Pathology of The Fallopian Tube: Fimbria Facts & Fictions

Pacific Northwest Society of Pathologists
Vancouver, B.C.
September 26, 2015

Teri A. Longacre, M.D.
longacre@stanford.edu
Stanford University, Stanford, CA
Topics For Discussion

• Hereditary “ovarian” cancer: BRCA 1/2
• Tubal serous carcinoma: tubal intraepithelial carcinoma & “p53 signature”
• Differential diagnosis of tubal carcinoma
Historic Perspective

- Ovarian cancer one disease – one treatment
- Most ovarian cancer is serous – all serous carcinomas are the same
- Most ovarian cancers arise in the ovary or peritoneum – rarely fallopian tube
Ovarian Surface Epithelial Neoplasms (SEN)

- Serous (tubal-like)*
- Mucinous
- Endometrioid
- Clear cell
- Brenner
- Squamous

* Prototype for surface epithelial tumors
*** Normal surface epithelium
Fallopian Tube Primary Neoplasia: Conventional Rules

- No concomitant ovarian or endometrial tumor
- Transition from tubal carcinoma to tubal dysplasia
- Tubal carcinoma considered to be very rare
Hereditary Ovarian Cancer

• Hereditary breast-ovarian cancer (HBOC)
• Lynch syndrome [Hereditary nonpolyposis colorectal cancer (HNPCC)]
Hereditary Breast-Ovarian Cancer

- Germline mutations in BRCA 1/ BRCA 2
- Breast & ovary
- High grade: triple negative, basal-like phenotype in breast
- High grade: serous carcinoma in ovary
BRCA-1

• Dominant inheritance pattern of susceptibility
• Mutation in 17q21 (>100 mutations)
• 85-90% lifetime risk of breast cancer
• 40 to 60% lifetime risk of ovarian cancer
• Possible gastric & pancreas cancer risk
BRCA-2

• Dominant inheritance pattern of susceptibility
• 13q12-13
• 85-90% lifetime risk of breast cancer – including male
• 20% lifetime risk of ovarian cancer
• Possible prostate, pancreas, gastric cancer risk
Hereditary Ovarian Cancer (BRCA)

- Early screening (25 years of age)
- Risk reducing salpingo-oophorectomy for BRCA 1/2 at age 40
Fallopian Tube Serous Carcinoma: BRCA Lessons

- High incidence of serous tubal intraepithelial serous carcinoma (STIC) in BRCA1/2
- STIC also seen in tubal mucosa from patients with ovarian & peritoneal high grade serous carcinoma
- STIC assoc with p53

"Ovarian" Cancer: Possible Tubal Origin

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Cancer</th>
<th>STIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell et al</td>
<td>BRCA</td>
<td>7/67 (10%)</td>
<td>57%</td>
</tr>
<tr>
<td>Finch et al</td>
<td>BRCA</td>
<td>7/159 (4%)</td>
<td>86%</td>
</tr>
<tr>
<td>Callahan et al</td>
<td>BRCA</td>
<td>7/100 (4%)</td>
<td>100%</td>
</tr>
<tr>
<td>Leeper et al</td>
<td>BRCA</td>
<td>5/30 (17%)</td>
<td>60%</td>
</tr>
<tr>
<td>Kindelberger</td>
<td>Ovary</td>
<td>All (43)</td>
<td>47%</td>
</tr>
<tr>
<td>Carlson et al</td>
<td>Peritoneum</td>
<td>All (19)</td>
<td>47%</td>
</tr>
<tr>
<td>Roh et al</td>
<td>Ovary</td>
<td>All (87)</td>
<td>36%</td>
</tr>
</tbody>
</table>

Gynecol Oncol 2009;113:391-396
Serous Tubal Intraepithelial Carcinoma

- Nuclear pleomorphism
- Increased nuclear/cytoplasmic ratio
- Increased proliferation
- Disorganized growth
- Nucleoli often present
- Typically fimbria or distal tube
The p53 Signature: Possible Precursor Lesion

- Histologically normal tubal epithelium
- At least 12 consecutive p53 positive secretory cell nuclei
- Normal proliferative index (Ki-67/mib1)
The "p53 Signature"
### How Common Is p53 Signature?

