

Oral manifestations of systemic disease

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Abstract

While the majority of disease of the mouth is centred upon the direct action of plaque, the oral tissues can be subject to change or damage as a consequence of disease that predominantly affects other body systems. Such oral manifestations of systemic disease can be highly variable in both frequency and presentation. As lifespan increases and medical care becomes ever more complex and effective it is likely that the numbers of individuals with oral manifestations of systemic disease will continue to rise. The present article provides a succinct review of oral manifestations of systemic disease. In view of it being one of a series on Oral Medicine, this review focuses upon oral mucosal and salivary gland disorders that may arise as a consequence of systemic disease.

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Introduction

Disorders of almost any body system can adversely impact upon the mouth. Oral manifestations may be (1) the first, only or most severe feature of systemic disease (2) the principle focus of therapy and/or (3) the dominant cause of a lessening of the affected person's quality of life. The oral features that an oral health care provider may witness will often be dependent upon the nature of their clinical practice. For example specialists of paediatric dentistry and orthodontics are likely to encounter the oral features of patients with congenital disease while those specialties allied to disease of adulthood may see manifestations of infectious, immunologically-mediated or malignant disease. The present article aims to provide a succinct review of the oral manifestations of systemic disease of patients likely to attend oral medicine services. The review will focus upon disorders affecting the oral mucosa and salivary glands – as these are tissues of greatest interest to practitioners of Oral Medicine. Although systemic disease relevant to Oral Medicine can impact upon the teeth, periodontal tissues or cause altered orofacial sensory or motor function these fall out with the scope of the present review.

Oral mucosal manifestations of systemic disease

The oral mucosa is perhaps the most likely oral tissue to be compromised by acquired systemic disease. The following sections will focus upon ulceration and white lesions of the oral mucosa – as these are the most likely abnormal signs that will be observed by oral health care providers.

Oral ulceration

A plethora of local and systemic disorders can give rise to ulceration of the oral mucosa (Table 1).

Solitary ulcers

Longstanding solitary oral mucosal ulceration should always initially be considered to reflect repeated local trauma or malignancy (usually oral squamous cell carcinoma (OSCC; Figure 1)). Of course many other disorders that give rise to oral ulceration may initially manifest as single ulcers but over time they evolve into more extensive disease. Local oral mucosal trauma in relation to systemic disease can arise as a consequence of physical (e.g. movement disorders (1) or chemical causes (e.g. the now rare instances of placing acidic aspirin at sites of oral pain, and the very rare examples of deliberate self-harm by swallowing caustic agents (2)).

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Other rare causes of traumatic ulceration could be due to reduced pain and/or touch sensation as might occur in trigeminal neuropathy secondary to metastatic deposits in the mandible or less commonly maxilla, multiple sclerosis, connective tissue disease (e.g. scleroderma), diabetes mellitus or drug therapy (e.g. with anti-malarials and some chemotherapy regimens). In most instances of suspected traumatic ulceration there will be an identifiable local and/or systemic cause, the ulcers will not be causing notable tissue destruction and the surrounding oral mucosa will be normal in appearance.

Malignancy of the mouth is typically OSCC related to lifestyle factors (tobacco, alcohol, some beta nut preparations and Human papillomavirus oncogenic types) (3) however rare congenital disorders such as dyskeratosis congenita (4) Fanconi anaemia (5) as well as the acquired diseases oral lichen planus (6) possibly scleroderma (7) and syphilis (8) are risk factors for the development of this malignancy. In contrast to traumatic ulceration OSCC does not have any identifiable local cause, may cause local destruction and have abnormal surrounding mucosa (e.g. speckling). Oral squamous cell carcinoma, and indeed all most malignancies of the mouth, may just appear plain odd.

