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Review Article

Oral Mucosal Manifestation of Lupus Erythematosus: A Short Review

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ABSTRACT

Lupus Erythematosus (LE) is a chronic autoimmune inflammatory disease, characterized by a wide spectrum of manifestations of variable evolution. Among the various organs involved, the skin is one of the most frequent site, sometimes being the first manifestation of the disease. The frequency of oral mucosal manifestations is variable, between 9 to 45% of SLE and 3 to 20% of Chronic Cutaneous Lupus Erythematosus. Oral mucosal manifestation of LE can present themselves in different ways and their description is varied in different studies. Oral Lupus Erythematosus is histopathologically characterized as an interface mucositis with hyperkeratosis, alternating epithelial hyperplasia with atrophy, changes in epithelial maturation, vacuolization of the basal layer, thickening of the basement membrane by Schiff's periodic acid staining and superficial and deep lymph-histiocytic infiltrate in the lamina propria, which can show focal, interstitial, perivascular location or in a tight epithelial band. The etiopathogenesis of LE is the result of a complex interaction between various pathogenic factors and remains unclear. Several mechanisms are known to participate in the process, such as: genetic, hormonal, environmental, autoantibodies and cellular components of the skin and the immune system. The treatment of LE, including oral mucosal manifestation, is a complex and multidisciplinary process, which is based on preventive measures, inflammatory process modulation and control, organ injury prevention, relief of the symptoms. The oral mucosal manifestation of LE is a rare condition, it could be observed and diagnosed by many health professionals, mainly by dentist, stomatologist, dermatologist and otolaryngologist, knowledge and depth study of OLE is needed by these professionals, thus, the sooner the disease is diagnosed, the better prognosis and quality of life can be given to the patient.

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Introduction

Lupus Erythematosus (LE) is a chronic autoimmune inflammatory disease, of unknown cause, characterized by a wide spectrum of manifestations of variable evolution [1-3]. LE is more common among females between the 2nd and 3rd decade of life, although it can occur at any age in both genders [1, 2, 4]. LE has been considered as a spectral disease by many authors, affecting multiple organs (Systemic Lupus Erythematosus) or being confined only to the skin (Cutaneous Lupus Erythematosus) [1-3]. Among the various organs involved, the skin is one of the most frequent site and its manifestations can occur at any stage of the disease, with skin lesions sometimes being the first manifestation of the disease [5].

Cutaneous Lupus Erythematosus (CLE) are classified as specific (diagnostic) and non-specific (non-diagnostic), the first being subdivided into acute, subacute and chronic, according to their clinical and histological characteristics observed only in LE [6-9]. Specific lesions may be present in both cutaneous and systemic forms of LE [3]. Mucous involvement in LE can be present in different presentations of the disease, and its prevalence is uncertain, in general, it is underestimated in the different case series. Lesions in the oral, conjunctival, nasal, vaginal and perianal mucosa have been described [10]. The present article reviewed some clinical and histopathological characteristics of oral mucosal manifestations of LE.

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Oral Lupus Erythematosus (OLE)

Lupus Erythematosus involving the oral mucosa is uncommon. In addition, it could be clinically asymptomatic, this explain why it is usually underestimated. Moreover, it is difficult to diagnose because presentations may vary and simulate other diseases. Mucous involvement showing oral and/or nasal ulcers is one of the 4 criteria for the diagnosis of SLE, additionally OLE can be found in SLE and CLE, which may be the only clinical manifestation of the disease in some patients.

I Epidemiology

In the literature, the frequency of oral mucosal manifestations is variable, between 9 to 45% of SLE and 3 to 20% of Chronic Cutaneous Lupus Erythematosus [10-12]. Burge *et al.* found 9% to 45% of oral involvement in SLE, and 3% to 20% in chronic cutaneous LE [10]. Lourenço *et al.* (2006) found 11.9% of oral lesions in 188 patients with LE [13].

