Review Article

Oral Lichen Planus: An Updated Review of Etiopathogenesis, Clinical Presentation, and Management

Abstract

Lichen planus (LP) is a chronic idiopathic immune-mediated inflammatory condition. LP is a heterogeneous disease with varied clinical presentations having different natural history, prognosis, sequelae, and outcomes. It can affect skin, hair, nails, and mucosae. Mucosal LP (including oral LP) tends to be persistent and resistant to treatment, compared to cutaneous LP. Oral LP (OLP) is broadly divided into two main categories: hyperkeratotic (usually asymptomatic) and erosive (commonly symptomatic). It can present with symptoms including odynophagia, dysphagia, dysgeusia, and sensitivity to hot spicy foods. Apart from the superficial epidermal changes, which vary with the type of clinical presentation, histopathologically oral LP shows a unifying similar and consistent feature of a lichenoid interface dermatitis. Recently, researchers have highlighted the critical role played by IL-17 in the pathogenesis of OLP. World Health Organization has categorized oral LP as one of the oral potentially malignant disorders (OPMD), albeit with a low risk of malignant transformation. Also, in the last couple of years there have been various reports on the usage of newer drugs like anti-IL17, anti-IL12/23, anti-IL 23, PDE4 inhibitors, and JAK inhibitors in the management of refractory OLP. The principal aim of treatment still remains to resolve the symptoms, prolong the symptoms free period, and reduce the risk of potential malignant transformation. We have described many new revelations made in recent times regarding the etiopathogenesis, associated conditions as well as management of OLP. Thus, the objective of this review is to present a comprehensive up-to-date knowledge including the recent advances made regarding OLP.

Keywords: *New pathogenesis, Oral lichen planus, patterns*

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Introduction

Lichen planus (LP) is a chronic idiopathic immune-mediated inflammatory disorder involving skin, hair, nails and mucosae (oral, genital, esophageal, and ocular). It derives its name from the Greek word λειχήν (lichen) for "tree moss" and the Latin word planus for "planar."[1] LP is a heterogeneous disease with widely varying clinical presentations having different natural history, prognosis, sequelae, and outcomes. Several variants of LP and a couple of overlap syndromes with other autoimmune diseases have also been described.[1]

All types of LP show a unifying similar and consistent histopathological feature of lichenoid interface dermatitis.[1] Classic cutaneous LP (CCLP) is characterized by 6 ps (purple, plane, polygonal, pruritic, papules, and plaques), whereas oral LP (OLP) is broadly divided into two main categories: hyperkeratotic (usually asymptomatic) and erosive (commonly symptomatic). The hyperkeratotic form includes reticulate (the most common type of OLP), papular, and plaque/verrucous forms, whereas erosive types can be erosive erythematous or erosive atrophic OLP. Bullous OLP is the rarest form of OLP. All these types of OLP can occur alone or as part of CCLP.[2] Symptoms of OLP include odynophagia, dysphagia, dysgeusia, and sensitivity to hot spicy foods.[3] Mucosal LP (including OLP) tends to be persistent and resistant to treatment compared to CCLP. OLP belongs to the category of oral potentially malignant disorders (OPMD) albeit with a low risk of malignant transformation according to WHO.[4]

The exact etiopathogenesis of OLP is not known. However, various factors like immune dysregulation, genetic, psychological factors, oral microbiome, mechanical and chemical injury from dental

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amalgam, prosthesis, teeth, denture, viral infections [HCV and HPV in some geographic locations], pro-inflammatory and pro-apoptotic milieu of cytokines, interleukins, and hormones in the saliva, all are speculated to play some role in OLP.[1-2] Differentiating OLP from oral lichenoid lesions (OLL) is of paramount importance where history, examination, biopsy, and direct immunoflourescence (DIF) play a great role.[5]

A wide variety of treatments have been used to treat OLP. Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs) constitute the first line therapy of OLP followed by immunosuppressives such as oral corticosteroids (OCS), methotrexate (MTX), azathioprine, cyclosporine, dapsone, and mycophenolate mofetil (MMF) recommended in severe recalcitrant cases as the second line therapies.[2,6,7] Different energy-based therapies (low-level laser light, lasers, photodynamic therapy)[8] and biologics[6] have also been tried. Bioactives such as platelet-rich plasma (PRP)[9] and novel plant-derived therapies[10] offer newer adjuvant safer treatment options that can help avoid side effects associated with prolonged use of immunosuppressants.

Distinct epidemiology, putative etiologic factors, significant role of psychological factors, persistent, relapsing recurrent nature of the disease, and malignant transformation potential have prompted discussion that OLP, especially isolated form, could be an entity different from idiopathic cutaneous LP.[1-3] Some authors have even considered OLP as a spectral systemic disease because of association with under-diagnosed esophageal and pharyngeal involvement[11], association with autoimmune, and systemic disorders.[12] Association with systemic co-morbidities in OLP patients is being recognized as an important aspect.[13] OLP leads to a significantly adverse psychological impact that impairs the quality of life because of its recurrent relapsing symptomatic nature, resistance to treatment, and potential risk of malignant transformation requiring life-long follow-up.[14]

Epidemiology

The exact prevalence and incidence of LP are not certain due to the paucity of uniform diagnostic criteria and heterogeneity of clinical presentations. Classic cutaneous LP is a relatively uncommon condition affecting little less than 1% of the total population (0.4 to 1.2% of all dermatology and hospital referrals).[1] OLP in the majority of cases (around 2/3rd) occurs as a part of classic idiopathic LP. But, in up to 25% cases, it can occur alone[15], or rarely as part of plurimucosal orogenital LP syndromes.[16] Out of the total estimated global prevalence of OLP of 1.01%, India at 0.49% has the lowest reported prevalence, whereas the highest prevalence of 1.43% is reported from Europe. The prevalence is higher in non-Asian females more than 40 years of age. High prevalence of tobacco chewing-associated oral keratosis appears to mask OLP, probably resulting in lower reported prevalence in India. Oral medicine physicians report a significantly higher prevalence of OLP (1.80%) than dentists (0.61%) and dermatologists (0.33%) ($P < 0.001$).[17] OLP in children is extremely rare.[18]

Etiopathogenesis

The precise etiopathogenesis of LP is unknown, complex, and multifactorial.[1] Immune dysregulation, infections, environmental, and genetic factors are the four major areas invoked to play a role in the pathogenesis of LP.[1] Currently, available data favor LP to be primarily due to T-cell (Th1) mediated targeting of basal keratinocytes, although other inflammatory cells may also be contributing in the process.[1,6] Thus, in a genetically predisposed person, environmental factors, namely drugs, infections, vaccines, contact allergens, stress, or other unknown agents, may trigger the immune system, initiating the inflammatory cascade leading to LP.[1]

Role of various inflammatory cells

Apart from the various populations of T-cells (CD4+, CD8+, T-regs), plasmacytoid dendritic cells (PDCs) and mast cells also participate in a complex interplay to bring about the inflammatory cascade, damaging the basal keratinocytes.[19] Self-antigens in the basal cell layer are exposed, initiating inflammatory pathways through molecular similarity, that lead to the pathologic changes and lesions of LP. PDCs and keratinocytes stimulated by external agents (drugs, infections, contact allergens, or hitherto unknown) release type 1 interferons (IFN) such as IFN–α, leading to activated CD8 + cytotoxic T-cells causing damage to the epidermal basal cells with the help of CD4 T-helper.[19]

