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Chapter 11

Mucosal diseases

Overview

Oral mucosa shows considerable variation in its normal structure and can be affected by a wide range of conditions. The identification of oral mucosal abnormalities is important because they can be harmless, minor primary conditions and secondary indications of systemic disease. The situation is further complicated by the multiple causes for many mucosal lesions: for example ulceration can reflect simple trauma, a habit tic with psychiatric implications, lichen planus, infection, gastrointestinal disease such as Crohn's disease or a side-effect of a drug.

11.1 Normal oral mucosa

Learning objectives

You should:

- know the structure of the mucosa and what constitutes normal mucosal anatomy.

Three divisions of oral mucosa are recognised.

Masticatory. This is firm, pink and keratinised. It forms the hard palate and gingivae.

Lining. This division is extensible, red and non-keratinised. It forms the buccal and labial mucosa, vestibular, floor of mouth, ventral tongue and soft palate.

Specialised mucosa. This includes filiform, fungiform and circumvallate papillae of the dorsal tongue.

Normal structures

In order to be able to recognise mucosal abnormality it is necessary to be familiar with normal anatomical structures that patients may notice and become concerned about. These include:

- lingual papillae, especially circumvallate papillae
- incisive papilla and rugae, which are easily traumatised
- fordyce granules, which may be prominent in atrophic mucosa
- pterygoid hamulus, mandibular and palatal tori
- lingual veins
- parotid and submandibular duct openings
- mucogingival junction.

Leukoedema

Leukoedema is a variant of normal mucosa. It is a bilateral, diffuse, whitish translucency of the buccal mucosa found commonly in Black and variably in White people. It is caused by intracellular oedema of the prickle cell layer. Recognition of leukoedema is important because it may be mistaken for a clinically significant disorder.

11.2 Conditions related to friction or trauma

Learning objectives

You should:

- understand which diseases are caused by friction/trauma and can be treated by removal of the irritant
- be able to distinguish friction-related hyperplasia from neoplasia.

Frictional keratosis

Chronic mechanical, thermal or chemical trauma may induce a keratinising response in buccal mucosa (which is normally non-keratinising) and hyperkeratosis (excessive keratinisation) elsewhere (Fig. 142). This may occur through activation of keratin genes. The keratin becomes swollen, resulting in a spongy appearance. Diagnosis is clinical and treatment normally involves eliminating the cause and reviewing to ensure resolution. There may be a local cause such as a sharp tooth or it may be habit related. Biopsy is undertaken where doubt exists. The principal histopathological features are:

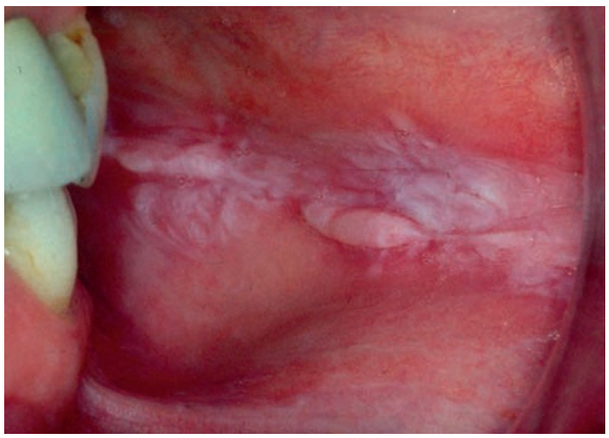

Fig. 142 Frictional keratosis in a patient who habitually chewed the buccal mucosa, particularly when stressed.

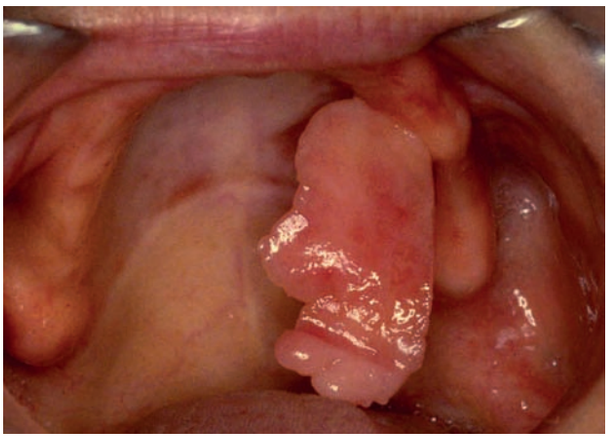

Fig. 143 Leaf-like fibrous hyperplasia of the palate caused by chronic irritation from an ill-fitting upper denture.

- regular epithelial maturation pattern
- hyperkeratosis, usually hyperparakeratosis
- parakeratin layer appears macerated and bacterial plaque is adherent
- acanthosis (widening of prickle cell layer).

Smoker's palatal keratosis

Smoker's palatal keratosis is also known as stomatitis nicotina. It is associated with any smoking habit but tends to be most florid in pipe smokers. The diagnosis is restricted to palatal lesions.

The principal features are:

- palatal mucosa appears white and crazed as a result of keratosis
- red spots occur through blockage of minor salivary gland ducts
- histopathology shows keratin plugs in duct openings
- reversible if smoking habit stopped
- not regarded as a potentially premalignant disorder.

Fibrous hyperplasia and neoplasia

Chronic irritation to the oral mucosa is common and often results in fibrous hyperplasia. Elimination of the cause of irritation may reverse the process, resulting in shrinkage or resolution. Many fibrous hyperplastic lesions are excised, however, because this is a simple and rapid method of treatment. All such tissue should be forwarded for histopathological examination to confirm the diagnosis.

Fibroepithelial polyp

A fibroepithelial polyp is typically a firm sessile or pedunculated polyp that arises most commonly on the labial and buccal mucosa as a result of mechanical trauma from the teeth or dentures (Fig. 143). It is easily excised under local analgesia but will recur unless the source of trauma is corrected.

Histopathologically there is a core of dense fibrous tissue covered by stratified squamous epithelium. The latter often shows keratinisation, reactive to trauma. Secondary ulceration may be seen.

Denture irritation hyperplasia

Denture irritation hyperplasia often forms in relation to denture flanges that have become overextended because of alveolar resorption. Folds of fibroepithelial tissue form in the vestibule. Papillary hyperplasia may be seen in the palatal mucosa covered by a poorly fitting denture.

Connective tissue neoplasms

Connective tissue neoplasms are uncommon in the oral mucosa, but benign tumours including lipoma, neuroma and fibroma may occur and mimic fibrous hyperplasia clinically. Malignant soft tissue neoplasms are extremely rare but may arise from any connective tissue in the oral cavity.

11.3 Ulceration

Learning objectives

You should:

- know the causes of ulceration
- know what drugs are likely to cause ulcers
- be aware of comorbid conditions associated with mouth ulcers
- understand the management of ulcers.

Oral ulceration is commonly caused by mechanical trauma. It is also associated with systemic diseases, drug side-effects and with infections (see Section 11.4).

Traumatic ulceration

An ulcer is a breach in the integrity of the covering epithelium. Traumatic ulceration is common in the oral cavity. The most frequent cause is mechanical injury from the teeth; such ulcers occur on the buccal mucosa, lateral tongue and lower lip in the occlusal plane. Ill-fitting dentures may also cause traumatic ulceration. Ulcers at other sites can be caused by habits (e.g. fingernail picking in children) or even deliberate self-harm. Sharp foodstuffs may cause traumatic ulceration of the palate. Thermal injuries are common at this site from over-hot drinks. Chemical causes of

traumatic ulceration include placing aspirin in the vestibule, and rinsing with astringent chemicals. Traumatic ulcers are common on the lower lip and may follow mechanical or thermal injury after inferior alveolar nerve block.

Clinical features

On clinical examination, traumatic ulcers typically are painful and surrounded by erythema. The base is covered by fibrinous exudate and at a later stage by granulation tissue and regenerating epithelium (see Fig. 9, p. 14). Shape and location often give a clue as to the cause. On gentle palpation, traumatic ulcers lack induration and are tender.

Management

Management is to elicit an accurate history, document the features of the ulcer, eliminate the cause if possible, provide symptomatic treatment and review to ensure that healing takes place. Any ulcer that does not heal within 3 weeks should be considered as suspicious and fast-track referred for specialist opinion to exclude carcinoma.

Drug-related ulceration

An increasing number of drugs cause oral ulceration as an unwanted effect. Examples include nicorandil, indometacin (indomethacin) and phenytoin. These tend to produce solitary or multiple ulcers, often recurring at fixed sites. Often a lichenoid pattern is seen in biopsy specimens. Where such a drug reaction is suspected, the possibility of changing the medication believed to be responsible should be raised with the patient's general practitioner, who needs to balance any risks associated with such a change against the benefits to the patient. Cytotoxic drugs cause oral ulceration through toxicity to the rapidly turning over cell population in the oral epithelium. Direct application of legal and illegal drugs for extended periods to the oral mucosa can produce severe ulceration at the site.

Recurrent aphthous ulceration: aphthous stomatitis

Aphthous stomatitis or recurrent aphthous ulceration (RAU) is an extremely common disorder of the oral cavity, estimated to affect 20% of the population. There is some evidence of a familial tendency to RAU. The disorder first manifests in early childhood but more frequently is noticed at around the time of puberty. Three clinical patterns are recognised.

Minor RAU. Ulcers are up to 5 mm in diameter with a yellow–grey base and halo of erythema (Fig. 144). It affects only non-keratinised mucosa. Ulcers tend to occur in crops of two to three but variable patterns are seen, ranging from occasional single ulcers to over 20 at any one time. Individual ulcers heal without scarring in 10–14 days.

Herpetiform RAU. Pinhead-size ulcers occur in crops (Fig. 145). Typically, the ulcers become confluent and healing takes up to 40–50 days. Any mucosal site can be affected. The severity of symptoms is greater than in minor RAU, with some patients experiencing a continuous pattern of ulceration.

Major RAU. Ulcers progressively enlarge and can be up to 3 cm in diameter (Fig. 146). They can persist for up to 3 months and often heal with scarring. Any mucosal site can be involved; often the oropharynx is affected. This causes particularly severe symptoms, including pain on swallowing and gagging.

