Chapter 9
Clinical Presentation of Oral Mucosal Premalignant Lesions

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This chapter is concerned with the clinical presentation of premalignant oral mucosal lesions and identification of lesions as high or low risk for malignant transformation. In 2005, the WHO renamed the premalignant lesions as "oral potentially malignant disorders", a term that suggests malignant transformation may not be an inevitable consequence, rather a possibility, and may occur at a site distinct from the original presenting lesion. Evidence suggests that for dysplastic oral potentially malignant lesions, approximately 40% change very little with time, 20% can regress spontaneously and a further 20% may increase in size. Overall, 20% are at risk of malignant transformation. Unfortunately, there are currenty no highly sensitive or specific biomarkers available that can accurately predict malignant transformation. Management decisions are therefore decided by evaluating individual patients' risk in relation to known clinical and pathological risk factors. Accurately describing the clinical appearance of lesions is critical for communication with colleagues and for individual clinicians to follow up patients longitudinally.

In order to describe the clinical presentation of potentially malignant disorders, it is necessary to briefly explain the historical and current nomenclature used in clinics worldwide. Much of the difficulty in concluding optimal management strategies for patients with oral potentially malignant disorders in systematic reviews and meta-analysis of studies on oral potentially malignant disorder outcomes has arisen from differences used in the nomenclature of lesions.

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Nomenclature of Potentially Malignant Disorders

In 1972, the WHO distinguished a precancerous lesion as "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart". In contrast, a precancerous condition is defined as a "generalised state associated with a significantly increased risk of cancer" [1, 2].

In the late 1970s, precancerous lesions included leukoplakia (Fig. 9.1), erythroplakia and palatal lesions in reverse smokers, whereas precancerous conditions included submucous fibrosis, actinic keratosis, lichen planus and discoid lupus erythematosus. There was however confusion surrounding this terminology because it did not accurately predict which lesions or conditions were high or low risk.

In 2005, the WHO Collaborating Centre for oral cancer and precancer came up with consensus views on working terminology to help with the classification of lesions of the oral mucosa based on the following observations:

1. Longitudinal studies showed that some areas of the oral mucosal tissue with alterations in clinical appearance underwent malignant change at follow-up.
2. The coexistence of red and white areas at the peripheral margins of squamous cell carcinoma suggests that squamous cell carcinoma may have a precursive state.
3. Some lesions show evidence of dysplasia (morphological and cytological changes without invasion of the basement membrane), but are not frankly invasive so may represent a precursive state.
4. Chromosomal, genomic and molecular alterations found in oral squamous cell carcinomas have also been found in oral mucosal precursor lesions.

In 2007, the WHO identified the term "potentially malignant disorders" to denote what had previously been termed precancer, precursor lesions, premalignant intraepithelial neoplasia or potentially malignant lesions. It was also suggested that precancerous conditions and lesions should not be subdivided because the subdivision gave little indication of the risk of malignant transformation. Given that patients with single precancerous lesions can develop cancerous lesions at contralateral previously healthy sites and molecular aberrations can occur at sites of normal clinical appearance, there appears to be little prognostic value in labelling patients as having oral precancerous lesions or conditions [3, 4].

Potentially malignant disorders therefore include patients with leukoplakia, proliferative verrucous leukoplakia (PVL), erythroplakia, palatal lesions in reverse smokers, chronic hyperplastic candidosis, sideropenic dysphagia, oral submucous fibrosis, actinic keratosis, lichen planus, discoid lupus erythematosus and hereditary disorders that have an increased risk of malignancy in the mouth including dyskeratosis congenita and epidermolysis bullosa. Within the potentially malignant disorders is a spectrum of disease encompassing single discrete lesions to multiple lesion disease which may or may not be associated with a systemic disorder.

Assessment of the Patient with Potentially Malignant Disorders

In general, the majority of patients present with lesions to their general dental practitioner with the presenting complaint of a red or white patch of the oral mucosa. A minority of patients present to a general medical practitioner. In the Western world, patients are mostly subsequently referred to a specialist clinic for management in a secondary or tertiary referral centre.

Evaluating the Patient with Oral Potentially Malignant Disorders (OPMDs)

Patients commonly present with incidental painless white or red patches of the oral mucosa found at routine dental check-up appointments. A minority of patients will present with painful red patches or nonhomogeneous white patches for which they have used various home or over-the-counter remedies to alleviate the lesion.

When taking a history from a patient with a new suspected oral potentially malignant disorder, it is important to try and assess whether the patient indeed has an oral potentially malignant disorder rather than a reversible lesion that could be due to tooth trauma, for example. There is therefore a need to assess the size and site of the lesion; the length of time a lesion has been present; previous lesions that have been treated and resolved; any changes in colour, shape and size; or surface characteristics of a new lesion in recent weeks or months. Patients should also be questioned as to whether they remember the onset of the lesion coinciding with tooth trauma event or use of topical medication for another mucosal condition. An assessment of the patient at the first visit aims to diagnose patients at high risk for having an oral potentially malignant disorder or a high risk for malignancy as this will determine management strategies for each individual patient.

Within the medical history, it is important to ascertain whether the patient is immunocompromised or has been so in the past as this could pose a higher risk for a patient developing a OPMD or squamous carcinoma. The drug history may also suggest medications that could be responsible for reversible mucosal ulceration and lesions that mimic oral potentially malignant disorders (e.g. nicorandil ulceration of the oral mucosa). The drug history may also highlight immunocompromising medications that could accelerate the development of OPMDs and squamous cell carcinoma (SCC).

An allergy history will inform the clinician if the lesion in their mouth could be reversible (e.g. amalgam related) if the allergen is avoided, reducing the need for biopsies and further investigation.

