



A Case of Proliferative Verrucous Leukoplakia With Insidious Transformation Into Oral Verrucous Carcinoma

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Proliferative verrucous leukoplakia (PVL) is a rare and aggressive subtype of oral leukoplakia characterized by multifocal progression, frequent recurrence, and a high risk of malignant transformation. Diagnosis is often delayed due to non-linear clinical course and evolving histopathologic features. We report a case of PVL-associated verrucous carcinoma in a 68-year-old non-smoking woman. The lesion initially presented as a localized elevated plaque on the left buccal mucosa and was diagnosed as squamous papilloma. Over a 6-year period, it progressively expanded with prominent verrucous changes, and repeated biopsies showed variable histologic findings. Wide transoral excision was performed, and the final pathology revealed verrucous carcinoma with a pushing growth pattern without cytologic pleomorphism or infiltrative invasion, which is consistent with the malignant transformation of long-standing PVL. This case highlights the diagnostic challenges of PVL and underscores the importance of prioritizing clinical suspicion over isolated histologic findings.

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Introduction

Proliferative verrucous leukoplakia (PVL) is a rare and distinct subtype of oral leukoplakia, first described by Hansen et al. in 1985. Clinically, PVL is characterized by slow progression and extensive, multifocal involvement.^{1,2)} It initially presents as a simple white keratotic lesion. Over time, however, the lesion gradually enlarges and may demonstrate a broad morphologic spectrum, from a flat plaque to papillary or verrucous forms.^{3,4)} This progressive spread and morphological heterogeneity are key features that distinguish PVL

from other oral premalignant lesions.

Clinically, PVL predominantly occurs in elderly women with a long-standing history of oral leukoplakia. It has also been reported to have no significant association with smoking or alcohol consumption.⁵⁾ Other proposed contributing factors include chronic irritation, viral infections such as Human Papillomavirus (HPV) and Epstein-Barr virus (EBV), *Candida* infection, specific oncogenes, and genetic and immunologic factors. However, no single etiologic factor adequately explains its pathogenesis, and a multifactorial mechanism is presumed to be involved.^{1,2)}

PVL frequently recurs after treatment and has a markedly higher rate of malignant transformation than conventional oral leukoplakia, with reported rates of approximately 40%–70%.^{2,6)}

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The World Health Organization (WHO) defines PVL as a clinicopathologic subtype of oral leukoplakia characterized by a multifocal, persistent, and progressive course, frequent recurrence, and a high risk of progression to squamous cell carcinoma. It is also regarded as an independent and aggressive oral potentially malignant disorder.^{7,8)} Malignant transformation in PVL occurs over several years and is resistant to various treatments, a phenomenon that has been interpreted as related to field cancerization across the oral mucosa.⁹⁾

Herein, we report a case of oral verrucous carcinoma arising from PVL in a patient whose lesion had initially been diagnosed as squamous papilloma on incisional biopsy 7 years earlier. Over time, the lesion gradually expanded and became symptomatic, and a repeat biopsy performed in 2025 suggested malignant transformation. The patient subsequently underwent surgical treatment, and the final diagnosis was verrucous carcinoma arising from long-standing PVL. We present this case along with a review of the relevant literature. This retrospective case report was approved by the Institutional Review Board of Catholic Kwandong University International St. Mary's Hospital (NON2026-001), and the requirement for informed consent was waived owing to the retrospective nature of the study.

Case

A 68-year-old woman with no significant medical history and no history of smoking or alcohol consumption presented in April 2019 with a painless lesion on her left buccal mucosa. Physical examination revealed a broad, elevated mucosal lesion involving most of the buccal mucosa anterior to the left retromolar trigone. The lesion demonstrated focal leukoplakic change without tenderness (Fig. 1). An incisional biopsy

of the lesion revealed squamous papilloma. Immunohistochemical staining for p16 was negative, with no evidence suggestive of high-risk HPV association. The patient was subsequently lost to follow-up for several years.

The patient returned in July 2023, presenting with paresthesia around the lesion. Compared with the findings in 2019, the lesion had become more irregular in shape and showed prominent verrucous exophytic growth. A repeat incisional biopsy was performed. Histologic examination revealed prominent epithelial hyperplasia, but no definitive evidence of malignancy was identified (Fig. 2). Because the possibility of malignancy could not be entirely excluded, complete excision of the lesion was recommended. However, the patient declined surgery and was once again lost to follow-up.

