Management of Oral Lichen Planus with Levamisole Monotherapy :Report of 2 Cases

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Introduction

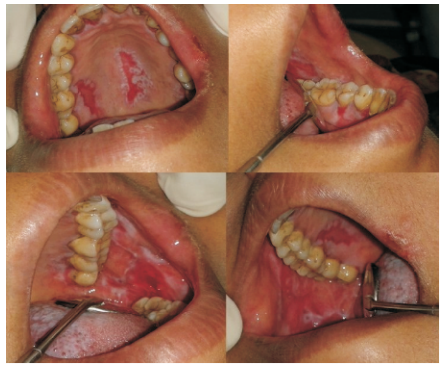
Lichen planus is a chronic inflammatory disorder demonstrating some immune pathology. It is a cell- mediated immune condition of unknown etiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and increase the rate of differentiation of stratified squamous epithelium, resulting in hyperkeratosis and erythema with or without ulceration. Oral Lichen Planus has little potential for malignant transformation, but it can serve as a source of severe morbidity.[2] It is prevalent round the globe, mostly in the fifth to sixth decades of life, and affects females twice as common as males.[2]

Case Report

Case 1: A 48 year old female patient reported with the chief complaint of burning sensation in mouth since 1 year on consuming hot and spicy foods. A diagnosis of Lichen Planus was established and she was under the treatment of a dermatologist who prescribed 4 mg Methylprednisolone for 2 months. Since the patient was diabetic and had poor control over the disease, she was prescribed topical Tacrolimus with an oral antioxidant which was taken by the patient for 4 months but there was no relief. She was then advised to take Hydroxy-chloroquine 400 mg once a day for 6 months, but the patient was still not relieved of the symptoms.

Intraoral examination revealed erythematous, desquamated lesions lined by fine keratotic striae involving the hard palate, right and left buccal mucosa, lingual attached gingiva around the premolars of left side and palatal gingiva in relation to the molars. (Fig 1.1).

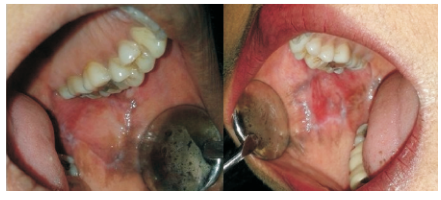
The patient was diabetic and hypertensive since 10 years, and had an insignificant family



history. This patient being diabetic, hypertensive and of late developed lichen planus was suggestive of Greenspan Syndrome.

Case 2: A 37 year old female patient reported with a chief complaint of severe discomfort in mouth since 7 months while taking hot and spicy food. She consulted a local dentist who diagnosed the condition as Lichen Planus and prescribed Triam-cinolone for topical application 3-4 times a day along with an oral antioxidant. She continued the treatment for 2 months and reported less discomfort during the treatment but started experiencing the symptoms a week after stopping the medication.

Intraoral examination revealed an erythematous area with fine, white, radiating striations involving right buccal mucosa with fine, white, radiating striations on left buccal mucosa. (Fig 2.1)

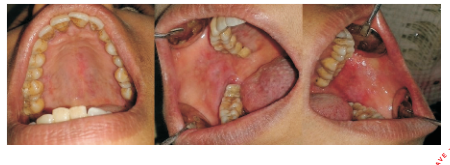


There were no cutaneous lesions present. The past medical and family history of the patient were insignificant. The patient was found to be having amalgam fillings, porcelain fused to metal and metal crown, which are known to be associated with incidence of Lichen Planus. But in this case, they were not replaced as they were 12 years old and were not to be associated with the lesion.

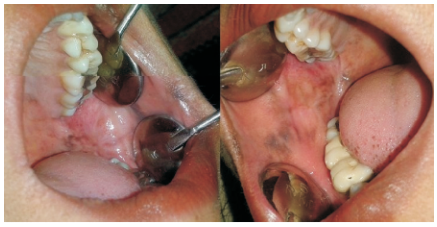
Both cases were prescribed systemic Levamisole for the management. We performed some tests for complete blood cell count, liver and renal function before initiating Levamisole drug therapy.