Aetiology

The aetiology of RAU is unknown, though there are strong associations with having a family history of RAU, stress, smoking cessation and haematinic deficiency. RAU is also seen in gastrointestinal disease, particularly Crohn's disease (which may involve the oral mucosa directly or induce oral ulceration secondary to malabsorption), coeliac disease and other disorders of malabsorption. Oral ulceration is additionally observed in immunological disorders. Behçet's disease is a multisystem autoimmune disorder for which RAU is one of the major diagnostic criteria. Classically, it is accompanied by genital ulceration and eye lesions (e.g. uveitis); however, the skin, joints, gastrointestinal tract, blood vessels and central nervous system may also be affected in various combinations. Severe unusual RAU is a recognised manifestation of infection with the human immunodeficiency virus (HIV).

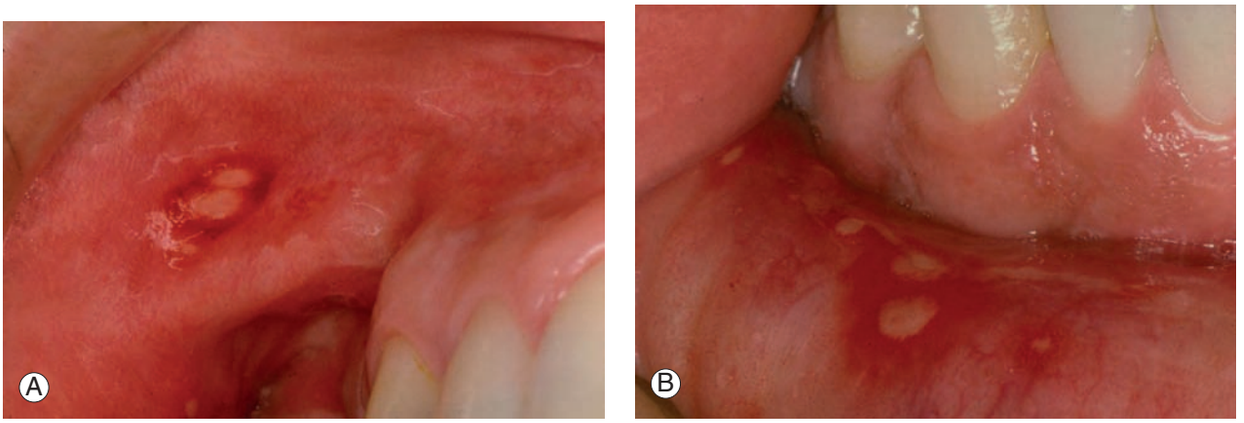

Fig. 144 Minor recurrent aphthous ulceration. Crops of ulcers up to 5 mm in diameter may involve the lining mucosa.

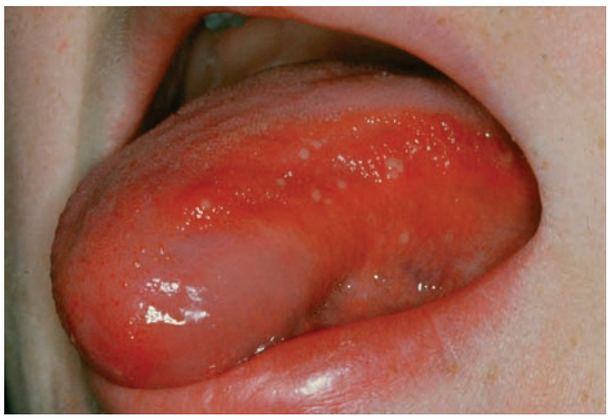

Fig. 145 Herpetiform recurrent aphthous ulceration. Pinhead-sized ulcers tend to become confluent with time.

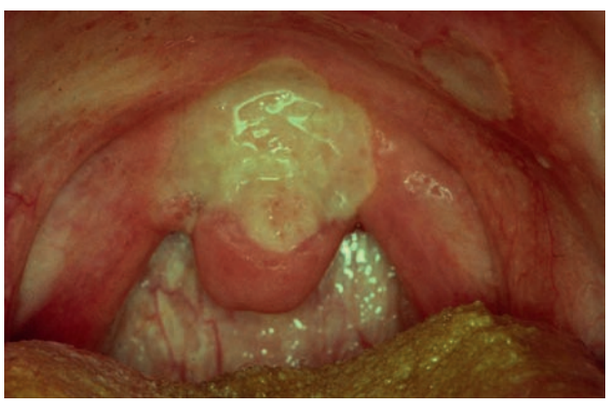

Fig. 146 Major recurrent aphthous ulceration. Ulcers tend to occur in the posterior part of the oral cavity and oropharynx.

Diagnosis

The diagnosis of RAU is made on clinical grounds. Because of its association with disease of the gastrointestinal tract, specific enquiry should be made into signs and symptoms of gastrointestinal problems. Similarly, the possibility of Behçet's disease leads to enquiry concerning the presence of other signs and symptoms of this disease. A full blood count and haematinics (serum vitamin B_{12}, ferritin (an iron-binding protein), folate and red blood cell folate) should be carried out. Where vitamin B_{12} deficiency is detected, the possibility of pernicious anaemia should be investigated by checking the blood for antibodies to intrinsic factor. Low levels of folate, often accompanied by low ferritin, are suggestive of coeliac disease (even in childhood) and the patient's blood should be checked for the presence of endomyseal or transglutaminase antibody. An increasing number of adult RAU patients with mild coeliac disease are identified nowadays. Other causes of folate deficiency (e.g. alcoholism) and vitamin B_{12} deficiency (e.g. diet) should also be considered. The most common cause of a low ferritin level is chronic blood loss. While correction of haematinic deficiencies can bring about resolution or improvement of the patient's oral ulceration this is pointless if the underlying cause of the deficiency is not addressed.

Management

It is difficult to prevent ulceration from occurring in susceptible individuals; however, limiting trauma to the oral mucosa by eliminating sharp foods, in particular crisps, from the diet can be of benefit. Similarly, where trauma from the teeth as a result of parafunctional habits is suspected, the provision of a soft bite guard for night-time wear may help. Unfortunately, the treatment of RAU lacks a robust evidence base. In terms of medication, some relief of symptoms may be obtained by the use of benzydamine mouthwash or spray. Both chlorhexidine and tetracycline mouthwashes can be of benefit; the latter seems to be of particular value in the treatment of herpetiform ulceration. Topical steroid preparations are widely used (see Section 11.5) and hydrocortisone lozenges seem to be particularly effective, if used on a daily basis, when episodes of ulceration are frequent. For severe cases, systemic medication is indicated, for example thalidomide, colchicine or systemic steroids; such agents should only be prescribed by a hospital-based specialist.

11.4 Infections

Learning objectives

You should:

- know the bacterial, viral and fungal infections that affect the oral mucosa
- be aware of the lesions associated with human immunodeficiency virus (HIV)
- understand the features of oral candidiasis.

Bacterial infections

Bacterial infections of the oral mucosa are rare. *Treponema pallidum* causes syphilis and mucosal lesions include primary chancres, secondary snail track ulcers and tertiary areas of focal necrosis (termed gumma). Syphilitic leukoplakia may also result. Tuberculosis infection is usually secondary to pulmonary lesions and presents as granular ulceration of the posterior palate and dorsal tongue. Raised red–white mucosal plaques termed lepromas are seen in established leprosy.

Viral infections

Herpes simplex

Oral involvement in herpes simplex (HSV) infection is commonly encountered, especially in children, and is most often due to HHV-1 (Fig. 147).

Primary herpetic gingivostomatitis

Initial infection results in primary herpetic gingivostomatitis. Grey blisters, which rapidly break down to form small ulcers, may be present anywhere on the oral mucosa and most frequently involve the gingivae. Crusted blisters may also appear on the circumoral skin. Infection is usually accompanied by a febrile illness, and bilateral tender cervical lymphadenopathy is frequently present. Infection

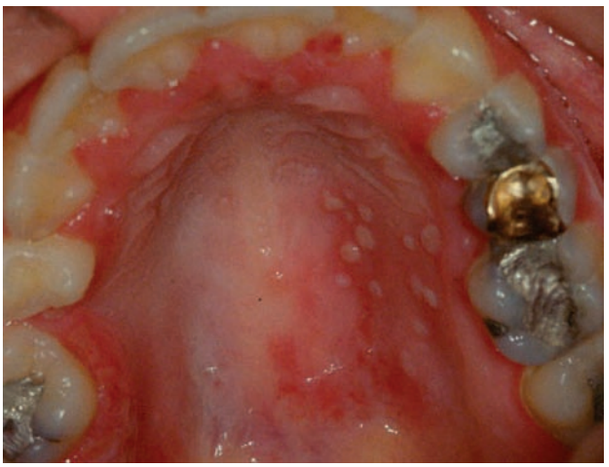

Fig. 147 Primary herpetic gingivostomatitis, showing vesicles and erythema of the palatal mucosa and gingivae.

can be spread to the fingers and conjunctiva by direct contact with the oral lesions, and advice should be given to avoid this. Resolution occurs within 2 to 3 weeks. Rest, maintaining fluid intake, chlorhexidine mouthwash to prevent secondary infection of the oral lesions and advice about cross-infection risks should be given. Infants under 6 months are at special risk of developing central nervous system infection and contact with infected siblings should be avoided. Prescription of systemic acyclovir is only of benefit in the early stages of the infection; a reasonable guide to this is the presence of intact vesicles. Diagnosis is usually made on clinical grounds, where doubt exists, serology performed on samples of acute and convalescent (2–3 weeks after onset of symptoms) blood should reveal a significant rise (of the order of fourfold or greater) in IgG antibodies against HSV in the later sample. Swabs, for culture or identification of viral DNA by polymerase chain reaction (PCR), and smears for cytology (showing ballooning of epithelial nuclei and/or multinucleate epithelial cells) may be useful but usually only if taken early in the course of the disease, ideally from an intact vesicle.

Herpes labialis (cold sores)

After primary infection, HHV-1 may remain in the trigeminal ganglion and low levels of virus are shed into the axoplasm thereafter. Local factors, such as exposure of the lip to intense sunlight, and systemic factors, such as depressed general immunity, result in herpes labialis (cold sores) in about 20–30% of individuals. Crusted vesicular patches appear on the lips, nose and circumoral skin. Acyclovir or pencyclovir cream applied immediately to new sores is an effective therapy. In a small number of individuals, recurrent intra-oral HSV infection may occur, lesions most commonly affect the hard palate and attached gingivae. Severe recurrent HSV infection may occur in the immunocompromised and further investigation to exclude this possibility should be performed.

