

## Follow up protocol in proliferative multifocal leukoplakia to avoid malignant transformation. A case report

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**Abstract:** Proliferative multifocal leukoplakia (PML) is considered one of the oral potentially malignant disorders (OPMD) with the highest malignant transformation rate. Therapeutics is extremely difficult since, in most cases, the lesions are refractory. This study aims to report a case of PML and its evolution, highlighting the importance of clinical monitoring through comprehensive follow-up protocols. A 75-year-old female with multiple keratotic and verrucous lesions with a proliferative growth pattern throughout the oral mucosa. The biopsies and the clinical context allowed clinicians to diagnose it as PML. The patient adhered to a strict protocol and so far has no carcinomatous lesions. This report highlights the careful monitoring of patients with PML to achieve early detection of oral squamous cell carcinoma and, consequently, improve prognosis.

**Keywords:** leukoplakia, oral squamous cell carcinoma, follow-up, proliferative leukoplakia.

## Introduction and background

Many potentially malignant disorders (PMDs) present in the oral mucosa usually manifest clinically as white lesions<sup>(1)</sup>. Among them, leukoplakia, and a very aggressive variant called *proliferative verrucous leukoplakia* (PVL), or better called *proliferative multifocal leukoplakia* (PML)<sup>(2)</sup>, has the highest malignancy rate. PML was described by Hansen et al.<sup>(3)</sup> in 1985; its diagnostic criteria have been optimized by many authors to date<sup>(4-5)</sup>. The World Health Organization (WHO) defined PML as an aggressive variety of leukoplakia characterized by a high recurrence and malignancy transformation rate<sup>(6)</sup>.

PML initially presents as a white lesion and may correspond to a keratotic spot or plaque, which gradually becomes proliferative, covering different oral mucosa areas, becoming multifocal, with diffuse and uncontrollable growth. The lesions can become

bulkier and resemble warts and become verrucous carcinomas or squamous cell carcinomas<sup>(7)</sup>.

PML lesions tend to resist treatment, including modalities such as laser excision, conventional surgery, radiation, and chemotherapy. However, strict patient follow-up, monitoring, and early biopsies are the best tool to prevent carcinomatous transformation<sup>(5)</sup>. This paper aims to report a clinical case of a patient with PML lesions and the strict clinical follow-up over three years (current status).

## Description

In March 2017, a 75-year-old female patient was referred by a head and neck surgeon to Stomatology Department "A" of the School of Dentistry of Universidad Nacional de Córdoba, Argentina. She had white lesions on the edge of the tongue, without associated symptoms.

The woman, a total edentulous patient, had a health history of osteoarthritis and hypertension, with no other relevant personal, family, or genetic history. Associated habits such as tobacco, alcohol, and drug use were not reported. Her diet was rich in vegetables and fruits, and she had one liter of *mate* daily, whose temperature did not exceed 75°.

The intraoral exam showed an extensive white lesion of five years of evolution; it did not detach with the scraping and was located in the anterior sector of the inferior alveolar ridge, dorsal and ventral face, edges and tip of tongue, compromising the buccal mucosa equally on both sides. The lesions appeared by sectors as true keratotic plaques, which tend to become verrucous, as shown in Fig. 1.

Fig. 1:



A: Keratotic lesions that are located on the lingual dorsum towards the tip and lateral edges, with a loss of filiform papillae. In the periphery, there are irradiated lesions similar to the striations in pathologies such as lichen planus. 1B. Keratotic lesions on the lower edentulous ridge reach the bottom of the lip sulcus and extend all over the lower residual ridge. 1 C and D: Tongue edge with keratotic lesions, showing areas that tend to become verrucous. Incisional biopsies were performed on these areas as we noticed increased consistency.

Presurgical laboratory tests were run, and we decided to perform serial incisional biopsies of the most representative areas stained with toluidine blue (Figure 2). This pigment does not easily penetrate the epithelium's deep layers, so its use would be limited to verrucous or hyperkeratotic lesions. However, it remains a useful complementary tool to select the representative area before the surgical procedure. In addition, cells were collected by smear or brush. They were then deposited in a specific transport medium, the Polymerase Chain Reaction (PCR) was run to test for Human Papillomavirus (HPV) and its subsequent genotyping.

**Fig. 2:**



A, B, C: Staining with toluidine blue showed no positive areas for suspected malignant or proliferative transformation. The areas dyed in blue in Figure 1 A correspond to pigment retention areas in filiform papillae. Figures 2 B and C show slight retention at the tongue edges at the sites indicated for biopsy. Site selection was based on palpation and not on toluidine blue staining. Figure 2 D. One-week postoperative view of right tongue edge at the biopsy site. Note the keratinizing pattern in the region that is healing post-surgically.

The anatomic pathology of the biopsied specimens showed similar images: a hyperplastic, acanthotic epithelium with superficial hyperkeratosis, hypergranulosis, and some cellular alterations affecting the basal layer, compatible with mild dysplasia. Clinical-pathological manifestations can correspond to the diagnostic criteria for proliferative multifocal leukoplakia. The PCR-HPV result was negative; therefore the presence of viral DNA in the lesions was ruled out.