Other malignancies related to systemic disease include several types of non-Hodgkin's lymphoma (NHL) and Kaposi's sarcoma (KS). Non-Hodgkin's lymphoma usually presents as a mass or area of destructive ulceration of the pharynx, palate or gingivae sometimes being driven by a background of immunodeficiency (e.g. HIV disease, iatrogenic immunosuppression) (9). Some types of oral NHL are almost specific for certain situations (e.g. plasmablastic lymphoma tends to be associated with HIV disease (10,11)) or may arise without obvious underlying cause (e.g. Natural Killer T cell lymphoma (NKTCL) (12)). Oral KS tends to arise on the palate and/or gingivae, is blue, red or purple and does not blanch with local pressure. Prior to the advent of anti-retroviral therapy (ART) KS was the most common oral malignancy of HIV disease but as the numbers of patients receiving this therapy have climbed so there has been a substantial fall in the prevalence of this oral tumour (13). Nevertheless oral KS can be the first clinical manifestation of unknown (and advanced) HIV disease and can arise in patients receiving long-term immunosuppressive therapy. Metastatic disease generally does not give rise to ulcers of the mouth, although as noted above can manifest within the mandible as a swelling and/or paraesthesia/anaesthesia (14).

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Other rare causes of solitary ulceration of possible systemic origin include syphilis (e.g. tertiary disease), primary or secondary infection of *Mycobacteria tuberculosis* or *Mycobacteria* other than *Tuberculosis* (MOTT) (15,16) and systemic mycoses (e.g. *Mucormycosis*, *Aspergillosis*, *Histoplasmosis* and *Parracocidiomycosis*) (17). Solitary ulceration secondary to neutropenias are also possible, although extensive ulceration might be more likely than single ulcers (18).

Multiple ulcers

Recurrent aphthous stomatitis is the most common cause of multiple superficial ovoid ulcers of the oral mucosa (19) but this is characterized by the patients being otherwise well (Figure 2). The multisystem inflammatory disorder Behcet's disease (BD) gives rise to near identical oral ulcers as RAS but also comprises genital ulceration, uveitis, erythema nodosum and other cutaneous features as well as a plethora of other gastrointestinal, urogenital, neural, musculoskeletal, cutaneous and vascular features (20). The uncommon autoinflammatory syndrome of Periodic fever, aphthous ulceration, pharyngitis and adenitis (PFAPA) that usually arises in pre-pubertal children gives rise to episodes of superficial aphthous-like ulceration. Unlike RAS this disorder tends to spontaneously remit in the teenage years (21). Other autoinflammatory diseases (i.e. periodic fevers) such as Familial Mediterranean Fever (FMF) may also sometimes give rise to superficial oral ulceration (22).

Ulceration similar to RAS, but without the same periodicity, can be a feature of anaemia of almost any cause. An important diagnostic rule is to always investigate for anaemia as being the cause of sudden onset superficial ulceration in an adult who does not have a history of RAS and has no signs of common bullous disease (see below) (23).

Several mucocutaneous disorders give rise to multiple areas of oral ulceration, lichen planus being without doubt the most common to do so. The ulceration of oral LP (OLP) is usually bilateral, has a background of different white patches and arises bilaterally on the buccal, lingual and/or gingival surfaces. Up to 40% of patients with OLP will also have cutaneous or other mucosal features of LP (24,25). Lichen planus usually arises without identifiable cause although may rarely be secondary to medication (e.g. β blockers, sulphonylureas, some anti-malarials (e.g. hydroxychloroquine for the management of lupus disease) and a

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spectrum of other agents) - when disease is termed lichenoid drug reaction (LDR)) or be a manifestation of graft versus host disease (GvHD) (24). Associations between LP and HCV disease are tenuous. Regardless of any association with systemic disorders or therapy OLP-like disease is considered potentially malignant, this cancer risk being independent of known causative factors of OSCC or therapy of OLP (6). Lupus disease (e.g. discoid and systemic) may give rise to oral mucosal and/or gingival features similar to those of OLP, although lesions of lupus may not be bilateral and may be more likely to affect the palate than OLP. "Sun-ray" pattern lesions that comprise a central area of erosion or ulceration from which white linear areas radiate have been described on the oral mucosa of patients with lupus disease (26,27).

The pemphigoid group of immunobullous disorders can give rise to bullae and/or ulceration of the palatal, buccal or lingual surfaces (28). Desquamative gingivitis is common (29). Intact blood or fluid filled bullae may be observed in patients with pemphigoid disease as the immune-mediated attack is targeting antigens of the basement membrane zone (BMZ) (30). Depending upon the type of pemphigoid patients may have blistering and/or ulceration of other mucocutaneous sites with oral involvement being most likely with mucous membrane pemphigoid (31). The IgA dermatoses (e.g. dermatitis herpetiformis [DH; often associated with gluten sensitive enteropathy] and linear IgA disease) can give rise to oral features similar to those of pemphigoid (32-35). Dapsone, often employed for the treatment of DH (and sometimes for pemphigoid) may rarely cause blue discolouration of the tongue secondary to methaemoglobinaemia.

