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Non–plaque-induced gingival diseases

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Abstract

While plaque-induced gingivitis is one of the most common human inflammatory diseases, several non–plaque-induced gingival diseases are less common but often of major significance for patients. The non–plaque-induced gingival lesions are often manifestations of systemic conditions, but they may also represent pathologic changes limited to gingival tissues. A classification is proposed, based on the etiology of the lesions and includes: Genetic/Developmental disorders; Specific infections; Inflammatory and immune conditions and lesions; Reactive processes; Neoplasms; Endocrine, Nutritional and metabolic diseases; Traumatic lesions; and Gingival pigmentation.

KEYWORDS

classification, diagnosis oral, epulis, gingiva, gingival diseases, immunological, inflammation, mouth mucosa, oral manifestations, oral medicine, periodontal disease, rare diseases

Human gingiva as well as other oral tissues may exhibit several non–plaque-induced pathologic lesions, which may in some instances be manifestations of a systemic condition or a medical disorder. They may also represent pathologic changes limited to gingival tissues. Although these lesions are not directly caused by plaque, their clinical course may be impacted by plaque accumulation and subsequent gingival inflammation. Dentists are the key healthcare providers in establishing diagnoses and formulating treatment plans for patients affected by such lesions. Specialists in periodontology should be familiar with and be able to diagnose, treat, or refer for treatment any such lesion.

A review of non–plaque-induced gingival lesions was presented at the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions,[1] and the present review aims to add available additional literature as well as diseases and conditions which were not included in the former review. Several of the diseases and their treatment have been reviewed recently.[2–4] The purpose of the current review is not to repeat the details of such texts, but to present a contemporary classification of the most relevant non–plaque-induced gingival diseases and conditions (Table 1) and to discuss briefly the more common of these. The major difference between the present classification proposal and that of the 1999 workshop is creation of a more comprehensive nomenclature and inclusion of ICD-10 diagnostic codes. Because some of the conditions seldom manifest in the oral cavity and some even more seldom present gingival manifestations, detailed appraisal is included within Table 2.

DESCRIPTION OF SELECTED DISEASE ENTITIES:

1 | GENETIC/DEVELOPMENTAL ABNORMALITIES

1.1 | Hereditary gingival fibromatosis (HGF)

Clinically, gingival fibromatosis may present gingival overgrowth in various degrees. Compared to drug-related gingival overgrowth, hereditary gingival fibromatosis is a rare disease which may occur as

TABLE 1 Classification table summary: non–plaque-induced gingival diseases and conditions

1 Genetic/developmental disorders
- 1.1 Hereditary gingival fibromatosis (HGF)

2 Specific infections
- 2.1 Bacterial origin
  - Necrotizing periodontal diseases (*Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., *Prevotella intermedia*, and others)
  - *Neisseria gonorrhoeae* (gonorrhea)
  - *Treponema pallidum* (syphilis)
  - *Mycobacterium tuberculosis* (tuberculosis)
  - Streptococcal gingivitis (strains of streptococcus)
- 2.2 Viral origin
  - Coxsackie virus (hand-foot-and-mouth disease)
  - Herpes simplex 1/2 (primary or recurrent)
  - Varicella-zoster virus (chicken pox or shingles affecting V nerve)
  - Molluscum contagiosum virus
  - Human papilloma virus (squamous cell papilloma, condyloma acuminatum, verrucca vulgaris, and focal epithelial hyperplasia)
- 2.3 Fungal
  - Candidosis
  - Other mycoses (e.g., histoplasmosis, aspergillosis)

3 Inflammatory and immune conditions and lesions
- 3.1 Hypersensitivity reactions
  - Contact allergy
  - Plasma cell gingivitis
  - Erythema multiforme
- 3.2 Autoimmune diseases of skin and mucous membranes
  - Pemphigus vulgaris
  - Pemphigoid
  - Lichen planus
  - Lupus erythematosus
- 3.3. Granulomatous inflammatory conditions (orofacial granulomatosis)
  - Crohn's disease
  - Sarcoidosis

4 Reactive processes
- 4.1 Epulides
  - Fibrous epulis
  - Calcifying fibroblastic granuloma
  - Pyogenic granuloma (vascular epulis)
  - Peripheral giant cell granuloma (or central)

5 Neoplasms
- 5.1 Premalignant
  - Leukoplakia
  - Erythroplakia
- 5.2 Malignant
  - Squamous cell carcinoma
  - Leukemia
  - Lymphoma

6 Endocrine, nutritional, and metabolic diseases
- 6.1 Vitamin deficiencies
  - Vitamin C deficiency (scurvy)

7 Traumatic lesions
- 7.1 Physical/mechanical insults
  - Frictional keratosis
  - Toothbrushing-induced gingival ulceration
  - Factitious injury (self-harm)
- 7.2 Chemical (toxic) insults
  - Etching
  - Chlorhexidine
  - Acetylsalicylic acid
  - Cocaine
  - Hydrogen peroxide
  - Dentifrice detergents
  - Paraformaldehyde or calcium hydroxide
- 7.3 Thermal insults
  - Burns of mucosa

8 Gingival pigmentation
- Gingival pigmentation/melanoplakia
- Smoker's melanosis
- Drug-induced pigmentation (antimalarials; minocycline)
- Amalgam tattoo

an isolated disease or as part of a syndrome. It has a genetic basis in mutations of the *Son of Sevenless* gene[5] (see Table 2).