Levamisole was administered with a dosage of 50 mg thrice a day for three consecutive days, and was discontinued for the following four days. This treatment regime was repeated until the lesion disappeared. Both the patients were evaluated after every 2 weeks. When complete clearance was achieved, Levamisole was withdrawn with progressive taper in the following fashion - 1st and 2nd week 50 mg twice daily for three consecutive days with four days break, 3rd week 50 mg once daily for three consecutive days followed by four days break, 4th week 50 mg once daily for two alternate days of 1st three days of week followed by four days break. The drug was then discontinued completely.

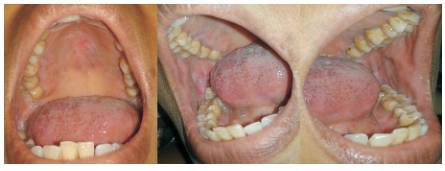
Case 1 showed response towards therapy in 2 weeks with total remission in 2 months. (Fig 1.2)

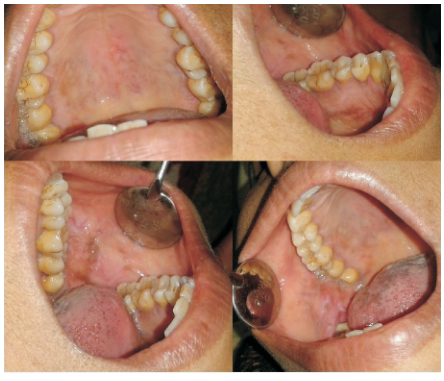


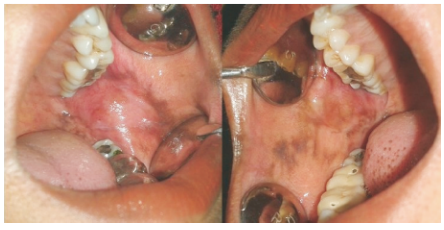
The dose was then tapered and stopped at the end of 3rd month follow-up while Case 2 showed response towards therapy with total remission in 1 month. (Fig 2.2)

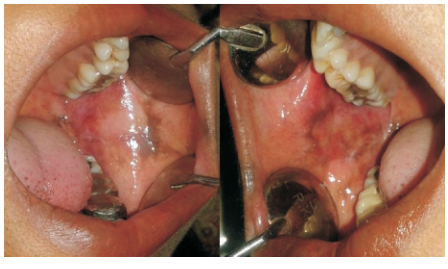


The dose was then tapered and stopped at the end of 2nd month follow up. There was no recurrence of the lesion in both cases at subsequent 4th and 6th month follow up (Fig 1.3, 1.4, 2.3 & 2.4) making up a post treatment disease free period of 3 and 4 months in Case I and II respectively without any medicinal support.









Both patients were advised complete blood cell count, liver and renal function tests at regular intervals. No infections or any other complications were reported during the treatment or on completion.

Discussion

Lichen planus is a common dermatologic disorder with either mucosal involvement may appear with cutaneous lesions. The disease was first described by Wilson in 1869. Globally, Oral Lichen Planus affects about 1-2% of population and prevalence in India ranges from 0.1-1.5%.[3]

Lichen Planus commonly appears bilaterally affecting buccal and labial mucosa, tongue, gingiva, and vermilion borders of the lower lip.[2] Andreason in 1968 divided Oral Lichen Planus into 6 clinical forms: reticular, papular, plaque-like, atrophic, erosive and bullous.[3]

