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IP Indian Journal of Clinical and Experimental Dermatology

Journal homepage: www.ijced.org/

Review Article

Lichen planus – A refractory autoimmune disorder

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ARTICLE INFO

Article history:
Received 25-01-2023
Accepted 04-03-2023
Available online 04-04-2023

Keywords:
Oral lichen planus (OLP)
Autoimmune
Steroids
Methotrexate
Tacrolimus
Phototherapy
Surgical excision
Laser usage

ABSTRACT

Lichen planus (LP) is a chronic inflammatory mucocutaneous disease of unknown aetiology with an estimated incidence of 0.5%–4.0% having a female preponderance at a ratio of 1.5:1. Oral lichen planus (OLP) is commoner than the cutaneous form and tends to be more persistent and more refractory to the treatment. The prevalence of oral lichen planus in Indian population is around 3% with more female predilection. Oral lesions occur in 50%–70% of the patients with lichen planus. LP is considered to be a T-cell-mediated autoimmune skin disease, in which CD8+ cytotoxic T lymphocytes are major mediators. TNF-α and IL-10, interferon-gamma (IFN-γ), IL-4, and IL-8, have been suggested to have an important role in the pathogenesis of OLP. The complications of Lichen Planus include post-inflammatory hyperpigmentation, scarring alopecia, dyspareunia, oesophageal stenosis & possible malignant transformation. Mucocutaneous site biopsy can confirm the diagnosis when taken from the edge of a plaque. There is no cure for Lichen Planus, the management is often performed with the use of antihistamines, corticosteroids, retinoids, immunomodulators, phototherapy and immunosuppressives. Inconsistent results are shown by griseofulvin and chloroquine derivatives. (further prospective studies are needed).

1. Introduction

Lichen planus (LP) typically presents as pruritic, polygonal, violaceous flat-topped papules and plaques. LP has a typical symmetric distribution that favors flexural surfaces of the forearms, wrists, and ankles; the dorsal surface of the hands; the shins; trunk; and sacral region.[1]

1.1. Types

Oral lichen planus (OLP) is a chronic mucocutaneous disorder of stratified squamous epithelium of unknown aetiology which affects oral and genital mucous membranes, most common between ages of 30 – 60 years, with greater preponderance in females. OLP is considered a potentially malignant disorder that shows 0.5% to 2% of malignant transformation. The causes attributed are poor oral hygiene,[2] tobacco which supports tissue destruction in OLP through irritation by elevating levels of TNF, PGE_2, neutrophil elastase, and MMPs, along with the vasoconstrictor effect.[2] H. pylori infection (common in dental plaques) significantly correlated with the pathogenesis of erosive OLP. Persistent survival of H. pylori within gastric mucosa induces dysregulation of immune system[3]

1.2. Pathogenesis

Lichen planus is a T-cell mediated autoimmune disease.

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https://doi.org/10.18231/j.ijced.2023.003

