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Oral lichenoid disease as a premalignant condition: The controversies and the unknown

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Abstract

We grouped as oral lichenoid disease (OLD) a series of chronic inflammatory processes with autoimmune base that affect the epithelium of the oral mucosa. This disease is present in 2% of the population with a marked predilection for the female gender, especially perimenopausal women. Clinically, it is characterized by the presence of lineal reticular papules and histologically by liquefaction degeneration of the basal layer of the epithelium associated with an inflammatory infiltrate with a "band-like" disposition on the lamina propria, composed primarily of T lymphocyte cells. Its pathogenicity is associated with deregulation of the cellular immune system, where the activated cytotoxic CD8 and the CD4 T helper lymphocytes induce apoptosis of the epithelial cells. Classically it has been considered a precancerous condition, although the malignant transformation does not exceed 1% of the cases. In recent years the differentiation between oral lichen planus (OLP) and oral lichenoid lesions (OLL) has become important, since the latter might have a greater malignant potential. In this paper, we analyse and update some controversial aspects of this frequent oral disease in relation to the diagnosis and malignant potential.

Key words: *Oral, lichen planus, lichenoid lesions, malignant potential, histopathology.*

Introduction

Classically "oral lichen planus" (OLP) has always been considered a chronic inflammatory mucous process of autoimmune origin that affects primarily perimenopausal women (1-3). Recently, we have proposed a new nomenclature and classification for these processes that we denominate generically as "oral lichenoid disease" (OLD) (4).

The basic clinical lesion that groups these processes is the white lineal papule that reveals a reticular pattern, generally asymptomatic (Fig.1) (2,5). The most frequent sites are the buccal mucosa, tongue, gingiva and lips, with a bilateral and symmetrical pattern characteristic of typical cases (1,2). The etiology of the majority of these processes is unknown, although there is general agreement in considering it an autoimmune process in which cytotoxic CD8 T lymphocytes (CD8TL) and CD4 T lymphocytes (CD4TL) participate, accumulate and are activated by different mechanisms inducing cellular apoptosis, degeneration of the basal layer and destruction of the epithelial basal membrane (2,6-8).

There are other processes similar to OLP that do not

gather the entire typical clinicopathological requirements and are denominated as "oral lichenoid lesions" (OLL) (9). These OLL can be reactive when there is a known cause (i.e. related to an amalgam restoration), or idiopathic (4). The OLL have been the object of special interest due, apparently, to a greater risk of malignant transformation than the classic OLP (3,10-12). Without any doubt, the most important complication of the processes grouped as OLD, is its possible malignant transformation (2,12-18).

In this paper we carry out a review and update of some controversial aspects of these processes, related to etiopathogenicity, as well as the diagnosis and prognosis.

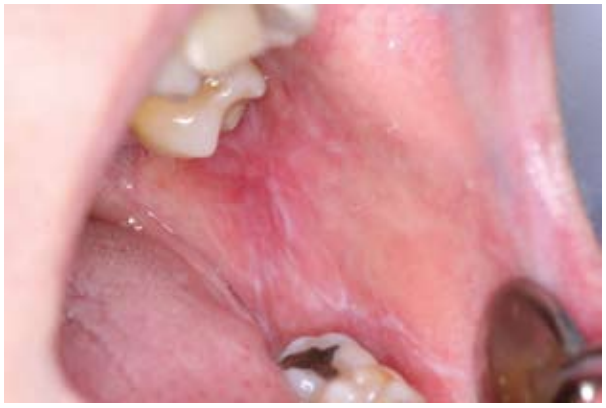

Fig. 1. White reticular papules in buccal mucosa with an erosive-ulcerative central area in a typical case of oral lichenoid disease.

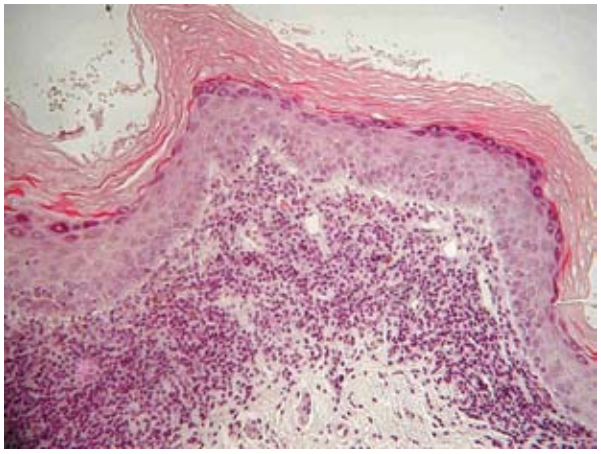

Fig. 2. Hyperorthokeratosis, granulosis, epithelial atrophy, associated with a band-like lymphocyte inflammatory infiltrate of the lamina propria, are classical histopathological data of the lichenoid disease (H&E 20x).

