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ORIGINAL PAPER

Architectural Alterations in Oral Epithelial Dysplasia are Similar in Unifocal and Proliferative Leukoplakia

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Abstract

The current WHO histopathologic criteria for oral epithelial dysplasia (ED) are based on architectural and cytologic alterations, and do not address other histopathologic features of ED. Here we propose new diagnostic criteria including *architectural*, *organizational*, and *cytologic* features for oral ED. Cases of unifocal leukoplakia (UL) and proliferative leukoplakia (PL) with clinical photographs and follow-up information were identified. Only cases that showed minimal cytologic atypia or mild ED were used to demonstrate critical architectural changes as defined in this study. Eight biopsies from eight UL patients and 34 biopsies from four PL patients were included. The biopsies showed (a) corrugated, verrucous or papillary architecture, (b) hyperkeratosis with epithelial atrophy, (c) bulky squamous epithelial proliferation, and (d) demarcated hyperkeratosis and "skip" segments. The *architectural* alterations defined here are as important as the currently used criteria for the diagnosis of ED. Clinicopathologic correlation when diagnosing oral ED is also of the utmost importance in accurate diagnosis.

Keywords Oral epithelial dysplasia · Malignant transformation · Architectural alteration · Leukoplakia · Proliferative verrucous leukoplakia

Introduction

Oral leukoplakia is a precancerous condition [1]. It was defined in 2005 as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer," and this definition still stands today [1, 2]. As such, a true leukoplakia is a clinical term only after having ruled out other specific diagnoses. Histopathologically, leukoplakia exhibits hyperkeratosis or parakeratosis, epithelial atrophy or hyperplasia, epithelial dysplasia (ED), carcinoma-in-situ or invasive squamous cell carcinoma (SCC) [2, 3]. Leukoplakia progresses to malignancy in 0.1–36.4% of cases and the time to malignant transformation varies depending on the study, the severity of ED, and the length of follow-up [4–8]. Leukoplakias that exhibited ED at the time of biopsy showed malignant transformation in 6.6–36.4% of the cases, while lesions without ED at the time of biopsy showed malignant transformation rate of 0.1–14.0% [9–13].

Histopathologic signs of ED are currently divided into *architectural* and *cytologic* features [2]. Leions are divided into low, moderate, and severe ED depending on whether $< 1/3$, $> 1/3$ but $< 2/3$, or $> 2/3$ of the epithelium (but not full thickness) is affected by dysplastic cells, respectively (Table 1) [14]. In keeping with the assessment of ED at other sites, a binary system of low- and high-grade ED has been proposed [15]. However, other aspects of *architectural* changes, such as corrugated, verrucous or papillary morphology, are not part of the current criteria for diagnosing and grading ED [2, 14]. Verrucous hyperplasia (clinically verrucous leukoplakia) is characterized by verrucous or papillary epithelial hyperplasia with an exophytic growth pattern where cytologic features of dysplasia are variable and may be minimal to absent [14, 16, 17]. Malignant transformation

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Table 1 Histopathologic features of oral epithelial dysplasia

	Proposed criteria	WHO criteria
Architectural features	Corrugated/verrucous/papillary morphology Hyperkeratosis and epithelial atrophy Bulky squamous proliferation, exophytic/endophytic growth Skip segments and demarcated hyperkeratosis Drop-shaped rete ridges	Irregular epithelial stratification Loss of polarity of basal cells Drop-shaped rete ridges Increased number of mitotic figures Abnormally superficial mitotic figures Premature keratinization of single cells Keratin pearls within rete ridges Loss of epithelial cell cohesion
Organizational features	Loss of upward maturation in the epithelium Dyscohesion Premature keratinization/dyskeratosis Keratin pearls within rete ridges Suprabasal mitotic figures	
Cytologic features	Cellular/nuclear pleomorphism Basal cell hyperplasia Increased nuclear:cytoplasmic ratio Atypical mitotic figures Enlarged and multiple nucleoli Hyperchromasia and coarse chromatin Dyskeratosis and/or glassy cytoplasm	Abnormal variation in nuclear size Abnormal variation in nuclear shape Abnormal variation in cell size Abnormal variation in cell shape Increased nuclear:cytoplasmic ratio Atypical mitotic figures Increased number and size of nucleoli Hyperchromasia

occurs in up to 10% of cases in verrucous hyperplasia [18]. However, some of such verrucous hyperplasia called "mass-type," likely already represents verrucous carcinoma or papillary SCC [18]. In addition, proliferative verrucous leukoplakia, a form of proliferative leukoplakia (PL, a more accurate term since many but not all lesions are verrucous) is an uncommon form of oral leukoplakia that often shows verrucous hyperplasia with minimal to no ED in biopsies performed in the early stage of the disease [19–21]. PL is characterized by the multifocal geographic expansion of white plaques, sometimes verrucous, and development of SCC in 70–100% of cases with long-term follow-up [20–23]. Most patients undergo multiple biopsies over years and decades. These show hyperkeratosis and often verrucous hyperplasia or epithelial atrophy without evidence of ED in the beginning, and subsequently varying degrees of ED and finally invasive SCC [20, 23–25].

This histopathologic progression of PL is particularly useful in understanding oral ED because of the high rate of malignant transformation despite early lesions showing no microscopic evidence of dysplasia. Such hyperkeratotic lesions without obvious ED have been referred to as keratosis of uncertain significance to emphasize that these lesions may look innocuous histopathologically, but when evaluated in the context of the clinical presentation, raise suspicions for early ED [3]. Furthermore, verrucous carcinoma which is characterized by an endophytic squamous epithelial proliferation with a blunt and pushing pattern of invasion on a broad front rather than the conventional invasion pattern of single cells or tumor islands, exhibits minimal-to-mild cytologic atypia and the diagnosis is rendered primarily on the bulky verruciform or papillary morphology and its endophytic growth pattern [14, 17, 26–29]. Verrucous hyperplasia illustrates the significance of *architectural* changes in determining the fate of lesions.

The objective of this study is to demonstrate *architectural* alterations of oral ED, defined here as gross morphologic changes noted on low microscopic magnification with

respect to four criteria illustrated through a series of cases of unifocal leukoplakia (UL) and PL (defined here as multifocal non-contiguous leukoplakias).

Materials and Methods

Cases were selected from the patient archives of the Division of Oral Medicine and Dentistry and Department of Pathology at the Brigham and Women's Hospital (BWH), Boston, MA, and StrataDx Inc., Lexington, MA. This study was approved by the Institutional Review Board of BWH. We included only cases of UL and PL with clinical photographs and follow-up information. The current features described as *architectural* by WHO are given the term *organizational* to reflect how keratinocytes relate to each other and to where they normally reside within the spinous layer [14]. *Cytologic* features mostly remain unchanged and are features that are best seen at high magnification and always seen on exfoliative cytology (Table 1).

Only cases that showed minimal cytologic atypia or mild ED with the following *architectural* alterations were included in the study.

1. Corrugated, verrucous or papillary architecture.
2. Hyperkeratosis and/or parakeratosis with epithelial atrophy and minimal/no interface inflammation, bearing in mind that different intra-oral sites have different baseline thickness of the epithelium. For example, epithelial atrophy for the buccal mucosa may be the normal thickness of epithelium for the ventral tongue, floor of mouth, and soft palate.
3. Bulky squamous epithelial proliferation with an exophytic and/or endophytic growth pattern (the former often associated with corrugated/verrucous/papillary architecture). Downward epithelial proliferation for at least three times the normal thickness of the epithelium was considered bulky endophytic proliferation. Spongiosis and leukocyte exocytosis should be minimal.
4. Demarcated hyperkeratosis and "skip" segments where the hyperkeratosis was sharply demarcated and there