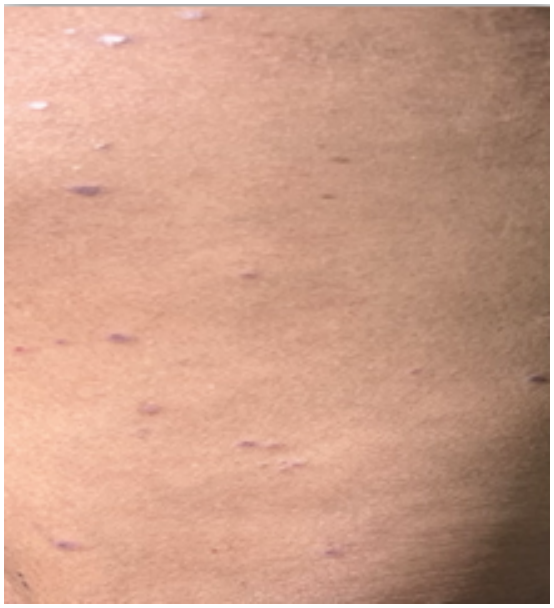

Fig. 1: Lichen planus

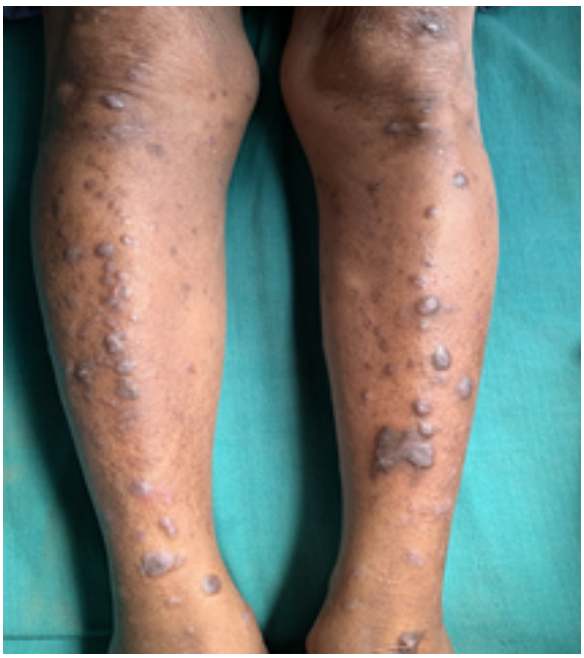

Fig. 2: Koebner phenomenon

CD8 + T cells trigger apoptosis of the basal cells of the oral epithelium. The activated CD8 + T cells in turn lyse the basal keratinocytes by releasing tumor necrosis factor (TNF)-α, there is more expression of the vascular adhesion molecules (VAM), that is, CD62E, CD54, and CD106, by the endothelial cells. Raised levels of IL 17 have also been reported. The JAK/STAT pathway, is activated by which cytokines downstream their inflammatory signal.[4,5]

