Review

Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation

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Abstract: Lichen planus, a chronic autoimmune, mucocutaneous disease affects the oral mucosa (oral lichen planus or OLP) besides the skin, genital mucosa, scalp and nails. An immune mediated pathogenesis is recognized in lichen planus although the exact etiology is unknown. The disease most commonly affects middle-aged females. Oral lichenoid reactions (OLR) which are considered variants of OLP, may be regarded as a disease by itself or as an exacerbation of an existing OLP, by the presence of medication (lichenoid drug reactions) or dental materials (contact hypersensitivity). OLP usually presents as white striations (Wickham's striae), white papules, white plaque, erythema, erosions or blisters. Diagnosis of OLP is established either by clinical examination only or by clinical examination with histopathologic confirmation. Direct immunofluorescence examination is only used as an adjunct to the above method of diagnosis and to rule out specific autoimmune diseases such as pemphigus and pemphigoid. Histopathologic features of OLP and OLR are similar with suggestions of certain discriminatory features by some authors. Topical corticosteroids are the treatment of choice for OLP although several other medications have been studied including retinoids, tacrolimus, cyclosporine and photodynamic therapy. Certain OLP undergo malignant transformation and the exact incidence and mechanisms are still controversial. In this paper, etiopathogenesis, diagnosis, management and malignant transformation of OLP and OLR have been reviewed. (J. Oral Sci. 49, 89-106, 2007)

Introduction

Lichen planus is a chronic autoimmune, mucocutaneous disease which can affect the oral mucosa, skin, genital mucosa, scalp and nails. The disease has most often been reported in middle-aged patients more commonly in females than males (1). Oral lichen planus is also seen in children although rare (2,3). The prevalence of OLP in the general population ranges between 0.5% in a selected Japanese population (4), 1.9% in the Swedish population (5) and 2.6% in the Indian population (6). It is a relatively uncommon mucosal disorder in Malaysia, affecting 0.38% of the population (7).

Clinically, it can present as white striations (Wickham's striae), white papules, white plaque, erythema, erosion or blisters (8). The buccal mucosa, dorsum of tongue and gingiva are commonly affected. OLP usually presents as a symmetrical and bilateral lesion or multiple lesions. It can occur in six types of clinical variants namely reticular, papular, plaque like, erosive, atrophic and bullous (8,9) and some variants can co-exist in the same patient. Burning sensation and sometimes pain usually accompany the erosive, atrophic or bullous type lesion.

The clinical differential diagnoses include lichenoid

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drug eruptions, lichenoid lesions associated with contact hypersensitivity to restorative materials, leukoplakia, lupus erythematosus and graft versus host disease (GVHD). Direct immunofluorescence can aid in distinguishing OLP from other lesions especially vesiculo-bullous lesions such as pemphigus vulgaris, benign mucous membrane pemphigoid and linear IgA bullous dermatosis.

Oral lichenoid reactions (OLR) are considered variants of OLP. They may be regarded as a disease by itself or as an exacerbation of an existing OLP, by the presence of medication or dental materials. Oral and cutaneous involvements have been reported. It has been associated with numerous drugs, although only some of these have been confirmed. Drugs such as beta blockers, dapsone, oral hypoglycemics, non-steroidal anti-inflammatory drugs (NSAIDs), penicillamine, phenothiazines, sulfonylureas and gold salts have been associated with lichenoid reactions (10). Other than drugs, lichenoid reactions have also been associated with dental materials. Lichenoid reaction as an allergic reaction to dental materials has been widely reported. Many studies have documented contact hypersensitivity to dental materials such as amalgam (11-13), composite (14) and dental acrylics (15) presenting as lichenoid reactions. Some studies also showed resolution of oral lichenoid lesions following replacement of causative restorations (13,16). In most cases, OLR are indistinguishable from idiopathic OLP, clinically or histologically. Indirect immunofluorescence study and cutaneous patch test may play a role in differentiating these lesions.

The diagnosis of OLP is usually made by clinical and

histological examinations. In classic lesions, it is possible to make a diagnosis based on its clinical appearance alone. However, OLP and OLR lack distinguishing features, clinically and histopathologically. The diagnosis of OLR is difficult and the pathognomonic features of OLR are yet to be identified.

Although the exact etiology is unknown, OLP is recognized as a chronic disease of cell-mediated immune damage to the basal keratinocytes in the oral mucosa that are recognized as being antigenically foreign or altered. The erosive and atrophic types most commonly undergo malignant transformation (17). Malignant transformation of OLP is still controversial and further prospective studies are required. Management of OLP remains palliative and topical corticosteroids remains the treatment of choice although several other medications have been studied including retinoids, tacrolimus, cyclosporine and photodynamic therapy.

Etiology of OLP and OLR

The precise etiology of this condition is unknown. Cell-mediated immune dysregulation has been associated with the pathogenesis of OLP. Current data suggest that OLP is a T-cell–mediated autoimmune disease in which autocytotoxic $CD8^+$ T cells trigger the apoptosis of oral epithelial cells. The nature of the antigen is uncertain. However, several predisposing factors have been implicated in the pathogenesis of OLP and OLR (Table 1).

Systemic medications

Systemic medications such as, anti-malarial drugs (18,19), non-steroidal anti-inflammatory drugs (NSAIDs) (20,21), antihypertensive agents (22,23) and angiotensin converting enzyme inhibitors (24) have been associated with oral lichenoid reactions. Other drugs that have been reported to cause oral lichenoid drug reactions are diuretics (25), oral hypoglycaemic agents (26), gold salts (27,28), penicillamine (29) and beta-blockers (30,31). More recently, oral lichenoid reactions induced by antiretroviral medications for treatment of human immunodeficiency virus (HIV) have been reported (32).

