

# Lichen planus and lichenoid reactions of the oral mucosa

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**ABSTRACT:** Oral lichenoid reactions represent a common end point in response to extrinsic agents (drugs, allergens), altered self-antigens, or superantigens. Oral lichen planus, a common and under-recognized inflammatory disorder, shares many clinical and histopathological features with oral lichenoid drug reaction and oral lichenoid contact reaction. Clinical presentation can vary from asymptomatic white reticular striae to painful erythema and erosions. Cutaneous and additional mucosal involvement is common. Delay in diagnosis of extraoral mucocutaneous lichen planus (LP) results in conjunctival scarring; vaginal stenosis; vulvar destruction; and stricture of the esophagus, urethra, and external auditory meatus. Although the etiology of LP is idiopathic, oral lichenoid reactions may be caused by medications or exogenous agents such as cinnamates and other flavorings. The clinical features, evaluation, and management of these oral lichenoid reactions are discussed.

**KEYWORDS:** lichenoid mucositis, lichen planus, oral lichenoid contact reaction, oral lichenoid drug reaction, treatment

## Introduction

Oral lichenoid reactions represent a common end point in response to extrinsic agents (drugs, allergens), altered self-antigens, or superantigens. Oral lichen planus (OLP) is a chronic, inflammatory disorder of unknown etiology. Patients experience mild to severe oral pain which may impede oral intake and compromise nutritional status. The varied morphologies of OLP mandate consideration of a broad differential diagnosis. A complete mucocutaneous examination and extensive review of systems should be performed on all OLP patients in order to identify additional sites of involvement, many of which cause severe morbidity. There is no cure for lichen planus (LP). Many topical and systemic treatment options have been utilized with variable success, but efficacy studies are lacking. Malignant transformation of OLP has been reported, but the absolute risk has not been well

defined. Thus, long-term surveillance at regular intervals is recommended for these patients. Oral lichenoid reactions may also result from systemic drug exposure (oral lichenoid drug reaction (OLDR)) or local allergic contact hypersensitivity (oral lichenoid contact reaction (OLCR)). Oral lichenoid lesions share common clinical and histological features; a detailed history and additional diagnostic testing are crucial to obtaining an accurate diagnosis and to directing management. Unlike OLP, most cases of OLDR and OLCR resolve after discontinuation of the causative agent. Given the overlapping clinical and histopathological features, similar therapies may be used in all of these conditions. This article presents a review of OLP, OLDR, and OLCR including a practical approach to the diagnosis, evaluation, and management of these challenging oral conditions.

## LP

### Epidemiology

LP, a common mucocutaneous inflammatory disorder, occurs at sites of stratified squamous epithelia. LP affects 0.5–2% of the population, with

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notable variation by geography and diagnostic criteria (1–4). The prevalence of OLP is unknown. Epidemiological studies are hampered by the lack of clear diagnostic criteria; varied clinical presentation; and the fact that the most common form of OLP, reticular, is asymptomatic and therefore underdiagnosed. Women are affected more commonly than men. Onset of disease occurs between 30 and 60 years of age (mean at 50 years) (5–7). In a retrospective study of 723 patients with biopsy-confirmed OLP, mean age at presentation was 57 years for women and 47 years for men (overall age range of 13–82 years). Seventy-five percent were women and 25% were men (5).

### Pathogenesis

The etiology of OLP is unknown; however, OLP appears to be a T cell-mediated autoimmune disease (8). Current evidence suggests that OLP reflects perturbation of cell-mediated immunity, precipitated by endogenous or exogenous factors, and results in altered response to self-antigen (9,10). Precipitating factors may include trauma, stress, and infectious agents (i.e., hepatitis C virus (HCV)) (11). The majority of T cells within the inflammatory infiltrate of OLP are activated CD8+ lymphocytes (12,13). Activated T cells in the inflammatory infiltrate in combination with increased Th1 cytokine production (IL-1, IL-8, IL-10, IL-12, TNF- $\alpha$ ) increase the expression of intercellular adhesion molecule-1 on Langerhans cells and macrophages, and major histocompatibility complex antigens by keratinocytes. Antigen presentation (including possible aberrant presentation of self-antigen) to keratinocytes ensues (9). Genetic polymorphism of the first intron of the IFN- $\gamma$  promoter is an important risk factor for the development of OLP, and further reinforces the role of Th1 cytokines (10). Furthermore, the peripheral immune suppressor function is altered in OLP, and the balance between help and suppression by T cells may determine disease activity (14,15). This altered immune response results in keratinocyte apoptosis (16–19).

### Clinical presentation

OLP is classified morphologically as reticular (white, 23%), erythematous (atrophic, 40%), and erosive (bullous, ulcerated, 37%) (5). Multiple morphologies may present simultaneously, and the predominant clinical morphology may change over time with more severe forms (erythematous/atrophic, erosive) occurring in older patients (2).

OLP characteristically presents with multiple lesions in a bilateral and roughly symmetric distribution, which assists in its distinction from OLCR (see below). Unilateral presentation of OLP is atypical (20). OLP most commonly involves the buccal mucosa (up to 90%), gingiva, dorsum of the tongue, labial mucosa, and lower vermilion lip. Less common sites include the palate, upper lip, and floor of the mouth (2,5,7,21). Approximately 10% of patients have disease confined to the gingiva (5,22). OLP confined to a single site other than the gingiva (i.e., tongue, lip) is uncommon; patients who present with isolated lesions develop multiple sites of involvement over time (5,20,23).

OLP develops in sites of trauma (Koebner phenomenon) and can be exacerbated by mechanical factors including biting/chewing habits, dental procedures, and rubbing of malpositioned or ill-fitting dental appliances (i.e., dentures, partials, and mouth guards). Heat and irritants from tobacco smoking may also aggravate lesions.

