

Update on Precancerous Lesions

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Abstract: Oral cancer continues to be a serious problem in the UK and it is well known that prevention and early recognition of potentially malignant lesions will provide the best prognosis. This article discusses recent changes in the nomenclature of lesions and current concepts in diagnosis and management.

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Clinical Relevance: Appropriate management and early detection of pre-cancerous lesions may eliminate the possibility of oral cancer developing or reduce the morbidity associated with treatment of such lesions.

The timely diagnosis of a malignant lesion, and its subsequent management, is well known to provide the best prognosis.¹ Despite increasing awareness among the healthcare profession and the public, the incidence of oral cancer is steadily increasing in the UK.² It may be considered that dental professionals are ideally situated to recognize potentially malignant lesions in the oral cavity. Primary oral cancer continues to be diagnosed at a late stage and is often, therefore, well advanced. Accordingly, despite advances in therapy, it continues to have a high mortality rate.³ The value of a formal screening programme for oral cancer as yet has not been proven, but dentists, particularly in general dental practice, are in an ideal situation to regularly 'screen' their patients' oral mucosa for the early signs of oral malignancy or potentially malignant lesions. Some cases of oral cancer, perhaps as many as one-third, are preceded by often relatively innocent-appearing lesions.

Leukoplakia or erythroplakia are the two most common, although most cases of oral cancer are thought to arise *de novo* from a background of apparently normal epithelium.⁴ Less often, other apparently benign lesions prove to be either premalignant or malignant. The purpose of this article is to highlight some lesions that dental professionals should suspect to be premalignant or malignant in order for the appropriate management to be implemented. This will therefore allow earlier treatment measures to be undertaken.

Many questions remain unanswered:

- Will a precancerous lesion always become malignant?
- How long will this process take?
- How can we, as dental professionals, prevent this process?
- What is the best method of diagnosis of these lesions?
- How should we then manage these lesions?
- Should all oral dermatoses be regarded as premalignant until proven otherwise?

Some of these questions will take a number of years to be solved. At present, the knowledge of some white

and/or red oral lesions is better than that of others.

AETIOLOGY OF ORAL CANCER

Numerous factors have been suggested in the aetiopathogenesis of oral cancer. The most commonly associated ones are:

- tobacco;
- alcohol;
- nutrition;
- genetics;
- viruses;
- ultraviolet radiation;
- mouthwashes; and
- occupational hazards.

The roles of tobacco and alcohol, and their synergistic effects in the aetiology, of oral cancer are well established.² In addition to conventional smoking, other methods of tobacco usage such as reverse smoking, tobacco chewing, and PAN usage must be considered as important aetiological factors. It is therefore important to question patients from differing ethnic and social backgrounds not only whether or not they smoke, but also if they use alternative tobacco forms. Only then will the dental professional be able to advise each individual patient of the risks.

Less information is available regarding the effects of other potential carcinogens and their interactions in the transformation of normal oral epithelium into either a premalignant lesion or a malignant lesion. The role of sunlight in the development of lip cancer will be further discussed below.

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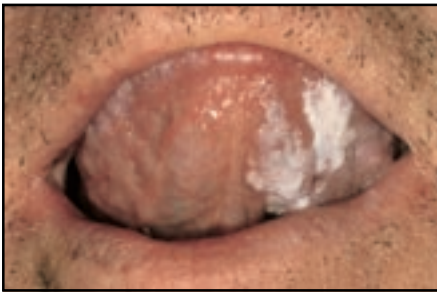


Figure 1. Homogeneous leukoplakia affecting the ventral surface of the tongue. Biopsy is required for histological diagnosis.

TERMINOLOGY

A symposium in Sweden⁵ sought to clarify the terminology used for precancerous lesions, leukoplakia in particular, which will help communication between clinicians and accurate prediction of the prognosis of these lesions. The terms *precancerous* and *premalignant* are synonymous; however, the terms *precancerous lesion* and *precancerous condition* cannot be interchanged.

A precancerous lesion is a morphologically altered tissue in which cancer is more likely to occur than in an apparently normal counterpart. An example is leukoplakia. A precancerous condition, on the other hand, is a generalized state associated with a significantly increased risk of developing malignancy. A good example is oral submucous fibrosis.

SPECIFIC LESIONS

The clinical lesions commonly considered to be premalignant or that can simulate premalignant lesions are:

- leukoplakia;
- erythroplakia;
- leukoerythroplakia;
- smoker's keratosis;
- oral submucous fibrosis;
- actinic keratosis/cheilitis;
- inherited conditions (e.g. dyskeratosis congenita);
- lichen planus/lichenoid.

