Cytology and Histology of Malignant Glandular Lesions of the Uterine Cervix

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9th Annual Meeting,
Hong Kong Society of Cytology,
Hong Kong,
December 6, 2008
Goal

• **Know the key** cytopathologic and histopathologic features of usual and unusual malignant glandular lesions of the uterine cervix
Classification

• Malignant Lesions
  – Premalignant lesions
    • Adenocarcinoma in situ: AIS
    • Endocervical glandular dysplasia: EGD
    • Stratified mucin producing intraepithelial lesion: SMILE
  – Adenocarcinoma
Glandular Premalignancy

• Precursor lesions of adenocarcinoma
  – AIS: good evidence
  – Dysplasia: poor evidence

• AIS incidence: 0.6/100,000
  – CIN III: x50 more frequent

• AIS prevalence: increasing
AIS: risk factors

- 50% AIS: concomitant SIL
- Risk factors similar to SIL
- HPV 16 and 18
- Multiple sexual partners
- OCP
- Early onset sexual activity
- Low socio-economic status

AIS: clinical features

• Mean age: 29 years
• Symptoms
  – None, discharge, abnormal Pap test
• Location: 65% T zone
• Mostly unifocal
• Colposcopy: no specific pattern
AIS

- Frequency: 10% of glandular malignancies
- Histological types: not clinically significant
  - Mucinuous
  - Intestinal
  - Adenosquamous
  - Clear cell
  - Endometrioid
  - Ciliated

AIS

Key pathology

- Normal glandular architecture
- Decreased mucin
- Stratified columnar cells
- Hyperchromatic nuclei
- Mitoses
- Absent stromal invasion
AIS: HPV status and IHC

• **HPV DNA**
  – 66% (40-90%) positive
  – HPV 16 and 18
  – Predominance of HPV 18

• **Antibody positive**
  – CEA (70%) and Steroid receptors
  – P16 and p53
  – Ki67: high index (>30%)

• **Antibody negative**
  – Vimentin and bcl2

AGC and HSIL

• Approximately 16% of AGC in follow up = HSIL

• Reasons
  – Co- incidental lesions
    • AIS and HSIL: 50%
  – Glandular mimics
    • HSIL in endocervical glands
AIS and HSIL: 2 cell types
HSIL involving endocervical glands

SMILE

- Uncommon lesion
- Resembles SIL with full thickness cytoplasmic vacuolization
- Described in association with cervical adenocarcinoma
- Also associated with HSIL, AIS or squamous cell carcinoma

Key pathology
• Dysplastic nuclei
• Mucin vacuoles
• Mitoses

Cytology features
• Not reported
Endocervical Dysplasia

- Controversial lesion
  - No outcome studies
- Alternate terminologies
  - Low CGIN: UK
  - Superficial (early) AIS
- Investigation
  - HPV testing
  - P16 positive
  - Steroid receptor positive

Endocervical dysplasia: criteria

- Hyperchromatic nuclei
- Occasional mitoses
- Minimal stratification
- AIS in one gland
- Other criteria

- Management
  - controversial

Adenocarcinoma: epidemiology

- 20-25% cervical carcinomas
- Mean age at presentation
  - Microinvasive adenocarcinoma: 39-44 years
  - Invasive adenocarcinoma: 44-54 years
- Incidence increasing in Canada and elsewhere
  - 1994-96: 1.83/100,000
    - 41% relative increase in 22 years
    - Higher Pap test false negative rate due to sampling error

Adenocarcinoma: risk factors

• Sexual behavior
  – Early age of onset of sexual activity
  – Lifetime number of sexual partners
  – Early age of first birth and increasing parity

• Oral contraceptives

• Obesity and body fat distribution

• No association with cigarette smoking

Adenocarcinoma: risk factors

• **Human Papilloma Virus (odds ratio=81)**
  - 88% HPV DNA positive
  - Types 16/18 in 82%
    - Type 16 predominant in endometrioid and VGA
    - Type 18=16 or slight predominance in others

• **Genetic**
  - Ovarian carcinoma
  - Peutz Jegher’s syndrome

Adenocarcinoma: classification

• 57% Mucinous
• 30% Endometrioid
• 11% Clear cell
• 2% Rare types
  – Minimal deviation
  – Serous
  – Mesonephric
  – Well differentiated villoglandular
Classification System
Deficiencies

