Dr. Amirah Alnour

DDS, MSD (oral pathology), Ph.D/ Damascus university

DUPO (Saint Josef University)

MMSc- medical education

Pathology of oral mucosa

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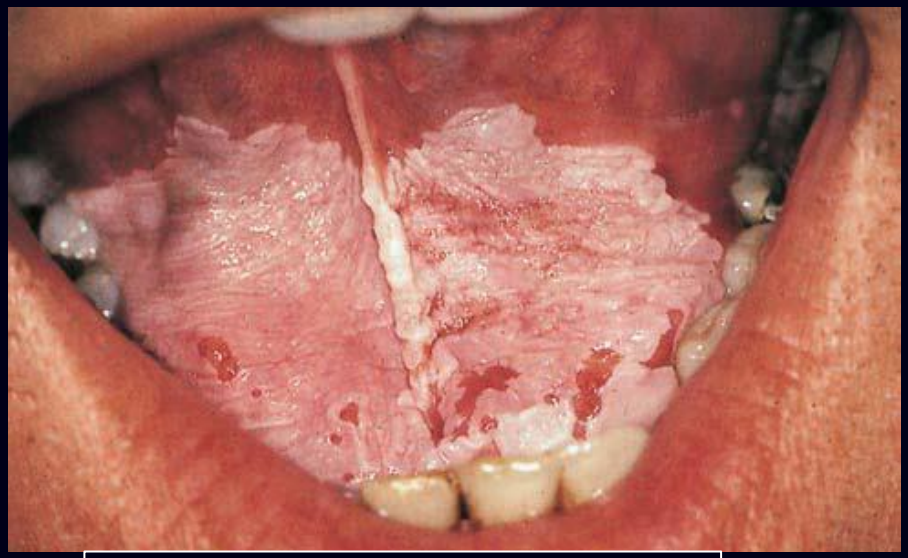
Lecture outlines

- Clinical view of oral lesions
- Oral potentially malignant disorders (OPMDs) & Oral epithelial dysplasia
- HPV- related oral epithelial dysplasia

Clinical classification

1. White lesions
2. Red lesions
3. Black and brown lesions
4. Vesiculobullous Lesions
5. Ulceration lesions
6. Papillary lesions

1. White lesions



Leukoplakia



Hairy Leukoplakia



Lichen planus

2. Red lesions



Sturge-Weber Angiomatosis



Erythematous Candidiasis



Erythroplakia

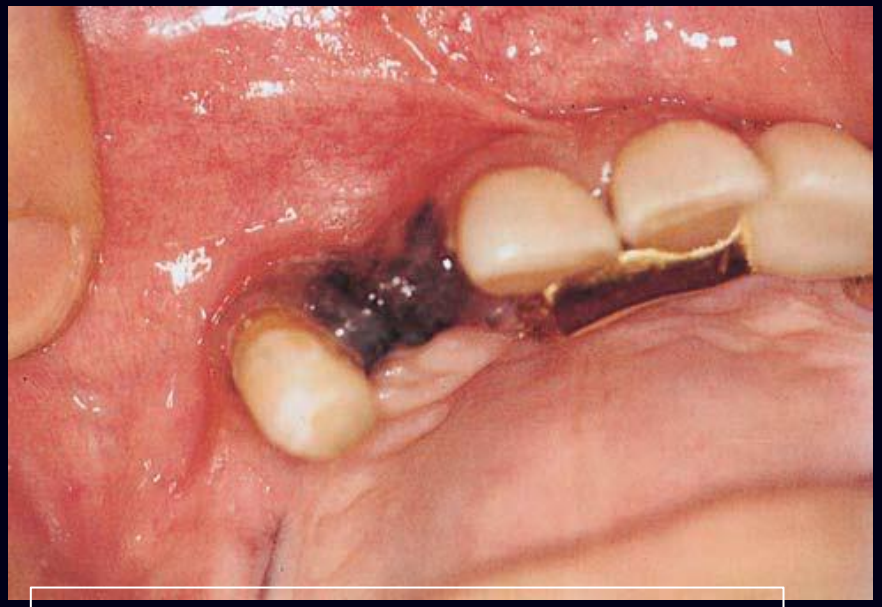
3. Black and brown lesions



Black Hairy Tongue



Peutz-Jeghers Syndrome

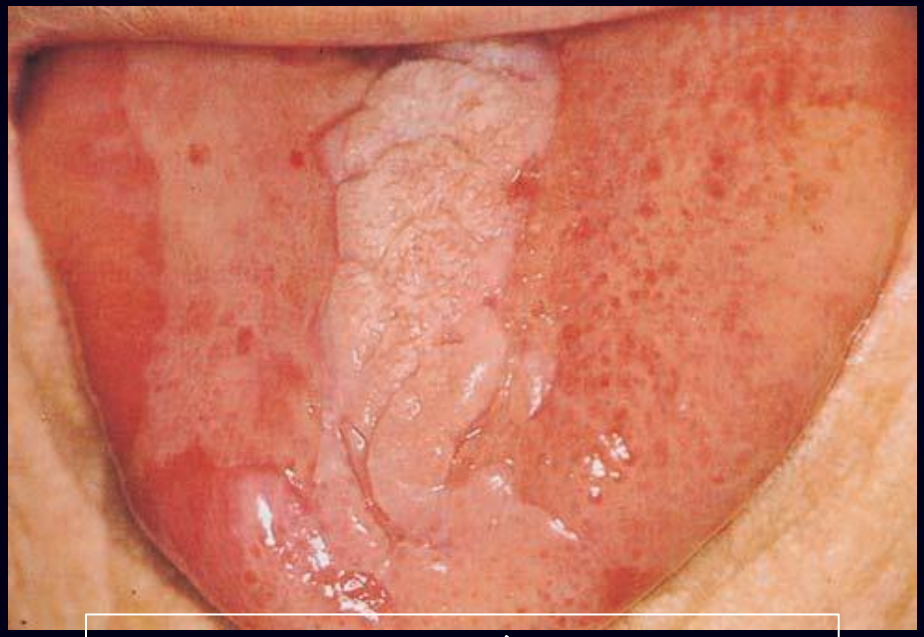


Melanoma

4. Vesiculobullous Lesions

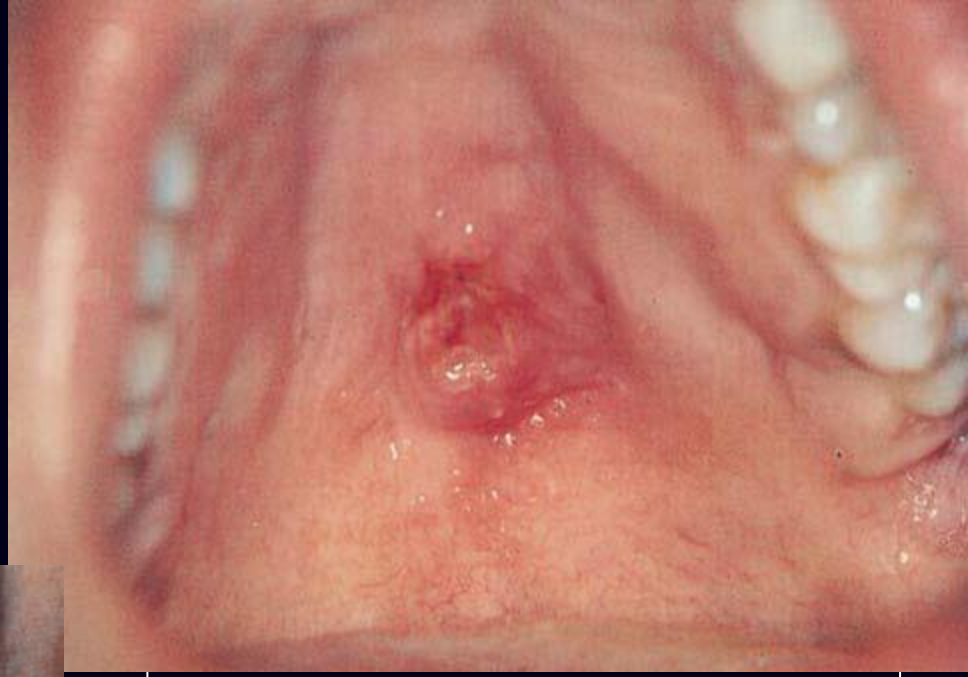


Herpetic Stomatitis



Pemphigus

5. Ulceration lesions



Necrotizing Sialadenometaplasia



Tuberculosis

6. Papillary lesions



Papilloma



Verrucous Leukoplakia

Oral Potentially Malignant Disorders (OPMDs)

OPMDs

Defines a *group* of lesions that carries an increased *risk of cancer* progression.





2017 *World Health Organization* (WHO) definition of OPMDs is:

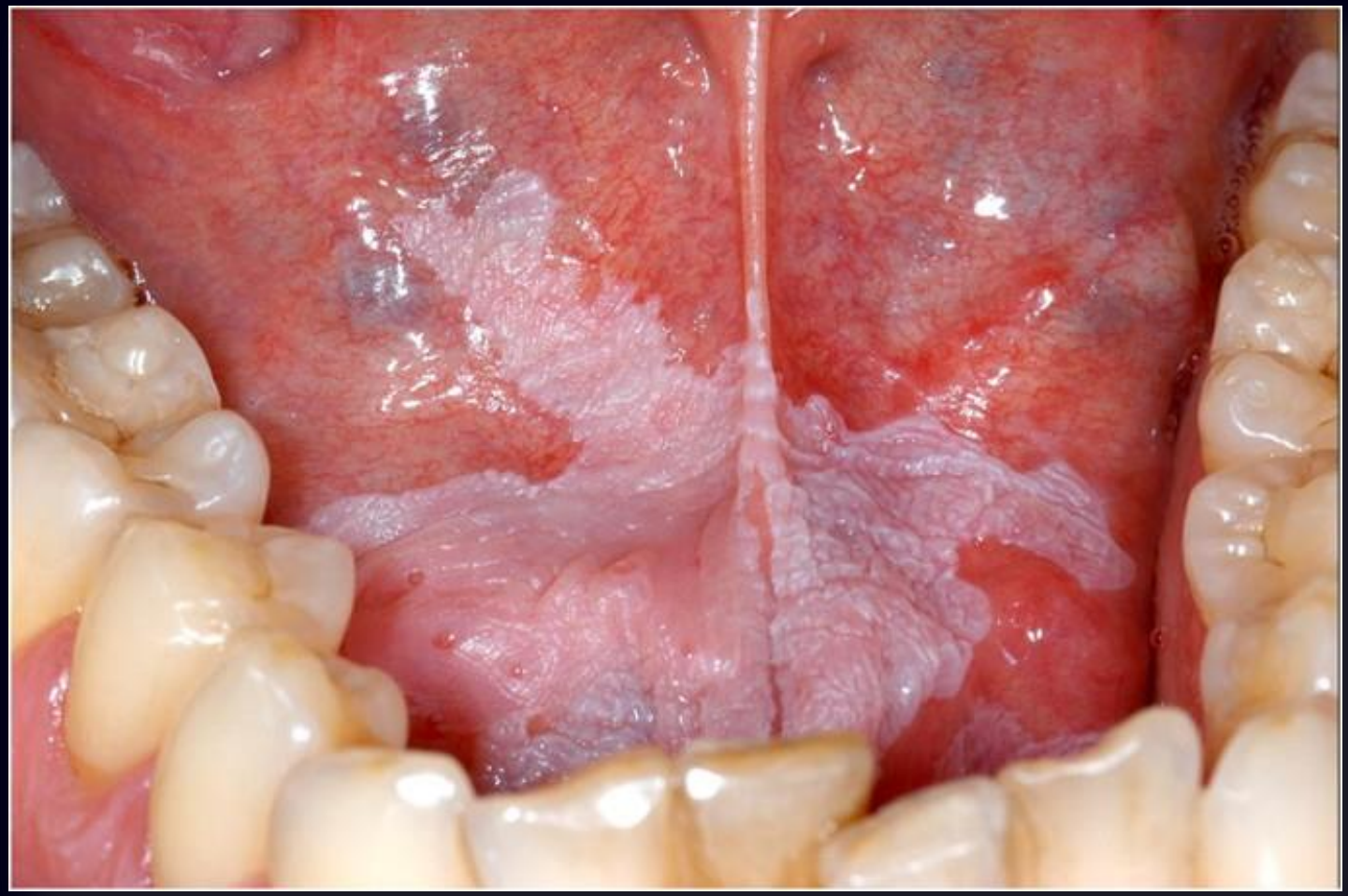
"clinical presentations that carry a *risk of cancer* development in the oral cavity, whether in:

1. a clinically definable precursor lesion
2. clinically normal mucosa.





Oral leukoplakia, the *most common* OPMD, has a 1% prevalence and reported malignant transformation rates of 2% to 5%.



