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Oral lichen planus: clinical features and management

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Oral lichen planus (OLP) is a relatively common chronic inflammatory disorder affecting stratified squamous epithelia. Whereas in the majority of instances, cutaneous lesions of lichen planus (LP) are self-limiting and cause itching, oral lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially premalignant and are often a source of morbidity. Current data suggest that OLP is a T cell-mediated autoimmune disease in which auto-cytotoxic CD8+ T cells trigger apoptosis of oral epithelial cells.The characteristic clinical aspects of OLP may be sufficient to make a correct diagnosis if there are classic skin lesions present. An oral biopsy with histopathologic study is recommended to confirm the clinical diagnosis and mainly to exclude dysplasia and malignancy. The most commonly employed and useful agents for the treatment of lichen planus (LP) are topical corticosteroids but other newer agents are available.
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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disorder affecting stratified squamous epithelia. The disease is relatively common, affecting approximately 1–2% of the population (Bouquot and Gorlin, 1986; Scully *et al*, 1998), an incidence equal to well-known diseases such as psoriasis and Barrett's esophagus.

Whereas in the majority of instances, cutaneous lesions of lichen planus (LP) are self-limiting and cause itching, oral lesions in OLP are chronic, rarely undergo spontaneous remission, are potentially premalignant and are often a source of morbidity. Furthermore, oral lesions, unlike cutaneous lesions, are difficult to palliate.

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Oral manifestations

Although OLP develops most commonly in the fifth to sixth decades of life, and in women more than twice as often as in men, patients of all ages may develop the disorder (Bagan-Sebastian *et al*, 1992; Carrozzo and Gandolfo, 1999; Eisen, 2002a). The clinical features of OLP in children, recently highlighted in several publications (Sharma and Maheshwari, 1999; Alam and Hamburger, 2001), are identical to those in adults, and the disease should be considered when evaluating oral mucosal lesions in children. Children with OLP often have concomitant cutaneous disease (Sharma and Maheshwari, 1999; Nanda *et al*, 2001), and those of Asian descent may be predisposed to the development of the disease (Alam and Hamburger, 2001).

Oral lichen planus lesions usually have recognizable and distinctive clinical features and a characteristic distribution. OLP may manifest in one of three clinical forms: reticular, erythematous (atrophic) and erosive (ulcerated, bullous). Whereas reticular lesions occur as isolated lesions and are often the only clinical manifestation of the disease, erythematous lesions are accompanied by reticular lesions, and erosive lesions are accompanied by reticular and erythematous lesions in almost all cases (Eisen, 1993; Scully *et al*, 2000). This feature helps clinically differentiate OLP from other vesiculo-erosive diseases such as pemphigus and pemphigoid, which are characterized by isolated areas of erythema and/or erosions.

The reticular lesions, the most recognized form of OLP, encompass white lesions, which appear as a network of connecting and overlapping lines, papules or plaques (Figure 1). Although some patients may display an impressive array of diffuse and widespread reticulated lesions, they rarely complain of symptoms and often, are unaware of their presence.

Erythematous (Figure 2) and erosive (Figure 3) OLP lesions result in varying degrees of discomfort. The number of ulcerations is variable as are their size and location; rarely, bulla that rupture easily may be observed in the erosive form of OLP (Thorn *et al*,

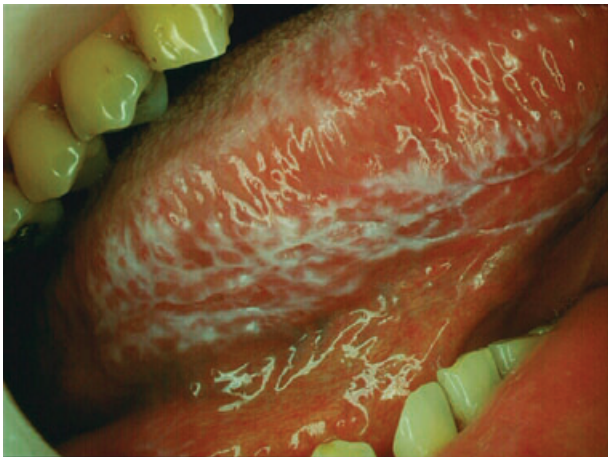

Figure 1 Reticular lesions may be papular, plaque-like, and lacy and are the most recognized form of OLP

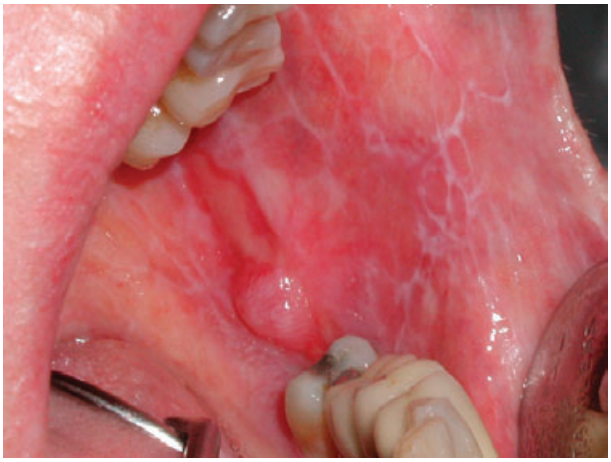

Figure 2 Erythematous OLP lesions, when present, are almost always accompanied by reticulated lesions

1988). The erosive lesions hardly ever remit spontaneously and may lead to confusion with other autoimmune mucosal, vesiculo-erosive diseases, which share similar clinical features.

