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Proliferative Verrucous Leukoplakia Progressing to Squamous Cell Carcinoma: A Case Report

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Proliferative Verrucous Leukoplakia Progressing to Squamous Cell Carcinoma: A Case Report

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Abstract

Proliferative verrucous leukoplakia (PVL) is an uncommon type of oral leukoplakia characterized by white patches featuring verrucoid areas. It is a condition of idiopathic origin, displaying a strong tendency of transforming into squamous cell carcinoma, verrucous carcinoma, or the newly described barnaculate carcinoma. PVL is more commonly found in elderly women who have had leukoplakic lesions for many years. Although PVL may be found virtually anywhere in the oral cavity, the buccal mucosa, gingiva, and tongue are the most-common sites. In this case we describe a lesion of this nature found in an elderly male patient. PVL is difficult to control over time as areas become more exophytic, wartlike, and apparently resistant to all forms of therapy. Recurrence is frequently observed. Notably, a higher incidence of recurrence and malignant transformation has been recorded with lesions involving the gingiva.

Methods and results: A 72-year-old Caucasian male patient presented with widespread, white patches on his maxillary alveolar gingiva without presence of any risk factors for oral squamous cell carcinoma. The initial biopsy specimen exhibited a markedly thickened layer of epithelium with hyper-orthokeratosis, micropapillary surface architecture, basilar hyperplasia, and epithelial rete ridges that varied from abbreviated to elongated. The histology and clinical features were highly suggestive of PVL. Three months later, a subsequent biopsy in the same region showed areas of invasive squamous cell carcinoma. Partial maxillectomy was performed and the patient was provided with a maxillary obturator.

Conclusions: PVL is a relentless condition with a high rate of malignant transformation. Early detection and treatment, which may include surgical resection, are of utmost importance. After treatment of PVL, patients must be monitored closely and regularly, and any suspicious lesions should be biopsied to check for potential early cancer development.

Keywords: Oral leukoplakia; biopsy; oral cancer; verrucous carcinoma; squamous cell carcinoma.

White lesions are frequent in the oral cavity, with a prevalence rate of approximately 24.8%, with 0.2 to 3.6% of these being classified as oral leukoplakia.[1,21]

Proliferative verrucous leukoplakia (PVL) is a distinct and less-common form of oral leukoplakia notable for a high recurrence and malignant transformation rates.[2,19,23] PVL is an uncommon type of oral leukoplakia frequently characterized by white patches featuring verrucoid areas. PVL may also have homogenous/fissured and erythroplakic components without the verrucoid component. Considering this varied appearance, Villa et al. suggested changing the name proliferative verrucous leukoplakia to simply proliferative leukoplakia.[3]

The World Health Organization (WHO) initially defined leukoplakia as a "precancerous lesion." Later, the 2005 workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the United Kingdom proposed changing the term "precancerous lesion" to "potentially malignant disorders," which is defined as a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer."[4] This change in nomenclature shows that not all lesions described under this term will transform into cancer.[4]

PVL most frequently affects females, especially at the age of 55-70 years old, with an average age at diagnosis of 63.9 years.[5] Typically, PVL

does not show a racial predilection, and it is not associated with the traditional risk factors for oral squamous cell carcinoma (OSCC).[6,27] It is important to emphasize that tobacco use has not been directly associated with PVL. The initial lesion usually presents clinically as hyperkeratosis without significant dysplasia and with low mitotic activity when examined microscopically. Over time, the white lesions may slowly grow and progress into persistent, multifocal lesions.[6]

PVL usually begins as a single leukoplakic lesion that then spreads and becomes multifocal. The lesions are slow-growing, persistent, progressive, and irreversible. The presence of wartlike and exophytic areas may represent transformation into verrucous carcinoma and/or squamous cell carcinoma, which supports the indication for an incisional biopsy to rule out a malignant transformation.[19] In this scenario, early biopsy and more extensive treatment, including lesion ablation, are of utmost importance for a successful case management. Long-term follow up, including photographic documentation to detect any clinical changes, is crucial to monitor lesion progression even after wide surgical excision is performed. Here we present a case of a male patient with significant clinical and histopathological signs of PVL that progressed to OSCC.

MATERIAL AND METHODS

Clinical presentation

A 72-year-old Caucasian male patient was referred by his private practice periodontist to the Oral Medicine Clinic at the University of Michigan School of Dentistry for evaluation of gingival leukoplakia suspicious for proliferative verrucous leukoplakia.

