Arch Dermatol Res (2016) 308:539–551
DOI 10.1007/s00403-016-1667-2

REVIEW

Oral lichen planus: a literature review and update

Mohammad S. Alrashdan[1] · Nicola Cirillo[2] · Michael McCullough[2]

Received: 23 January 2016 / Revised: 16 March 2016 / Accepted: 17 June 2016 / Published online: 27 June 2016

Abstract Lichen planus (LP) is a common chronic inflammatory condition that can affect skin and mucous membranes, including the oral mucosa. Because of the anatomic, physiologic and functional peculiarities of the oral cavity, the oral variant of LP (OLP) requires specific evaluations in terms of diagnosis and management. In this comprehensive review, we discuss the current developments in the understanding of the etiopathogenesis, clinical-pathologic presentation, and treatment of OLP, and provide follow-up recommendations informed by recent data on the malignant potential of the disease as well as health economics evaluations.

Keywords Oral lichen planus · Oral lichenoid reactions · Oral lichenoid lesions

Introduction

The term lichen planus (LP) is derived from the Greek word leichen meaning tree moss and the Latin planus meaning flat. Erasmus Wilson first described the condition LP in 1869, as a chronic disease affecting the skin, scalp, nails, and mucosa, with possible rare malignant transformation [30, 70]. LP may involve the hair follicles (lichen planopilaris, resulting in scarring alopecia), nails and more seldom, the eyes, urinary tract, nasal mucosa and larynx [30].

The oral variant; oral lichen planus (OLP) is a chronic inflammatory disease affecting the oral mucosa with characteristic relapses and remissions [25, 58, 78]. While cutaneous lesions of LP can be self-limiting and pruritic, oral lesions are commonly chronic, non-remissive and can be a source of morbidity [70]. OLP may frequently be associated with involvement of the esophagus and therefore an endoscopy may be indicated if dysphagia was a concomitant presenting feature [72].

The diagnosis of OLP is usually made by clinical and histological examinations. However, in classical lesions (bilateral, reticular pattern), it is possible to make a diagnosis based on the clinical appearance alone [44]. Additionally, there is a spectrum of oral lichenoid lesions (OLL) that may confuse the differential diagnosis. These include lichenoid contact lesions, lichenoid drug reactions and lichenoid lesions of graft versus host disease. For example, systemic medications, such as nonsteroidal anti-inflammatory drugs, certain antihypertensives, and oral hypoglycemics, can contribute to the development of oral lichenoid reactions (OLR) [25, 44, 78]. Dental restorative materials, including amalgam, gold and nickel may also be related to localized OLR in a number of patients [27]. It is noteworthy that several dermatoses (e.g., lupus erythematosus, erythema multiforme) may exhibit some lichenoid features, clinically or histologically. However, the discussion of these conditions is beyond the scope of this review.

Treatment of symptomatic OLP varies considerably and ranges from elimination of precipitating or provoking

✉ Mohammad S. Alrashdan
msalrashdan3@just.edu.jo

[1] Department of Oral Medicine and Surgery, Faculty of Dentistry, Jordan University of Science and Technology, Irbid 22110, Jordan

[2] Melbourne Dental School, The University of Melbourne, Victoria, Australia

factors—local or systemic, psychosocial interventions, to long-term pharmacological therapies. Thus, although OLP localizes to the oral cavity, there are broader implications in terms of patient management that warrant careful consideration. The ongoing controversy as to whether OLP is associated with an increased risk of malignant transformation adds further complexity to this disease. This review aims at presenting an overview of the accumulated knowledge and evidence on the different aspects of OLP, as well as the recent advances in each aspect.

Literature search was performed using MEDLINE/PubMed/Ovid databases with "oral lichen planus", "oral lichenoid lesions", "oral licheoid reactions" as key words. Exclusion criteria included articles irrelevant to the oral variant of LP and those published in languages other than English. No restrictions on articles types were applied. Additionally, individual articles retrieved manually from the reference list of the relevant papers were also included.

Epidemiology

The estimated prevalence of OLP in general adult population is 0.5 to 2 % [25, 70, 78]. The reported female/male sex ratio is 2 to 1 and the age of onset is generally between 30 and 60 years [1, 30, 78]. However, there have been case reports of OLP occurring in children [49].

Genital and cutaneous LP are associated with approximately 20 and 15 % of OLP cases, respectively, while it is estimated that OLP occurs in 70 to 77 % of patients with cutaneous LP [30, 70, 79].

Etiology

The precise etiology of OLP is unknown and only few predisposing factors are currently thought to potentially have a role in its pathogenesis.

Genetic background

Genetic background may play a role in OLP pathogenesis as several familial cases have been reported [7], however, the association has not been consistent. Genetic polymorphisms of several cytokines have been postulated to be associated with the clinical presentation of LP. It has been reported that genetic polymorphisms of the first intron of the promoter gene of Interferon-gamma (IFN-γ) may be an important risk factor to develop OLP, whereas an increase in the frequency of 308A tumor necrosis factor-alpha (TNF-α) allele may contribute to the development of additional skin involvement [16].

