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CURRENT ASSESSMENTS REGARDING THE PATHOGENESIS AND TREATMENT STRATEGIES OF ORAL LICHEN PLANUS – A REVIEW

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ABSTRACT

Oral Lichen planus (OLP) is an autoimmune chronic inflammatory disease of mucous membrane. It is mostly CD8+T-cell mediated autoimmune response with unknown etiology and pathogenesis. It generally affects approximately 1% to 2% of the world's population. OLP affects women more than men at a ratio of approximately 1.4:1. The prevalence of OLP ranges between 0.5% and 3% and in Indian populations it is 2.6%. In recent years, many possible causes regarding the pathogenesis of OLP have been suggested, the exact nature is still unclear. Most data suggests that some specific antigen and nonspecific mechanism are involved. Antigen presentation by basal keratinocytes and antigen-specific keratinocyte killing by CD8+ cytotoxic T-cells are said to be antigen-specific mechanisms. It is still not clear whether antigen is exogenous or endogenous in origin and what specific antigen is responsible for triggering the inflammatory responses. Mast cell degranulation and activation of matrix metalloproteinase (MMP) specific mechanisms. This paper explains how these two mechanism work together and also the current understanding regarding other factors which are responsible for its pathogenesis.

KEYWORDS: Pathogenesis, Oral lichen Planus, Treatment.

Introduction

Lichen planus in greek means tree moss and planus means flat. Lichen planus was first described by Erasmus Wilson in 1869[1]. Lichen planus is a chronic disease which affect the hair follicles, nails, esophagus, and, less frequently, the eyes, urinary tract, genitals, nasal mucosa, and larynx.

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Involvement of scalp causes violaceouspapupules known as lichen planopilaris and results in complete hair loss. In case of nails it causes pitting, pterygium formation and nail loss. First oral lichen planus case was reported by francoishenrihallopeau in 1910[1]. OLP constitutes 9% of all white lesions. In general OLP affects 0.5-2% of the population.The question of malignant transformation of oral lichen planus remains debatable [2].

Clinical criteria

Usually women are more affected than male with a ratio of 1.4:1[3]. It also occurs at age between 30 and 60 years, sometimes children and young adults may also get affected[1].
Presence of bilateral, more or less symmetrical lesions. Presence of a lace-like network of slightly raised gray-

white lines (reticular pattern) (Fig-1). Erosive, atrophic, bulbous and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa[4,5]. In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term 'clinically compatible with' should be used[4].

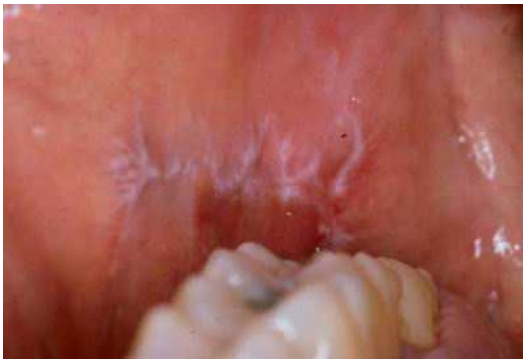

Fig 1: Demonstrate presence of lace like network – wickham straie

Etiology

The cause of OLP is unknown. It is said some certain factors mention below may trigger an inflammatory disorder.

- Hepatitis C infection and other types of liver disease.
- Allergy-causing agents (allergens), such as foods, dental materials or other substances.
- Genetic background.
- Immunodeficiency disorder.
- Some bacterial and viral diseases.
- Certain medications for heart disease.
- High blood pressure or arthritis.
- Certain drugs like ibuprofen and naproxen.
- Stress.
- Graft versus host disease [5,6,7].

Histopathologic criteria

It was first described by Dubreuill in 1906 and later by Shklar[8]. The criteria includes the presence of a well-defined band-like zone of cellular infiltration that is confined to thesuperficial part of the connective tissue, consisting mainly of lymphocytes (Fig 2).There will be signs of 'liquefaction degeneration' in the basal cell layer.However, there will be an absence of epithelial dysplasia. When the histopathologic features are less obvious, the term 'histopathologically compatible with' should be used[5, 9].

