Oral White Lesions: Who, What, Where, When, How and Why?

by

Peter Thomson

Author: *Peter Thomson, Head of Dentistry & Professor of Oral & Maxillofacial Sciences, College of Medicine & Dentistry, James Cook University, Australia*

peter.thomson1@jcu.edu.au

Keywords: Oral white lesions, potentially malignant disorders

Abstract

Diagnosis and management of oral white lesions can be challenging in clinical practice, owing to their highly variable aetiology and different prognoses ranging from benign, often reactive mucosal lesions through to potentially malignant conditions or frankly invasive oral cancers. In this paper, the author proposes a pragmatic, clinically based approach to assessment, diagnosis and treatment based upon a diagnostic decision-making tree and six classic information-gathering questions: who, what, where, when, how and why?

Introduction

Identification of a white lesion arising from the surface of the oral mucosa is a frequent clinical finding during comprehensive oral examination but can present a diagnostic challenge to oral health care practitioners. This is because oral white lesions, many of which are entirely asymptomatic, actually comprise a wide and complex spectrum of many different conditions, ranging from surface collections of debris and/or fungal infections (pseudo-membranes), that can be gently wiped off the mucosal surface with damp gauze, to persistent spots or plaques of thickened keratin (hyperkeratinisation) whose white and opaque appearance results from enhanced absorption of fluid from saliva and, as intrinsically altered epithelial tissue, are adherent and non-wipeable[1].

The significance, of course, is that whilst most lesions represent benign, often reactive conditions, other more sinister lesions develop due to histopathological abnormalities including epithelial dysplasia (essentially unstable tissue disorganisation and dysmaturation) that highlight the presence of an underlying potentially malignant disorder (PMD). PMD are defined as recognizable mucosal diseases that share an unpredictable but significantly increased risk of oral squamous cell carcinoma (OSCC) development. Oral leukoplakia, a non-wipeable white plaque that cannot be characterized clinically or pathologically as any other disorder, is by far the commonest PMD accounting for between 60 to 70% of cases, although others may present as red (erythroplakia) or mixed red-and-white lesions (erythroleukoplakia). It is well recognized that clinical identification of a PMD offers potential for both early diagnosis of malignancy and low-morbidity therapeutic intervention. The ultimate priority during the diagnostic approach to oral white lesions, therefore, must be to exclude the possibility, however rare it may seem, of an underlying oral malignancy[1,2].

In 2021, the Dentistry discipline at James Cook University (JCU) introduced a new course in Oral & Maxillofacial Sciences, combining and integrating several previously ‘stand-alone’ subjects including Oral & Maxillofacial Surgery, Medicine and Pathology, and Human Disease. With a focus on diagnosis and management of the presenting patient, the aim was to shift the focus of learning to the applied application of knowledge in clinical scenario-based situations. Whilst preparing educational material on oral white lesions, it became apparent how potentially useful this approach might be to assist inexperienced or non-specialist clinicians in the assessment of newly presenting lesions[3].

The question I therefore posed, both to myself and to my cohort of enthusiastic new Year 3 BDS students, was: How can we assist the practising clinician in reliably distinguishing between PMD and the more common benign oral white lesions? This paper aims to explore this issue further and to offer some practical advice to healthcare practitioners.

A Diagnostic Decision-Making Tree

Mortazavi et al[4] recently published a proposed clinical diagnostic decision tree for oral white lesions based upon their mode of development and individual clinical presentation, offering a stepwise diagnostic progression through putative lesion origin as either a congenital or an acquired condition, clinicians' ability in practice to wipe the lesion off the mucosal surface and, finally, the presence or absence of specific distinguishing clinical features as determined by oral examination. Whilst both an interesting and pragmatic tool to help distinguish between more than 20 different clinical entities, ability to accurately delineate benign conditions from PMD remains somewhat obscure with this method. A modified Clinical Decision Tree designed to specifically emphasize PMD risk was thus developed and is presented in Figure 1; this, as we shall see, is of especial relevance for some congenital and several acquired, non-wipeable lesions.