• Variable frequency of endometrioid
  – 7-50%

• Interobserver agreement
  – Endocervical, endometrioid, clear cell, serous: moderate-good
  – Mixed carcinomas: fair-poor
  – Villoglandular, adenosquamous: poor

Mucinous Adenocarcinoma

• Synchronous premalignancy
  – 66% AIS
  – 16% HSIL

• Synchronous mucinous tumors of ovary and fallopian tube
  – Primary or metastatic

• 3 morphologic types
  – Endocervical, intestinal, signet ring
    • Pure
    • Mixed

Endocervical adenocarcinoma

Key pathology
• Complex racemose glands
• Surface and intraluminal papillae
• Pale granular cytoplasm
• Brisk mitotic activity
• Apoptotic bodies

Young. Histopathol 2002; 41: 185.
Endocervical adenocarcinoma

• Mostly neutral mucin: content variable
  – Pas/al blue: red/purple mixed cytoplasmic stain
  – Mucicarmine: cytoplasmic positivity

• Antibody positive
  – CEA: cytoplasmic
  – P16 positive: diffuse and strong

• Antibody negative
  – Vimentin
  – Estrogen receptor

Endocervical adenocarcinoma
Cytology: endocervical adenocarcinoma

- Hypercellular smears
- Cells
  - Single
  - Sheets
  - Clusters
- Cell features of AIS
- Additional features
  - Perinuclear clearing
  - Macronucleoli
  - Tumor Diathesis

Intestinal adenocarcinoma

Key pathology
- Glands and papillae
- Pseudostratified mucin poor cells
- Goblet cells

Signet ring carcinoma

Key pathology
• Signet ring cells
• Pure form is rare
• Usually mixed with other types

Young. Histopathol 2002; 41: 185.
Endometrioid Adenocarcinoma

• Resembles endometrial counterpart
• Synchronous premalignancy
  – Higher compared to non endometrioid carcinomas
    • 81% AIS
    • 54% HSIL
• Difficult to distinguish from mucin poor mucinous carcinomas
• Lower frequency of squamous differentiation
• Better prognosis than mucinous carcinoma

Endometrioid adenocarcinoma

Key pathology
• Glandular architecture
• Benign squamous differentiation
• Stratified, oval nuclei
• No cytoplasmic mucin

Young. Histopathol 2002; 41: 185.
Endometrioid carcinoma

Cytology features
- Similar to mucinous carcinoma
Clear cell Carcinoma

- **DES exposed**
- Young women
- Location
  - Ectocervical
- HPV status
  - Usually negative
  - Rare cases HPV 31 positive
- **Sporadic**
- Post menopausal women
- Location
  - Endo or ectocervical

Clear cell Carcinoma

Key pathology
- Solid, tubulocystic, papillary
- Glycogenated clear cytoplasm
- Intracystic mucin
- Hobnail cells

Young. Histopathol 2002; 41: 185.
Clear cell Carcinoma

Cytology features
- Large cells
- Abundant cytoplasm
- Round nucleus
- Prominent nucleolus
**Minimal Deviation Adenocarcinoma**

- Rare tumor
  - 3 types
- Associations
  - Not HPV related: 1 report of type 16 and 18+
  - Lobular endocervical hyperplasia (PGM)
  - AIS with a gastric immunophenotype
  - Adenoma malignum (AM)
    - Mucinous ovarian tumors
    - SCTAT
    - Peutz Jeghers Syndrome

Adenoma Malignum

• Symptoms
  – Profuse watery discharge/bleeding

• Difficult on cytology and small biopsies

• Cytology features
  – Irregular sheets of benign glandular cells
  – Rare malignant cells with large nucleoli

• Prognosis
  – Worse than mucinous carcinoma

Adenoma malignum

Key pathology
• Atypical glands: shape, size, location
• Desmoplasia near outpouchings
• Single layer of low grade mucinous cells
• Rare gland with malignant cells
Adenoma Malignum versus Normal or Benign Endocervix

<table>
<thead>
<tr>
<th>Stain</th>
<th>Adenoma Malignum</th>
<th>Normal or Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS/Al Blue</td>
<td>Mostly red</td>
<td>Purple/ violet</td>
</tr>
<tr>
<td>HIK1083-PGM</td>
<td>+</td>
<td>-*</td>
</tr>
<tr>
<td>CEA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>P16</td>
<td>30% +</td>
<td>-</td>
</tr>
<tr>
<td>Alpha SMA</td>
<td>Increased + stroma</td>
<td>- stroma</td>
</tr>
<tr>
<td>ER</td>
<td>- stroma</td>
<td>+ stroma</td>
</tr>
</tbody>
</table>

