Endoscopic Ultrasound-guided FNA Cytology of the Pancreas

67th Annual California Society of Pathologists
2014

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Overview

• Review EUS-FNA technique and equipment
• Recognize contaminating GI elements introduced by EUS technique
• Review cytological features of selected lesions of the pancreas
• Understand the benefits and limitations of ancillary tests in the evaluation of pancreatic FNA samples
Endoscopic Ultrasound FNA Equipment
Endoscopic Ultrasound FNA

Trans-duodenal approach: most pancreatic head lesions

Trans-gastric approach: most pancreatic body & tail lesions

Courtesy JHMI
Endoscopic Ultrasound Technique

• Advantages
  – Ability to image/sample small lesions (< 2 cm)
  – Accurate preoperative staging through imaging of the neurovascular axis and sampling of peripancreatic lymph nodes
  – Ability to sample more than one site during the same procedure
  – Use of Doppler ultrasound to identify and avoid nearby vascular structures
  – Continuous visualization of the needle tip during aspiration
  – Lower complication rate than CT-guided FNA (1-2% compared to 5%)
  – Lower costs than CT-guided FNA

• Disadvantages
  – High operator learning curve (more time consuming)
  – Higher rate of GI epithelial contamination than CT-guided FNA
Pancreas EUS-FNA Cytology

• Sensitivity: 60 - 100%
  – lesional size, lesional characteristics (solid vs. cystic),
    operator experience, number of passes, and the
    availability of rapid on-site evaluation.

• Specificity: 86 - 100%
  – potential causes of false positive diagnoses include
    misinterpretation of gastrointestinal contaminants and
    over interpretation of reactive atypia.
Sample Preparation

• **Rapid On-Site Evaluation**
  – direct communication between the pathologist and endoscopist
  – triaging and obtaining of additional material for ancillary testing when needed (increases the diagnostic yield of cytological specimens)
  – discontinue the procedure once diagnostic material is obtained
  – Fixed, Toluidine blue or Rapid Pap stain

• **Smears: Pap stain, Romanowsky stain**

• **Additional material for ancillary studies**
  – Cell block (10% formalin-fixation)
  – Fluid Chemistry Analysis (1mL, red top tube, CEA & Amylase)
  – Flow Cytometry
Primary Role of Pathologist in Pancreatic FNA Cytology

• Rule out malignancy
  • 85 - 90% of pancreatic malignancies are ductal adenocarcinomas or one of its variants

• For cystic lesions, distinguish between lesions that may be managed conservatively (benign or indolent)
  – Pseudocyst, lymphoepithelial cysts
  – Serous cystadenoma

• from those that may need resection (pre-malignant or malignant)
  – Neoplastic Mucinous Cysts (IPMN, MCN)
  – Solid epithelial neoplasms with cystic degeneration
Assessment Prior to Cytomorphological Evaluation

• Location (head, body, or tail), size, and sampling approach (transduodenal or transgastric)?
• Patient age & gender
• Presentation & History: incidental, pancreatitis, alcoholism, autoimmune disease, or neoplastic process
• Solitary or multiple
• Infiltrative or well-circumscribed
• Invasion of adjacent structures or lymphadenopathy
• Solid or cystic
  – If cystic
    • Dilation of or connection to Main duct?
    • mural nodules?
    • Unilocular, multilocular, microcystic or oligocystic?
    • Evaluate quality & quantity of fluid
    • Request additional sample for cell block, fluid chemistry analysis (CEA, Amylase), or molecular analysis if necessary
Solid Pancreatic Lesions

• Ductal adenocarcinoma and variants (85%)
• Cellular epithelial neoplasms
  – Neuroendocrine tumor (2-4%)
  – Solid pseudopapillary neoplasm (1-2%)
  – Acinar cell carcinoma (1-2%)
  – Pancreatoblastoma (<1%)
• Metastases
Cystic Pancreatic Lesions

• Mucinous Cysts (*precursors to adenocarcinoma*)
  – Mucinous Cystic Neoplasm (MCN)
  – Intraductal Papillary Mucinous Neoplasm (IPMN)

• Non-mucinous Cysts
  – Pseudocyst (75%)
  – Serous cystadenoma
  – Squamous-lined cysts (Lymphoepithelial, dermoid, splenic epithelial inclusion cyst)
  – Solid tumors with cystic degeneration
    • Neuroendocrine tumor, Solid pseudopapillary neoplasm, Acinar cell carcinoma
Normal Pancreas

Duct, acini, and islets

Islets (arrow) are rarely seen in cytological samples.
Normal Pancreas: Ductal Cells

Flat, organized, orderly, “Honeycomb” sheets of non-mucinous epithelial cells.

