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

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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)

Despite the awkward phrase "oral potentially malignant disorders" (OPMDs), the term accurately defines a group of lesions that carries an increased risk of cancer progression[1-3] and underscores the complexity and the frustration for clinicians, pathologists, and their patients in assessing cancer risk. The 2017 World Health Organization (WHO) definition of OPMDs is "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal mucosa."[4] 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."[3] Other OPMDs include erythroplakia, erythroleukoplakia, submucous fibrosis, lesions of reverse smokers, and, less commonly, lichen planus. Fanconi anemia, dyskeratosis congenita, and xeroderma pigmentosa are rare inherited genetic syndromes that are associated with elevated oral cancer incidence. Immunosuppression in the setting of graft-versus-host disease and HIV infection is also associated with increased oral cancer. High risk for human papillomavirus (HPV) infection has been identified in a subset of oral epithelial dysplasia (OED) cases.

This review will focus specifically on the histologic features of OED as well as the histologic features of atypical verrucous keratoses/hyperplasia, particularly those that arise in the setting of proliferative verrucous leukoplakia (PVL). Several excellent recent reviews on the histology of submucous fibrosis have been published and will not be covered here.[5-9] Actinic keratosis, which can be considered an OPMD, will not be reviewed.

ORAL EPITHELIAL DYSPLASIA

It is a truth universally acknowledged that grading of oral dysplasia suffers from both intrarater variability and interobserver variability.[10-12] The WHO (2017) maintains a 3-tiered grading system for OED: mild, moderate, and severe dysplasia.[4] Carcinoma in situ is synonymous with severe dysplasia in this grading system.

Grading of OED suffers from subjective division into 3 types because it does not imply a continuous progression and does not predict its malignant potential.[13] Mild dysplasia is confined to the lower one-third of the epithelium (basal and parabasal layers) exhibiting cytologic and/or architectural alterations. Moderate dysplasia exhibits disordered maturation from the basal layer extending to the midportion of the spinous layer (middle third). Severe dysplasia/carcinoma in situ reveals abnormal maturation extending from the basal cells to a level above the midpoint of the epithelium (upper third) to the entire thickness of the epithelium. Most oral dysplasias are of the keratinizing type, and the criterion for full-thickness dysplasia as applied to nonkeratinizing dysplasia is inappropriate. Hyperplasia and/or hyperkeratosis without architectural or cytologic atypia is not considered an

Statement of Clinical Relevance

The term *oral potentially malignant disorders* (OPMDs) describes a recognizable group of mucosal diseases that have a risk of progressing to squamous cell carcinoma. This review paper discusses the histologic features of OPMDs as well as OPMD mimics.

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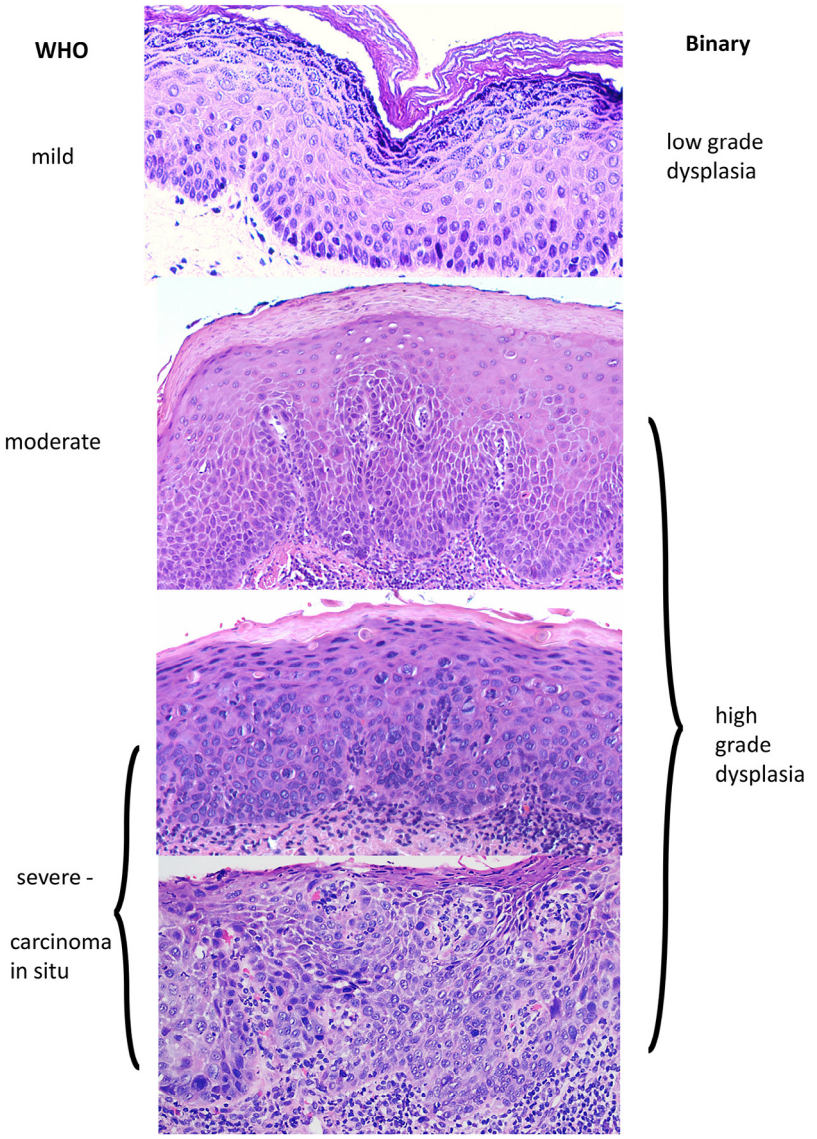

Fig. 1. Comparing World Health Organization (WHO) and binary systems of grading oral epithelial dysplasia.

OPMD. This excludes atypical verrucous lesions, which will be discussed later.

