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British Journal of Oral and Maxillofacial Surgery 51 (2013) 377–383

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Review

How should we manage oral leukoplakia?

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Accepted 26 October 2012
Available online 14 November 2012

Abstract

The aim of this article is to review the management of oral leukoplakia. The topics of interest are clinical diagnosis, methods of management and their outcome, factors associated with malignant transformation, prognosis, and clinical follow-up. Global prevalence is estimated to range from 0.5 to 3.4%. The point prevalence is estimated to be 2.6% (95% CI 1.72–2.74) with a reported rate of malignant transformation ranging from 0.13 to 17.5%. Incisional biopsy with scalpel and histopathological examination of the suspicious tissue is still the gold standard for diagnosis. A number of factors such as age, type of lesion, site and size, dysplasia, and DNA content have been associated with increased risk of malignant transformation, but no single reliable biomarker has been shown to be predictive. Various non-surgical and surgical treatments have been reported, but currently there is no consensus on the most appropriate one. Randomised controlled trials for non-surgical treatment show no evidence of effective prevention of malignant transformation and recurrence. Conventional surgery has its own limitations with respect to the size and site of the lesion but laser surgery has shown some encouraging results. There is no universal consensus on the duration or interval of follow-up of patients with the condition.

Keywords: Oral leukoplakia; Oral precancerous lesions

Introduction

Potentially malignant disorders of the oral cavity can be broadly classified into precancerous lesions and precancerous conditions.[1] The purpose of identifying potentially malignant disorders of the oral cavity is to initiate timely and adequate intervention and, where possible, to prevent malignant transformation, or enable early diagnosis of malignancy.

Oral leukoplakia

Much of the published data on the prevalence of potentially malignant disorders varies by the geographical location and population studied. Estimates of the global prevalence of oral leukoplakia range from 0.5 to 3.4%.[2] The point prevalence is estimated to be 2.6% (95% CI 1.72–2.74)[2] with a reported malignant transformation rate that ranges from 0.13 to 17.5%.[3,4] Prevalence increases with advancing age; it is less than 1% in men younger than 30 years, but 8% in men and

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0266-4356/$ – see front matter
http://dx.doi.org/10.1016/j.bjoms.2012.10.018

2% in women over 70 years. Smoking is the most commonly associated aetiological factor but there are other possible factors such as alcohol, HPV infection, candidiasis, and reduced concentrations of serum vitamin A and beta-carotene.[5]

Definition

Leukoplakia is a common precancerous lesion of the oral cavity. Oral leukoplakia is defined as: "a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion".[1,6,7] A report by Warnakulasuriya proposed that: "OL should be used to recognise white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer".[1]

Classification

Considering the macroscopic appearance, oral leukoplakia is broadly classified into homogeneous and non-homogeneous subtypes. Homogeneous plaques are predominantly white, of uniform flat, thin appearance with shallow cracks of surface keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout.[7] Non-homogeneous plaques are predominantly white, or white and red (erosive leukoplakia, erythroleukoplakia) and may be either irregularly flat, nodular (speckled), or verrucous.[1,8,9] Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia, and is characterised by a multifocal presentation, resistance to treatment, and high rate of malignant transformation.[8]

Histopathology

Oral leukoplakia can be distinguished as dysplastic and non-dysplastic lesions based on histological examination. The presence of dysplasia has been associated with a risk of progression to cancer.[10] It has been widely acknowledged that the grading of dysplasia is subjective, and there is little agreement among and between observers because of the lack of objectivity in the evaluation of established criteria, arbitrary division of grades, lack of calibration of criteria and grading, and not enough knowledge about which criteria best predict malignant potential.[10–13] The binary system for histopathological grading was proposed to reduce variability between observers. In this system the lesions are graded as low risk (mild and moderate dysplasia) and high risk (severe dysplasia and carcinoma in situ) depending on the architecture and cytological changes. The sensitivity and specificity of the new binary grading system for predicting malignant transformation in oral epithelial dysplasia were 85% and 80%, respectively, and the accuracy was 82%.[14]

Malignant transformation

Several factors have been associated with an increased risk of malignant transformation. Multivariate analysis has shown that age, site and type of lesion, and dysplasia are independent risk factors.[15]

