

## IN BRIEF

- Cancer and some systemic diseases may present with ulceration.
- Disorders of the blood, infections, gastrointestinal disease and skin diseases may cause mouth ulceration.
- Biopsy or other investigations may be indicated.

# 2

## Oral Medicine – Update for the dental practitioner. Mouth ulcers of more serious connotation

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This series provides an overview of current thinking in the more relevant areas of oral medicine for primary care practitioners, written by the authors while they were holding the Presidencies of the European Association for Oral Medicine and the British Society for Oral Medicine, respectively. A book containing additional material will be published. The series gives the detail necessary to assist the primary dental clinical team caring for patients with oral complaints that may be seen in general dental practice. Space precludes inclusion of illustrations of uncommon or rare disorders, or discussion of disorders affecting the hard tissues. Approaching the subject mainly by the symptomatic approach – as it largely relates to the presenting complaint – was considered to be a more helpful approach for GPs rather than taking a diagnostic category approach. The clinical aspects of the relevant disorders are discussed, including a brief overview of the aetiology, detail on the clinical features and how the diagnosis is made. Guidance on management and when to refer is also provided, along with relevant websites which offer further detail.

### ORAL MEDICINE

1. Aphthous and other common ulcers
2. Mouth ulcers of more serious connotation
3. Dry mouth and disorders of salivation
4. Oral malodour
5. Oral white patches
6. Oral red and hyperpigmented patches
7. Orofacial sensation and movement
8. Orofacial swellings and lumps
9. Oral cancer
10. Orofacial pain

### MALIGNANT ULCERS

A range of neoplasms may present with ulcers, most commonly these are carcinomas (Fig. 1), but Kaposi's sarcoma, lymphomas and other neoplasms may be seen and are discussed in Article 9. Most present with a single persistent ulcer. Biopsy is usually required to establish the diagnosis.

### SYSTEMIC DISEASE

A wide range of systemic diseases, especially mucocutaneous diseases, blood, gut, and miscellaneous uncommon disorders, may cause oral lesions which, because of the moisture, trauma and infection in the mouth, tend to break down to leave ulcers or erosions. Most present with multiple often persistent ulcers. Biopsy is often required to establish the diagnosis.

### MUCOCUTANEOUS DISORDERS

Mucocutaneous disease that may cause oral

erosions or ulceration (or occasionally blisters) include particularly Behçet's syndrome, and a number of skin diseases including lichen planus (Fig. 2; see Article 5), occasionally erythema multiforme or pemphigoid, and rarely pemphigus.

### BEHCET'S SYNDROME

Behçet's syndrome (BS) is a rare condition. It is the association of recurrent aphthous stomatitis (RAS) with genital ulceration and eye disease, but other systemic manifestations may also be seen. The disease is found worldwide, but most commonly in people from Eastern Mediterranean countries (particularly Greeks, Turks, Arabs and Jews) and along the Silk Route taken by Marco Polo across eastern Asia, China, Korea and Japan.

### Aetiopathogenesis

Behçet's syndrome is a vasculitis that has not been proved to be infectious, contagious or

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Fig. 1 Squamous cell carcinoma



Fig. 2 Lichen planus

sexually transmitted. There are many immunological findings in BS similar to those seen in recurrent aphthous stomatitis, with T suppressor cell dysfunction and increased polymorphonuclear leucocyte motility (Article 1). There is a genetic predisposition. Many of the features of BS (erythema nodosum, arthralgia, uveitis) are common to established immune complex diseases.

**Clinical features**

Behcet’s syndrome is a chronic, sometimes life-threatening disorder characterised mainly by:

- Recurrent aphthous stomatitis (RAS) in 90–100%
- Recurrent painful genital ulcers that tend to heal with scars
- Ocular lesions: iridocyclitis, uveitis, retinal vascular changes, and optic atrophy may occur
- CNS lesions
- Skin lesions: erythema nodosum, papulopustular lesions and acneiform nodules.

The joints, epididymis, heart, intestinal tract, vascular system and most other systems may also be involved.

However, very non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulcerations by six months to five years.

