

Oral Lichen Planus: Clinical Profile and Determination of Oral Epithelial Dysplasia

Liquen Plano Oral: Perfil Clínico y Determinación de la Displasia Epitelial Oral

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ABSTRACT: Oral lichen planus (OLP) is the most common noninfectious oral disease and is considered a potentially malignant disorders (OPMDs). The etiology and pathogenesis of OLP are not completely understood and the malignant transformation remains under discussion. The aim was to assess the cytological and histological features of OLP, and establish relationship between clinical and microscopic profiles. A total of 10 patients diagnosed with OLP were investigated. Slides were prepared and stained with Hematoxylin–Eosin to identify 8 histological features and 8 cytological alterations. Finally, oral epithelial dysplasia degree was determined. Hyperplasia and loss of polarity of basal cells were detected in 90 % of cases. Anisonucleosis, nuclear pleomorphism and hyperchromasia affected 100 % of the sample. Six cases were classified as mild-grade OED, with no cases of severe-grade. Microscopic alterations were higher in women ($P < 0.0001$) and moderate-grade OED was diagnosed only in this group ($P < 0.0014$). The findings demonstrated that microscopic and clinical data association should be analyzed to a better understand of disease behavior. OED was absence only in one case, so the periodic follow-up of patients diagnosed with OLP is mandatory to avoid the malignant transformation.

KEY WORDS: oral epithelial dysplasia, oral lichen planus, potentially malignant disorders.

INTRODUCTION

The lesions or conditions of oral cavity with potential malignancy were defined as “potentially malignant disorders” (OPMDs) in a workshop coordinated by World Health Organization (Barnes *et al.*, 2005). It is well accepted that OPMDs could precede oral squamous cell carcinoma (OSCC) (Warnakulasuriya *et al.*, 2007). In a wide range of different OPMDs, lichen planus (OLP) is an autoimmune chronic disease mediated by T lymphocytes that involves the stratified squamous epithelial tissue which etiology and pathogenesis is not completely understood. It's the most common noninfectious oral disease, often detected in mucosa, tongue and gum, and is estimated to affect 0.5% to

2.0% of general population (Ismail *et al.*, 2007; Roopashree *et al.*, 2010; Gupta & Jawanda, 2015).

The age ranges from 30-60 years, and is more common in women (Wang *et al.*, 2015). Unlike OSCC, risk factors implicated as potential initiators and/or promoters include tobacco, alcohol, ultraviolet radiation, human papillomavirus (HPV), immunosuppression, areca nut (betel nut or quid), and socioeconomic status are not directly linked to OLP development (Huber & Tantiwongkosi, 2014). On the other hand, there is growing interest in non-smoking non-drinking (NSND) patients presenting with OSCC. Koo *et al.* (2013) identified a distinct subgroup of elderly

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female patients presenting with OSCC not associated with the traditional risk factors, who have a worse prognosis. There are, however, few published reports of OSCC in the elderly.

Although OLP demonstrated benign behavior, the malignant transformation remains under discussion. According to van der Meij *et al.* (1999) there is a tendency to accept its potential transformation, with a rate amounting less than 0.5 %. In a systematic review, Fitzpatrick *et al.* (2014) evaluated evidence of malignant transformation, and in a total of 7,806 patients with OLP, 85 developed OSCC, which represents 1.09 percent of transformation rate. Other reports also associated OLP with oral cancer (Roopashree *et al.*; Gorsky & Epstein, 2011). It is widely accepted that early diagnosis and treatment of OPMDs are relevant to prevent OSCC. In the last years, diagnosis has been based mainly on clinical and histological data. Therefore, a detailed microscopic analysis of those lesions is critical for a better understanding of distinct clinical behavior and evolution. In this context, the detection and degree determination of epithelial dysplasia represent an important feature that could lead to a more accurate diagnosis of OPMDs, such as OLP.

Essentially, oral epithelial dysplasia (OED) has been considered the most important microscopic aspect of those disorders and it is defined by the presence of specific histological and cytological alterations. Oral pathologists need to detect a combination of architectural changes in epithelium before grading dysplasia (Warnakulasuriya *et al.*, 2008; Pitiyage *et al.*, 2009; Liu *et al.*, 2011). However, defining OED degree and malignancy transformation is still a challenge. Diagnosis of individual features of epithelial dysplasia is required to design systems of high predictive value, especially in the upper aerodigestive tract, where there is considerable variation in epithelial structure (Tilakaratne *et al.*, 2011).

