Pancreatic cystic lesions (PCLs) comprise a broad spectrum of entities and can be categorized into neoplastic and nonneoplastic. They differ greatly in their clinical behavior and malignant potential. Neoplastic cystic lesions such as intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and solid pseudopapillary neoplasms (SPNs) can undergo malignant transformation, whereas cystic pancreatic neuroendocrine tumors (cNETs) already harbor metastatic potential. On the other hand, pseudocysts, lymphoepithelial cysts, and retention cysts behave indolently and almost never progress into malignancy. The frequency of detection of pancreatic cysts has varied widely in the literature, ranging from 0.7% to 36.7%.1–3 The current use of advanced imaging techniques with improved spatial resolution4,5 has led to increased incidence of unsuspected small PCLs. The prevalence of PCLs correlates with increasing age; however, there is no significant difference in prevalence of cysts with respect to sex.3,6 Early detection of the cysts has increased the dilemma of how to triage and manage these lesions. Multiple algorithms7 have been developed to guide the clinicians’ decision to which of the cysts should be ignored, which should be observed without intervention, or which require medical or surgical intervention. These algorithms would ideally incorporate a constellation of findings that uses the clinical history, radiologic studies, and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) cytology with cyst fluid analysis to best classify, diagnose, and manage the PCLs. This review will summarize currently available data regarding primary PCLs.

NONNEOPLASTIC CYSTS

Pseudocyst

Pseudocysts are the most common pancreatic nonneoplastic cystic lesions.8 Pseudocyst is defined as a collection of amylase-rich fluid that contains debris, blood, and inflammatory cells, and is surrounded by a fibrous wall with no epithelial lining. Pancreatic pseudocysts can exist within the pancreatic tissue or adjacent to the pancreas.8 They occur after episodes of acute pancreatitis, or superimposed on chronic pancreatitis due to alcoholic, biliary, or traumatic cause.9,10 The diagnosis of pseudocysts is based primarily on the patient’s history and imaging. On abdominal computed
tomography scan, a diagnosis of a pseudocyst is suggested if a thick-walled, rounded, fluid-filled mass adjacent to the pancreas is identified in a patient with history of acute or chronic pancreatitis. EUS-FNA and cyst fluid analysis can also aid in the differentiation between pseudocysts and mucinous neoplastic cysts. Most pseudocysts will have an elevated concentration of amylase, typically thousands of units per liter. On the other hand, an elevation of more than 200 ng/mL in cyst fluid carcinoembryonic antigen (CEA) level will favor a mucinous cystic lesion. Low amylase levels are also expected in serous cysts and cystic neuroendocrine tumors.

In addition to the abundant inflammatory cells and histiocytes, fine-needle aspirate of a pseudocyst may show yellow pigment (Figure 1, A) and crystals (Figure 1, B). While most pancreatic pseudocysts resolve spontaneously owing to lack of epithelial source of fluid, those greater than 4.0 cm may need drainage or surgical resection. Resection specimens display a debris-filled space surrounded by granulation tissue or a fibrous capsule. Neoplastic lesions with extensive cystic degeneration and superimposed infection can clinically and histologically mimic pseudocysts. Solid pseudopapillary neoplasm and MCN can show extensive cystic degeneration and commonly get infected. Adenocarcinoma may also undergo extensive necrosis and clinically mimic pseudocyst. It is crucial to recognize the true nature of the cyst to avoid incorrect diagnosis and improper management. Adequate sampling of the cyst and recognition of any epithelial element will entertain an alternative diagnosis to pseudocyst.

Retention Cyst

Retention cysts are associated with pancreatic duct obstruction or narrowing with upstream smooth dilation of the pancreatic duct. They are commonly associated with chronic pancreatitis, stones, mucus plug, or a neoplasm. They are small (0.5 cm–1.0 cm) cysts and most are found incidentally on imaging. Retention cysts are lined by nonciliated simple cuboidal or columnar epithelium, usually reflecting attenuation of the native duct lining, which may contain mucin; the characteristic communication of the cyst with the pancreatic duct has been emphasized in several studies. Mucin-containing retention cysts may raise the possibility of IPMN and caution should be taken in these instances. Retention cysts in contrast to IPMN should not have mural nodules or a solid component, and the latter often has downstream dilation of the pancreatic duct. Other neoplastic processes causing the obstruction and leading to the formation of a retention cyst should also be ruled out.