Reticular lesions consist of white papules and striations that form a lacy network (Wickham's striae) on the buccal mucosa, gingiva, alveolar sulcus, and lower vermilion lip (FIGS 1 and 2). This presentation may be an isolated finding without concomitant erythema or erosions. Being asymptomatic, reticular OLP is often discovered incidentally during oral examination. Involvement of the



FIG. 1. Reticular and atrophic (erythematous) oral lichen planus involving the dorsal and lateral tongue.



**FIG. 2.** Reticular and erosive oral lichen planus involving the lower vermillion lip. Photograph courtesy of Dr. Susan Muller.



**FIG. 4.** Diffuse erythema and erosions of the maxillary gingiva typical of desquamative gingivitis. Photograph courtesy of Dr. Susan Muller.



**FIG. 3.** Hypertrophic reticular plaques involving the dorsum of the tongue.

dorsum of the tongue may cause dysgeusia. Large reticular plaques, which may be hyperkeratotic, show a predilection for the dorsum of the tongue (FIG. 3).

Erythematous and erosive OLP is almost always accompanied by reticular white papules/striae, a clinical clue that facilitates diagnosis (11,24). Rarely, intact vesicles may be observed (bullous OLP) (25). Erosive OLP often presents as desquamative gingivitis in which the gingival epithelium is easily peeled away from the underlying submucosa



**FIG. 5.** Flat-topped violaceous thin papules on the lower back characteristic of cutaneous lichen planus.

(26) (FIG. 4). Erythema and erosions can cause significant pain (burning, irritation), swelling, and bleeding (5).

Concomitant involvement of extraoral sites (i.e., scalp, skin, nails, conjunctiva, esophagus, larynx, urethra, vulva and vagina, and perianal area) is common and results in severe morbidity reinforcing the importance of a multidisciplinary approach to care. Cutaneous LP classically presents as pruritic, purple, polygonal, flat-topped papules and plaques with predilection for the flexural wrists, dorsal feet, and pretibia (FIG. 5). Cutaneous lesions typically exhibit fine, lacy white striations (Wickham's striae) similar to reticular OLP. Papules and plaques may occur in linear or angulated configurations demonstrating the isomorphic response (koebnerization). Generalized involvement may occur. Significant post-inflammatory mucocutaneous hyperpigmentation may result. Cutaneous LP



**FIG. 6.** Severe erosive vulvovaginal lichen planus. Note complete loss of the right labium minus and agglutination/resorption of the left labium minus.

was observed in 15% of an OLP population (27). Cutaneous LP lesions usually develop within several months of OLP lesions. There is no correlation between extent or severity of OLP and cutaneous LP (27). More than 50% of patients with cutaneous LP have concomitant OLP.

While post-inflammatory hyperpigmentation is disfiguring, scarring is not seen in cutaneous or oral LP. However, scarring is typical for involvement of other sites (nails, scalp, genitalia). Nail involvement is associated with nail plate dystrophy (thinning, ridging), splitting of the distal free edge of the nail plate, and pterygium formation with possible permanent loss of the nail. Lichen planopilaris of the scalp causes cicatricial alopecia.

LP often affects the genitalia. Approximately 25% of women with OLP have vulvovaginal involvement (27–29). Erosive lesions predominate and can be associated with severe morbidity including dyspareunia, dysuria, burning, and pain (FIG. 6). Asymptomatic reticular vulvar lesions may also be present, but are rarely the sole manifestation of vulvovaginal LP (30). Agglutination (scarring with resorption of tissue) affects the clitoral hood, labia minora, and vaginal introitus. Although erythematous and erosive OLP rarely scars, vulvovaginal LP often scars with resulting vulvar destruction and vaginal stenosis. Severe introital scarring may pre-

cipitate acute urinary obstruction, a medical emergency. Reticular and papulosquamous lesions of the glans penis are common, but erosive LP is rare. Vulvovaginal–gingival syndrome consists of erosive or desquamative vulvitis, vaginitis, and gingivitis, and was originally described in 1982 (29,31). Women with vulvovaginal–gingival syndrome may demonstrate reticular or erosive OLP involving the gingiva, buccal mucosa, labial mucosa, or tongue; 25% present with desquamative gingivitis. OLP may precede or occur simultaneous with vulvovaginal LP (29). The male corollary, the penogingival syndrome, typically presents with erosive LP of the glans penis, with or without reticular or erythematous lesions of the glans and shaft of the penis. Patients also have reticular, erosive, or erythematous OLP; 42% present with desquamative gingivitis (29,32).

The conjunctiva (33), nasal mucosa, larynx, esophagus (34), urethra, and anus are rare sites of erosive LP (3,27). Such involvement is under-recognized by practitioners and may result in life-altering sequelae.

### Differential diagnosis

The differential diagnosis of OLP varies by lesion morphology. White reticular OLP must be distinguished from candidiasis, discoid lupus erythematosus, leukoplakia, morsicatio buccarum et labium, mucous patches of secondary syphilis, oral hairy leukoplakia, lichenoid dysplasia, squamous cell carcinoma (SCC), and poor oral hygiene.

The differential diagnosis of oral erosive lesions is broad and includes OLP, immunobullous and connective tissue disorders, and lichenoid reactions to drugs and infections (Table 1). In the absence of classic reticular lesions, the diagnosis can be especially challenging, and biopsy is required. Biopsy of lesional skin for routine histopathology and perilesional skin for direct immunofluorescence (DIF) is essential to obtaining an accurate diagnosis. Indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assays for specific autoantibodies can provide additional diagnostic information. Desquamative gingivitis, characterized by patchy or confluent erythema and/or erosions of the gingiva, can most often be attributed to OLP, mucous membrane pemphigoid, pemphigus vulgaris, or systemic lupus erythematosus.

