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A REVIEW OF LICHEN PLANUS: ETIOPATHOGENESIS AND MANAGEMENT

Health Science

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ABSTRACT

Oral lichen planus (OLP) is a chronic mucosal condition usually experience in clinical practice. Lichen planus is expected to show an unusual reaction in which epithelial cells are perceived as outsider or foreign to, secondary to the change in the antigenicity of cell surface. OPL is a mucocutaneous disorder of stratified squamous epithelium of unknown etiology that effects oral and genital mucosal layer, skin, nail, and scalp. Lichen Planus (LP) is evaluated to influence 0.5 to 2 percent of the all inclusive community. With this illness has regularly been accounted for in moderately aged patient with 30 to 60 year old and shows female predilection. It has different oral appearances; reticular structure is most widely recognized. The erosive and atrophic type are less common, yet are destined to cause symptom. Tropical corticosteroids comprise back bone of treatment for symptomatic lesion of OLP. The present article is review on etiology, clinical features, histopathology and management of OLP. We hereby reviewed papers published from year 1983 to 2018 for better understanding of etiopatogenesis of development of OLP and its treatment modalities which includes modern medicine, laser and ayurveda. The articles selected for reviewing consist of both old and recent concept of pathogenesis and treatment plan of oral lichen planus. It also flashes some light on clinical characters and histopathological features of the oral lesion (OLP).

KEYWORDS

oral lichen planus, mucocutaneous, precancerous condition, pathogenesis.

INTRODUCTION:

OLP is chronic disorder of stratified squamous epithelium estimated to influence 0.5 to 2 percent of the all general population[1,2]. It is an chronic inflammatory disorder effecting mucosal and cutaneous tissues. OLP is mucosal counterpart of cutaneous LP and is progressively persistent and resistant to treatment [2, 3]. In perspective on the prevalence of OLP and the capability of this chronic lesion to cause significant discomfort it is essential for the clinician to known about its clinical presentation and the treatment.

Etiology

Although the exact etiology is still unknown but some factors associated with it. These are as follows

1. Hereditary: familial cases are unknown. An association has been seen with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1 and DRW9 [4,5,6,7,8].
2. Dental material: a considerable number of materials regularity utilized in restoration and treatment in oral cavity have been distinguished as activating components for OLP – including silver amulgum, gold, Co, palladium, chromium and even nonmetal eg epoxy saps (composite) and delayed utilization of denture wear [9,10,11,12].
3. Medication- Oral lichenoid drug responses might be activated by fundamental medications including NSAIDs, beta blockers, sulfonylureas, somel ACE inhibitors, and a few antimalarials, contact allergens including toothpaste flavourings, particularly cinnamates [4,9,13].
4. Infectious agent- HCV infection have been associated with OLP pathogenesis in certain ethnic populations, especially in Mediterranean area. The pathogenetic mechanism that connect OLP and HCV were based on the finding that circulating antibodies against the oral epithelium were identified in OLP patients with HCV infection, and that OLP mediating cytokinase are triggered by HCV infection[14].
5. Autoimmunity OLP may sometimes be related with immune system issue, for example, primary biliary cirrhosis, chronic hepatitis, ulcerative colitis, myasthenia gravis, and thymoma[15].
6. Gut disease: Gut ailments once in a while depicted associative with OLP incorporate coeliac sickness, ulcerative colitis and Crohn's disease[16].
7. Food allergy: Food substances and some of the additives of food, for example, cinnamon aldehyde have been observed to be related with OLP[11].
8. Stress: One of the variables variable factors for the development of OLP is nervousness and stress. Some of the studies in literature reveal the role of the psychological stress in the etiology of OLP[17,18,19].
9. Diabetes and hypertension: Studies have uncovered that both diabetes mellitus (DM) and hypertension are related with OLP [20,21,22,23]. (Greenspan disorder: Triad of DM, hypertension and OLP)
10. Malignant neoplasms: LP has been seen on the skin and additionally mucosae of patients influenced by a range of various neoplasms, for example, with breast cancer and metastatic adenocarcinoma [11].
11. Other factors: OLP has occasionally been related with different conditions, including psoriasis, lichen sclerosis, urolithiasis, and specialists used to treat nerve stones, Turner's disorder, and so on [11].

Pathogenesis-

Lichen planus is accepted to result from abnormal T cell mediated immune reaction in which basal epithelial cells are perceived as forgein on account of change in antigenicity of their cell surface[14]. The reason of this immune mediated basal cell damage is obscure.