Etiopathogenical Aspects

Although the exact etiology of OLP is unknown in the majority of the cases, it is considered as a multifactorial process related to many factors such as genetic influence, and psychological or infectious conditions, among others. Some of these factors would act as causal agents long before others that would be precipitant of the processes (2,6,15).

Nowadays, it is considered an autoimmune disease by which the cytotoxic CD8TL are attracted and activated by one or more antigens associated to a major histocompatibility complex class I (MHC-I) expressed by keratinocytes, together with helper CD4TLs, that would be attracted and activated by the major histocompatibility complex class II (MHC-II) associated with Langerhans cells (Lc) and/or keratinocytes (6). In these cases, different cytokines (IL-2, IL-12), gamma interferon (IFN-gamma) and the tumor necrosis factor-alpha (TNF-alpha), participate being secreted by the different cellular elements involved. The TNF-alpha secreted by the cytotoxic CD8TL cause apoptosis of the keratinocytes and stimulate an over-expression of the adhesion molecules (ELAM-I, ICAM-I, VCAM-I) by the endothelial cells of the subepithelial vascular plexus that participate in the inflammatory process in an important way (2,6).

The chronic character of this inflammatory process can be explained by two ways of tissue damage (7,8). The first way would be by an antigen-specific mechanism where the basal keratinocytes and the Lc would present antigens associated with CMH-I and CMH-II. The CMH-I antigens stimulate the cytotoxic CD8TL to secrete TNF-alpha and the CMH-II antigens stimulate the CD4TL to secrete IL-2 and gamma-IFN, that would cause continuous damage to the keratinocytes (6-8). The second way would be by non-specific mechanisms that cause degranulation of the mastocytes and a posterior activation of metalloproteinases (MMP), which degrade components of the extracellular matrix and basal membrane (7,19).

It has been pointed out that more than 60% of the mastocytes of the OLP lesions are degranulated when compared with the non-affected mucosa (6,20). The degranulation of the mastocytes is an important source of chymase and tryptase, which are MMP 1, 3 and 9 activator proteases (19). Also mediators liberated by the mastocytes participate in the migration of lymphocytes through the epithelium (6).

Specifically, TNF-alpha stimulates the over-expression of some adhesion molecules (CD62E, CD54, and CD106), necessary for the adhesion of the lymphocytes to the vascular wall for its posterior extravasation (19). MMP-9, from T lymphocytes, is activated by chymase and tryptase, and cause damage to the type IV collagen and the basal membrane (6,19).

Histopathological Aspects

Classic OLP is histopathologically characterized by the presence of hyperkeratosis and/or atrophy, hydropic degeneration of the basal layer, apoptotic keratinocytes (Civatte bodies) and a "band-like" chronic inflammatory infiltrate in the lamina propria constituted primarily by T lymphocyte cells (Fig.2) (8). Nevertheless, this histological aspect is not pathognomonic for OLP as can be observed in other chronic mucocutaneous processes (11).

OLLs are hard to define entities and differentiate from OLP by revealing similar clinical and histopathological characteristics. For this reason, it is essential to make a detailed clinical examination, since histopathological diagnostic errors may be associated with the omission of clinical data (11). In 2003, Van der Meij, et al. (9) described a series of clinical and histopathological criteria typical for OLP (Table 1), to be considered as "clinically and histopathologically compatible with OLP". Following these criteria, we should denominate OLL for all those atypical clinical situations. Characteristically, OLLs are unilateral, near dental restorations or associated with drugs (3,4).

Some authors (11) point out, that it is almost impossible to differentiate between OLP and OLL only by using histopathological data. Nevertheless, there are other suggestive characteristics, such as, a deeper inflammatory infiltrate from the lamina propria to the submucosa, in some areas or in the totality of the sample, or the existence of perivascular inflammation with plasmatic cells and neutrophils, which are absent in OLP. It is important to rule out the presence of *Candida* and to avoid ulcerated areas that could lead to a misdiagnosis by inducing secondary accumulation of plasmatic cells and neutrophils (11).

In recent years, many studies based on immunohistochemistry have tried to differentiate and to predict the malignant potential of these processes, obtaining a similar expression of ki67 on OLP and OLL, and a greater expression of p53 on OLP lesions (10,21).

The lichenoid lesions that present epithelial dysplasia on the biopsies should be treated as any other oral dysplastic lesion, and should be excluded from the diagnosis of OLP or OLL, as well as for the equivocal diagnosis of "lichenoid dysplasia" (9).

Pronostical Aspects

The most important complication of all these processes is the possible malignant transformation, reason for which it has been considered a precancerous condition (2,3,21). Many series of cases have been published in relation to the malignant transformation in this controversial pathology (5,12,14,16,18,22). Although the malignant transformation rate varies widely in the literature from 0.4 to 6.5%, in most studies it does not exceed 1% (2,5,16).

