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REVIEW ARTICLE

Malignant transformation of oral lichen planus by a chronic inflammatory process. Use of topical corticosteroids to prevent this progression?

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Abstract

Background: Oral lichen planus is a potentially malignant disorder with a capacity, although low, for malignant transformation. Of all the factors related to the process of malignant transformation, it is believed that the chronic inflammatory process plays a key role in the development of oral cancer. This inflammatory process is capable of providing a microenvironment based on different inflammatory cells and molecules that affect cellular growth, proliferation and differentiation. ***Objectives:*** The objectives of our study are: to review the available evidence about the possible relationship between the chronic inflammatory process present in oral lichen planus and its malignant transformation, to discuss the potential therapeutic implications derived from this relationship and to study the role that topical corticosteroids play in the control of oral lichen planus inflammation and its possible progression to malignant transformation. ***Conclusion:*** The maintenance of a minimum dose of topical corticosteroids could prevent the inflammatory progression of oral lichen planus to oral cancer.

Key Words: *cancer-associated inflammation, inflammation, oral lichen planus, oral squamous cell carcinoma, triamcinolone acetonide*

Introduction

'What if taking aspirin could reduce the risk of developing cancer?' [1]. We have seen this question repeatedly over the past few years, due to the fact that recent studies have published that daily treatment with aspirin for 5 years or more has a protective effect against death caused by cancer [2]. We know that inflammation represents the seventh distinctive characteristic of cancer and its importance in the pathogenesis has been demonstrated by a decrease in the risk of developing cancer in adults who have taken NSAIDs over a long period of time [3]; therefore, if we administer selective anti-inflammatory drugs, we would be acting against one of the pathogenic factors of cancer, possibly preventing its progression.

The relationship between cancer and inflammation is based on specific transcription factors that, once activated, have the ability to enhance the expression of common genes in the regulation and production of inflammatory mediators and also in the regulation of the survival and proliferation of carcinogenic cells [4]. This translates into clear evidence that persistent inflammation promotes cell proliferation and can induce DNA damage; and that, in the initial stages of carcinogenesis, the inflammatory factors mediate the development of a stroma associated with the tumor. At the same time, the activated cells in this stroma promote angiogenesis, cancer growth and metastasis [4].

There are authors who consider oral lichen planus (OLP) to be a unique model of a disease to study the relationship between inflammation and cancer [5], whose hypothesis is that inflammatory mediators such as cytokines and chemokines released from T-cells induce fundamental changes in the proteins of the oral epithelial cells that drive the progression of OLP to oral squamous cell carcinoma (OSCC) [5].

Keeping all of this in mind, the objectives of our study are: to review the available evidence about the

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possible relationship between the chronic inflammatory process present in OLP and its malignant transformation, to discuss the potential therapeutic implications derived from this relationship and to study the role that topical corticosteroids play in the control of OLP inflammation and its possible progression to malignant transformation.

Malignant transformation of OLP

Lichen planus is a chronic inflammatory disease of unknown etiology that affects skin and mucous membranes. At the oral level it tends to be more common, chronic and recalcitrant than at the cutaneous level, causing widespread erosions of the oral mucosa associated with pain and discomfort, which in turn leads to significant deterioration in the patient's quality-of-life [6,7].

In spite of multiple attempts carried out in the past few years to elucidate the etiology and pathogenesis of this disease, it is not yet entirely known, and new factors that might be involved in its etiology continue to be explored, such as: genetic factors, dental materials, drugs, infectious bacterial and viral agents, autoimmunity associated with other autoimmune diseases, immunodeficiency, food allergies, stress, habits, trauma, diabetes and hypertension, malignant neoplasms and inflammatory bowel disease [8]; thus proposing various hypotheses in relation to its pathogenesis. One of them is the probable relationship with an immune reaction mediated by cells in response to an unknown antigenic shift [9]. The exact knowledge of its pathogenesis would explain many unknown factors about OLP, including its capacity for malignant transformation.

Since the first published case of a gingival cancer in a patient with OLP [10], various cases of malignant transformation have been published. Although there are opposing views, most authors agree that it is a disease with a low risk of malignant transformation [6,11–13]. First of all, it is necessary to clearly define the meaning of OLP and, in order to do that, some authors [14] have established clinical–pathological criteria that differentiate OLP from oral lichenoid lesions. Secondly, in order to be able to speak about malignant transformation of OLP and in accordance with the criteria established by Krutchkoff et al. [11], there must be a clinical and histological diagnosis of OLP, as well as a follow-up period of 2 years and the absence of carcinogenic factors. If we review the literature related to the fulfillment of these criteria, there are few cases that meet all of the criteria and these few cases do not reach the 35% mark [11,15].