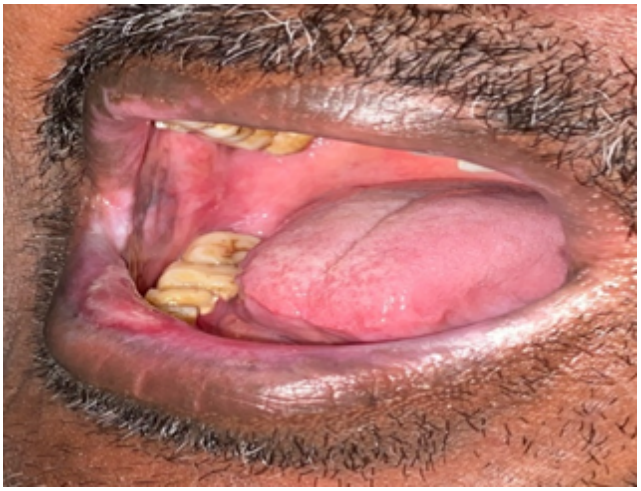

Fig. 3: Erosive lichen planus

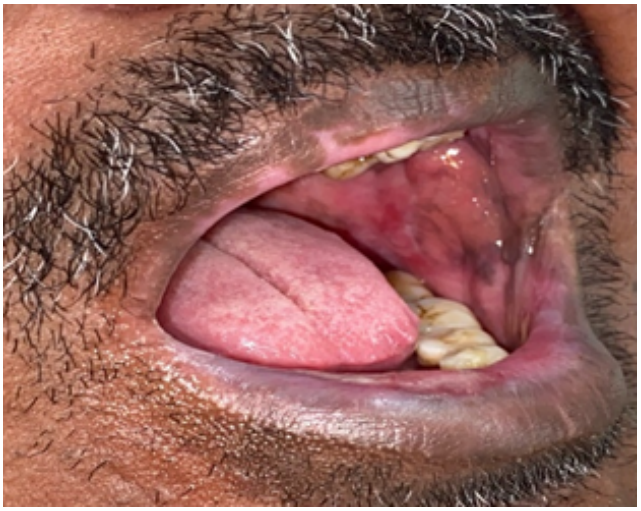

Fig. 4: Wickams striae and Post inflammatory hyperpigmentation

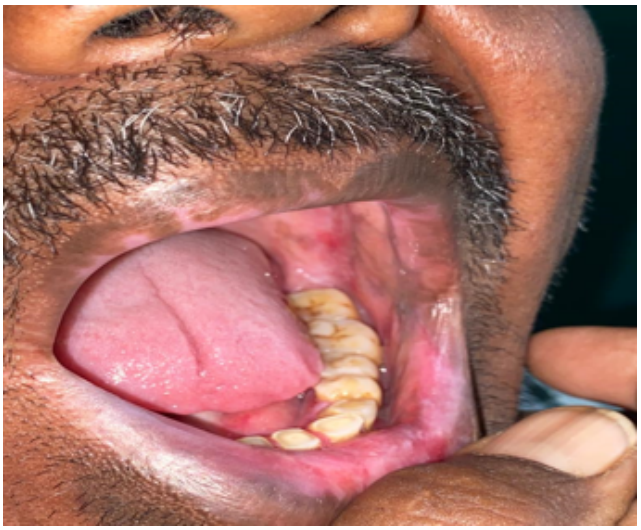

Fig. 5: Extensive LP of oral cavity

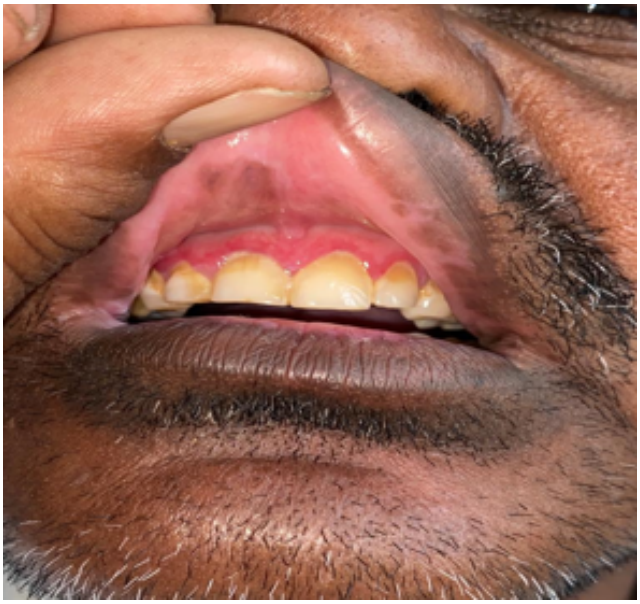

Fig. 6: Upper mucosal Involvement

The differential diagnosis of erosive OLP includes squamous cell carcinoma, discoid lupus erythematosus, benign mucous membrane pemphigoid, pemphigus Vulgaris, chronic cheek chewing, lichenoid reaction to dental amalgam or drugs, graft-versus-host disease (GVHD), hypersensitivity mucositis and erythema multiforme and benign candidiasis[6]

LP has an association with autoimmune disorders such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, and thymoma, bowel diseases such as coeliac disease, ulcerative colitis, and Crohn's disease, food additives such as cinnamon, viral infections such as human papillomavirus (HPV), Epstein Barr virus (EBV), human herpes virus 6, human immunodeficiency virus (HIV), factors such as anxiety and stress, can precipitate LP. Betel nut chewing, psoriasis, urolithiasis, diabetes and hypertension, drugs such as NSAIDs, beta blockers, sulfonylureas, some angiotensin-converting enzyme (ACE) inhibitors, and some antimalarials, can precipitate Lichenoid reactions. HLA-A3, A11, HLA-DR9, and Te 22 antigens have shown positive associations.[7]

The other clinical variants of LP are: Nail LP appearing in later life, involving fingernails more predominantly. Pitting of the nail matrix and trachyonychia is commonly observed. Nail LP occurs in 10% of patients.[8,9] Linear LP where papules along a line or band pattern are observed. Annular LP lesions clinically present as red to purple circular macules or plaques with raised borders with or without central atrophy Atrophic LP is one of the rarer variants of LP and typically affects the legs, with progressively enlarging papules with central atrophy. Hypertrophic lichen planus (HLP) is characterized by hyperkeratotic plaques and nodules. Inverse, Bullous, Eruptive variants are also observed. Lichen planopilaris (LPP) involves hair follicles. Actinic LP, affects sun-exposed areas of the skin. Vulvovaginal LP most commonly affects women in their late 50s or early 60s., similarly, Penile LP affects elderly males.

1.3. Diagnosis

Brocq′s phenomenon is a condition where there is a subepidermal haemorrhage, occurring on careful scraping of a classical lesion of lichen planus.

