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EDITORIAL

ORAL LICHEN PLANUS: NOVEL ACQUISITIONS IN THE PATHOGENESIS AND TREATMENT

R. SARACENO[1], B. LORÈ[2], A. VENTURA[1], S.P. NISTICÒ[3], C. PERUGIA[4], S. CHIMENTI[1] and L. BIANCHI[1]

[1]U.O.C. of Dermatology, University of Rome Tor Vergata, Rome, Italy; [2]Department of Oral and Maxillo-Facial Surgery, University of Rome Tor Vergata, Rome, Italy; [3]Department of Dermatology, University of Catanzaro "Magna Græcia", Catanzaro, Italy; [4]Department of Paediatric Dentistry, University of Rome Tor Vergata, Rome, Italy

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Lichen planus (LP) is a mucocutaneous disease of chronic inflammatory nature, commonly seen in dermatological and dental clinics; it is a relatively common disorder of stratified squamous epithelia, frequently exclusively involving the oral cavity. 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. Lichen planus is regarded as a premalignant lesion. This review discusses the role of hepatitis C virus (HCV), bacterial and fungal infection in LP. Analysing the seroprevalence of HCV infection in LP patients and patients with oral OLP in particular, which was the case in the vast majority of studies, the association varied from 0% to 62% and seemed to be connected to the high HCV seroprevalence in the general population. *Candida albicans* is present in about 37% of oral LP lesions. The aim of this review is to summarize what is new in the pathogenesis and treatment of OLP.

Lichen planus (LP) is a mucocutaneous disease of chronic inflammatory nature, commonly seen in dermatological and dental clinics; it is a relatively common disorder of stratified squamous epithelia, frequently exclusively involving the oral cavity. In 15% of the cases, the lesions are only seen in the oral cavity and no cutaneous involvement is present (1). OLP typically affects adults in the fifth decade of life with a female to male ratio of 3:2 (2). The disease is rarely seen in children. Prevalence of cutaneous and oral lichen planus have been reported to be 0.2–1% and 0.1–2.3% in western countries, respectively (3, 4). The aim of this review is to summarize what is new in the pathogenesis and treatment of OLP.

Clinical features

OLP was first described clinically by Wilson in 1869 as a chronic mucocutaneous disorder (5). Andreasen in 1968 classified oral lichen planus into six clinical forms, including reticular (92%), plaque-like (36%), papular (11%), atrophic (44%), erosive (9%), and bullous (6, 7). The most common type of OLP is reticular form with the characteristic feature of slender white lines (Wickham's striae) radiating from the papules.

Clinical lesions of OLP normally include white reticular lesions, typically in the posterior buccal mucosa (about 90% of cases), tongue (20%), alveolar ridge/gengiva (13%), rarely on the palate or

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Mailing address: Prof. Steven Nistico,
Dermatologist Associate Professor of Dermatology,
University Magna Graecia, Catanzaro
Viale Europa, Germaneto (CZ)
88100 Catanzaro, Italy
Tel./Fax: +39 09613694001
e-mail: steven.nistico@gmail.com

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lip vermilion (8).

Although OLP is often asymptomatic, the atrophic-erosive form can cause symptoms ranging from burning sensation to severe pain, interfering with speaking, eating, and swallowing. Patients with symptomatic OLP often require therapy and should be treated if symptoms are significant. The main complication of OLP is the reduced quality of life related to soreness or pain, particularly in atrophic or ulcerative/erosive lesions. Candidosis can also complicate OLP, especially when the more potent topical corticosteroids are used. Most important, however, is the risk of malignant change which has been recognized over recent years. OLP may also have associations with systemic diseases. The clinical history confirms the relationship between OLP and oral cancer, although the degree of the risk involved is controversial. Therefore, OLP should be considered a precancerous lesion, emphasizing the importance of periodic follow-up visits for all patients. Lichen planus is regarded as a premalignant lesion. Prevalence of squamous cell carcinoma (SCC) has been reported to be between 0.4% and 2% in various groups during a 15-year study period among lichen planus patients.

