Oral mucosal dysplasia vs reactive atypia

Benign hyperplasia vs verrucous carcinoma

Alison M Rich, Feb 2019
ORAL SQUAMOUS CELL CARCINOMA (OSCC)

‘A carcinoma with squamous differentiation arising from the mucosal epithelium’ WHO 2017

• Must be distinguished from oropharyngeal carcinoma
Oral Potentially Malignant Disorders

All clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa’ WHO 2017

- Erythroplakia
- Erythroleukoplakia
- Leukoplakia
- Oral submucous fibrosis
- Dyskeratosis congenita
- Smokeless tobacco keratosis
- Palatal lesions associated with reverse smoking
- Chronic candidosis
- Lichen planus
- Discoid lupus erythematosus
- Syphilitic glossitis
- Actinic keratosis (lip only)
Leukoplakia

‘white plaques of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer’  Warnakulasuriya et al 2007 J Oral Pathol Med
How can we predict the behaviour of this lesion?

- Clinical examination
- BIOPSY to assess presence or absence of dysplasia

BUT

- Is it ‘true’ dysplasia or reactive atypia?
- How is dysplasia best assessed and communicated?
- Does the presence of ‘true’ dysplasia imply malignant transformation?
- What adjuncts are available to predict prognosis?
Assessment of clinical features: 

**COLOUR**

- ↑ redness: ↑ risk of transformation
- ? association with candidal infection
Assessment of clinical features:

**TEXTURE**

- homogeneous: little risk of transformation
- non-homogenous: ↑risk of transformation
Assessment of clinical features: SITE

- FOM: ↑ risk of transformation
Assessment of Biopsy

Faculty of Dentistry
Te Kaupeka Pūniho
New Zealand’s National Centre for Dentistry
‘True’ dysplasia vs reactive atypia

• Clinical correlation
  – Proximity to ulcer
  – Physical trauma
  – Candidal infection
  – Lichen planus/lichenoid reaction

• Degree of dysplasia
  – Extent
  – Features
Clinical correlation: ulcer
Clinical correlation: fibrous hyperplasia
Clinical correlation: candidal infection
Clinical correlation: lichen planus/lichenoid reaction
• Often mild dysplasia in association with an interface mucositis
• Which came first?
• Check
  – Clinical features: bilateral? buccal mucosa involved?
  – Basal cell lysis
• Be cautious and recommend review ‘sufficient evidence that the presence of mild dysplasia in OLP is indicative of malignant potential’ Raj et al. Medical Hypotheses 2018
### Table 1. Epithelial dysplasia: criteria for diagnosis

<table>
<thead>
<tr>
<th>Architectural features</th>
<th>Cytologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular epithelial stratification</td>
<td>Abnormal variation in nuclear size (anisonucleosis)</td>
</tr>
<tr>
<td>Loss of basal cell polarity</td>
<td>Abnormal variation in nuclear shape (nuclear pleomorphism)</td>
</tr>
<tr>
<td>Drop-shaped rete ridges</td>
<td>Abnormal variation in cell size (anisocytosis)</td>
</tr>
<tr>
<td>Increased number of mitotic figures</td>
<td>Abnormal variation in cell shape (cellular pleomorphism)</td>
</tr>
<tr>
<td>Abnormally superficial mitoses</td>
<td>Increased nuclear/cytoplasmic ratio</td>
</tr>
<tr>
<td>Premature keratinization in single cells</td>
<td>Atypical mitotic figures</td>
</tr>
<tr>
<td>(dyskeratosis)</td>
<td></td>
</tr>
<tr>
<td>Keratin pearls within rete ridges</td>
<td>Increased number and size of nucleoli</td>
</tr>
<tr>
<td>Loss of epithelial cell cohesion</td>
<td>Hyperchromasia</td>
</tr>
</tbody>
</table>

Adapted from Reibel et al.⁴
Degree of dysplasia: extent

WHO 2017
• Mild dysplasia
• Moderate dysplasia
• Severe dysplasia

Binary grade
• Low-grade dysplasia
• High-grade dysplasia (4 architectural and 5 cytological features, Speight et al. 2018)
Most discriminatory:

- Drop-shaped rete ridges
- Mitoses above basal layer
- Loss of basal cell polarity

Kujan et al 2007 Oral Oncol.; Muller 2018 OOO
Does dysplasia imply malignant transformation?

