Difficult Diagnostic Problems in Pancreatobiliary Neoplasia

Jacob R. Bledsoe, MD; Shweta A. Shinagare, MD; Vikram Deshpande, MD

Pancreatic cancer is the fourth most-common cause of cancer-related death in the United States, with an estimated 46,420 new cases and 39,590 deaths in 2014. Cancers of the extrahepatic biliary tract and gallbladder are relatively less common, with an estimated 10,650 new cases in 2014. Pancreatobiliary carcinomas have a notoriously poor prognosis with an overall 5-year survival rate of less than 5% for pancreatic ductal adenocarcinoma (PDAC), and few of these tumors are resectable at presentation because of the concomitant presence of metastasis or involvement of regional vital structures, such as the superior mesenteric or portal vasculature. In those pancreatic tumors that are resectable, the clinical and radiologic presentation demonstrates a high degree of overlap with a number of other neoplastic and pseudoneoplastic processes that can confound the clinical diagnosis. Furthermore, the histologic differentiation of pancreatic neoplasms from each other, from extrapancreatic tumors involving the pancreas, and even from benign processes, can be a challenge for the pathologist, especially on small biopsies or frozen sections. Nevertheless, careful correlation of clinical presentation, gross pathology, and histopathologic findings allows distinction in most cases.

Arguably, the most-common diagnostic problem encountered in the pancreas by the practicing pathologist is distinguishing PDAC from chronic pancreatitis and from extrapancreatic carcinomas involving the pancreas, such as distal common bile duct or ampullary carcinomas. A less-common diagnostic dilemma in the pancreas, but one that is potentially underrecognized, is the differentiation among nonclassic intraductal pancreatic neoplasms, specifically intraductal tubulopapillary neoplasms (ITPNs), intraductal oncocytic papillary neoplasms (IOPNs), and acinar cell carcinoma with intraductal growth. Outside the pancreas, difficult diagnostic predicaments are often encountered with intrahepatic biliary proliferations, such as the distinction of intrahepatic cholangiocarcinoma from metastases to the liver.

This review presents a brief discussion of these common diagnostic dilemmas with an overview of each entity and tools that may be useful to avoid some of the diagnostic pitfalls encountered in the course of routine surgical pathology sign out.

**Conclusions.**—Important diagnostic features for a few challenging problems in pancreatobiliary pathology are reviewed. Careful study of the microscopic features along with awareness of differential diagnoses and diagnostic pitfalls generally allows distinction of these entities. We also highlight established and novel ancillary studies that help to arrive at an accurate diagnosis.


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**Context.**—Many common diagnostic dilemmas are encountered in pancreatobiliary pathology, frequently resulting in uncertainty on behalf of the pathologist and referral for a second opinion.

**Objectives.**—To review 4 common diagnostic dilemmas encountered in the practice of pancreatobiliary pathology:

1. Pancreatic ductal adenocarcinoma versus chronic pancreatitis;
2. Pancreatic ductal carcinoma versus adenocarcinomas arising in the ampulla and intrapancreatic common bile duct;
3. The distinction of uncommon intraductal neoplasms—intraductal oncocytic papillary neoplasm, intraductal tubulopapillary neoplasm, and intraductal acinar cell carcinoma; and
4. Intrahepatic cholangiocarcinoma versus metastatic carcinoma.

**Data Sources.**—A review of pertinent literature, along with the authors’ personal experience, based on institutional and consultation materials.

**Conclusions.**—Important diagnostic features for a few challenging problems in pancreatobiliary pathology are reviewed. Careful study of the microscopic features along with awareness of differential diagnoses and diagnostic pitfalls generally allows distinction of these entities. We also highlight established and novel ancillary studies that help to arrive at an accurate diagnosis.
and surgery performed without a tissue diagnosis. Therefore, pathologists may encounter pancreatic resection specimens that fail to harbor malignancy, much to the surprise of the surgeon. The histologic overlap between PDAC and chronic pancreatitis often further complicates the issue.