The Six Honest Serving Men

In 1902, as part of his volume of 'Just So Stories', the prolific author Rudyard Kipling published his famous poem, 'I Keep Six Honest Serving Men'. Referencing primarily his early life and work as a journalist, the first lines of Kipling's classic read:

'*I keep six honest serving-men,*

They taught me all I know,

Their names are What and Why and When,

And How and Where and Who.'

The Six Honest Serving Men eloquently summarize the fundamental investigative questions considered essential during basic information-gathering, critical analysis and problem solving. To complement our proposed clinical decision tree, these specific questions require consideration during the clinical assessment of newly presenting oral white lesions. The clinical relevance of the information gathered by asking Who, What, Where, When, How and Why is summarized in Table 1.

Applying our Six Honest Serving Men further, and working through the various decision tree categories, Tables 2 to 5 distinguish the aetiopathogenesis, clinical presentation, significance, and management approach to nineteen of the most commonly presenting oral white lesions seen in contemporary practice.

Congenital White Lesions

Congenital lesions, which are present at birth, and which may or may not have an underlying genetic basis, are often only clinically recognized later in life. These lesions, which are summarized in Table 2, comprise not only relatively common benign, incidental findings such as *leukoedema* (a milky-white appearance of the buccal mucosa) and *white sponge naevus* (diffuse, spongy thickened plaques at various oral sites), but also the much rarer and highly significant PMD, *dyskeratosis congenita*. The latter is an X-linked recessive trait comprising a triad of mucous membrane leukoplakia, nail dystrophy and skin pigmentation; premature mortality results from bone marrow failure and/or malignant transformation within mucosal lesions. Other congenital disorders include *Hereditary Benign Intraepithelial Dyskeratosis, Pachyonychia Congenita* and *Darier's disease*, although the latter two primarily present as widespread dermatological disorders rather than specific oral complaints[4,5].

Acquired White Lesions – Wipeable

Table 3 lists the two principal causes of non-adherent patches that can be wiped off the oral mucosal surface. *Acute pseudomembranous candidiasis* (thrush) classically presents with white papules or confluent plaques, often presenting in elderly or immunocompromised individuals but more frequently encountered in dental practice on the soft palate of patients failing to oral rinse after corticosteroid inhaler use; when wiped away, the underlying mucosa exhibits a raw, reddened or bleeding surface. Also commonly observed are the various *pseudo-membranes* that result from the build-up of extraneous debris associated with poor oral hygiene (Materia alba), or the necrotic mucosa and fibrin clots seen as a consequence of thermal, chemical and frictional injury or during ulcer healing. Often located at buccal mucosa sites or accumulating on the dorsum of the tongue, careful history taking assists in distinguishing the likely cause of such lesions[1,4].

Acquired White Lesions – Non-Wipeable / Benign

Accounting for some of the most frequently observed clinical presentations, Table 4 lists seven conditions that give rise to non-wipeable white lesions, all of which are essentially benign in nature and often require no, or only minimal, treatment intervention. *Frictional keratosis* is a response to chronic mechanical irritation of the mucosa and is most often seen on the buccal mucosa and/or lateral tongue due to the sharp edges of teeth, restorations or prostheses, or may arise on edentulous alveolar ridges suffering masticatory trauma from unopposed teeth. Whilst an obvious cause is often identifiable, incisional biopsy may be indicated to confirm the diagnosis and exclude a dysplastic element; removal or reduction of the irritant factor usually facilitates lesion resolution[1,4].

Stomatitis nicotina (sometimes known as smoker's keratosis) presents as a confluent white patch on palatal mucosa distinguished by the presence of multiple red orifices from swollen minor salivary glands and is a direct consequence of chronic thermal irritation; whilst there is no increased risk of cancer development, patients should be cautioned regarding such direct evidence of tobacco smoke damage and smoking cessation is to be encouraged[1].

The chronic mucocutaneous disorder *lichen planus* and its variants relating to contact or drug induced mucosal reactions provide a range of distinctive reticular, papular or plaque-like patches, often interspersed with erythematous or erosive areas that may prove symptomatic; they are highly recognisable by their clinical appearance and characteristic histopathological features of lichenoid inflammation seen under microscopy. In the absence of identifiable epithelial dysplastic change in biopsy specimens, controversy exists in the literature regarding the potential for malignant transformation, especially for classic oral lichen planus, whilst OSCC development is most definitely a risk in some solitary oral lichenoid lesions, as detailed further in Table 5[1,2].

