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Proliferative leukoplakia: Proposed new clinical diagnostic criteria

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Objective: We aimed to characterize proliferative verrucous leukoplakia (PVL) from a clinical and histopathological standpoint and suggest an updated classification.

Subjects and Methods: Records of patients seen at three oral medicine centers with a clinical diagnosis of PVL were reviewed for clinical and histopathological features and malignant transformation (MT).

Results: There were 42 patients (median age: 69 years [range: 36–88]; 35 females). 12.2% were current smokers. Family history of cancer was present in 43.7% of patients. Partial demarcation of lesion margins was present in 31.3% of lesions, followed by verrucous (27.5%), smooth (22.7%) erythematous (22.3%), and fissured (18.3%) appearance. Large and contiguous and multisite and non-contiguous lesions comprised 57.1% (24/42) and 35.7% (15/42) of PVL cases, respectively. 19.1% had prominent erythema (erythroleukoplakia). The most common histopathological diagnosis at first visit was hyperkeratosis without dysplasia (22/42; 56.4%). MT occurred in 71.4% patients after a median of 37 months [range: 1–210] from initial visit; erythroleukoplakia exhibited MT in 100% of cases.

Conclusion: The generic term "proliferative leukoplakia (PL)" may be more appropriate than PVL because 18.3% were fissured and 22.7% erythematous. We also propose the term proliferative erythroleukoplakia to more accurately describe the subset of PL with prominent erythema, which had the highest MT rate.

KEYWORDS
malignant transformation, proliferative, proliferative verrucous leukoplakia

1 | INTRODUCTION

Leukoplakia as defined by the World Health Organization (WHO) is "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" (Warnakulasuriya, Johnson, & van der Waal, 2007).

Oral proliferative verrucous leukoplakia (PVL) is a term first introduced by Hansen, Olson, and Silverman (1985) in 1985 as a variant of leukoplakia; it is a slow-growing, aggressive form of leukoplakia which is associated with a high malignant transformation (MT) rate (Hansen et al., 1985). PVL is a form of non-homogenous leukoplakia that generally affects multiple sites, frequently the gingiva and the buccal mucosa, and slowly progresses to involve contiguous or non-contiguous areas (Bagan, Scully, Jimenez, & Martorell, 2010; Bagan et al., 2003; Pentenero, Meleti, Vescovi, & Gandolfo, 2014; Warnakulasuriya et al., 2007).

Since the definition by Hansen et al. (1985), others have suggested additional criteria for diagnosis. Ghazali, Bakri, and Zain (2003) suggests that PVL "begins as homogenous leukoplakia with no dysplasia on histological examination" and progresses to a verrucous appearance with multiple lesions, either at a single site or at multiple sites. More recently, Cerero-Lapiedra, Balade-Martinez, Moreno-Lopez,

Esparza-Gomez, and Bagan (2010) proposed a new classification system based on major and minor criteria (Table 1; Cerero-Lapiedra et al., 2010).

Lesions of PVL have a nodular/verrucous appearance and occur more frequently in females with no racial predilection (Cabay, Morton, & Epstein, 2007; Ghazali et al., 2003; Villa, Kerr, & Woo, 2016). The mean age at the time of diagnosis is in the seventh decade (Abadie, Partington, Fowler, & Schmalbach, 2015), approximately two-thirds occur in never-smokers, and there is no substantial association with alcohol consumption (Pentenero et al., 2014).

In 2003, Petti estimated the pooled prevalence of oral leukoplakia to be between 1.5% (1.4%–1.6%, 95% confidence interval [CI]) and 2.6% (1.7%–2.7% 95% CI) (Petti, 2003). These data are from cohort studies, largely based on the more common form of leukoplakia which is typically localized to a single site such as the ventral tongue and designated here as unifocal leukoplakia (UL). PVL is a comparatively uncommon condition, and therefore, similar prevalence data do not currently exist.

The etiology of PVL remains unknown; it is a potentially malignant disorder and almost all initial biopsies show hyperkeratosis without dysplasia or verrucous hyperplasia. In terms of molecular profile, overexpression of p53 and deletions or mutations of the *p16INK4a* and *p14ARF* have been noted (Fettig et al., 2000; Gopalakrishnan et al., 1997; Kresty et al., 2008). Lesions also develop aneuploidy and alterations in the Mcm2 complex (Gouvea et al., 2013; Klanrit et al., 2007). An etiologic role of human papillomavirus and PVL has not been established (Campisi et al., 2004; Femiano, Gombos, & Scully, 2001; Gopalakrishnan et al., 1997; Palefsky, Silverman, Abdel-Salaam, Daniels, & Greenspan, 1995). Data from a recent systematic review showed that patients with PVL had a malignant transformation (MT) rate of 61.0% over an average follow-up period of 7.4 years with an overall 40.0% mortality rate (Abadie et al., 2015; Pentenero et al., 2014). The annual MT rate of PVL is approximately 10.0% per year (Villa & Woo, 2017).

There are still controversies surrounding the clinical diagnosis of PVL. Some centers consider all gingival leukoplakias regardless of size to be PVL, and some render a clinical diagnosis of PVL to patients presenting with multifocal lesions that are devoid of a verrucous appearance (Fettig et al., 2000; Hansen et al., 1985; Silverman & Gorsky, 1997). Furthermore, some cases of PVL that have an erythematous component are diagnosed as lichen planus because biopsies show a "lichenoid" lymphocytic band on microscopy. The demographics, management, and prognosis of lesions of PVL are distinctly different from the more commonly occurring UL. As such, the objectives of this retrospective study were to determine whether there are clinical variants of PVL, and if so, to determine whether there are differences in the behavior of such variants with regard to MT, and to propose new diagnostic criteria.

2 | MATERIAL AND METHODS

2.1 | Study design

A retrospective review of all medical records for patients with a clinical diagnosis of PVL was performed at three Oral Medicine centers (Brigham and Women's Hospital, Boston, USA; New York University, New York City, USA; and AC Camargo Cancer Center, San Paolo, Brazil) between August 1996 and October 2016. Inclusion criteria were as follows:

1. the presence of white plaques, with or without an erythematous component, at multiple sites (Hansen et al., 1985)
2. a lesion >3 cm at a single/contiguous site (Cerero-Lapiedra et al., 2010)
3. photographic documentation of the lesions
4. documented histopathological evaluation
5. documentation of at least one follow-up visit

Exclusion criteria were as follows:

1. Histopathological diagnosis of lichen planus although the term "lichenoid" used in the diagnosis is acceptable

TABLE 1 Proliferative verrucous leukoplakia: the Cerero-Lapiedra et al. (2010) classification

Major criteria	Minor criteria
A leukoplakia with more than two different oral sites, usually seen on the gingiva, palate, and alveolar ridge.	An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.
Verrucous appearance.	Being a female.
Progression and spreading of the PVL.	Never-smoker regardless of gender.
Presence of recurrence in a previously treated area.	A disease evolution longer than 5 years.
Oral epithelial hyperkeratosis or verrucous hyperplasia, verrucous carcinoma, or squamous cell carcinoma at histological examination.	

According to this classification a diagnosis of PVL is made when three major criteria (with the histopathological criterion being one of them) are present or with two major and two minor criteria (Cerero-Lapiedra et al., 2010).

2. Patients without follow-up

Socio-demographic information including gender, age, past medical history, family history of cancer, tobacco and alcohol habits, and oral symptoms was entered into an electronic database.