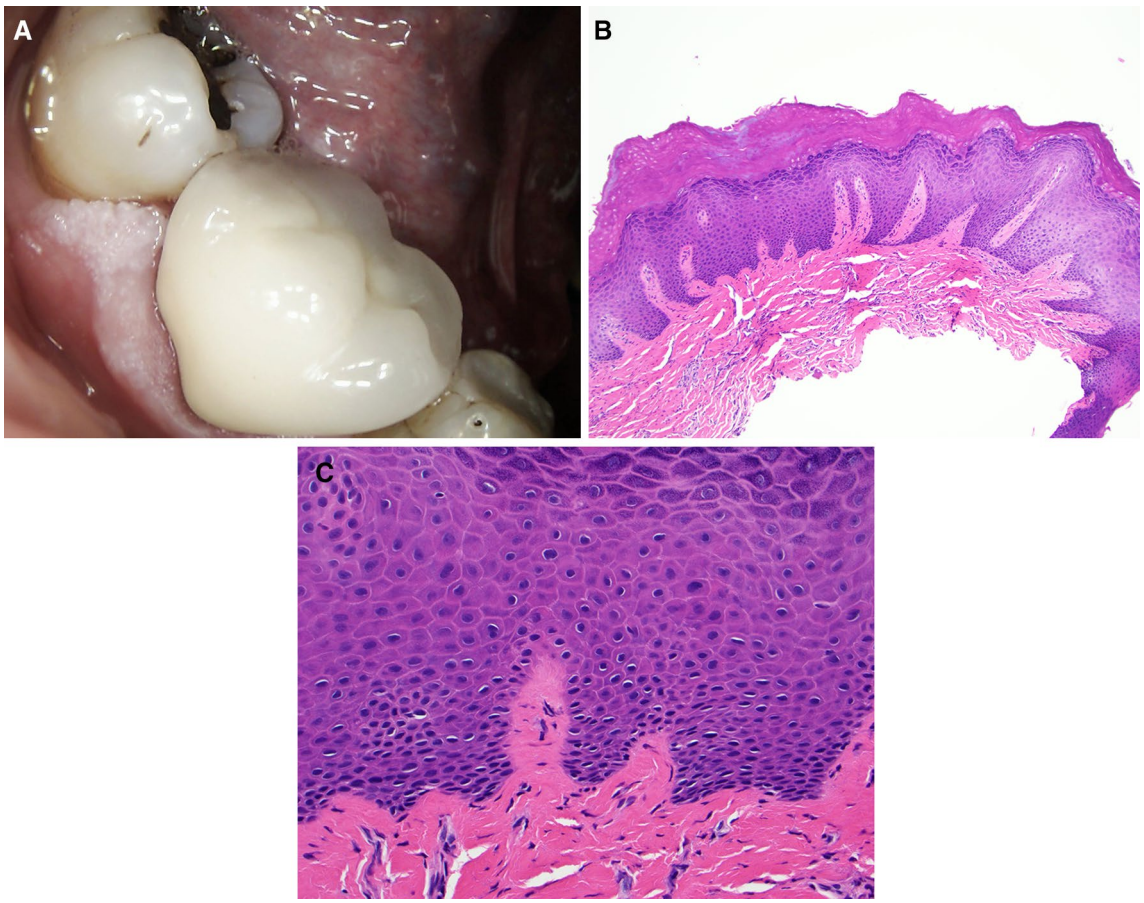

Fig. 1 Case 1 **a** Unifocal non-homogenous leukoplakia on the mandibular gingiva exhibiting corrugated surface. **b** Corrugated hyperkeratosis, hypergranulosis and epithelial hyperplasia (H&E, original magnification ×40). **c** No ED present (H&E, original magnification ×400)

was multifocal hyperkeratosis with intervening non-keratinized or normally keratinized epithelium.

These features were correlated with clinical findings and follow-up information was available on cases of PL where progression was defined as development of invasive SCC.

Results

Eight biopsies from eight patients with UL (Figs. 1, 2, 3, 4, 5, 6, 7, 8) and 34 biopsies from four patients with PL (Figs. 9, 10, 11, 12) were included in the current study. Demographic and follow-up information of the cases is provided in Tables 2 and 3. In the UL group, four cases were non-homogenous leukoplakia (verrucous and speckled) and four were homogenous leukoplakia (fissured and non-fissured).

Corrugated, Verrucous or Papillary Architecture

In the UL group, Cases 1–3 exhibited a corrugated/verrucous/papillary configuration with minimal ED which corresponded to clinical lesions of verrucous leukoplakias while Case 4 exhibited focal corrugations and was clinically a homogenous leukoplakia (Figs. 1a–c, 2a–c, 3a–d, 4a–d). In the PL group, Cases 9 and 10 exhibited papillomatosis and corrugated architecture (Figs. 9a–f, 10a–d). In the PL group, 23/34 (67.6%) of lesions showed a corrugated/verrucous/papillary configuration.

Hyperkeratosis with Epithelial Atrophy and Minimal/No Interfacial Inflammation

In the UL group, Cases 2, 4, and 5 presented with hyperkeratosis, epithelial atrophy, and mild chronic inflammation, without significant ED (Figs. 2a–c, 4a–c, 5a–c). Clinically, Case 2 was a verrucous leukoplakia, Case 4 was a

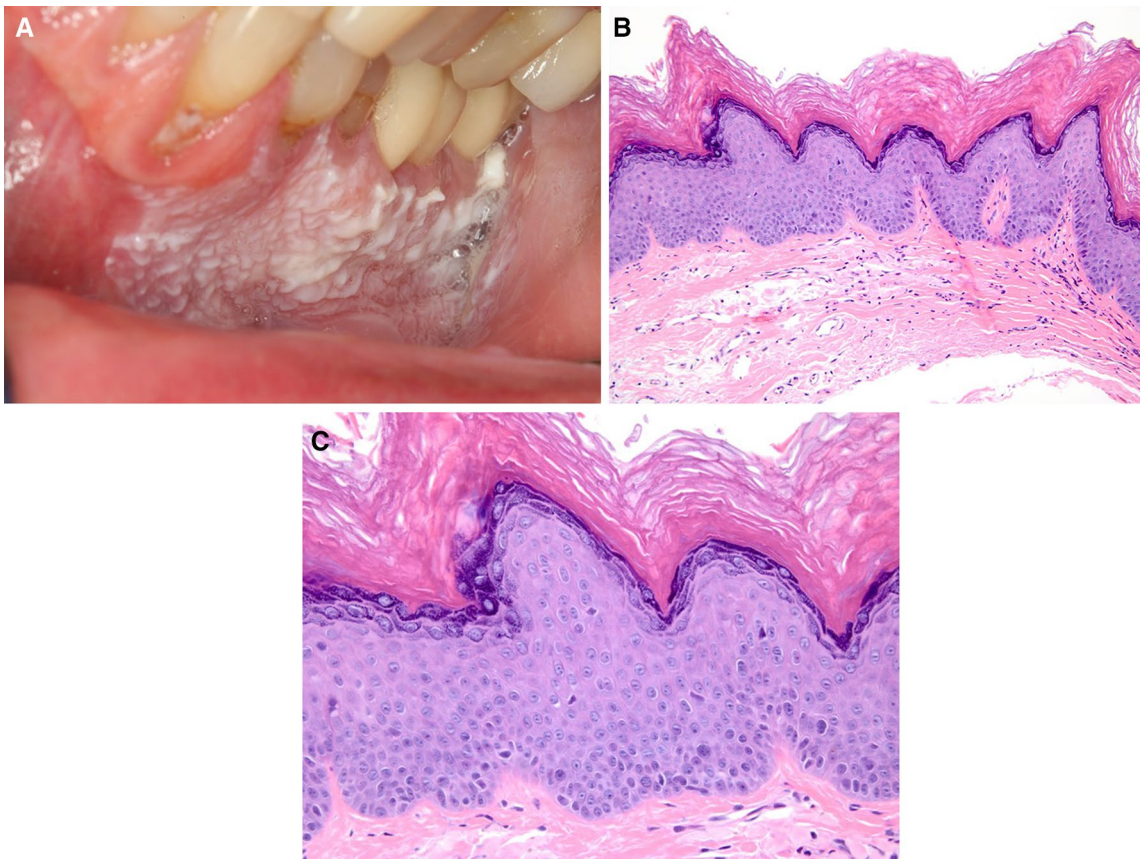

Fig. 2 Case 2 **a** Unifocal non-homogenous leukoplakia on the mandibular gingiva exhibiting corrugated surface. **b** Atypical verrucous hyperkeratosis and epithelial atrophy (H&E, original magnification ×100). **c** Minimal cytologic atypia present (H&E, original magnification ×400)

