Clinical History:
75-year old male presented with worsening epigastric pain, bloating, nausea, vomiting, fever, and chills. Lab tests showed CEA <1, CA19-9=4. MRI abdomen showed gastric outlet obstruction secondary to a 21 cm multilocular cystic epigastric mass of unclear origin. Biopsy diagnosis: spindle cell proliferation and low-grade epithelial proliferation worrisome for low-grade pancreatic adenocarcinoma.
An Unusual Papillary Neoplasm

New Frontiers in Pathology 2019
Case #16

Jiaqi Shi
GI Pathology
Case Presentation

- 75 yo male
- Worsening epigastric pain, bloating, nausea, vomiting, fever and chills
- 3+ years of constipation, diarrhea, and bloating, and 2 years of slow progressive weight loss
- CEA <1, CA19-9: 4
- MRI: gastric outlet obstruction 2/2 a 21 cm multilocular cystic epigastric mass of unclear origin. ?connect to pancreatic neck
- Bx at OSH: spindle cell proliferation and low grade epithelial proliferation worrisome for low grade pancreatic adenocarcinoma
Great news: resectable!

Whipple vs Distal pancreatectomy
During surgery...

Spilled some cyst content while dissecting it off a wall.

Created a full-thickness injury to colon while dissecting if off the tumor.

Tumor arising from the neck of the pancreas to the left of PV.

Decided distal pancreatectomy.

Lesions in the liver.
Large 25 cm cystic mass
Papillary excrescences
Tan/yellow thick purulent fluid and grumous material
Pancreas
Liver met
Liver met
Differential Diagnosis

- Intraductal papillary mucinous neoplasm (IPMN) with or w/o associated invasive adenocarcinoma
- Intraductal oncocytic papillary neoplasm (IOPN) with or w/o associated invasive adenocarcinoma
- Intraductal tubulopapillary neoplasm (ITPN) with or w/o associated invasive adenocarcinoma
- Solid pseudopapillary neoplasm
New WHO 2-tier grading:

- LG dysplasia
- HG dysplasia
Intraductal Tubulopapillary Neoplasm (ITPN)

An intraductal, grossly visible, tubule-forming epithelial neoplasm with high grade dysplasia and ductal differentiation without overt production of mucin. Focal tubulopapillary growth may be seen.

Courtesy of Drs. Volkan Adsay and Bahar Memis
Intraductal Tubulopapillary Neoplasm of the Pancreas
An Update From a Pathologist’s Perspective

Introduction—Intraductal tubulopapillary neoplasm (ITPN) is a rare intraductal epithelial neoplasm of the pancreas recently recognized as a distinct entity by the World Health Organization classification in 2015. It is often difficult to distinguish from intraductal papillary mucinous neoplasms (IPMNs), especially in small biopsies. It is important to recognize the disease as it is often indistinguishable from intraductal papillary mucinous neoplasms (IPMNs) on imaging, histology, and immunohistochemical studies, but it is discussed separately due to its clinical course and management.

Objectives—To provide a clinical, pathologic, and molecular update on ITPN with respect to clinical presentation, imaging findings, histopathologic features, differential diagnosis, biological behavior, molecular characteristics, and treatment options.

Materials and Methods—The PubMed database was searched for articles published between 2010 and 2020 using the terms “intraductal tubulopapillary neoplasm” and “ITPN.” The search was limited to English-language articles and included both clinical and basic science studies.

Results—Intraductal tubulopapillary neoplasm of the pancreas

Intraductal tubulopapillary neoplasm is a recently recognized distinct and rare entity of the pancreas, which may be indistinguishable from IPMNs. It is a rare entity of the pancreas and is often misdiagnosed as IPMNs. It is characterized by the presence of tubulopapillary structures lined by columnar epithelium with variable amounts of mucin production. The neoplasm is often indistinguishable from IPMNs on imaging, histology, and immunohistochemical studies, but it is discussed separately due to its clinical course and management.

Conclusion—Intraductal tubulopapillary neoplasm is a rare entity of the pancreas and is often misdiagnosed as IPMNs. It is characterized by the presence of tubulopapillary structures lined by columnar epithelium with variable amounts of mucin production. The neoplasm is often indistinguishable from IPMNs on imaging, histology, and immunohistochemical studies, but it is discussed separately due to its clinical course and management.

