

Lichen Planus –A Review

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Abstract: Lichen planus is a fairly distinctive, chronic, immunologically mediated mucocutaneous disease, of uncertain etiology that was first described as a disease of the skin that can also affect mucosal surfaces, including those that line the oral cavity. The prevalence of LP in the general population is of the order of 0.9 to 1.2%. It is stated that approximately 40% of lesions occur on both oral and cutaneous surfaces, 35% on cutaneous and 25% on mucosal surfaces alone. Oral lichen planus known to affect both men and women, usually between the ages of 30 and 70 years. This paper presents a review on lichen planus with its, pathophysiology, clinical features, and different modes of treatment.

Key Word: Oral lichen planus; Lichen planus.

I. Introduction

Lichen planus is a chronic inflammatory mucocutaneous disease which frequently involves the oral mucosa that affects approximately 1-2% of the general population. ^{1,2} About half of the patients with skin lesions have oral lesions, whereas about 25% present with oral lesions alone³. Cutaneous lesions typically present as small (2 mm) pruritic, white to violaceous flat-topped papules, which can increase in size to as much as 3 cm. They often occur bilaterally on the flexor surfaces of the extremities.³

Oral lichen planus has been described as “a common immunologic inflammatory mucocutaneous disorder that varies in appearance from keratotic to erythematous and ulcerative”.⁴

The disease was first described in 1869 by Erasmus Wilson as leichen planus, "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development, their habitat, their local and chronic character, and for the melasmic stains which they leave behind them when they disappear".⁵

The oral lesions in lichen planus were noted by Unna and Crocker and described as white lines and white spots on the buccal mucosa and symmetric plaques on the sides of the tongue in several cases.⁵

A clear and detailed description of the peculiar striae and dots found on the surface of a lichen planus papule was given by Louis Frederic Wickham in 1895 which currently bear his name and are referred as “Wickham’s Striae”.⁶

PREVALENCE:

Mehta, Pindborg and Hamner found the prevalence to be around 0.1 – 1.0% among rural inhabitants of India and reported a prevalence of 0.3% among 50,915 Indian villagers aged 15 years and above.^{7,8}

AGE:

“LP predominantly is a disease of the middle aged and elderly with ages ranging from 30-70 years. The age range for males with LP has been about a decade lower than for the females and overall 35% of patients are aged 50 years and more. Children occasionally are affected and LP has been described in an infant under the age of 6 months”.⁹

GENDER:

The sex distribution of OLP has a predilection for female predominance. Scully C and EL-Kom M in their comprehensive review stated that “LP affects both sexes, although occasional surveys have suggested a male predominance, the vast majority, from several different countries, have revealed that some 60 to 65 % of patients are females”.⁹

In a study of course of various clinical forms in 611 OLP patients reported female predominance with female: male ratio of 2:1.¹⁰

ETIOLOGY

The cause of the OLP is not well understood; although cell mediated immunity appears to play a major role in the pathogenesis of OLP it may be possibly initiated by the endogenous or exogenous factors in persons with a genetic predisposition to the development of LP.¹¹

Various factors have been implicated in the etiology of this disease entity, but few have stood up to the critical analysis, and correlations do not necessarily imply causation. These mainly include¹¹,

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|-----------------------|-----------------------------|
| 1. Genetics | 8. Psychological factors |
| 2. Dental materials | 9. Habits |
| 3. Drugs | 10. Trauma |
| 4. Infectious agents | 11. Diabetes & hypertension |
| 5. Immunology | 12. Miscellaneous |
| 6. Immunodeficiencies | |
| 7. Food allergies | |

1) GENETICS:

Familial LP has been defined as “LP that affects two or more family members”. There are few reports of familial LP, with less than 100 patients being reported in the literature.¹² The cause of familial LP is still unknown. An infective cause seems unlikely as familial LP often occurs in family members not living together and presents at intervals ranging from 6 weeks to 30 years. In addition, because LP is not uncommon, such cases may be merely coincidental or perhaps related to a common but unidentified environmental factor.¹² It is more likely that lichen planus is a multifactorial disease which requires interplay of genetic and particularly environmental factors for its initiation, perpetuation and perhaps resolution.¹³

2) DENTAL MATERIALS:

Metal restorations:

Lesions resembling OLP may occur in direct relation to amalgam restorations and some of these oral lesions may improve after substitution of the amalgam by other materials.^{14,15}

