Chapter 6

# Oral Lichen Planus

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Additional information is available at the end of the chapter

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## 1. Introduction

Lichen planus is a chronic systemic disease of established immune-mediated pathogenesis. [1] It most commonly, protractedly and persistently, involves the mucosa of the oral cavity, but it can involve other sites, namely the skin, the scalp (with inflammation around and affecting the hair follicles) resulting in alopecia), the nails as well as the genital area - the vulval and vaginal mucosa, and the glans penis. Other sites of involvement that are far less frequently described include the oesophagus and conjunctiva. There are seven recognized oral presentations of lichen planus: (1) reticular, (2) papular, and (3) plaque-form and the (4) atrophic, (5) ulcerative (erosive) and rare (6) vesiculo-bullous form [2] and (7) desquamative gingivitis, this latter term is a clinical descriptor, used to describe inflammation, with a mix of erythema, erosion and/or ulceration of the gingival tissues and the immediately adjacent alveolar mucosa, not incited by the presence of dental bacterial plaque. These latter four forms of OLP can be associated with significant discomfort requiring either topical and/or systemic immunosuppressive therapy.

The cause(s) of the various oral lichenoid lesions, ranging from idiopathic oral lichen planus (OLP) to the "contact" lesion, is not understood, but all the lesions are characterized histologically by a typical "lichenoid tissue reaction" featuring (1) a bandlike lymphohistiocytic infiltrate that fills the lamina propria; and (2) liquefactive degeneration of the basal keratinocytes. [3] These reactions may be the result of several diverse possible triggers, but all culminate in a common pathologic process, that of T-lymphocyte directed, immune mediated, damage to the oral epithelial basal cells.[1, 2]

## 2. Historical overview

Ferdinand Ritter von Hebra (1816-1880), famed dermatologist and co-founder of the renowned Vienna School of Dermatology, is credited with the first scientific description of the skin disease, he termed leichen ruber planus (in 1860). [4] But it was the famed British Dermatologist, Erasmus Wilson (1809-1884), who originally used the term lichen planus in his publication in 1869, noting the disorder in a group of 50 patients. [5] Lichen planus obtained its name because of the lacy white lines that bear a close resemblance to the symbiont, lichen, a composite organism consisting of a fungus (the mycobiont) and a photosynthetic partner (the photobiont or phycobiont, usually, a green algae) living together in a symbiotic relationship, seen growing on rocks (Figure 1). However, Ferdinand Ritter von Hebra used the term "lichen" to denote skin lesions which are exclusively nodular, that is characterised by a macular-papular skin eruption, hence, terms such as lichen pilaris (better known as Keratosis pilaris), and lichen nitidus are still used for other skin diseases, whose appearance differs markedly from that of lichen planus. [4] Heinrich Köbner (1838–1904) described the phenomenon that bears his name in 1872, at a meeting of the Silesian Society for National Culture. Four years later (1876) he published a paper describing his original patient describing the development of isomorphic pathologic lesions in response to trauma in previously uninvolved sites of patients with skin diseases, most often seen in patients with psoriasis, but also in eczema and lichen planus. [6] These new lesions are clinically and histopathologically identical to those in the diseased skin and/or mucosa. Louis Frédéric Wickham (1861-1913) is acknowledged as the first to describe the characteristic, fine, white or grey lines known as Wickham's striae (striae is derived from Latin for groove) or dots seen on the top of the pruritic papular rash of lichen planus of the skin, and also seen with OLP. [7] In 1910 François Henri Hallopeau reported the first case of OLP-related oral carcinoma. [8]

**Figure 1.** Foliose lichens growing on rock

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### 2.1. Epidemiology

OLP is a common condition, with a prevalence of between 0.5-2.2% of the population. [1, 9] However, a recent review of epidemiological studies specific to OLP, found only one study as being the most useful, being the most free of error and bias and so, is regarded as the most reliable estimation of population prevalence of OLP, at least in European populations with a reported prevalence of 1.27%. [10, 11] However, OLP most frequently presents in women, aged 40 years and above, by a ratio of approximately 3:1 to 3:2 compared with men, of the same age.

### 2.2. Pathogenesis

The oral mucosa appears to have a limited immunological repertoire, predominantly a lichenoid-type reaction. This is characterised by delayed-type IV hypersensitivity reaction, dominated by cytotoxic $CD8^+$ T-lymphocyte induced apoptosis of the basal keratinocytes, being the final common immunopathological pathway due to variety of insults, such as the development of autoantibodies against self-antigens, interaction with allergens, such as various drugs or dental materials, viruses, namely Hepatitis C (HCV), trauma (mechanical and chemical) and even stress. [12] However, the specifics, including the precise triggering factors, remain unknown and elusive.

The mechanisms involved in the aetio-pathogenesis of OLP are multifactorial and likely to be synergistic:

1. antigen-specific cell-mediated immune response
2. loss of tolerance evidenced by the development of autoantibodies against self-antigens and the promotion of autoimmunity
3. role of the humoral immune response
4. non-specific immune mechanisms; and
5. genetic factors.

## 3. Antigen-specific cell-mediated immune response

The antigen that serves as the trigger and/or driver of the immune responses seen in OLP is unknown. It is likely, in the majority of cases, to be an endogenous peptide, a protein sequence innate to the basal keratinocyte; therefore, OLP can be characterised as an auto-immune condition. It is also likely that supposed exogenous triggers for OLP, such as dental materials, certain drugs, viruses and even trauma serve to expose such self-antigens, or, alter the normal innate peptide sequences so that they are perceived by the immune-surveillance cells and system as being “non-self, that is “foreign”. The immune responses to this, as yet, unidentified antigen develops in three stages: (1) T-cell migration into the epithelium, (2) T-cell activation, followed by (3) induction of basal keratinocyte apoptosis. [12]

**T-Cell Migration into the Epithelium:** Two hypotheses have been proposed to explain this occurrence. The "chance encounter" hypothesis suggests that normally circulating, antigen-specific CD8+ cytotoxic T-cells enter the epithelium for routine surveillance and by chance encounter the putative antigen when it is present in the epithelium. Alternatively, the keratinocytes direct the CD8+ cytotoxic T-cells to migrate into the epithelium by the release of cytokines that allow the lymphocytes to "home-in" on the antigen-bearing basal keratinocyte, the so called "directed migration" hypothesis. [12, 13]

**T-cell Activation:** The lymphocytic infiltration that characterises the OLP lesion histologically, is comprised predominantly of T-cells. The majority of the T-cells in proximity to the damaged and dying basal keratinocytes and within the epithelial layers are overwhelmingly activated cytotoxic $CD8^+$ T-cells. [14] Cytotoxic CD8+ T-cells binding of antigen on the MHC Class I site of keratinocytes releases cytokines that attract other lymphocytes and immune-cells into the site of the developing OLP lesion. The cytotoxic CD8+ T-cells are also activated by the $CD4^+$ helper cells found in the lamina propria. In OLP lesions, helper CD4+ T cells may be activated by antigen associated with Class II MHC presented by the professional antigen-presenting cells, the Langerhans cells, or, by the keratinocytes themselves, which are induced to present antigens on their Class II MHC sites. Langerhans cells are not only increased in number in OLP lesions but also have up-regulated Class II MHC expression. [14] Interleukin-12 (IL-12) is secreted by Class II MHC expressing Langerhans cells and keratinocytes which in turn promotes CD4+ T-cell secretion of interleukin-2 (IL-2) and interferon-$\gamma$ (IFN- $\gamma$). These cytokines (IL-12, IL-2 and IFN- $\gamma$) and probably others, together with the presentation of an antigen associated with MHC class I on basal keratinocytes, promote cytotoxic CD8+ T-cell induction of keratinocytes apoptosis. So it would appear that within the OLP lesion there is a cycle of self-inducing and self-perpetuating T-lymphocyte activation.

