Pancreas Fine Needle Aspiration (FNA)

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• No relevant financial relationships with ineligible companies to disclose
Outlines

- Top 3 pancreas FNA challenges:
  1. Normal elements vs neoplasms
  2. Mucinous cyst vs contaminants
  3. Adenocarcinoma vs other
Case 1

27 year old woman with a 0.7 cm well circumscribed solid-cystic pancreatic body neoplasm
Imaging

Solid lesions:
- Ductal adenocarcinoma
- NET including NEC
- Acinar cell carcinoma

Solid-Cystic:
- SPN
- NET
- Acinar cell carcinoma
- Adenocarcinoma

Cystic lesions:
- Pseudocyst
- Mucinous cysts including IPMN and MCN
- Serous cystadenoma
ROSE

Suspicious for neoplasm, possibly solid pseudopapillary neoplasm (SPN) or pancreatic neuroendocrine tumor (PanNET)
Standardized Terminology and Nomenclature for Pancreato- Biliary Cytology

• I. Non-Diagnostic

• II. Negative for malignancy

• III. Atypical

• IV. Neoplastic:
  • Benign (serous cystadenoma)
  • Other:
    • Mucinous cysts (low- and high- grade dysplasia)
    • Well- differentiated neuroendocrine tumors
    • Solid- pseudopapillary neoplasm

• V. Suspicious for malignancy

• VI. Positive for malignancy
Solid Pseudopapillary Neoplasm (SPN)

- Highly cellular, dyscohesive cells
- Pseudopapillary structures
- Loosely cohesive clusters, surrounding hyalinized to myxoid stroma with fibrovascular stroma
- Irregular nuclear contours, grooves
- Extracellular hyaline globules
SPN (CB) + Beta- Catenin

Images by Dr. Longwen Chen
Case 1 Vs SPN
Case 1 Vs SPN
??? Neoplastic vs Non- Neoplastic
Case 1 Final Diagnosis:
- Non-diagnostic

B9 pancreatic cells only, likely not representative of the lesion seen on imaging.
Case 1: Normal Pancreas Misdiagnosed as Neoplastic

- Predominance of acinar cells:
  - Cohesive, small grape-like, rosette-like clusters adhesed to fibrovascular stroma, scattered single cells and naked nuclei
  - Abundant granular cytoplasm (DQ: small vacuoles)
  - Basally located, round nuclei, central to eccentric, uniform chromatin, single prominent nucleoli
Case 1: Normal Pancreas Misdiagnosed as Neoplastic

- **Architecture:** Key to differentiate B9 acinar cells (small uniform grape-like, adhesed to fibrovascular stroma) from neoplasm
Case 1: Normal Pancreas Misdiagnosed as Neoplastic

- **Architecture:** Key to differentiate B9 acinar cells (small uniform grape-like, adhesed to fibrovascular stroma) from neoplasm
Normal Pancreas

- Ductal cells
- Acinar cells
- Islet cells

Slide by Dr. Matthew Zarka
Islet Cells in Chronic Pancreatitis (CP) Misdiagnosed as PanNET on FNA

- Isolated and loosely cohesive cells with eccentrically located bland appearing nuclei
- Background of lymphocytes
- Resection:
  - CP with Predominance of islet cells

B9 Pancreas FNA

The Great Imitator
SPN vs B9 Pancreas

- Loosely cohesive clusters
- Cells surround hyalinized to myxoid stroma with fibrovascular stroma
- Majority of groups more cohesive and uniform clusters
- "Grape-like" architecture
- Uniform cells adhesed to fibrovascular core
SPN vs B9 Pancreas

• Mild nuclear enlargement

• Nuclei: irregular contours, bean shaped, grooves

• Cytoplasmic tails

• Extracellular PAS+ hyaline globules

• Nuclear (N) size = RBC

• Basally located N

• Round, smooth membranes
Acinar Cell Carcinoma
B9 Acinar Cells Misdiagnosed as Acinar Cell Carcinoma
ACC vs B9 Acinar Cells

- Cellular aspirate
- Ovoid cells, round smooth nuclear contours
- N enlargement, high N/C, coarse chromatin
- Prominent nucleoli
- Large Cytoplasmic granules

- More cohesive
- Uniform cell aggregates
- N = size RBC
Bonus Case: “Non-diagnostic”

Rare non-neoplastic acinar cells
Non-diagnostic
B9 Pancreas vs PanNET
B9 Pancreas vs PanNET