The *2017 WHO definition* of leukoplakia is “white plaques of *questionable risk*, once other specific conditions and *other OPMDs* have been *ruled out*





Other OPMDs include :

1. Erythroplakia,
2. Erythroleukoplakia,
3. Submucous fibrosis,
4. Lesions of reverse smokers,
5. Lichen planus











Rare *inherited genetic syndromes* that are associated with elevated *oral cancer* incidence:

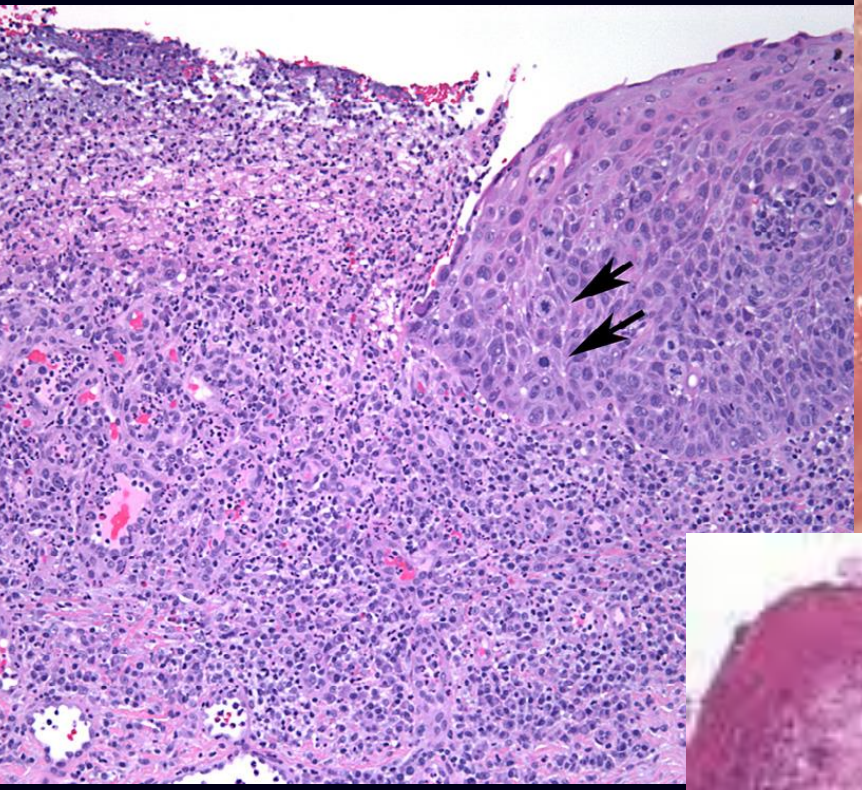
1. Fanconi anemia,
2. Dyskeratosis congenita,
3. Xeroderma pigmentosa

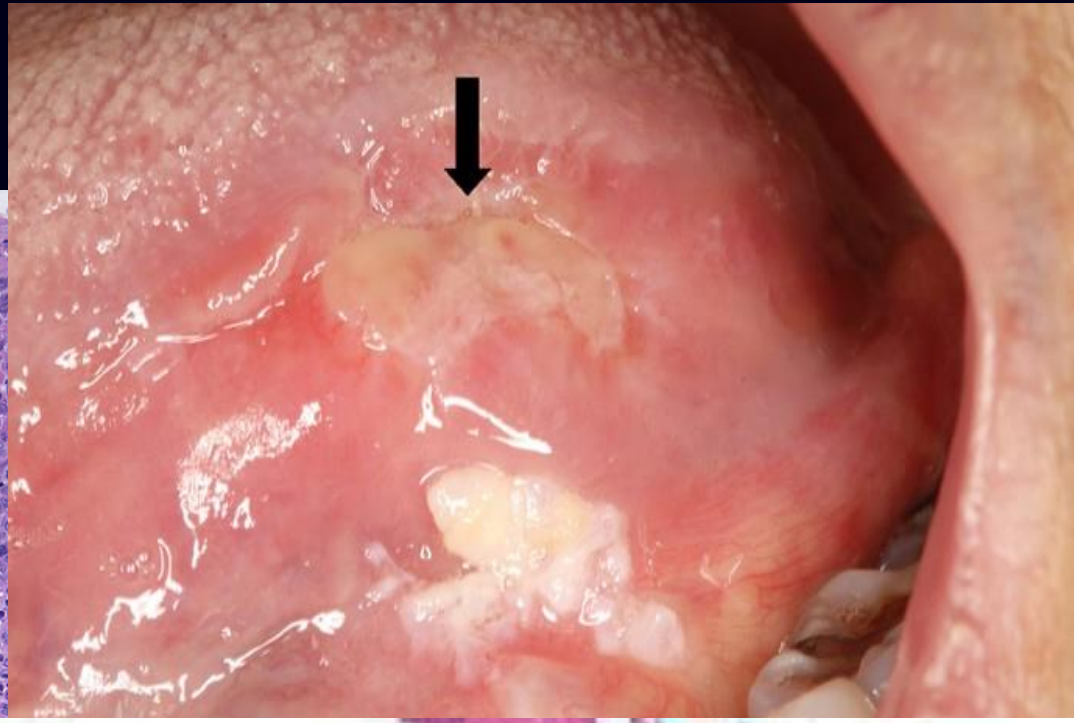


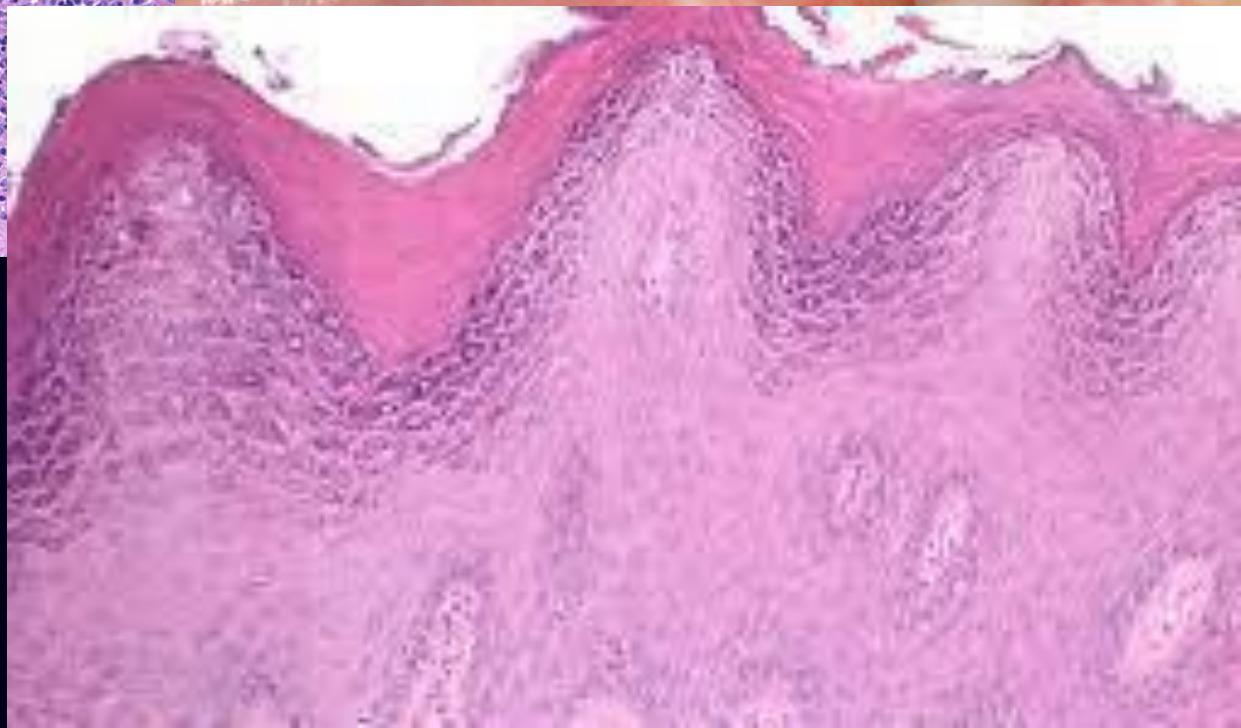


Oral Epithelial Dysplasia

OED

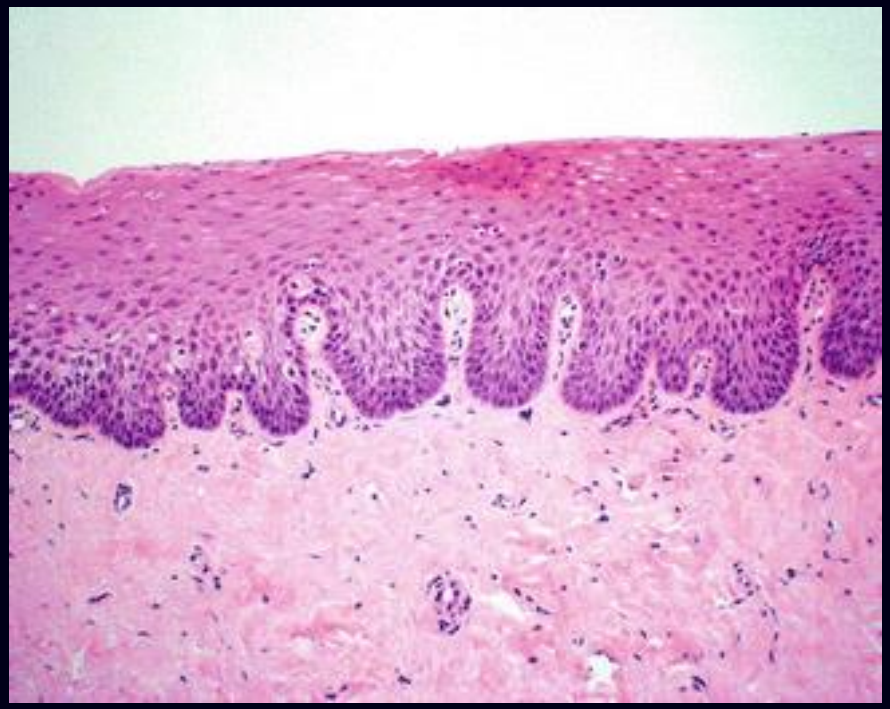


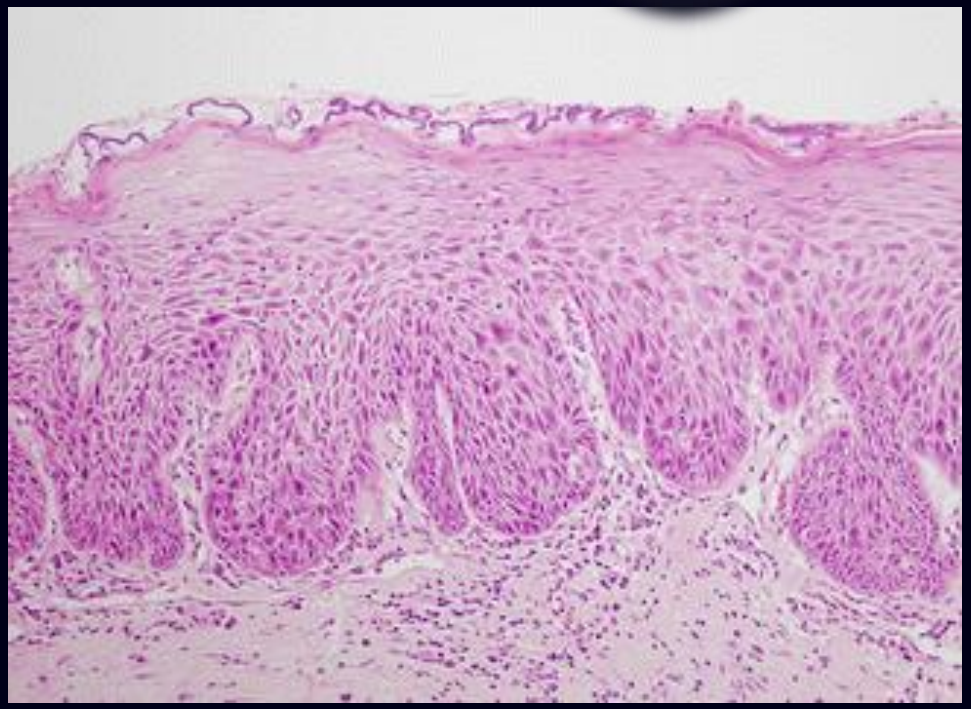




Grading of oral dysplasia suffers from both intrarater variability and interobserver *variability*.







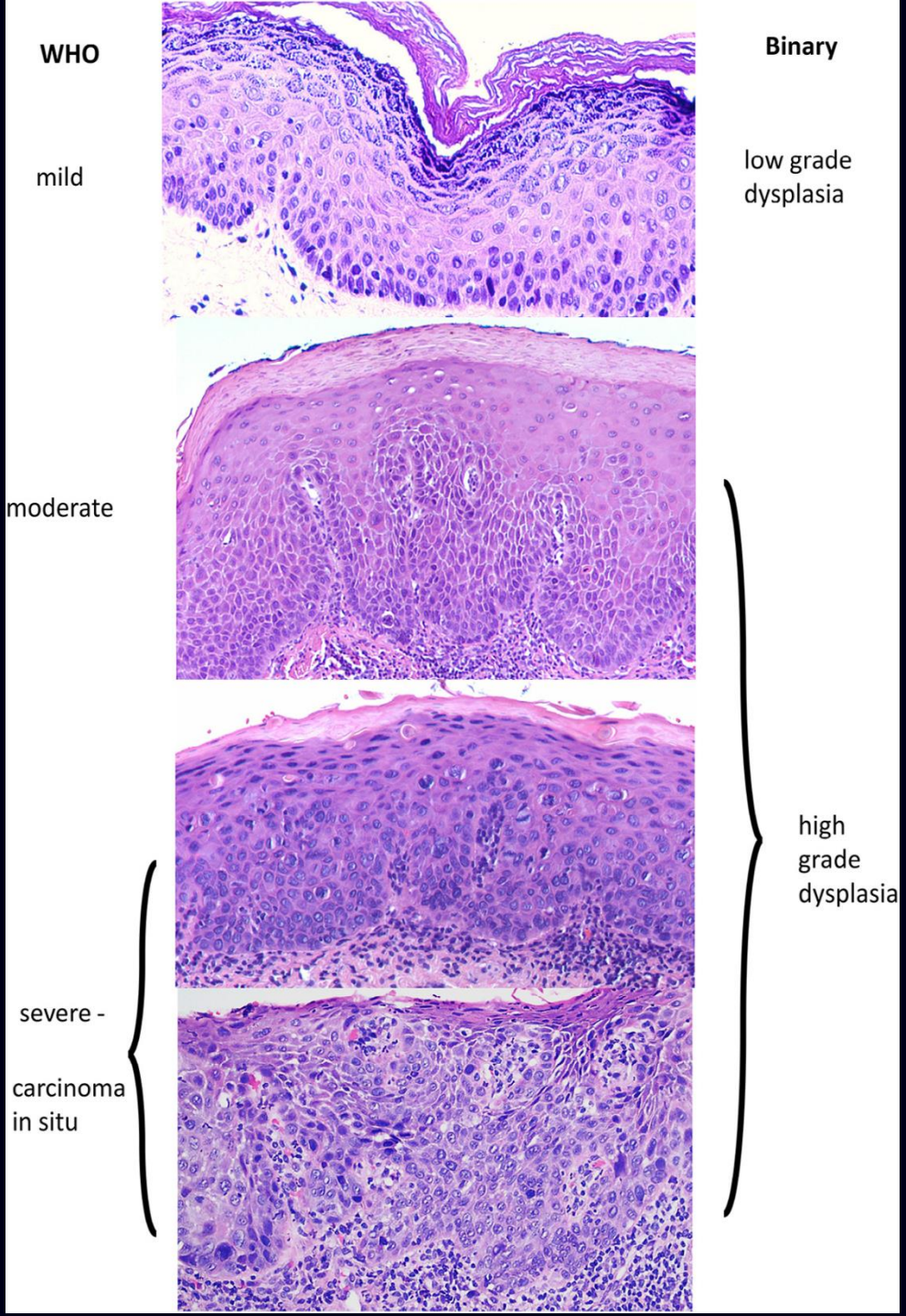
The WHO (2017) grading:

