Incidental Pancreatic Duct Dilation on Imaging

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Disclosures

- Consultant Boston Scientific
Objectives

- Discuss the magnitude of the problem.
- Differential Diagnosis.
- Diagnostic testing.
- Future developments.
- Conclusion.

Differential Diagnosis of Ductal Dilation

- Chronic Pancreatitis.
- Tumor obstructing the main duct.
- IPMN: MPD vs BD vs Mixed.
- Pancreatic Cystic Neoplasm.
- Dilation > 10 mm.
Abnormal MR Pancreatogram
“Ductectatic” Pattern

Chronic Pancreatitis

Side branch ectasia
6mm Pancreatic Adenocarcinoma

Late phase enhancing

Complex cystic mass MCAdenoca
Incidental Pancreatic Cystic Lesion

Pancreas Cysts: An Epidemic?

- 2.4% of all individuals harbor a pancreas cyst by screening MRI
- 20% of clinically indicated abdominal MRI studies demonstrate a cyst in the pancreas
- Prevalence is on the rise due to improved detection with increasingly sophisticated imaging
- 37% of cysts referred for evaluation are discovered incidentally

De Jong et al. Clin Gastro Hep 2010; 8(9) 806-11

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Pancreas Cysts...What Are They?

- Non-neoplastic cysts
  - Congenital cyst
  - Retention cyst
  - Inclusion cyst
  - Endometriotic cyst
  - Inflammatory cysts
    - Pseudocyst

- Cystic neoplasms
  - Serous Cystadenoma
  - Mucinous Cystadenoma
  - IPMN
  - Lymphangioma
  - Hemangioma
  - Lymphoepithelial cyst

- Solid tumors containing cystic spaces
  - Ductal adenocarcinoma
  - Solid-pseudopapillary neoplasm
  - Cystic endocrine tumor

Pancreatic Cystic Neoplasia

- Benign / Low Risk
  - Serous cystadenoma
  - Lymphoepithelial cyst/Endometriotic cyst
  - Hemangioma/lymphangioma

- Malignant potential / High Risk
  - Mucinous cystadenoma
  - Intraductal papillary mucinous neoplasm
    - Main duct
    - Side branch

- Early identification and intervention can prevent the development of cancer and/or metastasis
Serous Cystadenoma

- 30% of Pancreatic Cysts, Head/Body/Tail.
- Central Calcification in 30%.
- Cuboidal Cells, glycogen-rich (PAS+).
- Highly Vascular.
- Benign.
- Fluid analysis: CEA<5, low amylase.


Mucinous Cystadenoma

- Most common pancreatic cystic neoplasm.
- Female predominance (>75%).
- Mean age of diagnosis = 60’s.
- Macrocystic, often unilocular, eggshell calcification, mural nodule.
- Located in body/tail (90%).
- Do not communicate with the pancreatic duct.
  - Distinguishes from IPMN

Mucinous Cystadenocarcinoma with Liver Mets

Mucinous Cystadenoma

- Columnar mucin producing epithelium
  - Variable degrees of cellular atypia
  - Unique ovarian stroma

WHO Classification
- Benign
- Low-grade malignant
- Malignant
- Other classifications proposed

Reddy et al. Clin Gastro Hep 2(11); 1026-1031
Mucinous Cystadenoma: Fluid aspirate

- CEA
  - Elevated
- Amylase
  - Low
- Viscous fluid
  - String sign
- Cytology
  - Mucin producing epithelium
  - Atypia/dysplasia/carcinoma
- Genetic data
  - High amount of DNA
  - k-ras mutation
  - Loss of heterozygosity

FINAL DIAGNOSIS:

PANCREAS, FINE NEEDLE ASPIRATE WITH QUICK EVALUATION:

FRAGMENTS OF ATYPICAL GLANDULAR CELLS IN A MUCIN PRODUCING EPITHELIUM

IPMN: Clinical Presentation

- Mean age of diagnosis = 60-70's.
- Male predominance.
- Most commonly located in the pancreatic head.
- Clinical presentation
  - Asymptomatic
  - Recurrent pancreatitis
  - Abdominal pain
  - Jaundice
- Commonly initially misdiagnosed as obstructive pancreatitis.
IPMN: Main vs. Branch Duct

**Main Duct IPMN**
- Arises from the main duct
- Prevalent cancer risk 23-70%
- 10 year risk of progression = 63%
- Tends to be unifocal although may extend along duct

**Branch Duct IPMN**
- Arises in a side branch
- Prevalent cancer risk 0-36%
- 10 year risk of progression 15%
- Unifocal or multifocal (39-64%)

Tanaka et al. Pancreatology 2006;6;17-32

IPMN: Histology

- Benign
- Borderline
- Carcinoma in situ

Side Branch IPMN: MRCP

- Bile Duct
- MPD
- Cyst

Main Duct IPMN

- Arrow indicating lesion in the main duct.
Focal dilation
Present in 25% of cases, is a diagnostic finding

IPMN: Fluid aspirate

- CEA
  - Elevated
- Amylase
  - High
  - Due to communication with MPD
- Cytology
  - Mucin producing epithelium
  - Atypia/dysplasia/carcinoma
- Viscous fluid
  - String sign
- Genetic data
  - High amount of DNA
  - K-ras and p53 mutations
  - Loss of heterozygosity
Pancreas Cyst Fluid Aspirate
In a perfect world....