Systemic Lupus Erythematous, a multisystem autoimmune disorder involving skin and mucosa, may present intra-orally with erythematous lesions surrounded by stellate white striae similar in appearance to lichenoid lesions, and arising commonly at buccal mucosa sites. Whilst regular review of oral lesions is recommended, there is little evidence to confirm a definitive PMD risk. *Hairy Leukoplakia*, the presence of thickened, furrowed white bands arising on the lateral tongue and linked with Epstein-Barr virus infection in immunocompromised patients, is less frequently observed nowadays due to effective antiviral therapies; there is no malignant transformation risk for these lesions[1,2,4].

Figure 2 illustrates three examples of acquired, non-wipeable white lesions shown, for comparative purposes, all arising on buccal mucosa sites.

Acquired Lesions – Non-Wipeable / Potentially Malignant

Table 5 is of especial relevance considering our stated diagnostic priority to exclude potential malignancy. This table highlights seven white lesion presentations that are directly associated with either PMD or, in some cases, frankly invasive OSCC. PMD exhibit an overall 12% cancer risk over a mean transformation time of 4 years, with severe or 'high-grade' dysplasia considered most at risk. Oral carcinogenesis is a complex, multi-step process involving the sequential accumulation of gene mutations, either spontaneously or via the action of exogenous carcinogens, leading to de-regulation of normal cell proliferation mechanisms. As the natural history of any individual PMD remains unpredictable, contemporary clinical management is based upon initial incision biopsy for provisional histological assessment and dysplasia severity grading, followed by targeted surgical excision by CO_2 laser to facilitate definitive diagnosis and to remove lesions deemed at 'high risk' for malignant transformation[1,6-9].

Careful inspection of the lower lip vermilion and labial mucosa is an important component of every oral examination, especially for fair-skinned individuals living in climates with excessive ultra-violet radiation exposure such as Australia. Resultant tissue damage leads to a*ctinic cheilitis*, which is recognised clinically by dryness, crusting, erosions or leukoplakic patches; early-stage cheilitis may appear very similar to lichenoid change so that incision biopsy to facilitate histopathological examination helps avoid diagnostic uncertainty and guide appropriate treatment[1].

Solitary oral lichenoid lesions, especially those arising on ventro-lateral tongue sites, often exhibit significant dysplasia on incision biopsy and are at particular high risk of malignant transformation; early excision surgery with laser is thus strongly recommended. *Chronic hyperplastic candiadisis* (classically termed candidal leukoplakia) is common in smokers and usually presents as non-homogenous lesions at labial commissure sights; an example is shown in Figure 3A. Although it remains unclear whether candida initiates dysplastic change or represents secondary infection within abnormal tissue, lesions require urgent recognition, patients should be advised to eliminate tobacco use and systemic anti-fungal medication prescribed to eradicate deep-seated hyphae within hyperkeratinised epithelium. Laser excision is used for persistent and/or dysplastic lesions[1,7,8].

Statistically, PMD most frequently present in practice as *oral leukoplakia* arising on ventrolateral tongue, floor of mouth and buccal mucosa sites, as illustrated in Figure 3B, and are often linked to long-term tobacco and alcohol misuse. Large, non-homogenous, multi-focal lesions and the presence of significant dysplasia in incision biopsy specimens are all features associated with a higher risk of malignant transformation; such lesions should undergo interventional laser excision surgery and long-term active surveillance to monitor for both recurrent (same site) and further (new site) disease post-operatively[1,2,7].

