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## Case Report

# Multifocal intraductal tubulopapillary neoplasm of the pancreas with total pancreatectomy: report of a case and review of literature

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**Abstract:** Intraductal neoplasms of the pancreas are classified as intraductal tubulopapillary neoplasms (ITPNs) and intraductal papillary mucinous neoplasm (IPMNs) in the current WHO classification. ITPN is a rare tumor and there are only a few cases of ITPN reported in the literature. We present the case of an otherwise healthy 42-year-old male, who presented with upper abdominal pain. He was subsequently diagnosed with multifocal ITPN and underwent total pancreatectomy. The pathological report showed invasive growth. The postoperative course was uneventful and the patient received 6 months of adjuvant chemotherapy with gemcitabine-capecitabine. The patient is still alive 19 months after the procedure with no signs of recurrence. Literature review revealed only 30 individual cases of ITPN in the pancreas including our reported case. Mean age was 61 years (16 males/14 females; ratio 1.14:1). Mean tumor size was 3 cm. Immunohistochemical staining was positive for CK-7 in 100% of the patients, CK-19 in 95% and for MUC-1 in 88%. Trypsin was negative in all cases.  $\beta$ -catenin was negative in 94% and MUC-2 was negative in 96% of the cases. BRAF, KRAS, TP53 and PIK3CA mutations were infrequently seen. Invasive growth was present in 54% of the cases. Tumor size and Ki-67 index showed a statistically significant association with invasive growth. Survival rate could not be determined, due to short follow-up, and further research is needed to establish prognostic factors for disease recurrence and survival.

**Keywords:** Intraductal tubulopapillary neoplasm, pancreas, invasive growth

## Introduction

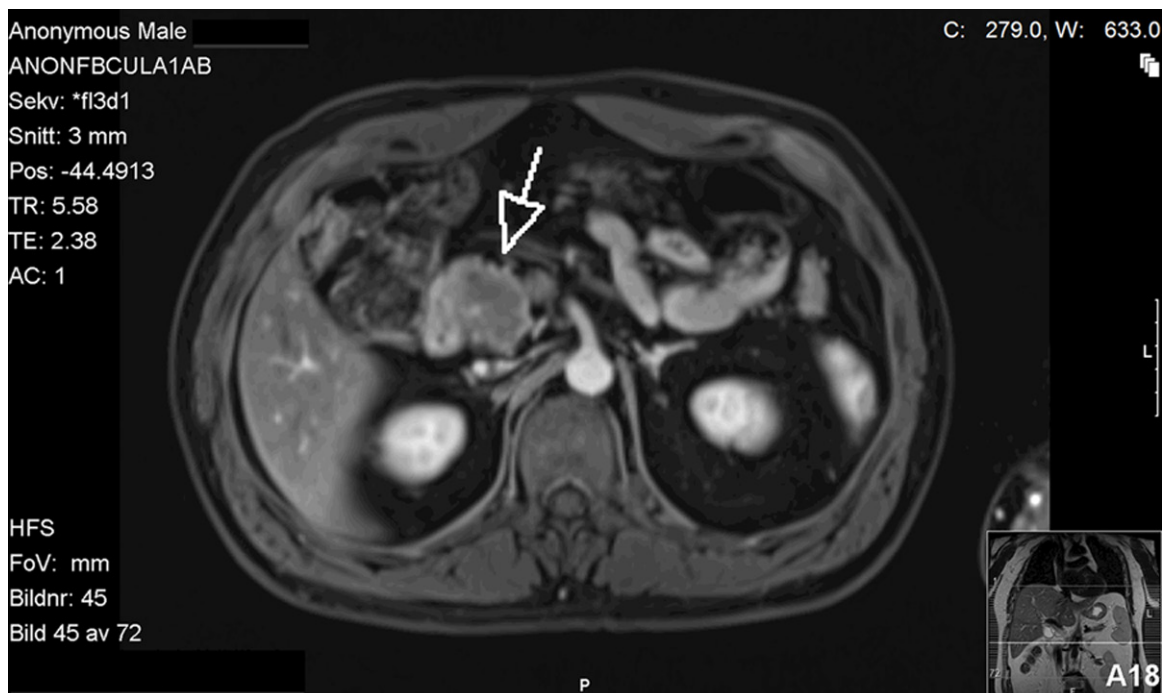
Intraductal tubulopapillary neoplasm (ITPN) is a rare epithelial neoplasm of the pancreas. According to the current World Health Organization (WHO) classification from 2010, ITPN is defined as an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin [1]. Because of the rarity of the disease, information regarding both clinical and molecular aspects of this newly described entity is limited [2-4]. It has become recently evident that ITPN is less aggressive than other pancreatic malignancies, and that it is important to distinguish ITPN from both IPMN and ductal adenocarcinoma as ITPN has a more favorable prognosis [5]. A greater insight into ITPN would make diagnosis, treatment and clinical surveillance more precise, which would aid in patient management.

