CLINICALLY RELEVANT DIAGNOSTIC PITFALLS IN UTERINE PATHOLOGY

W. DWAYNE LAWRENCE M.D.
WOMEN & INFANTS HOSPITAL OF RI
BROWN UNIVERSITY

“THINGS ARE SELDOM WHAT THEY SEEM, SKIM MILK MASQUERADES AS CREAM”
- W.S. Gilbert

CHANGES IN CLAIMS AGAINST PATHOLOGISTS FROM 1995-2003; DATA FROM THE DOCTOR’S COMPANY

- SURGICAL PATHOLOGY IS A “GROWTH INDUSTRY” AMONG MALPRACTICE ATTORNEYS
- INCREASED SPECTRUM OF CLAIMS AS TO ORGAN SYSTEMS AND DIAGNOSES
- SLIGHT DECREASE IN FNA CLAIMS
- SLIGHT INCREASE IN MELANOMA CLAIMS
- NEW AREAS OF LITIGATION: SOFT TISSUE, BLADDER, PULMONARY AND GYNE PATH

-- courtesy of Mark Wick MD

<table>
<thead>
<tr>
<th>Tissue</th>
<th>% Claims</th>
<th>% FN</th>
<th>% FP</th>
<th>Total Claims (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast bx</td>
<td>42</td>
<td>48</td>
<td>52</td>
<td>15.5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>44</td>
<td>95</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>14</td>
<td>57</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>FNA misc</td>
<td>10</td>
<td>40</td>
<td>60</td>
<td>3.5</td>
</tr>
<tr>
<td>FNA breast</td>
<td>5</td>
<td>60</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Gastric bx</td>
<td>12</td>
<td>42</td>
<td>58</td>
<td>4.5</td>
</tr>
<tr>
<td>Prostate bx</td>
<td>9</td>
<td>67</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Lung bx</td>
<td>12</td>
<td>50</td>
<td>50</td>
<td>3.5</td>
</tr>
<tr>
<td>GYN PATHOLOGY</td>
<td>31</td>
<td>74</td>
<td>16</td>
<td>11.5</td>
</tr>
<tr>
<td>Bladder pathology</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&quot;Cysts&quot;</td>
<td>3</td>
<td>100</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>48</td>
<td>65</td>
<td>19</td>
<td>26</td>
</tr>
</tbody>
</table>

**Summary: Number of Major Disagreements by Organ System and Clinical Impact**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Major Discrepancies</th>
<th>Documented Effect on Rx or Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female reproductive tract</td>
<td>32</td>
<td>16 (50.0%)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>27</td>
<td>14 (51.9%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>16</td>
<td>11 (68.8%)</td>
</tr>
<tr>
<td>Skin</td>
<td>24</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>14</td>
<td>6 (42.9%)</td>
</tr>
<tr>
<td>Hematolymphoid</td>
<td>5</td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td>Breast</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other (soft tissue, lung, and brain)</td>
<td>9</td>
<td>4 (-44.4%)</td>
</tr>
</tbody>
</table>

**Mandatory Second Opinion in Surgical Pathology Referral Material: Clinical Consequences of Major Disagreements.** Manion, Elizabeth MD; Cohen, Michael B. MD; Weydert, Jamie MD 32(5), Am J Surg Pathol May 2008, pp 732-737

### Nature of Change in Management in Major Disagreement Cases

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Surgical</th>
<th>Medical</th>
<th>Follow-up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td>18</td>
<td>2</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hematolymphoid</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>11</td>
<td>4</td>
<td>37</td>
</tr>
</tbody>
</table>

**Mandatory Second Opinion in Surgical Pathology Referral Material: Clinical Consequences of Major Disagreements.** Manion, Elizabeth MD; Cohen, Michael B. MD; Weydert, Jamie MD 32(5), Am J Surg Pathol May 2008, pp 732-737
ENDOMETRIAL EPITHELIAL CHANGES ("METAPLASIAS")

- SQUAMOUS
- MUCINOUS
- CILIARY
- TUBO-ENDOMETRIOID
- CLEAR CELL (ARIA-STELLA)
- EOSINOPHILIC (ONCOCYTIC)
- PAPILLARY
- PAPILLARY SYNCYTIAL
CLEAR CELL (SECRETORY) "METAPLASIA"

44 YOF RX FOR DUB

CLEAR CELL (SECRETORY) "METAPLASIA"