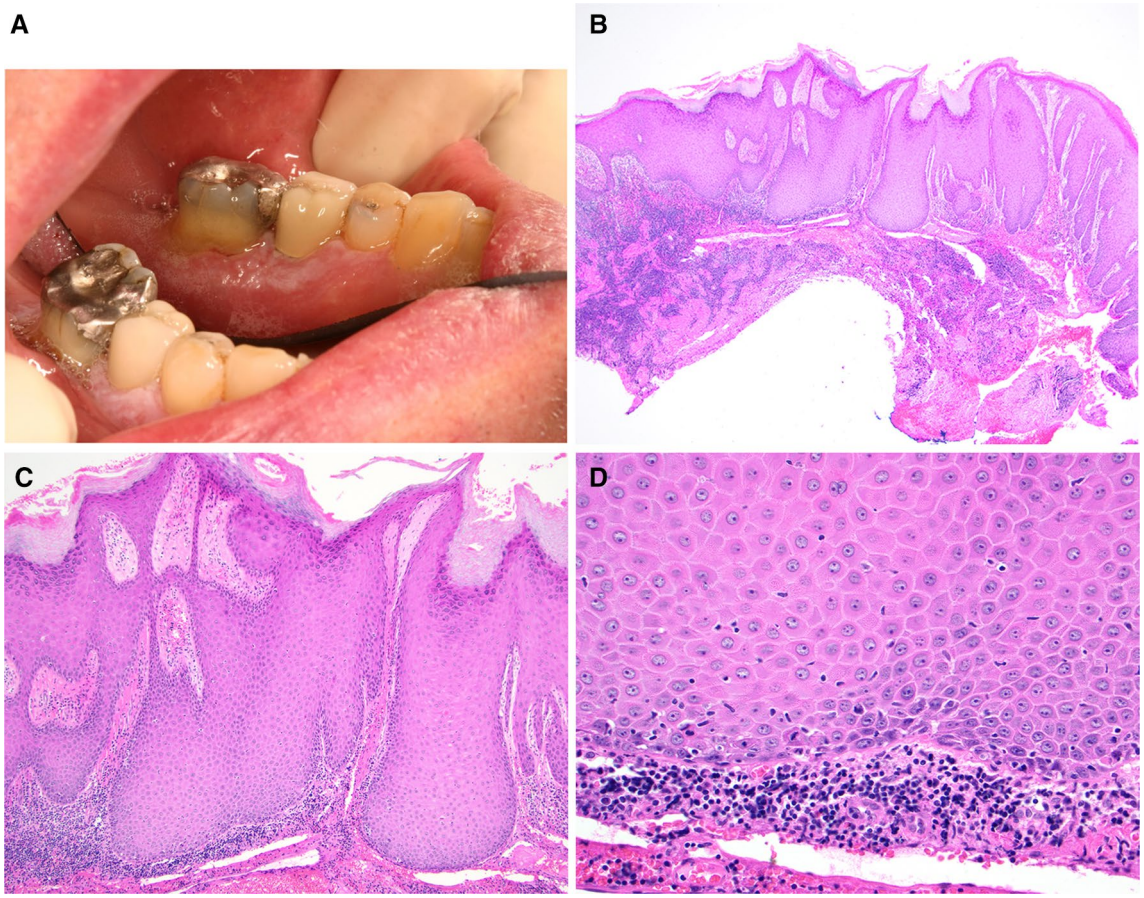

Fig. 3 Case 3 **a** Unifocal non-homogenous leukoplakia on the mandibular gingiva with a focally corrugated surface. **b** There is bulky, verrucous proliferation slightly exo- and endo-phytic forming bulbous rete ridges (H&E, original magnification ×40). **c** Bulbous rete ridges (H&E, original magnification ×200). **d** Minimal cytologic atypia and minimal chronic inflammatory infiltrate present (H&E, original magnification ×400)

non-fissured homogenous leukoplakia, and Case 5 was a fissured mostly homogenous leukoplakia. In the PL group, there were 15/34 (44.1%) specimens with hyperkeratosis, epithelial atrophy, and mild chronic inflammation; 12 of those were hyperkeratotic, and three were parakeratotic (Fig. 10a–d).

Bulky Squamous Epithelial Proliferation

In the UL group, Cases 3, 6, and 7 showed a bulky endophytic growth pattern with minimal ED (Figs. 3a–d, 6a–c, 7a–c). Case 3 was clinically a verrucous leukoplakia and Cases 6 and 7 were homogenous leukoplakias. In the PL group, 9/34 (26.5%) of specimens showed a bulky squamous proliferation (Fig. 12a–c) and 7/34 (20.6%) of specimens showed an exophytic growth pattern. Some specimens had both endophytic and exophytic components.

Demarcated Hyperkeratosis and "Skip" Segments

In the UL group, all the cases clinically showed a sharp demarcation (partially in some cases) of the hyperkeratotic

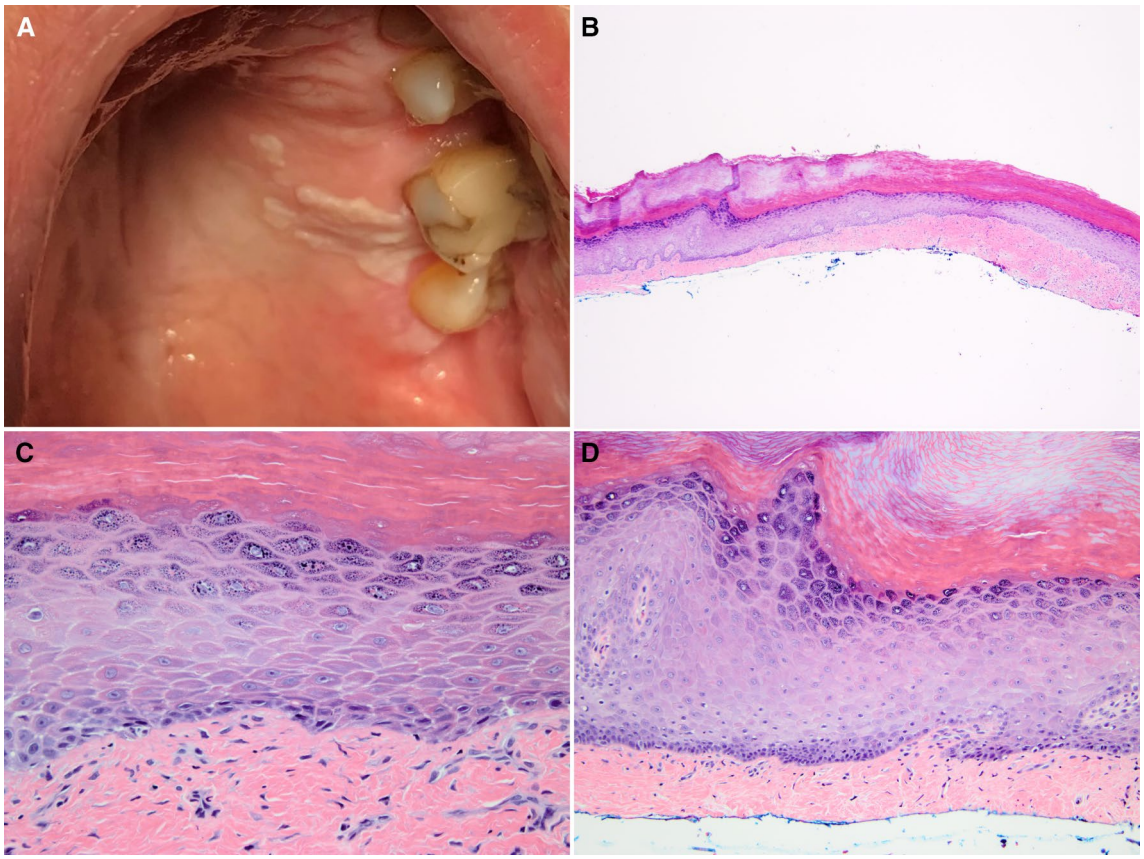

Fig. 4 Case 4 **a** Unifocal homogenous leukoplakia on the hard palatal mucosa. **b** Hyperkeratosis with hypergranulosis and epithelial atrophy (H&E, original magnification ×40). **c** No ED present (H&E, original magnification ×400). **d** Focal surface corrugation is identified (H&E, original magnification ×400)

area from the normal mucosa. Histopathologically, there is demarcated hyperkeratosis in Case 5 (Fig. 5d, e) and "skip" segments in Case 8 (Fig. 8a–c). In the PL group, lesions were at least partially demarcated in all cases, and 6/34 (17.6%) lesions exhibited skip segments or sharp demarcation (Figs. 10c, 11a–f).