Herpes zoster

Herpes zoster (HHV-3), the causative agent of chickenpox and shingles (Ch. 14), may involve the oral mucosa. Shingles tends to affect one or more dermatomes of the trigeminal nerve and is an important cause of facial pain. In the oral mucosa, rashes of grey vesicles restricted to the distribution of the sensory nerves are seen. High-dose systemic acyclovir or famcyclovir is usually prescribed.

Coxsackievirus

Coxsackieviruses cause hand, foot and mouth disease and herpangina. These manifest as vesicular eruptions and the management is conservative. Lifelong immunity is normally conferred.

Epstein–Barr virus

Epstein–Barr virus (HHV-4) causes hairy leukoplakia (see below).

Human papillomavirus

Human papillomaviruses produce focal proliferative lesions referred to as squamous papillomas (warts). They may be sessile or show finger-like projections. Histologically, fronds of keratotic squamous epithelium are supported by delicate fibrovascular stroma. Papillomas on the fingers can be the source of human papillomavirus, particularly for lesions on the lips and circumoral skin. Orogenital transmission is also possible. Intra-oral papillomas can be readily excised under local analgesia. HPV types 16 and 18 are an important cause of oral and particularly oro-pharyngeal carcinoma (see Ch. 12).

Human immunodeficiency virus

Initial infection by HIV may be asymptomatic or may cause a febrile illness with diarrhoea. An oral eruption clinically similar to primary herpetic stomatitis may occur at this time.

Numerous manifestations of established HIV infection are recognised. There are several with strong associated oral manifestations.

Kaposi's sarcoma. This is caused by human herpesvirus 8 (HHV-8), which is endemic in Mediterranean regions. Initial mucosal lesions are flat brown spots, which show haemosiderin deposition and vascular proliferation on biopsy. They progress into raised plaques and then nodular purple–red lesions, most often found on the palate, retromolar areas and gingivae. Oral lesions may precede the appearance of skin lesions.

Hairy leukoplakia. This lesion has been associated with progression from HIV infection to AIDS (acquired immunodeficiency syndrome) as the CD4 T lymphocyte count falls. It is caused by proliferation of Epstein–Barr virus (HHV-4) in the lateral tongue epithelium and rarely elsewhere in the oral cavity. Warty ridged or smooth white plaques are typical: sometimes extended papillary projections are seen. The lesion is also found in HIV-negative immunosuppressed patients, for example in renal transplant recipients. No treatment is required and the lesion is not premalignant.

Erythematous candidiasis. This is a frequent manifestation of HIV infection. It presents as white speckles on an erythematous background. Tongue and palate are frequently affected. Treatment can be a problem because of the development of resistant fungal strains in some patients. Hyperplastic and pseudomembranous forms of candidiasis are also common in HIV infection.

HIV-related gingivitis. This may resemble acute necrotising ulcerative gingivitis or present as a red lesion, termed linear gingival erythema.

HIV-related periodontitis. This manifests as unusual focal alveolar destruction. Severe alveolitis and osteomyelitis with sequestration of teeth and surrounding tissue may be seen in patients with advanced AIDS.

Other mucosal manifestations in HIV infection. Purpura results from thrombocytopaenia; bacillary angiomatosis, atypical ulceration, melanotic pigmentation, unusual infections and multiple viral papillomas are also seen.

Fungal infections

Candida albicans is the most common cause of fungal infection in the oral cavity (Fig. 148). It is a commensal organism carried by roughly half the population and disease is caused by opportunistic overgrowth. Oral candidiasis has been described as the 'disease of the diseased'. Local or systemic predisposing factors should be identified and corrected whenever possible (Table 13). Diagnosis is generally based on clinical features and can be confirmed by laboratory methods using material from oral swabs, smears or rinses. Where quantification is required, saliva samples, the oral rinse or the imprint culture techniques may be used. Other *Candida* sp. may also cause oral infection, particularly in the immunocompromised.

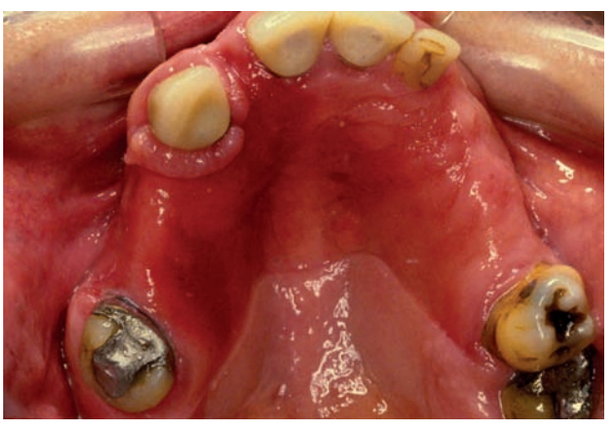

Fig. 148 Denture-related stomatitis. The oral mucosa of the denture-bearing area is erythematous, oedematous and hyperplastic. *Candida albicans* was recovered from the fitting surface of the denture.

Treatment is based on the use of topical antifungal agents. Amphotericin is available in the form of lozenges and nystatin in the form of a suspension. Patients suffering from **xerostomia** may find the latter or miconazole gel more pleasant to use; similarly this gel is convenient for the treatment of denture-induced stomatitis as it can be applied directly to the fitting surface of the denture. In addition to the use of an antifungal agent, the patient should be advised to leave the denture out at night. Acrylic dentures should be soaked overnight in a 0.1% solution of hypochlorite. If a cobalt chromium denture is worn, it should be soaked for 15 minutes twice daily in chlorhexidine. These measures should eradicate those microorganisms adherent to the denture, which may be more heavily colonised than the mucosa.

Systemic antifungal agents (e.g. fluconazole) should be reserved for those cases of oral candidiasis where topical antifungal agents are not appropriate. There are an increasing number of reports of resistance to azole antifungal drugs. These drugs play a significant role in the treatment of candidal infections in the immunocompromised. In contrast to nystatin and amphotericin triazole or imidazole antifungal agents, including miconazole, are readily absorbed via the gastrointestinal tract thus care should be taken to check for possible drug interactions.

Angular cheilitis

Candida sp. alone, bacteria alone or a combination of *Candida* and bacteria (*Staphylococcus aureus*, β-haemolytic

Table 13 Classification of *Candida*-related oral lesions

Lesion	Characteristics
Thrush (acute pseudomembranous candidiasis)	Friable white plaques that can be scraped off; often involves oropharynx; affects infants, elderly and immunosuppressed adults
Antibiotic sore mouth	Generalised erythematous and sore oral mucosa; caused by elimination of bacterial competition; related to prolonged use of wide-spectrum antibiotics
Denture-induced candidiasis	Related to continuous wearing of acrylic dentures; mucosa over fitting surface appears erythematous and oedematous; patient should improve denture hygiene and leave dentures out at night
Chronic hyperplastic candidiasis	Fixed, white, folded plaques, commonly behind the angle of the mouth; smoking and poor denture hygiene are common predisposing factors; candidal hyphae invade the parakeratin layer
Erythematous candidiasis	Red patchy areas, typically on palate and dorsum of tongue; associated with low CD4-cell counts, particularly in HIV infection; may be a cause of linear gingival erythema
Angular cheilitis	Crusted cracked lesions at the angle of the mouth; may be infected by *Candida* sp. or *Staphylococcus aureus*; predisposing factors include anaemia and saliva spreading to skin
Median rhomboid glossitis	Lozenge-shaped erythematous patch on the midline dorsal tongue; usually symptomless; epithelial hyperplasia with neutrophils in the parakeratin layer
Mucocutaneous candidiasis	Generalised chronic oral candidiasis resulting in fixed mucosal white patches; immune defect may be detected but sometimes idiopathic; some types associated with endocrine or thymus disease; nails often affected, other mucosal sites may also be involved

streptococci) may cause angular stomatitis. Unless the classic golden yellow crusts associated with *S. aureus* are present, treatment should be commenced with antifungal drugs, e.g. a combined miconazole/hydrocortisone cream (miconazole has some antibacterial properties). When clinical features indicate *S. aureus* infection, fusidic acid cream is appropriate. If intra-oral candidiasis is present, this must be treated concurrently or recurrence of the angular stomatitis will occur. Iron deficiency is a significant aetiological factor in angular cheilitis.

Aspergillosis

Aspergillus sp. infection is sometimes encountered in the maxillary sinus in severe immunosuppression or in association with zinc-containing endodontic material inappropriately extruded through the roots of maxillary molars.

Chronic hyperplastic candidiasis

Oral white and red lesions may be seen in oral infections with *C. albicans*. Chronic hyperplastic candidiasis is a particular form of candidiasis that presents as a persistent white plaque that cannot be scraped off. Smoking and continuous denture wearing are the main predisposing factors, although the condition may also be associated with reduced immunity.

Clinical features

- Dense white rough or nodular patch
- Typically found on the buccal mucosa adjacent to the angle of the mouth
- Often bilateral, may be multifocal
- Associated with smoking and poor denture hygiene habits.

Histopathological features

- Epithelial acanthosis and parakeratosis resulting in broad, blunt rete processes
- Candidal pseudohyphae penetrate the parakeratin layer
- Neutrophils form microabscesses in the parakeratin layer
- Intense diffuse chronic inflammatory infiltrate present in the lamina propria
- May regress following elimination of local predisposing factors and antifungal therapy (often systemic antifungal drugs are used)
- If microscopic dysplasia found (~40% cases) then the lesion may be clinically classified as **candidal leukoplakia**.

Median rhomboid glossitis

Median rhomboid glossitis is an abnormality of the midline dorsal tongue where a lozenge-shaped, smooth or nodular red flecked area of depapillated mucosa is found. A corresponding area of erythema may be present on the palate. It is often (but not always) associated with candidal infection and *Candida* can often be recovered. Further investigation and treatment are usually unnecessary. Treatment, with topical antifungal agents, is only normally indicated if the lesion gives rise to discomfort.

11.5 Lichen planus

Learning objectives

You should:

- know the types of lesion that can occur
- know how to diagnose lichen planus
- understand the possible aetiology and, therefore, the management.

