REVIEW

Oral lichen planus (OLP): clinical and complementary diagnosis *

Líquen plano oral (LPO): diagnóstico clínico e complementar

Alan Motta do Canto [1]
Helena Müller [2]
Ronaldo Rodrigues de Freitas [3]
Paulo Sérgio da Silva Santos [4]

Abstract: Lichen planus is a common disorder of the stratified squamous epithelium that affects oral and genital mucous membranes, skin, nails, and scalp. Oral Lichen Planus (OLP) affects middle-aged women and shows distribution patterns and characteristics such as white striations, white plaques or papules, erythema, blisters and erosions, and may be associated with medication and/or dental materials used by the patient. The clinical diagnosis can only be made if the disease presents classical patterns such as concomitant lesions in the oral mucosa and skin. The laboratory diagnosis is histopathologically characterized by the presence of projections of the epithelium in the form of sawtooth and Civatte bodies and allows the exclusion of dysplasia and malignancy. Direct immunofluorescence is used when there is suspicion of other diseases, such as pemphigus and pemphigoid. OLP is treated with anti-inflammatory agents, particularly topical corticosteroids; new agents and techniques have proved effective. The malignant transformation of OLP and its exact incidence remain controversial. This work aims at presenting, through literature review, the etiopathogenesis, clinical diagnosis, laboratory tests, and complications of OLP.
Keywords: Diagnosis, oral; Lichen planus, oral; Mucositis

Resumo: O líquen plano é uma desordem comum do epitélio escamoso estratificado que acomete as mucosas oral e genital, a pele, as unhas e o couro cabeludo. O líquen plano oral (LPO) afeta mulheres de meia-idade e apresenta padrões e distribuição característicos, como estriações brancas, pápulas ou placas brancas, eritema, erosões e bolhas, que podem estar associadas a medicações e/ou materiais dentários no paciente. O diagnóstico clínico somente poderá ser feito se a doença apresentar padrões clássicos, como lesões concomitantes na mucosa oral e na pele. O diagnóstico laboratorial por meio do exame histopatológico se caracteriza pela presença de projeções do epitélio em forma de dentes de serra e corpos de Civatte, e possibilita excluir condições de displasia e malignidade. A imunofluorescência direta é utilizada em suspeita de outras doenças, como pênfigo e penfigoide. O LPO é tratado com agentes anti-inflamatórios, principalmente, corticosteroides tópicos, e novos agentes e técnicas têm-se demonstrado eficazes. A transformação maligna do LPO e sua incidência exata permanecem controversas. Este trabalho tem como objetivo apresentar, com base na revisão da literatura, a etiopatogenia, o diagnóstico clínico, exames complementares e complicações do LPO.
Palavras-chave: Diagnóstico bucal; Líquen plano bucal; Mucosite

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[1] Dental Surgeon; Resident at the Oral and Maxillofacial Surgery Service, Santa Casa de Sao Paulo – Sao Paulo (SP), Brazil.
[2] Specialist in General Pathology; Professor (Ph.D.) of Pathological Sciences, Faculty of Medical Sciences, Santa Casa de Sao Paulo – Sao Paulo (SP), Brazil.
[3] Ph.D. in Medicine; Head of the Oral and Maxillofacial Surgery Service, Santa Casa de Sao Paulo – Sao Paulo (SP), Brazil.
[4] M.Sc., Ph.D. in Oral Pathology; Assistant at the Oral and Maxillofacial Surgery Service, Santa Casa de Sao Paulo – Sao Paulo (SP), Brazil.