<table>
<thead>
<tr>
<th></th>
<th>Amylase</th>
<th>CEA</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous Cystadenoma</td>
<td>Low</td>
<td>Low</td>
<td>Cuboidal cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PAS +</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>High</td>
<td>Low</td>
<td>Debris</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutrophils                   Hemosiderin laden macrophages</td>
</tr>
<tr>
<td>Mucinous Cystadenoma</td>
<td>Low</td>
<td>High</td>
<td>Mucin producing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>columnar epithelium, ovarian stroma</td>
</tr>
<tr>
<td>IPMN</td>
<td>High</td>
<td>High</td>
<td>Mucin producing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>columnar epithelium</td>
</tr>
</tbody>
</table>

Back to reality.....

- FNA is performed through the stomach or duodenal wall
  - Contamination of sample
- Some IPMN (especially branch duct) harbor cells identical to gastric mucosa
- Insufficient fluid for cytology
  - Who wins CEA? Molecular analysis?
- CEA frequently non-diagnostic
  - Mild elevation
  - Elevated in benign processes
  - Absent in pre-malignant/malignant
- CEA cutoff levels vary among laboratories
- 20% of BD IPMN harbor main duct component

Correa-Gallego et al. Pancreatology 2010;10:144-150
CEA: How good is it?

- Cooperative Pancreas Cyst Study
  - Optimal CEA cutoff to maximize AUC = 192
    - Sensitivity 73%
    - Specificity 84%
    - Accuracy 79%
  - Median CEA for non-mucinous lesions = 284
  - Other studies with similar or worse results

Brugge et al. Gastro 2004;126:1330–1336
Khalid et al. Am J Gastro 2006; 101:2493-2500
Park et al. Pancreas. 2010 Oct 13

Limitations of CEA

- Pooled analysis of 450 patients (no IPMN) from 12 studies
  - CEA > 800  48% sensitivity 98% specific for mucinous cystadenoma and cystadenocarcinoma

CEA cutoff = 192 missed 25% (4/12) of malignant mucinous cysts


Cyst Fluid Cytology

- Sensitivity 35%
- Specificity 83%
- Accuracy 59%

Combination Cytology + CEA

- Sensitivity 82%
- Specificity 71%
- Accuracy 77%

Brugge et al. Gastro 2004;126:1330–1336
Khalid et al. GastrointestEndosc 2009; 69(6) 1095-1102
Strategies to Improve Diagnostic Accuracy

- Molecular analysis
- Cyst wall tissue acquisition
  - Brush cytology
  - Cyst wall puncture/biopsy
- Intracystic imaging
  - Confocal endomicroscopy
  - Direct visualization (Spyglass)
- PET scan
  - Sensitivity poor (57%)
- Serial cross sectional imaging and/or EUS FNA

Pancreatic Cyst Fluid DNA Analysis

- Genetic mutations occur early in the process of pancreatic carcinogenesis
- The molecular process of pancreatic carcinogenesis is being increasingly elucidated
  - Similarity in some pathways with heterogeneity in others
Pancreatic Cyst

Integrated analysis of DNA/mutational change.

- DNA QUANTITY
- DNA QUALITY
- KRAS POINT MUTATION (ONCOGENE)
- LOSS OF HETEROZYGOSITY (LOH) MUTATION (TUMOR SUPPRESSOR GENE)

Analysis of free DNA and protein can help assess sampling variation

**Final Diagnosis**

Pancreas (cyst fluid from body and tail, and head cyst), endoscopic, ultrasound-guided fine needle aspiration, x 2 (specimens “A” and “B”):
- Both samples are basically acellular

<table>
<thead>
<tr>
<th>Pancreatic Cyst Fluid-Body &amp; tail</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylase</td>
<td>61,948.5</td>
<td>U/L</td>
</tr>
<tr>
<td>CEA</td>
<td>206.3</td>
<td>ng/ml</td>
</tr>
<tr>
<td>Pancreatic Cyst-Head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>49,368.5</td>
<td>U/L</td>
</tr>
<tr>
<td>CEA</td>
<td>8,718.0</td>
<td>ng/ml</td>
</tr>
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</table>

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Commercially available DNA analysis

- Quantity of DNA - optical density
- Quality of DNA - cycle threshold value
- Degree of allelic imbalance - allelic loss amplitude (ALA), loss of heterozygosity
- k-ras-2 mutation
- Number of mutations
- Sequence of mutations
  - k-ras followed by allelic loss

**DIAGNOSTIC CATEGORIES**

**BENIGN:** NON-MUCINOUS & MUCINOUS (LACKS AGGRESSIVE MOLECULAR FEATURES)

**STATISTICALLY INDOLENT** (SINGLE AGGRESSIVE MOLECULAR FEATURE)

**STATISTICALLY INDOLENT SHOWING GREATER RISK FOR NEOPLASTIC PROGRESSION** (SINGLE AGGRESSIVE FEATURES WITH CLINICAL CORRELATIVE SUPPORT FOR AGGRESSIVE BIOLOGY)

