Gingival Pathology
Anne Hegarty and Alison Rich

Abstract
The normal anatomy and physiology of the periodontium is well known to dentists and dental specialists, as are the effects on the periodontium of plaque-associated bacterial infections. However, the gingivae may be involved in many other local and systemic conditions. The purpose of this chapter is to describe some of the less common pathological conditions that may affect one or more of the components of the periodontium and to discuss how clinicians can ensure these lesions are diagnosed and managed in a timely manner.

Keywords
Gingival lesions • Periodontium • Periodontal diseases and conditions • Non-plaque gingival pathology • Immunological • Lichen planus • Infectious • Drug-induced • Leukoplakia • Erythroplakia • Neoplastic

Contents
Introduction .......................................... 2
Gingival Lesions of Developmental/Genetic Origin ............................................. 2
Hereditary Gingival Fibromatosis ....................................................... 2
Ligneous Gingivitis ................................................................. 2
Gingival Hamartoma ............................................................... 4
Reactive Gingival Lesions ............................................................. 5
Gingival Epulides ........................................................................ 6
Localized Juvenile Spongiotic Gingival Hyperplasia ................................................. 9
Peripheral Giant Cell Lesions .......................................................... 9
Drug-Induced Gingival Lesions ........................................................ 11
Gingival Lesions of Infectious Origin ................................................... 12
Viral Infections ........................................................................... 12
Human Immunodeficiency Virus (HIV) Infection ........................................... 12
Immune-Mediated Gingival Lesions ....................................................... 13
Oral Lichen Planus ........................................................................ 13
Mucous Membrane Pemphigoid .......................................................... 14
Linear IgA Disease ....................................................................... 16
Pemphigus Vulgaris ....................................................................... 17
Orofacial Granulomatosis and Oral Crohn’s Disease ....................................... 18
Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) ....................... 19
Pyostomatitis Vegetans ................................................................... 19
Plasma Cell Gingivitis/Gingivostomatitis ................................................. 19

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© Springer International Publishing AG 2017
C.S. Farah et al. (eds.), Contemporary Oral Medicine,
DOI 10.1007/978-3-319-28100-1_15-1
### Introduction

A wide variety of lesions may arise from the oral mucosa, fibrous connective tissue, bone, and cementum of the periodontium. The commonest pathology is a result of bacterial infection and is very well known to dental practitioners and is covered in other chapters of this text and detailed in the classification of periodontal diseases and conditions (Table 1) (Armitage 1999). Rarer conditions, however, also present as gingival pathology. The pathogenesis of these non-plaque-related lesions and conditions comprises genetic, traumatic, immunological, and neoplastic etiologies including benign, malignant, and metastatic. This chapter outlines these conditions, describing them in terms of four categories related to their pathogenesis: Genetic, Reactive, Immunological, and Neoplastic. Using this framework, and with careful consideration of both the clinical features and use of appropriate special tests, should enable the clinician to make a timely and accurate diagnosis. Plaque-related gingival and periodontal conditions are covered in more detail in separate chapters on “► Odontogenic Bacterial Infections” and “► Odontogenic Pathology.” Given the wide spread of conditions affecting the gingival tissues, more detailed exploration of conditions covered in this chapter can also be found in separate chapters on “► Oral Lichen Planus,” “► White and Red Lesions of the Oral Mucosa,” “► Oral Mucosal Malignancies,” “► Oral Ulcerative Lesions,” “► Oral and Maxillofacial Viral Infections,” and “► Oral Vesicular and Bullous Lesions” among others.

#### Gingival Lesions of Developmental/Genetic Origin

**Hereditary Gingival Fibromatosis**

Hereditary gingival fibromatosis is an uncommon condition characterized by generalized extensive fibrous enlargement of the gingivae which have a normal or slightly paler color and which are firm to touch (Fig. 1). It is inherited, usually as an autosomal dominant trait, and is associated with mutation of the son-of-sevenless (SOS-1) gene which encodes a guanine-nucleotide exchange factor that is important for Ras activation and hence activation of various receptors relating to cell proliferation (Hart et al. 2002; Poulopoulos et al. 2011). It may be associated with hypertrichosis and/or sensorineural hearing loss (Hartsfield et al. 1985) with or without learning disability and/or epilepsy (Witkop 1971). Care with oral hygiene may be all that is required for treatment, but surgical reduction may be necessary with recurrences to be expected.