Histopathology of Typical papules of lichen planus is used to confirm the diagnosis which shows (1) compact orthokeratosis with very few, if any, parakeratosis that is important for diagnosis, (2) wedge-shaped hypergranulosis with coarse and abundant keratohyalin granules, (3) irregular acanthosis giving rise to dome-shaped dermal papillae and to pointed pressure saw-toothed rete ridges, (4) damage to the basal cell layer with bacillary degeneration and apoptosis of the basal cells giving rise to characteristic round Eosinophilic apoptotic bodies and (5) a band like dermal lymphocytic infiltrate.

Dermoscopy allows visualisation of wickham striae in most cases. A network of white lines with red globules along the periphery is the classic finding.

OLP near dental restoration prompts patch testing to determine if any allergy to one of the metals used is associated.

Direct immunofluorescence is helpful in differentiating lichen planus and lupus erythematous.[10]

2. Dermoscopy showing the lesions of Lichen Planus

2.1. Treatment options

LP has a highly unpredictable course, typically clears spontaneously within 24 months, so treatment is aimed at reducing pruritus and early resolution. Restricted or limited LP would require first-line treatment with topical steroids. Inadequate response to topical steroids may be augmented with intralesional corticosteroids. For diffuse LP, first-line treatment is oral corticosteroids. If no change is seen, second-line therapy should be considered. Second-line therapy may include isotretinoin (10 mg twice daily for 2 months), acitretin, PUVA, UVB, topical calcineurin inhibitors, or methotrexate. Third line treatment may include trimethoprim-sulfamethoxazole, griseofulvin, terbinafine, antimalarials, tetracyclines, ciclosporin, mycophenolate mofetil, azathioprine, biologics such as etanercept, adalimumab. Enoxaparin or LMWH has been so far evaluated for its clinical efficacy in LP.

Oral LP may spontaneously resolve within 5 years, but many cases are chronic which never resolve. Asymptomatic oral LP usually not treated as the side-effects with treatment would overweight the benefits. Remission