By gross examination, ductal adenocarcinomas are typically poorly circumscribed, solid, firm masses that are difficult to distinguish from surrounding fibrotic tissue. Although usually located in the head of the pancreas, approximately 15% arise from the body or tail, and a similar proportion diffusely involve the pancreas. The cut surface is typically white-tan and fibrotic appearing and, occasionally, contains areas of necrosis. Rarely, the tumors undergo cystic degeneration or are associated with cystic dilation of the ducts and may, therefore, mimic primary cystic neoplasms of the pancreas. The tumors often involve the distal common bile duct and main pancreatic duct, classically resulting in abrupt stenosis with upstream duct dilation. Similarly, involvement of the ampulla or wall of the duodenum occurs not infrequently and may suggest an extrapancreatic carcinoma invading the pancreas (discussed below). A thoughtful dissection of the specimen will generally locate the epicenter of the tumor in the head of the pancreas, a finding that argues for a primary pancreatic carcinoma. In contrast, chronic pancreatitis is grossly characterized by uneven and poorly circumscribed fibrosis of the parenchyma, which usually involves the pancreas more diffusely than it does in PDAC and is often associated with calculi in the ducts and pseudocyst formations. Other forms of pancreatitis, such as autoimmune pancreatitis and paraduodenal pancreatitis, may be associated with a discrete mass. Stenosis of the common bile duct and pancreatic duct may occur in chronic pancreatitis but is typically tapering rather than abrupt.6

Useful histologic features for establishing the malignant nature of pancreatic lesions are well documented (Table 1)7 and include poorly circumscribed, irregular, or angulated malignant glands associated with abundant desmoplastic stroma and ducts outside of their normal lobular distribution (Figure 1, A and B). The presence of ducts at an aberrant location constitutes an important diagnostic parameter—normally only a few medium-to-large caliber ducts should be found in the interlobular septa. Thus, the presence of ducts adjacent to an artery (unlike in the liver where ducts accompany arteries) or at a perineural location is highly suggestive of malignancy (Figure 1, C and D).8,9 Other helpful parameters for a diagnosis of malignancy include incomplete duct lumina, the presence of intraluminal mucin or necrotic glandular debris, and single-cell infiltration (Figure 1, E).9,11 The architectural features are often emphasized at the expense of cytologic parameters, primarily because, in many cases, the cells have a rather banal appearance. Cytologically, the 2 most-reliable features in PDAC are markedly irregular nuclear outlines and anisonucleosis (>4:1 variation in nuclear size within a single gland).11

### Biomarkers of Pancreatic Ductal Adenocarcinoma

There are a host of markers that may be of assistance in distinguishing benign from malignant pancreatic glands. Some of these, such as mucins, including Muc4 and Muc16, mesothelin, and clusterin-β, are either not widely available or have not been rigorously validated.12,13 A number of markers, for example mucin-1 (MUC1) and mesothelin, among many others, may be useful for prognostication in PDAC, but their utility for diagnosis is not well studied.14,15 Arguably, the most robust immunohistochemical marker of PDAC is SMAD4. The protein is lost in approximately one-half of all PDACs,16 whereas nuclear reactivity is preserved in reactive and inflammatory diseases of the pancreas, such as chronic pancreatitis. Total loss of protein expression in PDAC results from biallelic mutations or mutation in one copy of the gene followed by either deletion or epigenetic silencing of the second copy. There is a strong correlation between SMAD4 mutations and loss of immunoreactivity, and thus, immunohistochemistry serves as a robust surrogate marker for the mutation (Figure 1, F). When evaluating this stain, adjacent benign tissue, such as stroma and inflammatory cells, should be regarded as an internal control. Interestingly, the SMAD4 wild-type tumor has been shown to have a better prognosis when compared to tumors with SMAD4 mutations.17 Finally, a number of genetic mutations are also observed in pancreatic carcinomas, which distinguish them from benign processes (Table 2) but not necessarily from noninvasive pancreatic neoplasia, such as pancreatic intraepithelial neoplasia.18 The most frequent among those genetic mutations are KRAS, TP53, SMAD4 and CDKN2A/p16.19,20 Virtually all pancreatic carcinomas will have one or more of these mutations.

