Non mucinous cystic lesions of the pancreas

PRESENTED BY
Irene Esposito
Institute of Pathology – Heinrich Heine University and University Hospital of Duesseldorf, Germany
Disclosure of Relevant Financial Relationships

The faculty, committee members, and staff who are in position to control the content of this activity are required to disclose to USCAP and to learners any relevant financial relationship(s) of the individual or spouse/partner that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the CME content. USCAP has reviewed all disclosures and resolved or managed all identified conflicts of interest, as applicable.

Irene Esposito reported no relevant financial relationships
Spectrum of cystic lesions of the pancreas

**Neoplastic, epithelial**
- Intraductal papillary mucinous neoplasm (IPMN)
- Mucinous cystic neoplasm (MCN)
- Intraductal tubulo-papillary neoplasms (ITPN)
- Serous cystic neoplasm (SCN)
- Solid pseudopapillary neoplasm (SPN)
- Cystic neuroendocrine tumor (cNET)
- Cystic pancreatic ductal adenocarcinoma
- Cystic acinar cell carcinoma

**Non-neoplastic, epithelial**
- Lymphoepithelial cyst
- Simple mucinous cyst
- Acinar cystic transformation
- Enterogenous cyst
- Retention cyst
- Peri-ampullary duodenal wall cyst
- Endometrial cyst
- Congenital cysts in malformation syndromes

**Neoplastic, non-epithelial**
- Benign (e.g. lymphangioma)
- Malignant (e.g. sarcoma with cystic changes)

**Non-neoplastic, non-epithelial**
- Pancreatitis-associated pseudocyst
- Parasitic cyst
**Spectrum of cystic lesions of the pancreas**

**Neoplastic, epithelial**
- Intraductal papillary mucinous neoplasm (IPMN)
- Mucinous cystic neoplasm (MCN)
- Intraductal tubulo-papillary neoplasms (ITPN)
- Serous cystic neoplasm (SCN)
- Solid pseudopapillary neoplasm (SPN)
- Cystic neuroendocrine tumor (cNET)
- Cystic pancreatic ductal adenocarcinoma
- Cystic acinar cell carcinoma

**Non-neoplastic, epithelial**
- Lymphoepithelial cyst
- Simple mucinous cyst
- Acinar cystic transformation
- Enterogenous cyst
- Retention cyst
- Peri-ampullary duodenal wall cyst
- Endometrial cyst
- Congenital cysts in malformation syndromes

**Neoplastic, non-epithelial**
- Benign (e.g. lymphangioma)
- Malignant (e.g. sarcoma with cystic changes)

**Non-neoplastic, non-epithelial**
- Pancreatitits-associated pseudocyst
- Parasitic cyst
Frequency of resected pancreatic cystic lesions

- IPMN
- MCN
- SCN
- cNET
- SPN
- Others

Sources:
- Valsangkar et al, Surgery 2012
- Gaujoux et al, J Am Coll Surg 2011
- Kleeff…Esposito, HPB Surg 2015
Serous cystic neoplasms

- **Frequency**: ~16% of the resected cystic tumors
- **Gender**: F>M (3:1), Age: 16-99 y (mean 58)
- **Symptoms**: abdominal or back pain, abdominal mass, nausea, vomiting, incidental (up to 60%)
- **Localization**: 60% in the body-tail region, mean size 4.2 cm (0.2-18)
- **Prognosis**: Excellent (SCN are mostly **benign**)
- **Other features**: association with other neoplasms, especially NET

Reid et al, Am J Surg Pathol 2015
Jais et al, GUT 2016
SCN: macroscopic types

Microcystic (45-77%)
Oligocystic (32-21%)
Solid (2-5%)

Reid et al, Am J Surg Pathol 2015
Jais et al, GUT 2016
Serous microcystic adenoma
Serous microcystic adenoma
**Immunohistochemistry**

- CK 7, 8, 18, 19 +
- Inhibin +
- MUC6 +
- NSE +
- CEA -
- MUC1 -
- MUC2 -
- SYN -
SOIA: Serous Oligocystic and Ill-demarcated Adenoma

26 cases
F>M (4:1)
Body-tail
Younger patients (~ 50y)

Often misdiagnosed: MCN
IPMN
simple mucinous cyst
choledocal cyst

...
Serous adenoma, solid variant

DD with PEComa (MelanA+, HMB45+), clear cell NEN (Syn+, Chrom+) and metastasis of renal cell carcinoma, clear cell type (Vimentin+, PAX 8+)
Multiple SCN in VHL syndrome

87% rate of pancreas involvement in VHL

Park et al, Scand J Gastroenterol 2015
VHL in serous cystic tumors

Useful in the preoperative assessment of pancreatic cysts!

