Oral Lichen Planus

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KEYWORDS
- Lichen planus • Oral • Autoimmune disease • Reticular • Erosive

KEY POINTS
- Lichen planus is an immunologically mediated mucocutaneous disease, affecting 0.1% to 4% of the general population.
- Several reports suggest an association of hepatitis C virus and human papilloma virus with oral lichen planus.
- Oral lichen planus predominately affects females, with most patients aged between 30 and 70 years.
- Common treatment options include systemic and topical corticosteroids, topical retinoids, cyclosporine, tacrolimus, and pimecrolimus.
- The potential malignant transformation of lichen planus remains highly controversial; periodic observation of these lesions for dysplastic changes remains prudent.

INTRODUCTION

Lichen planus is an immunologically mediated mucocutaneous disease. A complex series of immunologic events is purported to cause the initiation and perpetuation of the condition. It is a common disease, affecting 0.1% to 4.0% of the general population. Patients often have concomitant cutaneous and oral lesions (Fig. 1).1,2 Oral lesions may be chronic in nature, remitting and relapsing with varying degrees of morbidity; they range from asymptomatic to debilitating pain.

Clinically and histologically similar entities, including lichenoid drug reaction (Fig. 2), lichenoid mucositis (Fig. 3), and lichenoid dermatitis, can make the diagnosis of lichen planus challenging. These lesions are associated with the administration of a drug or direct contact with a metal and often, but not always, resolve when the offending agent is removed. Antibiotics, antihypertensives, gold, diuretics, antimalarials, and nonsteroidal antiinflammatory drugs may precipitate these conditions.3 Oral lichenoid reactions in chronic graft-versus-host disease are also well recognized.4,5 It is not possible to distinguish such lesions from oral lichen planus (OLP) clinically or histologically; there is, however, a significantly higher frequency of CD25+ cells in the epithelium and the connective tissue of OLP than in chronic graft-versus-host disease. This variance in frequency indicates differences in regulatory mechanisms of the immunologic response in the two conditions.6 Genetic involvement in OLP is yet to be determined.7,8

Several reports suggest an association of hepatitis C virus and human papilloma virus with OLP.9,10 In Spain and Japan, there is a reported incidence of coinfection of 20% and 62%, respectively, with HCV; but this has not been shown in the American population.11–13

CLASSIFICATION

The classification of lichen planus is based on clinical presentation and is divided into 3 main...
forms: reticular, erosive, and atrophic (or erythematous) lesions. Many other descriptors have also been used, including bullous, plaquelike, and papular. There is often overlap between types, with a combination of reticular, erosive, and erythematous lesions.

**CLINICAL FEATURES**

OLP predominately affects females, with most patients aged between 30 and 70 years. It is a rare occurrence in children; but in men, lesions often develop at an earlier age. The presentation is varied in clinical appearance, with most lesions being bilateral and located on the buccal mucosa. Lesions can appear, however, on the tongue, in the vestibule, and on the gingivae. Isolated gingival lichen planus may be seen in up to 8.6% of patients.

Malignant transformation of lichen planus is highly controversial. The term *premalignant* implies eventual malignant transformation, but lichen planus may better be described as having “malignant potential.” There has been a reported incidence of 0.4% to 1.5% malignant transformation to squamous cell carcinoma in patients with lichen planus. The World Health Organization’s (WHO) criteria describe lichen planus as a condition predisposed to malignant transformation.

Others have suggested that another entity, known as lichenoid dysplasia, is responsible for the conversion to malignancy. These lesions are dysplastic leukoplasias with a secondary lichenoid infiltrate but are often misdiagnosed as lichen planus. It is also purported that patients with erosive lichen planus are more susceptible to known carcinogenic agents because of the lack of an epithelial barrier. Regardless, most investigators advocate periodic observation for dysplastic changes.

**Reticular Lichen Planus**

Reticular lichen planus is the most common type and is often found incidentally. Lesions are asymptomatic and located on the buccal mucosa. Lesions can appear, however, on the tongue, in the vestibule, and on the gingivae. Isolated gingival lichen planus may be seen in up to 8.6% of patients.

**Erosive Lichen Planus**

Erosive lichen planus appears atrophic, with areas of ulceration, erythema, and keratotic white striae. There can be pseudomembranes, and in the gingival region it often appears similar to desquamative gingivitis. There is a range of symptoms, from a mild burning sensation to debilitating pain. Lesions can interfere with speech, chewing, and...
swallowing. These lesions can be mixed with reticular lesions, which are not seen in other vesiculoerosive diseases, such as pemphigus, pemphigoid, and linear immunoglobulin A (IgA) disease.\textsuperscript{19}

**Erythematous, Atrophic Lichen Planus**

This form of lichen planus presents as a red, diffuse lesion with mucosal atrophy.

**Plaquelike Lichen Planus**

Solitary, slightly raised, or flat white lesions appear similar to leukoplakia; a common oral location is on the tongue (Fig. 4).

**Bullous Form**

This rare form of OLP exhibits bullae that rupture, progressing to erosive lichen planus.