### Chronic Pancreatitis

In benign conditions such as chronic pancreatitis, other than an occasional large duct, few glands should be seen in the interlobular septae (Figure 2, A). Glands located within lobules, regardless of the degree of atypia, would suggest a “benign” interpretation. It should be remembered that a high percentage of pancreata, particularly those in elderly individuals, can show intrapancreatic fat, and thus, the presence of atypical ducts within fat is not diagnostic for carcinoma and does not constitute extrapancreatic invasion—a detail that is relevant in the staging of pancreatic carcinoma, specifically the distinction of PT2 from PT3 tumors. In chronic pancreatitis, reactive nuclear atypia is seen, but variation in nuclear size should be minimal. Benign and reactive ducts typically show dense eosinophilic cytoplasm (Figure 2, B). In contrast, many adenocarcinomas, especially well-differentiated carcinomas, show abundant, pale, apical cytoplasm (Figure 1, E), which gives the cells a low nuclear to cytoplasmic ratio, a

<table>
<thead>
<tr>
<th>Table 1. Helpful Diagnostic Features of Chronic Pancreatitis and Pancreatic Ductal Adenocarcinoma</th>
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<tbody>
<tr>
<td><strong>Feature</strong></td>
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<tr>
<td>Desmoplastic stroma</td>
</tr>
<tr>
<td>Irregular ducts with incomplete lumina</td>
</tr>
<tr>
<td>Nuclear variation of &gt;4:1 within a gland</td>
</tr>
<tr>
<td>Cytoplasma</td>
</tr>
<tr>
<td>Lobular architecture maintained</td>
</tr>
<tr>
<td>Nonlobular distribution of glands</td>
</tr>
<tr>
<td>Association of ducts with arteries</td>
</tr>
<tr>
<td>Perineural invasion</td>
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2. Diagnostic Problems in Pancreatobiliary Neoplasia—Bledsoe et al
Figure 1. Pancreatic ductal adenocarcinoma. A, Atypical angulated ducts with abundant surrounding desmoplastic stroma. B, Haphazardly organized glands outside of the normal ductal distribution, within fat and fibrous tissue adjacent to a large muscular vessel. C, The presence of isolated glands adjacent to a medium-sized artery on frozen section is highly suggestive of an invasive carcinoma. D, Perineural invasion is a useful diagnostic feature of pancreatic ductal adenocarcinoma, particularly in cases with deceptively benign-appearing malignant glands. E, Conventional features of pancreatic ductal carcinoma include angulated glands with incomplete lumina, pale cytoplasm, intraluminal necrotic debris, and surrounding desmoplastic stroma. F, Loss of SMAD4/DPC4 expression in atypical glands is the most useful biomarker for pancreatic ductal adenocarcinoma. Note that the islets provide a robust positive internal control (hematoxylin-eosin, original magnifications ×100 [A and B], ×200 [C], ×400 [C inset, D, and E]; SMAD4, original magnification ×400 [F]).
common finding in PDAC and one that can create a deceptively bland appearance. Islets can be especially problematic mimics of carcinoma in chronic pancreatitis. Typically, islets are relatively unaffected by the inflammatory process and appear as small, benign-appearing nests of cells embedded in fibrotic stroma. However, in pancreatitis islets may become hyperplastic or diffuse and can be closely associated with nerves and muscular vessels, mimicking endocrine neoplasia or poorly differentiated carcinoma, particularly on frozen section.