Appearance

In general, homogeneous lesions are thought to have a low risk of malignant transformation, mixed white and red lesions (or speckled leukoplakia) an intermediate risk, and pure erythroplakia (red lesions) the highest risk. However, none of these macroscopic features is reliably diagnostic of any histological grade of precursor lesion, and histological analysis of the lesions is mandatory to discover their biological potential.[8,13,16]

Site and age

Lesions on the tongue or floor of the mouth, and larger lesions (more than 200 mm^2) have also been known to be predictive indicators of malignant transformation,[3,8] and it has been reported that in non-smokers they carry an increased risk. Elderly patients (over 60 years of age) with lesions on the lateral or ventral tongue, and who had non-homogeneous lesions with high-grade dysplasia, correlated a much higher risk of transformation.[15]

Dysplasia

Epithelial dysplasia has been regarded as one of the most important indicators of malignant potential. It has been reported that dysplastic oral leukoplakia carries a 5-fold greater risk of malignant transformation than non-dysplatic oral leukoplakia,[16] and its predictive value depends on the prevalence of leukoplakia in a given population.[10] In patients with histologically confirmed disease, oral cancer-free survival has been reported as 86.6% at 3 years and 82.0% at 5 years. High-grade dysplasia had a considerably higher incidence of malignant change than low-grade dysplasia (5-year oral cancer-free survival 59% compared with 90.5%).[15]

Over the years, it has been suggested that DNA content (DNA ploidy) is an important predictor of the malignant potential of leukoplakia or erythroplakia. In a case-control study, multivariate analysis of time to progression showed that abnormal DNA content was a significant predictor for progression to cancer with a hazard ratio (HR) of 3.3 (95% CI 1.5 to 7.4) corrected for site and grade of dysplasia.[17] Results of a study by Bremmer et al.[18] showed that DNA aneuploidy was associated with the development of cancer (HR 3.7, 54% sensitivity and 60% specificity). They also found no association between patient-related clinical factors and the risk of malignant transformation, and a relatively low correlation between ploidy and grade of dysplasia. A combination of aneuploidy with dysplasia seemed to improve the specificity to almost 100%, but this was at the expense of a lower sensitivity. They concluded that lesions that show DNA aneuploidy have a significantly higher risk of malignant transformation, although DNA diploid lesions are not

exempt from malignant progression. For individual patients, DNA ploidy as a single biomarker has limited value to predict progression to cancer.

Despite advances in molecular biology, there are no reliable markers to predict the malignant transformation of oral leukoplakia.[19] It has been reported that a few markers such as Ki-67(Mib-1) and bromodeoxyuridine, and the combined biomarker score of chromosomal polysomy, p53, and loss of heterozygosity might be strong predictors for malignant transformation, but this is not generally adopted in clinical practice.[7]

The molecular events that induce a premalignant lesion to progress to carcinoma are still unknown, and the over-expression (or under-expression) of biomarkers alone adds little predictive value over standard histological analysis.[13] The detection of dysplastic lesions using oral cytological examination is promising, but has been limited so far by variable false-positive and false-negative results.[13]

Diagnosis

A provisional diagnosis of oral leukoplakia is made when other possible aetiological factors, including use of tobacco, have been ruled out. An arbitrary period of 2–4 weeks seems to be an acceptable time to look for regression after possible causative factors have been eliminated.[1,8,16] In practice this could mean – for example, smoothing the edges of a sharp tooth or a restoration. It is also well recognised that lesions sometimes take longer to regress or disappear.[8,16] A biopsy examination is essential if a lesion persists beyond this period to rule out any other specific disorder.[1]

Incisional biopsy with scalpel and histopathological examination of the suspicious tissue is the gold standard. Punch biopsy is a useful alternative and can be used in multiple and diffuse mucocutaneous lesions; incisional biopsy is done for large (more than 1.0 cm), multiple, or diffuse lesions. In those that contain areas of erythroplakia and leukoplakia, lesions with erythroplakia must be given priority because they have the most cellular activity.[20]

Oral transepithelial brush biopsy with computer-assisted analysis (OralCDx®, CDx Diagnostics™, Suffern, USA) helps to differentiate between precancerous and cancerous cells, and has 52% sensitivity and 29% specificity.[21] The drawback is that if it is positive or inconclusive then a tissue biopsy is indicated. It can also be used as a follow-up tool[21] but its usefulness in everyday practice is limited.

