Oral Lichen Planus: A Review with Emphasis on Etiopathogenesis and Differentiating Features from Lichenoid Lesions

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Received : 26.02.2016
Review Completed : 10.03.2016
Accepted : 17.03.2016

ABSTRACT

Lichen planus (LP) is an mucocutaneous disease affecting mainly the skin and oral mucosa of unknown etiology. The various mechanisms hypothesized to be involved in immunopathogenesis are immune response mediated by antigen-specific cells, autoimmune response, Humoral immunity, Nonspecific mechanisms and other etiologies like viruses. Lichen planus also has a tendency for malignant transformation. Oral Lichenoid Lesions share the clinical features of OLP and presentations as plaques or erosive patches with presence of Wickham's striae. However, there are certain distinctive features that the lichenoid lesions exhibit that differentiate them from OLP. This article hightlights the key features essential for lichen planus diagnosis and its etiopathogenesis.

Introduction

Lichen planus (LP) is an inflammatory disease of unknown etiology that affects mainly the skin and oral mucosa. Other mucous membranes, such as those of the genitalia, esophagus, and conjunctiva, as well as skin appendage areas such as the scalp and nails may also be affected. It is a common mcocutaneous disease, first described by Wilson in 1869[1]. It Affects 0.5-1% of world's population. Annual Age adjusted incidence rate was 2.1 and 2.5 per 1000 among men and women. Prevalence in Indian Population is 2.6%.[2]

Etiopathogenesis of Lichen Planus

The antigens that trigger the inflammatory immune response in oral lichen planus, remains unknown. Countless factors have been proposed as relevant to the etiology of the lesions, including genetic history, dental materials, drugs, infectious agents such as bacteria and viruses, autoimmunity, associations with other autoimmune diseases, immunodeficiency, food, allergies, stress, habits, trauma, diabetes and hypertension, malignant neoplasms, and intestinal diseases. The T-Cell autoimmune disease in which cytotoxic CD8+ T cells trigger the apoptosis of oral epithelial cells (Type IV Hypersensitivity reaction)

The various mechanisms hypothesized to be involved in immunopathogenesis are:
(i) An immune response mediated by antigen-specific cells;
(ii) An autoimmune response;
(iii) Humoral immunity;
(iv) Nonspecific mechanisms.

Immune response mediated by antigen-specific cells

The lymphocytic infiltrate in lesions of LP consists mainly of T cells, including CD4+ and CD8+ lymphocytes, that migrate to the epithelium either by random antigen match during routine surveillance or in a process mediated by cytokines. The degeneration of basal keratinocytes observed in LP is attributed to cytotoxic CD8+ T lymphocytes, which represent the main component of the infiltrate located within the epidermis and adjacent to damaged keratinocytes. As the disease progresses, a gradual accumulation of CD8+ T lymphocytes occurs. The main event in the pathogenesis seems to be the increased production of cytokines that induce recruitment of Langerhans cells and clonal expansion of cytotoxic cells.[3]

Cytotoxic lesional CD8+ T cells can be activated by keratinocyte basal antigen associated with class I MHC, which releases many cytokines such as interleukin-2 (IL-2), tumor necrosis factor (TNF), and interferon-a (IFN-a), which induce not only the expression of HLA-DR in basal keratinocytes but also the activation of dendritic cells, including Langerhans cells thereby attracting more lymphocytes. The possible mechanisms that induce keratinocyte apoptosis by CD8+ T cells are [3]:
(I) TNF-a secreted by T cells, binding to TNF-a1 receptor on the surface of keratinocytes;
(ii) expression of CD95L (Fas ligand) on the surface of T cells, binding to CD95 (Fas) on the surface of keratinocytes;
(iii) Entry through the pores of the membrane induced by perforin in granzyme B keratinocytes, secreted by T cells.

