ORAL LICHEN PLANUS: A DISEASE OR A SPECTRUM OF TISSUE REACTIONS? TYPES, CAUSES, DIAGNOSTIC ALGORHYTHMS, PROGNOSIS, MANAGEMENT STRATEGIES

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Abstract

Oral lichen planus and lichenoid lesions (OLP/OLL) comprise a group of disorders of the oral mucosa that likely represent a common reaction pattern to one or more unknown antigens. The coexistence of hyperkeratotic striation/reticulation, varying degrees of mucosal inflammation from mild erythema to severe widespread ulceration and a band-like infiltrate of mononuclear inflammatory cells including activated T lymphocytes, macrophages and dendritic cells are considered suggestive of OLP/OLL. Several classification systems of OLP/OLL have been attempted, though none seem to be comprehensive. In this paper we present a classification of OLP/OLL that includes oral lichen planus, oral lichenoid contact lesions, oral lichenoid drug reactions, oral lichenoid lesions of graft versus host disease, discoid lupus erythematosus, and systemic lupus erythematosus, lichen planus-like variant of paraneoplastic pemphigus/paraneoplastic autoimmune multi-organ syndrome, chronic ulcerative stomatitis, lichen planus pemphigoides, solitary fixed drug eruptions and lichen sclerosus. We present the clinical and diagnostic aspects of OLP/OLL and discuss related treatment options.

Introduction

Oral lichen planus and lichenoid lesions (OLP/OLL) comprise a group of disorders of the oral mucosa that likely represent a common reaction pattern in response to extrinsic antigens, altered self-antigens or super antigens (89). Historically, there have been unresolved debates and controversies around the OLP/OLL terminology. The latter term has been frequently used to refer to oral lesions that have clinical and histopathological features similar to OLP but no risk of malignant transformation or to indicate an uncertain diagnosis of OLP. However, definitive clinical and histological diagnostic criteria able to distinguish OLP from OLL are still lacking (89). Furthermore, there remains no consensus regarding the possible different clinical behaviour of the disorders in the OLP/OLL group with respect to cancer development. In Dermatology, the concept of "lichenoid tissue reaction/interface dermatitis" (LTR/IFD) was introduced a long time ago to define a number of distinct inflammatory cutaneous diseases sharing common histopathological features including liquefactive/vacuolar changes of the basal keratinocytes and a sub-epithelial band-like array of mononuclear inflammatory cells including activated T lymphocytes, macrophages and dendritic cells (89,156). During the 2006 World Workshop in Oral Medicine IV, it was proposed to classify the OLP/OLL group in four distinct disorders including OLP, oral lichenoid drug reactions (OLDR) caused by systemic drug exposure, oral lichenoid contact lesions (OLCL) triggered by local hypersensitive reaction to dental materials and oral lichenoid lesions of graft-versus-host disease (GVHD) (2). Although a step forward, this classification failed to provide clear and reliable clinical and histological criteria to properly differentiate these three types of OLL from OLP. In addition, several other disease entities characterised by clinical and/or histological features of LTR/IFD were excluded from the classification. Other authors have proposed alternative classifications (42,76,173). Overall, there remains no consensus on classification, diagnostic criteria, clinical behaviour and management of the OLP/OLL (1,28,174).

In this review, we have attempted to (i) update the classification of OLP/OLL, (ii) suggest pragmatic diagnostic criteria and (iii) define a management strategy.

Classification

Table 1 lists the main disorders displaying histological and/or clinical characteristics of this OLL/OLP group. Some of these disorders are apparently uncommon whereas others are poorly defined or may simply represent a misnomer.

Oral Lichen Planus

OLP is the prototype disorder of the group. Despite the lack of reliable epidemiological data, OLP is thought to be relatively common, affecting approximately 1–2% of the population (147). OLP lesions are chronic and rarely undergo spontaneous remission (28); they can cause significant pain and morbidity and most authors would agree that they can undergo malignant transformation (52). OLP most commonly affects middle-aged adults of both sexes, with a slight female predominance, and without any apparent racial predilection (48). The distinctive clinical features of OLP are represented by the presence of white papules that enlarge and coalesce to form a reticular, annular or plaque-like pattern, the so-called Wickham's striae (28). Erythema, erosion and ulceration can also occur, often in association with white striae (Figure 1). The most commonly affected sites are the buccal mucosa bilaterally, the borders and dorsum of the tongue and the gingiva, whereas the palate (either hard or soft), the lips and the floor of the mouth are less commonly affected. Reticular/papular lesions are rarely symptomatic and patients are often unaware of their presence, whereas erythematous and erosive/ulcerative lesions usually result in a varying degree of discomfort or pain. When erosive/ulcerative lesions are predominant, confusion with diseases such as pemphigus vulgaris, mucous membrane pemphigoid (MMP) and persistent erythema multiforme (EM) is common (28,48,147). Long lasting OLP lesions can be predominantly plaque-like, particularly in smokers; in the absence of typical reticular/papular lesions, this can raise significant diagnostic difficulties with other diseases such as oral leukoplakia. It should also be mentioned that dyskeratosis congenita can sometimes present with lichenoid features (64), and therefore all putative paediatric OLP cases should be carefully investigated for nail dystrophies, abnormal reticulate skin pigmentation, and haematological abnormalities. Individuals with OLP

