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Proliferative verrucous leukoplakia: An aggressive form of oral leukoplakia

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Proliferative verrucous leukoplakia (PVL) is an aggressive form of oral leukoplakia that is persistent, often multifocal, and refractory to treatment with a high risk of recurrence and malignant transformation. This article describes the clinical aspects and histologic features of a case that demonstrated the typical behavior pattern in a long-standing, persistent lesion of PVL of the mandibular gingiva and that ultimately developed into squamous cell carcinoma. Prognosis is poor for this seemingly harmless-appearing white lesion of the oral mucosa.

Keywords: Leukoplakia, proliferative verrucous, Leukoplakia, oral, Disease, premalignant, Cancer, oral

Introduction

Proliferative verrucous leukoplakia (PVL) is a recently delineated entity that is defined as a diffuse, white and smooth or papillary or wartlike area of the oral mucosa caused by varying degrees of epithelial hyperplasia.[1]In its early stages it is often clinically so bland that it is dismissed as frictional hyperkeratosis or as candidiasis, but, even though the clinical course is slow, it possesses a propensity for malignant transformation. Although PVL is well documented in the oral pathology literature, it is not documented in the dental hygiene or periodontic literature. Therefore, the purpose of this paper is twofold: (1) to acquaint dental health professionals, including dental hygienists and periodontists, with this highly significant variant of oral leukoplakia and (2) to document a case of PVL with gingival involvement that progressed to malignancy.

Literature Review

PVL was first described and segregated from other forms of leukoplakia by Hansen et al. in 1985.[2] It is significant because it has a high recurrence rate and the potential to develop into verrucous carcinoma or squamous cell carcinoma in 60% to 70% of the affected patients.[3] PVL is more commonly found in elderly females and is associated with tobacco use or alcohol abuse one-third to one-half of the time.[3,4] The most common locations are the gingiva or alveolar ridge (often extending into the vestibule), tongue, and buccal mucosa-sites that traditionally have not been considered high-risk areas for the development of oral squamous cell carcinoma, with the exception of the tongue. According to Haley et al. the

gingiva is the most likely site for the malignant transformation of PVL.[5] PVL often begins as a focal lesion spreading laterally over time and can be multifocal.[6] Early in its course it is a flat hyperkeratotic lesion that becomes progressively verrucous and histologically often exhibits varying degrees of epithelial dysplasia.

PVL Case Report

A 48-year-old Caucasian female was referred to a periodontist by her general dental practitioner for a biopsy to rule out oral lichen planus. The patient presented with a chief complaint of "a new white spot on my gum that is spreading and thickening." The patient stated that she first noticed the asymptomatic lesion 3 months ago. It involved the facial gingiva of the right mandibular incisors. She related a 9-year history of multifocal oral leukoplakia that had been clinically diagnosed as lichen planus, but during the nine years it was never biopsied. She had never used tobacco products or alcohol. She was taking prednisone for myasthenia gravis. At her referral appointment with the periodontist, oral examination disclosed multiple white plaques and rough-surfaced to verrucous-appearing lesions that involved the mandibular gingiva, right buccal mucosa, dorsum of tongue (Fig 1), hard palate, and floor of mouth. Based on the clinical findings, the differential diagnosis included hyperplastic candidiasis, lichen planus, and carcinoma arising from leukoplakia. However, over the ensuing two-year period, three biopsies of lesions from the anterior mandibular facial gingiva, right buccal mucosa, and dorsum of the tongue were microscopically diagnosed as "cyst with chronic inflammation," "leukoplakia," and "leukoplakia," respectively. Because there was no clinical evidence of a cyst and leukoplakia is strictly a clinical term, the periodontist sought a second opinion. An oral and maxillofacial pathologist was consulted and believed that the microscopic findings in all three specimens, although free of cytologic dysplasia, represented the early changes found in proliferative verrucous leukoplakia. The lesions were closely monitored for any changes suspicious for invasive squamous cell carcinoma or verrucous carcinoma. A biopsy was then performed on a spreading lesion involving the buccal gingiva in the premolar-molar area of the right mandible (Fig 2). The specimen from the buccal gingiva showed marked hyperorthokeratosis with verrucous epithelial hyperplasia (Fig 3). Periodic acid Schiff staining was negative for *Candida albicans*. There was no epithelial dysplasia present in the surgical specimen. Following the results of the last biopsy, the patient was referred to a head and neck cancer surgeon for follow-up and management of her oral condition. Two years after the last biopsy was performed, the patient developed gingival squamous cell carcinoma at the site (Fig 4). The patient expired 6 years after the original diagnosis. The cause of death is unknown to the authors.