Lymphoepithelial Cyst

Pancreatic lymphoepithelial cysts (LECs) are benign cysts that constitute 0.5% of pancreatic cysts and occur predominantly in middle-aged men (male to female ratio: 4:1). On imaging, they are well circumscribed, sharply demarcated from the pancreas, can be multilocular or unilocular, and range in size from 1.2 cm to 17.0 cm. The viscosity of the cyst contents of LECs often depends on the amount of keratin debris content and ranges from thin serous to thick white and cheesy. Both CEA and CA19.9 can be elevated in LECs and caution should be taken to avoid potential confusion with mucinous neoplasms. Fine-needle aspirate typically shows mature squamous cells, anucleate squamous cells, keratin debris, lymphocytes, macrophages, and cholesterol crystals (Figure 2, A and B). On histologic examination, LECs are lined by stratified squamous epithelium surrounded by dense lymphoid tissue with lymphoid follicles (Figure 2, C). Mucous cells and sebaceous differentiation can rarely be seen in LECs (Figure 2, D, inset); however, a diagnosis of dermoid cyst should be entertained if the mucous cells and/or the sebaceous differentiation is prominent. A careful search for cartilage or hair follicles will confirm a diagnosis of dermoid cyst. The presence of a bandlike lymphoid tissue on the other hand will favor the diagnosis of lymphoepithelial cyst. Pseudocysts and lymphangiomatas will also enter the differential diagnosis. The former will not have the dense lymphoid tissue and usually have acute inflammatory cells, which are not present in LECs. The latter will be lined by a single cell layer of flat to cuboidal epithelium that can be highlighted by immunohistochemical stains for endothelial markers, such as CD31 and D2-40. Unlike their counterpart in the head and neck, pancreatic LECs do not appear to be associated with autoimmune disorders, HIV infection, or lymphoma.
Cystic Pancreatic Lymphangioma

Cystic lymphangiomas are congenital malformations of the lymphatic system with obstruction of the lymph flow and formation of multiloculated cystic lesions. Cystic pancreatic lymphangiomas are indolent, incidentally discovered, and tend to occur more commonly in women.33 The increased incidence in females may partially be attributed to oral contraceptive use, pregnancy, or other hormonal influences.34 They can reach a large size (average size: 12.7 cm)35,36 and cause a palpable mass and abdominal pain. On imaging, they appear as well circumscribed, often multilocular lesions with enhancing capsule and thin septa.37 The cyst fluid is usually serous, serosanguineous, or chylous. Fine-needle aspiration will show nonspecific features including scattered lymphocytes and histiocytes in a background of amorphous proteinaceous material (Figure 3, A). The latter should not be misinterpreted as mucin, leading to an erroneous diagnosis of mucinous cystic lesion. Mucicarmine special stain can be used in this circumstance. The differential diagnosis also includes dermoid cysts, pseudocysts, and serous cystic neoplasms (SCNs). High triglyceride content of the cyst fluid can confirm the diagnosis of lymphangioma; however, it is not always present. On histologic examination, the cysts are composed of enlarged lymphatic vessels lined by cuboidal epithelium that stains positively for the endothelial markers CD31, D2-40 (Figure 3, B), and occasionally CD34. The lining cells are typically negative for cytokeratin. The cyst wall frequently contains smooth muscle cells, lymphocytes, and foamy histiocytes. The prognosis of cystic pancreatic lymphangio-

Figure 2. Lymphoepithelial cyst. A, Aspirate smear with keratinous debris. B, Cyst contents that stain for mucicarmine can represent a diagnostic challenge. This can be misdiagnosed as mucinous cystic lesion. C, Resection of the same case demonstrating keratin debris within the cyst lumen. Cyst wall with lymphoid follicles and sebaceous glands. D, Keratinizing squamous epithelium is separated from the normal pancreas (lower right) by a band of lymphoid tissue. Note the mucin-containing cells (inset [arrows]) (Papanicolaou, original magnification ×200 [A]; mucicarmine special stain, original magnification ×200 [B]; hematoxylin-eosin, original magnifications ×40 [C], ×200 [D], and ×400 [D, inset]).
mas is excellent with complete resection; however, recurrence may occur in cases that are incompletely resected. 36,38