The pemphigus group, in particular pemphigus vulgaris (PV), characterized by the generation of a series of anti-epithelial antibodies give rise to highly superficial ragged-bordered ulcers of the palatal, lingual and buccal mucosa as well as desquamative gingivitis (Figure 3). The mouth is the first site of involvement of PV in about 50% of affected individuals and without therapy perhaps 95% of patients will develop oral lesions (36,37).

Of concern has been the realization that bullous disease can arise on a background of systemic malignancy, this group of disorders being termed Paraneoplastic pemphigus (PNP; sometimes also termed paraneoplastic autoimmune multi-organ syndrome (PAMS)). About two thirds of the associated cancers are haematological (e.g. non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and Castleman's disease) although PNP has been observed in association with sarcomas, thymoma, lung cancer and OSCC. The mouth, pharynx and larynx

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are usually the first sites of involvement although the conjunctivae and genitals may also be affected. The oral features are similar to those of PV, although there can be notable labial involvement. Desquamative gingivitis presumably occurs. Confusingly oral lichen planus-like features can sometimes arise in PAMS. Of concern PAMS can cause bronchiolitis obliterans and early death. The variable presentation of PAMS reflects the wide range of autoantibodies with different epithelial targets that may be generated (38). Finally several groups of drugs may cause pemphigus-like disease, for example angiotensin converting enzyme (ACE) inhibitors (39).

Erythema multiforme (EM) can often give rise to areas of irregular superficial ulceration of the mouth particularly the anterior oral mucosa. There can also be areas of non-specific erythema, occasional vesicles or blisters or desquamative-like gingivitis. Target-like lesions may very rarely arise on the oral mucosa. This group of disorders includes EM minor, EM major, Stevens Johnson syndrome and Toxic Epidermal Necrolysis Syndrome (TENS) that often, but not always, are secondary to an increasingly wide range medications. The risk of EM type disease clearly increases with the numbers of different drugs that a patient receives - but in some instances EM disease can arise in the absence of drug therapy (40).

White patches

White patches of the oral mucosa can be categorized clinically into adherent (i.e. do not easily wipe off) and non-adherent. The range of systemic disorders that can give rise to oral mucosal (and sometimes gingival) white patches is summarized in Table 2.

Non-adherent white patches

Pseudomembranous candidiasis (Thrush) is a non-adherent white or cream coloured non-adherent pseudomembrane that tends to arise on the posterior palate or pharynx, although when disease is severe almost any oral surface can be affected (Figure 4). Thrush is usually painless and typically reflects present or recent therapy with broad spectrum antibiotics, corticosteroids or other immunosuppressants, other immunodeficiencies or long standing oral dryness (e.g. medication induced, Sjogren's syndrome). Thrush is perhaps most commonly observed in patients receiving long-term corticosteroid inhaler therapy (e.g. for the management of asthma). While *Candida albicans* is the most common species associated with oral thrush

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several other types may also give rise to this clinical feature, some of which can be particularly insensitive or indeed resistant to antifungal therapy (41,42).

Adherent white patches

The most common causes of white patches of the mouth are local physical trauma, oral lichen planus (discussed above), hyperkeratosis of unknown cause, epithelial dysplasia or neoplasia. Some of these can arise in association with systemic disease (e.g. traumatic keratosis secondary to cerebral palsy or oral lichen planus due to medication) and white patches of the oral mucosa and to a lesser extent the gingivae may be a significant feature of systemic disease. Perhaps the most important of these is Chronic Mucocutaneous Candidiasis (CMC), a group of often congenitally driven disorders characterized by recurrent mucocutaneous candidal infection (43). In CMC the complete spectrum of presentations of oral candidal infection can occur (e.g. pseudomembranous, erythematous, chronic hyperplastic). Patients with Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED) not only have chronic candidal infection but may have diabetes mellitus (which presumably will increase the risk or severity of periodontitis), enamel hypocalcification (secondary to hypoparathyroidism) and hypermelanotic pigmentation of the oral mucosa (secondary to autoimmune-driven destruction of the adrenal cortex) (44-47). Late-onset chronic mucocutaneous candidiasis (Good's syndrome) is accompanied by thymoma, myasthenia gravis and bone marrow abnormalities and thus affected individuals may have abnormal movement of the eyes, mouth and/or face (48). Chronic mucocutaneous candidiasis may be considered to be a rare risk factor for OSCC (49).

