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Cytologic Assessment of Cystic/Intraductal Lesions of the Pancreatobiliary Tract

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• **Context.**—Because of new and improved imaging techniques, cystic/intraductal pancreatobiliary tract lesions are increasingly being discovered, and brushings or endoscopic ultrasound/computed tomography/magnetic resonance imaging–guided fine-needle aspiration biopsies from these lesions have become an integral part of pathologists’ daily practice. Because patient management has become increasingly conservative, accurate preoperative diagnosis is critical. Cytologic distinction of low-risk (psuedocysts, serous cystadenomas, lymphoepithelial cysts, and squamoid cysts of the pancreatic duct) from high-risk pancreatic cysts (intraductal papillary mucinous neoplasm and mucinous cystic neoplasm) requires incorporation of clinical, radiologic, and cytologic findings, in conjunction with chemical and molecular analysis of cyst fluid. Cytopathologists must ensure appropriate specimen triage, along with judiciously use and interpret ancillary studies, and ensure that cytopathologists appropriately triage specimens, judiciously use and interpret ancillary studies, and incorporate the studies into reporting.

Pancreatic cystic lesions are increasingly being identified as incidental findings during highly sensitive computed tomography and magnetic resonance imaging for unrelated etiology. Their detection rate reportedly ranges from 2.4% to 49.1%, depending on imaging modality and population.1–3 This has created a major management problem for clinicians and an urgent need for noninvasive diagnostic tests that can better stratify risk and tailor management.

Pancreatic cystic lesions comprise a broad spectrum of pathologic cyst types ranging from completely benign and innocuous to frankly malignant. The vast majority are evaluated by endoscopic ultrasound (EUS)–guided fine-needle aspiration (FNA). Newly designed EUS needles and needle tips have significantly improved the diagnostic yield of FNA.4,5 These needles’ back-facing bevels and larger cutting surfaces, along with new fanning, wet-suction, and slow-pull techniques, are just some of the recent changes that have enhanced procurement of larger tissue fragments and corelets.6–7 The EUS-guided through-the-needle forceps biopsy device (Moray Microforceps, US Endoscopy, Mentor, Ohio) was specifically introduced for the evaluation of pancreatic cysts.8 It can be advanced through the lumen of a 19-gauge EUS-FNA needle for actual tissue biopsy and is superior to FNA in diagnosing, classifying, and even grading some cysts.8,9

Endoscopic ultrasound-guided FNA is known to have variable sensitivity (60%–96%) and excellent specificity (nearing 100%) in diagnosing pancreatic lesions.10–12 However, its performance is significantly challenged in pancreatic cystic lesions. As a result, definitive diagnosis and triage of aspirated cystic lesions requires an integrated multidisciplinary approach that involves clinical evaluation, radiologic assessment, cyst fluid biochemistry, and molecular/genetic testing as well as cytologic evaluation, which must all be incorporated to best stratify patients for surveillance or surgical intervention.

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TYPES OF PANCREATIC CYSTIC LESIONS

Pancreatic cysts may be nonneoplastic or neoplastic. The most common nonneoplastic pancreatic cystic lesions represent the post inflammatory sequelae of acute and/or chronic pancreatitis and result in the formation of non-epithelial degenerative cysts (ie, pseudocysts), which account for 75% of all cystic pancreatic lesions. Other nonneoplastic cysts with true epithelial lining include squamous epithelium-lined lymphoepithelial cysts (LECs) and squamoid cysts of the pancreatic duct.

Neoplastic pancreatic cysts include serous cystadenomas (SCAs), mucinous cysts, cystic teratomas, solid-pseudopapillary neoplasms (SPNs), and cystically degenerated solid tumors. Mucinous cysts account for the vast majority of nonneoplastic pancreatic cystic lesions and include intraductal papillary mucinous neoplasm (IPMN), which arises from and connects with the pancreatic duct system, and mucinous cystic neoplasm (MCN), which does not. Non-mucinous intraductal neoplasms, such as intraductal oncocytic papillary neoplasm (IOPN) and intraductal tubulopapillary neoplasm (ITPN), are less frequently encountered and may or may not be associated with pancreatic duct dilatation and cyst formation. Serous cystadenoma and SPN are nonmucinous, nonductal cystic pancreatic neoplasms that spare the duct system. Cystically degenerated solid epithelial malignancies, such as ductal adenocarcinoma and neuroendocrine and acinar neoplasms, are even less frequently encountered but must be included in the differential. Table 1 summarizes the different types of cysts in the pancreas and/or biliary tract.

REPORTING TERMINOLOGY FOR PANCREATOBILIARY CYTOLoGY SPECIMENS

In the laboratory setting, the cytologic assessment of pancreaticobiliary tract samples begins with the standardized reporting system endorsed by the Papanicolaou Society of Cytopathology. There are 6 diagnostic categories: nondiagnostic, negative (for malignancy), atypical, neoplastic (benign or other), suspicious and positive. Most pancreatic cysts fall within the negative and neoplastic categories (Table 2), and the latter are subdivided into (1) neoplastic: benign (which includes SCA and teratoma) and (2) neoplastic: other, where the bulk of the high-risk pancreatic cystic lesions fall, particularly neoplastic mucinous cysts (IPMN and MCN) and SPN. Intraductal oncocytic papillary neoplasm, which was originally classified as a subtype of IPMN but is now classified as a distinct entity (because of its distinctive molecular associations and biologic behavior), also belongs to the neoplastic: other category. Also included in this category are well-differentiated pancreatic neuroendocrine tumors (PanNETs), which may present as cystic lesions. The risk of malignancy increases with each Papanicolaou Society of Cytopathology category, and ranges from 7.7% for nondiagnostic to 1% for negative; 28% for atypical; 0% for neoplastic: benign; 30.3% for neoplastic: other; 90.0% for neoplastic: other with high-grade atypia; 100% for suspicious; and 100% for positive. Mucinous cysts with high-grade atypia (which are part of the neoplastic: other group), suspicious, and positive categories have high sensitivity, specificity, and positive and negative predictive values (92.2%, 98.8%, 98.3%, and 94.3%, respectively).

Table 1. Cystic and/or Intraductal Lesions of the Pancreas and Bile Duct

| Type of Lesion | Subtype |
|---------------|---------|
| Pancreas—intraductal | Mucinous: Intraductal papillary mucinous neoplasm (IPMN) |
| | Nonmucinous: Intraductal oncocytic papillary neoplasm (IOPN) |
| Bile duct—intraductal | Mucinous: Intraductal papillary neoplasm of bile duct (IPMN) |
| | Nonmucinous: Intraductal oncocytic papillary neoplasm (IOPN) |
| | Degenerative cyst |
| | Neoplastic: Solid tumor with cystic degeneration |
| | Acinar cell carcinoma |
| Pancreas—intraductal | Mucinous: Intraductal papillary mucinous neoplasm (IPMN) |
| | Degenerative cyst |
| | Neoplastic: Intraductal papillary mucinous neoplasm (IPMN) |
| | Solid tumor with cystic degeneration |
| | Acinar cell carcinoma |
| | Ductal adenocarcinoma |
| | Neuroendocrine neoplasm |
| | Nonneoplastic: Pseudocyst |
| | Paracortical cyst |
| | Intraductal oncocytic papillary neoplasm (IOPN) |
| | Intraductal tubulopapillary neoplasm (ITPN) |
| | Squamous cyst of pancreatic duct (SPN) |
| | Metastasis |

ASSESSMENT OF PANCREATIC CYSTIC LESIONS: A MULTIMODAL APPROACH

The goal of preoperative evaluation of pancreatic cysts is first to exclude malignancy, and then to distinguish low-risk from high-risk pancreatic cysts. In order to ensure accurate diagnosis and classification, one must use an integrated, multidisciplinary approach that incorporates clinical, radiologic, and cytologic findings with (chemical/molecular) cyst fluid analysis and ancillary stains (where applicable).

