

## Oral lichen planus: a narrative review

Dario Di Stasio<sup>1</sup>, Agostino Guida<sup>1</sup>, Carmen Salerno<sup>1</sup>, Maria Contaldo<sup>1</sup>, Vincenzo Esposito<sup>1</sup>, Luigi Laino<sup>1</sup>, Rosario Serpico<sup>1</sup>, Alberta Lucchese<sup>1</sup>

<sup>1</sup>Multidisciplinary Department of Medical-Surgical and Odontostomatological Specialties; 6 L. De Crecchio Street, 80138 Naples, Italy

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Scientific literature revision
4. Discussion
  - 4.1. Epidemiology
  - 4.2. Aetiopathogenesis
  - 4.3. Clinical presentation and diagnosis
  - 4.4. Current treatment modalities in Oral Lichen Planus
5. Acknowledgements
6. References

## 1. ABSTRACT

Oral Lichen Planus (OLP) is a common disease of unknown aetiology affecting oral mucosae by T-cell mediated chronic inflammation. OLP diagnosis is made by evaluating both clinical and histological criteria. Pharmacological treatment is useful in symptomatic cases. Life-long clinical follow-up is essential, due to low-risk of malignant transformation. *In vivo* Reflectance Confocal Microscopy (RCM) offers a real-time virtual biopsy of the being tissues and does not require surgical excision nor histopathological processing. RCM was used to capture OLP lesions in order to clinically differentiate them from other clinical entities.

## 2. INTRODUCTION

Lichen planus (LP) is an idiopathic inflammatory disease of skin and mucous membranes, characterised by an autoimmune epidermis attack by skin-infiltrating T cells. It remains unknown, however, how such aggressive T cells could be activated *in vivo* to cause epidermal damage (1).

The disease has a predominance in the general population of 1-2%, 50% of which has both skin and oral lesions, while 25% of patients shows only oral lesions (OLP) (2). Extra-oral sites (i.e. scalp, skin, nails, conjunctiva, esophagus, larynx urethra, vulva and vagina, and perianal area) are commonly involved. Skin lesions

## Oral lichen planus

include flat-topped violaceous papules affecting wrists, ankles and genitalia (3). It results in severe morbidity, thus a multidisciplinary approach is needed. OLP mainly affects women between their fifth and sixth decade. Approximately, 18-25% of patients are smokers and 24-29% uses alcoholic beverages (4, 5). The oral sites generally involved are buccal mucosa, tongue and gingiva. Usually OLP lesions are multiple, symmetrical and bilateral. OLP is generally classified into six clinical variants: reticular (23%), papular, plaque-like, erosive (37%), atrophic (40%) and bullous. Its development is chronic, and a spontaneous remission is rare (3). Although atrophic and erosive OLP are considered premalignant conditions, their malignant transformation rate is low (about 0–5,3%) (6). In the present work, scientific literature has been reviewed in order to produce an update on the current state of art on OLP.

### 3. SCIENTIFIC LITERATURE REVISION

Medline (www.pubmed.com), Scopus (www.scopus.com) and ISI Web of knowledge (www.webofknowledge.com) were used as search engines to investigate literature and review OLP. Key Words used were “oral lichen planus”. Results were then restricted to papers on *in vivo* or *in vitro* studies in humans, that had been published in English until January 2013. MEDLINE search produced 2972 citations for “oral lichen planus”. Scopus and ISI Web of knowledge databases and bibliographies of review articles did not reveal any relevant studies that had not been identified by the MEDLINE search. Results were then restricted to papers in English, on humans, *in vivo*, and similar articles were excluded, favoring first published articles. Results were this way restricted to 60 articles.

### 4. DISCUSSION

#### 4.1. Epidemiology

Predominance of OLP may vary according to the country. In India, it has been reported to range from 0.0.2% (7) to 0.4.0% (8), more recently 0.1.5% (9). Another East Asian study showed a prevalence of 2.1.5% in Malaysia and 3.8.5% in Thailand (10) with a further study in Thailand reporting 2.8.% (11). Saudi Arabian studies reported a predominance of 0.5.9% (12) and 1.6.8% (13). A German study reported the prevalence as 0.6.0% (14). An Italian paper reported prevalence of OLP was 1.4.6% (15). Studies on patients attending screening clinics for extra-oral disease have been conducted in Europe and the USA. A Hungarian paper has shown predominance of 0.0.8% (16). Two USA studies based in screening clinics reported predominance of 0% (17) and 1.1.% (18). A Japanese report showed prevalence as 1.0.% (19). In the UK, it has been showed predominance of 2.5.9% (20). In most of these studies, the division of age and sex to allow proper standardization was insufficient.

