

# World Journal of *Gastrointestinal Surgery*

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## Benign vs malignant pancreatic lesions: Molecular insights to an ongoing debate

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### Abstract

Several benign conditions such as chronic pancreatitis, autoimmune pancreatitis, and paraduodenal pancreatitis can present as mass lesions and may mimic pancreatic ductal adenocarcinoma (PDAC) clinically and radiologically. Thorough histologic examination with attention to certain morphologic features can assist in deciphering neoplastic from reactive, however small biopsies often remain a challenge. Variable histologic patterns in conventional PDAC may also confound the diagnosis of PDAC. Uncommon subtypes of pancreatic carcinoma such as adenosquamous and squamous cell carcinoma, colloid carcinoma, medullary carcinoma, hepatoid carcinoma and signet ring cell carcinoma necessitate excluding metastasis from other sites prior to rendering the diagnosis of pancreatic carcinoma. The use of immunohistochemical staining and molecular markers can aid in separating benign from malignant and PDAC from metastasis. PDAC expresses a few non-specific epithelial and mucin immunomarkers such as CK7, CK19, MUC1, MUC4 and MUC5AC. However, the only immunohistochemical marker that is specific for PDAC in the right clinical context is SMAD4. Loss of SMAD4 within atypical glands and ducts supports the diagnosis of PDAC in a limited sample. Unfortunately, this finding is seen only in 50% of PDAC cases. The identification of certain mutations can help support a diagnosis of PDAC when benign conditions are in the differential. At the molecular level, KRAS oncogene mutations are seen in approximately 93% of PDACs. Subsequent neoplastic progression is driven by additional mutations of tumor suppressor genes, such as CDKN2A, TP53, and SMAD4. Molecular markers can also provide an insight to the prognosis. For instance, the loss of SMAD4 is associated with a poor outcome whereas mutations in MLL, MLL2, MLL3, and ARID1A are associated with improved survival.

**Key Words:** Pancreas; Pancreatitis; Autoimmune; SMAD4; Molecular

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**Core Tip:** Multiple benign entities share clinical and radiological features with pancreatic ductal adenocarcinoma requiring histologic examination to render the final diagnosis. However, the diagnosis of well differentiated adenocarcinoma can be challenging in a limited sample. Certain morphologic features and molecular markers can be used to resolve this issue.

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## INTRODUCTION

In the pancreas, several benign conditions such as chronic pancreatitis (CP), autoimmune pancreatitis (AIP), and paraduodenal pancreatitis (PDP) can present as mass lesions and mimic pancreatic ductal adenocarcinoma (PDAC) clinically and radiologically[1]. The diagnosis of PDAC is relatively straightforward in resection specimens as multiple sections with large cut surfaces are available for microscopic examination. However, in small biopsy specimens (*e.g.*, core needle biopsy) and intraoperative frozen sections, distinguishing PDAC from mass-forming benign lesions can be extremely challenging. Misdiagnosis in these settings may lead to an unnecessary surgical resection of a benign condition with resultant surgery-related complications. Alternatively, if one is too conservative at the microscope a diagnosis of resectable PDAC may be delayed with potentially adverse oncologic outcomes[2-4]. The aim of this review is to describe the microscopic, immunohistochemical and molecular features that can help distinguish PDAC and benign mass-forming entities, especially CP. Also, we will review a few subtypes of non-conventional PDAC that may further confound the diagnosis with their differing morphologies.

## WELL-DIFFERENTIATED PDAC AND ITS MIMMICKS

Smoking and CP are well-established risk factors of PDAC[4,5]. Early stage PDAC can be asymptomatic. However, at an advanced stage, patients usually present with variable symptoms ranging from painless jaundice, anorexia, weight loss and abdominal pain to pancreatic endocrine and exocrine insufficiency[6]. On magnetic resonance imaging and computed tomography, PDAC is usually seen as hypointense mass. However, PDAC not uncommonly shows similar intensity with surrounding tissue. In these cases, other features such as structural deformity, abrupt obstruction of the ducts, obstruction of both common bile duct and pancreatic duct (also known as "double duct sign") and atrophy proximal to the lesion, may be helpful in rendering a correct diagnosis[3].

PDAC is derived from the epithelium of the pancreatic ductal tree. "Differentiation" of a malignant tumor is the degree of histomorphologic resemblance between the neoplastic cells and their origin. Therefore, a well-differentiated PDAC shows duct-like glands recapitulating the benign pancreatic ducts. Less differentiated (moderately, poorly, to undifferentiated) PDACs show more disorganized growth compared to well-differentiated tumors, with sheet-like, nested or single cell patterns of architecture. The invasion of neoplastic cells into surrounding tissue with a breach of the ductal basement membrane is usually accompanied by a proliferation of fibroblasts and fibrotic reaction of the neighboring stroma, called desmoplasia[2,3].

## CP

CP is a progressive form of pancreatic injury subsequent to inflammation, fibrosis and atrophy[4,7]. Risk factors of CP include alcoholism, mechanical obstruction of the biliary tract and hyperlipidemia. As stated above, CP can be a risk factor for PDAC. Conversely, PDAC may lead to CP in the background pancreas[4,5,7]. Therefore,



coexistence of CP and PDAC is not a rare occurrence and distinguishing these two is crucial given the differing management and prognosis[8]. Unfortunately, there is a high degree of overlap in clinical signs and symptoms between CP and PDAC[4,7]. Radiologically, dilation of the main pancreatic duct and branches with diffuse atrophy and calcification would favor CP over PDAC. However, again, focal atrophy and duct dilation can also be seen in PDAC and may be misleading[7].

