Gynecologic Pathology: Lower Female Genital Tract

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Pathology of the Lower Female Genital Tract

- HPV related pathology

- Selected Pathology
  - Vulva
  - Vagina
  - Cervix

HPV – Human Papillomavirus

- Characteristics
  - DS-DNA
  - over 100 subtypes based upon nucleic acid sequence homology
  - ~30 are genital-specific
  - sexually transmitted

condyloma acuminata
Epidemiology of HPV: 
...a silent epidemic

- HPV: the most common STD in the U.S.
  - >5 million new cases per year (¼ of all STD)
  - 70% Americans have never heard of HPV!
  - DNA can be carried by spermatocytes

- Association with Neoplasia
  - recovered in "virtually all" cervix cancer
  - "immortalized" keratinocytes in culture
    - HeLa cell line → HPV 16

HPV Subtypes – Associated Risk

- Low Risk ≈ Low Grade Lesions
  - 6/11
  - episomal

- High Risk ≈ High Grade Lesions
  - 16, 18
  - DNA integration

Lorincz et al., 1991

Condyloma – the Prototype of HPV Pathology

- histology
  - papillary epithelial projections
  - koilocytosis
    - perinuclear halo (clearing) and nuclear atypia
Viral Cytopathic effect of HPV

Carcinoma in-situ

Range of Pathologic Findings

- HPV DNA positive — no physical findings
- Condyloma Acuminata
- Intraepithelial Neoplasia = SIL*
  - VIN (vulvar) 1.0 per 100,000
  - VaIN (vaginal) 0.3 per 100,000
  - CIN (cervical) 38 per 100,000
- Carcinoma
  - Squamous (vulva, and vagina, and cervix)
  - Glandular (cervix only)
  
  *squamous intraepithelial lesion

Vulvar Dermatoses – Nomenclature

Vulvar Dermatoses
- Lichen sclerosus
- Squamous Hyperplasia
- Other Dermatoses "Atypical" Lesions
  - VIN 1 (LSIL)
  - VIN 2-3/CIS (HSIL)
- Paget's Disease

Leukoplakia
Lichen Sclerosus

- pruritic white lesion
  - aka kraurosis vulvae, LS & A, senile vulvitis
  - primarily menopausal women
  - can occur at any age
- Etiology unknown
  - HLA predisposition
  - autoimmune?

Lichen Sclerosus: at any age

[Images of post-menopausal and pre-pubertal cases]

Lichen Sclerosus: Histology

histologic triad:
- epidermal thinning
- collagenized upper dermis
- “lichenoid” lymphocytic infiltrate
Pre-malignant & Malignant Vulvar Neoplasms

- squamous
  - intraepithelial (VIN)
  - HPV-associated carcinoma
  - non-HPV associated carcinoma
- Extramammary Paget’s disease
- Melanoma

“Typical” VIN 3

VIN - Types

Warty Basaloid
Vulvar Malignancies – Incidence by Histologic Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>86.2%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4.8%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2.2%</td>
</tr>
<tr>
<td>Basal Cell Carcinoma</td>
<td>1.4%</td>
</tr>
<tr>
<td>Bartholin’s Gland squamous cell carcinoma</td>
<td>0.4%</td>
</tr>
<tr>
<td>Adenocarcinoma, NOS</td>
<td>0.6%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>3.9%</td>
</tr>
</tbody>
</table>


Vulvar Carcinoma

Radical Vulvectomy

Vulvar Carcinoma

- 3-5% female genital malignancies
- recent increase incidence in younger women
- risk factors:
  - diabetes
  - hypertension
  - obesity
  - HPV type 16 – young women
Keratinizing SCC

Vagina – Carcinoma
- metastatic squamous cell carcinoma
  - most common
  - extension from cervix or vulva
  - recurrent from endometrium
- primary vaginal carcinoma ~ rare
  - <1% gynecologic malignancies
  - squamous cell carcinoma

Pathology of the Cervix
- Inflammatory Processes
- Cervical Neoplasia
  - intraepithelial (dysplasia)
  - carcinoma
Terminology of the Transformation Zone (T-Z)

- Squamo-columnar junction
- Transformation zone (T-Z)
- Original squamous epithelium

The “T-Z”

- Squamo-columnar junction
- Squamous metaplasia
- Reserve cell hyperplasia

Cervix — Inflammation

- Acute & Chronic
  - present in all women
  - varying degrees
- Pathophysiology
  - hormonal effects
    - commensal bacteria
    - pH
  - infectious
  - traumatic
  - environmental

- Menarche
  - Estradiol
- Glycogen Storage

- Commensal Bacteria
  - lactobacillus
  - streptococcus
  - E. coli
  - anaerobes
- acid pH
- squamous metaplasia
The T-Z and HPV/CIN

“The Neoplastic Continuum”

Age Adjusted Cancer Death Rate – Uterus

modified from American Cancer Society Statistics, 1992
PAP Smear Terminology

Abnormal Cervical Cytology

Abnormal PAP Smear: Guidelines for Management
Colposcopy of HSIL

Cervical Neoplasia: Risk Factors

- age at first intercourse
- number of sexual partners
  - number of partners of the male partner
- smoking
- immune status
  - HIV
  - diabetes
  - immunosuppression

...and human papilloma virus infection

Natural Course of HPV-related Cytology

### Long Term Follow-Up of Cervical Dysplasia: Summary

<table>
<thead>
<tr>
<th>Extent of Disease</th>
<th>Regression (%)</th>
<th>No Change (%)</th>
<th>Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>50-75%</td>
<td>27%</td>
<td>10%</td>
</tr>
<tr>
<td>HSIL</td>
<td>2-25%</td>
<td>45%</td>
<td>30-50%</td>
</tr>
</tbody>
</table>


### Carcinoma of the Cervix

- squamous cell carcinoma ~75%
- other carcinomas 10-25%
  - adenocarcinoma (5-15%)
  - adenosquamous carcinoma
  - undifferentiated
  - others

### Microinvasive Squamous Carcinoma
Exophytic Cervical Carcinoma

Squamous Cell Carcinoma

LCNK — large cell, non-keratinizing
LCK — large cell, keratinizing

Large Cell Non-Keratinizing SCC
Cervix — Adenocarcinoma

- Adenocarcinoma In-situ (ACIS)
  - "skip lesions"
- Invasive Adenocarcinoma
- Adenosquamous Carcinoma
  - higher association with HPV 18

ACIS & Invasive Adenocarcinoma

Cervical Carcinoma: Barrel Shaped
Cervical Cancer

- Prognostic Indicators
  - Stage
  - Histology
  - Lymph Node Status
- Survival
  - all stages: 69%
  - Stage I: 91%
  - pre-invasive: 100%

Lower Genital Tract Pathology Summary

- HPV is a ubiquitous infection with a variety of manifestations in the female genital tract
- early diagnosis of HPV-related neoplasia is life saving