Intraductal Tubulopapillary Neoplasm of the Pancreas

An Update From a Pathologist's Perspective

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• ***Context.***—**Intraductal tubulopapillary neoplasm (ITPN) is a rare intraductal epithelial neoplasm of the pancreas recently recognized as a distinct entity by the World Health Organization classification in 2010. It is defined as an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. The diagnosis can be challenging owing to morphologic overlap with other intraductal lesions and its rarity. While recent advances in molecular genetic studies of ITPN have provided new tools to facilitate clinical diagnosis, the limited number of cases has yielded limited follow-up data to guide management.**

Objective.—**To provide a clinical, pathologic, and molecular update on ITPN with respect to clinical presentation, imaging findings, histopathologic features, differential diagnosis, biological behavior, molecular characteristics, and treatment options.**

Data Sources.—**Analysis of the pertinent literature (PubMed) and authors' research and clinical practice experience based on institutional and consultation materials.**

Conclusions.—**Clinical presentation, imaging findings, histopathology, immunohistochemistry studies, molecular characteristics, prognosis, and treatment options of ITPN are reviewed. Important differential diagnoses with other intraductal neoplasms of the pancreas—especially intraductal papillary mucinous neoplasm—using histopathologic, molecular, and immunohistochemical studies, are discussed. Despite the recent progress, more studies are necessary to assess the biology and genetics of ITPN for a better understanding of the prognostic factors and treatment options.**

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The intraductal neoplasms of the pancreas are defined by the current 4th edition of the World Health Organization (WHO) classification as macroscopic epithelial neoplasms with ductal differentiation that grow in the pancreatic ductal system. The 2 entities included in this category are intraductal papillary mucinous neoplasm (IPMN) and intraductal tubulopapillary neoplasm (ITPN). Note that intraductal lesions with nonductal differentiation, such as acinar cell carcinoma, are not included in this category. Interestingly, before the current WHO classification, intraductal neoplasms of the pancreas were classified into 3 groups: IPMN, pancreatic intraepithelial neoplasia (PanIN), and intraductal tubular neoplasm.[1,2] Intraductal tubular neoplasm was then further classified into intraductal tubular adenoma and intraductal tubular carcinoma, with intraductal tubular adenoma considered as the precursor of intraductal tubular carcinoma.[3] Both IPMN and ITPN can be either cystic or solid-mass forming. The distinction between the intraductal neoplasms and PanIN is that PanIN is microscopic. On the contrary, by definition, both IPMN and ITPN are grossly and radiographically detectable lesions with an arbitrary minimal size criterion of 1 cm. Intraductal tubulopapillary neoplasms can have variable components of tubular and/or papillary histologic growth patterns. These neoplasms are considered to be premalignant owing to their common association with and demonstrated progression to invasive carcinoma.

Intraductal tubulopapillary neoplasm is a rare intraductal epithelial neoplasm of the pancreas recently recognized as a distinct entity by WHO classification in 2010.[4–10] It was actually first recognized by Japanese investigators in the mid 1990s and then was proposed to be named *intraductal tubular carcinoma* by the Japan Pancreas Society in 2002.[11,12] In 2009, Yamaguchi et al[13] proposed renaming this entity as *intraductal tubulopapillary neoplasm*. It accounts for less than 1% of all pancreatic exocrine neoplasms and approximately 3% of intraductal pancreatic neoplasms. According to the most recent 4th edition of WHO, the definition of ITPN is as follows: an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. The confusing change in nomenclature, in conjunction with infrequent exposure to these lesions that can have histologic overlap, poses a diagnostic challenge for practicing pathologists. Nevertheless, careful correlation of clinical presentation, imaging, gross pathology, and histopathologic and immunohistochemistry findings allows for correct diagno-

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sis in most cases. This review provides a brief update on the current knowledge of ITPN with an overview of clinical, radiologic, histopathologic, and molecular features. Furthermore, we will discuss prognosis and treatment options in ITPN.