Microscopically, there is a striking morphologic resemblance between CP and well-differentiated PDAC that may lead to diagnostic challenges. In CP, benign acinar components frequently undergo atrophy. While their lobular architecture tends to be maintained, atrophic acini may resemble small ducts and the native small branch ducts may appear relatively prominent within the atrophic acini. Fibrosis in CP often encases the atrophic small duct-like acini and native small ducts. Consequently, those elements appear as ductular structures embedded in fibrotic stroma, mimicking well-differentiated invasive PDAC in desmoplastic stroma[8] (Figure 1).

The latest World Health Organization (WHO) classification of digestive system tumors listed relevant morphologic criteria in distinguishing PDAC and advanced CP. Architectural findings that are in favor of PDAC include the presence of irregular, ruptured, haphazard ducts in the immediate vicinity of neural structures or within the vessels[9]. Also, “naked” ducts in the adipose tissue favor PDAC over CP[10]. The presence of neutrophils and necrotic debris, rather than calculi and secretory plugs, is another histologic clue that supports the diagnosis of malignancy. Moreover, classic cytologic features of malignancy within the glands and ducts such as pleomorphism, nuclear hyperchromasia and increased mitotic rate support PDAC[9].

### AIP

AIP is a rare form of CP. Type I AIP predominantly affects older males and type II affects younger patients without gender predilection[11-14]. Clinically, AIP commonly presents with painless obstructive jaundice and/or pancreatic mass similar to PDAC, thus is prone to misdiagnosis[11,12].

Two histologic patterns had been recognized and later designated as type I and type II, respectively[15,16]. Commonly found in the head of the pancreas, AIP is an important mimicker of PDAC, also commonly found in the head of the pancreas [11-13,17]. Radiologically, AIP can present as a mass lesion with three radiologic patterns described: diffuse, focal and multifocal[12]. Similar to pancreatic cancer, the most common clinical presentation is jaundice, but it can present with abdominal discomfort/pain and less commonly with weight loss[11,13].

Type I and type II AIP have distinct histologic appearances. Type I is characterized by a dense lymphoplasmacytic infiltrate with an increased IgG4 expression, storiform fibrosis and obliterative phlebitis[16,18,19] (Figure 2). Type II AIP is seen in a younger age group compared to AIP type I. It is histologically characterized by the presence of granulocytes in the ductal epithelium with or without granulocytic involvement of the acini with low or absent IgG4 positive cells[16,18,19] (Figure 3).

The diagnostic approach of AIP is complex, thus an interdisciplinary approach combining clinical, laboratory, and radiological features and typical pathologic findings, when available, is warranted[14,18,20]. The HISORT criteria consisting of histology, imaging, serology, other organ involvement and response to therapy components are commonly used for a diagnosis of AIP by clinicians[7,18,20].

### PDP

Also known as groove pancreatitis, PDP represents a localized type of CP affecting the region of pancreas between the pancreatic head, the duodenum, and the common bile duct [21,22]. The term PDP was introduced to include multiple pathologic entities such as cystic dystrophy of heterotopic pancreas and para-duodenal cysts[23]. Increased alcohol intake is a risk factor for PDP, which predominantly affects middle aged men [22,24]. Clinically PDP can manifest with a spectrum of symptoms including pain, vomiting, jaundice and weight loss[23,25].

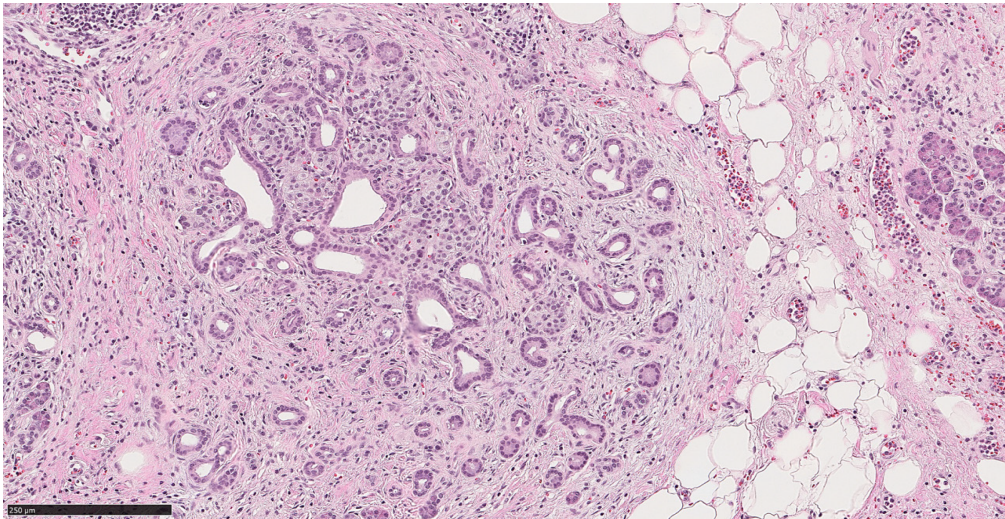
Variable imaging modalities can be utilized to identify PDP. However, it is not uncommon to have an inconclusive radiologic diagnosis, with carcinoma of the pancreas as a differential diagnosis[25-27]. Duodenal wall thickening, Brunner gland hyperplasia and inflammation are typical features of PDP, in addition to proliferation of myofibroblasts, smooth muscle hyperplasia, edema and heterotopic pancreatic tissue (Figure 4). Cyst formation is also a common histologic finding[21,23-25].

