Pathology of the Female Genital Tract-I
Cervix | Vagina | Vulva

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- Cervix
  - Histology, transformation zone
  - Pap smear
  - Human Papillomavirus, CIN/SIL
  - Squamous cell carcinoma

- Vulva
  - Squamous cell carcinoma
  - Lichen sclerosis vs Lichen simplex chronicus
  - Paget disease

- Vagina
  - Squamous cell carcinoma
  - Clear cell carcinoma
  - Embryonal rhabdomyosarcoma

Normal Ectocervix
Normal nulliparous Ectocervix
Normal vaginal cuff

Stroma=dense connective tissue; Small amount smooth muscle
Cervix:
- Ectocervix: Stratified Squamous Epithelium
- Endocervix: Simple Columnar Epithelium

Squamocolumnar Junction

Cervical Transformation Zone
- Squamous metaplastic change
- Transformation Zone = band of squamous metaplasia lying between the original SCJ and new SCJ

Source: Rubin's Pathology: Clinicopathologic Foundations of Medicine, 7e, 2014
Squamous Metaplasia

Early stages of squamous metaplasia of transformation zone: Reserve cells begin to proliferate (arrow).

Later stage: the proliferating reserve cells displace the glandular epithelium.

Final step: cells mature into glycogen-rich squamous cells.

A B C

Transformation zone where two types of epithelia coexist
Glandular epithelium
Columnar epithelium
Squamocolumnar junction
Squamous epithelium
Vagina
Relevance?
The transformation zone is the site of cervical squamous carcinoma

No woman should die of cervical cancer
Screening leads to fewer deaths

https://www.cdc.gov

PAP Smear
Screening for cervical cancer

Ideal Screening Test:
Always correct
Repeatable
Safe, painless, quick, inexpensive
Results make clinical difference
Understanding the PAP Smear

- Cervical Transformation Zone
  - Cervical Intraepithelial Neoplasia (CIN)/Squamous Intraepithelial Lesion (SIL)
  - Role of Human Papillomavirus (HPV)

Human Papillomavirus (HPV)

- Oncogenic DNA virus
- Multiple types
  - High risk: 16, 18, 31, 33
  - Low risk: 6, 11

Factors related to HPV infection:
- Early age at first intercourse
- Multiple sexual partners
- Male partner with multiple previous sexual partners
HPV Oncogenicity

• HPV oncoproteins E6, E7
  – Bind to Rb and p53
    (key tumor suppressor proteins)
  • Neutralize their function

High Risk HPV

• Tropism for immature squamous cells of the transition zone (infection)
• Integrate into host genome
• Inactivate tumor suppressor gene (p53, Rb)
• Promote monoclonal outgrowth of squamous cells

Condyloma

• Low risk HPV 6, 11
• “Characteristic cell = koilocyte

Source: Webpathology.com
Exophytic Condyloma
“Condyloma Acuminatum”

Cervical Intraepithelial Neoplasia (CIN)
Squamous Intraepithelial Lesion (SIL)

Natural History SIL

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Regress</th>
<th>Persist</th>
<th>Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL (CIN I)</td>
<td>60%</td>
<td>30%</td>
<td>10% (to HSIL)</td>
</tr>
<tr>
<td>HSIL (CIN II, III)</td>
<td>30%</td>
<td>60%</td>
<td>10% (to carcinoma, usually within 10 years)</td>
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</table>
HPV Infection Summary

• Early phases of infection with all HPV types likely involve episomal viral propagation throughout a polyclonal epithelial field, with an LSIL cytology.

• Oncogenic types of HPV are prone to subsequent genomic integration of virus and promote monoclonal outgrowth of cells driven by transforming viral proteins (E6/E7) with progression to HSIL.

PAP Smear

Cytologic Features of CINS/SIL
CIN/SIL Management

- Biopsy
  - Via Colposcopy
  - Contour, color, and vascular pattern distinguish LSI, HSIL
- LSI – observation
- HSIL – surgical excision, long-term follow-up
Prevention: HPV Vaccine

- **Bivalent**
  - HPV vaccine against HPV types 16 and 18
- **Quadrivalent**
  - HPV vaccine against HPV 16/18, HPV 6/11

- Ideally, patients should be vaccinated before onset of sexual activity, when they may be exposed to HPV.