There are many other potential oral mucosal manifestations of systemic disease, as summarized in Table 3. Perhaps the most notable of these is Addisonian pigmentation. This is actually very rare but manifests as areas of hypermelanotic pigmentation of the buccal mucosae. A similar appearance (together with palatal pigmentation) can arise with some small cell carcinomas of the lung.

Salivary gland manifestations

Disease of the salivary glands broadly manifests as local swelling and/or oral dryness (the symptom of xerostomia). The disorders likely to give rise to salivary gland manifestations are summarized in Tables 4 and 5.

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Salivary gland swelling(s)

Mucoceles of the minor salivary glands of the lower lip and sialolithiasis of the submandibular gland are probably the most common causes of swellings salivary glands. Mucoceles have no association with systemic disease and ranulas, swellings of the submandibular and/or sublingual glands akin to that of mucoceles, do not seem to have any consistent association with systemic disease – although have been observed in patients receiving ART. Sialolithiasis tends to arrive *de novo* but a number of systemic disorders or therapies have been linked to this disorder including include diabetes mellitus, hypertension and/or chronic liver disease, nephrolithiasis, hyperparathyroid disease and therapy with the anti-HIV agent atazanavir (50).

Acute suppurative sialadenitis, that usually manifests as a painful swelling of one parotid gland is typically secondary to longstanding oral dryness such as Sjogren's syndrome or radiotherapy-associated salivary gland disease (see below). However neonatal disease has been reported in association with prematurity, orogastric feeding and/or immunodeficiency. In adults links with systemic disease have included diabetes mellitus, HIV disease and a plethora of surgical interventions as well as the very rare coprophagia (the consumption of faeces).

Mumps will often cause short term salivary gland swelling although hopefully the return of the high compliance with appropriate vaccination will lessen the frequency of this and the much more significant consequences of this disorder. Hepatitis C virus (HCV) infection can cause both salivary gland enlargement (typically the parotid glands) and reduced salivary output (see below also) and importantly there is a risk of NHL of salivary glands (50).

Salivary gland disease associated with HIV infection tends to arise in late advanced disease although may rarely be the first manifestation of previously unknown HIV infection. There can be swelling and/or xerostomia, the former being most common in the parotid glands. Within the gland there is inflammation (sialadenitis) that is being driven by infection with BK polyomavirus (BKPyV) (51,52). Multicystic lymphoepithelial lesions, sometimes termed cystic lymphoid hyperplasia (CLH) or Benign Lymphoepithelial Lesion (BLEL) or Benign Lymphoepithelial cysts (BLEC), may also occur in 6% of adults and 10% of children infected with HIV. Transformation to non-Hodgkin's lymphoma is a rare complication of CLH. Other causes of salivary swellings of

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patients with HIV disease include intraglandular lymphadenopathy, Kaposi's sarcoma, NHL and acute suppurative sialadenitis. As noted above sialolithiasis possibly secondary to ART has been documented and some HIV protease inhibitors can cause salivary gland enlargement of unknown cause.

Salivary gland swelling (often only of the submandibular glands) sometimes with xerostomia can arise in IgG4-related disease. This is a rare fibroinflammatory disorder characterised by elevated serum levels of IgG4 and multi-organ inflammation (lacrimal glands, pituitary gland, thyroid, pancreas, biliary tract, lungs, prostate gland and retroperitoneal cavity). The disease has predominantly been described in Asian patients (particularly from Japan) but affected individuals have been reported in the Western World. In the past the features were termed "Mikulicz' disease" "Kuttner tumour" or "Chronic sclerosing sialadenitis"(53,54).

