International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: 10.7439/ijbar
CODEN: IJBABN

Review Article

Clinical and Genetic Aspects of Oral Lichen Planus

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Abstract

Lichen planus (LP) is a chronic inflammatory muco-cutaneous disease. Oral Lichen Planus (OLP) is often asymptomatic; the atrophic-erosive form can cause symptoms ranging from burning sensation to severe pain, interfering with speaking, eating, and swallowing. OLP can be a source of severe morbidity and has a small potential to be malignant. The prevalence of OLP varies from 0.5% to 4% of the general population and in spite of extensive research; exact etiology of OLP remains unclear. A proper understanding of the clinical presentation, pathogenesis and diagnosis of the disease becomes important for providing the right treatment. The present review draws together aspects of Epidemiology, Clinical Features, Etiopathogenesis with emphasis on Genes involved in OLP pathogenesis and the clinical management of OLP.

Keywords: Oral Lichen Planus, Genetics, pathogenesis

1. 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 (LP) is derived from the Greek “leichen” meaning tree moss and the Latin “planus” meaning flat. {Lichens are primitive plants composed of symbiotic algae and fungi and Planus in Latin for flat. Term suggests flat fungal condition}[2] Lichen planus (LP) is an inflammatory mucocutaneous disease, which can involve the skin, hair, nails, and mucosal surfaces.[3]

The World Health Organization’s (WHO) criteria describe lichen planus as a condition predisposed to malignant transformation.[4] Mucosal sites of involvement include oral, genital, ocular, otic, esophageal, and less commonly, bladder, nasal, laryngeal, and anal surfaces.[5] Oral lichen planus (OLP) is a relatively common, chronic, inflammatory, immunological potentially premalignant condition which is a rather common disease in the middle-aged and elderly populations.[6]

2. Historical Background

Erasmus Wilson first described LP in 1869, as a chronic disease affecting the skin, scalp, nails, and mucosa, with possible rare malignant degeneration and is thought to affect 0.5 to 1% of the world’s population.[7] He considered this to be the same disease as "lichen ruber," previously described by Hebra[8] and characterized the disease as "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development."[9]

In 1892, Kaposi reported the first clinical variant of the disease, lichen ruber pemphigoides.[10] WICKHAM 1895 described the characteristic appearance of whitish striae and punctuations that develop atop the flat surfaced papules Text book of oral medicine and radiology –ongole first edition.[11]

Darier is credited with the first formal description of the histopathological changes associated with LP.[12] Although oral lichen planus recognized by the World Health Organization, the premalignant potential of OLP is still a much debated issue, in this article we will review the Epidemiology, Clinical Features, Etiopathogenesis, and the clinical management of OLP.

3. Epidemiology

The prevalence of OLP varies from 0.5% to 4% of the general population, and the malignant transformation rate is 0–2%.[13] It tends to be more chronic in nature than cutaneous disease, affecting women more commonly than men, with age of onset on average around 60 years. OLP in childhood is rare. The extent of involvement with OLP is variable.[14] The relative risk is 3.7% in people with mixed oral habits, lowest (0.3%) in non-users of tobacco and highest (13.7%) among those who smoked and chewed tobacco.[15] It affects all racial groups.[16] However, according to some literature white individuals are five and a half time more likely to develop this disease compared to other races.[17]

4. Clinical Features

OLP is characterized by orthokeratotic hyperkeratosis, acanthosis, or epithelial atrophy, basal cell degeneration, subepithelial eosinophilic amorphous band and dense well-defined infiltrate of lymphocytes in the superficial dermis. The clinical and histopathologic features of OLP are often undistinguishable from that of graft-vs-host (GVH) disease.[18] Several subtypes have been described, but the following six clinical types of OLP lesions were more observed, individually or combined: papular, reticular, plaque-like, atrophic, erosive, and bullous.[19]

The presentation is varied in clinical appearance, with most lesions being bilateral and located on the buccal mucosa. Lesions can appear, however, on the tongue, in the vestibule, and on the gingivae. Isolated gingival lichen planus may be seen in up to 8.6% of patients.[20]

The term premalignant implies eventual malignant transformation, but lichen planus may better be described as having "malignant potential."[21] Patients with oral LP should be examined for other mucosal lesions, such as genital lesions. Such mucous membrane lesions are more resistant to conventional therapies than cutaneous lesions and malignant transformation of longstanding, non-healing oral LP has been reported. Even in cutaneous LP, chronic erosive lesions are at risk of developing squamous cell carcinoma.[22]

5. Etiopathogenesis

In spite of extensive research, exact etiology of OLP remains unclear.