OLP has always been considered to be a disease with a capacity for malignant transformation, from the first WHO classifications of pre-cancerous lesions and statuses [16], to the most recent classification of Warnakulasuriya et al. [17] in 2007, which includes OLP as a potentially malignant disorder.

The potential for malignant transformation is low, if we review the most recently published papers with a significant number of patients and if we follow Krutchkoff's criteria, it stands somewhere between 0.1–2.5% [13,18,19]. It seems that the lesions with increased risk of malignant transformation are atrophic–erosive lesions, which pre-dispose the oral mucosa to the effects of other carcinogenic agents [20,21]. Even so, it is not exclusive of atrophic-erosive OLP, as it has been described in cases of malignant transformation in plaque-like or even reticular form OLP [22,23]. Although it can affect any location of the oral mucosa, the tongue is of greater predilection [13,19].

There are various factors that have been associated with this process of malignant transformation: virus (HPV, others), chronic inflammation, immunosuppression, diet, advanced age, candida superinfection, genetic predisposition, etc. [24].

The relationship between the chronic and persistent inflammatory process present in OLP and its progression to OSCC is something that we consider to be fundamental.

Relationship between inflammation and cancer

Since 1863, when Virchow attributed the formation of tumors to chronic irritation for the first time [25], numerous studies have been developed that attempt to explain the possible association between the chronic inflammatory process and the development of different disorders that present epithelial alterations. These studies have led to the general acceptance that inflammation is a major risk factor for the development of cancer [5,26,27]. Some examples described relating to this type of association include, among others, inflammatory bowel disease and colorectal cancer, atrophic gastritis and gastric cancer, gallbladder cancer associated with chronic cholecystitis, cancer of the esophagus related to esophageal reflux [26,27] and, as has been recently published, bilateral carcinoma *in situ* Wharton's duct after chronic obstructive sialadenitis, in which the inflammation is attributed to the cause of malignant transformation [28]. However, currently, many of the aspects related to the knowledge of the molecular and cellular mechanisms that connect both processes have not yet been clarified [29] and it is thought that, by doing so, it might be able to open many doors in the field of cancer prevention and treatment.

OLP, chronic inflammation and cancer

In spite of the fact that there is great controversy in regard to this topic, there is a lot of available evidence that supports the role of the immune dysregulation in

the pathogenesis of OLP [6]. From this point of view, OLP has been described as a chronic inflammatory disorder mediated by T-cells characterized on the histopathological level by a sub-epithelial lymphocytic infiltration, disruption of the basal membrane and degeneration of keratinocytes, giving rise to the so-called Civatte bodies, parakeratosis and acanthosis [26].

In the last few years numerous works have been published that consider the hypothesis that the microenvironment, based on the cells and molecules that participate in the chronic inflammatory process present in OLP, could be responsible for the malignant transformation that this disease undergoes [5,7,25]. This inflammatory process is mainly mediated by T-lymphocytes. Many other inflammatory cells and molecules participate (macrophages, mast cells, lymphocytes, cytokines, interleukins 1 and 6, tumor necrosis factor, fibroblasts, cellular immunosuppression, chemokines RANTES) that are at the same time involved, in many cases, in the development of various malignant neoplasms [26].

Inflammatory cells

Macrophages. Macrophages are phagocytic cells that form part of the first line of defense against pathogens. Additionally, they also help other cells of the adaptive immune system, contributing to the activation of T-cells. They are capable of producing anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TNF-β), as well as collaborating in tissue regeneration after inflammatory damage through the production of matrix metalloproteinases (MMPs) and their inhibitors [30]. This wide range of functions has led to the classification of macrophages in two specific sub-types: macrophages with pro-inflammatory (M1) and anti-inflammatory (M2) activity [31].

M1 macrophages can exacerbate chronic inflammatory diseases such as OLP. M1 can help the progression of the disease through three mechanisms: initiation of the inflammation, activation and priming of T-cells and direct destruction of the basal membrane [32]. On the other hand, it is known that M1 macrophages can help to initiate the process of malignant transformation and the production of reactive oxygen and nitrogen species (superoxide and hydrogen peroxide), which, although they may have a beneficial effect in the short-term, these reactive species have mutagenic ability due to their cytotoxicity against many pathogens and in the chronic inflammatory process (as occurs in LP) they may be responsible for the progress of the disease and for the malignant transformation of epithelial cells [30].

In OSCC, the macrophages (called macrophages associated with tumors or MATs) constitute a substantial portion of the leukocyte infiltration characteristic of OSCC [30].