can also have extra-oral manifestations of lichen planus. The most frequent extra-oral site in females is the genital mucosa, with lesions developing in approximately 20% of women with OLP (61). The association of concomitant lichenoid lesions/lichen planus on the vulva, vagina and gingiva has been termed "vulvo-vaginal-gingival syndrome". Conversely, cutaneous lesions develop in just approximately 15% of patients with OLP (48). OLP is suggested to represent a T-cell-mediated immunological response to an unknown antigenic change in the skin or oral mucosa in predisposed patients (89). A key, early event in OLP pathogenesis is the genetically enhanced increased production of TH1 cytokines, particularly interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α). However, a recent study has suggested that Th2-mediated inflammation can also contribute to OLP pathogenesis and progression through and can be induced by myeloid dendritic cells (mDCs), which in turn are activated by Thymic stromal lymphopoietin (TSLP) secreted by epithelial cells (185). Cytokine polymorphisms seem also to influence whether lesions would develop just in the mouth (IFN-γ associated) or also on the skin (TNF-α associated) (26). A recent meta-analysis has confirmed the association between -308 G/A polymorphism in TNF-α gene and OLP (84). Studies of T cell receptor-variable region genes have also highlighted that OLP is likely to be the common outcome of a limited combination of extrinsic antigens, altered self-antigens or super antigens (167). Three meta-analyses have confirmed that OLP is associated with hepatitis C virus (HCV) (98,100,132), which could be also involved in disease pathogenesis (133). Although the malignant potential of OLP remains controversial, a number of small uncontrolled studies and three large retrospective controlled studies from Denmark, Sweden and Italy, using strict diagnostic criteria, have strongly suggested that OLP patients do carry a significantly higher risk of developing oral squamous cell carcinoma (OSCC) than the general population (57,71,140). A recent systematic review has suggested an overall rate of transformation of up to 3.5% (52). The clinical manifestations alone, particularly when presenting in the 'classic' bilateral keratotic reticular or papular form, may sometimes allow diagnosis (28) (Figure 1). However, given the chronic course and pleomorphic clinical manifestations, the need for long-term treatment and monitoring, and the risk of malignant

transformation, a confirmatory surgical biopsy appears to represent prudent clinical practice. Histopathological confirmation is also important before starting an active treatment, as a common cause of therapy failure is inappropriate diagnosis (28). Histopathological assessment of OLP can however be difficult (173), although the assessment of the presence of dysplasia or malignancy is usually straightforward. Direct immunofluorescence (DIF) testing may be of diagnostic help in patients presenting with predominantly erosive/ulcerative OLP, so as to exclude other autoimmune blistering/ulcerative diseases. DIF of OLP is usually negative or can show shaggy fibrinogen deposits at the epithelial basement membrane zone or the so-called cytoid bodies (Russell bodies) (67). Sometimes, further immunological testing such as salt-split-skin, indirect immunofluorescence, immunoblot/immunoprecipitation and ELISAs are needed in order to achieve a definitive diagnosis and differentiate OLP from other blistering disorders, especially MMP (17). However, these techniques are costly, time-demanding and not widely available (25).

Oral Lichenoid Contact Lesions (OLCL)

Oral lichenoid contact lesion (OLCL) is a term used to describe oral lesions that resemble OLP both clinically and histopathologically but are thought to be caused by a localised (contact) hypersensitivity reaction to dental restorative materials, mainly amalgam (8,112). Dental amalgam alloy is composed of a mixture of approximately equal parts of liquid mercury and a powder consisting of silver (~22–32%), tin (~14%), copper (~8%), and other trace metals, including zinc (81). OLCLs to amalgams are supposed to represent a delayed hypersensitivity reaction (Coombs and Gell classification: type IV) to low-level mercury exposure (112). However, an animal model has failed to definitively prove that amalgam fillings can cause OLCL (46). A more recent study using the same animal model (Brown-Norway Rats) but with different exposure modalities, suggests that non-toxic mercury can rather cause lupus-like oral mucosal lesions (149).

Patch tests are commonly used to identify patients with suspected hypersensitivity reactions but their usefulness in OLCL have shown conflicting results (167). Skin testing is preferable to

mucosal testing due to a higher sensitivity and specificity and because allergen concentration on mucosa needs to be 5–12 times higher than skin, potentially exposing patients to the risk of a toxic reaction. In vitro lymphocyte proliferation has been employed as an adjunctive tool in the diagnosis of allergies to various drugs (124) and metals (12), with the aim of re-stimulating antigen-specific lymphocytes (memory cells) from peripheral blood. The assay has a variety of modifications and names, for example, LTT (lymphocyte transformation test), LST (lymphocyte stimulation test), LPT (lymphocyte proliferation test), or MELISA® (memory lymphocyte immunostimulation assay). However, this test seems of limited utility to OLCL (29). The clinical appearance of OLCL has been rarely described in details. It is thought that OLCLs are less symmetrical and more commonly unilateral than OLP but supporting evidence remains scarce. Similarly, the close proximity of the lesions with amalgam restorations is commonly but not invariably reported (Figure 2). According to the published pictures, OLCLs might lack the typical reticular appearance of OLP and be more commonly patch-like or atrophic. They are usually located on posterior buccal mucosae and borders of the tongue. Histopathology could aid diagnosis if it shows a mixed cell sub-epithelial infiltrate and a deeper diffuse distribution in lamina propria. However, OLCL are often undistinguishable from other OLLs and OLP on histopathology assessment. There is also insufficient evidence to support routine removal of all amalgam restorations in patients with OLP/OLCL (8), although some authors have reported an improvement in 90% of the lesions after amalgam replacement in individuals with positive patch tests and lichenoid lesions in close contact with amalgam fillings (167).