- 10 year prospective study of 1357 patients with biopsy proven PMODs in UK
- 35 (2.6%) developed OSCC

- Patients with severe dysplasia > risk of malignant transformation than those with no dysplasia, independent of other variables (Warnakulasuriya et al., 2011, J Oral Pathol Med.)

- Similar trend with lower grades of dysplasia but less certainty

- Reports of lack of association between dysplasia grading and malignant transformation (Dost et al 2014, OOO)
Clinical adjuncts: Toluidine blue
Toluidine blue

- Cheap and simple
- Used for yrs to detect occult oral mucosal lesions and/or to demarcate extent of lesion
- Quite good at detecting oral carcinomas i.e. shows good sensitivity and reasonable specificity

BUT

- Subjective interpretation ? how blue
- Less sensitive and specific in detecting lesions with dysplasia
- Meta-analysis of 77 publications* ⇒ toluidine blue was positive in ~50% dysplastic lesions and ~50% non-specific ulcers etc. were positive

*Lingen et al., 2008, Oral Oncol
Clinical adjuncts: Tissue fluorescence imaging (VELscope)

- Autofluorescence viewed after application of blue excitation light
- Based on principle that autofluorescence is altered in abnormal tissues (viewed as dark regions) compared with normal tissue (pale green autofluorescence)
Tissue Fluorescence Imaging
Tissue Fluorescence Imaging

• Does appear to distinguish lesions from healthy mucosa*

• VELscope system demonstrated high sensitivity and specificity identifying occult lesional tissue, using dysplasia as gold standard**

• Useful to detect margins*

*De Veld et al., 2005, Oral Oncology
** Onizawa et al., 1996, Cancer Lett.
Laboratory adjuncts: Brush biopsy
Brush biopsy

- Reported as positive when atypical cells found
- Scalpel biopsy must follow

- Good sensitivity and specificity with clinically detected high-risk lesions (BUT would biopsy them anyway)*

- Less accurate and ↑ false positives in low-risk lesions*

Fedele, 2009 Head & Neck Oncol
Laboratory Adjuncts: DNA ploidy

• Assessment relatively easy

• Oral SCC often have aneuploid cell population

• Ploidy status prognostic factor for SCC

• ? Role in predicting behaviour of potentially malignant lesions but recent studies confirming value
Loss of Heterozygosity (LOH)

- LOH is loss of genomic material in one of a pair of chromosomes
- Deleted regions likely to contain TSG
- LOH at 3p common in oral SCC and potentially malignant oral lesions, LOH at 17p (p53), LOH at 9p early event
Analysis of multiple variables

- 10 yr prospective study patients with PMODS by patient characteristics, histology and biomarkers  n=61

Significant predictors of malignant transformation were:

- **Patient characteristics:** cancer history
- **Histology:**
- **Biomarkers:** ploidy, p53, LoH

Cancer history 0.13
Histology 0.001
Ploidy, p53, LOH 0.012

Lee *et al.*, 2000, Clin Cancer Res.
Analysis of multiple variables

- 4 yr prospective study patients with PMODS by patient characteristics and histology, n=91

Significant predictors of malignant transformation were:
- Non-smoking status
- Site
- Non-homogeneous appearance
- Size of lesion
- Dysplasia grade p=0.06

Ho et al., 2012, Oral Oncol.
Saliva

Oral Fluid NanoSensor Test,
Handheld, automated, easy-to-use integrated system that will enable simultaneous and rapid detection of multiple salivary protein and nucleic acid targets

Wong, 2006, JADA
Key Message: Reactive atypia vs true dysplasia

- Clinical correlation
- Clinical review and re-biopsy if necessary
- Potentially ploidy, LoH, p53 status
Verrucous hyperplasia vs verrucous carcinoma
ORAL VERRUCOUS CARCINOMA

A subtype of OSCC which is a ‘well differentiated, non-metastatic variant with pushing superficial invasion, exophytic, lacks atypia, good prognosis; may progress to conventional SCC’ WHO 2017

Histology image from Moutasim et al Diag Histopath. 2017
Verrucous carcinoma

- Buccal mucosa, mandibular gingivae, tongue most commonly affected
- Elderly and ~ equal male: female
- Tobacco-associated
- Not HPV-associated

- Rete ridges broad and long ‘elephant feet’
- Cytologically bland
- No invasion through the basement membrane
- Extension of abnormal rete ridges relative to adjacent epithelium
But what is **VERRUCOUS HYPERPLASIA**?