Pathogenesis

The role of immune system as a primary factor in the pathogenesis of lichen planus has become clearer in recent years. Although the etiology and pathogenesis of OLP are not fully understood, current data suggest that oral lichen planus is a T-cell-mediated autoimmune disease in which autocytotoxic CD8+ T cells trigger the apoptosis of oral epithelial cells. The CD8+ cytotoxic T cells may trigger keratinocyte apoptosis through activation of the cells by an antigen associated with major histocompatibility (MCH) class I on basal keratinocytes. Evidence of this comes from the histology of the lesional lymphocytic infiltrate in OLP that is comprised principally of T cells, including $CD4^+$ and $CD8^+$ lymphocytes. Many antigen-specific mechanisms may be involved in the pathogenesis of OLP, including MHC class I and MHC class II restricted antigen presentation by lesional keratinocytes, activation of antigen-specific $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells, clonal expansion of antigen-specific T cells, and keratinocyte apoptosis triggered by antigen-specific $CD8^+$ cytotoxic T cells. Chemokines produced by T cells and keratinocytes may attract various inflammatory cells into the site of the developing OLP lesion. In OLP, Langerhans cells and macrophages in the basal epithelium provide antigenic information for autocytotoxic CD8 T-cell activity against the epithelial basal layer, resulting in its liquefaction, apoptosis of the basal keratinocytes, acanthosis, thickening of the granular cell layer and often hyperkeratosis. Although the nature of the antigens responsible for OLP development is uncertain, an increased keratinocyte expression of heat shock proteins (HSP) has been reported, suggesting that these proteins could be an auto-antigen. The upregulation of HSP could be induced by agents, such as drugs and infections, implicated in lichenoid diseases.

TNF-alpha is also involved in the pathogenesis of OLP, and may be activated and released from the CTL surface by lesional MMPs. Activated T cells undergo intra-lesional clonal expansion and release RANTES and other cytokines that up-regulate mast cell CCR1 expression and stimulate intra-lesional mast cell migration and degranulation. Degranulating mast cells release TNF-alpha which up-regulates endothelial cell adhesion molecule expression for lymphocyte adhesion and extravasation. Mast cell TNF-alpha also up-regulates RANTES and MMP-9 secretion by OLP lesional T cells. Activated lesional T cells (and possibly keratinocytes) secrete chemokines which attract extravasated lymphocytes toward the OLP epithelium. Degranulating mast cells release chymase that damages the epithelial basement membrane directly or indirectly via activation of MMP-9 secreted by OLP lesional T cells. Epithelial basement membrane disruption facilitates the passage of lymphocytes into the OLP epithelium and denies keratinocytes a cell survival signal, resulting in further keratinocyte apoptosis.

New pathogenetic hypotesis

Th 17 cells, a novel T helper cell subpopulation that was first characterized in 2005 as a distinct T-cell lineage that differed from Th1 and Th2 cells in function and pathological role. The unique cytokine of Th17 is IL-17 which has several isoforms of which IL-17A and IL-17F appear to be important

in regulating immune responses in autoimmunity. Pouralibaba et al. Found that serum IL-17 levels were higher in patients with both erosive and non-erosive lichen planus compared to healthy individuals. Serum levels of IL-17 were significantly higher in patients compared with controls, suggesting that IL-17 can contribute to the pathogenesis of lichen planus by enhancing T-cell-mediated reactions and inducing production of chemokines and other cytokines. Implications of Th1 and Th17 cells in pathogenesis of oral lichen planus and suggested Th1 cells in OLP lesions play a crucial role in the activation of cytotoxic $CD8^+$ T cells. The data revealed that IL-17-mediated immune response may correlate with OLP subtypes and play an important role in the pathogenesis of OLP, as the level of this interleukin was lower in the reticular form compared to the erosive form. This high level may be the reason for higher inflammation and atrophy in the erosive type.

