Case 3
Young woman with a cystic pancreatic mass

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I declare that I have no conflicts of interest to disclose

• 31 year old woman with recent onset of abdominal pain, some weight loss, and diarrhea
• Patient herself noted she had a palpable abdominal mass which pulsated
• Physical examination: BMI 41.6. Large palpable mass in left abdomen through which one could feel the pulsations of the aorta

• Outside CT: large complex cystic and solid mass replacing most of the tail of the pancreas. No splenic mass. Associated collaterals around spleen
• Outside clinical and radiographic impression: pancreatic pseudocyst
• Pathologist to pathologist phone consultation. My clinical impression: solid pseudopapillary neoplasm
• Referred to our institution for further evaluation
• Underwent endoscopic ultrasound (EUS) with transgastric FNA
• Aspirated fluid sent for CEA, amylase and cytology
Endoscopic ultrasound

Findings and impressions

- Cystic lesion in tail of pancreas, 110 x 100 mm, with many thickly septated compartments
- No communication with pancreatic duct
- Intrinsic associated mass and associated mural nodule
- Most c/w solid pseudopapillary neoplasm, but cannot exclude intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN)

Diff-Quik air-dried smears
Solid pseudopapillary neoplasm

- Mainly in young women, late teens and 20’s
- Often present with abdominal pain or discomfort
- Indolent tumor, most behave benignly
- Most cured with surgery. May recur
- 10-15% metastasize, mostly to liver and peritoneum; nodal metastases rare
- Can survive many years with metastases

What do you next?

- Feel overwhelmed or panic
- Take a deep breath
- Review clinical and radiographic findings
- Check on results of cyst fluid biochemical analysis
Endoscopic ultrasound

- EUS FNA has essentially replaced percutaneous radiographically-guided FNAs
- Transducer right next to pancreas, so smaller lesions detected
- Radial scans for cross-sectional images
- Curved linear array for real-time visualization of needle during FNA

EUS FNA OF THE PANCREAS

- Lesions in head of pancreas aspirated through the duodenum
- Lesions of body or tail of pancreas lesions aspirated through the stomach

EUS FNA OF THE PANCREAS

- How do you distinguish contaminating GI tract epithelium from pancreatic ductal epithelium?
- Presence of goblet cells supports duodenal epithelium
- Branch duct IPMNs lined by gastric foveolar type epithelium may be difficult to distinguish from contaminating gastric epithelium
- Most branch duct IPMNs occur in head of pancreas so accessed through duodenum

EUS FNA: Duodenal epithelium
**EUS FNA: Gastric epithelium**

**Cyst fluid chemical analysis**
- Serum CEA 7250 ng/mL
- Serum amylase 3983 U/L
Pancreatic cyst fluid analysis

<table>
<thead>
<tr>
<th></th>
<th>Amylase</th>
<th>CEA</th>
<th>K-ras mutation</th>
<th>GNAS mutation</th>
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</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>Very high</td>
<td>Low</td>
<td>Absent</td>
<td>Absent</td>
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<tr>
<td>Serous cystadenoma</td>
<td>Low</td>
<td>Low</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>MCN</td>
<td>Variable</td>
<td>High</td>
<td>Frequent</td>
<td>Absent</td>
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<tr>
<td>IPMN</td>
<td>High</td>
<td>High</td>
<td>50-80%</td>
<td>57-79%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Variable</td>
<td>High</td>
<td>90%</td>
<td>Associated with IPMN</td>
</tr>
</tbody>
</table>

CEA cut-off of >192-200 ng/mL ~ 80% accurate for diagnosis of mucinous cyst (Tanaka et al, 2012)

Papanicolaou Society of Cytopathology System for Reporting Pancreatobiliary Cytology

- Nondiagnostic
- Negative (for malignancy)
- Atypical
- Neoplastic
  - Benign – serous cystadenoma
  - Other – well differentiated NET, IPMN, MCN, solid pseudopapillary neoplasm
- Suspicious (for malignancy)
- Positive/Malignant

Multidisciplinary group
- Drafts on interactive web-based open forum, presented at national and international meetings
- Published in 2014
- Standardized approach to diagnosis and reporting of pancreatobiliary cytology
- Addresses ancillary testing and clinical management
PSC System: Reporting Pancreatobiliary Cytology
- Nondiagnostic
- Negative (for malignancy)
- Atypical
- Neoplastic
  - Neoplastic mucinous cyst with high grade atypia. Epithelium represents at least high grade dysplasia; invasion cannot be excluded
- Suspicious (for malignancy)
- Positive/Malignant

Patient underwent resection of pancreatic mass with splenectomy
- Resected portion of pancreas 18 x 12.5 x 6.5 cm, 526 g, with 15 cm multiloculated cystic mass

