Oral leukoplakia and erythroplakia: a protocol
for diagnosis and management

Coordinator: Prof. Isaäc van der Waal

Pedro Diz¹, Meir Gorsky², Newell W. Johnson³, Camilla Kragelund⁴, Maddalena Manfredi⁵, Edward Odell⁶, Kobkan Thongprasom⁷, Saman Warnakulasuriya⁸, José V. Bagan⁹, Isaäc van der Waal¹⁰

¹ Santiago de Compostela University, School of Medicine and Dentistry, Special Needs Unit, Santiago de Compostela, Spain
² Tel-Aviv University, School of Dental Medicine, Tel-Aviv, Israel
³ Griffith Health Institute, Gold Coast Campus, Queensland, Australia
⁴ University of Copenhagen, Department of Oral Medicine, Section of Oral Pathology & Medicine, Copenhagen, Denmark
⁵ University of Parma, Oral Medicine, Oral Pathology and Laser Assisted Surgery Unit, Parma, Italy
⁶ King’s College London, Guy’s Hospital, Department of Oral Pathology, London, UK
⁷ Chulalongkorn University, Faculty of Dentistry, Oral Medicine Department, Bangkok, Thailand
⁸ King’s College London, Dental Institute at Guy’s, King’s and St Thomas’ Hospitals, Department of Oral Medicine, London, UK
⁹ Valencia University, University General Hospital, Service of Stomatology, Valencia, Spain
¹⁰ VU University Medical Center (VUmc)/Academic Centre for Dentistry Amsterdam (ACTA), Department of Oral and Maxillofacial Surgery, Amsterdam, The Netherlands

Corresponding author:
Professor Isaäc van der Waal
VU University Medical Center/ACTA
Department of Oral and Maxillofacial Surgery/Pathology
P.O. Box 7057
1007 MB Amsterdam, The Netherlands
Tel: +31-20-4440539/+31-20-4441023
Fax: +31-20-4440467/+31-20-4441024
E-mail: i.vanderwaal@vumc.nl
1. Introduction; terminology and definitions

The terms ‘precancer’, ‘precursor’, ‘premalignant’ and ‘potentially malignant’ have been used in the literature to describe clinical manifestations that have a potential to become cancer. In the WHO monograph on Head and Neck Tumours the term ‘epithelial precursor lesions’ has been used.\(^1\) In a workshop, coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the UK, held in 2005, the term, potentially malignant, has been recommended;\(^2\) this term will be used in the present text.

Recognized potentially malignant disorders are leukoplakia, erythroplakia, palatal lesions in reverse smokers, submucous fibrosis, actinic cheilitis and lichen planus; rare potentially malignant disorders include Fanconi’s anaemia, discoid lupus erythematosus, dyskeratosis congenita and xeroderma pigmentosum. The emphasis in this paper will be on leukoplakia and erythroplakia.

In the past, a distinction was made between potentially malignant lesions and potentially malignant conditions, based on the assumption that cancer in a patient with a potentially malignant lesion would arise at the site of the lesion and that in potentially malignant conditions, the cancer could arise in any anatomical site. Since it is known that in patients with a potentially malignant lesion dysplasia may be present in a distinct separate anatomic site suggestive of a pathway to malignant transformation, the recommendation was made to refer to all clinical presentations that carry a risk of cancer as potentially malignant disorders.

The term leukoplakia should be used to recognize ‘predominantly white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer’.\(^2\) Examples of such benign lesions are listed in Table 1.

Erythroplakia has been defined as ‘a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease’.\(^2\) An example of such ‘definable disease’ is erythematous candidiasis.

2. Epidemiology and aetiology

The prevalence of oral leukoplakia, worldwide, is approximately 1%-2% for all ages together.\(^3\) There are geographical differences with regard to gender distribution. Leukoplakias are usually diagnosed after the fourth decade of life and are six times more common among smokers than among non-smokers.\(^4\) Alcohol may be an independent or