References—The references are not included in this summary.
Solid Pseudopapillary Neoplasm

- Solid
- Hyalinized stroma
- Hemorrhage
Solid
Hyalinized stroma
Foamy macrophages
Uniform nuclei

Nuclear groove
Perinuclear vacuoles
Oncocytic changes
Clear cell changes
Nuclear β-catenin
Other Papillary Neoplasms?
Majority of PDAC are solid and characterized by small infiltrating tubules in desmoplastic stroma.
PDAC can have papillary pattern

Cystic Papillary Pattern in Pancreatic Ductal Adenocarcinoma: A Hereetofore Undescribed Morphologic Pattern That Mimics Intraductal Papillary Mucinous Carcinoma

Paul J. Kelly, MB, BCH, FRCPath,* Shweta Shinagare, MD,† Nisha Sainani, MD,‡
Xiao Hong, MD,† Cristina Ferrone, MD,§ Omer Yilmaz, MD, PhD,‡
Carlos Fernández-del Castillo, MD,§ Gregory Y. Lauwers, MD,† and Vikram Deshpande, MD†

- 10 cases of PDAC with intraluminal papillary pattern
- Can be the predominant pattern
- 7 died of disease, 1 alive with widely metastatic disease, 2 lost follow up
Histologic Evaluation

Papillary changes in PDAC
Majority of pancreatic ACC are solid tumor
ACC can have papillary pattern

Intraductal and Papillary Variants of Acinar Cell Carcinomas

A New Addition to the Challenging Differential Diagnosis of Intraductal Neoplasms

Olca Basturk, MD,* Giuseppe Zamboni, MD, † David S. Klimstra, MD, ‡ Paola Capelli, MD, †
Aleodor Andea, MD,* Nabil S. Kamel, MD,* and N. Volkan Adsay, MD*

- 7 cases of ACC with intraductal or papillary growth pattern
- Relatively small and less metastasis than traditional ACC

Papillary pattern
Intraductal papillocystic pattern

Acidophilic secretions

Am J Surg Pathol
2007;31:363–370
Coming back to our case...

Papillary Acidophilic secretions
Acidophilic secretions
Papillary
Uniform nuclei
Prominent nucleoli
Eosinophilic cytoplasm
Mitosis
Acinar pattern

Prominent nucleoli

Eosinophilic cytoplasm
Flat cyst lining

Acinar pattern
Flat cyst lining
Acinar pattern
Basophilic cytoplasm
Prominent nucleoli
Trypsin
If you are still not convinced:

BCL-10
Trypsin+ secretions
Acinar Cell Carcinoma with papillary and cystic features
Patient Follow Up

- Started Gemcitabine and later Capecitabine
- CT after 6 cycles and 9 months after surgery: stable disease
- Molecular testing:
  - Sequencing analysis of 20 genes (Invitae Pancreatic Cancer Panel): Negative
  - PanCAN referred to Perthera (molecular profiling and precision medicine): NRAS (no KRAS), CTNNB1, SMAD4, MSS
Acinar Cell Carcinoma

- Highly cellular
- Lobular
- Scant fibrous stroma
- Necrosis
Acinar Cell Carcinoma

Different architectural patterns, often mixed

Acinar and solid most common
Acinar Cell Carcinoma

BE AWARE!

- Rare subtypes:
  - Oncocytic
  - Spindle
  - Clear
  - Pleomorphic
  - Intraductal
  - Papillary

Acinar Cell Carcinoma

Ideally...

- Eosinophilic granular cytoplasm
- Basally located nuclei
- Prominent nucleoli
Acinar Cell Carcinoma

Real life - Uniform nuclei

Acinar

Eosinophilic/ basophilic cytoplasm
# Acinar Cell Carcinoma IHC

<table>
<thead>
<tr>
<th>ACCs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromogranin A*</td>
<td>0/49</td>
</tr>
<tr>
<td>Synaptophysin*</td>
<td>0/49</td>
</tr>
<tr>
<td>Trypsin</td>
<td>46/48 (96%)</td>
</tr>
<tr>
<td>COOH-terminal BCL10</td>
<td>40/47 (85%)</td>
</tr>
<tr>
<td>CEL</td>
<td>29/32 (91%)</td>
</tr>
<tr>
<td>Amylase</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>Lipase</td>
<td>9/30 (30%)</td>
</tr>
<tr>
<td>p53</td>
<td>6/28 (21%)</td>
</tr>
<tr>
<td>CK19</td>
<td>29/34 (85%)</td>
</tr>
<tr>
<td>CK7</td>
<td>25/28 (89%)</td>
</tr>
<tr>
<td>β-Catenin</td>
<td></td>
</tr>
<tr>
<td>Membrane</td>
<td>24/25 (96%)</td>
</tr>
<tr>
<td>Nuclear</td>
<td>1/25 (4%)</td>
</tr>
<tr>
<td>PDX1</td>
<td>21/24 (87%)</td>
</tr>
</tbody>
</table>

