Proliferative Leukoplakia

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KEYWORDS

• Proliferative leukoplakia • High-risk leukoplakia • Oral potentially malignant disorder • Malignant transformation • Diagnostic criteria • Oral dysplasia • Multi-modality treatment

KEY POINTS

- Proliferative leukoplakia (PL) is an aggressive oral potentially malignant disorder with a malignant transformation rate of 65% to 100%.
- PL affects mostly non-smoking individuals in the 7th decade, and females are affected more than males.
- PL may present clinically as multifocal plaques or a single large (>4 cm) plaque with or without a verrucous surface.
- Histopathology of PL lesions may not demonstrate frank cytologic dysplasia especially in early lesions, but rather shows architectural dysplasia.
- Surgical management of PL can be challenging and non-surgical and multimodality management approaches are being explored.

INTRODUCTION

Oral leukoplakia (OL) is the most common potentially malignant lesion of the oral cavity with an estimated global pooled prevalence of 1.4% to 4.1%.[1,2] The malignant transformation (MT) rate of conventional OL has been reported to be 4.0% to 10.0% with non-homogenous lesions (verrucous, nodular, or speckled) exhibiting a higher rate of up to 40.0%.[3–6] A particularly aggressive but uncommon form of OL, with distinct demographic features and prognosis, was first described by Hansen *and colleagues* in 1985.[7] The authors coined the term "proliferative verrucous

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Abbreviations	
CPS	combined positive score
HkNR	hyperkeratosis, not reactive
ICI	immune checkpoint inhibitor
MT	malignant transformation
OED	oral epithelial dysplasia
OL	oral leukoplakia
OSCC	oral squamous cell carcinoma
PD-L1	programmed death-ligand 1
PEL	proliferative erythroleukoplakia
PL	proliferative leukoplakia
PVL	proliferative verrucous leukoplakia
TPS	tumor proportion score
WHO	World Health Organization

leukoplakia (PVL)" to describe leukoplakias that progressed over time from mostly solitary flat lesions to multifocal or diffuse verrucous lesions, with many lesions undergoing MT.

The World Health Organization (WHO) defines PVL as a "clinicopathological subtype of OL that is multifocal, persistent, and progressive, with a high rate of recurrence and a high risk of progression to squamous cell carcinoma".[8] Although there is a lack of consensus on the clinical and histopathologic diagnostic characteristics of PVL, there is general agreement that PVL has the highest MT rate among oral potentially malignant disorders.[9] The estimated annual MT rate is approximately 9.3% to 10.0% per year,[4,10] and the overall MT rate ranges from 65.0% to 100%.[11,12] The higher end of the range was reported in a study describing proliferative erythroleukoplakia.[12]

TERMINOLOGY

Since the initial description of PVL, other names have been suggested, such as "proliferative multifocal leukoplakia"[13] and "proliferative leukoplakia" (PL).[11] Although all these terms refer to the same entity, they differ in whether a verrucous appearance or multifocality is the defining feature. PL is the most inclusive of the proposed terminology and will be used throughout this article.

The diagnostic criteria proposed by Villa *and colleagues*,[11] and Carrard *and colleagues*,[14] include a unifocal lesion > 4.0 cm or a lesion affecting contiguous sites >3.0 cm as possible presentations of PL and these criteria have been accepted by the WHO (**Table 1**).[8] Despite lack of multifocality, these lesions have a higher rate of MT compared to conventional OLs and should be categorized under the umbrella of PL.[7,11] This is in keeping with historic studies, which showed that larger lesions >2 cm have a higher MT rate.[15] Although 3 cm and 4 cm are arbitrary numbers, the hypothesis is that a larger lesion is likely to harbor more genetic and epigenetic events compared to a smaller lesion and would therefore account for the higher rate of MT.

The other conundrum is whether lesions of the buccal/facial gingiva and lingual/palatal gingiva should be considered a contiguous site since the leukoplakia often extends between teeth via the interdental gingiva, or whether they should be considered multifocal sites (**Fig. 1**A, B). The term "ring around the collar" has been used to describe lesions affecting the marginal gingiva[16]; however "linear gingival leukoplakia" is a more accurate designation as these lesions do not always present in a distinct circumferential pattern.

