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Pancreatic ductal adenocarcinomas associated with intraductal papillary mucinous neoplasms (IPMNs) versus pseudo-IPMNs: relative frequency, clinicopathologic characteristics and differential diagnosis

Takashi Muraki[1], Kee-Taek Jang [2], Michelle D. Reid[1], Burcin Pehlivanoglu[1], Bahar Memis[1], Olca Basturk [3], Pardeep Mittal[4], David Kooby[5], Shishir K. Maithel[5], Juan M. Sarmiento[5], Kathleen Christians[6], Susan Tsai[6], Douglas Evans[6] and Volkan Adsay[7✉]

The literature is highly conflicted on what percentage of pancreatic ductal adenocarcinomas (PDACs) arise in association with intraductal papillary mucinous neoplasms (IPMNs). Some studies have claimed that even small (Sendai-negative) IPMNs frequently lead to PDAC. Recently, more refined pathologic definitions for mucin-lined cysts were provided in consensus manuscripts, but so far there is no systematic analysis regarding the frequency and clinicopathologic characteristics of IPMN-mimickers, i.e., pseudo-IPMNs. In this study, as the first step in establishing frequency, we performed a systematic review of the pathologic findings in 501 consecutive ordinary PDACs, which disclosed that 10% of PDACs had associated cysts ≥1 cm. While 31 (6.2%) of these were IPMN or mucinous cystic neoplasm (MCN), 19 (3.8%) were other cyst types that mimicked IPMN (pseudo-IPMNs) per recent WHO/consensus criteria. As the second step of the study, we performed a comparative clinicopathologic analysis by also including our entire surgical pathology/consultation databases that was comprised of 60 IPMN-associated PDACs, 30 MCN-associated PDACs and 40 pseudo-IPMN-associated PDACs. We found that 84% of true IPMNs were pre-operatively recognized, whereas IPMN was considered in differential diagnosis of 33% of pseudo-IPMNs. Of the 40 pseudo-IPMNs, there were 15 secondary duct ectasias; 6 large-duct-type PDACs; 5 pseudocysts; 5 cystic tumor necrosis; 4 simple mucinous cysts; 3 groove pancreatitis-associated paraduodenal wall cysts; and 2 congenital cysts. Microscopically, pseudo-IPMNs had at least partial mucinous-lining mimicking IPMN but had smaller cystic (mean = 1.9 cm) and larger PDAC (mean = 3.8 cm) components compared to true IPMNs (cyst = 5.7 cm; PDAC = 2.0 cm). In summary, in this pathologically verified analysis that utilized refined criteria, 10% of PDACs were discovered to have cysts ≥1 cm, about two-thirds of which were IPMN/MCN but about one-third were pseudo-IPMNs. True IPMNs underlying the PDACs are often large and are already diagnosed pre-operatively as having an IPMN component, whereas only a third of the pseudo-IPMNs receive IPMN diagnosis by imaging and their cysts are smaller. At the histopathologic level, pseudo-IPMNs are highly prone to misdiagnosis as IPMN, which presumably accounts for much higher association of IPMNs with PDAC as reported in some studies. The subtle but salient characteristics of pseudo-IPMNs elucidated in this study should be combined with careful radiological/clinical correlation in order to exclude pseudo-IPMNs.

INTRODUCTION
Pancreatic ductal adenocarcinoma (PDAC) is now the third leading cause of cancer-related death in the U.S.[1]. The vast majority of PDACs are solid tumors presumed to arise from microscopic dysplastic lesions termed pancreatic intraepithelial neoplasia (PanIN)[2], which are, by definition, radiologically and grossly invisible. A subset of PDACs arise from cystic precursor lesions, i.e., mucinous cystic neoplasms (MCNs) and intraductal neoplasms,

in particular, intraductal papillary mucinous neoplasms (IPMNs) and other related entities, which by definition form grossly visible tumors that are typically larger than 1 cm. These are thought to represent a separate PDAC evolution pathway, which can be viewed as the tumoral intraepithelial neoplasm pathway, and have distinct molecular, biological, and prognostic characteristics[2–10]. The reported frequency of PDAC-associated IPMN (and similar tumoral intraepithelial neoplasms) is highly variable, and ranges

[1]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA. [2]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. [3]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [4]Department of Radiology, Emory University School of Medicine, Atlanta, GA, USA. [5]Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA. [6]Department of Surgery, Medical College of Wisconsin, Wauwatosa, WI, USA. [7]Department of Pathology, Koç University Hospital and Koç University Research Center for Translational Medicine (KUTTAM), Istanbul, Turkey. ✉email: vadsay@kuh.ku.edu.tr

from <1% to 15%[11–14]. This is presumably due to definitional differences in what represents a true IPMN, and has contributed to vastly divergent views on the clinical significance of IPMNs and their role in PDAC formation. This becomes highly pertinent when an IPMN is detected in isolation or incidentally in terms of how best to manage them. Some schools have found that even small IPMNs accompany PDACs, and consequently now advocate resecting all IPMNs.

Incidental pancreatic cysts are increasingly being discovered in the general population (up to 15% in the elderly[15–20]), and the frequency of what percentage really lead to PDAC has very significant population-wide implications. In most studies, small, incidental, non-complex IPMNs (also called "Sendai-negative"[21] referring to the radiologic criteria used in evaluation of these cysts) have been found to be innocuous processes for which "watchful waiting" is mostly adequate[22–24]. However, as mentioned above, some studies have recently claimed that PDACs are not uncommonly associated with even small "branch-duct" IPMNs[21,25–29], including even those that are ≤1 cm[21,27–29]. These reports have led some observers to propose that all IPMNs may require resection, even if they are very small[21,25,26].

Concurrently, several international consensus meetings have recently been held to achieve more unified terminology and concepts in diagnosis and differential diagnosis of IPMNs including the Baltimore and Verona consensus meetings[3,5,10,23,30], and the criteria put forth in these studies were also covered in the World Health Organization (WHO)-2019 classification[31].

In this study, we investigated the frequency, clinical and histopathologic characteristics of ≥1.0 cm cystic lesions associated with PDAC using recently refined criteria. Towards this goal, we reviewed the pathology material of 501 consecutive pancreato-duodenectomies that contained PDAC in order to determine the true frequency of this occurrence. Separately, we evaluated the clinicopathologic findings of all the PDACs associated with ≥1 cm cysts in our entire institutional and consultation files.

METHODS
The cases subjected to deeper analysis were identified as below.