#### 4.2. Aetiopathogenesis

OLP, whose aetiology is still unknown, has a multifactorial pathogenesis. It is an inflammatory disease characterized by cell-mediated autoimmune reaction (1) in

which lesions are result of T CD8+lymphocytes-induced apoptosis of the epithelial basal cells (21).

Activated T-cells and amplified Th1 cytokine production (interleukin (IL) -1, IL-8, IL-10, IL-12, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )) enhance the expression of intercellular adhesion molecule-1 (ICAM-1) on Langerhans cells and macrophages, and major histocompatibility complex type I (MHC I) antigens on keratinocytes (22). Furthermore, cytokine activity may be facilitated by an over-expression of their receptors; a study showed that receptors for chemokines CXCR-3, CXCL-10 and CXCL-11 are up-regulated in OLP (23). These events determine the initiation of lymphocytic infiltration that characterizes OLP. T lymphocytes migrate from extravascular environment to epithelium, where they remain due to adhesive interactions between lymphocyte function-associated antigen-1 (LFA-1) on T-cells and ICAM-1, both expressed on keratinocytes and lymphocytes. Hence, lymphocytes influence development and extension of lesions through their products, such as histamine releasing factor, which promotes mast cells degranulation and interferongamma (IFN- $\gamma$ ). IFN- $\gamma$  induces ICAM-1 expression on endothelial cells, ICAM-1 and MHC class II expression on keratinocytes, MHC class II up-regulation, and CD4 antigen expression on intraepithelial lymphocytes (15), thus auto-fostering the inflammatory process. Moreover, it has been demonstrated that TNF- $\alpha$  and IFN- $\gamma$  polymorphisms contribute to OLP/ OLP susceptibility. In detail, the higher IFN- $\gamma$  production could be considered an important risk factor for OLP lesions development. Likewise, the cytokine polymorphisms seem to influence the clinical presentation of the pathology (24). Thus, it has been hypothesised that lesional cytotoxic T-CD8+ cells may be activated by a basal keratinocyte antigen associated with MHC class I (25), promoting, consequently, keratinocyte apoptosis. The triggering antigen has not been identified yet. Interaction (cross-reactivity after non-self antigen immunization) between endogenous or exogenous agent (allergens, drugs, viruses) and keratinocytes has been hypothesised. There is robust evidence that Hepatitis C Virus (HCV) is associated with OLP and that this virus may be involved in OLP pathogenesis. It has been hypothesised that a peculiar genetic predisposition might facilitate the incidence of OLP in a subgroup of patients with HCV (26).

Associations between genetic polymorphisms of the first intron of the interferon- $\gamma$  promoter gene and progression of oral lesions of lichen planus have been observed.

Furthermore, a retrospective study on 124 HCV+ patients confirmed a statistically significant presence of OLP and other oral lesions (aphtous stomatitis, angular cheilitis) in HCV+ patients (27) and three meta-analyses confirmed the association between HCV and lichen planus. For these reasons, it seem reasonable to screen patients with LP/OLP for HCV antibodies (28). OLP has been also correlated with other diseases. In a study, data from 956 patients with OLP and 1029 controls showed that the use of levothyroxine was associated with OLP, thus suggesting a

## Oral lichen planus

possible connection with hypothyroidism. Specifications of the nature of the thyroiditis could have been interesting (29).

In addition to cell-mediated autoimmunity, in recent years, the role of autoantibodies has been considered. Autoantibodies against p63 (30,31) - which is important in homeostasis of normal epithelium and regulates proliferation and differentiation of keratinocytes (32) - and E74-like factor 3 (ELF-3) - which is exclusively expressed in epithelial cells and promotes differentiation of keratinocytes through transactivation of a variety of genes (33,34) - have been found in sera from patients with OLP. The authors have considered these findings as supportive evidence of the autoimmune origin of this disease, confirming dysregulation of proliferative mechanisms of basal keratinocytes, where ELF-3 and p63 are mainly expressed (23).