Psychological factors

Psychological factors are thought to play a role in the pathogenesis of OLP. OLP patients were shown to exhibit higher levels of anxiety, greater depression and increased vulnerability to psychological disorders, as opposed to healthy controls [83]. Moreover, exacerbations of OLP have been linked to periods of psychological stress and anxiety in some studies [46, 73].

In addition to the chronic discomfort that can result in stress, patients with OLP were shown to be concerned about the possibility of malignancy, the contagious nature of the disease and the lack of available patient educational materials [11].

The levels of anxiety and salivary cortisol measured in a group of OLP patients were statistically correlated and significantly higher than a control group [50].

In spite of the presence of higher levels of psychological stress and anxiety among OLP patients, the question remains whether the psychological factors contribute to the etiology of OLP or are merely driven by the morbidity associated with the condition.

Trauma

Trauma as such has not been reported as an etiological factor in OLP, although it has been postulated as a mechanism by which other etiological factors may exert their effects [78]. The Koebner phenomenon, whereby OLP lesions develop in response to mechanical trauma, may partially explain why OLP lesions develop commonly in sites prone to trauma, i.e., the buccal mucosa or lateral surfaces of the tongue [25].

Systemic associations

OLP may be associated with some systemic diseases; however, few have been thoroughly investigated.

Hepatitis C virus (HCV)

Along with porphyria cutanea tarda and cryoglobulinemia, OLP is one of the three dermatologic diseases that have been most frequently reported in patients infected with HCV [30]. The first report suggesting an association between OLP and HCV seropositivity appeared in 1991 [67]. Since then, the association has been well documented in some Mediterranean populations [4, 15, 28], in Japan [68] and in a United States metropolitan population [5, 6]. Nevertheless, an association between OLP and HCV-seropositivity could not be demonstrated in other areas of the world including France [21, 24], the United Kingdom

[42], and countries with high HCV prevalence, such as Egypt [39] and Nigeria [23].

A systematic review of HCV prevalence in LP patients and in matched controls without LP yielded 25 relevant studies, including eight with only OLP [57]. A significantly higher proportion of HCV-seropositivity was documented in patients with OLP (OR 5.7, 95 % CI 3.5–9.4). This association was stronger in Mediterranean countries and disappeared in Northern Europe such as in Germany and United Kingdom (OR 2.14, 95 % CI 0.6–7.7).

In a study from Italy, 44 OLP patients positive for HCV were compared to a group of 144 OLP patients negative for HCV. HCV-related OLP group showed a significantly higher association with HLA class II allele HLA-DR6 (52 versus 18 %) [14]. This finding may partially explain the peculiar geographical heterogeneity of the association between HCV and OLP, probably depending on the presence of certain HLA subtypes.

Hypertension and diabetes mellitus

An association between OLP, diabetes mellitus, and hypertension was first described by Grinspan in a small series of seven patients [35]. The triad was later named as Grinspan's syndrome. Although Grinspan's syndrome may be seen clinically, the association between the three conditions may simply represent an OLR to medications used to treat hypertension and/or diabetes rather than a true syndrome.

Thyroid dysfunction

The association between OLP and thyroid dysfunction was investigated in a retrospective Finnish study that confirmed a link between OLP and hypothyroidism in particular [81]. This study revealed that 10 % of OLP patients versus 5 % of the controls had hypothyroidism (OR 2.39, 95 % CI 1.05–5.61).

Other studies suggested a relationship between OLP and hyperthyroidism [20].

Graft versus host disease (GVHD)

Nearly 15,000 patients worldwide receive allogenic hematopoietic stem cell transplants (HSCT) each year, and GVHD will eventually develop in about 40 to 70 % and will represent the leading cause of death in such patients [41].

Acute GVHD occurs within the first 100 days of transplantation and comprises dermatitis, enteritis, and hepatitis with immunosuppression and cachexia while chronic GVHD develops after day 100 and comprises an autoimmune-like syndrome comparable to ulcerative colitis, primary biliary cirrhosis, Sjögren's syndrome, rheumatoid arthritis, and lupus-like disease with glomerulonephritis. The skin is a primary target in chronic GVHD and exhibits either lichenoid eruptions or sclerodermatous changes [58].

Oral involvement occurs in 33 to 75 % of patients with acute GVHD and up to 80 % of patients with chronic GVHD [41]. Oral mucosal GVHD resembles OLP both clinically and histologically.

Although the antigen specificity of OLP and mucocutaneous GVHD is probably distinct, it is likely that they share similar immunological effector mechanisms resulting in T cell infiltration, epithelial basement membrane disruption, basal keratinocyte apoptosis and clinical disease [58].