Radiologic/Clinical Assessment

The extent of radiologic assessment of pancreatic cysts is beyond the scope of this text however cytologic assessment actually begins with imaging. Certain radiologic findings should prompt consideration of particular differentials. A pancreatic cyst that involves the main and/or branch pancreatic ducts on imaging should raise concern for an IPMN. This is in contrast to MCN, SCA, and LEC, which do not typically involve the duct system. Additionally, in a perimenopausal woman with a cystic pancreatic tail mass and no obvious duct involvement, the differential diagnosis includes MCN and to a lesser extent SCA. In elderly women with circumscribed unicystic, oligocystic, or multicystic...
lesions, with a soap bubble appearance, central stellate scar (with or without calcification), and absence of duct involvement, the primary differential is a SCA. In young adults, particularly women, the presence of a cystic and solid pancreatic (body/tail) mass should raise the differential of SPN.

### Rapid On-Site Evaluation of Pancreatic Cysts

Cyst fluid analysis typically begins during rapid on-site evaluation where one can potentially assess fluid viscosity. Cyst fluid that is more viscous than serum has been shown to correlate with mucinous cysts. These often contain thick, mucoid material that is difficult to express from the needle, smears as gelatinous sticky material, and takes a longer time to dry on the slide. This information can be shared immediately with the gastroenterologist, who can then send fluid for biochemical and molecular analysis. Measuring maximum length of stretch between thumb and index finger from a droplet of cyst fluid has been used as an indirect measure of viscosity, and lengths of 3.5 mm or more correlate with mucinous cysts. Nonmucinous cysts (LEC and squamoid cysts of the pancreatic duct) may, however, have high viscosity.

Although the role of rapid on-site evaluation in evaluating solid pancreatic masses is indisputable (ensuring acquisition of adequate material for ancillary studies), its utility in the evaluation of pancreatic cysts has become controversial, as it can potentially waste fluid that could be submitted for molecular and chemical analysis. The success rate of cyst fluid analysis is also partly dependent on the volume of fluid aspirated. Because fluid volume is often limited it is probably best to triage samples to cytology and ancillary biochemical and molecular analysis rather than making smears. If the cyst aspirate is grossly dry, then rapid on-site evaluation should be attempted with smears along with needle rinses for cell block preparation. In a cystic and solid lesion, rapid on-site evaluation should be performed on the solid component.

### Biochemical Analysis of Pancreatic Cyst Fluid

Carcinoembryonic antigen (CEA) measurement is a mainstay of cyst fluid analysis and requires approximately 0.5 mL of fluid. Carcinoembryonic antigen levels have a higher sensitivity, specificity, and accuracy than cytology or EUS-FNA alone. A cutoff value of 192 ng/mL has 80% accuracy, 84% specificity, and 75% sensitivity. Values of 110 to 200 ng/mL are strongly associated with neoplastic lesions, with a soap bubble appearance, central stellate scar (with or without calcification), and absence of duct involvement, the primary differential is a SCA. In young adults, particularly women, the presence of a cystic and solid pancreatic (body/tail) mass should raise the differential of SPN.

Although this is promising, verification in larger studies is needed. Recently, an Italian group analyzed cyst fluid glucose concentration and found that glucose levels lower than 50 mg/dL were more sensitive than a CEA higher than 192 ng/mL (93.6% versus 54.8%; P = .003). Although typically higher in IPMN than MCN (because of the connection to the duct system), amylase cannot be used to distinguish between mucinous and pseudocystic cysts and may be high in both.

Other analytes may be helpful in identifying specific cyst types. Vascular endothelial growth factor A (VEGF-A) has been shown to be elevated in SCA, which typically has a low amylase level. Amylase levels are often markedly elevated in pseudocysts (>1000 ng/mL), and levels lower than 250 U/L are thought to exclude pseudocysts. Although typically higher in IPMN than MCN, elevated CEA may rarely be seen in nonmucinous cysts, and thus other differentials should always be entertained in the differential (pseudocysts, squamoid cysts of the pancreatic duct, SCA, and LEC), and correlation with clinical, radiologic, and cytologic findings is critical.

Although the role of rapid on-site evaluation in evaluating solid pancreatic masses is indisputable (ensuring acquisition of adequate material for ancillary studies), its utility in the evaluation of pancreatic cysts has become controversial, as it can potentially waste fluid that could be submitted for molecular and chemical analysis. The success rate of cyst fluid analysis is also partly dependent on the volume of fluid aspirated. Because fluid volume is often limited it is probably best to triage samples to cytology and ancillary biochemical and molecular analysis rather than making smears. If the cyst aspirate is grossly dry, then rapid on-site evaluation should be attempted with smears along with needle rinses for cell block preparation. In a cystic and solid lesion, rapid on-site evaluation should be performed on the solid component.

### Molecular Analysis of Pancreatic Cyst Fluid

Recent advances in discoveries of key molecular alterations in cyst fluid have been extremely critical in distinguishing different pancreatic cysts preoperatively, and have shown high concordance with diagnosis on resection. KRAS mutations and loss-of-heterozygosity events involving tumor suppressor genes CDK2NA, RNF43, SMAD4, TP53, and VHL can be extremely useful in distinguishing mucinous from nonmucinous cysts, with VHL mutations being seen in SCA. Recently PRKACA and PRKACB gene fusions were described in the cyst fluid of pancreaticobiliary IOPN, as well as their invasive counterparts. Aneuploidy in mucinous cysts has been linked to malignant transformation, and although molecular testing is not widely available, it is now an integral part of cyst fluid analysis. Molecular alterations in specific cyst types will be discussed in each individual cyst section.
Cytologic Evaluation of Pancreatic Cysts

Cytopathology represents the primary preoperative modality for investigating the majority of pancreatic cysts. Its primary goal is to exclude malignancy and distinguish innocuous (neoplastic and nonneoplastic) cysts from those prone to harboring or progressing to malignancy. If the cyst is neoplastic, then one needs to determine whether it is low risk and therefore unlikely to progress, or is frankly malignant (like SPN or cystic adenocarcinoma) or has a high risk of harboring high-grade dysplasia or invasive carcinoma (IPMN, MCN, IOPN, ITPN). Because low-risk pancreatic cysts have a low risk of harboring malignancy, they are typically resected only if patients are symptomatic or if a definitive diagnosis cannot be rendered on cytology or imaging. In contrast, because high-risk pancreatic cysts (like IPMN and MCN) have a high risk of harboring high-grade dysplasia or invasive carcinoma or a high risk of harboring high-grade dysplasia or invasive carcinoma (IPMN, MCN, IOPN, ITPN), because low-risk pancreatic cysts have a low risk of harboring malignancy, they are typically resected only if patients are symptomatic or if a definitive diagnosis cannot be rendered on cytology or imaging. In contrast, because high-risk pancreatic cysts (like IPMN and MCN) have a high risk of harboring carcinomatous change, they should ideally be resected. In the clinical setting, resection is typically dependent on clinical factors (presence of comorbidities), cyst size, pancreatic duct diameter, and presence of a mural nodule, along with cytologic findings and/or molecular alterations suggestive of malignancy.41

