Oral lesions in lupus erythematosus: correlation with cutaneous lesions

Oral lesions in the context of lupus erythematosus (LE) have long been described. However, definitive agreement on about the exact nature and correct classification of these manifestations is lacking in published studies. Controversy exists on the significance of oral LE lesions regarding patient outcome. In this article, medical and dental literature on clinical and histopathological aspects of oral LE lesions are reviewed and critically discussed. A clinico-pathological correlation of oral lesions (interface mucositis-lupus mucositis) with cutaneous lesions (interface dermatitis-lupus dermatitis) is established, for those represent the mucosal counterparts of cutaneous LE. Validity about widely used but imprecise terms such as “oral ulcers”, “ulcerative plaques”, and others, in the context of LE, is discussed, and the uncertain relationship of these alterations to systemic disease with a worse outcome is commented. Furthermore, insights about the nature, differential diagnosis, and prognosis of oral lesions in LE patients are presented.

Key words: lupus erythematosus, oral lesions

Oral lesions in lupus erythematosus

Different studies of oral lesions in the course of LE have shown a frequency varying from 9 to 45% in systemic disease and 3 to 20% in localized cutaneous disease [4-6]. Our group reported 26 patients with oral lesions among 188 LE patients studied, 13 of these had SLE according to the ACR criteria. Nineteen patients were female and 7 were male [7]. Burge et al. reported 10 female and 4 male patients with oral lesions of LE, of these, 5 were considered to have SLE and 9 had localized cutaneous LE [1]. In a further study by our group, oral lesions were diagnosed in 46 patients, only 13 had SLE according to established criteria [8]. A possible reason for the lower frequency of oral lesions when compared with skin lesions may be the lack of ultraviolet radiation incidence in the oral cavity in contrast to the skin.

Clinical descriptions of oral LE lesions vary enormously in the different studies. Terms used include: “oral discoid lesion”, “chronic plaque”, “lupus chelitis”, “acute ulcer”, “oral ulcer”, “red ulcer”, “ulcerative plaques”, “pebbly red areas”, “honeycomb lesion”, “keratotic lesion” “white keratotic plaques”, “purpuric lesions” and “diffuse palatal petechial erythema” [2, 3, 9-12]. Thus, in contrast to cutaneous LE, no uniformity exists in classifying oral LE lesions, and an adequate clinical categorization is lacking. Additionally and yet more confusing, oral ulcerations in LE patients have for a long time been considered as a sign of “vasculitis” and predictors of severe systemic flares of the disease [12, 13]. This misconception brings no light to the knowledge of such lesions and has created myths among physicians about the true significance of oral lesions of LE.

Classification of oral LE and correlation with cutaneous LE

Cutaneous manifestations of LE are divided in non-specific (non-diagnostic lesions) and specific (diagnostic lesions) [14]. Non-specific lesions usually indicate systemic disease with consequent cutaneous repercussions and include vasculitis, Raynaud’s phenomenon, non-scarring alopecia and livedo racemosa. Non-specific manifestations are not observed in the oral cavity. Specific LE lesions indicate lupus dermatitis (analogous to “lupus arthritis”, “lupus nephritis”, “lupus serositis” etc) and are represented by interface dermatitis. These are classified as cutaneous acute, subacute and chronic LE [14, 15]. These categories represent variants of the lupus process on the skin, with specific clinical, histopathological, genetic and immunoserological features [14-16].

As with many other skin diseases with mucosal manifestations, oral lesions of LE represent the exact mucosal counterpart of skin lesions, and should be similarly classified.
(consequently no “follicular pluggings”, so typical of discoid LE) and scarring (atrophy) is difficult to assess because of better mucosal regeneration when compared to skin. Moreover, some patients may present with exclusively oral lesions, making an immediate correlation with cutaneous LE less obvious.