Toluidine blue, Lugol's iodine,[22–26] and whitening of the oral mucosa induced by acetic acid[27] have been used to help to identify and demarcate potentially malignant mucosal lesions, but subjective interpretations make them unreliable and there is no convincing evidence available to support their use in clinical practice.[28]

Optical diagnostic techniques detect a change in the optical property at a molecular level, and an alteration in the interaction between light and tissue is used to differentiate normal from malignant tissue. These techniques overcome some of the limitations of standard techniques (being invasive and time consuming, and lacking uniformity in reporting) by offering objective data analysis, which may reduce variations in pathological diagnosis. They also provide real-time assessment of tissue structure and metabolism through a minimally invasive approach. The benefits of optical technologies are limited in current daily clinical use, but with developing technological advances they have the potential to revolutionise the diagnosis and surveillance of precancerous and cancerous lesions at the early stage of development.[29]

Autofluorescence spectroscopy and imaging systems can differentiate normal oral mucosa from abnormal tissue (82–100% sensitivity, 63–100% specificity) but there is a lack of evidence to support their ability to distinguish different types of lesions.[30] When probed, the cancerous and precancerous lesions show less green fluorescence than the surrounding normal mucosa. A study by Awan et al.[31] showed that autofluorescence had 84.1% sensitivity and 15.3% specificity for detecting dysplastic lesions, but they also commented that it could not be used for screening, and could not dictate the biopsy site in a large and heterogeneous lesion.

Multispectral imaging systems (fluorescence, narrow band imaging, orthogonal polarised reflectance)[28] and trimodal spectroscopy (fluorescence spectroscopy, elastic scattering spectroscopy, Raman spectroscopy)[32] have been shown to diagnose precancerous or cancerous tissue accurately. Even though they can diagnose precancerous lesions reliably, they can be expensive and time consuming, which limits their efficacy in daily clinical practice.

Management

The presence of epithelial dysplasia is the still the strongest predictor of future malignant transformation.[1] Some groups think that it is safe to treat all lesions irrespective of the presence of dysplasia, even though there has been no documented evidence that treatment of any kind prevents the possible future development of malignancy.[8,33]

Various non-surgical and surgical treatments have been reported, but currently there is no consensus on which is best. Outcomes seem to vary, and long-term follow-up studies are few. Operation can include conventional surgery,[6,16,34] electrocauterisation, laser ablation,[35,36] or cryosurgery.[6]

Non-surgical treatments to prevent malignant transformation may also be considered.[6,37] They cause minimal adverse effects, particularly in patients with widespread oral leukoplakia that involves a large area of the oral mucosa, or in those with medical problems who have high surgical risks.[6] The use of carotenoids (beta-carotene,[38] lycopene), vitamins A, C, and K, fenretinide,[39] bleomycin, and photodynamic therapy have been reported, but at this time randomised controlled trials for non-surgical treatment have not shown evidence

that they effectively prevent malignant transformation and recurrence.[6]

Invasive procedures include conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation). Conventional surgery involves excision of the lesion with or without a skin graft or other dressing material, but often is not feasible for extensive lesions or those in certain anatomical locations. The associated morbidity of surgery also makes it less appealing for extensive lesions. Electrocoagulation produces thermal damage in the underlying tissue, which causes postoperative pain and oedema, and leads to considerable scarring. Postoperative pain and oedema are also severe after cryosurgery.[35]

Carbon dioxide, neodymium:yttrium-aluminium garnet (Nd:YAG), argon, and potassium-titanyl-phosphate (KTP) lasers are used in the management of oral leukoplakia.[35] Advantages are haemostatic effects, minimal electrocontractility, and minimal damage to the surrounding tissue, which reduces acute inflammatory reaction and postoperative pain. Wound healing is excellent because of limited contraction; it produces satisfactory mobility of the oral mucosa and minimum oral dysfunction.[35] The reported cure rates after laser surgery vary between 33.9% and 82%, and recurrence between 7.7% and 66%.[40] Another large retrospective study reported cure rates of 82%, local recurrence of 9.9%, and 1.1% malignant transformation.[35] Various factors such as surgical technique, selection of patients, and follow-up periods may account for the wide range of results. The laser evaporation technique has a disadvantage, as no tissue is available for histopathological examination.