We herein report a case of multifocal ITPN of the pancreas and review additional ITPN cases that exist in the medical literature. We have collected and analyzed 30 cases of ITPN, which, to our knowledge, is the largest series presented so far. We have sought to determine how many cases that evolve into invasive carcinomas and distinguish the clinicopathological, immunohistochemical and molecular features of ITPN.

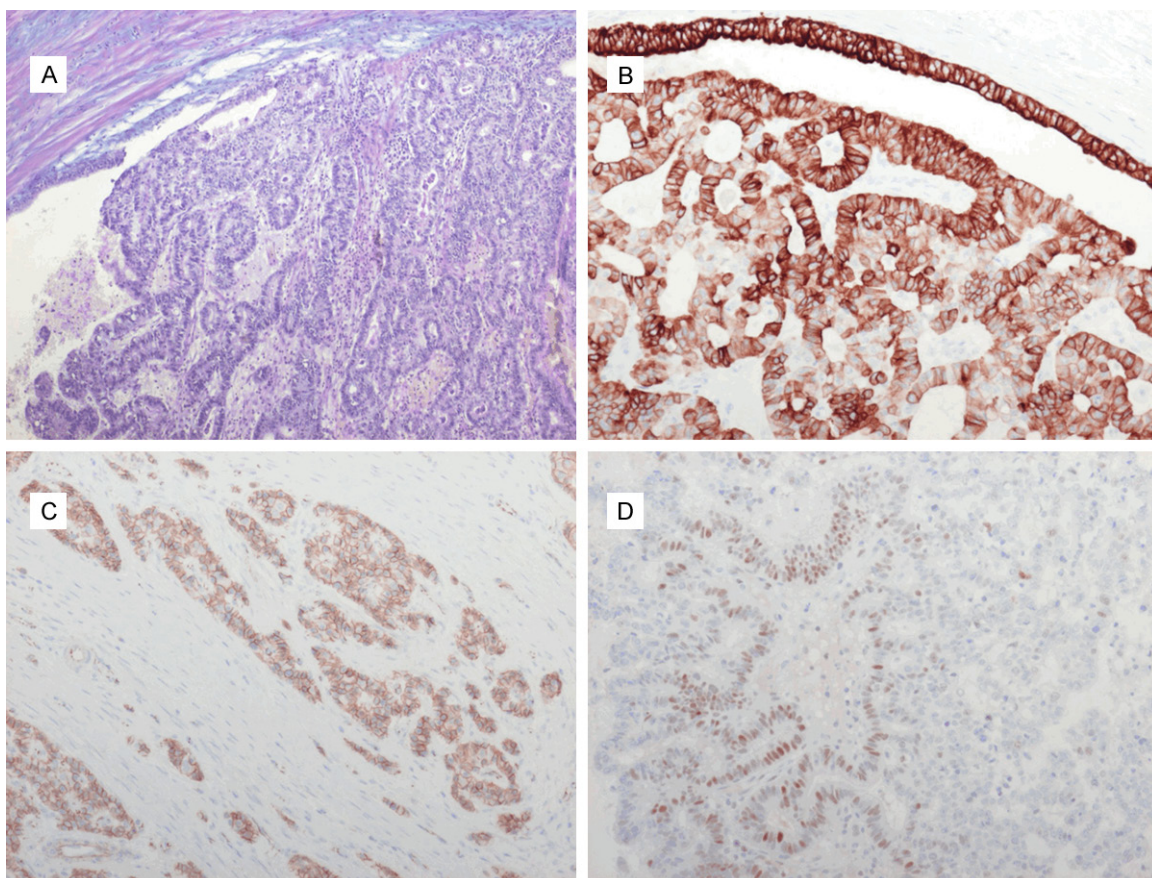
## Case report

A 42-year old man with no significant past medical history presented with upper abdominal pain at a local hospital. On physical examination, mild tenderness in the epigastric and right upper hypochondriac region was noticed. Initial laboratory work-up showed the following abnormal findings: total bilirubin 2.7 mg/dL, alanine aminotransferase 647 IU/L, alkaline phosphatase 518 IU/L, pancreatic amylase 4.7 U/L and

