PROLIFERATIVE VERRUCOUS LEUKOPLAKIA: LITERATURE REVIEW WITH EMPHASIS ON DIAGNOSIS, MANAGEMENT AND TREATMENT.

LEUCOPLASIA VERRUCOSA PROLIFERATIVA: REVISÃO DA LITERATURA COM ÊNFASE NO DIAGNÓSTICO, MANEJO E TRATAMENTO

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Resumo

As Desordens Potencialmente Malignas Orais (DPMO) descrevem um grupo de doenças com risco aumentado de desenvolver o Carcinoma Espinocelular (CEC), e a mais comum é a Leucoplasia Oral (LO), que apresenta uma variante agressiva denominada Leucoplasia Verrucosa Proliferativa (LVP). Descrita pela primeira vez em 1985 por Hansen et al., a LVP é considerada uma forma multifocal incomum da doença, com curso clínico agressivo e implacável para malignidade, sem associação com os fatores de risco tradicionais da LO. O diagnóstico e manejo dessa variante é um desafio, pois, além da ausência de biomarcadores comprovados que possam predizer seu curso evolutivo, a subjetividade existente na sua avaliação clínica e histopatológica, faz com que a presença ou grau de Displasia Epitelial Oral (DEO) não consiga determinar se haverá ou não transformação maligna da lesão. O objetivo desse trabalho foi realizar uma Revisão da Literatura Tradicional, focando especificamente nos aspectos sobre diagnóstico, transformação maligna, manejo e tratamento da LVP, variante agressiva da LO. Concluímos que, ainda hoje, não existem biomarcadores que possam predizer o avanço das LO, tornando-se obrigatório o acompanhamento e/ou tratamento de toda e qualquer LO, inclusive os casos de Queratose de significado incerto.

Palavras-chave: Leucoplasia oral. Câncer bucal. Carcinoma Espinocelular. Líquen Plano Bucal. Eritroplasia.

Abstract

Oral Potentially Malignant Disorders (OPMDs) describe a group of diseases at increased risk of leading to Squamous Cell Carcinoma (SCC). The most common is Oral Leukoplakia (OL), which presents itself through an aggressive variant known as Proliferative Verrucous Leukoplakia (PVL). First described in 1985 by Hansen et al., PVL is considered an uncommon multifocal form of the disease, with an aggressive and relentless clinical course towards malignancy, and lacks association with traditional OL risk factors. The diagnosis and management of this disease form posits a significant challenge since, in addition to the absence of proven biomarkers that can predict its evolutionary course, the subjectivity existing in its clinical and histopathological evaluation means that the presence or degree of Oral Epithelial Dysplasia (OED) is not enough to determine whether or not the lesion will undergo a malignant transformation. The objective of this work was to carry out a Traditional Literature Review focused specifically on aspects of diagnosis, malignant transformation, management and treatment of PVL, an aggressive variant of OL. Our conclusion is that, to this day, there are no biomarkers able to predict the progress of OL, making it necessary to monitor and/or treat all OL cases, including cases of Keratosis of unknown significance.

Keywords: *Oral leukoplakia. Oral cancer. Squamous cell carcinoma. Oral lichen planus. Erythroplasia.*

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INTRODUCTION

In 2018, oral and labial cancers had a worldwide incidence in excess of 350,000 new cases, causing approximately 177,000 deaths (1), among which 90-95% (2-5) were associated with Squamous Cell Carcinoma (SCC). Because its initial symptoms are vague and it provides for minimal physical findings (2), SCC is often diagnosed during advanced stages of the disease, leading to a very low average 5-year survival rate of approximately 50%. It is considered a lethal and deforming disease due to its capacity for tissue invasion, orofacial destruction and the production of distant metastases (2,3,6). However, it is well established that an important portion of oral cancers are preceded by tissue changes that can be observed during an oral clinical examination and diagnosed through histopathological examination (2,4,6,7). Described as Oral Potentially Malignant Disorders (OPMDs), such epithelial changes have varying potentials to progress into malignancy, making it difficult to predict their evolutionary course (2,5,8,9). OL is the most common form of OPMD (5,10-12). Among its clinical phenotypes, it presents a particularly aggressive variant known as Proliferative Verrucous Leukoplakia (PVL) (13). Currently, there is a need for greater precision in the diagnosis and management of both OL and PVL. This advancement, however, is limited by excessive subjectivity in the clinical and histopathological assessment of cases (14). This is because there are no proven biomarkers able to predict the lesion's evolution (9,15,16), while the presence or degree of Oral Epithelial Dysplasia (OED) are not enough to determine whether malignant transformation will occur (14).