1. Mild dysplasia
2. Moderate dysplasia
3. severe dysplasia

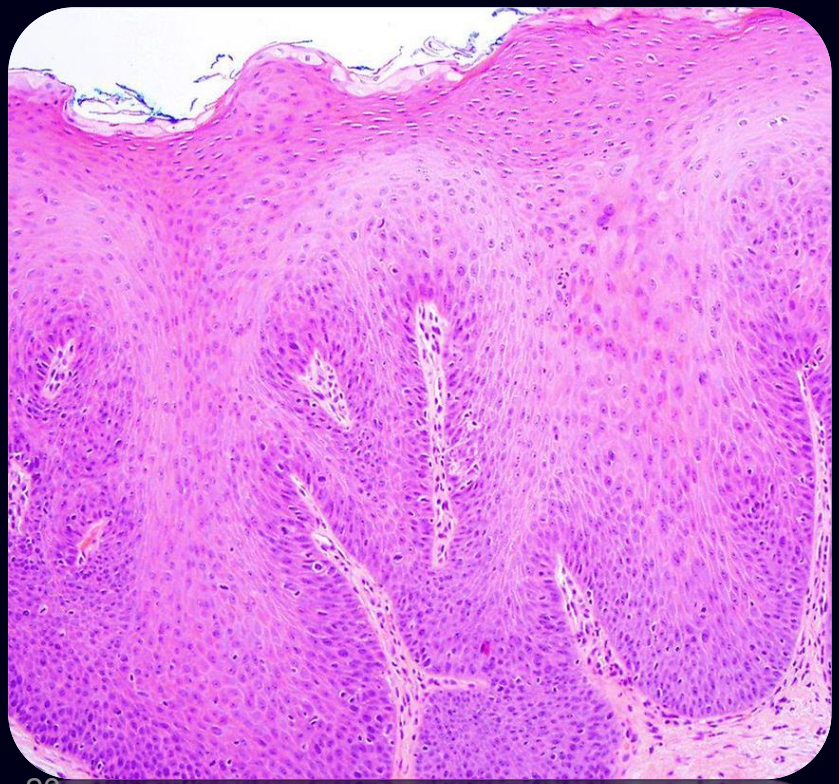
Binary grading system:

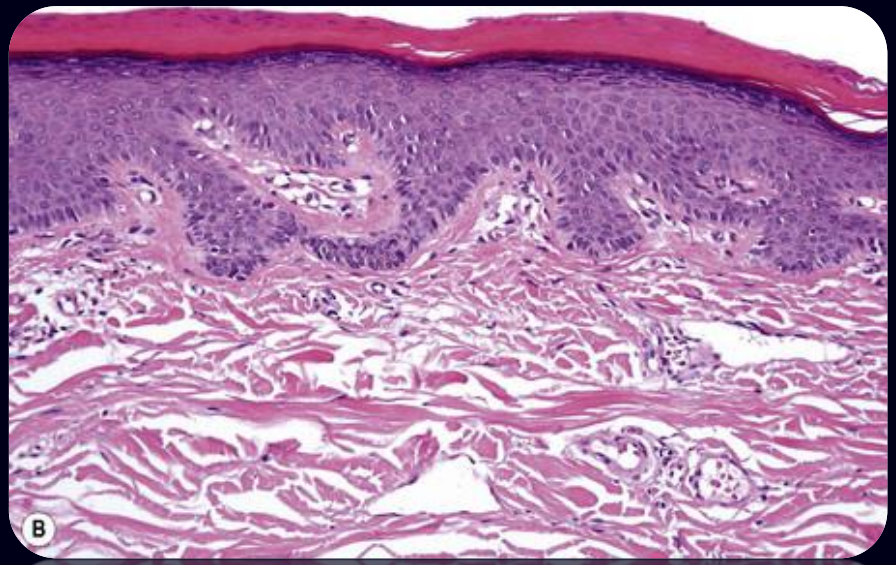
1. Low-grade dysplasias
2. High-grade dysplasias

Carcinoma in situ is synonymous with *severe dysplasia* in this grading system.


WHO
Binary
mild
low grade dysplasia
moderate
high grade dysplasia
severe -
carcinoma in situ

Hyperplasia and/or *hyperkeratosis* without architectural or cytologic atypia is *not considered as OPMDs.*





There are some ***moderate dysplasias*** that may fall into the *low-grade dysplasia* category when using the binary system.

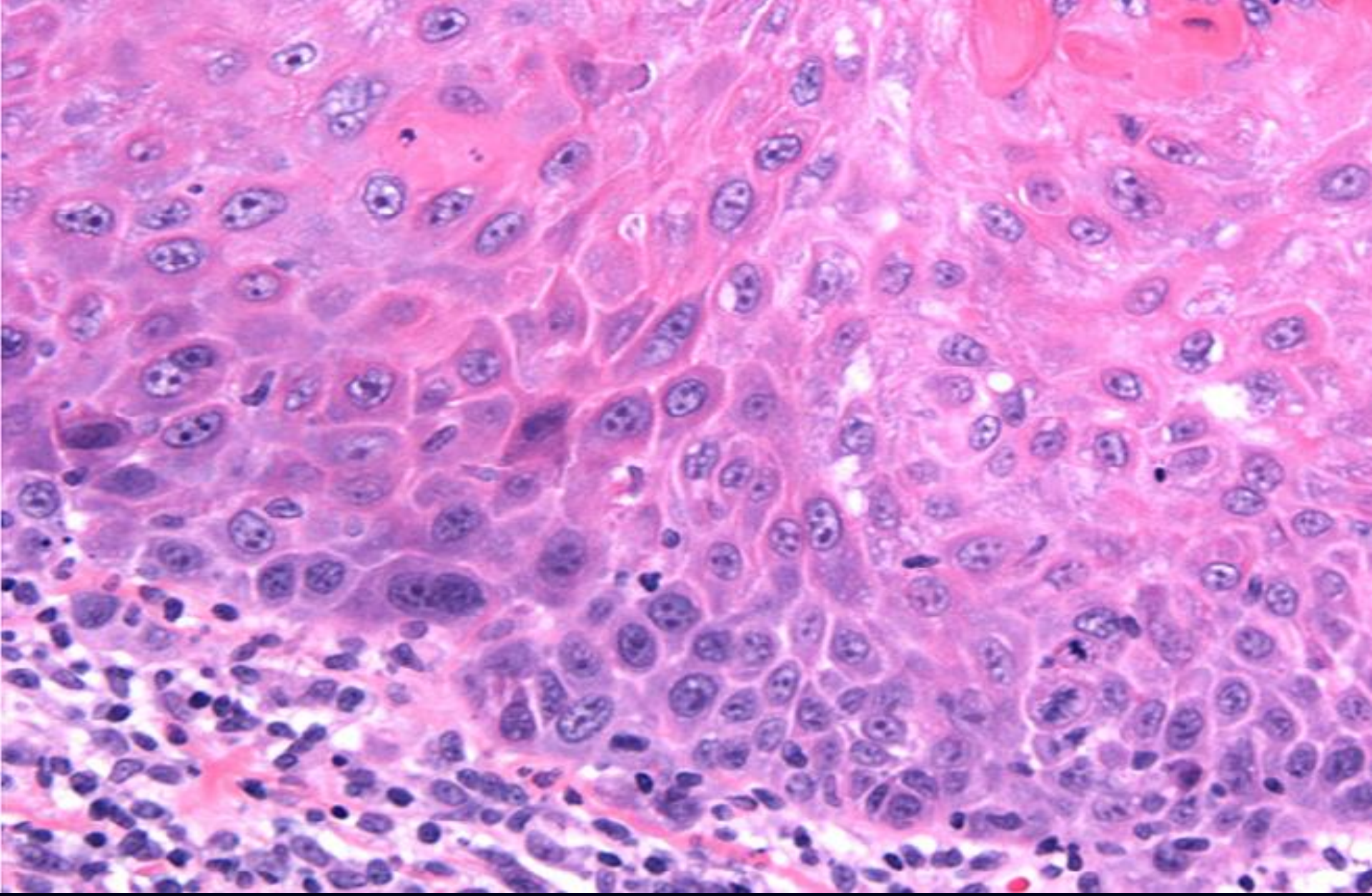
BUT, ***WHO*** has recommended that *more validation* is required before adopting the *binary* system.



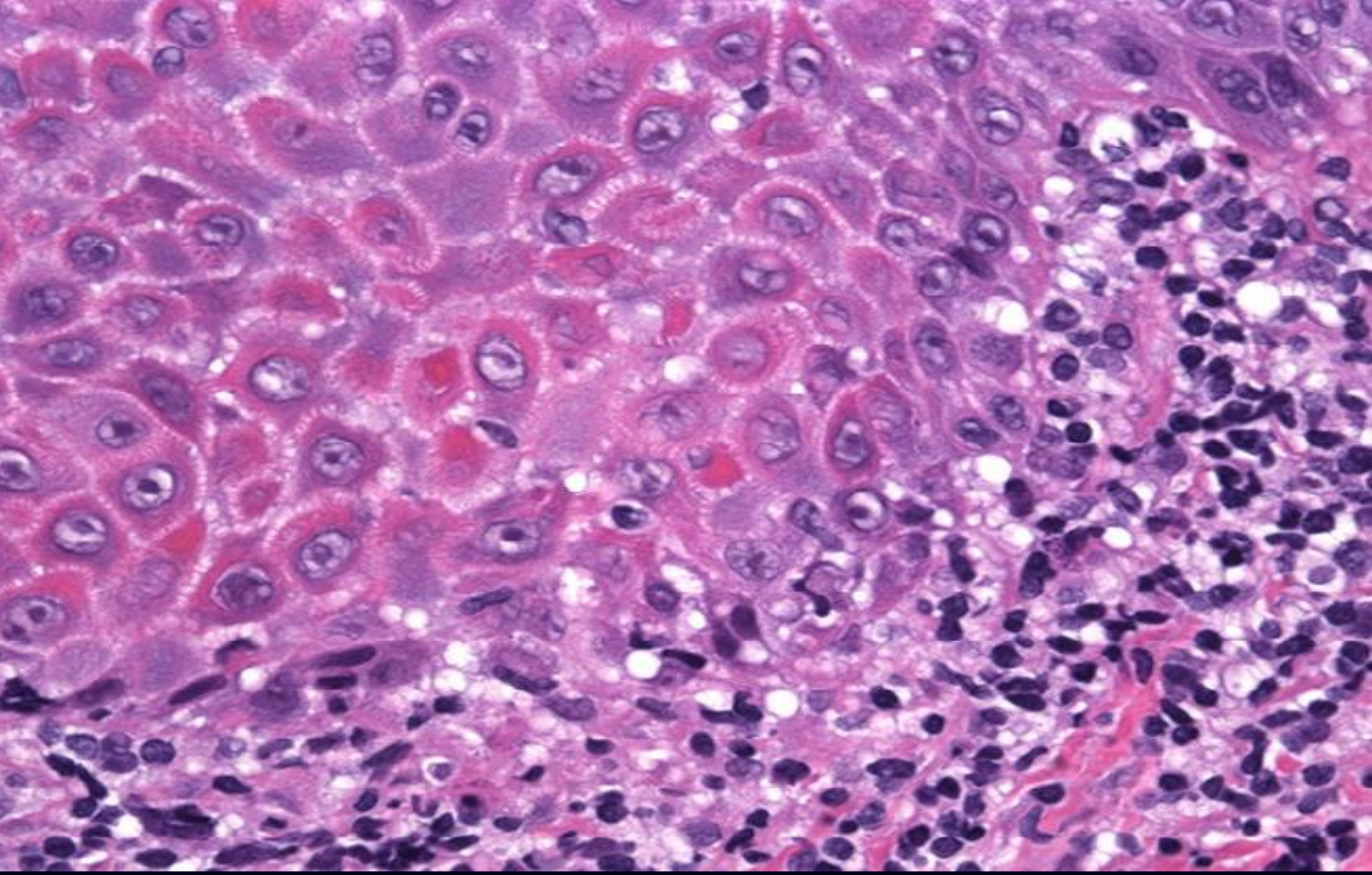
Architectural features	Cytologic feature
Irregular epithelial stratification	Abnormal variation in nuclear size (anisonucleosis)
Loss of basal cell polarity	Abnormal variation in nuclear shape (nuclear pleomorphism)
Drop-shaped rete ridges	Abnormal variation in cell size (anisocytosis)
Increased number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