Invasive Carcinoma of the Cervix

- Majority Squamous Cell Carcinoma (75%)
  - Adenocarcinoma (15%)
- HPV plays a role in all
- ~20% somatically acquired mutations in tumor suppressor gene LKB1
- Most often seen in women who have never had PAP smear or not screened in many years

Invasive Carcinoma of the Cervix

- Peak incidence ~45 years
- Symptoms: vaginal bleeding, leukorrhea, dyspareunia, dysuria
- Key risk factor – high risk HPV Infection
  - Other risk factors: smoking, immunodeficiency (AIDS defining illness)
Cervical Carcinoma

- Treatment
  - Hysterectomy, lymph node dissection
- Mortality strongly correlated to tumor stage
- Advanced disease = local invasion, obstruction of ureters and urinary bladder
“Other” Squamous Epithelium Covered Structures/Organs of the Female Genital Tract:

- **Vulva**
  - Skin and mucosa of genitalia external to the hymen
    - Labia major, Labia minora, mons pubis, vestibule

- **Vagina**
  - Canal leading to cervix
Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Vulva</th>
<th>Vagina</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common?</td>
<td>3%</td>
<td>Extremely uncommon</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>High risk HPV 16-18</td>
<td>Non-HPV related</td>
</tr>
</tbody>
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Vulva: Lichen Sclerosus

- Postmenopausal women > other ages
- Uncertain etiology, but suspect autoimmune
- Symptoms: none, pruritus, soreness, irritation
- Histology: Thinning of Epidermis, Fibrosis of Dermis
- Physical Exam: Leukoplakia - thin white plaques on Vulva

*white patch

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Vulva: “Condyloma”

- “Wart”
- Condyloma acuminata
  - HPV 6,11 / Low risk of progression to cancer

Source: Robbins

Vulva: Lichen Simplex Chronicus

- Epidemiology: Associated with chronic irritation, scratching
- Histology: Hyperplasia of vulvar epithelium
- Exam: Leukoplakia; thick leathery skin
- NO increased risk of malignancy

Summary: Vulvar Leukoplakia

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<thead>
<tr>
<th></th>
<th>Lichen Sclerosis</th>
<th>Lichen Simplex Chronicus</th>
<th>Squamous Cell Carcinoma</th>
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</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Thinning of Epithelium</td>
<td>Hyperplasia of Epithelium</td>
<td>Infiltrating nests of malignant cells arising from squamous epithelium of vulva</td>
</tr>
<tr>
<td>Etiology</td>
<td>Likely autoimmune</td>
<td>Chronic irritation</td>
<td>HPV Non-HPV (Lichen Sclerosis)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Small risk of progression to cancer, elderly women</td>
<td>Benign</td>
<td>Invade and spread, regional LN and beyond</td>
</tr>
</tbody>
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Paget Disease of the Vulva (Extramammary Paget Disease)

- Intra-epidermal proliferation of malignant cells
  - Can also occur in breast nipple
- Usually no underlying tumor
- Arises from intra-epidermal progenitor cells
- Presents as RED, scaly, crusted plaque

Paget Disease of Vulva

Single cells with pale vacuolated cytoplasm with abundant glycosaminoglycans

Clear Cell Adenocarcinoma of Vagina

- Rare malignancy associated with Diethylstilbestrol (DES) exposure in-utero
- Malignant proliferation of glands with clear cytoplasm
  - Precursor lesion = vaginal adenosis
    - Persistence of columnar epithelium in upper 1/3 vagina
- Clinical examination: red, granular areas adjacent to normal pale pink vaginal mucosa
Embryonal Rhabdomyosarcoma of Vagina

• “Rhabdomyosarcomas”
  – STEP BACK to early MHD I
  – What is the cell of origin?
  – Soft tissue neoplasms
    • Usually appearing before age 20
    • Head and neck, genitourinary (bladder and vagina)

Embryonal Rhabdomyosarcoma of Vagina

• Aka “Sarcoma Botryoides”
• Rare, primary vaginal cancer
• Children < 5 years old
• Presentation: Bleeding, soft, grape-like masses protruding through vagina
• Histology: Rhabdomyoblast
  – Demonstrate skeletal muscle differentiation
    • Immunohistochemistry: Desmin, myogenin

Embryonal Rhabdomyosarcoma of Vagina

Source: Robbins Pathologic Basis of Disease, 8th edition
Source: Pathology Outlines
FIN

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