In April 2025, the patient returned because the lesion had rapidly increased in extent, extended to the mandibular gingiva, and was accompanied by pain (Fig. 3). Biopsies were performed at multiple sites, including the buccal and gingival areas. Compared with the previous histologic findings, the biopsies revealed features suggestive of possible progression to verrucous carcinoma. Neck computed tomography and positron emission tomography showed no evidence of cervical lymph node or distant metastasis. Neck magnetic resonance imaging showed diffuse thickening of the soft tissue in the left buccal area but no invasion into the deep buccal space.

On June 26, 2025, a transoral wide excision was performed. A 1 cm safety margin was secured around the grossly visible lesion, which was excised to approximately half the depth of the buccalis muscle. The lesion, including the portion extending to the mandibular gingiva, was removed en bloc. The interdental mucosa was curetted, and a frozen section examination confirmed the absence of cancer cells. Further frozen section examinations were performed on a total of eight mar-

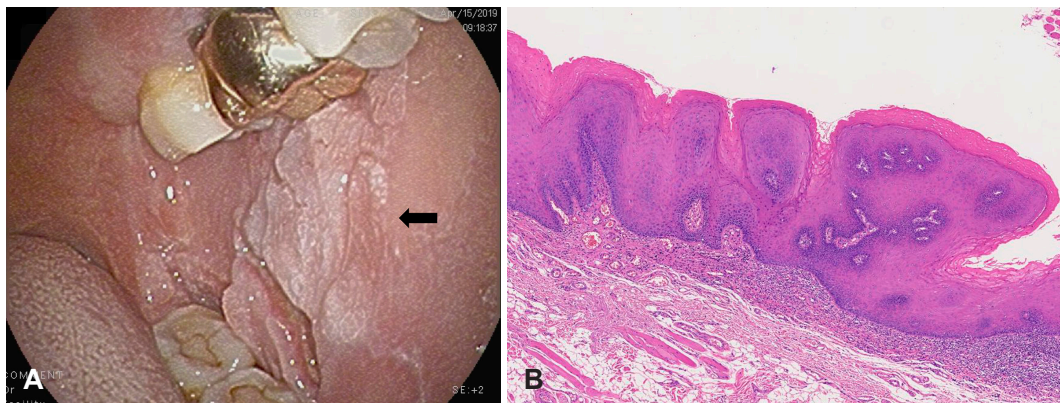


Fig. 1. Clinical and histopathologic findings of the initial lesion in 2019. A: Diffuse, non-tender, white plaque on the left buccal mucosa (arrow). B: Histopathologic examination showing mild epithelial hyperplasia with hyperkeratosis (H&E stain, ×40).

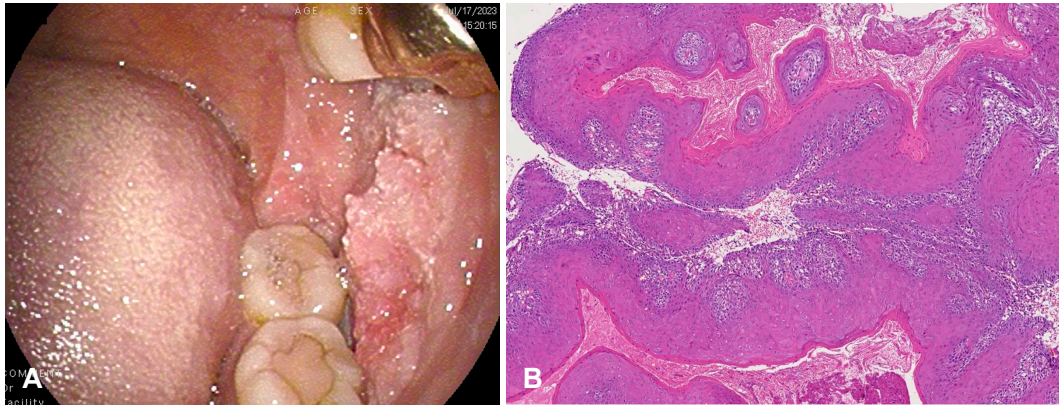


Fig. 2. Clinical and histopathologic findings of the aggravated lesion in 2023. A: Irregularly shaped, prominently verrucous, exophytic lesion involving the left buccal mucosa. B: Histopathologic examination showing marked epithelial hyperplasia with complex and convoluted rete ridges, without evidence of stromal invasion (H&E stain, ×40).

