Clinical History:
A 45-year-old female with anemia and abnormal pap screening.
Gynecologic Pathology

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Disclosures

• Nothing to disclose
Learning Objectives

• Present, as an “index case”, a high-grade endometrial carcinoma

• Review differential diagnostic entities as they pertain to the index case

• Apply morphologic queues and ancillary studies to reconcile tough cases
Outline of Presentation

1. Present our index case

2. Detailed look at the clinicopathological characteristics

3. Review the differential diagnosis relative to our index case
Index Case

45F with Anemia and Abnormal Pap Screening
Index Case

• 45 year-old woman presented with anemia and abnormal Pap test
  – Anemia thought to be secondary to heavy periods
  – Pap test was high-risk HPV positive and showed atypical glandular cells

• Colposcopic exam and pelvic ultrasound:
  – Some acetowhite lesions, but no cervical mass
  – Abnormal; thickened (3.2 cm) and heterogeneous endometrial lining

• Endometrial biopsy:
  – Endometrioid adenocarcinoma, FIGO grade 1
Definitive Therapy

Hysterectomy, Bilateral Salpingo-oophorectomy, Pelvic Lymphadenectomy
• Myoinvasive tumor with two different components

• Poorly-differentiated component:
  – Dominant component; grows in sheets with some alveolar areas
  – Discohesive round cells; ugly, but homogeneous cytology
  – Eccentric nucleus, prominent nucleoli

• Well-differentiated component:
  – Endometrioid adenocarcinoma, FIGO grade 1
  – Abrupt transition to the poorly-differentiated component
Diagnosis

“Dedifferentiated Endometrial Carcinoma”

Mixed Undifferentiated and Endometrial Carcinoma
“Dedifferentiated Carcinoma”

- Undifferentiated carcinoma with well-differentiated component
  - Silva EG, et al. *Int J Gynecol Pathol* 2006;25:52-58
  - 25 cases

- Presents with abnormal uterine bleeding w/wo pelvic pain

- Wide age-range (30-82)

- Occasionally, undifferentiated component not present on biopsy

- Aggressive clinical course (15 patients DOD, median 6 months)
Undifferentiated Carcinoma (UCEC)

• **Classic morphology:**
  – Cytologically monotonous proliferation of medium-large round cells
  – Diffuse, sheet-like pattern of growth
  – Discohesive appearance
  – No epithelial organization (i.e., no nesting, gland formation, papillae, etc.)

• **Variants:**
  – Rare cases with marked nuclear pleomorphism; almost always a focal finding
  – Extracellular mucin or myxoid matrix
  – Areas of abrupt extracellular keratinization
Extremely cellular
Sheets of cells without epithelial organization
Discohesive arrangement
Gaps between cells
Uniform cytology
Medium-sized round cells
“Squared-off” cell borders
Eccentric, round nuclei; prominent nucleoli
Vaguely alveolar arrangement
Areas with extracellular mucin
Undifferentiated Carcinoma (UEC)

• Variable immunophenotype:
  – EMA, keratins (CAM 5.2, OSCAR, broad spectrum) = patchy at best
  – Synaptophysin = some cases with patchy expression
  – Desmin, high molecular weight keratins (CK 5/6) = usually negative
  – PAX8, chromogranin, E-cadherin = usually negative
  – SMARCB1 (INI1) = retained in most cases
  – SMARCA4 and SMARCA2 = lost (up to 33% of cases)

• Molecular genetic profile:
  – Dedifferentiated carcinoma = often hypermutated, MSI-H
  – Pure UEC = TP53, PTEN, POLE, ARID1A, PIK3CA, CTNNB1 mutations reported
Dedifferentiated Carcinoma

• Dedifferentiated carcinoma is likely an under-recognized entity:
  – 2% of all endometrial carcinomas
  – 10% of all high-grade endometrial carcinomas

• Significance of diagnosis:
  – Behaves worse than FIGO 3 endometrioid carcinoma
  – Very few studies reporting outcome, but almost always extremely aggressive
  – MSI-H cases common (usually due to MLH1 promoter hypermethylation)
  – Broad differential diagnosis with major treatment implications
Differential Diagnosis

