Vesiculobullous disorders affecting the oral cavity

Vesiculobullous disorders of the oral cavity managed by oral medicine specialists include erythema multiforme, pemphigus vulgaris, paraneoplastic pemphigus and mucous membrane pemphigoid. These conditions can have significant effects on quality of life and potentially serious sequelae if not identified early.

Immune-mediated vesiculobullous disorders affecting the oral mucosa are rare but can lead to significant morbidity and mortality. It is important that these disorders are recognized and treatment instituted in a timely manner. Oral medicine physicians play an important role in accurate diagnosis and management of the oral manifestations of these disorders, and will liaise with other specialties including dermatology and ophthalmology. A multidisciplinary approach to patient care is often necessary and dedicated joint clinics have been established in some centres.

This article gives an overview of the most common and important vesiculobullous disorders affecting the oral cavity. These include erythema multiforme, pemphigus vulgaris, paraneoplastic pemphigus and mucous membrane pemphigoid (*Table 1*). Genodermatoses and the rarer vesiculobullous disorders are outside the scope of this article.

The aetiopathogenesis, epidemiology, clinical features, investigations and management for each condition will be discussed, but the focus will be on the management of oral mucosal features of these disorders. Comprehensive review articles regarding the management of cutaneous and/or ocular involvement exist in the literature and these should be referred to for further detail.

Erythema multiforme

Epidemiology and aetiopathogenesis

Erythema multiforme is an immune-mediated vesiculobullous disorder that commonly presents with oral mucosal involvement. It is more common in males than females, and usually occurs in young adults aged 20–40 years (Farthing et al, 2005). Up to 70% of cases are associated with herpes simplex virus reactivation (Schofield et al, 1993). A smaller proportion of cases are associated with other infective agents, such as *Mycoplasma pneumonia*, and rarely with medications (Farthing et al, 2005). In some cases, the trigger cannot be identified. The pathogenesis of erythema multiforme is unknown, but appears to involve a cell-mediated immune response to the causative agent.

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Clinical features

Erythema multiforme may be sub-classified into minor and major forms, with the minor form of lesser severity and only involving one mucosal surface, in addition to cutaneous involvement. Erythema multiforme major is more severe and more than one mucosal site is involved. There is a wide spectrum of severity of the disease, and it can be episodic or recurrent. The oral mucosa is involved in 70% of cases (*Figures 1* and *2*), and oral mucosal involvement can occur without cutaneous signs (Ayangco and Rogers, 2003; Farthing et al, 2005). In herpes simplex virus-related erythema multiforme, clinical features develop 10–14 days after clinically evident herpes virus infection, such as herpes labialis (Lemak et al, 1986). Erythema multiforme is generally a self-limiting disease and most cases will resolve within 2–3 weeks (Al-Johani et al, 2007).

Skin lesions are classically targetoid (*Figure 3*), developing from macules or erythematous papules that are usually symmetrical and in an extensor distribution (Farthing et al, 2005). A variety of 'atypical' cutaneous lesions have also been reported. Ulceration of the oral mucosa typically involves the non-keratinized and mobile mucosa of the anterior part of the oral cavity. The oral ulceration is irregular, ragged and shallow, often covered with a white slough of desquamated epithelium (Al-Johani et al, 2007). Classically the lips are involved, with extensive ulceration, swelling, cracking and haemorrhagic crusting (Lozada-Nur et al, 1989; Ayangco and Rogers, 2003). In more severe forms, other mucosal surfaces may be involved, including the conjunctivae, and the genital, laryngeal and oesophageal mucosae (Schofield et al, 1993; Farthing et al, 2005).

Investigations

Erythema multiforme is primarily a clinical diagnosis, particularly in cases where classical targetoid skin lesions are present or the characteristic pattern of irregular oral ulceration with lip involvement and crusting is evident.