The purpose of this study was to identify the histological and cytological alterations of epithelial dysplasia in OLP cases and define OED degree. The correlation between microscopic findings with clinical data was also performed.

MATERIAL AND METHOD

Study population. The retrospective study was approved by Ethics Committee of the Institution where

it was developed (protocol 071/10– Federal University of Espírito Santo/UFES, Brazil). Written informed consent was obtained from each participant and the study was performed in accordance with the Declaration of Helsinki. Paraffin-embedded tissue samples of OLP were obtained by biopsies from different sites of oral mucosa from the archives of the Oral Pathology Laboratory of Dentistry School/UFES between 2004–2010. Clinical and histopathological data were collected from medical records and included: gender, age, lesion site and history of tobacco exposure. Exclusion criteria were: incomplete clinical data and insufficient sample for microscopic analysis.

Microscopic analysis. Slides of OLP samples were prepared and stained with Hematoxylin–Eosin (HE) to identify histological and cytological alterations and to define OED degree. The criteria applied for diagnosis are consistent with Warnakulasuriya *et al.* The histological features studied were: irregular epithelial stratification, loss of polarity of basal cells, basal cells hyperplasia, drop-shaped rete ridges, increased number of mitotic figures, abnormally superficial mitoses, dyskeratosis and keratin pearls. The cytological feature variables considered were: anisonucleosis, nuclear pleomorphism, cellular pleomorphism, increased in nuclear-cytoplasmic ratio, increased nuclear size, increased number and size of nucleoli, hyperchromasia and atypical mitotic figures. Each feature was classified as present or absent. After that, lesions were scored for epithelial dysplasia degree as mild, moderate or severe-grade. Images were acquired with a light microscope (Primo Star, Zeiss, Germany) coupled to a digital camera system (Axiocam HRP, Zeiss, Germany) at 100X magnification

Statistical Analysis. Statistical analysis was performed using the GraphPad Prism 5.01 program (GraphPad Software, Inc., San Diego, CA, USA). Association between clinical data with microscopic features was tested by Two-way ANOVA. The results were considered significant when $p < 0.05$.

RESULTS

Clinical data: From the 797 oral and maxillofacial lesions retrieved from the files of Oral Pathology Laboratory, 13 cases were diagnosed as OLP. Of these total cases, 3 were excluded due to incomplete clinical data and/or insufficient sample for microscopic analysis. OLP lesions represented 1.63 % of oral diseases

diagnosed in the Oral Pathology Service (UFES, Brazil). Age range 26–94 years (median, 47.5 years) and most of patients were older than 40 years (60 %), women (80 %) and the most affected site was jugal mucosa (60 %). Regarding habits, 60 % of patients related no smoking. Table I summarized patient data.

Microscopic findings: Regarding histological features, hyperplasia and loss of polarity of basal cells were the most common (90 %). Anisonucleosis, nuclear pleomorphism and hyperchromasia represented the cytological variables that affected 100 % of the cases (Table II). After microscopic variables identification, the OED was determined and 60% of lesions were classified as mild-grade with no cases of severe-grade (Table I). The clinical and histopathological features are presented in Figure 1.

Presence of OLP with mild-grade (A) and moderate-grade (B) dysplasia in jugal mucosa. Loss of polarity of basal cells, anisonucleosis and nuclear pleomorphism is observed in mild-grade lesion (C), on other hand, irregular epithelial stratification, loss of polarity of basal cells, anisonucleosis, nuclear and cellular pleomorphism could be detected in moderate-grade lesion (D).

Association of clinical and microscopic data: Some epithelial dysplasia variables were tested to identify possible associations between microscopic features and gender. It was possible to observe that histological and cytological alterations were found in a higher frequency in female patients ($P < 0.0001$) (Fig. 1E). Still, OLP with moderate-grade epithelial dysplasia was diagnosed only in women ($P < 0.0014$) (Fig. 1F).