Some pathologists advocate a binary grading system for OED, similar to that for laryngeal precursor lesions, and published reports have demonstrated improved diagnostic agreement in grading OED with a 2-tiered system—that is, low-grade and high-grade dysplasias.[14] Figure 1 illustrates the overlap of the 2017 WHO OED grading system and the binary system. It should be noted that in the most recent 2017 WHO laryngeal dysplasia grading system, low-grade dysplasia is limited to the lower one-third of the epithelium similar to OED mild type.[14] Moderate or severe dysplasia or carcinoma in situ is considered high-grade dysplasia.[14] The WHO OED grading system acknowledges that there are some moderate dysplasias that may fall into the low-grade dysplasia category when using the binary system.[4] Although we favor a binary system for grading OED at our institution, at this time, the WHO has recommended that more validation is required before adopting the binary system.[4]

Both architectural and cytologic changes are utilized when developing criteria for grading OED (Table I). Figure 2 presents some of the architectural criteria. Admittedly, some diagnostic criteria are easier to identify compared with others; however, even on low-power microscopic examination, the architectural features of budding or drop-shaped rete can be appreciated (see Figure 2A). Figure 3 illustrates some of the cytologic features, including increased nuclear/cytoplasmic ratio and nuclear pleomorphism, which can be readily identified in OED. Some of the other architectural and cytologic features listed in Table I, such as loss of basal cell

Table I. Epithelial dysplasia: criteria for diagnosis

Architectural features	*Cytologic features*
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

Adapted from Reibel et al.[4]

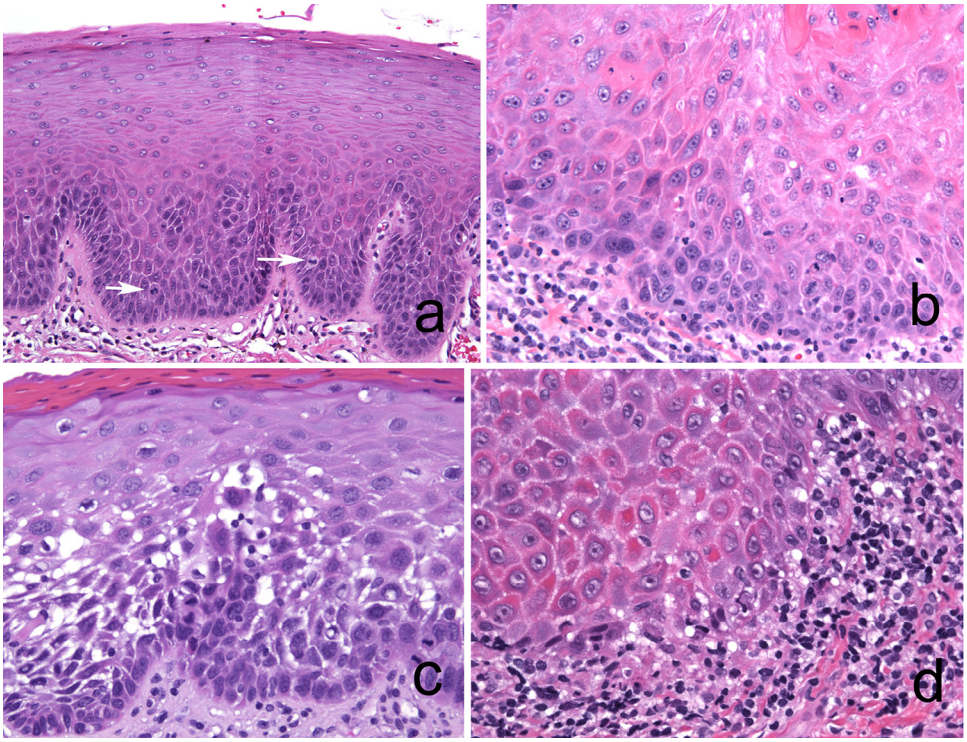

Fig. 2. Architectural features of oral epithelial dysplasia include budding of the rete and increased number of mitotic figures. **A,** Original magnification ×200; loss of basal cell polarity. **B,** Original magnification ×200; irregular epithelial stratification and loss of epithelial cell cohesion. **C,** Original magnification ×200; premature keratinization seen in the lower third of the epithelium along with loss of basal cell polarity. **D,** Original magnification ×300.

polarity (see Figure 2B), irregular epithelial stratification and loss of epithelial cell cohesion (see Figure 2C), dyskeratosis (see Figure 2D), atypical mitotic forms and nuclear pleomorphism (see Figures 3A and 3B), can at times be more difficult to identify.

Kujan et al. using the 2005 WHO criteria for diagnosing dysplasia developed a binary system of grading based on the combination of architecture and cytology changes.[15] The cutoff points for a high-risk lesion defined as "potential susceptibility for malignant transformation" and a low-risk lesion defined as "does not have the potential susceptibility for malignant transformation" were at least 4 architectural changes and 5 cytologic changes, respectively. Using this grading scheme, those authors showed that not all high-risk lesions were synonymous with severe dysplasia/carcinoma in situ. Indeed, 16 of 30 moderate dysplasias were identified as high-risk lesions, which, at follow-up, showed malignant transformation. Despite this, Kujan et al. recognized the weaknesses in their proposed grading classification with κ-values for interobserver agreement to be similar in both the WHO grading system and their binary system.[15]

In an attempt to duplicate and validate Kujan et al.'s study of a binary OED grading system, Nankivell et al. refined the diagnostic threshold using 4 architectural and 4 cytologic criteria for moderate dysplasia.[16] The study

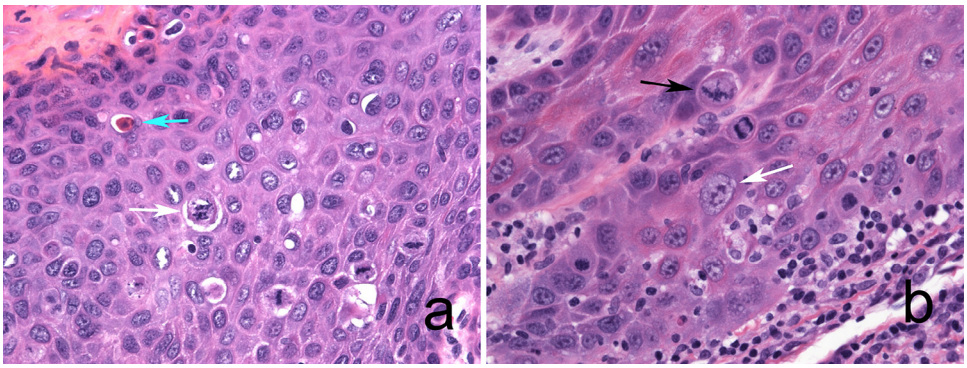

Fig. 3. Cytologic features of oral epithelial dysplasia include atypical mitotic figures *(white arrow)* and apoptotic cells characterized by eosinophilic cytoplasm and pyknotic nucleus *(blue arrow)*. **A,** Original magnification ×400; marked cellular and nuclear pleomorphism, multiple nucleoli *(white arrow)*, atypical mitotic figures *(black arrow)*, increased nuclear/cytoplasmic ratio and hyperchromasia. **B,** Original magnification ×400.

