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REVIEW

Oral lichen planus: A look from diagnosis to treatment.

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Abstract: Oral lichen planus (OLP) is a chronic mucocutaneous disease of unknown etiology. Its pathogenesis is multifactorial and it may affect the oral mucosa, skin and other mucous membranes. Diagnosis is based on clinic and histopathology; direct immunofluorescence techniques can also be of use. It affects about one to two percent of the population, mainly women between the fifth and sixth decades of life. In the mouth, the most affected area is the buccal mucosa, followed by the gums, tongue and/or palate. Its three most representative clinical forms are reticular, erythematous and erosive; evolution depends on the type it is. Lesion treatment is determined by the clinical form and, since no fully effective treatment has been found yet, it is directed towards controlling the disease. The treatment of choice involves topical or systemic corticosteroids, but other drugs may also be used.The aim of this paper is to gather current and relevant information about oral lichen planus: its pathogenesis, diagnosis, treatment and management.
Keywords: Oral Lichen Planus, Clinical/Histopathology Diagnosis, Corticosteroids, Neoplasms.

Pablo Córdova[1, 2], Aida Rubio[2], Paula Echeverría[1].

1.- Facultad de Odontología, Universidad Andrés Bello, Chile.

2.- Facultad de Odontología, Universidad de Valencia, España.

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Corresponding author: Dr. Pablo Córdova G. Echaurren 237 – Santiago de Chile. Phone: +56968496998. Email: pab.cordova@gmail.com

Liquen plano oral: Una mirada desde el diagnóstico al tratamiento.

Resumen: El liquen plano oral (LPO) es una enfermedad crónica mucocutánea de etiología poco conocida, cuya patogénesis es multifactorial, y puede afectar a la mucosa oral, piel y otras mucosas. El diagnóstico está basado en la clínica y la histopatología. Además, técnicas como la inmunofluorescencia directa pueden contribuir al diagnóstico de la enfermedad. Afecta del 1 al 2% de la población, principalmente mujeres, entre la quinta y sexta décadas de la vida. En boca, la zona más afectada es la mucosa yugal, seguido de encías, lengua y/o paladar. Las tres formas clínicas más representativas son: reticular, eritematosa y erosiva, cuya evolución varía según el tipo. El tratamiento de las lesiones depende de la forma clínica y está dirigido hacia un control de la enfermedad, ya que en la actualidad no se conoce un tratamiento del todo efectivo. El tratamiento de elección es la utilización de corticoides, en forma tópica o sistémica, aunque otros fármacos también pueden ser utilizados para el manejo de la enfermedad. El objetivo del presente artículo es recopilar información actualizada y relevante del liquen plano oral en su etiopatogenia, diagnóstico, tratamiento y manejo de la enfermedad.
Palabras clave: Liquen Plano Oral, Diagnóstico Clínico/ Histológico, Corticoides, Neoplasia.

Introduction.

Oral lichen planus (OLP) is a mucocutaneous disease which can alter the skin, oral mucosa and other mucous membranes. It affects approximately one to two percent of the population, mainly women, and it occurs most frequently during the fifth and sixth decades of life. Usually, oral lesions appear before skin lesions and, sometimes, they expose themselves only in the oral mucosa. In the mouth, the most affected area is the buccal mucosa, although it can present itself on the tongue, gums and/or palate as well.[1-7]

The course is chronic with frequent recurrences. Diagnosis is based on clinic and histology, but techniques such as direct immunofluorescence (DIF) can provide a valuable additional criterion. There is no fully effective treatment.[1, 8]

Etiology and pathogenesis.

Today, it is considered a disease of obscure etiology, although various triggers are proposed. Besides, there is a considerable controversy about OLP pathogenesis.[2, 9] Current evidence presents multifactorial pathogenesis of various immune mechanisms[2, 3, 10-13]:

1. Antigen - specific immune response: CD8+ cytotoxic cells are activated in OLP by major histocompatibility complex class I and II molecules when antigens are presented.

2. The proposed mechanisms involved in non-specific immune response are mast cell degranulation and marked matrix metalloproteinases activation.

3. Another hypothesis is the autoimmune response. It is supported by various OLP characteristics such as chronicity, adult onset, association with other autoimmune diseases, female predilection, lack of TGF-ß1expression, overexpression of heat shock proteins, keratinocytes apoptosis and Langerhans cell maturation.

Among others, these factors have been proposed as causative agents: genetic component, trauma, drugs, both viral and bacterial infectious agents, food allergy, autoimmunity, stress, immunodeficiency, dental materials

and diabetes.

Some authors have described its relationship with hepatitis C, however, this aspect has generated discrepancies. In this sense, it has been possible to describe such association in some geographic areas while, in others, evidence has not been found.[1, 3, 11, 12, 14-16]

There is a close relationship between OLP and psychosomatic disorders, mainly anxiety and stress. Some researchers suggest that the combination of psychiatric and OLP treatment can be effective in reducing the lesion size or even their remission in patients with OLP.[1, 3, 12, 17]

Diagnosis and classification.