Nuclei are evenly spaced, round to oval, with fine, evenly dispersed chromatin
Normal Pancreas: Acinar Cells

Small grape-like clusters of cells with voluminous granular cytoplasm & small round nuclei

Predominate in normal pancreatic aspirates and in early pancreatitis

Cytoplasm stains blue-green on Pap stain and purple on Romanowsky stain
Normal Pancreas: Lobule

Intact pancreatic lobules (on the left) may be seen on aspirate smears of normal pancreas and in pancreatitis.
GI Contaminant: Duodenum

Trans-duodenal sampling approach used for lesions of pancreatic head

Large flat sheets of non-mucinous cells with regularly dispersed goblet cells imparting a “starry-sky” appearance.

Nuclei are round and regular with even chromatin.
Crypt and villous architecture of duodenal mucosa can be seen as slender tubular or finger-like projections.
GI Contaminant: Duodenum

Lamina propria elements may be attached to duodenal epithelial groups and should not be confused with “cellular stromal fragments” of autoimmune pancreatitis.

The edge of the lamina propria is smooth and defined by an overlying basement membrane (arrow).
GI Contaminant: Duodenum

Brush border may be seen on lumenal edge (arrow).
GI Contaminant: Gastric Mucosa

Trans-gastric sampling approach used for lesions of pancreatic body & tail

Flat sheet or small clusters of bland appearing glandular cells with basally located small, round nuclei. Cytoplasmic mucin may be present and often confined to the upper third of the cytoplasmic compartment, forming “mucin cups” (arrow). Nuclear grooves and mild irregularities may be present. Similar epithelium, if present in a cystic pancreatic head lesion sampled via a trans-duodenal approach, may represent low-grade neoplastic mucinous cyst.
High Grade Adenocarcinoma

- 3D cell clusters
- Marked pleomorphism
- Hyperchromasia
- Nuclear enlargement, overlapping/crowding
- Single atypical cells
- Necrosis
Adenosquamous Carcinoma

- Defined histologically: >30% squamous differentiation
- Look for malignant glandular groups to exclude metastatic squamous cell ca from lung, cervix, esophagus (primary squamous cell ca of pancreas is extremely rare)
- Squamous differentiation (whether <, =, or >30%) is a poor prognostic indicator and should be mentioned in the report if present.
Undifferentiated Carcinoma with Osteoclastic-type Giant Cells

Non-neoplastic osteoclast type giant cells (CD68+, CK-)

Neoplastic epithelioid to spindle cell component (CK+/-, CD68 -/+)

May be associated with typical ductal adenocarcinoma (40%)

Rule out metastasis
Well-Differentiated Adenocarcinoma

- Minimal criteria:
  - Anisonucleosis (4:1)
  - Nuclear membrane irregularity
  - Architectural disarray
  - Nuclear enlargement (>2x size of red blood cells)
  - Other minor criteria: coarse or cleared chromatin, mitoses (atypical or several in one or more fields), macronucleoli

Lin F, Staerkel G. Cancer Cytopathol 2003; 99:40-50

If only rare clusters of cells with these features are present, a “suspicious” diagnosis can be considered.
Case 1

• 57 year old man with history of weight loss, alcohol use, and recurrent pancreatitis.