also found less interrater variability when using the binary system, rather than the WHO classification. Importantly, despite improved correlation among pathologists, when both grading systems were evaluated in terms of prognosis, no significant differences were found between the WHO system and the binary system. Speight et al.[17] also looked at interobserver OED differences when using the WHO defined criteria as published by Kujan et al. The goal of the study was to improve diagnostic agreement, specifically for use in creating new quantitative tools, such as oral cancer molecular and morphometric biomarkers. The agreement of OED grading by 2 experienced oral pathologists ranged from 62% to 81% ($\kappa = 0.251$-0.706).[17] Having a third reviewer act as adjudicator increased the diagnostic agreement by 30%. Consensus scoring also improved interrater reliability in OED grading in a follow-up study by Kujan et al.[18] This study reported that the highest agreement among the pathologists in the study were with regard to increased mitotic figures, drop-shaped rete, increased nuclear size, and cellular pleomorphism. The highest disagreement among the scorers was with regard to irregular epithelial stratification, loss of basal cell polarity, nuclear pleomorphism, atypical mitotic figures, and hyperchromatism. Importantly, when the study looked at the architectural features associated with the clinical outcomes, only drop-shaped rete, loss of basal cell polarity, and abnormally superficial mitoses were statistically associated. Likewise, atypical mitoses, nuclear and cellular pleomorphism, and multiple nucleoli were cytologic features associated with clinical outcome. In this study, the features of 4 architectural changes and 5 cytologic changes were associated with disease progression, confirming the authors' earlier study.

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*.[19] Some of these cases of koilocytic dysplasia were most likely multifocal epithelial hyperplasia (Heck disease). However, 64% of cases were positive for high-risk HPV (HPV-16/18) on in situ hybridization. In 2013, Woo et al. described a unique subset of OED associated with high-risk HPV, which they termed *HPV-associated oral intraepithelial neoplasia*.[20] Since then, other studies have added to our understanding of this entity.[21-23] Most cases of HPV-OED are associated with HPV-16, and other HPV types reported include HPV-33, -45, and -58. Clinically, the lesions of HPV-OED are indistinguishable from non–HPV-OED (Figure 4). Most cases occur on the tongue and the floor of the mouth, although other oral anatomic sites, including the buccal mucosa and the gingiva, have been reported.

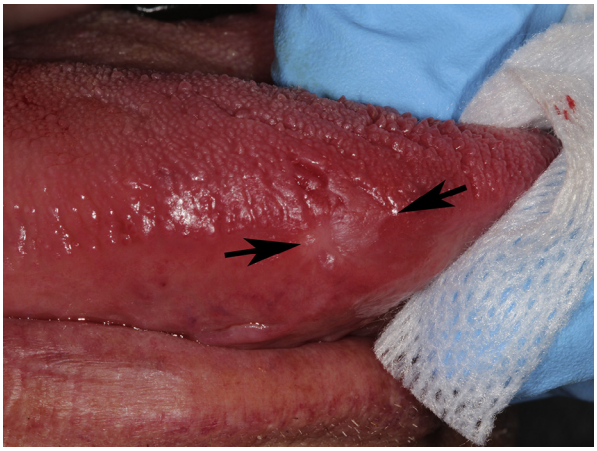

Fig. 4. Human papillomavirus (HPV)-16–associated oral epithelial dysplasia arising on the lateral tongue of a 70-year-old white male. The clinical presentation is indistinguishable from non-HPV dysplasia.

The microscopic features of OED, in addition to conventional features, are distinctive. The epithelial