**Basal Keratinocyte Apoptosis:** The apoptosis of the basal keratinocytes that characterises all forms of lichen planus, appears to be mediated predominantly by particularly active, cytotoxic CD8+ T-cells. [14] In one study of testing the reactivity of lesional versus non-lesional T-cell clones from LP patients against lesional and non-lesional autologous keratinocytes, the lesional T-cells lines derived from patients with LP were significantly more active and cytotoxic against autologous lesional keratinocytes than the T-cell lines obtained from clinically normal skin. [14] In this same study, it was also shown that the most cytotoxic T-cell clones were $CD8^+$ and the least cytotoxic clones, were $CD4^+$. [15] However, in this same study, the cytotoxicity of some of these activated $CD8^+$ T-cell clones was shown to be partially inhibited by anti-MHC class I monoclonal antibody (Dako clone W6/32). This antibody targets a monomorphic epitope on the 45 kDa polypeptide products of the HLA-A, B and C loci. [16] These findings indicated that the apoptosis of the basal keratinocytes so characteristic of LP (and OLP) is induced by the cytotoxic CD8+ T-lymphocytes activated by a putative basal keratinocyte antigen associated with the MHC Class I.

The induction of keratinocytes apoptosis by CD8+ T-cells can occur by three established pathways: Firstly, secretion by T-cells of tumour necrosis factor-$\alpha$ (TNF-$\alpha$), which binds TNF-$\alpha$ receptor 1 on the keratinocytes surface [16] ; secondly, expression on the T-cell surface of CD95L (Fas ligand), which binds CD95 (Fas) on the keratinocytes surface. Fas ligand (FasL or

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CD95L) is a type-II transmembrane protein that belongs to the TNF family that on binding with its receptor induces apoptosis in the target cell. [17] Fas-induced apoptosis by the perforin pathway are the two main mechanisms by which cytotoxic T lymphocytes induce cell death in cells expressing foreign antigens. Thirdly, by the infusion of granzyme B by T cells into the keratinocytes. Granzymes are serine proteases that are released from cytoplasmic granules within cytotoxic T cells (and natural killer cells) and whose usual role is to induce apoptosis within virus-infected cells, thus destroying them. [18] Cytotoxic T-cells release a protein called perforin, which attacks the target cells forming multimeric complex (of granzyme B, perforin, and granulysin) that enters cells through the mannose 6-phosphate receptor. [19] Granzyme B is then released, to cause apoptosis by various pathways, including the cleaving of caspases (especially caspase-3), which in turn activates caspase-activated DNase and this enzyme degrades DNA, so inducing the apoptotic cascade culminating in cell death. [18, 19]

## 4. Development of autoantibodies against self-antigens and the promotion of autoimmunity

The autoimmune nature of OLP is evidenced by the chronic and protracted course of the disease, its later age of onset, its higher prevalence in women, its association with other autoimmune diseases, proven demonstration of the T-cell auto-reactivity and increased auto-cytoxicity against basal keratinocytes, its clinical, histological and immunological similarity to graft-versus host disease (GVHD) and the effectiveness of immunosuppressive therapies. Two theories have been advanced to explain the autoimmune nature of OLP, specifically the loss of self-tolerance of the basal keratinocytes: (1) impaired immune-suppression in OLP due to lack of Transforming Growth Factor-β1 (TGF-β1); and (2) loss of "immune-privilege" in OLP. [14, 20]

**Impaired Immune-Suppression in OLP (deficient TGF-β1):** TGF-β is believed to be important regulator of the immune system by inducing and increasing the differentiation of both Foxp3+ regulatory T cells (Tregs) (and Th17 cells). FOXP3 (forkhead box P3) also known as scurfin, is a protein involved in immune system responses. A member of the FOX protein family, FOXP3 appears to function as a master regulator (transcription factor) in the development and function of regulatory T cells. [21, 22]

TGF-β also appears to block the activation of lymphocytes and monocyte derived phagocytes. TGF-β1 levels and/or activity may be deficient for some of the following reasons: insufficient numbers of TGF-β1-secreting Th3 regulatory T cells; blockage of TGF-β1secretion; secretion of defective, non-functional TGF-β1; defective or inadequate TGF-β1receptor expression; or defective intracellular downstream signalling from the TGF-β1 receptors. Local overproduction of IFN-γ by Th1 $CD4^+$ T cells in OLP lesions would down-regulate the immunosuppressive effect of TGF-β1and so up-regulate keratinocyte MHC class II expression and CD8+ cytotoxic T cell activity explaining the immune responses to antigens including self antigens and the chronicity of OLP.

**Loss of "Immune-Privilege" in OLP:** The normal oral epithelium, similar to the eye, testes and placenta, may represent an immune-privileged site, by being able to induce apoptosis of infiltrating T-lymphocytes. In these sites, the stromal cells possess Fas Ligand (CD95L) that can trigger the apoptosis of infiltrating inflammatory and immune cells that express Fas (CD95). [20] Keratinocytes themselves can also trigger T-cell apoptosis by the release of the cytokine TNF-$\alpha$, which on binding the TNF-receptor-1 of T-cells triggers their apoptosis. Loss or impairment of either of these two mechanisms to induce T-cell apoptosis may have a role in the pathogenesis of OLP.

Langerhans cells may also contribute to the loss of self-tolerance. Langerhans cells phagocytose the apoptotic bodies and debris of basal keratinocytes, but in doing so, may process and present to the $CD4^+$ T helper cells a self-antigen derived from the remains of the basal keratinocyte. In turn, this may activate self-reactive $CD4^+$ T cells that differentiate into Th1 or Th2 phenotypes and promote cell- or antibody-mediated autoimmune reactions against basal keratinocytes, including the stimulation of the cytotoxic T cells against the basal keratinocytes. [14]

## 5. Role of the humoral immune response

The humoral immune response is thought to have some role in the pathogenesis of OLP, even though it is dominated by the T-cell-mediated immune response. Circulating autoantibodies to desmoglein 1 and 3 have been identified, but again the exact role of such autoantibodies remains uncertain. [23 Further evidence of the potential role of humoral immune response in OLP, is a single case report, dating back to 2008, of full resolution of muco-cutaneous lichen planus with oral and oesophageal involvement, following a course of anti-CD20 monoclonal antibody therapy (rituximab) directed against pre-B and mature B lymphocytes, so preventing their evolution to antibody-releasing plasma cells. [24]

## 6. Non-specific immune mechanisms in OLP pathogenesis

Some of the T-cells in the T-cell dominant lymphocytic infiltrate so pathognomonic for OLP are not specific or targeted. Their presence may be due to pre-existing inflammation that favours the movement of such non-specific T-lymphocytes into the epithelium, which in turn, causes destruction of the keratinocytes. The mechanisms involved include: (1) basement membrane disruption; (2) increased presence of matrix metalloprotienases (MMP); (3) Chemokine (C-C motif) ligand 5 (CCL5) (previously termed RANTES - Regulated on Activation, Normal T cell Expressed and Secreted) activity; and (4) Mast cell activation and degranulation. [14, 15]

**Basement Membrane Disruption:** Integrity of the epithelial basement membrane is maintained by the keratinocytes, which release collagen IV and laminin V into the basement membrane zone, but the keratinocytes require a basement membrane-derived signal to prevent their apoptosis. Thus, the basement membrane is needed for keratinocyte survival and its

integrity is maintained by the keratinocytes. Apoptosis of the keratinocytes by the $CD8^+$ cytotoxic T-cells results in the loss of the maintenance function by performed the keratinocytes, leading to disruption of the basement membrane, thereby allowing the non-specific T-cell to infiltrate the epithelial cell layers. [14, 23] The disruption of the basement membrane also leads to apoptosis of the keratinocytes, due to the loss basement-membrane derived signal to prevent their apoptosis, and so on. This ongoing, self-perpetuating cycle may explain the chronicity of OLP.

**Matrix Metalloprotienases (MMPs):** MMP-9 concentrations have been found to be increased in culture supernatants taken from patients with OLP compared with normal controls. [25] MMP-9 is one member of a family of some 20 MMPs identified to date, which are all zinc-containing proteinases. [26] MMP-9 (together with MMP-2) are gelatinases that cleave collagen IV. Other MMPs can cleave collagen IV and laminin. The MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs) that form stable complexes with MMPs or pro (precursor) MMP's. [27] T-cells release activators of MMP-9, resulting in disruption of the basement membrane.