The role of TNF-α as a major effector molecule in GVHD has been confirmed in a number of experimental systems. Importantly, neutralizing anti-TNF-α antibodies have been shown to alleviate cutaneous and intestinal GVHD in both mice and humans [10, 38].

OLR

OLR are considered variants of OLP. They may be regarded as a disease by itself or as an exacerbation of an existing OLP, by the presence of medication or dental materials [44, 79].

OLR have been associated with numerous medications as well as dental materials, although only some of these have been experimentally confirmed.

Dental materials

OLR as an allergic reaction to dental materials has been widely reported, with many studies documenting contact hypersensitivity to dental materials such as amalgam, composite, dental acrylics, cobalt and nickel presenting as OLR [44, 55, 82, 88].

A theory attempting to explain the pathogenesis of OLR was suggested on the assumption that dental materials in direct contact with the oral mucosa may directly alter the antigenicity of basal keratinocytes by the release of mercury or other products, triggering a type IV/delayed hypersensitivity immune reaction [8].

Diagnosis of OLR will commonly depend on the topography and distribution of the lesions as in most cases OLR are indistinguishable from idiopathic OLP, clinically or histologically [88]. Cutaneous patch testing may also play a role in differentiating these lesions [44, 79]. Thornhill et al. [88] found that 70 % of amalgam contact hypersensitivity lesions (presented as lichenoid reactions) were patch test positive for amalgam or mercury compared with only 3.9 % of OLP cases. Unfortunately, there is no

clear evidence that patients with either OLP or OLR would routinely benefit from having their amalgam restorations replaced [3].

Systemic medications

Medications, such as anti-hypertensives (i.e., beta blockers, ACE inhibitors, diuretics), dapsone, oral hypoglycemics, non-steroidal anti-inflammatory drugs (NSAIDs), penicillamine, phenothiazines, anti-malarials, sulfonylureas and gold salts have been associated with OLR [1, 44, 78].

OLR induced by antiretroviral medications for treatment of HIV have also been reported [80]. Clinical identification of lichenoid drug reactions has been based largely on subjective criteria although there may sometimes be a tendency for the oral lesions to be unilateral and erosive [25]. Histology may be beneficial as lichenoid lesions may have a more diffuse lymphocytic infiltrate and contain eosinophils and plasma cells and there may be more colloid bodies than in classical OLP [79].

Pathophysiology

In OLP, cellular-mediated immunity, initiated by endogenous or exogenous factors, is thought to result in the production of TNF-α, IFN-γ and keratinocyte/T cell/antigen-presenting cell associations [25, 58, 71]. The increased production of T-helper 1 (Th1) cytokines is a key and early event in OLP and genetic polymorphism of cytokines seems to govern whether lesions develop in the mouth alone (IFN-γ associated) or in the mouth and skin (TNF-α associated) [16, 79].

TNF-α may stimulate the activation of nuclear factor kappa B (NF-κB) whose increased expression has been seen in OLP [76]. Because NF-κB translocation in keratinocytes can induce the production of several inflammatory cytokines, it could be partially responsible for the characteristic, chronic course of OLP similar to other chronic inflammatory diseases such as psoriasis and rheumatoid arthritis [25].

The mechanisms thought to be involved in OLP pathogenesis have been classically described as specific and non-specific ones [84]. Specific mechanisms highlight the pivotal role of helper and cytotoxic T lymphocytes in OLP, while non-specific mechanisms are thought to be mediated by the epithelial basement membrane, matrix metalloproteinases (MMPs), chemokines, and mast cells.

A unifying hypothesis of the pathogenesis of OLP was introduced by Sugerman et al. [84] and is based on a theoretical interaction between CD8+ T cells and CD4+ T cells through a "request cytotoxic activity" (RCA) cell-surface molecule expressed by CD8+ T cells and a RCA receptor expressed by the CD4+ T cells to allow confirmation and initiation of cytotoxic activity by CD8+ T cells. The hypothesis stresses that this interaction can only take place after each type of the T cells antigen receptors is engaged with a related foreign antigen, i.e., antigen 1 in the context of MHC class I engaged by CD8+ T cells antigen receptors and antigen2 in the context of MHC Class II engaged by CD4+ T cells antigen receptors. Ultimately, activated CD8+ T cells can trigger keratinocytes apoptosis via TNF-α or a Fas–Fas Ligand mechanism.

MHC class II antigen presentation in OLP may be mediated by Langerhans cells or keratinocytes. Increased numbers of Langerhans cells have been reported in OLP lesions with up-regulated MHC class II expression [32, 94, 95]. Keratinocytes in OLP have also been shown to express MHC class II [31, 40, 43].

High levels of antigen expression, CD40 and CD80 expression, and IL-12 secretion by MHC class II+ antigen-presenting cells in OLP are thought to promote a Th1 CD4+ T cell response with IL-2 and IFN-γ secretion [19, 84].

