DIAGNOSTIC CHALLENGES:
Cytology Slide Seminar
Pancreas FNAB
Dr. M. Weir
May 2015

CONFLICT OF INTEREST DISCLOSURE

- I have not had in the past 3 years, a financial interest, arrangement or affiliation with one or more organizations that could be perceived as a direct or indirect conflict of interest in the content of this presentation.

OBJECTIVES

- Recognize diagnostic approaches to complex cytological problems
- Expand knowledge & skills in interpretation of advanced cytology sampling techniques & ancillary tests
AGENDA

- 2 cases
- Pancreas eus fnabs
- Posted online prior to session
- Approach, diagnostic differentials

Photos:
Hologic, PathologyOutlines, Icytology.wordpress.com

Case 1

- 55 year old female
- Head of pancreas (HOP) mass
- Solid, 5 x 4 cm
- Transduodenal EUS FNAB
Approach

- Clinical & imaging important
  - if solid – use algorithm for DDX

- Microscopic approach
  - Adequacy
    - Background
    - Contamination
    - Diagnosis
**ALGORITHM:**
Solid Pancreas Mass EUS FNAB

<table>
<thead>
<tr>
<th>Non-neoplastic</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal contaminant</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Pancreatic endocrine neoplasm</td>
</tr>
<tr>
<td>- chronic</td>
<td>Acinar cell carcinoma</td>
</tr>
<tr>
<td>- autoimmune</td>
<td>Solid pseudopapillary neoplasm</td>
</tr>
<tr>
<td>- acute</td>
<td>Pancreaticoblastoma</td>
</tr>
<tr>
<td>Infection</td>
<td>Metastasis</td>
</tr>
</tbody>
</table>

**ADEQUACY: ROSE**

- Define adequacy to accommodate threshold differences in interpretation

- **Solid lesion:**
  - Epithelial predominant: > 10 groups
  - Inflammation: may not be lesional

**BACKGROUND**

- Fat necrosis & chronic pancreatitis
- Coagulative necrosis: malignant
CONTAMINATION

- Esophagus
- Stomach
- Duodenum
- Biliary duct
- Pancreas

DIAGNOSIS: LO POWER

<table>
<thead>
<tr>
<th>Mucosal Contamination</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low to high cellularity</td>
<td>High</td>
</tr>
<tr>
<td>Cohesive, 2-D, flat</td>
<td>Loosely cohesive, 3D</td>
</tr>
<tr>
<td>Polarized groups</td>
<td>Drunken honeycomb</td>
</tr>
<tr>
<td>Naked grooved nuclei</td>
<td>Single abN cells</td>
</tr>
<tr>
<td>In mucus blobs</td>
<td>Necrosis (coagulative)</td>
</tr>
</tbody>
</table>

- Duodenal epithelium: Cohesive, honeycomb, goblet cells
- Adenocarcinoma: Drunken honeycomb, atypia
Gastric epithelium polarized, organized, bare grooved nuclei

Mucin, upper 1/3 cell

Adenocarcinoma drunken honeycomb, atypia

DIAGNOSIS: LO POWER

**Chronic pancreatitis***
- Low to high cellularity
- Polymorphous-acini, ducts
- Cohesive clusters - acini
- Polarized groups
- Absence/rare single cells
- Inflammation
- Necrosis (fat)

**Adenocarcinoma**
- High
- Monomorphous
- Loosely cohesive
- Drunken honeycomb
- Single cells
- Necrosis (coagulative)

* may be perilesional

Chronic pancreatitis

Lobular

Tangies

Intermixed lymphocytes

Lobular
**DIAGNOSIS: HI POWER**

<table>
<thead>
<tr>
<th>Chronic pancreatitis</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No to min crowding</td>
<td>Nuclear crowding, overlap</td>
</tr>
<tr>
<td>Hypochromatic, even</td>
<td>Irregular chromatin</td>
</tr>
<tr>
<td>Regular contours</td>
<td>Irregular nuclear contour</td>
</tr>
<tr>
<td>Less nuclear enlargement</td>
<td>Nuclear enlargement</td>
</tr>
<tr>
<td>Tiny nucleoli, not abN</td>
<td>AbN nucleoli</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mitoses: numerous, abN</td>
</tr>
<tr>
<td>- in epith, background</td>
<td>Mucin vacuoles</td>
</tr>
<tr>
<td></td>
<td>- indent nuclei, fill cell</td>
</tr>
</tbody>
</table>

**DIAGNOSTIC CRITERIA: CA**

**Major**
- Crowding & overlap
- Irregular chromatin clearing & clumping
- Irregular nuclear contours

**Minor**
- Nuclear shape/size
  - 2-3x increase
  - aniso 4:1 rule
- Single malignant cells
- Necrosis, mitoses

Robins et al, 1995

2 or more major OR 1 major, 3 minor = hi sens/spec/accuracy

**Positive for Malignancy**

Ductal Adenocarcinoma

**Poorly differentiated CA**

Nuclear molding
- 2-3x size N ductal nucleus
- Aniso 4:1 = hi sens/spec

Cohen et al, 1991
DIAGNOSTIC CRITERIA

Well differentiated CA
Subtle nuclear atypia
Slight nuclear crowding, overlap
Drunken honeycomb

DIAGNOSIS

- Diagnosis of pancreatic adenocarcinoma
  - significant
    - Whipple’s vs palliation
  - be sure it is positive!
    - consult liberally
    - internal or external
    - LHSC: 40% rate