* >30% positive. 14/49 have <30% positivity

### Key Genetic Alterations in Pancreatic Tumors

**SMAD4, BRCA2, RASSF1, ID3, ARID1A, CDKN2A, CTNNB1** are also frequently affected in ACC.

#### Table 1
Pancreatic neoplasms with their key genetic alterations

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Major Genetic Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>KRAS, CDKN2A, GNAS, RNF43, SMAD4, TP53,</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor/carcinoma</td>
<td>MEN1, ATRX, DAXX, TSC2, PTEN, Rb, TP53, VHL</td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>CTNNB1</td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>TP53, APC, SND1-BRAF, allelic loss on chromosome 11p</td>
</tr>
<tr>
<td>Pancreatoblastoma</td>
<td>Loss of chromosome 11p, CTNNB1, APC</td>
</tr>
</tbody>
</table>
Acinar Cell Carcinoma Treatment

Surgery significantly improves OS

25% 5-yr survival

Resected 5-yr survival:
ACC-72%
PDAC-16%

Only stage related to prognosis

SND1-BRAF fusion:
sensitive to MEK inhibitors
Take Home Message

- Not all papillary neoplasms of the pancreas is IPMN
- Not all acinar cell carcinomas have prominent nucleoli
- Pay close attention to cytological and architectural features
- IHC can be helpful to confirm your H&E impression
Thank you!
CASE #16

DIAGNOSIS: Acinar cell carcinoma with papillary and cystic features

CLINICAL HISTORY:
75-year old male presented with worsening epigastric pain, bloating, nausea, vomiting, fever and chills. Lab tests showed CEA <1, CA19-9=4. MRI abdomen showed gastric outlet obstruction secondary to a 21 cm multilocular cystic epigastric mass of unclear origin. Biopsy diagnosis: spindle cell proliferation and low grade epithelial proliferation worrisome for low grade pancreatic adenocarcinoma

MICROSCOPIC DESCRIPTION:
At low magnification, there is mostly a papillary proliferation of an epithelioid neoplasm with abundant eosinophilic secretions. Cystic areas are also present. At higher magnification, the neoplastic cells are columnar and have abundant eosinophilic cytoplasm, uniform oval nuclei, and prominent nucleoli. Mitotic figures are frequently seen. Some areas of the cyst lining are composed of epithelial cells with acinar architecture, basophilic granular cytoplasm and prominent nucleoli. Immunohistochemical stains showed the neoplastic cells are positive for acinar markers trypsin and Bcl-10.

DISCUSSION:
Although the diagnosis of pancreatic acinar cell carcinoma (ACC) is relatively straightforward most times, rare variants of ACC can be easily misdiagnosed as other pancreatic neoplasms, including malignant ductal adenocarcinoma, neuroendocrine neoplasms (NEN), and benign precursor lesions such as intraductal papillary mucinous neoplasm (IPMN). Classic ACC is characterized by a hypercellular and lobular epithelial neoplasm with cells that have eosinophilic granular cytoplasm, uniform nuclei, and a single prominent nucleolus. However, ACC variant with cystic, intraductal, and papillary growth patterns have been described. Distinguishing a papillary variant of ACC from IPMN or other papillary neoplasms of the pancreas can be challenging with limited sampling and in the absence of ancillary studies.

Histological features that are consistent with ACC include eosinophilic granular cytoplasm, uniform nuclei, and prominent nucleoli. The eosinophilic secretions and absence of mucin are also clues that point to ACC. Looking for areas with more typical acinar morphology is also helpful for differential diagnosis. IPMN often has more mucin and lack of eosinophilic secretion. Immunohistochemical stains with acinar markers (trypsin, chymotrypsin, and Bcl-10) can further confirm the morphologic impression.

Genetically, TP53, APC, SMAD4, SND1-BRAF, BRCA2, CDKN2A, CTNNB1 mutations or fusions are some of the most frequently discovered alterations in
ACC. Microsatellite instability has also been identified in 8-14% of ACC. However, the most common molecular alterations found in ductal adenocarcinoma (KRAS), cystic neoplasms (GNAS and RNF43), and NENs (MEN1, DAXX, and ATRX) are rarely found in ACC.

REFERENCES


