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Large-duct pattern invasive adenocarcinoma of the pancreas–a variant mimicking pancreatic cystic neoplasms: A minireview

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Abstract

Pancreatic cancer currently has no subtypes that inform clinical decisions; hence, there exists an opportunity to rearrange the morphological and molecular taxonomy that guides a better understanding of tumor characteristics. Nonetheless, accumulating studies to date have revealed the large-duct type variant, a unique subtype of pancreatic ductal adenocarcinoma (PDA) with cystic features. This subtype often radiographically mimics intraductal papillary mucinous neoplasms (IPMNs) and involves multiple small cysts occasionally associated with solid masses. The "bunch-of-grapes" sign, an imaging characteristic of IPMNs, is absent in large-duct PDA. Large-duct PDA defines the mucin profile, and genetic alterations are useful in distinguishing large-duct PDA from IPMNs. Histologically, neoplastic ducts measure over 0.5 mm, forming large ductal elements. Similar to classic PDAs, this subtype is frequently accompanied by perineural invasion and abundant desmoplastic reactions, and *KRAS* mutations in codon 12 are nearly ubiquitous. Despite such morphological similarities with IPMNs, the prognosis of large-duct PDA is equivalent to that of classic PDA. Differential diagnosis is therefore essential.

Key Words: Large-duct pattern invasive carcinoma of the pancreas; Pancreatic ductal adenocarcinoma; Pancreatic cystic disease; Clinicopathological features of pancreatic cancer; Pancreatic cancer subtype

Core Tip: This review integrates the current knowledge about large-duct pattern invasive adenocarcinoma of the pancreas [large-duct pancreatic ductal adenocarcinoma (PDA)]. This subtype is a rare exocrine pancreatic neoplasm and often mimics intraductal papillary mucinous neoplasms (IPMNs). However, its prognosis is notably different from that of IPMNs, and distinguishing this subtype from IPMNs preoperatively is crucial. We summarized the morphological features and genetic landscape of large-duct PDA, with a primary focus on its differences from other types of pancreatic cystic neoplasms. The information aid in making appropriate decisions when tackling atypical pancreatic cystic neoplasms.

INTRODUCTION

Pancreatic cancer is one of the most devastating and fatal diseases in humans, with pancreatic ductal adenocarcinoma (PDA) being the most common exocrine pancreatic neoplasm[1]. With the increase in the number of patients, PDA is expected to become the second leading cause of cancer-related mortality worldwide[2,3]. Advances in multidisciplinary treatment have improved patient survival and have enhanced the effectiveness of modalities for the early detection and identification of cancer subtypes. Despite all efforts to prolong survival, PDA represents one of the worst tumors, with a 5-year overall survival rate of only 2%-9%[4]. Molecular subtyping of this tumor based on genetic signatures has been developed over the past 10 years; nevertheless, the correlation of such information with clinical phenotypes has been somewhat evasive.

Macroscopically, PDA is characterized by yellowish-white masses, usually without hemorrhagic necrosis[5,6]. On histological examination, typical PDA exhibits duct-like glandular structures infiltrating the pancreatic parenchyma, eliciting a strong desmoplastic stromal response[7,8]. The neoplastic cells are columnar to cuboidal and produce various mucins, depending on differentiation and histotypes. Several genetic alterations such as *KRAS* (chromosome 12p), *SMAD4* (chromosome 18q), *CDKN2A* (chromosome 9p), and *TP53* (chromosome 17p) are responsible for causing PDA[9-11] that progresses from low-grade pancreatic intraepithelial neoplasia (PanIN) to higher-grade PanIN and invasive PDA[12-16].

PDA accounts for up to 90% of pancreatic neoplasms and is typically visualized as a solid mass accompanied by abundant desmoplasia[17]. However, tumors with cystic components occasionally compose a small subset in approximately 4%-5% of patients. Colloid carcinoma, a subtype of PDA that is often conjugated to intraductal papillary mucinous neoplasms (IPMNs), is characterized by extracellular mucin pools. Morphologically, colloid carcinoma tends to exhibit a large, well-demarcated cystic lesion[18]. This subtype of PDA originates, at least in part, from IPMNs, which are well-known pancreatic cystic neoplasms[19-21]. IPMNs can be categorized into two morphologically distinct types — namely, the branched type and main duct type[22,23]. Furthermore, multiple subsets, including gastric, intestinal, and pancreatobiliary types, are histologically defined[24]. These types have unique paths during development and progression to invasive tumors[25], and specific genetic alterations observed in IPMNs may be responsible for tumor phenotypes and ultimately influence the patients' outcome[26,27]. In most cases, other pancreatic lesions with cystic features, such as solid cystic neoplasm (SCN)[28,29], mucinous cystic neoplasm (MCN) [30], and solid pseudopapillary neoplasm (SPN)[28], can be easily distinguished from classic PDA[31]; however, atypical imaging findings of patients occasionally impair proper diagnosis. Knowledge and use of relevant genetic alterations unique to these cystic neoplasms may aid patients and physicians in making appropriate decisions.

Recent studies have revealed a histological subtype of PDA with cystic features mimicking pancreatic cystic diseases[32]. This PDA variant is referred to as large-duct pattern invasive adenocarcinoma of the pancreas (large-duct type) and is characterized by invasive PDA forming large, sometimes dilated glands. Nevertheless, this entity

is considered rare and often leads to the misdiagnosis of several pancreatic cystic neoplasms, including IPMNs. This review compares the clinical characteristics, gross morphology and histopathology, and genetic alterations of large-duct PDA and other pancreatic cystic neoplasms.