44 YOF RX FOR DUB

“CLEAR CELL” METAPLASIA (HYPERSECRETORY CHANGE)

55 YOF
OXYPHILIC (ONCOCYTIC) CHANGE OF THE ARIAS-STELLA PHENOMENON

ENDOMETRIAL EPITHELIAL CHANGES (“METAPLASIAS”)
- SQUAMOUS
- MUCINOUS
- CILIARY
- TUBO-ENDOMETRIOID
- CLEAR CELL (ARIAS-STELLA)
- EOSINOPHILIC (ONCOCYTIC)
- PAPILLARY
- PAPILLARY Syncytial

“PINK CELL” ENDOMETRIAL METAPLASIAS
- “EOSINOPHILIC METAPLASIA”
- “PURE” CILIARY METAPLASIA
“NATIVE ATYPIA” OF CILIARY EPITHELUM IN A HYPERPLASTIC ENDOMETRIAL POLYP

EVERY DAY TERRORS OF TEM IN ENDOCERVICAL CURETTINGS: ALL MOST LIKELY FROM THE LUS

“ATYPICAL” TUBOENDOMETRIOID METAPLASIA
"METAPLASTIC" MAYHEM: CONFUSING ENDOMETRIAL EPITHELIAL "METAPLASIAe"

- Papillary eosinophilic normal metaplasia
- Menstrual cysts
- Papillary syncytial metaplasia
- Polyp with small nonvillosus papillae

HOBNAIL METAPLASIA: A WORRISOME MIMIC OF CARCINOMA

- Different types of normal metaplasia
- Histological images of ho cnail metaplasia

"SHEDDING" ENDOMETRIUM WITH FEATURES WORRISOME FOR A SEROUS NEOPLASM

- Histological images of endometrium with serous features
ENDOMETRIAL INTRAEPITHELIAL CARCINOMA: SEROUS CARCINOMA IN SITU

- EIC IS DIFFERENT FROM EIN (ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA)
- PRECURSOR TO INVASIVE SEROUS CARCINOMA
- ARISES IN ATROPHIC ENDOMETRIUM AND MAY BE MISSED
- NOT ASSOCIATED WITH UNOPPOSED ESTROGEN
- p53 IMMUNOPosITIVE
- SEROUS EPITHELIUM IN TUBE ALSO FREQUENTLY SHOWS SEROUS INTRAEPITHELIAL CARCINOMA ("FIELD EFFECT")

ATYPICAL TUBOENDOMETRIOID METAPLASIA OR ENDOMETRIAL GLANDULAR DYSPLASIA/CARCINOMA?

P53 immunonegative

Occurrence of endometrial glandular dysplasia precedes uterine papillary serous carcinoma. 2006 Int J Gynec Pathol 26: 38-52
ENDOMETRIAL EPITHELIAL CHANGES ("METAPLASIAS")

- SQUAMOUS
- MUCINOUS
- CILIARY
- TUBO-ENDOMETRIOID
- CLEAR CELL (ARIA-S-STEDELLA)
- EOSINOPHILIC (ONCOCYTIC)
- PAPILLARY
- PAPILLARY SYNCYTIAL

SURFACE SEROUS PAPILLARY "METAPLASIA" MIMICKING SEROUS CARCINOMA IN A SMALL POLYP

Simple and complex hyperplastic papillary proliferations of the endometrium: a clinicopathologic study of nine cases of apparently localized papillary lesions with fibrovascular stromal cores and epithelial metaplasia.
THE SPECTRUM OF MUCINOUS ENDOMETRIAL LESIONS

• BENIGN MUCINOUS METAPLASIA IN ENDOMETRIAL CURETTINGS
• MUCINOUS METAPLASIA IN ENDOMETRIAL HYPERPLASIA
• MUCINOUS CHANGES IN SURFACE EPITHELIAL CHANGES OVERLYING WELL DIFF ENDOMETRIOID CAs
• "TRUE" MUCINOUS CARCINOMAS (END'OID & MICROGLANDULAR)

BENIGN PAPILLARY MUCINOUS METAPLASIA IN A PMP WOMAN
THE SPECTRUM OF MUCINOUS ENDOMETRIAL LESIONS

- Benign Mucinous Metaplasia in Endometrial Curettings
- Mucinous Metaplasia in Endometrial Hyperplasia
- Mucinous Changes in Surface Epithelial Changes Overlying Well Diff Endometroid CAs
- "True" Mucinous Carcinomas (End’oid & Microglandular)