### Diagnostic evaluation

The extent and nature of the diagnostic evaluation required for patients with possible OLP will vary

**Table 1.** Differential diagnosis of erythematous and erosive oral lichen planus (OLP)

Disease	Characteristic features
Aphthous ulcers	Non-keratinized mucosal of the lip, buccal, ventral tongue, floor of mouth Single or multiple discrete oval ulcers Erythematous halo, yellow pseudomembrane Rarely herpetiform (10–100 1–2 mm ulcers clustered) H&E: necrosis, ulceration, PMN dust DIF: negative
Bullous pemphigoid	Oral involvement in 10–35% Erosions, rare intact bullae Cutaneous urticarial plaques, tense bullae H&E: subepithelial blister with eosinophils and possibly neutrophils DIF: linear C3, IgG at BMZ IIF: linear IgG at BMZ SSS: linear IgG at roof of blister
Chronic ulcerative stomatitis	Clinically very similar to OLP H&E: lichenoid mucositis DIF: speckled or granular perinuclear IgG in lower third of epithelium IIF: IgG antinuclear antibodies
Dermatitis herpetiformis	Oral lesions common Subtle, diffuse erythema and superficial ulcerations Tooth enamel defects (pits) common H&E: neutrophilic mucositis DIF: granular IgA at BMZ
Discoid lupus erythematosus	Mucosal involvement in 25% Buccal mucosa most common, also palate, tongue Erythematous plaques with radiating white striae and telangiectases (“sunburst”) Secondary ulceration H&E: vacuolar interface mucositis DIF: linear band or continuous granular IgG, IgA, IgM and complement components (C3, etc.) at BMZ
Epidermolysis bullosa acquisita	Traumatic oral ulcers and bullae Desquamative gingivitis H&E: pauciinflammatory subepithelial bulla DIF: linear IgG at BMZ SSS: linear IgG at base of blister ELISA: autoantibodies to type VII collagen
Erythema multiforme	Erosions with white pseudomembrane Hemorrhagic cheilitis Often recurrent H&E: vacuolar interface mucositis DIF: negative
Familial benign pemphigus (Hailey–Hailey disease)	Rare ulcers, painful vegetative papules H&E: intraepithelial acantholysis, no dyskeratosis DIF: negative IIF: negative
Graft versus host disease	Appropriate clinical setting Diffuse erythema and mucositis (both keratinized and non-keratinized mucosa) White reticular plaques and erosions Loss of filiform papillae Loss of gingival stippling H&E: basal vacuolar degeneration, subepithelial lymphocytic infiltrate
Primary herpes simplex stomatitis	Erosive gingivostomatitis Small, punched out ulcers that may coalesce to large ulcers with scalloped borders Recurrent on gingiva, hard palate, and dorsal tongue Positive Tzanck, DFA, viral culture, serology for HSV1 and 2 H&E: intraepidermal bulla with neutrophils, keratinocyte necrosis, multinucleated giant cells, positive immunohistochemistry for HSV 1 or 2
Recurrent herpes simplex stomatitis	Small, punched out ulcers that may coalesce to large ulcers with scalloped borders Recurrent on gingiva, hard palate, and dorsal tongue
Linear IgA bullous dermatosis	Oral lesions common (up to 70%) Large ulcers on tongue, palate, buccal mucosa Desquamative gingivitis DIF: linear IgA at BMZ, less often also IgG, C3 IIF: linear IgA at BMZ SSS: linear IgA at roof of blister

**Table 1.** Continued

Disease	Characteristic features
Mucous membrane pemphigoid	Most often presents as patchy desquamative gingivitis Rare intact bullae Investigate other mucosal sites H&E: subepithelial bulla with mixed dermal inflammatory infiltrate, may be "cell poor" DIF: linear IgG and C3 at BMZ, less often IgA, IgM and/or fibrin IIF: low-titer linear IgG and/or IgA at BMZ SSS: linear IgG and/or IgA at roof of blister, linear IgG and/or IgA at floor of blister in anti-laminin 332
Paraneoplastic pemphigus	Predominant labial mucosa and vermilion involvement Underlying malignancy H&E: suprabasilar acantholysis, interface/lichenoid mucositis DIF: intercellular IgG, C3 with or without BMZ deposition of IgG, C3 IIF: intercellular staining of transitional epithelium (rat bladder) ELISA: autoantibodies to BP180, BP230, dsG1, dsG3 Immunoprecipitation: antiplakin autoantibodies
Pemphigus vulgaris	Desquamative gingivitis Soft palate, buccal and labial mucosa H&E: suprabasilar acantholysis, "tombstoning" DIF: intercellular IgG and C3 in "chicken wire pattern" IIF: intercellular IgG, C3 ELISA: autoantibodies to desmoglein 3, desmoglein 1
Systemic lupus erythematosus	Oral involvement in 25% of patients Hard palate involvement Recurrent ulcers and erythema Discoid lesions may be present H&E: vacuolar interface mucositis DIF: linear band or continuous granular IgG, IgA, IgM and complement components (C3, etc.) at BMZ

BMZ, basement membrane zone; DFA, direct fluorescent antigen; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; H&E, hematoxylin and eosin staining; IIF, indirect immunofluorescence.

based on lesion morphology, extent and severity of oral involvement, review of systems, and the presence and severity of cutaneous and/or non-oral mucosal involvement.

