Differential Diagnosis of Ovarian Mucinous Tumours

Sigurd F. Lax
Mucinous tumours of the ovary

• Primary
  ➢ Seromucinous tumours
  ➢ Mucinous tumours
  ➢ Benign, borderline, malignant

• Secondary (metastatic)
  ➢ Metastases (from gastrointestinal tract)

• Metastases can mimic primary ovarian tumour
Mucinous tumours: General

- 2nd largest group after serous tumours
- Gastro-intestinal differentiation (goblet cells)
- Endocervical type > seromucinous tumours
- Majority is unilateral, particularly cystadenomas and borderline tumours
- Bilaterality: rule out metastatic origin
- Adenoma > carcinoma sequence reflected by a mixture of benign, atypical proliferating and malignant areas within the same tumour
Sero-mucinous ovarian tumours

- Previous endocervical type of mucinous tumor
- Mixture of at least 2 cell types: mostly serous
- Association with endometriosis; multifocality
- Similarity with endometrioid and serous tumours, also immunophenotype
- CK7, ER, WT1 positive; CK20, cdx2 negative
- Most cystadenoma and borderline tumours
- Carcinomas rare and difficult to diagnose

Shappel et al., 2002; Dube et al., 2005; Vang et al. 2006
Seromucinous Borderline Tumour
ER
Seromucinous carcinoma being discontinued?

- Poor reproducibility: Low to modest agreement from 39% to 56% for 4 observers
- Immunophenotype not unique, overlapped predominantly with endometrioid and to a lesser extent with mucinous and low-grade serous carcinoma
- Molecular features overlap mostly with endometrioid and low-grade serous carcinomas

Rambau et al., Am J Surg Pathol 2017;41:685–69
# Immunphenotype and Mutations

<table>
<thead>
<tr>
<th>Histotype</th>
<th>Immunphenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>ER/PR+, WT1-, PTEN-/+</td>
<td>ARID1A, PIK3CA, PTEN, CTNNB1, POLE, PPP2R1A, K-RAS, MMR deficiency</td>
</tr>
<tr>
<td>Clear cell</td>
<td>ER/PR-, WT1-, PTEN+/-.</td>
<td>ARID1A, PIK3CA</td>
</tr>
<tr>
<td>Low grade serous</td>
<td>ER/PR+, WT1+, PTEN+</td>
<td>K-RAS, N-RAS, B-RAF, c-erbB2</td>
</tr>
<tr>
<td>Mucinous</td>
<td>ER/PR-, WT1-, PTEN+</td>
<td>K-RAS, CDKN2A, ARID1A, PIK3CA</td>
</tr>
<tr>
<td>Seromucinous</td>
<td>ER/PR+, WT1-/-, PTEN+</td>
<td>All above</td>
</tr>
</tbody>
</table>

Rambau et al., 2017, modified
Challenge for Differential Diagnosis

- Biology: Invasion
- Site of origin: primary versus metastatic
Origin of ovarian mucinous neoplasms: 3 proposals

• Derived from surface epithelium of ovaries and inclusion cysts through metaplasia
• Development from transitional epithelium at the tuboperitoneal junction (Walthardt nests)
• Development from mucinous epithelium in teratomas
Tubo-peritoneal Junction

Site of transitional cell metaplasia (Walthardt nests) from which mucinous neoplasms and Brenner tumors arise
Molecular Pathology of MOC

- Distinct molecular features
- Development from precursors (MBOT)
- Major drivers: Mutant K-RAS, CDKN2A, p53
- Copy number aberrations, amplicon at 9p13
- High copy number aberration reflects high stage and poorer prognosis
- Distinct from metastasis on molecular level
Pathogenetic model for ovarian mucinous carcinomas

Mucinous and seromucinous carcinomas: Adenoma-carcinoma Pathway

Cystadenoma

Borderline-tumor

- K-RAS
- B-RAF
- CDKN2A (p16)

- HER2
- PIK3CA
- P53

Low grade carcinoma
- p53

High grade carcinoma
- P53
Sampling is crucial to find MOC

Sufficient number of samples (1/cm DM) from the right areas
Mucinous cystadenoma

- Less frequent than serous cystadenoma
- Bilateral in ca. 10-20%
- Multilocular
- May recur if treated by cystectomy
Mucinous Borderline Tumors