**Chemokine (C-C Motif) Ligand 5 (CCL5 (RANTES)):** CCL5 is a key chemokine released by various cells including, activated T-lymphocytes, oral keratinocytes and mast cells and has a critical role in the recruitment of various immune and inflammatory cells, including lymphocytes, monocytes, eosinophils, basophils and mast cells. CCR1, CCR3 to CCR5, and CCR9 and CCR10 are key cell surface receptors for CCL5 and have also been identified in lichen planus. [28] CCL5 attracts mast cells which degranulate, releasing TNF-$\alpha$ and chymase, which in turn up regulates OLP lesional T-cell release of CCL5, leading again to the development of a self-perpetuating cycle, that further contributes to the chronicity of OLP.

**Mast Cell Activation and Degranulation:** Mast cells are not only increased in numbers, but most are degranulated in OLP (compared with normal tissues). [14, 23, 28] Mast cell degranulation results in the release of variety of pre-inflammatory mediators, including TNF-$\alpha$, chymase and typtase. TNF-$\alpha$ can up-regulate endothelial cell adhesion molecules required for the lymphocytes to adhere to luminal surfaces of blood vessels and their subsequent extravasation. Chymase, a mast cell protease, activates MMP-9, so contributing to basement membrane disruption. Both chymase and TNF-$\alpha$ can stimulate CCL5 secretion by lesional T-lymphocytes, which in turn can trigger further mast cell degranulation. [28]

## 7. Genetic factors

Genetic factors clearly must have a role in the pathogenesis of OLP. Recently, the identification of genetic polymorphisms of cytokine/receptor gene loci has been shown to act as clear-cut genetic risk factors for a number of autoimmune diseases. [29] Polymorphism of several cytokines has been shown to be associated with the clinical presentation of LP. [30] Genetic polymorphisms of the first intron of the promoter gene of interferon-$\gamma$ and development of oral lesions of LP and an association between the –308A TNF-$\alpha$ allele and the development of cutaneous lesions of LP. [30] The occurrence of OLP has also been linked to MHC class II allele

DR6. in those patients who also have HCV. [31] To date no specific HLA antigen profile has been found associated with idiopathic OLP.

In summary, despite the oral mucosa only being capable of a limited immunological response, the immuno-pathogenesis of OLP is complex. OLP appears to be predominantly a delayed-type IV hypersensitivity reaction, due in large measure to cytotoxic CD8+ T-lymphocyte induced apoptosis of the basal keratinocytes of the oral epithelium. There are also a number of aspects, best characterised as immune-deregulation that leads to a self -inducing, self-perpetuating cycle that may explain the chronicity of OLP. However, despite a limited comprehension of the pathogenesis of OLP, therapeutic stratagems are being pursued, based on this understanding, including the trialling of TNF-$\alpha$ inhibitors, interleukin-1 inhibitors, mast cells stabiliser agents, to prevent their degranulation, and the use of agents that can induce the up-regulation of key immune-suppressive cytokines such as TGF-$\beta$ and interleukin-8, or the *in-vitro* production of these cytokines for use as therapeutic agents.

## 8. Clinical manifestations of OLP

The diagnosis of OLP is usually made on clinical features alone. However, careful attention to the clinical history is essential, to ensure assessment, and if warranted, the appropriate management, of the extra-oral manifestations of lichen planus. [1, 32, 33]

OLP is classified morphological into seven different clinical presentations: Predominantly white, usually slightly raised lesions consisting of a (1) reticular form (2) papular, and (3) plaque-form seen in about 23% of patients, [34, 35] the predominantly erythematous presentations, with (4) atrophic mucosa, which is seen in some 40% of patients, (5) ulcerative (erosive) lichen planus, seen in some 37% of presenting patients and the rare (6) vesiculo-bullous form (Figures 2a – 4b). [2] In some 10% of patients have their OLP confined to the gingivae, termed (7) "desquamative gingivitis". This term is a clinical descriptor, used to describe inflammation, with a mix of erythema, erosion and/or ulceration of the gingival tissues and the immediately adjacent alveolar mucosa, not incited by the presence of dental bacterial plaque (Figures 5a and 5b). These latter predominantly erythematous forms of OLP can be associated with significant discomfort requiring either topical and/or systemic immunosuppressive therapy. [33] When patients do present with pain, it usually is not spontaneous, but they tend to complain of mild, but noticeable intolerance to particularly salty, spicy or acidic foods (such as any form of curry) brushing of their teeth, which can be made worse and is generalised, on the use of flavoured toothpastes. Rarely, patients will present with widespread oral mucosal ulceration that is spontaneously very painful and so elicit their presentation. The asymptomatic, predominantly white appearing, striated, papular and plaque forms of OLP tend to be found incidentally during the course of an oral examination. They commonly take the form of minute white papules that gradually enlarge and coalesce to form either a reticular, annular, or plaque-like pattern. A characteristic feature is the presence of slender white lines (Wickham's striae) radiating from the papules. In the reticular form, there is a lace-like network of slightly raised white lines, often interspersed with papules or rings. The plaque-like form may

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be difficult to distinguish from leukoplakia. Oral lesions of lichen planus may also include bullae, but this is rare. These different forms can merge or coexist in the same patient. [1, 34, 35] The commonest sites are inevitably bilateral and include the buccal mucosa (seen in some 90% of patients), gingiva, dorsal tongue, lateral tongue, labial mucosa and the lower lip. Uncommon sites include the palate (Figure 6), upper lip, and floor of the mouth. [34] The gingivae are commonly the site of erythematous/erosive OLP. Involvement of the gingivae is described clinically as desquamative gingivitis, but is not unique to OLP and may feature in the presentation of other oral dermatoses, especially pemphigoid and pemphigus. [34]

