Oral lichen planus and its recent management: A review
Iqbal M. A., Yesmin S, Maaisha F, Ibrahim S, Gotame P

AFFILIATION:
1. Dr. Md. Ashif Iqbal 
Associate Professor, 
Department of Periodontology & Oral Pathology 
Update Dental College, Dhaka, Bangladesh
2. Dr. Suraiya Yesmin 
Lecturer 
Department of Periodontology & Oral Pathology 
Update Dental College, Dhaka, Bangladesh
3. Dr. Fathimath Maaiasha 
Intern Doctor 
Department of Periodontology & Oral Pathology 
Update Dental College, Dhaka, Bangladesh
4. Dr. Shaama Ibrahim 
Intern Doctor 
Department of Periodontology & Oral Pathology 
Update Dental College, Dhaka, Bangladesh
5. Dr. Puja Gotame 
Intern Doctor 
Department of Periodontology & Oral Pathology 
Update Dental College, Dhaka, Bangladesh

ABSTRACT:
Background: Oral Lichen Planus (OLP) is one of the most common dermatological disease which is present in the oral cavity. It is a chronic autoimmune, mucocutaneous disease that affects oral mucosa as well as the skin, genital mucosa and other sites of the body. Method: In this review study, various databases such as Google Scholar, PubMed Central, Hinari and Cochrane library were searched for articles with keywords lichen planus, oral lichen planus, premalignant lesions, management of Lichen planus. Articles were searched from January 2015 to 5th November 2020. Result: From the 34 articles obtained after reviewing the abstracts, most relevant 32 articles were evaluated in this study. Conclusion: The etiology, pathophysiology, clinical presentation, histopathological features, diagnosis and various management for oral lichen planus is discussed. This article also compares the existing and the most recent treatment modalities that are available throughout the world that are discussed in the literatures. However, more intensive studies must be carried out to find the best treatments which are cost-effective in the long run.

KEYWORDS: lichen planus, oral lichen planus, premalignant lesions, Management of oral Lichen planus

INTRODUCTION:
Oral lichen planus is an auto immune chronic mucocutaneous disease. The prevalence rate of OLP is reported as 0.5–2.2% with a malignant transformation rate of 1.09% 
It usually affects middle-aged women but occurs in both sexes with a female to male ratio of 1.4:1. Lichen planus can affect the skin, hair, scalp, esophagus, nails, genital areas and oral mucosa. Oral lichen planus can be seen in the mucous membrane of buccal mucosa, tongue, palate and tongue. OLP is commonly seen as symmetrical and bilateral lesions with multifocal involvement in the oral mucosa. It can also show periods of recurrence and recovery. There are six clinical patterns of oral lichen planus. They are reticular, plaque-like, atrophic, erosive/ulcerative, papular and bullous form. But the most common is reticular, papular and plaque forms which are usually painless and similar to other white disorders such as leukoplakia, and appears as white hyperkeratotic striae or plaques. Erosive and atrophic forms can cause discomfort, pain, burning sensation and intolerance to spicy and hot food. Also long lasting form of erosive OLP is associated with a significant potential for malignant transformation with an estimated risk of 0.5-2%.

Citation
DOI: https://doi.org/10.3329/updcj.v10i2.50179
Prominent lymphocyte penetration at the epithelium connective tissue interface, hyperparakeratosis, cytid body, acanthosis and hydropic epithelial layer transition are some histopathologic characteristics of OLP.  

So far, OLP appears to be an incurable disease, and most clinical practice focuses on inflammation control and reduction. Despite multiple treatment modalities, most cases of OLP appear to be more resistant to treatment, such as topical steroids (considered as the first line of treatment), systemic steroids, retinoids, calcineurin inhibitors, lasers, phototherapy, immunosuppressants, natural agents such as curcumin, aloe vera, vitamin A, laser biomodulation. Although there are many proposed treatment modalities, a permanent cure is not yet available. Unfortunately, most of the therapeutic modalities are associated with adverse effects; some of them are serious, which limits their use.

