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REVIEW ARTICLE

Malignant potential and associated risk factors of oral lichen planus

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Abstract:

Introduction: Oral Lichen Planus (OLP) is a chronic, immune-mediated inflammatory disease of uncertain pathogenesis, which affects about 0.5-2% of the world population, being more frequent in middle-aged women. The clinical presentations are reticular, erosive, atrophic, bullous, papular, and plaque-like forms. Its malignant potential, and its risk factors, are topics of clinical importance, although controversial. **Aim:** To perform a literature review about the malignant potential of OLP and the main risk factors involved. **Material and Method:** The Scielo and Pubmed databases were used for search the articles, using the combinations "oral lichen planus AND malignancy" and "oral lichen planus AND malignant neoplasm" were selected 19 articles published in English and Spanish, over the last ten years, in addition to classic papers. **Results and Discussion:** Studies report that the malignant potential of OLP is low (around 1.12%), although it is still uncertain, due to the lack of consistent diagnostic criteria. However, there is a suggestion that the malignant potential occurs when OLP shows as the erosive form or when it is on the tongue. An association between tobacco and alcohol consumption and the Hepatitis C virus is a topic that still needs to be clarified. Also, studies suggest that the release of inflammatory cytokines from chronic inflammation may contribute to this process. **Final Considerations:** Although questionable, the potential for malignant transformation of OLP, as well as its risk factors, should be further studied. Therefore, it is necessary to standardize the diagnostic criteria and documentation. Also, more longitudinal studies are essential to elucidate the role of different carcinogens in the pathogenesis and malignant potential of OLP.

Keywords: Oral Lichen Planus; Carcinoma, Squamous Cell, Neoplasms; Risk factors

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INTRODUCTION

Oral Lichen Planus (OLP) is a chronic, immune-mediated inflammatory mucocutaneous disease that is characterized by a T-cell-mediated response against epithelial basal cells, resulting in subepithelial band infiltration and degeneration of basal cells[1]. It affects about 0.5 to 2% of the general population, and the most frequently affected are women from the fourth or fifth decades of life[2-5]. According to Giuliani et al, although OLP still has an unknown etiology, it has been argued that its etiopathogenesis is due to some causes, the main ones being psychological stress, cell-mediated hypersensitivity, and the individual's immune response[5]. Several anatomical sites can be affected, the buccal mucosa is the most common site, followed by the tongue, lips, and gingival mucosa. Clinically, OLP may present in reticular, erosive, atrophic, bullous, papular, and plaque-like forms, and the reticular variant is the most common, and in general, asymptomatic [2]. Unlike erosive and atrophic forms, which usually cause discomfort and painful symptoms[6].

The diagnosis of Oral Lichen Planus is usually made by assessing the clinical and histopathological aspects so that it is possible to differentiate it from other similar pathologies. Bilateral classic lesions that present a reticular pattern are often diagnosed based on their clinical aspects[7]. However, they can be easily confused with so-called Oral Liquenoid Lesions (OLL), which are associated with local factors, which trigger the inflammatory response[8]. Besides, some diseases with clinical and histopathological characteristics similar to OLP may confuse the diagnosis, such as lupus erythematosus, leukoplakia, and graft versus host disease. The clinical presentation of erosive and atrophic may also be confused with other diseases, such as pemphigus, pemphigoid, herpetiform dermatitis, among others, requiring mandatory histopathological analysis[7].

Regarding the treatment, as the cause of OLP is still not known, there is no specific and efficient protocol. For this reason, the treatment intends to relieve symptoms and minimize their impacts. Therefore, the dimension of the lesion and the severity of the symptoms should be regarded, enabling individualized treatment. Some lesions do not require treatment, such as the reticular pattern, which is asymptomatic. Atrophic lesions, on the other hand, may leave sequels and may not respond quickly to treatment. Erosive lesions are usually treated with systemic corticosteroids to reduce inflammation and severe pain. Adequate oral hygiene is also necessary to avoid the evolution of the inflammatory process[9].

One of the most worrying complications that can arise from an OLP lesion, depending on its evolution and prognosis, is the development of Squamous Cell Carcinoma (SCC). In 1978, the pathology was considered a Potentially Malignant Disorder, according to WHO [10], after the first report of SCC from a case of OLP in 1910. Since then, studies have been written to clarify its malignancy rate and possible risk factors[11].