A summary of distinctive morphologic features of PDAC and its benign mimics is outlined in Table 1.

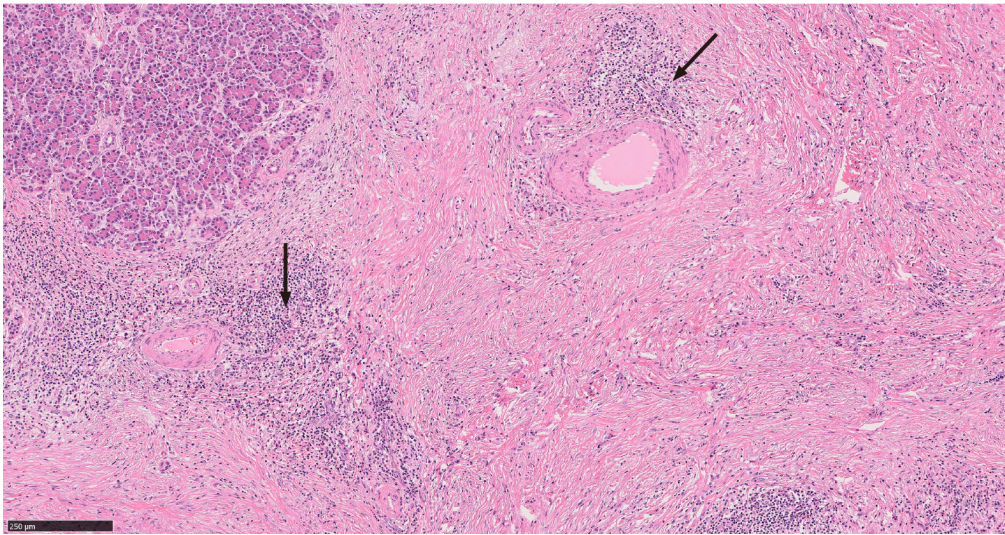
**Table 1 Distinctive histologic features of pancreatic ductal adenocarcinoma and its benign mimics**

PDAC	CP	AIP	PDP
Perineural invasion; perivascular invasion; naked glands in adipose tissue; desmoplasia; anisonucleosis (4:1 nuclear size variation)	Intact lobular architecture; fibrosis; secretory plugs	<b>Type I:</b> Dense lymphoplasmacytic infiltrate with an increased IgG4 expression; storiform fibrosis; obliterative phlebitis. <b>Type II:</b> Granulocytes in the ductal epithelium; absent IgG4 positive cells.	Duodenal wall thickening; brunner gland hyperplasia; smooth muscle hyperplasia; heterotopic pancreatic tissue

PDAC: Pancreatic ductal adenocarcinoma; CP: Chronic pancreatitis; AIP: Autoimmune pancreatitis; PDP: Paraduodenal pancreatitis.



**Figure 1 Atrophic glands in a background of chronic pancreatitis (hematoxylin & eosin, 150 ×, scale 250 µm).** In a biopsy material it can be challenging to distinguish this morphology from well differentiated pancreatic ductal adenocarcinoma.

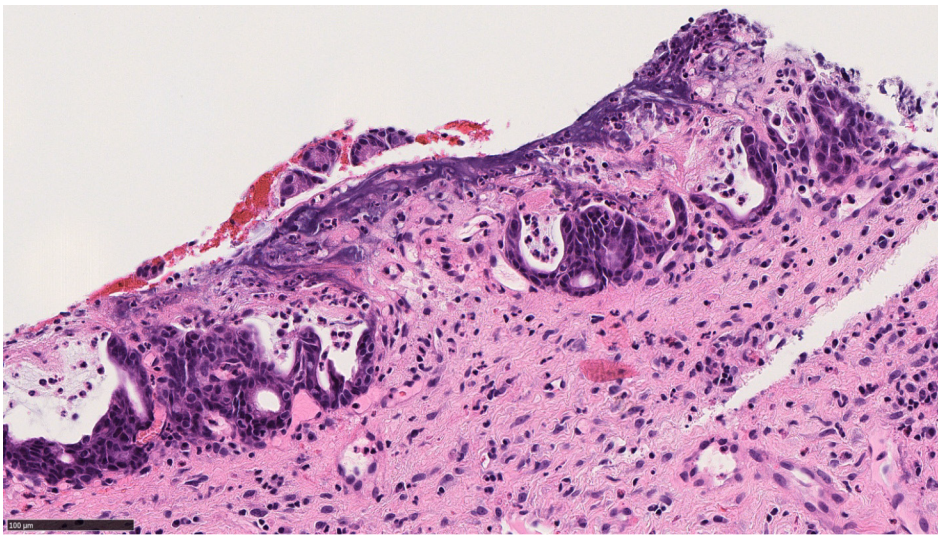


**Figure 2 Autoimmune pancreatitis type 1.** This image shows characteristic histologic features of this entity: lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis (arrows) (hematoxylin & eosin, 100 ×, scale 250 µm).