CLINICAL MANIFESTATIONS

Epidemiology
Large-duct PDA has been estimated to occur in < 7% of all PDA cases. It has been reported in only 63 patients in the past literature[33-35]. Large-duct PDA has been initially diagnosed as IPMN in most cases[34]; hence, the incidence of large-duct PDA has not been clearly recognized. Thus, regarding incidence, large-duct PDA of the pancreas is considered rare[36]. The median age of these patients with large-duct PDA was 63.0 years, and the sex ratio was female-dominant, with a female-to-male ratio of 1.74 (Table 1). The female-to-male ratio was higher in patients with large-duct PDA than in those without large-duct PDA[18]. A previous study reported no specific and unique risk factors.

Tumor location and symptoms
Generally, 60% of classic PDAs develop in the pancreatic head[37], and the majority of the patients exhibit symptoms associated with obstructive jaundice. A summary of previously reported cases with large-duct PDA indicated similar tumor locations (Table 1). Kelly *et al*[34] reported that 2 out of 9 patients with large-duct PDA had jaundice. Other patients had acute pancreatitis (*n* = 1) and abdominal pain (*n* = 5).

IMAGING FINDINGS

Computed tomography imaging
Dynamic contrast-enhanced computed tomography imaging is an essential modality for assessing cystic lesions in the pancreas. Typical PDA presents as a solid and hypovascular tumor, and the most common radiographic finding of PDA is dilatation or stricture of the main pancreatic duct. In contrast, large-duct PDA usually presents as a cluster of small cystic lesions. The diameter of cysts generally measures 5-7 mm, although they sometimes exceed 10 mm[38]. However, large-duct PDA does not have a "bunch-of-grapes" appearance[39], commonly detected in IPMNs. Given the multiple small cysts visualized on cross-sectional images, distinguishing them from SCN is more complicated, particularly in cases with macrocystic-type cysts[40]. SCN typically has a spongy or honeycomb-like appearance; one previous report described a large-duct PDA case showing a honeycomb-like morphology[36]. Large-duct PDA lacks either a star-shaped scar or calcification at the center of the cyst, commonly observed in SCN[38,41,42]. Considering the female-dominated epidemiology, MCN is also a significant differential diagnosis. MCN has an orange-like appearance and sometimes forms cystic lesions measuring over 10 cm; these features are not typical in large-duct PDA[42,43].

Another critical finding suggestive of the large-duct pattern is the slightly diminished enhancement of the parenchyma surrounding cystic components (Figure 1). Similar to typical PDA, such enhancement gradually increases with time after contrast media injection. Furthermore, walled-off necrosis (WON) should be excluded. WON often contains debris and hemorrhage in cysts, resulting in a mixed density change in the fluid[44,45]. These findings are not usually observed in large-duct PDA. Retention cysts often occur along with PDA and are also important in distinguishing it from large-duct PDA. Retention cysts are typically unilocular and tend to be larger than the cysts observed in large-duct PDA[46,47] (Table 2).

Magnetic resonance imaging
Magnetic resonance cholangiopancreatography is another essential modality for diagnosing pancreatic cystic diseases, except in claustrophobic individuals and those with implanted magnetic resonance imaging-unsafe foreign bodies. Crucial findings for large-duct PDA include small cysts in the pancreas[48], with each cyst usually having a diameter of 0.5-0.7 cm[49]. It should be noted that pancreatic duct stricture is more intense than that observed in other cystic neoplasms. Stricture of the main pancreatic duct and bile duct closely associated with a cluster of small cysts is another

Table 1 Patient characteristics of large-duct pancreatic ductal adenocarcinoma

Ref.	Number of cases	Median age	Sex		Tumor location	
			Female	Male	Head	Body or tail
Kelly *et al*[34], 2012	10	67	6	4	9	1
Bagci *et al*[33], 2012	28	67	19[1]	8[1]	16	11
Kosmahl *et al*[35], 2005	24	58	15	9	12[2]	9[2]
Total	63	63.0	40	23	37	21

[1]One case with missing information on sex.

[2]Three cases with missing information on tumor location.

finding that we may consider when diagnosing large-duct PDA (Figure 2). In making a differential diagnosis of IPMNs, communication with the main pancreatic duct is crucial. Both typical main duct-type and branched duct-type IPMNs communicate with the main pancreatic duct and often show dilatation of the main pancreatic duct [41,50,51].

Moreover, diffusion-weighted imaging and apparent diffusion coefficient map on magnetic resonance cholangiopancreatography is helpful in diagnosing PDA. Considering the high intensity of cystic lesions on T2-weighted images[52,53], diffusion-weighted imaging may not help distinguish large-duct PDA from other pancreatic cystic diseases (Figure 2).