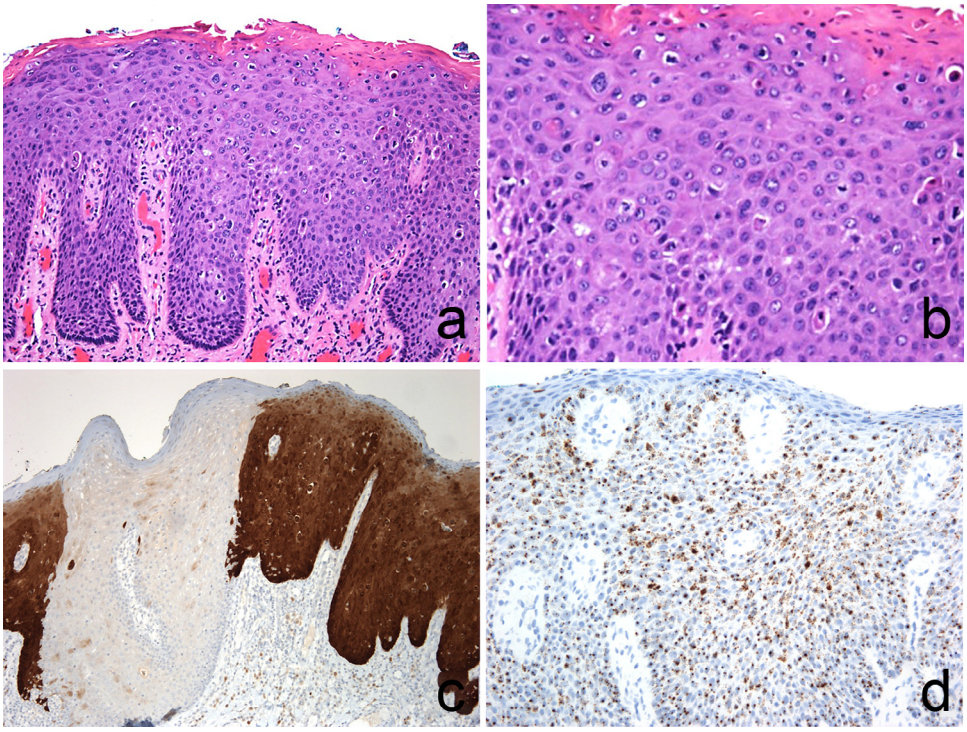

Fig. 5. The pathology from the patient in Figure 3 illustrates the typical findings in human papillomavirus (HPV)–associated oral dysplasia. There is epithelial hyperplasia surfaced by eosinophilic compacted parakeratin. **A,** Original magnification ×100; marked karyorrhexis (mitosoid figures) and numerous apoptotic cells involving the full-thickness of the epithelium is present. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04723.* **B,** Original magnification ×400; p16 immunohistochemistry shows strong and diffuse cytoplasmic and nuclear staining with an abrupt transition to nondysplastic epithelium presenting as discontinuous staining (skip lesion). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04722.* **C**, Original magnification ×100; nuclear positivity for high-risk HPV infection, using RNA in situ hybridization. **D,** Original magnification ×100.

surface may be corrugated and both parakeratosis and orthokeratosis may be present. The parakeratin is brightly eosinophilic and often compacted (Figure 5A). 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 (Figure 5B). p16 immunohistochemistry demonstrates 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 (Figure 5C). Similar to non–HPV-associated OED, skip lesions, whereby discontinuous p16 immunostaining is observed correlating to abrupt transitions in dysplasia, can occur.

There are many types of HPV testing, and sensitivity and specificity vary greatly. Polymerase chain reaction amplification of HPV DNA is more sensitive but lacks specificity, possibly resulting in false positives. HPV E6/E7 mRNA expression by in situ hybridization has higher sensitivity and specificity in the oropharynx compared with HPV DNA in situ hybridization.[24] When evaluating in situ hybridization for high-risk HPV infection, only nuclear staining is considered positive (Figure 5D).

At this time, unlike in the oropharynx, p16 immunohistochemistry in the oral cavity is not considered a surrogate marker for high-risk HPV infection. Khanal et al. examined p16 immunoreactivity and high-risk HPV infection in OED, which fulfill the cytologic features of HPV-associated dysplasia.[23] The goal of their study was to use p16 and polymerase chain reaction –based HPV genotyping to identify specific HPV types. Using the cutoff of greater than 70% of cells showing p16 positivity, either strong and diffuse or patchy, they observed a good correlation among p16 expression, histologic features of mitotic figures, karyorrhectic and apoptotic cells, and positivity for HPV. Greater than 90% of cases were HPV-16 but HPV types 6, 33, and 45 were also present. Despite the good correlation among p16 immunoexpression, cytologic features of HPV-OED, and positivity for HPV, these authors, as well as others, have found outliers, whereby OED is strongly p16 + /HPV– or p16–/HPV + .

No defined protocol exists to establish when p16 and/or HPV testing should be done for OED that fulfills the cytologic criteria of HPV-OED. There is no consensus on nomenclature for these unique dysplastic lesions. A variety of terms, including *HPV-associated oral intraepithelial neoplasia* and *high-risk HPV-associated oral epithelial dysplasia*, have been advocated. As these terms do not use the conventional dysplasia grades familiar to treating clinicians, it may be confusing and could potentially result in mismanagement.

The significance of HPV-OED with regard to biologic behavior is uncertain. 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. In addition, it is unknown how HPV driven OSCC differs from HPV-associated oropharyngeal carcinoma. There is improved survival for HPV-positive oropharyngeal carcinomas compared with HPV-negative tumors.[25] Too few cases of HPV-positive OSCC have been reported to determine if prognosis is improved, although to date, studies have shown no survival advantage in the rare HPV-positive cancers outside of the oropharynx, including the larynx and the oral cavity.[25] The current recommendation is that HPV-positive OSCC be treated with protocols for oral cavity cancer and not that for HPV-positive oropharyngeal cancer.

ATYPICAL VERRUCOUS HYPERPLASIA/KERATOSIS/PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

There are many verrucous and papillary lesions of the oral cavity, including the benign lesions papilloma, verruca vulgaris, verruciform xanthoma, and condyloma. These lesions are not considered OPMDs, rarely are diagnostically challenging, and will not be discussed here. The recognition of atypical verrucous hyperplasia and/or keratoses (AVH/AVK) as a distinct subset of OPMDs has long been acknowledged.[1-3,26,27] Even more so than OED, AVK is fraught with disparities in diagnostic clinical and histologic criteria, and the microscopic diagnosis cannot be made without knowledge of the clinical presentation. This is particularly true when applied to the diagnosis of PVL. PVL is a unique OPMD that is not associated with the traditional risk factors for OPMDs and OSCC, including tobacco smoking, alcohol, and areca nut/betel leaf chewing.[4] No evidence for a viral association and PVL has been established.[26] A disorder of older individuals with a female predilection, PVL is a clinically distinct OPMD with a multifocal presentation and relentless progression to malignancy. In a 2014 systematic literature review of PVL, Pentenero et al. assessed clinical findings to determine if particular features were defining characteristics of PVL.[28] When the data on malignant transformation from 347 patients were merged, the malignant transformation rate was 56.2%. Furthermore, when looking at the literature where clinical follow-up was available, 272 patients with PVL on an average follow-up of 7.4 years had a malignant transformation rate of 60.7%. Multiple cancers were identified in 37.3% of patients, with an average time lapse of 1.5 to 2 years from the initial cancer diagnosis to the secondary cancer. The gingiva/alveolar ridge was the anatomic site of malignant transformation in 38.2% of patients, followed by the tongue (22.8%), palate (15.4%), and buccal mucosa (11.8%).[28] These findings are in striking contrast to non–PVL-associated OSCC, where the lateral border of the tongue is involved in the majority of cancers, and the overall malignant transformation rate is 2% to 5%.[29]

