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LITERATURE REVIEW

Oral Leukoplakia: Diagnosis And Management Revisited

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ABSTRACT

The definition of oral leukoplakia has not much changed during the past five decades and is still a definition by exclusion of ‘known’ lesions. Therefore, a diagnosis of leukoplakia is not always a straightforward one for the clinicians and, to some extent, also for the pathologists. The traditional clinical classification in homogeneous and nonhomogeneous leukoplakia may just be simplified into leukoplakia (thin and thick/verrucous) and erythroleukoplakia. In spite of numerous reported predictive molecular and genetic parameters of malignant transformation, the presence and grade of epithelial dysplasia as assessed by histopathological examination is still the most important one. Of the various treatment modalities, surgery and CO₂ laser evaporation are still the most common ones. Treatment may delay or prevent recurrence, but does not seem to prevent malignant transformation or the occurrence of cancer development elsewhere in the mouth or the head and neck region or beyond. There is a strong need for randomized prospective studies and uniform reporting of treatment results.

Key words: diagnosis, management, oral leukoplakia, potentially malignant disorder of the oral mucosa, premalignant oral diseases

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INTRODUCTION

Leukoplakia is the most common potentially malignant lesion or disorder of the oral mucosa. The adjectives ‘potentially malignant’, ‘premalignant’, ‘potentially premalignant and ‘precancerous’ are all synonyms and indicate an increased risk of malignant transformation. Unfortunately, ‘increased risk’ has not been specified in the literature. The present, somewhat simplified, definition reads: ‘a potentially malignant, predominantly white lesion or disorder of the oral mucosa, having excluded well-defined (‘known’) predominantly white lesions or disorders’. Several notes should be added to this definition: 1) a diagnosis of leukoplakia is primarily based on clinical features and does not necessarily require histopathological examination as a routine, 2) if biopsied or excised, the histopathological findings are not pathognomonic; epithelial dysplasia may or may not be present, 3) absence of epithelial dysplasia does not preclude potential malignant behaviour, 4) in case of an underlying squamous cell carcinoma or verrucous carcinoma, the clinical term leukoplakia is replaced by the respective diagnosis, and 5) since a malignancy may not always occur within or close to the leukoplakia but also may arise in other parts of the mouth or elsewhere in the head-and-neck region and even in the esophagus, there is some merit in considering leukoplakia a disorder rather than a lesion.

The reported prevalence of oral leukoplakia varies between 1%-3%. Oral leukoplakia usually occurs above the age of 30-40 years. In some parts of the world there is a strong male preference. Tobacco habits and, in some parts of the world, betel quid use with or without smokeless tobacco, are the most important etiological factors. However, in some cases no etiologic factors can be identified. Leukoplakia may occur in every part of the mouth; the sites of preference may differ in various parts of the world. Symptoms may or may not be present.

The reported annual malignant transformation rate varies widely but an estimated rate in the range of a few percent seems a reasonable one.
EXCLUSION OF WELL-DEFINED (‘KNOWN’) LESIONS FROM A DIAGNOSIS OF LEUKOPLAKIA

It is well recognized that the definition of oral leukoplakia is one by exclusion of well-defined (‘known’) white lesions or disorders. Therefore, a diagnosis of leukoplakia strongly depends on the experience of the clinicians and, to a lesser degree, of the pathologists (Table 1).

Nonreticular lichen planus and hyperplastic candidiasis may be difficult to separate from leukoplakia both clinically and histopathologically. An issue of debate is the question whether frictional keratosis and alveolar ridge keratosis are benign lesions, that should be excluded from a diagnosis of leukoplakia.\(^1\) Based on a preliminary study, using clinical pictures, application of texture analysis on leukoplakic lesions has shown to be a promising diagnostic method.\(^2\) A somewhat similar observation has been reported in another study using machine learning.\(^5\)