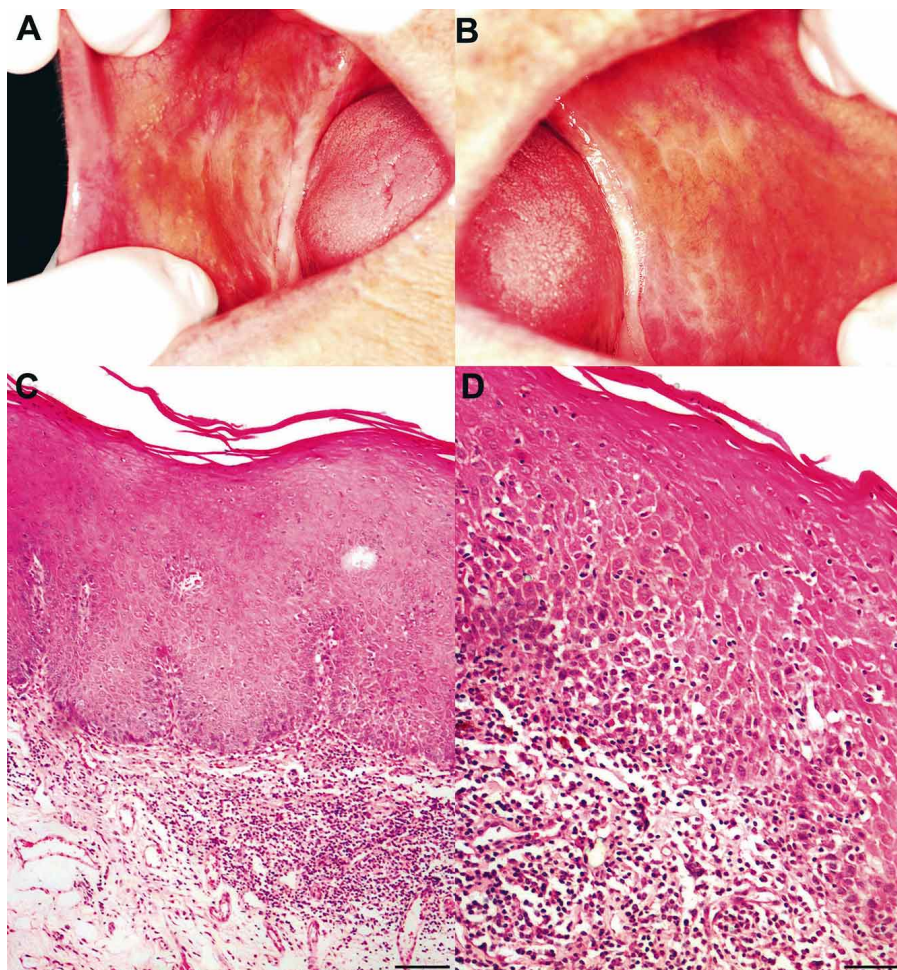
Table I. Data from patient's included in this study.

Patient	Sex	Age	Site	Smoking	OED
1	F	29	Jugal mucosa	N	Mild
2	M	26	Jugal mucosa	NI	Mild
3	F	57	Jugal mucosa	N	Absence
4	M	50	Gum	N	Mild
5	F	53	Gum	NI	Mild
6	F	39	Jugal mucosa	N	Mild
7	F	22	Jugal mucosa	N	Mild
8	F	94	Gum	NI	Mild
9	F	56	Jugal mucosa	Y	Moderate
10	F	49	Tongue	N	Moderate

N= No; Y= Yes; NI= No Informed; OED= oral epithelial dysplasia; F= female and M= male.

Table II. Frequency of histological and citological variables of OLP cases.

	n (%)	
Histological variable	Irregular epithelial stratification	2 (20 %)
	Loss of polarity of basal cells	9 (90 %)
	Basal cells hyperplasia	9 (90 %)
	Gout formations	3 (30 %)
	Increased number of mitotic figures	2 (20 %)
	Abnormally superficial mitoses	1 (10 %)
	Dyskeratosis	1 (10 %)
	Keratin pearls	0
Citological variable	Abnormal variation in nuclear size (anisonucleosis)	10 (100 %)
	Nuclear pleomorphism	10 (100 %)
	Cellular pleomorphism	8 (80 %)
	Increased nuclear-cytoplasmic ratio	5 (50 %)
	Increased nuclear size	5 (50 %)
	Increased number-size of nucleoli	7 (70 %)
	Hyperchromasia	10 (100 %)
Atypical mitotic figures	6 (60 %)	