Table 1. Presentation and management of vesiculobullous disorders of the oral cavity

	Erythema multiforme	Pemphigus vulgaris	Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome	Mucous membrane pemphigoid
Age/gender	M>F, 20–40 years	M=F, mean age 70 years but wide range including paediatric	M>F, 45–70 years	F>M, 50+ years
Pattern of oral mucosal involvement	Lips: blood crusting, swollen and cracked; mobile mucosa in anterior parts of mouth, irregular superficial ulceration	Irregular superficial ulceration, may affect all intra-oral mucosal surfaces, generally discrete lesions	Diffuse, generalized erosive stomatitis, often involving lips, continuous pattern of ulceration	Gingival erythema and desquamation, vesicles and bullae of oral mucosa, irregular deep ulceration of hard palate and alveolar mucosa, may heal with scarring of soft palate and/or uvula
Extra-oral features	Skin: target lesions, macules or papules, ocular, genital, pharyngeal, oesophageal ulceration	Skin: blisters and erosions on face, scalp, flexures, extremities; other mucosae: conjunctival, nasal, genital, oesophageal, pharyngeal crusting and ulceration	Skin: polymorphic eruption which may be erythematous macules or papules, targetoid or lichenoid lesions,blisters, erosions, commonly involves trunk, extremities, palms, soles, spares the scalp; other sites: conjunctivae, respiratory epithelium, oesophagus, stomach, possibly kidney	Skin: rarely involved; other mucosae: ocular involvement common, can lead to significant scarring, pharyngeal and oesophageal ulceration and strictures, genital ulceration and strictures
Key history points	Herpes simplex virus infection before onset, medication exposure, recurrent episodes	Onset of oral ulceration before skin lesions, medication exposure	Comorbid malignancy	Intact bullae in oral cavity, gingival erythema not related to plaque, ocular symptoms – redness, pain, ulceration
Key investigations	Nil required	Biopsy of oral mucosa or skin for histopathology and direct immunofluorescence, serum for indirect immunofluorescence	Biopsy of oral mucosa or skin for histopathology and direct immunofluorescence, serum for indirect immunofluorescence, serum for immunoprecipitation, screening for malignancy	Biopsy of oral mucosa for histopathology and direct immunofluorescence, serum for indirect immunofluorescence, ophthalmological examination
Acute management	Supportive therapy, may require oral corticosteroids	Corticosteroids, supportive therapy	Corticosteroids, supportive therapy, treatment of malignancy	Corticosteroids – systemic and topical
Ongoing management	May require prophylaxis against herpes simplex virus infection	Maintenance therapy with adjunctive immunosuppressants	Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome may persist after treatment of malignancy	Dapsone, doxycycline/nicotinamide, immunosuppression for ocular disease
Complications	Scarring related to ocular, oesophageal or pharyngeal involvement	Risk of sepsis associated with extensive skin involvement, conjunctival injury with ocular involvement	Respiratory involvement often progressive, high mortality as a result of underlying malignancy or respiratory involvement with paraneoplastic autoimmune multiorgan syndrome	Ocular scarring, oesophageal or pharyngeal scarring, genital scarring

Mucosal biopsy is rarely diagnostic as the disease has many different histopathological variants. Histopathology of skin and mucosal specimens may show liquefactive degeneration of basal cells, necrotic keratinocytes and lymphocyte exocytosis. A lichenoid infiltrate may be observed on oral mucosal biopsies (Sokumbi and Wetter,

Figure 1. Ulceration of soft palate in erythema multiforme.

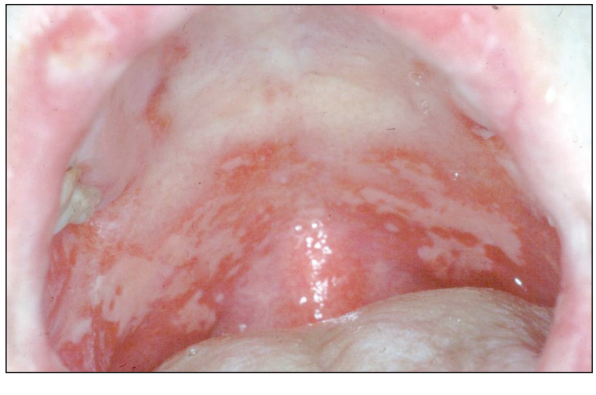
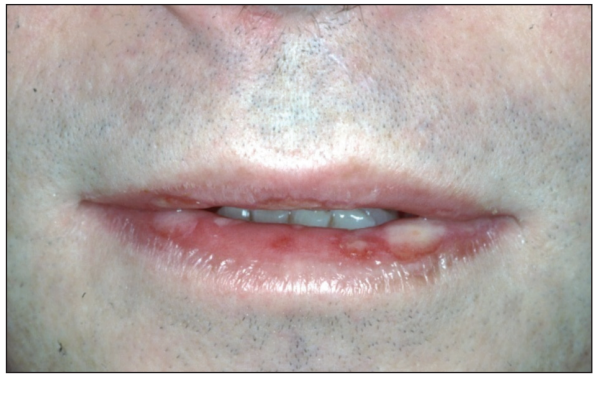


Figure 2. Lip ulceration in erythema multiforme.