Is It a Cystic Adenocarcinoma?.—Because up to 8% of pancreatic ductal adenocarcinomas (PDACs) can present as cystic masses, the first goal of cytologic evaluation of cyst fluid is aimed at identifying adenocarcinoma.13,42 This is especially common in large duct–type PDAC (Figure 1, A and B), PDACs with squamous differentiation, and some undifferentiated carcinomas.17,43,44 If frank carcinoma is identified then the case should be signed out as “malignant: adenocarcinoma.” Cytologic features of PDAC are dependent on differentiation. Poorly differentiated PDAC has 3-dimensional clusters and singly dispersed intact cells with high nuclear to cytoplasmic ratio, hyperchromasia or hypochromasia (resembling papillary thyroid carcinoma), nuclear membrane folding or irregularity, prominent or large nucleoli (Figure 1, C and D), 3- to 4-fold anisonucleosis, single-cell necrosis, background necrosis, and intracytoplasmic vacuoles that may or may not contain central targetoid eosinophilic granules. Although the features of poorly differentiated PDAC are straightforward, those of well-differentiated PDACs are more challenging. Well-differentiated PDAC may show only minimal deviation from normal duct morphology. Cytologic features include drunken honeycomb sheets of crowded overlapping

Figure 1. A, Large-duct variant of pancreatic ductal adenocarcinoma composed of large sheet of cells with minimal anisonucleosis. B, High power of the same case shows drunken honeycomb sheets of crowded, overlapping, irregular, hypochromatic nuclei. C, Colloid carcinoma composed of abundant pools of thick orange mucin and scattered cell clusters. D, High power of same case shows 3-dimensional cluster of cells with high nuclear to cytoplasmic ratio, hypochromasia and macronucleoli (Papanicolaou stain, original magnifications ×200 [A and C] and ×400 [B and D]).
but minimally atypical epithelial cells with minimal loss of polarity or nuclear membrane irregularity (Figure 1, B). Cellular dissociation, single cells, and nuclear anisonucleosis are helpful features, but may not be present.

When evaluating FNAs with abundant extracellular mucin, another malignant differential to consider is colloid or mucinous carcinoma. Colloid carcinoma is the most common type of invasive carcinoma to arise in intestinal-type IPMNs. The latter are morphologically similar to colonic villous adenomas and express CK20, as well as the mucin glycoprotein MUC2 and caudal homeobox 2 (CDX2).35 On aspiration of colloid carcinoma, there is abundant dense mucin that is stretched andropy or forms defined loculated pools even on smear (Figure 1, C and D). These pools contain entrapped 3-dimensional clusters and strips of cells with variable cytoplasmic mucin and other features of adenocarcinoma (Figure 1, D). If these cytologic findings are seen in a radiologically solid mass, then colloid carcinoma is a possibility. However, in a cyst or dilated duct, the differential includes MCN or IPMN with high-grade atypia. Demarcated mucin pools and overt malignant cytology should raise strong suspicion of colloid carcinoma, particularly if IPMN is also present in the pancreas. In some situations, however, it will be virtually impossible to distinguish colloid carcinoma from a mucinous cyst, and it is best to classify such cases as neoplastic mucinous cyst with high-grade atypia” (see below), because the clinical/management implications are the same for both.

**Is It a Mucinous Cyst? — Neoplastic Mucinous Cysts.** Mucinous pancreatic cysts are of ductal lineage, and, because they may progress to invasive adenocarcinoma, they are the most important of the cystic pancreatic neoplasms. They are of 2 main types, IPMN and MCN. Both are composed of thick mucin and may have a mucinous epithelial lining, which can show a spectrum of dysplasia ranging from low to high grade, and can eventually progress to invasive carcinoma (seen in 30% of IPMNs and 17% of MCNs). Intraductal papillary mucinous neoplasms by definition arise from and involve the main and/or branch pancreatic ducts (most frequently) in the pancreatic head, followed by the body/tail, and present as multifocal, multilocular cysts (so-called cyst-aside-cyst appearance) in men and women in the sixth decade.44 The lining epithelium of IPMNs is of 3 types: gastric, intestinal, and pancreatobiliary (Figures 2, A through D, and 3, A through D). In contrast, MCNs do not involve the duct system, and typically present as solitary, unicellular or multilocular cysts (so-called cyst-in-cyst appearance) in the pancreatic body/tail of perimenopausal women. Mucinous cystic neoplasms are also lined by mucinous epithelium and are distinguished from IPMNs (and defined) by their subepithelial ovarian-type stroma, which is rarely sampled on FNA.47 Intraductal papillary mucinous neoplasm and MCN cumulatively fall under the umbrella cytologic term neoplastic mucinous cysts because the MCN-defining ovarian-type stroma is rarely sampled on cytology, and the 2 cysts are otherwise indistinguishable on FNA.

Preoperative assessment of suspected mucinous cysts is used to identify those with high-risk features or high-grade atypia (encompassing high-grade dysplasia and/or invasive carcinoma). This determination is based on clinical history, gender, imaging characteristics, cytology, and cyst fluid biochemical and mutational analysis. The 2017 revised international consensus Fukuoka guidelines for management of IPMN define high-risk stigmata (worrisome for, or supportive of, malignancy) as a solid component, main pancreatic duct diameter 10 mm or more, cysts 3 cm or more with thick walls, mural nodules, main duct size 5 to 9 mm (considered worrisome), suspicious or positive cytology, and abrupt pancreatic duct caliber change with distal atrophy, among others.41 If worrisome features are present, EUS-guided FNA biopsy is recommended. If the aspirate is neoplastic with high-grade atypia, or suspicious/positive for malignancy, then surgery is recommended.44

Aspirated material from neoplastic mucinous cysts is typically composed of variable amounts of thick viscous mucin that is magenta to blue on Diff-Quik (Figure 2, A) and greenish pink to orange on Papanicolaou stain (Figure 1, C and D). In scant samples thick mucin may appear as stretchy, radiating projections/pseudopods on the slide, which are a visual clue to its viscous nature. It should be noted that in the appropriate clinical/radiologic context, thick, “ropy” mucin alone (without associated epithelium) is also diagnostic of a neoplastic mucinous cyst, particularly if cyst fluid CEA is elevated. This is because some mucinous cysts are lined by more attenuated epithelium that is less likely to be sampled on FNA. Aspirates from mucinous cysts can show variable cellularity, but are typically composed of flat, folded, or branching sheets, papillae, and clusters of epithelial cells with variable intracytoplasmic mucin and well-defined cell walls (resembling vegetable cell walls) (Figures 2, A through D, and 3, A and C). Psammomatous calcifications and papillae (Figures 2, B, and 3, A) may be seen, but are more frequent in IPMN than MCN.