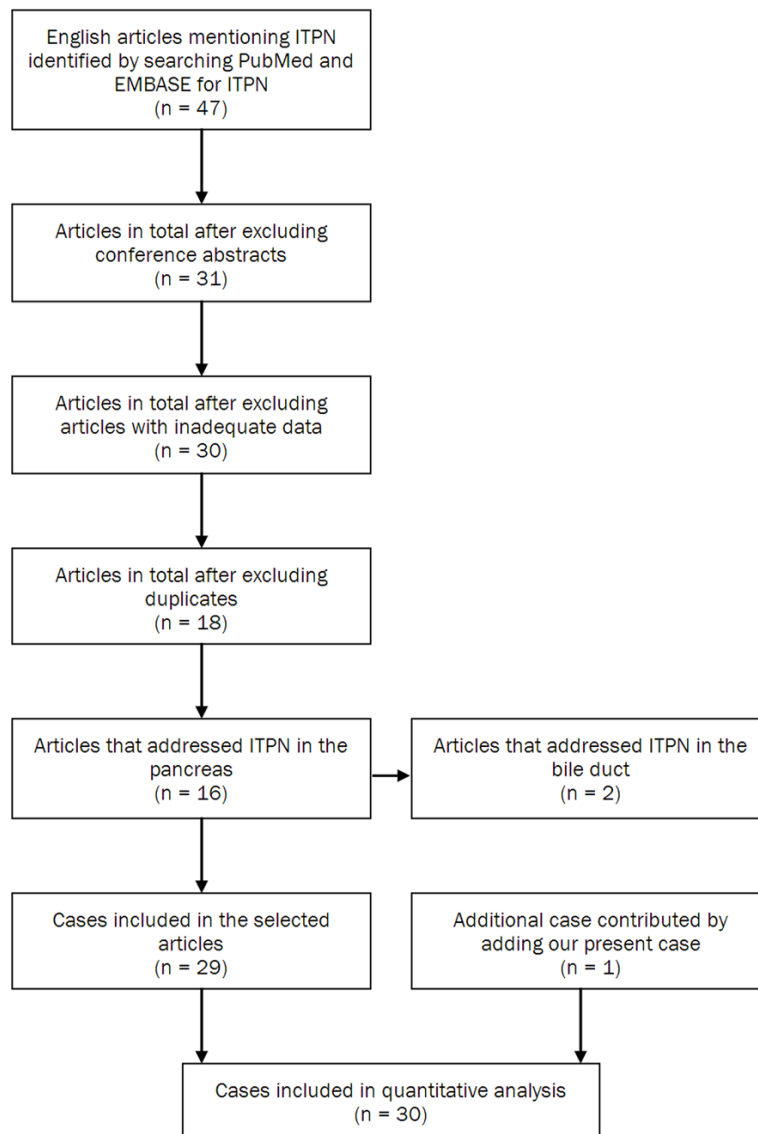
## Intraductal tubulopapillary neoplasm of the pancreas



**Figure 1.** 42-year-old patient with ITPN. MRI shows a round and inhomogeneous mass in the uncinate process of the pancreas measuring 4.1 cm in diameter (arrow).



**Figure 2.** Microscopic findings of the tumor. A. ABPAS-staining showed minimal or no mucin. B. Immunohistochemical staining of the ductal component of the tumor demonstrated positive result for CK-19. C. Staining of the infiltrative portion showed positive result for  $\beta$ -catenin. D. Overexpression of TP53 was focally observed in the intraductal component.