With a predilection to present in female non-smokers, and thereby erroneously considered to be ‘low risk’, *proliferative verrucous leukoplakia* (PVL) appears as fissured, exophytic and warty-looking patches on the gingiva and alveolar mucosa, as shown in Figure 3C. In reality, however, these lesions exhibit progressive behaviour, considerable treatment resistance and, ultimately, a very high 70 to 100% malignant transformation risk. Although often requiring repeated treatments, laser ablation offers a pragmatic management technique to both vapourise abnormal epithelium and facilitate low morbidity healing. *Verrucous carcinoma* is a slow growing warty-looking malignancy that primarily exhibits local tissue invasion with only limited potential for metastasis and may arise de-novo intra-orally or as evolution of a pre-existing PVL. Interestingly, it is increasingly recognised that there probably exists an important continuum of progressive histopathological change involving hyperkeratosis and lichenoid inflammation, PVL, verrucous hyperplasia and verrucous carcinoma, and ultimately culminating in frankly invasive and metastasizing OSCC[1,10,11].

Although *OSCC* most commonly presents as non-healing ulcerative and/or irregular, exophytic lesions, up to 12% of clinically diagnosed PMD have been shown to already harbour foci of early invasive

carcinoma. Initial presentation of OSCC as an oral leukoplakia, therefore, should always be considered a potential risk during clinical decision making[2,7,12].

Conclusions

Although sharing a similar clinical appearance, oral white lesions represent a complex mixture of benign and potentially malignant mucosal lesions. Whilst this paper does not attempt to compete with the vast clinico-pathological detail available in contemporary textbooks of oral medicine and pathology, the aim has been to rationalize a diagnostic approach to newly presenting white lesions that prioritizes identification and interventional management for those conditions most at risk of OSCC development. It is hoped that this approach will provide pragmatic assistance to busy clinicians in their day-to-day decision making and in the delivery of care for patients presenting with this common oral conundrum.

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Figure 1: Clinical Decision Tree for Oral White Lesions (modified from Mortazavi et al*)

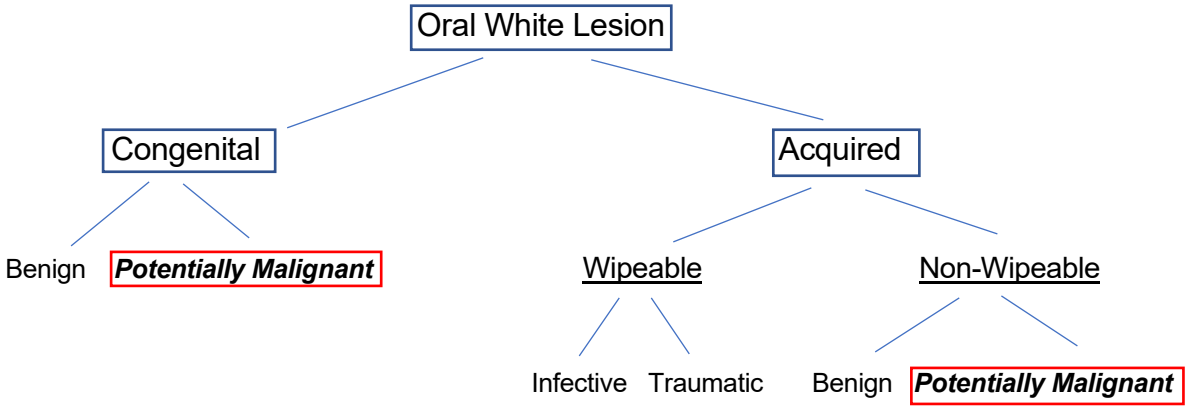
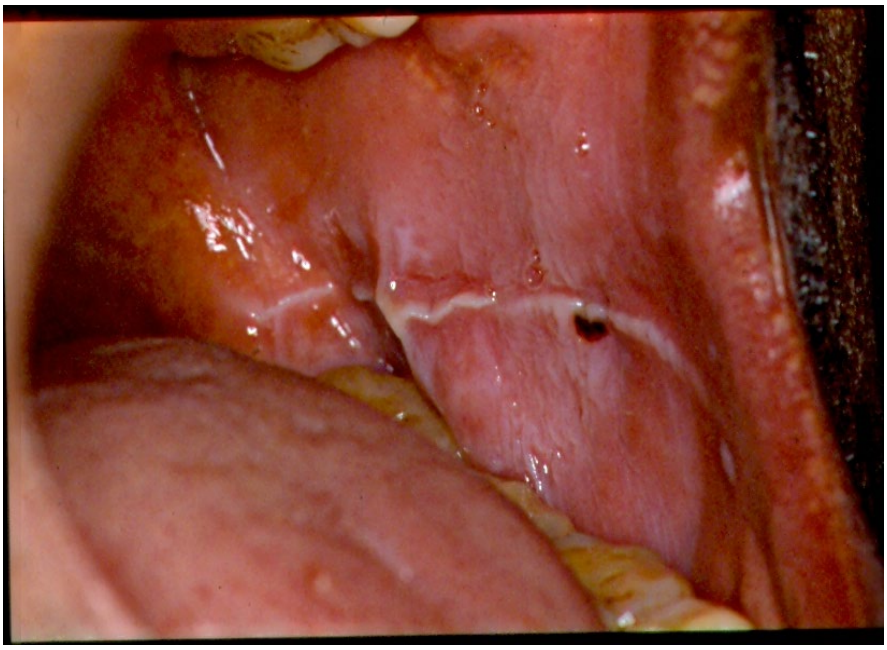


