
David H Felix


Jane Luker


Crispian Scully

*This series provides an overview of current thinking in the more relevant areas of Oral Medicine, for primary care practitioners.*
*The series gives the detail necessary to assist the primary dental clinical team caring for patients with oral complaints that may be seen in general dental practice. Space precludes inclusion of illustrations of uncommon or rare disorders.*
*Approaching the subject mainly by the symptomatic approach, as it largely relates to the presenting complaint, was considered to be a more helpful approach for GDPs rather than taking a diagnostic category approach. The clinical aspects of the relevant disorders are discussed, including a brief overview of the aetiology, detail on the clinical features and how the diagnosis is made, along with guidance on management and when to refer, in addition to relevant websites which offer further detail.*

# Oral Medicine: 6. White Lesions

Specialist referral may be indicated if the Practitioner feels:
- The diagnosis is unclear;
- A serious diagnosis is possible;
- Systemic disease may be present;
- Unclear as to investigations indicated;
- Complex investigations unavailable in primary care are indicated;
- Unclear as to treatment indicated;
- Treatment is complex;
- Treatment requires agents not readily available;
- Unclear as to the prognosis;
- The patient wishes this.

Truly white oral lesions appear white usually because they are keratotic (composed of thickened keratin, which looks white when wet) or may consist of collections of debris (materia alba), or necrotic epithelium (such as after a burn), or fungi (such as candidosis). These can typically be wiped off the mucosa with a gauze swab.

Other lesions, which cannot be wiped off, also appear white usually because they are composed of thickened keratin (Figure 1). A few rare conditions that are congenital, such as white sponge naevus (Figure 2), present in this way, but most white lesions are acquired and many were formerly known as 'leukoplakia', a term causing misunderstanding and confusion. The World Health Organization originally defined leukoplakia as a 'white patch or plaque that cannot be characterized clinically or pathologically as any other disease', therefore specifically excluding defined clinicopathologic entities such as candidosis, lichen planus (LP) and white sponge naevus, but still incorporating white lesions caused by friction or other trauma, and offering no comment on the presence of dysplasia. A subsequent international seminar defined leukoplakia more precisely as:

*'…a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and which is not associated with any physical or chemical causative agent except the use of tobacco.'*

There is a range of causes of white lesions (Table 1), but morphological features and site may also give a guide to the diagnosis.

For example, *focal* lesions are often caused by keratoses; *multifocal* lesions are common in thrush (pseudomembranous candidosis) and in LP; *striated* lesions are typical of LP; and *diffuse* white areas are seen in the buccal mucosa in leukoedema and some LP, in the palate in stomatitis nicotina and at any site in keratoses. White lesions are usually painless but this may not be the case in burns, candidosis, LP, or lupus erythematosus.

## Local causes of white lesions

Debris, burns (from heat, chemicals such as mouthwashes), grafts and scars may appear pale or white. Materia alba can usually easily be wiped off with a gauze.

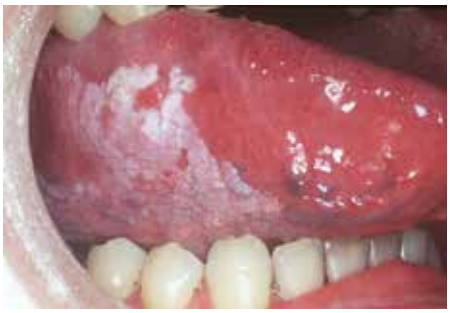
**Figure 1.** Leukoplakia, ventral tongue.

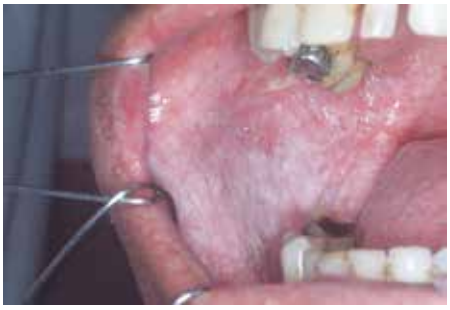
**Figure 2.** White sponge naevus.

### Furred tongue

Tongue coating is common, particularly in edentulous adults on a soft, non-abrasive diet, people with poor oral hygiene, and those who are fasting or have febrile diseases. The coating appears more obvious in xerostomia. The coating consists of epithelial, food and microbial debris and the tongue is the main reservoir of some micro-organisms, such as *Candida albicans* and some Streptococci, and the various anaerobes implicated in oral malodour (Article 5).