**Figure 3.** PRISMA diagram showing selection of articles and patient cases for review.

C-reactive protein 2.3 mg/dL. Abdominal ultrasonography revealed a mass in the head of the pancreas. Computed tomography (CT) confirmed the findings of a low-attenuation mass, 4 × 3 cm, located in the uncinate process of pancreas. The tumor abutted the superior mesenteric vein for a distance of 15 mm. There were no signs of liver or lung metastases. Subsequent magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatog-

raphy (MRCP) revealed a solid lesion (4.1 cm in diameter) located in the uncinate process of the pancreas with close proximity to the descending duodenum (**Figure 1**). The main pancreatic duct (MPD) was dilated up to 8 mm and there was marked atrophy of the pancreatic parenchyma in the body and tail of the pancreas. The distal part of the common bile duct was slightly dislocated due to compression from the tumor. As part of the diagnostic work-up, an upper gastrointestinal endoscopy was also performed but without any remarkable findings. Serum tumor markers showed elevated levels of CEA (10 ng/mL) and extraordinarily high levels of AFP 1788 (ng/mL), while levels of CA 19-9, chromogranin A and IgG4 were normal.

The patient was referred to our hospital and surgery was planned. The operation started as a classical Whipple procedure. The pancreas was accessed via an extensive Kocher mobilization and entrance through the lesser sac. A solid tumor was found in the pancreatic head. At the transection of the pancreas, large amounts of necrotic

debris were observed in the MPD and sent for cytological examination. The results showed malignant cells. Due to the risk of malignant cells throughout the entire MPD the decision was made to convert the operation to a total pancreatectomy. Thus, total pancreatectomy was performed concomitant with duodenectomy, cholecystectomy and splenectomy. Total bleeding loss during surgery was 1000 mL. Total operation time was 8.5 hours.

# Intraductal tubulopapillary neoplasm of the pancreas

**Table 1.** Clinicopathological features

| Case  | Authors                  | Age | Sex    | Symptoms                           | Location | Size**  | Invasion | Prognosis          |
|-------|--------------------------|-----|--------|------------------------------------|----------|---------|----------|--------------------|
| 1     | Yamaguchi et al. [4, 13] | 60  | F      | None                               | H        | 6       | No       | 7 mo AN 19 mo DO   |
| 2     | Yamaguchi et al. [4, 13] | 35  | F      | Abdominal pain                     | B        | 1       | No       | 72 mo (AN)         |
| 3     | Yamaguchi et al. [4, 13] | 68  | F      | None                               | H        | 2.5     | No       | 29 mo (AN)         |
| 4     | Yamaguchi et al. [4, 13] | 53  | M      | Abdominal pain                     | B        | 2       | No       | Re 12 mo, 36 mo AN |
| 5     | Yamaguchi et al. [4, 13] | 60  | F      | Abdominal pain                     | H        | 4.5     | No       | 24 mo (AN)         |
| 6     | Yamaguchi et al. [4, 13] | 73  | F      | None                               | H        | 5.2     | No       | 33 mo (AN)         |
| 7     | Yamaguchi et al. [4, 13] | 72  | M      | None                               | B        | 1       | Yes      | 33 mo (AN)         |
| 8     | Yamaguchi et al. [4, 13] | 44  | M      | Abdominal pain                     | H        | 6       | Yes      | 72 mo (AN)         |
| 9     | Yamaguchi et al. [4, 13] | 48  | M      | Jaundice                           | H, B, T  | 15      | Yes      | DD 7 mo            |
| 10    | Yamaguchi et al. [4, 13] | 70  | M      | Exacerbation of DM                 | H, B     | 4       | No       | 24 mo (AN)         |
| 11    | Someya et al. [14]       | 74  | M      | Fever                              | H        | 7       | Yes      | -                  |
| 12    | Ahls et al. [15]         | 43  | F      | Abdominal pain                     | H        | 2.6     | No       | 24 mo (AN)         |
| 13    | Kasugai et al. [5]       | 69  | F      | Excessive thirst                   | H, B, T  | 12      | Yes      | 24 mo (AN)         |
| 14    | Del Chiaro et al. [16]   | 78  | M      | Abdominal pain                     | H, B, T  | 1.1     | No       | -                  |
| 15    | Tajiri et al. [3]        | 66  | M      | Appetite loss                      | H        | >1      | No       | 12 mo (AN)         |
| 16    | Urata et al. [17]        | 78  | F      | None                               | B, T     | 2.2     | Yes      | Re 34 mo, 43 mo AD |
| 17    | Furuhata et al. [11]     | 74  | M      | Fever                              | H        | 7       | Yes      | -                  |
| 18    | Guan et al. [12]         | 41  | F      | None                               | H        | 2.3     | No       | -                  |
| 19    | Jokoji et al. [2]        | 68  | M      | -                                  | B, T     | 10      | Yes      | 15 mo (AN)         |
| 20    | Kitaguchi et al. [18]    | 61  | M      | None                               | H        | 1.2     | Yes      | 22 mo (AN)         |
| 21    | Kitaguchi et al. [18]    | 75  | F      | None                               | B        | 10      | Yes      | 51 mo (AN)         |
| 22    | Bhuva et al. [19]        | 50  | M      | Abdominal pain, jaundice, anemia   | -        | -       | Yes      | Re 18 mo, 28 mo AD |
| 23    | Matthews et al. [20]     | 55  | M      | Abdominal pain                     | T        | 10      | Yes      | Re 24 mo, 36 mo AD |
| 24-29 | Chang et al.* [9]        | 64  | 2M /4F | 4 abdominal pain/1 none/1 jaundice | 4H/1B/1T | 1.5-4.5 | -        | -                  |
| 30    | Kölby et al.             | 42  | M      | Abdominal pain                     | H, B, T  | 3.5     | Yes      | 19 mo (AN)         |