Dental materials

Dental materials such as amalgam (11-13), metals (33-36), gold (37) and composite restorations (14,38) have been associated with OLR. Amalgam fillings inducing oral lichenoid lesions have been reported in many studies (12,39). Thornhill et al. (13) found that 70% of amalgam contact hypersensitivity lesions (presented as lichenoid reactions) were patch test positive for amalgam or mercury compared with only 3.9% of OLP cases. Replacement of

Table 1 List of causative/exacerbation factors for OLP and OLR (References: 11-14, 18-64)

1) Drugs
- *Anti-malarials*
- *Non-steroidal anti-inflammatory drugs*
- *Angiotensin- converting enzyme inhibitors*
- *Diuretics*
- *ß-blockers*
- *Oral hypoglycemics*
- *Gold salts*
- *Penicillamine*
- *Anti-retrovirals*

2) Dental materials
- *Dental amalgam*
- *Composite and resin-based materials*
- *Metals* (eg: *nickel*)

3) Chronic liver disease and Hepatitis C virus
4) Stress
5) Genetics
6) Tobacco chewing
7) Graft-versus-Host disease

amalgam has resulted in improvement in 93% of amalgam contact hypersensitivity lesions. Although rare, OLR related to composite or resin-based materials have been reported (14,38). Overwhelming evidence from many case reports has shown that allergy may be the cause for adverse reactions towards dental cast alloys. Lichenoid lesions of oral mucosa and of the gingiva have also been reported (40,41). Metals like nickel, gold, palladium, cobalt or copper released from certain dental cast alloys were thought to be the cause of reaction such as lichenoid reactions and gingival inflammation. The most common reported metal is nickel, which is of special interest in dentistry because nickel containing metals are commonly used in orthodontic appliances and crown/bridge restorations (42).

In the past, lichenoid reactions caused by contact hypersensitivity to dental materials have been attributed to galvanic reactions between dissimilar metals in close contact. However, recent findings have suggested the lesions appear to be the result of cell-mediated contact hypersensitivity to dental materials, in susceptible individuals who have been sensitized through long exposure. Dental materials in direct contact with the oral mucosa may directly alter the antigenicity of basal keratinocytes by the release of mercury or other products. Contact allergy to dental materials (presented as lichenoid reactions) mostly involved type IV/delayed hypersensitivity reaction (43). Type IV hypersensitivity involved cell mediated immunity primarily macrophages and T lymphocytes which are sensitized to antigen (haptens), but it is unknown how mercury or other metallic haptens released from dental materials are capable of triggering immune reactions.

Chronic liver disease and hepatitis C virus

The association between OLP and chronic liver disease is still controversial. It was first reported by Mokni et al. in 1991 (44). Carrozzo et al. (45) have demonstrated a strong association between hepatitis C viral infection and OLP. High prevalence rates of HCV infection in patients with OLP have been reported, as high as 62% in Japan (46) and 27% in Southern Italy (47). However, a causal role for viral infection in OLP has not been identified. The presence of HLA-DR6 allele has been implicated as the possible cause of the peculiar geographic heterogeneity (48). Lodi et al. (49), in their recent systematic review showed that the proportion of hepatitis C virus-positive subjects was higher in the lichen planus group compared with controlled subjects in 20 of the 25 studies. The results showed a statistically significant difference in the proportion of hepatitis C virus seropositive subjects among lichen planus patients, compared with control patients. The association

of OLP with HCV infection appears to be dependent on geographical heterogeneity and is more common in the Mediterranean and Japan (48). On the other hand, the association was not observed in other studies done in Britons (50), French (51), and Americans (52). The treatment rendered for Hepatitis-C viral infection, namely, interferon and ribavirin therapy itself has been thought to aggravate OLP (53).

Stress

Exacerbations of OLP have been linked to periods of psychological stress and anxiety (52,54-56). In contrast, Humphris (57) and Macleod (58) reported no statistically significant association between OLP and anxiety. In another study by Ivanovski et al. in 2005, prolonged emotive stress in many OLP patients have been proposed to lead to psychosomatization which in turn may contribute to the initiation and clinical expression of oral lichen planus (55). However, the study was unable to determine whether the observed psychological alterations constitute a direct cause of OLP or a consequence of OLP.

Genetics

Genetic background seems to play a role in OLP pathogenesis as several familial cases have been reported (59). Lowe et al. (60) first reported a significantly raised frequency of HLA-A3 in a group of British patients with cutaneous lichen planus. However, Porter et al. (61) reported no significant association with a particular HLA has been demonstrated in familial lichen planus.

Tobacco chewing

Daftary et al. (62) have reported an OLP-like lesion in Indian betel-tobacco chewers during an epidemiologic study of oral cancer and precancerous lesions of Indian population in Kerala, India. This OLP-like lesion consisted of white, linear, wavy, parallel, non-elevated streaks which could not be scraped off. In some instances the lesions radiated from a central erythematous area. The fine white lines however, did not overlap or criss-cross as in classical OLP. The lesion generally presented at the site of placement of the betel quid. Zain et al. (63) have proposed the term 'betel-quid lichenoid lesion' to describe this OLP-like lesion. A causal role for betel quid in OLP has not been identified.

Graft-versus-host disease

Oral lichenoid lesions are part of the spectrum of chronic graft-versus-host disease that occurs after allogeneic bone marrow transplantation (64). Although the etiology of oral lichenoid lesions and chronic graft-versus-host disease

is different, the clinical and histological appearances are quite similar (65). Both lesions show immune system involvement in their pathogenesis. Despite their different antigen specificity, it is likely that they share similar immunologic effector mechanisms resulting in T cell infiltration, epithelial basement membrane disruption and basal keratinocyte apoptosis.

Pathogenesis of OLP and OLR

OLP is a chronic inflammatory oral mucosal disease in which cell mediated immunity plays a major role. At the cellular level, OLP probably results from an immunologically induced degeneration of basal layer. It is characterized by cytotoxic CD8$^+$ cell response on modified keratinocytes surface antigen (66).

Basal cells of epithelium are the target cells in lichen planus and it is believed that the initial event is recognition of an antigen by mucosal Langerhans cells. Keratinocyte antigen expression is probably induced by systemic drugs (lichenoid drug reaction), contact allergens in dental restorative materials (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), bacterial or viral infection or unidentified agent. The CD8$^+$ cytotoxic T cells may trigger keratinocyte apoptosis through activation of the cells by an antigen associated with major histocompatibility (MHC) class I on basal keratinocytes.

Keratinocytes are thought to express an antigen in lichen planus. However, the nature of the antigen is uncertain. There is increased expression of heat shock protein on oral mucosal keratinocytes in OLP (67). Heat shock protein therefore, has been proposed as autoantigen. The upregulation of heat shock protein may be triggered by diverse exogenous agent such as systemic drugs, viral infection, bacterial product and mechanical trauma. However, until now, the exact lichen planus antigen is still unknown.