<table>
<thead>
<tr>
<th>Lesion or disease</th>
<th>Main diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin burn (including other types of chemical burns)</td>
<td>History of prolonged application of aspirin tablets or other chemical agents</td>
</tr>
<tr>
<td>Candidiasis, hyperplastic</td>
<td>Somewhat questionable entity; some authors refer to this lesion as candida-associated leukoplakia</td>
</tr>
<tr>
<td>Hairy leukoplakia (A rather unfortunate term, because 1) it is a well known entity, and 2) the lesion is not premalignant)</td>
<td>Usually bilateral on the borders of the tongue; histopathology is diagnostic, particularly by the immunohistochemical presence of EBV.</td>
</tr>
<tr>
<td>Keratotic lesions (include reversed smoking keratosis and tobacco pouch keratosis); it is an issue of debate whether or not frictional keratosis and alveolar ridge keratosis to exclude from a diagnosis of leukoplakia</td>
<td>Different etiologies and various clinical presentations; in some cases the taking of a biopsy is indicated.</td>
</tr>
<tr>
<td>Lesion caused by prolonged, direct contact of the oral mucosa with an amalgam restoration or other dental restorations; often referred to as a lichenoid lesion</td>
<td>Disappearance of the lesion within an arbitrarily chosen period of 2-3 months after removal of the restoration; the taking of a pretreatment biopsy should be considered.</td>
</tr>
<tr>
<td>Leukodema</td>
<td>Primarily a clinical diagnosis of a veil-like aspect of the buccal mucosa, bilaterally; tends to disappear when stretched. Occurs almost exclusively in dark-skinned people.</td>
</tr>
<tr>
<td>Lichen planus and lichenoid lesion</td>
<td>Often a clinical diagnosis; occasionally difficult to distinguish from leukoplakia, particularly in nonreticular subtypes of lichen planus. A biopsy may be helpful.</td>
</tr>
<tr>
<td>Morsicatio</td>
<td>History of habitual chewing or biting. Clinical aspect of irregular whitish-yellowish flakes. Often bilateral. A biopsy is rarely indicated.</td>
</tr>
<tr>
<td>Skin graft, e.g. after vestibuloplasty</td>
<td>History of a previous graft</td>
</tr>
<tr>
<td>Snuff dipper’s lesion</td>
<td>See keratotic lesions (tobacco pouch keratosis)</td>
</tr>
<tr>
<td>Syphilis, secondary (“mucous patches”)</td>
<td>Medical history; clinical aspect. Demonstration of T. pallidum; serology.</td>
</tr>
<tr>
<td>White sponge nevus</td>
<td>May occur on a young age; often family history. The clinical aspect is more or less diagnostic. Occasionally, a biopsy may be helpful.</td>
</tr>
</tbody>
</table>

| Table 1. Some well-defined (‘known’) predominantly white lesions or disorders that should be excluded from a diagnosis of leukoplakia. |

CLINICAL CLASSIFICATION

Leukoplakia, erythroleukoplakia, erythroplakia

Traditionally, a clinical classification has been used, consisting of homogeneous leukoplakia (thin, flat or wrinkled) and nonhomogeneous leukoplakia (thick, verrucous leukoplakia or leukoplakia intermingled with red areas, often referred to as erythroleukoplakia). It seems appropriate to abandon the adjectives ‘homogeneous’ and ‘nonhomogeneous’ and, instead, to recognize 1) leukoplakia, being a predominantly white lesion or disorder, irrespective of the texture, being either thin or thick/verruceous (Figure 1), and 2) erythroleukoplakia, in case of a mixture of white and red changes of the oral mucosa (Figure 2). With regard to management guidelines it seems relevant to identify a) thin, and b) thick/verruceous leukoplakia, although it is well acknowledged that the distinction between thin, thick and verrucous can not be accurately described. In case of erythroleukoplakia, subtyping in erosive, granular and speckled, does not seem to be relevant. At the end of the spectrum of leukoplakia
THE ROLE OF THE BIOPSY IN THE DIAGNOSIS OF LEUKOPLAKIA

A diagnosis of leukoplakia may often be made on the clinical appearance alone. There is not much room for the use of adjunctive diagnostic tests other than a biopsy, although some promising preliminary results have been reported on the use of colcoscopy to detect dysplastic changes.

A biopsy of an asymptomatic predominantly white lesion may be indicated when the clinical differential diagnosis includes a ‘known’ lesions or condition, as has been shown in Table 1. In a proven flat, otherwise asymptomatic leukoplakia, the taking of one or more biopsies is not mandatory for establishing the diagnosis. Nevertheless, a biopsy may be taken in such circumstances for reassurance of the patient or on the request by the patient, or because of medicolegal reasons, particularly when treatment will consist of CO₂ laser evaporation where no surgical specimen will become available.