Amalgam in the oral cavity is prone to corrosion and may be responsible for sensitization and allergic reactions (type IV, T-cell dependent) by releasing metal ions. This process may lead to long-term antigenic stimulation, with mucosal changes, and ultimately to OLP. A less favorable hypothesis is that close contact between dissimilar metals (e.g., amalgam and gold) may produce different potentials and lead to electrochemical reactions, corrosion and increased release of metal ions, also leading to mucosal changes.¹⁶

Non-metallic restorations:

Lichenoid lesions topographically related to resin-based composite restorations were observed in 17 patients. Total remission occurred in four cases after the composite was replaced, and partial remission was observed in five patients.¹⁷

3) DRUGS:

The possible association of drugs with lesions similar to LP was noted when quinacrine and mepacrine used as antimalarials during World War II were seen to cause lichenoid lesions¹⁸.

Certain drugs such as mepacrine have been associated with a incidence rate of around 47% with oral lichenoid reactions and statistically significant association was found between nonsteroidal anti-inflammatory drug intake and erosive oral lichen planus.¹⁹ Nonsteroidal anti-inflammatory drugs are believed to produce mucosal ulceration in other parts of the gastrointestinal tract and there have been reports of stomatitis and ulceration of the aphthous type related to NSAID and the possibility exists that in some cases nonsteroidal anti-inflammatory drugs provoke erosions in patients with preexisting lichen planus.²⁰

The cause remains unknown and the drugs that are known to induce lichenoid responses act as agents which amplify a disorder predating the use of the drug rather than by inducing the disease de novo and it could be argued that the implicated drug acts to increase temporarily the specific antigenic stimulus and hence increases the reaction.²¹

4) INFECTIOUS AGENTS:

A viral aetiology of LP was suggested on the basis of the degenerative changes seen in the epithelial basal cells but culture of lesions of LP has not revealed any viruses. In a study on association between Human papilloma viruses (HPV) and 20 patients with erosive lichen planus, it was found that 13 out of 20 samples (65%) were positive for some HPV type, predominantly HPV-II. Thus the association between HPV and these lesions has provided a basis for suggestion of etiological role of HPV.²² Though different agents have been proposed their role remains speculative.

5) IMMUNOLOGY:

Biochemical epithelial alterations coupled with genetic factors related to major histocompatibility profiles appears to render persons susceptible to either true LP or a spectrum of similar, benign LP - like reactions.²³

In a study that was conducted to find out whether oral lichen planus patients exhibited aberrations regarding immunoelectrophoresis or levels of immunoglobulin G, A and M and possible presence of autoantibodies. Total of 10 patients showed abnormal immunoelectrophoresis as compared to control and reported a possible etiological background to the immunological aberration noted in oral lichen planus patients.²⁴

Immune Mediated Chronic Liver Diseases:

The possible association between LP and HCV is still controversial and various researchers have suggested that the simultaneous appearance could be genetic, environmental, geographic or other factors. If this is a true association OLP in certain population can be used as a marker of HCV infection in asymptomatic patients leading to diagnosis and early treatment and possibly a better prognosis.^{25,26}

Autoimmune diseases:

Associations of LP with several different autoimmune diseases have been documented which mainly include Alopecia areata, Dermatomyositis, Dermatitis herpetiformis, Hashimoto's thyroiditis, Keratoconjunctivitis sicca, Xerostomia, Morphea, Myasthenia gravis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, Systemic sclerosis, Thymoma and Vitiligo etc.²⁷

6) IMMUNODEFICIENCIES:

Cutaneous LP is more strongly associated with defects of T-cell function such as thymoma or HIV, than it is with humoral immunodeficiencies. OLP may also be seen in HIV disease and a few cases have been reported of lichenoid lesions in patients with HIV infection, but most of them could be related to zidovudine or ketoconazole therapy.²⁸

7) FOOD ALLERGIES:

A small minority of patients with OLP and lichenoid lesions have been shown to react to certain foods. Toothpaste flavorings, especially cinnamates may trigger lichenoid contact sensitivity reactions.²⁹

8) PSYCHOLOGICAL FACTORS:

Psychological factors have been strongly associated with lichen planus, in particular high stress and anxiety levels.³⁰ In conditions involving pain, anxiety, fright or acute tissue damage, a rise in the levels of blood cortisol is one of the most important physiological effects and salivary cortisol levels were found to be high in OLP patients, leading to a conclusion that this disease entity has close association to stress.³¹

9) HABITS:

The etiological role of habits in OLP is still a matter of controversy. A number of studies have been conducted in this aspect, but failed to propose a definite etiological role. In India a study conducted in Kerala, out of 27,599 individuals studied 21,096 were tobacco users in any form. 10.5% of the tobacco users and 0.8% of the non users developed OLP. Lesions occurred in 1% smokers, 5.1% chewers and 4.4% of individuals with both chewing and smoking habits. Out of all the (722) OLP patients, 93% (672) were tobacco users.³²

10) TRAUMA:

Trauma as such has not been quoted as an etiological factor in LP, although it may be the mechanism by which other etiological factors exert their effects.. Almost any type of irritant, for example, burns, lacerations, friction, or UV light may provoke the isomorphic response.

11) DIABETES AND HYPERTENSION:

The prevalence of OLP in patients with DM varies from 0% to 5.7%. The prevalence of DM in patients with OLP varies from 1.6% to 38.9%.

In 1963 and 1966 Grinspan suggested an association between Lichen planus, Diabetes mellitus and vascular hypertension. This triad was named as "Grinspan syndrome" by Grupper in 1965³³.

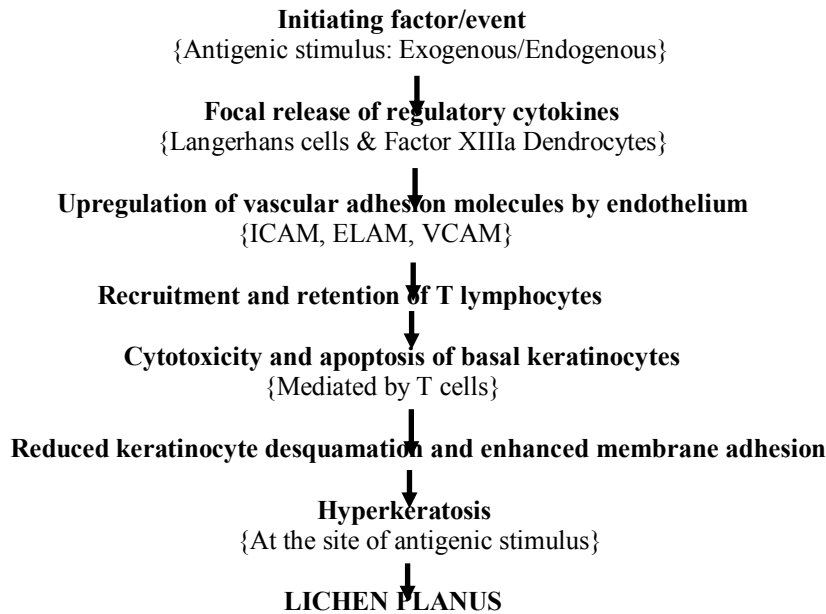
12) MISCELLANEOUS:

The triad of erosive or desquamative vulvitis, vaginitis and gingivitis (the vulvo-vaginal-gingival syndrome) has been recognized and described by Pelisse. Also LP has occasionally been associated with other conditions including psoriasis, lichen sclerosis, urolithiasis, agents used to treat gallstones,

mesangioproliferative glomerulonephritis, erythema dyschromicum, Turner’s syndrome with endocrinopathies.^{34,35.}

PATHOGENESIS:

OLP is a cell-mediated immune condition and can be envisaged as a delayed-type hypersensitivity reaction. The disease mechanism appears to involve several steps that could be described as follows:³⁶



The initial reaction whether progresses to the development of OLP, or is switched off, probably depends on a number of factors like,

- i) The nature of the antigen
- ii) The ability of the individual to present the antigen (HLA type)
- iii) The presence of T cells capable of recognizing the antigen (T cell receptor repertoire)
- iv) Possibly the inheritance of a profile of cytokine and other gene polymorphisms that promote, rather than suppress, a cell-mediated response to the antigen.³⁷

FORMS OF LICHEN PLANUS:

Several OLP classifications have been proposed with different degrees of complexity. The various authors have classified OLP in various clinical forms as follows,³⁸

