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ORIGINAL PAPER

Oral Leukoplakia. A Five-Year Follow-Up Study

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ABSTRACT

Background: *Oral leukoplakia (OLK) is the most studied oral potentially malignant disorders in the scientific literature. Its malignant transformation (MT) rate varies between 1.1% and 40.8%, depending on the type of study and population group studied. There is no universal agreement to treat or manage these lesions, so it is up to each clinician's experience and expertise in how he/she manages these patients.*

Objectives: *The aim of this retrospective study was to assess the clinical aspects and pattern of evolution of OLK in 30 patients five years or more after the initial diagnosis.*

Materials and methods: *We selected 30 OLK patients from our database. Demographic, clinical and evolutive data was retrieved from the medical files. The following variables were analysed: age and sex, smoking habits, clinical features (form, dimension, site of the lesion), result of mycological examination, treatment and outcomes of the lesions over a follow-up of more than five years.*

Results: *For a follow-up of 119.63 months, we detected a value of 0.2% MT rate per year. Outcomes varied from the complete disappearance of the lesion to recurrence and malignant transformation with a variety of treatment methods applied.*

Conclusion: *Despite the low MT rate for a long follow-up, it is hard to say which treatment method is the best, due to the heterogeneity of the clinical aspects of the lesions and because there is no standardised test method, either genetic testing or immunohistochemical testing. We recommend a varied approach, suitable for each patient's needs and medical context, always when possible histopathological confirmation for grading epithelial dysplasia, which remains the most reliable method of checking the process of malignant transformation.*

Keywords: oral leukoplakia, OPMD, oral potentially malignant disorder, oral cancer, oral disease, oral medicine.

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INTRODUCTION

Oral leukoplakia (OLK) is an oral mucosal lesion that is defined by WHO as „a predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" (1). It is one of the most studied oral potentially malignant disorders (OPMD), oral lesions with high risk of malignancy. The prevalence of leukoplakia was most recently reported in a systematic review and meta-analysis from 2023 within the general population and in clinical studies. The prevalence of OLK in the general population was 1.35%, with an overall pooled estimated prevalence of 2.23% (95% CI 1.44–3.18%) and variations depending on the geographical regions (1.82% for Europe). Regarding the OLK prevalence in clinical-based studies, the total prevalence was 0.64%, with a pooled overall estimated prevalence of 1.36% (95% CI 0.82–2.02%) and local geographic variation (0.38% for Europe). For specific population studies, the reported total OLK prevalence was 4.67%, with a pooled overall estimated prevalence of 9.10% (95% CI 4.85–14.47%) and local geographic variation (4.85% for Europe) (2).

A recent meta-analysis shows the malignant transformation rate of OLK varies between 1.1% and 40.8% (3). The exact mechanisms that are involved in its occurrence are still unknown, but major molecular events concerning cell life-cycle and cell division are explored to date (4). It sometimes occurs in correlation with well-studied risk factors, including tobacco smoking, alcohol consumption and areca nut chewing (5). Chronic oral candidiasis has also been linked to oral leukoplakia, with the non-homogenous type being due to the presence of endogenous nitrosamines produced by some species of *Candida albicans* (6). Other factors, such as human papillomavirus infection, periodontal pathogenic microbes, nutritional deficiencies and some hereditary conditions, are also described in the literature (7). Clinically OLK is subdivided into homogenous and non-homogenous. The homogenous lesion is uniformly white, while the non-homogenous one may either be mixed red and white and is called erythroleukoplakia or it may be verrucous (8).

There is no consensus regarding the best treatment option for OLK so far, and there is no evidence of a treatment that is effective in preventing malignant transformation (MT) (9). Some studies have tested the beneficial effects of vitamin A or retinoids as well as those exhibited by non-steroidal anti-inflammatory drugs, herbal extracts, bleomycin and Bowman-Birk inhibitor but with no clear results (10). A recent meta-analysis suggests that photodynamic-therapy (PDT) has beneficial effects and may be a useful therapeutic strategy in the management of oral leukoplakia as a non-surgical treatment (11). Other authors suggest that CO_2 laser excision is a good treatment for OLK due to its effectiveness and low associated morbidity (12) but it does not avoid the clinical outcomes of recurrence or malignancy (13). One study shows that CO_2 laser excision has better results than the Nd:YAG laser evaporation (14).