The phenotype of the MATs varies with the development of the disease: the M1 could collaborate at the beginning, while the M2 could help the progression of the disease in advanced stages [33].

Therefore, taking into account that macrophages clearly play a very important role in the development of inflammatory diseases and cancer of the oral cavity, they could be considered as potential therapeutic targets for these types of conditions.

Mast cells. It has been observed in several studies that there is a significant increase in the count and degranulation of the mast cells in OLP lesions [34], which confirms the importance of this cell type in the pathogenesis of this disease. During degranulation various cytokines and chemokines are released that act through different mechanisms influencing the chronicity of the disease [35]: TNF-α, that regulates the expression and extravasation of lymphocytes, as well as the secretion of RANTES and MMP-9 by damaged T-lymphocytes, which in turn secrete chemokines that attract more extravasted lymphocytes towards the epithelium; and *chymase*, a protease that damages the basal membrane directly or indirectly through the activation of MMP-9 by damaged T-cells.

On the other hand, it has been demonstrated that mast cells actively contribute to tumor growth. Coussens et al. [36] demonstrated in animal models that specific proteases are released that regulate angiogenesis in epithelial squamous cell carcinoma [36].

The mast cells could act synergistically with macrophages, perhaps contributing to the malignant transformation of OLP, giving rise to changes in the stroma through the activation of the MMPs and of the control of the cell cycle and angiogenesis through the release of TNF [26].

Lymphocytes and immune response. In OLP, the majority of T-cells present in the epithelium and adjacent to the damaged keratinocytes are activated CD8+ lymphocytes; however, on the level of the lamina propia, the majority of the lymphocytes are CD4+ or Th [6].

In general, the immune response has been divided into two major categories depending on the profile of cytokines produced by the CD4 T lymphocytes or collaborators (Th): cellular immunity (CI) and humoral immunity (HI). The CI is characterized by the production of IL-2, TNF-α and IFN-γ by the Th CD4+ lymphocytes profile (Th1), while the humoral immunity shows production of IL-4, IL-6 and IL-10 (cytokine profile Th2) [37]. All malignant tumors studied so far, related to conditions of chronic inflammation, have been associated with the suppression of the CI and predominance of HI [38]. From

this observation the hypothesis is derived that the microenvironment characterized by the chronic suppression of the CI and the predominance of the HI could play a key role in the initiation, development and tumor spread [26]. In the case of OLP it has been shown that there is a mixture of the two profiles of immunity (Th1 and Th2) in inflammatory infiltrate [39].

Cytokines

Cytokines are soluble proteins that play an important role in the initiation and maintenance of inflammation and the immune response, as well as in intercellular communication [7,40].

There is currently sufficient evidence to accept that the chronic inflammatory process *per se* is capable of providing a microenvironment, based on cytokines, capable of influencing the survival, growth, proliferation and differentiation of the cells, thus contributing to the initiation, progression, invasion and metastasis of the cancer [26].

In OLP the participation of several types of cytokines has been described and, even in recent years, several studies have shown that the serological and salivary concentrations of some types are significantly higher in the patients with OLP when compared to healthy subjects.

Interleukins 1 and 6 (IL-1, IL-6). They are promoting factors in tumor growth, invasion and metastasis. They are able to stimulate angiogenic factors such as VEGF (vascular endothelial growth factor) [27]. Additionally, it appears that both cytokines are, in turn, involved in the production of other cytokines in the inflammatory infiltrate of OLP, such as tumor necrosis factor alpha (TNF-α) [26].

Recently, a large number of oral diseases, such as oral cancer, lichen planus and periodontal disease, have been associated with the regulation of IL-6. In fact, it is thought that the individual variability in the production of IL-6 may modulate the susceptibility, development and progression of a large number of autoimmune and inflammatory diseases, as well as malignant lesions [7,41–44].

In recent years, IL-6 is gaining importance as a mediator and new therapeutic target for chronic inflammatory diseases and cancer [7]. Several studies have demonstrated that patients with OLP have elevated levels of IL-6 in saliva and serum, in comparison with healthy controls, especially in the ulcerative forms [45,46]. The same thing happens in patients with oral cancer and with other tumors of the head and neck, in comparison with controls, thus allowing us to observe elevated levels of IL-6 in saliva and serum in the first group of patients [47]. Additionally, from a research point of view, it has been suggested that the determination of the serological and salivary concentrations of IL-6 could be particularly useful in the monitoring of disease activity and response to therapy, associating the reduction of these levels after receiving treatment with a significant improvement in symptoms [48,49]. Thus, the serological levels of IL-6 in patients with OLP who had received treatment [49] are reduced during the period of remission of the disease, but are elevated again in periods of its exacerbation.

