INTRODUCTION

Since Hansen and colleagues\(^1\) defined the term proliferative verrucous leukopla-kia (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 leukopla-kia 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...
rate was reported by Zakrzewska and colleagues and Cabay and colleagues. 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 and Silverman and colleagues, 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. More recently, however, the relationship between PVL and oncogenic HPV has been challenged. In contrast, Beltiol and colleagues 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. 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.

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. 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.

DIAGNOSIS AND HISTOPATHOLOGY

A working diagnosis of proliferative leukoplakia is clinically based. It is supported by the progression
from initially smooth, uniform, and homogeneous lesions to those that are granular, and finally to warty or verrucous lesions with an erythematous or erythroplastic component. The latter features develop over a variable time frame without intervention, and often in a multifocal distribution.

The pathologic nature of this entity is characterized by variation from one area to another within the region being sampled when an incisional biopsy is performed. It has been noted by way of general experience, and reported in the literature, that a wide range of abnormality can be found, from simple benign hyperkeratosis to invasive squamous cell carcinoma. Other forms of abnormality include ranges of dysplasia, verrucous hyperplasia, verrucous carcinoma, and, uncommonly, papillary squamous cell carcinoma.1,4,19

### Treatment

#### Photodynamic Therapy

The concept of photodynamic therapy is based on the activation of a photosensitizer by light of various wavelengths on superficial malignant or premalignant lesions. The photosensitizer is administered systemically, generating cytotoxic effects when the cells are exposed to light. One of the significant limitations of PDT is the marginal depth of penetration to the cutaneous or mucosal level.

Hematoporphyrin (Photofrin) was used initially at the Mayo Clinic in 1960 by Lipson and Schwartz.20 They observed that administration of hematoporphyrin generated fluorescence of neoplastic lesions; this was used during surgery for tumor detection.20 One of the targets of photodamage by Photofrin was the mitochondria of cells, with no accumulation in the nuclei. This process resulted in diminished risk for DNA mutation or additional carcinogenesis. In addition to targeting the tumor cells, however, PDT has an effect on the microvasculature of the tumor bed and the inflammatory and immune systems, resulting in apoptosis and tumor control.21 Photodynamic therapy has been effective in ablation of early superficial lesions of head and neck cancers, with up to 75% of the complete responses sustained at 2 years.22

Although PDT has been a viable treatment option, the side effects of dihematoporphyrin ether include hypersensitive skin reactions, local edema, nausea, and liver toxicity. Skin photosensitivity may last for up to 14 weeks; therefore, a topical option with fewer side effects was investigated. Topical application of 5-aminolevulinic acid activated with a 585-nm pulsed dye laser showed a 78% average reduction of laryngeal keratosis, with no significant differences between

### Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Alveolar ridge</td>
<td>66.6%</td>
</tr>
<tr>
<td>Tongue</td>
<td>50%</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>41.6%</td>
</tr>
<tr>
<td>Gingiva</td>
<td>33.3%</td>
</tr>
<tr>
<td>Oral floor</td>
<td>25%</td>
</tr>
<tr>
<td>Gingival sulcus</td>
<td>25%</td>
</tr>
<tr>
<td>Labial mucosa</td>
<td>16.6%</td>
</tr>
<tr>
<td>Hard &amp; soft palate</td>
<td>8.3% each</td>
</tr>
</tbody>
</table>

the outpatient and the operating room settings. Aminolevulinic acid (ALA) is not a photosensitizer but rather a precursor of protoporphyrin in the heme biosynthesis pathway.\textsuperscript{23}

Chen and colleagues\textsuperscript{24} evaluated ALA in the management of 8 oral verrucous hyperplasias and 24 oral leukoplakia lesions. All 8 oral verrucous hyperplastic lesions were treated weekly and showed complete response after an average of 3.8 treatments. No recurrence was seen within a mean follow-up of 10.6 months. The oral leukoplakia lesions were treated twice a week (because of limited response in a previous study administering topical ALA and PDT once a week). Complete response was achieved in 8 and partial response in 16 lesions after an average of 3.5 treatments. Of the 8 complete responses in the oral leukoplakia group, 2 recurred after 9 and 11 months. The remaining 6 complete responses showed no evidence of relapse after a mean follow-up period of 7.2 months.

Chen and colleagues\textsuperscript{25} also reported the case of a patient with verrucous carcinoma in the commissure of the lip; the patient was a smoker and areca quid chewer also treated with ALA and PDT. The lesion showed complete remission in the extraoral aspect of the lip after 6 treatments and after 22 treatments to the intraoral tumor. No recurrence was identified after 6 months of follow-up.

Enough evidence exists to initiate treatment of PVL, and possibly even verrucous carcinoma, using photodynamic therapy. Longer follow-up and further identification of dosage and regimens, along with well-designed prospective randomized clinical trials are necessary to give additional validity to this treatment modality.

**Surgery**

Surgery has been considered the preferred treatment for PVL and verrucous carcinoma, but the recurrence rate for both types of lesions has been high. This finding calls into question the operative management of the disease.