Prognosis

Although clinical appearance such as non-homogeneous oral leukoplakia or erythroplakia,[41,42] and anatomical site (notably the floor of the mouth and the ventral tongue) can help to identify lesions with a high risk of transformation,[41] there are no reliable ways to predict the behaviour of individual lesions or to guide clinical management without biopsy examination. Patients with multiple oral precancerous lesions and extensive areas of mucosa that may show signs of dysplastic change are particularly difficult to manage.[41] Modern concepts of carcinogenesis have emphasised the existence of molecularly altered preneoplastic fields from which multiple lesions can develop.[43] Widespread lesions have been shown to have higher rates of malignant transformation than those that are more localised.[1,6]

A study by Holmstrup et al. identified 2 factors that are of prognostic value: size and type of lesion.[3] Logistic regression analysis showed that other factors that characterise lesions were insignificant in most instances. Non-homogeneous leukoplakia had an odds ratio of 7.0 for cancer to occur compared with homogeneous leukoplakia. There is no substantial reported evidence for the size of the lesions to develop into cancer but this study showed that in those that exceeded 200 mm^2 the odds ratio for cancer to occur was 5.4 as opposed to smaller lesions. There was no correlation between histological features and clinical outcome, which may be explained by the biopsy site not being representative of the entire lesion.

The risk of malignant transformation has been reported to be between 6.6% and 36.4%, although a recent meta-analysis indicated a rate of 12.1%.[44–46] A recent study reported a relatively high malignant transformation rate (22%) at 5 years among patients diagnosed with oral epithelial dysplasia. Factors such as not smoking, lateral tongue site, and non-homogeneous appearance were all associated with a 5-year malignant transformation rate of around 40% or more. The study showed that the lesions on the lateral border of the tongue had the highest rate of malignant transformation (53% at 5 years) and the floor of the mouth was the commonest site of epithelial dysplasia (44%) with a malignant transformation rate of 8% at 5 years.[47]

Recurrence of oral leukoplakia after surgical treatment has been reported in 10–35% of cases,[6] and development of cancer after operation in 3–9% of cases[3]; 2.6–9% were after laser surgery.[35,48] Several reports have suggested that operation does not seem to prevent premalignant lesions from developing malignancy. The only significant factors associated with malignant transformation are clinical type and size of lesion. Other factors including site, demarcation, presence of any type of epithelial dysplasia, smoking, and operation seem to be insignificant with respect to future development of malignancy.[3] The lack of success of surgical treatment may be because of a multiclonal origin of the affected areas as seen in field cancerisation.[6] Such a concept includes the persistence of cells invaded by cancer outside the removed lesions.[49,50] This hypothesis is supported by studies on the DNA content in cells of oral leukoplakia,[3,17,18] which showed karyotypic changes in the oral mucosa other than those visible clinically and histologically.

Follow-up

A retrospective study to find out if biopsy examinations of oral premalignant lesions showed findings representative of the whole excised specimen concluded that the biopsy examinations might not be reliable. Thirty-five percent of the total lesions had a more severe histopathological diagnosis, and compared with biopsy specimens taken on average 10.4 months earlier, 7% showed the presence of carcinoma. Therefore, if an incisional biopsy has been taken the lesions should be followed up by observations at close intervals (every 3–6 months) independent of the presence or absence of epithelial dysplasia. The study also concluded that none of the associated variables including presence of any degree of epithelial dysplasia in the whole lesion, site, demarcation, and smoking, influenced the risk of malignant development.[51]

No strict guidelines are followed regarding duration and frequency of follow-up examinations in patients with oral leukoplakia. Some authors recommend lifelong follow-up at