**Ligneous Gingivitis**

Ligneous gingivitis, also known as destructive membranous periodontal disease or (erroneously) amyloidaceous gingival hyperplasia, is another rare disorder that should be included in the differential diagnoses for patients presenting with generalized or focal gingival enlargement in the absence of the use of medications. Females are affected more frequently than males (F:M ratio ~3:1), and while the initial cases were reported in people of Turkish ethnicity, it is now clear there is a worldwide distribution (Sivolella et al. 2012). The gingival enlargement has a generalized nodular appearance with surface ulceration which may begin in childhood (Fig. 2). The soft tissue hyperplasia may be associated with significant alveolar bone loss and severe periodontal disease. Histological examination shows the deposition of eosinophilic acellular material, demonstrated to be fibrin, in the connective tissue (Fig. 3). Amyloid is not present. A small number of patients have similar conjunctival lesions, known as
<table>
<thead>
<tr>
<th>I. Gingival diseases</th>
<th>3. Gingival diseases of fungal origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Dental plaque-induced gingival diseases</td>
<td>a. Candida-species infections</td>
</tr>
<tr>
<td>1. Gingivitis associated with dental plaque only</td>
<td>1. Generalized gingival candidosis</td>
</tr>
<tr>
<td>a. Without other local contributing factors</td>
<td>b. Linear gingival erythema</td>
</tr>
<tr>
<td>b. With local contributing factors (See VIII A)</td>
<td>c. Histoplasmosis</td>
</tr>
<tr>
<td>2. Gingival diseases modified by systemic factors</td>
<td>d. Other</td>
</tr>
<tr>
<td>a. Associated with the endocrine system</td>
<td>4. Gingival lesions of genetic origin</td>
</tr>
<tr>
<td>b. With local contributing factors (See VIII A)</td>
<td>1. Puberty-associated gingivitis</td>
</tr>
<tr>
<td>c. Histoplasmosis</td>
<td>a. Hereditary gingival fibromatosis</td>
</tr>
<tr>
<td>3. Pregnancy associated</td>
<td>b. Other</td>
</tr>
<tr>
<td>a. Gingivitis</td>
<td>5. Gingival manifestations of systemic conditions</td>
</tr>
<tr>
<td>b. Associated with blood dyscrasias</td>
<td>1. Leishmaniasis</td>
</tr>
<tr>
<td>1. Leukemia-associated gingivitis</td>
<td>a. Lichen planus</td>
</tr>
<tr>
<td>2. Other</td>
<td>2. Pemphigoid</td>
</tr>
<tr>
<td>4. Gingival diseases modified by malnutrition</td>
<td>3. Pemphigus vulgaris</td>
</tr>
<tr>
<td>a. Ascorbic acid-deficiency gingivitis</td>
<td>1. Erythema multiforme</td>
</tr>
<tr>
<td>b. Other</td>
<td>2. Lupus erythematosus</td>
</tr>
<tr>
<td>5. Gingival diseases modified by medications</td>
<td>6. Drug-induced</td>
</tr>
<tr>
<td>a. Drug-influenced gingival diseases</td>
<td>1. Dental restorative materials</td>
</tr>
<tr>
<td>1. Drug-influenced gingival enlargements</td>
<td>b. Allergic reactions</td>
</tr>
<tr>
<td>b. Other</td>
<td>b. Nickel</td>
</tr>
<tr>
<td>4. Gingival diseases modified by malnutrition</td>
<td>c. Acrylic</td>
</tr>
<tr>
<td>a. Ascorbic acid-deficiency gingivitis</td>
<td>d. Other</td>
</tr>
<tr>
<td>b. Other</td>
<td>2. Reactions attributable to</td>
</tr>
<tr>
<td>B. Non-plaque-induced gingival lesions</td>
<td>a. Toothpastes/dentifrices</td>
</tr>
<tr>
<td>1. Gingival diseases of specific bacterial origin</td>
<td>b. Mouthrinses/mouthwashes</td>
</tr>
<tr>
<td>a. Neisseria gonorrhoea-associated lesions</td>
<td>c. Chewing gum additives</td>
</tr>
<tr>
<td>b. Treponema pallidum-associated lesions</td>
<td>3. Other</td>
</tr>
<tr>
<td>c. Streptococcal species-associated lesions</td>
<td>6. Traumatic lesions (factitious, iatrogenic, accidental)</td>
</tr>
<tr>
<td>d. Other</td>
<td>a. Chemical injury</td>
</tr>
<tr>
<td>2. Gingival diseases of viral origin</td>
<td>b. Physical injury</td>
</tr>
<tr>
<td>a. Herpesvirus infections</td>
<td>c. Thermal injury</td>
</tr>
<tr>
<td>1. Primary herpetic gingivostomatitis</td>
<td>7. Foreign body reactions</td>
</tr>
<tr>
<td>2. Recurrent oral herpetic</td>
<td>8. Not otherwise specified (NOS)</td>
</tr>
<tr>
<td>3. Varicella-zoster infections</td>
<td>b. Other</td>
</tr>
<tr>
<td>B. Generalized</td>
<td>7. Other</td>
</tr>
<tr>
<td>II. Chronic periodontitis</td>
<td>VIII. Developmental or acquired deformities and conditions</td>
</tr>
<tr>
<td>A. Localized</td>
<td>(continued)</td>
</tr>
<tr>
<td>B. Generalized</td>
<td>A. Combined periodontic-endodontic lesions</td>
</tr>
<tr>
<td>VII. Periodontitis associated with endodontic lesions</td>
<td>VIII. Developmental or acquired deformities and conditions</td>
</tr>
</tbody>
</table>
ligneous (woody) conjunctivitis. These patients should be investigated to exclude an association with inherited type 1 plasminogen deficiency since hypoplasminogenaemia is present in a high proportion of cases (Schuster et al. 1997; Scully et al. 2007; Sivolella et al. 2012). In cases with or without hypoplasminogenemia, surgical removal of the hyperplastic gingival tissue tends to be followed by recurrence (Kurtulus et al. 2007; Sivolella et al. 2012). Topical and/or systemic plasminogen supplementation has been attempted with variable success (Sivolella et al. 2012).

**Gingival Hamartoma**

Odontogenic gingival epithelial hamartoma (OGEH) is a rare benign hamartoma believed to arise from epithelial remnants of the dental lamina (rests of Serres) (Kitano et al. 1991). It usually

### Table 1 (continued)

<table>
<thead>
<tr>
<th>III. Aggressive periodontitis&lt;sup&gt;b&lt;/sup&gt;</th>
<th>A. Localized tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Localized</td>
<td>1. Tooth anatomic factors</td>
</tr>
<tr>
<td>B. Generalized</td>
<td>2. Dental restorations/appliances</td>
</tr>
<tr>
<td>IV. Periodontitis as a manifestation of systemic diseases</td>
<td>3. Root fractures</td>
</tr>
<tr>
<td>A. Associated with hematological disorders</td>
<td>4. Cervical root resorption and cemental tears</td>
</tr>
<tr>
<td>1. Acquired neutropenia</td>
<td>B. Mucogingival deformities and conditions around teeth</td>
</tr>
<tr>
<td>2. Leukemias</td>
<td>1. Gingival/soft tissue recession</td>
</tr>
<tr>
<td>3. Other</td>
<td>a. Facial or lingual surfaces</td>
</tr>
<tr>
<td>B. Associated with genetic disorders</td>
<td>b. Interproximal (papillary)</td>
</tr>
<tr>
<td>1. Familial and cyclic neutropenia</td>
<td>2. Lack of keratinized gingiva</td>
</tr>
<tr>
<td>2. Down syndrome</td>
<td>3. Decreased vestibular</td>
</tr>
<tr>
<td>3. Leukocyte adhesion deficiency syndromes</td>
<td>4. Aberrant frenum/muscle position</td>
</tr>
<tr>
<td>4. Papillon-Lefèvre syndrome</td>
<td>5. Gingival excess</td>
</tr>
<tr>
<td>5. Chediak-Higashi syndrome</td>
<td>a. Pseudopocket</td>
</tr>
<tr>
<td>6. Histiocytosis syndromes</td>
<td>b. Inconsistent gingival margin</td>
</tr>
<tr>
<td>7. Glycogen storage disease</td>
<td>c. Excessive gingival display</td>
</tr>
<tr>
<td>8. Infantile genetic agranulocytosis</td>
<td>d. Gingival enlargement (See I.A.3 and I.B.4)</td>
</tr>
<tr>
<td>10. Ehlers-Danlos syndrome (Types IV and VIII)</td>
<td>C. Mucogingival deformities and conditions on edentulous ridges</td>
</tr>
<tr>
<td>11. Hypophosphatasia</td>
<td>1. Vertical and/or horizontal ridge deficiency</td>
</tr>
<tr>
<td>12. Other</td>
<td>2. Lack of gingiva/keratinized tissue</td>
</tr>
<tr>
<td>C. Not otherwise specified (NOS)</td>
<td>3. Gingival/soft tissue enlargement</td>
</tr>
<tr>
<td>V. Necrotizing periodontal diseases</td>
<td>4. Aberrant frenum/muscle position</td>
</tr>
<tr>
<td>A. Necrotizing ulcerative gingivitis (NUG)</td>
<td>5. Decreased vestibular depth</td>
</tr>
<tr>
<td>B. Necrotizing ulcerative periodontitis (NUP)</td>
<td>6. Abnormal color</td>
</tr>
<tr>
<td>VI. Abscesses of the periodontium</td>
<td>D. Occlusal trauma</td>
</tr>
<tr>
<td>A. Gingival abscess</td>
<td>1. Primary occlusal trauma</td>
</tr>
<tr>
<td>B. Periodontal abscess</td>
<td>2. Secondary occlusal trauma</td>
</tr>
<tr>
<td>C. Pericoronal abscess</td>
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<sup>a</sup>Can occur on a periodontium with no attachment loss or on a periodontium with attachment loss that is not progressing