Six clinical forms of OLP have been proposed: white striations (reticular), white plaques, white papules, erosive, atrophic and bullous. For this review, the three most representative clinical forms were considered: reticular, erythematous and erosive.

The reticular form is usually presented with a symmetrical character in both mucous membrane areas, especially in buccal mucosa, and few symptoms. It is common to observe the erythematous type in the jugal mucosa, tongue and/or gums; the latter often in the form of desquamative gingivitis. The erosive form is painful; on the contrary, erythematous causes discomfort but no pain, manifesting itself mainly in the buccal mucosa and dorsal tongue. It is part of the clinical criteria to find reticular lesions peripherally to the atrophic-erosive lesions.[1, 7, 9, 18, 20]

In patients with lichen planus, diagnosis should always be made by combining clinical findings with histopathology.[18] A DIF study, which usually gives positive results in basement membrane with fibrinogen, can also be performed. Biopsy is necessary because it allows confirming clinical and differential diagnosis with other lesions such as lichenoid reaction, lupus, pemphigus, pemphigoid and leukoplakia, among others.

There are a series of lesions which are both clinically and histologically similar to idiopathic lichen planus, the so-called *"lichenoid reactions"*.[19] These include lichenoid lesions by contact, drug-induced lichenoid reactions, and lichenoid reactions associated to graft versus host reaction.[18] Often, clinical and histology alone are not able to differentiate an idiopathic lichen planus from a lichenoid reaction.[20-22]

Clinical criteria comprise presence of bilateral symmetrical lesions and white reticular lesions. Lesions may be atrophic, erosive, blistering or take the form of plaque which appears along with reticular lesions in a specific area of the oral cavity. When both criteria are met, it is considered a typical lichen planus. Lesions simulating lichen planus, but not meeting the previous criteria, are considered clinically compatible with lichen planus.

Histological criteria include: a band of lymphocytic inflammatory infiltrate in the subepithelial connective tissue, liquefaction degeneration of the basement membrane and the absence of epithelial dysplasia. If these three criteria are met, the injury is considered a typical lichen planus from a histopathological point of view. Those not meeting any of the histopathological criteria are considered histologically consistent with lichen planus.[1, 22, 23]

By contrast, lichenoid reaction includes patients with typical lichen planus clinically but not histologically, those with histological level but not clinical, and the ones who are clinically and histologically compatible.[22, 23]

Malignant potential.

One of the potential complications of OLP is the chance of malignant transforming. However, this phenomenon is still the subject of much controversy.[24-27] Literature contains a growing number of clinical series in relation to the malignant potential of OLP, although some authors question the current evidence.[28-30]

Since 1910, when the first case of oral squamous cell carcinoma (OSCC) in a patient with OLP was reported, these published series have displayed a malignancy rate of 0 to 12.5%.[22, 31, 32]

In literature reviews, comparisons are difficult because of differences in the criteria used for OLP diagnose, lack of information about oral exposure to carcinogenic agents, variability in the selection, lesion identification and location, and differences in monitoring patients. Nevertheless, most studies indicate that OLP patients may develop oral cancer, increasing the risk of incidence (10 times) compared to general population.[24, 33, 34]

Furthermore, oncogenesis has been associated with other risk factors which should also be taken into account. Nowadays, not only tobacco and alcohol but also Candida infection and the possible role of different oncogenic virus like human papilloma virus (HPV) and Epstein Barr virus (EBV) have to be considered. Also, the possible influence of nutrition, genetics and heredity, and immune suppression induced by certain treatments used for OLP should be taken into consideration.[27, 32, 33, 35]

In particular, erythematous and erosive forms of OLP are most likely considered to malignify, although the evidence for this hypothesis is weak. From different intraoral sites, tongue seems to be the preferred place for malignant transformation, according to observations by Tizeira Lanfranchi *et al.*[31] Nevertheless, Mignogna *et al.*[25] reported an increase in the frequency of carcinomas in the midline palate, gums and lips; and, conversely, Rajentheran *et al.*[36] indicated the buccal mucosa

as the most affected area.

Considering patient's sex and age, there seems to be agreement o the fact that the risk is higher in women between the sixth and seventh decades of life.[27, 31]

It was found that OLP-OSCC subjects are more likely to develop a second or third oral cancer, and have lymph node metastases, compared to OSCC-only control subjects. This observation would be consistent with a field cancerization phenomenon.[26] Therefore, clinical follow-up for these patients is essential in order to establish an early malignant transformation diagnosis.[3, 25, 26]

Van der Meij *et al.* considered the following criteria for lichen planus malignant transformation[22]:

A. It typically requires clinical lichen planus diagnosis with histopathology including at least two of the following four signs:

- Hyperkeratosis or parakeratosis.
- Serrated-shape interpapillar gingival crest.
- Subepithelial infiltration band.
- Hydropic degeneration of the basal layer.

