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CASE REPORT

Proliferative verrucous leukoplakia and its progression to oral carcinoma: report of three cases

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Proliferative verrucous leukoplakia (PVL) is a distinct clinical form of oral leukoplakia defined by its progressive clinical course, changing clinical and histopathologic features, and potential to develop into cancer. PVL behaves in a more aggressive and relentless manner than the more innocuous white oral lesions that it can resemble clinically. We present three cases of PVL that progressed to carcinoma and discuss the histopathologic findings that may either hinder or assist in the diagnosis.
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Introduction

Proliferative verrucous leukoplakia (PVL) is a clinical diagnosis for leukoplakias that encompass a spectrum of clinical and histopathologic stages prone to exhibit recurrence and, at times, the clinical and microscopic features of malignancy (1). Several studies have examined the long-term characteristics of PVL and its propensity to develop into carcinoma. We present three cases of PVL (Table 1) in order to add to the cases of PVL previously described in the literature, discuss some salient features of PVL not previously discussed, and point out some potential pitfalls in the diagnosis of these lesions. The cases reported here involve tissue submitted to the University of Washington School of Dentistry's Oral and Maxillofacial Pathology Service, Seattle, WA, USA.

Case 1

Three biopsies from a 78-year-old Caucasian male patient were taken of a white verrucoid plaque on the gingiva of the right upper quadrant, a white papillomatous/verrucoid plaque on the gingiva of the left lower quadrant, and a white plaque on the buccal mucosa and oral commissure. He had a 10 pack-year history of cigarette smoking but reported no tobacco use in the 20 years prior to his presentation. The histopathologic diagnoses were 'non-specific immunofluorescent findings, suggestive of lichen planus' and 'suggestive of lichen planus', respectively. Over 4 years later, biopsies were taken from an area of several white to light pink, raised areas of the right buccal mucosa and a red area on attached gingiva in the left upper quadrant. The diagnoses were 'epithelial hyperplasia, mild atypia, and focal lichenoid inflammation' for both sites. Two years later, biopsies were taken from white, patchy, leathery changes of the right buccal mucosa and the attached gingiva of the left lower quadrant. The diagnoses were 'lichen planus with verrucoid hyperorthokeratosis and epithelial atrophy' for both biopsies (Fig. 1). Over a year later, a biopsy was taken of a white, thickened area from left lower quadrant attached mucosa. The diagnosis was 'verrucous hyperkeratosis, acanthosis, and basilar hyperplasia with mild dysplasia consistent with a late stage of proliferative verrucous leukoplakia'. One month later, a biopsy was taken of a rough white lesion on left lower quadrant gingiva. The diagnosis was 'proliferative verrucous leukoplakia with areas suggestive of verrucous carcinoma'. This was followed shortly by surgical excision of the entire lesion. The histopathologic diagnosis of the definitive surgical specimen was 'verrucous carcinoma' (Fig. 2).

Case 2

A 73-year-old Caucasian female patient presented with a chief complaint of slight soreness and bleeding upon brushing of interproximal gingiva in the left lower quadrant. She had no history of tobacco use. Seven months earlier, the associated gingival papilla had been removed without submission of the tissue for histopathologic examination and diagnosis. A biopsy was taken of this region with a diagnosis of 'atypical epithelial hyperkeratosis, acute and chronic mucositis, and areas questionable for dysplasia'. Two months later, a second

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Table 1 Clinical and histopathologic characteristics

	Case 1	*Case 2*	*Case 3*
Sex	Male	Female	Female
Age (years)	78	73	89
History of tobacco use	Yes	No	No
Initial site(s) of disease	Gingiva, buccal mucosa, oral commissure	Gingiva	Hard palate
Clinical presentation	White verrucoid plaque	Soreness, bleeding	Red/white rough lesion
Initial diagnosis	Suggestive of lichen planus	Atypical epithelial hyperkeratosis	Squamous cell carcinoma arising in proliferative verrucous leukoplakia
Number of recurrences	4	4	0
Final diagnosis	Verrucous carcinoma	Squamous cell carcinoma arising in proliferative verrucous leukoplakia	Squamous cell carcinoma arising in proliferative verrucous leukoplakia
Length of follow-up (years)	7.5	3.5	0.2

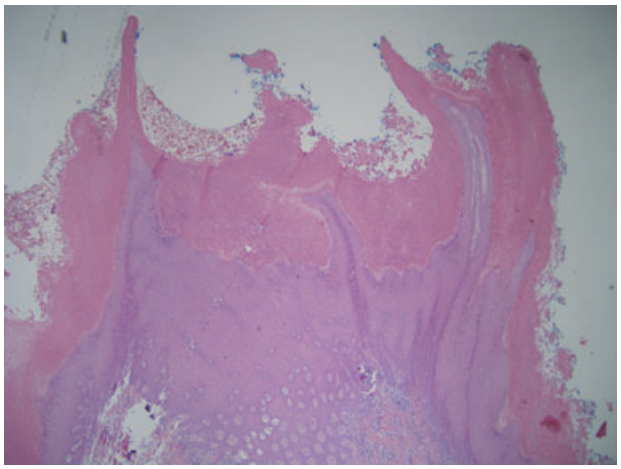

Figure 1 Transition from lichenoid inflammation to an area with corrugated to slightly verruciform keratosis (hematoxylin and eosin stain, ×100).

