Cystic and Intraductal Neoplasms of the Pancreatobiliary Tract

Pancreatobiliary Pathology Society
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Michelle Reid reported no relevant financial relationships
Cytologic Assessment of Cystic/Intraductal Lesions of the Pancreatobiliary Tract

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Cystic and Intraductal Pancreatic (and biliary) lesions

1. Mucinous
   - IPMN
   - MCN

2. Non-mucinous (minimally mucinous)
   - Intraductal
     - IOPN
     - ITPN
     - SCOPD
   - Others
     - Serous
     - SPN

Others

Degenerative
- PDAC
- Acinar cell carcinoma
- NENs
Case for Discussion

- 35 yo female
- Abdominal “fullness”
- Serum CA 19-9 > 100,000 U/mL
- 15cm cystic and solid pancreatic mass
- CT-guided FNA performed
Smear with thick colloid-like mucin
Evenly spaced epithelial cells present in a large flat sheet with cytoplasmic mucin.

Honeycomb sheets of bland cells with cytoplasmic pink mucin, round nuclei and low N/C ratio.
Cells with mild nuclear pleomorphism, high N/C ratio, no mucin, background debris
Cell block has bland mucin-filled epithelial cells as well as cells with irregular hyperchromatic nuclei and high N/C ratio.
Cytopathology Report

• Pancreas, CT-guided FNA biopsy:
  • Neoplastic cells present.
  • Neoplastic mucinous cyst with high-grade atypia (at least high-grade dysplasia; suspicious for invasion)
Terminology & Nomenclature for Pancreatobiliary Cytology (PSC Guidelines, 2014)

Classification Scheme:
- Non-diagnostic
- Negative (for malignancy)
- Atypical
- Neoplastic
- Suspicious (for malignancy)
- Positive/malignant

A) Neoplastic: Benign
- Serous cystadenoma, teratoma, schwannoma

B) Neoplastic: Other
- IPMN, MCN, SPN
- Well differentiated PanNET

Pitman et al. Standardized Terminology and Nomenclature for Pancreatobiliary Cytology:
The Papanicolaou Society of Cytopathology Guidelines.
Diagn Cytopathol 2014;42:338-350
Pancreatic Cysts

- Incidental pancreatic cysts have an annual incidence of ~12%
  - Increases with patient age
- Major management problem for clinicians
- Need for non-invasive diagnostic tests for risk/management stratification

Lee et al. Am J Gastroenterol. 2010 Sep;105(9):2079-84.
Interdisciplinary work-up is required to identify **high risk cysts**

**Low-risk pancreatic cysts**
- Low risk of harboring malignancy
- Resected:
  - If symptomatic
  - When definitive diagnosis is impossible on imaging/cytology

*Examples:*
- Pseudocyst
- Serous cystadenoma
- Squamoid cyst of pancreatic duct

**High-risk pancreatic cysts**
- High risk for carcinomatous change
- Resection is dependent on:
  - Clinical factors
  - Radiology, size, mural nodule, duct
  - Cytology, cyst fluid analysis

*Examples:*
- **Intraductal papillary mucinous neoplasm (IPMN):** 30% harbor invasion
- **Mucinous cystic neoplasm (MCN):** 17% harbor invasion
Interdisciplinary Work-up of Cystic Pancreatic Lesions

1. Imaging
   - Ductal (main vs branch duct) vs non-ductal cyst

2. Cyst fluid analysis
   - CEA, amylase
   - Molecular studies

3. Cytologic evaluation
Interdisciplinary Work-up of Cystic Pancreatic Lesions

1. Imaging

2. Cyst fluid analysis
   - CEA, amylase
   - Molecular studies (covered later)

3. Cytologic evaluation
Role of Rapid onsite evaluation (ROSE) in the Evaluation of Pancreatic Cysts

- Cyst fluid analysis begins at the time of ROSE
- Use of ROSE in pancreatic cyst evaluation is now controversial
- ROSE can assess for presence of thick mucin on smears
  - Allows immediate feedback to gastroenterologist

**BUT**

- ROSE can potentially waste precious cyst fluid
  - Cyst fluid needed for CEA, amylase, molecular studies
- ROSE is helpful in sampling/evaluating a solid component within a cyst
#2: Cyst Fluid Analysis: CEA is still useful (but imperfect)

- Requires ~ 0.5 ml of fluid
- Categorical cut-offs vary from lab to lab
  - 192 ng/ml historically, or 30 – 800 ng/ml
- Elevated CEA is suggestive of a mucinous cyst
- **BUT** non-mucinous cysts may also have elevated CEA levels

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<thead>
<tr>
<th></th>
<th>EUS</th>
<th>Cytology</th>
<th>CEA</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>56%</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>Specificity</td>
<td>45%</td>
<td>83%</td>
<td>84%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>51%</td>
<td>59%</td>
<td>80%</td>
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</tbody>
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Interdisciplinary Work-up of Cystic Pancreatic Lesions

1. Imaging
2. Cyst fluid analysis
   • CEA, amylase
   • Molecular studies
3. Cytologic evaluation
3. Cytologic Evaluation of Cystic and Intraductal Pancreatobiliary Lesions
Task #1: Exclude Cystic Adenocarcinoma (PDAC)

Large duct variant of adenocarcinoma often has a cystic component.
Task #2: Is it mucinous or not?
Is it a neoplastic mucinous cyst?