The posterior buccal mucosa is the most frequent site of involvement followed by the tongue, gingiva, labial mucosa, and vermilion of the lower lip (Silverman *et al*, 1985; Bagan-Sebastian *et al*, 1992; Eisen, 2002a). Lesions on the palate, floor of the mouth, and upper lip are uncommonly noted.

Approximately 10% of patients with OLP have the disease confined to the gingiva (Scully and el Kom, 1985). Gingival LP presenting as small, raised white, lacy papules or plaques, may resemble keratotic diseases such as leukoplakia. Erythematous lesions affecting the gingiva result in desquamative gingivitis (Figure 4), the most common type of gingival LP (Scully and Porter, 1997). Erosive lesions resembling those observed in other vesiculo-erosive diseases including pemphigoid, pemphigus, linear IgA disease, and foreign body gingivitis (Gordon and Daley, 1997) also produce desquamative gingivitis not easily identified as lichen planus unless there are coexistent reticular lesions on the gingiva or elsewhere in the oral cavity.

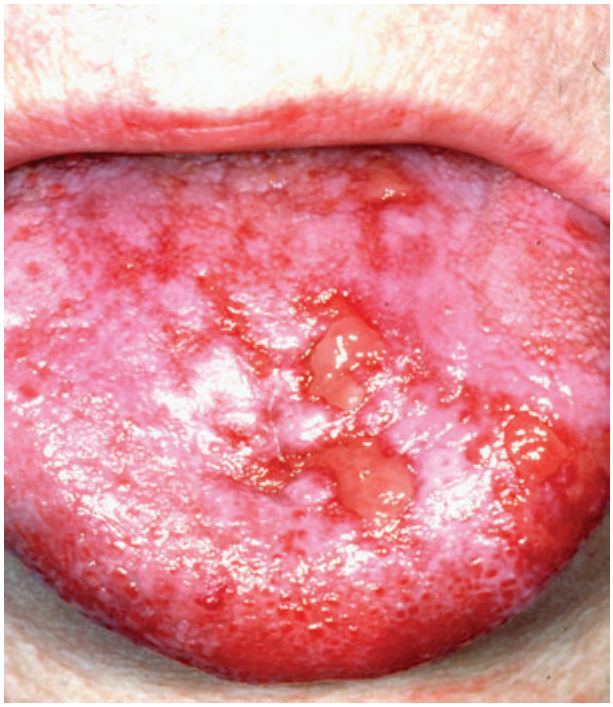

Figure 3 The most severe and painful lesions of OLP develop in the erosive form of the disease

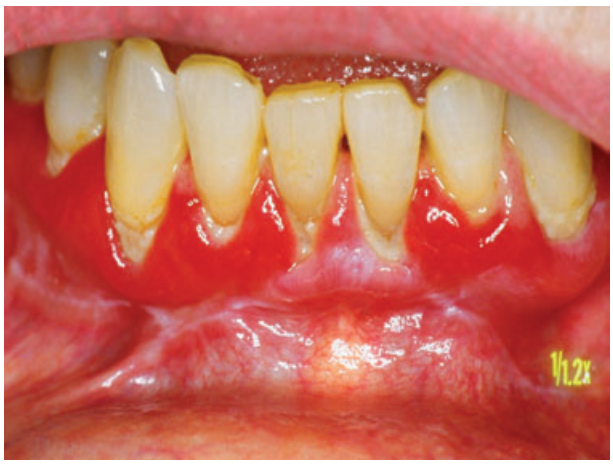

Figure 4 Up to 10% of patients with OLP have the disease confined to the gingiva, typically with atrophic and erosive lesions resulting in desquamative gingivitis

Lichen planus isolated to a single oral site other than the gingiva is uncommon. Patients with isolated lip lesions (Allan and Buxton, 1996) and tongue lesions (Andreasen, 1968) have been described although many patients who present with isolated lesions eventually develop more widespread disease.

Extraoral manifestations

Patients with OLP frequently have concomitant disease in one or more extraoral sites. Therefore, a thorough

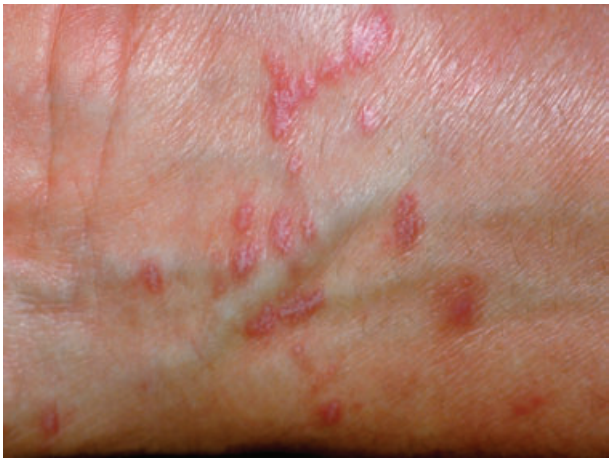

Figure 5 Cutaneous LP: violaceous papules that are flat topped and polygonal in form covered with a network of fine lines (Wickham's striae)

evaluation and multidisciplinary approach is required to uncover potential sites of extraoral involvement.

