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# Cystic lesions of the pancreas

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**Although cystic tumors of the pancreas are relatively rare, they constitute an increasingly important category. Advances in imaging and interventional techniques and the sharp drop in the mortality rate of pancreatic surgery have rendered pancreatic biopsies and resections commonplace specimens. Consequently, in the past two decades, the nature of many cystic tumors in this organ has been better characterized. The names of some existing entities were revised; for example, what was known as papillary-cystic tumor is now regarded as *solid-pseudopapillary tumor*. New entities, in particular, *intraductal papillary mucinous neoplasm* and its variants, such as oncocytic and intestinal subtypes were recognized. The importance of clinical and pathologic correlation in the evaluation of these lesions was appreciated, in particular, with regards to the multifocality of these lesions, their association with invasive carcinomas, and thus their 'preinvasive' nature. Consensus criteria for the distinction of these from the ordinary precursors of adenocarcinoma, the pancreatic intraepithelial neoplasia, were established. The definition of mucinous cystic neoplasms was refined; ovarian-like stroma has now become almost a requirement for the diagnosis of mucinous cystic neoplasia, and defined as such, the propensity of these tumors to occur in perimenopausal women became even more striking. The validity and clinical value of classifying the pancreatic cysts of mucinous type as adenoma, borderline, CIS and invasive have been established. Related to this, the importance of thorough sampling in accurate classification of these mucinous lesions was recognized. Greater accessibility of the pancreas afforded by improved invasive as well as noninvasive modalities has also increased the detection of otherwise clinically silent cystic tumors, which has led to the recognition of more innocuous entities such as acinar cell cystadenoma and squamoid cyst of pancreatic ducts. As the significance of the cystic lesions emerged, cystic forms of otherwise typically solid tumors were also better characterized. Thus, significant developments have taken place in the classification and our understanding of pancreatic cystic tumors in the past few years, and experience with these lesions is likely to grow exponentially in the coming years.**
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Dorland's Medical Illustrated dictionary defines a cyst as 'any closed cavity or sac, normal or abnormal, lined by epithelium, and especially one that contains a liquid or semisolid material'.[1] In the pancreas, however, this term has been applied to a variety of lesions, ranging from radiologically low-attenuated tumors, to any process that forms a cavity, and in some cases, whether it has an epithelial lining or not. Therefore, the term *cyst* has become associated with some pancreatic lesions that do not fulfill the dictionary definition of the term.

Overall, cystic tumors of the pancreas are significantly less common than solid ones. It is estimated that less than 1% of pancreatic tumors seen in oncology clinics are cystic; however, in resection specimens cystic ones are becoming increasingly more common, reportedly up to 15% of the cases in some institutions. There are important reasons for this increase in frequency, particularly among resection specimens: (1) recent developments in imaging techniques have led to increased detection of clinically silent tumors, (2) most cystic lesions are noninfiltrative, and are thus resectable, (3) most cystic tumors are biologically curable, (4) advances in surgical and perioperative care have decreased the mortality rate of pancreatectomy procedures from 20 to 30% in 1980s to below 5% in 'very high-volume' institutions, and therefore, most cystic tumors undergo resection, such that there is a remarkable increase in the exposure of surgical pathologists to these lesions. This contrasts with invasive ductal (pancreatobiliary-type) adenocarcinoma in this organ, which is the most common tumor type (>85% of all cases), is

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**Table 1** Estimated relative frequency of the cystic lesions in the pancreas

| | | |
|---|---|---|
| I. No lining | 'Pseudocyst': pancreatitis-associated | 30[a] |
| II. True lining | Mucinous | |
| | Intraductal papillary mucinous neopl. | 20 |
| | Mucinous cystic neopl. | 10 |
| | Serous | 20 |
| | Others (squamous, acinar, endothelial…) | <5 |
| III. Degenerative/necrotic change in a neoplasm | Solid-pseudopapillary neoplasm | <5 |
| | Cystic ductal adenocarcinoma | <5 |
| | Others (endocrine, mets., etc) | <5 |

[a]Numbers reflect approximate percentages.

**Table 2** Types of cystic lesions in the pancreas based on their lining

*Pseudocysts (no lining)*
- Conventional pseudocysts
- Paraduodenal wall cyst (cystic dystrophy)
- Infection-related pseudocysts

*Cysts with mucinous epithelium*
- Intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms
- Mucinous cystic neoplasms
- 'Mucinous non-neoplastic cysts', 'mucoceles' and 'retention cysts'

*Serous (clear-cell) cystic tumors*
- Serous cystadenoma
- VHL-associated pancreatic cysts
- Serous cystadenocarcinomas

*Squamous-lined cysts*
- Lymphoepithelial cysts
- Epidermoid cysts within intrapancreatic accessory spleen
- Dermoid cysts
- Squamoid cyst of pancreatic ducts

*Cysts lined by acinar cells*
- Acinar cell cystadenocarcinomas
- Acinar cell cystadenomas (cystic acinar transformation)

*Endothelial-lined cysts*
- Lymphangiomas

*Degenerative or necrotic changes in solid tumors*
- Solid-pseudopapillary tumor
- Cystic change in ordinary ductal adenocarcinoma
- Cystic pancreatic endocrine neoplasia (islet cell tumors)
- Cystic change in other invasive carcinomas
- Cystic mesenchymal neoplasms

*Other rare cystic lesions*
- Cystic hamartomas
- 'Enterogenous' (congenital; duplication) cysts and duodenal diverticula
- Endometriotic cyst
- Secondary tumors
- Congenital or developmental cysts
- Others
- Unclassified cysts

mostly unresectable (80%), and associated with a dismal prognosis (5-year survival <5%).

The relative frequencies of cystic lesions in the pancreas vary substantially from institution to institution, from primary *vs* tertiary care centers, and presumably even from region to region.[2,3] The lesions below are discussed in an order that reflects both the frequency and clinical significance of different cystic lesions in this author's experience based upon a large surgical and autopsy database from an institution that serves both as a primary and tertiary care center, as well as the author's consultation material and the published data in the literature. Estimated relative frequency of cystic lesions accordingly is shown in Table 1.

There is no formal classification of cystic neoplasms of the pancreas. For the purpose of this text, they will be categorized based on the presence and type of cyst lining at the microscopic level (Table 2).

## Pseudocysts (no lining)

### Conventional Pseudocysts

Most cavity-forming lesions of the peripancreatic region are pseudocysts.[4–6] The entity referred to as 'pseudocyst' is a non-neoplastic complication of pancreatitis caused by alcoholic, biliary, or traumatic acute pancreatitis.[7,8] It develops when a focus of peripancreatic fat necrosis is resorbed, producing a debris-filled space rich in pancreatic exocrine enzymes. Pseudocysts may measure up to several centimeters. The pathologic findings may vary depending on the stage of the process. The cyst contents, originally necrotic fat, transform into a mixture of necrotic cells, enzymes, scavenger cells, hematoidin pigment, cholesterol clefts, and sometimes neutrophils. There is no epithelial lining. The adjacent stroma may be hypercellular (Figure 1). The tissue that surrounds the necrotic material first produces granulation tissue, and eventually becomes a fibrotic pseudocapsule. Depending on the severity and duration of the pancreatitis, the pseudocyst may resolve spontaneously, or may achieve a size that is no longer self-resorbable, and require surgical intervention.

Pseudocysts do not present a risk of malignant degeneration, and the treatment of pseudocysts differs dramatically from that of cystic neoplasms of the pancreas. Fortunately, the clinical diagnosis of a pseudocyst is usually straightforward; however, neoplasms may mimic a pseudocyst and conversely. There are case reports of virtually every pancreatic neoplasm presenting like a pseudocyst.[9–14] Solid-pseudopapillary neoplasms often undergo massive cystic degeneration, and mucinous cystic neoplasms.[15] have a tendency to become infected and exhibit suppurative contents. The ovarian stroma characteristic of the latter may be confused microscopically with the granulation tissue of pseudo-

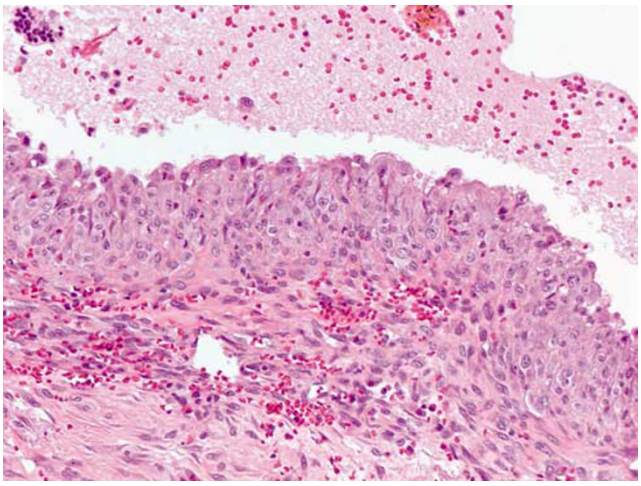

**Figure 1** Pseudocyst. Pseudocyst is defined by the lack of an epithelial lining. The constituents of the wall vary depending on the stage of the lesion; in the earlier phase, necrotic debris and precipitated acinar secretions are present in the lumen, and granulation tissue on the wall. Later on, fibrosis becomes more prominent. In this example, histiocytes are prominent adjacent to the lumen of the cyst, and there is a cellular stroma around it. This can mimick ovarian-type stroma of mucinous cystic neoplasms.

cysts and vice versa. Proper sampling is essential for the correct diagnosis in such cases. It should also be kept in mind that ductal adenocarcinoma, although rarely, may undergo central necrosis and clinically mimic pseudocysts.[2,16–19]