Figure 2: Clinical Examples of Acquired, Non-Wipeable, Benign White Lesions arising on the Buccal Mucosa showing: (A) Frictional Keratosis in response to a sharp and irregular dentition (with an especially prominent Linea alba), (B) Oral Lichen Planus (classic reticular white striae pattern), and (C) Lichenoid Contact Reaction (immediately adjacent to an old amalgam restoration).

A



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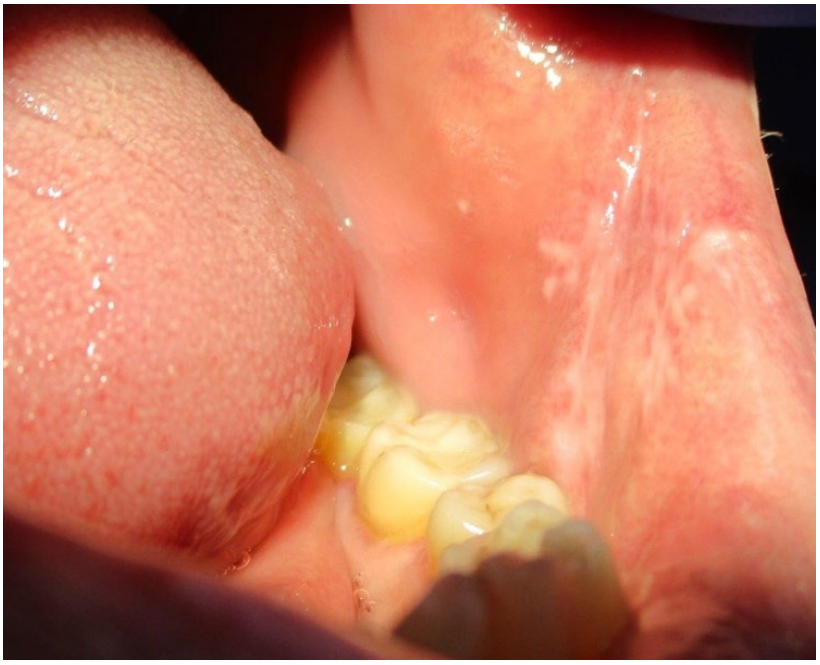