Data from the initial visit and all subsequent follow-up visits were recorded with respect to oral manifestations and histopathological diagnosis. Oral features of PVL cases were reviewed, and each case was evaluated according to number and location(s) of involved sites (maximum of 22 possible anatomic sites), size of the largest lesion (in mm), and presence of the following clinical parameters: keratotic lesions (smooth vs. fissured vs. verrucous); demarcation (well-delineated borders around at least part of the lesion); erythema; ulceration; and striation (Table 2). Lesions were then classified as involving a single site, multiple contiguous sites, and multiple non-contiguous sites. If more than six of 22 sites (>25%) showed erythema, a diagnosis of proliferative erythroleukoplakia (PEL) was made. Histopathological data were recorded from the pathology reports of all previous biopsies.

All study members (S.B.W., A.R.K., F.D.A.A, A.V.) received training with a PowerPoint presentation to classify lesions in a systematic manner. All clinical photographs used in the training were curated by two oral medicine specialists (A.V.; S.B.W.) for image quality and for clinical features of PVL lesions.

The study was approved by the Institutional Review Board of the Partners Human Research Committee (2014P002040/MGH—October 30, 2014) and the New York University School of Medicine Institutional Review Board.

2.2 | Statistical analysis

Descriptive statistics were used to characterize PVL both clinically and histopathologically, and MT rates were calculated from the date of the initial visit. Median time to MT was calculated from the date of the first visit. The association between erythema, demographic characteristics, and the risk of MT was calculated using the Pearson's chi-square test. Statistical significance was defined as

TABLE 2 Data collection tool for oral lesions in patients with proliferative verrucous leukoplakia

Intraoral findings

Size (specify in cm for the largest lesion)

LEFT SIDE

			MAXG		MANDG						
	ULB	LLB	PALATAL	BUCCAL	LINGUAL	BUCCAL	BM	VT	DT	FOM	SP
Keratotic											
Fissured	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Smooth	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Verrucous	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Demarcated (at least partially)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Erythema	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ulcer (s)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Striations	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

RIGHT SIDE

			MAXG		MANDG						
	ULB	LLB	PALATAL	BUCCAL	LINGUAL	BUCCAL	BM	VT	DT	FOM	SP
Keratotic											
Fissured	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Smooth	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Verrucous	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Demarcated (at least partially)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Erythema	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ulcer (s)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Striations	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

ULB, upper labial mucosa; LLB, lower labial mucosa; MAXG, maxillary gingiva; MANDG, mandibular gingiva; BM, buccal mucosa; VT, ventral tongue; DT, dorsal tongue; FOM, floor of the mouth; SP, soft palate.

$p < .05$. All analyses were performed using JMP® (version 12; SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

There were 42 patients with a median age of 69 years at initial visit (range: 36–88). Thirty-five subjects were females (83.3%) with a female-to-male ratio of 5:1. The median age at diagnosis was 70 years for females and 59 for males ($p < .05$). Five patients (12.2%) were current smokers with a median of one pack per day (range: 0.2–2.5 packs/day), 12 patients (29.3%) were former smokers, and 58.5% of patients were never-smokers; 31.0% of patients consumed alcohol (median of eight alcoholic beverages/month) (Table 3). A positive family history of any cancer was reported by at least 46.9% of patients, although this number is likely an under-representation because these data were not collected for every patient.

TABLE 3 Socio-demographic characteristics

	n (%)
Gender	
Female	35 (83.3)
Male	7 (16.7)
Age (median [range])	68.5 [36–88]
Smoking status	
Current[a]	5 (12.2)
Former	12 (29.3)
Never	24 (58.5)
Years of smoking (median [range])	21 [6–57]
Pack per day (median [range])	1 [0.2–2.5]
If former, years since smoking (median [range])	8.5 [0–32]
Other habits	
Areca nut	1 (2.4)
None	41 (97.6)
Alcohol consumption	
Current	13 (31.0)
Former	1 (2.4)
Never	28 (66.6)
Drink/month (median [range])	8 [1.5–32]
Family history of cancer[b]	
No	17 (53.1)
Yes	15 (46.9)
Malignant transformation	
No	12 (28.6)
Yes	30 (71.4)
Malignant transformation (months; since diagnosis) (median [range])	37 [1–210]

[a]Including one individual smoking cigars.
[b]Including missing numbers.

3.2 | Clinical and histopathological features

The median number of anatomic sites involved was 9 (out of 22) (range: 1–17). Large contiguous and multifocal non-contiguous PVLs constituted 57.1% and 35.7% of cases, respectively. Single-site involvement was present in 7.1% of the cases. Gingival/alveolar mucosal lesions were present in 33/42 patients (78.5%), and the buccal mucosa was the second most common site of involvement (72.7%) followed by the ventral tongue (57.1%) (Table 4). Three cases involved the gingiva exclusively.

The most common clinical features of the lesions were demarcation (at least partially; 31.3%), followed by verrucous appearance (27.5%) (Figure 1a–d), smooth appearance (22.7%) (Figure 2), presence of erythema (22.3%), and fissured appearance (18.3%; Figure 3a–d) (Table 5). Gingival lesions had the highest frequency of showing verrucous (15.6%) and erythematous components (12.0%). Ten of 42 cases (23.8%) had prominent verrucous features (defined as involvement of at least six sites of 22). Eight cases (19.1%) showed prominent erythema and, as such, qualified for a diagnosis of PEL (Figure 4a–d). Of interest, 3/42 cases (7.1%) of cases had no verrucous features.

Three cases had been originally diagnosed as having lichen planus based on the biopsy results, two diagnosed as outright lichen planus and one as lichenoid mucositis. On reviewing the clinical images, there were no classic signs of white reticular changes and the margins of the white lesions were sharply demarcated (Figure 5). There were also no previous clinical images available to evaluate for the presence of reticulations, and the biopsies could not be reviewed because they were evaluated at an outside institution.

3.3 | Histopathological features

There were a total of 222 biopsies performed across multiple clinical visits. By far, the most common histopathological diagnosis from

TABLE 4 Anatomic distribution of by number of sites involved and patient

Anatomic distribution	By sites (%)	By patient *n* (%)
Buccal mucosa	15.0	32 (72.7)
Gingiva[a]		
Buccal mandibular	14.7	31 (73.8)
Lingual mandibular	12.2	24 (57.1)
Palatal	11.6	22 (52.4)
Buccal maxillary	11.2	19 (42.2)
Tongue		
Dorsal	9.9	21 (50.0)
Ventral	9.0	24 (57.1)
Floor of the mouth	5.0	18 (42.9)
Soft palate	4.7	6 (14.3)
Labial mucosa		
Lower	4.3	16 (38.1)
Upper	2.4	4 (9.5)

[a]Gingival/alveolar mucosa involvement.