#### *Diagnosis*

The history is important to exclude a congenital or hereditary cause of a white lesion. The clinical appearances usually strongly suggest the diagnosis: biopsy is only required if the white lesion does not scrape away from the mucosa with a gauze.

**David H Felix**, BDS, MB ChB, FDS RCS(Eng), FDS RCPS(Glasg), FDS RCS(Ed), FRCP(Edin), Postgraduate Dental Dean, NHS Education for Scotland, **Jane Luker**, BDS, PhD, FDS RCS , DDR RCR, Consultant and Senior Lecturer, University Hospitals Bristol NHS Foundation Trust, Bristol, **Professor Crispian Scully,** CBE, MD, PhD, MDS, MRCS, BSc, FDS RCS, FDS RCPS, FFD RCSI, FDS RCSE, FRCPath, FMedSci, FHEA, FUCL, DSc, DChD, DMed(HC), Dr HC, Emeritus Professor, University College London, Hon Consultant UCLH and HCA, London, UK.

**Local causes**

- Materia alba and furred tongue (debris from poor oral hygiene)
- Burns
- Keratoses
  - Frictional keratosis (and cheek/lip biting)
  - Smoker's keratosis
  - Snuff-dipper's keratosis
- Skin grafts
- Scars

**Congenital**

- Fordyce spots
- Leukoedema
- Inherited dyskeratoses (rare, eg white sponge naevus, dyskeratosis congenita, Darier's disease)

**Inflammatory**

**Infective**

- Fungal (eg pseudomembranous and hyperplastic candidosis)
- Viral
  - Hairy leukoplakia (Epstein-Barr virus)
  - Human papillomavirus infections
- Bacterial (eg syphilitic mucous patches and keratosis)

**Non-infective**

- Lichen planus
- Lupus erythematosus

**Neoplastic and possibly pre-neoplastic**

- Leukoplakia
- Keratoses
- Carcinoma

**Table 1.** Causes of oral white lesions.

**Figure 3.** Fordyce spots.

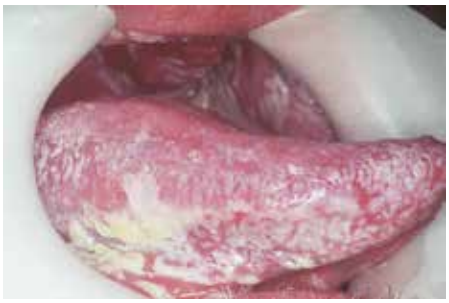

**Figure 4.** Pseudomembranous candidosis.

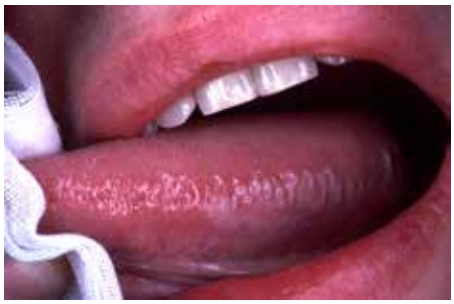

**Figure 5.** Oral hairy leukoplakia.

***Management***

Treatment is of the underlying cause where this can be identified.

## Congenital causes of white lesions

**Fordyce spots**

Some common whitish conditions, notably Fordyce granules (ectopic sebaceous glands), are really yellowish, but may cause diagnostic confusion (Figure 3). This condition is entirely benign and does not require any further intervention, though there is some evidence they may become more prominent in hereditary nonpolyposis colorectal cancer.

**Leukoedema**

Leukoedema is a common benign congenital whitish-grey filmy appearance of the mucosa, seen especially in the buccal mucosae bilaterally in people of African or Asian descent. Diagnosis is clinical; the white appearance disappears if the mucosa is stretched. No treatment is available or required.

**Inherited dyskeratoses**

Inherited disorders of keratin are rare, but may be diagnosed, especially if there is a positive family history or other associated features, such as lesions on other mucosae, or skin appendages such as the nails.

White sponge naevus, the commonest of the inherited dyskeratoses, is an autosomal dominant condition with variable expression and a high degree of penetrance. It generally presents during childhood and is characterized by thickened, folded white patches, most commonly affecting the buccal mucosae. Other mucosal sites in the mouth may be involved and some patients may have similar lesions affecting genital and rectal mucosa. Since the other dyskeratoses may have wider implications and, in particular the risk of malignant transformation, specialist care is indicated.