Endoscopic findings

Endoscopic ultrasonography (EUS) has the highest sensitivity for detecting PDA lesions[54], specifically small-sized tumors. Irrespective of the size of PDA, non-neoplastic cystic changes associated with PDA include retention cysts caused by ductal obstruction, and pseudocysts attributable to tumor-associated pancreatitis may be considered to distinguish it from large-duct type tumors[55,56]. A "mucinous clot," which is a hyperechoic lesion inside cysts, is sometimes visualized using EUS in patients with IPMNs, but not in those with large-duct PDAs[57,58]. Furthermore, large-duct PDAs typically lack mural nodules and papillary growth, signatures of high-risk stigmata, and worrisome features in the Fukuoka criteria[41,59]. Youn *et al* [38] described a case of large-duct PDA with a solid mass inside a dilatated glandular cyst[38]. Such atypical findings make a differential diagnosis between large-duct PDAs and IPMNs with high-risk stigmata confusing among endoscopists; nonetheless, surgical resection should be performed for either disease. Considering the multifocality of IPMNs, performing EUS for multifocal lesions, which are not observed in large-duct PDA, is crucial (Table 2)[41,51]. The morphology of "cyst by cyst" appearance can be observed in typical IPMNs using EUS[41].

No report has specifically described EUS-guided fine-needle aspiration (EUS-FNA) in patients with large-duct PDA. In the case of pancreatic tumors with cystic components, concerns related to tumor cell dissemination from the cystic fluid (needle tract seeding)[60] may need to be pointed out (Figure 3). Thus, drawing a distinction between large-duct PDA and IPMN-associated cancer using EUS-FNA can become highly challenging, which will be explained well in the "Pathology" section. The requirements for preoperative histological diagnosis of PDA have increased in the neoadjuvant chemotherapy era; therefore, an ingenious solution for the safe and accurate diagnosis of large-duct PDA using EUS-FNA needs to be considered. No report regarding endoscopic retrograde cholangiopancreatography has described specific findings for large-duct PDA. For tumors developing in the pancreatic head, transpapillary biopsy for histological diagnosis can be useful if massive bile duct invasion is evident.

PATHOLOGY

Macroscopic features

Bagci *et al*[33] described 28 cases of large-duct PDA. Macroscopically, 10 patients had a cyst measuring < 10 mm, whereas 1 patient had a large cyst over 70 mm[33]. Pathologically, each small cyst is a dilatated glandular carcinoma. Similarly, Kosmahl *et al*[35].

Table 2 Clinical and morphological characteristics of pancreatic diseases

Ref.	Diseases	Median age	Sex (%, females)	Tumor location (%, pancreatic head)	Multifocality	Gross appearance	Cyst diameter	Main pancreatic duct communication	Internal structure	Other features	Key genetic alterations
Bagci *et al*[33], 2012 Kelly *et al*[34], 2012 Kosmahl *et al* [35], 2005 Youn *et al*[38], 2018	Large-duct PDA	63	68.3	56.2	No	Multiple small cysts	0.5–0.7 cm in each cyst	No	Dilatated glandular cyst (duct)	Dilatated glandular cyst (duct) is > 0.5 mm in diameter. Easily invades to the perineural plexus and shows desmoplastic reaction	*KRAS* (codon 12)
Seidel *et al*[18], 2002 Adsay *et al* [24], 2016	Colloid carcinoma	61	52.9	66.7	Infrequent	Single or multiple cysts, well demarcated	1.2–16 cm	No	Well-defined pools of mucin, contained scanty malignant epithelial cells	Associated with intestinal-type IPMN	*KRAS, BRAF, PIK3CA*; MSIs are more frequently observed than non-colloid cancer PDA
Tanaka *et al* [41], 2012 Kim and Cho [46], 2015 Laurent *et al* [51], 2016	Branched duct-type IPMN	65–70	55.2	62.3	Yes	Bunch of grapes	Up to 30 mm for non-invasive IPMN; 30 mm or greater for IPMN with worrisome features	Yes	Cyst by cyst	Main pancreatic duct; normal or dilatated to > 5 mm, suggesting combined type with main duct IPMN	*KRAS* (codon 12), *GNAS, RNF43*
Hecht *et al*[19], 2021 Tanaka *et al* [41], 2012 Salvia *et al*[50], 2010	Main duct-type IPMN	60 s	41.3	59.6	Yes	Bunch of grapes	Up to 30 mm for non-invasive IPMN; 30 mm or greater for IPMN with worrisome features	Yes	Cyst by cyst	Main pancreatic duct; partial or diffuse dilatation > 5 mm	*KRAS* (codon 12), *GNAS, RNF43, TP53*
Ånonsen *et al* [42], 2019 Wu *et al*[80], 2011	SCN	60–70	70	50	No	Spongy or honeycomb-like	3.7–5.1 cm	No	Microcystic or macrocystic		*VHL*
Ånonsen *et al* [42], 2019 Yamao *et al*	MCN	40–50	95	5	Infrequent	Orange-like	1.0–26.4 cm	No	Cyst by cyst	Ovarian-like stroma	*KRAS, RNF43*

[43], 2011											
Wu *et al*[80], 2011											
Kim and Cho [46], 2015	Retention cyst	60 s	?	?	No	Unilocular	2.8–12 cm	Yes	No cellular dysplasia	Main pancreatic obstruction in should be observed downstream	?
Assifi *et al*[47], 2014											
Singhi *et al* [61], 2012	Pancreatic neuroendocrine neoplasms with cystic changes	50 s	42	24	Infrequent, except MEN1-related neuroendocrine neoplasms	Pinkish-tan to yellowish in color, well demarcated	0.8–18.0 cm	No	Well circumscribed and surrounded by a thin-to-thick fibrous capsule	Larger cysts tend to show hemorrhage	*MEN1, PTEN, DAXX, ATRX, MUTYH, CHEK2*
Halfdanarson *et al*[62], 2008											
Scarpa *et al* [86], 2017											
Tanaka *et al* [41], 2012	Walled-off necrosis	40–50	25	45	Rare	Variable	Variable	Yes	Unilocular	Main pancreatic duct; normal or irregularly dilatated. Observed no later than 6 wk after the occurrence of acute pancreatitis	
Cohen *et al* [45], 2003											

