Pancreatitis: A Potential Pitfall in Endoscopic Ultrasound-Guided Pancreatic FNA

Jack Yang, MD
Department of Pathology, Medical University of South Carolina

Objectives

• Understand the indication of EUS-guided Pancreatic FNA
• Know the cytologic features of chronic pancreatitis
• Know the differential diagnoses of chronic pancreatitis
• Know the limitations of pancreatic cytology

Indication of EUS-Guided Pancreatic FNA

• Clinical evaluation and imaging study suggestive of pancreatic neoplasia
• Imaging study reveals definitive evidence of unresectability for pancreatic or biliary tract cancer
• A nonoperative candidate due to comorbidities
• Pre-operative neoadjuvant chemotherapy and/or radiation
• EUS-guided FNA can be performed as an integral part of EUS examination, allowing definitive tissue acquisition and rapid diagnosis
Pancreatobiliary Terminology Classification Scheme
Proposed By The Papanicolaou Society of Cytopathology

- I. Nondiagnostic
- II. Negative (for malignancy)
- III. Atypical
- IV. Neoplastic: benign and other
- V. Suspicious (for malignancy)
- VI. Positive/malignant

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Chronic Pancreatitis?

Normal Components in EUS-guided Pancreatic FNA

- GI contaminants
  - Gastric wall
    - Gastric epithelium
    - Chief cells and parietal cells
    - Smooth muscle
  - Duodenal wall
    - Small intestinal epithelium
    - Brunner's glands
    - Smooth muscle
- Pancreatic parenchyma
  - Ductal cells
  - Acinar cells
  - Islet cells
Gastric mucosal components

- Foveolar cells
  - Sheets and strips; occasional isolated cells and gastric pits
  - Visible mucin (foveolar cells)
  - Grooved naked nuclei

Gastric foveolar cells IPMN
Gastric mucosal components

- Gastric chief and parietal cells
  - Cuboidal or pyramidal shaped cells with eccentrically/basally located nuclei
  - Granular or fine vacuolated cytoplasm
  - Single, acinar, or small tubular configurations
Duodenal components

Gastrointestinal Mucosal Contaminants

- **Duodenal mucosa**
  - Flat, cohesive monolayer sheets with a honeycomb pattern
  - Non-mucinous glandular cells with brush border
  - Sporadically placed goblet cells appear as "fried eggs" within the sheet
Brunner’s Gland

- Columnar with basally located nuclei and abundant foamy cytoplasm

Brunner’s Glands

Normal Pancreas

- Acinar cells: two-tone cytoplasm-basophilic at the base and eosinophilic at the apical pole
- Ductal cells: Columnar epithelial cells
- Langerhans islet cells: loosely packed pale staining cells.
Acinar Cells

- Cohesive acinar or grapelike aggregates
- Eccentrically placed round nucleus with evenly distributed, finely granular chromatin
- Small nucleoli
- Abundant granular cytoplasm
- Indistinct cell borders in clusters

Acinar Cells

- Tissue fragments attached to fibrovascular stroma

Acinar Cells

- Abundant granular cytoplasm
- Indistinct cell borders in clusters
Ductal cells

- Flat, cohesive sheets (few isolated cells) with evenly spaced nuclei
- Round to oval nucleus with evenly distributed, finely granular chromatin
- Cuboidal or columnar shape
- Inconspicuous nucleolus
- Well-defined cytoplasmic borders

Langerhans Islet Cells

- Rarely identified in aspirates of normal pancreas
- Isolated cells, bare nuclei and small loosely cohesive clusters
- Plasmacytoid appearance
- Stippled (“salt and pepper”) chromatin with or without nucleoli

Chronic Pancreatitis

- Chronic pancreatitis is a progressive inflammatory processes of the pancreas of various etiology
  - Lymphocyte infiltration
  - Progressive atrophy of acinar parenchyma
  - Pancreatic Duct changes
    - Duct dilatation
    - Protein plugs
  - Fibrosis
Chronic pancreatitis