CLINICAL PRESENTATION

Owing to the rare occurrence and relatively recent recognition and classification of ITPN, there are only limited data on this entity so far. According to the limited cases reported, ITPN occurs as commonly in males and females.[4] The mean age at diagnosis is 61 years (range, 35–78 years).[4] Risk factors have not been elucidated; however, a case of ITPN in a field of irradiation has been reported.[14] In another case report, an ITPN occurred in a 78-year-old man with a family history of pancreatic cancer.[9] Approximately two-thirds of patients present with nonspecific symptoms including abdominal pain, vomiting, weight loss, exacerbation of diabetes, jaundice, and fever. About one-third of patients are asymptomatic with incidental discovery of their lesions. Nearly half of ITPNs are located in the head of the pancreas. However, a literature review shows that ITPNs also occur in other pancreatic sites, including the body (5 of 30, 17%), tail (2 of 30, 7%), head and body (1 of 30, 3%), body and tail (2 of 30, 7%), and with diffuse involvement (4 of 30, 14%).[4] These tumors are usually slow growing and are therefore relatively large at the time of diagnosis. The size of the tumor ranges from 1 to 15 cm (3 cm in average). Laboratory tests are often nonspecific, including serum tumor antigens. Treatment is surgery in most cases (22 of 30, 73%), with the most frequent procedures being pylorus-preserving pancreatoduodenectomy and distal pancreatectomy.[4] Total pancreatectomy was performed in 18% of the patients.

IMAGING STUDIES

Radiographic studies, including endoscopic ultrasonography, dynamic contrast-enhanced computed tomography (CT), magnetic resonance (MR) imaging including MR cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP), are often performed before surgery and are helpful in assisting diagnosis in most cases. Intraductal tubulopapillary neoplasms are usually visualized as poorly enhancing lesions throughout the scanned phase.[15] Motosugi et al[16] described a 2-tone duct sign in ITPNs on the dynamic CT (7 of 10, 70%) and MR images (5 of 8, 63%), with a slightly higher density area representing the tumor in the main pancreatic duct and a lower density area representing dilated upstream duct. Most ITPNs arise in the main pancreatic duct with ductal dilation; only about 5% (2 of 41) of the cases arise in branch ducts.[15] Branch-duct ITPNs have neither a dilated main pancreatic duct nor 2-tone duct sign. Another characteristic feature of ITPN is a "cork-of-wine-bottle sign" that was observed on MRCP and ERCP images, indicating intraductal growth.[16] Rare ITPN cases have coarse calcification that can be mistaken for a neuroendocrine tumor.[17] However, concurrent obstruction and dilation of the main pancreatic duct would suggest an intraductal lesion. Knowledge about fluorodeoxyglucose–positron emission tomography findings for ITPN is limited. The degree of uptake varies depending on the characteristics within a tumor. For example, intratumoral hemorrhage can cause interval decrease in the metabolic activity and uptake within the tumor.[18] Many of the abovementioned findings are also characteristic of IPMNs, which makes diagnosis by imaging alone nearly impossible. A more solid growth pattern favors ITPN over IPMN.

HISTOPATHOLOGY

By definition, ITPNs are macroscopic (≥1 cm and mass forming), intraductal, tubule-forming epithelial neoplasms. Compared to IPMNs, they are less often cystic. Intraductal tubulopapillary neoplasms typically have uniform high-grade dysplasia and frequent mitotic figures. They consist of closely apposed tubules forming complex cribriform structures in dilated pancreatic ducts with focal areas of papillary architecture (Figure 1, A and B). Mucin is minimal to nonexistent. The tubules are lined by predominantly cuboidal to low columnar epithelial cells with a moderate amount of eosinophilic or amphophilic cytoplasm and round to oval nuclei with moderate to marked atypia. Rare clear cell changes and stromal osseous and cartilaginous metaplasia have been reported in ITPN.[19,20] Sometimes, apical apocrine snouts are present. Occasionally, there are intraluminal secretions or comedolike necrosis. Approximately 40% to 50% of ITPN cases are associated with invasive carcinoma.[4,21] A higher risk of invasion is associated with male sex, larger tumor size, and high Ki-67 proliferation.[4]