In case of thick or verrucous leukoplakia or in the presence of induration, a biopsy is indicated to rule out verrucous carcinoma or squamous cell carcinoma. Erythroleukoplakias should always be biopsied. It should be no surprise that a biopsy of an (erythro) leukoplakic lesion may not be representative.

Histopathological Aspects

As has been mentioned before, a diagnosis of leukoplakia may be based on clinical aspects alone. If a biopsy or a surgical specimen is available, the histopathological features of leukoplakia may vary from hyperorthokeratosis or hyperparakeratosis (Figure 3) to various grades of epithelial dysplasia (Figure 4). The absence of epithelial dysplasia does not preclude a diagnosis of leukoplakia. Based on histopathological features, a few authors distinguish three types of keratosis: 1) reactive, e.g. frictional keratosis, 2) dysplastic/malignant, and 3) keratosis of unknown significance.

Epithelial dysplasia (ED) is based on cytological abnormalities and/or architectural ones. Reported subtypes include, a.o., adenoid ED, koilocytic ED, and lichenoid ED, the use of the latter subtype being discouraged. The clinical relevance of these subtypes is unknown.

Various grading systems of ED have been reported in the literature. Most systems recognize mild, moderate and severe ED. The histopathological assessment of ED and the absence or presence and its grade, carries a high degree of intra- and interobserver variation. The application of artificial intelligence may be helpful to obtain a reproducible histopathological
judgement, including the assessment of the grade of epithelial dysplasia, if present. 

There is no universal agreement on the distinction between the histopathological features of verrucous hyperplasia and verrucous carcinoma, which is a cause of confusion among and between pathologists, as has been mentioned already. 

In case of an underlying carcinoma (in situ), an (exophytic) squamous cell carcinoma or a verrucous carcinoma, the term leukoplakia is replaced by the respective histopathological diagnosis.

**PREDICTORS OF MALIGNANT TRANSFORMATION**

At the statistical level, there are numerous clinical, histopathological, immunohistochemical and genetic predictors of future malignant transformation, none of these being reliable for use in the management of an individual patient (Table 2). In most studies, erythroleukoplakia, location on the borders of the tongue and the floor of the mouth- in some parts of the world the buccal mucosa is at risk- and the presence of epithelial dysplasia are regarded as ominous signs. It is well accepted, that the risk of malignant transformation increases with the severity of the dysplasia. Immunosupression, including the use of topical steroids, seems to be associated with malignant transformation.

In one study, comprising over 600 patients, erythroleukoplakia (‘nonhomogeneous’ leukoplakia) and a size >200 mm² were shown to be the only relevant predictors of malignant transformation, while epithelial dysplasia was less predictive. In thick/verrucous leukoplakia, often running a protracted clinical course, there may be a highly increased risk of malignant transformation. However, because of poor clinical and histopathological definitions (see section 3.2) it is difficult to come up with science-based conclusions. In some studies, the presence of C. albicans was shown to be of importance, at least in what the authors called ‘chronic hyperplastic candidiasis’, while in another study it was not. Also age and female gender may be associated with an increased risk of malignant transformation. 

Deep learning-based pathology image analysis may be useful to predict cancer progression risk.

**MANAGEMENT**

**Leukoplakia**

The main reason to treat leukoplakia and erythroleukoplakia is to try to prevent malignant transformation. Although spontaneous regression has been reported in screening-detected leukoplakia, such event seems rather rare in patients who have been admitted for consultation of their leukoplakia. In the decision to treat or not to treat, the size and the location of the lesion, as well as the absence or presence of epithelial dysplasia, play an important role. This also applies to the morbity of the treatment and patient’s factors, such as physical and mental condition. In all cases, proper patient information should lead to a ‘shared-decision’.

It is well recognized that all types of leukoplakia and erythroleukoplakia may coexist, often requiring a modified type of treatment as being outlined below.
Furthermore, the feasibility of management protocols very much depends on clinical skills, available treatment facilities, financial aspects and transport facilities for patients. Furthermore, the interest and compliance of patients may vary widely all over the world, even within single countries and even between citizens and people living in rural areas.