In the review made by Lodi, et al. (5) that gathered studies published between 1985 and 2004, with a follow-up of 4.5 to 7.5 years, they observed a malignant transformation rate between 0 and 5.3%.

Table 1. Diagnostic criteria for oral lichen planus (OLP) and oral lichenoid lesions (OLL). Modified by (Van der Meij E, et al. J Oral Pathol Med. 2003;32:507-12).

Clinical criteria*: • Presence of bilateral symmetrical lesions. • Presence of white-grey lineal reticular papules (reticular pattern). • Erosive-ulcerative, atrophic, bullous and plaque-like lesions (accepted only in the presence of reticular papular lesions in any location of the mucosa).
Histopathological criteria †: • Presence of a well-defined "band-like" cellular infiltrate, confined to the superficial portion of the connective tissue and composed primarily of lymphocytes. • Signs of "liquefactive degeneration" of the epithelial basal cell layer. • Absence of epithelial dysplasia.
Final diagnosis: • The clinical and histopathological criteria should be included for a final diagnosis. • OLP diagnosis should include both criteria, clinical and histopathological. • LLO diagnosis should be used when: 1. Clinically typical for OLP but histologically compatible with OLP. 2. Histologically typical for OLP but clinically compatible with OLP. 3. Clinically and histopathologically compatible with OLP.

WHO, World Health Organization; OLP: Oral Lichen Planus; OLL: Oral Lichenoid Lesion

* In other lesions similar to OLP, but that do not completely fit the criteria, should be used "clinically compatible with".

† When the histopathological characteristics are less obvious, should be used "histologically compatible with".

Classically a greater risk has been described for malignant transformation of the "atypical" clinical presentation, specially the atrophic and erosive-ulcerative types (16,23). Eisen (15), found that the 6 (0.8%) patients who developed a malignant transformation had atrophic-erosive lesions. This circumstance could be related to a greater chronic inflammatory response, behaving similarly to other inflammatory diseases also associated with neoplastic malignant growth, such as inflammatory intestinal disease, chronic esophagitis or chronic colicystitis (7,24,25). Chronic inflammation would play an important role in the possible carcinogenesis of this process, causing genetic damage and inducing tissular proliferation (26). The increase of cytokines and growth factors, promote and/or facilitate oral carcinogenesis (7,25,26). Chronic inflammation produces oxidative damage of the DNA by products derived from inflammatory induced enzymes, such as nitric oxide synthase (iNOS) (27).

Another inducible inflammation enzyme is cicloxigenase-2 (COX-2) that acts inhibiting apoptosis of the keratinocytes and in so doing, facilitating carcinogenesis (28).

In recent years, the process of malignant transformation of the lichenoid lesions has been related to a possible "field cancerization" phenomena, by which all associated events would predispose these patients to a greater risk of multiple and/or multifocal neoplastic malignancies in the oral cavity (25).

One of the major problems of interpretation of malignant potential studies of this disease is the inexistence of strict diagnostic criteria to differentiate lichenoid processes (9). Some studies have included cases of OLP with OLL and vice versa. For this reason it is fundamental to establish precise clinical and histopathological diagnostic criteria to differentiate the lesions and in this way to assess the real malignant potential (4,9). A Holland group (14), studied 67 patients with OLP and 125 with OLL, using previous diagnostic criteria to differentiate them from one another, and an average follow-up of 55.9 months, finding a malignant transformation in 4 patients (2.1%), all diagnosed as OLL. Previously, this group (12) obtained similar results, having 3 patients (1.7%) with malignant transformation of the lesions, all of them diagnosed as OLL. These studies would confirm the existence of a greater risk of malignant transformation of "atypical lesions" diagnosed as OLL, which would support the need to always make a careful clinical and histopathological diagnostic separation (4).

There are no definitive and reliable criteria that would allow us to determine which patients present a greater risk of malignant transformation. For this reason, a clinical surveillance protocol would be of great importance. Therefore, Mignogna et al. (18) applied a surveillance protocol with periodic examinations every 4 months for 12 years, denominated "Neoplasia/Dysplasia" in 45 patients with OLP that had developed 117 malignant neoplastic events. With this system, they detected 94.9% of the carcinomas at the initial stage (intraepithelial or microinvasive) and obtained a 100% survival rate in a 3 year period and a 96.7% survival rate in a 5 year period, suggesting a surveillance protocol of twice a year (18). Other authors (13) do not justify the protocols based on several visits per year, since on comparing other studies with 1, 2 or 4 examinations per year in patients with malignant transformation, the number of recurrences and deaths was constant regardless of the different protocols. We conclude in this review on "oral lichenoid disease", that there is a need to study in depth the understanding of the disease and its different variants, and to establish clear diagnostic and therapeutic guidelines that would lead us to a reliable prognosis.

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