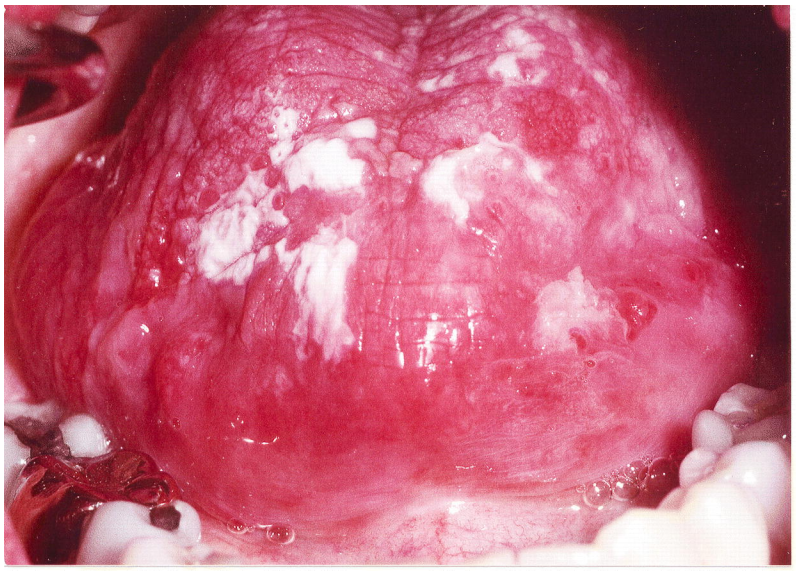

Figure 1. Patient with multifocal smooth and verrucous plaques on the dorsal tongue.

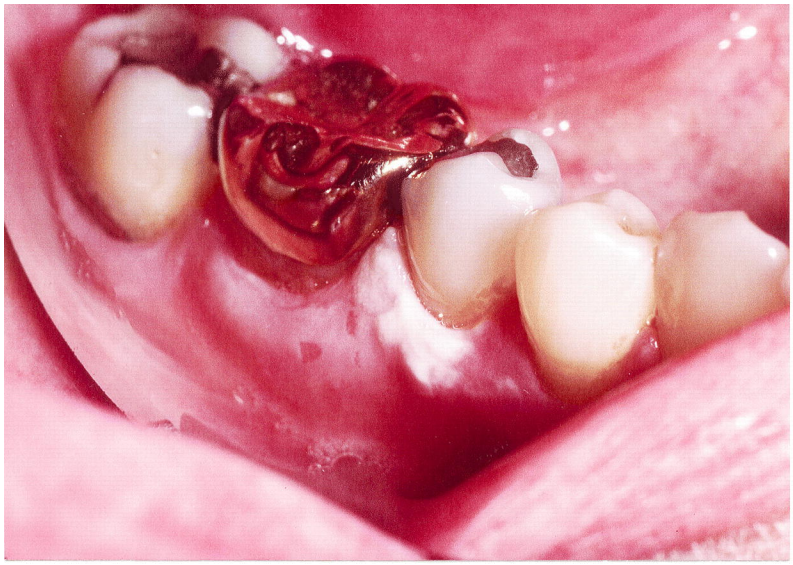

Figure 2. PVL of the mandibular gingiva. Note the transition from a smooth plaque in the first molar area to an exophytic verrucous lesion involving the free and attached gingiva of the bicuspid.

