Review

Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management

Isaäc van der Waal*

VU University Medical Center (VUmc)/Academic Centre for Dentistry Amsterdam (ACTA), Department of Oral and Maxillofacial Surgery/Pathology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

ARTICLE INFO

Available online xxxx

Keywords:
Oral leukoplakia
Oral lichen planus
Actinic cheilitis
Submucous fibrosis
Potentially malignant oral disorders

S U M M A R Y

In a recently held WHO workshop it has been recommended to abandon the distinction between potentially malignant lesions and potentially malignant conditions and to use the term potentially malignant disorders instead. Of these disorders, leukoplakia and erythroplakia are the most common ones. These diagnoses are still defined by exclusion of other known white or red lesions. In spite of tremendous progress in the field of molecular biology there is yet no single marker that reliably enables to predict malignant transformation in an individual patient. The general advice is to excise or laser any oral or oropharyngeal leukoplakia/erythroplakia, if feasible, irrespective of the presence or absence of dysplasia. Nevertheless, it is actually unknown whether such removal truly prevents the possible development of a squamous cell carcinoma.

At present, oral lichen planus seems to be accepted in the literature as being a potentially malignant disorder, although the risk of malignant transformation is lower than in leukoplakia. There are no means to prevent such event. The efficacy of follow-up of oral lichen planus is questionable. Finally, brief attention has been paid to oral submucous fibrosis, actinic cheilitis, some inherited cancer syndromes and immunodeficiency in relation to cancer predisposition.

Introduction

In a World Health Organization (WHO) Workshop, held in 2005, the terminology, definitions and classification of oral lesions with a predisposition to malignant transformation have been discussed. The term “potentially malignant” was preferred above “premalignant” or “precancerous”,1 furthermore, it has been recommended to abandon the traditional distinction between potentially malignant lesions and potentially malignant conditions and to use the term “potentially malignant disorders” instead.

In this treatise, attention will be mainly paid to leukoplakia and erythroplakia. Furthermore, lichen planus and submucous fibrosis will be discussed, as well as a number of miscellaneous potentially malignant disorders.

Leukoplakia

Definition and terminology

Leukoplakia is at present defined as “A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer”.1 Examples of white or predominantly white diseases of the oral mucosa that carry no increased risk for cancer development are shown in Table 1.

The term leukoplakia can be used at different levels of certainty (C-factor) as a clinical term only (C1 or C2) or as a clinicopathological term (C3 or C4), as shown in Table 2.

Epidemiology and etiology

The estimated reported prevalence of oral leukoplakia, worldwide, is approximately 2%.2 However, when viewed in relation to an annual malignant transformation rate of 1%, this prevalence figure would result in development of oral cancer in 20 per 100,000 populations per year. Obviously, this cancer incidence figure, based on malignant transformation of oral leukoplakia alone is much too high. Probably, the prevalence of oral leukoplakia has to be set at a more realistic figure of less than 0.5%. There are some geographical differences with regard to the gender distribution.

Leukoplakia is six times more common among smokers than among non-smokers.3 Alcohol is an independent risk factor, regardless of beverage type or drinking pattern.4 There are conflicting results of studies related to the possible role of human papillomavirus infection.5–7
Evidence following excision and pathological examination of the resected tissue is necessary to confirm the diagnosis of leukoplakia. This is especially important when there is no history of mechanical irritation (e.g. habit of vigorous toothbrushing) to suggest a frictional lesion, as this type of lesion can be considered cured once it has been treated and the etiological factor removed. Histopathologically, a distinction can be made between dysplastic and non-dysplastic leukoplakia. The assessment and severity of dysplasia are based on architectural disturbance accompanied by cytological atypia. The WHO 2005 classification recognizes five histopathological stages in epithelial precursor lesions (Table 3). The criteria used for diagnosing dysplasia are shown in Table 4. 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. Furthermore, there may be a substantial interobserver and intraobserver variation in the histopathological assessment of the presence and severity of epithelial dysplasia. Perhaps a better consensus can be reached by modifying the WHO five tier system into a binary one, recognizing “low-risk” versus “high-risk” lesions. It has been suggested that an AgNOR cut-point may be helpful to distinguish mild and moderate dysplasia. In Table 5 two other grading systems – the Squamous Intra-epithelial Neoplasia (SIN) system and the Ljubljana classification of Squamous Intraepithelial Lesions (SIL) – are shown. Occasionally, koilocytic changes in dysplastic lesions (“koilocytic dysplasia”) can be observed, apparently related to the presence of intermediate and high-risk human papillomavirus; the clinical significance and potential for malignant transformation is as yet unclear. Yet another subtype of dysplasia is “lichenoid dysplasia” (see discussion on lichen planus).