Neoplastic mucinous cyst (NMC) = both IPMN and MCN
Distinction between IPMN and MCN is not realistic on cytology (and not required)!

Ovarian type stroma is required for diagnosis of MCN but is rarely sampled on cytology samples.
Less complex NMCs may only yield MUCIN on FNA.

Aspiration often yields “thick mucin” only, which is a significant finding in the right clinical context.
Cytologic Findings in Neoplastic Mucinous Cysts

Diff-Quik stain

Thick colloid-like magenta mucin is difficult to express from needle

Papilla

Note nuclear atypia with crowding and hyperchromasia

H&E stain
Task #3: If NMC, is there high-grade atypia?

A MCN with areas of low and high-grade dysplasia.
Histologic classification

- 2-tier system of LGD vs HGD ("intermediate" is now LGD)

Cytologic classification

- 2-tier system of low-grade vs high-grade "atypia"
- High-grade atypia = HGD/CIS and invasive carcinoma

Low-Grade Atypia

- Bland mucin-containing cells in sheets
- Round nuclei, low N/C
- Even chromatin
- Inconspicuous nucleoli
Low-Grade Atypia in a NMC Case

- Cell block had gastric type mucinous epithelium
- Bland columnar cells in honeycomb sheets, with cytoplasmic mucin, low N/C
- Branching papillae, broad fronds
“High-Grade Atypia” in NMCs

• Incorporates high-grade dysplasia (CIS) AND invasive carcinoma

• High-risk of invasive carcinoma on resection
  • Sensitivity 72%, Specificity 85%, Accuracy 80%

High-Grade Atypia in NMCs

Single cells (small cells with high N/C, irregular nuclei)

3-D clusters of small cells with high N/C, change in chromatin pattern

Necrosis
Caveats in the Cytologic Diagnosis of NMCs

• GI contaminants can mimic NMCs cytologically
• Some IPMN subtypes are “less mucinous” than others
Epithelial Contaminants in Pancreatic FNA Samples

1. Duodenal; seen with FNAs of head/uncinate lesions
   - Honeycomb sheets (no detached cells/3-D clusters);
   - 2-cell population of enterocytes and goblet cells

2. Gastric; seen with FNA of body/tail lesions
   - Goblet cells
Gastric epithelial contaminants vs Gastric IPMN ??
Major dilemma

Canned comment:
“If truly from the cyst, then it may represent gastric type IPMN”

Gastric foveolar cells have U shaped mucin cups in superficial 1/3 of cell
Follow-Up on 35 yo: Distal Pancreatectomy: 25 cm MCN

Ovarian-type stroma c/w MCN
Case for discussion

- 56 yo F
- Pancreatic head cystic and solid mass (6cm)
- EUS-FNA performed
Flat sheet of “Hurthle”-loid cells
Note the lack of cytoplasmic mucin and the sheets of granular cells with prominent peripheral nucleoli.
Numerous sheets and papillae lined by pseudostratified oncocytic epithelium.
• Pancreas, EUS-guided FNA biopsy:
  • Neoplastic cells present.
  • Intraductal oncocytic papillary neoplasm (IOPN) with high-grade atypia (*by definition*)
3 Histologic Subtypes of IPMN

Oncocytic Type has been moved
Cystic and Intraductal Pancreatic lesions

Mucinous
- IPMN
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Non-mucinous (minimally mucinous)
- IOPN
- ITPN
- SCOPD

Intraductal
- IOPN

Others
- Serous
- SPN

Degenerative
- PDAC
- Acinar cell carcinoma
- NENs
• IOPN is considered a NMC with “high-grade atypia”

• Classical cytologic features make definitive diagnosis possible on FNA
  • Oncocytic cells with scant mucin, large nuclei, prominent eccentric nucleoli
  • Papillae and punched out intercellular spaces

• BUT always exclude degenerative solid neoplasms
  • Oncocytic NET, acinar cell carcinoma, and metastatic hepatocellular carcinoma
**Cytologic distinction of IOPN from Cystic PanNET and Acinar cell carcinoma**