<sup>b</sup>Can be further classified on the basis of extent and severity. As a general guide, extent can be characterized as Localized = ≤30% of sites involved and Generalized = >30% of sites involved. Severity can be characterized on the basis of the amount of clinical attachment loss (CAL) as follows: Slight = 1 or 2 mm CAL, Moderate = 3 or 4 mm CAL, and Severe = ≥5 mm CAL
presents as an asymptomatic gingival lump in adults, mostly females. Histologically OGEH shows multiple islands and clusters of bland epithelial cells surrounded by condensed fibrous connective tissue, without significant hyalinization typical of epithelial-mesenchymal inductive interactions seen in odontogenic neoplasms (Fig. 4). It is a completely innocuous lesion but is an important differential histological diagnosis for localized gingival lesions containing odontogenic epithelium when a diagnosis of a peripheral odontogenic tumour is being considered (see below).

Reactive Gingival Lesions

Acute physical trauma to the gingiva is common and is easily recognized by the patient and clinician, although low-level chronic trauma may not elicit a clear history. The first part of this section will describe gingival reactions to various local irritants. The second part will describe reactions of the gingival tissues to the use of some systemic medications.
Gingival Epulides

Gingival epulis refers to a lump on the gingiva and includes angiogranuloma (also known as vascular epulis or erroneously as pyogenic granuloma) (Fig. 5), pregnancy epulis (Fig. 6) and fibrous epulis (sometimes known as peripheral fibroma despite the fact the lesion is traumatic in origin) (Fig. 7). Angiogranuloma is a relatively common tissue response to localized irritation or trauma often seen in the gingiva and presents as a localized swelling. It is a reactive inflammatory process filled with proliferating vascular channels, immature fibroblastic connective tissue, and scattered inflammatory cells. Pregnancy can
predispose the patient to gingival hyperplasia and induce a large localized vascular lesion (pregnancy epulis), particularly when oral hygiene is poor. A fibrous epulis, a localized hyperplastic fibrous gingival mass formed as a response to chronic irritation, shows much less vascularity histologically with more mature fibrous tissue and little inflammation. Mineralization within a fibrous epulis is relatively common and, in these cases, the surface is often ulcerated. There may be dystrophic calcification or recognizable woven bone or cementum (Fig. 7c). These are known as mineralizing or ossifying fibrous epulides to reflect their reactive nonneoplastic nature.

Fig. 7 Fibrous epulis between the lower left canine and first premolar teeth (33 and 34) (a). The surface mucosa is of the same color and texture as surrounding tissue. (b) shows another fibrous epulis, in this case involving the labial gingiva of the lower left first and second molar teeth (36 and 37), in a 14-year-old female. Histologically this was shown to contain mineralized areas within the connective tissue similar to that shown in (c). (Clinical images courtesy of Professor Camile Farah, Queensland Oral Medicine & Pathology, Brisbane, QLD, Australia)
For all gingival epulides management involves treating the cause and usually requires excisional biopsy as definitive treatment and to confirm the diagnosis. The excision should extend to periosteum, and the region should be thoroughly scaled and root planed (Fig. 8). This is usually curative, but recurrences do occur. Although many of these lesions can be excised without raising a flap (b). Healing at 2 weeks post-surgery (c). (Images courtesy of Professor Camile Farah, Queensland Oral Medicine & Pathology, Brisbane, QLD, Australia)

Fig. 8 Surgical removal and debridement of angiogranuloma. Angiogranuloma involving labial gingival margin between upper left central and lateral incisor teeth (21 and 22) (a). Lesion is excised completely down to periosteum and periodontal tissues debrided thoroughly without raising a flap (b). Healing at 2 weeks post-surgery (c). (Images courtesy of Professor Camile Farah, Queensland Oral Medicine & Pathology, Brisbane, QLD, Australia)

Fig. 9 Clinical presentation of localized juvenile spongiotic gingival hyperplasia involving the labial gingiva of the upper right first and second incisors and canine teeth (11, 12, 13) in a 12-year-old female (a). (Image courtesy of Professor Camile Farah, Queensland Oral Medicine & Pathology, Brisbane, QLD, Australia). The small vessels in the superficial connective tissue are typically dilated and engorged in this condition, contributing to the clinical appearance (b)

For all gingival epulides management involves treating the cause and usually requires excisional biopsy as definitive treatment and to confirm the diagnosis. The excision should extend to periosteum, and the region should be thoroughly scaled and root planed (Fig. 8). This is usually curative, but recurrences do occur. Although many of these lesions can be excised without extensive periodontal surgery with adequate healing, occasionally coronally repositioned flaps are required to provide adequate tissue coverage, healing, and esthetics. For pregnancy epulis, treatment is best deferred until after parturition when the vascularity of the lesion will regress.
Localized Juvenile Spongiotic Gingival Hyperplasia

Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a painless solitary localized sessile or pedunculated swelling of the attached gingivae with a characteristic bright red color (Fig. 9a). It bleeds easily and usually affects the maxillary anterior labial gingivae in children and adolescents. Histologically the lesion is covered by nonkeratinized epithelium with elongated rete ridges with pronounced edema of the stratum spinosum and neutrophil exocytosis. Numerous small dilated blood vessels and a mixed inflammatory cell infiltrate are conspicuous in the connective tissue papilla (Fig. 9b). Sometimes the surface has a granular or papillary texture. LJSGH is considered to be a reactive lesion, but it is not simply a response to plaque (Darling et al. 2007), and there is no convincing evidence to support a viral etiology (Argyris et al. 2015). The histological features and pattern of cytokeratin expression in the epithelium of LJSGH are similar to that of junctional epithelium, rather than mature gingival epithelium, leading to the suggestion that these lesions might represent exteriorized junctional epithelium from the gingival sulcus (Chang et al. 2008; Allon et al. 2016). The exposed junctional-type epithelium is then vulnerable to local irritants and the reactive LJSGH ensues. Localized surgical excision with careful scaling and root planning of the adjacent teeth is the treatment of choice (Chang et al. 2008).