The patient has had asymptomatic white lesions since 2018. He reported no allergies, no history of tobacco use, occasional consumption of alcoholic beverages, and no significant

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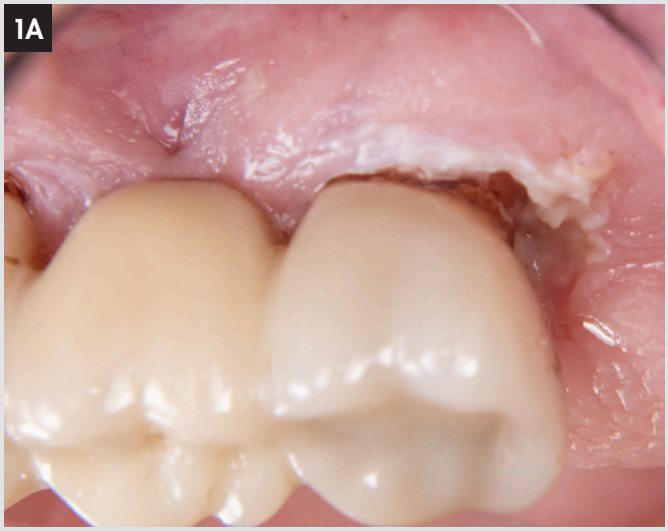
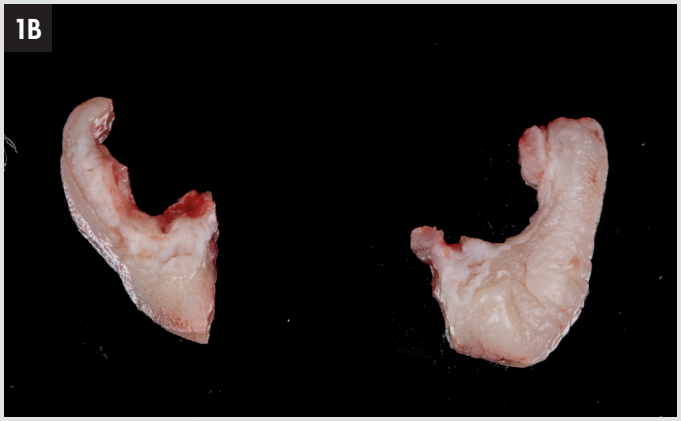
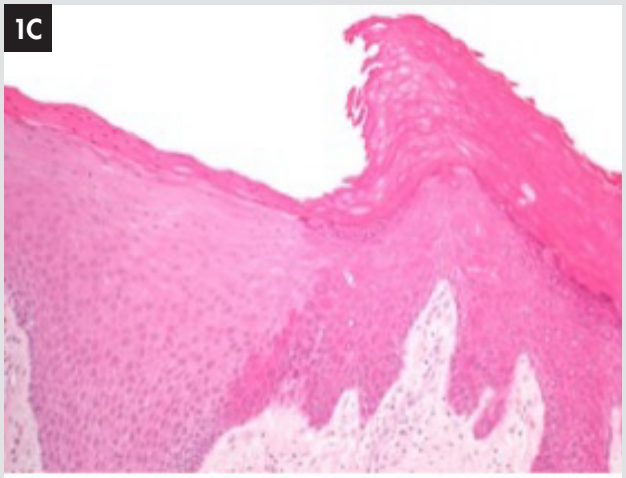
Figure 1



Clinical presentation before the second biopsy procedure. Leukoplakia with verrucoid appearance on the marginal gingiva of tooth #2 (distal surface).



Excised tissue sectioned for histological and DIF analysis.



Representative microscopic image showing an abrupt transition from parakeratinized to hyperorthokeratinized stratified squamous epithelium with a verrucoid surface.

Squamous Cell Carcinoma

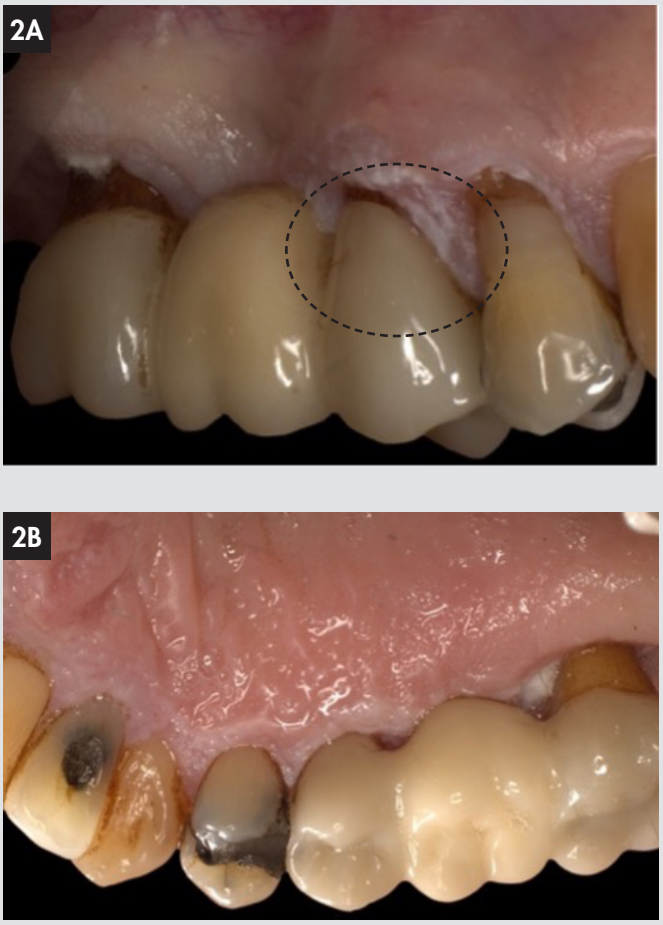
(Continued from Page 49)

medical history. His only current medication was daily 81 mg aspirin.