\*Chang et al. did not report information about individual cases. \*\*Size is presented in centimeters. AD, alive with disease; AN, alive with no evidence of disease; DO, died from other disease; DD, died from disease; Re, recurrence; F, female; M, male; DM, diabetes mellitus; H, head; B, body; T, tail.

Macroscopically, soft tissue obstructed the MPD and necrotic papillary neoplastic material could be seen. No mucin production was observed. Multiple tumors were seen in the head, body and tail of pancreas, with the largest mass measuring 3 × 3.5 cm in the head of the pancreas. Microscopically, intraductal growth with low- and high-grade dysplasia was seen. Infiltrative cylinders expanded into loose connective tissue near small blood vessels and nerves. The infiltration was approximated to 3 cm. ABPAS-staining showed minimal or no mucin. Immunohistochemical staining showed positive results for CK-7, CK-19 and  $\beta$ -catenin. Staining for TP53 demonstrated overexpression in the ductal component of the tumor (**Figure 2**). Mutational analyses of KRAS and BRAF were negative. Proliferation activity was highly irregular throughout the tumor and Ki-67 labeling index was determined to 10-65%. No mitotic figures were observed within the specimen. Analysis of the transection margins showed at least 0.5 mm distance to the anterior resection margin, 0.5 mm to the superior mesenteric artery margin and more than 1 mm to the posterior resection margin and superior mesenteric vein

margin. In total 30 lymph nodes were examined, without evidence of metastasis. Perineural invasion was observed in position 8. Tumor staging was classified as pT<sub>3</sub>N<sub>0</sub>M<sub>0</sub>.

Postoperatively, the patient recovered well without any complications and was discharged 9 days after the surgery. He was placed on pancreatic enzyme replacement therapy and insulin due to the nature of the operation. The patient was referred to the oncological outpatient clinic and received gemcitabine combined with capecitabine for 6 months as adjuvant treatment. The chemotherapy was tolerated well and no severe complications were observed. CEA and AFP levels were normalized after surgery. The patient has shown no signs of recurrence 19 months after the surgery.

## Literature review

### Search strategy

The electronic search was carried out in PubMed and EMBASE (inception-April 2015) to identify articles that addressed ITPN of the