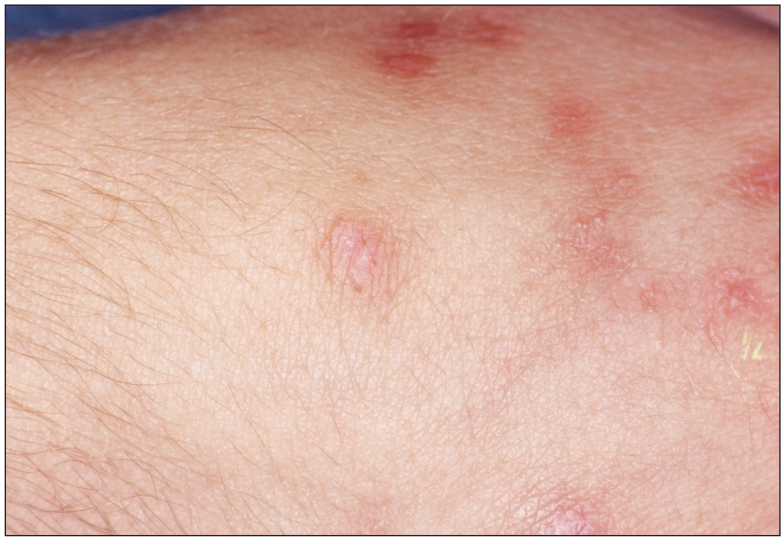


Figure 3. Targetoid lesions in erythema multiforme.

2012). Immunofluorescence (direct and indirect) is not useful diagnostically, although it may help rule out the presence of other immunologically-mediated vesiculobullous disorders (Al-Johani et al, 2007; Sokumbi and Wetter, 2012). Careful history taking may reveal the causative agent, such as herpes simplex virus reactivation, other infections or a drug reaction, although in some cases no trigger can be identified. In more severe forms of the disease review by both ophthalmology and dermatology teams is important.

Management

In the acute setting, management will depend on the severity of the disease and the extent of mucosal and skin involvement. Cases with oral involvement should be managed by oral medicine specialists. Oral medicine teams are also involved in assessing oral lesions and providing advice on oral care and management for patients requiring admission for more severe or extensive disease. Initial management consists of supportive care including oral hygiene and oral comfort measures, nutritional support and maintenance of hydration. This may include topical anaesthetic mouthrinses or gels for pain relief, topical antibacterial and antifungal agents to reduce the risk of super-infection of ulcerated oral mucosa, oral hygiene procedures with the assistance of oral health professionals, and topical corticosteroids to assist with resolution of ulceration. A soft or puree diet may be more comfortable in the acute phase. More severe cases may require admission and intravenous fluid supplementation until patients are able to maintain oral intake. Appropriate management of cutaneous and/or ocular involvement should also be instituted.

If a trigger can be identified, it should be managed appropriately, including withdrawal of medication. Herpes simplex virus-related erythema multiforme should be managed with systemic antiviral therapy, although this is likely to be most effective if commenced at the first appearance of herpes simplex virus infection. Prophylaxis with long-term low dose acyclovir reduces the frequency of recurrent herpes simplex virus-related erythema multiforme episodes (Lemak et al, 1986; Tatnall et al, 1995).

Administration of corticosteroids is viewed with some controversy. Mild cases may respond to topical corticosteroid mouthrinses or ointments, but patients with significant oral ulceration secondary to erythema multiforme will recover more rapidly with systemic corticosteroids (Sokumbi and Wetter, 2012). In the majority of cases oral corticosteroids such as prednisolone 1–1.5 mg/kg/day are appropriate. The extent of ocular and cutaneous involvement should be used as a guide to the dose and nature of corticosteroid therapy.

