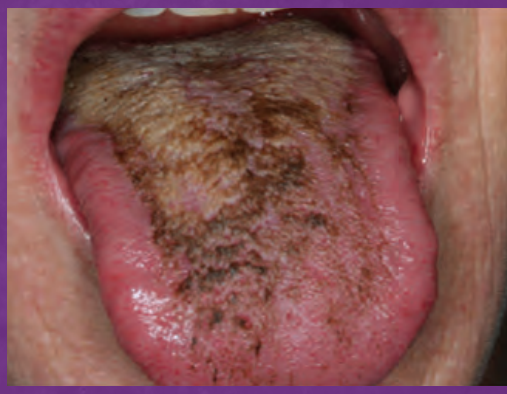
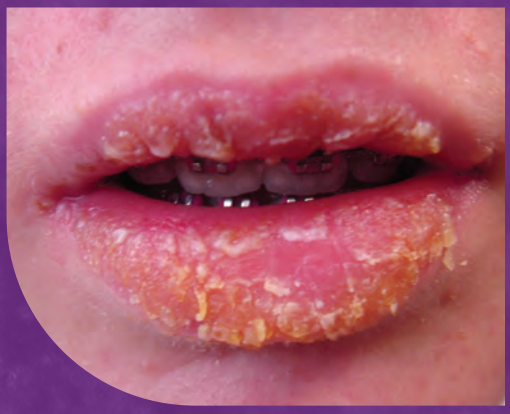
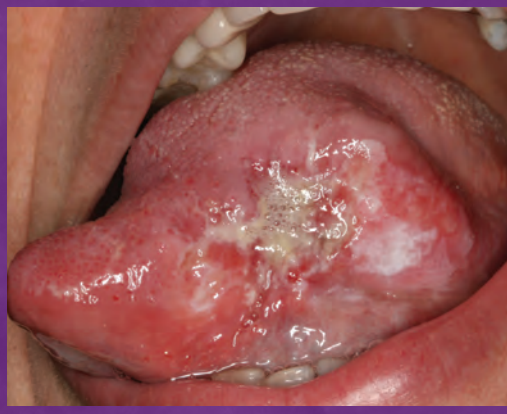
Oral Dermatology

A practical guide for dermatologists and medical practitioners

S R Prabhu, Amanda Oakley & Sue-Ching Yeoh

Oral Dermatology

In memory of our colleague and friend,
Newell Walter Johnson CMG

Oral Dermatology

A practical guide for dermatologists and medical practitioners

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FOREWORD

It has been a pleasure and an honour to be asked to write a foreword to this new publication, *Oral Dermatology: A practical guide for dermatologists and medical practitioners*, a reference book primarily targeted at dermatologists.

Often, dermatologists encounter patients with oral mucosal diseases. In some cases, the presenting oral lesion may be the sole clinical presentation. A range of oral lesions may also appear as the only or early manifestations of underlying mucocutaneous diseases. In such circumstances, dermatologists may be uncertain of diagnosing and managing oral mucosal and mucocutaneous presentations. Diagnosing and managing mucosal or mucocutaneous disease demands logical structuring of clinical information. It is also important not to miss an oral cancer at its first presentation. *Oral Dermatology* provides a systematic approach to address these challenging issues.

Oral Dermatology contains ten chapters, offering readers in-depth information about oral mucosal disease encountered in dermatology practice or in primary care. It begins with chapters discussing anatomical structures of the oral cavity and variants of the oral mucosa, diagnostic procedures for evaluating diseases of the oral mucosa, differential diagnosis of the oral lesions, reactions of the oral mucosa to local or exogenous factors, oral mucosal disease of developmental and genetic origin, infections of the oral mucosa, oral mucosal inflammatory diseases and conditions, oral mucosal non-inflammatory diseases and conditions, oral mucosal manifestations of systemic diseases, and oral neoplastic lesions: benign, potentially malignant, and malignant. This book offers essential knowledge to understand the aetiology, clinical features, and differential diagnosis and management protocol of oral mucosal diseases. The book provides clear advice to arrive at a working diagnosis. It includes over 200 clinical images to aid in complementing the text.

This book is a welcome addition to the available resources in dermatology and medicine. I highly recommend this valuable reference book to every dermatologist, primary care physician, postgraduate student of dermatology and medicine, and any other physician who deals with oral and skin care.

This book is authored jointly by internationally reputed oral medicine experts and a dermatologist. I wish to congratulate Professors S R Prabhu, Amanda Oakley, and Sue-Ching Yeoh for compiling this thorough and easy-to-read book that covers all significant aspects of oral mucosal and mucocutaneous diseases.

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PREFACE

The idea for this book was conceived in 2021 by Oral Medicine Specialist and Honorary Associate Professor S R Prabhu (University of Queensland), who recognized a gap in the market for an up-to-date guide to oral diseases targeted at dermatologists and medical practitioners. He soon co-opted Dermatologist, Adjunct Associate Professor Amanda Oakley (now Honorary Professor, University of Auckland) and a practising Oral Medicine Specialist, Associate Professor Sue-Ching Yeoh (Sydney), to help with the task.

We recognized that often patients with oral mucosal diseases and conditions consult a dermatologist or a family doctor, who are frequently unfamiliar with acute and chronic mucosal disorders and lesions within the oral cavity. In this book, we start with a chapter about oral anatomical features and another containing a brief outline of investigations and procedures available. Our readers should find *Chapter 3* particularly helpful, where we have assembled lists of diseases and conditions and their key points according to their morphology or location. *Chapters 4* to *10* provide greater detail about individual topics and are accompanied by clinical illustrations. Many of these illustrations come from the authors' own collections or their institutions (in particular, Health New Zealand | Te Whatu Ora – Waikato). Others have been acquired from Open Access online resources or published works, after gaining permission for copyrighted works. We have tried to acknowledge the copyrighted material for the images used. If copyright infringement has occurred unintentionally, we wish to tender our apologies.

Our goal is to provide an easy-to-read textbook where readers can quickly find what they need to confidently assess symptoms and signs of lesions within and around the mouth.

S R Prabhu
Amanda Oakley
Sue-Ching Yeoh

ABOUT THE AUTHORS

Professor S R Prabhu is an Honorary Associate Professor at the University of Queensland School of Dentistry, Brisbane. His expertise is in Oral and Maxillofacial Pathology and Oral Medicine, with a special interest in tropical oral diseases. Professor Prabhu formerly held academic positions in Oral Medicine and Oral Pathology at university dental schools in India, Kenya, Sudan, Trinidad and Tobago, Malaysia, Saudi Arabia, and the UAE and administrative positions as Director and Dean of Dental Schools in Trinidad and Tobago West Indies, and the UAE, respectively. Professor Prabhu is a Fellow of the dental faculties Royal Colleges of Surgeons in the UK and Ireland and the International College of Dentists. He was an external examiner for the Royal College of Surgeons of Edinburgh, UK dental membership examinations. He received the Commonwealth Medical Scholarship awarded by the British Council and the Rotary Foundation award for teaching in developing countries. Professor Prabhu has conducted workshops on HIV/AIDS for oral healthcare professionals in several countries in the Asian and Caribbean regions. He has published numerous papers in refereed journals, edited/co-edited, and authored/co-authored over fifteen books. Prominent among these include *Oral Diseases in the Tropics*, *Textbook of Oral Medicine*, *Textbook of Oral Anatomy Histology and Embryology*, *Textbook of Oral Diagnosis*, *Oral Diseases for Medical Practitioners* (all with Oxford University Press), *HIV/AIDS for Dental Practice* (Dental Council of India), *Clinical Diagnosis in Oral Medicine* (Jaypee Bros Medical Publishers), *Handbook of Oral Pathology and Oral Medicine* (John Wiley & Sons), and *Sexually Transmissible Oral Diseases* (John Wiley & Sons). Professor Prabhu is on the editorial board of the *International Dental Journal* (IDJ), published by the FDI World Dental Federation, Geneva.

Professor Amanda Oakley is an experienced medical dermatologist in Hamilton, New Zealand. She is Head of the Department of Dermatology at Health New Zealand | Te Whatu Ora – Waikato and an Honorary Professor for the Department of Medicine of the University of Auckland. Her research interests include artificial intelligence, teledermatology and dermoscopy, aiming to improve the equity of dermatological care to patients in New Zealand and worldwide. Professor Oakley is passionate about medical education, authoring several textbooks, including *Dermatology Made Easy*, publishing numerous papers in peer-reviewed dermatological journals, writing a regular column for the primary care medical magazine *New Zealand Doctor Rata Aotearoa,* and contributing to several online resources. She serves on several Editorial Boards and medical committees. Dr Oakley was Editor in Chief of DermNet for 25 years, for which she received several Honorary Memberships and awards, including the Companion of New Zealand Order of Merit in 2018. She has been President of Waikato Postgraduate Medical Incorporated (1999–2004), New Zealand Dermatological Society Incorporated (2011–13), Australian and New Zealand Vulvovaginal Society (2011–13), and the International Society of Teledermatology (2020–3).

Professor Sue-Ching Yeoh is an Associate Professor at Sydney Dental School, University of Sydney and maintains an Oral Medicine specialist practice with a clinical appointment at the Royal Prince Alfred Hospital and Chris O'Brien Lifehouse. Associate Professor Yeoh is the Head of Training in Oral Medicine at the University of Sydney. She is a Fellow of the Royal Australasian College of Dental Surgeons (General and Special Fields Stream), the International College of Dentists, the Pierre Fauchard Academy and the Royal College of Physicians and Surgeons of Glasgow.

Associate Professor Yeoh is currently the President of the Oral Medicine Academy of Australasia (OMAA) and the Chair of the Australian Dental Association Therapeutics Committee and is a contributing author to the *Therapeutic Guidelines: Oral and Dental V3* (2019). She is committed to continuing professional development and has been a frequently invited speaker for the Australian Dental Association CPD programme. Associate Professor Yeoh has presented nationally and internationally at various conferences, generated publications in peer-reviewed journals, and contributed to and edited several oral medicine textbooks. Associate Professor Yeoh's clinical interests include oral mucosal disease, odontogenic pathology, salivary gland pathology, orofacial pain, and temporomandibular dysfunction. Her current research focus is the autoimmune vesiculobullous disease.

ACKNOWLEDGEMENTS

AIPDerm (www.aipderm.com) utilized its expertise in computer vision techniques based on pixel interpolation to enhance certain images within this book (these are clearly indicated in the figure legend). These images were manipulated individually and without utilizing external images for deep learning AI. Subsequently all images were deleted to prevent unintentional usage or incorporation into deep learning databases in the future. AIPDerm is a company headquartered in Europe which is striving to transform dermatology care through its proprietary AI and technology platform.

Editorial assistance from Jonathan Ray of Scion Publishing is gratefully acknowledged.

TERMINOLOGY

The following terms describe mucosal lesions based on their clinical appearance.

Bulla (plural **bullae**): a bulla is a blister containing clear fluid >1cm in diameter.

Erosion: erosion is a partial-thickness loss of epithelium. Typically, erosions follow the rupture of vesicles or bullae, or are due to trauma. Mucosal erosions may also result from an inflammatory disease of infection.

Macule: a macule is flat and is noticeable because of its difference in colour from normal skin or mucosa. Macules may be red due to increased vascularity or inflammation, or pigmented due to melanin, haemosiderin, or foreign material.

Nodule: a nodule develops within the deep mucosa and may protrude above the mucosa, forming a dome-shaped structure. A nodule is >1cm in diameter.

Papule: a papule is raised above the mucosal surface and is <1cm in diameter. Papules may be dome-shaped or flat-topped.

Plaque: a plaque is a raised or thickened lesion >1cm in diameter, often composed of coalescing papules.

Purpura: purpura is a reddish-purple discolouration caused by blood leaking into the connective tissue. They do not blanch when pressure is applied. They are classified by size as petechiae (<0.3cm), purpura (0.4–0.9cm), or ecchymoses (>1cm).

Pustule: pustules are blisters containing purulent material. They appear turbid and yellow.

Ulcer: an ulcer is a well-circumscribed, full-thickness epithelial defect covered by a fibrin membrane, resulting in a yellow-white depressed centre.

Vesicle: vesicles are small blisters that contain clear fluid, each <1cm in diameter.

ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ANCA	antineutrophil cytoplasmic antibodies
CBC	complete blood count
CMV	cytomegalovirus
CN	cranial nerve
CT	computerized tomography
DIF	direct immunofluorescence
EB	epidermolysis bullosa
EBA	epidermolysis bullosa acquisita
EBV	Epstein–Barr virus
ELISA	enzyme-linked immunosorbent assay
EM	erythema multiforme
ESR	erythrocyte sedimentation rate
GvHD	graft-versus-host disease
HAART	highly active antiretroviral therapy
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
IBD	inflammatory bowel disease
IHC	immunohistochemistry
IIF	indirect immunofluorescence
LE	lupus erythematosus
MEN	multiple endocrine neoplasia
MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphoma
NSAID	non-steroidal anti-inflammatory drug
OLP	oral lichen planus
OPMD	oral potentially malignant disorder
PCR	polymerase chain reaction
PET	positron emission tomography
SCC	squamous cell carcinoma
SJS/TEN	Stevens–Johnson syndrome / toxic epidermal necrolysis
SSSS	staphylococcal scalded skin syndrome
TB	tuberculosis
TMJ	temporomandibular joint
UV	ultraviolet
VZV	varicella-zoster virus

CHAPTER 4

REACTIONS OF THE ORAL MUCOSA TO LOCAL OR EXOGENOUS FACTORS

See also:
- *Section 6.4.1: Angular cheilitis; Section 6.1.1: Denture-related stomatitis*
- *Section 7.1: Aphthous ulcers; Section 7.2.4: Graft-versus-host disease*
- *Section 9.3: Angioedema due to anaphylaxis; Section 9.7: Aphthous ulcers due to coeliac disease; Section 9.8.1: Aphthous ulcers due to inflammatory bowel disease; Section 9.16: Drug-induced osteonecrosis of the jaw*
- *Section 10.3.1: Actinic keratosis of the lip; Section 10.3.4: Reverse smoker's palate*

Specific oral mucosal diseases can be due to local debris, trauma (including sharp teeth or dentures, and burns), and the effects of toxins associated with tobacco and areca nut.

4.1 Dental and oral hygiene

Dental and oral hygiene aims to care for the oral mucosa, tongue, teeth, lips, gums, and dentures. The goal is to remove or prevent the build-up of plaque and tartar, to prevent dental caries and periodontal disease, and to decrease the incidence of halitosis.

4.1.1 Adults

- Patients should see their dentist and dental hygienist once or twice a year.
- Brush teeth for 2–3 minutes twice daily using a manual or electric soft-bristle toothbrush and fluoride toothpaste. An electric toothbrush requires less effort. Remove plaque and remnants of food and drink from teeth and gums by vertical or horizontal scrubbing, rolling, or using the Bass technique.
- Use a tongue scraper to clean the tongue's surface.
- Avoid brushing your teeth straight after consuming acidic drinks and foods, to reduce the chance of dental enamel erosion.
- Replace your toothbrush every 3–4 months.
- Remove biofilm and debris between the teeth once a day using floss or an interdental brush to prevent gum disease and tooth decay.
- As bacteria, fungi, plaque, and tartar can become deposited on removable dentures, these must be taken out after every meal and cleared of food remnants under running water. They should be cleaned using a denture brush without toothpaste at least once daily.

- Oral rinses with anti-plaque, anti-cavity, anti-tartar and anti-bacterial agents reduce oral discomfort, provide moisture, and help with bad breath.

4.1.2 Children

- Children should be introduced to tooth brushing at 2 years of age with a pea-sized amount of low-fluoride toothpaste. A parent or caregiver should help with the brushing until the child is at least 3 years old. After the age of 6 years, children can safely use regular fluoridated toothpaste.
- Flossing in toddlers should be commenced as soon as primary teeth establish proximal contact.
- Mouthwashes are not recommended for children under 6 years because of the risk of swallowing.

4.1.3 Patients with oral mucositis due to radiotherapy or chemotherapy

- When pain prevents using an ordinary toothbrush, use a gauze pad, a swab stick, or a foam toothbrush (dental swab).
- To avoid mucosal irritation, select a toothpaste without menthol, cinnamon, peppermint oil, and sodium lauryl sulphate.
- Patients with a bleeding tendency should avoid interdental cleaning with dental floss.
- Use antibacterial mouthwash to prevent gingivitis and periodontitis.
- For dry mouth, choose a mouth rinse with mucin, carboxymethylcellulose and hydroxymethyl cellulose, xanthan, linseed oil and polyethylene oxide to improve viscosity and wettability.
- Patients with mucositis should avoid mouthwashes containing alcohol and chlorhexidine. Replace with salt-and-soda solution or rinse with 0.5% lignocaine.
- Using sugar-free chewing gum after eating can accelerate the clearance of dietary substances and microorganisms, promote buffers to neutralize plaque acids, and provide antibacterial substances.
- Patients with ulceration or neutropenia must not wear dentures during and after radiotherapy or chemotherapy except while eating.