2 | SPECIFIC INFECTIONS

2.1 | Bacterial origin

Necrotizing periodontal disease

Necrotizing gingivitis (NG), necrotizing periodontitis (NP), and necrotizing stomatitis (NS) are severe inflammatory periodontal diseases caused by bacterial infection in patients with specific underlying risk factors (poor oral hygiene, smoking, stress, poor nutrition, compromised immune status [e.g., HIV]).

Although the necrotizing diseases often run an acute, rapidly destructive course, the term acute has not been included in the diagnoses since 1999. Since superficial necrosis always involves an ulcer, it is requested to delete the term "ulcerative." The term "gingivitis" is used for lesions only involving gingival tissue and characterized by no loss of periodontal attachment.[6] Central necrosis of the papillae may result in considerable tissue destruction with formation of a crater. If loss of attachment is established, the diagnosis consequently becomes NP.[7] For lesions with ulceration extending >1.0 cm from the gingival margin, including tissue beyond the mucogingival junction, the term NS has been used.[8] The three necrotizing diseases appear to represent various stages of the same disease process,[9] and a distinction between the different manifestations has not always been made in the literature. As a result, the term "necrotizing periodontal disease" (NPD) is proposed as a common term encompassing NG, NP, and NS. Further details are presented in Table 2. A constant and variable part of the microflora in NPD lesions have been described. The constant flora primarily contains *Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Prevotella intermedia*; the variable flora consists of a heterogeneous array of bacterial types.[10,11]

Other bacterial infections

Non–plaque-associated bacterial infections of the gingiva are uncommon. Gingivitis caused by a specific bacterial infection may, however, arise due to a loss of homeostasis between non–plaque-related pathogens and innate host resistance.[12] Acute streptococcal gingivitis is an example of a rare acute non–plaque-associated gingival inflammation.[13–15] Other examples of specific bacterial infections of the gingiva may also be due to *Neisseria gonorrhoeae*[16,17] and *Treponema pallidum*.[12,16–18] Orofacial tuberculosis is a rare manifestation of extrapulmonary tuberculosis, occurring in approximately 0.1% to 5% of all tuberculosis infections.[19]

2.2 | Viral origin

The most important viruses to cause gingival manifestations are Coxsackie viruses and the herpes viruses including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus.[20]

Although these viruses most often infect individuals in childhood, primary infections may occur in adult life as well. They may give rise to oral mucosal disease followed by periods of latency and sometimes reactivation.

Coxsackie viruses

Coxsackie viruses may cause herpangina and hand-foot-and-mouth disease (synonym: vesicular stomatitis with exanthema). While herpangina does not involve gingiva, hand-foot-and-mouth disease is a common contagious vesicular viral disease affecting skin and oral mucosa including gingiva. The lesions are primarily seen in children and mainly caused by coxsackie viruses A6, A10, and A16 (see Table 2).[21]

HSV-1 and HSV-2

HSV-1 usually causes oral manifestations, in contrast to HSV-2, which is primarily involved in anogenital infections and only occasionally in oral infections.[20]

Herpetic gingivostomatitis

Primary herpetic infection typically occurs in infants and has an incubation period of 1 week. It may run an asymptomatic course in early childhood, but it may also give rise to gingivostomatitis with severe manifestations. A characteristic feature is the formation of few or many vesicles, which rupture, coalesce, and leave fibrin-coated ulcers often of irregular extension (Table 2).[20,22]

Recurrent intraoral herpes simplex lesions typically occur in adults and have a much less dramatic course (Table 2). As a result, they may remain undiagnosed or mistaken for aphthous ulcerations[23,24] despite the fact that aphthous ulcers do not typically affect keratinized mucosa.[23]

Varicella-zoster virus

The primary infection of varicella-zoster virus causes varicella (chicken pox), which occurs mainly in children (Table 2). Later reactivation of the virus in adults causes herpes zoster (shingles) with unilateral lesions following the distribution of an infected nerve. If the second or third branch of the trigeminal nerve is involved, skin lesions may be associated with intraoral lesions, including gingival lesions,[25,26] and intraoral lesions may occur alone.[26] Initial symptoms are pain and paresthesia, which may be present before lesions appear.[27] The initial lesions are vesicles, which soon rupture and leave fibrin-coated small ulcers, often coalescing to irregular forms (Table 2).[28]

Molluscum contagiosum virus

Molluscum contagiosum virus of the poxvirus family causes molluscum contagiosum, which is a contagious disease with infrequent oral manifestations (Table 2).[29,30] It is seen in infants with immature immune systems and manifests as discrete umbilicated papules on the skin. In adults, the disease appears in the genital areas and is often sexually transmitted.

