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Various Treatment Modalities of Oral Lichen Planus: A Concise Review

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ABSTRACT

Oral Lichen Planus (OLP) is an autoimmune, mucocutaneous disorder present in the oral cavity. Besides oral mucosa, skin, scalp and genital mucosa can also get affected. Middle aged females are mostly affected. It is a precancerous lesion and its atrophic and erosive forms are painful. The patient can experience burning sensation and discomfort in such cases. It is chronic inflammatory disorder and it mostly affects adults. Cytotoxic T cells play an important role in its pathogenesis. This disorder is also triggered by viral and bacterial infections. The treatment plan aims in reducing the inflammation and include various treatment modalities such as corticosteroids, retinoids, immunosuppressants, antifungals, calcineurin inhibitors, vitamin A, curcumin and lasers. The corticosteroids, in the form of intralesional injections, topical agents and systemic drugs, are an important part in the management of this disorder. The photodyanamic therapy is also an important treatment option to control this disease.

Keywords: mucocutaneous, disorder, inflammation, treatment, corticosteroids

INTRODUCTION

In 1869, Wilson explained this disease as a chronic, autoimmune, mucocutaneous disorder. It mostly affects adult females and common oral sites are buccal mucosa, tongue, gingival and palate.[1] However, this disorder can affect any mucosal surface including larynx and oesophagus and prevalence in India ranges from 0.1-1.5%. In this disorder, the lymphocytes are activated by antigens and cytokines are generated, which further lead to the apoptosis of basilar keratinocytes.[2] The predisposing factors include stress, genetic factors, infective substances, systemic disorders, viral infections, bacterial infections, vitamin deficiency, abnormal drug reactions and hypersensitivity to dental material.[3] Both CD-4 (helper)(where CD stands for cluster of differentiation) and CD-8(cytotoxic) cells are present but activation of CD-8 cells cause cell-mediated immunological damage to the basal epithelium. The immune reaction is enhanced by keratinocytes and modified Langerhans cells.[4]

ETIOPATHOGENESIS

Immune dysregulation, genetic factors and environmental factors play an important role in the pathogenesis of this disease.[5] The reaction is mediated by Tcells, mostly CD8 positive T cells, that generate cytokines, which leads to distortion of basement membrane and cause apoptosis of basal epithelial cells.[3] There is appearance of keratinocyte antigens and invasion of T cell lymphocytes. Oxidative stress plays an important role in the engaging of lymphocytic infiltrate, increased generation of reactive oxygen species and apoptosis

initiation.[6] There is unusual cell mediated immune reaction of both T4 and T8 lymphocytes in basal epithelial cells, which is enhanced by Langerhans cells.[7] The main factors include stress, cell mediated hypersensitivity, autoimmune reaction to local antigens, hypertension, diabetes, bacterial and viral infections. Certain autoimmune disorders, systemic medications, such as NSAID (nonsteroidal anti-inflammatory drugs), antihypertensives, oral hypoglycemic agents, and amalgam restorations can enhance the severity of this disease.[6] It is observed that hepatitis C virus (HCV) and human papilloma virus (HPV) have strong connection with this disease and can cause cancerous alteration of this disease.[5]

CLINICAL FEATURES

The lesions are multiple, bilateral, mostly symmetrical, well-defined white bands with a framework of mild erythema affecting buccal mucosa and tongue.[3] These are the clinical forms as follows:

1. Reticular-There is a lacelike pattern of slightly elevated grayish white lines, called Wickham's striae, with a framework of papules or rings. It is mostly asymptomatic and is most common.[5]
2. Erosive-There is presence of pseudomembrane with erythema, ulceration and keratotic white lines. The patient suffers burning sensation and pain, along with difficulty in speech and swallowing.[5]
3. Atrophic-The lesions are reddish in colour and diffused, with intermixed areas of white lines and erythema of the oral mucosa.[5]
4. Plaque like-There is presence of white, homogenous areas on the oral mucosa, resembling oral leukoplakia. The common sites affected are buccal mocosa and dorsal surface of tongue.[5]
5. Papular-There is presence of minute papules in the oral cavity, which are white in colour. Indented streaks, which are white, are present at the border of the lesion.[5]
6. Bullous-These lesions are initiated as blisters, which are painful. These blisters expand and break, which further leads to ulceration in the oral cavity. One of the major signs of this form is presence of positive Nikolsky's sign.[5]
7. Vulvovaginal gingival syndrome-In this disorder, there is presence of lichen planus lesions in vulva, vagina and gingiva. The genital disorder is erosive and erythematous. The clinical features include discomfort, pain, burning sensation, dyspareunia and vaginal discharge.[8]