4.2 Debris

4.2.1 Hairy tongue

A hairy tongue has a white, brown, or blue-black mid-dorsal surface in front of the circumvallate papillae.

- A hairy tongue affects around 13% of the general population.
- It affects about 8% of children and young adults and 57% of imprisoned drug addicts.

Causes

A hairy tongue is characterized by hypertrophy and elongation of filiform papillae, which fail to desquamate because of a lack of mechanical stimulation and debridement. Associations include the following factors:

- Edentulism
- Heavy smoking and excessive coffee drinking
- Poor oral hygiene
- A soft diet that prevents the shedding of the papillae
- Dehydration due to fasting or a febrile disease
- Dry mouth due to medication or radiotherapy
- A prolonged course of an antibiotic
- Mouthwash containing oxidizing agents
- Sometimes, *Candida albicans* or bacterial infection.

Clinical features

A hairy tongue has varying colours (see *Figs. 4.1a* and *b*) due to retained pigment from tobacco smoking, food, beverages, and candies or pigment-producing bacteria. The hairy area cannot be wiped off with gauze.

- Some patients complain of glossodynia (a burning sensation without signs), taste aberration, halitosis, gagging, and nausea.
- Cytologic smears and swabs for culture for candida are usually negative.

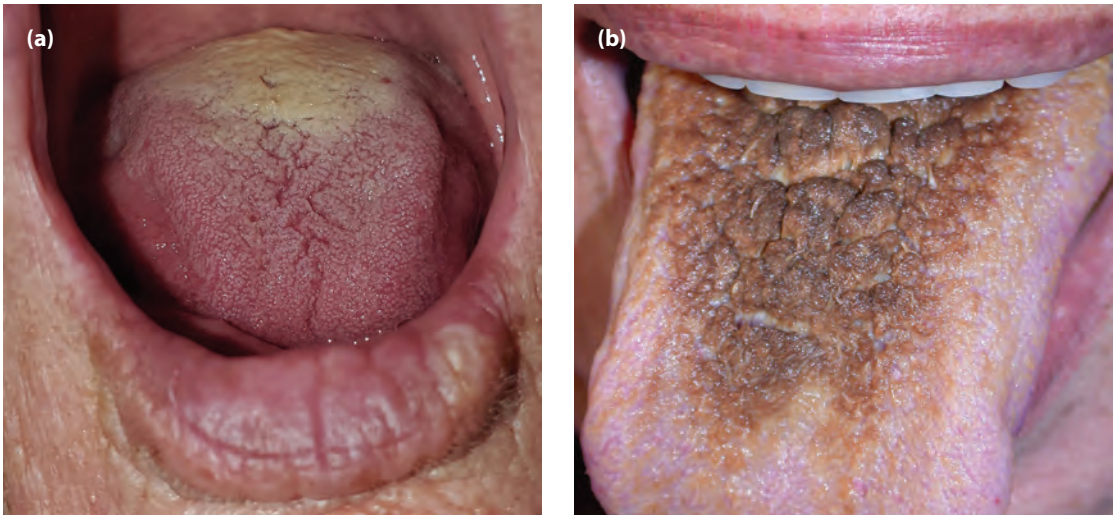

Figure 4.1 (a and b). Hairy tongue. The brown colour in image (b) was due to heavy smoking.

(a) Reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission.

Treatment

When treatment of hairy tongue is considered necessary, options include the following:

- Eliminate causative/predisposing factors such as anticholinergic medications or broad-spectrum antibiotics.
- Maintain oral hygiene by tooth brushing daily and scraping the tongue.
- Attempt to increase saliva production if the patient has xerostomia.
- Topical 30% urea solution and trichloroacetic acid are reported effective for severely elongated papillae.

- Treat candida-associated glossodynia with an antifungal agent.
- Clip or remove the papillae by electrodesiccation or carbon dioxide laser.

4.2.2 Materia alba

Materia alba is a soft non-mineralized whitish deposit on the tooth surface around the gingival margins.

- It is an accumulation of food debris, microorganisms, and dead cells.
- It may be associated with gingival inflammation.
- It is common among those with poor oral hygiene.

Treatment

- Remove debris by water irrigation or gentle scaling.
- Prevent recurrence by brushing the teeth daily.

4.3 Acute injury

4.3.1 Traumatic ulceration

Localized trauma results in acute ulceration (see *Fig. 4.2*).

Figure 4.2 (a–c). Traumatic ulcers on the left lateral tongue.

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4.3.2 Extravascular blood

Extravascular blood results from trauma or a surgical procedure, particularly if the patient has a blood disorder, is prescribed an anticoagulant/antiplatelet drug, or has an infection such as meningococcal disease, SARS-CoV-2 infection, and others. Tissue bleeding or purpura does not blanch on pressure.

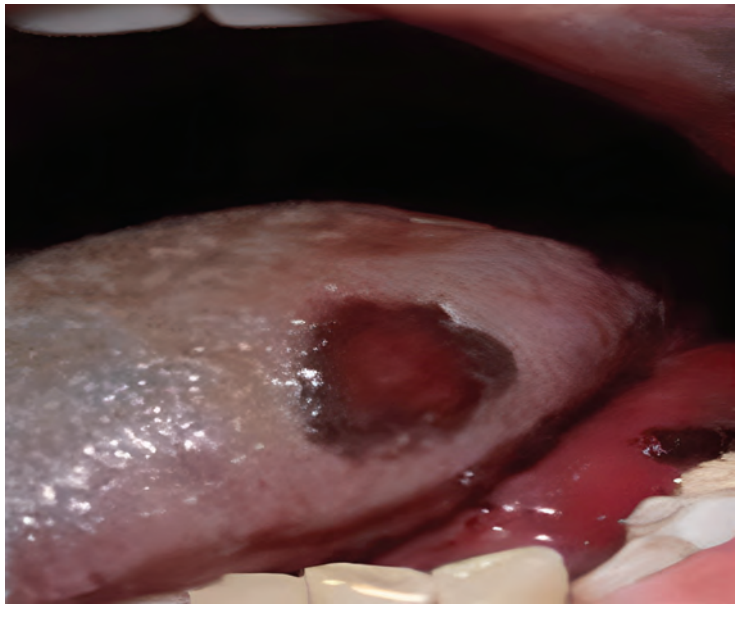

Figure 4.3. Ecchymosis of the dorsolateral tongue.

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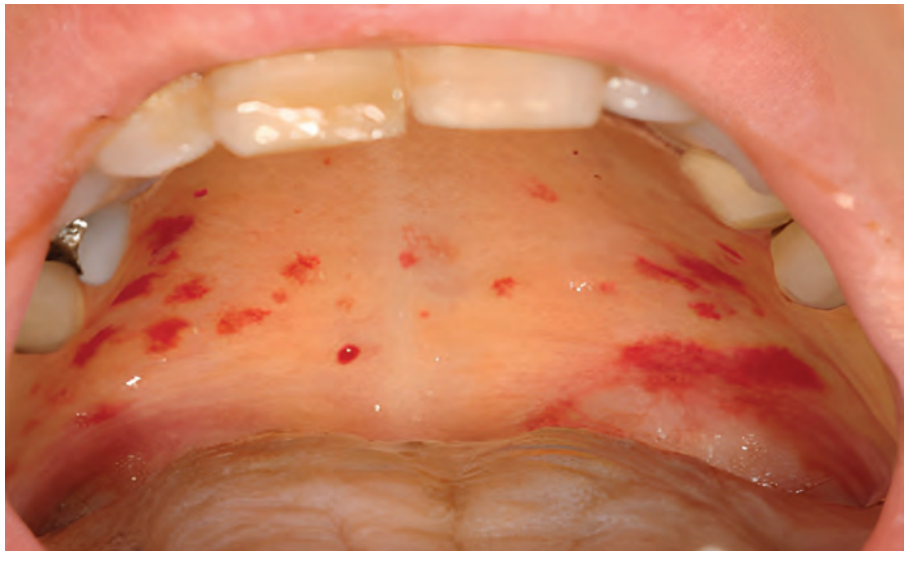

Figure 4.4. Petechiae of the marginal gingiva in a patient with severe thrombocytopenia secondary to acute leukaemia.

Reproduced with permission from *Pocket Dentistry* (Chapter 9, Bleeding disorders; www.pocketdentistry.com), and included here after enhancement by AIPDerm (www.aipderm.com).

- Ecchymosis is a flat, red, purple, or blue discolouration >1 cm due to bleeding under the skin (see *Fig. 4.3*).
- Petechiae are pinpoint 1–2mm haemorrhages (see *Fig. 4.4*).
- Spontaneous gingival haemorrhage presents as a slow ooze of blood flow.

No treatment is necessary. Tissue bleeding will resolve spontaneously in several weeks.

4.3.3 Traumatic haemorrhagic bulla

A haemorrhagic bulla is an oral blood-filled blister known as angina bullosa haemorrhagica. Traumatic haemorrhagic bulla is usually observed in adults aged 50–70.

Causes

Traumatic haemorrhagic bulla is due to masticatory trauma, especially chewing hard and crispy food. Diabetes, hypertension, and long-term steroid inhaler use may be contributory factors.

Clinical features

Traumatic haemorrhagic bulla presents as a blood-filled, red or purple subepithelial blister of the oral cavity that quickly expands and ruptures spontaneously within 24–48 hours.

- The blisters are usually observed on the soft palate (see *Fig. 4.5*). Occasionally, they may arise on the buccal mucosa, the lateral border of the tongue, or the lip.
- Although usually painless, the ruptured blister forms an ulcer, which may be painful. It heals without scarring.

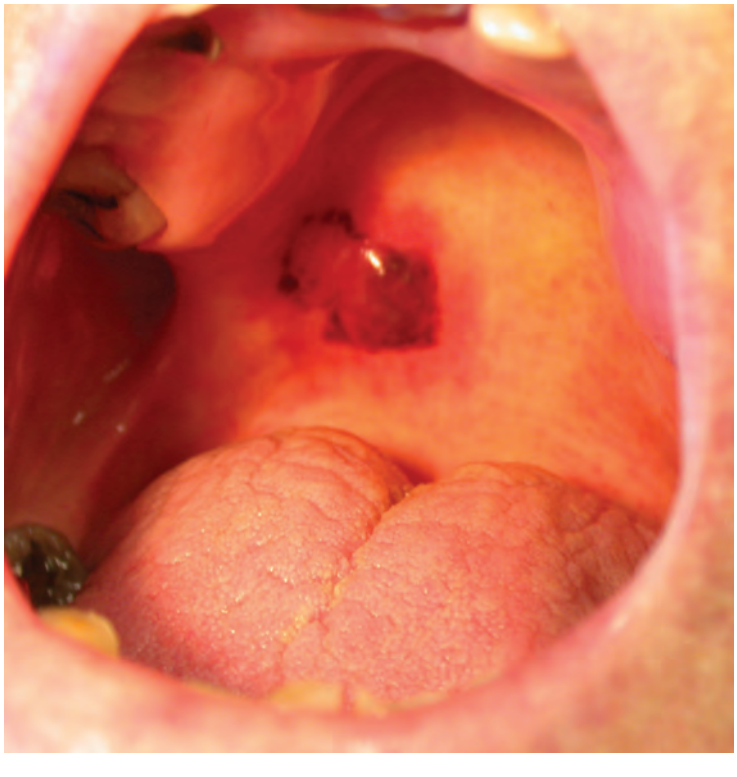

Figure 4.5. Traumatic blood-filled bulla right soft palate.

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Treatment

No treatment is required for traumatic haemorrhagic bulla, which resolves spontaneously.

4.3.4 Mucosal burn

A mucosal burn may be due to heat (thermal burn), cold (frostbite or cryotherapy burn) (see *Fig. 4.6a*), chemicals, or radiation.

See also *Section 10.3.4* on reverse smoker's palate.

- The affected site may blister initially and then develop into an ulcer.
- The blister is short-lived, usually only lasting a few hours before rupturing and ulcerating.

Thermal burn

A thermal burn is a painful lesion caused by intense heat. Examples include the following:

- Scorching hot and sticky foods such as cheese or pizza.
- The burning end of the smoking device (chutta, a homemade cigar) in a reverse smoker.
- An injury during a dental procedure from an overheated impression compound.

Mucosal thermal burns are especially common in children.

Clinical features

The burn is initially red and may form a short-lasting, fluid-filled bulla. A severe burn presents as a white necrotic plaque overlying an ulcer. Frequent sites for thermal burns include the palate (see *Fig. 4. 6b*) and tip of the tongue.

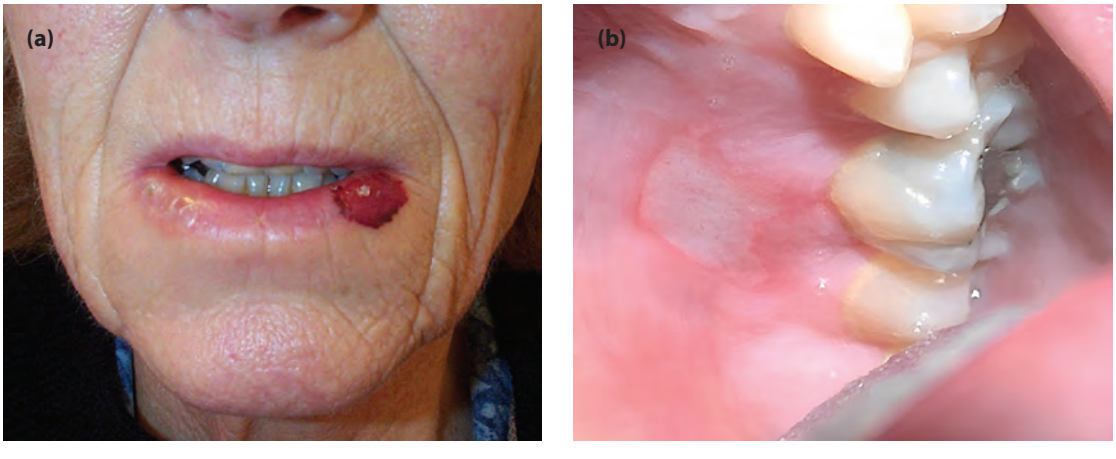

Figure 4.6 (a and b). (a) Cryotherapy burn on the left lower lip manifesting as a blood-filled blister. (b) Thermal burn of the palatal mucosa caused by microwave-heated cheese pie.

(b) Reproduced from *Cases Journal*, 2008;1:191 (https://doi.org/10.1186/1757-1626-1-191) under a CC-BY 2.0 licence, and included here after enhancement by AIPDerm (www.aipderm.com).

Treatment

Treatment of a mucosal thermal burn is symptomatic.
- Apply or spray topical lignocaine and benzydamine.
- Avoid contact with irritants and food.

The healing time depends on the size and depth of the burn.

Chemical burn

A chemical burn is a painful lesion caused by a noxious chemical agent in direct contact with the mucosa. Examples include the following:
- Aspirin that has been applied to the vestibule adjacent to a painful decayed tooth.
- A mouthwash containing chlorhexidine, alcohol, or acetone.
- Dental treatment solution containing sodium hypochlorite, formalin; an endodontic paste containing arsenic; or improper use of silver nitrate or hydrogen peroxide.

Other causative agents include acids, alkalis, urea, and organic substances.
- Acids act by coagulation necrosis through protein denaturation.
- Alkalis act by liquefaction necrosis and cause more damage than acids.

Clinical features

A chemical burn is initially erythematous, then presents as a painful, irregular ulcer covered by a white pseudomembrane (see *Fig. 4.7*). A shallow lesion has a whitish and wrinkled appearance, and a deeper one is necrotic.

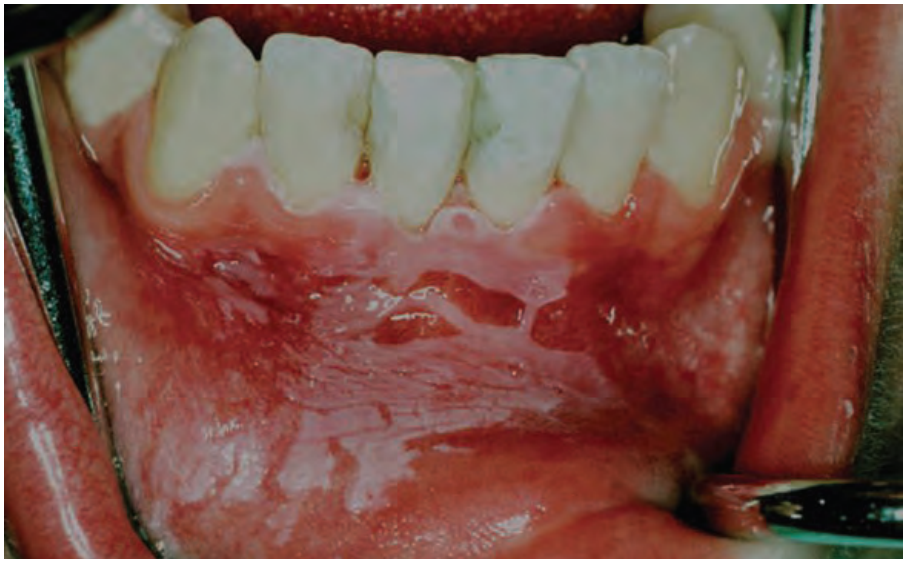

Figure 4.7. Aspirin-induced chemical burn noted on the labial mucosa and the gingiva showing white pseudomembrane.