II Clinical Features

There is a wide variety of poorly objective clinical terms, which have been used to describe oral mucosal lesions, such as: "Oral discoid lesions"; "lupus cheilitis"; "ulcerative plaques"; "honeycomb plaques"; "lichen planus like lesions"; and other terms [12, 14]. Oral mucosal manifestation of LE can present themselves in different ways and their description is varied in different studies. In order to correlate oral lesions with skin lesions of LE, Nico *et al.* (2008), classified oral manifestations into: acute, subacute and chronic, concluding that they represent the mucosal analog of CLE [14].

i Acute Oral Lupus Erythematosus (AOLE)

Acute Oral Lupus Erythematosus comprises several clinical presentations that are preferably located on the palate. They correspond to the lesions of acute cutaneous LE, however, they can occur even in their absence. They may present as erythematous macules or purpuric erythematous located on the palate and erosions or ulcerations with symmetrical or asymmetric distribution through the mucosa. They also can present with aphthoid and bullous lesions, haemorrhages and gingivitis [14]. Although some authors consider oral ulcerated lesions to be a warning sign for a possible systematization of the disease, suggesting a worse prognosis [15]. Jorizzo *et al.* demonstrated that these lesions represent specific lesions of LE (interface mucositis) without prognostic implications [16].

ii Subacute Oral Lupus Erythematosus (SOLE)

The Subacute Oral Lupus Erythematosus, on the other hand, presents as a well-defined, slightly depressed erythematous macula, usually located on the palate. On the lips, they appear as scaly erythematous plaques, ill-defined in the vermillion. It is a very rare form, further SOLE is characterized by photosensitivity, thus intraoral lesions are very uncommon [14].

iii Chronic Oral Lupus Erythematosus (COLE)

According to Nico *et al.* classification, we can define that the most common manifestation of the chronic oral form of LE is the discoid lesion, characterized by a well-defined, rounded or irregular erythematous lesion, with an atrophic or ulcerated surface with white radiated streaks and telangiectasias. In general, they are most commonly located in the buccal mucosa [10, 14]. Variants of the chronic oral form are keratotic, verrucous and "honeycomb" lesions. The "honeycomb" aspect occurs in long-lasting lesions and represents a scar. The lips may have well-defined or diffuse discoid lesions that, in general, exceed the vermillion limit [14].

III Histopathological Features

Oral Lupus Erythematosus is histopathologically characterized as an interface mucositis with hyperkeratosis, alternating epithelial hyperplasia with atrophy, changes in epithelial maturation, vacuolization of the basal layer, thickening of the basement membrane (evidenced by PAS histochemical staining - Periodic Acid-Schiff) and superficial and deep lymph-histiocytic infiltrate in the lamina propria, which can show focal, interstitial, perivascular location or in a tight epithelial band. These same characteristics are commonly found in other diseases; thus it requires accurate differential diagnosis [1, 10, 17, 18]. There are significant histological differences between OLE and oral lichen planus (OLP), determined by Schiodt in 1984 and confirmed by Karjalainen *et al.* in 1989. The histological features of OLE differ from OLP due to the presence of keratinocyte vacuolization, subepithelial positive Schiff's periodic acid reaction by immunoglobulin deposition, edema in the upper part of the lamina propria, positive PAS for thickening in the blood vessel walls, and perivascular or deep intense inflammatory infiltrate presence [19].

In the lichen planus, there are epithelial cones as "sawtooth", intense hydropic degeneration of the basal layer, focal or disseminated destruction of the basement membrane by the inflammatory infiltrate, which presents with a superficial lichenoid aspect, with a predominance of lymphocytes. Lichenoid reactions to drugs differ from LE by the presence of necrotic cells in the suprabasal layer and by the widespread destruction of the basement membrane by the lymphocytic inflammatory infiltrate, and the presence of eosinophils [19]. The histopathological diagnosis of oral lesion in LE can be increased by direct immunofluorescence examination. Immunoglobulins (Ig) IgA, IgM, IgG and complement C3 can be found as focal or continuous deposition in the basal membrane zone of OLE lesions, there is a variety of patterns such as: homogeneous, fibrillar, linear and granular [12, 20, 21].