TREATMENT MODALITIES

CORTICOSTEROIDS

Some of the commonly used steroids are hydrocortisone, methyl prednisolone, dexamethasone, prednisone, triamcinolone and clobetasol. Some of the major actions of glucocorticoids are anti-inflammatory action, immunosuppressive action, affecting metabolism of proteins, carbohydrates and lipids, stabilization of lysozyme membrane, reduction in the production of inflammatory mediators, for example prostaglandins and suppression of the activity of white blood cells There is reduction in edema and fibrin deposition, which leads to reduced leucocyte activity, reduced kinin production, reduced production of hydrolytic enzyme and reduced destruction of tissues. Phagocytosis is suppressed.[9]

A study was done in which twenty patients suffering from oral lichen planus were given triamcinolone acetonide in forms of mouthwash and or abase. They were instructed to consume the medication four times a day. The results showed that the mouthwash had better shelf life and is more suitable for the patient.[10] The treatment of oral lichen planus comprises the use of topical steroid preparations in the form of ointment, cream, gel, adhesive paste, sprays and rinsing solutions.[11] They are first line therapy for erosive lichen planus.[12] The

following table includes topical steroid preparations in relation to their potency [11]:

Corticosteroids having low potency	**1% hydrocortisone acetate, 0.25% methylprednisolone acetate**
Corticosteroids having mild potency	0.05%clobetasone butyrate,0.1%hydrocortisone butyrate
Corticosteroids having high potency	0.025%beclomethasone dipropionate, 0.05%beclomethasone dipropionate,0.1%betamethasone valerate
Corticosteroids having very high potency	0.05%clobetasol propionate

Oral prednisone is a systemic corticosteroid that is used in severe cases of oral lichen planus.[12] For a normal adult, prednisone should be administered in the dosage of 10-20mg/day (milligram per day) but if the case is uncontrollable, it should be administered in the dosage of 35mg/day. It is advised to be consumed as a single dose in morning, after consuming food, in order to avoid peptic ulceration and insomnia.[13] 0.05%clobetasol propionate gel,0.1% triamcinolone acetonide ointment,0.1% betamethasone valerate gel, and fluticasone propionate spray are mostly used. Prednisolone (dose-40 to 80 mg for one week) is a systemic corticosteroid which is commonly used to treat ulceration and erythema in patients suffering from erosive lichen planus.[9] In cases of severe pain,1.0 mg/mL aqueous triamcinolone acetonide is preferred. During night and after meals, patient should gargle with 5mL(millilitre) of solution for two minutes. When the rising is done, the patient should be instructed to spit out the solution and should not consume food for at least one hour. Adrenal obstruction, distortion of oral mucosa, candidiasis and discomfort are some of the adverse effects of using topical corticosteroids. In cases of uncontrollable lesions, intralesional, subcutaneous injection of 0.2-0.4 mL of a 10 mg/mL solution of triamcinolone acetonide is recommended.[13] Betamethasone and methyl prednisolone are systemic corticosteroids, which obstruct the conversion of phospholipids to arachidonic acid, which leads to obstruction of the cyclooxygenase and lipoxygenase pathways and stops the generation of inflammatory mediators. They are administered in the dosage of 1-1.5 mg/kg/day (where kg is kilogram) and 0.5mg OD (once a day) is given after breakfast on two consecutive days every two weeks for a duration of ten weeks. The side effects include diarrhea, weakness, hypertension, fluid retention, insomnia and nervousness.[1] Contraindications include patients who are breast feeding, or pregnant, and extensive care and monitoring should be done in immunocompromised patients, diabetic patients, hypertensive patients and patients suffering from tuberculosis.[13]