Note

Severe cytonuclear atypia and dyskeratosis may be presented and restricted to the bottom third of an epithelial surface. Such lesions may give rise to so-called " drop-down carcinomas that seemingly drop from the base of relatively mature bland epithelium without gradual transition.



loss of basal cell polarity



premature keratinization seen in the lower third of the epithelium along with loss of basal cell polarity

Oral Oncology (2006) 42, 987–993

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ORAL ONCOLOGY

Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation

Omar Kujan [a], Richard J. Oliver [a], Ammar Khattab [b], Stephen A. Roberts [c], Nalin Thakker [a], Philip Sloan [a,*]

[a] School of Dentistry, The University of Manchester, Manchester M15 6FH, United Kingdom
[b] Trafford General Hospital Trust, Manchester, United Kingdom
[c] Biostatistics Group, The University of Manchester, Manchester M15 6FH, United Kingdom

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KEYWORDS
Oral epithelial dysplasia;
Grading systems;
Prediction;
Malignant transformation;
Potentially premalignant oral lesions

Summary The aim of this paper is to assess the reproducibility of a novel binary grading system (high/low risk) of oral epithelial dysplasia and to compare it with the WHO classification 2005. The accuracy of the new system for predicting malignant transformation was also assessed. Ninety-six consecutive oral epithelial dysplasia biopsies with known clinical outcomes were retrieved from the Oral Pathology archives. A pilot study was conducted on 28 cases to determine the process of classification. Four observers then reviewed the same set of H&E stained slides of 68 oral dysplastic lesions using the two grading systems blinded to the clinical outcomes. The overall inter-observer unweighted and weighted kappa agreements for the WHO grading system were $K_s = 0.22$ (95% CI: 0.11—0.35), $K_w = 0.63$ (95% CI: 0.42—0.78), respectively, versus $K = 0.50$ (95% CI: 0.35—0.67) for the new binary system. Interestingly, all pathologists showed satisfactory agreement on the distinction of mild dysplasia from severe dysplasia and from carcinoma in situ using the new WHO classification. However, assessment of moderate dysplasia remains problematic. The sensitivity and specificity of the new binary grading system for predicting malignant transformation in oral epithelial dysplasia were 85% and 80%, respectively and the accuracy was 82%. The new binary grading system complemented the WHO Classification 2005 and may have merit in helping clinicians to make critical clinical decisions particularly for the cases of moderate dysplasia. Histological grading of dysplasia using established criteria is a reproducible prognosticator in oral epithelial dysplasia. Furthermore, the present study showed that more consensus scoring on either the degree of dysplasia, assessment of risk or the presence

High-risk lesion defined as:

at *least 4 architectural* changes.

Low-risk lesion defined as:

5 cytologic changes

weaknesses in their proposed grading classification: interobserver *agreement to be similar* in both the *WHO* grading system and their *binary* system

Vol. 115 No. 1 January 2013

The binary oral dysplasia grading system: validity testing and suggested improvement

Paul Nankivell, BA, BMBCh, MRCS,[a,c] Hazel Williams, BDS, FDS, FRCPath, MSc, PhD,[b] Paul Matthews, BSc, FRCPath,[c] Sari Suortamo, FRCPath,[c] David Snead, MBBS, FRCPath,[c] Christopher McConkey, MSc,[d] and Hisham Mehanna, PhD, BMedSc (hons), MBChB (hons), FRCS,[a] Coventry, United Kingdom

Objectives. A binary system is reputed to be superior to the World Health Organization (WHO) system in grading oral

nostic ability over the WHO system. Importantly, it was also reported to improve differentiation of cases of moderate dysplasia into those most or least likely to transform. If true, this has important clinical implications. A workshop coordinated by the WHO Collaborating Center for Oral Cancer and Precancer in the U.K. identified the need for the reproducibility and prognostic ability of this new system to be independently validated. Only 1 study has independently assessed this system, but it neither evaluated the system's reproducibility nor compared its prognostic ability with the existing WHO system.[9]

We had 4 main aims for the present study: first, to validate the prognostic ability of the binary system proposed by Kujan et al. compared with the WHO system and in particular the ability of the binary system to separate moderate dysplasia into high and low risk groups; second, to independently evaluate in a larger cohort the interobserver variability of the binary system compared with the WHO system and establish which features may be contributing to the discrepancies; third, to assess whether the addition of clinical factors to the

Table I. Individual architectural and cytologic features assessed with the WHO grading system for oral epithelial dysplasia

Architecture	*Cytology*
Stratification	Abnormal variation in nuclear size
Loss of polarity	Abnormal variation in nuclear shape
Drop-shaped rete ridges	Abnormal variation in cell size
Mitoses increased	Abnormal variation in cell shape
Abnormally superficial mitoses	Increased nuclear-cytoplasmic ratio
Premature keratinization	Increased nuclear size
Keratin pearls within rete ridges	Atypical mitotic figures
	Increased nucleoli
	Hyperchromatism

from the initial biopsy showing dysplasia were included. To assess the prognostic abilities of the grading systems, only cases with ≥12 months of follow-up were included in this cohort. Clinical data on tobacco and alcohol use along with lesion morphology and site were obtained from patient records. Ethical approval was granted for this study (10/H1210/9) and the research carried out in compliance with the Helsinki

Refined the diagnostic threshold for moderate dysplasia using:

1. A *4 architectural*
2. A *4 cytologic* criteria

Found *less interrater variability* when using the *binary system*, rather than the WHO classification.

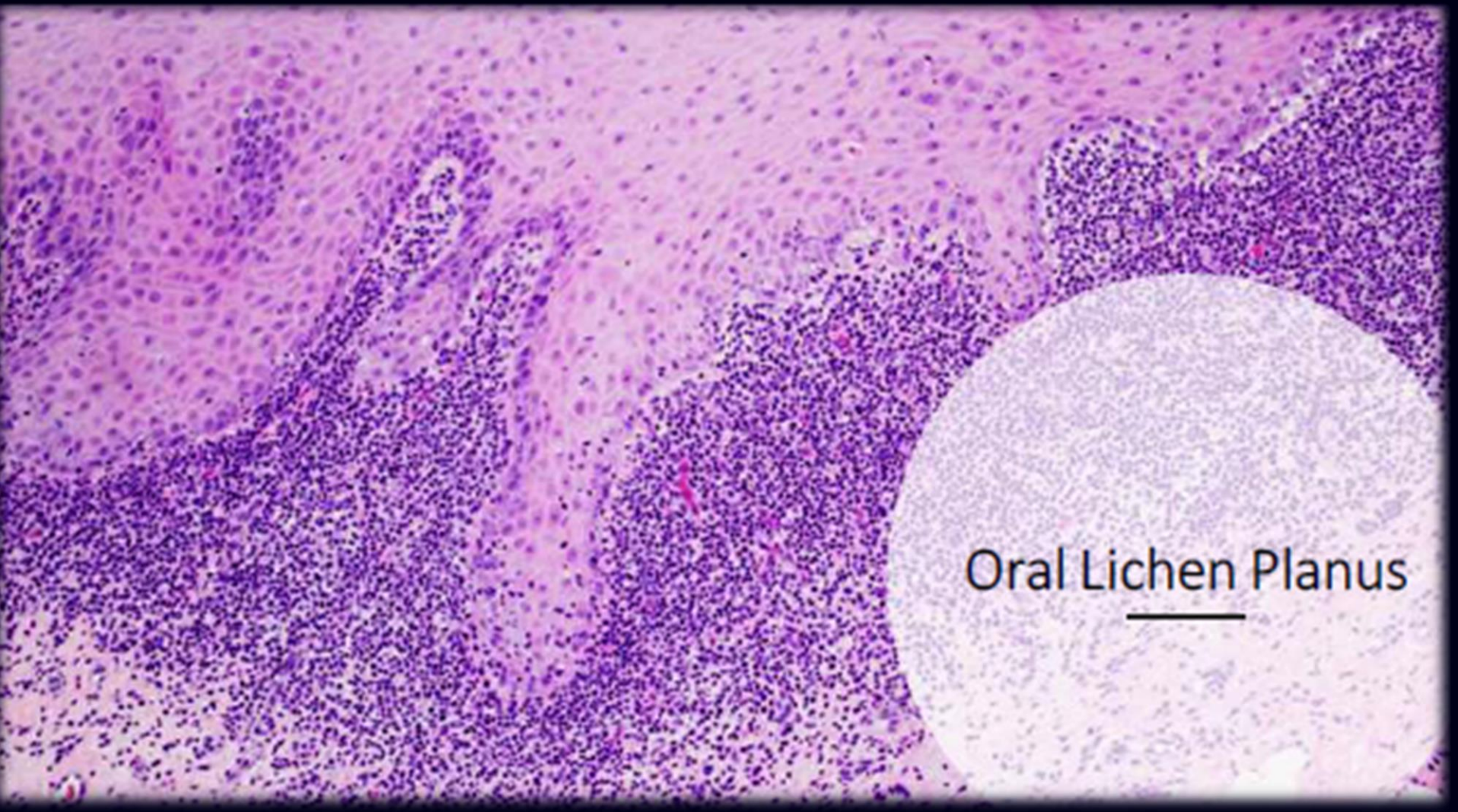
Vol. 125 No. 6 June 2018

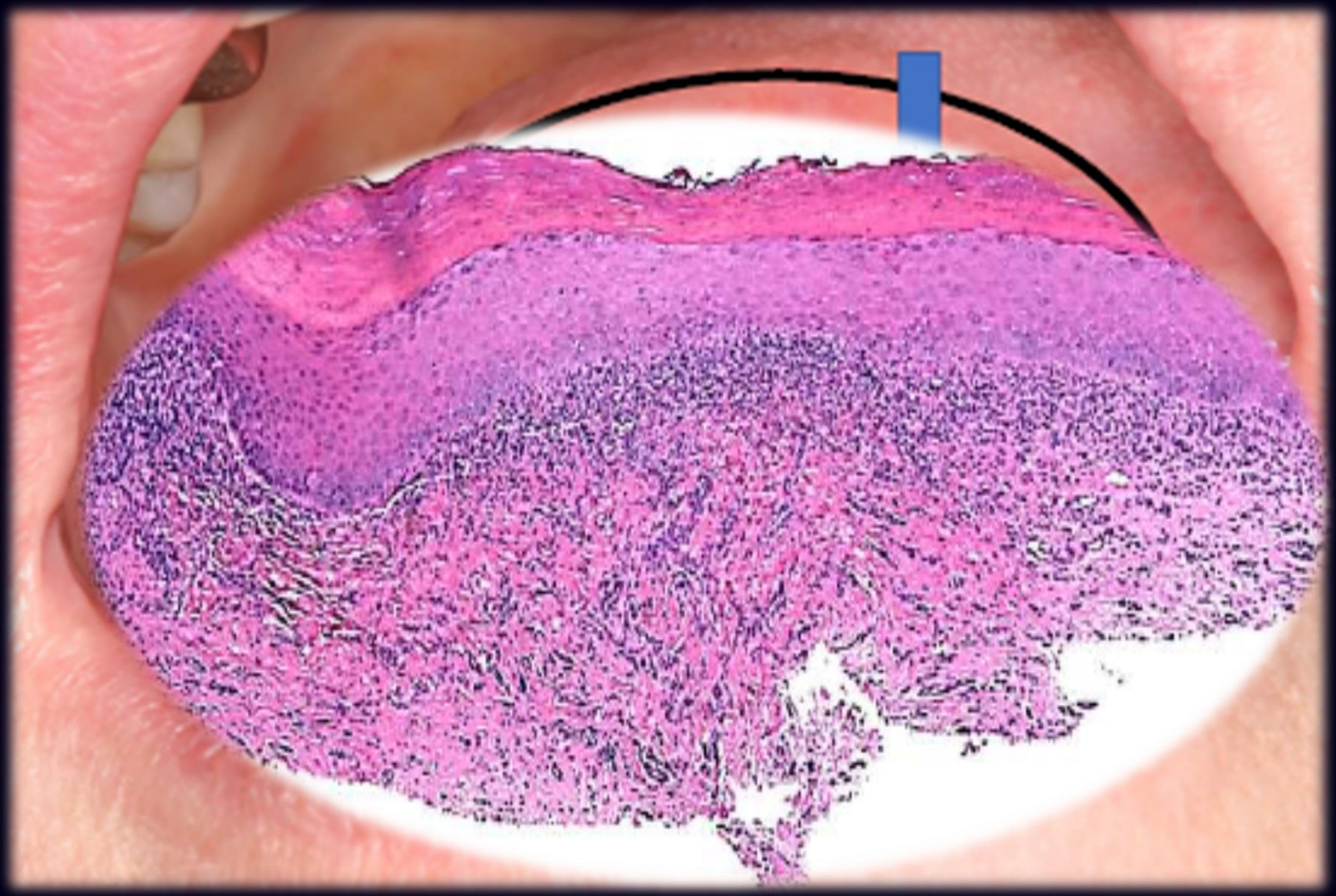
Oral epithelial dysplasia, atypical verrucous lesions and oral potentially malignant disorders: focus on histopathology