PDA: Pancreatic ductal adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasms; MCN: Mucinous cystic neoplasm; SCN: Solid cystic neoplasm.

described 24 cases of large-duct PDA and reported a diameter ranging from 4 to 18 mm for each cyst; the gross tumor size was not different from ordinary PDA[35]. The entire cystic lesion size is crucial, and the cystic component of large-duct PDA is less than 100 mm generally. In comparison, the size of cysts in MCN, SCN, or pancreatic neuroendocrine neoplasms (PanNENs) sometimes exceeds 100 mm (Table 2)[61,62].

Microscopic features

Microscopically, large-duct PDA shows dilatated glands that range in size from 5 to 10 mm. The term "large duct" is defined as dilatation greater than 0.5 mm among ≥ 50% of glands in PDA[33]. Hematoxylin–eosin staining has revealed some essential pathological findings for large-duct PDA. The nuclei of the epithelial carcinoma (dilatated glands) are irregular, wrinkled, and basally located. The cytoplasm exhibits a foamy or microvesicular pattern, and the glands are jagged and irregular[34]. While a papillary growth pattern is typically absent, discrimination of large-duct PDA from other cystic neoplasms, especially gastric-type IPMNs, is crucial[63,64]. In contrast to mucinous carcinoma, large-duct PDA lacks signet ring cells or mucinous lakes[65,66].

Perineural invasion is another important finding for diagnosing large-duct PDA to discriminate from other cystic neoplasms. Bagci *et al*[33] reported that perineural invasion occurred in 88% of large-duct PDAs[33] but was less commonly observed in
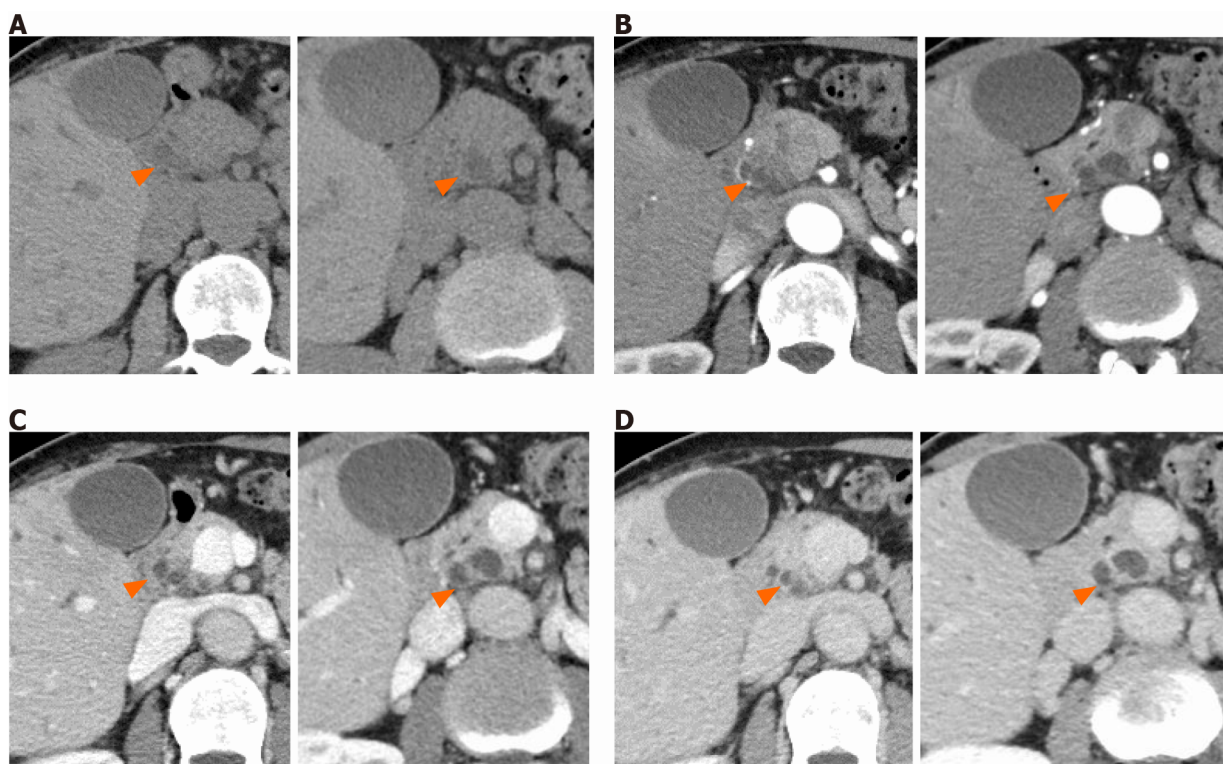
Figure 1 Typical computed tomography imaging of large-duct pancreatic ductal adenocarcinoma. The orange arrowheads show the cystic lesion in large-duct pancreatic ductal adenocarcinoma. A: Plain computed tomography indicates low attenuation area in the pancreas; B: Arterial phase reveals multiple cystic lesions in the pancreatic head without enhancement; C: Portal phase shows multiple cystic lesions in the pancreatic head with parenchymal enhancement; D: Equilibrium phase shows slight ring enhancement of the lesion.