SURFACE EPITHELIAL (MATURATIONAL) CHANGES

CASE STUDY: 70 YOP SURFACE (MATURATIONAL) EPITHELIAL CHANGES
- Dec 2005: Endometrial Ctos: Microglandular Hyperplasia
- May 2006: Endometrial Ctos: MGH With Glandular Atypia
- June 2007: LeeP Biopsy DCX: Reactive Changes
- July 2007: Consultation

"SURFACE EPITHELIAL CHANGES IN ENDOMETRIAL ADENOCARCINOMA: DIAGNOSTIC PITFALLS IN CURETTAGE SPECIMENS"

- 116 Endometrioid Cancers
- 49% with "Surface Epithelial Changes"
- Microglandular Pattern Most Prominent
- Syncytial/Papillary/Squamous
- Largely FIGO Grade 1
- Mild to Moderate Cytologic Atypia
- In Postmenopausal Women: Caution Making Benign Dx of MGH in Endometrial Cages!
“NORMAL” ENDOCX IN THE EMC OF A POSTMENOPAUSAL PT?
SECs UNTIL PROVEN OTHERWISE!

"SURFACE EPITHELIAL CHANGES"

PUTATIVE CARCINOMA

56 YOF
EM CTG5

56 YOF
EM CTG5
THE SPECTRUM OF MUCINOUS ENDOMETRIAL LESIONS

- Benign Mucinous Metaplasia in Endometrial Curettings
- Mucinous Metaplasia in Endometrial Hyperplasia
- Mucinous Changes in Surface Epithelial Changes Overlying Well Diff Endometrioid CAs
- "True" Mucinous Carcinomas (End'oid & Microglandular)

WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- Endometroid Adenocarcinoma
  - With Squamous Differentiation
  - Villo glandular Type
  - Secretory Type
  - Ciliated Cell Type
- Serous Carcinoma
- Clear Cell Carcinoma
- Mucinous Adenocarcinoma
- Squamous Carcinoma
- Mixed Carcinoma
- Undifferentiated Carcinoma

ENDOCERVICAL TYPE MUCINOUS ADENOCARCINOMA

- Can Mimic Well Diff Adenoca of Cx (Especially Adenoma Malignum)
- Variants of Well Differentiated Endometrioid Carcinoma
- Can Be Confused with Sec's But No Clinical Difference
- Can Be Confused with Microglandular Cervical Hyperplasia and Result in Delay in Diagnosis and Treatment
**ENDOMETRIOID CARCINOMA, “MUCIN RICH” TYPE**

**THE SPECTRUM OF MUCINOUS ENDOMETRIAL LESIONS**

- BENIGN MUCINOUS METAPLASIA IN ENDOMETRIAL CURETTINGS
- MUCINOUS METAPLASIA IN ENDOMETRIAL HYPERPLASIA
- MUCINOUS CHANGES IN SURFACE EPITHELIAL CHANGES OVERLYING WELL DIFF ENDOMETRIOID CAs
- “TRUE” MUCINOUS CARCINOMAS (END’OID & MICROGLANDULAR)

**COMPLEX ATYPIICAL ENDOMETRIAL HYPERPLASIA (ENDOCERVICAL TYPE MUCINOUS METAPLASIA)**
VAGARIES IN THE HISTOLOGIC TYPING AND GRADING OF ENDOMETRIAL CARCINOMAS

GRADING ENDOMETRIAL CANCER
FIGO GRADE 1 OR 2 ENDOMETRIOID CARCINOMA (ARCHITECTURAL GRADE) CAN BE UPGRADED BY 1 GRADE IN THE FACE OF SEVERE (GRADE 3) NUCLEAR ATYPIA

HOW DO YOU DEFINE SEVERE NUCLEAR ATYPIA?
SUPREME COURT JUSTICE POTTER STEWART: "I CAN'T DEFINE (PORNOGRAPHY*) BUT I KNOW IT WHEN I SEE IT"
* SEVERE NUCLEAR ATYPIA
FIGO GRADING OF ENDOMETRIAL CARCINOMA: HOW DO YOU DEFINE SEVERE NUCLEAR ATYPIA?