Acinar groups in B9 may look like pseudorosettes in PanNET
Normal vs PanNET

- More cohesive clusters
- Predominance of single cells
- Loosely cohesive clusters

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B9 Pancreas vs PanNET

Occasional single cells  Single cells predominate
Bonus Case Vs Normal
Bonus Case Vs PanNET
Bonus Case CB
Follow up: PanNET

- CK
- Ki-67
- Necrosis
- Atypia
### WHO 2017 Classification of Well-Differentiated Pancreatic Endocrine Tumors

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ki67 (%)</th>
<th>Mitotic index (per 10 hpf)</th>
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<tr>
<td>1</td>
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<td>&lt;2</td>
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<tr>
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<tr>
<td>3</td>
<td>&gt;20</td>
<td>&gt;20</td>
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</table>
Neuroendocrine Tumors Cytology

- Loosely cohesive clusters with fibro vascular core/stroma, but single cells predominate, bare nuclei in the background, pseudorosettes
- Uniform tumor cells with round to oval nuclei, some cells out of proportion to others
- Plasmacytoid, binucleate cells
- Regular nuclear membranes
- “Salt and pepper” chromatin
- Moderate cytoplasm with fine granules (pink granules DQ)

Images by Dr. Matthew Zarka
Case 2

69 year old male
EUS: 30 x 20 mm septated cystic lesion in pancreatic head communicating with pancreatic duct, consistent with IPMN
No worrisome findings on imaging
Case 2

69 year old male
EUS: 30 x 20 mm septated cystic lesion in pancreatic head communicating with pancreatic duct, cw IPMN
No worrisome findings on imaging
ROSE: solid lesions only
Any visible mucin is pathologic; overtly mucinous ductal cells from pancreas represent either MCN/ IPMN or adenocarcinoma.
Standardized Terminology and Nomenclature for Pancreato-Biliary Cytology

• I. Non-Diagnostic

• II. Negative for malignancy

• III. Atypical

• IV. Neoplastic:
  • Benign (serous cystadenoma)
  • Other:
    • Mucinous cysts (low- and high-grade dysplasia)
    • Well-differentiated neuroendocrine tumors
    • Solid-pseudopapillary neoplasm

• V. Suspicious for malignancy

• VI. Positive for malignancy
Neoplastic cells present

Mucinous epithelium present in a background of abundant mucin, consistent with IPMN
No high-grade dysplasia or malignancy
Mucinous Cystic Neoplasms

- Thick mucous
- Low cellularity
- Columnar cytoplasm with mucin and basally located nuclei
- Some nuclear stratification, single mucous cells
- Atypia depends on degree of differentiation

Images by Dr. Matthew Zarka

Pitman et al. Cancer Cytopathol. 2010;1181-13
Mucinous Background

- **Benign**
  - Gastric epithelium
  - Duodenal epithelium

- **Neoplastic**
  - Mucinous cystic neoplasm (MCN)
  - Intraductal papillary mucinous neoplasm (IPMN)

- **Malignant**
  - Mucinous non-cystic adenocarcinoma
  - Signet ring carcinoma

Image by Dr. Matthew Zarka
Common Pancreatic Cystic Lesions

- Serous Cystadenoma
- Mucinous Cystadenoma
- Cystic Islet Cell Tumor
- Intraductal Papillary Mucinous Neoplasm (Main Branch)
- Intraductal Papillary Mucinous Neoplasm (Side Branch)

Slide by Dr. Matthew Zarka
Pseudocyst vs Serous Cyst

Images by Dr. Matthew Zarka
Fluid Chemistry and Molecular Analysis in Cystic Lesions

- Very helpful in cystic lesions with:
  - Atypical diagnosis
  - Normal appearing or non-diagnostic
- \( \text{CEA} > 192 \text{ ng/ml} \): highly suggestive of MCN

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>Amylase</th>
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<tbody>
<tr>
<td>IPMN</td>
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<td>Variable</td>
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<tr>
<td>MCN</td>
<td>High</td>
<td>Variable</td>
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<td>Serous cystadenoma</td>
<td>Low, &lt;5 ng/ml</td>
<td>Low</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>Low</td>
<td>High</td>
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</table>
Molecular Analysis in Cystic Lesions

- Helpful if CEA level low
- Does not distinguish B9 from malignant
- KRAS mutations: IPMN (61%) and MCN (21%)
- GNAS mutations almost exclusive in IPMN (also in SCA, but not in MCN)
- VALUE: helps distinguishing IPMN from MCN (MCN always resected)
- KRAS and GNAS:
  - If + together: suggest IPMN
  - No prognostic indication
  - Seen in low and high grade dysplasia
PSC Category IV, other: Mucinous cystic neoplasm, favor IPMN