Table 1
Comparison of diagnostic criteria proposed for PL

Criterion	Cerero-Lapiedra et al,[25] 2010	Carrard et al,[14] 2013	Villa et al,[11] 2018	de Mendoza et al,[12] 2022
Number of sites	Multifocal separate	Multifocal separate or contiguous sites	Multifocal separate or contiguous sites or single large lesion	Multifocal separate
Minimum cumulative size	3.0 cm	3.0 cm	3.0 cm (contiguous sites) and 4.0 cm (single lesion)	X
Verrucous	✔	✔	X	X
Progressive[a]	✔	✔	X	✔
Period of evolution > 5 y	✔	✔	X	X
Recurrence in treated site	✔	✔	X	✔
Histopathology of dysplasia or hyperkeratosis	✔	X	✔	X
Female sex	✔	X	X	X
Non-smoker	✔	X	X	X

[a] Progressive refers to size enlargement and/or development of multifocality documented by the clinician over time.

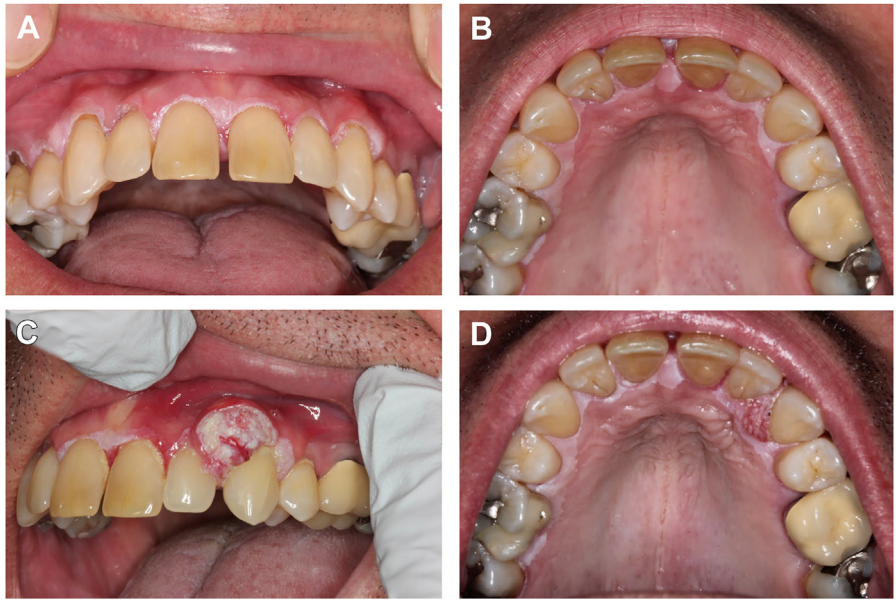

Fig. 1. Proliferative leukoplakia manifesting with circumferential involvement of the gingival margin. (*A*) Linear gingival leukoplakia involving the maxillary facial gingival margin extending to (*B*) the palatal gingiva. (*C, D*) The patient developed carcinoma in the facial and lingual interdental papilla between teeth #10 to 11.

DEMOGRAPHICS

In contrast to conventional OLs, PLs occur more frequently in females (66.7%) with a mean age in the 7th and 8th decades.[17] Furthermore, females are approximately 3 times more likely to develop oral squamous cell carcinoma (OSCC) than males with PL.[17–19] The majority of patients affected by PL are non-smokers (66.6%) and most patients with PL who developed OSCC were non-smokers.[17,18] Additionally, studies have found no association between alcohol consumption and PL development.[11,15]

On the other hand, similar to conventional OLs, personal and family histories of cancer are recognized as associated risk factors. Family history of cancer was observed in 43.7% to 87.9% of OLs, mainly among 1st degree relatives, with lung, breast, and prostate cancer being the most common.[11,20]

LOCATION

It is well-recognized that the most common sites of involvement for PL are the gingiva (44.5% – 50.9%) and buccal mucosa (25.0% – 44.9%).[15,21] However, any site may be involved, such as the tongue (19.4% – 40.6%) and palatal mucosa (11.1% – 18.2%).[15,21]