The social history is important to evaluate the amount and type of tobacco use, preferential site of placement and historical use of tobacco products because refrain-

ing from the use of these products may prevent development of SCC or even reverse a OPMD. An alcohol history evaluating units and type of alcohol consumed with or without concurrent tobacco use is useful to evaluate whether the patient is at higher risk of OPMD development or rapid progression to SCC. Diet, fruit and vegetable consumption has been shown to influence the development of OPMDs in a number of studies particularly in conjunction with alcohol drinking [5, 6]. Poor oral health and hygiene has been shown to be an independent risk factor for oral cancer in China, the USA and Brazil [7–10], but poor oral health and hygiene is often found in individuals with multiple confounding risk factors, so the exact influence of oral health as an independent variable is unknown.

The family history for a patient with a OPMD may give some indication of high risk for inherited disorders that might give an increased risk for malignancy, e.g. epidermolysis bullosa, or identify a benign condition that could be confused for a OPMD, e.g. white sponge naevus with autosomal dominant inheritance present in a direct relative.

Adjunctive diagnostic aids such as VELscope® or methylene blue may also be used during the clinical examination, but their lack of specificity and sensitivity in comparison to the gold standard of clinical examination means they are of limited use in assessing a new clinical presentation.

In [11], Goodson and Thomson reported an evaluation of the VELscope in identifying high-risk patients who might benefit from interventional surgical treatment of OPMDs. In this study, 296 patients were evaluated to see whether VELscope could improve diagnostic accuracy. The study found that there was a marginal improvement in diagnostic accuracy as far as assessing the extent of a lesion for biopsy, but VELscope was not very sensitive at identifying worsening dysplasia grades and could not differentiate inflammation consistently from dysplasia. In conclusion, it was stated that at best, VELscope could be used as a clinical adjunct to aid examination, but could not replace the gold standard of standard clinical examination.

A photograph of the lesion(s) however may be useful as they can be used as a record to assess the change of lesions at subsequent appointments.

Clinical Presentation of Oral Potentially Malignant Disorders

Potentially malignant disorders are commonly described by clinicians as leukoplakia (homogeneous or nonhomogeneous) or erythroplakia.

Leukoplakia

Leukoplakia is the most common clinical presentation of an oral potentially malignant disorder comprising around 60–70% oral potentially malignant disorders with prevalence rates of 3–105 cases per 1000 population worldwide. Higher prevalence

rates are found in New Guinea, China and India, and in general, rates are higher in rural than urban populations.

Leukoplakia can be defined as "plaques of questionable risk having excluded (other) known diseases or disorders that carry increased risk for cancer". Leukoplakia is purely a clinical condition, and there are no histological requirements for a lesion to fulfil this definition.

Leukoplakia can exist in a homogeneous or nonhomogeneous form where homogeneous types are purely white patches and nonhomogeneous are speckled, nodular or verrucous lesions with speckled nonhomogeneous lesions being those at greatest risk of malignant transformation.

Leukoplakia on standard clinical examination appears white because keratin in the lesion absorbs water from saliva giving a white appearance. As a consequence, it is not until the lesions are around 1 cm in size or more that they are recognised by patients or the general practitioner as visible mucosal keratinisation and thickening. Diagnostic aids such as methylene blue and VELscope may help to diagnose smaller or less visible lesions, but the prognostic value of these diagnostic adjuncts is uncertain.

The risk factors for development of leukoplakia include tobacco use, alcohol consumption, dietary factors, oral health, immune suppression and low socioeconomic status.

The sites of clinical presentation may therefore be influenced by these factors. Tobacco can be used in smoked or smokeless forms, and the site of leukoplakia may be related to habitual placement of the tobacco product. Clinically, a lesion may start as an area of wrinkled slightly whitened mucosa often in the floor of the mouth or ventral surface of the tongue but progress through a thickened smooth plaque to an irregular thickened plaque (sometimes described as verrucous) which may show yellow or blackened discolouration from tobacco products (Figs. 9.1 and 9.2).

Leukoplakia has an overall prevalence of around 2–3% but is more common in males and is most common in the 50–70-year-old age group. There is however evidence in Western populations of an increased number of younger patients presenting with leukoplakia and subsequent malignant transformation in the absence of common risk factors.

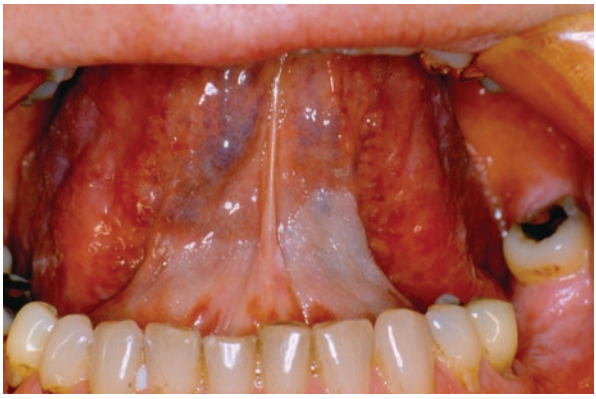

Fig. 9.1 Early faint leukoplakia of the floor of the mouth (@ John Wiley & Sons, reproduced with permission)

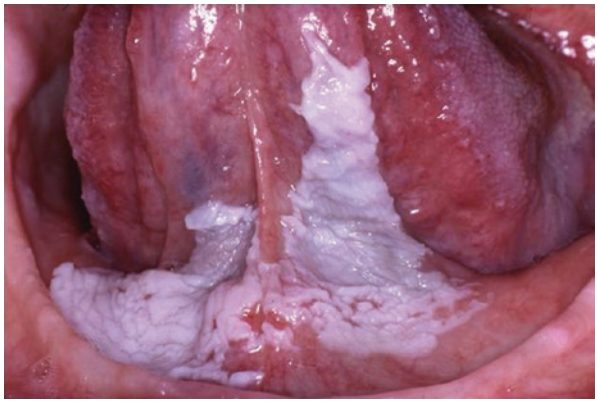

Fig. 9.2 Thickened irregular leukoplakia of the floor of the mouth (@ John Wiley & Sons, reproduced with permission)