Study objective

The objective of this retrospective clinical study was to assess the clinical features of OLK in 30 patients and the pattern of evolution during a minimum period of five-year follow-up since the initial diagnosis. ❑

MATERIALS AND METHODS

For this retrospective research, we revisited the medical charts of patients with the diagnosis of OLK from the database of the Oral Medicine and Pathology Department of the Faculty of Dentistry, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

Thirty-seven files of patients diagnosed with OLK were selected for the current study. The main inclusion criterium was a minimum follow-up period of five years mentioned/documented in the medical files.

The diagnosis of OLK was done based on the recommendations of WHO, which included the clinical and histopathological criteria (1). Oral mycological testing was recommended in cases where there was a clinical suspicion of the *Candida albicans* co-infection (the presence of symptoms related by the patients or a speckled aspect of the lesion).

All patients were adults and a preliminary diagnosis was established by the oral medicine specialist of the department. Each patient was contacted by phone and asked to return for a follow-up consultation. Seven patients refused to return for follow-up and were not included in

the present study. For the remaining 30 patients, demographical data such as age and sex, smoking habits and clinical data (form, dimension, site of the lesion, evolution), mycological examination result and treatment options were all retrieved from the medical files. Nine patients had no histological evaluation for the OLK lesion as they refused to have a biopsy taken.

The annual MT rate was calculated based on the period of follow-up as it is mentioned in the medical files of all patients.

All participants consented to participate in this research. The study was approved by the Ethics Committee of Research of "Carol Davila" University of Medicine and Pharmacy with the number 1139/13.01.2023, according to the principle of the Helsinki Declaration. ❑

RESULTS

The main demographic and clinical characteristics are summarised in Table 1. Study participants comprised 17 females (57%) and 13 (43%) males with a mean age of 47.27 years (standard deviation 11.90). Of the total number of patients, 67% (n=20) were smokers, 20% (n=6) non-smokers and 13% (n=4) former-smokers.

Regarding the clinical form of OLK, 67% (n=20) were homogenous, while the remaining 33% (n=10) were non-homogenous. Most lesions [67% (n=20)] were smaller than 2 cm^2, 23% (n=7) ranged between 2-4 cm^2 and 10% (n=3) were larger than 4 cm^2. Most lesions were single lesions [70% (n=21)], while the remaining 30% (n=9) were lesions that appeared on multiple sites in the oral cavity. The most highly affected topographic region of the mouth was the gingiva (n=13), followed by buccal mucosa (n=12), flour of the mouth (n=7), tongue (n=2) and other regions (n=2).

In 30% (n=9) of patients, *Candida* testing was not required due to lack of clinical suspicion. Of those who underwent testing, 43% (n=13) had negative results, whereas the remaining 27% (n=8) had positive results.

Nine patients (30%) refused to have a biopsy taken. The majority of cases (n=11.37%) had no dysplasia, nine cases (30%) had mild dysplasia and one case (3%) moderate dysplasia. No severe dysplasia was detected.

Variable	Value
Age	47.27±11.90 (years)
Sex	
Males	13 (47%)
Females	17 (57%)
Smoking habit	
Current	20 (67%)
Former	4 (13%)
Never	6 (20%)
Lesion size	
>2cm^2	20 (67%)
2-4 cm^2	7 (23%)
<4cm^2	3 (10%)
Candida albicans test	
Positive	8 (27%)
Negative	13 (43%)
Not-done	9 (30%)
Number of OLK lesions	
Single	21 (70%)
Multiple	9 (30%)
Clinical form	
Homogenous	20 (67%)
Non-homogenous	10 (33%)
Location	
Buccal	12
Gingiva	13
Floor of mouth	7
Tongue	2
Other	2
Histology	
No dysplasia	11 (37%)
Mild dysplasia	9 (30%)
Moderate dysplasia	1 (3%)
Severe dysplasia	0
Not done	9 (30%)
Follow-up	119.63±40.67 (months)
Treatment	
No treatment	7 (15%)
Quit smoking	11 (24%)
Local treatment	12 (27%)
Systemic treatment	3 (7%)
Surgical removal	12 (27%)
MT	Two cases (0.2% per year)