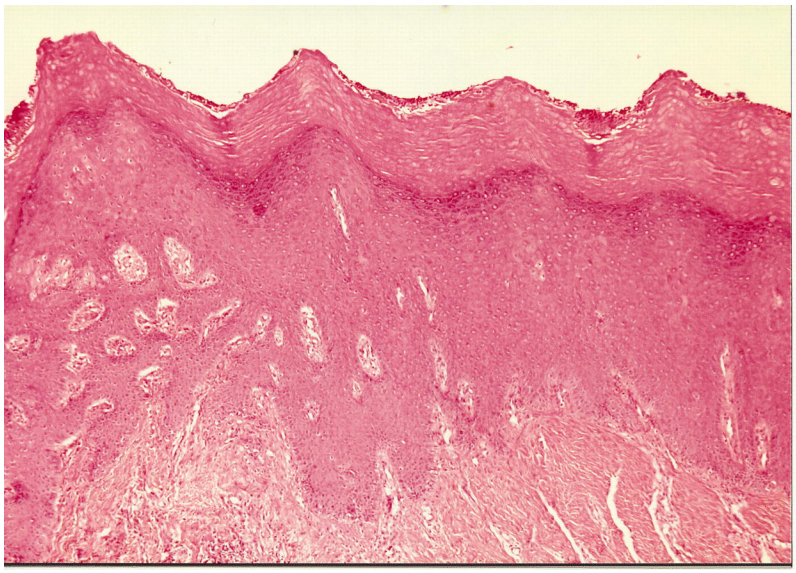

Figure 3. The lesion exhibits a verrucous pattern characterized by a thick hyperkeratotic surface, epithelial acanthosis, and no evidence of cytologic atypia (hematoxylin-eosin stain; original magnification x 100).

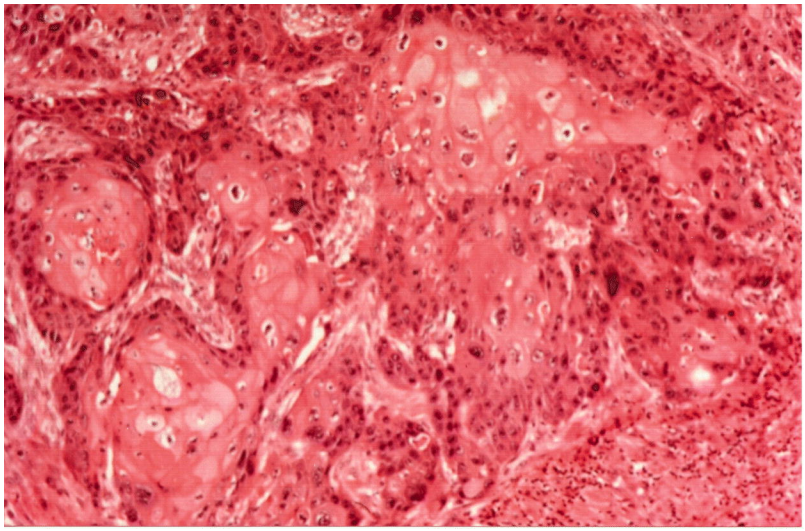

Figure 4. Photomicrograph showing islands of carcinomatous squamous epithelium invading the connective tissue (hematoxylin-eosin stain; original magnification x 50).

Discussion

Comparison and etiology

As this case illustrates, PVL is a high-risk variant of oral leukoplakia with a propensity for malignant transformation. Differences exist between PVL and homogeneous forms of leukoplakia with regards to epidemiology, clinical presentation, histopathology, and biologic behavior (Table I).[5]The etiology of PVL is unknown. Tobacco does not appear to play a major role, nor does the coexistence of *Candida spp*.[3] Human papilloma virus, subtype 16, may be suspected to be a cofactor in PVL.[6,7]

Table I. Comparison of Proliferative Verrucous Leukoplakia and Leukoplakia*

Proliferative verrucous leukoplakia	Leukoplakia
Relatively uncommon	Common
Women > men (4:1)	Men > women (2:1)
Lower correlation with tobacco and alcohol use	Higher correlation with tobacco and alcohol use
High rate of malignant transformation (70% to 80%)	Moderate rate of malignant transformation (3% to 25%)
High mortality	Moderate mortality

*Modified from data presented by Haley et al.[5]

Clinical features

The patient, reported in this case was 48-years-old. This is consistent for the age range of PVL, (36 - 90 years with a mean of 70.2 years of age).[2] The clinical course of PVL is deceiving because it evolves very slowly (often over the course of several years), progressing from a flat white plaque to an exophytic plaque with a papillary or verrucous surface. In addition, multifocal lesions typically develop. The nine-year history of multiple oral white lesions that were clinically interpreted as lichen planus in our patient in fact represented a multifocal distribution of PVL. PVL can involve any oral site with the buccal mucosa, gingiva, and tongue being the most common locations.[3] Interestingly, Fettig et al.[6] have recently described

what they think is a subset of oral PVL that is limited to the gingiva. The study was composed of 10 patients (mean age 65 years) with recurrent lesions that were solitary or regional involving the free and attached gingiva, especially in the anterior regions. Multiple lesions did not develop. The gingival lesions in six of the 10 patients progressed to either squamous cell carcinoma or verrucous carcinoma.