The main aim of this article is to combine the latest information and findings regarding oral lichen planus

ETIOLOGY

The specific etiology of oral planus lichen is uncertain. But some potential initial triggering factors which determine keratinocytes destruction are considered to be the following: such as, inducers of cell-mediated hypersensitivity, autoimmune response to local antigens, stress, and microorganisms. The manifestation of disease plays an important role in genetic and environmental factors, such as anxiety, pathogens (e.g. HPV16, HSV17), & changes in the mucosal microbiota (e.g. Candida species, various other bacteria) Medical conditions such as auto immune disease, diabetes, chronic liver disease, intestinal diseases, increases cholesterol level, hypertension and infections can also cause onset of oral lichen planus.

Systemic medicines can also contribute to the production of oral lichenoid reactions (OLR) and lichen planus, such as nonsteroidal anti-inflammatory drugs, antihypertensives, and oral hypoglycemics. Amalgam, copper, , and nickel from dental restorative content can also be related to the localization of OLR in some patients.

The table below briefly describes some of the etiological features of oral lichen planus.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic background</td>
<td>Genetic polymorphism of cytokines, IFN-gamma, increase in frequency of 308A TNF-alpha allele [SKIN]</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>Stress and anxiety Increase in salivary cortisol and stress</td>
</tr>
<tr>
<td>Trauma</td>
<td>Koebner phenomenon</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>HCV Hypertension, diabetic (Grispan syndrome) Thyroid dysfunction GVHD</td>
</tr>
<tr>
<td>Oral lichenoid reactions</td>
<td>Dental materials systemic medications</td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGY

While various studies have shown that OLP is a widely recognized chronic inflammatory autoimmune response-driven disorder, the precise pathogenesis remains unknown. Some researchers found that emotional stress, infection and hypersensitivity contribute to OLP onset. There has also been reported genetic vulnerability by haplotypes, such as HLA – A3, -A5, -A28, -B8, -B16, -Bw35, -B7, -B18, -Aw19, -Cw8 associated with different variants of LP.

OLP is considered a T cell-mediated autoimmune disorder in which apoptosis of basal epithelial cells is caused by clusters of differentiation 8 (CD8)+ T cells. Its function is uncertain, but in the exacerbation and continuation of the oral lichen planus, a cytokine complex network (such as TNF- α, IFN-γ, TGF-β, IL-1, 2, 4, 5, 6, 8, 10, 12, 17, 18, and IL-22) plays a significant role. Other researchers suggest that the cell-mediated immune system starts with the expression of keratinocytes antigen; this step is accompanied by the movement of T cell lymphocytes directly activated by an antigen binding to the main histocompatibility complex (MHC)-1 on keratinocytes or activated CD4 + lymphocytes. In exchange, the activated CD8 + T cells kill the basal keratinocytes by tumor necrosis factor (TNF)-alpha, Fas-FasL-mediated or granzyme B-activated apoptosis. Researchers conclude that oxidative stress influences molecules and pathways involved in the recruitment of lymphocytic infiltrates in OLP lesions and apoptosis induction, including ICAM-1, p53, TNF-alpha, NF-kB, Fas / FasL and granzyne B pathways.

Others assume that OLP’s inflammatory pathways activate T-cells to release reactive oxygen species (ROS) alone or to enhance ROS production by activating keratinocytes, causing damage to neighboring cells.

Interleukin and renin has been reported to play a potential pathogenic role in autoimmune disease. In fact in the biopsies and serum of OLP patients, elevated levels of IL-17 have been identified. IL-17 can activate different cells to release potent inflammatory molecules, such as epithelial cells, fibroblasts, and chondrocytes. In response to stimulus, oral keratinocytes are able to produce renin. The activated NF-kB pathway greatly increases the production of renin, which is dramatically enhanced in the epithelial layer and lamina propria of OLP keratinocytes. Immunohistochemistry staining data showed that renin was present in cytoplasm rather than the nucleus. In the microenvironment of inflamed tissues, some recent studies indicate that renin is strongly elevated, and RAS plays a role in activating Th17 cells and increasing the production of IL-17.

To induce CCL-20, IL-8, and TNF-a development, exogenous IL-17 has been documented in oral keratinocytes. Previous experiments have shown that elevated levels of IL-17 mRNA and protein are found in OLP relative to unaffected samples. There may be a crucial role in OLP disease in indicating IL-17.