- Acinar atrophy
- Duct dilatation and proteinaceous plug

Chronic pancreatitis

- Pseudocyst

Chronic Pancreatitis

- Fibrosis
**Chronic Pancreatitis**

- Frequent mucinous metaplasia/Pancreatic intraepithelial neoplasia (PanIN)
- Residual islet and islet hyperplasia

**Cytologic Features of Chronic Pancreatitis**

- Low cellularity
- Lymphocytes
- Normal pancreatic parenchyma
**Nondiagnostic**

A nondiagnostic cytology specimen is one that provides no diagnostic or useful information about the solid or cystic lesion sampled.

- Unsatisfactory for evaluation
  - Mucin
  - Artifacts
- Satisfactory for evaluation, but cannot explain mass lesion seen on imaging
  - Gastrointestinal (GI) contamination
  - Normal acinar and ductal epithelium
  - Cyst contents with insufficient cyst fluid volume for ancillary testing

**Cytologic Features of Chronic Pancreatitis**

- Pancreatic parenchyma and lymphocytic infiltration
- Plasma cells

**Cytologic Features of Chronic Pancreatitis**

- Fragments of fibrous tissue with lymphocytic infiltration
- Pseudocyst contents
Cytologic Features of Chronic Pancreatitis

- Fat necrosis
- Granulation tissue fragments

Negative (for Malignancy)

- A negative cytology sample is one that contains adequate cellular and/or extracellular tissue to evaluate or define a lesion that is identified on imaging.
- When using the negative category one should give a specific diagnosis
  - Benign pancreatic/biliary tissue in the setting of vague fullness and no discrete mass
  - Acute pancreatitis/Chronic pancreatitis/Autoimmune pancreatitis
  - Benign cyst
    - Pseudocyst
    - Lymphoepithelial cyst
    - Serous cyst
    - Splenule/accessory spleen
  - False negative rate is approximately 15% for solid and up to 60% on cystic pancreatic lesions

Cytologic Features of Chronic Pancreatitis

- Enlarged nuclei and variation in size in the same sheet (less than 4:1 diameter ratio)
- Nuclear groove
- Small prominent nucleoli
Atypical

- Cells present with cytoplasmic, nuclear, or architectural features that are not consistent with normal or reactive cellular changes of the pancreas, and are insufficient to classify them as a neoplasm or suspicious for a high-grade malignancy
  - Scant atypical cells
  - Mucinous neoplasm vs. gastric mucosal contamination
  - High grade pancreatic intraepithelial neoplasia (PanIN) vs. mucinous neoplasm (IPMN, MCN, Mucinous adenocarcinoma)
  - Benign acinar cells and islet cells vs. pancreatic neuroendocrine tumor

Suspicious (for malignancy)

- Some but an insufficient number of the typical features of a specific malignant neoplasm are present, mainly pancreatic adenocarcinoma.
- The morphologic features must be sufficiently atypical that malignancy is considered more probable than not

Case 1

- 56 year old man with long history of abdominal pain
- CT showed 2 cm mass at the tail of pancreas
Case 1

A. Chronic Pancreatitis
B. Atypical Lymphocytes, send for flow cytometry study
C. Large cell lymphoma
D. Small cell carcinoma
E. Intrapancreatic spleen

Case 1

- Cytologic diagnosis
  - Atypical lymphocytes, cannot exclude lymphoma
  - Correlate with flow cytometry result

Case 1

- Histological diagnosis
  - Follicular pancreatitis
Diagnosis?

Case 1
A. Chronic Pancreatitis
B. Atypical Lymphocytes, send for flow cytometry study
C. Large cell lymphoma
D. Small cell carcinoma
E. Intrapancreatic spleen

Small Cell Carcinoma
- Scant cytoplasm
- Hyperchromatic nuclei with stippled ("salt and pepper") chromatin
- Nuclear molding
- Mitosis or apoptosis
- No nucleoli
Small Cell Carcinoma

Diagnosis?

