

Leukoplakia and erythroplakia of the oral mucosa – a brief overview

SADJ November 2012, Vol 67 no 10 p558 - p560

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SUMMARY

Leukoplakia and erythroplakia are the two most common potentially malignant disorders of the oral cavity. The prognosis and overall survival of a patient with oral cancer is dependent on the early detection of any lesion that might identify a patient with higher risk than normal or with early infiltration before metastatic disease. The role of the general dentist cannot be overstressed and the aim of this brief summary is to give the general practitioner an overview on the current concepts relating to these disorders.

Leukoplakia and erythroplakia were traditionally known as two "precancerous lesions of the oral mucosa". The term "precancer" defines all lesions classified as such to have a "precancerous nature" implying that all of them will eventually become malignant. Through the years it became known that even clinically normal mucosa may show features of dysplasia and in some instances molecular aberrations of early malignant transformation may be found in the mucosa of a patient without any clinical lesions or dysplasia. The consensus view then was to introduce the term: "potentially malignant disorders" (PMD) reflecting the more generalised mucosal involvement in these patients. It remains a challenge to predict the behaviour of any of these lesions but early detection thereof remains the best chance any oral cancer patient will have for survival.

LEUKOPLAKIA

In 1978 the World Health Organisation (WHO) defined leukoplakia as "a white patch or plaque that cannot be characterised clinically or pathologically as any other disease".¹ Subsequent changes to the definition briefly included reference to "tobacco"² but that was soon discarded and permanently excluded as there seems to be no clinical rationale for distinguishing tobacco-associated from idiopathic leukoplakia. The current definition is that of "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer".³ Leukoplakia is a clinic-pathological diagnosis that can only be made after histological examination of the tissue. Other white mucosal lesions such as frictional keratosis, lichenoid lesions, lichen planus and other autoimmune diseases associated with white lesions (discoid lupus erythematosus), nicotine stomatitis, morsicatio, tobacco pouch keratosis, leukoedema and

ACRONYMS

PMD: Potentially Malignant Disorders
PVL: Proliferative Verrucous Leukoplakia

hyperplastic candidiasis should be excluded. The white appearance of all of these lesions is the combined effects of increased surface keratin production, thickened epithelial layers and resultant obscured sub-epithelial vascularity. This implies that a biopsy is mandatory when a clinical diagnosis cannot be made with certainty.

Epidemiology

Leukoplakia represents the most commonly encountered PMD of the oral mucosa. The reported prevalence varies geographically but also reflects differences in study design and populations studied. To make things worse, the term leukoplakia is used indiscriminately in the literature and the true incidence and malignant transformation potential is uncertain. "Candidal leukoplakia", "sanguinaria-induced leukoplakia", "syphilitic leukoplakia" and "oral hairy leukoplakia", amongst others, are all specific disease entities with well-described pathogeneses and the term "leukoplakia" seems inappropriate and confusing. Most authorities agree the worldwide prevalence rate of PMD to be somewhere between 1% and 5% with leukoplakia responsible for more than 80% of these.^{4,5} The transformation rate of leukoplakia into oral cancer is controversial but certain clinical factors have been identified which seem to be relatively good indicators of higher risk. These include older age, female gender; anatomical location (high risk areas) and large size of the lesion (involving more than one anatomical area) as well as tobacco and alcohol usage. The presence of heterogeneity within the clinical lesions, such as areas alternating in thickness and colour (speckled leukoplakia or erythroleukoplakia), is associated with an increased risk of malignant change.

Clinical and microscopic features

Leukoplakia may affect any mucosal location. High-risk areas for malignant transformation have been identified as floor of the mouth, lateral borders of the tongue and the soft palate/retromolar areas. Clinically, two main types of leukoplakia are recognised, namely: homogenous and non-homogenous types. Homogenous leukoplakia is flat, thin and has a uniformly vague or definitive white colour mimicking white paint brushed onto the mucosa (Figure 1). Non-homogenous leukoplakia is heterogeneous. It may be flat with a speckled red and white appearance, nodular with a more granular appearance (Figure 2) seen as small polypoid outgrowths or verrucous with a wart-like, "wrinkled" or cor-

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Figure 1: Small homogenous leukoplakia (arrow) on the floor of mouth.



Figure 2: Nodular leukoplakia on the ventral surface of the tongue, floor of mouth and alveolar ridge.



Figure 3: Erythroleukoplakia (arrow) of the soft palate.

rugated appearance. Non-homogenous lesions, especially erythroleukoplakia (Figure 3) should be managed with great caution. A sub-type of verrucous leukoplakia that deserves special mention is proliferative verrucous leukoplakia (PVL). The diagnosis of this non-homogenous form of leukoplakia can only be made retrospectively. It is characterised by a long history of recurrent verrucous leukoplakias presenting in various locations, seen predominantly in older females without a tobacco history and most importantly (Figure 4). PVL has a high rate of malignant transformation.⁶

Diagnosis

On initial discovery of a white lesion the clinician should aim to find an explanation for its presence. If any possible cause is evident, such as local mechanical irritation by a broken restoration, remove it and recall the patient in two to four weeks. If no change in the clinical appearance of the lesion is visible after the waiting period or if no explanation for its presence could be found in the first place, a diagnosis of provisional leukoplakia is made and a biopsy is mandatory. The role of histological analysis of the leukoplakia is twofold: (1) to exclude other pathologies that might be responsible for the white lesion and (2) to evaluate the presence and degree of epithelial dysplasia within the lesion.

Microscopically, leukoplakia is subdivided into those with and those without epithelial dysplasia. Epithelial dysplasia



Figure 4: **A:** Patient with PVL presenting with non-homogenous leukoplakia involving several anatomical areas. **B:** Same patient developed a squamous cell carcinoma at a later stage.