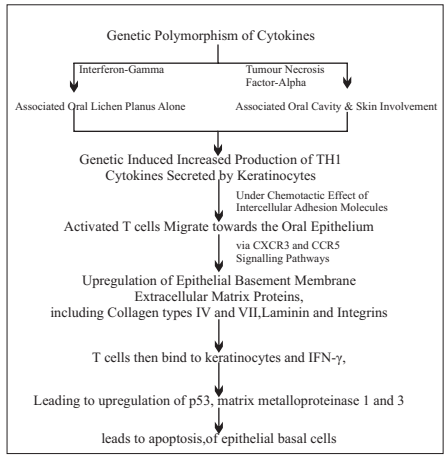
Reticular form presents as white fine striae to annular/circular patterns with peripheral erythemous zone, which reflects sub-epithelial inflammation.[4] Papular form is present in initial phase of disease, characterised by small white dots which at most of the times intermingle with reticular form[4] whereas plaque-like are homogeneous, well demarcated often, but not always surrounded by striae.[4]

Erythematous and erosive lichen planus are most enfeebling form of disease. Erythematous or Atrophic form is characterised by homogeneous red area with frequent striae at periphery while Erosive form clinically present with fibrin coated ulcers surrounded by erythematous zone frequently displaying radiating white striae.[4]

The classic appearances of cutaneous lesions are described by the six P's: Planar, Plaque, Pruritic, Purple, Polygonal and Popular.[4]

Recent studies have demonstrated association of Lichen Planus with hepatitis C virus infection (HCV).[1,2] Though Lichen Planus is a benign lesion there is a reported risk of malignant transformation varying between 0.4 and 2.5% over periods of observation from 0.5 to 20 years.[1,2,3]

Pathophysiology of Oral Lichen Planus is follows[2]



The chronic course of OLP may result from the activation of the inflammatory mediator nuclear factor kappa B, and the inhibition of the transforming growth factor control pathway (TGF-beta/smad) may cause keratinocyte hyperproliferation that leads to the white lesions.[2]

Lichen Planus mimics number of lesions hence differential diagnosis includes: Plaque-like forms - Leukoplakia, particularly proliferative verrucous leukoplakia.[2] Erosive Oral Lichen Planus - Squamous cell carcinoma, Discoid lupus erythematosus, Chronic candidiasis, Benign mucous membrane Pemphigoid, Pemphigus vulgaris, Chronic cheek bite, Lichenoid reaction to Dental amalgam or Drugs, Graft-versus-host disease (GVHD), Hypersensitivity mucositis and Erythema multiforme.[5]

Various treatment modalities are being subjected to treat lichen planus of which corticosteroid therapy is the first line therapy because of their activity in dampening cell mediated immune activity there by modulating the immune function.[3] These drugs can be administered topically, intralesionally or systemically and are as given in Table I

Table-I Drugs Used To Treat Lichen Planus

S. No.	Drugs	Dosages
1.	Tab Levamisole[4]	150 mg/day * 3 days then break for 4 days Repeat the regimen for 6 weeks
2.	Tab Prednisolone[1]	40-80 mg/day
3.	Oint Triamcinolone 0.1%[4]	Apply 3-4 times/day
4.	Oint Flucinonide 0.05%[4]	
5.	Hydrocortisone Hemisuccinate Aqueous Solution[4]	
6.	Fluticasone Propionate Spray[4]	
7.	Betamethasone Na Phosphate Mouth Wash[4]	
8.	Mometasone Furoate Microemulsion[4]	
9.	Oint Clobetasole Propionate 0.05%[4]	
10.	Pimecrolimus 1% Cream[4]	
11.	Fluocinolone Acetonide 0.1% Orabase[4]	
12.	Inj. Triamcinolone	5 mg/ml + LA to inject 0.1 ml/cm^3 intralesionally[4] 10 mg/ml inject 0.2-0.4 ml/cm^3 intralesionally[5]
13.	Cyclosporin Mouth Rinses (Containing 100 mg/ml)[4]	TID
14.	Oint Tacrolimus 0.1%[5]	Apply 2 times a day
15.	Tab Dapsone[4]	100 mg OD * 3 Months
16.	Tab Azathioprine[1]	150 mg/day
17.	Tab Thalidomide[2]	200 mg/day
18.	Oint Thalidomide 1%[4]	
19.	Tab Giesofulvin[3]	500 mg TID * 10 Weeks
20.	Cap Retinol[1]	10,000 IU
21.	Oint Tretinoin 0.1%[4]	Apply 4 times/day
22.	Tab Cyclosporin[1]	6 mg/kg body weight/day
23.	Tab Hydroxychloroquine Sulphate[3]	200-400 mg/day * 6 Month
24.	Cap Retinoids[3]	25-75 mg * 8 Weeks
25.	Tab Curcumin[3]	Upto 6000 mg/day
26.	Green Tea (Epigallactechin-	