Website: https://www.banglajol.info/index.php/UpDCJ
Interestingly, in erosive OLP patients, serum IL-17 concentrations are higher than in the non-erosive subtype, indicating a favorable association between IL-17 levels and OLP severity. By destroying the extracellular matrix and causing apoptosis of oral keratinocytes, over expression of renin and IL-17 in OLP can influence the onset and pathogenesis of this disease.

Decreased renin development has been associated with genetic or chemical involvement of the NF-kB pathway. The active NF-kB pathway is identified as mediated by pro-inflammatory cytokines. Chinese researchers have found that the signaling of vitamin D / VDR inhibits the NF-κB pathway and also improves MicroRNA-26, 27 a / b production. As a consequence, epithelial cell apoptosis and the risk of OLP lesions are decreased.

**CLINICAL FEATURES:**

Lichen planus is a distinct condition with normal colour, morphology and distribution, representing skin and mucosal lesions. LP affects about 0.5-2% of the general population, especially women, and occurs most frequently in middle age. Usually, numerous lesions occur in the disorder, often of bilateral and symmetric distribution. The classification of Andreasen distinguishes six OLP clinical manifestations, including reticular, plaquelike, atrophic (erythematous), erosive-ulcer and erosive. It may occur alone in the mucosa of the oral cavity, alone in the skin, concurrently in the oral cavity and skin, or in other extra-oral locations, such as the scalp, esophagus, nails, and genitals. Erythematous lesions are frequently associated with reticular lesions, while both reticular and erythematous lesions are associated with erosive lesions in most cases. In addition, within the mouth, in the buccal and lingual mucosa and on the dorsal tongue, lesions are prominent. Clinically, cutaneous lichen planus is distinguished by purple, polygonal, pruritic papules on the flexor surface of the wrist, shins, trunk, and medial thighs, mostly hidden by Wickham striae. In around one third of cases, a generalized incidence of oral frequently associated with discomfort and burning symptoms and can cause issues with feeding, communicating, and swallowing. Moreover with an expected risk of 0.52 percent, erosive longlasting OLP is associated with a substantial malignant transformation potential. Of all cases, there should be a differential diagnosis of burning mouth syndrome (BMS). Burning sensations and discomfort in the tongue and/or oral mucosa are characteristic signs of BMS. After ingestion of food and liquid, these symptoms may change, but are, however, constant for a duration of 4-6 months. Xerostomia, dysgeusia, metallic taste, mood swings, and variations in chemosensory perception are additional signs linked to BMS. The key distinction between OLP and BMS is that in patients with BMS, abnormal variations in the oral mucosa are not found. The reported incidence of malignant transformation of OLP ranged from 0 to 10 percent.

A new metaanalysis has found that 1.1% of OLP lesions advance to OSCC, with a higher occurrence of cigarettes, alcohol users and hepatitis C virus infected individuals. Erosive OLP tends to be the form with the highest frequency to advance to OSCC. Malignant transformation happens most often in lesions that are found on the tongue. Muñoz et al. also shown that it takes an average of 5.5 years to turn OLP lesions into an existing OSCC. The clinical features are summarized in [Table 1.]

<table>
<thead>
<tr>
<th>Table 1: Clinical features of oral lichen planus</th>
</tr>
</thead>
<tbody>
<tr>
<td>RETICULAR</td>
</tr>
<tr>
<td>EROSIVE</td>
</tr>
<tr>
<td>ULCERATIVE</td>
</tr>
<tr>
<td>PLAQUE LIKE</td>
</tr>
</tbody>
</table>

The progression of OLP is marked by periods of recovery and exacerbation, where it will last several weeks or even months with both the signs and the symptoms. Classical cutaneous LP is self-limited and typically resolves within 6 (> 50 percent) to 18 months (85 percent). Some of the infected patients can be fully asymptomatic (about 20 percent). OLP diagnosis can be made clinically in many cases, particularly when viewed in reticular form. Leukoplakia subtype, erythroplakia, lichen sclerosis, pemphigoid lichen planus, lupus erythematosus, linear IgA syndrome, chronic ulcerative stomatitis, pemphigoid mucous membrane, and also the second stage of syphilis. A biopsy can be useful in such cases for histopathological evaluation and, if possible, for immunohistochemical analysis.