**Differential diagnosis**

This is from a range of other syndromes that can affect the eyes, mouth and skin – such as various dermatological disorders and infections.

**Diagnosis**

BS can be very difficult to diagnose, but the International Study Group for Behcet’s Disease (ISGBD) criteria suggest the diagnosis be made on clinical grounds alone on the basis of RAS plus two or more of the following:

- Recurrent genital ulceration
- Eye lesions
- Skin lesions
- Pathergy – a >2 mm diameter erythematous nodule or pustule forming 24–48 hours after sterile subcutaneous puncture of the forearm.

**Investigations**

There is no specific diagnostic test, but typing for specific human leukocyte antigens (HLA B5101) can help. Disease activity may be assessed by serum levels of various proteins, such as the acute phase proteins (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) or antibodies to intermediate filaments.

**Management**

In the face of the difficult diagnosis and serious potential complications, patients with suspected BS should be referred early for specialist advice.

**Websites and patient information**

<http://www.aarda.org/indexf.html>

**LICHEN PLANUS**

Lichen planus is discussed in Article 5.

**ERYTHEMA MULTIFORME**

Erythema multiforme (EM) is an uncommon acute often recurrent reaction affecting mucocutaneous tissues, seen especially in younger males.

The aetiology of erythema multiforme (EM) is unclear in most patients, but it appears to be an immunological hypersensitivity reaction, leading to sub- and intra-epithelial vesiculation. There may be a genetic predisposition with associations of recurrent EM with various HLA haplotypes.

EM is triggered by a range of usually exogenous factors, such as:

- Infective agents, particularly HSV (herpes-associated EM: HAEM) and the bacterium *Mycoplasma pneumoniae*
- Drugs such as sulfonamides (e.g. co-trimoxazole), cephalosporins, aminopenicillins, and many others
- Food additives or chemicals.

**Clinical features**

EM ranges from limited disease (Minor EM) to severe, widespread life-threatening illness (Major EM). Most patients (70%) in either form, have oral lesions, which may precede lesions on other stratified squamous epithelia (eyes, genitals or skin), or may arise in isolation. Oral EM typically presents with macules which evolve to blisters and ulcers. The lips become swollen, cracked, bleeding and crusted.

Minor EM affects only one site and may affect mouth alone, or skin or other mucosae. Rashes are various but typically ‘iris’ or ‘target’ lesions or bullae on extremities.

Major EM (Stevens-Johnson syndrome; SJS) almost invariably involves the oral mucosa and causes widespread lesions affecting mouth, eyes, pharynx, larynx, oesophagus, skin and genitals.

**Diagnosis**

There are no specific diagnostic tests for EM. Therefore, the diagnosis is mainly clinical, and it can be difficult to differentiate between it and viral stomatitis, pemphigus, toxic epidermal necrolysis, and sub-epithelial immune blistering disorders. Serology for HSV or *Mycoplasma pneumoniae*, or other micro-organisms, and biopsy of perilesional tissue, with histological and immunostaining examination, are essential if a specific diagnosis is required.

**Management**

Spontaneous healing can be slow – up to two to three weeks in minor EM and up to six weeks in major EM.

Treatment is thus indicated but controversial and thus specialist care should be sought. Supportive care is important; a liquid diet and even intravenous fluid therapy may be necessary. Oral hygiene should be improved with 0.2% aqueous chlorhexidine mouthbaths.

The use of corticosteroids is controversial but minor EM may respond to topical corticosteroids. Patients with major EM such as the Stevens-Johnson syndrome may need to be admitted for hospital care. Major EM patients should be

referred for treatment with systemic corticosteroids or other immunomodulatory drugs.

#### Websites and patient information

<http://www.emedicine.com/EMERG/topic173.htm>

#### PEMPHIGOID

Pemphigoid is the term given to a group of uncommon sub-epithelial immunologically-mediated vesiculobullous disorders (SEIMD) which can affect stratified squamous epithelium, characterised by damage to one of the protein constituents of the basement membrane zone (BMZ) anchoring filaments components. A number of other sub-epithelial vesiculobullous disorders may produce similar clinical features (Table 1).

