PROLIFERATIVE VERRUCOUS LEUKOPLAKIA: AN ELUSIVE DISORDER

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SORT SCORE

A	B	C	NA

SORT, Strength of Recommendation Taxonomy

LEVEL OF EVIDENCE

1	2	3

See page A8 for complete details regarding SORT and LEVEL OF EVIDENCE grading system

ABSTRACT

Proliferative Verrucous Leukoplakia (PVL) is a multifocal form of progressive leukoplakia with a high rate of malignant transformation that requires early recognition by oral health care providers for proper management.

Background and Purpose

PVL will frequently appear as an innocuous white lesion or lesions that can easily be overlooked or considered clinically insignificant, yet it has a high rate of malignant transformation. There is limited in-depth knowledge about the pathobiology of PVL. Oral health care providers lack familiarity with this lesion; consequently the intent of this article is to increase awareness of the clinical aspects of PVL.

Methods

Case reports, case series and review articles provide a profile of PVL.

Conclusion

It is essential that health care providers performing intraoral examinations are aware that PVL is a distinct and rare form of multifocal oral leukoplakia. PVL commonly affects females above the age of 62. Currently, little is known about its etiopathogenesis. Additionally, no specific treatment modality has proven to be effective in aborting its progression. Because of its high recurrence potential and relentless progression to squamous cell carcinoma, all recurrent and multifocal white lesions of the oral cavity should be viewed with suspicion.

Key words: proliferative verrucous leukoplakia, oral pathology, human papillomavirus, lesion, mutifocal oral leukoplakia

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INTRODUCTION

The World Health Organization Collaborating Center for Oral Cancer and Pre-Cancer have described leukoplakia as "a white plaque of questionable risk having excluded all known diseases or disorders that carry no risk for cancer."[1,2] The prevalence of oral leukoplakia is estimated to be between 2–5% worldwide and most lesions pursue a benign course.[2–4] There are many clinical variants of oral leukoplakia.[3] In 1985, Hansen et al described 30 cases of a simple hyperkeratosis which evolved to affect multiple oral sites over a variable period of time. These investigators claimed the observed white plaques were slow growing, persistent and eventually manifested as exophytic and wart-like lesions that had a high tendency to undergo malignant transformation to Oral Squamous Cell Carcinoma (SCC).[4] Hansen et al described these lesions as 'Proliferative Verrucous Leukoplakia' (PVL).[4] The World Health Organization (WHO) has further described PVL as a rare yet distinctive high-risk (with high potential for malignant transformation) leukoplakia without a single pathognomonic criterion, but with characteristic combined histologic and clinical features and behavior.[5] Prior to the description by Hansen et al, this condition was referred to as oral florid papillomatosis.[6]

DEMOGRAPHICS

Hansen et al reported that majority of the patients with PVL in their study were females (24/30), with ages ranging from 27 to 74 years (mean ages 49 years).[4] Silverman and Gorsky reported similar findings.[7] Most individuals with PVL are in the sixth decade of life.[5] There is no racial predilection.[8]

ETIOLOGY

The etiology of PVL is not fully understood. Common causes for a conventional leukoplakia do not appear to be strongly associated with PVL.[3] Tobacco use is not a consistent finding in patients affected by PVL.[9] Out of the 30 patients with PVL described by Hansen et al, 62% used some form of tobacco product (primarily cigarettes), while the rest of the study group had no history of tobacco use.[4] Silverman et al identified that 31% of the studied patients with PVL used tobacco products.[7] Approximately half of the group of PVL patients evaluated by Fettig et al used tobacco.[10] A meta-analysis by Cabay et al identified that 37% of PVL patients studied were tobacco users.[11] The role of tobacco in PVL lesions is unclear since these lesions can be seen in both smokers and nonsmokers.[12,13]

The role of alcohol in PVL has not been extensively addressed.[14] Approximately 17% of patients with PVL evaluated by Campisi et al consumed alcohol.[15]