Oral Lichenoid Drug Reactions (OLDR)

OLDR are caused by or associated with exposure to certain medications (2). They are thought to be uncommon compared to cutaneous lichenoid drug reactions but reliable data are scarce and OLDR are likely to be under-reported. The list of drugs that can cause OLDR is vast and includes angiotensin-converting enzyme inhibitors (ACE), non-steroidal anti-inflammatory inhibitors (NSAIDs), oral hypoglycaemic drugs, penicillamine, gold, beta-blockers,

methyldopa, quinidine and quinine (109), diuretics (in particular hydrochlorothiazide), antifungals (e.g. ketoconazole), anticonvulsants (e.g. carbamazepine), immunomodulatory drugs (e.g. gold salts and penicillamine), sulfasalazine, and lithium (188). Recently, tumour necrosis factor alpha (TNF-α) inhibitors infliximab and adalimumab have been reported in association with OLDR (5). OLDR may occur at any time, even years after the start of a certain drug therapy (163), although in many cases there seems to be a relatively clear temporal association between the use of the suspected medication and the onset of the oral lesions (2). There is currently no specific test for OLDR. Clinical appearance is unclear particularly compared to other OLLs, though the unilateral location may aid diagnosis (91). Histopathologically OLDR can present a sub-epithelial inflammatory infiltrate containing conspicuous eosinophils and/or plasma cells, which is more diffuse and extends more deeply than OLP, or has a perivascular appearance (45). Notably, none of these characteristics has been consistently reported and other OLL may present similar histopathological features, such as discoid lupus erythematosus (DLE) (109). The most reliable method of diagnosing an OLDR is to notice resolution after the withdrawal of the putative drug and the reappearance when the same drug is reintroduced. However, this is both impractical and potentially detrimental for the patient as some reactions may take weeks or months to resolve and the medication could be life-saving (2).

Circulating basal cell cytoplasmic antibodies (BCCA) are known to appear in drug eruptions and they have been studied in OLDR [38], but outcomes remain unclear. Autologous and allogeneic immunofluorescence tests seeking for lichen planus specific antigen (LPSA) seem not to aid diagnosis of OLDR (108).

Oral Lichenoid Lesions of Graft Versus Host Disease (OLL-GVHD)

Graft versus host disease (GVHD) is a major complication in patients receiving hematopoietic cell transplant (74). GVHD can be classified in acute or chronic (cGVHD), depending on the time to onset from the transplant (threshold is of the order of 100 days); however, the latest NIH consensus criteria recommend that classification should be based on characteristic

symptoms and signs rather than a rigid temporal definition (51). Both acute and chronic GVHD can involve the mouth but lichenoid lesions are more common in the latter (74). Oro-facial manifestations occur in up to 80% of patients with cGVHD (74) and include three separate disease patterns that can coexist: (i) oral lichenoid lesions (OLL-GVHD) including reticulation, ulcerations and mucosal atrophy, (ii) salivary gland dysfunction with hyposalivation and persistent dry mouth symptoms and oro-facial fibrosis with restricted mouth opening (51,182). The mucosal lesions are very similar to those found in OLP (Figure 3), the salivary gland infiltrates mimic those found in Sjögren's syndrome, and the fibrosis and reduced mouth opening are similar to the orofacial manifestations of scleroderma, that is also classified as a LTR/IFD (74). Histologically OLL-GVHD can be very similar to OLP. The typical clinical features of lichenoid lesions together with the history of allogeneic bone marrow transplant are often sufficient for the diagnosis of OLL-GVHD. Histological confirmation of OLL-GVHD is indicated in the absence of signs and symptoms of other systems or organs involvement and in cases of atypical clinical presentation. It is also important to consider development of dysplasia or malignancy, especially in patients with long-standing chronic disease.

Lichen planus-like variant of Paraneoplastic Pemphigus/Paraneoplastic autoimmune multi-organ syndrome

Paraneoplastic pemphigus (PNP) is an autoimmune syndrome, first described in 1990 (3), characterized by the development of muco-cutaneous lesions in individuals with a neoplastic, often malignant, disease. Although affected patients often present with blisters and ulceration similar to those of pemphigus vulgaris (hence the term PNP), the disorder can present a spectrum of clinical and histopathological manifestations that have been classified into 5 variants: 1) pemphigus-like, 2) pemphigoid-like, 3) erythema multiforme-like, 4) graft-vs-host disease-like, and 5) lichen planus-like. More recently, due to increasing evidence of the involvement of internal organs as one of the potential manifestations of the disease, the term "paraneoplastic autoimmune multiorgan syndrome" (PAMS) was introduced (119). Lichen planus-like variant of PNP/PAMS is frequently associated with Castleman's disease, which is

a rare non-clonal neoplasm of lymphatic origin, also known as giant lymph node hyperplasia or benign giant cell lymphoma (122). Castleman's disease most commonly develops in lymphatic areas in the retroperitoneal spaces or in the chest and there is evidence that lesions may be present for very long periods of time before PNP/PAMS develops. The most common histological variant of Castleman's disease associated with PNP/PMAS is the hyaline vascular type (122).