In the induction phase, the damaged basal keratinocytes attract more CD8+ T-cells resulting in a self-perpetuating cycle and chronicity seen in LP.[19] Cytokines typical of a type 1 IFN response released by keratinocytes cause up-regulation of the cell surface adhesion molecule expression and migration of T-cells to the initial site of damage. RANTES released by T-cells leads to degranulation of mast cells releasing TNF-α which in turn up-regulates RANTES secretion by T-cells which is another contributor to a positive feedback loop causing persistence or recurrence of inflammation and lesions. The innate immune response also participates through pro-inflammatory myeloid dendritic cells (mDCs), T-regulatory cells (T regs), polyfunctional T-cells, and toll-like receptors (TLRs).[1,19]

In the evolution phase, matrix metalloproteinase 9 (MMP 9) is secreted from activated effector T-cells and degranulation products from mast cells damage the basement membrane zone (BMZ). This helps the entry of CD8+ T-cells into the epidermis.[1,19] Matricellular protein inflammosome tenascin-C also plays a role in trafficking of T-lymphocytes to the BMZ in OLP.[20] Also, the accumulation of B-cells near the BMZ reported recently indicates their possible role in the pathogenetic pathway of OLP.[21]

Role of cytokines and chemokines axes

Cytokines are tiny regulatory proteins playing a significant role in infection, immune responses, and inflammation. Cytokines such as interleukins (α, 4, 6, 8, 17), IFN-γ, TNF-α, VEGF, TGF-β 1, caspase 3, and bcl 2 are up-regulated.[1,19] Various chemokine and chemokine receptor axes such as CXCR3/CXCL9-11[22], CCL17/CCR4[23], and CCL5/CCR5[24] act to direct T-lymphocytes, antigen presenting CD1a+ Langerhans cells, and factor XIII-a positive cells to the site of the lesions.[15] Transforming growth factor BMP-4 causes apoptosis of cells through up-regulation of p53, MMP1, and MMP3 in OLP.

Humberto *et al*[25] in a recent review on the role of cytokines, cortisol, and nitrous oxide found significantly elevated levels of cytokines (IL-4, IL-6, IL-8, IL-17, IFN-γ, and TNF-α) in 17 studies, cortisol in 5/9 (55.5% studies), and nitrous oxide (NO) in all the six studies compared to healthy controls, in the saliva of OLP patients, pointing to their role in the causation and potential use as biomarkers for OLP. Topical steroids led to the reduction of cytokines TNF-α, IL-1α, IL-6, and IL-8, and oral steroid treatment in IFN-γ, TNF-α, and sTNFR-2 levels in the saliva.[26]

Role of micro-RNAs

Micro-RNAs (mRNAs) are a group of small RNAs involved in regulating the expression of protein-coding genes that have pro-inflammatory and pro-apoptotic actions. Elevated levels of pro-inflammatory and pro-apoptotic mRNAs 21, 31, and 155 in the serum and saliva OLP patients have been found.[27] However, mRNA-26a/b may have a protective role in OLP.[27]

Type II IFN response and potential new target therapeutic pathways

Although LP is primarily a type 1 IFN disease, recently Shao *et al*[28] demonstrated JAK STAT dependent type II interferon inflammatory response. Wherein, they showed the involvement of Janus kinase 2 (JAK2) and signal transducer and activator of transcription 1 (STAT1), thus providing the basis for the therapeutic use of JAK inhibitors in the management of LP.

IL17/Th17 role in pathogenesis of OLP is well established.[29] Th9/IL9 pathway synergistically potentiates the cytotoxic effects of Th17 cells through induction of MMP 9.[30]

Role of humoral immune response

The occurrence of various autoantibodies in patients of OLP has been studied.[31] The role of humoral immunity in LP is indicated by increased levels of anti-keratinocyte, anti-nuclear, anti-desmoglein-1 and 3, anti-mitochondrial, and anti-thyroglobulin antibodies found in LP patients.[32] Chiang *et al*[32] found elevated levels of serum autoantibodies in 61% of their 320 OLP patients. They discovered that a significant proportion of these patients (21.9%, 13.6%, 7.1%, 0.3%) had low hemoglobin, iron, vitamin B12, and folic acid, respectively. 14.8% abnormally had high serum homocysteine level. They recommended to investigate the serum autoantibody, hematinic, and homocysteine levels in OLP patients. Autoimmune thyroid disease has been significantly associated with OLP in some studies and reviews,[12,33] but not confirmed by others.[34]

Auto-antigens in LP

Although LP is considered an autoimmune condition, no definitive antigen consistently triggering the disease has been discovered as yet. However, Shimada *et al*.[35] recently found decreased expression of keratin-19 and increased expression of desmoglein-1 demonstrating loss of basal cell phenotype in OLP. T_h1/T_h17 cell recognition of desmoglein-3 and bullous pemphigoid antigen 180 in LP was discovered by Schmidt *et al*.[36]

External triggers

Certain viral infections especially HCV[37], HPV[38], and others (HBV, HHV 6, HHV 7, VZV)[1], drugs[1], dental amalgam[1], other chemicals,[1] and vaccines[39] are some of the well-known triggers for LP. In Japan, Middle East, and southern Europe, HCV is significantly associated with OLP. The patients with LP have a higher prevalence of HCV and vice versa in these regions. A 6-times higher risk of HCV infection is found in OLP patients in some areas. Patients with HCV have a 2 to 4 times higher risk of developing OLP.[38] The exact mechanism about how HCV induces LP in some just started to unravel now. Well-documented cases of vaccine-induced CCLP, but not OLP has been reported worldwide.[39] Hepatitis B, influenza, and herpes zoster vaccines are the three most common vaccines implicated in the causation of CCLP. Most cases of hepatitis B vaccine-induced LP are reported after the second dose. The median time of onset of LP following vaccination is 2 weeks.[39] Very recently, few reports of cases of CCLP post-COVID vaccination have been published.[40,41] Also, reported are couple of cases of isolated OLP triggered by mRNA COVID vaccine.[42]

Role of oral infection and salivary microbiome

Salivary microbiome, mycobiome, and their alterations are also speculated to play a role in causation of OLP.[43] There are conflicting reports in this regard. Some investigators have found oral candida may be playing an etiologic role as an initial antigen in OLP, whereas others have not.[44] A recent analysis of a large number of studies concluded that no infectious agent including oral candida infection in the oral cavity is consistently associated with OLP and thus does not fulfill Koch' criteria of casualization.[45]

Role of psychological factors

Stress, anxiety, and depression, through various neuroendocrine and neuroimmunologic mechanisms, can trigger, exacerbate, and perpetuate OLP.[18] The association between stress and LP has been shown by elevated levels of IL2r, sFasL, neopterin, sIL6R, and IL 8.[1,46] Also, stress hormone levels are increased in OLP patients during activity and reduce after successful treatment.[46]

Drug-induced OLP and OLL

Drug-induced LP, commonly referred to as lichenoid drug eruption (LDE), is a well-known entity. Antimalarials, antibiotics, non-steroidal antiinflammatory drugs (NSAIDs), oral hypoglycemics, antiepileptics, diuretics and various biologics are the drugs that have commonly caused LP.[1,19] Drugs can trigger lesions resembling classic cutaneous LP, OLP, or LP occurring in a photo-distributed area.[1] OLL must be differentiated from OLP.[5] A recent meta-analysis questioned the existence of drug-induced oral lichenoid reaction (OLR) including drug-induced OLP as an entity based on weak chronological association with any particular drug (s).[47]