Dermoid/Epidermoid Cyst

Dermoid cysts are extremely rare in the pancreas, with fewer than 50 reported cases. 39 They are frequently located in the head/body of the pancreas. Most patients present with abdominal pain or a palpable mass. Imaging has limited utility in the diagnosis of dermoid pancreatic cysts. 40 The fine-needle aspirate will demonstrate both nucleated and anucleated benign squamous cells, inflammatory cells, and abundant keratin debris (Figure 4, A). Cholesterol crystals are not uncommon. These features can be seen in any squamous-lined cysts of the pancreas including LEC, dermoid cyst, and epidermoid cyst. 41 It would be difficult even for the experienced pathologist to distinguish between them. The most important task is to exclude a mucin-producing neoplasm. Mucicarmine stain, or other histochemical and immunohistochemical stains for intracellular mucin, should be used to rule out mucinous lesions, as a potentially misleading keratin debris can be mistaken for background mucin. On histologic examination, squamous-lined cysts can be separated on the basis of their cyst wall constituents. While LEC contains smooth muscle and lymphoid tissue with germinal centers, dermoid cyst demonstrates adnexal tissue within the cyst wall (Figure 4, B). Epidermoid cyst lacks the adnexal structures and is frequently accompanied by splenic tissue. 42,43

Duplication Cyst/Ciliated Foregut Cyst

Enteric duplication cysts are very rare congenital malformations of the foregut that are usually detected in children and have an overall predominance in females (2:1). Most duplication cysts are found in the head of the pancreas and can cause pancreatitis. 44 The aspirate smear is typically composed of a mix of mucinous material, histiocytes, and amorphous proteinaceous debris (Figure 5, A). 45-47 The epithelial lining varies between squamous, columnar,
gastric, or normal intestinal and is frequently ciliated (Figure 5, B). Duplication cyst can be distinguished from bronchogenic cyst by the presence of cartilage and respiratory glands within the latter. The absence of bronchogenic features—namely, respiratory glands and cartilage—and absence of muscle layers within the cyst wall, in an intra-abdominal cyst lined by ciliated columnar epithelium, should be designated as ciliated foregut cyst (CFC).48,49 The cyst fluid of CFC might contain elevated CEA and CA19.9 levels and the aspirate smear can have mucin. These features can lead to inappropriate interpretation and therefore CFCs are frequently misdiagnosed as pancreatic cystic mucinous lesions. EUS-FNA plays an important role to avoid this pitfall. The aspirate smear of CFC will demonstrate predominantly degenerated cells, amorphous debris, and may contain cohesive groups of pseudostratified ciliated columnar epithelium (Figure 5, C) with or without goblet cells.50 A characteristic feature of CFC is the presence of detached ciliary tufts, which represent ciliated, anucleated fragments of cytoplasm from the top of columnar epithelial cells.45,51 On histologic examination, the cyst wall characteristically contains layers of smooth muscle that may theoretically recapitulate those of normal gut (Figure 5, D).48,52,53 Surgical excision remains the mainstay of therapy for pancreatic duplication cysts; however, the biologic behavior of this entity and the propensity for malignant transformation are still relatively unknown.54

**NEOPLASTIC CYSTS (PANCREATIC CYSTIC NEOPLASMS)**

**Mucinous Cystic Lesions**

**Intraductal Papillary Mucinous Neoplasm.**—IPMNs are papillary proliferations within the pancreatic duct that lead to the dilatation of the pancreatic duct and the

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**Figure 5.** Ciliated foregut cyst/duplication cyst. A, Amorphous proteinaceous debris and scattered histiocytes. B and C, Cyst lining composed of ciliated squamous columnar epithelium. D, Cyst wall of duplication cyst will characteristically contain layers of smooth muscle that may theoretically recapitulate those of normal gut (Diff-Quik, original magnification ×200 [A]; Papanicolaou, original magnification ×400 [B and C]; hematoxylineosin, original magnification ×200 [D]).
formation of a detectable mass. IPMNs are commonly found in the head of the pancreas, characterized by the production of thick mucin and measure more than 1.0 cm according to the World Health Organization 2010 classification.\textsuperscript{55} During the performance of endoscopic ultrasonography, extrusion of mucin from the ampulla of Vater is almost always diagnostic of IPMN. Evaluation of cyst fluid CEA levels has high specificity for differentiating mucinous (CEA > 192 ng/mL) from nonmucinous PCLs. However, the cutoff of CEA level may differ among institutions and should be validated. IPMNs are divided into ‘‘main duct type,’’ which arise from the main pancreatic duct, and ‘‘branch duct type,’’ which arise in one of the branches of the main pancreatic duct and are considered the most common pancreatic cyst.\textsuperscript{7} The risk of malignancy transformation in main duct type and branch duct type IPMNs are approximately 38\% to 68\% and 22\%, respectively.\textsuperscript{56–58}