**Chronic lesions**

Chronic cutaneous LE (CCLE) includes, among others, the classic discoid lesion. This is characterized by round, well-circumscribed, infiltrated, scaly and atrophic plaques with follicular plugging, mainly on the face, scalp, ears, and, more rarely, on the chest and arms (disseminated discoid LE) (figure 1A). Discoid lesions develop severe scarring in most cases; scalp lesions typically show scarring alopecia. Verrucous LE refers to intensely keratotic discoid lesions. Other variants of CCLE include tumid, lupus panniculitis and chilblain LE [14, 16, 17].

The commonest mucosal presentation of chronic LE is the oral discoid lesion. The typical clinical picture is of a well-demarcated, round or irregular red area that can be atrophic or ulcerated, with white radiating keratotic striae and telangiectases. This aspect represents the very same lesion as the classic cutaneous discoid LE (figure 1B and C). Morphologic variants of chronic oral LE include the so-called “honeycomb plaques” (a clinical aspect of mucosal scarring) (figure 2A) [1] intensely keratotic white lesions (corresponding to verrucous CCLE) (figure 2B), and linear fissured, ulcerative and keratotic lesions that may occur in buccal mucosa [10]. Most patients will have simultaneous cutaneous lesions, but exclusive mucosal manifestations are not rare. Isolated palatal lesions can be seen (figure 1C). Pain is variable. Lesions are more often asymmetrically distributed in the oral cavity (palate, buccal mucosa, tongue). This asymmetry is important in differential diagnosis since lesions of clinically similar diseases such as oral lichen planus (LP) are almost always symmetric. Tumid and subcutaneous chronic LE have not been described in the oral cavity.

Lip involvement is frequent. Clinical manifestations include well-demarcated discoid lesions or a diffuse cheilitis [2]. Lesions typically tend to spread from the vermilion to the surrounding lip skin, obscuring the limits of the vermilion (figure 3A and B). This feature is useful in differentiating LE from lichen planus of the lip and from other types of cheilitis, as LP lesions are characteristically limited to the vermilion area. The designation “lupus cheilitis” is used at times [1, 2], but it may suggest a different or special manifestation instead of a typical LE lesion on that location.

Squamous cell carcinoma may, rarely, arise in longstanding scarring lesions of oral LE, as well as in long established scars of other chronic mucosal diseases (LP, syphilis) [14, 16] (figure 3C).

**Subacute lesions**

Subacute LE represents a subtype of LE with characteristic clinical, serological and prognostic features [14]. Subacute

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**Figure 1.** Cutaneous and oral discoid LE: **A)** Typical discoid LE-round plaques with keratosis, central atrophy and follicular plugging. **B)** Intra oral discoid lesion in the same patient—an erythematosus round ulcer with surrounding keratotic striae. **C)** Discoid lesions are common on the palate.

**Figure 2.** Clinical aspects of longstanding oral discoid lesions: **A)** Well-established scarring lesions often display a typical “honeycomb” aspect. **B)** Longstanding intensely keratotic plaque—this is akin to cutaneous verrucous LE.

**Figure 3.** Clinical aspects of lip lesions in LE: **A)** Discoid lesion on the lip characteristically spreading from the vermilion to adjacent skin. **B)** Diffuse vermilion evolution spreading to lip skin in a patient with subacute cutaneous LE. **C)** Squamous cell carcinoma can develop on longstanding scars of LE.
cutaneous LE (SCLE) includes psoriasiform (erythematopapulo-squamous) and polycyclic (erythema multiforme-like) photosensitive eruptions and is more commonly associated to mild systemic disease (figure 4A). “Rowell’s Syndrome” refers to the coexistence of erythema multiforme and LE, but its identity is widely discussed. Subacute LE lesions heal without scarring; vitiligo-like hypopigmentation is common [14, 16, 17]. Although SCLE lesions characteristically appear on sun-exposed areas, intra oral manifestations may rarely be present. Lesions consist of well-demarcated, round, red patches that on close inspection may appear slightly depressed. Due to moisture, scaling is not evident (figure 4B). Lip lesions may occur as diffuse erythematous scaling plaques on the vermilion that typically spread towards the skin of the lip and are almost always associated with more generalized SCLE (figure 3B).

