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ORAL LEUKOPLAKIA WITH EPITHELIAL DYSPLASIA: REPORT OF TWO CASES WITH PROLONGED AND RIGOROUS FOLLOW-UP AND NO MALIGNANT TRANSFORMATION

Leucoplasia oral com displasia epitelial: relato de dois casos com anos de acompanhamento rigoroso e sem história de transformação maligna

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RESUMO

Objetivo: Relatar dois casos de leucoplasia oral (LO) com diagnóstico histopatológico de displasia epitelial, acompanhados por mais de dez anos em um serviço de Estomatologia de um Hospital Universitário. **Relato do caso**: O primeiro caso refere-se a uma mulher de 89 anos com LO não homogênea na borda lateral da língua. O segundo caso trata de um homem de 55 anos diagnosticado com LO não homogênea na região de ventre da língua. Ambos os locais são considerados de alto risco para transformação maligna. Os pacientes foram acompanhados por avaliações clínicas regulares e múltiplas biópsias realizadas em diferentes intervalos, com achados de displasia epitelial intensa. O segundo paciente apresentava histórico de tabagismo e etilismo prolongados, fatores que aumentam o risco de progressão maligna. **Discussão**: Apesar do potencial de transformação, não houve evidência clínica ou histopatológica de malignização em nenhum dos casos. O acompanhamento prolongado de mais de 10 anos juntamente com controle rigoroso dessas lesões do grupo das desordens potencialmente malignas e uma vigilância ativa foram essenciais para a detecção de alterações histológicas e prevenção de desfechos desfavoráveis. Esses casos reforçam a importância da conduta conservadora e do papel da Estomatologia no diagnóstico e monitoramento das desordens potencialmente malignas da cavidade oral. **Conclusão**: O seguimento clínico rigoroso e multidisciplinar, juntamente com o manejo e orientações sobre fatores de risco, desempenha papel fundamental na vigilância de lesões potencialmente malignas, favorecendo a identificação precoce de sinais de progressão para o câncer.

Palavras-chave: Leucoplasia Oral; Diagnóstico Bucal; Prognóstico; Medicina Bucal; Patologia Bucal.

ABSTRACT

Aim: To report two cases of oral leukoplakia (OL) with histopathological evidence of epithelial dysplasia, monitored over a ten-year period through a collaborative, service-based learning model in the Stomatology Department of a University Hospital. **Case Report**: The first case describes an 89-year-old woman with a clinical diagnosis of non-homogeneous OL on the lateral border of the tongue. The second case concerns a 55-year-old man with a non-homogeneous OL on the ventral surface of the tongue. Both lesion sites are considered high-risk for malignant transformation. The patients underwent regular clinical follow-up and multiple biopsies at different intervals, which revealed severe epithelial dysplasia. The second patient had a prolonged history of smoking and alcohol consumption, known risk factors for malignancy. **Discussion**: Despite the malignant potential of the lesions, no clinical or histopathological signs of transformation were observed in either case. Long-term follow-up, with close monitoring and serial biopsies, was essential for the detection of histological changes and prevention of unfavorable outcomes. These cases highlight the importance of a conservative and preventive clinical approach, and the essential role of Oral Medicine specialist in the diagnosis, monitoring, and management of oral potentially malignant disorders. **Conclusion**: Systematic and multidisciplinary follow-up, combined with risk factor control, may prevent malignant transformation even in lesions located in anatomically high-risk areas and with severe dysplastic changes.

Keywords: Leukoplakia, oral; Diagnosis, Oral; Prognosis; Oral Medicine; Pathology, Oral.

INTRODUCTION

Oral leukoplakia (OL) is defined as a lesion characterized by “a white plaque in the oral mucosa, which does not have any other microscopic or clinical definition”. The condition is related to an unknown etiology and, in the most recent update by the World Health Organization, remains a potentially malignant disorder[1]. Different clinical presentations of OL have been reported. One of the most recent classifications identified two major types: homogeneous (characterized by a flat and uniform white plaque with well-defined margins) and non-homogeneous (with areas of erythematous foci or accompanied by nodular and verrucous areas)[2,3].

OL prevalence has remained relatively stable over the years. A recent systematic review from 2023 reported a prevalence of 1.39%, ranging from 0.12 to 33.33%[4], based on data from 69 studies. Another systematic review from 2003 revealed a prevalence of de 1.49% in well-designed studies and of 2.60% in studies of lower methodological quality[5].