# Intraductal tubulopapillary neoplasm of the pancreas

**Table 2.** Immunohistochemical and molecular features

| Case   | Ki-67 (%) | Mitotic count** | MUC      |   |           |   | CK |    | Trypsin | β-catenin*** |
|--------|-----------|-----------------|----------|---|-----------|---|----|----|---------|--------------|
|        |           |                 | 1        | 2 | 5AC       | 6 | 7  | 19 |         |              |
| 1      | 30.5      | 6               | +        | - | -         | - | +  | +  | -       | -            |
| 2      | 6.1       | 1               | +        | - | -         | + | +  | +  | -       | -            |
| 3      | 9.2       | 0               | +        | - | -         | + | +  | +  | -       | -            |
| 4      | 21.4      | 1               | +        | - | -         | - | +  | +  | -       | -            |
| 5      | 24.6      | 0               | +        | - | -         | - | +  | +  | -       | -            |
| 6      | 19.1      | 1               | +        | - | -         | + | +  | -  | -       | -            |
| 7      | 33.4      | 2               | +        | - | -         | + | +  | +  | -       | -            |
| 8      | 43        | 7               | +        | - | -         | + | +  | +  | -       | -            |
| 9      | 28.7      | 9               | +        | - | -         | - | +  | +  | -       | -            |
| 10     | 10.8      | 1               | +        | - | -         | + | +  | +  | -       | -            |
| 11     | 5-20      |                 | +        | - | -         | + | +  | +  | -       | -            |
| 12     | 10-15     | 1               | +        | - | -         | + | +  |    | -       | -            |
| 13     | 20-30     |                 | +        |   | -         | + | +  | +  | -       |              |
| 14     |           |                 | +        | - | -         | + |    |    |         |              |
| 15     | 9         |                 | +        | - | -         | + | +  | +  | -       |              |
| 16     | 32        | 6               | +        | + | +         | + | +  | +  | -       | -            |
| 17     | 24.6      | 2-3             | +        | - | -         | + | +  | +  | -       | -            |
| 18     | 5         |                 | +        | - |           |   |    |    | -       |              |
| 19     |           | 0.6             | +        | - | -         | - | +  | +  | -       | -            |
| 20     |           |                 |          |   |           |   | +  |    | -       |              |
| 21     |           |                 |          |   | -         |   |    |    |         |              |
| 22     |           |                 |          | - | -         | + | +  | +  |         |              |
| 23     |           | 1               | +        | - | -         |   | +  | +  |         | -            |
| 24-29* | >20       |                 | ++ +/--- |   | +++ +/--- |   |    |    |         |              |
| 30     | 10-60     | 0               |          |   |           |   | +  | +  |         | +            |

\*Chang et al. did not report individual cases. \*\*Counted in 10 HPF. \*\*\*In β-catenin staining, + indicates overexpression and - indicates normal expression.

pancreas. Keywords used were 'ITPN', 'intraductal tubulopapillary neoplasm' and 'pancreas'. A manual search of references in eligible articles was also performed to identify additional pertinent articles. The search was limited to original articles based on human studies and written in English. Published case series or case reports that did not include individual patient data were excluded. Conference abstract were excluded since they did not provide detailed information. Articles addressing ITPN in the bile duct were excluded. The process of selection of articles for review is summarized in **Figure 3**.

## Statistical analysis

Data are expressed as mean or median with range or as frequencies with percentage. Parametric continuous data were analyzed with

independent two-sample t-test. Non-parametric continuous data were analyzed with Mann-Whitney U-test. Categorical data were analyzed with Fisher's exact test. A *p*-value (two-sided) less than 0.05 was considered statistically significant. Graphpad Prism 6 (GraphPad Software Inc, San Diego, Ca, USA) was used for all statistical calculations.

## Clinical characteristics

Including our patient, 30 individual cases of ITPN were collected for analysis. The mean age at the time of diagnosis was 61 years (ranging from 35-78 years). Gender distribution was balanced, 16 males and 14 females. Tumors were most frequently located in the head of pancreas, as seen in 15 cases (52%). Other sites were in the body (17%), in the tail (7%), in both the head and body (3%), in both the body and tail

**Table 3.** Mutational analyses

| Case   | KRAS             | BRAF     | TP53             | PIK 3CA  |
|--------|------------------|----------|------------------|----------|
| 1      | Wild             | Wild     | Wild             | Wild     |
| 2      | Wild             | Wild     | Wild             | Wild     |
| 3      | Wild             | Wild     | Wild             | Wild     |
| 4      | Wild             | Wild     | Mutated          | Wild     |
| 5      | Wild             | Wild     | Wild             | Mutated  |
| 6      | Wild             | Wild     | Wild             | Wild     |
| 7      | Wild             | Wild     | Wild             | Mutated  |
| 8      | Wild             | Wild     | Wild             | Wild     |
| 9      | Not done         | Not done | Wild             | Wild     |
| 10     | Not done         | Not done | Wild             | Not done |
| 11     | Not done         | Not done | Not done         | Not done |
| 12     | Wild             | Wild     | Wild             | Wild     |
| 13     | Wild             | Not done | Not done         | Not done |
| 14     | Not done         | Not done | Not done         | Not done |
| 15     | Wild             | Mutated  | Not done         | Not done |
| 16     | Wild             | Mutated  | Mutated          | Wild     |
| 17     | Not done         | Not done | Not done         | Not done |
| 18     | Wild             | Not done | Wild             | Not done |
| 19     | Not done         | Not done | Wild             | Not done |
| 20     | Not done         | Not done | Not done         | Not done |
| 21     | Not done         | Not done | Not done         | Not done |
| 22     | Not done         | Not done | Wild             | Not done |
| 23     | Not done         | Wild     | Not done         | Not done |
| 24-29* | 2 Mutated/4 Wild | Not done | 3 Mutated/3 Wild | Not done |
| 30     | Wild             | Wild     | Mutated          | Not done |