EUS-FNA is widely used to diagnose IPMNs. However, the cytologic features should be interpreted in the context of the clinical and radiologic findings. In the right clinical setting, the presence of abundant thick mucin solely (Figure 6, A through D) can suggest the diagnosis of IPMN. Contrarily, the presence of limited mucin and low-grade mucinous epithelium could be indistinguishable from that of normal gastric epithelium. It is crucial for the cytopathologist to distinguish between IPMN with low-grade dysplasia (Figure 7, A and B) and IPMN with high-grade dysplasia (Figure 8, A and B), as the latter is more likely to progress to invasive cancer if left untreated. Significant features that favor high-grade over low-grade IPMN include background necrosis, abnormal chromatin pattern (hypochromasia or hyperchromasia), marked nuclear irregularity, large vacuolated single cells, increased nuclear to cytoplasmic ratio, and cell size smaller than that of a 12-μm duodenal enterocyte.\textsuperscript{59} IPMNs with high-grade atypia are more likely to be large (>30 mm), have enhancing mural nodules (>5 mm)\textsuperscript{60} or have a solid component, with dilated main pancreatic duct (>5 mm).\textsuperscript{57} CA19.9 (>37 U/mL) is an independent predictor of malignancy in IPMN.\textsuperscript{61–63} Another challenging aspect to the cytopathologist is to distinguish IPMN from MCN. The latter is less likely to form papillary clusters and if present, they are not as tall, abundant, and striking as those in the former.\textsuperscript{64} Correlation with radiologic findings can significantly favor a diagnosis over the other, as communication with the pancreatic duct is seen with IPMN, but not with

**Figure 6.** Thick mucin. Fine-needle aspiration of pancreatic cysts with different morphology of thick mucin (A through D) that occasionally show distinctive patterns that can be described as ferning (B) and fanlike (D) (Diff-Quik, original magnifications ×100 [A and B] and ×400 [C]; hematoxylin-eosin cell block, original magnification ×400 [D]).
MCN. Mucinous cystic neoplasm is also seen almost exclusively in women and the presence of ovarian stroma is pathognomonic. Genetic analysis showing double mutation of \( \text{KRAS} \) and \( \text{GNAS} \) is very specific for IPMNs. In contrast to MCNs and SCNs, which lack the \( \text{GNAS} \) codon 201 mutation, several studies have shown that mutation in \( \text{GNAS} \) codon 201 is found in 41% to 66% of IPMNs and can reach 74% to 100% in the intestinal-type IPMN.65–67

On histologic examinations, IPMNs show variable morphologies including gastric, intestinal, pancreaticobiliary, and oncocytic.68 Gastric foveolar-type IPMN shows papillae lined by columnar cells with basally located nuclei and abundant apical mucin (Figure 7, B). Intestinal-type is morphologically similar to villous adenomas of the colon with their characteristic cigar-shaped nuclei and variable amount of apical mucin. When the papillae are more complex and the lining of the papillae is composed of cuboidal cells with round nuclei and occasional prominent nucleoli, IPMN is categorized as pancreaticobiliary-type. The oncocytic type of IPMN demonstrates a complex papillary architecture with papillae lined by round monotonous cells exhibiting abundant eosinophilic granular cytoplasm and prominent central nucleoli.68,69 The latter is frequently misinterpreted in cytology specimens as pancreatic ductal adenocarcinoma.70