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**CAUSE**

Although the exact cause is not known, the literature supports an inflammatory immune cause for OLP.\textsuperscript{20–23} An antigen-specific cell-mediated immune response, autoimmune response, and humoral immunity have been previously described as mediating factors along with nonspecific mechanisms.\textsuperscript{24–27} The antigen-specific cell-mediated immune response involves CD8$^+$ T cells triggering keratinocyte apoptosis via the caspase cascade pathways.\textsuperscript{28–30} Keratinocyte apoptosis further triggers alteration in the basement membrane, causing nonspecific T-cell migration into the epithelium from the subepithelial layer. Altered basement membrane, matrix metalloproteinase (MMP), chemokines,\textsuperscript{25} and mast cells are part of the nonspecific mechanisms proposed in the development of OLP.\textsuperscript{27,31} T cells produce and secrete regulated on activation, normal T-Cell expressed and secreted (RANTES), a chemokine that enhances mast cell destruction, leading to the release of tumor necrosis factor–\(\alpha\) and chymase. This loop is a positive feedback loop that further stimulates RANTES production.\textsuperscript{32} RANTES is also involved in the recruitment of lymphocytes, monocytes, natural killer cells, eosinophils, basophils,\textsuperscript{32} and mast cells. Chymase activates MMP-9 that, in turn, causes basement membrane disruption.\textsuperscript{33} Keratinocyte-derived transforming growth factor–\(\beta_1\) mediates a weak immune response and upregulation of heat shock proteins and of circulating humoral antibodies against desmogleins 1 and 3 in OLP.\textsuperscript{25,34} The response may be autoimmune in nature\textsuperscript{35} or may be associated with exogenous antigens.\textsuperscript{26,36,37}

**HISTOLOGY**

Dubreuil was the first to describe the histopathology of OLP in 1906; in 1972, Shklar reported the classic histologic features of overlying keratinization, a dense bandlike layer of lymphocytic infiltrate within the underlying connective tissue, and liquefaction degeneration of the basal cell layer.\textsuperscript{38} Current literature supports common findings of dense, well-defined infiltrate of lymphocytes in the superficial dermis, orthokeratotic hyperkeratosis, parakeratosis, acanthosis, epithelial atrophy, basal cell degeneration\textsuperscript{39} and saw-tooth rete pegs.\textsuperscript{20,25} Homogeneous eosinophilic globules, known as colloid bodies (Civatte, hyaline, or cytoid), are found at the degenerating basal keratinocyte layer.\textsuperscript{20,25} The dense bandlike lymphocytic infiltration of the superficial stroma, basal epithelial cell liquefactive degeneration, and colloid bodies are considered the key features of OLP.\textsuperscript{24} The presence of plasma cells and B cells
is uncommon. Hemidesmosomes, filaments, and fibrils forming the epithelial anchoring system at the basal layer show disturbances. These disturbances produce deterioration of the epithelial-connective tissue junction leading to the formation of clefts called Max-Joseph spaces. Fibrin and fibrinogen in a linear pattern at the basal membrane layer is a common finding on direct immunofluorescence. Colloid bodies stain positively with IgM, C3, and C4. These immunofluorescence findings are highly suggestive of, although not diagnostic for, OLP when associated with other histologic features. The final diagnosis of OLP is concluded by clinical and histopathologic presentation.

TREATMENT AND PROGNOSIS

The management of lichen planus can be difficult. Cochrane evidence is weak for all interventional modalities. There is no cure, and most therapeutic modalities aim for symptomatic relief. This disease is a chronic disease, with periods of remission and relapse. The reticular form of lichen planus, when asymptomatic, does not require treatment. Common treatment options include systemic and topical corticosteroids, topical retinoids, cyclosporine, tacrolimus, and pimecrolimus.

Eisen found that exacerbation of the disease was precipitated by stress, foods, dental procedures, systemic illness, and poor oral hygiene. Oral lesions improved or resolved when the exacerbating factor was removed. Avoidance of irritating factors and improvement of periodontal health can aid in the management of these lesions. Systemic corticosteroids are an important form of treatment of diffuse erosive lichen planus or in patients who are refractory to topical steroids. There are, however, many side effects, even with short-term use. These side effects include hyperglycemia, diabetes, osteoporosis, cataracts, depression, hypertension, hypothyroidism, and amenorrhea. Systemic steroids can be used alone or in combination with topical corticosteroids, but they have not been found to be more effective than topical triamcinolone acetonide alone. In fact, topical triamcinolone acetonide alone has been shown to be an equally or more effective treatment in patients with erosive lichen planus. There are many effective formulations, including Orabase, lozenges, pastes, or mouthwash. Other topical corticosteroids (fluocinonide, betamethasone, clobetasol gel) have also been used with success. The side-effect profiles of topical corticosteroids are less severe than systemic corticosteroids but can include opportunistic candidiasis; mucosal atrophy; and, in cases of high-potency topical steroids, adrenal suppression.