The diagnostic challenge posed by IPMN's histologic overlap with ITPN, especially the pancreatobiliary-type and oncocytic-type IPMN (Figure 1, C and D), needs to be addressed. A comparison between these 2 entities is listed in Table 1. Intraductal papillary mucinous neoplasms are typically cystic, have more abundant mucin, and their architecture is predominantly papillary. The cytologic atypia ranges from low- to high-grade and comedolike necrosis in the lumen is rare. By contrast, ITPNs are typically not cystic, have no or minimal mucin, and architecture is predominantly tubular. They have uniformly high-grade cytologic atypia, and comedolike necrosis in the lumen is frequently seen. However, it is important to note that diffuse high-grade dysplasia and cribriform complex architecture are found in many pancreatobiliary- and oncocytic-type IPMNs. For example, we have encountered a pancreatobiliary-type IPMN that histologically resembles ITPN with predominant tubular and cribriform complex architecture and comedolike necrosis in the lumen (Figure 2, A and B). In difficult cases such as this, immunohistochemistry studies may be helpful to confidently differentiate them, since most IPMNs are positive for MUC5AC and negative for MUC6 (Figure 2, C and D).

The differential diagnosis for ITPN may also include intraductal acinar cell carcinoma, which sometimes has an intraductal growth pattern, mimicking intraductal neoplasms.[22] They typically consist of sheets of back-to-back acinar structures, but papillary structures can be seen. The cells classically contain round uniform nuclei with a single prominent central nucleolus and eosinophilic zymogen granule–containing cytoplasm, characteristic features of acinar cell differentiation. Unfortunately, these typical cytologic features are not always present, in which case immunohistochemical studies for trypsin, chymotrypsin, and BCL10—all of which show positivity in acinar cell carcinoma—are necessary.