### 4.3. Clinical presentation and diagnosis

Various morphologies may occur in the same patient at the same time, and the prevailing clinical form may mutate over time. An evolution towards more serious forms (erythematous/atrophic, erosive) can present as the patients grow older (4). The imbalance, between regenerative epithelial reaction and T-cells mediated destruction, is responsible for the clinical varieties of OLP forms. If the regenerative epithelial reaction overcomes the destructive T-cells action, lesions appear “proliferative” (mainly striae and/or papulae); otherwise, when lymphocytes prevail, lesions are mainly represented by erythematous/erosive forms. Reticular lesions are constituted by white papules and striations, often forming a lacy network (Wickham’s striae) on the buccal mucosa, alveolar sulcus and lower vermillion lip.

Wickham’s striae can be found with or without concomitant erythema or erosions. Being asymptomatic, reticular OLP is often accidentally discovered during routine oral examination. When symptomatic, involvement of the dorsum of the tongue may cause dysgeusia. Large reticular plaques, which may be hyperkeratotic, show a predilection for the dorsum of the tongue and buccal mucosa. Erythematous and erosive OLP may cause pain (burning, irritation), swelling, and bleeding (35). In some cases, vesicles may be also observed (bullous OLP) (36). Erosive OLP may present also as desquamative gingivitis, in which the gingival epithelium is easily detachable from the underlying submucosa (37).

Diagnosis of OLP should be made by evaluating both clinical and histological features. Indeed, because the histopathological criteria of OLP are not truly reproducible, a final diagnosis of OLP cannot be made on histopathological grounds alone. Criteria of OLP diagnosis have been established by World Health Organization and are reported in Tables 1 and 2 (38).

In recent years, reflectance confocal microscopy (RCM) has demonstrated to be a valuable tool for the ‘*in vivo*’ characterization of various skin diseases with cellular level resolution (39,40). In particular has been

demonstrated that RCM might be helpful to follow the therapeutic evolution of the LP in a non-invasive manner in real-time (41).

Lesions that simulate a lichen planus, but do not meet the above criteria, are considered to be clinically compatible with lichen planus (lichenoid reaction) (42).

The clinical differential diagnosis of OLP includes squamous cell carcinoma, chronic candidiasis, benign mucous membrane pemphigoid, pemphigus vulgaris, lichenoid drug eruptions, contact lichenoid reactions, leukoplakia, lupus erythematosus, graft-versus-host disease (GVHD), hypersensitive mucositis, and multiform erythema (6).

### 4.4. Current treatment modalities in oral Lichen Planus

Medical treatment should be personalised according to patient's general status, age, and symptoms, evaluating type and extent of mucosal lesion. It is generally accepted that patients with asymptomatic reticular lesions may only necessitate follow-up (2).

Optimisation of oral hygiene is fundamental to treat OLP, as dental plaque and calculus implement intraoral inflammation and can intensify both extension and symptoms of OLP lesions. Patients should be instructed to clean their teeth using a soft bristle toothbrush and toothpaste, without irritants like mint or cinnamon, avoiding accidental trauma on soft tissues; daily use of alcohol-free chlorhexidine mouthwash may reduce bacterial plaque, thus helping to prevent opportunistic fungal infection, especially in patients with dentures (43). In addition, accidental toothbrush trauma, pointed cusps, cracked teeth or worn dental restorations may worsen symptoms or even be a “trigger” for new lesions. Acidic, spicy, hard/crunchy, and hot foods and beverages may be not tolerated during active phases of the disease. Alcohol and tobacco consumption, known carcinogens, should be reduced/eliminated, especially in erythematous/erosive forms (44). Weak evidence from potentially very biased, small, non-randomized, unblinded studies suggests that a small fraction of OLP or oral lichenoid lesions patients may benefit from amalgam restoration replacement (34). Generally, medical treatment is instituted for atrophic, erosive or symptomatic OLP.

Moreover, because of the fact that atrophic and erosive forms present a risk, although low, of malignant transformation a long-term follow-up is required. Administration of topical steroids must be preferred, thus reserving systemic steroids for severe and refractory OLP, for short periods, switching, then, to topical drugs as soon as possible. Furthermore, a study did not find significant differences in the use of systemic prednisone plus topical clobetasol and topical clobetasol alone (45). The use of systemic corticosteroids is indicated, as well as in patients refractory to topical therapy, when disease manifestations are spread in extra-oral locations such as skin, genitals or oesophagus (2,44). Clobetasol is the most effective topical steroid. It has been reported that complete remission rate of OLP treated with clobetasol ranges from 47% to

## Oral lichen planus

75%(2,24). A big issue in using topical medicaments in the mouth is making them adherent to oral mucosa for a sufficient absorption time (2).