In 1978, WHO proposed clinical and histopathological diagnostic criterion for the recognition of OLP, to standardize the established criteria, enabling the production of more uniform and comparable studies[12], as well as assess its potential for malignant transformation[10]. However, Van Der Meij and Van der Waal highlighted the need for diagnostic criteria that would allow the differentiation between the OLL and OLP and suggested modifications in such criteria, to make them more rigorous[13]. They also highlighted the importance of histopathological examination at the time of diagnosis since the use of only clinical criteria could give false-positive results, mainly for lesions that resemble OLP and bring with it a malignant potential[5]. The WHO recommended the creation of new diagnostic criteria to differentiate OLP from OLL in 2005. However, must be considered the risk of malignant transformation in both until the stabilization of the criteria[14].

The malignancy rate of Oral Lichen Planus has been the subject of several studies. It is still quite controversial in literature since the value usually varies once it depends on the studied population and the used diagnostic criteria. Using another criterion may confuse the comparison between the studies. Therefore, it can be considered biases methodological[15], as well as the adequate documentation of this information[5]. Differences in initial diagnosis, follow-up, and information regarding exposure to different oral carcinogens are also factors that end up making studying the malignant transformation of OLP difficult[16]. Among the analyzed studies, the rate of malignant transformation varied from 0.44% to 2.15%[1-5,10,12,17-25].

The real reason for the malignant transformation of OLP, as the risk factors involved in this malignancy, are still inconsistent in the literature. However, it is supposed that chronic inflammatory processes, such as OLP, would be capable to create a microenvironment based on cytokines that may influence cell survival, altering its growth and differentiation, to promote the initiation, promotion, and progression of a neoplasm[17-20]. Most studies indicate that the clinical form of OLP that suffered the malignant transformation was erosive[3,5,

[10,12,17-20]. Also, some studies indicate that lesion on the tongue could turn into an oral carcinoma more quickly [3,5,10,12,17,20,22]. They also mention the possibility of some association with seropositivity for the Hepatitis C virus, smoking, and alcohol consumption. However, it is still something that needs to be further clarified[1,2,4,5,10,19,22].

Some patients with OLP develop SCC, so that regular monitoring of these patients is so important[1]. There is no consensus in the literature about the number of visits to the dentist. However, two visits per year may be adequate and efficient to detect cancer in the early stages[11] since the early treatment offers satisfactory results[4]. Therefore, this article aims to review the information found in the literature to elucidate the malignant potential of the Oral Lichen Plan. Also, the risk factors that may be involved in this malignancy. Thus, to enable the monitoring and adequate therapeutic plan as well as facilitate future studies.

MATERIAL AND METHODS

It is an integrative literature review, which is a method that allows synthesizing information obtained from a theme or question in a systematic, comprehensive, and orderly way, providing more extensive information on a subject/problem. The papers were found on the electronic databases National Library of Medicine (Pubmed), Scientific Electronic Library Online (Scielo), and Science Direct. The search descriptors in English were combined with Boolean operators, resulting in: "oral lichen planus AND malignancy" and "oral lichen planus AND malignant neoplasm".

The papers published between 2010 and 2020 were chosen if available for reading in full in English and Spanish. Also, classic relevant studies to the theme were selected. Studies that indicate the average rate of malignant transformation of Oral Lichen Planus and suggest the risk factors were also selected. High-level scientific evidence studies were preferred, such as systematic reviews - with and without meta-analysis - and cohort studies, which study individuals with a confirmed diagnosis of OLP based on WHO criteria, and subsequent development of SCC. Cases reports, thesis, and dissertations were excluded from the study. Also, studies that do not distinguish between Lichenoid Reactions/Lesions and Oral Lichen Planus lesions were not selected.

The selection of studies was in two stages: stage I, from the reading of the title and summary, which agreed with the inclusion criteria, and stage II, reading the articles in full, discarding those that did not agree with the eligibility criteria. The methodological design of the research is in a flowchart, in annex 1. The data were tabulated in an Excel sheet and ordered by title, authors, type of study, mean rate of malignant transformation (%), and risk factors.