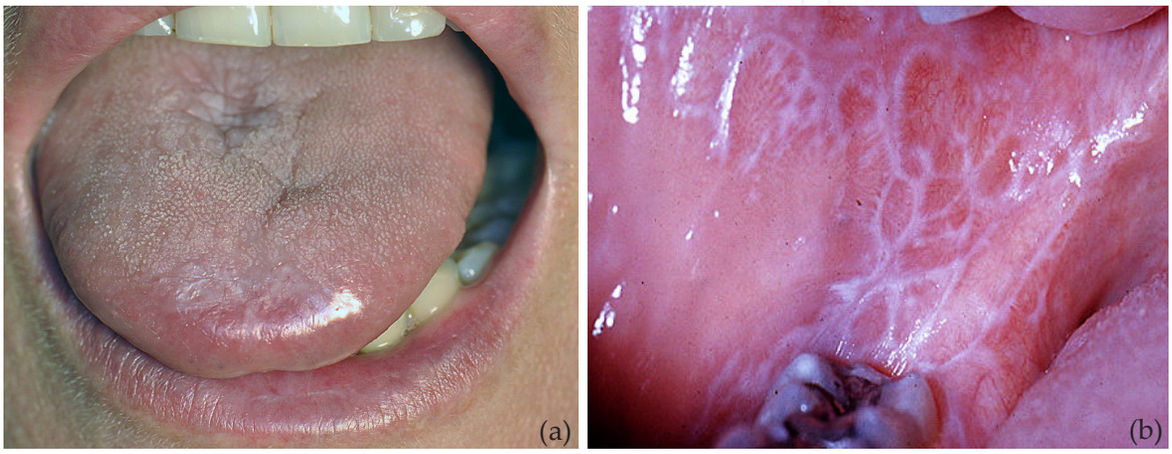


**Figure 2.** a) Reticular OLP (tongue); b) Reticular OLP (buccal mucosa)

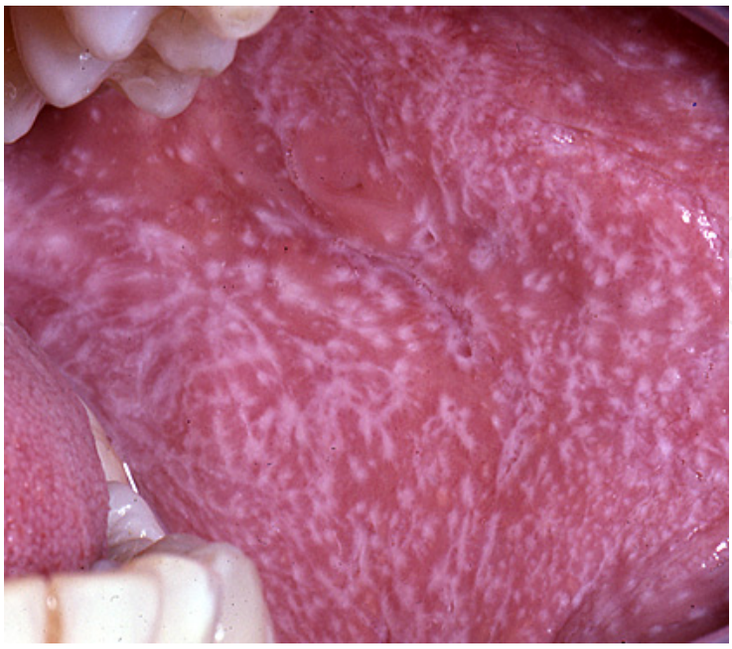

**Figure 3.** Paupular OLP

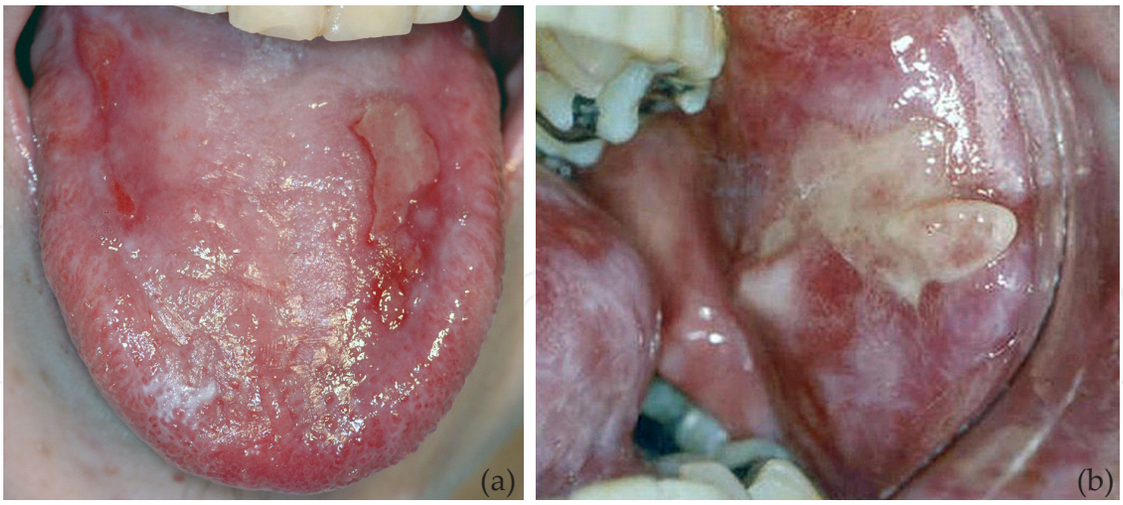


**Figure 4.** a) Ulcerative (erosive) OLP (dorsal tongue); b) Ulcerative (erosive) OLP (buccal mucosa)

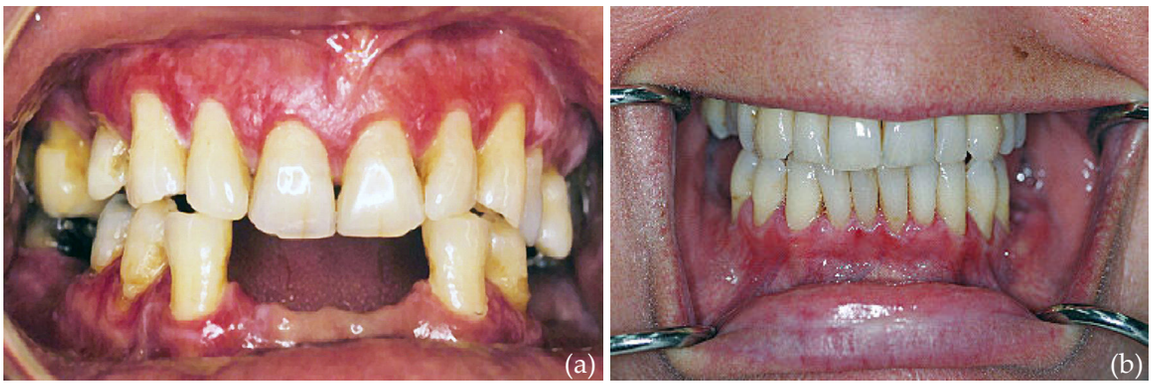


**Figure 5.** a) Desquamative gingivitis; b) Desquamative gingivitis with plaque form of OLP of central lower lip

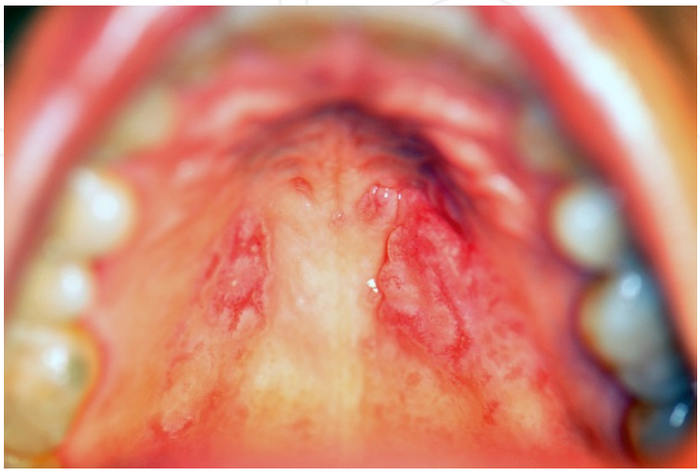

**Figure 6.** OLP of the hard palate

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OLP not only tends to develop in sites of trauma (Koebner phenomenon) but tends to be exacerbated by mechanical factors including biting/chewing habits, dental procedures and rubbing of malpositioned or ill-fitting dentures, teeth and fillings.

## 9. Clinical subtypes of oral lichenoid reactions

Oral lichenoid reactions encompass several clinical entities. [33-36]

**Oral Lichen Planus (OLP):** in which patients present with oral lichenoid lesions not readily attributable to any defined cause, that is to say "idiopathic" OLP. OLP represents one aspect of the spectrum of mucocutaneous lichen planus, which can affect potentially any mucosal surface, and/or the skin and its appendages.

**Oral Lichenoid Contact Lesions (OLCL):** due to allergic contact stomatitis (delayed immune mediated hypersensitivity) and seen in direct topographic relationship to dental restorative materials, most commonly amalgam (Figure 7). [36, 37]

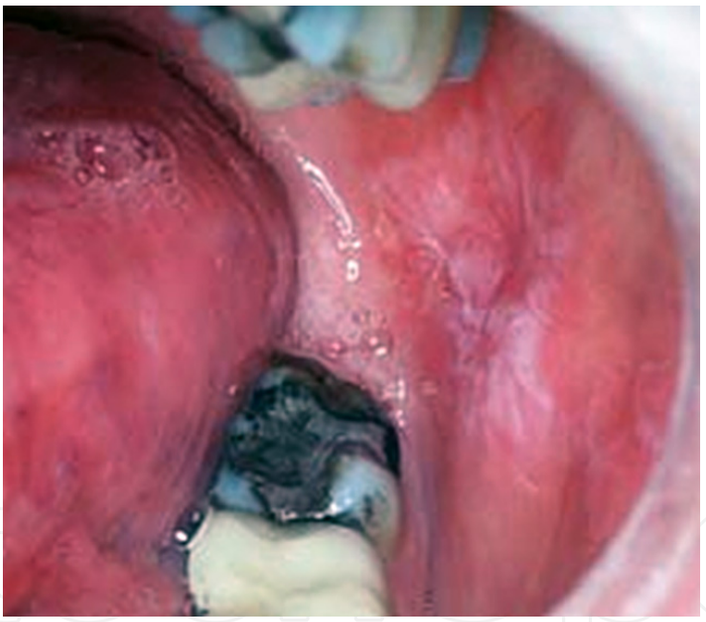

**Figure 7.** Oral Lichen Contact Lesion (OCLC) – left buccal mucosa

**Oral Lichenoid Drug Reactions (OLDR:** in which oral and/or cutaneous lesions occur, temporally associated with the taking of certain medications, such as oral hypoglycaemic drugs, angiotensin converting enzyme (ACE) inhibitors, and non-steroidal anti-inflammatory agents (NSAIDS), but historically has been seen with the previous more wide-spread use of gold salts and penicillamine for the management of rheumatoid arthritis. [38]