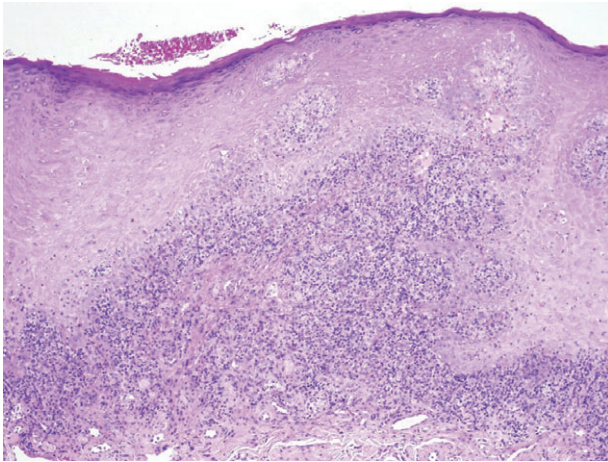
An extensive review of systems should be obtained. Specific attention should be given to dysphagia, swallowing difficulty, change in vision, ocular foreign body sensation, hoarseness, stridor, dysuria, dyspareunia, and hematuria in order to assess for esophageal, conjunctival, laryngeal, vulvar, and vaginal LP. These mucosal sites are well-described and under-recognized, but carry severe morbidity. Dermatologists should have a low threshold to consult appropriate specialists (dentists, gastroenterologists, ophthalmologists, otolaryngologists, urologists, and gynecologists) in order to ensure a complete diagnostic evaluation and to devise an appropriately comprehensive therapeutic regimen that addresses the needs of the patient.

Patients who present with classic reticular lesions of OLP in a bilateral, symmetric distribution may not require biopsy. Patients who present with erythema or erosions should undergo biopsy for both routine histopathology and DIF. Histological confirmation can provide reassurance of the diagnosis to the patient and physician, and also reinforce the appropriateness of aggressive therapeutic regimens. Repeat biopsy during follow-up should be considered when the clinical

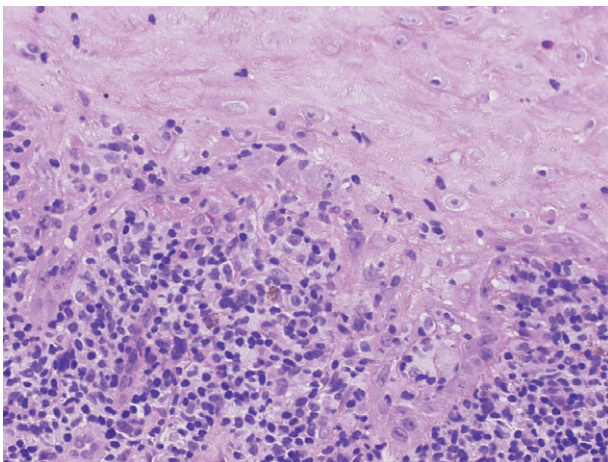
presentation changes, when lesions do not respond to appropriate therapy as predicted, or when dysplasia or malignancy is suspected. Patients who present with an acute exacerbation should be evaluated for other causes of oral pain and discomfort including reactivation of herpes simplex virus infection and oral candidiasis.

Histologically, OLP is characterized by a dense, band-like, lymphocytic, superficial inflammatory infiltrate which may obscure the junction of the epithelium and lamina propria, liquefaction degeneration, and necrosis of basal keratinocytes (FIGS 7 and 8). These degenerated keratinocytes form Civatte (colloid, hyaline, or cytoid) bodies that appear as homogenous eosinophilic globules in the lower epithelium and superficial lamina propria. Dysplasia is not present. With erosive OLP, the histopathological findings may be less distinct and not diagnostic. Reticular lesions may provide greater diagnostic yield (5,35). Evaluation of OLP histopathology specimens is subjective and insufficiently reproducible; in approximately 50% of OLP cases, there is a lack of clinicopathological correlation (36,37). Clinicopathological correlation should be emphasized especially when there is concern for malignancy.

DIF microscopy of perilesional mucosa is essential to exclude other autoimmune vesiculoerosive disorders that are clinically indistinguishable par-



**FIG. 7.** Biopsy of oral lichen planus shows a dense, band-like, lymphocytic infiltrate in the superficial submucosa and wedge-shaped hypergranulosis of the epithelium (100× magnification).



**FIG. 8.** Biopsy of oral lichen planus shows scattered necrotic keratinocytes and basal keratinocyte vacuolar degeneration (400× magnification).

ticularly in the context of desquamative gingivitis (38,39) (Table 1). The gingiva may represent the best site for obtaining a biopsy for DIF microscopy in patients with OLP; however, biopsy of the gingiva should be performed after consideration of the risks of anatomical defect, permanent scarring, and technical challenges (see “Art and Science of the Oral Exam” by Agha and Mirowski) (39). Immunofluorescence demonstrates fibrin and shaggy fibrinogen in a linear pattern at the basement membrane zone (BMZ) (40).

The role that HCV plays in the initiation of OLP has yet to be resolved. Studies of the link between HCV infection and OLP have yielded mixed results which may be due to variability in diagnostic and

inclusion criteria. An association between HCV infection and/or chronic hepatic disease and OLP has been demonstrated in several studies of geographically diverse populations with different rates of endemic HCV infection (21,41–45). HCV DNA sequences have been detected in oral tissue specimens and sera of OLP patients, and HCV replication in OLP tissue has been demonstrated (41,46–48). Prevalence rates of HCV infection in OLP vary significantly by geography, ranging from 20% in Spain to as high as 62% in Japan (49,50). However, several studies of OLP patients in Northern and Western Europe have shown no association (51–55). Prospective laboratory evaluation for liver abnormalities in 195 consecutive OLP patients in the midwestern United States revealed no cases of hepatitis B or C virus infection or other liver abnormality (5). However, Chuang et al. (43) did demonstrate a positive correlation in a case-control study of 340 patients in Indianapolis, IN. HCV-associated OLP occurs more commonly in HLA-DR6-positive patients which may in part explain the observed geographic variability of this association (56,57). Screening of OLP patients for hepatic abnormality and/or HCV infection should be performed after consideration of patient demographics, review of systems, and geographic location.

