Ovarian Serous Borderline Tumors

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Pathology:

- Left ovary: Serous borderline tumor, with micropapillary pattern,
  - endophytic and exophytic components are seen,
- Omentum & uterine serosa: positive for invasive implants.
- Lymph nodes: negative
- Cytology: positive for serous neoplasm.
Ovarian Serous Borderline Tumors

- Identified more than 100 years ago
- Popularized in 1960s-70s
- Initially controversial
- Adopted in classifications of international organizations (FIGO, WHO, ISGP)
- Continues to be challenged
Ovarian Serous Borderline Tumors

Historical Synonyms,

- Semimalignant tumor
- Low potential malignancy
- Borderline malignancy (carcinoma of LMP)
- Tumor of LMP
- Atypical proliferative tumor
WHO Classification of Ovarian Tumors

Surface Epithelial-Stromal Tumors

Degree of Epithelial Proliferation

Benign

Borderline

Malignant
World Health Organization Classification of Ovarian Tumors

Borderline Tumors - Criteria

- Epithelial proliferation greater than that seen in benign tumors of the same cell type
- Destructive or obvious stromal invasion is **not** present
Borderline Tumors
Microscopic Criteria

Cellular stratification
Detached cell clusters
Mitotic activity
Nuclear atypia
**ABSENT** of destructive stromal invasion
# Serous Borderline Tumor

## Clinicopathologic Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>9-15%</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>38 yrs</td>
</tr>
<tr>
<td>Bilateral</td>
<td>40%</td>
</tr>
<tr>
<td>Exophytic surface growth</td>
<td>48%</td>
</tr>
<tr>
<td>Peritoneal/omental implants</td>
<td>32%</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>7-23%</td>
</tr>
<tr>
<td>Stage</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Stage I</td>
<td>41-83%</td>
</tr>
<tr>
<td>Stage II</td>
<td>7-22%</td>
</tr>
<tr>
<td>Stage III</td>
<td>4-40%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Serous Borderline Tumor

- Clinical behavior (According to R. Kurman):
  - 5 year survival = 90 -95% patients with no extraovarian disease
Serous Borderline Tumors Survival

Review of the Literature

2,104 cases

Stage I 99.5%
Stage II and III 70%

Surveillance, Epidemiology and End Result (SEER)

2818 women 1988-1997

10 yr relative survival by stage

Stage I 97%
Stage II 90%
Stage III 88%
Stage IV 69%
Total II-IV 82%

Seidman JD, Kurman RJ
Hum Pathol 31:539-577, 2000

Trimble CL et al Gynecol Oncol 86:34, 2002
# Serous Borderline Tumors

## Prognosis - Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0-20%</td>
</tr>
<tr>
<td>III</td>
<td>14-50%</td>
</tr>
</tbody>
</table>
Ovarian Serous Borderline Tumors

- Micropapillary/cribriform pattern
- Peritoneal implants
- Microinvasion, new data
- Lymph node involvement
- Recurrent serous borderline tumor
Serous Borderline Tumors

• Typical
• Micropapillary/cribriform
<table>
<thead>
<tr>
<th>Architecture</th>
<th>Typical</th>
<th>Micropapillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchical branching</td>
<td>Micropapillae (5x longer than wide) arise</td>
<td></td>
</tr>
<tr>
<td>Irregular papillae</td>
<td>directly from smooth papillae</td>
<td></td>
</tr>
<tr>
<td>Detached tufts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology</td>
<td>Columnar, eosinophilic cells, low N:C ratio</td>
<td></td>
</tr>
<tr>
<td>Polygonal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>high N:C ratio</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Serous Borderline Tumors with Micropapillary Pattern

- Usually arise in association with typical serous borderline tumor
- Must measure at least 5 mm in one dimension on at least one slide
Johns Hopkins Group

- Low grade serous carcinoma
- Micropapillary serous carcinoma
## Micropapillary tumors: Clinicopathologic findings

### Survival, Stage I

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deavers</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prat</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Slomovitz</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
# Micropapillary tumors: Survival Stage II+

<table>
<thead>
<tr>
<th>Sig?</th>
<th>MP</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deavers</td>
<td>No</td>
<td>72</td>
</tr>
<tr>
<td>Noninv</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>Inv Impl</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>Prat</td>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Noninv</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Inv Impl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slomovitz</td>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Noninv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longacre</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
If there is no difference in survival stage by stage-

Should micropapillary tumors be separated from typical serous borderline tumors?
### Micropapillary tumors: Clinicopathologic findings

<table>
<thead>
<tr>
<th></th>
<th>Bilaterality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MP</td>
</tr>
<tr>
<td>Deavers</td>
<td>72</td>
</tr>
<tr>
<td>Prat</td>
<td>67</td>
</tr>
<tr>
<td>Slomovitz</td>
<td>71</td>
</tr>
</tbody>
</table>
Micropapillary tumors: Clinicopathologic findings

<table>
<thead>
<tr>
<th>Stage II+</th>
<th>MP</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deavers</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prat</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Slomovitz</td>
<td>43</td>
<td>34</td>
</tr>
</tbody>
</table>
## Micropapillary tumors: Clinicopathologic findings