CLINICAL FEATURES AND DIAGNOSTIC CRITERIA

PL is a form of OL that enlarges or spreads over time or develops synchronous or metachronous multifocal lesions. Similar to conventional OLs, PLs can present as homogenous lesions, with an erythematous component, proliferative erythroleukoplakia (PEL), or they can be verrucous as in PVL, but not all are verrucous.[11] Early lesions may start out smooth and develop verrucous areas, and any 1 lesion may have verrucous,

smooth, or erythematous components at different parts of the lesion or at different sites.[9,11,21,22] Although the presence of a verrucous area had been considered a sine qua non for the diagnosis of PL, this concept is now questioned and other proposed terminology include multifocal leukoplakias, although even the concept of multifocality is questioned.[9,11,21,22] The development of verrucous, nodular, and erythematous areas may indicate a higher grade of oral epithelial dysplasia (OED) or progression and all such areas should be biopsied.[11]

One way to classify these lesions is to use the criteria that WHO has set out for conventional OL namely, homogenous, verrucous-nodular, and erythroleukoplakia types. This would simplify the clinical diagnosis and still be clinically accurate. It is important to differentiate PEL, which may be bilateral and somewhat symmetric, from other multifocal mixed white/red lesions of the oral mucosa, such as oral lichen planus, given PEL's particularly high MT rate of almost 100%.[10,11,23] Lichenoid reactions may also appear adjacent to areas of PL.[24]

Table 1 shows a comparison between the 4 most commonly accepted diagnostic criteria.[11,12,14,25] Each of these criteria incorporates a combination of demographic, clinical, and histopathologic characteristics to aid in the diagnosis and uniform reporting of PL. While it is well-documented that PL exhibits a female predominance, it is unnecessary to use it as a specific criterion since even a male patient who smokes may present with PL. Recurrence should also not be a criterion since even conventional OL recur with some frequency and much depends on whether margins are clear of OED by new criteria, as well as the location and accessibility of the entire lesion to therapy. If the patient presents at first visit with all the features of PL, it is probably unnecessary to wait several years to see progression to confirm the diagnosis.

ETIOPATHOGENESIS

Understanding the etiopathologic mechanisms of PL is crucial, and recent studies are addressing this. DNA aneuploidy was observed in 66.7% to 92.0% of PL cases, highlighting it as a potential biomarker for PL.[26,27] DNA aneuploidy has been associated with MT in 55.6% of a small series of PLs.[27]

TP53, a tumor suppressor gene, is one of the most commonly mutated genes in PL.[28–30] These alterations have been found to become increasingly prevalent as lesions progress histopathologically from hyperplasia to dysplasia and carcinoma.[31] Another tumor suppressor gene detected in PL is *CDKN2A*.[30,32,33] One study reported that the concurrent loss of these proteins was observed in 45% of PL cases.[32] Additionally, research has shown that OLs exhibit copy-number loss and loss of heterozygosity in 9p21, and this may be utilized as a tool for cancer risk assessment.[34–36]

Missense or frameshift mutations in *KMT2C* (which regulates gene transcription) have also been reported as a frequent molecular finding.[37] One study on the molecular profile of OLs demonstrated the genomic overlap between lesions "without OED" and lesions with OED reporting no significant difference in the mutational frequency of genes, which have a $\geq$15% rate of alteration.[37] The observations from these studies, reinforce the concept of genomic instability in PL.

Immune evasion is recognized as a crucial mechanism in carcinogenesis.[33,38] Increased expression of programmed death-ligand 1 (PD-L1) in dysplastic oral epithelial cells, and PD-L1 positivity has been significantly associated with MT.[39–41] Furthermore, immunophenotyping revealed that PD-L1 was overexpressed in PL (combined positive score [CPS] of 2.45 and tumor proportion score [TPS] of 0.1), specifically in comparison to conventional OL (CPS of 0 and TPS of 0).[33] Moreover, PL showed a higher presence of CD8 + T-cells and T-regulatory cells compared to conventional

OL.[33] The checkpoint interaction between PD-L1 expressed by epithelial cells and the programmed cell death protein 1 on T-cells and other immune cells may play a role in PL progression via immune evasion and could present a target for therapy.[33] Human papillomavirus does not play a role in the etiopathogenesis of PL.[28,42–44]

