Uterine pathology:
Selected topics

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Case 1

• 60 year old woman diagnosed with FIGO grade 1 endometrioid adenocarcinoma on biopsy
• Hysterectomy showed a large endometrial tumor with a range of cytologic appearances
Case 1

- Diagnosis: Mixed endometrioid and serous carcinoma
- Discussion points:
  - Why it’s important to recognize serous differentiation
  - How to recognize serous differentiation in unexpected circumstances
  - How to handle difficult cases in practice
Why it's important to recognize serous differentiation

- “Aggressive”--extrauterine spread
- Staging
- Chemotherapy

Examples:
- “Complex atypical hyperplasia” followed by peritoneal carcinomatosis
- “FIGO grade 1 endometrioid adenocarcinoma”, unstaged, followed by serous carcinoma metastatic to supraclavicular lymph nodes
- Endometrial intraepithelial carcinoma (intraepithelial serous carcinoma); omentectomy revealed metastatic serous carcinoma
How to recognize serous differentiation in unexpected circumstances

• Clinical history
• Background endometrium
• Low- and intermediate-power architecture
• Nuclear features


How to recognize serous differentiation in unexpected circumstances

• Clinical history
  – Breast cancer
  – Tamoxifen >5 years
  – Pelvic radiation
  – AGUS or adenocarcinoma on pap smear

How to recognize serous differentiation in unexpected circumstances

• Clinical history
• Background endometrium
  – Atrophy
  – Atrophic endometrial polyp
  – No hyperplasia
  – Endometrial intraepithelial carcinoma (EIC)
How to recognize serous differentiation in unexpected circumstances

- Clinical history
- Background endometrium
- Low- and intermediate-power architecture
  - Micropapillae (BUT may be glandular, solid)
  - Tufting, budding, dyscohesion
  - Ragged luminal profiles
  - Gaping gland myometrial invasion

How to recognize serous differentiation in unexpected circumstances

- Clinical history
- Background endometrium
- Low- and intermediate-power architecture
- Nuclear features
  - Diffuse nuclear pleomorphism
  - High nucleus/cytoplasmic ratios
  - Abundant mitotic activity
  - Atypical mitotic figures
How to handle difficult cases in practice

- Consensus diagnosis with experienced gynecologic pathologists
  - 85% concordance (kappa=0.74)
  - Correlations with adverse outcomes, p53 overexpression and peritoneal dissemination


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- Consensus diagnosis with experienced gynecologic pathologists
  - 85% concordance (kappa=0.74)
  - Correlations with adverse outcomes, p53 overexpression and peritoneal dissemination

- General surgical pathologists:
  - Kappa=0.2-0.33
  - Correlation with p53: not significant

How to handle difficult cases in practice

- Consensus diagnosis with experienced gynecologic pathologists
- Immunohistochemical stains
  - p53: “All or none”
    - Overexpression: >75% tumor nuclei
    - Patchy staining does not support serous carcinoma
  - Mib-1: >75% tumor nuclei
  - PR: <10% tumor nuclei
  - p16: Essentially every cell positive

IHC summary table

<table>
<thead>
<tr>
<th></th>
<th>Serous Grade 1 and 2 Endometrioid</th>
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<tbody>
<tr>
<td>p53</td>
<td>“All or none”</td>
</tr>
<tr>
<td>mib-1</td>
<td>Almost all</td>
</tr>
<tr>
<td>PR</td>
<td>Almost none</td>
</tr>
<tr>
<td>p16</td>
<td>Almost all</td>
</tr>
<tr>
<td>PTEN</td>
<td>Some staining</td>
</tr>
<tr>
<td>β-catenin</td>
<td>No nuclear</td>
</tr>
</tbody>
</table>

P53 prognosis data

- Univariate analysis of adverse prognostic features for problematic endometrial cancers:
  - High FIGO stage (p=0.02)
  - Lymphovascular invasion (p=0.05)
  - Serous carcinoma diagnosis rendered by GYN specialist (p=0.008)
  - p53 overexpression (p=0.008)

How to handle difficult cases in practice: “managerial classification”

- Biopsy and curettage material
- Hysterectomy

How to handle difficult cases in practice: “managerial classification”

- Biopsy and curettage material
  - What type of staging surgery?
- Hysterectomy
  - Adjuvant therapy?