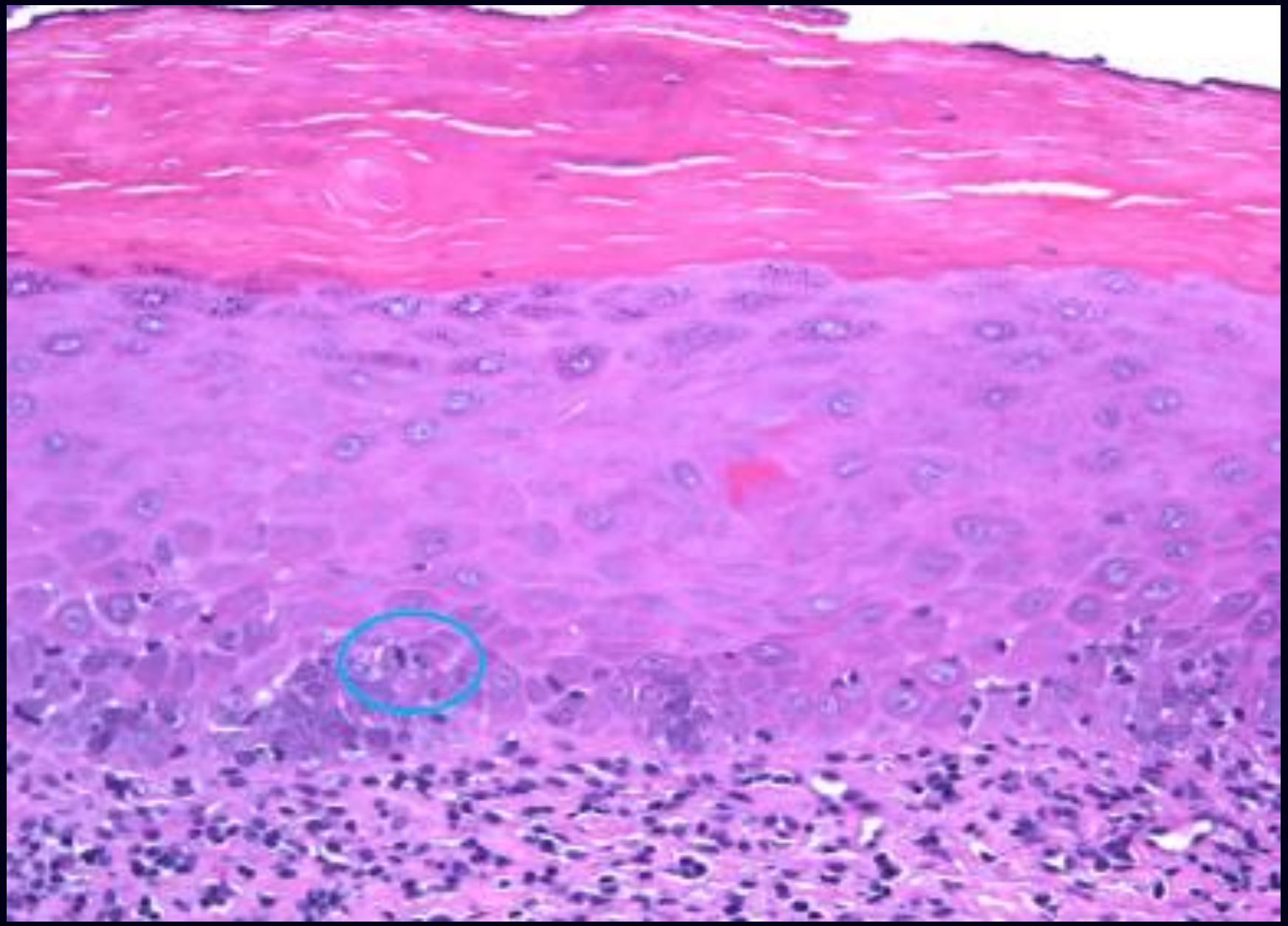
Susan Müller, DMD, MS

The term *oral potentially malignant disorders* (OPMDs) describes a recognizable group of mucosal diseases that have a risk of progressing to squamous cell carcinoma. Oral leukoplakia, the most common OPMD, has a 1% prevalence and reported malignant transformation rates of 2% to 5%. Other OPMDs include erythroplakia, erythroleukoplakia, submucous fibrosis, lesions of reverse smokers, and inherited genetic disorders, such as Fanconi anemia. The histopathologic assessment of OPMDs is an area of subjectivity, and oral epithelial dysplasia (OED) is fraught with both interrater variability and intrarater variability. Both architectural and cytologic changes are utilized when developing criteria for grading OED. However, the concept of atypical verrucous lesions, particularly as it pertains to proliferative verrucous leukoplakia, suffers from lack of histopathologic diagnostic criteria. Histopathologic mimics of OPMDs, including reactive/regenerative epithelium, frictional keratosis, and infection, can result in patient mismanagement. This review will focus specifically on the histologic features of OED, including human papillomavirus–associated dysplasia, as well as the histologic features of atypical verrucous keratoses/hyperplasia, particularly those that arise in the setting of proliferative verrucous leukoplakia along with OPMD mimics. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:591–602)

Diagnostic Challenges of Oral Epithelial Dysplasia and Precursor Lesions


Oral Lichen Planus





Dysplasia should NOT be present on lichen planus

Lichen planus is bilateral and/or multifocal disease

Should we make the diagnosis: lichenoid dysplasia?

The term may cause confusion and this may result in inadequate patient management

MODERN PATHOLOGY (2017) 30, S54–S67

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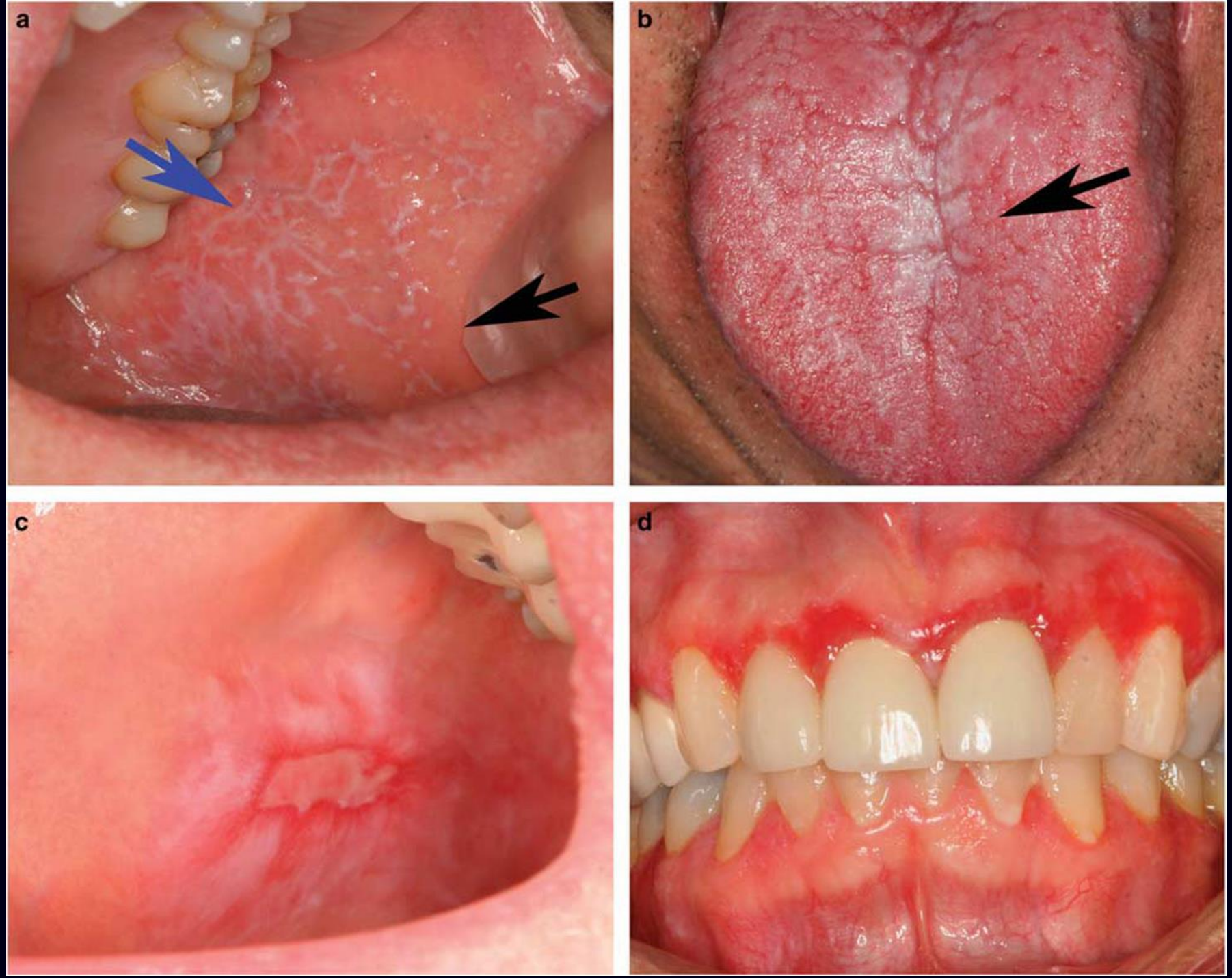
Oral lichenoid lesions: distinguishing the benign from the deadly

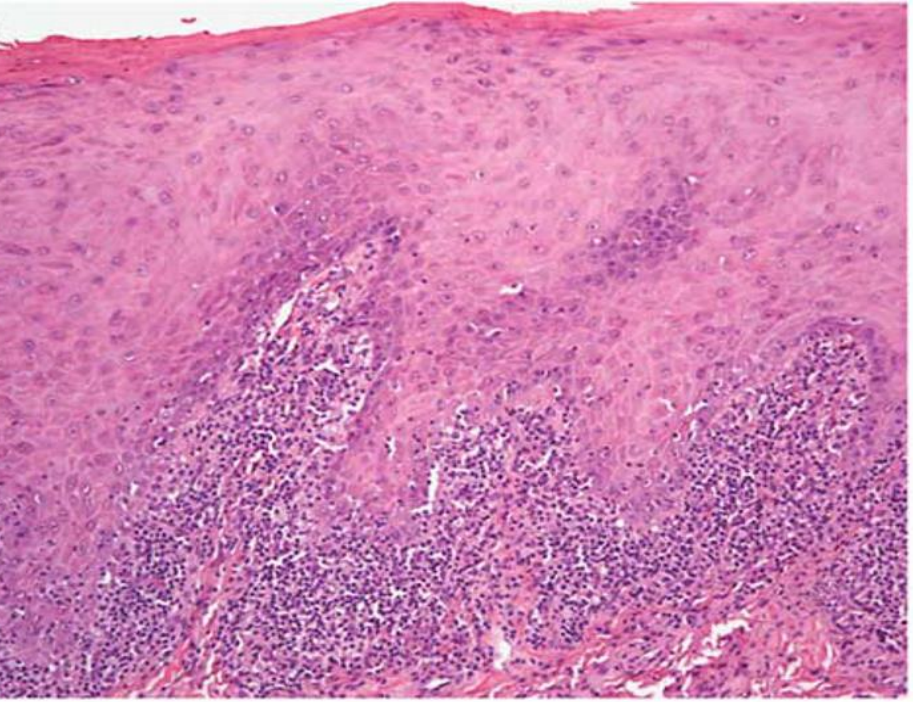
Susan Müller

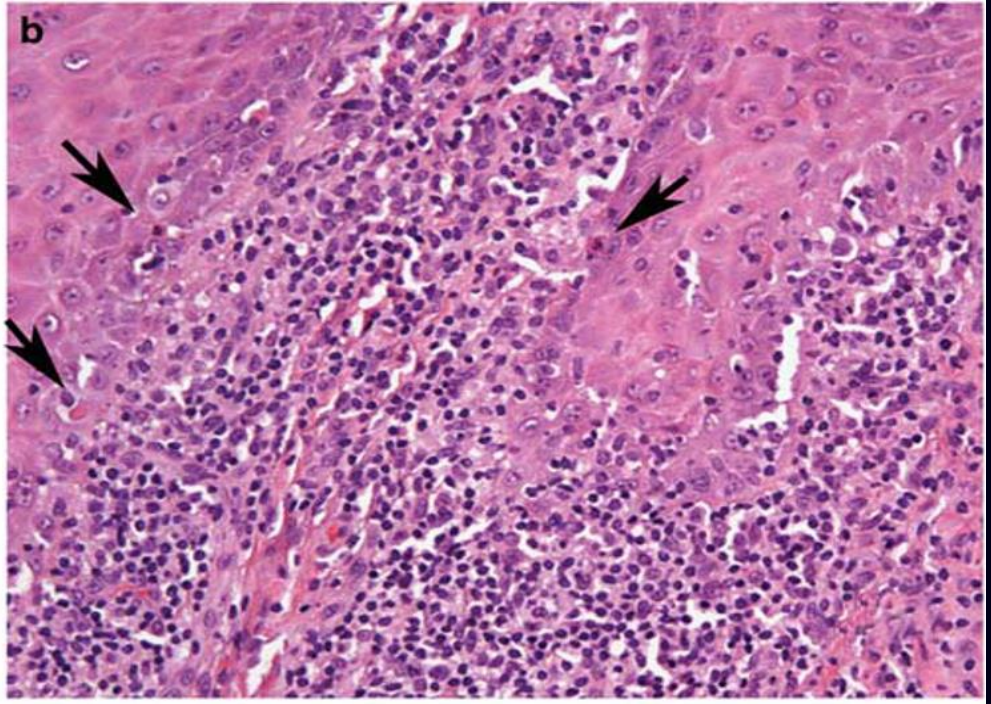
Professor Emeritus, Emory University School of Medicine: Atlanta Oral Pathology, Decatur, GA, USA