| Local factors influencing oral immunity or ecology | Systemic immune defects |
|---|---|
| Hyposalivation | Malnutrition |
| Smoking | Immunosuppressant drugs such as corticosteroids |
| Corticosteroids | T lymphocyte defects, especially HIV infection, leukaemias, lymphomas and cancers |
| Broad spectrum antimicrobials | Neutrophil leukocyte defects, such as in diabetes |
| Cytotoxic chemotherapy | Cytotoxic chemotherapy |
| Irradiation involving the mouth/salivary glands | Anaemia |
| Dental appliances | |

**Table 2.** Factors predisposing to candidosis.

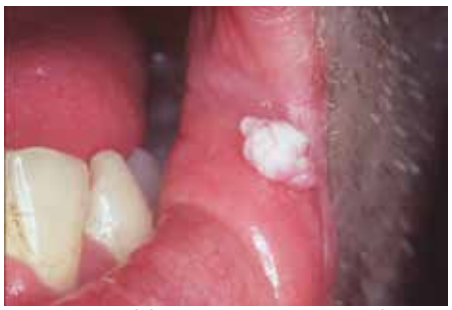

**Figure 6.** Condyloma acuminatum (genital wart).

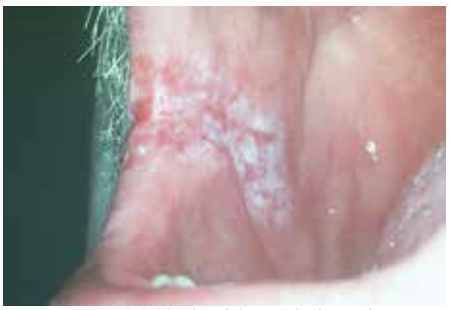

**Figure 7.** Candidal leukoplakia, right buccal mucous.

## Inflammatory causes of white lesions

### Infections

White lesions which can result from infections include candidosis (Figure 4), hairy leukoplakia caused by Epstein-Barr virus (Figure 5), warts and papillomas (caused by human papillomaviruses) (Figure 6), and the mucous patches and leukoplakia of syphilis. Specialist care is usually indicated.

#### *Candidosis* (candidiasis; moniliasis)

The importance of Candida has increased greatly, particularly as the HIV pandemic extends, since this common commensal can become opportunistic if local ecology changes, or the host immune defences fail. *Candida albicans* is the most common cause but occasionally other species may be implicated; in decreasing order of frequency these are:

- *C tropicalis*;
- *C glabrata*;
- *C parapsilosis*;
- *C krusei*;
- other Candida species and other genera.

Some 50% of the normal healthy population harbour (carry) *C albicans* as a normal oral commensal, particularly on the posterior dorsum of the tongue, and are termed Candida carriers. Candidal carriage is more common in smokers and people who wear oral appliances.

Candidosis is the state when *C albicans* causes lesions and these can be mainly white lesions (thrush particularly; Figure 4) or candidal leukoplakia (Figure 7) in which hyphal forms are common, or red lesions (denture-induced stomatitis, median rhomboid glossitis, erythematous candidosis), in which yeast forms predominate, and which may be symptomless though antibiotic stomatitis and angular cheilitis can cause soreness (Article 7).

Circumstances that cause susceptibility to candidosis include local factors influencing oral immunity or ecology, or systemic immune defects, or a combination of more than one factor (Table 2).

#### *Diagnosis*

The diagnosis of candidosis is primarily clinical but a Gram-stained smear (looking for hyphae), a microbiological swab or oral rinse for culture may help to confirm the diagnosis.

#### *Management*

Possible predisposing causes should be looked for and dealt with, if possible. Topical polyene antifungals, such as nystatin or amphotericin or imidazoles, such as miconazole or fluconazole, are often indicated.

### Non-infective causes

Lichen planus (LP) is a very common cause of oral white lesions. It affects up to 2% of the adult population. Accordingly most dental practitioners will have patients afflicted with LP. It is the main skin disease that can present with oral white lesions but lupus erythematosus can present similarly. Up to 44% of patients with oral lichen planus will have skin lesions and more than 70% of patients with skin lesions will have co-incident oral lesions.

## Lichen planus

Lichen planus (LP) usually affects people between the ages of 30 and 65 and there is a slight female predisposition.

### Aetiopathogenesis

Lichen planus is an inflammatory autoimmune-type of disease but it differs from classic autoimmune disorders in having no defined autoantibodies, and only rarely being associated with other autoimmune diseases. There is also no definitive immunogenetic basis yet established for LP and familial cases are rare.

