Squamous Cell Carcinoma

Precursors
- Squamous intraepithelial lesions

Mimics
- Herpes infection, Syphilis
- Papillomatosis
- Multinucleated Atypia

Squamous cell carcinoma and variants

Condyloma of the Vulva

- Condylomata acuminata
- Papular warts
- “Subclinical” acetowhite macules

Perianal region, and vagina/cervix may also be affected
- HPV types 6/11 most common
Diagnostic Criteria for Condyloma of Vulva

- **Koilocytosis** – cavitated cytoplasm
- **Nuclear atypia** – enlargement, hyperchromasia, pleomorphism, multinucleation, membrane irregularity
- **Architectural abnormalities** – papillomatosis, acanthosis, hyperkeratosis, parakeratosis
- **MIB-1 staining**: Group of 2 or more stained nuclei in same HPF in upper 2/3 of epithelium
- **More specific**: HPV immunohistochemistry and in situ hybridization
Positive HPV Immunostain

**High Grade SIL (VIN)**

*Classic, or Bowenoid Type*

- Young women - 30’s and 40’s - increasing in incidence
- History of condylomas, herpes infection, HIV disease, smoking
- Linked to HPV, usually HPV 16
- Varied appearance:
  - Papules, plaques, polyps
  - White, red, or pigmented
- Multicentric disease in vagina or cervix

Vulvar intraepithelial neoplasia

Vulva - VIN III
**Pagetoid Lesions of the Vulva**

<table>
<thead>
<tr>
<th></th>
<th>HMWK</th>
<th>LMWK</th>
<th>CK 7</th>
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<tr>
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<td><strong>Paget’s</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>
High Grade SIL

Results of Therapy

• Treatment: Excision, laser ablation, topical imiquimod
• Local recurrence - up to 35%
• Occult invasion - up to 20%
• Invasive carcinoma develops in
  – 3-10% of treated patients
  – 9% to up to 90% of untreated patients
  – Invasive carcinoma is basaloid or condylomatous type, some keratinizing
• Bowenoid papulosis

The Problem with Low Grade SIL (VIN)

• Less than 50% of cases of VIN I confirmed on review
• 70% of cases associated with low risk HPV
• MIB-1 positive nuclei in upper epithelium correlate with VIN I

Status of VIN Classification Pre-LAST

• Category of VIN I eliminated
  – ISSVD
  – WHO 2004
• Most cases VIN I flat condyloma or reactive
• Diagnosis of VIN refers to high grade lesions only
• Classical and Differentiated types

Low Grade SIL of the Vulva

• Some papillomatous with prominent koilocytic atypia (~ 1/3)
• Some flat with minimal koilocytic atypia (~ 2/3)
• No difference in HPV type distribution
• 91% had detectable HPV

Logani S, et al. Mod Pathol 2003;16(8):735-741
VIN 1 with extensive koilocytic atypia found to have HPV 59

VIN 1 with minimal koilocytic atypia found to have HPV 68

VIN 3 with HPV 16


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**HPV Types in Low Grade SIL of Various Sites**

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Vulva</th>
<th>Vagina</th>
<th>Cervix</th>
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<tr>
<td>Low risk</td>
<td>67%</td>
<td>35%</td>
<td>6%</td>
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<td>6 or 11</td>
<td>42%</td>
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<td>6%</td>
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<tr>
<td>High risk</td>
<td>42%</td>
<td>76%</td>
<td>94%</td>
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<tr>
<td>16</td>
<td>6%</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>24%</td>
<td>17%</td>
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**HPV Types in High Grade SIL of Various Sites**

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Vulva</th>
<th>Vagina</th>
<th>Cervix</th>
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<td>3%</td>
<td>6%</td>
<td>0%</td>
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<tr>
<td>6 or 11</td>
<td>3%</td>
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<td>High risk</td>
<td>100%</td>
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<td>75%</td>
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<tr>
<td>18</td>
<td>6</td>
<td>0%</td>
<td>4%</td>
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**VIN Simplex or Differentiated Type**

- 2-10% of VIN
- Postmenopausal women, average age late 60’s
- Small lesions, roughened gray white, or white plaques, may be multifocal
- Lichen sclerosis may also be present
- Not associated with HPV
- ? Greater potential for progression to invasive carcinoma; invasive carcinoma is keratinizing squamous cell type

Differentiated vulvar intraepithelial neoplasia contains TP53 mutations and is genetically linked to vulvar squamous cell carcinoma.