The referring periodontist completed an initial incisional biopsy of the marginal gingival distal to the maxillary right second molar, which was described as "white with a rough irregular surface." The biopsy revealed epithelial changes (hyperkeratosis and a micropapillary surface architecture), which did not meet the criteria for epithelial dysplasia, but raised suspicion for PVL.

The patient was seen in the University of Michigan Graduate Periodontics and Oral Medicine Clinic in February of 2022. Clinical examination revealed white plaque-like lesions in the maxillary gingiva bilaterally, with a more-pronounced presentation on the right posterior gingiva. One month later, during a follow-up appointment, a decision was made to order a second biopsy based on the irregular and wart-like (verrucoid) appearance of the leukoplakic areas. The second incisional biopsy, with borders extending further to the buccal and palatal of the maxillary right second molar, was performed in March of 2022. The excised tissue was divided into two parts; the palatal section was placed in formalin for routine histological analysis, and the buccal section was placed in Michel's solution for direct immunofluorescence (DIF) studies (Fig. 1A-C). DIF was considered to rule out a potential autoimmune condition considering the multifocal and progressive clinical presentation of this case.

Figure 2 — Clinical presentation before the third surgical procedure. Leukoplakic lesions featuring verrucoid surface and areas of erythroleukoplakia (black circle) on the marginal and attached gingiva (buccal and palatal views).



Microscopic examination revealed a specimen surfaced by hyperorthokeratinized stratified squamous epithelium with a prominent granular layer and mild verrucoid surface showing an abrupt transition to hyperparakeratinizing stratified squamous epithelium (Fig. 1C). The overall maturation of the epithelium was within the range of normal. The underlying variably dense fibrocollagenous connective tissue showed blood vessels, nerve twigs, and scattered chronic inflammatory infiltrates. The abrupt transition from orthokeratinized to parakeratinized epithelium and a verrucoid surface seen focally were features suggestive of proliferative verrucous leukoplakia. The immune deposition pattern seen in the DIF specimen was nonspecific. Based on the clinico-pathologic findings, the patient was placed in a regular monthly follow-up protocol.

In June 2022, three months after the second biopsy procedure, there were changes in the clinical appearance of the leukoplakic lesions in the region of teeth #2-#6, featuring an irregular/verrucoid surface and focal areas of erythema/erythroplakia (Fig. 2). This clinical presentation supported the decision to perform an excisional biopsy with broader margins in the form of gingivectomy.

RESULTS/CASE MANAGEMENT

Surgical procedure

After written and oral consent was obtained for the gingivectomy procedure, the patient rinsed with a 3% hydrogen peroxide rinse for 60 seconds for pre-procedural oral disinfection. Lidocaine with epinephrine was administered for regional block local anesthesia and hemostasis of the maxillary right quadrant. Gingivectomy was performed using gingivectomy knives** (Fig. 3 A, B, C) to excise all white lesions in the maxillary right posterior quadrant, from the tuberosity to the maxillary right canine buccally and palatally, with the border of at least 2 mm of normal tissue, leaving a thin layer of connective tissue overlying the periosteum. Electrocautery## was used to control the bleeding at the end of the surgical procedure (Fig. 3D). A surgical dressing∝∝ was placed, and post-operative instructions were given to the patient regarding oral hygiene and pain control. The patient was instructed to take three tablets of ibuprofen 200 mg every six hours for three days to prevent pain, and as needed thereafter.

Microscopic findings

The gingivectomy specimen was placed on a flat, sterile piece of paper to facilitate histological orientation, and a ballpoint pen was used to map the mesial, distal, buccal, and lingual sides (Fig. 4 A, B, see Page 52) prior to placing it in formalin. The fixed specimen was inked and sectioned in four separate fragments for histological processing. Microscopic examination revealed a malignant neoplastic proliferation of surface epithelial origin. The focal neoplastic epithelial proliferation exhibits small tumor islands with increased nuclear to cytoplas-