PNP/PAMS is characterized by the presence of autoantibodies against multiple antigens, particularly the plakin family of proteins, which are part of the intracellular plaque of the desmosomes and/or hemidesmosomes. These include the 210 kDa envoplakin (EP), the 190 kDa periplakin (PP), the 230 kDa bullous pemphigoid antigen BP230, the 250 and 210 kDa desmoplakins I and II (DSPI and DSPII), and the 500 kDa plectin. Other antigens include the desmogleins (Dsg) 1 and 3, plakophilin 3, desmocollins 1-3 and the previously described 170 kDa autoantigen recently identified as the protease inhibitor alpha-2-macroglobulin-like-1 (A2ML1) (146). There seems to be an association with HLA-Cw*14 and in DRB1*03 in Chinese and French patients, respectively (68,97), which is yet to be confirmed in other populations. In case of any recent or suspicious history of a neoplasm in patients developing oral or mucocutaneous lichenoid lesions a diagnosis of PNP/PAMS should be considered. Clinically, these patients have severe mucocutaneous lesions and can develop respiratory failure. They are typically refractory to standard treatment. Oral and skin manifestations are usually pleomorphic and can show a confusing and overlapping array of lesions (Figure 4). Histopathology is normally not of great aid. Routine immunologic tests such as direct and indirect immunofluorescence (IIF) can be either negative or controversial showing features of more than one disease entity. IIF analysis of PNP/PAMS sera demonstrates the presence of anti-epidermal antibodies that recognize both the epithelial cell surface of keratinocytes, typically seen in pemphigus vulgaris, and the basement membrane zone, seen in pemphigoid. The use of special substrates such as rat bladder epithelium that does not contain Dsg1 and 3 but does contain DSP, EP and PP greatly increases sensitivity (75-86%) and specificity (83-98%) (68,97). Several commercially available ELISAs are able to detect reactivity against

some PNP antigens. In particular, an ELISA based on the N–terminal domain of EP is able to detect reactivity of 80.6% PNP patient sera (135). Immunoblotting can show a distinctive profile of antibodies directed toward the plakin family that include EP, PP, DSP, BPAG1, and plectin. However, the gold standard for diagnosis is still represented by immunoprecipitation (IP) of keratinocyte extracts. Historically, the first technique used to identify PNP autoantibodies was IP using radioactively labelled keratinocyte extracts (3). The sensitivity of this technique is superior to immunoblotting, IIF on rat bladder, and EP-ELISA. In addition, IP is able to identify anti-A2ML1 reactivity that is not detected by IB with PNP sera (146). However, because of the use of radioactive material, this technique is not widely available. Recently, non-radioactive IP has been introduced and it seems to have similar diagnostic performance (134).

Lichenoid lesions of Discoid Lupus Erythematosus

The term lupus erythematosus (LE) refers to a group of connective tissue disorders comprising at least three major disease subsets: 1) Systemic lupus erythematosus (SLE); 2) Subacute cutaneous LE (SCLE) and 3) Discoid lupus erythematosus (DLE). SLE and DLE can give rise to oral lichenoid lesions, which may appear similar if not identical to those of OLP. Immunofluorescent studies may be occasionally useful to distinguish oral lesions of LE from OLP (121) but they cannot always distinguish between the two disorders (117). The presence of mixed clinical and histopathological features of LE and LP, has been referred to as lupus erythematosus/ lichen planus overlap syndrome (LE/LP overlap syndrome) (117).

DLE is the common form of chronic cutaneous LE and can be separated into two groups: localized and generalized. The widespread disease is more frequently associated with abnormalities detected in laboratory tests (125). DLE has been associated with HLA region genes and non-MHC loci (see Table1) but the evidence is weaker than in SLE (79,80,118).

The disease may be confined to the skin, especially on sun-exposed areas, such as face, ears and scalp, but there may be also mucosal involvement which is usually limited to the oral and anogenital mucosae (18,82,113,141,166,172,179,181). Up to 28% of patients with DLE are

susceptible to developing SLE (35). Oral lichenoid lesions occur in 15–20% of DLE cases but the prevalence of DLE limited to the oral mucosa is unknown and rarely studied. The buccal mucosa, the vermilion, the gingiva and palate are usually affected. Typical oral lesions are characterised by central atrophic areas or shallow erosions, radiating white striae at margins, characteristically far less sharply defined than in OLP. They are often unilateral, and may be on the hard and soft palate, and outer aspect of the lips which OLP usually spares. They can be the sole manifestation of the disease. Lip lesions can tend to spread from the vermilion to the surrounding lip skin, obscuring the limits of the vermilion but this is not a constant feature (120). Squamous cell carcinoma may rarely arise in longstanding lesions of oral DLE (99). Patients with DLE rarely fulfil 4 or more of the criteria used to classify SLE (161). Serologic abnormalities are particularly uncommon in localized disease. The predominant autoantibody in DLE patients remains unknown and only low-titre anti-Ro (60 kDa) antibodies have been found in DLE patients (36). Histopathology can sometimes be of help but frequently is equivocal or not specific, particularly in distinguishing DLE from OLP (168). On direct immunofluorescence testing granular deposition of immunoglobulin and/or complement can be seen at the dermo-epidermal junction, the so called lupus band test (LBT): this is characteristic but not pathognomonic of either DLE or SLE. The LBT is neither sensitive nor specific and has mostly been replaced by advances in serologic testing (73).