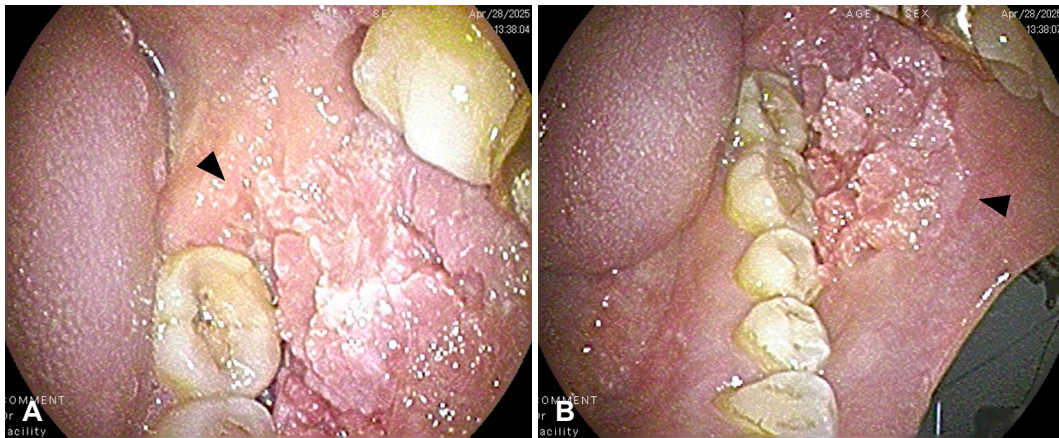


Fig. 3. Endoscopic images demonstrating rapid progression and extension of the lesion in 2025. A: Extension of the lesion to the mandibular gingiva (arrowhead). B: Further extension toward the labial mucosa near the oral commissure (arrowhead).



Fig. 4. Intraoperative and postoperative findings. A: Operative field after transoral wide excision of the left buccal lesion. Surgical bed demonstrating preservation of partial thickness of the buccalis muscle (arrow). B: Reconstruction of the defect using a full-thickness skin graft harvested from the thigh. C: Postoperative appearance at 2 months, showing a well-healed defect with complete re-epithelialization and graft take.

gins, including the deep margin, all of which were negative. The buccal defect was reconstructed with a full-thickness skin graft, measuring approximately 8×6 cm, harvested from the left thigh (Fig. 4).

Final histopathologic examination revealed a 3.1×2.3 cm lesion. No epithelial dysplasia was identified throughout the

lesion. Compared with the adjacent normal epithelium, the lesion demonstrated verrucous epithelial hyperplasia with hyperkeratosis. Consistent with the preoperative biopsy findings, broad bulbous rete ridges with pushing borders compressing the underlying connective tissue were clearly identified, supporting the diagnosis of verrucous carcinoma. These features

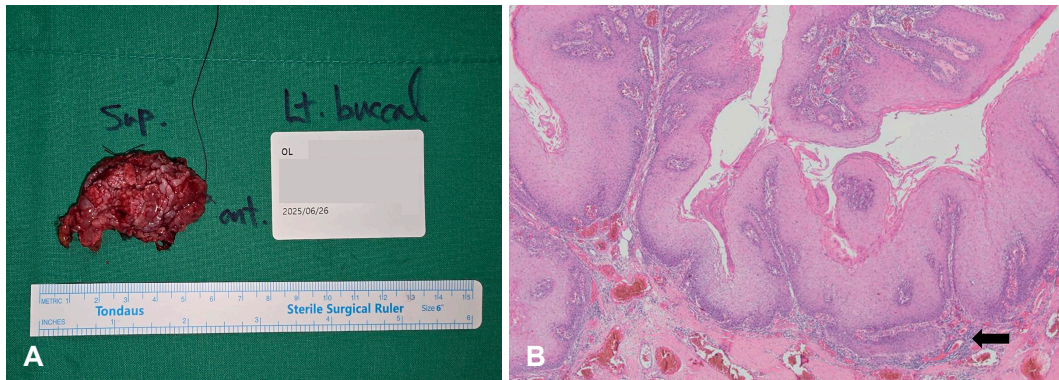


Fig. 5. Postoperative pathologic findings. A: Gross specimen obtained after wide excision. B: Histopathologic examination showing thick, club-shaped epithelial projections with complex architecture and broad, pushing bulbous rete ridges extending into the underlying connective tissue (arrow) (H&E stain, $\times 40$).

were absent in the 2019 and 2023 biopsy specimens. Comprehensive review of the previous biopsy slides and the surgical specimen suggested gradual downward progression of the hyperplastic epithelial lesion, distinct from simple verrucous hyperplasia. Based on the long-term clinical course and histopathologic progression, the lesion was ultimately diagnosed as verrucous carcinoma arising from PVL (Fig. 5). The lesion was excised with peripheral margins of 6–7 mm and a deep margin of 2 mm. The maximum pushing depth below the basement membrane was 1 mm. No infiltrative invasion, which is commonly observed in squamous cell carcinoma, was present, and no lymphovascular or perineural invasion was identified.