- Most unilateral (stage I)
- Extraovarian disease uncommon
- Recurrences very rare if completely removed, also in case of intraepithelial carcinoma (IEC)
- Cave: Metastases from mucinous cystic lesions of the appendix and from intestinal carcinomas may “occur as” mucinous BLT
- Pseudomyxoma peritonei (PP) rare (most are in fact metastatic neoplasms)
MBOT: Diagnostic Criteria

- Cellular atypia and proliferation of the mucinous epithelium
- Pseudostratification with elongated hyperchromatic nuclei
- Pseudopapillae and papillae
- Mitoses
Mucinous Borderline Tumors

• No prognostic impact:
  ➢ Intraepithelial carcinoma (subjective)
  ➢ Microinvasion (≤ 5 mm)

• Important: Exclusion of
  ➢ Metastasis mimicking a borderline tumour
  ➢ Invasion > 5mm
MBT with intraepithelial carcinoma
Patterns of Invasion of Mucinous Tumors

• Confluent (cribriform or back to back glands)
  ➢ Most frequent in mucinous carcinoms
• Infiltrative (small nests in spaces, desmoplastic stromal reaction)
• Nodular
  ➢ Typical for metastases
    (Pancreas, colon, upper GI tract, biliary system)
Mucinous carcinoma
Confluent growth pattern ("maze-like")
Infiltrative growth pattern
Immunohistochemistry: Mucinous

- ER, PR negative
- WT-1 negative
- CK7 positive
- CK20, cdx2 variable
- P53 mutant pattern frequent in carcinomas
Immunohistochemistry for Typing

WT-1

PTEN

CK7

CDX2
Intramural Nodules

• Cellular nodules in the wall of MBT and MOC
• Extremely rare
• Size from mm to cm
• 2 types:
  ➢ Neoplastic (carcinosarcoma-a or anaplastic carcinoma-like) with spindle, rhabdoid or pleomorphic cells
  ➢ Reactive (pseudotumour-like with foreign body giant cells)
• Cytokeratin positive or negative
• Outcome may be favorable
Ovarian Mucinous Tumors Associated With Mature Cystic Teratoma

- Mostly cystadenomas & BOT; carcinomas rare
- Derived from gastrointestinal, sinunasal or bronchial epithelium
- CK7/CK20 pattern heterogenous, also CDX2 and villin expression vary
- CK7-/CK20+ pattern frequently associated with pseudomyxoma ovarii
- If CK7-/CK2+/CDX2+ a lower GI origin needs to be ruled out; interpreted as primary ovarian tumour, when non-ovarian mucinous tumor not identified

Vang et al., AJSP 2007
Pseudomyxoma ovarii
High grade and high stage MOC

- High grade mucinous carcinomas are unusual
- High stage mucinous carcinomas are very rare
Outcome of high stage mucinous ovarian tumours

- Stage III/IV mucinous carcinomas very rare
- Outcome very pure, similar to that of ovarian metastases, less favorable than stage III/IV high grade serous carcinoma
- Many mucinous adenocarcinomas that are diagnosed as primary ovarian neoplasms appear to be metastatic to the ovary

Zaino et al., Cancer 2011
Metastatic mucinous tumours

- Most frequent in “Western” countries: Colorectal adenocarcinoma and carcinomas of the pancreato-biliary system
- Historically: Gastric adenocarcinoma, diffuse type (“Krukenberg tumor”)
- Mucinous tumors of the appendix
- Endocervical adenocarcinoma
- Endometrioid carcinoma with mucinous differ.
Metastases to the ovary

- Diagnosed
  - before (18 %),
  - synchronously (33 %)
  - after (49 %) the primary tumor was identified
- 25 % were single,
- 40 % were unilateral
- 47 % were ≥13 cm
- Therefore, always consider a metastasis

Lobo et al., VIAR 2017
Mucinous ovarian tumors: Important gross and microscopic features