RESULTS AND DISCUSSION

To the study, have been selected 71 articles. After complete the reading and application of the respective eligibility criteria, 19 were selected. From them, it was possible to observe that the malignant potential of OLP and the possible risk factors involved are themes that have been widely discussed in the literature. Both still are inconsistent and controversial due to the variation of studies and lack of standardization criteria used to diagnose the pathology. To clarify the topics related to OLP, such as the malignant potential and the risk factors involved in malignancy, retrospectives and prospective longitudinal studies have been performed. Table 1 shows the results of these studies.

It is suggested to use the diagnostic criteria modified by WHO and proposed by Van der Meij and Van der Waal, to obtain reliable and reproducible data[13]. The clinical criteria require reticulated, lacy, gray-white linear lesions, called Wickham striae, which is typically bilateral, relatively symmetrical, with histopathological signs of degeneration by liquefaction of basal layer, absence of epithelial dysplasia, as well as lymphocytic infiltrate confined to the superficial chorion. Lesions that do not correspond with the above criteria are Oral Lichenoid Lesions (OLLs)[11]. Standardizing the use of these criteria allows not only to reduce the diagnostic heterogeneity present in studies that study the malignancy of OLP but also the confusion that permeates the subject[13].

The present study has an average rate of malignant transformation of 1.12%, corroborating with most of the authors, who have a similar average rate[1,4,5,12,14,21,22]. According to Gonzalez-Moles et al (2019), the application of restrictive diagnostic criteria for OLP may be responsible for underestimating its true malignancy. It would be inducing authors to consider OLP and OLL lesions as potentially low-risk malignant disorders, lead to inadequate surveillance and delay in the diagnosis of oral carcinomas resulting from these lesions[14]. On the other hand, for Giuliani et al. (2019), future studies must follow the modified WHO diagnostic criteria, so that it is possible to reach a correct diagnosis. Cases of dysplasia and/or carcinomas diagnosed simultaneously

Table 1. Results found in longitudinal studies included in the research.

	QUANTITY OF LPO CASES	CLINICAL SUBTIPES	DIAGNOSIS	MALIGNI ZATION RATE (%)	RISK FACTORS*
Van der Meij EH, Van der Waal I. (2003)	62 patients	-	Clinical and histopathological (Following WHO criteria)	1,70%	Atrophic, erosive and ulcerative lesions; Candida Albicans infection
Torrente-Castells E, Figueiredo R, Berini--Aytés L, Gay-Escoda C. (2010)	65 patients	66% white lichen (n=43); 34% Red lichen (n=22).	Clinical and histopathological (Following WHO criteria, modified by Van der Meij et al.)	1,50%	Smoking
Shen ZY, Liu W, Feng JQ, Zhou HW, Zhou ZT. (2011)	518 patients	White lichen 52.3% (n=271) - reticular, papular or plaque-like lesions; Red lichen 47.7% (n=247) -atrophic, erosive or bullous lesions	Clinical and histopathological (Following WHO criteria)	0,96%	Erosive lesions; Use of topical and systemic corticosteroids
Bombeccari GP, Guzzi G, Tettamanti M, Giannì AB, Baj A, Pallotti F, et al. (2011)	327 patients	-	Clinical and histopathological (Following WHO criteria, modified by Van der Meij et al.)	2,45%	Erosive and atrophic OLP; tongue injuries
Bardellini E, Amadori F, Flocchini P, Bonadeo S, Majorana A. (2012)	204 patients	Reticular lichen 46.56% (n=95); Lichen on plate 23,03% (n=47); Atrophic lichen 16,17% (n=33); Erosive lichen 10,29% (n=21); Papular lichen2,94% (n=6); Bullous lichen 0,98% (n=2)	Clinical and histopathological (Following WHO criteria)	0,98%	Red forms of OLP (erosive, atrophic and ulcerative) and patients with Hepatitis C
Budimir V, Richter I, Andabak-Rogulj A, Vučićević- Boras V, Budimir J, Brailo V. (2014)	414 patients	Reticular lichen 64,8% (n=365; Erosive lichen 22,9% (n=129); Lichen on plate 5,7% (n=32); Atrophic / erythematous lichen 4,3% (n=24) and Papular lichen 2,3% (n=13)	Clinical and histopathological (Following WHO criteria)	0,70%	Erosive and atrophic OLP
Tomaz A, Jacomacci WP, Quinto JHS, Veltrini VC, Iwaki LCV, Tolentino ES. (2015)	85 patients	Reticular lichen 76,5% (n=65); Erosive lichen 14,1% (n=12); Reticular lichen and erosive associated 7% (n=6); Papular Lichen 1,2% (n=1); Bullous lichen 1,2% (n=1)	Clinical and histopathological (Following WHO criteria)	0,85%	Smoking, erosive OLP, cytokines resulting from chronic inflammation and old age