Lichenoid Lesions of Systemic Lupus Erythematosus

SLE is regarded as a prototypic systemic autoimmune disease, which can affect multiple organs and systems. Genome-wide association studies and mapping of candidate regions have allowed a better understanding of the genetic basis of SLE (65). A meta-analysis found the most consistent HLA association with HLA-DR3 and DR2 in European populations (50), whereas a genome-wide association study (GWAS) revealed a greater association with MSH5 gene, which is in the class III region (66). Table 1 lists the candidate gene associations confirmed by GWAS. Given the large number of SLE susceptibility loci known, it seems that the genetic risk of SLE is derived from variations in several genes, each being of modest effect

size (65). SLE most often manifests as a mixture of constitutional symptoms, with skin, musculoskeletal, and hematologic involvement. However, some patients present with predominantly hematologic, renal, or neuropsychiatric manifestations (58). Cutaneous manifestations of SLE are present in 85% of patients during the course of the disease. The most typical skin lesion of LE is erythema over the malar eminences of the face and bridge of the nose (the so called butterfly rash). Oral lesions appear in up to 40 % of cases of SLE and can rarely be the presenting sign of the disease (85,86). Oral manifestations of SLE can be similar to DLE: oral lichenoid lesions with atrophy, erosion and hyperkeratotic reticulation and striation (Figure 5). Histopathological and immunofluorescence features have been discussed above in the DLE section. Otherwise unspecific oral ulcerations can also be seen and they are an American College of Rheumatologists (ACR) criterion for SLE diagnosis (111). According to the ACR, the diagnosis of SLE requires the presence of four or more of 11 criteria, serially or simultaneously, during any period of observation (58). Diagnosis of SLE is also challenging because typical symptoms and signs could take long time to establish. The diagnosis should be confirmed by the pattern of autoantibodies, particularly anti-nuclear antibodies (ANA). Further to double-stranded DNA autoantibodies other autoantibodies are commonly detected in SLE. Some SLE autoantibodies are pathogenic and others are protective and some appear to be neutral, indifferent, and/or have roles that may not be directly traced to pathogenesis or protection (55).

Chronic Ulcerative Stomatitis

In 1990 Jaremko et al. (78) described a disease, which they named chronic ulcerative stomatitis (CUS), characterized by chronic oral ulcerations that occasionally can involve the skin (23,38,43,53,75,152,153,155,183). The clinical appearance of oral lesions of CUS is reminiscent of OLP and specific features able to differentiate CUS from OLP are virtually non-existant. Some authors report that CUS should be considered in patients unresponsive to glucocorticosteroid therapy (53). No more than 40 cases have been reported since the original description and it is still unclear if this disease exists as a separate entity from OLP. The

histologic features are non-specific, with a chronic inflammatory infiltrate, often appearing similar to OLP. Diagnosis of CUS requires immunofluorescence (IF) microscopic examination (138). Direct IF reveals the presence of IgG antibodies bound to of keratinocytes nuclei of the basal and lower one-third cell layers, with a unique stratified epithelial specific-antinuclear antibody (SES-ANA) pattern (78). However, other disorders such as SLE, scleroderma and CREST (Calcinosis, Raynaud's phenomenon, Oesophageal involvement, Sclerodactyly and Telangectasia) syndrome, and mixed connective tissue disease (MCTD), may demonstrate a similar ANA pattern (152). CUS patients also have circulating antibodies which exhibit the SES-ANA pattern on indirect IF (IIF) using an oesophagus substrate (78). Circulating IgG in SLE, CREST, and MCTD patients (38,127,175) are usually detected using human neoplastic HEp-2 cells or rodent kidney cells as substrates but they are not suitable for IIF of suspected CUS cases. SLE, scleroderma and MCTD may also be positive for ANA on oesophagus substrates but the pattern is different because the antibodies should be distributed through the superficial epithelial layers (152). Immunoblot studies led to the recognition of a 70-kDa keratinocyte protein in some CUS cases (16,24,128). Further studies identified a nuclear protein normally present in basal and parabasal cells of stratified squamous epithelia called deltaNp63alpha (Δnp63α), which is thought to be the putative specific CUS antigen (93). Δnp63α is a member of a family of nuclear transcription factors, including p63, p73, and the p53 tumor suppressor gene, which share considerable sequence homology (34). It is still debated if Δnp63α is specific of CUS as some Authors reported that OLP patients could have circulating autoantibodies against this protein (128). Two novel non-commercial ELISA systems have been developed to detect antibodies against Δnp63α (47,154).