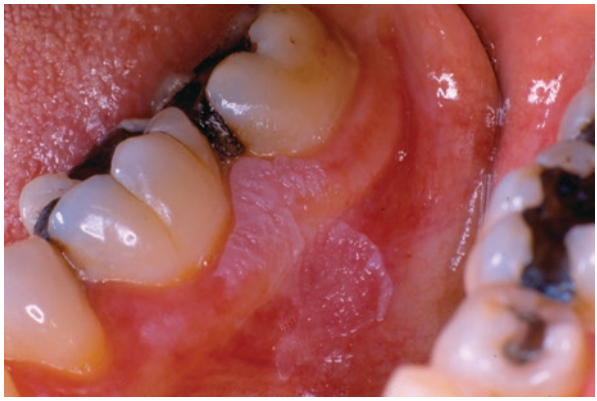

Fig. 9.3 Early localised proliferative verrucous leukoplakia of the buccal gingivae and left buccal sulcus (@ John Wiley & Sons, reproduced with permission)

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (Figs. 9.3 and 9.4) is a clinical entity that appears to behave more aggressively than erythroplakia with malignant transformation rates of 60–100% [12–14]. Proliferative verrucous leukoplakia differs from leukoplakia in general in the way it progresses from a flat lesion through increasing degrees of thickening, fissuring and warty proliferation until the eventual development of squamous cell carcinoma. Even if lesions are surgically removed, they have a high chance of recurrence and new lesion development [15]. PVL commonly presents with multiple lesions involving more than one site. Signs suggesting malignant transformation are new areas of redness or erosions within a lesion, induration and rapid growth of a verrucous patch.

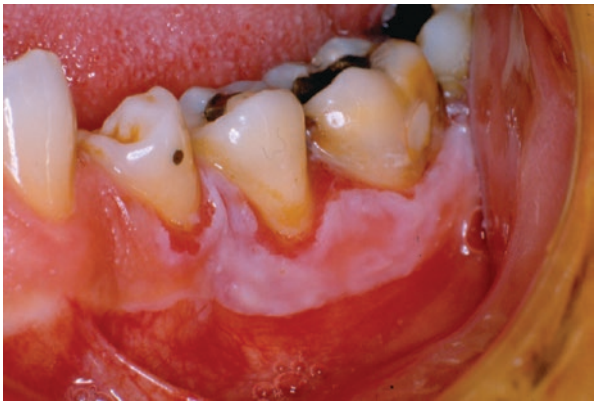

Fig. 9.4 More extensive proliferative verrucous leukoplakia of the left buccal gingivae and buccal sulcus (@ John Wiley & Sons, reproduced with permission)

Risk Factors for Leukoplakia and Erythroplakia

Tobacco Use

Tobacco use and smoking are common risk factors. The type of tobacco used usually determines the site of the leukoplakia lesion. Leukoplakia is around six times more common in smokers than non-smokers and can affect any part of the oral mucosa, although the buccal mucosa, floor of the mouth and ventrolateral tongue are commonly affected. Some patients however use smokeless forms of tobacco. Snuff, tobacco chewing and use of tobacco products mixed with areca nut and lime/additives can result in different site presentations depending on the site where the tobacco is usually placed on the oral mucosa.

Alcohol Consumption

Long-term alcohol use has also been cited as a risk factor for leukoplakia. For patients with dysplastic oral premalignant lesions that have been excised, there is evidence that continued alcohol intake of more than 28 units per week increases the risk of recurrent disease at the same site [16].

Immune Compromise

Immune suppression has long been known to be a risk factor for oral cancer, but evidence supporting a role in precancer is largely anecdotal and related to case reports of leukoplakia in transplant patients and patient with HIV/AIDS. In HIV/

AIDS patients, dormant Epstein-Barr virus can be reactivated when the immune system is weakened resulting in a condition called hairy leukoplakia.

Socioeconomic status has been found to be an independent predictor of oral leukoplakia in the US Third National Health and Nutrition Examination Survey (NHANES III) along with diabetes, age and tobacco smoking. Alcohol use, race/ethnicity, years of education and BMI however showed no independent effects. There is however no evidence that socioeconomic status of a patient can predict the site of a lesion [17].

Diet

The influence of dietary factors on precancerous lesions has been assessed in India [5] where low intakes of iron and vitamin C in women were associated with the presence of leukoplakia and precancer. Again, the site of presentation of leukoplakia was not influenced by these variables. In erythroplakia, a case-control study of 100 cases found that there was a multiplicative effect between alcohol consumption and low vegetable intake or low fruit intake [6].

Oral Health

There is no evidence that oral health and hygiene is an independent predictor of oral precancer development at the present time although poor oral hygiene may coexist in patients with many of the other precancer risk factors previously described.

Human Papilloma Virus

There is conflicting evidence of HPV-16 and 18 in oral potentially malignant disorder development. Observational studies suggest it is present in up to 20% of lichen planus lesions which could be described clinically as leukoplakia. Chen et al. [18] found that HPV-18 was a significant risk factor for leukoplakia and squamous papilloma and the site of leukoplakia was more often in the oropharynx.

The ARCAGE study in 2013 [19] looked at more than 1400 cases and controls with upper aerodigestive tract cancers and found an important role for HPV-16 infection in oropharyngeal cancer and supported a marginal role for HPV-18 in oropharyngeal cancer and HPV-6 in laryngeal cancer, but not oral cancer specifically.

Erythroplakia

Erythroplakia (Fig. 9.5) is less commonly seen than leukoplakia and has a reported prevalence of 0.2–1.9 per 1000 population from studies in the USA and Mexico [20, 21]. It is defined as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease". It is more common to see patients with erythroleukoplakia—a lesion that is a combination of red and white in appearance, sometimes termed speckled leukoplakia (Fig. 9.6). Again, erythroplakia is a clinical diagnosis, and the term gives no indication of histological findings [22].

Erythroplakia and erythroleukoplakias have greater potential for malignant transformation than homogeneous leukoplakia, so identification of red areas within a lesion is important clinically (Table 9.1).

Erythroplakias are considered to be very high-risk lesions for malignant transformation. They are more commonly symptomatic lesion, presenting with soreness or sensitivity. Erythroplakia is, again, purely a clinical diagnosis, presenting with almost equal prevalence in men and women. Erythroplakia is red in colour because lesions commonly have atrophic epithelium and histologically may demonstrate dysplasia or even carcinoma in situ. It is not uncommon to find early carcinoma in erythroplakic lesions.

