50 ENCORE! Pancreas: Surgical Pathology and Cytopathology of Pancreatic Neoplasms

N Adsay MD
Michelle Reid MD

2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
33 W. Monroe, Ste. 1600
Chicago, IL 60603
With recent advances in imaging and interventional techniques and a dramatic decline in mortality and morbidity of pancreatic operations, pancreatic resection specimens are now seen more often by surgical pathologists. Endoscopic ultrasound-guided fine needle aspiration has significantly increased the number of preoperative cytologic specimens reviewed by cytopathologists. Changes in terminology and classifications add to the new information one must now absorb. This session will provide an overview of challenges and practical clues in the diagnosis of pancreatobiliary specimens, with an algorithmic approach to differential diagnosis. Discussions will include: Pancreatic adenocarcinoma and its distinction from its mimics; Differential diagnosis of solid cellular/fleshy tumors of the pancreas; Clinicopathologic characteristics and biologic behavior of cystic tumors of the pancreas; Cytopathologic diagnosis of solid and cystic pancreatic lesions.

- Accurately differentiate problematic cases in surgical pathology of the pancreas, including solid-scirrhous lesions, solid/fleshy circumscribed lesions and cystic and traductal pancreatic tumors.
- Recognize the most common solid and cystic pancreatic lesions/tumors encountered on pancreatic fine needle aspiration; Evaluate the usefulness of ancillary studies in their cytologic diagnosis; Recognize key gastrointestinal contaminants in endoscopic ultrasound-guided pancreatic fine needle aspiration, that may lead to misdiagnosis on cytology.
- Distinguish and diagnose tumors of the ampulla, gallbladder and extrahepatic bile duct; Describe the grossing of pancreatoduodenectomy specimens.

**FACULTY:**

N. Adsay MD
Michelle Reid MD

**Practicing Pathologists**
Surgical Pathology
Surgical Pathology (GI, GU, Etc.)

3.0 CME/CMLE Credits

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EUS-Guided Fine Needle Aspiration and Cytopathology of Cystic and Solid Lesions of the Pancreas

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Emory University Hospital
Atlanta, GA

NEEDLE ASPIRATION OF THE PANCREAS

1. Percutaneous fine needle aspiration (FNAB)
   - Performed by a radiologist
   - A. Trans-abdominal ultrasound
   - B. CT-guided
   - Better resolution of smaller lesions

2. Endoscopic ultrasound-guided (EUS) FNAB (B 1 technique)
   - Performed by a gastroenterologist
   - An echoendoscope is placed against stomach/duodenum
   - High-resolution image obtained

INTRODUCTION

Endoscopic ultrasound-guided (EUS) FNAB

Advantages:
- Most cost effective and sensitive diagnostic modality
- Higher resolution of sub-centimeter (0.5 cm) lesions than CT
- Real-time visualization of needle during FNA
- Simultaneously diagnose and stage patients
DIAGNOSIS OF PANCREATIC LESIONS

• Can be challenging - SO WHY DO IT?
  • Because cytologic diagnosis affects surgical management
    • Pseudocysts, serous cystadenoma, pancreatitis - NO SURGERY REQUIRED
    • All other lesions/neoplasms - SURGERY REQUIRED

• Initial assessment of pancreatic lesions is radiologic
  • Lesions are either cystic, solid or mixed

ABRIDGED CLASSIFICATION OF SOLID AND CYSTIC PANCREATIC NEOPLASMS

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Entities in parentheses only rarely exhibit this gross configuration

Modified from Klimstra et al. Archives of Pathology and Laboratory Medicine 2009; 133(3):454-64.

INTRODUCTION

• FNA diagnosis of pancreatic lesions requires correlation of:
  • Cytologic and clinical findings
  • Radiologic findings
  • Ancillary studies
    • Immunohistochemistry
    • Flow cytometry
    • Cyst fluid analysis
INTRODUCTION
Accuracy of FNAB

- Immediate cytologic assessment IS A MUST
  - Best performed by cytopathologist or cytotechnologist
  - Reduces number of passes
  - Reduces inadequate samples
  - Saves time and money

Accuracy of Pancreatic FNAB

- Sensitivity for detecting malignancy:
  - 86% - 98% for percutaneous FNAB
  - 75% - 94% for EUS-FNAB
- Specificity for both approaches 100%
- False-negative and false-positive results occur
- False-negative results more common