Dental restorative materials, mechanical factors, and OLP

In the past, metals in the dental amalgam, especially mercury, were considered a common cause for inducing OLP or OLR (supported by clearance on removal and positive patch test results). However, due to the increasing use of other newer substitutes, the incidence of mercury amalgam-induced OLP has reduced significantly in dental practice.[48]

Role of genetic factors

The role of genetic influences in the etiology of LP is highlighted by reports of familial cases (up to 10% in certain studies) and also the identification of high association of certain specific HLA genetic loci in different populations (like HLA DR10 in Arabs, DsR BI*01:01 in Sardinia and Mexico, HLA-a28 in Israel, and HLA A3, A5, A7, B7, DR1 in different regions of the world).[1]

Genetic polymorphism in OLP

Polymorphism in a number of putative genes encoding proteins involved in the pathogenesis of LP has been discovered.[49] A significant association of 308 G/A single nucleotide polymorphism in TNF-α (a mediator that plays a significant role in LP pathogenesis) with OLP but not CLP has been documented.[49] Similarly, the association between polymorphisms in interleukins and OLP is also indicated in a recent meta-analysis.[50] A recent study has found new genetic associations on HLA complexes in LP and seven other diseases.[51]

OLP and malignancy (epidemiology and etiopathogenesis)

Malignant transformation (MT) in OLP is a matter of concern for the patient as well as the treating physician. WHO proposed and adopted the term oral potentially malignant disorders (OPMD), which includes conditions such as oral leukoplakia, erythroplakia, OLP, and oral submucous fibrosis for categorizing and quantifying their premalignant potential, risk, and rate of MT into the most common and devastating oral malignancy, squamous cell carcinoma (SCC). Leukoplakia (42%) and OLP (23%) are the two most common OPMD.

Wide variation in figures of incidence of MT in OLP ranging from 0 to 6.5% has been reported in various hospital/clinic-based studies.[52,53] However, the only population-based study comparing OLP patients with healthy control from the same population revealed MT rate of 3.1% at 20-years after the first diagnosis of OLP. Patients with OLP were around 5 times more likely to have OSCC. The median time to development of oral squamous cell carcinoma (OSCC) was 14.7 years earlier for the OLP patients, compared to the general population. The transformation of OLP to OSCC took an average of 5.5 years. Also, the patients developing OSCC on OLP lesions had a higher tumor recurrence rate in comparison with those with primary OSCC. The type of OLP (erosive more likely than other), location (tongue > buccal > lip mucosa), and extent of involvement have bearing on risk of MT. Most of the recent meta-analyses and systematic reviews have found an MT rate of around 1%.[52,53] A recent meta-analysis of all reported studies and cases till January 2020 (33 studies, 12838 patients) concluded that the risk of MT in OLP is exaggerated. Out of 151 cases of OLP initially considered to have undergone malignant transformation, only 56 cases (0.44%) were true, after applying strict criteria. The risk of MT was found to be significantly higher among those who were smokers, consumed alcohol, HCV positive, and/or had a erosive OLP.[54]

Pathogenetic factors in malignant transformation of OLP

Matrix metalloproteinases 1, 2, and 9 and enhanced c-myc expression, salivary cortisol, nitric oxide, and certain interleukins are implicated in malignant transformation in OLP.[19,49]

HCV, HPV, and EBV, and known carcinogens such as smoking, tobacco and alcohol as etiological co-factors, and p16, p21, p53, mRNA26, at molecular/cellular levels could be playing a role in initiating MT in OLP.[19,55,56] There is still doubt about the potential of MT, whether it is because of OLP itself, or due to the various risk factors implicated in its pathogenesis, including oncogenic viruses.[57]

Chronic inflammation seen in OLP is now being considered to be a definite factor in malignant transformation, as seen

in colitis-associated cancer.[58] Various inflammatory cells and cytokines associated with OLP not only cause DNA damage, promote cell proliferation, and inhibit apoptosis, but, also cause fundamental changes in the proteins of oral epithelial cells.[59]

Hanahan *et al*, were the first to suggest the concept of tumor microenvironment, considered as a characteristic feature of tumors.[60] Four main types of microenvironment in tumors have been identified: hypoxic, inflammatory, immune, and acid microenvironments.[61-63] It is believed that it is the microenvironment that provides intercellular communication and interaction among several distinct cell types[60] and has been highlighted to clarify the bioactivity of tumor cells. Similarly, it has been speculated that a tumor-like microenvironment exists in OLP and plays a key role in its malignant transformation. Recurrent epigenetic alterations such as methylation of DNA but not chromosomal alterations were found significantly in OLP undergoing such change. Characteristic altered chromosomal patterns were found in OSCC but not in OLP. However, the large number of alterations in the DNA methylation pattern detected in OLP, when compared to normal controls, that were also observed in OSCC, supports the hypothesis that OLP is a precursor of OSCC, and it shares multiple epigenetic alterations with it.[64]

Clinical Features: OLP is one of the most common mucosal conditions affecting the oral cavity. It predominantly occurs in the fourth–fifth decade of life, is more often seen in women (four times as common as in males) and initially reported to affect 2–5% of the general population.[65] A current meta-analysis showed the global prevalence of OLP to be 1.01%, which showed wide variations depending upon the geographic location, being the lowest in India (0.49%) and the highest in Europe (1.43%).[17] Although reported in children, OLP is quite rarely seen in younger age group.[18,66]

In large majority of the cases, OLP follows a chronic course punctuated by recurrent episodes and aggravations, which can sometimes last for many years. It is associated with significant morbidity, unlike cutaneous disease. OLP occurs more frequently than the cutaneous form, and it is generally much more difficult to treat. Up to 50% of patients of OLP also have skin lesions; the presence of these characteristic cutaneous lesions can be of great help in establishing the diagnosis of OLP in atypical or doubtful cases.[67] The characteristic clinical presentation of OLP is almost always bilaterally symmetrical on sites like buccal mucosa, tongue, gums, lips, and palate. It commonly involves multiple sites. However, the buccal mucosa is the typical site of involvement. Although very uncommon, single site OLP cases with localized gingival or isolated lip[68] involvement is also reported.

Clinically, there are six different well-established variants of OLP, which can either occur independently or in varying combinations. They are as follows: reticular, erosive, ulcerative (bullous), papular, plaque-like white patches, erythematous, and atrophic,[1-3,65,66] the most common being reticular and erosive-ulcerative.[69]

Clinical classification of OLP

Hyperkeratotic types

a. Reticular (most common) [Figure 1 and 2]
b. Plaque/verrucous [Figure 3 and 4]
c. Papular

Erosive types

d. Erosive (resistant, recurrent, the type with highest risk of malignant transformation) [Figure 5].
e. Erythematous atrophic
f. Bullous: Rare

Reticular: It is largely asymptomatic and often presents as a lace-like network of slightly raised gray-white lines (known as Wickham's striae), interspersed with papules or rings.