- **Histological diagnosis**
  - Exophytic
  - No endophytic ‘invasive’ component
  - Rete ridges relatively slender
  - May be dysplastic
  - May progress to OSCC (or VC)

- **Excludes**
  - Proliferative verrucous leukoplakia (PVL)
  - Verrucous hyperplasia associated with betel use
<table>
<thead>
<tr>
<th></th>
<th>Verrucous hyperplasia</th>
<th>Verrucous carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expophytic</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Endophytic</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rete</td>
<td>Slender, anastomosing, at ~ same level of adjacent epithelium</td>
<td>Broad, elongated, extend as broad front deeper than adjacent epithelium- may involve muscle</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Maybe</td>
<td>No (? Papillary SCC)</td>
</tr>
<tr>
<td>Progression</td>
<td>OSCC (sometimes)</td>
<td>OSCC (sometimes)</td>
</tr>
<tr>
<td>HPV associated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oral Mucosal Papillary Carcinoma

‘A variant of OSCC which has ’keratinizing and non-keratinizing types, often arises on the gingiva; better prognosis than conventional OSCC’. WHO 2017

– Some features in common with laryngeal and oropharyngeal papillary carcinoma, but not HP V-related

– Has ‘conventional’ invasion

– Oral mucosal papillary carcinoma occurs in anterior oral cavity, has an exophytic and endophytic invasive component, keratin production, atypia and dysplasia (Fitzpatrick et al 2013 Head Neck Pathol)
Proliferative verrucous leukoplakia

A distinct and aggressive OPMD which is multifocal, has a progressive course and is associated with high recurrence and malignant transformation rates  

WHO 2017

Clinical diagnosis over time
Proliferative Verrucous Leukoplakia Continuum

From Greer et al. J Calif Dent Assoc 1999
Verrucous hyperplasia associated with betel use

REVIEW

Exophytic Verrucous Hyperplasia of the Oral Cavity – Application of Standardized Criteria for Diagnosis from a Consensus Report

Rosnah Binti Zain¹*, Thomas George Kallarakkal¹, Anand Ramanathan¹, Jin Kim², WM Tilakaratne³, Takashi Takata⁴, Saman Warnakulasuriya⁵, Vinay Kumar Hazarey⁶, Alison Rich⁷, Haizal Mohd Hussaini⁷, Ajura Jalil⁸

Abstract

Verruco-papillary lesions (VPLs) of the oral cavity described in the literature involve a spectrum of conditions including squamous papilloma, verruca vulgaris, focal epithelial hyperplasia, condyloma, proliferative verrucous leukoplakia and verrucous carcinoma. A majority of the VPLs are slow growing, benign in nature and have a
45 y/o female with incidental finding of a gingival white patch
55 y/o female, non-smoker, no alcohol intake, presented to local dentist for routine treatment
67 y/o female with asymptomatic white patches on gingivae, palate and buccal mucosa. Non smoker, no alcohol.
52 y/o male with oral mucosal white patches first noticed about five years previously. Ceased tobacco smoking ~ 3 yrs ago, no alcohol.
64 y/o female with ~5 yr history of white/red lesions on right lateral tongue. P
How to distinguish VH, VC, PC

- Clinical features
- Histology
- But not always possible ~ 25% can’t be categorised
- Need to get appropriate message to clinicians- VC and PC need complete local excision with 5mm margin without neck dissection (Moutasim et al 2017)
Key messages

• Adequate biopsy-representative and with border
• Clinical correlation
• Communication with treating clinician
Thank you