Common non-premalignant white and red lesions are:

- frictional keratosis;
- oral candidal lesions;
- chemical burns (e.g. by aspirin);
- thermal burns;
- pericoronitis;
- gingivitis;
- viral papillomata;
- haemangiomas;
- intra-oral skin grafts restoring surgical defects;
- lingua erythema migrans (geographic tongue);
- epulides;
- glossitis (drug related or due to deficiency disease);
- sublingual varicosities;
- intra-oral tattoos and foreign bodies;
- Fordyce's spots.

Leukoplakia

Recent advances in research into white patches have stimulated a great deal of interest into these lesions. The definition of oral leukoplakia has been updated following the Uppsala conference in 1994.⁵ This has now been adjusted to encompass those 'predominately white lesions of the oral mucosa, which cannot be characterized clinically or pathologically as any other disease: some oral leukoplakias will transform into oral cancer.' Leukoplakia should therefore be regarded as a clinical diagnosis until a definitive pathological diagnosis has been established following biopsy.

Categorization of White and Red Lesions of the Oral Mucosa

Homogeneous

A homogeneous lesion is a predominately white lesion which is uniformly flat and thin (Figure 1). Some small cracking may be evident. The surface may appear crinkled or corrugated, but must be of a similar texture throughout.

Non-homogeneous

A predominately white or white and red lesion (leukoerythroplakia) which may be flat, nodular or exophytic including

the clinical lesion of speckled leukoplakia (Figure 2).

Erythroplakia

These lesions are the red counterparts of leukoplakias and should be regarded in the same manner as leukoplakia. Many early oral cancers manifest as red patches, which are asymptomatic and are found at high-risk sites.⁶

Early Oral Cancer

This is a term used by some to describe a minimally invasive squamous cell carcinoma of the oral cavity, which is asymptomatic; most commonly presenting as erythroplakia with or without patches of keratosis, and found most often in the floor of the mouth, the soft palate complex or the lateral border of tongue. Such lesions do not tend to be ulcerated or indurated in comparison to more advanced lesions.⁶ Although these lesions have a similar clinical appearance to some precancerous lesions, histological investigation would reveal early invasion—emphasizing the importance of biopsy of such lesions (see below).

Other Leukoplakias

Hairy leukoplakia is almost exclusively associated with immunocompromised individuals; Epstein-Barr virus can usually be demonstrated within the epithelial cells. Although not premalignant, it is nevertheless an important lesion to recognize because of the potentially serious underlying condition. *Candidal leukoplakia* (Figure



Figure 2. Clinically speckled leukoplakia affecting the buccal mucosa. Following biopsy this was diagnosed as lichenoid reaction.



Figure 3. Candidal leukoplakia, typically affecting the mucosa in the commissure region. The clinical diagnosis was confirmed following biopsy.

3), although often demonstrating dysplasia histologically, will resolve following appropriate management. It is not in its own right considered to have any propensity for malignant transformation but lesions with a smoking and alcohol aetiology could coincidentally have candidal organisms present and therefore should be regarded with some suspicion.

Smoker's Keratosis

This condition is characterized by a general whiteness of the palatal mucosa with interspersed red areas, which are, in fact, the orifices of minor salivary glands that have become inflamed (Figure 4). It is thought to be a result of the thermal trauma from smoking, particularly from using a pipe. This condition itself is not premalignant, but continuation of the causative smoking habit could lead to malignant transformation in the future; possibly at sites distant from the palatal mucosa. Smoker's keratosis is therefore a precancerous condition. Mucosal biopsy may help diagnosis in cases for which elimination of carcinoma from the differential diagnosis is difficult.

Although uncommon in the UK, the condition known as reverse smoker's palate is occasionally seen. It results from smoking with the lit end of a hand-rolled cigarette within the mouth and is a definite premalignant lesion. Other white lesions attributable to smoking may occur at various sites in the mouth and may also be referred to as smoking-related keratosis but, according to the

above, should strictly be referred to as leukoplakia clinically if no other causative factors are identifiable.