Human papilloma virus (HPV)

More than 100 types of HPV have been identified, and at least the following 25 types have been detected in oral lesions: 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 31, 32, 33, 35, 40, 45, 52, 55, 57, 58, 59, 69, 72, 73. The benign oral lesions, associated with HPV infection, include squamous cell papilloma, condyloma acuminatum, verruca vulgaris, and focal epithelial hyperplasia, and they appear to be associated with different distinct HPV subtypes. Oral benign HPV lesions are mostly asymptomatic, and may persist or regress spontaneously (Table 2).[31]

2.3 | Fungal origin

A number of fungi may give rise to oral infections, including candidosis, histoplasmosis, aspergillosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, cryptococcosis, geotricosis, mucormycosis.[32] Several of these are uncommon, and oral manifestations may more likely occur with immune deterioration.[33,34] Oral mycoses can cause acute, chronic, and mucocutaneous lesions.[35] Candidosis is the most common mouth mycosis, while histoplasmosis and aspergillosis are less common (Table 2).

Candidosis

Several candida species may be isolated from the mouth of humans, including *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. guillermondii*. The most common fungal infection of the oral mucosa is candidosis mainly caused by *C. albicans*. *C. albicans* is a normal commensal organism of the oral cavity but also an opportunistic pathogen.[36] While candidal infection can be seen anywhere in the oral mucosa, lesions of the gingiva are seldom seen in otherwise healthy individuals. The most common clinical characteristic of gingival candidal infection is redness of the attached gingiva, often with a granular surface.

Nodular gingival lesions are uncommon and are characterized by slightly elevated nodules of a white or reddish color.[37] Diagnosis of candidal infection can be accomplished on the basis of culture, smear, and biopsy. "Linear gingival erythema" described in the 1999 International Workshop, sometimes associated with HIV infection, is now generally regarded as gingival candidosis and has therefore been removed from this classification.

3 | INFLAMMATORY AND IMMUNE CONDITIONS AND LESIONS

3.1 | Hypersensitivity reactions

Contact allergy

Oral mucosal manifestations of hypersensitivity (allergy) are very uncommon. As mentioned in the 1999 classification review,[1] such

TABLE 2 Features of the more common non–plaque-induced gingival lesions and conditions

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
1. Genetic/developmental disorders					
1.1. Hereditary gingival fibromatosis	K06.1	Generalized fibrous gingival enlargement of tuberosities, anterior free/attached gingiva and retro-molar pads	Mutation localized to 2p21-p22 (HGF1) & 5q13-q22 (HGF2) Mutations of "Son of Sevenless" genes (SOS 1, SOS2)[119]	N/A	Excisional biopsy for histopathology
2. Specific infections					
2.1. Bacterial origin					
Necrotizing periodontal diseases	A69.0	Ulceration with central necrosis of the papillae may result in considerable tissue destruction with formation of a crater[7,8]	*Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Prevotella intermedia* and others[10,11]	Poor oral hygiene, smoking, stress, poor nutrition, immune compromise e.g. HIV	Characteristic clinical features
Gonorrhea	A54.8	Unspecific lesions with ulcers or fiery red mucosa and white pseudomembrane with or without symptoms[120]	*Neisseria gonorrhoeae*	May be associated with painful pharyngitis and lymphadenopathy. Genital infection of sexual partner.	Microbiological identification of pathogen
Syphilis	A51.2	Fiery red, edematous and often painful ulcerations, asymptomatic chancres or mucous patches, or atypical non-ulcerated, inflamed gingivitis	*Treponema pallidum*		Clinical features combined with dark-field examination of smear. Serologic reactions are present after few weeks.
Tuberculosis	A18.8	Nodular or papillary proliferation of inflamed gingival tissues[19]	*Mycobacterium tuberculosis*	Most often combined with pulmonary infection	Biopsy demonstrating granulomas with multinucleated giant cells
Streptococcal gingivitis	K05.01	Acute gingivitis not associated with plaque	Strains of streptococcus	Sometimes preceded by upper respiratory infection	Biopsy combined with microbiologic examination
2.2. Viral origin					
Hand-foot-and-mouth disease		Small vesicles that after rupture leave fibrinous coated ulcers. Usually in children	Coxsackie virus A 6, A 10 and A 16	Similar skin lesions of hands and feet; sometimes fever	Clinical features with lesions of skin and oral mucosa
Primary herpetic gingivostomatitis	B00.2	Gingivostomatitis with severe manifestations including painful gingivitis, ulcerations, edema and stomatitis	Herpes simplex virus types 1 and 2	Lymphadenitis, eventually fever	Few or many vesicles, which rupture, coalesce, and leave fibrin-coated ulcers often of irregular extension
Recurrent intraoral herpes simplex	B00	Cluster of small painful ulcers in attached gingiva and hard palate[23]	Herpes simplex virus types 1 and 2		Characteristic lesions combined with patient history
Chicken pox (varicella)	B01.8	Usually affecting children: small yellowish vesicles which rapidly rupture	Varicella-zoster virus	Fever, malaise, and a skin rash	Clinical features