HISTOPATHOLOGIC FEATURES

It is crucial to emphasize that PL is solely a clinical diagnosis, and the term should not be used when reporting the histopathologic diagnosis. Overall, OED was noted in 23.5% to 85.0% of PL biopsies, of which 30.8% to 83.3% were mild OED, 8.8% to 43.5% were moderate OED, 0.0% to 29.2% were severe OED, and 3.9% to 19.0% were OSCC.[11,12,21,23,24,45–49] However, 9.0% to 73.5% of cases were reported to show "no dysplasia".[11,12,21,23,24,46–50] This wide range is likely attributed to: (1) time at which the biopsy was performed (early lesion vs late lesion), (2) site of biopsy, (3) low interobserver reliability in evaluating PL biopsies, and (4) use of cytologic criteria only for the diagnosis of OED.[51] Silverman and Gorsky[52] reported absence of cytologic dysplasia in 51.9% of early PL biopsies, while last biopsies in their study period lacked cytologic dysplasia in 20.4% of cases.[52] A recent study of 86 early/initial PL biopsies showed that 31.4% of cases lacked the standard cytologic-based features of OED and were described as "hyperkeratosis, not reactive (HkNR)" and approximately one-fifth of such HkNR lesions progressed to OED, implying that HkNR is the earliest presentation of OED.[49] Furthermore, in a review of a large series of patients who developed OSCC at the site of a previous biopsy, 28% had biopsies that initially showed only "hyperkeratosis", which should be designated as HkNR.[53]

In the original paper on PL in 1985,[7] 10 histopathologic stages were described, based on both clinical and histopathologic findings with stages 1 to 2 being "clinical leukoplakia" at one end that showed "simple hyperkeratosis with little to no dysplasia" to stage 9 to 10 being "less differentiated squamous carcinoma exhibiting dysplasia", at the other end. Most of the intervening stages up to stage 8 showed little cytologic atypia. The 2021 PL expert consensus guidelines[54] emphasized that "architectural distortion is greater than cytologic atypia" similar to what was described in the original paper by Hansen *and colleagues*[7] and described several histopathologic features under the heading of "corrugated ortho (para) hyperkeratotic lesion, not reactive" (**Fig. 2**A, B):

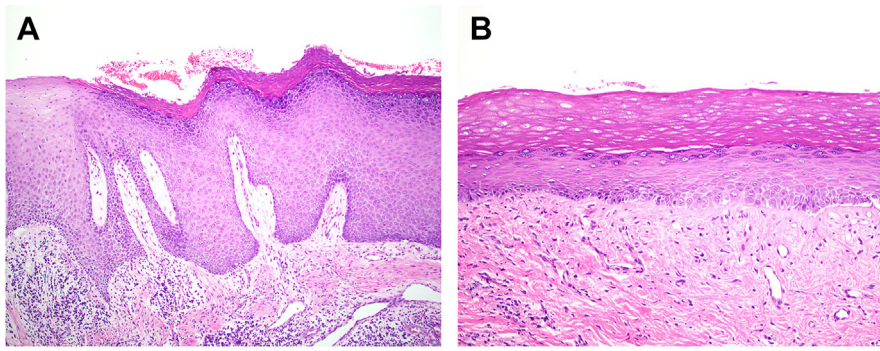

Fig. 2. (*A*) Sharply demarcated and corrugated hyperkeratosis with minimal cytologic atypia (H&E original magnification x200). (*B*) Marked hyperkeratosis with epithelial atrophy. The keratin is as thick as the epithelium (H&E original magnification x200).

1. Corrugations, undulations, and crests and spikes of keratin; this includes verruciform architecture.[55]
2. Marked hyperkeratosis (>½ the thickness of the underlying epithelium) with epithelial atrophy; this is particularly subject to the misdiagnosis of "hyperkeratosis, no dysplasia".
3. Sharp demarcation and skip segments.

Some lesions showed "bulky epithelial proliferation, not reactive" and lesions "suspicious for squamous cell carcinoma" where the epithelial proliferations are usually >3 to 4 times the thickness of uninvolved epithelium.[54] Such bulky epithelial proliferation is reported in 4.7% to 26.5% of PL biopsies.[49,56] It is likely that the earliest changes of OED are architectural in appearance and progress to cytologic evidence of OED and lastly carcinoma (**Fig. 3**).[49]

A lymphocytic band at the interface referred to as "lichenoid" has been reported in 26.4% to 61.1% of biopsies (**Fig. 4**),[21,44,48–50,57] and this has led the clinicians to erroneously believing that PL and oral lichen planus/lichenoid mucositis are indistinguishable.[11,47,55,58] The lymphocytic band likely represents T-cells within the microenvironment of OED that recognize neo-antigens within dysplastic epithelium, similar to the lymphocytes seen in the microenvironment of OSCC and for which checkpoint inhibition may be employed for therapy.