The objective of this work was to conduct a literature review on the most recent criteria for the diagnosis of PVL, including information on its capacity for malignant transformation as well as the suggested protocols for its management and treatment. To this end, a Traditional Literature Review of the State of the Art type was carried out in order to gather the most current and relevant information on this pathology by means of a bibliographic survey in the Medline, Lilacs, SciELO and Google Scholar databases. This initial survey was supplemented by the analysis of information available on websites of national and international organizations that research the topic.

LITERATURE REVIEW

In 1967, the World Health Organization (WHO) created a collaborating center for the study of neoplasms, which aimed to characterize and define oral lesions that should be considered premalignant and determine their relative risk of becoming malignant (17). Since then, the study and interpretation of these injuries has evolved significantly. In 2017, the WHO defined them as OPMDs, "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa" (18). Malignant Transformation (MT) occurs through various histopathological stages (19). As such, the transition from the normal mucosa to the premalignant, dysplastic and malignant mucosa is a complex interaction between the environment and the host, which may include genetic aspects, immune system function, and exposure to carcinogens (4,20). Currently, researchers posit that the development of cancer is driven by the accumulation of genetic and epigenetic changes in a clonal population of cells, so that these genotypic changes are liable to affect hundreds of genes, causing phenotypic and cellular-function changes – such as resistance to cell death, increased cell proliferation, induction of angiogenesis, as well as the development of invasive and metastasizing abilities (6,7,20-22). However, these changes may evolve into progression, elimination, persistence or regression, making it extremely difficult to predict their clinical evolution (22).

OPMDs are relatively common, with a worldwide prevalence ranging between 0.9 and 5% (5,19,23). The majority present clinically as white, red or reddish-white lesions (9,18). Their MT rates – depending on the study design and the characteristics of the population – vary between 0.13% to 50% of cases (9,10). Despite prevalence-rate variations according to the studied population, OL is still the most common OPMD described in the literature. (5,10-12).

As a clinical term, Leukoplakia describes a "white plaque or spot which cannot be diag-

nosed clinically and histologically like any other disease, but which carries an increased risk of MT." In that sense, its diagnosis is carried out by excluding other conditions with similar clinical presentation, in addition to mandatorily requiring a a biopsy for risk status assessment (4,12,17,18,22,24). Although most authors regard this definition as insufficient, it remains the most accepted worldwide (9).

OLs are divided into two broad types and their subtypes, depending on texture, thickness, color and regularity. The first type is the homogeneous (thin and thick) OL, and the second is the non-homogeneous OL (in the form of erythroleukoplakia, verrucous, ulcerated or nodular lesions), which presents a higher risk of MT (4,12,20,25). Its prevalence ranges between 1% and 6.2% of the population, with MT rates between 0.13 and 36.4% of cases (10,20,22,23,26,27). Histopathologically, it is characterized by hyperkeratosis of the stratified squamous epithelium, of the ortho or parakeratotic type, with or without acanthosis and/or epithelial dysplasia (4,11). However, since there are no pathognomonic microscopic characteristics, in order to arrive at a final diagnosis it is necessary to associate clinical characteristics with histopathological changes (4,10). Thus, researchers posit that leukoplakia evolves from hyperkeratosis or hyperplasia into varying degrees of epithelial dysplasia, which may finally develop into a Carcinoma in situ (CIS), Verrucous Carcinoma (VC) or SCC (19,28).

A. Diagnosis

The diagnosis and assessment of OPMDs' MT risk are based on clinical evaluation accompanied by histopathological confirmation of epithelial changes (5,9). In addition to ruling out other clinical entities, this also enables the assessment of the presence and extent of morphological changes – cell atypia, loss of maturation and normal stratification of the epithelium – which define the OED condition (3,9,17,20,23). Currently, the most accepted OED classification system is the WHO's. The latter is based on criteria that describe architectural and cytological alterations in the diseased epithelium, according to three degrees: mild, moderate and severe. Mild dysplasia exhibits changes in the epithelium affecting its lower third (basal and parabasal layers), while moderate dysplasia also affects the middle third, and intense dysplasia reaches the upper third of the epithelium (18). The term carcinoma in situ, meanwhile, is equivalent to severe dysplasia, in which changes affect the entire thickness of the epithelium, with the underlying connective tissue remaining uninvaded (18). The presence of OED is considered the main factor in the assessment of the OPMD's malignancy potential (3,9,19,23), and this risk increases as the degree of epithelial dysplasia progresses (9,23). The general rate of OED MT ranges between 4.8 and 6% in mild dysplasias, 15.7 and 18% in moderate dysplasias, and 26.7 and 39% in severe dysplasias (8,18). Although the presence of OED indicates that a lesion is at an increased risk of malignant transformation, this cannot be regarded as a predictor of malignant changes (27,29), since such epithelial characteristics are not necessarily a reflection of progress towards malignancy. Conversely, the absence of dysplasia does not exclude the hypothesis of the OPMD being pre-malignant (6,23).