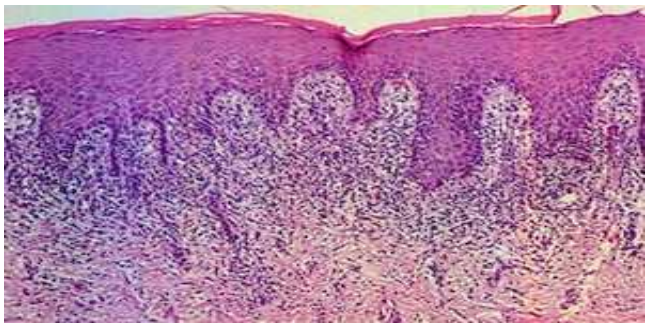

Fig 2: Demonstrate zone of cellular infiltration mainly lymphocytes and liquefaction degeneration in basal layers.

Pathogenesis

Many controversies exist about the pathogenesis of oral lichen planus. A large body of evidence supports a role of immune dysregulation in the pathogenesis [6, 10, 11, 12]. The various mechanisms hypothesized to be involved in the immunopathogenesis are:

- Antigen-specific mechanism.
- Non-specific mechanisms.
- Autoimmune response.
- Humoral immunity.

Antigen-specific cell-mediated immune response

Antigen related lichen planus is still unidentified, even though the antigen may be a self-peptide. It was suggested that keratinocyte expresses lichen planus antigen which is in relation with amount of lichen planus lesion present. Keratinocyte antigen expression may be the first event in lichen planus formation or exposing at the future lesion site induced by all the etiological factors mentioned above. Heat shock proteins may also be considered as unknown antigen but there over expression may link the other common factors like trauma, drugs and infectious agents in pathogenesis of OLP. Heat shock proteins (HSP), a highly conserved class of protective cellular proteins that are produced under various conditions of environmental challenge, have been implicated as the antigenic stimulus in autoimmune diseases as lichen planus is considered to be autoimmune mediated by T cells[13]. Heat shock proteins (HSP) usually expressed by stressed oral keratinocytes may result from dysregulated HSP gene expression from an inability tosuppress an immune response following self-HSP recognition which is more likely due to decreased immune response [6,14]. There is still confusion regarding the number of antigen; whether one or both antigens are involved. CD4+ T helper cells and CD8+ cytotoxic T cells are activated when presented with antigens by MHC class II and I molecules respectively. Antigens related to MHC class II are managed through an endosomal cellular pathway[10]. In contrast, antigens related to MHC class I are managed through a cytosolic cellular pathway. Hence, the antigen obtainable by MHC class II may differ from that existing MHC class I. Otherwise, one antigen may gain access to both the endosomal and cytosolic cellular pathways of antigen presentation. Cell-mediated immunity appears to play a major role in the pathogenesis of oral lichen planus. Majority of T cells adjacent to damaged basal keratinocytes are CD8+ T cells which may further trigger apoptosis[6,14]. The specific immune response to this unknown antigen involves the following steps[10].

- Movement of T lymphocytes into the epithelium;
- Initiation of the T-lymphocytes;
- Killing of keratinocytes.

Movement of T lymphocytes into the epithelium

Two hypotheses have been proposed for the migration of T cells into the epithelium they are,

- Chance encounter' hypothesis – it is basically based on identifying CD8+ cytotoxic T cells and its encounter with specific antigen in the oral epithelium. It may enter the oral epithelium on routine surveillance or may come across them by chance.
- Directed migration' hypothesis– Chemokines secreted by the damaged keratinocyte direct the T cells to drift into the epithelium[6,10].