---

Table 1. Benign disorders that need exclusion to diagnose leukoplakia*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Diagnostic features</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>White sponge naevus</td>
<td>Noted in early life, family history, large areas involved</td>
<td>Biopsy not indicated</td>
</tr>
<tr>
<td>Frictional lesion</td>
<td>History of trauma, mostly along the occlusal plane, an aetiological cause apparent, mostly reversible on removing the cause</td>
<td>Biopsy if persistent after elimination of cause, particularly in a tobacco user</td>
</tr>
<tr>
<td>Morsicatio buccarum</td>
<td>Habitual cheek – lip biting known, irregular whitish flakes with jagged out line</td>
<td>Biopsy not indicated</td>
</tr>
<tr>
<td>Chemical injury</td>
<td>Known history, site of lesion corresponds to chemical injury, painful, resolves rapidly</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Acute pseudomembranous candidosis</td>
<td>The membrane can be wiped off leaving an erythematous/raw surface</td>
<td>Swab for culture</td>
</tr>
<tr>
<td>Leukoedema</td>
<td>Bilateral on buccal mucosa, could be made to disappear on stretching (retracting)</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Hairy leukoplakia</td>
<td>Bilateral tongue leukoplakic lesions</td>
<td>Not indicated in an identified HIV infected patient; otherwise a biopsy should be considered Specific histopathology with koilocytosis; EBV demonstrable on in situ hybridization</td>
</tr>
<tr>
<td>Smokers' palate (”Nicotine stomatitis”)</td>
<td>Smoking history, greyish white palate</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

*Oral lichen planus and some of the lichenoid lesions are considered a potentially malignant disorder. The clinical and histopathological features may occasionally resemble those of leukoplakia.
synergistic risk factor. There may be a potentially important and causal association between human papillomavirus and oral potentially malignant disorders.\textsuperscript{5}

Erythroplakia is much less common than leukoplakia. No reliable prevalence figures are available; estimated figures vary from 0.02\% to 0.83\%.\textsuperscript{6} The aetiology is unknown, but tobacco and alcohol are probably predisposing factors.\textsuperscript{6}

3. Clinical aspects
Two main clinical types of leukoplakia are recognized, being homogeneous and non-homogeneous leukoplakia. The distinction is, based on surface color and morphological (thickness and texture) characteristics. 

Homogeneous lesions are uniformly flat and thin (Fig. 1). Homogeneous leukoplakias are otherwise usually asymptomatic. 

Non-homogeneous leukoplakias are often symptomatic. Non-homogeneous varieties include: speckled: mixed, white and red (‘erythroleukoplakia’) (Fig. 2), but retaining predominantly white character; nodular: small polypoid outgrowths, rounded red or white excrescences (Fig. 3); verrucous or exophytic: wrinkled or corrugated surface appearance (Fig. 4); proliferative verrucous leukoplakia (PVL) remains a controversial entity since its first description in 1985.\textsuperscript{7} This definition is actually based on a combination of features such as morphology, multifocality, progression in time, and resistant to therapy.

Additional clinical descriptions that may assist in the characterization of oral leukoplakia are:
* aetiological description: clearly associated with tobacco or areca nut use; idiopathic.
* site description giving anatomical sub-site in the mouth.\textsuperscript{8}
* size or extent of the lesion(s). Some have recommended a classification system based on <2 cm, 2-4 cm and >4 cm,\textsuperscript{9} while others have recommended a cut off size of 200 mm\textsuperscript{2}.\textsuperscript{10}

The clinical appearance of erythroplakia (fiery red) may be flat or even depressed with a smooth or granular surface (Fig. 5). In the case of a mixture of mostly red and some white changes such lesion is usually categorized as non-homogeneous leukoplakia (‘erythroleukoplakia’). The generally solitary presentation is helpful in clinically distinguishing erythroplakia from erythematous lichen planus and erythematous candidiasis, since these lesions often manifest multiple sites, almost always in a bilateral, more or less symmetrical pattern.

![Image of erythroplakia of the palate.](image-url)

### 4. Histopathological aspects

In biopsies of leukoplakias a distinction can be made histopathologically between dysplastic and non-dysplastic lesions. The assessment and severity of dysplasia is based on architectural disturbance accompanied by cytological atypia. It should be emphasized that dysplasia is a spectrum and that no criteria exist to precisely divide this spectrum into mild, moderate and severe categories.\textsuperscript{11} A somewhat confusing subtype of dysplasia is ‘lichenoid dysplasia’ in which there is the presence of a subepithelial bandlike infiltrate, somewhat mimicking lichen planus.\textsuperscript{12} It should be realized that a lichenoid host response is a normal feature of dysplasia, making distinction from lichen planus difficult in some cases.

Occasionally, a diagnosis of verrucous carcinoma, carcinoma in situ or invasive squamous cell carcinoma is made in the initial clinical presentation of leukoplakia; in such event the histopathological diagnosis replaces the clinical diagnosis of leukoplakia. It is well recognized that (proliferative) verrucous leukoplakia may show a spectrum of histopathological changes, ranging from hyperkeratosis with or without dysplasia to verrucous hyperplasia.

