Case # 4

Low-Grade Serous Carcinoma (Macropapillary) of the Ovary Arising in an Atypical Proliferative Serous Tumor

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School of Medicine
Case History

- A 53 year old woman presented with a pelvic mass and underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy
- At surgery bilateral ovarian tumors were found one measuring 8 cm and the other 6 cm in greatest dimension
- Microscopically, the tumors were similar
- Slides were from one of the ovarian tumors
Issues to be Discussed

- Typical micropapillary serous carcinoma (MPSC) - Background
- Relationship of MPSC to low-grade serous carcinoma
  - Molecular genetic findings
- Macropapillary variant
- Lymph node involvement
- Sampling
Issues to be Discussed

• Typical MPSC - Background
Can SBTs be divided into benign and malignant subtypes?

Hierarchical Branching
Atypical Proliferative Serous Tumor

Nonhierarchical Branching
Micropapillary Serous Carcinoma, Noninvasive “Medusa”

Compared to APSTs, MPSCs had a significantly poorer outcome

Atypical Proliferative Serous Tumor

Noninvasive Micropapillary Serous Carcinoma
Noninvasive Micropapillary Serous Carcinoma

Medusa

Micropapillary

Cribriform

Cribriform
Issues to be Discussed

• Typical MPSC
• Relationship to low-grade serous carcinoma
  – Molecular genetic findings
Intraepithelial MPSC with focus of early invasion

Frankly Invasive MPSC
## Frequency of Functional p53 and KRAS or BRAF Mutations in Ovarian Serous Tumors

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<tr>
<th>Tumor</th>
<th>KRAS/BRAF</th>
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* Includes Atypical Prolif Tumor and noninvasive MPSC

I-M Shih et al
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Pathogenesis of Low Grade Serous Carcinoma or Invasive MPSC

APST → Noninvasive LGSC → Noninvasive LGSC with invasion → Invasive LGSC
Low-grade Serous Carcinomas are relatively uncommon
The Usual Type of Serous Carcinoma

High-grade
High-grade Serous Carcinoma Pathogenesis

- The precursors of high-grade serous carcinomas are not well characterized
- It has been proposed that they develop “de novo” from the surface epithelium or inclusion cysts

Bell DA, Scully RE
Cancer 73:1859-64, 1994
Low-grade pathway

Borderline → Low-grade carcinoma
High-grade pathway

Low-grade pathway

cystadenoma

APST

MPSC

SBT

Low-grade carcinoma

inclusion cyst

High-grade carcinoma

High-grade pathway
Issues to be Discussed

• Typical MPSC
• Relationship to low-grade serous carcinoma
  – Molecular genetic findings
• Macropapillary variant
Low-grade serous carcinoma, macropapillary type

Figure 3-41
SEROUS PAPILLARY ADENOCARCINOMA, LOW GRADE
The papillae lie within nonlymphatic spaces separated by stroma derived from ovarian stroma.

FIG. 6. Atypical proliferative serous tumor (not shown in...
Issues to be Discussed

• Typical MPSC
• Relationship to low-grade serous carcinoma
  – Molecular genetic findings
• Macropapillary variant
• Lymph node involvement
Lymph Node Involvement

- Historically thought to have little if any prognostic significance
- Two types –
  - Endosalpingiosis
  - Clusters of eosinophilic cells in lymph node sinuses
## Lymph Node Involvement and Outcome
### 43 Patients

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<th>No. of Series</th>
<th>No. of Cases</th>
<th>Last Known Status</th>
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<td>25</td>
<td>63</td>
<td>43 pts, 6.5 yr mean FU</td>
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1 patient DOD

**Survival – 98%**

Seidman JD, Kurman RJ
Hum Pathol 31:539-557, 2000
Lymph Node Involvement Endosalpingiosis
Atypical Proliferative Serous Tumor Lymph Node Involvement
Lymph Node Involvement

– In fact there are not two types of involvement but
– Three types –
  • Endosalpingiosis
  • Clusters of eosinophilic cells in lymph node sinuses
  • *Metastatic carcinoma*
The Debate

Micropapillary Serous Tumors
Borderline or Carcinoma?
Consensus

• The noninvasive micropapillary tumor compared to the typical SBT is more often associated with invasive as opposed to noninvasive implants and
• Has a higher rate of recurrence
Consensus

• There is no difference in survival between typical SBTs and MP tumors once corrected for the presence of invasive implants
Disagreement

• It has been reported that occasionally typical SBTs are associated with invasive implants
• Therefore some argue that the MP tumors should not be classified as carcinoma
Issues to be Discussed

• Typical MPSC
• Relationship to low-grade serous carcinoma
  – Molecular genetic findings
• Macropapillary variant
• Lymph node involvement
• Sampling
Bilateral SBTs – one 10 cm, the other 9 cm
10 blocks taken from each tumor

“Noninvasive” Implant

“Invasive” Implant
An additional 10 blocks were obtained from each tumor. A 1 cm MPSC was identified on each side.
Do Invasive Implants Ever Arise from Atypical Proliferative Serous Tumors (Typical SBTs)?

• Very unlikely!
• Invasive implants allegedly associated with typical SBTs probably contain occult areas of carcinoma (micro or rarely macropapillary serous carcinoma) that were not sampled.
Take Home Message

- Implants associated with typical SBTs are noninvasive for all practical purposes.
- If implants appear to be invasive, obtain additional sections of the primary tumor.
- If areas of MPSC are not found, question whether the implants are truly invasive.
What is the Significance of the Micropapillary Pattern?

- Recognition of micropapillary tumors has elucidated the nature of SBTs.
- They are not a distinct entity, separate from invasive carcinoma, but in fact are precursors of low-grade serous carcinoma.
What is the Significance of the Micropapillary Pattern?

- New understanding of ovarian serous carcinogenesis
  - *Low-grade* serous carcinomas develop slowly in a stepwise fashion from a morphologically recognizable precursor (SBT)
  - *High-grade* serous carcinomas develop rapidly without intermediate stages “*de novo*”
The difficulty is not so much in developing new ideas as in escaping from old ones

John Maynard Keynes