INTRODUCTION

Lichen planus is an autoimmune chronic disease mediated by T lymphocytes that involves the stratified squamous epithelial tissue. The designation and description of the pathology were presented by the English physician Erasmus Wilson in 1866. In addition, he suggested that its etiology could result from "nervous tension". [1] Louis-Frédéric Wickham added to the description of the lesion *stries et punctuations grisatres* (grayish striae and dots), named Wickham striae in 1895. [2]

This dermatosis normally affects the oral mucosa, but it may involve the skin, nails, and genital mucosa. It is common in middle-aged women and affects men and women in the ratio of 2:3, respectively. It rarely affects children. [3,4,5]

The etiology of the disease remains unclear, but many causal factors have been associated, among which: anxiety, diabetes, autoimmune diseases, intestinal diseases, drugs, stress, hypertension, infections, dental materials, neoplasms, and genetic predisposition. [4,6] Even though its etiology has not been fully understood, its pathogenesis is more clearly defined. The main occurrence is the lymphocytic attack to the keratinocytes of the basal layer of the mucosa. T Lymphocytes induce apoptosis and cell degeneration and perpetuate the process by releasing chemokines in the inflammatory site. [4,6]

Clinical diagnosis

The diagnosis of oral lichen planus (OLP) should be done by clinical and histological examination. However, in classical lesions, it is possible to achieve the diagnosis based solely on clinical appearance. The clinical presentations of this pathology vary widely and may, in some cases, have a silent onset and be overlooked in the examination. [4]

OLP lesions normally last for years, alternating periods of exacerbation and quiescence. During the exacerbation period, both the erythematous or ulcerated areas and the pain increase. [4] Exacerbations of OLP are associated with periods of psychological stress, anxiety and mechanical trauma (*Koebner phenomenon*). The low intensity chronic irritation resulting from the plaque or dental calculus may also worsen gingival lichen planus and is considered *Koebner phenomenon*, as well as the mechanical trauma of odontological procedures, heat and cigarette irritants, friction of sharp points, rough dental restorations, and oral habits, like chewing gum. [7,8]

Upon inspection, OLP may present with white striae (Wickham striae) in the surface of the mucosa, white papules or plaques, atrophic, erosive or vesicular lesions. The erosive, atrophic or bullous OLP has diverse painful symptoms. [8] The gingival variant often presents erythemas or ulcers limited to the gingiva. Due to the clinical similarity with gingival inflammation, it is denominated desquamative gingivitis. The most commonly affected areas are the mucosa of the cheek, dorsum of the tongue, gingiva, labial mucosa and lower lip (redness). [3,4,5,6]

The diagnosis of OLP is usually achieved by clinical and histological examination. Nevertheless, in classical lesions (bilateral white striae in the mucosa of the cheek), it is possible to accomplish the diagnosis based solely on clinical appearance. Differential diagnosis includes lichenoid reactions to drugs or dental materials, leukoplakia, lupus erythematosus, and graft vs. host disease in bone marrow transplantation patients. Desquamative gingivitis may also be mistaken for other diseases, such as pemphigus, pemphigoid, dermatitis herpetiformis or linear IgA disease. Therefore, complementary exams are essential for the diagnosis and exclusion of malignancy in all the cases. [3,4,6]

Among complementary exams, the most important is direct immunofluorescence, which helps in difficult cases of bullous OLP lesions that may resemble other diseases. [3,4,9]

In some cases, patients with OLP may present concomitant lesions in the skin (15%), genital mucosa (25% of women and 2-4% of men), scalp (lichen planopilaris), nails, esophageal mucosa, larynx, and conjunctivae. [10]

Intraoral lesions

OLP has six classical clinical presentations described in the literature: reticular, erosive, atrophic, plaque-like, papular and bullous. [11,12]

Reticular: it is the most common clinical form of the disease and it presents with fine, intertwined white striae, called "Wickham striae". Often, these lesions are not static, improving and worsening within weeks or months. Lesions are usually asymptomatic with a bilateral pattern, symmetrical, and involve the posterior mucosa of the cheek in most cases (Figures 1 and 2). [3,8,13]

Erosive: this is the most significant form of the disease because it shows symptomatic lesions. Clinically, a central irregular ulceration covered or not by a fibrin plaque or pseudomembrane. The lesion is often surrounded by fine radiant keratinized striae with a network appearance [3] (Figures 3 and 4).