Patients must be instructed to dry the mucosa first and then apply the topical corticosteroid to adhesive patches or swabs. When gingival mucosa is involved, dental trays that cover the gingiva may be used(44). Topical steroids usually do not lead to systemic adverse effects, but a common intraoral reaction is candidiasis, which may be minimized through the use of [0]prophylactic antifungal therapy (44–46). During severe OLP, if steroid treatment has failed or has not been tolerated or indicated, cyclosporine should be considered as the third-line treatment (47).

It has been reported the efficacy of local (mouthwash) and systemic cyclosporine (45), but its prescription is restricted by its price, systemic adverse effects and because it may not always give greater help than topical corticosteroids (44). Furthermore, oral cyclosporine rinse has a bad taste and may give transient burning sensation (46). Still, it does not lead to mucosal atrophy as topical steroids do, even if used for a long time. Because of weak cost/benefit ratio, its use is usually confined to patients with severe manifestations or those who have failed conventional treatments (2). Steroids and cyclosporine are effective in the treatment of symptomatic OLP, even if their mechanisms of action are still unclear. In the same study, dexamethasone (DeX) and cyclosporine A (CsA) were showed to down-regulate NF- $\kappa$ B signaling pathway in T cells by inhibition of TLR4 expression, inducing apoptosis of T cells (47).

Other drugs tested for OLP treatment have been topical calcineurin inhibitors, tacrolimus and pimecrolimus (44). Topical tacrolimus administration may lead to local irritation and possible recurrences after drug removal (46). Oral cancer onset has been reported in a OLP patient treated by tacrolimus (48). Pimecrolimus, the newest calcineurin inhibitor tested for OLP treatment, has mechanisms of action similar to tacrolimus, but shows no effect on Langerhans cells (2).

Biological agents such as basiliximab, etanercept, efalizumab and alefacept have been introduced for OLP treatment. Basiliximab, a chimeric (of human and murine origins) monoclonal antibody to interleukin 2 receptor, can prevent T-cell activation, and it is supposed to be helpful in patients affected by T cell-mediated autoimmune diseases such as OLP (49); etanercept (Enbrel) is a TNF receptor fusion protein composed by the extracellular portion of two TNF type II (p75) receptors joined to the Fc portion of IgG1. It primarily binds to soluble TNF- $\alpha$  as well as TNF- $\beta$  (lymphotoxin). Etanercept prevents TNF binding to its receptor, blocking its action (50); Efalizumab (Raptiva) is a monoclonal antibody that binds the CD11a subunit of leukocyte function-associated antigen type 1 (LFA-1). LFA-1 is a T lymphocytes surface molecule. Efalizumab, by binding to CD11a, reversibly interrupt the interaction between LFA-1 and ICAM-1, which is necessary for several cell functions, such as activation, migration into the skin, and cytotoxic effects (51); alefacept is a recombinant protein that binds to CD2 on memory-effector T

lymphocytes, inhibiting their activation and reducing the number of CD4+ and CD8+ cells. It is a fusion protein composed by a LFA-3 protein and human IgG1 fragment crystallizable (Fc) domain (52).

Topical retinoids have been reported to be efficient for reticular or hyperkeratotic OLP (53); tazarotene (54) has been shown to be effective in a randomized triple-blind placebo-controlled clinical trial, allowing to avoid corticosteroids' topical adverse reactions. Topical retinoids may be used in combination with corticosteroids in OLP mixed forms (45). Although mild, their adverse events comprehend burning sensation, dryness, erythema, and desquamation (47). Other treatments such as laser therapy have been tested in patients refractory to the previously mentioned drug administrations, but its efficacy has not been established (2).

Recent studies tried to assess efficacy of photodynamic therapy (PDT) on OLP lesions (55). Chlorin e6-PDT was effective to reduce significantly (on average by 55 %) clinical size of the lesions (effects better on lining mucosa than on masticatory mucosa) (56), and so as protoporphyrin IX (PpIX) PDT in a 6 months period and after a 4 years follow-up after 1 session (57). T-cells absorption of PpIX was histologically demonstrated. Last but not least, since OLP is a chronic disease with alternation of exacerbation and remission periods, long drug therapies and unpredictability of prognosis can cause great stress for patients. It has been demonstrated that OLP patients have a higher levels of anxiety and depression and show increased vulnerability to psychological disorders. It is still unclear if psychological factors play a role in the pathogenesis or are consequences of the disease (45). Therefore, OLP patients may require supportive psychological care (57).