Oral Submucous Fibrosis

This condition has not received much attention, probably because it is not common in Western countries. The signs are a response to the use of a betel quid, common practice in the Indian subcontinent and within some ethnic communities in the UK. Many leading authorities now consider oral submucous fibrosis to have a considerable genetic input. It is characterized by dense bands of fibrous tissue, which replace elastic tissue in the submucosal tissues and render the mucosa rigid (due to substances released from the areca nut). The mucosa can also show petechiae, melanosis and vesicles, which are thought to be caused by prolonged contact with the tobacco, which is often mixed with the areca nut in the quid. Severely affected individuals are unable to move the tongue and the most serious cases are handicapped by severe trismus. Those affected are at significantly increased risk of developing a malignancy, which is due to the carcinogenic effects of the tobacco. Unfortunately, cessation of the habit is not associated with regression of the condition, and regular follow up is mandatory. Other treatment, such as intralesional corticosteroids and surgery to release tight banding, may be successful although surgical intervention will result in further fibrous scarring.

Actinic Keratosis

The cumulative effect of ultraviolet radiation on exposed areas of skin and oral mucosa is the cause of this condition. Clinically, irregular scaly plaques on an erythematous background are the main features, although a keratin horn is occasionally felt on palpation. It is therefore a premalignant lesion and should be treated with respect. Surgical excision or cryosurgery are the preferred means of treatment. Long-term follow up is also advisable. Malignant transformation is estimated to occur in

about 0.25% of patients and the prognosis is good if the condition is treated early. Actinic cheilitis, which affects the oral mucosa, is analogous to the condition. Application of an adequate sunscreen to the lips is advisable for all patients.

Genetically Determined Mucosal Lesions

White Sponge Naevus

This is an entirely benign condition, which presents as diffuse raised plaques on the oral mucosa. It is inherited as an autosomal dominant trait but may not manifest clinically until adulthood.

Pachyonychia Congenita

This autosomal dominant benign condition is characterized by oral keratosis and palmar-plantar keratosis with no tendency to malignant transformation.

Xeroderma Pigmentosum

This rare genetically acquired condition is manifested by numerous cutaneous and oral malignancies in middle age.

Dyskeratosis Congenita

This is rare and thought to be X-linked due to the preponderance of males affected. The tongue and buccal mucosae develop bullae, which become erosions and finally leukoplakic lesions. These are considered premalignant: approximately one-third undergo malignant transformation.



Figure 4. Classical smoker's keratosis affecting the palate. The openings of the ducts of the minor salivary gland are erythematous and are superimposed upon a background of keratotic mucosa. No biopsy is required.

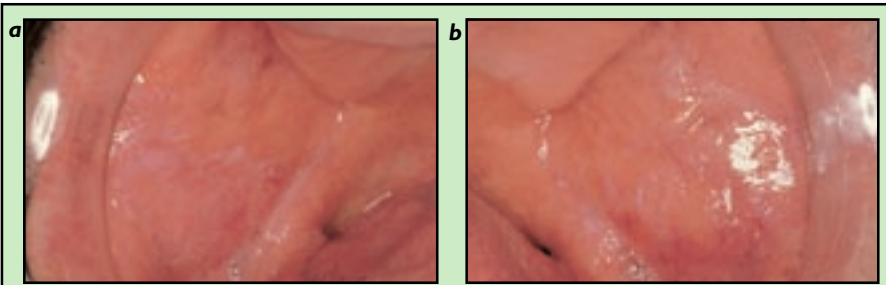


Figure 5a and 5b. Non-erosive lichen planus with faint white striae affecting the buccal mucosa bilaterally. The histological diagnosis supported the clinical findings.

Patients also often develop aplastic anaemia and severe periodontal disease.

Lichen Planus and Lichenoid Eruptions

Lichen planus classically has a bilateral distribution of white striae, particularly on the buccal mucosa and tongue (Figure 5); less often the gingivae are also involved. Lesions with a similar clinical appearance that are caused by drugs or topical agents (such as amalgam) often have a more localized distribution and are known as lichenoid eruptions or reactions (Figure 6). A potential for these lesions to undergo malignant transformation has been claimed but this is a rather contentious issue and widely debated in the literature: malignant transformation rates of between 1 and 5% have been quoted.⁷ Malignant transformation appears to be predominantly associated with the atrophic forms. It would therefore be sensible to monitor such lesions over a protracted period, even though the

potential for malignant change is very small.