Approximately 15% of patients with OLP develop cutaneous lesions (Eisen, 1999). The classic appearance of skin lesions consists of erythematous to violaceous papules that are flat topped and occasionally polygonal in form (Figure 5). A network of fine lines (Wickham's striae) often overlies many of the papules. Cutaneous LP may also appear in several atypical forms that are not easily recognizable.

Typically, cutaneous lesions develop within several months after the appearance of the oral lesions, and the severity of the oral lesions does not seem to correlate with the extent of cutaneous involvement (Eisen, 1999).

Undoubtedly, the most frequent extraoral site of involvement in female patients with OLP is the genital mucosa with lesions developing in 20% of women with OLP (Rogers and Eisen, 2003). The association of LP of the vulva, vagina and gingiva is recognized as the vulvovaginal-gingival syndrome (Pelisse, 1989). When LP affects the genital mucosa, the erosive form of the disease is the predominant type (Figure 6) although

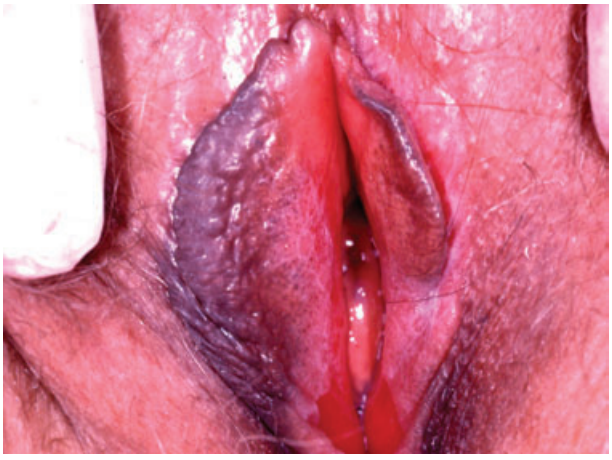

Figure 6 Vulvovaginal LP: the characteristic lesion is a tender, painful, erythematous atrophic or eroded introitus of the vulvovaginal area

asymptomatic reticular lesions can be identified in a quarter of all patients (Eisen, 1994). Various symptoms including burning, pain, vaginal discharge, and dyspareunia are frequent and are noted in patients with erythematous and erosive disease. Not uncommonly, patients with mild oral involvement display severe erosive vulvovaginal disease, and patients afflicted with severe oral involvement develop only mild asymptomatic genital disease. Reports of malignant transformation of genital lichen planus in women (Dwyer *et al*, 1995; Franck and Young, 1995) underscore the need for an early diagnosis and the institution of prompt treatment for these patients.

The penogingival syndrome represents the male equivalent of the vulvovaginal-gingival syndrome of LP (Cribier *et al*, 1993). Although the concomitant involvement of oral and genital LP is much less common in males than females, recognition and treatment of the disease are important as malignant transformation of penile LP has been reported (Bain and Geronemus, 1989).

Lichen planopilaris represents LP involvement of the scalp and hair follicles causing a scarring alopecia. Lichen planus may also involve the nails producing thinning and ridging of the nail plate and splitting of the distal free edge of the nail. Healing with a scar produces a ptyergium, an uncommon but characteristic LP nail manifestation. Lichen planus of the nails and scalp are uncommon in patients with OLP (Eisen, 1999).

The clinical features of esophageal LP have been well documented (Harewood *et al*, 1999; Abraham *et al*, 2000; Evans *et al*, 2000), and the disease appears to develop most commonly in patients with OLP. The overwhelming majority of patients with esophageal LP are diagnosed as a result of painful symptoms, with dysphagia being the predominant complaint. Although malignant transformation has not been reported, untreated esophageal LP may result in chronic pain and strictures (Souto *et al*, 1997).

Patients with OLP may also develop the disease in one or more sites including the ocular, bladder, nasal, laryngeal, otic, gastric, and anal structures although these sites of involvement are uncommon.

Etiology and associations

Pathogenesis

Current data suggest that OLP is a T cell-mediated autoimmune disease in which auto-cytotoxic CD8+ T cells trigger apoptosis of oral epithelial cells (Eversole, 1997; Porter *et al*, 1997). Cell mediated immunity, possibly initiated by endogenous or exogenous factors, results in the production of tumor-necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) and keratinocyte/T cell/antigen-presenting dendritic cell associations (Scully *et al*, 2000, Lodi *et al*, 2005a,b). OLP lesional T-cells do not secrete interleukin 4 and 10 (IL-4, IL-10) or transforming growth factor-beta (TGF-β) (Simark-Mattsson *et al*, 1998, 1999). The dominant role of CD8+ T cells in OLP pathogenesis is confirmed by the expression in infiltrating lymphocytes of the chemokines

CCR5 and CCR3 and their respective ligand RANTES/CCL5 and IP-10/CXCL10 (Iijima *et al*, 2003).

