Breakout session: Gynecologic Pathology

Tao Huang, MD, PhD
Serous Borderline Tumor

• Definition: hierarchical branching, tufting, and detachment of cells and cell clusters; lined by columnar, ciliated and eosinophilic cells

• Serous borderline tumor (SBT) = Atypical proliferative serous tumor (APST)

• Serous cystadenoma (cystadenofibroma) with focal proliferation
  • Focal borderline change <10% of tumor volume
  • Considered benign with no risk of recurrence or disease progression
Disease Specific Survival

• >95% for stage I disease
• 65% for stage II-IV
• 6-7% transform to low-grade serous carcinoma
• Rarely transform to high-grade serous carcinoma
Features Associated with Disease Progression

- Bilaterality
- Surface involvement
- Capsular rupture
- Micropapillary/cribriform pattern
- Microinvasion
- Advanced stage at presentation
- Implant type
  - invasive implants a/w the highest risk of predicting poor outcome
- Residual disease
Micropapillary / Cribriform Pattern

- Micropapillary architecture:
  - Non-hierarchical branching of elongated papillae that are at least five times as long as they are wide

- Cribriform pattern: a variant of micropapillary pattern

- Cytology:
  - More uniform/monomorphous appearance than the usual SBT
  - Small but conspicuous nucleoli; increased mitotic activity
  - Less frequent pink cells and ciliated cells
  - Higher degree of cytologic atypia than the usual SBT
SBT, Micropapillary Variant

• AKA, non-invasive low-grade serous carcinoma (LGSC)

• Definition:
  • The micropapillary or cribriform elements occupy a continuous 5 mm linear extent

• SBT with focal micropapillary features
  • Lessor degree (<5 mm in linear extent) of micropapillary or cribriform elements
Stromal Microinvasion

• Individual eosinophilic cells and cell clusters (most common)
  • occurs disproportionally in pregnant patients with SBT, usually with low-stage disease, and does not appear to be associated with any risk of progression in that setting.

• Simple and non-complex branching papillae

• Less common: inverted macropapillae, micropapillary, or cribriform

• Each focus has to be < 5 mm

Malpica A and Longacre TA. Pathology. 2018;50(2):205-213
Microinvasive Carcinoma

• Destructive invasion of ovarian stroma by cytologically malignant cells, i.e. small foci (< 5 mm) of low-grade serous carcinoma
Current WHO Definition for Microinvasion and Microinvasive Carcinoma

• “The term “microinvasion” has been applied to clusters of cells in the stroma with abundant eosinophilic cytoplasm, similar to the eosinophilic cells on the surface of papillae, that measure < 5 mm in the greatest dimension.”

• “On rare occasions, small foci of low-grade serous carcinoma, which differ from the clusters of eosinophilic cells that are typically classified as “microinvasion,” are detected in the stroma of an SBT/APST. To distinguish these small carcinomas from microinvasion, some pathologists refer to them as “microinvasive carcinoma””
Implants

• Implants (rather than metastases) have been used in extraovarian disease
• Noninvasive vs invasive implants
• Classification of implants is the most important prognostic factor in patients with high-stage disease
• Invasive implant = Low grade serous carcinoma (LGSC)
## Implants

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Implants (non-invasive)</strong></td>
<td></td>
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<tr>
<td>Epithelial implants</td>
<td>Smooth interface with underlying/surrounding normal tissue. Implant composed of branching papillae, glands with complex papillary infoldings, and single cell and small cell clusters. Mild to moderate atypia. Minimal or no reactive stroma.</td>
</tr>
<tr>
<td>Desmoplastic implants</td>
<td>Smooth interface with underlying/surrounding normal tissue. Implant composed of branching papillae, simple and complex glands with papillary infoldings, and single cell and small cell clusters. Mild to moderate atypia. Oedematous, reactive fasciitis-like stroma.</td>
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<td>Indeterminate implants</td>
<td>Implants with desmoplastic-type stromal response, but focal encroachment into underlying or adjacent parenchymal tissue, imparting a subtle irregular interface at low power magnification or Implants with focal micropapillary architecture but no evidence of infiltration into underlying parenchyma (i.e., exhibit a smooth interface) or Implants with no evidence of infiltration into underlying parenchyma, but with cytological atypia that exceeds that of the usual implant (i.e., moderate atypia, insufficient to warrant a diagnosis of carcinoma)</td>
</tr>
<tr>
<td>Low-grade serous carcinoma</td>
<td>Jagged and irregular interface with underlying/surrounding normal tissue, often entrapping fat lobules in omentum. Typically formed by branching papillae and simple and/or complex glands with papillary and micropapillary infoldings. Abundant epithelial component. Moderate to marked atypia.</td>
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### Table 1  Classification of extra-ovarian disease in serous borderline tumours

