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# Lichen planus, lichenoid drug reactions, and lichenoid mucositis

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## Epidemiology

Lichen planus (LP) is a common mucocutaneous disease affecting 1% to 2% of the population. Forty percent of lesions occur on both oral and cutaneous surfaces, 35% occur on cutaneous surfaces alone, and 25% occur on mucosa alone. Oral LP occurs in men and women, usually between the ages of 30 and 70 years. Children and adolescents are rarely affected.

The name "lichen planus" was provided by the British physician, Erasmus Wilson, who first described the condition in 1869. Because lichens are primitive organisms of symbiotic algae and fungi, it can be assumed that the clinical appearance of lesions seen by Wilson were reminiscent of lichens growing on rocks. Although the term "lichen planus" suggests a flat fungal infection, current evidence suggests a mucocutaneous disorder, mediated by numerous complex immunologic events.

Varying in its clinic appearance, oral LP (OLP) can appear keratotic (reticular or plaquelike) or erythematous and ulcerative and is often accompanied by skin lesions [1–3]. Spontaneous remission of cutaneous LP after 1 year occurs in approximately 70% of cases. Spontaneous remission of OLP is much less common, occurring in less than 5% of patients over a 7.5-year follow-up. The reticular form of OLP has the best prognosis, because spontaneous remission occurs in 40% of cases. The reported mean duration of OLP is 5 years, but the erosive form of the disease can persist for up to 15 to 20 years [4,5].

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## Cause and pathogenesis

Currently, the exact cause of LP remains unclear. Research exploring the pathogenesis of LP has yielded much data suggesting that immunologic mechanisms are fundamental to the initiation and perpetuation of LP [6]. Primarily, focus has on the role of the epithelial antigenic processing macrophage, Langerhans' cells [7], mast cells, [8–14], and their interactions with the abundant T-cell population accumulated in the underlying connective tissue [15–18].

Current evidence suggests that LP is a T-cell–mediated process [15–18]. Lesional LP tissue demonstrates massive local activated T-cell populations with increased local expression of cytokines and altered adhesion molecule expression [7,11,15,19]. In addition, therapies that suppress cell-mediated immune responses such as cyclosporine and etretinate reduce the lymphocyte infiltrate and cause clinical improvement of LP lesions [20]. Other evidence supporting the immunologic pathogenesis of LP includes the deposition of fibrinogen along the basement membrane and the cell-mediated autoimmune destruction of basal keratinocytes [21]. Analysis of the lesional cell populations has revealed that T lymphocytes are the main component of the inflammatory infiltrate with a significant number of CD4+ helper T cells in the lamina propria and CD8+ cytotoxic T cells in close proximity to the epithelial basement membrane [8,9]. Accumulations of CD8+ cells seem to increase gradually with disease progression. Potential imbalance between the T helper and suppressor activity may be the fundamental determinant of the immunologic activity of this infiltrate [15,19]. These cells both produce and respond to a range of cytokines and inflammatory mediators, and variations in the clinical presentation of OLP may be the result of differing cytokine profiles that in turn affect epithelial cells and stimulate cell proliferation and cell death [13,22].

Studies of T-cell receptor gene expression have not revealed the use of a restricted number of different variable region genes. Keratinocytes are the main target of damage by these T cells because of their expression of foreign or altered self-antigens on their surface. This finding suggests that OLP is probably caused by a limited range of extrinsic antigens, altered self-antigens, or superantigens. Important in these processes are the cytokines, chemokines, and adhesion molecules including tumor necrosis factor–$\alpha$ (TNF-$\alpha$), interferon-$\gamma$, and intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM)-1, which serve to recruit T cells, foster their adhesion to blood vessels, or direct their migration from the vasculature to the tissues [22].