Mast cells and antigen-presenting Langerhans cells are also involved in the cellular event. There is an increase in the number of activated antigen-presenting Langerhans cells in both connective tissue and epithelium, even though the total number of Langerhans cell is unchanged (68). It is likely that they initiate the local immune response. Cytokines released from various cells lead to chronicity of the disease. Exogenous agents are believed to be the stimulant for activation of mast cells and antigen-presenting Langerhans cells. Recently, a T cell-secreted regulated upon activation normal T cells expressed and secreted (RANTES) has been associated in the pathogenesis of OLP (69). Degranulation of mast cell and macrophage activation release cytokines (tumour necrosis factor-Éø and chymase) which induce expression of endothelial leukocyte adhesion

molecule-1 (ELAM-1), intercellular adhesion molecules (ICAM) and leukocyte adhesion molecules (70). Endothelial leukocyte adhesion molecule-1 and leukocyte adhesion molecules facilitate adhesion and migration of lymphocytes. Chymase is a mast cell protease which can function as matrix metalloproteinases (MMPs). Therefore, chymase may directly or indirectly cause basement membrane disruption in OLP (71).

Apoptosis has been proposed as a mechanism of keratinocytes death (72). CD8$^+$ cytotoxic T cells may secrete TNF-α which trigger keratinocytes apoptosis (73). However the precise mechanism is unclear. Possible mechanisms include (66):

   i. T cell secreted TNF-α which binds to TNF-α R$_1$ receptor on the keratinocyte surface.
   ii. T cell surface CD95L (Fas ligand) binds to CD95 (Fas) on the keratinocyte surface.
   iii. T cell secretes granzyme B entering the keratinocyte via perforin induced membrane pores.

All these mechanisms are thought to activate the caspase cascade resulting in keratinocyte apoptosis. On the contrary, reduced or absent apoptotic rate in inflammatory cells in OLP have been thought to contribute to development of malignancy in OLP (74,75).

Humoral immunity seems to play a role in the pathogenesis of oral lichen planus. Circulating autoantibodies have been identified including autoantibodies to desmogleins 1 and 3 (76). Sugerman et al. proposed a unifying hypothesis for the pathogenesis of oral lichen planus with both antigen mediated mechanisms and non-specific mechanisms such as involvement of TNF-α, CD40, Fas, MMPs and mast cell degranulation in disease pathogenesis (1).

As many studies are being performed to understand the pathogenesis, potential biomarkers are being proposed to predict the onset and severity of OLP in individuals, which include CD275 (77), serum autoantibodies to desmogleins 1 and 3 (76), urinary prokallikrein, PLUNC (78), biomarkers to predict the malignant transformation of OLP including 8-nitroguanine (79), and biomarkers to monitor therapeutic response of OLP (80).

The pathogenesis of lichenoid drug eruptions appears to involve different routes of antigen presentation (81). However, the exact mechanism is still unknown. Patch tests in subjects with lichenoid eruptions appear to indicate that the majority are in fact allergic to the substance. However, because of its inconsistent findings it is difficult to ascertain whether the disease could be classified as an allergic reaction or not. Penicillamine is known to change surface antigen (29) and the sulphydryl groups of captopril change enzyme systems. These aberrations may precipitate

an immune response to epidermal antigens leading to lichenoid drug eruptions.

Diagnosis of OLP and OLR

The diagnosis of OLP, oral lichenoid drug reactions and lichenoid reactions induced by dental materials contact hypersensitivity is based on clinical and histopathologic characteristics. In addition, OLR may be further confirmed with patch testing findings.

Clinical Presentation of OLP and OLR

The clinical presentation of OLP varies. In many patients, the onset of OLP is insidious, and patients are unaware of their oral condition. Some patients report a roughness of the lining of the mouth, sensitivity of the oral mucosa to hot or spicy foods, painful oral mucosa, red or white patches on the oral mucosa, or oral ulcerations. Some patients present with concurrent lesions on the skin, scalp, nails, genital mucosa, esophageal mucosa, larynx, and conjunctivae. In approximately 15% of patients with OLP, concurrent skin lesions are present (82). The genitals are involved in as many as 25% of women with OLP, compared with only 2-4% of men with OLP. The features are similar to those of the oral lesions. In patients with OLP, scalp (lichen planopilaris), nail, laryngeal, esophageal and conjunctivae involvement is uncommon.

Six clinical forms of OLP have been described which are white forms (Fig. 1a) namely reticular, papular, plaque-like and the red forms (Fig. 1b) namely the erosive (ulcerated), atrophic (erythematous) and bullous (8,9). The most common type is the reticular pattern which present as fine white striae known as 'Wickham's striae'. The striae are typically symmetrical and bilateral. The buccal mucosa is the most commonly affected, although any site can be affected. Patients with reticular lesions are often asymptomatic (52,83). Atrophic OLP presents as a diffuse red lesion. The lesions may appear as a mixture of clinical subtypes. For example, white streaks and gray streaks may form a linear or reticular pattern on an erythematous background (84). Alternatively, a central area of shallow ulceration (erosion) may have a yellowish surface (fibrinous exudate) surrounded by an area of erythema. Erosive OLP present as irregular erosion or ulceration covered with a fibrinous plaque or pseudo-membrane. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae. Atrophic (erythematous) or erosive (ulcerative) OLP are often associated with a burning sensation and pain (52). The oral pain is variable and exacerbated by trauma and foods, particularly those that are hot, spicy or acidic. Plaque type OLP appears as homogenous white patches which resemble leukoplakia. However, the presence of white striation and histologic confirmation will allow for the definitive diagnosis of OLP to be made. This type commonly affects the dorsum of the tongue and buccal mucosa. The lesions can appear multifocal. Plaque type OLP may range from a slightly elevated and smooth to a slightly irregular form. This form is more common among tobacco smokers (85). The papular type is rarely seen. This type shows small (0.5 to 1.0 mm) white, raised papules with fine white striation at the periphery of the lesion. The papular type usually coexists with another type. It is rare and sometimes overlooked during clinical examination due to the small size of the lesion (86). Bullous OLP is the least common type of OLP (87). The bullae range from a few millimeters to several centimeters in diameter. They tend to rupture leaving ulcerated and painful surfaces. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae.

Gingival lichen planus can present with reticular, erosive or atrophic type (52,84,88). Eisen (52) noted that 8.6% of patients with OLP have the lesions confined to the gingiva. In a recent study, Mignogna et al. noted that 7.4% of a cohort of 700 patients had OLP lesions confined exclusively to the gingiva (88). Gingival lichen planus frequently present with erythematous area or ulceration that affects the entire width of the attached gingiva, a condition called desquamative gingivitis (Fig. 1c). Hyperkeratotic radiating striae can be found at the periphery of the erosive or erythematous regions, simplifying diagnosis. However, this clinical appearance of desquamative gingivitis is not pathognomonic of oral erosive lichen planus and may represent the gingival manifestation of many other diseases such as cicatricial pemphigoid, pemphigus vulgaris, epidermolysis bullosa acquisita, and linear IgA disease (89,90). Pelisse (91) and Eisen (92) described a triad of erosive or desquamative lichen planus involving the vulva, vaginal and gingival which was termed as vulvo-vaginal-gingival syndrome.