[Figure: Reticular, Plaque like, atrophic and erosive type of lichen planus from left to right and upper to lower]
within the epithelium. A rete ridge resembles of progressive remodeling over time, resulting in decreased thickness and, rarely, tissue are the microscopic criteria for lichen planus. The epithelium undergoes kertinocyes

Histopathology: Hyperkeratosis, basal layer vacuolization of apoptotic keratinocytes and a T cell infiltrate at the interface of the epithelium-connective tissue are the microscopic criteria for lichen planus. The epithelium undergoes progressive remodeling over time, resulting in decreased thickness and, rarely, a rete ridge resembles of saw tooth. There are growing numbers of T cells within the epithelium.

MANAGEMENT AND TREATMENT.
Management of OLP should be done in a systematic manner. The first step is to develop a history-based diagnosis, clinical evaluation and complex histo-pathology testing, direct immunofluorescence (DIF), indirect immunofluorescence (IIF), skin patch testing 21. The second stage is to advise the patient of the following: OLP is a persistent condition with predicted flare-up times and symptom-free periods; each patient will have variations in disease activity 21. The targets of therapy are to relieve unpleasant signs, eradicate ulcerative lesions, decrease the risk of oral cancer, prolong symptom-free times and promote proper oral and dental hygiene 21. Owing to its recalcitrant disposition and also its idiopathic etiology, multiple drugs will need to be tried. At present, topical and systemic immuno- suppressants are typically administered to relieve clinical symptoms, but most of the cases of OLP tend to be more persistent and more resistant to treatment despite of many treatment modalities like topical and systemic steroids, anti-inflammatory coating gels, topical calcineurin inhibitors, retinoids and immunosuppressants. While some of these leave significant side effects such as dysgeusia, tachyphylaxis, oral mucosa thinning, adrenal suppression, systemic absorption and secondary candidiasis up on long term management 3,5,6,10,11. Hence numerous studies are being carried out throughout the world to find alternative treatments for OLP using non-pharmacological approaches and other therapeutic strategies. Topical steroids are considered as the first line of treatment as well as the gold standard in OLP treatment for decades 3,5,6,10,11. In mild cases of OLP, topical steroids can be used but systemic corticosteroids must be given in cases where topical corticosteroid doesn’t work, such as in recalcitrant, erosive and erythematous OLP. Here, 40-80 mg of prednisolone is prescribed for 5-7 days 5. Some immunosuppressants and immunomodulatory agents are indicated in cases of contraindications for systemic steroids (breast-feeding, herpetic diseases, glaucoma, breastfeeding, HIV, asthma, diabetes mellitus, or hypertension): calcineurin inhibitors (cyclosporine, tacrolimus, pimecrolimus), mycophenolate mofetil, efalizumab 21. Cyclosporine can be used as a mouth rinse. However due to its high cost, it should be reserved for recalcitrant cases. Tacrolimus is a more powerful inhibitor of calcineurin that can be used in the treatment of recalcitrant and erosive OLP safely and efficiently 5,21. It has an immunosuppressive effect similar to cyclosporine and can readily penetrate into the mucosa. It is highly advised to use it two times/day (ointment of Protopic 0.1%) 21 for a limited period of time because of its ability to facilitate malignant transformation in long term use 21. When steroids are contraindicated, Dapsone, a steroid-sparing medication with reduced side effects (usual adult dose of 100 mg a day for 3 months), is an important medicine in erosive OLP 21. In case of isolated plaques and non healing erosive OLP, surgical excision is recommended 5. In clustered erosive and symptomatic OLP, free gingival grafts were used, indicating a complete eradication of the disease after 3.5 years 5. Micronutrients, like antioxidants, modify the role of the immune system and are perceived appealing substitutes of negligible side effects while handling OLP 11. Oral lichen planus being hypothesized to be an autoimmune disease, several researches have been carried out to treat lichen planus by micronutrients including antioxidants that modify the immune system function. Such studies involve the impact of vitamins A, D, E 3,11

Vitamin A: Topical retinoids like tretinoin, isotretinoin or fenretinide have been reported to induce transient reversal of white striae in OLP. However, relative to topical corticosteroids, topical retinoids are usually less effective since they are associated with side effects such as cheilitis and elevated serum triglyceride and liver enzyme levels 5,21

Vitamin D: One study showed that subjects who took vitamin D supplements in addition to the routine treatment improved the clinical appearance of the lesion in the 1st week and completely disappeared on a period of 4 weeks. In another study of OLP treatment, 3 groups of patients were put on psychiatric counseling and vitamin D along with topical corticosteroid. The result of this study showed that patients receiving vitamin D supplements with or without the psychiatric counseling, improved their symptoms 5.