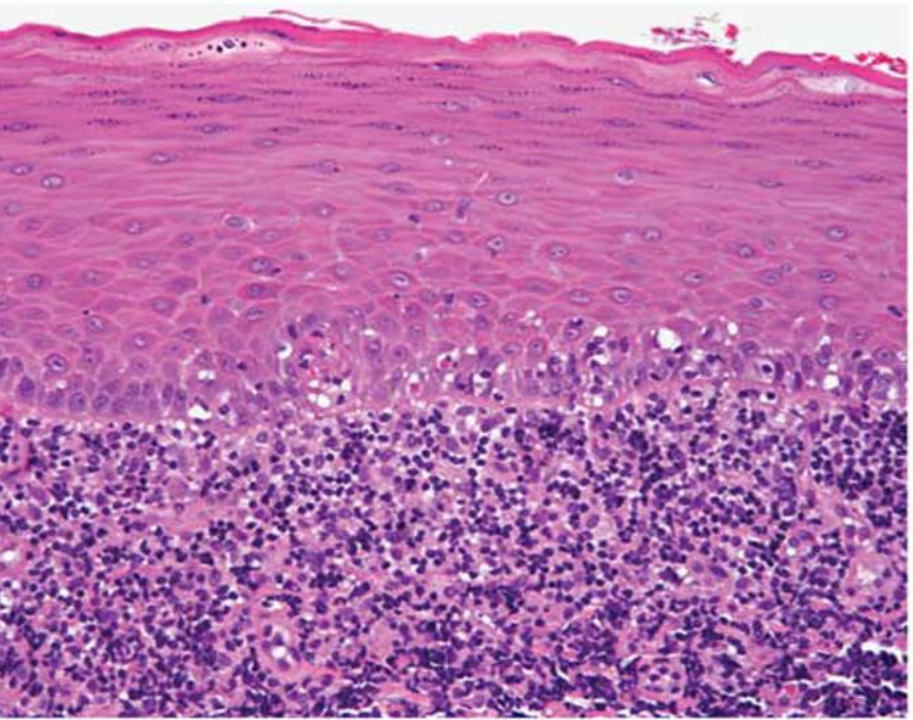
Oral lichen planus is a chronic inflammatory disease of unknown etiology or pathogenesis with varied disease severity that waxes and wanes over a long period of time. Although a common oral mucosal disease, accurate diagnosis is often challenging due to the overlapping clinical and histopathological features of oral lichen planus and other mucosal diseases. Other immune-mediated mucocutaneous diseases can exhibit lichenoid features including mucous membrane pemphigoid, chronic graft-*versus*-host disease, and discoid lupus erythematosus. Reactive changes to dental materials or to systemic medications can mimic oral lichen planus both clinically and histologically. In these situations the clinical presentation can be useful, as oral lichen planus presents as a multifocal process and is usually symmetrical and bilateral. Dysplasia of the oral cavity can exhibit a lichenoid histology, which may mask the potentially premalignant features. Proliferative verrucous leukoplakia, an unusual clinical disease, can often mimic oral lichen planus clinically, requiring careful correlation of the clinical and pathologic features.

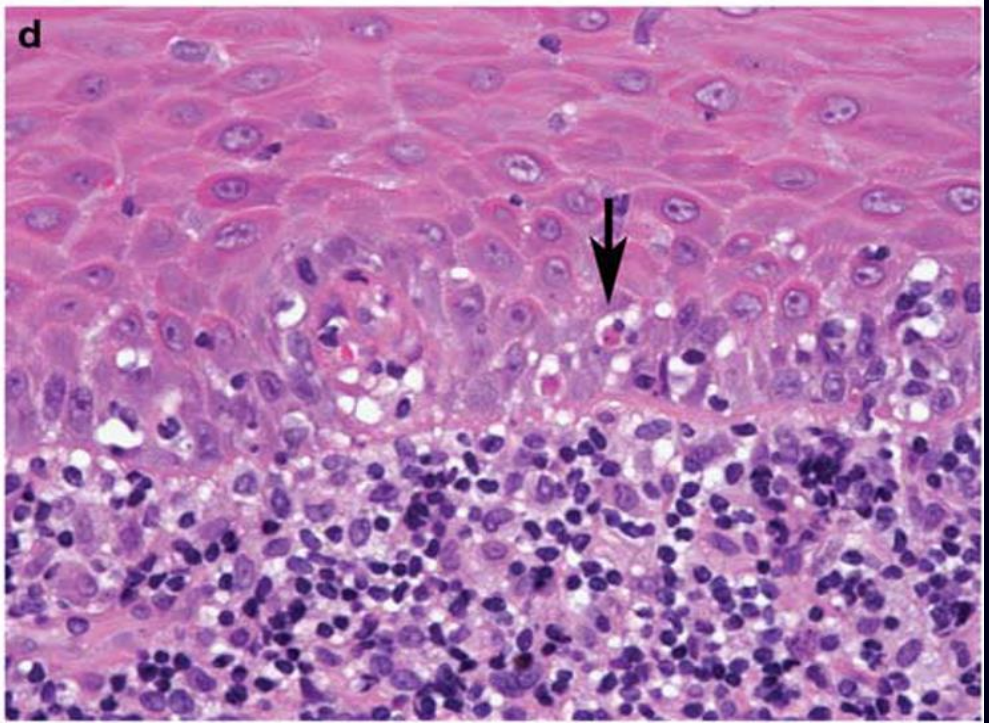
Modern Pathology (2017) **30,** S54–S67; doi:10.1038/modpathol.2016.121

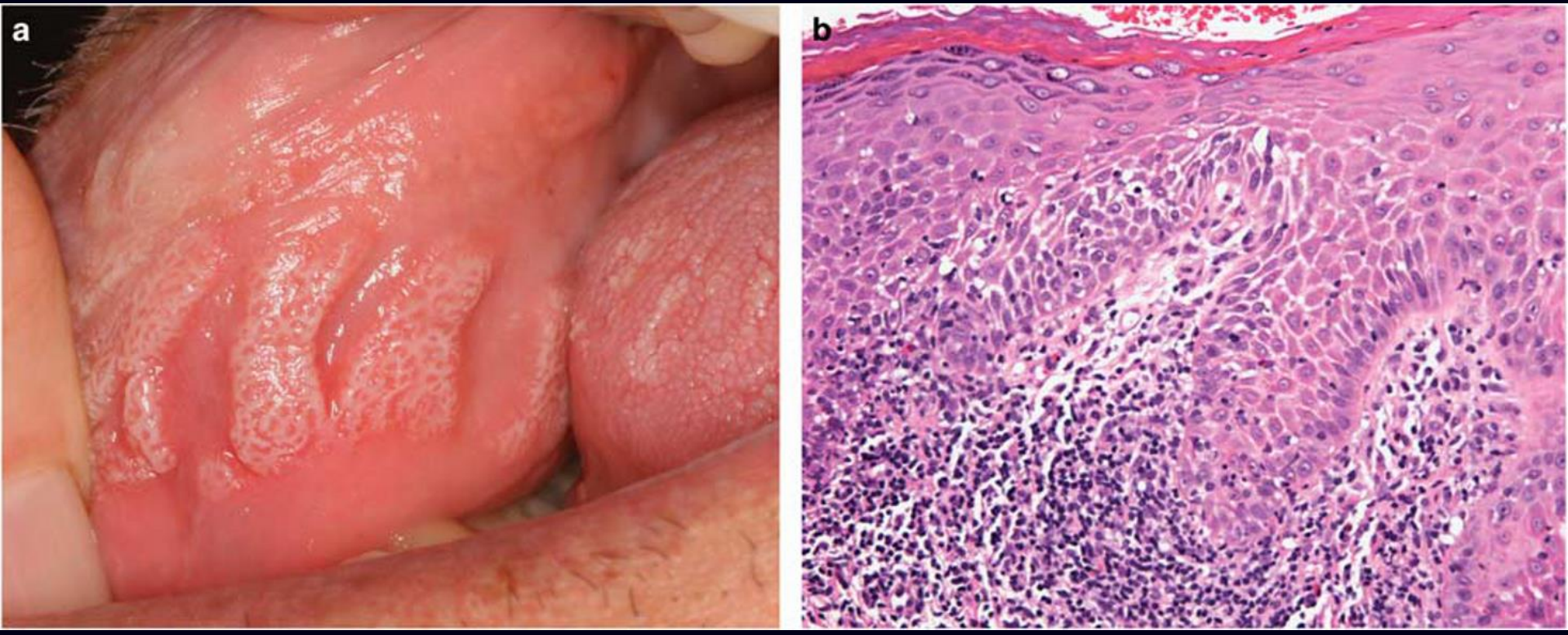

a
b
c
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b




d

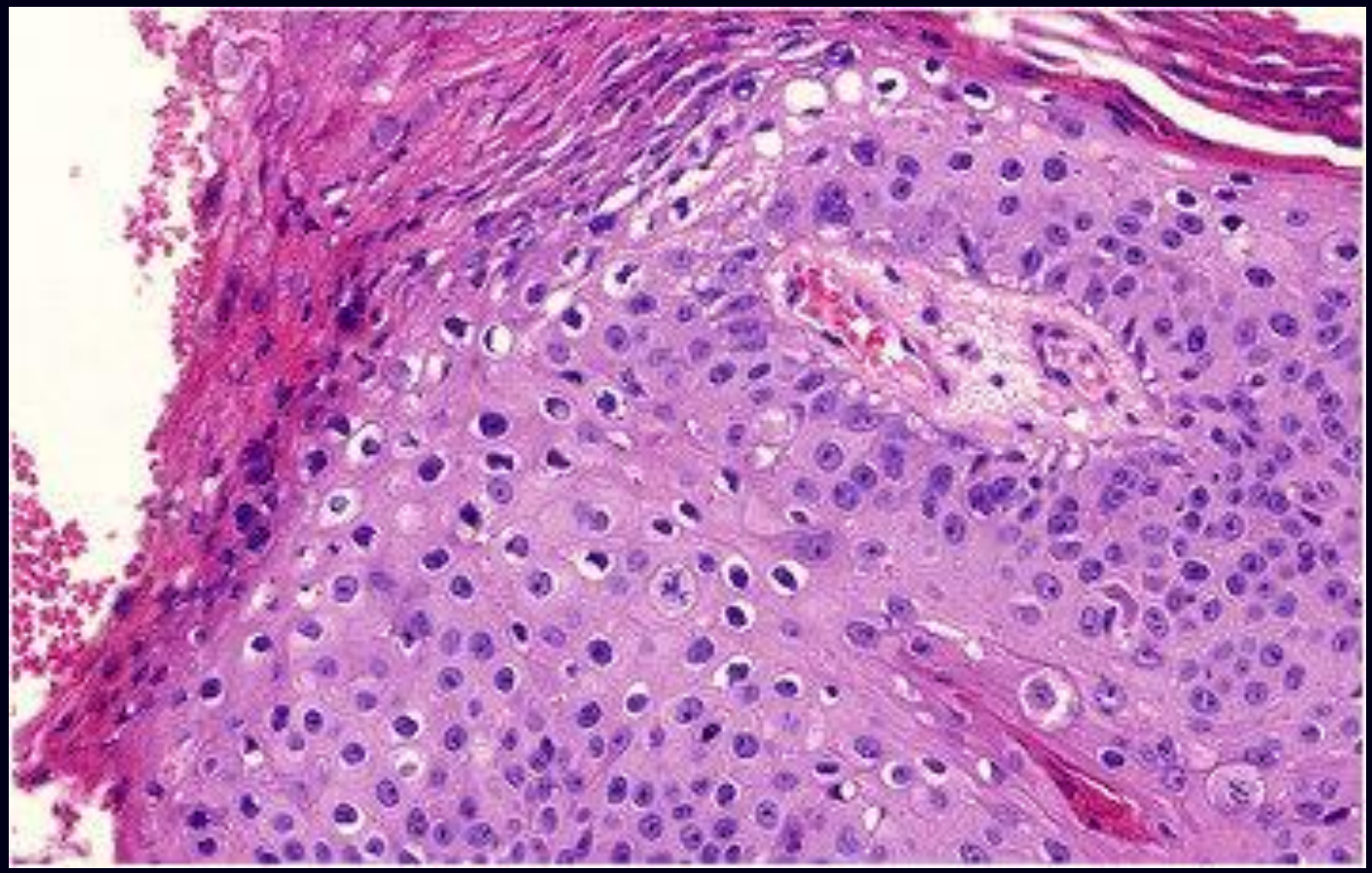


Oral lichenoid contact reaction to cinnamon flavored chewing gum. Within 10 days of discontinuing the gum, the lesion completely resolved. (a) The microscopic features of oral lichenoid contact reaction to cinnamon show marked epithelial acanthosis with elongation of the rete. Perivascular inflammatory cell infiltrate can be present as well as an occasional eosinophi