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Shingles (herpes zoster)	B02	Unilateral painful ulcers preceded by vesicles. Lesions coalesce to form irregular ulcers.[28]	Varicella- zoster virus	Sometimes combined with skin lesions	Affecting second or third branch of trigeminal nerve
Molluscum contagiosum virus	B08.1	Molluscum contagiosum is a skin and mucosal disease of viral origin with infrequent oral mucosal involvement[30]	Molluscum contagiosum virus, which is a virus of the poxvirus family	Discrete umbilicated papules on the skin of face and[29] trunk or in adults, in the genital areas due to sexual transmission	Clinical features
Squamous cell papilloma, condyloma acuminatum, verrucca vulgaris and focal epithelial hyperplasia	B07.8	Asymptomatic exophytic papillomatosis, verrucous or flat lesions[31]	Human papilloma virus (HPV)		Histopathology of removed lesion
2.3. Fungal					
Candidosis	B37	Various types of clinical manifestations including: • pseudomembranous (also known as thrush in neonates) • erythematous • plaque-like • nodular[37]	Various Candida-species, most commonly *Candida albicans*	Sometimes oral involvement is secondary to a more serious systemic infection	Definitive diagnosis is confirmed with histologic review of biopsied tissue as well as pertinent culture results
Histoplasmosis	B39	Nodular, papillary or granulomatous lesions, which develop loss of tissue with ulcerations and pain[32]	*Histoplasma capsulatum*		Clinical features, histopathologic examination and/or culture
Aspergillosis	B44	Early stage characterized by violaceous marginal gingiva. More advanced lesions become necrotic and covered by a pseudomembrane containing fungal hyphae.	*Aspergillus spp.*	Oral involvement is commonly secondary to more serious systemic infection[33]. In the late stage, the lesions may progress and include destruction of the alveolar bone and surrounding facial muscles.	Clinical features, histopathologic examination and/or culture[34]
3. Inflammatory and immune conditions and lesions					
3.1. Hypersensitivity reactions					
Contact allergy	K08.55/ Z91.01/ Z91.04	Redness and sometimes lichenoid lesions	Type IV hypersensitivity to dental restorative materials, dentifrices, mouthwashes and foods		Histopathology shows chronic inflammatory reaction often lichenoid infiltration of primarily lymphocytes

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Plasma cell gingivitis	C90	Erythematous gingiva with a velvety texture usually affecting the anterior maxillary gingiva[39]			Histopathology reveals dense infiltrate of plasma cells in lamina propria.[121] Allergen to be identified by dermatologist.
Erythema multiforme	L51	The manifestations are varied, the most characteristic having a rounded shape with a central red area, a paler pink or edematous zone, and a red periphery. May also present only with erythema, erosions and ulcers.		May be associated with skin lesions usually appearing symmetrically on the distal extremities and progressing proximally	Clinical manifestations combined with patient history and biopsy
3.2. Autoimmune diseases of skin and mucous membranes					
Pemphigus vulgaris	L10	Gingival manifestation is usually described as desquamative gingivitis and/or as vesiculo-bullous lesions of the free and attached gingiva characterized by intraepithelial bullae which, after rupture, leave erosions[42,62]	The intraepithelial bullae in skin and mucous membranes are due to formation of autoantibodies directed against desmosome-associated protein antigens (desmoglein-3) residing in epithelial and epidermal intercellular substance	Bullous lesions of the skin are common	Diagnosis is based on clinical presentation and confirmed by histopathology and the presence of circulating autoantibody titers to desmoglein 1 and 3 which can be detected by enzyme-linked immunosorbent assay
Pemphigoid	L12.1	Desquamative lesions of the gingiva presenting as intensely erythematous areas. Rubbing of gingiva may precipitate bulla formation, which is called a positive Nicholsky sign and is caused by the destroyed adhesion of the epithelium to the connective tissue.	Caused by autoantibodies towards hemidesmosome or lamina lucida components resulting in detachment of the epithelium from the connective tissue in the basement membrane zone	Scarring is a serious concern for ocular lesions	Clinical features and histopathology. Circulating antibodies are not always found by indirect immunofluorescence.
Lichen planus	L43.8	Papular, reticular, plaque type, erythematous (atrophic), ulcerative (erosive) or bullous lesions[55]	Inflammatory reaction towards an unidentified antigen in the basal epithelial layer/basement membrane zone		Presence of papular or reticular lesions are characteristic of lichen planus. Diagnosis based on clinical features and histopathology[49]
Lupus erythematosus (LE)	L93	The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae. Ulcerations may be a sign of systemic LE.[57,59]	Deposits of antigen−-antibody complexes appear to play a role in the tissue damage characteristic of the disease[122]	The dark-red "butterfly" skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks[60]	Clinical features and histopathological findings
3.3 Granulomatous inflammatory conditions (orofacial granulomatosis)					
Crohn's disease	K50	Cobblestone appearance of the oral mucosa, linear ulceration and gingival overgrowth[60]	Granuloma in the soft tissue of the oral cavity or the intestinal soft tissue	General complications, intestinal pain, anal fissures, diarrhea. Labial enlargement is common.	Clinical and histopathological findings