Case 1
A. Chronic Pancreatitis
B. Atypical Lymphocytes, send for flow cytometry study
C. Large cell lymphoma
D. Small cell carcinoma
E. Intrapancreatic spleen
Intrapancreatic Accessory Spleen

- Accessory spleens are estimated to be present in approximately 10% of the general population and 15%-20% of them are present in the pancreatic tail
- Mimic solid pancreatic tumor, especially pancreatic neuroendocrine tumor on imaging
- Gross and histological appearances are similar to normal spleen
- Epidermoid cyst can be seen in pancreatic accessory spleen
Intrapancreatic Accessory Spleen

- Cytologic Features
  - Scattered tissue fragments comprised of tangles of small blood vessels surrounded by small lymphocytes embedded in perivascular tissue
  - Single cell population of polymorphous hematopoietic cells
  - CD8 stains the splenic sinus endothelial cells
  - CD56 stains a subset of T-cells
Case 2

- 29 year-old female patient with a history of autoimmune pancreatitis
- Imaging study showed 3 cm mass in the tail of pancreas

Case 2

A. Chronic pancreatitis
B. Atypical cells, cannot exclude Pancreatic neuroendocrine tumor (PanNET)
C. PanNET
D. Acinar cell carcinoma
E. Solid pseudo-papillary neoplasm
Case 2

- Histological diagnosis
  - Chronic Pancreatitis

Pancreatic Neuroendocrine Tumor (PanNET)

- Cytologic Features of PanNET
  - Predominantly isolated cells, bare nuclei, pseudorosettes and small clusters
  - Eccentric nuclei (plasmacytoid appearance) with finely stippled (“salt and pepper”) chromatin and with or without nucleoli
  - Moderate to abundant granular cytoplasm

Pancreatic Neuroendocrine Tumor (PanNET)

- Cytologic Features of PanNET
  - Nuclei are usually uniform, but may be pleomorphic
Acinar Cell Carcinoma

- Cytologic Features of Acinar Cell carcinoma
  - Highly cellular
  - Numerous isolated cells, loose cell aggregates, naked tumor nuclei
  - Loose granules in the background

Acinar Cell Carcinoma

- Cytologic Features of Acinar Cell carcinoma
  - Prominent nucleoli
  - Naked Nuclei

Acinar Cell Carcinoma

Mixed acinar cell carcinoma and PanNET
Solid-Pseudopapillary Neoplasm (SPN)

- Monomorphic, uniform epithelial cells forming solid nests and sheets, together with pseudopapillae
- Hyalinized and myxoid stroma containing small thin-walled blood vessels
- Degenerative changes include hemorrhage, cystic spaces, and foamy macrophages
Solid-Pseudopapillary Neoplasm (SPN)

- Cytologic Features of SPN
  - Myxoid or hyalinized vascular stalks lined by neoplastic cells
  - Delicate, finely vacuolated cytoplasm with indistinct cell borders
  - PAS-D–positive hyaline globules
  - Round/oval, bean-shaped nuclei
  - Foam cells and necrotic debris
### Immunohistochemistry of PanNET, ACC, and SPN

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<th>ACC</th>
<th>SPN</th>
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<tr>
<td>Pan-Cytokeratin</td>
<td>+</td>
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PanNET: Pancreatic neuroendocrine tumor
ACC: Acinar cell carcinoma
SPN: Solid-pseudopapillary neoplasm

### Case 3

- A 66-year-old male patient with history of chronic pancreatitis
- Imaging study show large mass at the head of pancreas

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Case 3

A. Chronic pancreatitis
B. Atypical cell, cannot exclude mucinous neoplasm
C. Mucinous neoplasm
D. Adenocarcinoma with signet-ring features
Case 3

Histological Diagnosis
- Chronic pancreatitis with extensive high grade PanIN
Take Home Messages

- Chronic pancreatitis can mimic solid pancreatic neoplasm radiologically, cytological, and histologically
- Both the degree of atypia and quantitation of atypical cells are important in the diagnosis of pancreatic solid tumors in patients with history and cytologic features of chronic pancreatitis