Classification of VIN

Â VIN, usual type
  ï Low-grade SIL (HPV only, VIN 1)
  ï High-grade SIL (VIN 2/3)

Â VIN, differentiated type

Â VIN, unclassified type (including Paget’s disease)
WHO Classification of VIN, 2014

- Low-grade SIL (HPV only, VIN 1)
- High-grade SIL (usual type VIN 2/3)
- Differentiated type VIN
Two Pathways to Vulval Neoplasia

HPV-related

- Young women
- Warty/basaloid (undifferentiated) vulvar intraepithelial neoplasia (VIN)
- Warty/basaloid carcinoma
- Associated with other intraepithelial lesions
- Same HPV types as CIN
- Predominance of HPV 16
- Mechanisms probably similar
- p16 surrogate marker?
HSIL
(Usual-type VIN)
HSIL (Usual-type VIN)
Two Pathways to Vulval Neoplasia

Non-HPV-related

- Older women
- Associated with lichen sclerosus
- Differentiated (simplex type) VIN
- Often well differentiated squamous cell carcinoma but clinically aggressive
- p16 negative
- ? p53 mutation important (Pinto et al, Mod Pathol 2010; 23: 404-412)
Lichen sclerosus

VIN

VIN

Squamous cell carcinoma
HPV and Morphology

- 69.5% basaloid SCC HPV positive (n=326)
- 11.5% keratinising SCC HPV positive (n=1234)

- 90.3% usual type VIN HPV positive (n=535)
- 48.9% differentiated type VIN HPV positive (n=48)

Does This Matter?

- Potential therapeutic relevance
  - Imiquimod
  - Other agents

- Should we classify on the basis of HPV?

- Further molecular investigation of differentiated type VIN needed
Two main pathways – HPV-related and non-HPV-related

WHO classification
- Low-grade and high-grade SIL (−IN)
- Differentiated type VIN included
- HPV positive and negative lesions recognised but do not form the basis of the classification

HPV vs non-HPV-associated lesions
- Prognostic difference?
- Therapeutic implications?
- p16 or HPV typing?
Verrucous Carcinoma of the Vulva

A Verrucous carcinoma is warty appearing, highly differentiated, variably keratinized and invades in the form of bulbous pegs with a pushing border. There is minimal atypia, abundant eosinophilic cytoplasm, normal mitotic figures and no increased p53 or p16 staining. Using these criteria, lesions with prominent koilocytotic atypia and HPV positivity are better classified as giant condyloma

WHO, 2014
Verrucous Carcinoma of the Vulva

Å Differential diagnosis
  ï Warty squamous cell carcinoma of usual type
  ï Giant condyloma

Å p16 immunostaining
  ï Positive in high-risk HPV-associated carcinoma
  ï Negative in non- verrucous non-HPV-associated carcinoma
  ï Negative in giant condyloma
  ï So of limited use

Å HPV typing
  ï Giant condyloma and usual type SCC both positive (low and high risk HPV respectively)
  ï Does not distinguish between non-HPV-related usual type SCC and verrucous carcinoma
<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Location</th>
<th>Original diagnosis</th>
<th>Consensus diagnosis</th>
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</tbody>
</table>

From del Pino M et al Mod Pathol 2012; 25: 1354-63
Verrucous Carcinoma of the Vulva

- Difficult diagnosis
- p16 immunostaining helpful if positive as indicates HPV-driven carcinoma
- p16 does not distinguish between giant condyloma and verrucous carcinoma
- HPV typing can help to identify giant condyloma (HPV 6, 11 positive)
- In most cases, diagnosis is morphological
VIN can arise via HPV-related and non-HPV-related pathways.

Two morphological types of VIN are recognised: usual-type VIN (uVIN) and differentiated type VIN (dVIN). The WHO recommends replacing the term uVIN with squamous intraepithelial lesion (SIL).

Although uVIN is typically associated with HPV infection, and dVIN is not, this relationship is not clear-cut.
Summary

Å TP53 mutation has been associated with dVIN but, again, this relationship is not clear-cut.

Å There is a case for classifying VIN lesions on the basis of their association with HPV.

Å Specific markers of non-HPV-associated VIN are needed, not only to distinguish it from HPV-associated VIN, but also to distinguish it from non-neoplastic squamous hyperplasia.

Å Verrucous carcinoma can be difficult to distinguish from non-HPV-related usual-type SCC, and from giant condyloma