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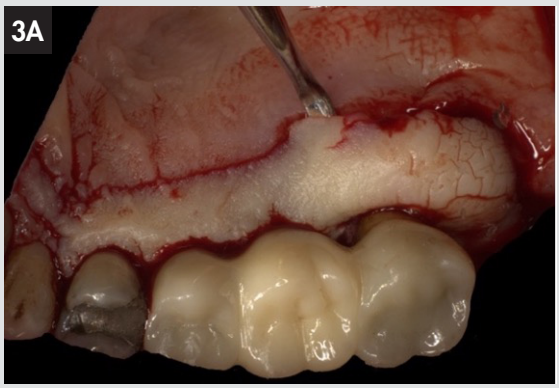
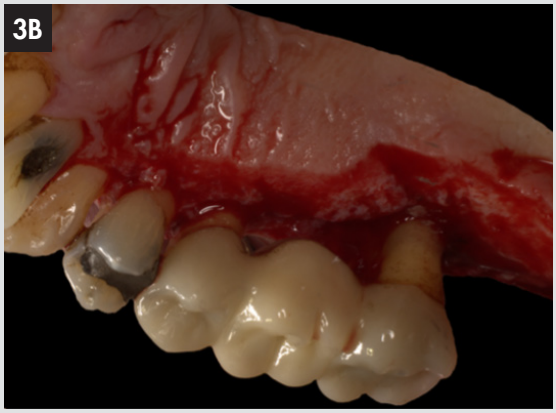
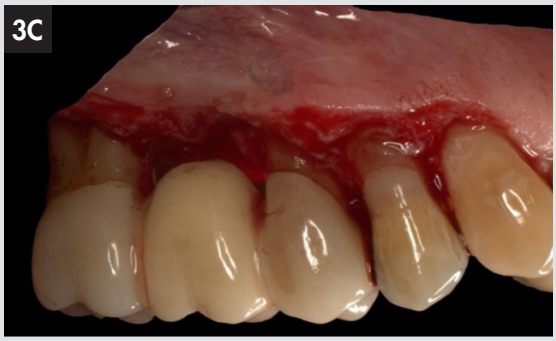
Figure 3 — Gingivectomy/biopsy.



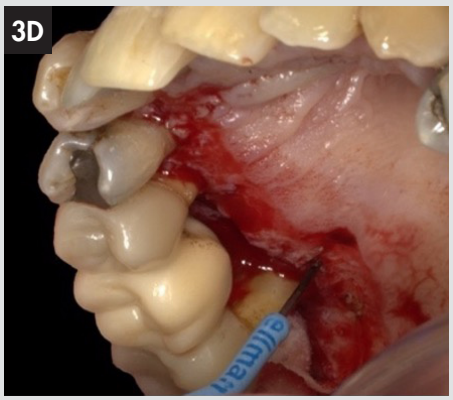
Maxillary right palatal gingiva. Slot surgical knife used.



Palatal side.



Buccal side after gingivectomy.



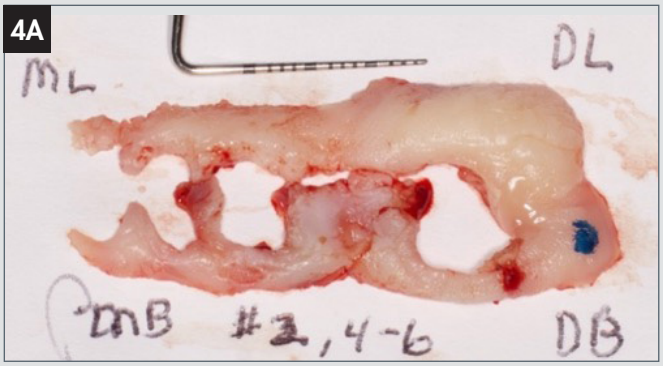
Palatal side, coagulation for bleeding control.

**Solt ½, Orban ½; Hu Friedy, Chicago, Ill.

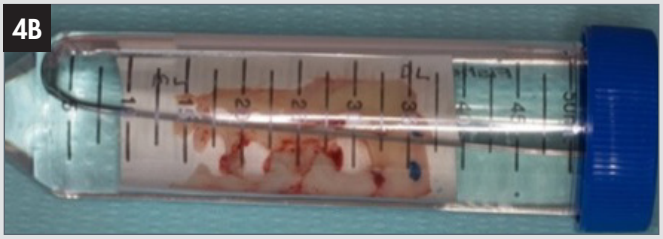
##Surgitron, Ellman International, Inc., Hicksville, N.Y.

∝∝ Coe Pak, GC America Inc., Alsip, Ill.

Figure 4

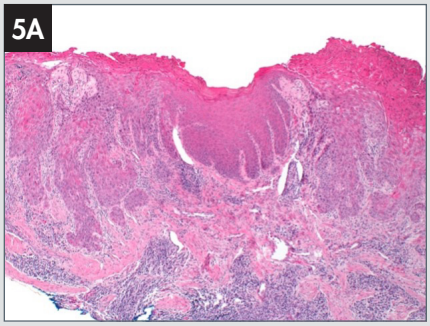


4A Fragment of the excised maxillary right gingiva, palatal, and buccal side with mapping details;

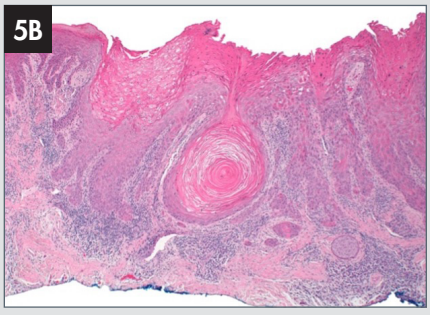


4B Sample placed in formalin for fixation.

Figure 5 — Microscopic analysis of the third biopsy procedure.



5A Hematoxylin and eosin-stained slides (at 40x magnification) showing downwardly directed rete peg projections of the surface epithelium featuring areas of invasion into the adjacent connective tissue.



