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Oral Leukoplakia – an Update

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ABSTRACT

The main purpose of this paper was to assess the current state of science on oral leukoplakia. Although it is considered a potentially malignant disorder the overall malignant progression of oral leukoplakia is of the order of 5% and even more. Nowadays there are no currently accepted markers to distinguish those that may progress to cancer from those that may not. The current golden standard is considered the presence of epithelial dysplasia on the tissue biopsy of the lesion. Proliferative verrucous leukoplakia is a rare form of OL which has multiple recurrences, is refractory to treatment and has malignant transformation in a short period. It is considered a true premalignant lesion. The management of oral leukoplakia varies from a "wait and see" attitude and topical chemopreventive agents to complete surgical removal.

Keywords: oral leukoplakia, potentially malignant disorder

INTRODUCTION

It has been reported that oral squamous cell carcinoma is associated with the presence of potentially malignant disorders in 15-48% cases (1). Oral leukoplakia (OL) is the most frequent potentially malignant disorder of oral mucosa. Although OL is mentioned in clinical reviews since 1969 (2), it was first defined by World Health Organization in 1978 (3) as a white patch or plaque which cannot otherwise be characterized clinically or pathologically as any other disease. Since then until now, the meaning of oral leukoplakia is not very much changed. In 1994 (4), after an international symposium held in Uppsala, Sweden in the definition, was added that oral leukoplakia is not associated with any physical or chemical cause, excepting smoking and it can become cancer. In 2007 it was decided that the name of leukoplakia should be limited only to a clinical diagnosis defined by exclusion of other white lesions such as oral lichen planus, white sponge nevus, nicotine stomatitis, leukoedema etc (5). In 2012 van der Waal (6) proposed a new definition which seems more oportune as it includes the histological confirmation "A predominantly white lesion or plaque of questionable behavior having excluded, clinically and histopathologically, any other definable white disease or disorder". This one hasn't been assessed yet by WHO but it has good chances for acceptance.

Incidence. Demographic distribution

The pooled estimated prevalence rate of oral leukoplakia in 2003 varied between 1.7 to 2.7% in general population (7). For this estimated rate, the author- Stefano Petti, in a meta-analysis including 23 primary studies from all over the world published in the period 1986-

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2002 found no difference between geographical areas and between younger and older patients. It has been reported that between 16% and 62% of oral squamous carcinomas are associated with oral leukoplakia (6).

OL is often found among men, and its prevalence increases with age advancement. It has been estimated that it mainly affects men over 40 years (8).

Etiology

The etiology of OL is considered multifactorial, but smoking is appreciated to be a frequently involved factor. It is much more common among smokers than among non-smokers (5). Alcohol is thought to be an independent risk factor (4) but definitive data are still lacking. There are conflicting results of studies related to the possible role of human papillomavirus infection. As OL can mimic a large variety of lesions, in case a possible causal factor is suspected such as dental restoration, mechanical irritation. In the later case a subsequent evaluation in 4 weeks is needed (6).

Clinical appearance

OL is classified in two main types: homogeneous type which appears as a flat white lesion and non-.homogeneous type which includes speckled, nodular and verrucous leukoplakia (5). The homogeneous leukoplakia is a uniform, thin white area altering or not with normal mucosa (Figure 1). The speckled type is a white and red lesion, with a predominantly white surface (Figures 2 a and 2 b). Verrucous leukoplakia has an elevated, proliferative or corrugated surface appearance (Figure 3). The nodular type has small polypoid outgrowths, rounded predominantly white excrescences (5) (Figure 5).

Proliferative verrrucous leukoplakia is a subtype of verrucous leukoplakia characterized by an aggressive evolution, a multifocal appearance, resistance to treatment, higher degree of recurrence and a high rate of malignant transformation (9).