**Thin, otherwise asymptomatic leukoplakia**

In case of suspected mechanical irritation or a possibly amalgam related lesion in an otherwise asymptomatic, thin white lesion, one may await the result of the elimination of such lesions for an arbitrarily chosen period of 6-8 weeks. A similar period may be observed for the result of cessation of tobacco habits, if applicable. In leukoplakias at the commissures, short term, e.g. two weeks, topical antifungal treatment should be considered in an attempt to reduce the size of the leukoplakia or to downstage erythroleukoplakia. No long-term results have been reported.

In the absence of possible causes, management may consist of observation, even without taking a biopsy or active treatment, such as surgical removal, laser excision or CO\(_2\), laser evaporation. In case of removal, a margin of at least five millimeters in all directions is recommended, if feasible. An important advantage of surgical removal or laser excision is the availability of a surgical specimen for thorough histopathological examination.

**Thick/verrucous, otherwise asymptomatic leukoplakia**

In case of thick or verrucous leukoplakia or in the presence of induration, an incisional or, in case of a small lesion, an excisional biopsy with a margin of at least five millimeter, if feasible, is indicated to rule out verrucous carcinoma or squamous cell carcinoma. In the latter case, additional oncologic work-up and management will be required. In widespread or multiple thick/verrucous, otherwise asymptomatic leukoplakia, observation or surgical excision may be considered, if feasible, with or without being combined with nonsurgical treatments, such as anti-inflammatory drugs, carotenoids, lycopene, vitamins (A, C, E), bleomycin, methotrexate and photodynamic therapy. One may also consider laser excision or CO\(_2\) laser evaporation in one more sessions; another option consists of photodynamic therapy. Also intravenous administration of methotrexate may be useful, particularly in elderly patients.

**Erythroleukoplakia and symptomatic leukoplakia**

Erythroleukoplakias and symptomatic leukoplakia, being either thin or thick/verrucous, should be removed, preferably by surgical excision in order to obtain a surgical specimen for histopathological examination. In Figure 5 an example is shown of a selective excision of a clinical suspicious leukoplakia of the tongue without an attempt to remove the entire lesion.

**TREATMENT RESULTS**

The outcome of whatever treatment remains uncertain. Recurrences and development of new leukoplakias elsewhere in the oral cavity may arise in a matter of months or years (Figure 6). Such events can most likely be explained by the concept of field cancerization. Wider excisions or wider CO\(_2\) laser evaporation may reduce or delay local recurrences, but do not decrease the risk of cancer development. In a large study from Sweden, some 50 years ago, the statement has already been made that “there is no evidence that the incidence of oral carcinoma can be diminished by surgical removal”. Nevertheless, surgical removal was advised mainly for obtaining a more accurate histopathologic diagnosis than based on a biopsy specimen alone. Cessation of tobacco habits has been reported to reduce the number of unfavorable events after surgical treatment. Some authors have raised the question whether surgery may actually be a cancer promotional stimulus. To the best of my knowledge this subject has not been elaborated in other publications.

Unfortunately, there is a lack of uniform reporting of treatment results.
FOLLOW-UP

Both treated and untreated patients should be followed-up, lifelong, at intervals of 3-6 months, depending on the presence or absence of epithelial dysplasia. Some authors suggested to limit the follow-up to five years. Overall, there are hardly any scientific data about the true value of follow-up programs, other than reassurance of the patient.

CONCLUSION

A diagnosis of leukoplakia is not always a straightforward one. The traditional clinical classification in homogeneous and nonhomogeneous leukoplakia may just be simplified into leukoplakia (thin and thick/verrucous) and erythroleukoplakia. Proliferative verrucous leukoplakia is a poorly defined subtype of leukoplakia. Epithelial dysplasia is still the most important predictive marker of future malignant transformation of all types of leukoplakia. Of the various treatment modalities, surgery and CO₂ laser evaporation are still the most common ones. Treatment may delay or prevent recurrence, but does not seem to prevent malignant transformation. There is a strong need for randomized prospective studies and uniform reporting of treatment results.

CONFLICT OF INTEREST

The author declared no conflict of interests.

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