SAMPLE PREPARATION AND EVALUATION

1. Prepare air-dried and alcohol-fixed slides
   A. Air-dried slides
      - Stain with a Romanowski stain (Diff-Quik®)
      - Determine adequacy
      - Triage specimens
         - Flow cytometry
         - Cyst fluid collection for analysis
   B. Alcohol-fixed slides
      - Papanicolaou and hematoxylin and eosin (H&E)

2. Collect needle rinses for:
   - Cell blocks (place specimen in 95% alcohol or formalin)
   - Immunohistochemical stains
## Pancreatic Cyst Fluid Analysis

<table>
<thead>
<tr>
<th>1. Enzymes</th>
<th>Pseudocyst or Non-Neoplastic Cyst</th>
<th>Neoplastic Cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase</td>
<td>High</td>
<td>low*</td>
</tr>
<tr>
<td>Lipase</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>High</td>
<td>Low</td>
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<tr>
<th>2. Viscosity</th>
<th>Non-Mucinous Cyst</th>
<th>Mucinous Cyst</th>
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<tbody>
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<td>Viscosity</td>
<td>&lt; serum</td>
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<th>3. Tumor Markers</th>
<th>Non-Mucinous Cyst</th>
<th>Mucinous Cyst</th>
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<tbody>
<tr>
<td>CA19-9</td>
<td>Not elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>CA125</td>
<td>Not elevated</td>
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<th>4. Molecular Markers</th>
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<tbody>
<tr>
<td>K-ras gene</td>
<td>Not elevated</td>
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</tr>
<tr>
<td>LOH mutation</td>
<td>Not elevated</td>
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### Molecular Markers in Pancreatic Cyst Fluid Analysis

- RedPath Integrated Pathology developed a commercially available molecular kit for pancreatic cyst fluid and cell block analysis.
- Called “PathFinderTG”
  - Includes 3 tests
    1. **K-ras** gene point mutation (on chromosome 12p12)
    2. Loss of heterozygosity (LOH) analysis for mutations in ≥2 of 15 genomic loci
      - 1 and 2 are considered high amplitude mutations if they involve >75% of total DNA content
    3. Measurement of DNA quantity and quality

### Use of Immunohistochemical Stains in Diagnosis of Pancreatic Neoplasms

| Table 7: Immunohistochemical Staining of Solid, Cellular Pancreatic Neoplasms |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| Neoplastic Ductal Neoplasms | Acinar Cell Carcinoma | Pancreatinomas | Solid/Papillary Neoplasms |
| KIT (CD117)                  | ++               | ++              | ++               |
| Vimentin                     | –                | –               | –                |
| Transforming growth factor    | –                | –               | –                |
| p53                          | ++               | ++              | ++               |
| MIB1                         | –                | –               | –                |
| CA19-9 tumor antigen         | ++               | ++              | ++               |
| CA125                        | ++               | ++              | ++               |
| GA43                          | –                | –               | –                |

**Legend:**

- +: focal positive
- ++: usually positive
- +++: may be positive
- –: usually negative

**Source:**

- Table from Levine et al., *Archives of Pathology 2010; 139(3):454-64.*
REPORTING TERMINOLOGY
Six diagnostic categories
• 1) Non-diagnostic
• 2) Negative for malignancy
• 3) Atypical cells present
• 4) Suspicious for malignancy
• 5) Positive for malignant cells
• 6) Neoplastic cells present

Diagnostic Categories
1. Non-diagnostic:
   • Material is unsatisfactory:
     – Because of low cellularity
     – Because it does not represent the site biopsied

2. Negative for malignancy:
   • Benign pancreatic epithelium

3. Atypical cells present:
   • Atypia is mild
     • Background pancreatitis
     • A COMMENT should be added

4. Suspicious for malignancy:
   • Atypia ≥ moderate
     • Worrisome for malignancy but:
       • Qualitatively insufficient
       • Quantitatively insufficient
       for a definite diagnosis of malignancy
Diagnostic Categories

5. Positive for malignant cells
   • Cells show obvious malignant features

6. Neoplastic cells present:
   • When the cells are obviously “neoplastic” but not definitely benign or malignant
   • E.g. Mucinous cysts