Activated T cells in the OLP infiltrate migrate to oral epithelium mediated by intercellular adhesion molecules (ICAM-1 and VCAM) (Eisen *et al*, 1990b). Upregulation of ELAM-1, ICAM-1, and VCAM-1, especially by endothelial cells in the subepithelial vascular plexus, could play a role in the pathogenesis of LP (Regezi *et al*, 1996). Cytokines (IL-1, -8, -10, -12 and TNF-α), secreted by keratinocytes are chemotactic for lymphocytes ultimately leading to tissue destruction (Sugermann *et al*, 1996). Recently, the basis of the peculiar Th1 cytokine bias observed in OLP was shown to have a genetic background. Indeed, genetic polymorphism of the first intron of the promoter gene of IFN-γ was shown to be an important risk factor for the development of oral lesions of LP, whereas an increase in the frequency of the – 308ATNF-α allele was demonstrated in patients who displayed LP of the mouth and skin (Carrozzo *et al*, 2004). Significantly, TNF-α stimulates the activation of nuclear factor kappa B (NF-κB) whose increased expression has been seen in OLP (Santoro *et al*, 2003). Because NF-κB translocation in keratinocytes may induce the production of several inflammatory cytokines including TNF-α, the activation of NF-κB could be partially responsible for the characteristic, chronic course of OLP similar to other chronic inflammatory diseases such as psoriasis and rheumatoid arthritis. Recent data also suggests pathogenic differences between erythematous and reticular lichen planus, with the former linked to the inhibition of TGF-β/smad pathway leading to hyperproliferation of keratinocytes (Karatsaidis *et al*, 2003).

In addition, there is upregulation of epithelial basement membrane extracellular matrix (ECM) proteins, including collagen types IV and VII, laminin and certain integrins – serving as pathways for T cell migration (Eversole, 1997). T cells then bind to keratinocytes and programmed cell death (apoptosis) is implicated in the basal cell destruction of LP (Tanda *et al*, 2000).

Systemic associations

Patients infected with the hepatitis C virus (HCV) often have extrahepatic manifestations, which significantly contribute to HCV-related morbidity. Many studies have demonstrated an association of OLP and HCV in southern Europe and in Asia (Bagan *et al*, 1994; Nagao *et al*, 1995; Carrozzo *et al*, 1996; Chuang *et al*, 1999; Roy and Bagg, 1999; Klanrit *et al*, 2003). HCV infection is more frequently found in patients with erosive OLP than in patients with non-erosive OLP (Carrozzo *et al*, 1996). The HCV related OLP association is supported by the fact that HCV viral sequences have been found in the serum of patients with OLP, and HCV was shown to occasionally replicate in oral lichen planus tissue, possibly contributing to the pathogenesis of mucosal damage (Jubert *et al*, 1994; Carrozzo *et al*, 1996, 2002; Arrieta *et al*, 2000;). Moreover, recent data has shown that HCV-specific T cells can be found in the oral mucosa of patients with chronic hepatitis C and OLP (Pilli *et al*, 2002).

The association of OLP with both HCV infection and liver disease appears to be partially dependent on geographic factors. Some, but not all studies of American patients (Eisen, 2002a), as well as British (Ingafou *et al*, 1998), Irish (Roy *et al*, 2000), Dutch (van der Meij and van der Waal, 2000), and German (Grote *et al*, 1999; Friedrich *et al*, 2003) patients failed to demonstrate an association between LP and liver abnormalities. However, in studies from countries with a high HCV prevalence (Egypt and Nigeria), there were negative or insignificant associations with OLP, suggesting that a LP-HCV association cannot always be explained on the basis of high prevalence in the general population (Carrozzo and Gandolfo, 2003).

The HCV-related OLP appears to be associated with the HLA class II allele HLA-DR6, which would partially explain the peculiar geographical heterogeneity of the association between HCV and OLP (Carrozzo *et al*, 2001; Petruzzi *et al*, 2004). Even in countries where HCV infection appears to play an etiologic role in the pathogenesis of OLP, the majority of patients suffering from OLP are not infected by HCV (del Olmo *et al*, 2000).

Although OLP patients do not appear to have an increased risk of diabetes, diabetics who develop OLP have an increased frequency of atrophic-erosive lesions and a greater proportion of lesions on the tongue (Bagan *et al*, 1993).

Psychological factors

Patients with OLP exhibit higher levels of anxiety, greater depression and increased vulnerability to psychic disorders (Soto Araya *et al*, 2004). OLP patients with erosive LP exhibit higher depression scores than patients with non-erosive lichen planus (Rojo-Moreno *et al*, 1998). In addition to the chronic discomfort that can result in stress, patients with OLP are concerned about the possibility of malignancy, the contagious nature of the disease, and the lack of available patient educational materials (Burkhart *et al*, 1997). Psychological intervention may be warranted given the fact that the level of anxiety and salivary cortisol of OLP patients are high, supporting the relationship of OLP with stress (Koray *et al*, 2003).

Oral lichenoid reactions

The concept of oral lichenoid reactions or lesions (OLR or OLL), eruptions in the oral cavity that have an identifiable etiology and that clinically and histologically resemble OLP, is well recognized but controversial. Indeed, some authors use the term OLR when several clinical or histological features are present but the diagnosis remains inconclusive (van der Meij *et al*, 2003). Others consider OLR when there is an adverse effect to dental materials only (Karatsaidis *et al*, 2003).

Dental restorative materials including amalgams, composite resins, cobalt and gold, have been implicated as causes of oral lichenoid reactions. Even flavorings and plastics can be important in the pathogenesis and management of patients with OLR (Yiannias *et al*, 2000).

