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Teri Longacre declares no conflict(s) of interest to disclose.
Introduction

- Terminology
- Diagnostic features
- Superficial invasion
- Ancillary studies
- Reporting

<table>
<thead>
<tr>
<th>LAST</th>
<th>WHO 2003</th>
<th>ISSVD 2004</th>
<th>SYNONYMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade SIL (condyloma)</td>
<td>Condyloma acuminatum</td>
<td>Condyloma acuminatum</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>VIN/ANI 1</td>
<td>N/A</td>
<td>Flat condyloma, mild dysplasia</td>
</tr>
<tr>
<td></td>
<td>VIN/AIN 2</td>
<td></td>
<td>Moderate dysplasia</td>
</tr>
<tr>
<td>High-grade SIL (VIN2-3; AIN2-3)</td>
<td>VIN/AIN 3</td>
<td>VIN, usual type</td>
<td>Severe dysplasia, CIS, Bowen’s disease</td>
</tr>
<tr>
<td>N/A</td>
<td>Carcinoma in situ (simplex type)</td>
<td>VIN, differentiated (simplex) type</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Hart 2001, Scurry 2006, Darragh 2012*
LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL)

Vulvar (& Anal Skin) Condyloma

- **Condyloma acuminatum**
  - Common, not pre-neoplastic
  - Associated with HPV 6 and 11
  - Frequently multiple, often coalesce
  - Diagnostic criteria are not particularly robust

- **Condyloma with features of seborrheic keratosis**
  - Strong association with HPV 6

*APMIS 2012;120:477-83*
Vulvar (& Anal Skin) Condyloma

- Flat condyloma with koilocytes
  - Uncommon in vulva
  - Associated with intermediate and high-risk HPV types
  - Classified as low-grade based on morphology
Vulvar Condyloma
Anal Condyloma: Is It A Risk Lesion?

• In contrast to anal skin condyloma, anal canal condyloma may exhibit foci of HSIL (AIN 1-2)
• Anal canal condyloma may harbor high risk HPV 16, 18 types
• Anal canal condyloma may progress

NOT ALL ANAL CONDYLOMAS ARE INNOCUOUS!

Proposed Common Terminology

- **Intra-anal** = not visualized or incompletely visualized (anal canal)
- **Perianal** = completely visualized & within 5 cm of anal opening (anal margin)
- **Anal skin** = completely visualized & > 5 cm from anal opening (cutaneous)

*J Low Genit Tract Dis.* 2012;16:205-42
HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

High Grade Squamous Intraepithelial Lesion (HSIL)

- HPV-related:
  - High grade squamous intraepithelial lesion (VIN 2,3/AIN 2,3)
  - VIN, usual type

- Not to be confused with non HPV-related (vulva)
  - Differentiated (simplex) type
HSIL (VIN2-3/AIN2-3)

- Strong association with high-risk HPV, especially HPV16 (70% cases)
- Commonly multicentric with extension to perineum and skin, as well as involvement of cervix and vagina
- Old terminology:
  - Bowen’s disease, bowenoid papulosis, bowenoid dysplasia – not recommended for use
HSIL (VIN2-3/AIN2-3)

- 2/3 to full thickness atypia
  - Disorganization
  - High N:C ratios with dark, irregular nuclei
  - Numerous and abnormal mitotic figures
  - Dyskeratotic cells
- Can extend down pilosebaceous units (1/2 to 2/3 cases)
- VIN 2-3/AIN2-3
HSIL (VIN2-3/AIN2-3)

• Subtypes
  – Warty: prominent koilocytosis or warty architecture
  – Basaloid: more poorly differentiated
  – Pagetoid: rare variant, involves mature squamous epithelium as single cells or clusters with pale cytoplasm

• Precursor lesion for warty or basaloid invasive SCC

Hart 2001, Medeiros 2005
HSIL (VIN2-3) – basaloid
DIFFERENTIATED (SIMPLEX) VIN
Differentiated (Simplex) VIN

- Post-menopausal women
- Associated with lichen sclerosus, not HPV-related
- Typically identified adjacent to well-differentiated keratinizing carcinoma
- Infrequently identified prospectively
- No counterpart in the cervix
Differentiated (Simplex) VIN

• Clinical appearance:
  – Rough area with gray-white discoloration, 
    or
  – Ill-defined raised white plaque
Differentiated (Simplex) VIN: Architecture