Erythroleukoplakia or speckled leukoplakia presents as leukoplakia on a background of erythroplakia most commonly found at the labial commissures or the floor of the mouth. It is often superimposed with chronic candidal infection.

The Differential Diagnosis of Leukoplakia and Erythroplakia

There are a number of benign white and red lesions that can be confused with leukoplakia and erythroplakia.

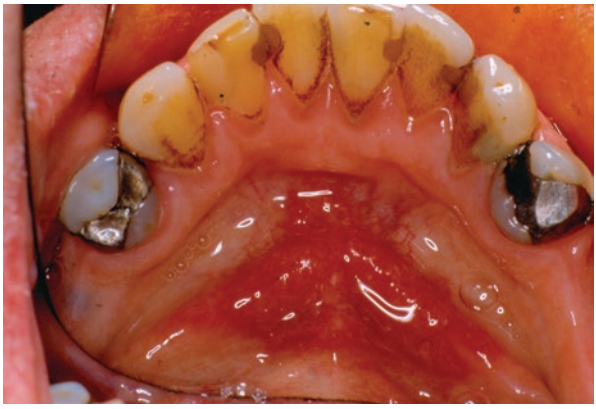

Fig. 9.5 Erythroplakia of the floor of the mouth (@ John Wiley & Sons, reproduced with permission)

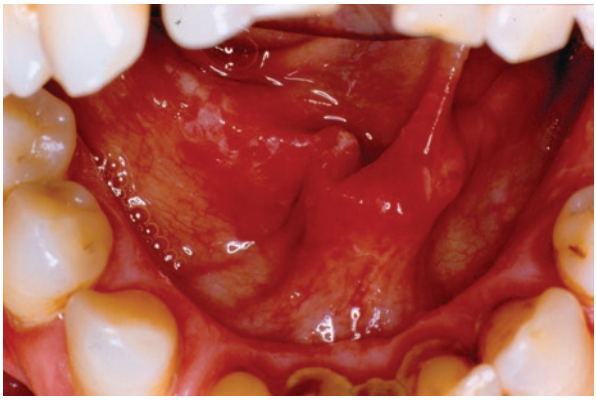

Fig. 9.6 Erythroleukoplakia of the floor of the mouth (@ John Wiley & Sons, reproduced with permission)

Table 9.1 Worldwide prevalence rates of oral potentially malignant disorders per 1000 population

Lesion	Prevalence rate per 1000
Leukoplakia	4–105
Erythroplakia	0.2–1.9

The differential diagnosis of leukoplakia could be one of a number of hereditary conditions (including oral epithelial white sponge naevus, leukoedema, pachyonychia congenita, tylosis, follicular keratosis, hereditary benign intraepithelial dyskaryosis) or chronic inflammations (oral lichen planus, frictional keratosis, chemical or thermal trauma).

The differential diagnosis of erythroplakia includes inflammatory disorders such as desquamative gingivitis, erosive lichenoid lesions, pemphigoid, and hypersensitivity reactions; infections including candidosis, purpura and trauma; or tumours such as Kaposi's sarcoma and haemangioma.

Premalignant Lesions Versus Premalignant Conditions

Premalignant lesions (leukoplakia, erythroplakia and erythroleukoplakia) present as single isolated lesions of morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart (WHO, 1978), but there are a number of more generalised medical conditions which may result in the development of potentially malignant lesions. In contrast to oral precancerous lesions where a discrete mucosal lesion may present, these more generalised states are associated with a significantly increased risk of cancer, and this includes a range of systemic disorders where the oral manifestations are one of the many signs or symptoms of disease. The oral precancerous conditions include immune suppression, lichen planus (Fig. 9.7) and lichenoid lesions, oral submucous fibrosis (Fig. 9.8), sideropenic

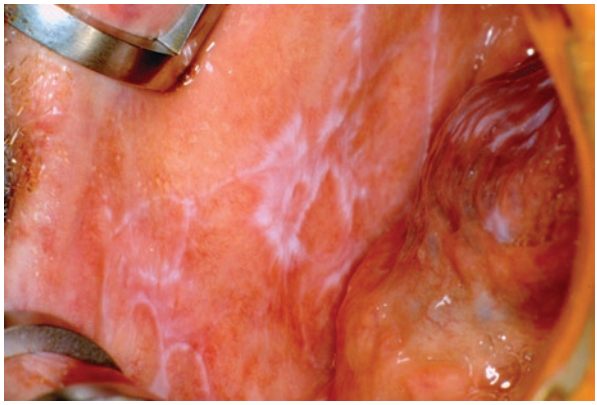

Fig. 9.7 Reticular lichen planus of the buccal mucosa (@ John Wiley & Sons, reproduced with permission)

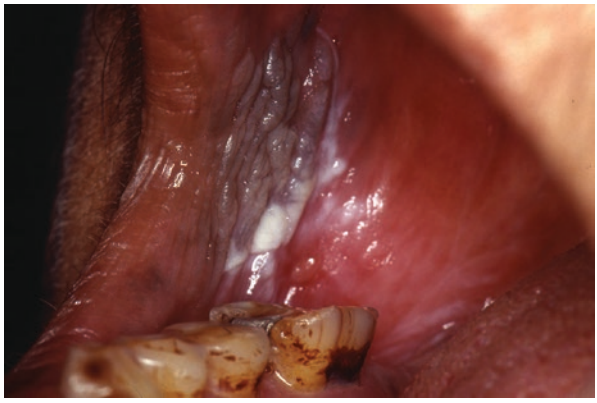

Fig. 9.8 Oral submucous fibrosis of the right buccal mucosa (@ John Wiley & Sons, reproduced with permission)

dysphagia, discoid lupus erythematosus, actinic cheilitis (Fig. 9.9), syphilis (Fig. 9.10) and dyskeratosis congenita.