Some authors report a low frequency of sensitization to mercury and no beneficial effects from removal of amalgam fillings (Hietanen *et al*, 1987), whereas others suggest that sensitization to mercury is an important cause of all OLR (Koch and Bahmer, 1999). Although uncommon, they should be suspected when OLP lesions are confined to areas of the oral mucosa in close contact with or proximity to the filling materials. A positive patch test reaction to more than one mercurial allergen and a strong clinical association between lesions and amalgam restorations may increase the likelihood of the correct diagnosis and may justify the removal and replacement of all amalgam fillings with those made of other materials (Thornhill *et al*, 2003).

In cases where patch test negative patients improve with amalgam replacement, mercury may be acting as an irritant in the pathogenesis of OLR (Wong and Freeman, 2003). Patch testing and biopsies however, cannot accurately predict the response to removal of amalgam fillings (Skoglund, 1994; Ostman *et al*, 1996).

Drug-induced oral lichenoid reactions have been reported most commonly to non-steroidal anti-inflammatory agents and the angiotensin-converting enzyme inhibitors (Potts *et al*, 1987; Robertson and Wray, 1992). A review of the subject suggests that the evidence linking drugs and lichenoid eruptions is strongest for beta blockers, methyldopa, penicillamine and non-steroidal anti-inflammatory agents (Thompson and Skaehill, 1994). Although numerous other drugs have been linked with oral lichenoid reactions, the reports have been based upon a single case or poor documentation.

Clinical identification of lichenoid drug reactions has been based largely on subjective criteria although there may sometimes be a tendency for the oral lesions to be unilateral (Lamey *et al*, 1995) and erosive (Potts *et al*, 1987). Histology may be beneficial as lichenoid lesions may have a more diffuse lymphocytic infiltrate and contain eosinophils and plasma cells, and there may be more colloid bodies than in classical LP (Lamey *et al*, 1995; Scully *et al*, 2000). Moreover, the detection of autoantibodies binding to cytoplasm of basal keratinocytes has been proposed as a means of identifying lichenoid lesions but it lacks both specificity and sensitivity (Lamey *et al*, 1995; McCartan and Lamey, 2000). The most reliable method to diagnose lichenoid drug reactions is to note if the reaction resolves after the offending drug is withdrawn, and if it returns when the patient is challenged again. As this is both impractical and potentially unsafe, empiric withdrawal of the offending drug and substitution with another agent may be warranted. After the offending drug is withdrawn, it may be months before the lichenoid reaction resolves. OLR may develop months or even years after a patient takes a drug, and fortunately, reports of OLR are considerably fewer than drug-induced cutaneous lichenoid reactions (McCartan and McCreary, 1997).

Precipitating factors

The Koebner phenomenon characteristic of cutaneous LP, whereby lesions develop in response to trauma, is also observed in the oral cavity. Mechanical trauma from dental procedures, heat and irritation from tobacco products, friction from sharp cusps, rough dental restorations and poorly fitting dental prostheses, and oral habits including lip and cheek chewing are exacerbating factors (Conklin and Blasberg, 1987). The Koebner phenomenon may explain why erosive lesions develop most commonly in areas subjected to trauma, such as the buccal mucosa and lateral surfaces of the tongue. When such factors are minimized or eliminated, oral lesions either revert to the less severe forms of the disease or, rarely, resolve completely (Eisen, 2002b).

When atrophic or erosive lesions are present, especially where there is desquamative gingivitis, there are particular problems because toothbrushing may be complicated by gingival pain and bleeding. This situation frequently results in the accumulation of dental plaque, which may adversely influence the course of OLP. Dental plaque and calculus can also result in worsening gingival lichen planus and are associated with a significantly higher incidence of erythematous and erosive gingival lesions (Ramon-Fluixa *et al*, 1999).

Gingival OLP can ultimately result in gingival recession, advanced periodontal disease and, rarely, in tooth loss. Periodontal surgical procedures, which are required to correct these defects, may themselves exacerbate OLP (Katz *et al*, 1988). Therefore, oral hygiene procedures in OLP patients must be gentle but effective – when there can be subjective and objective improvement of the lesions (Holmstrup *et al*, 1990).

Malignant potential

The most important complication of OLP is the development of oral squamous cell carcinoma. The reported frequency of malignant transformation varies greatly, between 0.4% to over 5%, over periods of observation from 0.5 to over 20 years (van der Meij *et al*, 1999b). The significantly increased risk of oral cancer appears to be independent of the clinical type of OLP and therapy administered (Gandolfo *et al*, 2004).

There is considerable controversy regarding the malignant transformation of OLP. Despite the fact that more than 25 follow-up studies have focused on this topic, as recently reviewed by Barnard et al (Barnard *et al*, 1993), many investigators have questioned the criteria utilized for diagnosing OLP in published reports (Krutchkoff *et al*, 1978; Eisenberg, 2000). For example, while some studies included patients diagnosed with OLP based on clinical and histological criteria, others included patients that were based solely on clinical features (Murti *et al*, 1986). Consequently, some published cases of OLP associated with malignant transformation, diagnosed clinically as OLP, may actually have been lichenoid dysplasia, a premalignant condition with lichenoid features. It is known that patients with lichenoid dysplasia often display erythematous and erosive lesions clinically identical to OLP lesions (Eisenberg and Krutchkoff, 1992). However, the results of three studies (Holmstrup *et al*, 1988; Gandolfo *et al*, 2004; Rodstrom *et al*, 2004) with strict diagnostic

criteria for the disease demonstrated a statistically significant risk for OLP patients to develop squamous cell carcinoma. Unfortunately, these studies failed to identify factors that would modify the risk of developing oral cancer among OLP patients.