B. History and monitoring.

- Clinical and histological data showing the transformation must be properly documented (both previous lesions and when malignant transformation occurred).
- Clinical data such as age, sex and lesion location must be registered.
- At least, two year follow-up.

C. Exposure to tobacco.

- Those patients who smoke and have a carcinoma, attributed to tobacco, should be discarded.

Corticosteroids and other treatments.

The main goal of any treatment is OLP symptomatic control. In general, patients with reticular OLP lesions and other asymptomatic lesions do not require active treatment.[11, 20, 21]

It is important to eliminate potential triggers and irritants such as dental malocclusion or fractured carious teeth, poorly fitting dentures; alcohol and tobacco consumption should be identified and avoided/eliminated whenever possible.[3, 37] Good oral hygiene, alongside with the use of chlorhexidine mouthwashes and plaque reduction, may have beneficial effects on lesions; therefore, they should also be indicated.[3, 38, 39]

As OLP is a chronic disease, patient history, psychological status, treatment compliance and drug interaction should be considered when evaluating any treatment modality.[17, 37, 39]

There are various treatments which have been proposed to improve symptomatic OLP evolution, but none exists to cure the disease. In particular, some treatment modalities suggest lichenoid lesions induction, and do not improve their previous state. Topical treatment is generally preferred because it has fewer adverse effects. However, systemic agents may be necessary if lesions are generalized, they occur essentially in the skin or other non-oral mucosa.[1, 40]

Most published studies consider topical corticosteroids as the most useful drug for OLP treatment. A positive response to medium-potency corticosteroid treatment, such as acetate triamcinolone 0.1%, powerful fluorinated steroids as fluocinolone acetonide 0.05% and 0.1%, and more high-potency halogenated corticosteroids, like clobetasol propionate 0.05%, has been reported in most treated patients.[1, 11, 21, 41]

In particular, clobetasol propionate appears to be the most effective topical steroid, reporting a high remission rate (56-75%) of OLP signs and symptoms. Moreover, clobetasol has shown to be more effective than triamcinolone acetate and fluocinolone in comparative studies.[37]

The main problem when using topical corticosteroids is for adhering them to the mucosa for a sufficient period of time.[11] Adhesive pastes such as sodium carboxymethylcellulose (Orabase), hydroxyethyl cellulose and special drug delivery systems such as lipid laden microspheres have been suggested for this purpose.[42]

Aditionally, adrenal suppression is not found in the long term, even with oral application of topical corticosteroids such as triamcinolone acetonide, fluocinolone and clobetasol propionate.[41, 43, 44]

Pseudomembranous candidiasis is the only common side-effect of treatment with topical corticosteroids. This can be prevented by using antifungals such as miconazole gel[4, 16] or chlorhexidine rinses.[42] Topical steroids can be applied using splints where there are gingival lesions.[45]

Prolonged use of these drugs can sometimes result in a decrease in biological effectiveness (tachyphylaxis).[11] This can be avoided by using a high-potency steroid (i.e. clobetasol) at first and then a moderate corticosteroid (i.e. triamcinolone) for maintenance therapy.[20]

Systemic corticosteroids are usually reserved for cases where OLP is widespread, involving the skin, genitals, esophagus or scalp. Prednisone doses of 40 to 80 mg per day are usually enough to achieve response both when taken for short periods of time (five-seven days) and then abruptly withdrawn, or 5-10 mg dose per day which is gradually reduced over two to four weeks.[11, 20, 39, 41, 46]

Immunomodulatory agents, such as calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus or tacrolimus) or retinoids, may be beneficial, especially if the lesions are resistant to the highest- potency steroids.