Lichen planus is a common condition affecting around 1% of the population and involving skin and mucous membranes. The peak incidence is in the third to sixth decades, 60% in females.

Clinical features

Oral lesions

Oral lesions are classically bilateral and affect the buccal mucosa and lateral aspects of tongue; gingivae may show red atrophic appearance ('desquamative gingivitis'). The palatal mucosa is usually spared. Atypical distribution of lesions is suggestive of a lichenoid reaction; the possibility of lupus erythematosus should also be considered in these circumstances. Three clinical variants of oral lichen planus are recognised:

- non-erosive type: most common, typically painless
- minor erosive type: areas of redness and superficial ulceration
- major erosive type: atrophy, redness and extensive ulceration.

Oral lesions of various types may occur in any of the variants of lichen planus:

- reticular lesions: network or linear white bands (Fig. 149)
- plaque lesions: white patches
- papular lesions: small white spots, which may join up
- annular lesions: circular arrays of white lines
- atrophic lesions: diffuse red areas
- erosive lesions: extreme atrophy leading to ulceration (Fig. 150)
- bullous lesions: blood-filled blisters, rare type.

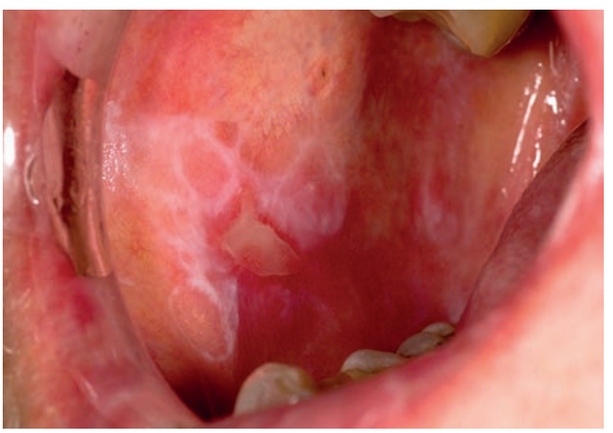

Fig. 149 Lichen planus, showing typical reticular lesions.

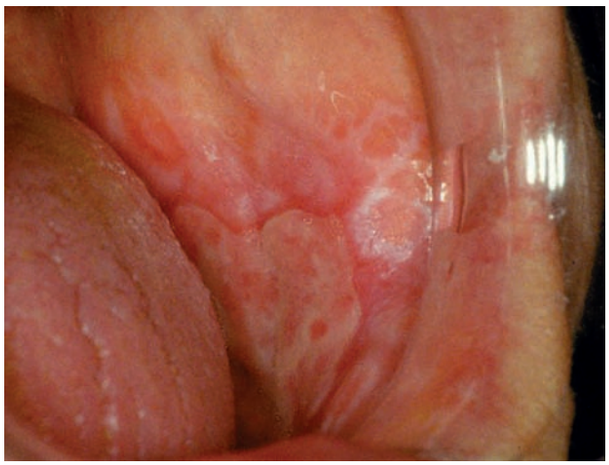

Fig. 150 Lichen planus showing erosive and superficially ulcerated lesions.

Skin lesions

Skin lesions are classically violaceous, itchy macules and papules on the flexor surfaces. The papules show distinctive white lines, termed Wickham's striae. They may be more widespread on the trunk. Fingernails may be ridged or atrophied. The scalp may be involved, leading to hair loss. In females, the vulva and, far less commonly, the vagina may be affected.

Lichenoid mucositis

Lichenoid mucositis is a clinical term for conditions that have similar clinical features, such as lichenoid reaction (drugs and restorative materials), lupus erythematosus and graft-versus-host disease. Lichenoid reaction due to amalgam is increasingly recognised clinically where restorations are in direct contact with the oral mucosa.

Histopathological features

Appearances vary and successful diagnosis depends on adequate biopsy from a representative site (Fig. 151):

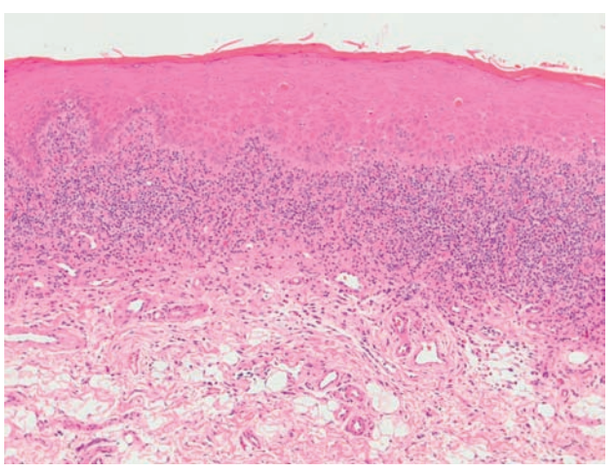

Fig. 151 Lichen planus, showing the subepithelial band of lymphohistiocytic infiltrate and basal-cell degeneration.

- epithelium varies in thickness and may show keratosis or atrophy
- subepithelial band of T lymphocytes and histiocytes
- T lymphocytes 'cross' the basement membrane into epithelium
- basal-cell liquefaction and degeneration
- apoptosis of basal cells results in Civatte (colloid) bodies
- 'sawtooth' rete processes, typical of skin lesions, not always seen.

Ulceration may alter the characteristic features.

Aetiology

The cause of lichen planus is not known, though it has been linked with hepatitis C infection in southern European peoples. Skin lesions tend to be transitory, while oral lesions are more persistent. Non-erosive lichen planus is often not symptomatic. Biopsy is required, however, to establish a tissue diagnosis. Erosive lichen planus is also considered as a premalignant condition and appropriate advice about alcohol, paan and tobacco as risk factors for oral cancer should be given. Regular review may be required in some cases.

Management

Treatment is indicated for those patients who experience oral discomfort. It is important that patients appreciate that such treatment should alleviate their symptoms but will not 'cure' the condition, which may persist for several years. Treatment should be adjusted to match the fluctuations in disease severity that characterise oral lichen planus. Modification of diet by avoiding foods that are acidic, spicy, salty or that have a rough texture can reduce discomfort at meal times, and changing to a bland toothpaste makes good oral hygiene easier to maintain. The latter is particularly important when the gingivae are involved as plaque and calculus act as aggravating factors. Mild symptoms may be controlled by the use of an analgesic mouthwash or spray such as benzydamine hydrochloride; however, topical steroids are often required. These are available as:

- pastes, e.g. triamcinolone dental paste
- lozenges to be dissolved in the mouth, e.g. hydrocortisone lozenges
- soluble tablets used to make up a mouthwash, not to be swallowed, e.g. betamethasone sodium phosphate
- inhalers sprayed onto the affected areas, e.g. beclomethasone diproprionate.

If the latter two types of preparation are felt to be necessary, a specialist oral medicine opinion should be sought prior to their prescription.

Choice of medication is determined by disease severity and the sites involved. If the painful lesions are localised to one or two areas that are easily accessible to the patient, then triamcinolone paste is a reasonable choice. If, however, the lesions are generalised, then a steroid mouthwash would be more appropriate. For severe cases, systemic medication is indicated, for example systemic steroids in combination with the immunosuppressant azathioprine, which should only be prescribed by a hospital-based specialist.

Where a lichenoid drug reaction is suspected, the possibility of changing the medication believed to be responsible should be raised with the patient's general practitioner, who needs to balance any risks associated with such a change against the benefits to the patient. Patch testing to restorative materials can be carried out but may not always be indicated if there is a close anatomical relationship between the restorations and the patient's lesions. Again the decision to replace any restoration must take into account the possible benefits to the patient.

11.6 Pigmented lesions

Learning objectives

You should:
- know how to distinguish extrinsic and intrinsic pigmentation
- know which lesions require further investigations.

Pigmentation of the oral mucosa can be extrinsic or intrinsic. Extrinsic pigmentation is usually easily recognised and common causes are regular chlorhexidine rinsing and paan chewing, which produces an orange–brown discoloration. Natural racial oral pigmentation is prominent in dark-skinned races and sometimes can be a confusing finding in individuals of mixed race.

Black hairy tongue

Black hairy tongue is caused by overgrowth of filiform papillae accompanied by bacterial pigmentation from commensal flora. In reality, it is often brown in colour and, although harmless, may cause anxiety for the patient. Increasing friction to the dorsal mucosa by gentle rubbing with a toothbrush or sucking a peach stone can be effective remedies.

Amalgam tattoos

Amalgam tattoo presents as an area of grey–black discoloration of the mucosa (Fig. 152). It is caused by entry of dental amalgam into the mucosa at the time of placement of amalgam restorations or during dental extractions. As the amalgam corrodes, particles are taken up by macrophages and collagen fibres become stained by the silver component. The lesion may appear to enlarge clinically.

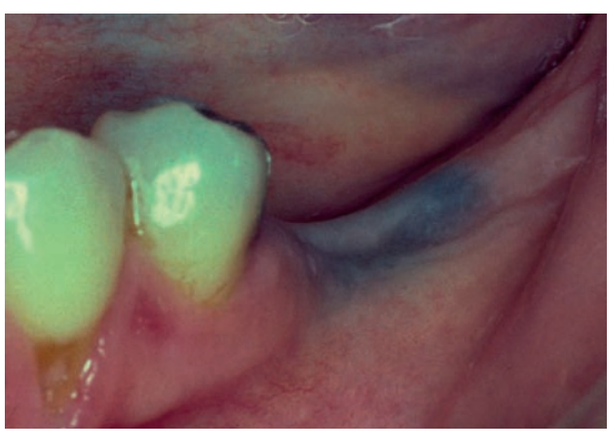

Fig. 152 An amalgam tattoo on the alveolar ridge.

Radiographs will usually reveal amalgam particles in the tissue, but sometimes excision biopsy is performed to exclude a melanotic lesion.

Melanotic lesions

Melanotic lesions can be focal or diffuse.

Discrete melanin-pigmented lesions. Intra-oral pigmented naevi or oral focal melanosis are discrete lesions. Multiple pigmented oral and circumoral macules can be a manifestation of Peutz–Jeghers syndrome. Oral and nail pigmentation is found in Laugier–Hunziker syndrome.

Malignant melanoma. This is a diffuse lesion, presenting mostly on the palate or gingivae as a spreading area of pigmentation, which may evolve into a nodular ulcerated tumour. Early diagnosis can lead to excision and cure but nodular lesions have a poor prognosis.