Lichen Planus Pemphigoides

Lichen planus pemphigoides (LPP) is a rare clinical variant of bullous pemphigoid (BP), which is characterized by clinical and histological features of both LP and BP. This immuno-bullous disorder usually occurs on skin and occasionally involves the oral mucosa (154,180,189). Less than 80 cases have been reported so far and about 40% reported oral lesions similar to those

of OLP (189). Only 3 cases of LPP limited to the oral mucosa have been published (114,154), though similar clinical appearance and immunological testing led to a MMP diagnosis in at least another published case (92). LLP seems to have a similar demographic to OLP, with a slight female predominance and mean age at diagnosis of 54 years (189). LPP has been associated with a wide variety of conditions including malignancies such as lymphoma, haemangiopericytoma, and colon cancer, and other conditions and therapies such as viral hepatitis, phototherapy (UVA, UVB/psoralen-UVA), and therapy with simvastatin, furosemide, ramipril, captopril, cinnarizine, paracetamol and ibuprofen (63,105,114,123,158). Clinically, LPP is characterized by formation of blisters or tense bullae prior to, during, or after a papular eruption of cutaneous LP. The bullae arise on both normal and LP affected skin (39,154). Clinical features of oral involvement in LPP are lichenoid striation, erythematous and ulcerative lesions involving gingiva, buccal mucosa but also the palate (Figure 6). Classic diagnosis of LPP is made by clinical, histopathologic and immunologic features that suggest the concurrence of both LP and BP (39,154,160). Histopathology shows features of orthokeratosis, hypergranulosis, irregular acanthosis, hydropic degeneration of basal keratinocytes with citoid body formation and subepidermal clefting (at the level of the lamina lucida). The dermal inflammatory infiltrate is inconstant and may be cell-rich or cell-poor, lichenoid or perivascular; in addition, eosinophilic spongiosis may also be a feature (144,154,187). The sub-epidermal blister shows linear deposition of IgG and/or C3 along the dermal-epidermal junction (DEJ) upon DIF. In addition, more than 50% of LPP cases have circulating IgG anti-BMZ antibodies that are deposited on the epidermal side of 1.0 M sodium chloride split skin indirect immunofluorescence. By immunoblot, sera of LPP patients react against BP180, a component of the hemidesmosome involved in the dermo-epidermal anchoring complex. In particular, autoantibodies bind to the C-terminal portion of NC16A, a non-collagenous region of BP180 recognized by the vast majority of BP and MMP patients (10,190). In this context, the commercially available ELISA based on NC16A can contribute to the diagnosis.

Mixed Group

Lichenoid lesions on the inner side of the lip, possibly initiated by microbial plaque accumulation on the buccal surfaces of the anterior teeth, have been reported as a possible new disease entity (9,107). All subjects presented with a localized erythematous patch on the labial mucosa of the upper lip and microscopically the lesions were characterized by the presence of lichenoid inflammation with concomitant granulomatous inflammation.

Solitary fixed drug eruptions on the lip have been rarely reported. They are characterized by a peculiar sudden onset of solitary, or occasionally multiple, well demarcated erythematous lesions on the mucous membranes which may or may not become ulcerated. The histopathology shows lichenoid interface dermatitis that includes plasma cells and tends to surround small vessels (130). The diagnostic hallmark is the reappearance of the lesion precisely over the previously affected site when the offending agent is reused.

Lichen sclerosus (LC) is clinically characterized by the development of well-delimited hyperkeratotic lesions to the skin and genitals, and very rarely to the oral mucosa, followed by fibrosis/sclerosis (7,83). It can mimic other disorders causing hyperkeratotic patches including OLP. Histopathology of LC shows epithelial atrophy, local hydropic degeneration of the basal cells, loss of the epithelial crests, and homogenization of the underlying connective tissue with a reduction in elastic fibre presence, hyalinization and connective tissue sclerosis. Lichenoid lymphocytic infiltrate is often present but does not show a distinct band of lymphocytes at the epithelial–connective tissue junction as in OLP and other lichenoid lesions (7).

Differential Diagnosis of OLL

Occasionally the diagnosis of a specific OLL may be made on visual inspection without any further test but in most instances other investigations are warranted (Figure 7). OLL often present overlapping clinical and histopathological features and diagnosis is frequently challenging. A complete history and clinical assessment by a multidisciplinary group of specialists may be required to investigate oral, skin, nail, scalp, genital, oesophageal, laryngeal and conjunctival involvement.

The clinical features alone, particularly when presenting in the "classic" hyperkeratotic reticular bilateral form, would often support the exclusion of other oral keratotic disease such as leukoplakia, frictional keratosis and proliferative verrucous leucoplakia (156). The latter is particularly difficult to address as available reports suggest that it can show histological "lichenoid" features. Biopsy would be prudent clinical practice in most, if not all, patients. Histopathology, however, can be subjective and nonspecific (28); also it is unlikely to allow differentiation between OLL. Further investigations such as direct and salt-split skin indirect immunofluorescence and ELISA tests may be needed when a bullous disorders or LPP and CUS are suspected. In cases of recalcitrant and atypical muco-cutaneous manifestations, further investigations are warranted including a PET-scan for total body cancer screening if PNP/PAMS is suspected. Immunoblotting, IP and ELISAs may also assist diagnosis (Figure 7).

When medical history, clinical features and immunological findings (for example positive ANA test) suggest SLE, testing fro anti-DNA antibodies as well as and other autoantibodies including Anti-Sm, anti-RNP, anti-Ro/SSA and La/SSB, anti-antiphospholipid and anti-cardiolipin should be considered (Table 1) (Figure 7) (55). For some OLL such as DLE, OLDR and OLCL, reliable diagnostic tests are not available and further research is warranted.

Management of OLP/OLL

Some OLL such as OLP, OLCL, OLDR, DLE and CUS are more amenable to topical therapy than PNP/PAMS, SLE and LPP, which usually require systemic medications and multidisciplinary management. This chapter will focus upon topical therapy of OLP/OLL.