Malignant transformation (MT) has been associated whit the non-homogeneous type of OL, higher grades of epithelial dysplasia, and certain anatomical location. A systematic review and meta-analysis of 26 studies found a pooled MT rate of 7.20%[6]. Excessive alcohol consumption and smoking habits are major risk factors for MT, particularly with prolonged exposure. In patients who do not use tobacco or alcohol, the lesion’s evolution time has also been identified as a relevant risk factor[7].

There are limited literature reporting OL cases with long-term follow-up exceeding 10 years, especially those monitored through multiple biopsies at different time intervals, alongside consecutive clinical evaluations. Although surgical removal is clearly indicated for lesions with epithelial dysplasia, this approach is not always feasible. Treatment planning must consider factors such as the patient’s comorbidities and opinion, lesion location, and risk profile[8].

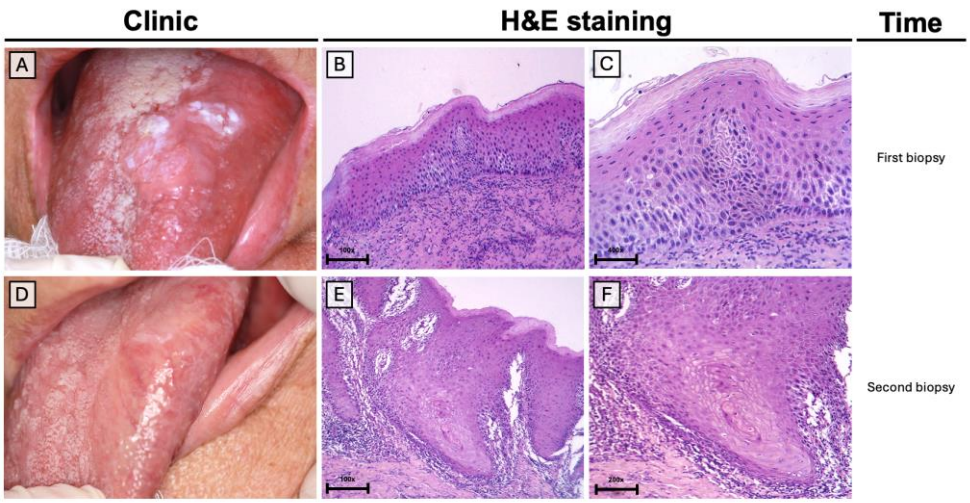
The responsibility of maintaining long-term clinical follow-up of OL is substantial and highly dependent on patient adherence — including attending periodic visits, undergoing repeated biopsies, and eliminating risk factors. In this context, the present study aims to describe two cases of patients diagnosed with OL associated with epithelial dysplasia, which followed for over ten years, which did not progress to oral cancer.

CASE REPORT

Case 1

A Caucasian female patient with 89 years old complains of an oral lesion with no pain or other symptoms. The patient was in medical care because of a vitiligo diagnosis for more than 20 years. An erythroleukoplakic lesion was observed on the tongue border and was characterized as a white plaque associated with erythematous areas and a focal area with a nodule of a hard consistence, located on the dorsum (Fig. 1A). The clinical diagnosis was of a non-homogeneous OL and an incisional biopsy was performed. Histopathological results were compatible with OL, with hyperkeratosis and epithelial dysplasia (Fig. 1B-C). Subsequently an excisional biopsy was performed on the whole plaque lesion. After one year, the patient reported a new lesion, again with the clinical diagnosis of a non-homogeneous OL, which was again confirmed through histopathological analysis. The biopsies procedures were performed in two different sites because the differential diagnosis includes oral squamous cell carcinoma. Histopathological results showed acanthosis, hyperkeratosis, and severe epithelial dysplasia (Fig. 1E-F). The patient was then followed under consecutive clinical evaluation for more than 19 years, and at the 20th year follow-up, clinical evaluation revealed absence of a well-defined white plaque lesion and a nodule, and at the border of the tongue in the previous operated area, only a whitish discrete plaque with striate aspect was found (Fig. 1D). During the period of 20 years there were no signs of MT.

Figure 1. Clinical and histopathological aspects of the two biopsy procedures in the patient of case 1.



Legend:
First biopsy (A-C)
A show the clinical appearance of oral leukoplakia on the left lateral border of the tongue. B and C correspond to histological sections from the first biopsy, revealing parakeratinized stratified squamous epithelium with moderate epithelial dysplasia.
Second biopsy (D-F) (20-year follow-up)
D shows the clinical aspect after 20 years of follow-up, with no visible leukoplakic lesion. E and F correspond to histological sections from the second biopsy, revealing parakeratinized stratified squamous epithelium with severe epithelial dysplasia.