Histopathological features

Histological appearance of oral leukoplakia varies between no dysplasia and carcinoma. Dysplasia reflects histological changes which are followed by the loss of uniformity or of the architecture of the epithelial cells. It can be related to disturbed cell proliferation (mentioned as 1-9 in Table 1) or to a disordered maturation

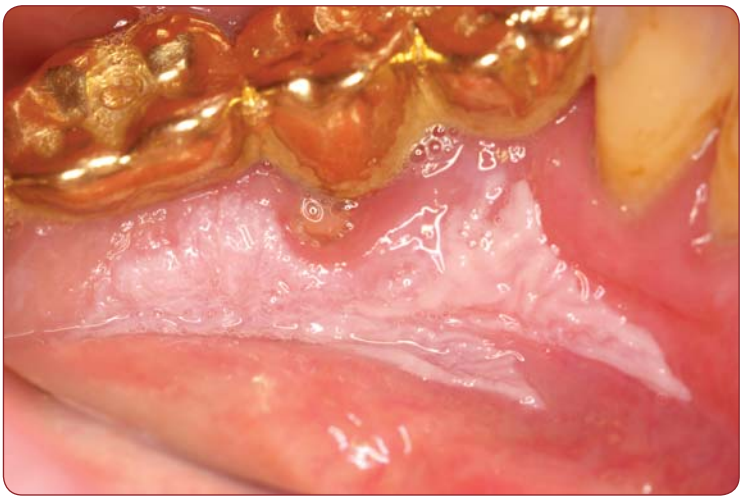

FIGURE 1. Homogenous leukoplakia of the lingual versant of the gingiva.

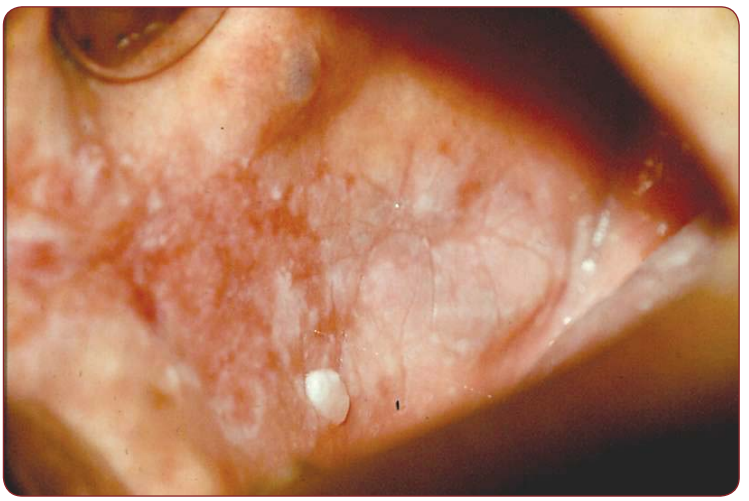

FIGURE 2A. Speckeled leukoplakia on the right retrocomisural mucosa in a hard smoker.

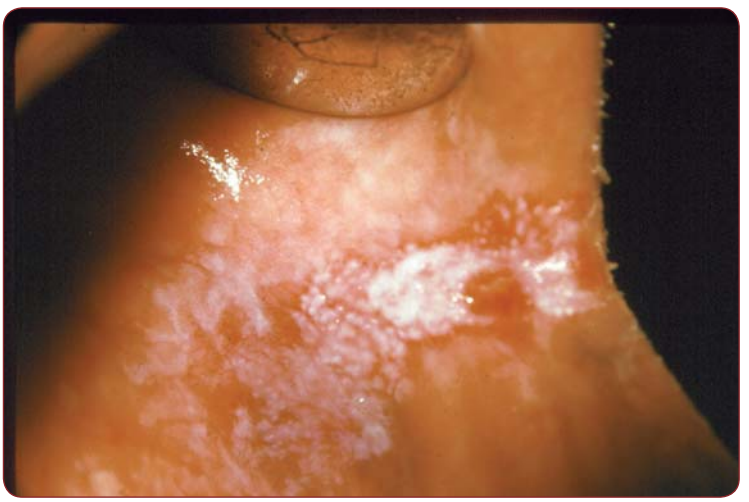

FIGURE 2B. Speckeled leukoplakia on the left retrocomisural mucosa in the same patient (Candidal leukoplakia).