The distinction of autoimmune and paraduodenal pancreatitis from PDAC may be especially difficult clinically and radiologically but is usually straight forward histologically. Details of these entities have been previously described in depth. The presence of storiform-type fibrosis and obliterator phlebitis would indicate type 1 autoimmune pancreatitis, whereas a periductal infiltrate accompanied by neutrophilic abscesses would support type 2 autoimmune pancreatitis. The key ancillary test for the diagnosis of type 1 autoimmune pancreatitis is an immunohistochemical assay for immunoglobulin G4 (IgG4). Notably, approximately 10% of pancreatic adenocarcinomas are associated with increased IgG4 plasma cells, so correlation with histomorphology is required. In paraduodenal, or groove, pancreatitis, the mass lesion is located in the groove between the duodenum, the common bile duct, and the pancreatic head, adjacent to the minor papilla. Fibrosis involves both the duodenal wall and the adjacent pancreas. Embedded within the lesion are cystic spaces lined by granulation tissue, prompting the designation cystic dystrophy of heterotopic pancreas, or paraduodenal wall cyst, and exuberant Brunner gland hyperplasia is invariably seen. Although this form of pancreatitis may mimic pancreatic carcinoma clinically, the histologic features are generally unequivocally benign and the few “atypical” pancreatic ducts embedded within the lesion do not raise a concern for malignancy. However, similar to other mass-forming variants of chronic pancreatitis, the strong clinical suspicion for malignancy may bias the pathologist into suspecting a well-differentiated adenocarcinoma.

### PANCREATIC DUCTAL ADENOCARCINOMA VERSUS DISTAL BILE DUCT AND AMPULLARY CARCINOMA

The ampullary region is anatomically and histologically complex because it serves as the confluence of the common bile duct, pancreatic duct, duodenum, and pancreas. Therefore, adenocarcinomas arising from these extrapancreatic structures and invading the pancreas may be difficult to distinguish from PDAC, although the latter is encountered considerably more often. Although the distinction is not easily made on a biopsy sample, the distinction is obligatory on a Whipple resection because each site has a specific TNM staging system, and the site of origin may affect the choice of adjuvant therapy and entry into clinical trials. An accurate diagnosis is contingent upon identification of the primary site of tumor involvement, which is accomplished through a proper gross dissection in which sections are taken that demonstrate the relationship between tumor, ampulla, periampullary duodenum, distal common bile duct, and pancreas. We find that is best accomplished through probing and opening anteriorly along both the common bile duct and pancreatic duct.

### Ampullary Carcinoma Versus Pancreatic Ductal Adenocarcinoma

Grossly, identification of the epicenter of the tumor in an extrapancreatic location such as the ampulla strongly suggests a nonpancreatic malignancy (Figure 3, A). Most pathologists refer to tumors arising from the ampullary papilla, the distal-most common bile duct and the pancreatic duct, and the common channel as ampullary carcinomas. Identification of the pattern of ampullary involvement is often possible and prognostically relevant categorization of ampullary carcinomas has recently been established. These 4 categories of ampullary carcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Role in Tumorigenesis</th>
<th>Pancreatic Cancers Showing Alteration, %</th>
<th>Mechanisms of Activation/Inactivation</th>
<th>Diagnostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Oncogene</td>
<td>&gt;90</td>
<td>Activating mutation in codons 12, 13, or 61</td>
<td>May provide supportive evidence for pancreatic adenocarcinoma and intraductal papillary mucinous neoplasms Caveat: Virtually all pancreatic intraepithelial neoplasia lesions also harbor KRAS mutation</td>
</tr>
<tr>
<td>TP53</td>
<td>Tumor suppressor gene</td>
<td>50</td>
<td>Mutation in one allele and loss of other allele</td>
<td>Strong reactivity for p53 is seen in 50% of PDACs Caveat: Immunoreactivity for p53 does not always correlate with p53 mutation, ie, p53 reactivity may be seen in reactive lesions</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Tumor suppressor gene</td>
<td>50</td>
<td>Homozygous deletion or mutation in one allele and loss of other allele</td>
<td>On immunohistochemistry, loss of SMAD4 is diagnostic for PDAC Caveat: Technically difficult stain, ensure positive control on tissue before reporting</td>
</tr>
<tr>
<td>CDKN2A/p16</td>
<td>Tumor suppressor gene</td>
<td>95</td>
<td>Homozygous deletion or mutation in one allele and loss of other allele or promoter methylation</td>
<td>Not helpful diagnostically</td>
</tr>
</tbody>
</table>