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Diameter (cm)</th>
<th>Bilateral</th>
<th>Atypia +++</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLT (incl. IEC)</td>
<td>20</td>
<td>6%</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>BLT with microinvasion</td>
<td>17</td>
<td>0</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>18</td>
<td>21%</td>
<td>75%</td>
<td>58%</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>8</td>
<td>51%</td>
<td>71%</td>
<td>23%</td>
</tr>
</tbody>
</table>

\( p \)-value

<0.0001 \quad <0.0001 \quad <0.0001 \quad <0.002

## Criteria for Differential Diagnosis of Primary and Metastatic Ovarian Tumors

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraovarian tumor in history</td>
<td>(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Mucin deposits outside the ovary</td>
<td>(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>(+)</td>
<td>++</td>
</tr>
<tr>
<td>Size &gt;15 cm</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Gross tumor on the ovarian surface</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Microscopic surface involvement</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Nodular pattern</td>
<td>(+)</td>
<td>+++</td>
</tr>
<tr>
<td>Association with Brenner tu, teratoma, adenofibroma</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Association with endometriotic cyst or endometriosis</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Seidman’s rule: DD mucinous tu

• all bilateral mucinous carcinomas metastatic
• unilateral mucinous carcinomas <10 cm metastatic
• unilateral mucinous carcinomas >10 cm as primary
• correctly classified 90% of the neoplasms

• Does not work properly on other metastases

Seidman et al., AJSP 2003
# Immunohistochemistry for DD

<table>
<thead>
<tr>
<th></th>
<th>Colon</th>
<th>Stomach</th>
<th>Pancreas</th>
<th>Cervix</th>
<th>Ovary muc</th>
<th>Ovary seromuc</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>-/+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>CK20</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>++/-</td>
<td>-</td>
</tr>
<tr>
<td>CDX2</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+++/+</td>
<td>-</td>
</tr>
<tr>
<td>SATB2</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DPC4</td>
<td>++</td>
<td>++</td>
<td>-/+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>P16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ER</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>WT1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Clue for DD: Pattern of invasion

Confluent: primary ovarian

Nodular: metastasis
Metastatic colorectal adenocarcinoma: BOT-like areas
Metastatic Adenocarcinoma from Colon
Metastatic ductal adenocarcinoma of the pancreas
62 yr. old F, left adnexal mass, 10 cm; history of pancreatic adenocarcinoma
Omental lesion
Loss of DPC4 (SMAD4): characteristic for metastatic pancreatic adenocarcinoma
Metastatic gastric carcinoma, poorly cohesive type
Synchronous Mucinous Tumours of Ovary and Appendix

• Rare; usually low grade appendiceal mucinous neoplasm (LAMN) and ipsilateral mucinous cystic ovarian tumour (right)
• Continuous spread: Ruptur usually not found
• Identical K-RAS mutations
• Pseudomyxoma peritonei und pseudomyxoma ovarii: unusual for primary mucinous neoplasms (except association with teratoma)
Appendix
Mucinous tumors from 333 patients: 38 borderline tumors, 295 invasive ca.

Almost certainly cases of ovarian and non-ovarian origin included

45 gene panel on NGS, targeted immunohistochemistry

Most common mutations in a subset (n = 128) of invasive cancers KRAS (60%), TP53 (38%), PIK3CA (13%) and PTEN (9%).

Borderline tumors had higher rates of BRAF mutations, and PGP and TOP2A overexpression than invasive cases.

KRAS mutant invasive cancers had lower expression of thymidylate synthase (p = 0.01) and higher expression of TUBB3 (p = 0.01) than KRAS wildtype tumors.

Given the difficulty recruiting patients to histotype- specific trials in rare subsets of ovarian cancer, it may be more important to focus on identifying potential treatment targets and to personalise treatment and design clinical trials in MO-CUPS agnostic of primary site to overcome these issues.
Take Home message

• Mucinous ovarian tumors are distinct
• Seromucinous tumours differ from usual gastrointestinal type mucinous tumours
• Metastases may mimick ovarian borderline tumours and carcinomas
• Nodular pattern, bilaterality, extraovarian spread, tumour on surface... favor metastasis
• Immunohistochemistry helpful but may vary
Thank you very much for your attention!