OLP lesions usually persist for many years with periods of exacerbation and quiescence. During periods of exacerbation, the area of erythema or erosion increases, with concomitant increase in pain and sensitivity. During periods of quiescence, the area of erythema or erosion decreases, with decreased pain and sensitivity. Patients are often unaware of quiescent OLP, which may present with only faint white striations, papules, or plaques. Exacerbations of OLP have been linked to periods of psychological stress, anxiety and mechanical trauma (the Koebner phenomenon). Chronic low-grade irritation from dental plaque and calculus may cause exacerbation of gingival lichen planus, presumably by the Koebner

phenomenon (93). Likewise, mechanical trauma of dental procedures, heat and irritants from cigarettes, friction from sharp cusp, rough dental restorations and oral habits such as lip chewing are frequent exacerbating factors that cause flare-up of the lesions (52).

Lichenoid reactions usually have the same clinical features as those of idiopathic OLP. However, few clinical features suggestive of OLR include atypical sites for OLP such as the palate, unilaterality (94) and erosions (95), but only few data support this possibility. Rarely, lichenoid reactions of the oral mucosa occur on the oral mucosa that is in contact with or close to an amalgam, a composite resin dental restoration, or a denture component (Fig. 1d). This lesion is likely to be the result of contact sensitivity to the dental materials. In most cases, the cause for OLR cannot be identified; hence the diagnosis by exclusion is 'idiopathic OLP' (66).

Histopathology

The histological features of OLP are similar to those of cutaneous lichen planus. It was first described by Dubreuill in 1906 and later by Shklar (96). Shklar described three classic histological features which are overlying keratinization, a dense band-like layer of lymphocytic
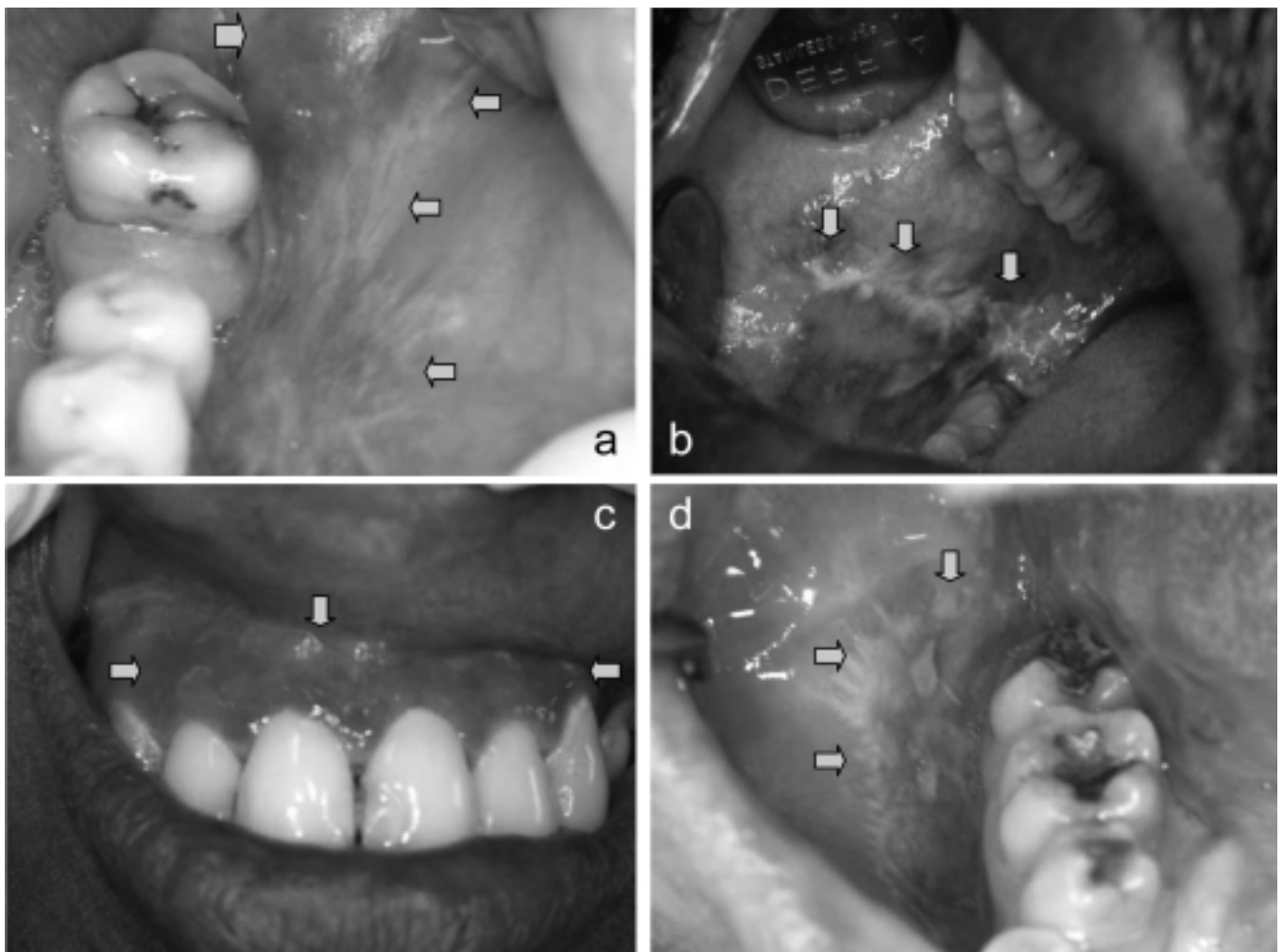

Fig. 1 a) Oral lichenoid drug reaction or an atrophic/erythematous oral lichen planus. An erythematous area in the buccal mucosa is surrounded by white striations (arrows). A history of drug intake for a chronic condition would lead to the diagnosis of a lichenoid drug reaction. A negative history of associated drug intake would lead to a diagnosis of atrophic/erythematous oral lichen planus.
b) White, reticular pattern of OLP at the buccal mucosa (Arrows showing the white striae).
c) Desquamative gingivitis – Erythematous area of the gingiva with faint white striae (Arrows showing the lesional margin). Histological features and direct immunofluorescence (DIF) were consistent with OLP.
d) Oral lichenoid lesion consisting of ulcerations (yellowish areas) surrounded by red areas with white striae radiating (arrows) out of the ulcerated and red areas. Clinically presentation is suggestive of oral lichenoid lesion and further defined by the presence of the lesion adjacent to teeth filled with restorative materials (amalgam).

infiltrate within the underlying connective tissue and liquefaction degeneration of basal cell layer. Pindborg et al. (9) have further described the histological features of idiopathic OLP which have similar features to that described by Shklar above. Within the basal cell layer, degenerating basal keratinocytes form colloid (civatte, hyaline or cytoid) bodies that appear as homogenous eosinophilic globules. The ultrasructure of colloid bodies suggests that they are apoptotic keratinocytes. An eosinophilic band which represents thickened basement membrane may also be present. B cell and plasma cells are rare features of idiopathic lichen planus. The presence of a mixed and sometimes more diffused infiltrate may suggest lichenoid reactions, rather than true idiopathic lichen planus.