TABLE 1. Demographic and clinical features of the study population

The mean follow-up period was 119.63 months, with a standard deviation (SD) of 40.67 (Figure 1). As the OLK management is individualised for each patient, treatment options and outcomes varied throughout the study group. Of all patients, 27% (n=12) underwent surgical removal of the lesions, 27% (n=12) received local treatment, 24% (n=11) discontinued smoking, 15% (n=7) had no treatment and 7% (n=3) had systemic treatment. Results are summarised in Table 2. In 19% (n=7) of cases, the lesions had not changed clinically during follow-up, while in 17% (n=6) of patients, the lesions extended in dimension and in 14% (n=5) they re-occurred after surgical removal. Only in 31% (n=11) of patients, OLK lesions totally remitted. In the present study group, we detected

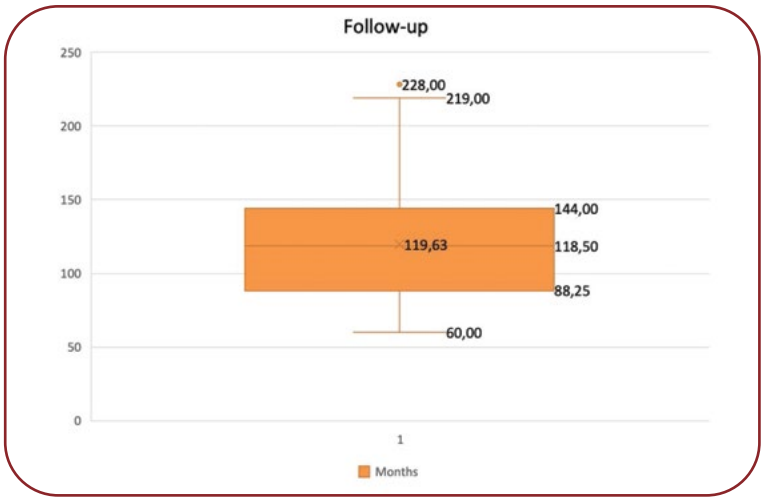

FIGURE 1. Box-plot showing the distribution of months of follow-up for the studied group

TABLE 1. Demographic and clinical features of the study population

Outcomes	
No change	7 (19 %)
Partial remission	5 (14%)
Total remission	11 (31%)
Re-occurrence	5 (14%)
Extended lesion	6 (17%)
Malignization	2 (5%)

two patients who developed MT from the OLK lesions. The first patient was a 56-year-old male smoker with a non-homogenous verrucous OLK lesion on the buccal mucosa; mild dysplasia was revealed by the initial biopsy, and 144 months later MT occurred. The second patient, a 36-year-old female smoker, had a non-homogenous speckled OLK lesion located on the buccal mucosa; thus, no dysplasia was detected on the histopathological evaluation and the lesion malignancy was detected after 228 months.

The calculated MT rate was 6.6% for the group, with 0.2% rate *per* year.

Figure 2 displays the evolution of OLK in a patient who gave up smoking after initial clinical diagnosis but resumed smoking by the time of the last follow-up. The patient was not willing to undergo a biopsy of the lesion; thus, no histopathological evaluation was available. ❑

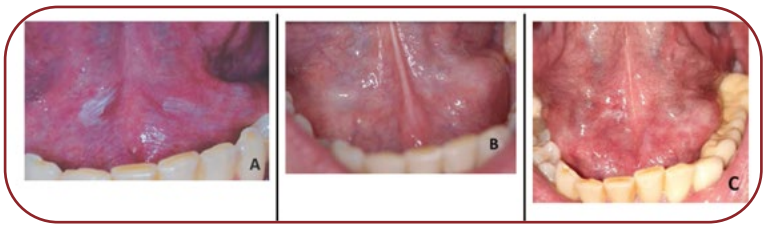

FIGURE 2. Clinical evolution of oral leukoplakia on the floor of the mouth in patient number 5 (C.D, male, 34-year-old, smoker). **A:** First visit clinical aspect of homogeneous OLK (18.04.2014); **B:** Clinical aspect after cease of smoking (28.07.2014); **C:** Clinical aspect during the last follow-up – partial recurrence of OLK; patient started smoking again between visits (19.07.2022).