Figure 5: Erythroplakia (arrow) of the soft palate

is defined by the presence of abnormal architectural and cytological features but also the absence of invasion by malignant cells. The presence of dysplasia in leukoplakia is believed to be associated with a higher probability to transform into oral cancer which increases with the grade.^{7,8} Unfortunately non-dysplastic lesions may also transform into cancer⁹ but even so, the presence and severity of dysplasia in such a lesion currently remains the best predictive marker available.⁷ That said, microscopic grading of dysplasia is subjective and substantial inter- and intra-observer variation in the interpretation of the grade or even the presence of dysplasia has been shown.¹⁰

The WHO classification recognises five discernible stages of dysplasia: squamous hyperplasia, mild, moderate and severe epithelial dysplasia and carcinoma *in situ*.¹¹ A binary system that divides epithelial dysplasia into “low-risk” (no/questionable/mild dysplasia) and “high-risk” (moderate or severe dysplasia) complements the WHO system and has proven superior in correlation and reproducibility between pathologists.¹² The inclusion of molecular markers into the grading of dysplasia has been proposed^{13,14} but most pathologists still use only light microscopic assessment.

ERYTHROPLAKIA

Erythroplakia is the PMD with the highest risk of malignant transformation defined as “a fiery red patch that cannot be characterised clinically or pathologically as any other definable disease”.³ As is the case with leukoplakia, the clinical diagnosis of erythroplakia does not carry any microscopic connotations and is therefore a diagnosis by exclusion.

Epidemiology

There is a lack of literature dealing purely with erythroplakia. It is discussed mainly with leukoplakia under the heading of erythroleukoplakia and in epidemiologic studies dealing with oral mucosal lesions and under oral squamous cell carcinomas due to the fact that a large percentage of erythroplakia lesions already have infiltrating carcinoma.¹⁵⁻¹⁷ The true prevalence is therefore uncertain but is reported to be between 0.02% and 0.83%.^{16,18} Studies showed 85-90% of early oral squamous cell carcinomas presented initially as erythroplakia¹⁹ and up to 50% of erythroplakias do transform into carcinoma.¹⁶

Clinical and microscopic features

Erythroplakia is usually seen in adults over 45 years¹⁸ where it most commonly involves the soft palate, floor of the mouth or buccal mucosa.¹⁶ Quantification of the amount of red versus white areas in non-homogenous lesions (“erythroleukoplakia” or speckled leukoplakia versus “leukoerythroplakia” or speckled erythroplakia) seems to be redundant as almost all PMD’s with red areas will show either severe epithelial dysplasia or microinvasive carcinoma on microscopic assessment of these areas.²⁰ If one adheres strictly to its defini-



Figure 6: **A:** Patient presents with erythroplakia (arrow) on the ventral surface of the tongue. **B:** Same lesion showing toluidine blue uptake (arrow). **C:** Loss of fluorescence (arrow) on Velscope examination.

tion, erythroplakia presents either as a solitary flat, velvety red macule, an erythematous area depressed below the level of the surrounding oral mucosa or as a plaque-like patch (Figure 5). The usually solitary presentation of erythroplakia helps to distinguish it from other more generalised red lesions such as erosive lichen planus and erythematous candidiasis.

IMPORTANT ASPECTS IN THE MANAGEMENT OF PMD

The gold standard for the diagnosis and management remains histopathologic assessment of a biopsy from a suspicious lesion. This depends on the quality of the biopsy obtained, pertinent clinical information to the pathologist, interpretation of the biopsy by a pathologist knowledgeable in oral mucosal histology and pathology and the correct action by the clinician.

The microscopic structure of the oral mucosa varies in different areas and what might be considered normal epithelial thickness and features in keratinising mucosa of the palate will be diagnosed as dysplasia when present in the thin, non-keratinising mucosal areas of the ventral surface of the tongue or floor of mouth. The dental status, presence of any local irritants (fractured restorations or dentures), systemic or genetic diseases, patient habits (morsicatio), history of tobacco use (as well as type of tobacco used) are all important aspects that need to be considered together with microscopic examination. The pathologist can only confirm that no other pathology is present and comment on the presence and degree of dysplasia or infiltration after taking all of the above information into careful consideration.

Selection of the biopsy site

It is important to select the biopsy site that will be representative of the most significant epithelial pathology present in the mucosa at that time. If the clinician feels uncomfortable with the practice of taking biopsies, the patient should be referred as selection for ease of access by the clinician might not be representative of the areas with highest risk for malignant transformation with under-management as a result. Multiple biopsies are advisable in a patient with large or extensive involvement of the mucosa. Each sample should be submitted in separate, clearly labelled containers.

The most commonly used diagnostic aids purported to assist the clinician in selection of the most appropriate biopsy site include Toluidine blue mouth rinse and tissue autofluorescence (VELscope). Toluidine blue is a vital dye that stains nucleic acids and has been used as an aid to identify mucosal abnormalities for many years. In principle, the higher the DNA contents of a cell, the bluer the staining of the tissue which should at least guide the clinician's decision. Tissue autofluorescence rests on the principle that exposure of tissue to a certain excitation wavelength should result in autofluorescence of cellular fluorophores, seen as a light green fluorescent colour. In the case of abnormal tissue,

there is a change in the concentration of fluorophores which should result in colour changes observed usually as loss of the green fluorescence (Figure 6). These techniques have low sensitivity due to uptake of dye and loss of fluorescence in inflamed and ulcerated tissue due to non-neoplastic pathology.²¹ It is important to realise that these modalities can only be used as meaningful adjuncts in the armamentarium of a clinician competent to interpret the clinical lesions present and never as screening tools.

Declaration: No conflict of interest declared

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