Acute lesions

Acute cutaneous LE (ACLE) includes the classic malar edematous butterfly lesion (figure 5A), a corresponding widespread eruption and bullous LE. These presentations almost always indicate systemic LE, with its diagnostic serological changes and manifestations in other organs. These cutaneous lesions tend to heal without scarring since inflammatory component is scarce [14-18]. Oral lesions in the setting of systemically ill LE patients are very common. There are many possible clinical presentations: circumscribed red macules, diffuse or palatal erythema, purpuric macules (figure 5B), and erosions or ulcers that may or may not be symmetrically distributed in the mucosa [2, 14]. These can occasionally be present in the absence of skin lesions.

There is still controversy as to whether bullous LE represents specific acute or non-specific LE dermatitis [14] but histopathological and immunofluorescence data [14-16] favor specific acute manifestation because they are diagnostic. Patients with bullous LE may present with linearly arranged blisters along the lip vermilion or with intact or, more often, ruptured blisters on the palate or buccal mucosa [21] (figures 6A and B). There is a rare variant of LE in which lesions have a widespread erosive bullous aspect similar to Stevens-Johnson disease or toxic epidermal necrolysis, these patients usually present with hemorrhagic crusts and erosions on the lips and mucous epithelial detachment. The question as to whether these manifestations represent a hyper-acute type of specific lupus dermatitis/mucositis or a non-specific indicator of severe activity is still under debate [19, 20].

Oral ulcerations or ulcers in the setting of SLE have long been considered to be predictors of systemic vasculitis and worse prognosis [12, 13]. Jorizzo et al. proved that these lesions represent, in fact, specific lupus lesions clinically and histopathologically (interface mucositis), without prognostic implications [18] (figure 7). Curiously, though, the same group of authors, in a latter review, stated that these ulcers are non-specific manifestations of SLE heralding serious disease. However, no explanation is offered on their nature or histopathological findings [22]. Established prognostic indexes for systemic LE in the rheumatological literature, such as the “Systemic Lupus Activity Measure” (SLAM) [11, 12], equivocally classify oral LE ulcers together with “peri-ungual erythema, photosensitive rash and nail fold infarcts” (mostly non specific LE lesions), and separated from “erythematous rash, discoid lesions, lupus paniculitis, bullous lesions” (specific LE lesions). This classification probably provides unnecessary additional value to muco-cutaneous specific LE lesions in establishing systemic prognosis. These oral lesions of LE are summarized in table 1.
Clinical differential diagnosis

Clinical differential diagnosis of LE mucositis will depend on the morphology of the lesion analyzed. The main differential diagnoses for keratotic discoid lesions are LP, lichenoid reactions to dental fillings, traumatic and smoker’s keratoses, and verrucous carcinoma. Ulcerated discoid lesions should be differentiated from aphtha, erosive LP, traumatic ulcers, deep mycoses, Langerhans cells histiocytosis and SCC (SCC can develop in old scarring LE lesions). Lip lesions may simulate contact cheilitis, factitious cheilitis, actinic cheilitis, LP, psoriasis, erythema multiforme, pemphigus vulgaris and SCC. Erythematous or purpuric macules may resemble LP, erythema multiforme, mucous patches of syphilis, petechiae of viral exanthem, and negative pressure purpura (“fellatio syndrome”). Finally, differential diagnoses for oral bullous LE include pemphigus vulgaris, mucous membrane pemphigoid, herpes simplex, varicella, and erythema multiforme with its variants (Stevens-Johnson disease and toxic epidermal necrolysis).