IPMNs, even though the tumor had invasive compartments. In large-duct PDA, the stroma has a rich desmoplastic appearance[33,34]. These features are commonly observed in PDA compared to IPMNs; however, they are more remarkable in large-duct PDA. Additionally, hypercellular stroma or ovarian-like stroma is present in some cases. As for the differential diagnosis of colloid carcinoma or PanNENs, the cysts in these lesions are relatively well-demarcated relative to those in large-duct PDA. PanNENs sometimes have a thick fibrous capsule with hemorrhage[61]. WON usually shows necrotic debris in cysts. Macroscopically, this finding is usually not observed in large-duct PDA and can be a point to distinguish one from other cystic lesions[67].

Immunohistochemistry

Immunohistochemistry (IHC) may be a crucial diagnostic tool that can be utilized to discriminate large-duct PDA from other pancreatic cystic neoplasms[36]. Among the immunostaining widely used in the diagnosis of tumors, mucin (MUC) staining is particularly important and may play a key role in diagnosing large-duct PDA. Gastric-type IPMN exhibits relatively low papillary growth[64] and is typically low grade. However, in tumors with high-grade gastric IPMN, distinction from the large-duct type PDA is sometimes uncertain pathologically. IPMNs present unique MUC staining patterns, depending on the epithelial subtypes[63]. Gastric-type IPMNs show MUC5AC-positive staining patterns and are negative for MUC1, MUC2, and MUC6. Kelly *et al*[34] and Kosmahl *et al*[35] reported MUC staining for large-duct PDAs (Table 3)[34,35]; the positivity rates of MUC1, MUC2, MUC5AC, and MUC6 immunostaining were 79.4%, 8.8%, 78.8%, and 60.6%, respectively. Thus, MUC1 and MUC6 IHC may help make to a differential diagnosis from IPMNs[68].

Furthermore, p53 IHC is beneficial in diagnosing lesions with malignant potential. Bagci *et al*[33] showed that 73% of all large-duct PDAs positively stained for p53. Another point of IHC for large-duct PDA is whether the dilatated glands are dilatated glandular carcinomas or dilatated glands resulting from the occlusion of upper-stream pancreatic ducts. To presume the origin of anatomical localization of the dilated pancreatic ducts, Elastica–Masson staining may be suitable (Figure 4). In addition to the main pancreatic duct, elastin fibers in these normal pancreatic ducts can be stained with Elastica–Masson. Typically, the dilatated glands in large-duct PDA are negative

Table 3 Mucin staining profiles of large-duct pancreatic ductal adenocarcinoma

Ref.	MUC1	MUC2	MUC5AC	MUC6
Kelly *et al*[34], 2012	10/10 (100.0%)	1/10 (90.0%)	9/10 (90.0%)	8/10 (80.0%)
Kosmahl *et al*[35], 2005	17/24 (70.8%)	2/24 (8.3%)	17/23 (73.1%)	12/23 (52.2%)
Total	27/37 (73.0%)	3/37 (8.1%)	26/36 (72.2%)	20/36 (55.6%)

No. of staining-positive cases/available cases. MUC: Mucin.
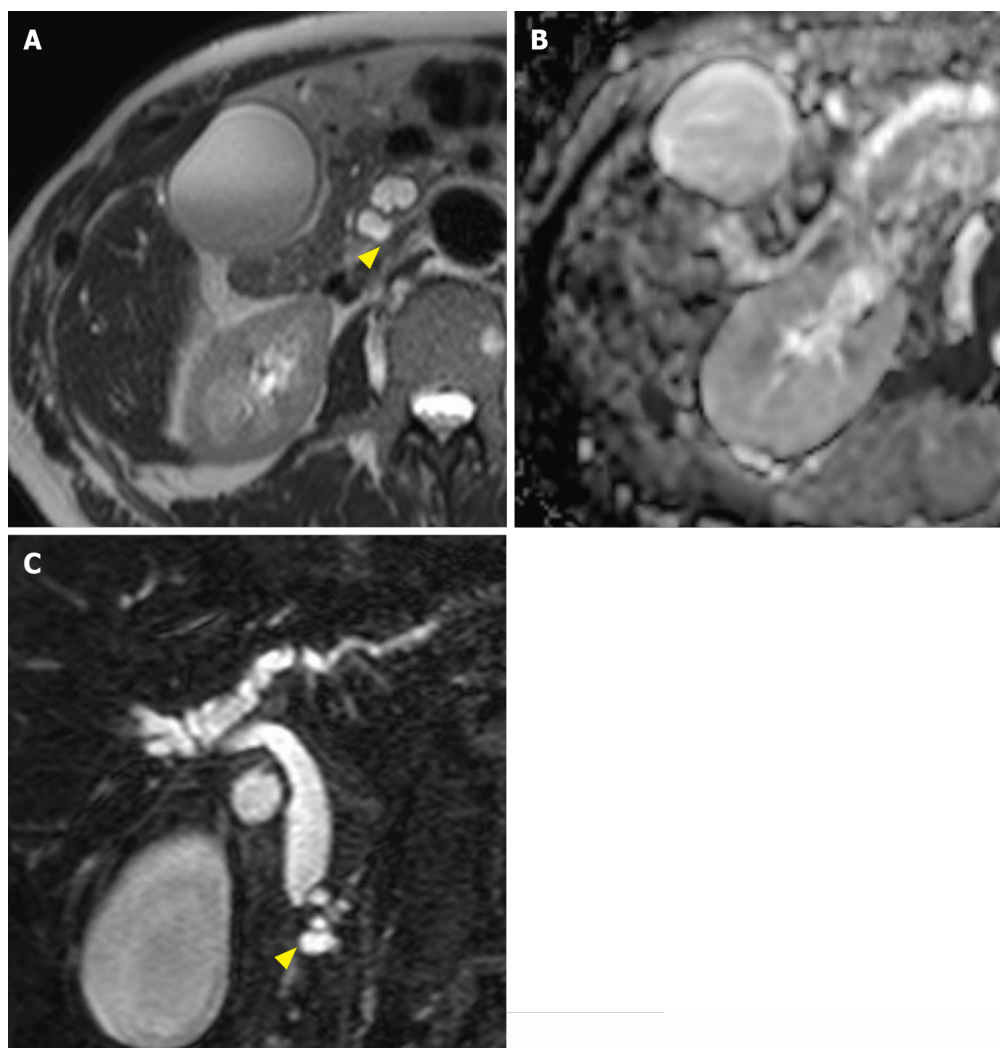
Figure 2 Typical magnetic resonance imaging of large-duct pancreatic ductal adenocarcinoma. The yellow arrowheads show the cystic lesion in large-duct pancreatic ductal adenocarcinoma (PDA). A: T2-weighted imaging reveals high intensity in the large-duct PDA lesion; B: Diffusion-weighted imaging shows no significant signal increase/decrease in the lesion; C: Magnetic resonance cholangiopancreatography (coronal view) reveals multiple cystic lesions in the pancreatic head and compressed bile duct.