Apoptosis also plays a role in the pathogenesis of OLP. Apoptosis, or programmed cell death, is a normal component of the development and health of multicellular organisms. Cells die in response to a variety of stimuli, and during apoptosis they do so in a controlled, regulated fashion. This controlled process distinguishes apoptosis from another form of cell death, necrosis, in

which uncontrolled cell death leads to lysis of cells, inflammatory responses, and, potentially, to serious health problems. Apoptosis also has been referred to as "cell suicide" because the cells play an active role in their own death. It is unclear which process is responsible for the basal cell damage seen in OLP; however, two mechanisms seem to play a role in cytotoxic T-cell apoptosis: apoptosis of the target cell and T-cell secretion of granzyme B. TNF-α may also promote apoptosis in OLP through direct induction or enhancement of a Fas/Fas-L–mediated process. Here, molecules (Fas ligand or FasL) bind to specific receptors (CD95 or Fas) on the cell surface and signal the cell to begin the apoptosis program [8,13,22].

Although there is sizable literature on T-cell populations in OLP, recent research has focused on other immunocompetent cells. An increased number of mast cells is a consistent finding in lesions of OLP [14], leading investigators to examine the potential contribution these cells and their mediators to chronic inflammation. T-cell cytokine RANTES (for *r*egulated on *a*ctivation *n*ormal *T*-cell *e*xpressed and *s*ecreted) has also been the focus of recent research in OLP. RANTES is a chemoattractant for eosinophils, monocytes, and lymphocytes. It is a potent and selective eosinophil chemotaxin that is stored in and released from platelets, activated T cells, and other cells. Oral keratinocytes secrete T-cell RANTES following cytokine stimulation [16]. RANTES is a prototypical T-cell-derived chemokine and potent inflammatory mediator that activates basophils and mast cells and attracts T cells [19]. Zhao and colleagues [9] demonstrated that stimulation of OLP lesional T-cell RANTES secretion from mast cell-derived TNF-α was responsible for the activation of mast cells and T cells in OLP. The postulated confounding and complex interactions between mast cells and T cells may determine the chronicity of OLP lesions.

Reports of hepatitis C infection associated with OLP have frequently appeared in the literature [23–25]. Although a majority of these reports come from Asian or Mediterranean countries, anecdotal evidence suggests that an association exists in both the United States and Great Britain. The relationship of hepatitis C to dermatologic diseases is not limited to OLP and seems to be related to the increased expression of the immune response by the virus. In an Italian study, the prevalence of different genotypes was equal to that in a population with chronic hepatitis C without LP [24]. The prevalence of autoantibodies is not higher in anti-HCV–positive patients than in negative patients; however, the positive patients have higher levels of immunoglobulins, which could be related to cryoglobulinemia. The virus replicates in epithelial cells whether LP is present or not, indicating that liver disease may be a prerequisite for LP to develop in anti-HCV–positive patients.

## Clinical features

LP has a wide range of clinical appearances that correlate well with disease severity [1,26,27]. Three distinct clinical presentations most often are

described: reticular, erosive, and plaquelike. Often, patients have a combination of the reticular and erosive forms, whereas plaquelike LP usually occurs as a solitary, white plaque resembling leukoplakia, and may or may not occur with other forms.

### Reticular lichen planus

Reticular LP has a distinct and characteristic clinical appearance of thin, slightly raised white lines that connect in a pattern resembling lacework or a reticular, annular appearance. This arcuate pattern of white lines can be on erythematous or nonerythematous mucosa and is referred to as Wickham's striae (Fig. 1). Patients with reticular LP rarely experience symptoms and only become aware of their condition when it is noticed by a dental health professional. If the underlying mucosal becomes more inflamed, atrophic, or ulcerated, patients often complain of soreness of the area, made worse with the consumption of certain foods or use of certain oral hygiene products. The most common locale for reticular LP is the buccal mucosa, followed by the buccal vestibule, tongue, gingiva, and labia. Reticular LP commonly occurs bilaterally.