Contaminants in Pancreatic FNAB

• EUS-FNAB introduces gastrointestinal (GI) tract contaminants
• GI tract contaminants include:
  - 1. Duodenal epithelium
  - 2. Gastric epithelium
  - 3. GI tract mucin
• Distinguishing GI contaminants from pancreatic ductal adenocarcinoma and neoplastic mucinous cysts can be challenging

CONTAMINANTS IN PANCREATIC FNAB

• Must know location of lesion to determine likely contaminant
• Lesions in head and uncinate process → duodenal epithelial contaminants
• Lesions in body/tail → gastric epithelial contaminants
1. Duodenal Epithelial Contaminants

- Form flat honeycomb sheets with interspersed goblet cells
- Tissue edges have distinct brush border best seen at very high power
- Distinction from well differentiated ductal carcinoma or a neoplastic mucinous cyst can be difficult

Well Differentiated Ductal Adenocarcinoma vs Duodenal Contaminants

- Well differentiated ductal carcinoma: overlapping cells with loss of brush border
- Duodenal epithelium: with distinct brush border

Duodenal Contaminants vs Mucinous Neoplasm

- Duodenal epithelium: 2-dimensional honeycomb sheets with goblet cells interspersed
- Neoplastic mucinous cyst: pure population of mucin-filled cells often crowded together
2. Gastric Epithelial Contaminants

Gastric epithelial mucin does not fill the entire cell but is confined to the superficial 1/3rd of the cell where it forms a distinct "mucin cup".

2. Gastric Epithelial Contaminants

It is even more challenging to distinguish gastric epithelium from mucinous cystic lesions. Note the distinct mucin "cups" in superficial 1/3rd of cell (on the left).

3. GI Tract Mucin

- GI tract mucin may also be seen in EUS-FNAB
- Thin, watery and scant
- Not abundant or thick like mucin in cystic mucinous neoplasms
- "Neoplastic" mucin may have tumor cells admixed
Normal Exocrine Pancreas - Acinar Cells

- Cells form acinar structures without distinct lumens
- Cells are bland, pyramidal/triangular with low N/C ratio, granular (zymogen-rich) cytoplasm, round nuclei, inconspicuous or prominent nucleoli

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CYTOLOGY OF THE NORMAL EXOCRINE PANCREAS

- Ductal cells
  - Form monolayer sheets
  - Cells are evenly dispersed
  - Well-defined cell borders
  - Round nucleus with fine chromatin
  - Inconspicuous or absent nucleoli

Ductal cells in honeycomb sheet

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Endocrine pancreas

- Islet cells
  - Rarely sampled on a FNA
  - Form loose aggregates with ill-defined cell borders
  - Wispy cytoplasm
  - Round nucleus
  - Fine chromatin
  - Nucleoli are absent or inconspicuous

Endocrine cells are small, monotonous with low N/C ratio and bland nuclei
CYSTIC PANCREATIC LESIONS

The majority are non-neoplastic or benign
- Pancreatic pseudocysts account for the majority (75%)
- Lymphoepithelial cysts
- Serous cystadenoma
- Mucinous cystic neoplasm
- Intraductal papillary mucinous neoplasm
- Solid neoplasms with cystic degeneration

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The primary goal of FNAB of cystic lesions is to distinguish low from high-risk pancreatic cysts

- **Low-risk pancreatic cysts**
  - Less likely to harbor malignancy
  - Resected only if:
    - Symptomatic
    - When definitive diagnosis impossible

- **High-risk pancreatic cysts**
  - Have a higher risk of high-grade dysplasia or malignancy
  - Managed surgically with partial/total pancreatectomy

- **Low-risk pancreatic cysts**
  - Pancreatic pseudocysts
  - Serous cystadenomas
  - Lymphoepithelial cysts

- **High-risk pancreatic cysts**
  - Intraductal papillary mucinous neoplasm (IPMN)
    - 10% harbor carcinoma
  - Mucinous cystic neoplasm (MCN)
CYSTIC LESIONS OF THE PANCREAS

Serous cystadenoma
Solid pseudopapillary neoplasm
Mucinous Cystic Neoplasm

LOW-RISK PANCREATIC CYSTS

Pancreatic Pseudocyst - FNA

• Collection of amylase-rich secretions, debris and blood
• Lacks a true epithelial lining
• Paucicellular smears with granular debris, macrophages, yellow bile/hematoidin pigment and fat necrosis