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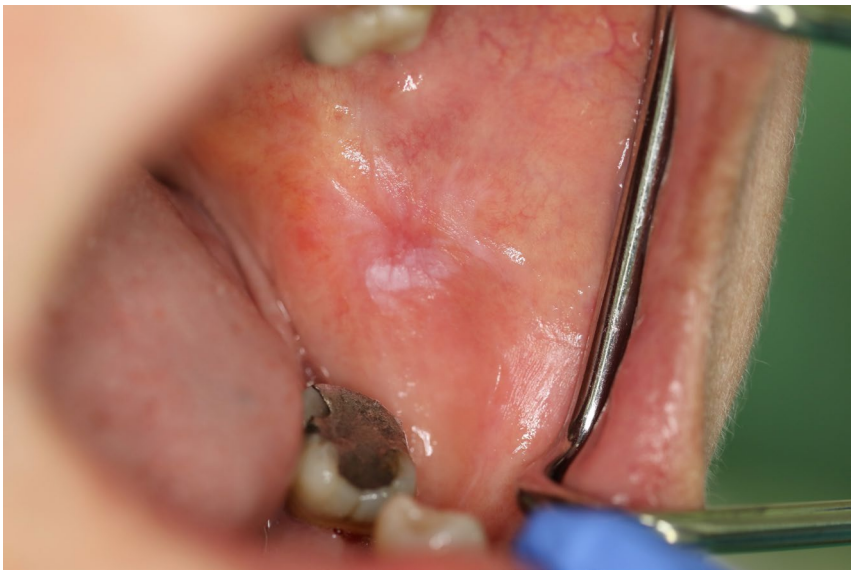
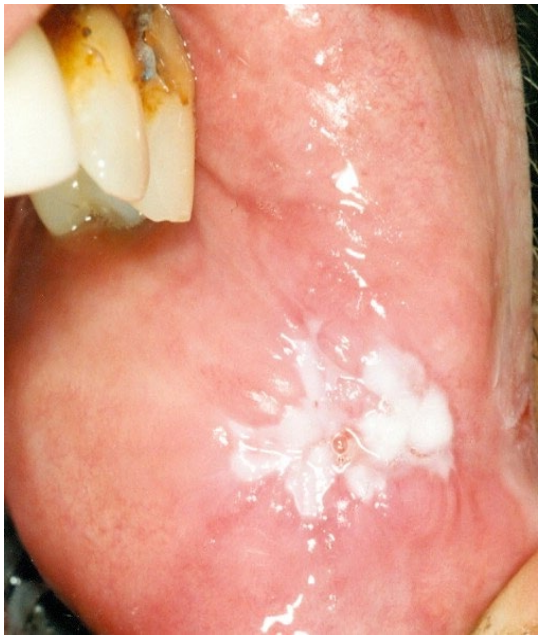


Figure 3: Clinical Examples of Acquired, Non-Wipeable, Potentially Malignant White Lesions showing: (A) Chronic Hyperplastic Candidiasis (arising at the labial commissure region), (B) Non-Homogenous Leukoplakia (on the floor of mouth and ventral tongue) and (C) Proliferative Verrucous Leukoplakia (maxillary buccal gingiva).

A



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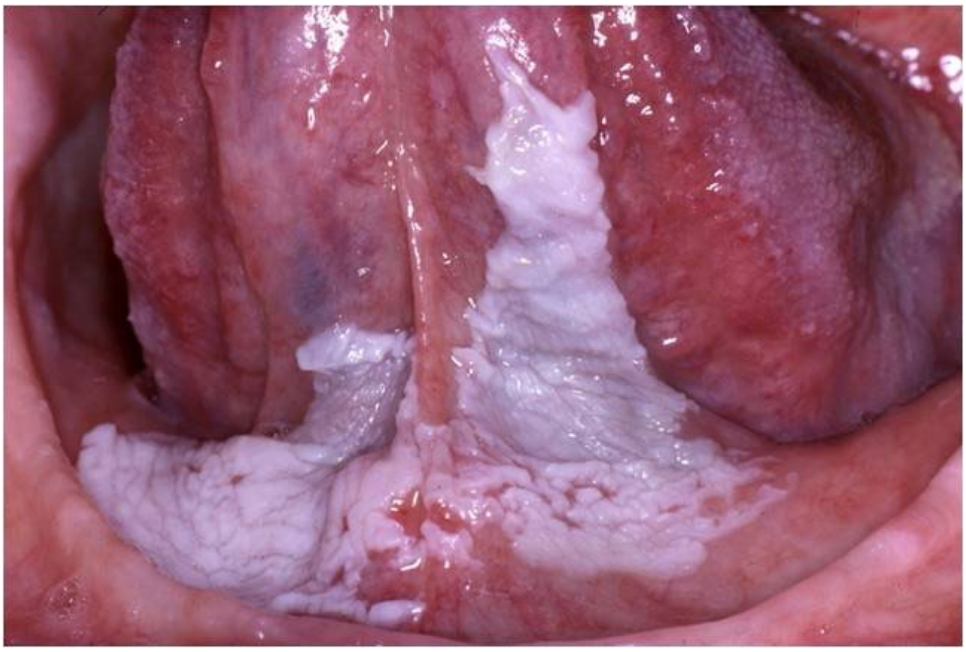