First described in 1985 by Hansen et al., PVL (13) is classified as a non-homogeneous subtype of OL. It is considered an uncommon form of the disease, which, in its initial stage, often presents verrucous hyperplasia with minimal or no dysplasia (4,20). Despite its more aggressive clinical course and its lack of association with traditional risk factors such as smoking, alcohol, betel-quid chewing or viruses, it has a slow multifocal evolution that may or may not involve contiguous areas. These areas may be verrucous, and the disease exhibits a predilection for older individuals, especially women, often affecting the gums, cheek mucosa, and tongue. Its progression into malignancy is relentless. However, some authors have suggested changing its description to "Proliferative Leukoplakia" (PL). Since not all lesions are clinically verrucous, this would be a more precise terminological choice. Such a change would result in dissociating this clinical entity from OL, considering that, in addition to the fact that its etiology remains unclear, it can also exhibit a differentiated spectrum of histopathological changes, ranging from hyperkeratosis without dysplasia to verrucous hyperplasia or VC (4,15,24,28,30). As for its molecular profile, p53 overexpression and de-

letions or mutations of p16INK4a and p14ARF have been observed, in addition to aneuploidy and changes in the Mcm2 complex (30). In any case, these findings have not yet become relevant for daily clinical practice.

The OPMD subtype described as "Verrucous Hyperplasia" (VH) or "clinically verrucous leukoplakia" is characterized by verrucous or papillary epithelial hyperplasia with an exophytic growth pattern. In this subtype, the cytological characteristics of dysplasia vary significantly and may even be minimal or absent (24,27). There are still no standardized criteria for the histological diagnosis of VH, and biopsies at various anatomical sites may show different histological patterns, usually correlating with clinical characteristics (27). OED diagnosis in these lesions is riddled with disparities regarding clinical and histological criteria. Their microscopic diagnosis, meanwhile, cannot be carried out without previous knowledge of clinical presentation, especially when a PVL diagnosis is suggested (27). However, during its evolution, PVL may also exhibit a VH-like clinical aspect, with or without dysplasia. This unique pattern of epithelial progression can have characteristics similar to VC. Procedures for distinguishing between them are not well established, but the former shows exophytic growth with epithelial hyperplasia and elongated/thin epithelial projections, and may present anastomosis absent the bulbous growth typical of VCs. In the latter, the projection extends below the epithelial level, epithelial cells have abundant eosinophilic cytoplasm, and normal mitotic figures can be seen in the basal or parabasal layer, with no cytological atypia. Nevertheless, it is a known fact that VH can evolve into VC, exhibiting minimal dysplasia and invasion, with less aggressive clinical behavior than SCC (27).

Currently, the gold standard for assessing OL as well as PVL malignant transformation risk and predictive factors are inhomogeneous clinical appearance (3) and histopathological determination of the OED in the altered epithelium, collected through a biopsy of the lesion (8,9,14 ,31).

It is important to note that certain conditions may exhibit histological aspects similar to those found in PVL, potentially leading to overdiagnosis and inadequate management. Possible confounders are Reactive Keratoses that may resemble precocious PVL, especially Alveolar Ridge Keratosis, Smokeless Tobacco Keratosis, and Frictional Keratosis (caused by bites on the cheek mucosa/tongue) (27).