“The category of “Neoplastic: Other” should be used when the cyst has been classified as a neoplasm, which may be based solely on ancillary tests.” — Pitman M B, Layfield L. The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology. Springer 2015
IPMN – “Quadruple” Test

• **Clinical-EUS/ Gross:**
  - Thick mucin

• **Radiographic:**
  - Dilated duct system, cyst communicate with pancreatic duct

• **Cytology:**
  - Mucinous epithelium

• **Ancillary tests:**
  - Fluid chemistry (CEA, amylase), molecular

Images and partial content by Dr. Matthew Zarka
Contaminants in EUS-Fine Needle Aspiration

Transgastric: body and tail of pancreas
Transduodenal: head of pancreas
Stomach

- Thin, watery mucin
- Small /intermediate/large clusters
- Apical mucin cups
- Grooved naked nuclei within mucin
- Cell types:
  - Mucinous, parietal, chief cells

Slide by Dr. Matthew Zarka
Apical mucin cups in foveolar cells

Images: left side Dr. Miguel Perez (left) ASC Meeting 2021 (right)
Duodenum

- Generally thin mucus
- Large tissue fragments
- Goblet cells ("fried eggs"), lymphocytes ("sesame seeds")
- Brush borders

Images by Dr. Matthew Zarka
Which images correspond to GI contaminants and which to pancreatic mucinous cyst???
GI Contaminant vs Mucinous Neoplasm

- No “colloid-like” mucin
- Identifiable gut epithelium in background
- +Thick “colloid-like” mucin (mucinous neoplasms may lack mucin in +/− 50% of cases)
- +INC (1/3 of IPMN)

Images by Dr. Matthew Zarka
Which of the following is IPMN?

ASC Meeting 2020
Which of the following is IPMN?
What if not sure???
When unsure if lesion or contaminant and no supportive evidence for mucinous cyst:

• “Negative for malignancy: Non-specific cyst fluid negative for high-grade epithelial atypia”
Which of the following is IPMN?
Which of the following is IPMN?
All of them
Which of the following is IPMN? All of them, but...
Which of the following is IPMN? All of them, but...

+ High Grade Dysplasia
High Grade Dysplasia

- High N/C ratio (variable amount of cytoplasm w or w/o mucin or vacuoles)
- Nuclear atypia (irregularity), hypo or hyperchromasia, variable nucleoli
- Loss of nuclear polarity, small single cells (< duodenal enterocyte)
- Complex architecture (3D, 2-4 tight buds of cells)
- Less/ scant background mucin, +/- necrosis

Images by Dr. Matthew Zarka
High Grade Dysplasia (HGD) in IPMN

- HGD Important to distinguish:
  - Resection

- LGD lesions:
  - Followed clinically EUS/ imaging
  - Resected if worrisome imaging findings appear
High Grade Dysplasia (HGD) in IPMN

- HGD Important to distinguish:
  - Resection

- LGD lesions:
  - Followed clinically EUS/ imaging
  - Resected if worrisome imaging findings appear

- If not sure: conservative approach
IPMN with High Grade Dysplasia
IPMN with High Grade Dysplasia
IPMN HG vs LG Dysplasia

- High N/C ratio, “small” cells, variable cytoplasm
- Nuclear atypia (irregularity, hyper or hypochromasia)
- Loss of nuclear polarity
- Single cells or complex architecture (3D, 2-4 tight buds of cells)
- Less/ scant background mucin, -/+ necrosis
- Uniform cells
- Bland or mild nuclear atypia
- No architectural complexity
- Intracytoplasmic mucin
- Abundant extracellular mucinous material
IPMN with HGD

- Increased N/C ratio
- Nuclear atypia
- Loss of nuclear polarity
- Complex architecture
- Less/ scant mucin

Adenocarcinoma

- Discohesion, many single tumor cells
- Anisonucleaosis with >4 times variation in nuclear size
- Necrosis
- Pleomorphism with nuclear outline irregularity
Case 3

Provided information “Suspicious for IPMN”
Positive for Neoplasm

Mucinous epithelium present, suggestive of IPMN
No high-grade dysplasia or malignancy
CB: Is this IPMN???
Follow up:
Lesion not cystic, but mostly SOLID

• Final Report:

• Atypical
  • Markedly paucicellular sample with atypical mucinous cells cannot exclude malignancy
Resection: Adenocarcinoma arising from IPMN with high grade dysplasia
Resection vs CB
Adenocarcinoma vs Mucinous Lesions