Discussion

The diagnosis of mild ED has always been challenging with large inter-examiner variability [30–33]. Unlike mild ED, moderate and severe ED usually demonstrate higher inter-examiner agreement (Fig. 13a, b). Trauma, candidiasis, and inflammation may cause reactive epithelial atypia that shares many features with ED. As such, no single feature is diagnostic for ED but rather a constellation of features, correlated with the degree of inflammation and the clinical appearance of the lesion [34]. The importance of clinical correlation cannot be overstated, and this is particularly well-illustrated in the condition of PL. The recognition of this entity in 1985 was a result of realizing that the innocuous histopathology did not correlate with the clinical appearance of large, often multifocal lesions that progressed over years and decades from hyperkeratosis with epithelial atrophy, to dysplasia or/and invasive SCC in 70–100% of cases

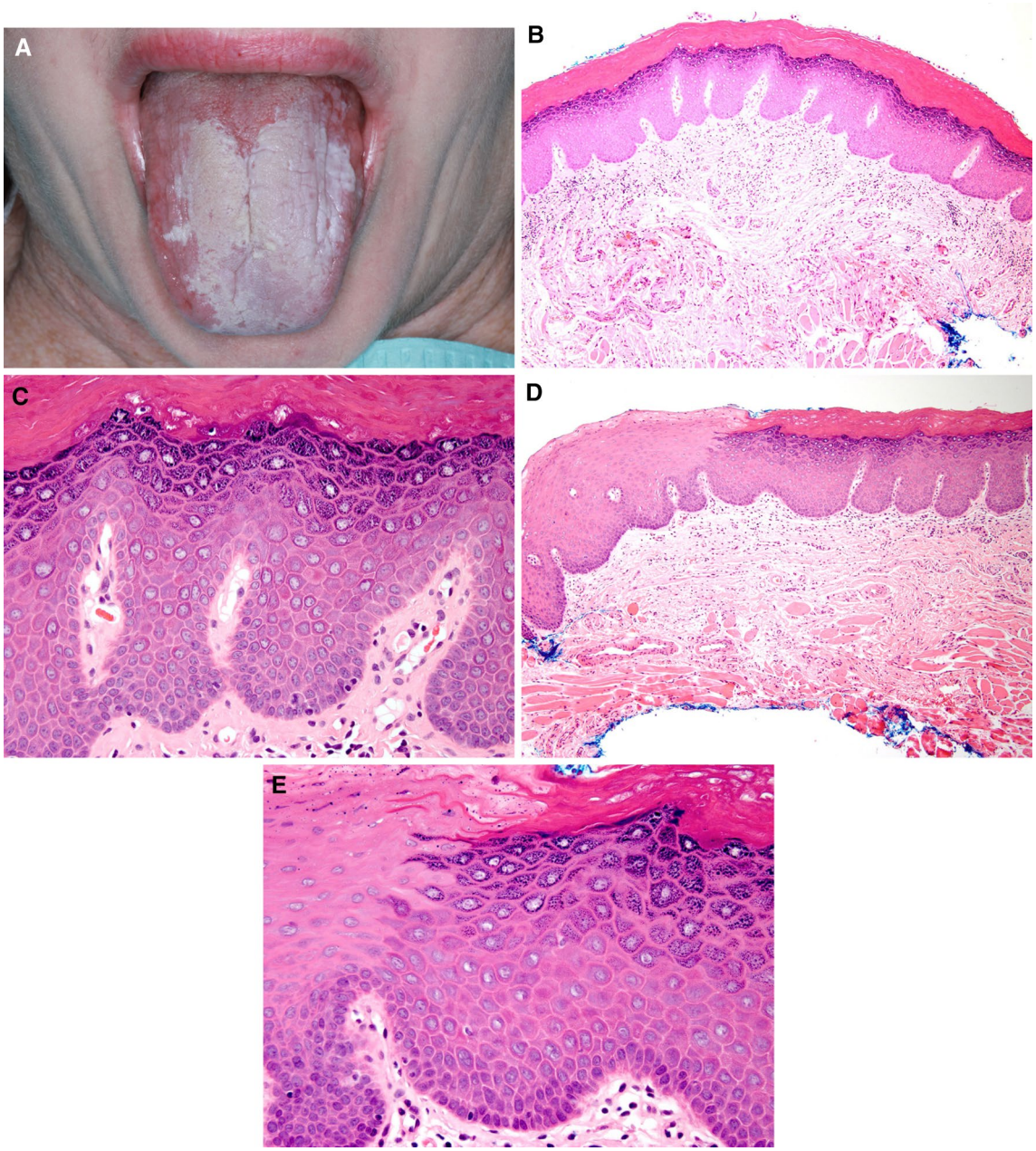

Fig. 5 Case 5 **a** Unifocal fissured homogenous leukoplakia on the dorsal tongue. **b** Demarcated and corrugated hyperkeratosis with hypergranulosis, and epithelial atrophy (loss of papillae) (H&E, original magnification ×100). **c** Minimal cytologic atypia present (H&E, original magnification ×400). **d** Demarcated hyperkeratosis is noted (H&E, original magnification ×100). **e** Minimal ED with mild chronic inflammation present (H&E, original magnification ×400)

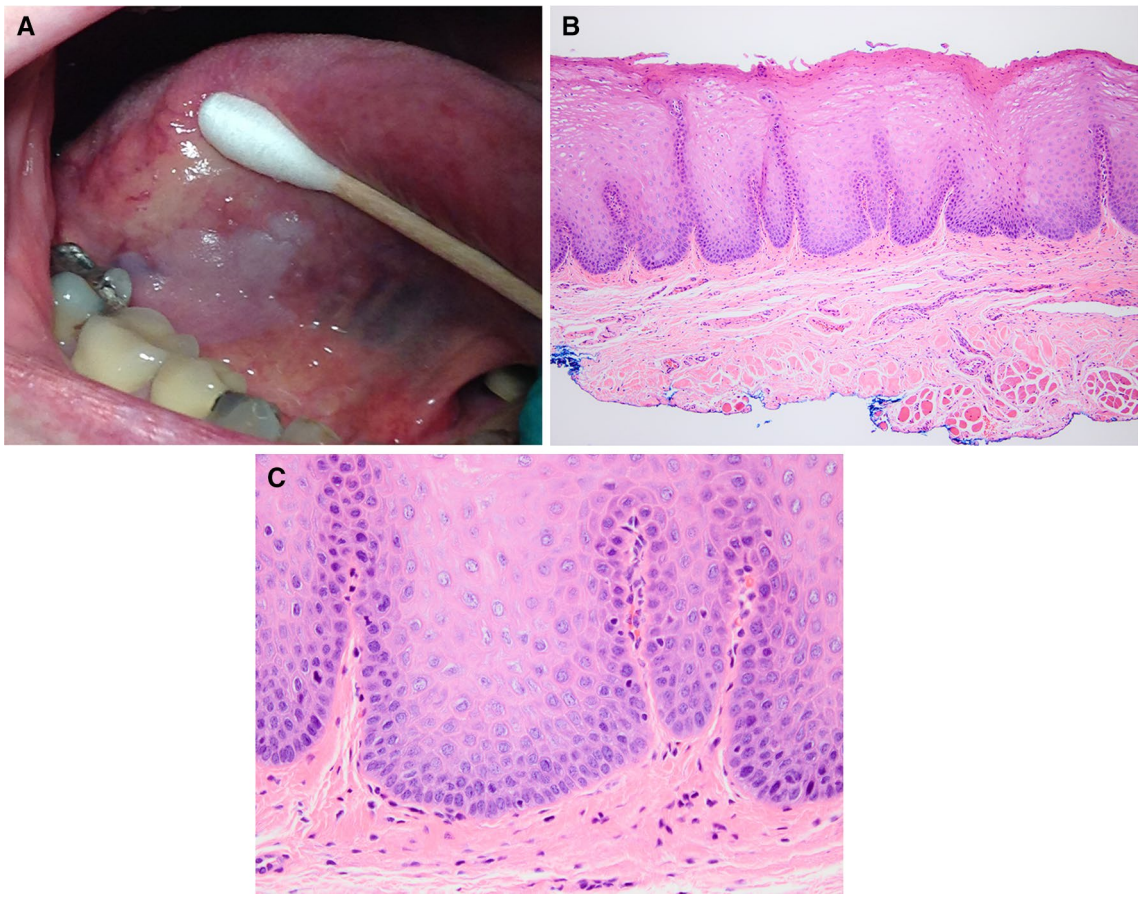

Fig. 6 Case 6 **a** Unifocal homogenous leukoplakia on the ventral tongue. **b** There is bulky squamous epithelial proliferation (H&E, original magnification×100). **c** Minimal ED present (H&E, original magnification×400)

[19, 25, 35, 36]. Support for this finding can be found in previous studies that showed lesions greater than 200 mm^2 correlated with poorer prognosis even if there was no ED on biopsy [37]. In this regard, the histopathologic features of early stage of PL inform the features of very early ED. PL and UL share similar histopathologic features, whether *architectural*, *organizational*, or *cytologic* [34].

We believe that the assessment of oral ED should be based on three categories of findings, namely *architectural* (readily seen at low power), *organizational* (readily seen at intermediate to high power) and *cytologic* which are the conventional features best identified on high power microscopy and on exfoliative cytology (Table 1) [2, 31, 32, 34]. The *architectural* features described by Kujan et al. [15] and in the WHO classification [14] fall primarily into the category of *organizational* changes within the epithelium as described here. *Organizational* features show how keratinocytes have lost their normal relationship to each other (e.g. dyscohesion), and to their abnormal position within the epithelium such as location of basal cells and mitoses beyond the usual 1–2 layers of the basal and parabasal cells. We suggest that the term "*architectural* features" as defined in this study be used for features that are clearly discernible with low power microscopy and refer to gross microscopic morphology.