Immunosuppression

Drug-induced immunosuppression which may occur following organ transplant is more common than congenital immune suppression, but acquired immune deficiency in HIV/AIDS, for example, is increasingly common worldwide. It is common for immunosuppressed patients to present with multiple oral leukoplakias with the lips and labial commissure as common sites. These lesions may occur synchronously or at different times. Immunosuppressed patients are at high risk of developing squamous cell carcinoma and as such need close monitoring for progression or recurrence of disease.

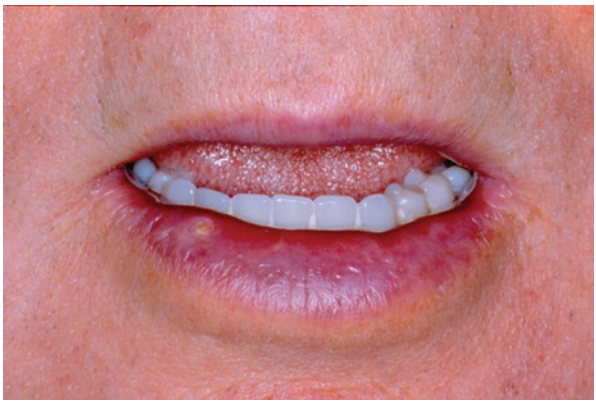

Fig. 9.9 Actinic cheilitis of the lower labial mucosa (@ John Wiley & Sons, reproduced with permission)

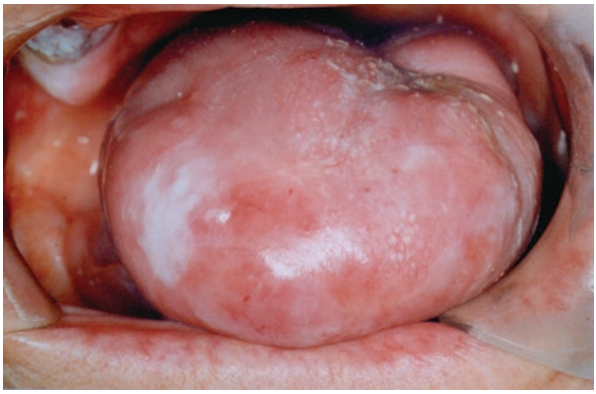

Fig. 9.10 Mucosal atrophy in tertiary syphilis (@ John Wiley & Sons, reproduced with permission)

Bone marrow transplant patients with graft-versus-host disease are also a vulnerable group as far as leukoplakia and erythroplakia are concerned. These patients are at high risk of malignant transformation.

Lichenoid Lesions and Lichen Planus

There are varying reports of the malignant potential of lichenoid lesions. Lichen planus is a multifactorial disorder which typically presents bilaterally with hyperkeratotic lesions comprising striae, nodules and plaques. Below the keratinised, atrophic superficial epithelial layers are acanthosis and a T cell infiltrate. If lesions undergo severe atrophy and basal cell liquefaction, red lesions containing erosions or bullae may appear. Lichenoid lesions can occur almost anywhere on the oral mucosa, but the most common sites are the buccal mucosa, the gingivae or the floor of the mouth and ventral tongue. The overall risk of malignant transformation for lichen planus is thought to be around 1%, with higher rates in atrophic or erosive

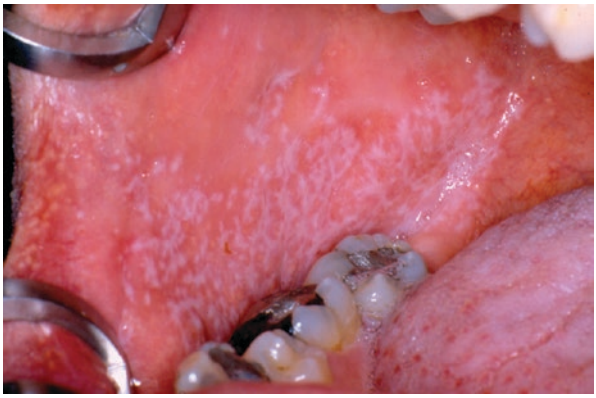

Fig. 9.11 A lichenoid lesion of the right buccal mucosa (@ John Wiley & Sons, reproduced with permission)

lichen planus where there is not a layer of protective surface keratinisation. It is not uncommon to see multiple oral premalignant lesion disease in patients with lichen planus or lichenoid lesions because extensive mucosal disease may predispose to a high risk of "field cancerisation".

Lichenoid lesions (Fig. 9.11) are clinically indistinguishable from lichen planus but can arise as hypersensitivity reactions to amalgam restorations or drugs. Unlike lichen planus, they do not tend to occur with bilateral presentation.

Given that lichenoid lesions and lichen planus can affect multiple sites of the oral mucosa, it is generally advised that all sites containing such lesions should be biopsied to rule out early malignant transformation or dysplastic changes which may give certain sites a predisposition to cancer development. It is not known why some lichenoid or lichen planus lesions undergo malignant transformation and others do not, but there is a tendency for dysplastic lesions especially those with an inflammatory cell infiltrate in the adjacent subepithelial tissue to be at high risk.

Goodson and Thomson reported in [23] a cohort of 88 patients with lichenoid inflammation who underwent excisional laser surgery. Of these, 60 displayed lesions with varying grades of dysplasia; despite interventional laser surgery, they, as a group, were significantly less likely to be disease-free after the follow-up period than other forms of OPMDs, and consequently this group may be prone to worse clinical outcome and poorer long-term prognosis.

Oral Submucous Fibrosis (OSMF)

This condition is commonly seen in South East Asia and related to betel quid use. Betel quid comprises areca nut mixed with slaked lime mixed in a betel vine leaf which is held in the mouth and acts as a stimulant. It is primarily used by manual labourers who may consume up to 30 quids a day but is also unfortunately consumed by children. The most obvious effects of betel quid are tooth discolouration and redness of the oral mucosa which may also exist in conjunction with

erythroplakia or leukoplakia. Over time, the oral mucosa becomes pale with less vascularity and hardened or fibrotic giving it a rubbery firm texture. The overlying epithelium becomes atrophic and has a high risk of malignant transformation of 0.5% [24]. Consequentially, OSMF and squamous cell carcinomas are commonly found at the site of betel quid placement in the sulcular epithelium and buccal mucosa.

