HPV-Independent Vulvar Squamous Cell Carcinoma and Differentiated VIN

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Dr. Anthony Karnezis declares he/she has no conflict(s) of interest to disclose.

Objectives - Understand the Clinicopathological Features of HPV-Independent VSCC

- Utility and limitations of morphology and p16 IHC in determining HPV status
- Clinical behavior by HPV status
- Difficulties in diagnosis of dVIN and the use of p53 IHC

Case Presentation

- 73 year old woman with peri-citloral thickening

[Images of histological sections]
Diagnosis

- Moderately differentiated keratinizing SCC arising in a background of dVIN
- Extensive lichenoid infiltrate with reactive epithelial atypia

<table>
<thead>
<tr>
<th></th>
<th>HPV (1/3rd)</th>
<th>Non-HPV (2/3rd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Fourth to sixth decade</td>
<td>Sixth to ninth decade</td>
</tr>
<tr>
<td>Etiology</td>
<td>High-risk HPV (HPV16 &gt;&gt; HPV33, HPV18)</td>
<td>Chronic inflammation (lichen sclerosus)</td>
</tr>
<tr>
<td>Precursor</td>
<td>HSIL (uVIN)</td>
<td>dVIN</td>
</tr>
<tr>
<td>Morphology</td>
<td>Basaloid, warty, koilocytic change</td>
<td>Keratinizing</td>
</tr>
<tr>
<td>Biomarker expression</td>
<td>p16 overexpression</td>
<td>Abnormal p53 expression (~2/3rd)</td>
</tr>
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Predict HPV: p16 negative
Predict non-HPV: p16 positive
Confirmed by HPV PCR
**p16 IHC – Marker of High-Risk HPV in the Appropriate Clinical Context**

- Marker of inactivation of RB1 tumor suppressor
  - HPV E7
  - RB1 mutation
- **Positive = diffuse 'block' pattern nuclear and cytoplasmic staining of basal and parabasal epithelial cells**
- HPV PCR or HPV ISH for discordant or equivocal results

**Positive p16 – assess (para)basal cells**

- HPV positive confirmed by HPV PCR

**Prognostic Significance of HPV Status**

- **Prognostic: worse prognosis for HPV-negative tumours**
  - Ansink Gynecol Oncol 1994
  - Monk Obstet Gynecol 1995
  - van de Nieuwenhof Cancer Epidemiol Biomarkers Prev 2005
  - Lindell Gynecol Oncol 2010
  - Dong AJSP 2015
  - Lee Gynecol Oncol 2016
  - Hay / Low Gent Tact Div 2016
  - *Afs, Clarke, unpublished
  - McAlpine Histopathol 2017, in press
- **Not prognostic**
  - Pinto Gynecol Oncol 2004
  - Santos AJSP 2006
  - Alonso Gynecol Oncol 2011

**p16 and Outcome in VSCC**

<table>
<thead>
<tr>
<th>OS</th>
<th>DSS</th>
<th>PFS</th>
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<tbody>
<tr>
<td><img src="image" alt="Graph" /></td>
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*In multivariable analysis, prognostic effect independent of age and stage. McAlpine Histopathol 2017, in press.

**Survival by p16 Status and Surgical Era**

- ![Graph](image)

**Differentiated VIN**

- Precursor of HPV-independent VSCC
- Difficult to diagnose, easy to confuse with benign dermatoses
  - (atypical squamous hyperplasia, 'reactive atypia')
- More likely to progress to cancer than HSIL
HPV-Independent VSCC and dVIN

**HSIL vs. dVIN Progression Free Survival**

<table>
<thead>
<tr>
<th>Time</th>
<th>Survival Probability</th>
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<tbody>
<tr>
<td>0.00</td>
<td>0.75</td>
</tr>
<tr>
<td>0.25</td>
<td>0.50</td>
</tr>
<tr>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>0.75</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Log Rank p < 0.001

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**dVIN Pathology**

- Yang and Hart AJSP 2000
  - Epidermal hyperplasia with parakeratosis
  - Anastomosing rete ridges
  - Dysplastic basal and parabasal cells
  - Enlarged keratinocytes with premature eosinophilic cytoplasmic differentiation
  - Prominent intracellular bridges


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**Molecular Features of dVIN**

- p53 mutation in most cases
- **p53 IHC – score basal and parabasal cells**
  - Increased expression
  - Loss of expression in up to ~25% of cases (Singh AJSP 2016)
  - Normal expression
- Proper interpretation requires:
  - Normal epidermis for comparison
  - Optimized p53 IHC conditions
  - Validated scoring criteria (ongoing)

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**p53 IHC?**

- Degraded upon maturation
- Reactive Atypia
- Adjacent dVIN
- Normal

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**Altypical Squamous Lesions**

- p53 IHC?
  - Other?
Summary – HPV status in VSCC

- Morphology leads to misclassification of HPV status in 15-20%
- p16 is an excellent marker of HPV status
  - Sensitivity = 100%
  - Specificity = 98%
- HPV PCR or HPV ISH for indeterminate clinicopathological results
- Accumulating evidence suggests a possible role for subtyping
  - Informing patient prognosis
  - Predicting recurrence (Bosse, Ordi, unpublished)
  - Identifying potential therapeutic targets in HPV-negative tumors
    - EGFR amplification (Dong AJSP 2016, Liang/Yemelyanova, Poster 1194)

Summary – dVIN

- Difficult to diagnose
- p53 IHC to support morphologic impression of dVIN
- Communicate to clinicians the limitations of current histopathologic evaluation of dVIN
- Future studies
  - Rigorous p53 IHC scoring criteria
  - p53 IHC and prognosis of atypical squamous lesions

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