Received: 2 July 2024 | Accepted: 5 October 2024

DOI: 10.1002/cap.10320

CASE STUDY

Proliferative verrucous leukoplakia: Case study of 24 years and outcome of treatment with CO_2 laser

Charles M. Cobb[1] | **Nabil E. Beaini**[2] | **Jessica Scully**[3] | **Tanya M. Gibson**[4]

[1]Department of Periodontics, School of Dentistry, University of Missouri-Kansas City, Kansas City, Missouri, USA

[2]Private Practice, Columbia, Missouri, USA

[3]Private Practice, Washington, Missouri, USA

[4]Department of Oral Pathology, Radiology and Medicine, School of Dentistry, University of Missouri-Kansas City, Kansas City, Missouri, USA

Correspondence
Charles M. Cobb, Department of Periodontics, School of Dentistry, University of Missouri-Kansas City, 424 West 67th Terrace, Kansas City, MO 64113, USA.
Email: cobbc@umkc.edu

Abstract

Background: Proliferative verrucous leukoplakia (PVL) is a rare and refractory form of oral leukoplakia. The etiology of PVL remains unknown. The lesion is characterized by a high rate of malignant transformation. There is no definitive treatment for PVL.

Methods: This case study presents a patient diagnosed in 2000 with a localized hyperkeratinized/verrucous lesion involving the facial gingivae of teeth #6–#8. Over the next 24 years, the lesion was biopsied five times. Further, two attempts to ablate the lesion with a CO_2 laser (10.6 μm wavelength) were performed. Both ablation treatments were unsuccessful as the lesion recurred and progressed to involve more areas of gingival tissue. To date, biopsy has not revealed transformation into verrucous or squamous cell carcinoma (SCCA).

Results: This case study demonstrates that two attempts at ablation of PVL using a CO_2 laser had no short- or long-term benefit. The patient eventually lost all maxillary teeth due to root caries and inability to maintain adequate oral hygiene. The PVL lesion currently involves the entire maxillary edentulous ridge, extending from the 2nd molar site to the opposite corresponding site. During the 24 years encompassed by this report, the patient has not experienced a malignant transformation.

Conclusion: The results of CO_2 laser ablation of the PVL lesion in this case provided no short- or long-term benefit. Given the potential for a sinister outcome, PVL patients require frequent clinical evaluation and biopsy for early detection of a malignant transformation into oral verrucous or SCCA.

KEYWORDS
carbon dioxide laser, gingiva, oral cancer, oral leukoplakia, oral pathology, precancerous conditions

Key points

- Proliferative verrucous leukoplakia (PVL) is a clinical diagnosis and represents a refractory form of multifocal oral mucosal leukoplakia of unknown origin.
- Currently, there is no reliable and successful treatment for PVL.
- PVL may undergo transformation to a verrucous or squamous cell carcinoma, thereby necessitating frequent oral examination and biopsy of sinister-appearing mucosal sites.

Plain language summary

Proliferative verrucous leukoplakia (PVL) is a rare disorder that affects the gum tissue around the teeth. PVL is a pre-cancerous disorder for which the cause is unknown and there is no treatment that yields a consistently successful result. This

case study presents a patient diagnosed in 2000 with PVL involving the facial gum tissue of the upper right cuspid, lateral, and central incisor teeth. Over the next 24 years, the lesion was biopsied five times and two attempts to irradicate the lesion with a CO_2 laser were performed. All attempts at treatment were unsuccessful and the lesion slowly progressed to involve more areas of gum tissue. The last biopsy taken in February 2024 did not reveal any areas of developing cancer. During the 24 years covered in this report, the patient did not develop oral cancer. However, treatment with the CO_2 laser afforded no measurable benefit. Given the potential for developing cancer of the gum tissues, PVL patients should receive frequent oral exams and periodic biopsies for the detection of early cancer.