• EUS: An ill-defined mass in the pancreatic head measuring 2 cm by 1.5 cm. The borders are well-defined suggesting lack of invasion without regional lymph node enlargement.
Case 1

Ductal epithelial groups with mild architectural disarray, mild anisonucleosis, nuclear enlargement & focal membrane irregularities. The background is ‘dirty’ with scattered stromal fragments. Acini are sparse to absent.
Case 1

• Cytological diagnosis:
  – Cellular atypia in a background of chronic pancreatitis
  – Note: The degree of atypia in this sample is mild to focally moderate. Although these changes may be seen as part of a reactive process in the setting of chronic pancreatitis, a well-differentiated adenocarcinoma cannot be entirely excluded. Close clinical follow-up with additional sampling is recommended if clinical suspicion persists.
Chronic Pancreatitis

• Clinical
  • Abdominal pain radiating to the back, weight loss, diarrhea
  • May present as mass lesion and mimic carcinoma similarly to Autoimmune pancreatitis

• Cytology
  • Depends on stage of disease
    – earlier lesions: more cellular with acinar cells
    – later lesions: less cellular with ductal and fibrotic fragments
  • Grungy background, calcific debris, mild mixed inflammation
  • Mild ductal epithelial atypia without significant nuclear membrane irregularity or anisonucleosis
    – The presence of significantly atypical cell clusters should be reported in this setting and ductal adenocarcinoma mentioned as a possibility, with repeat biopsy suggested if there is evidence of disease progression or high index of suspicion
  • Autoimmune pancreatitis: cellular stromal fragments with plasma cells (correlate with serum IgG levels)
Case 2

• 67 year old man with back pain, abdominal discomfort, and weight loss.

• EUS: 2.3 cm by 2.8 cm mass in head of pancreas with ill-defined borders. The remainder of the pancreas has an appearance consistent with chronic pancreatitis.
The majority of the ductal groups show uniform oval nuclei with smooth borders and evenly distributed chromatin. Focally, there is irregular spacing, 3-4:1 anisonucleosis, nuclear enlargement, and nuclear membrane irregularity. Abundant mitoses were identified.
Case 3

- 58 year old woman with history of acute and chronic pancreatitis presents with vague abdominal pain.

- EUS: An irregular mass in the pancreatic head, measuring 2.6 cm by 3.2 cm. The borders are well-defined suggesting lack of invasion.
Case 3

Ductal cells with marked nuclear membrane irregularities, nuclear enlargement, 3-4:1 anisonucleosis, and architectural disarray with irregular internuclear spacing.
### Ancillary Studies to Distinguish Benign vs. Malignant Ductal Epithelium


<table>
<thead>
<tr>
<th>marker</th>
<th>Benign/Chronic Pancreatitis (%)</th>
<th>Ductal Adenocarcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCEA (+ cytoplasmic staining)</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>B72.3 (+ cytoplasmic staining)</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>p53 (&gt;20% nuclear staining)</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>DPC4 (lack of nuc. &amp; cyto. staining)</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Mesothelin (+ nuc. or cyto. staining)</td>
<td>5</td>
<td>95</td>
</tr>
</tbody>
</table>

- Beware of small sample size & staining heterogeneity
- Panel of markers necessary for adequate interpretation
- Cell block tissue material needed
Case 4

• 42 year old man with incidental pancreatic mass.

• EUS: A solitary, well-circumscribed, predominantly solid mass in the pancreatic body measuring 2.3 cm by 2.6 cm without evidence of invasion.
Case 4

Discohesive monomorphous cells

Plasmacytoid cells with fine, stippled chromatin

Arrangement in cords, ribbons & pseudorosettes

Granular cytoplasm with red metachromatic granules on Romanowsky stain
Case 4

• Cytological diagnosis:
  Pancreatic Neuroendocrine Tumor
Pancreatic Neuroendocrine Tumor

Background: Clean
Nuclei: Eccentric/plasmacytoid, small, round, oval, “salt-pepper”, small to prominent nucleoli, marked atypia may be seen.
Cytoplasm: Moderate to scant, cyanophillic to granular.