**IOPN**
- Papillae covered by multilayered oncocytic epithelium

**Oncocytic PanNET**
- NET with oncocytic cytoplasm and oval nuclei
- Synaptophysin

**Classical PanNET**
- NET with prominent nucleoli and papillae: Salt & pepper chromatin

**ACC**
- Irregular nuclei, pink cytoplasmic zymogen granules, prominent nucleoli; No papillae
- Trypsin+, BCL10 +
Other Non-Mucinuous Intraductal Lesions
Cystic and Intraductal Pancreatic lesions

Mucinous
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- MCN

Intraductal
- ITPN
- SCOPD

Non-mucinous

Others
- Serous
- SPN
- Degenerative
- PDAC
  Acinar cell carcinoma
- NE Neoplasms
Intraductal Tubulopapillary Neoplasm (ITPN)

• Intraductal predominantly tubule-forming neoplasm
• Composed of non-mucinous epithelium with high-grade dysplasia
• May occur in pancreatic duct or biliary tree
• May be sampled on FNA or bile duct brushing depending on location
Cytologic Findings in an FNA of ITPN

Cellular FNA with branching sheets of crowded cells with back to back punched out tubular spaces and no mucin

Crowded cells, back to back tubules

Cell block showed cribriform tubules
Cytologic Findings in Bile duct Brushing of an ITPN

Back to back tubules are more difficult to appreciate in liquid-based samples.

High-grade cytology.

Corresponding cell block with back to back non-mucinous tubules.
Case for Discussion

• 51 year old female had an incidental 3cm pancreatic tail cyst
• Cyst fluid analysis:
  • Amylase 38,161 U/L
  • CEA 131.5 ng/ml
• FNA performed
Paucicellular sample with scattered honeycomb sheets of bland non-mucinous epithelium
Squamoid Cyst of the Pancreatic Duct

Cell block with strips of eosinophilic cells in a syncytial arrangement

P63+ (brown)/CK5+(red) mucicarmine negative

Layered p63 + cells
Columnar cell layer on the right and squamoid layer on the left.
Squamoid Cyst of Pancreatic Duct (SCOPD)

- Non-mucinous cystic dilatation of pancreatic duct
- Often misdiagnosed as mucinous cysts on imaging
- Associated with **CEA** and amylase (which is misleading)
- Lined by 2 types of epithelium
  - *Glandular* epithelium on the **luminal** surface
  - *Squamous* /transitional epithelium beneath (**basal** location)
    - Lacks granular layer and keratinization

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    - Degenerative
      - PDAC
      - Acinar cell carcinoma
      - NE Neoplasms
Central stellate scar, radiating septa and cyst locules lined by clear cuboidal epithelial cells

Reid et al. Serous cystic neoplasms of pancreas: Clinicopathologic and molecular characteristics. Sem Diag Pathol. 2014.
Serous Cystadenoma

• During ROSE cyst fluid is thin and clear not mucoid and thick
• Cyst fluid analysis shows low amylase and CEA
• Unfortunately many of these are non-diagnostic on FNA
• Clear cells are PAS, Keratin, GLUT1, α-inhibin (+)
• Accuracy of imaging, cytology and cyst fluid analysis is ONLY 20%
Solid Pancreatic Tumors Can Undergo Cystic Degeneration
Branching FVCs lined by bland cells with high N/C ratio, open, vesicular chromatin on Papanicolaou stain

Solid-Pseudopapillary Neoplasm (SPN)
Fibrovascular Cores in SPN

Magenta colored myxoid stroma on Diff Quik

Bluish-grey myxoid stroma on Pap; Nuclear grooves

Cell Block

β-catenin is + (nuclear)

LEF1 +, keratin -
• Mucinous cysts are the most common type of pancreatic cyst
  • Distinction between IPMN vs MCN is difficult (and not required) on cytology
  • Always grade the degree of atypia in mucinous cysts

• Non-mucinous cystic and intraductal pancreatic/biliary lesions:
  • IOPN and ITPN
  • SCOPD (extremely rare)

• Non-mucinous non-ductal pancreatic lesions include:
  • Benign (Serous cystadenoma)
  • Malignant (degenerative) cysts
    • PDAC, Acinar cell carcinoma, solid-pseudopapillary neoplasm (SPN), NET
    • Metastatic tumors should be considered in patients with prior h/o malignancy
Cytologic Evaluation of Cysts

• Correlation of imaging and chemical/molecular analysis with cytology is important for accurate diagnosis of cysts
• Always grade atypia/dysplasia in mucinous cysts
• Some intraductal lesions are non-mucinous
• Cystic forms of solid tumors should be kept in differential diagnosis when evaluating cysts

THANK YOU!
References

• Lee et al. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010 Sep;105(9):2079-84.
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