*Paraduodenal wall cyst (cystic dystrophy)*
This is one of the complications of a subset of chronic pancreatitis that we refer to as paraduodenal pancreatitis.[20] These cysts appear to occur as a consequence of chronic fibrosing inflammation in the periampullary region in which one or more of the accessory ducts form a cyst on the duodenal wall, and mimic duodenal duplication.[5,21,22] This usually occurs in the background of microcystic trabeculation of the duodenal wall by 'myo-adenomatosis' type changes that form a 'pseudotumor' which may also involve the adjacent pancreas in the groove area (the so-called groove pancreatitis[23]). The cyst wall may be partly lined by ductal epithelium and partly by inflammation as well as granulation tissue.[24] In our experience,[21,22] this process is often located in the second portion of the duodenum, (Figure 2) centered around the accessory ampulla, and may be associated with the scarring of common bile duct, mimicking pancreas cancer. We believe paraduodenal wall cysts are closely related to the so-called cystic dystrophy.[25] In our experience, they occur predominantly in males, at age 40–50 years, often with a history of alcohol abuse, and in the context of severe abdominal symptoms.[20] Some were interpreted to be associated with 'pancreatic heterotopia' in the duodenal wall.[26]

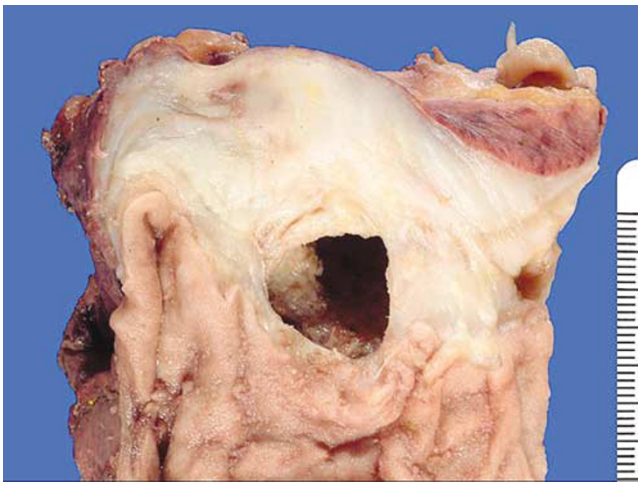

**Figure 2** Paraduodenal wall cyst. In some patients with pancreatitis, in particular of the paraduodenal type (also called cystic dystrophy of duodenal wall), one or more of the cysts may become fairly large, and located on the duodenal wall, mimicking duodenal duplication. These may be partly lined by ductal epithelium, but are mostly lined by granulation tissue.

*Infection-related pseudocysts*
Other rare inflammatory cysts that can occur in the pancreas include parasitic cysts such as echinococcal cyst[27–29] and necrotic tuberculous infections.[30,31]

## Cysts with mucinous epithelium

### Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by cystic dilatation of pancreatic ducts in which an intraductal proliferation of neoplastic mucin-producing cells is usually arranged in papillary patterns[14,32–51] (Figure 3). The papillae may range from microscopic to large nodular masses. Mucin production by the neoplastic cells is usually associated with intraluminal mucin secretion which leads to cystic dilatation of the ducts, and at times, to mucin extrusion from the ampulla of Vater, a finding that is virtually diagnostic of an IPMN. Depending upon the location of the primary process and subsequent mechanical changes in the ducts, IPMNs may present as a spectrum of multilocular cystic masses, villous/papillary nodules or with mucin extrusion from the ampulla. This spectrum is reflected in the variety of designations that had been given to these neoplasms including mucinous duct ectasia[52] (ductectatic mucinous cystadenoma),[53] mucin-producing tumor,[54,55] and villous adenoma[56] or papillary carcinoma.[57,58] The term coined by Günter Klöppel, IPMN, is now widely accepted as the designation of these neoplasms.[44,50,59] IPMNs are estimated to account for ~5% of pancreatic neoplasms, however, they are being reported in increasing numbers and may be more common than previously recognized.[35,39]

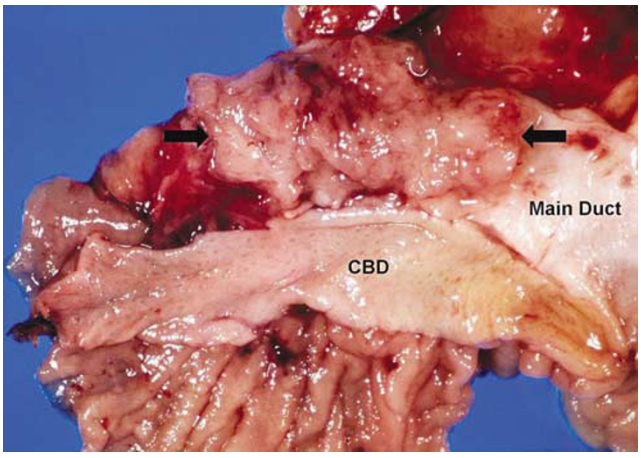


**Figure 3** IPMNs. In this example, the main duct is markedly dilated, and there is a polypoid nodule filling the lumen of the proximal segment of the duct (arrows).

Clinically, patients with an IPMN usually present in the 7–8th decade of life with nonspecific abdominal symptoms, although in some, a history of pancreatitis is noted. Approximately, 30% of the patients have tumors in other organs, some synchronous and others metachronous.[34,60,61] Endoscopic findings, particularly mucin extrusion from the ampulla of Vater, and radiologic findings, especially ectasia of the pancreatic ducts, are virtually diagnostic for these neoplasms. IPMN occurs predominantly in the head of the pancreas.

Macroscopic examination of IPMNs is imperative for documenting involvement of the pancreatic ductal system and the distribution of the disease within the ductal system, especially since there are no basal or myoepithelial cells in pancreatic ducts to distinguish native ducts. In some cases, the IPMN primarily involves the main pancreatic duct, (Figure 3) and in others the branch ducts; the latter is predominant particularly in those that arise in the uncinate process. The latter have been referred to as 'branch-duct'-type IPMNs.[49,62–65] Some authors believe this variant is a biologically distinct entity, and therefore every attempt should be made during macroscopic examination to determine the distribution of the lesion.[47,49,60,62,64–67] IPMNs may be localized, multicentric or, rarely, the entire ductal system may be involved. Careful examination and sampling of the specimen for an invasive carcinoma component is of vital importance.

Microscopically, the cystically dilated ducts of IPMNs contain mucin-producing cells with various degrees of atypia (Figure 4). Papillae with three distinct morphologic patterns may be seen[34,68–73] (1) intestinal, which is morphologically similar to that of colonic villous adenomas of the colon (Figure 5) and (2) pancreatobiliary, in which the papillae are more complex and are lined by cuboidal cells with prominent nucleoli. (3) gastric, rarely some papillas have gastric foveolar appearance (Figure 6). As this phenotype is also common in the nonpapillary areas of these tumors, it is also referred to as 'null' type. The first group does in fact show molecular characteristics of intestinal differentiation as evidenced by MUC2 and CDX2 expression, which are regarded as having key roles in intestinal programming, in addition to their tumor-suppressor properties.[73] Invasive carcinomas associated with this group is typically of colloid type, (Figure 7) and conversely, colloid carcinoma is also often associated with intestinal type papillae.[73] Papillae with the pancreatobiliary pattern, on the other hand, typically do not express CDX2 and MUC2, but may instead express MUC1, a 'marker' of aggressive phenotype in the pancreas.[73]

Although IPMNs and mucinous cystic neoplasms have some features that overlap, the two can be distinguished by clinical, gross, and microscopic findings[74] (see Table 3). Mucinous cystic neoplasms occur predominantly in perimenopausal female subjects and in the tail of the pancreas. IPMNs are seen predominantly in the head of the pancreas and in elderly males.[33,75,76] Whereas IPMNs involve the pancreatic ducts, mucinous cystic neoplasms typically do not communicate with the ductal system. Mucinous cystic neoplasms often have thick cyst walls. The presence of ovarian stroma is diagnostic for mucinous cystic neoplasms and has almost become a requirement for the diagnosis of this tumor type.[74] The differential diagnosis of IPMNs should also include ampullary adenomas that may extend intraluminally into the pancreatic ducts.

IPMNs also need to be distinguished both conceptually and practically from the smaller (microscopic) lesions of the pancreatic ducts known as pancreatic intraepithelial neoplasia (PanIN),[77] and from non-neoplastic localized duct-ectasia (Kimura lesions[78] and retention cysts). The separation of IPMNs and PanIN is based primarily on size.[79] IPMNs are larger ($>1$ cm) and usually form a macroscopic and/or radiologic detectable mass.[79,80] This is analogous to the dichotomy[80] in other organs, for example, flat-type urothelial CIS *vs* papillary urothelial neoplasms, and mammary intraductal proliferations *vs* intracystic papillary carcinoma of the breast, which incidentally, is also seen in elder patients.[81,82]

As advocated by the World Health Organization classification,[83,84] noninvasive IPMNs are graded as adenoma, borderline-tumor and *in situ* carcinoma.[35,36] Invasive adenocarcinoma, which is seen in $\sim$30% of cases is usually either of the colloid[85] or tubular (ordinary ductal) types.[33,34] The former has been found to have indolent behavior, analogous to the colloid carcinomas of the breast, regardless of whether it is associated with IPMN or not.[85]

Overall 5-year survival for patients with an IPMN is $>$70%.[32–40,42–44,86,87] This is not surprising, considering that most IPMNs are noninvasive. Interestingly, some patients with surgically resected noninvasive IPMNs later develop recurrence and