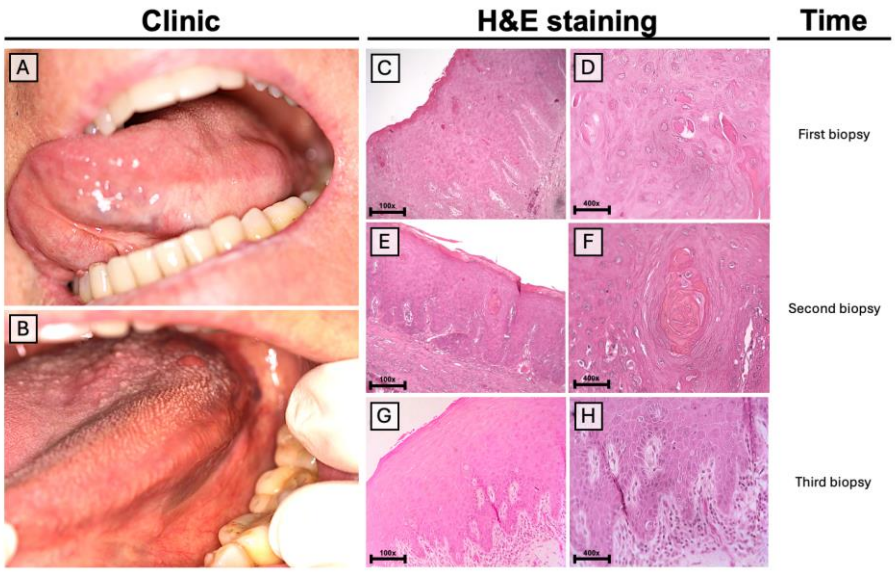
Case 2

A 55-year-old Caucasian male patient had a previous diagnostic hypothesis of oral lichen planus, however, this diagnosis was later reconsidered due to the absence of typical signs and symptoms of the disease, such as bilateral symmetrical reticular lesions (Wickham's striae), ulcerated or erosive areas, and subjective complaints of pain or burning sensation. Furthermore, no cutaneous manifestations characteristic of lichen planus, such as violaceous, pruritic, and papular skin lesions, were observed. The patient reported being a former smoker, with a 24-year history of tobacco use, accompanied by alcohol consumption for 28 years. Extraoral clinical examination revealed two homogeneous white plaques with well-defined borders on the lower lip, diagnosed as actinic cheilitis. Intraoral examination showed white plaque-like lesions on the right buccal mucosa and along the lateral border of the tongue on the same side. During follow-up over the course of one year, the absence of bilateral lesions suggested oral leukoplakia (OL) as a differential diagnosis. The white plaque exhibited

a heterogeneous texture and varying shades of whiteness, leading to a clinical diagnosis of non-homogeneous OL.

Consecutive biopsy procedures (incisional biopsies followed by surgical excision of the lesion) performed over time revealed a progression of histopathological findings: mild epithelial dysplasia, moderate to severe epithelial dysplasia, and again moderate to severe epithelial dysplasia (Fig. 2C–H). The interval between the first and second biopsy was 422 days, while 312 days elapsed between the second and third biopsy. Thus, the total time between the first intervention and the final excisional surgery was 734 days. At the ten-year follow-up, the patient remains free of the tongue lesion, with no clinical or histological evidence of malignant transformation (Fig. 2A–B).

Figure 2. Clinical and histopathological aspects of the three biopsy procedures in the case of patient 2.



Legend:
A and B - Lateral border of the tongue without signs of recurrence of the patient at 10th year of follow-up.
C - Parakeratinized stratified squamous epithelium with severe epithelial dysplasia.
D - Same case showing presence of dyskeratosis in the middle and upper parts of the epithelium.
E - Parakeratinized stratified squamous epithelium with severe epithelial dysplasia.
F - Same case showing presence of keratin pearls in the middle and upper parts of the epithelium.
G-H - Histopathology of the last biopsy showing stratified squamous epithelium with mild epithelial dysplasia.

DISCUSSION

In this study, we report two cases of oral leukoplakia with epithelial dysplasia that were followed for more than 10 years, showing no evidence of malignant transformation. Despite the complete removal of the lesion, recurrence had occurred, and the most prudent approach was to maintain regular follow-ups with biopsies when necessary. Patient 1 underwent clinical monitoring for approximately 20 years, with quarterly follow-up visits due to the presence of epithelial dysplasia, resulting in an estimated total of 80 visits. Patient 2 was followed for 10 years, also with three-month intervals, totaling approximately 40 visits. Throughout the entire period of continuous care, our stomatology service provided periodic evaluations, which were crucial for the close monitoring of these patients, and in both cases, no signs of progression to oral cancer were observed over time During the whole time on continuous care, our stomatology service provided periodic evaluations which were crucial to closely monitor these patients and for more than 10 years, and in our cases, the patients did not reveal signs of a transformation into oral cancer.