Treatment

Treatment of a mucosal chemical burn is symptomatic.

- Apply or spray topical lignocaine or benzydamine.
- A severely necrotic lesion may be treated by topical/intralesional corticosteroid injection.

Most mucosal chemical burns heal within 7–14 days.

Chemotherapy-induced oral mucositis

Chemotherapy-induced oral mucositis affects 40–60% of cancer patients undergoing chemotherapy.

Causes and risk factors

Chemotherapy-induced oral mucositis results from a complex interaction of local tissue damage, the specific drug or drugs, the level of myelosuppression, and the patient's predisposition.

- Patients with haematological malignancies have an increased rate of oral mucositis compared with those with solid tumours.
- The occurrence and severity of mucositis depend on the intensity and duration of the chemotherapy regimen.
- The most stomatotoxic agents include the antimetabolites 5-fluorouracil, methotrexate, and cytarabine.
- Concomitant radiation therapy to the head and neck increases the risk of oral mucositis, as does hyposalivation or dry mouth from any cause.
- Younger age is associated with more severe oral mucositis.
- Chronic irritation from ill-fitting prostheses or faulty restorations predisposes patients to develop oral mucositis.

Clinical features

Mucositis occurs 7–10 days after chemotherapy, commencing with erythema that progresses towards erosion and ulceration (see *Fig. 4.8*).

Chemotherapy-induced mucositis is painful, restricts oral intake, and promotes local or systemic infection. It resolves slowly 2–3 weeks after cessation of treatment.

Diagnosis

The diagnosis of chemotherapy-induced oral mucositis is based on a history of chemotherapy for cancer, the clinical findings, and the chronology of the development of lesions.

A biopsy is not routinely necessary for diagnosis, and histopathological features may be non-specific.

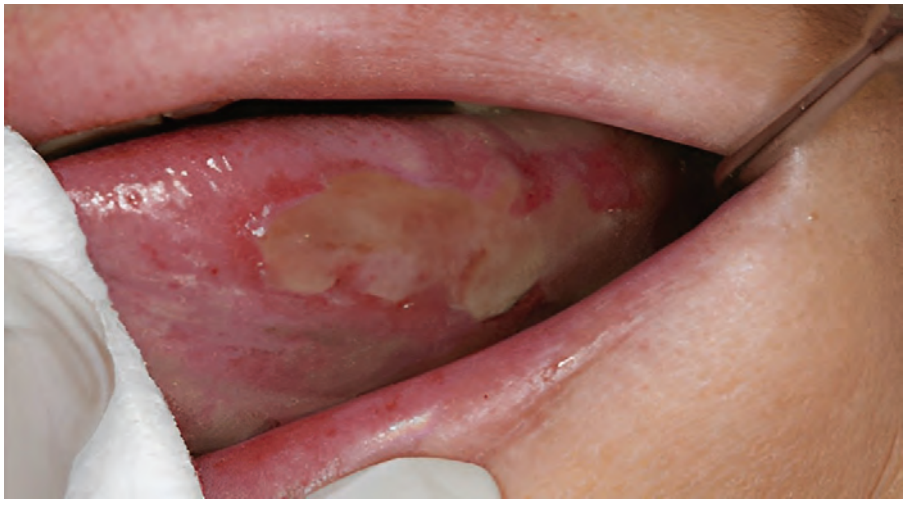

Figure 4.8. Chemotherapy-induced mucositis. Widespread mucositis of the non-keratinized mucosa of the lateroventral side of the tongue induced by chemotherapy.

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Treatment

Management of oral mucositis may include:

- Oral debridement (e.g. brushing, flossing) and mucolytic agents to help dislodge dried secretions
- An antimicrobial mouthwash
- Topical and systemic pain relief
- Sucking ice chips or sipping cold water during infusions of chemotherapy.

Where available, palifermin (endogenous keratinocyte growth factor) may reduce the incidence, duration, and severity of mucositis.

Radiation mucositis

Radiation mucositis is an expected tissue injury induced by ionizing radiation, and it affects up to 90% of head and neck cancer patients treated with radiotherapy. It is also called radiation-induced oral mucositis.

Risk factors and causes

Patient-related risk factors include concomitant chemotherapy, poor oral hygiene, poor nutritional status, periodontal disease, hyposalivation, smoking, alcohol abuse, low body mass index (BMI <18.5), and immunosuppression due to co-morbidities such as diabetes mellitus, old age, and female gender.

Treatment-related risk factors include radiation source, total dose, daily fractionation, previous radiotherapy, chemotherapy (dependent on dosage, type of drug and timing), and medications designed to target cancer cells without affecting normal cells (targeted therapy).

The pathogenesis of radiation mucositis consists of four phases:
1. Initial inflammatory/vascular phase
2. Epithelial phase
3. Pseudomembranous ulcerative/bacteriological phase
4. Healing phase.

Clinical features

Radiation mucositis causes pain, odynophagia, and reduced oral intake.

Four phases follow oral radiotherapy:
1. Grade I mucositis during the second week — erythema, intolerance to spices, and burning pain
2. Grade II mucositis during the third week — erosions and desquamation
3. Grade III mucositis in the fourth and fifth weeks — ulceration covered by pseudomembrane composed of cell debris, keratin, and fibrin (see *Fig. 4.9*)
4. Grade IV mucositis in the fifth and sixth weeks — ulceration, necrosis, and sometimes bleeding.

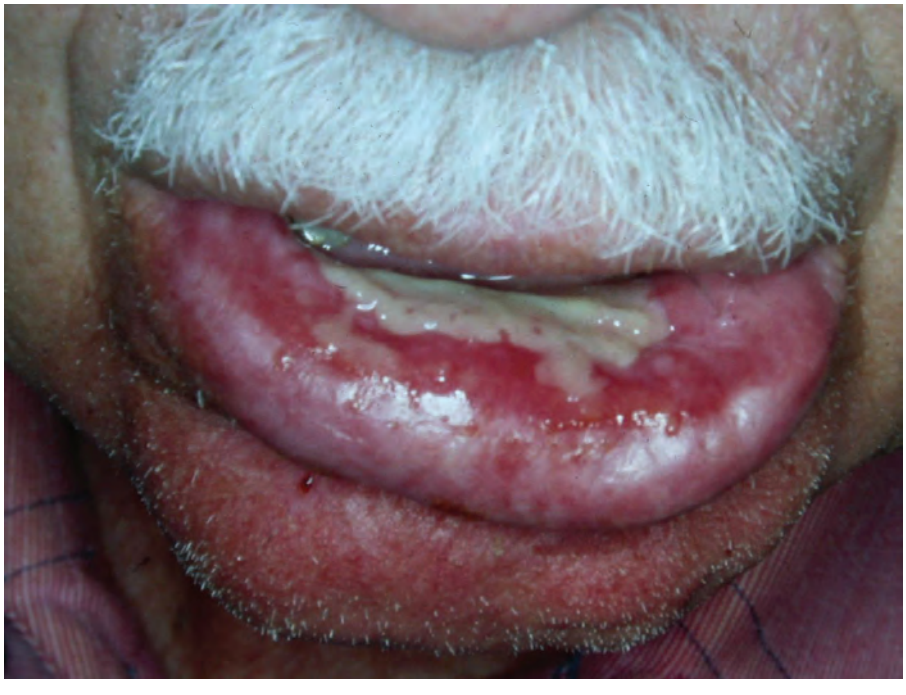

Figure 4.9. Radiation mucositis shows ulceration covered by pseudomembrane.

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Treatment

Pre-treatment preparation:
- Dental assessment of the oral cavity
- The patient should use a soft-bristle toothbrush to maintain oral hygiene
- Avoid hot and spicy food, alcohol, and smoking

- Rinse mouth with normal saline, alkali (soda bicarbonate), benzydamine, or aloe vera
- Apply sucralfate or granulocyte–macrophage colony-stimulating factor to treated areas.

Pain management:
- Liquid/semi-solid high-calorie and high-protein food
- Application of honey (not suitable for people with diabetes)
- Apply local anaesthetic (2% lignocaine gel) before food
- Topical rinse with aspirin, doxepin, or benzydamine
- Analgesics, including opioids, if necessary
- Treatment of bacterial or candida infection.

4.3.5 Traumatic neuroma

Traumatic neuroma, also known as amputation neuroma, is a localized proliferation of neural tissue.

Causes

Traumatic neuroma follows an injury. The nerve bundle degenerates distal to the severed or damaged nerve. As the proximal end of the nerve regrows along the old nerve pathway, it may be blocked by scar tissue. The continued growth of the nerve then produces a nodule.

Clinical features

A traumatic neuroma of the oral mucosa is a smooth-surfaced nodule.
- Symptoms may include altered nerve sensation (numbness, tingling) or pain, which can be spontaneous or triggered by manipulation of the lesion.
- The most common intraoral site is the mental foramen due to traumatic tooth extraction.
- They may also arise on the tongue and lower lip.

Treatment

A traumatic neuroma and a small portion of the proximal nerve bundle can be surgically excised. Recurrence is uncommon.

4.3.6 Pyogenic granuloma / vascular epulis

Pyogenic granuloma is a reactive inflammatory lesion that may arise on the skin, lips, or oral mucosa. A gingival pyogenic granuloma is also known as a vascular epulis or angiogranuloma.

Causes

Oral pyogenic granuloma is more common in females than males.
- A history of minor trauma is commonly elicited.
- Irritation from calculus or an overhanging restoration may cause gingival pyogenic granuloma.
- Pregnancy predisposes to pyogenic granuloma on the gingiva, when the lesion is called a pregnancy tumour or epulis (see *Fig. 4.10a*).

Clinical features

- A pyogenic granuloma can occur anywhere in the oral cavity, but most commonly occurs on the maxillary anterior facial surfaces of the gingiva.
- It is a smooth or lobulated soft red–purple papule that may be pedunculated or sessile (see *Fig. 4.10b*). It bleeds on slight trauma.
- The lesion's surface may be smooth, ulcerated, or lobulated and often covered with a yellowish fibrinous membrane.
- During pregnancy, pyogenic granuloma usually starts in the first trimester and peaks in the third trimester. It may resolve postpartum.
- Dermoscopy shows red–purple structures separated by white strands.
- Histopathology reveals proliferating vascular channels, immature fibroblastic oedematous connective tissue, and scattered inflammatory cells.

Figure 4.10 (a–c). (a) Pregnancy tumour; (b) and (c) pyogenic granuloma of the gingiva in a non-pregnant woman. Histologically both lesions show similar features.

(b) Reproduced with permission from Professor Nagamani Narayana, University of Nebraska Medical Centre, NE, USA. (c) Reproduced with permission from *Pocket Dentistry* (Chapter 9; www.pocketdentistry.com), and included here after enhancement by AIPDerm (www.aipderm.com).

Treatment

Pyogenic granuloma is treated by conservative surgical excision. Gingival lesions should be excised down to the periosteum with scaling of adjacent teeth to remove any calculus and plaque.

The prognosis is excellent, and recurrence is uncommon.

4.4 Chronic repetitive injury

Irritation within the mouth can cause a hyperplastic response, with the specific name relating to its location or appearance.

4.4.1 Fibroepithelial polyp and fibrous epulis

A fibroepithelial or fibrous polyp is a common finding on the buccal mucosa, along the occlusal line, lip, or the tip of the tongue (see *Fig. 4.11*).

A gingival fibroepithelial polyp is also known as a fibrous epulis. They are most often diagnosed in children and young adults.

Causes

Fibroepithelial polyp arises as a reaction to habitual biting or irritation.

Clinical features

Fibroepithelial polyps are painless, firm, pink, dome-shaped pedunculated or sessile papules ranging from a few millimetres to a centimetre or more.

- Usually painless, they may ulcerate following trauma.
- Histopathology shows dense, hypovascular and hyperplastic fibrous tissue.

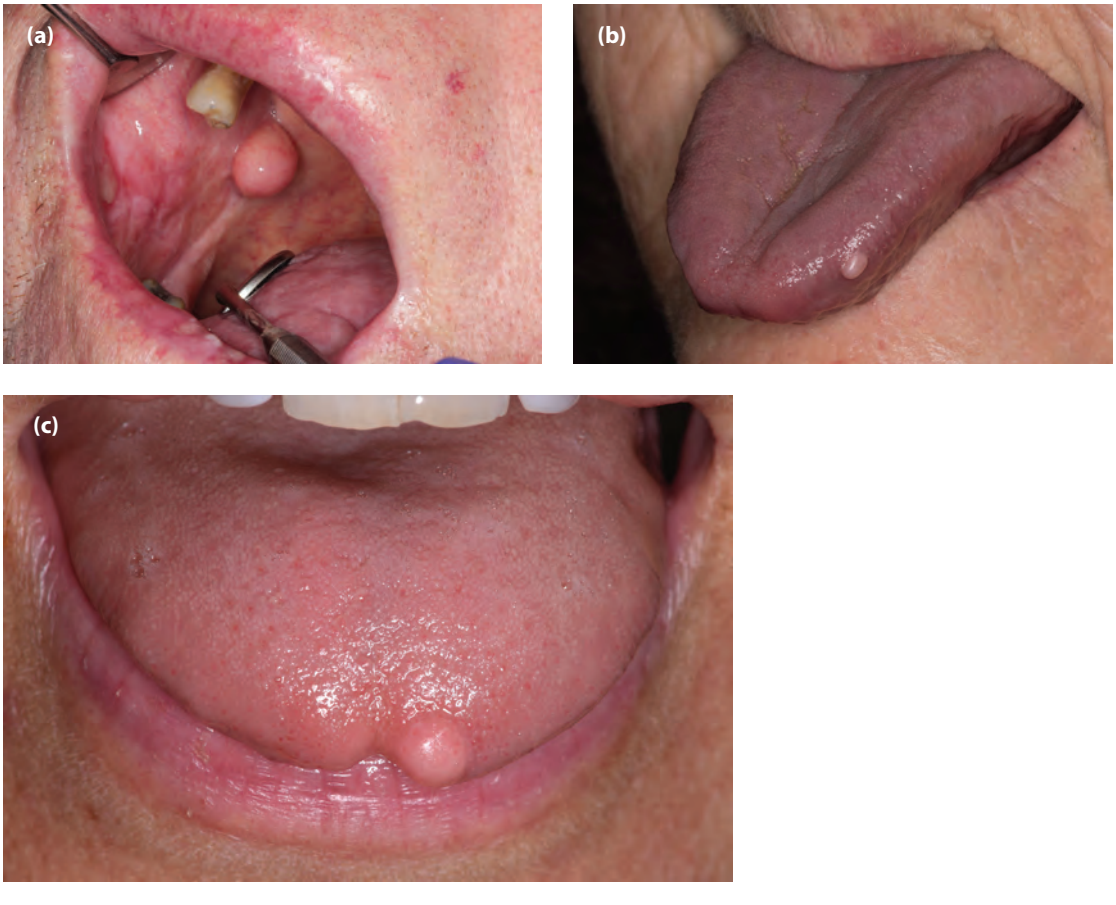

Figure 4.11 (a–c). Fibroepithelial polyp on (a) buccal mucosa, (b) left lateral tongue, and (c) tip of the tongue.

Treatment

Fibroepithelial polyps can be surgically removed. Recurrence is uncommon.

4.4.2 Giant cell epulis

Giant cell epulis is also known as peripheral giant cell granuloma. It occurs on the gingiva and alveolar mucosa, usually interdentally. It most often affects women aged 30–60.

Causes

Giant cell epulis is due to chronic low-grade local irritation or trauma to the periodontal ligament or periosteal tissues.

Clinical features

A giant cell epulis is more prominent and darker red than a fibrous epulis.

- It is a circumscribed soft, painless, dark-red or purple nodule and is sessile or pedunculated.
- It is usually located anterior to the permanent molars (see *Fig. 4.12*).
- It may grow up to 2cm in diameter.
- It can push teeth aside or erode alveolar bone.
- Histopathology shows inflammatory cells, foreign body giant cells, haemorrhage, and fibroangiomatous stroma.