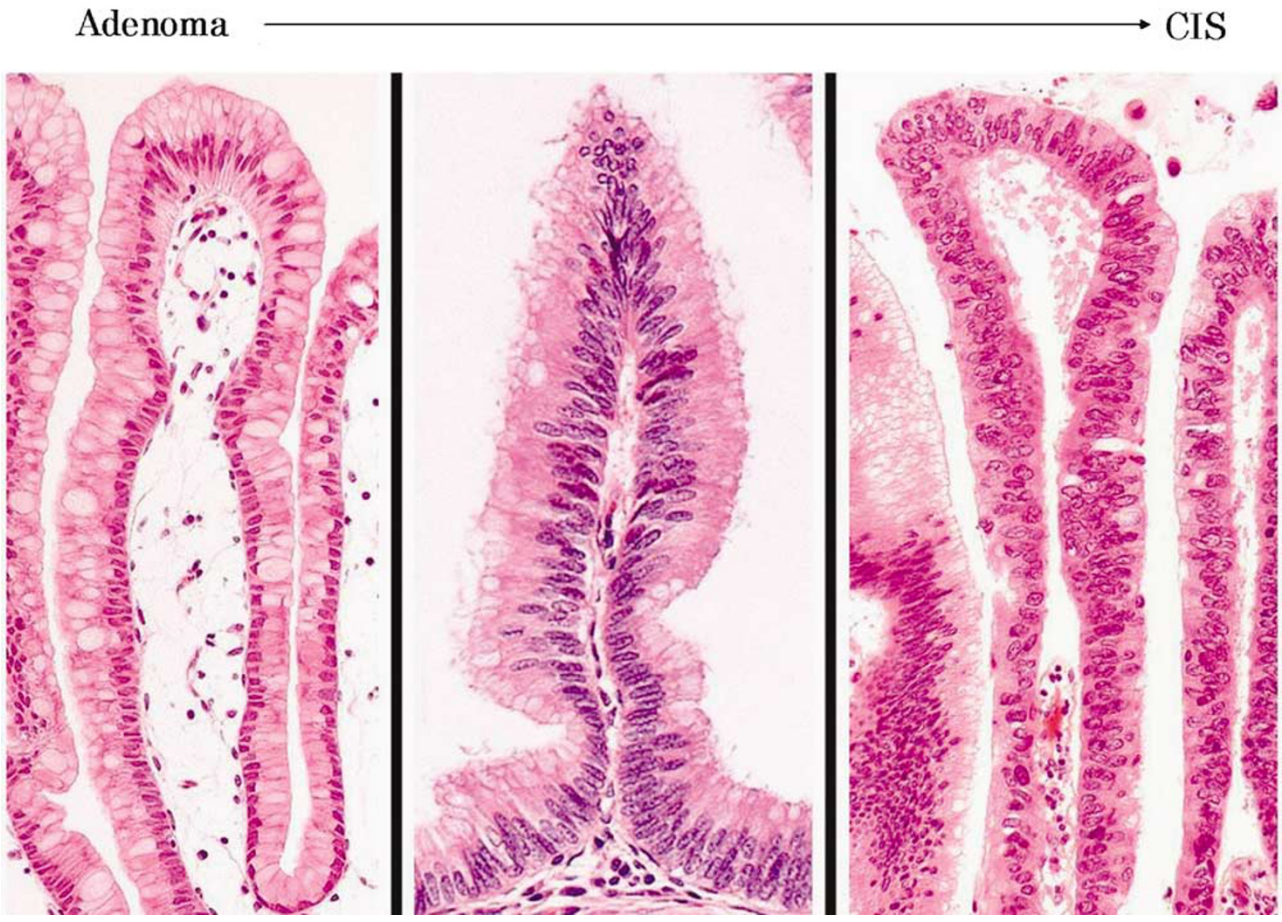


**Figure 4** IPMNs, adenoma (left), borderline (middle) and carcinoma *in situ* (right). The papilla on the left shows virtually no atypia and exhibits a gastric foveolar appearance. The one in the middle is reminiscent of villous adenoma, and exhibits low-grade dysplastic changes that fall into the 'borderline' category. The papilla on the right shows marked cytologic disorganization and atypia (ie CIS).

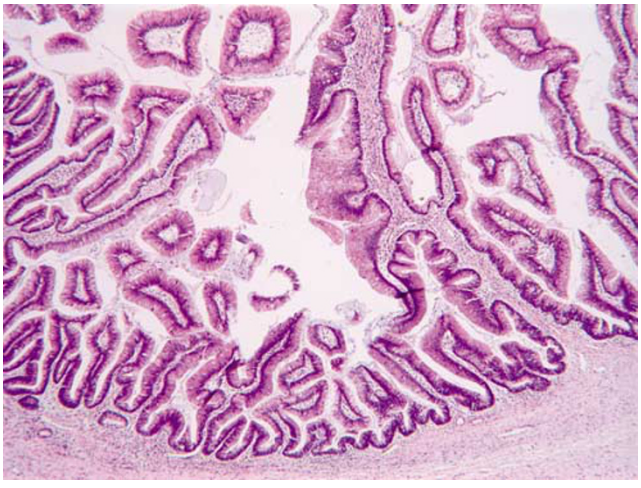

**Figure 5** IPMN. Many examples exhibit a pattern virtually indistinguishable from colonic villous adenomas.

some even develop metastases. These cases most likely represent multifocal disease, a finding uncommon with mucinous cystic neoplasms.[88] Multi-

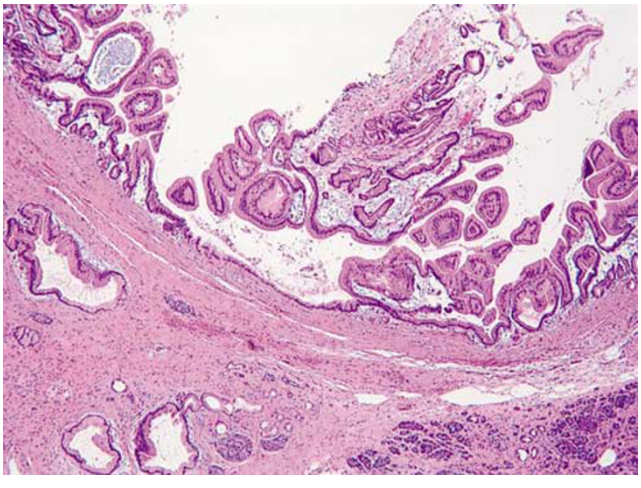

**Figure 6** IPMN in smaller ducts. These tumors can involve any component of the ductal system. The larger cyst in this example is in fact a markedly dilated branch duct. Smaller units are often involved (lower left) with what is presumed to be pagetoid spread of the lesion. In some cases, it can be difficult, if not impossible, to distinguish these from incidental/independent PanINs. This example also illustrates the gastric foveolar-type of papillae.

focality of disease and haphazard distribution of carcinoma, which can be grossly invisible, necessitates the careful evaluation of these neoplasms, with complete removal and thorough pathologic examination.[34,38]

That invasive carcinoma may develop both adjacent to and away from the IPMN,[89] as well as its potential for multifocal disease, have rendered the management of these tumors rather problematic. A multidisciplinary approach by experts familiar with this tumor type may be crucial. It seems that IPMNs that are of the branch-duct type (as determined by their location and radiologic findings), and those that are simple (small, predominantly cystic, and without complex nodularities) usually prove to be adenomas and are highly amenable to conservative approach.[74] On the other hand, main-duct type IPMNs, and those that are large, complex and nodular often prove to be carcinomas, and require more aggressive therapy. Some authors advocate even total pancreatectomy for some cases.[38]

Another problematic area in the management of IPMNs is the status of surgical resection margins.[38] In general, it is felt that the presence of carcinoma at the surgical margins bears too high a risk for the patient, and further therapy is probably warranted for these patients, if clinically feasible. On the other hand, the presence of 'adenomatous' epithelium at the pancreatic parenchymal margin is probably negligible[49,62–65] (based on what we extrapolate from the branch-duct literature); however, the relative risk of later developing an invasive carcinoma in these patients is also rather difficult to determine.

IPMNs appear to be genetically much more stable than conventional infiltrating ductal adenocarcinomas, and lack (or exhibit at much lower levels) the molecular/genetic alterations of the latter. Mutations in the *KRAS, p16* and *TP53* genes are significantly less common in IPMNs, and *SMADH4/DPC4* loss is not usually detected.[44,90–93] Also, as noted earlier, IPMNs frequently express MUC2 and CDX2,[73] which have tumor-suppressor activity and encode for intestinal type mucin-related glycoproteins. The molecular alteration characteristic of Peutz-Jeghers syndrome is detectable in one-third of IPMNs.[94] There are also differences in the molecular phenotype of IPMNs *vs* PanINs. PanINs lack MUC2 expression, and high-grade PanINs may show MUC1 expression and *SMADH4/DPC4* loss. Whether some of these molecular alterations may have utility in prognostication and stratification of patients into different treatment categories is too soon to tell. Some studies have found MUC1 expression,[70,80,95] p53 overexpression[96] and telomerase activity[97] to be associated with a more aggressive clinical course. These and other potential markers ought to be studied further.

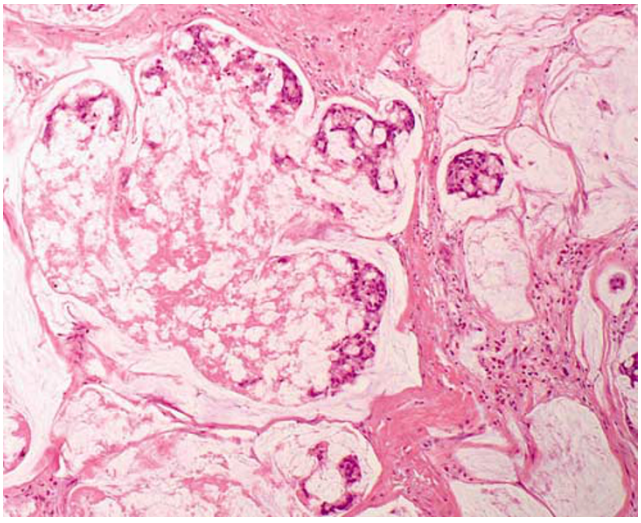

**Figure 7** Colloid carcinoma. Invasive colloid carcinomas are often associated with IPMNs. These are indistinguishable from colloid carcinomas of the breast, and have been found to have an indolent prognosis.

