The International Society of Gynecological Pathologists

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New Developments in Cervical Pathology:

NHPVA Types of Endocervical Adenocarcinoma

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Based on descriptive morphologic features

2013 WHO

Glandular tumours and precursors
Adenocarcinoma in situ
Adenocarcinoma
- Endocervical adenocarcinoma, usual type
- Mucinous carcinoma, NOS
  - Gastric type
  - Intestinal type
  - Signet-ring cell type
- Villoglandular carcinoma
- Endometrioid carcinoma
- Clear cell carcinoma
- Serous carcinoma
- Mesonephric carcinoma
- Adenocarcinoma admixed with neuroendocrine carcinoma
Based on morphologic features linked to etiology (ie, human papillomavirus infection)
Distinction of HPV-from non HPV related adenocarcinomas based on:

Presence of luminal mitoses and apoptoses

Classification based on pathogenesis as reported in vulva and oropharynx likely to be more informative
Endocervical Adenocarcinoma Subtypes

Much higher frequency of gastric-type carcinoma in Japan
Younger age at presentation if HPV related (42 vs 55 years)
Larger size (3.8 vs 2.1 cm) if non-HPV-related
Greater frequency of advanced stage (II or higher) if non-HPV related
Precursor lesions by far much more common in HPV related tumors
HPV HR ISH superior sensitivity, specificity, and negative predictive values than p16
NON-HUMAN PAPILLOMA ASSOCIATED CARCINOMA

- Gastric
- Clear cell
- Mesonephric
- Endometrioid
- Miscellaneous and NOS
GASTRIC TYPE ADENOCARCINOMA
May be associated with Peutz Jeghers Sde

- Low N/CP ratio
- Clear, foamy, pale cytoplasm
- Distinct cytoplasmic borders
  - Basally located nuclei
- +/- intestinal diff (goblet or neuroendocrine-like cells)
Signet ring cells if poorly differentiated
Focal/equivocal HPV features at 200x

ENDOMETRIAL CURETTING
P16 and HPV negative
GASTRIC-TYPE ENDOCERVICAL ADENOCARCINOMA COLONIZING ENDOMETRIAL GLANDS
SECONDARY INVOLVEMENT OF FALLOPIAN TUBE WITH STROMAL INVASION
OVARIAN METASTASES
ADENOMA MALIGNUM
(Minimal deviation gastric-type adenocarcinoma)

ABNORMAL CERVIX ON INSPECTION:

Often barrel shaped cervix
ADENOMA MALIGNUM

ABNORMAL GLANDS:
- Number
- Distribution
- Shape

ENDOCERVICAL CANAL
## A Detailed Immunohistochemical Analysis of a Large Series of Cervical and Vaginal Gastric-type Adenocarcinomas


<table>
<thead>
<tr>
<th>Protein</th>
<th>Positive</th>
<th>Diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>47/47</td>
<td>45</td>
</tr>
<tr>
<td>MUC6</td>
<td>17/21</td>
<td>6</td>
</tr>
<tr>
<td>CEA</td>
<td>25/31</td>
<td>2</td>
</tr>
<tr>
<td>CA125</td>
<td>36/45</td>
<td>5</td>
</tr>
<tr>
<td>PAX8</td>
<td>32/47</td>
<td>20</td>
</tr>
<tr>
<td>CK20</td>
<td>23/47</td>
<td>6</td>
</tr>
<tr>
<td>CDX2</td>
<td>24/47</td>
<td>4</td>
</tr>
<tr>
<td>p16</td>
<td>18/47</td>
<td>4</td>
</tr>
<tr>
<td>p53</td>
<td>19/46</td>
<td>19</td>
</tr>
<tr>
<td>HNF-1b</td>
<td>13/14</td>
<td>6</td>
</tr>
<tr>
<td>ER, PR, PAX2, HER2</td>
<td>Mostly negative</td>
<td></td>
</tr>
</tbody>
</table>

- SKT11 mut
- TP53 mut (50%)
- 3q gain
- 1p loss
Although called gastric type due to pyloric mucin, morphologically resemble pancreatobiliary carcinoma with similar immunohistochemical profiles.
Overall, poorer survival when compared to HPV-related adenocarcinomas (~40% versus 90%; 62% vs 96% if stage I tumors; chemoresistant). Metastases to adnexa, omentum, liver, brain and bone in contrast to HPV-related adenocarcinomas (typically pelvis).
ADENOMA MALIGNUM
(Minimal Deviation Adenocarcinoma)

Differential Diagnosis

• Deep endocervical glands and Nabothian cysts
• Tunnel clusters
• Endocervical hyperplasia, NOS
• Lobular endocervical gland hyperplasia or pyloric gland metaplasia
• Cervical adenomyoma
• Endocervicosis
LOBULAR ENDOCERVICAL GLAND HYPERPLASIA
NOT ALWAYS PERFECT BUT TENDENCY TO BE LOBULATED
## ADENOMA MALIGNUM vs LEGH