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Sarcoidosis	D86.8	Gingival swelling, nodules, ulcerations and gingival recession, loosening of teeth and swelling of salivary glands	Granuloma in the soft tissue of the oral cavity or in the intestinal soft tissue		Clinical and histopathological findings
4. Reactive processes					
4.1 Epulides					
Fibrous epulis	K06.8	Exophytic smooth-surfaced pink masses of fibrous consistency attached to the gingiva[65,66]	Presumably the result of continued physical trauma [65,66]		Clinical and histopathologic features
Calcifying fibroblastic granuloma	L92.8	Pedunculated or sessile red to pink mass usually derived from the interdental papilla			Clinical and histopathologic features
Pyogenic granuloma (vascular epulis)	L98	Ulcerated, smooth or lobulated pedunculated or sessile mass, red to pink in color depending on the duration of the lesion			Clinical and histopathologic features
Peripheral giant cell granuloma (or central)	M27.1	Well-defined, sessile or pedunculated soft tumor-like process with a purple, sometimes bluish to brownish color[123,124]			Clinical and histopathologic features
5. Neoplasms					
5.1 Premalignant					
Leukoplakia	K13.21	Not-removable white spot in the oral mucosa with smooth, corrugated or verrucous surface[72,73]	Tobacco and alcohol usage may be involved		Clinical and histopathologic features ruling out other diagnoses
Erythroplakia	K13.29	Red, often sharply demarcated with the surface below the surrounding mucosa	May be associated with oral lichen planus[125]		Clinical and histopathologic features ruling out other diagnoses.
5.2 Malignant					
Squamous cell carcinoma	44.02	Gingival squamous cell carcinoma often presents as painless exophytic masses, red and white speckled patches or non-healing ulcerations involving the keratinized gingiva	Tobacco and alcohol usage may be involved in the pathogenesis		Clinical and histopathologic features
Leukemia	C95	Various changes including pallor of the oral mucosa, pain, petechiae and ecchymosis, gingival bleeding and gingival swelling due to leukemic cell infiltration.[82–84] Deep punched-out ulcerations and necrosis on gingiva and tooth mobility.[126,127]	Immunosuppression due to malignant transformation of leukocyte production in the bone marrow	Dysphagia, facial paralysis, and paresthesia of the face, lips, tongue and chin, and trismus may occur	Differential blood cell analysis of the venous blood, bone marrow biopsy

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
Lymphoma	C85.91	Non-specific gingival swelling may be the first manifestation of non-Hodgkin lymphoma, mimicking a periodontal abscess or pyogenic granuloma[128–130]	Hodgkin lymphoma is associated with Epstein-barr virus and an increased incidence is seen in immunocompromised patients[131,132]	Swelling of lymph nodes	Histopathology of biopsy
6. Endocrine, nutritional and metabolic diseases					
6.1. Vitamin deficiencies					
Vitamin C deficiency (Scurvy)	E64.2	Enhanced gingival bleeding, ulceration, swelling	Changes in connective tissue metabolism due to lack of ascorbic acid	Malaise	Reduced plasma ascorbic acid concentration
7. Traumatic lesions					
7.1. Physical/mechanical insults					
Frictional keratosis	K13.29	White lesion sharply demarcated, leukoplakia-like asymptomatic, homogeneous whitish-plaques that are irremovable usually presenting on facial attached gingiva[92]	Limited trauma often due to inappropriate toothbrushing		Clinical and histopathological features
Toothbrushing-induced gingival ulceration	K05.10	Superficial, often horizontal gingival laceration to major loss of tissue often resulting in gingival recession[93,94]	Excessive trauma, due to inappropriate toothbrushing		Clinical findings
Factitious injury (self-harm)	F68.1	Unusual tissue damage with ulceration in areas that can easily be reached by fingers and instruments[91]	Pressure from fingernails, application of pencils, pocket knives or other types of instruments[91]		Clinical findings combined with patient history
7.2. Chemical (toxic) insults					
Etching, chlorhexidine, acetylsalicylic acid, cocaine, hydrogen peroxide, dentifrice detergents, paraformaldehyde or calcium hydroxide	L43.8	Surface slough or ulceration	May be related to patient's use of chlorhexidine,[97,98] acetylsalicylic acid,[99,100] cocaine,[101] hydrogen peroxide,[102,103] dentifrice detergents,[104] paraformaldehyde or calcium hydroxide		Clinical findings combined with patient history
7.3. Thermal insults					
Burns of mucosa	K13.7	Erythematous lesions that may slough a coagulated surface. Vesicles and sometimes ulceration, petecchia or erosion.[108]			Clinical findings combined with patient history

(*Continues*)

TABLE 2 (continued)

Subheading and diagnosis	ICD-10 code	Clinical presentation	Etiology	Associated conditions	Diagnostic investigations
8. Gingival pigmentation					
Gingival pigmentation/ melanoplakia	L81.9	Brownish to black diffusely pigmented areas	Most often physiologic pigmentation in persons with a dark skin complexion	Sometimes combined with endocrine disturbances (Addison's disease), syndromes (Albright syndrome, Peutz Jegher syndrome)	Clinical findings eventually combined with laboratory investigation
Smoker's melanosis	K13.24	Brownish areas most often on mandibular facial gingiva[111,112]	Deposits of melanin synthesized due to influence of smoking		Clinical findings in smokers
Drug-induced pigmentation (antimalarials, minocycline)	L83	Bluish grey or brownish to black diffuse pigmentation	Accumulation of melanin, deposits of drug or drug metabolites, or synthesis of pigments under the influence of a drug or deposition of iron following damage to the vessels		Clinical finding combined with patient history
Amalgam tattoo	L81.8	Usually small bluish or grey to black localized pigmentation, which is not elevated	Accumulation of amalgam fragments or small amalgam particles. May be result of fracture of amalgam filling during extraction or due to small particles of amalgam being spilled into wounds during restorative procedures.		Clinical findings eventually combined with radiographs to identify larger fragments. In cases where amalgam tattoo cannot be differentiated from other causes of oral pigmentation, a biopsy may be performed.[118]

reactions may be due to dental restorative materials, dentifrices, mouthwashes, and foods and are most often type IV hypersensitivity reactions (contact allergy).