- 6 of 10 dVIN cases had at least 1 VIN focus with 1 or more TP53 mutations
- 4 were p53 immunopositive (missense or splice) and 2 were p53 negative (deletions)
- 5 had SCC associated with dVIN, 4/5 had TP53 mutations
  - 2 missense, p53 positive
  - 2 nonsense, p53 negative
- 2/4 cases had same TP53 mutation in dVIN and SCC
- Multiple foci dVIN with different mutations in some cases

Expanding the morphologic spectrum of differentiated VIN (dVIN) through detailed mapping of cases with p53 loss.


- p53 negative dVIN and SCC, when present, in 14 specimens from 10 patients
- 27% of dVIN cases at Vancouver General Hospital
- 1 case reclassified as not dVIN
- In 5/13 the p53 negative areas corresponded to the morphologic dVIN
- In 8/13 the p53 negative areas were more extensive than the morphologic dVIN and in some were at margins
FIGURE 1. A, Simplex vulvar intraepithelial neoplasia, grade 3 of basaloid type. Diffuse replacement of the entire epithelium by a homogeneous population of small, "undifferentiated" keratinocytes with scanty cytoplasm extending throughout the entire thickness of the epidermis, showing no or only minimal maturation in superficial layers. Normal vulvar squamous epithelium is present on the left. B, The epidermis is thickened and shows a parakeratotic surface reaction. The rete ridges are elongated and markedly enlarged and coalescent. C, Small cells, with scant cytoplasm, showing large vesicular nuclei, with visible nucleoli. D, Moderate to severe atypia, with nuclear pleomorphism, multinucleation, and dyskeratosis.

LAST Project
Lower Anogenital Squamous Terminology Standardization
Project for HPV-associated Lesions

- Single set of diagnostic terms for all lower anogenital sites
- Two-tiered nomenclature for intraepithelial lesions
  - Low grade generally self-limited lesions
  - High grade potentially progressive lesions
- Recommended terminology:
  - Low grade SIL
  - High grade SIL
- Use p16 only to improve accuracy
- Vulvar SISCCA = FIGO IA cancer

Int J Gynecol Pathol 2013; 32:76-115

Current Classification of Vulvar Squamous Intraepithelial Lesions

<table>
<thead>
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<th>WHO, 2014</th>
<th>ISSVD, 2015</th>
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<td>Low grade SIL</td>
<td>Low grade SIL (vulvar LSIL, flat condyloma or HPV effect)</td>
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<tr>
<td>High grade SIL</td>
<td>High grade SIL (vulvar HSIL, VIN usual type)</td>
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<tr>
<td>Differentiated type VIN</td>
<td>Differentiated type VIN</td>
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</table>

- WHO Classification of Tumours of the Female Reproductive Organs, 4th Ed, 2014

Squamous Cell Carcinoma of the Vulva

- **Type I**
  - Younger women, average age 55
  - VIN, HPV associated, usually HPV 16
  - Basaloid, condylomatous types

- **Type II**
  - Older women, average age 77
  - No or simplex VIN, no HPV, some LS or SH
  - Keratinizing squamous cell carcinoma

After analyzing all options, the committee concluded that the 2 concerns regarding the LAST could be addressed by accepting a modified form of the WHO classification. The version that was finally adopted by the ISSVD (Table 4) does contain LSIL. However, the word “neoplasia” is not used, replaced by “lesion,” and in parentheses, it is stated that the meaning of this term is a flat condyloma or HPV effect. This expresses the approach of the ISSVD that LSIL is not precancerous and does not need to be treated, unless symptomatic.
HPV and Squamous Cell Carcinoma of the Vulva