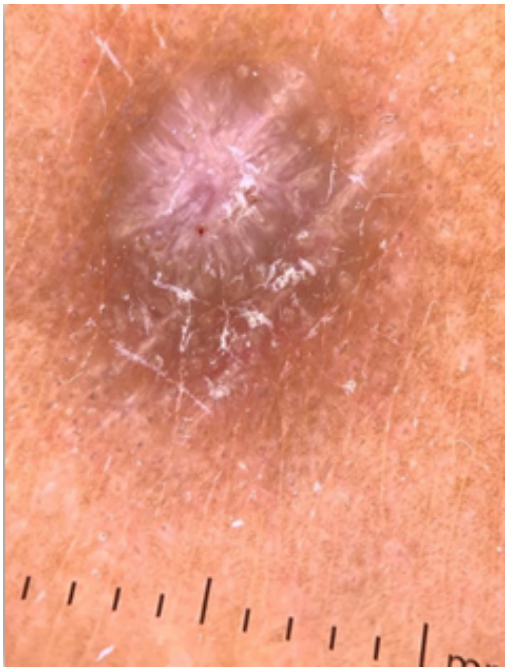

Fig. 7: Classic lichen planus

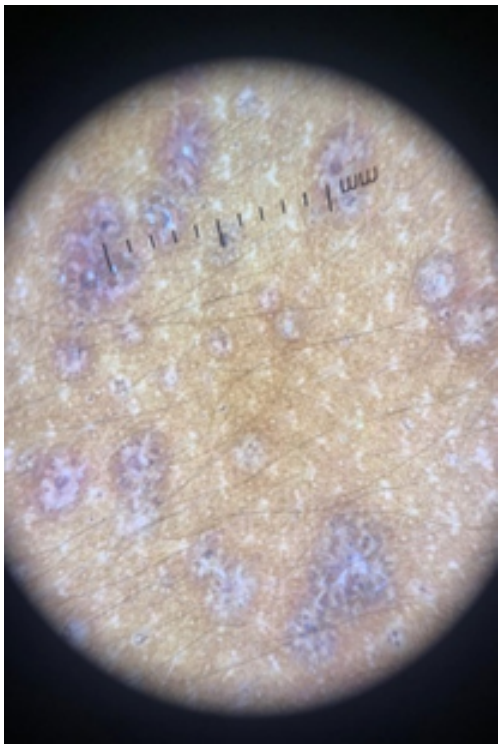

Fig. 8: Generalised lichen planus

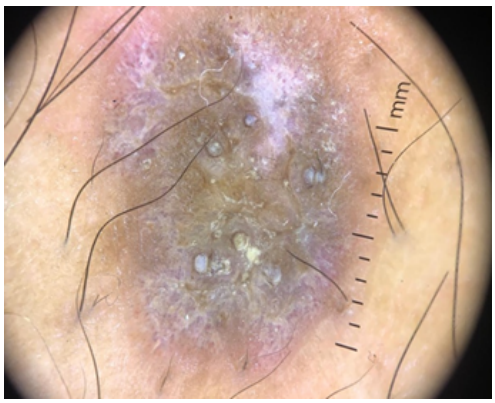

Fig. 9: Hypertrophic lichen planus

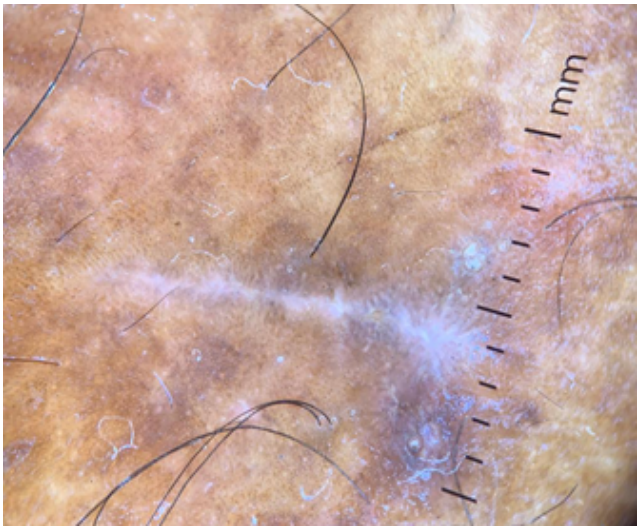

Fig. 10: Koebners phenomenon

Table 1: Lichen planus management

First line	• Topical corticosteroids
	• Oral antihistamines
	• Immunomodulators
	• Topical minoxidil
Second line	• Systemic corticosteroids
	• Oral retinoids
	• Phototherapy
Third line	• Immunosuppressives

following treatment is typically followed by relapse. Thus, the ultimate goal for treatment of symptomatic oral LP is to heal erosive lesions to reduce pain and allow normal food intake. Avoiding spicy or acidic foods as well as alcohol and tobacco, is to be executed. First-line treatment is topical steroids, lidocaine I/L steroids, retinoid gel, topical immunomodulators until remission. No improvement after 6 weeks should prompt escalation of therapy. Second-line treatment is cyclosporine mouth

wash, extracorporeal photochemotherapy, photodynamic therapy. Third-line treatment may include cyclosporine, azathioprine, mycophenolate mofetil, or methotrexate.

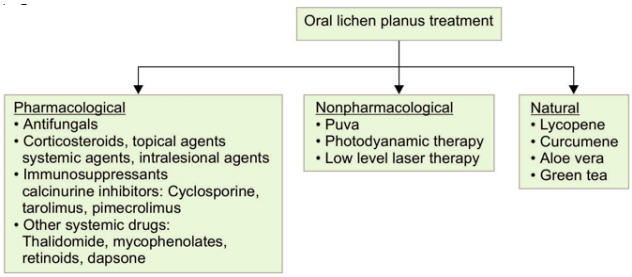

Fig. 11: Plan of treatment

3. Pharmacological Intervention

3.1. Corticosteroids

Topical corticosteroids are the most useful agents for the treatment of OLP but there is a lack of adequate studies determining their efficacy and optimal dose, duration of treatment, and type of formulation. High-potency topical corticosteroids are first-line therapy for all forms of lichen planus, including genital, cutaneous, and mucosal erosive lesions. The most frequent topical corticosteroids were triamcinolone acetonide followed by fluocinolone acetonide and clobetasol propionate. The daily regimen mostly employed was 3 times a day. Steroids reduce pain and inflammation in the areas affected by Lichen Planus. During the therapy, candidiasis was commonly found and in addition, bad taste, nausea, dry mouth, sore throat, and swollen mouth may occur as minor side effects from some topical steroids. A topical corticosteroid is always considered first-line therapy for patients with oral lichen planus.[11,12] Intralesional Triamcinolone injection in ulcerative OLP is effective and safe in achieving lesion and pain regression. Nail Lichen Planus responds better to intralesional steroids as compared to IM steroids. IM triamcinolone acetonide 60 mg per month for 3 months, provided better results. Combined therapy of topical steroids and systemic antihistamines was more effective in the active reduction of disease.[13]