### Intraductal Oncocytic Papillary Neoplasms

Intraductal oncocytic papillary neoplasm (IOPN)[98] is regarded a special subtype of IPMN,[74] although recent molecular findings suggest that it may be different from IPMNs.[93] Grossly, these neoplasms exhibit cystic dilatation of the pancreatic ducts, many of which contain large, tan and friable nodular proliferations. The neoplasms are relatively large (mean size: 5.2 cm) at the time of diagnosis. The papillae of IOPNs exhibit a 'pancreaticobiliary (PB)' pattern[99] (also called compact cell type), which is characterized by exuberant, arborizing papillae lined by 1–5 cell layers of cuboidal cells (Figure 8).

**Table 3** The differential diagnosis of mucinous cystic neoplasms and intraductal papillary mucinous neoplasms

| *Features* | *Mucinous cystic neoplasms* | *Intraductal papillary mucinous neoplasms* |
|---|---|---|
| Age | 50 | 68 |
| Gender | Females (>95%) | Males ~ Females |
| Specific endoscopic finding | None | Mucin extrusion from ampulla |
| Specific radiologic finding | Multilocular thick-walled cyst ('CYST IN CYST') | Cystically dilated ducts ('CYST BY CYST') |
| Location | Tail (>90%) | Head (>80%) |
| Gross ductal communication | No | Yes |
| Specific histologic findings | Ovarian Stroma (almost a requirement) | Cystically dilated native ducts with villous nodules |

The nuclei in IOPNs contain single, prominent, and eccentric nucleoli (Figure 9). One distinctive feature that appears to be relatively specific for these neoplasms is the presence of *intraepithelial lumina* which are round, punched-out spaces within the epithelium that often give the proliferation a cribriform architecture, similar to that seen in oncocytic schneiderian papillomas of the sinonasal tract. These intraepithelial lumina often contain mucin. The cells of IOPNs are *oncocytic*, due to an abundance of mitochondria and the paucity of other organelles, which is reflected histologically as abundant, granular, acidophilic cytoplasm. In most cases, the degree of cytoarchitectural atypia, the exuberance of the papillae, and the presence of mitoses qualify for the diagnosis of at least carcinoma *in situ*.

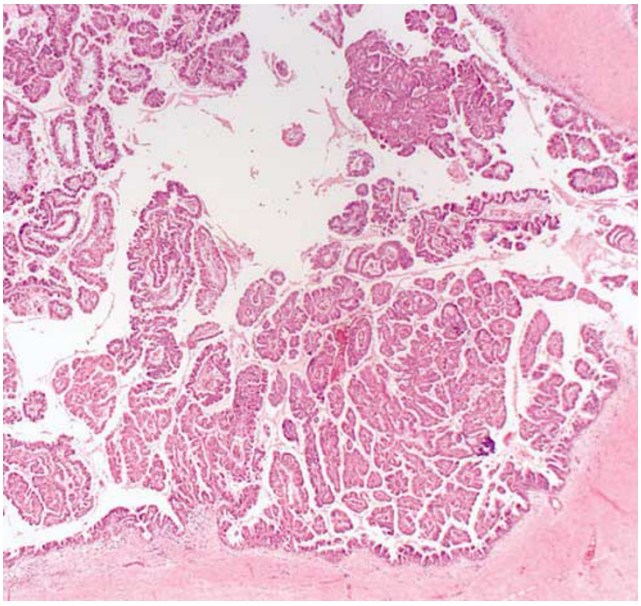

**Figure 8** IOPN. This cystically dilated duct is filled with complex (arborizing) papillae characteristic of this tumor type. Often, the papillary cores show edematous changes.

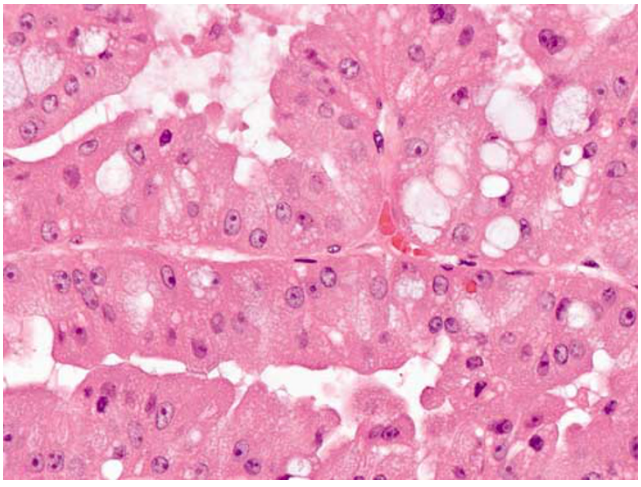

**Figure 9** IOPN. Even more so than the complexity of the papillae, these tumors are characterized by oncocytic cells (with abundant acidophilic cytoplasm, round nuclei with fine chromatin, single prominent and eccentric nucleoli, and distinctive intraepithelial lumina formation.

In other organs, oncocytic change (which is probably a degenerative phenomenon secondary to oxidative stress on the cells) is associated with a different biologic behavior than the nononcocytic counterparts of these neoplasms. Whether this applies also to the pancreas remains to be seen. Preliminary molecular analyses have shown that IOPNs may differ from the conventional IPMNs, by the lack of *KRAS* gene mutations and alternate MUC phenotypes. Furthermore, IOPNs have a much higher incidence of HepPar-1 expression, and MUC6 is more diffuse and strong than any other types or components of IPMNs.[100,101]

The data on the clinical course of IOPNs is limited,[98,102–105] however, it seems to be similar to that of IPMNs, but may be even more indolent.

## Mucinous Cystic Neoplasms

Mucinous cystic neoplasms are presumably *de novo* cystic tumors (unlike IPMNs which give rise to cystic dilatation of native ducts), and they are characterized by an ovarian type of stroma. Mucinous cystic neoplasms have distinctive clinicopathologic characteristics: they are seen almost exclusively in perimenopausal female patients (mean age = 48 years, M/F = <1/20; only rare male patients with ovarian-stroma are on record) and the neoplasm is most often located in the tail of the pancreas.[76,106–110] Macroscopically, these neoplasms are composed of large multilocular cysts ranging in size from one to several centimeters. The cysts have thick fibrotic walls (Figure 10). Unless there is fistula formation, the cysts do not visibly communicate with the pancreatic ductal system (although recent reports from Japan indicate that there is often subtle communication at the microscopic level evidenced by the passage of dye injected into the ducts into the cysts). The wall of the cysts may have velvety papillations, appear trabeculated, and thickened. The cyst contents are often mucoid, but hemorrhage and a more watery consistency may also be noted. Solid areas within the neoplasm should be sampled extensively for microscopic examination, as they may harbor an invasive component. Morphologically, mucinous cystic neoplasms of the pancreas are similar to mucinous cystic neoplasms that occur in the retroperitoneum, ovary, and liver. This resemblance includes the presence of a distinctive stroma (referred to as ovarian-like) around the cysts (Figure 11). This stroma is a very common and an entity-defining feature of these neoplasms, to an extent that it has almost become a requirement for the diagnosis.[74] There are two

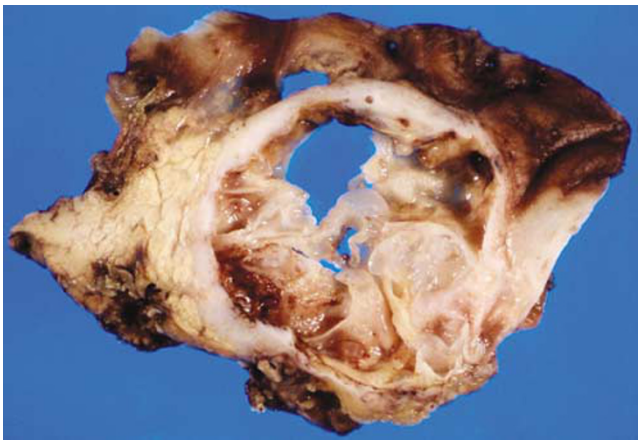

**Figure 10** Mucinous cystic neoplasm. A thick-walled multilocular cystic tumor is a characteristic finding of mucinous cystic neoplasms.

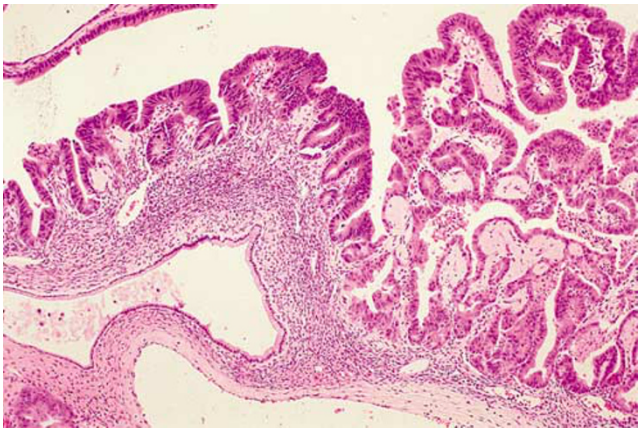

**Figure 11** Mucinous cystic neoplasm (with ovarian-type stroma). The distinctive hypercellular stroma, which shows all the morphologic and immunophenotypic characteristics of ovarian stroma, has become nearly a requirement for the diagnosis of this tumor type. The epithelium in mucinous cystic neoplasia may show various degrees of atypia, ranging from adenoma (lower left) to frank carcinoma *in situ* (upper).

hypotheses on the origin of a neoplasm in the pancreas with ovarian-type stroma. The first hypothesis is that these neoplasms arise from rests of embryologic ovarian tissue deposited in the pancreas. This hypothesis is supported by the close proximity of the left ovarian primordium to the tail of the pancreatic anlage in fetal life. The second hypothesis proposed to account for these neoplasms is that the stroma represents a recapitulation of periductal fetal mesenchyme, the primitive mesenchyme seen around the pancreatic and hepatic ducts in the developing fetus.[111] Regardless of its origin, it is clear that this stroma is hormone sensitive; it is often admixed with luteal-type cells and it regularly expresses progesterone receptors. Moreover, some mucinous cystic neoplasms are reported to be associated with ovarian thecomas,[112] further suggesting a hormone influence in the pathogenesis of these neoplasms.