Erosive: It appears atrophic, with areas of ulceration, erythema, and keratotic white striae with a network appearance. There can be the presence of pseudomembranes. Its symptoms can range from a mild burning sensation to debilitating pain, to even interfere with speech, chewing, and swallowing.

Atrophic: It presents as diffuse erythematous lesions, with mixed features of two different clinical forms, such as the presence of white striae characteristic of the reticular type surrounded by an erythematous area.

Plaque-like: It presents as whitish homogeneous irregularities akin to leukoplakia, mostly involving the dorsal surface of the tongue, and cheek mucosa.

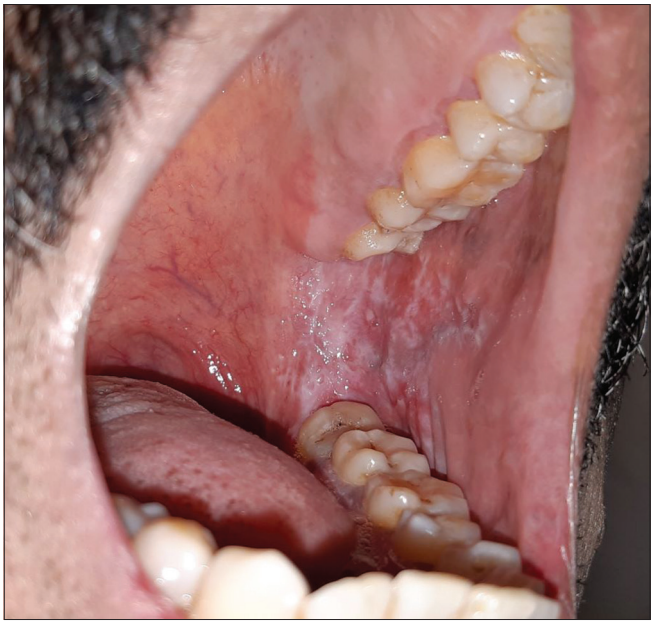

Figure 1: Classical white lacy reticular pattern of lesions on left buccal mucosa

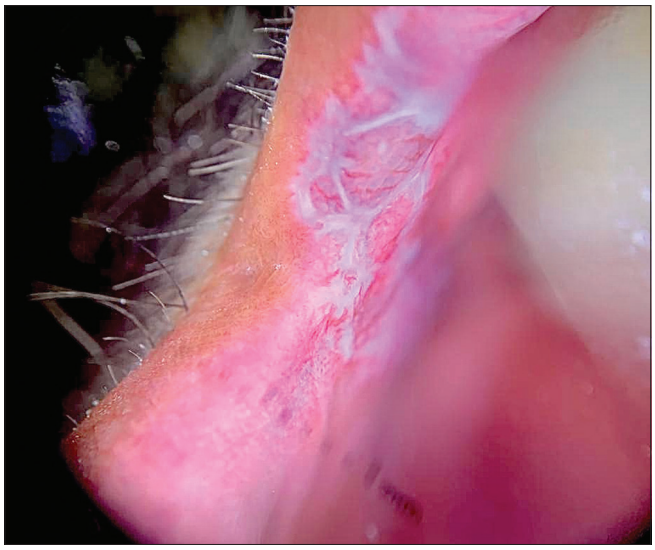

Figure 2: Classical white lacy reticular pattern of lesions on lip and adjoining left buccal mucosa. (Dermoscope ILLUCO IDS-1100;Polarized 10X)

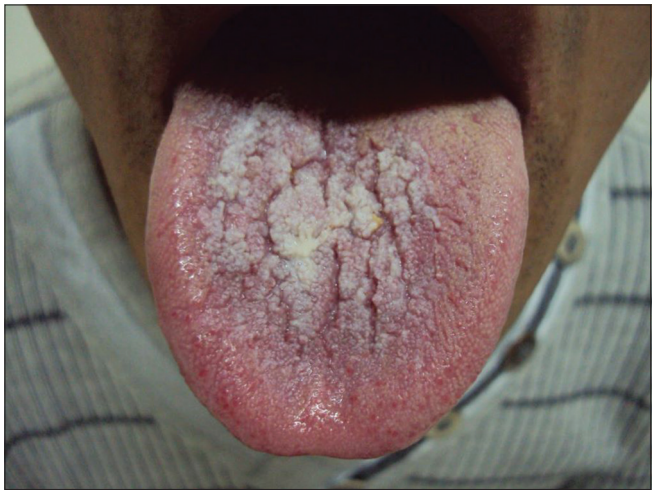

Figure 4: OLP lesions characterized by hypertrophic plate on the central part of dorsal aspect of tongue

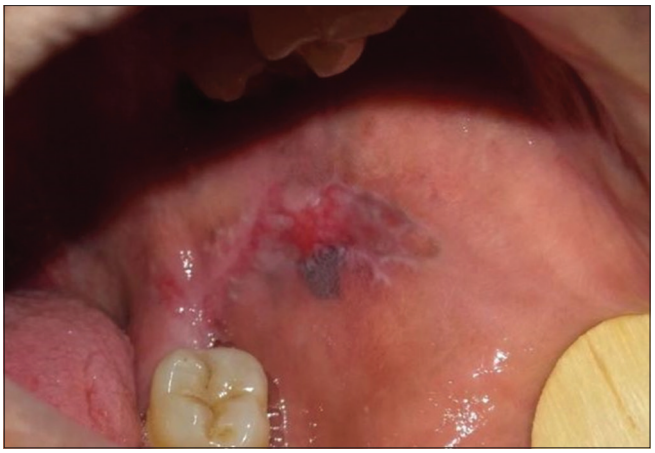

Figure 3: White lacy reticular pattern with pigmented area on periphery at lower end and central healing erosion on left buccal mucosa

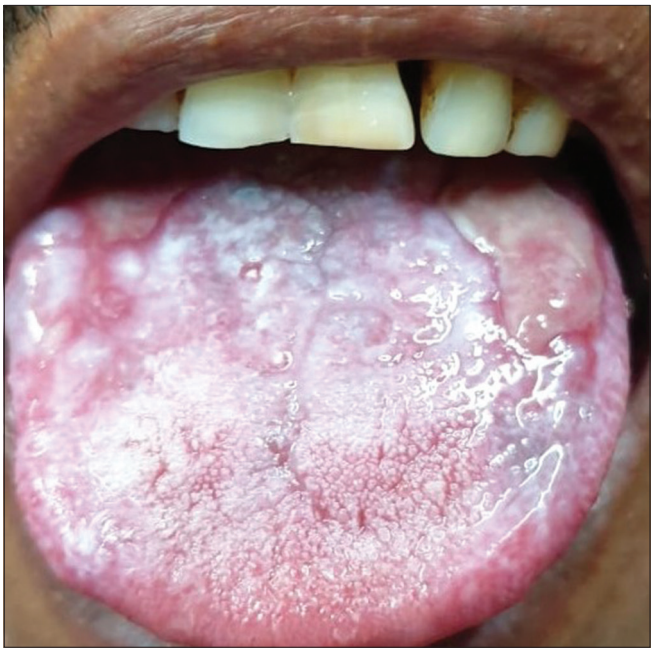

Figure 5: Large erosive plaques of OLP on posterior dorsal aspect of the tongue on both sides

Papular: Rare presentation is normally followed by some other type of clinical variant described. It presents with small white papules with fine striae in its periphery.