## 6. ACKNOWLEDGEMENTS

The authors declare that they have no conflict of interest.

## 7. REFERENCES

1. T Shiohara, Y Mizukawa, R Takahashi, Y Kano: Pathomechanisms of lichen planus autoimmunity elicited by cross-reactive T cells. *Curr Dir Autoimmun* 10, 206–226 (2008)
2. M Carrozzo, R Thorpe: Oral lichen planus: a review. *Minerva Stomatol* 58, 519–537 (2009)
3. S Silverman, M Gorsky, F Lozada-Nur: A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. *Oral Surg Oral Med Oral Pathol* 60, 30–34 (1985)
4. J-L Xue, M-W Fan, S-Z Wang, X-M Chen, Li Y, L Wang: A clinical study of 674 patients with oral lichen planus in China. *J Oral Pathol Med* 34,467–472 (2005)

## Oral lichen planus

5. MG Oliveira Alves, JD Almeida, I Balducci, LA Guimarães Cabral: Oral lichen planus: A retrospective study of 110 Brazilian patients. *BMC Res Notes* 3,157 (2010)
6. SB Ismail, SKS Kumar, RB Zain: Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. *J Oral Sci* 49, 89–106 (2007)
7. JJ Pindborg, M Bhatt, KR Devanath, HR Narayana, S Ramachandra: Frequency of oral white lesions among 10,000 individuals in Gangalore, South India. A preliminary report. *Indian J Med Sci* 20, 349–352 (1966)
8. J Zachariah, B Mathew, NA Varma, AM Iqbal, JJ Pindborg: Frequency of oral mucosal lesions among 5000 individuals in Trivandrum, South India. Preliminary report. *J Indian Dent Assoc* 38, 290–294 (1966)
9. T Saraswathi, K Ranganathan, S Shanmugam, R Sowmya, P Narasimhan, R Gunaseelan: Prevalence of oral lesions in relation to habits: Cross-sectional study in South India. *Indian J Dent Res* 17, 121 (2006)
10. T Axéll, RB Zain, P Siwamogstham, D Tantiniran, J Thampipit: Prevalence of oral soft tissue lesions in out-patients at two Malaysian and Thai dental schools. *Community Dent Oral Epidemiol* 18, 95–99 (1990)
11. A Jainkittivong, V Aneksuk, RP Langlais: Oral mucosal conditions in elderly dental patients. *Oral Dis* 8, 218–223 (2002)
12. NJ Mani: Preliminary report on prevalence of oral cancer and precancerous lesions among dental patients in Saudi Arabia. *Community Dent Oral Epidemiol* 13, 247–248 (1985)
13. G Salem: Oral lichen planus among 4277 patients from Gizan, Saudi Arabia. *Community Dent Oral Epidemiol* 17, 322–324 (1989)
14. PA Reichart, H Kohn: Prevalence of oral leukoplakia in 1000 Berliners. *Oral Dis* 2, 291–294 (1996)
15. V Crincoli, MB Di Bisceglie, M Scivetti, A Lucchese, S Tecco, F Festa: Oral lichen planus: update on etiopathogenesis, diagnosis and treatment. *Immunopharmacol Immunotoxicol* 33, 11–20 (2011)
