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PROLIFERATIVE VERRUCOUS LEUKOPLAKIA: A PERSISTENT AND HIGH-RISK ORAL DISORDER

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ABSTRACT

Proliferative verrucous leukoplakia (PVL) is a unique form of oral leukoplakia characterized by its tendency to expand and develop new lesions, often displaying a warty surface texture. It is typically diagnosed in individuals from their fifth decade onward and is more prevalent in women. The most commonly affected sites include the gingiva, followed by the buccal mucosa and the lateral border of the tongue. PVL is considered an oral potentially malignant disorder with a significant risk of progressing to malignancy. Given its aggressive nature, general dental practitioners (GDPs) must recognize these lesions early to ensure timely referral for further evaluation and diagnosis. Managing PVL remains challenging, requiring long-term monitoring and, when necessary, surgical excision, although recurrence after surgery is common. This article offers an updated review aimed at GDPs, summarizing current knowledge on PVL and discussing management complexities through clinical case examples.

KEY WORDS: Proliferative verrucous leukoplakia, malignant, aggressive lesion.

INTRODUCTION

Proliferative verrucous leukoplakia (PVL) is a progressive and multifocal disorder of the oral mucosa, distinguished by persistent, heterogeneous white lesions with a strong tendency for malignant transformation[1]. First described by Hansen in 1985, PVL is now recognized as a high-risk variant of oral leukoplakia, characterized by a relentless clinical course and a significant potential for recurrence and progression to squamous cell carcinoma (SCC). Given its aggressive nature, early identification and appropriate management are critical for improving patient outcomes. Proliferative verrucous leukoplakia represents a significant clinical challenge due to its persistent nature, resistance to treatment, and high malignant potential. Unlike other oral potentially malignant disorders (OPMDs)[2,3],

PVL typically presents as focal, adherent white lesions in the early stages, later evolving into multifocal and multicentric proliferations. The gingiva is a common site of involvement, often extending circumferentially around teeth, but lesions may also appear on the buccal mucosa, tongue, and other intraoral locations[4]. Unlike conventional leukoplakia, PVL follows an

unpredictable trajectory, alternating between quiescent and active phases over several years. Most cases exhibit slow, persistent progression before undergoing sudden rapid growth, with some lesions even emerging de novo as carcinoma.

One of the defining characteristics of PVL is its resistance to standard interventions, suggesting a field cancerization phenomenon, wherein multiple areas of the mucosa exhibit pre-neoplastic changes, increasing the likelihood of malignancy. Studies indicate that approximately 50% of PVL cases ultimately progress to SCC, underscoring the need for long-term surveillance[5-7].

The World Health Organization (WHO) initially classified leukoplakia as a "precancerous lesion." However, recent recommendations suggest replacing the terms "precancerous" and "premalignant" with "potentially malignant", consolidating all such lesions and conditions under the broader category of "potentially malignant disorders" (PMDs). Following the 2005 WHO Collaborating Centre for Oral Cancer workshop on oral precancer, oral leukoplakia has been redefined as "a white plaque of questionable risk, after excluding other known diseases or disorders that do not increase cancer risk.[8-10]

Despite these updates in terminology and classification, oral leukoplakia remains the most common potentially malignant disorder affecting the oral cavity. Studies indicate that its malignant transformation rate varies widely, ranging from 0.13% to 17.5%, with an estimated annual transformation rate of approximately 1% across all leukoplakia types[11-13].

Given the high risk of malignant transformation, early recognition of PVL is crucial for timely intervention. However, diagnosis can be challenging due to its variable clinical presentation and histopathological complexity. The lack of universally accepted diagnostic criteria has led to inconsistent terminology and reporting, complicating both clinical management and research efforts. This article reviews about the etiopathogenesis, diagnostic criteria and treatment modalities for proliferative verrucous leukoplakia.

ETIOPATHOGENESIS

Unlike many other oral lesions, PVL does not appear to show any racial predilection. Furthermore, tobacco use does not seem to play a significant role in the disease, as PVL occurs in both smokers and non-smokers, distinguishing it from traditional leukoplakia and other potentially malignant oral disorders.

The precise cause of PVL remains unclear; however, a potential link to viral infections—particularly human papillomavirus (HPV) types 16 and 18—has been suggested. Palefsky et al. (1995) analyzed lesions from seven PVL patients and found that 89% tested positive for HPV, with HPV-16 detected in most cases. Similarly, Gopalakrishnan et al. (1997) examined mucosal samples from PVL, oral squamous cell carcinoma (OSCC), and normal controls, identifying

HPV-16 and HPV-18 in two out of eight p53-positive PVL cases and in two out of seven p53-positive OSCC cases, but none in normal tissues. These findings indicate a possible role of high-risk HPV strains in PVL pathogenesis.