Autoimmune Response

Deficiency of transforming growth factor-a1 (TGF-a1) may predispose to autoimmune lymphocytic inflammation. In 2014, Shen et al. demonstrated the increased expression of Foxp3 and IL-17 in LP lesions including oral and cutaneous variants. The expression of Foxp3 in oral LP was higher than that in cutaneous LP, a finding that may reflect the difference in clinical behaviour between the two variants of the disease. [3]

Humoral Immunity

Autoantibodies have been identified in OLP patients. Anti-smooth muscle antibody (SMA) occurs at a significantly higher frequency in patients with OLP than in healthy control subjects. In the erosive form of OLP, the concentrations of circulating antibodies against desmoglein 1 and 3 are significantly increased in comparison with those in healthy controls.[3]

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Nonspecific mechanisms

Some of the T cells in OLP lymphocyte infiltrates are unspecific. They can be attracted and retained within OLP lesions by various mechanisms associated with the pre-existing inflammation. The non specific mechanisms include the following [3]:

Epithelial basal membrane: Keratinocyte apoptosis by CD8+ cytotoxic T lymphocytes may result in disruption of the basal membrane in OLP, which allows nonspecific T lymphocytes present in the subepithelial area to migrate to the epithelium.

Metalloproteinases: In OLP, activation of MMP-9 results in the disruption of the basal membrane.

Chemokines: Chemokines play a critical role in OLP through the recruitment of lymphocytes, monocytes, natural killer cells, eosinophils, basophils, and mast cells. Eg: RANTES, secreted by OLP lesional T cells, can attract mast cells that, by undergoing degranulation, release TNF-a and chemokines that stimulate more RANTES secretion.

Mast cells: Studies show an increase in the density of mast cells in OLP, 60% of which have undergone degranulation.

Vascular endothelial growth factor: serum levels of VEGF to be significantly elevated in patients with OLP.

Langerhans cells: These cells produce greater amounts of IFN-a to induce more apoptosis mediated by cytotoxic cells via a cascade of caspase.

Viruses and oral Lichen Planus

Viruses that are suspected of having an association with Oral Lichen Planus (OLP) can be divided into two groups. The first group includes viruses for which associations have been anecdotally suggested, such as varicella zoster virus, Epstein–Barr virus, cytomegalovirus, herpes virus, human papillomavirus (HPV), and human immunodeficiency virus (HIV). The second group includes viruses for which an association with LP has been documented, such as HCV. The relationship between HCV and OLP remains controversial.

Several studies suggest that the relationship between the two diseases may be the result of genetic, environmental, geographic, and other factors. It is estimated that patients with hepatitis C are twice as likely to develop LP than the general population HCV is not sufficient by itself as a causative agent in the development of OLP and that host factors play an important role in the pathogenesis of HCV associated with OLP. HCV-positive patients with HLA-DR6 are more prone to develop OLP lesions. Figueiredo et al. observed the rate of HCV infection to be six times higher among patients with OLP and the rate of OLP to be eight times higher in patients with HCV than in the general population. [3][4]

Diagnosis of Lichen Planus

In 1968, Andreasen divided OLP into 6 clinical forms [5,6]:

1. Reticular
2. Papular
3. Plaque like
4. Atrophic
5. Erosive
6. Bullous

The reticular form is the most common type. It clinically presents as papules and plaques with interlacing white keratotic lines (wickham's striae) surrounded by an erythematous border. Wickham's striae are usually bilateral and seen on buccal mucosa, mucobuccal fold, gingiva and rarely on palate, tongue and lips. This type is reportedly more common in males than females and it is usually asymptomatic. OLP usually present as a bilateral symmetrical lesion or involves multiple areas individually. OLP involving the gingival is termed as "desquamative gingivitis" which clinically manifest as a fiery red erythema of attached gingiva. OLP lesions which are associated with patchy brown melanin deposits in the oral mucosa are termed as inflammatory melanosis. Reticular form of oral lichen planus is usually asymptomatic [5,6,7].

Atrophic/erythematous and erosive/ulcerative lesions are symptomatic. Symptoms include mucosal sensitivity, burning sensation and continuous debilitating pain. Oral lichen planus lesions usually persist for many years. OLP patients have periods of exacerbation and quiescence. Periods of exacerbation are generally associated with psychological stress and anxiety and during this time there is increased erythema or ulceration with increased pain and sensitivity. OLP resulting from mechanical trauma either during dental treatments or due to cheek biting is termed as koebner phenomenon.[5,6,7]

The 6 P's of Lichen Planus [7,8]:

1. Pruritic
2. Purple
3. Polygonal
4. Planar
5. Papules
6. Plaques

The key histological features include, Liquefaction degeneration of basal layer, overlying keratinisation, Lymphocytic infiltrate within the connective tissue that is dense and resembles a band. Hyper orthokeratosis or hyperparakeratosis, with acanthosis, which is thickening of the granular layer with intercellular edema., Rete pegs characteristically are "saw tooth" in appearance. Mononuclear infiltration of the T-cells and histiocytes form a typical band like an appearance subepithelially. The intraepithelial T-cells and degenerating ketatinocytes form the colloid bodies, the homogeneous globules that are eosinophilic in nature called the civette, cytoid, hyaline bodies are seen. The characteristic feature of Max-Joseph space that is formed from the degeneration of basal keratinocytes and anchoring units disruption. They are regarded as histologic clefts. The colloid bodies ultrastructurally are apoptotic keratinocytes revealing DNA fragmentation in these cells. The basement membrane of when examined under electron microscope reveal duplications, branches, and breaks.

The investigations include Direct Immunofluorescence that show positive linear and/or granular IgG, IgA, IgM and complement at BMZ, and exhibit positive fluorescence with antifibrinogen. IgA, IgG, complement C3 are seen on

colloid bodies. Indirect immunofluorescence: shows "annular fluorescence" or the "string of pearls" appearance.[8]

Corticosteroids have been the mainstay of management of OLP; yet, other modalities like calcineurin inhibitors, retinoids, dapsone, hydroxychloroquine, mycophenolate mofetil and enoxaparin have contributed significantly toward treatment of the disease. Oral photochemotherapy and extracorporeal photochemotherapy are indicated in low doses in the treatment of oral lichen planus. 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.[4,9]

Oral lichen planus is a potentially malignant disorder with a capacity, although low, for malignant transformation. Of all the factors related to the process of malignant transformation, it is believed that the chronic inflammatory process plays a key role in the development of oral cancer. This inflammatory process is capable of providing a microenvironment based on different inflammatory cells and molecules that affect cellular growth, proliferation and differentiation.[10] The Overall frequency of malignancy is 0.3-3.5% . c-Jun, a transcription factor, activation in human skin is involved in proliferation and could potentially participate in the transformation of LP from an inflammatory to a carcinogenic state. [11] In a recent systematic review, by Fitzpatrick, the most common subsite of malignant transformation was the tongue. They also demonstrated slight female predilection of Lichen planus [12, 13]. The average time from diagnosis of OLP to transformation was 51.4 months.[14,15]

Differentiating Features of Oral Lichen Planus from Lichenoid Lesions

Oral Lichenoid Reactions or Lesions (OLRs/OLLs) are clinical and histological contemporaries of Oral Lichen Planus (OLP) often indistinguishable in manifestations. The benchmark of differentiation between the two groups is the association of the former with known inciting factors, which when identified and eliminated, often cause a regression of the lesion. The classification of lichenoid lesions is highlighted in table 1 below. The associated factors with OLRs may broadly be divided into four groups[16]:

a. Dental restorative materials (modified from original description)
b. Drugs and medications
c. Graft-versus-host disease (GVHD)
d. Other factors

Oral Lichenoid Lesions share the clinical features of OLP and presentations as plaques or erosive patches with presence of Wickham's striae are seen. OLLs are known to occur in all clinical varieties of presentation seen in OLP like reticular, atrophic, erosive, bullous, and keratotic. However, there are certain distinctive features that the lichenoid lesions exhibit that differentiate them from OLP. OLLs are usually unilateral, have a topographical association with a dental restorative material and a causative association with a drug or medication, if it is the inciting factor, and rarely occur in sites like tongue and palate. The causal effect can be confirmed by withdrawal of the suspected drug, if medically feasible, and observation of the regression of the lesion. Occasionally, when dental material association is suspected then epicutaneous patch tests and replacement of the material may bring about the desired result.[17,18]

Table 1: Classifications of Oral Lichenoid Lesions[16]