Diffuse oral melanosis. A diffuse melanosis can be seen in melanin incontinence. This is caused by increased release of melanin in response to chronic irritation, such as smoking, or chronic inflammatory disease involving the oral mucosa. Increased adrenocorticotrophic hormone secretion in Addison's disease may cause diffuse mucosal pigmentation particularly in areas subject to chronic low-grade trauma, e.g buccal mucosa at and around the level of the occlusal plane. Drugs and heavy metal exposure can cause increased oral pigmentation.

Other lesions

Drugs, HIV infection and ingestion of heavy metals can cause oral pigmentation. Blood breakdown products may be deposited in the oral mucosa in jaundice and haemochromatosis.

11.7 Vesiculo-bullous lesions

Learning objectives

You should:
- know the potential causes for oral vesicles or bullae
- know the features of the main diseases producing oral vesiculo-bullous lesions.

A vesicle is a small fluid-filled lesion (blister) affecting skin or mucosa; larger fluid-filled lesions are referred to as bullae. Vesiculo-bullous lesions involving the oral mucosa may be seen in:

- viral infections
- traumatic injury
- drug reactions
- genetic disorders
- autoimmune conditions.

Immune-mediated conditions

Benign mucous membrane pemphigoid

Benign mucous membrane pemphigoid (cicatricial pemphigoid) is an autoimmune disease, characterised by blisters and erythematous lesions affecting the oral mucosa, conjunctiva and vulvovaginal region. The oral mucosa may be the only site affected clinically but

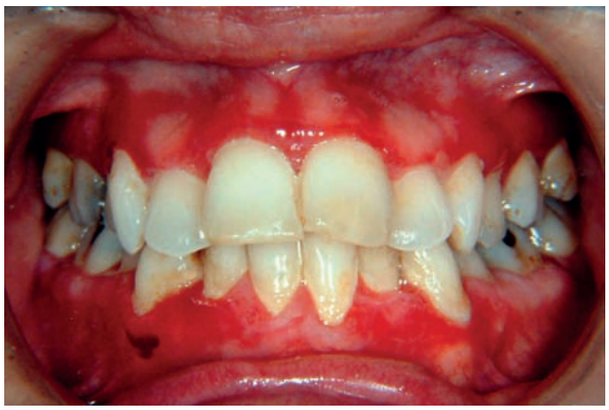

Fig. 153 Desquamative gingivitis. The atrophic, erythematous appearance can be caused by a number of diseases. This example is cicatricial pemphigoid.

examination by an ophthalmologist is always indicated. Pemphigoid may present as desquamative gingivitis (Fig. 153), though other disorders such as lichen planus may also cause red, shiny, tender attached gingivae. Autoantibodies, most commonly IgG, react with a variety of targets around the basement membrane causing loss of adherence of epithelial hemidesmosomes, and formation of a **subepithelial blister**. Laminin V is a common antigenic target, but molecular heterogeneity is recognised and accounts for the variations in clinical features. Diagnosis is based on direct immunofluorescence testing of a fresh biopsy of perilesional mucosa. Circulating autoantibodies may be detected but only if a sensitive indirect immunofluorescence technique is used employing salt-split skin. Specialist referral is necessary when this diagnosis is suspected, particularly in view of the scarring, which may lead to blindness if there is conjunctival involvement. Where oral involvement alone is present, topical steroid treatment may be sufficient to control the disease. As with lichen planus, the maintenance of good oral hygiene is an important adjunct to treatment when desquamative gingivitis is present. When oral lesions are unresponsive to topical steroids, or present in conjunction with other manifestations of the disease, systemic treatment is appropriate. There is evidence for the efficacy of dapsone and drugs drawn from the sulphonamide group of antibiotics, such as sulfapyridine and sulfamethoxypyridazine.

Pemphigus vulgaris

Pemphigus vulgaris is a less common autoimmune vesiculo-bullous disease with life-threatening potential. In approximately 50%, blisters appear first in the oral cavity, but the skin may be involved at the outset or later. The oral mucosa is painful, and blisters appear readily at sites of minor injury. Sloughing may occur and the appearances can resemble a burn. Autoantibodies, most commonly IgG, react with a component of desmosomes called desmogleins, in particular desmogleins 3 and 1. This causes stearic hindrance within the desmosomal attachment and the suprabasal oral epithelial cells separate, forming an **intra-epithelial blister**. Separation in this way is known as acantholysis. Diagnosis is made by direct immunofluorescence on fresh biopsy or cytological material. Referral to a specialist is essential when this diagnosis is suspected. The use of topical steroids may be of benefit for oral lesions but is only an adjunct to systemic treatment, most commonly with steroids and a steroid-sparing immunosuppressant such as azathioprine.

Other autoimmune conditions

Bullous pemphigoid, linear IgA disease, dermatitis herpetiformis and epidermolysis bullosa acquisita are characterised by the presence of skin lesions but oral involvement is often reported in each.

Erythema multiforme

Erythema multiforme is typified by recurrent bullous eruptions. Crusted haemorrhagic bullae are often seen on the lips, the oral mucosa, eyes and genital area. Target lesions sometimes occur on the skin. Sites may be affected in isolation or in combination. In rare severe disease, there may be febrile illness and hospital admission may be needed. Diagnosis is primarily made on clinical grounds, although the oral lesions may mimic primary herpetic gingivostomatitis. The disorder is believed to be an immunologically mediated hypersensitivity reaction. Attacks may be triggered by recurrent herpetic lesions, drugs or chemicals. During the acute phase, systemic steroids may be prescribed if not contraindicated, and it is important to ensure that fluid intake is maintained. Antiseptic mouthrinses may be used to prevent secondary infection. It is then important to establish the cause and prevent exposure to the causative agent if possible. Prophylactic acyclovir is generally prescribed to prevent herpetic-induced attacks.

Genetic disorders

Genetic disorders where there is derangement of the components of the mucosa may cause oral blisters. An example is one form of epidermolysis bullosa, where there is a mutation of the collagen VII gene resulting in defective anchoring fibrils.

Angina bullosa haemorrhagica

Angina bullosa haemorrhagica is characterised by the appearance of recurrent blood blisters in the oral mucosa. The most commonly affected site is the posterior hard and soft palate, where the blood-filled blisters suddenly appear and may reach 2 cm in diameter. Other sites in the oral cavity can be affected. It is necessary to exclude bleeding disorders and autoimmune diseases, but then patients can be reassured that the condition is harmless. Associations with the use of steroid inhalers applied without a nebuliser, the eating of rough foodstuffs and the taking of very hot drinks have been reported, and these risk factors should be considered in providing advice. Some clinicians advise pricking any fresh lesions with a sterilised needle to release the blood and speed healing. If discomfort is experienced the use of an analgesic mouthwash such as benzydamine hydrochloride may be of benefit.

11.8 Granulomatous disorders

Learning objectives

You should:
- know what a granuloma is and how to investigate it
- know the potential causes of granuloma.

A granuloma is a collection of macrophages in tissue and granulomas are found in a number of local and systemic disorders of the oral mucosa.

Investigation

A deep mucosal biopsy is needed for diagnosis because granulomas may only be seen in the underlying muscle. Granulomas are typically non-caseating and consist of mononuclear macrophages, epithelioid macrophages and Langhans giant cells. Lymphoedema, dilated lymphatic channels and scattered chronic inflammatory cells are also found in the lamina propria, often around small vascular channels. When patients present with the oral features of Crohn's disease, referral to a gastroenterologist or other specialist is necessary.

Causes of granulomas

Foreign body

Foreign-body granulomas can form around implanted materials such as retained sutures, restorative materials and even vegetable pulses, the last sometimes resulting in a proliferative periostitis.

Orofacial granulomatosis

Orofacial granulomatosis is a generic and rather imprecise term used to describe a number of disorders characterised by the presence of granulomas in the oral mucosa. It has been associated with food allergies, such as to benzoates and cinnamaldehydes used as preservatives or flavourings. Minor changes may be present in the gastrointestinal tract on endoscopy.

Crohn's disease

Crohn's disease is a chronic granulomatous disorder of the gastrointestinal tract. Lesions are most common in the terminal ileum. Skip lesions are characteristic. The oral manifestations (Fig. 154) are:

- diffuse swelling of the lips and cheeks
- cobblestone mucosa
- mucosal tags and folds resembling irritation hyperplasia
- angular cheilitis
- aphthous or deep slit-like non-healing ulcers
- granular gingivitis
- glossitis, related to haematinic deficiency.

Sarcoidosis

Sarcoidosis is a multisystem chronic granulomatous disorder affecting predominantly young adults. Pulmonary, lymph node, skin, salivary and eye lesions are most common. Oral lesions present as submucosal nodules, erythema, or granular gingival patches.

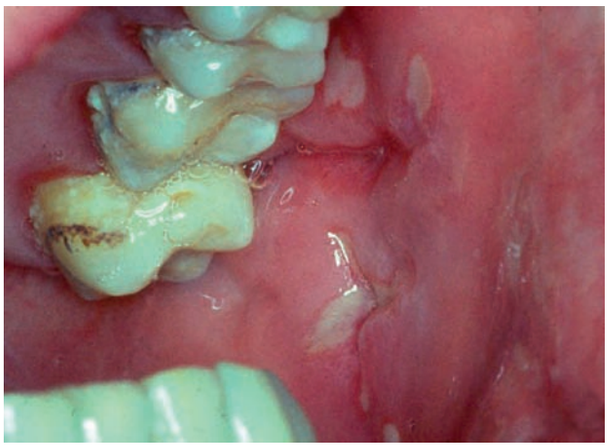

Fig. 154 Crohn's disease, showing cobblestone mucosa and slit-like fissure ulcers.

Wegener's granulomatosis

Wegener's granulomatosis is an autoimmune vasculitic disorder. Strawberry hyperplastic gingival lesions, palatal ulceration and delayed healing may all be presenting signs. Antineutrophil cytoplasmic antibodies (ANCA) can be detected in the circulation. Histopathologically, fibrinoid necrosis of vessels, dense active chronic inflammatory infiltrate and multinucleated giant cells may be found.

11.9 Other mucosal conditions

Learning objectives

You should:
- know how to identify white sponge naevus
- know how to identify geographic tongue
- know how to identify epulides
- be able to differentiate the harmless or minor conditions from potentially serious diseases with similar appearance.

