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Original Article

Pathogenesis of Oral lichen Planus

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ABSTRACT:
Oral lichen planus (OLP) is a T-cell-mediated chronic inflammatory oral mucosal disease of unknown etiology. OLP presents as white striations, white papules, white plaques, erythema, erosions, or blisters affecting predominantly the buccal mucosa, tongue and gingiva. Both antigen-specific and non-specific mechanisms may be involved in the pathogenesis of oral lichen planus (OLP). Antigen-specific mechanisms in OLP include antigen presentation by basal keratinocytes and antigen-specific keratinocyte killing by CD8(+) cytotoxic T-cells. Non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions. These mechanisms may combine to cause T-cell accumulation in the superficial lamina propria, basement membrane disruption, intra-epithelial T-cell migration, and keratinocyte apoptosis in OLP. A wide spectrum of treatment modalities is available, from topical corticosteroids to laser ablation of the lesion. In this review, we discuss the various concepts in the pathogenesis and current treatment modalities of OLP.
Keywords: oral lichen planus, pathogenesis, Apoptosis, autoimmune, basal keratinocytes

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INTRODUCTION

The mouth is a mirror of health or disease, a sentinel or early warning system. The oral cavity might well be thought as a window to the body because oral manifestations accompany many systemic diseases. In many instances, oral involvement precedes the appearance of other symptoms or lesions at other locations[1].

Lichen planus is a comparatively common, mucocutaneous disorder that is mediated immunologically. It can also be autoimmune in pathogenesis. It is chronic in occurrence, with periods of exacerbations and remission. It was first described by British Physician Wilson Erasmus in 1869. Lichens are primitive plant that consists of symbiotic algae and fungi and the word planus in Latin means flat.[1]

Lichen planus is a chronic inflammatory disease that affects the skin and the mucus membrane. Oral lichen planus (OLP), the mucosal counterpart of cutaneous lichen planus, presents frequently in the fourth decade of life and affects women more than men in a ratio of 1.4:1.[2] Lichen planus (LP) is a chronic mucocutaneous disorder of the stratified squamous epithelium that affects oral and genital mucous membranes, skin, nails, and scalp. [3]Oral lichen planus (OLP) is the mucosal counterpart of cutaneous LP. [4] It is derived from the Greek word "leichen0" means tree moss and Latin word "planus" means flat. [4]

The designation and description of the pathology were first presented by the English physician Erasmus Wilson in 1866. [5] He considered this to be the same disease as "lichen ruber," previously described by Hebra[6] and characterized the disease as "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development."OLP has been suggested to be related to bacteria such as a Gram-negative anaerobic bacillus and spirochetes but this has not been confirmed. [7] Some of the studies reveal the role of Helicobacter pylori (HP) in the etiology of OLP. [8],[9] However, no evidence of its role has been detected in OLP in some recent studies[10]

HISTOPATHOLOGY

LP is characterized by lichenoid interface dermatitis.

The classic histopathological features include a dense, continuous, and band-like lymphohistiocytic infiltrate at the dermal-epidermal junction and in the upper dermis. Characteristically, the infiltrate disguises the dermal-epidermal junction and makes it difficult to recognize the basal layer at the early stages of the disease [11]Epidermal changes in LP lesions include irregular epidermal hyperplasia with a jagged "sawtooth" appearance, compact hyperkeratosis or orthokeratosis, foci of wedge-shaped hypergranulosis, basilar vacuolar degeneration, slight spongiosis in the spinous layer, and squamatization. The dermal papillae between the elongated rete ridges are frequently dome shaped [12].Vacuolar degeneration at the basal layer may be noted leading to focal subepidermal clefts (Max Joseph spaces) .Whickham striae are usually seen in the areas of hypergranulosis [13]

EPIDEMIOLOGY

The exact incidence and prevalence of LP is unknown. In 1895, Kaposi noted the disease as "rather frequent" with 25 to 30 cases presenting annually. [14] In the United States, the incidence of LP is reported to be approximately 1% of all new patients seen at health care clinics. [15] The Indian subcontinent has a particularly high incidence of disease. LP is estimated to affect 0.5% to 2.0% of the general population.