- Grade 1 Nuclear Atyopia
- Internal Nuclear Control
- Grade 3 Nuclear Atyopia

WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- Endometrioid Adenocarcinoma
  - With Squamous Differentiation
  - Villoglandular Type
  - Secretory Type
  - Ciliated Cell Type

- Serous Carcinoma
- Clear Cell Carcinoma
- Mucinous Adenocarcinoma
- Squamous Carcinoma
- Mixed Carcinoma
- Undifferentiated Carcinoma

FOUR EXAMPLES OF UTERINE SEROUS CARCINOMA (WITH PROMINENT GLANDULAR PATTERN)

- Hobnails
- Hobnails & Clefts
- Hobnails
SEROUS CARCINOMA vs CILIATED CELL ADENOCARCINOMA

WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- ENDOMETRIOID ADENOCARCINOMA
  - WITH SQUAMOUS DIFFERENTIATION
  - VILLOGLANDULAR TYPE
  - SECRETORY TYPE
  - CILIATED CELL TYPE

- SEROUS CARCINOMA
- CLEAR CELL CARCINOMA
- MUCINOUS ADENOCARCINOMA
- SQUAMOUS CARCINOMA
- MIXED CARCINOMA
- UNDIFFERENTIATED CARCINOMA

ENDOMETRIOID CARCINOMA, CILIATED CELL TYPE

WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- ENDOMETRIOID ADENOCARCINOMA
  - WITH SQUAMOUS DIFFERENTIATION
  - VILLOGLANDULAR TYPE
  - SECRETORY TYPE
  - CILIATED CELL TYPE

- SEROUS CARCINOMA
- CLEAR CELL CARCINOMA
- MUCINOUS ADENOCARCINOMA
- SQUAMOUS CARCINOMA
- MIXED CARCINOMA
- UNDIFFERENTIATED CARCINOMA
CONSULTATION: MIXED PAPILLARY SEROUS AND CLEAR CELL ENDOMETRIAL CARCINOMA IN A 76 YOF
DX: MIXED PAPILLARY ENDOMETRIOID AND SECRETORY CARCINOMA

DX: MIXED PAPILLARY SEROUS AND CLEAR CELL ENDOMETRIAL CARCINOMA IN A 76 YOF
DX: MIXED PAPILLARY ENDOMETRIOID AND SECRETORY CARCINOMA

DX: WELL DIFFERENTIATED MIXED VILLOGLANDULAR AND SECRETORY TYPE ENDOMETRIOID CARCINOMA

SAME PATIENT SHOWING THE RELATIVELY BLAND APPEARING NUCLEI AND MORE COLUMNAR STRATIFIED APPEARANCE OF THE CELLS

“PENGUIN CELLS” IN SECRETORY TYPE ENDOMETRIOID CARCINOMA

SECRETORY HYPERPLASIA
SECRETORY CARCINOMA CAN BE HIGHER GRADE AND MIMIC CLEAR CELL CARCINOMA

‘HIGHLY GLYCOGENATED’ ADENOSQUAMOUS CARCINOMA

WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- ENDOMETRIOID ADENOCARCINOMA
  - WITH SQUAMOUS DIFFERENTIATION
  - VILLOGLANDULAR TYPE
  - SECRETORY TYPE
  - CILIATED CELL TYPE
- SEROUS CARCINOMA
- CLEAR CELL CARCINOMA
- MUCINOUS ADENOCARCINOMA
- SQUAMOUS CARCINOMA
- MIXED CARCINOMA
- UNDIFFERENTIATED CARCINOMA
THE MANY FACES OF ENDOMETRIAL SEROUS CARCINOMA

THE DIFFERING PAPILLARITY OF ENDOMETRIAL SEROUS CARCINOMA

PAPILLARY TUMORS OF THE ENDOMETRIUM: A CONTINUING SOURCE OF CONFUSION

- Chunky
- Elongate papillae
- Finely filigree pattern
- Pinched off buds similar to ovarian serous carcinoma
THE VALUE OF p53 IN MAKING THE DIAGNOSIS OF ENDOMETRIAL SEROUS CARCINOMA?

PRICELESS! FOR EVERYTHING ELSE, THERE'S PTEN...