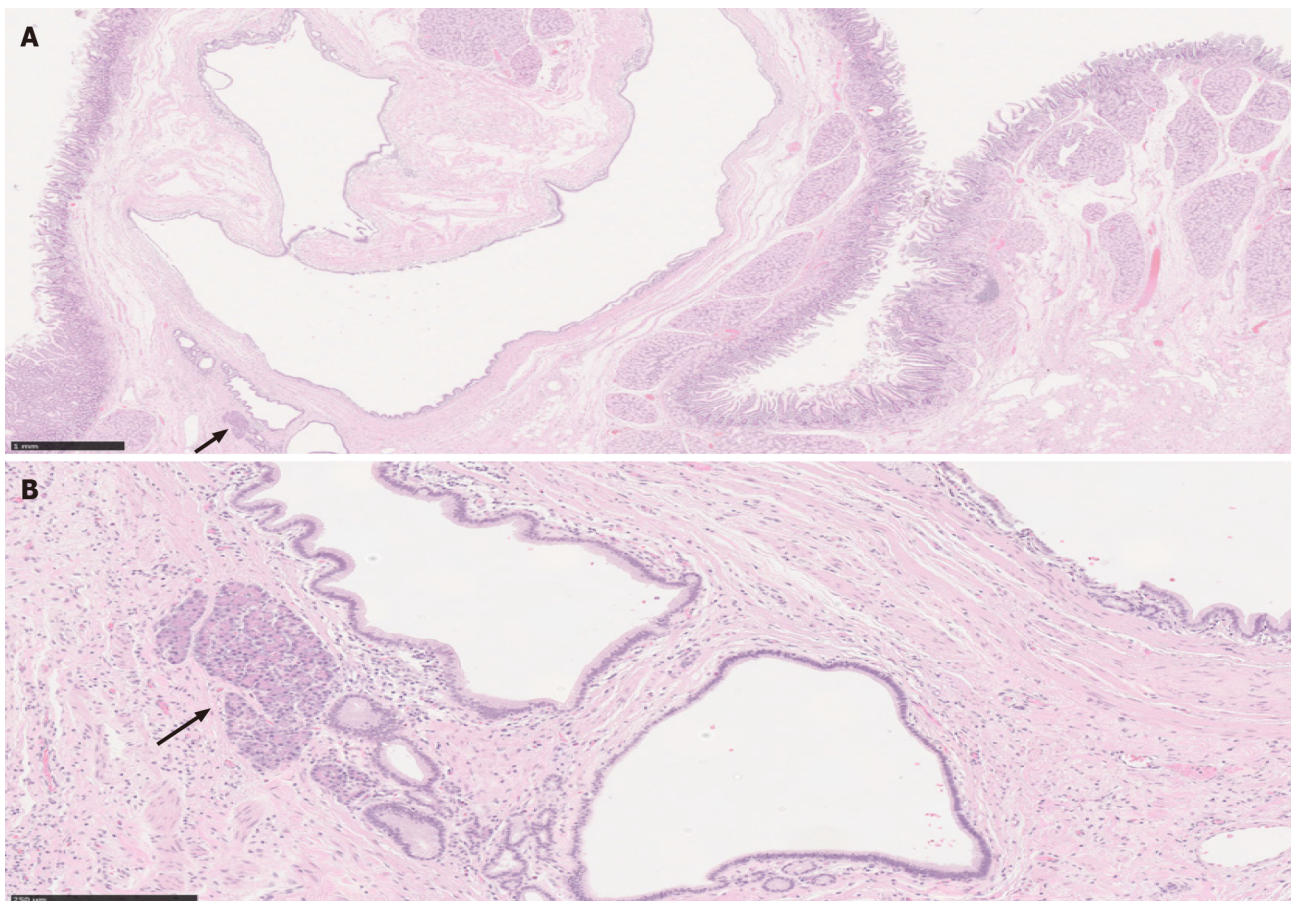
**IMMUNOHISTOCHEMICAL MARKERS OF PDAC**

PDAC originates from ductal epithelium. Therefore, PDAC expresses a number of non-specific epithelial and mucin immunomarkers such as CK7, CK19, MUC1, MUC4 and MUC5AC. However, these markers can also be expressed in any benign ducts. Hence, none of these markers is useful in differentiating between PDAC and CP. The only immunohistochemical marker that confirms malignancy is SMAD4; loss of SMAD4 within atypical glands or ducts would be useful in making a diagnosis of