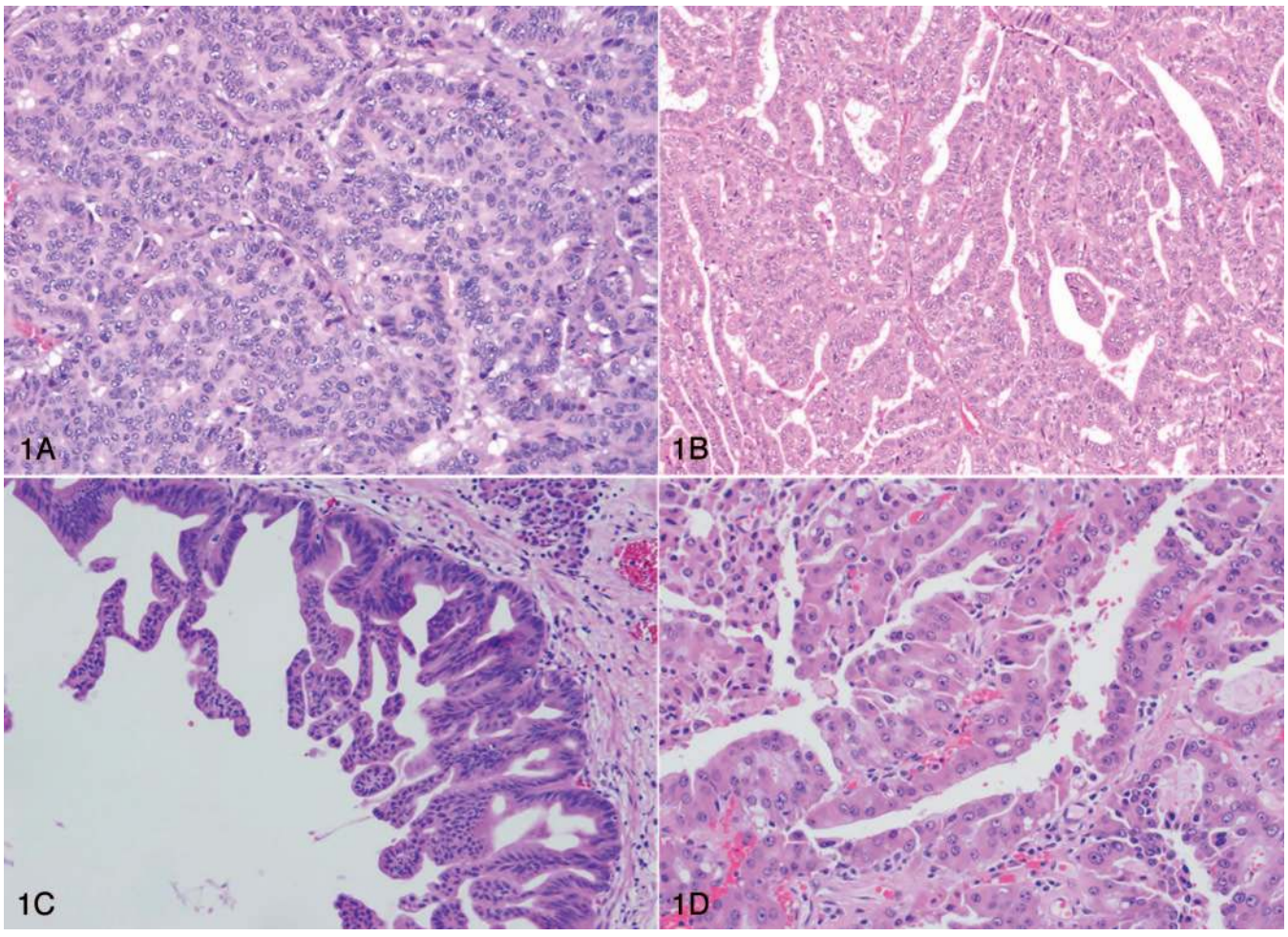

Figure 1. *Histologic comparison between intraductal tubulopapillary neoplasm and pancreatobiliary- and oncocytic-type intraductal papillary mucinous neoplasm (IPMN). A and B, Intraductal tubulopapillary neoplasm. C, Pancreatobiliary-type IPMN. D, Oncocytic-type IPMN (hematoxylin-eosin, original magnification ×200 [A through D]).*

IMMUNOHISTOCHEMISTRY

Immunohistochemical studies are useful in rendering the diagnosis of ITPN in rare cases that lack classic morphology or overlap histologically with IPMNs. In these cases the differential typically includes a combination of ITPN, various IPMN subtypes, and/or intraductal acinar cell carcinoma. Knowledge of the characteristic immunohistochemical profiles of these lesions can be very helpful in this situation. Typically, ITPNs are positive for cytokeratin (CK) 7 (21 of 21, 100%), CK19 (18 of 19, 95%), MUC1 (23 of 26, 88%), and MUC6 (14 of 19, 74%), and they are negative for MUC2 (25 of 26, 96%), MUC5AC (23 of 27, 85%), trypsin (19 of 19, 100%), and β-catenin (16 of 17, 94%).[4] However, rare cases of MUC5AC-positive ITPNs have been reported.[23] Mucin glycoproteins MUC6 and MUC5AC are the most useful markers to differentiate between ITPN and IPMN, since most IPMNs are positive for MUC5AC and negative for MUC6 (Figure 2, C and D). An exception is the oncocytic-type IPMN, which is usually positive for MUC6 and MUC1, and negative for MUC5AC and MUC2 (as is ITPN) (Table 2). Mitochondrial stains such as phosphotungstic acid–hematoxylin, Novelli stain, or apoptin 111.3 antibody in oncocytic IPMN may be helpful in this situation.[5] In addition, the cystic gross appearance with mucin production and the oncocytic cytology is also helpful in distinguishing oncocytic-type IPMN from ITPN. Gastric-type IPMNs can also be MUC6 positive, but should also express MUC5AC. MUC1 typically shows positivity in the pancreatobiliary-type IPMNs and negativity in other types of IPMN. MUC2 typically shows positivity in the intestinal-type IPMNs and negativity in other types of IPMN (Table 2).