**Mucinous Cystic Neoplasm.**—Mucinous cystic neoplasms are distinctive entities of the pancreatic cysts with unique characteristics. Mucinous cystic neoplasms occur almost exclusively in middle-aged females with a mean age of 48 years and are located in the tail and body of the pancreas (90%–95%). They are multilocular with variable septations that vary in thickness and show peripheral calcifications on imaging in contrast to serous cystic neoplasms, which contain central, stellate calcifications.15 Mucinous cystic neoplasms do not communicate with the pancreatic ductal system, which can be used as a differentiating point from IPMN. Similar to IPMN, increased cystic

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**Figure 7.** Intraductal papillary mucinous neoplasm with low-grade dysplasia. A, Benign-appearing mucinous epithelium with honeycomb morphology consistent with a mucinous cyst low-grade dysplasia. B, Abundant columnar mucin and basally located nuclei (Papanicolaou, original magnification ×100 [A]; hematoxylin-eosin, original magnification ×100 [B]).

**Figure 8.** Intraductal papillary mucinous neoplasm with high-grade dysplasia. A, Large vacuolated single cells with hyperchromasia and increased nuclear to cytoplasmic ratio. B, Marked nuclear atypia and complex architecture with an unorganized cellular arrangement and acinar formation; background necrosis is present (Diff-Quik, original magnification ×600 [A]; hematoxylin-eosin, original magnification ×600 [B]).

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Pancreatic Cystic Lesions—Abdelkader et al 53
fluid CEA level can be helpful in discerning MCN from other nonmucinous cystic lesions. However, a low CEA level does not exclude a mucinous cystic lesion. Aspirates of low-grade MCN (mucinous cystadenoma), which comprise more than 75% of MCNs, will demonstrate honeycomb sheets of bland mucin-containing epithelium (Figure 9, A), usually lacking the complex papillary architecture that can be seen in high-grade MCN. The mucin-containing cells have smooth nuclear contour, fine chromatin, and inconspicuous nucleoli. The risk of harboring invasive carcinoma is low in MCNs and is estimated to be approximately 7% to 12%. Cysts that are larger than 4 cm and those containing mural nodules that can be seen on radiologic imaging are more likely to be associated with malignancy.

On histologic examination, the cysts are composed of mucin-containing tall columnar epithelium and the lining can be focally flat or cuboidal. The cyst wall characteristically contains densely cellular ovarian-type stroma (Figure 9, B and C), which is a requirement for the diagnosis of MCN. The ovarian stroma stains positively for progesterone receptor (Figure 9, C, inset), estrogen receptor, inhibin, and calretinin immunostains. To distinguish MCNs from other cystic neoplasms such as IPMN and SPN, multiple studies have shown that MCNs do not have GNAS mutations and typically do not have CTNNB1 mutations. KRAS mutation has been reported in MCNs (50%–75%).

Surgical resection for all surgically fit candidates with MCN is recommended by the international consensus guidelines. For MCNs smaller than 4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

**Nonmucinous Cystic Neoplastic Lesions**

**Serous Cystic Neoplasm.**—Serous cystic neoplasms represent less than 1% of all primary pancreatic lesions and about 30% of all cystic neoplasms of the pancreas. They tend to occur in the fifth to seventh decade of life with female predilection. Given the indolent biologic behavior of SCNs, most of these tumors present as incidental radiographic findings in asymptomatic patients, usually in the body-tail region of the pancreas. They are divided into benign serous cystadenoma (SCA) with no metastatic potential, and malignant serous cystadenocarcinoma, which is extremely rare. The latter can only be diagnosed in the presence of metastases. The EUS-FNA of SCNs has low sensitivity and specificity, and tends to be paucicellular with clear or hemorrhagic background and hemosiderin-laden macrophages (Figure 10, A). The hemorrhagic nature of the specimen is due to the highly vascularized fibrous septa of SCNs. The cysts are usually filled with clear-yellow serous fluid with low viscosity; and in contrast to IPMNs, SCNs do not communicate with the pancreatic duct and have low CEA levels. The cells of SCNs are bland with round nuclei, smooth contours, evenly distributed chromatin, and inconspicuous nucleoli. When mucin is present in the background, correlation with CEA levels and radiologic imaging would be prudent to exclude MCNs. Gastrointestinal contaminants can be also challenging to distinguish from SCNs, particularly with transgastric approach. Owing to denudation of cyst wall epithelium and the presence of cystic degenerated material, SCN can be misdiagnosed as a pseudocyst. The latter will have a high level of cyst fluid.