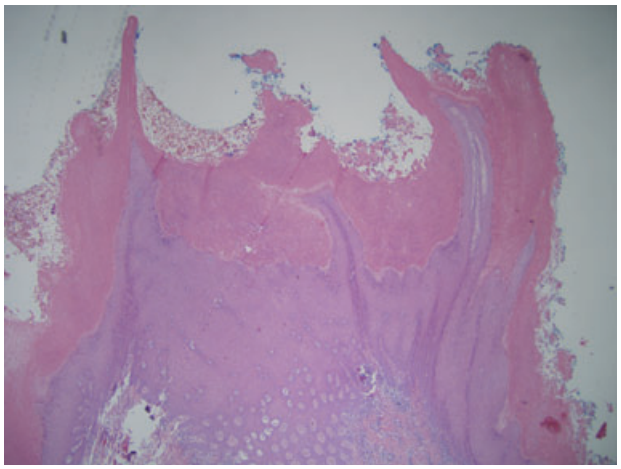

Figure 2 Verrucous carcinoma in excised lesion (hematoxylin and eosin stain, ×40).

biopsy was taken from the same area because of similar clinical findings. The diagnosis was 'verruciform epithelial hyperplasia with mild to moderate atypia and areas questionable for dysplasia'. Over a year later, a third biopsy was taken of a raised lesion from the same area with a diagnosis of 'atypical epithelial proliferation with significant dysplasia' with a comment that superficially invasive squamous cell carcinoma could not be ruled out. The involved teeth were extracted at that time. Over a year later, the patient presented with a submucosal swelling of the residual alveolar ridge extending posterior to the retromolar pad, where a 'cheesy' exudate was observed. Clinically, the lesion was considered an infected cyst. An incisional biopsy was taken with a diagnosis of 'verrucous keratosis with moderate to severe dysplasia consistent with proliferative verrucous leukoplakia and areas suggestive of squamous cell carcinoma'. An external consultation of that specimen was returned with a diagnosis of 'atypical papillary-verruciform proliferation suggestive of proliferative verrucous leukoplakia and verrucous carcinoma'. Two months later, the definitive surgery was performed with a diagnosis of 'multifocal well-differentiated squamous cell carcinoma arising in proliferative verrucous leukoplakia'. At the time of surgery, there was evidence of extensive epithelial folding forming pseudocysts arising from the surface epithelium in the edentulous areas with extension into and resorption of the subjacent mandible (Fig. 3).

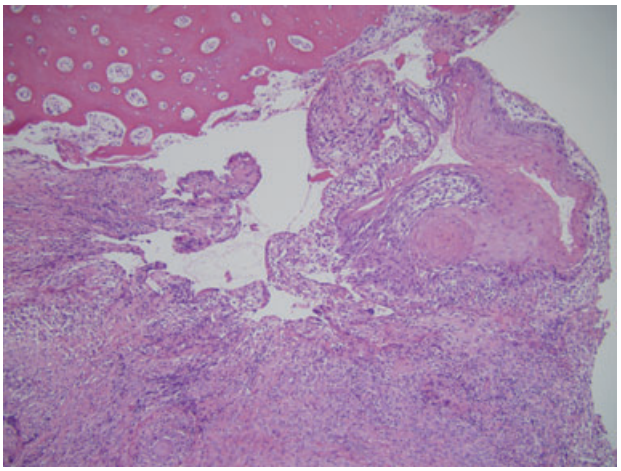

Figure 3 Bone invasion with pseudocyst formed by invagination from tumor surface (hematoxylin and eosin stain, ×100).

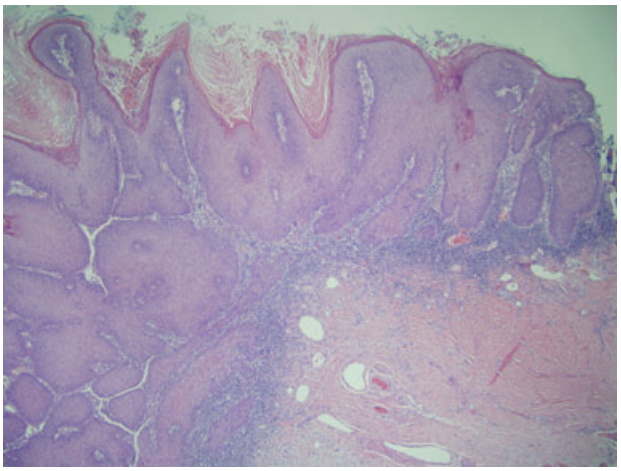

Figure 4 Squamous cell carcinoma arising in proliferative verrucous leukoplakia (hematoxylin and eosin stain, ×40).

