STEPHY Publishers

SOJ Medical and Clinical Case Reports

Case Report

ISSN: 2834-5517

Proliferative Verrucous Leukoplakia and/or HPV Lesion: Clinical, Histopathological, Molecular Biology, and Evolutionary Correlation: A Detailed Case Study

Chicatun M,[1] Brandizzi D[2,3]*

[1]Independent researcher, Argentina

[2]Department of Nuclear Medicine, National Atomic Energy Commission, Argentina

[3]School of Dentistry, Universidad Maimónides, Argentina

Abstract

Introduction: Proliferative verrucous leukoplakia (PVL) is a rare and progressive form of oral leukoplakia, first described in 1985. It is characterized by its multifocal presentation, progressive clinical course, and high propensity for malignant transformation. The diagnosis of PVL can be challenging due to its clinical resemblance to other white lesions, such as leukoplakia, oral lichen planus, and lichenoid lesions, particularly when multiple risk factors are involved.

Aim: This case report presents a clinically significant case of PVL at the lateral border of the tongue, associated with human papillomavirus (HPV) infection, and discusses the diagnostic challenges and management strategies involved.

Case report: A 49-year-old male presented with a white lesion on the left lateral border of his tongue, which was initially detected during a routine oral examination by his dentist. His medical history revealed that he had been a smoker for 15 years, consuming about 10 cigarettes daily until he quit 14 years ago. Additionally, he had a habit of regular alcohol consumption. Upon clinical examination, the lesion was found to be white and irregular, measuring 42 mm by 21 mm, with both flat and palpable areas. Histopathological evaluation indicated mild epithelial dysplasia. Further testing using polymerase chain reaction (PCR) confirmed the presence of low-risk HPV genotypes 6, 44, and 55. Although these HPV types are generally associated with a lower risk of malignancy, their presence in a progressive lesion such as PVL necessitates close monitoring. The lesion was partially removed using a shave biopsy technique specifically adapted for the oral mucosa.

Conclusion: This case of Proliferative Verrucous Leukoplakia (PVL) is presented with a thorough clinical, histopathological, and molecular biology correlation over a 9-year follow-up period. Key carcinogenic risk factors in this patient include a history of smoking, co-infection with HPV types 6, 44, and 55, and chronic mechanical irritation. The complete recurrence of the lesion at the third stage of surgical treatment demonstrates the more aggressive nature of PVL, as reported in the literature. The recurrence also highlights the complexity of therapeutic decision-making during the first two years of treatment. Ongoing clinical follow-up and the lesion's evolution have reaffirmed the soundness of the initial treatment approach and its successful outcome.

Keywords: Proliferative verrucous leukoplakia, Oral leukoplakia, Human papillomavirus, Malignant transformation, Shave biopsy, Oral cancer

Introduction

Proliferative verrucous leukoplakia (PVL) was first described in 1985,[1] with its diagnosis based on a combination of clinical and histological features. In subsequent years, specific clinical diagnostic criteria were proposed,[2,3] including the involvement of more than two distinct oral sites and the presence of a verrucous area. Initial clinical presentations may present as flat, white lesions without any verrucous components.

Other terms, such as proliferative multifocal leukoplakia and proliferative leukoplakia, have also been used in the literature.[4,5] These terms were introduced to reflect the multifocal nature and progressive behavior of the condition, distinguishing it from localized leukoplakia. However, PVL has gained wider acceptance due to its emphasis on the verrucous and highly recurrent characteristics, which are key to its clinical and histopathological identification.

Quick Response Code:

***Corresponding author:** Daniel Brandizzi, Juncal 657 - Martinez -CP1640 - Provincia de Buenos Aires – Argentina

Received: January 27, 2025 **Published:** 18 February, 2025

Citation: Chicatun M, Brandizzi D. Proliferative Verrucous Leukoplakia and/or HPV Lesion: Clinical, Histopathological, Molecular Biology, and Evolutionary Correlation: A Detailed Case Study: Case Report. *SOJ Med Clin Case Rep*. 2025;5(1):1–9.
DOI: 10.53902/SOJMCCR.2025.05.000530

The World Health Organization (WHO) consensus reports on Oral Potentially Malignant Disorders (OPMD) recognize PVL as a distinct form of multifocal oral leukoplakia.[6,7] It is characterized by a progressive clinical course, evolving clinical and histopathological features, and a higher likelihood of developing oral cavity cancer compared to other OPMDs.

Although it may resemble other white lesions like oral lichen planus and lichenoid lesions, there is consensus that PVL significantly increases the risk of oral cancer. A recent systematic review estimated the malignant transformation rate of PVL at 49.5% (95% CI: 26.7% – 72.4%).[8-10] PVL patients may progress to conventional squamous cell carcinomas or verrucous carcinomas, with multiple primary carcinomas, particularly affecting gingival sites, having been documented.[11]

This paper presents a compelling case of PVL located at the tongue border, associated with HPV infection, which has shown favorable evolution over a period of more than nine years.