Postoperatively, oral intake was withheld until a soft diet was initiated on postoperative day 6, after which oral intake was gradually advanced. The patient was discharged on postoperative day 13 without significant complications after adequate pain control was achieved. Although the skin graft healed well, limitation of mouth opening developed due to graft-site contracture, requiring two adhesiolysis procedures in the outpatient clinic. The symptoms subsequently improved, and the patient remains under regular follow-up without evidence of recurrence at 8 months postoperatively.

Discussion

PVL is a subtype of oral leukoplakia with a distinctive clinical course. Its clinical and histopathologic findings are known to change over time, and it carries a high risk of malignant transformation.⁹ PVL initially presents as a slowly growing, simple keratotic lesion. After a prolonged period, however, the lesion gradually increases in extent and may progress to multifocal disease, with verrucous, exophytic, or erythema-

tous changes. Some cases may exhibit sudden rapid growth or malignant transformation.^{1,5} Because of this nonlinear clinical and histopathologic progression, PVL is difficult to diagnose based solely on a pathologic assessment at a single point in time. In many cases, the diagnosis is made retrospectively by integrating the long-term clinical course with findings from repeated histopathologic examinations.^{3,10}

The diagnosis of PVL remains challenging because its precise etiology and molecular pathogenesis have not yet been clarified, which limits the establishment of consistent criteria for interpreting pathologic findings.^{3,9} Since PVL was first recognized in 1985, various diagnostic criteria have been proposed. However, no internationally accepted uniform diagnostic criteria has been established to date. In this context, several diagnostic systems that integrate clinical and pathologic findings have been proposed, among which the criteria proposed by Cerero-Lapiedra, et al.¹¹ and Villa, et al.¹² are the most widely used worldwide.

The diagnostic criteria proposed by Cerero-Lapiedra, et al.¹¹ in 2010 include quantifiable indicators of the clinical course and pathologic features, facilitating clinical application and contributing to their widespread use. The major criteria include the presence of multiple oral lesions, enlargement and progression of the lesion over time, recurrence after treatment, and a characteristic pathologic spectrum ranging from simple hyperkeratosis to verrucous carcinoma and invasive squamous cell carcinoma. The minor criteria include a cumulative lesion size of 3 cm or greater, female sex, non-smoking status, and a disease duration of 5 years or longer. However, these criteria have limitations when applied to early-stage or solitary lesions. To address these limitations, Villa, et al.¹² proposed supplementary criteria in 2018. They recommended that a lesion be evaluated within the PVL spectrum, even

without a typical verrucous pattern, if it is a large solitary lesion (e.g., 4 cm or greater in diameter), continuously involves adjacent oral sites with a cumulative extent that exceeds a defined threshold, or shows persistent clinical progression or recurrence.¹²⁾ Additionally, because not all cases present with a verrucous pattern, they proposed the broader term “proliferative leukoplakia,” which has been adopted in many subsequent studies.^{12,13)} This approach appears consistent with the recent WHO classification, which defines PVL primarily by its clinical characteristics rather than by a specific pathologic morphology.⁸⁾

In the present case, the lesion developed in a female non-smoker and initially presented as a localized leukoplakic lesion. Over an approximately 6-year clinical course, it exhibited gradual enlargement and progression, and repeated biopsies demonstrated a pathologic spectrum demonstrating a histopathologic spectrum ranging from papillomatous change and epithelial hyperplasia to verrucous carcinoma. These findings correspond to the major Cerero-Lapiedra criteria of lesion progression and characteristic pathologic change, as well as the minor criteria of female sex, non-smoking status, a disease duration of more than 5 years, and a cumulative lesion size of 3 cm or greater. Even when applying the supplementary criteria of Villa, et al., the lesion can reasonably be interpreted as PVL, as it was a large, single entity that continuously involved adjacent sites and showed persistent clinical progression.^{11,12)} Furthermore, because PVL lesions can present with various morphologies, ranging from an initial leukoplakic lesion to an exophytic papillary one,⁵⁾ the initial diagnosis of squamous papilloma in this case can be interpreted as reflecting the early pathologic spectrum of PVL. This case highlights the limitations of relying on a single biopsy specimen for the diagnosis of PVL.