**Figure 9.** Mucinous cystic neoplasm with low-grade atypia. A, Benign-appearing mucinous epithelium in cohesive groups, often indistinguishable from gastric epithelium contaminant. B and C, The lining epithelium is composed of a single layer of mucin-producing columnar cells with basally oriented nuclei. The cyst wall contains the characteristic densely cellular “ovarian-like” stromal layer highlighted by the positivity of immunohistochemical stain progesterone receptor (C, inset) (Papanicolaou, original magnification ×400 [A]; hematoxylin-eosin, original magnifications ×200 [B] and ×400 [C]; original magnification ×200 [C, inset]).
amylase. Macroscopically, SCN shows cysts with distinctive spongy or honeycomb appearance, often arranged around a stellate scar. On histologic examination, the serous cystadenomas are composed of microcysts lined by a single layer of cuboidal epithelium (Figure 10, C). Epithelial tufting or focal papillary architecture can be seen (Figure 10, B) and does not indicate worse prognosis. The epithelial cells are glycogen rich with clear cytoplasm, which can be highlighted by periodic acid–Schiff stain. Serous cystadenomas are thought to arise from centroacinar cell and stain positively for cytokeratins and calretinin, and stain negatively for CEA, mucin, estrogen receptor, and progesterone receptor immunostains. Recently, inhibin and calponin have been shown as helpful immunostain markers to distinguish SCN from ductal adenocarcinoma and neuroendocrine tumors.77–79 The absence of CTNNB1 mutation in serous cystadenomas can separate them from SPNs. KRAS and GNAS mutations are rarely detected in SCNs, which are often expressed in IPMNs and MCNs. Serous cystadenomas, on the other hand, are associated with von Hippel–Lindau (VHL) syndrome, and all SCAs in patients with VHL syndrome harbor mutation in the VHL gene. VHL loss-of-function mutations may also play a role in the development of sporadic SCAs.80 The diffuse involvement of the pancreas or the presence of multiple foci of SCAs should raise the possibility of associated VHL disease. Other rare types of SCNs are the macrocystic (oligocystic) variant with fewer but larger number of cysts and without the central stellate scar; solid variant, which is devoid of cysts; and mixed serous-neuroendocrine variant.79

The prognosis of SCNs is excellent and resection of these indolent tumors is recommended only in symptomatic patients or patients with neoplasms larger than 4.0 cm, and if there is uncertainty about the true nature of the cystic neoplasm.75

**Solid Pseudopapillary Neoplasm.**—Solid pseudopapillary neoplasms are indolent solitary tumors with low malignant potential. They represent less than 3% of all primary pancreatic neoplasms.81 They tend to occur in women in their second and third decade of life.82 A line of differentiation of SPNs has not been defined. Some authors suggest that SPNs arise from pluripotent stem cells of the pancreas, while others hypothesize that SPNs originate from primitive ovarian tissue that is incorporated into the pancreatic parenchyma during embryogenesis.82–84 Solid pseudopapillary neoplasm appears on computed tomography scan as a poorly enhancing, encapsulated, well-circumscribed, and heterogeneous mass with central necrosis.85,86 EUS-guided FNA can aid in the diagnosis of SPNs and can differentiate SPNs from other radiologically similar neoplasms such as pancreatic neuroendocrine tumors (PanNETs) and acinar cell carcinoma (ACC). EUS-guided FNA of SPNs demonstrates a hypercellular smear consisting of delicate papillary fragments with fibrovascular stalks and perivascular myxoid matrix, lined by monomorphic cuboidal cells and arranged in cohesive groups and isolated cells (Figure 11, A and B). The neoplastic cells are round to oval and have ill-defined cytoplasmic borders. The nuclei are occasionally grooved or bean shaped with finely granular chromatin and inconspicuous or small nucleoli (Figure 11, C). This is in contrast to the salt and paper chromatin and the prominent nucleoli that are seen in PanNET and ACC, respectively. PanNET and ACC are less likely to show papillary architecture with perivascular myxoid substance.87–89 Macroscopically, SPNs are large, round to oval, well-demarcated masses, with fibrous pseudocapsule. Solid pseudopapillary neoplasms are complex neoplasms with solid, cystic, hemorrhagic, and necrotic