Sialosis (sometimes termed sialoadenosis) is an uncommon non-neoplastic and non-inflammatory disorder possibly associated with some systemic disorders that gives rise to bilateral non-painful enlargement of the major salivary glands – typically the parotids. Xerostomia is not a common or dominant accompanying symptom. The precise cause is unknown although it may reflect a neuropathy by which unopposed sympathetic drive causes an increase in protein content within the acinar cells (55). This would perhaps explain the association of sialosis with diabetes mellitus and perhaps hypothyroidism, malnutrition, alcoholic and other causes of hepatic cirrhosis. Sialosis has also been observed in Bulimia nervosa, the degree of salivary gland enlargement possibly correlating with the frequency of bulimic symptoms and with levels of serum amylase.

A wide range of drugs can cause salivary gland enlargement. Transient and mild acute sialadenitis (sometimes termed "Iodide mumps") can arise in response to iodine based contrast media (e.g. for percutaneous coronary interventions) (56-59). Similarly radioactive iodine, used for the treatment of thyroid cancer, can cause salivary gland swelling and xerostomia that may arise within 24 hours of therapy and persist for a few weeks. Other agents that may cause salivary gland enlargement include l-asparaginase, clozapine, phenylbutazone, methyldopa, interferon alpha, oxyphenbutazone, ramipril, trimethoprim/sulfamethoxazole, nifedipine, chlormethiazole, methimazole, naproxen, nitrofurantoin, sulfadiazine, captopril, cytarabine, cimetidine, ranitidine, and thioridazine (60).

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Oral dryness

The symptom of oral dryness does not always accord with loss of salivary gland function, indeed many individuals report some degree of usually transient or mild oral dryness without objective evidence of reduced salivary gland function. Reduced salivary function gives rise to dysarthria, dysphagia, dysgeusia, some mucosal soreness, an increased liability to caries, gingivitis (but perhaps not periodontitis (see above)), candida infection (e.g. pseudomembranous, erythematous and angular chielitis), acute suppurative sialadenitis and reduced retention of upper full dentures. It can thus greatly lessen quality of life (50).

The most common cause of persistent oral dryness is drug therapy - with late-aged patients receiving polypharmacy being at greatest risk of this problem (Table 5). Medication-related xerostomia reflects anticholinergic and/or sympathomimetic actions, hence the drugs most commonly implicated in xerostomia are tricyclic antidepressants, benzodiazepines, atropinics, beta-blockers and anti-histamines. Morphine- derived agents cause oral dryness and while often promoted as having less anticholinergic actions than the tricyclics, the selective serotonin reuptake inhibitors (SSRI's) still cause some dry mouth. Some other newer drug therapies including omeprazole, anti-HIV protease inhibitors, the nucleoside analogue HIV reverse transcriptase inhibitor didanosine, trospium chloride, elliptinium, and new generation antihistamines may also cause drug-induced xerostomia.

Xerostomia is the most common persistent adverse side effect of radiotherapy (RT) of the head and neck, affecting up to 85% of patients (61). The prevalence of RT-induced xerostomia varies with respect to RT field, dose, regimen, and technique. Although the introduction of Intensity modulated RT has led to a significant reduction in the frequency and severity of this iatrogenic problem, many patients still experience the consequences of irreversible salivary gland dysfunction there being a fall in salivary outflow and altered salivary content. (90,91).

Oral dryness is a dominant symptom of Sjogren's syndrome (Figure 5). This disorder is classified as primary disease in which there are symptoms and signs of ocular and oral dryness and secondary Sjögren's syndrome in which there is also a connective tissue disorder – most frequently rheumatoid arthritis or systemic lupus erythematosus. However patients with primary Sjogren's syndrome have a spectrum of other systemic, and

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often autoimmune phenomena, while those with secondary Sjogren's syndrome may also have oral manifestations of any accompanying Connective Tissue Disease (62).

The oral features of primary or secondary SS are those of oral dryness (as described previously) and salivary gland enlargement due to the inflammation of the actual disease, episodes of acute suppurative sialadenitis and NHL. With regard to this last feature it is important to appreciate that SS is a potentially malignant disorder having a 4.3% risk of malignancy with a standardised incident rate of 18.9. The tumours are usually low grade marginal zone lymphoma (MALT), but can also be Follicle Centre, Diffuse B cell lymphoma (DBCL) or Lymphoplasmacytoid lymphoma (63,64).