A recently identified sub-group of CD4+ T lymphocytes, namely Th17 CD4+ sub-group, has been to shown to produce IL-26 and IL-22, in addition to IL-17 which are all known to be inducers of the inflammatory response, when uncontrolled, in different autoimmune conditions, such as multiple sclerosis, psoriasis and lupus [71]. The proportion of lesional Th1 and Th17 cells and serum IL-17 levels in patients with OLP were shown to be significantly greater than controls, especially in the atrophic-erosive forms, suggesting that Th17 cells and their cytokine IL-17 may play a role in OLP pathogenesis [97].

The possible role of MMPs and tissue inhibitors of metalloproteinases (TIMPs) in OLP has been investigated in a number of studies. Culture supernatants from OLP lesional T cells were shown to contain a higher concentration of MMP-9 and TIMP-1 than those obtained from peripheral blood T cells in both the same OLP patients group and the healthy controls, suggesting the presence of additional MMP-9 activators in the OLP lesional T cell supernatants [99].

MMP-9 activators released from the OLP T cells are believed to help in activating pro-MMP-9, resulting in basement membrane disruption [74]. Rubaci et al. [75] showed that the expression of MMP-2 and MMP-7 in epithelium and connective tissues from OLP lesions were greater than normal oral mucosa and that MMP-2/TIMP-1 and MMP-7/TIMP-1 ratios were higher in the OLP patient group than in the control group. These results support the view that increased MMPs expression and imbalance between MMPs and TIMPs may also contribute to the pathology of OLP.

RANTES (regulated on activation, normal T cell expressed and secreted) is a member of the CC chemokine family and is produced by various cells, including activated T lymphocytes, bronchial epithelial cells, rheumatoid synovial fibroblasts, oral keratinocytes and mast cells. RANTES is thought to have a role in the recruitment of lymphocytes, monocytes, natural killer cells, eosinophils, basophils, and mast cells in OLP. This chemokine has a number of cell surface receptors (CCR1, CCR3, CCR4, CCR5, CCR9, and CCR10) that have been identified in OLP [84].

Studies have shown increased mast cell density in OLP with approximately 60 % of them being degranulated, compared with 20 % in normal buccal mucosa [48]. They were shown to be preferentially located in the lamina propria, near blood vessels and nerves [47].

Furthermore, mast cell density in OLP was found to be markedly higher in the basement membrane rupture sites as compared to intact sites, suggesting that this cell might play a direct role in the basement membrane destruction, as well as in the CD8+ T-lymphocyte migration to the intra-epithelial region [99].

Mast cells degranulation in OLP releases a range of pro-inflammatory mediators such as TNF-α, chymase and tryptase. TNF-α has been shown to up-regulate endothelial cell adhesion molecule (CD62E, CD54, and CD106) expression in OLP that is required for lymphocyte adhesion to the luminal surfaces of blood vessels and subsequent extravasation [47, 98]. Moreover, Chymase, a mast cell protease, is a known activator of MMP-9 [29]. Basement membrane disruption in OLP may be mediated by mast cell proteases directly or indirectly via activation of T cell-secreted MMP-9 [84].

Finally, pro-inflammatory macrophages might exacerbate OLP manifestation through the production of agents such as TNF-α or IL-1β [71]. It has also been shown that the production of TNF-α by the macrophages can initiate the basal keratinocyte apoptosis and indirectly, increase the disruption rate of the basement membrane by MMP-9, produced by T cells [61].

Clinical-pathologic features

Distribution

The classic presentation of OLP is in a bilateral, symmetrical pattern with the buccal mucosa being the most typical site of involvement, however, any other oral mucosal site can also be involved [1, 44]. Other common sites of involvement include the tongue, gingiva and labial mucosa while lesions of OLP affecting the palate, floor of the mouth, and upper lip are not common [25, 70]. If the erosive/ulcerative subtype of OLP only affects the gingival tissue, the descriptive clinical term (desquamative gingivitis) is often used. OLP is confined to the gingiva in about 10 % of patients [65, 79].

Clinical patterns

Clinically, there are six clinical subtypes of OLP that can be seen individually or in combination: reticular, plaque-like, atrophic, erosive/ulcerative, papular and bullous (Fig. 1). The most common of these are the reticular, erosive/ulcerative and plaque-like subtypes [30, 79].

The reticular lesions, the most recognized form of OLP, are often asymptomatic and appear as multiple papules with a network of small, raised, whitish–gray, lacy lesions referred to as Wickham striae [25]. In the absence of the classic reticular pattern on oral mucosal surfaces, it is challenging to clinically diagnose OLP [79]. Histological confirmation of the diagnosis is thus required. The erosive form of OLP may present with erythema caused by inflammation or epithelial thinning and ulceration/pseudomembrane formation can also be seen, with the periphery of the lesion surrounded by reticular keratotic striae [44]. Atrophic and erosive/ulcerative OLP lesions result in varying degrees of discomfort. These particular OLP lesions hardly ever remit spontaneously and may lead to confusion with other vesiculo-bullous diseases, which share similar clinical features [25].