Association between gender and histopathological features

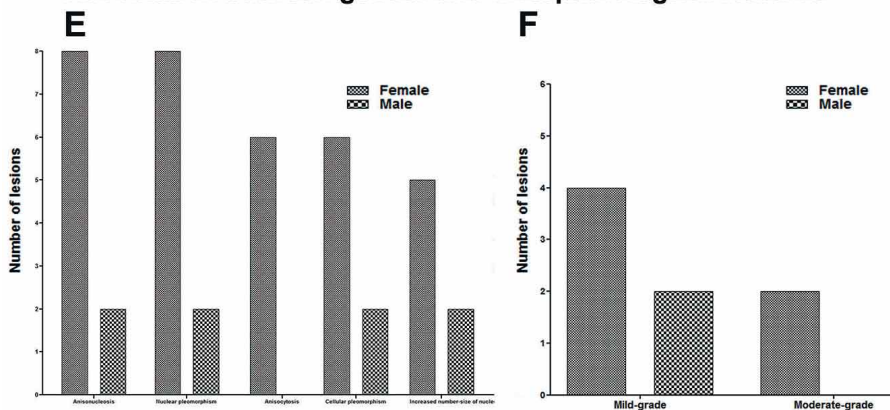


Fig. 1. Clinical and histopathological features of OLP. (A and B) OLP in bilateral jugal mucosa. (C) Loss of polarity of basal cells, anisonucleosis and nuclear pleomorphism in mild-grade OLP. (D) Irregular epithelial stratification, loss of polarity of basal cells, anisonucleosis, nuclear and cellular pleomorphism in moderate-grade OLP. In both cases a rich inflammatory infiltrate is observed. H&E, Scale bar= 50 μ m. Graphs of association between smoking and microscopic data. (E) Appearance of anisonucleosis, nuclear and cellular pleomorphism, anisocytosis, and increased number-size of nucleoli were positive associated with female patients ($P < 0.0001$). (F) The same was observed to OED degree ($P < 0.0014$).

DISCUSSION

Early diagnosis and treatment of OPMDs is essential to prevent the development of cancer. For a better understanding of malignant transformation, the association between clinical and histological features could be a determination to achieve a more accurate prognosis. In this context, epithelial dysplasia represents an important aspect in OPMDs diagnosis. Besides, the OED grade is considered crucial (Shailaja *et al.*, 2015), there is a lack of universally accepted guidelines for treatment of those lesions (Balasundaram *et al.*, 2014).

OLP represented 1.63 % of lesions diagnosed in Oral Pathology Service between 2004–2010, a percentage compatible with literature, that estimated 0.5 % to 2.0 % (Ismail *et al.*; Roopashree *et al.*; Gupta & Jawanda). The clinical findings showed that women were the most affected gender, which is in agreement with other reports (Roopashree *et al.*; Wang *et al.*; Coelho *et al.*, 2000; Corrêa *et al.*, 2006; Carvalho *et al.*, 2011). Regarding age, patients older than 40 years were the major group, consistent with Carvalho *et al.* The main affected site was jugal mucosa, as mentioned by others studies in Brazil and different countries (Fernández-González *et al.*, 2010; Oliveira Alves *et al.*, 2010; Werneck *et al.*, 2015).

When frequency of histological and cytological feature was analyzed, some dysplastic variables were presented in a higher frequency, such as, hyperplasia and loss of polarity of basal cells, anisonucleosis, nuclear pleomorphism and hyperchromasia. Tilakaratne *et al.* analyzed the individual features of epithelial dysplasia in 86 oral lesions and determined the reproducibility of scoring for each. The authors emphasized that some microscopic findings presented a wide variation in the scoring, including anisonucleosis, basal dyscohesion and dyskeratosis. Despite this, it is important to emphasize that OED degree determination of OPMDs is crucial as an indicator of malignant transformation risk. We detected 60 % of OLP with mild-grade and 30 % as moderate-grade. Any case was diagnosed as severe-grade. Wei Liu *et al.* demonstrated that patients diagnosed with severe-grade dysplasia had a higher oral cancer incidence than those with mild-grade. Whereas the cutaneous lichen planus is described with no risk of malignant transformation (Sigurgeirsson & Lindelöf, 1999; Ramos-e-Silva *et al.*, 2010), the oral forms had been documented as a potentially lesion for cancer, with rates

reaching 5.8 % (Wei *et al.*; Ramos-e-Silva *et al.*; Rajentheran *et al.*, 1999). Other rates of malignant transformation were reported, amounting to less than 0.5 % (Warnakulasuriya *et al.*).