INTRODUCTION

Proliferative verrucous leukoplakia (PVL) is a clinical diagnosis and represents a refractory form of multifocal oral mucosal leukoplakia of unknown origin.[1] Clinically, the lesion is characterized by a slowly progressing and confluent exophytic surface texture. The histology of PVL can exhibit considerable variation in surface features, ranging on a spectrum from hyperkeratosis to verrucous hyperplasia with dysplasia to verrucous and squamous cell carcinoma (SCCA). Consequently, the differential diagnosis should include irritational hyperkeratosis, leukoplakia, chronic hyperplastic candidiasis, verrucous hyperplasia, verrucous carcinoma, and SCCA.[2]

PVL has a high propensity for malignant transformation into oral SCCA or verrucous carcinoma, with estimates ranging from 50% to 100%.[3–6] Although considered a premalignant lesion, PVL is not associated with the traditional risk factors for oral carcinoma such as the use of alcohol and tobacco products. Another enigma is PVL's resistance to treatment, whether it be aggressive surgical removal,[7] topical medications such as retinoids, or laser ablation procedures.[8–10] In contrast, there are several single case studies claiming short-term success using topical applications of imiquimod[11] or photodynamic therapy.[12] Viewed collectively, there appears to be no specific treatment that will predictably control the progression of PVL.[3,13,14]

The following case presents a 24-year history of slowly progressive PVL and failure to ablate the lesion with multiple applications of a CO_2 laser. Ultimately, the patient lost all maxillary teeth with the PVL lesion remaining to involve the edentulous maxillary ridge.

MATERIALS AND METHODS

Background

The University of Missouri-Kansas City (UKMC) Institutional Review Board (IRB) for human research determined that a case study is not considered Human Subjects Research and thus outside the purview of an IRB. Since no patient-identifying information is included in this report the Privacy Rule does not apply. Further, over the 24 years that the patient was under care, multiple consents were obtained from the patient, both oral and written, for treatment and biopsy.

The patient, an 83-year-old Caucasian female, was initially diagnosed in 2000 with a hyperkeratotic/verrucous leukoplakia lesion involving the facial gingivae of the maxillary teeth #6–#8. She remained under the care of her general dentist until 2015 at which time she was referred to the Department of Periodontics, School of Dentistry, UMKC for evaluation and treatment of a clinical diagnosis of proliferating verrucous leukoplakia.

Initial clinical presentation

The 2015 oral examination revealed a white, thickened leukoplakia with a distinct verrucous surface texture that involved facial and lingual gingivae of all maxillary teeth except for the molars (Figure 1). The patient was missing teeth #1, #16, #17, and #30; teeth #3, #13, and #29 had Class I amalgam restorations and teeth #4, #9, #10, #19, and #20 were restored with full-coverage porcelain-nonprecious metal crowns. There were diastemas between teeth #8–#9 (2.0 mm) and #9–#10 (1.8 mm). Probing depths ranged between 2 and 3 mm for all teeth except #6 through #10 which had interproximal 4 mm depths. Bleeding on probing was 8.6% (14 of 162 sites). There were no furcation involvements and none of the teeth exhibited mobility. The patient's chief complaint concerned the appearance of the maxillary gingival tissues and difficulty in executing oral hygiene due to irregular gingival contours, pain, and bleeding.

Dental history

The patient stated she had been seen by her general dentist for periodic oral examinations and dental prophylaxis every four months since early 2000. Biopsies were done by the general dentist in 2004, 2010, and 2013. Histology on the biopsies ranged from epithelial acanthosis with chronic inflammation to hyperkeratosis with chronic inflammation

FIGURE 1 Presentation at initial examination (January 2016). Proliferative verrucous leukoplakia (PVL) lesion involved facial and lingual gingivae of all maxillary teeth except for the molars.

FIGURE 2 Patient in February 2024. Proliferative verrucous leukoplakia (PVL) lesion involved all mucosa of the edentulous maxillary arch.

to verrucous hyperkeratosis suggesting PVL. As the lesion continued to spread and involve the gingivae of more maxillary teeth, she was referred to the UMKC School of Dentistry in December 2015.