Many patients afflicted with LP have a conscientious type of personality with obsessive-compulsive traits and suffer mild chronic anxiety, suggesting neuro-immunological mechanisms may be at play. Stress has been held to be important in LP: patients have a tendency to be anxious

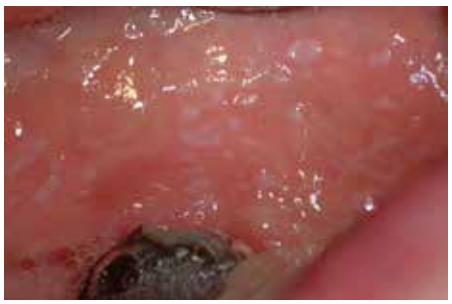

**Figure 8.** Papular lichen planus.

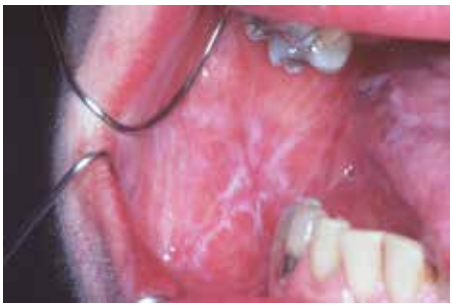

**Figure 9.** Reticular lichen planus.

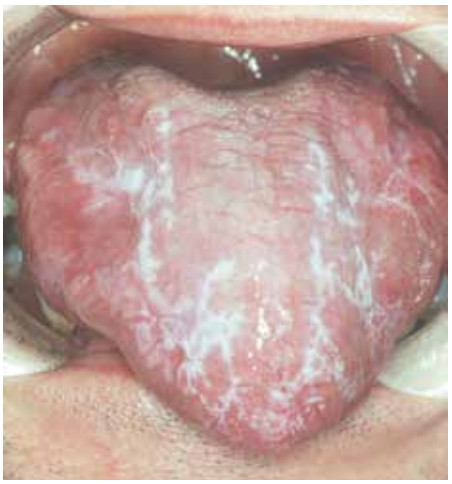

**Figure 10.** Reticular lichen planus, dorsum of tongue.

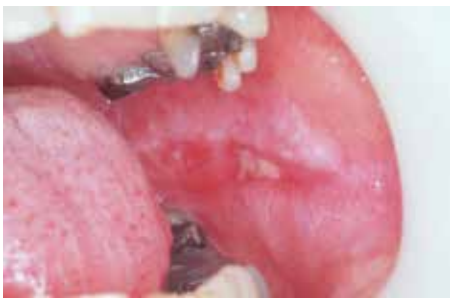

**Figure 11.** Erosive lichen planus, buccal mucosa.

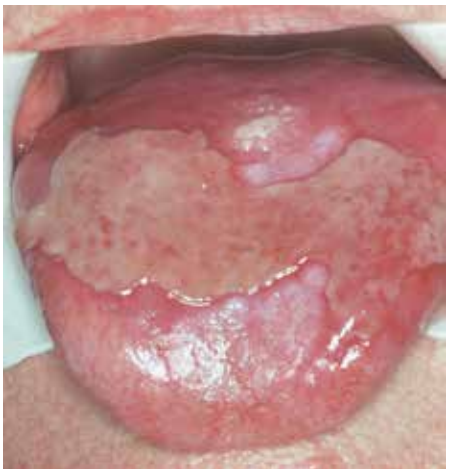

**Figure 12.** Erosive lichen planus, dorsum of tongue.

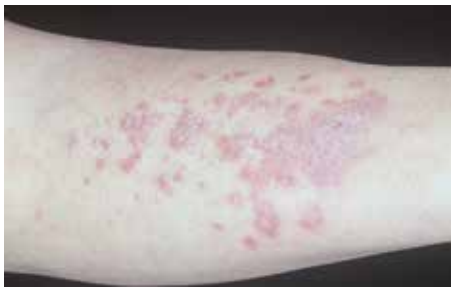

**Figure 13.** Lichen planus, skin.

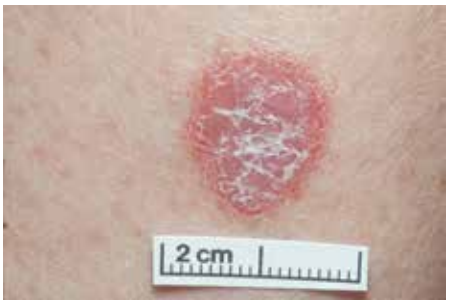


**Figure 14.** Cutaneous lichen planus.

and depressed, but of course the chronic discomfort may partially explain some cases in which this association has been documented.

Pathologically, there is a local cell-mediated immunological response characterized by a dense T-lymphocyte inflammatory cell infiltrate in the upper lamina propria causing cell death (apoptosis) in the basal epithelium, probably caused by the production of cytokines such as tumour-necrosis factor alpha (TNFα) and interferon gamma (IFN-γ).