The plaque form of OLP mimics leukoplakia in that it appears as a white, homogeneous, slightly elevated, multifocal, smooth lesion. The plaque form of OLP commonly affects the tongue and buccal mucosa [44].

In general, bullous and papular forms are rare in the oral mucosa [70]. OLR have similar features, clinically and histologically to OLP, but have a less characteristic morphology or have a distinct cause, unlike OLP. OLR therefore need to be distinguished because treatment modalities are different from those for OLP [1].

To better define the criteria for diagnosis of OLP, the World Health Organization (WHO) devised a set of clinicopathological criteria in 1978 [51] (Table 1). However, these criteria lacked consensus regarding a clinical and histological diagnosis of OLP, and so modifications were proposed to the WHO criteria in 2003 [93] (Table 2), which resulted in a substantial increase in consensus and clinicopathological correlation.

Signs, symptoms, and clinical behavior

The clinical signs and symptoms of OLP vary. In many patients, the onset of OLP is insidious and patients are unaware of their oral condition. Some patients report roughness of the lining of the mouth, sensitivity of the

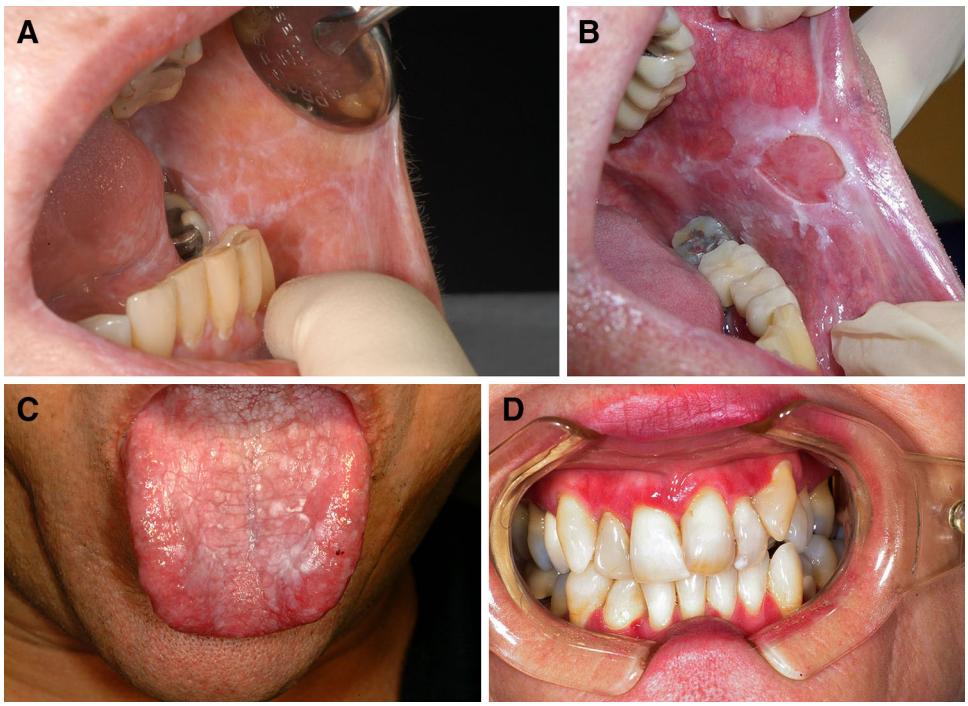

Fig. 1 Clinical patterns of OLP. **a** reticular, **b** erosive/ulcerative, **c** atrophic and plaque-like, and **d** desquamative gingivitis (atrophic and erosive forms)

Table 1 Original WHO diagnostic criteria of OLP (1978)

WHO diagnostic criteria of OLP
Clinical criteria
Presence of white papule, reticular, annular, plaque-type lesions, gray–white lines radiating from the papules
Presence of lacelike network of slightly raised gray–white lines (reticular pattern)
Presence of atrophic lesions with or without erosion, and possibly also bullae
Histopathological criteria
Presence of thickened ortho- or parakeratinized layer in sites that are normally keratinized, and, if site is normally nonkeratinized, this layer may be thin
Presence of Civatte bodies in basal layer, epithelium, and superficial part of connective tissue
Presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of liquefaction degeneration in the basal cell layer

Adopted from Ref. [51]

oral mucosa to hot or spicy foods, painful oral mucosa, red or white patches on the oral mucosa or oral ulcerations [44]. Approximately two-thirds of the patients affected with OLP experience some degree of oral discomfort [70].