The patient was seen every 3–4 months in the UMKC graduate periodontal clinic from December 2015 through December 2017, after which she was referred to her general dentist with instructions to map and biopsy suspicious areas and keep the patient on a 3 month maintenance schedule. The patient requested a referral back to the general dentist for convenience as she had to travel a significant distance for appointments.

In June 2018 the general dentist removed the maxillary incisor teeth due to root caries, inserted an acrylic partial denture, and referred the patient to a periodontist near her residence. She was under the care of the periodontist until 2021 at which time the patient became noncompliant regarding appointments. In June 2021, the general dentist removed tooth #13 (root caries) and noted the lesion had spread into the edentulous space. The periodontist again saw the patient in February 2024 for a biopsy, by which time she had a complete maxillary denture. The lesion had persisted over the intervening years and had spread to involve the entire maxillary edentulous ridge (Figure 2).

Medical history

The patient was ambulatory, emotionally stable, and talkative with a great attitude. Her medical history included type II diabetes, hypothyroidism, and osteoarthritis. Prescribed medications included insulin and glipizide for diabetes, celecoxib for arthritis, and levothyroxine for thyroid dysfunction. Her most recent A1c was 7.0 (February 2024) and she reported no allergies. She reported a history of limited alcohol intake, that is, <2 exposures per week, and a negative history of tobacco use.

Case management

It was explained to the patient that currently there was no definitive treatment for her clinical condition and that wide surgical excision was the usual method of treatment. It was emphasized that due to the relatively high rate of recurrence and potential for malignant transformation,[15] it would be necessary to undergo periodic oral exams, repeated biopsy of suspicious areas, and mapping of biopsy sites. The patient was already aware that a clinical diagnosis of PVL carried the possibility of transformation to a verrucous or SCCA. Due to the extensive tissue involvement, the possibility of a multiple ablation procedure using a CO_2 laser was suggested, with the caveat that the case study literature was conflicting regarding the use of lasers for the treatment of PVL.[8–10,16–19] The patient stated a willingness to try laser therapy in lieu of surgical excision and signed an informed consent to that effect.

A dental CO_2 laser* (10.6 μm wavelength) fitted with a flexible waveguide and a 0.8 mm ceramic delivery tip was used for ablation of affected gingival tissues of the maxillary dentition. The laser energy was delivered as a focused beam, 1–2 mm from the target surface. Laser parameters were 6 W of power, a pulse rate of 20 Hz, and a 0.01 s pulse length which yielded a laser fluence of 240 J/cm^2. At this fluence, the depth of tissue ablation was approximately 600 μm. The laser ablation procedures were done using a local anesthetic (lidocaine) delivered by local infiltration.

The first laser ablation procedure done in February 2016 involved the facial and lingual gingivae of all maxillary teeth showing visual signs of PVL with an extension to include one tooth distal of affected tissues (Figure 3). The patient was instructed to take 600 mg ibuprofen, q. 8 h., as needed for pain. Oral hygiene during the healing phase consisted of rinsing with a chlorhexidine mouth rinse, q. 8 h., gentle flossing, and brushing using an ultrasoft textured brush.

* LX-20 C02 Laser, Luxar Corp., Bothell, WA.

FIGURE 3 Immediate post-first CO_2 laser ablation procedure in April 2016.

FIGURE 5 Area identified as potential biopsy, prior to toluidine blue staining, during the April 2017 appointment.

FIGURE 4 Staining with toluidine blue solution prior to 2nd CO_2 laser ablation procedure (April 2017) in an attempt to identify suspicious areas requiring biopsy.