There are a number of harmless or minor conditions that give rise to mucosal lesions very similar to those associated with serious disorders. Some of these have been covered earlier in the chapter in association with the diseases of similar appearance:

- leukoedema
- median rhomboid glossitis
- some pigmented lesions
- angina bullous haemorrhagica.

White sponge naevus

White sponge naevus is an autosomal dominant condition in which the oral mucosa is white, soft and shows irregular thickening (Fig. 155). Often, the entire oral cavity is affected, but the condition may manifest in patches. In some patients, the anus and genital mucosa is also affected.

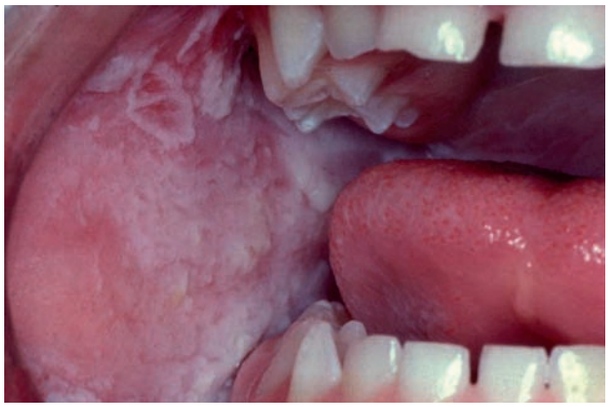

Fig. 155 White sponge naevus. The buccal mucosa appears folded and spongy.

Mutations in keratin genes 4 and 13 have been identified as a cause.

Diagnosis

Diagnosis is by family history and clinical features. The white areas are diffuse and characteristically folded.

Biopsy is only undertaken in cases of doubt; it shows epithelial hyperplasia, parakeratosis and typical 'basket-weave' appearance.

Management

No treatment is needed; patients can be reassured that there is no risk.

Geographic tongue

Geographic tongue is also known as erythema migrans. It is a common benign disorder of uncertain aetiology sometimes associated with soreness and discomfort of the tongue. Irregular smooth red areas with sharply defined edges appear on the dorsal surface of the tongue. These extend, heal and are then replaced by new lesions in other areas. Sometimes a pale white or yellow raised margin is seen. Rarely other areas of the mucosa may be affected.

Diagnosis

Diagnosis is usually based on clinical features alone; biopsy is only undertaken in cases of doubt. The histopathological appearances are of epithelial thinning and active chronic inflammatory inflammation, with neutrophils in the oral epithelium.

Management

Control of symptoms may be achieved by using an analgesic mouthwash such as benzydamine hydrochloride.

Epulides

An epulis is defined as a localised swelling on the gingivae. A variety of diseases may present as a localised gingival swelling, including primary and metastatic cancers and peripheral extensions of underlying bone lesions. For this reason, a radiograph should always form part of the investigations for an epulis and excised epulides should be examined by a histopathologist. Generally the term epulis is reserved for three common reactive lesions, which arise most often in the anterior part of the oral cavity.

Fibrous epulis. This is the equivalent of fibro-epithelial polyp arising on the gingiva. Chronic irritation, from calculus and defective restorations, is a common cause. Fibrous epulis has a core of dense collagenous tissue. Calcification and even ossification may be present and these features are linked with recurrence. The core is covered by epithelium, which may be ulcerated or keratotic.

Vascular epulis. This presents as a red, fleshy gingival swelling, which sometimes has a thick fibrinous crusted surface and a collar of regenerating epithelium at its base (Fig. 156). It is associated with hormonal changes in puberty and pregnancy but may arise as a result of local irritative factors. Growth is usually rapid and recurrence is possible, especially in pregnancy. It is the histopathological equivalent of pyogenic granuloma, being composed of a core of vascular granulation tissue with a variable chronic inflammatory infiltrate and fibrinous crust.

Giant-cell epulis (peripheral giant-cell granuloma). It arises as a red or brown–purple friable swelling. Histopathologically, there are foci of osteoclast-like multinucleated giant cells in a background of fibroblasts and mononuclear precursor cells. A rich vascular plexus composed of thin-walled channels is characteristic. The lesion is covered by mucosa. This lesion must be distinguished from central giant-cell granuloma and hyperparathyroidism; this can be achieved in the first instance radiographically with subsequent biochemical investigations if a central lesion is identified.

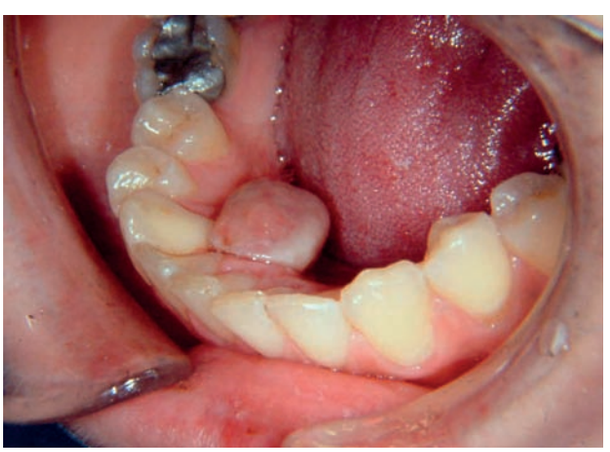

Fig. 156 Vascular epulis. Note the epithelial collarette at the base and ulcerated surface.

Self-assessment: questions

Multiple choice questions

1. In vesiculo-bullous disorders involving the oral cavity:
   a. A positive Nikolsky's sign is only found in pemphigus vulgaris
   b. Mucous membrane pemphigoid is typified by subepithelial bullae
   c. Circulating autoantibodies are present at a high titre in mucous membrane pemphigoid
   d. Mucous membrane pemphigoid (MMP) is the most common cause of desquamative gingivitis
   e. Prompt fixation of a mucosal biopsy is required for successful direct immunofluorescence testing
2. Recurrent aphthous ulceration (RAU):
   a. Affects up to 10% of the population
   b. Usually onsets during the first 2 years of life
   c. Is nearly always related to underlying iron, folate or vitamin B_{12} deficiency
   d. Herpetiform aphthae may involve the hard palate
   e. Severe aphthous stomatitis may be a feature of HIV infection
3. The oral lesions of lichen planus:
   a. Typically exhibit sawtooth rete ridges in biopsies
   b. On the gingiva are most commonly reticular in nature
   c. Are most commonly bilateral and often symmetrical
   d. Are typically associated with a subepithelial band of infiltrating B lymphocytes
   e. Often improve clinically with topical corticosteroid therapy
4. In oral candidiasis:
   a. Most pathogenic *Candida* species involving the oral cavity are dimorphic
   b. *Candida* species never invade the oral epithelium
   c. Diffuse chronic mucocutaneous candidiasis may be associated with endocrine abnormalities
   d. Miconazole can be absorbed systemically from its oral gel preparation (Daktarin oral gel)
   e. *Candida* carriage rates are higher in smokers than in non-smokers
5. Oral manifestations of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS):
   a. Initial infection is not associated with oral manifestations
   b. Hairy leukoplakia is an AIDS-defining lesion
   c. Kaposi's sarcoma is caused by cytomegalovirus
   d. HIV infection may result in salivary gland lesions
   e. Oral candidiasis is the most common oral manifestation of AIDS
6. Gingival enlargements:
   a. Generalised gingival overgrowth may be caused by tacrolimus
   b. An epulis may occur in any part of the oral cavity
   c. Chronic lymphatic leukaemia is the most frequent type of leukaemia associated with gingival enlargement
   d. May be caused by an autosomal dominant gene
   e. Excessive gingival overgrowth in transplant recipients should be trimmed away under local anaesthesia in the dental surgery
7. Mucosal manifestations of systemic disease:
   a. Coeliac-associated recurrent oral ulceration can be detected by testing for α-gliadin autoantibodies
   b. Cobblestone mucosa, fissure ulcers and mucosal tags are found exclusively in Crohn's disease
   c. Chronic iron deficiency may be linked to the finding of oral epithelial dysplasia in mucosal biopsies
   d. Pyostomatitis vegetans is a manifestation of ulcerative colitis
   e. Diffuse mucosal pigmentation may be seen in Addison's disease
8. Herpes virus infections of the oral mucosa:
   a. Herpes simplex virus type II infections may cause primary herpetic gingivostomatitis
   b. Acyclovir cream applied twice daily is the most appropriate treatment for recurrent intra-oral herpes simplex infection
   c. Herpes simplex is an RNA retrovirus
   d. Herpes simplex infection may rarely cause serious gastroenteritis in neonates
   e Herpangina is a clinical variant of herpes simplex infection that results in painful vesicles affecting the soft palate and oropharynx.
9. White sponge naevus:
   a. Is an autosomal recessive disorder
   b. Is restricted to the oral mucosa
   c. Exhibits hyperparakeratosis, spongiosis and a basketweave appearance in biopsies
   d. Is caused by a mutation in the gene *APC*
   e. Is a premalignant condition
10. The tongue may:
    a. Become enlarged in amyloidosis
    b. Show migratory glossitis as an indicator of systemic disease
    c. Develop a lozenge-shaped red patch on the midline dorsal mucosa as a result of candidiasis
    d. Become smooth and red as a result of sickle cell anaemia
    e. Become covered by pigmented hyperkeratotic filiform papillae in Peutz–Jeghers syndrome.

Extended matching items

EMI 1. Theme: Pathology of gingival erythematous lesions

Options:

A Lichen planus
B Mucous membrane pemphigoid
C Erythroplakia
D Plasma-cell mucositis
E Pemphigus vulgaris
F Leukaemia

G Linear gingival erythema
H Primary herpetic gingivostomatitis
I Wegener's granulomatosis
J Peripheral giant-cell granuloma

Lead in: Match the case history from the list below that is most appropriate for each diagnosis above.

