

Clinical and pathologic patterns of oral leukoplakia: A retrospective study of surgical management and clinical outcome

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Abstract—The aim was to evaluate the clinical-pathological characteristics and to assess the outcomes of the clinical management of oral leukoplakia (OL), considering the clinical-pathological characteristics as predictors of OL progression. This retrospective observational analysis was conducted with patients referred to our university between the years 1998 to 2013. Only the medical records containing age, gender, smoking status, alcohol consumption, clinical, pathological and management documentation were included. A new biopsy was performed in cases in which recurrence or changes in clinical parameters were observed. The association between the clinical, demographic and histologic characteristics and the clinical fate of OL was analyzed with the Fisher exact test. Of 120 patients, 22 presented demographic and clinicopathologic data eligible for further analysis, of which 54.5% were female and 45.4% were male. The mean age was 52.5 ± 13.11 years, and the follow-up period ranges from 12-180 months. Tongue dorsum and buccal mucosa were the most affected sites, with predominance of lesions with $<200 \text{ mm}^2$ (77.3%) in size, with a majority representing the homogeneous type (95.4%). Twenty two percent presented changes in the clinical/histological behavior. Most of the surgically treated cases presented no signs of changes in the behavior. Clinical, demographic and pathologic variables were not significantly associated with remission/stabilization or recurrence of OL ($p > 0.05$). Although the possible bias related with retrospective studies, our results suggests that surgical removal of OL should be performed even in cases without OED. None of the studied clinical traits were reliable in the prediction of the risk of OED worsening.

Keywords—Epidemiology, Oral leukoplakia, Prognosis, Risk factors, Surgery, Treatment.

I. INTRODUCTION

More than 90% of the head and neck malignant neoplasms are Oral squamous cell carcinoma (OSCC), with more than 300.000 arising annually worldwide [1-3]. Over the last 3 decades the survival rates of OSCC have not improved significantly [4], remaining in a 50% to 55% range. Prevention of malignant transformation by the detection and treatment of oral potentially malignant disorders (PMDs) could influence dramatically the patient's survival rates and may contribute to reducing the burden of oral cancer [5].

PMDs can be defined as morphological tissue changes in which there is a higher probability of emergence of malignancies in comparison with normal oral mucosa [5]. Although there is a statically increased risk for PMDs to progress to cancer, malignant transformation rate of these disorders could vary from 0.3 to 27% [6,7]. Oral leukoplakia (OL) is the most common PMD of oral cavity and has been reported as a lesion with an increased risk of progressing to cancer [8-10]. The most recent definition of OL describe this condition as “predominantly white plaques of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk

for cancer” [11]. Clinically OL is classified into homogenous and non-homogenous types, with the former characterized by a uniformly and thin white plaque, with a flat and smooth surface, with occasional shallow cracks, and the latter characterized by the presence of a speckled (white and red in color, also called erythroleukoplakia), nodular (small red or white polypoid outgrowths) or verrucous lesion (white corrugate plaque) [12]. Histologically, this condition may show normal epithelium or varying degrees of oral epithelial dysplasia (OED) [13].

The presence of OED in OL could be associated with a possible progression to malignancy. However, the histologic assessment of OED can carry intra and interobserver variability, and such method should not be considered the only tool to evaluate the risk of malignant transformation [10]. In fact, there are some clinical features that could be also useful in the OL prognosis assessment [14], as anatomical site, size of lesion, clinical type, gender, age and habits¹⁰. According to Van Der Waal (2009) [9] OL localized at tongue or floor of mouth, larger than 200 mm², categorized as non-homogeneous, in female patients, in patients with >50 years-old and/or in non-smokers have an increased risk of malignant progression.

Despite the variety factors that could be related with an increased risk of OL malignant transformation, the prediction of the outcome of an individual patient is a challenging task, since the clinical risk factors could vary between different population, and the histologic grading system could not predict with accuracy the malignant transformation [15]. These factors point out that there is a need for studies to reinforce which clinical features constitute risk factors for OL and OL malignant transformation in the different populations. It is also emphasized that there is no consensus about OL management [5], with a lack of information about the impact of interventions in the prevention of the progression of OL into cancer [14]. The study of clinical and histopathological characteristics of OL, allied to the analysis of the impact of the management modality in the prevention of malignant progression, could aid in the identification of malignant transformation risk factors in different population. Thus, the aim of this study was to evaluate the clinical-pathological characteristics of OL and to assess the outcomes of its clinical management, considering the clinical-pathological characteristics, smoking habit and alcohol consumption habit as predictors of OL progression.