Case 1
Positive for Malignancy
Ductal Adenocarcinoma
Duodenal contamination
Consider benign mimics for pancreas ca - pancreatitis, GI contaminants

Case 2

- 60 year old male
- BOP mass
- Cystic on imaging, unilocular
- Transgastric EUS FNAB
**APPROACH**

- Clinical & imaging important
  - if cystic - use algorithm for DDX
  - check cyst chemistry

- Microscopic approach
  - Adequacy
  - Background
  - Contamination
  - Diagnosis

**ALGORITHM:**

**Cystic Pancreas Mass EUS FNAB**

<table>
<thead>
<tr>
<th>Non-neoplastic</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal contaminant</td>
<td>Neoplastic Mucinous Cyst - MCN, IPMN</td>
</tr>
<tr>
<td>- mucus</td>
<td>- Serous Neoplasm</td>
</tr>
<tr>
<td>- GI epithelium</td>
<td>- Any solid neoplasm - PanNET, SPN, AC</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td></td>
</tr>
<tr>
<td>Other benign cysts</td>
<td></td>
</tr>
</tbody>
</table>

**CYST CHEMISTRY**

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Amylase</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PanNET, serous cystad, SPN</td>
<td>low (&lt; 250 U/L)</td>
<td>low (&lt; 0.5 ng/mL) may be elevated - serous</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>high (&gt; 1000s U/L)</td>
<td>low, may be elevated</td>
</tr>
<tr>
<td>IPMN</td>
<td>high, but variable</td>
<td>&gt; 200 ng/mL, may be low</td>
</tr>
<tr>
<td>MCN</td>
<td>low or high</td>
<td>&gt; 200 ng/mL, may be low</td>
</tr>
</tbody>
</table>

Our case: high amylase, elevated CEA
ADEQUACY: ROSE

Cystic lesion:
- cyst fluid characteristics (vol, type)
  - viscous (mucinous)
  - watery (serous)/ turbid (pseudocyst)
- cyst protocol: no microscopic ass’t
  - 4 smears: 1 air dried, 1 alcohol, Pap
    2 mucin stains (PASd, AB2.5)
  - 1 ThinPrep +/- cell block

BACKGROUND: Mucus/Mucin

GI luminal mucus
- watery, thin, dirty
- food, heterogeneous

Mucin
- thick, uniform
- cracked, colloid-like

BOTH = mucin stains

BACKGROUND

Mucin = neoplastic mucinous cyst
Cystic contents
Not in GI mucus

Serous cystadenoma
Clean, hemosiderin, histios

Pancreatic pseudocyst
Debris, acute inflammation

WHO: Pitman
Gastric epithelium polarized, organized, bare grooved nuclei

Mucin, upper 1/3 cell

Neoplastic mucinous epithelium

**CONTAMINATION**
Beware - gastric type IPMN mimics N: hard to tell

**CYSTIC LESION**
2 issues

1. Mucinous or not?
2. High grade atypia or not?

**DIAGNOSIS**
Mucinous or not?
- smears best (esp air dried)
- ThinPrep – mucolytic, never alone
- may be wispy, thin
- 1/3 mucinous cysts lack mucin
- mucin = lesional
  Call it neoplastic mucinous cyst
DIAGNOSIS
High grade atypia or not?
- never ignore atypia
- atypia in cyst = pancreatic neoplasm
- malignant features (adenocarcinoma)
  - call it positive
- atypia < overtly malignant
  - call it neoplastic (lo vs hi gr atypia)
  - hi grade includes: mod & hi gr dysplasia

ATYPIA
High Grade Atypia Criteria
- Small cells
- Inc N/C ratio
- Hyperchromasia
- Nuclear elongation
- Crowding, loss polarity
- Papillary or tight clusters
- Single cells

Types IPMN/MCN
**Gastric**
Lo or hi grade
**Intestinal**
At least intermediate grade
**Pancreatobiliary***
**Oncocytic***
***High grade by definition (cytology)***
### Cyst Contents Template

<table>
<thead>
<tr>
<th>Cyst contents:</th>
<th>Present/Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucin:</td>
<td>Present/Absent</td>
</tr>
<tr>
<td>Mucin Stains:</td>
<td>Positive/Negative/NA</td>
</tr>
<tr>
<td>Lesional Cells:</td>
<td>Mucinous/Serous/Other</td>
</tr>
<tr>
<td>Atypia:</td>
<td>Low/High grade</td>
</tr>
<tr>
<td>Mucosal Contamination:</td>
<td>Gastric/Duodenal</td>
</tr>
<tr>
<td></td>
<td>Present/Absent</td>
</tr>
</tbody>
</table>

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**Case 2: Neoplasm**

**Neoplastic Mucinous Cyst**

**Clinically:** IPMN, unilocular

Cyst contents: present
Mucin: present
Mucin stains: positive
Lesional cells: NA
Contamination: gastric

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**Consider benign mimics for neoplastic mucinous cysts**

- GI mucus & epithelium
Take home points

For solid pancreas EUS FNAB
- use malignancy criteria
- consider benign mimics
- consult liberally

For cystic pancreas EUS FNAB
- identify mucin – it’s enough for dx
- consider benign mimics
- look for mucinous epi, atypia

“Being challenged in life is inevitable, being defeated is optional.”
Roger Crawford