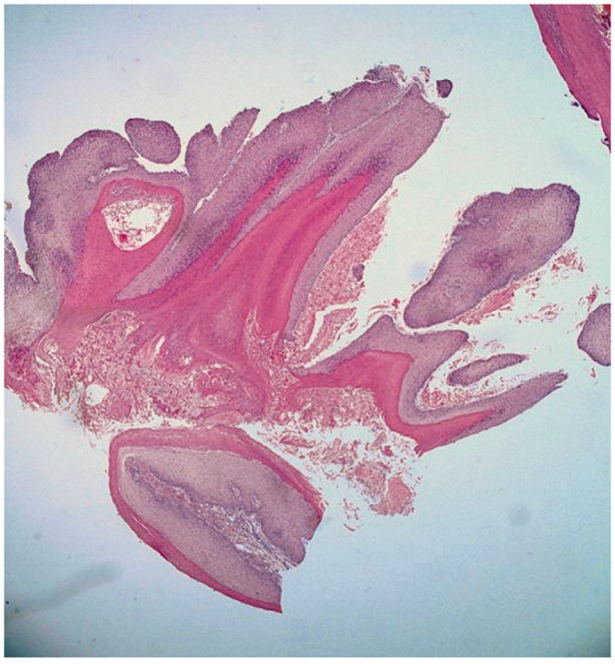

FIGURE 6 Low power view of April 2017 biopsy showing verrucous epithelial proliferation. Hematoxylin & eosin stain; original magnification of 25x.

The patient returned in 10 days for post-surgery follow-up and reported she had not needed the pain medication having experienced no discomfort or any adverse events.

In situ, staining of oro-pharyngeal soft tissues using toluidine blue (TB) has been reported as useful in the identification of early premalignant and malignant lesions.[20,21] To that end, a second laser ablation session, done in April 2017, was preceded by the application of a 1% solution of TB to all visual PVL lesion areas for 20 s, using a cotton-tip applicator, as described by Mashberg.[20] The TB application was followed by rinsing with 1% acetic acid followed, in turn, by a final rinse with sterile water (Figure 4). Based on the staining pattern, the interdental papilla between the maxillary teeth #5–#6 was biopsied (Figure 5). The second attempt at lesion ablation used the same laser, parameters, and post-treatment recommendations as the first session.

Histologic diagnosis

The histologic diagnosis of the April 2017 biopsy was "atypical verrucous epithelial proliferation with focal epithelial dysplasia (Figures 6 and 7). Recommend frequent oral examinations and biopsy of suspicious areas."

The most recent biopsy was procured on February 28, 2024, at which time the patient was 91 years old. The histologic diagnosis of this biopsy was "atypical verrucous epithelial proliferation with focal areas of epithelial dysplasia characterized by dyskeratosis" (Figures 8 and 9). The case was then referred to another pathology service for extramural consultation and received the same diagnosis with the following comments: "…. papillary epithelial proliferation with a dominant exophytic component and to a lesser extent, endophytic growth." And, "… anticipated progression over time, so continued follow-up is advised, with interval re-biopsy."

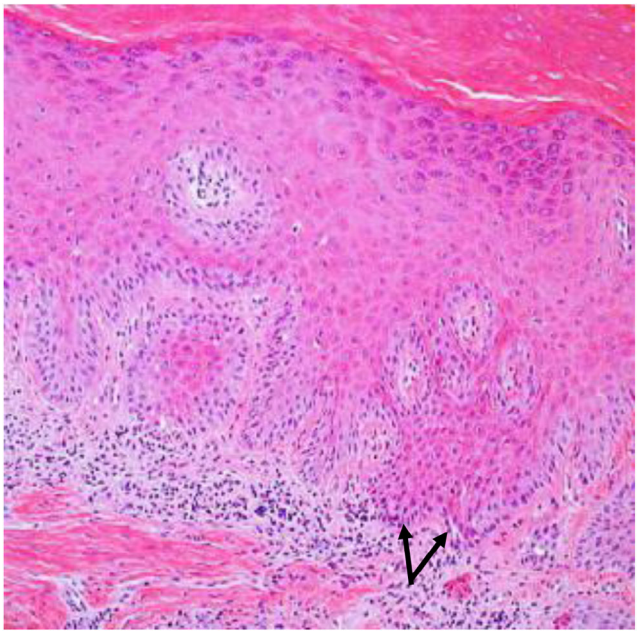

FIGURE 7 View of April 2017 biopsy showing epithelial proliferation with mild dysplasia (arrows). Hematoxylin & eosin stain; original magnification of 100x.