Peripheral Giant Cell Lesions

Peripheral giant cell lesions (giant cell epulis) are relatively common and present as a red, bluish, or purple gingival mass, sometimes ulcerated. Initially they usually involve the buccal interdental papillae but they may extend lingually/palatally and separate the adjacent teeth (Fig. 10a). They occur over a wide age range with a reasonably even gender distribution. Peripheral giant cell lesions are considered to be derived from cells in the periosteum or periodontal ligament as a reactive response to local trauma (Lester et al. 2014). There have been reports of their development adjacent to dental implants (Hirshberg et al. 2003; Brown et al. 2015). Histological examination shows mononuclear cells and numerous multinucleated giant cells, thought to be of osteoclastic origin, in vascular cellular connective tissue (Fig. 10b). There have been numerous reports describing the immunohistochemical profiles of mononuclear cells and giant cells in...

![Image](a)

**Fig. 10** Peripheral giant cell granuloma of the gingiva between the lower left first and second incisors (32 and 33) causing displacement of tooth 32 lingually. (a) The surface mucosa is erythematous and easily traumatized (Image courtesy of Professor Camile Farah, Queensland Oral Medicine & Pathology, Brisbane, QLD, Australia).

![Image](b)

Numerous multinucleate giant cells are present in vascular immature fibrous connective tissue, typical of a giant cell lesion (b). More mature fibrous tissue containing hemosiderin and a mild chronic inflammatory cell infiltrate is present in the top right side of the photomicrograph.
peripheral and central giant cell lesions in anticipation of variation in expression reflecting differences in behavior and response to treatment modalities such as calcitonin, interferons, and bone resorption inhibitors (Tobón-Arroyave et al. 2005; Kujan et al. 2015; Martins et al. 2015). It is important that radiographs of the region are obtained since, while these lesions can cause minor resorption “cupping” of the adjacent cortical bone, more extensive bony involvement indicates the presence of a central giant cell lesion with peripheral extension. A peripheral giant cell lesion should be treated in the same way as a fibrous epulis. Clinical review is recommended since recurrences do occur. The clinical and histological appearance of the “brown tumors” of hyperparathyroidism (Fig. 11) may be the same as that of giant cell lesions and hence hyperparathyroidism should be excluded for central giant cell lesions and for multiple or recurrent peripheral lesions. The oral lesions in these cases may not need surgical intervention once the parathyroid hormone levels are stabilized.

Fig. 11 Brown’s tumour of hyperparathyroidism presenting as a gingival lump on the maxillary alveolus (a). The lesion demonstrates a strongly enhancing soft tissue mass eroding bone within the right anterior maxilla extending into the nasopalatine canal and into the overlying gingiva on MDCT (b) and MRI (c). (Images courtesy of Professor Camile Farah, Perth Oral Medicine & Dental Sleep Centre, Perth, WA, Australia)
Drug-Induced Gingival Lesions

One of the most troublesome drug-induced gingival lesions is gingival enlargement, which may be so marked as to interfere with mastication and cause esthetic problems. Agents associated with gingival enlargement include phenytoin (Fig. 12a), calcineurin inhibitors such as cyclosporine (Fig. 12b) and tacrolimus, and calcium channel blockers such as nifedipine, diltiazem, oxidipine, and amlodipine. A common link between these drugs is cation flux inhibition, leading to decreased uptake of folate by gingival fibroblasts and subsequent changes in matrix metalloproteinase metabolism and lack of collagenase activation. Thus, the excess collagen formed in association with inflammatory gingivitis cannot be degraded effectively (Brown et al. 1991; Brown and Arany 2014). Careful attention to oral hygiene remains an important treatment modality. The putative drug should be withdrawn by the treating physician if possible, but regression of the gingival hyperplasia is often slow. Surgical debulking may assist but should not be performed until after the drug has been ceased for some months. If the drug cannot be altered, gingival recontouring, either by conventional surgery or laser, may be helpful but is likely to relapse. Despite a number of reports recommending the use of topical or systemic folic acid supplementation, or azithromycin to manage drug-induced gingival enlargement, there is currently insufficient evidence to confirm their value (Brown and Arany 2014).

Drug-induced hyposalivation may be associated with increased susceptibility to cervical caries and gingivitis/periodontitis due to prolonged adherence of plaque at the tooth-gingival interface (Lam et al. 2009). Drug-induced hyposalivation may be associated with many medications, particularly antidepressants and diuretics. Mouth-breathing has been associated with higher levels of plaque and gingival inflammation (Wagaiyu and Ashley 1991).

Drug-induced oral ulceration has been reported with numerous medications (Scully and Bagan 2004) and, in more recent times, secondary to nicorandil, a potassium channel activator used in the treatment of unstable angina (Yamamoto et al. 2011). Although more common on the tongue, lesions may affect the gingivae and edentulous ridge mucosa (Fig. 13).
Gingival Lesions of Infectious Origin

Viral Infections

Herpes Simplex Infection
Primary herpetic gingivostomatitis presents usually in young children as a painful acute viral illness with intraoral vesicles and erythematous, swollen gingiva (Fig. 14). The generalized gingival involvement is a fairly constant and conspicuous clinical feature of primary herpetic gingivostomatitis and may assist in distinguishing it from other viral infections that involve the oral mucosa such as herpangina and hand, foot and mouth disease. Treatment is usually symptomatic, ensuring adequate hydration, while an antiviral agent such as acyclovir (also known as acyclovir) may be necessary in immunocompromised hosts. Acyclovir is prescribed for primary herpetic gingivostomatitis at a dose of 200 mg five times daily for 5 days in adults and for a child, 1 month to 2 years old, half the adult dose is given. Potential adverse effects include nausea, vomiting, rash and photosensitivity and very rarely hepatitis, acute renal failure, neurological reactions, and hematological effects. Valaciclovir, a pro-drug of acyclovir, may be used if there are adverse effects to acyclovir is ineffective. A usual dose for adults is 500 mg twice daily for 5 days, and for children consultation with pediatric medical specialists is advised. Adverse reactions are similar to those related to acyclovir but neurological reactions are more likely with higher doses. Other herpesviruses, e.g., varicella-zoster rarely affects the gingiva, but if gingival herpes zoster does occur, treatment should take into account the possibility of post-zoster osteonecrosis, since alveolar bone necrosis and tooth exfoliation is a rare complication of intraoral herpes zoster infection, particularly in immunocompromised patients (Mendieta et al. 2005; Jain et al. 2010).