The microscopic criteria for OLP and its epithelial dysplasia diagnosis represent a challenge and are controversial. However, is important to considered that epithelium in this kind of disease may develop dysplasia during carcinomatous transformation process (Gonzalez-Moles *et al.*, 2008). When OED is presented, some authors classified the lesion as lichenoid dysplasia (LD) (Van der Meij *et al.*, 2003). Lodi *et al.* (2014) distinguished LD in 2 groups of conditions: those with clinical features similar to OLP but with dysplasia; and those with lichenoid microscopic features (band-like lymphocytic infiltration in particular) and clinical aspect which do not resemble classic OLP (unilateral distribution absence of reticular lesions). The first one could be an early phase in OLP malignant transformation, while the latter could represent various clinical conditions including lichenoid reactions, lupus erythematosus, leukoplakia, erythroleukoplakia, and proliferative verrucous leukoplakia (PVL). The importance of dysplasia presence or absence diagnosis is clear, and when the presence is confirmed, the determination degree might be procedure, even for lesions considered benign with low potential malignancy transformation (Pereira *et al.*, 2011). In Oral Pathology Service (UFES, Brazil) since 2011, in most cases of OLP there has been a biopsy to identify and document a possible OED, and the follow-up of those patients became more frequent.

A large number of studies connected lifestyle habits with transformation of OPMDs into cancer, especially smoking, known as the most important factor (Wei *et al.*; Pereira *et al.*; Goodson *et al.*, 2010). Although habits are not considered independent risk factors and their roles in malignant transformation are conflicting, the identification is important since treatment could be compromised. Many studies reviewed case reports of cancer in patients affected by OLP, however, most of that was rejected due to lack of criteria (Lodi *et al.*). The Krutchokoff's criteria adopted by scientific literature in cases of OLP, tobacco exposure might be properly documented to help distinguish between a true malignant transformations and conventional carcinomas (Van der Meij *et al.*, 1999). In our sample, only one related smoking habit. OLP is an autoimmune disease with inflammatory feature and the presence of microscopic alterations may be the result of inflammation more than habit

(Sousa & Rosa, 2008). Furthermore, the identification of a distinct clinical subgroup of NSND patients with OSCC and different demographic distribution it must be analyzed. Absence of risk factors and female gender are important features of OLP, predominant profile found in our cases, in agreement with other reports (Wang *et al.*; Werneck *et al.*). When the association of dysplastic cell factors and clinical data was analyzed, the presence of anisonucleosis, nuclear and cellular pleomorphism, anisocytosis, and increased number-size of nucleoli were influenced by gender, as well as the OED degree. A lack of clinicopathological correlation in the diagnosis leads towards the need for more investigation to clarify the malignant transformation of OLP.

The gold standard for the assessment of those lesions remains the microscopic evaluation of HE slides. The microscopic profile is only possible through the

identification of OLP and performing the biopsy, which has been recommended in many services of oral diagnosis, as well as in our service.

The findings demonstrated that microscopic and clinical data association should be analyzed to a better understand of disease profile and behavior. The patients of our study sample showed similar features of other reports and OED was absent in only one case. So the periodic follow-up is mandatory for early detection of oral cancer.

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PAIVA, S. N.; BRAGA, C. C.; ALMEIDA-COBURN, K. L.; BAUTZ, W. G.; DE BARROS, L. A. P. & DA GAMA-DE-SOUZA, L. N. Liqueen plano oral: perfil clínico y la determinación de la displasia epitelial oral. *Int. J. Odontostomat.*, 10(1):99-106, 2016.

RESUMEN: El liquen plano oral (LPO) es la enfermedad no infecciosa más común y se considera un trastorno potencialmente maligno. La etiología y la patogénesis del LPO no se conoce y la transformación maligna sigue siendo objeto de debate. El objetivo de este estudio fue evaluar las características citológicas e histológicas del LPO y establecer la relación entre los perfiles clínicos y microscópicos. Un total de 10 pacientes diagnosticados con LPO fueron investigados. Secciones histológicas se prepararon y tiñeron con hematoxilina-eosina para identificar 8 características histológicas y 8 alteraciones citológicas. Finalmente, se determinó el grado de displasia epitelial. La hiperplasia y la pérdida de la polaridad de las células basales se detectaron en el 90 % de los casos. Anisonucleosis, pleomorfismo nuclear e hiper cromasia afectaron al 100 % de las muestras. Seis casos fueron clasificados como displasia epitelial oral (DEO) de grado leve y no se reportaron casos de grado severo. Las alteraciones microscópicas fueron mayores en las mujeres ($p < 0,0001$) y DEO de grado moderado fue diagnosticado sólo en este grupo ($p < 0,0014$). Los resultados demostraron que la asociación de datos microscópicos y clínicos deben ser analizados para una mejor comprensión del comportamiento de la enfermedad. La DEO estuvo ausente sólo en un caso, por lo que el seguimiento periódico de los pacientes diagnosticados con LPO es necesario para evitar la transformación maligna.

PALABRAS CLAVE: displasia epitelial oral, liquen plano oral, trastornos potencialmente malignos.

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