Abbreviation: PDAC, pancreatic ductal adenocarcinoma.
ampullary carcinoma about the spectrum of tumors that should be designated
use of this classification scheme may decrease confusion
ulceration. Among these groups, the ampullary-ductal
 localized at the tip of the ampullary papilla, often with
wise specified (papilla of Vater), in which the carcinoma is
intra-ampullary component; and (4) ampullary-not other-
involvement of the ampullary orifice but a relatively small
growth on the duodenal surface of the papilla with
duodenal carcinoma, which shows prominent exophytic
fibrous thickening of the ampullary duct; (3) periampullary-
pancreatobiliary type and shows invasion associated with
ampullary-ductal type carcinoma, which is usually a
primary site is not always possible in large tumors. At a
minimum, documentation of differentiation (intestinal,
ampulla usually have the opposite staining pattern, which is
shared with PDAC. Among these markers, CDX2, MUC1,
and MUC2 are particularly reliable, and the keratin stains
are relatively unreliable. However, these markers may be
less effective in distinguishing among phenotypes in
ampullary neoplasia than in pancreatic intraductal papillary
mucinous neoplasms (IPMNs) given the mix of cell types
normally found at the ampulla. Notably, cancerization of
the ampullary, bile ductular, and duodenal epithelium by
PDAC may occur and can be difficult to distinguish from
primary carcinoma in situ. The aforementioned immuno-
stains may be of use in distinguishing such colonization
from a primary dysplastic process of these sites. Like
PDAC, loss of DPC4 (SMAD4) expression has been
documented in ampullary carcinomas, and expression of
CEA and CA 19–9 is often seen and cannot be used to
differentiate these tumors.

Given the prominent fibrotic response and poor circum-
scription that can be seen in tumors arising at or near the
ampulla, gross and histopathologic distinction of the
primary site is not always possible in large tumors. At a
minimum, documentation of differentiation (intestinal,
ampullary, or mixed) should be reported because
studies have shown that intestinal-type ampullary carcino-
mas carry a better prognosis than do pancreatobiliary-type
tumors. However, the optimal method of distin-
guishing the intestinal from the pancreatobiliary phenotypes
remains to be determined—through morphology alone or
through a combination of morphology and immunohisto-
chemistry. A recent analysis used a combination of CDX2,
MUC1, and morphology to separate pancreatobiliary
(MUC1<sup>+</sup> CDX2<sup>−</sup>) from intestinal (MUC1<sup>−</sup> CDX2<sup>+</sup>) tumors
and showed that the phenotype, particularly when com-
bined with lymph node status, was highly predictive of
prognosis. Although pure forms of intestinal and pancreat-
obiliary phenotypes exist, many cases show elements of
both. Finally, it may be difficult or impossible to determine
the phenotype of non-tubule forming variants, such as
medullary or signet ring cell carcinomas.

**Distal Bile Duct Carcinoma Versus Pancreatic Ductal
Adenocarcinoma**

Distinction of PDAC from distal bile duct carcinoma
involving the pancreas may be even more problematic than
distinguishing ampullary tumors because of their intraran-
creatic location and identical pancreatobiliary-type mor-
phology and immunophenotype. The distinction between

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**Figure 2.** Chronic pancreatitis. A, Although atypical glands can be
seen in chronic pancreatitis, they are limited to a normal lobular
distribution and do not extend into interlobular fibrous septae. B, High-
power view of the A inset. In comparison to pancreatic ductal
adenocarcinoma, reactive ducts show complete lumina, more uniform-
ity in nuclear size, open chromatin, and relatively dense eosinophilic
cytoplasm (hematoxylin-eosin, original magnifications ×100 [A] and
×400 [B]).
these entities may be important for stratification of patients into clinical trials or treatment groups and has prognostic significance. Distal bile duct carcinomas are frequently misclassified as either PDAC or ampullary carcinoma, and survival in cases reclassified from PDAC is better than it is in true PDAC. The distinction may also have therapeutic implications; in one study, treatment of patients who have bile duct carcinoma (including advanced or metastatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer) with cisplatin plus gemcitabine (the latter being a key agent used to treat PDAC) was associated with a significant survival advantage as compared with use of gemcitabine alone, without the addition of substantial toxicity.