AUTHORS	CLASSIFICATION
Andreasen (1968)	Reticular, papular, plaque, atrophic, ulcerative and bullous.
Axell (1987)	White forms : Papular, reticular, plaque Red Forms : Atrophic, Ulcerous, bullous
Silverman (1985)	Reticular (Lacy like keratotic) Atrophic (reticular, keratotic and erythema) Erosive (ulcerative and atrophic)
Silverman (1991)	Reticular Atrophic (reticular keratosis with an erythematous mucosa) Erosive (reticular and atrophic with mucosal ulceration)
Began – Sebastian (1992)	Group 1 : Exclusively white reticular lesions Group 2 : Atrophic and/or ulcerative lesion with or without reticular lesions
Eisen (2002)	Reticular (White line, plaque and papules) Atrophic or erythematous Erosive (ulcerations and bullae)

RETICULAR LP:

Reticular LP is the most common type. It has a distinct and characteristic clinical appearance of thin, slightly raised white lines that connect in a pattern resembling lacework or a reticular, annular appearance.

Characteristically, it presents as a series of fine, radiant, white striae known as ‘Wickham striae’ in an interlocking pattern (Honiton lace) or in an annular pattern which may be surrounded by a discrete erythematous border. The striae are typically bilateral in a symmetrical form on the buccal mucosa. Lesions may be localized to the area of the interdental line or involve the entire buccal mucosa, extending to the vestibular areas and the retromolar areas. They may also be seen on the lateral border of the tongue and less often on the gingiva and the lips.³⁹

EROSIVE OR ULCERATIVE TYPE:

Erosive oral lichen planus is the second most common type. It most often appears as a mixture of intensely erythematous mucosa with large areas of irregularly shaped ulceration with a whitish-yellow pseudomembrane. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae. It is painful when the pseudomembrane or fibrinous plaque is disturbed. The ulcerative lesions are usually noted at the line of occlusion.⁴⁰

PAPULAR TYPE:

papular lesions occur as isolated lesions and are often the only clinical manifestation of the disease. In this type, the papules of about 0.5 mm in size are spaced apart and yet close enough that the lesion has a pebbled white or gray appearance. 41

PLAQUE TYPE:

The plaque-like forms of LP may resemble leukoplakia, particularly proliferative verrucous leukoplakia.41

BULLOUS FORM:

Bullous oral lichen planus is a rare form of LP characterized by large bullae ranging in size from 1 to 2 mm to several cm in diameter. The larger vesicles or bullae are fluctuant and appear white or gray - purple in color. The fluid in the vesicles is usually clear but may be hemorrhagic or even purulent upon secondary infection. These tend to rupture easily and when they rupture leave an ulcerated, painful surface. The bullous form is commonly seen on the lateral borders or undersurface of the tongue. The lesions are also common on the buccal mucosa, particularly in the posteroinferior areas adjacent to the second and third molar teeth.⁴¹

II. Histological Features:

The histopathological features of OLP are similar to those of cutaneous lichen planus and were first described by Dubreuill in 1906.⁴²

The essential and exclusionary histologic features must be met to make a definitive diagnosis of OLP. The essential histologic features of OLP are:⁴³

- i) Liquefactive degeneration of basal epithelial cells
- ii) Dense, band-like inflammatory infiltrate consisting of lymphocytes
- iii) Normal maturation epithelium
- iv) Saw-tooth appearance of rete ridges
- v) Civatte bodies (colloid bodies)
- vi) Hyperkeratosis

III. Immunofluorescent Features

The immunofluorescence technique is one of the most widely used adjunctive diagnostic procedures for the clarification of OLP when the diagnosis may sometimes pose histopathologic problems, especially when the mucosal lesions are ulcerated with secondary inflammation. It proved to be a valuable additional tool in the diagnosis of bullous, erosive and ulcerative lesions. It combines histochemical and immunologic methods to pinpoint specific antigen-antibody complexes formed in tissue sections or cellular smears with the reaction of fluorochrome-labeled antibody.⁴⁴

A study was conducted in which direct immunofluorescence was used to examine the fluorescence patterns in OLP and oral lichenoid reactions and to compare the degree of intensity of their fluorescence. It was found out that deposition of fibrinogen at the basement membrane zone was present in both OLP and suspected oral lichenoid reaction but the fluorescence was less intense in oral lichenoid reactions. It was also found out that pattern of fluorescence was more ragged fibrillar (band like pattern) in OLP while it was homogenous (linear) in suspected oral lichenoid reaction.⁴⁴