**Table 1 Uncommon sub-epithelial vesiculobullous disorders**

Pemphigoid variants
Acquired epidermolysis bullosa (EBA)
Toxic epidermal necrolysis (TEN)
Erythema multiforme
Dermatitis herpetiformis
Linear IgA disease
Chronic bullous dermatosis of childhood

The main types of pemphigoid that involve the mouth are:

- Mucous membrane pemphigoid (MMP), in which mucosal lesions predominate but skin lesions are rare
- Oral mucosal pemphigoid – patients with oral lesions only, without a progressive ocular scarring process and without serologic reactivity to bullous pemphigoid (BP) antigens
- Bullous pemphigoid (BP) – which affects mainly the skin
- Ocular pemphigoid – which is sometimes termed cicatricial pemphigoid (CP) since it may cause serious conjunctival scarring.

However, most of the literature has failed to distinguish these variants, since their distinction has only recently been recognised, and therefore the following discussion groups them together.

#### MUCOUS MEMBRANE/ORAL PEMPFIGOID

Mucous membrane pemphigoid (benign mucous membrane pemphigoid) is an uncommon chronic disease, twice as common in females, and usually presenting in the fifth to sixth decades.

Mucous membrane pemphigoid is an autoimmune type of disorder with a genetic predisposition. The precipitating event is unclear in most cases, but rare cases are drug-induced (eg by furosemide or penicillamine). It is characterised immunologically by deposition of IgG and C3 antibodies directed against the epithelial basement membrane zone (BMZ). There are also circulating autoantibodies to BMZ components present in hemi-desmosomes or the lamina lucida.

The antibodies damage the BMZ and histologically there is a sub-basilar split. The pathogenesis probably includes complement-mediated sequestration of leukocytes with result-

ant cytokine and leukocyte enzyme release and detachment of the basal cells from the BMZ.

#### Clinical features

The oral lesions (Figs 3–5) affect especially the gingivae and palate, and include bullae or vesicles which are tense, may be blood-filled and remain intact for several days. Persistent irregular erosions or ulcers appear after the blisters burst and, if on the gingivae, can produce desquamative gingivitis – the most common oral finding. This is characterised by erythematous, ulcerated, tender gingivae in a patchy, rather than continuous distribution.

The majority of people with MMP have only oral lesions, but genital involvement can cause great morbidity and untreated ocular involvement can lead to blindness. Nasal, laryngeal and skin blisters are rare.



Fig. 3 Pemphigoid



Fig. 4 Mucous membrane pemphigoid



Fig. 5 Pemphigoid: desquamative gingivitis

#### Diagnosis

The oral lesions of pemphigoid may be confused clinically with pemphigus, or occasionally erosive lichen planus, erythema multiforme or the sub-epithelial blistering conditions shown in Table 1.

Biopsy of perilesional tissue, with histological and immunostaining examination can therefore be essential to the diagnosis.

#### Management

Spontaneous remission is rare, and thus treatment is indicated. Specialist advice is usually needed.

Systemic manifestations must be given attention. For this reason, an ophthalmology consultation can be needed.

The majority of cases respond well to topical corticosteroids. Non-steroidal immunosuppressive agents such as tacrolimus may be needed if the response is inadequate.

Severe pemphigoid may need to be treated with immunosuppression using systemic azathioprine or corticosteroids.

**Website and patient information**

<http://www.dent.ucla.edu/pic/members/MMP/index.html>

**PEMPHIGUS**

Pemphigus is a group of fortunately rare, potentially life-threatening chronic diseases characterised by epithelial blistering affecting cutaneous and/or mucosal surfaces. There are several variants with different autoantibody profiles and clinical manifestations (Table 2) but the main type is pemphigus vulgaris; this includes an uncommon variant pemphigus vegetans. Pemphigus vulgaris is seen mainly in middle aged and elderly females of Mediterranean, Ashkenazi Jewish or South Asian descent.

Pemphigus vulgaris is an autoimmune disorder in which there is fairly strong genetic background. Rare cases have been triggered by medications (especially captopril, penicillamine, rifampicin and diclofenac) or other factors.