Early PVLs can be indistinguishable from Benign Keratoses and from OLs that do not come accompanied by dysplasia. This is because they often do not express many dysplastic cytological characteristics but only architectural changes, exhibiting a wavy or verrucous architecture related to their clinical presentation (27). They may also present alongside interface mucositis with lymphohistiocytic infiltrates adjacent to basal cells, in addition to dyskeratotic cells, often leading to a false diagnosis of oral lichen planus (OLP). Nevertheless, it is important to note that hyperorthokeratosis with a wavy surface is not a typical histological finding for OLP (27). Likewise, PVLs that have an erythematous component (erythroleukoplakia morphology) – especially those with bilateral and multifocal lesions (specifically in the jugal mucosa) – can also clinically mimic OLP. For Villa et al., this is an important aspect of the disease: in the latter's study, patients with the prominent erythematous component had MT in 100% of cases, as compared to 62.5% of cases when the erythematous component was absent. Therefore, the author suggests the use of the term "Proliferative erythroleukoplakia" to better describe PLs with prominent erythema (30). OLP may also exhibit hyperkeratosis with epithelial atrophy or erosion, but these findings are commonly associated with degeneration of basal cells, colloid bodies and lymphohistiocytic infiltrate at the interface, as well as other reactive changes within the epithelium caused by inflammation. However, when these characteristics are found in well-demarcated areas they should be interpreted with caution, since this "lichenoid" pattern has been observed in 29% of lesions with OED (32). Such an infiltrate is likely to represent a lymphocytic response to OED or a tumor-promoting inflammation, which is a hallmark of cancer (24,30).

There have been suggestions towards changing the term "hyperkeratosis without dysplasia" to "non-reactive hyperkeratosis" in cases of lesions without dysplasia, in which the epithelial changes are not a result of inflammation (24). Moreover, new architectural criteria for the diag-

nosis of OED have also been suggested – including wavy, verrucous or papillary architecture, hyperkeratosis with epithelial atrophy, voluminous epithelial proliferation with exophytic and/or endophytic growth, and "bulging" hyperkeratosis between areas with normal epithelium – in due consideration to characteristics commonly found in early PL before the development of OED or SCC (24). A systematic review on PVL by Abadie et al. concluded that, in the first biopsy, instead of epithelial dysplasia, more than half of the cases (56.4%) exhibited hyperkeratosis or parakeratosis with either epithelial atrophy or acanthosis (33). Similarly, since very early dysplastic lesions are potentially treatable, it has also been suggested that the term "Keratosis of unknown significance" be adopted for clinical leukoplakias that exhibit hyperkeratosis and/or parakeratosis, acanthosis or atrophy, minimal cytological atypia without inflammation, with discrete papillomatosis accompanied by "bulging" segments between keratin and normal epithelium but lacking characteristics of traumatic keratosis (25). However, an important point described by Woo is that local trauma, candidiasis and inflammation can also lead to forms of reactive epithelial atypia that share many characteristics with OED. In that sense, there is no single characteristic that is conducive to accurate OED diagnosis, but rather a set of characteristics that must be correlated with the degree of inflammation and with the lesion's clinical appearance (25). In a study that explored the transcriptomic differences between dysplastic and non-dysplastic OL, Farah et al. identified a subset of OL that presents "genotypic dysplasia" without histopathological evidence of "phenotypic dysplasia" (34), corroborating the study by Villa et al. which concluded that leukoplakia without dysplasia (which Woo calls Keratosis of unknown significance) shares genomic characteristics with dysplastic OL (35). These studies support the theory that some leukoplakias can be precancerous regardless of the presence of dysplasia (16).

Controversies persist regarding the precise clinical diagnosis of PVL. Some may equate it to gingival leukoplakia of any size across multiple sites, while others define it strictly as the occurrence of multifocal lesions without a verrucous appearance, and others still regard it as a PVL with an erythematous component – such as OLP – insofar as the microscopically analyzed biopsies show a "lichenoid" lymphocytic band (30).

Villa et al. gathered findings from several studies and suggested the following criteria for PL diagnosis:

- white/keratotic, smooth, fissured, verrucous or erythematous lesions;
- multi-focal noncontiguous lesions OR a single large lesion > 4.0 cm involving one site OR a single large lesion > 3 cm involving contiguous sites;
- lesions that progress/expand in size and/or develop multifocality over time.
- lesions showing hyperkeratosis, parakeratosis, atrophy or acanthosis with minimal or no cytologic atypia, with or without a lymphocytic band or verrucous hyperplasia (after excluding frictional or reactive keratoses) (30).

B. Malignant Transformation x Management

It is well established that OPMDs are statistically more likely to become malignant. However, lesions with dysplasia may or may not progress to carcinoma, while histologically normal lesions may in fact be benign and lesions with pre-malignant molecular aspects may have not yet developed morphological/cytological changes typical of dysplasia (9,20,21). Studies have shown that benign hyperkeratosis/epithelial hyperplasia suffered MT in 1% to 30% of cases, demonstrating that non-dysplastic lesions can also become malignant (36,37). In the case of PVL, studies have shown a MT rate ranging from 40 to 100% of cases, with an average follow-up of 7 years, and an overall mortality rate of 40% (4 ,15,20,25,27).