Cohesive pseudo-acinar arrangement

Bi-nucleation & prominent nucleoli

Pseudo-rosette, elongated cytoplasm, nuclear grooves
Pancreatic Neuroendocrine Tumor

- **Clinical**
  - 2-4% of pancreatic neoplasms
  - M=F
  - Any age, but typically in adults
  - Mostly in tail or body
  - Increasingly detected as incidental mass

- **Imaging**
  - Well-defined, well-circumscribed mass, usually < 3cm
  - May appear cystic

- **Cytology**
  - Cellular smears with intermediate sized cells arranged singly, in cords, ribbons, pseudorosettes, or pseudoacini. Thin delicate capillaries.
  - Smooth “salt-pepper” chromatin, occasional nucleoli, plasmacytoid & binucleated forms, metachromatic granules, occasional marked nuclear atypia
  - May rarely be oncocytic, clear, or pigmented

- **Ancillary Studies:** Chromogranin, Synaptophysin, CD56, Cytokeratin, ki-67
2010 WHO/ENETS Grading System for Pancreatic Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitoses (per 10 HPF)*</th>
<th>Ki-67 (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>G2</td>
<td>2-20</td>
<td>2-20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

* HPF = 2mm², at least 40 fields (at 40x magnification) evaluated in area of highest mitotic density and reported as number of mitoses per 10 HPF.

** Ki-67 labeling reported as % of 2000 tumor cells positive in area of highest nuclear labeling.

If grade differs based on mitotic count compared to ki-67 index, the higher grade is assigned.

Although additional studies are needed, preliminary studies show good correlation of grade between cytological and histological material (89%) based on assessment of ki-67 index.

Case 5

- 59 year old woman with vague abdominal pain and discomfort.

- EUS: 6.7 cm well-circumscribed mass in the pancreatic tail. The remainder of the pancreas has a normal appearance.
Clustered and dispersed cells with delicate round to elongated/spindled cytoplasm

Uniform round, oval, to elongated nuclei with fine chromatin, nuclear grooves & small nucleoli

Perivascular myxoid change and hyaline globules better seen in Romanowsky stain
Case 5

Ancillary Studies:

**Beta Catenin** + (nuclear)
CD10+
PR+

Chromogranin: –
Synaptophysin: rare weak +
CK: rare weak +
Alpha-1-anti-chymotrypsin: rare weak +
Alpha-1-anti-trypsin: +

Cytological diagnosis:
Solid Pseudopapillary Neoplasm
Solid Pseudopapillary Neoplasm

• Clinical
  – 1-2% of all pancreatic exocrine tumors
  – Almost exclusively in women
  – Younger to middle-age group (mean age, 35 years)
  – More commonly in tail, but can occur anywhere
  – Larger size (average 10 cm)
  – More commonly solid and cystic
  – Excellent prognosis (95% behave in benign fashion)

• Imaging
  – Well-demarcated, variably cystic mass in body or tail ± calcification

• Ancillary Studies:
  – Beta-catenin+, CD10+, PR+, CD56+, Synaptophysin -/+ , CK -/+ , Alpha-1-antitrypsin+, Alpha-1-antichymotrypsin+
Case 6

- 65 year old man with painless jaundice and abdominal pain.

- EUS: A 4.2 cm by 3.6 cm solid mass in the pancreatic head concerning for adenocarcinoma.
Case 6

- Prominent nucleoli
- Acinar formation
- Cellular smears with naked nuclei
- Moderate amounts of granular basophilic cytoplasm
- CB with plasmacytoid cells, prominent nucleoli, naked nuclei, granular debris
Acinar Cell Carcinoma

Clinical
Rare (1-2%)
M>F
5-7th decade, but can occur in younger patients (teenagers)
Most common in pancreatic head, but may involve body or tail

Imaging
Well-circumscribed mass with pushing rather than infiltrative borders

Ancillary testing
**Trypsin**+ (most useful), PASD+, CK+, Chymotrypsin+, Lipase+, Alpha-1-antichymotrypsin+, Alpha-1-antitrypsin+, CD56-, Chromogranin-, Synaptophysin-
Acinar cell ca & Neuroendocrine tumors can be subtle and mimic each other or mimic normal acinar groups

Look for nuclear & cytoplasmic features, architectural disarray, & obtain material for immunostains
Helpful Immunostains for Cellular Epithelial Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>Synapto</th>
<th>Chromo</th>
<th>CD56</th>
<th>CD10</th>
<th>beta-Catenin</th>
<th>Trypsin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SPN</td>
<td>-/+</td>
<td>-/focal</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+ (nuclear)</td>
<td>-</td>
</tr>
<tr>
<td>ACC</td>
<td>+</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
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Cystic Pancreatic Lesions