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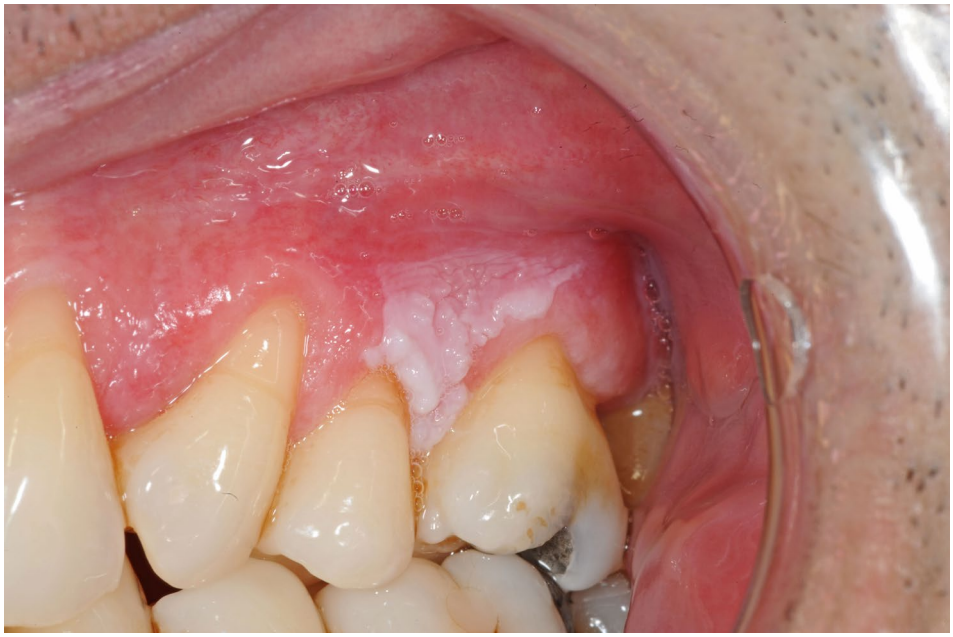

Table 1: Clinical Relevance of Who, What, Where, When, How and Why?

Investigative Question	Clinical Relevance
Who?	Male or Female Predominance
What?	Characteristic Clinical Appearance of Mucosal Lesion
Where?	Principal Oral Sites Involved
When?	Most Common Patient Age at Presentation
How?	Aetiopathogenesis
Why?	Clinical Significance & Patient Management

Table 2: Congenital White Lesions

Lesion	Who	What	Where	When	How	Why
Oral Epithelial (White Sponge) Naevus	Males & Females (Any)	Shaggy, folded, diffuse, spongy plaques	Any Oral Site	Childhood Adolescence	• Autosomal Dominant • Dyskeratotic Hyperplasia due to Gene Mutation	• Benign • No Treatment
Leukoedema	Males & Females	Milky, opalescent folds Disappear temporarily upon Mucosal Stretching	Buccal Mucosa	Childhood Adolescence	• Normal Variant	• Normal Variant • Benign • No Treatment
Dyskeratosis Congenita	Males > Females	Bullae Erosions Oral Leukoplakia	Buccal Mucosa Tongue Oropharynx	Children 5-12 Years of Age	• X-Linked Recessive	• PMD • 30% Malignant Transformation Risk • Interventional Therapy & Active Surveillance

Table 3: Acquired White Lesions – Wipeable

Lesion	Who	What	Where	When	How	Why
Acute Pseudomembranous Candidiasis	Females > Males	Creamy White Plaques	Palate Buccal Mucosa Tongue	Infants Elderly	• Candida Super-Infection • Immuno-Compromised Host	• Benign • Correct Predisposing Factors • Anti-Fungal Treatment
Non-Specific Pseudomembrane (Trauma, Ulceration, Burns, Debris)	Males & Females (Any)	Yellow or Grey-White Coating	Buccal Mucosa Tongue Dorsum	Any Age	• Trauma • Necrotic Tissue + Fibrin Clot	• Benign • Debridement • Monitor Healing