The cysts in mucinous cystic neoplasms are lined by tall, columnar, mucin-producing epithelium, which may exhibit gastric foveolar-type intracellular mucin or goblet cells. Scattered neuroendocrine cells are present in the majority of cases and they can be demonstrated by immunohistochemical labeling for neuroendocrine markers such as chromogranin and synaptophysin.

The epithelium in the predominantly cystic and adenoma components of MCNs are virtually indistinguishable from those of IPMNs, or for that matter, also from those of PanINs. The papillary components, however, show some differences. MCN-papillae do not typically have the full-blown villous adenoma-like appearance and diffuse MUC2/CDX2 expression characteristic of the 'intestinal' (dark-cell, columnar-cell) subset of IPMNs.[113] Instead, they often show MUC1 expression similar to the pancreatobiliary subtype of IPMNs.

Some mucinous cystic neoplasms have purulent contents and these may be misdiagnosed as *pseudocysts* both intraoperatively as well as histopathologically especially if the epithelium is denuded, and the remaining ovarian stroma resembles the granulation tissue of pseudocysts. Inflammation may also impart a more complex architecture to an otherwise simple mucinous cystic neoplasm and raise the suspicion of malignancy.[114]

Mucinous cystic neoplasms can show a wide range of cytologic and architectural atypia: Some are histologically bland, with uniform, basally oriented nuclei, and minimal architectural atypia, while others exhibit prominent papillary proliferations that form intraluminal polypoid masses with cribriform architecture and substantial cytologic atypia (Figure 11). The epithelial atypia may be patchy, and there is often an abrupt transition between histologically bland epithelium and epithelium with severe atypia. Numerous sections may be required to properly evaluate these neoplasms. This may explain why the studies from the Armed Forces Institute of Pathology (AFIP),[106,110] a referral center where the diagnosis is generally based on a few selected slides submitted for consultation, have failed to demonstrate that dysplasia and even the presence of an invasive cancer are prognostically relevant. For that reason, the authors from the AFIP regard all MCNs, regardless of their grade, as 'low-grade malignant neoplasms,' that is, cystadenocarcinoma.[106,110] However, more recently, a number of studies from other authors who performed more complete examination and extensive sampling of the neoplasms concluded that grade does accurately predict the outcome.[76,108,109,115] It is also our experience that patients with completely resected mucinous cystic neoplasms without atypia (mucinous cystadenomas) are almost always cured. These tend to be small as well ($<3$ cm). Mucinous cystic

neoplasms with moderate atypia are classified as mucinous cystic neoplasms with moderate dysplasia, while those with significant architectural and cytologic atypia are classified as mucinous cystic neoplasm with carcinoma *in situ*[83,116] (Figure 11). Patients with these latter two grades of noninvasive mucinous cystic neoplasms are also often cured if their tumors are resected completely.

If an invasive carcinoma is present, the neoplasm should be classified as a mucinous cystadenocarcinoma.[83,116] In fact, we prefer to report these as 'invasive carcinoma of—type,—cm, arising in association with mucinous cystic neoplasms (—cm),' just as we do for IPMNs or *in situ* neoplasia of other organs such as the breast. The invasive carcinomas that arise in association with mucinous cystic neoplasms are usually tubular/ductal type. Interestingly, these have been found to pursue a more indolent course than ordinary infiltrating ductal adenocarcinoma.[110] It is difficult to determine whether this implies that the invasive carcinomas arising from MCNs are biologically different (although they may look morphologically identical to ductal adenocarcinoma) or whether MCN allows for earlier diagnosis of invasive carcinoma. The same concept also holds true for IPMNs (as previously discussed).

In addition to its association with invasive tubular adenocarcinomas, some MCNs may be associated with undifferentiated carcinoma with osteoclast-like giant cells,[117,118] or high-grade sarcoma.[119] Pure colloid carcinoma, which is the predominant type of invasive carcinoma in IPMNs, is exceedingly uncommon in MCNs,[113] once the latter is defined by the presence of ovarian-stroma.

#### Intraductal Tubular Adenocarcinomas

This is an emerging entity that has yet to be fully characterized.[120] These are mostly solid tumors, but fall into the differential diagnosis of cystic neoplasia because of their intraductal growth. Some examples do show cystic changes in the ducts (cavity without intraluminal nodules). These tumors are characterized by intraductal neoplasia that have prominent tubular growth, morphologically resembling acinar tumors, but also showing ductal features. Mucin formation is minimal. Many examples have densely packed tubular units tightly packed with only minimal intervening stroma, but in some, there is significant desmoplastic-type stroma. In a subset of these cases, squamoid zones and comedo-like necrosis are seen in the ducts.

#### 'Mucinous Non-Neoplastic Cysts,' 'Mucoceles', and 'Retention Cysts'

In general, the vast majority of 'mucinous cysts' (cysts lined by mucinous epithelium) in the pancreas are considered neoplastic. However, it is known that obstruction and fibrosis may lead to cystic dilatation of the upstream ducts[5,121] (ie a retention cyst, or if mucus filled, a mucocele).[122,123] Epithelial-lined examples of paraduodenal wall cysts can be regarded as part of the same phenomenon. Mucinous non-neoplastic cyst is also possibly a related concept.[124,125] There is no precise definition for these lesions or specific criteria to distinguish them from IPMNs, mucinous cystic neoplasms, or for those that are small, from PanIN. Our approach to these lesions is to accept them as 'non-neoplastic' only if they are simple (unilocular), lined by either low-cuboidal, or attenuated cells. In these cases, finding an obstruction of the pancreatic duct helps establish the diagnosis. However, we classify those lesions lined by *tall-columnar-mucinous cells,* forming papillae or that are more complex (multilocular) as neoplastic (PanIN if they are smaller than 1 cm and IPMN if they are $>1$ cm). Admittedly, these criteria are rather arbitrary and may not be widely agreed upon.

## Serous (clear-cell) cystic tumors

In the pancreas, the term serous is defined somewhat differently than it is in some other sites, in particular, the female reproductive tract. In the pancreas, it describes a distinctive cell type with clear cytoplasm, and immunophenotypic characteristics suggestive of centroacinar/intercalated-duct differentiation.

#### Serous Cystadenoma

Serous cystadenoma is a benign neoplasm composed of uniform cuboidal glycogen-rich epithelial cells that form small cysts containing serous fluid. Serous cystadenomas are the prototypical and almost sole example of microcystic pancreatic neoplasms. In fact, the gross appearance of most serous cystadenomas—numerous, tightly packed small cysts and a stellate scar, creating a sponge-like appearance—is diagnostic of the entity (Figure 12). Serous cystadenomas usually present as relatively large masses measuring up to 25 cm, mostly in the body or tail of the pancreas, and are seen predominantly in female patients (F:M = 3:1). The mean age of the patients is 61 years.[126–132] Microscopically, these neoplasms have distinctive morphologic features. The cells lining the small cysts have clear cytoplasm, well-defined cytoplasmic borders, and small, round uniform nuclei with dense, homogeneous chromatin (Figure 13). These cytologic features are also characteristic and very helpful in needle biopsies. A rare macrocystic variant of the serous cystadenoma has been reported[133–135] (discussed below) as has a solid variant.[136]

Serous cystadenomas are presumed to arise from (or recapitulate) the centroacinar cell-intercalated duct system,[137] and accordingly express MUC6.

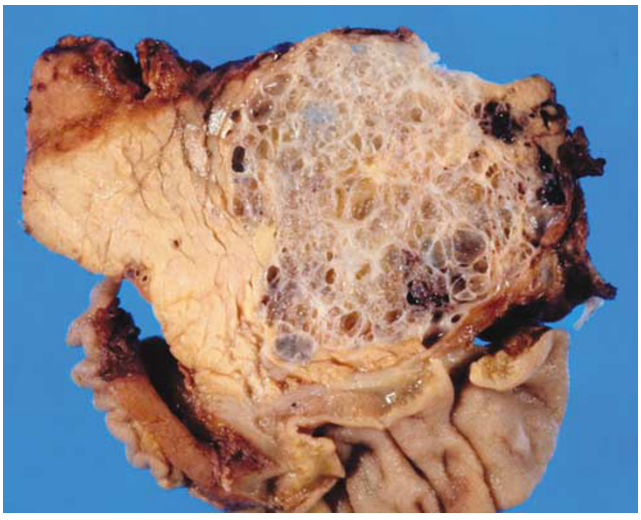

**Figure 12** Serous cystadenoma. Serous cystadenomas are typically composed of innumerable small cysts, most of which are in the range of millimeters, hence the synonym 'microcystic' adenoma. This sponge-like appearance of serous adenomas is so characteristic that these tumors can virtually be diagnosed by their gross appearance alone.

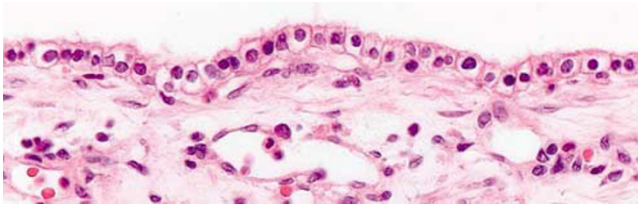

**Figure 13** Serous cystadenoma. The cytologic features of serous adenomas are also as characteristic and specific as their gross appearance. The cells have glycogen-rich clear cytoplasm, distinct cytoplasmic borders, and round, uniform nuclei with dense homogenous chromatin.