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Invasive Implants

• Traditional tissue-destructive stromal invasion
• Expanded criteria (with no obvious infiltration into underlying normal stroma)
  • Implants showing micropapillary or cribriform/confluent patterns similar to SBT, micropapillary variant (non-invasive LGSC)
  • Solid nests and small papillae surrounded by a clear space

<table>
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<tr>
<th>Clinical outcome</th>
<th>Invasive (n = 31)</th>
<th>Noninvasive* (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of disease (NED)</td>
<td>12 (39%)</td>
<td>25 (86%)</td>
</tr>
<tr>
<td>Alive with progressive disease (AWPD)</td>
<td>13 (42%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Dead of disease (DOD)</td>
<td>6 (19%)</td>
<td>2 (7%)</td>
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</table>
A

Overall Survival

Noninvasive

Invasive

\( p = 0.04 \)

B

Overall Survival

Invasive

Noninvasive

Micropapillary & clefts only

\( p = NS \)

C

Disease-free survival

Noninvasive

Invasive

Micropapillary & clefts only

\( p = 0.005 \)

D

Disease-free survival

Noninvasive

Invasive

Micropapillary & clefts only

\( p = 0.03 \)
In this series, 4 pts with indeterminate implants based on destructive tissue invasion but had prominent micropapillary architecture; each of these patients had recurrence or persistent disease.
Current WHO Definition for Implants

• “Although the presence of unequivocal invasion is an important prognostic feature, this may be difficult to establish in some cases. Some studies have shown that implants that do not infiltrate underlying tissue but display cytologic features of invasive implants, especially small, solid nests of cells surrounded by a space, micropapillary and/or cribriform growth, behave in a similar manner to clear-cut invasive implants as described above. Because the latter and invasive implants behave like low-grade serous carcinoma (LGSC) they should be designated as such.”
Implants with No Attached Normal Tissue

- Classified as non-invasive, provided the atypia is moderate at most and the architecture is not overly complex (e.g., cribriform or florid micropapillary).

- When marked cytological and architectural atypia are present, the lesion should probably be classified as invasive implant (low-grade serous carcinoma), or alternatively as indeterminate.
Lymph Node Involvement

• Not an independent prognostic factor to predict adverse outcome.
• Patterns of lymph node involvement
  • Most common: single cells, cell clusters and papillae similar to that seen in typical SBT
  • Presence of discrete, solid (not enlarged cyst) and confluent (not interrupted by lymphoid cells), nodular aggregate of SBT greater than 1 mm is a/w decreased disease-free survival; often a/w desmoplastic stromal reaction and micropapillary architecture
• Should be distinguished from endosalpingiosis and benign mesothelial inclusions.
Low Grade Serous Carcinoma (LGSC)

- Exuberant epithelial proliferation with > 5 mm destructive stromal invasion
- Invasion patterns:
  - Reminiscent of the single cell and simple papillary-pattern of stromal microinvasion, but is widely invasive
  - Nested or small papillae with surrounding retraction, resembling invasive micropapillary carcinoma of the breast
  - Fused or cribriforming glands, resembling invasive ductal carcinoma of the breast
  - Inverted macropapillary
- Moderate cytologic atypia
- Mitotic figures: < 12 / 10 HPF
Papillary Tubal Hyperplasia (PTH)

- Small rounded clusters of tubal epithelial cells and small papillae, with or without associated psammoma bodies
- It is speculated that PTH implants on ovarian and peritoneal surfaces to produce SBT
- Other terminology: Secretory cell outgrowths (SCOUTs); loss of PAX2
- Other study did not confirm the correlation of tubal mucosal proliferation with low-grade serous tumors

TWO PATHOGENETIC PATHWAYS TO OVARIAN SEROUS CARCINOMA

Type I pathway

Type II pathway

Courtesy of Drs. Ie-Ming Shih and Kathleen Cho
Molecular Study

• Pathogenesis of low-grade serous tumor:
  • Serous cystadenoma/adenofibroma to SBT/APST to SBT, micropapillary variant / non-invasive LGSC to LGSC rarely to HGSC

• Most common gene mutations: mutually exclusive KRAS and BRAF mutations

• Concordant KRAS/BRAF mutations in SBT and subsequently developed serous carcinoma argues for tumor progression

• Rare cases show discordant mutations, arguing for clonally unrelated, independent primary neoplasm

• Not all HGSC associated with SBT/LGSC contain TP53 mutation, but often has KRAS mutation (uncommon in conventional HGSC)

Sarcoma-Like Mural Nodules (SLMN)

• Histologically, sharply-demarcated without vascular invasion, small in size, and exhibit a heterogeneous cell population
• Need to separate from true sarcomatous nodules and anaplastic carcinoma
• Favorable behavior
• May represent a reactive phenomenon within a neoplasia
• Possible origin of submesothelial mesenchymal cells
• While SLMNs are often a/w mucinous ovarian tumors, it can be seen in SBT/LGSC

Case 8

Calretinin

PAX8