* Risk factors that influence the malignant transformation of OLP.

with OLP should be excluded, assess the true rate of malignant transformation of OLP[5]. Furthermore, Idrees et al. (2020) emphasize that the diagnosis of OLP must be performed based on clinical and histopathological criteria, since many studies have ignored the importance of microscopic confirmation, to result in high rates of incorrect diagnoses, contributing to the controversy surrounding the malignant transformation of OLP[10].

Van der Meij, et al. (2003), in their study, states that the erosive clinical presentation was present in all

cases of SCC from lesions of OLP[13]. It is believed that atrophic and erosive clinical presentation tend to predispose the mucosa to damage caused by carcinogenic agents, for this reason, malignant transformations are more likely to occur in these types[3,5,10,12,14,17,18,19]. The tongue stands out as the anatomical site most commonly involved in malignant transformations[3,5,10,12,14,17,22]. The relationship between smoking and alcohol with the malignancy of OLP is highly debatable. There are debates in the literature that raise the question of whether smoking can cause SCC independently or whether it interacts with OLP to increase its malignant potential[1]. It is known that tobacco may influence the malignant transformation of OLP by increasing the density of microvessels[26]. On the other hand, alcohol promotes an increase in the permeability of the oral mucosa and consequent epithelial atrophy, which helps the entry of carcinogens[27]. Both can still act synergistically, improving their harmful effect[14].

Several authors state that there is no association between smoking and alcohol consumption and malignant development of OLP since none of the patients in their studies had such habits[2,13,17]. However, Aghbari et al. (2017) reported a positive correlation between smoking and malignant transformation. But, he says that future studies are necessary for a more careful assessment of cases[1]. Some authors mentioned Hepatitis C virus (HCV) seropositivity but it is still controversial. Scientific evidence reports that HCV infection is likely to induce a specific direct immune response to infected epithelial cells[5], behaving as a potentiating factor for malignant transformation. However, it still needs to be better elucidated, as some authors claim to have an association[1,14], while others deny its association[3,5,10].

Candida Albicans infection is also a factor mentioned by some authors[5,13,22]. Although it is still unclear, it is supposed that Candida may colonize and penetrate the epithelium deeply, catalyzing the formation of carcinogens and generating chronic inflammation, and may also act synergistically with other risk factors[28]. Furthermore, chronic stimulation from inflammatory and stromal cells in the OLP may provide signals that promote disorganized growth control of epithelial cells. Also, added to oxidative stress, generated by oxidative and nitrative products, it may cause damage to cellular DNA, resulting in neoplastic changes[29]. Immunosuppression, although questionable, is also a factor considered in the literature. As OLP is an immune-mediated disease, the management of patients is most often through immunosuppressive therapy[5]. However, it depresses immune-mediated by local cells and promotes the progression of malignant development. It would reduce the symptoms and increases the chance of advance before the diagnosis and treatment. As a result, it would be hiding the disease's existence[13].

This study had some limitations, such as the limited availability of prospective studies, which enable a more consistent and comprehensible evaluation of the pathology and the risk factors. Also, the controversy in both the value of the malignant transformation rates of OLP and in the risk factors involved in its malignancy makes it hard to understand the results.

FINAL CONSIDERATIONS

Although the malignant transformation of OLP is still controversial, we believe that it is a low probability event, however, the risk must be considered. Therefore, it is essential to apply appropriate, rigorous, and careful monitoring strategies with all affected patients to detect suggestive changes of malignant development as early as possible[17,21]. The follow-up interval varies from two months to a year[17,20]. If erosive changes are present in the lesions during follow-up visits, it should reduce the period of visits, and additional biopsies are mandatory[17]. Also, it is appropriate to standardize the diagnostic criteria and adequate documentation of clinical and histopathological information. As a result, it would be possible to carry out new longitudinal long-term studies, such as prospective[2,4,5,10,17,24], enabling to clarify the actual malignancy rate of OLP, which patients are at potential risk of malignant development, as well as to investigate the true influence of carcinogens in this malignant transformation.