<table>
<thead>
<tr>
<th>Feature</th>
<th>LEGH</th>
<th>AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucous discharge</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Mass</td>
<td>Rarely</td>
<td>Typically</td>
</tr>
<tr>
<td>Depth of involvement</td>
<td>&lt;50%</td>
<td>Often &gt;&gt;50%</td>
</tr>
<tr>
<td>Demarcation</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Lobulation</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Minimal</td>
<td>Prominent (at least focally)</td>
</tr>
<tr>
<td>Stromal response</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
LOBULAR ENDOCERVICAL GLAND HYPERPLASIA with SEVERE CYTOLOGIC ATYPIA
CARCINOMA ARISING IN LEGH

GASTRIC-TYPE ADCA
HPV-negative Gastric Type Adenocarcinoma In Situ of the Cervix

A Spectrum of Rare Lesions Exhibiting Gastric and Intestinal Differentiation

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Marisa R. Nucci, MD,‡ and W. Glenn McCluggage, FRCPath§

CLEAR CELL CARCINOMA

- Biphasic age distribution (<5%)
- 1/3 associated with in utero exposure to diethylstilbestrol (DES) and non-steroidal estrogen before 18\textsuperscript{th} week of gestation (exocervical location)
- Frequent coexistence with vaginal adenosis > transverse vaginal or cervical ridges
- 2/3 not associated with DES (endocervical location)
CLEAR CELL CARCINOMA: TUBULOCYSTIC PATTERN

Great variability in number and distribution

- Polygonal cells
- Highly atypical but uniform nuclei
ARCHITECTURAL DISTORTION DUE TO HYALINIZATION

DECEPTIVE APPEARANCE
HNF-1B and Napsin A variably expressed in clear cell carcinoma

Overall, HNF-1b less specific than Napsin A:
- HNF-1b ubiquitously expressed in gastric-type and most HPV-related adenocarcinomas
- Napsin A expressed in 1/4 of gastric type adenocarcinomas and all intestinal type HPV-related adenocarcinomas

p16 and p53 may be positive

CEA is negative (in contrast to gastric-type adenocarcinoma)
Remember that:

Arias Stella reaction may occur in postmenopausal women and a history of hormones does not always exist.
UNUSUAL APPEARANCES IN MICROGLANDULAR HYPERPLASIA
MESONEPHRIC CARCINOMA

< 1% of cervical carcinomas

Mixed growth patterns
Eosinophilic secretions

Aggressive behavior
Pseudoendometrioid appearance; most common
DIFFUSE HYPERPLASIA

CARCINOMA
No cytologic atypia
Incidental finding
Dx of exclusion if coexistent endometrioid carcinoma
ENDOMETRIOID CA EXTENDING TO CERVIX
SIMULATING MESONEPHRIC HYPERPLASIA

ER and PR positive
<table>
<thead>
<tr>
<th>Protein</th>
<th>EEC</th>
<th>Mesonephric Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD10</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AR</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Calretinin</td>
<td>-/+</td>
<td>+/-</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>ER</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>p16</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>PAX2</td>
<td>Loss</td>
<td>+</td>
</tr>
<tr>
<td>PAX8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GATA3</td>
<td>- (rarely positive)</td>
<td>+ (except carcinoma)</td>
</tr>
</tbody>
</table>
• PAX8, CD10, p16, calretinin - not helpful to separate mesonephric lesions from EEC extending to cervix

• Vimentin and HNF1b may be + in mesonephric lesions

• GATA3 only rarely positive in EEC but in ~10% of usual type endocervical adenocarcinoma. Mesonephric carcinomas less positive than mesonephric hyperplasia
GATA3 in MESONEPHRIC PROLIFERATIONS

Remnant

Hyperplasia

Carcinoma

Targeted genomic profiling reveals recurrent KRAS mutations and gain of chromosome 1q in mesonephric carcinomas of the female genital tract.
MOLECULAR ALTERATIONS IN MESONEPHRIC TUMORS

No PTEN or PIKCA mutations

RAS/MAPK pathway targeting inhibitors

13 (81%)
Most adenocarcinomas originally diagnosed as endometrioid reclassified as usual-type, showing similar rates of p16 overexpression and HPV positivity to usual type adenocarcinoma (78 vs 83% and 82 vs 87%).

- Low-grade endometrioid glands
- Columnar cells and pseudostratified nuclei
- Squamous, ciliated diff and/or endometriosis
  - No mucin
  - No HPV features
SEROUS CARCINOMA = NON-EXISTENT

ALWAYS EXCLUDE:

- ENDOCERVICAL ADCA WITH PAPILLARY FEATURES
- SEROUS CARCINOMA FROM UPPER GYNECOLOGIC TRACT
CONCLUSIONS:

- Most NHPVA related adenocarcinomas are associated with an aggressive behavior
- The morphologic and immunohistochemical spectrum of gastric-type carcinoma is very wide and it resembles pancreatobiliary carcinomas
- Gastric-type and clear cell carcinoma may show deceptive appearance
- Before establishing a diagnosis of endometrioid carcinoma, exclude a mucin poor endocervical adenocarcinoma and look for HPV cytologic features or a corpus endometrioid carcinoma
- Before establishing a diagnosis of primary serous carcinoma of the cervix, exclude a metastases or a papillary cervical adenocarcinoma
- p16 positivity may be seen in NHPV related carcinomas, if in doubt use ISH
THANK YOU!
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