• Mucinous Cysts (*precursors to adenocarcinoma*)
  – Mucinous Cystic Neoplasm (MCN)
  – Intraductal Papillary Mucinous Neoplasm (IPMN)

• Non-mucinous Cysts
  – Pseudocyst (75%)
  – Serous cystadenoma
  – Squamous-lined cysts (Lymphoepithelial, dermoid, splenic epithelial inclusion cyst)
  – Solid tumors with cystic degeneration
    • Neuroendocrine tumor, Solid pseudopapillary neoplasm, Acinar cell carcinoma
Clinical and Imaging Characteristics of Neoplastic Pancreatic Cysts

<table>
<thead>
<tr>
<th>Type</th>
<th>Age - Gender</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN Benign</td>
<td>75% women 60-70 y Grandma</td>
<td>Lobulated microcystic 18% central scar with Ca++</td>
</tr>
<tr>
<td>MCN Malignant potential</td>
<td>99% women 40-50 y Mother</td>
<td>Macrocystic Usually 1 cyst 25% peripheral Ca++ 95% in tail and body</td>
</tr>
<tr>
<td>Main-duct IPMN Malignant potential</td>
<td>M=W 60-80 y</td>
<td>Dilated Pancreatic duct Protruding papil of Vater</td>
</tr>
<tr>
<td>Side-branch IPMN Malignant potential</td>
<td>M=W 60-80 y</td>
<td>Bunch of grapes connection to PD</td>
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</tbody>
</table>
# Cyst Fluid Chemistry

## General Trends

<table>
<thead>
<tr>
<th></th>
<th>Pseudocyst</th>
<th>Serous Cystadenoma</th>
<th>Neoplastic Mucinous Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross</strong></td>
<td>Turbid</td>
<td>Clear, Watery</td>
<td>Thick, Viscous</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>Low</td>
<td>Low (&lt; 5ng/mL)</td>
<td>High (&gt;200 ng/mL)</td>
</tr>
<tr>
<td><strong>Amylase</strong></td>
<td>High</td>
<td>Low (&lt;250 U/L)</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Cyst Fluid Molecular Analysis

- **Analysis**
  - DNA quality & quantity
  - *KRAS* mutation
  - LOH mutations
- **Correlation of accumulated mutational damage with disease process**
  - Benign non-mucinous
    - Low quality/quantity DNA
    - No *KRAS* mutation
    - LOH at <2 genomic loci
  - Benign mucinous
    - High quality/quantity DNA or
    - *KRAS* mutation positive or
    - LOH ≥ 2 genomic loci
  - Malignant mucinous
    - High amplitude *KRAS* mutation (>75% total DNA) or
    - LOH ≥ 2 genomic loci at high amplitude (>75%)
Mutation Analysis

- KRAS mutations present in ductal adenocarcinomas, MCN and IPMN
- p16/CDNK2A loss occurs with increasing dysplasia
- TP53 and SMAD4 inactivation in high grade precursors and invasive cancers
- GNAS mutations present in IPMN
- Sensitivity of these tests parallel sensitivity of cytology & specificity has been shown to be inferior to cytology
- *Cytology remains gold standard for diagnosis*
Case 7

• 48 year old man with history of alcoholism and abdominal pain

• EUS: 3.4 cm solitary unilocular thick-walled cyst in the pancreatic tail. There are no mural nodules or septations.