IL-6 contributes to the pathogenesis of oral cancer through different mechanisms and biological processes [7]. The chronic inflammation alters the DNA methylation and the expression of the genes associated with OSCC. The capacity of IL-6 to induce hypomethylation has been demonstrated *in vitro*. Thus, Gasche et al. [50] suggest that IL-6 promotes carcinogenesis by altering DNA methylation in the oral cancer cells.

OLP treatment

Although there are no randomized controlled clinical trials that compared steroids with placebo in patients with symptomatic OLP [51], topical corticosteroids (TC) constitute the first line of treatment of atrophic–erosive OLP because of its anti-inflammatory and immunosuppressive action [52]. The main goal of treatment with TC in oral pathology is to ensure that the symptoms of the disease disappear, so that patients can regain the ability to eat, talk and carry out proper oral hygiene. The exclusively reticular and/or plaque-like forms only require adequate information and periodic revision.

Corticosteroids administered at therapeutic doses present a powerful anti-inflammatory and immunosuppressive action:

- They decrease the number of surrounding lymphocytes, monocytes, eosinophils and basophils (migration);
- They increase the number of neutrophils (loss of capacity of migration);
- They decrease the synthesis of collagen (the proliferation of fibroblasts is inhibited);
- The production of interleukins is inhibited (the function of leukocytes and macrophages is inhibited);
- The activity of phospholipase A and, therefore, the production of prostaglandins, leukotrienes and other derivatives of arachidonic acid with powerful chemotactic and pro-inflammatory activity is inhibited; and
- The expression of cyclooxygenase is reduced and, therefore, the capacity for production of prostaglandins in response to inflammatory stimuli is reduced.

Several studies support the use of TC as compared to systemic corticosteroids in the oral lesions of the LP, as it clearly decreases the emergence of the possible side-effects; and additionally the therapeutic effect is even better. Carbone et al. [53] observe that 69.6% of the OLP patients with TC treatment improve, compared to 68.2% of patients with systemic corticosteroids treatment.

We consider the best choice to be the topical use of an aqueous solution of triamcinolone acetonide between 0.3–0.5%, starting 3-times a day for 1 month, and decreasing the dose as the symptoms continue to improve and functional capacity is regained. It has been proved that the triamcinolone acetonide in a rinse is an appropriate treatment in erosive OLP because of its high efficiency and low risk of fungal superinfection [54].

The treatment of OLP with different TC significantly decreases the levels of various pro-inflammatory cytokines involved in the development of the OSCC such as TNF-α, IL-1-α, IL-6 and IL-8 [48]. Thongprasom et al. [51] demonstrated in 18 patients with ulcerative and erosive forms of OLP that, after 4 weeks of topical treatment with fluocinoloneacetonide at 0.1% in orabase, the number of positive mononuclear cells for TNF-α before treatment was significantly higher than after having received treatment and in comparison with the normal oral mucosa. Rhodus et al. [48], in a study conducted in 13 patients with erosive OLP, demonstrated that after 6 weeks of treatment with dexamethasone 0.1% rinses, the salivary levels of TNF-α, IL-1-α, IL-6 and IL-8 significantly decreased, even the levels of IL-1-α and IL-8 were not significantly different from those detected in the control patients. Additionally, the patients experienced an improvement in the symptoms in positive correlation with the decline in the levels of IL-1-α and IL-8.

Eisen [55] suggests that, taking into account that the microenvironment based in cytokines associated with OLP can promote tumor progression, by eliminating the inflammatory response through treatment, the restoration of the normal immune response is achieved and the progression of the cancer is interrupted.

It is considered that, in the case of diseases that are accompanied by very chronic or recurrent erosive lesions (as in some cases of OLP or pemphigoid), the correct treatment pattern is based on the use of TC for a prolonged course of unpredictable duration [56]. Some authors suggest that it would be prudent to maintain the treatment at least a few days per week to prevent recurrence [57], even for 1 year after the remission of the lesions, performing a follow-up every 6 months [56]. Keeping all of this in mind, we might consider that the maintenance with a minimum dose of TC could inhibit the chronic inflammatory processes present in OLP and, in this way, avoid the malignant progression of the disease; and that the cessation of the treatment could promote the inflammatory progression and the development of an OSCC. We know that the topical corticosteroid therapy involves local side-effects such as candidiasis, burning mouth syndrome, hypogeusia, hairy leukoplakia and drug hypersensitivity; and for systemic therapy such side-effects include: facial edema (moon face), hirsutism, capillary fragility, diabetes, hypertension, hormonal deregulation [56,58]. All of these possible side-effects will have to be monitored and corrected when they appear.