Case presentation

A 49-year-old male from Buenos Aires visited clinical practice in December 2015 due to a white lesion on the left border of his tongue. His dentist initially observed the lesion during the first oral examination, prompting a referral to an oral medicine specialist.

Medical history

The patient reported allergies to insect bites and a specific juice brand.

Risk factors for oral cancer

Tobacco Use: Smoked 10 cigarettes daily for 15 years, quit 14 years ago.

Alcohol Consumption: Consumed high-proof alcohol, amount unspecified.

Mate Consumption: Drank mate 2-3 times daily, water temperature not recorded.

Mechanical Irritation/Trauma

The patient exhibited signs of tongue border indentations associated with swallowing habits (lingual protrusion) and anxiety-related behaviours, such as pressing the tongue against dental structures. He also presented with mucosal trauma, particularly along the tongue lateral border, due to dental origins and suction habits, along with dysfunctional swallowing exacerbated by significant anxiety.

Fungal infection

o evidence of *Candida albicans* infection was observed, and there was no therapeutic response to local antifungal treatment.

Microbiological factors

During the initial consultation, the presence of oral sepsis means, dental calculus, along with mild to moderate periodontal disease.

Oral examination

The lesion measured 42 mm in length and 21 mm in width and had an irregular appearance. In some areas, it was non-palpable (clinically characterized as a white patch), while in others, it was palpable on the surface (clinical keratosis or plaque). The edges were irregular, with micro verrucous zones. The surface was white and moist in appearance and allowed a certain translucency of the chorion. From a semiological point of view, some authors have called this particular lesion "*clinical acanthosis*" Figure 1- Figure 9.[12,13]

Diagnostic studies

Histopathological Examination: An initial biopsy showed mild epithelial dysplasia, with no koilocytic changes.[13]

Polymerase Chain Reaction (PCR): PCR and reverse hybridization identified HPV DNA with three low-risk genotypes (HPV 6, 44, 55) detected among the high-risk and probable high-risk types.[14]

Direct Immunofluorescence (DIF): DIF on fresh biopsy samples fixed with Michel's medium tested negative for Anti-IgG, Anti-IgM, Anti-IgA, Anti-fibrinogen, and Anti-C3 antibodies.[15]

Diagnosis and treatment

Based on the conducted studies and the latest OPMD consensus, the diagnosis was proliferative verrucous leukoplakia with mild epithelial dysplasia and co-infection with HPV types 6, 44, and 55.

Proposed Treatment

The treatment plan involved:

Local application of 2% ketoconazole in an oral base, 100,000 IU vitamin A, and 300 mg vitamin E three times daily. For nighttime application, 1% gentian violet aqueous solution was applied locally before the oral base application.

Partial lesion removal using the shave biopsy technique adapted for oral mucosa.[12] Preliminary 3 mm punch biopsies were performed in the target area for histopathological correlation. Electrofulguration at low intensity created blisters, which were removed using a surgical curette.

Post-surgical care included continued application of the above treatment with hydrocortisone 1% in oral base until epithelialization.

Given the extent of the lesion, treatment was staged, with clinical and histopathological follow-ups. Six stages were necessary. The treatment spanned 12 months, after which the patient remained under periodic monitoring for nine years, showing no recurrence.

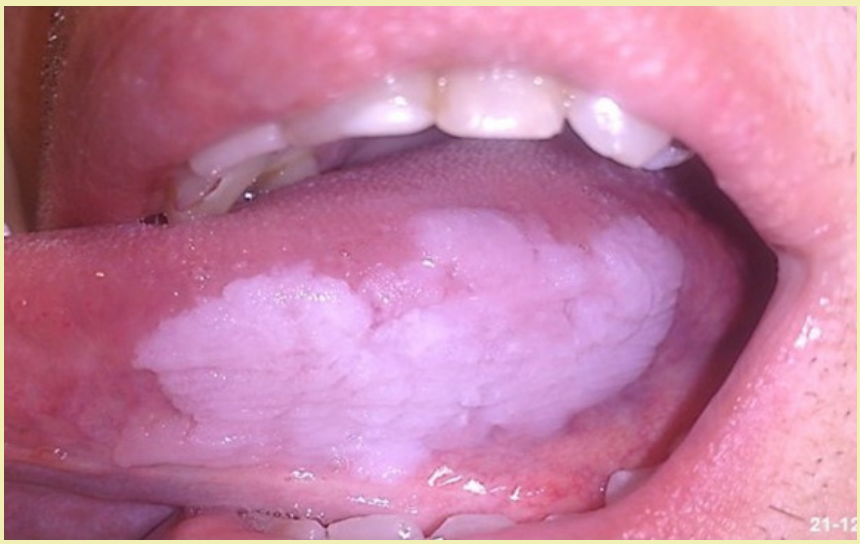

Figure 1: Image of the lesion at the patient's first consultation on the left tongue border, white in color and with irregular edges. The lesion measured 42 mm in length and 21 mm in width. The semiological evaluation allowed the identification of the following elementary lesions: “white spot, clinical keratosis or plaque, areas of microverrugosity”. The general appearance of the lesion showed “clinical acanthosis”[13]