- Expansion of basal layer with elongated, narrow rete ridges
- Epithelial thickness: acanthotic to atrophic
- Prominent parakeratosis
Differentiated (Simplex) VIN: Cytology

• Abnormal maturation
  – Enlarged keratinocytes with abundant, markedly eosinophilic cytoplasm in mid-to-superficial layers
  – Superficial cell enlargement with pallor
• Nuclear atypia of the basal cell layer
  – Enlarged, pleomorphic nuclei or
  – Relatively small, hyperchromatic irregular nuclei
Differentiated (Simplex) VIN: Dermal Changes

- Fibrosis
- Lymphocytic infiltrate, may be lichenoid

Scurry, 2006
Are There “Hybrid” Types?

- Usual HPV-related VIN in patients with lichen sclerosus
- Usual HPV-related VIN and non-HPV-related (differentiated [simplex]) VIN in same lesion

*J Clin Pathol. 2007;60;504–509*
INVASIVE SQUAMOUS CELL CARCINOMA
Invasive Squamous Cell Carcinoma

- HPV-dependent (40-50%)
  - Warty or basaloid SCC
  - Associated with HSIL (VIN2-3)
- HPV-independent:
  - Well-differentiated keratinizing SCC
  - Associated with differentiated VIN and lichen sclerosus
- Rare variant: Verrucous carcinoma
Well-differentiated Keratinizing SCC
LAST: Superficially Invasive SCC (SISCCA)

- Term applies across lower anogenital tract sites
- Definition varies by site
- Must have negative margins
- Report should include information about LVI and multifocality

*J Low Genit Tract Dis.* 2012;16:205-42
Vulva: SISCCA

• Definition T1a (FIGO IA):
  – ≤ 2 cm size and ≤ 1 mm stromal invasion
  – Confined to vulva or perineum

• Measuring depth (AJCC):
  – Epithelial-stromal junction of adjacent-most superficial dermal papilla to deepest point of invasion
  – Include measurement of tumor thickness

Note that the presence or absence of lymphatic invasion does not impact the assessment of invasion per se, although it should always be noted in the pathology report.
Anal: SISCCA

• Definition T1a:
  – ≤ 7 mm size and ≤ 3 mm stromal invasion

• Measuring depth (AJCC):
  – Basement membrane of point of origin to deepest point of invasion
  – Include measurement of tumor thickness

Note that the presence or absence of lymphatic invasion does not impact the assessment of invasion per se, although it should always be noted in the pathology report.
Well-differentiated keratinizing SCC
VERRUCOUS CARCINOMA
Verrucous Carcinoma (Giant Condyloma of Buschke-Lowenstein)

- HPV 6, 11 often reported in these lesions
- A second, high risk HPV type may be present in a portion of the lesion
- Alternatively, alteration in control genes for low risk HPV type may occur
Verrucous Carcinoma

- Large size > 10 cm
- Thick stratum corneum
- Exophytic, hyperkeratotic fronds
- Cytologically bland squamous epithelium
- Circumscribed border with displacement of deep tissue
- Non-metastasizing
Ancillary Studies

HPV-related
• p16
• Ki-67 (MIB-1) +/-

Non-HPV-related
• p53 +/-

*J Low Genit Tract Dis. 2012;16:205-42*
p16 Immunohistochemistry

- Diffuse (>80%) strong nuclear or nuclear and cytoplasmic reactivity block positive involving at least 1/3 basal layer:
  - Correlates with presence of HR-HPV and diagnosis of dysplasia
  - Grading of dysplasia must be based on histology

- Focal strong (5-80%) reactivity
  - Equivocal: Atypical

*J Low Genit Tract Dis.* 2012;16:205-42
p16 Immunohistochemistry: Indications

- LSIL versus HSIL (VIN 2/AIN2)
- HSIL versus benign mimic
- Interobserver disagreement
- Persistent abnormal Pap but no noticeable abnormality

_J Low Genit Tract Dis._ 2012;16:205-42
The Pathology Report

- LSIL versus HSIL (separate terminology if differentiated)
- Margin status
- Ancillary studies (p16 +/- Ki-67), if performed
- Suspicious for invasion
- Lymphovascular space invasion (LVSI)
- Lichen sclerosus present
The Pathology Report: Invasive Squamous Cell Carcinoma

- Focal vs multifocal
- Depth of invasion
- Margin status – measure
- Lymphovascular space invasion (LVSI)
Thank you

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