MANAGEMENT

Any white or red patch that does not quickly resolve should be investigated. Clinical examination must include all of the oral mucosa: it is suggested that all patients should undergo a full oral mucosal examination at every dental visit. Visual examination may reveal the extent of any white or red area; this should be supplemented with palpation, which will reveal any induration or hardness. Sometimes drying the mucosa will reveal any subtle changes that may have been disguised by saliva. Mucosal stains (e.g. OraScan; Germiphene, Canada) are claimed to aid in the diagnosis of premalignant or malignant lesions. However, although showing a high sensitivity for carcinoma and being relatively sensitive for dysplasia, the specificity of mucosal stains is low and the only feasible use is in the surveillance of high-risk subjects.⁸

Definitive Diagnosis

The provisional diagnosis (or diagnoses) will have been reached following the clinical examination. In order to determine the definitive diagnosis, all aetiological factors should be excluded, and if the lesion persists the most appropriate special investigation is incisional or excisional biopsy. Owing to the polyaetiological nature of many potentially premalignant lesions, the histological diagnosis will often be at variance to that determined clinically. Biopsy is therefore regarded

as mandatory for all undiagnosed lesions, as most are diagnosable only histologically.

Often biopsy will be carried out following referral to a specialist centre; however, increasing numbers of general dental practitioners are performing biopsies. Whether the biopsy is carried out by the general dental practitioner before referral or by the specialist centre following referral will depend on local arrangements. Individual referral centres may operate a 'fast-track' referral system for suspicious lesions, and this should be used where possible to save valuable time in reaching the definitive diagnosis and instituting appropriate management. However, as biopsy shows many suspicious lesions to be relatively innocent, there is a real danger of clogging the 'fast-track' system.

Presence of Dysplasia

The histopathological report should include an estimation of the level of dysplasia within the lesion and exclude the possibility that invasion has already occurred. Dysplasia is the disordered maturation of mucosa in response to physical, chemical and microbiological irritants. Dysplastic epithelium may become neoplastic if the causative stimulus is not promptly discontinued. The level of dysplasia (often quantified by the pathologist as mild, moderate or severe) is of crucial significance to the clinician in regard to the management. There remains a 'grey' area as to the appropriate management of those lesions described as exhibiting lesser



Figure 6. The appearance of a lichenoid reaction to the amalgam restoration in 6]. Histological diagnosis confirmed the clinical diagnosis.



Figure 7. Leukoplakia on the ventral surface of the tongue. Following excision, histology revealed the presence of an early invasive squamous cell carcinoma.

degrees of dysplasia or those with no dysplasia at all, as a proportion do progress to malignancy.

Location of Lesion

The exact site of the lesion within the mouth should also be considered at the outset. Lesions of the tongue and floor of mouth should be regarded with the greatest suspicion as, at these sites particularly, there is a higher rate of transformation to malignancy (Figure 7). It is important to recognize lesions on the posterior aspect of the tongue, oropharynx and retromolar areas early, as tumours arising in these areas are notoriously difficult to manage and may have a worse prognosis than others.

Other Investigations

Other pertinent investigations include blood tests (full blood count, vitamin B₁₂ assay, folic acid assay, and random glucose sample). Clinical photography should also be considered in the monitoring of these lesions: this is an excellent method of recording changes in lesions. Microbiological investigations are only of use if a superimposed infection, typically candidal, is suspected.

Treatment

Treatment is fraught with difficulty. There is little consensus within the profession as to the best method of treatment. Between 3 and 36% of lesions may progress to malignancy (the higher figure quoted for

lesions exhibiting dysplasia).⁹ Lesions which exhibit red areas or are predominantly red (erythroleukoplakia) should usually be regarded with the greatest suspicion and, if possible, erythematous regions should be biopsied. Complete elimination of the lesion should be considered: either by excisional biopsy or by laser treatment. Alternatively, observation on a regular basis with serial biopsy (if required) may be the best recourse for large lesions.

The use of vitamin A analogues or other antioxidants has received much attention recently,¹⁰ but there is insufficient evidence to comment on the efficacy of these compounds in the prevention of oral carcinomas.

Prevention is better than cure and this is true in the case of oral cancer as it is well established that tobacco use and alcohol consumption play a significant role in the aetiology of oral cancer; their synergistic effects are well recognized.² The dental team therefore has a role in encouraging patients to cease these habits, although the help of medical practitioners and other healthcare workers may be needed.

CONCLUSION

- Arrange for biopsy of all white and red patches if in doubt, or if no resolution occurs after removal of all possible causative factors.
- Refer early where possible.
- Most cases of oral cancer arise *de novo* but could mimic precancerous lesions.
- Regular, systematic clinical evaluation of the oral cavity is mandatory for all

patients so that precancerous lesions can be recognized and treated.

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