As the lesions were multifocal and extensive, a follow-up protocol was implemented. This protocol—agreed with the patient and her relatives—established monthly appointments in the first semester, bimonthly in the second semester, and quarterly in the second year of follow-up. After that, and according to the evolution of the clinical picture, it was agreed to space appointments or reduce the time between appointments. Initially, a local antifungal treatment was provided, any traumatizing elements from the patient's complete dentures were removed, and the patient was instructed on hygiene techniques. The importance of periodic check-ups was emphasized.

Subsequently, oral medicine residents were calibrated to standardize the follow-up criteria and follow a strict working methodology at the follow-up appointments. A general dental exam was performed, photographs of the affected and healthy oral mucosa were taken, and the area was stained with toluidine blue. A biopsy specimen was taken if there were new verrucous areas, nodular lesions with increased consistency, areas of rapid growth compared to the previous appointment, and erythroplasia that did not improve after trauma elimination or fungal infection treatment, or which was unrelated to these conditions). Fig.3

The patient remained stable for three years. A new biopsy specimen was taken due to the appearance of the above indication criteria, with a histopathological diagnosis of hyperkeratosis with mild dysplasia, similar to the initial lesions.

**Fig. 3:**



Photos taken eight months after the first appointment with clear lesion stability. 3B and 3C show complete keratinization of biopsied areas. The lesions have hardly

changed in disposition or presence compared to the first appointment. In each follow-up session, these items were controlled in addition to the above procedures.

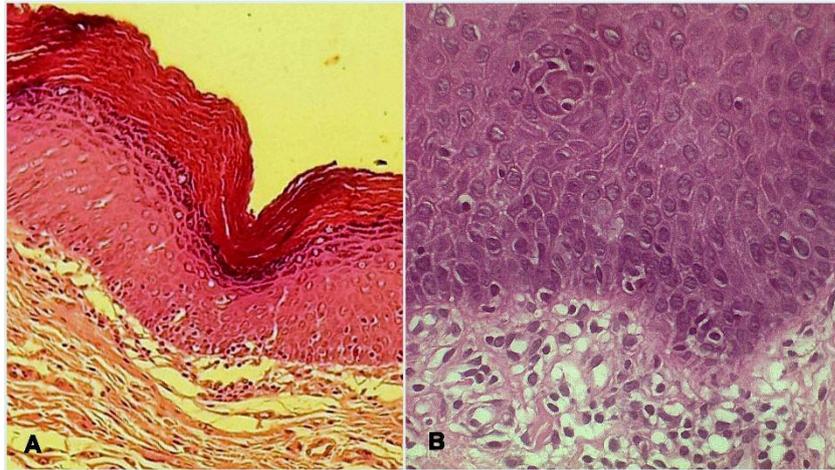
The patient attended the follow-up appointments in the first year; however, she did not in the following years due to mobility issues associated with her osteoarthritis. Until the time this paper was written, no focal points of carcinomatous transformation were observed. Fig. 4 shows the latest follow-up visit.

**Fig. 4:**



A and B. The latest follow-up visit showed a discrete change in the proliferative pattern of the lingual dorsum and right edge compared to previous visits. C. In addition, a lesion on the lingual face of the lower edge, left sector not present before was observed. D. Toluidine blue staining was positive, and an incisional biopsy with a similar diagnosis of hyperkeratosis with mild dysplasia was immediately scheduled. To date, the patient attends follow-up visits with no significant changes in her lesions.

**Fig. 5:** Histopathology of the first tongue edge biopsy.



It must be noted that only three incisional biopsies were necessary throughout the follow-up: two at the start of the treatment and a third one when a suspicious lesion appeared. All the histopathological analyses showed hyperkeratosis and mild epithelial changes. A: Acanthotic epithelium with hypergranulosis and hyperorthokeratinization. Low focal inflammatory activity was observed in the connective tissue. B: some hyperchromatic nuclei and cytological and architectural signs of mild epithelial dysplasia are observed.

## Discussion

PML is one of the pathologies that has promoted the most debate on its nomenclature, nature, and treatment. Over the past decades, different diagnostic criteria have been proposed (Ghazali et al., Gandolfo et al., Cerero-Lapiedra et al., Villa et al.). In many cases, it may begin as a single homogeneous leukoplakia<sup>(8)</sup> that proliferates into a multicenter entity, with or without malignant changes at diagnosis. One of the most commonly used diagnostic criteria are those proposed by Cerero-Lapiedra et al. in 2011<sup>(4)</sup>. Our patient was a 70-year-old woman with no associated risk factors such as tobacco and alcohol. Clinically it was a white plaque measuring over 3 cm, with verrucous areas that involved more than two different sites in the oral cavity: dorsal and ventral face, edges and tip of the tongue, buccal mucosa, and lower alveolar ridge, showing that the lesions spread throughout the evolution. All these characteristics coincide with similar cases of PML reported in the literature over the years and met all the major and minor criteria of proliferative multifocal leukoplakia proposed by Cerero-Lapiedra et al. in 2011.