5B Focal areas of deep keratinization supporting the diagnosis of squamous cell carcimona.

Squamous Cell Carcinoma

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mic ratio and nuclear pleomorphism near the advancing front, featuring proliferative and bulbous rete ridges that extend into the underlying connective tissue. The adjacent stratified squamous epithelium was papillary, severely hyperkeratotic, acanthotic, and featuring broad rete ridges. The underlying fibrovascular connective tissue showed foci of chronic inflammatory cells and aggregates of multinucleated giant cells. A Periodic acid-Schiff (PAS) special stain was negative for fungal organisms (Fig. 5A, B). The final diagnosis was made of well-differentiated squamous cell carcinoma. According to the mapping of the specimen, it was possible to identify the area of malignant transformation correspondent to the buccal aspect of tooth #4, where verrucous and erythroleukoplakic areas were observed clinically (Fig. 2). The histopathologic findings of the entire specimen when combined with the clinical presentation were consistent with a background of proliferative verrucous leukoplakia.

Follow-up

At the two-week post-operative visit healing was within normal limits (Fig. 6). The periodontal dressing was removed. The patient's reported pain level was 3-4 on the scale from 1 to 10. A new periodontal dressing was applied to decrease discomfort. At the four-week post-operative visit, the dressing was removed. The patient was referred to the University of Michigan Oral and Maxillofacial Surgery and Hospital Dentistry Department for further treatment. A staff oral surgeon performed a right hemi maxillectomy to remove all potential dysplastic cells and a dentist trained in maxillofacial prosthetics fabricated a maxillary obturator for the patient (Fig. 7, see Page

54). Follow-up is scheduled every four months with the oral surgeon and oncologist. Biopsy is planned for the left maxillary gingiva to rule out any neoplastic changes in the area.

DISCUSSION

The etiology of PVL remains poorly understood. According to Bagan et al. 2010,[6] none of the meta-analyses published to date have established the possible role of microbiological agents (Candida albicans, human papilloma virus HPV, Epstein Barr virus EBV) in the pathogenesis of PVL.[6,25,26] Silverman et al. reported 68% of PVL patients were positive for Candida albicans but did not find that fungal infection was linked to PVL occurrence or progression to carcinoma.[8] In their meta-analysis, Cabay et al. found only 37% of patients with PVL reported a history of tobacco use.[7,17] Also, existing literature has shown no correlation between the immunodeficiency disorders and PVL.[1] Kresty et al. were the first to report that the cell cycle regulatory genes p16INK4a and p14ARF are frequently altered in PVL.[11] Irrespective of its causation, the malignant transformation rate of PVL is high, affecting 48% to 71.2% of patients.[2,13,14,16] The reported mortality rate may be as high as 40%.[10]

A recent systematic review and meta-analysis by Palaia et al. reinforced that PVL is an aggressive lesion that undergoes malignant transformation in almost 50% of cases, mainly to squamous cell carcinoma.[2,27] Over a year's time, up to 10% of PVLs may undergo such MT.[25] Elderly women are more often diagnosed than men, and usually have a negative history of alcohol and tobacco consumption.[2]

Several classifications have been proposed for PVL lesions.[18,20,22,24] In 1985, Hansen et al. distinguished 10 grades of PVL. Grades 1 to 3 consist of a simple hyperkeratosis with or without dysplasia; Grades 3 to 5 represent verrucous hyperplasia; Grades 5 to 7

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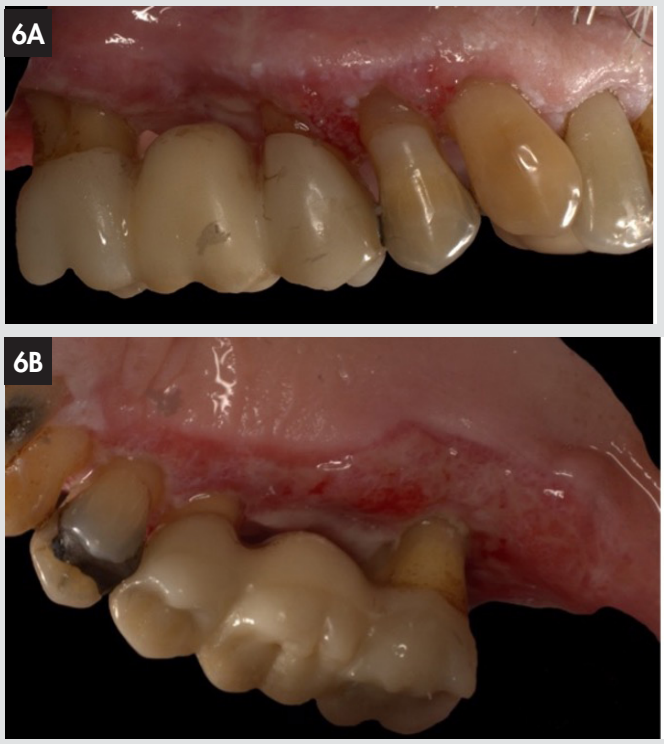
Key Points

Why is this case new information?
This case demonstrates that the clinical appearance of proliferative verrucous leukoplakia (PVL) does not always correspond with the histopathological outcome and analysis. Prompt biopsy is required for any suspicious lesions.