As previously mentioned, intraductal acinar cell carcinoma can sometimes enter the differential diagnosis of ITPN,

Table 1. Histopathology and Molecular Comparison Between Intraductal Papillary Mucinous Neoplasm (IPMN) and Intraductal Tubulopapillary Neoplasm (ITPN)

	IPMN	ITPN
Luminal mucin	Abundant	Minimal to none
Atypia	Low–high-grade	Uniform high-grade
Predominant growth pattern	Papillary	Tubular
Comedolike necrosis	Rare	Frequent
KRAS mutation	+/−	−
PIK3CA mutation	−	+/−

Abbreviations: −, absent; +/−, present or absent.

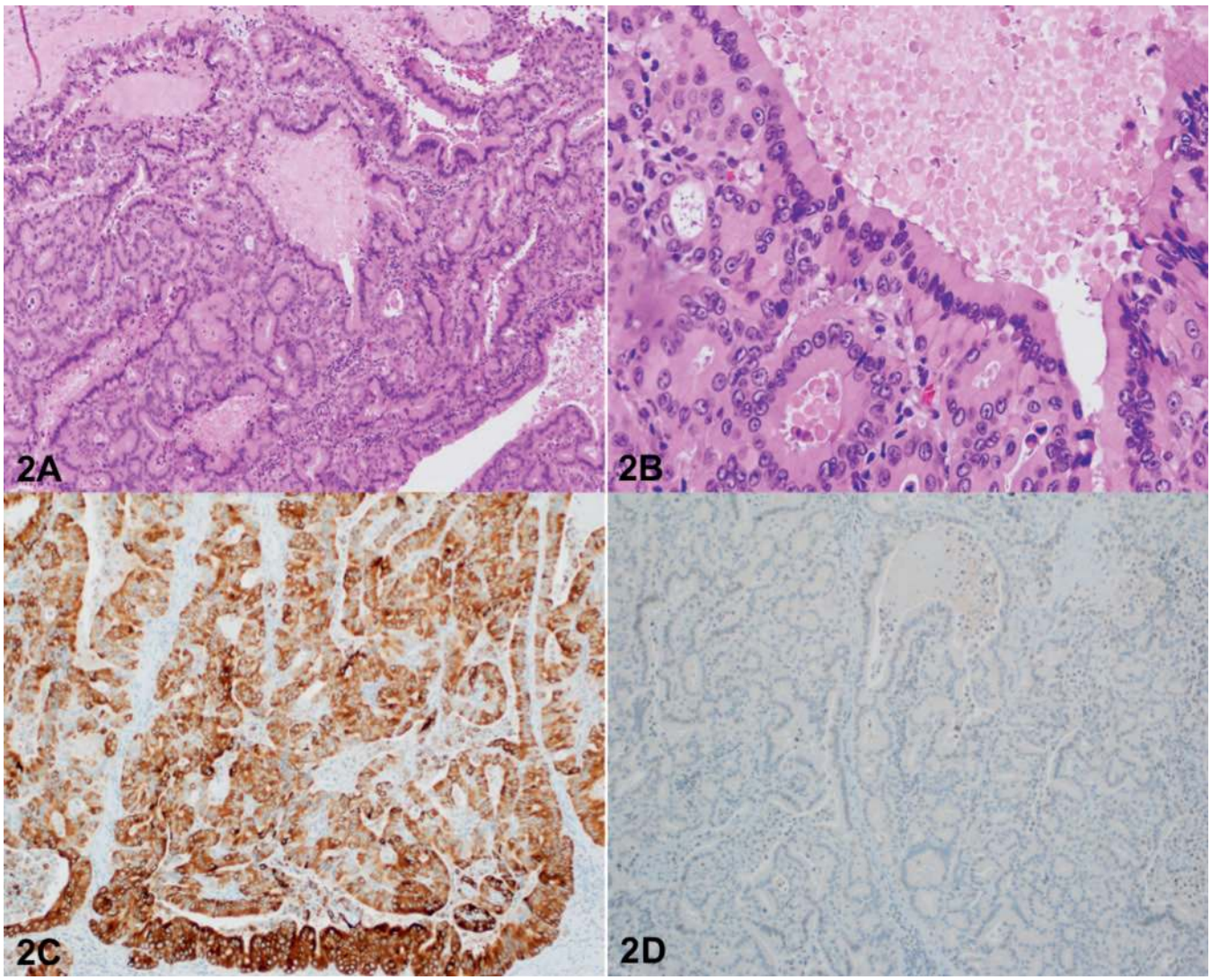

Figure 2. *A pancreatobiliary-type intraductal papillary mucinous neoplasm (IPMN) histologically mimicking intraductal tubulopapillary neoplasm (ITPN). A, Back-to-back tubules with cribriform complex architecture and frequent comedolike necrosis in the lumen, histologically resembling ITPN. B, Higher magnification of the same lesion as in (A) showing the tubules lined by cuboidal/columnar epithelial cells with eosinophilic cytoplasm and atypical nuclei. Apical apocrine-like snouts and comedolike necrosis in the lumen are present. C and D, The neoplastic epithelial cells are diffusely positive for MUC5AC (C) and negative for MUC6 (D), supporting a diagnosis of pancreatobiliary-type IPMN (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]; original magnification ×100 [C and D]).*