Mechanism involves keratinocyte antigen expression or unmasking of an antigen that may be a self peptide or heat shock protein

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T cells (mostly CD8 cells and some CD4 cells) migrates into the epithelium through chemokines mediated migration

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These migrated CD8 cells are activated directly by antigen binding to major histocompatibility complex -1 on keratinocytes or through activated CD4 lymphocytes

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The activated CD8 Tcell in turn kills the basal keratinocytes through tumor necrosis factor (TNF)-α

Cell Cycle control in OLP

Cell cycle control in oral lichen planus Apoptosis of basal keratocyste, caused by the activity of cytotoxic t cells could be a possible explanation for one of the histopathological Hallmark of OLP that is the vascular degeneration of basal membrane Supported by several molecular studies demonstrating the presence of apoptotic signals in OLP is apoptosis was the main cellular event then all cases of untreated 0lp would end up with fever and extensive oral mucosa erosion however this is not the case in the majority of 0lp as the most common clinical form of OLP is reticular lichen planus while the erosive form

usually are limited in one or two oral sites authors have demonstrated mixed pattern of both apoptosis and increased cellular proliferation occurring simultaneously. Gonz alez etal. suggested that possibly epithelial cells in OLP respond to the inflammatory chronic Attack by exhibiting senescent phenotype instead of apoptosis this hypothesis was based on the observed positive p21 expression in OLP which is indicative of cell cycle arrest and possibly of senescence Cell cycle arrest helps in maintaining tissue integrity and facilitating DNA repair mechanism but at the same time entry into senescence could favour malignant transformation[10].

THE ROLE OF P53 IN OLP-

The tp53 gene was discovered in 1979 and and codes are tumor suppressor protein.Cellular stress such as DNA damage can lead to activation of p53. Inactivation of p53 is a frequent phenomena in OS cc. this is caused by mutations presence of HPV virus and other molecular alterations occurring in the p53 pathway as p53 expression has been identified as a response to DNA damage the identification of p53 in o l p tissue is interpreted as an indication of precancerous potential by some researchers. The higher expression of p53 in ALP is a result of the highest cellular proliferation it is tempting to speculate that 0lp as an inflammatory condition along with the accompanying oxidative stress probably induces genotoxic stress. the higher proliferation rate reported for the oral epithelium turnover in OLP may also create a replication stress which leads to activation of the DNA damage response checkpoint. continuous activation of this checkpoint will eventually surface these cell repair capacity predicting the emergence of genomic instability and finally selective p53 inactivation[10].

MATRIX METALLOPROTEINASES (MMPs) AND OLP –

Sutinen et al. where among the first to investigate the expression of MMPs and there inhibitors TIMPs in clinical samples with Oral squamous cell carcinoma (OSCC), OLP, dysplasia lymph nodes metastasis and normal oral mucosa. Their findings showed significantly higher expression in OSCC in comparison to the other regions they first noted a weak MMP1 and 2 expressions in OLP the role of MMPs in OLP was initially associated with apoptosis of epithelial cells and the level of inflammation[14].

Chen et al, studied MMPs, TIMPs and TGF-b in the OSCC that developed from previous 0LP and found constant expression with levels comparable to those detected in atrophic OLP, which is the form of OLP reported to have the higher malignant potential[10].

The Role Of Nf-kappa B And Associated Cytokines (I L 1 Alpha I L 6 I L 8, Tnf)

The transformation factor nuclear factor KAPPAB (NF KAPPA B) has been described as a major molecular associating chronic inflammation and cancer. By inhibiting apoptosis, promoting cellular proliferation and favouring metastatic phenotypes. The level of NF- KAPPA B associated cytokines (IL-1 alpha IL-6, IL-8, TNF) have been found increased in hole an unstimulated saliva and other oral fluids of OLP patience and also in OSSC patients[10].

A Cytokine-Mediated Lymphocyte Homing Mechanism

In OLP, there is over expression of the vascular adhesion molecules (VAM), that is, CD62E, CD54, and CD106, by the endothelial cells of the sub-epithelial vascular plexus. The invading lymphocytes express reciprocal receptors (CD11a) to these VAM. A portion of the cytokines that are incharge of the upregulation of the VAM are: TNF-α, IFN-γ and IL-1[14,24].

Nonspecific components like mast cell degranulation and MMP-1 activation further disturb the T-cell accumulation, BM interruption by mast cell proteases and keratinocyte apoptosis[4,25]. The integrity of the BM is kept up by a living basal keratinocyte because of its secretion of collagen 4 and laminin 5 into the epithelial BM zone. Thus, keratinocytes require a BM-derived cell survival signal to keep the beginning of its apoptosis. Apoptotic keratinocytes are no longer able to perform this function, which results in damage of the BM. A non intact basement membrane cannot send a signal for cell survival. This sets in an endless loop which identifies the chronic nature of disease[20]. The matrix metalloproteinase (MMP) are primarily associated with tissue matrix protein degradation. MMP-9, which separates collagen 4, alongside its activators is upregulated in OLP lesional T cells, bringing about more BM disturbance[4, 27].RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) is an individual from the CC chemokine family which assumes a basic job in the enrollment of lymphocytes and mast cells in OLP. The selected mast cell experiences degranulation affected by RANTES, which discharges chymase and TNF-α. These substances upregulate RANTES secretion by OLP lesional T cells[4,28].