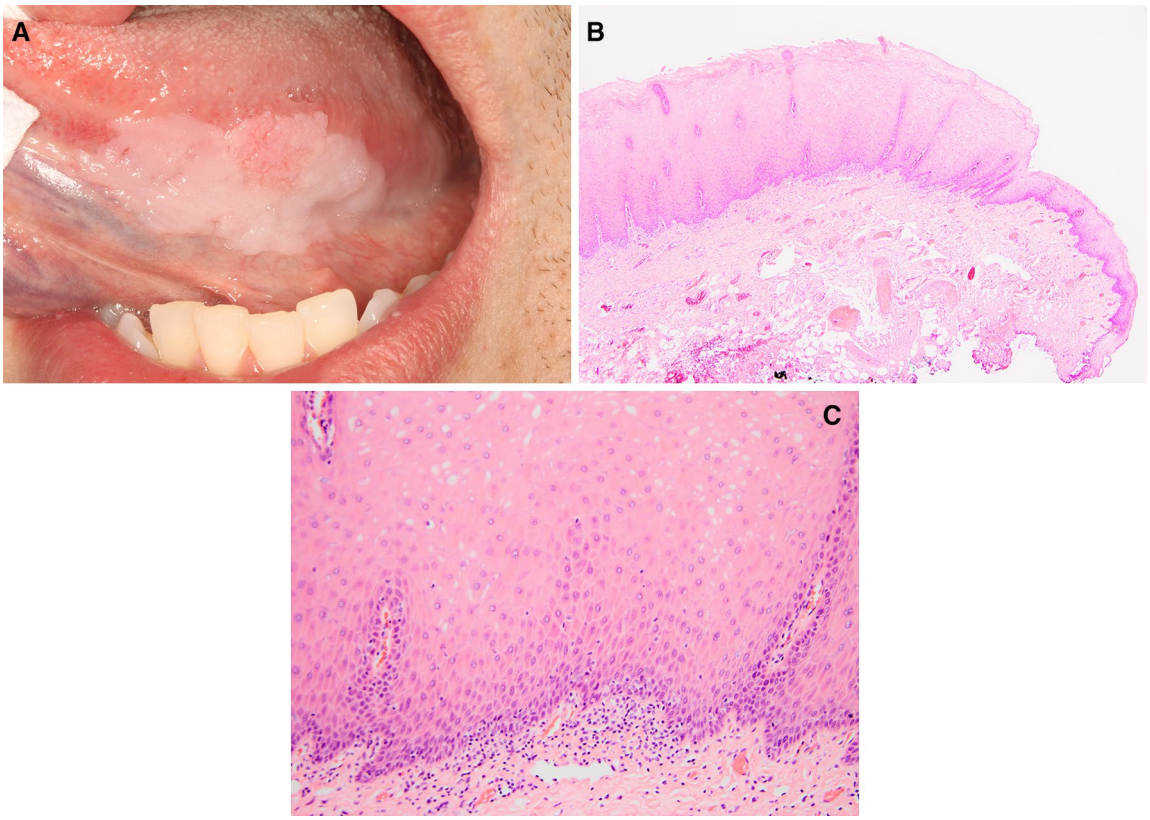

Fig. 7 Case 7 **a** Unifocal homogenous leukoplakia on the left ventral tongue. **b** There is bulky, exophytic squamous epithelial proliferation (H&E, original magnification ×100). **c** No ED present (H&E, original magnification ×400)

These include the well-recognized corrugated/verrucous/papillary architecture, hyperkeratosis with epithelial atrophy, bulky and usually endophytic squamous proliferation, sharply demarcated keratinization and "skip" segments, as well as bulbous and drop-shaped rete ridges, this last feature being already well-established. These *architectural* features are seen in both PL and UL lesions, often with ED and as such, should be considered worrisome even in the absence of cytologic dysplasia in the leukoplakic lesions.

Corrugated/verrucous/papillary architecture was noted in 67.6% of biopsies of PL, and this often occurred without, or with minimal evidence of cytologic dysplasia. Historically, non-homogenous leukoplakias with a verrucous/nodular appearance progress to SCC in 33 per 1000 cases every year with an overall transformation rate 50–60% [14, 38, 39]. This architecture is a common predictor of malignant transformation especially to verrucous carcinoma and must be included in any system for grading ED [14, 17, 40].

In the original and seminal article on PL by Hansen, many PL cases showed hyperkeratosis with epithelial atrophy [25]. In our PL cohort, 15/34 cases (44.1%) showed hyperkeratosis and epithelial atrophy. Most classifications focus on epithelial hyperplasia as precursors to ED [41, 42]. However, such hyperplasia or acanthosis is seen frequently in response to local irritation and injury (e.g., morsicatio mucosae oris and benign alveolar ridge keratosis) (Fig. 13c, d) [43–45]. It would be highly unusual to see epithelial atrophy in reaction to local irritation. In addition, the clinical appearance of a

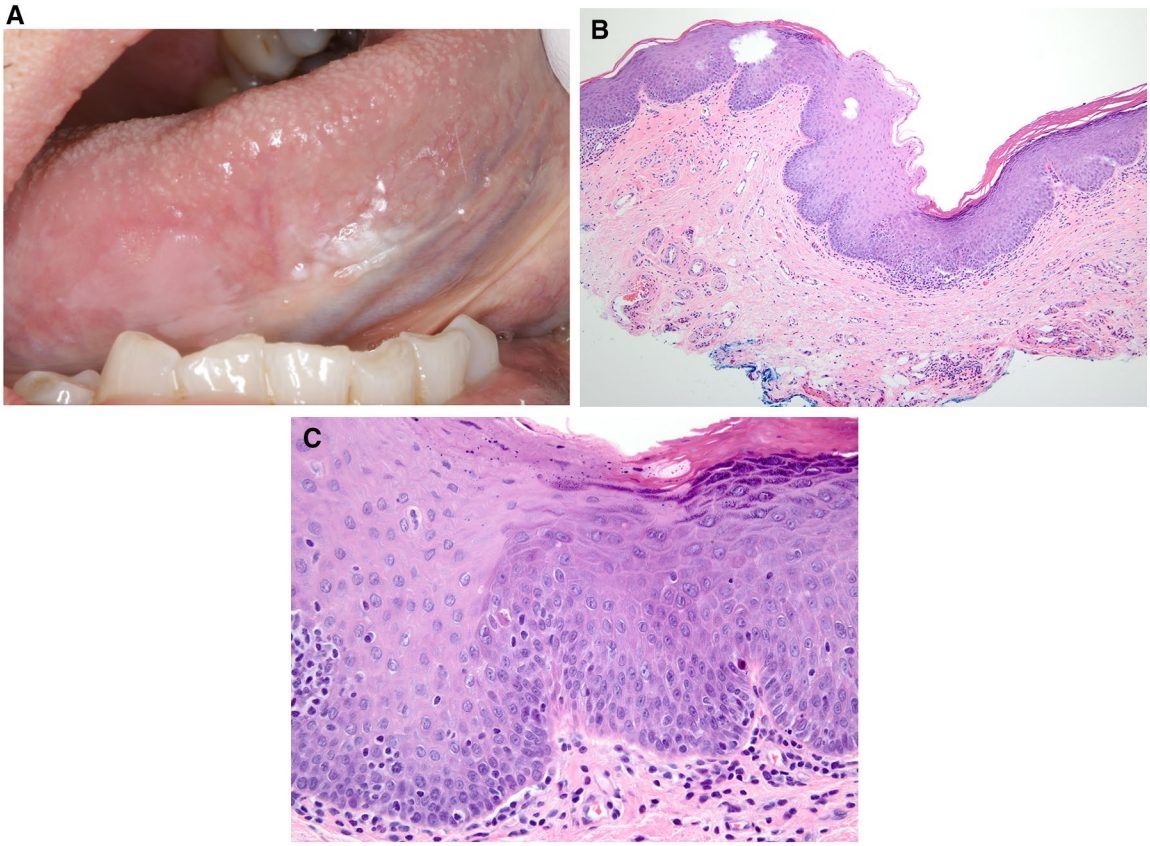

Fig. 8 Case 8 **a** Unifocal non-homogenous leukoplakia on the right ventral tongue. **b** Demarcated hyperkeratosis with "skip" segments (H&E, original magnification ×100). **c** Mild ED and a mild chronic inflammatory infiltrate is identified (H&E, original magnification ×400)

demarcated plaque also speaks against local injury and suggests clonal proliferation. Lichen planus may show hyperkeratosis and epithelial atrophy or erosion but these findings are always associated with degeneration of the basal cells, colloid bodies and a lymphohistiocytic infiltrate at the interface, as well as other reactive changes within the epithelium due to inflammation (Fig. 13e). Furthermore, hyperkeratotic lesions with epithelial atrophy and a lymphocytic band at the interface in the clinical setting of a demarcated plaque should be viewed with caution because such a "lichenoid" pattern has been noted in 29% of ED [46]. It is likely that such infiltrates represent a lymphocytic host response to ED or tumor-promoting inflammation, a hallmark of cancer as noted by Hanahan and Weinberg [47]. Such lymphocytes, well recognized in invasive carcinoma, are the basis for the immunotherapy in head and neck cancer [48].