**AGGRESSIVE**
Incremental Value of Molecular Analysis for Pancreatic Cyst Management using Endoscopic Ultrasound

- Provides a separate source of multiparameter information to diagnosis and better understand pancreatic cyst biology
- Capable of identifying aggressive disease relatively early in development prior to other clinical evidence
- Assist in the evaluation when conflicting data on biological aggressiveness is present after first line testing
- Possible to plot the trajectory of pancreatic cyst biology through serial integrated molecular/clinical analysis

Performance of Molecular Analysis for Diagnosis of Mucinous Cysts

- Multicenter analysis of 113 patients undergoing EUS FNA for evaluation of pancreas cysts with histologic confirmation
  - 88 mucinous
- Fluid cytology
  - Insufficient in 1/3 of cases
  - Acellular/non-diagnostic in 43%
- CEA @ 192 cutoff for mucinous cysts
  - Sensitivity 64%, Specificity 83%
- CEA @ 192 + k-ras mutation
  - Sensitivity 82%, Specificity 83%
- K-ras alone specificity 96% for mucinous cysts

Khalid et al. GastrintestEndosc 2009; 69(6) 1095-1102
Incremental Value of Molecular Analysis for the Diagnosis of Mucinous Cysts

- Single center of 100 patients with FNA of cysts (0.8-14cm)
  - Quantity not sufficient for CEA = 16%
  - CEA > 192 in 33% of cysts, sensitivity 82%
  - Molecular analysis consistent with mucinous cyst in 49%, sensitivity 77%
  - CEA + molecular, sensitivity 100%, specificity 100%
    - Histology proven cysts

Small Cysts - The real problem

- Single center cyst registry
  - 69% of cysts 3cm or smaller
  - Cytology, CEA, DNA analysis

<table>
<thead>
<tr>
<th></th>
<th>Cytology</th>
<th>CEA</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory</td>
<td>18 (28.6%)</td>
<td>16 (25.4%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Benign/serous</td>
<td>17 (27.0%)</td>
<td>31 (49.2%)</td>
<td>14 (22.2%)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>26 (41.3%)</td>
<td>16 (25.4%)</td>
<td>43 (68.3%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>2 (3.2%)</td>
<td>N/A</td>
<td>4 (6.3%)</td>
</tr>
</tbody>
</table>

Sawhney et al. Gastrointest Endosc 2009; 69(6) 1106-10

Incremental Value of Molecular Analysis in Cysts < 3cm

- CEA & Molecular analysis
  - All cases with CEA > 192 had concordant molecular results
    - Includes cytology non-diagnostic but CEA elevated (n=4)
    - 75% confirmed histologically, and concordant
    - K-ras mutations only seen in mucinous cysts

- Additional value of molecular analysis
  - 31% with non diagnostic cytology/CEA obtained a diagnosis based on molecular analysis alone
    - 84% agreed with clinical impression
  - One patient with non-mucinous histology/CEA and aggressive molecular profile had repeat EUS FNA identified adenocarcinoma

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Practical considerations of cyst fluid analysis....

- Cyst fluid mismanagement
  - Splitting of samples to more than one location
  - CEA, amylase

- Variability among institutions in determining optimal cutoff

- One test is not the answer, especially for small cysts
  - Clinical + CEA + molecular
  - Enhancing the knowledge base

- Cost
  - CMS approved molecular analysis for patients with pancreatic cysts where “traditional” fluid chemistry and/or cytology evaluations were inconclusive.
Cyst Wall Puncture

- Hypothesis: Puncture of the cyst wall will provide greater cytologic yield than fluid aspirate

- Retrospective review 107 cysts
  - Insufficient fluid for analysis = 30%
    - CWP diagnosis of mucinous cyst 47%
  - Cyst fluid CEA <192
    - CWP diagnosis of mucinous cyst = 31%
  - Overall incremental diagnosis of mucinous cysts based on CWP = 37%

- Complications 2.8%

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Incremental Yield of CWP for the Diagnosis of Mucinous Cysts

**Mucinous Cysts As Percent of Total**

- **Total**
- **QNS**
- **CEA<192**

**Without CWP** vs **With CWP**

Prospective collection of 39 cysts
- 28% inadequate cyst fluid for cytologic analysis
- 20/39 had findings consistent with non-mucinous cyst (CEA < 192 & Non-mucinous cytology)
  - 40% (8/20) CWP diagnosed mucinous cyst
- 7 cysts with insufficient fluid for cytology/CEA
  - 5/7 mucinous by cyst wall puncture
- Incremental diagnostic yield of CWP = 33%
  - 2 adenocarcinoma
- Pancreatitis n=1

Summary
- Accurate diagnosis of pancreas cysts is paramount to determine appropriate management strategy
- Combination of tests hold promise for the best performance characteristics
  - CEA
  - Molecular DNA analysis
  - Cyst wall puncture
- Further insights into molecular carcinogenesis hold promise for future refinements