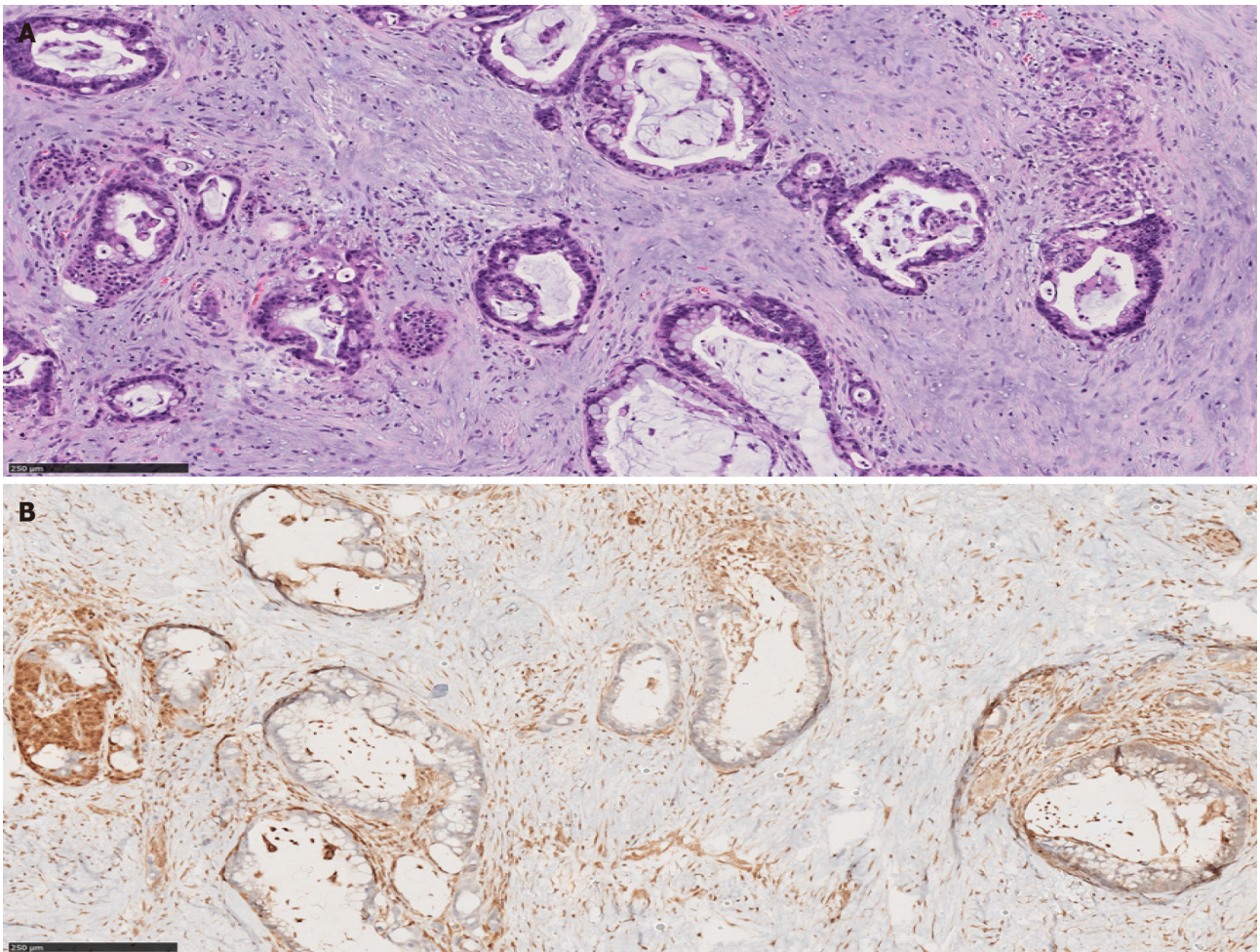
**Figure 3 Autoimmune pancreatitis type 2.** This image shows granulocytic infiltration of pancreatic ductal epithelium (hematoxylin & eosin, 300 ×, scale 100 μm).



**Figure 4 Paraduodenal pancreatitis.** A: This image shows cyst formation, Brunner gland hyperplasia, and ectopic pancreatic tissue (solid arrow) with associated inflammation, consistent with paraduodenal pancreatitis, in a patient with history of significant alcohol use [hematoxylin & eosin (H&E), 20 ×, scale 1 mm]; B: A higher magnification to show the ectopic pancreatic tissue in association with other elements (H&E, 130 ×, scale 250 μm).

PDAC in a limited sample. Unfortunately, this finding is seen only in 50% of PDAC cases (Figures 5 and 6). Consequently, positive (retained) SMAD4 staining within the glands does not exclude a diagnosis of PDAC[28-30].





**Figure 5 Pancreatic ductal adenocarcinoma.** A: The ducts show features of malignancy including cytologic atypia and incomplete gland formation with loss of lobular architecture, in a prominent desmoplastic stroma (hematoxylin & eosin, 130 ×, scale 250 µm); B: SMAD4 immunostaining shows loss of SMAD4 expression in the malignant glands (SMAD4, 120 ×, scale 250 µm).