If It Is a Mucinous Cyst Then What Is the Grade of Atypia? — In order to improve pathologists’ concordance and link clinical and molecular observations, a 2-tiered histologic classification system (of low- versus high-grade dysplasia) was proposed for all precursor pancreatobiliary lesions, including neoplastic mucinous cysts (IPMN, MCN) and pancreatic intraepithelial neoplasia. Intermediate-grade dysplasia is now classified as low grade (and clinically innocuous), whereas the high-grade dysplasia category is reserved for carcinoma in situ-type lesions, which have a strong association with invasive cancer and thus warrant clinical intervention.49,50 Membrane-bound glycosylated phosphoproteins (MUC1, MUC2, MUC5AC, and MUC6) can help in subclassifying mucinous cysts.

**Low-Grade Epithelial Atypia in Neoplastic Mucinous Cysts.**—The cytologic term low-grade epithelial atypia encompasses low- and intermediate-grade dysplasia. Low-grade mucinous epithelium typically forms sheets or papillae of bland columnar cells with low nuclear to cytoplasmic ratio and basally polarized rounded to oval nuclei (Figure 2, B through D), with even chromatin, inconspicuous nucleoli, and cytoplasmic mucin (Figure 2, C and D). Gastric-type IPMNs are more likely to show low-grade atypia (Figure 2, C and D), stain positively for MUC5AC and variably for MUC6, and are negative for MUC1 (EMA), MUC2, CDX2, and CK20.

**High-Grade Epithelial Atypia in Neoplastic Mucinous Cysts.**—High-grade cytologic atypia encompasses high-grade dysplasia and invasive adenocarcinoma, because cytology material typically lacks the required stromal component necessary to assess invasion.38,54 Additionally, distinction between high-grade dysplasia and invasive carcinoma is not required for management, as both ideally require resection. Cytologic features in high-grade examples include crowded (drunken honeycomb) sheets, papillae, and 3-dimensional cell clusters with high nuclear to cytoplasmic
ratio, irregular nuclei, and change in chromatin (hyperchromasia and/or hypochromasia) (Figure 3, A and B). Prominent nucleoli, single cells, and “punched-out” cytoplasmic mucin vacuoles (that displace the nuclei peripherally) may also be seen (Figure 3, A and B). Single-cell necrosis and necrotic debris are also seen in high-grade atypia. An example of a pathology report from such a case is shown in Table 3. Pancreatobiliary IPMN and IOPN are by definition high grade (Figure 3, A through D), whereas intestinal-type IPMNs show a spectrum of dysplasia ranging from low to high grade. Pancreatobiliary-type IPMN stains positively for MUC1 (Figure 3, D) and variably for MUC5AC and MUC6, and is negative for MUC2, CDX2, and CK20, whereas intestinal-type IPMN is positive for MUC2, CDX2, and CK20 and negative for MUC1 and MUC6.46

**Caveats in the Cytologic Diagnosis of Neoplastic Mucinous Cysts.**—Gastrointestinal epithelial contaminants may mimic neoplastic mucinous cysts. The type of epithelial contaminant seen depends on the cyst’s location and the structures traversed during EUS-FNA. For uncinate and pancreatic head lesions, the aspirating needle traverses the duodenal wall, resulting in duodenal epithelial contaminants. Duodenal epithelium is composed of flat or folded sheets with a 2-cell population of evenly spaced columnar cells or enterocytes admixed with pale goblet cells resembling fried eggs (Figure 3, E). Duodenal epithelium’s characteristic appearance makes distinction from a neoplastic mucinous cyst relatively straightforward. For lesions in the pancreatic body or tail, the aspirating needle traverses the stomach wall, resulting in gastric epithelial contaminants. Gastric foveolar epithelium contains intracytoplasmic mucin that forms U-shaped cups in the superficial third of the cell (Figure 3, F). The latter may mimic a low-grade gastric-type IPMN, and distinction may be impossible on cytology. In such cases, one must rely on cyst fluid analysis (elevated CEA and amylase levels would favor neoplastic mucinous cyst). However, if this is unavailable or inconclusive, then a diagnosis of “atypical findings. See comment,” with a comment stating, “If truly from the cyst, then this may represent a gastric-type IPMN,” may be required (Table 3). Luminal gastrointestinal tract mucin may be abundant in some EUS-FNA samples, and if increased may mimic a mucinous cyst. Unlike neoplastic mucin, gastrointestinal tract mucin is thin and watery, easy to extricate from the needle/syringe, and dries quickly on smearing. Luminal

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**Figure 2.** Neoplastic mucinous cyst (gastric-type intraductal papillary mucinous neoplasm [IPMN]) with (A) thick ropy magenta mucin, (B) complex branching papillae with thin fibrovascular cores, and (C and D) sheets of cells with well-defined cell borders, polarized basal nuclei and pink cytoplasmic mucin (low-grade atypia) on (C) smear and (D) cell block (Diff-Quik, original magnifications ×40 [A] and ×200 [B]; Papanicolaou stain, original magnification ×200 [C]; hematoxylin-eosin, original magnification ×200 [D]).
Figure 3. Case of pancreatobiliary-type intraductal papillary mucinous neoplasm (neoplastic mucinous cyst) with high-grade atypia with (A) complex branching papillae lined by overlapping hypochromatic high-grade nuclei (Papanicolaou stain ×200), and (B) 3-dimensional clusters and single high-nuclear to cytoplasmic ratio cells with folded hypochromatic nuclei in a necrotic background. (C) Cell block from the same case shows papillae lined by overlapping cells with cytologic features resembling foamy gland-type adenocarcinoma and (D) MUC1 positivity. (E) Duodenal epithelium composed of flat honeycomb sheet of enterocytes admixed with pale halved goblet cells. (F) Normal gastric epithelium with strip of bland cells with basal nuclei and cup-shaped cytoplasmic mucin occupying the upper half of the cell (Papanicolaou stain, original magnifications ×200 [A and B] and ×400 [F]; hematoxylin-eosin, original magnification ×400 [C]; original magnification ×400 [D]; Diff-Quik, original magnification ×200 [E]).
### Table 3. Examples of Cytopathology Reports in Cystic Pancreatobiliary Lesions

| Sample Site | Cytology Findings | Molecular Findings |
|-------------|-------------------|--------------------|
| Pancreas, CT-guided FNA biopsy | Neoplastic cells present | KRAS mutation |
| Pancreas, EUS-guided FNA biopsy | Neoplastic cells present | GNAS mutation |
| IPMN with high-grade atypia | Neoplastic cells present | PRKACA/PRKACB |
| ITTPN with high-grade atypia | Neoplastic cells present | TP53, p16/CDKN2A, SMAD4/DPC4 |

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; ITTPN, intraductal tubulopapillary neoplasm.

mucin covers slides evenly and lacks the so-called pseudopods of a neoplastic mucinous cyst.