## Treatment

There is no cure for OLP. Current treatments are palliative and have varied efficacy; management is commonly empirical. Evidence-based recommendations are lacking (11). A systematic review of the literature for randomized controlled trials revealed only 11 trials with placebo control; studies were limited by small sample sizes, lack of replication, and lack of standard outcome measures. To further assess efficacy of therapies for OLP, larger placebo-controlled trials with standard outcome measures are needed (58).

Practitioners should discuss the chronic relapsing course of OLP, as well as the potential unpredictability of acute flares with patients. Treatment goals include reducing symptoms, healing erosive lesions, and minimizing the functional impact of OLP. Patients should be educated that asymptomatic, reticular lesions do not require treatment. Chronic palliation of symptoms can be challenging. Therapeutic decisions should be made after careful consideration of potential risks and benefits by the patient and physician.

Generally, treatment is instituted for atrophic, erosive, or symptomatic OLP. Patients with mild

disease may respond to topical corticosteroids or other topical medications. Once disease control is achieved, patients should titrate the frequency of medication use based on symptoms and ability to tolerate food. The ability to titrate medications offers patients some degree of control; other patients, however, may feel uneasy and overwhelmed by this ambiguity. Patients with widespread OLP, desquamative gingivitis, or multiple mucocutaneous sites of disease may require systemic immunomodulatory therapy. Physicians need to consistently educate patients about the proper use of medications, both topical and systemic, as well as side effects and the risk of concomitant infection.

### Oral care and hygiene

Optimization of oral hygiene is fundamental to the treatment of OLP as dental plaque and calculus stimulate intraoral inflammation and can exacerbate OLP activity (59,60). Patients should be instructed to brush their teeth twice daily using a soft bristle toothbrush and toothpaste devoid of mint or cinnamon flavorings. Patients should floss at least once daily using unflavored dental floss or tape. Professional dental cleanings should be performed every 3–6 months. The use of alcohol-free chlorhexidine gluconate mouth rinses may reduce bacterial plaque (59,61). Long-standing gingival OLP can cause gingival recession requiring periodontal surgery, and periodontal surgical procedures can exacerbate OLP (Koebner phenomenon) (62). Thus, oral hygiene measures are especially important in patients with prominent gingival disease.

Attempts should be made to minimize all mechanical and chemical trauma. Dentition should be examined for sharp cusps and cracked or worn dental restorations. The condition and fit of dental appliances should be evaluated and replaced if needed. Patients should be advised to avoid acidic, spicy, hard/crunchy, and hot foods and beverages (61,63). Elimination of exacerbating factors can result in reversion to less severe, asymptomatic reticular lesions or remission. Exposure to alcohol and tobacco products, known carcinogens, should be reduced if not eliminated completely. Marijuana and other illicit substance use should also be addressed as their use may contribute to poor oral hygiene.

### Topical corticosteroids

Topical corticosteroids are the mainstay of OLP treatment and are considered first-line therapy.

The intraoral use of topical corticosteroids is off-label. Patients should be advised that despite labels stating “for external use only,” topical corticosteroids can be used safely for oral mucosal disease with appropriate monitoring.

Positive response to treatment with medium- to super-potency topical corticosteroids has been reported (61). Potent topical corticosteroid gels or ointments (clobetasol propionate 0.05%, betamethasone propionate 0.05%) are initially applied to affected areas three to four times daily; as symptoms improve, patients may taper the frequency of application as tolerated. Alternatively, topical corticosteroids formulated in an adhesive base can be utilized although some patients may not like or tolerate the gritty texture. Adhesive bases have not been shown to be more effective than other topical corticosteroid preparations (64,65). Patients should be instructed to dry the oral mucosa and apply the topical corticosteroid using a Q-tip or fingertip. Patients with prominent gingival involvement may be best served using dental trays that cover the gingiva, as well as the teeth, as a delivery mode for topical corticosteroids or other topical medications (66). For more widespread oral mucosal lesions or for patients who cannot apply corticosteroids directly to oral lesions, dexamethasone elixir (5 mL of a 5 mg/5 mL suspension) can be used as a mouth rinse; elixir can be used four to six times daily when symptoms are severe with tapering as OLP improves. Patients who use topical corticosteroids should be instructed to avoid eating, drinking, and excessive speaking for at least 60 minutes after each use. The topical corticosteroid potency and frequency of use should be reduced as clinical disease and symptoms improve. Intraoral use of topical steroids is safe and well tolerated (67–69). The most common adverse effect is candidiasis, which may be minimized with use of prophylactic antifungal therapy (70,71).

### Topical cyclosporine

Topical cyclosporine (100 mg/mL solution, 5 mL swish and spit three times daily) may be used as a mouth rinse in OLP patients who do not respond to topical corticosteroids (72). The utility of cyclosporine solution may be limited by its cost. Lower doses of cyclosporine (500 mg once daily swish and spit or low-dose cyclosporine in an adhesive base) have demonstrated benefit in OLP and may reduce the cost of therapy (6,73). Cyclosporine may not always provide greater benefit than topical corticosteroids; a double-blind, randomized compari-

son of clobetasol and cyclosporine demonstrated greater clinical improvement with clobetasol (68). Blood levels of cyclosporine were low or undetectable after 8 weeks of use with no systemic side effects (72).