Walvekar and colleagues\textsuperscript{26} reported on 101 oral verrucous carcinomas treated with surgery; 68% of the patients experienced local recurrence. On univariate analysis, tumor location (in the upper alveolar-palatal complex), presence of a premalignant lesion (ie, leukoplakia or submucous fibrosis), smoking, and positive margins were statistically significant for worse outcomes. The overall disease-free survival with surgical therapy was 77.6%. The incidences of cervical node metastasis and tumor invading bone were extremely low, consistent with data from Oliveira and colleagues.\textsuperscript{27}

Femiano and colleagues\textsuperscript{28} reported similar recurrence rates after excision of PVL. This study prospectively and randomly assigned 2 groups of 25 patients with HPV+ PVL paired and matched to 2 different treatment modalities. Group A was treated with surgical scalpel excision with normal surrounding mucosa, whereas Group B was treated with similar surgery in addition to Viruxan (methisoprinol), a synthetic agent with immunomodulatory properties and antiviral activity against HPV. After 18 months of follow-up, 18 recurrences (72%) were seen in Group A compared with 4 relapses (16%) in Group B.

Surgical resection may be the intuitive approach to eliminate the lesion, but the biologic behavior of PVL and verrucous carcinoma probably requires addressing the possible underlying viral infection, if it exists, in addition to the excisional procedure.

**Radiation Therapy**

For a long time there was a perception that radiotherapy changed the biologic behavior of verrucous carcinoma into a more aggressive squamous cell carcinoma.

In 1988, Nair and colleagues\textsuperscript{29} reported on 52 cases of oral verrucous carcinoma treated with radiation. Fifteen patients with well-circumscribed T1 through T2 and early T3 lesions were treated with interstitial brachytherapy with single plane radium implants. Thirteen (87%) of the 15 patients treated with brachytherapy were alive with no evidence of disease after 3 years. Eight (25%) of 31 patients treated with external radiation survived, disease-free. The difference in survival rates may have been related to selection bias. The group receiving brachytherapy had smaller tumors with negative cervical node metastasis, whereas the group receiving external-beam radiation had larger tumors and a high incidence of cervical metastasis.

A report by the Commission on Cancer at the American College of Surgeons in 2001 reviewed the National Cancer database and identified 2350 cases of verrucous carcinoma. The most common treatment was surgery alone (69.7%), followed by surgery with irradiation (11%), and irradiation alone (10.3%). The 5-year relative survival rate was 77.9%. For localized disease, survival after surgery was 88.9% compared with 57.6% after irradiation. The rate of anaplastic transformation after irradiation was 6.7%. The conclusion of the Commission supported surgical treatment, especially for cases originating in the oral cavity.\textsuperscript{30}

**Laser Ablation**

The authors did not find evidence of reliable data on laser ablation when compared with surgical
excision or just the “wait and see” approach in the management of PVL.

Although oral leukoplakia likely has a different origin and progression, one group compared laser ablation versus the wait-and-see approach in 200 patients (100 patients in each group) and followed them for 10 years. They didn’t find differences in outcomes between the treatment group and the control group.31

In the case of verrucous lesions, the authors believe that laser ablation eliminates the ability to identify whether the lesion had any area of invasive squamous cell carcinoma, and therefore they do not advocate its use.

Medical Management: Chemoprevention

Initial data from MD Anderson Cancer Center in the early 1980s supported the use of cancer chemoprevention through administering systemic 13-cis-retinoic acid to patients with premalignant lesions.32

Only recently a study reported the result in 2 small groups of patients with PVL treated with either topical or systemic retinoid therapy. The evaluators of the outcomes were blinded to the treatment modality. Eleven patients were treated with systemic retinoids and 5 with topical; 1 received both topical and systemic therapy. Seven lesions (6 in the systemic treatment group and 1 in the topical) improved, but 7 became worse (5 in the systemic therapy group and 2 in the topical group); the balance remained unchanged.33 Although the study was preliminary, the results suggest a possible role for prospective chemoprevention studies in PVL. These studies should address the proposed viral association with PVL and verrucous carcinoma, especially considering that the combination of surgery and antiviral agents showed significant success.28

SUMMARY

Proliferative verrucous leukoplakia, a lesion of unknown origin and with no strictly defined diagnostic criteria, is worthy of great clinical concern and scrutiny. The rate of malignant transformation associated with this entity was as high as 74% in one series.11

A wide range of pathologic findings characterize the clinically diverse presentation and slow evolution of the stated abnormalities. Treatment options are varied, with no consensus regarding the most efficient and effective strategy. Further complicating the unusual biology and behavior of this lesion is the usual multifocal presentation and progression observed, with lifelong vigilance required after treatment.

Verrucous carcinoma is a progressive lesion with high recurrence and 5-year survival rates. It has a low incidence of bone invasion, and cervical node metastasis is unusual. Surgery is still the preferred treatment. Further investigation into the combination of surgery and antiviral agents may bring additional improvement in patient care.

REFERENCES