IgG and IgA deposits are the most specific for oral discoid lesions, and IgM deposits show greater sensitivity [12]. OLE lesions commonly demonstrate reactivity to IgM and complement C3, however, Lourenço *et al.* (2007) reported a predominance of IgG with or without complement C3 in a linear pattern [21]. Direct immunofluorescence assists in the differential diagnosis of oral lesions of LE and lichen planus [10, 12, 21]. The deposit of immunoreactants in the basal membrane zone can be demonstrated in SLE (in 100% of the injured mucosa and in 75% of the uninjured) and in discoid LE (in 73% of the injured mucosa). It is rarely present in lichen planus (4%) and leukoplakia (3%) [12]. The presence of the lupus band (joint deposit of IgA, IgG, IgM and

complement c3 in the basal membrane zone) can be investigated by the lupus band test, an important method for the diagnosis of SLE [20].

IV Etiopathogenesis

The etiopathogenesis of LE is the result of a complex interaction between various pathogenic factors and remains unclear. Several mechanisms are known to participate in the process, such as: genetic, hormonal, environmental, autoantibodies and cellular components of the skin and the immune system. It is believed that for the LE development, a genetic predisposition condition for the disease is necessary. And in a genetically predisposed person, there are risk factors such as: infections, hormones, ultraviolet radiation and drug exposures, which could initiate inflammatory processes. Concomitantly, autoantigens are formed, probably through antigens released by apoptotic cells. Moreover, there are many cells that play important role at the beginning of the disease, such as neutrophils and dendritic cells (DC) [9, 15, 22-24].

It is known that numerous cytokines are also involved in this process. They promote the inflammatory response spreading and the suppression of tolerogenicity of the immune system, recruiting and promoting the activation of T cells. The self-reactive B cells start to produce autoantibodies, which are an important part of the diagnostic criteria and the key to some clinical manifestations of LE. Then, several mechanisms amplify and feedback the immune response, and culminate in the onset and perpetuation of LE lesions in various organs, such as the skin [15, 25, 26].

V Treatment

The treatment of LE, including oral mucosal manifestation, is a complex and multidisciplinary process, which is based on preventive measures, inflammatory process modulation and control, organ injury prevention, relief of the symptoms [27]. Prevention could be done by managing and monitoring patient's lifestyle habits. Patient education on ultraviolet radiation exposure, smoking cigarettes and drug avoidance should be an important part of the treatment plan [27-30]. There are many different options for topical therapy, mainly when patient shows localized cutaneous or mucosal lesions, such as: topical corticosteroids (methylprednisolone, triamcinolone acetonide, betamethasone valerate, clobetasol, hydrocortisone, fluocinolone acetonide); calcinerium inhibitors (calcinerium inhibitor, tacrolimus, pimecrolimus); Imiquimod [27-30].

Systemic therapy is usually indicated in cases that patient shows widespread or scarring disease, or in cases when patient revealed refractory to topical therapies. Thus, when systemic therapies are prescribed, topical agents become as adjunctive treatment [29]. There is no specific drug to treat CLE or OLE, usually the same drugs are used for SLE. Firstly, it is recommended the use of antimalarial drugs (hydroxychloroquine, chloroquine and quinacrine) associated to or not with systemic corticosteroids (prednisone) in activated disease. Moreover, in cases to avoid corticosteroids or in refractory cases, it is possible to prescribe immunomodulators (dapsons, thalidomide, lenalidomide) and/or oral retinoids (acitretin, isotretinoin, alitretinoin) and/or immunosuppressives (methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, mycophenolate sodium, cyclosporine). Recently, it is suggested the use of biological agents

(rituximab, belimumab) as an optional treatment for severe cases [27-30].

Conclusion

Lupus erythematosus is a very complex disease and it needs a multi-professional diagnosis and treatment. The oral mucosal manifestation of LE is a rare condition, it could be observed and diagnosed by many health professionals. Most of the time, dentist, stomatologist, dermatologist or otolaryngologist would be the first professional to note oral lesions of LE, and knowledge and depth study of OLE is needed by these professionals, thus, the sooner the disease is diagnosed, the better prognosis and quality of life can be given to the patient.

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Conflicts of Interest

None.

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