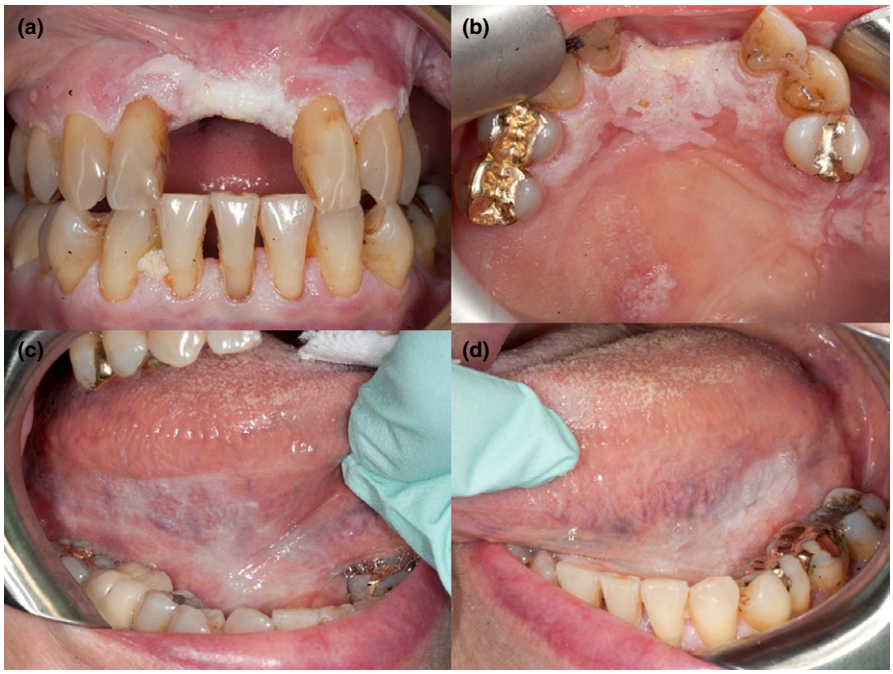

FIGURE 1 Proliferative leukoplakia with a predominant keratotic/verrucous appearance (a–d; note sharply demarcated margins and multiple non-contiguous sites) [Colour figure can be viewed at wileyonlinelibrary.com]

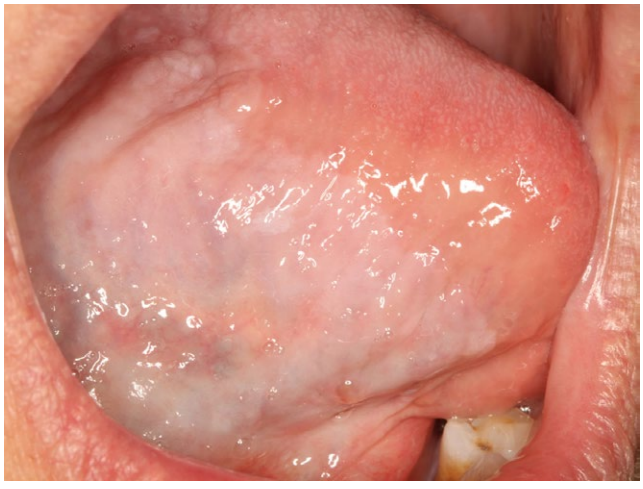

FIGURE 2 Proliferative leukoplakia of the right ventro-lateral tongue with a keratotic/smooth appearance (single site, >4 cm) [Colour figure can be viewed at wileyonlinelibrary.com]

biopsies taken at the initial visit (i.e., baseline) was hyperkeratosis without dysplasia (n = 22; 56.4%); this has been referred to in the literature as "keratosis of unknown significance" (KUS; Woo, Grammer, & Lerman, 2014).This was followed by mild (n = 14; 35.9%), moderate (n = 2; 5.1%), and severe dysplasia (n = 1; 2.6%). Verrucous hyperplasia was noted in five biopsies. A median of three biopsies (range: 1–26) was performed before MT occurred, and only eight patients received one biopsy prior to MT. A median of two biopsies (range: 1–5) was performed for the cases with a baseline diagnosis of hyperkeratosis without dysplasia/KUS before moderate or severe dysplasia developed (median time: 5 months; range: 2–60; Figure 6). A median of four biopsies (range: 4–10) was performed for cases with a baseline diagnosis of mild dysplasia before development of invasive squamous cell carcinoma (SCC).

3.4 | Malignant transformation

MT to invasive SCC occurred in 71.4% patients (30/42) after a median of 37 months (range: 1–210) from their initial visit. This is compared with a median of 17.5 months (range: 1–108) of patients who did not develop cancer ($p < .05$). All eight cases of PEL (100.0%) underwent MT (median time: 49 months [range: 9–111]), while the PVLs without an erythematous component showed MT in 62.5% of cases (median time: 24 months [range: 9–120]). Twenty-five cases (78.1%) were conventional invasive SCC, and five cases (15.6%) were verrucous carcinomas. Twenty patients developed one cancer, eight developed two cancers, and two patients developed three synchronous cancers.

There was no significant association between MT and the presence of prominent erythema, gender, age, and tobacco or alcohol consumption ($p > .05$; data not shown).

4 | DISCUSSION

The WHO defines leukoplakia as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" PVL is considered a non-homogenous form of leukoplakia (Warnakulasuriya et al., 2007). Hansen et al. (1985) was the first one to identify PVL as a separate form of leukoplakia and described it as a "slow-growing, persistent, irreversible" lesions with erythematous components and "exophytic and wart-like" areas resistant to most forms of therapy (Hansen et al., 1985).

This study of 42 patients showed a female predilection of 5:1, very similar to the 4:1 ratio reported by Silverman and Gorsky (1997) in their large cohort of 54 cases, but compared with only 2.5:1 in a recent review (Pentenero et al., 2014). While 1/3 (Silverman & Gorsky,

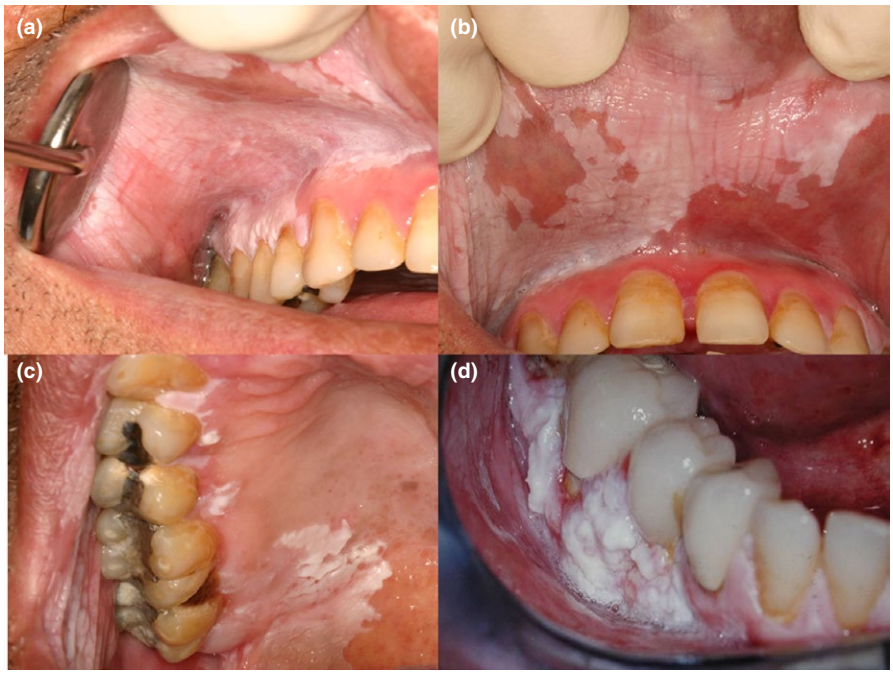

FIGURE 3 Proliferative leukoplakia with a predominant keratotic/fissured appearance (panels a, b, c) (note sharply demarcated margins and multiple non-contiguous sites) and subsequent development of gingival verrucous carcinoma (panel d) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Oral features of proliferative verrucous leukoplakia

	Total[a] (%)	Left side (%)	Right side (%)	LM (%)	Gingiva/hard palatal mucosa (%)	BM (%)	VT (%)	DT (%)	FOM (%)	SP
Keratotic lesions										
Fissured	18.3	10.1	8.2	1.1	7.8	3.1	2.3	2.1	1.3	0.6
Smooth	22.7	13.2	9.5	1.7	8.6	3.4	2.1	4.0	1.3	1.5
Verrucous	27.5	13.7	13.7	1.5	15.6	3.6	2.1	2.9	0.8	1.0
Demarcated (at least partially)	31.3	16.0	15.3	1.9	16.6	5.0	2.7	2.1	1.7	1.3
Erythema	22.3	10.9	11.5	2.1	12.0	3.1	1.9	1.1	0.8	1.3
Ulcer (s)	5.3	2.1	3.2	0.0	3.1	0.8	0.6	0.2	0.6	0.2
Striations[b]	2.1	1.3	0.8	0.2	0.8	0.6	0.0	0.4	0.0	0.2

LM, labial mucosa; BM, buccal mucosa; VT, ventral tongue; DT, dorsal tongue; FOM, floor of the mouth; SP, soft palate.
[a]The total % represents the proportion of lesions with these oral features.
[b]Three patients were diagnosed as lichenoid mucositis in the past.

