Today’s Topics

- Peritoneal mesothelioma: pathology, treatment, results
- Selected benign mesothelial tumors
- Mesothelial hyperplasia vs mesothelioma and carcinoma
- Peritoneal serous carcinoma: clinical features, pathology, etiology

Malignant Peritoneal Mesothelioma in Women

- Wide age range (17-92), average 47 years
- Presentation
  - Abdominal or pelvic pain
  - Abdominal swelling due to ascites
  - Pelvic mass
- Operative findings
  - Mainly widespread disease
  - Some have more limited or even localized tumors
- No association with asbestos exposure in most cases
- Poor prognosis (12.5 months median survival) generally reported, but Kerrigan et al reported that up to 40% have indolent behavior

Figure 4a. Gross pathologic features of a peritoneal malignant mesothelioma


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Classification of Mesothelioma

- Epithelial
  - Epithelioid – solid sheets of tumor cells
  - Tubulopapillary – tubular or papillary growth
  - Deciduoid – large polygonal cells with abundant eosinophilic cytoplasm
  - Microcystic
  - Small cell
  - Clear cell
  - Localized malignant mesothelioma – a distinctly localized nodular tumor without gross or microscopic evidence of diffuse peritoneal spread
- Sarcomatous
  - Sarcomatous
  - Transitional
  - Lymphohistiocytoid
  - Desmoplastic
- Mixed Epithelial and Sarcomatous

<table>
<thead>
<tr>
<th>Type</th>
<th>Number (total = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelial Types</strong></td>
<td></td>
</tr>
<tr>
<td>Tubular</td>
<td>56, predominant 24</td>
</tr>
<tr>
<td>Papillary</td>
<td>45, predominant 23</td>
</tr>
<tr>
<td>Epithelioid (solid)</td>
<td>45, conspicuous 23</td>
</tr>
<tr>
<td>Deciduoid</td>
<td>2</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1, focal in others</td>
</tr>
<tr>
<td>Localized</td>
<td>3</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
<td>4</td>
</tr>
</tbody>
</table>


Figure 4b. Gross pathologic features of a peritoneal malignant mesothelioma

Appearance of mesothelioma cells

# Immunohistochemistry in the Diagnosis of Mesothelioma

**Immunostains that are typically positive in mesothelioma:**
- Calretinin; D2-40 (podoplanin); thrombomodulin; cytokeratin 5/6; WT1; h-caldesmon; VIM; CK; CK7

**Immunostains that are typically positive in adenocarcinoma**
- MOC-31; Ber-EP4; B72.3; CD15; CEA; CK; CK7 (some types); WT-1 (serous, TCC); ER/PR

## Mesothelioma Markers

*Mesothelioma vs Serous Carcinoma*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mesothelioma</th>
<th>Serous Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calretinin</td>
<td>88-100% +</td>
<td>9-31%+, focal</td>
</tr>
<tr>
<td>D2-40</td>
<td>93-100%</td>
<td>13-65%+, focal</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>33-74%</td>
<td>2-35%</td>
</tr>
<tr>
<td>CK5/6</td>
<td>53-100%</td>
<td>22-55%</td>
</tr>
<tr>
<td>WT1</td>
<td>43-93%</td>
<td>83-100%</td>
</tr>
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</table>

## Adenocarcinoma Markers

*Mesothelioma vs Serous Carcinoma*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mesothelioma</th>
<th>Serous Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>0%+</td>
<td>65-89%+</td>
</tr>
<tr>
<td>MOC 31</td>
<td>4-25%, focal</td>
<td>98%</td>
</tr>
<tr>
<td>Ber-EP4</td>
<td>9-13%, focal</td>
<td>50-100%</td>
</tr>
<tr>
<td>B72.3</td>
<td>0%</td>
<td>65-98%</td>
</tr>
<tr>
<td>CD15</td>
<td>0%</td>
<td>30-80%</td>
</tr>
<tr>
<td>CEA</td>
<td>0%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Carcinoma markers that can show focal staining in mesothelioma – Ber-EP4 and MOC-31