Plasma cell gingivitis

Plasma cell gingivitis is an uncommon inflammatory condition usually affecting the anterior maxillary gingiva and of uncertain etiology. While some authors have associated plasma cell gingivitis with a hypersensitivity response to antigens in various substances,[38] others have raised doubt whether plasma cell gingivitis is a distinct clinicopathologic entity.[39]

Erythema multiforme (EM)

EM is an uncommon, self-limiting, acute immune-inflammatory disorder of the oral mucosa (Table 2). The etiology of EM is unclear in most patients, but it appears to be an immunologic hypersensitivity reaction mediated by T-lymphocytes. The disorder may present a diagnostic dilemma because infections (particularly, herpes simplex and mycoplasma pneumoniae) and some drugs seem to predispose toward the development of erythema multiforme, in what are believed to be immune complex disorders.[40]

3.2 | Autoimmune diseases of skin and mucous membranes

Pemphigus vulgaris (PV)

PV is an autoimmune vesiculo-bullous disease of skin and mucous membranes. Involvement of the oral mucosa is common, and in about 54% of cases, the oral cavity has been reported to be the primary site of involvement.[41] The disease is characterized by intraepithelial bullae in skin and mucous membranes due to auto-antibodies directed against desmosome-associated protein antigens (desmoglein-3). Oral mucosal lesions, including gingival lesions, may precede skin involvement.[42] In the literature, gingival localization of PV usually manifests as desquamative gingivitis and/or as vesiculo-bullous lesions of the free and attached gingiva; early lesions only rarely appear as extensive erythema and erosions (Table 2).[43]

Pemphigoid

Pemphigoid is a group of mucocutaneous disorders caused by autoantibodies toward antigens of the basement membrane, resulting in detachment of the epithelium from the connective tissue. If only mucous membranes are affected, the term mucous membrane pemphigoid (MMP) is often used.[44] Scarring is an important ocular complication but not for oral mucosal lesions.[43] Any area of the oral mucosa may be involved in MMP, but the main clinical manifestation is desquamative lesions of the gingiva presenting as intensely erythematous areas (Table 2).[45–47] Usually the bullae rupture rapidly, leaving fibrin-coated ulcers. The separation of epithelium from connective tissue at the basement membrane area is the main diagnostic feature of MMP, and circulating serum antibodies are not always revealed by indirect immunofluorescence.[48]

Lichen planus

Lichen planus is a common mucocutaneous disease with frequent manifestation on the gingiva. Oral involvement alone is common, and concomitant skin lesions in patients with oral lesions have been found in 5% to 44% of the cases.[49,50] The major characteristic of this disease is an inflammatory reaction toward an unidentified antigen in the basal epithelial layer/basement membrane zone. The disease may be associated with severe discomfort. Because it has been shown to possess a premalignant potential,[51–53] it is important to diagnose, treat, and follow patients through regular oral examinations.[51,52,54] Six types of clinical manifestation have been described (Table 2).[55] The lesions, usually bilateral, often involve the gingiva and present as desquamative gingivitis causing pain and discomfort during eating and toothbrushing. The clinical diagnosis is based on the presence of papular- or reticular- type lesions, eventually supported by histopathologic findings of hyperkeratosis, degenerative changes of basal cells, and subepithelial inflammation dominated by lymphocytes and macrophages.[49] In a recent randomized controlled trial, a tailored plaque-control regime was shown to be beneficial in reducing symptoms of gingival lichen planus and improving overall quality of life.[56]

Lupus erythematosus (LE)

LE is a group of autoimmune disorders characterized by autoantibodies to various cellular constituents, including extractable nuclear antigens and cytoplasmic membrane components. Two major forms are described: discoid LE (DLE) and systemic LE (SLE), which may involve a range of organ systems. DLE is a mild chronic form, which involves skin and mucous membranes, sometimes including the gingiva as well as other parts of the oral mucosa.[57,58] The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae (Table 2). Eight percent of patients with DLE develop SLE, and ulcerations may be a sign of SLE.[57,59] The characteristic dark red “butterfly” skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks.[60] The systemic type may also include skin lesions located on the face, but they tend to spread over the entire body.