Atrophic: it exhibits diffuse red lesions and it may resemble the combination of two clinical forms, such as the presence of white striae characteristic of the reticular type surrounded by an erythematous area. [14]

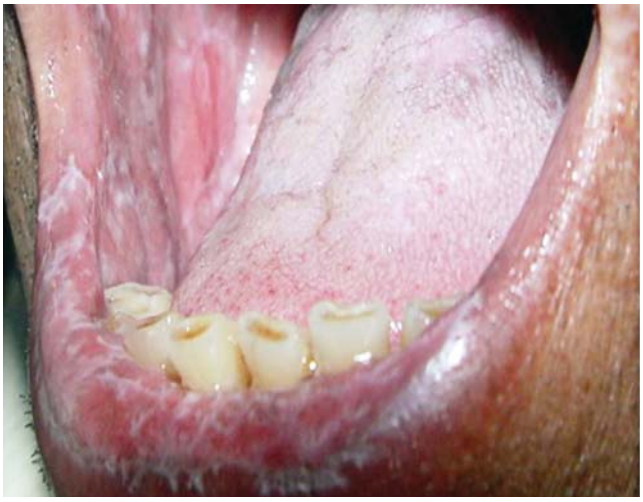

Figure 1: Reticular lichen planus – reticular aspect on the lips and mucosa of the cheek

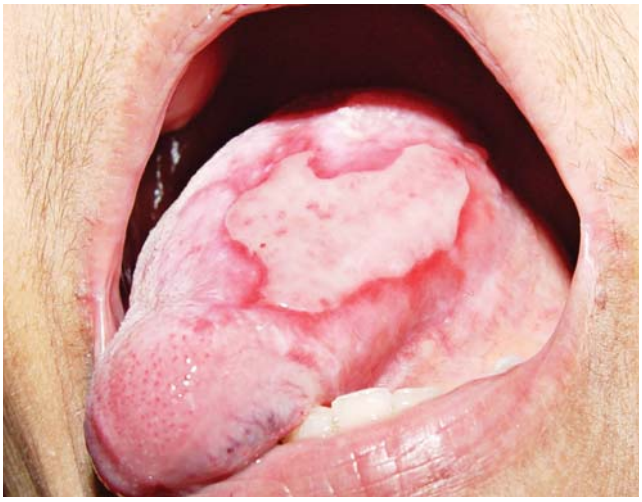

Figure 3: Erosive lichen planus – ulcerated lesion in the lateral area of the tongue with erythematous borders

Plaque-like: this type shows whitish homogeneous irregularities similar to leukoplakia; it mainly involves the dorsum of the tongue and the mucosa of the cheek. Lesions can be multifocal, changing aspect and becoming elevated and/or rugous (especially in smokers). [6]

Papular: this form is rarely observed and is normally followed by some other type of variant described. It presents with small white papules (0.5mm to 1.0 mm of diameter) with fine striae in its periphery. [15]

Bullous: it is the most unusual clinical form, exhibiting blisters that increase in size and tend to rupture, leaving the surface ulcerated and painful. The periphery of the lesion is, in general, surrounded by fine keratinized striae. [3,16]

Desquamative gingivitis

Approximately 10% of the patients with OLP present lesions only in the gingiva. [1] Gingival lichen planus is characterized by an erythematous or ulcerated area localized in the attached gingiva associated with small whitish areas, a disease called desquamative gingivitis. [4]

When bullous lesions are present, desquamative gingivitis is not a pathognomonic sign of OLP, since it may be associated with other diseases, such as pemphigoid, pemphigus vulgaris, dermatitis herpetiformis or linear IgA disease. [17,18]

The triad constituted by desquamative or erosive lichen planus involving the vulva, vagina and gingiva was denominated vulvovaginal-gingival syndrome. [19] In a study by Di Fede et al., the presence of