Other oral manifestations of systemic disease

The present article has focused upon the impact of systemic disease upon the oral mucosa and salivary glands but a very wide range of other symptoms and/or signs of systemic disease can arise in the mouth or adjacent face as a consequence of disorders of non-oral structures (summarized briefly in Table 6).

Conclusion

Oral features of systemic disease can be helpful in the diagnosis and management of the underlying disorder – and indeed the oral symptoms may be those that most lessen the quality of life of affected individuals. The providers of primary oral health care have an essential role in the management of patients who may have oral consequences of systemic disease – as they are often likely to be the first clinicians to observe such abnormalities. They may not know exactly what the disease is but timely referral of patients to specialist Oral Medicine units will ensure that any potential oral manifestation of systemic disease is managed quickly and appropriately to improve the patient's quality of life. A simple rule to perhaps apply is "It looks different thus I will refer the patient to someone who may know what to do"

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Table 1. Systemic causes of oral mucosal or gingival ulceration

Trauma (physical, chemical, radiation, thermal)

Disorders causing aphthous-like ulceration

Behçet disease

PFAPA syndrome, other autoinflammatory disorders

Others

Infections

Primary or recurrent herpes simplex virus infection

Varicella-zoster virus

Epstein-Barr virus

Cytomegalovirus (very rare)

Coxsackie virus

Echovirus

Treponema pallidum

Mycobacterium tuberculosis (and rarely mycobacteria other than tuberculosis (MOTT))

Gram-negative infections (rare)

Chronic mucocutaneous candidiasis

Dermatoses

Lichen planus

Mucous membrane pemphigoid (and occasionally other types)

Pemphigus vulgaris (and occasionally other types)

Dermatitis herpetiformis

Linear IgA disease

Epidermolysis bullosa acquisita

Erythema multiforme

Hematologic disorders

Neutropenia(s)

Non-solid haematological malignancies: Leukaemia(s) and myeloproliferative disorders

Solid haematological malignancy: non-Hodgkin's lymphoma

Haematinic deficiencies

Others

Gastrointestinal disorders

Crohn's disease and related disorders

Ulcerative colitis

Drugs

Cytotoxics and very many others

Malignancy

Kaposi's sarcoma

non-Hodgkin lymphoma

Others

Others

Hypoplasminogenemia

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Table 2. Oral mucosal white patches associated with systemic disease

Non-adherent

- Pseudomembranous candidosis (thrush)
- Other mycoses
- Food debris
- Furred tongue
- Drug-associated necrotic debris (e.g., aspirin, cocaine)

Adherent

- Papillomas (warts—these are rarely of sexual origin)
- White sponge naevus
- Geographic tongue (erythema migrans – sometimes associated with type I hypersensitivity disorders or psoriasis)
- Frictional keratosis (e.g. as a consequence of abnormal orofacial movement)
- Lichen planus
- Lupus disorders
- Oral hairy leukoplakia
- Chronic mucocutaneous candidiasis
- Others (e.g. the rare dyskeratosis congenita)

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Table 3. Other oral mucosal manifestations of systemic disease

Swellings

Granulomatous disease (e.g. Crohns disease; sarcoidosis)

 Cobblestoning

 Mucosal tags and/or nodules

 “Stag horn” type swellings of the floor of mouth

 Swelling of the lips and/or face (angioedema)

Tuberous sclerosis

Sturge Weber syndrome

Neurofibromatosis type 1

Cowden’s syndrome

Others

Pigmentation (usually hypermelanotic)

Physiological (i.e. racially based)

Neurofibromatosis type 1

Albright syndrome

Laugier-Hunziker syndrome

Haemochromatosis

Incontinentia pigmenti

Metastatic malignant melanoma

Hypoadrenocortical deficiency

 Autoimmune

 Infection of the adrenal cortex (eg. TB, CMV, others)

Ectopic ACTH production (e.g. with some lung malignancies)

Peutz-Jegher’s syndrome (usually per-oral rather than oral hyperpigmented areas)

Drugs (rare, but many can do this – e.g. buspulfan, minocycline, zidovudine, others)

[other types of pigmentation include central cyanosis (blue), Kaposi’s sarcoma (blue, red purple) and congenital bilirubinaemias (brown – but usually on the gingivae only).