Studies have shown that "hyperkeratosis without dysplasia" may progress to dysplasia and carcinoma from 0.1 to 14.0% of cases [9–13]. It is unclear whether such reports relied exclusively on the use of cytologic criteria, resulting in an under-diagnosis of dysplasia. A recent study showed that such lesions harbored the same mutations as lesions with moderate and severe ED used as controls [49]. As such, we suggest that the term "hyperkeratosis, not reactive"

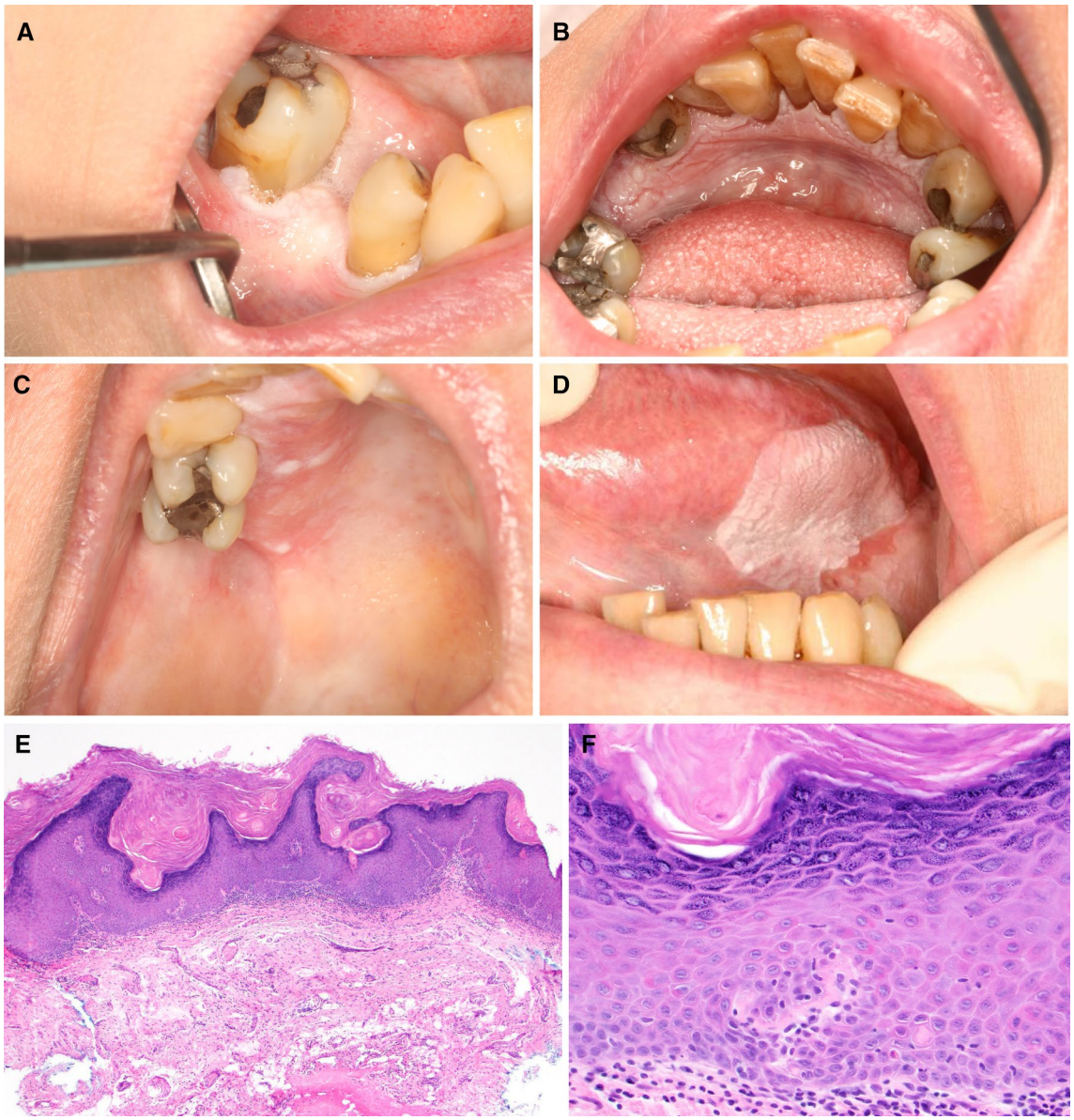

Fig. 9 Case 9 Proliferative leukoplakia on **a**, **b** the mandibular gingiva, **c** the hard-palatal mucosa, and **d** the latero-ventral tongue. **e** Biopsy of tongue lesion exhibits atypical verrucous hyperplasia (H&E, original magnification ×40). **f** Minimal cytologic atypia and minimal inflammatory infiltrate present (H&E, original magnification ×400)

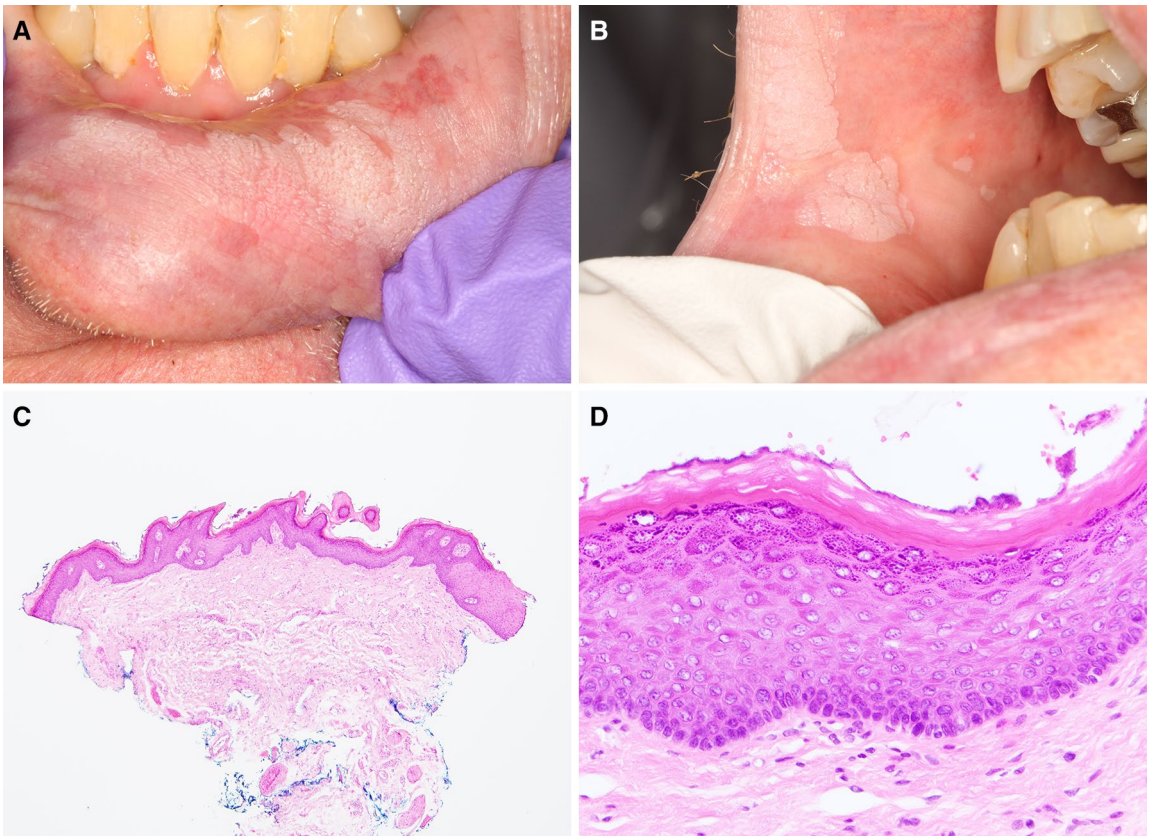

Fig. 10 Case 10 Proliferative leukoplakia on **a** the lower lip mucosa and **b** the buccal mucosa. **c** There is atypical verrucous hyperkeratosis and epithelial atrophy (H&E, original magnification ×40). **d** ED is not identified (H&E, original magnification ×400)

should be applied in the absence of ED and where the histopathologic features are unlikely to be a result of inflammation rather than "hyperkeratosis, no dysplasia" which may lead to patients being discharged from follow-up.