However, conflicting studies challenge this association. Campisi et al. (2004) detected HPV DNA in 24.1% of PVL cases and 25.5% of oral leukoplakia (OL) cases, with no significant difference between the two groups, suggesting that HPV may not be uniquely linked to PVL. Further, Fettig et al. (2000) and Bagan et al. (2007) found no evidence of HPV in PVL lesions using polymerase chain reaction (PCR) analysis, adding to the uncertainty regarding the virus's role in the disease.

In addition to HPV, PVL has also been investigated for potential associations with Epstein–Barr virus (EBV) and Candida infections. In one study, EBV was detected in 60% of PVL cases, 40% of OSCC cases, but was absent in normal oral mucosa, indicating a possible link. However, further research is needed to establish the significance of these findings and determine whether viral infections contribute to PVL's progression or simply represent incidental co-infections.[14-16]

MOLECULAR CHARACTERIZATION

Despite the aggressive nature of proliferative verrucous leukoplakia (PVL) and its high malignant potential, molecular research on this condition remains scarce. This is likely due to its low prevalence and the tendency for delayed diagnosis, which complicates comprehensive genomic investigations. However, existing studies have demonstrated that DNA ploidy abnormalities are frequently observed in PVL and are closely associated with the severity of oral epithelial dysplasia (OED).

Targeted molecular analyses have provided crucial insights into the genetic alterations underlying PVL. Notably, CDKN2A, a tumor suppressor gene, is often inactivated in PVL at a higher frequency than in dysplastic oral leukoplakia (OLK), indicating a distinct oncogenic trajectory. Additionally, PVL exhibits a substantial mutational burden in key regulatory genes such as TP53, CDKN2A, and KMT2C, which are involved in tumor suppression and epigenetic modifications. These findings suggest that PVL shares significant molecular characteristics with oral squamous cell carcinoma (OSCC), reinforcing its classification as a high-risk potentially malignant disorder[17`] .

Recent advancements in global methylation profiling and transcriptomic analysis have further illuminated the molecular landscape of PVL. These studies have identified gene expression alterations associated with epigenetic dysregulation, aligning PVL's molecular signature with that of OSCC. Such parallels highlight the need for early detection and precise classification, as the disease's genetic predisposition to malignancy necessitates proactive management.[18]

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Due to its propensity for malignant transformation and the absence of well-defined diagnostic markers, there is a critical need for reliable molecular biomarkers to facilitate early and accurate identification of PVL. Current research aims to compare the transcriptomic signatures of PVL lesions—both with and without dysplasia—to those of conventional OLK. By delineating the pathognomonic molecular pathways that differentiate PVL from other leukoplakic conditions, these efforts seek to establish a definitive molecular diagnostic framework and uncover novel therapeutic targets. Such advancements hold the potential to revolutionize PVL diagnosis and treatment, ultimately improving patient outcomes through precision medicine and early intervention strategies[19].

CLINICAL PROGRESSION

Proliferative verrucous leukoplakia (PVL) typically begins as one or more homogeneous leukoplakic lesions, which progressively enlarge and spread to multiple oral sites over time, particularly affecting the gingivae, buccal mucosa, and alveolar ridges. According to Reichart and Philipsen (2003), these locations are the most frequently involved, although some studies suggest that the gingiva and tongue are more commonly affected. In a study by Bagan et al. (2003), 87% of PVL cases exhibited gingival lesions, whereas Gandolfo et al. found that lesions predominantly occurred on the alveolar crest (87.2%), with gingival involvement in 46.8% of cases. Additionally, nearly all PVL lesions tend to be bilateral, primarily affecting the lower alveolar ridge and buccal mucosa.

Clinically, PVL often presents in its early stages as a benign, localized lesion, but it exhibits a strong tendency to become diffuse and multifocal. Over time, the lesions may develop into exophytic, wart-like, or erythroplakic areas, eventually transforming into oral squamous cell carcinoma (OSCC). This progressive malignant potential underscores the necessity for early recognition and proactive management.[20]

HISTOPATHOLOGICAL FEATURES

The microscopic characteristics of Proliferative Verrucous Leukoplakia (PVL) vary depending on the stage of the disease, biopsy site, and sample adequacy. Due to its progressive nature, PVL encompasses a broad histopathological spectrum, ranging from hyperkeratosis to invasive squamous cell carcinoma.

Hansen et al.'s Classification

Hansen et al. described a continuum of histological changes in PVL, categorizing lesions into six progressive stages, with intermediate transitions between them:

- Grade 0: Normal oral mucosa.

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- Grade 2: Hyperkeratosis, corresponding to clinical leukoplakia.
- Grade 4: Verrucous hyperplasia, indicating a proliferative, thickened epithelial layer.
- Grade 6: Verrucous carcinoma, a locally invasive but non-metastasizing malignancy.
- Grade 8: Papillary squamous cell carcinoma, demonstrating greater architectural disruption.
- Grade 10: Poorly differentiated squamous cell carcinoma, exhibiting aggressive malignant transformation.