3.3 | Granulomatous inflammatory conditions (orofacial granulomatosis)

Persistent enlargement of the soft tissues in the oral cavity as well as the facial region can occur concomitant with various systemic conditions like tuberculosis, Crohn's disease (CD),[61] and sarcoidosis. These changes are also seen as a typical symptom of the Melkersson-Rosenthal syndrome (MRS). In 1985, Wiesenfeld introduced the

term orofacial granulomatosis (OFG) to describe granulomas in the absence of any recognized systemic condition (Table 2).[62] The clinical symptoms of OFG are so similar to CD that OFG may be related to or may be CD. There is still no consensus whether OFG is a distinct clinical disorder, or an initial presentation of CD or sarcoidosis, or indeed an allergic reaction.[63]

4 | REACTIVE PROCESSES

4.1 | Epulides

Epulis is a term often applied to exophytic processes originating from the gingiva. The term is non-specific and histopathology is the basis of a more specific diagnosis. Several of these processes are reactive lesions, i.e., non-neoplastic proliferations with very similar clinical appearance to benign neoplastic proliferations.[64] Usually there are no symptoms, although the reactive processes are thought to represent an exaggerated tissue response to limited local irritation or trauma, and they are classified according to their histology. True epulides include:

- Fibrous epulis
- Calcifying fibroblastic granuloma
- Pyogenic granuloma (vascular epulis)
- Peripheral giant cell granuloma (or central)

Among 2,068 cases of reactive lesions of the oral cavity, the attached gingiva with 1,331 (64.36%) cases was the most frequently affected location.[64]

Fibrous epulis

Fibrous epulides (focal fibrous hyperplasia, irritation fibroma) are common exophytic smooth-surfaced pink masses of fibrous consistency attached to the gingiva. The size varies from small to large tumorlike processes with a diameter of several cm (Table 2).[65,66]

Calcifying fibroblastic granuloma

Calcifying fibroblastic granuloma (ossifying fibroid epulis, peripheral ossifying fibroma) occurs exclusively on the gingiva (Table 2). The lesion, although usually smaller than 1.5 cm in diameter, can reach a larger size and rarely cause separation of the adjacent teeth and resorption of the alveolar crest.[67,68]

Pyogenic granuloma

The pyogenic granuloma (telangiectatic granuloma, pregnancy granuloma, pregnancy tumor, vascular epulis) is rather common and shows a striking predilection for the gingiva, which accounts for 75% of all cases (Table 2).[66] When occurring during pregnancy, the influence of female sex hormones may result in a biologic behavior distinct from other pyogenic granulomas.

Peripheral giant cell granuloma (or central)

Peripheral giant cell granuloma (giant cell epulis, peripheral giant cell reparative granuloma) usually develops from the marginal gingiva. Among 2,068 cases of reactive lesions of the oral cavity, peripheral giant cell granuloma was the most prevalent lesion (30.12%).[64] The swelling may be sessile or pedunculated, sometimes ulcerated, and the appearance may resemble pyogenic granulomas (Table 2).[69,70]

5 | NEOPLASMS

5.1 | Premalignant

Leukoplakia

The term "leukoplakia" refers to a white lesion of the oral mucosa that cannot be characterized as any other definable lesion. It is a clinical diagnosis arrived at by exclusion in that all other potential causes of a white lesion have been ruled out or addressed.[71] Lesions are generally asymptomatic and cannot be rubbed off. Approximately 20% of leukoplakic lesions demonstrate some degree of dysplasia or carcinoma upon biopsy and most oral cancers are preceded by a long-standing area of leukoplakia. As a result, leukoplakia can be considered a premalignant condition. The prevalence of malignant transformation in leukoplakia ranges from 0.13% to 34%.[72] Lesions occur most frequently on the buccal mucosa, mandibular gingiva, tongue, and floor of the mouth.

Leukoplakia manifests clinically as homogeneous and non-homogenous subtypes. The size of the lesions and clinical features are determinants of the prognosis.[73] Thus, larger lesions and non-homogenous types of lesions imply a greater risk of malignant transformation than homogenous leukoplakia.[73,74]

Verrucous leukoplakia is characterized by white papillary lesions that are covered with a thick keratinized surface. Lesions exhibiting exophytic growth and invasion of the surrounding tissues are referred to as proliferative verrucous leukoplakia, a high-risk subtype of non-homogenous leukoplakia.[75]

Erythroplakia

Erythroplakia is the red counterpart of leukoplakia in the sense that it is a red lesion, which cannot be diagnosed as any other disease. Erythroplakia usually has a higher premalignant potential.[76] The lesions are uncommon and seldom affect the gingiva (Table 2).[73]

5.2 | Malignant

Squamous cell carcinoma

Squamous cell carcinoma of the gingiva represents about 20%[77,78] of intraoral carcinomas and occurs most frequently in the mandibular premolar and molar regions. Lesions commonly occur in edentulous areas, but they may also occur at sites in which teeth are present. Mobility of

adjacent teeth is common, and invasion of the underlying alveolar bone is apparent in approximately 50% of cases. Gingival squamous cell carcinoma may mimic other oral lesions affecting the periodontium, most of which are reactive or inflammatory in nature.[79–81]

Leukemia

Leukemias can be classified as acute- or chronic-based on their clinical behavior, and lymphocytic/lymphoblastic or myeloid depending on their histogenetic origin. Oral lesions occur in both acute and chronic leukemia but are more common in the acute form. The signs and symptoms are varied (Table 2). Bacterial, viral, and fungal infections including candidosis, and herpes simplex infection may also be present.[82–84]

Lymphoma

Lymphoma is a general term given to tumors of the lymphoid system and represents the most common hematologic malignancy. Lymphoma may originate from B-lymphocyte and T-lymphocyte cell lines. There are two main types of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma, the former being one-sixth as common as non-Hodgkin lymphoma. In contrast to non-Hodgkin lymphoma (Table 2), oral manifestations of Hodgkin lymphoma are extremely rare.[85–87]