They are negative for mucin stains, and the glycogen can be highlighted by the PAS stain. They do not harbor the molecular genetic alterations that are characteristic of mucinous-type ductal neoplasia of the pancreas, such as mutations in the *k-ras, SMADH4/DPC4, TP53,* and *p16* genes.[138,139] Instead, von Hippel-Lindau gene alterations, detected in 40% of the cases[137,140] have been implicated in the pathogenesis of serous cystadenomas. Glut-1, a molecule involved in glycogen metabolism, is also expressed consistently in serous tumors.[141]

Of interest, serous cystadenomas are often reported to coexist or 'collide' with other pancreatic neoplasms[142–148] and with congenital pathologic conditions.[149,150]

*Oligocystic (macrocystic) variant of serous cystadenoma*

Although the vast majority of serous cystadenomas exhibit a microcystic growth pattern, rare examples are oligocystic (megacystic, macrocystic), that is, composed of fewer but larger loculi.[133–135,137,151] The epithelial lining of these cysts may become denuded, and it may be difficult to distinguish oligocystic serous cystadenomas from mucinous neoplasms or pseudocysts.[152] unless the lesion is extensively sampled and examined carefully to identify the characteristic glycogen-rich clear cells.

### VHL-Associated Pancreatic Cysts

The cysts seen in the pancreas of the patients with von Hippel-Lindau disease are virtually indistinguishable from those of serous cystadenomas, but instead are distributed more irregularly (hamartomatously), rather than forming a distinct lesion. VHL gene alterations are present in these lesions.

### Serous Cystadenocarcinomas

Most serous cystic neoplasms of the pancreas are benign serous cystadenomas. A handful of malignant serous cystic neoplasms, serous cystadenocarcinomas, have been reported.[129,153–161] Most of these were microscopically identical to serous cystadenomas, and no morphologic findings, other than behavior, have been found to distinguish these malignant variants from their benign counterparts. In fact, in some, the diagnosis of malignancy was established only after metastases to the liver were detected. The possibility of these liver lesions representing a metachronous neoplasm rather than a metastasis is difficult to exclude and renders 'serous cystadenocarcinoma' a dubious entity. On the other hand, in two other reported cases, an otherwise classical serous cystadenoma showed focal malignant appearing morphologic features;[155,159] however, in these cases, the clinical and biologic significance of these morphologic changes could not be determined due to the lack of follow-up information. For practical purposes, although the vast majority of serous cystic neoplasms are benign, there are very rare examples of metastasis developing from these neoplasms.[129,154] We have seen examples of metastatic ovarian clear-cell adenocarcinoma and clear-cell renal cell carcinoma that were mistaken for serous cystadenocarcinomas.

## Squamous-lined cysts

### Lymphoepithelial Cysts

Lymphoepithelial cysts (LECs) are benign cystic lesions seen predominantly in males, in the fifth to sixth decade of life.[162] They may be unilocular or multilocular. The cyst contents may vary from serous to cheesy/casseous-appearing (Figure 14) depending on the degree of keratin formation. The cyst wall and trabeculae are usually thin. Microscopically, the cysts are lined by well-differentiated stratified squamous epithelium, which may or may

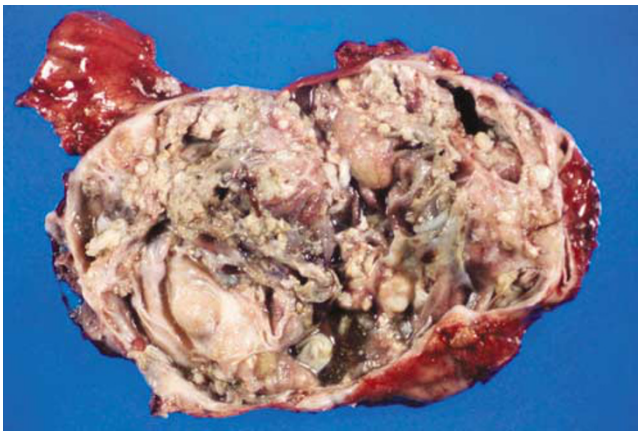

**Figure 14** LEC. Some cases have abundant keratinization that leads to granular debris in the lumen, as seen in this example, creating a picture reminiscent of 'sebaceous cyst,' although some have serosangineous contents.

not have prominent keratinization. In some areas, the lining may appear more transitional, and in others, flat, cuboidal, and focally denuded. Cases with denuded epithelium may cause diagnostic problems. Sebaceous elements and mucinous cells are uncommon. The squamous epithelium is surrounded by a band of dense lymphoid tissue composed of mature T-lymphocytes with intervening germinal centers formed by B cells, which may be abundant in some cases. In many cases, the lymphoid tissue is immediately adjacent to the epithelium, while in others, there is a band of fibrous tissue separating them. In some examples, the lymphoid tissue has a thin capsule and a subcapsular sinus, suggesting that the process may have arisen in a peripancreatic lymph node. Solid lymphoepithelial islands (microscopic clusters of epithelial cells admixed with lymphocytes, akin to the so-called 'epimyoepithelial islands' in the salivary gland LECs) may also be present. Some of these epithelial nests form microcysts. It is uncommon for LECs to become infected or acutely inflamed; however, the adjacent pancreas may contain granulomas, collections of foamy histiocytes and fat necrosis, thereby mimicking acute pancreatitis. LECs of the pancreas do not appear to be associated with any autoimmune conditions, human immunodeficiency virus infection, lymphoma, or carcinoma, all of which have been documented to occur in their salivary gland counterparts.

### Epidermoid Cysts within Intrapancreatic Accessory Spleen

These are rare. They occur almost exclusively in the tail of the pancreas[163–165] where accessory spleens are not too uncommon. They are seen in younger patients (2nd–3rd decades). The cysts are lined by

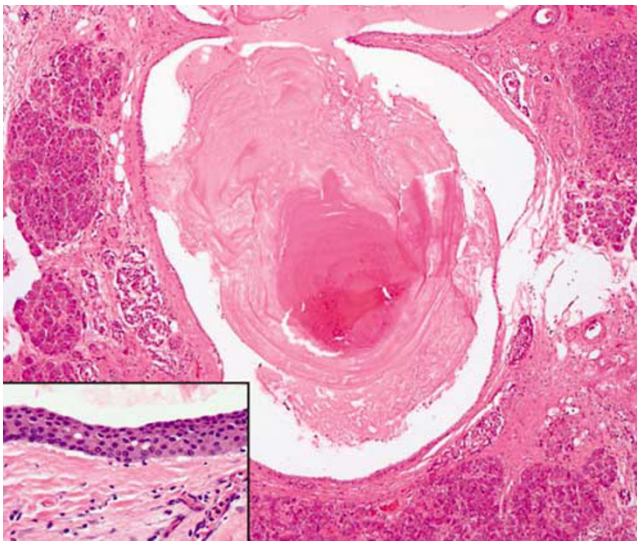

**Figure 15** Squamoid cyst of pancreatic ducts. These usually have a thin wall lined by transitional/squamous cells without keratinization or granular layer (see inset). The cysts are more commonly unilocular and typically contain concentric enzymatic concretions as seen in this example, which indicates their communication with the acinar system.

attenuated squamous cells, usually nonstratified, surrounded by normal-appearing splenic tissue.

### Dermoid Cysts

Dermoid cysts are also exceedingly rare tumors in the pancreas region.[163] They are reported in younger patients (2nd–3rd decades) and are morphologically similar to the teratomas seen in other sites, although some examples are composed predominantly of epidermal elements, such that they are difficult to distinguish from LECs. The presence of sebaceous glands or hair follicles is more typical for dermoid cysts.

### Squamoid Cyst of Pancreatic Ducts

This is a recently recognized type of cystic lesion in the pancreas,[166] in which cystically dilated ducts are lined by a squamous/transitional epithelium (Figure 15) without keratinization. The larger and clinically manifested examples reported were unilocular. The cells in the basal/parabasal region express p63 (transitional/squamous cell marker, not detected in any normal pancreas or nonsquamous neoplasia). The superficial cells are positive for MUC1 and MUC6 (markers present in intercalated duct cells), and negative for GLUT-1 (consistent marker of serous adenomas, another tumor of presumed centroacinar cell origin). These cystic lesions are believed to be the larger versions of a relatively common incidental change in the acinar lobules. These microscopic lesions have abortive septae, irregular contours, are found lying within compact

acinar tissue, and appear to be transforming from intercalated ducts, often showing adjacent tightly packed clusters of ducts with similar morphology. The cysts typically contain distinctive acidophilic acinar secretions that form concretions (Figure 15), more evident in medium-sized examples, confirming their communication with the acinar system, and suggesting a localized obstruction in their pathogenesis.