\*Chang et al. did not report information about individual cases.

### Microscopic findings

Immunohistochemical examination showed positive staining for CK-7 (100%), CK-19 (95%), MUC-1 (88%) and MUC-6 (74%). Negative immunohistochemical staining was observed for trypsin (100%),  $\beta$ -catenin (94%), MUC-2 (96%) and MUC-5AC (85%). Genetic mutations in BRAF were detected in 15% of the patients, 10% had KRAS-mutations, 23% showed TP53-mutations and 18% demonstrated PIK3CA-mutations (**Tables 2 and 3**).

Invasive growth was present in 54% of the cases. Age did not affect the frequency of invasive growth. Men had a strong tendency to higher risk of invasive growth,  $P = 0.095$ . Two cases showed metastases to regional lymph nodes and both these cases also showed distant metastases. The size of the tumor and the Ki-67 labeling index could be significantly correlated to a higher risk of invasiveness, ( $P = 0.023$ ,  $P = 0.006$ , respectively) (**Table 4**).

### Survival

Our patient was alive and free of disease at last follow-up 19 months after the operation. In the 29 cases from the literature, 20 presented survival. Fourteen patients were alive and free of disease at last follow-up between 7 months and 6 six years after the operation. One patient died of multiple liver metastases from ITPN after 7 months and another patient died of other disease after 19 months. Two cases had recurrence after 12 and 34 months, respectively, but after treatment they had no signs of disease during the rest of the follow-up period. Two other patients had recurrence after 18 and 24 months, respectively, and due to distant metastases they were treated with palliative care. They were alive, but showed signs of disease at their latest check-up at 28 and 36 months after diagnosis, respectively.

### Discussion

ITPN is a rare pancreatic neoplasm, with a frequency of approximately 0.4% among pancre-

(7%) and in the whole pancreas (14%). The mean tumor size was 3 cm (ranging from 1-15 cm). All articles, except one, reported symptoms. Twenty out of 29 of these cases were symptomatic (69%) and nine cases were asymptomatic (31%). The most frequent symptoms were abdominal pain (42%), jaundice (10%) and fever (7%). Excessive thirst, anemia, loss of appetite and exacerbation of diabetes mellitus were present in single cases (**Table 1**).

In 22 of the 30 cases, type of surgery was reported. The most frequent procedures were pylorus-preserving pancreatoduodenectomy (PPPD), and distal pancreatectomy (DP), performed in 27% of the cases, respectively. Total pancreatectomy (TP) was performed in 18% of the cases and 14% had pancreatoduodenectomy (PD). Spleen-preserving distal pancreatectomy (SPDP), subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) and subtotal pancreatectomy (Sub-TP) were performed in 5% of the cases, respectively.

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**Table 4.** Comparison of invasive and non-invasive ITPN

|                      | Invasive (n = 13)  | Non-invasive (n = 11) | p-value |
|----------------------|--------------------|-----------------------|---------|
| Age (yrs)            | 64                 | 59                    | 0.535   |
| Sex                  | 10 males/3 females | 4 males/7 females     | 0.095   |
| Size (cm)            | 7.0                | 2.5                   | 0.023   |
| Ki-67 index (%)      | 30.4               | 11.7                  | 0.006   |
| KRAS                 | 0 mutated/5 wild   | 0 mutated/9 wild      | 1.000   |
| BRAF                 | 1 mutated/4 wild   | 1 mutated/7 wild      | 1.000   |
| TP53                 | 2 mutated/5 wild   | 1 mutated/8 wild      | 0.550   |
| Mitotic count/10 HPF | 2.3                | 1.0                   | 0.177   |
| PIK3CA               | 1 mutated/3 wild   | 1 mutated/6 wild      | 1.000   |