- It can be extremely challenging to distinguish well-differentiated PDCA and IPMN/MCN on cytology due to:
  - Subtle cytologic atypia and
  - Low N/C that can occur in both cases
- FAVORS Adenocarcinoma:
  - DISTINCT MASS on imaging
Cytology of Adenocarcinoma

- Crowding/overlapping/3D, single cells, drunken honeycomb
- Nuclear features:
  - Enlargement, anisonucleosis (4:1), membrane irregularity, clearing/hyperchromasia, macronuclei
- Cytoplasm:
  - Scant or abundant-mucinous
- Necrosis, mitosis, single cells

Image by Dr. Matthew Zarka
Adenocarcinoma

- **Major criteria**
  - Nuclear overlap and crowding
  - Nuclear contour irregularity
  - Chromatin clearing or clumping

- **Minor criteria**
  - Single epithelial cells
  - Necrosis, mitosis
  - Nuclear enlargement

Acta Cytol, 1995; 39:1-10
Differential Diagnosis

• Autoimmune pancreatitis (AIP)/ chronic pancreatitis (CP)
• Pancreatic Neuroendocrine Tumor (PanNET)
Autoimmune Pancreatitis (AIP)

- Clinical presentation as mass, mimics malignancy
- Associated with autoimmune diseases
- Responds well to steroids
- Lymphoplasmacytic infiltrate and fibrosis, Increased IgG and IgG4
AIP Cytology

- Decreased ductal-type groups, abundant acinar epithelium
- Ductal atypia (nuclear enlargement, prominent nucleoli)
- Cellular stromal fragments rich in lymphocytes or lymphoid tangles
- Variable background inflammation: nil to moderate
AIP
<table>
<thead>
<tr>
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<th>AIP</th>
<th>Adenocarcinoma</th>
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<tbody>
<tr>
<td>Nuclear atypia</td>
<td>Mild to moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Cell Crowding, 3D</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Single cells</td>
<td>Likely GI contamination</td>
<td>Single tumor cells</td>
</tr>
<tr>
<td>IgG4/ IgG positive cells</td>
<td>May be elevated</td>
<td>Not elevated</td>
</tr>
<tr>
<td>Serum IgG4</td>
<td>May be elevated</td>
<td>Not elevated</td>
</tr>
<tr>
<td>Serum ANA</td>
<td>May be elevated</td>
<td>Not elevated</td>
</tr>
</tbody>
</table>

Chronic Pancreatitis (CP)

- Low cellularity
- Flat cohesive sheets, slight crowding
- Low N/C ratio
- Slightly enlarged nuclei w little variation in size (<4x)
- **Round smooth nuclear membranes**
- Prominent nucleoli
- **Background: fat necrosis and calcific, inflammatory stroma or saponified debris**
CP vs Adenocarcinoma

- Round smooth nuclear membranes

- Irregular nuclear membranes

Images by Dr. Miguel Perez
CP vs Adenocarcinoma

- Background: fat necrosis, “grundgy material”, calcification, inflammatory stroma, saponified debris

- Coagulative necrosis

Left side image by Dr. Miguel Perez
<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear enlargement</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Mitosis</td>
<td>Present</td>
<td>Present</td>
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<tr>
<td>Anisonucleosis</td>
<td>&lt;4x</td>
<td>&gt;4x</td>
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<tr>
<td>Chromatin pattern</td>
<td>Even</td>
<td>Clumpy, paranucleolar clearing</td>
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<td>Amylase, lipase</td>
<td>Elevated</td>
<td>Normal</td>
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<tr>
<td>SMAD4 IHC</td>
<td>Retained</td>
<td>Lost in up to 50% of cases</td>
</tr>
<tr>
<td>Nuclear membrane contour</td>
<td>Slightly irregular</td>
<td>Markedly irregular</td>
</tr>
</tbody>
</table>

Adenocarcinoma

• AVOID a definitive diagnosis:
  • Scant atypical cells
  • Acute or chronic inflammation in the background
  • Fibrotic fragments with lymphoid tangles
PanNET challenges

- Nuclei may be pleomorphic due to endocrine atypia
- Pseudorosettes may be confused with glands
- Lipid rich variant: foamy/vacuolated cytoplasm
- Oncocytic variant: abundant granular, oncocytic cytoplasm, prominent nucleoli
PanNET vs Adenocarcinoma