Acitretin a synthetic retinoid, is the pharmacologically active metabolite of etretinate. has been shown to act all three retinoic acid receptors (RARs), namely, alpha, beta, and gamma. Acitretin is preferred in the hyperkeratotic variant of lichen planus for its modulating effect on keratinization. Acitretin hinders the expression of proinflammatory cytokines like interleukin-6 (IL-6), migration inhibitory factor-related protein-8 (MRP-8), and interferon-gamma. An initial daily dose of 25 or 30 mg of acitretin, for 2 to 4 weeks is recommended. After this initial phase, it may be necessary in some cases to increase the dose up to a maximum of 75 mg of acitretin per day. Redness, itching, skin scaling, peeling and dry skin during the first several weeks are common side effects.[14,15]

Topical Tacrolimus has been shown to inhibit T-lymphocyte activation by inhibiting the phosphatase activity of calcineurin. The anti-inflammatory molecular mechanism of action of tacrolimus is similar to cyclosporine, which inhibits the production of IL-2 by T lymphocytes. Tacrolimus 0.1% is a safe and effective medication that improves the clinical appearance of the lesion, reduces pain as well as the histopathological features of OLP. It's a second line therapy, for patients refractory to potent steroids.[16,17]

Pimecrolimus 1% cream seems to be an effective and well-tolerated treatment for oral erosive lichen planus. This is a suitable alternative to steroids if side effects are encountered. Pimecrolimus was well tolerated and successful in decreasing the pain and symptoms of the disease. Some patients do not tolerate this medication due to local irritation. Pimecrolimus seemed to be more effective in providing long-term resolution of signs and symptoms, as compared to Tacrolimus.[18]

Cyclosporine: It inhibits chronic inflammatory reactions by inhibiting T-cell activation and proliferation, inhibits lymphokine production and releases of interleukin-2. Topical cyclosporine can be used either in the form of mouthwashes or in the form of an adhesive base. Patients are advised to swish and spit 5 ml of medication (l00 mg cyclosporin/ml) three times daily for 4 weeks. Severe chronic lichen planus were successfully treated with oral cyclosporine (6 mg/kg/day). The administration of cyclosporine may result in a relatively prolonged remission in patients with lichen planus.[19,20]

Levamisole seems to have a preferential effect on T helper-1 cells with subsequent upregulation of interleukin-2, interleukin-12 and interferon-γ. Levamisole reduces the levels of tumor necrosis factor-α, interleukin-6 and interleukin-8 in patients with oral lichen planus and it has been found to be effective in oral lichen planus either alone or as an adjuvant to Systemic corticosteroids. Levamisole 150 mg thrice weekly and low-dose oral corticosteroids is often recommended.[21,22]

Mycophenolate Mofetil or MMF may be a treatment to consider for severe corticosteroid-dependent or corticosteroid-resistant LP. Mycophenolate mofetil (MMF) is an immunosuppressive drug that specifically and reversibly inhibits the proliferation of activated T cells. 0.5 g of oral MMF twice daily for 4 weeks and reported an 83% decrease in symptoms of refractory lichen planus .MMF may be a viable treatment for refractory or generalised lichen planus.[23]

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP) and is therefore classed as a purine analog which has been shown to be an effective

steroid sparing treatment for generalized lichen planus. The recommended dosage of azathioprine for dermatological indications is 1–3 mgkg.[24]

Dapsone 50-150 mg once a day and for children 1-2 mg/kg once a day, is effective for erosive lichen planus. Screening for G6PD deficiency is required before prescribing dapsone. When used for the treatment of skin diseases, it probably acts as an anti-inflammatory agent by inhibiting the release of chemotactic factors from mast cells, thus can be used for erosive LP.[25]

Interferon in noncontrolled studies have suggested that a topically applied gel preparation containing human fibroblast interferon (HuIFN-beta) and interferon-alpha (IFN-alpha) cream may improve outcome of erosive oral LP. A response was observed within 2 to 3 weeks. Itching and erythema decreased first, followed by gradual flattening and disappearance of papules and plaques after 8 to 10 weeks of treatment.[26]