<table>
<thead>
<tr>
<th></th>
<th>BRCA 1/2</th>
<th>Low Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al</td>
<td>10/41 (24%)</td>
<td>19/58 (33%)</td>
</tr>
<tr>
<td>Shaw et al</td>
<td>19/176 (11%)</td>
<td>12/64 (19%)</td>
</tr>
</tbody>
</table>
Normal tubal secretory cells

p53 signature

Serous tubal intraepithelial lesion in transition

Serous tubal intraepithelial carcinoma

Invasive serous carcinoma
Courtesy of A. Folkins
Fallopian Tube Serous Carcinoma: Surgical Pathology

- Serial sections of entire fallopian tube for risk reducing prophylactic salpingo-oophorectomy (longitudinal sections of fimbria) at 2-3 mm
- Serial (longitudinal) sectioning of fimbria for apparent low stage uterine and ovarian serous carcinoma; at least 3 sections to include fimbria
- Do not rely on p53! Use standard morphologic criteria

*Virchows Arch 2007;450:25-29*
Prevalence of BRCA1/BRCA2 in Fallopian Tube Carcinoma

Vicus D et al, Gynecol Oncol. 2010 Jun 4. [Epub ahead of print]

- Mutation in BRCA1 or BRCA2 in 30%
- Highest frequencies associated with diagnosis before age 60, Jewish ethnicity, family history of breast or ovarian cancer, & personal history of breast cancer
- Recommend all patients diagnosed with invasive fallopian tube cancer be considered candidates for genetic testing
Tubal Carcinoma

- Serous (75%)
- Endometrioid (10%)
- Transitional (5%)
- Mixed (5%)
- Clear cell – very rare
- Mucinous – exclude appendix

*Pathology 2007;39:112-124*
Histology of BRCA-1 Hereditary “Ovarian” Cancer

- High grade serous, undifferentiated or endometrioid
- Nuclear anaplasia
- High mitotic index
- Tumor intraepithelial lymphocytes (TILs)
Pelvic Serous Phenotype

- CK7 positive/CK20 negative
- WT1 positive
- ER+/-
- PAX8 positive
- PAX2 negative
- p53+ due to mutation
- p16+/-
Tubal Serous Carcinoma: Differential Diagnostic Problems

- Serous adenofibroma - S-LMP – Low grade serous carcinoma
- Metaplastic papillary tumor
- Papillary clear cell cystadenoma
- Metaplasia: transitional, squamous, etc
- ‘Hyperplasia’
- Inflammatory processes
- Mesothelioma
- FATWO
- Other histology: endometrioid
- Other primary sites of serous carcinoma
- Other metastases: breast
Metaplastic Papillary Tumor

- Very rare
- Noninvasive, mitotically inactive, and cytologically bland
- Resembles exuberant serous tumor of low malignant potential with abundant eosinophilic cytoplasm
Metaplasia

- Transitional
- Squamous
- Mucinous
Transitional Cell Metaplasia

- Common (25%)
- Multifocal (2/3) with involvement of the tip, edges, or base of the fimbrial plicae
- Small: mean 1.3 mm (range, 0.1 to 10 mm)
- Histologically identical to Walthard rests

*Am J Surg Pathol 2009;33:111-9*
Squamous Metaplasia

- Diffuse pattern associated with band-like subsurface fibrosis in peritoneal dialysis patients
- Micronodular pattern associated with inflammatory conditions.

*Int J Gynecol Pathol* 2008;27:465-74
Papillary Clear Cell Cystadenoma

- Rare, usually broad ligament – more common in men
- Von Hippel-Lindau syndrome
- Benign
- Can pose problem on frozen section: clear cell carcinoma vs serous borderline tumor vs metastasis
Mesothelioma, Papillary Type

- Diffuse thickening of peritoneum & mesentery, multiple small nodules or abdominal mass – but may be focal
- Asbestos exposure strongly linked in men, but not women
- Cuboidal cells with eosinophilic cytoplasm
- Vesicular nuclei with prominent nucleoli, cytoplasmic vacuoles
Well Differentiated Papillary Mesothelioma
Well Differentiated Papillary Mesothelioma
## Recognition of Mesothelial Lesions in the Peritoneum