The antigen responsible for this immune response is unclear but lesions very similar to LP, termed lichenoid lesions, are sometimes caused by:

- Dental restorative materials (mainly amalgam and gold);
- Drugs (non-steroidal anti-inflammatory agents, antihypertensive agents, antimalarials, and many other drugs);
- Chronic graft-versus-host disease seen in bone marrow (haemopoietic stem cell) transplant patients;
- Infection with hepatitis C virus( in some populations such as those from southern Europe and Japan);
- A variety of other systemic disorders such as hypertension and diabetes (probably a reaction to the drugs used).

**Clinical features**

Lichen planus can affect stratified squamous epithelium of the skin, the oral mucosa and genitalia.

Oral LP may present a number of different clinical pictures (Figures 8–13), including:

- Papular LP, white papules (Figure 8);
- Reticular LP, a network of raised white lines or striae (reticular pattern) (Figures 9, 10);
- Plaque-like LP, simulating leukoplakia;
- Atrophic red atrophic areas, simulating erythroplasia (Figure 11; mixed atrophic/erosive form): lichen planus is one of the most common causes of desquamative gingivitis;
- Erosive erosions, less common, but persistent, irregular and painful, with a yellowish slough (Figure 12).

White lesions of LP are often asymptomatic, but there may be soreness if there are atrophic areas or erosions.

Lichen planus typically results in lesions, which are usually in the posterior buccal mucosa bilaterally, but the tongue or gingivae are other sites commonly affected.

On the skin, lichen planus frequently presents as a flat-topped purple polygonal and pruritic papular rash most often seen on the front (flexor surface) of the wrists (Figure 13) in which lesions are often crossed by fine white lines (Wickham's striae; Figure 14). Nail lesions may be seen (Figure 15). Oral LP may be accompanied by vulvovaginal lesions (the vulvovaginal-gingival syndrome).

**Prognosis**

Often, the onset of LP is slow, taking months to reach its peak. It usually clears from the skin within 18 months but in a few people persists for many years. Oral lesions often persist. There is no sign or test to indicate which patients will develop only oral,

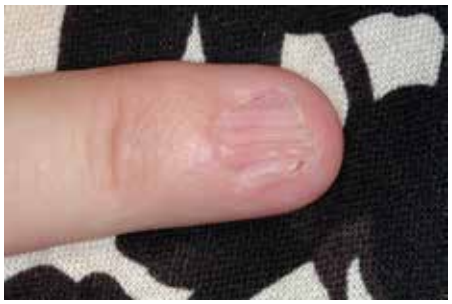

**Figure 15.** Nail lichen planus.

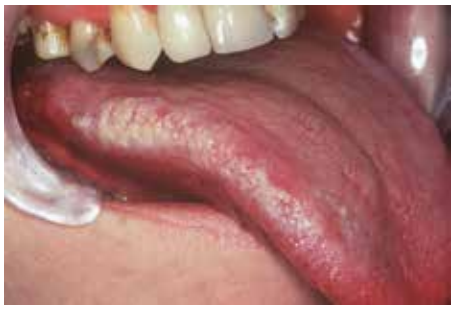

**Figure 16.** Frictional keratosis, lateral tongue.

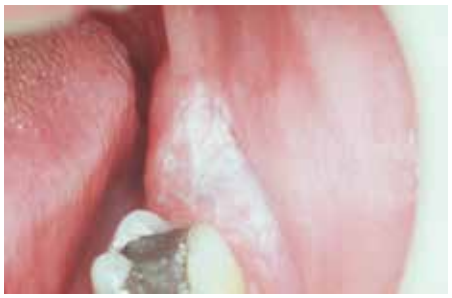

**Figure 17.** Frictional keratosis, retromolar pad.

or oral and extra-oral lesions of LP.

Non-reticular oral LP in particular has a small malignant potential, probably of the order of 1%.

#### Diagnosis

LP is often fairly obviously diagnosed from the clinical features but, since it can closely simulate other conditions such as:

- Lupus erythematosus;
- Chronic ulcerative stomatitis;
- Keratosis; or even
- Carcinoma;

biopsy and histopathological examination of lesional tissue, occasionally aided by direct immunostaining, are often indicated.

## Keypoints: lichen planus

- Some patients also have the condition on the skin, hair, nails or genitals;
- Diabetes, drugs, dental fillings and HCV should be excluded;
- Blood tests may therefore be required;
- Biopsy is usually in order;
- Non-reticular lichen planus *may rarely*, after years, lead to a tumour;
- Removal of the affected area does not necessarily remove the problem;
- Therefore, the best management is usually to ensure the mouth is checked by a healthcare professional at least at 6-monthly intervals.