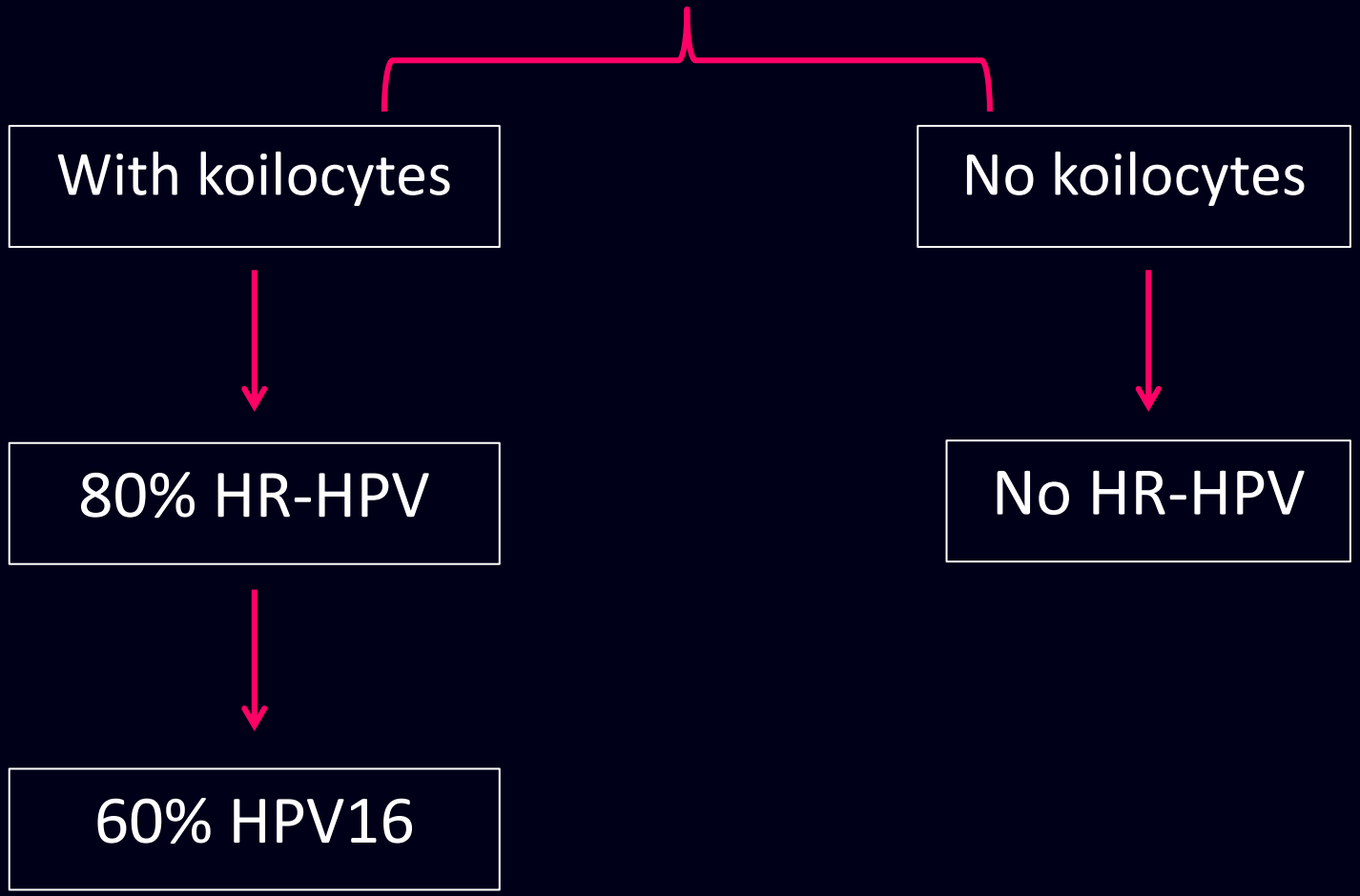
- Histologic grading based on morphology remains the accepted method for the diagnosis of oral dysplasia.
- Oral lichenoid lesions can be a diagnostic challenge for the pathologist due to the tremendous overlap in the clinical and pathologic presentation of many inflammatory, reactive, and immune-mediated disorders than commonly involve the oral mucosa.

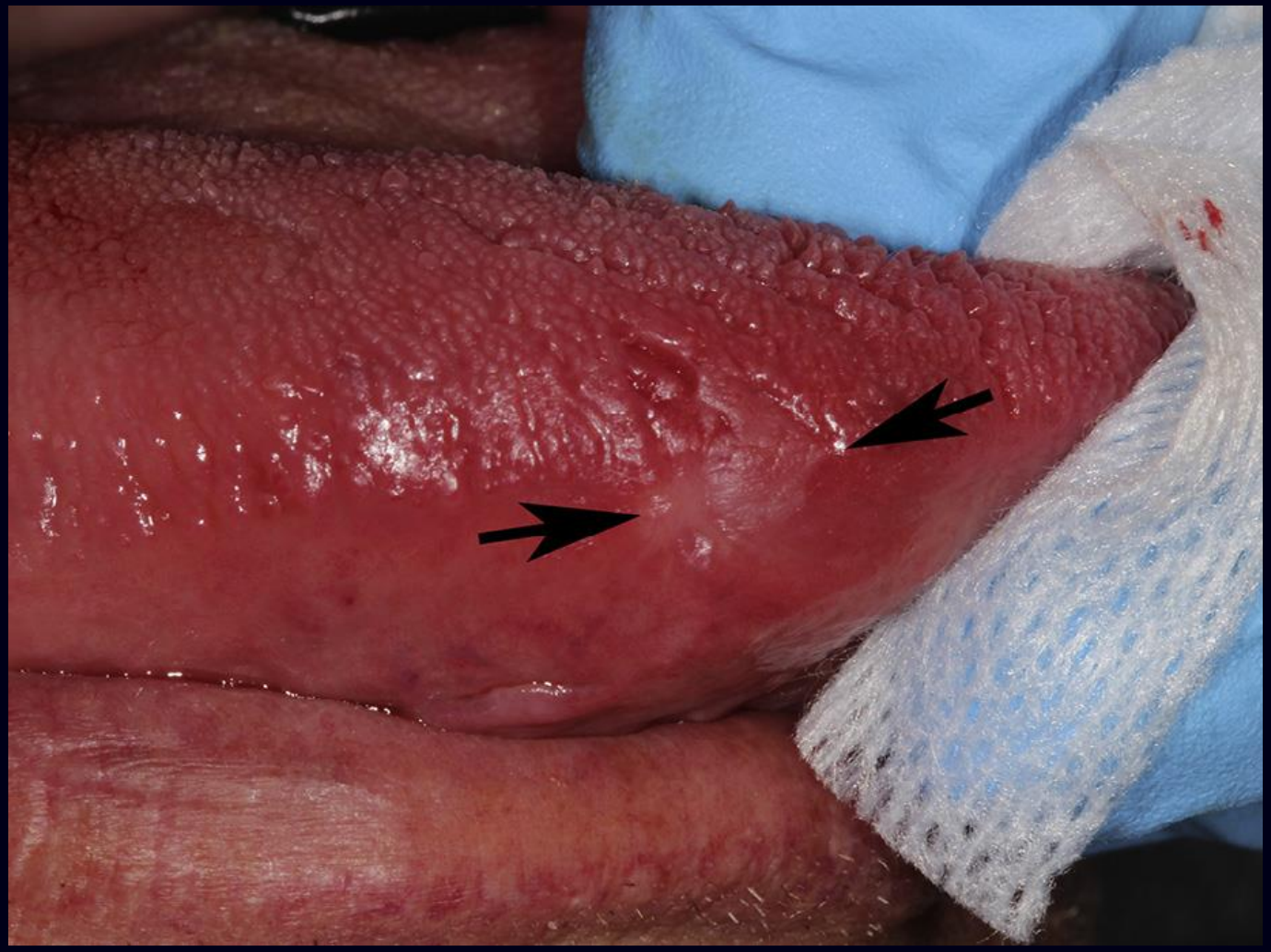
High-risk HPV-associated OED

In 1996, Fornatora et al. described 31 cases exhibiting histologic features of both high- and low-grade OED. BUT with prominent koilocytes, which they termed *koilocytic dysplasia*.



OED

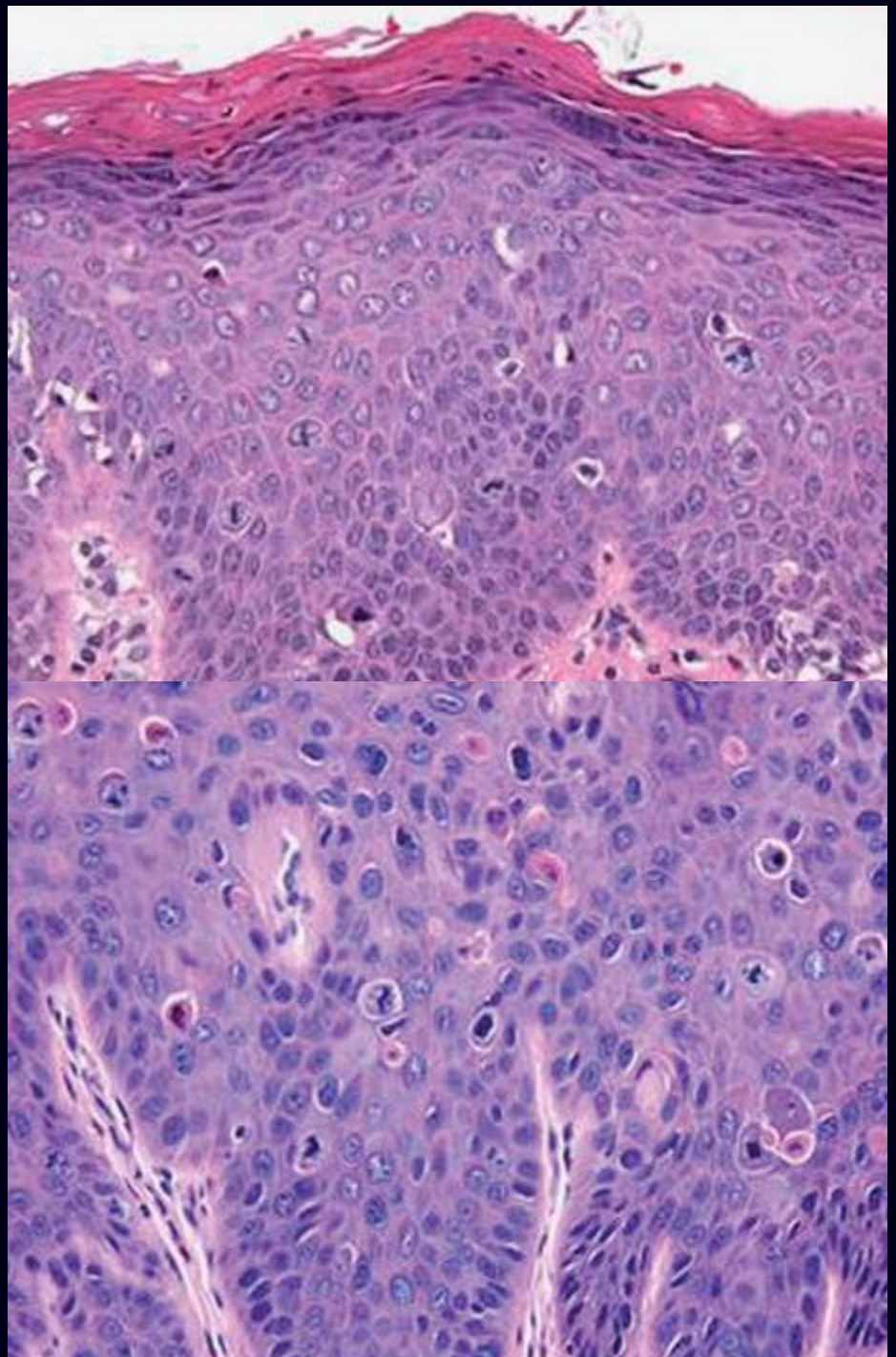




Human papillomavirus (HPV)-16–associated oral epithelial dysplasia arising on the lateral tongue of a 70-year old white male. The clinical presentation is indistinguishable from non-HPV dysplasia.

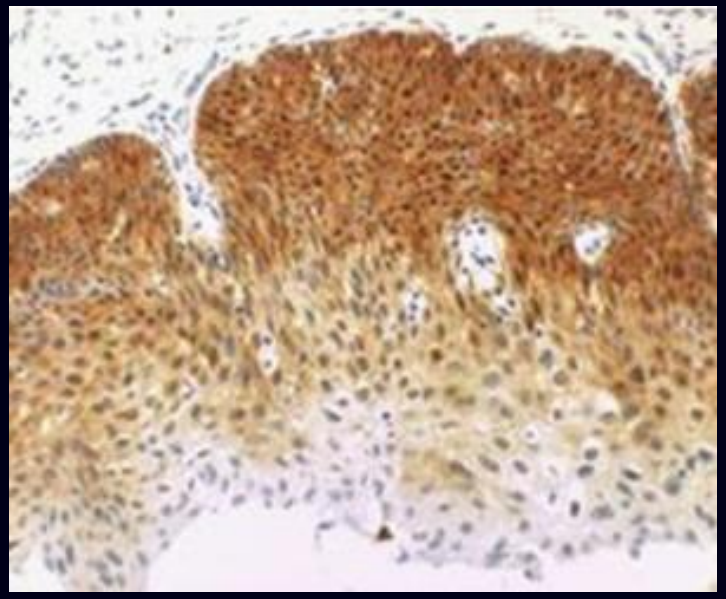
Koilocytes may or may not be present or, if present, usually in *small numbers*.