II. METHODS

This study was approved by the Human Ethics Committee of our Institutional Review Board at number 015/2010. Informed consent was obtained from all eligible subjects. A retrospective observational analysis was conducted with patients referred to the oral medicine clinic of our university between the years 1998 to 2013. Only the medical records containing age, gender, smoking status, alcohol consumption, clinical (anatomic location, color and size of the lesion), pathological and management documentation were included. Records of patients under 12 months of follow-up or with uncertainty in OL diagnosis were excluded. Of 120 patients, 22 presented demographic and clinicopathologic data eligible for further analysis (Table 1). The patients were then reassessed in order to update the overall health status, smoking and drinking habits, and physical clinical status (anatomic location, size, color and surface). A new biopsy was performed in cases in which recurrence or changes in clinical parameters were observed.

2.1 Clinical evaluation, management and outcome of Oral Leukoplakia

The management proposed for this sample were assessed according the evolution of lesions, resulting in remission/stabilization or change in behavior/recurrence of the lesion.

Evaluation criteria

1. Remission: when surgical excision was performed, and no signs of recurrence was observed;
2. Stabilization: the lesion remained unchanged during the follow-up period, where the complete excision was not performed;
3. Change in lesion behavior: the lesion had clinical or pathological changes (increase in size, development of erythematous areas or/and progression of dysplastic grading), where the complete excision was not performed;
4. Recurrence: recurrence of the lesion at the primary site or the development of lesions in other sites as a result of field change.

2.2 Histopathological analysis and histological grading of OED

The histological slides of the first biopsies were reviewed by two independent oral pathologists and the histological grades of OED were determined according to the World Health Organization (WHO) [16] criteria in a blinded fashion. According to the clinical evaluation criteria proposed in this study, new biopsy specimens were obtained from 5 patients. The specimens were fixed in

10% buffered formalin (pH 7.4), embedded in paraffin, submitted to 5 µm histological sections for routine staining with hematoxylin eosin (H&E) and analyzed under light microscopy. The histological grades of OED in the new biopsies were also determined by two independent oral pathologists in agreement with WHO criteria. Any disagreement in the findings was discussed among the pathologists to render a final evaluation.

2.3 Statistical Analysis

Descriptive statistics was used to summarize patients clinical, demographic and pathological data. The association between the clinical, demographic and histologic characteristics and the clinical fate (remission/stabilization/recurrence) of leukoplakia was statistically analyzed with the Fisher exact test. Statistical significance was established at $p < 0.05$. Statistical analysis was carried out using the software SPSS version 19.0 (Statistical Package for the Social Sciences, Chicago, IL, USA).

III. RESULTS

The total of 22 patients was included in the present research, of which 54.5% were female and 45.4% were male. The mean age was 52.5 ± 13.11 years, and the follow-up period ranges from 12-180 months (mean= 96.54 ± 52.56). Tongue dorsum and buccal mucosa were the most affected sites, with predominance of lesions with $< 200 \text{ mm}^2$ (77.3%) in size, with a majority representing the homogeneous clinical type (95.4%) (Table 1).

Table 1- Clinical, demographic and histological profile of the patients.

Clinical/demographic/Histologic characteristics	n
<i>Gender</i>	
Female (F)	12
Male (M)	10
<i>Age</i>	
<50.0	11
50.0-59.11	6
≥ 60	5
<i>Site (including recurrences)</i>	
Tongue dorsum	6
Buccal mucosa	5
Mandibular/Maxillary alveolar ridge	5
Lateral border of the tongue	4
Vestibule	3

Retromolar area	3
Hard palate	2
Mandibular/Maxillary gingivae	2
<i>Size of lesion (largest in cases with multiple lesions)</i>	
<200mm ²	5
≥200mm ²	
<i>Clinical appearance</i>	
Homogenous	21
Non – Homogenous	1
<i>Epithelial Displasia</i>	
Without dysplasia	7
Mild dysplasia	9
Moderate dysplasia	6
Severedysplasia	0
<i>Number of lesions</i>	
Single	12
Multiple	10
<i>Smoking history</i>	
Never	8
Past or present	14
<i>Alcohol consumption</i>	
Never	11
Past or present	11
<i>Follow-up</i>	
1 year	2
5 years	9
10 years	7
15 years	4

Among the 22 evaluated patients, 77.3% had complete remission/stabilization of the lesions, and 22.7% presented changes in the clinical/histological behavior or recurrence (Figure 1). Most of the surgically treated cases presented no signs of changes in the behavior or recurrences (Table 2). From all sample, 68.1% presented dysplasia, 45.4% presented multiple lesions, 63.6% were smokers and 50% were drinkers. The characteristics of patients who had changes in behavior/recurrence at the primary site or other sites are presented in Table 3. Clinical, demographic and pathologic variables (age, gender, smoke habit, drink habit, clinical appearance and grade of OED) were not significantly associated with remission/stabilization or

recurrence of OL ($p>0.05$). Conservative and non-conservative management do not differ in respect of OL

clinical outcome ($p>0.05$).