1. In order to determine the true frequency of ≥1 cm cysts accompanying ordinary PDACs and the relative frequency of lesions contributing to this phenomenon, the pathology material from 501 consecutive pancreatectomies with ordinary PDAC resected in one institution (Emory University) between 2009 and 2016 were carefully reviewed by the authors. Both the radiologic images and pathology reports of these cases were investigated (T.M.) as well as detailed microscopic examination of the slides (V.A., B.M., T.M., B.P., and M.D. R).
2. Separately, all the PDACs with documentable cyst(s) ≥1 cm, and all the IPMNs and MCNs with an associated invasive pancreatobiliary-type carcinoma in the authors' institutional databases as well as the surgical and consultation files of the authors (in addition to those identified in the systematic review mentioned above) were also retrieved and added to the analysis for the clinicopathologic comparison component of the study.

Only conventional PDACs (with tubular, ordinary pancreatobiliary-type adenocarcinoma pattern) were included. Other carcinoma subtypes biologically different than PDAC (e.g., colloid carcinoma) and non-ductal neoplasms (neuroendocrine carcinoma, acinar carcinoma, etc.) were excluded, as were carcinomas arising from the ampulla and common bile duct, and other secondary carcinomas by careful histologic evaluation and correlation with clinical findings. PDACs resected post-neo-adjuvant therapy were also excluded to have a more uniform cohort.

The ≥1 cm cyst size was selected because of its known usage as a definitional cut-off size criterion for distinguishing IPMNs (which are typically >1 cm) from PanINs (which are <1 cm)[5,31]. The cyst size in radiology reports as well as imaging studies themselves (where available) was recorded by the authors (T.M. and P.M.); however, the documentation of existence and size of a cystic component was highly variable in

radiology reports, and in addition, radiology images were not completely accessible to the authors in all cases. Accordingly, the final cyst size was defined by pathological examination.

For the diagnosis of IPMN and distinction from its mimics, the definitions outlined in the WHO tumor classification book and recent Baltimore and Verona consensus meetings were applied[3,5,31]. For MCN, the presence of ovarian stroma was required[10,32]. For the diagnosis of simple mucinous cyst (SMC), the definitions provided by the Baltimore and Verona consensus meetings[3,5] and later detailed by Krasinskas et al.[30] were utilized. Paraduodenal wall cysts were defined as arising in a background of paraduodenal pancreatitis and showing the characteristic features of this entity[33]. Large-duct-type PDAC was defined as previously described[34,35]. Colonization (cancerization; intraductal spread of invasive carcinoma cells) was defined using Baltimore consensus conference guidelines[5]. The initial histopathological assessment of the cases in terms of the diagnostic classification, verification of PDAC, and the presence of a cyst ≥1 cm was conducted by two pathologists (B.M. and V.A.). The final classification of the cyst type was done in a consensus setting including V. A., B.M., M.D.R., B.P, and T.M., and in controversial cases a vote was taken in order to place the given case to a more specific category.

RESULTS
The findings in the institutional cohort of 501 consecutive PDAC resections (utilized for the frequency determination) and those in the overall cohort (i.e., all-comers including consultation cases and those in surgical databases spanning over a larger time frame), which was analyzed for clinicopathologic characteristics, are provided separately below.

Frequency of ≥1 cm cysts with PDACs
In 501 consecutive pancreatectomies analyzed systematically by the authors, 10% of these ordinary PDACs were found to be accompanied by a cyst ≥1.0 cm. These were 25 IPMNs (5.0%), 6 MCNs (1.2%), and 19 other cyst types (3.8%) (Table 1).

Clinicopathologic characteristics of different groups
When all the PDACs accompanied by a cyst ≥1 cm in the authors' entire files (including consultation cases) were analyzed and classified per the current criteria, 90 PDACs were IPMN/MCN associated, and 40 had other cyst types that mimicked IPMNs which, for the purpose of this study, we grouped as pseudo-IPMNs. The clinicopathologic characteristics of these were as follows.

Table 1. Clinicopathologic comparison of cysts ≥1 cm accompanying ordinary PDACs classified as IPMN/MCN versus pseudo-IPMN ($n = 130$).

	PDAC with IPMN/MCN	PDAC with pseudo-IPMN
Total number of the cases	90	40
True frequency in 501 systematically evaluated cases	6.2%; $n = 31$	3.8%; $n = 19$
Mean age (range), years	65 (29–82)	67 (50–87)
Male gender, %	39	44
Cysts located in body/tail, %	44	50
Mean size of PDAC (range), cm	2.0 (0.1–7.0)	3.8 (1.2–7.0)
Mean size of cystic component (range), cm	5.7 (1.0–25.2)	1.9 (1.0–11.0)
Pre-operative diagnosis of IPMN	84% (94%, after 2010)	33%*

PDACs pancreatic ductal adenocarcinomas, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm.
*Results of pre-operative imaging studies were available to the authors in 27 of 40 patients with pseudo-IPMN, and in 9 of these (33%) pre-operative diagnosis was IPMN.

IPMN/MCN-related PDACs (*n* = 90)

There were 60 IPMN-associated PDACs (i.e., IPMN with associated tubular/ductal-type adenocarcinoma) and 30 MCN-associated PDACs in the authors' files that were verified and re-classified histologically by the authors. In these 90 cases, the PDAC represented a smaller component of the overall tumor (mean, 2.0 cm; range, 0.1–7.0) while the cystic component was fairly large (mean, 5.7 cm; range, 1.0–25.2) (Table 1).

Among the cases in this group that had adequate pre-operative radiologic documentation available, the majority (84%) had been diagnosed as IPMN/MCN pre-operatively, and this frequency was even higher for the cases diagnosed after 2010 (94%, 31/33).

Pseudo-IPMN-related PDACs (*n* = 40)

Clinical findings. The mean age of this heterogenous group was 67 years (range, 50–87), there was no gender predilection (56% were female) and, of note, half of them (50%) occurred in the body/tail (Table 1).

Detailed pre-operative imaging data was available to the authors in 27 of 40 patients with pseudo-IPMN, and in 9 of these, the diagnosis for the cystic component had been designated as IPMN pre-operatively although none could be verified as IPMN on subsequent histologic examination (Table 2). Additionally, 2 had been classified pre-operatively as pseudocyst, which histologically proved to be central necrosis and paraduodenal wall cyst, and 1 as metastatic renal cell carcinoma (proved to be pseudocyst). The remaining 15/27 with adequate data available had been diagnosed pre-operatively as PDAC with retention cyst or pseudocyst (Table 1).