MANAGEMENT

There are several treatment options for PL:

Active Surveillance

Careful periodic observation with surveillance biopsies is an option especially if patients are older and treatment may be too morbid. Biopsies are indicated when there are changes in the clinical appearance of the lesion, such as development of thickness or a mass, verrucous/nodular architecture, and erythematous areas since this may indicate progression to a higher grade of OED or MT. Even without such changes, periodic surveillance biopsies should be performed.

Surgery

Studies that compared surgical excision to observation of OL showed MT rates of 1.2% to 8.9% versus 8.8% to 14.6%, respectively.[59–61] Surgical or laser removal of PL lesions yields a recurrence rate of 67.3%.[62] Surgical excision of all PL lesions is impractical because of size and/or multifocality. Excision of OSCCs as they occur is performed with the understanding that there is usually microscopic or gross residual OED left behind. It is also difficult to completely excise gingival lesions without the extraction of associated teeth.[48] The high recurrence rate often leads to multiple surgical procedures for some patients with continued progression of residual leukoplakia and development of carcinomas.[62,63]

Laser Therapy and Photodynamic Therapy

Studies have shown high recurrence rates of up to 54.0% using laser therapy.[64] A mean MT rate of 3.5% has been reported.[65,66] Additionally, laser ablation does not allow for the histopathologic evaluation of tissue following removal. A meta-analysis on the efficacy of photodynamic therapy suggests that it may be a potentially effective treatment option for conventional OL.[67] However, several factors can influence the treatment outcome, such as the wavelength used, photosensitizer employed, and the duration of application.[67] More recently, the use of nanoparticles in photodynamic