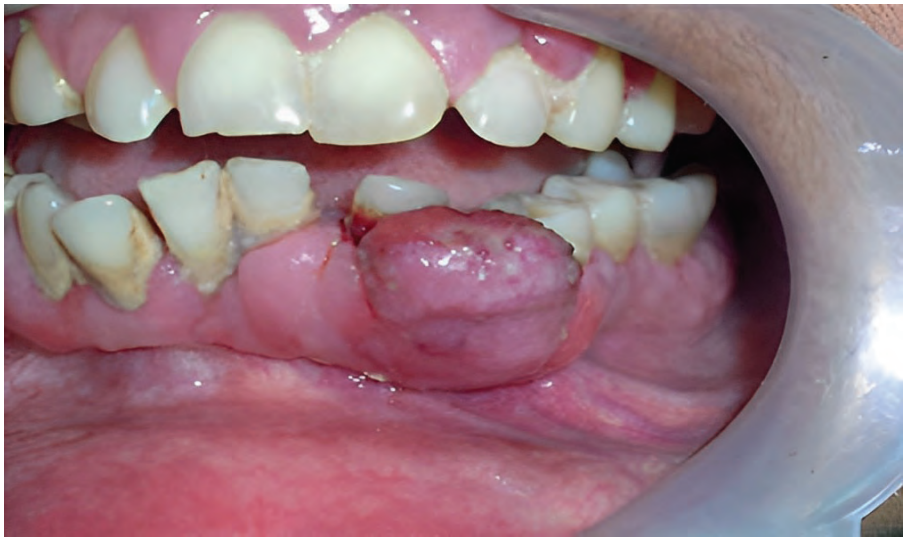

Figure 4.12. Peripheral giant cell epulis anterior to the lower premolars.

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Treatment

The treatment of giant cell epulis is surgical excision. Curettage of the underlying bone may be required to prevent a recurrence.

4.4.3 Denture-induced hyperplasia

Denture-induced mucosal hyperplasia is also known as inflammatory fibroepithelial hyperplasia of the oral mucous membrane caused by a denture, denture granuloma, and epulis fissuratum.

Causes

Chronic trauma from the flange of ill-fitting dentures results in exuberant fibrous tissue.

Clinical features

Denture-wearing may induce pink, broad-based, firm, lobulated and leaf-like hyperplastic tissue on the buccal mucosa, gingiva, or labial sulcus (see *Fig. 4.13*).

- Single or multiple sites may be affected.
- The posterior edge of the upper denture may irritate the palate, causing a 'leaf fibroma'.
- Fissuring may occur, but ulceration is uncommon.
- Histopathology shows fibrous hyperplasia with a mild inflammatory cell infiltrate.

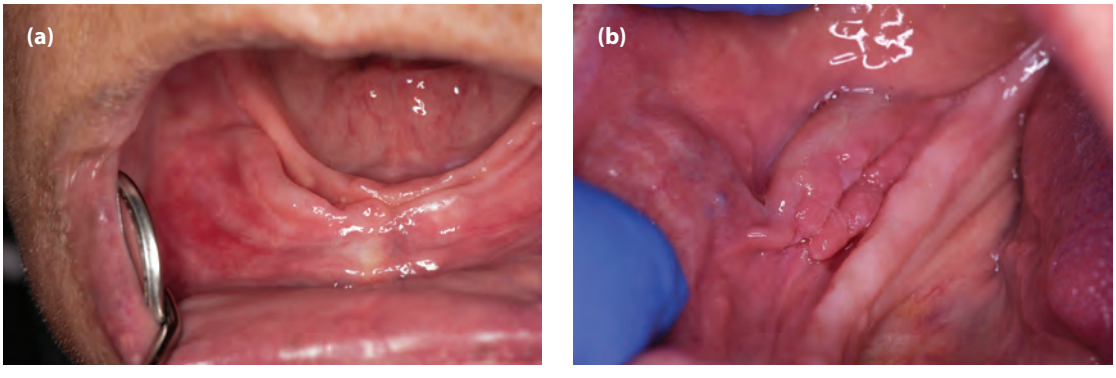

Figure 4.13 (a and b). Denture-induced hyperplasia (epulis fissuratum). Note leaf-like hyperplastic tissue in the buccal mucosa.

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Treatment

The hyperplastic tissue can be removed surgically or by laser ablation. Ill-fitting dentures must be corrected or replaced.

4.4.4 Papillary hyperplasia

Dentures can also cause papillary hyperplasia on palatal mucosa covered by a denture.

- Papillary hyperplasia is also known as denture stomatitis or denture sore mouth.
- It occurs in 50–60% of denture wearers.
- Non-denture-bearing mucosal surfaces may rarely develop similar pathology.

Causes

Papillary hyperplasia of the palate in complete denture wearers is attributed to chronic infection by *Candida albicans* and mechanical irritation.

Clinical features

Oral papillary hyperplasia presents as asymptomatic diffuse erythema, oedema, and multiple pinpoint papules on the palate (see *Fig. 4.14*).

- Occasional white spots or petechiae may be observed.
- Lesions should be differentiated from leukokeratosis nicotina palati.

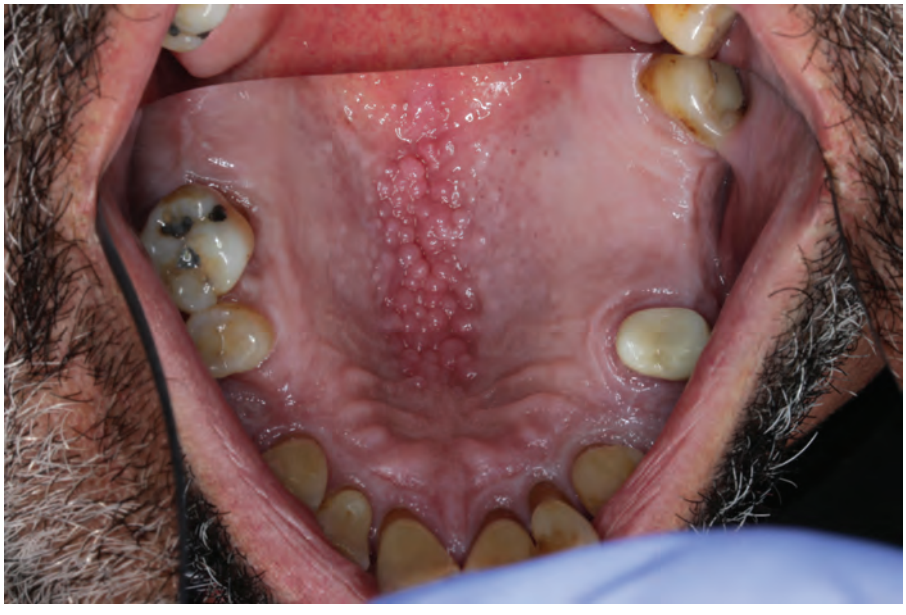

Figure 4.14. Oral papillary hyperplasia of the palate.

Treatment

Denture hygiene: soft brush twice daily, using toothpaste free of sodium lauryl sulphate.

Oral papillary hyperplasia may respond to topical antifungal therapy.

4.4.5 Peripheral ossifying fibroma of the gingiva

Peripheral ossifying fibroma, also known as cementifying or calcifying fibroma, is reactive gingival hyperplasia containing mineralized tissues, bone, cementum-like material, or dystrophic calcification. Peripheral ossifying fibroma is more common in females than in males, with a peak in the second decade of life.

Causes

Peripheral ossifying fibroma is thought to be due to irritating local agents such as dental calculus, plaque, orthodontic appliances, and ill-fitting restorations. The growth arises from the periodontal ligament.

Clinical features

Peripheral ossifying fibroma is a solitary, slow-growing nodule with an ulcerated or smooth surface (see *Fig. 4.15*).

- A peripheral ossifying fibroma is usually <1.5 cm in size.
- It may be pedunculated or sessile.
- The most common site is the anterior maxilla.
- Histopathology shows areas of dystrophic calcification within a cellular fibrous connective tissue covered by stratified squamous epithelium. An inflammatory infiltrate is usually present.

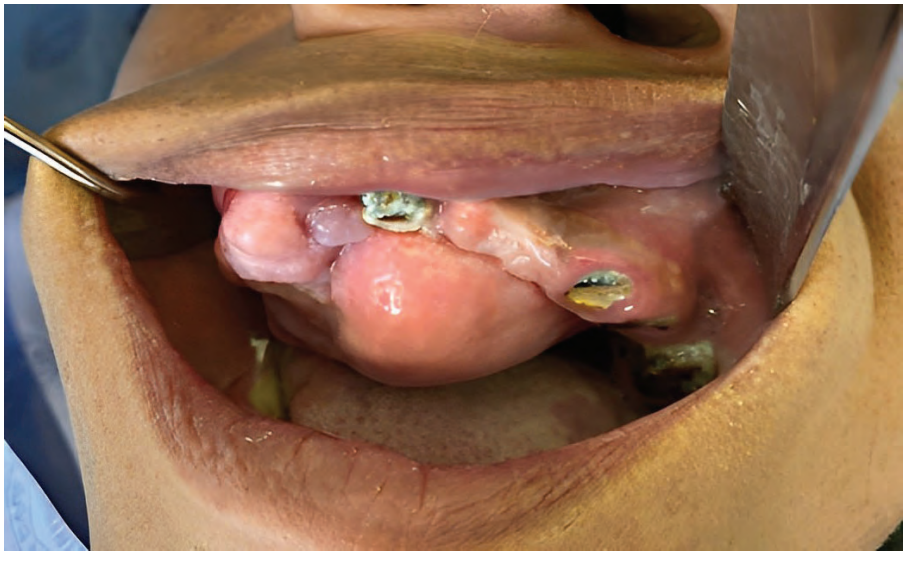

Figure 4.15. Peripheral ossifying fibroma.

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Treatment

Peripheral ossifying fibroma is removed surgically down to the bone, with the adjacent periosteum and the periodontal ligament.

Recurrence rates after surgery range from 8% to 45%.

4.4.6 Frictional keratoses

Frictional keratoses are a group of hyperkeratotic white patches or plaques on the buccal mucosa. The surface of frictional keratoses can be rough, warty, wrinkled, or corrugated. Frictional keratoses are asymptomatic, and they may be unilateral or bilateral.

They are classified by their site and cause. Some examples include the following:

- Chronic cheek biting. A white plaque inside the cheeks may be due to chronic cheek biting (morsicatio buccarum) (see *Fig. 4.16*).

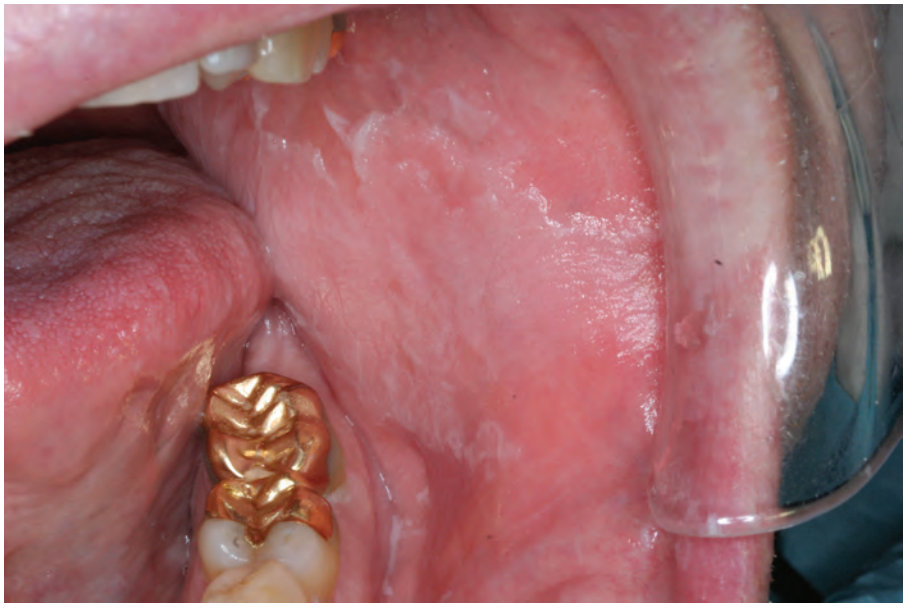

Figure 4.16. Chronic cheek biting showing keratotic white lesion on the buccal mucosa.

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- Alveolar ridge keratosis. This affects the retromolar trigone (60%) or the edentulous alveolar ridge (40%) and is caused by chewing without natural teeth or a dental prosthesis (see *Fig. 4.17*).
- Linea alba. This is a white keratotic line on the buccal mucosa at the occlusal plane (see *Fig. 4.18a*) or on the lateral border of the tongue and is due to contact with teeth (see *Fig. 4.18b*).
- Excessive tooth brushing. White plaques on the attached gingiva, especially the maxillary arch, may be due to excessive and inappropriate tooth brushing.

Alveolar ridge keratosis tends to affect edentulous middle-aged males at a mean age of 50–55 years. It is less common in females, with a reported ratio of 3.7:1. Other forms of oral frictional keratoses affect males and females of all ages. Prevalence has been reported to range between 2.7% and 11.5%.

Causes

Frictional keratosis is due to chronic repetitive trauma, which stimulates epithelial acanthosis, a granular layer, and the production of excessive keratin, i.e. a white plaque.

The trauma may be due to the following:
- Habitual cheek/lip/tongue biting
- Broken appliances or teeth
- Improper tooth brushing
- Teeth grinding (bruxism).

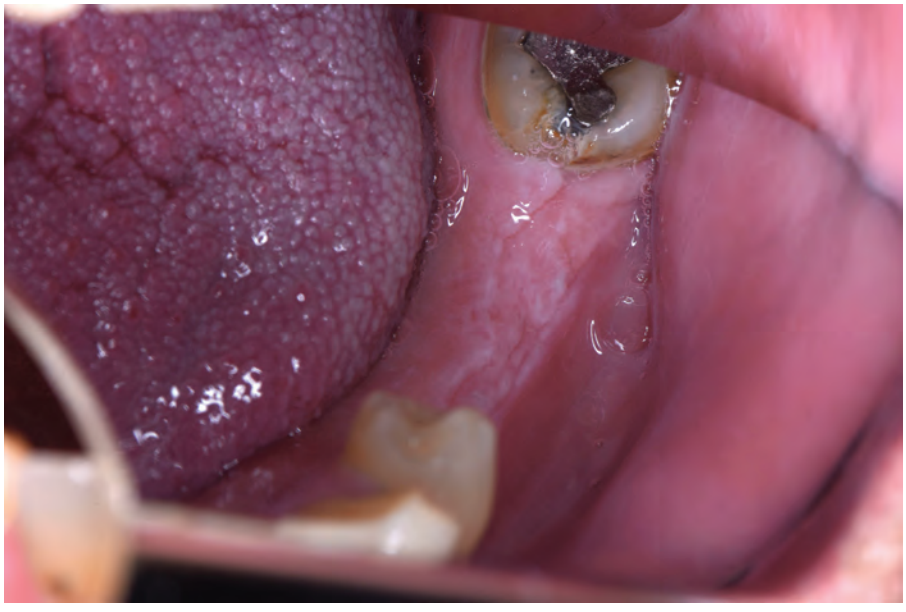

Figure 4.17. Alveolar ridge keratosis showing a white lesion with a corrugated surface on the retromolar trigone.

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Diagnosis

Frictional keratoses are usually diagnosed clinically.

- A biopsy is recommended if there are atypical features, the lesion fails to resolve when friction is eliminated, or there is ulceration.
- Histopathology of frictional keratosis shows orthokeratosis, parakeratosis, hypergranulosis, and acanthosis of the surface epithelium. A patchy chronic inflammatory infiltrate may occur in the dense, fibrous connective tissue.

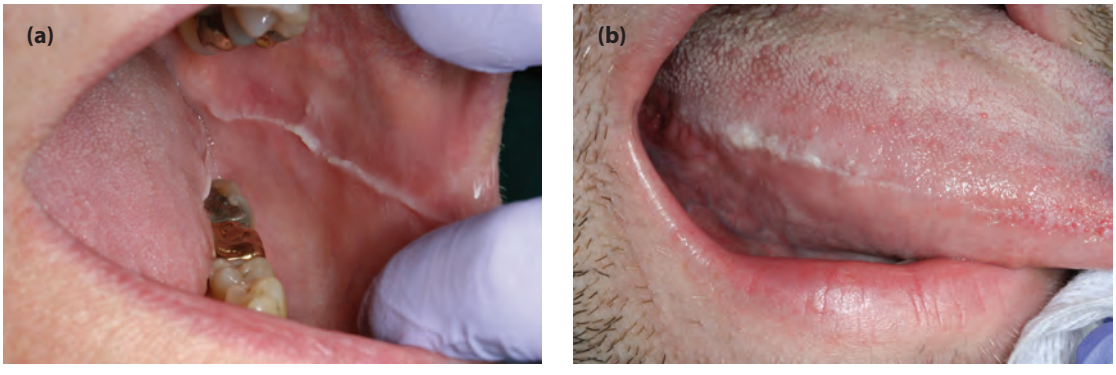

Figure 4.18 (a and b). Linea alba. Note keratotic linear line on the buccal mucosa at the level of occlusal line (a) and the lateral border of the tongue.