Human Immunodeficiency Virus (HIV) Infection
Antiretroviral therapy (ART) has dramatically improved the management of patients infected with human immunodeficiency virus and has reduced the incidence and severity of linear gingival erythema and necrotizing periodontitis as well as intraoral neoplasms associated with acquired immunodeficiency syndrome (AIDS). Human papillomaviruses may induce a number of lesions in patients with HIV/AIDS including gingival papillomas, warts, condyloma acuminatum, and focal epithelial hyperplasia (Fig. 15). Carbon dioxide laser treatment may reduce the HPV-related lesions but the underlying immune impairment reduces its effectiveness (Limeres Posse and Scully 2016). Malignant transformation in gingival papillary lesions in HIV/AIDS is rare. It is interesting to note that
the incidence of HPV-associated malignancies in other sites, specifically anus and cervix, has not declined since the introduction of ART indicating that ART confers little benefit in the prevention and management of HPV-related pathology (Palefsky 2016).

**Immune-Mediated Gingival Lesions**

**Oral Lichen Planus**

Oral lichen planus (OLP) can present as white, red, and/or ulcerative lesions usually presenting bilaterally on the buccal mucosa, the lateral margins of the tongue or the gingivae. White striated, papular, or plaque-like forms (Fig. 16) are often asymptomatic, but the atrophic and ulcerative forms may cause significant discomfort. When OLP affects the gingivae and gives rise to generalized gingival erythema, desquamation, and edema, the term “desquamative gingivitis” may be used (Fig. 17). This is a general term describing a clinical situation and is not a diagnosis. Because other conditions can have a similar clinical appearance, biopsy is recommended to confirm the diagnosis, but it is advisable to avoid a gingival biopsy if there are other sites of involvement, since the inflammatory infiltrate associated with concomitant gingivitis may disrupt the typical histological features of OLP (Fig. 18) leading to difficulties in obtaining a definite diagnosis. The cause of OLP is not fully understood, but it is thought to represent a T cell-mediated immune response to an unknown trigger, whereby cytotoxic T-cells damage basal epithelial keratinocytes (Zhou et al. 2002), in a microenvironment where there is an altered balance of immune regulatory cells and signalling pathways (Firth et al. 2015; Sinon et al. 2016). OLP is considered a potentially malignant condition (Al-Hashimi et al. 2007), and it is prudent that patients be reviewed at regular intervals by an oral medicine specialist because of an increased likelihood of oral squamous cell carcinoma occurring in association with OLP, particularly of the atrophic or ulcerative variety. Treatment is aimed at relieving symptoms and is usually provided to patients with painful, erosive, and ulcerative forms of disease (Hegarty 2012; Ryan et al. 2014). Maintenance of good oral hygiene and attention to routine dental care should be reinforced to patients. Due to the paucity of randomized controlled clinical trials to evaluate therapies, there is a lack of strong evidence supporting the effectiveness of any palliative therapy for symptomatic OLP (Chan et al. 2000; Zakrzewska et al. 2005). Topical corticosteroids are still considered first line therapy (Thongprasom et al. 2011). Preparations include betamethasone sodium phosphate as a mouthrinse, fluticasone propionate as spray, mouth rinse, or cream, beclomethasone spray, fluocinolone cream, and clobetasol ointment or cream, or dexamethasone mouth rinse. As OLP can present as desquamative gingivitis, improvement and maintenance of oral hygiene should be a
priority in the management of this disease, but pain may be a limiting factor to good oral hygiene measures and therefore must be taken into account when designing a preventive program for these patients (Scattarella et al. 2011; Hegarty 2012). Topical immunomodulators such as tacrolimus and cyclosporine may be useful second line therapies in recalcitrant OLP (Elad et al. 2010; Thongprasom et al. 2011). Systemic immunosuppressants that have been used successfully in the treatment of recalcitrant symptomatic OLP include azathioprine, mycophenolate mofetil, and systemic corticosteroids (Al-Hashimi et al. 2007; Ryan et al. 2014). The use of laser therapy and ultraviolet light phototherapy has been reported less frequently in the treatment of OLP with limited effectiveness (Ryan et al. 2014). Topical aloe vera, topical pimecrolimus, and oral curcuminoids are the most promising of the new therapies reported (Thongprasom et al. 2013). Other interesting modalities are topically applied thalidomide and amlexanox. Regular monitoring of patients with OLP is recommended due to the potentially malignant nature of the condition although the optimum frequency of review appointments is uncertain (Mattsson et al. 2002; Ryan et al. 2014).

**Mucous Membrane Pemphigoid**

Mucous membrane pemphigoid (MMP) is a rare chronic blistering autoimmune disease, where autoantibodies are formed against components of
hemidesmosomes. Target antigens in MMP include bullous pemphigoid antigen 1 (BP 230) and 2 (BP180), and laminins (Chan et al. 2002) with antibodies to human α6 integrin being identified as important in the pathogenesis of oral MMP (Rashid et al. 2006). The condition commonly affects middle-aged and elderly females and the usual presentation is oral mucosal vesicle/bulla formation with or without gingival involvement. Gingival involvement usually manifests as painful erythema with desquamation (Fig. 19), either spontaneously or following minor trauma such as tooth-brushing. Blood or fluid-filled blisters may be seen. The diagnosis should be confirmed by biopsy for routine microscopic evaluation and immunofluorescence where possible, understanding that a biopsy of an already ulcerated region is likely to provide a nonspecific result and the typical subepithelial split, with intact basal keratinocytes remaining on the epithelial surface, will not be seen (Fig. 20). Perilesional and lesions early in their evolution will show linear deposition of IgG and/or C3 in the basement membrane zone (Fig. 21). Because of potential ocular involvement, as shown in Fig. 22, an ophthalmological examination should be organized given the risk for blindness. Treatment of MMP may be difficult due to the complexity of the disease, diversity of pathogenic pathways seen, and the lack of large scale, well-controlled studies regarding therapy for MMP (Chan et al. 2002; Di Zenzo et al. 2014; Taylor et al. 2015). Patients with oral disease including involvement of the gingivae can often be managed with local therapies, namely,
topical corticosteroids and calcineurin inhibitors (Taylor et al. 2015). With gingival involvement, avoidance of trauma and improvement of oral hygiene should be part of the management regime (Bagan et al. 2005). For gingival lesions application of topical therapy in a vacuum-formed custom tray may be more effective (Bagan et al. 2005). The choice of medication use in the treatment of MMP depends on the site, severity, and rapidity of progression. If gingival MMP is recalcitrant to local measures and topical therapies, systemic immunosuppressants and immunomodulators may be required. Azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, and cyclophosphamide have been used in the management of severe disease to reduce inflammation, and biological agents such as rituximab are used to reduce autoantibody production (Taylor et al. 2015). Dapsone and other sulphonamides which suppress neutrophil adherence modulate severe vesiculobullous disease (Bagan et al. 2005). Tetracyclines which have anti-inflammatory and immunosuppressive activity and nicotinamide have also been used successfully in managing oral MMP (Chan et al. 2002; Bagan et al. 2005). Systemic corticosteroids either alone or combined with other systemic therapy are effective in achieving rapid control of severe disease; however, the adverse effects tend to limit their long-term use (Bagan et al. 2005; Taylor et al. 2015).