ETIOLOGY

1. STRESS

The main etiological factor of lichen planus is stress. There are reported exacerbations of the lesion associated with anxiety and psychological stress.[16,17,18] Psychosomatization arising from prolonged emotional stress contributes greatly to initiation and clinical expression of the lesion.[19,01]

2. GENETIC BACKGROUND

Familial cases are rare. An association has been observed with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1, and DRW9.21,22,23,24] In Chinese patients, an increase in HLA-DR9 and Te 22 antigens has also been noted

3. INFECTIOUS AGENTS

OLP has been suggested to be related to bacteria such as a Gram-negative anaerobic bacillus and spirochetes but this has not been confirmed. [25] Some of the studies reveal the role of Helicobacter pylori (HP) in the etiology of OLP. [26],[27] However, no evidence of its role has been detected in OLP in some recent studies. [28]OLP has been found to be associated with various viral agents such as human papilloma virus (HPV), [29],[30],[31],[32] Epstein Barr virus (EBV), [33] human herpes virus 6 (HHV-6) and human immunodeficiency virus (HIV). [34].

4. AUTOIMMUNITY

OLP may occasionally be associated with autoimmune disorders such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, and thymoma. [35]

5. SYSTEMIC MEDICATIONS

Systemic medications such as beta blockers,[36] nonsteroidal anti-inflammatory drugs, anti malarials,[37] diuretics, oral hypoglycemics,[38] penicillamine,[39] oral retroviral medications are reported to initiate or exacerbate oral lichen planus and oral lichenoid reaction

6. DIABETES AND HYPERTENSION

Studies have revealed that both diabetes mellitus (DM) and high blood pressure are associated with OLP. [40],[41],[42],[43](Greenspan syndrome: Triad of DM, hypertension and OLP)

PATHOGENESIS

OLP is T - cell mediated autoimmune disease in which the auto-cytoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epethelium.Intially keratinoocyte antigen expression or unmasking of an antigen may occur followed by migration of T cells(mostly CD8+ and some CD4+ cells) into the epethellium either due to random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes. These migrated CD8 + cells are activated directly by an antigen binding to major histocompatibility complex (MHC)-1 on keratinocyte or through activated CD4 + lymphocytes. In addition, the number of Langerhans cells in OLP lesions is increased along with upregulation of MHC-II expression; subsequent antigen presentation to CD4 + cells and interleukin (IL)-12 activates CD4 + T helper cells which activate CD8 + T cells through receptor interaction, interferon γ (INF-γ) and IL-2. The activated CD8 + T cells in turn kill the basal keratinocytes through tumor necrosis factor (TNF)-α, Fas-FasL-mediated or granzyme B-activated apoptosis.

A CYTOKINE-MEDIATED LYMPHOCYTE HOMING MECHANISM

In OLP, there is increased expression of the vascular adhesion molecules (VAM), that is, CD62E, CD54, and CD106, by the endothelial cells of the sub-epithelial vascular plexus. The infiltrating lymphocytes express reciprocal receptors (CD11a) to these VAM. Some of the cytokines that are responsible for the upregulation of the VAM are: TNF-α, IFN-γ and IL-1.[44]