**Figure 10.** Serous cystic neoplasm. A, Paucicellular specimen consists of bland and nonmucinous tumor cells with hemorrhagic background. B, Focal papillary architecture can be seen and does not indicate worse prognosis. C, Microcysts lined by a single layer of cuboidal epithelium (Papanicolaou, original magnification ×400 [A]; hematoxylin-eosin, original magnifications ×100 [C] and ×200 [B]).
components. They frequently undergo cystic degeneration and the larger the tumor the more prominent is the cystic component. On histologic examination, SPNs also appear as encapsulated tumors with cystic and solid components. The solid component shows a delicate microvasculature. The pseudopapillary pattern is attributed to the swelling and degenerative changes that affect the cells farthest from the tumor blood vessels, and possibly the alteration of the cell adhesion molecules causing cell dyshesion away from the vessels. This pattern can resemble pseudorosettes (Figure 11, D) that mimic ependymoma or PanNETs. Cholesterol crystals and calcifications/ossification are occasionally seen. Immunohistochemically, SPNs strongly and diffusely express vimentin, α-1 antitrypsin, CD56, and neuron-specific enolase. Solid pseudopapillary neoplasms can show expression of estrogen receptor, progesterone receptor, and CD10. Synaptophysin can be focally positive in SPNs, a pitfall that can lead to misdiagnosis as a PanNET; however, PanNETs will stain positively for chromogranin, while SPNs will not. Activating mutation in exon 3 of the β-catenin gene is a consistent genetic alteration that is seen in SPNs, resulting in nuclear β-catenin staining (Figure 11, D, inset). Absence of KRAS, GNAS, or RNF43 can discern SPNs from other PCLs. The prognosis of SPNs is excellent and complete resection of these indolent tumors is curative. Although 10% to 15% of SPNs are malignant (defined by angioinvasion, neural invasion, or pancreatic parenchymal invasion), they have excellent prognosis after complete resection.

**Cystic Pancreatic Neuroendocrine Tumor.**—Cystic neuroendocrine tumors represent approximately 8% of all primary pancreatic cystic neoplasms and about 10% to 17% of all PanNETs. EUS-guided FNA is considered the most accurate method to diagnose cNETs as compared to imaging and cyst fluid analysis. On computed tomography scan, cNETs appear as a cystic lesion with peripheral enhancing rim because of their rich blood supply. The
Cyst fluid is thin and clear with low CEA and amylase levels; however, an increase in CEA and amylase levels does not exclude NETs. The aspirate smear will display the classic endocrine morphology including predominantly isolated cells, loosely cohesive groups, and occasionally pseudorosettes. The cells are uniformly round or polygonal, often with plasmacytoid morphology, and the nucleus is round with finely stippled (salt and paper) chromatin (Figure 12, A and B). Imaging cannot reliably distinguish between cNET and other pancreatic cysts such as SPNs. The distinction between NET and SPN can also be challenging on FNAs. Fine-needle aspiration cytology showing the classic endocrine morphology in conjunction with immunostains can provide a definitive confirmation. NETs express chromogranin and will show only cytoplasmic expression of β-catenin, in contrast to SPNs, which express nuclear staining of β-catenin, show reactivity to CD10 and vimentin, and are negative for chromogranin. Approximately 25% of cNETs are associated with multiple endocrine neoplasm syndrome. The biologic behavior of cNETs is somewhat less aggressive than that of their counterpart solid pancreatic NETs when applying the same criteria of grading and staging. Therefore, observation only is suggested for those cNET tumors that are smaller than 2.0 cm in asymptomatic patients.

Cystic Acinar Cell Neoplasm.—The pancreatic parenchyma is composed predominantly of acinar cells; however, acinar cell neoplasms are rare. Acinar cell cystadenomas are indolent tumors that are discovered incidentally at a mean age of 49 years with female predilection. Imaging generally demonstrates a unilocular or multicystic cystic lesion ranging in size from 1.5 to 10 cm. The lesion can diffusely involve the pancreatic parenchyma and is frequently multicentric. These neoplasms are not connected to the pancreatic main or branch duct. The cyst fluid typically contains a CEA level with a mean of 248.6 ng/mL. As expected from the acinar differentiation of these neoplasms, amylase level can be very high with a mean level of 86,139 U/L. EUS-FNA of acinar cystadenoma is characterized by single cells and clusters of cells with high nuclear to cytoplasmic ratio (Figure 13, A), occasional prominent nucleoli, and slightly coarse chromatin (Figure 13, B). Amorphous debris (Figure 13, C) resembling mucin can be seen and should not be interpreted as mucinous neoplasm.