#### Management

Treatment of LP is not always necessary, unless there are symptoms. Predisposing factors should be corrected:

- It may be wise to consider removal of dental amalgams if the lesions are closely related to these, or unilateral, but tests such as patch tests will not reliably indicate which patients will benefit from this. Accordingly, empirical replacement of amalgam restorations may be indicated.
- If drugs are implicated, the physician should be consulted as to the possibility of changing drug therapy.
- If there is HCV infection, this should be managed by a general physician.
- Improvement in oral hygiene may result in some subjective benefit; chlorhexidine or triclosan mouthwashes may help. Symptoms can often be controlled, usually with topical corticosteroids or sometimes with tacrolimus.
- If there is severe or extensive oral involvement, if LP fails to respond to topical medications, or if there are extra-oral lesions, specialist referral may be indicated.
- Patients with non-reticular lichen planus should be monitored to exclude development of carcinoma. Tobacco and alcohol use should be minimized.

## Keypoints for patients: lichen planus

- This is a common condition;
- The cause is unknown;
- Children do not usually inherit it from parents;
- It is not thought to be infectious;
- It is sometimes related to diabetes, drugs, dental fillings, or other conditions;
- It sometimes affects the skin, hair, nails or genitals;
- Blood tests and biopsy may be required;
- The condition tends to persist in the mouth but it can be controlled;
- Most lichen planus is benign but *some forms may rarely*, after years, lead to a tumour;

Therefore, the best management is usually to:

- Avoid habits such as use of tobacco, alcohol or betel (and, for lips, sun-exposure);
- Take a healthy diet rich in fresh fruit and vegetables;
- Have your mouth checked by a healthcare professional at least at 6-monthly intervals;
- Changes that might suggest a tumour is developing could include any of the following persisting more than 3 weeks:
  - A sore on the lip or in the mouth that does not heal;
  - A lump on the lip or in the mouth or throat;
  - A white or red patch on the gums, tongue, or lining of the mouth;
  - Unusual bleeding, pain, or numbness in the mouth;
  - A sore throat that does not go away, or a feeling that something is caught in the throat;
  - Difficulty or pain with chewing or swallowing;
  - Swelling of the jaw that causes dentures to fit poorly or become uncomfortable;
  - Pain in the ear;
  - Enlargement of a neck lymph gland.

#### Websites and patient information

**http://www.bcd.tamhsc.edu/outreach/lichen/index.html**
**http://www.aad.org/pamphlets/lichen.html**

## Keratoses and leukoplakias

#### Frictional keratosis

Frictional keratosis is quite common and caused particularly by friction from the teeth and seen mainly at the occlusal line in the buccal mucosae, particularly in adult females, especially in those with temporomandibular pain-dysfunction syndrome. It is also commonly seen on the lateral borders of the tongue (Figure 16). Patients with missing teeth may develop keratosis on the alveolar ridge simply related to trauma when eating (Figure 17).

Malignant change is very rare but any sharp edges of teeth or appliances should be removed and the patient counselled about the habits.

| Tobacco habit | Common sites affected | Occasional sites affected | Malignant potential |
|---|---|---|---|
| **Cigarette** | Lip (occasionally nicotine-stained) and commissures | Palate<br>Others | Rare |
| **Pipe smoking** | Palate (termed smoker's keratosis or stomatitis nicotina) | Others | Rare |
| **Cigar** | Palate (termed smoker's keratosis or stomatitis nicotina) | Others | Rare |
| **Snuff** | Gingival (together with recession) | Lip | Rare |
| **Reverse smoking (Bidi)** ***cigarettes are smoked with the lit end within the mouth*** | Palate | Others | Common |
| **Tobacco chewing** | Buccal | Others | Common |