On the other hand, bulky squamous epithelial proliferation that expands the epithelial thickness at least three-fold is concerning for developing ED. In this series, this feature was noted in 16/34 (47.1%) of PL cases. These often exhibit an endophytic growth pattern and the term "atypical endophytic squamous proliferation" is often used. Bulky squamous proliferation borders on neoplasia in many cases, and verrucous carcinoma is a prime example of such a pattern of squamous proliferation and yet, is still a carcinoma with a "blunt" pattern of invasion [50]. Corresponding to the at least partially demarcated clinical lesions of both UL and PL, biopsies taken from the margin of such lesions will show demarcated hyperkeratosis, and "skip" segments in 20.6% of PL cases.

These *architectural* features may occur alone or in combination; for example, it is common to see verrucous/papillary hyperplasia exhibiting bulky endophytic growth pattern, and hyperkeratosis with atrophy exhibiting "skip" segments. We have consolidated some of the WHO criteria here. Irregular epithelial stratification and loss of polarity of basal cells is recognizable at medium power and is characterized by loss of upward maturation, an *organizational* criterion. The four *cytologic* criteria of variation of nuclear and cell shape and size are consolidated into a single feature of pleomorphism

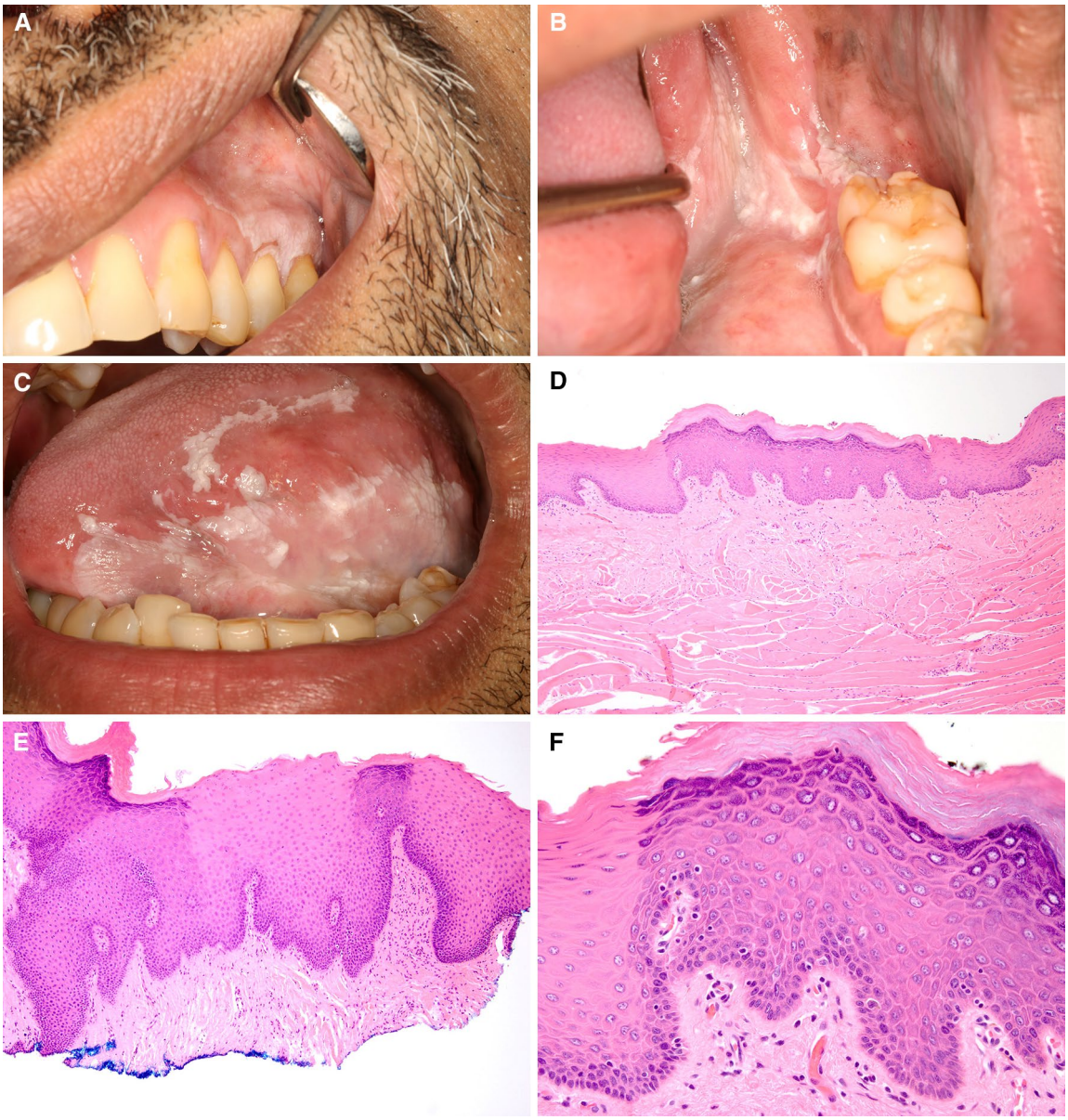

Fig. 11 Case 11 Proliferative leukoplakia on **a** the gingiva, **b** retromolar trigone extending to the anterior tonsillar pillar, and **c** the latero-ventral and dorsal tongue. **d** Biopsy from the tongue exhibits demarcated hyperkeratosis (H&E, original magnification ×100). **e** A later biopsy from the tongue exhibits demarcated corrugated hyperkeratosis and acanthosis with skip segments (H&E, original magnification ×100). **f** Mild ED is focally present (H&E, original magnification ×400)

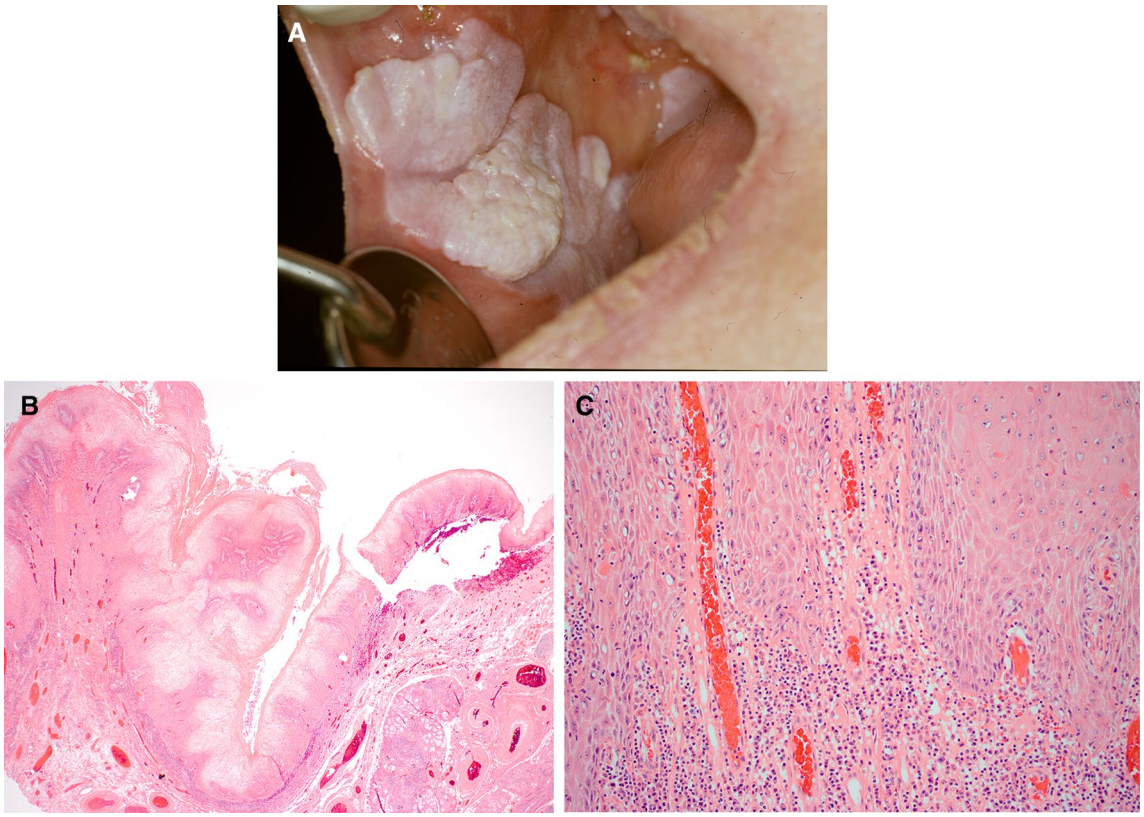

Fig. 12 Case 12 **a** Proliferative leukoplakia on the buccal mucosa extending to the commissure area with a second lesion further posteriorly. **b** There is bulky squamous epithelial proliferation (H&E, original magnification ×20). **c** No ED present (H&E, original magnification ×400)