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Treatment

- Remove any frictional irritants where possible. Repair fractured or rough tooth surfaces or irregularly fitting dentures or other appliances.
- Encourage the patient to discontinue biting, sucking, or chewing; a psychological evaluation may be appropriate.

If causative factors are eliminated, frictional keratoses resolve in 1–3 weeks. Avoidance of further friction will prevent a recurrence.

4.4.7 Verruciform xanthoma

Verruciform xanthoma is an uncommon benign reactive lesion. It is also known as verrucous xanthoma.

- It can occur at any age, most often in the fifth to seventh decades, with equal sex incidence.
- It has been reported in the oral cavity of about 300 individuals.
- A smaller number of similar lesions have been reported in anogenital sites.

Causes

Verruciform xanthoma is an immune response to local trauma or inflammation.

Clinical features

Oral verruciform xanthoma usually presents as an asymptomatic solitary, sessile or pedunculated, red or white papule 2–15 mm in size.

- Oral verruciform xanthoma commonly involves the gingiva, alveolar mucosa, and palate.
- The lesion surface can be rough or pebbly.

Diagnosis

Histopathological examination is essential to make a definitive diagnosis of oral verruciform xanthoma.

It is histologically characterized by epithelial parakeratosis and lipid-laden macrophages (foam cells) in the connective tissue papillae.

Treatment

The treatment of verruciform xanthoma is surgical excision. Recurrence is rare.

4.4.8 Contact stomatitis

Contact stomatitis is inflammation of the oral mucosa caused by external substances.

- Irritant contact stomatitis is usually due to acidic or sharp food. It can complicate other inflammatory disorders, such as lichen planus.
- Allergic contact stomatitis is a T-cell-mediated delayed hypersensitivity reaction to a specific allergen. It is much less common than allergic contact dermatitis.
- Lichenoid contact reaction to mercury in an amalgam filling.

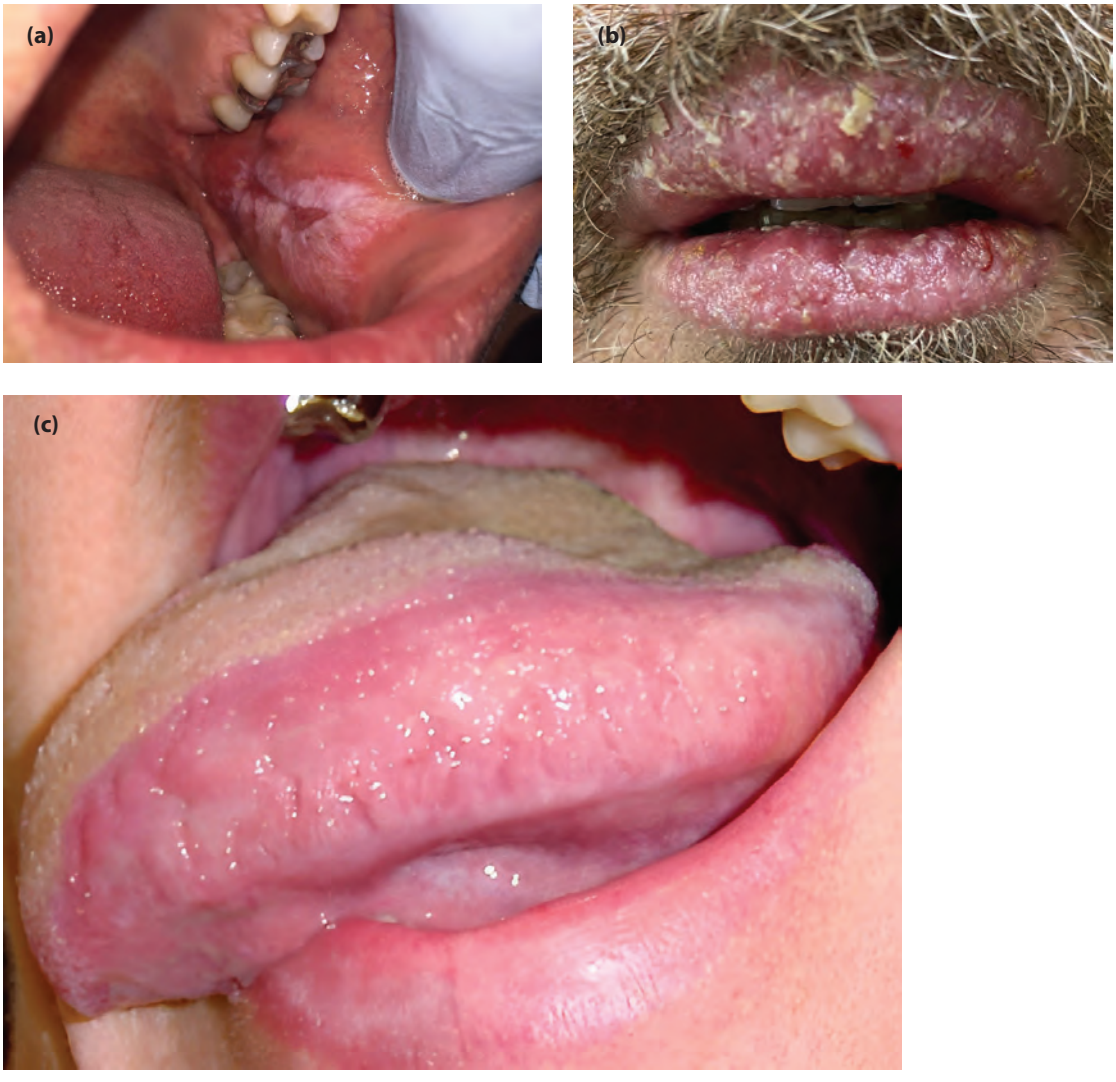

Figure 4.19 (a–c). (a) Lichenoid contact stomatitis of the buccal mucosa due to amalgam; (b) contact allergic cheilitis caused by propolis; (c) contact reaction on tongue caused by cinnamon.

(a) Reproduced with permission from Professor Yeshwant Rawal, University of Milwaukee School of Dentistry, Milwaukee, WI, USA; (b) reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission; (c) reproduced from *Diagnosis and Management of Oral Lesions and Conditions: A resource handbook for the clinician*; Eds: CA Migliorati and FS Panagakos (http://dx.doi.org/10.5772/57597) under CC BY 3.0 licence. © 2014 InTech.

Causes of allergic contact stomatitis

Contact allergy to oral flavourings, preservatives, metals, rubber compounds, propylene glycol, and many other substances may cause stomatitis.

- Allergens are found in oral hygiene products, foods, dental restorations, and topical medications.
- Oral fragrances include balsam of Peru, cinnamon, cinnamic aldehyde, menthol, and peppermint.

- Preservatives such as parabens are found in various foods, including salad dressing, spicy sauces, mustard, jellies, jams, fruit juices, syrups, and candies. They are also used in lipsticks, toothpaste, and dental hygiene products.
- Allergens in dental prostheses include metals (e.g. nickel, palladium, gold, mercury, and zinc), formaldehyde, acrylate monomer, resins, rubber accelerants, and colophonium.
- Propylene glycol is found in tobacco formulations, food colours, and flavouring agents.

Clinical features

Contact stomatitis presents with pain, burning sensation, or itchiness. A contact allergy should be suspected when oral examination reveals erythematous plaques, vesiculation, and ulceration (see *Fig. 4.19*). A lichenoid reaction presents as a white plaque adjacent to the amalgam.

Diagnosis

Contact stomatitis may be suspected based on history and examination. Investigations include the following:

- Patch testing to identify a contact allergen
- A mucosal biopsy to exclude other causes of stomatitis.

Treatment

Contact irritants and any identified or potential allergens should be identified and avoided.

Contact stomatitis is treated with topical corticosteroids. Severe and extensive stomatitis may require short-term systemic corticosteroids. Oral antihistamines are ineffective.

4.5 Toxins

4.5.1 Areca nut

Oral submucous fibrosis

Oral submucous fibrosis is a chronic debilitating disorder characterized by inflammation and progressive fibrosis of the submucosal tissues. It is potentially malignant.

The incidence of oral submucous fibrosis differs with diet, habits, and culture.

- In India, the incidence ranges from 0.2–2.3% in males and 1.2–4.6% in females, with an age range of 11–60 years.
- Sporadic cases of South Asians have also been reported in South Africa, the UK, and Europe.

Causes

The main cause of oral submucous fibrosis is areca nut chewing.

- 'Paan' (in India) is a betel leaf filled with chopped areca nut and slaked lime (calcium hydroxide).

- Areca nut is a confirmed carcinogen, genotoxin, and mutagen.
- Areca nut contains alkaloids (arecoline, arecaidine, guvacine, and guvacoline), flavonoids, and copper. These alkaloids stimulate fibroblasts to produce collagen.
- Oral submucous fibrosis results from increased biosynthesis and reduced clearance of collagen.

Other associated factors include the following:
- Chewing smokeless tobacco
- Autoimmunity
- Vitamin B, vitamin C, and iron deficiencies
- Consumption of spicy foods
- HPV infection.

Clinical features

The initial symptoms of oral submucous fibrosis include xerostomia, mucosal burning sensation, and the formation of vesicles.

With continued exposure to areca nut:
- mouth opening becomes progressively limited (the normal range is 40–74mm in males and 35–70mm in females)
- palpable fibrous bands arise in the buccal mucosa, retromolar areas, and around the mouth
- the tongue appears smooth as the papillae on the tongue involute
- tongue protrusion is impaired
- the mucosa appears marble white (see *Fig. 4.20*).

Diagnosis

The diagnosis of submucous fibrosis depends on a history of habitual chewing of areca nut, the clinical findings, and biopsy features.
- Histopathology of submucous fibrosis reveals an atrophic epithelium, chronic inflammation, excessive collagen, local inflammation in the lamina propria and deep connective tissues, and degenerative changes in the underlying muscles.
- Occasionally, oral submucous fibrosis may show epithelial dysplasia.

Treatment

Cessation of the use of betel quid (paan) and areca nut chewing is essential. Iron and vitamin B complex deficiencies should be corrected.

In patients with moderate oral submucous fibrosis, treatment may include:
- topical steroids and weekly submucosal intralesional steroid injections
- topical hyaluronidase
- submucosal administration of aqueous human placental extract (unapproved).

Surgical treatment (simple excision of fibrous bands) is indicated in patients with severe trismus or biopsy, revealing dysplastic or neoplastic changes. Oral submucous fibrosis is not curable.
- Monitor the patient long-term.
- Oral squamous cell carcinoma develops in 1.9–9% of patients with submucous fibrosis (see also *Section 10.4.1*).

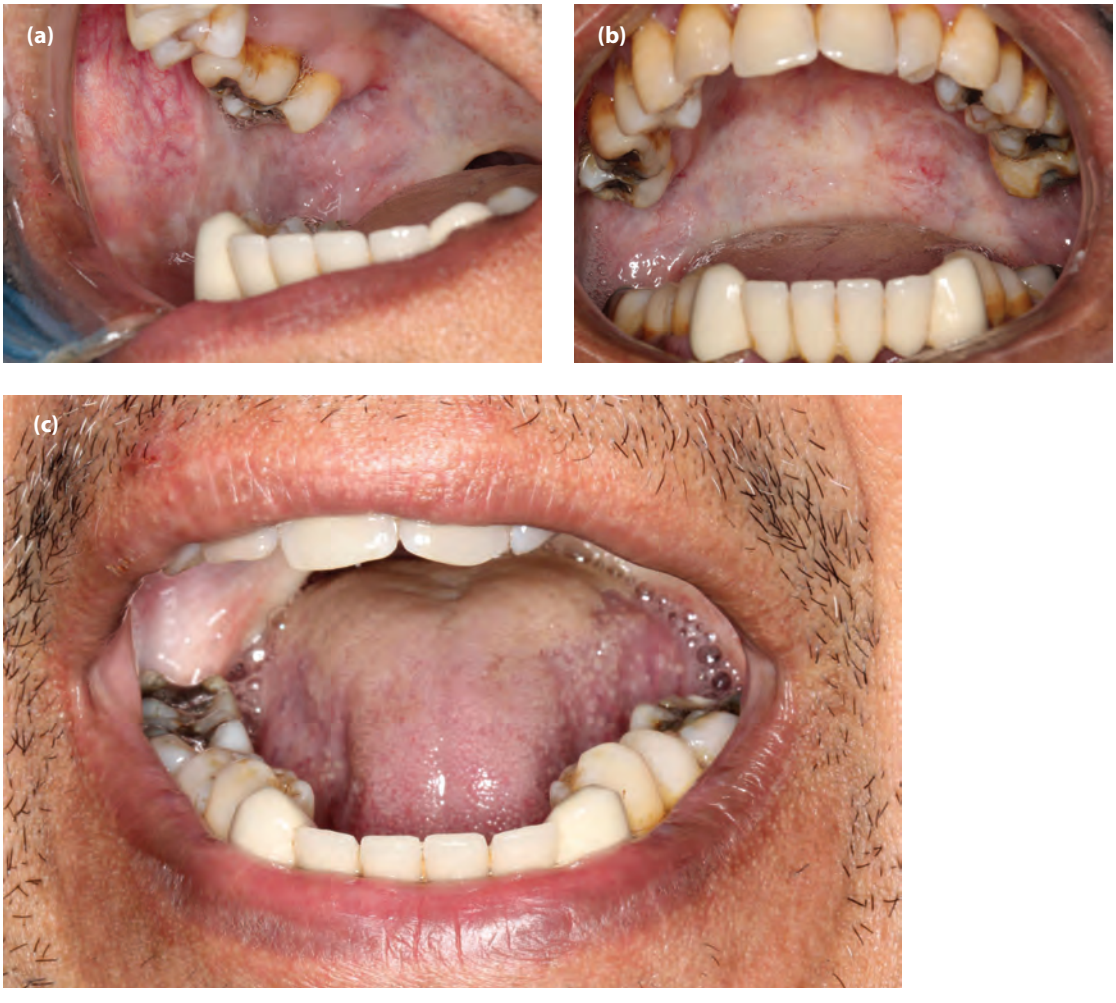

Figure 4.20 (a–c). Oral submucous fibrosis; pallor and fibrous bands on (a) the buccal mucosa and (b) the palate; (c) reduced mouth opening.

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Oral verrucous hyperplasia

Oral verrucous hyperplasia is a histopathological diagnosis. It resembles verrucous carcinoma clinically and histologically and may evolve into frank verrucous carcinoma over time (see also *Section 10.4.1* on verrucous carcinoma).

Causes

Oral verrucous hyperplasia is strongly associated with tobacco smoking and areca nut chewing.

Clinical features

Oral verrucous hyperplasia presents as a solitary whitish or pink plaque or exophytic mass >1cm in an intraoral site (see *Fig. 4.21*).

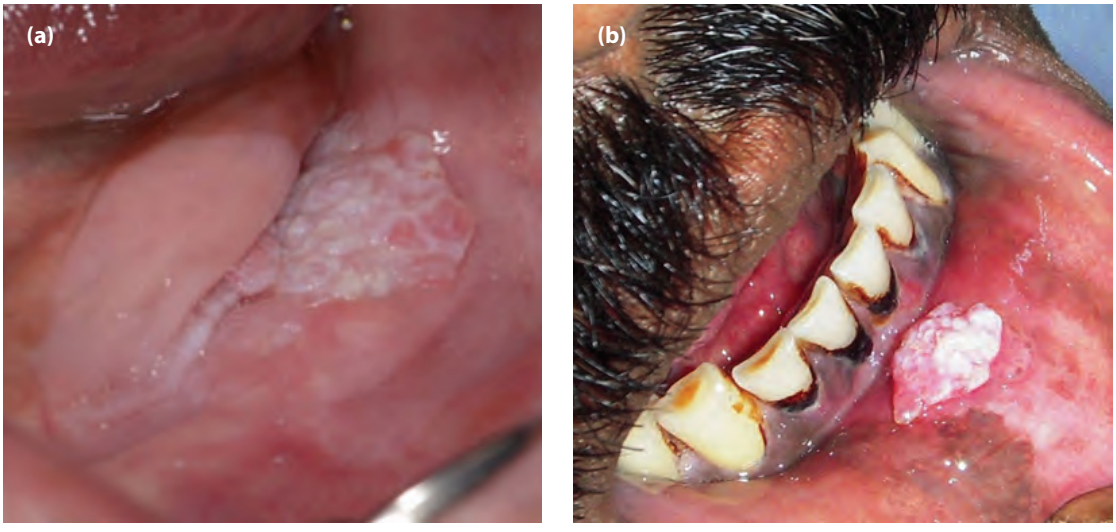

Figure 4.21 (a and b). Oral verrucous hyperplasia.