but it should be trypsin, chymotrypsin, and BCL10 positive. BCL10 is a newly developed marker of acinar cell differentiation in pancreas.[24,25] The antibody recognizes the C-terminal portion of the BCL10 protein, which is homologous to an enzyme (carboxylic ester hydrolase) produced by pancreatic acinar cells. It is more sensitive than other pancreatic enzyme markers in detecting acinar cell carcinoma. Studies also show that BCL10 is specific to acinar cells of normal and ectopic pancreas, of pancreatic metaplasia, and of acinar cell carcinoma, and is not expressed in pancreatic ductal adenocarcinoma, IPMN, mucinous cystic neoplasm, neuroendocrine tumor, solid-pseudopapillary neoplasm, or serous cystic tumor. One caveat is that some of the adenosquamous carcinomas of the pancreas can be positive for BCL10.[24]

Table 2. Immunohistochemistry Comparison Between Intraductal Papillary Mucinous Neoplasm (IPMN) and Intraductal Tubulopapillary Neoplasm (ITPN)

	IPMN				
MUC	Gastric	Intestinal	PB	Oncocytic	ITPN
MUC1	−	−	+	Focal +	+
MUC2	−	+	−	−	−
MUC5AC	+	+/−	+	−	−
MUC6	+/−	−	−	+	+

Abbreviations: PB, pancreatobiliary type; +, positive; focal +, focal area positive; −, negative; +/−, positive or negative.

Interestingly, an unusually strong and diffuse immunohistochemical staining pattern for vimentin was observed in a case of branch-duct lesion with morphologic features of ITPN.[26] The lesion was also positive for CK7 and MUC1, but negative for MUC5AC, chymotrypsin, CK20, chromogranin, synaptophysin, β-catenin, and PAX8. The authors stained 3 cases of IPMNs, none of which were positive for vimentin.