OLP has periods of relapses and remissions, during a period of exacerbation there will be an increase in symptoms and clinical signs while during periods of quiescence, symptoms and signs of OLP are diminished [44]. Factors such as stress may aggravate the clinical presentation of the disease. Precipitating factors similar to the Koebner phenomenon, which is characteristic of cutaneous LP whereby lesions develop in response to trauma, can also affect the oral cavity where sharp cusps and ill-fitting dental prosthesis may be the triggers.

Accumulation of plaque and calculus was also shown to exacerbate OLP [65]. Gingival OLP can eventually lead to gingival recession and advanced periodontal disease [25].

Oral post-inflammatory pigmentation has been described in patients with OLP and OLR as diffuse brown or black pigmentation following the lichenoid lesions distribution [60].

Table 2 Modified diagnostic criteria for OLP and OLL (2003)

Modified WHO diagnostic criteria of OLP and OLL
Clinical criteria
Presence of bilateral, more or less symmetrical lesions
Presence of a lacelike network of slightly raised gray–white lines (reticular pattern)
Erosive, atrophic, bullous, and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa
In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term "clinically compatible with" should be used
Histopathologic criteria
Presence of a well-defined, band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of liquefaction degeneration in the basal cell layer
Absence of epithelial dysplasia
When the histopathological features are less obvious, the term "histopathologically compatible with" should be used
Final diagnosis of OLP or OLL
To achieve a final diagnosis, clinical as well as histopathological criteria should be included
OLP
A diagnosis of OLP requires fulfillment of clinical and histopathologic criteria
OLL
The term OLL will be used in the following conditions:
1. Clinically typical of OLP but histopathologically only compatible with OLP
2. Histopathologically typical of OLP but clinically only compatible with OLP
3. Clinically compatible with OLP and histopathologically compatible with OLP

Data from Ref. [93]

Histopathology

Definite diagnostic histological findings of OLP include; liquefactive degeneration of the basal cells, colloid bodies (Civatte, hyaline, cytoid), homogeneous infiltrate of lymphocytes and histiocytes in a dense, band-like pattern along the epithelium-connective tissue interface in the superficial dermis, cytologically normal maturation of the epithelium, saw-tooth rete ridges and hyperkeratosis (orthokeratosis or parakeratosis) [25, 44, 70] (Fig. 2). In addition, the surface epithelium may show signs of erosion/ulceration, typically seen in erosive/ulcerative OLP.

Several histologic criteria that are considered as exclusionary in diagnosing OLP include the absence of basal cell liquefaction degeneration, polyclonal inflammatory infiltrate, abnormal cytology suggestive of dysplasia, abnormal keratinization, flat rete ridges, and absence of colloid bodies [26, 44].

Diagnosis

The characteristic clinical aspects of OLP (symmetry, bilateral distribution) are thought, by some researchers, to be sufficient to make a correct diagnosis especially if classical skin lesions are present [25].

However, an oral biopsy with histopathological study is usually recommended to confirm the clinical diagnosis and mainly to exclude dysplasia and malignancy [1, 44].

Gingival OLP may be more difficult to diagnose and direct immunofluorescence of perilesional mucosa may facilitate the diagnosis and exclude other causes such as vesiculobullous diseases [25]. The value of direct immunofluorescence for confirmation of the disease is well accepted, especially with non-diagnostic histopathological features and for the desquamative gingivitis form of OLP [79].

Direct immunofluorescence studies of OLP show a linear pattern and intense positive fluorescence with antifibrogen outlining the basement membrane zone and cytoid-like bodies with positive immunoglobulin M labeling [36]. Indirect immunofluorescence studies are not routinely used in the clinical diagnosis of OLP.

It has been proposed that allergy to dental materials is common in patients with OLR [44]. Therefore, cutaneous patch testing is a recognized and accepted method to identify allergens responsible for type IV allergic reactions in OLR associated with dental materials. However, skin patch testing to investigate contact sensitivity responses to mercury and amalgam produced conflicting results with variable numbers of patients being positive in different studies and are not routinely used in the diagnosis of OLP.