Issa *et al.*, 2005[34]
a) Classified clinically into three groups:
White patches, striated, plaque, or reticular lesions
Erosive or atrophic lesions
Ulcerative lesions
b) Classified according to their relationship with restorations:
OLLs only in contact with restorations
OLLs in clinical contact, and at least one additional site without clinical contact with restorations
OLLs without clinical contact with restorations
c) Classified according to their oral location:
OLLs located on the buccal mucosa (unilateral or bilateral)
OLLs located on the tongue (lateral or dorsal surface)
Gingival lichenoid lesions
Other part of oral mucosa; lips, floor of the mouth, and palate
Van der Waal (2009)[35]
1. Amalgam restoration topographically-associated OLL
2. Drug-related OLL
3. OLL in chronic graft-versus-host disease
4. OLL, unclassified (e.g., erythematous changes limited to the gingiva without signs of "classic" OLP elsewhere in the oral cavity, or lesions that have a lichen planus like aspect, but that lack one or more characteristic clinical features, such as bilateral presentation)
Modified World Health Organization criteria for the diagnosis of OLRs, OLLs, and oral lichen planus (OLP) (Van de Meij *et al.*, 2007)[36]
Clinical criteria
1. Bilateral presentation, more or less symmetrical lesions
2. Presence of white striae (reticular pattern)
3. Erosive, atrophic, bullous, or plaque manifestations are only accepted as subtypes when always accompanied by reticular lesions located anywhere in the mucosa. The term "clinically compatible with" is to be used with all lesions similar to OLP that do not meet the mentioned criteria
Histological criteria
1. Well-defined, mainly lymphocytic band infiltration in the most superficial zone of the connective tissue
2. Signs of degenerative liquefaction in epithelial basal layer.
The term "histologically compatible with" is to be used in application to all histopathological findings less clearly compliant with the mentioned criteria
Final diagnosis of OLP and OLLs
1. The clinical and histopathological criteria must be included in order to establish a final diagnosis
2. Both the clinical and histopathological criteria must be met in order to diagnose OLP
3. The term OLLs is to be used under the following conditions:
(1) Clinically characteristic of OLP, but histologically only "compatible with" OLP
(2) Histologically characteristic of OLP, but clinically only "compatible with" OLP
(3) Both clinically and histologically "compatible with" OLP

OLP: Oral lichen planus, OLLs: Oral lichenoid lesions

The Histological features include, The subepithelial infiltrate in OLP is limited to the lamina propria, it is more diffuse and penetrating in OLLs.The nature of the infiltrate is also lymphohistiocytic compared with the mixed variety of OLP. There is a tendency for perivascular congregration of the inflammatory cells.Epithelial changes include focal parakeratosis, focal interruption of the granular layer, and presence of cytoid bodies in the granular and keratinized layers. Mast cell presence in OLL is more subdued. Various minor features like increased vascularity and increased positivity of periodic acid-schiff (PAS) material in the basement membrane of OLP are not usually found in OLLs. The malignant transformation rate of OLP is variably listed as 0.5-2% in various studies. [19,20] The key differentiating factors have been highlighted in Table 2 below.

Key differentiating features between oral lichen planus (OLP) and oral lichenoid lesions [16]:

Criteria	OLP	OLL
Clinical	Usually bilateral and symmetrical	Usually unilateral
	In established well-defined sites like buccal mucosa, tongue	In less well-established sites like gingiva, lips, and palate in addition to the well-established sites
	Idiopathic	Association with factors listed in Table 1
	Classical white striae (Wickham's striae), and in various manifestations like reticular, papular, erosive, erythematous, and bullous	Mostly similar in clinical presentation
Histopathological	Mixed subepithelial infiltrate	Strict lymphohistocytic infiltrate
	Limited to lamina propria	Diffuse and more deeper distribution in lamina propria and superficial submucosa
	No such changes usually seen	Focal parakeratosis, focal interruption of granular layer, cytoid bodies in keratinized and granular layers
	Increased numbers of granulated mast cells in areas of basement membrane degeneration	No such changes
	Increased vascularity	No such changes
	Increased PAS-positive basement membrane thickness	No such changes
Malignant transformation rate	0-2% (0 cases in 65 patients)[36]	2.7% (3 cases in 111 patients)[36]

PAS: Periodic acid-schiff, OLP: Oral lichen planus, OLL: Oral lichenoid lesions

Conclusion

Lichen planus (LP) is a mucocutaneous disease with well-established clinical and microscopic features. The oral mucosa and skin may present clinical and microscopic alterations similar to those observed in LP, called lichenoid reactions (LRs), which are triggered by systemic or topical etiological agents. Differentiation between the two diseases allows an effective and correct therapeutic approach. Clinically and histologically, LP and lichenoid reactions cannot be distinguished with certainty in many cases. Treatment is mainly symptomatic and can be difficult. The first-line therapies for LP are topical or systemic corticosteroids; however, some studies have mentioned acitretin leading to similar improvement. Medical treatment, together with patient education and psychosocial support, can significantly benefit patients' quality of life.

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