To date, there are no standardized criteria for the histologic diagnoses of AVK/AVH, particularly as it relates to PVL. Biopsies from various anatomic sites in the same patient may exhibit a variety of histologic patterns, generally correlating with the clinical features.[4,27,30] Early lesions of PVL may be indistinguishable from benign keratoses and leukoplakia without dysplasia (Figure 6). Most early PVL lesions do not express many of the defined cytologic features of OED, and therefore, focus on the architectural features of PVL is required. Subtle histologic features can raise the consideration that the biopsy may be associated with PVL. With progression, lesions display a corrugated or verrucous architecture often surfaced by orthokeratin corresponding to the clinical presentation (Figure 7).[30] Interface mucositis with a lymphohistiocytic infiltrate adjacent to the basal cells and dyskeratotic cells may be present (Figure 8).[4,13] These lichenoid features can be misdiagnosed as oral lichen planus (OLP).[31] However, marked orthokeratosis with a corrugated surface is not a typical histologic finding in

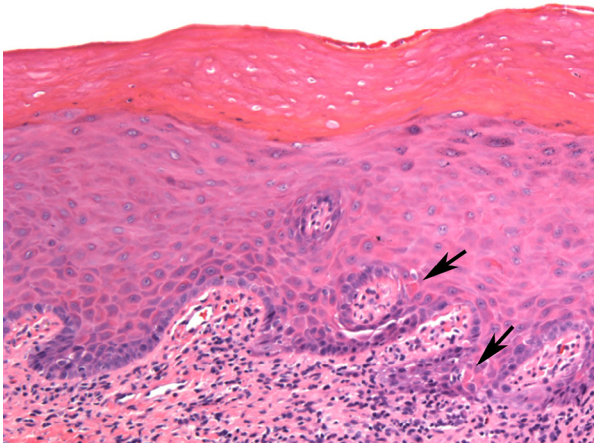

Fig. 6. Biopsy of early oral proliferative verrucous leukoplakia. Epithelium surfaced by orthokeratin with a slight corrugated surface. Dyskeratosis present in the basal/parabasal layer *(arrows)*. (Original magnification ×200).

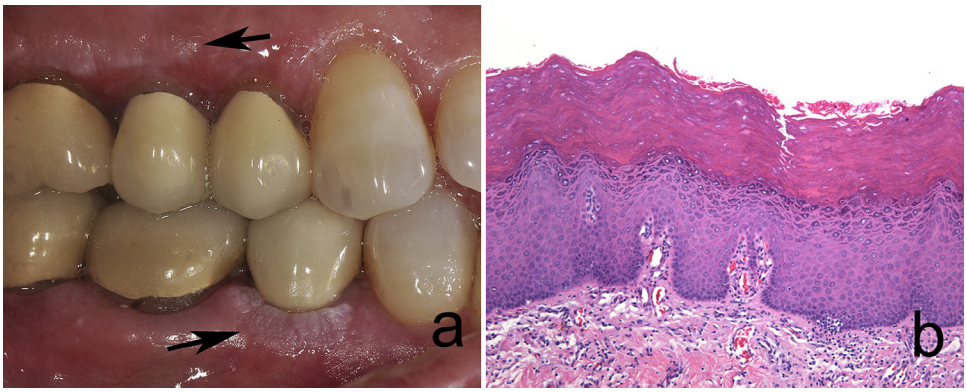

Fig. 7. Clinical presentation of proliferative verrucous leukoplakia illustrating the varied keratinization. With progression, the lesions can become more hyperkeratotic and verrucoid *(arrows)* (**A**); the histology often corresponds to the clinical appearance: marked orthokeratosis with a verrucous architecture. A normal epithelial maturation is present (**B**) (original magnification ×100).

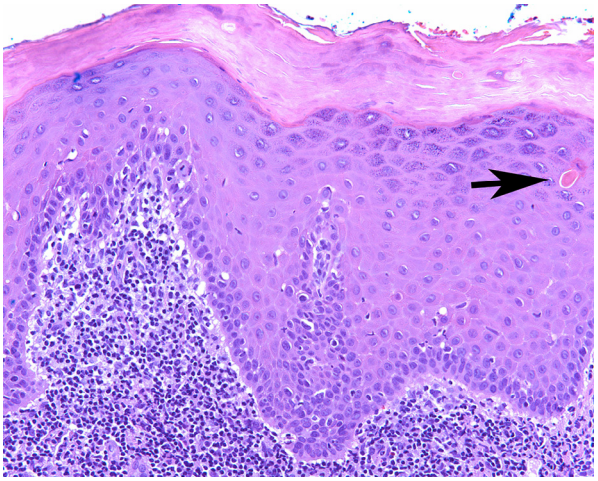

Fig. 8. Proliferative verrucous leukoplakia with lichenoid features: prominent orthokeratosis, dyskeratosis *(arrow)* and a lymphohistiocytic infiltrate subjacent to the basal cells (original magnification ×200).

OLP.[32,33] The presence of any dysplasia also precludes a diagnosis of OLP. Clinically, these 2 entities can share some features but the thickened homogeneous leukoplakia, particularly of the gingiva in PVL, is distinct from gingival OLP (Figure 9).[32,33] Alveolar ridge keratosis can also exhibit marked orthokeratosis, although usually without inflammation unless there is secondary ulceration (Figure 10).[34,35] This entity is considered to represent a frictional, reactive keratoses. The retromolar pad is a common site for these lesions, most of which are benign hyperkeratosis. However, because there are microscopic similarities between alveolar ridge keratoses and early PVL, clinical correlation is essential.