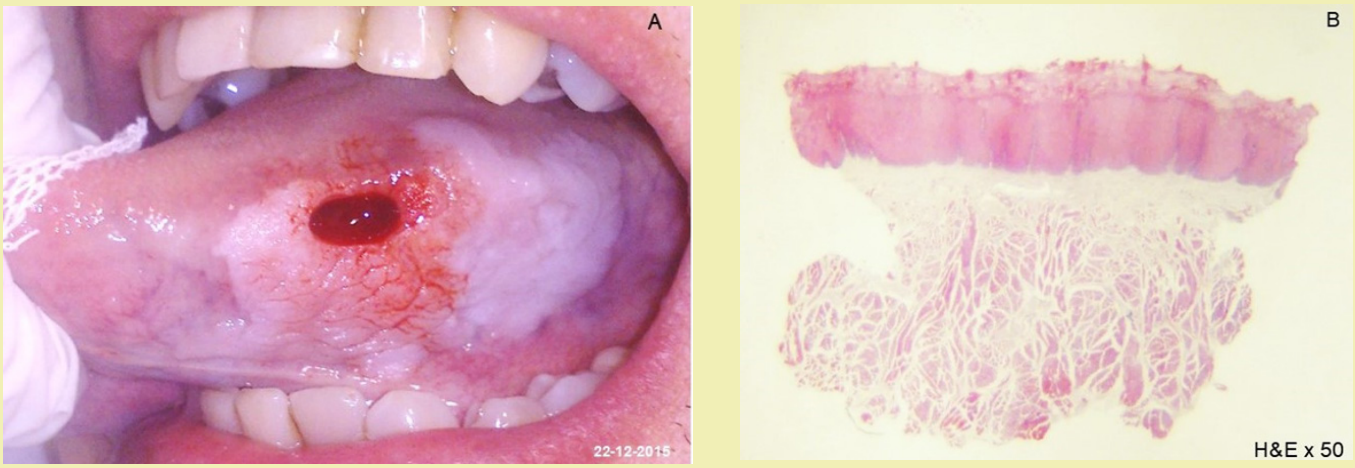

Figure 2: A. Clinical image of the area chosen for the biopsy **B**. Microphotograph corresponding to the biopsy area

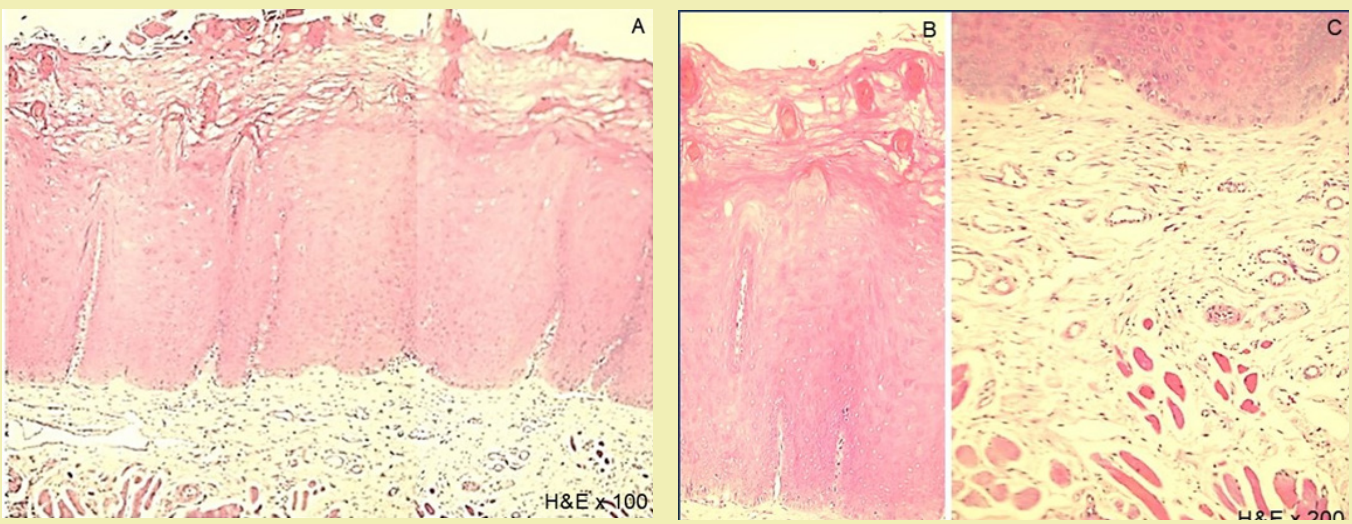

Figure 3: Micrograph of the first biopsy sample showing mild epithelial dysplasia. **A.** Marked hyper parakeratosis, ballooning of epithelial ridges. **B.** Stratification of the basal layer, irregularities in the arrangement of intermediate and deep layers of the epithelium and increased proliferative activity. No koilocytic images are observed. **C.** The chorion shows discrete angiogenesis.