Weak expression of transforming growth factor (TGF)- β1 has been found in OLP. TGF-β1 lack may incline to autoimmune lymphocytic inflammation. The harmony between TGF-β1 and IFN-γ decides the level of immunological activity in OLP lesion. Nearby overproduction of IFN-γ by CD4 + T cells in OLP lesion downregulates the immunosuppressive impact of TGF-β1 and upregulates keratinocyte MHC class II expression and CD8 + cytotoxic T-cell activity[4].

Clinical Features

Lichen planus is a disease of middle age that affects men and women in nearly equal numbers (0.2 % to 2%). Children are really affected. many of these cases likely represent lichenoid drug reactions to the medications used to manage these conditions which may mimic lichen planus clinically .Several types of lichen planus within the oral cavity have been described. The most common type is the-

a) Reticular form which is characterized by numerous interlacing white keratotic lines or striae (so called wickham's striae) that produces an annular or lacy pattern. The buccal mucosa is the site most commonly involved. The striae, although occurring typically in a symmetric pattern on the buccal mucosa bilaterally, may also be noted on the tongue and less commonly on the gingiva and the lips.

b) Plaque form of lichen planus tends to resemble leukoplakia clinically but has a multifocal distribution. Such plaques generally range from slightly elevated to smooth and flat. The primary site for this variant are the dorsum of the tongue and the buccal mucosa.

c) Erythematous or atrophic form of lichen planus appears as Red patches with very fine white striae. It may be seen in conjunction with reticular or erosive variants. The proportion of keratinized area to atrophic area varies from one area to another. The attached gingiva commonly involved in this form of lichen planus, exhibits patchy distribution often in four quadrants. Patients may complain of burning sensitivity and generalized discomfort.

d) Erosive form of lichen planus the central area of lesion is ulcerated. A fibrinous plaque or pseudo membrane covers the ulcer. The process is a rather dynamic one, with changing patterns of involvement noted from week to week. Careful examination usually demonstrates keratotic striae, peripheral to the site of erosion and erythema.

A rarely encountered form of lichen planus is the bullous variant. The bullae range from a few millimetre to cm in diameter. Such bullae are generally short lived and on rupturing leaves a painful ulcer. Lesions are usually seen on the buccal mucosa specially in the posterior and inferior region adjacent to the second and third molars. The lesions are less commonly seen on the tongue, gingiva and inner aspect of the lips. Reticular or striated keratotic areas should be seen with this variant of lichen planus.

On the skin lichen planus is characterized by the presence of small violaceous polygonal flat topped pruritic papules on the flexures surface. Other clinical variants include hypertrophic, follicular, bullous, atrophic and linear forms. Cutaneous lesions have been reported in 20% to 60% of patients with oral lichen planus.

Histopathology

The microscopic criteria for OLP includes hyperkeratosis liquefactive degeneration of the basal cells followed by caspas mediated cell death (apoptosis) of keratocytes dance band of t-lymphocyte that is lymphophagocytotic infiltrate at the epithelial connective tissue interface. The epithelium undergoes gradual remodeling resulting in reduced thickness and occasionally sawtooth rete ridge pattern. Discrete oesnophilic ovoid bodies representing the apoptotic keratocytes are seen at the basal zone[29].

These degenerating keratinocytes form colloid (Civatte bodies or hyline or cytoid) bodies, that appear as homogeneous eosinophilic globules[1]. Degeneration of the basal keratinocytes and disruption of the anchoring components basement membrane and basal keratinocytes (e.g. hemi desmosomes, filaments, fibrils) weaken the

interface between epithelium and connective tissue. As a result, histological clefts (Max-Joseph spaces) might form and blisters on the oral mucous membrane (bullous LP) is seen at clinical examination[30].

Differential Diagnosis

The differential conclusion can incorporate cheek biting/frictional keratosis, leukoplakia, lichenoid responses, leukoplakia, lupus erythematous, pemphigus, bodily fluid film pemphigoid, para neoplastic pemphigus, erythematous candidiasis and unending ulcerative stomatitis, Graft versus have malady[31].