Sideropenic Dysphagia

This uncommon condition commonly manifests in middle-aged women who have symptoms of dysphagia from oesophageal web formation, iron deficiency anaemia, glossitis and dysplastic lesions of the oral mucosa.

Discoid Lupus Erythematosus

Discoid lupus erythematosus is a chronic autoimmune condition predominantly affecting females with a characteristic red facial "butterfly rash" across the nose and cheeks. The classical premalignant oral lesion in DLE is a stellate lesion of the buccal mucosa, but patients may also present with circular areas of redness or ulceration of the oral mucosa, and these lesions characteristically have white borders so may be confused with lichen planus or erythroplakia.

Actinic Cheilitis

These lesions are usually crusted ulcerated lesions covering the lower lip. They are commonly found in people who have spent a lot of time outdoors in prolonged periods of exposure to UV and sunlight. The malignant transformation rates for actinic cheilitis are unclear, but most studies suggest squamous cell carcinoma develops from dysplastic tissue. There is some evidence that the absence of cytokeratin 10 predisposes to malignant transformation [25].

Clinically, actinic cheilitis can be confused with lichen planus and lip leukoplakia due to immune compromise.

Chronic Hyperplastic Candidosis (Candida Leukoplakia)

This condition commonly presents bilaterally with nonhomogeneous leukoplakia or erythroplakia at the labial commissures in smokers. Candida hyphae invade parakeratinised mucosa and can give rise to cellular atypia or varying degrees of dysplasia.

It is not clear whether dysplastic tissue provides a foundation for candida growth or whether the reverse is true, and tobacco and candida carcinogens create tissue dysmaturation and disorganisation (dysplasia).

Syphilis

This is an uncommon condition in the west but more common in Asian countries. The clinical presentation of tertiary syphilis may include leukoplakia of the dorsum of the tongue with a very high risk of malignant transformation.

Dyskeratosis Congenita

This rare condition of likely recessive inheritance affects males. The presentation may include greyish-brown skin pigmentation, immune deficiency, nail dystrophy and oral leukoplakia. The commonly affected sites in children are the tongue and buccal mucosa with vesicles or ulcerations. In later life, there is reddening of the mucosa and then erosive leukoplakia with high malignant potential in men aged 20–30.

Multiple Lesion Disease (Fig. 9.12)

A particularly difficult group of potentially malignant disorder patients to manage are those with multiple precancerous red and/or white lesions often comprising tissue that exhibits dysplastic change. Multifocal disease was first described by Slaughter [26] who popularised the idea that some patients have molecularly altered preneoplastic fields of the oral mucosa from which multiple lesions can develop either synchronously or metachronously. Multiple lesion disease has been reported to affect between 3% and 24% of patients with oral precancerous lesions and demonstrates malignant transformation rates of more than 20% [27–29].

In the study by Hamadah et al. [27] undertaken in the northeast of England, 78 patients with single and 18 with multiple lesions were assessed to see how many developed oral squamous cell carcinoma. Oral squamous cell carcinoma developed in 3/78 single lesions and 4/18 multiple lesions. Single lesions were most common on the floor of the mouth and ventrolateral tongue, and multiple lesions were more common on the buccal mucosa. Interestingly, the most severe dysplasia was found in single lesions, and these lesions had higher cyclin-A and Ki-67 labelling indices than the multiple lesions, yet a smaller proportion developed cancer over the 5-year follow-up period (3.8% of single lesions versus 22.2% of multiple lesions).

In contrast to single potentially malignant lesions which predominantly affect the floor of the mouth and ventral tongue, multiple lesion disease is more common

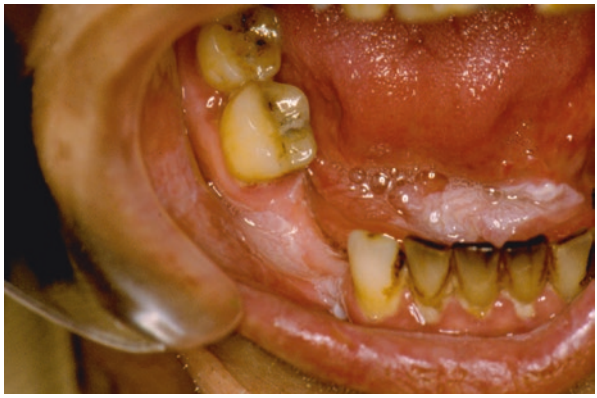

Fig. 9.12 Multiple lesion disease affecting the floor of the mouth and mandibular alveolus (@ John Wiley & Sons, reproduced with permission)

on the buccal mucosa, soft palate retromolar area and dorsum of the tongue. While precancerous conditions associated with systemic illness may be responsible for some cases of multiple lesion disease, there is also evidence that diet (high intake of fruit and vegetables) can have a protective effect on the development of multiple lesion disease [30, 31].

High- and Low-Risk Lesions

Risk Profiling of Oral Potentially Malignant Lesions

Assessment of malignant transformation risk for potentially malignant disorders is crucial and fundamental to the management of these conditions. Unfortunately, in clinical practice, the risk of malignant transformation remains obscure and highly variable, with quoted rates ranging from 0.13% to 36.4%. Mehanna et al. [32] reported an overall malignant transformation rate of around 12%, rising to 14.6% in patients whose lesions were left in situ, versus only 5.4% when the lesions were surgically excised. Thomson et al. reported transformation rates of between 2% and 4% in laser-treated patient cohorts, supporting the hypothesis that appropriate intervention helps to reduce the risk of cancer development.