Nonspecific mechanisms like mast cell degranulation and MMP-1 activation further aggravate the T-cell accumulation, BM disruption by mast cell proteases and keratinocyte apoptosis.[45] The normal integrity of the BM is maintained by a living basal keratinocyte due to its secretion of collagen 4 and laminin 5 into the epithelial BM zone. In turn, keratinocytes require a BM-derived cell survival signal to prevent the onset of its apoptosis. Apoptotic keratinocytes are no longer

able to perform this function, which results in disruption of the BM. Again, a non-intact BM cannot send a cell survival signal. This sets in a vicious cycle which relates to the chronic nature of the disease.[46]The matrix metalloproteinase (MMP) are principally involved in tissue matrix protein degradation. MMP-9, which cleaves collagen 4, along with its activators is upregulated in OLP lesional T cells, resulting in increased BM disruption[66].RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) is a member of the CC chemokine family which plays a critical role in the recruitment of lymphocytes and mast cells in OLP. The recruited mast cell undergoes degranulation under the influence of RANTES, which releases chymase and TNF-α. These substances upregulate RANTES secretion by OLP lesional T cells.[47]Weak expression of transforming growth factor (TGF)-β1 has been found in OLP. TGF-β1 deficiency may predispose to autoimmune lymphocytic inflammation. The balance between TGF-β1 and IFN-γ determines the level of immunological activity in OLP lesions. Local overproduction of IFN-γ by CD4 + T cells in OLP lesions downregulates the immunosuppressive effect of TGF-β1 and upregulates keratinocyte MHC class II expression and CD8 + cytotoxic T-cell activity.

CLINICAL FEATURES

The cutaneous lesions of LP are characterized by 5 ps: Purple, polygonal, pruritic papules and plaque. [48] Initially, LP is evident as a cutaneous and mucosal eruption, though rarely it can manifest with only oral or nail findings. LP usually begins as discrete, flat-topped papules that are 3 to 15 mm in diameter which may coalesce into larger plaques. Cutaneous lichen planus may present in different forms. Linear lichen planus manifests as closely aggregated linear lesions on the limbs that may develop the Koebner phenomenon. Annular lichen planus accounts for approximately 10 percent of lichen planus cases. It commonly appears as arcuate groupings of individual papules that develop rings or a peripheral extension of clustered papules with central clearing. In addition to the usual sites of distribution, this form of lichen planus may occur on male genitalia and buccal mucosa.[49]

THE SIX P'S TO DESCRIBE LICHEN PLANUS LESIONS

1. Planar (flat-topped)
2. Purple
3. Polygonal
4. Pruritic
5. Papules
6. Plaques

DIAGNOSIS

Lichen planus can be diagnosed clinically in classic cases, although biopsy is often helpful to confirm the diagnosis and is required for more atypical presentations. A 4-mm punch biopsy should be adequate on the skin or in the mouth. The histology shows a characteristic "saw-tooth" pattern of epidermal hyperplasia; hyperparakeratosis with thickening of the granular cell layer; and vacuolar alteration of the basal layer of the epidermis, with an intense infiltration (mainly T cells) at the dermal-epidermal junction, 4-mm punch biopsy should be performed when diagnosis is uncertain.

DIFFERENTIAL DIAGNOSIS OF ORAL LICHEN PLANUS

Condition	Distinguishing features	Diagnostic method	Treatment
Bite trauma	White area on buccal mucosa where the teeth occlude	Clinical appearance	Reassurance
Leukoplakia	White adherent patch or plaque on oral mucosa that does not rub off	Punch or shave biopsy	Surgical excision or cryotherapy with liquid nitrogen
Thrush	White adherent patch or plaque on oral mucosa that rubs off	Clinical appearance and potassium hydroxide (KOH) preparation	Antifungal suspension or troches

TREATMENT OF ORAL LICHEN PLANUS

Treatment	Severity of case	Dosage
1.High-potency topical corticosteroids a)Clobetasol (Temovate) b)Fluocinonide	First-line therapy	Clobetasol 0.05% ointment Fluocinonide 0.05%
2.Topical calcineurin inhibitors† a)Pimecrolimus (Elidel) b)Tacrolimus (Protopic	For cases unresponsive to topical corticosteroids	Pimecrolimus 1% cream Tacrolimus 0.1% ointment
3.Oral corticosteroids (prednisone)	For severe, widespread lichen planus	

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