- HPV prevalence in vulvar intraepithelial neoplasia: 52% to 100%
- HPV prevalence in invasive squamous cell carcinoma: 15% to 79%

Histopathology 2013; 62:161-175

HPV Testing in Vulvar Carcinoma
Toki, Kurman, et al 1991

<table>
<thead>
<tr>
<th></th>
<th>Ave. Age</th>
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<th>Adj. SH, LS</th>
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<td>BC</td>
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</table>

VIN and LS adjacent to thin vulvar SCC

<table>
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<td>Warty SCC-6</td>
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<td>Basaloid SCC-4</td>
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<tr>
<td>LS</td>
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<td>9/16</td>
<td>4/9</td>
</tr>
<tr>
<td>Age Pt.</td>
<td>62</td>
<td>78</td>
<td>75</td>
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</table>


HPV in SCC of the Vulva

- Worldwide study of 2296 cases, 587 VIN and 1709 invasive SCC
  - 25.1% SCC were HPV related
  - Prevalence of HPV related highest in young women
  - Basaloid and warty most likely to be HPV positive
  - HPV 16 most common (72.5%, followed by HPV 33 (6.5%) and HPV 18 (4.6%)

Squamous Cell Carcinoma of the Vulva

- Most occur on labia
- Clitoris involved in <15%
- Multifocal in <10%
- Exophytic papillary mass or endophytic ulcer

Grading of Vulvar Squamous Cell Carcinoma

- Grade 1: No poorly differentiated component
- Grade 2: < 50% poorly differentiated component
- Grade 3: > 50% poorly differentiated component

Squamous Cell Carcinoma of the Vulva Subtype

<table>
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<td>Basaloid</td>
</tr>
<tr>
<td>Warty (Condylomatous)</td>
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<tr>
<td>Verrucous</td>
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</table>
Basaloid Type of Squamous Cell Carcinoma
Condyomatous Type of Squamous Cell Carcinoma

Squamous Cell Carcinoma of the Vulva

Therapy and Results

- Radical vulvectomy in the past
- Treatment now more conservative - wide excision, hemivulvectomy for lateralized tumors
- About 30% of patients have LN metastases, lymphadenectomy generally performed; role for SLN Bx
- Survival 75% overall, 90-100% stage I

Superficially Invasive Squamous Cell Carcinoma of the Vulva (Stage IA)

- The term “microinvasive carcinoma” is not used in the vulva
- The category of stage IA is an attempt to define a group with a very low risk of lymph node metastasis
- Definition: ≤ 1 mm in depth and ≤ 2 cm diameter
- Lymphovascular invasion, growth pattern do not exclude tumors from this category

Histologic Features Suggestive of Invasion

- Rete ridges are irregular in size, shape and distribution
- Rete ridges extend deeply into the dermis
- Complex budding or branching of the rete ridges
- Paradoxical keratinization deep in the rete ridges or in dermal nests
- Prong like buds of epithelium grow into the dermis
- Irregular, often angulated nests of atypical squamous cells in the dermis
- Too many (crowded) nests of cells, often irregularly distributed
- Single or small clusters of atypical cells in the dermis
- Cells in the dermis have vesicular nuclei, prominent nucleoli, eosinophilic cytoplasm – different from adjacent VIN
- Desmoplastic or edematous stroma around dermal nests
- Growth adjacent to or around thick walled blood vessels or nerves
Squamous Cell Carcinoma of the Vulva

Measurements of Invasion

Depth = From the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

Verrucous Carcinoma of the Vulva

- Condyloma misclassified as verrucous carcinoma
- Verrucous carcinoma misclassified as carcinoma
- Well differentiated SCC misclassified as verrucous carcinoma
- Verrucous carcinoma misclassified as well differentiated SCC
Verrucous Carcinoma of the Vulva

- Elderly women
- Locally aggressive with eventual formation of a large warty tumor
- Lymph node metastases are rare
- Treatment is by wide local excision; vulvectomy may be necessary
- 5-year survival ~ 80%