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- Oral verrucous hyperplasia has a verrucous or papillary surface.
- It is classified as sharp or blunt:
  - sharp verrucous hyperplasia has long, narrow, heavily keratinized white structures
  - blunt verrucous hyperplasia has broader, flatter structures that are not heavily keratinized.
- Oral verrucous hyperplasia may co-exist with oral submucous fibrosis.

Diagnosis

Histopathology is necessary to distinguish oral verrucous hyperplasia from oral verrucous carcinoma.

- Verrucous hyperplasia is best distinguished from verrucous carcinoma in a biopsy taken at the margin of the lesion. In the former, the verrucous processes and the greater part of the hyperplastic epithelium are superficial to adjacent normal epithelium.
- Oral verrucous carcinoma has an exophytic and an endophytic growth pattern with broad, elongated rete processes resembling an elephant's feet.
- Oral verrucous hyperplasia has an exophytic growth pattern with pointed, ragged, slender, and anastomosing rete processes.

Treatment

Treatment options for verrucous hyperplasia include surgical excision and laser ablation.

4.5.2 Smokeless tobacco keratosis

Smokeless tobacco keratosis is a grey/white plaque on oral mucosa that is in frequent contact with a smokeless tobacco product such as chewing tobacco, moist snuff, or dry snuff.

It is also known as:
- tobacco pouch keratosis
- snuff dipper's keratosis.

Smokeless tobacco keratosis is common among adult smokeless tobacco users. The reported prevalence in the USA is 1.5% in smokeless tobacco users. Young men and males over 65 are affected more commonly than females.

The severity of smokeless tobacco keratosis is dependent on the following:
- Habit duration
- Brand of tobacco
- Early onset of use
- Total hours and amount of daily use
- The number of sites used for tobacco placement.

It usually takes 1–5 years to develop a smokeless tobacco keratosis.

Clinical features

Smokeless tobacco keratosis has a wrinkled or fissured corrugated surface. The most common locations are the lower labial or buccal vestibule (see *Fig. 4.22*). The plaque cannot be wiped off with gauze.

Diagnosis

Smokeless tobacco keratosis is usually diagnosed clinically.
- A biopsy is required if the lesion shows ulceration or does not resolve within 2–6 weeks of smokeless tobacco use.

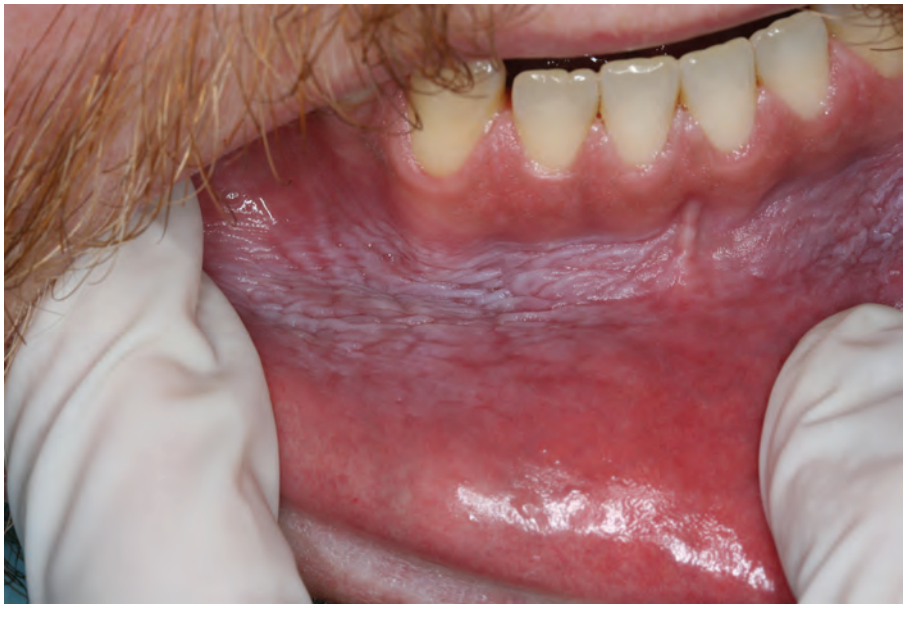

Figure 4.22. Smokeless tobacco keratosis showing a wrinkled white lesion in the labial vestibule.

- Histopathology of smokeless tobacco keratosis reveals hyperkeratosis, parakeratin chevrons (V-shaped pattern), glycogen-rich clear superficial epithelial cells, and acanthosis. The connective tissue may show amorphous material, increased sub-epithelial vascularity, and vessel engorgement.

Treatment

No treatment is required.
- Encourage patients with smokeless tobacco keratosis to stop using tobacco.
- Epithelial changes resolve in 90% of lesions within 2–4 weeks of quitting smokeless tobacco use.

Verrucous carcinoma and squamous cell carcinoma have rarely been reported at the site of smokeless tobacco keratosis (see *Chapter 10* for more).

4.5.3 Tobacco smoking

Leukokeratosis nicotina palati

Leukokeratosis nicotina palati is an asymptomatic benign diffuse white lesion covering most of the hard palate.

It is also known as:
- nicotine stomatitis
- nicotinic stomatitis
- nicotine palatinus
- stomatitis palatini
- smoker's palate
- smoker's keratosis
- palatal leukokeratosis.

Leukokeratosis palati is common in smokers. A study in Saudi Arabia showed leukokeratosis nicotina palati affected 29.6% of all smokers and 60% of pipe smokers. It occurs in middle-aged and older individuals, with a male preponderance.

Causes

Leukokeratosis nicotina palati is mucosal hyperkeratosis due to the combined effects of tobacco products and heat.

It is associated with the following:
- Heavy, long-term pipe smoking
- Cigar smoking
- Hand-rolled reverse cigarette/cigar smoking.

It is less common with cigarette smoking.

Clinical features

Leukokeratosis nicotina palati presents as uniform white plaques on the palatal mucosa, sometimes with fissuring. The mid-palate inflamed mucous glands appear as umbilicated papules with red centres (see *Fig. 4.23*). Leukokeratosis nicotina palati cannot be wiped off.

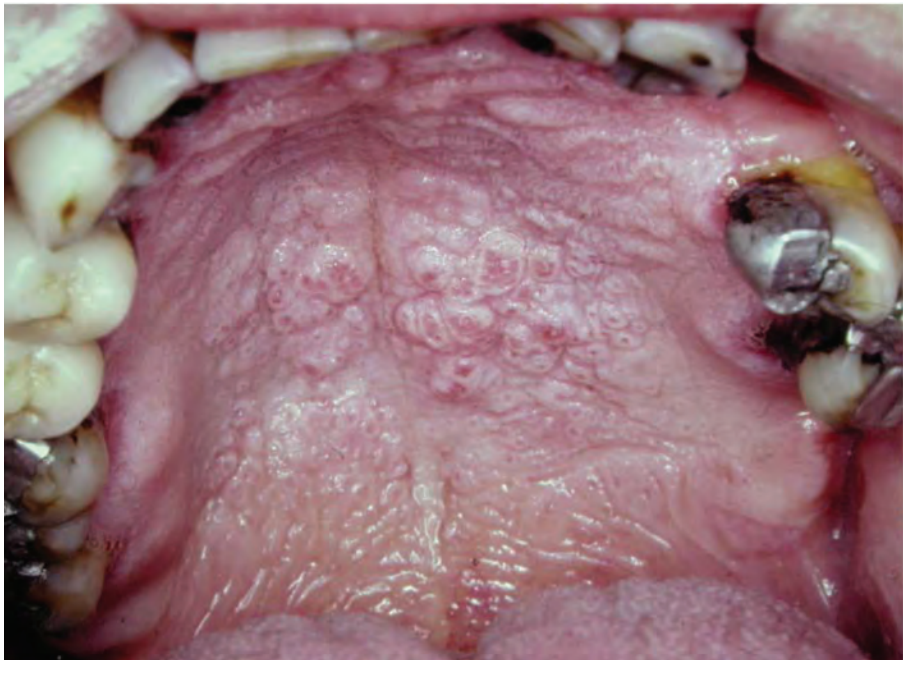

Figure 4.23. Nicotinic stomatitis (smoker's palate).

Diagnosis

Leukokeratosis nicotina palati is usually diagnosed clinically.

- A biopsy is warranted if the structure is irregular and ulcerated or if the patient places the burning end of the smoking device inside the mouth (see *Section 10.3.4* on reverse smoker's palate).
- Histopathology of leukokeratosis nicotina palati reveals acanthosis and orthokeratosis without cellular atypia or loss of polarity. Fibrosis of the lamina propria is a consequence of chronic inflammation.

Treatment

No treatment is required.

- Encourage patients with leukokeratosis nicotina palati to stop smoking.
- Leukokeratosis nicotina palati is reversible with smoking cessation.

Smoker's melanosis

Smoker's melanosis is a characteristic pigmentary change to the oral mucosal surfaces because of tobacco habits. It is due to increased melanin production by melanocytes in the basal cell layer of the epithelium and the accumulation of melanophages within the connective tissue.

- Smoker's melanosis is common among dark-skinned adult smokers.
- In females, it has been associated with birth control pills.

Figure 4.24 (a–c). Smoker's melanosis. Brown and black pigmentation of the oral mucosa in a heavy smoker.

(a) and (b) Reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission; (c) Reproduced from Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Smoker%27s_melanosis.jpg) under a CC-BY-SA 3.0 Unported licence.

- It usually presents as a diffuse hyperpigmented patch on the attached gingiva and buccal mucosa and is less common in other mucosal areas (see *Fig. 4.24*).
- Pigmentation decreases following cessation of smoking and other tobacco habits.

4.6 Adverse drug reaction

An oral mucosal adverse drug reaction to a topical or systemic medication usually presents as ulceration. Diagnosis is based on the chronology of an ulcer appearing after drug administration or dose escalation.

Causes

Adverse drug reactions are classified as Type A and Type B.

- Type A reactions are dose-dependent, based on drug pharmacology.
- Type B reactions are idiosyncratic and may be immunological (either T-cell or antibody-mediated) or non-immunological (for example, direct mucosal toxicity due to conventional and targeted anti-cancer therapy).

Pharmacogenetics influences the risk of some adverse drug reactions. For example, in Han Chinese and South-East Asian populations, the HLA-B*1502 polymorphism is associated with an increased risk of SJS/TEN with anticonvulsants.

Clinical features

Drug-induced oral mucosal ulceration may present with cheilitis (for example dryness due to isotretinoin) (see *Fig. 4.25*), aphthous-like ulcers, a lichenoid eruption, lupus-like ulcers, or trigger an immunobullous eruption. The ulcers may closely resemble an inflammatory disease that is not induced by a drug (see *Sections 7.1*, *7.2*, and *7.4*).

- Ulceration may occur within days, weeks, or months of starting the responsible medication, such as methotrexate (see *Fig. 4.26*).
- Fixed drug eruptions recur at the same site with further exposure to the causative drug.

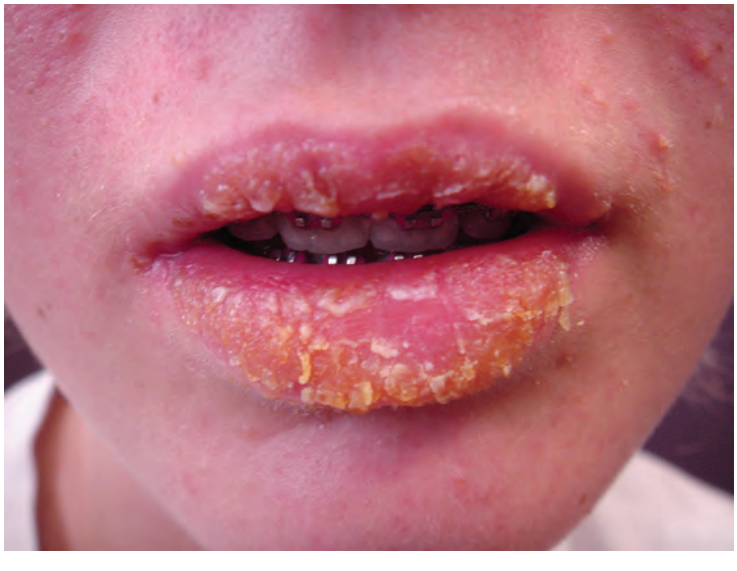

Figure 4.25. Cheilitis due to oral isotretinoin.

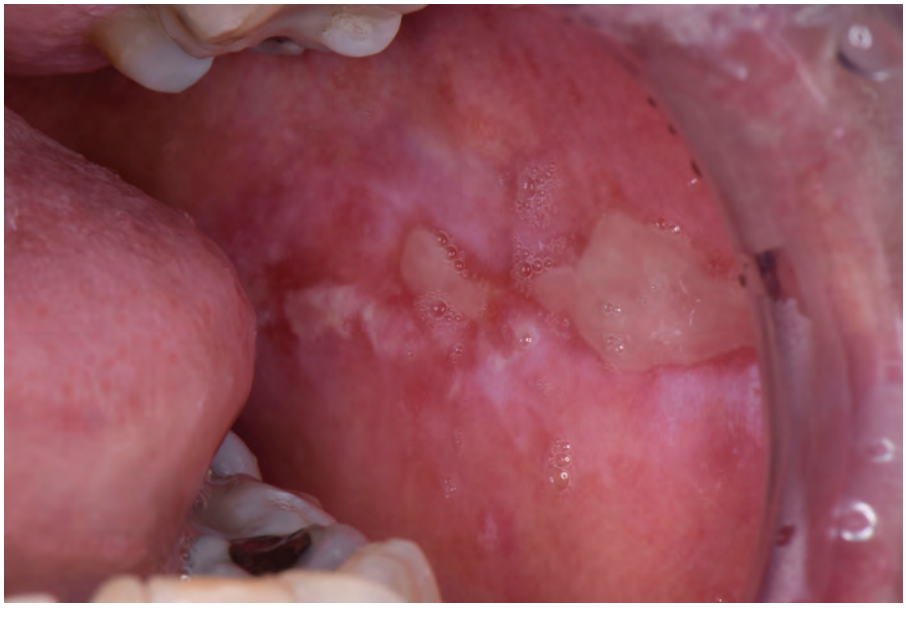

Figure 4.26. Ulceration of the left buccal mucosa due to methotrexate.

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4.6.1 Chemical burn

A chemical burn is due to direct contact of the mucosa with a causative drug, such as aspirin or cocaine.

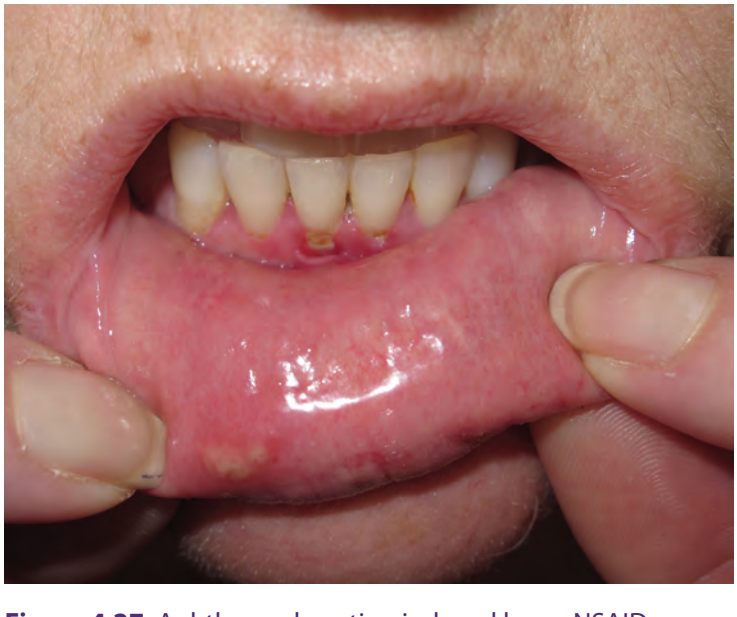

Figure 4.27. Aphthous ulceration induced by an NSAID.

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4.6.2 Aphthous-like ulceration

Aphthous or aphthous-like ulcers (see *Fig. 4.27*) can result from an oral non-steroidal anti-inflammatory drug (NSAID: naproxen, piroxicam, indomethacin), the anti-anginal nicorandil, an antihypertensive (captopril, labetalol, losartan), an antibiotic (trimethoprim-sulfamethoxazole), a bisphosphonate (alendronate, etidronate, risedronate), or an mTOR inhibitor (sirolimus, everolimus).