### Topical calcineurin inhibitors

The topical calcineurin inhibitors, tacrolimus and pimecrolimus, have been employed as steroid-sparing topical immunosuppressives in OLP (74). Most studies included small numbers of patients, lacked controls, and lasted for a short duration (i.e., 2 months). A prospective double-blind 30-day trial of pimecrolimus cream 1% versus vehicle in erosive OLP showed complete healing of erosions in 7 of 10 pimecrolimus-treated patients versus 2 of 10 vehicle-treated patients (75). Pimecrolimus cream 1% has demonstrated benefits similar to triamcinolone acetonide paste 0.1% (76). Tacrolimus ointment 0.1% was shown to be as effective as clobetasol ointment 0.05% (77). Side effects include temporary burning or stinging at the site of application (78,79). Systemic levels of pimecrolimus and tacrolimus have been detected after oral mucosal application (79,80). The potential for systemic absorption and the potential for malignancy reinforce the need for additional long-term evaluation.

### Topical retinoids

Topical retinoids have been reported to be effective for OLP (81–83). When compared directly, topical fluocinolone acetonide 0.1% is more effective than topical tretinoin 0.05% in the treatment of atrophic/erosive OLP ( $n = 33$ ) (84). A randomized, placebo-controlled study ( $n = 12$ ) of tazarotene gel 0.1% used for hyperkeratotic OLP twice daily for 8 weeks showed significant benefit compared to placebo (85). Side effects of topical retinoids may include irritation and inflammation. Topical retinoids may yield greatest benefit when used frequently with topical corticosteroids for reticular or hyperkeratotic OLP (86).

### Intralesional corticosteroids

Intralesional injection of triamcinolone acetonide (10–20 mg/mL, repeated every 2–4 weeks) can be performed for persistent localized erosive OLP (8,21,61,87). Intralesional injections may be associated with systemic absorption (61).

### Systemic corticosteroids

The use of systemic corticosteroids should be reserved for patients with recalcitrant OLP or

extensive OLP with additional extraoral involvement (11). Prednisone (40–80 mg, or 1 mg/kg, as a single morning dose) can improve OLP lesions and associated pain in a short period of time (88). A study of patients with atrophic-erosive OLP ( $n = 49$ ) demonstrated equivalent rates of remission in those patients treated with either clobetasol ointment 0.05% or prednisone (50 mg/day) followed by clobetasol ointment 0.05%; systemic adverse effects were noted more frequently in patients who received prednisone (69). Systemic corticosteroids are gradually tapered and used for the shortest duration possible (typically for 2–4 weeks). OLP is typically more recalcitrant to treatment than cutaneous LP, and may require longer treatment courses. Relapse of disease activity is frequently noted after discontinuation of systemic corticosteroids. Thus, patients should be maintained on topical corticosteroids.

### Other systemic therapies

A number of systemic medications including antimicrobial agents (89–92), immunomodulatory agents (93–104), and retinoids (105,106) have been reported to be beneficial for OLP (Table 2). Efficacy studies are lacking; most reports are limited to isolated cases and small series. None of the systemic agents used for OLP results in long-term remission reinforcing the need for concomitant topical therapy during and after systemic medication use.

### Concomitant oral candidiasis

Patients who use intraoral topical corticosteroids frequently develop secondary candidiasis (107). New or recalcitrant white or erythematous mucosal lesions should be evaluated for *Candida* using potassium hydroxide microscopy and/or fungal culture. The use of systemic antifungal agents is preferred as topical antifungal formulations may be irritating. In addition, the need for multiple applications of both topical corticosteroids and antifungals may result in decreased efficacy and poor compliance. Given the chronic use of topical and/or systemic immunosuppressive therapy, prophylactic antifungal therapy should be considered. Meticulous care of dental appliances should include removal of all appliances at bedtime and soaking them in dilute (0.02%) sodium hypochlorite solution, 0.12% chlorhexidine gluconate, or nystatin suspension (100,000 U/mL) overnight (108,109).

**Table 2.** Additional systemic therapies for oral lichen planus (OLP)

Name	Dose	Comments
Antimicrobial agents		
Dapsone (92)	100–150 mg daily	Isolated case reports Benefit in erosive OLP
Griseofulvin (89,90)	1 g daily	Minimal improvement Significant adverse effects
Metronidazole (91)	500 mg twice daily	Greater benefit for cutaneous LP than OLP
Immunomodulatory agents		
Alefacept (93)	15 mg/week intramuscular	Case report
Azathioprine (94,95)	75–150 mg daily	May require 3–6 months before maximal benefit achieved
Cyclosporine (97–99)	1–3 mg/kg/day	Limited duration of use Potential for severe adverse effects
Hydroxychloroquine (96)	200–400 mg daily	Open label Symptoms improved in 1–2 months Erosions required 3–6 months
Methotrexate (100)	2.5–12.5 mg weekly	Retrospective case series
Mycophenolate mofetil (101,102)	2–4 g daily	Isolated case reports Used initially with prednisone or cyclosporine
Thalidomide (103,104)	50–100 mg daily	Limited by adverse effects
Retinoids		
Acitretin (105)	30 mg daily	Less effective for OLP than for cutaneous LP Limited by adverse effects
Isotretinoin (106)	10–60 mg daily	Only slight improvement Limited by adverse effects

### Supportive therapy

OLP is chronic with periods of exacerbation and remission. The lack of cure and unpredictability of course can cause stress for patients. There is conflicting evidence that anxiety and stress may contribute to the pathogenesis and course of OLP (110–113). OLP patients demonstrate higher levels of anxiety, greater depression, and increased vulnerability to psychological disorders; it is unclear whether these psychological factors play a role in the pathogenesis or are consequences of OLP (113,114). Referral to psychologists and psychiatrists can provide psychosocial support and help patients develop skills for coping with this chronic illness. Patients may have concerns about the possibility of malignancy or the potential contagious nature of the disease; patient education is vital to alleviating these fears (115).