### Erosive lichen planus

Erosive LP most often appears as a mixture of intensely erythematous mucosa with large areas of irregularly shaped ulceration with a whitish-yellow pseudomembrane (Fig. 2) [28,29]. Often, the junction of the red and normal mucosa exhibits faint, white, radiating striae. The degree of atrophy, erythema, and central ulceration can vary from lesion to lesion. In some patients, the atrophy and ulceration are confined to the gingival mucosa, producing a pattern called "desquamative gingivitis" (Fig. 3). Clinically, chronic desquamative gingivitis may represent mucous membrane pemphigoid or pemphigus vulgaris, making histopathologic evaluation essential.

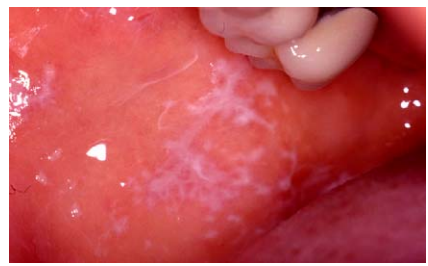

Fig. 1. Lacelike pattern of white lines classically referred to a Wickham's striae.

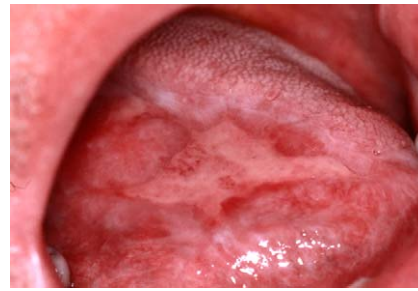

Fig. 2. Erosive lichen planus with an irregularly shaped ulcer with yellowish pseudomembrane and moderate erythema.

## Plaquelike lichen planus

Plaquelike LP appears as a slightly raised or flat white area on the oral mucous membranes. It cannot be rubbed off and is indistinguishable from other focal leukoplakias (Fig. 4). The most common location for plaquelike LP is the tongue, and more than one location can be involved.

Bullous LP is a rare form of LP characterized by large bullae ranging in size from 4 mm to 2 cm. The bullae, like pemphigus vulgaris, rupture almost immediately in the oral cavity, leaving an ulceration on a bed of inflamed mucosa. Bullous LP seems most commonly to affect the posterior buccal mucosa.

## Diagnosis and histopathologic features

Reticular LP often is diagnosed based on clinical information alone because of the distinct characteristic Wickham's striae in a lacework or annular pattern on an inflamed or uninflamed background. The erosive and plaquelike forms always require laboratory evaluation, because they can clinically resemble other oral mucosal lesions, including malignancy [30,31].

Because other mucocutaneous diseases, including pemphigus, pemphigoid, lichenoid reactions, and contact allergy, among others, are included in

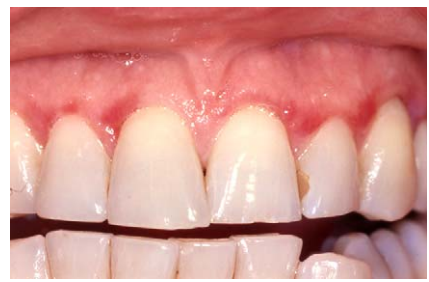

Fig. 3. Mild lichen planus manifesting as a desquamative gingivitis.

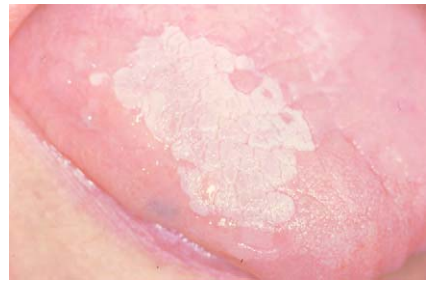

Fig. 4. Well-delineated, slightly raised white patch of plaquelike lichen planus.

a differential diagnosis of LP, it is important that a biopsy be performed to confirm a diagnosis. Often two distinct specimens are obtained, one for hematoxylin-eosin staining and the other for direct immunofluorescent (DIF) study to rule out lupus, mucous membrane pemphigoid, and pemphigus.