6 | ENDOCRINE, NUTRITIONAL, AND METABOLIC DISEASES

6.1 | Vitamin deficiencies

Vitamin C deficiency (scurvy)

Ascorbic acid (vitamin C) is necessary for various metabolic processes in the connective tissue as well as in the formation of catecholamines. Clinically, scurvy is characterized by gingival bleeding and soreness (Table 2), as well as by a depressed immune response. In gingival health, the concentration of ascorbic acid in gingival crevicular fluid is higher than in plasma.[88]

7 | TRAUMATIC LESIONS

Traumatic lesions of the gingiva may be due to a wide range of causes.[89] Such lesions may be self-inflicted, iatrogenic, or accidental. Lesions, whether physical, chemical, or thermal in nature, are probably among the most common in the mouth, yet the periodontal literature contains few references on the topic.[89–91]

7.1 | Physical/mechanical insults

Frictional keratosis

Inappropriate toothbrushing can be injurious to the gingival tissues. Some patients believe they should actively brush the gingiva. Limited physical trauma from brushing may result in gingival hyperkeratosis, a white leukoplakia-like lesion referred to as frictional keratosis (Table 2).[92]

Toothbrushing-induced gingival ulceration

In cases of more violent trauma, toothbrushing damage varies from superficial gingival laceration to major loss of tissue resulting in gingival recession (Table 2).[93,94] Characteristic findings in these patients are extremely good oral hygiene, cervical tooth abrasion, and unaffected tips of the interdental papillae in the site of injury. The condition has been termed traumatic ulcerative gingival lesions.[93] Inappropriate dental flossing may also cause gingival ulceration and inflammation primarily affecting the tip of the interdental papillae. The prevalence of such findings is unknown.[95] Diagnosis of the lesion is based on clinical findings, and an important differential diagnosis includes NG.[96]

Factitious injury (self-harm)

Self-inflicted injury to the gingival tissue is usually seen in young patients, and the lesions may present unusual tissue damage in areas that can easily be reached by fingers and instruments (Table 2).[91]

7.2 | Chemical (toxic) insults

Etching

Toxic chemical products may result in mucosal surface erosions, including reactions of the gingiva. Surface sloughing or ulceration may be related to the use of chlorhexidine,[97,98] acetylsalicylic acid,[99,100] cocaine,[101] hydrogen peroxide,[102,103] or to dentifrice detergents.[104] These lesions are reversible and resolve after removing the toxic influence. Injury to the gingival tissue may also be caused by dentists' incorrect use of substances used for endodontic purposes that may be toxic to the gingiva, including paraformaldehyde or calcium hydroxide, which may give rise to inflammation, ulceration, and necrosis of the gingival tissue if the cavity sealing is insufficient.[105,106] In most instances, the diagnosis is obvious from the combination of clinical findings and patient history (Table 2).

7.3 | Thermal insults

Thermal burns of the gingiva may be prevalent due to a hurried lifestyle with intake of microwave-heated foods and drive-through coffee shops.[89] Any part of the oral mucosa can be involved, including the gingiva.[107] The lesion is erythematous with sloughing of a coagulated surface. Vesicles may also occur,[108] and sometimes the lesions present as ulceration, petechia, or erosions, which may be painful. The clinical characteristics and the history are important for the correct diagnosis (Table 2). Gingival injury due to cold has been described but appears to be very uncommon.[109]

8 | GINGIVAL PIGMENTATION

Gingival pigmentation/melanoplakia

Oral pigmentation (Table 2) is associated with a variety of exogenous and endogenous factors including drugs, heavy metals, genetics, endocrine disturbances (Addison's disease), syndromes (Albright syndrome, Peutz-Jegher syndrome), and postinflammatory reactions.[110] Physiologic pigmentation is usually symmetric, occurring on the gingiva, buccal mucosa, hard palate, lips, and tongue.

Smoker's melanosis

A primary etiologic factor in melanocytic pigmentation of the oral mucosa is cigarette smoking. Smoker's melanosis occurs most frequently on the mandibular anterior facial gingiva.[111,112] Melanosis gradually improves or may completely resolve upon cessation of smoking.

Drug-induced pigmentation (DIP)

DIP may be caused by the accumulation of melanin, deposits of drug or drug metabolites, synthesis of pigments under the influence of a drug, or deposition of iron following damage to the vessels.

Quinine derivatives such as quinolone, hydroxyquinolone, and amodiaquine are antimalarial drugs that cause bluish grey or black mucosal pigmentation occurring most frequently on the hard palate including the palatal gingiva.[113,114]

Long-term use of minocycline is associated with pigmentation of the alveolar bone and teeth. When changes in bone are viewed through relatively thin overlying mucosa, the gingiva may appear grey and is seen primarily in the maxillary anterior region. True minocycline-induced soft tissue pigmentation is much less common and occurs primarily on the tongue, lip, buccal mucosa, and gingiva.[115,116]

Amalgam tattoo

Pigmentation of the oral mucosa due to amalgam is frequently seen in the gingiva and alveolar mucosa. The lesion is a well-defined bluish, blackish, or greyish discoloration, which is not elevated (Table 2).[117,118] Radiographic imaging may demonstrate underlying amalgam debris.

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