• Gross: 1.5 cc of thin, turbid, brown fluid.
Case 7

Hemosiderin-laden macrophages, neutrophils, and lymphocytes in a proteinaceous, granular, debris-filled background

Fluid Chemistries:
Amylase = 146,000 U/L
CEA= 0.5 ng/mL
Pancreatic Pseudocyst

• Clinical
  – Acute or Chronic pancreatitis
  – Alcohol use, trauma, obstruction
  – Small to very large size
  – Tail preponderance, usually extrapancreatic
  – Men > Women (3:1)

• Imaging
  – Thin or thick-walled, unilocular, well-circumscribed cystic lesion ± calcification

• Cytology
  – Hemosiderin-laden macrophages, neutrophils, and lymphocytes in a proteinaceous, granular, debris-filled background

• Ancillary
  – High Amylase (>800 U/L)
  – Low CEA (<5ng/mL)

• By definition, pseudocysts lack epithelial lining; however, GI and ductal epithelial contaminants are commonly seen in cytology samples and may pose as a diagnostic pitfall.
A 57 year old man with history of pancreatitis presents with abdominal pain.

EUS findings: A 2.7cm unilocular cystic lesion is noted in the pancreatic body. There are no septations or mural nodules. The pancreatic duct is of normal caliber.

Gross findings: 1.2 cc of thick fluid submitted for fluid analysis and smears.
Case 8

Bland non-mucinous glandular epithelium

Background: abundant, thick proteinaceous to keratinous-like debris

Fluid Chemistries:
Amylase = 152,000 U/L
CEA= 45 ng/mL
Case 8

• Cytological diagnosis:
  – Benign non-mucinous cyst; see note.
    Note: The sample consists of rare bland non-mucinous epithelial cells consistent with GI or ductal contaminant in a background of thick debris and rare histiocytes. The differential diagnosis includes a pseudocyst versus a benign squamous lined epithelial cyst such as lymphoepithelial cyst, splenic epidermal inclusion cyst, or dermoid cyst. Features of a mucinous cyst or malignancy are not identified.
Lymphoepithelial Cyst

Squamous epithelial lining
Case 9

- 69 year old healthy woman with incidental pancreatic lesion found during imaging following a car accident
- EUS: 4.1 cm well-defined oligocystic lesion in pancreatic tail. The remainder of the pancreas appears normal.
- Gross: 1.5 cc of clear, watery fluid.
Case 9

Paucicellular sample with rare bland cuboidal epithelial cell clusters in a clean background.

Fluid Chemistry: Amylase = 25 U/L, CEA = <5 ng/mL
Case 9

• Cytological diagnosis:
  – Rare groups of bland non-mucinous epithelial cells consistent with serous cystadenoma; see comment.
  – Comment: The sample is paucicellular without evidence of intra- or extra-cellular mucin. The rare epithelial cells show bland nuclei with even chromatin and scant cuboidal non-mucinous cytoplasm. This, together with low fluid CEA and Amylase levels are consistent with serous cystadenoma.
Serous Cystadenoma

Cystic spaces lined by bland low cuboidal epithelial cells

Lobulated mass with central calcification
Serous Cystadenoma

- **Clinical**
  - Older age
  - Usually asymptomatic
  - F>M (9:1)
  - Body or Tail
  - Excellent prognosis
  - Resected if symptomatic or > 4cm

- **Imaging**
  - Microcystic type: central scar, numerous small cysts, "sunburst" type calcification
  - Macrocystic type: non-specific, multiloculated cyst

- **Cytology**
  - Paucicellular sample with rare bland cuboidal epithelial cell clusters in a clean background.
  - Rare histiocytes

- **Ancillary Studies**
  - Cellblock: PAS+/PASD-
  - Fluid Chemistry: Low CEA (≤5 ng/mL), Low Amylase (<100 U/L)
Neoplastic Mucinous Cysts (IPMN & MCN)

- Distinguishing low-grade lesions from contaminating GI epithelium can be challenging
- MCN and IPMN cannot be distinguished based on cytomorphology

<table>
<thead>
<tr>
<th>IPMN</th>
<th>MCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Communication with pancreatic ducts</td>
<td>• Not associated with pancreatic ducts</td>
</tr>
<tr>
<td>• Papillary architecture</td>
<td>• Ovarian Stroma (ER+, PR+, Inhibin +), not seen on cytology</td>
</tr>
<tr>
<td>• M&gt;F (1.5:1)</td>
<td>• Female preponderance (9:1)</td>
</tr>
</tbody>
</table>
International Consensus Guidelines 2012 for the Management of IPMN and MCN of the Pancreas