In support of the criteria of OLP given by Pindborg et al. (3), Eisenberg (97) suggested that essential and exclusionary histologic features must be met to make a definitive diagnosis of OLP. The essential histological features of OLP are: liquefactive degeneration of basal epithelial cells; dense, band-like inflammatory infiltrate consisting of lymphocytes; normal maturation epithelium; saw-tooth appearance of rete ridges; civatte bodies (colloid bodies) and hyperkeratosis (Fig. 2a). The histological features considered as exclusionary criteria of OLP are: absence of basal cell liquefaction degeneration; heterogeneous population of infiltrate; atypical cytomorphology, nucleus enlargement, increased mitotic figures; blunted rete ridges; absence of civatte bodies and abnormal keratinization.

The features of atypical cytomorphology, nucleus enlargement, increases mitotic figures, blunted rete ridges and abnormal keratinization are among the features accepted for the diagnosis of dysplasia. If these features of exclusionary criteria were included in the diagnosis of OLP, would then lead to some authors considering dysplasia as a common feature of OLP. In 1985, Krutchkoff and Eisenberg (98) have suggested a term lichenoid dysplasia to describe lesions that resemble OLP but are dysplastic. Some cases of OLP that progressed to squamous cell carcinoma were misdiagnosed as OLP from the beginning and many lichenoid lesions with epithelial dysplasia were called OLP. The term lichenoid dysplasia defines an 'entity' solely on the basis of microscopic findings limited to the area of biopsy. Based on these arguments, Eisenberg (97) has suggested that the term lichenoid dysplasia should be avoided as it can create more confusion. The dysplastic OLP is best categorized as other dysplastic conditions.

Histological appearances of idiopathic lichen planus and lichenoid drug eruption are very similar. However, several studies have shown some distinguishing features of lichenoid drug eruption (10,99) such as: an inflammatory infiltrate located deep to superficial infiltrate in some or all areas; a focal perivascular infiltrate; plasma cells in the connective tissue and neutrophils in the connective tissue. These findings of distinguishing features of OLP and lichenoid lesions cannot be fully substantiated with clinical findings as these distinguishing histological features can also be seen in other clinically non-lichenoid white lesions. Thus, the World Health Organization (100) criteria for OLP do not differentiate between the two conditions (9). Thus, the current acceptance of the features of OLP/oral lichenoid reaction are those features as described by WHO (3) and
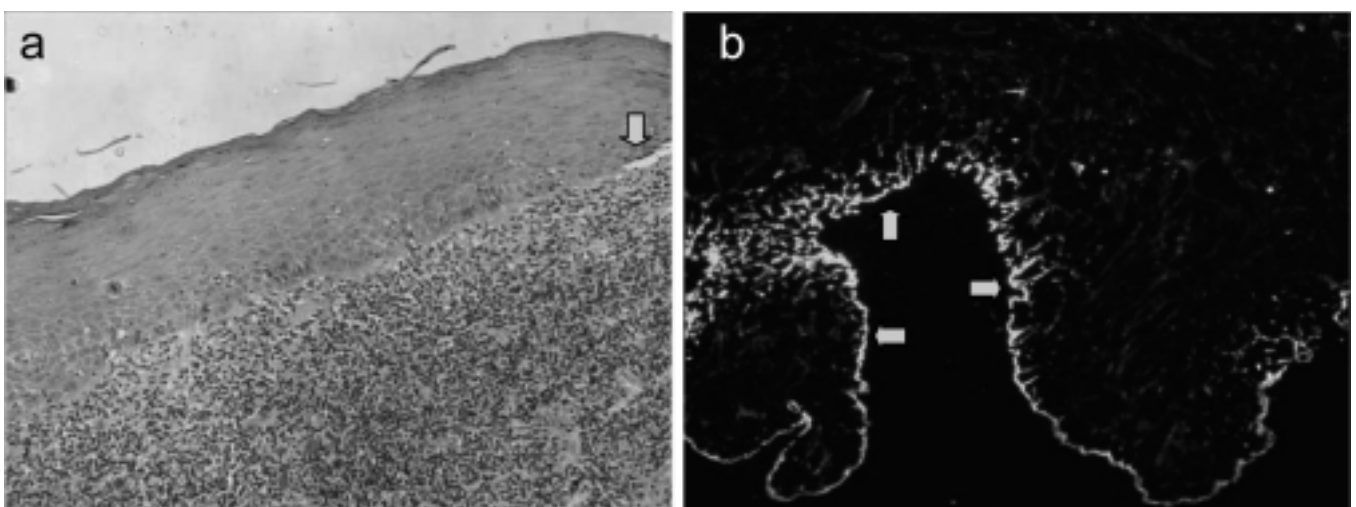

Fig. 2 a) Histology of oral lichen planus showing a parakeratinized stratified squamous surface epithelium surface with characteristic subepithelial band of lymphocytes, an area showing a cleft at the epithelium/connective tissue junction suggestive of basal cell liquefaction degeneration (arrow).
b) Direct immunofluorescence (DIF) for OLP – Intense positive linear fluorescence along the basement membrane with anti-fibrinogen (arrows) (Courtesy: Dr. John R. Kalmar & Dr. Parish P. Sedghizadeh)

Eisenberg's essential criteria except for the 'saw-tooth' appearance of the rete pegs as it is not as routinely observed in OLP/oral lichenoid lesion as compared to skin lichen planus.