Long-term management of recurrent erythema multiforme can include prophylactic and/or treatment dose antiviral agents such as acyclovir or valacyclovir (Tatnall et al, 1995). In some cases systemic immunosuppression may be necessary in order to reduce the frequency of erythema multiforme episodes where the trigger cannot be identified. The evidence base for management of erythema multiforme is limited, but studies have shown efficacy of azathioprine, mycophenolate mofetil, cyclophosphamide, dapsone, thalidomide and intravenous immunoglobulin in the management of erythema multiforme (Davis et al, 2002; Sokumbi and Wetter, 2012).

Pemphigus vulgaris

Epidemiology and pathogenesis

Pemphigus vulgaris is an autoimmune vesiculobullous condition affecting the skin and mucous membranes, which is characterized by autoantibodies generated against cell-cell adhesion molecules, including desmosome components desmogleins 3 and 1 (DSG3/DSG1). Autoreactive IgG-type antibody deposition on intercellular adhesion components results in an inflammatory process leading to acantholysis and intra-epidermal or intra-epithelial clefting, forming fragile bullae which rapidly break down into erosions (Black et al, 2005). Pemphigus vulgaris is a rare disorder, with an estimated incidence rate of 0.7 per 100 000 person years (Langan et al, 2008). Until the advent of corticosteroid therapy, the mortality rate was close to 100%. Current mortality rates range from 5–20%, but a significant proportion of this is the result of complications of therapy (Herbst and Bystryn, 2000). The disease can affect a wide range of age groups but is most common in the middle-aged to elderly (Black et al, 2005).

Clinical features

In the majority of patients, the presenting feature is oral mucosal ulceration (Harman et al, 2003). This takes the form of irregular, superficial erosions of the oral mucosa (*Figures 4* and *5*) and lips, which can be very extensive. Intact bullae are rarely seen as they are fragile given the

intra-epithelial nature of the clefting. Oral mucosal involvement occurs in almost all cases of pemphigus vulgaris (Harman et al, 2003). Development of skin involvement may occur weeks to months after the onset of oral ulceration, and this presents as flaccid blisters or erosions on the skin, particularly affecting the face, scalp, flexures and extremities. Involvement of the periungual area can also occur (Joly and Litrowski, 2011). The blistering process may also include the nasal and genital mucosae, conjunctivae, oesophageal, pharyngeal and laryngeal mucosae (Black et al, 2005).

Investigations

The gold standard for pemphigus vulgaris diagnosis is a combination of histopathology and direct immunofluorescence of a biopsy of oral mucosa or skin. Histopathology findings include epithelial acantholysis and supra-basal clefting, and direct immunofluorescence shows IgG deposition in an intercellular pattern (Harman et al, 2003). Indirect immunofluorescence is positive in 90% of cases of active pemphigus vulgaris (Mutasim and Adams, 2001). ELISA (enzyme-linked immunosorbent assay) techniques may be used to quantify DSG1 and DSG3 auto-antibody titres (Amagai et al, 1999). However, indirect immunofluorescence and antibody titres do not always correlate well with clinical disease activity, with a proportion of patients having positive titres while in clinical remission (Cheng et al, 2002). Anti-DSG3 antibodies are found in all cases of pemphigus vulgaris, but up to 50% of patients also develop anti-DSG1 antibodies, and this appears to correlate with a more severe disease phenotype and more significant cutaneous involvement (Amagai et al, 1999; Miyagawa et al, 1999).

Figure 4. Oral pemphigus vulgaris.

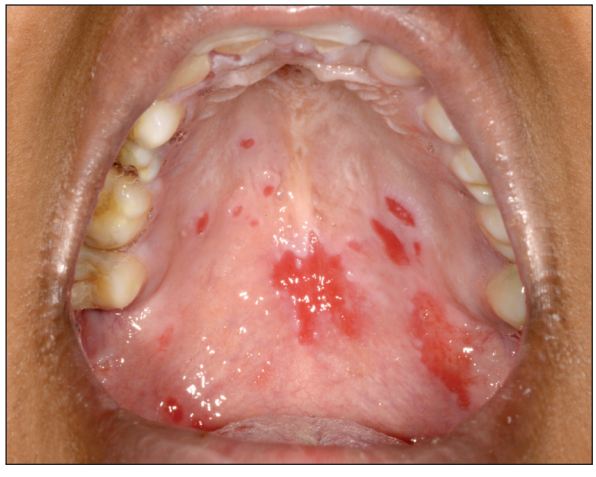


Figure 5. Oral pemphigus vulgaris.