**Oral Lichenoid Lesions of Graft versus Host Disease (OLL-GVHD):** in the setting of patients with acute, but predominantly, chronic graft versus host disease (cGVHD). [33]

Lichenoid responses or reactions ("lichenoid stomatitis") of the oral cavity may also be noted with other autoimmune or inflammatory diseases including connective tissue diseases and other immuno-bullous disorders. The cause(s) of the various oral lichenoid lesions, ranging from idiopathic oral lichen planus (OLP) to the "contact" lesion, is not understood, but all the lesions are characterized histologically by a typical "lichenoid tissue reaction" culminating in a common pathologic process, that of T-lymphocyte directed, immune mediated, damage to the oral epithelial basal cells. [1,2]

The diagnosis of OLP is usually made on clinical features alone. However, careful attention to the clinical history is essential, to ensure assessment, and if warranted, the appropriate management, of the extra-oral manifestations of lichen planus (Figures 8a and 8b). [1, 33-35]

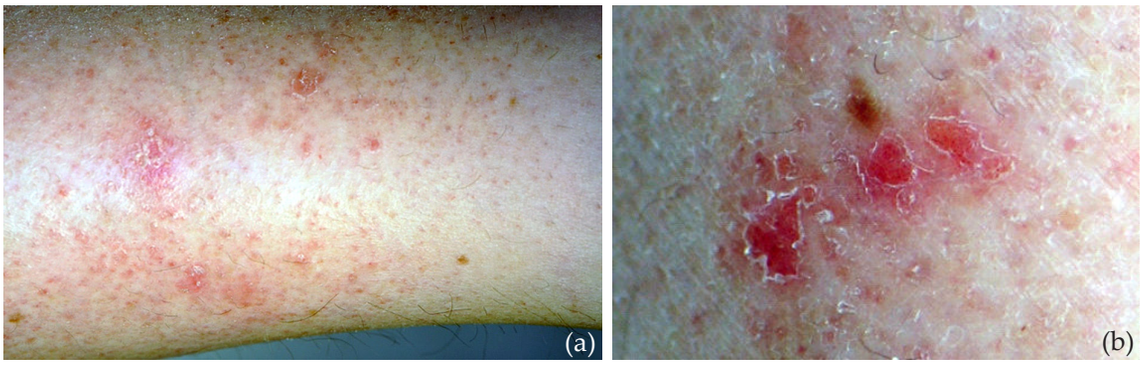


**Figure 8.** a) LP of the skin; b) LP of the skin (close up)

## 10. Special investigations

**Biopsy (Histopathological and Direct Immune-Fluorescence Investigations (DIF))**: The clinical features alone may be sufficiently diagnostic, particularly when presenting with the "classic" reticular form. The evidence regarding the need and value of biopsy for histological confirmation of the diagnosis is not definitive. Studies have shown variability in both inter-observer and intra-observer reliability in the clinicopathological assessment of OLP. [39] As OLP is a chronic disorder that often requires long-term treatment and monitoring, biopsy would be prudent clinical practice, particularly when the disease does not present with its typical manifestations, or when there is concern and therefore need, to exclude dysplasia or malignancy. [1] Furthermore, in severe disease warranting treatment with high-dose systemic corticosteroid therapy or potent "'steroid-sparing" immune-suppressant agents, then a confirmatory biopsy would be appropriate. The histopathological features are shown in Table 1. The findings on direct immune-fluorescence (DIF) are of a fibrin deposition in a linear pattern in the basement membrane zone. Colloid bodies may be positive for fibrin, IgM, and C3. The DIF findings, however, are not diagnostic of OLP, but DIF is certainly useful in differentiating OLP from other oral dermatoses, such as pemphigoid, or immune disorders, such as lupus (both discoid and systemic lupus) given their similar clinical presentation in the oral cavity. [34]

| |
|---|
| Essential Features (for histopathological diagnosis): |
| • Signs of "liquefaction degeneration" in the basal cell layer |
| • Presence of well-defined bandlike zone of cellular infiltration confined to the superficial part of the connective tissue, consisting mainly of T-lymphocytes |
| • Normal epithelial maturation pattern (absence of epithelial dysplasia) |
| Non-Essential Histopathological Features that may also be seen: |
| "Candle-dripping" or "saw-tooth"-like rete ridge conformation |
| Parakeratosis |
| Civatte bodies |
| Separation of epithelium from lamina propria due to basal cell destruction |
| **Exclusionary Histopathological Features (the presence of which would preclude a definitive histopathological diagnosis of OLP).** |
| •Epithelial Dysplasia/Atypia |
| →Atypical cytomorphology |
| →Nuclear enlargement or hyperchromasia |
| →Prevalent dyskeratosis |
| →Increased number of mitotic figures; aberrant mitosis |
| →Disordered stratification |
| •Heterogeneous inflammatory infiltrate |
| Heterogeneous inflammatory infiltrate with plasma cells and eosinophils |
| Deep extension below superficial stroma |
| or perivascular infiltration |
| • Blunt rete ridges |

**Table 1.** Histopathological features of OLP (adapted from Eisenberg, E. Clinicopathologic patterns of oral lichenoid lesions. Oral Maxillofac Surg Clin North Am, 1994, 6, 445.) [3] (Figures 9a, 9b and 9c)

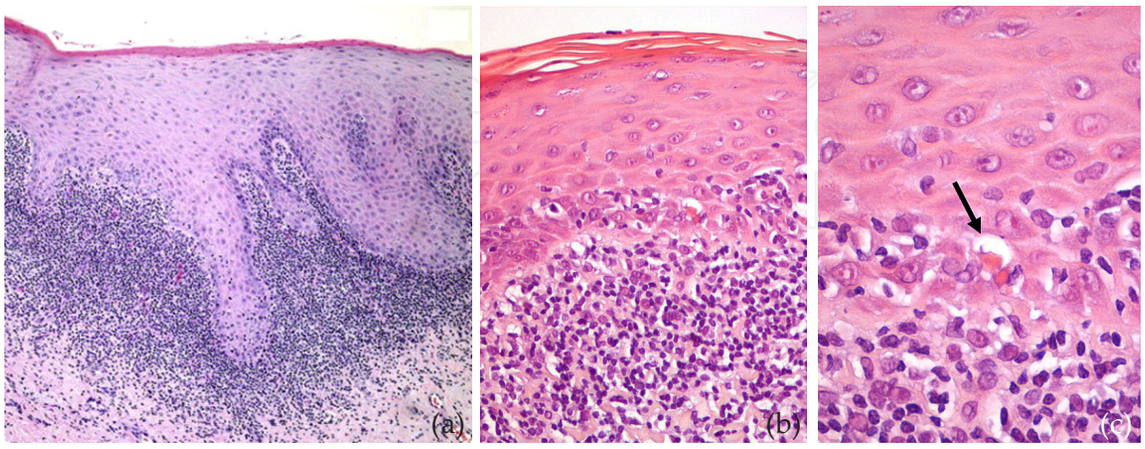


**Figure 9.** a) Histopathology (low power) band-like inflammatory infiltrate; b) Histopathology – vacuolar degeneration of the basal keratinocytes; c) Histopathology – civatte body

**Laboratory Investigations:** Generally are not required, except in patients with severe OLP warranting high-dose systemic corticosteroids, with the need to exclude underlying latent infectious diseases that can be reactivated by the corticosteroids (HIV, Hepatitis B and C, and tuberculosis). Again generally not required, except if considering treatment with a suitable 'steroid-sparing systemic agent (e.g.: hydroxychloroquine (Plaquenil), azathioprine or methotrexate) then routine full blood count, and assessment of liver and renal function may be warranted, for baseline assessment and monitoring in patients needing long-term management. [33]

**Patch Testing and the Removal of Lichenoid-Inducing Dental Restorative Materials:** Idiopathic OLP needs to be distinguished from oral lichenoid contact lesions (OLCL), most commonly seen in direct topographic relationship with amalgam. Cutaneous patch testing, undertaken by a clinician skilled and experienced in "reading" the cutaneous response to a variety of test agents can be useful to confirm the diagnosis of a OLCL, [36, 37] especially in severe, symptomatic cases, in which wide-spread replacement of the amalgam fillings is being considered, given the expense in time and money to the patient concerned. The benefit of such patch testing is to ensure that the alternate dental restorative materials also, in turn, do not incite a lichenoid contact reaction (e.g.: as has been seen with gold and even composite materials). In select cases, and if practical, consideration should be given to the replacement of those isolated restorations, seemingly to be in direct topographic relationship with a lichenoid oral mucosal lesion, particularly if symptomatic, with an alternate material, but the patient needs to be counselled that this may not necessarily prove beneficial. As an interim step, temporary coverage of the suspecting inciting material may be considered to determine if resolution of the OLCL occurs before undertaking definitive removal and replacement of the suspected inciting material.