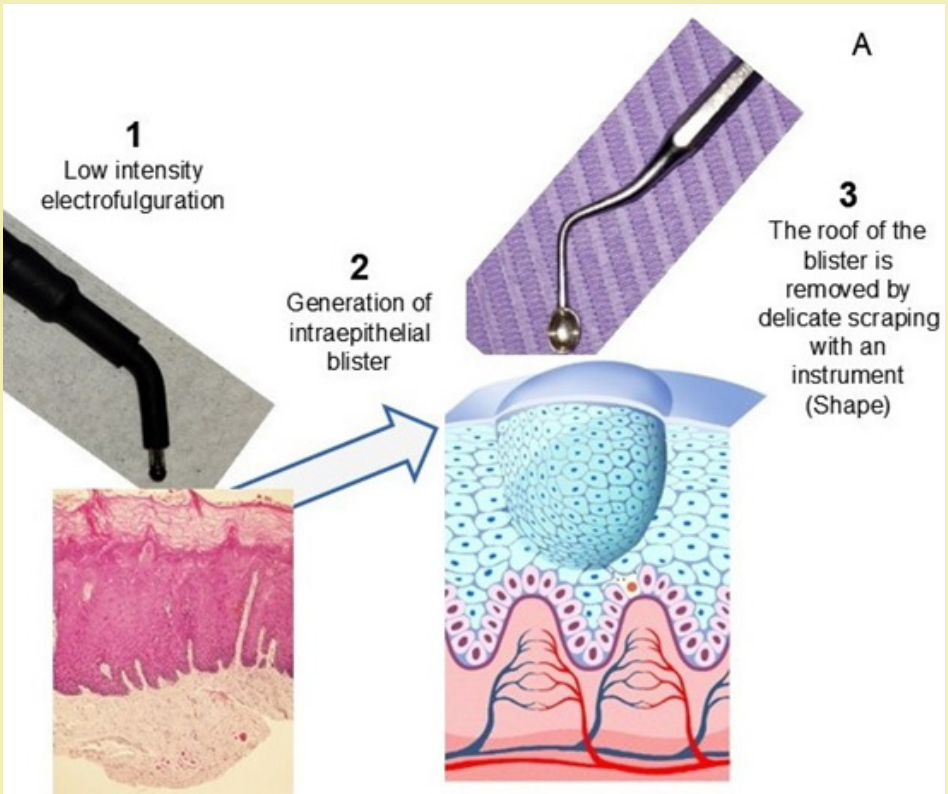

Figure 4: Details of the shave biopsy[12] technique adapted for buccal mucosa[13]