In [33], Goodson et al. reported findings from a retrospective study of 1248 patients with oral cancer identified over a 13-year period. Of these, 58 patients had identifiable precursor lesions that became malignant, but only 25 had been dysplastic on initial biopsy. Nineteen of the 33 non-dysplastic lesions exhibited lichenoid inflammation only. SCC arose most often on the ventrolateral tongue and floor of the mouth, with a mean transformation time of 29.2 months. Transformation time was significantly shorter in men ($p = 0.018$) and those over 70 years of age ($p = 0.010$). Patients who consumed more than 21 units of alcohol/week and those

who had had interventional laser surgery to treat precursor lesions had higher-staged tumours ($p = 0.048$). This study showed that the results of incisional biopsy and grading of dysplasia had limited use as predictive tools and supported the view that cancer may arise in the absence of recognisable epithelial dysplasia. Consequently, risk profiling individual patients is difficult due to the lack of objective definitive clinical or pathological markers for malignant transformation and the unknown additive interactions in patients with multiple known clinicopathological risk factor variables.

There are currently no definitive studies quantifying risk for individual patients. Ideally, risk could be evaluated by a scoring system where patients were assessed for risk using weighted variables. The best evidence for risk factors comes from publications summarising findings of cohort and case-control studies where patients have been prospectively followed or retrospectively analysed to look at the effects of known or proposed risk factors on malignant transformation. It has however been difficult to examine the weighted effects of individual variables because many patients possess a number of risk factors that make them susceptible to malignancy. The combined effects of multiple risk factors can be difficult to quantify because they may not be additive but multiplicative and there are insufficient numbers of studies to accurately quantify these combined effects.

When assessing patients at presentation for high- or low-risk status, the assessment is based on the clinical history and examination findings as well as pathological examination of a biopsy specimen. As a consequence, overall risk profiling requires the clinician to take into account both clinical and histopathological factors.

Clinical Risk Profiling

In 2007, van der Waal identified factors that would suggest a patient is at statistically significant higher risk of malignant transformation of potentially malignant disorders (Table 9.2).

Almost 10 years later, these and other risk factors were further stratified into high- and low-risk categories. Diajil and Thomson [34] undertook a systematic review of 300 papers on oral cancer risk factors published between 1982 and 2009 and stratified 14 different risk factors as high or low risk. The higher-risk factors were tobacco use, excess alcohol consumption, use of betel quid, predisposing genetic factors and inherent susceptibility, immunodeficiency, diet low in fresh fruit and vegetables, old age and marijuana use. Low-risk factors in an individual patient included low socioeconomic status, poor oral health, use of shammah/toombak, human papillomavirus infection, *Candida albicans* infection and diabetes mellitus (Table 9.3).

The INHANCE study [35], published in 2012, looked at diet and head and neck cancer risk. In this analysis, pooled data included 22 case-control studies with

Table 9.2 Statistically significant risk factors for malignant transformation of oral potentially malignant disorders

Female gender
Long duration of leukoplakia
Nonhomogeneous leukoplakia or erythroplakia
Peripheral verrucous leukoplakia
Lesion size >200 mm^2
Presence and severity of epithelial dysplasia and dyskaryosis
Presence of *Candida albicans*
History of previous head and neck carcinoma or previous recurrent potentially malignant lesions
Multiple lesion disease
Patients with immune compromise
Tobacco smoking
Alcohol consumption
Low socioeconomic status and educational attainment
Unemployment
Age >40 years

Table 9.3 High- and low-risk factor profiling

High risk	Low risk
Tobacco use	Low socioeconomic status
Excess alcohol consumption	Poor oral health
Use of betel quid	Use of shammah/toombak
Predisposing genetic factors and inherent susceptibility	Human papillomavirus infection
Immunodeficiency	*Candida albicans* infection
Diet low in fresh fruit and vegetables	Diabetes mellitus
Old age	
Marijuana use	

14,520 cases and 22,737 controls. Centre-specific quartiles among the controls were used for food groups, and frequencies per week were used for single food items. A dietary pattern score combining high fruit and vegetable intake and low red meat intake was created. The study found that higher dietary pattern scores, reflecting high fruit/vegetable and low red meat intake, were associated with reduced head and neck cancer risk.

Regarding employment and socioeconomic status in risk factor profiling, the ARCAGE study evaluated the association between occupational history and upper aerodigestive tract (UADT) cancer risk in the ARCAGE European case-control study [36]. The study included almost 2000 cases and controls with cancer of the oral cavity, oropharynx, hypopharynx, larynx or oesophagus. The study found that among men, there were increased risks for cancer in painters, bricklayers, workers employed in the erection of roofs and frames, reinforced concreters, dockers and

workers in road construction and cargo handling. Increased risks were also found for loggers and cattle and dairy farmers. Among women, there was no clear evidence of increased risks of upper aerodigestive tract cancer in association with occupations or industrial activities.

Pathological Risk Profiling

The risk of malignant transformation for an individual patient however also may depend on pathological features of a biopsied lesion. The gold standard for assessment of oral potentially malignant lesions is microscopic examination of haematoxylin- and eosin-stained sections for architectural and cytological features of epithelial dysplasia, but only 50% leukoplakias actually demonstrate features of dysplasia, and malignant transformation rates of dysplastic mucosa can range from 0% to 50%.

The diagnostic gold standard for oral potentially malignant disorders is the WHO classification. The 2005 classification identifies cytological and histological features of dysplasia shown in Table 9.4, but there is little evidence to suggest which architectural and cytological features should be weighted more highly to identify high- and low-risk OPMDs. There is also no category of provision within these features for the diagnosis of proliferative verrucous leukoplakia which is often multifocal and has very high risk of malignant transformation. Dysplasia grading remains subjective and is prone to inter- and intraobserver variability.