Pancreatic Pseudocyst

• Fluid is turbid/necrotic
• NOT mucinous or gelatinous
• Granular background debris
• Inflammatory cells
• Pigment is important for diagnosis
  • Yellow pigment = bile/hematoidin
  • Brown pigment = hemosiderin

Cell blocks
**Pancreatic Pseudocysts vs Mucinous Cystic Lesions**

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<th>Mucinous Cystic Lesions</th>
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<tr>
<td>Fluid is turbid or necrotic</td>
<td>Fluid is gelatinous</td>
</tr>
<tr>
<td>Mucicarmine negative</td>
<td>Mucicarmine positive</td>
</tr>
<tr>
<td>Amylase</td>
<td>Amylase</td>
</tr>
<tr>
<td>High (&gt;250ng/mL)</td>
<td>– Low **</td>
</tr>
<tr>
<td>CEA</td>
<td>CEA</td>
</tr>
<tr>
<td>Low (&lt;5ng/mL)</td>
<td>High (&gt;200ng/mL)</td>
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**LOW-RISK PANCREATIC CYSTS**

- Serous Cystadenoma
  - Cystic spaces lined by bland cuboidal or low columnar clear epithelial cells

- Mucinous Cystic Neoplasm
  - Intraductal

- Solid pseudopapillary neoplasm
Serous Cystadenoma - FNA

- Cyst fluid is usually thin and clear
- Aspirates are often hypocellular
- AE1/AE3 and CA19.9 are +, EMA is focally +
- Amylase and CEA levels are low
- Mucicarmine negative
- Accuracy of diagnosis by imaging, cytology and chemical analysis is ONLY 20%**

Serous Cystadenoma

Sheets and clusters of cells with clear cytoplasm, defined borders, PAS+ cytoplasm

LOW-RISK PANCREATIC CYSTS

Lymphoepithelial cyst
Lymphoepithelial Cyst - FNA

- Has thick, white, cheesy fluid
- Lined by mature squamous epithelium
- Surrounded by dense lymphoid infiltrate +/- follicles
- Smears have:
  - Nucleated/anucleated squames
  - Keratinous debris
  - Lymphocytes, histiocytes, giant cells
- Aspirates are usually DIAGNOSTIC
- Accurate FNA diagnosis obviates the need for radical surgery
  - Cyst fluid has high CEA and amylase levels

HIGH-RISK PANCREATIC CYSTS
“NEOPLASTIC MUCINOUS CYSTS”
NEOPLASTIC MUCINOUS CYSTS

• Mucinous cystic neoplasm (MCN)
  – Primary mucin-producing cystic neoplasm
  – Lined by bland mucin-filled columnar cells
  – Has classical sub-epithelial ovarian-type ER+, PR+ stroma

• Intraductal papillary mucinous neoplasm (IPMN)
  – Primary mucin-producing cystic neoplasm
  – Arises from the main or branch pancreatic ducts
  – Lined by papillary mucinous epithelium with variable atypia

Key Differences Between the Two Cysts

• MCN
  – Large, circumscribed, solitary cystic lesion
  – Not connected to the main pancreatic duct or its branches
  – Because they are not connected to the main pancreatic duct/branches
    amylase levels are usually low
  – Most patients are females between 40-50 yrs
  – F: M 20:1
  – Malignant features include:
    • Size >3 cm
    • Thick wall, peripheral calcifications
    • Intramural mass/nodules

• IPMN
  – Diffuse ectasia involving the main and/or branch pancreatic ducts
  – Always connected to the main pancreatic duct and branches
  – Because they are connected to main pancreatic duct/branches
    amylase levels are high
  – Most patients are males above 50 yrs
  – M > F or are slight > females
  – Malignant features include:
    • Size >3 cm
    • Dilated main pancreatic duct
    • Intramural mass/nodules

Cytologic Similarities

• Both IPMN and MCN have abundant thick mucin
• Difficult to express from needle
• Difficult to spread on the slide
• Smear cellularity is variable
• Higher the grade of dysplasia, the greater the cellularity
• Psammomatous calcifications may be seen in IPMN
Similarities Between MCN and IPMN

Both contain sheets and clusters of columnar cells with abundant intracytoplasmic mucin.

Similarities between MCN and IPMN

The mucin fills the entire cytoplasm and displaces the nucleus peripherally – note limited nuclear atypia in this example.