A. Technique diagram

B. Equipment used

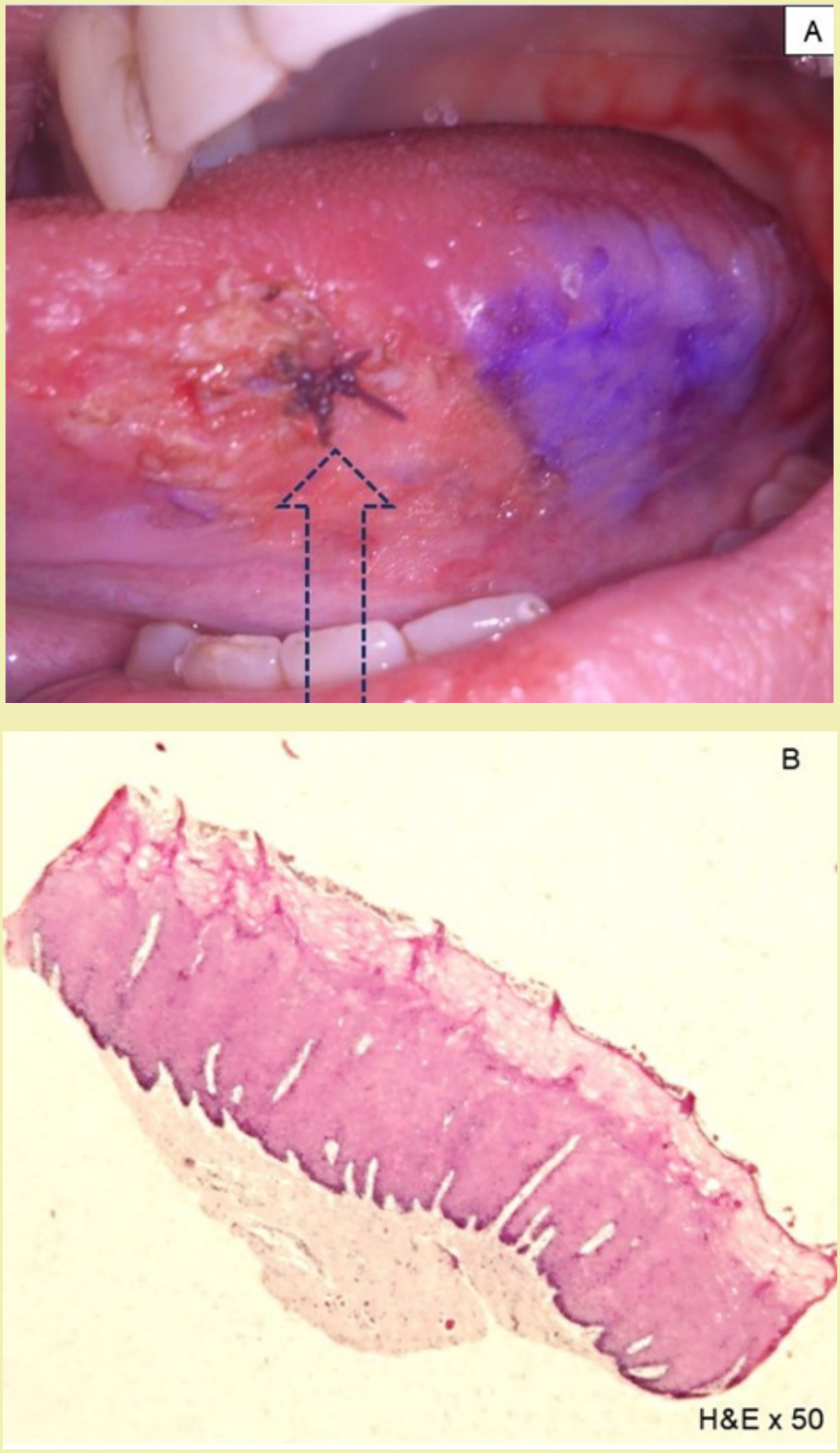

Figure 5: Partial lesion removal using the shave biopsy technique adapted for oral mucosa[12,13]

A. Clinical image of the chosen site. A 3 mm punch biopsy was previously performed to allow histopathological evaluation. Low-intensity electrofulguration was then performed to remove the blister roofs generated. See figure 4

B. Microphotograph of the image of the biopsied area

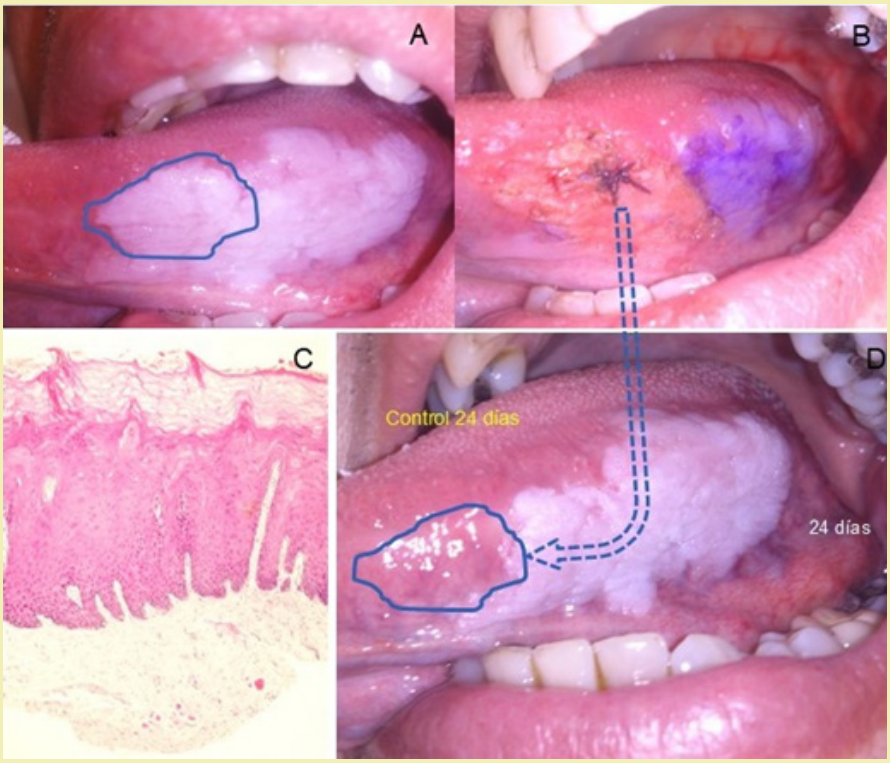

Figure 6: The first stage of therapeutic surgery is shown
A. Image of the lesion before removal. The treated area is shown in blue line
B. Immediate post-surgical image. We can see the surgical bed left by the shave and some stitches can be seen in the areas where the punch biopsy was performed
C. Microphotograph of the biopsied area of a case of mild epithelial dysplasia
D. Clinical image of the evolution in 24 days. The good response and normal buccal mucosa can be seen in blue post-treatment