Occasionally, a diagnosis of verrucous carcinoma, carcinoma in situ or invasive squamous cell carcinoma is made in the clinical presentation of leukoplakia; in such event the histopathological diagnosis replaces the clinical diagnosis of leukoplakia. It is well
Table 5

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Squamous intraepithelial neoplasia (SIN)</th>
<th>Ljubljana classification squamous intraepithelial lesions (SIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell hyperplasia</td>
<td>Squamous cell (simple) hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>Basal/parabasal cell hyperplasia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Atypical hyperplasia&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>SIN 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Atypical hyperplasia&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>SIN 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Carcinoma in situ</td>
</tr>
</tbody>
</table>

<sup>a</sup> Basal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually a benign lesion and the latter the lower grade of pre-cursor lesions.

<sup>b</sup> “Risky epithelium”. The analogy to moderate and severe dysplasia is approximate.

<sup>c</sup> The advocates of SIN combine severe dysplasia and carcinoma in situ.

Although the presence of *Candida albicans* has been mentioned as a risk factor,<sup>22</sup> it is remarkable that this microorganism seems to be particularly present in leukoplakias at the commissures of the mouth and at the dorsum of the tongue, while these sites are rarely involved in cancer development. 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 this is not the case in India.<sup>19</sup> In a study from Denmark also size was shown to be of importance, particularly when exceeding 200 mm<sup>2</sup>.<sup>20</sup>

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,<sup>11,23</sup> perhaps with the exception of expression of podoplanin<sup>24</sup> suprabasal expression of p53,<sup>25</sup> angiogenesis,<sup>26</sup> the presence of high-risk HPV types, such as HPV 16,<sup>27</sup> the immunohistochemically expression patterns of cyclin D1, p27 and p63,<sup>28</sup> or the expression of cytokeratin 8,<sup>29</sup> The use of non-invasive genetic tests, using exfoliated or brushed cells of lesional tissue,<sup>30–32</sup> or molecular markers from saliva<sup>33,34</sup> may prove to be a step forward in the search for relevant prognosis markers.

Management

A flowchart for the management of leukoplakia has been presented in Table 7. In the presence of possible etiological factors, including tobacco habits,<sup>25</sup> an observation period of not more than a somewhat arbitrarily chosen 2–4 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 more time. On the other hand, one would not like to postpone a biopsy for a too long time in case a biopsy has not been taken already at the first visit. In patients with multifocal or widespread leukoplakia multiple biopsies (“field mapping”), if needed using general anesthesia, should be considered.<sup>36</sup> Particularly in case of a non-homogeneous leukoplakia an incisional biopsy may not be representative.<sup>37,38</sup> In small leukoplakias, e.g., <2–3 cm, an excisional biopsy may be considered.

The diagnostic value of oral brush cytology is still a subject of controversy.<sup>39–41</sup> This technique may have value as a screening tool, but histopathologic examination is at present still the gold standard for diagnostic purposes. This is also true for the use of toluidine blue.<sup>42–44</sup> Nevertheless, toluidine blue may be useful in identifying potentially malignant disorders as a risk of progression to squamous cell carcinoma.<sup>45</sup> Optical spectroscopy may become an attractive non-invasive diagnostic tool to identify dysplasia.<sup>46</sup> This also applies to direct fluorescence visualization,<sup>47,48</sup> and to visual assessment of oral cavity luminescence following a chemical reaction, i.e., chemiluminescence.<sup>49</sup>

The reason to treat leukoplakia may be the presence of symptoms and an attempt to prevent malignant transformation. Reasons not to treat may consist of a large extent or a diffuse pattern of the lesion. Furthermore, patient’s factors, such as poor general condition, may hinder optimal treatment. Although there is no scientific evidence that treatment, of whatever modality, truly prevents the possible future development of a squamous cell carcinoma,<sup>50</sup> it seems safe practice to actively treat leukoplakias, irrespective of the absence or presence of epithelial dysplasia.<sup>21</sup>

Apart from surgical excision, various treatment modalities are available such as cryosurgery, laser surgery (including evaporation),<sup>52,53</sup> administration of retinoids, either topically or systemically,<sup>54–56</sup> mouthwash therapy containing an attenuated adenovirus<sup>57,58</sup> and photodynamic therapy.<sup>59</sup> The most commonly used treatment modalities consist of surgical excision or laser therapy. The width of the margin that should be taken into account has never been discussed in detail; probably most clinicians will