IV. Malignant Potential

A case of carcinoma arising in lichen planus of the oral mucosa was first described in 1910, by Hallopeau. Ever since, several mainly retrospective studies and case reports have been published on this subject⁴⁵. It has been suggested that the erosive or atrophic forms of oral lichen planus undergo malignant transformation more commonly than other variants of lichen planus.⁴⁶ It is stressed that the OLP patients should be under a regular follow up, at least two to four times a year, with an extremely meticulous clinical examination, especially in atrophic, erosive and keratotic forms.^{47,48}

TREATMENT

The aim of current OLP therapy is to eliminate mucosal erythema and ulceration, alleviate symptoms and reduce the risk of oral cancer in OLP patients. There is no cure and so the treatment is mainly directed towards symptomatic relief. The large number of agents used in the management of the disease reflects the inadequacy of any agent to control the symptoms in all patients.⁴⁹

General considerations in the management of OLP:

Atrophic or ulcerative / erosive lesions poses problem in cases of gingival involvement, as the lesions will interfere with tooth brushing and leads to accumulation of dental plaque. In such patients oral hygiene procedures are essential and can enhance healing. Intensive oral hygiene procedures may produce subjective and objective improvement of the lesions and can also eliminate Candida from most lesions.⁵⁰

The Koebner phenomenon or isomorphic response is a common feature in lichen planus, characterized by the occurrence of LP changes in areas subjected to trauma. Almost any type of irritant may provoke a Koebner reaction. Mechanical trauma or irritants such as sharp cusps, sharp filling margins or rough surfaces and even poorly fitting dental prostheses can be exacerbating factors of OLP and should therefore receive attention.⁵⁰

The psychological profile of the OLP patient should be taken into account. Studies have reported higher levels of anxiety, greater depression and increased psychic disorders in OLP compared to control groups. So stress is one of the most frequent causes of acute exacerbation in OLP patients and should therefore receive attention.⁵⁰

Pharmacological Management:

Various treatment regimens have been designed to improve management of symptomatic OLP, but a permanent cure is not yet possible.⁵⁰ The various treatment modalities that have been used are:⁵⁰

A) Immunomodulators

1) Immunosuppressors

- i) Cyclosporin
- ii) Corticosteroids

a) Topical:

Betamethasone
Clobetasol
Fluciclonide
Hydrocortisone
Triamcinolone

b) Intralesional:

Dexamethasone
Hydrocortisone
Methyl prednisolone
Triamcinolone

c) Systemic:

Prednisolone
Methyl prednisolone

2) Cytotoxics

Azathioprine

3) Hormone

ACTH

4) Immunostimulants

Levamisole

B) Retinoids

Topical:

Fenretinide
Isotretinoin
Tazarotene
Tretinoin

Systemic:

Acitretin
Etretinate
Isotretinoin
Tazarotene

C) Antimicrobials

Antibiotics

Doxycycline
Tetracycline
Dapsone

D) UV radiation

UV Light
PUVA

Anti-fungal	
Azoles	
Polyenes	
Griseofulvin	
Antimalarials	
Hydroxychloroquine	
Antivirals	
Interferon β	
F) Others	
Phenytoin	Magnetism
Basiliximab	Psychotherapy
Diethyldithiocarbamate	Reflexotherapy
Phenytoin	Photopheresis
Basiliximab	Mesalazine
Diethyldithiocarbamate	Thalidomide
Enoxaparin	Tacrolimus
	E) Surgery
	Conventional
	Cryosurgery
	Laser surgery
	Grafting

1. **Corticosteroids:**

Are the mainstay of treatment, which can be used topically, intralesionally or systemically.