for the immunostaining, suggesting they were derived from tumor glands rather than the secondary dilation of the normal main pancreatic duct and associated large branch duct[69].

GENETIC ALTERATIONS

KRAS is mutated in the great majority of PDA, and approximately 90%-95% of PDA patients have major hot spot mutations in codons 12, 13, and 61[9]. This genetic event has been identified at the earliest stages of PanIN, and studies in genetically
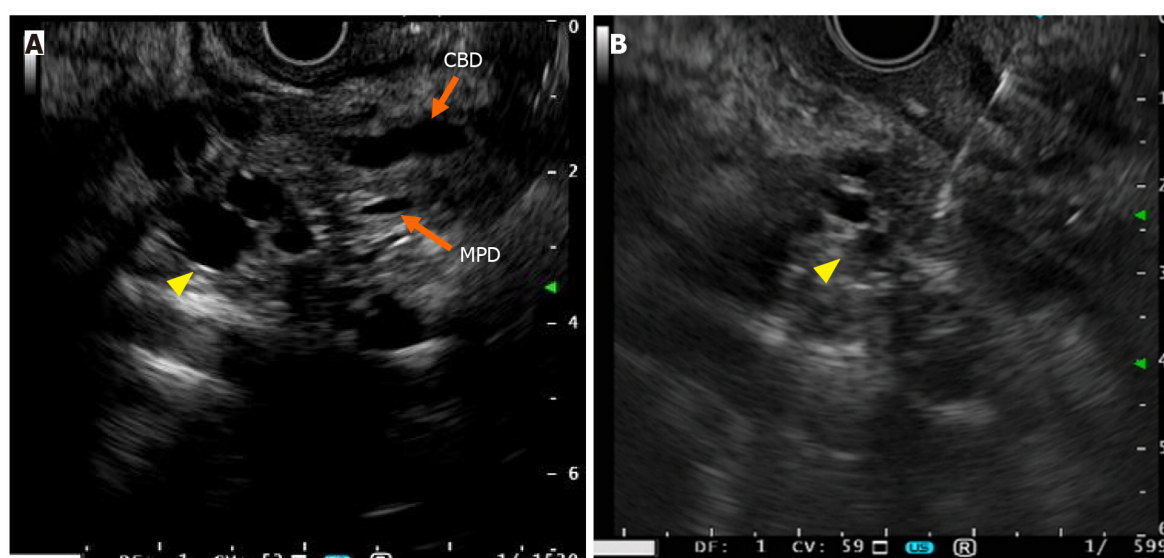
Figure 3 Endoscopic ultrasonography findings of large-duct pancreatic ductal adenocarcinoma. The yellow arrowhead shows the cystic lesion in large-duct pancreatic ductal adenocarcinoma (PDA). A: Endoscopic ultrasonography (EUS) reveals multiple echoic lesions in the pancreatic head; B: EUS-fine-needle aspiration was performed in the parenchyma of the cystic lesion in large-duct PDA. The EUS model used was GF-UE260-AL5 (Olympus, Tokyo, Japan). The ultrasonic diagnostic equipment used was EU-ME2 (Olympus, Tokyo, Japan). CBD: Common bile duct; MPD: Main pancreatic duct.

engineered mice models (GEMMs) indicate that PanINs arise from pancreatic acinar cells that incur Kras mutations (Ptf1a-induced Kras activation). In the Kras^{G12D}-expressing mice, PanIN formation coincides with acinar-to-ductal metaplasia (ADM), characterized by the replacement of acinar cells with cells expressing ductal markers, such as CK19 and the ductal fate determinant Sox9[70]. Further, propensity of ductal and centroacinar cells to give rise to PanINs is demonstrated by GEMM with Sox9^{CreER}-mediated Kras activation, although considerably less frequent relative to Ptf1a^{CreER}-induced Kras activation[71].