The possible effect of treatment with immunosuppressive agents in the malignant transformation of OLP is not yet clear and there is currently a lot of controversy. The immunosuppressive agents affect the severity and progression of OLP. Some authors believe that they might trigger the malignant transformation [6], decrease the anti-tumor activity of the patient and increase the risk of oral cancer [59].

The transforming growth factor beta 1 (TGF-β1) has been identified in the sub-epithelial lymphocytic infiltrate of OLP. The level of TGF-β1 is crucial in the pathogenesis and evolution of OLP: low levels of TGF-β1 can promote increased immune responses, and high levels of TGF-β1 seem to suppress the anti-tumor immune response and, therefore, promote carcinogenesis [59].

The integrated signal of tumor inhibitors (TGF-β1, TNF-α, IFN-α, IL-12) and promoters (MIF, MMP-9, TGF- β1 of the keratinocytes) can sensitize oral keratinocytes against oral mutagens and regulate tumor growth and metastasis in OLP [59]. It has been observed that the atrophic and erosive forms are those that are associated with an increased risk of oral cancer, this is interesting since they are the ones that normally receive immunosuppressive therapy [59].

Unfortunately, we have little information about the long-term effects of the treatment of OLP in relation to its potential of malignant transformation [6] and there is no general consensus between the different research contributions. On the one hand, it has been observed that therapies that induce immunosuppression appear to be beneficial for OLP, but they can decrease the patient's anti-tumor response and increase the risk of oral cancer [59,60].

However, in a recent study in which a follow-up of a cohort of 402 patients with OLP was carried out, for the majority treated with topical and/or systemic steroids, it was observed that the treatment did not influence the risk of malignant transformation [61]. Bombeccari et al. [18], in a longitudinal study, also found no relationship between the possible influence of immunosuppressive therapy and cancer.

What is clear is that patients with OLP must be meticulously controlled over time to allow for the early detection of a possible malignant transformation [62] and the most important indicator of transformation is the change in the aspect of the lesion, not the

symptoms themselves. Thus, when changes occur in the lesions, the period between revisions should be reduced and a biopsy should be performed [63].

If during one of these biopsies an epithelial dysplasia were to appear, although the epithelial dysplasia is not considered a typical diagnostic criterion of OLP [14], we suggest surgically removing the 'area of dysplasia' and continuing with and/or increasing the dosage of topical corticosteroids, basing this suggestion primarily on its local anti-inflammatory effects.

In the field of cancer, Balkwill and Mantovani [27] confirm that, in terms of the inflammatory reactions, the neoplastic disorders constitute a real paradox, since, on the one hand, it has been observed that the tumors produce inflammatory cytokines and chemokines and there is a leukocyte infiltrate; however, on the other hand, the neoplastic disorders have been associated with a faulty capacity to trigger inflammatory reactions in different places at the location of the tumor and it has been observed that circulating monocytes of patients with cancer are defective in their ability to respond to chemotactic stimuli [64]. Several factors caused by the tumor microenvironment could contribute to the 'systemic anti-inflammation' associated with cancer. For example, the chemokines released into the systemic circulation could desensitize the circulating leukocytes [65] and even the tumors can produce anti-inflammatory cytokines.

Mignogna et al. [26] concluded that, since the crucial role played by inflammation in tumor development is clear, there is a need for more studies channeled mainly in two directions: on the one hand, research to try to find the underlying mechanisms in the development of malignant neoplasms and, on the other hand, studies focused on the investigation of the molecular aberrations, since it is very likely that the carcinomas associated with OLP will develop through a molecular path that is different from sporadic OSCC.

The pathogenesis of cancer is clearly associated with genetic alterations. OSCC has been shown to occur via a multistep process driven by the accumulation of carcinogen-induced genetic changes [66]. It has even been postulated that there are two different types of OSCC, OSCC-L associated with high-stage cancer and OSCC-S associated with low-stage cancer, which arise from different types of dysplasia via different genetic pathways [67].

As conclusions of this work, we could say that:

- Lichen planus is a chronic inflammatory disease with a risk, although low, that is clinically significant of malignant transformation.
- Chronic inflammation is a risk factor for the development of cancer, because it promotes cell proliferation and angiogenesis and it inhibits apoptosis.
- The treatment with topical corticosteroids has an anti-inflammatory and immunosuppressive effect. The maintenance of this therapy may inhibit the chronic inflammatory processes present in OLP and in this way prevent the progression to malignant transformation.
- Patients with OLP must be meticulously controlled over time in order to allow for the early detection of a possible malignancy.

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