Table 3. Molecular Genetic Comparison Between Intraductal Papillary Mucinous Neoplasm (IPMN) and Intraductal Tubulopapillary Neoplasm (ITPN)

	IPMN, %	ITPN, %
KRAS	47–81	0–10
GNAS	41–66	0–25
TP53	10 (5/52, high-grade)	0–23
BRAF	6 (3/52, high-grade)	0–15
SMAD4/DPC4	2 (1/52)	0–10
RNF43	75	N/A
PIK3CA	3–11	0–27
CDKN2A/p16	18	54

Abbreviation: N/A, not available.

Data derived from Kolby et al,[4] Kloppel et al,[6] Yamaguchi et al,[13] Reid et al,[28] Amato et al,[29] Urata et al,[36] Esposito et al,[38] Wu et al,[39] and Furukawa et al.[40]

Pancreatic neoplasms are rarely positive for vimentin, except for solid-pseudopapillary neoplasm. It is not known whether this is an incidental finding in a single case or whether this is applicable to all ITPNs. Larger studies in ITPNs are necessary to clarify this finding.

MOLECULAR CHARACTERISTICS

Evidence that ITPN and IPMN are distinct entities also lies in their differing molecular genetic characteristics (Table 3). Whole exome sequencing of IPMNs revealed about 26 mutations per neoplasm, with mutations in *KRAS* (47%–81%), *GNAS* (41%–66%), and *RNF43* (ubiquitin E3 ligase ring finger 43) (75%) observed most frequently.[27] Consistently, *KRAS* mutations are the most frequent, which supports the hypothesis that *KRAS* is an important driver gene during IPMN progression. Second most common are mutations in *GNAS*, typically at codon 201. Nearly 100% of intestinal-type IPMNs harbor a *GNAS* mutation. Interestingly, *GNAS* mutations have been found in invasive adenocarcinomatous components associated with IPMNs but not in de novo, isolated ductal adenocarcinomas.[28] *RNF43* is a potential tumor suppressor gene and a negative regulator of the Wnt signaling pathway; it is inactivated in 75% of IPMNs.

Recently, Amato et al[29] sequenced 52 intraductal papillary neoplasms, including 48 IPMNs and 4 ITPNs to assess mutational profile in 51 cancer-associated genes by using Ion Torrent semiconductor-based next-generation sequencing technique (Life Technologies, Carlsbad, California). At least 1 somatic mutation was found in 96% (46 of 48) of IPMNs, and 60% (29 of 48) had multiple gene mutations. Again, 92% (44 of 48) of IPMNs were found to have *KRAS* and/or *GNAS* mutations. In addition, *KRAS* and *GNAS* mutations coexist in 37.5% (18 of 48) of IPMNs. *RNF43* was the third most commonly mutated gene in IPMNs and it was always associated with *KRAS* and/or *GNAS* mutations. On the contrary, only 1 of 4 ITPNs contained *GNAS* and *NRAS* mutations. Interestingly, the gastric-type IPMNs had the most frequent *GNAS*, *KRAS*, and *SMAD4* mutations, compared to other types of IPMNs, although the sample number was relatively low ($n = 6$).[29] *TP53* (5 of 52, 10%) and *BRAF* (3 of 52, 6%) mutations were only found in high-grade IPMNs, with *TP53* mutations most often detected in pancreaticobiliary type. Other less common mutations in IPMNs include *PIK3CA* (3%–11%), *AKT1* (3 of 36, 8%), *CDKN2A/p16* (18%), *SMAD4* (1 of 52, 2%), *CTNNB1/β-catenin* (2 of 52, 4%), *IDH1* (2 of 52, 4%), *STK11* (2 of 52, 4%), *PTEN* (2 of 52, 4%), *ATM* (1 of 52, 2%), *CDH1* (1 of 52, 2%), *FGFR3* (1 of 52, 2%), and *SRC* (1 of 52, 2%).[6,29,30] Most of these low-frequency mutations are found concurrent with a *GNAS* and/or *KRAS* mutation.[29] Some of these additional mutations may reflect more advanced, higher-grade lesions, as *CDKN2A/p16* and *SMAD4* mutations and/or loss of expression has been shown to correlate with higher-grade lesions.[31–33] Increased microRNA expression, such as miRNA-21, in IPMNs has also been reported.[34]