4.6.3 Fixed drug eruption

Oral mucosal fixed drug eruption has been reported from a single exposure or multiple exposures to a causative drug, which includes analgesics (paracetamol, naproxen, etoricoxib, piroxicam), the antihistamine levocetirizine, an antimicrobial agent, (trimethoprim-sulfamethoxazole fluconazole, clarithromycin, ornidazole, tetracycline), gabapentin, or simvastatin.

Fixed drug eruption presents as one or more acute blisters on an erythematous or purplish base resolving with hyperpigmentation. It recurs in identical sites on re-exposure to the causative drug. Fixed drug eruption can present with painful ulcers on the lips and tongue (see *Fig. 4.28*).

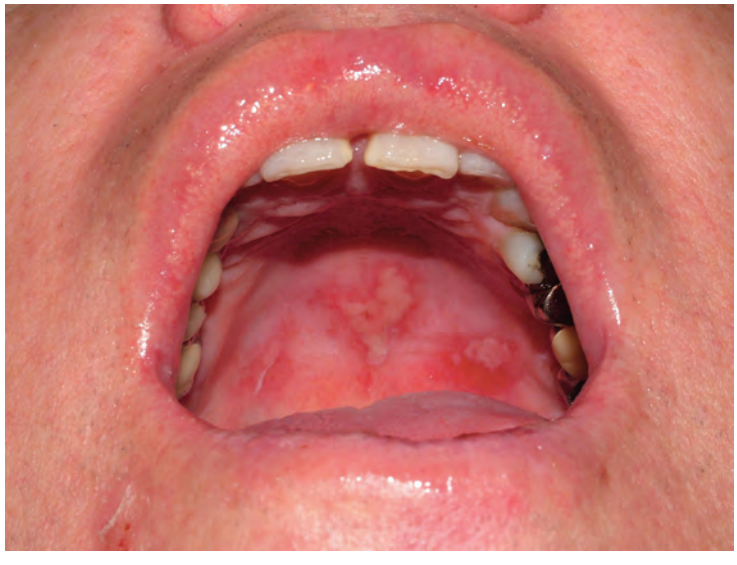

Figure 4.28. Fixed drug eruption.

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4.6.4 Lichenoid drug eruption

The wide range of drugs causing oral lichenoid reactions includes:

- analgesics – aspirin, diclofenac, ibuprofen, indomethacin, naproxen, piroxicam
- antidiabetics – glibenclamide, glipizide, metformin, tolbutamide
- antihypertensives – atenolol, captopril, enalapril, methyldopa, nifedipine, prazosin, propranolol

- antimicrobials – chloroquine, ethambutol, isoniazid, ketoconazole, rifampicin, sulfamethoxazole, tetracyclines
- antirheumatics – gold, penicillamine, sulfasalazine
- biologic agents – imatinib, sunitinib, etanercept, abatacept, adalimumab, infliximab, nivolumab, pembrolizumab
- diuretics – bendrofluazide, frusemide, hydrochlorothiazide
- other drugs – carbamazepine, allopurinol, lithium, pravastatin, simvastatin, and levothyroxine.

They present as painful lichen planus-like white streaks and ulcers, most often affecting the buccal mucosa (see *Fig. 4.29*).

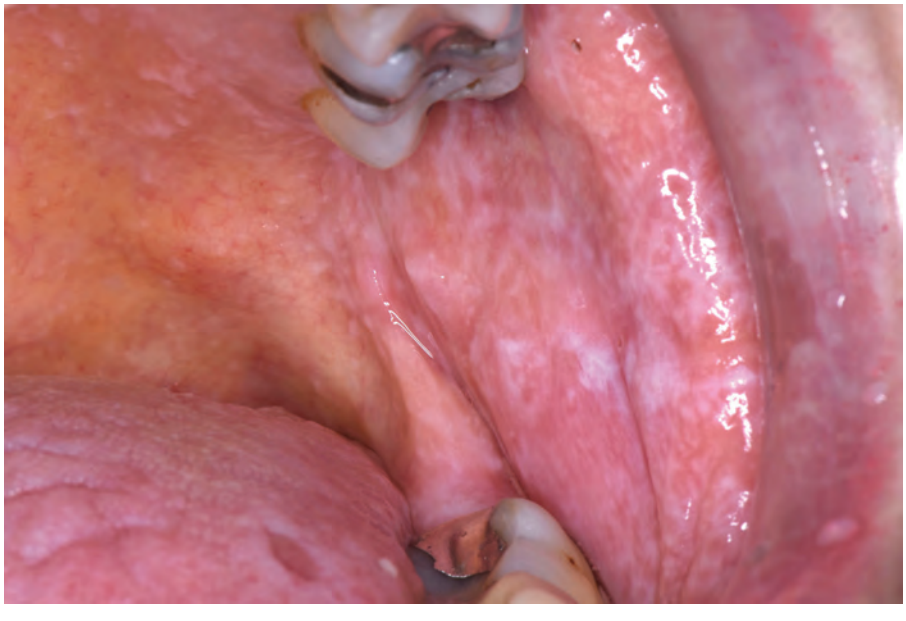

Figure 4.29. Lichenoid drug reaction associated with nivolumab. Nivolumab is used in the treatment of non-small cell lung cancer, kidney cancer, head and neck cancer, melanoma, Hodgkin disease, and liver cancer.

4.6.5 Lupus-like reaction

Drugs that may cause oral lupus-like ulceration include antihypertensives (captopril, hydralazine), antimicrobials (minocycline, isoniazid), and others (carbamazepine, chlorpromazine, penicillamine, sulfasalazine, anti-TNF-α inhibitors, procainamide).

4.6.6 Immunobullous reaction

A bullous adverse reaction to a drug may present as an acute SCAR (a severe cutaneous adverse reaction such as SJS/TEN or bullous drug hypersensitivity syndrome (see *Fig. 4.30*). Drugs that can also induce bullous pemphigoid (e.g. vildagliptin) or pemphigus vulgaris (e.g. vancomycin) may involve the oral mucosa. Other drugs reported to cause bullous eruptions include

anticonvulsants (carbamazepine, lamotrigine, phenytoin), antibiotics (amoxicillin/clavulanic acid, trimethoprim-sulfamethoxazole, rifampicin), xanthine oxidase inhibitor (allopurinol), NSAID (diclofenac), or others (chlorpromazine, frusemide, spironolactone, and penicillamine.

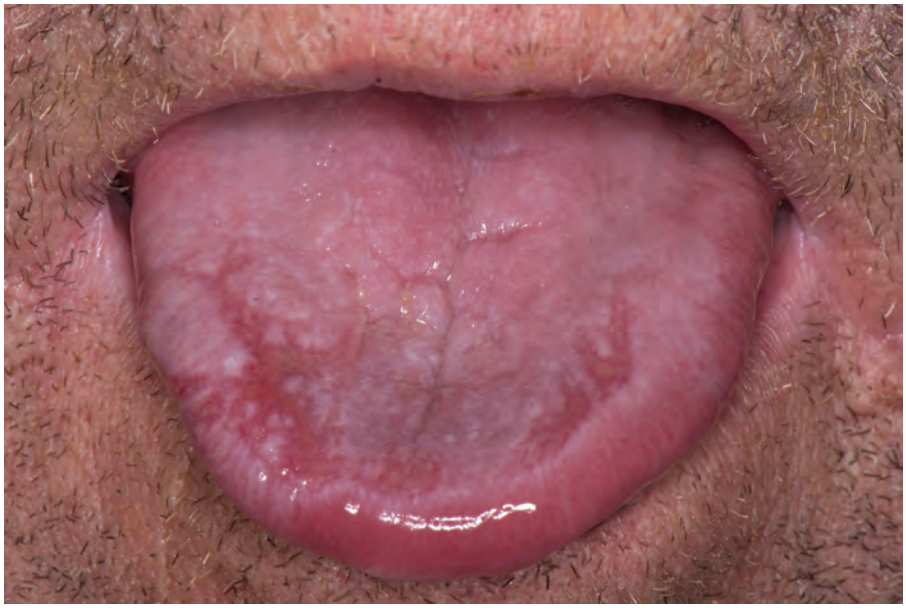

Figure 4.30. Bullous drug eruption due to sulfamethoxazole-trimethoprim, with widespread cutaneous bullae, oral blisters, and erosions seen here on the tongue.

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4.6.7 Drug-induced gingival hyperplasia

Drug-induced gingival hyperplasia is a peri-dental side-effect of certain drugs, causing swelling, bleeding, and problems with chewing, aesthetics, and pronunciation.

The drugs causing gingival hyperplasia include the following:

- Anticonvulsants, particularly phenytoin (50%)
- Immunosuppressants, particularly ciclosporin (30%)
- Calcium channel blockers, such as nifedipine (20%).

Clinical features

Drug-induced gingival hyperplasia presents as a firm, pale pink, painless, nodular enlargement of the interdental papilla, limited to the keratinized gingiva and extending to the facial and lingual gingival margins (see *Fig. 4.31*).

- Typically, it does not affect edentulous areas.
- The gingival overgrowth resolves when teeth are extracted.
- Histopathology shows an excessive accumulation of extracellular matrix-like collagen.

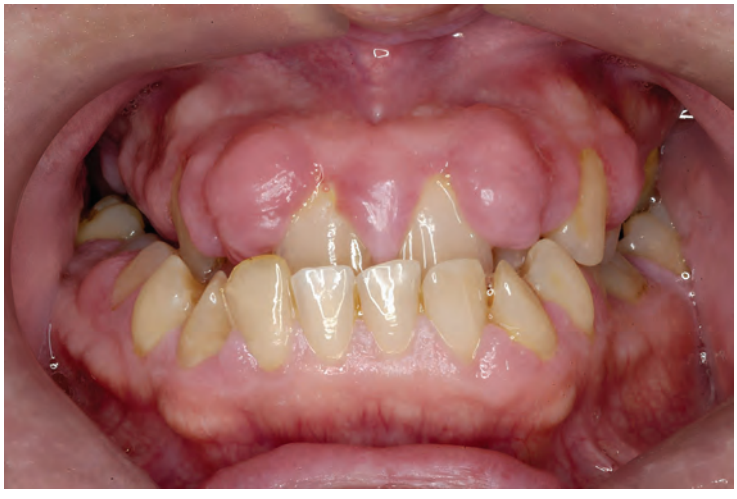

Figure 4.31. Drug-induced gingival hyperplasia (ciclosporin). Ciclosporin is an immunosuppressant medication.

Image reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission, and included here after enhancement by AIPDerm (www.aipderm.com).

Treatment

Options for treatment include:
- plaque control
- discontinuing or changing the inducing drug
- scalpel gingivectomy.

4.6.8 Stevens–Johnson syndrome / toxic epidermal necrolysis

Stevens–Johnson syndrome / toxic epidermal necrolysis (SJS/TEN) is a rare acute mucocutaneous emergency requiring hospitalization. The area of detached skin classifies the disease.
- SJS: skin detachment of <10% of body surface area
- Overlap SJS/TEN: detachment between 10% and 30% of body surface area
- TEN: skin detachment of >30% of body surface area.

SJS/TEN can affect children and adults. Incidence is equal in males and females, involving about 1 to 2 cases per million per year. It is more commonly experienced in people of Chinese ancestry than in Europeans.

Causes

SJS/TEN is a severe cutaneous adverse reaction, most often to a drug, such as an antibiotic (40%), an anticonvulsant, allopurinol, or targeted immunotherapy.
- In about 20% of cases, the cause is an infection or vaccination.
- There is a genetic predisposition with HLA associations for reactions to specific drugs in certain races.
- Cytotoxic lymphocytes mediate skin detachment.

Clinical features

The prodrome varies from a few days to two months, depending on the causative drug. The patient rapidly becomes extremely ill.

- Initial symptoms of SJS/TEN are high fever, sore throat, conjunctivitis, myalgia, and arthralgia.
- A tender, painful rash begins abruptly on the trunk and rapidly extends to the face and limbs over 4 days.
- It comprises erythematous macules, diffuse erythema, blisters, and targetoid lesions.
- The Nikolsky sign is positive. The skin detaches, exposing bright red, oozing dermis.
- The oral mucosal disease presents with haemorrhagic crusting of the lip, painful blisters, crusted erosions, and ulceration (see *Fig. 4.32*) causing odynophagia and dysphagia.
- The disease may affect ocular, oesophageal, anogenital mucosa, respiratory and gastrointestinal tracts, heart, liver, and kidneys.
- The acute stage of the illness lasts 1 or 2 weeks, but re-epithelialization can take weeks.

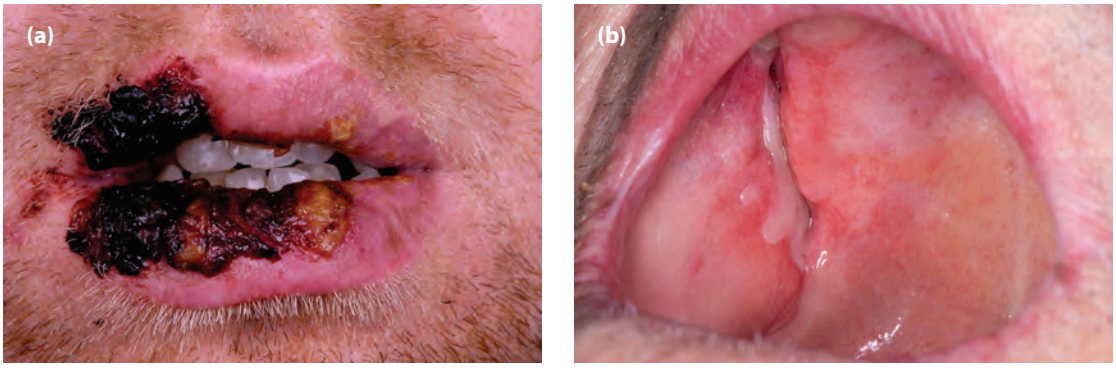

Figure 4.32 (a and b). Lip and oral mucosal crusting and ulceration in Stevens–Johnson syndrome / toxic epidermal necrolysis.

Image reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission.

Diagnosis

The diagnosis of SJS/TEN is clinical.

- Typical histopathological features are full-thickness epithelial necrosis and keratinocyte apoptosis. Intra-epithelial vesicles and perivascular lymphocytic infiltration are characteristic.
- Investigations are undertaken to identify and monitor systemic effects of the reaction.

Treatment

Stop the causative drug immediately; the patient should avoid it lifelong. The patient should be referred to a hospital, ideally to a burns unit.

Prognosis

The prognosis of SJS/TEN depends on the extent of epidermal detachment, patient age, and systemic co-morbidities.

- Mortality is up to 10% for SJS and >30% for TEN.
- Recovery may be accompanied by blindness and scarring of skin, nails, and mucosa.

4.7 Reaction to infection or vaccination

4.7.1 Infection-related mucositis

Erythema, oedema, and erosions can rarely arise in association with a viral infection (see *Fig. 4.33*).

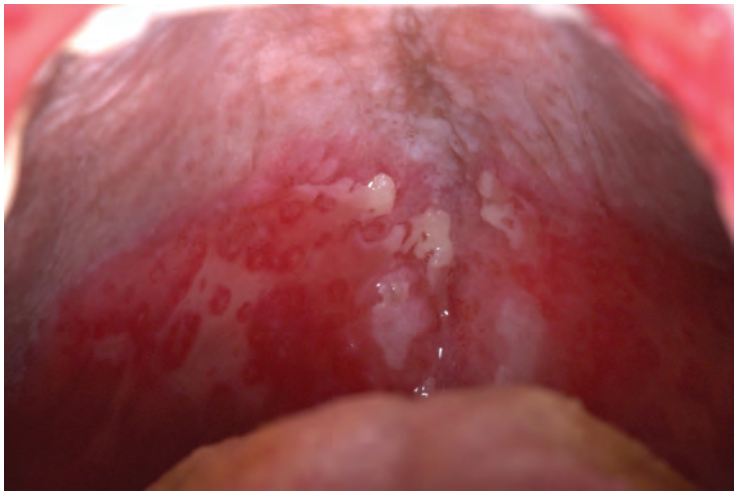

Figure 4.33. Acute mucositis associated with Covid-19 infection.

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4.7.2 Erythema multiforme

Erythema multiforme (EM) is an uncommon mucocutaneous reaction to an infection or other trigger. It usually affects young adults, with an annual incidence of about 1%.

Classification is based on the degree of mucosal involvement and the nature and distribution of skin lesions.

1. EM minor – affects only one mucosa and is associated with symmetrical target lesions on the extremities.
2. EM major – affects two or more mucous membranes with more variable skin involvement.

Causes

Erythema multiforme is often due to HSV infection (~70%).

- Other viral infectious triggers include orf and Covid-19.