• Nuclei: “salt and pepper” chromatin, elongated, plasmacytoid, spindled

• Even in the presence of atypia, retain uniformity of the nuclei

• More cohesive fragments, glandular differentiation

• More pleomorphism and nuclear atypia, mitosis, necrosis

Right side image Dr. Matthew Zarka
Extra/ Final Case: Outside consult for Second Opinion- Surgeon’s Request

81 year old male with a large solid mass
Unresectable pancreatic mass at presentation
Patient very ill and another EUS- FNA not feasible
Outside Diagnosis

• Suspicious for neoplasm

• Differential diagnosis
  • Low grade neuroendocrine tumor
  • Serous cystadenoma
IHC

- Negative:
  - PASD
  - Mucin
  - CK7/ CK20
  - PAX8
  - TTF1
  - Chromogranin
  - Synaptophysin
Synaptophysin
Serous Cystadenoma

- Markedly hypocellular, clear fluid
- Small cuboidal cells
- Imaging: “soap bubble”, central scar, “star burst” pattern of calcifications
Serous Cystadenoma: Inhibin+
Serous Cystadenoma vs Outside Case
Serous Cystadenoma vs Outside Case
Next steps:

??Request Block and do more stains
### IHC Solid Pancreatic Epithelial Neoplasms

<table>
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<th>Diagnosis</th>
<th>Immunostains</th>
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<td>Pancreatic adenocarcinoma</td>
<td>SMAD-4 loss (50%) Mesothelin expression</td>
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<tr>
<td>Neuroendocrine tumor</td>
<td>CK+ve, CD56, synaptophysin, chromogranin, PAX-8*</td>
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<tr>
<td>Acinar cell carcinoma</td>
<td>CK+ve, Trypsin, chymotrypsin</td>
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<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>CK negative, b-catenin (nuclear localization), CD56, CD10, Trypsin, chymotrypsin,</td>
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Next steps:

- Request the Block and do more stains
  
- OR...

- Look at the case again...
Back to Outside Case: Fibrotic areas
Outside Case: ThinPrep
Summary- Pancreas FNA Pitfalls

- Normal Pancreas vs Neoplasm
  - Preserved acinar/ normal lobulated architecture

- Cystic lesions:
  - Low cellularity
  - GI contamination
  - Very helpful:
    - Correlation with imaging, fluid chemistry (CEA, Amylase), molecular analysis
    - Thick colloid like extracellular mucin favors mucinous neoplasm
  - IPMN: LG vs HG very important distinction

- Adenocarcinoma:
  - Low N/C ratio
  - Difficult to distinguish from reactive conditions (AIP, CP)
  - Look for fibrotic fragments, lymphoid tangles
  - Correlation with imaging and clinical findings essential
The glomerulus shows mesangial expansion with nodular homogeneous acellular eosinophilic deposits. Vascular wall deposits are also present (arrows).

Thanks!

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References


- ASC Meeting 2020: Images and content

- ASCP Meeting 2021: Images and content
Normal

- Predominance of acinar cells (except chronic pancreatitis)
- Acinar cells: cohesive, small grape-like clusters of cells, scattered polygonal single cells, occasional stripped nuclei
- Round regular Nuclei, central to eccentric, uniform chromatin, often prominent nucleoli
- Abundant granular cytoplasm (DQ: small vacuoles)
- Architecture: Key to differentiate B9 acinar cells from neoplasm (small uniform grape-like)
**IVA Neoplastic Benign**
- Serous cystadenoma
- Cystic teratoma
- Schwannoma
- Lymphangioma

**IVB Neoplastic Other**
- Intraductal papillary mucinous neoplasm
- Mucinous cystic neoplasm
- Neuroendocrine tumor*
- Solid pseudopapillary tumor

**Benign behavior**

Not definitive benign but warrants distinction from high grade malignancy
Case 1 Vs SPN
Case 1 Vs SPN
SPN vs Case 1

- Mild nuclear enlargement (CHECK)
- Irregular nuclear contours
- Intranuclear grooves
- Cytoplasmic tails
- Extracellular PAS+ hyaline globules

- Nuclear (N) size = RBC
- Basally located N
- Round, smooth membranes
- Key: architecture “grape-like”, uniform cells adhesed to fibrovascular core
Thanks

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Case 1
Duodenal papilla Reactive
Duodenal papilla Reactive
Cystic Neuroendocrine Neoplasms: Cytology

Patterns: Loosely cohesive tissue fragments with predominately dispersed single cells; Epithelial proliferations with fibrovascular stroma or cores within epithelial tissue fragments