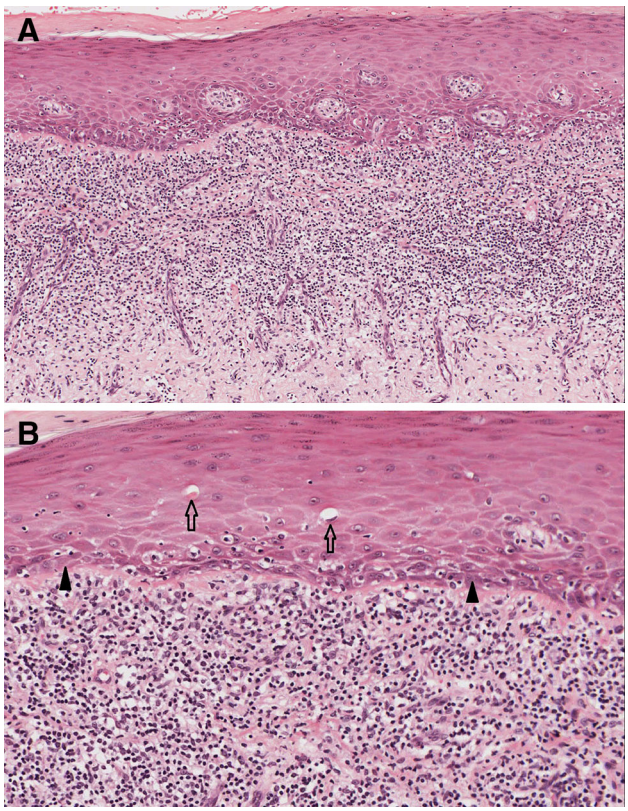

Fig. 2 Histopathology of OLP. **a** Low power photomicrograph showing parakeratosis, band-like subepithelial chronic inflammatory infiltrate and saw-tooth rete ridges (H & E, original magnification X100). **b** High power photomicrograph showing several colloid bodies (*arrows*) and liquefactive degeneration of basal keratinocytes (*arrowheads*) (H & E, original magnification X200)

In a systematic review that analyzed data from 14 cohort and 5 case–control studies with a total of 1158 with OLR associated with amalgam; 16–91 % of patients were patch test positive for at least one mercury compound [45].

Original and modified diagnostic criteria for OLP and OLL are reported in Tables 1 and 2, respectively.

Management

Reticular lesions that are asymptomatic generally require no therapy but only observation for change. In general, management should be aimed at treating atrophic and erosive/ulcerative lesions, alleviating accompanying symptoms and reducing the potential risk of malignant transformation [1, 25, 79].

Mechanical trauma or irritants such as sharp filling margins, rough surfaces or badly fitting dentures should receive attention. A drug history should be obtained to identify reversible causes of lichenoid eruptions as discontinuation of the offending agent, when possible, can be curative [25].

An optimal oral hygiene program should be instituted in patients with gingival disease. Drug treatment with topical agents is preferred as it has fewer adverse effects. The most commonly employed and useful agents for the treatment of OLP are topical corticosteroids. A response to treatment with midpotency corticosteroids such as triamcinolone, potent fluorinated corticosteroids such as fluocinolone acetonide and fluocinonide and superpotent halogenated corticosteroids such as clobetasol has been reported in 30–100 % of treated patients [12, 86].

Topical corticosteroids are available in adhesive vehicles or can be used as mouth rinses. Empirical evidence seems to suggest that mouth rinses are of value in patients with widespread symptomatic OLP where the lesions are not easily accessible to the placement of ointments or gels. The evidence also suggests that higher potency corticosteroids, such as clobetasol are probably more effective [1].

Few serious side effects arise with topical corticosteroids as they are generally well tolerated. Side effects reported include; secondary candidosis; nausea; oral use not tolerated; refractory response; mucosal atrophy; oral dryness; sore throat; bad taste; and delayed healing [77, 85].

Systemic absorption has been reported and it is thought that absorption of small amounts through the oral mucosa can take place but clinical experience and laboratory studies have shown this not to be of clinical significance in almost all cases [77].

Other topical agents that can be alternatively used to manage recalcitrant OLP include calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and less commonly retinoids [1].

A recent systematic review and meta-analysis has shown comparable effects of topical tacrolimus (0.01 %) and clobetasol in the treatment of OLP [17]. Although not widely accepted as a complication of the use of topical calcineurin inhibitors on the oral mucosa, the potential carcinogenicity of these agents remains a concern.

Several studies have reported that systemic corticosteroids are the most effective treatment for OLP; however, a comparative study that involved a total of 49 OLP patients did not find differences in response between systemic prednisone (1 mg/kg/day) with topical clobetasol in an adhesive base and topical clobetasol after a mean follow-up period of 36 months [13]. Systemic corticosteroids are, therefore, usually reserved for cases where topical approaches have failed, where there is recalcitrant, erosive, or erythematous OLP, or for widespread OLP when skin, genitals, oesophagus or scalp are also involved [1]. Systemic mycophenolate mofetil was also shown to be effective in managing recalcitrant erosive OLP in some studies [22, 96]. Other reported helpful systemic agents include azathioprine and methotrexate [1, 54].

However, it is noteworthy that the literature on the use of systemic agents in OLP management is generally limited to non-randomized clinical trials and is generally inconclusive [59].

Newly emerging treatment modalities to manage OLP are under investigation and these include; topical aloe vera, biologics, low intensity laser and oral curcuminoids [69, 87].

Several studies showed resolution of OLR following replacement of causative restorations [53, 88]. Gingival OLR lesions, in particular, were reported to be nonresponsive to amalgam replacement for unknown reasons [37]. The most reliable method to diagnose and manage lichenoid drug reactions is to note if the reaction resolves after the offending drug is withdrawn, and if it returns when the patient is challenged again. However, as this is both impractical and potentially unsafe, empiric withdrawal of a potentially offending drug and substitution with another agent may not be warranted [25].