What are the keys to successful management of this case?
- Early clinical diagnosis and biopsy are necessary to confirm PVL.
- Once PVL is diagnosed, the patient receives regular follow-up visits to monitor for any change in the lesions, and an additional biopsy with wider margins is performed as soon as change is detected. In this case, the gingiva of the right maxillary tuberosity and marginal gingiva became intensely white with focal areas of erythroplakia/erosion.
- When squamous cell carcinoma was detected within an area of PVL, the patient was promptly referred to OMFS, who performed hemi-maxillectomy and arranged for a maxillofacial prosthetics-trained dentist to construct an obturator for the patient.

What are the primary limitations to success in this case?
PVL has a high rate of transformation to squamous cell carcinoma. Failure to monitor patients for recurrent lesions may lead to unfavorable outcomes.

Figure 6 — Two weeks follow-up after gingivectomy.



Squamous Cell Carcinoma

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represent verrucous carcinoma; Grades 7 to 9 represent papillary squamous cell carcinoma; and Grade 10 represents less differentiated squamous carcinoma.[9]

In 1999 Batsakis et al. reduced the number of stages to four: clinical flat leukoplakia without dysplasia, verrucous hyperplasia, verrucous carcinoma, and squamous cell carcinoma.[1]

In a recent expert consensus guideline for standardized assessment and reporting of PVL, Thompson et al. recognized four histological categories of PVL, which include corrugated ortho(para) hyperkeratotic lesion, bulky hyperkeratotic epithelial proliferation, squamous cell carcinoma, and any lesion that does not fit any other category.[12] This classification of PVL lesions is based on a combination of clinical findings and histologic description, which helps guide clinical management, standardize reporting, and aid in future research.[12]

The clinico-pathologic spectrum of PVL may vary. According to Thompson et al.,[12] not all lesions are warty or verrucoid; however, warty or verrucoid lesions have a high risk for malignant transformation to several types of carcinomas (e.g., squamous cell carcinoma, verrucous carcinoma, and barnaculate carcinoma)[12] (Fig. 8). Following transformation to squamous cell carcinoma the patient death rate has been reported as high as 40%.[10]

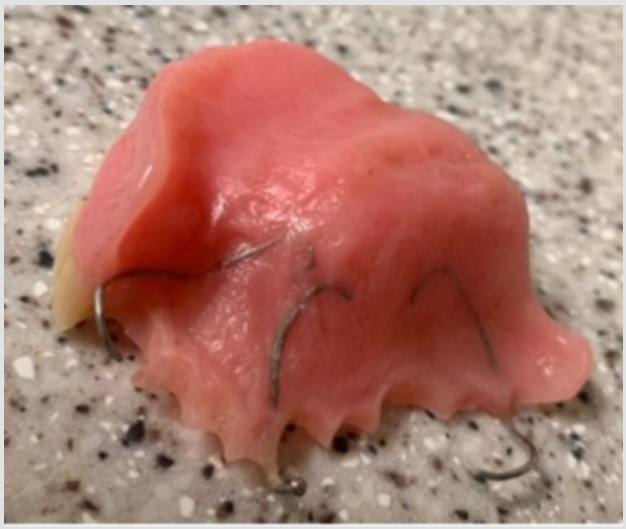
To date, there is no effective, standardized treatment protocol for proliferative verrucous leukoplakia; however, multiple treatment approaches have been proposed in the literature. Regardless of the chosen treatment, the recurrence rate remains high. Schoelch et al. reported on the use of lasers, including CO^2 and Nd: YAG (neodymium-doped yttrium aluminum garnet); however, the recurrence rate was still high at 83%.[15] Bagan et al. also reported a similar recurrence rate of 86.7% after treatment with CO^2 laser and or/scalpel surgery.[6]

PVL lesions are usually painless, and their appearance is not suggestive of a high rate of malignancy. They are often misdiagnosed.[23] This is especially true for a solitary lesion or those not exhibiting dysplasia microscopically. They may also be confused with frictional keratosis lesions or conventional leukoplakia. Misdiagnosis may lead to delays in appropriate treatment.

In the present case, the white lesions were diagnosed as PVL, but clinically they were not indicative of squamous cell carcinoma. However, the clinical evolution of the lesions in a relatively short period of time and the presence of intensely white verrucoid areas combined with erythroleukoplakia warranted additional biopsy. This revealed an early-stage squamous cell carcinoma. The patient was referred for definitive multi-disciplinary treatment to the University of Michigan Medicine departments of Oral and Maxillofacial Surgery, Oncology, and Hospital Dentistry for partial maxillectomy, fabrication of an oral obturator by a maxillofacial prosthodontics-trained dentist and follow-up care for OSCC. The obturator restores the patient's lost maxillofacial contours, oral structures, and function (including speaking, swallowing, and mastication), as well as esthetics.