Cellularity: varies

Perivascular/coronal pattern

Monomorphic appearance; some cells out of proportion to others

Plasmacytoid, bi-nucleate; stripped nuclei

Salt and pepper chromatin

Pink granules with air dry stains

Synaptophysin +; chromogranin+ patchy
Liver mass, needle biopsy
Liver mass, needle biopsy: Well-differentiated neuroendocrine tumor with focal hepatoid differentiation. Ki67 performed on the outside biopsy = WHO grade 2 of 3 (Ki-67 = 14.35%).
Recent Updates on Neuroendocrine Tumors From the Gastrointestinal and Pancreatobiliary Tracts

Jin Young Kim, MD, PhD; Seung-Mi Hong, MD, PhD

• Context.—Gastrointestinal (GI) and pancreatobiliary tracts contain a variety of neuroendocrine cells that constitute a diffuse endocrine system. Neuroendocrine tumors (NETs) from these organs are heterogeneous tumors with diverse clinical behaviors. Recent improvements in the understanding of NETs from the GI and pancreatobiliary tracts have led to more-refined definitions of the clinicopathologic characteristics of these tumors. Under the 2010 World Health Organization classification scheme, NETs are classified as grade (G) 1 NETs, G2 NETs, neuroendocrine carcinomas, and mixed adeno-neuroendocrine carcinomas. Histologic grades are dependent on mitotic counts and the Ki-67 labeling index. Several new issues arose after implementation of the 2010 World Health Organization classification scheme, such as issues with well-differentiated NETs with G3 Ki-67 labeling index and the evaluation of mitotic counts and Ki-67 labeling.

Hereditary syndromes, including multiple endocrine neoplasia type 1 syndrome, von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis, are related to NETs of the GI and pancreatobiliary tracts. Several prognostic markers of GI and pancreatobiliary tract NETs have been introduced, but many of them require further validation.

Objective.—To understand clinicopathologic characteristics of NETs from the GI and pancreatobiliary tracts.

Data Sources.—PubMed (US National Library of Medicine) reports were reviewed.

Conclusions.—In this review, we briefly summarize recent developments and issues related to NETs of the GI and pancreatobiliary tracts.


In addition to the typical features of NETs, some pancreatic NETs show morphologic variations, including clear cell, oncocytic, and pleomorphic types. Clear cell NETs will be discussed in the section on von Hippel-Lindau syndrome (Figure 3, A). Oncocytic pancreatic NETs contain large polygonal cells with eosinophilic granular cytoplasm and prominent nucleoli (Figure 3, B). Some studies reported that oncocytic tumors have a malignant clinical behavior. In the setting of liver metastasis of oncocytic pancreatic NETs, immunohistochemical staining
Neuroendocrine Tumors
PSC Categories

- I: Non-diagnostic
- II: Benign
- III: Atypical
- IVb: Neoplastic, other
- IV: Suspicious
Cysts of the pancreas

- Non-neoplastic
  - Pseudocyst
  - Retention cyst
  - Congenital cyst
  - Foregut cyst
  - Endometriotic cyst

- Cystic nonepithelial neoplasms
  - Lymphangioma
  - Hemangioma

Adsay NV. ModPathol (2007): 20:S71-S93
- KRAS seen in about 61% of IPMN and 21% of MCN
- GNAS mutation almost exclusively found in IPMN but has been found in SCA
- KRAS and GNAS seen together suggests IPMN
- KRAS or GNAS has no prognostic indication, can be seen in both low and high grade dysplasia

Mucinous cystic neoplasm:

cytology

Pattern: Mucinous background

- Thick mucous, if present, extremely helpful
- Low cellularity
- Flat sheet or single mucous cells
- Ovarian-type stroma often absent
- Cytologic atypia depends on degree of differentiation
  - Cytology often underestimates the final histologic grade

Is this a mucinous cyst?

Neoplastic mucin or GI mucin?