Management:

The primary line of treatment of OLP has been corticosteroids[33, 34], however due to there adverse effects alternate therapeutic approaches are being administered. Numerous new agents to treat OLP are the following: Amlexanox (AX), Aloe vera gel, tricyclic antidepressant, green tea, curcuminoids, ignatia, low-intensity optical laser , hyluronic acid (HA), propolis, herbaceous plant extract, lycopene, pimecrolimus, and topical thalidomide. tricyclic antidepressant, AX, aloe vera, HA, thalidomide, and propolis are used as topical agents, whereas herbaceous plant, lycopene, green tea, and ignatia are used systemically[32,33,34]

Corticosteroid administered locally, intralesionally, or systemically for the management of OLP, since it dampens the cell-mediated immunity. Numerous researchers have found that the combination of topical and general steroids is effective. Topical application of corticosteroids [33,35] daily is suggested to treat topical oral lesion;0.025% clobetasol propionate, 0.1% corticosteroid acetonide, and 0.05% fluocinonides are the main topical agents used [33,35].

Amitriptyline is a tricyclic antidepressant drug, that can be used along with other drugs in a combine drug therapy to treat OLP. Javadzadeha et al[36] prepare a solution that contains ketoconazole, clobetasol, and tricyclic antidepressant which are compared with dexamethasone tablet (0.5 mg in five cubic centimetre water), thirty Mycostatin drops, and five cubic centimetre antihistamine syrup for purpose of mouth wash. The combination was found to be effective among the patients with OLP

Amlexanox is a medicine and is available in the form of a paste. It is highly effective against the oral tissue layer lesions and there aren't any visible sideeffects. It will increase the content of cyclic AMP in inflammatory cells thereby inhibiting the assembly and secretion of tumour necrotic factor-alpha (TNF-α), leukotrienes, and aminoalkane[32].

Curcuminoids are the basic elements of Curcuma longa (turmeric). it's been an element of Ayurvedic medication for hundreds of years in ancient India, because it is nontoxic and encompasses a type of healing properties together with inhibitor, analgesic, antiseptic, and anticarcinogenic activity. Numerous studies have shown that higher doses of curcuminoids (6000 mg/day) are effective in the management of OLP but according to few researchers there is 40 percent chances of side effects[37].

The low-intensity lasers are being employed in health care studies since 3 decades. It causes local vasodilatation thereby inflicting the immune cells to manoeuvre into the tissue. It helps in controlling the inflam-mation of the oral cavity by modulating the function of mast cells A study conducted by Elshenawy et al showed complete remission of symptoms with no associated side effects[38,39].

Thalidomide is associate immunomodulatory drug. It's anti-immunologic and anti inflammatory properties. it's getting used within the management of aphthous stomatitis, erythema leprosum, atrophic arthritis, myelodysplastic syndromes, and Crohn's disease because it has the potential to cut back the formation of TNF-α [40,41]. It's found to be effective within the management of OLP due to its varied therapeutic properties, like medicament, anti-angiogenesis, and immuno-modulatory properties. Wu et al compared the efficacy of 1% thalidomide paste with 0.043% dexamethasone paste and found both have same efficacy in treatment of erosive OLP[42].

Lycopene is a red-colored antioxidant, which supplies red color to tomatoes and a number of other other fruits. It's therapeutic properties like inhibition of neoplastic cell proliferation, anitioxidant activity, inducing phase II enzymes, interference with protein stimulation, regulation of transcription, and restoration of gap junc-tions[43, 44]. Saawarn et al, conducted a study in which they found that Lycopene 8 mg/day reduces the symptoms of OLP[45].

Aloe vera gel has therapeutic properties which include, antifungal, antiviral, and hypoglyce-mic effects[46, 47]. It inhibits the inflammatory method either by reducing the extent of TNF-α and blood corpuscle adhesion or it interferes with the action of arachidonic acid pathway via Cox[48].

Hyaluronic acid: A study performed by Nolan et al[49] to judge the effectiveness of HA gel preparation (topical) within the treatment of OLP found that topical application of HA has improved the pain scores as compared with placebo.

Green tea: It inhibits migration, activation, and proliferation of T-cell, and additionally controls different inflammatory mediators, thereby managing OLP by regulating the nonspecific and antigen-specific mechanisms involved in the etiopathogenesis of OLP[50,51]. Zhang et al [52] hypothesized that consumption of tea would possibly cut back the incidence of OLP and provides a way of harmless and economical useful medical aid for OLP.

Propolis: Propolis or bee glue is getting used since cen-turies in Ayurvedic drugs. It consist of, antiviral, antifungal, antitumor, antiradiation, and immunomodulating effect. These properties have prompted investigators to test its efficaciousness on OLP.

A study was done by Zyada et al [53] to assess the effectuality of topical mucoadhesive gel containing propolis within the treatment of OLP and proven that propolis showed to be a promising medical specialty agent for inhibiting cell proliferation and found effective on OLP lesions

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