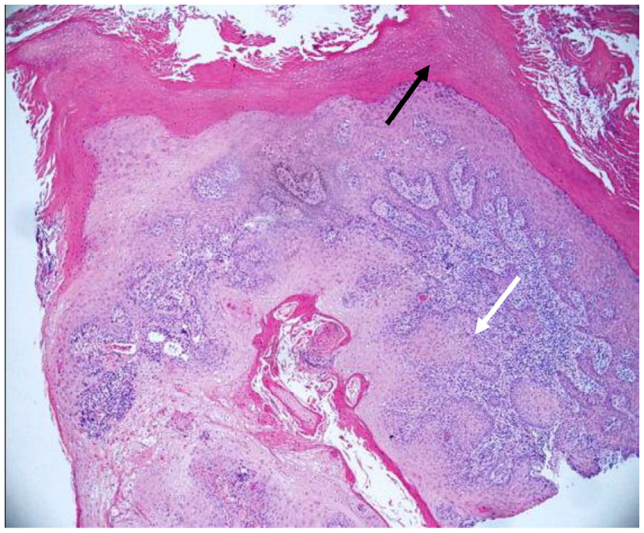

FIGURE 8 Low power view of the February 2024 biopsy showing atypical epithelial hyperplasia (white arrow) and a hyperkeratotic layer (black arrow). Hematoxylin & eosin stain; original magnification of 25x.

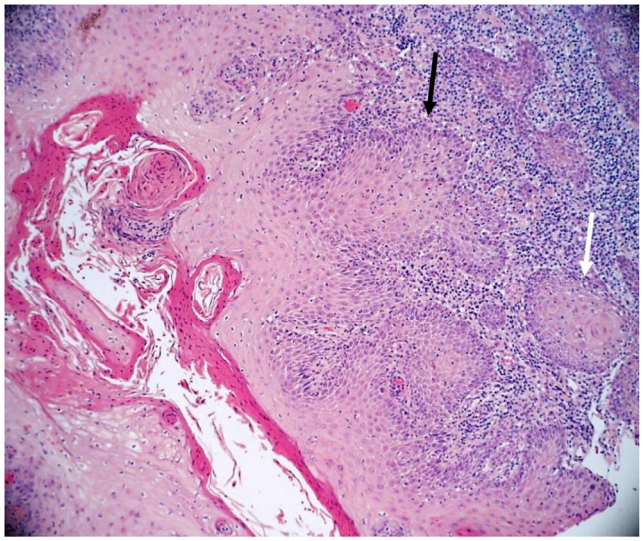

FIGURE 9 View of epithelial hyperplasia and epithelial dysplasia (black arrow) with dyskeratosis (white arrow) in the February 2024 biopsy specimen. Hematoxylin & eosin stain; original magnification of 100x.

FIGURE 10 Maxillary anterior view showing recurrence of proliferative verrucous leukoplakia (PVL) at 3 months following the 2nd ablation attempt using the CO_2 laser (April 2017).

RESULTS

Clinical outcome

Following two attempts at lesion ablation using the CO_2 laser within a 6 month period, the PVL lesion recurred and extended to involve the facial and lingual gingivae of all anterior and posterior teeth, except 2nd molars. (Figure 10)

Beginning in 2018 the patient began losing teeth due to root caries. Over the next 6 years, she lost all maxillary teeth and was converted to a maxillary complete denture in 2024. Interestingly, over the approximately 24-year period the lesion was evident (2000–2024), the patient has never experienced a transformation of the PVL into a verrucous or SCCA. Currently, the PVL lesion involves the entire maxillary edentulous ridge (Figures 2 and 11).