- *Mycoplasma pneumoniae* causes an erythema multiforme-like distinct syndrome known as *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM).
- Rare triggers of EM include vaccination, systemic illness, and medication such as an NSAID, antibiotic, or anti-epileptic.

Clinical features

Erythema multiforme is an acute reaction characterized by target lesions, oral or lip ulceration, and mild systemic symptoms.

- Lesions are present in the oral mucosa, other mucosal sites, and the skin.
- Oral lesions most frequently affect the buccal mucosa and vermilion border. They range from minor erythema to extensive and painful, deep haemorrhagic bullae, crusted erosions, and ulcers (see *Fig. 4.34*).
- EM may also affect ocular, nasal, pharyngeal, laryngeal, upper respiratory, and anogenital mucosa.
- Classic target lesions are concentric rings of central epidermal blistering/necrosis, intermediate zone oedema, and peripheral erythema. They are pruritic and painful. Target lesions and atypical erythematous plaques start on the hands and feet and appear on the distal limbs. Target lesions may also affect the cheeks, ears, and chest. The distribution is symmetrical.
- Recurrent EM is uncommon and is nearly always triggered by herpes labialis.
- Chronic EM is rare.

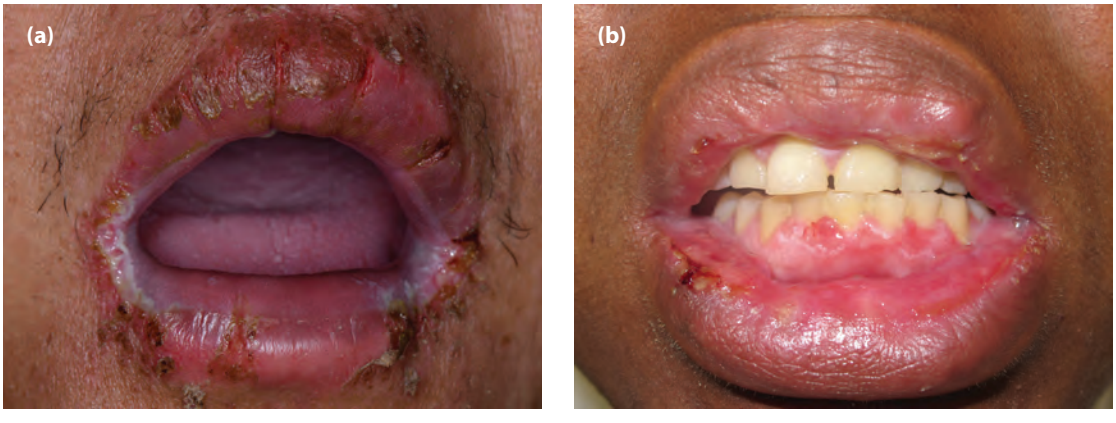

Figure 4.34 (a and b). Erythema multiforme showing (a) crusted vermilion, and (b) vesicles and erosions on gingiva and lips.

Image reproduced from Health NZ – Waikato (www.waikatodhb.health.nz) with permission.

Diagnosis

The diagnosis of EM is clinical. Typical histopathological features are dermal oedema and individual keratinocyte necrosis, but the histology is often non-specific.

Treatment

Supportive therapy includes analgesics, local anaesthetic/antiseptic mouthwash, hydration, nutritional supplementation, a topical corticosteroid, and bed rest.

Systemic steroids may be prescribed in patients with EM major, but their use is controversial.

Prognosis

In most cases, EM resolves within 3 weeks, but recovery may take up to 6 weeks for EM major.

- EM does not usually cause scarring except for rare ocular or pharyngeal involvement.
- Episodes of recurrent EM associated with HSV may be reduced by prophylactic oral aciclovir or valaciclovir.

4.8 Pigment

4.8.1 Amalgam tattoo

Amalgam tattoo, also known as focal argyrosis, is the impregnation of amalgam particles into focal areas of the oral mucosa during tooth extraction or replacement of an existing amalgam restoration.

Clinical features

Amalgam tattoos are the most common focal pigmented lesions of the oral mucosa.

- An amalgam tattoo is usually an incidental clinical finding during a routine oral examination.
- Typically, there is a solitary, blue–black, well-defined, or diffuse pigmented macule (see *Fig. 4.35*).
- Most amalgam tattoos are found on the gingivae or edentulous ridges.

Diagnosis

Clinical diagnosis is usually sufficient.

- An X-ray may reveal a large tattoo to be radiodense due to metal in the paradental tissues.

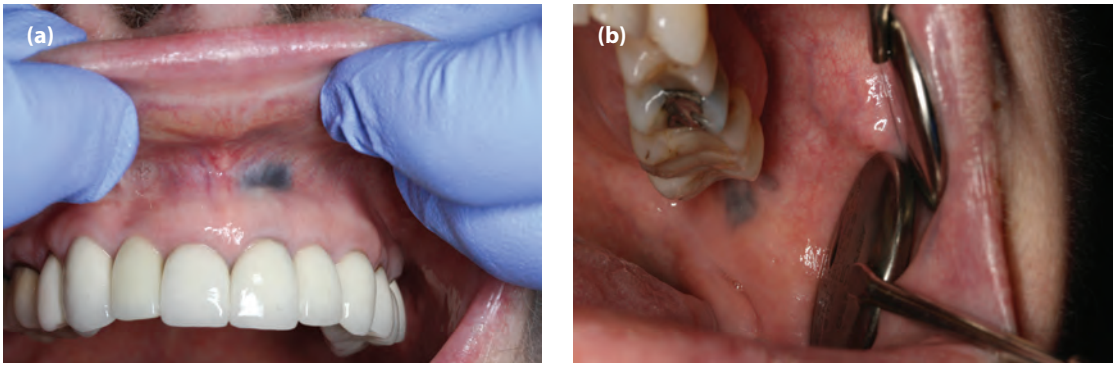

Figure 4.35 (a and b). Amalgam tattoo showing blue–black pigmentation in the missing lower premolar region.

(a) Reproduced with permission from Professor Nagamani Narayana, University of Nebraska Medical Centre, NE, USA.

- Histology shows foreign particulate material within macrophages and multinucleated giant cells or extracellularly around blood vessels in the connective tissue.

Treatment

No treatment is required for most amalgam tattoos, but they may be excised; for example, to exclude mucosal melanoma.

4.8.2 Cosmetic tattoo

Tattooing of soft tissues is popular in many countries, and it may be culturally significant in developing countries, while in developed countries, it is a social custom. While cutaneous tattooing is more common, mucosal tattooing may also be observed.

Clinical features

Tattoos should be differentiated from physiologic pigmentation and smoker's melanosis.

- The tattoo colour may vary from dark green to black.
- The gingiva, labial mucosa, and palate are the most common intraoral sites for tattooing.
- Periodontal disease increases the risk of procedure-related infection.
- The colour fades more rapidly in the mouth than when implanted in the skin.

Treatment

The pigment used for tattoos is usually harmless, and no treatment is required. Contact allergy, granulomas, and lichenoid reactions to intraoral cosmetic tattoos have been rarely described.

4.8.3 Drug-induced pigmentation

Pigmentation of the oral mucosa is reported to be induced by many medications:

- Antimalarial (chloroquine phosphate, hydroxychloroquine, quinidine, quinacrine)
- Chemotherapy (doxorubicin, busulfan, bleomycin, cyclophosphamide, clofazimine, imatinib)
- Antiretroviral agent (zidovudine, azidothymidine)
- Antibiotic (tetracycline, minocycline)
- Tranquillizer (chlorpromazine)
- Antifungal (ketoconazole)
- Laxative (phenolphthalein).

Clinical features

Drug-induced mucosal pigmentation may present as linear, diffuse, or multifocal discrete macules. Brown or grey pigmentation may affect the gingivae or other mucosal sites (see *Fig. 4.36*).

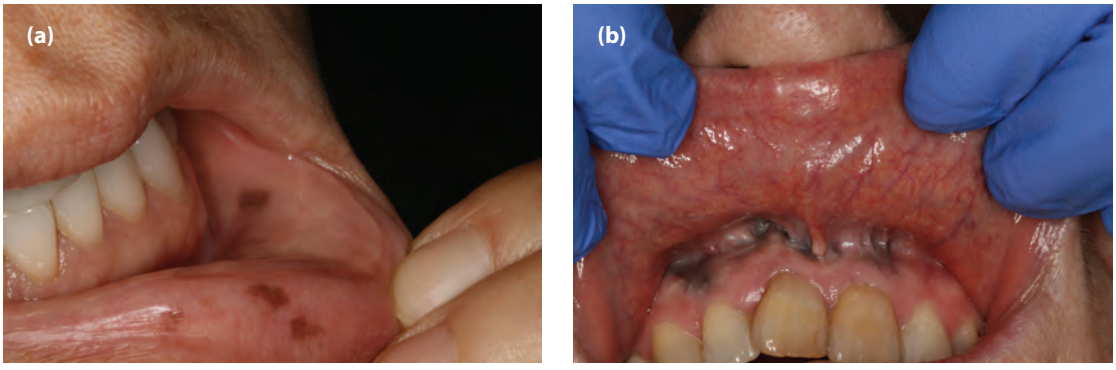

Figure 4.36 (a and b). Drug-induced pigmentation. Multifocal discrete macules (a) and patchy diffuse pigmentation (b).

- Diagnosis is usually on clinical grounds and a history of chronic drug use.
- Intraoral fixed drug eruption and lichenoid drug eruption may also result in pigmentation following an inflammatory phase.
- A biopsy may be required for confirmation.

Treatment

No treatment is required for asymptomatic drug-induced pigmentation. Patient education and reassurance are recommended.

4.8.4 Postinflammatory pigmentation

Inflammatory skin conditions such as lichen planus may result in localized hyperpigmentation as they resolve, especially in patients with skin of colour.

4.8.5 Heavy metal pigmentation

Heavy metal pigmentation is rare and is caused by excessive ingestion or exposure to bismuth, lead, mercury, and silver.

Clinical features

Pigmentation appears on the skin and oral mucosa in a patient with a metallic taste, gastrointestinal disturbance, and a history of exposure to heavy metals.

- A thin linear deposit of the gingiva is the most common sign of heavy metal pigmentation. Diffuse pigmentation may also occur.
- A biopsy reveals black particulate deposits in the lamina propria. These are the products of the oxidation of the metal within the tissues.

Treatment

Treatment involves avoiding further exposure to heavy metals and referral to a hospital facility.

4.9 Reaction to an underlying disease

4.9.1 Acanthosis nigricans

Acanthosis nigricans refers to hyperpigmented velvety plaques affecting the skin folds in the neck, groin, and axillae. Acanthosis nigricans may also affect the oral cavity.

- Acanthosis nigricans is more commonly observed in people of African and Polynesian descent than in Europeans and Asians.
- Acanthosis nigricans may become apparent at any age. When associated with malignancy, it most frequently occurs after 40 years of age.

Causes

Acanthosis nigricans is a sign of insulin resistance and is most often associated with obesity and systemic diseases such as diabetes. Elevated levels of insulin and insulin-like growth factor cause epithelial cells to proliferate.

- Acanthosis nigricans is sometimes caused by a medication (e.g. insulin, glucocorticoids, niacin, oral contraceptive, or a protease inhibitor).
- It may be inherited as an autosomal dominant trait due to mutations in fibroblast growth factor receptor 3.
- Malignant or paraneoplastic acanthosis nigricans is most often associated with gastric adenocarcinoma and less commonly with lung, ovary, and breast cancers.
- Malignant acanthosis nigricans is related to the secretion of various tumour products such as epidermal growth factor, transforming growth factor-alpha, and hormones that stimulate the growth of melanocytes, keratinocytes, and fibroblasts.

Clinical features

Acanthosis nigricans is characterized by hyperpigmentation and abnormal thickening of the sides and back of the neck, axillae, groin, and anal/genital region. Oral involvement is rare.

- Acanthosis nigricans of the oral mucosa is characterized by painless soft, papillomatous plaques on the lips, perioral region, palate, gingiva, and tongue (see *Fig. 4.37*).
- The mucosal lesions have the same colour as the surrounding mucosa.
- Oral acanthosis nigricans may be the first clinical sign of internal cancer.

Diagnosis

The diagnosis of acanthosis nigricans is based on personal and family history and clinical evaluation. Endocrine tests and imaging may follow.

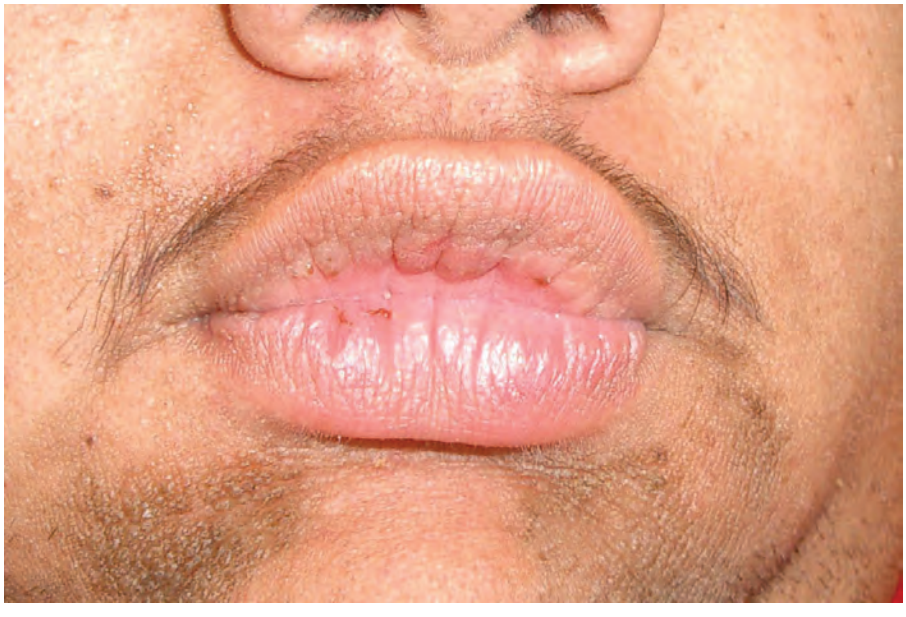

Figure 4.37. Acanthosis nigricans affecting vermilion.

Image shown here after enhancement by AIPDerm (www.aipderm.com).

Treatment

There is no specific treatment for oral acanthosis nigricans. Treatment of any underlying medical problem is helpful, such as weight loss in those with obesity.

4.9.2 Plummer–Vinson syndrome

Plummer–Vinson syndrome (also known as the Paterson–Kelly syndrome) is a triad of:

1. dysphagia
2. iron-deficiency anaemia
3. oesophageal webbing.

It is associated with an increased risk of oral squamous cell carcinoma (SCC) and SCC of the pharynx and oesophagus, with 3–15% of patients developing upper gastrointestinal tract cancer.

- Plummer–Vinson syndrome is rare, with most patients of Caucasian background, middle-aged, and female.
- Its causes are unknown.
- Dysphagia may be painless and intermittent or progressive over many years. It may limit dietary options and, in some cases, result in significant weight loss.
- Anaemia may result in weakness, pallor, and fatigue.
- Oral manifestations of long-standing anaemia include glossitis and angular cheilitis (see *Section 6.4.1*).

4.9.3 Mouth ulcers due to underlying bowel disease

Aphthous or aphthous-like ulceration is sometimes associated with underlying bowel disease, when treatment of the bowel disease can result in improvement or resolution of the mouth ulcers. See also *Section 9.7* on coeliac disease and *Section 9.8* on inflammatory bowel disease.

4.10 Reactive gingival hyperplasia

4.10.1 Localized juvenile spongiotic gingival hyperplasia

Localized juvenile spongiotic gingival hyperplasia primarily affects children and young adults. Its cause is unknown.

Clinical features

Juvenile spongiotic gingival hyperplasia results in bright red plaques on the attached gingiva.

- They have a papillary or granular surface.
- Histopathological examination shows subtle papillary epithelial hyperplasia with spongiosis, neutrophil exocytosis and engorged capillary vascular spaces in the lamina propria.

Treatment

Persistent juvenile spongiotic gingival hyperplasia can be surgically excised and does not recur if completely excised.

4.10.2 Hormone-related gingivitis

According to the US CDC, 60–75% of pregnant women have gingivitis.

Causes

Gingival disease in pregnancy is initiated by dental plaque and changes in oral microbiota due to fluctuations in oestrogen and progesterone levels. Oral contraceptive medications can provoke similar features, and hormone-related gingivitis may occur in postmenopausal women.

Clinical features

Gingivitis in pregnancy is characterized by erythematous swollen gingiva with increasing periodontal probing depths and bleeding upon probing.

Treatment

Maintenance of good oral hygiene is essential.

Consider surgical reduction of gingival hyperplasia.