16. J Bánóczy, O Rigó: Prevalence study of oral precancerous lesions within a complex screening system in Hungary. *Community Dent Oral Epidemiol* 19, 265–267 (1991)
17. NM Ross, E Gross: Oral findings based on an automated multiphasic health screening program. *J Oral Med* 26, 21–6 (1971)
18. JE Bouquot, RJ Gorlin: Leukoplakia, lichen planus, and other oral keratoses in 23,616 white Americans over the age of 35 years. *Oral Surg Oral Med Oral Pathol* 61, 373–381 (1986)
19. N Ikeda, MC Downer, T Ishii, H Fukano, T Nagao, K Inoue: Annual screening for oral cancer and precancer by invitation to 60-year-old residents of a city in Japan. *Community Dent Health* 12, 133–137 (1995)
20. MC Downer, AW Evans, CM Hughes Hallet, JA Jullien, PM Speight, JM Zakrzewska: Evaluation of screening for oral cancer and precancer in a company headquarters. *Community Dent Oral Epidemiol* 23, 84–88 (1995)
21. LJ Walsh, NW Savage, T Ishii, GJ Seymour: Immunopathogenesis of oral lichen planus. *J Oral Pathol Med* 19, 389–396 (1990)
22. G Scardina, A Ruggieri, P Messina, E Maresi: Angiogenesis of oral lichen planus: A possible pathogenetic mechanism. *Med Oral Patol Oral y Cir Bucal* 14, 558–562 (2009)
23. K Danielsson, L Boldrup, M Rentoft, PJ Coates, M Ebrahimi, E Nylander, YB Whalin, K Nylander: Autoantibodies and decreased expression of the transcription factor ELF-3 together with increased chemokine pathways support an autoimmune phenotype and altered differentiation in lichen planus located in oral mucosa. *J Eur Acad Dermatol Venereol* 27, 1410–1416 (2013)
24. M Carrozzo, M Uboldi de Capei, E Dametto, ME Fasano, P Arduino, R Brocchetto, D Vezza, S Rendine, ES Curtioni, S Gandolfo: Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. *J Invest Dermatol* 122, 87–94 (2004)
25. D Eisen, M Carrozzo, J-V Bagan Sebastian, K Thongprasom: Number V oral lichen planus: clinical features and management. *Oral Dis* 11, 338–349 (2005)
26. M Carrozzo, E Dametto, ME Fasano, P Arduino, G Bertolusso, F Uboldi de Capei, S Rendine, A Amoroso: Cytokine gene polymorphisms in hepatitis C virus-related oral lichen planus. *Exp Dermatol* 16, 730–736 (2007)
27. Y Nagao, K Hashimoto, M Sata: Candidiasis and other oral mucosal lesions during and after interferon therapy for HCV-related chronic liver diseases. *BMC Gastroenterol* 12, 155 (2012)
28. L Baccaglini, K Thongprasom, M Carrozzo, M Bigby: Urban legends series: lichen planus. *Oral Dis* 19, 128–143 (2013)
29. J Robledo-Sierra, U Mattsson, M Jontell: Use of systemic medication in patients with oral lichen planus - a possible association with hypothyroidism. *Oral Dis* 19, 313–319 (2013)