Given the uncertainty of the premalignant nature of OLP and the fact that early detection of oral cancer results in improved survival, it seems prudent to monitor all patients with OLP carefully and over the long-term.

Diagnosis

The characteristic clinical aspects of OLP may be sufficient to make a correct diagnosis if there are classic skin lesions present. An oral biopsy with histopathologic study is recommended to confirm the clinical diagnosis and mainly to exclude dysplasia and malignancy. However, the histopathologic assessment of OLP is a rather subjective and insufficiently reproducible process (van der Meij *et al*, 1999a) and in about 50% of OLP cases, there is a lack of clinicopathologic correlation in the diagnostic assessment of OLP (van der Meij and van der Waal, 2003).

Gingival LP may be more difficult to diagnose, and direct immunofluorescence of perilesional mucosa may facilitate the diagnosis and exclude other causes such as bullous diseases (Firth *et al*, 1990). The value of direct immunofluorescence for confirmation of the disease is well accepted, especially with non-diagnostic histopathologic features and for the desquamative gingivitis form of LP. The histopathologic and immunofluorescent findings in OLP are provided in Table 1.

Treatment

General considerations

Treatment should be directed at achieving specific goals after considering the degree of clinical involvement, the predominant clinical type of lesions, the patient's symptoms, and age. Reticular lesions that are asymptomatic generally require no therapy but only observation for change. In general, all treatment should be aimed at eliminating atrophic and ulcerative lesions, alleviating symptoms, and potentially decreasing the risk of malignant transformation.

Table 1 Histopathologic and immunofluorescent features OLP

Histology (Eisenberg, 2000)
Essential features
Superficial band-like infiltrate of T lymphocytes
Basal cell liquefaction degeneration
Normal epithelial maturation pattern
Additional features
Jagged, spindly rete ridges
Civatte bodies
Separation of epithelium from lamina propria
Immunofluorescence of perilesional mucosa (Helander and Rogers, 1994)
Fibrin and shaggy fibrinogen in a linear pattern at the basement membrane zone
Cytoids in the absence of deposition of fibrinogen

Mechanical trauma or irritants such as sharp filling margins or rough surfaces or badly fitting dentures should receive attention. A drug history should be obtained to identify reversible causes of lichenoid eruptions as discontinuation of the offending agent is often curative. Hypersensitivity reactions should be suspected when the lichenoid lesions are confined to oral mucosal sites in close proximity to dental restorations.

An optimal oral hygiene program should be instituted in patients with gingival disease. Patients with OLP who are elderly and have poor nutrition could have folate deficiency, even when they are not found to be anemic when screened (Thongprasom *et al*, 2001).

Drug therapy

Patients with oral LP are managed with medications that were neither developed nor intended for oral diseases and, consequently, most lack adequate efficacy studies. Thus, such factors as optimal dose, duration of treatment, safety, and true efficacy remain unknown (Scully *et al*, 2000).

Corticosteroids

The most commonly employed and useful agents for the treatment of LP are topical corticosteroids. A response to treatment with midpotency corticosteroids such as triamcinolone, potent fluorinated corticosteroids such as fluocinolone acetonide and fluocinonide and superpotent halogenated corticosteroids such as clobetasol has been reported in 30–100% of treated patients (Lozada-Nur *et al*, 1994; Aleinikov *et al*, 1996; Carbone *et al*, 1999; Buajeeb *et al*, 2000; Thongprasom *et al*, 2003). The greatest obstacle in using topical corticosteroids in the mouth is the lack of adherence to the mucosa for a sufficient length of time. For this reason, some investigators prefer using topical corticosteroids in adhesive pastes although there is no data that topical steroids in adhesive bases are more effective than as base preparations (Buajeeb *et al*, 2000; Lo Muzio *et al*, 2001). Elixir forms of corticosteroids, such as dexamethasone, triamcinolone and clobetasol have been used as an oral rinse for patients with diffuse oral involvement or for elderly patients who may find it technically difficult to apply medication to various active locations of the oral cavity. Careful consideration should be given to the vehicle as unlike skin compounds, which have been well-studied, clinical trials that have compared the strength of corticosteroids in various bases in the oral cavity are generally lacking.

Few serious side-effects arise with topical corticosteroids. Unlike the skin, atrophy in the oral mucosa is rarely observed. As many as one third of OLP patients treated with topical corticosteroids develop secondary candidiasis which necessitates treatment (Vincent *et al*, 1990) or instituting antifungal therapy before the patient begins using topical steroids (Lozada-Nur *et al*, 1994; Carbone *et al*, 1999). Prolonged use of these drugs may occasionally result in diminished biological effectiveness (tachyphylaxis), which can be avoided by using alternate day therapy

or by using a very potent steroid (e.g. clobetasol) initially and then a moderately potent corticosteroid (e.g. triamcinolone) for maintenance therapy. Patients should be warned about the off-label use of topical corticosteroids and the accompanying package inserts which state for 'external use only'.