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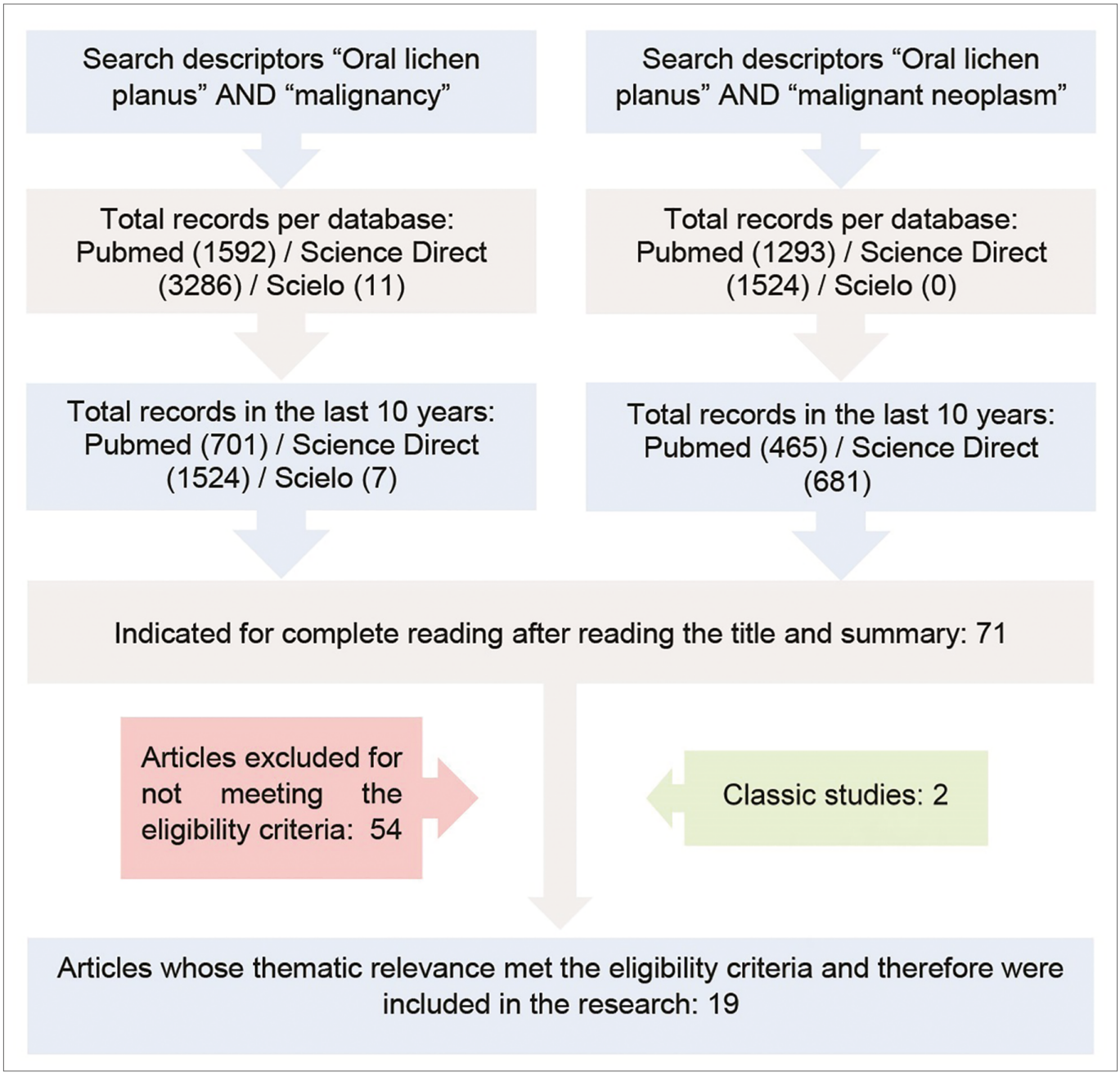

Annex 1. Flowchart methodological design of the research.