General pathologic features. The mean size of PDAC in the pseudo-IPMN group was 3.8 cm (range, 1.2–7.0) and the mean size of cystic component was 1.9 cm (range, 1.0–11.0) (Table 1). Histologically, all examples had ductal epithelial lining, and in most (37/40; 93%), the cyst lining was at least partially mucinous, making IPMN a differential diagnosis. In 64% these, the mucinous lining of the cysts was due to colonization by carcinoma (i.e., cancerization; Fig. 1) mimicking high-grade dysplasia of IPMN. Also, degenerative changes were frequently present including granulation tissue, hemorrhage, and myxoid stroma.

Adequate sections of uninvolved pancreas away from tumor were available for examination to the authors in 18 of the pseudo-IPMN cases. While 4 of these showed low-grade PanINs, 11 had high-grade PanINs, and there was no PanIN identified in the remaining 3 cases.

Classification of pseudo-IPMNs

Pseudo-IPMNs were classifiable into 2 groups (Table 2).

Mucinous epithelial or carcinoma-lined cysts

Secondary duct ectasia (retention cysts) (n = 15). Mean cyst size was 1.3 cm (range, 1.0–2.2) and 36% (*n* = 5) occurred in the tail (although <20% of PDACs were in the tail). The cystic component was typically localized upstream to the PDAC and displayed the distinctive architecture of secondary dilatation (Fig. 2). Magnetic resonance imaging (MRI) revealed a homogeneous cyst with high intensity on T2-weighted images (Fig. 2). Of the 11 cases with adequate imaging, 4 had been diagnosed as IPMN radiologically.

By pathologic examination, they typically formed multiple smaller round and distinct cysts that were located within the parenchyma (unlike primary cysts such as SMCs and IPMNs, which often protruded to the soft tissues). A characteristic finding was the formation of a chain at the periphery creating a pattern similar to that of polycystic ovary. They (15/15) had at least partial low-cuboidal lining by unremarkable epithelium unlike many other cyst types, but colonization by the adjacent invasive carcinoma was also a very common finding (14/15). This typically created PanIN-like mucinous epithelium with abrupt transition to normal epithelium. They often showed direct continuity with or spatial relationship to the invasive carcinoma. In some cases, the colonized areas displayed foamy cytology as well as atypical patterns such as cribriforming and irregular tufting, characteristic of colonization and not seen in PanINs.

Large-duct type PDAC (n = 6). Mean cyst size was 1.1 cm, with the largest cyst measuring 1.4 cm and the PDAC was relatively large (mean, 4.8 cm, range, 2.7–7.0). All were in the body/tail. Radiologically, multiple cystic structures, some ≥1 cm, were noted within the PDAC bed. MRI showed relatively high intensity in the cysts but less than that of cerebrospinal fluid (CSF) on T2-weighted image (Fig. 3A, B). All showed histologic features of large-duct type adenocarcinoma (Fig. 3C, D) as previously described[34,35].

Simple mucinous cyst (SMC) (n = 4). The cysts of this group were relatively larger (mean, 2.3 cm, range, 1.8–3.1). Radiologically, they were usually unilocular and round with high-intensity areas similar to CSF on T2-weighted MRI (Fig. 4A). Microscopically, they had smooth internal lining composed mostly of flattened simple mucinous epithelium without florid papillae. They tended to protrude into peripancreatic soft tissues (Fig. 4B, C). Pericystic pancreatic parenchyma was relatively unremarkable. By definition, they had mucinous lining. All 4 had focal mild atypia (low-grade PanIN-type changes) in this epithelium; however, none showed high-grade PanIN or colonization (Table 2). They were in the vicinity of the invasive carcinoma but were solitary, isolated cysts showing all the characteristics described in recent studies on this topic[30].

Congenital cyst (n = 2). Both the cysts were fairly large (6.0 and 11.0 cm) with a relatively small (1.6 and 2.5 cm, respectively) PDAC component. They had been initially diagnosed as IPMN, both radiologically and pathologically. However, cyst walls contained a band of smooth muscle and the lining epithelium showed few areas of respiratory-type epithelium with associated accessory mucous glands (Fig. 5), which are pathognomonic of congenital cysts. Both cases displayed papillary in situ neoplasia mimicking IPMN.

Paraduodenal wall cyst of paraduodenal/groove pancreatitis (n = 3). The cystic component was relatively large (1.4, 2.2, and 2.5 cm, respectively). These patients were all males and were significantly older (63, 66, and 80 years) than the typical paraduodenal pancreatitis patient (mean age, 50s)[33,36]. Radiologically, cystic lesions were located in the groove area or duodenal wall, and displayed typical characteristics of paraduodenal (groove) pancreatitis (Fig. 6A). History of pancreatitis was documented in one-third. Microscopically, cysts were partially lined by epithelium and hypercellular stroma showing acinar secretions and inflammatory/fibroblastic reaction, features characteristic of paraduodenal pancreatitis (Fig. 6B, C). No colonization by carcinoma was seen in this group.

Cysts related to necrosis/degeneration

Pseudocyst (n = 5). The cysts measured up to 2.5 cm (mean, 1.5 cm). Radiologically, they were demarcated unilocular peripancreatic cysts with a heterogeneous interior on MRI (Fig. 7A, B). Of the 3 cases with available imaging, 1 was pre-operatively diagnosed as IPMN-associated PDAC. Microscopically, cyst contents were partly hemorrhagic and necrotic, and the cyst walls were composed of granulation tissue and fibro-inflammatory debris, typical of pseudocysts (Fig. 7C). In 3 cases, carcinoma colonized the cysts, with carcinoma cells invading into and partially lining the cyst wall.

Table 2. Radiological and pathological characteristics of pseudo-IPMNs.