Table I. *Differential diagnosis of OLP.*

DIFFERENTIAL DIAGNOSIS
Squamous cell carcinoma
Discoid Lupus erythematosus
Chronic Candidiasis
Benign mucous membrane pemphigoid
Pemphigus vulgaris
Chronic cheek chewing
Graft-versus-host disease (GVHD)
Erythema multiforme and mucositis
Lichenoid reaction to dental amalgam or drugs

Table II. *Topical and systemical treatments.*

TOPICAL TREATMENTS	SYSTEMIC TREATMENTS
Corticosteroids	Corticosteroids
Vitamin A derivates	Vitamin A derivates
Cyclosporine rinse	Cyclosporine
NB-UVB 308 Excimer light	PUVA
CO2 laser	Biologics
PRP	Thalidomide
Cryotherapy	ECP
ND:YAG laser	
Tacrolimus	

Hepatitis C virus and lichen

Oral lichen planus has been found to be associated with diseases and agents, such as viral and bacterial infections, autoimmune diseases, medications, vaccinations and dental restorative materials. An important issue regarding OLP is its reported association, in some populations, with hepatitis C virus (HCV) infection.

However, since 1991, more than 80 case reports world-wide have supported the link between LP and HCV infection. HCV is presently considered as the main etiologic agent of both blood-borne and sporadic non-A and -B hepatitis, and is one of the major causes of chronic liver disease worldwide. There are 170 million chronic HCV carriers throughout the world and HCV is the major cause of hepatocellular carcinoma. Analysing the seroprevalence of HCV infection in LP patients and patients with OLP in particular, which was the case in the vast majority of studies, the association varied from 0% to 62% and seemed to be connected to the high HCV seroprevalence in the general population, which is high in the Mediterranean countries and Japan and low in Scandinavia, United Kingdom, France and Germany. However, few studies investigated LP in HCV-infected persons, showing the prevalence of LP generally higher than expected ranging from 1.6% to 20% (9). A pathogenetic link between HCV infection and some extrahepatic manifestations was confirmed by their responsiveness to antiviral treatment, as was the case in mixed cryoglobulinaemia, interferon-alpha and, most recently pegylated IFN-α (Peg-IFN-α) plus ribavirin (RBV) being the first choice to consider (10). HCV-related OLP appears also associated mainly with the HLA-DR6 allele in specific populations and this could partially explain the peculiar geographic heterogeneity in the association between HCV and LP (11). The putative pathogenetic link between LP and HCV is still under investigation but molecular mimicry between the virus and host epitopes is unlikely as are viral factors such as genotype or viral load (12). The prevalence of HCV infection in LP appears to be higher in persons with oral lesions from Southern Europe (mainly Italy and Spain),

Japan and USA than among patients from Northern Europe. Carrozzo et al. have demonstrated a strong association between hepatitis C viral infection and OLP in Italy (13). High prevalence rates of HCV infection in patients with OLP have been reported, as high as 62% in Japan (14). These geographical differences appear unrelated to the particular HCV genotypes or to any co-infection with hepatitis G virus or transfusion transmitted virus (TTV) or to molecular mimicry, and seem only partially related to the level of the HCV endemicity in the general population (15). A possible link between hepatitis viruses and LP has been suggested by the fact that LP has been frequently associated with chronic liver disease (CLD) in Mediterranean but not in northern European patients (16).

In OLP, HCV replication has been reported in the oral mucosa of anti HCV/HCV-RNA positive patients. In fact, some studies showed that both the plus and minus strands of viral RNA are detectable in epithelial cells from normal oral mucosa and from the LP lesions by reverse transcription/polymerase chain reaction or *in-situ* hybridization (17).

However, HCV is unlikely to cause direct damage to epithelial cells in OLP lesions, as it was also found in normal mucosa (18). The lympho-mononuclear infiltrate typically found in oral lichen lesions suggests that the progressive destruction of the oral mucosa lining is on account of local immune aggression. A recent study showed that HCV-specific $CD4^+$ and/or $CD8^+$ T lymphocytes can be found in the oral mucosa of patients with chronic hepatitis C and LP. $CD4^+$ polyclonal T-cell lines were generated more efficiently from lichen-infiltrating lympho-mononuclear cells than from peripheral blood mononuclear cells from the same patients, suggesting a higher frequency of HCV-specific T cells in the oral compartment. However, T-cell clones present in the oral mucosa showed a different TCR (T-Cell Receptor)-Vb chain usage than those circulating in the peripheral blood, suggesting a specific compart-mentalization at the site of the LP lesions.