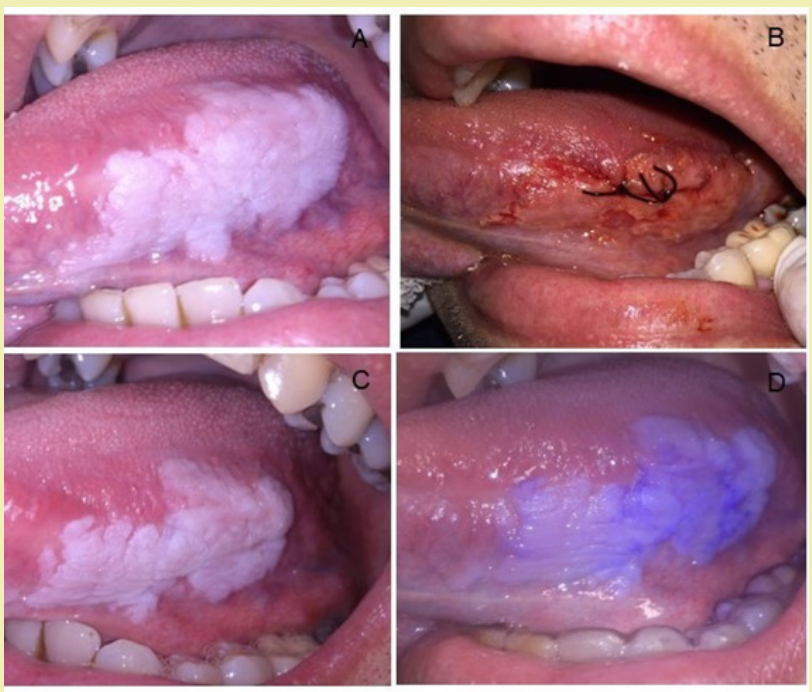

Figure 7: The 3rd stage of therapeutic surgery is shown with complete recurrence in 21 days
A. Image of the lesion prior to removal
B. Immediate post-surgical image with removal of the entire lesion and stitches in the areas where the punch biopsy was taken
C. Image of the evolution at 21 days
D. Evolutionary Control at 27 days

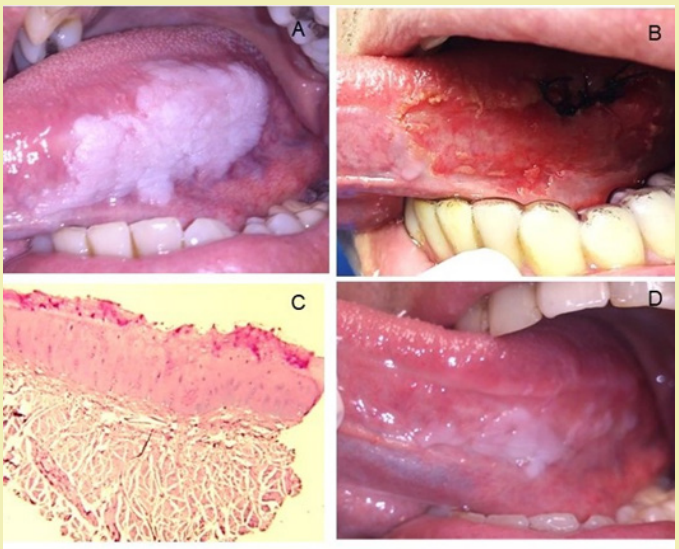

Figure 8: The 4th surgical therapeutic stage is shown with a good response and little partial recurrence
A. Image of the lesion prior to removal
B. Immediate post-surgical image with total removal and stitches in the areas where the punch biopsy was taken
C. Microphotograph of the sample taken
D. Monitoring at 90 days