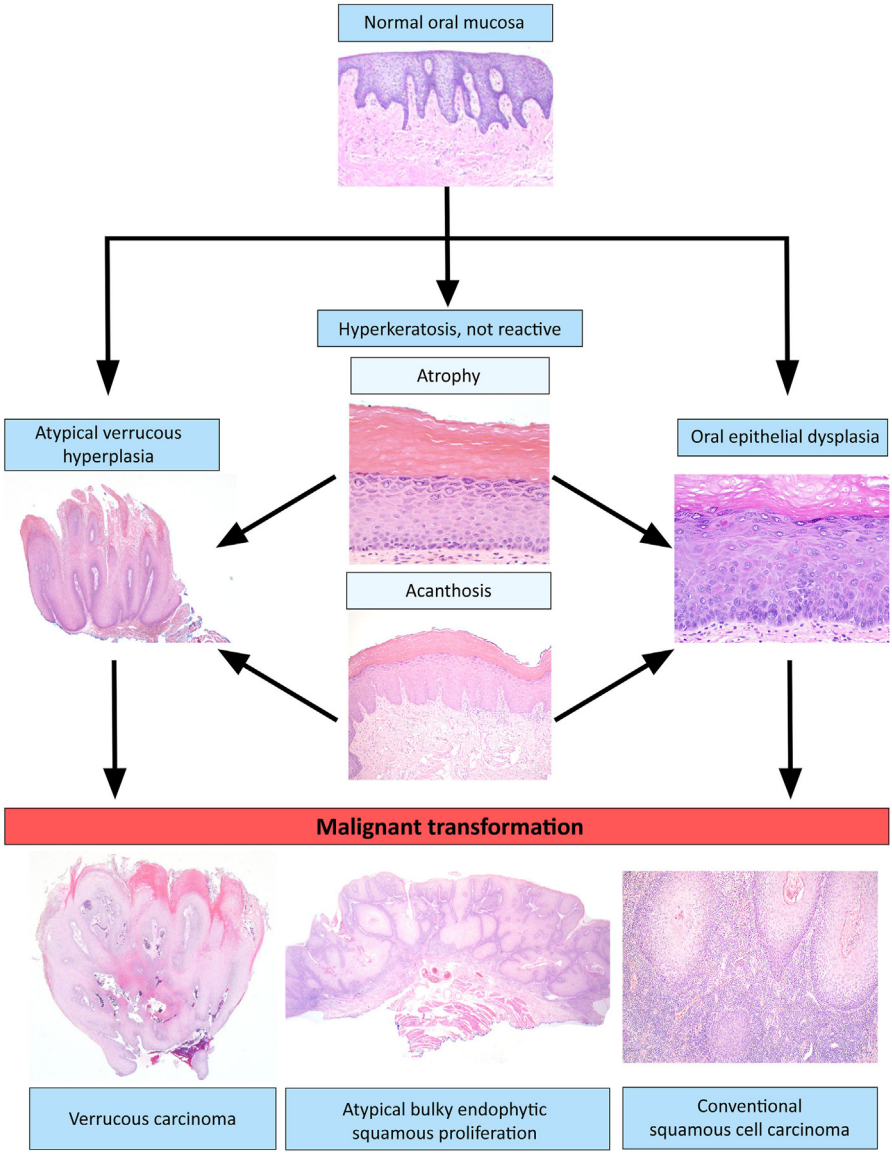

Fig. 3. The spectrum of histologic diagnoses of proliferative leukoplakia. (*Reused from* Alabdulaaly L, Villa A, Chen T, et al. Characterization of initial/early histologic features of proliferative leukoplakia and correlation with malignant transformation: a multicenter study. Mod Pathol 2022;35(8):1034–44 with permission from Springer Nature.)

drug delivery systems has gained considerable attention and holds potential as a treatment option for PL.[68]

Pharmacologic Therapy

Systemic therapies including vitamin A, nonsteroidal anti-inflammatory drugs, lycopene, beta-carotene, curcumin, green tea extract, and Bowman-Birk inhibitors have

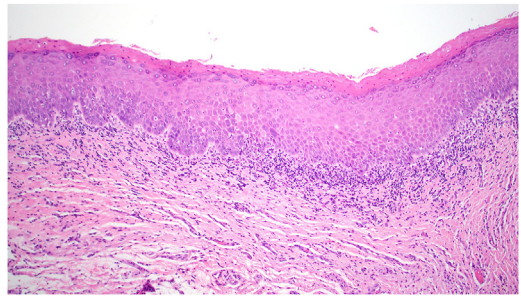

Fig. 4. Parakeratosis and moderate cytologic dysplasia. Note the focal basal cell degeneration, and the presence of a lymphocytic band at the epithelium-lamina propria interface in the center of the lesion, and typical dysplasia on the left (H&E original magnification x200).

not demonstrated clear evidence of efficacy.[69,70] Topical agents, such as bleomycin, isotretinoin, ketorolac, and dried black raspberries have also been evaluated in chemoprevention trials but have revealed only modest success.[69,70]

Imiquimod cream is a topical immunomodulatory agent that is used for the treatment of actinic keratosis, a precancerous lesion of the skin, as well as superficial basal cell carcinoma and genital warts.[71,72] Case reports and a pilot study using imiquimod to treat mostly conventional OL showed resolution[73,74] or regression to statistical significance.[75] In a recent retrospective study, topical 5% imiquimod was noted to reduce the size of conventional OL and PLs by $\geq$ 50.0% in two-thirds of cases, with 42.1% showing complete resolution at 6-month follow-up.[20] The majority of lesions included in the cohort were PLs on the gingiva,[20] which have a high-rate of recurrence and MT. It is possible that imiquimod cream can flow into the gingival sulcus, which may harbor dysplastic cells, potentially reducing recurrence.[20]

A recent phase 2 clinical trial using intravenous nivolumab showed that 36.0% of subjects had at least a partial response, which was assessed by the reduction in the composite score of target lesion size and degree of OED.[34] During the trial, 27.0% of patients developed OSCC within a median time of 6.6 mo.[34] Notably, the majority of subjects who developed OSCC had 9p21.3 copy number loss in the pre-treatment sequencing of their biopsy tissue specimens.[34] Deletions related to 9p21 have been proven to be predictors of immune checkpoint inhibitors (ICI) resistance in advanced OSCC,[76] and suggest that 9p21.3 chromosomal loss could be used for subject stratification in future investigations.[34] Ongoing clinical trials are further investigating the use of systemic and intralesional ICIs for OL (NCT03603223, NCT04504552, NCT05327270).[77–79] However, patients have been shown to develop OSCC shortly after discontinuation of systemic ICI,[34] which raises the question of a potential cancer-promoting effect.

Metformin has been shown to regress OL in up to 17.0% of cases,[80] and clinical trials are underway to further investigate this (NCT05727761).[81] A recent report showed PL resolution and regression in 2 allogenic stem cell transplant recipients after initiating ibrutinib, a Bruton tyrosine kinase inhibitor, for the management of chronic graft-vs-host disease.[82] A study using erlotinib on OL lesions did not show a difference in cancer-free survival in patients with aneuploidy and high *EGF* gene copy number.[83]

It may be that PL in the future will be managed with multi-modality treatments, reducing the size of the lesion with one modality and using a second modality to

completely remove the lesion. Alternatively, one modality may be utilized to expose the neo-antigens and sensitize the immune system, and a second modality may be used to boost the immune response.