NEOPLASTIC MUCINOUS CYSTS

A. Mucin +

B. Nuclei are slightly pleomorphic with coarse chromatin and prominent nucleoli

C. Macrophages may be present
**NEOPLASTIC MUCINOUS CYSTS**

- Papillary clusters may be seen in IPMN but are not typical in MCN
- Nuclear and architectural atypia can be seen in both IPMN and MCN
  - Includes hypercellularity
    - Nuclear crowding
    - Loss of polarity
    - Hyperchromasia, pleomorphism
    - High N/C ratio and nucleoli
    - Single epithelial cells in mucin
- Nuclear atypia is more often seen in IPMN than MCN

**Pancreatic Neoplastic Mucinous Cyst with High-Grade Dysplasia**

**Interesting Case - Pancreatic Tail Cyst**
Diagnosis? – Adenocarcinoma (at least in situ) possibly arising in a neoplastic mucinous cyst

NEOPLASTIC MUCINOUS CYSTS
- Necrosis, inflammation and signet ring cells more common in high-grade dysplasia/carcinoma
- Best correlate of invasion in pancreatic mucinous cysts is necrosis
- Single highly atypical cells are also suggestive of malignancy

Key Point In Daily Practice
Thick gelatinous mucin is DIAGNOSTIC of a neoplastic mucinous cyst even if diagnostic cells are not identified.
- Correlation with imaging is required.
PANCREATIC MUCIN-PRODUCING CYSTS

- Definitive cytologic distinction between MCN and IPMN is discouraged
- The best diagnosis for such lesions is:
  - “Neoplastic cells present.”
  - “Neoplastic mucinous cyst”
  - A comment should be made regarding the presence and grade of cytologic atypia/dysplasia

SOLID PANCREATIC LESIONS

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Modified from Herro et al., Archives of Pathology and Laboratory Medicine 2009; 133(3):454-64.
Ductal Adenocarcinoma

- 60% - 70% occur in the pancreatic head
- Well - poorly differentiated
- Poorly differentiated carcinoma is straightforward
- Well and moderately differentiated carcinoma may be difficult to distinguish from reactive ductal cells and GI tract contaminants

Poorly Differentiated Ductal Carcinoma

- Not a diagnostic challenge
  - 3-dimensional groups
  - 4-fold anisonucleosis is characteristic
  - Irregular nuclei
  - High N/C ratio
  - Macronucleoli
  - Abnormal mitoses
  - Necrosis
  - Single intact tumor cells are common
Poorly Differentiated Ductal Adenocarcinoma

- 3-D crowded groups
- 4-fold anisonucleosis
- Disorganized sheets with hyperchromatic cells with irregular nuclei

Poorly Differentiated Ductal Adenocarcinoma

- MALIGNANT
- BENIGN

Well Differentiated Ductal Carcinoma

- Disorganized sheets similar to normal ductal cells
- Slight nuclear crowding
- “Drunken” honeycomb sheets
- Mild nuclear enlargement
- N/C ratio may remain low
- Anisonucleosis not as pronounced
- Normal pancreatic acini and endocrine cells are rare to absent
Interesting Case - FNAB Pancreatic Mass

Slightly "drunken" honeycomb sheet and cellular dissociation

Irregular nuclear contours, hypochromasia and prominent nucleoli

An extremely bland-appearing well differentiated adenocarcinoma with voluminous foamy cytoplasm

Cells have abundant mucinous vacuoles and very bland almost benign cytologic appearance

Closer examination revealed single intact malignant cells with nuclear irregularity

Diagnosis?

Foamy Gland Variant of Well Differentiated Ductal Adenocarcinoma
Foamy Gland Ductal Adenocarcinoma

Ductal Adenocarcinoma
- Immunohistochemical markers:
  - CK7, CK8, CK18, CK19
  - CA 125
  - DUPAN-2 (pancreatic cancer-associated antigen)
  - Mucin glycoproteins are variably expressed
    - MUC1, 3, 4 and MUC5AC
- Molecular markers:
  - K-ras mutation
  - Loss of heterozygosity (LOH) mutation
  - p53 mutation

Other Variants of Ductal Carcinoma
Squamous Cell Carcinoma of Pancreas

- Extremely rare variant of pancreatic carcinoma
  - Incidence ranges from 0.5% - 5%
- Only diagnose after metastasis has been excluded and after a glandular component has been excluded (i.e. adenosquamous carcinoma)
- Similar biologic behavior to ductal adenocarcinoma