Immunofluorescence
Direct immunofluorescence

The immunofluorescence technique is one of the most widely used adjunctive diagnostic procedures for mucocutaneous disorders. Direct immunofluorescence is used to detect autoantibodies that are bound to the patient's tissue. Direct immunofluorescence studies have shown a linear pattern and intense positive fluorescence with anti-fibrinogen that outlined the basement membrane zone in OLP frozen sections (101-104) (Fig. 2b). In some cases, deposition of IgM, and less often IgA, IgG and complement C3, were found exclusively on the colloid bodies. Some authors (105,106) have suggested that immunofluorescence changes in lichen planus are secondary events, following damage to the lower epithelial and membrane zone. Direct immunofluorescence finding in lichenoid drug reactions appears to be identical to those in idiopathic OLP (107).

Indirect immunofluorescence

Indirect immunofluorescence is used to detect the presence of antibodies that are circulating in the blood. This technique however, is not a useful technique singly or as an adjunct to the clinical diagnosis of OLP/oral lichenoid lesion. Despite the inability of this technique to be used as an adjunct to clinical diagnosis of OLP, there have been studies which indicated its use in the diagnosis of lichenoid drug reactions. For instance, in cutaneous drug reactions, the circulating antibodies reactive with basal cells of skin give rise to an annular fluorescence pattern, sometimes termed the 'string of pearls' reaction or basal cell cytoplasmic autoantibody (BCCA) which aids in diagnosis of these drug reactions (108,109).

Allergic patch test

It has been proposed that allergy to dental materials is common in patients with OLR. A toxic reaction may also occur, however, clinically, localized toxic reactions are hard to distinguish from contact allergic reactions. The diagnosis has usually been based on a negative patch test. Cutaneous patch testing is a recognized and accepted method of identifying allergens responsible for type I and IV allergic reactions. The Dental Series Epicutaneous Test Battery (Trolab) of patch test allergens has commonly been used. The test substances were applied to normal skin on the back and read after 72 hours exposure. The patients are considered to be patch test positive to an allergen if they develop erythematous, edematous (vesicular) or bullous (ulcerative) reaction at the site of contact.

In spite of the widespread use of amalgam as a restorative material, reported cases of hypersensitivity to amalgam are relatively infrequent. Skin patch testing studies to investigate contact sensitivity responses to mercury and amalgam have produced conflicting results, with between 8% and 78.9% of OLP patients being positive. Lind et al. (11) reported 34% of patients with OLP (topographically related to amalgam restorations) were tested positive for mercury compounds.

Laine et al. (110) studied 118 patients with oral lichenoid lesions topographically related to dental fillings. They found eighty patients (67.8%) with positive patch test reactions to metals of dental filling materials. The patients were positive to various mercury compounds including to sodium aurothiosulphate, stannic chloride and silver nitrate. The positive patch test reactions appeared more commonly in patients with restricted contact lesions as compared to patients with lesions exceeding to the adjacent areas, indicating association of OLR lesion and the filling material. Complete healing of OLP was observed after a mean follow-up of 16 months, in 45.2% (28/62) of patients patch tested positive and 20% (3/15) of patients patch tested negative when dental fillings were replaced.

Management of OLP and OLR

Most patients with OLP are usually asymptomatic. However, atrophic-erosive forms are painful and also due to the fact that there is a risk of malignant transformation although low (111,112), long term follow-up is necessary. Ramon-Fluixa et al. (113) reported a significantly higher incidence of erythematous and erosive gingival OLP lesions in patients with plaque and calculus deposits. Maintenance of good oral hygiene can enhance healing and lessen the symptoms. Mechanical trauma such as from dental procedures, friction from rough dental restorations, sharp cusps and poorly fitting dental prostheses can exacerbate the lesions. All these exacerbating factors should be minimized or removed. Although OLP is often asymptomatic, the atrophic-erosive form can cause symptoms ranging from burning sensation to severe pain. In the symptomatic cases, many drugs have been tried including corticosteroids (114-116), griseofulvin (117,118), topical retinoids (119,120), cyclosporine (114,121), clobetasol (122), tacrolimus (123), sulodexide (124), pimecrolimus (125), oxpentifylline (126), photo-chemotherapy (127) and photodynamic therapy (128,129) with variable success. Table 2 summarizes the findings of a number of reports on treatment modalities used for OLP/OLR and its outcome.

Table 2 Review of management of OLP and OLR (1978 - August 2006)

Authors & Year	No. of cases	Lesion	Diagnostic criteria	Management	Follow-up Period
Non-surgical					
Greenspan et al. 1978 (131)	19	OLP	Clinical; HPE only in 6 cases	Topical Betamethasone valerate 400µg/day (aerosol vs pellets)	8 weeks
Lozada-Nur 1980 (133)	67	OLP	Clinical & HPE	Topical fluocinonide 0.1%	3-6 months
Aufdemorte et al. 1983 (117)	3	OLP	Clinical & HPE	Griseofulvin 500-250mg	9-15 months
Bagan et al. 1985 (118)	7	OLP	Clinical & HPE	Griseofulvin 500mg twice daily	21/2 months
Vincent et al. 1990 (149)	63	OLP	Clinical; HPE only in 16 cases	Topical triamcinolone acetonide 0.1-0.2%	9.1 months (average)
Thongprasom 1992 (116)	40	OLP	Clinical & HPE	Fluocinolone acetonide 0.1% vs triamcinolone acetonide 0.1%	6-8 months
Voute et al. 1993 (134)	20	OLP	Clinical & HPE	Fluocinonide 0.025%	3-17 months
Tradati et al.1994 (120)	2	OLP	Clinical & HPE	Topical retinoid	1 month
Lundquist et al. 1995 (127)	16	OLP	Clinical & HPE	Psoralen & long-wave ultraviolet light (PUVA)	12 months
Harpenau et al. 1995 (158)	14	OLP	Clinical & HPE	5ml (500mg) Cyclosporine once daily for 4 weeks	4 weeks
Kaliakatsou et al. 2002 (136)	19	OLP	Clinical & HPE	Topical tacrolimus 0.1%	30 weeks
Swift et al. 2005 (125)	10	OLP (Erosive)	Clinical & HPE	1% pimecrolimus ointment	4 weeks
Ungphaiboon et al. 2005 (135)	11	OLP	Clinical & HPE	Triamcinolone acetonide mouthwash	4 weeks
Wongwatana et al. 2005 (126)	15	OLP	Clinical & HPE	Oxpentifylline (400mg three times daily)	8 weeks
Donovan et al. 2005 (138)	1	OLP (Erosive)	Clinical & HPE	Topical tacrolimus 0.1% ointment	2 weeks
Femiano & Scully 2006 (124)	20	OLP	Clincal & HPE	Oral (systemic) sulodexide (250 units) twice each day between meals for 40 days and then once a day for a further 40 days.	1 year
Xia et al. 2006 (132)	45	OLP	Clincal & HPE	Intralesional injection of 0.5 ml lidocaine 2% with 0.5 ml TA (40 mg/ml) to the experimental lesion. Over 2 weeks, if the treated ulceration regressed <81% in size, one more injection was given and was reassessed after 2 weeks.	4 weeks
Aghahosseini et al. 2006 (128)	2	OLP	Clinical & HPE	Methylene blue mediated photodynamic therapy (MB-PDT)	9 months
Shichinohe et al. 2006 (137)	2	OLP	Clinical & HPE	Topical tacrolimus	5 weeks
Aghahosseini et al. 2006 (129)	13	OLP	Clinical & HPE	Methylene blue mediated photodynamic therapy (MB-PDT)	12 weeks
Yoke et al. 2006 (114)	139	OLP	Clinical & HPE	Triamcinolone acetonide vs. cyclosporine (RCT)	8 weeks
Laeijendecker et al. 2006 (123)	40	OLP	Clinical & HPE	Topical tacrolimus (0.1% ointment 4 times daily) (group I) vs. triamcinolone acetonide ointment (0.1% ointment 4 times daily) (group II)	9 weeks
Conrotto et al. 2006 (122)	40	OLP	Clinical & HPE	Clobetasol propionate vs. cyclosporine	2 months
Surgical					
Horch et al. 1986 (143)	7	OLP	Clinical	CO₂ laser surgery	37 months (average)
Kok 1999 (146)	6	OLP	Clinical & HPE	CO₂ laser surgery	3-10 months
Tal & Rifkin 1986 (145)	1	OLP	Clinical & HPE	Cryosurgery	2 years
Vedtofte et al. 1987 (144)	5	OLP	Clinical & HPE	Surgical excision	Not specified
Removal of causative agent					
Potts et al. 1987 (95)	38	OLR (drug induced)	Clinical & HPE	Drug (NSAIDs) withdrawal in 12 patients	Not specified
Laine et al. 1992 (16)	91	OLP/OLR (amalgam related)	Clinical, HPE & patch testing	Amalgam replacement in 15 patients patch tested +ve for mercury compounds	3.2 years (average)
Thornhill et al. 2003 (13)	81	OLP/OLR (amalgam related)	Clinical, HPE & patch testing	Amalgam replacement in 28 patients	3-12 months
Bagan et al. 2004 (21)	3	OLR (drug induced)	Clinical	Drug (COX-2 inhibitor) withdrawal in all 3 patients	2 weeks - 1 year