Differential diagnosis

Baughman and Boland[8] and Eversole[9] have provided in-depth discussions on the clinical differential diagnosis for oral PVL. The late or advanced stages of PVL cannot be differentiated clinically from verrucous carcinoma or an exophytic papillary form of squamous cell carcinoma.[9] However, in many instances, as in our patient's, the clinical differential includes chronic hyperplastic candidiasis, lichen planus, and leukoplakia. The hyperplastic form of candidiasis is characterized by multifocal thickened white plaques that may have a verrucoid appearance.[9] The clinical features and history of prednisone use in this case warranted a consideration of hyperplastic candidiasis. However, multiple biopsies did not confirm the presence of candidal hyphae associated with the lesion. Although the patient had been told over a nine-year period that she had oral lichen planus, the lesions at the time of the first biopsy did not clinically show the characteristic lacy pattern (Wickham's striae) of lichen planus. Lichen planus involving the dorsal tongue may appear as smooth, white plaques sans the lacy straie.[10] However, they are not verrucous as they are in this case. The multiple biopsies did not support lichen planus as well. Last in the differential for this patient was carcinoma arising in a pre-existing leukoplakia, which the aforementioned biopsies ruled out. Patients who use mouth rinses or toothpastes containing sanguinaria have developed leukoplakia that, in some instances, have had a corrugated surface and, therefore, have resembled PVL. This was not an issue in this case. The vast majority of these so-called sanguinaria-associated leukoplakias have occurred in the maxillary vestibule and alveolar mucosa.[11]

Diagnosis

The definitive diagnosis of PVL is a clinicopathologic correlation, typically in retrospect, following multiple biopsies and a prolonged clinical course. The histologic findings are variable and usually a function of time or age of the lesion.[4] The early lesions are deceptively bland exhibiting only hyperkeratosis, but over time they become progressively verrucous and often show varying degrees of epithelial dysplasia.[12,13]The advanced lesions have a propensity for conventional squamous cell carcinoma and verrucous carcinoma within the histologic spectrum.

Treatment

The lesions of PVL are persistent, progressive, and relentless and have a high recurrence rate regardless of the treatment method employed.[14] Complete surgical excision is difficult because of the diffuse, multifocal nature of the condition and the inability to assess accurately surgical margins clinically and microscopically. The presence of the dentition also complicates complete removal of gingival lesions. Other modalities, such as laser ablation, external beam radiation, and chemotherapy, have been unsatisfactory.[4,5] However, Femiano et al. have recently claimed a significant degree of success in controlling recurrences using surgery in combination with methisoprinol, an antiviral agent in 25 patients.[15] We believe that early-stage, small lesions should be treated with surgical (scalpel) excision. However, in late-stage lesions, which can extend over large areas and encompass multiple anatomic sites, the treatment becomes much more complex. Marx and Stern have provided a detailed discussion on the treatment rationale and various modalities used in the management of PVL.[16] Nevertheless, the biological profile of PVL remains elusive, and the various modalities of treatment that have been used have resulted in variable success at best. We are in agreement with the conclusions of Reichart and Philipsen that multicenter studies are essential to determine etiologic factors and concepts for therapy.[17]

Conclusions

The biologic behavior of PVL is decidedly more aggressive than the other forms of leukoplakia. However, the initial clinical presentation of PVL is so innocuous that one can easily dismiss it as insignificant until there is widespread oral involvement and carcinomatous transformation. Moreover, PVL has a high predilection for the gingiva, which is also the most common site for its malignant transformation. We hope that this case report will alert dental practitioners, including dental hygienists and periodontists, to this dangerous form of leukoplakia so that patients can be identified early in the course of their disease and managed appropriately. With any questionable lesion, it is imperative that the clinician ask the pathologist to review the microscopic findings if a diagnosis is not consistent with the clinical findings. As the clinician did in this case, a request for an independent second microscopic opinion is warranted if the clinician continues to have concerns about an inconsistent clinicopathologic correlation.

Notes

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