Dysplasia, Mimics and Other Controversies

Mary S. Richardson, MD
Dept. of Pathology
Medical University of South Carolina
Charleston, SC

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  Mary Richardson, MD

Pseudoneoplasia lesions

• Lesions that simulate malignancy

• A single perspective may cause concern: radiologic, clinical and/or pathologic findings
• May require multidisciplinary approach
65 yo male with 3 week history of non healing ulceration with induration of floor of mouth. History positive for smoking and P/DH.

Traumatic granuloma

50 yo male with resection for squamous cell carcinoma
Nerve

Juxtacoronal organ of Chievitz

54 yo female with gradually increasing intranasal mass and occasional epistaxis
45 yo male with painless lesion of the tongue with bleeds occasionally
Granular cell tumor

Pseudoepitheliomatous hyperplasia
Figure 1
General incidence trends of head and neck squamous cell carcinoma (HNSCC) as a function of yearly cigarette consumption. In the United States, the overall incidence of HNSCC over the past 50 years has paralleled yearly annual cigarette consumption, with a peak incidence in the 1970s. A distinct divergence from this trend has been observed among white males under 50, in whom the incidence of oropharyngeal carcinoma (red arrow) has been on the rise since the early 1970s.
Dysplasia “disordered growth”

- Abnormality in maturation of cells within a tissue above the basement membrane

- Development of cytological atypia within cells

- Change in understanding:
  “pre-cancerous lesion” ➔ “potentially malignant disorder (PMD)”
Clinical management

What do we know the natural history of dysplasia?

- Dysplasia is often seen clinically as leukoplakia (1-17%), erythroplakia (~50%)
- Patients with oral dysplasia have a greater risk of developing cancer
- Meta-analysis showed higher rate of transformation in oral dysplasia not treated surgically vs excised (14.6% vs 5.4%)
- Recurrence rates range from 10% to 34% even after excision
### Epithelial precursor lesion classification schemas

<table>
<thead>
<tr>
<th>Oral epithelial dysplasia</th>
<th>Squamous Intraepithelial Neoplasia (SIN)</th>
<th>Squamous Intraepithelial lesions (Ljubljana System)</th>
<th>WHO 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial hyperplasia</td>
<td>n/a</td>
<td>Simple hyperplasia</td>
<td>Low grade dysplasia</td>
</tr>
<tr>
<td>NIL dysplasia</td>
<td>SIN 1</td>
<td>Basal/Paranuclear hyperplasia</td>
<td>High grade dysplasia</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
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</tr>
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<td>Severe dysplasia</td>
<td>SIN 3</td>
<td>Carcinoma in situ</td>
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Modified from WHO 2005 & WHO 2017

### WHO 2017

#### Criteria for Diagnosing Dysplasia

**Low grade**

- **Architectural Disturbances**
  - Normal epithelial stratification: transition of basal cells with perpendicular orientation to basement membrane
  - Spinous layer: may be increased in thickness
  - Basal/parabasal layer spectrum of change is 2-3 unchanged layers to augmentation of the lower half of the epithelium

- **Cytology**
  - Normal nuclear size and shape
  - Rare mitoses
  - Few dyskeratotic cells

**High grade**

- **Architectural Disturbances**
  - Abnormal maturation
  - Irregular epithelial stratification and polarity of basal cells
  - Two subtypes: keratinizing (spinous-type) and non-keratinizing (basal cell-type)
  - Increased number of mitoses beyond cells of basal one third of the epithelium
  - Formation of irregular tear drop rete ridges with intact basement membrane

- **Cytology**
  - Abnormal nuclear size and shape
  - Cellular pleomorphism
  - Increased nuclear to cytoplasmic ratio
  - Increased mitoses at or above suprabasal layer
  - Dyskeratotic and apoptotic cells are frequent throughout the epithelium
Criteria for Diagnosing Dysplasia

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Keratinizing dysplasia features

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Non-Keratinizing Dysplasia - Cervix Progressive

Classification System

- Dysplasia
  - Mild Dysplasia
  - Moderate Dysplasia
  - Severe Dysplasia
  - Carcinoma in Situ

- Classification
  - Low Grade
  - Intermediate
  - High Grade

- Histologic
  - Low Grade Squamous Intraepithelial Lesion (LSIL)
  - High Grade Squamous Intraepithelial Lesion (HGSIL)
Cervical non-keratinizing dysplasia

Keratinizing Dysplasia UADT-spontaneous

Mild

Moderate

Severe

Table 4.3: Diagnostic criteria for epithelial dysplasia, adapted from Bynes et al. (146)

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<thead>
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<th>Cytological changes</th>
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<tbody>
<tr>
<td>Loss of polarity of basal cells</td>
<td>Abnormal nuclear shape</td>
</tr>
<tr>
<td>Drop-shaped nuclei</td>
<td>Abnormal variation in cell size</td>
</tr>
<tr>
<td>Reduced number of mitotic figures</td>
<td>Abnormal variation in cell size</td>
</tr>
<tr>
<td>Premature keratinization in single cells</td>
<td>Increased N/C ratio</td>
</tr>
<tr>
<td>Keratin pearls within cell lumens</td>
<td>Hyperchromasia</td>
</tr>
</tbody>
</table>