Bullous: It is the most unusual clinical form and presents with painful lesions starting as blisters that grow and tend to rupture, leaving behind ulceration. Positive Nikolsky's sign can sometimes be demonstrated in these lesions.

Vulvovaginal-gingival syndrome: OLP commonly occurs alone, or as part of CCLP, and however rarely occurs as part of orogenital LP syndromes. The combination of LP of the vulva, vagina, and gingiva is recognized as vulvovaginal-gingival syndrome.[70] The most common type of LP lesion affecting the genitalia in these cases is erosive form.

Penogingival syndrome: The male counterpart of the vulvovaginal-gingival syndrome of LP is known as the penogingival syndrome.[71] In this variant, the oral mucosal involvement is characteristically limited to gingiva, often as desquamative gingivitis. Penile involvement is typically characterized by erosions of the glans penis, although reticular and erythematous lesions have also been described. In around three-fourth of the cases, oral lesions occur simultaneously with genital lesions. It does not typically leave behind scars or have extraorogenital involvement. Early recognition and initiation of treatment are important because of the reports of malignant transformation of penile LP.[72]

Recognizing the importance of OLP due to reports of its malignant transformation, WHO in the year 1978 came out with a set of clinicopathologic criteria to differentiate it from the other closely resembling dermatoses affecting the oral mucosa.[73] In 2003, these criteria were modified due to the absence of

consensus regarding the clinical and histologic diagnosis of OLP [Table 1].[74]

The severity of the symptoms of OLP is directly proportional to the degree of inflammation and clinical erythema. Minimally inflamed OLP lesions are painless, whereas erosive/ulcerative forms the most painful lesions.[75] In addition, the formation of bacterial plaque because of the discomfort associated with brushing the teeth in patients with gingival involvement may also increase the severity of symptoms.

LP and co-morbidities

Chronic long-lasting inflammation creates a milieu that is conducive to the development of metabolic syndrome (MS).[76] Chronic inflammatory skin diseases like psoriasis, hidradenitis suppurativa, and LP are increasingly linked to the risk of having MS.[77] In comparison with CCLP, the patients with OLP have severe lipid metabolism derangement and possess much higher atherogenic indexes.[78]

Co-morbid conditions: Various other systemic diseases have been associated with LP with oral involvement.[12] The strongest linkage has been found with hepatitis C virus (HCV).[37,79] Isolated OLP has been shown to be associated with numerous systemic diseases such as diabetes mellitus (DM)[80], hypertension[12], metabolic syndrome (MS)[76-78], thyroid diseases[34], liver disease[12], gastrointestinal diseases[13], psychosomatic ailments[14], chronic, and genetic susceptibility to cancer.[12]

a) ***HCV and other viral infections*:** Mokni *et al* were the first one to suggest a possible association between OLP and chronic liver diseases.[81] The prevalence of HCV infection in patients with OLP varies widely between 0.5% and 35% depending upon the geographical areas.[79] Studies from southeast Asia and southern Europe have found the coexistence of HCV infection and OLP to be more relevant.

Unlike LP, the association of herpes group of viruses with OLP has not been substantiated. However, a much stronger association has been determined recently between human papilloma virus (HPV) and OLP. This association has been found to vary with different geographic locations. It suggests a causal role of HPV in the potential risk of malignant transformation of OLP, although it may not apply in all cases.[46]

b) ***Autoimmune diseases:*** A recently published meta-analysis has vividly analyzed the association of OLP with various autoimmune diseases.[77] One of the studies has shown that 7% of the patients of OLP were found to have associated autoimmune disease.[15]

OLP, diabetes mellitus, hypertensions, and carbohydrate metabolism

The association with DM was initially reported by Grinspan *et al*.[82] Later on, a meta-analysis confirmed that patients with DM were more likely to have OLP when compared with the controls (1.37% Vs 0.75%).[80] Atrophic-erosive OLP of tongue has been reported more commonly in patients with diabetes. The triad of OLP, diabetes mellitus, and hypertension has been described as Grinspan syndrome.[82] Dreiher *et al* demonstrated that a majority of patients with OLP had dyslipidemia.[83]

Table 1: Modified WHO diagnostic criteria of OLP and oral lichenoid lesions (2003)[74]

Clinical criteria

- Presence of bilateral, more or less symmetric lesions
- Presence of a lacelike network of slightly raised gray-white lines (reticular pattern)
- Erosive, atrophic, bullous, and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa

In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term "clinically compatible with" should be used.

Histopathologic criteria

- Presence of a well-defined, bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
- Signs of liquefaction degeneration in the basal cell layer
- Absence of epithelial dysplasia

When the histopathologic features are less obvious, the term "histopathologically compatible with" should be used.

Final diagnosis of OLP or oral lichenoid lesions (OLL)

To achieve a final diagnosis, clinical as well as histopathologic criteria should be included.

A diagnosis of OLP requires fulfillment of clinical and histopathologic criteria.

The term OLL will be used in the following conditions:

1. Clinically typical of OLP but histopathologically only compatible with OLP
2. Histopathologically typical of OLP but clinically only compatible with OLP
3. Clinically compatible with OLP and histopathologically compatible with OLP

OLP and thyroid disease

Kurgansky, *et al*. in 1994 were the first to report the association of thyroid disease and OLP.[84] Li *et al*[85] in a recent meta-analysis showed a statistically significant difference in the prevalence of thyroid diseases between the OLP and the control population. They showed that hypothyroidism and Hashimoto thyroiditis were the two most commonly associated thyroid diseases.

Among gastrointestinal diseases, OLP has been shown to be associated with celiac disease, ulcerative colitis, and Crohn's disease.[6]

C) Stress and anxiety

OLP has been regarded as a psychosomatic disorder,[14] and an increased rate of psychiatric ailments especially depression and anxiety have been reported in patients with OLP.[86] Stress has also been shown to be a major contributory factor for the acute exacerbations in patients with OLP.[87] A recent systematic review by Cerqueira *et al*. has confirmed the strong association between the prevalence of OLP in patients with psychological disorders.[14]

Histopathology [Figure 6]: Although diagnosis of OLP is often made clinically, biopsy and histopathological examination are needed when it presents with atypical manifestations, or when there is suspicion of dysplasia or malignancy needs to be ruled out.

Histopathological features of OLP were first described by Dubreuil in 1906.[88] Shklar *et al* in 1972[89] reported the characteristic histologic features of dense band like layer of lymphocytic infiltrate in the upper dermis and degeneration of the basal cell layer. The key histopathological features include the following: in the epidermis orthokeratotic hyperkeratosis, parakeratosis, acanthosis, epithelial atrophy, basal cell layer degeneration, and saw-tooth rete pegs. The presence of homogeneous eosinophilic globules is known as colloid bodies, in the degenerating basal keratinocyte layer. In the dermis there is dense, well-defined band-like infiltrate of lymphocytes in the reticular dermis, and the presence of plasma cells and B cells.

The term "lichenoid dysplasia" is used to describe a dysplastic surface epithelium accompanied by a band-like lymphocytic infiltrate in the subjacent lamina propria. It indicates a premalignant process and should not be misconstrued as lichen planus with dysplastic changes.[90]

Immunofluorescence: Immunofluorescence test is one of the most commonly used adjunctive diagnostic methods for the diagnosis of mucosal diseases, including OLP. It can either be done on the biopsy specimen (direct immunofluorescence: DIF) or in the serum (indirect immunofluorescence: IIF). It, basically, detects the presence of autoantibodies.