- Raise the possibility of serous differentiation in a note
  - This should encourage comprehensive staging with omentectomy
- Do NOT grade the tumor using FIGO
  - “FIGO grade 2” carcinomas may be understaged
How to handle difficult cases in practice: “managerial classification”

- Biopsy and curettage material
- Hysterectomy
  - Stakes are high for FIGO stages I and II
    - Do NOT grade the tumor using FIGO
      - “FIGO grade 2” carcinomas may be undertreated
    - Consider using p53 as a surrogate for adverse clinical outcome and peritoneal dissemination


Grading

- FIGO grading for *endometrioid* and *mucinous* carcinomas ONLY
- Serous and clear cell carcinomas are not graded
- Gilks’ grading when histologic subtype is uncertain
  - Binary scheme (high grade versus low grade)
  - Architecture (solid or papillary); nuclear grade (grade 3); mitotic rate (>6 mf/10 hpf)
  - High grade tumors show 2 or more of the above

Case 2

- 65 year old woman diagnosed with MMMT (carcinosarcoma) on biopsy
- Hysterectomy revealed a large, polypoid tumor that filled the endometrial cavity
Case 2

• Diagnosis: Endometrioid carcinoma with spindle cell features (spindle cell carcinoma)
• Discussion points:
  – Examples of carcinosarcoma mimics
  – Why it’s important to exclude these mimics
  – How to diagnose typical examples of carcinosarcoma
  – How to handle difficult cases in practice

Carcinosarcoma (CS)

• WHO definition:
  – Neoplasm composed of an admixture of malignant epithelial and mesenchymal components

  CS, as diagnosed historically, is an extremely heterogeneous entity

Carcinosarcoma (CS) mimics

• Spindle cell carcinoma
• “Dedifferentiated endometrial carcinoma”
• Combined adenocarcinoma and neuroendocrine carcinoma
• Adenosarcoma and atypical polypoid adenomyoma
• Mesonephric carcinoma
• Collision tumors

Carcinosarcoma (CS) mimics

• Spindle cell carcinoma
• “Dedifferentiated endometrial carcinoma”
• Combined adenocarcinoma and neuroendocrine carcinoma
• Adenosarcoma
• Mesonephric carcinoma
• Collision tumors
Carcinosarcoma vs spindle cell carcinoma

Problem: Biphasic
Spindled carcinoma:
Epithelial/stromal merging; low grade
Carcinosarcoma: Distinct epithelial and stromal elements; high grade

Spindle cell carcinoma

- FIGO grade 1 or 2 endometrioid carcinoma intimately admixed with low grade spindle cell proliferation
  - Endometrium>ovary

*Grade only the glandular component


Spindle cell carcinoma

- FIGO grade 1 or 2 endometrioid carcinoma intimately admixed with low grade spindle cell proliferation
- Frequently polypoid?
- Trabeculae, cords and hyalinized stroma
- Osteoid, chondroid, squamous


Carcinosarcoma vs de-differentiated endometrial carcinoma

Problem: Biphasic
Carcinosarcoma: Both elements are high grade
DDEC: One element is low grade and one is high
De-differentiated endometrial carcinoma

- Epithelial component is low grade
- Undiff component has small, round cells

Silva EG. Int J Gynecol Pathol 25:52-8, 2006

Undifferentiated component

- Morphology:
  - Small, round cells; not overtly pleomorphic
  - Solid sheets; no glands, no squamous
  - Myxoid stroma and rhabdoid cells

**Undifferentiated component**

- **Morphology:**
  - Small, round cells; not overtly pleomorphic
  - Solid sheets; no glands, no squamous
  - Myxoid stroma and rhabdoid cells
- **Immunohistochemistry:**
  - Relative loss of keratin, ER/PR, EMA, CK18
  - Minor neuroendocrine marker expression allowed


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**De-differentiated endometrial carcinoma**

- Well- or moderately-differentiated endometrioid carcinoma juxtaposed with an undifferentiated carcinoma
- Endometrium>>ovary
  - Synchronous or metachronous
- Stage: 10/24 FIGO III or IV
- Prognosis: 20/21 patients DOD or AWD
- Biology: ~2/3 DNA MMR abnormalities*


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**Carcinosarcoma vs high-grade endometrial adenocarcinoma**

Disease-free survival in women with stage I carcinosarcoma vs stage I high-grade endometrial carcinoma, $P = 0.001$
Why it’s important to exclude CS mimics

- Spindle cell carcinoma—low grade, low risk tumor (i.e. FIGO grade 1 or 2 CA)