Cyclosporin has been used as a mouthwash or

Drug treatment		Indications / Side effects
Costicosteroids	Triamcinolone acetonide 0.1% Fluocinolone acetonide 0.05% - 0.1% Clobetasol Propionate 0.05% Betamethasone Dipropionate 0.05%	Cream or gel. It can be used with gingival splints In oral solution. (Mouthwash). Use in case of localized or generalized atrophic-erosive lesions. Do not swallow.
	Triamcinolone Depot 10-20 mg	Perilesional injections for lesions which do not respond to local measures.
	Prednisone 1mg/kg/day 5-80 mg/day	Atrophic-erosive lesions which are unresponsive to the above measures.
Calcineurin inhibitors	Ciclosporin 50-100 mg/day Tacrolimus 0.03%-0.1% Pimecrolimus 1% Sirolimus	Oral solution and adhesive base. Consider them only as second-line treatments.
Retinoids	Tretinoin Isotretinoin Fenretinide	Recommended only for topical use, not systemic. Consider them only as second-line treatments.
Dapsone	Dapsone 200-300 mg/day	Antiinflammatory effects. Risk of hemolytic anemia and hypersensitivity reactions.
Azatropine	Azatropine 50-100 mg/day	In case of involvement of other mucous membranes and skin. Side effects, such as retinal damage and bone marrow suppression, should be considered.
Micophenalate	Mofetil Micophenolate	It is not recommended at this time
Other immunosupresors	Basiliximab Etanercept Efalizumab Alefacept	Low cost/benefit ratio. Their use is limited to patients with severe manifestations which are unresponsive to treatment with corticosteroids or calcineurin inhibitors.
No drug treatment	Photodynamic therapy (PDT) Therapy with ultraviolet longwave radiation (PUVA) Surgical treatment with CO2 laser	PUVA therapy is not used due to its oncogenic potential. PDT has an immunomodulatory effect. CO2 laser effectiveness is unsubstantiated.
Auxiliary treatments		
Antifungal	Ergosterol synthesis Inhibitors: Nystatin / amphotericin B. Azole derivatives: Miconazole, fluconazole, ketoconazole, itraconazole.	They are concurrently used with corticosteroids or for treating candidiasis occurrence by prolonged use of corticosteroids form.
Antiseptics	Clorhexidine 0.12%	Reduce plaque level.
Alternative drugs.	Aloe Vera gel	Anti-inflammatory, antibacterial, antiviral and antifungal properties.
Psychiatric/psychological therapy.	Muscle relaxants , anxiolytics , benzodiazepines , psychological therapy	In combination with drug therapy. Reduce anxiety and stress level identified as one of the etiologic factors. In addition, patients may develop "cancer phobia".

Table 1. Summary of pharmacological, non-pharmacological and auxiliary therapies and main indications for treating oral lichen planus

adhesive bases, but it is expensive, not always effective, and less potent than topical clobetasol to induce OLP clinical improvement.[13, 47, 48]

Tacrolimus is 10-100 times more potent than cyclosporine.[11] Several studies have documented this agent efficacy and safety (at a concentration of 0.03% to 0.1%) in the erosive OLP evolution.[13, 49, 50, 51] However, tacrolimus therapeutic levels in OLP patients have been associated with oral absorption after topical application, leading to systemic side effects.[53, 54] In addition, OLP relapses after tacrolimus discontinuation are common.[13, 50]

Pimecrolimus is another calcineurin inhibitor used in OLP treatment. Its action is similar to tacrolimus, but it has no effect on the Langerhans cells. Pimecrolimus immunosuppressive capacity is weaker than cyclosporin or tacrolimus, and it has lower permeability through the skin compared to topical steroids and tacrolimus.[13, 53]

However, the FDA issued a "black box" warning on the use of tacrolimus and pimecrolimus due to an increased theoretical risk of cancer (squamous cell

carcinoma and lymphoma) in patients treated with tacrolimus/pimecrolimus for psoriasis.[3, 11, 54, 55]

Topical Rapamycin (sirolimus) has been recently proposed in refractory erosive OLP cases, because it has immunosuppressive properties and is a tumoral inhibitor, thus decreasing LPO malignancy risk.[13, 56]

Topical retinoids such as tretinoin, isotretinoin and fenretinide, often cause side effects and are generally less effective than topical corticosteroids. Moreover, their use should be limited to topical and second-line treatments should be considered.[1, 11, 57]

Various systemic immunosuppressive agents have been used for treating OLP. Biological agents as basiliximab, etanercept, efalizumab, and alefacept have been proposed for OLP treatment. However, due to the low cost/benefit ratio, its use is limited to patients with severe disease manifestations or those who have failed with traditional treatments such as topical corticosteroids and calcineurin inhibitors.[11, 58-60]

As immunosuppressive drugs used for OLP have not been developed for oral diseases, there is need for appropriate studies to determine their efficacy and optimal dose, treatment duration and safety to avoid side effects.[61]

Non-pharmacologic methods, such as photodynamic therapy (PDT), ultraviolet longwave radiation (PUVA), and surgical treatment with CO2 laser have been proposed, especially for patients with recurrences after more conventional therapies. Yet, their effectiveness has not been tested and, apparently, the surgery also induces OLP.[11, 59, 60, 62-64]

Table 1 shows the main treatments for OLP.

Conclusion.

Lichen planus is a chronic mucocutaneous disease of multifactorial etiology and pathogenesis. OLP is considered a potentially malignant lesion, so lesion monitoring must be periodic even in asymptomatic patients, and symptomatic ones should be treated. Corticosteroids are considered as first-line treatments since their topical form has better benefits and fewer side effects over time. Alternative therapies efficacy has not been demonstrated yet.

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