1. A 55-year-old woman presented with oral soreness progressively worsening over a 3-month period. The attached gingivae were brightly erythematous and small haemorrhagic blisters were seen in places. She also had redness of the conjunctiva and an ophthalmologist found that symblepharon was present.
2. A 60-year-old man presented with velvety red gingival patches. He smoked 10 cigarettes per day and drank 40 units of alcohol each week. An incisional biopsy was reported as showing basal-cell hyperplasia with formation of drop-shaped rete processes and moderate cellular atypia.
3. A 30-year-old woman developed enlarged gingival papillae that were strawberry red. Ulceration of the soft palate was present and she experienced nose bleeds. The cANCA test was positive and a biopsy of mucosal tissue showed vasculitis, multinucleated giant cells and accumulations of neutrophils.
4. A 50-year-old woman developed itchy red-purple raised and flat lesions on her wrists and ankles. Her dentist diagnosed desquamative gingivitis and referred her to an oral medicine specialist. Faint white striae were noticed on the buccal mucosa and a biopsy was performed.
5. A 26-year-old Yemeni man presented with widespread bright red granular lesions on the gingivae and palate. He chewed Khat (Qat) leaf, a habit that is popular in the Yemen. The lesions regressed when he abstained from chewing.
6. A 9-year-old child presented to the dentist with sore red gums, coated tongue, and tender cervical lymphadenopathy of 1 week's duration. On close examination a few recently ruptured vesicles were spotted on the hard palate.
7. A 25-year-old HIV positive man who was non-compliant with therapy presented with redness of the attached gingivae. A direct smear showed a tangled mass of *Candida albicans* pseudohyphae.
8. A 70-year-old man developed enlarged red gingival papillae, with continuous oozing of blood from the crevice. He also had been experiencing haematuria and had been unwell for 3 weeks.
9. A 53-year-old woman presented with an increasingly sore mouth over a 6-month period. The oral mucosa peeled away with light pressure and a biopsy showed suprabasal intra-epithelial splitting.
10. A 38-year-old man presented with an enlarged interdental papilla that was red-brown in colour. An excision biopsy was performed and the pathologist reported the presence of foci of multinucleated giant cells, haemosiderin, thin-walled vessels and red cells in the tissue.

EMI 2. Theme: Pathology of oral mucosa

Options:

A Hairy leukoplakia
B Minor aphthae
C White sponge naevus
D Haemangioma
E Nicorandil-related ulceration
F Smoker's keratosis
G Chronic hyperplastic candidosis
H Fordyce spots
I Amalgam tattoo
J Traumatic ulcerative granuloma with stromal eosinophils

Lead in: Match the case history from the list below that is most appropriate for each diagnosis above.

1. A 63-year-old man with severe angina complained of deep painful and persistent ulcers in the mouth.
2. A 29-year-old man who had had a renal transplant 2 years ago noticed bilateral white plaques and papillary lesions on the lateral borders of his tongue.
3. A 13-year-old boy complained of crops of ulcers affecting the buccal mucosa, vestibule and undersurface of tongue.
4. The parents of a 4-year-old child noticed that his entire oral lining had a white folded appearance. The child had not experienced any oral symptoms.
5. A 60-year-old man presented with an indurated ulcer on the lateral border of the tongue. He was a heavy smoker and a biopsy was taken to exclude squamous carcinoma.
6. A vocational trainee dentist noticed that one of her new patients had widespread areas of 1–2 mm yellowish lesions on the buccal mucosa on both sides of the oral cavity.
7. A 47-year-old patient was referred because the dentist was concerned about a pigmented patch on the alveolus that had increased in size since the patient's last visit.
8. White lesions with a crazy-paving appearance and red spots were noticed on the soft palate of a 53-year-old man. The patient said that he smoked in the past but had given up.
9. A 23-year-old woman complained of pigmented raised lumps on the tongue. On examination these were found to blanch under gentle pressure.
10. A 55-year-old complete denture wearer presented with white lesions on the buccal mucosa at behind the angle of the mouth. On biopsy the pathologist noted acanthosis, hyperrparakeratosis and broad blunt test-tube-shaped rete processes. Microabscesses were present in the parakeratin layer.

Case history questions

Case history 1

A 68-year-old woman developed severe mouth ulcers, some of which tended to recur at the same sites. Her medical history was clear apart from angina, which was poorly controlled. She took 75 mg aspirin daily and nicorandil.

1. How might the drug therapy relate to her oral ulceration?
2. What investigations should be undertaken?
3. Which agents might be prescribed for symptomatic relief?

Case history 2

A 46-year-old schoolteacher noticed white thickening of the buccal mucosa after reading about oral leukoplakia on a health website. He consulted his general dental practitioner who reassured him and referred him for specialist opinion. At the clinic, the specialist found that there were white bands at the level of the occlusal plane on the buccal mucosa and noted marked wear facets on the teeth.

1. What clinical diagnosis is most likely?
2. Why might the teeth show marked wear facets?
3. How could the diagnosis be established without recourse to mucosal biopsy?
4. If a biopsy of the buccal mucosa was taken, which features would you expect to be present?

Case history 3

A 36-year-old bank clerk was concerned about the sudden appearance of blood-filled blisters, which were occurring with increasing frequency on the roof of his mouth. Some reached to 2 cm across and were painful until they burst. He was medically fit and well and his asthma, present since childhood, was well controlled.

1. What is the most likely diagnosis?
2. What investigations should be undertaken?
3. What is the possible link with his asthma?
4. What advice should be given to prevent further lesions?

Case history 4

An 8-year-old boy presented with soreness and crusting at the angles of the mouth. Swabs and smears were taken which revealed *Candida* species and *Staphylococcus aureus* infection. The condition responded well to cream applied daily. One year later he returned with persistent swelling of the lips and on examination was found to have lobulated buccal mucosa, ulceration and red, granular gingivitis. A biopsy of the buccal mucosa was taken and he was subsequently referred to a paediatric gastroenterologist.

1. Suggest suitable creams which might be used to treat the initial complaint.
2. Which condition is present at re-presentation?
3. What might be seen in the biopsy?
4. Why was referral to a physician needed?

Case history 5

Figure 157 shows the buccal mucosa of an Italian member of the tifosi. He was otherwise fit and well although he felt stressed when his favourite motor racing team was losing, at which times his condition tended to flare up. His medical history was clear apart from his having had rheumatic fever and hepatitis C in childhood.

1. What lesions are present on the buccal mucosa?
2. List the features you would expect to see in a biopsy of the buccal mucosa.
3. What is the link with his medical history?

Viva questions

1. What are the common causes of diffuse oral pigmentation?
2. Which topical steroid preparations are available for use in the mouth? How would you advise patients to apply them?
3. What factors should you take into account when taking a mucosal biopsy to aid the pathologist?
4. Why are both swabs and smears taken for the diagnosis of suspected *Candida* infection?
5. How would you manage an elderly patient with submucous fibrosis?
6. What are the three common histological types of epulis?
7. Which mucosal lesions are strongly associated with HIV infection?
8. What are the possible oral manifestations of leukaemia?

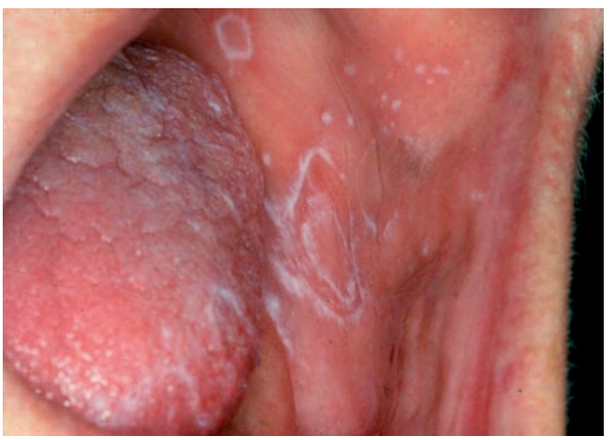

Fig. 157 The buccal mucosa of the patient in Case history 5.

Self-assessment: answers

Multiple choice answers

1. a. **False.** Nikolsky's sign is the formation of a blister when lateral pressure is applied to skin or mucosa. It is found in pemphigus, some forms of mucous membrane pemphigoid and other vesiculo-bullous dermatoses.
   b. **True.** The antigenic targets are located in and around the hemidesmosome/basement membrane complex.
   c. **False.** Sensitive detection systems are required to detect circulating autoantibodies in MMP. Mucosal biopsy is usually performed.
   d. **False.** Lichen planus is the most common cause of desquamative gingivitis. It may also be caused by mucous membrane pemphigoid, pemphigus, plasma cell mucositis and allergic reactions.
   e. **False.** Perilesional mucosa is required for direct immunofluorescence and the tissue must be snap-frozen or submitted to the laboratory in special transport medium.

2. a. **False.** Most estimates suggest that over 20% of the population are affected by RAU.
   b. **False.** Onset can be at any age but most commonly occurs at puberty.
   c. **False.** Haematinic deficiency may be found in up to 25% of RAU patients, in some populations.
   d. **True.** Herpetiform and major RAU may involve keratinised oral mucosa.
   e. **True.** Severe and atypical RAU has been reported in HIV sufferers.

3. a. **False.** Sawtooth rete ridges are characteristic of lichen planus in skin biopsies and are found in less than one-third of oral biopsies.
   b. **True.** Striae may be conspicuous or evident on close examination of gingival lesions in desquamative gingivitis caused by lichen planus.
   c. **True.** Solitary patches of lichenoid mucositis may be a reaction to dental materials.
   d. **False.** The subepithelial infiltrate typically comprises mostly T lymphocytes and histiocytes. A few B lymphocytes may be present.
   e. **True.** Topical corticosteroids are often used to treat symptomatic erosive lichen planus.

4. a. **True.** Most candidal infection is caused by *C. albicans*; other species such as *C. glabrata*, *C. krusei*, *C. tropicalis* and *C. parapsilosis* may cause oral infection. All are dimorphic.
   b. **False.** In chronic hyperplastic candidiasis (candidal leukoplakia), pseudohyphae invade the parakeratin layer.
   c. **True.** Autoimmune polyendocrinopathy syndrome is a rare autosomal recessive disorder; it is one form of diffuse mucocutaneous candidiasis.
   d. **True.** Significant systemic absorption of miconazole may occur and has been reported to potentiate the action of warfarin, resulting in severe purpura.
   e. **True.** Carriage rates are also increased in pregnancy and in denture wearers.