Management

Induction of remission and resolution of ulceration are the initial aims of treatment in the acute phase, and supportive care may be necessary to maintain oral intake and skin integrity (Harman et al, 2003). Provision of oral hygiene advice, periodontal debridement and supportive symptomatic measures are often prescribed by the oral medicine team as adjunctive therapy. Following induction of remission, immunosuppressive therapy is required to maintain this status. Studies report a remission rate of approximately 50% at 5 years (Herbst and Bystryn, 2000).

The mainstay of management of pemphigus vulgaris in the acute phase is systemic corticosteroids, and the introduction of these therapeutic agents is responsible for the dramatic decrease in mortality related to pemphigus vulgaris (Bystryn and Steinman, 1996). However, given the adverse effects of long-term corticosteroid use, focus is now on the use of corticosteroid-sparing agents for the management of pemphigus vulgaris. Published evidence supporting any one agent is relatively weak, and the literature is generally limited to case reports and case series. However, some evidence exists for the use of agents such as azathioprine, mycophenolate mofetil, cyclophosphamide (oral and intravenous), intravenous corticosteroids, intravenous immunoglobulin, plasmapheresis and biological agents such as rituximab (Ahmed, 2001; Harman et al, 2003; Martin et al, 2009, 2011; Kasperkiewicz et al, 2012).

Adjunctive topical therapy for oral ulceration includes the use of mouthrinses containing corticosteroids as well as antifungal and antibacterial prophylaxis. Areas of recalcitrant ulceration may respond to the application of high potency corticosteroid ointments mixed with the thickening paste orabase. Topical tacrolimus may also be of some benefit for oral ulceration.

Paraneoplastic pemphigus

Epidemiology and pathogenesis

Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome is an uncommon vesiculobullous disorder affecting the oral mucosa, in association with an underlying malignancy. It is most commonly associated with lymphoproliferative disorders, usually non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or Castleman disease (Anhalt, 2004). Reports also exist regarding diagnoses of paraneoplastic autoimmune multiorgan syndrome associated with solid organ tumours

and other malignancies (Billet et al, 2006). The exact pathogenesis is unclear, but it may be related to dysregulated production of cytokines by malignant cells (Anhalt, 2004).

Clinical features

Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome is characterized by severe oral mucosal ulceration primarily affecting the tongue and lips. The ulceration demonstrates more necrosis than that seen in pemphigus vulgaris, and the lesions are clinically distinct from the ragged superficial erosions in pemphigus vulgaris (Anhalt, 2004). Skin lesions are variable in appearance, ranging from bullous pemphigoid-like tense blisters, to erythema multiforme-like blisters with surrounding erythema, to confluent erosions similar to toxic epidermal necrolysis (Anhalt, 2004). Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome is often mistaken for these diagnoses, but its continuous and progressive course differentiates it from these self-limiting conditions (Anhalt, 2004). Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome can also affect non-stratified squamous epithelium, including the bronchial epithelium, leading to respiratory failure in some cases (Nguyen et al, 2001).

Investigations

Paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome can be difficult to diagnose, particularly when the underlying malignancy has not yet been identified. Oral medicine specialists are often the first clinicians to suspect this condition from the appearance of the oral lesions, and may initiate further investigations and management. In cases of suspected paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome a careful physical examination and appropriate investigations are required to reveal the type of malignancy.

Biopsy of skin and/or mucosal lesions for histopathology and direct immunofluorescence, and analysis of serum for indirect immunofluorescence may reveal markers of paraneoplastic pemphigus. Histopathological findings vary with the clinical presentation, but classically include an interface reaction with dyskeratotic and necrotic keratinocytes (Czernik et al, 2011). Direct immunofluorescence staining may occur in one of three patterns – intercellular, linear (basement membrane zone) or entire cell (Czernik et al, 2011). Indirect immunofluorescence is most sensitive when performed using rodent bladder as a substrate, and antibodies may be identified in an intercellular or basement membrane pattern (Billet et al, 2006). Circulating antibodies to proteins of the plakin family may be detected by immunoprecipitation (Billet et al, 2006). Antibodies to DSG1 and DSG3 are not always present (Billet et al, 2006).