Historically, pathologists took into account a combination of microscopic features from those listed above and arrived at a grade; the worst site of a biopsy was scored although sampling errors may have affected reporting. Before grading of dysplasia became more standardised, lesions were described as mild, moderate or

Table 9.4 Cytological and architectural features of dysplasia (Adapted from [37])

Cytological features of dysplasia	Architectural features of dysplasia
Abnormal variation in nuclear size and shape (anisonucleosis and pleomorphism)	Loss of polarity
Abnormal variation in cell size and shape	Disordered maturation from basal to squamous cells
Enlarged nuclei and cells	Includes top to bottom change of carcinoma in situ
Hyperchromatic nuclei	Increased cellular density
Increased mitotic figures	Basal cell hyperplasia
Abnormal mitotic figures (abnormal in shape or location)	Dyskeratosis (premature keratinisation and keratin pearls deep in epithelium)
Increased number and size of nucleoli	Bulbous drop-shaped rete pegs
	Secondary extensions (nodules) on rete pegs

severe dysplasia relatively subjectively. Pathologists in different units would make their own grading systems and sometimes only diagnosed dysplasia when only two of the listed features were observed [38]. Others scored lesions depending on how many dysplastic features a biopsy expressed providing weighted scores for 13 microscopic features of dysplasia, namely:

1. Loss of polarity of basal cells
2. Presence of more than one layer having basaloid appearance
3. Drop-shaped rete ridges
4. Increased nuclear cytoplasmic ratio
5. Nuclear hyperchromatism
6. Enlarged nucleoli
7. Increased number of mitotic figures
8. Mitotic figures in abnormal form
9. The presence of mitotic figures in the superficial half of the epithelium
10. Cellular and nuclear pleomorphism
11. Irregular epithelial stratification
12. Loss of intercellular adherence
13. Keratinisation of single cells or cell groups in the prickle cell layer

Smith and Pindborg [39] weighted these features in lesions, and a maximum score of 75 for any one lesion could be obtained. They considered mild dysplasia to include scores of 11–25, moderate dysplasia from 26 to 45 and severe dysplasia in excess of 45, but the appropriate weighting given to each of the features was largely guesswork on what the authors felt was more or less indicative of severity. Some of the features were not specific for dysplasia and could be found in other conditions such as inflammation.

To reduce ambiguity in reporting, the WHO further subdivided categories of mild, moderate and severe dysplasia and carcinoma in situ with features they felt were appropriate for each category, but not all features had to be present for a lesion to be given a particular grade.

There is some controversy on whether carcinoma in situ is actually a premalignant condition as many believe it to be actual malignant change but without invasion. Microinvasive carcinoma is also difficult to diagnose as it is difficult to visualise in the early stages.

In addition to difficulties assigning weightings to various cytological and histological features of dysplasia, there is a considerable amount of evidence suggesting that dysplasia grading is subjective and prone to interobserver variability [40–42]. In one study by Karabulut et al. [41], interobserver agreement rates were in the range of 49–69% between four pathologists with kappa values showing poor to moderate agreement between pathologists. Diagnostic difficulty is particularly associated with grading of moderate dysplasia where features are not unilaterally mildly dysplastic or severely dysplastic. Malignant transformation rates for mild dysplasia may be less than 5% but for moderate dysplasia are 3–15% and for severe dysplasia around 16% with variability of 7–50% [43]. Decisions on management of the entire precancerous lesions is

often based on grading of dysplasia from incisional biopsy which has also been reported as fairly inaccurate with reports of only 56% agreement in diagnosis between incisional and definitive biopsies from 200 patients with single premalignant lesions. Discrepancies in diagnosis in 42 patients with multiple lesions totalled 11.9%. Holmstrop et al. [44] undertook a similar study and found that incision biopsy reports gave different degrees of dysplasia compared to the whole lesions with variability of around 49% again confirming that biopsies may not be being taken from the most severely dysplastic area of a lesion visible with the naked eye.

For patients with multiple lesion disease, field mapping biopsies are advocated [45]. Multifocal disease may ultimately affect up to 24% of oral cancer patients, and for holistic patient management, all sites where there are visible epithelial abnormalities should be biopsied, if necessary under general anaesthesia.

Diagnostic accuracy is also problematic with verrucous hyperplasia and proliferative leukoplakia (PVL). These lesions have gross hyperkeratosis with a verrucous or papillomatous surface. The lesions are exophytic and spread laterally. Verrucous hyperplasia is more localised, but the recurrent multifocal and progressive type, PVL, occurs at an average age of diagnosis of 62 years, and women are more commonly affected than men. PVL usually affects multiple sites but most commonly the buccal mucosa in women and the tongue in men. Many cases are resistant to all forms of medical and surgical treatments including laser surgery.

While PVL lesions do not demonstrate many features of cytological atypia and only 50% show evidence of dysplasia, 70% of lesions may progress to squamous cell carcinoma [14, 46]. Clinical history, multifocality and extent of the lesion are all important factors in diagnosis. The exophytic nature and lack of pushing invasive front distinguish it from verrucous carcinoma [37]. Another area of diagnostic difficulty, also reported by Speight [37], includes pseudoepitheliomatous lesions. Granular cell tumours are typical examples along with chronic hyperplastic candidosis, median rhomboid glossitis and necrotising sialometaplasia. Reactive inflammatory cell atypia is common in these lesions and should be differentiated from atypia in oral dysplasia.

In an attempt to standardise dysplasia classification and use it to predict risk of malignant transformation, Kujan et al. [47] developed a novel binary grading system where lesions were reclassified as low or high risk for malignant transformation. There was some success in using this classification in that it reduced the number of categories for a lesion down to two. Using the binary system, four pathologists showed satisfactory agreement on the distinction of mild dysplasia from severe dysplasia and from carcinoma in situ, but the assessment of moderate dysplasia was more difficult. 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 reported as 82%. It was felt that the new binary grading system complemented the WHO Classification 2005 but needed further evaluation on a larger sample size.

In summary, there is no single dysplasia classification system at present that is more or less accurate than the WHO system. All systems use similar features to classify dysplasia, but there needs to be consensus agreement on which features are more indicative of more severe tissue dysmaturation and disorganisation. This combined with introduction of clinical factors to stratify risk may provide a more encompassing system that provides prognostic as well as diagnostic information.

A considerable amount of work has been undertaken trying to find biomarkers that predict malignant transformation at the molecular level, but to date, no accurate biomarkers have consistently been able to predict malignant transformation of oral potentially malignant disorders, and these are largely a research tool. They are not in routine use for individual patient management.

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