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Diagnosis and Management of Proliferative Verrucous Leukoplakia

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Abstract

Proliferative verrucous leukoplakia is a distinct oral potentially malignant disorder characterized by multifocal white lesions with progressive clinical behavior and exceptionally high malignant transformation rates. This condition presents unique diagnostic and therapeutic challenges for dental practitioners owing to its resistant nature and propensity for recurrence. This evidence-based review synthesizes the current knowledge on proliferative verrucous leukoplakia, examining its diagnostic criteria, clinical presentations, histopathological features, and management approaches. The disorder predominantly affects elderly women, exhibits resistance to conventional therapies, and demonstrates malignant transformation rates approaching 44-50%. Recent consensus guidelines have established standardized histopathological categories to improve diagnostic accuracy and clinical management. Proliferative verrucous leukoplakia requires lifelong surveillance with serial biopsies to detect early malignant transformation. No therapeutic intervention has been proven to be consistently effective in preventing disease progression. Clinicians must maintain heightened awareness of this aggressive disorder to ensure appropriate patient management and timely detection of malignancies.

Keywords: Leukoplakia, proliferative verrucous leukoplakia, oral potentially malignant disorder, white lesions, malignant transformation, recurrence

INTRODUCTION

Proliferative verrucous leukoplakia (PVL) is one of the most aggressive forms of oral potentially malignant disorders. It was first described by Hansen et al. in 1985 as a distinct clinical entity [1]. The 2020 WHO Collaborating Centre for Oral Cancer consensus meeting defined PVL as a distinct form of multifocal oral leukoplakia characterized by a progressive clinical course, changing clinical and histopathological features, and association with the highest proportion of oral cavity cancer development compared with other potentially malignant oral disorders [2].

The malignant transformation rate of PVL has been reported to be approximately 44-50%, significantly higher than that of conventional oral leukoplakia [3,4]. This aggressive behavior, combined with characteristic multifocality and treatment resistance, necessitates a

comprehensive understanding among dental professionals for early recognition and appropriate management [5]. The lesions often involve the gingiva adjacent to and sometimes circumferential to the teeth and mucosa in other intraoral locations, pursuing a relentless clinical course with high rates of recrudescence and progression to squamous cell carcinoma [6]. This review synthesizes evidence-based insights into the epidemiology, clinical presentation, histopathology, diagnosis, and management of PVL, compiled from recent open-access literature.

EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS

Demographics and Risk Factors

PVL primarily affects women, with research indicating a female prevalence rate of approximately 64-66%, and an average age of over 60 years [3,7]. Typically, female patients are diagnosed at an average age of 70.2 years, whereas male patients are diagnosed at 59.6 years [7]. Notably, in contrast to traditional oral squamous cell carcinoma, the majority of patients with PVL do not smoke or consume alcohol [7]. Some authors have suggested excluding tobacco use as a minor diagnostic criterion, even though pooled analyses have shown that approximately 38% of patients with PVL were smokers [2]. These epidemiological characteristics distinguish PVL from conventional tobacco-related oral cancers.

Anatomical Distribution

The gingiva and alveolar ridge are the most frequently affected sites (39-51% of cases), followed by the buccal mucosa (22-45%) and tongue (33-41%) [3,8]. The gingiva/alveolar ridge mucosa is the most common site for malignant transformation of PVL lesions [7]. This anatomical predilection contrasts sharply with that of conventional oral leukoplakia, which predominantly affects the lateral tongue and floor of the mouth [9]. A characteristic clinical feature includes marginal gingival leukoplakia progressing to circumferential lesions surrounding the teeth, described as a "ring around the collar" appearance [6].

Clinical Presentation

PVL manifests as multifocal white plaques that are progressive and persistent throughout evolution [2]. Clinical descriptions report PVL lesions as white, multifocal (affecting 91% of documented cases), and progressive (70% of cases), with varying surface textures, including smooth, fissured, verrucous, or erythematous presentations [2]. The lesions demonstrate wave-like undulations of the epithelium or keratosis, with some areas exhibiting 'basket-weave' patterns or prominent crests, formerly termed "Christmas tree keratosis" [6]. Sharp and abrupt demarcation from the surrounding tissues is an important clinical feature that is not generally observed in reactive oral lesions [6].