HPE: Histopathological examination; RCT: Randomized controlled trial
(Most studies did not report on exacerbation and recurrence of the lesions.)

Corticosteroids are the most widely used agent in the treatment of OLP because of their action in suppressing cell mediated immune activity. They can be used topically, intralesionally or systemically. Betamethasone valerate (115,130,131), triamcinolone acetonide (116,123,132) and fluocinolone acetonide (133,134) have been used as topical corticosteroids. Topical fluocinolone acetonide is recommended as the first choice of treatment because there will be no permanent adrenal cortical suppression seen (after 6 months treatment) and it is more effective than triamcinolone acetonide (116). Adrenal suppression and secondary oral candida infection have been reported after the use of topical steroids. Triamcinolone acetonide can be used as an ointment (116) and a mouthwash (135), while betamethasone valerate can be used as a mouthwash (132). Improvement in signs and symptoms was noted in patients treated with topical corticosteroids therapy, with follow-up ranges from 6 months to 1 year. Systemic corticosteroids (i.e. Prednisolone) are usually reserved for severe and more widespread lesions. Adrenal cortical suppression is common even with short courses of systemic corticosteroids therapy (111).

Tacrolimus, a potent immunosuppressive agent used in organ transplant patient has been used in the management of recalcitrant ulcerative OLP. Kaliakatsou et al. (136) reported a significant improvement of symptoms within 1 week of commencement of topical 0.1% tacrolimus in a paraffin ointment base with a decrease of the ulcerated area of 73.3% over the 8 week study period. However, relapse of OLP occurred in the majority of patients (13/17) within 2 to 15 weeks of cessation of tacrolimus therapy. Two other recent studies have also reported success with tacrolimus treatment in recalcitrant erosive OLP (137,138). There are also adverse effects of tacrolimus reported in the literature (135-138). These includes local irritation (135), the possibility of inducing the development of squamous cell carcinoma where it has been shown to impact the cancer signaling pathways of MAPK and the p53 (139) and mucosal pigmentation (140).

Psoralens and long-wave ultraviolet-A (PUVA) is commonly used for treatment of various dermatoses, including cutaneous lichen planus (141). Healing or improvement of OLP lesions with PUVA therapy in 81.2% (13/16) of patients have been shown by Lundquist et al. (127). However, side effects including nausea, dizziness, paresthesia and headache were observed in the majority of the patients. It has also been reported that long term PUVA therapy for patients treated for cutaneous lichen planus and OLP can increase squamous cell carcinoma incidence (142) and risk for oral cancer (142) respectively.

Aghahosseini et al. reported use of methylene blue-mediated photodynamic therapy (MBPDT) for the treatment of OLP (128,129). Photodynamic therapy (PDT) involves *in situ* photo-activation of photosensitizers (PSs) by light at appropriate wavelength, generating cytotoxic oxygen species, which induce direct oxidative damage to cellular organelles, destruction of microvasculature, and promotion of apoptosis. Thirteen patients with 26 OLP lesions were included in their study and they reported improvement in sign scores for 16 lesions with four keratotic lesions disappearing completely. The authors reported a statistically significant decrease in sign and symptom(pain) scores 1 week after treatment and at follow-up sessions up to 12 weeks (129).

Surgical management including cryosurgery and carbon dioxide (CO_2) laser (143-146) has been performed in OLP lesions. Despite these reported cases, surgical excision is not recommended as first choice treatment due to the inflammatory condition which can recur (147).

A recent systematic review of 11 randomized clinical trials of treatments used in oral lichen planus (topical cyclosporins, topical or systemic retinoids, topical steroids and phototherapy) cautioned that the results are not entirely reliable due to the small study samples, lack of replication, lack of standardized outcome measures and the very high likelihood of publication bias. There is only circumstantial evidence for the superiority of the assessed interventions over placebo for the palliation of symptomatic OLP and there is a need for larger placebo-controlled RCTs with carefully selected and standardized outcome measures (148).