**Molecular Alterations in Neoplastic Mucinous Cysts (IPMN and MCN).**—Of 96 IPMNs recently studied by Springer et al., almost all had at least 1 mutation, loss of heterozygosity, or aneuploidy, with KRAS mutation being most prevalent. KRAS mutation has a specificity and sensitivity of 54% and 100%, respectively, for detecting PDAC, IPMN, and MCN. A commercially available molecular kit was used to assess KRAS mutations, loss of heterozygosity, DNA quality, and DNA quantity in pancreatic cyst fluid and had 83% sensitivity and 100% specificity for malignancy. GNAS oncogene mutations (codon 201) are seen in up to 60% of IPMNs, with intestinal-type ones showing the highest prevalence followed by gastric and pancreatobiliary, but not IPMN or MCN. GNAS mutations are even detectable in duodenal pancreatic juice. More than 90% of IPMNs have either GNAS or KRAS mutations, and almost half show both, whereas SCAs show neither. In fact, KRAS/GNAS mutations have an 89% sensitivity and 100% specificity for mucinous cysts. Assays containing both GNAS and KRAS amplicons can potentially distinguish between these mucinous and serous cysts. Somatic RNF43 mutations are also seen in IPMNs and MCN. Other PDAC-related driver gene mutations (TP53, p16/CDKN2A, SMAD4/DPC4) may occur in IPMNs and MCNs, particularly those with high-grade dysplasia or invasive carcinoma.

**Other (Intra)Ductal Cystic Tumors of Pancreas**

**Intraductal Oncocytic Papillary Neoplasm.**—Intraductal oncocytic papillary neoplasm is another intraductal (but mucin depleted) cystic neoplasm that involves the main (and/or branch) pancreatic duct. It was formerly classified as an IPMN subtype; however, because its molecular associations and biologic behavior are different from other IPMN subtypes, it is now classified as a separate entity and in current Papanicolaou Society guidelines falls under the neoplastic: other category. Although typically considered a mucinous cyst, IOPNs often present as complex solid and cystic masses, rather than pure cysts, and are typically mucin depleted of both intracellular and extracellular mucin, unlike their IPMN and MCN counterparts.

The cytologic features of IOPN in the pancreas and biliary tree are quite distinct, making definite diagnosis possible on cytology. Smears from IOPNs at either site are usually hypercellular with/without thick background mucin, and composed of crowded sheets, clusters, or papillae of Hurthleoid polygonal cells with abundant granular cytoplasm, well-defined cell borders, relatively low nuclear to cytoplasmic ratio, and large central oval or irregular nuclei with prominent, slightly eccentric nucleoli (Figure 4, A through E). Cytoplasmic mucin is a very rare finding in IOPN. Tumor cells lining papillae are often pseudostratified and have interspersed punched-out intercellular spaces (Figure 4, E). Papillae may be broad, edematous, and basophilic or hyalinized (Figure 4, E). Abnormal mitoses, degenerative atypia, and coagulative necrosis are common and may be extensive (Figure 4, E). By definition IOPNs have high-grade atypia. An example of a pathology report is shown in Table 3.

Invasive carcinoma may develop in IOPN and on cytology may show classical pancreaticbiliary-type features or be more oncocytic in appearance (Figure 4, F). Intraductal oncocytic papillary neoplasm is positive for MUC6, MUC5AC, and MUC1 and negative for intestinal markers (only goblet cells show staining with intestinal markers). Tumors may also rarely express HepPar1. Newly described molecular alterations have been found in pancreaticobiliary IOPN, including PRKACA and PRKACB gene fusions, which can also be seen in their invasive counterparts, and in cyst fluid and brushings.

The differential diagnosis of IOPN includes other neoplasms with granular eosinophilic cytoplasm, including cystic PanNET (particularly its oncocyctic variant), acinar cell carcinoma, and metastatic carcinomas in pancreas (oncocytic thyroid and hepatocellular carcinoma). Oncocytic PanNETs have more abundant granular cytoplasm and may have papillae and fibrovascular cores mimicking IOPN. However, oncocytic PanNET cells have eccentric nuclei, which, along with salt-and-pepper chromatin and positive staining for neuroendocrine markers, should facilitate distinction. Acinar cell carcinoma also has granular cytoplasm and prominent nucleoli resembling IOPN. Unlike IOPN, tumor cells in acinar cell carcinoma express trypsin, chymotrypsin, and BCL10.

**Intraductal Tubulopapillary Neoplasm.**—Intraductal tubulopapillary neoplasm is a relatively recently recognized, rare (<2%), but separate intraductal neoplasm. It may arise in the pancreatic ducts or the biliary tree. Tumors may present as cystic or solid pancreatic masses on imaging. Histologically, ITPN forms intraductal neoplasms that are composed of back-to-back tubules with minimal papillae. Tubules are lined by mucin-depleted, mitotically active cuboidal cells with high-grade cytology, closely mimicking acinar cell carcinoma morphologically.
Figure 4. Pancreatic intraductal oncocytic papillary neoplasm (IOPN) with (A) crowded sheets and (B and C) large cells with granular cytoplasm, central oval nuclei, and prominent nucleoli. (D) Intraductal oncocytic papillary neoplasm on ThinPrep showing cells with abundant granular cytoplasm, central oval nuclei, and prominent cherry-red nucleoli. (E) Cell block from IOPN case shows broad basophilic edematous papillae lined by pseudostratified oncocytic cells with punched-out intercellular spaces and pleomorphic hyperchromatic nuclei. (F) This invasive carcinoma arose in an IOPN and shows a 3-dimensional cluster of pleomorphic oncocytic cells (Diff-Quik, original magnifications ×100 [A] and ×400 [F]; Diff-Quik and Papanicolaou stain, original magnification ×400 [B and C]; Papanicolaou stain, original magnification ×400 [D]; hematoxylin-eosin, original magnification ×400 [E]).
also be seen in ITPNs.

The cytologic features of ITPN have only rarely been described and are the same in the pancreas and biliary tree. They include hypercellularity and branching sheets or clusters of overlapping cells with back-to-back cribriform spaces representing tubular units (Figure 5, A). Tumor cells are cytologically high grade with high nuclear to cytoplasmic ratio, hyperchromatic or hypochromatic nuclei, prominent cherry-red nucleoli, brisk mitoses, and single-cell/confluent necrosis. In contrast to the cytoplasmic mucin in intestinal- and gastric-type IPMN, ITPN tumor cells lack cytoplasmic mucin (Figure 5, B). Tumor cells are positive for CK7, CK19, MUC1, and MUC6 and negative for MUC2 and MUC5AC.

The differential diagnosis for ITPN includes acinar cell carcinoma and high-grade mucinous cysts (particularly pancreateobiliary-type IPMN), which usually have cytoplasmic mucin (even if focally) and do not have back-to-back cribriform tubules like ITPN. Like ITPN, acinar cell carcinoma may present as a cystic/intraductal pancreatic mass, with tumor cells that show red cytoplasmic zymogen granules, large nuclei, and cherry-red nucleoli, reminiscent of ITPN. Luminal proteinaceous material in the tubules of ITPN may resemble enzymatic concretions seen in acinar cell carcinoma. Although the acini in acinar cell carcinoma are morphologically similar to those of ITPN, they express acinar markers trypsin, chymotrypsin, and BCL10, which are negative in ITPN. Invasive carcinoma is common in ITPN (approximately 70%), and is of tubular type, similar to that seen in pancreatobiliary-type adenocarcinoma. A third of biliary ITPNs show somatic mutations in the phosphatidylinositol 3-kinase pathway, a potential diagnostic/therapeutic target.