## Cysts lined by acinar cells

### Acinar Cell Cystadenocarcinomas

A cystic form of acinar cell carcinoma is well documented but is extremely uncommon; only a handful of cases have been documented in the literature.[167–170] It should be kept in mind, however, that the term 'cystic acinar cell carcinoma'[171–173] had also been erroneously applied during the 1980s to the neoplasm currently known as 'solid-pseudopapillary neoplasm,' at which time *solid-pseudopapillary tumors* (SPTs) were mistaken to be of acinar origin. True acinar cell cystadenocarcinomas[167–170,174] are composed of neoplastic cells that form acini with prominent lumen formation (Figure 16) (in contrast to ordinary acinar cell carcinomas which have a more solid growth pattern[175]). Some show significant cystic dilatation that may measure up to several centimeters. In fact, some ACCs show prominent intraductal growth and/or papillary/papillocystic patterns that fall into the differential diagnosis of intraductal neoplasia.[176] The cysts in these neoplasia are true cysts with an epithelial lining composed of cells with acinar differentiation rather than a degenerative phenomenon. The cells often contain abundant apical, acidophilic (zymogenic) granules, and immunolabeling will reveal the expression of pancreatic exocrine enzymes. In the examples we have seen, the cysts contained enzymatic concretions (Figure 16) admixed with crystalline material, presumably composed of enzymatic secretions. Acinar cell cystadenocarcinomas are often large. Their biology seems not to be significantly different from their solid counterparts, with liver metastases developing early in the course of the disease, although some with intraductal growth had protracted clinical courses.[176]

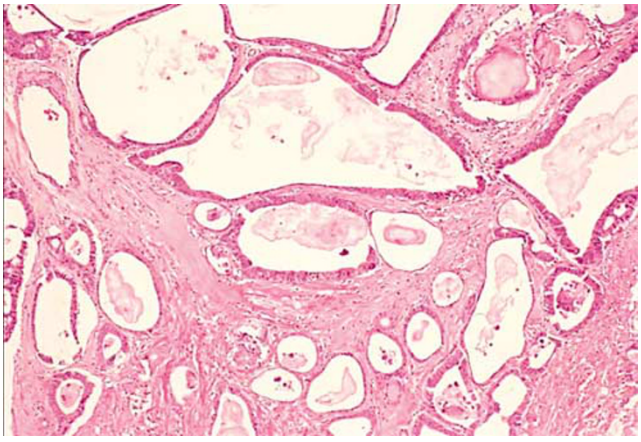

**Figure 16** Acinar cell cystadenocarcinoma. The cysts contain precipitated secretory material composed of pale acidophilic mucoproteinaceous substance with concentric laminations, which is characteristic of enzymatic secretions of acinar cells.

### Acinar Cell Cystadenomas

Until recently, the conventional thought was that all acinar neoplasms in the pancreas are malignant, albeit solid or cystic. In 2000, however, an entity referred to as acinar cell cystadenoma (also called cystic acinar transformation) was described.[5,177] This phenomenon is uncommon, often incidental, but may on occasion produce a clinically detectable cystic mass (measuring up to several centimeters), in which the cysts are lined by cytologically bland acinar cells.[177–180] Immunohistochemical labeling for markers of acinar differentiation (trypsin and others) are positive. Interestingly, they are also cytokeratin 7 positive while normal acinar cells are negative for this marker. Acinar cell cystadenoma is seen in young adults and children, and the consensus is that it is a benign process.

## Endothelial-lined cysts

### Lymphangiomas

Lymphangiomas may also present as pancreatic and peripancreatic cystic masses,[181,182] and may closely mimic LECs (especially those with denuded epithelium) because they also contain prominent lymphoid tissue. Lymphangiomas are lined by endothelial cells as demonstrated by immunohistochemical labeling for endothelial markers (CD31, CD34 or D2–40) and lack staining for epithelial markers (cytokeratins). Lymphangiomas may become very large, measuring up to 25 cm.[183] They are benign.

## Degenerative or necrotic changes in solid tumors

Degenerative necrotic changes with cavity formation have been described virtually in all otherwise typically solid pancreatic tumors.[184] Altogether, this group constitutes an estimated 10% of the pancreatic cysts (Table 1). It is important to recognize this group, because unlike the tumors in the other categories discussed, these are often either low-grade malignancies as in the case of SPT, or even true carcinomas as in the case of *cystic change in ductal adenocarcinoma*.

## Solid-Pseudopapillary Tumor (SPT)

SPT is the most recent name advocated by the WHO[83,84] for a distinctive tumor type in the pancreas that often presents as a cystic mass, and for this reason was previously (and is sometimes still) referred to as 'solid and cystic',[185,186] 'solid and papillary'[187] 'cystic and papillary' and 'papillary-cystic'.[188,189] The plethora of names used previously for SPT reflects the enigmatic nature of this neoplasm. It is now known that the cavities that form in SPTs are not 'true' cysts (there is no epithelial lining) but rather represent a necrotic/degenerative process[59,190] (Figure 17). The cystic areas often contain blood, necrotic debris, and clusters of foamy macrophages. In the cavity wall, characteristic morphologic features of these neoplasms include pseudopapillary architecture (that creates an ependymoma-like appearance), hyaline globules, clusters of uniform cells mimicking neuroendocrine neoplasia (but lacking neuroendocrine chromatin), and grooved nuclei (Figure 18).

SPT remains somewhat of an enigma although its clinical and pathologic features are well characterized and the tumors show remarkable fidelity from one case to another. However, it is one of very few neoplasms in which the direction of differentiation of the neoplastic cells has yet to be established. SPT is practically unique to the pancreas, with no close kindred in any other organ. Meanwhile, it does not show clear-cut pathogenetic relationship to any of the cells normally found in the pancreas; there is no evidence for ductal, acinar, or frank endocrine differentiation.[59,190] Even the epithelial differentiation of this tumor type is incomplete and dubious. Immunohistochemically, the neoplastic cells express nonspecific markers such as vimentin, CD56, alpha-1-antitrypsin and neuron-specific ('non-specific') enolase; meanwhile, epithelial markers (keratins) can be focal or weak. Synaptophysin and NSE are commonly positive in SPTs; however, chromogranin, the most specific endocrine marker, is typically negative. SPTs reported to be diffusely/strongly chromogranin-positive in the literature most likely represent pancreatic endocrine neoplasms with cystic degeneration. Similarly, the reports on high-grade pancreatic tumors that expressed CD99 (Ewing's marker) and t(11:22) translocation, in our opinion, may represent primitive neuroectodermal tumor of this organ.[191] Recently, CD10 expression and APC/$\beta$-catenin pathway and cyclin-D1 alterations were found to be almost uniformly present (>90%) in SPTs. This interesting finding is very helpful diagnostically, and may prove to be important in unraveling the pathogenesis of this peculiar tumor. Recently, c-kit (CD117) expression was detected in a substantial portion of SPTs.[192]

Another puzzling aspect of SPTs is that they almost exclusively occur in young female subjects[186,190] (mean age, 25 years, M/F<1/20). Moreover, the neoplastic cells consistently express progesterone receptors[10] and also the beta form of estrogen receptors,[193] suggesting a role for hormones in the evolution of these neoplasms.

Yet another peculiar aspect of the SPT is its clinical behavior.[190] More than 80% of SPTs are cured by surgical resection. Metastases (either to liver or peritoneum, but only seldom to lymph nodes) may be seen in a small percentage of patients, but even some patients with metastases are cured. Seldom has any death been attributed to solid-pseudopapillary neoplasm. There do not appear to be any reliable histopathologic criteria to distinguish SPTs that can metastasize from those that do not.[194] Perineural invasion and infiltration to the

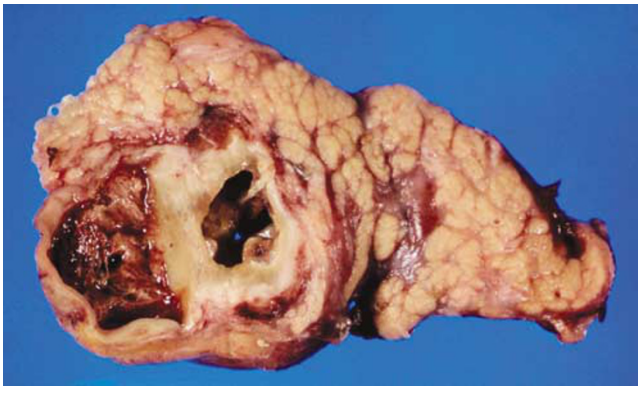

**Figure 17** SPT. Typical macroscopic appearance of this tumor type with solid areas showing hemorrhagic material, patchy fleshy areas, and a cystic component. The tumor appears deceptively well-demarcated, but often proves to have streaks of neoplastic cells projecting beyond the gross boundaries of the lesion.

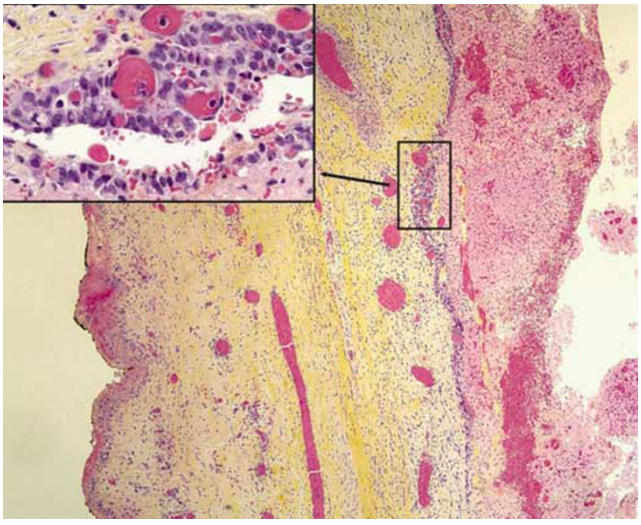

**Figure 18** SPT. These lesions often present clinically like a 'pseudocyst,' and the reasons for this may also be reflected at the microscopic level as seen in this example. The cyst wall is inflamed and congested, and there are fibrinous changes on the external surfaces (lower left). The cyst contents are granular and hemorrhagic. There is only a thin rim of neoplastic tissue clinging to the cyst wall (box and inset).

adjacent pancreas are common findings even in non-metastastasizing examples. Recently, cases with anaplastic transformation and aggressive clinical course were reported.[195]

### Cystic Change in Ordinary Ductal Adenocarcinoma

Rarely, conventional infiltrating ductal adenocarcinoma of the pancreas may undergo cystic change.[2,16–19] In our experience, this occurs in less than 1% of the cases.[16] In some pancreatic cancers, a large, radiologically detectable cyst may form because of central necrosis. In these cases, what appears radiologically to be a cyst (a macrocyst), however, often proves microscopically to be solid, nonviable tissue surrounded by a cuff of viable carcinoma. Such cases can be misdiagnosed preoperatively as 'pseudocysts'.[18] In other cases, infiltrating ductal adenocarcinoma can obstruct the pancreatic duct and lead to cystic dilatation of the upstream duct. The dilated upstream duct can show reactive epithelial changes, which may be indistinguishable from IPMNs or mucinous cystic neoplasms. There is also a large-duct (microcystic) variant of ductal adenocarcinoma[196] in which the infiltrating tubular units are larger than those of ordinary ductal adenocarcinoma. This variant mimics IPMNs or mucinous cystic neoplasms at the microscopic level, but not at the clinical or macroscopic levels,[197] because the dilatation in the infiltrating tubules is of a minimal degree, and creates a microcystic pattern at most.