**Linear IgA Disease**

Linear IgA disease is a rare chronic, subepithelial blistering disease that is associated with the presence of linear deposits of IgA along the basement membrane zone. Oral mucosal lesions may occur similarly to oral MMP with gingival involvement rarely seen (Fig. 23). Management is similar to that of MMP but should include exclusion of inflammatory bowel disease (IBD), because of its occasional association with linear IgA disease (Shipman et al. 2012).
**Pemphigus Vulgaris**

Pemphigus vulgaris (PV) is a rare but important autoimmune disease, which frequently first occurs intraorally. Gingival involvement may be in the form of mild erythema, desquamative gingivitis, and/or ulceration (Fig. 24). Antibodies are formed against cell adhesion molecules, particularly desmoglein 3 in the case of oral mucosal disease, leading to progressive bulla formation and subsequent ulceration and desquamation. A biopsy is mandatory to confirm the diagnosis prior to the institution of systemic and topical immunosuppressive therapy, but care should be taken with obtaining an adequate specimen since the tissue is fragile and the epithelium can easily be lost. A perilesional site, not directly involving the gingivae, should be chosen if possible. Histology will show an intraepithelial split with acantholysis (Fig. 25) and with direct immunofluorescence, a rim of IgG may be seen around the suprabasal cells (Fig. 26). Early diagnosis of oral lesions and hence early initiation of appropriate therapy appears to minimize the chance of later severe cutaneous disease in some instances, in part by reducing the likelihood of epitope spread and introduction of antibodies to desmoglein 1 (Endo et al. 2008). Treatment usually involves use of systemic immunosuppressants and benefits.
have been reported from use of systemic corticosteroids, azathioprine, mycophenolate mofetil, plasmapheresis, intravenous immunoglobulins, methotrexate, and the monoclonal antibody to CD20 on B cells, rituximab (Black et al. 2005; McMillan et al. 2015; Cholera and Chainani-Wu 2016). There is still a lack of evidence from good quality clinical studies regarding best interventions for PV (McMillan et al. 2015; Cholera and Chainani-Wu 2016). The response to treatment varies and the incidence of remissions in pemphigus is unclear (Black et al. 2005). If there is gingival involvement, local measures must be included in the management plan and attention to improving and maintaining good oral hygiene and minimizing irritation is essential along with the adjuvant use of topical immunosuppressive therapies in the form of corticosteroids and/or calcineurin inhibitors (Black et al. 2005).

Orofacial Granulomatosis and Oral Crohn’s Disease

Orofacial granulomatosis (OFG) is a term used to describe a group of conditions with a clinical presentation of diffuse swelling of the lower half of the face, particularly the lips, hyperplastic mucosal tags in the buccal mucosa, and diffuse gingival enlargement and/or erythema (Fig. 27). Biopsy shows non-caseating granulomata. A proportion of these patients have underlying Crohn’s disease or sarcoidosis. While the oral lesions may pre-date gastrointestinal Crohn’s disease where investigations have ruled out Crohn’s disease or sarcoidosis, a search for an allergic etiology, particularly to cinnamaldehyde and benzoates, should be undertaken. Management of OFG and oral Crohn’s disease is challenging. Topical and systemic immunosuppressants including intralesional injections of triamcinolone have been used successfully but many patients require systemic interventions to achieve partial or complete remission of signs and symptoms. Topical corticosteroids and tacrolimus have been reported to be beneficial, and systemic therapies include systemic corticosteroids, azathioprine, thalidomide, methotrexate, and in recalcitrant cases biologic agents such as infliximab and adalimumab (monoclonal antibodies against TNF-alpha) have been used (Hegarty et al. 2003; Kolho et al. 2011; Zbar et al. 2012; O’Neill and Scully 2012). A cinnamon and benzoate-free diet has been reported to be beneficial and plays a role in management of OFG (Campbell et al. 2011). Gingival erythema and enlargement can be managed additionally by attention to oral hygiene and dental scaling and debridement. If gingival enlargement persists following treatment of the condition, then surgical intervention may be appropriate in some cases (Bansal et al. 2015).
Granulomatosis with Polyangiitis (Wegener’s Granulomatosis)

Granulomatosis with polyangiitis (GPA), previously known as Wegener’s granulomatosis, is a severe systemic vasculitis affecting medium and small arteries (Falk et al. 2011; Wojciechowska et al. 2016). It is characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract with glomerulonephritis, although many systems may be involved. Approximately one third of patients with GPA will have oral involvement, which, in a small number of cases, can first manifest in the oral mucosa (Almouhawis et al. 2013). The gingivae are the usual site of oral involvement, with the development of a characteristic reddish purple granular hyperplasia, known as “strawberry gingivitis” (Fig. 28) (Cohen and Meltzer 1981; Almouhawis et al. 2013). Diagnosis in clinical practice is based on a combination of the clinical manifestations suggestive of a vasculitis, a biopsy of the affected organ showing necrotizing granulomatous inflammation with vasculitis and the presence in serum of anti-neutrophil cytoplasmic antibodies (ANCA) (Lutalo and D’Cruz 2014; Wojciechowska et al. 2016). The particular pattern of ANCA in GPA is cytoplasmic (c-ANCA), where the antibody binds to proteinase 3 (Relle et al. 2016). Immunosuppression with corticosteroids and cyclophosphamide is used to induce remission with azathioprine and methotrexate for remission maintenance. Rituximab (monoclonal antibody against CD20) is used for severe GPA (Relle et al. 2016).

Pyostomatitis Vegetans

Pyostomatitis vegetans (PyoV) is a rare oral disorder that may affect the gingivae and is associated with Inflammatory Bowel Disease (IBD), in particular ulcerative colitis (Hegarty et al. 2004). It is considered a specific marker of disease activity in ulcerative colitis (Lankarani et al. 2013). The term Pyostomatitis vegetans was first introduced by McCarthy in 1949 and considered the oral counterpart of pyoderma vegetans and since then more than 50 cases have been reported (Hegarty et al. 2004; Clark et al. 2016). Males are affected two to three times more often than females with an average age at presentation of 34 years (Lankarani et al. 2013). Bowel disease may precede the onset of oral lesions by months or years. The condition presents as erythematous, thickened oral mucosa with multiple pustules and superficial erosions and may involve the gingivae (Fig. 29), labial and buccal mucosae, and palate. As vegetating lesions progress, the mucosa may develop thickened folds particularly in the labial and buccal mucosa (Hegarty et al. 2004). Immunological and microbial factors have been suggested as possible etiological factors (Femiano et al. 2009). Skin lesions of pyoderma vegetans may appear at the same time as oral lesions, and liver dysfunction has also been reported in association with PyoV (Hegarty et al. 2004). Histopathologically, PyoV is characterized by intraepithelial and/or subepithelial abscesses containing large numbers of eosinophils (Fig. 30). Peripheral eosinophilia is seen in up to 90% of cases (Lankarani et al. 2013; Wu et al. 2015). Topical and systemic corticosteroids are the mainstay of treatment but medical and/or surgical treatment of any coexisting bowel disease may be effective in controlling oral lesions (Hegarty et al. 2004; Femiano et al. 2009; Lankarani et al. 2013).