If there is abundant “gut” epithelium, be careful!
Pancreatic pseudocyst

- Clinical
  - Age: All ages (pancreatitis – older)
  - Males > Females
  - Tail more common
  - 2-30 cm
- Gross: fibrous, necrotic wall
- Chemistry: high amylase (usually in the 1000s U/l) and lipase, low CEA

Adsay NV. ModPathol (2007): 20:S71-S93
Pancreatic pseudocyst cytology

Patterns: **Inflammatory cells predominating without epithelial tissue fragments; Stromal fragments without epithelial tissue fragments**

Hypocellular and lack epithelial cells; no serous or mucinous or lining epithelium

- GI contaminant common

Nonspecific cystic contents

Necrosis, protein debris, mixed inflammatory cells, mostly lymphocytes and histiocytes, including hemosiderin laden macrophages, cholesterol crystals

- granulation tissue uncommon
Serous cystadenoma

- Gender: more common in women than men (7:3)
- Older (average 61-68)
- Location: anywhere, ? predilection in the head
- Symptoms: abdominal pain and weight loss
- Prognosis: vast majority benign

- Gross: Numerous tightly packed small cyst and stellate scar; sponge-like
- Chemistry: low amylase (<250 ng/ml and CEA (<5ng/ml)
Serous Cystadenoma:

Pattern: Predominately discohesive epithelial cells with single cells.

Usual scant cellularity

Bloody aspirate; possible strands of fibrous, vascularized tissue. Histiocytes and histiocytes with hemosiderin common

- usually absent in mucinous cysts

Delicate flat sheet of cuboidal, bland, serous-type epithelium

- often not present

- liquid based preps may preserve lining cells better

Lining cells with bland, centrally located nuclei, and may have nuclear grooves

- mimic benign mesothelial cells
Mucinous Background

- Benign
  - Gastric epithelium
  - Duodenal epithelium
  - Squamoid cyst of pancreatic ducts

- Neoplastic
  - Mucinous cystic neoplasm
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm

- Malignant
  - Mucinous non-cystic adenocarcinoma
  - Signet ring carcinoma
Mucinous Cystic Neoplasm

- **Clinical**
  - Gender: much more common in women than men
  - Age: mean age at diagnosis 50
  - Location: Tail > head
  - Gross: Thick fibrous wall, multicystic; usually larger than 2cm
  - Lined by glandular cells and ovarian stroma; septae; may show calcifications
  - Chemistry: low amylase, high CEA

Adsay NV. ModPathol (2007): 20:S71-S93
Intraductal Papillary Mucinous Neoplasm (IPMN)

**Clinical**
- Male >> Female
- Mean age 68
- Location: Head (89%)
- Gross: Localized, multicentric, important to document relation with pancreatic ductal system
  - Cystically dilated ducts containing mucin with various degrees of atypia
- Chemistry: High amylase, high CEA (>192 ng/ml)
- Imaging: communicate with pancreatic duct system
  - mucin oozing from the ampulla of Vater
Intraductal Papillary Neoplasm: Cytology

Pattern: Mucinous background
- Thick mucus; foamy histiocytes
- Single cells, flat sheets, small clusters
- Low vs high cellularity
- Goblet cells
- Atypia

Low grade (low-intermediate dysplasia)
- 3D architecture
- Variable amount of cytoplasm w/o visible mucin or vacuoles
- 2-4 tight buds of cells
- High N/C ratio

High grade (high grade dysplasia)
- Mild-moderate nuclear irregularity
- Hypo or hyperchromasia, variable nucleoli
- Scant to moderate cellular necrosis
- Small single cells (< 12 micron duodenal enterocyte)
Case …

63 yo male with UC
Multiple cystic pancreatic lesions since 2018
2019 Pancreas FNA
Atypical cells present

Atypical mucinous epithelium, cannot exclude high grade dysplasia
Follow up MRI

- Stable pancreatic tail cystic lesions communicating with pancreatic duct measuring up to 1.4 cm
- No pancreatic ductal dilatation, no atrophy.
- Clinical impression “IPMN indeterminate for atypia”
- Distal pancreatectomy recommended, but patient decided on conservative management.
- Patient still alive 2022
- No worrisome imaging findings
- Follow-up MRI/MRCP in 1 year
Invasive ductal adenocarcinoma, moderately differentiated arising in a background of high grade pancreatic intraepithelial neoplasia (PanIN-3)
Standardized Terminology and Nomenclature for Pancreato-Biliary Cytology

I. Non-Diagnostic
II. Negative for malignancy
III. Atypical
IV. Neoplastic:
   - Benign (serous cystadenoma)
   - Other:
     - Mucinous cysts (low- and high- grade dysplasia)
     - Well-differentiated neuroendocrine tumors
     - Solid- pseudopapillary neoplasm
V. Suspicious for malignancy
VI. Positive for malignancy
LG IPMN

- Flat sheets, papillary groups
- Bland nuclei or mild atypia
- Abundant colloid like thick mucin in the background
- Radiology:
  - Cystic lesions with communication with the main duct, or main duct IPMN
- Chemistry/ molecular analysis:
  - High CEA (196ng/mL), amylase is variable
- KRAS mutation common in mucinous neoplasms
Another IPMN
Another case (same as prior)
Another case ipmn w hgd
IPMN HG vs LG Dysplasia