- Dedifferentiated EC—fulminant clinical course, DNA MMR abnormalities

Why it’s important to exclude CS mimics

- Examples:
  - “MMMT” patient treated with whole pelvic RT, ifosfamide and platinum
  - “MMMT” patient with explosive, systemic lymph node recurrences heralded by high LDH
  - “MMMT” patient with peritoneal and lymph node recurrence diagnosed as “small cell carcinoma”
How to diagnose typical examples of CS

Epithelial components

Serous or hi grade NOS: 2/3
Endometrioid: 1/3
FIGO G3: >3/4
Mesenchymal components

Essentially all are histologically high-grade

“Histologically high-grade stroma”

“High grade” stroma:
- Nuclear pleomorphism at scanning mag
- Easily found mitotic figures at scanning mag
- Atypical mitotic figures

How to handle difficult cases in practice

- WHO criteria, excluding:
  - Monophasic tumors
    - Monophasic tumor that coexpresses keratin and vimentin
  - Biphasic tumors without a mesenchymal component
    - De-differentiated endometrial carcinoma

How to handle difficult cases in practice

• WHO criteria, excluding:
  – Monophasic tumors
  – Biphasic tumors without a mesenchymal component
  – Biphasic tumors other than CS
    • Adenosarcoma or atypical polypoid adenomyoma


How to handle difficult cases in practice

• CS is NOT a default diagnosis
  – Do not feel afraid to miss a diagnosis of CS

How to handle difficult cases in practice

• WHO criteria, excluding:
  – Monophasic tumors
  – Biphasic tumors without a mesenchymal component
  – Biphasic tumors other than CS
  – Biphasic tumors that are reportedly less aggressive than CS
    • Spindle cell carcinoma


How to handle difficult cases in practice

• CS is NOT a default diagnosis
  – Do not feel afraid to miss a diagnosis of CS
  • Recognize that biopsy or curettage may not contain diagnostic material
How to handle difficult cases in practice

- CS is NOT a default diagnosis
  - Do not feel afraid to miss a diagnosis of CS
- Recognize that biopsy or curettage may not contain diagnostic material
- Avoid an unequivocal diagnosis of CS when:
  - Spindle cell elements are very rare, merge with epithelium (squamous), not atypical
  - You cannot exclude histologic mimics

Summary

<table>
<thead>
<tr>
<th>Spread</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Low grade CA → Undiff</td>
<td></td>
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<tr>
<td>Dedifferentiated carcinoma</td>
<td>Nodes &gt; visera</td>
</tr>
<tr>
<td>LG CA → LG spindle cell</td>
<td>Local</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>Peritoneum &gt;</td>
</tr>
<tr>
<td>HG CA → HG spindle cell (homologous)</td>
<td>nodes &gt; visera</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td></td>
</tr>
<tr>
<td>HG CA → HG spindle cell (heterologous)</td>
<td>Peritoneum &gt;</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>nodes &gt; visera</td>
</tr>
</tbody>
</table>

Case 3

- 20 year old pregnant woman underwent transvaginal ultrasound during the second half of the first trimester
- The ultrasound was abnormal—a fetus was not identified—even though the uterine size was consistent with dates; a urine pregnancy test was positive; and an ectopic gestation was not noted
Case 3

- Diagnosis: Early complete hydatidiform mole (ECM)
- Discussion points:
  - What is ECM?
  - Why it’s important to recognize ECM
  - How to recognize ECM in unexpected circumstances
  - How to handle difficult cases in practice
Early Complete Mole (ECM)

- Biology identical to complete hydatidiform mole
  - Hydropic change of chorionic villi
  - Trophoblastic proliferation
  - Excess of paternal DNA, typically diploid
  - Usually diagnosed in the 2nd trimester

Early Complete Mole (ECM)

- Complete hydatidiform mole
  - Clinical (<12 weeks gestation)
    - Ultrasound
      - Delayed 1st trimester miscarriage
      - Anembryonic pregnancy
    - Uterus not enlarged
    - Variable beta-hCG

Why it’s important to recognize ECM

<table>
<thead>
<tr>
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<th>Complete Mole (Classic &amp; Early)</th>
<th>Partial Mole</th>
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<tbody>
<tr>
<td>Persistent Disease</td>
<td>20%</td>
<td>&lt;5%</td>
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<tr>
<td>Progression to Choriocarcinoma</td>
<td>2-5%</td>
<td>Case reports</td>
</tr>
</tbody>
</table>

Why it’s important to recognize ECM

- Examples:
  - “Hydropic abortus” followed by choriocarcinoma
Why it’s important to recognize ECM