Initiation of the T-lymphocytes

The lymphocytic infiltrate in OLP is composed almost exclusively of T cells, and the majority of T cells within the epithelium and adjacent to damaged basal keratinocytesare activated CD8+ lymphocytes. CD4+ T cells were not increased in areas of basement membrane disruption [6, 14].

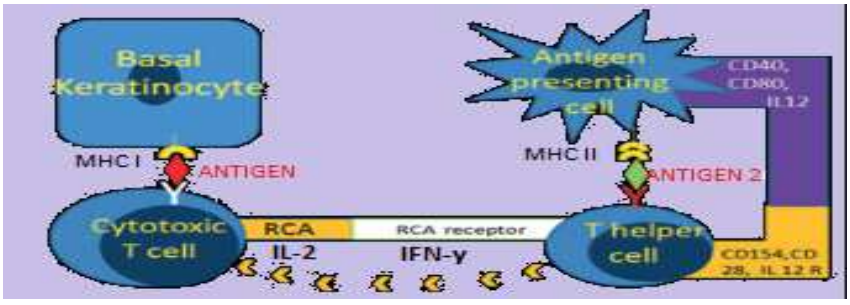

Fig 3: Demonstrate activated CD8+ T cells and CD4+ T cells by binding with MHC I and MHC II respectively [10].

Binding of antigen to MHC-1 on target cell (keratinocyte) activates CD8+ cytotoxic T cell directly (Fig 3). Activated CD8+ T cells (and possibly keratinocytes) may release chemokines that attract additional lymphocytes and other immune cells into the developing OLP lesion [6, 10,14].

Binding of antigen to MHC-1 on target cell (keratinocyte) activates CD8+ cytotoxic T cell directly. They express request for cytotoxic activity (RCA) on their surface. MHC class II antigen presentation in OLP may be mediated by Langerhans cells (LCs) or keratinocytes. There are increased numbers of LCs in OLP lesions with upregulated MHC class II expression. Binding of antigen to MHC-2 present on antigen presenting cells along with secretion of IL-12 activates CD4+ T helper cells. Most lymphocytes in the lamina propria are CD4+ helper T cells. They inturn activate CD8+ T cells by RCA R receptor interaction with RCA expressed on CD8+ cells, and IL-2 and IFN-γ secretion[6, 10, 14].

Killing of keratinocytes

The activated cytotoxic T cells kill the basal keratinocytes. Apoptosis has been proposed as mechanism of keratinocyte death. Cytotoxic T cells secrete TNF-α which triggers keratinocyte apoptosis (Fig 4). The precise mechanism is unclear.

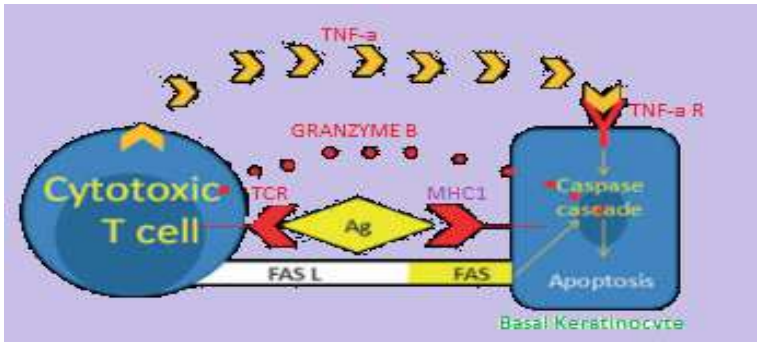

Fig 4: Demonstrate killing of basal keratinocytes through apoptosis [10].

Possible mechanisms of keratinocyte apoptosis are:

- T-cell secreted TNF-a binding to TNF-a R1 receptor on keratinocyte surface.
- T-cell surface CD95L (Fas ligand) binds to CD95 (Fas) on the keratinocyte surface.
- T-cell-secreted granzyme B entering the keratinocyte via perforin induced membrane pores.