Management

Management of paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome involves treatment of the underlying malignancy as well as management of the mucosal and respiratory disease. In some cases treatment of the malignancy will result in resolution of paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome, but often the disease will be ongoing and progressive, particularly in cases with respiratory involvement (Billet et al, 2006). Management involves the use of high-dose corticosteroids and adjunct immunomodulatory agents such as azathioprine, mycophenolate mofetil, cyclophosphamide and ciclosporin (Billet et al, 2006).

Adjunctive topical management of oral mucosal ulceration is similar to that used for pemphigus vulgaris, with a combination of topical corticosteroids and anti-infective agents used as mouthrinses or ointments. The mucosal disease in this condition is often slow to respond to any therapy and may indicate to the oral physician the need to search for an underlying malignancy.

Mucous membrane pemphigoid

Epidemiology and pathogenesis

Mucous membrane pemphigoid comprises a group of rare autoimmune chronic inflammatory subepithelial blistering diseases primarily affecting mucous membranes, particularly the oral mucosa and conjunctivae. The nasal, pharyngeal, laryngeal, oesophageal and genital mucosae may also be involved. Skin involvement is rare. Mucous membrane pemphigoid usually affects adults over 50 years of age and is more common in females (Bagan et al, 2005). Mucous membrane pemphigoid is the most common vesiculobullous disorder diagnosed and managed in oral medicine units in the UK.

The mechanism of disease is subepithelial clefting secondary to binding of pathogenic autoantibodies and complement to a variety of targets in the basement membrane zone, with a subsequent inflammatory process. The target antigens include BP180, BP230, laminins 5 and 6, type VII collagen and integrin β4 subunit (Chan et al, 2002). Disease involving the ocular, laryngeal and genital mucosae may heal with scarring, giving rise to severe complications including airway obstruction, blindness and genitourinary dysfunction (Chan et al, 2002). The oral cavity has the highest frequency of involvement, followed by ocular disease. There is a wide spectrum of disease severity, but disease involving the oral cavity alone appears to be more responsive to medical therapy (Chan et al, 2002).

Clinical features

Oral mucosal involvement in mucous membrane pemphigoid is characterized by the formation of vesicles and/or bullae on mucosal surfaces, which break down to form irregular areas of ulceration. Involvement of the gingivae

(*Figure 6*) with dense erythema or desquamative gingivitis is common, as is ulceration of the alveolar and/or palatal mucosa (*Figure 7*) (Bruch-Gerharz et al, 2007). The condition is often readily diagnosed clinically by an oral medicine specialist, because of the classical oral mucosal presentation. Ocular involvement may present as recurrent episodes of conjunctival inflammation, with scarring sequelae including symblepharon, entropion, trichiasis and corneal opacification (Chan et al, 2002; Bagan et al, 2005).

Scarring and altered anatomy of the pharyngeal arches and soft palate, or obliteration of the buccal vestibule may also occur. In cases of pharyngeal, laryngeal or oesophageal involvement strictures may form which can lead to airway obstruction or dysphagia (Bruch-Gerharz et al, 2007). Genital mucosal involvement can lead to strictures of the urethral, vaginal or anal orifices and adhesions of the labia (Chan et al, 2002). Following confirmation of the diagnosis based on the oral mucosal appearance and appropriate investigations, the oral medicine specialist will request a formal ocular assessment.

Figure 6. Gingival involvement in mucous membrane pemphigoid.

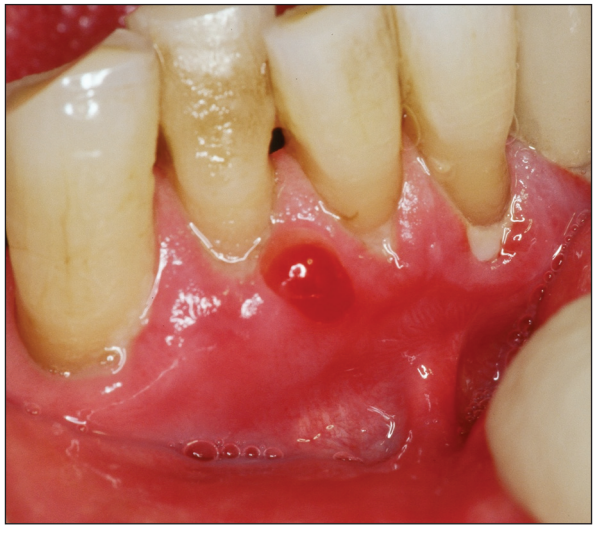
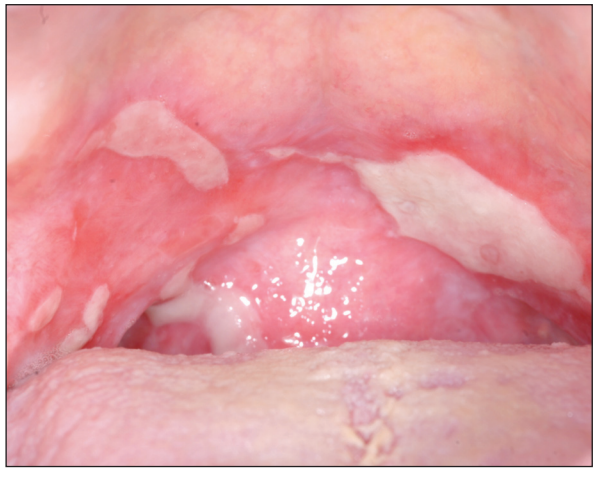