**Additional Measures:** Referral for examination by a dermatologist or gynaecologist should be considered, depending on the presenting signs and symptoms reported by the patient.

## 11. Differential diagnoses

There is a spectrum of oral lesions that resembles OLP both clinically and histopathologically. [33, 34] These "lichen planus–like" ("lichenoid") lesions include the following conditions: (1) Oral lichenoid contact lesions (OLCL) as a result of allergic contact stomatitis (delayed immune mediated hypersensitivity). They are seen in direct topographic relationship to dental restorative materials, such as amalgam. In regards to the approach to oral lichenoid contact lesions, the value of patch testing remains controversial. (2) Oral lichenoid drug reactions (OLDR), wherein oral and/or cutaneous lesions arise in temporal association with the taking of certain medications, for example, oral hypoglycaemic agents, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory agents. Confirmation of the diagnosis of an oral lichenoid drug reaction may be difficult, since empiric withdrawal of the suspected drug and/or its substitution by an alternative agent may be complicated. [38] (3) Oral lichenoid lesions (OLL-GVHD) of graft-versus-host disease are confined to allogeneic haematopoietic

stem transplant recipients who have developed acute, or more commonly, chronic graft-versus-host disease (cGVHD). There is evidence that there is a greater risk of malignant transformation with OLL-GVHD than seen with OLP. [40]

The oral presentation of discoid lupus erythematosus (DLE) can also present with reticular or plaque-like lesions, but it is an uncommon condition that tends to present very much unilaterally, so meriting biopsy for histopathological and direct immune-fluorescence investigations, the latter being most useful in distinguishing OLP from DLE. [34]

### 11.1. Treatment

An essential first step is patient education as to the chronic nature of OLP and that therapy is not curative, but directed at relieving their symptoms. For treatment to be effective, patients need educated regarding the need to be patient and persistent with the recommended therapy. Instilling in patients the need for ongoing monitoring, not only for patients' response to treatment, but for malignant transformation is also important.

### 11.2. Supportive measures

The elimination of precipitating or provoking factors is an important initial step in the management of symptomatic OLP. The undertaking of active measures to resolve or minimize mechanical trauma from dental procedures, sharp cusps, rough dental restorations, and ill-fitting prostheses, or chemical trauma from acidic, spicy, or strongly flavoured foods and beverages should be encouraged. Of themselves, such supportive measures can lead to symptomatic improvement, or, more rarely, resolution of the disease.

The accumulation of bacterial plaque, often as a result of the discomfort associated with oral hygiene procedures in patients with gingival involvement, may also exacerbate the condition. The use of supplemental oral hygiene measures, including the use of alcohol-free chlorhexidine gluconate mouth rinses, may be helpful in such cases. [41]

### 11.3. Pharmacotherapy

Given the immune-mediated aetiology of OLP (and similar conditions such as mucous membrane pemphigoid (MMP)), the aim of therapy, is to minimise or "restrain" the body's immune-mediated inflammatory response, but without risking the activation of opportunistic infections. Treatment should be kept as simple as possible and should not inordinately burden the patient with expensive, complex, unwieldy or protracted treatments that result in non-compliance; therefore, topical corticosteroids remain the mainstay of treatment. [1, 33] Unfortunately, there are only limited evidence-based studies regarding the therapeutic interventions in OLP, and so treatment remains largely empirical. [1]

**Topical Treatment:Home Remedies and Over-the-Counter (OTC) Preparations:** patient prepared "salty" (saline) mouthwashes are of very limited clinical utility, somewhat palliative, and do not address the aetiological factors seen in OLP, but may facilitate oral hygiene. Patients also often self-prescribe and use any of the variety of OTC anti-microbial mouthwashes, in the

mistaken understanding that OLP may be infective in nature, but often complain of their astringency, especially the alcohol containing mouthwashes (and a useful clue as to the diagnosis).

Kenalog in Orabase® is one topical corticosteroid (0.1% triamcinolone) preparation that has the distinct advantage of being mixed with a vehicle for applying medication to the oral surfaces – Orabase® (composed of gelatin, pectin and carmellose in a Plastibase (hydrocarbon gel ointment base)). [1] The use of such an adhesive addresses an important therapeutic issue in treating OLP; that is having sufficient "contact time" between the medicament and the mucosal lesion(s) of OLP. It maintains the medication in close contact with the lesion and provides a protective covering that augments the effects of the corticosteroid. [33]

**Prescription Treatments: Topical Corticosteroid Preparations**. Topical corticosteroids come in a range of strengths, rated from mild – e.g.: hydrocortisone, to moderate – e.g.: betamethasone valerate, to highly potent, e.g.; clobetasone and means of delivery: pastes, ointments, gels or as inhaled agents (as used in asthma treatment). All agents, used in a variety of delivery methods have demonstrated some efficacy in treating OLP.[1] However, the basic principles guiding topical corticosteroids therapy, is firstly, to use the lowest strength agent possible to achieve a therapeutic benefit, and secondly, for oral mucosal lesions, (as opposed to skin conditions) to favour the use of adhesive containing preparations to prolong contact time, and so avoid the agent being simply washed away by the ever-present saliva.

**Compounded Preparations**: Empirically, patients report modest to good responses, to the use of moderate, to highly potent topical corticosteroids such as betamethasone valerate mixed with an equal amount (by weight) of Orobase, used 3-4 times daily (after meals) given they are suitably adhesive. One limitation is that they often need to be prepared by specialist compounding pharmacists. A second limitation is that many patients often complain how unpleasant and "tacky" they find this mixture. Use of specially fabricated modified topical fluoride trays, with extended coverage of the gingiva and adjacent alveolar mucosa to hold topical agents in place in the treatment of the desquamative gingivitis form of OLP are reported to be helpful, but again, patient compliance can be poor. [1]

Potent corticosteroids, such as dexamethasone, compounded as a mouthwash suspension (0.1% strength - 40 mg Dexamethasone mixed with 400 ml sterile water) are better tolerated by patients. However, patients must be carefully instructed in their use, emphasising that it is to be used as rinse, for at least 3 minutes (for sufficient therapeutic contact time), at most four times a day (after meals) and to spit out well, to minimise systemic uptake of this highly potent corticosteroid and thereby avoid its adverse effects.

Antifungal Agents: supplemental use of an antifungal agents, such as Daktarin® (miconazole) Oral Gel, or chlorhexidine-containing mouthwashes is warranted given the risk of candidial overgrowth and possible infection secondary to the use of the corticosteroids (whether they be used topically or systemically).

**Systemic Agents:** Corticosteroids: systemic corticosteroids are used in two ways mainly: firstly, as short-term "pulse" dose of prednisolone up to 0.5 mg per kilogram (of the patient's) body weight for a short period of time (i.e.: 4 days or less and then rapidly tapered) to bring

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about control of severe ulcerative OLP or in patients with multiple, highly active, sites of lichen planus. Secondly, longer-term, to supplement topical therapies, at sub-physiological doses (equal or less than 7.5 mg prednisone (or equivalent) daily). [1] Monitoring for the principle side-effects (and other adverse effects) of systemic corticosteroid therapy, such as, hypertension, cataract formation, diabetes mellitus, gastric ulceration, osteoporosis, and infection, is needed.

**Corticosteroid Alternatives: Retinoids (Topical and Systemic):** overall, the published studies suggest that retinoids are potentially effective in the treatment of OLP, but probably inferior to corticosteroids. [42] Systemic retinoids are associated with a number of serious adverse effects that would prohibit their routine use for the management of OLP, and include elevated/deranged transaminase levels, hyper-lipidemia, cheilitis, dryness and desquamation of the skin, alopecia, and dystrophic nail formation, and as well, being teratogenic and therefore their use in women of childbearing age would be contraindicated.