Histopathological aspects

Several studies have focused on the histopathological aspects (figures 8A-C) of cutaneous and mucosal lesions of LE [5, 7-9, 15, 16, 23, 24]. Characteristically, features of cutaneous and mucosal LE are of perivascular and interface dermatitis/mucositis. Histopathological distinction between acute, subacute and chronic cutaneous LE lies in the intensity of epithelial affection, severity of follicular damage, nature and level of the inflammatory infiltrate in the dermis [15, 16, 24]. The histopathologic features of oral LE represent the mucosal counterpart to the described aspects of cutaneous LE. The most important differences lie in the absence of pilosebaceous units and the frequent finding of an absent epithelium that may be lost during the biopsy procedure or due to the high frequency of ulcerated lesions inside the mouth (marked basal cell liquefaction associated with mechanical trauma). In a study of 46 oral LE patients by our group, the most consistent findings corresponded to an interface mucositis with a superficial and deep perivascular lymphocytic inflammation; edema in the lamina propria is constantly present. The covering epithelium presented areas of acanthosis alternated with atrophy. Occasional pseudoepitheliomatous hyperplasia was observed. Variable degrees of spongiosis were present (a common finding in oral mucosa biopsies, not important for diagnosis). Foci with hydropic degeneration of the basal layer were evident.

Table 1. Clinical presentations of oral LE lesions

<table>
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<tr>
<th>Chronic lesions: discoid lesions</th>
<th>Subacute lesions</th>
<th>Acute lesions</th>
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<td>Note- lesions are almost always asymmetrically distributed on buccal cavity.</td>
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<td>– Atrophic or ulcerated round lesions with peripheral keratotic striae (figure 1B)</td>
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<td>– Linear ulcers with keratotic striae</td>
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<td>– “Honeycomb plaques” (longstanding scarring lesions) (figure 2A)</td>
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<td>– Intensely keratotic lesions (verrucous LE) (figure 2B)</td>
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<td>– palatal discoid lesions (figure 1C)</td>
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<td>– Labial discoid lesions (figure 3A)</td>
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<td>– Squamous cell carcinoma may arise in longstanding scarring lesions (figure 3C).</td>
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<td>– Discrete red patches, (much rarer and more discrete than cutaneous subacute LE) (figure 4B).</td>
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<td>– Diffusely scaly labial patches (figure 3B).</td>
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<tr>
<td>– Erythematous-purpuric macules (figure 5B).</td>
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<td>– Palatal erythema.</td>
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<td>– Petechiae.</td>
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<td>– Ulcerations (figure 7A).</td>
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<td>– Bullous LE: labial blisters (figure 6A), intra-oral intact or ruptured blisters (figure 6B).</td>
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Lesions could indicate systemic vasculitis and have prognostic implications [18].

These authors demonstrated that oral ulcerations in SLE represent the ulcerated form of mucositis with no signs of vasculitis, these findings demonstrated that all biopsies of these ulcers revealed interface LE who presented with oral ulcers. These authors demonstrated by our and previous studies using immunohistochemical labelling of cytokeratins [7, 25]. Occasional identification of immuno-reactants are IgM and C3, the most common immuno-reactive patterns include colloid (apoptotic) bodies and continuous (linear) or granular basement membrane fluorescence that can be found on up to 100% of biopsies studied [7, 8]. These findings can also be found in other diseases and in sun damaged skin and thus are considered non-specific. IgG and IgA immuno-reactivity is most specific for LE, typically in linear basement membrane pattern.

These are observed on up to 29% of oral lesions [26].

Table 2. Histopathological comparison between oral LE, oral LP and oral lichenoid drug reactions