• High Risk Stigmata ➔ Surgery
  • Obstructive jaundice in a patient with cystic lesion in the pancreatic head
  • Enhancing solid component within cyst
  • Main duct dilation ≥ 10mm

• Worrisome Features ➔ EUS-FNA
  • Cyst ≥ 3 cm
  • Thickened/enhancing cyst wall
  • Main duct size 5-9 mm
  • Non-enhancing mural nodule
  • Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy

• EUS-FNA ➔ Surgery
  • Definite mural nodule
  • Main duct features suspicious for involvement (thickened walls, mural nodules, intraductal mucin)
  • “Positive or Suspicious” Cytology
Cytological Atypia/Dysplasia

• Low Grade Features
  – Scant cellularity
  – Flat, honeycomb sheets; small, flat groups
  – Low N/C
  – Round, regular, orderly nuclei

• High Grade Features
  – High.cellularity
  – Three-dimensional or papillary clusters, crowded cellular groups
  – Single dysplastic cells with high N/C
  – Nuclear irregularity, anisonucleolis, nuclear overlapping, elongation, stratification
  – Necro-inflammatory debris
  – Abnormal chromatin

Neoplastic mucinous cysts are heterogeneous and cytologic sampling may under-represent the histological grade.
Case 10

- 42 year old woman with vague abdominal discomfort found to have cystic lesion in pancreas
- EUS: 4.3 cm unilocular cystic lesion in pancreatic body-tail. Well-circumscribed, without mural nodules or septations. The pancreatic duct is marginally dilated.
- Gross: 1 cc of thick, viscous, clear fluid submitted for direct smears.
Case 10

Specimen is paucicellular with abundant thick, colloid-like mucinous background with scattered macrophages. Only rare muciphages seen on Pap.
Case 10

• Cytologic Diagnosis:
  – Abundant, thick mucin consistent with neoplastic mucinous cyst; see comment.
  – Comment: The sample shows abundant thick extracellular mucin and scattered macrophages. In the setting of a cystic lesion, the findings are consistent with a neoplastic mucinous cyst.

*Thick, viscous mucin with macrophages, even if lacking neoplastic cells, in the appropriate clinical and imaging context is sufficient for a diagnosis of a neoplastic mucinous cyst.*
Case 10

Histological diagnosis: Mucinous Cystic Neoplasm

Low-grade gastric-type mucinous epithelial lining

Subepithelial ovarian stroma
Mucinous Cystic Neoplasm

- Clinical
  - Predominantly middle-aged or older women (mean age 49 years)
  - Body and Tail (90%)
- Imaging
  - No communication with main duct
  - Rim of peripheral calcification (20%)
- Ovarian stroma on histology (not sampled in FNA material)
- Ancillary
  - Highly variable, but generally high CEA levels (>200 ng/mL)
Case 11

- A 60 year old woman with vague abdominal pain for 8 months was found to have a lesion in the pancreatic head.
- EUS: 3 cm thin-walled cystic lesion in pancreatic head with possible mural nodules but no mass. The pancreatic duct is dilated from tail (1.9 cm) to head (2.4 cm).
- Gross: 1 cc of thick viscous mucoid fluid submitted for smears.
Case 11

Neoplastic mucinous cyst with *at least* low to moderate grade dysplasia

Papillary-like cluster and flat sheets of glandular epithelium with mild to focally moderate nuclear atypia in a background of abundant, thick, viscous mucin and histiocytes. The cells have moderate to abundant cytoplasm.
Case 11

• Cytological diagnosis:
  – Neoplastic mucinous cyst; see comment.
  
  Comment: The differential diagnosis includes IPMN and MCN. The location of the lesion in the pancreatic head, and a diffusely dilated main pancreatic duct favors the former. The overall cellularity and cytological features suggest at least a low to moderate grade dysplasia; higher grade of dysplasia cannot be excluded.