Regular follow-up is absolutely mandatary to detect any potential new cancer or a recurrence at the previous site of the disease. According to Hansen et al., the permanent elimination of the PVL is not possible, as the disease recurs after a few months regardless of the treatment option.[9] In patients with multifocal lesions, the prognosis is poor as it is extremely difficult to remove all the involved sites that may approach vital structures.[19] In addition, the heterogeneous clinical presentation may complicate early diagnosis of malignant transformation. When diagnosed in the late stage, PVL-

Figure 7 — Maxillary interim obturator. The prosthesis device allows the patient function after the surgical hemisection surgery.



associated malignancy is often advanced and refractory to treatment.

Conclusions

This well-documented case demonstrates that the apparent benign clinical appearance of proliferative verrucous leukoplakia does not always correlate with the microscopic features. For this reason, a close follow-up and incisional biopsy of any suspicious lesion is crucial to rule out early malignant transformation. This case highlights the importance of a multidisciplinary approach to manage cases of PVL that transform to cancer. ●

References

1. Batsakis JG, Suarez P, El-Naggar AK. Proliferative verrucous leukoplakia and its related lesions. Oral Oncol 1999;35:354–359.

2. Palaia G, Bellisario A, Pampena R et al. Oral proliferative verrucous leukoplakia: progression to malignancy and clinical implications. Systematic review and meta-analysis. Cancers (Basel) 2021;13;13(16):4085.

3. Villa A, Menon RS, Kerr AR, De Abreu Alves F, Guollo A, Ojeda D, Woo SB. Proliferative leukoplakia: proposed new clinical diagnostic criteria. Oral Dis 2018 Jul;24(5):749-760.

4. Axell T. Occurrence of leukoplakia and some other oral white lesions among 20,333 adult Swedish people. Community Dent Oral Epidemiol 1987;15:46–51.

5. Schepman KP, Van der Meij EH, Smeele LE, Van der Waal I. Prevalence study of oral white lesions with special reference to a new definition of oral leucoplakia. Eur J Cancer B Oral Oncol 1996;32(B)6:416-9.

6. Bagan J, Scully C, Jimenez Y, Martorell M. Proliferative verrucous leukoplakia: a concise update. Oral Dis 2010;16(4):328-32.

7. Cabay RJ, Morton TH Jr, Epstein JB. Proliferative verrucous leukoplakia, and its progression to oral carcinoma: a review of the literature. J Oral Pathol Med 2007;36(5):255-61.

8. Silverman S Jr, Gorsky M. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:154-7.

9. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol 1985;60:285-98.

10. Abadie WM, Partington EJ, Fowler CB et al. Optimal management of proliferative verrucous leukoplakia: a systematic review of the literature. Otolaryngol Head Neck Surg 2015;153(4):504–511

11. Kresty LA, Mallery SR, Knobloch TJ et al. Frequent alterations of p16INK4a and p14ARF in oral proliferative verrucous leukoplakia. Cancer Epidemiol Biomarkers Prev 2008;17(11):3179-87.

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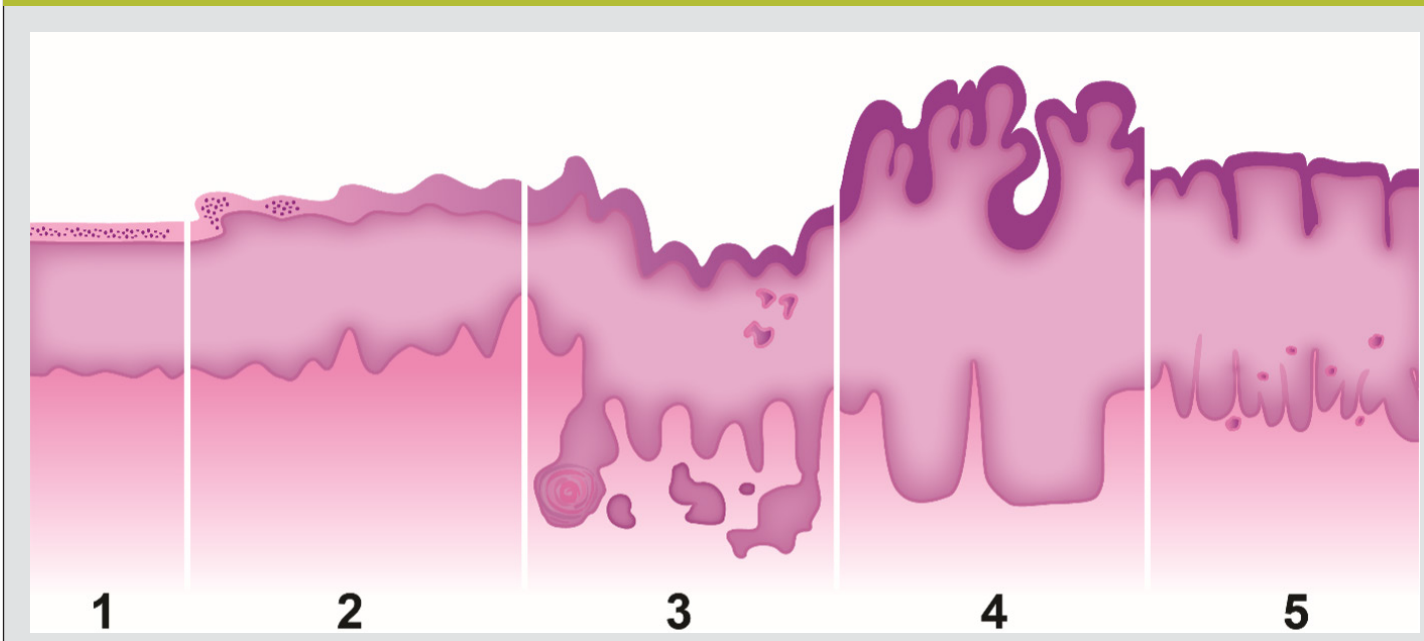
Figure 8 — Schematic drawing summarizing the main histological features of proliferative verrucous leukoplakia and the spectrum of malignant transformation. At early stages, the normal adjacent mucosa (1) becomes hyperkeratotic, featuring an abrupt transition from parakeratinized (dots represent the cells that characterized this type of keratinization) to orthokeratinized epithelium (no dots or cells) along with a verrucoid surface (2). The three most-common types of cancer arising in the setting of PVL are squamous cell carcinoma (3), verrucous carcinoma (4), and the newly described barnaculate carcinoma (5).