Malignant squamous cells are admixed with benign pancreatic ductal cells. This was a case of primary pancreatic squamous cell carcinoma

- Most cases represent metastases
  - From the lung, followed by cervix then esophagus
- Correlation with clinical information is paramount to accurate diagnosis
Osteoclastic- Giant Cell Carcinoma of Pancreas

- Extremely rare primary malignant pancreatic tumor.
- Associated with ductal adenocarcinoma (40% of cases).
- May be focal or predominant.
- Prognosis is controversial:
  - Some say not as dismal as ductal carcinoma.
  - Others say more aggressive than ductal carcinoma.
  - Mean survival ≤ 12 months – related to quantity of ductal carcinoma.

Osteoclastic- Giant Cell Carcinoma of Pancreas

- 3 cell types:
  1. Benign-appearing osteoclast-like giant cells
     - CD68+, Cytokeratin-
  2. Pleomorphic giant carcinoma cells
     - CD68-, Cytokeratin+
  3. Small round/spindle histiocytelike carcinoma cells
     - CD68+/−
     - Cytokeratin +/-, EMA/+/-
     - P53+/−, ki-67+.

Osteoclastic-Giant Cell Carcinoma of Pancreas

- Cell block with benign giant cells.
- Conventional ductal adenocarcinoma – same case.
Mucinous “Colloid” Carcinoma of Pancreas

- Accounts for <1% of pancreatic malignancies
- Commonly associated with IPMN
- Clusters and singly dispersed malignant cells in thick colloid-like mucin
- Signet ring cells are present
- Cytologic diagnosis is straightforward

Note clusters of slightly pleomorphic, hyperchromatic malignant cells in thick mucin

Chronic Pancreatitiss

- Can present as solid pancreatic head lesion
- Distinction from carcinoma challenging on radiology
- Reactive ductal cells may be challenging

Lymphohistiocytic infiltrates

Fat necrosis

Stromal fragments
Chronic Pancreatitis

- Atypical reactive ductal cells can be confused with ductal carcinoma
- Distinction between the 2 may require immunohistochemistry

FNA: “Atypical Cells Present”
Reactive Ductal Cells vs. Ductal Carcinoma

Note the sheet-like arrangement, round nuclear contours and similarity between cells.
This is marked reactive atypia

Benign ductal cells – in honeycomb
Well differentiated ductal carcinoma

Abnormal mitosis

Drunken honeycomb sheet

Reactive ductal cells – in honeycomb sheets
Well differentiated ductal carcinoma
Immunohistochemical Distinction between Adenocarcinoma, Chronic Pancreatitis and GI Tract Contaminants

<table>
<thead>
<tr>
<th>Atypical Ductal Cells</th>
<th>SMAD4</th>
<th>p53</th>
<th>CDX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal Adenocarcinoma</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GI tract contaminants</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Key Point In Daily Practice

- If atypical glandular cells are present and one cannot determine whether they are neoplastic or reactive the best diagnosis is:
  - "Atypical cells present" with COMMENT
    - Correlate clinically and radiologically

Autoimmune Pancreatitis

- "Lymphoplasmacytic sclerosing pancreatitis"
- Can produce a mass effect in pancreas
- Associated with RA, IBD, primary sclerosing cholangitis
- ↑ serum IgG4 antibody
- Antinuclear antibody (ANA) +
- Rheumatoid factor +
**Autoimmune Pancreatitis (AIP)**

- Few reports on cytologic features
- Range from paucicellular to hypercellular aspirates
- Contain stromal fragments, lympho-plasmacytic infiltrate, eosinophils
- Minimal ductal epithelium
- IgG4 immunostain is positive in plasma cells

**Pancreatic Neuroendocrine Tumors**

- Range from well - poorly differentiated
- Well differentiated pancreatic neuroendocrine tumor (Pan NET) is the most common
- Poorly differentiated neuroendocrine carcinoma (Pan NEC) is extremely rare
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma

**Well Differentiated Pancreatic Neuroendocrine Tumor**

- Hypercellular smears
- Uniform, dyscohesive cells
- Fragile, easily stripped cytoplasm
- Often have eccentric nuclei → plasmacytoid appearance
- May resemble lymphocytes
- Classical “salt-n-pepper” chromatin on Pap/H&E stain
- Indistinct nucleoli usually
- May have prominent nucleoli
- Variable nuclear atypia