All these mechanisms activate a caspase cascade resulting in keratinocyte apoptosis. On the contrary reduced or absent apoptotic rate in inflammatory cells in OLP have been thought to contribute to development of OLP[6, 11].

Non-specific mechanisms in oral lichen planus

Some of the T cells in the oral lichen planus lymphocytic infiltrate are not specific. They may be attracted to and retained within oral lichen planus lesions by various mechanisms associated with pre-existing inflammation.These mechanisms are aimed at movement of lymphocytes into the epithelium to cause destruction of keratinocytes [6, 12, 15]. The various factors proposed to be responsible for non-specific immune response are:

- The epithelial basement membrane
- Matrix metalloproteinases
- Chemokines
- Mast cells

The epithelial basement membrane

Keratinocytes is important for the structure of the epithelial basement membrane as it secretes collagen IV and laminin V into the basement membrane zone (Fig 5). A sevidence suggested from the mouse mammary gland model, that keratinocytes require a basement membrane which is ensuing cell survival signal to stop the onset of apoptosis [6]. Thus basement membrane is required for keratinocyte survival and keratinocyte for normal basement membrane production. So if there is apoptosis then the basement membrane will not function properly leading to basement membrane disruption. Hence intra-epithelial

CD8+ cytotoxic T cells may result in epithelial basement membrane disruption in OLP due to apoptosis, which allows the non-specific T lymphocytes present in the subepithelial zone to migrate into the epithelium. Both keratinocyte apoptosis and basement membrane disruption plays an important role in the pathogenesis of OLP[6, 10].

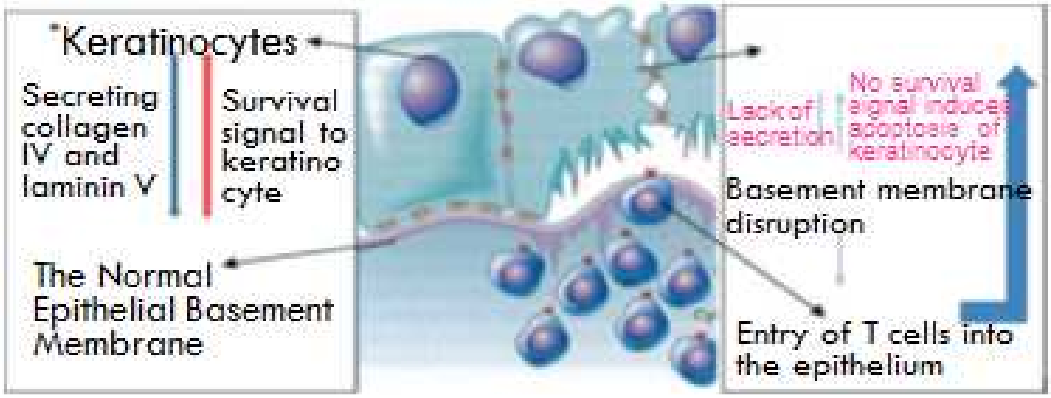

Fig 5: demonstrate lack of secretion of collagen IV and laminin V leading to epithelial basement membrane disruption [10].

Matrix metalloproteinases

Matrix metalloproteinases(MMPs) are a family of zinc-containing endo-proteinases with at least 20 members. The principal function of MMPs is the proteolytic degradation of connective tissue matrix proteins. MMPs share biochemical properties but retain distinct substrate specificities [6]. The gelatinases (e.g. MMP-2 and -9) cleave collagen IV and the stromelysins (e.g. MMP-3 and -10) cleave collagen IV and laminin. Action of endogenous inhibitors is necessary to regulate MMP proteolysis, including the tissue inhibitors of metalloproteinases (TIMPs), which form stable inactive enzyme-inhibitor complexes with MMPs or proMMPs[6, 14]. MMP-9 activators released from the T cell helps in activating pro MMP 9 resulting in basement membrane disruption[6, 10, 14].MMP-9 was identified within the inflammatory infiltrate in the lamina propria, with occasional positive cells in the epithelium[6].