5.1 Genetic background

The genetic predisposition has been hypothesized in OLP etiology.[23] In this context, Genetic factors influencing immune function may contribute to OLP pathogenesis. many studies have focused on the relationship between HLA and OLP, demonstrating that an association has been observed with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1, and DRW9.[13,24-26] the HLA-DR1 is frequently associated with cutaneous idiopathic LP, but not in OLP and the HLA-DR6 is usually linked to hepatitis C virus-associated OLP.[27-29]

A significant increase in genetic polymorphism of the first intron of the promoter gene of interferon-gamma was found in patients with OLP compared with controls.[30] While a Chinese study found an association between a polymorphism in the TNF-α gene and genetic risk for OLP in a subset of patients.[31] Understanding of involved genes in the pathogenesis of OLP can be used in the genetic counseling and better management. [32]

5.2 Genes network involved in OLP pathogenesis

The physio-pathology of multi-factorial disease like OLP is characterized by various biologic pathways, dependent upon the contribution of a large number of genes [33]. Therefore, the knowledge of molecular mechanisms of complex diseases must deal with a large array of genes and gene products.[34] These genes form complex networks of interactions, which may be direct (that is to say, physical interactions between the proteins, confirmed by experimental techniques, such as NMR or crystallography), or indirect (involvement in the same metabolic pathway or co-expression under different conditions).[35]

At present, several studies have analyzed the role of different genes (132 genes in total) involved or potentially involved in the pathogenesis and evolution of OLP. However, these studies were in most cases dealing with one single gene or with a single gene family.[36-44] However, only few of them have a high number of interactions with the other genes in the network and therefore they may play a major role. These genes were identified and termed as ''leader genes''. JUN, EGFR, FOS, IL2, ITGB4 genes are defined as leader genes involved in human OLP pathogenesis base on bioinformatics studies. The established or putative role of these genes is summarized in Table 1.[45]

Table1: leader genes involved in human OLP pathogenesis

	leader genes and their molecular functions
Gene	**function**
JUN	Encodes a protein which interacts directly with specific target DNA sequences to regulate gene expression. This gene is mapped to 1p32-p31, a chromosomal region involved in both translocations and deletions in human malignancies.
EGFR	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand leads to cell proliferation.
FOD	Encodes leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1. As such, the FOS proteins have been implicated as regulators of cell proliferation, differentiation, and transformation. In some cases, expression of the FOS gene has also been associated with apoptotic cell death.
IL2	The protein encoded by this gene is a secreted cytokine that is important for the proliferation of T and B lymphocytes.
ITGB4	Integrins mediate cell-matrix or cell-cell adhesion, and transduced signals that regulate gene expression and cell growth. This gene encodes the integrin beta 4 subunit, a receptor for the laminins. This subunit is likely to play a pivotal role in the biology of invasive carcinoma.

6. Molecular markers and OLP

The transformation of normal oral mucosa to lichen planus or other mucosal disease is a complex multistep process, in which expression of various molecular markers have been studied, in order to understand the molecular mechanisms involved in this issue. they include Cell cycle markers like *Cdk family, Rad-51 enzyme, p53 and* Cell proliferation markers such as *Ki-67 (Mib-1), Topoisomerase II alpha, Proliferating cell nuclear antigen (PCNA), Cyclin D1 and* Apoptosis pathway marker namely Bcl-*2 and* Cell-to-cell adhesion marker for instance *Ck-19, E-cadherin family, Desmocollin-1*.[46]

6.1 Dental materials

A great many materials commonly used in restoration treatments in the oral cavity have been identified as triggering elements for OLP, including silver amalgam, gold, cobalt, palladium, chromium and even non-metals such as epoxy resins (composite) and prolonged use of denture wear.[47-49]

6.2 Stress

Stress is thought to play a role in the pathogenesis of OLP, because anxiety and depression are reportedly more common in OLP patients relative to normal controls and OLP exacerbations correlate with episodes of anxiety.[50-51]

6.3 Autoimmunity

OLP is sometimes detected in the same patient simultaneously with a known autoimmune disease, such as systemic lupus erythematosus and Sjögren's syndrome, and it arises predominantly in older females, which is characteristic of autoimmune disease.[52]

The most accepted and current data suggests that OLP is a T cell mediated inflammatory disease in which there is a production of cytokines which leads to apoptosis. Auto cytotoxic CD8 and Tcells trigger apoptosis of oral epithelial cells. [53-54]

6.4 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.[48] OLP has been found to be associated with various viral agents such as human papilloma virus (HPV), Epstein Barr virus (EBV), human herpes virus 6 (HHV-6) and human immunodeficiency virus (HIV).[55-57]