Table 6

<table>
<thead>
<tr>
<th>Reported risk factors of statistical significance for malignant transformation of leukoplakia, listed in an at random order (not applicable in the individual patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Long duration of leukoplakia</td>
</tr>
<tr>
<td>Leukoplakia in non-smokers (idiopathic leukoplakia)</td>
</tr>
<tr>
<td>Location on the tongue and/or floor of the mouth</td>
</tr>
<tr>
<td>Size &gt; 200 mm&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-homogeneous type</td>
</tr>
<tr>
<td>Presence of <em>C. albican</em></td>
</tr>
<tr>
<td>Presence of epithelial dysplasia</td>
</tr>
</tbody>
</table>
include a margin of just a few millimetres, although it is conceivable and actually demonstrated that nuclear changes in the epithelium are present well beyond clinically visible leukoplakia. This phenomenon most likely explains the risk of local recurrence and the development of new leukoplakias. Recurrence rates vary in various papers from almost zero up to 30%. There are no scientific data available about the possible value of follow-up and the optimal intervals after treatment of leukoplakia; nevertheless, some suggestions have been provided in Table 7.

**Uniform reporting; classification and staging system**

In order to promote uniform reporting, the use of a classification and staging system is recommended in which the size and the histopathological features are taken into account (Table 8). In addition, gender, age at the time of diagnosis, any etiologic factors, if identified, and the oral or oropharyngeal subsite(s) should be recorded. The system presented in Table 8 has been slightly modified from a previously reported proposal; it has not been validated yet.

The recording of treatment results should be standardized as much as possible, including the length of the follow-up intervals and the total length of follow-up. After surgical excision (including laser surgery or evaporation) recurrences are not uncommon. When the recurrence is at the site of the primary lesion, the term recurrence seems justified, indeed, irrespective of the time span between the excision and the recurrence. When the recurrence develops at a distinct different oral subsite, it seems appropriate to refer to such lesion as a new leukoplakia.

In case of non-surgical treatment or observation, the findings should be expressed as a percentage related to the original size of the leukoplakia as follows: no change (stable disease), partial regression (>50%), complete regression, and progressive disease (>25%). The most suitable criterium to measure such changes seems, indeed, to be the size of the leukoplakia and not so much the whiteness and/or the texture of the lesion (Table 9). In case of monitoring the lesion by one or more biopsies during follow-up, the possible change in the histopathological findings could then be reflected in the staging system shown in Table 8.

**Erythroplakia**

Erythroplakia is defined as “A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease”. The clinical appearance may be flat or even depressed with a smooth or granular surface. In case of a mixture of red and white changes such lesion is usually categorized as non-homogeneous leukoplakia ("erythroleukoplakia"). Tobacco and alcohol use are considered important etiologic factors. The possible role of *C. albicans* is at present still unclear.

Prevalence figures of erythroplakia are only available from studies performed in South- and Southeast Asia and vary between 0.02% and 0.83%. Erythroplakia mainly occurs in the middle aged and the elderly. There is no distinct gender preference. Any site of the oral and oropharyngeal cavity may become involved, usually in a solitary fashion. This solitary presentation is often helpful in clinically distinguishing erythroplakia from erosive lichen planus, lupus erythematosus and erythematous candidiasis, since these lesions occur almost always in a bilateral, more ore less symmetrical pattern.

Histopathologically, erythroplakia commonly shows at least some degree of dysplasia and often even carcinoma in situ or...
There is an ongoing debate in the literature whether patients with oral lichen planus (OLP) carry an increased risk of developing a squamous cell carcinomas. Nevertheless, there is a tendency to accept that there is.67–70 The reported annual malignant transformation rate is usually well below 1%. Apparently, such event may occur in all clinical types of OLP.71 Unfortunately, the issue of malignant transformation in OLP is blurred by the often present lack of clinicopathologic correlation in the diagnosis.72,73 Furthermore, there is the somewhat confusing histopathological term “lichenoid dysplasia”,74 probably mainly used in case of a bandlike lymphocytic infiltrate underneath dysplastic epithelium. When one accepts that oral lichen planus may transform into a squamous cell carcinoma, then it is conceivable that in such event dysplastic changes may occur, justifying the use of the term lichenoid dysplasia. However, based on personal experience there is rarely clinical evidence for pre-existing lichen planus in case of lichenoid dysplasia; this has also been confirmed by others.75