<table>
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<tr>
<th>Oral LE</th>
<th>Oral LP</th>
<th>Lichenoid drug reactions</th>
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<tr>
<td>Epithelial alterations</td>
<td>Hyperkeratosis, granulosis, acanthosis and atrophy, spongiosis, hydropic degeneration (patchy or widespread), colloid bodies, hyperproliferation of basal layer, sometimes with presence of atypical keratinocytes.</td>
<td>Hyperkeratosis, granulosis, acanthosis and atrophy, epithelial cones in &quot;saw-tooth&quot;, spongiosis, hydropic degeneration (patchy or widespread). In severe cases, complete destruction of basal layer is seen.</td>
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<td>Basement membrane (epithelial and vascular wall)</td>
<td>Regular or focal thickening of epithelial basement membrane associated with thickening of vascular wall.</td>
<td>Focal or widespread destruction of basement membrane by inflammatory infiltrate.</td>
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<tr>
<td>Lamina propria</td>
<td>Lymphocytic predominant inflammatory infiltrate of variable intensity with limited or widespread aggression to the basal keratinocytes. Inflammatory infiltrate is seen both in the superficial lamina propria (lichenoid) and deep perivascular.</td>
<td>Lymphocytic predominant lichenoid infiltrate with presence of Langerhans cells.</td>
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Basal necrotic keratinocytes, widespread or focal, were frequent. Thickening of epithelial and vascular basement membranes was visible on haematoxylin-eosin (HE) and PAS stains [8, 9]. The presence of epithelial atypia is not rare and has been observed by other authors [18]. This is probably due to a hyperproliferative status of the mucosa as demonstrated by our and previous studies using immunohistochemical labelling of cytokeratins [7, 25]. Occasional interlobular minor salivary gland inflammation is present, and this has been inappropriately labelled “Sjögren’s syndrome associated phenomenon” [3, 22].

Histopathological changes in mucosal LE lesions must be differentiated from similar alterations that may occur in other instances of perivascular and interface mucositis, such as lichen planus (LP), lichenoid mucositis and drug reactions [16, 23]. Karjalainen et al. compared histopathological features of oral LE with those of LP and concluded that the most important differences included: thicker basement membrane in LE (HE and PAS), edema in the lamina propria more pronounced in LE, PAS positive thickening of blood vessel walls in LE, deeper perivascular infiltrates in LE, more pronounced epithelial atrophy in LP [9].

The presence of mucin in the lamina propria is an important clue in differentiating LE from LP [14, 16]. These differences are summarized in Table 2.

Jorizzo et al. [18] studied 10 patients diagnosed with SLE who presented with oral ulcers. These authors demonstrated that all biopsies of these ulcers revealed interface LE mucositis with no sign of vasculitis, these findings demonstrate that oral ulcers in SLE represent the ulcerated form of specific LE mucositis, probably without prognostic implications [18] (figure 7B), contrary to the view that these lesions could indicate systemic vasculitis and have prognostic implications [3, 11-13].

Immunofluorescence studies

Direct Immunofluorescence (DIF) studies are often performed when diagnosing cutaneous and mucosal lesions of LE [24, 26-28]. These are particularly useful in differential diagnosis between LE and other possibly similar clinical and histopathological conditions such as LP. The three major classes of immunoglobulins IgG, IgA and IgM as well as complement components may be found in basement membrane zone deposits of cutaneous and oral LE, in a linear and/or granular pattern [24, 26-28]. DIF in oral LE lesions is frequently positive and the most commonly identified immuno-reactants are IgM and C3, the most common immuno-reactive patterns include colloid (apoptotic) bodies and continuous (linear) or granular basement membrane fluorescence that can be found on up to 100% of biopsies studied [7, 8]. These findings can also be found in other diseases and in sun damaged skin and thus are considered non-specific. IgG and IgA immuno-reactivity is most specific for LE, typically in linear basement membrane pattern. These are observed on up to 29% of oral lesions [26].

Conclusion

Oral lesions are not a rare event in the clinical context of LE. These are better understood if considered as the mucosal counterpart of cutaneous LE (“lupus dermatitis” and “lupus mucositis”), for they represent those very same lesions in the mucosa. Identical to cutaneous LE, clinical and histopathological subtypes of oral LE lesions represent diversity in intensity and in chronological phases of interface inflammation on the mucosa [15, 29]. When compared to cutaneous LE, differences concern mostly the anatomic and functional peculiarities of oral tissues: lack of pilosebaceous units, lack of scaling due to moisture and frequent ulceration due to friction. These limitations make use of strict clinical-pathological criteria essential for differentiating oral LE from other possibly similar conditions such as LP, and other lichenoid eruptions such as drug reactions. There is no definite evidence that oral LE lesions of any type may herald a worse outcome or systemic vasculitis.
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References