	Retention Cyst (secondary duct ectasia)	Large-duct-type PDAC	Simple mucinous cyst	Congenital cyst	Paraduodenal wall cyst of PDP	Pseudocyst of conventional type	Necrosis within the tumor
Distribution, body/tail, n*	5/14	5/5	1/2	1/2	0/3	3/4	1/4
Mean size of cystic component (range), cm	1.3 (1.0–2.2)	1.1 (1.0–1.4)	2.3 (1.8–3.1)	6 and 11	1.4, 2.2, and 2.5	1.5 (1.0–2.5)	1.8 (1.0–3.4)
Pre-operative diagnosis of IPMN, n***	4/11	0/3	1/2	1/1	2/3	1/3	1/5
MRI findings	Unilocular and concentric at the distal side of the PDAC. High intensity on T2-WI.	Multiple cystic structures, some >1 cm within the PDAC. Relatively high intensity but less than that of cerebrospinal fluid on T2-WI.	Unilocular and round. High-intensity fluid on T2-WI.	N/A	Cysts in the groove area or duodenal wall.	Demarcated unilocular peripancreatic cysts with heterogeneous occasionally un-enhanced components.	Heterogeneous cystic lesions within the PDAC.
Pathologic findings	Round, unilocular, with smooth lining and open lumina. No contour irregularities. No papillary configuration. No classical cell types.	Irregularly distributed large ducts with jagged edges. Lined by columnar mucinous cells often having deceptively bland cytological features. Variable degrees of papillomatosis.	A smooth internal lining composed of simple mucinous lining with occasional folding and atypia. No florid papilla formation.	A band of muscle coat and other epithelia (respiratory) and accessory mucous glands.	Cysts were lined partially by epithelium and hypercellular reactive tissue with stromal deposition of acinar secretions associated with inflammatory/fibroblastic reaction.	Partly hemorrhagic and necrotic. Cyst wall composed of granulation tissue and fibro-inflammatory elements. Carcinoma cells were seen invading into and partially lining the inner layer of the fibro-inflammatory cyst wall.	In 3, the cystic component corresponded to acellular hyalinized material and the cyst wall also showed partially hyalinized and paucicellular stroma but also contained carcinoma cells. In 2 others, the cyst wall was composed of hypercellular inflammatory stroma.
Partial mucinous cyst lining, n**	15/15	6/6	4/4	2/2	2/3	4/5	3/5
Colonization by carcinoma, n	14/15	–	–	–	0/3	3/5	0/5
PanIN in the uninvolved pancreas, n**,***	6/6 (4 HG-PanIN, 2 LG-PanIN)	3/3 (2 HG-PanIN, 1 LG-PanIN)	2/2 (1 HG-PanIN, 1 LG-PanIN)	0/2	2/2 (HG-PanIN)	2/3 (HG-PanIN)	1/2 (HG-PanIN)

PDAC pancreatic ductal adenocarcinoma, PDP paraduodenal pancreatitis, IPMN intraductal papillary mucinous neoplasm, MRI magnetic resonance imaging, T2-WI T2-weighted image, N/A no available data, LG-PanIN low-grade pancreatic intraepithelial neoplasia, HG-PanIN high-grade pancreatic intraepithelial neoplasia.

*Results of pre-operative imaging studies were available to the authors in 27 of 40 patients with pseudo-IPMN.

**One case had both paraduodenal wall cyst and cystically necrotic tumor.

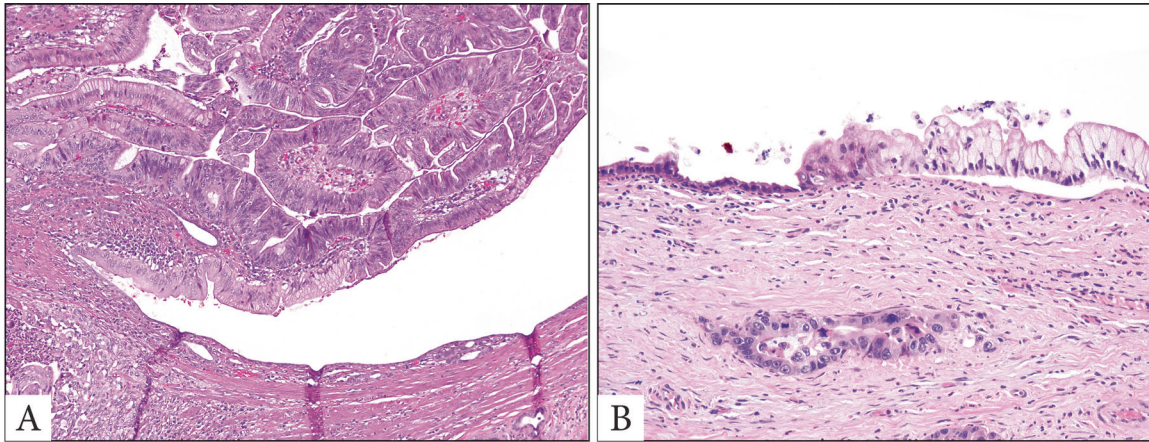***Adequate slides representing the uninvolved pancreas were available in 18 patients.

Fig. 1 Pseudo-IPMNs characterized by cysts showing papillary and mucinous linings. A Invasive carcinoma invading to a secondary (retention) cyst is forming a compact papillary nodule virtually indistinguishable from an IPMN. **B** This retention cyst is lined partially by normal ductal epithelium (left), and partially by invasive carcinoma colonizing the surface (cancerization, right) mimicking IPMN (H&E stain). Invasive carcinoma is typically seen on the wall of these cysts (lower left in (**A**), and middle-lower in (**B**)).
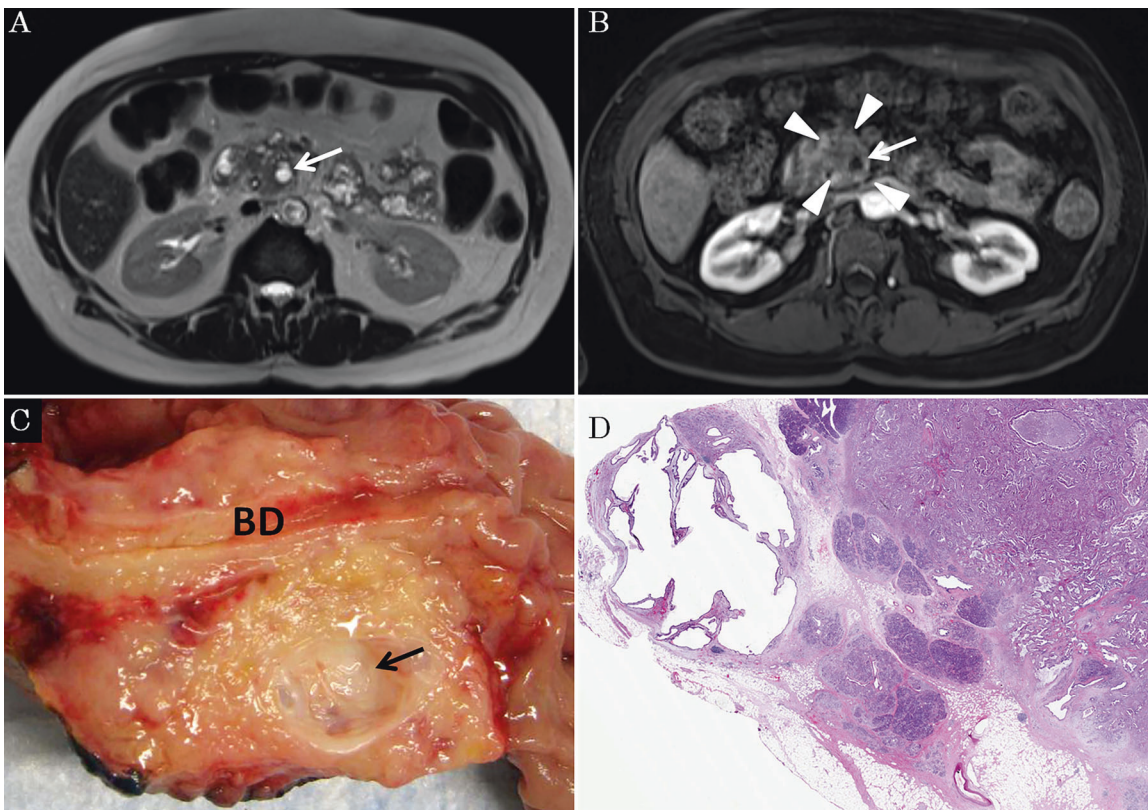
Fig. 2 Secondary duct ectasia (retention cyst) forming a pseudo-IPMN. A, **B** The cystic component (arrow) bordered on pancreatic ductal adenocarcinoma (arrow head) was usually unilocular-appearing, a homogeneous cyst with high intensity on T2-weighted image (**A** HASTE-MRI and **B** T1-weighted image, arterial phase). **C** Retention cysts (arrow) were round and unilocular with smooth lining and open lumina on gross examination (H&E stain). **D** Whole-mount photomicrograph of the upstream dilatation at the periphery of the pancreas (left), and solid carcinoma component (right; H&E stain). Note the atrophic parenchyma surrounding the retention cyst.