### Cystic Pancreatic Endocrine Neoplasia (Islet Cell Tumors)

Cystic pancreatic endocrine neoplasms are rare.[184,198–208] They constitute 5–10 % of pancreatic endocrine neoplasms.[184,209] In contrast to the cystic change in other solid tumors (especially those in ductal adenocarcinomas), the cyst formation in pancreatic endocrine neoplasms does not appear to be due to necrosis. Rather, the cysts are lined by a ragged cuff of well-preserved neoplastic endocrine cells, (Figure 19) and filled with a clear serosanguineous fluid instead of necrotic debris. The cyst formation is usually unilocular and at the center of the tumor. In some cases, however, the process is more microcystic with multiple small cysts.[210] Some cystic pancreatic endocrine neoplasms achieve significant sizes, up to 25 cm.[211] Cystic pancreatic endocrine neoplasms are predominantly clinically nonfunctioning. The pathologic diagnosis of these cystic pancreatic endocrine neoplasms is relatively simple if attention is paid to the cytologic features of the lesion. Microscopic examination of the solid areas of the tumors reveal characteristic cytomorphologic features of a well-differentiated pancreatic endocrine neoplasm, including round, monotonous cells with a moderate amount of cytoplasm and distinctive nuclear chromatin pattern. Often the neoplastic cells have a trabecular pattern of growth (Figure 19).

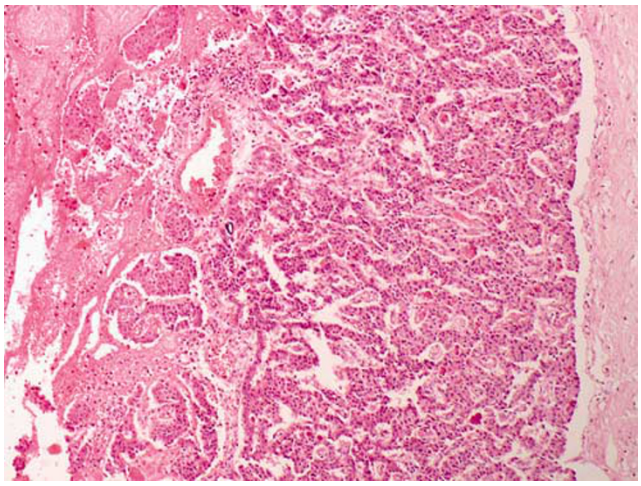

**Figure 19** Pancreatic endocrine neoplasm. Approximately 5% of pancreatic endocrine neoplasms (islet cell tumor) present as a cyst containing degenerative serosangineous fluid which is reflected as granular material on the left in this picture. The cuff of tumor shows the characteristic trabecular pattern and monotonous cells of endocrine neoplasia.

### Cystic Change in other Invasive Carcinomas

Other invasive malignant neoplasms of the pancreas such as undifferentiated carcinoma with osteoclast-like giant cells[12] or squamous cell carcinomas.[212] have also been occasionally reported to present as cystic masses.

### Cystic Mesenchymal Neoplasms

Some mesenchymal neoplams that occur in the pancreatic region may present as cystic lesions. Schwannomas in the pancreas especially tend to be cystic.[213–215] We have seen an example in which the spindle cells surrounding the cysts mimicked the ovarian-like stroma of the mucinous cystic neoplasms. Some sarcomas,[216] especially GISTs, may also be cystic. Other nonepithelial tumors of this region such as paragangliomas have also been reported to present as a cyst.[2,217]

## Other rare cystic lesions

### Cystic Hamartomas

Most cases reported in the literature as hamartomas appear to be examples of chronic pancreatitis in which pancreatic elements are haphazardly distributed (in a hamartomatous fashion). Recently, true hamartomas of this organ have been characterized, and some are cystic.[218,219] These 'solid and cystic

hamartomas' form a sharply delimited lesion similar to the multicystic hamartomas of children, and is composed of haphazardly distributed cystic ductal elements lined by cuboidal to flattened epithelium, surrounded by well-differentiated acini embedded in fibro-inflammatory stroma. Scattered ill-formed clusters of endocrine cells composed predominantly of PP-cells type and unaccompanied by any insulin positive cells are also present and support the hamartomatous nature of the process.

### 'Enterogenous' (Congenital; Duplication) Cysts and Duodenal Diverticula

Congenital cysts of foregut derivation may also occur in the pancreas[220–222] although very rarely. Essentially, these are regarded as gastrointestinal (enteric) duplications,[223] and some appear to be true diverticula.[224] They may have respiratory (bronchogenic) or simple ciliated epithelium.[225–227] We have also seen two examples with ciliated epithelium. One of these contained inner and outer muscular coats typical of intestinal wall, and had an associated high-grade papillary adenocarcinoma with pancreatobiliary-type features. Although the carcinoma in this case appeared to be confined to the cyst wall, the patient developed widespread metastases.

### Endometriotic Cyst

Endometriotic cysts,[228] some with massive hemorrhage[229] may be seen in the pancreas.

### Secondary Tumors

Rarely, metastatic neoplasms (or neoplasms that secondarily involve the pancreas) can exhibit cystic change.[217,230] We have seen examples of metastatic ovarian and renal cell carcinoma in the pancreas that presented as cystic masses. Cystic lesions of the common bile duct (eg, choledochal cyst) and duodenum may also mimic pancreatic cysts.[14,224,231]

### Congenital or Developmental Cysts

A variety of congenital or developmental disorders may be associated with cyst formation in the pancreas, in addition to vHL-associated cystic changes discussed previously in the 'serous' lesions section. Some of the others are the following:

*Polycystic kidney disease and medullary cystic kidney*: Patients with polycystic kidney disease, both adult and infantile types, may have cystic lesions in the pancreas.[232] Rarely, patients with medullary cystic kidneys may also have pancreatic cysts.[233]

*Cystic fibrosis*: In patients with cystic fibrosis, the genetic defect in the cystic fibrosis transmembrane conductance regulator protein increases the viscosity of pancreatic secretions, which in turn leads to the cystic dilatation of the pancreatic ducts[121,234] by causing intraluminal impaction, in addition to lobular atrophy and parenchymal fibrosis. This dilatation in the ducts, however, is generally not clinically detectable.

*Other congenital syndromes*: Cystic transformation of the pancreas has been described in a variety of congenital syndromes[235] including Ivemark, trisomy 13 or 15, Meckel-Gruber, Elejalde, glutaric aciduria, chondrodyplasia, short rib polydactyly (Jeune's and Saldino-Noonan),[236] a newly described syndrome (Balci[237]) and others with no specific name.[238] A patient with choledochal cyst was also reported to have multiple pancreatic cysts.[239]

*Familial fibrocystic pancreatic atrophy*: This is an interesting phenomenon described in a pancreas cancer family from Seattle, Washington, USA, and is characterized by a lobulocentric pancreatic atrophy associated with fibrocystic (microcystic) changes and endocrine cell proliferation.[240] These do not appear to form clinically detectable cysts. In the background of this peculiar fibrocystic process, PanINs and a variety of invasive neoplasia including anaplastic carcinoma as well as small cell carcinoma have developed in some members of this family. Other pancreas cancer families may also show similar cystic changes.[241]

*Cysts associated with congenital infections*: Cytomegalovirus infection has also been implicated in cyst formation in the pancreas of newborns.

### Unclassified Cysts

Some cysts cannot be classified into one of the well-documented entities. An example is the case reported by HD Friedman as nonmucinous, glycogen-poor cystadenocarcinoma of the pancreas.[242] We have also seen cases that do not fit pathologically into any of the well-described categories. If such a case is encountered, an attempt ought to be made to determine the potential biologic nature of the lesion based on the degree of cellularity, atypia, and architectural complexity of the process. Needless to say that, such cases ought to be examined completely, and the possibility of an invasive neoplasm effectively ruled out.

## Conclusions

Cystic neoplasms of the pancreas are relatively rare but constitute an increasingly important category with a challenging differential diagnosis. In contrast with solid tumors of this organ, most of which are ductal adenocarcinomas with dismal outcomes, the vast majority of cystic neoplasia is either benign tumors or low-grade malignancies with indolent behavior. Serous and squamous cystic lesions of the pancreas are typically benign. Cysts with mucinous lining, however, carry the risk of

malignant transformation. Many are associated with invasive carcinoma, and therefore their thorough sampling and careful examination are of utmost importance.

Macroscopic examination plays a crucial role in the diagnosis of cystic neoplasia, especially those of the mucinous type. First of all, it is important to document the lesion is cystic or has a cystic component, which may not be as appreciable on the slides. Identifying and documenting the suspect foci (granular, irregular areas within or on the cyst wall) are essential to rule out papillary nodules or carcinomas. Also, subclassification of IPMNs into branch or main duct types relies heavily on macroscopic examination and guided sampling. Along the same lines, the lack of gross ductal communication, an important criterion for the diagnosis of MCNs, is also established by the macroscopic findings.

The importance of careful examination and thorough sampling in the evaluation of pancreatic cysts cannot be overemphasized. This is especially true for the mucinous lesions for which some authors even advocate total sampling. For serous tumors, on the other hand, the macroscopic features are so characteristic and the likelihood of unexpected findings in microscopic examination is so low that few random sections may be adequate.

It is also important to examine a cystic lesion thoroughly before it can be diagnosed as a 'pseudocyst'. SPTs commonly appear clinically (and grossly) like a pseudocyst, and even ordinary ductal adenocarcinomas or endocrine neoplasia may present as a pseudocyst.

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