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Table 4. Non-neoplastic systemic causes of salivary gland swelling

Unilateral	Bilateral
Acute suppurative sialadenitis	Mumps
Recurrent parotitis of childhood	HIV salivary gland disease (and related disorders)
Sialolithiasis and other causes of ductal obstruction	HCV sialadenitis
Sjogren's syndrome (and associated non-Hodgkin's lymphoma)	Sjogren's syndrome (and rarely bilateral non-Hodgkin's lymphoma)
IgG4 related disease	IgG4 related disease
Sarcoidosis	Sarcoidosis
Chronic non-specific sialadenitis	Sialosis
Xanthogranulomatous sialadenitis	Pneumoparotitis
Amyloidosis	Iodine containing contrast media and radioactive iodine
Others	Drugs (rare)
	Others

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Table 5. Systemic causes of longstanding oral dryness

Drugs (many)
Radiotherapy of the head and neck
Sjogren's syndrome and related disorders
Chronic graft versus host disease
IgG4 related disease
Sarcoidosis
Salivary gland agenesis
HIV salivary gland disease
HCV sialadenitis
Others (e.g. longstanding anxiety, depression)

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Table 6. Other oral signs and symptoms of systemic disease relevant to oral medicine

Oral pain

Any disorder that increases the risk of painful dental caries

Dental pain secondary to sickle cell disease (very rare)

Trigeminal neuralgia-like disease with:

Multiple sclerosis

Systemic lupus erythematosus

Osteopetrosis

Infection/tumours around the central parts of the trigeminal nerve

Glossopharyngeal neuralgia-like disease with:

Multiple sclerosis

Infection/tumours around the central or peripheral parts of the glossopharyngeal nerve

Post-herpetic neuralgia (rare in the mouth)

Giant cell arteritis

Migrainous disorders

Temporomandibular disorder (TMD) –like features with:

Ehler Danlos syndrome

Persistent idiopathic facial pain (sometimes termed idiopathic facial pain) with:

Others

Loss of sensation (trigeminal neuropathy)

Metastatic deposits

Diabetes mellitus (diabetic neuropathy)

Connective tissue disease (e.g. scleroderma, Sjogren's syndrome, others)

Sickle cell disease

Familial dysautonomia

Drugs (e.g. anti-malarials)

Others

Abnormal orofacial movement

Facial weakness (usually unilateral)

Upper motor nerve

Stroke

CNS malignancy

Others

Lower motor nerve

Lyme disease (*Bartonella burgdoferi*)

Meningioma/neurofibroma/infections within the internal auditory meatus

Middle ear/temporal bone malignancy/destruction

Tumours/infection in other parts of the nerve

Orofacial dyskinesias

Trigeminal neuralgia-like disease (as above)

Parkinson's disease

Tardive dyskinesia (e.g. secondary to some anti-psychotic agents). Note that metronidazole can cause tardive and other dyskinesias of the face)

Rabbit syndrome (secondary to drugs)

Chin tremor (e.g. with paroxetine)

Reduced/altered tongue movement

Bulbar palsy (i.e lower motor) – malignancy/infection/trauma of lower CNS/base of skull/tongue

Pseudobulbar palsy (i.e upper motor) – malignancy/infection of CNS, some types of motor neurone disease (also described in variant Creutzfeldt Jakob disease)

Oral malodour

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Upper respiratory tract infection/malignancy

Pulmonary TB, abscesses, bronchiectasis, malignancy

Occasionally H.pylori-associated gastric erosion

Trimethylaminuria

Hypermethioninaemia

Diabetic ketoacidosis

End stage renal failure

End stage hepatic failure

Halitophobia/pseudohalitosis/olfactory reference syndrome (symptoms but no clinically detectable evidence of altered breath smell)

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Figure legends

Figure 1. Oral squamous cell carcinoma – probably one of the most significant causes of solitary ulceration of the oral mucosa

Figure 2. Recurrent aphthous stomatitis – episodic superficial oral mucosal ulceration in otherwise well children and adults.

Figure 3. Superficial ulceration of pemphigus vulgaris – the most common type of pemphigus to affect the oral mucosae or gingivae

Figure 4. Pseudomembranous candidiasis (thrush) of the oral mucosa

Figure 5. Oral dryness secondary to Sjogren's syndrome – this tongue is notably fissured and also has signs of mild oral lichen planus.

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