On histologic examination, acinar cystadenoma is composed of a cystic lesion with single or multiple cell layers. The cell lining consists of bland, low cuboidal to columnar cells (Figure 13, D), with apical eosinophilic zymogen granules that can be highlighted with periodic acid–Schiff stain with diastase pretreatment (Figure 13, D, inset). Cyst walls lack ovarian-type stroma and are hyalinized. Occasionally the lining of the cyst wall appears flat/cuboidal, resembling ductal cells without obvious morphologic features of acinar cells, which can lead to misinterpretation as unclassified pancreatic cyst, retention cyst, or unilocular SCA. Immunohistochemical stains can assist in confirming the acinar cell differentiation.

Acinar cell cystadenocarcinoma is an extremely uncommon entity with only a handful of cases described in the literature. The lesions are large and multicystic, with a mean size of more than 17 cm. On histologic examination, there is marked atypia, necrosis, easily identified mitotic figures, and single prominent nucleoli. Rarely, cystic ACCs can show prominent intraductal growth and should be distinguished from IPMN. Immunohistochemically they express trypsin, chymotrypsin, and lipase; they usually lack the expression of neuroendocrine markers such as synaptophysin and chromogranin, and Ki-67 proliferation index is typically low in acinar cell cystadenoma.

Cystic acinar neoplasms are generally treated with surgical resection. The prognosis of acinar cystadenoma appears to be good even when the lesion is not completely resected. On the other hand, the prognosis of acinar cell cystadenocarcinoma is generally poor, and patients commonly have metastasis at the time of diagnosis. Resection is the treatment of choice in surgically fit patients with localized tumors; however, the recurrence rate is similar high to that seen in the solid variant ACC (72%).
Pancreatic Ductal Adenocarcinoma With Cystic Degeneration

Ductal adenocarcinoma of the pancreas can rarely undergo cystic degeneration with central necrosis. These can appear as cystic lesions on imaging and can be misinterpreted preoperatively as pseudocysts. Ductal adenocarcinoma can also obstruct the pancreatic duct, causing upstream dilatation and reactive changes in the epithelial lining that can be misinterpreted as a mucinous cystic lesion. Another type of ductal carcinoma is the large duct variant. This variant can mislead the pathologist to a false diagnosis of IPMN. This misguidance can be avoided with a multidisciplinary approach to these lesions with incorporation of the clinical, radiologic, and pathologic features before reaching a definite diagnosis. Pancreatic ductal adenocarcinomas (PDACs) are more likely to harbor KRAS mutation than other cystic neoplasms and most PDACs lack the GNAS mutation. This is in contrast to IPMNs, which are more likely to harbor GNAS than KRAS and can show mutation in both KRAS and GNAS simultaneously.

Intraductal Tubulopapillary Neoplasm of the Pancreas

Intraductal tubulopapillary neoplasm (ITPN) is a rare intraductal neoplasm of the pancreas that causes dilatation of the pancreatic duct and represents 0.9% of exocrine pancreatic neoplasms and 3% of intraductal neoplasms. EUS-FNA typically shows branching papillae, tubules, and cribriform patterns. Neoplastic cells are uniform with paranuclear clearing and distinct nucleoli. Mucin is absent or scant in comparison to the abundant mucin seen in IPMN. On histologic examination, ITPN appears as an intraductal neoplasm with tubular, papillary, solid, and cribriform architecture. Neoplastic cells are cuboidal to columnar with eosinophilic cytoplasm, nuclear enlargement, and prominent nucleoli (Figure 14, A and B). They demonstrate high-grade dysplasia. Necrosis, which is rarely found in IPMN, is frequently seen in ITPN.
Intratubular variant of ACC can mimic ITPN and shows tubulopapillary growth pattern with similar cytomorphology. The former would express exocrine markers, including trypsin. ITPNs are unlikely to harbor KRAS and B-Raf mutations. Although there are limited data on the prognosis of ITPN, surgical resection is recommended in cases that show invasion or potential invasion. Ki-67 proliferative index can be used as an indicative of invasiveness of ITPN.

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