- FIGO grade 3 endometrioid adenocarcinoma
- Carcinosarcoma (malignant mixed Müllerian tumor, MMMT)
- Undifferentiated uterine sarcoma (UUS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- High-grade Müllerian adenosarcoma
- Hematolymphoid neoplasm
- Metastasis (lobular carcinoma of the breast, melanoma)
Dedifferentiated carcinoma

Grade 3 endometrioid carcinoma
Grade 3 Endometrioid Carcinoma
Grade 3 Endometrioid Carcinoma
Glandular and solid areas
Can appear like two separate components
Grade 3 Endometrioid Carcinoma
Solid areas are cohesive
Epithelial structures (glands, nests)
Grade 3 Endometrioid Carcinoma
Solid areas are cohesive
Glandular spacing, nests
Most cases strongly positive for CKCKTL
Most (80%) of cases PAX8 positive
<table>
<thead>
<tr>
<th>Dedifferentiated carcinoma</th>
<th>Carcinosarcoma (MMMT)</th>
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![Dedifferentiated carcinoma](image1.jpg)

![Carcinosarcoma (MMMT)](image2.jpg)
Weird MMMT
Carcinosarcoma (MMMT)
Rare cases can have round cell components
Carcinosarcoma (MMMT)
High-grade serous component common

Carcinosarcoma (MMMT)
Heterologous elements, spindled elements
Carcinosarcoma (MMMT)
Cell-to-cell pleomorphism
Heterologous elements
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<th>UUS</th>
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[Image: Microscopic images of Dedifferentiated carcinoma and UUS tissue samples.]
Undifferentiated Uterine Sarcoma
Undifferentiated Uterine Sarcoma
Can show prominent growth
Necrosis, unequivocally high-grade
Undifferentiated Uterine Sarcoma
Tends to be a spindle cell malignancy
Sheeting growth, but also vaguely fascicular
Undifferentiated Uterine Sarcoma
Extreme pleomorphism
Dedifferentiated carcinoma

HGESS
HGES S
Uniform cytology
Sheet-like growth
HGESS
Cohesive cells
Spiral-like arterioles
HGESS
Open chromatin pattern
No prominent nucleoli
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<th>High-grade adenosarcoma</th>
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![Dedifferentiated carcinoma](image1)

![High-grade adenosarcoma](image2)
High-grade Adenosarcoma
High-grade adenosarcoma
Polypoid with finger-like projections
High-grade adenosarcoma
Epithelial component benign
High-grade adenosarcoma
Stromal component is a spindle cell process
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<th>Hematolymphoid neoplasm</th>
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![Dedifferentiated carcinoma](image1)

![Hematolymphoid neoplasm](image2)
MALT Lymphoma of the Uterus
Lymphoma
No epithelial structures
Nodular (often multinodular)
**Lymphoma**
Coarse chromatin pattern
No nucleoli
Immunophenotypic differences (CD45, etc)
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<th>Metastatic lobular carcinoma</th>
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- Dedifferentiated carcinoma
- Metastatic lobular carcinoma
Metastatic Lobular Carcinoma
Metastatic lobular carcinoma
Low-power hypercellularity within stroma
**Metastatic lobular carcinoma**

- Monotonous cytology
- Cells with eccentric nuclei
- Signet-ring appearance with ample mucin
Metastatic lobular carcinoma
Pleomorphic variant less atypical appearing
Not as cellular as dedifferentiated carcinoma
Immunophenotypic differences
Summary

• Dedifferentiated endometrial carcinoma:
  – Undifferentiated carcinoma + differentiated endometrial carcinoma
  – Accounts for up to 10% of high-grade endometrial carcinomas
  – Highly aggressive tumor

• Extremely broad differential diagnosis
  – Gynecologic carcinomas: Grade 3 endometrioid, high-grade serous, MMMT
  – Gynecologic sarcoma: UUS, HGESS, high-grade adenosarcoma
  – Hematolymphoid tumors
  – Melanoma, diffuse-type carcinomas

• Immunohistochemistry used to exclude other entities
Questions
Other Helpful References


• Ramalingam P, Croce S, McCluggage WG. Loss of expression of SMARCA4 (BRG1), SMARCA2 (BRM), and SMARCB1 (INI1) in undifferentiated carcinoma of the endometrium is not uncommon and is not always associated with rhabdoid morphology. *Histopathology* 2017;70:359-366