1997) to 2/3 (Hansen et al., 1985) of patients have been reported to smoke, the recent review noted that approximately 35.3% were ever smokers which is similar to what we reported in our study of 40.5% [3]. The most common sites in our study were gingiva/alveolar mucosa (78.5%), buccal mucosa (72.7%), and ventral tongue (57.1%). Silverman and Gorsky (1997) found that the buccal mucosa was the most frequently site affected (57%) follow by the gingiva or tongue (54%). In a study of 55 patients by Bagan et al. (2011), 89.9% of patients had a gingival involvement followed by the tongue in 49.1% of patients and the buccal mucosa in 47.3%. In a study of 47 cases, 87.2% had involvement of the mucosa of the alveolar crest and 46.8% of the gingiva (Gandolfo, Castellani, & Pentenero, 2009).

Multisite involvement is one of the most important and an undisputed major criterion for the diagnosis of PVL. One of the minor criteria proposed by Cerero-Lapiedra et al. (2010) is that a lesion >3.0 cm (presumably at a single site) should be considered PVL. van der Waal, Schepman, and van der Meij (2000) have long been a proponent of size being an important predictor of behavior. They reported that lesions >4.0 cm with benign histopathology tend to progress to dysplasia and SCC (van der Waal, Schepman, van der Meij, & Smeele, 1997; van der Waal et al., 2000). Whether the cutoff is 3.0 cm or 4.0 cm is arbitrary because the crucial point is that a larger lesion would generally connote a more progressive lesion that is more difficult to excise with clear margins. In our study, large lesions that involved contiguous sites (Figure 7) constituted 57.1% of cases, while 7.1% of cases involved a single site. In the series of 30 cases by Hansen et al., three (10.0%) of cases involved a single site.

An important aspect of size of a lesion at a single site is reflected in yet another controversy regarding gingival leukoplakia, one of the most common sites involved by PVL (Figure 8a–d; Bagan et al., 2003).

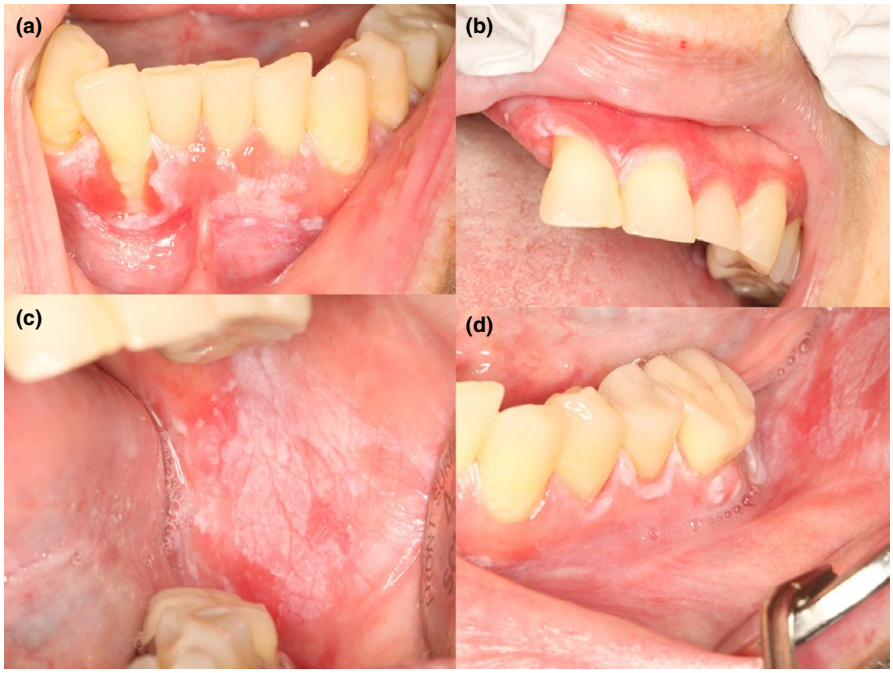

FIGURE 4 Proliferative erythroleukoplakia with multisite involvement [Colour figure can be viewed at wileyonlinelibrary.com]

These are localized lesions of the gingiva that initially involve one tooth but over time, extend to involve the marginal (usually facial) gingivae of adjacent teeth, and often also the lingual or palatal gingiva, possibly from spread through the interdental periodontal membrane (Figure 9a,b). The first question therefore is whether this should be regarded as two non-contiguous sites or a single contiguous site. Its length may be 1.0–2.0 cm if it involves the marginal gingiva of 1 or 2 teeth, but may be as much as 5.0–6.0 cm if multiple teeth are involved, even though the visible width may be <0.5 cm. The second question therefore is whether the greatest linear dimension determines its classification as PVL. Studies have demonstrated that these gingival leukoplakias tend to "recur" after excision. In our opinion, this is likely a function of incomplete removal of lesional tissue within the crevicular epithelium which then repopulates the biopsy site, leading to progression of residual disease, rather than a true recurrence. Margins are often not reported on pathology reports, especially if the margins show only hyperkeratosis without obvious dysplasia/KUS (Bagan et al., 2003; Kuribayashi, Tsushima, Sato, Morita, & Omura, 2012). This issue of incomplete removal and "recurrence" is further complicated by the lack of consensus among pathologists on reporting the

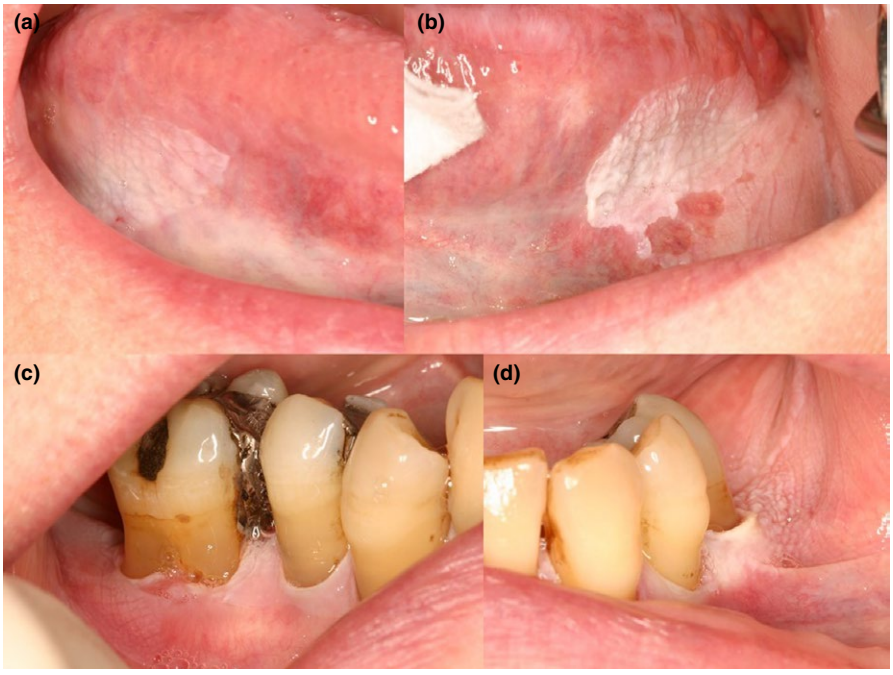

FIGURE 5 Proliferative leukoplakia with keratotic/fissured plaques of the ventral tongue, very well demarcated on the left side (a, b), and poorly demarcated plaques on the mandibular posterior gingiva (c, d) [Colour figure can be viewed at wileyonlinelibrary.com]