**Topical Calcineurin Inhibitors.** Cyclosporine, is one of the oldest such agents, but it is relatively expensive and unpleasant tasting, with studies showing an improvement in the oral symptoms that is not significantly better than 1% triamcinolone paste. [43]

Tacrolimus and pimecrolimus are newer calcineurin inhibitors, [44] with an improved safety profile in comparison with cyclosporine, but there are only limited studies as to their benefits, they are expensive and the United States Food and Drug Administration (FDA) has a "Black Box" warning attached to the use of these agents because of a theoretical increased risk of malignancy (squamous cell carcinoma and lymphoma) in patients using topical tacrolimus/pimecrolimus for cutaneous psoriasis. Therefore, the use of these agents should be restricted and patients should be made aware of these concerns. [45]

**Phototherapy:** there is one study of the benefits of phototherapy using psoralen ultraviolet A light (PUVA) and was included in a recent Cochrane review. However, UV light has a known oncogenic potential and therefore, its use for OLP is questionable. [46

**Other and/or "Steroid-Sparing" Systemic Medications:** These agents are indicated in patients with refractory LP, confined to the oral cavity, or also involving extra-oral sites, requiring systemic corticosteroids for control. There is only limited evidence supportive of only few potentially useful agents and the use of such agents is best restricted to clinicians highly familiar with these drugs and importantly their adverse effects: (1) *Lysosomotropic amines (the antimalarials chloroquine and hydroxychloroquine):* hydroxychloroquine, at doses of 200 to 400 mg daily, has also been shown to be effective for OLP. [47] (2) *Azathioprine* has been reportedly successful as a "steroid-sparing agent" for cutaneous lichen planus, and there is limited published evidence suggesting it may have a similar role in recalcitrant OLP at doses ranging from 1-2 mg per kilogram (patients' bodyweight), daily. [48] (3) *Mycophenolate mofetil (MMF)* has been employed for treatment of OLP. It is a newer immunosuppressive agent introduced for treatment of immune-mediated skin disorders and also for chronic GVHD. [49, 50] Side effects related to its use are consistent seen with other steroid-sparing alternate immune-suppressive therapies, including a risk of infections and malignancy, in particular, lympho-proliferative neoplasms. MMF, at moderate dosage, appears to be more effective than

azathioprine in treatment of cutaneous LP. [51] This is probably due to the fact that MMF has also anti-inflammatory properties exerted by inhibition of leukocyte recruitment and adhesion to endothelial cells. MMF has been used for treatment of severe, erosive-ulcerative oral and genital lichen planus recalcitrant to other systemic therapies. [52, 53] It induced complete, long-lasting remissions without flare-ups over a follow-up period of 4 years. However, the improvement of lesions was delayed, evident only after 4–6 week of treatment. No short-or long-term side effects were experienced, except minor gastrointestinal disturbances. (4) *Methotrexate*. Lundqvist et al carried out an open trial with methotrexate, which has an anti-inflammatory and immunomodulating activity, supplemented with steroid ointments for severe erosive lichen. [54] Four patients were given methotrexate in a dosage of 10–15 mg/week for about 17 months and they all improved their symptoms. This and another case series demonstrated that methotrexate was a well-tolerated and effective treatment for severe OLP. [54, 55] However, there was a delay in the effect of the methotrexate, so ongoing treatment with systemic corticosteroids may be needed, which are then weaned as the methotrexate becomes increasingly effective. (5) *Other Systemic Agents*: a variety of other immune-suppressant or immune-modifying agents have been trialled in OLP, including Dapsone (diaminodiphenyl sulfone – an anti-tuberculotic/anti-leprotic medication), [56] and thalidomide, [57, 58] but only in the context of isolated, case reports.

Evidence for the use of "'steroid-sparing" and/or "alternate" systemic immune-suppressant agents is poor, limited to case series or case reviews and these agents all have significant side effects that would suggest caution in their use for OLP. However, this needs to be balanced against the known and significant adverse side-effects of high dose corticosteroids needed for recalcitrant OLP, or patients with LP active in several sites. The limitation of much of the literature pertaining to the treatment of OLP is the lack of any unified or agreed objective measures for disease activity and outcomes, which needs to be urgently addressed, so that the various treatments used in OLP can be usefully compared.

### 11.4. Biological therapies

Biologic therapies, more commonly referred to as "biologics", is a medicinal product such as a vaccine, blood or blood component, allergenic, somatic cell, gene therapy, tissue, recombinant therapeutic protein, or living cells that are used as therapeutics to treat diseases. [59] Biologics are produced by means of biological processes involving recombinant DNA technology, rather than being chemically synthesized. These medications are usually one of three types: (1) Substances that are (nearly) identical to the body's own key signalling proteins, for example are the blood-production stimulating protein erythropoietin; (2) Monoclonal antibodies. These are similar to the plasma-cell derived antibodies that are produced in response to infection, but they are "custom-designed" (using hybridoma technology or other methods) and can therefore be made specifically to counteract or block any given substance in the body, or to target any specific cell type, for example rituximab that selectively targets $CD20^{+}$ B-cells; and (3) Fusion proteins (receptor constructs), usually based on a naturally-occurring receptor linked to the immunoglobulin frame wherein, the receptor provides the construct with detailed

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specificity, and the immunoglobulin-structure imparts stability and other useful features in terms of pharmacology.

The management of various immune-mediated disorders has been changed dramatically by the advent of biologic therapies. Biologics are designed to target every stage, as presently understood, in the pathogenesis of immune-inflammatory diseases, by either modulation of T-cells and T-cell functions, or cytokines. However, the future use of biologics will depend on whether they have the ability to truly treat and modify disease, to prevent disease progression and chronicity, or, merely offer more sophisticated, but more expensive palliation, a particular concern in chronic conditions, such as OLP. The other concern is by interfering in the fundamental processes of the immune system, are patients at risk of previously rare and indeed fatal infectious disease, such as progressive multifocal leukoencephalopathy, and is this warranted for a disease such as OLP, which is associated with distress and discomfort, but not serious morbidity or mortality. To date, there have only been limited case reports and case series using biologics for OLP. As with other, more potent immune-suppressive agents now used for OLP, caution is required and patience needed to await and observe the benefits, safety and long-term adverse effects of biologic therapies used in immune-mediated diseases with greater morbidity and potential mortality, such as rheumatoid arthritis, Behçet's disease and the inflammatory bowel diseases, before their use in patients with OLP.

The rationale for the use of biologics in OLP is based on our present understanding of that activated CD8+ and CD4+ lymphocytes play a pivotal role in the pathogenesis of OLP and cytokines such as TNF-$\alpha$, IL-2 and IFN-$\gamma$ are involved in the activation and persistence of OLP.

**Efalizumab (Raptiva):** a humanized monoclonal antibody that binds the CD11a subunit of Lymphocyte function-associated antigen-1 (LFA-1). LFA-1 is a T-cell surface molecule and Intercellular Adhesion Molecule-1 (ICAM-1) is its partner molecule. The interaction between LFA-1 and ICAM-1 regulates many normal T-cell functions. Binding of efalizumab to CD11a on T cells blocks the interaction between LFA-1 and ICAM-1, thus interfering with T-cell activation, migration and cytotoxic functions. This blockade is reversible, and seemingly does not deplete T cells or cause end-organ toxicity, opportunistic infections or malignancy. [60] Cheng and Mann, in 2006, reported a case of a 54-year-old woman with recalcitrant OLP resistant to topical and systemic corticosteroid therapy treated with efalizumab (Raptiva) reported an improvement of oral and cutaneous lesions at 5 weeks after commencement efalizumab therapy (initial dose of 0.7 mg/kg/week, followed by 1.0 mg/kg per week). [61] However, of interest and concern is that efalizumab has been withdrawn from both the American and European markets over safety concerns following the development of three fatal cases of progressive multifocal leucoencephalopathy (PML), a condition linked to immunosuppression that emerged after 3 years of continuous treatment in patients with psoriasis. [62]

**Etanercept (Enbrel):** This is an example of a fusion protein, consisting of a fully humanised TNF soluble receptor composed of the extracellular portion of two TNF type II receptors joined to the Fc portion of IgG1. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNF receptor (TNFR), preventing TNF mediated cellular responses by rendering TNF biologically inactive. [63] Etanercept may also modulate biological responses controlled by additional downstream molecules (e.g. cytokines, adhesion

molecules or proteinases) that are induced or regulated by TNF. It was the first TNF antagonist approved for treatment of psoriasis and psoriatic arthritis and is administered as subcutaneous injection. Yarom published a case report in 2007 of a 56-year-old woman with resistant to treatment to the usual immune-suppressant drugs and whose diabetes and hypertension precluded the use of high dose corticosteroids. [64] Subcutaneous etanercept (25 mg twice weekly) was administered with a 90% symptomatic improvement lesions documented 4 week after beginning therapy. After 10 weeks, the patients stopped the treatment because of the expense, which highlights another concern with the use of the new biologic therapies, their cost.