Wu et al, PNAS 2011
Singhi et al, Gut 2018
Serous cystadenocarcinoma (does it exist?)

- WHO requires the presence of liver metastasis for the diagnosis

- Direct infiltration of other organs or lymph nodes occurs but does not justify the diagnosis of malignancy

Serous cystic lesion in the liver? Consider multifocality!
However…

Carcinoma Ex Microcystic Adenoma of the Pancreas: A Report of a Novel Form of Malignancy in Serous Neoplasms

Signet-ring morphology

Squamous-like nests

Solid-pseudopapillary neoplasms

- **Frequency:** ~5% of the resected cystic tumors
- **Gender:** F>M (10:1) Age: 8-85 y (mean 28)
- **Symptoms:** abdominal or back pain, abdominal mass, incidental
- **Localization:** no predilection, mean size 8.6 cm
- **Behavior:** 10-15% with recurrence or metastasis (peritoneum, liver, lung)
- **Prognosis:** 97% 5-year-survival

Kosmahl et al, Virchows Arch 2004
Law et al, Pancreas 2014
Female patient, 11 years-old
Car accident with blunt abdominal trauma
Clin. diagnosis: Hematoma

Male patient, 55 years-old
Abdominal discomfort
Clin. diagnosis: chronic pancreatitis with pseudocyst

Female patient, 17 years-old
Recurrent upper-GI bleeding
Clin. diagnosis: duodenal cancer

Schlitter et al, Dtsch med Wochenschr 2013
Female patient, 21 years-old
liver metastases of SPN 10
years after resection of the primary tumor

Sumida et al, J Ped Surg 2007
SPN Histopathology

Solid areas

Pseudopapillary areas
Hyaline globules
### SPN Immunohistochemistry

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin</td>
<td>- to weak +</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>(focal +)</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
</tr>
<tr>
<td><strong>Beta-catenin</strong></td>
<td>+ (nuclear)</td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td>+ (hyaline globules)</td>
</tr>
<tr>
<td>α1-antichymotrypsin</td>
<td>+ (hyaline globules)</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>+</td>
</tr>
<tr>
<td>PR</td>
<td>+</td>
</tr>
<tr>
<td>Ki67</td>
<td>low</td>
</tr>
</tbody>
</table>

**Immunohistochemistry Images:**

- **Vimentin**
- **CK18**
- **Beta-catenin**

**Islets**

**Syn**
Molecular Pathology of SPN

CTNNB1 activating exon 3 mutation

Illustration from: Jeong et al, Precision Oncology 2018

Abraham et al, Am J Pathol 2002
Tanaka et al, Cancer Res 2001
Molecular Pathology of SPN

Nanostring: activated Wnt-pathway (DKK4, LGR5, CCND1…)

Methylation profile of epithelial cells

Selenica et al, Mol Oncol 2019
SPN Immunohistochemistry: New markers

- **SPN: 100%**
  - LEF1: 100%
  - TFE 3: 94% of SPN, 23% of NET
  - CD200: 100% of SPN, 96% of NET

Pancreatoblastoma: 4/4 (100%)

References:
- Singhi et al, Mod Pathol 2014
- Jiang et al, Hum Pathol 2018
- Lawlor et al, Virchows Arch 2019
SPN: Markers of aggressive behavior

- Cases with components of undiff. carcinoma (solid growth, necroses, high Ki-67-index, sarcomatoid morphology)

- Possibly more aggressive in male patients?