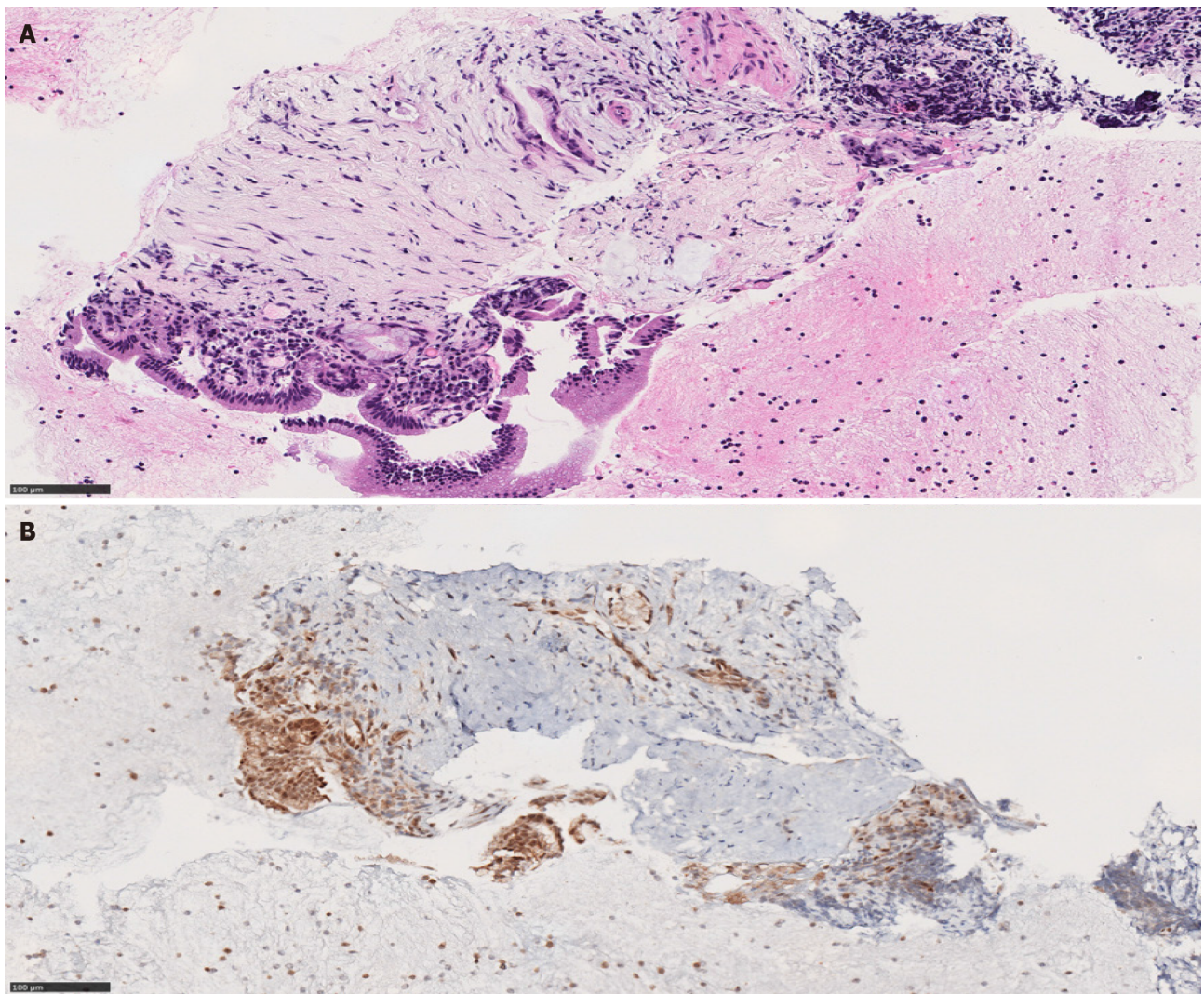
## MOLECULAR MARKERS OF PDAC

Next generation sequencing (NGS) is a technique by which millions of nucleotide sequences are simultaneously deciphered and mutations or other genomic aberrations are detected. Using NGS, an entire human genome can be sequenced within a single day[31]. The Cancer Genome Atlas (TCGA) is a project that aims to discover then classify major cancer-causing genomic alterations called drivers. A few potential drivers of PDAC have been identified[32]. When a driver mutation is found in a pancreatic mass, a neoplastic process, such as PDAC, would be favored over CP.

According to the TCGA, *KRAS* oncogene mutations are seen in approximately 93% of PDACs. This mutation is usually seen early in the neoplastic process. Subsequent neoplastic progression is driven by mutations of tumor suppressor genes, such as *CDKN2A*, *TP53*, and *SMAD4*. Furthermore, genetic and epigenetic alterations lead to invasion and metastasis. These mutations are by far less frequent than *KRAS* mutation. For example, *TP53* mutations and loss of *SMAD4* are limited to approximately 50% of the cases[33-35]. The loss of *SMAD4* is also associated with a poor outcome[36] whereas mutations in *MLL*, *MLL2*, *MLL3*, and *ARID1A* are associated with an improved survival[37].

A multitude of other genetic alterations have been suggested to drive neoplasia in *KRAS* wild-type PDACs. These alterations are sub-grouped into three categories: (1) Tumors with an activated MAPK pathway associated with *BRAF* mutation; (2) Tumors with microsatellite instability due to defective DNA mismatch repair (MMR) featuring a high tumor mutational burden; and (3) Tumors with kinase gene fusions[38].





**Figure 6** Pancreatic mass biopsy showing a minute focus of atypical glandular structure, highly suspicious for carcinoma. A: The atypical glands are surrounded by desmoplastic stromal reaction (hematoxylin & eosin, 190 ×, scale 100 μm); B: The atypical glands retain SMAD4 expression; this staining pattern does not rule out malignancy (SMAD4, 190 ×, scale 100 μm).

## SELECTED SUBTYPES OF PDAC

The following subtypes share a similar mutational profile with PDAC. Some of these may show additional pathognomonic or targetable mutations. [Table 2](#) provides a summary of morphologic features and altered genes for PDAC subtypes.

### **Non-classified conventional PDAC**

Conventional PDAC may exhibit any of the morphologic patterns listed below; currently, these patterns are not classified as separate categories by the WHO[9].

**Large duct pattern:** Macroscopically, tumors with a large duct pattern show cysts (5 to 7 cysts) that are > 0.5 cm in diameter. These cysts may mimic intrapancreatic mucinous neoplasm (IPMN) radiologically and macroscopically. Microscopically, these neoplastic cysts are lined by atypical cuboidal epithelium with occasional papillary projections[39].

**Foamy gland pattern:** The foamy gland pattern poses a diagnostic challenge especially on frozen section as the cytoarchitectural features of malignancy are subtle in this particular pattern. Tumors are composed of glands resembling benign endocervical glands or gastric foveolar glands, with foamy (microvesicular) cytoplasm. Condensed brush border-like bands are noted at the luminal aspect of the glands, and the raisinoid, small nuclei are basally located[40].