Cystic necrosis of carcinoma (n = 5). Mean cyst size was 1.8 cm (1.0–3.4) and by MRI these were heterogeneous cystic lesions within the PDAC (Fig. 8A, B). In 3 cases, this corresponded partly to acellular hyalinized material with cavitary changes rather than a cyst formed by conventional tumor necrosis. In the other 2, the cyst wall contained inflammatory stroma (Fig. 8C, D).

DISCUSSION

Of the resected PDACs, 5% are associated with IPMNs

This study elucidates that 10% of ordinary PDACs are accompanied by mucin/carcinoma-lined cysts ≥1 cm. However, histologically verifiable IPMNs account for only half of these (5%). More than 30% of ≥1 cm cysts accompanying PDACs are, in fact, not
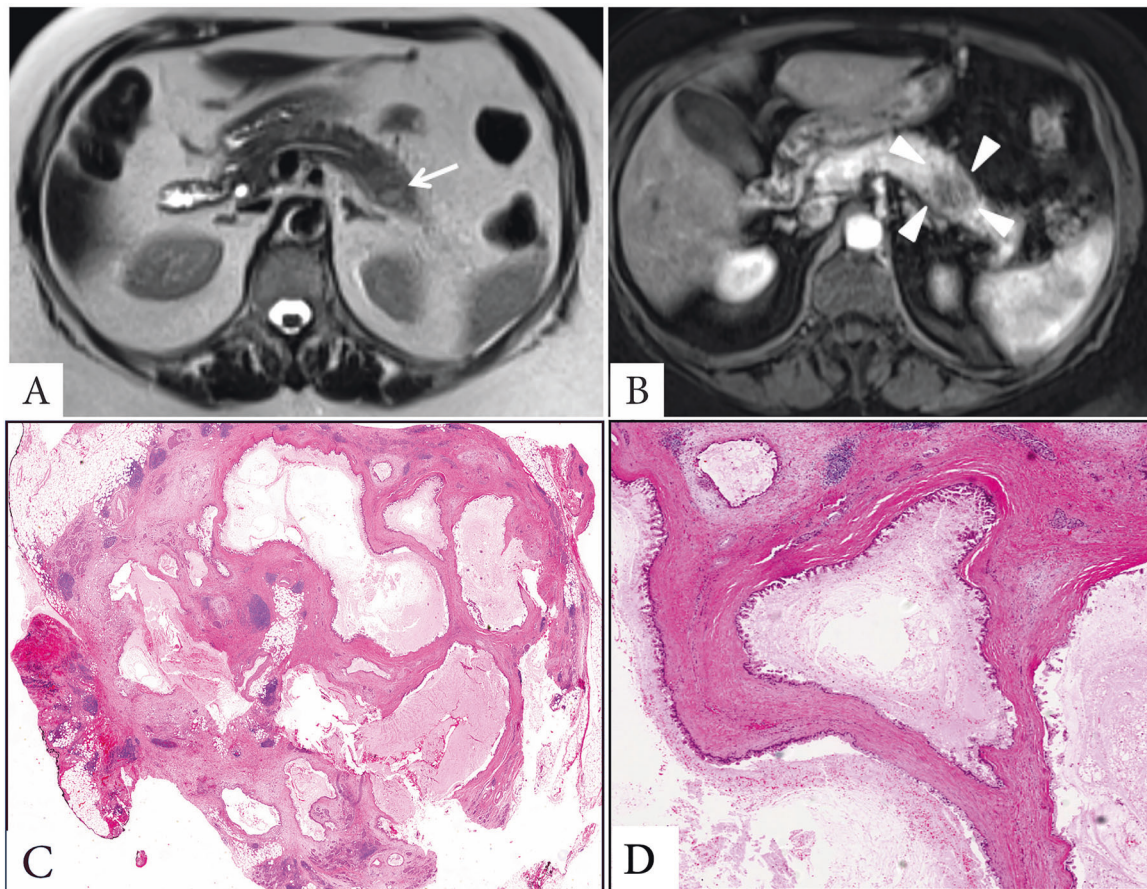
Fig. 3 Large-duct type PDAC forming a pseudo-IPMN pattern. All the cystic structures depicted in this photomicrograph are in fact invasive units of a pancreatic ductal adenocarcinoma (**A** HASTE-MRI; **B** T1-weighted image, arterial phase; **C**, **D** H&E stain).

precursor-type lesions (not IPMNs or MCNs) and presumed not to be the cause of PDAC, but rather other cystic lesions, often the result of PDAC, but that can mimic IPMNs on imaging, and even microscopically (i.e., pseudo-IPMNs, which accompany 3.8% of all PDACs).