Helpful features that point to a distal bile duct origin include the finding of an in situ component, such as prominent biliary intraepithelial neoplasia or a biliary intraductal papillary neoplasm, as well as circumferential involvement of the bile duct by invasive carcinoma (Figure 3, D). In tumors situated near the bile duct, circumferential and symmetric involvement was found to be associated with bile duct dysplasia, whereas tumors with their epicenter away from the common bile duct were more likely associated with pancreatic intraepithelial neoplasia, suggesting a pancreatic origin. Therefore, when a tumor is centered in the bile duct, we are inclined to favor the diagnosis of bile duct carcinoma. Otherwise, we are hesitant to make a diagnosis of distal bile duct carcinoma, regardless of the extent of bile duct involvement. Currently, other than careful gross and histologic examination, reliable markers that can distinguish distal bile duct carcinoma from PDAC are lacking.

**UNCOMMON PANCREATIC INTRADUCTAL PAPILLARY LESIONS**

Intraductal papillary mucinous neoplasms are often seen in clinical practice, and although they may cause some diagnostic dilemmas, such as the differential with mucinous cystic neoplasms, the characteristic features of classic gastric-type, intestinal-type, and pancreatobiliary-type IPMNs are generally widely known and have been reviewed previously. In contrast, the diagnosis of oncocyty-type...
IPMNs, such as IOPNs and other infrequently encountered intraductal papillary lesions, such as intraductal tubulopapillary neoplasms and acinar cell carcinoma with intraductal growth, may cause more of a diagnostic dilemma given their degree of morphologic overlap and most pathologists’ lack of familiarity with these entities. Knowledge of the typical histology and characteristic immunohistochemical profiles of these lesions (Table 3) is helpful.

**Intraductal Oncocytic Papillary Neoplasm**

Intraductal oncocytic papillary neoplasms, like the other types of IPMNs, are often grossly cystic with mucin production and duct dilation. Histologically, they are characterized by a multilayered proliferation of atypical oncocytic cells with large nuclei, prominent nucleoli, and distinctive eosinophilic cytoplasm (Figure 4, A and B). Intraductal oncocytic papillary neoplasms show complex arborizing papillae, cribriform formations, and solid nests within the lumen of a dilated duct. Mucin-containing intraepithelial and intracellular lumina, as well as scattered goblet cells, may be seen (Figure 4, B). These neoplasms show diffuse high-grade dysplasia and may evolve into invasive carcinoma with similar oncocytic features. Intraductal oncocytic papillary neoplasms are typically positive for MUC6 (Figure 4, C) and MUC1, may be focally positive for MUC5AC, and are usually negative for MUC2 and CDX2, except in interspersed goblet cells. Intraductal oncocytic papillary neoplasms characteristically lack the KRAS mutations that are found in PDAC and many nononcocytic IPMNs.

**Intraductal Tubulopapillary Neoplasm**

Intraductal tubulopapillary neoplasms are relatively rare, making up approximately 3% of the intraductal neoplasms of the pancreas, and they are clinically and histopathologically distinct from IPMNs. Radiologically and grossly, they form solid masses with no mucin production. Histologically, the intraductal nodules are predominantly made up of closely apposed, tubule-forming glands and cribriform structures with uniform high-grade dysplasia (Figure 4, D and E). There is morphologic overlap with the pancreaticobiliary type of IPMNs, but the latter do not show complex tubulopapillary proliferations expanding and clogging the pancreatic duct, which are characteristic of ITPNs. The cuboidal cells show a modest amount of eosinophilic to amphophilic cytoplasm (Figure 4, E). Mitoses are frequently seen, and necrosis is more commonly seen than is seen in IPMNs. In contrast to IPMNs, mucin is absent, and the broad range of atypia is typically not seen. An associated invasive tubular carcinoma is often present. Stains for mucins, such as MUC1 and MUC6, can be positive but are more often negative than they are in IPMNs, including IOPN, and trypsin and chymotrypsin staining should be absent (Figure 4, F). Unlike IPMNs, these tumors are negative for KRAS mutations and, instead, show mutations in the PI3K pathway.