With progression, PVL lesions can exhibit marked AVH with or without dysplasia (Figure 11). This is a unique pattern of epithelial progression that can share features of verrucous carcinoma (VC) (Figure 12).[27,30] The method to make that distinction is not well defined and may be ambiguous. AVH has an exophytic growth pattern with epithelial hyperplasia. The epithelial rete are elongated and slender and may show anastomosis. AVH rete lack the bulbous downgrowth typical of VC, where the rete extend below the level of the adjacent epithelium. The epithelial cells in VC are composed of bland cells with abundant eosinophilic cytoplasm. Cytologic features of dysplasia can be present in AVH and is not typical of VC (Figure 13A). In VC, normal mitotic figures may be appreciated in the basal or parabasal layer, but not cytologic atypia (Figure 13B). However, it is recognized that VC can exhibit minimal dysplasia and minimal invasion, but the clinical behavior is comparable with that of VC, rather than that of OSCC.[36] Furthermore, oral verrucous hyperplasia (OVH) can transform into VC.[2,3,13,32]

In an attempt to standardized and apply criteria to the clinical and histologic features of OVH in patients in the Asian region, a consensus meeting was held in 2013 in Malaysia. The working committee comprised of clinicians and pathologists with expertise in OPMDs and oral cancer. Rosnah et al. developed standardized criteria for the diagnosis of exophytic verrucous hyperplasia to ascertain the potential for malignant transformation.[37] These proposed criteria defined exophytic verrucous hyperplasia as a discrete and solitary lesion; PVL was not included in the study. The study evaluated both clinical and histologic diagnostic criteria to distinguish OVH from VC, papillary squamous cell carcinoma (SCC) and SCC with papillary features. The working committee's proposed criteria for OVH were keratinized exophytic verrucapapillary surface, +/– keratin plugging, epithelial hyperplasia with acanthosis and basal cell hyperplasia, lack of downward growth compared with the adjacent normal epithelium, +/– OED, and +/– lymphocytic infiltrate.[37] The authors acknowledged diagnostic pitfalls that could be encountered when reviewing incisional biopsy specimens. In their series, some surgical specimens

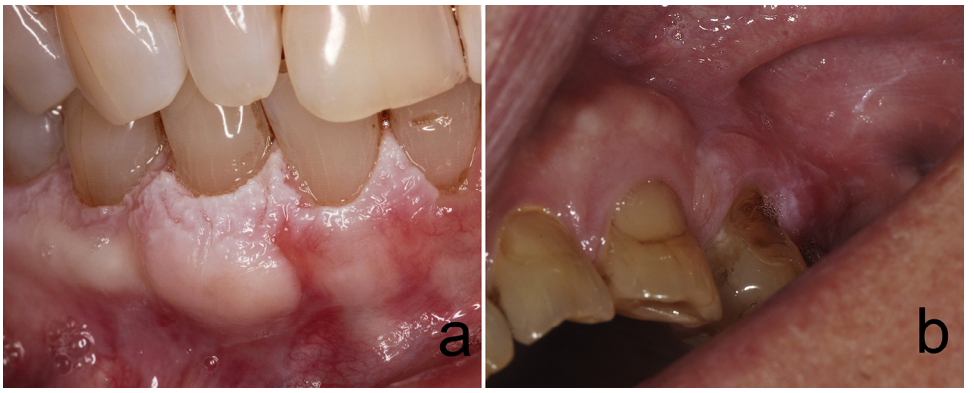

Fig. 9. Proliferative verrucous leukoplakia often affects the attached gingiva and with progression presents as diffuse white thickened plaques with a corrugated surface. **A**, This is dissimilar to oral lichen planus of the gingival that will have an erythematous component and lacks the thickened plaques (**B**).

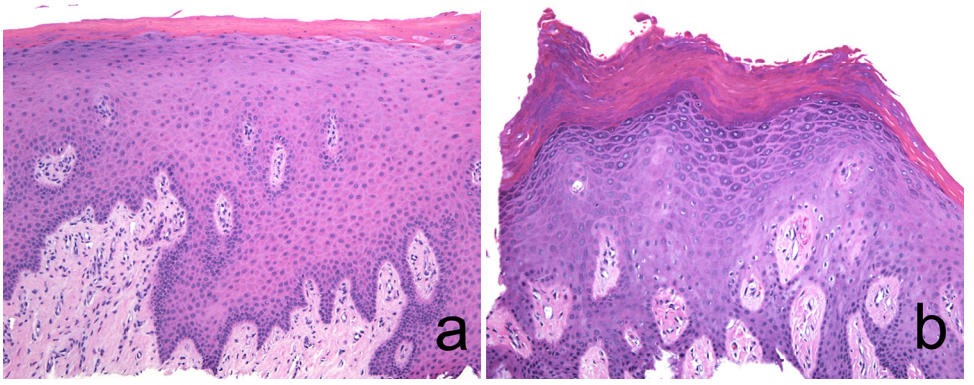

Fig. 10. Alveolar ridge keratosis can exhibit either parakeratosis (**A**) or orthokeratosis (**B**). The surface configuration can be flat or showed mild papillomatosis. There are long and anastomosing epithelial rete and lack of inflammation. No epithelial dysplasia is seen (original magnification ×200).

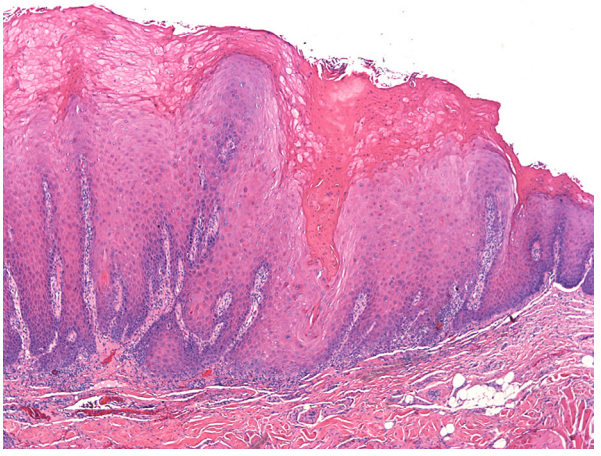

Fig. 11. Atypical verrucous hyperplasia in a patient with proliferative verrucous leukoplakia. Prominent keratosis with a verrucous architecture, hyperplastic elongated epithelial rete (original magnification ×100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04721.*

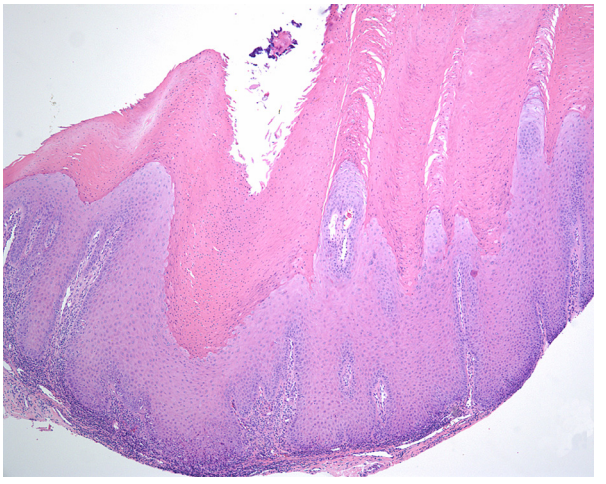

Fig. 12. Verrucous carcinoma exhibiting the typical bulbous rete (original magnification ×100).