Histopathologically, erythroplakia most commonly shows at least some degree of dysplasia and often even carcinoma in situ or invasive carcinoma.

### 5. Diagnosis

The diagnosis of leukoplakia can be made at different levels of certainty, as a clinical term only or as a clinico-pathological diagnosis;\textsuperscript{9} the same applies to a diagnosis of erythroplakia.

A provisional diagnosis of leukoplakia is made when a predominantly white lesion at clinical examination can not be clearly diagnosed as any other disease or disorder of the oral mucosa as being listed in Table 1; a definitive diagnosis of leukoplakia is made when any aetiological cause, e.g. tobacco, C. albicans, mechanical irritation, has been excluded and histopathologic examination has not disclosed any other specific disorder. At times, it may be difficult to exclude other disorders, even when a biopsy specimen is available. For instance, the histopathology of a white lesion may be compatible with both a clinical diagnosis of leukoplakia and lichen planus. In other words, some lesions are difficult to diagnose with certainty, even in the availability of a biopsy specimen. Nevertheless, the taking of a biopsy is strongly recommended not only to exclude any other specific disorder, but also to assess the absence or presence and degree of epithelial dysplasia or even carcinoma in situ or frank squamous cell carcinoma.

The biopsy should be taken at the most clinically suspicious area, if any, such as redness, an area of surface thickening or a symptomatic area. In patients with multifocal or widespread leukoplakia multiple biopsies (‘field mapping’) should be considered.\textsuperscript{13} Particularly in the case of a non-homogeneous leukoplakia an incisional biopsy may not be representative.\textsuperscript{14} In small leukoplakias, e.g. < 2–3 cm, an excisional biopsy may be considered. The value of oral brush cytology is a subject of controversy, as is the use of toluidine blue, and
other adjuncts.\textsuperscript{15,16} Histopathologic examination is at present still the gold standard for diagnostic purposes. DNA ploidy measurements may be helpful in identifying lesions that carry a high risk of malignant transformation.\textsuperscript{17}

6. Malignant transformation

In a study from India, an annual malignant transformation rate of leukoplakia of 0.3\% has been reported.\textsuperscript{18} In studies from Western countries somewhat higher figures have been mentioned; an annual malignant transformation rate of approximately 1-2\% is probably a reasonable average figure for all types of leukoplakia together. It is well appreciated that this figure is much higher for non-homogeneous types, including proliferative verrucous leukoplakia. The latter entity probably nearly always transforms into one or more verrucous carcinomas or squamous cell carcinomas, but may do so in a protracted course of many years. Many leukoplakias probably may not progress over time; spontaneous regression is rare.

Malignancies may develop at the site of treated or untreated leukoplakia, but may also occur elsewhere in the oral cavity or upper aerodigestive tract. The commonly recognized factors that statistically carry an increased risk of malignant transformation into a squamous cell carcinoma are listed in Table 2. Of these risk factors, the presence of epithelial dysplasia – often correlating with a clinically non-homogeneous, erythroleukoplakic subtype – is in general regarded the most important indicator of malignant potential. Nevertheless, it should be recognized that some dysplastic lesions may remain unchanged or may even show complete regression.\textsuperscript{18}

Furthermore, carcinomatous transformation may also take place in non-dysplastic leukoplakia.\textsuperscript{19} In several studies from the Western world, the borders of the tongue and the floor of the mouth have been mentioned as high-risk sites, while in a study from Denmark also size was shown to be of importance, particularly when exceeding 200 mm\textsuperscript{2}.\textsuperscript{10}

In spite of tremendous progress in the field of molecular biology, there is as yet no single marker or set of markers that reliably enables to predict malignant transformation of leukoplakia in an individual patient with leukoplakia,\textsuperscript{1} perhaps with the exception of DNA ploidy measurements.\textsuperscript{17} The use of non-invasive genetic tests, using exfoliated or brushed cells of lesional tissue,\textsuperscript{19} or molecular markers from saliva may prove to be a step forward in the search for relevant prognostic markers.\textsuperscript{20}

Most erythroplakias will probably undergo malignant transformation. There are not enough documented series that would allow to calculate a reliable annual malignant transformation rate.