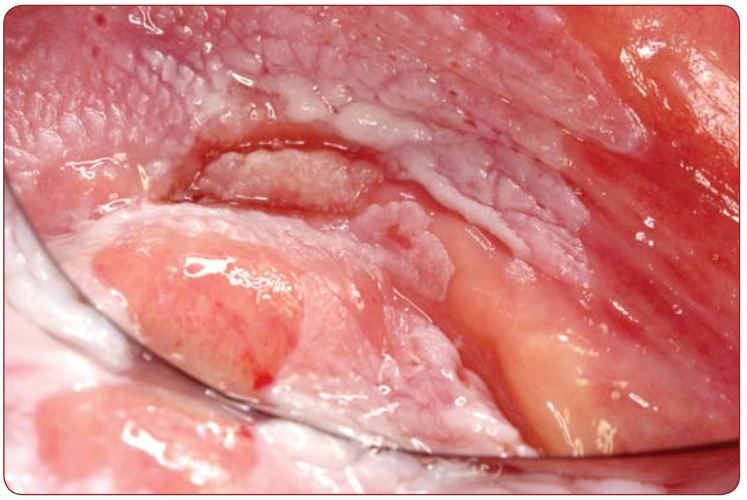

FIGURE 3. Verrucous leukoplakia on the floor of the mouth.

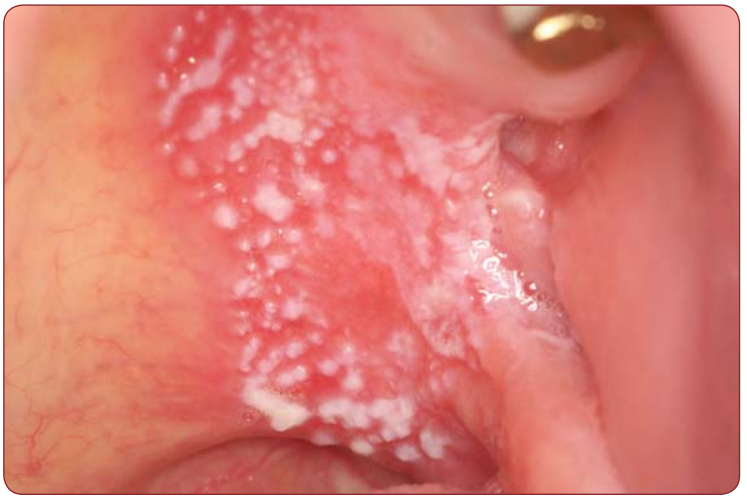

FIGURE 4. Nodular leukoplakia of the soft palate.

(10-13 in the Table 1) (10).

At the last world seminar of Oral Medicine about potentially malignant lesions, London 2010 (11), it has been recommended a binary classification of histological changes (without risk or low risk and moderate or severe risk). This aims to reduce subjectivity in grading dysplasia, thus increasing the possibility of conformity between histological interpretations of different pathologists (5). Lesions are classified as non-dysplastic and dysplastic (mild dysplasia, moderate or severe). Some authors have already tested this system for grading dysplasia and confirmed these views (11).

	Histological changes
1.	Loss of polarity of basal cells
2.	More than one layer of cell with basaloid appearance
3.	Drop-shaped rete-ridges
4.	Increased nuclear-cytoplasmic ratio
5.	Nuclear hyperchromatism
6.	Enlarged nucleoli
7.	Increased number of mitotis
8.	Abnormal form of mitosis
9.	The presence of mitotic cells in the superficial epithelium
10.	Cellular and nuclear pleomorphism
11.	Irregular epithelial stratification
12.	Loss of intercellular adherence
13.	Keratinization of single cells or cell groups in the prickle cell layer

TABLE 1. Histological types of parotid tumor.