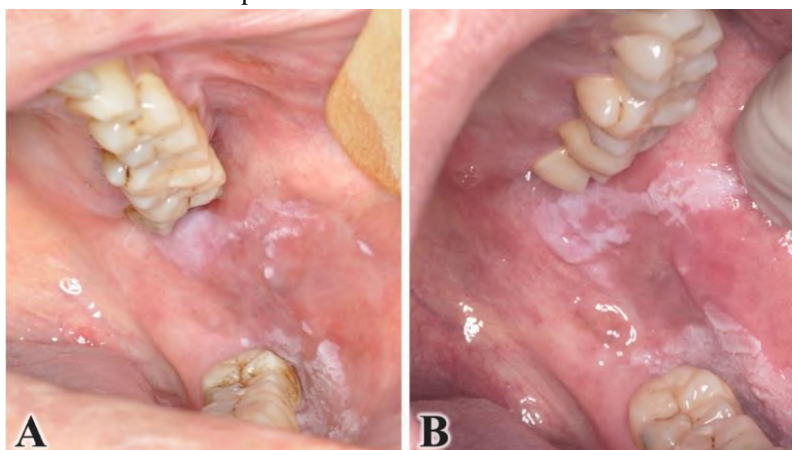


Fig.1: Clinical image of oral leukoplakia characterized by a white homogeneous patch in the left buccal mucosa. (A) Initial clinical presentation. (B) Clinical aspect 1 year after the initial biopsy: Increasing in size and changes in the clinical appearance.

Table 2: Patients outcome according to the management modality.

Clinical/pathological progression	N (%)	Conservative Treatment	Non-conservative treatment (surgical)
Remission/Stabilization	17 (77,3%)	8	9
Change in the behavior /Recurrence	5 (22,7%)	4	1

Table 3 - Clinical, demographic and histological characteristics of lesions that presented changes in the behavior/recurrence

Patients	1	2	3	4	5
Gender	F	M	F	F	F
Age	83	57	40	50	57
Site	Right mandibular alveolar ridge	Lateral border of the tongue	Buccal mucosa	Tongue dorsum	Left mandibular alveolar ridge
Size of lesion	>200mm ²	<200mm ²	>200mm ²	<200mm ²	<200mm ²
Clinical appearance	Homogenous	Homogenous	Homogenous	Homogenous	Homogenous
Smoking history	No	No	Yes	Yes	No
Alcohol consumption	No	No	Yes	No	No
Epithelial dysplasia (first biopsy)	Mild dysplasia	Without dysplasia	Without dysplasia	Without dysplasia	Without dysplasia
Epithelial dysplasia (Follow-up biopsy)	Moderate dysplasia	Mild dysplasia	Mild dysplasia	Moderate dysplasia	Mild dysplasia
Treatment	Conservative treatment	Non-conservative treatment	Conservative treatment	Conservative treatment	Conservative treatment

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<i>Time to recurrence</i>	4 years	11 years	2 years	7 months	6 years
<i>Clinical fate</i>	Progression of the grade of epithelial dysplasia + Recurrence at another site (left mandibular alveolar ridge)	Progression of the grade of dysplasia	Progression of the grade of dysplasia	Progression of the grade of dysplasia + Recurrence at another site (Tongue dorsum)	Progression of the grade of dysplasia + Increased size (4mm – 8mm)

IV. DISCUSSION

The management of OL could be a real dilemma for the clinician, varying from just a long-term observation to surgical excision [9]. Many risk factors should be considered when the treatment modality of OL is debated, this include clinical, demographic and histological characteristics, such as anatomical site, size of lesion, clinical type, gender, age, smoke or drink habits, and the grade of OED [10, 14]. Although some of the mentioned risk factors are apparently established in the current literature, there is a strong variation of these features in the different population [17-20]. This emphasizes the importance of additional studies to reinforce which clinical/demographic features constitute risk factors for malignant transformation of OL in specific population and which management modality could be considered in the presence of the mentioned risk factors.

