this article can provide pathologists and clinicians with more detailed ITC diagnosis ideas and avoid misdiagnosis and mistreatment.

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