Plasma Cell Gingivitis/ Gingivostomatitis

Plasma cell gingivitis is a rare condition which presents as diffuse or more localized erythema and swelling of the gingiva (Fig. 31) characterized by infiltration of polyclonal plasma cells into the subepithelial gingival tissues (Fig. 32). Occasionally the plasma cell proliferation may extend beyond the gingiva in which case the terms plasma cell gingivostomatitis, orofacial plasmacytosis, or oropharyngeal mucosal plasmacytosis are more appropriate (Tong et al. 2008; Madhavarajan and Tighe 2015). The etiology is uncertain but thought to represent an immunological reaction to an allergen (Joshi and Shukla 2015) such as components of toothpaste and
Fig. 28 Granulomatosis with polyangiitis presenting as friable erythematous gingiva in a 63-year-old female on initial presentation (a), post-systemic prednisolone therapy (b), and post-systemic methotrexate and cyclophosphamide therapy (c). Hematoxylin and eosin stained histopathological specimen demonstrating widespread nonspecific inflammatory infiltrate with extravasated red blood cells (d). (Images courtesy of Professor Camile Farah, Perth Oral Medicine & Dental Sleep Centre, Perth, WA, Australia)
tooth powders, chewing gum, and certain foods. Treatment is with topical and/or systemic immunosuppression, in addition to identification of offending agent and its exclusion where possible.

**Cysts, Potentially Neoplastic and Neoplastic Gingival Lesions**

**Odontogenic Cysts and Neoplasms**

Cysts and neoplasms peculiar to the odontogenic tissues may present with gingival involvement when they arise in an intrabony site and expand or erode the cortical plate. Less commonly these lesions can arise within the soft tissues of the gingival complex such as the gingival cyst of the adult (Fig. 33). These occur most often as an asymptomatic elevated dome-like lesion in the mandibular canine and premolar gingivae, without underlying bony involvement. The histology shows a cyst with a thin epithelial lining, usually with focal epithelial thickenings known as plaques. Excision is curative.

Peripheral ameloblastoma (PA), also known as extraosseous ameloblastoma is a type of ameloblastoma that occurs exclusively in the soft tissues of the gingiva or edentulous alveolar areas, showing microscopic features of ameloblastoma and without bone involvement (Vered et al. 2017). It has a predilection for the lingual gingiva in the premolar region of the mandible (Philipsen et al.
PA can mimic nonspecific ulceration and/or pyogenic granuloma/angiogranuloma clinically (Fig. 34a). It shares similar histological features with intraosseous ameloblastomas and retains an unencapsulated and infiltrative histopathological growth pattern (Fig. 34b). However, the recurrence rate is lower, and PA is generally regarded to be less aggressive than intrabony ameloblastomas.

Other benign odontogenic tumours such as calcifying epithelial odontogenic tumour and adenomatoid odontogenic tumour very rarely have peripheral counterparts in the absence of an intrabony component. Benign cementum-producing neoplasms such as benign cementoblastoma and cemento-ossifying fibroma, as well as non-neoplastic bone lesions such as fibrous dysplasia and the osseous dysplasias, may also present as a diffuse swelling of the alveolar bone. These lesions are covered in more detail in separate chapters on “Odontogenic Pathology” and “Non-Odontogenic Bone Pathology.”

Leukoplakia and Erythroplakia

Oral potentially malignant lesions of the gingiva include leukoplakia, erythroleukoplakia, and erythroplakia. Homogeneous and non-homogeneous leukoplakia may develop on the gingiva (Fig. 35) and are considered to be at risk
of malignant transformation. Less commonly, erythroplakia may be diagnosed which has a higher malignant potential than leukoplakia (Fig. 36). Biopsy is necessary to establish the degree of epithelial dysplasia (Warnakulasuriya et al. 2011). Proliferative verrucous leukoplakia (PVL) is a rare form of leukoplakia which progresses, often over many years, from a single localized homogeneous leukoplakia to multiple widespread nonhomogeneous verrucous leukoplakic lesions with a high rate of change to verrucous and/or squamous cell carcinoma. It is characterized by extensive and multifocal white adherent lesions which frequently involve the gingiva (Fig. 37), in addition to the palate and buccal mucosa (Bagan et al. 2003; Gondalfo et al. 2009). The diagnosis can only be made retrospectively and the underlying etiopathogenesis is poorly understood. PVL requires close monitoring, and adequate management is difficult. There is some evidence to suggest carcinoma arising in PVL have a better prognosis than other intraoral carcinomas (Akrish et al. 2015). Oral potentially malignant lesions are covered in more detail in separate chapters on “▶ White and Red Lesions of the Oral Mucosa” and “▶ Oral Mucosal Malignancies.”
Oral Squamous Cell Carcinoma

Over 90% of oral cancers are squamous cell carcinomas and the gingivae or edentulous alveolar mucosa are sites that may be involved. Oral squamous cell carcinoma (OSCC) may present as a persistent nonhealing ulcer (Fig. 38a), a persistent white, red, or mixed white and red patch or an exophytic mass (Fig. 38b). Patients may be asymptomatic or present with pain, bleeding, altered sensation, difficulty eating, speaking, swallowing and/or cervical lymphadenopathy.

OSCC, including gingival SCC, is seen most frequently in patients with a history of tobacco and alcohol use, although gingiva was a relatively frequent site of carcinoma in elderly females who had never smoked or drank alcohol (Dahlstrom et al. 2008). Any lesion on the gingivae which does not show significant resolution following elimination of possible causes should be biopsied within 3 weeks. A degree of urgency in management is advisable, because, while early gingival SCC can usually be treated successfully by local surgery, the proximity of the gingival soft tissues to alveolar bone can lead to early bone involvement. Invasion of the underlying bone, particularly invasion of the mandibular canal, presents a difficult surgical problem and poor 5-year survival (Okura et al. 2016).