Compared with IPMNs, molecular genetic studies of ITPN are relatively limited owing to the small number of cases available. According to a literature review, mutational analysis revealed *TP53* mutations in 27% (6 of 22), *PIK3CA* mutations in 18% (2 of 11), *BRAF* mutation in 15% (2 of 13), and *KRAS* mutation in 10% (2 of 20) of the ITPN cases.[4] However, other studies[6] have found lower frequency of *KRAS* mutation (0%–7%) in ITPNs. Although mutations of *PIK3CA* were described in 3% to 11% of IPMNs, they are among the most frequent mutations in ITPN (up to 27%, 3 of 11).[3,35] Therefore, *KRAS* mutations are much more common in IPMN, whereas *PIK3CA* mutations are much more common in ITPN (Table 1).[5] Of note, *PIK3CA* mutations are often associated with an increase in phosphorylated AKT, suggesting the activation of the PI3K-AKT signaling pathway and a potential therapeutic target in ITPN.[28] Altered expression of CDKN2A/p16 was seen in 54% of ITPNs, and p53 was overexpressed in 20% of ITPNs. Rare *BRAF* V600E mutations have also been reported.[36] Recent deep coverage, targeted next-generation sequencing was performed on 11 ITPN cases with a panel of 300 key cancer-associated genes and none of the known IPMN-associated genetic alterations were found in ITPN.[37] Two histone H3 methyltransferase genes, *MLL2* and *MLL3*, each were mutated in 2 cases of ITPN. Six ITPN cases had *MCL1* (a member of the Bcl-2 family) amplification, while 3 ITPN cases contained no mutations in the tested genes. Taken together, the data indicate that there are definitive genetic differences between ITPN and IPMN, which makes genetic analysis another valuable tool for diagnosis.

PROGNOSIS AND TREATMENT

There are limited follow-up data available in the literature for ITPNs. Invasive carcinoma was reported in 54% (13 of 24) of the ITPN cases.[4] Male sex, large tumor size, increased mitosis, and high Ki-67 proliferative index, but not age, are associated with a higher risk of invasive growth.[4,13] Therefore, one study[4] proposed that imaging-guided core needle biopsy followed by Ki-67 immunohistochemical staining, together with imaging to determine the tumor size, should be used to stratify the risk of invasion before surgery. Rare cases of death from multiple ITPN liver metastases have been reported. Therefore, surgery is currently preferred to treat patients with ITPN to prevent malignant transformation. The tumor can recur years after surgery, which is thought to be due to intraductal colonization. However, other cases of ITPN resected via distal pancreatectomy did not have recurrence in the follow-up period, suggesting that total pancreatectomy is not always necessary. Nevertheless, close clinical follow-up is considered essential to detect early recurrence. Fortunately, the prognosis of ITPN-associated invasive carcinoma is much better than that of traditional pancreatic

ductal adenocarcinoma, even in patients with recurrent and metastatic disease.[6] The 5-year survival is more than 30%.

CONCLUSIONS

Intraductal tubulopapillary neoplasm is a newly recognized type of pancreatic intraductal neoplasm. It is defined as an intraductal, grossly visible, tubule-forming epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Intraductal tubulopapillary neoplasm is a rare entity and thus there are limited clinical, pathologic, and molecular genetic data regarding this disease. As these neoplams are considered to be precursor lesions to carcinomas, surgery and close clinical follow-up is generally recommended. Morphologically, they can mimic some subtypes of IPMN. However, molecular studies revealed that they are distinct entities. Further studies are needed to elucidate the clinical, pathologic, and molecular features of ITPN, which could be used as guidance for the management of patients.

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