**Table 2. Main types of pemphigus involving the mouth**

Variant	Oral lesions	Main antigens	Localisation of antigens	Antibodies
Pemphigus vulgaris localised to mucosae (Mucosal)	Common	Dsg 3	Desmosomes	IgG
Pemphigus vulgaris also involving skin/ other mucosae (Muco-cutaneous)	Common	Dsg 3 Dsg 1	Desmosomes	IgG

The autoantibodies are directed against stratified squamous epithelial desmosomes, particularly the proteins desmoglein-3 (Dsg3) and plakoglobin (Table 2). Damage to the desmosomes leads to loss of cell-cell contact (acantholysis), and thus intra-epithelial vesiculation.

**Clinical features**

Pemphigus vulgaris typically runs a chronic course, causing blisters, erosions and ulcers on the mucosae and blisters and scabs on the skin. Oral lesions are common, may be an early manifestation and mimic those of pemphigoid in particular. Blisters rapidly break down to leave erosions seen mainly on the palate, buccal mucosa, lips and gingiva.

**Diagnosis**

To differentiate pemphigus from other vesiculobullous diseases, a careful history and physical

examination are important, but biopsy of perilesional tissue, with histological and immunostaining examination are crucial. Serum should be collected for antibody titres.

**Management**

Before the introduction of corticosteroids, pemphigus vulgaris typically was fatal, mainly from dehydration or secondary systemic infections. Current treatment, by systemic immunosuppression, usually with steroids, or azathioprine or mycophenolate mofetil, has significantly reduced the mortality to about 10%. Specialist care is mandatory.

**Websites and patient information**

<http://www.pemphigus.org>

**Blood disorders** that can cause ulcers include mainly the leukaemias, associated with cytotoxic therapy, viral, bacterial or fungal infection, or non-specific. Other oral features of leukaemia may include purpura, gingival bleeding, recurrent herpes labialis, and candidosis.

**Gastrointestinal disease** may produce soreness or mouth ulcers. A few patients with aphthae have intestinal disease such as coeliac disease causing malabsorption and deficiencies of haematinics, when they may also develop angular stomatitis or glossitis. Crohn's disease and pyostomatitis vegetans may also cause ulcers. Orofacial granulomatosis (OFG), which has many features reminiscent of Crohn's disease, may also cause ulceration.

**Miscellaneous uncommon diseases** such as lupus erythematosus can cause ulcers.

**DIFFERENTIAL DIAGNOSIS OF ORAL ULCERATION**

The most important feature of ulceration is whether the ulcer is single, multiple or persistent.

**Multiple non-persistent ulcers** are most commonly caused by viral infections or aphthae, when the ulcers heal spontaneously, usually within a week to a month. If this is not the case, or if the ulcers clinically do not appear to be aphthae, an alternative diagnosis should be considered.

**A single ulcer that persists** may be caused by neoplasia such as carcinoma or by chronic trauma, a chronic skin disease such as pemphigus, or a chronic infection such as syphilis, tuberculosis or mycosis.

**Multiple persistent ulcers** are mainly caused by skin diseases such as lichen planus, pemphigoid or pemphigus, gastrointestinal disease, blood disease, immune defect or drugs.

In cases where the diagnosis is unclear, or where there is a single persistent ulcer, specialist referral is usually indicated.

**DIAGNOSIS OF ORAL ULCERATION**

Making a diagnosis of the cause for oral ulceration is based mainly on the history and clinical features. The number, persistence, shape, character of the edge of the ulcer and the appearance of the ulcer base should also be noted. Ulcers should always be examined for

induration (firmness on palpation), which may be indicative of malignancy. The cervical lymph nodes must be examined.

Unless the cause is undoubtedly local, general physical examination is also indicated, looking especially for mucocutaneous lesions, other lymphadenopathy or fever, since it is crucial to detect systemic causes such as leukaemia or HIV infection (Fig. 6).



Fig. 6 HIV-associated ulceration

### Biopsy

Informed consent is mandatory for biopsy, particularly noting the likelihood of post-operative discomfort, and the possibility of bleeding or bruising or sensory loss. Care must be taken not to produce undue anxiety; some patients equate biopsy with a diagnosis of cancer. Perhaps the most difficult and important consideration is which part of the lesion should be included in the biopsy specimen.

