Proliferative verrucous leukoplakia
A follow-up study of 54 cases

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Objectives. Proliferative verrucous leukoplakia is a unique form of oral leukoplakia that has a high risk for becoming dysplastic and transforming into squamous cell carcinoma. The purpose of this review is to update patient profiles, pathogenesis, and survival.

Study design. Fifty-four patients with proliferative verrucous leukoplakia (17 from a previous report) were followed prospectively in our clinic for a mean of 11.6 years after initial biopsy.

Results. In the patient population studied, the mean age was 62 years, and women outnumbered men 4 to 1. Multiple intraoral sites were involved (mean, 2.6 per patient); the most common sites were buccal mucosa in women and tongue in men. In a mean time of 7.7 years, 70.3% of the patients developed a squamous cell carcinoma at a proliferative verrucous leukoplakia site, most frequently the gingiva and tongue. Twenty-one of the patients with proliferative verrucous leukoplakia died of proliferative verrucous leukoplakia-associated carcinoma. Only 31% of the 54 patients used tobacco in any form. Radiation did not appear to enhance surgical control.

Conclusions. Proliferative verrucous leukoplakia is a high risk precancerous lesion with a high mortality rate. Because of both the propensity for progression to dysplasia and malignancy, as well as a high recurrence rate, these patients must be treated aggressively and followed carefully.


In 1985 we first described a unique form of leukoplakia found in 30 patients.1 Because of the characteristics in appearance as a progressively expanding exophytic/verrucal predominantly white lesion, we coined the name proliferative verrucous leukoplakia (PVL). This group of lesions had a high risk for malignant transformation with 86.7% developing carcinoma at a lesion site in a follow-up time of up to 20 years (mean, 6 years).

An added complexity of these growths was the variable histologic appearances within patient specimens that could range from a benign hyperkeratosis, through degrees of epithelial dysplasia to verrucous or squamous cell carcinoma. The white blood cell inflammatory infiltrate in the connective tissue also appeared quite variable, ranging from mild and diffuse to dense subepithelial clustering.

The ratio of women to men was 4 to 1. Half of the women and 83% of the men smoked; only one patient used snuff. Control of PVL was unsatisfactory; 13 (43.3%) of the patients died of their disease.

Recently, our findings have been supported by a report of 10 PVL cases from London.2 The purpose of this article is to describe the clinical findings and assess risk factors in a larger group of PVL patients, as well as update management approaches, progression, and prognosis.

MATERIAL AND METHODS
The study group comprised 54 patients seen in the Oral Medicine Clinic, University of California, San Francisco, who met our criteria for PVL. Clinically, the lesions were slowly increasing in size or extending to other oral mucosal sites over the period of observation; there was progression to wart-like, verrucal, exophytic features; and primarily the lesion had a keratotic, white appearance. Histologic findings were quite variable and consistent with PVL, ranging between and within patients from hyperkeratosis, dysplasia with degrees of severity, to verrucous or squamous carcinoma, and subepithelial inflammatory infiltrates that varied from sparse and diffuse to dense. Seventeen of the patients, who were part of the initial study and available, were included and followed with this group.

After obtaining initial incisional biopsies and histories, all patients were periodically followed in our clinic (examinations, measurements, and photos) until either lost to follow-up or death (mean, 11.6 years; range, 1 to 39 years). The number and sites of biopsies depended on clinical judgment, variable findings such as red components, induration or ulceration, and positive toluidine blue staining reactions. Repeat biopsies on follow-up were obtained when changes in signs or symptoms occurred.
The biopsies were prepared for routine hematoxylin and eosin staining. Oral swabs were plated on Candida BCG agar (PML Media, Sacramento, Calif.) to evaluate for candidal colonization; and histologic specimens were stained additionally with the periodic acid-Schiff stain.

Speciation of positive candidal cultures was accomplished by germ tube production or carbohydrate assimilations (API 20C bioMerieux, Hazelwood, Mo.). In addition, nine specimens (six paraffin-imbedded and three frozen) were processed by polymerase chain reaction to assess for the presence of human papilloma virus (HPV). This was performed in our stomatology virology laboratory and reported by Palefsky et al., using radioactive phosphorus-labeled oligonucleotide probes specific to HPV 6, 11, 16, 18, 31, 33, and 45.

Treatment by surgical removal was performed on the basis of histologic findings, aggressiveness of the growth, and patient concurrence. Radiation therapy was administered postsurgically in some cases of carcinoma when surgical margins were questionable or because of tumor staging, postoperative radiotherapy was deemed advisable.

Although this was primarily a descriptive study of a relatively small group of patients, statistical analysis with the Fisher’s exact test (2-tail) was used to test for differences in proportions.

RESULTS

Table I shows the predominance of women with PVL compared with men (4 to 1). There was no apparent association with smoking as 69% never used tobacco in any form or had discontinued smoking at least 1 year before the occurrence of PVL. There was no significant difference between the number of women (33%) and men (27%) who smoked (p = 1.00). Only 15% had complaints of discomfort. Table II indicates the extent of the PVL lesions with an average occurrence of 2.6 mucosal sites per patient in both women and men. Although the most common site in women was the buccal mucosa, the tongue was the most frequent site in men.