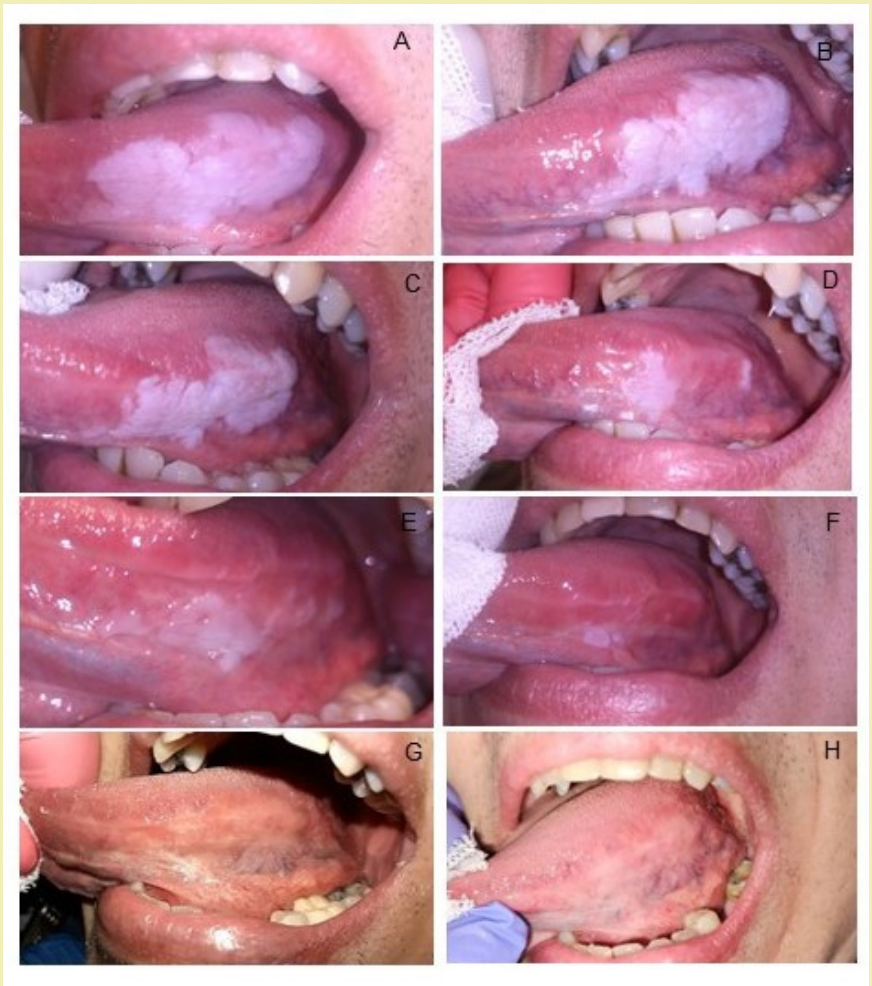

Figure 9: Images of evolutionary controls at 9 years after the start of treatment. **A.** Initial. **B.** End of 2nd stage (3 months from start). **C.** End of 3rd stage 3 (4 months from start). **D.** End of 4th stage (12 months from start) **E.** End of 5th stage (14 months from start) **F.** End of 6th stage (19 months from start) **G.** Evolutionary control at 2 years **H.** Last evolutionary control at 9 years

Discussion

The role of HPV infection in PVL pathogenesis remains unclear and contradictory.[14-16] Studies by Smith[17] and Johnson.[18] suggested that high-risk HPV subtypes, such as HPV 16 and 18, may increase malignant transformation through viral oncoproteins E6 and E7, which inactivate tumor suppressor proteins p53 and pRb.

This case presents PVL associated with low-risk HPV infection, with over nine years of clinically favorable outcomes. The Argentine School of Oral Medicine, observed similarities between clinical HPV lesions of the cervix and oral lesions, referring to this as "clinical acanthosis".[13] This semiological term has been controversial, especially among pathologists. The objective is to support clinical presumption of HPV infection in these lesions and then arrive at a diagnosis supported by histological and molecular biology findings. This approach allows targeted therapy to control viral infection, which may contribute to lesion aggressiveness.

These particular clinical features described are different from other white lesions related to tobacco alone or may be confused in patients with oral lichen planus and a history of smoking habits.[13] The latest WHO consensus[6,7] incorporates different forms of leukoplakia, including PVL, aligning with literature for this clinical case.

At the time, molecular biology tools were not available to confirm these hypotheses. Research on PVL should focus on risk factors rather than naming entities with multiple risk factors, such as oral lichen planus, smoking, and HPV infections. The Argentine oral medicine school classifies leukoplakia into primary and secondary, considering tobacco-induced leukoplakia as primary due to a characteristic clinical histopathological picture, while secondary leukoplakia is associated with other risk factors such as candida, lichen keratoticus in patients with a history of smoking, alcohol consumption, chronic mechanical irritation and HPV.[13] This perspective helps to adapt treatments based on the associated risk factors., considering tobacco Leukoplakia as primary due to a characteristic clinical histopathological picture, while secondary Leukoplakia are associated with other risk factors like candida, lichen keratoticus in patients with a tobacco history, alcohol use, chronic mechanical irritation, and HPV.[13] This perspective helps tailor treatments based on associated risk factors.

The surgical shave technique adapted for oral mucosa showed excellent results in this case, being conservative and leaving minimal sequelae. Further study is warranted on laser therapy's potential as a microbicidal and immunomodulatory treatment.[19]

Long-term clinical follow-ups are crucial for managing PVL due to their high recurrence and transformation potential. Tailored therapeutic approaches can effectively address complex conditions.

Diagnoses of white lesions should consider reasonable evolutionary times, as shown by the 9-year follow-up of this case. Interpreting lichenoid lesions clinically and histologically could reveal other white lesions in their evolution.[8,20,21] This interpretation aligns with the understanding of lichenoid lesions and their potential transformation into oral carcinomas or other white entities of the oral mucosa.[5,7,8,20,21,22]

Conclusion

This case stresses the clinical and histopathological complexity of PVL with HPV coinfection, highlighting the need for a multidisciplinary approach to diagnosis and management. Specifically, it presents PVL associated with low-risk HPV infection, demonstrating clinically favourable outcomes over a nine-year follow-up period- This case reinforces the importance of integrating clinical, histopathological, and molecular findings to guide targeted therapeutic interventions aimed at controlling viral infection, which may contribute to lesion aggressiveness.