### Course and prognosis

OLP is chronic with variable disease activity; remission is rare. Exacerbations may be accompanied

by changes in morphology. Precipitants for acute flares include stress, foods (most often tomatoes, citrus, and spicy foods), dental procedures, systemic illness, heavy alcohol consumption, and tobacco use in any form. Stress was identified most frequently by patients as a cause of their acute disease flares (5,116).

OLP rarely undergoes spontaneous remission. A retrospective study of 808 Italian patients with OLP revealed that less than 2.5% of patients experienced complete remission over the 6- to 204-month follow-up period (median of 47.4 months for males, median of 44.8 months for females) (21). Close follow-up and monitoring with monthly visits are necessary for patients with severe symptoms, poorly controlled erosive disease, and those on systemic therapy. Once disease activity and symptoms are fairly well controlled, OLP patients should continue to be evaluated every 6–12 months with more frequent assessment as symptoms warrant (8).

The potential for malignant transformation of OLP is controversial (117–119). Most data have been provided by follow-up and retrospective studies, many of which demonstrate heterogeneity

within the subject population and lack of standardized inclusion criteria, both clinical and histological. Patients with dysplasia at the time of diagnosis of OLP should be excluded. Noting these limitations, malignant transformation of OLP has been shown to occur in 0.4% to greater than 5% of patients over variable durations of follow-up (118,120–123). Carbone et al. reported that 15 of 808 (1.85%) OLP patients developed oral SCC with a mean time of 52.33 months after the initial diagnosis of OLP; only four patients had carcinoma develop in the same site of the initial OLP biopsy (21). Higher rates of malignant transformation in erythematous (atrophic) and erosive lesions have been reported, although this is not uniformly noted throughout the literature (21,122). In a large retrospective review of US OLP patients ( $n = 723$ ), six (0.8%) developed oral SCC at sites previously diagnosed clinically as erosive or erythematous OLP (5). In spite of the limitations of the current literature, the potential risk of malignant transformation of OLP must be addressed. The prognosis of oral SCC improves with early diagnosis and treatment. Therefore, routine surveillance of OLP patients is warranted (124).

## OLDR

Lichenoid drug reactions may involve the skin, oral mucosa, or both (125). OLDR is less common than cutaneous lichenoid drug reaction, and may occur without skin involvement (125–127). OLDRs are common in adults, but have been rarely reported in pediatric patients (128–130). The interval between initial medication use and development of OLDR is highly variable, ranging from weeks to months, with an average of 2–3 months (127). Delay of onset of greater than 1 year has been reported. Therefore, a clear temporal relationship between initiation of medication and onset of OLDR lesions may not be readily apparent (128,131). A thorough history of systemic medication use over the preceding 12–24 months should be obtained. OLDR lesions present as white reticular papules or erythematous erosions, depending on the drug involved, and can be associated with significant oral pain (132). Sites of predilection are similar to OLP. Unlike OLP, however, OLDR lesions tend to be unilateral (133–135).

OLDRs have been reported in association with many systemic medications, the most common of which include nonsteroidal anti-inflammatory drugs (126,136), antihypertensives (125–127), and HIV antiretrovirals (137,138) (Table 3). HIV

**Table 3.** Causes of oral lichenoid drug reaction

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Antibiotics	<ul style="list-style-type: none"> <li>• Tetracycline</li> </ul>
Anticonvulsants	<ul style="list-style-type: none"> <li>• Carbamazepine</li> <li>• Oxcarbazepine</li> <li>• Phenytoin</li> <li>• Valproate sodium</li> </ul>
Antidiabetics	<ul style="list-style-type: none"> <li>• Chlorpropamide</li> <li>• Glipizide</li> <li>• Insulin</li> <li>• Tolbutamide</li> </ul>
Antidiarrheals	<ul style="list-style-type: none"> <li>• Bismuth</li> </ul>
Antifungals	<ul style="list-style-type: none"> <li>• Amphotericin B</li> <li>• Ketoconazole</li> </ul>
Antihypertensives	<ul style="list-style-type: none"> <li>• Atenolol</li> <li>• Enalapril</li> <li>• Hydrochlorothiazide</li> <li>• Methyldopa</li> <li>• Metoprolol</li> </ul>
Antimalarials	<ul style="list-style-type: none"> <li>• Chloroquine</li> <li>• Hydroxychloroquine</li> <li>• Quinidine</li> <li>• Quinine</li> </ul>
Antimycobacterials	<ul style="list-style-type: none"> <li>• Aminosalicylate sodium</li> <li>• Isoniazid</li> <li>• Rifampin</li> <li>• Streptomycin</li> </ul>
Antiretrovirals	<ul style="list-style-type: none"> <li>• Zidovudine</li> </ul>
Chemotherapeutics	<ul style="list-style-type: none"> <li>• Dactinomycin</li> <li>• Imatinib</li> </ul>
Immunomodulatory drugs	<ul style="list-style-type: none"> <li>• Gold salts</li> <li>• Interferon-<math>\alpha</math></li> <li>• Penicillamine</li> </ul>
NSAIDs	<ul style="list-style-type: none"> <li>• Aspirin</li> <li>• Diflunisal</li> <li>• Ibuprofen</li> <li>• Indomethacin</li> <li>• Naproxen</li> <li>• Rofecoxib</li> <li>• Sulindac</li> </ul>
Psychiatric	<ul style="list-style-type: none"> <li>• Benzodiazepines</li> <li>• Tricyclic antidepressants</li> <li>• Lithium</li> </ul>

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antiretroviral medications may directly cause oral lichenoid lesions consistent with OLDR; in addition, improved immunocompetence in HIV-positive patients treated with antiretrovirals may contribute to oral lichenoid lesion formation (139). Hepatitis B vaccination has been reported to cause OLDR in pediatric patients (140,141).