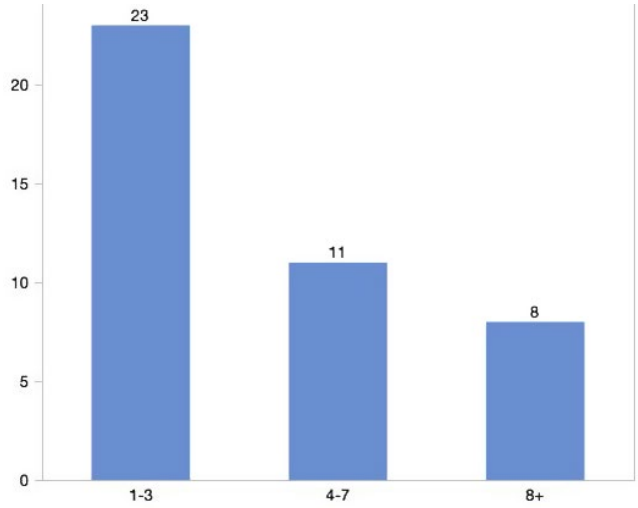

FIGURE 6 Number of biopsies prior malignant transformation [Colour figure can be viewed at wileyonlinelibrary.com]

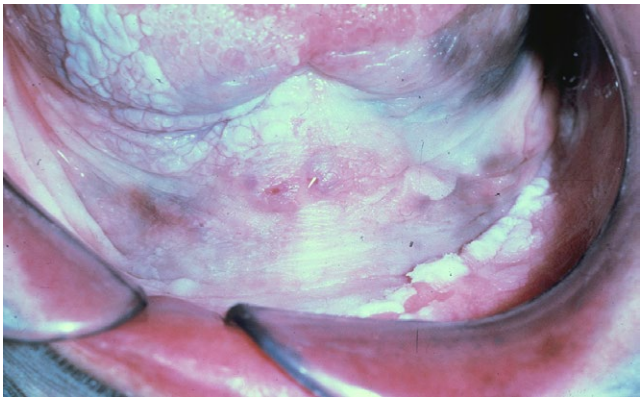

FIGURE 7 Proliferative leukoplakia of the dorsal tongue, ventral tongue, floor of the mouth, and alveolar ridge mucosa (multisite involvement, contiguous) [Colour figure can be viewed at wileyonlinelibrary.com]

involvement of margins by dysplasia and by hyperkeratosis. Whether such gingival leukoplakias should be regarded de facto as PL will continue to be debated.

For multifocal PVL, it is almost impossible to surgically eradicate the condition because of the difficulty of obtaining disease-free margins, also with the understanding that margins may show hyperkeratosis without dysplasia/KUS. It is possible that these lesions of KUS may already contain genetic mutations, and studies are ongoing in our institution to investigate this. Recurrence is one of the major criteria put forward by Cerero-Lapiedra et al. (2010). However, if recurrence is a major criterion, even a 0.5-cm lesion that recurs from incomplete removal (a frequent occurrence on the gingiva) would be considered PVL which is not an accurate depiction of this condition.

Only 10 of our PVL cases (10/42; 23.8%) had prominent keratotic verrucous features, and the majority of patients showed smooth or fissured appearance (30/42; 71.4%). As such, verrucous appearance is not a requirement for the diagnosis of this form of leukoplakia. PVL with both an erythematous and white component (erythroleukoplakic form) with bilateral and multifocal lesions (specifically those affecting the buccal mucosa) may mimic oral lichen planus clinically (Fernandes, Santos-Silva, Vargas, & Lopes, 2017). Previous studies have shown that some cases of oral lichen planus that underwent MT were likely misclassified and were probably lesions of PVL that exhibited a lymphocytic band at the interface, often referred to as "lichenoid mucositis" (Cortes-Ramirez, Gainza-Cirauqui, Echebarria-Goikouria, & Aguirre-Urizar, 2009). Such a bandlike lymphocytic response may also be associated with both epithelial dysplasia and oral SCC (Hanahan & Weinberg, 2011; Muller, 2017; van der Meij, Mast, & van der Waal, 2007), and therefore, the use of the term "lichenoid" by a pathologist may erroneously lead the clinician to assume that the dysplasia or SCC arose within oral lichen planus (Goodson, Sloan, Robinson, Cocks, & Thomson, 2015). This was noted in three of the current cases. In one study, 33.0% of cases of "lichenoid inflammation" developed squamous cell carcinoma (Goodson et al., 2015). It is well known that such "tumor-related lymphocytic response" is often seen around carcinomas and should not be surprising when seen adjacent to dysplasias.

Proliferative verrucous leukoplakia is recognized as an aggressive variant of leukoplakia with a higher malignant potential than UL (Bagan et al., 2010). A recent systematic review of 25 studies showed a mean MT rate of 63.9% with a mean follow-up time of 7.4 years (Abadie et al., 2015). The annual MT rate of PVL is approximately 10% per year (Villa & Woo, 2017). This is in keeping with our 42 cases of PVL that showed a MT rate of 71.4% (followed up for a median of 70 months; range: 9–56). Prominent erythema was present in about 19% of the cases. In this study, patients with a prominent erythematous component showed 100% MT compared to a rate of 62.5% in those without an erythematous component. Even Hansen et al. (1985) indicated that some of their PVL cases had an erythroleukoplakic appearance similar to what we report here. Patients who developed SCC and those who did not were followed up for a median of 70.0 and 17.5 months, respectively, suggesting that the longer the patients are followed, the more likely they are to develop SCC which is not surprising. As such, all patients must receive lifetime follow-up.

A recent systematic review on the treatment of PVL showed that patients with PVL typically would have undergone nine biopsies with a mean follow-up of 7.4 years, until a diagnosis of cancer is made (Abadie et al., 2015). More than half of the cases of PVL in this series (56.4%) exhibited no evidence of epithelial dysplasia at first biopsy, but hyperkeratosis or parakeratosis with epithelial atrophy or acanthosis. This is similar to the data reported by Garcia-Chias, Casado-De La Cruz, Esparza-Gomez, and Cerero-Lapiedra (2014) where 50% of cases exhibited hyperkeratosis without dysplasia (KUS) and 50% showed dysplasia. In their systematic review Pentenero et al. (2014) showed that 47.7% of patients with PVL had a diagnosis of dysplasia, but did not comment on other histopathological stages. The assumption therefore is that 52.5% did not show dysplasia. However, it is also well established that leukoplakias with "benign hyperkeratosis" may develop dysplasia and SCC in 15%–30% of cases (Goodson et al., 2015; Holmstrup, Vedtofte, Reibel, & Stoltze, 2006; Schepman, van der Meij, Smeele, & van der Waal, 1998; Silverman & Gorsky, 1997), and leukoplakias with these benign histopathological features have