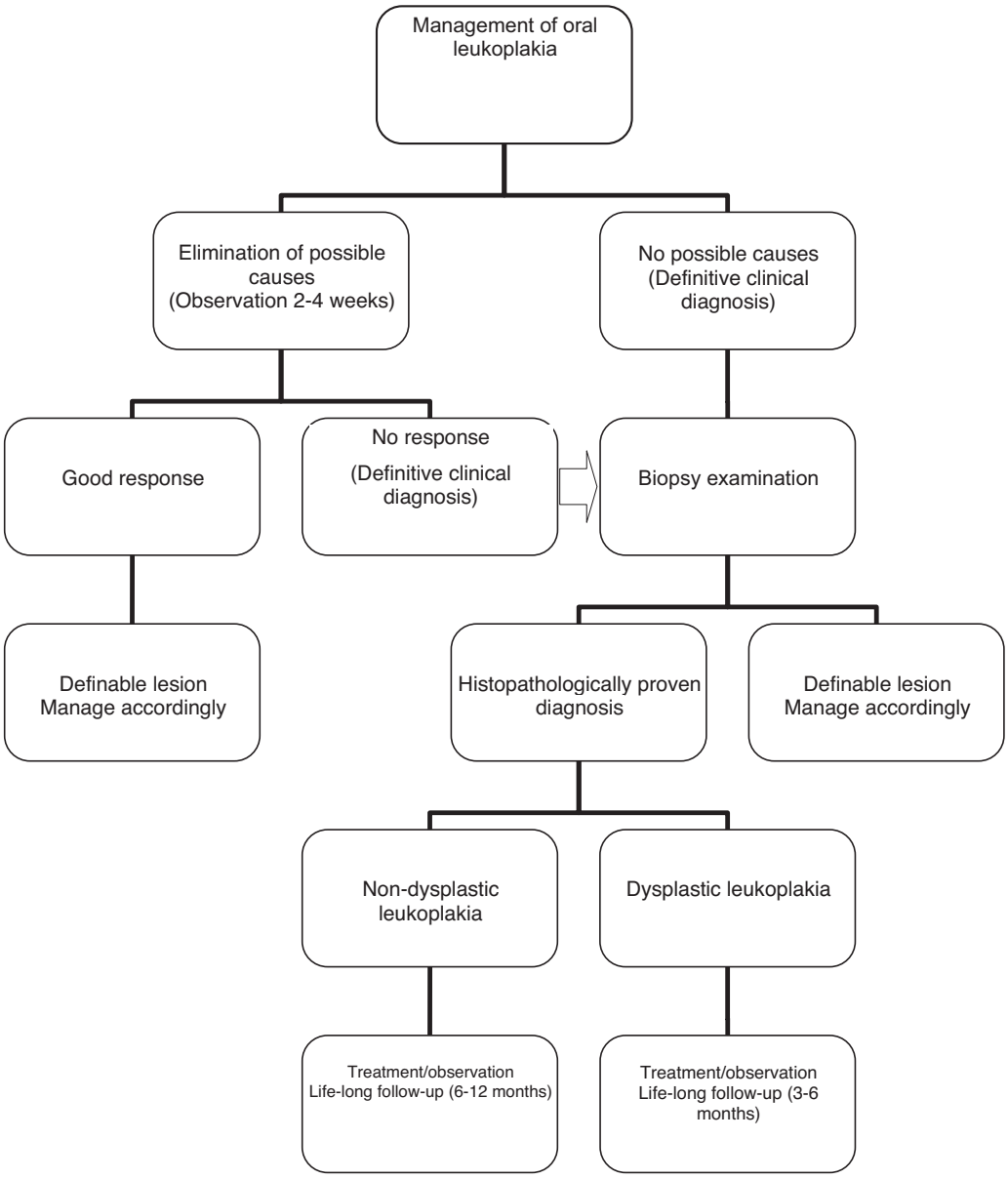

Fig. 1. Management of leukoplakia.

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intervals of 6–12 months in patients who have, and have not had treatment. Occasionally – for example, in an untreated patient with dysplastic leukoplakia, one may feel the need for follow-up visits at 3-month intervals (Fig. 1).[9]

Summary

Oral leukoplakia is a common premalignant condition. Although it is generally accepted that early detection and screening for oral cancer have the potential to reduce the morbidity and mortality of disease, methods of screening have yet to be proved successful. Incisional biopsy is mandatory for diagnosis, planning treatment, and for ascertaining the prognosis of the lesion. The risk factors for malignant transformation include age, site, size, appearance, presence of dysplasia, and abnormal DNA content, but there is no single predictive factor or any reliable biomarker predictive of malignant transformation.

There is no universal consensus on the most appropriate treatment, and despite treatment the disease can recur, undergo malignant transformation, or new lesions can develop in patients treated previously. Site, size, dysplastic features, and the patient's preference dictate the surgical options available. Complete excision of high-risk lesions is recommended, and specialists should closely follow up these patients for life. Life-long follow-up by a specialist is also necessary when complete excision is not possible

and non-surgical options are used. For low-risk lesions and those that have been treated successfully, follow-up can be arranged in the primary care setting by the general dental practitioner as part of their routine check up.

Factors associated with increased risk of malignant transformation are patients who do not smoke and are over 60 years of age; lesions that are non-homogeneous or are wide spread; lesions on the lateral border of the tongue and those larger than 200 mm^2; and histopathologically confirmed epithelial dysplasia.

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