**Alefacept (Amevive):** a recombinant protein that, binds to CD2 on the T cell membrane thereby blocking the costimulatory molecule LFA-3/CD2, inhibiting the activation of $CD4^+$ and $CD8^+$ T cells by interfering and inducing apoptosis of memory-effector T lymphocytes. It is composed of an LFA-3 protein and human IgG1 fragment crystallizable (Fc) domain. [65] The rationale for alefacept use in the treatment of lichen planus is the established role for $CD4^+$ T-cells and alefacept induces T-cells apoptosis through natural-killer cells release of granzyme with a reduction in the $CD4^+$ T-cell lymphocyte numbers. Fivenson et al in 2006, reported two cases of generalized lichen planus, with OLP, treated with alefacept, with both patients having full resolution of their lesions and remaining free of lesions and symptoms with completion of the course alefacept therapy, suggesting that it may have a disease modifying effect, negating the need for ongoing therapy for patients with seemingly recalcitrant lichen planus, including OLP. [66]

**Rituximab:** was approved for the treatment of malignancy by the US Food and Drug Administration in 1997, has been used in certain B-cell lymphomas and treatment resistant rheumatoid arthritis. It is a chimeric murine–human monoclonal antibody to CD20 that depletes normal as well as malignant B cells. Currently, rituximab has been introduced into therapies of numerous immune-mediated conditions in dermatology. [67] Parmentier et al reported in 2008, successful treatment with rituximab for muco-cutaneous LP with oesophageal involvement. [24] There has been no follow-up cases reported since. It is controversial that rituximab targeting B cells could improve T-cell mediated OLP, but it suggests that the humoral arm of the immune system may have some role in the immune-pathogenesis of OLP.

## 12. Prognosis and outcome

Protracted involvement is typical for OLP, averaging on 8 years, and ranging up to 20 years. In many cases, OLP inexplicably "burns out" allowing for the cessation of any therapeutic interventions. However, some patients may suffer from the cycle of chronic inflammation followed by healing with scarring, with resultant microstomia, if the bucco-labial mucosa is involved, or loss of buccal sulcal depth, making the provision of oral hygiene by the use of a toothbrush difficult for the patient. In such cases, elective removal of the more posteriorly placed teeth, especially unopposed, non-functional, molar teeth may merit consideration. Plastic surgery interventions to relieve the microstomia are indicated, but are painful and can be of limited benefit (Figure 10).

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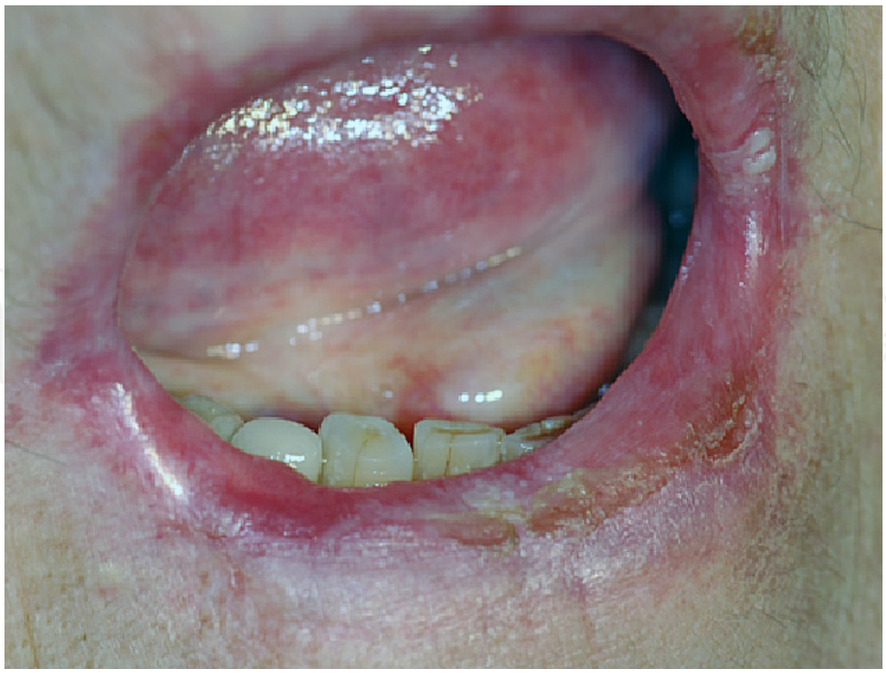

**Figure 10.** Microstomia secondary to long-standing OLP

### 12.1. Malignant transformation

The potential for OLP to undergo malignant transformation is controversial. If there is a risk, the risk is very difficult to quantify and possibly so low that it is very difficult to determine if OLP is truly associated with a significant risk for malignant transformation. Prudence would dictate to treat OLP as a potentially malignant lesion. [1, 33] If this approach is favoured, then ongoing, and at the least, annual monitoring, of the oral mucosa, by a clinician experienced in the management of OLP, is indicated. Any lesion suspected to harbour dysplasia and/or frank malignancy (oral squamous cell carcinoma) merits biopsy, and histopathological assessment, preferably by a pathologist experienced in oral pathology. Clinical suspicion should be aroused in the case of a lesion (or lesions) not typical for OLP, a lesion that is heterogeneous in texture and colour (a mixture of erythema and keratosis), or, any isolated area of mucosa that appears to be distinctly unresponsive to therapeutic interventions - such as persistent ulceration - despite clinical improvement in the remainder of the mucosa affected by the OLP. Before undertaking a biopsy, consideration should be given to a trial of topical (and if indicated systemic) corticosteroids and anti-fungal treatments to lessen any associated inflammatory or infectious changes that on histopathological assessment may mask the degree of dysplasia or malignancy within the lesion. [33, 34]

## 13. Conclusion

Oral lichen planus is a disease that results from CD8+ T cell-mediated apoptosis of basal keratinocytes in response to an unknown endogenous or at times a known exogenous antigen.

The resultant raised white lesions tend to develop in sites of trauma (Koebner phenomenon) and may exhibit the presence of slender white lines (Wickham's striae) radiating from the lesions that are generally asymptomatic, observed often by chance and do not warrant ongoing treatment. However, the predominantly erythematous forms of OLP that is the atrophic, ulcerative (erosive) and desquamative gingivitis presentations of OLP can be significantly symptomatic and warrant treatment. A biopsy is prudent, particularly when the disease does not present with its typical manifestations, or when dysplasia or malignancy needs to be excluded. Signs of "liquefaction degeneration" in the basal cell layer, presence of a well-defined band-like zone of cellular infiltration confined to the superficial part of the connective tissue consisting mainly of T-lymphocytes and normal epithelial maturation pattern are hallmarks of OLP. Patch testing may be employed by a specialist with sufficient expertise in the area to differentiate between idiopathic OLP and oral lichenoid contact lesions OLCL if for instance amalgam is suspected as an allergen.

Therapy, for symptomatic patients, initially should focus on patient education on the elimination of precipitating or provoking factors. Pharmacotherapies are largely empirical and initially potent topical corticosteroids (betamethasone in Orobase, clobetasone in Orobase, or dexamethasone as a mouthwash suspension) are trialled. Topical calcineurin inhibitors are effective but inferior to topical corticosteroids. Low-dose systemic corticosteroids are useful. Hydroxychloroquine, azathioprine, methotrexate, and mycophenolate may be effective in refractory disease. The efficacy (as well as their long-term safety) of biologic agents remains to better evaluated by larger, prospective studies.

OLP inexplicably burns out after a mean period of 8 years. The risk of malignancy is controversial but regular surveillance is advisable with biopsies of suspicious areas recommended to detect early dysplastic changes.

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