Chemokines

Chemokines are pro inflammatory cytokines. RANTES (regulated on activation, normal T cell expressed and secreted) is a member of the CC chemokine family and is produced by various cells, including activated T-lymphocytes, bronchial epithelial cells, rheumatoid synovial fibroblasts, oral keratinocytes and mast cells. RANTES plays a critical role in the recruitment of lymphocytes, monocytes, natural killer cells, eosinophils, basophils, and mast cells in OLP. CCR1, CCR3, CCR4, CCR5, CCR9 and CCR10 which are cell surface receptors for RANTES have been identified in lichenplanus[6, 10, 16]. RANTES secreted by OLP lesional T cells may attract mast cells into the developing OLP lesion and subsequently stimulate mast cell degranulation. Degranulating mast cells in OLP would release TNF-a and chymase which in turn upregulates OLP lesional T cell RANTES secretion. Such a cyclical mechanism mayunderlie OLP chronicity.ICAM-1 and RANTES are expressed by oral keratinocytes in OLP and amalgam-induced OLR suggests that keratinocytes may play a key role in the pathogenesis of these chronic inflammatory diseases[17].

Mast cells

Studies have shown increased mast cell density in OLP [18, 19, 20]. Approximately 60% of mast cells were degranulated in OLP, compared with 20% in normal buccal mucosa (7). Thus mast cells have been proposed to be involved in the pathogenesis of OLP. Mast cell degranulation in OLP releases a range of pro-inflammatory mediators such as TNF-a, chymase and tryptase. TNF-a may upregulate endothelial cell adhesion molecule (CD62E, CD54 and CD106) expression in OLP that is required for lymphocyte adhesion to the luminal surfaces of blood vessels and subsequent extravasation [6, 9, 18, 19, 20]. TNF-a also upregulates, CCR1 expression by a variety of

inflammatory cells (including T cells and mast cells). It also stimulates RANTES secretion by lesional T cells. As already described the RANTES attracts CCR + mast cells and inflammatory cells into developing oral lichen planus lesion and triggers further mast cell degranulation[10].

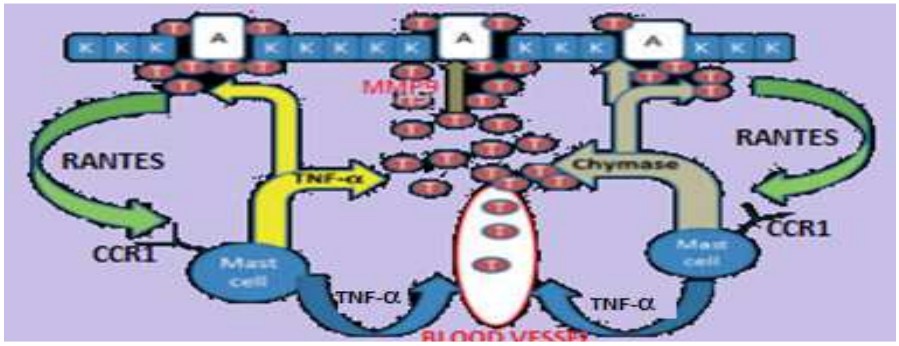

Fig 6: Demonstrate role of mast cell and chemokines in the pathogenesis of oral lichen planus[10].

Autoimmunity

OLP is hypothesized to be an autoimmune disease. The role of autoimmunity in disease pathogenesis is supported by many autoimmune features of OLP, including disease chronicity, adult onset, female predilection, association with other autoimmune diseases, occasional tissue-type associations, depressed immune suppressor activity in OLP patients, and the presence of autocytotoxic T cell clones in lichen planus lesions [6, 10].