ENDOMETRIAL SEROUS CARCINOMA: HISTOLOGY

“GAPING” GLANDS AND “CRAB CLAW” CONFIGURATIONS

ENDOMETRIAL SEROUS CARCINOMA WITH PROMINENT GLANDULAR PATTERN

MISDIAGNOSED AS ENDOMETRIOID FIGO GRADE I BECAUSE OF WELL-FORMED GLANDS
WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- ENDOMETRIOID ADENOCARCINOMA
  - WITH SQUAMOUS DIFFERENTIATION
  - VILLOGLANDULAR TYPE
  - SECRETORY TYPE
  - CILIATED CELL TYPE
- SEROUS CARCINOMA
- CLEAR CELL CARCINOMA
- MUCINOUS ADENOCARCINOMA
- SQUAMOUS CARCINOMA
- MIXED CARCINOMA
- UNDIFFERENTIATED CARCINOMA

ENDOMETRIAL CARCINOMAS ARISING IN SMALL POLYPS: SIZE DOESN’T MATTER!

SMALL SEROUS CARCINOMAS IN SMALL ENDOMETRIAL POLYPS:
BETTER TO SWEAT THE SMALL STUFF

- MD ANDERSON STUDY
- SIZE RANGE 0.5 UP TO 4 CM
- 5-70% OF POLYP
- ABSENT/RARE MYOMETRIAL INVASION OR LVS
- STG 1 PTS: RECURRENT DZ PERITONEUM
- STG 1 PTS: 40% DOD
- FIELD EFFECT OF SEROUS NEOPLASIA?

EXAMINE CAREFULLY & IN THEIR ENTIRETY
SMALL SEROUS CARCINOMA ARISING IN A BENIGN SENILE ENDOMETRIAL POLYP

CONSULTATION CASE: 54 YOF SMALL HYPERPLASTIC ENDOMETRIAL POLYP ON EMC. TWO YEARS LATER HAD HIGH GRADE ADENOCARCINOMA IN PAP SMEAR

ENDOMETRIAL EPITHELIAL CHANGES ("METAPLASIAS")

- SQUAMOUS
- MUCINOUS
- CILIARY
- TUBO-ENDOMETRIOID
- CLEAR CELL (ARIA-STELLA)
- EOSINOPHILIC (ONCOCYTIC)
- PAPILLARY
- PAPILLARY SYNCYTIAL
SURFACE SEROUS PAPILLARY “METAPLASIA” MIMICKING SEROUS CARCINOMA IN A SMALL POLYP


WHO/ISGP CLASSIFICATION OF TUMORS OF THE UTERINE CORPUS

- ENDOMETRIOID ADENOCARCINOMA
  - WITH SQUAMOUS DIFFERENTIATION
  - VILLOGLANDULAR TYPE
  - SECRETORY TYPE
  - CILIATED CELL TYPE

- SEROUS CARCINOMA
- CLEAR CELL CARCINOMA
- MUCINOUS ADENOCARCINOMA
- SQUAMOUS CARCINOMA
- MIXED CARCINOMA
- UNDIFFERENTIATED CARCINOMA

ENDOMETRIAL SEROUS CARCINOMA AND CLEAR CELL CARCINOMAS: FIRST COUSINS...TWICE REMOVED?

Clear cell carcinoma of the endometrium, like serous carcinoma, is estrogen independent and shows a high Ki-67 proliferation index.

In contrast to serous carcinoma, strong p53 expression occurred less frequently in clear cell carcinomas and predominantly in clear cell carcinomas with serous features.

The findings suggest that the molecular events that underlie the development of clear cell carcinoma differ from those of endometrioid and serous carcinoma.
ENDOMETRIAL POLYPS WITH BIZARRE STROMAL CELLS


ATYPICAL POLYPOID ADENOMYOMA: THE “DISAPPEARING” INVASIVE CANCER

APAs MAY CONTAIN CARCINOMA SO SAMPLE, SAMPLE, SAMPLE

KEMPSON’S LAW: IF IT LOOKS LIKE CARCINOMA, CALL IT CARCINOMA
CLINICAL HISTORY:
68 YOF WITH ENLARGED UTERUS AND VAGINAL BLEEDING

METASTATIC COLON CARCINOMA INVADING THE UTERUS

‘COLONOID’ ENDOMETRIOID CARCINOMA, UTERUS
CONSULTATION: 68 YOF WITH VAGINAL BLEEDING AND HYSTERECTOMY

- LARGE POLYPOID ENDOMETRIAL MASS
- CLEAR CELL CARCINOMA

YOLK SAC TUMOR ARISING FROM MIXED ENDOMETRIOID AND CLEAR CELL CARCINOMA

- SCHILLER-DUVAL BODIES
- RETICULAR PATTERN OF YST
- SERUM AFP: 68,000 ng/ml
- IHC: AFP, SCHILLER-DUVAL BODIES

FINIS