Topical corticosteroids:

Corticosteroids may be applied topically as ointments, pastes, lozenges or mouthwashes or through an inhaler with a special adapter. Ointments, pastes, lozenges or creams should be applied as a thin coating over the lesion after meals and at bedtime. One should not eat or drink for 30 minutes after use of topical preparations.⁵¹

Ointments or gels may be best for localized lesions, while dexamethasone 0.5 mg/mL elixir may be best for widespread lesions.⁵¹

Intralesional corticosteroids:

Intralesional injection of triamcinolone acetonide suspension was first used by Sleeper in 1967 on seven patients with a dosage of 5 to 7 mg of triamcinolone and all patients experienced relief of symptoms within two weeks. Further, the efficacy of depot solutions (methylprednisolone acetate 40 mg/ml) in the treatment of erosive OLP was documented by Ferguson (1977) and since then intralesional hydrocortisone, dexamethasone, betamethasone, triamcinolone acetonide and methylprednisolone have been used in the treatment of OLP.⁵²

Systemic corticosteroids:

They are indicated in cases of moderate to severe OLP or in cases unresponsive to topical therapy and their use should be reserved for acute exacerbations. They most often are used in combinations with topical corticosteroids, as their effects are immediate and can be maintained with topical agents.⁵²

2. **Antifungals:**

Studies have demonstrated that *Candida* is present in roughly a half to third of all oral lichen planus patients, the prevalence not statistically different from the normal population. Vincent *et al* (1990), in a study of 100 patients with oral lichen planus, reported secondary candidiasis in 31% of symptomatic patients. *Candida* treatment often resulted in resolution of pain and clinical improvement.⁵² Systemic ketoconazole at doses of 200 mg daily for 2 to 3 weeks at the initiation of therapy will augment the effects of most therapies employed.⁵²

3. **Cyclosporine:**

Is a potent immunosuppressant that may be beneficial in the treatment of OLP. Some studies have suggested that cyclosporine is effective when applied either topically or in the form of mouth rinse, but others have reported little or no benefit^{51,52}.

4. **Tacrolimus:**

Is a potent immunosuppressive agent used in the treatment of recalcitrant ulcerative OLP. It is known to inhibit T-cell activation at 10-100 times lower concentration than cyclosporine and seems to penetrate skin better than topical cyclosporine.⁵²

5. **Retinoids:**

The use of retinoids for the treatment of oral lichen planus was first reported in 1973 by both Gunther and Ebner *et al* in which they applied vitamin A locally to white, reticulated lesions with good results.^{51,52}

Systemic and topical forms of retinoids have been used in the treatment of OLP.

a) Topical retinoids:

The most widely available and employed topical retinoid for the treatment of OLP is tretinoin, a metabolite of vitamin A which may be beneficial because of the antikeratinization and immunomodulation

effects. Sloberg et al in 1979 tested this agent at a concentration of 0.1% in 23 patients. Although he got good results relapses were common within 3 months of discontinuing therapy and similar results were also obtained by Giustina et al in their study where relapses were noted within 3 months of discontinuing therapy.⁵²

b) Systemic Retinoids:

The first ever to report beneficial results with systemic isotretinoin for oral lichen planus was Handler. He used 0.25 mg/kg/d and observed "excellent" results in seven patients after 2 months of therapy. This is also supported by Woo in his treatment of two patients of refractory erosive OLP with isotretinoin at doses of 0.5 to 1.0 mg/Kg/d.⁵²

6. Ultraviolet Irradiation (Photochemotherapy):

UVA without systemic or topical photosensitizers is also found to be effective. UVA without psoralens may be selectively efficacious in OLP. A similar treatment was described by Chen in 1989. Weekly treatments of ultraviolet-A without systemic or topical photosensitizers were received by 35 patients. After eight treatments, 87% of patients were either cured or had significantly improved clinically, and resolution of pain also was achieved in most patients.⁵²

7. Miscellaneous treatment:

Mainly includes antibiotics, antimalarials, azathioprine, dapsone, glycyrrhizin, interferon, levamisole, mesalazine and phenytoin. Any definitive conclusion regarding the efficacy of these agents was not possible, as adequate number of controlled studies or open trials have not been performed.⁵²

8. Surgery:

Surgical excision has been recommended for isolated plaques or non healing erosions. Conventional surgical excisions, cryosurgery and CO₂ lasers all have been used. Surgical treatment of selected oral lichen planus lesions was done in four patients with symptomatic lesions by Emslie and Hardman in 1970. Vedtofte et al excised dysplastic lesions in five patients with oral lichen planus with minimal complications and no recurrences.⁵²

Cryosurgery has been used successfully in cases of erosive OLP resistant to most treatment modalities. As an alternative to scalpel surgery, the CO₂ laser has been used in the treatment of multicentric lesions or in difficult areas of OLP.⁵²

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