In individuals with potential OLDR, the causing medication should be discontinued where possible. This is often difficult because the drug is usually important to the patient's health and effective alternative drugs may not be available. Moreover, the lesions may persist for several months following withdrawal of the medication (109). Patients suspected to have OLCL may benefit from targeted amalgam replacement, although it is possible that simple polishing of the restorations and improvement of the patient's oral hygiene may minimize plaque

accumulation and frictional trauma to the mucosa and therefore results in an improvement of the OLCL. Patients obviously should be counselled on benefits and risks of amalgam removal. Also, the cyclic nature of the disease characterized by periods of spontaneous remission and exacerbation, the limited evidence supporting amalgam replacement, and the unpredictability of the amalgam removal procedure should be described. Risks should be fully disclosed: these include potential iatrogenic dental damage, the possibility of the worsening of the lesions immediately after amalgam replacement (especially if a rubber dam is not used), shorter life span of some alternative materials, and possible additional allergic reactions involving any of the newly placed restoration materials (8).

The main aim of any therapy of OLP/OLL is symptomatic control (28,164). Usually, patients with reticular and other asymptomatic lesions do not require active treatment. The elimination of potential precipitating or provoking factors is an important initial step in the management of symptomatic OLP/OLL. Precipitating factors and irritants (sharp or fractured teeth, poorly fitting dentures, alcohol and tobacco consumption) should be identified and avoided or eliminated where possible (73). Good oral hygiene along with the use of chlorhexidine mouth rinse should also be advocated, as plaque reduction may have beneficial effects on the lesions (70).

As many cases of OLP/OLL are chronic, the patient's medical history, psychological state, and treatment compliance as well as possible drug interaction must be considered when evaluating the cost effectiveness of any treatment modality (27).

Although a permanent cure is not available, various treatment regimens (Table 2) have been introduced to reduce and control painful symptoms of OLP/OLL. Curiously, several suggested treatment modalities are also suspected to induce lichenoid lesions (Table 2). Topical agents are usually the first line of therapy as they have few adverse side effects. However, systemic agents may be required if lesions are widespread and involve the skin or other mucosae, or if there is recalcitrant disease. The medications that are commonly used for OLP/OLL are immunosuppressive and few were developed specifically for oral disease. As a result, there is a lack of adequate studies determining their efficacy (164). Moreover, several aspects of the

therapy such as optimal dose, duration of treatment, safety, and true efficacy remain largely unknown (148). Patients should be warned about the off-label use of the medications used to treat OLP/OLL.

Topical corticosteroids

Topical corticosteroids (TCS) are universally recognized as first-line treatment of symptomatic OLP/OLL. However it remains unclear which steroid potency, formulation, concentration or dosage regimen represents "standard of care" (164).

Commonly, ointments and suspensions are preferred whereas creams can have a bitter taste and do not melt well with adhesive pastes whereas gels almost invariably contain alcohol and sting. Sprays, normally used for nasal allergy and asthma, can be also used intra-orally.

A reduction in painful symptoms with mid-potency corticosteroids, such as triamcinolone acetonide 0.1% and betamethasone, potent fluorinated corticosteroids such as fluocinolone acetonide 0.1% and fluocinonide 0.05%, and super potent halogenated corticosteroids, such as clobetasol propionate 0.05%, have been reported in 30–100% of treated patients (15,20,21,103,139,165,177). The adherence to the oral mucosa for a sufficient length of time can be enhanced using adhesive pastes, such as sodium carboxymethyl cellulose (Orabase®) and hydroxyethyl cellulose, or special drug delivery systems, such as lipid-loaded microspheres (19,21,103,116). Iatrogenic Cushing's syndrome has been rarely reported using TCS (44,59,94) whereas acute pseudo-membranous candidiasis is the most common adverse side effect. This can be prevented with the use of antifungals (miconazole gel) or chlorhexidine mouthwashes (21,101). When lesions of OLP/OLL are limited to the gingivae topical steroids may be best delivered using custom made trays (60).

Other topical agents

Other topical immunosuppressants or immunomodulatory agents such as calcineurin inhibitors (TCI) (cyclosporine, tacrolimus, or pimecrolimus) or retinoids have been reported to be beneficial for symptomatic OLP/OLL, especially if the lesions are recalcitrant to

corticosteroids. Cyclosporine has been used as a mouthrinse (50-1500 mg/day) (127) or in adhesive bases (26-48 mg/day) (40,49,77,96,151,178) but is expensive, not always effective, and less beneficial than topical clobetasol in inducing clinical improvement (40). Tacrolimus is 10–100 times as potent as cyclosporine and has greater percutaneous absorption. Several uncontrolled, not randomised studies have documented the efficacy and safety of this agent in the management of recalcitrant erosive OLL at concentrations ranging from 0.03% up to 0.1% (41,69,87,95,115,126,142). Burning on application is a common side-effect and is observed in <20% of patients. Circulating therapeutic levels of tacrolimus can be demonstrated after topical application and occasionally they can cause systemic adverse events (41). Pimecrolimus is the newest calcineurin inhibitor used in OLP/OLL treatment. Its immunosuppressive potency is thought to be weaker than cyclosporine and tacrolimus and it has lower permeation through the skin than topical steroids or topical tacrolimus. Nevertheless, a recent RCT comparing pimecrolimus 1% versus tacrolimus 0.1% in adhesive ointment in the management of symptomatic OLP/OLL did not show any difference in clinical efficacy (4). Although four small placebo-controlled randomised trials suggested that 1% pimecrolimus cream can be an effective and well-tolerated treatment for erosive OLP/OLL (110,129,159,176), a very recent meta-analysis (129,159,176) reported that in fact there is no robust evidence that pimecrolimus is more effective than placebo (164).

