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Oral Lichen Planus- A Review

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Abstract: *Lichen planus is a disease involving skin and mucosal membranes of various parts of the body. The exact etiology of oral lichen planus (OLP) still remains partially understood. According to the literature, pathogenesis of OLP is due to cell-mediated immunopathological response to antigenic alterations of keratinocytes in the skin and mucosa.The World Health Organization (WHO) has defined OLP as a potentially precancerous disorder, representing a generalized state associated with a significantly increased risk of cancer. OLP affects 0.5% to 2.2% of the population and is more frequent in women than men, from 2:1 to 3:1, respectively. The common age at presentation is 30 to 60 years, predominantly involves middle-aged women and younger-aged men.OLP is relatively not so common among the pediatric population, and it usually appears along with cutaneous Lichen Planus (LP). Only 17% of the affected patients recover totally from OLP, however remission seen in 39% of the OLP lesions.*

Keywords: *Oral Lichen Planus, Wickham's Striae, Autoimmume Disorder, T- Lymphocytes.*

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I. Introduction

Ferdinand Ritter von Hebra a renowned dermatologist is credited with the first scientific description of this skin disease; he termed the lesions as leichen ruber planus (1). The term Lichen planus (LP) was first coined by the Dermatologist, Sir William James Erasmus Wilson to describe the lesions in his publication which involved a group of 50 patients (2). He characterized the disease as "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development"(2).

In 1892, a variant of the disease, lichen ruber pemphigoides was described by Kaposi. In 1895, Wickham noted the typical and characteristic reticulate white lines on the surface of LP papules. Today the white lines are recognized as Wickham striae (3). Darier is credited with the first formal description of the his to pathological changes associated with Lichen Planus (LP).

Oral lichen planus is a chronic inflammatory condition that specifically affects mucous membranes inside the oral cavity. Oral lichen planus appears as white, lacy patches; red, swollen tissues; or open sores. These lesions may lead to burning sensation, pain and discomfort. Oral lichen planus is not a communicable or contagious disease. The disorder occurs when the immune system mounts an attack against cells of the oral mucous membranes.

II. Oral Lichen Planus

Clinically, OLP appears in various combinations of reticular or papular forms with or without the expression of plaque-type, atrophic, erosive and bullous forms. It presents bilaterally in the posterior buccal mucosa (about 90% of the cases), or on the tongue (about 30%), or alveolar ridge or gingiva (about 13%), but rarely on the labial mucosa, palate, floor of the mouth or lip vermilion. The reticular type is the most common form of OLP lesions. Wickham's striae classically appear as bilateral and interlacing white hyperkeratotic lines with an erythematosus border. Papular and plaque-like forms are variants of the reticular form, which resemble multiple leukoplakia areas and vary from smooth, flat areas to irregular, elevated areas (4).

EXTRA-ORAL LICHEN PLANUS

- **Skin.** Lesions in cutaneous LP usually appear as purplish, polygonal, flat-topped bumps that are often itchy.
- **Genitals.** Lesions on the female genitalia often cause painful intercourse. These lesions on genitalia are usually red and eroded and sometimes appear as white or gray-white areas. Similar type of lesions also can occur on male genitalia.
- **Ears.** Lichen planus involving the ears can lead to hearing loss depending upon the severity of the disease.
- **Scalp.** Occurrence of lesions on the scalp is very rare, when occurs it may lead to temporary to permanent hair loss.
- **Nails.** Lichen planus of the toe nails or fingernails may result in ridges on the nails, thinning or splitting of nails and sometimes lead to temporary or permanent nail loss.
- **Eyes.** Rarely, lichen planus may involve the mucous membrane surfaces of the eyes, and if not treated on time can cause scarring and blindness.
- **Esophagus.** Lichen planus of the esophagus also is rare, but when it occurs, it may result in a narrowing of the esophagus or the formation of tightened, ringlike bands in the esophagus that can make swallowing difficult.

ETIOLOGY

The exact etiology of this disease is still remains unspecified, but according to the clinicians and researchers some factors are associated with oral lichen planus (OLP) as listed below.

1) Genetic predisposition

According to the authors Ognjenovic et al and Porter K et al, an relatively strong association has been observed with Human leukocyte Antigen (HLA), HLA- A3, A11, A26, A28, B3, B5, B7, B8, DR1, and DRW9 (5,6)**.** However there is no sufficient evidence and documentation that OLP runs in families. An increase incidence of OLP with HLA DR9 and Te22 antigens has been established in a Chinese population, documented in a study done by Sun et al, in HLA- DR9 and Te 22 antigens has also been noted (7).