Notably, the treatment strategies implemented during the initial two years were pivotal, as the disease progressed to stage three, emphasizing its aggressive nature. The surgical shave technique, adapted for the oral mucosa, proved to be an effective and conservative approach, minimizing sequelae. Given the high recurrence and malignant transformation potential of PVL, long-term clinical surveillance remains essential. Additionally, further research into laser therapy as a microbicidal and immunomodulatory treatment is warranted. This case ultimately highlights the efficacy of a combined surgical and pharmacological approach, demonstrating that early intervention and sustained follow-up can lead to favourable long-term outcomes.

Acknowledgments

We would like to thank the following colleagues for their participation in the resolution of this case: Sebastian Lista, a doctor and dentist specializing in oral and maxillofacial surgery; María Luisa Paparella, who carried out the pathological anatomy of all biopsy samples and direct immunofluorescence; colleagues from the molecular pathology area of the Pathological Anatomy service of the Italian Hospital of Buenos Aires; and Mariana Gandolfo and Claudia Giacco, who collaborated in the discussion of decisions in the evolutionary process.

Funding

This article received funding from the National Atomic Energy Commission.

Conflicts of Interest

Regarding the publication of this article, the authors declare that they have no conflict of interest.

References

1. Hansen LS, Olson JA, Silverman S. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol.* 1985;60:285-298.
2. Cerero Lapiedra R, Balade Martinez D, Moreno Lopez LA, et al. Proliferative verrucous leukoplakia: A proposal for diagnostic criteria. *Medicina Oral Patología Oral y Cirugia Bucal.* 2010;15(6):e839-845.
3. Carrard VC, Brouns ER, van der Waal I. Proliferative verrucous leukoplakia; a critical appraisal of the diagnostic criteria. *Med Oral Patol Oral Cir Bucal.* 2013;18(3):e411-3.
4. Aguirre Urizar JM. Proliferative multifocal leukoplakia better name that proliferative verrucous leukoplakia. *World J Surg Oncol*. 2011;9:122.
5. Villa A, Menon RS, Kerr AR, et al. Proliferative leukoplakia: Proposed new clinical diagnostic criteria. *Oral Dis.* 2018;24(5):749-760.
6. Warnakulasuriya S, Kujan O, Aguirre Urizar JM, et al. Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. *Oral Dis.* 2021;27(8):1862-1880.
7. 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):575-580.
8. Gilligan G, Garola F, Piemonte E, et al. Lichenoid proliferative leukoplakia, lichenoid lesions with evolution to proliferative leukoplakia or a continuum of the same precancerous condition? A revised hypothesis. *J Oral Pathol Med.* 2021;50(2):129-135.
9. 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):255-261.
10. Iocca O, Sollecito TP, Alawi F, et al. Potentially malignant disorders of the oral cavity and oral dysplasia: A systematic review and meta-analysis of malignant transformation rate by subtype. *Head Neck.* 2020;42(3):539-555.
11. Bagan J, Murillo Cortes J, Poveda Roda R, et al. Second primary tumors in proliferative verrucous leukoplakia: a series of 33 cases. *Clin Oral Investig*. 2020;24(6):1963-1969.
12. Kopf AW, Popkin GL. Letter: Shave biopsies for cutaneous lesions. *Arch Dermatol.* 1974;110(4):637.
13. Grinspan D. Enfermedades de la boca (Tomo IV). Ed. Grinspan D. Editorial Mundi. Buenos Aires. 1983:Pp.2811-2864
14. Borgna SC, Clarke PT, Schache AG, et al. Management of proliferative verrucous leukoplakia: Justification for a conservative approach. *Head Neck*. 2017;39(10):1997-2003.
15. Campisi G, Giovannelli L, Ammatuna P, et al. Proliferative verrucous vs conventional leukoplakia: no significantly increase risk of HPV infection. *Oral Oncol.* 2004;40:835-840
16. Bagan JV, Jimenez Y, Murillo J, et al. Lack of association between proliferative verrucous leukoplakia and human papillomavirus infection. *J Oral Maxillofac Surg*. 2007;65:46-49
17. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Res.* 2002;89(2):213-228.
18. Herrero R, Castellsagué X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst.* 2003;95(23):1772-1783.
19. Bombeccari GP, Garagiola U, Candotto V, et al. Diode laser surgery in the treatment of oral proliferative verrucous leukoplakia associated with HPV-16 infection. *Maxillofac Plast Reconstr Surg*. 2018;40(1):16.
20. Batsakis JG, Suarez P, el Naggar AK. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol.* 1999;35(4):354-359.
21. Garcia Pola MJ, Llorente Pendás S, González Garcia M, et al. The development of proliferative verrucous leukoplakia in oral lichen planus. A preliminary study. *Med Oral Patol Oral Cir Bucal.* 2016;21(3):e328-334.
22. Gilligan G, Piemonte E, Lazos J, et al. Oral squamous cell carcinoma arising from chronic traumatic ulcers. *Clin Oral Investig.* 2023;27(1):193-201.