Besides these drugs CO_2 Laser, Photodynamic Therapy and Cryotherapy are also advocated to treat Lichen Planus. Photodynamic Therapy is given after administration of 0.6 mg/kg of Methoxsoralen 2 hrs prior to UVA exposure with a beginning dose of 0.75 J/cm^2 with total dose of 11.6-16.5 J/cm^2.[1]

All drugs have their possible merits and demerits and hence must be used taking risk v/s benefit ratio into consideration. Possible side effects of these drugs are described in Table II

Table-II Adverse Effect Of Drugs Used To Treat Lichen Planus(Page-36)

Of these our drug of choice was Levamisole owing to its lesser side effects and moreover both cases were recalcitrant. Levamisole (levo isomer of 2,3,5,6-tetrahydro-6-phenylimidazo (2,1-b) thiazole) is a broad-spectrum antihelminthic with property of immunomodulation hence in use

Drugs	Side Effects
Corticosteroids	Topical – Secondary Candidiasis, Thinning of Oral Mucosa, Discomfort on application. Prolonged use with occlusal dressing may lead to Adrenal Suppression.[3]
	Intralesional – Atrophy[3]
	Systemic – Insomnia, Diarrhoea, Mood Swings, Nervousness, Fluid Retention, Muscle Weakness, Hypertension, Decreased resistance to infections, [3] Adrenal Crisis,[5] Hyperglycemia.[1]
Azathioprine	Nausea, Vomiting, Diarrhoea, Pancreatitis, Bone Marrow Suppression, Hepatotoxicity, Arthralgia, Retinopathy.[3]
Cyclosporine	Hypertension, Nephrotoxicity
Retinoids	Pruritus, Chelitis, Dry Skin, Headache, Rash, Desquamation of hands, feet, Paronychia.[3]
Dapsone	Haemolysis, Nausea, Headache.[3]
	Nausea, Vomiting, Dizziness, Headache,
Levamisole	Rash,, Agrnulocytosis(in patients with HLA-B27 Positivity or Long Term Therapy)[3]
Curcumin	Diarrhoea, GI Discomfort[3]
Hydroxychloroquine	Long term use may lead to Altered eye pigmentation, Acne, Anaemia, Blood disorders, Convulsions, Vision Difficulties, Diminished Reflexes, Emotional Changes, Excessive Colouring of the Skin, Hives, Itching, Liver problems, Loss of hair, Muscle paralysis, Weakness or atrophy

to treat some autoimmune diseases.[6]

Studies have indicated that levamisole (1) restores normal phagocytic activity of macrophages and neutrophils, (2) immunomodulates or immunopotentiates host defenses (T cell-mediated immunity), (3) potentiates the activity of human interferon and interleukin-2, (4) inhibits fumarate reductase, (5) potently inhibits mammalian alkaline phosphatase, (6) inhibits aerobic tumor glycolysis, and (7) alters the natural course of chronic, recurrent, inflammatory diseases.[7]

Sun et. al. in 2006 evaluated the effect of levamisole on the immune system of patients with recurrent aphthous ulcers (RAU) or oral lichen planus (OLP) in an open trial found a significant improvement in clinical symptoms and normalization of the decreased CD4/CD8 ratio after levamisole treatment. The serum ANA detected in 3 patients with erosive OLP disappeared after 1-22 months of levamisole treatment. The disappearance of serum anti-BCA was also observed in 50%, of the anti-BCA-positive patients with erosive OLP after 3–13 months of levamisole treatment. These findings suggest that levamisole has modulating effects on both cell-mediated and humoral immunity in patients with Oral Lichen Planus.[8]