Batsakis et al.'s Simplified Staging System

Batsakis et al. (1999) proposed a more streamlined classification, reducing the number of histological stages to four while retaining intermediate variations:

- Grade 0: Flat leukoplakia without dysplasia.
- Grade 2: Verrucous hyperplasia, an early proliferative stage.
- Grade 4: Verrucous carcinoma, characterized by exophytic, wart-like growths.
- Grade 6: Conventional squamous cell carcinoma, representing malignant transformation.[2,21,22,23]

DIAGNOSTIC FRAMEWORK

The diagnosis of Proliferative Verrucous Leukoplakia (PVL) is guided by a combination of clinical presentation and histopathological progression. Various diagnostic models have been proposed to standardize identification and enhance early detection.

Cerero-Lapiedra et al.'s Major and Minor Criteria

Cerero-Lapiedra et al. established two sets of diagnostic criteria: major criteria, which reflect the primary clinical and histological features of PVL, and minor criteria, which provide supportive diagnostic indicators.

Major Criteria

1. Multifocal Leukoplakia: Lesions affecting at least two distinct oral sites, most commonly the gingiva, alveolar processes, and palate.
2. Verrucous Transformation: The presence of wart-like or verrucous areas.
3. Lesion Expansion: Evidence of progressive spreading or enlargement over time.
4. Recurrence: The reappearance of lesions in a previously treated area.
5. Histopathological Spectrum: Lesions ranging from simple hyperkeratosis to verrucous hyperplasia, verrucous carcinoma, or oral squamous cell carcinoma (OSCC), either in situ or infiltrating.

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Minor Criteria

To confirm a PVL diagnosis, one of the following combinations must be met:

- Three major criteria (including Criterion E)
- Two major criteria (including Criterion E) + Two minor criteria

Minor Diagnostic Indicators:

1. Lesion Size: The combined affected area must exceed 3 cm.
2. Gender: The patient is female (not a definitive factor but a common trend).
3. Smoking Status: The patient is a non-smoker (PVL occurs in both smokers and non-smokers, but non-smoking status has been observed in some cases).
4. Disease Duration: The condition has been evolving for at least five years.

Ghazali et al.'s Diagnostic Criteria

Ghazali et al. proposed a set of sequential diagnostic indicators, emphasizing the progressive nature of PVL:

1. Initial Presentation: The lesion begins as homogeneous leukoplakia without dysplasia.
2. Verrucous Transformation: Over time, some areas develop a verrucous morphology.
3. Expansion and Multifocality: The disease progresses, forming multiple isolated or confluent lesions at either the same or different intraoral sites.
4. Histopathological Progression: The lesion evolves through distinct histopathological stages as described by Hansen et al.
5. Recurrence: New lesions appear even after treatment, signifying a persistent and recurrent nature.
6. Long-Term Follow-Up: Diagnosis requires a minimum follow-up period of one year to confirm disease evolution.

Gandolfo et al.'s Diagnostic Criteria

Gandolfo et al. focused on clinical and histopathological evolution, defining PVL as:

1. A seemingly benign lesion that initially presents as a homogeneous plaque.
2. Progressive Transformation: Over time, the lesion becomes exophytic, diffuse, multifocal, and verrucous in appearance.
3. Histopathological Continuum: PVL progresses from hyperkeratosis without dysplasia to more severe stages, including verrucous hyperplasia, verrucous carcinoma, or oral squamous cell carcinoma (OSCC).

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Recognizing limitations in early detection, Carrard et al. proposed a simplified diagnostic model, eliminating the distinction between major and minor criteria. Their revised framework includes:

1. Multifocal Leukoplakia: Presence of verrucous or wart-like lesions in at least two different oral sites.
2. Size Criterion: The total affected area must measure at least 3 cm.
3. Long-Term Progression: A minimum disease evolution period of five years, characterized by lesion spreading, enlargement, and recurrence after treatment.
4. Histopathological Evaluation: At least one biopsy must confirm the absence of verrucous carcinoma or OSCC before diagnosing PVL[24-26].

DIFFERENTIAL DIAGNOSIS

PVL must be carefully distinguished from other oral lesions with similar clinical and histopathological presentations.