OPMDs have a higher risk of MT in the first 5 years after diagnosis (9). However, the moment of malignant transformation is unpredictable and, therefore, clinically suspicious lesions have to be managed on the basis of active surveillance. On the other hand, lesion management must consider clinical aspects as well as patient risk factors, being liable to expedient transition between careful observation and surgical intervention (10,20,21). A recent systematic review analyzed the clinical aspects of PVL and was

unable to obtain reliable data on this injury's MT rate due to the short follow-up periods found in the literature (28). There are no universally accepted guidelines or recommendations on follow-up frequency for patients diagnosed with OED, and new lesions may occur adjacent to previously excised lesions or at different sites (3,20). For Villa et al., cases must be monitored closely and the verrucous or nodular areas must be biopsied to rule out dysplasia or SCC (30).

C. Treatment

The most used treatments for OPMD are surgical excision and CO2 laser vaporization. However, these methods are not fully effective for dysplastic lesions, which reoccur in up to 40% of cases (15,30,36,38,39). Bagan et al. treated 34 patients (61.8% of cases) with CO2 laser vaporization, and saw injury reoccurrence in 85% (40). Mehanna et al., Carried out a systematic review with meta-analysis encompassing studies that followed patients with OED and concluded that unexcised lesions had a higher rate of MT (14.6% of cases) as compared to excised lesions (5.4% of cases). This suggests that surgical excision reduces the risk of MT by more than half, but does not eliminate it (38). In any case, lesion recurrence rates after surgical excision remain high, reaching 71.2% (33).

For over 30 years, leading authors have stated that the practice of "clinical observation of OL without biopsy" could be dangerous and should be discouraged, advising the complete removal, whenever possible, of all lesions that exhibit more than mild degrees of dysplasia, especially in cases of leukoplakia involving the floor of the mouth or the tongue (17,26). Some time later, the indication for surgical excision evolved to encompass any OL, regardless of the presence or absence of dysplasia (15). More recently, complete surgical excision of the lesion has been indicated for leukoplakias that present moderate or severe dysplasia, in addition to non-homogeneous leukoplakias, especially leukoerythroplakias and PVLs (20,29). A recent systematic review concluded that no treatment seems to be effective (laser, retinoids, photodynamic therapy or chemotherapy). Furthermore, since PVL is multifocal, its surgical eradication is difficult, especially when it comes to obtaining disease-free margins with no dysplasia (28).

Recently, Villa et al. recommended a treatment protocol for patients with PL (30):

a. photograph the lesions during every appointment and send them to the pathologist together with the biopsy;

b. monitor the patient every 3 or 6 months (depending on histopathological diagnosis), performing periodic biopsies when there is a change in the aspect of the lesion (development of red and/or nodular/verrucous areas, hardening and involvement of other sites);

c. monitor keratoses of unknown significance, treating gingival leukoplakia on a case-by-case basis, as other factors can affect treatment indication, such as age, physical health, the area's degree of involvement, bone loss, tooth mobility, appearance and behavior of the lesion;

d. observe mild to moderate dysplasias when extension or location impedes excision, or remove them when the area is discreet;

e. excise in cases involving severe dysplasia or carcinoma in situ;

f. in the histopathological reports of excisional biopsies, describe the characteristics of the lesion margins.

The available methods for the diagnosis, management and treatment of PVL are still a challenge for most stomatologists. Due to their persistent characteristic of developing into and progressing towards malignancy, in order to obtain a more favorable outcome for the patient, the constant search for early diagnosis is crucial. This is made possible by means of continuous screening exams of every patient who is undergoing a dental exam, in association with active surveillance of clinically suspect lesions, in addition to aggressive treatment of existing lesions.

CONCLUSIONS

Because PVL is an aggressive variant of OL that exhibits malignant capacity in virtually all cases, the management and/or treatment of any and all OL – including cases of keratosis of unknown significance – is absolutely mandatory. Photographic control of the entire oral mucosa at each follow-up visit of suspected cases has become an indispensable tool for

arriving at a PVL diagnosis during the disease's early stages. PVL's modified description as a Proliferative Leukoplakia – per which it is no longer regarded as a variant of OL – may prompt further research on this specific condition, resulting in more accurate and conclusive information about its diagnosis, management, and treatment.

The author declare no conflict of interest.

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