Benign – serous cystadenoma
Other – WD NET, IPMN, MCN, SPN

Suspicous for malignancy
- Cystic mucinous neoplasm with high grade epithelial atypia; at least high grade dysplasia. Abundant necrosis, suspicious for invasive carcinoma
- Positive/Malignant
**IgG4-associated sclerosing autoimmune pancreatitis**

- Over 95% in women
- Mean age at diagnosis 40-50 years, range 14-95 years
- Over 95% in body & tail of pancreas
- Resection recommended in surgically fit patients bcs of risk of harboring or progression to malignancy
- Prevalence of invasive ca <15% (6-33%)
- Consider conservative resection for MCN <4 cm without mural nodules

**Mucinous cystic neoplasm**

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- Mean age at diagnosis 40-50 years, range 14-95 years
- Over 95% in body & tail of pancreas
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**MCN with focal high grade dysplasia**

- Pancreas and spleen, distal pancreatectomy
  - Mucinous cystic neoplasm (MCN), 15 cm, with focal high grade dysplasia
  - 102 sections of mass examined
  - Margins involved by MCN
  - Negative lymph nodes (0/22)
Mucinous cystic neoplasm

- Imaging: well-circumscribed cystic mass with one or several loculations
- Does not communicate with ductal system
- Ovarian-like stroma
- Cytologic features overlap those of IPMN

Mucinous cystic neoplasm (MCN)
Intraductal papillary mucinous neoplasm (IPMN)
2010 WHO classification

- With low or intermediate grade dysplasia
- With high grade dysplasia
- With associated invasive adenocarcinoma

A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas

Olca Basturk, MD, Seung-Mo Hong, MD, PhD, Laura D. Wood, MD, PhD, N. Volkan Adsay, MD, Jorge Albores-Saavedra, MD, Andrew V. Biankin, MD, Lodewijk A.A. Brosens, MD, PhD, Noriyoshi Fukushima, MD, Michael Goggins, MD, Ralph H. Hruban, MD, Yo Kato, MD, David S. Klimstra, MD, Gunter Kloppel, MD, Alyssa Krasinskas, MD, Daniel S. Longnecker, MD, Hanno Matthaei, MDG, Johan A. Offerhaus, MD, PhD, Michio Shimizu, MD, Kyoichi Takaori, MD, PhD, Benoit Terris, MD, Shinichi Yachida, MD, PhD, Irene Esposito, MD, and Toru Furukawa, MD, PhD

Multidisciplinary consensus meeting of international experts held in Baltimore at Johns Hopkins in 2014

Revised classification system for neoplastic precursor lesions in pancreas

- PanIN, low grade and high grade
- MCN/IPMN with low grade dysplasia
- MCN/IPMN with high grade dysplasia (geographic option: w/carcinoma in situ)
- MCN/IPMN with associated invasive adenocarcinoma

Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract. Recommendations of the Verona Consensus meeting


International multidisciplinary consensus met in Verona in 2013, followed by consultations with other experts

Intraductal papillary mucinous neoplasm
- Until recently defined as a grossly and radiographically visible noninvasive, mucin-producing, epithelial neoplasm arising from the main pancreatic duct or branch ducts
- May be multiloculated or multicystic if branch ducts involved

Revised classification system for neoplastic precursor lesions in pancreas
- IPMN classically defined as > 1cm
- PanIN classically defined as < 0.5 cm
- Never-never land: lesions 0.5-1.0 cm
- In revised classification, incipient IPMN for lesions 0.5-1.0 cm with long papillae, intestinal or oncocytic differentiation; or GNAS mutation


Intraductal papillary mucinous neoplasm
- Duct involved
  - Main duct type
  - Branch duct type
  - Both

- Histologic type
  - Intestinal
  - Gastric
  - Pancreatobiliary
  - Oncocytic
  - Mixed
Intraductal papillary mucinous neoplasm

- **Main duct type**
  - Involve the main pancreatic duct
  - Mainly in head of pancreas
  - May involve the entire pancreatic duct

- **Branch duct type**
  - Most in head of pancreas or uncinate process
  - About 30% in body or tail of pancreas

**IPMN: Association with carcinoma**

- About 30% of IPMN have associated invasive adenocarcinoma
- Mean risk of associated invasive cancer
  - Main duct IPMN: 43-50%
  - Branch duct IPMN: 16-18%
- Risk of associated high grade dysplasia >60% for main duct IPMN

**Pancreatic cysts**

- By CT scan, pancreatic cysts in 1.2-2.6% of individuals without symptoms of pancreatic disease
  - Up to 10% in those 70 and over
- By MRI, reported prevalence of pancreatic cysts 2-38%, overall 15%
- Most incidental
- Ddx: non-neoplastic, neoplastic mucinous cysts, serous cystadenomas, cystic NET, solid tumors with cystic change
Pancreatic cysts