2) Dental materials

A variety of materials commonly used in day to day restoration treatments in the oral cavity such as amalgamated silver, gold, cobalt, palladium, chromium and to some extent non-metallic compounds such as epoxy resins (composite) and also prolonged use of dentures (8-11).

3) Microbial agents

OLP has been associated in the individuals who have recurrent infections with gram-negative anaerobic bacillus, spirochetes and Helicobacter pylori (HP) (10, 12, and 13). According to the research and recent studies done by various authors, few periodontopathogenic microorganisms are also associated with the patients of OLP (14). 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) (15-20). Epidemiological evidences from various studies worldwide strongly suggest that hepatitis C virus (HCV) may be an etiologic factor in OLP (21, 22).

4) Autoimmunity

OLP is associated with autoimmune disorders such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, and thymoma (23).

5) Bowel disease

Incidence of OLP is high with the autoimmune diseases of intestines such as celiac disease, ulcerative colitis and Crohn's disease (24).

6) Drugs

Oral lichenoid drug reactions may be triggered by systemic drugs including Non steroidal anti-inflammatory drugs, beta blockers, sulfonylureas, some angiotensin-converting enzyme (ACE) inhibitors,and some antimalarials, contact allergens including toothpaste flavorings, especially cinnamates (8,25).

7) Stress

One of the factors responsible for the development of OLP is anxiety and stress. Some of the studies in literature reveal the role of the psychological stress in the etiology of OLP (26,27,28)

8) Habits

Smoking and betel nut chewing have strong association with development of Oral Lichen Planus.

9) Diabetes and hypertension

Diabetes mellitus (DM) and high blood pressure are associated with OLP (29-32).

Triad of DM, hypertension and OLP is known as Greenspan Syndrome.

10) Malignant neoplasms

Incidence of the OLP is more among the patients suffering from breast and Gastrointestinal malignancies

PATHOGENESIS

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8 + T cells trigger apoptosis of the basal cells of the oral epithelium. An early event in the disease mechanism involves keratinocyte antigen expression or unmasking of an antigen that may be a self-peptide or a heat shock protein. Following this, T cells (mostly CD8+, and some CD4 + cells) migrate into the epithelium either due to random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes. Activation of the migrated CD8 + cells occur directly by an antigen binding to major histo-compatibility complex (MHC)-1 on keratinocytes or indirectly 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 causes killing of the basal keratinocytes through tumor necrosis factor (TNF)-α, Fas–FasL-mediated or granzyme B- activated apoptosis (33).

A Cytokine- Mediated Lymphocyte Homing Mechanism

In OLP, there is overexpression of the vascular adhesion molecules (VAM), particlularly, CD62E, CD54, and CD106, by the endothelial cells of the sub-epithelial vascular plexus. The infiltrating lymphocytes express reciprocal receptors (CD11a) to these VAM. TNF-α, IFN-γ and IL-1 are responsible for the up-regulation of the VAM (34).

T-cell accumulation, Basement membrane (BM) disruption by mast cell proteases and keratinocyte apoptosis occurs mainly due to mast cell degranulation and MMP1 activation (35).

BM integrity is normally maintained by a living basal keratinocytes which secrete 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 become helpless to perform this function, which causes 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 (36).

Tissue matrix protein degradation is brought about by the group of matrix mettaoproteinases (MMP). MMP-9, which cleaves collagen 4, along with its activators is up-regulated in OLP lesional T cells, resulting in increased BM disrupion.

Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES) 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 cells undergo a process of degranulation under the influence of RANTES, which release of chymase and TNF-α. These substances up-regulate RANTES secretion by OLP lesional T cells. 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 down-regulates the immunosuppressive effect of TGF-β1 and upregulates keratinocyte MHC class II expression and CD8 + cytotoxic T-cell activity (37).

CLINICAL FEATURES

Oral Lichen Planus (OLP) is characterized by lesions consisting of radiating white gray, velvety, thread-like papules in a linear, annular and retiform arrangement forming typical lacy, reticular patches, rings and streaks. A tiny white elevated dot is present at the intersection of white lines known as Wickham's striae (38). The lesions are asymptomatic, bilaterally/symmetrically anywhere in the oral cavity, but most common on buccal mucosa, tongue, lips, gingiva, floor of mouth, palate and may appear weeks or months before the appearance of cutaneous lesions.