**Cystic papillary pattern:** This pattern may be related to the large duct pattern. It is characterized by a papillary cystic architecture intermixed with intervening areas of conventional PDAC. The biologic behavior of PDAC with this pattern is similar to that of poorly differentiated adenocarcinoma[9,41].

**Table 2 Summary of morphologic features and altered genes of pancreatic ductal adenocarcinoma subtypes**

Subtype	Colloid	Medullary	Adenosquamous	Hepatoid	Signet ring cell
Morphologic features	More than 80% of extracellular mucin; focal signet-ring cells can be seen	Minimal glandular differentiation; syncytial growth pattern; abundant inflammatory infiltrate	More than 30% of squamous differentiation	More than 50% of hepatocellular differentiation	More than 80% of signet ring cell component
Altered genes	<i>GNAS</i> ; <i>ATM</i>	MMR genes; <i>POLE</i>	<i>SMAD4</i> ; <i>CDKN2A</i>	<i>BAP1</i> ; <i>Notch1</i>	NA

MMR: Mismatch repair; NA: Not available.

### **Adenosquamous and squamous cell carcinoma**

Adenosquamous carcinoma is a tumor composed of both adenocarcinoma and squamous carcinoma components (Figure 7), with a poor prognosis. Some authors have suggested an arbitrary cut-off of 30% of the squamous component for the diagnosis[42-44]. The proportion of squamous component had no effect on overall survival in Voong *et al*[45]'s study. However, the presence of any degree of squamous differentiation in a PDAC appears to confer a worse outcome[44-46]. Pure squamous cell carcinomas of the pancreas are extremely rare, and a metastasis should always be ruled out before establishing this diagnosis[44,47]. At the molecular level, both adenosquamous and pure squamous carcinoma show the classic molecular alterations of PDAC[44,48-50].

### **Colloid carcinoma**

More than 80% of extracellular mucin is required to establish the diagnosis of colloid carcinoma. Although focal signet-ring cells can be seen in this subtype, the overall prognosis of colloid carcinoma is more favorable than conventional PDAC[51-53]. Studies have shown similar molecular profiles between the colloid carcinoma and intestinal-type IPMN; both of which harbor somatic mutations in *GNAS*. Thus, intestinal-type IPMN is considered to be a precursor of this particular subtype of PDAC[54-57]. At the germline level, heterozygous mutations in the *ATM* gene seems to predispose patients to the development of the colloid subtype of PDAC[58]. Furthermore, germline *ATM* aberrations are shown to increase the efficacy of antineoplastic drugs that induce synthetic lethality such as platinum drugs and PARP inhibitors (*e.g.*, Olaparib)[59,60].

### **Signet-ring cell carcinoma**

The diagnosis of signet-ring cell carcinoma is rendered when more than 80% of the tumor demonstrates signet ring cells. This subtype is extremely rare in the pancreas therefore its prognosis is unknown. Similar to the other uncommon subtypes listed above, metastatic malignancies with a signet ring cell component, notably gastric and mammary carcinomas, must be excluded before such a diagnosis is rendered[61,62]. Due to its extreme rarity, molecular data on this subtype is currently unavailable in the literature[5].