Malignant transformation and specific biomarkers

Oral squamous cell carcinoma is a common malignancy worldwide and the most encountered oral malignant tumor (12,13). It has a multifactorial etiology but the most important factors are tobacco and alcohol, separately and synergically (13).

The cohort studies about oral leukoplakia are very rare, so it is difficult to appreciate its real malignant transformation rate due to various regional habits (6,14). Malignant transformation of oral leukoplakia in annual average is 1% in different populations and geographic areas with the higher risk reported by 43% (15), hence the follow up in these patients should be active and long termed.

The risk factors for malignancy of OL such as vicious habits (smoking, alcohol intake), clinical form, location of lesions were studied. Among them, tobacco cigarette smoking was reported to be the most important etiological factor for the development of oral premalignant lesions and to their progression into oral carcinoma (16).

Napier and Speight have recently revised predictive clinical factors -age, gender, location of lesions but results vary between different study populations (12). In an Italian population oral premalignant lesions located on the tongue were more frequently dysplastic compared with the buccal mucosa. Conversely in the Indian population oral leukoplakia of the buccal mucosa is more involved in malignisation.

Despite enormous progress in molecular biology at present there is no certain marker to predict malignant transformation of oral leukoplakia in a particular patient. As it was 20 years ago, epithelial dysplasia is still currently considered "the gold standard" for determining the risk of malignant transformation (15). According to Silverman (17), 36% of dysplastic lesions progress to carcinoma, and 16% of non-dysplastic lesions. However it is known that epithelial dysplasia is correlated with clinically het-

erogeneous lesions that are considered to have the greatest risk.

As histological examination has a degree of subjectivity, there is the need to improve its capacity to assess the dysplasia. This can be done using other markers or by the cross examination of two pathologists.

Identification of biomarkers for oral carcinogenesis is based on markers of proliferation (Ki-67) and component of cell cycle control such as tumor suppressor proteins p53, the retinoblastoma protein (pRb) and cycline D1. But none of these markers are used in routine diagnosis. Expression of p53 and loss of expression of p16 are shown to be the earliest events in the malignisation process. In non-dysplastic leukoplakia a combined alteration of p53/Ki67/p16INK4a was proven to be a risk of progression (18).

Another valuable predictive method is a morphometric computer-assisted analysis was used the measure the size of the cell perimeter and the nuclear perimeter of normal mucosa, oral leukoplakia and oral carcinoma. This technique used computer images of histological stained sections. It showed that these dimensions increased gradually with significant difference from normal mucosa, oral leukoplakia and the highest level in oral carcinoma (19).

Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) was first described by Hansen (1985) has a high risk of transformation in oral carcinoma. PVL begins as one or more homogeneous leukoplakic areas and, in time it extends to more oral sites. It slowly grows and has a high tendency to recur after treatment. It has been reported that most frequently it affects the gingivae (20). But other authors also mention the buccal mucosa, gingiva, and alveola ridges (21). Proliferative verrucous leukoplakia has an uncertain etiology. The association of PVL and presence of Human Papilloma Virus has been suggested previously but wasn't confirmed by further studies so far (21). Also the association of PVL and Epstain-Barr virus (EBV) has been studied. Epstain-Barr virus is the proven etiologic cause of nasopharyngeal carcinoma, oral hairy leukoplakia, lymphoproliferative disease, B-cell lymphomas and lymphoepithelial carcinoma. EBV was examined by nested PCR in 10 cases of PVL, five with oral squamous carcinoma, and five normal mucosa samples. Epstein–Barr virus was detected in 60% of the PVL cases and in 40% of oral carcinoma, but in none of the normal mucosa samples (22).