T**halidomide** is useful for erosive lichen planus have responded at a dosage of 150 mg/d and have maintained improvement at a dosage of 50 mg every other day. The side effects reported are headache, nausea, constipation, rash, sedation, dry mouth, erythema nodosum–like lesions, weight gain, and peripheral edema. The mechanism of action of Thalidomide is mediated by (1) anti-inflammatory effects, particularly an inhibition of neutrophil chemotaxis, (2) immunosuppressive effects.[27]

Griseofulvin in the dose of 500mg daily for about 6 months provided improvement in patients with recalcitrant, symptomatic oral lichen planus. The chance of complete remission or significant improvement in patients with protracted uncomfortable or unremitting oral lichen planus treated with griseofulvin appears to be about 50% of cases.[28]

Adalimumab caused improvement of LP after 2 weeks of adalimumab treatment. Lesions on the extremities and the buccal mucosa improved in appearance, and the pruritic vulvar lesions resolved. Adalimumab may be a promising biologic treatment option for patients with LP who have failed conventional therapies. Adalimumab was administered subcutaneously for 3 months at the recommended dose 80 mg induction dose followed by 40 mg every second week from day 7. Itching decreased after 2 weeks, accompanied by a slow regression of the skin symptoms. The cutaneous lesions healed in 2 months.[29]

Enoxaparin sodium 3-mg subcutaneous injections of weekly for 4 to 14 weeks and then followed up for 1 year. Most patients had been previously treated with topical corticosteroids and/or oral antihistamines. Complete response was seen in patients as assessed by the disappearance of skin lesions.[30]

Basiliximab, Etanercept, Efalizumab and Alefacept have been proposed for the treatment of OLP. especially for patients with severe manifestations or those who have failed traditional first- and second-line therapy such as topical corticosteroids/topical calcineurin inhibitors. Basiliximab binds to and blocks the alpha chain of interleukin-2 receptors (IL-2R alpha), also known as CD25 antigen, on the surface of activated T-lymphocytes. Paradoxically LP developed after 8 months therapy of with Etarnecept. TNF-α inhibitor, Ustekinumab indirectly blocks TNF-α, as well as other proinflammatory cytokines such as IFN-γ, IL-17, and IL-22.[31]

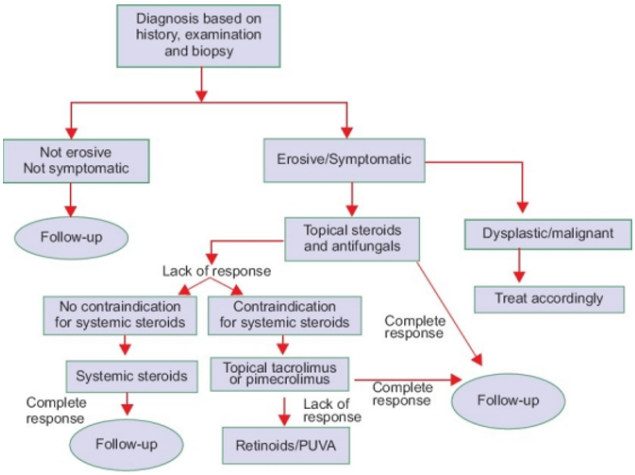

Fig. 12: Algorithm of treating lichen planus[32]

4. Non Pharmacological Intervention

4.1. Lower level laser therapy

Oral Lichen Planus was treated using a Low-Level Laser Therapy with a 660 nm diode laser. The treatment was performed once per week for two sessions of five minutes each. Laser was found to be effective in the management of OLP, without any reported adverse effects. The results of the studies confirm that low-level laser therapy is effective in management of symptomatic OLP and can be used as an alternative to corticosteroids[33]

4.2. Photodynamic therapy

Photodynamic therapy (PDT) has been considered as an alternative/complementary therapeutic modality for the management of premalignant lesions. Methylene blue-mediated photodynamic therapy (MB-PDT) was used as a possible alternative method for the treatment of OLP. [34]

4.3. PUVA

Photochemotherapy with 8-methoxy psoralen and long-wave ultraviolet light (PUVA) has become a useful alternative in LP.[35]

Cryotherapy with nitrous oxide gas is as effective as topical triamcinolone acetonide in the treatment of OLP with no systemic side effects and needs less patient compliance.[36]

5. Natural Modes of Management: Herbal Drugs

Curcumin is extracted from Curcuma plant, which is the main ingredient of turmeric root. Various studies have found curcumin as a suppressant of many diseases due to its anti-inflammatory, antioxidant, and antineoplastic properties. The curcumin is found to be an effective treatment in oral lichen planus even in the cases where topical steroids have been used and recurrence was seen. The efficacy is similar to triamcinolone cream in reducing pain & healing lesions. Dose of curcumin is 2000mg / day.