5. a. **False.** Initial HIV infection may be asymptomatic or may be associated with a 'flu-like illness, diarrhoea and a generalised stomatitis.
   b. **False.** Hairy leukoplakia is a warty plaque caused by Epstein–Barr virus overgrowth and occurs in CD4-cell lymphopenia related to HIV and non-HIV disorders.
   c. **False.** Kaposi's sarcoma is caused by human herpesvirus 8 (HHV-8), endemic in Mediterranean regions.
   d. **True.** HIV infection is associated with lymphoepithelial salivary cysts, dry mouth and malignant lymphoma.
   e. **True.**

6. a. **False.** Drug-induced gingival overgrowth (DIGO) is associated with phenytoin, ciclosporin and calcium-channel-blocking drugs such as nifedipine.
   b. **False.** An epulis is a localised swelling of the gingivae.
   c. **False.** Acute leukaemia more typically results in enlargement of the gingivae, through infiltration by leukaemic cells.
   d. **True.** Hereditary gingival fibromatosis is known to be caused by mutation of the SOS-1 gene on chromosome 2p.
   e. **False.** Excessive bleeding has been reported and such cases are best referred for specialist care.

7. a. **False.** Testing for α-gliadin antibody has been replaced by testing for endomysial or tissue transglutaminase antibody. A positive result should trigger referral to a gastroenterologist for further investigation.
   b. **False.** These features may be seen in orofacial granulomatosis.
   c. **True.** This is important particularly in the Plummer–Vinson syndrome.
   d. **True.**
   e. **True.**

8. a. **True.** However, herpes simplex type I is the more common cause.
   b. **False.** Acyclovir cream is not suitable for intra-oral use; systemic acyclovir may be prescribed if necessary.
   c. **False.** Herpes simplex is a DNA virus.
   d. **False.** It may rarely cause encephalitis.
   e. **False.** Herpangina is caused by coxsackievirus A.

9. a. **False.** White sponge naevus is an autosomal dominant disorder.
   b. **False.** It may also involve the anogenital region, nose and oesophagus.
   c. **True.** Biopsy is only made if there is doubt about the diagnosis.

d. **False.** It is caused by mutations in the genes for keratin 4 and 13.
e. **False.** Other very rare forms of hereditary white patch, such as those associated with tylosis and dyskeratosis congenita, are associated with malignancy.

10. a. **True.**
b. **False.** Migratory glossitis (geographic tongue) is not linked to systemic disease.
c. **True.** This is termed median rhomboid glossitis.
d. **False.** A red, beefy tongue is seen in haematinic deficiency.
e. **False.** Black hairy tongue is not a manifestation of a syndrome. Peutz–Jeghers is a syndrome of mucocutaneous melanotic pigmentation and gastrointestinal polyposis.

Extended matching items answers

EMI 1

1. **B.** Mucous membrane pemphigoid can affect the oral cavity, conjunctive and genital mucosa. Testing by indirect and direct immunofluorescence can be helpful in establishing the diagnosis.
2. **C.** Dysplasia and even invasive oral cancer can present clinically as a red patch. All such suspicious oral lesions should be biopsied or referred for consultant opinion.
3. **I.** Strawberry gingival papillae are a classical sign of a vasculitic disease, Wegener's granulomatosis. Ulceration may be present and prompt referral to a specialist unit is indicated.
4. **A.** Desquamative gingivitis is a clinical term describing red atrophic-looking gums. The most common underlying disease process is lichen planus, but vesiculo-bullous disorders can have similar clinical appearances.
5. **D.** Plasma-cell mucositis is a rare condition that affects the oral mucosa and that can extend into the supraglottic larynx. Mature plasma cells expand connective tissue papillae and this can result in a spongy appearance. Allergy to herbal and leaf products may be the cause in some patients.
6. **H.** Dentists may see children with primary herpetic gingivo stomatitis. Small grey vesicles are typical but quickly break down into small ulcers.
7. **G.** Linear gingival erythema is a recognised oral manifestation of HIV infection and is variant or erythematous candidiasis.
8. **F.** Leukaemia may present with gingival swelling or bleeding and may be confused with chronic periodontitis.
9. **E.** Over half of patients suffering from pemphigus present first with oral disease. Autoantibodies against desmoglein 3 occur and cause suprabasal oral keratinocytes to separate, resulting in intra-epithelial blisters. Testing by direct and indirect immunofluorescence may be helpful to establish the diagnosis.
10. **J.** These histological features are typical of giant-cell granuloma. The differential diagnosis should include central giant-cell granuloma and hyperparathyroidism.

EMI 2

1. **E.** Nicorandil is a drug given for intractable angina. Some individuals develop deep painful and persistent oral ulcers, often at fixed sites.
2. **A.** Hairy leukoplakia is caused by proliferation of Epstein–Barr virus (HHV4) in the upper layers of the oral epithelium in immunosuppressed patients. HIV infection or drugs given to prevent transplant rejection can predispose to HL.
3. **B.** Minor aphthae (recurrent oral ulceration) occurs on lining oral mucosa. Ulcers tend to last for less than 2 weeks and rarely exceed 5 mm in size. They are common in children and teenagers. Sudden onset in adult life may indicate an underlying systemic disorder.
4. **C.** White sponge naevus is caused by a mutation in keratin genes (often K4) and is autosomal dominant. No treatment is needed.
5. **J.** Traumatic ulcerative granuloma with stromal eosinophils (TUGSE) is caused by crush injury to tongue muscle. A thick fibrinous crust is present and the deeper muscle fibres are separated by histiocytic cells and eosinophils. Clinically the disorder can mimic carcinoma. Spontaneous resolution with conservative measures is observed.
6. **H.** Fordyce spots are normal sebaceous glands that occur in oral mucosa and oesophagus. In older patients or where atrophy is present they can be quite prominent.
7. **I.** When dental amalgam enters mucosal tissue it can form a pigmented lesion. Corrosion leads to spread of the particles with time and clinically the lesion appears to enlarge. Other causes of discrete pigmented lesions are melanotic macules, naevi and malignant melanoma.
8. **F.** Stomatitis nicotina or smoker's keratosis is a distinctive lesion of the soft palate. The red spots represent salivary duct openings. The lesion is not premalignant. Patients often give an unreliable smoking history.
9. **D.** Haemangiomas are blood-filled developmental lesions and are common in the tongue. Blood can be displaced by pressure or a fine needle can be used to sample contents to confirm the diagnosis.
10. **G.** Chronic hyperplastic candidosis is seen most often in denture wearers and smokers. *Candida* pseudohyphae extend into the keratin and provoke active chronic inflammation. Predisposing factors should be eliminated and systemic antifungal drugs can be prescribed if not contraindicated clinically.

Case history answers

Case history 1

1. Severe oral ulceration has been linked to nicorandil therapy. This is prescribed for uncontrollable angina and often cannot be substituted.
2. A full history should be obtained; full blood count and haematinics would be requested and other investigations may be needed.

3. Benzydamine hydrochloride (Difflam oral rinse or spray) may relieve pain and carmellose sodium (Orabase or Orahesive) may be used as a protective barrier. Topical steroids may be of benefit.

Case history 2

1. The features suggest frictional keratosis.
2. Marked wear facets are often seen in bruxism (habitual teeth grinding); a thickened band is often seen on the lateral tongue and buccal mucosa at the level of the occlusal plane owing to chronic trauma.
3. Provision of a protective splint may reverse frictional keratosis by eliminating mechanical trauma to the mucosa and correcting uncontrolled jaw movements or habitual chewing.
4. Classical histopathological features of frictional keratosis are acanthosis, hyperparakeratosis and maceration of the parakeratin layer with formation of bacterial plaque on its surface. Epithelial maturation is regular.

Case history 3

1. The features strongly suggest angina bullosa haemorrhagica.
2. Full blood count and coagulation screen to exclude a bleeding disorder.
3. A link between inhaled steroids and angina bullosa haemorrhagica has been suggested.
4. Reassure the patient and advise use a nebuliser, rinse out mouth after using inhaler, avoid excessively hot drinks and hard or rough foods.

Case history 4

1. Miconazole nitrate (Daktarin cream) has antifungal and antistaphylococcal activity. It is also available in a combined preparation with hydrocortisone (Daktacort). Nystatin cream may also be used.
2. Lip swelling, cobblestone mucosa, ulceration and granular gingivitis suggest a diagnosis of oral Crohn's disease (orofacial granulomatosis).
3. Mucosal biopsy would show non-caseating granulomas, scattered chronic inflammatory infiltration and dilated lymphatic vessels with lymphoedema.
4. It is important to investigate for Crohn's disease in the gastrointestinal tract.

Case history 5

1. Reticulated lesions of lichen planus are shown. The white lines are often referred to as Wickham's striae.
2. A band-like subepithelial lymphohistiocytic infiltrate, basal-cell liquefaction degeneration, Civatte bodies and sometimes sawtooth rete processes.
3. Hepatitis C infection has been linked with oral lichen planus.

Viva answers

1. Normal racial pigmentation; extrinsic causes such as paan chewing, smoking, chlorhexidine rinses and drugs; intrinsic causes such as melanin incontinence in Addison's disease, haemochromatosis and jaundice.
2. Triamcinolone as Adcortyl in Orabase, hydrocortisone as Corlan pellets, applied as directed in the British National Formulary, and betamethasone as Betnosol mouthwash.
3. A representative area should be selected and the biopsy should be of adequate size and depth. Crushing should be avoided and local anaesthetic solution must not be injected directly into the biopsy site. Normally biopsies are fixed in 10% neutral buffered formalin; at least 10 times the volume of the biopsy must be used. The specimen pot must be labelled and the request card should be completed carefully, providing full clinical details.
4. Swabs are taken to estimate growth, perform speciation and other microbiological tests. Smears are employed for rapid detection of pseudohyphae by periodic acid-Schiff base or Gram staining; this indicates candidal proliferation and is a good indicator of candidal infection.
5. Submucous fibrosis is related to paan chewing. Advice should be given to discontinue this habit and avoid other risk factors for oral cancer. Regular checking of the oral cavity is advised.
6. Fibrous, vascular and giant-cell types. Other disorders, including primary and secondary cancers, can present as a localised gingival swelling.
7. Erythematous candidiasis, hairy leukoplakia, HIV gingivitis, Kaposi's sarcoma.
8. Gingival and mucosal bleeding and purpura from thrombocytopenia; gingival enlargement caused by infiltration by leukaemic cells (especially in acute myeloid types); dry mouth; mucosal atrophy; and ulceration.