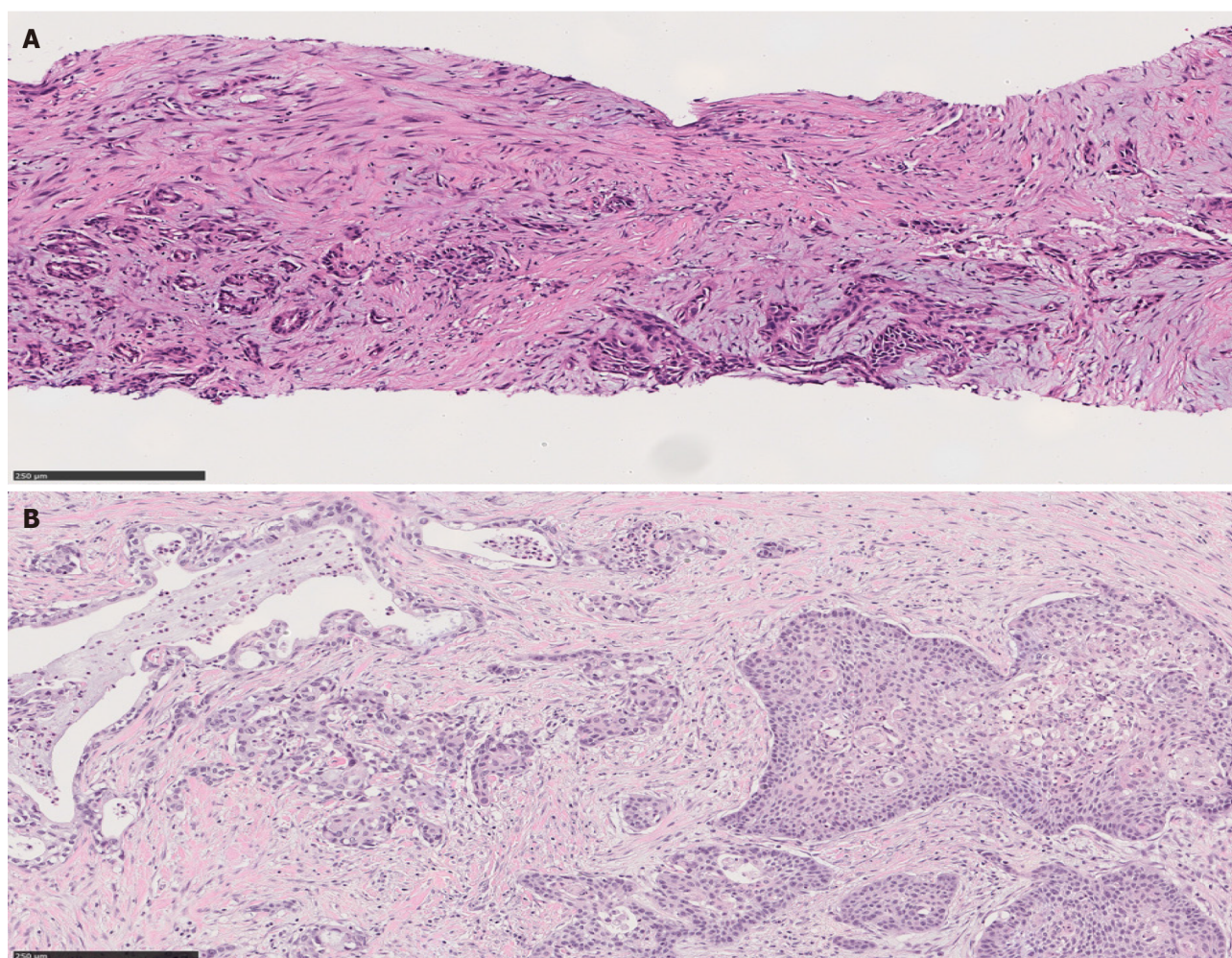
### **Medullary carcinoma**

The histologic hallmarks of this subtype include minimal glandular differentiation, a syncytial growth pattern and abundant inflammatory infiltrate[63]. MMR deficiency is common in this subtype (up to 20%) conferring a better response to immune checkpoint inhibitors and a slightly better prognosis compared to conventional PDAC [9,63,64]. Due to its rarity, molecular data are limited to some case reports. Kryklyva *et al*[65] recently reported a case of pancreatic medullary carcinoma without MMR deficiency. However, a somatic mutation in the *POLE* gene was noted resulting in a high tumor mutation burden and theoretically, increased neoantigen exposure with potential responsiveness to immune checkpoint inhibitor therapy.

### **Hepatoid carcinoma**

The diagnosis of hepatoid PDAC requires that over 50% of the lesion shows hepatocellular differentiation[9]. This is another extremely rare subtype. Due to its extreme rarity, a metastatic hepatocellular carcinoma should always be considered first[66,67]. Data on the prognosis of this subtype are limited[9]. In the literature, molecular profiling of one case of pancreatic hepatoid carcinoma is available. This showed somatic mutations of *BAP1* and *NOTCH1*. Both targets are considered not actionable



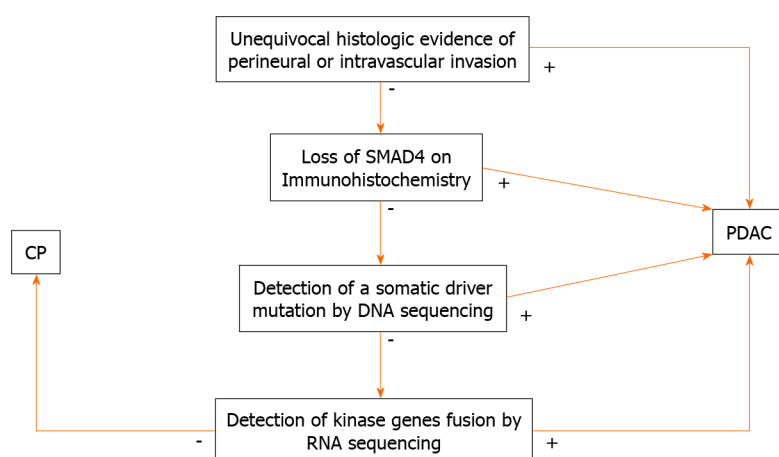


**Figure 7 Adenosquamous carcinoma of the pancreas.** A: Adenosquamous carcinoma of the pancreas in a biopsy material. Both squamous component (right) and glandular component (left) are found in this field [hematoxylin & eosin (H&E), 140 ×, scale 250 µm]; B: Adenosquamous carcinoma of the pancreas in a resection material. Squamous nests are noted (right). The glandular counterpart shows typical features of pancreatic ductal adenocarcinoma (left) (H&E, 136 ×, scale 250 µm).

by current precision immunotherapy[68].

## CONCLUSION

While risk factors, clinical presentation and imaging studies can be helpful in the diagnosis of a mass lesion in the pancreas, there is a significant overlap between benign and malignant lesions. Therefore, histologic examination is a crucial component in the work-up of pancreatic mass. However, in a limited sample, histologic examination can be challenging due to paucity of glandular structures in PDAC, limited ability to evaluate architecture, and nonspecific stromal changes. In this review we outlined the clinical presentation, imaging findings and histologic findings of PDAC, CP, AIP and PDP in order to highlight the inherent difficulties we face in our daily practice. Making a correct diagnosis of these different entities can be extremely challenging, and surgical resection may be still required for the final diagnosis in some cases. Recently discovered molecular alterations in PDAC may help clear ambiguity, serve as prognosticators and broaden treatment options. The algorithm outlined in [Figure 8](#) summarizes the steps in the workup of PDAC *vs* CP.



**Figure 8** An algorithm outlining the steps for the microscopic, immunohistochemical and molecular work up of pancreatic ductal adenocarcinoma vs chronic pancreatitis. CP: Chronic pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.

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