As a general rule, the biopsy should include lesional and normal tissue. In the case of ulcerated mucosal lesions, most histopathological information is gleaned from the peri-lesional tissue since by definition most epithelium is lost from the ulcer itself. The same usually applies for skin diseases affecting the mouth, where the epithelium in the area mainly affected will, more often than not, separate before it ends up under the microscope, and results will be compromised. In the case of a suspected potentially malignant or malignant lesion, any red area should ideally be included in the specimen. In some cases where no obvious site can be chosen, vital staining with 'toluidine blue' may first be indicated.

A biopsy punch has the advantage that the incision is controlled, an adequate specimen is obtained (typically 4 mm or 6 mm diameter) and suturing may not be required. However, in the skin disorders, the punch can sometimes split the epithelium or detach it from the lamina propria. When a scalpel is used, a specimen of elliptical shape is usually taken, most commonly from an edge of the lesion.

### Procedure

A local analgesic should be given, although in a few cases, conscious sedation may also be necessary.

Make the incisions using a scalpel with a number 15 blade. Do not squeeze the specimen with forceps while trying to dissect the deep margin. A suture is best used for this purpose (and also to protect the specimen from going

down the aspirator). Place the biopsy specimen on to a small piece of paper before immersing in fixative, to prevent curling.

Put the specimen into a labelled pot, ideally in at least 10 times its own volume of buffered formalin, and leave at room temperature.

Suture the wound if necessary, using resorbable sutures (eg Vicryl).

### MANAGEMENT OF ORAL ULCERATION

- Treat the underlying cause
- Remove aetiological factors
- Prescribe a chlorhexidine 0.2% mouthwash
- Maintain good oral hygiene
- A benzydamine mouthwash or spray or other topical agents (Table 3) may help ease discomfort.

Table 3 Topical agents which may reduce pain from mucosal lesions

Agent	Use	Comments
Benzydamine hydrochloride	Rinse or spray every 1.5 to 3 hours	Effective in reducing discomfort
Lidocaine	Topical 4% solution may ease pain	Also reduces taste sensitivity
Carboxymethylcellulose	Paste or powder used after meals to protect area	Available containing triamcinolone

### REFERRAL OF PATIENTS WITH ORAL ULCERATION

Patients with single ulcers persisting more than three weeks, indurated ulcers, or multiple persistent ulcers may benefit from a specialist opinion.

Patients with recalcitrant ulcers, or a systemic background to mouth ulcers, or needing investigation, may also benefit from a specialist referral.

Features that might suggest a systemic background to mouth ulcers include:

- **Extraoral features** such as skin, ocular, or genital lesions (suggestive of Behcet's syndrome); purpura, fever, lymphadenopathy, hepatomegaly, or splenomegaly (which may be found in leukaemia), chronic cough (suggestive of TB or a mycosis), gastrointestinal complaints (eg pain, altered bowel habits, blood in faeces), weakness, loss of weight or, in children, a failure to thrive.
- **An atypical history or ulcer behaviour** such as onset of ulcers in later adult life, exacerbation of ulcers, severe aphthae, or aphthae unresponsive to topical steroids.
- **Other oral lesions**, especially infections suggestive of HIV/AIDS (candidosis, herpetic lesions, necrotising gingivitis or periodontitis, hairy leukoplakia or Kaposi's sarcoma), glossitis or angular cheilitis (suggestive of a haematinic state), or petechiae or gingival bleeding or swelling (raising the possibility of leukaemia).

Investigations sometimes indicated include:

- blood tests to exclude haematinic deficiencies, leukaemia or HIV infection
- microbiological and serological investigations to exclude infection
- biopsy
- immunological studies to exclude skin diseases and HIV
- imaging to exclude TB, deep mycoses, carcinoma, or sarcoidosis.

### Patients to refer

Malignancy  
HIV related ulceration  
Syphilis  
TB  
Drug related ulceration  
Systemic disease  
Mucocutaneous disorders