• Histology:
  – IPMN with low to high grade dysplasia, gastric and pancreatobiliary type
Intraductal Papillary Mucinous Neoplasm (IPMN)

• Clinical
  – Predominantly older patients (7th-8th decade), M>F (1.5:1)
  – Head>Body
  – Main duct, branch duct, or mixed

• Imaging
  – Connection to ductal system
  – Main duct dilatation may not be seen in all cases, especially branch-duct type IPMN
  – Mucin extrusion from ampulla of Vater virtually diagnostic

• Ancillary
  – Highly variable, but generally high CEA and high Amylase levels
Case 12

- A 57 year old woman was found to have incidental lesion in the pancreatic head.
- EUS: 2.6 cm cystic lesion in pancreatic head with pancreatic duct dilation.
- Gross: 2.5 cc of thick viscous fluid submitted for smears and fluid chemistries.
Case 12

Neoplastic mucinous cyst with at least low to moderate grade dysplasia

Fluid Chemistries:
Amylase = 10,543 U/L
CEA= 1672 ng/mL

Papillary clusters of atypical mucinous epithelium in a background of abundant, thick mucin and macrophages. Nuclear crowding & enlargement present. Majority of nuclei are basally oriented, round. Single tumor cells have low N/C ratios.
Case 12

Histological Diagnosis:
IPMN with low to moderate grade dysplasia, gastric type
Case 13

- A 74 year old man with abdominal pain found to have a pancreatic head mass.
- EUS: 2.8 cm cystic lesion in pancreatic head with pancreatic duct dilation.
- Gross: 3 cc of thick bloody fluid.
Papillary clusters of atypical mucinous epithelium in a background of mucin and macrophages. Focally, there is marked nuclear atypia, cellular apoptosis and single atypical cells.

Fluid Chemistries:
Amylase = 11,603 U/L
CEA= 1846 ng/mL
Case 13

Histological Diagnosis: IPMN with moderate to high grade dysplasia, intestinal type.
Case 14

• A 66 year old man with weight loss and back pain found to have a pancreatic head mass.
• EUS: 2.8 cm cystic lesion in pancreatic head with possible mural nodule and pancreatic duct dilation.
• Gross: 1.8 cc of thick bloody fluid.
Case 14

Neoplastic mucinous cyst with high grade dysplasia; cannot exclude invasive ca

Sheets and papillary groups of neoplastic mucinous epithelium with nuclear membrane irregularities, anisonucleosis, and abnormal arrangement in a background of extracellular mucin and marked necro-inflammatory debris.

Fluid Chemistries: Amylase = 863 U/L, CEA = 126 ng/mL
Case 14

Histological Diagnosis:
IPMN, high grade, with invasive colloid ca.
Case 15

• A 60 year old woman with abdominal pain found to have a pancreatic head mass.

• EUS findings: 3.1 cm complex solid and cystic lesion in pancreatic head with pancreatic duct dilation.

• Gross: 2.6 cc of thick bloody fluid submitted for fluid chemistry analysis and smears.
Case 15

Sheets of atypical mucinous epithelium with mitoses, nuclear chromatin clearing, irregular nuclear borders, anisonucleosis, and necro-inflammatory background debris.

Fluid Chemistries:
Amylase = 12,824 U/L
CEA= 5892 ng/mL
Case 15

Histological Diagnosis:
IPMN, high grade, with invasive adenocarcinoma.
Summary Notes

- A comprehensive approach to incorporate clinical, imaging, and cytological findings is necessary to arrive at the best interpretation in pancreatic cytology.

- Atypia in the setting of chronic pancreatitis should be noted with suggestion of follow-up with additional sampling if clinical suspicion persists.

- Solid masses, particularly NET, SPN, and ACC can undergo cystic degeneration and should always be considered in the differential diagnosis of cystic lesions. Cell block material for immunostaining in these cases is very helpful.

- Care should be taken not to over-interpret GI contaminant or under-interpret mucinous neoplastic cell groups.

- Thick, viscous mucin with macrophages, even if lacking neoplastic cells, in the appropriate clinical and imaging setting, is sufficient to suggest a neoplastic mucinous cyst.

- The tumor grade or degree of dysplasia in neoplastic mucinous cysts may be under-estimated in cytology samples.

- High CEA levels and the presence of GNAS (in IPMN) or KRAS mutation support mucinous neoplasm but do not necessarily correlate with malignancy or grade of dysplasia. Cytology remains the gold standard.
References


References