DIAGNOSTIC CRITERIA AND HISTOPATHOLOGY

Evolution of Diagnostic Criteria

Multiple diagnostic criteria for PVL have been proposed since Hansen's original description, creating challenges in standardizing the diagnosis [1,10,11,12]. There are four major proposals: Hansen et al. (1985), Cerero-Lapiedra et al. (2010), Carrard et al. (2013), and Villa et al. (2018) [2]. Inconsistent diagnostic criteria have been identified as significantly related to the variable malignant transformation rates reported (ranging from 0% to 100%), with studies of lower methodological quality tending to report lower transformation rates (27.60%) [2].

The Cerero-Lapiedra criteria propose five major and four minor criteria, requiring either three major criteria (including histopathology) or two major and two minor criteria for diagnosis [2,10]. Villa et al. proposed four mandatory criteria: white/keratotic lesions, multifocal non-contiguous lesions or a single large lesion >3-4 cm; lesions progressing over time, and specific histopathology excluding reactive keratoses [2,12]. The recent diagnostic criteria for PVL are presented in Table 1.

Criteria Set	Major Criteria	Minor Criteria	Diagnostic Requirements
Cerero-Lapiedra et al. (2010) [10]	A. Lesion at >2 oral sites (especially gingiva/palate) B. Verrucous area present C. Lesion spread/enlargement D. Recurrence after treatment E. Histology: hyperkeratosis to carcinoma	a. Lesion ≥3 cm total size b. Female patient c. Non-smoker d. Disease evolution >5 years	3 major criteria (including E) OR 2 major (including E) + 2 minor
Villa et al. (2018) [12]	All four required: 1. White/keratotic lesions (smooth, fissured, verrucous, or erythematous) 2. Multifocal non-contiguous lesions OR single lesion >3-4 cm 3. Lesions progress/expand over time 4. Histology: hyperkeratosis, parakeratosis, atrophy, or acanthosis without supporting reactive/frictional diagnosis	None specified	All 4 criteria must be fulfilled
Thompson et al. (2021) Histopathologic Categories [6]	Three standardized categories: 1. "Corrugated ortho(para)hyperkeratotic lesion, not reactive" 2. "Bulky hyperkeratotic epithelial proliferation, not reactive" 3. "Suspicious for" or "squamous cell carcinoma"	Combined with clinical findings for diagnosis	Classification based on combination of clinical and histologic features

Table 1: Diagnostic Criteria for Proliferative Verrucous Leukoplakia.

Consensus Histopathologic Guidelines

In 2021, an expert consensus guideline supported by the American Academy of Oral and Maxillofacial Pathology and North American Society of Head and Neck Pathologists established three standardized histopathologic categories: (1) "corrugated ortho(para)hyperkeratotic lesion, not reactive;" (2) "bulky hyperkeratotic epithelial proliferation, not reactive;" and (3) "suspicious for," or "squamous cell carcinoma" [6].

The first category demonstrates disproportionate orthokeratosis exceeding half the epithelial thickness, wave-like undulation with corrugation, a prominent granular layer, loss of rete pegs, and sharp demarcation with abrupt transitions from the adjacent epithelium [6]. The bulky epithelial proliferation category shows amplified bulkiness, where the epithelial compartment rather than surface hyperkeratosis accounts for lesion thickness, with bulbous rete pegs sometimes appearing confluent and architectural abnormalities overshadowing cytological findings [6].

Histopathological Spectrum

Histopathological analysis reveals hyperkeratosis in 71% of patients, epithelial dysplasia in 58%, verrucous hyperplasia in 44%, verrucous carcinoma in 21%, and squamous cell carcinoma in 29% of documented cases [2]. Importantly, frank cytological dysplasia is uncommon in early PVL lesions, with 84% showing no dysplasia or only mild dysplasia. Architectural disturbances are often more diagnostically significant than cytological atypia [6].

MALIGNANT TRANSFORMATION AND PROGNOSIS

Transformation Rates and Patterns

Meta-analyses report pooled malignant transformation proportions of 43.87-44% (95% CI: 31.93-56.13) [3,2]. A total of 320 PVL patients (45.8%) developed oral verrucous carcinoma or conventional oral squamous cell carcinoma through malignant transformation, with a statistically significant 3.8-fold higher risk of progression to conventional squamous cell carcinoma compared with that of verrucous carcinoma [7].