Thus, our results bring a different perspective to the recent studies that found PDACs to be commonly associated with Sendai-negative IPMNs, and which consequently advocated the removal of even small cysts. Interestingly, these studies included cysts that were <1 cm in their analysis[25–27]. It should be reiterated here that cysts that are smaller than 1 cm were not even included in our analysis[3,31]. If carefully sought out, cysts smaller than 1 cm are extremely common in normal pancreata and even more so in pancreata with tumors as a secondary change (see below). If these small cysts are also regarded as IPMN, then one may indeed arrive at the erroneous conclusion that a majority of PDACs arise from cysts/IPMNs, and as such IPMN loses its value as a distinct entity.

In this study, we also found that when a PDAC arises from an IPMN/MCN, the IPMN/MCN component is typically recognized pre-operatively, and is often the predominant lesion in the entire tumor, while the PDAC represents a minor component. The majority of PDACs (84%) that proved to have a histologically convincing IPMN/MCN component on resection had indeed been diagnosed as IPMN/MCN pre-operatively, and this figure was even more striking for cases operated on after 2010 (94%, 31/33). This goes to the heart of the original definition of IPMNs, where it was required that the cysts be clinically/radiologically diagnosable, a requirement confirmed and supported by our findings. In contrast, the vast majority of cysts that had not been recognized clinically as IPMN or MCN indeed proved to be other cyst types, i.e., pseudo-

IPMNs rather than true IPMNs on careful histologic evaluation using the updated criteria[3,5,10,30–32]. Therefore, if a lesion is not radiologically recognizable as having an IPMN component, careful pathologic scrutiny is warranted before designating that cyst as an IPMN.

Pseudo-IPMNs: characteristics and differential diagnosis
The non-IPMN/MCN cyst types that accompany PDACs are a heterogeneous group of lesions. However, they have some common characteristics. By their nature of development, with a few exceptions (such as the congenital cysts and paraduodenal/groove pancreatitis-associated cysts), they tend to have smaller cystic components (typically <2 cm) and larger invasive components. This should not be surprising considering they are often, in particular retention cysts, necrosis and large-duct pattern, secondary to the PDAC, not the underlying pathologic process. In contrast, the inverse is true for true IPMN/MCN-associated PDACs, because, IPMN/MCNs typically achieve large sizes before they become invasive, and also, because they are large (and now also have invasion), they come to clinical attention, albeit a little too late.

The most common of these IPMN-mimickers are retention cysts (secondary duct ectasia), which appear to occur due to the duct obstruction caused by PDAC. They have a distinctive architecture, which is appreciable both radiologically and histopathologically. Retention cysts are located in upstream areas of the tumor, and in contrast with the primary cystic lesions that presumably develop due to inherent abnormalities in those given ducts, which consequently show smooth undulating contours, they are typically round and rigid-appearing, presumably because they were ducts
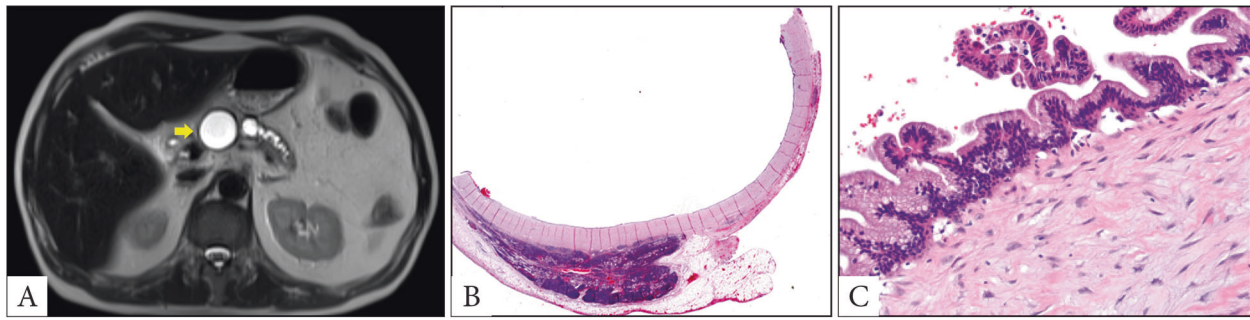
Fig. 4 Simple mucinous cyst presenting as pseudo-IPMN. The cysts are usually unilocular and round (**A** HASTE-MRI, arrow) and relatively large with a smooth internal lining, typically protruding from the pancreas into the adjacent soft tissues (**B** H&E stain). The lining is mucinous and shows some stubby low/micro papillary architecture as well as mild cytologic atypia (**C** H&E stain) but lacks the characteristic papillary nodules and cytologic features of a true IPMN (**B**, **C** H&E stain).

filled and distended by fluid that gets washed off during processing. Unlike primary cystic lesions, they often form a chain at the periphery of the parenchyma creating a picture reminiscent of polycystic ovary. They have low-cuboidal lining, although they may show PanIN-type changes or even colonization by the carcinoma. The colonizing tumor cells, however, are usually flat or tufted, or at most low-papillary, with high-grade cytology different than that of even high-grade IPMNs. In IPMNs (and PanINs), the architectural and cytologic atypia often go hand in hand (the degree of atypia is in sync for cytology and architecture), whereas in colonization observed in retention cysts, typically there is cyto-architectural dissociation phenomenon with the cytologic atypia overbearing the architectural complexity. High-grade IPMNs are characterized by true papilla formation (with fibrovascular cores) in contrast to diminutive, micro papilla formation in occasional retention cysts colonized by carcinoma. Also, atypia is more striking in colonization by carcinoma.

Since retention cysts are secondary cystic changes, they are not precursors. Therefore, it is presumed that these particular PDACs must be arising from traditional PanIN pathway. Indeed, PanIN changes were detected in 15 of 18 pseudo-IPMN cases in which adequate sections of the uninvolved normal pancreas were available for the authors' examination. This figure is not different than what is typically observed in ordinary PDACs, and as such may support this impression[37]. On the other hand, it is difficult to derive a definitive conclusion on this issue considering low-grade PanINs are very frequent in general population[37–40], and, for what is qualified as "high-grade PanIN" it is difficult to absolutely exclude the possibility of colonization (intraductal spread from invasive carcinoma) phenomenon.