Direct immunofluorescence: It is considered to be very helpful, especially in cases of OLP showing non-diagnostic histopathological features on biopsy[5], and also in cases presenting clinically as desquamative gingivitis where it is difficult to make the diagnosis on routine histopathological examination.[91] DIF plays an invaluable role in distinguishing erosive/ulcerative form of OLP from other diseases presenting with oral lesions of similar morphology, especially vesiculobullous diseases like pemphigus vulgaris, benign mucous membrane pemphigoid, and linear immunoglobulin A (IgA) bullous dermatosis. In cases of OLP, it classically shows a linear pattern with antifibrogen at dermo-epidermal junction and positive immunofluorescence of cytoid bodies in epidermal basal layer with IgM.[92]

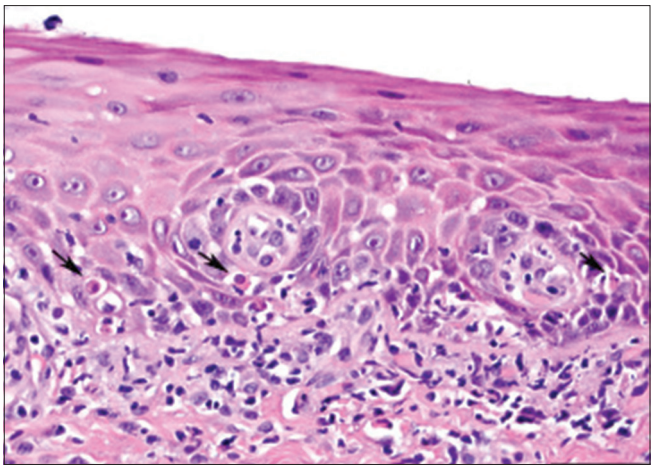

Figure 6: Band like upper dermal lymphocytic infiltrate admixed with few plasma cells

Indirect immunofluorescence: It is not routinely used in the diagnosis of OLP. Lin *et al* have reported the presence of serum anti-basal cell antibodies in more than half of the 63 patients with OLP that they studied.[93]

Patch tests: These are helpful in cases where contact sensitivity to dental material is suspected to be the case of oral lichenoid reaction. The Dental Series Epicutaneous Test Battery (Trolab) of patch test allergens is used commonly. The test substances are applied securely on normal looking skin on the upper back for 72 h. The test is considered positive if a patient develops erythematous, edematous, or bullous reaction at the site of contact with allergen after 72 h of application of the allergen.[90]

Differential diagnosis and prognosis: The differential diagnosis of OLP includes a group of oral lichen planus-like lichenoid (OLL) lesions that may clinically resemble OLP and at times may be difficult to differentiate from OLP clinically. Three main dermatoses included in this group are lichenoid contact lesions, lichenoid drug reactions, and lichenoid lesions of graft versus host disease.[48]

Lichenoid contact reactions have been usually due to the use of dental materials such as amalgam, composite, and dental acrylics.

The commonly implicated drugs for oral lichenoid reaction are dapsone, non-steroidal anti-inflammatory drugs (NSAIDs), sulphonylureas, penicillamine, phenothiazines, gold salts, beta blockers, and oral hypoglycemics. The most reliable method of confirming a lichenoid drug reaction is to record complete resolution of the lesion after the suspected drug is stopped and recurrence of lesions when the patient is administered the same drug again.

Graft versus host disease (GVHD) is a major complication seen in the recipients of allogeneic hematopoietic stem cells or bone marrow transplantation cases. Acute OLL-GVHD is often painful, ulcerated, and presents with marked de-epithelialization, whereas chronic OLL-GVHD presents as whitish hyperkeratotic plaques, with areas of erythema, erosion, or even ulceration.[47]

Diagnosis: Most of the cases of OLP can be easily diagnosed based only on the clinical features, particularly "classic" reticular form, which is also the most common clinical presentation of OLP. However, in some difficult or atypical cases, biopsy for routine histopathology and DIF has to be performed to confirm the diagnosis.

Also, some serum markers are being investigated for their role in diagnosing the cases of OLP. Oxidants and antioxidants level is one of the potential biomarkers being developed to diagnose OLP. Increase in the level of oxidants and reduction in antioxidant levels may indicate the diagnosis of OLP. Also, other potential biomarkers like Gastric Parietal Cell Antobody (GPCA), immunoglobulins like IgA and IgG, and cortisol levels are being used to predict OLP. These biomarkers can be measured in both serum and saliva. And thus, it may help in making the diagnosis of OLP without using invasive procedure.

Elevated levels of several pro-inflammatory molecules (cytokines, stress hormones, etc.) in saliva of patients of OLP that are supposed to play a role in causing lesions of LP as compared to healthy controls have prompted them to be considered for use as biomarkers for diagnosis, disease activity, therapeutic response, and malignant transformation.[25]

A new and innovative field of salivary diagnostics (metabolomics) is emerging that utilizes saliva as an easily, non-invasively accessible source of pro- and anti-inflammatory proteins such as cytokines or stress hormones for screening of oral disorders. It involves identification of one or more biomarkers that can serve as a simple laboratory test facilitating the early detection of OSCC in OPMD patients.[94] Saliva provides a non-invasive, easy, and rapidly accessible source of such biomarkers (various proteins, microbes, cytokines, hormones, etc.) for diagnosis and follow-up of diseases affecting oral mucosa including OLP and oral cancers.

Chitinase-3-like protein-1 (YKL-40) is one of the 18-glycosyl hydrolases, whose levels were found significantly elevated in serum of patients of LP compared to healthy controls. The highest levels were found in patients having CLP and OLP both followed by those having OLP and CLP alone, respectively.[95]

Complications

Infection: Erosive/ulcerative variant of OLP is prone to develop superinfection with candida.[96] It causes severe symptoms and does not respond to treatment, unless the candida infection is treated.

Malignancy: The occurrence of malignancy in OLP has been a controversial topic, with widely varying MT rates reported in the literature (0.2% up to 12.5%), which are up to 60 times higher as compared to the general population[97] Krutchkoff *et al* first linked malignant transformation of OLP with the development of OSCC.[98] Although, it was Francois Henri Hallopeau who first reported OLP-related carcinoma in 1910.[99]

In 2005, the World Health Organization (WHO) classified OLP as a potentially malignant disorder.[100] Most of the recently published have confirmed that the rate of MT is not as high as had been reported in some of the earlier studies. The overall rate of MT in OLP is less than 1% which is much less compared to submucosal fibrosis and leucoplakia.[54]

Besides, tobacco and alcohol consumption, intraoral localization of lesions, different clinical forms, genders, and ages have been reported as other important factors in the malignant transformation of OLP.

The malignancy associated is squamous cell carcinoma (SCC), seen in 0%–5.8% of patients.[101] Age range reported is 56–79 years (mean 70.5 years).[102] Although all OLP forms can potentially become malignant, it is the atrophic and erosive forms that possess the greatest risk for potential malignant transformation.[103] The occurrence of new ulcerated or infiltrated lesions in a long-standing case of OLP are considered to be the clinical red flag of an evolving SCC.

