Current Management Strategies for Verrucous Hyperkeratosis and Verrucous Carcinoma

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KEYWORDS

• Verrucous carcinoma • Proliferative verrucous leukoplakia • Hyperkeratosis

KEY POINTS

- Verrucous carcinoma is a progressive lesion with high recurrence and high 5-year survival rates.
- It has a low incidence of bone invasion and cervical node metastasis is unusual.
- Most proliferative verrucous leukoplakia cases begin as homogeneous smooth plaques of leukoplakia that slowly increase in surface area to involve other areas either in continuity or anatomically separated, ultimately assuming a multifocal distribution.
- Surgery remains the preferred treatment.
- Further investigation into the combination of surgery and antiviral agents may bring additional improvement in patient care.

INTRODUCTION

Since Hansen and colleagues[1] defined the term *proliferative verrucous leukoplakia* (PVL) in 1985, many reviews and reports of this unusual form of oral leukoplakia have been published. Before this study, the term *oral florid papillomatosis* was used to describe and characterize PVL.[2] More recently, the term *proliferative multifocal leukoplakia* was suggested to emphasize the early proliferative and multifocal nature of this entity and to indicate that initial manifestations are not warty or verrucous. When they finally become so, they histologically correspond to verrucous carcinoma, much as in the earlier descriptions by Batsakis and colleagues.[3,4] They emphasized that so-called verrucous hyperplasia was a precursor to verrucous carcinoma, conventional squamous cell carcinoma, and possibly papillary squamous carcinoma.

In a similar fashion, Shear and Pindborg[5] coined the term *verrucous hyperplasia* in 1980, which would represent PVL according to the currently accepted criteria for its definition. In their series of cases, they reported a 39% incidence of either squamous cell carcinoma or verrucous carcinoma, and microscopic evidence of dysplasia in 66% of cases.

Silverman and colleagues[6] subsequently published a large series of cases in which a subset of patients presenting with verrucous hyperplasia demonstrated a similar high rate of malignant transformation. Furthermore, a 100% transformation

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Oral Maxillofacial Surg Clin N Am 25 (2013) 77–82
http://dx.doi.org/10.1016/j.coms.2012.11.008
1042-3699/13/$ – see front matter

rate was reported by Zakrzewska and colleagues[7] and Cabay and colleagues.[8]

The cause of this clinical entity remains obscure. There is an anatomic and gender predilection, poor response to treatment, and a significant risk for progression to verrucous carcinoma or invasive squamous cell carcinoma. This condition comprises a histologic continuum from hyperkeratosis to carcinoma, and neither attempts at prevention nor clinical intervention yield predictable results. Of importance is the notion that PVL remains a clinically based diagnosis without specific histologic connotation in the same fashion as typical oral leukoplakia.

From a demographic perspective, PVL is significantly more common in elderly women from age 62 to older than 70 years, as noted reported by Bagan and colleagues[9] and Silverman and colleagues,[6] with those cases reporting a long history of lesions characterized as leukoplakia.

ETIOLOGY

PVL has no known origin. Unlike typical oral leukoplakia, PVL is more commonly noted in individuals without the usual risk factors of smoking, other forms of tobacco use, and excess alcohol consumption. Fungal and viral origins have not been proven, although earlier studies suggested that human papilloma virus (HPV) was of significance.[10,11] More recently, however, the relationship between PVL and oncogenic HPV has been challenged.[12–14] In contrast, Beltiol and colleagues[15] identified HPV in 100% of the patients with PVL, but in only 8.75% of the group without mucosal lesions. Clearly, the role of HPV in the origin of oral PVL remains undetermined.

Any site in the oral cavity may be involved with these lesions, but the most commonly affected areas, in descending orders of frequency, are the alveolar ridge, tongue, buccal mucosa, attached gingiva, floor of mouth, gingival sulcus, labial mucosa, and hard and soft palate.

From a genetic standpoint, PVL has been shown to demonstrate cell cycle alterations secondary to dysregulation of p16INK4a and p14ARF genes. Homozygous deletions, loss of heterozygosity, and mutational changes have been frequently shown. Although ploidy alterations have been considered a tool to predict malignant transformation, some have questioned this on the grounds of data validity.[16,17] High expression of cell cycle proteins Mcm-2 and Mcm-5 could help predict the long-term behavior and risk of malignant transformation of PVL. These markers could be useful diagnostic tools, superior to the Ki-67 proliferation marker.[18]

CLINICAL PRESENTATION

Most PVL cases begin as homogeneous smooth plaques of leukoplakia that slowly increase in surface area to involve other areas either in continuity or anatomically separated, ultimately assuming a multifocal distribution (**Figs. 1–3**). The authors' combined anecdotal experience confirms the essential unifocal initial presentation, apparent inexorable progress to the more typical multifocal distribution, and the associated high rate of dysplasia or invasive cancer developing over a few years. In a reported large series, the alveolar ridge is most frequently affected, followed by the tongue and buccal mucosa (**Table 1**).

DIAGNOSIS AND HISTOPATHOLOGY

A working diagnosis of proliferative leukoplakia is clinically based. It is supported by the progression

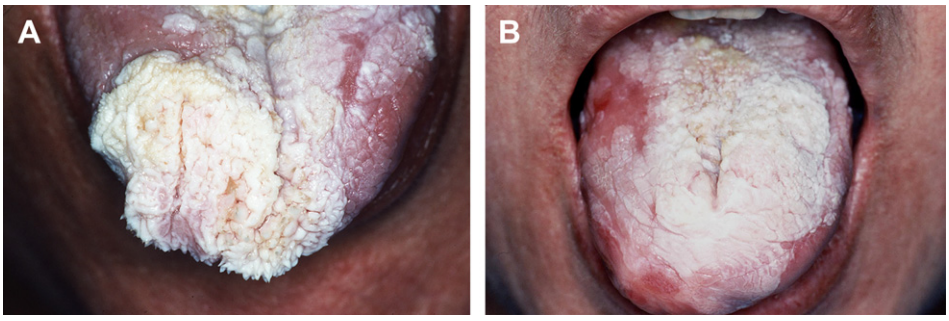

Fig. 1. (*A*) Broadly distributed lesions of proliferative verrucous leukoplakia over the dorsum of the tongue with variable surface textural features, including homogeneous, fissured, and prominent verrucous features. Microscopically, the features were reported as "consistent with verrucous carcinoma." (*B*) Persistent leukoplakia after conservative surgical resection approximately 14 months earlier. Moderately developed verrucous qualities are evident on either side of the midline, whereas toward the periphery a thinner more homogeneous pattern of keratinization is seen.