Follow-up

A regular screening for oral cancer in OLP patients is potentially cost-effective [89]. Follow-up protocols ranging from every 2 months to annually may be accepted as part of long-term care for patients with OLP largely to screen for changes that may indicate malignant transformation [62]. At a minimum, annual monitoring is recommended and favorably two to four reviews depending on OLP signs and symptoms [1, 70]. If changes are noted in a lesion at follow-up visits, then an additional biopsy or biopsies should be performed and the follow-up intervals shortened [44]. However, it should be noted that the effect of sensitivity and specificity of an oral examination in detecting oral cancer on cost-effectiveness seems to be substantial. This on one end suggests that the screening should be performed by oral medicine specialists and, on the other, calls for the development of novel diagnostic tools to support conventional oral exploration.

OLP malignant potential

Since the first report of the malignant transformation of OLP in 1910 [34], numerous studies have attempted to address this issue. Several authors agreed to a frequency of malignant transformation between 0.4 % and 5 %, over periods of observation from 0.5 to over 20 years with an annual rate between 0.2 and 0.5 % [1, 91]. However, other reviews limited to selected studies on malignant potential of OLP with a follow-up of more than 2 years showed that when strict criteria were applied, the malignant transformation rate is 0–2 % [44].

In 1985, Krutchkoff and Eisenberg coined the term lichenoid dysplasia (LD) to describe lesions that resemble OLP histologically and also show features of dysplasia [52]. They suggested that OLP has no inherent predisposition to become malignant and that reported cases of malignant transformation in OLP lesions were due to lack of discrimination between OLP and LD or failure to identify a concomitant exposure to known carcinogens.

van der Meij et al. [93] proposed the designation OLL for cases that are clinically characteristic and histologically compatible, clinically compatible and histologically characteristic, or clinically and histologically compatible with OLP (Table 2). It is currently proposed by some key authors that OLL rather than OLP are at high risk of developing cancer [9, 34, 90].

The World Health Organization, in its latest volume on the Pathology and Genetics of Head and Neck Tumors, has recommended the development of diagnostic criteria to differentiate between OLP and OLL but declared that both lesions should be considered at risk of malignant transformation until such criteria become available [33].The possible effect of OLP treatments, most commonly immunosuppressive agents, on malignant transformation of OLP is not clear. Immunosuppressive agents affect the severity and progression of OLP, but theoretically they could also trigger malignant transformation [59].

An important reported feature of the presentation and clinical course of carcinomas that arise on OLP is their tendency of multiplicity. It has been reported that 29 % of patients developing carcinomas in OLP had two or more independent neoplastic lesions (19 % with a second tumor, 10 % with >2 metachronous tumors) [66]. Histopathologically, most tumors detected in OLP are well-differentiated squamous cell carcinomas (SCC) [56].

Several risk factors for malignant transformations in OLP have been proposed. These include; erosive/ulcerative forms, tongue lesions, female gender and 6–7th decades of life, but none of these have gained significant agreement among researchers [34].

In some series, plaque-like OLP lesions were also relevant, both when they appeared alone and when associated with atrophic-erosive lesions [64].

The mean interval between OLP diagnosis and cancer diagnosis ranges widely from 20.8 months to 10.1 years, although the maximum risk is reportedly between 3 and 6 years after OLP diagnosis [34].

Some infectious factors have also been implicated in cancers developing in OLP. It is thought that *Candida albicans* may represent a risk factor in OLP malignant

transformation probably as a consequence of N-nitrosobenzylmethylamine production [92]. Therefore, the treatment of oral fungal infection has been specifically recommended for OLP patients [34]. Interestingly, the correlation between common risk factors for oral SCC (i.e., smoking and alcohol) and malignant transformation of OLP has not been well defined in literature. A recent study showed that smoking habits are associated with an alteration of the inflammatory infiltrate in OLL, which may in turn affect the immune surveillance and the malignant transformation mechanisms [2].

Finally, chronic inflammation is believed to be associated with various types of cancer [18], and OLP as a chronic inflammatory condition was proposed by some authors to represent an oral model for such an association [63].

Conclusion

OLP and OLL are common oral mucosal lesions with several predisposing factors and systemic associations but poorly identified etiology. These lesions were shown to be the result of a T cell-mediated immune response leading ultimately to keratinocytes apoptosis. Several clinical patterns of OLP and OLL are encountered and the diagnosis is commonly based on a combination of clinical and histopathological features. For symptomatic lesions, management is largely based on topical immunosuppressants particularly corticosteroids. Some new treatment modalities have been recently introduced; however, the clinical evidence for their use is still inconclusive. In the light of the ongoing debate regarding the potentially malignant nature of OLP and OLL, a long-term follow-up protocol is essential.

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