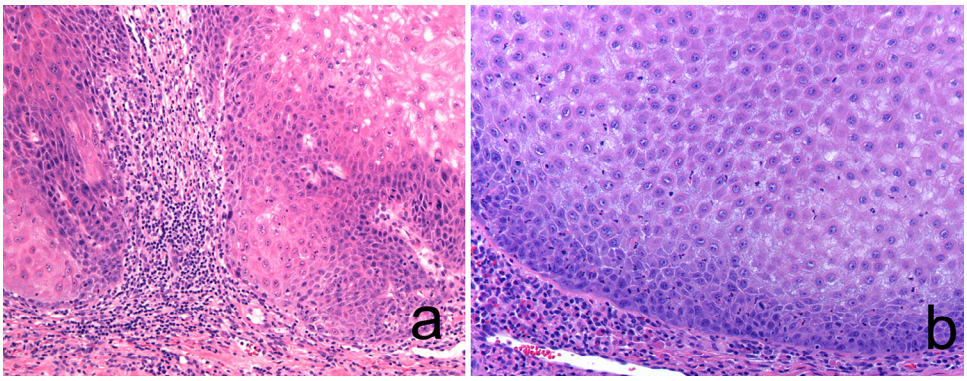

Fig. 13. High-power image of Figure 11 shows epithelial dysplasia with nuclear hyperchromasia and pleomorphism, dyskeratosis, and loss of normal maturation sequence (**A**) (original magnification ×200); high-power image of verrucous carcinoma (see Figure 12) shows occasional normal mitotic figures in the basal/parabasal layer, but cytologic atypia is not present. The epithelial cells are bland with prominent eosinophilic glassy cytoplasm (**B**) (original magnification ×200).

diagnosed as OVH on incisional biopsy had features of VC or SCC, papillary variant. The study's population comprised almost exclusively betel quid users (personal communication) who had solitary lesions, as already stated. However, these proposed standards could be a springboard for future studies developing histologic criteria for the diagnosis of PVL.

PITFALLS IN DIAGNOSIS OF OED AND OTHER OPMDS

Histologic mimics of OED and PVL can be seen in a variety of settings which can result in overdiagnosis and mismanagement. In addition to OLP, as discussed above, reactive keratoses that may resemble early PVL include previously described alveolar ridge keratosis, early smokeless tobacco keratosis (STK), and frictional keratosis (cheek/tongue biting). The histology of lichenoid lesions/OLP has been discussed in detail in recently published articles and will not be duplicated here.[31,33] Frictional keratosis usually demonstrates marked shaggy parakeratosis, epithelial hyperplasia, and ballooned cells with intracellular edema (Figure 14).[38] Shredding of the superficial keratin consistent with a parafunctional habit of biting is apparent, and often bacteria are noted on the keratin surface, particularly in biopsy specimens from the tongue. No epithelial dysplasia is present, and unless secondarily ulcerated, inflammation is not significant. Early STK related to tobacco products used in North America and western Europe, rather than products typically associated with Southeast Asian countries, is usually reversible on cessation of use of these products.[39] In early lesions, the epithelium shows marked parakeratosis with a focal wavy or chevron keratinization (Figure 15). Similar to frictional keratosis, intracellular edema with ballooned cells are often seen. Epithelial dysplasia is generally absent, although increased basal cell hyperchromasia is often present. These histologic features are in no way specific to STK; however, with the corresponding clinical information, a pathologist can generally make the observation that the histology is consistent with that of STK.

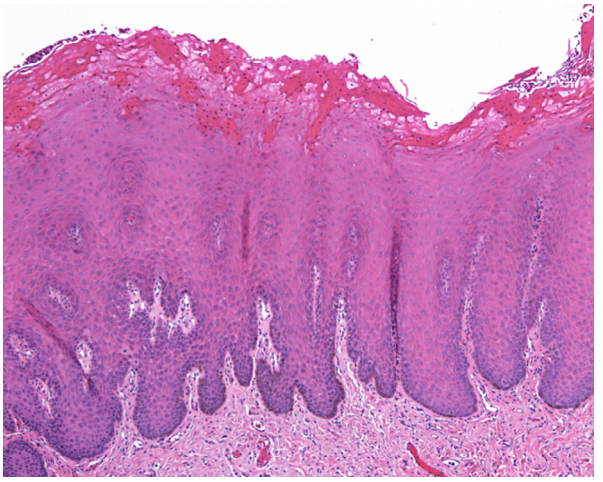

Fig. 14. Typical findings of frictional keratosis include a shaggy, hyperparakeratosis surface often with surface bacteria. The epithelium is acanthotic, and ballooned cells with intracellular edema are evident. Inflammation is usually absent (original magnification ×100).

Both inflamed epithelia and regenerative epithelia, a common occurrence in the oral cavity, can show reactive epithelial changes. There is a paucity of reports on this topic specific to the oral cavity, although attempts have been made to describe atypia versus true dysplasia in the setting of Barret esophagus.[40,41] In the milieu of an active ulcer, such as an aphthous ulcer or traumatic ulcerative granuloma, distinguishing reactive atypia from true dysplasia may be difficult. Nuclear hyperchromatism and pleomorphism are usually less severe in the regenerating epithelium, and generally, a normal to

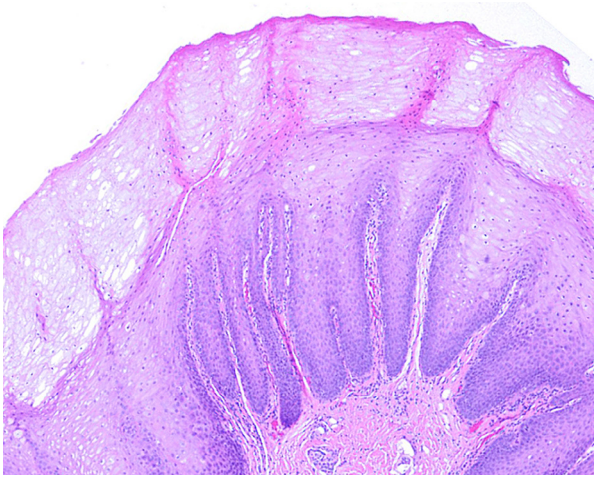

Fig. 15. Smokeless tobacco keratosis with chevron keratinization, hyperparakeratosis, and intracellular edema. The epithelium is acanthotic with elongated rete. No dysplasia is seen (original magnification ×100).