PROGNOSIS

In general, PL lesions have a higher tendency to recur than conventional OLs (67.2% vs 30.0%)[62,63] and it has been suggested that this is related to positive margins during surgical removal.[52] This is particularly important if margins show no cytologic dysplasia but architectural dysplasia and are inaccurately evaluated as "hyperkeratosis, no dysplasia". Another possible explanation is the concept of field cancerization, which posits that a field of tissue may harbor genetic mutations rendering it prone to precancerous and cancerous changes, even after the complete excision of existing lesions.[84,85]

The gingiva is the site with the highest rate of recurrence.[62,63,86] It has been hypothesized that this may be attributed to limited accessibility and incomplete removal of dysplastic cells within the sulcular epithelium, which can lead to repopulation of the gingival surface.[48] Furthermore, it has been reported that up to 37.5% of PL lesions that progressed to carcinoma were located on the gingiva.[18,21,52] It is also the site with the highest frequency of developing >1 primary OSCC in patients with PL (**Fig. 1**C, D).[84] This emphasizes the importance of careful monitoring of gingival lesions, including measuring periodontal pocket depths around involved teeth and assessing for tooth mobility to evaluate the extent of peri-radicular involvement.

The rate of malignant transformation of PL overall is 65.0% to 100.0% while the annual rate of malignant transformation is up to 10%.[10,11] Most commonly, MT takes the form of conventional OSCC (60.0% – 94.4% of malignant tumors) and less commonly, verrucous carcinoma (5.6% – 40.0%).[21,23,49,50,57,87] Furthermore, second primary malignancies are not uncommon in PL[23,49,50,57] and patients may develop 1 to 5 carcinomas.[84]

NEED FOR CONSENSUS

Several issues exist that deserve attention for more accurate clinical and histopathologic diagnosis, uniform reporting, timely management of patients, and conduct of clinical trials. These include:

a. Moving to more accurate terminology for the name of this entity and we propose using the term proliferative leukoplakia for reasons discussed earlier.
b. Deciding whether the definition should be limited to multifocal noncontiguous lesions only, or whether large single site or contiguous/adjacent sites should be included.
c. Deciding whether synchronous buccal/facial and lingual/palatal lesions should be considered a single contiguous site or 2 distinct noncontiguous sites. This would be moot if multi-site involvement is no longer a criterion.
d. Adopting the new architectural criteria proposed by WHO and other investigators to replace either "hyperkeratosis" or "hyperkeratosis, no dysplasia" for histopathologic diagnosis.

SUMMARY

PL, although uncommon, represents a precancerous oral mucosal disorder with high MT rates and limited treatment options at this time, currently without international consensus on a clinical definition. Fortunately, there are now histopathologic criteria

for the diagnosis of early lesions based mostly on architectural alterations often in the absence of cytologic atypia/dysplasia. Recent advances in the genomics and immunoprofiling of PL have improved our understanding of these lesions and provide a foundation for future research into potential pharmacologic therapies.

CLINICS CARE POINTS

- A unifocal lesion > 4.0 cm or a lesion affecting contiguous sites > 3.0 cm should be considered proliferative leukoplakia, even in the absence of multifocality, as these larger lesions have a higher malignant transformation rate compared to smaller leukoplakias.
- Proliferative leukoplakia is a clinical diagnosis, and biopsy is essential for confirming the histopathological features of oral epithelial dysplasia.
- The development of verrucous, nodular, or erythematous areas indicates lesion progression and warrants a biopsy, as these changes suggest a higher grade of dysplasia.
- Biopsies may show architectural dysplasia without cytologic dysplasia, and "hyperkeratosis, not reactive" is considered the earliest manifestation of oral epithelial dysplasia.
- Management of proliferative leukoplakia currently includes active surveillance, surgical excision, and laser ablation.
- Pharmacological treatment options are under investigation, including topical imiquimod, immune checkpoint inhibitors, and metformin.
- Proliferative leukoplakia has a higher recurrence rate than conventional leukoplakia, underscoring the need for monitoring of affected patients.

DISCLOSURE

The authors have no disclosures related to this article.

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