DISCUSSIONS

As WHO anticipated that the oral cancer incidence was expected to increase, early detection and treatment of OPMDs in order to avoid malignant transformation has become even more important (15). Oral lesions included in OPMDs are currently statistically associated with a risk of cancer progression. A consensus report by WHO Collaborating Centre for Oral Cancer (1) categorised these disorders as follows: oral leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, palatal lesions in reverse smokers, lupus erythematosus, epidermolysis bullosa, and dyskeratosis congenita.

From these, oral leukoplakia (OLK) has a global prevalence of 2.23% for population-based studies, 1.36% for clinic-based population studies and 9.10% for specific populations (16). The prevalence of OLK in a dental hospital in Romania is 3.47%, as shown in a recent study (17).

The main problems regarding OLK are in connection with its dynamic evolution and prognosis. A scoping review of the literature aiming to determine which parameters were used for follow-up emphasised the lack of standardised parameters and the absence of consensus on determining the appropriate management to reduce OLK aggravation (18).

The present study analyses the OLK evolution in 30 Romanian patients. Our results are generally consistent with those reported by other studies, despite the small number of participants.

Although in the literature OLK has been more frequently seen in males than females (16, 19), in the present study it predominantly affected women (57% of our study subjects were females). Other clinical studies conducted in European countries, including Spain (20), Northern Ireland (21) and the Netherlands (22), reported similar findings. This may be due to the fact that women usually have a heightened concern for their oral health and health in general than men.

In our study group, 67% of patients were currently smoking, which was in line with other reported studies (17, 23). Although smoking is a

major risk factor for oral cancer, OLK studies describe particular demographic features that carry a risk for malignant development, including females, non-smoking status, age over 50 years (24).

The most commonly encountered clinical form was the homogenous form (67%). This outcome is in line with other studies (20, 25). Rupert *et al* (20) analysed the clinical features and evolution of OLK in 412 patients with 86.8% of homogeneous lesions. In our study group, the most commonly found size was smaller than 2 cm^2 (67%). Evren *et al* reported similar findings in 140 OLK cases, of which 74 (53%) were smaller than 2 cm2 (22). A scoping review conducted by Saldivia-Siracusa *et al* included 18660 OLK patients in whom there was also a predominance of OLK lesions smaller than 2 cm^2 (74.4%) and of those with a homogeneous form (60.8%) (18).

The 0.2% MT rate for the present study group was different than that reported by other studies. Some studies showed that variations of MT rates were caused by multiple factors and some clinical predictors (24). In a thorough meta-analysis that included 17830 OLK patients, Iocca *et al* reported an OLK MT rate of 9.5% (99% CI 5.9%–14.00%) cumulative score and 1.56% each year (26). Other authors calculated an MT percentage of 13%, while noting that in the international scientific literature there was no consensus regarding parameters to be reported in order to provide a standardisation proposal of follow-up study (18).

Van der Waal also emphasised the lack of reliable clinicopathological or molecular predicting factors of malignant transformation that can be used in individual patients was a major downside of OLK research, MT reporting and patients' quality of life (27). Although we recommend a histopathological evaluation of the OLK lesions for determining the epithelial dysplasia grade, it was difficult to establish a standardised treatment from the first visit. Thus, it rests on the experience and skill of each clinician in how they manage the OLK lesions. It would be useful to have a set of standardised tests that we can use to predict the relative risk of malignant transformation. To date, the histological grading of epithelial dysplasia remains the best predictor of MT, although it remains to be seen if the classical WHO system (28) or the binary system (29) can predict the MT rate more accurately.

Our study has a few limitations that must be addressed: firstly, the limited sample size for the selected group, and the other one, the lack of histopathological diagnosis for patients who refused biopsy. Due to these factors, the results need to be interpreted carefully. ❑

CONCLUSIONS

We found a small MT rate among our study participants compared to other studies for the mean follow-up of almost 10 years. It is difficult to state which treatment method is better; it depends on the clinical features of the lesions and the general health status of each patient. In addition, it is challenging to predict the outcome of OLK lesions in the absence of genetic investigations or immunohistological markers that might alert you to any risk or even occurrence of MT. We recommend biopsy and histological grading of epithelial dysplasia, which remains the best predictor of MT process in OLK lesions.

Ethics approval: Institutional Review Board statement: The present study was approved by the Committee of Ethics in Research of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania (No. 1139/13.01.2023).

Patients' informed consent: obtained from all patients involved in the present study.

Conflicts of interest: none declared.

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Data availability: Datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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