Sun et. al. in 2007 studied the effect of Levamisole treatment on the levels of Serum Tumour Necrosis Factor α concluded that levamisole can reduce high serum TNF-α levels to normal in patients with Erosive Oral Lichen Planus.[9]

Hung-Pin Lin et. al. found significantly higher frequencies of serum anti-thyroglobulin and anti-thyroid microsomal autoantibody in Chinese Oral Lichen Planus patients than in healthy control subjects. After 1 year of levamisole treatment, serum anti-thyroglobulin and anti-thyroid microsomal autoantibody levels were reduced partially or became undetectable in approximately 88% of anti-thyroglobulin-positive and 96% of anti-thyroid microsomal autoantibody-positive Oral Lichen Planus patients.[10]

Hung-Pin Lin et. al. in another study reported significantly higher frequency of serum Anti-Nuclear Antibody (23.2%) in Taiwanese Oral Lichen Planus patients than in healthy control subjects. Treatment with levamisole for 2–38 months reduced the high serum Anti-Nuclear Antibody to an undetectable level, and significantly improved the signs and symptoms in all treated Oral Lichen Planus patients.[11]

Shin-Yu Lu et. al. in 1995 in their prospective study over 23 patients of Lichen Planus who had been treated unsuccessfully with other modalities were given 150 mg/day levamisole and 15 mg/day prednisolone for 3 consecutive days each week. Twelve patients showed dramatic remission of signs and symptoms within 2 weeks, whereas 11 had partial remission. All 23 reported significant pain relief and showed no evidence of erosive oral lichen planus after 4 to 6 weeks of treatment. All 23 also remained free from symptoms for 6 to 9 months after the treatment ended. There were few side effects from this treatment besides minor skin rash, headache, and insomnia from the levamisole in three cases. They concluded that the addition of levamisole to prednisolone may produce improved results in the management of erosive oral lichen planus.[7]

We observed subjective as well as clinical improvement after 2 weeks of levamisole therapy in both the cases with complete clearance of the lesion after 2 months of treatment in Case I while Case II responded with complete clearance in 1 month time from the initiation of treatment.

In another study in 1998 they evaluated the short-term and long-term clinical efficacy of levamisole used with low-dose prednisolone in 30 patients with oral lichen planus, 6 patients with erythema multiforme, 3 patients with mucous membrane pemphigoid, and 2 patients with early pemphigus vulgaris. Concluded that the addition of levamisole to prednisolone may produce improved results in the management of erosive lichen planus, erythema multiforme, mucous membrane pemphigoid, and early pemphigus vulgaris.[12]

Levamisole has been reported to have many adverse effects of which Agranulocytosis is of biggest concern. Agranulocytosis is commonly seen in those patients with HLA-B27 positivity and in those patients who have undergone long term levamisole therapy.[13]

We advocated the intermittent administration of Levamisole hence might not have encountered such adverse effects. Similar observation was made by Tai Hyok Won et. al.[13], J Scott et. al.[14] in their study.

Conclusion

The chronic nature and autoimmune characteristic of Oral Lichen Planus, patients have to be educated and informed about the alternating periods of symptomatic remission and exacerbation, in order to motivate the patient to continue the treatment without leaving it after a few months. A wide range of medication has been documented for treating Oral Lichen Planus, but a number of studies do not yield any conclusive findings. All treatment modalities are oriented to eliminate inflammation but are nonspecific.

Even today, corticosteroids remain the first line drug for the management of Oral Lichen Planus, but for the recalcitrant type of lesions, we propose the use of Levamisole as a single drug treatment regime. Even though the effect of Levamisole monotherapy is slower, it can be accelerated by the addition of a low dose of corticosteroid. Levamisole monotherapy was fruitful in achieving complete remission of the disease in both the cases.

Reference

References are available on request at editor@healtalkht.com