The high rate of malignant transformation in PVL has been consistently reported since early studies, and recent research suggests the risk of malignancy is approximately 8-fold higher than that of conventional oral leukoplakia.^{6,10)} No significant association has been identified with common risk factors such as smoking or alcohol consumption. Evidence regarding other factors, including HPV or EBV infection, graft-versus-host disease, and DNA ploidy, remains inconclusive.²⁾ More recently, it has been proposed that malignant transformation in PVL may be associated with dysregulation of the immune microenvironment, such as abnormal T-cell proliferation.¹⁴⁾

In PVL lesions, carcinoma is diagnosed when epithelial invasion through the basement membrane is observed or when

a pushing encroachment toward deep submucosal structures is present, as in this case. This structural growth pattern is a key pathologic finding in the diagnosis of verrucous carcinoma arising from PVL and distinguishes it from verrucous hyperplasia, in which epithelial proliferation remains confined to the epithelial layer.⁴⁾ Both verrucous carcinoma and squamous cell carcinoma arising from PVL reportedly differ from conventional oral squamous cell carcinoma, as cytologic pleomorphism and epithelial dysplasia are not prominent. Instead, architectural changes characterized by bulky pushing growth are the main features rather than cellular infiltration.^{2,4,9)} There is no consistent conclusion as to whether verrucous carcinoma or squamous cell carcinoma is the predominant form of malignant transformation in PVL, but the risk of verrucous carcinoma is reported to be significantly higher than in the general population.^{2,10)} In a 2015 study, Akrish, et al. suggested that PVL-associated carcinoma is clinically distinct from conventional oral squamous cell carcinoma because it is often detected at a relatively early stage, lymph node metastasis is rare, it occurs mainly in the gingiva and buccal mucosa, and it has a favorable 4-year survival rate of 100% despite a high recurrence rate.¹⁰⁾ However, a recent systematic review and meta-analysis reported that approximately 33.8% of patients died from disease progression. These findings should be interpreted in light of methodological limitations in the analyzed studies, including insufficient follow-up duration and limited survival data.²⁾

PVL is known to show a limited response to treatment over its long clinical course, making curative treatment difficult to achieve.¹⁵⁾ Various treatment modalities, including surgical excision, CO₂ laser cauterization, and radiation therapy, have been attempted, but no standard treatment has been established that can achieve durable control of disease progression or recurrence.^{1,2)} Accordingly, recent studies commonly identify prophylactic excision, regular follow-up at 3–6-month intervals, and repeated biopsies of clinically changed or newly developed lesions as key management strategies.^{2,6,10)} For PVL-associated carcinoma, early diagnosis and aggressive surgical excision are recommended as the main treatment approach, with the extent of resection and margin assessment considered important for preventing recurrence.²⁾

Cervical lymph node metastasis from oral verrucous carcinoma is reported to be very rare in most studies. A recent meta-analysis reported a cervical lymph node metastasis rate of 0% (95% confidence interval 0%–2.3%) for verrucous carcinoma without concomitant invasive carcinoma.¹⁶⁾ In clinical-

ly node-negative cases, elective neck dissection (END) has been reported not to improve survival, regardless of T stage.¹⁷⁾ In the present case, the pathologic findings were consistent with typical verrucous carcinoma without an infiltrative growth pattern, and preoperative imaging showed no findings suspicious for cervical lymph node metastasis. Therefore, END was not performed.

In summary, a realistic goal in managing PVL is not a cure but rather the early recognition and minimization of disease progression and malignant transformation.¹⁵⁾ Ensuring the patient's adequate understanding of this chronic course and the need for long-term management should also be considered an important component of treatment. The present case involves a verrucous carcinoma arising from typical PVL in a 68-year-old non-smoking woman, demonstrating long-term clinical and pathologic progression. It reflects disease characteristics distinct from those of conventional oral leukoplakia or squamous cell carcinoma and highlights the importance of early recognition of PVL in clinical practice. At the time of this case report, the postoperative follow-up period of 8 months was relatively short, which limits an adequate assessment of the long-term disease course, including recurrence. Given the limited treatment response and chronic clinical course of PVL, further studies on its pathophysiology and mechanisms of malignant transformation are warranted, along with the development of standardized long-term management strategies. In this context, we report this case with a review of the literature.

Supplementary Materials

Korean translation of this article is available with the Online-only Data Supplement at <https://doi.org/10.3342/kjorl-hns.2026.00094>.

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Conceptualization: Hye Ran Lee. Data curation: Hyeon Jin Kim, Hye Ran Lee. Investigation: Hyeon Jin Kim, Hye Ran Lee. Supervision: Hye Ran Lee. Visualization: Hyeon Jin Kim, Hye Ran Lee. Writing—original draft: Hyeon Jin Kim, Hye Ran Lee. Writing—review & editing: Hye Ran Lee.

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