- Frictional Keratosis
- Homogeneous Leukoplakia
- Squamous Papilloma
- Verrucous Hyperplasia
- Verrucous Carcinoma
- Squamous Cell Carcinoma (SCC)
- Chronic Hyperplastic Candidiasis

Distinguishing PVL from Other Mimicking Lesions

- Frictional Keratosis: Has an identifiable mechanical cause (e.g., dental trauma, cheek biting), resolving upon elimination of the source.
- Squamous Papilloma: Caused by HPV infection, exhibiting exophytic papillary projections.
- Verrucous Hyperplasia: Shares histological overlap with PVL but lacks its progressive nature and is less likely to become malignant.
- Verrucous Carcinoma: A slow-growing, well-differentiated carcinoma, usually with a broad-based pushing invasion pattern, as opposed to PVL's stepwise progression.
- Squamous Cell Carcinoma (SCC): Shows invasive growth and atypical cellular features with potential metastasis. PVL often transforms into SCC over time.
- Chronic Hyperplastic Candidiasis: Fungal infection leading to a white plaque that does not rub off, confirmed by periodic acid–Schiff (PAS) staining for Candida hyphae[20,27].

CURRENT TREATMENT APPROACHES AND LIMITATIONS

Timely detection and intervention are crucial in managing Proliferative Verrucous Leukoplakia (PVL) to prevent malignant transformation and improve patients' quality of life. Given its aggressive and recurrent nature, early diagnosis allows for proactive therapeutic measures, minimizing disease progression and associated morbidity.

A variety of treatment modalities have been explored for PVL, including:

- Conventional surgical excision
- Cryosurgery
- Electrosurgery
- Laser surgery
- Cytotoxic drug administration
- Photodynamic therapy (PDT)

Among these approaches, PDT has emerged as a promising alternative. Romeo et al. successfully treated an elderly female patient with 5-aminolevulinic acid (5-ALA)-based PDT, demonstrating its potential efficacy in managing PVL. While traditional surgical techniques remain the mainstay of treatment, minimally invasive approaches like PDT offer targeted therapy with reduced morbidity. Further research is needed to establish optimal treatment protocols and improve long-term outcomes for PVL patients.

Due to PVL's progressive nature, conventional treatment methods used for oral leukoplakia have often yielded unsatisfactory outcomes. The following interventions have been attempted, with varying degrees of success:

- Carbon dioxide (CO_2) laser therapy
- Radiation therapy
- Topical bleomycin solution
- Systemic chemotherapy
- Oral retinoids and beta-carotene

Despite temporary improvements, recurrence rates remain high, with many lesions reappearing within months of discontinuing treatment.

Methisoprinol and HPV-Associated Lesions

Methisoprinol, an antiviral agent that inhibits viral RNA synthesis and stimulates cell-mediated immune responses, has shown some promise in HPV-related lesions. However, its effectiveness in PVL remains uncertain, and recurrence continues to be a challenge[16,28,29].

Laser Ablation and Photodynamic Therapy (PDT)

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- Laser ablation has shown limited success in a small group of patients observed over 6–178 months.
- Photodynamic therapy (PDT), which involves topical application of photosensitizing agents followed by light activation, may offer benefits, including:
    - Low morbidity
    - No scarring
    - Ability to treat multiple mucosal sites simultaneously However, multiple treatment sessions may be required over the disease's course.

Surgical Excision

Given PVL's resistance to most treatment modalities, complete surgical excision with clear margins is currently the most effective approach. However, due to PVL's multifocal nature, surgery alone may not prevent recurrence. Lifelong follow-up remains essential.

Malignant Transformation and Recurrence

PVL is highly aggressive, with a malignant transformation rate of up to 74%. The disease is associated with:

- High recurrence rates (87–100%)
- Multiple oral cancers developing over time
- Significant mortality (30–50%)

The gingiva and palate are the most frequently affected sites for PVL-associated malignancies. Due to the high risk of oral squamous cell carcinoma (OSCC) development, lifelong monitoring is strongly recommended, with follow-up visits at least every six months.[3]

CONCLUSION

Proliferative Verrucous Leukoplakia (PVL) remains a rare yet highly aggressive oral disorder characterized by multifocal involvement, high recurrence rates, and a significant risk of malignant transformation. Despite extensive research, its etiology remains unclear, and no universally effective diagnostic criteria or treatment approach has been established. Diagnosis primarily relies on a combination of clinical presentation, histopathological evaluation, and disease progression over time.

Treatment strategies for PVL have largely been unsatisfactory, with conventional therapies such as laser ablation, topical agents, and systemic medications failing to provide long-term remission. Surgical excision with clear margins remains the most effective approach, but even

this method does not guarantee a cure due to PVL's persistent and recurrent nature. Given its high rate of malignant transformation, particularly into oral squamous cell carcinoma (OSCC), early detection and long-term monitoring are crucial.

To improve patient outcomes, future research should focus on identifying reliable molecular markers for early diagnosis, developing targeted therapies, and refining existing treatment protocols. Until more effective interventions are established, lifelong surveillance of PVL patients is essential, with regular follow-up visits to detect disease progression and potential malignancy at the earliest stage possible.

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