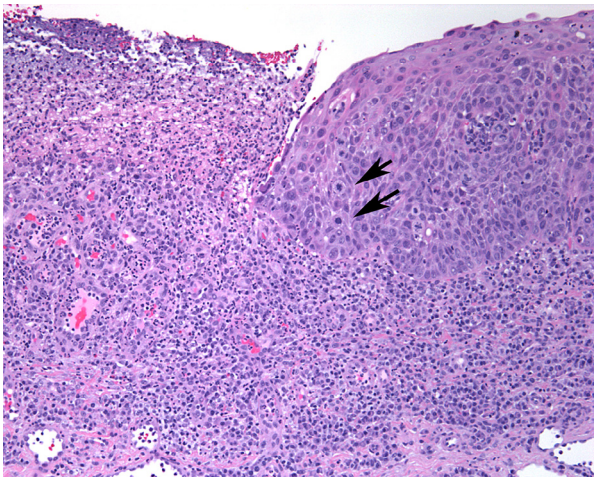

Fig. 16. Traumatic ulcerative granuloma. Cytologic atypia comprised of nuclear hyperchromasia and mitotic figures adjacent to the ulcer bed are present *(arrows)*. These cytologic findings can be a normal component of regenerative epithelium.

near-normal nuclear/cytoplasmic ratio is maintained (Figure 16). High-grade OED, as discussed earlier, usually should not be seen. Nuclear polarity should be maintained. Herpetic ulcers may also show epithelial atypia, but viral cytopathic features, including virally altered acantholytic epithelial cells (Tzanck cells) with ballooning degeneration of the nuclei with chromatin condensation around the periphery and multinucleation, are often present, thus excluding true OED.

Candida, a commensal organism, is an opportunistic yeast that can cause oral infection. Although these fungi do not normally cause pathology, in settings of immunosuppression, ranging from antibiotic use to diabetes

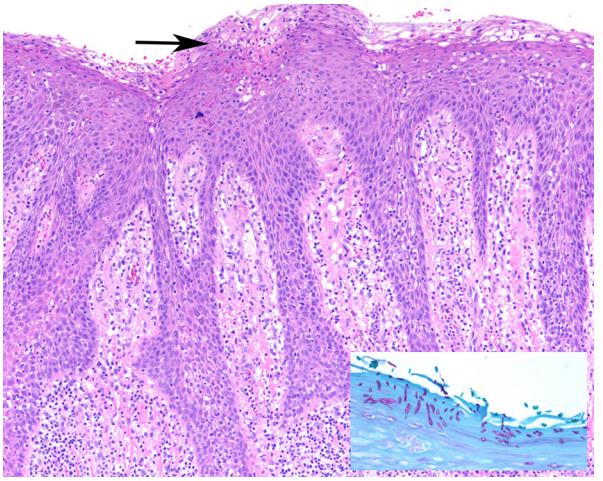

Fig. 17. Hyperplastic candidiasis. Markedly elongated epithelial rete with inflammatory cell transmigration and neutrophilic microabscesses in the superficial keratin *(arrow)*. Periodic acid–Schiff staining highlights the fungal pseudohyphae and spores *(inset)* (original magnification ×100).

to HIV infection, an overgrowth of *Candida* can occur, resulting in morbidity. *Candida* spp. can form biofilms on dentures and dental implants and may not respond to treatment even after appropriate antifungal treatment.[42,43]

In cervical cytologic specimens associated with candidal colonization features of epithelial cells, including nuclear enlargement, hyperchromasia, perinuclear halos, and cytoplasmic orangeophilia, are reported.[44] As these findings are in Papanicolaou-stained cytology specimens, these cytologic features may not translate to hematoxylin and eosin–stained biopsy specimens. Histologic features of *Candida* colonization are epithelial hyperplasia with parakeratosis and superficial neutrophilic microabscesses (Figure 17).[43] Periodic acid–Schiff staining highlights spores and pseudohyphae in the superficial keratin (see Figure 17, inset). Variable inflammation in the connective tissue can be incited by the organism, and interface mucositis may be prominent and mistaken for an OPMD. Basal cells may show enlarged hyperchromatic nuclei, causing concerns about OED. Attempts to link OED and/or OSCC to *Candida* infection have been investigated. No studies have demonstrated that *Candida* infection has a direct role in the development of OED or OSCC, although some studies have demonstrated increased oral yeast colonization in patients with oral cancer.[45] However, because oral cancer is a multifactorial disease, distinguishing yeast infection as a causative factor from other causative factors, including tobacco use, may be difficult.

Admittedly, in some situations, it may not be possible to distinguish between reactive changes from true dysplasia in an oral biopsy specimen. Unlike other mucosal sites, the oral cavity is easily visualized without the need for anesthesia or specialized equipment. After

appropriate treatment or the anticipated healing time, the clinician can re-evaluate the questionable area. Repeat biopsy should be performed on any suspicious lesions or they should be clinically monitored, depending on clinical findings. It should be emphasized that in these situations, clear communication among the clinician, surgeon, and pathologist is imperative to ensure appropriate patient management.

CONCLUSIONS

Despite its shortcomings, histologic grading based on morphology remains the accepted method for the diagnosis of OED. One caveat when grading OED on the basis of an incisional biopsy is to recognize that the "worse" area may not be available for evaluation. Furthermore, OED grading is not a predictive tool for progression to malignancy. Active surveillance of clinically suspicious lesions therefore remains the mainstay of patient management.[46]

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