- Based on CT scan prevalence, it has been estimated that up to 55% of these incidental pancreatic cysts are branch duct IPMNs
- But pathologic confirmation not there
- Not clear how many are the simple mucinous cysts defined in the Baltimore consensus classification (Basturk O et al. Am J Surg Pathol 2015;39:1730–1741)

Simple mucinous cysts

- Baltimore consensus group recommends this term for macroscopic cysts with flat mucinous epithelial lining, usually gastric type, lacking ovarian stroma
- Some of these formerly called retention cysts, mucinous non-neoplastic cysts)
- Not directly addressed in the 2012 International consensus guidelines
- Not addressed in PSC System for Reporting Pancreatobiliary Cytology

Pancreatic cystic lesions

- Goal: identify cystic lesions with higher malignant potential which need closer surveillance and/or resection
- 2006 International consensus ("Sendai") guidelines for management of IPMNs and MCNs of pancreas (Tanaka et al. Pancreatology 2006;617-32)
- ACG practice guidelines for diagnosis and management of neoplastic pancreatic cysts (Am J Gastro 2007;102:2339-2349)

2012 International Consensus Guidelines

- 2012 International consensus guidelines for management of IPMNs and MCNs of pancreas
- Update of 2006 guidelines based on 1) increasing role of EUS FNA and 2) indications for more observation of branch duct IPMNs and more conservative approach to resection

Tanaka et al. Pancreatology 2012;183-197
Pancreatic cyst fluid analysis
What are we trying to determine?

- Is the cyst mucinous or non-mucinous?
- Is there high grade atypia?
- ? other prognostic factors to guide clinical management

High grade atypia in mucinous cyst fluid

- Specificity 85-88%
- Sensitivity 67-72%
- For detection of malignancy
- Small cell size with increased N:C ratio
- Hypochromatic or hyperchromatic
- Background necrosis
- Encompasses HGD and adenocarcinoma

Pitman et al. Cancer Cytopath 2014;122:40-7

International Consensus Guidelines 2012 for the management of IPMN and MCN

Recommend surgical resection for surgically fit patient with main duct IPMN or MCN; for BD-IPMN with high risk stigmata

EUS for BD-IPMN with worrisome features

Surgical resection for BD-IPMN with definite mural nodule, suspicious for main duct involvement, cytology suspicious or positive for malignancy

Algorithm for surveillance of other BD-IPMN


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Pitman et al. Cancer Cytopath 2014;122:40-7
Triple negative test for pancreatic cysts

- Absence of high risk stigmata or worrisome features by 2012 Internat’l guidelines
- Absence high grade atypia
- 99% neg pred value

Wu RI et al. Cancer Cytopath 2014;122:412-419

EUS of cystic pancreatic lesions

Cell blocks

- Provide additional material to examine
- Can be used for IHC
- Loss of SMAD4 expression, expression of mesothelin support diagnosis of carcinoma
- IHC for MUCs – data not clear
- Immunoreactivity for chromogranin and synaptophysin support NET

Is there a role for molecular studies?

- Cyst aspirate often paucicellular, cells degenerated
- What do you with int. grade atypia?
- Variable sensitivity of cytology for detection of IPMN/ MCN – as low as 32% in some studies
- CEA, radiology not specific for malignancy

Pancreatic cyst fluid: Molecular analysis

- DNA quantity
- DNA quality
- K-ras codon 12 mutation – by itself, not specific for malignancy
- Loss of heterozygosity (LOH):
  2 or more loci of allelic loss
- GNAS – supports dx of IPMN, but does not distinguish pre-malignant from malignant IPMN
Pancreatic cyst fluid: Molecular analysis

- Multi-institutional prospective PANDA trial: data did not provide support for use
- Molecular tests have variable sensitivity and specificity for addressing:
  - Mucinous vs nonmucinous
  - Benign vs high risk/malignant
- Future directions: Next gen sequencing, microRNAs, other

Take Home Points

- Pancreatic cysts are common and most do not need resection
- Review the clinical history, EUS, other imaging studies
- Correlate cytologic findings with results of cyst fluid biochemical analysis
- Cell blocks can be helpful – additional morphology, material for IHC
- K-ras mutations in neoplastic mucinous cystic lesions (IPMN, MCN)
- GNAS mutations in IPMN
- K-ras and GNAS do not distinguish benign from malignant

Take Home Points

- Likely more molecular studies in future, e.g., next-generation sequencing
- Morphologic examination helpful in identification or exclusion of high grade atypia
- Effective communication key
  - PSC System for Reporting Pancreatobiliary Cytology
  - Multidisciplinary approach