Although the histopathologic features of LP vary slightly among the various clinical types, three hallmark features are considered necessary for an LP diagnosis [1]: (1) Hyperortho- or hyperparakeratosis, usually with a thickening of the spinous cell layer (acanthosis) and shortened, pointed, saw-toothed appearance of the rete ridges. These thickened areas are clinically seen as Wickham's striae. Between these areas, the epithelium is often atrophic with loss of rete ridge formation. (2) Necrosis of the basal cell layer often referred to as "liquefaction degeneration." (3) A dense subepithelial band of chronic inflammatory cells, usually T lymphocytes in the subjacent connective tissue that can transgress the basement membrane and can be seen in the basilar or parabasilar layers of the epithelium.

Scattered within the epithelium and superficial connective tissue, Civatte's bodies are isolated epithelial cells, shrunken with eosinophilic cytoplasm and one or multiple pyknotic nuclear fragments. These Civatte's bodies are thought to represent apoptotic keratinocytes and other necrotic epithelial components that are transported to the connective tissue for phagocytosis [32].

The tissue diagnosis of LP can be difficult but may be greatly aided by the use of immunofluorescence. Immunofluorescent studies of biopsy specimens from lesions of LP reveal features that suggest the pathogenesis of these lesions and aid in the differentiation of LP from other mucocutaneous diseases [12]. Specifically, DIF demonstrates a ragged band of fibrinogen in the basement membrane in nearly 100% of cases. Occasionally, specimens demonstrate IgM-staining cytoid bodies in the dermal papilla or peribasilar areas. When present in large numbers or clusters, these cytoid bodies are highly suggestive of LP. Immunohistochemical staining using the antibody to the S-100 protein indicates an increase in Langerhans' cells in the midlayers of the epithelium [12].

In erosive LP, there is thinning and ulceration of the epithelium with complete loss of rete ridge formation and a dense T-cell infiltrate extending

well into the middle and upper levels of the epithelium. Liquefaction of the basement membrane and vacuolization and destruction of the basal cell is seen in most areas. Often the epithelium is lost, revealing underlying connective tissue.

Plaquelike LP histologically is similar to the striae of the reticular form, without the intermittent areas of epithelial atrophy. Ortho- and parakeratosis are seen in combination with acanthosis. The basement membrane is thickened, with a band of T lymphocytes that is less dense than in the reticular form.

## Treatment

To date, no cure for OLP or its dermal counterpart exists. The treatment goal is always twofold: (1) alleviation of symptoms, and (2) monitoring for dysplastic changes [33]. Small areas of the reticular or plaquelike form of LP are rarely treated unless they become symptomatic, persist, or become widespread. For cases of lichenoid reaction, elimination of the offending agent is imperative.

Corticosteroids have been shown to be the most predictable and effective medications for controlling the signs and symptoms of OLP. Topical corticosteroids such as fluocinonide 0.05% and clobetasol 0.05% are frequently prescribed as gels and applied daily according to disease severity [34,35]. Topical medications can be applied to the lesions with cotton swabs or gauze pads impregnated with steroid. Extensive erosive lesions on the gingiva can be treated two or three times daily with occlusive splints that hold the steroid medication on the affected areas. Long-term studies demonstrate no adverse systemic side effects of topical steroids, but occlusive splint therapy can lead to systemic absorption of steroid. Candidal overgrowth with clinical thrush is an occasional side effect, requiring concomitant topical or systemic antifungal therapy. In lesions recalcitrant to topical therapy, intralesional injections of steroid can be effective. Often, triamcinolone, 5 mg/ml, is combined with local anesthetic to inject 0.1 ml/$cm^3$ of lesion.

No controlled studies have evaluated the efficacy of systemic corticosteroids in OLP. Occasionally, systemic steroids are indicated for brief treatment of severe exacerbations or for short periods to treat recalcitrant lesions that fail to respond to topical therapy. Many clinicians recommend prednisone, 0.50 to 0.75 mg/kg/day for less than 10 days without tapering [3]. Often, combination topical and systemic therapy may prove more beneficial than any single modality.