Recent data have shown that HCV-specific T cells can be found in the oral mucosa of patients with chronic hepatitis C and LP (19). *In situ* and peripheral blood-derived T-cell lines were able to proliferate and to produce interferon gamma upon stimulation with structural and non-structural HCV antigens, and showed the same specificity.

HCV infection is not a direct causal factor of OLP because replication of HCV was observed in both mucosa with and without OLP. In addition, the authors found a mononuclear cell infiltrate around the epithelial cells of HCV-seropositive patients with and without OLP. However, the authors did not rule out the possibility of HCV inducing changes in the host that may have led to an autoimmune response. (20)

Bacterial and fungal infections and OPL

Although it has been determined that OLP and viruses are related, the roles of bacteria and fungi in the etiology of OLP have not yet been determined. However, it is known that OLP is related to periodontal diseases. It is known that patients with OLP are more likely to be infected by many other microorganisms (21).

Ertugrul et. al investigated the role of periodonto-pathogenic microorganisms (*A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *T. denticola*) in the pathogenesis of OLP using the micro-IDent kit to compare periodontopathogenic microorganisms in OLP and controls. The authors found that the amounts of periodontopathogens in OLP patients were higher in comparison to non-OLP patients explaining the relationship between OLP and periodontopathogenic microorganisms can be explained by two hypotheses. The first is the increase in the numbers of periodontopathogens following the formation of OLP lesions. The second relationship is that periodontopathogeniv microorganisms play a direct role in the etiology of OLP and could cause the formation of OLP lesions (22). Several studies have reported a possible relationship between *Helicobacter pylori* and OLP (23, 24). Among these studies Moravvej et al. found statistically significant differences in *H. Pylori* infection between patients with lichen planus and a control group (25). Numerous studies have investigated the prevalence of candidal infection in erosive lichen planus. However, according to the results of the larger studies, candida infection is not currently considered an etiologic factor for OLP (26, 27). On the other hand, *Candida albicans* is present in about 37% of oral LP lesions (28) and symptoms of oral LP may

be exacerbated by candidal overgrowth or infection. OLP may be exacerbated by candidal overgrowth or infection, while antifungal treatment of erosive lesions with Candida can change the lesions to the reticular form. Theoretically the use of antifungal treatment in some cases of oral LP could reduce the potential of *Candida albicans*.

Treatment: conventional and new treatments

Generally, no medication is necessary for the benign form of this disease (reticular lichen planus). In the case of severe pain and a burning sensation, high-potency topical corticosteroids remain the most reliably effective treatment. Oral hygiene and corrective dentistry play a major role in the management of OLP and consultation with a dentist or oral medicine specialist is helpful. Excellent oral hygiene maintenance is believed to reduce the degree of severity of the symptoms and duration associated with OLP. Treatment of OLP is difficult as complete eradication of the disease is rare. Currently, treatment for OLP is focused mainly to eliminate mucosal erythema, ulcerations and alleviate disease symptoms during periods of activity and, if possible, increase the periods of disease quiescence. Reticular type is often asymptomatic and seldom requires treatment. Various treatment modalities for lichen planus have been tried including topical and systemic steroids, retinoids, immunosuppressive drugs, surgery, lasers and photochemotherapy (Tables I and II).

Currently, corticosteroids are the drug of choice for the treatment of OLP. It may be employed in the form of topical superficial application or intralesional injection; or systemic or combination of topical and systemic. Topical corticosteroids are widely used in the treatment of OLP to reduce pain and inflammation. Triamcinolone acetonide is commonly used either in Orabase or as lozenges. Systemic corticosteroids may be indicated in patients whose condition is unresponsive to topical steroids or in patients with mucocutaneous disease and may be administered in high doses (1.5-2 mg/kg/daily), however, adverse effects are possible even with short courses.