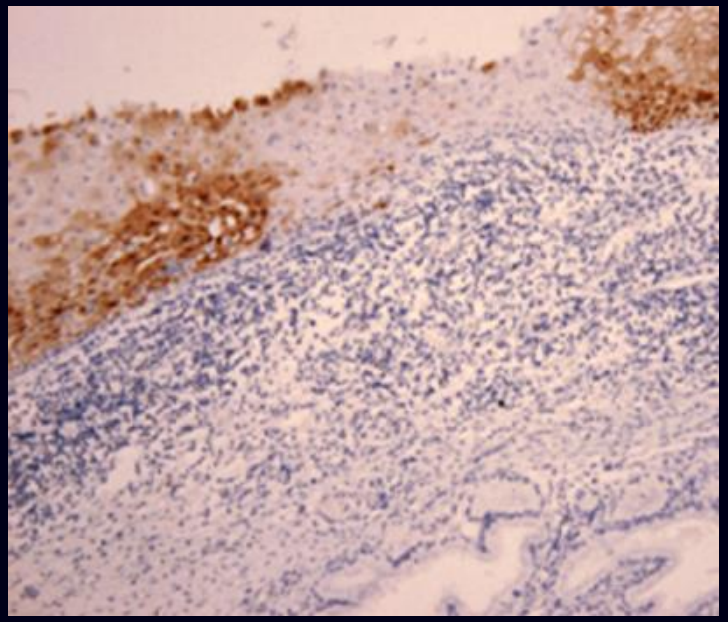
Prominent karyorrhexis, sometimes referred to as *mitosoid cells*, and *apoptosis* throughout the epithelium are the *hallmark of HPV-OED*

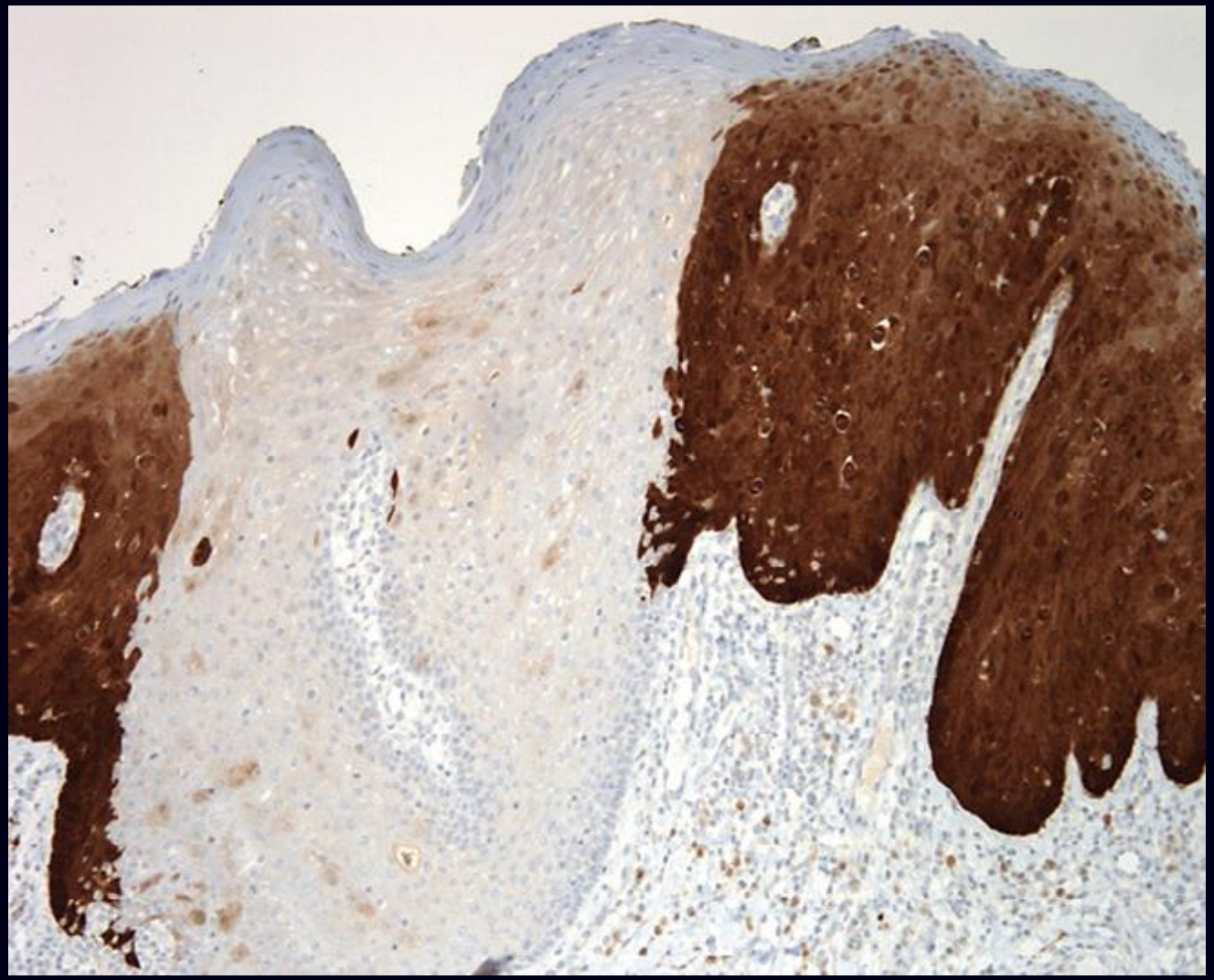


p16 IHCs: diffuse and strong *nuclear and cytoplasmic* staining, usually as a *continuous band* with full thickness of the epithelium, excluding the keratin layer.

Often, the *demarcation* between the *affected epithelium* and the *normal* epithelium is striking.





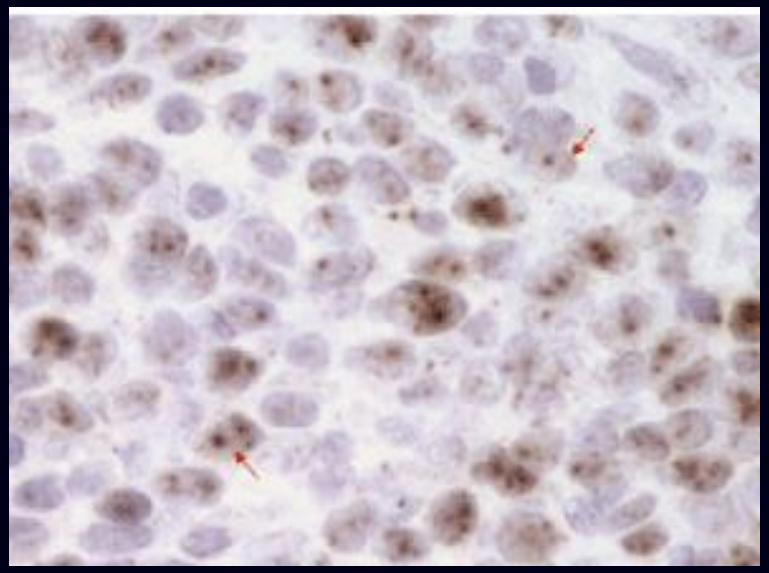


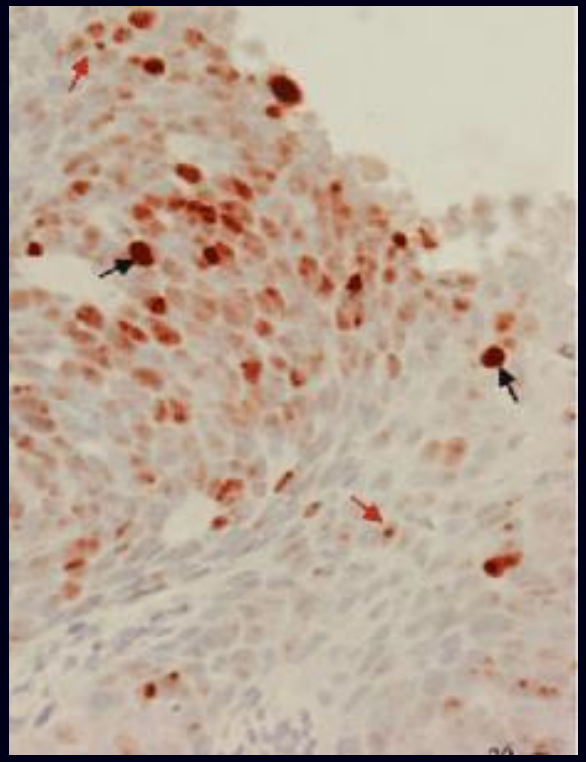
strong and diffuse cytoplasmic and nuclear staining with an abrupt transition to nondysplastic epithelium presenting as discontinuous staining (skip lesion).

PCR amplification of HPV DNA is more sensitive but lacks specificity (*false positives*).

≠

HPV E6/ E7 *mRNA expression by in situ hybridization* has higher sensitivity and specificity in the oropharynx.





Vol. 123 No. 5 May 2017

Histologic variation in high grade oral epithelial dysplasia when associated with high-risk human papillomavirus

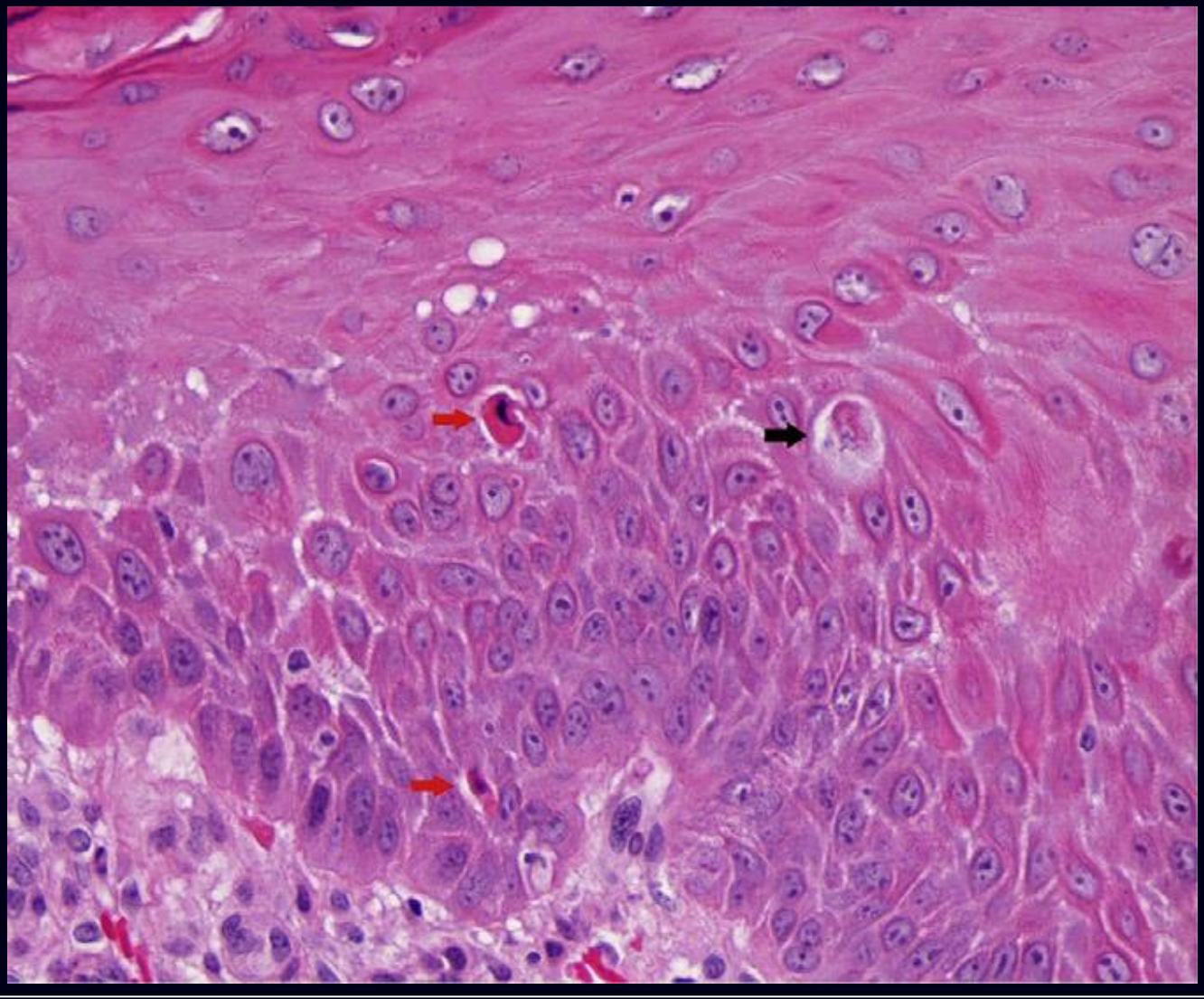
Sujita Khanal, MS, PhD,[a] Patrick J. Trainor, MS, MA,[b] Maryam Zahin, PhD,[c] Shin-je Ghim, PhD,[d] Joongho Joh, PhD,[d] Shesh N. Rai, PhD,[e] Alfred Bennett Jenson, MD, MS, FACP,[f] and Brian S. Shumway, DDS, MS[g]

Objectives. Reported cytologic alterations associated with high-risk human papillomavirus (HR-HPV) in oral epithelial dysplasia (HPV-OED) need further characterization.

Study Design. Archival cases of high-grade oral epithelial dysplasia (hgOED) (N = 38) were assigned a cytologic score (CS) based on the average number of mitotic, karyorrhectic, and apoptotic cells per high-power field. Three groups were then generated on the basis of increasing CS: Focal (group 1, N = 14), Intermediate (group 2, N = 12), and Diffuse (group 3, N = 12). Polymerase chain reaction–based HPV genotyping and p16 immunohistochemistry were performed.

Results. HR-HPV was found significantly more in group 3 (83.3%) compared with groups 1 and 2 (group 1&2; 42.9% and 41.7%, respectively; $P = .047$). HPV16 predominated in HR-HPV-positive cases (90.5%). By location, the tongue or the floor of mouth was associated with all groups ($P = .04$). Increasing CS was associated with a slightly younger age ($P = .04$) and increased expression of p16 ($P = .005$). CS and p16 expression were not sensitive but were highly specific predictors for HR-HPV presence. Based on limited follow-up information, HPV-OED does not differ in clinical aggressiveness compared with conventional OED.

Conclusions. Increased CS in hgOED is strongly associated with HR-HPV (mostly HPV16) and p16 expression. CS and p16 expression are specific predictors of HR-HPV presence. Further molecular study and long-term follow-up of HPV-OED are needed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:566-585)



A few apoptotic cells (red arrows) and karyorrhectic cells (black arrows).

- P16 *positivity*: *strong* and *diffuse* or *patchy*
- Good *correlation* among *p16 expression*, and *positivity* for HPV.
- Despite the good correlation, have found ***outliers***, whereby OED is strongly p16 + /HPV– or p16–/HPV + .

Currently, *limited data* exist to determine if HPV-OED has a higher or lower *malignant transformation* to oral squamous cell carcinoma (OSCC) than non–HPV-OED





Now we have a clear view of OPMDs…


Thank you!