Resolution of OLR usually follows the removal of causative agent (21,95). It is important to find out whether the patient is on any medication known to be associated with oral lichenoid drug reactions especially cardiovascular, anti-arthritic, anti-malarial and non steroidal anti-inflammatory drugs. A change of medication should be considered after consultation with the patient's general medical practitioner. In some cases, physicians may be reluctant to change patient's medication especially when the drug is being given for potentially life threatening diseases such as cardiovascular diseases. With such situations where the offending drug cannot be withdrawn, the management of oral lichenoid lesion would be similar to the management of OLP.

Resolutions of OLR following replacement of causative restorations in patients allergic to dental materials have been reported in some studies. Thornhill et al. (13) found that 70% of amalgam contact hypersensitivity lesions (presented as OLR) were patch tested positive for amalgam or mercury compared with only 3.9% of OLP cases. Replacement of amalgam has resulted in lesion improvement in 93% of

amalgam contact hypersensitivity lesions.

Malignant Transformation of OLP

The best evidence of the potentially malignant nature of OLP currently available is from follow-up studies and retrospective incidence studies. There are a number of studies of OLP with regards to malignant transformation in the last few decades. Table 3 summarizes the studies from the English literature (up to Aug 2006) indicating the risk of malignant transformation. However, there is still considerable controversy regarding the malignant potential of OLP. The frequency of malignant transformation ranges from 0% to 5.3% with the highest rate noted in erythematous and erosive lesions (84,112,149-151). The World Health Organization (9,100), has categorized OLP as a precancerous condition, which is "*a generalized state associated with a significant increased risk of cancer*".

The main problem in studying the malignant potential of OLP is that there are no universally accepted specific diagnostic criteria of oral lichen planus. Krutchkoff et al. (152) reviewed a total of 223 reported cases of malignant transformation of OLP and concluded that there was insufficient evidence to consider OLP as a premalignant condition. A major problem in the follow-up studies was the inclusion criteria since there is no universally accepted specific diagnostic criterion. Some studies were based on a diagnosis established solely on clinical features, whereas others included both clinical and histologic criteria. Furthermore, many oral lesions diagnosed clinically and/or histologically as OLP in the published series may actually have been dysplastic lesions with lichenoid appearances (Fig. 1a). Another problem with the previous studies is that there is lack of documentation on the use of tobacco (152).

The importance of presence or absence of dysplasia in the initial presentation of OLP is clearly seen in the study by Bornstein et al. who reported 4 cases of malignant transformation in 141 OLP patients. In the 4 cases which underwent malignant transformation, dysplasia was present at the initial diagnosis of OLP in 3 cases. The actual malignant transformation rate of 2.84% among the 141 patients drops to 0.71% if the 3 patients with initial dysplasia are excluded. Hence, the potential malignant nature of OLP lesions still remains inconclusive (153). On the other hand, few authors have recorded no malignant transformation of OLP in their follow up studies (8,149).

Reviewing selected studies on malignant potential of OLP/OLR with a follow-up period of more than 2 years (Table 3), showed that if strict criteria (based on diagnosis,

Table 3 Development of oral squamous cell carcinoma in studies of patients with oral lichen planus

Authors	Year	Type of study	No. of cases	Diagnostic criteria	Follow-up period (year)	Malignant transformation No. of cases (%)
Andreasen (8)	1968	Retrospective	115	Non-strict	10.0	0 (0%)
Silverman et al. (84)	1985	Prospective	570	Non-strict	5.6	7 (1.2%)
Vincent et al. (149)	1990	Prospective	100	Non-strict	9.1 months	0 (0%)
Silverman et al. (111)	1991	Prospective	214	Non-strict	7.5	5 (2.3%)
Barnard et al. (17)	1993	Retrospective	241	Non-strict	10	8 (3.3%)
Lo Muzio et al. (112)	1998	Retrospective	263	Non-strict	5.7	14 (5.3%)
Rajentheran et al. (150)	1999	Retrospective	832	Non-strict	11.0	7 (0.8%)
Eisen (52)	2002	Retrospective	723	Strict	4.5	6 (0.8%)
Yaacob et al. (159)	2002	Retrospective	19	Non-strict	3.6	1 (5.2%)
van der Meij et al. (160)	2003	Prospective	62(OLP)111 (OLR)	Strict	2.6	0 (0%) in OLP 3 (2.7%) in OLR
Gandolfo et al. (151)	2004	Retrospective	402	Non-strict	4.9	9 (2.2%)
Roosaar et al. (161)	2006	Retrospective	327	Non-strict	28	1 (0.3%)
Bornstein et al. (153)	2006	Retrospective	145	Non-strict	6	4 (2.84%) (3 had dysplasia) 1 (0.71%) (excluding 3 patients with dysplasia)
Laeijendecker et al. (162)	2005	Retrospective	200	Non-strict	12	3 (1.5%)
Ingafou et al. (83)	2006	Retrospective	690	Non-strict	7	1.9%
Larsson and Warfvinge (163)	2005	Retrospective	724 (OSCC)	Non-strict	15	4 (0.5%)

Strict criteria: Clinical & histopathological diagnosis (with exclusion of dysplasia & OLR) and well documentation of habits & alcohol consumption (with the exclusion of the patients with habit/s).
Non-strict criteria: No clear documentation of clinical & histopathological diagnosis, habits and alcohol consumption or clear documentation but included those with habits.

histological, follow-up and tobacco exposure) were applied, the risk of malignant transformation of OLP (excluding oral lichenoid reaction) is only in the range of 0-2 percent and the overall malignant transformation is about 1 percent, which is similar to a review by van der Meij et al. (154). A prospective follow-up study with strict criteria applied (including the documentation of tobacco and alcohol consumption) and long term follow-up (not less than 5 years) is required to establish the putative premalignant nature of OLP. A uniform and accepted criteria to diagnose OLP need to be established before a proper long-term prospective studies can be conducted. To this end, a recent report by Mignogna et al. suggested a dysplasia/neoplasia surveillance with an excellent, clinical criteria to monitor for malignant transformation in OLP patients (155). However, some patients did not benefit from such surveillance and developed advanced-stage oral carcinomas.

Mignogna et al. (155,156) have suggested that regular follow-up of patients with OLP be performed up to 3 times a year. OLP with dysplasia should be examined more frequently, every 2-3 months. However, patients with asymptomatic, mainly reticular type may be assessed annually. The signs that may be indicative of transformation, such as the extent of symptoms and loss of homogeneity should be assessed thoroughly at each appointment. Scoring systems such as those suggested by Mignogna et al. (155) and Piboonniyyom et al. (157) can be adopted by clinicians treating OLP patients on a regular basis. When there is evidence of changes in clinical appearance, the follow-up period should be shortened and additional biopsy should be performed.

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