Although observations in these mice models have not been validated in humans, multiple PanIN-like lesions with various grades of atypia can often be observed in the "normal area" of the resected specimens of pancreatic cancer. These lesions are usually solitary and localized in the normal acinar compartment without pancreatitis. However, PanINs associated with a cluster of ADM can also be seen[9]. Nevertheless, it remains to be determined if the PDA, including large-duct type, originated from either differentiated duct or duct-like cells associated with ADM. Such hypothesis may be clarified based on the particular mutation profiles and molecular signature related to cellular origin.

Moreover, genetic analysis is valuable in establishing a differential diagnosis between large-duct PDA and IPMNs. Bagci *et al*[33] conducted a mutation analysis of *KRAS* codon 12, which is the most frequent mutation point in PDA, using specimens from 28 large-duct PDA patients compared to ordinary ductal adenocarcinoma of the pancreas[33]. The results indicated 82% of large-duct PDAs harbored *KRAS* codon 12 mutations, a bit less frequency observed in classic PDAs (generally over 90%)[33,72]. Since the authors utilized slot-blot Southern analysis of polymerase chain reaction-amplified samples, *KRAS* mutation in codon 12 might be missed in case of the tumor with low tumor cellularity, and latest methods may also identify other hotspots at codons 13 and 61. Additionally, IPMN can be initiated by *KRAS* mutation[9], although less frequently than PanIN[73,74] . *KRAS* mutations are observed in 53%-87% of gastric-type IPMNs and approximately 40% in intestinal-type IPMNs. In contrast to PDAs including large-duct type, IPMNs frequently harbor multiple different types of *KRAS* mutations, suggesting poly-clonal diseases[25]. Therefore, specifying the variation in *KRAS* mutation types may be valuable in determining a subset of patients with large-duct PDA.

TP53 gene is also frequently mutated around 75% of pancreatic carcinoma patients [75], and Bagci *et al*[33] reported that abnormal immunostaining of p53 was observed in 73% of large-duct type PDA, a higher frequency relative to classic PDA (60%). Moreover, *TP53* mutation can be seen in 10%-40% of high-grade IPMNs and 40%-60% of IPMN-associated invasive carcinomas[73,76]. Given the strong gain-of-function of particular missense mutations in *TP53* relative to the truncating mutations[77,78], further studies will be required if such *TP53* mutation types are associated with the
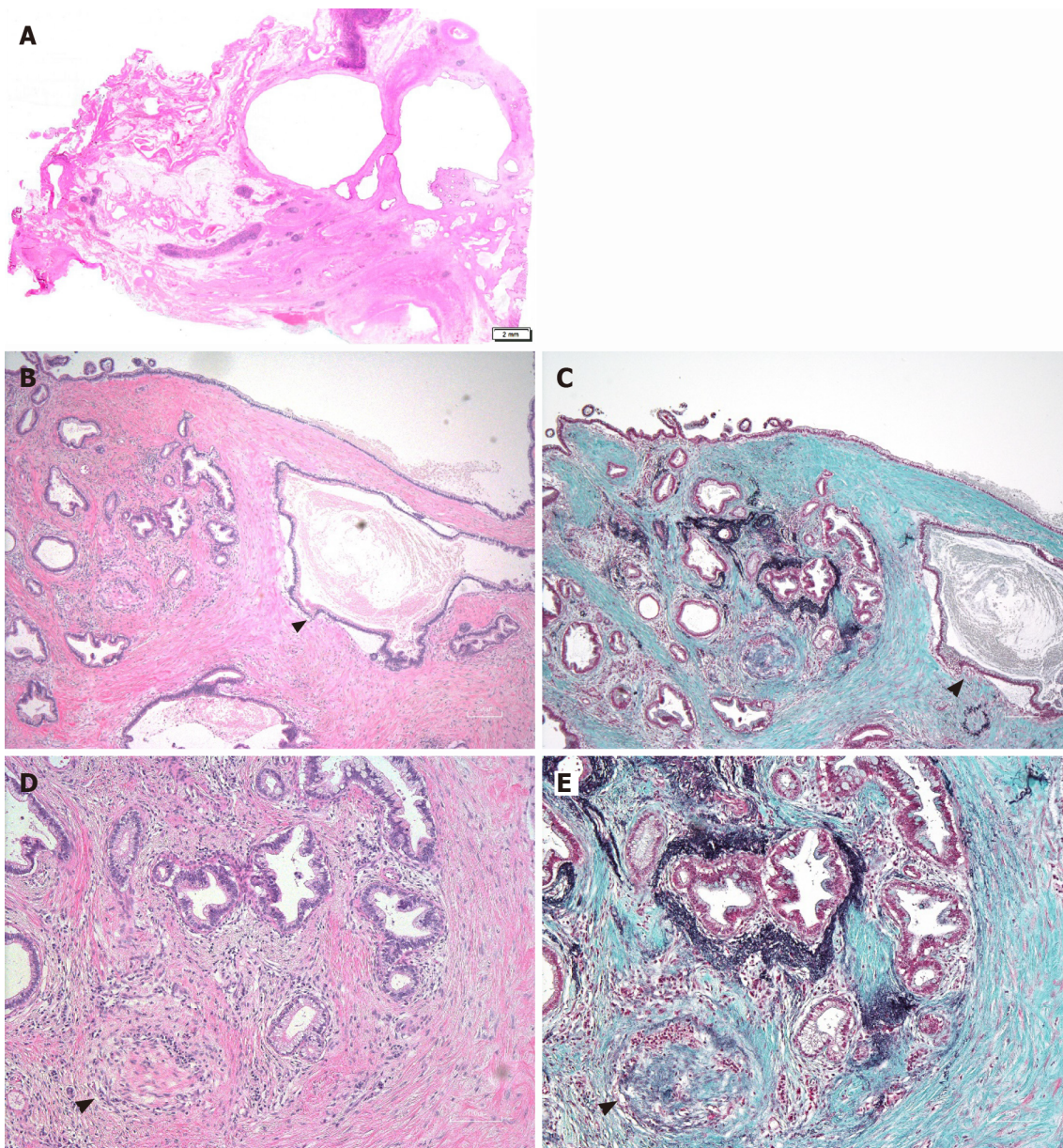
Figure 4 Pathological findings of large-duct pancreatic ductal adenocarcinoma. A: Hematoxylin–eosin (HE) staining of the lesion (× 4); B: HE staining of the lesion (× 200) shows a dilatated glandular carcinoma > 0.5 mm in diameter (black arrowhead); C: Elastica–Masson immunohistochemistry (× 200) reveals that the dilatated glands lack elastic fibers (black arrowhead); D: HE staining of the carcinoma invading the myelin sheath (× 200; black arrowhead); E: Elastica–Masson immunohistochemistry (× 200) reveals that the dilatated glands invading the myelin sheath lack elastic fibers (black arrowheads show the myelin fiber).