Squamous Cell Carcinoma

(Continued from Page 55)

12. Thompson LDR et al. Proliferative verrucous leukoplakia: an expert consensus guideline for standardized assessment and reporting. Head Neck Pathol 2021;15(2):572-587.

13. Villa A, Woo SB. Leukoplakia — a diagnostic and management algorithm. J Oral Maxillofac Surg 2017 Apr;75(4):723-734.

14. Borgna SC, Clarke PT, Schache AG, Lowe D, Ho MW, McCarthy CE, Adair S, Field EA, Field JK, Holt D, Risk JM, Rajlawat BP, Triantafyllou A, Shaw RJ. Management of proliferative verrucous leukoplakia: justification for a conservative approach. Head Neck 2017;39(10):1997-2003.

15. Schoelch ML, Sekandari N, Regezi JA et al. Laser management of oral leukoplakia: a follow-up study of 70 patients. Laryngoscope 1999;109:949–953.

16. Bagan JV, Jimenez Y, Sanchis JM et al. Proliferative verrucous leukoplakia: high incidence of gingival squamous cell carcinoma. J Oral Pathol Med 2003;32:379–382.

17. Ghazali N, M.M. Bakri, R.B. Zain Aggressive, multifocal oral verrucous leukoplakia: proliferative verrucous leukoplakia or not. J Oral Pathol Med 2003;32(7):383-92.

18. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007;36(10):575-80.

19. Bagan JV, Murillo J, Poveda R, et al. Proliferative verrucous leukoplakia: unusual locations of oral squamous cell carcinomas, and field cancerization as shown by the appearance of multiple OSCCs. Oral Oncol 2004;40(4):440–3.

20. Celentano A, Glurich I, Borgnakke WS, Farah CS. World Workshop on Oral Medicine VII: Prognostic biomarkers in oral leukoplakia and proliferative verrucous leukoplakia — A systematic review of retrospective studies. Oral Dis 2021;27(4):848-880.

21. Villa A, Celentano A, Glurich I, Borgnakke WS, Jensen SB, Peterson DE, Delli K, Ojeda D, Vissink A, Farah CS. World Workshop on Oral Medicine VII: Prognostic biomarkers in oral leukoplakia: a systematic review of longitudinal studies. Oral Dis 2019;25(1):64-78.

22. Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization Classification of Tumours. Pathology and genetics of head and neck tumours. Lyon: IARC Press;2005:180.

23. Gupta RK, Rani N, Joshi B. Proliferative verrucous leukoplakia misdiagnosed as oral leukoplakia. J Indian Soc Periodontol 2017;21(6):499-502.

24. Villa A, Menon RS, Kerr AR, De Abreu Alves F, Guollo A, Ojeda D, Woo SB. Proliferative leukoplakia: Proposed new clinical diagnostic criteria. Oral Dis 2018 Jul;24(5):749-760.

25. Bagan J, Jiménez Y, Murillo J, et al. Epstein-Barr virus in oral proliferative verrucous leukoplakia and squamous cell carcinoma: a preliminary study. Med Oral Patol Oral Cir Bucal 2008;13(2):E110-3.

26. Palefsky JM, Silverman S Jr, Abdel-Salaam M. et al. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. J Oral Pathol Med 1995;24(5):193-7.

27. Gouvêa AF, Santos Silva AR, Speight PM, Hunter K, Carlos R, Vargas PA, de Almeida OP, Lopes MA. High incidence of DNA ploidy abnormalities and increased Mcm2 expression may predict malignant change in oral proliferative verrucous leukoplakia. Histopathology 2013;62(4):551-62.

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