There are no possibilities to truly prevent malignant transformation of oral lichen planus. The efficacy of continuous follow-up of oral lichen planus patients is questionable.68 although such follow-up has been recommended by various authors.76–78

**Oral submucous fibrosis**

The occurrence of oral submucous fibrosis (OSF) is more or less restricted to Southeast Asia, although a number of cases have been reported in other parts of the world, such as South Africa, Greece and the United Kingdom. The disease is most likely caused by the habit of chewing areca and betel quid or substitute.80 Clinically, OSF is characterized by a burning sensation, blanching and stiffening of the oral mucosa and oropharynx, and trismus. In advanced stages vertical fibrous bands appear in the cheeks, fa- cial pillars, and encircle the lips. Through an as yet unknown process, fibrosis and hyalinization occur in the lamina propria, which results in atrophy of the overlying epithelium. The atrophic epidermis apparently predisposes to the development of a squamous cell carcinoma in the presence of carcinogens. In a long-term follow-up study the annual malignant transformation rate was approximately 0.5%.81

**Some miscellaneous potentially malignant disorders**

**Actinic cheilitis**

Actinic cheilitis is a clinical term for an ulcerative, sometimes crust-forming lesion of the mucosa of part or entire vermilion border of the lower lip. The histopathologic spectrum varies from hyperkeratosis with or without epithelial dysplasia to early squamous cell carcinoma in the presence of basophilic changes in the lamina propria. There may be a marked inflammatory cell infiltrate present. The disease mainly occurs in elderly men. There are no incidence figures available from the literature. Depending on the clinical signs and symptoms, and the result of a biopsy, treatment usually consists of superficial surgical excision (“lip shave”) or CO2-laser evaporation.82 The advantage of surgical excision is the availability of a specimen for histopathologic examination. If CO2-laser is used, a pretreatment biopsy should be taken. Other treatment modalities such as photodynamic therapy, seem less effective.83 There are no follow-studies of untreated actinic cheilitis that would allow to present annual malignant transformation rates.

**Lichen planus**

There is an ongoing debate in the literature whether patients with oral lichen planus (OLP) carry an increased risk of developing a squamous cell carcinomas. Nevertheless, there is a tendency to accept that there is.67–70 The reported annual malignant transformation rate is usually well below 1%. Apparently, such event may occur in all clinical types of OLP.71 Unfortunately, the issue of malignant transformation in OLP is blurred by the often present lack of clinicopathologic correlation in the diagnosis.72,73 Furthermore, there is the somewhat confusing histopathological term “lichenoid dysplasia”,74 probably mainly used in case of a bandlike lymphocytic infiltrate underneath dysplastic epithelium. When one accepts that oral lichen planus may transform into a squamous cell carcinoma, then it is conceivable that in such event dysplastic changes may occur, justifying the use of the term lichenoid dysplasia. However, based on personal experience there is rarely clinical evidence for pre-existing lichen planus in case of lichenoid dysplasia; this has also been confirmed by others.75

There are no possibilities to truly prevent malignant transformation of oral lichen planus. The efficacy of continuous follow-up of oral lichen planus patients is questionable.68 although such follow-up has been recommended by various authors.76–78

**Oral submucous fibrosis**

The occurrence of oral submucous fibrosis (OSF) is more or less restricted to Southeast Asia, although a number of cases have been reported in other parts of the world, such as South Africa, Greece and the United Kingdom. The disease is most likely caused by the habit of chewing areca and betel quid or substitute.80 Clinically, OSF is characterized by a burning sensation, blanching and stiffening of the oral mucosa and oropharynx, and trismus. In advanced stages vertical fibrous bands appear in the cheeks, fa- cial pillars, and encircle the lips. Through an as yet unknown process, fibrosis and hyalinization occur in the lamina propria, which results in atrophy of the overlying epithelium. The atrophic epidermis apparently predisposes to the development of a squamous cell carcinoma in the presence of carcinogens. In a long-term follow-up study the annual malignant transformation rate was approximately 0.5%.81

**Some miscellaneous potentially malignant disorders**

**Actinic cheilitis**

Actinic cheilitis is a clinical term for an ulcerative, sometimes crust-forming lesion of the mucosa of part or entire vermilion border of the lower lip. The histopathologic spectrum varies from hyperkeratosis with or without epithelial dysplasia to early squamous cell carcinoma in the presence of basophilic changes in the lamina propria. There may be a marked inflammatory cell infiltrate present. The disease mainly occurs in elderly men. There are no incidence figures available from the literature. Depending on the clinical signs and symptoms, and the result of a biopsy, treatment usually consists of superficial surgical excision (“lip shave”) or CO2-laser evaporation.82 The advantage of surgical excision is the availability of a specimen for histopathologic examination. If CO2-laser is used, a pretreatment biopsy should be taken. Other treatment modalities such as photodynamic therapy, seem less effective.83 There are no follow-studies of untreated actinic cheilitis that would allow to present annual malignant transformation rates.