It is recommended that photographs be taken at each visit as part of the clinical management and follow-up to record lesions and areas of clinically healthy mucosa. Biopsies are indicated when there are clinical findings of red, nodular, or verrucous areas or induration areas. In cases of reported dysplasia, lesions should be surgically removed, and pathologists should always inform the PML margins, even in the absence of dysplasia<sup>(5)</sup>. This patient underwent a strict follow-up during the first years, with detailed clinical monitoring of the lesions and ongoing check-up of the prosthesis condition to avoid chronic mechanical irritation and fungal superinfection. The pathogenesis of the disease has not yet been established<sup>(9)</sup>. Given the verrucous clinical appearance of PML-associated lesions, HPV infection was possible; various HPV infection rates in PML are found in the literature<sup>(10)</sup>. In addition, aberrations have

been found in cell cycle regulatory genes, with deletions, loss of heterozygosity, and mutations in some of these lesions<sup>(11)</sup>. In our case, PCR for molecular diagnosis of HPV was negative and the pathology could not be linked to patient habits or other external factors (such as living in an area with high consumption of water contaminated with arsenic, frequent in our country), associated with the presence of oral leukoplakia.

Some authors have proposed that some PML could initially have clinical forms similar to those reported in oral lichen planus (OLP) and lichenoid lesions<sup>(12)</sup>. The following might link PML and OLP: PML frequency in female patients, non-smokers, multifocal lesions, usually over the age of 50, and the similarity of this clinical scenario with OLP<sup>(13)</sup>. In this case, the patient's characteristics coincide with the features described above. In addition, there are clinical details that led clinicians to believe that this PML was associated with a previous OLP. The lingual dorsal lesion showed a true keratotic zone with a striated pattern, more so towards the tip, similar to those described in OLP. However, as there were no oral mucosal biopsies before the patient's first appointment, OLP could not be initially diagnosed. Some authors have also proposed similar clinical findings, where PML lesions can coexist with lichenoid areas<sup>(5,14-15)</sup>. In some reported cases of PML, a juxtaepithelial interface lymphocytic infiltrate similar to that of OLP was observed<sup>(16-17)</sup>, sparking some controversy on the true nature of PML. The juxtaepithelial infiltrate present in many white lesions would not be exclusive of pathologies such as OLP or lichenoids, as it is a non-specific histological finding present in dysplastic, allergic lesions associated with mechanical irritation<sup>(14)</sup>.

PML is not only characterized by its high rate of post-surgical recurrence, but by its high rate of carcinomatous transformation: it is the PMD with the most significant potential to become a carcinoma. Transformation rates range from 60 to 100%, with the gingiva and palate being the two areas with the highest frequency of transformation<sup>(8-9,16,18-19)</sup>. In our case, the lesions appeared in the edentulous ridge, tongue, buccal, and lip mucosa, and there were no palatal lesions. We also observed how the mucosa quickly healed with a keratinizing pattern once the lesions in the incisional biopsies were surgically removed. Strict follow-up protocols and the patient's adherence to them allowed for a careful examination of the lesion's evolution by performing early biopsies in the event of significant changes. As it is a refractory pathology, it is essential to monitor the patient over time.

Finally, follow-up procedures for patients with PML were systematized, including this case. Controls included: a systematic exam of the entire oral mucosa, both visual and through palpation, functional static and dynamic control of prosthesis, periodontal health (not necessary since the patient was edentulous), and possible fungal superinfection. The presence of new lesions or increased lesions compared to the previous visit is evaluated. In these patients, medical records and photographic material of pathological and healthy mucosa are carefully studied to establish if the pathology is progressing or if there are moments of remission of the proliferative pattern. Once all these aspects have been evaluated, lesions and healthy mucosa are stained with toluidine blue, as these patients are considered at high risk of developing carcinomas, specifically on the edges of the tongue and floor of the mouth. Then the staining results are observed and complemented with lesion palpation. Based on the analysis of all these variables during follow-up, incisional biopsies are performed if any suspicious lesions are found.

## Conclusion

PML is an oral mucosa disease that has the highest rate of carcinomatous transformation. Successful treatment of these patients entails avoiding such transformation. In cases as widespread as the one presented here, where total removal of the lesion is impossible, a comprehensive follow-up is the most critical preventive-therapeutic measure.

In these cases, efforts should aim to create the necessary conditions for patients and their environment to foster empathy with the oral medicine service where they are being treated to achieve adherence to the follow-up plan. Early biopsies, when there are clinical alert changes, are the first step in preventing PML carcinomatous transformation.

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**Authors' contribution note:**

- 1.Conception and design of study
  - 2.Acquisition of data
  - 3.Data analysis
  - 4.Discussion of results
  - 5.Drafting of the manuscript
  - 6.Approval of the final version of the manuscript.
- FL has contributed in 1, 2, 3 y 5.  
TM has contributed in 1, 2, 3 y 5.  
GG has contributed in 1, 5 y 6.  
PR has contributed in 5 y 6.

**Editor's opinion:**

This article has been accepted by the Odontostomatología's editor Dra. Vanessa Pereira-Prado