Mean was calculated for age. Medians were calculated for Ki-67 LI, size and mitotic count.

atic resections in our institution. Prior to the current WHO classification, pancreatic intra-ductal neoplasms were classified into three groups; intraductal papillary mucinous neoplasm (IPMN), pancreatic intraepithelial neoplasm (PanIN) and intraductal tubular neoplasms (ITN) [4, 6, 7]. The latter was further divided into intraductal tubular adenoma (ITA) and intraductal tubular carcinoma (ITC) based on the grade of dysplasia. This classification indicated that ITA was a precursor lesion to ITC [8]. ITA has been considered to be a variant of IPMN and ITC has been recognized, by some authors, to be a type of ITPN [5, 8]. However, this translation of diagnoses is not supported by definite evidence. For this reason we chose to include only cases that were diagnosed as ITPN, resulting in fewer but expectantly more uniform cases.

IPMN is often compared to ITPN for its similar characteristics. They are both intraductal and have an ability to become invasive. They share some of the same symptoms, such as epigastric pain and jaundice. ITPN shows a uniform high-grade atypia, while IPMN shows 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 in IPMN, whereas ITPN does not show this characteristic. Another difference is the tubule-forming epithelium only observed in ITPN. Immunohistochemical properties and genetic mutations of ITPN differ from those of IPMN. IPMN, in contrast to ITPN, is usually positive for MUC-5AC but often negative for MUC-1. IPMN has a lower Ki-67 labeling index and KRAS-mutations are more common in IPMN compared to ITPN [4, 9]. These criteria could be

used to distinguish ITPN from IPMN, together with the macroscopical growth patterns and mucin production.

Pancreatic ductal adenocarcinoma (PDAC) is another differential diagnosis that is important to distinguish from ITPN. The two neoplasms share some of the same characteristic features such as being located in the MPD, commonly in the head of the pancreas. Symptoms such as epigastric pain and jaundice can be observed in

both diseases. In contrast to ITPN, nearly all PDAC express KRAS-mutations [10]. Our result shows that mutations of KRAS are much more uncommon in ITPN, with a mutation frequency of 10%. This difference makes genetic analysis of KRAS a valuable factor when distinguishing ITPN from PDAC.

Previous literature has requested studies with larger groups to determine if Ki-67 labeling index and mitotic count could be used as predictive factors for invasiveness [4]. Ki-67 is a protein that could be used as a cellular marker for proliferation. We report that a high Ki-67 labeling index could be associated with a higher risk of invasiveness. The size of the tumor also showed a correlation to invasiveness, making it another factor to take into consideration when assessing the risk of invasiveness. Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) has been used to diagnose ITPN by cytological immunohistochemistry [11, 12]. However, we suggest that imaging-guided core needle biopsy (CNB) could be used instead to enable histological examination. A biopsy, used to determine Ki-67 labeling index, together with diagnostic imaging to estimate the size of the tumor, could be used for both diagnosis and to assess the risk of invasion in the pre-operative period.

Limited clinical follow-up data restricted an analysis of survival. However, one patient died of the disease from multiple liver metastases that originated from an invasive carcinoma. This may indicate that radical surgery before the neoplasm evolves into an invasive carcinoma is preferable. In two other patients, recurrence of the tumor appeared after 12 and 34

months respectively. They may have occurred by intraductal colonization, since distal pancreatectomy was performed in both cases. There are several other cases that underwent distal pancreatectomy and they did not show any signs of recurrence in the follow-up period, suggesting that total pancreatectomy is not always necessary and could be avoided to minimize the associated complications of surgery. However, we consider a close clinical follow-up for all ITPN cases is needed to improve the prognosis by detecting recurrences at an early stage.

In conclusion, we report the largest series of ITPN to date, together with the clinical, immunohistochemical and molecular characteristics that could be used for diagnosis of ITPN. We also report that Ki-67 labeling index and size of the tumor could be used as predictive factors for invasiveness. Further studies are necessary to determine the 5-year survival, as well as to find clinical and molecular factors that could be used as predictive factors for tumor recurrence and survival.

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## Disclosure of conflict of interest

None.

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