- High N/C ratio, "small" cells, variable cytoplasm
- Nuclear atypia (irregularity, hyper or hypochromasia)
- Loss of nuclear polarity
- Single cells or complex architecture (3D, 2-4 tight buds of cells)
- Less/scant background mucin, -/+ necrosis

- Uniform cells
- Bland or mild nuclear atypia
- No architectural complexity
- Intracytoplasmic mucin
- Abundant extracellular mucinous material
Another case highly atyp cells susp colloid ca CEA 11500 cw IPMN clinically
Same case
Same
Same
DO NOT DELETE MCN (ASC Meeting)
DO NOT DELETE EP slimier to CB of case w atyp cannot r/o adeno, but this MCN ASC Meeting more organized, no loss of polarity
Adenocarcinoma

Patterns: Predominately cohesive epithelial or ductal-type tissue fragments; Mucinous background; Predominantly discohesive epithelial cells with single cells; Dirty or Necrotic Background

Major criteria
- Nuclear overlap and crowding
- Nuclear contour irregularity
- Chromatin clearing or clumping

Minor criteria
- Single epithelial cells
- Necrosis, mitosis
- Nuclear enlargement

Acta Cytol, 1995; 39:1-10
Adenocarcinoma

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Minor criteria
Single epithelial cells
Necrosis, mitosis
Nuclear enlargement

Acta Cytol, 1995; 39:1-10
Crowding/ overlapping/ 3D, single cells, drunken honeycomb

Nuclear features:
- Enlargement, anisonucleosis (4:1), membrane irregularity, clearing/ hyperchromasia, macronucloli

Cytoplasm:
- Scant or abundant- mucinous

Necrosis, mitosis, single cells
Adenoca
Adenoca
AIP Cytology

- Decreased ductal-type groups, abundant acinar epithelium
- Atypia
- Cellular stromal fragments rich in lymphocytes or lymphoid tangles
- Variable background inflammation: nil to moderate
AIP
AIP
AIP
AIP
AIP CB
AIP vs Adenocarcinoma
Cystic Pancreatic Neuroendocrine Tumors (PanNET)

- Rare; 5-10% of pancreatic neoplasms
- Cyst formation not due to necrosis in contrast to cystic adenocarcinoma
- Usually unilocular; up to 25 cm
Somastatinoma
Somastatinoma CB
Somastatinoma CB
Summary- Pancreas FNA Pitfalls

• Normal Pancreas
• May mimic neoplasms
• Preserved acinar architecture
• Cystic lesions:
• Low cellularity
• Correlation with imaging, CEA, Amylase
• Adenocarcinoma:
• Low N/C ratio
• Look for ….
Summary- Pancreas FNA Pitfalls

- Normal Pancreas vs Neoplasm
  - Preserved acinar/ lobulated architecture

- Cystic lesions

- Challenges:
  - Low cellularity
  - GI contamination

- Helpful:
  - Correlation with imaging, fluid chemistry (CEA, Amylase), molecular analysis very helpful
  - Thick colloid like extracellular mucin favors mucinous cystic neoplasm
  - Cell block, IHC

- Adenocarcinoma:
  - May have low N/C ratio
  - Chronic pancreatitis, AIP: false positive
  - Look for fibrotic fragments with lymphoid tangles
NOTES IF ENOUGH TIME ADD

• Slide w solid pseudopap neopl (SSP) before slide w IHC
• Slide w descriptive comparison ssp vs normal
• TABLEs W KI-67 AND NET (ASC pg 59)
• Table PNT vs acinar pg60 (for keeping)
• Slide w NET vs adeno text and pictures comparison
SSP Cytology
CP Misdiagnosed as PanNET on FNA

- Isolated and loosely cohesive cells with eccentrically located bland appearing nuclei
- Background of lymphocytes
- Resection:
  - Predominance of islet cells

Duodenal and gastric epithelium contaminant in EUS-FNA of pancreas
Cell block section
Stomach

- Thin, watery mucin
- Small /intermediate/large clusters
- Apical mucin cups
- Grooved naked nuclei within mucin
- Cell types:
  - Mucinous, parietal, chief cells

Slide by Dr. Matthew Zarka
Which of the following is IPMN?
IPMN, LOW GRADE

GASTRIC FOVEOLAR CELLS

BENIGN PANCREATIC DUCTAL CELLS
Foto de ratoeira ou tap