Women have a 1.7 times higher likelihood of developing oral cancer from PVL progression than men, with a statistically significant higher likelihood of developing conventional squamous cell carcinoma in females [7]. The tendency to develop multiple carcinomas is an important consequence of the underlying field cancerization of the affected mucosa [2]. Studies have reported that 40.74% of patients develop multiple tumors, with 5-year mortality rates ranging from 34.70% to 50% [13].

Prognostic Factors

No conclusive associations have been found between malignant transformation and sex, age distribution, tobacco consumption, or alcohol consumption [2,3]. The malignant transformation rate has been reported to be 43.87% to 65.8%, establishing PVL as the oral potentially malignant disorder with the highest propensity for malignancy [14]. The high variability in reported malignancy rates (0-100%) is significantly related to inconsistent diagnostic criteria and short follow-up periods in primary studies [2].

MANAGEMENT STRATEGIES

Treatment Modalities

Various treatment strategies have been proposed, although most have demonstrated high recurrence rates [5]. A literature review showed that surgery and laser ablation are the most commonly used modalities, with surgery applied in 136 cases across ten studies and laser ablation in 64 cases across seven studies. According to studies with at least 30 patients, a mean recurrence rate of 85% was observed for all treatment modalities, whether isolated or associated [5].

Systematic reviews examining recurrence following PVL treatment reported pooled proportions of 67.2% (232/397 treated patients) with a mean follow-up of 6 years [15,16]. Modalities such as surgery, laser ablation, photodynamic therapy, retinoids, radiation, and chemotherapy are ineffective in reducing relapse and malignant transformation [5]. No therapies are known to lower malignant transformation rates or prevent recurrence [17].

Surveillance Protocols

PVL may progress to verrucous or squamous cell carcinoma over time despite numerous treatment interventions, suggesting an association with diffuse submicroscopic changes in the oral mucosa described as "field cancerization." Patients with a whitish harmless appearance and recurrence episodes should be followed up every six months, with frequent and repetitive biopsies when changes in color, appearance, and size occur, or when new lesions appear [5].

Given the unpredictable disease progression and high malignancy risk balanced against the potential for radical overtreatment, conservative management with close surveillance by multidisciplinary teams has been suggested [6,18]. The high risk of oral cancer in patients with PVL should be clearly communicated to patients, reinforcing that PVL requires careful lifelong follow-up to achieve an early diagnosis of malignancy [2].

DIFFERENTIAL DIAGNOSIS

Important differential diagnoses include oral lichen planus, traumatic hyperkeratosis, alveolar ridge hyperkeratosis, tobacco pouch keratosis, and unifocal dysplasia [6]. Differentiation from oral lichen planus is particularly problematic as lichenoid lesions may mimic PVL both clinically and histologically, with approximately one-third of verrucous hyperplasia cases showing band-like lymphocytic response and basement membrane degeneration [6].

Oral lichen planus requires the destruction of basal cells, strict absence of epithelial dysplasia, and absence of verrucous epithelial architectural changes, with an estimated malignant transformation rate of less than 2%, compared to PVL's approximately 50% overall transformation rate and up to 10% annual transformation rate. Unifocal leukoplakia more commonly affects males and favors the lateral/ventral tongue and floor of the mouth, in contrast to PVL's female predominance and gingival/buccal predilection for PVL [6].

Limitations

This concise clinical review, intended for practicing dentists, does not address the etiopathogenesis of the PVL. Instead, it provides only an outline of the clinical presentation, diagnosis, and management strategies for PVL, rather than a comprehensive approach.

Conclusion

Proliferative verrucous leukoplakia is a highly aggressive oral potentially malignant disorder that requires increased clinical awareness among dental practitioners. PVL is characterized by multifocal, progressive, and persistent white plaques and is typically diagnosed around the age of 60 years, with malignant transformation rates reaching

approximately 50%. The implementation of standardized diagnostic criteria, which encompass both clinical and histopathological features, has enhanced diagnostic consistency, although significant inter-observer variability persists. No treatment modality has demonstrated efficacy in preventing disease progression or recurrence, thereby requiring lifelong surveillance with serial biopsies. Classification based on a combination of clinical findings and standardized histologic categories is advocated to standardize reporting, facilitate future research and guide clinical management. Ongoing research into the molecular pathways and prognostic biomarkers of this complex disorder may eventually enable risk stratification and the development of targeted therapeutic interventions for this condition.

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