Lymphoma

Lymphoma is a term used to describe a heterogeneous group of malignant disorders derived from lymphoid cells and their precursors. Extranodal Hodgkin’s lymphoma is uncommon and most primary oral lymphomas are B-cell non-Hodgkin’s lymphoma (NHL), particularly diffuse large B cell NHL (Iguchi et al. 2012; Silva et al. 2016). Lymphoma is the second most common intraoral malignancy after SCC (Epstein et al. 2001). Waldeyer’s ring is the most frequent oropharyngeal site involved, but gingival lesions occur in otherwise healthy people (Fig. 39a, b), as well as in those with immunodeficiencies. A study of 68 extranodal B cell NHL in the head and neck reported that 30 were intraoral; and the most frequent intraoral location was the gingiva (Bagan et al. 2015). Gingival NHL may be associated with alveolar bone loss, edema, and pain mimicking dental periapical and/or periodontal infections and leading to a delay in diagnosis (Spatafore et al. 1989; Jessri et al. 2013). The conventional histopathology findings need to be interpreted along with immunohistochemistry with a panel of appropriate antibodies and molecular investigations for various translocations (Fig. 40a, b). Prognosis is grade-dependent and ranges from sustained long-term survival to a 5-year mortality rate of around 60%. Hematologists are the primary specialists involved in provision of treatment for lymphoma.

Other Primary Malignant Neoplasms

Rarely other primary oral malignant neoplasms may involve the gingivae. Oral malignant melanoma usually presents as a pigmented lesion on the gingivae or palate (Fig. 41a). It is an aggressive neoplasm derived from malignant transformation of oral mucosal melanocytes. Early in its evolution, it is likely to be a dark brown to black irregular macule which progresses to a raised nodule with ulceration and soon involves the underlying alveolar bone (Fig. 41b, c). An observational study of 46 new cases involving intraoral malignant melanoma emphasized their clinical
Fig. 38  Persistent gingival ulcer which histologically was found to be a squamous cell carcinoma (a). Note the leukoplakia around the gingival margin of the adjacent teeth. Gingival squamous cell carcinomas can present in a variety of forms including as an erythematous somewhat exophytic lesion as shown in (b).

Fig. 39  Intraoral lymphomas may be part of disseminated disease, but the first indication of lymphoma may be presentation with a painless soft tissue swelling involving the gingivae, as shown in a, b, or posterior hard palate.

Fig. 40  (a) is a photomicrograph from an incisional biopsy of a gingival mass in a 63-year-old female and shows a dense infiltrate of neoplastic lymphoid cells which were CD3 positive (b). The diagnosis was diffuse large B-cell lymphoma.
and histological diversity. The greater majority of these were found in the maxillary mucosa with clinicians’ impressions of these varying from benign fibrous growths to high grade malignancies. The histopathological features also varied widely among cases, with two cell types predominating, namely, epithelioid cells and spindle cells, often in combination. Only 53.1% demonstrated melanin pigmentation (Housley Smith et al. 2016).

Leukemia, a group of malignancies of hematopoietic stem cells, may occasionally manifest as diffuse gingival swelling when leukaemic cells infiltrate the gingival soft tissues (Fig. 42a, b). As the normal hematopoietic stem cells in the bone marrow are displaced by malignant cells, the oral mucosa, including the gingivae, may show evidence of neutropenia with increased susceptibility to infection and ulceration and thrombocytopenia with petechial hemorrhages and a tendency to spontaneous or prolonged bleeding.

Kaposi sarcoma (KS), an AIDS defining malignancy, may present as oral mucosal red, brown, or purple macules and/or swellings which may affect the gingivae (Fig. 43). Kaposi sarcoma-associated herpesvirus (KSHV) is necessary for the development of KS which usually occurs in a setting of immunosuppression (Chang et al. 1994; Dittmer and Damania 2016). This virus also causes other diseases in AIDS patients, including multicentric Castleman’s disease, a B cell lymphoproliferative disorder, and specific lymphomas (Goncalves et al. 2017). Most primary KSHV infections are asymptomatic. The virus infects endothelial cells, epithelial cells, B cells, monocytes, and dendritic cells where it becomes latent, but it can be reactivated and induced to replicate in certain circumstances in response to severe T cell depletion or inactivation (Dittmer and Damania 2016; Goncalves et al. 2017). The diagnosis is made by demonstrating KSHV in lesional spindle cells in a biopsy sample.
While the incidence and mortality from Kaposi sarcoma has dropped significantly since the use of ART, it remains the most common AIDS-associated malignancy in both developed and developing nations (Wen and Damania 2010).

**Metastases to the Gingiva**

Metastases to the oral regions are rare and are usually associated with widespread metastatic disease. Bony metastases are the most likely, particularly to the mandible, but soft tissue metastases do occur, and in these instances the gingival mucosa is the most common oral mucosal site involved (Allon et al. 2014). An association has been noted between gingival metastases and the presence of teeth, leading to the suggestion that cytokines related to periapical and periodontal inflammation facilitate the development of a suitable niche for circulating tumour cells to thrive (Allon et al. 2014; Hirshberg et al. 2014). The most common clinical presentation of a gingival metastasis is a painful swelling, with or without surface ulceration, which rapidly increases in size. If bone is involved and the lesion is located in the vicinity of the inferior alveolar nerve, labial paresthesia or anesthesia may develop. In these instances, radiographs are likely to show radiolucency with poorly defined margins. In males, the most common primary sites that metastases to the oral region are lung, kidney, liver, and prostate, and in females, metastases are most likely to be from breast, female genital organs, kidney, and colorectum (Hirshberg et al. 2014).

**Conclusions and Future Directions**

Gingival lesions may be of a simple local nature or may be an indication of severe local or systemic disease. Recognizing the signs and/or symptoms of gingival pathology will ensure prompt and appropriate management for the patient. Careful clinical observation will continue to be critical to the development of a clinical diagnosis for gingival pathology. However, diagnostic techniques are
changing. Biopsy of a lesion for conventional histopathology remains the gold standard for most diagnoses, but this is often interpreted in conjunction with the results of immunofluorescence and immunohistochemistry studies. We are increasingly looking beyond the tissue architecture and cellular features to study genetic and protein-related biomarkers from lesional tissue, blood, and potentially saliva. The diagnostic applications of saliva as a biofluid are beginning to be understood but reliable cost-effective technology is not yet available.

Cross-References

▶ Clinical Evaluation of Oral Diseases
▶ Clinical Immunology in Diagnoses of Maxillofacial Disease
▶ Diagnostic Imaging Principles and Applications in Head and Neck Pathology
▶ Head and Neck Malignancies
▶ Laboratory Medicine and Diagnostic Pathology
▶ Non-odontogenic Bone Pathology
▶ Normal Variations in the Anatomy, Biology and Histology of the Maxillofacial Region
▶ Odontogenic Bacterial Infections
▶ Odontogenic Pathology
▶ Oral and Maxillofacial Viral Infections
▶ Oral Lichen Planus
▶ Oral Manifestations of Systemic Diseases and Their Treatments
▶ Oral Mucosal Malignancies
▶ Oral Ulcerative Lesions
▶ Oral Vesicular and Bullous Lesions
▶ Pediatric Oral Medicine
▶ Pharmacotherapeutic Approaches in Oral Medicine
▶ Pigmented Lesions of the Oral Mucosa
▶ White and Red Lesions of the Oral Mucosa

References