According to one study, 46%–54% of SCC from OLP lesions occur in the buccal mucosa, 30% in the tongue, 16% in the lower lip, and 8% in other sites.[104] The evolution of a benign lesion into SCC may take from 1–11 years.[105] There are suggestions for a more aggressive treatment approach for SCC related to OLP, because it has a greater chance of metastases, and therefore carries worse prognosis.[104]

Apart from monitoring the disease activity, measuring the serum levels of IL 6 is also useful in predicting the prognosis, since it has been found to correlate with the malignant transformation of OLP. It has been shown that in case of malignancy, it induces B-cell and cytotoxic cell differentiation by acting as an autocrine growth factor.[25] Similarly, protooncogene C-MYC isolation in patients with severe

OLP can predict patients with a high risk of progression to OSCC.[106] Detection of inflammatory molecules in saliva or serum is emerging as a novel non-invasive way of detecting development of malignancy in OLP.[25,94-95]

OLP Severity Scoring Systems [Table 2][107]: At least 22 different scoring systems have been developed to grade the severity of OLP. Thongprasom *et al*, probably developed the first scoring system for OLP, referred to as white striae, erythema, and atrophy (WEA), used a simple 0–5 scores for each criteria.[108] Another widely used scoring system developed by Pibooniyom *et al* scores ten sites for reticulations, erythema, and ulceration, commonly referred to as REU system (stands for reticulations, erythema, and ulceration).[109] The scale developed by Escudier *et al.* is more complex, scores 17 different sites, and combines them with activity scores for calculating the final scores[110] The system developed by Malhotra *et al*. does not differentiate between various clinical types of OLP, unlike its predecessors.[111] The newer scales being developed, in general, use more sites, and they also take into consideration the severity of symptoms like pain, for the purpose of calculating the final scores.

Impact of OLP on quality of life (QoL)

Odynophagia, dysphagia, dysgeusia, chronic, relapsing recurrent nature, and fear and anxiety from the risk of MT

Table 2: Scoring systems in OLP

Author	Objective morphological findings	Subjective findings (symptoms)
Thongprasom *et al*., 1992[108]	Scale from 0 to 3: 0=no lesion 1=mild white striae, no erythema 2=white striae with atrophic area (≤1 cm^2)	Scale from 0 to 1: 0=not cured 1=cured: no erythema, no white striae or other symptoms
Pinboonniyom *et al*., 2005[109]	Ten oral subsites Reticular lesions (0=none; 1=presence of white striae) Erosive lesions (0=none; 1=lesion ≤1 cm^2; 2=lesions from 1 to 3 cm2; 3=lesions ≥3 cm^2) Ulcerative lesions (0=none; 1=lesion ≤1 cm^2; 2=lesions from 1to 3 cm2; 3=lesions ≥3 cm^2) For each of the three clinical signs (R, E, U), a score was derived by summation of the scores of all ten areas	No scale
Escudier *et al*., 2007[110]	Seventeen oral subsites Subsite score (A) 0=no lesion 1=evidence of lichen planus 2 = ≥50% of buccal mucosa, dorsum of tongue, floor of mouth, hard palate, soft palate, or oropharynx affected Severity score (B) 0=keratosis only 1=keratosis with mild erythema (≤3 mm from gingival margin) 2=marked erythema (e.g. full thickness of gingivae, extensive with atrophy or oedema on nonkeratinized mucosa) 3=ulceration present The activity score was calculated as the result of multiplying the subsite score A by the severity score B	Numerical rating score The total score was the result of the summation of the activity score and the pain score
Malhotra *et al*., 2008[111]	Five oral subsites Areas involved ≤50% (1) or ≥50% (2) of tongue and buccal mucosa; for lips, gingiva and palate just uninvolved (0) or involved (1) was used A total score was obtained by adding the scores of all subsites Based on the total score, a grade was assigned (Grade 0=0 points; grade I=1–3 points; grade II=4–6 points; grade II=7–12 points) The severity was expressed as: Mild (asymptomatic grade I) Moderate (symptomatic grade I or grade II) Severe (grade III or erosive lesion of any grade)	No separate score was used

in OLP requiring life-long follow-up affect QoL adversely in OLP.[112]

Follow-up: Follow-up of these cases is largely for the early detection of any suspicious change in the morphology, indicative of malignant transformation. Although, various protocols have been suggested varying from once every two months to once a year. At least once a year follow-up visit is recommended, depending on the signs and symptoms. If any change is noticed, the follow-up visits have to be made more often and even biopsy has to be considered.[69] The patients with OLP must be followed for years, preferably life-long to allow for early detection of evolution to SCC, which is the only chance to treat the disease with efficacy.

Recent advances in diagnostics

Several non-invasive diagnostic methods are being investigated to diagnose, follow treatment response, and for early detection and prognostication of the risk or actual appearance of malignancy in LP. They include dermoscopy, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), diffuse reflection spectrophotometry (DRS) and ultrasound (USG).[113]

These *in vivo* techniques allow identification of specific aspects in LP lesions and to correlate them with histological findings. The aim is to improve the accuracy of diagnosis. Their advantages are painless, immediate interpretation, documentation, enhanced compliance and easy repeatability. They are capital-intensive, require special sophisticated equipment, and training. Uses of RCM, OCT, DRS, and USG in LP are still at infancy primarily being employed in research and academic settings.

Recently, mucoscopy which refers to the use of dermoscope for the evaluation of mucosal surfaces has been utilized in the diagnosis of OLP.[114] However, it is still in the developing phase and has not been used to its full potential yet. And, there is a dearth of published literature on its use in oral mucosal lesions. In a recently published study on oral mucoscopy, oral LP was the most common disease.[115] Wherein, the authors reported the findings of Wickham striae (WS), vascular patterns and pigment patterns were considered diagnostic of OLP. WS was reported to appear as shiny, pearly, white structures. Other features of OLP reported were blue-white veils at the periphery of WS and veil-like Structure less area (SLA). The presence of combination of leukoplakia-like areas (LLA), and well-demarcated, brightly erythematous shiny erosions present adjacent to the LLA has been reported in erosive OLP in another study.[116]

Treatment

OLP is chronic, recurrent, relapsing, and many a times resistant condition unlike CCLP that resolves in 2/3rd of patients within two years. Association of OLP with various systemic diseases including thyroid disorders, hypertension, diabetes mellitus, anemia, metabolic syndrome, and dyslipidemia is being increasingly recognized. Psychological factors also play a role in causation/triggering/exacerbation of OLP in many patients and in turn result in psychiatric morbidity (anxiety, depression). Finally, there is a small risk of malignant transformation in some patients. All these factors warrant a thorough work-up and holistic approach in management of OLP. The principal aim of treatment is to resolve painful symptoms of OLP, prolongation of symptoms free period, and potentially reduce the risk of malignant transformation. However, there are no universal guidelines, and therapy varies from individual to individual depending upon their clinical presentation and symptoms.

A. General Measures

The elimination of precipitating or provoking factors is an important initial step to manage symptomatic OLP. The importance of maintaining good oral hygiene and avoiding trauma to oral mucosa needs to be explained to the patient. Depending on the severity of disease, regular personal and dental care, replacement of amalgam or gold dental restoration, avoidance of smoking, spicy food, and alcohol may be indicated for some patient of OLP[117] Biofilm, tarter, damaged filling, and ill-fitted dentures all may worsen lesions. Professional treatment helps in improving the local aggravating factors. Soft brushes and non-abrasive toothpaste are to be used and helpful in few.