tumor phenotypes. *SMAD4* is also inactivated in 55% of PDA cases; of these, 35% are inactivated by homozygous deletion, whereas 20% show loss of one allele[10]. Inactivation of *SMAD4* enhances the rapid progression of *Kras*[G12D]-initiated mice pancreatic neoplasms, showing IPMN-like phenotypes[79], and a significant fraction of IPMN-associated human pancreatic cancer harbors *SMAD4* mutation and the abnormal immunostaining[25]. Whether *SMAD4* inactivation can influence the progression or promotion of large-duct PDA remains unclear.

GNAS mutations are unique to IPMNs[80,81] and are more frequently identified in intestinal-type IPMNs than in gastric- and pancreatobiliary-type IPMNs[9]. The mutation can progress to IPMN-associated PDA, and recent studies demonstrated that about 8%-11% of pancreatic cancers[9], including cases considered not related explicitly to IPMN, harbor *GNAS* mutations or amplifications. Since *GNAS* mutation can lead to entirely distinct transcriptional and metabolic reprogramming to *KRAS*-driven circuitry[82], identification of *GNAS* mutations may discriminate large-duct PDA from IPMN-related pancreatic cancer.

RNF43 encodes an E3 ubiquitin ligase. *RNF43* mutations are observed in IPMNs and MCNs and are detected in approximately 50% of all IPMNs[83]. Nonetheless, a recent

meta-analysis has suggested that *RNF43* mutations are not associated with clinicopathologic parameters in patients with IPMN[83,84]. Approximately 50% of MCNs present *RNF43* mutations, including loss of heterozygosity[85]. Other cystic neoplasms in the pancreas exhibit specific genetic mutations. Genetic alterations such as *VHL* mutations and loss of heterozygosity in SCN, *CTNNB1*, and *PIK3CA* mutations in SPN and PanNEN-associated mutations (*MEN1*, *PTEN*, *DAXX*, and *ATRX*) have been specifically identified in SCNs and PanNENs, particularly in cases with cystic components resembling retention cysts[85,86] (Table 2).

Further genetic analysis should be performed in the large-duct PDA, considering whether the cellular origin of the large-duct PDA was the branch or main pancreatic duct and pathways of carcinogenesis[87,88]. Whole-genome sequencing may be helpful in determining the genes responsible for forming large-duct glands[87,89].

TREATMENT AND PROGNOSIS

Large-duct PDA has been recognized as an uncommon subtype of PDA. Hence, in previous reports, large-duct PDA was mainly diagnosed from surgically resected specimens[33,34]. Preoperative diagnosis was variable, including IPMN, MCN, and "PDA with solid and cystic mass." Furthermore, the patients in these reports were diagnosed at an advanced stage, and the period of survival after resections was about 7-16 mo. These reports were published in the era when adjuvant or neoadjuvant chemotherapy for PDA was not established. The outcome is worse than that of surgically resected IPMNs, reported as 37.0 mo[90], and chemotherapy is not generally considered if the invasive component in IPMN-associated cancer is not evident. Therefore, distinguishing large-duct PDA from other cystic neoplasms, including IPMNs, is essential. Accurate histological and genomic information related to the tumor will help decide between appropriate therapeutic options before surgery[91-93]. Currently, how standard chemotherapy against PDAs, including both adjuvant and neoadjuvant chemotherapy, can effectively eradicate large-duct PDAs remains unclear.

CONCLUSION

Large-duct PDA is a subtype of PDA that mimics IPMNs or other pancreatic cystic neoplasms. Given the rarity of this disease, the diagnostic approach is sometimes challenging. Considering the estimated prognosis of the patients, it is crucial to distinguish large-duct PDAs from IPMNs using macroscopic and pathological findings. When an atypical cystic lesion is identified in the pancreas, both symptomatic and asymptomatic, the differential diagnosis should include large-duct PDA. Given their advantages, genetic analysis of PDAs and IPMNs, exploration of *KRAS* mutations, and mutation profiling of other cancer-related genes may help establish an accurate diagnosis.

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