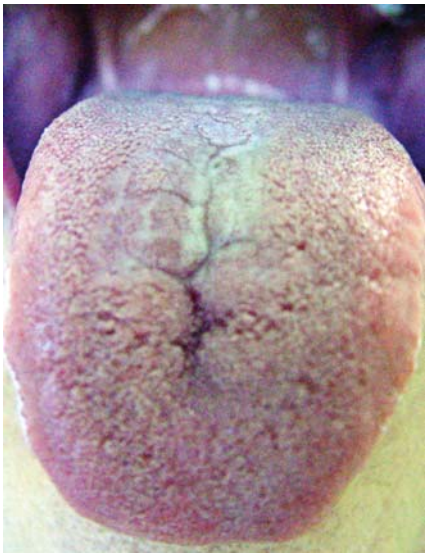

Figure 2: Reticular lichen planus– reticular aspect on the dorsum of the tongue

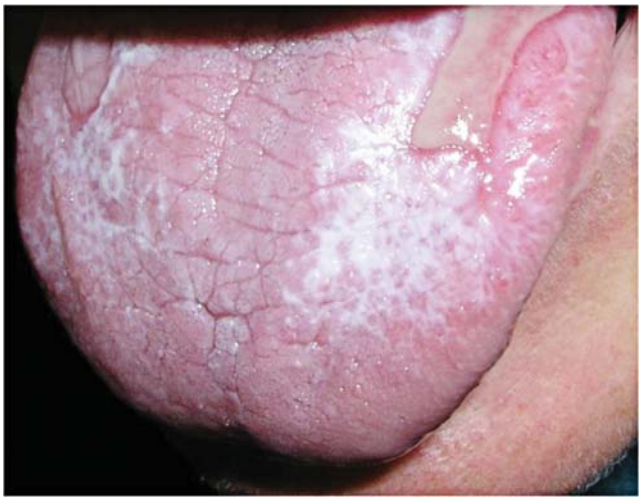

Figure 4: Erosive lichen planus – ulcerated lesion on the dorsum of the tongue surrounded by reticular striae

vaginal lichen planus was observed in 88% of the 41 patients with OLP. Oddly, 92.3% of the patients reported absence of genital symptoms. Therefore, every woman with OLP lesions should be submitted to a multidisciplinary evaluation, even if genital symptoms are absent. This procedure aims at diagnosing genital lichen planus. [20]

Gingival lesions may be keratinized, vesicobullous, atrophic, and erosive. [21]

keratinized: keratinized lesions are often found in attached gingiva in the form of small whitish elevations with a flat surface. They may be classified as papular, plaque-like, linear, reticular (Honilton striae) or annular.

Vesicobullous: these lesions are more common in the gingiva and, when present, may difficult the diagnosis.

Atrophic: atrophic lesions produce the most common type of gingival lesion of OLP, the desquamative gingivitis.

Erosive: erosive lesions also produce desquamative gingivitis.

Extraoral lesions

Skin lesions normally occur in individuals between 25 and 60 years old, do not have predilection for race or sex and affect from 2 to 3% of the patients with OLP. [6] They are divided into cutaneous, genital, ungueal, actinic, hypertrophic, vesicobullous and mixed.

Complementary diagnoses

Optical microscopy

Histopathologically, lichen planus has typical, unspecific characteristics, since lichenoid reaction to drugs and amalgam [22], lupus erythematosus, ulcerative chronic stomatitis and reaction of the oral mucosa to cinnamon leaf may also show a similar histopathological pattern. [3]

Predilection for the epidermis, MHC specificity and T cells produce a histopathological result similar to that of lichen planus and may be present in graft vs. host disease (GVHD) in bone marrow transplantation individuals. [6]

The classical histopathological characteristics must be identified for a conclusive diagnosis of OLP. They are: liquefactive degeneration of the basal layer (hydropic degeneration), band-like dense inflammatory infiltrate of T lymphocytes, normal epithelial maturation, saw-toothed anatomical prominences, Civatte bodies (coloids) and hyperkeratosis (orthokeratosis or parakeratosis) (Figures 5 and 6). [23]

Some lesions may be infected by candida; however, for an appropriate histopathological interpretation, the infection should be treated before. [3]