PTK3CA mutations are associated with overexpression of phosphorylated AKT. p16/CDKN2A mutations may also be seen in ITPNs.

NONMUCINOUS NEOPLASTIC CYSTS OF PANCREAS

Serous Cystadenoma

Serous cystadenoma is a benign, nonmucinous, cystic pancreatic neoplasm and the second most common type of pancreatic cystic neoplasm. It may arise sporadically or in von Hippel–Lindau disease. Cysts occur in the pancreatic body or tail of older women (mean age 66 years). Most SCAs have a spongelike, microcystic soap-bubble appearance and a central stellate scar. Macrocytic (oligocystic or unicystic) variants have fewer, larger cyst locules and may be mistaken for mucinous cysts on imaging.

Because of their prominent subepithelial capillary meshwork, aspiration of SCAs often yields nondiagnostic paucicellular bloody specimens. Cyst fluid is clear or serosanguinous, with low CEA and amylase levels on cyst fluid analysis. Smears often show only proteinaceous or hemorrhagic debris with hemosiderin-laden macrophages. When present, serous epithelium typically forms monolayered sheets of bland epithelial cells with well-defined cell borders; abundant, glycogen-rich, clear cytoplasm (best seen on Papanicolaou stain); and round/oval bland nuclei (Figure 5, C and D). Necrosis, extracellular or cytoplasmic mucin, and pleomorphism are not features of SCA. Tumor cells stain positively for pancytokeratin, PAS (with diastase digestion), inhibin, and glucose uptake and transporter 1 (GLUT1) (Figure 5, E and F). Because cytologic material often lacks the requisite serous epithelium (hence low FNA sensitivity), knowledge of the radiologic appearance, which may be diagnostic, is helpful.

VHL mutations have been identified in SCA cyst fluid (and in some PanNETs), but not IPMN, MCN, or SPN. Other alterations include aneuploidy of chromosome 3p, but not KRAS, GNAS, and RNF43. VEGF protein levels are also elevated in SCAs.

Solid-Pseudopapillary Neoplasm

Solid-pseudopapillary neoplasm is the most common nonmucinous cystic pancreatic neoplasm (frequency 12%). Solid-pseudopapillary neoplasm occurs predominantly in young adult women (female to male ratio = 9; mean age, 30s), but can rarely be seen in men and older women. Tumors are typically large (mean 8–10 cm) and well demarcated. The cytomorphology of SPN is so distinctive that definitive diagnosis is often possible on cytology. Fine-needle aspiration typically yields hypercellular smears with clusters and delicate, fingerlike, branching papillae containing delicate fibrovascular cores covered by crowded tumor cells (Figure 6, A through E). Tumor cells are epithelioid with coffee bean–shaped nuclei, longitudinal nuclear grooves, indistinct small peripheral nucleoli, and papillary thyroid carcinoma–like vesicular chromatin (Figure 6, B through D). This papillary thyroid carcinoma–like chromatin is in stark contrast to the salt-and-pepper chromatin seen in PanNETs and the large cherry-red nucleoli in ITPN or acinar cell carcinoma. Fibrovascular cores in SPN are often covered by dense myxoid stroma that is magenta colored on Diff-Quik and blue-green on Papanicolaou stain (Figure 6, A, B, and E). Foamy macrophages and clear cells with cytoplasmic tails may also be seen. Tumor cells may be extremely discohesive and plasmacytoid, mimicking PanNET (Figure 6, C), but unlike PanNET, they lack the salt-and-pepper chromatin.

Solid-pseudopapillary neoplasms show somatic mutations of β-catenin (CTNNB1) in 95% to 100%, which affects the Wnt signaling pathway. As such, they show cytoplasmic and eventual nuclear β-catenin accumulation, resulting in nuclear and cytoplasmic overexpression of β-catenin protein on immunohistochemistry (Figure 6, E inset). Nuclear β-catenin expression is the most helpful profile in distinguishing SPN from PanNETs. Solid-pseudopapillary neoplasm also shows diffuse nuclear positivity for transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) and lymphoid enhancer binding factor 1 (LEF1), other proteins involved in the β-catenin/Wnt signaling pathway. Solid-pseudopapillary neoplasm tumor cells overexpress androgen and progesterone receptor and cyclin D1. Despite their epithelioid appearance, tumor cells are negative or only focally positive for pancytokeratin. CTNNB1 alterations also cause loss of expression for e-cadherin and resultant cellular discohesion. Synaptophysin and CD56 may be focally positive in SPN, but unlike PanNET, SPN is negative for chromogranin and typically negative (or only focally positive) for epithelial markers, VHL, GNAS, and RNF43 alterations are not usually seen in SPN.

Cystically Degenerated Solid Tumors of the Pancreas

Whether primary or metastatic, practically every solid tumor type that involves the pancreas may undergo cystic degeneration and thus present as a cystic mass. Some form
Figure 5. (A) Fine-needle aspiration of pancreatic intraductal tubulopapillary neoplasm shows crowded cells with high-grade atypia and back-to-back cribriform tubules. (B) Corresponding cell block showing back-to-back tubules with angulated nuclei, cherry-red nucleoli, and granular cytoplasm without mucin. (C) Serous cystadenoma (SCA) with bland tumor cells with round nuclei, even chromatin, and clear cytoplasm. (D) Cell block from SCA showing hyalinized tissue fragment surrounded by clear cells with low nuclear to cytoplasmic ratio and small hyperchromatic nuclei. Tumor cells showed cytoplasmic positivity for pancytokeratin (E) and GLUT-1 (F) (Papanicolaou stain, original magnification ×400 [A and C]; hematoxylin-eosin, original magnifications ×200 [B] and ×400 [D]; original magnification ×200 [E and F]).
of cystic change larger than 1 cm can be found in up to 10% of ordinary PDACs. Most represent cystic necrosis, large-duct variant of PDAC, or secondary changes such as obstructive duct dilatation (retention cysts). The cytomorphologic features of the large-duct variant of PDAC are the same as those of its smaller tubular counterparts and have been described above (Figure 1, A and B). Where they differ is in the abundance of large, complex sheets of cells, which are more common in large-duct variant than classical PDAC. At low power, these sheets can easily be dismissed as benign ductal cells or duodenal epithelium. However, on close inspection, nuclear crowding and irregularity, anisokaryosis, and change in chromatin can be seen, supporting the PDAC diagnosis (Figure 1, B). Additionally, other invasive carcinomas such as squamous cell carcinoma and undifferentiated carcinoma with osteoclast-like giant cells may occasionally present as cystic masses. Similarly, cystic degeneration occurs in 10% to 17% of neuroendocrine tumors and 2% of acinar carcinomas.