<table>
<thead>
<tr>
<th>Site</th>
<th>Total n=38</th>
<th>Women n=43</th>
<th>Men n=11</th>
<th>Smokers n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>11 (29%)</td>
<td>9 (21%)</td>
<td>2 (18%)</td>
<td>1</td>
</tr>
<tr>
<td>Tongue</td>
<td>10 (26%)</td>
<td>8 (19%)</td>
<td>2 (18%)</td>
<td>5</td>
</tr>
<tr>
<td>Buccal</td>
<td>6 (16%)</td>
<td>5 (13%)</td>
<td>1 (9%)</td>
<td>3</td>
</tr>
<tr>
<td>Floor</td>
<td>5 (13%)</td>
<td>5 (13%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Palate</td>
<td>5 (13%)</td>
<td>4 (11%)</td>
<td>1 (9%)</td>
<td>2</td>
</tr>
<tr>
<td>Lip</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

In a mean time of 7.7 years (range, 1 to 27 years) from the time of diagnosis or recognition of their PVL, carcinoma developed in 38 (70.3%) of the patients in one of the PVL sites (Table III). The most common site of transformation to malignancy was the gingiva (mean time, 7.3 years), followed by the tongue (mean time, 5 years). When compared with all other oral sites, the tongue and gingiva appeared to have a greater tendency for malignant transformation (p = 0.13). Although women were more likely to develop a malignancy than men (74.4% and 54.4%, respectively), statistical significance was not reached (p = 0.27).

Table IV shows the progressive histologic nature of PVL with the microscopic appearance of dysplasias and malignancies increasing from 48% at the initial diagnosis to 80% at the last biopsy reading. In the 44 patients who had never previously been known to have a PVL-associated malignancy, carcinomas developed in 28 (64%) during the follow-up period of up to 27 years from the time when PVL was first noted.

In addition, during the follow-up visits of the 38 patients with initial or subsequent first PVL-associated carcinomas, a second malignancy was found in another PVL oral site in 12 (31.5%) of the cases. In comparing smokers and nonsmokers, cancer transformation rates were identical (70%).

Nineteen of 38 specimens stained for Candida were positive. Speciation showed all were Candida albicans. Malignancies developed in 13 (68%) of the 19 cases
with positive fungal cultures; this was similar to the 74% that developed carcinomas that did not show *Candida* histologically (p = 0.78). Eight of nine specimens processed for HPV were positive: six for HPV-16 alone, one for HPV-18 alone, and one specimen was positive for both 16 and 18.

Twenty-one patients (39.6%) died of PVL-associated carcinoma. Surgery was the indicated and primary treatment, even though the outcome was poor (Table V). Adding radiation to the management offered no additional survival benefit.

**DISCUSSION**

This follow-up study of 54 PVL patients confirms our initial findings and impressions reported in 30 patients over a decade ago; PVL is a very high risk precancerous lesion with a high mortality rate. Longer term follow-up would not doubt result in an even higher than 70% transformation rate. The same would undoubtedly hold true for multiple cancers, which occurred in almost one third of those with PVL-associated carcinomas. If mortality data from our 1985 report are combined with our present group, the PVL-associated deaths would be 50%.

Therapeutic approaches have not been encouraging, although surgery with laser technology offers some hope. The surgical failures primarily appear to be related to subcellular molecular elements that in early stages are not reflected in either clinical or microscopic identifiable changes, thereby leading to recurrences because of “inadequate margins.” Although useful biomarkers for tissues at risk are being pursued, reliable markers have not as yet been identified. Conventional external beam radiation does not appear to be effective in controlling PVL-associated biologic factors of epithelial cell behavior. This is based on the lack of response in 8 of 11 patients treated with radiotherapy. An additional problem is the lack of experience by radiation oncologists with PVL lesions.

The role of HPV remains speculative regarding its presence and regulatory influence on PVL occurrence and progression. The fact that Palefsky et al. found HPV in eight of nine of our PVL specimens certainly indicates a potential role as a cofactor in the high malignant transformation rate. Furthermore, HPV-16 (identified in seven specimens) is the HPV type acknowledged to be associated with squamous carcinoma of the uterine cervix. Of interest, in the Palefsky et al. control group, four of eight non-PVL dysplasia specimens were positive for HPV 16. The possibility of a cofactor role for HPV is further enhanced by the known effects of HPV E6 protein, which can bind and inactivate p53 protein. This in turn may account for chromosomal instability, ineffective epithelial suppression of growth factors, and subsequent neoplasia.

Because of the broad spectrum in PVL appearance, natural history, histopathologic conditions, and outcome, it seems logical to believe that PVL is a multifactorial disease. But supportive findings are sparse. Clinical evidence of any immunologic disease(s) or associated immunodeficiencies have not been a feature. Vitamin A, vitamin A analogues, and antioxidant nutrients (vitamins C, E, and beta carotene), which have been shown to modify or reverse some oral leukoplasias, have shown no beneficial effects when randomly used in therapeutic dosages in six of our PVL patients.

Potentiating factors, such as smoking and the presence of *Candida*, have not demonstrated any evident influence on either occurrence or progression. Although the largest number of carcinomas (29%) and the highest transformation rate (38%) occurred in the gingiva, only 1 of the 11 patients smoked. In one of our previous studies on oral leukoplakia, patients who did not smoke paradoxically incurred a greater risk for malignant transformation than those who smoked. Reasons for gender and site differences are not apparent. Thus, at the present time, careful clinical and microscopic assessment combined with surgical intervention, clinical judgment, and close follow-up offer the best approaches to management and control.
REFERENCES


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