SMCs are lesions that were recently separated out as a category from IPMNs[3,5,30,31,41]. Previously also called "mucinous non-neoplastic cyst"[42], they are believed to be innocuous lesions. The pathogenesis of SMCs is not known. Theoretically, they may be viewed as an exaggerated and slowly evolved form of retention cysts that are not necessarily accompanied by any signs of obstruction or any signs of chronic changes in the vicinity. They show several features that distinguish them from the ordinary retention cysts analyzed in this study. Grossly and architecturally, they are more like an MCN without an ovarian stroma. They form relatively large, demarcated cysts that protrude into the peripancreatic tissues. In contrast, retention cysts are characterized by multiple smaller round and distinct cysts, in the background of fibrosis and atrophy, and obstructive findings. Retention cysts are typically confined to the parenchyma, and often form a chain at the periphery creating a pattern similar to polycystic ovary, especially in the setting of PDAC where the obstructive process is often rather swift.

SMCs can show a spectrum of dysplastic changes[30,41], all the cases analyzed here had low-grade PanIN-type changes but none
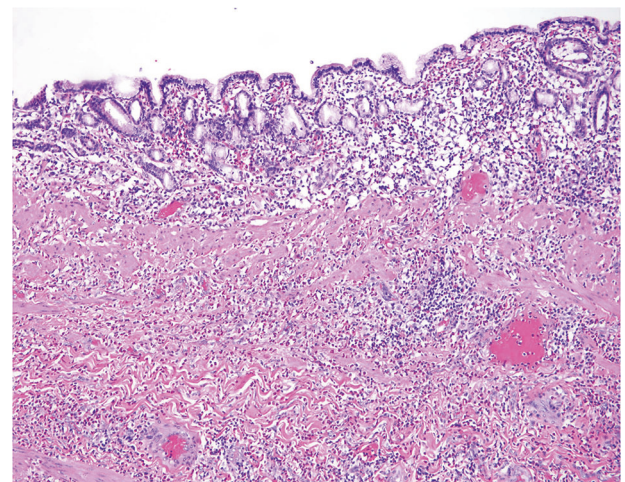

Fig. 5 Congenital cyst, originally misdiagnosed as IPMN. A well-formed band of muscle coat and the architecture of the mucosa with accessory mucous glands are characteristic of congenital cysts (H&E stain).

had high grade dysplasia or colonization. It is possible that SMCs in fact have some precursor (or marker) properties. After all, the concepts of PanIN and IPMN have established that once mucinous epithelium develops in the pancreas, it can acquire other mutations and lead to invasive carcinoma. There is no reason to believe that SMCs are immune to this phenomenon. The cases here accentuate this concern. More studies are needed to determine the malignant potential of SMCs.

The 2 congenital cysts diagnosed during verification analysis are also examples of primary cystic (peri)pancreatic lesions that are typically misdiagnosed as IPMNs, and as such emphasize the importance of examining PDAC-associated cysts carefully for other pathologic findings. A variety of congenital or developmental cysts may occur in the pancreas[43–45]. Choledochal cysts may also occur as duplication cysts[46]. The identification of an outer muscular coat as well as a lining by a relatively normal ciliated/respiratory, gastric or intestinal mucosa establishes the diagnosis of congenital cyst and distinguishes them from IPMNs. Of note, both of our congenital cysts were, not surprisingly, relatively large (6 and 11 cm). They both contained foci of in situ carcinoma transitioning from the native mucosa and not displaying features of colonization, thus illustrating that the invasive pancreatobiliary-type adenocarcinoma was indeed arising from the cyst. It is known that adenocarcinomas may arise in choledochal cysts and duplication cysts located in the pancreas[45–47]. In some cases, heterotopic pancreatic tissue/ductal system may be present in the
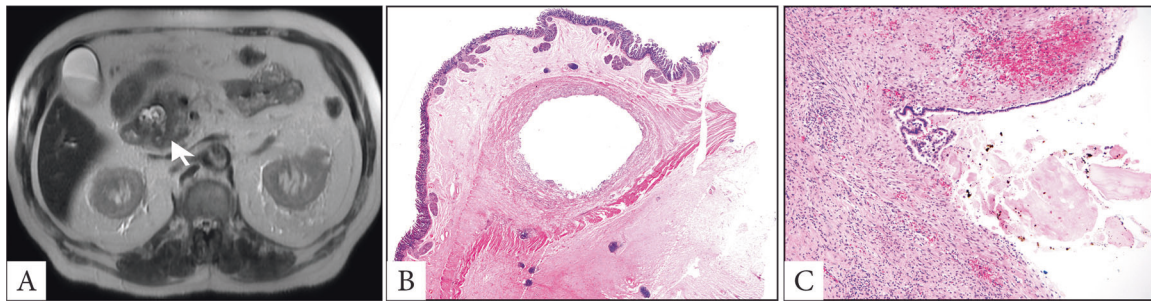
Fig. 6 Paraduodenal wall cyst of paraduodenal (groove) pancreatitis mimicking IPMN. A The cystic lesions were located in the groove area /duodenal wall (HASTE-MRI, arrow) **B**, **C** Microscopically, the cysts were lined partially by epithelium and partially by hypercellular reactive tissue with stromal deposition of acinar secretions. No colonization by carcinoma was seen in this group (H&E stain).
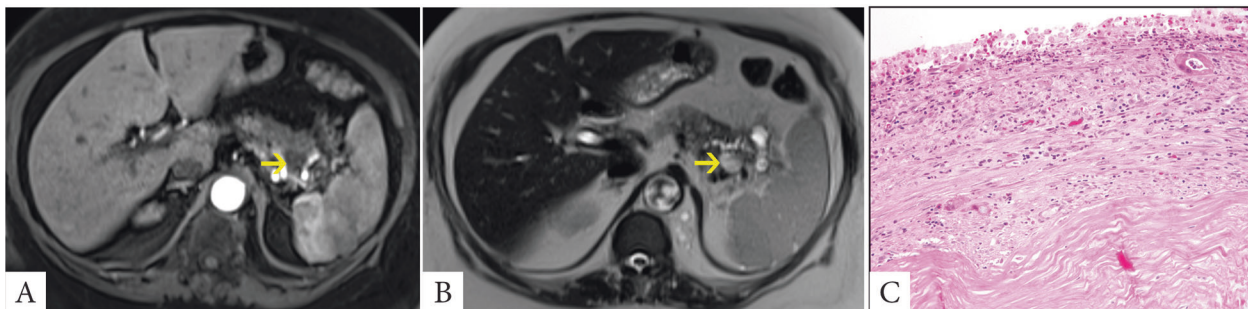

Fig. 7 Pseudocyst. A, **B** Cyst with heterogeneous, some un-enhanced components, which was bordered on pancreatic ductal adenocarcinoma (**A** MRI, T1-weighted image, arterial phase, **B** HASTE-MRI, arrows). **C** Microscopically, the cyst wall was composed of granulation tissue, enzymatic concretions, inflammation and evolving fibrosis, the characteristic elements typical of pseudocysts, with scattered carcinoma cells invading into the fibro-inflammatory cyst wall (H&E stain).

duplication cyst, which may explain the development of pancreatic cancer in these cysts[48,49]. Pre-operatively these are typically classified as cystic neoplasm of pancreas or pseudocyst[45,47,50], as happened in both of our cases.