The histopathological criteria for lichen planus exclusion are: absence of liquefactive degeneration of the basal cells, infiltrate with a heterogeneous cell population, atypical cell morphology, nuclear widening, intense mitotic activity, flat anatomic prominences, absence of Civatte bodies, and abnormal keratinization. If these criteria were included in the diagnosis, the dysplasia would be considered an ordinary finding in OLP. [4]

Biopsies of the gingival and cheek mucosa may be necessary and often show pathological similarity; however, biopsy of the gingiva should be avoided. When the gingival mucosa is biopsied, the histopathological characteristics of OLP may be altered by unspecific gingivitis, making the diagnosis more complicated. [24] In these cases, direct immunofluorescence should be used as an auxiliary diagnostic tool. [25]

Direct Imunofluorescence

The sensitivity of direct immunofluorescence depends on the disease investigated. This technique is positive for 65.8% of the patients with OLP. [9]

Positivity for OLP is considered when there is IgA, IgG, IgM or C3 deposition throughout the basement membrane zone, as well as fibrinogen in the basement membrane in an irregular pattern. The intraoral areas most sensitive to direct immunofluorescence are the buccal floor, upper labial mucosa, hard palate and mucosa of the cheek. The worst intraoral sites for the performance of direct immunofluorescence are the gingiva and the dorsum of the tongue. [9]

The use of *punch* instead of the scalpel blade was better to detect the disease in direct immunofluorescence. [9]

In lichen planus direct immunofluorescence is

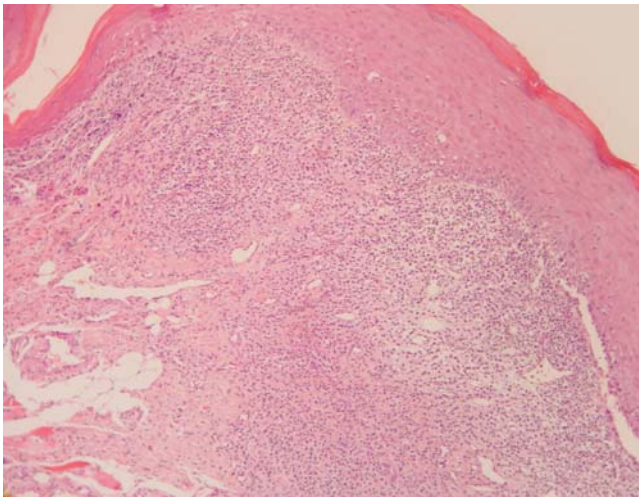

Figure 5: Histological aspects – hyperkeratosis, band-like dense lymphocytic inflammatory infiltrate and hydropic degeneration

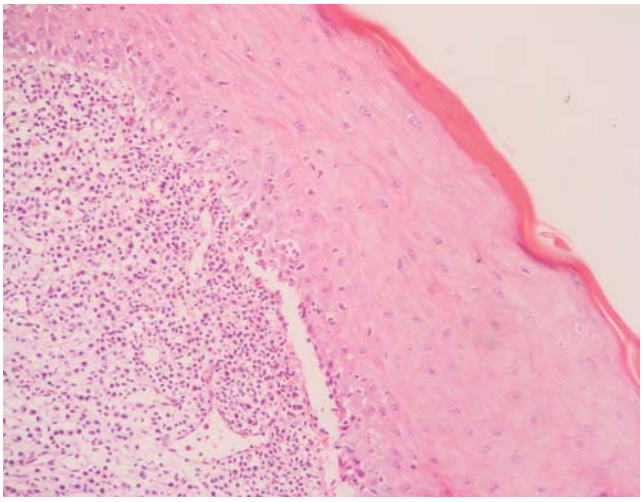

Figure 6: Histological aspects - hyperkeratosis, presence of vacuoled keratinocytes, band-like dense lymphocytic inflammatory infiltrate and deterioration of the epithelium-chorion interface

usually performed in the lesional mucosa. Nonetheless, biopsy of lesional tissue is often problematic in direct immunofluorescence. Immune deposits are degraded by the intense inflammation of the basement membrane, yielding a false negative result. [9]