**Intraductal Acinar Cell Carcinoma**

Acinar cell carcinomas occasionally have a component of intraductal polyoid growth, and when predominantly intraductal, they can mimic other intraductal neoplasms, such as ITPNs and IOPNs. Grossly, such tumors show a nodular or polyoid intraductal growth pattern accompanied by duct dilation and surrounding parenchymal sclerosis. Like ITPNs, acinar cell carcinomas are typically composed of sheets of back-to-back acinar structures (Figure 4, G and H). True tumor-lining papillary structures may be seen. The nuclei are round, relatively uniform, and typically contain a single prominent central nucleolus (Figure 4, H). The presence of PAS+, diastase-resistant, apical, eosinophilic zymogen granules and intraluminal concretions are helpful features in distinguishing acinar cell carcinomas from other intraductal lesions but are not always present. Immunohistochemistry for trypsin (Figure 4, I) and chymotrypsin, both of which are positive in acinar cell carcinoma, may be invaluable for distinguishing intraductal acinar cell carcinoma from other intraductal lesions, such as ITPNs, which can appear quite similar on hematoxylin-eosin. The absence of keratin 19 (positive in virtually all ductal neoplasms) may be the first clue to an acinar cell proliferation.

Other neoplasms that may show a prominent intraductal pattern of growth include pancreatic endocrine neoplasms and invasive pancreatic adenocarcinomas, which may show a cystic papillary pattern of growth, mimicking an IPMN.

**INTRAHEPATIC CHOLANGIOCARCINOMA VERSUS CARCINOMA METASTATIC TO THE LIVER**

The differentiation of an intrahepatic cholangiocarcinoma (IHCC) from a metastatic tumor of unknown primary constitutes a major unsolved problem in diagnostic surgical

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**Table 3. Comparative Immunohistochemistry of Intraductal Oncocytic Papillary Neoplasms, Intraductal Tubulopapillary Neoplasms, and Intraductal Acinar Cell Carcinoma Immunohistochemistry**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Acinar Growth</th>
<th>CK7</th>
<th>CK19</th>
<th>MUC1</th>
<th>MUC2</th>
<th>MUC5AC</th>
<th>MUC6</th>
<th>CDX2</th>
<th>Trypsin</th>
<th>Chymotrypsin</th>
<th>DPC4/SMAD4</th>
<th>Other</th>
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<tbody>
<tr>
<td>IOPN</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>focal/–</td>
<td>focal</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Retainedb</td>
<td>Mitochondrial stains: phosphotungstic acid hematoxylin, Novelli stain, 111.3 antibody42</td>
</tr>
<tr>
<td>ITPN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>Retainedb</td>
<td>Other exocrine markers</td>
</tr>
<tr>
<td>IACC</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>Retainedb</td>
<td>Other exocrine markers</td>
</tr>
</tbody>
</table>

Abbreviations: IACC, intraductal acinar cell carcinoma; IOPN, intraductal oncocytic papillary neoplasm; ITPN, intraductal tubulopapillary neoplasm.