Epidemiological evidences from various studies worldwide strongly suggest that hepatitis C virus (HCV) may be an etiologic factor in OLP. [58] In OLP, HCV replication has been reported in the epithelial cells from mucosa of LP lesions by reverse transcription/polymerase chain reaction or *in-situ* hybridization; also, HCV-specific CD4 and CD8 lymphocytes were reported in the subepithelial band. These probably suggest that HCV-specific T lymphocytes may play a role in the pathogenesis of OLP. The putative pathogenetic link between OLP and HCV still remains controversial and needs a lot of prospective and interventional studies for a better understanding.[59]

6.5 Drugs

Oral lichenoid drug reactions may be triggered by systemic drugs including NSAIDs, beta blockers, sulfonylureas, some angiotensin-converting enzyme (ACE) inhibitors, and some antimalarials, contact allergens including toothpaste flavorings, especially cinnamates.[60]

6.6 Food allergies

Food and some of food additives such as cinnamon aldehyde has been found to be associated with OLP.[48]

6.7 Habits

Although most patients with OLP show no increased prevalence of cigarette smoking [61], it has been suggested to be an etiological factor in some Indian communities.[62] Betel nut chewing is also more prevalent in Indian patients with OLP than in those without.[63]

6.8 Malignant neoplasms

LP has been observed on the skin and/or mucosae of patients affected by a range of different neoplasms such as with breast cancer and metastatic adenocarcinoma.[48]

6.9 Miscellaneous associations

OLP has occasionally been associated with other conditions, including psoriasis, lichen sclerosis, urolithiasis, agents used to treat gall stones, Turner's syndrome, etc.[48]

6.10 Diabetes and hypertension

Studies have revealed that both diabetes mellitus (DM) and high blood pressure are associated with OLP.

6.11 Trauma

Trauma as such has not been quoted as an etiological factor in lichen planus, although it may be the mechanism by which other etiological factors exert their effects.[48]

Together, major debates around the mechanisms by which lichen planus develops and why they occur. Although there is evidence that viral infections - especially those caused by the hepatitis C virus – and psychological disorder somatization, such as stress and anxiety, may be possible causes of this disease, information is lacking to definitively confirm these connections. Further debates have arisen about the possible malignant nature of oral lichen planus.[65]

7. Management of OLP

In general terms the management of lichen planus can be difficult. Cochrane evidence is weak for all interventional modalities so the treatment is often not warranted.[66]

There is no cure, and most therapeutic modalities aim for symptomatic relief, the extent of oral and extra-oral clinical involvement, medical history, and other factors.

7.1 Drug Therapy

Common treatment options include systemic and topical corticosteroids, topical retinoids, cyclosporine, tacrolimus, and pimecrolimus.in which, corticosteroids remain the mainstay of Immunomodulatory Agents for oral lichen planus treatment.[67]

Systemic corticosteroids are an important form of treatment of diffuse erosive lichen planus or in patients who are refractory to topical steroids. There are, however, many side effects, even with short-term use.[68]

A systemic corticosteroid with a short plasma half-life, such as prednisone,is generally used.[69] Topical corticosteroids (fluocinonide, betamethasone, clobetasol gel) have also been used with success.[70] 66 to 100% of treated patients respond at least partially to topical corticosteroids, with variation in efficacy mostly due to the different potency of the corticosteroids.[71] Intralesional injections of hydrocortisone, dexamethasone, triamcinolone acetonide, and methylprednisolone have also been used with short-term success.[72]

7.2 Nondrug Therapies

7.2.1 Ultraviolet Irradiation

UV radiation has been used with apparent success in oral lichen planus in a number of studies.[73-74] Carbon dioxide lasers have been used to treat multicentric lesions or difficult areas; and low-dose excimer 308-nm laser seems promising from the results of three small trials.

7.2.2 Surgery

Resection has been recommended for isolated plaques or non-healing erosions, because it provides excellent tissue specimens for histopathological confirmation of diagnosis, and is said to cure localised lesions. **Error! Reference source not found.**

7.3 Other Treatments

Several other therapies have been occasionally used in an attempt to control oral lichen planus. They include the use of diethyldithiocarbamate[77], psychotherapy[78], magnetism[79], and reflexotherapy.[80]

8. Conclusion

In the light of the above review, lichen planus can affect multiple cutaneous and mucosal surfaces, OLP continues to be a variant with a chronic course requiring long-term treatment and surveillance. While there have been numerous anecdotal reports and awareness of OLP and other manifestations of the disease but the pathogenesis of OLP is still not fully understood. This issue led to clear need for more multicenter randomized controlled trials for growing recognition of clinical features and treatment options and emphasizes the importance of a multidisciplinary approach to therapy.

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