IMMUNOSUPPRESSANTS

These are immunomodulatory agents such as calcineurin inhibitors, for example, cyclosporine, tacrolimus or pimecrolimus. Cyclosporine decreases the synthesis of lymphokines and can be used in the form of mouthrinse or ointment [2]. Nephrotoxicity, renal dysfunction, gingival hyperplasia and hypertension can occur. In patients suffering from severe and uncontrollable lesions,0.1% topical tacrolimus should be the first line of treatment, when the use of calcineurin inhibitors is considered.[14] It is a macrolide immunosuppressant whose functioning is similar to cyclosporine but it has certain advantages. It is safe, well tolerated, infiltrates oral mucosa more effectively and is 10 to 100 times more efficient drug than cyclosporine. In cases of patients suffering from erosive oral lichen planus, topical tacrolimus with small concentration, dissolved in distilled water, should be administered.[2] A comparative study was done which suggested that tacrolimus, when used topically, is as efficacious as corticosteroid with high potency, like clobetasol. When a randomized controlled trial was done, it was found that 1% pimecrolimus cream is successful in treating erosive oral lichen planus.[12] Topical calcineurin inhibitors, especially tacrolimus and pimecrolimus, are most suitable of

treating such lesions and in cases of psoriasis. They are anti-inflammatory drugs that suppress the activity of T lymphocytes and stop the generation of proinflammatory cytokines. The adverse effects include atrophy of skin, telangiectasia, acneiform eruptions and dermal scarring .Studies have shown that pimecrolimus penetrates the skin with slow speed than tacrolimus but is more lipophilic than tacrolimus and has comparatively more retention within the skin, so the systemic adverse effects are reduced in such patients.[15] However, there can be adverse effect of development of malignancy(squamous cell carcinoma and lymphoma) in patients who are administering topical tacrolimus or pimecrolimus for treatment of oral lichen planus and in cases of cutaneous psoriasis, according to the research done by US FDA(United States Food and Drug Administration).[8]

Azathioprine is an immunosuppressant drug and is given in the dosage of 50 to 100 mg/day. It is a steroid sparing agent which functions synergistically with prednisone. It decreases inflammation and is beneficial as the dosage of prednisone can be reduced in such cases. Nausea, vomiting, inflammation of pancreas, hepatotoxicity, distortion of bone marrow, diarrhea, joint pain and damage to retina are some of the adverse effects.[2]

Mycophenolate mofetil is morpholino ester and a derivative of mycophenolic acid, which comprises of immunosuppressive, antibacterial, antifungal, anti-cancerous and antiviral activities. There is decrease of guanosine nucleotides and disability of DNA, RNA and protein generation. The lymphocyte proliferation, glycosylation and antibody synthesis are stopped. The engaging of leukocytes to areas of inflammation is obstructed by this drug. It is administered in bullous and erosive forms of lichen planus with a dosage of 2gram per day in adults. Nausea, vomiting, diarrhea, anorexia, abdominal pain and hematuria are some of the side effects.[22]

RETINOIDS

Retinoids belong to the family of polyisoprenoid lipids and are derivatives of vitamin A(Retinol). It can be classified into for generations. The first generation comprises of retinol, tretinoin and isotretinoin. The second generation involves etretinate and its metabolite acitretin, and the third generation comprises of tazarotene and bexarotene. Seletinoid G belongs to the fourth generation. The mechanism of action includes attaching of retinoid ligands of certain nuclear receptors. It has the ability to up/downregulate transcription.[16] They initiate the activity of macrophages and cell mediated cytotoxicity, which is antibody dependent. The inflammatory mediators are inhibited.[1] Retinoids control epithelial cell growth and differentiation, decreases keratinization of epithelial cells, inhibit tumorigenesis and has anti-inflammatory action [16]

Ferguson et al conducted a study in which etritinate was suggested to have lowest value in treatment of erosive oral lichen planus. The dosage is 25-75 mg for 8 weeks and the side effects include pruritis, paronychia, cheilitis and skin peeling of limbs. Camisa and Allen conducted a study in which systemic isotretinoin was administered to six patients. The dosage was 10-60 mg/day for 8 weeks. Cheilitis, headache, dry skin and rashes were some of the side effects and the retinoid was of minimal use.[2] The dosage of etretinate is 0.6 mg/kg/day for a duration of 2 months. Its maintenance dose is 0.3 mg/kg/day.[1]