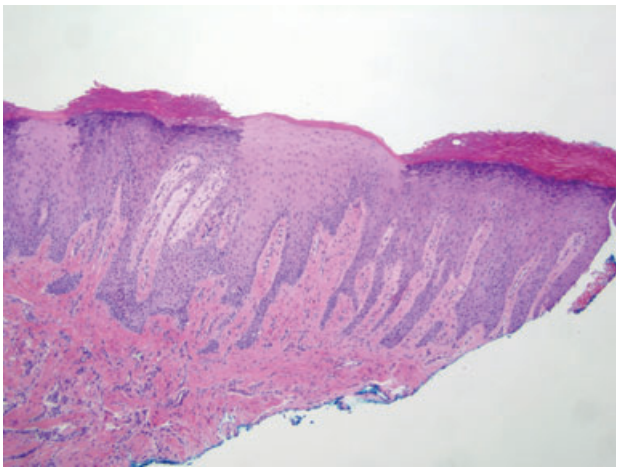

Figure 5 Abrupt transition between parakeratin and orthokeratin in proliferative verrucous leukoplakia (hematoxylin and eosin stain, ×100).

Case 3

An 89-year-old Caucasian female patient presented with rough, red to white lesions of the palate underlying her upper denture. She had no history of tobacco use. Two biopsies were taken, one from the right anterior palate and one from the left hard palate with diagnoses of 'proliferative verrucous leukoplakia with mild to moderate dysplasia and areas suspicious for superficial invasion' in the first and 'squamous cell carcinoma, well-differentiated, arising in proliferative verrucous leukoplakia' in the second (Fig. 4). At the time of biopsy, the lesion on the left palate extended into the maxillary sinus and nasal cavity. Two months later, a maxillary resection was performed with a diagnosis of 'squamous cell carcinoma, well-differentiated, with infiltration of bone and undermining of the respiratory mucosa'.

Comments

Proliferative verrucous leukoplakia exhibits progressive histopathologic features that may be observed in a single biopsy, multiple biopsies taken from a patient at the same time, or serial biopsies taken over time (1). In many cases, there is an interface lymphocytic infiltrate within the superficial lamina propria that is similar to and often mistaken for lichen planus. Basilar vaculopathy (hydropic, ballooning, or vacuolar degeneration) is usually not observed or is not a consistent feature (2). The lymphocytic infiltrate may be intense and focally obscure visualization of the basement membrane and the epithelial connective tissue interface. Apoptotic cells and eosinophilic ovoid (Civatte, colloid, cytoid, hyaline) bodies may occasionally be identified. With clinical evidence of increasing surface change observed over time (or within a single biopsy), there are corresponding histopathologic findings of increased keratosis with an increasingly corrugated or verruciform surface, with increasing acanthosis and basilar hyperplasia with or without dysplasia. Frequently, there is an abrupt transition from hyperparakeratosis to hyperorthokeratosis (Fig. 5).

Our three cases illustrate three important points. The first is that the progressive histologic features of PVL may include features that are mistaken for lichen planus or associated with areas that are or have been diagnosed as lichen planus (2, 3). A stage of PVL must be considered in the cases of lichenoid interface inflammation with basilar hyperplasia and hyperkeratosis without evidence of significant basilar vaculopathy. The second is that the various stages of PVL may be observed within a single specimen or in several specimens taken from the patient at the same time. The third is that, in advanced cases, the deeply folded tissue may erode and infiltrate the underlying bone forming pseudocysts between and around teeth and in edentulous areas that may be mistaken for odontogenic cysts. In an additional PVL case from the maxilla with a six-year history of multiple biopsies, the extension of the surface epithelium at one stage of the PVL formed radiolucent pseudocysts, one of which was diagnosed as an odontogenic keratocyst with dysplasia. The lesion continued to proliferate with the loss of several teeth, and the patient was eventually diagnosed with squamous cell carcinoma arising in PVL that required a hemimaxillectomy.

If the clinical lesions continue to grow horizontally and vertically, there are concurrent histopathologic changes of increasing hyperkeratosis with increased surface folding, verrucous papillomatosis, acanthosis, and basilar hyperplasia with or without dysplasia. Only if these latter histopathologic changes are observed and/or there is recurrence of a previously excised lesion should a white lesion be considered consistent with PVL clinically. Hyperkeratosis and verrucous hyperplasia (verrucous keratosis) are histological descriptions of lesions that do not meet the overall criteria of PVL but may represent an early stage of PVL if they persist and continue to follow the characteristic clinical and histological features. If lesions with the clinical and histological features of PVL are not aggressively treated, they will recur and may progress to verrucous carcinoma and/or squamous cell carcinoma.

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