a Typical staining patterns based on the authors’ experience. Staining defined as typically positive (+), typically negative (–), variable (±), typically focally positive (focal–), or typically negative or only focally positive (focal–).
b Loss of DPC4/SMAD4 expression can be seen in a corresponding invasive component.
pathology. The morphologic appearance is of some value in this distinction. Most IHCCs are composed of well-formed, round to oval glands lined by low cuboidal epithelium that is devoid of mucin. The tumor frequently displays a "never-ending" glandular pattern in which the glands appear to merge into each other without intervening stroma (Figure 5, A). A substantial proportion of IHCC cases have a bland morphology and thus often bear a superficial resemblance to bile duct adenomas. Other common patterns of growth include solid nests and glands with cribriform structures. Focal areas of clear cell change are commonly observed (Figure 5, B). The glands are present in the abundant stroma, which is often hyalinized. The IHCC cases tend to differ morphologically from peribiliary and distal bile duct carcinomas, which instead resemble PDACs. Despite these characteristics, the poorly differentiated variant of IHCC cannot be distinguished with confidence from a metastatic carcinoma by histology or immunohistochemistry. That conundrum can result in an extensive clinical workup to exclude a potential tumor of nonhepatic origin.

Although immunohistochemical confirmation is required for a definitive diagnosis of IHCC, there are no markers unique to cholangiocarcinoma, and the foremost role of an immunohistochemical panel is to exclude a metastatic adenocarcinoma. However, the keratin profile is identical to a host of other tumors: keratin 7\(^+\) and 19\(^+\), and keratin 20\(^+\). Access to a definitive marker for IHCC would allow the oncologist to forego the obligatory, and often extensive, immunohistochemical workup. The introduction of 2 markers may change the current diagnostic algorithm in IHCC: albumin and IDH1/2. Recent data from our group suggest that the presence of albumin in IHCC, detected using branch chain chromogenic in situ hybridization technology (ViewRNA, Affymetrix, Santa Clara, California), can distinguish this neoplasm from metastatic adenocarcinoma (Figure 5, C and D). Thus, detecting albumin in a gland-forming tumor that lacks histologic evidence of hepatocytic differentiation is

Figure 4. Uncommon intraductal neoplasms. A through C, Intraductal oncocytic papillary neoplasm consisting of papillae lined by oncocytic cells with prominent nucleoli projecting into the lumen of the duct. Characteristic intraepithelial and intracellular lumen formation is sometimes seen (B). Immunostains for MUC6 (C) and MUC1 are typically positive. D through F, Intraductal tubulopapillary neoplasm. Complex tubular and cribriform growth filling the duct lumen. Distinction from intraductal oncocytic papillary neoplasm and acinar cell carcinoma can be made based on hematoxylin-eosin morphology and immunohistochemistry. Intraductal tubulopapillary neoplasms should be negative for trypsin (F) and chymotrypsin. G through I, Acinar cell carcinoma with prominent intraductal growth. Acinar morphology is almost always apparent, but a papillary growth pattern may be seen (G). Apical eosinophilic granularity may be appreciable on high power. Immunostains for exocrine proteases trypsin (I) and chymotrypsin are positive (hematoxylin-eosin, original magnifications ×200 [A, D, and G] and ×400 [B, E, and H]; original magnification ×400 [C, F, and I]).
evidence of IHCC.\textsuperscript{57} Similarly the presence of IDH1/2 mutations in a gland-forming tumor in the liver is highly suggestive of IHCC, although such mutations are present in only one-third of these neoplasms.\textsuperscript{58} IDH1/2 mutations are identified in a variety of other tumor types, such as glioma, chondrosarcoma, and acute myeloid leukemia; however, none of those tumors are likely to be confused with IHCC.

References

Figure 5. Intrahepatic cholangiocarcinoma. A, Intrahepatic cholangiocarcinoma is typically composed of infiltrating tubular glands with a “never-ending” pattern, in which one gland merges imperceptibly with another in the setting of background fibrosis. B, Solid nests with cytoplasmic clearing are frequently seen in intrahepatic cholangiocarcinoma. C and D, Chromogenic in situ hybridization for albumin is diffusely positive in the tumors depicted in A and B (hematoxylin-eosin, original magnification ×200 [A and B]; original magnification ×200 [C and D]; original magnification ×400 [D inset]).