• Examples:
  – “Hydropic abortus” followed by choriocarcinoma
  – Diagnosis of “partial mole” followed by contraception for only 6 months. Subsequent rise in serum hCG, assumed to represent new pregnancy. Patient ultimately diagnosed with invasive complete mole

How to recognize ECM in unexpected circumstances

• Features generally associated with complete mole (attenuated in ECM)
  – Villous hydrops
  – Circumferential trophoblastic hyperplasia in at least some villi
  – Trophoblast atypia
How to recognize ECM in unexpected circumstances

• Features specifically associated with ECM
  – Bulbous or cauliflower like terminal villi
  – Distinctive myxoid stroma
  – Karyorrhexis

*Evidence of fetal development is allowed
Differential Diagnosis

- Partial mole (diandric triploidy)
- Hydropic abortus
- Trisomic or triploid (non-molar, digynic triploid placenta)
Partial Hydatidiform Mole

- **Clinical**
  - Moderately increased beta-hCG
  - Size < Dates
- **Microscopic**
  - Hydropic and fibrotic villi intermixed
  - Less marked trophoblastic proliferation
  - Fetal tissue more commonly identified
- **Biologic**
  - Diandric triploidy
- **Risk of persistent or recurrent GTD**
  - Less than with complete mole (early or otherwise)
Hydropic Abortus

- Variable villous size from small to hydropic
- Attenuated trophoblast without proliferation
- Polar trophoblastic proliferation

Triploidy and trisomy

- Digynic Triploidy
  - Can mimic partial mole
    * Dimorphic villi without hydrops
- Trisomy (particularly ch 7, 15, 21, 22)
  - Can mimic complete mole
    * Trophoblastic proliferation without uniform hydrops

How to handle difficult cases in practice

• Check clinical situation:
  – gestational age, hCG levels, ultrasound appearance, presence of fetus
• Submit ALL tissue for examination (minus that needed for ancillary tests)
• Exclude histologic mimics
• Ancillary tests

Ancillary studies

- Flow cytometry
- Image analysis
- FISH/CISH (ch10)
- Cytogenetics
- Immunohistochemistry (p57KIP2)

p57KIP2 immunohistochemistry

• Strongly paternally imprinted
• Expressed when a maternal allele is present
• Chromosome 11p15.5
• Inhibitor of cell cycle & negative regulator of cell proliferation
• Monoclonal antibody

p57KIP2

• Nuclear stain
• Positive Control
  - Decidua & extravillous trophoblasts
• Partial Moles & Hydropic Abortus
  – POSITIVE in cytotrophoblast and villous mesenchyme
• Complete Moles
  – NEGATIVE in cytotrophoblast and villous mesenchyme
**Acknowledgment**

- Melissa Murray, D.O.

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<table>
<thead>
<tr>
<th></th>
<th>ECM</th>
<th>CM</th>
<th>PM</th>
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<tr>
<td><strong>Trophoblast</strong></td>
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<td>Severe</td>
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<tr>
<td><strong>Villi</strong></td>
<td>Spectrum sizes</td>
<td>Spectrum sizes</td>
<td>2 populations (large &amp; small)</td>
<td>Similar sizes (balloon-like)</td>
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<td><strong>Scalloped villous</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td><strong>contours</strong></td>
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<tr>
<td><strong>Club-like</strong></td>
<td>+</td>
<td>-/+</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td><strong>projections</strong></td>
<td></td>
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<tr>
<td><strong>Cisterns</strong></td>
<td>Variable</td>
<td>Prominent</td>
<td>Variable</td>
<td>Absent/rare</td>
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<tr>
<td><strong>Stroma</strong></td>
<td>Cellular &amp; myxoid</td>
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<tr>
<td><strong>Pseudoinclusions</strong></td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>-</td>
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<tr>
<td><strong>Karyorrhexis</strong></td>
<td>Common</td>
<td>Absent or inconspicuous</td>
<td>Absent or inconspicuous</td>
<td>Absent or inconspicuous</td>
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<td><strong>p57kip2</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>+</td>
<td>+</td>
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<td><strong>Fetal tissue</strong></td>
<td>Usually none</td>
<td>Usually none</td>
<td>Usually present</td>
<td>Usually none</td>
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<td>Diploid (all paternal)</td>
<td>Diploid (all paternal)</td>
<td>Triploid (2:1 paternal:maternal)</td>
<td>Diploid or Triploid (2:1 maternal:paternal)</td>
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<td><strong>Behavior</strong></td>
<td>10-30% persistent GTD</td>
<td>10-30% persistent GTD</td>
<td>0.5% persistent GTD</td>
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