Another type of true primary cystic process which, in fact, may pre-date the development of PDAC is the paraduodenal wall cyst of which there were 3 examples in this study. Depending on which aspect of the lesion is examined microscopically, these can be interpreted as pseudocysts or IPMN or SMC, because they are partially lined by granulation tissue and partially by columnar mucinous epithelium. Interestingly, all 3 were in men older than 65 years, which is a decade older than the typical paraduodenal pancreatitis patient that is diagnosed[33,36], creating the impression that the PDAC may have been a long-term sequalae of the paraduodenal pancreatitis.

In this study, 6 PDACs of the "large-duct" variant (also called cystic-papillary adenocarcinoma) presented with cysts >1 cm. Paradoxically, it is in fact this group that typically exhibits a pattern and cytology that can very closely mimic IPMN[34,35], by virtue of their small papillae and relatively bland cytology. We have seen several examples misdiagnosed microscopically as IPMN in our consultation practice. However, the cystically dilated glands' infiltrative haphazard distribution, irregular contours, and high-grade cytology are divergent from the classical IPMN subtypes, albeit subtle, and should therefore allow their distinction from IPMNs[34,35].

Degenerative-type cysts developing as a secondary phenomenon in PDACs include necrotic cysts that can occur in any cancer and were seen in 10 cases in this study. The inner lining of these cysts often gets colonized and lined by carcinoma cells, and thus mimic IPMN histologically. In some, microscopic determination of whether these are pre-existing pseudocystic changes (complications of prior or ongoing acute pancreatitis) or fat necrosis (pseudocyst) induced by PDAC or therapeutic intervention, or mere tumor necrosis (or tumor's effect on the infiltrated vessels) can be very difficult.

Clinical and populational implication of these findings

Distinguishing whether a cyst ≥1 cm accompanying a PDAC is IPMN/MCN versus a pseudo-IPMN has far-reaching implications. First, literature suggests, and our preliminary observation supports (unpublished data) that IPMN/MCN-associated PDACs appear to have a better prognosis than those accompanied by pseudo-IPMN. This may partly be related to the size/stage at which they are detected and partly due to biologic differences. More detailed studies are needed to investigate this comparison.

Determining whether a cyst accompanying a PDAC represents IPMN/MCNs versus pseudo-IPMNs also has major implications for our understanding of the behavior of IPMNs. The recent literature indicating the frequent association of Sendai-negative IPMNs with PDACs is probably based, at least partly, on the inclusion of what is regarded now as pseudo-IPMN lesions per recently updated criteria. Research focusing on molecular genetic analysis of IPMNs versus PDACs should also be conducted with special attention to the pseudo-IPMNs which, in critical appraisal of the publications, appears to be a significant pitfall that greatly influences the impressions regarding the IPMN category.

In conclusion, approximately 5% of ordinary PDACs arise from IPMNs. An additional 3–4% of PDACs are accompanied by cysts ≥1 cm, which are entities that are prone to be misdiagnosed as IPMN both clinically and histopathologically. Many of these pseudo-IPMNs are not precursor lesions and most do not appear to be the cause of PDAC but rather a consequence or manifestation of it, including retention cysts, large-duct adenocarcinoma, and cystic necrosis secondarily lined by carcinoma cells. By their nature of development, most pseudo-IPMNs tend to have a smaller cystic component with a larger PDAC. Most true IPMNs (and MCNs) accompanying PDACs are typically diagnosable as such pre-operatively by radiologic examination, whereas for pseudo-IPMNs, attention to the characteristics of the entities highlighted in this study should allow their accurate diagnosis as something other than IPMN. The entities that present as pseudo-
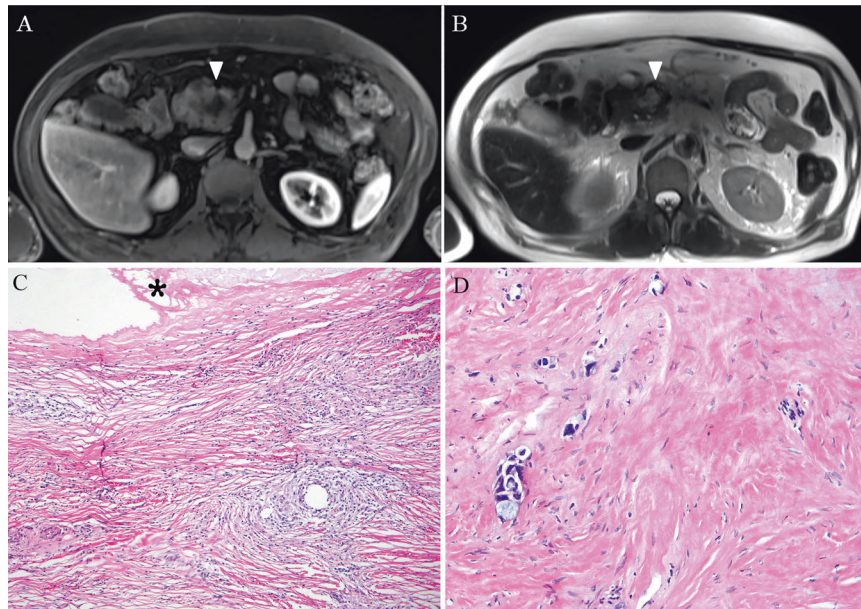
Fig. 8 Cystic tumor necrosis. A, B By MRI, these appeared as heterogeneous cystic lesions within the pancreatic ductal adenocarcinoma (**A** MRI, T1-weighted image, arterial phase, **B** HASTE-MRI). **C** In 2 cases, there was a cavitary lesion (asterisk) lined by hypercellular granulation tissue stroma (with inflammatory cells). **D** In 3 cases, the cyst wall showed partial hyalinization with trapped neoplastic glands (H&E stain).

IPMN closely mimic IPMNs at the microscopic level as well, and therefore, it is imperative that pathologists should familiarize themselves with the diagnostic characteristics of these entities.

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