<table>
<thead>
<tr>
<th>Invasive Implants</th>
<th>MP</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deavers</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Prat</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Slomovitz</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Micropapillary Serous Tumors: Conclusions

- Survival is most closely linked to invasiveness in implants
- Data fail to demonstrate a poorer prognosis in MPSBT
- These tumors should remain classified in the borderline category
Micropapillary Serous Tumors: Conclusions

- MPSBT have distinct features (age, bilaterality, stage, invasive implants)
- Warrant clear distinction from typical SBT in pathology report
Ovarian Serous Borderline Tumors

- Micropapillary/cribriform pattern
- *Peritoneal implants*
- Microinvasion, new data
- Lymph node involvement
- Recurrent serous borderline tumor
Serous Borderline Tumors
Peritoneal Implants

- **Noninvasive**
  Noninvasive of underlying tissue
- **Invasive**
  Irregular infiltration of underlying tissue

- *Bell, DA Hum Pathol 22:750, 1991*
Serous Borderline Tumors
Peritoneal Implants

• Outcome of patients with advanced stage disease (implants) correlates with Type of implant
  – Noninvasive
  – Invasive
# Implant Status and Outcome

## 467 Patients

<table>
<thead>
<tr>
<th>No. of Series</th>
<th>Total Stage II/III Patient</th>
<th>Noninvasive Deaths/Total</th>
<th>Invasive Deaths/Total</th>
<th>Follow up Mean Mean, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>467</td>
<td>17/363</td>
<td>35/104</td>
<td>89</td>
</tr>
</tbody>
</table>

**Survival**

- **Noninvasive**: 95.3%
- **Invasive**: 66%

*Seidman JD, Kurman RJ*  
*Hum Pathol 31:539-577, 2000*
## Tissue Invasion Criteria and Prognosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Noninvasive</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCaughey</td>
<td>11/13 (85)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>D. Bell</td>
<td>47/50 (94)</td>
<td>1/6 (17)</td>
</tr>
<tr>
<td>De Nictolis</td>
<td>10/10 (100)</td>
<td>5/9 (56)</td>
</tr>
<tr>
<td>Eichhorn</td>
<td>13/13 (100)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Prat</td>
<td>34/34 (100)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Gilks</td>
<td>39/42 (93)</td>
<td>3/6 (50)</td>
</tr>
<tr>
<td>Seidman</td>
<td>43/51 (84)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Deavers</td>
<td>78/91 (84)</td>
<td>4/8 (50)</td>
</tr>
<tr>
<td>Longacre</td>
<td>Highly sig, uni, multivariate</td>
<td></td>
</tr>
</tbody>
</table>
Non-invasive implant
Non-invasive implants
Non-invasive implant:
No invasion of underlying tissue
Cytologic atypia same as ovarian (borderline) tumor
Non-invasive implant: Papillae with fibrous or hyalinized cores
Epithelium of implants merges with stroma
Non-invasive implant:
Stroma has granulation tissue tissue appearance
Non-invasive implant, Desmoplastic type
Individual eosinophilic cells in the stroma are not indicative of an invasive implant

Stroma has granulation tissue appearance
Noninvasive Implant

- Ratio of epithelium to stroma is less than in invasive implants
- Epithelial cells often larger than those in invasive implants
  - Nuclei can be more atypical
  - Cytoplasm often abundant and eosinophilic
Invasive Implant

- Invasion of Normal Tissue
- “Micropapillary” Architecture
- Small Solid Epithelial Nests Surrounded By Clefts
- Cytologic atypia resembles that of a grade 1 serous carcinoma
Non-invasive desmoplastic implant

Invasive implant
Invasive Implant
Invasion Of Normal Tissue
Invasive Implant
Serous Borderline Tumors
Peritoneal Implants-Subtyping Criteria

• Relationship of the tumor and its surrounding stroma to underlying tissue invasion
• Characteristics of the tumor itself:
  • Micropapillarity
  • Solid nests of cells with clefts
  • Glands with extensive bridging
  • Marked cytologic atypia
  • Single cells
Invasive Implant,
“Micropapillary” Architecture
Micropapillary nests
• Solid nests of cells with clefts

Small Solid Epithelial Nests Surrounded By Clefts
Cytologic atypia resembles that of a grade 1 serous carcinoma
Solid nests of cells with clefts
<table>
<thead>
<tr>
<th>Feature</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasiveness (Tissue inv)</td>
<td>0.84</td>
</tr>
<tr>
<td>Micropapillarity</td>
<td>0.71</td>
</tr>
<tr>
<td>Single stromal cells</td>
<td>0.50</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>0.46</td>
</tr>
<tr>
<td>Periglandular Clefts</td>
<td>0.34</td>
</tr>
<tr>
<td>Prominent Nucleoli</td>
<td>0.20</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>0.03</td>
</tr>
<tr>
<td>Invasiveness (Inv, micr, clefts)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Peritoneal Implants
Conclusions

• Most reproducible feature is tissue invasion
• Micropapillarity and solid nests with clefts co-vary with invasion and are also reproducible
Peritoneal Implants
Conclusions