DISCUSSION

The demographics of PVL indicate the lesion is more common in women above 60 years of age than men.[22–24] Smoking and alcohol use appear to be low-level risk factors.[22–24] The more common lesion locations are the gingivae, buccal mucosa, and tongue.[22–24]

Transformation of PVL into verrucous or SCCA is the most sinister aspect of the lesion. Collectively, systematic reviews have reported malignant transformation of PVL ranging

FIGURE 11 View of the left maxillary edentulous ridge showing posterior extension of the proliferative verrucous leukoplakia (PVL) lesion (February 2024).

from 45.8% to 65.8%,[23–25] with the most frequent pathologic transformation being a conversion to conventional SCCA.[23,24]

Detection of suspicious areas requiring biopsy can, in many cases, be for the most part a subjective clinical decision based on visual appearance. The use of TB application to detect epithelial dysplasia has been suggested by several authors.[26–28] Use of TB in the current case provided little diagnostic benefit. We found the staining to be nonspecific and diffuse (Figure 4) with only a suggestion of concentration that would indicate an area requiring biopsy. Interestingly, Mills[29] reported TB had a sensitivity of 73% and specificity of 69% leading to the conclusion that TB was not reliable enough to warrant use as the sole diagnostic determinant.

Reports of successful ablation of PVL lesions using various laser wavelengths are conflicting. Schoelch et al.[30] reported the results of 70 consecutive laser-treated patients with various degrees of oral leukoplakia using the CO_2 or Nd:YAG lasers. Thirty-nine patients had some degree of microscopic dysplasia and six were diagnosed with PVL. Twenty-nine patients had no recurrence of their lesion; 19 patients had small areas of recurrence; two patients had complete recurrence; and five patients developed SCCA. Five of the six (83%) PVL lesions recurred following laser ablation.

Recurrence of PVL lesions following laser ablation was reported by Saibene et al.[31] and because of recurrence issues, Dong et al.[32] warns against using lasers for ablation of oral leukoplakia. Yet, Mogedas-Vegara et al.[33] claim the CO_2 laser to be a routine procedure for the treatment of oral leukoplakia. Additionally, there are isolated single-patient case studies of successful treatment of PVL using photodynamic therapy extending up to 12 months post-treatment.[34,35]

Other than surgical excision and laser ablation of PVL, the application of topical medications such as topical retinoic acid[36] or 5% imiquimod[37] have been reported as beneficial but with varying degrees of success. A promising treatment for PVL was recently reported by Hanna et al.[38] involving immune checkpoint inhibitor therapy with the drug nivolumab. The authors identified genetic mutations and immune cell response associations that will aid in future clinical trials. Interestingly, in terms of prognosis, it appears that PVL-derived SCCA has a better prognosis than conventional SCCA,[39] particularly with regard to mortality rate.[40]

CONCLUSION

This case demonstrates that two attempts at ablation of proliferative verrucous leukoplakia using a CO_2 laser (10.6 μm wavelength) had no short- or long-term benefit. Patients with PVL should receive periodontal maintenance therapy and re-evaluation at short intervals with a focus on periodontal status, caries incidence, and biopsy of mucosal lesions that exhibit a change in presentation from that of previous appointments. There is no definitive etiology or treatment for PVL. Consequently, patients require frequent clinical evaluation and biopsy for early detection of transformation into a more sinister lesion, such as oral verrucous or SCCA.

AUTHOR CONTRIBUTIONS

All authors contributed to the review, editing, and revision of the manuscript. The authors, Charles M. Cobb, Nabil E. Beaini, and Jessica Scully were involved in patient treatment at various times over the 11-year period. Tanya M. Gibson was the oral and maxillofacial pathologist responsible for the histologic diagnosis and procurement of photomicrographs.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request to the corresponding author.

ORCID

Charles M. Cobb https://orcid.org/0000-0003-0844-2738
Nabil E. Beaini https://orcid.org/0009-0000-4064-7915
Jessica Scully https://orcid.org/0009-0002-2445-2207
Tanya M. Gibson https://orcid.org/0009-0001-3241-6794

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How to cite this article: Cobb CM, Beaini NE, Scully J, Gibson TM. Proliferative verrucous leukoplakia: Case study of 24 years and outcome of treatment with CO_2 laser. *Clin Adv Periodontics*. 2024;1-8. https://doi.org/10.1002/cap.10320