Best Markers
Mesothelioma vs Serous Carcinoma
- Calretinin, D2-40
- ER
- Ber-EP4 and/or MOC 31
- Other markers as needed

Deciduoid Mesothelioma
- Initially described as peritoneal tumors in young women; sometimes mistaken for decidual reaction
- Subsequently reported in older women and men, and in pleura
- Predilection for peritoneum, females, young relative to mesothelioma in general
- Majority of tumor cells are large cells with eosinophilic cytoplasm: decidua-like or deciduoid
- EM reveals abundant intermediate filaments in cytoplasm
- Mesothelioma immunophenotype; also stain for NSE, PGP 9.5, NKI/C3
Deciduoid Mesothelioma DDx: Deciduosis (Decidual Rxn)

Decidual Reaction vs Deciduoid Mesothelioma

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Decidual Rxn</th>
<th>Deciduoid Meso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, drug</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor, ascites</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Other meso patt</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>No</td>
<td>Few</td>
</tr>
<tr>
<td>CK</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Calretinin</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
**Treatment of Mesothelioma**

- Surgery
- Systemic chemotherapy
- Radiotherapy
- Maximum debulking with intraperitoneal chemotherapy


**Possible Pathological Prognostic Markers**

- Histologic type
  - Sarcomatoid and mixed types have a poor prognosis
- Grade
  - Various grading systems: tubulopapillary vs. solid, nuclear grade, nuclear size, mitotic index
  - Grade 1=10-20µ; grade 2=21-30µ; grade 3=31-40µ; grade 4=>40µ
- Invasion beneath the surface

**Mesothelioma Involving the Ovary**

- Ovarian involvement common in diffuse peritoneal mesothelioma
- Presentation as a primary ovarian tumor is rare (Clement reported 9 cases)
  - 2 confined to ovaries; no f/u
  - 7 had widespread disease; 5/6 with f/u DOT
- Tumor generally involves serosa and parenchyma
- 7 epithelial, 2 mixed

Well Differentiated Papillary Mesothelioma

- First large report dates from 1990
- Median age of female patients 41 years, range 2-70’s
- Mesentery, omentum, bowel serosa, ovary surface most common sites
- A majority of patients have had multiple tumors
- Most are < 1 cm, but tumors > 3 cm have been reported
- Most patients NED
- Literature contains reports of patients with invasive disease, tumor requiring extensive surgery or chemotherapy, and tumor related deaths
Well Differentiated Papillary Mesothelioma
Criteria for Diagnosis

- Small (most < 2 cm)
- Consist entirely of papillae
- Papillae lined by uniform cuboidal cells
- Bland cytology
- No more than rare mitotic figures
- No evidence of invasion

- Complex morphology with multifocality more compatible with malignant mesothelioma.
- Significance of tumors with typical simple architecture but multifocality unclear.

Cystic Mesothelioma

- Mainly occur in women of reproductive age
- Present with abdominal pain, distention or a palpable mass
- Adherent to pelvic organs or abdominal structures
- Can be large (>20 cm)
- History of prior surgery, endometriosis, or PID is typical
- Recurrences are common and may be due to:
  - Ongoing inflammation and adhesions
  - Recurrence of incompletely removed tumor


Figure 20b. Multicystic mesothelioma in an asymptomatic 60-year-old woman with a palpable mass found at pelvic examination


Figure 15b. Gross pathologic features of multicystic mesothelioma

Cystic Mesothelioma

What is It?

- Low grade neoplasm of mesothelial cells
  - Multiplicity of lesions, spread and recurrence, transitions to adenomatoid tumor (Weiss and Tavassoli)
- Reactive mesothelial proliferative lesion
  - Resembles reactive mesothelial lesions; inflammation, hemorrhage, fibrosis; association with previous mesothelial injury; benign clinical course (Ross, Welch and Scully)

Mesothelial Hyperplasia

- Can cause differential diagnostic problems with
  - Mesothelioma
    - Mesothelial hyperplasia can be difficult to differentiate from epithelial mesothelioma
  - Epithelial tumors
    - Mesothelial hyperplasia can simulate metastatic carcinoma involving peritoneum or invasion in a borderline ovarian tumor
  - Lymph node metastases
    - Hyperplastic mesothelial cells in lymph node sinuses simulate metastatic carcinoma