Four hypothesis have been proposed implicating autoimmune reaction in oral lichen planus, they are:

- Deficient antigen-specific immunosuppression in oral lichen planus – lack of TGF-b1.
- Keratinocyte apoptosis and langerhans cell maturation in oral lichen planus (Fig 7).
- Breakdown of immune privilege in oral lichen planus(lack of keratinocyte induced apoptosis of T cells) (Fig 8).
- Heat shock proteins[6, 10].

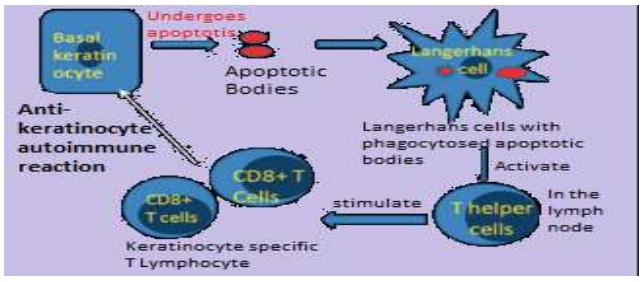

Fig 7: Demonstrate mechanism of anti keratinocyte autoimmune reaction [10].

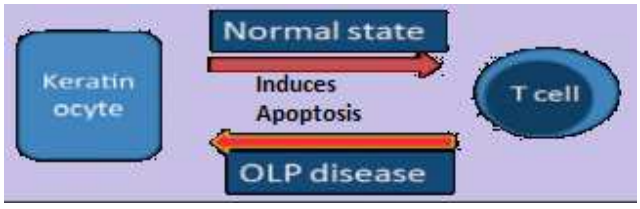

Fig 8: Demonstrate relation between keratinocytes and T Cell[10].

Humoral immunity

Circulating antibodies have been identified including autoantibodies against desmogleins 1 and 3. This indicates a role of humoral immunity in oral lichen planus. Further studies are needed to know the exact role of humoral immunity[6, 10].

Recent advances in treatment of oral lichen planus

Corticosteroids have been the pillar of management of OLP and yet, other modalities like calcineurin inhibitors, retinoids, dapsone, hydroxychloroquine, mycophenolatemofetil and enoxaparin have contributed significantly toward treatment of the disease.Analysis of current data on pathogenesis of the disease suggests that blocking IL-12, IFN-γ, TNF-α, RANTES, or MMP-9 activity or upregulating TGF-β1 activity in OLP may be of therapeutic value in the future[21].

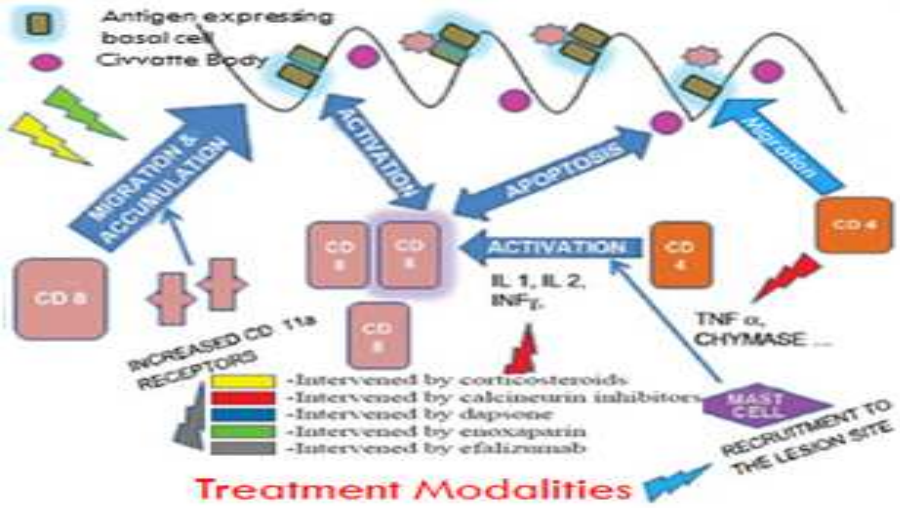

Fig 9: Demonstrate action of various drugs in oral lichen planus [21]

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