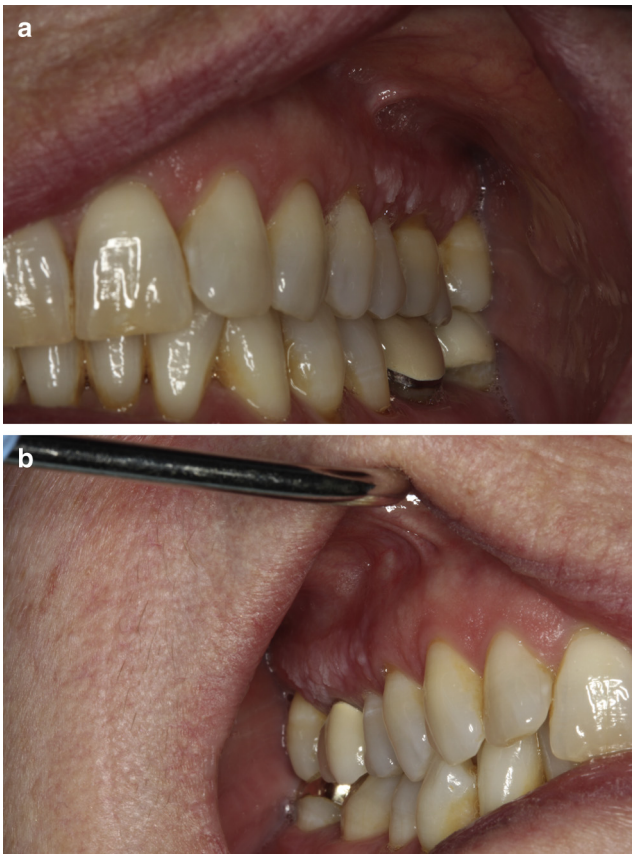
An association between PVL and Human Papillomavirus (HPV) has been suggested.[6] Palefsky et al found that 89% of 9 PVL lesions they evaluated were positive for HPV, primarily for HPV 16 (7/8 cases).[16] Similarly, Femiano et al confirmed using polymerase chain reaction testing that 50 patients with PVL had HPV positive lesions.[9] Gopalakrishnan also identified a link between PVL and HPV.[17] Interestingly, Campisi et al identified that 24.15% of PVL cases and 25.5% of conventional oral leukoplakia harbored HPV DNA,[15] while Fettig et al and Bagan et al could not establish any association between HPV and PVL.[10,18] There is preliminary evidence that Epstein–Barr virus (EBV) infection may have a link in some PVL cases.[19] Candida species were identified in the majority of PVL cases investigated by Marx et al.[20] It remains uncertain whether this identification of the candida species is a coincidental finding in such cases. The rough and corrugated surface morphology of PVL can favor entrapment of candida organisms, and this finding may not be causative.[20]

Specific gene aberrations and telomerase overexpression have also been identified in PVL cases.[14,20–26] Despite these findings, little is known about the applicability and significance of these molecular markers in PVL lesions.[8] The role of weakened/compromised immunity and PVL has also been proposed.[27]

CLINICAL FINDINGS

In its early clinical phases, PVL can present as a focal hyperkeratosis, which may easily be confused with conventional leukoplakia.[3] Over time, additional similar lesions may be observed, surrounding the initial lesion.[6,11] PVL often presents as a flat, white, rough, grainy or verrucous surfaced lesion[11] (**Figure 1**a and b). However, lesions can be erythematous rather than white.[12] PVL lesions progress and tend to follow 4 broad clinical phases: 1) focal early presentation; 2) geographic expansion with time; 3) development of a verrucoid/warty appearance (**Figure 2**a and b); and 4) development of cancer (**Figure 3**).[3] Although most initial lesions are asymptomatic, pain may be present.[20] Clinical evidence of ulceration and induration in longstanding PVL may indicate the possibility of malignant transformation.[20]

Figure 1. a) This patient with PVL presented with multiple diffuse white plaques with a grainy and verrucous surface affecting the left maxillary gingiva and vestibule. b) This patient had similar lesions affecting the right maxillary gingiva.



PVL can affect any oral mucosal surface and is frequently bilateral. The disease predominantly involves the buccal mucosa and tongue.[4,11,28] Although, some investigators opine that the gingiva and alveolar mucosa are frequently involved.[10,14] In one study, which evaluated 47 patients with PVL, 87.2% presented with lesions affecting the alveolar crest mucosa, with gingival involvement in 46.8%.[14] Similar findings of predominant alveolar crest involvement were documented