The US Food and Drugs Administration issued a "Black Box" warning regarding the use of tacrolimus and pimecrolimus because of a possible increased risk of malignancy development (squamous cell carcinoma and lymphoma) in patients using topical tacrolimus/pimecrolimus for cutaneous diseases. The decision has been heavily criticized in the medical community as the concern stemmed from case reports and animal data (150). A recent 'deductive meta-analysis' found no evidence of increased risk of skin cancer associated with the use of TCIs (162). The issue remains controversial, as two separate papers reported development of oral SCC in two patients with OLP/OLL and history of topical tacrolimus 0.1% therapy (11,106).

Topical rapamycin (Sirolimus), which inhibits the response to interleukin-2 (IL-2) and blocks activation of T- and B-cells, has been recently suggested to represent an effective alternative

therapy in refractory erosive OLP (157). Notably, rapamycin has both immunosuppressive and tumour inhibitor properties, and might theoretically control painful symptoms and at the same time lessen the risk of cancer development in OLP/OLL patients.

Topical retinoids such as tretinoin, isotretinoin, fenretinide and tezarotene are generally less effective than topical corticosteroids and more likely to cause adverse side effects (13,14,131,145,170).

Systemic therapy

Systemic corticosteroids are recommended for patients with severe painful OLP/OLL who have failed to respond to topical therapy or have widespread OLP/OLL involving skin, genitals, oesophagus, or scalp (22). Prednisolone at a starting dosage of 40 to 80 mg daily for 1-4 weeks is usually sufficient to achieve a notable response, often followed by slow reduction in dosage. However recurrences are common and therefore systemic corticosteroids do not represent a sensible therapeutic option in chronic OLP/OLL (102) due to their toxicity profile associated with long-term therapy. Corticosteroid-sparing agents and other immunosuppressants including azathioprine and mycophenolate mofetil are usually required for long-term therapy (32,33,54,136,169,186), though there has been little robust evaluation of their efficacy in the OLP/OLL population. Hydroxychloroquine sulphate is considered the first-line systemic therapy for severe DLE (82) but it could be also effective for CUS.

Also, very recently, biologic agents including Basiliximab, Etanercept, Efalizumab and Alefacept have been proposed for treatment of OLP/OLL (Table 2), especially for patients with severe manifestations or those who have failed traditional first- and second-line therapy such as topical corticosteroids/topical calcineurin inhibitors. Non-pharmacological modalities such as phototherapy (62), surgery (6) and laser treatment (with carbon dioxide and low-dose excimer 308-nm laser) (72,90,171) have been suggested but their effectiveness is yet to be proven. Of note, surgical intervention has been reported to worsen lesions of OLP/OLL (88).

Novel treatments

Topical aloe vera (AV) (37,104,137,143) and oral curcuminoids (OC) (30,31) have been suggested to represent promising therapeutic options for OLP/OLL. However, different AV formulations have been published so far and the amount of active product can vary greatly depending on the age of the plant, the growing and harvesting conditions, the parts of the plant, and the extraction methods used. Further, OC can cause adverse side effects in up to 40% of the patients, including liver dysfunction.

Amlexanox (56) and topical thalidomide (184) have also been investigated and were reported to be effective in controlling painful symptoms of OLP/OLL in comparison to weak topical corticosteroids, which are no longer commonly used for OLP/OLL management.

Conclusions

OLP/OLL represent a heterogeneous group of inflammatory disorders that are characterised by similar clinical manifestations and histopathological features. They probably share a common reaction pattern to one or more antigens, however the exact pathogenic mechanisms and the nature of antigenic triggers remain unknown. Oral manifestations typically include "lichenoid" hyperkeratotic striation/reticulation and/or a variable degree of erythema, blistering, erosion and ulceration, which are seen in oral lichen planus, oral lichenoid contact lesions, oral lichenoid drug reactions, oral lichenoid lesions of graft versus host disease, discoid lupus erythematosus, and systemic lupus erythematosus, lichen planus-like variant of paraneoplastic pemphigus/paraneoplastic autoimmune multi-organ syndrome, chronic ulcerative stomatitis, lichen planus pemphigoides, solitary fixed drug eruptions and oral lichen sclerosus. Histologically OLP/OLL are characterised by a "lichenoid" sub-epithelial inflammatory infiltrate of lymphocytes. With the exception of oral lichen planus and sclerosus, oral lichenoid contact lesions, oral lichenoid drug reactions, and chronic ulcerative stomatitis, affected patients often present a variety of extra-oral systemic manifestations that require assessment and management. Oral painful lesions of OLP/OLL are commonly managed with topical corticosteroids and immunosuppressants, although severe recalcitrant disease and extra-oral manifestations typically require systemic immunosuppression. Some of the

disorders in the OLP/OLL group are associated with an increased risk of oral cancer development and should be carefully and regularly monitored.

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