Retinoids can be useful and are frequently used in combination with topical corticosteroids as an adjuvant therapy. The indication for topical retinoids seems to be plaquelike and reticular lesions that are persistent or widespread. Lesions frequently recur after withdrawal of these medications. Systemic and topically administered β-all-*trans* retinoic acid, vitamin A, systemic etretinate, and systemic and topical isotretinoin all have

demonstrated some measure of efficacy in open studies or anecdotal case reports [3]. Topical retinoids are usually favored over their systemic counterparts because the latter may be associated with adverse side effects such as liver dysfunction and teratogenicity.

The topical use of cyclosporine seems to be beneficial in treating recalcitrant cases of OLP [20]. Despite encouraging results in double-blinded clinical trials, the use of cyclosporine is limited because of its hydrophobicity, high cost, and poor taste. In addition, concerns over its role in promoting viral reproduction and malignant change have restricted its use to patients with severe disease and otherwise intractable lesions.

Recently, numerous reports have suggested the use of topical tacrolimus or pimecrolimus in solutions, ointment, or cream form for OLP resistant to topical or systemic therapies [36–39]. These immunosuppressive agents are used in dermatology primarily to treat atopic dermatitis. Although their exact mode of action is unclear, they appear to inhibit T-cell activation and proliferation [36–39]. Side effects of these topical immunomodulators include carcinogenicity, mutagenicity, and infertility.

Other treatments for OLP have been reported to be useful; however, additional research data are necessary. Oral psoralen-UVA (PUVA) therapy with low-dose UV-A has been shown to be effective in treating OLP in several open studies [40]. PUVA is a combination treatment that consists of exposing patients to psoralens (P) and then exposing the skin to long-wave ultraviolet radiation (UVA). Additional medications including griseofulvin, levamisole, dapsone, and thalidomide have been reported to be effective in the treatment of OLP in various case reports throughout the literature [3,41].

## Lichen planus: a premalignant lesion

The possible premalignant character of LP is the subject of ongoing and controversial discussion in the literature [42–50]. The first identifiable case of carcinoma arising in LP of the oral mucosa was described by Hallapeau in 1910. Since that time, numerous retrospective studies and case reports have been published linking the development of carcinoma with LP. The range of malignant transformation of OLP per year, as described in the literature, is between 0.04% and 1.74% [42–50]. Controversy exists as to the true malignant potential of OLP, primarily because of lack of adequate data in the initial diagnosis of OLP, because of the lack of documentation as to the historical exposure to carcinogens, and because many of these retrospective studies and case reports describe the development of carcinomas at anatomic sites remote from the OLP. A study using strict diagnostic criteria for OLP and lichenoid lesions as outlined by the World Health Organization reported the development of squamous cell carcinoma in 3 of 173 patients (1.7%) [50].

It is generally accepted that the malignant transformation or development of malignancy in the presence of OLP is more likely to occur in atrophic, erosive, or ulcerative lesions. It had been postulated that these atrophic, erosive, and ulcerative lesions predispose the mucosa to damage from carcinogenic agents. Many patients who develop carcinoma lack a positive history for tobacco or alcohol use, however, suggesting that malignancy may be part of the natural course of the disease process or that other unknown extrinsic factors may be involved. Because Candida is a natural inhabitant of the oral mucosa in many patients and because it often develops secondary to topical corticosteroid therapy, Candida may be another extrinsic factor involved in the development of malignancy. It has been hypothesized that strains of *Candida albicans* are able to catalyze the formation of the known carcinogen *N*-nitrosobenzylmethylamine.

Other debates have revolved around the use of immunomodulating agents in the treatment of LP as a causative factor in the development of malignancy. Theoretically, the ability of these medications to depress local cell immunity could promote the progression of LP to malignancy; because of the potent anti-inflammatory effects of these agents, malignant progression would advance with reduced symptoms. Before a definitive, consensus statement regarding the malignant potential of LP can be made, longitudinal studies with larger number of patients should be performed. Clinically, it is important that patients with OLP, particularly patients who have erosive and ulcerative disease, undergo biannual follow-up evaluations.