Cystic degeneration in solid malignancies is often associated with necrosis, and aspirates may be composed predominantly of necrotic debris with only limited viable tumor cells. In the case of cystic PanNET and acinar cell carcinoma, this can be especially challenging, as immunohistochemical panels including neuroendocrine (synaptophysin, chromogranin, INSM1) and acinar markers (trypsin, chymotrypsin, and/or BCL10) are required for definitive diagnosis. The cytologic features of cystic PanNET and acinar cell carcinoma are similar to those of their solid counterparts. In PanNETs, tumor cells are monotonous and plasmacytoid with low nuclear to cytoplasmic ratio, oval nuclei, and salt-and-pepper chromatin. Red cytoplasmic neurosecretory granules may be seen, but cytoplasmic mucin or thick background mucin is not. Acinar cell carcinoma typically yields moderately cellular FNAs composed of cells with abundant granular cytoplasm, large hyperchromatic or hypochromatic nuclei, prominent cherry-red nucleoli, brisk mitoses, and cytoplasmic red zymogen.
granules. Again, the cytoplasmic mucin and thick background mucin of neoplastic mucinous cysts would not be seen. Cyst fluid CEA and amylase are low in PanNETs and acinar carcinoma, and they lack RNF43 and GNAS mutations, which would be seen in mucinous cysts.

**NONNEOPLASTIC CYSTS OF THE PANCREAS**

**Lymphoepithelial Cyst of the Pancreas**

Lymphoepithelial cysts of the pancreas are benign unicellular or multilocular cysts with male predominance. Most are discovered incidentally and have a classical radiologic appearance, which makes FNA unnecessary in some examples. Cytologic findings in LEC of pancreas are classical and diagnostic. Aspirates yield yellow-white material containing anucleated (and fewer nucleated) squamous cells, keratin debris, and cholesterol crystals (Figure 7, A). Lymphocytes and histiocytes are variable but usually scant because the cyst wall (where these are most abundant) is often not sampled. Cell blocks may show bland squamous cells or laminated keratin (Figure 7, B). Whereas the cytomorphology of LEC of pancreas is straightforward, cyst fluid analysis is not, and high CEA and amylase levels may cause misinterpretation as a mucinous cyst.

The differential diagnosis of LEC of pancreas includes pseudocysts as well as cystic lesions/neoplasms with a squamous lining, such as squamoid cyst of the pancreatic duct, epidermoid cyst involving intrapancreatic accessory spleen, and squamous and adenosquamous carcinomas. Differentiating an epidermoid cyst from LEC of pancreas may be impossible on cytology, as the 2 are cytologically bland. Malignant squamous lesions typically show high-grade cytology.

**Squamoid Cyst of the Pancreatic Duct**

Squamoid cyst of the pancreatic duct is characterized by dilatation of the main pancreatic duct and squamous metaplastic change of the lining epithelium. It is often misdiagnosed as a mucinous cyst on imaging. Cysts are typically lined by multilayered transitional-type epithelium. The basal layer resembles polygonal squamous cells, have abundant eosinophilic cytoplasm, and lack keratinization or a granular layer, but stain positively for p40, p63, and cytokeratin 5. The cyst-facing luminal epithelial layer is typically composed of columnar cells, which may or may not contain cytoplasmic mucin (Figure 7, C). The smear background may contain mucin, a possible pitfall that can lead to misdiagnosis as mucinous cyst if this differential is not considered. However, this mucin is thin and watery, unlike the thick mucin of neoplastic mucinous cysts. Cyst fluid analysis often shows elevated CEA and amylase levels (because of duct involvement), which may also lead to misdiagnosis as mucinous cyst.

**Pseudocysts**

Pseudocysts are the most common nonneoplastic cysts of the pancreas and may arise after acute alcoholic pancreatitis, among other causes. By definition they lack an epithelial lining. Aspiration of pseudocysts typically yields abundant turbid, brown to greenish fluid. This fluid typically has a markedly elevated amylase and low CEA. Smears are paucicellular and composed predominantly of blood, hemosiderin-laden macrophages, other mixed acute and chronic inflammatory cells or lymphocytes, fibrin, debris, and bile pigment (Figure 7, D). They lack an epithelial lining, but benign gastrointestinal epithelial contaminants may be seen, and should not be misinterpreted as neoplastic.

The differential diagnosis of pseudocysts includes other inflammatory or infectious cysts, as well as true cysts and cystic neoplasms. The presence of neoplastic mucinous epithelium and thick background mucin should raise concern for a neoplastic mucinous cyst. In addition to the cytology described above, finding elevated CEA levels and specific molecular alterations (GNAS, RNF43) would support a diagnosis of a mucinous cyst over pseudocyst.

**Acinar Cystic Transformation**

Acinar cystic transformation (formerly acinar cell cystadenoma) is a rare, unicellular or multilocular cystic mass (up to several centimeters) that is characterized by cysts that are lined by pseudostratified cytologically bland acinar cells and are not connected to the pancreatic ducts. Most arise secondary to obstructive processes and are thus not true neoplasms. In addition to the acinar cell component, the cyst lining may also have intermixed ductal cells and even foci mucinous change.

Acinar cystic transformation is often misdiagnosed on cytology, according to case reports. Although a recent case was correctly diagnosed as such by Moray forceps, the typical cytologic sample from acinar cystic transformation is paucicellular. Specimens are rich in inspissated enzymatic concretions that are robin’s-egg blue (Diff-Quik stain) or pale green (Papanicolaou stain) on smear, and have prominent artifactual cracking reminiscent of colloid in thyroid FNAs (Figure 7, E). Benign acinar cells may also be seen (Figure 7, E inset). These have variable nuclear to cytoplasmic ratio ranging from low to high, granular eosinophilic cytoplasm, round to oval nuclei, and coarse chromatin, and may have prominent nucleoli (Figure 7, E inset). Forceps biopsies, which take large bites of cyst wall, may allow definitive cytologic diagnosis by showing a cyst wall lined by bland single or multilayered acinar epithelium.

The differential diagnosis of acinar cystic transformation should include neoplastic mucinous cysts because the eosinophilic amorphous enzymatic concretions may resemble or be misinterpreted as mucin. Carcinoidembryonic antigen and amylase may be high (not surprisingly because of the acinar enzyme producing epithelial lining), causing misdiagnosis as neoplastic mucinous cyst.