Hyperplastic Mesothelial Cells in a Lymph Node


Cytokeratin

Calretinin
Mesothelial Hyperplasia vs Neoplasm (Mesothelioma or Carcinoma)

<table>
<thead>
<tr>
<th></th>
<th>Meso Hyperplasia</th>
<th>Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small, microscopic</td>
<td>Gross tumor</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>Granulation tissue</td>
<td>Desmoplasia</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Surface</td>
<td>Surface, invasion</td>
</tr>
<tr>
<td><strong>Pattern</strong></td>
<td>Papillary, linear</td>
<td>Irregular</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Marked atypia</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Atypical MF</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Desmin</strong></td>
<td>+ (&gt; 80%)</td>
<td>- (+ in &lt;20%)</td>
</tr>
<tr>
<td><strong>EMA</strong></td>
<td>- (+ in 15%)</td>
<td>+ (75%)</td>
</tr>
</tbody>
</table>

Attanoos RL et al. Histopathology 2003;43:231-238
Primary Peritoneal Carcinoma

WHO Definition

- Primary epithelial tumors of the peritoneum that resemble malignant ovarian surface-epithelial tumors.
- Both ovaries must be normal in size or enlarged by a benign process.
- The tumor in extraovarian sites must be larger than the tumor on the surface of either ovary.
- Ovarian tumor involvement must be either nonexistent, confined to the ovarian surface without stromal invasion, or involve the cortical stroma with tumor size < 5x5 mm.

Extraovarian Peritoneal Serous Papillary Carcinoma

A Clinicopathologic Study of 31 Cases


The characteristics of patients admitted to King George V Hospital with extraovarian peritoneal serous papillary carcinoma are described in this study. The criteria for diagnosis and the treatment of these patients have been reviewed.

Primary Peritoneal Carcinoma

- Same clinical presentation and age range as advanced ovarian cancer
  - Postmenopausal, abdominal pain or distention, GI symptoms, ascites
- Stage III or IV disease
- Almost always serous carcinoma
- Most patients have largest amount of tumor in omentum
- Same therapy as for ovarian cancer
- Response to therapy similar to that for matched ovarian cancer patients
Serous Carcinoma
Sites of Origin in 809 Cases
Australian Ovarian Cancer Study Group

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>627</td>
<td>78</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>129</td>
<td>16</td>
</tr>
<tr>
<td>Fallopian Tube</td>
<td>45</td>
<td>6</td>
</tr>
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</table>


Survival With Ovarian and Primary Peritoneal Carcinoma

Jaaback KS et al. Int J Gynecol Cancer 2006;16(Suppl. 1):123-128

Omental Masses
Clinically thought to be primary peritoneal serous carcinoma
Peritoneal serous papillary carcinoma, a phenotypic variant of familial ovarian cancer: Implications for ovarian cancer screening

Primary peritoneal carcinoma can be a BRCA associated tumor

Beth Y. Katin, MD,1 Rae Lynn Baldwin, PhD,2 Eloise Lopez-Arcarazo, RN, BSN,2 Leslie J. LaRuffa, MD,3 Denise Barbarito, MEI,4 Steven Nandi, MD,5 and Lawrence D. Platt, MD, MP6

1Los Angeles, California; and Toronto, Ontario, Canada;

2Our purpose was to report the cancers among during a familial ovarian cancer screening program and investigate the tumor's biology and association with BRCA1 and BRCA2 mutations.

STUDY DESIGN: Program participants with a diagnosis of ovarian cancer or peritoneal serous papillary carcinoma were identified and their demographic characteristics, ultrasonographic findings, CA-125 results, optimization results, and pathologic analysis revealed. Immunohistochemical analysis of CA-125, p53, p27kip1, and mesothelin expression was performed on tumor tissues from multiple metastatic sites, and germline BRCA1 and BRCA2 mutations were identified.