Aloe vera Gel, has anti-inflammatory effects via suppressing cyclooxygenase, analgesic effects, as well as anticoagulant, anticarcinogenic, and anti-infectious effects.

Glycyrrhizin from G. glabra shows Clinical improvements in two to three symptoms of OLP (decreased redness, fewer white papules, and fewer erosion).

Triptolide, a diterpenoid epoxide, is a major active component of extracts derived from Tripterygium wilfordii. Triptolide has multiple pharmacological activities including anti-inflammatory, immune modulation, and anti-proliferative activity. Supplementing with 8 mg/day of lycopene for 8 weeks showed favorable results in OLP patients, by reducing the burning sensation.[37]

Green Tea ie epigallocatechin-3-gallate, possesses anti-inflammatory and chemo preventive properties. It can inhibit antigen presentation, T-cell activation, proliferation and migration, keratinocyte apoptosis, nuclear factor-kappaB (NF-B) activation and MMP-9 activity, thus reduces symptoms of LP.[38]

5.1. Vitamins

Vitamin A acid has been used for topical treatment of lichen planus (LP.) 0.05% or 0.1% Vitamin A cream is found to have palliative effects. Complete resolution or improvement was seen in 85% of the lesions after first treatment, following use of Etretinate 0.3 mg/kg/day.[39]

Oxidative stress influence molecules and pathways implicated in recruitment of lymphocytic infiltrate in OLP lesions and induction of apoptosis including ICAM-1, p53, TNF-α, NF-κB, the Fas/FasL pathway and granzyme B-perforin system. Vitamin E has ability to modulate immune system function, prevent inflammation and inhibit cellular growth/differentiation.[40]

5.2. Surgical excision

Surgical excision of OLP is considered an effective treatment for isolated plaques or nonhealing erosions Patients had no irritation and pain in mucous membranes while eating acidic or spicy food. Patients' returned to normal within 2-6 months after surgery.[41]

6. Conclusion

Bilateral and Symmetrical lesions which are Pruritic, Purple, Polygonal with Papules, Planar, Plaques are the features of LP. Lichen Planus occurs in the oral cavity, hair, nails, and genital area. Lichen Planus is triggered by Hepatitis C infection, NSAIDs, and with the use of Viral vaccines. Lichen Planus lesions that resolve in a period of 6 months to 1 year after treatment. The chronic and erosive nature of LP can affect Quality of Life. Long-term follow-up is necessary to monitor disease activity and to exclude malignant transformation of the erosive lesions, hence periodic assessment of patients is suggested. Psychological stress can exacerbate or precipitate LP. LP is a T-cell-mediated disease. TNF-α, as well as other proinflammatory cytokines such as IFN-γ, IL-17, and IL-22. Many immune disorders are associated with LP, such as lupus erythematosus, primary biliary cirrhosis, Sjogren's syndrome, ulcerative colitis, alopecia areata, and myasthenia gravis, hence concomitant therapy is often required. Mayo clinic clearly mentions that there is no cure for this condition, it has to be treated symptomatically. The main aims are to help the severe lesions heal, reduce pain and discomfort and be a critical watch on the progression of lesions. In LP patients, narrowband UV-B phototherapy produced a good response that was well tolerated. There's no single treatment that can cure lichen planus completely and hence combination therapies are used**.** Surgical intervention is mainly used in cases with plaque-like lesions, not recommended for erosive or atrophic lesions. Oral Lichen Planus can be managed by 308-nm excimer laser to decrease the pain and the soreness with no potential adverse effects.

7. Conflict of Interest

None.

8. Source of Funding

None.

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Cite this article: Manmohan G, Yadav KA, Madhulika G, Chaudhry S. Lichen planus – A refractory autoimmune disorder. *IP Indian J Clin Exp Dermatol* 2023;9(1):20-27.