B. Medical Treatment

Although, topical agents are generally preferred as they have fewer side effects. However, systemic agents are required for extensive, recalcitrant lesions.

a. Topical Treatment

1. Topical corticosteroid (TCS)

Application of potent and super-potent TCS is the mainstay of treatment in the cases with localized OLP lesions. Orabase or gel formulations have proven to be more effective.[6,7] Different topical formulations (ointment, oral suspension, aqueous solution, pellets, aerosol, or spray, mouthwashes and in adhesive paste formulation) containing clobetasol propionate (0.05%), triamcinolone, betamethasone, fluocinolone, and fluticasone have all been found to be safe and highly effective.[118]

There are many published reports comparing either different topical steroid preparations or vehicles, or both.[7] Both, fluticasone propionate spray and betamethasone sodium mouth rinse are effective in reducing the pain. Similarly, fluocinolone acetonide 0.1% orabase was found to be superior to triamcinolone acetonide 0.1% orabase after 4 weeks of treatment. A novel lipid microsphere-based drug delivery system containing clobetasol (0.025%) has been found to be equally effective as an ointment base.[119] A mouthwash preparation of this molecule also yielded a good outcome.[120] Intralesional triamcinolone acetonide and betamethasone are also found to be efficacious. Pain is the main constraint.[7]

2. Topical Calcineurin inhibitors (TCI)

Both, tacrolimus and pimecrolimus, have emerged as useful alternatives to TCS.[121] In an investigator-blinded parallel group randomized clinical trial, 40 patients with oral LP were assigned into two equal groups to receive either pimecrolimus 1% or triamcinolone acetonide 0.1% paste 4 times daily for a total of 2 months.[122]

In one double-blind randomized controlled trial, tacrolimus 0.1% ointment has been found to be equally effective compared to triamcinolone acetonide 0.1%. Other formulations of tacrolimus 0.1%, such as rinse and powder, have also been successfully used in OLP.[121] Local irritation and burning sensation are the common side effects noticed with TCIs, more often experienced in erosive OLP.[121] Most studies found tacrolimus to be superior to pimecrolimus, whereas few observed vice versa and in some studies no differences were found among these two. A recent meta-analysis concluded that tacrolimus, pimecrolimus, and cyclosporine possessed similar efficacy as TCS, when used in the short-term treatment of OLP.[123] However, tacrolimus showed higher local adverse effects than with TCS. Few mild and tolerable systemic adverse events were reported with TCI's. Tacrolimus 0·1% should be the first drug of choice for the short-term management of recalcitrant OLP. However, well-designed long duration studies are needed to evaluate the long-term efficacy and safety of TCIs.

A recent Cochrane review of TCS, TCIs, placebo, and cyclosporine concluded that delivered topically as adhesive gels or similar preparations TCS (clobetasol propionate > triamcinolone > placebo) may be more effective than placebo for reducing the pain of symptomatic OLP, whereas the evidence to suggest that calcineurin inhibitors, specifically tacrolimus, may be more effective at resolving pain than corticosteroids is very weak. Although, there is some uncertainty about adverse effects and clinical response to tacrolimus that showed conflicting results.[124]

3. **Topical Cyclosporine** in OLP was found to be effective a double-blinded placebo-controlled trial[125]. However large, controlled trial comparing with clobetasol propionate (0.1% in orabase) found it to be inferior.[126] Cyclosporine should be formulated in orabase as other approaches as bioadhesive base and mouth wash have no or partial benefit.[7]
4. **Topical retinoids** mostly tretinoin 0.05% have been tried in OLP with good effect, but generally too irritating to recommend.[7]

5. Miscellaneous topical agents

Pharmacognosy-based plant-derived agents such as purslane, curcuminoids, aloe vera, propolis, and topical tocopherol have been tried with varying success. They have demonstrated to be clinically efficacious but more clinical studies needed to determine their role.[6,10,118,127]

b. Systemic Therapy

In cases that are recalcitrant and there is no satisfactory response to topical agents, systemic therapy can be tried after proper evaluation with agents having low risk of systemic side effects.

1. Systemic corticosteroids

Systemic corticosteroids, methylprednisolone, or prednisolone is the most effective treatment modality for patients with diffuse recalcitrant erosive OLP or multisite lesions with erosion. But they should be given for short periods only to prevent the long-term side effects. Prednisolone is administered at a dosage of 0.5-–1 mg/kg body weight for 3–6 weeks, and is then gradually tapered.

Oral mini pulse (OMP) therapy (betamethasone 5 mg/day on two consecutive days every week) is also effective and safer way of administering OCS in OLP.[111] The authors compared OMP with triamcinolone 0.1% paste and found that both are effective; however, the response is little faster with betamethasone pulse, while side effects were mild and transient.

2. Oral Retinoids

Acitretin is the only retinoid approved for LP treatment with level A evidence, as it has been shown to be effective in double blind study.[128] The risk benefit ratio needs to be assessed before starting with proper investigations especially in women of child bearing age group.[118] Kunz *et al* found oral alitretinoin 30 mg OD for 24 weeks to be effective in reducing disease severity in ten OLP cases refractory to standard therapy in a prospective open-label single arm pilot study.[129] Primary end point was reduction in signs and symptoms measured by the Escudier severity scoring system.

3. Oral Cyclosporine

It has been tried in dose of 3–5 mg/kg/day and found to be effective in different studies mostly in erosive OLP. Proper evaluation and monitoring for hypertension, renal, and other side effects of cyclosporine are needed.[130]

4. Methotrexate

In a case series, 7.5-20 mg once weekly methotrexate showed the most encouraging results.[117] Despite all evidence, large prospective controlled trials are needed to establish optimal dosage and duration of methotrexate therapy. Lajevardi, *et al*.[131] found oral methotrexate 15 mg once a week for 24 weeks in 18 patients of recalcitrant erosive OLP that had not responded to at least one previous oral or topical treatment to get benefit.

C. Novel treatments and techniques

A number of novel pharmacologic and non-pharmacologic treatments have been tried and reported as efficacious in few or small number of patients as an alternative to existing immunosuppressive and immunomodulatory agents anecdotally. They include photodynamic therapy, low-level light[132], lasers,[8] biomolecules such as platelet-rich plasma[9], topical thalidomide, topical hyaluronic acid,

piperine derived from black pepper, aloe vera gel, topical and oral curcuminoids,[10] zinc (oral and topical), selenium, and probiotics.[133] Randomized controlled trials involving large number of patients and for longer duration are needed to establish an evidence-based role for these modalities in treating LP in its myriad manifestations.[6] Although the majority of them still do not qualify to be targeted therapy for LP, they do offer an important advantage of being steroid sparing. In view of the oxidative stress in the oral cavity playing a role in causation of OLP, supplementing with antioxidants has also been recommended although more studies are needed.[13]

There are anecdotal reports of use of oral tacrolimus, sirolimus, intravenous immunoglobulin, biologics (secukinumab, ustekinumab, apremilast, JAK inhibitors, etc.) in severe recalcitrant cases of multi-drug-resistant OLP.[134-136] Effective treatment of OLP definitely improves oral and general health QoL in patients and regular long-term follow-up helps in early detection and prevention of malignant transformation that should be emphasized to the patient.[137]

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Conflicts of interest

There are no conflicts of interest.

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