Although a number of studies have demonstrated the safety of topical corticosteroids when applied to mucous membranes for short intervals (Lehner and Lyne, 1969; Plemons *et al*, 1990) and even up to 6 months (Carbone *et al*, 2003), the potential for adrenal suppression with prolonged use, especially for a disease that is chronic, necessitates careful and frequent follow-up examinations. When using super-potent steroids such as clobetasol, one should be aware that the drug is indicated for no longer than a 2 week period, occlusive dressing are contraindicated with its use (Abma *et al*, 2002), adrenal insufficiency following prolonged use in moderate dosages (at doses as low as 2 g day^{-1}) may be more common than previously recognized (Ohman *et al*, 1987), and the total amount of drug used per week and the duration of treatment should be carefully monitored by those familiar with its adverse effects.

In general, therapy should be initiated with a potent preparation to achieve a rapid response particularly in erosive OLP lesions (Thongprasom *et al*, 1992). Patients should be instructed to apply the agent several times daily, maintain prolonged contact of the medication with the mucosa, and refrain from eating and drinking for 1 h afterwards. It is advisable to lower the strength of the preparation as soon as erosions heal and erythematous lesions become asymptomatic. Once the disease becomes inactive and there is either an absence of lesions or the presence of only white reticular lesions, therapy may be temporarily discontinued.

For intractable erosive OLP lesions, intralesional steroids such as triamcinolone acetonide (10–20 mg ml^{-1}) injections can be effective and repeated every 2–4 weeks. Other steroids such as hydrocortisone may also be used but there are no studies to suggest which steroid is preferable. Frequent injections of steroids, however, are painful, not invariably effective, and may result in an unwanted systemic dose.

Although some consider systemic corticosteroids to be the most effective treatment modality to control OLP, the literature on their use is limited, and a recent comparative study did not find differences in treatment response between prednisone (1 mg kg^{-1} day^{-1}) plus clobetasol in an adhesive base and clobetasol alone (Carbone *et al*, 2003). Systemic corticosteroids should be reserved for recalcitrant erosive or erythematous LP, where topical approaches have failed, or for widespread oral LP with concomitant skin, genital, esophageal, or scalp involvement.

Daily doses of prednisone in the range of 40–80 mg is usually sufficient to achieve a response without the need for higher doses as in other mucocutaneous diseases such as pemphigus or pemphigoid. The toxicity of prednisone requires that it be used only when necessary, at the lowest dose possible and for the shortest duration of time. Therefore, prednisone should either be administered for brief periods of time, i.e. 5–7 days and then abruptly withdrawn, or the dose should be reduced by 5–10 mg day^{-1} gradually over a 2–4 week period. If patients are able to tolerate alternate day administration of the same total dose, adverse effects may be minimized.

Other topical agents

Patients who exhibit desquamative gingivitis, widespread oral disease, or diffuse ulcerations, may not respond adequately to topical corticosteroids alone. The addition of potent immunosuppressants or immunomodulatory agents such as cyclosporine, tacrolimus, pimecrolimus or tretinoin, in topical formulations, may be beneficial in this group of patients.

The standard solution of cyclosporine (100 mg ml^{-1}) intended for systemic use in organ transplant recipients may be used as a mouthrinse in oral LP (Eisen *et al*, 1990a). However, the solution is prohibitively expensive for routine use and should be reserved for patients recalcitrant to other treatments. Utilizing a smaller quantity of drug (500 mg day^{-1} *vs* 1500 mg day^{-1}) may reduce the cost of the drug (Harpenau *et al*, 1995); even finger rub application using very low doses of cyclosporine (48 mg day^{-1} or less) in an adhesive base preparation is beneficial (Carrozzo and Gandolfo, 1999). Systemic absorption is generally low with topical cyclosporine and the efficacy of the drug does not correlate with cyclosporine blood levels (Eisen *et al*, 1990b).

Tacrolimus, a steroid free topical immunosuppressive agent approved for the treatment of atopic dermatitis, is 10–100 times as potent as cyclosporine and has greater percutaneous absorption than cyclosporine. Several uncontrolled studies have documented the efficacy and safety of this agent in recalcitrant erosive OLP (Kaliakatsou *et al*, 2002; Olivier *et al*, 2002; Rozycki *et al*, 2002; Hodgson *et al*, 2003), although in one study, only 14% of patients had complete resolution of ulcers and erosions when the drug was applied over a 19 month period (Hodgson *et al*, 2003). Burning is the commonest side-effect with tacrolimus and is observed in $<20\%$ of patients (Hodgson *et al*, 2003). Therapeutic levels of tacrolimus can be demonstrated in OLP patients using the drug but are unrelated to the extent of oral mucosal involvement (Kaliakatsou *et al*, 2002). Relapses of OLP after cessation of tacrolimus therapy are common (Olivier *et al*, 2002). Notably, in a mouse model, topically applied tacrolimus has been shown to accelerate skin carcinogenesis (Niwa *et al*, 2003). The US Food and Drug Administration recently issued a health advisory to inform healthcare providers and patients about a potential cancer risk from use of tacrolimus. They recommended the drug be used in minimum amounts, only for short periods of time, not continuously, and only as labelled – for atopic dermatitis.