ANTIMALARIALS

Antimalarial agents include hydroxychloroquine (HCQ). It is derived from chloroquine (CQ) by hydroxylation. Both HCQ and CQ have anti-inflammatory activity and. immunostimulatory activity. HCQ goes across the cell membrane and deposits in lysosomes. So, there is decreases in the generation of cytokines and proinflammatory mediators, which leads to decrease in inflammation.[17] The side effects include nausea, vomiting, headache,

diarrhea, muscle pain, tiredness, cutaneous hyperpigmentation and damage to retina.[14]

ANTIFUNGALS

As overlapping candidal infection, candida albicans can be present in cases of oral lichen planus. This superimposed infection can worsen the lesion. Griseofulvin is an antifungal, which can be used in such cases. The dosage is 500 mg/day for six months, used in the form of tablet. Side effects include nausea, vomiting, headache, tiredness, diarrhea, sleepiness and abnormally low concentration of neutrophils in the blood.[1] A randomized, double-blind trial, was done, in which 35 patients suffering from oral lichen planus were administered either clobetasol propionate and miconazole or clobetasol propionate and placebo. The duration was six weeks. It was found that miconazole was not successful in treating oral lichen planus but it obstructed the emergence of candidiasis in the oral cavity. However, clobetasol propionate gel was successful in curing lesions associated with oral lichen planus.[18]

PHOTODYNAMIC THERAPY

Methylene blue is a photosensitizing element, which is activated by laser light at a particular wavelength.[6] The purpose is to eliminate targeted cells, with the help of powerful oxidizers, as they can lead to disintegration of cell by rupture of cell wall, cell destruction and deactivation of protein. In cases of oral lichen planus, psoriasis and malignancy, an abnormally high rate of proliferation of cells by rapid division, along with inflammation, can be observed. This therapy encourages selective absorption of photosensitizers into these hyperproliferating, inflammatory cells, which leads to apoptosis in these cells. This can cause reduction in hyperproliferation and inflammation, associated with this disease. Methylene blue is a phenothiazine dye, which has antibacterial property and very less tissue toxicity. At wavelengths longer than 620 nm, it has the ability of strong absorption, where piercing of light into tissue is most favourable.[19]

LASER

Laser treatment is successful in cases of erosive lichen planus, as it causes distortion of superficial epithelium, underlying connective tissue and epithelium with inflammatory elements. In this treatment, laser diode of 980 nm (nanometer), infrared rays of 904 nm, ultraviolet rays and laser biostimulation with pulsed diode, can lead to destruction of the outer epithelium which comprises of keratinocytes with denatured protein.[6]

ANTIOXIDANT

Lycopene is strong, polyunsaturated, fat soluble, beta carotenoid and is red in colour [20]. It is lipophilic antioxidant and has acyclic structure. It is found in red and pink fruits like tomato, watermelon and guava. The pro vitamin A activity is lacking and it scavenges singlet oxygen. It neutralizes hydroxyl radical and nitrogen dioxide.[21] It causes obstruction of proliferation of malignant cells. In conditions where there is elevation of oxidative stress and lipid peroxidation, and reduction in antioxidant property, like oral cancer or premalignant disorders like oral submucous fibrosis, oral leukoplakia and oral lichen planus, lycopene can be used .This is because it has strong antioxidant, free radical scavenging and immunomodulatory actions.[20] There is physical and chemical quenching of free radicals, and this drug is taken with a dose of 6-60 mg/day for a duration of 2-32 weeks.[1]

SURGICAL MANAGEMENT

Surgical excision and cryosurgery have proved to be efficacious in the management of erosive oral lichen planus but relapse can occur in such cases.[11] There is a risk of trauma in such cases which can lead to the development of new lesions (Koebner phenomenon).[2]

CONCLUSION

According to the nature and clinical form of this disease, guidance should be given to the patient. There is not enough evidence to prove the success of all these treatment modalities but the use of corticosteroids is the most common therapeutic approach in the treatment of this lesion.[2] A typical, symptomatic lesion of oral lichen planus in chronic condition can disturb the normal life of the patient and his/her attitude towards disease, causing stress, anxiety and fatigue.[1]

Declaration by Authors

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