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Mesothelial</th>
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<tbody>
<tr>
<td><strong>Calretinin</strong></td>
<td>〇〇</td>
<td>●●</td>
</tr>
<tr>
<td><strong>Ber-EP4</strong></td>
<td>●●</td>
<td>〇〇</td>
</tr>
<tr>
<td><strong>CK 5/6</strong></td>
<td>●●</td>
<td>●●</td>
</tr>
<tr>
<td><strong>mCEA</strong></td>
<td>●●</td>
<td>〇〇</td>
</tr>
<tr>
<td><strong>CD15</strong></td>
<td>●●</td>
<td>〇〇</td>
</tr>
<tr>
<td><strong>WT-1</strong></td>
<td>●●</td>
<td>●●</td>
</tr>
</tbody>
</table>

〇 = Pos  
〇〇 = Neg
Female Adnexal Tumor of Probable Wolffian Origin (FATWO)

- Paratubal (broad ligament) location
- Solid or solid & cystic (mean, 8 cm)
- Sieve-like pattern, but can have tubules mimicking Sertoli tubules or endometrioid tumor
- Immunoprofile: EMA-, CK7+ (but patchy), inhibin, calretinin
Tubal Hyperplasia
Adenomatoid Tumor
Tubal Carcinoma

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*Pathology 2007;39:112-124*
Endometriosis
Endometrioid Adenofibroma
Borderline Endometrioid Tumor
Mucosal Metastases
• Breast
• Appendix

Serosal Metastases
• Anything
Metastatic Breast Carcinoma
Serous Problems: Breast vs Ovary/Tubal/Peritoneum vs Endometrium

<table>
<thead>
<tr>
<th></th>
<th>WT1</th>
<th>BRST2</th>
<th>PAX8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>○</td>
<td>●</td>
<td>○</td>
</tr>
<tr>
<td>Ovary/Peritoneum/ Fallopian tube</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>Endometrium</td>
<td>○</td>
<td>○</td>
<td>●</td>
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</table>

○ = Negative
● = Positive
Tubal Carcinoma

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Pathology 2007;39:112-124
Tubal Low-Grade Serous Carcinoma
Tubal Low-Grade Serous Carcinoma
Serous Carcinoma: Dual Pathway

• Low grade
• High grade
Serous Carcinoma: Pathogenesis

Familial

- Inclusion cyst
- Fallopian tube
  - BRCA-1,2 mutation
  - BRCA-1,2 LOH
  - Dysplasia
    - p53 mutation
  - High grade carcinoma

Sporadic

- Surface Epithelium
  - BRAF, KRAS
  - Low Malignant Potential
  - Micropapillary LMP
  - Low grade carcinoma

- Low grade carcinoma

- Dysplasia
  - p53 mutation
  - Low Malignant Potential

- High grade carcinoma

- BRCA-1,2 mutation

- LOH
Gene Expression in S-LMP vs S-CA

(Gilks et al, 2005)
# Low Grade vs High Grade Ovarian Serous Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Stage</th>
<th>Recurrence (mos)</th>
<th>Survival (mos)</th>
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<tbody>
<tr>
<td>LG-SC</td>
<td>III/IV</td>
<td>19.5</td>
<td>81</td>
</tr>
<tr>
<td>HG-SC*</td>
<td>III/IV</td>
<td>18.5</td>
<td>60</td>
</tr>
</tbody>
</table>

*Optimally debulked, < 1 cm

*Gynecol Oncol 2006; 105:625-629*
Low Grade Serous Carcinoma

- Uncommon, but important to distinguish from high grade serous carcinoma
- Less aggressive
- Less responsive to standard platinum-based chemotherapy
- Different molecular pathway
- Often associated with foci of S-LMP
So...where is it coming from?

- Ovary
- Peritoneum
- Fallopian tube
- Endometrium
- Cervix
Pelvic Serous Carcinoma

- Tumors don’t come with arrows & they all look alike
- Patients treated similarly, but if tubal component consider BRCA1/2
- *Exclude uterine serous carcinoma*
Is Fallopian Tube Source of Ovarian & Peritoneal Carcinoma?

• Role of surface epithelium in ovarian carcinogenesis is largely circumstantial
• Epithelial inclusion cysts, peritoneal inclusion cysts are other strong contenders
• Tubal primary vs secondary involvement
• Role for “pelvic serous carcinoma”
Thank you

Stanford University