Table 4: Acquired White Lesions – Non-Wipeable / Benign

Lesion	Who	What	Where	When	How	Why
Frictional Keratosis	Any	Plaque Roughened Surface	Buccal Mucosa Lateral Tongue Alveolus	Any Age	Repetitive Minor Trauma	• Removal of Chronic Irritants
Stomatitis Nicotina	Males	Grey-White Plaque with Reddened Minor Salivary Gland Orifices	Palatal Mucosa	Middle Aged	Thermal Irritation	• Smoking Cessation
Oral Lichen Planus	Females	Reticular, Papular, Plaque-Like +/- Erythema, Erosions, Ulceration	Bilateral Buccal Mucosa & Dorsolateral Tongue	Middle Aged	Auto Immune Mucocutaneous Disorder	• Topical Corticosteroids for Symptomatic Lesions
Lichenoid Contact Reaction	Females	Reticular, Papular, Plaque-Like +/- Erythema, Erosions, Ulceration	Buccal Mucosa Lateral Tongue Adjacent to Dental Materials	Any Age	Delayed Hypersensitivity Reaction to Dental Materials	• Restorative Intervention
Drug-Induced Lichenoid Reaction	Any	Reticular, Papular, Plaque-Like +/- Erythema, Erosions, Ulceration	Unilateral Buccal Mucosa Tongue	Any Age	Delayed Hypersensitivity Reaction	• Identification & Withdrawal / Replacement of Drug
Systemic Lupus Erythematosus	Females	Discoid Stellate Lesions	Buccal Mucosa Palate Gingiva	Young Adult	Auto Immune	• Immune Modulating Treatments • Topical Corticosteroids for Symptomatic Lesions
Hairy Leukoplakia	Males	Furrowed, Thickened Vertical Bands	Lateral Tongue	Any Age	EB Virus Infection Immunocompromised Host	• Anti-Viral Medication

Table 5: Acquired Lesions – Non-Wipeable / Potentially Malignant

Lesion	Who	What	Where	When	How	Why
Actinic Cheilitis	Males	Dryness Crusting Plaques +/- Atrophy Ulceration	Lower Lip Vermilion	Middle Aged Elderly	U-V Irradiation Carcinogenesis	• PMD • U-V Protection • Laser Ablation
Solitary Oral Lichenoid Lesion	Females > Males	Reticular, Papular, Plaque-Like +/- Erythema, Erosions, Ulceration	Unilateral Buccal Mucosa Ventro-Lateral Tongue	Middle Aged	Auto Immune ? Carcinogenesis	• ? PMD • Laser Excision
Chronic Hyperplastic Candidiasis (Candidal Leukoplakia)	Any	Patches, Plaques +/- Erythema	Labial Commissure Tongue Dorsum	Middle Aged	Chronic Candida Infection Carcinogenesis	• PMD • Anti-Fungal Therapy • Smoking Cessation • Laser Excision
Oral Leukoplakia	Males > Females	Patch Plaque Homogenous or Non-Homogeneous	Floor of Mouth Ventro-Lateral Tongue Buccal Mucosa	Middle Aged	Carcinogenesis	• PMD • 12% Malignant Transformation Risk • Laser excision
Proliferative Verrucous Leukoplakia	Females	Plaque Warty, Verrucous Non-Homogenous	Gingiva Alveolus	Middle Aged Elderly	Carcinogenesis	• PMD • 70 – 100% Malignant Transformation Risk • Laser Ablation
Verrucous Carcinoma	Males	Plaque Warty, Verrucous Non-Homogenous	Gingiva Alveolus Buccal Mucosa	Elderly	Carcinogenesis	• Malignancy • Surgical Excision
Oral Squamous Cell Carcinoma	Males > Females	Patch Plaque Homogenous or Non-Homogeneous Ulceration	Floor of Mouth Ventro-Lateral Tongue Buccal Mucosa	Middle Aged Elderly	Carcinogenesis	• Malignancy • Multi-Disciplinary Management • Surgery, Chemoradiotherapy