The follow-up of OL is essential to monitor any changes or progression to oral cancer by clinical evaluation and histopathology assessment when necessary. There is no specific defined time to determine if an OL will transform into oral cancer. Traditionally, it has been stated that most of MT events will occur within the first 2 years after the diagnosis of oral leukoplakia, based on a primary paper which confirmed the precancerous nature of OL[9]. However, in a systematic review by Aguirre-Urizar et al.[10] (2021), the mean time for reports of malignant transformation in the studies was 3.2 ± 0.9 years until malignant transformation, with a range between 1.8 and 5.1 years. In another systematic review, the global media rate of malignant transformation was 9.7%, and the average time for this transformation varied between 11 and 132 months[11]. In another study, MT occurred at a median of 59 months follow-up (range: 14–244), and the authors reported that since until there is no effective management to prevent MT of OL lesions, patients with OL usually remain under regular periodic check-ups for many years or even lifelong. The monitoring at an oral medicine or head and neck cancer centers (inside or not of a hospital) was reported to be effective, meaning that with a clear and strict regular follow-up regime of patients with OL resulted in early detection of MT[12]. In agreement with their study, our cases did not

reveal MT, and our long and continuous follow-up regimen was effective in supervising these patients.

Some authors discuss the possibility that performing multiple biopsies on potentially malignant oral lesions might theoretically contribute to the activation of local inflammatory processes that stimulate cellular proliferation and tissue repair, which could ultimately favor malignant transformation. However, this hypothesis still lacks robust evidence and remains controversial in the current literature[13]. On the other hand, biopsy is essential for accurate histopathological evaluation, differential diagnosis, and monitoring of cellular changes that indicate progression or regression of the lesion, being critical for clinical decision-making[14]. Thus, the challenge lies in balancing the frequency and indication of invasive procedures to ensure effective follow-up while minimizing potential risks, which reinforces the need for rigorous and individualized clinical protocols for managing these lesions[13].

The two cases reported in this study revealed clinical and epidemiological characteristics which are classic for OL and the epithelial dysplasia was classified as severe in both cases. Also important, the oral sites the lesions are indeed considered at high risk for MT, both on the tongue border. In addition, the patient in the second case was exposed to risk factors for a long period, by smoking and alcohol consumption. Yet, there was no evidence of MT, and this was supported by the continuous care in our service, which takes place inside of a University Hospital, which includes the integration of dentists, professors, and students in the team.

Regarding the clinical findings, our two cases were classified as non-homogeneous OL. Guan (2023)[6] showed that the risk of malignant transformation (MT) in non-homogeneous oral leukoplakia (OL) is 4.93 times higher than in homogeneous OL. Non-homogeneous lesions tend to present oral epithelial dysplasia (OED), and the early stage of MT may represent the first of the "three strikes" in the multistep process of carcinogenesis. A previous recent study revealed that high-risk epithelial dysplasia was more frequently observed in non-homogeneous leukoplakia (OR:7.66; CI:1.43-41.04)[15]. Surprisingly, both cases with OED and classified as non-homogeneous can represent the cases of even with all the facts pointing to a worst outcome, it was not the case.

Thus, a follow-up period of 10 years is recommended, and yet, the fact is that they should be monitored for the rest of their lives, even when considering the concept

of oral field cancerization[1,16]. This concept suggests that clinically normal-appearing mucosa may harbor genetically altered fields susceptible to malignant transformation. These premalignant fields, often undetectable to the naked eye, can persist even after surgical excision, particularly when clear margins are not achieved, thereby contributing to local recurrence or the development of new lesions over time. Therefore, the extent of surgical margins may influence long-term outcomes, and close, lifelong surveillance remains essential regardless of the initial treatment approach[17].

CONCLUSION

It can be concluded that a long-term follow-up of two patients diagnosed with oral leukoplakia and severe epithelial dysplasia was crucial to monitor the absence of malignant transformation. The clinical care of patients with oral lesions is important and oral medicine experts have a pivotal role in evaluating patients with oral potential malignant disorders. Despite the successful long-term monitoring of these two cases, it is important to emphasize that not all patients adhere well to extended clinical follow-up protocols.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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