Table 4.4: Grading systems for epithelial dysplasia

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<th>Grade of dysplasia</th>
<th>Binary system</th>
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<td>Severe dysplasia</td>
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The cut-off point between low-grade and high-grade dysplasia, as suggested by Wani et al. (1988), is four architectural and five cytological changes [see Table 4.3, irrespective of the level within the epithelium. According to Blandford and Putman (1972), a subset of four architectural and four cytological changes may mirror microscopic characterization.
Epithelial precursor lesion classification schemas

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- Cytology
  - Normal nuclear size and shape
  - Rare mitoses
  - Few dyskeratotic cells

Hyperplasia with hyperkeratosis
WHO 2017 Criteria for Diagnosing Dysplasia

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- Cytology
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  - Dyskeratotic and apoptotic cells are frequent throughout the epithelium
Current Dilemmas for Clinicians

- Treatment options are limited, largely unproven
- Limited in ability to predict accurately which lesions will progress
- Overtreatment—unnecessary morbidity
- No consensus on appropriate follow up
Fig. 5 Survival curve (to invasive carcinoma) for patients with oral dysplasia


Index case

Table 4B: Diagnostic criteria for oral dysplasia, adapted from Bains et al. (148)

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<th>Cytological changes</th>
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<tbody>
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<td>Irregular epithelial stratification</td>
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<tr>
<td>Drop-shaped nuclei and巨型 nucleus</td>
<td>Abnormal variation in cell size</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>Increased nuclear:cytoplasm ratio</td>
</tr>
<tr>
<td>Premature keratinization in basal cells</td>
<td>Koilocytic figures</td>
</tr>
<tr>
<td>Keratin pearls within nuclear clefts</td>
<td>Increased number and size of nuclei</td>
</tr>
<tr>
<td>Loss of epithelial cell cohesion</td>
<td>Hyperchromasia</td>
</tr>
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Table 4A: Grading systems for epithelial dysplasia

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</thead>
<tbody>
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The cut-off point between low-grade and high-grade dysplasia, as proposed by Scan C et al. (1991), is four architectural and five cytological changes (see Table 4B), irrespective of the level within the epithelium. According to Bains LM et al. (1992), a subcellular level of four architectural and four cytological changes may indicate dysplasia.
Keratinizing Dysplasia: surface keratosis, dyskeratosis, pre-mature keratin "pink cell change".

Downward small complex "clubbing" epithelial pegs
Dysplasia caveats

- Pseudoepitheliomatous hyperplasia has bulbous rete, an etiologic agent may be present
- Tangential sections may cause a faulty diagnosis-need to carefully review
- Gland-duct extension is not invasion
- Parakeratosis and keratosis at certain sites may be abnormal (the oral cavity vs larynx)

Differential Diagnosis
Dysplasia

- Hyperplasia-thickened epithelium due to increased number of cells>10 cells thick, may be associated with subjacent granular cell tumor
- Regeneration-proliferating epithelium with features of basal and para basal cells lacking surface maturation
- Repair-epithelial atypia noted immediately adjacent an inflammatory reaction or ulcer
- Reactive changes-downward proliferation of epithelium regularity and but lacking complexity
Differential Diagnosis*

Dysplasia

- Intermediate epithelium of a squamo-ciliary junction- larynx, sinonasal tract
- Irradiation changes- enlarged nucleus and cytoplasm, note adjacent vessels often contain enlarged endothelial cells, connective tissue alterations
- Laser injury- adenoid dysplasia
- Necrotizing sialometaplasia- squamous hyperplasia within seromucous gland ducts with infarcted acini and retention of lobular architecture
Lichen planus vs Dysplasia vs "Lichenoid dysplasia"

Features of Lichen Planus:
Band-like lymphocytic inflammation
Bilateral or multifocal lesions
Dysplasia or atypia is absent
Lichen planus

Shear, M, et al, Cancer 1980; 46

Verrucous hyperplasia

VH
Proliferative verrucous leukoplakia (PVL)
Proliferative verrucous leukoplakia

Non-keratinizing squamous cell carcinoma in situ of upper aerodigestive tract
Key Points
Dysplasia

• Epithelium confined above the basement membrane which shows marked architectural disorder of basal to surface maturation and cytologic alteration
• Nuclear size and chromasia is inappropriate by cellular location within the epithelium
• Architectural alterations – irregular maturation, lack of nuclear polarity, dyskeratosis, increased cellularity
• Cytological alterations – increased nuclear to cytoplasm ratio, nuclear hyperchromasia, nuclear pleomorphism, increased and/or abnormal mitotic figures
• Precursor lesions may be self limiting and reversible while others may persist