Table 2 Clinical information of the cases

	Age	Gender	Number of lesions (homogenous or non-homogenous)	Lesions' location
Unifocal leukoplakia (UL)	74	M	1	G
	56	M	1	G
	75	M	1	G
	70	M	1	HP
	58	F	1	DT
	73	F	1	VT
	78	M	1	VT
	60	M	1	VT
Proliferative leukoplakia (PL)	55	F	6 (4,2)	G, VT, LT, HP, BM and LM
	53	M	6 (4,2)	G, VT, FOM, SP, HP and BM
	36	M	9 (8,1)	DT, BM and LM
	88	F	3 (0,3)	G, TP and BM

G gingiva, *DT* dorsal tongue, *LT* lateral border of tongue, *VT* ventral tongue, *FOM* floor of mouth, *TP* tonsillar pillar, *BM* buccal mucosa, *LM* labial mucosa, *SP* soft palate, *HP* hard palatal mucosa

Table 3 Follow-up information of the PL cases

	Follow up (years)	Clinical outcome
Case 9	11	3 SCCs, DoD
Case 10	8	No disease progression[a]
Case 11	14	3 SCCs, alive with disease undergoing palliative immunotherapy
Case 12	5	1 SCC, DoD

SCC squamous cell carcinoma, *DoD* dead of disease

[a]Last follow-up 2.5 years ago

for simplicity. The presence of atypical mitotic figures is more appropriately categorized as a *cytologic* feature while the location of normal-appearing mitotic figures beyond the basal and parabasal cells is an *organizational* feature of ED (Table 1).

Currently, the WHO grades oral ED into mild, moderate and severe depending on the thickness of epithelium [31], while grading of "squamous intra-epithelial neoplasia (SIN)" for laryngeal lesions designates lesions as SIN I (low grade) and SIN II (high grade) in increasing order of severity of dysplasia [51]. A binary system of grading oral ED into "high risk" and "low risk" has been proposed as is used for other mucosal sites and we believe that *architectural* features of ED as defined here must be included in any grading system for accuracy [15]. Larger scale studies with long term follow up information are needed to fully investigate the correlation between the architectural alterations, clinical outcome, and importantly, the molecular signature of oral ED. Finally, it cannot be overstated that clinical information is of the utmost importance in arriving at an accurate diagnosis namely size, multifocality and the appearance of lesions.

Conclusion

Oral ED is a precursor lesion of oral SCC. Here we propose that ED be diagnosed based on not only the well-recognized *organizational* and *cytologic* criteria but also on *architectural* features. Eight UL and four PL cases were presented to illustrate architectural features of ED that may occur with minimal evidence of cytologic atypia/dysplasia. These include corrugated, verrucous or papillary architecture, hyperkeratosis or parakeratosis with epithelial atrophy, bulky squamous epithelial proliferation with exophytic and/or endophytic growth pattern, and sharply demarcated hyperkeratosis and/or skip lesions. These features are commonly seen in lesions of PL in early stages and precede development of other features of ED and SCC which occur in the majority of patients over time.

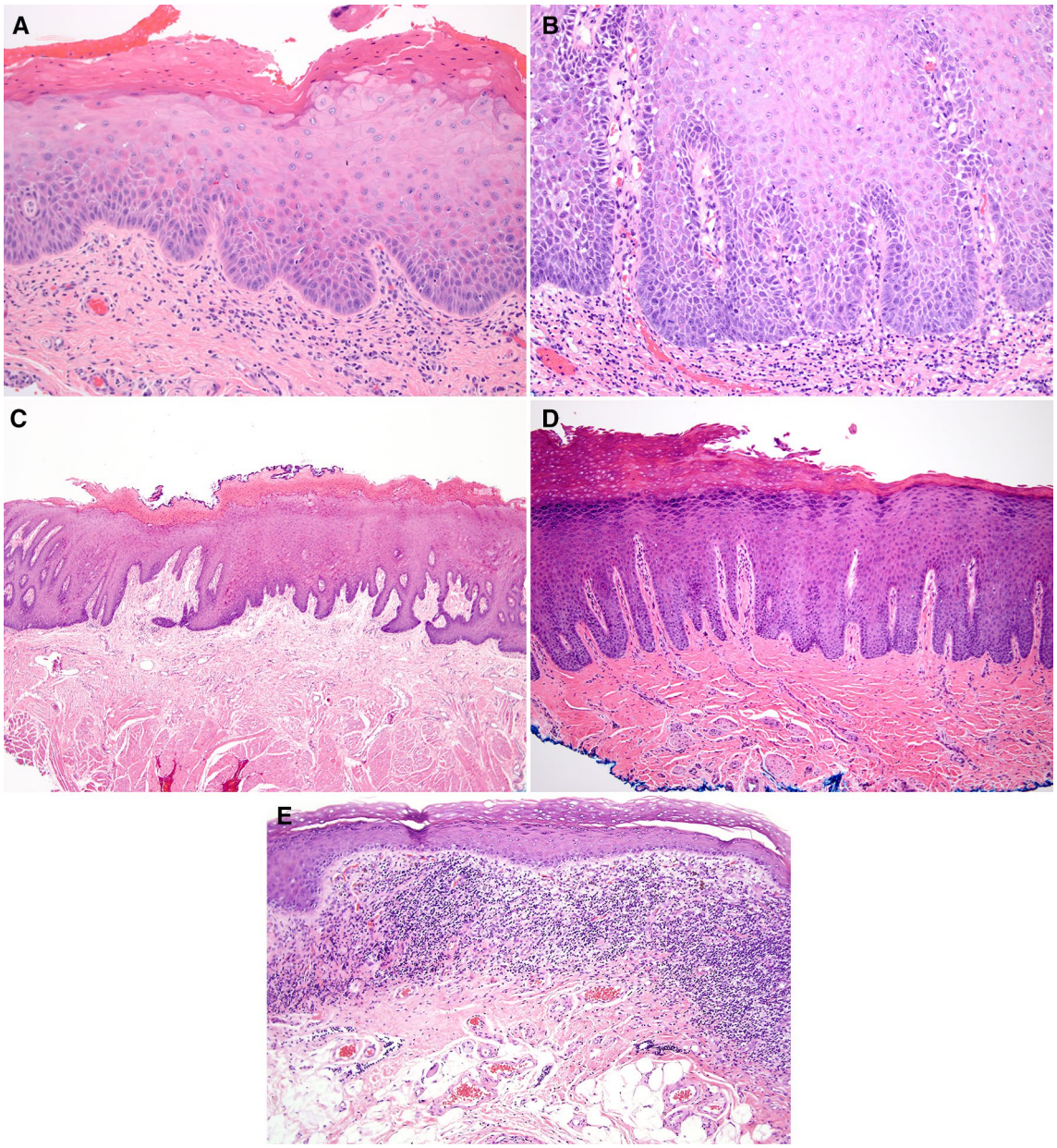

Fig. 13 **a** Moderate ED characterized by drop-shaped rete ridges, cells with increased nuclear:cytoplasmic ratio and dyskeratosis involving approximately half the thickness of the epithelium (H&E, original magnification ×200). **b** Severe ED characterized by bulbous rete ridges, dyscohesion, cells with increased nuclear:cytoplasmic ratio, dyskeratosis and slight nuclear pleomorphism and hyperchromasia involving greater than 2/3 the thickness of the epithelium (H&E, original magnification ×200). **c** Chronic bite/factitial keratosis (morsicatio mucosae oris) with parakeratosis and acanthosis (H&E, original magnification ×100). **d** Benign alveolar ridge keratosis with hyperkeratosis, wedge-shaped hypergranulosis and acanthosis (H&E, original magnification ×100). **e** Lichen planus exhibiting hyperkeratosis, epithelial atrophy, and interface inflammation (H&E, original magnification ×100)

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Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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