Figure 7. Oral ulceration in mucous membrane pemphigoid.



Investigations

Oral mucosal biopsy for histopathology and direct immunofluorescence of perilesional tissue is the primary diagnostic technique. Conjunctival biopsies should be avoided as this may worsen scarring (Chan et al, 2002). Histopathology may show subepithelial clefting. Direct immunofluorescence shows a linear pattern of staining of the basement membrane zone with IgG, IgA and/or C3 (Rogers et al, 1977). Indirect immunofluorescence is less sensitive but 50% of patients may have positive anti-basement membrane zone IgG or IgA on salt-split skin (Bruch-Gerharz et al, 2007). ELISA for BP180 and BP230 antibody titres may also be performed.

Management

Management of mucous membrane pemphigoid depends on the clinical presentation, as there is a very wide variation in severity of the disease. Mild presentations with involvement restricted to the oral mucosa may be managed with topical corticosteroids, with the addition of dapsone 50–200 mg daily for more extensive oral mucosal disease (Chan et al, 2002). Oral hygiene advice, periodontal debridement and supportive symptomatic measures are prescribed by the oral medicine team as adjunctive therapy. Some clinicians report effective management of oral mucosa-restricted disease with tetracyclines and nicotinamide (Reiche et al, 1998). Disease affecting extra-oral sites, particularly ocular, laryngeal or pharyngeal involvement, will require more intensive therapy. A combination of oral corticosteroids with dapsone or immunosuppression may be required in cases of aggressive ocular disease (Chan et al, 2002). Clinicians have reported efficacy of cyclophosphamide, azathioprine and mycophenolate mofetil in the management of severe mucous membrane pemphigoid (Chan et al, 2002). In cases of severe progressive disease, intravenous immunoglobulin and/or biological agents such as infliximab or etanercept have been used (Ciarrocca and Greenberg, 1999; Chan et al, 2002; Canizares et al, 2006).

It is important that patients diagnosed with mucous membrane pemphigoid are referred for appropriate ophthalmological screening, given the potentially severe sequelae of untreated ocular disease. The disease tends to run a chronic course and may exhibit periods of remission. Surgical management of the sequelae of the disease may be required if there is severe scarring affecting sight or function.

Conclusions

Immune-mediated vesiculobullous disorders of the oral mucosa are rare, and early identification and appropriate referral is essential for best management of these disorders. Patients with extensive or unusual oral ulceration, particularly in the presence of skin lesions and other systemic features, should be urgently referred to an oral

medicine specialist service. Differentiating clinically between different types of oral ulceration can be difficult for the non-specialist and in view of the serious nature of some of these disorders, it is important that referral is made to the appropriate clinical team in a timely manner for investigations and treatment. BJHM

Conflict of interest: none.

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KEY POINTS

- Vesiculobullous disorders affecting the oral mucosa are rare and may have serious sequelae.
- Oral medicine specialists are experienced in the clinical assessment and diagnosis of these disorders as well as their management.
- Multidisciplinary care for patients with vesiculobullous disorders affecting multiple sites is essential.
- Early recognition and appropriate referral are essential for reduction of morbidity and mortality related to vesiculobullous diseases.
- Oral medicine specialists play an important role in the identification of systemic diseases such as paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome based on the oral mucosal presentation.