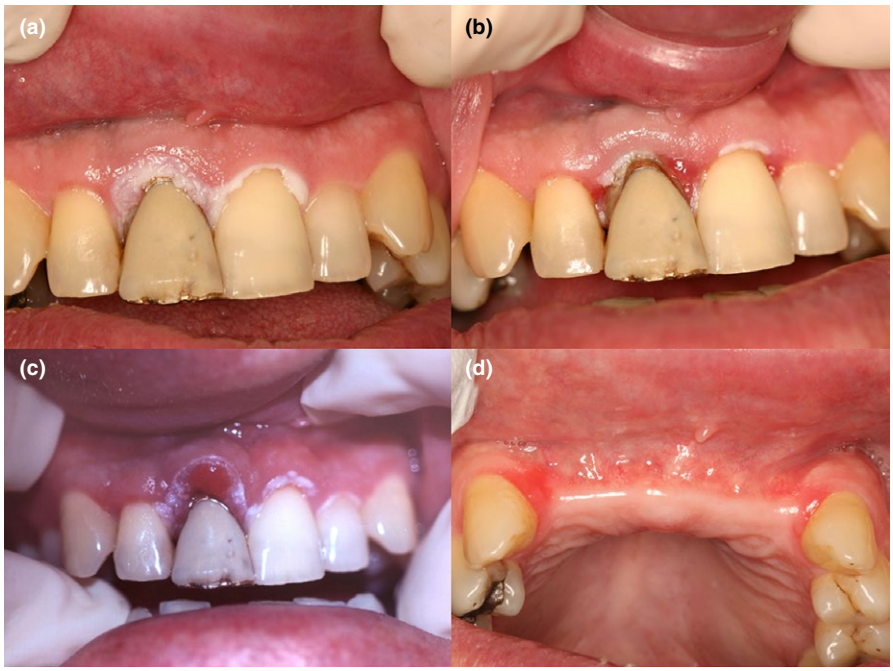

FIGURE 8 Gingival proliferative leukoplakia of the anterior maxillary marginal gingiva presurgical excision (a); recurrence postsurgical excision 2 weeks later (b); development of nodular and erythematous area 1 year later (c) (courtesy of Dr. John Sexton, MA); post-block resection (d) [Colour figure can be viewed at wileyonlinelibrary.com]

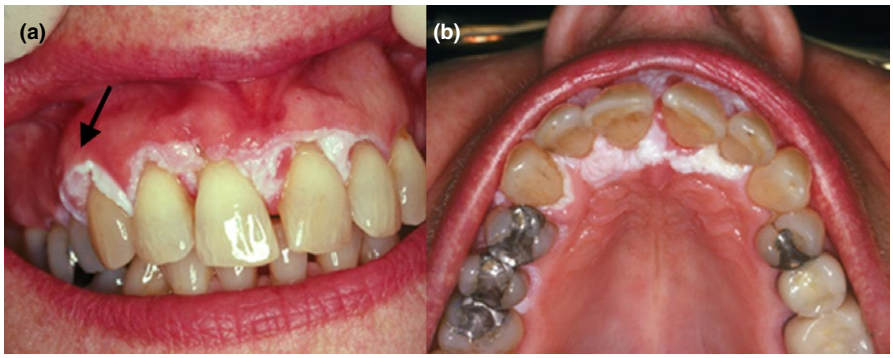

FIGURE 9 Gingival proliferative leukoplakia of the facial and palatal maxillary marginal gingiva (a and b); this patient had a verrucous carcinoma within the maxillary alveolus with one focus presenting superficially (see arrow) [Colour figure can be viewed at wileyonlinelibrary.com]

been termed KUS (Woo et al., 2014). KUS in well-demarcated keratotic lesions may already represent a precancerous state and such lesions should be biopsied periodically or even removed completely, based on the clinical presentation (size and anatomic site involved) and other patient-related factors (Villa & Woo, 2017; Woo et al., 2014). KUS lesions often show hyperkeratosis and epithelial atrophy, and epithelial atrophy was noted as an initial finding in the seminal paper by Hansen et al. (1985), while epithelial hyperplasia or acanthosis was considered Stage 2.

A recent study from Akrish, Ben-Izhak, Sabo, and Rachmiel (2015) has shown that SCC arising from PVL has different clinical behavior and epigenetic/genetic characteristics compared to SCC that did not arise from PVL Specifically, patients with PVL who underwent malignant transformation displayed early-stage SCC, with smaller tumor size, no lymph node metastasis, and no distant metastasis, and experienced significantly improved 4-year survival compared to non-PVL-associated SCC (100.0% vs. 56.9%). It is likely that frequent follow-up visits and surveillance contributed to early detection and, as such, early-stage lesions resulting in improved prognosis. In addition, P53 overexpression was more common in PVL-associated SCCs compared to those with non-PVL-associated SCC (Akrish et al., 2015). Other studies have shown increased incidence of p16INK compared to UL (Fettig et al., 2000; Gopalakrishnan et al., 1997; Kresty et al., 2008).

Management of PVL remains challenging due to the multifocality of this condition, and surgical treatment may not improve the rate of MT (Borgna et al., 2017). Patients should be monitored closely and all the verrucous/nodular areas biopsied to rule out dysplasia or SCC (Villa & Woo, 2017). Surgery is the most common treatment option, but recurrence rates remain high at 71.2% (Abadie et al., 2015). Other modalities of treatment that have been reported include laser ablation, photodynamic therapy, and medical therapy although none of these have shown complete efficacy (Chau et al., 2017; Lodi et al., 2016; Vohra et al., 2015).

Our study had several limitations because of its retrospective nature. First, patients may have had oral PVL months or years before the initial visit to our oral medicine clinics, and therefore, the duration of the lesion may not be accurate, although that would have been true even in prospective studies. Nevertheless, the median time reported to MT may be underestimated. Second, the clinical characterization

TABLE 6 Comparison between unifocal and proliferative leukoplakia

	Unifocal leukoplakia	Proliferative leukoplakia
Gender	Mostly in men (2–3.5:1)	Mostly in women (2.5–5:1)
Smoking association	Strong (>60%)	Weak (<30%)
Number of sites	Single site	Multifocal non-contiguous lesions
Location	Ventral tongue and floor of mouth	Gingiva, buccal mucosa
Prevalence of dysplasia	~40% at first biopsy	<10% at first biopsy and usually hyperkeratosis/KUS or verrucous hyperplasia
Malignant transformation	3%–15%	70%–100% (PEL: ~100%)
Deletion in $p14^{ARF}$ exon 1B (within CDKN2A locus)	3.8%	40.0%
Treatment	Usually amenable to ablation/excision if small and localized	Difficult to treat because multifocal and single-site lesions are very large

KUS, keratosis of unknown significance; PEL, proliferative erythroleukoplakia.

of the PVLs was based on photographic documentation and some anatomic sites may not have been photographed. Finally, there was no calibration of pathologists for the recognition of KUS and/or dysplasia. Of note, patients with a histopathological diagnosis of dysplasia at the first biopsy when seen at these three centers may have had a previous biopsy showing KUS, confirming the natural history of progression of these lesions from hyperkeratosis with no dysplasia to dysplasia to SCC. Future studies that characterize these lesions from a genomic standpoint to identify biomarkers that can be useful for early detection, risk stratification, prediction of MT and, importantly, for targeted therapy are needed.