Cyclosporine is a lipophilic cyclic polypeptide which produces calcium-dependent, specific, reversible inhibition of transcription of interleukin (IL)-2 and several other cytokines, most notably in T helper lymphocytes. This reduces the production of a range of cytokines, inhibiting the activation and/or maturation of various cell types, including those involved in several chronic inflammatory diseases.

Some studies have suggested that cyclosporin is effective applied either topically or in the form of a mouth rinse, but others have reported little benefit or no significant improvement. Cyclosporin can be an alternative to conventional treatments for initial control of oral LP. However, it should not be considered as a first drug of choice because of the high cost of long-term treatment and the availability of effective alternatives. Severe side effects of systemic cyclosporin, such as hypertension and nephrotoxicity, preclude its use for oral LP.

In oral LP patients, systemic absorption is probably low and most studies did not detect cyclosporin in peripheral blood. Although many studies have claimed the effectiveness of cyclosporin, the disadvantages of this medication are bad taste, transient burning sensation on initial application, and high cost.

Tacrolimus is a macrolide immunosuppressant with a mechanism of action similar to that of cyclosporine, but is 10 to 100 times more potent and is better able to penetrate the mucosal surface. Notably, topical tacrolimus seems to penetrate skin better than topical cyclosporin. This drug used topically can control symptoms and significantly improve refractory erosive oral LP. Local irritation is the most common adverse effect. Recently, the treatment of chronic erosive oral LP with low concentrations of tacrolimus has been found to yield a rapid and important palliative effect, but all patients relapsed after 12-month follow-up in this study (29).

Treatment with topical tacrolimus 0.1% ointment four times daily induced a better initial therapeutic response than triamcinolone acetonide 0.1% ointment in patients with symptomatic OLP. However, relapses occurred frequently in both groups within several weeks after the cessation of both these treatments (30).

Retinoids are metabolites of vitamin A. They have been noted to have antikeratinizing and immunomodulating effects (31-32). Retinaldehyde 0.1%, isotretinoin gel 0.1% have been tried in OLP and they showed good clinical efficacy. However, all the cases reported showed a relapse 2-5 weeks after discontinuation of treatment. Only transient

burning sensations or irritation on initial application have been reported. Moreover, following treatment with topical tretinoin, histologic examination demonstrated that keratinization may decrease significantly or even disappear (33).Narrow-band UVB known as monochromatic excimer light (MEL) emitting at 308 nm represents a new source of investigation. MEL 308 nm, emitted as either coherent (laser) or non-coherent light, has been used in the treatment of a range of skin conditions showing interesting clinical results (34-42). Excimer 308 nm lasers could be an effective choice in treating symptomatic OLP. Treatments with these lasers are painless and well tolerated (35-37). The authors in this study, did not observe problems with wound healing. In every case there was complete epithelialization within 3 weeks. They found out that when there is no further improvement with steroids, CO2 laser evaporation seems to be a good treatment option for oral lichen planus and may even be considered a first choice. CO2 laser as well as surgical excision, cryotherapy, and ND:YAG laser have all been used in the treatment of OLP. Surgery is reserved to remove high-risk dysplastic areas (39). Also photochemotherapy with 8-methoxypsoralen and long-wave ultraviolet light (PUVA) has been used successfully in the treatment of skin lesions and cutaneous LP. It was first used in the treatment of recalcitrant OLP. Eighty-seven percent of patients treated with ultraviolet-A, without a systemic or topical photosensitizer, improved significantly, but until more extensive studies are undertaken, it must be considered as an experimental method.

CONCLUSIONS

Patients with oral lichen planus should be informed of the causes, nature and course of the condition and response to different treatment modalities. Causative agents, such as dental restorations or drugs, must be identified and appropriate corrective measures should be taken. Patients experience high rates of recurrences after the cessations of treatment and this should not discourage them for receiving further treatment. Regular follow-ups allow the clinicians to examine and evaluate the patients thoroughly. Any suspicious lesions must be sent for biopsy for histopathological examination as in some forms of lichen planus there is a high chance of transformation into squamous cell carcinoma.

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