**Lichen planus**

There is an ongoing debate in the literature whether patients with oral lichen planus (OLP) carry an increased risk of developing a squamous cell carcinomas. Nevertheless, there is a tendency to accept that there is.67–70 The reported annual malignant transformation rate is usually well below 1%. Apparently, such event may occur in all clinical types of OLP.71 Unfortunately, the issue of malignant transformation in OLP is blurred by the often present lack of clinicopathologic correlation in the diagnosis.72,73 Furthermore, there is the somewhat confusing histopathological term “lichenoid dysplasia”,74 probably mainly used in case of a bandlike lymphocytic infiltrate underneath dysplastic epithelium. When one accepts that oral lichen planus may transform into a squamous cell carcinoma, then it is conceivable that in such event dysplastic changes may occur, justifying the use of the term lichenoid dysplasia. However, based on personal experience there is rarely clinical evidence for pre-existing lichen planus in case of lichenoid dysplasia; this has also been confirmed by others.75

There are no possibilities to truly prevent malignant transformation of oral lichen planus. The efficacy of continuous follow-up of oral lichen planus patients is questionable.68 although such follow-up has been recommended by various authors.76–78

**Oral submucous fibrosis**

The occurrence of oral submucous fibrosis (OSF) is more or less restricted to Southeast Asia, although a number of cases have been reported in other parts of the world, such as South Africa, Greece and the United Kingdom. The disease is most likely caused by the habit of chewing areca and betel quid or substitute.80 Clinically, OSF is characterized by a burning sensation, blanching and stiffening of the oral mucosa and oropharynx, and trismus. In advanced stages vertical fibrous bands appear in the cheeks, fa- cial pillars, and encircle the lips. Through an as yet unknown process, fibrosis and hyalinization occur in the lamina propria, which results in atrophy of the overlying epithelium. The atrophic epidermis apparently predisposes to the development of a squamous cell carcinoma in the presence of carcinogens. In a long-term follow-up study the annual malignant transformation rate was approximately 0.5%.81

**Some miscellaneous potentially malignant disorders**

**Actinic cheilitis**

Actinic cheilitis is a clinical term for an ulcerative, sometimes crust-forming lesion of the mucosa of part or entire vermilion border of the lower lip. The histopathologic spectrum varies from hyperkeratosis with or without epithelial dysplasia to early squamous cell carcinoma in the presence of basophilic changes in the lamina propria. There may be a marked inflammatory cell infiltrate present. The disease mainly occurs in elderly men. There are no incidence figures available from the literature. Depending on the clinical signs and symptoms, and the result of a biopsy, treatment usually consists of superficial surgical excision (“lip shave”) or CO2-laser evaporation.82 The advantage of surgical excision is the availability of a specimen for histopathologic examination. If CO2-laser is used, a pretreatment biopsy should be taken. Other treatment modalities such as photodynamic therapy, seem less effective.83 There are no follow-studies of untreated actinic cheilitis that would allow to present annual malignant transformation rates.
Some inherited cancer syndromes

In xeroderma pigmentosum and Fanconi’s anemia there is an increased incidence of malignancies, including oral cancer.\(^8\)

Immunodeficiency

In immunodepressed patients, e.g. due to the prolonged use of immunosuppressive drugs after solid organ transplants, there is an increased risk of cancer, particularly of the lower lip.\(^8\) In patients who underwent a liver transplant there was no increased prevalence of oral or oropharyngeal cancer.\(^8\) There has been a report of an immunosuppressed liver transplant recipient in whom oral leukoplakia rapidly progressed to carcinoma.\(^8\)

Particularly in the era before HAART therapy, but also more recently, a number of HIV-infected patients with oral cancer have been reported.\(^8\) Furthermore, oral cancer have been reported in patients suffering from chronic Graft Versus Host Disease after stem cell transplantation.\(^8\)

Conflict of interest statement

None declared.

References

Pindborg JJ, Reichart PA, Smith CJ, van der Waal I.  

Ishii J, Fujita K, Komori T. Laser surgery as a treatment for oral leukoplakia.  

van der Waal I, Axell T. Oral leukoplakia: a proposal for uniform reporting.  