We propose the term "proliferative leukoplakia (PL)" which may be more appropriate than PVL because approximately 18% are fissured and 22% erythematous, and these are also features of UL. The term "proliferative erythroleukoplakia (PEL)" may be used to better describe PL with prominent erythema, which has the highest MT rate similar to erythroleukoplakia which has a high association with dysplasia and SCC. The criteria for the diagnosis of this condition have evolved over time and will continue to do so as research provides further insight into this condition. At this time, we suggest the following four criteria, all of which must be met, for diagnosis of PL which are a distillation of findings by Cerero-Lapiedra et al. (2010), van der Waal et al. (2000), Hansen et al. (1985)), and others:

1. White/keratotic lesions that may be smooth, fissured, verrucous, or erythematous with or without ulcer
2. Multifocal non-contiguous lesions or a single large lesion >4.0 cm involving one site or a single large lesion >3 cm involving contiguous sites
3. Lesions that progress/expand in size and/or develop multifocality over time.
4. Histopathology that, if not overtly exhibiting dysplasia or carcinoma, shows hyperkeratosis, parakeratosis, atrophy, or acanthosis with minimal to no cytologic atypia (KUS), with or without a lymphocytic band, or verrucous hyperplasia; these features must not support a diagnosis of frictional or reactive keratoses

Whether or not the lesions are "progressive" is not a required criterion. By the time the lesions are multifocal, they obviously have progressed over time. Finally, neither gender nor smoking history is important although it is recognized that it is more common in non-smoking women, but not exclusively so. The diagnosis would not change if the lesion occurred in a male smoker. We hope that these criteria that we have proposed above, as well as the change in terminology, will help to further tighten and clarify diagnostic criteria for this condition. It may be useful for PL to be classified separately as its own entity because of the differences between this and UL, rather than being listed as a form of non-homogenous leukoplakia (Table 6).

Finally, we recommend the following as part of the management strategy for patients with PL:

1. Photographs should be taken at every visit, and these should be submitted to the pathologist with the biopsy. This is truly

a clinicopathologic entity that requires careful clinicopathologic correlation.

2. Patients should be closely followed up every 3–6 months (depending of the histopathological diagnosis) with periodic biopsies especially when there has been a change in the character of the lesion such as development of red and/or nodular/verrucous areas, induration, and involvement of other sites.
3. Biopsies that show only KUS, that is, hyperkeratosis, parakeratosis, epithelial atrophy, or acanthosis, with or without inflammation, may be followed only (Woo et al., 2014). Gingival leukoplakias will have to be treated on a case-by-case basis because many other factors impact treatment such as age, physical health, degree of involvement, bone loss, tooth mobility, and the appearance and behavior of the lesion.
4. Biopsies of areas that show mild-to-moderate dysplasia can likely be observed if it is felt that completely removing the area is not possible because of the extent or location of the lesion (Borgna et al., 2017). However, if the area is discrete, excision can be attempted.
5. Biopsies of areas that show severe dysplasia or carcinoma in situ should be excised especially if the area is discrete such as a nodular or verrucous mass within a fissured and relatively homogenous area, with the understanding that the margin will likely show KUS or mild-to-moderate dysplasia.
6. Pathology reports for excisional biopsies should always report on margins, even if the margins show KUS.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

All listed authors read the paper and provided feedback. A. Villa wrote the manuscript and performed data analysis. S. B. Woo and A. Villa drafted the rebuttal letter.

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REFERENCES

Abadie, W. M., Partington, E. J., Fowler, C. B., & Schmalbach, C. E. (2015). Optimal management of proliferative verrucous leukoplakia: A systematic review of the literature. *Otolaryngology - Head and Neck Surgery*, *153*, 504–511. https://doi.org/10.1177/0194599815586779

Akrish, S., Ben-Izhak, O., Sabo, E., & Rachmiel, A. (2015). Oral squamous cell carcinoma associated with proliferative verrucous leukoplakia compared with conventional squamous cell carcinoma–a clinical, histologic and immunohistochemical study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *119*, 318–325. https://doi.org/10.1016/j.oooo.2014.10.023

Bagan, J. V., Jimenez, Y., Sanchis, J. M., Poveda, R., Milian, M. A., Murillo, J., & Scully, C. (2003). Proliferative verrucous leukoplakia: High incidence of gingival squamous cell carcinoma. *Journal of Oral Pathology and Medicine*, *32*, 379–382. https://doi.org/10.1034/j.1600-0714.2003.00167.x

Bagan, J. V., Jimenez-Soriano, Y., Diaz-Fernandez, J. M., Murillo-Cortes, J., Sanchis-Bielsa, J. M., Poveda-Roda, R., & Bagan, L. (2011). Malignant transformation of proliferative verrucous leukoplakia to oral squamous cell carcinoma: A series of 55 cases. *Oral Oncology*, *47*, 732–735. https://doi.org/10.1016/j.oraloncology.2011.05.008

Bagan, J., Scully, C., Jimenez, Y., & Martorell, M. (2010). Proliferative verrucous leukoplakia: A concise update. *Oral Diseases*, *16*, 328–332. https://doi.org/10.1111/j.1601-0825.2009.01632.x

Borgna, S. C., Clarke, P. T., Schache, A. G., Lowe, D., Ho, M. W., McCarthy, C. E., … Shaw, R. J. (2017). Management of proliferative verrucous leukoplakia: Justification for a conservative approach. *Head and Neck*, *39*, 1997–2003. https://doi.org/10.1002/hed.24845

Cabay, R. J., Morton, T. H. Jr, & Epstein, J. B. (2007). Proliferative verrucous leukoplakia and its progression to oral carcinoma: A review of the literature. *Journal of Oral Pathology and Medicine*, *36*, 255–261. https://doi.org/10.1111/j.1600-0714.2007.00506.x

Campisi, G., Giovannelli, L., Ammatuna, P., Capra, G., Colella, G., Di Liberto, C., … D'Angelo, M. (2004). Proliferative verrucous vs conventional leukoplakia: No significantly increased risk of HPV infection. *Oral Oncology*, *40*, 835–840. https://doi.org/10.1016/j.oraloncology.2004.02.007

Cerero-Lapiedra, R., Balade-Martinez, D., Moreno-Lopez, L. A., Esparza-Gomez, G., & Bagan, J. V. (2010). Proliferative verrucous leukoplakia: A proposal for diagnostic criteria. *Medicina Oral Patología Oral y Cirugia Bucal*, *15*, e839–e845. https://doi.org/10.4317/medoral.15.e839

Chau, L., Jabara, J. T., Lai, W., Svider, P. F., Warner, B. M., Lin, H. S., … Fribley, A. M. (2017). Topical agents for oral cancer chemoprevention: A systematic review of the literature. *Oral Oncology*, *67*, 153–159. https://doi.org/10.1016/j.oraloncology.2017.02.014

Cortes-Ramirez, D. A., Gainza-Cirauqui, M. L., Echebarria-Goikouria, M. A., & Aguirre-Urizar, J. M. (2009). Oral lichenoid disease as a premalignant condition: The controversies and the unknown. *Medicina Oral Patología Oral y Cirugia Bucal*, *14*, E118–E122.

Femiano, F., Gombos, F., & Scully, C. (2001). Oral proliferative verrucous leukoplakia (PVL); open trial of surgery compared with combined therapy using surgery and methisoprinol in papillomavirus-related PVL. *International Journal of Oral and Maxillofacial Surgery*, *30*, 318–322. https://doi.org/10.1054/ijom.2001.0066

Fernandes, D. T., Santos-Silva, A. R., Vargas, P. A., & Lopes, M. A. (2017). Letter to the Editor: Development of proliferative verrucous leukoplakia (PVL) in oral lichen planus: Is it not a clinical spectrum of PVL? *Medicina Oral Patología Oral y Cirugia Bucal*, *22*, e142–e143.