RESULTS: Three (18.8%) of the 15 cases of peritoneal serous papillary carcinoma were stage IVb, and 1 (6.7%) was stage II. Ultrasonographic findings suggested peritoneal extension in all 5 cases of stage I disease. Clinical stage of CA-125 were the last diagnosis. In 2 of 7 cases of peritoneal serous papillary carcinoma, abdominal ultrasonography findings prompted diagnosis in 2 of 7 cases, and 9 of 11 months lead to abdominal symptoms. 0, 5, and 10 months after surgery. Results of immunohistochemical studies suggested multiorgan disease in 5 of 7 patients with peritoneal serous papillary carcinoma. At least 3 of the peritoneal serous papillary carcinoma carry BRCA1 1655A>20 mutations.

CONCLUSION: Multiple peritoneal serous papillary carcinomas may be a phenotypic variant of familial ovarian cancer and screening strategies for these patients warranting an ultrasound and CA-125 test.

Primary Peritoneal Carcinoma
Is it really Primary?
- Omentum
- Colon Serosa

Serous carcinoma in omentum

Serous carcinoma of the fallopian tube with TIC
Primary Peritoneal Carcinoma Does It Occur?

_Fallopian tube often contains tumor in cases of PPCa_

| Kindelberger et al found tubal tumor in 6/7 cases of PPCa (4 with TIC) in which tubes were totally sectioned (2007) |

<table>
<thead>
<tr>
<th>Sampling</th>
<th>N</th>
<th>Carcinoma in Endosalpinx</th>
<th>STIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete</td>
<td>26</td>
<td>13 (50%)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Complete</td>
<td>19</td>
<td>15 (79%)</td>
<td>9 (47%)</td>
</tr>
</tbody>
</table>

Carlson JW J Clin Oncol 2008; 26:4160-4165

P53 Mutation Analysis in PPCa

- Mutation analysis performed in 10 cases, testing tube and peritoneum
- 5 cases noninformative for technical reasons
- 4 cases had same mutation in STIC and PPCa
- 1 case had same mutation in p53 signature lesion and PPCa

Carlson JW J Clin Oncol 2008; 26:4160-4165
Peritoneal Serous Carcinoma

- Many have serous carcinoma +/- TIC in the fallopian tube
- Is this
  - FT → Peritoneum
  - Peritoneum → FT
  - Synchronous primary sites

Factors favoring fallopian tube primary
- Same genetic mutations at both sites
- Precursor lesions identified in tube, not in peritoneum
- TIC and serous carcinoma without peritoneal serous carcinoma are much more common than peritoneal serous carcinoma without FT TIC and serous carcinoma

Primary Peritoneal Carcinoma Does It Occur?

- Fallopian tube contains no tumor in at least 20% of cases of PPCa
- Peritoneal carcinomatosis can occur in women with EIC
  - Soslow et al reported 3 cases and found that the clinical and pathologic features of EIC-PCa were similar to those in PPCa (1 TIC in 9 PPCa)
- Primary peritoneal carcinoma can develop in women who have had previous BSO or Oophorectomy
  - Piver et al reported 9 cases from the Gilda Radner Familial Ovarian Cancer Registry
  - 8 had BSO, 1 bilateral oophorectomy
  - Peritoneal carcinoma developed 1, 1, 1, 2, 3, 5, 7, 15, and 15 years after oophorectomy

Primary Peritoneal Carcinoma New Definition

- Primary epithelial tumors of the peritoneum that resemble malignant ovarian surface-epithelial tumors.
- Both ovaries must be normal in size or enlarged by a benign process.
- The tumor in extraovarian sites must be larger than the tumor on the surface of either ovary.
- Ovarian tumor involvement must be either non-existent, confined to the ovarian surface without stromal invasion, or involve the cortical stroma with tumor size < 5x5 mm
- The Fallopian tubes are thoroughly studied and no intraepithelial or invasive carcinoma is present.
- The endometrium is thoroughly studied and no serous carcinoma or EIC is present.

Pathways to Pelvic Serous Carcinoma

Crum CP Molec Oncol; 2009; 3:165-170