## Oral lichen planus

30. M Ebrahimi, Y-B Wahlin, PJ Coates, A Wiik, G Roos, K Nylander: Detection of antibodies against p63 and p73 isoforms in sera from patients diagnosed with oral lichen planus. *J Oral Pathol Med* 36, 93–98 (2007)
31. M Ebrahimi, E Nylander, B Bäcklund, Y-B Wahlin, PJ Coates, K Nylander: The use of a novel ELISA method for detection of antibodies against p63 in sera from patients diagnosed with oral and/or genital and skin lichen planus. *J Oral Pathol Med* 39, 486–490 (2010)
32. Koster MI, Roop DR. Mechanisms regulating epithelial stratification. *Annu Rev Cell Dev Biol. Annual Reviews* 23, 93–113 (2007)
33. P Oettgen, RM Alani, M Barcinski, L Brown, Y Akbarali, J Boltax, C Kunsch, K Munger, T Libermann: Isolation and characterization of a novel epithelium-specific transcription factor, ESE-1, a member of the ets family. *Mol Cell Biol* 17, 4419–4433 (1997)
34. JM Andreoli, SI Jang, E Chung, CM Coticchia, PM Steinert, NG Markova: The expression of a novel, epithelium-specific ets transcription factor is restricted to the most differentiated layers in the epidermis. *Nucleic Acids Res* 25, 4287–4295 (1997)
35. D Eisen: The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol* 46, 207–214 (2002)
36. JJ Thorn, P Holmstrup, J Rindum, JJ Pindborg: Course of various clinical forms of oral lichen planus. A prospective follow-up study of 611 patients. *J Oral Pathol* 17, 213–218 (1988)
37. C Scully, SR Porter: The clinical spectrum of desquamative gingivitis. *Semin Cutan Med Surg* 16, 308–313 (1997)
38. M Rad, MA Hashemipoor, A Mojtahedi, MR Zarei, G Chamani, S Kakoei, N Izadi: Correlation between clinical and histopathologic diagnoses of oral lichen planus based on modified WHO diagnostic criteria. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 107, 796–800 (2009)
39. M Rajadhyaksha, S González, JM Zavislan, RR Anderson, RH Webb. *In vivo* confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. *J Invest Dermatol* 113, 293–303 (1999)
40. G Pellacani, M Vinceti, S Bassoli, R Braun, S Gonzalez, P Guitera, C Longo, AA Marghoob, SW Menzies, S Puig, A Scope, S Seidenari, J Malvehy: Reflectance confocal microscopy and features of melanocytic lesions: an internet-based study of the reproducibility of terminology. *Arch Dermatol* 145, 1137–1143 (2009)
41. E Moscarella, S González, M Agozzino, JLS Sánchez-Mateos, C Panetta, M Contaldo, M Ardigò: Pilot study on reflectance confocal microscopy imaging of lichen planus: a real-time, non-invasive aid for clinical diagnosis. *J Eur Acad Dermatol Venereol* 26, 1258–1265 (2012)
42. EH Van der Meij, I van der Waal: Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. *J Oral Pathol Med* 32, 507–512 (2003)
43. C Salerno, M Pascale, M Contaldo, V Esposito, M Busciolano, L Milillo, A Guida, M Petruzzi, R Serpico: Candida-associated denture stomatitis. *Med Oral Patol Oral y Cir Bucal* 16, 139–143 (2011).
44. BJ Schlosser: Lichen planus and lichenoid reactions of the oral mucosa. *Dermatol Ther* 23, 251–267 (2010)
45. M Carbone, E Goss, M Carrozzo, S Castellano, D Conrotto, R Broccoletti, S Gandolfo: Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. *J Oral Pathol Med* 32, 323–329 (2003)
46. D Farhi, N Dupin: Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. *Clin Dermatol* 28, 100–8 (2010)
47. Y Ge, Y Xu, W Sun, Z Man, L Zhu, X Xia, L Zhao, Y Zhao, X Wang: The molecular mechanisms of the effect of Dexamethasone and Cyclosporin A on TLR4 /NF- $\kappa$ B signaling pathway activation in oral lichen planus. *Gene* 508, 157–164 (2012)
48. JC Becker, R Houben, CS Vetter, EB Bröcker: The carcinogenic potential of tacrolimus ointment beyond immune suppression: a hypothesis creating case report. *BMC Cancer* 6, 7 (2006)
49. A Reborá, A Parodi, G Murialdo: Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 138, 1100–1101 (2002)
50. N Yarom: Etanercept for the management of oral lichen planus. *Am J Clin Dermatol* 8, 121 (2007)
51. A Cheng, C Mann: Oral erosive lichen planus treated with efalizumab. *Arch Dermatol* 142, 680–682 (2006)
52. ALS Chang, J Badger, W Rehms, AB Kimball: Alefacept for erosive lichen planus: a case series. *J Drugs Dermatol* 7, 379–383 (2008)
53. M Petruzzi, A Lucchese, C Lajolo, G Campus, D Lauritano, R Serpico: Topical retinoids in oral lichen planus treatment: an overview. *Dermatology* 226, 61–6 (2013)
54. M Petruzzi, M De Benedittis, R Grassi, N Cassano, G Vena, R Serpico: Oral lichen planus: a preliminary clinical study on treatment with tazarotene. *Oral Dis* 8, 291–295 (2002)

## Oral lichen planus

55. S Sobaniec, P Bernaczyk, J Pietruski, M Cholewa, A Skurska, E Dolińska, E Duraj, G Tokajuk, A Paniczko, E Olszewska, M Pietruska: Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus. *Lasers Med Sci* 28, 311–316 (2013)

56. SI Kvaal, E Angell-Petersen, T Warloe: Photodynamic treatment of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol* 115, 62–70 (2013)

57. P López-Jornet, F Camacho-Alonso: Quality of life in patients with oral lichen planus. *J Eval Clin Pract* 16, 111–113 (2010)

**Key Words:** Oral Lichen Planus, T-cell, Chronic Inflammation.

**Send correspondence to:** Dario Di Stasio, Multidisciplinary Department of Medical-Surgical and Odontostomatological Specialties; 6 L. De Crecchio Street, 80138 Naples, Italy, Tel: 0039 081 5667675, Fax: 0039 081 5667674, E-mail: dariodistasio@me.com