**Plasmacytoid cells**

**NET with prominent nucleoli**
Well Differentiated Pancreatic Neuroendocrine Tumor

- Plasmacytoid cells
- Salt-and-pepper chromatin, small nucleoli
- Prominent nucleoli and pseudorosettes

Pseudorosettes on cell block

Well Differentiated Pancreatic Neuroendocrine Tumor - Pleomorphic Variant

- Single plasmacytoid cells and cells with focal degenerative "endocrine" acini

Pseudorosettes are visible both on smear and cell block
Pancreatic Neuroendocrine Tumor

- Immunohistochemistry
- Positive for neuroendocrine markers
  - Synaptophysin, chromogranin, CD56, CD57
- Positive for keratin, CAM5.2

Poorly Differentiated Pancreatic Neuroendocrine Carcinoma (NEC)

- Extremely rare
- Include small cell and large cell NEC
- Rule out metastasis before making this diagnosis
- Small cell carcinoma resembles small cell carcinoma of the lung
  - Molding, salt and pepper chromatin, crush artifact
- Large cell NEC
  - Resembles poorly differentiated carcinoma
  - Expresses neuroendocrine markers

Acinar Cell Carcinoma

- Hypercellular smears
- Acinar formation and naked nuclei
- Abundant granular cytoplasm
- Nuclei with fine to coarse chromatin, inconspicuous nucleoli
- Normal pancreatic acini
Acinar Cell Carcinoma

- Tumor cells stain positively for:
  - Pancytokeratin
  - Pancreatic enzymes:
    - Lipase, trypsin, chymotrypsin, α 1-antichymotrypsin, α 1-antitrypsin
    - Do not confuse trypsin with α 1-antitrypsin
    - α 1-antitrypsin is not a very useful stain for acinar cells
    - Because it also stains solid-pseudopapillary neoplasm and pancreatic neuroendocrine tumors

Solid-Pseudopapillary Neoplasm

- Tumor cells form vague clefts or spaces lined by bland epithelial cells with intervening myxoid stroma, thin-walled vessels and vesicular, grooved nuclei
**Solid-Pseudopapillary Neoplasm**

- Rare low-grade solid and cystic pancreatic
- Usually arises in the pancreatic tail
- Almost exclusively in women (F:M 9:1)
- Third decade (mean age 28 years) or adolescence
- Cytologic features are distinctive
- Accurate diagnosis often made before resection

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**固形-類乳頭腫**

- Low-grade solid and cystic pancreatic tumors
- Usually occur in the tail of the pancreas
- Almost exclusively in women (F:M 9:1)
- Third decade (mean age 28 years) or adolescence
- Cytologic features are distinctive
- Accurate diagnosis is often made before resection

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**Vesicular nuclei with open, fine, powdery chromatin**

- Nuclear grooves
- Fibrovascular core

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**Vascular nuclei with open, fine, powdery chromatin**

- Nuclear grooves
- Fibrovascular core
Solid-Pseudopapillary Neoplasm

- Immunohistochemistry is characteristic and diagnostic
  - Positive for vimentin
  - Frequently negative for cytokeratin
  - Positive for:
    - Neuro specific enolase
    - CD56 (variable)
    - CD10
    - β-catenin
    - Progesterone receptor

Neoplasms in pancreatic tail include solid pseudopapillary neoplasm (SPN), acinar cell carcinoma, and metastatic mammary or mesothelial tumors.

Pancreatic Neuroendocrine Tumor (NET) vs Solid-Pseudopapillary Neoplasm (SPN)

- Fine, open chromatin
- Salt & pepper chromatin

Secondary Pancreatic Neoplasms

- Various tumors may metastasize to the pancreas
  - Lung (small cell and squamous cell carcinoma)
  - Breast
  - Kidney
  - Lymphoma
- Less commonly:
  - Ovary, colon and stomach
- History of previous malignancy and immunohistochemistry are helpful in diagnosis
SUMMARY - PANCREATIC FNAB
– Cytologic evaluation of pancreatic lesions is complex
– Knowledge of types and location of the most common solid and cystic lesions is helpful in diagnosis
– Correlation with clinical, imaging data is paramount
– Cytopathologist /cytotechnologist’s presence during immediate evaluation improves adequacy and diagnostic yield
– Be mindful that chronic pancreatitis and GI tract contaminants (in EUS-FNAB) may simulate carcinoma

References