The diagnosis of PVL based on clinical data is usually late, as the progressive evolution of the lesions from homogeneous leukoplakia spreading too many different locations and with the appearance of erythroplastic and verrucous forms takes time. Proliferative verrucous leukoplakia has a high rate of recurrences after treatment and a high rate malignant transformation. This is appreciated to 74% of cases, with a tendency of multicentric foci (23). Multiple location lesions are more prone to finally develop with single location leukoplakia they found that widespread lesions have a higher potential for the cancer development than unique lesions.

Adjunctive noninvasive methods of investigation

The usual clinical examination of oral mucosa is most frequently visual. It is the standard conventional method for oral cancer screening. It depends on the experience and skills of the clinician. But the risk level of the lesion is difficult to measure. There are many variants of adjunctive techniques for the detection of potentially malignant disorders, including oral leukoplakia.

Brush biopsy was designed for clinical lesions which initially based on clinical features did not require a biopsy. This is a noninvasive technique which collects the basal layer cells using a brush. It can be used for mass screening campaigns. It eliminates the need for surgical procedure in doubtful lesions (24). Since it was introduced in 1999, until now it shows great promise (25).

Toluidine blue is an intravital staining for nucleic acids and abnormal tissue. Initially was used for mucosal lesions of the cervix. In the oral cavity the method was used as guidance for biopsy site selection.

Chemiluminescence (reflective tissue fluorescence) was first applied for the detection of cervix dysplasia. It is based upon the normal fluorescence of the tissue when exposed to blue-white illumination. The technique has been adapted for oral mucosal inspection in the ViziLite system. It detects a variety of oral mucosa lesions including linea alba, hairy

tongue, leukoedema traumatic ulcers (25). Oral leukoplakia has a high degree of visibility and sharpness with proeminent and distinctive margins of the surrounding mucosa. ViziLite has a limitation in discriminating between benign, inflammatory and potentially malignant disorders and it has a low specifity (28%) in detection of dysplasia. As the test does not accurately distinguish between high risk and low risk leukoplakia it should be used with caution (26).

The limit of all these methods or techniques is that they do not provide a definitive diagnosis. They are useful in evaluating a multicentric lesion as well as in noncompliant patient for motivating them to return for further controls.

Treatment guidelines

The main objective in oral leukoplakia's management of care is to detect and to prevent malignant transformation. At the first, the ceasing of the risk activities such as smoking is recommended. Further, the histopathological evaluation is needed. The degree of dysplasia will guide the choice of the treatment. Oral leukoplakia presenting low malignant risk (no dysplasia or simple displasia) may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation (12). In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended (6). The surgical treatment can use conventional surgery or laser ablation, electrocauterization, or cryosurgery (27). Recurrence of OL after surgical treatment has been reported in more than 10% of cases (27). Surgical excision of OL does not lower the risk of subsequent malignant transformation but it brings the opportunity for a complete histolopathological examination of the lesion. Cryotherapy is not considered to be a first line therapy of oral leukoplakia. The risk of post-operative scarring, tissue contraction limit the use of the method (27).

The medical treatment uses local and systemic chemopreventive agents such as vitamin A and retinoids, systemic beta carotene, lycopene (a carotenoid), ketorolac (as mouthwash), local bleomycin, and a mixture of tea used both topically and systemically with a reduced benefit (27).

Another possible choice is an attitude of "wait and see" to keep oral leukoplakia under clinical and histological surveillance with frequent visits and biopsies without other treatment. This follow-up can observe an early malignant transformation and subsequent specific treatment (27). ❑

CONCLUSIONS

The role of the dentist and general practitioner is important in the early diagnosis when leukoplakia is usually asymptomatic and it is simple to remove possible factors involved in its etiology -smoking, thus reducing the rate of malignant transformation.

There is no satisfactory treatment for leukoplakia so far. It must be assumed that generally leukoplakia should be removed preferably totally, if possible and patients should be regularly monitored for any relevant mucosal change, and instructed to avoid the major risk factors of oral epithelial dysplasia, especially tobacco usage and alcohol consumption.

Conflict of interests: none declared.

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