Fettig, A., Pogrel, M. A., Silverman, S. Jr, Bramanti, T. E., Da Costa, M., & Regezi, J. A. (2000). Proliferative verrucous leukoplakia of the gingiva. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *90*, 723–730. https://doi.org/10.1067/moe.2000.108950

Gandolfo, S., Castellani, R., & Pentenero, M. (2009). Proliferative verrucous leukoplakia: A potentially malignant disorder involving periodontal sites. *Journal of Periodontology*, *80*, 274–281. https://doi.org/10.1902/jop.2009.080329

Garcia-Chias, B., Casado-De La Cruz, L., Esparza-Gomez, G. C., & Cerero-Lapiedra, R. (2014). Diagnostic criteria in proliferative verrucous leukoplakia: Evaluation. *Medicina Oral Patología Oral y Cirugia Bucal*, *19*, e335–e339. https://doi.org/10.4317/medoral.19424

Ghazali, N., Bakri, M. M., & Zain, R. B. (2003). Aggressive, multifocal oral verrucous leukoplakia: Proliferative verrucous leukoplakia or not? *Journal of Oral Pathology and Medicine*, *32*, 383–392. https://doi.org/10.1034/j.1600-0714.2003.00180.x

Goodson, M. L., Sloan, P., Robinson, C. M., Cocks, K., & Thomson, P. J. (2015). Oral precursor lesions and malignant transformation–who, where, what, and when? *British Journal of Oral and Maxillofacial Surgery*, *53*, 831–835. https://doi.org/10.1016/j.bjoms.2015.08.268

Gopalakrishnan, R., Weghorst, C. M., Lehman, T. A., Calvert, R. J., Bijur, G., Sabourin, C. L., … Stoner, G. D. (1997). Mutated and wild-type p53 expression and HPV integration in proliferative verrucous leukoplakia and oral squamous cell carcinoma. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *83*, 471–477. https://doi.org/10.1016/S1079-2104(97)90148-7

Gouvea, A. F., Santos Silva, A. R., Speight, P. M., Hunter, K., Carlos, R., Vargas, P. A., … Lopes, M. A. (2013). High incidence of DNA ploidy abnormalities and increased Mcm2 expression may predict malignant change in oral proliferative verrucous leukoplakia. *Histopathology*, *62*, 551–562. https://doi.org/10.1111/his.12036

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell*, *144*, 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hansen, L. S., Olson, J. A., & Silverman, S. Jr (1985). Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surgery, Oral Medicine, Oral Pathology*, *60*, 285–298. https://doi.org/10.1016/0030-4220(85)90313-5

Holmstrup, P., Vedtofte, P., Reibel, J., & Stoltze, K. (2006). Long-term treatment outcome of oral premalignant lesions. *Oral Oncology*, *42*, 461–474. https://doi.org/10.1016/j.oraloncology.2005.08.011

Klanrit, P., Sperandio, M., Brown, A. L., Shirlaw, P. J., Challacombe, S. J., Morgan, P. R., & Odell, E. W. (2007). DNA ploidy in proliferative verrucous leukoplakia. *Oral Oncology*, *43*, 310–316. https://doi.org/10.1016/j.oraloncology.2006.03.016

Kresty, L. A., Mallery, S. R., Knobloch, T. J., Li, J., Lloyd, M., Casto, B. C., & Weghorst, C. M. (2008). Frequent alterations of p16INK4a and p14ARF in oral proliferative verrucous leukoplakia. *Cancer Epidemiology, Biomarkers & Prevention*, *17*, 3179–3187. https://doi.org/10.1158/1055-9965.EPI-08-0574

Kuribayashi, Y., Tsushima, F., Sato, M., Morita, K., & Omura, K. (2012). Recurrence patterns of oral leukoplakia after curative surgical resection: Important factors that predict the risk of recurrence and malignancy. *Journal of Oral Pathology and Medicine*, *41*, 682–688. https://doi.org/10.1111/j.1600-0714.2012.01167.x

Lodi, G., Franchini, R., Warnakulasuriya, S., Varoni, E. M., Sardella, A., Kerr, A. R., … Worthington, H. V. (2016). Interventions for treating oral leukoplakia to prevent oral cancer. *Cochrane Database Systematic Review*, *7*, CD001829.

Muller, S. (2017). Oral lichenoid lesions: Distinguishing the benign from the deadly. *Modern Pathology*, *30*, S54–S67. https://doi.org/10.1038/modpathol.2016.121

Palefsky, J. M., Silverman, S. Jr, Abdel-Salaam, M., Daniels, T. E., & Greenspan, J. S. (1995). Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. *Journal of Oral Pathology and Medicine*, *24*, 193–197. https://doi.org/10.1111/j.1600-0714.1995.tb01165.x

Pentenero, M., Meleti, M., Vescovi, P., & Gandolfo, S. (2014). Oral proliferative verrucous leucoplakia: Are there particular features for such an ambiguous entity? A systematic review. *British Journal of Dermatology*, *170*, 1039–1047. https://doi.org/10.1111/bjd.12853

Petti, S. (2003). Pooled estimate of world leukoplakia prevalence: A systematic review. *Oral Oncology*, *39*, 770–780. https://doi.org/10.1016/S1368-8375(03)00102-7

Schepman, K. P., van der Meij, E. H., Smeele, L. E., & van der Waal, I. (1998). Malignant transformation of oral leukoplakia: A follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncology*, *34*, 270–275. https://doi.org/10.1016/S1368-8375(98)80007-9

Silverman, S. Jr, & Gorsky, M. (1997). Proliferative verrucous leukoplakia: A follow-up study of 54 cases. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *84*, 154–157. https://doi.org/10.1016/S1079-2104(97)90062-7

van der Meij, E. H., Mast, H., & van der Waal, I. (2007). The possible premalignant character of oral lichen planus and oral lichenoid lesions: A prospective five-year follow-up study of 192 patients. *Oral Oncology*, *43*, 742–748. https://doi.org/10.1016/j.oraloncology.2006.09.006

van der Waal, I., Schepman, K. P., & van der Meij, E. H. (2000). A modified classification and staging system for oral leukoplakia. *Oral Oncology*, *36*, 264–266. https://doi.org/10.1016/S1368-8375(99)00092-5

van der Waal, I., Schepman, K. P., van der Meij, E. H., & Smeele, L. E. (1997). Oral leukoplakia: A clinicopathological review. *Oral Oncology*, *33*, 291–301. https://doi.org/10.1016/S1368-8375(97)00002-X

Villa, A., Kerr, A. R., & Woo, S. B. (2016). Proliferative erythro-leukoplakia: A variant of proliferative verrucous leukoplakia? *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *122*, e160. https://doi.org/10.1016/j.oooo.2016.06.037

Villa, A., & Woo, S. B. (2017). Leukoplakia-A diagnostic and management algorithm. *Journal of Oral and Maxillofacial Surgery*, *75*, 723–734. https://doi.org/10.1016/j.joms.2016.10.012

Vohra, F., Al-Kheraif, A. A., Qadri, T., Hassan, M. I., Ahmed, A., Warnakulasuriya, S., & Javed, F. (2015). Efficacy of photodynamic therapy in the management of oral premalignant lesions. A systematic review. *Photodiagnosis and Photodynamic Therapy*, *12*, 150–159. https://doi.org/10.1016/j.pdpdt.2014.10.001

Warnakulasuriya, S., Johnson, N. W., & van der Waal, I. (2007). Nomenclature and classification of potentially malignant disorders of the oral mucosa. *Journal of Oral Pathology and Medicine*, *36*, 575–580. https://doi.org/10.1111/j.1600-0714.2007.00582.x

Woo, S. B., Grammer, R. L., & Lerman, M. A. (2014). Keratosis of unknown significance and leukoplakia: A preliminary study. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *118*, 713–724. https://doi.org/10.1016/j.oooo.2014.09.016

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