**Table 3.** Tobacco-induced keratoses.

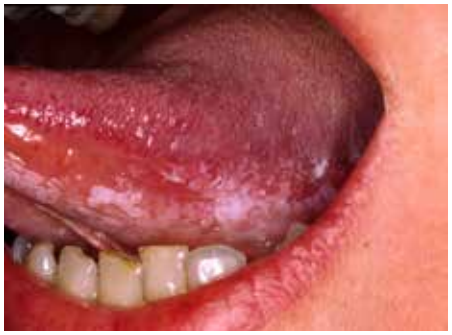

**Figure 18.** Speckled leukoplakia, lateral tongue.

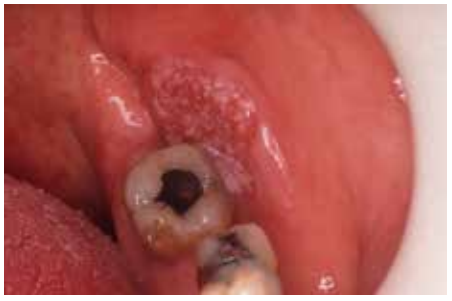

**Figure 19.** Nodular leukoplakia.

**Tobacco-induced keratoses**

Tobacco is a common cause of keratosis, seen especially in males, the teeth are usually nicotine-stained and there may be mucosal smoker's melanosis but malignant change is uncommon in most forms (Table 3).

**Idiopathic keratoses**

Many leukoplakias are uncommon and arise in the absence of any identifiable predisposing factors and most, up to 70% in large series, are benign without any evidence of dysplasia. However, the remaining 10–30% may be, or may become, either dysplastic or invasive carcinomas. Overall, the rate of malignant transformation of all keratoses and leukoplakias is of some 3–6% over 10 years.

The lesions of greatest malignant potential are those leukoplakias which are:

- Speckled (Figure 18), nodular (Figure 19) or verrucous lesions;
- In at risk sites – lateral tongue, ventral tongue (Figure 20), floor of mouth (Figures 21 and 22) and soft palate complex (Figure 23);
- Associated with *Candida* (Figure 7).

In these, rates of malignant transformation up to 30% have been reported in some series.

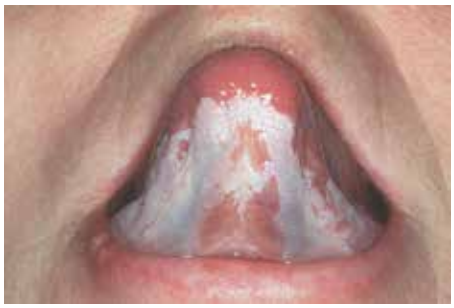

**Figure 20.** Leukoplakia, ventral tongue, floor of mouth.

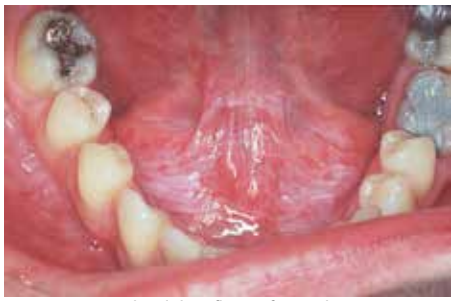

**Figure 21.** Leukoplakia, floor of mouth.

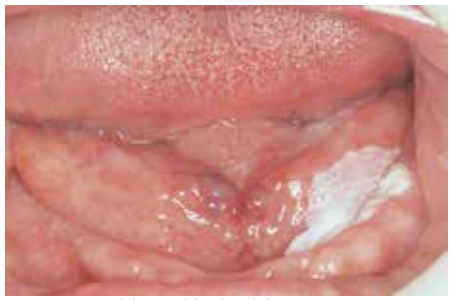

**Figure 22.** Sublingual leukoplakia.

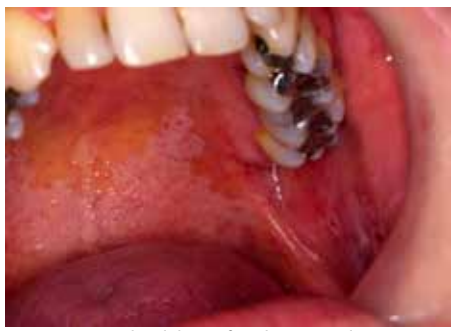

**Figure 23.** Leukoplakia soft palate complex.

***Diagnosis***

The nature of white lesions can often only be established after further investigation.

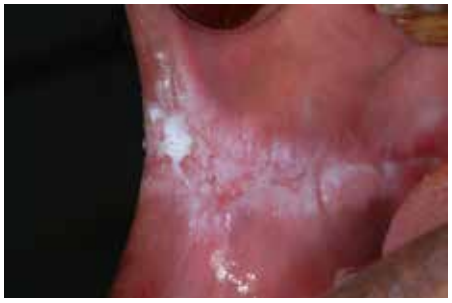

**Figure 24.** Betel chewing keratosis.

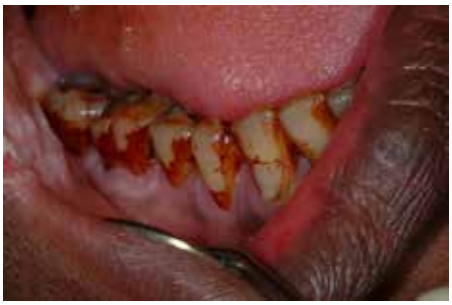

**Figure 25.** Same patient as Figure 23, showing tooth staining.

Biopsy is usually indicated, particularly where there is a high risk of malignant transformation, such as in lesions with:

- Any suggestion of malignancy;
- Admixture with red lesions (speckled leukoplakia or erythroleukoplakia);
- A raised lesion (nodular or verrucous leukoplakia);
- Candidal leukoplakia;
- Floor of mouth leukoplakia (sublingual keratosis);
- A rapid increase in size;
- Change in colour;
- Ulceration;
- Pain;
- Regional lymph node enlargement.

## Keypoints: keratosis (leukoplakia)

- Biopsy is mandatory in high risk lesions or high risk patients;
- In a *very small* number of keratoses, and after years, a tumour may develop;
- There is no universally agreed management;
- Removal of the affected area does not necessarily remove the problem but does permit better histological examination.

Therefore, the best management is usually to:

- Remove the lesion, where possible;
- Avoid harmful habits such as use of tobacco, alcohol or betel (and, for lips, sun exposure);
- Advise a healthy diet rich in fresh fruit and vegetables;
- Examine the oral mucosa at least at 6-monthly intervals.

***Prognosis***

The finding by the pathologist of epithelial dysplasia may be predictive of malignant potential, but this is not invariable, and there can be considerable inter- and intra-examiner variation in the diagnosis of dysplasia.

Thus there has been a search for molecular markers to predict exactly which lesions are truly of malignant potential and may develop into oral squamous cell carcinoma (OSCC).

The most predictive of the molecular or cellular markers thus far assessed for OSCC development, apart from dysplasia, include chromosomal polysomy, the tumour suppressor p53 protein expression, and loss of heterozygosity (LOH) at chromosome 3p or 9p. Routine use of these is, however, hampered by their complexity and lack of facilities in many pathology laboratories.

As a surrogate for individual molecular markers, measurement of gross genomic damage (DNA ploidy) may be a realistic option, and is now available in some oral pathology laboratories.

***Management***

The dilemma in managing patients with potentially malignant oral lesions and field change has been deciding which mucosal lesions or areas will progress to carcinoma. At present there are no reliable markers which predict which lesions will progress. Specialist referral is indicated.

Cessation of dangerous habits such as tobacco and/or betel use (Figures 24, 25), and the removal of lesions is probably the best course of action, particularly if they are the high risk lesions or in a high risk group for carcinoma (Article 3).

Perhaps surprisingly, management of leukoplakias is very controversial, since there are no randomized, controlled, double-blind studies that prove the best type of treatment. However, most specialists prefer removal of the lesion (by laser, scalpel or other means).

## Keypoints for patients: keratosis (leukoplakia)

This is an uncommon condition:

- Sometimes it is caused by friction or tobacco;
- It is not inherited;
- It is not known to be infectious;
- Blood tests and biopsy may be required;
- In a *very small* number, and after years, it may lead to a tumour;
- There is no universally agreed management and this can be by simple observation, drugs, or surgery;

Therefore, the best management is usually to:

- Avoid harmful habits such as use of tobacco, alcohol or betel (and, for lips, sun exposure);
- Take a healthy diet rich in fresh fruit and vegetables;
- Have your mouth checked by a healthcare professional at least at 6-monthly intervals;

Changes that might suggest a tumour is developing could include any of the following persisting for more than 3 weeks:

- A sore on the lip or in the mouth that does not heal;
- A lump on the lip or in the mouth or throat;
- A white or red patch on the gums, tongue, or lining of the mouth;
- Unusual bleeding, pain, or numbness in the mouth;
- A sore throat that does not go away, or a feeling that something is caught in the throat;
- Difficulty or pain with chewing or swallowing;
- Swelling of the jaw that causes dentures to fit poorly or become uncomfortable;
- A change in the voice; and/or
- Pain in the ear;
- Enlargement of a neck lymph gland.

**Useful websites and patient information**

**http://www.cochrane.org/cochrane/revabstr/ab001829.htm**

**http://www.emedicine.com/ent/topic731.htm**

**http://www.mayoclinic.com/health/leukoplakia/DS00458**

**Patients to refer:**

- Keratoses which do not regress after elimination of aetiological factors;
- Hairy leukoplakia, if underlying cause of immunosuppression not already identified;
- Carcinoma.