Table 1
Diseases, drugs, and materials commonly implicated in lichenoid reactions

| Category | Drug or material |
|---|---|
| Antiarthritics | Aurothioglucose, gold salts |
| Antihypertensives | Angiotensin-converting enzyme inhibitors, thiazide diuretics, mercurial diuretics, labetalol, practolol, methyldopa |
| Antimicrobials | Dapsone, ketoconazole, streptomycin, sulfamethoxazole, tetracycline |
| Antiparasitics | Chloroquine, quinacrine, pyramethamine, organic arsenicals |
| Anxiolytics | Lorazepam |
| Nonsteroidal anti-inflammatory agents | Ibuprofen, fenclofenac, naproxen, phenylbutazone |
| Oral hypoglycemic agents | Chlorpropamide, tolazamide, tolbutamide |
| Uricosuric agents | Allopurinol |
| Dental restorative materials and foodstuffs | Amalgam components, acrylic, casting alloys, betel quid, peppermint, cinnamon |
| Systemic disease | Graft-versus-host disease, hepatitis C, thymoma, lupus erythematosus |

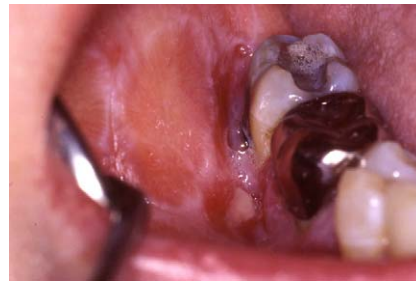

Fig. 5. Lichenoid lesions secondary to corroding amalgam.

## Lichenoid drug reactions

Lichenoid drug reactions and LP exhibit similar clinical and histologic findings [51–56]. The former are distinguished from the latter by two factors: (1) the association with the administration of a drug, contact with a metal or foodstuff, or systemic disease, and (2) their resolution when the offending agent is eliminated (although this resolution is not universal) [52]. The prevalence of oral lichenoid drug reactions seems to be increasing, perhaps because of the realization that the entity has a cause that is distinct from idiopathic LP [53,54]. The increased occurrence may also result, in part, from the introduction of numerous new categories of medications that have a greater tendency for lichenoid reactions as a side effect. Most often, antibiotics, antihypertensives, gold compounds, diuretics, antimalarial agents, and nonsteroidal anti-inflammatory agents are responsible for lichenoid reactions. Table 1 summarizes the drugs and materials commonly implicated in oral lichenoid reactions.

Clinically, lesions are indistinguishable from OLP, demonstrating erythematous erosions and ulceration with focal areas of radiating striae (Fig. 5). Because the histology is often indistinguishable from OLP, diagnosis often depends on establishing a temporal relationship between lesion onset and the use of the offending agent and resolution of symptoms upon withdrawal of the offending agent. A drug history can be one of the most important aspects of the assessment of a patient with oral lichenoid lesions. Occasionally, drug-induced lesions may show a deep and superficial perivascular lymphocytic infiltrate with the presence of eosinophils, plasma cells, and neutrophils. Treatment of lichenoid reactions, in addition to cessation or reduction in the dose of the offending medication, is usually restricted to topical corticosteroids. The resolution of lesions after removal of an offending agent may be prompt or may take months to clear.

## Summary

OLP and lichenoid reaction are a relatively common oral mucosal disease process encountered in clinical practice. This mucocutaneous disease can

manifest as desquamative gingivitis, asymptomatic Wickham's striae or plaques, or severe, painful erosions or ulcerations anywhere in the oral cavity. Although the exact agent initiating LP is unknown, current research points to a number of complex immunologic events and cells that are responsible for the inflammatory destruction and chronicity of these lesions. Currently, the mainstay of treatment remains topical corticosteroids, but newer therapies such a tacrolimus are available for recalcitrant lesions. In cases of lichenoid mucositis or reactions, treatment should always be directed toward identifying and removing the presumed causative agent. Given the apparent risk of squamous cell carcinoma in these patients, frequent follow-up and repeat biopsy when indicated are vital.

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