7. Treatment options

The reason for treating leukoplakia may be the presence of symptoms, but is mainly to eliminate

\begin{table}
\centering
\begin{tabular}{|l|}
\hline
\textbf{Table 2.} Reported risk factors of statistical significance for malignant transformation of leukoplakia, listed in an at random order (not reliable for use in the individual patient) \\
\hline
\begin{itemize}
\item Female gender
\item Long duration of leukoplakia
\item Leukoplakia in non-smokers (idiopathic leukoplakia)
\item Location on the tongue and/or floor of the mouth
\item Size > 200 mm\textsuperscript{2}
\item Non-homogeneous type
\item Presence of invasive \textit{C. albicans}
\item Presence of epithelial dysplasia
\item DNA aneuploidy
\item History of previous head-and-neck carcinoma
\end{itemize}
\hline
\end{tabular}
\end{table}
the lesion as an attempt to prevent malignant transformation. A large size or a diffuse pattern of the lesion and patient factors, such as a poor general condition, may hinder optimal treatment. The most commonly used treatment modalities consist of cold knife excision or CO₂-laser therapy (excision or vaporization). Although there is no strong preference for either modality, excision has the advantage of providing a specimen for additional histopathological evaluation. Some oral subsites are easier to treat with CO₂-laser, such as the floor of the mouth, the palate or the buccal mucosa. The width of the margin that should be taken into account has never been discussed in detail in the literature; most clinicians probably will include a margin of just a few millimeters. Recurrence rates vary in various papers ranging from almost zero up to more than 30%, largely depending on the selection of leukoplakias and the length of the follow-up period. Apart from cold knife excision and CO₂-laser therapy, various treatment options are available such as: Nd:YAG laser therapy, chemoprevention - either topically or systemically - with retinoids vitamins A, C, and E, carotenes or lycopene, mouthwash therapy containing an attenuated adenovirus, and photodynamic therapy. Since these treatment options are not universally available, these options will not be discussed here in detail.

8. Management protocol
The management protocol is designed for those who have a level of competence to clinically diagnose the most common lesions and disorders of the oral mucosa and, preferably, have a good understanding of the histopathology of such lesions. A flowchart for the management of leukoplakia is presented in Table 3. In the presence of possible aetiological factors, in particular tobacco habits,21 which may require professional habit intervention - an observation period of not more than a somewhat arbitrarily chosen six weeks seems acceptable to observe a possible regression after elimination of such factors. Of course, it is well appreciated that complete regression may take much longer. On the other hand, one would not like to postpone a biopsy for too long. Although there is no scientific evidence that treatment, of whatever type, truly prevents recurrences or the possible future development of a squamous cell carcinoma,22,23 it seems safe practice to actively treat leukoplakias, irrespective of the absence or presence of epithelial dysplasia,24 if feasible. There are no scientific data about the value of follow-up visits and the optimal intervals after treatment of leukoplakia; nevertheless, some suggestions have been provided in Table 3. In general, erythroplakia needs to be treated because of its high risk of malignant transformation. Besides, most erythroplakias are symptomatic. Surgery, either by cold knife or by laser, is the recommended treatment modality. As for excision of leukoplakia, no guidelines are available with regard to the width of the surgical margins. There are no data from the literature about the recurrence rate after excision of erythroplakias.

9. Some recommendations for future studies
There is a need for randomized controlled trials studying the effectiveness of management of the various types of oral leukoplakia. For various reasons such studies require a multicenter and probably also an international design in order to obtain a sufficient sample size. In order to promote uniform reporting, the use of a classification and staging system is recommended in which clinical type, size and the histopathological features are taken into account.9 In addition, gender, age at the time of diagnosis, any aetiologic factors, if identified, and the oral or oropharyngeal subsite(s) should be recorded.
Table 3. Diagnosis and management of leukoplakia

**LEUKOPLAKIA**
(Provisional clinical diagnosis)

- Elimination of possible cause(s), including tobacco habits, *C. albicans* (maximum six weeks to observe the result)
- No or only partial response (Definitive clinical diagnosis)

No possible cause(s) (Definitive clinical diagnosis)

- Biopsy

Definitive clinico-pathological diagnosis

- Non-dysplastic leukoplakia
  - Treatment (if feasible, e.g. < 2-3 cm)
  - Follow-up in both treated and untreated patients at intervals of 6 months; lifelong (?)

- Dysplastic leukoplakia
  - Treatment (if feasible, e.g. < 2-3 cm)
  - Follow-up in both treated and untreated patients at intervals of 3 months; lifelong (?)

Known lesion

Management accordingly
References