- Recent metaanalysis of „aggressive“ SPN:

  59 pts (F:M=7.4:1), mean age: 37.4 y
  81.4% with distant mets
  Disease-specific survival: 13 y, 5- and 10-year survival: 71% and 65.5%

Unresectable tumors and metastases within 3 years correlate with more aggressive course

Machado et al, Surgery 2008
Hao et al, Medicine 2018
CTNNB1 mutation is the only recurrent mutation in SPN.
- Epigenetic modulators are associated with metastatic disease.
- Mutations are shared between primary and mets.
- All primary SPN are diploid.

Loss of BAP1 and KDM6A and overexpression of Glut1 seems to be associated with mets.
Cystic pNET

- 6-27% of all pNET (13% in a metaanalysis)
- Sporadic or associated with MEN 1 (10%)
- 85% non-functional
- Often glucagon expression
- More frequently G1 than solid NET
- Better prognosis than solid NET in some studies

Nakashima et al, Pancreatology 2019
Carr et al, Pancreatology 2019
Hurtado-Pardo et al, Rev Esp Enferm Dig 2017
Konukiewitz et al, Virchows Arch 2011
Cystic pNET

T2W

T1W + CM

FNB

Courtesy of Prof. T. Lauenstein, EVK, Duesseldorf
Cystic NET

Synaptophysin

Ki67

Glucagon
Cystic NET

Courtesy of G. Klöppel
Ready for the rest?
Male, 57 y, vague abdominal complaint
CT scan: hypodense cystic lesion in the pancreas tail, 5 cm, no connection with the duct
Well-demarcated, peripancreatic cystic lesion

Squamous epithelium
Lymphatic stroma with lymph follicles (*)

The squamous epithelium has no atypia
Lymphoepithelial cyst

- Frequency: very rare!
- Patients: M>F (4:1); mean age: 55 y (21-74)
- Symptoms: abdominal pain, weight loss, incidental; CEA/Ca19-9 may be ↑
- Localization: body-tail, often peripancreatic
- Gross morph: well-demarcated cyst, size: 1.5-16 cm, mean 4 cm
  uni- (60%) or multilocular (40%), no connection with the ductal system
- Histology: stratified squamous epithelium, lymphoid tissue with germinal centers

Groot et al, HPB 2018
Squamous-lined cysts of the pancreas

- **Lymphoepithelial cysts**: M > F, mean age 55, squamous epithelium + lymphoid stroma
  
  Pathogenesis: misplaced branchial cleft,
  cystic transformation of metaplastic pancreatic duct
  *ectopic epithelium in a lymph node*

- **Epidermoid cyst** in ectopic spleen: no sex predilection, mean age: 38, **only** body-tail

- **Dermoid cyst**: no sex predilection, younger pts (mean age: 23), different type of epithelium (squamous/mucinous/respiratory), more prominent sebaceous units, no lymphoid stroma

Adsay et al, Semin Diag Pathol 2000
Female, 66 years-old, abdominal discomfort

In CT: multicystic lesion in the pancreas body-tail
Acinar cystic transformation

Gender: F>M (2-3:1)
Age: 47 ys (16-71)
Localization: Head > body-tail, possibly multifocal/disseminated
Symptoms: Abdominal discomfort, incidental finding

Gross anatomy: Uni- oder multilocular cysts (0.1-12 cm), rarely connection to the duct system
Histopathology: flat, non-descript epithelium, acinar, mucinous, squamous epithelium. Mural nodules.
IHC: CK8/18/7/19+, MUC1+, MUC6+, Trypsin+, Chymotrypsin+

Evidence of polyclonality with two methods:
- HUMARA (Singhi et al, Am J Surg Pathol 2013)
- Sequencing of mt-DNA (Bergmann et al, Oncol Lett 2014)
Conclusions

Non-mucinous cysts of the pancreas include numerous, but mostly rare entities

The most frequent are SCN, SPN, cNET and pseudocysts

A diagnosis can be reached taking into account the characteristic clinical context, the histomorphology and the typical immunohistochemical profile
Save the date

32nd Congress of the ESP and XXXIII International Congress of the IAP
29 August – 2 September 2020, Scottish Event Campus, Glasgow, UK
Thank you!

Düsseldorf, Media Harbor