OLDR may be indistinguishable, clinically and histologically, from OLP (142). As such, the differential diagnosis of OLDR and OLP is similar (see above and Table 1). Histological features which may favor the diagnosis of OLDR include a deep and diffuse subepithelial mixed infiltrate of lymphocytes, plasma cells, and neutrophils with or without eosinophils; perivascular inflammation; and intraepithelial colloid bodies (143). These histological features, however, are not specific for OLDR and may also be seen in oral lesions of discoid lupus erythematosus (143,144). DIF of both OLP and OLDR demonstrates shaggy deposition of fibrinogen along the BMZ and immunoglobulin M-positive colloid bodies (39). IIF studies of OLDR patient sera may detect circulating basal cell cytoplasmic autoantibodies in a “string of pearls” pattern (133,145). IIF is negative in OLP.

There are no standardized criteria for the diagnosis of OLDR. Proposed diagnostic criteria include a history of systemic medication intake, clinical and histological features of lichenoid mucositis, and resolution of lesions with drug discontinuation (142). A lengthy interval between initial medication use and onset of oral lesions does not exclude a diagnosis of OLDR. In patients taking multiple suspect medications, the medication initiated most recently should be the target of initial investigation. Provocation testing with drug rechallenge can be used to confirm the causative relationship between the suspect medication and OLDR, but understandably, may be deferred by patients because of the associated discomfort and fear.

Treatment of OLDR consists of discontinuation of the suspect medication and substitution with an alternate medication. OLDR lesions typically resolve within weeks to months of drug cessation, but delayed responses may also occur (146). This course cannot be distinguished from that of OLP which, by definition, may wax and wane. Residual, milder, reticular, and erosive lesions may persist (128,134). If the causative medication cannot be discontinued or if residual lesions persist after drug elimination, topical corticosteroids can be used with variable success. Therapy for OLP can be utilized in OLDR depending on the extent and severity of residual disease.



**FIG. 9.** Oral lichenoid contact reaction to dental amalgam. Note direct apposition of lichenoid lesion and dental amalgam. Photograph courtesy of Dr. Susan Muller.



**FIG. 10.** Oral lichenoid contact reaction to cinnamon flavoring in chewing gum. Lesions resolved 2 weeks after discontinuing chewing gum use. Photograph courtesy of Dr. Susan Muller.

## OLCR

Lesions of OLCR are located in apposition or in near proximity (within 1 cm) to the offending allergen, and lesions are limited to such sites of contact (147–149). Typical sites include the lateral borders of the tongue and buccal mucosa (FIGS 9 and 10). Dental restorative materials, most commonly mercury-containing amalgam, are the most frequent culprits (150). Older restorations that are cracked or worn may have increased predisposition for hypersensitivity induction. Cinnamon and other flavorings may also cause OLCR (150,151) (Table 4). Histopathological features of OLP and OLCR show considerable similarity, and biopsy may be of little help (152). Biopsy is recommended when lesions exhibit atypical clinical features or when there is concern for possible malignancy

**Table 4.** Causes of oral lichenoid contact reactions

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Dental adhesives	<ul style="list-style-type: none"> <li>• Acrylate compounds</li> <li>• Eugenol</li> </ul>
Dental metals	<ul style="list-style-type: none"> <li>• Beryllium</li> <li>• Cobalt</li> <li>• Copper</li> <li>• Chromium</li> <li>• Gold</li> <li>• Mercury</li> <li>• Nickel</li> <li>• Palladium</li> <li>• Silver</li> <li>• Tin</li> </ul>
Other dental restoration materials	<ul style="list-style-type: none"> <li>• Composite</li> <li>• Glass ionomer</li> <li>• Porcelain</li> </ul>
Flavorings	<ul style="list-style-type: none"> <li>• Balsam of Peru</li> <li>• Cinnamon, cinnamic aldehyde</li> <li>• Eugenol</li> <li>• Menthol</li> <li>• Peppermint</li> <li>• Vanillin</li> </ul>

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(153). Cutaneous patch testing can be very valuable; however, the selection of allergens to be tested and specific details surrounding interpretation are controversial (154–156). The combination of a positive patch test and a strong clinical association between OLCR lesions and amalgam restorations is an excellent predictor of improvement following amalgam replacement (152,157). The foundation of OLCR treatment is avoidance of the allergen. Symptoms typically resolve quickly after elimination of allergen exposure (158). Patients should be provided with detailed written instructions regarding allergens and cross-reactants to avoid, and a list of safe alternatives. The Contact Allergen Replacement Database, available from the American Contact Dermatitis Society, can be an invaluable tool ([www.contactderm.org](http://www.contactderm.org)). Therapeutic strategies used for OLP may be implemented for symptomatic OLCR.

## Conclusion

Lichenoid lesions of the oral mucosa present a diagnostic challenge. It may be difficult to distinguish OLP, OLDR, and OLCR on the basis of clinical and/or histological findings. It is essential to obtain

a thorough history and perform a complete mucocutaneous examination in addition to specific diagnostic testing (i.e., DIF, IIF, cutaneous patch testing). Generally, OLDR and OLCR resolve once the causative agent has been discontinued. OLP, however, is chronic with rare remission. OLP presents a therapeutic challenge to both the patient and physician, and long-term monitoring of OLP patients should be conducted given the potential for malignant transformation.

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