In the present study it was presented the clinical, demographic and histological data from 22 midwestern Brazilian patients diagnosed with OL with a follow-up period varying from 12 months to 180 months. It was found a slight tendency of OL to occur in female patients, mean age of 52.5 years old, with a predominance of the homogenous type. In relation with age and clinical type, our data are in accordance with the most part of the studies of the population of developed and developing countries, with the mean age above the fifth decade of life [21] with the homogenous form being the most common type of OL [22]. It was found a singular trace in the present sample, which was the higher prevalence of OL in female patients. Most reports showed that female was found to be much less likely to have OL [23]. These findings could be justified by the fact that men are more prone to have the smoking habit [24]. Apparently, in our sample, the female prevalence could be explained by the predominance of the smoke habit in these patients, supporting that local habits, which could vary from the different geographic regions,

could influence in the occurrence of OL. Despite the lack of studies demonstrating the relation of smoke habit with OL in a mechanistic way, a great number of investigations have pointed a relation between smoke and OL [25].

Here we also observed a tendency of OL to present changes in it behavior or to recurrence in female patients, even though there was no significant association between gender and the risk of OL progression. Despite the fact that OL is usually less frequent in females, it was observed previously that female gender has a greater risk of malignant transformation [24]. However, it has not been elucidated why women are more disposed to malignant transformation, and which habits or environmental or genetic factors are involved in this change in the behavior.

One of the main risk factors for progression of OL to malignancy is based on it clinical features, as the clinical type (homogeneous and non-homogenous), size and anatomical site. According to Speight et al. (2018) [26] there is strong association with an increased risk of malignant progression when the lesions are represented by the non-homogenous type, when exceeds 200 mm², and when occurs in the tongue or floor of mouth. In the present investigation the homogeneous type account 95.4% of our sample, with 77.3% of OL samples with less than 200 mm² in size, and tongue dorsum, buccal mucosa, alveolar ridge and lateral tongue the most prevalent oral sites for OL. It was also observed that the homogenous type has a potential to have changes in clinical or/and histological behavior. Although there is no statistical significance, all the cases that showed changes in the behavior or recurrence were homogeneous type at first. In fact, OL is a dynamic condition that could vary in it clinical and histological appearance over the time, and even having a lower risk of malignant transformation compared to the nonhomogeneous type, homogeneous OL carries an increased risk of progression to cancer in comparison with normal oral mucosa [26], indicating that this data should

not be underestimated. Additionally, OED could be more prevalent in specific anatomical sites, such as tongue [27], like we demonstrated in our sample.

There is some evidence that size of OL have a significant correlation with its progression to cancer [23, 28]. According to Warnakulasuriya and Ariyawardana (2016) [23] lesions with more than 200 mm² presents a higher risk to progress to malignancy. In the present study, even homogenous lesions with less than 200 m² progress in the grades of OED. Nevertheless, none of the 22 cases of this investigation presented malignant transformation. The prediction of risk of malignant progression of OL based on the clinical parameters, despite the evidence of its correlation, could be problematic, since these parameters usually are investigated through observational studies, which could present bias and could differ among the distinctive population.

In this report we also analyzed not only the clinical characteristics, but also the grade of OED. OED assessment can be a real challenge in order to predict the risk of progression of OL, owning a subjectivity related to its intraobserver and interobserver variability [29]. Anyway, OED histologic grading remains the accepted method for evaluate OL prognosis [15], with some evidence that the more severe the epithelial dysplasia is greater are the chances to progress to malignancy [20]. However, malignant transformation of mild dysplasia and complete regression of severe dysplasia could be also observed, which raises doubts as to the classification of risk of malignancy adopted in OL [15, 29]. In our findings it was observed that the majority of OL lesions which presented changes in the behavior or recurrence were initially graded as a lesion without epithelial dysplasia. In fact, OED progression could be related with various factors, since the duration of the lesion, habits and infection could influence the dysplasia status [15].

The management of OL should be carefully pondered because an aggressive treatment modality could not be reasonable, considering the related morbidities, and also the fact that lesions, even with mild or moderate OED, could not progress to malignancy. Our results suggested that intervening even in lesions without epithelial dysplasia could be considered, since the observation alone seems to be not satisfactory to prevent progression of OED. Comparably, Arnautakis et al. (2013) [30] evocated that an early excision of any PMD should performed, since they found a high recurrence rate or malignant progression of lesions that were passive observed over the time, even when they were classified as a mild OED.

V. CONCLUSION

Prospective studies with larger sample should be considered to expand our findings, since we evaluated just 22 cases. Although the possible bias related with retrospective studies, our results suggests that surgical removal of OL should be performed even in cases without OED. However, none of the studied clinical traits were reliable in the prediction of the risk of OED worsening.

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