*positive staining in lobular hyperplasia

Adenoma Malignum: Pas Al Blue

Adenoma Malignum

Normal Gland

*ph=2.5

Serous Carcinoma

• Histology similar to ovarian and endometrial counterparts
• Metastatic spread should be excluded
• Outcome
  – Stage 1 = Stage 1 endocervical adenocarcinoma
  – Advanced stage: rapidly fatal

Serous carcinoma

Key pathology
- Complex papillary proliferation
- Stratification and tufting
- High grade nuclei
  - P53 positive, CEA negative

Serous Carcinoma

Cytology features
- Single cells
- Sheets
- Tight balls
- Malignant features obvious
- Psammoma bodies
Mesonephric carcinoma

- Rare tumor
  - 30 documented cases
- Arise from mesonephric duct remnants
- Gross appearance
  - Cervical mass
- HPV negative
- Outcome
  - More indolent than mucinous carcinoma

Mesonephric carcinoma

Key pathology
- Variable pattern: mostly ductal
- Retiform, tubular, sex cord, spindle cell
- Eosinophilic mucinous secretion
- Mesonephric remnants
Mesonephric carcinoma: immunohistochemistry

• Pattern similar to mesonephric remnants
• Negative staining
  – mCEA, CTK 20, ER/PR
• Positive staining
  – EMA, CTK 7, CAM 5.2, CD10, Vimentin, Calretinin, Inhibin, p16
• CEA, CD10, and vimentin pattern is controversial

Well Differentiated Villoglandular Adenocarcinoma

- Rare tumor of young women
  - Average age: 35
- Presentation: vaginal bleeding/exophytic mass
- May be mixed with other types of carcinoma
- HPV status
  - 100% type 16/18 positive
  - Mostly type 16
- Prognosis usually excellent

Well differentiated villoglandular adenocarcinoma

Key pathology
• Papillary architecture
• Minimal cytological atypia
• Minimal stromal invasion
• No desmoplasia
Well differentiated villoglandular adenocarcinoma: cytology

- Not specific
- Atypical glandular cells
  - Papillary fragments
  - Nuclear crowding
  - Subtle atypia
- High false negative rate

Secondary Adenocarcinoma

• Genital tract
  – Endometrial carcinoma
  – Ovarian, tubal and peritoneal

• Extragential sites
  – Rare
    • Breast
    • Colorectal
    • Gastric

Endometrial carcinoma

• Stage II tumors
  – IIa: Surface cancerization
  – IIb: Stromal invasion

• Tumor source
  – Direct spread
  – Surface metastases
  – Embolic

Stage II endometrial carcinoma: histology

Stage IIa

Stage IIb
Endometrial endometrioid carcinoma: cytology

Key Pathology
- Watery diathesis
- Crowded groups
- Prominent nucleoli
- Ingested PMNs
# Cervical Primary versus Stage II Endometrial Carcinoma

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cervix</th>
<th>Endometrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR</td>
<td>83% -</td>
<td>70% +</td>
</tr>
<tr>
<td>CEA</td>
<td>86% +</td>
<td>89% -</td>
</tr>
<tr>
<td>Vimentin</td>
<td>86% -</td>
<td>59% +</td>
</tr>
<tr>
<td>P16</td>
<td>100% + strong/diffuse</td>
<td>30%+ Moderate/patchy</td>
</tr>
</tbody>
</table>

Stage II Endometrial Carcinoma

PTEN: tumor suppressor gene
- Endometrial carcinoma: somatic mutations
  - Expression is diminished
- Cervical adenocarcinoma
  - Expression retained

Extrauterine genital tract primaries

- Dissemination pathways
- Direct spread
- Embolic spread
- Transtubal migration

Metastatic Breast Carcinoma

- Frequency increasing
- Longer survival
- Lobular more frequent than ductal
- Pap test: rare malignant cells
- Histology: isolated metastasis

Metastatic colonic carcinoma

Key cytology features
- Dirty background
- Glandular groups
- Palisading of basal nuclei

The End

Thank you for inviting me