• Peritoneal tumor associated with SBT should be termed: “noninvasive and invasive implants”
• invasion of underlying tissue is the most important adverse prognostic factor
Ovarian Serous Borderline Tumors

- Micropapillary/cribriform pattern
- Peritoneal implants
- *Microinvasion, new data*
- Lymph node involvement
- Recurrent serous borderline tumor
Serous Borderline Tumors with Stromal Microinvasion

10-15% of tumors have small foci of invasion in tumor stroma with a minimal stromal reaction
Definition of microinvasion

- Less than 3 mm in diameter
- Less than 10 sq mm in area
- Less than 5 mm in greatest dimension
Serous Borderline Tumors with Microinvasion

Microinvasive foci present in:
- 10% of Stage I SBTs
- 56% of Stage II and III SBTs
- Pregnant women
Serous Borderline Tumors with Stromal Microinvasion

Morphologic patterns:
Common pattern: Eosinophilic cell pattern
Unusual patterns: Micropapillae, solid nests, cribriform nests - rare
Serous Borderline Tumors with Stromal Microinvasion
## Microinvasion and Outcome

### 94 Patients

<table>
<thead>
<tr>
<th>No. of Series</th>
<th>No. of Cases</th>
<th>Last Known Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>101</td>
<td>94 pts, 6,7 yrs means FLU</td>
</tr>
</tbody>
</table>

1 recurrence, pt AWD  
Survival-100%

---

Seidman JD, Kurman RJ  
*Hum Pathol* 31:539-577, 2000
Microinvasion: 2003

Eosinophilic cell pattern

• Does not convey a worse prognosis
• Should be designated “serous borderline tumor with microinvasion”
Microinvasion: New Data

Prat and De Nictolis (20/137):

<table>
<thead>
<tr>
<th>Survival</th>
<th>Typical</th>
<th>Microinvasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>100%</td>
<td>80% AW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% DOD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% A after rec CA</td>
</tr>
</tbody>
</table>
Microinvasion: New Data

Longacre et al.

• (10%) 28/276

• 8/28 patients DOD or alive with recurrent invasive serous carcinoma

• Univariate and multivariate analysis: Microinvasion associated with overall survival, independent of micropapillary and implant status.
Microinvasion: New Data

McKenney/Longacre

60 cases-34 Stage I, 26 Stage II/III
9/50 with follow-up died or developed progressive disease
Most strongly linked to MP, but most had common pattern
Microinvasion: Stanford Data

- Stromal microinvasion significant adverse prognostic factor
- independent of stage in nonpregnant patients
- Still classify as borderline
Ovarian Serous Borderline Tumors

- Micropapillary/cribriform pattern
- Peritoneal implants
- Microinvasion, new data
- **Lymph node involvement**
- Recurrent serous borderline tumor
Serous Borderline Tumors Lymph Node Involvement

- Patients who undergo lymph node sampling
- 21-25% of pelvic or paraaortic lymph nodes involvement
Serous Borderline Tumors
Lymph Node Involvement

- Tumor confined to lymph nodes
- Present in sinuses,
- Less frequently in sinuses and parenchyma

Two morphologic types

- Eosinophilic cells, singly or in papillae
- Columnar serous cells in clusters, papillae
# Lymph Node Involvement and Outcome

43 Patient

<table>
<thead>
<tr>
<th>No. of Slides</th>
<th>No. of Cases</th>
<th>Last Known Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>63</td>
<td>43 pts, 6.5 yrs mean FU</td>
</tr>
</tbody>
</table>

1 patient DOD
Survival –95%

*Seidman JD, Kurman RJ*
*Hum Pathol 31:539-577, 2000*
Lymph Node Involvement

Conclusions

Lymph node involvement at presentation is not associated with an adverse outcome in patients with peritoneal implants, as long as the tumor aggregates are not >1mm.

Ovarian Serous Borderline Tumors

- Micropapillary/cribriform pattern
- Peritoneal implants
- Microinvasion, new data
- Lymph node involvement
- *Recurrent serous borderline tumor*
Serous Borderline Tumors
Recurrent Tumor

Tumor may recur as:
Noninvasive serous borderline tumor
Invasive low grade carcinoma
## Molecular genetics

<table>
<thead>
<tr>
<th></th>
<th>S BLTs / LG</th>
<th>HG</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS / BRAF</td>
<td>Present (61 – 68 %)</td>
<td>Absent</td>
</tr>
<tr>
<td>P53</td>
<td>&lt; 10 %</td>
<td>&gt; 50 %</td>
</tr>
</tbody>
</table>
Serous Borderline Tumors

Recurrent Tumor

Tumor may recur as:

Noninvasive serous borderline tumor - good prognosis

Invasive low grade carcinoma - patients who develop clinically apparent progressive disease
Recurrent tumor should be histologically examined and classified as borderline or carcinoma.
Conclusions
Ovarian Serous Borderline Tumors

- Microinvasion
- Peritoneal implants
- Micropapillary/cribriform pattern
- Recurrent serous borderline tumor
- Lymph node involvement