Findings Adjacent to Verrucous Carcinoma of Vulva

- Lichen Sclerosis – 1
- LSC with verrucous features – 7
- VAAD – 7
  - Vulvar acanthosis with altered differentiation
  - Variable verruciform architecture
  - Plaque like parakeratosis
  - Cytoplasmic pallor due to loss of granular layer
- No Classic or differentiated VIN

Vulvar acanthosis with altered differentiation

Vulvar acanthosis with altered differentiation

VAAD

S = hyperplasia, sharp
B = hyperplasia, blunt
C = verrucous carcinoma

Despite the name “verrucous” carcinoma...

Most think that there is no good evidence of an association with HPV
Where Does This Information Come From?

- Edward J. Wilkinson, MD
- "Verrucous carcinoma may be associated with HPV, typically type 6 or variants of type 6."

Verrucous Carcinoma and HPV

- 27 cases initially classified as VC reviewed; after review 13 accepted
- 11 cases initially classified as VC of vulva/perineum
  - 5 accepted as VC – none had HPV
  - 4 reclassified as SCC – none had HPV
  - 2 reclassified as giant condylomas, 1 had HPV 6, 1 had HPV 11
- Conclusions
  - HPV unlikely to be causally related to VC
  - Positive HPV test favors giant condyloma over VC

Mod Pathol 2012; 25:1354-1363
Differences Between Verrucous Carcinoma and Condyloma

- Verrucous carcinoma is usually large, condyloma is smaller
- Verrucous carcinoma shows pushing invasion into the underlying dermis, condyloma grows off the surface
- Usually more abnormal cytology in verrucous carcinoma
- No koilocytosis in verrucous carcinoma, characteristic of condyloma
- No HPV in verrucous carcinoma, HPV present in condyloma

Not verrucous carcinoma; well differentiated squamous cell carcinoma

Not verrucous carcinoma!
“Pseudotumors” that Mimic Squamous Cell Carcinoma

Case 1
- 37 year old HIV positive woman
- Vulvar tumor excised
We present a case of a 40-year-old woman with a history of human immunodeficiency virus infection and a nodular, hyperkeratotic 3.5-cm vulvar mass that increased in size over a 2-month period. Histopathologic examination of the excised mass was diagnostic of chronic hypertrophic vulvar herpes simulating neoplasia. Hypertrophic vulvar herpes presents a diagnostic challenge for both pathologists and clinicians because of its unusual clinicopathologic features that mimic neoplasia and its rarity. There is therefore the need for the correct diagnosis of this entity, so that appropriate therapy can be given. The pertinent literature is reviewed and discussed.

Case 2

- 39 years old, HIV positive
- Clinical diagnosis: Malignant neoplasm
- 3 cm fragment of mucosal tissue excised
- Histology: ? Squamous cell carcinoma
Histologic Features of Condyloma Latum

- Acanthosis
- Elongation and broadening of rete pegs
- Neutrophil infiltration of the epidermis
- Mononuclear infiltration of the dermis
- Spirochetes in zone of PMN infiltrate

Freinkel AL Histopathology 1987, 11:819-831

Paget Disease of the Vulva
56 Cases Studied at Duke

- Mean age at diagnosis 69
- Pruritus, erythematous white plaque
- Average size 5.6 cm, 54% unilateral
- 68% had no recurrence
- 68% of curative resections had + margins
- Invasive Paget’s in 18%, 0.2-6mm
- Last seen: 43% NED, 43% DOC, 9% AwP, 3% lost, 2% (only 1 patient) DIP

**Paget’s Disease**

*Use of Immunohistochemistry*

<table>
<thead>
<tr>
<th>Stain</th>
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<th>Perianal No Assoc Ca</th>
<th>Perianal Assoc Ca</th>
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<td>GCDFP</td>
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**Key Observations:**
- **CK20+**, **CDX-2+** and **GCDFP-**
- Paget’s Disease is likely secondary