Website: https://www.banglajol.info/index.php/UpDCJ
**Vitamin E**: In another clinical trial, adjunctive systemic use of vitamin E with topical triaminolone acetonide adhesive paste has demonstrated positive results without any side effects\(^{11}\).

There are some alternative non-pharmacological treatments available such as PRP, PDT, laser, and ozone therapy\(^{5,21}\) recently emerged as a new and futuristic therapeutic modality, specially in severe cases and patients who are not reacting to conventional treatments\(^3\).

In PRP (platelet rich plasma) patients own plasma is used for the treatment. PRP showed to be effective in decreasing the symptoms and improvement in clinical signs of OLP, which was resistant to conventional therapy\(^3\). A case report of erosive OLP which showed resistance to conventional therapy was efficiently treated by PRP. There was significant reduction in patient’s symptoms and the clinical presentation of the lesion after 1st week and the lesion was completely regressed in terms of size and inflammation by the 4th week. On the follow up visit after 6 months, no recurrence of the lesion was observe\(^3\) The effect of PRP gel with cyclosporine mouthwash and retinoic acid lotion on various OLP phenotypes was contrasted in a pilot study. They concluded that PRP could be used in the erosive form, which proved to be successful once a week when implemented\(^4\).

In Photodynamic therapy, a photosensitizing compound (methylene blue), triggered by laser light at a certain wavelength, is used in photodynamic therapy to kill the targeted cell using powerful oxidizers that trigger cell destruction, membrane lysis and protein inactivation, and has been successfully used to relieve OLP symptoms in adult patients\(^5,23\). A systematic review of the effectiveness of (PDT) in symptomatic OLP treatment, however, revealed contradictory findings. Two trials, for instance, documented comparable efficacy of PDT and corticosteroids\(^14,25\).

Laser treatment trends to be more effective in treating painful erosive OLP. In contrast with topical super-potent corticosteroid numerous experiments have documented the effect of laser therapy on erosive OLP, including the use of 980 nm laser diode\(^9,13\). Carbon dioxide laser evaporation, pulsed diode laser photocoagulation with 980 nm pulsed infrared rays, low-dose 308 nm laser and UV rays. Their consequence is the degradation of the superficial epithelium (containing protein denaturation of the target keratinocytes); in addition, the diode laser also kills the underlying connective tissue along the epithelium with the inflammatory compound\(^13\). While several studies have reported positive findings, the efficacy of laser therapy in OLP has yet to be proven\(^9\).

Use of ozone (O3) has also gained a lot of interest in treating OLP. O3 is a very strong antioxidant that is being used as a disinfectant and a germicidal agent used in medical purposes. It also increases blood circulation and has healing effect\(^{10,23,26}\). A case-controlled study showed that Compared to the group treated with corticosteroids alone, lesion size, Thongprason score and discomfort dramatically reduced in the group treated with ozone and topical corticosteroids\(^{10}\). This was supported by another two studies carried out by Mostafa et al and Bayer et al (23,26). Ozonized water seems to be effective as an adjunct therapy, in combination with topical corticosteroids, for the treatment of eOLP\(^{10}\). Other natural agents like, lycopene, cur-cumin, purslane and aloe vera have also been assessed for management of OLP with varying outcomes\(^3,11\).

**CONCLUSION.**

Oral lichen planus is a chronic inflammatory condition of uncertain etiology. Patients who have a history of chewing tobacco, areca nut chewing, smoking and alcohol consumption should be monitored constantly as there is a higher chance of the lesion to undergo malignancy specially in case of atrophic and erosive type. Depending on the form and severity of the lesion and doctor’s own preference, the treatment could be non-surgical or surgical. However, more intensive studies must be carried out to find the best treatments which are cost-effective in the long run.

**REFERENCES:**

PMid:32678513

PMid:29534707 PMCid:PMC5851270


PMid:31803979

PMid:29984679 PMCid:PMC6087560


PMID:28190112