OLP has 6 clinical presentations such reticular variant, erosive variant, atrophic variant, plaque-like variant, papular and bullous variants.

MALIGNANT POTENTIAL OF OLP

OLP is considered as premalignant lesion but malignant transformation of OLP remains a very controversial issue till date (33).According to Pelisse et al, there was little evidence that chronic OLP lead to epithelial dysplasia (lichenoid dysplasia) which progressed subsequently to overt

Squamous cell carcinoma (SCC)(39). The OLP lesions are consistently more persistent than the dermal lesions and have been reported to carry a risk of malignant transformation to oral squamous cell carcinoma (OSCC) of 1-2% (reported range of malignant transformation

0– 12.5%) (40). Erythroplastic lesions may also occur in OLP in approximately 1% of the patients and are sharp with slight reddish depressions.In most cases, malignant transformation to carcinoma in situ (28.5%) and in micro invasive carcinoma (30-38%) is observed, less frequently stage I and II carcinoma. Oral cancer-correlated OLP predisposes to the development of multiple primary metachronous tumors of the oral cavity and of lymph node metastases (41, 42).

DIAGNOSIS

The clinical history, typical oral lesions with skin and/or nail involvement are sufficient for making the diagnosis of OLP. Biopsy and histopathological examination forms a definitive diagnostic tool for confirmation of OLP. The classical histopathological features of OLP includes the dense, band-like subepithelial inflammatory infiltrate consisting of lymphocytes beneath the basement membrane, increased number of intraepithelial lymphocytes and liquefactive degeneration of basal keratinocytes .

Griffin et al described that eosinophilic colloid bodies (Civatte bodies) are formed by degenerating basal keratinocytes and immunocomplexes, and they are often identified in the supra-basal epithelial area. The ultrastructure of these colloid bodies suggest that they are apoptotic keratinocytes, which is shown by demonstrating of DNA and nuclear fragmentation and immunoglobulins, especially IgM in these cells.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis can include 1) frictional keratosis, 2) leukoplakia, 3) lichenoid reactions, 4) leukoplakia, 5) lupus erythematous, 6) pemphigus, 7) mucus membrane pemphigoid, 8) para neoplastic pemphigus, 9) erythematous candidiasis and chronic ulcerative stomatitis,10) Graft vs. host disease (43).

TREATMENT

There is no specific treatment for OLP, and thus other diseases should always be excluded. Therefore, treatment of OLP patients depends on symptoms, the extent of oral and extra-oral clinical involvement, medical history, and other factors. Asymptomatic reticular lesions usually do not require active treatment. All the mechanical irritants, such as non-fitting dentures and sharp or rough fillings, especially dental amalgam restorations, in teeth should be repaired, and as well calculus and gingivitis should be treated. Thus, oral hygiene plays a major role in disease progression. It is also very important to exclude the possibility of oral candidiasis, since the medical components may aggravate candidal infection. Oral candidiasis itself causes soreness of the oral mucosa.

Drug treatment:

The most common treatment for OLP is topical corticosteroids- triamcinolone, potent fluorinated steroids- fluocinolone acetonide and fuocinonide, and superpotent halogenated steroids such as clobetasol. These midpotency corticosteroids are effective in most patients when applied according to the instructions, i.e. a thin layer of the steroid (ointment, gel, spray or rinse) several times daily. Patients who suffer from severe OLP lesions, desquamative gingivitis, widespread oral disease or diffuse ulcerations may need more potent immunosuppressants (cyclosporine) or immunomodulatory agents, such as calcineurin inhibitors (tacrolimus or pimecrolimus) or retinoids (tretinoin) in topical formulations.

Systemic treatment with corticosteroids are used for patients with severe atrophic and erosive OLP or multisite disease, where topical approaches have failed and skin, genital or scalp lesions are present.

Non-drug treatment:

Surgery, as well as CO2 laser, has been used with isolated plaque-like or non-healing erosive lesions to cure localized lesions. Cryosurgery is shown to specifically heal gingival lichen planus.

III. Conclusion

Lichen planus is a disease that can affect the skin and any lining mucosa. Involvement could be the oral, esophageal, vaginal mucosa as well as the skin. The exact etiology of lichen planus and oral lichen planus is not clearly till date, but genetics and immunological factors play a major role in the pathogenesis of the disease. Proper understanding of the pathogenesis, clinical presentation, diagnosis of the disease becomes important for providing the right treatment.

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