There is no difference in the sensitivity of direct immunofluorescence between biopsies performed in perilesional tissue (radius of up to 1 cm from the lesion) or distant tissue (radius greater than 1 cm). This occurs because the immune deposit may be present in the entire oral tissue, not only close to the lesion. This explains why biopsies done in tissues distant from the lesion yield positive results in direct immunofluorescence. Distant sites also provide more sample options when tissue extraction is difficult. [9]

Malignization of OLP

The malignancy potential of lichen planus, especially in the erosive form, is not yet fully understood. More concrete evidence of its malignant potential is found in long-term follow-up studies and retrospective incidence of the patients; however, the issue remains controversial. [4,6]

Studies about the development of squamous cell carcinoma in OLP lesions appear to have fairly uniform results. On average, the sample is constituted by 200 patients and the frequency of malignancy varies from 0 to 5.3% in follow-up studies of 6 months to 20 years. Based on the variant of OLP presented, the atrophic, ulcerated and erosive types show greater incidence of malignant transformation. The most common sites are the tongue, gingiva and mucosa of the cheek. [14,26-28]

Advances in the research about carcinogenesis are useful to study the malignization risk of OLP. Non-dysplastic lesions show reduced frequency of heterozygous loss (main sites of tumoral suppression) when compared to epithelial dysplasia and hyperplasia. As the dysplasia progresses and the carcinoma develops, the frequency of heterozygous loss increases. These findings suggest that non-dysplastic OLP is a disease with distinct molecular profile and etiopathogeny. In contrast, dysplastic OLP shows a high frequency of heterozygous loss, similar to what is observed in oral dysplasia. Hence, non-dysplastic OLP and lichenoid dysplastic lesions are completely separate entities. Dysplasia appears to be independent from lichen planus and is a risk to the progression of squamous cell carcinoma. [29] Still, the World Health Organization generally classified OLP as a pre-cancerous condition. For this reason, patients who develop this disease should be informed about the risk of cancer development. [4]

The greatest problem of studying the potential of malignancy of OLP is the lack of objective and unanimous criteria for its diagnosis. Some studies base the diagnosis only on clinical characteristics; others, on histopathological findings and others still on both. In addition, many lesions clinically and/or histologically diagnosed as OLP may, in reality, be dysplastic leukoplakias with lichenoid appearance and secondary lichenoid inflammatory infiltrate similar to lichen planus (lichenoid dysplasia). It is important to stress that histological characteristics of epithelial dysplasia are not exclusively premalignant. Changes in the histological pattern may occur in response to low intensity chronic stimuli; for instance, in the reactive hyperplasia induced by prosthesis with epithelial dysplasia. Another limiting factor of studies about the malignant transformation of OLP is the lack of documentation about the associated smoking. [4,6]

The importance of the presence or absence of dysplasia in the early presentation of OLP was described in a study that reported four cases of malignant transformation in 141 patients with OLP. Of the four cases in which malignant transformation occurred, dysplasia was present in the early diagnosis of three of them. [30]

Regular follow-up of patients with dysplastic OLP should be done every two to three months. However, patients with asymptomatic lesions, mainly observed in the reticular type, may be seen annually. The aggravation of symptoms and loss of the homogeneity of the lesion should be evaluated when the patient returns. If this occurs, follow-up should be more frequent and additional biopsies will need to be performed. For early monitoring and detection of

transformation signs, it will be necessary to use toluidine blue stain to better choose the biopsy site. This stain binds to DNA and to lesion areas with intense mitotic activity or abnormal DNA, resulting in the blue color. [4,29-31]

Erythroplastic lesions may also occur in OLP. They develop in approximately 1% of the patients and are sharp with slight reddish depressions. Histopathological analysis often reveals epithelial dysplasia, but some situations may camouflage squamous cell carcinoma or premalignant lesion. [32]

Even though progress has been made for the understanding of the malignization process of OLP lesions, the literature still lacks prospective studies with universally established diagnostic criteria. [4] ❑

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Alan Motta do Canto
Rua Dr. Cesário Motta Jr., 112 - Santa Cecília
01221-020 - São Paulo - SP, Brazil

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