Betamethasone as an oral mini-pulse therapy (2 consecutive days per week) has been shown

<table>
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<tr>
<th>Box 1</th>
<th>WHO diagnostic criteria (1978) for diagnosis of OLP</th>
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<tr>
<td><strong>Clinical Criteria</strong></td>
<td>Presence of white papule, reticular, annular, or plaque-type lesions, gray-white lines radiating from the papules</td>
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<td></td>
<td>Presence of a lacelike network of slightly raised gray-white lines (reticular pattern)</td>
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<td>Presence of atrophic lesions with or without erosion may also have bullae</td>
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<tr>
<td><strong>Histopathologic Criteria</strong></td>
<td>Presence of a thickened orthokeratinized or parakeratinized layer in sites that are normally keratinized; layer may be very thin if site is normally nonkeratinized</td>
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<td>Presence of Civatte bodies in basal layer, epithelium, and superficial part of the connective tissue</td>
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<td></td>
<td>Presence of a well-defined, bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes</td>
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<td>Signs of liquefaction degeneration in the basal cell layer</td>
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to be as effective as topical triamcinolone acetonide paste. This therapy has a lower side-effect profile than conventional systemic corticosteroids, and its use for exacerbations or as monotherapy has been described as effective.52

Intralesional injections of hydrocortisone, dexamethasone, triamcinolone acetonide, and methylprednisolone have also been used with short-term success.53 These injections are, however, often painful and can inadvertently cause mucosal atrophy.24

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**Box 2**  
Proposal for a set of modified WHO diagnostic criteria of OLP and OLL

**Clinical Criteria**

There is the presence of bilateral, more or less symmetric lesions.

There is the presence of a lacelike network of slightly raised gray-white lines (reticular pattern).

Erosive, atrophic, bullous, and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa.

In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term clinically compatible with should be used.

**Histopathologic Criteria**

There is the presence of a well-defined bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes.

There are signs of liquefaction degeneration in the basal cell layer.

There is an absence of epithelial dysplasia.

When the histopathologic features are less obvious, the term histopathologically compatible with should be used.

**Final Diagnosis OLP or OLL**

To achieve a final diagnosis, clinical as well as histopathologic criteria should be included.

OLP: A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria.

OLL: The term OLL will be used under the following conditions:

1. Clinically typical of OLP but histopathologically only compatible with OLP
2. Histopathologically typical of OLP but clinically only compatible with OLP
3. Clinically compatible with OLP and histopathologically compatible with OLP

**Abbreviation:** OLL, oral lichenoid lesions.


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**Fig. 5.** (A) Painful and ulcerated lesion of lichen planus before treatment. (B) Same patient as in (A), after treatment with chlorhexidine. Pain, ulcer, and erythema have resolved.
Patients with lichen planus can have superimposed candidiasis infections or can be secondarily infected with candidiasis from corticosteroid therapy. Treatment of *Candida* can help prevent exacerbations and can convert the erosive form to the reticular form. Further, corticosteroid-related candida infections can be treated with concomitant topical miconazole gel therapy.

Retinoids in topical or systemic forms have been used in the treatment of OLP. They are best used as an adjuvant therapy and have a significant recurrence rate after discontinuation of the drug. Retinoids in topical or systemic forms have been used in the treatment of OLP. They are best used as an adjuvant therapy and have a significant recurrence rate after discontinuation of the drug.

Cyclosporin is an immunosuppressant that affects T-cell cytokine production. Its use as a topical or mouth rinse in treatment of OLP has been reported with mixed results. Disadvantages include poor patient compliance because of taste, a burning sensation, and expense.

Pimecrolimus is an immunosuppressant agent in the ascomycin class of macrolactams. It inhibits T-cell activation and proliferation by acting on the calcineurin pathway. Found topical pimecrolimus cream four times a day to be as effective as triamcinolone acetonide paste. Tacrolimus is in the same drug class as pimecrolimus. Topical tacrolimus has a smaller molecular mass than cyclosporine and can better penetrate the epidermal barrier to exert its effect. It has been shown to have an equivalent or better initial therapeutic response than triamcinolone acetonide for treating erosive lichen planus but also shows greater relapse when therapy is discontinued.

Other treatments that have been reported include antibiotics, antimalarials, azathioprine, dapsone, glycyrrhizin, interferon, levamisole, mesalazine, and phenytoin. Many of these drugs, however, are also known to induce lichenoid reactions themselves. Recently, Mansourian and colleagues has shown aloe vera to be an effective substitute for triamcinolone acetonide for treating erosive lichen planus but also shows greater relapse when therapy is discontinued.

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**SUMMARY**

OLP is a very common immunologically mediated disease. It has varied clinical presentations and can appear on the buccal mucosa, tongue, gingivae, or in the vestibule. The common forms are reticular, erosive, and erythematous patterns. Management is aimed at symptomatic relief and includes systemic and topical corticosteroids, retinoids, tacrolimus, and pimecrolimus. The potential malignant transformation of lichen planus remains highly controversial. Periodic observation of these lesions for dysplastic changes remains prudent.

**REFERENCES**