Topical retinoids such as tretinoin have been reported to be effective for oral LP (Sloberg *et al*, 1979). However, topical corticosteroids (0.1% fluocinolone acetonide) are more effective than topical 0.05% tretin-

oin in the treatment of atrophic-erosive OLP (Buajeeb *et al*, 1997). Therefore, as a monotherapy, tretinoin has limited value in OLP but in combination with topical corticosteroids, especially for reticular lesions, modest benefits may be achieved with high doses and frequent applications (Eisen, 2002b). Retinoids applied to the skin often cause considerable irritation and inflammation, and the same is to be expected when applied to oral mucous membranes.

Systemic therapy

A number of systemic immunosuppressive agents have been reported to be beneficial in the treatment of OLP although rigorous evaluation of their efficacy is lacking. None of the agents used for OLP results in long-term remission, and when they are withdrawn, the disease usually recurs. Nevertheless, despite these shortcomings, systemic agents could produce significantly better results than topical agents alone although direct comparative studies are lacking. As with other diseases treated with these agents, such as cutaneous LP and psoriasis, topical therapy should be maintained while undergoing treatment with systemic agents. All of these agents require monitoring for laboratory abnormalities and should be administered only by specialists familiar with their adverse effects. Table 2 summarizes the drugs that have been anecdotally reported to be of value in the treatment of recalcitrant OLP and Table 3 highlights several of the non-pharmacologic approaches that have been employed.

Conclusion

As the term OLP represents a heterogeneous group of patients afflicted with mucosal disease, it is imperative to classify and identify subgroups of patients that may result in treatments that are effective. Identifying and eliminating the multifactorial agents associated with the disease is essential. The improvement and control of oral hygiene should be a primary consideration in the management of OLP as this can enhance the healing of the lesions (Thongprasom *et al*, 2003). As no therapy for OLP is curative, the goal for symptomatic patients is palliation. Relief can be achieved in the majority of patients with topical corticosteroids alone or in

Table 2 Drugs anecdotally utilized for OLP

Drug	*Dose*	*Comments*
Acitretin (Laurberg *et al*, 1991)	30 mg day^{-1}	Highly effective and acceptable therapy for severe cases of cutaneous LP; less effective and less tolerated for OLP
Azathioprine (Lear and English, 1996)	75–150 mg day^{-1}	Highly effective, requires frequent laboratory evaluation; useful as a corticosteroid sparing agent
Basiliximab (Rebora *et al*, 2002)	?	Very expensive; potentially severe adverse effect; only one case report
Cyclosporine (Levell *et al*,1992)	1–3 mg kg^{-1} day^{-1}	Severe adverse effects; should be reserved for severe and refractory cases
Dapsone (Beck and Brandrup, 1986)	100–150 mg day^{-1}	Few case reports; no improvement with gingival disease
Eiconol (Barer and Polovets, 1995)	6 g day^{-1}	Positive changes in 69% of patients with atrophic OLP
Enoxaparin (Hodak *et al*, 1998)	3 mg $week^{-1}$	Improvement of 25% of cases, no side-effects
Griseofulvin (Bagan *et al*, 1985; Naylor, 1990)	1 g day^{-1}	Mixed results; very safe but several studies show no improvement
Glycyrrhizin (Da Nagao *et al*, 1996)	40 ml day^{-1}	66.7% OLP patients improved clinically significant
Hydroxychloroquine (Eisen, 1993)	200–400 mg day^{-1}	Small open label study; response may take several months
Interferon alpha (Kovesi, 2001)	?	Effective and cured 90%
Levamisole (Lu *et al*, 1995)	150 mg $day^{-1} \times 3$ days $week^{-1}$	When administered with prednisolone, excellent response and long-term remission
Mycophenolate mofetil (Nousari *et al*, 1999)	2–4 g day^{-1}	New immunosuppressive; expensive; well tolerated; highly effective with long-term use
Thalidomide (Camisa and Popovsky, 2000; Macario-Barrel *et al*, 2003)	100–150 mg day^{-1}	Serious side-effects should restrict its use to the most severe forms of the disease

Adapted from Eisen (2002b). [Reproduced with permission from Blackwell Publishing, Eisen D (2002) Evaluating and treating patients with oral lichen planus. *Dermatol Ther* **15:** 206–217.]

Table 3 Non-pharmacologic approaches for OLP

Treatment	*Comments*
Psoralens and long wave ultraviolet A (PUVA) (Jansen *et al*, 1987; Lundquist *et al*, 1995)	Excellent results in several studies; PUVA has oncogenic potential limiting its use
Extracorporeal photochemotherapy (Becherel *et al*, 1998)	Limited by complexity and potential serious adverse events
308-nm UVB Excimer laser (Kollner *et al*, 2003; Passeron *et al*, 2004)	Preliminary benefits warrant further studies
Surgery (excision, CO2 laser, cryosurgery) (Emslie and Hardman, 1970; Tal and Rifkin, 1986; Loh, 1992; Huerta *et al*, 1999)	Effective for persistent or dysplastic lesions; surgery may lead to worsening OLP presumably via a Koebner phenomenon; high rate of recurrence

combination with other immunomodulatory topical agents. Infrequently, patients require the prolonged use of systemic medications to control the disorder. All treatments are non-specific and directed at eliminating inflammation and therefore, are only partially successful and their effects, temporary.

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