**Paraduodenal Wall Cysts (Paraduodenal or Groove Pancreatitis)**

Paraduodenal wall cysts of the paraduodenal groove may also form cysts in the pancreatic head region. They develop as a result of a unique form of chronic inflammation of the periampullary/paraduodenal region, aka groove pancreatitis, which leads to cysts on the pancreas-facing surface of the duodenal wall (paraduodenal wall cysts). Patients are typically male, range from 40 to 50 years old, and often have a history of alcohol abuse and smoking. Paraduodenal wall cysts may be misdiagnosed radiologically as IPMN or even PDAC. Groove pancreatitis causes thickening/fibrosis of the duodenal wall, trabeulation of duodenal muscularis, inflammatory stroma, myofibroblast proliferation, and duodenal wall/groove cysts that may, at least partially, be lined by ductal epithelium and granulation tissue, mimicking mucinous cysts or pseudocysts.
Figure 7. (A and B) Lymphoepithelial cyst with nucleated and anucleated squamous cells (A) and multilayered keratin and debris on cell block (B). Note absence of lymphocytes. (C) Cell block from squamoid cyst of pancreatic duct shows multilayered epithelium with columnar and squamoid cells with eosinophilic cytoplasm. (D) Cell block from pseudocyst composed of inspissated enzymatic concretions and bile pigment with scant inflammatory cells. (E) Aspirate from acinar cystic transformation shows dense cracked enzymatic concretions admixed with bland acinar cells (inset). (F) Cell block from cyst of paraduodenal pancreatitis shows bland spindle cells (Papanicolaou stain, original magnifications ×400 [A and E inset] and ×200 [E]; hematoxylin-eosin, original magnifications ×400 [B] and ×200 [C, D, and F]).
The cytologic features of groove pancreatitis have only rarely been described.\textsuperscript{86–88} Findings depend on the site sampled. Aspirates range from acellular to moderately cellular with bland spindled cells representing stromal fibrosis or proliferating myofibroblasts (Figure 7, F), acute or chronic inflammatory cells, multinucleated giant cells, and smooth muscle and cyst contents (debris and amorphous proteinaceous material, the latter representing enzymatic concretions from acinar cells).\textsuperscript{86–88} Spindle cells can be abundant and (even) mitotically active, leading to misdiagnosis as spindle cell neoplasms (Figure 7, F).\textsuperscript{86,88} In one example, multinucleated giant cells were so striking that the differential of undifferentiated carcinoma with osteoclast-like giant cells was considered.\textsuperscript{87} Hyperplastic Brunner glands may also be sampled and potentially misinterpreted as mucinous cells from a neoplastic mucinous cyst.\textsuperscript{86} On rare occasions, cyst fluid analysis has been performed and shown elevated amylase and CA19-9 levels but normal CEA levels.\textsuperscript{86,88}

**Cystic Lesions of the Biliary Tract**

The biliary tract is most frequently sampled by brush cytology along with fluorescence in situ hybridization and molecular studies. This triple-modality approach (brush cytology, forceps biopsy, and fluorescence in situ hybridization) significantly increases sensitivity and accuracy and allows sampling of strictures as well as solid intraductal biliary lesions.\textsuperscript{89} Endoscopic ultrasound-guided FNA of cystic (and solid) biliary lesions is less commonly performed. The most commonly encountered intraductal neoplasms in the biliary tract are summarized in Table 1.

**Intraductal Papillary Neoplasm of the Bile Duct**

Preinvasive tumoral intraepithelial bile duct lesions may cause duct ectasia or form cystic masses, and are called intraductal papillary neoplasms of the bile ducts (IPNBs). Intraductal papillary neoplasms of the bile ducts are extremely uncommon and may arise along the intrahepatic and/or extrahepatic biliary tree. They can cause bile duct obstruction, dilatation, and jaundice, or less commonly a solid mass. Tumors are typically composed of arborizing papillary or solid-tubular units lined by gastric, intestinal, oncocytic, or pancreatobiliary epithelium or a combination,\textsuperscript{90} and are thought to represent the biliary counterparts of IPMNs. Associated invasive adenocarcinoma is seen far more frequently than in pancreatic mucinous cysts, and is typically of tubular type.\textsuperscript{90,91} A new classification system (type 1 and type 2 IPNB) was recently proposed. Type 1 IPNBs are more frequently intrahepatic and mucinous, and resemble IPMNs, whereas type 2 IPNBs are more histologically complex, with irregular papillae or predominant solid-tubular component.\textsuperscript{92,93}

Cytologic samples of cystic biliary tract lesions include both FNA and bile duct brushing samples, depending on the tumor’s location in the biliary tree. Lesions in the distal extrahepatic bile duct are typically sampled by bile duct brushing (Figures 5, A and B, and 8, A through C), whereas hilar and intrahepatic biliary lesions are often sampled by FNA. Low-grade gastric-type IPNB is characterized by flat or folded honeycomb sheets of cells with abundant cytoplasmic mucin, low nuclear to cytoplasmic ratio, and round/oval or slightly indented nuclei with even chromatin. On aspiration, intestinal-type IPNB shows sheets and/or branching papillae lined by columnar cells with cytoplasmic mucin, nuclear elongation and pseudostratification, and variable nuclear atypia, most frequently high grade. Pancreatobiliary-type IPNB shows complex branching papillae lined by stratified cuboidal cells with high nuclear to cytoplasmic ratio, hypochromasia and hyperchromasia, and abnormal mitoses (Figure 8, A through C).

**Intraductal Oncocytic Papillary Neoplasm of the Bile Duct**

The cytomorphologic and immunocytochemical features of IOPN of bile duct are identical to those of their pancreatic counterparts that are described above. An example of this entity that was sampled by bile duct brushing is shown in Figure 8, D and E. Based on location, the bile duct type of IOPN differential should include other primary or metastatic oncocytic neoplasms that may involve the intrahepatic or extrahepatic biliary tree. Hepatocellular carcinoma may rarely infiltrate and grow along the bile ducts as a cystic or polypoid mass and may be sampled on cytology.\textsuperscript{94} Brushings or aspirates of hepatocellular carcinoma may resemble IOPN of bile duct and form oncocyctic sheets or papillae resembling IOPN. History of hepatocellular carcinoma and positivity for hepatocellular markers (HepPar and arginase) would favor the latter. Of note, IOPN may express HepPar immunostain and may show gene fusions that have been described in some hepatocellular carcinomas (fibrolamellar) variants.\textsuperscript{18,37,58} These represent potential pitfalls in diagnosis on limited cytologic samples. Liver metastases of oncocyctic-type PanNET may also resemble IOPN morphologically.

**Intraductal Tubulopapillary Neoplasm of the Bile Duct**

Intraductal tubulopapillary neoplasm may also develop in the bile ducts. Its cytologic features are the same as those of its pancreatic counterpart that were discussed and summarized in detail in the section above.

**Nonbiliary Tumors Involving the Bile Duct**

In addition to cholangiocarcinoma, other primary and metastatic tumors may extend into the bile ducts and be sampled on FNA or bile duct brushing. Duct involvement by hepatocellular carcinoma (which was mentioned above) is associated with a high mortality and rapid demise.\textsuperscript{17,94} Bile duct involvement by hepatocellular carcinoma should be conveyed clearly in pathology reports. Other tumors that may involve the intrahepatic and extrahepatic biliary tree include metastatic gallbladder, ampullary, gastrointestinal tract, and lung carcinoma; neuroendocrine tumor; and lymphoma.\textsuperscript{95,96} These may be sampled on brushing or FNA. Without appropriate clinical history they may be misdiagnosed as hepatic or biliary tract primaries. Their cytologic description is beyond the scope of this review.

**Conclusions**

The increased sensitivity of imaging modalities has led to an explosion in the incidence and frequency of discovery and sampling of cystic lesions of the pancreaticobiliary tract. These are now a routine part of pathologists’ daily practice. Accordingly, it is critical that cytopathologists understand the most common cytologic differentials to consider when they encounter FNAs and brushings from these lesions so as to more accurately diagnose, triage, classify (and in some cases grade) them using a multimodal approach that incorporates clinical, radiologic, and cytologic assessment in conjunction with chemical and more sophisticated molecular cyst fluid analysis, some complementary and
others superior to those in current use. The cytopathologist’s crucial role in reporting, using appropriate terminology, and incorporating judiciously selected ancillary studies cannot be overstated.

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