AN OVERVIEW OF VESICOBULLOUS CONDITIONS AFFECTING THE ORAL MUCOSA

EMMA HAYES, STEPHEN J CHALLACOMBE

ABSTRACT

Vesicobullous diseases are characterised by the presence of vesicles or bullae at varying locations in the mucosa. The most common occurring in the oral cavity are mucous membrane pemphigoid (MMP) and pemphigus vulgaris (PV). Both are autoimmune diseases with a peak age onset of over 60 years and females are more commonly affected than men. This paper reviews the structure of the oral mucosa, with specific reference to the basement membrane zone, as well as bullous conditions affecting the mucosa, including PV and pemphigoid, their aetiology, clinical presentation, and management.

Learning outcomes
• Understand the common presentation of vesicobullous diseases.
• Appreciate the role of investigations in diagnosis and its interpretation.
• Appreciate the roles of both primary and secondary care in patient management.

KEYWORDS
Bullous, Basement Membrane Zone, Pemphigus Vulgaris, Mucous Membrane Pemphigoid

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Introduction
Vesicobullous diseases are characterised by the presence of vesicles or bullae at varying locations in the mucosa. They often affect both the skin and oral mucosa, but can on occasion affect only oral mucosae. The most common of the vesicobullous diseases, which occur in the oral cavity are PV and MMP. Both are antibody-mediated autoimmune diseases but the target antigens of these two diseases are different. In MMP, blisters form owing to antibodies binding to components of the basement membrane zone (BMZ) and in PV to molecules on the surface of keratinocytes. The aetiology, pathology, clinical presentations, and the treatment of these conditions are discussed. It is outside the scope of this paper to include full details of the infectious causes of bullae, such as those seen in primary herpetic gingivostomatitis.

The structure of the oral mucosa
The oral mucosa is a specialised stratified squamous epithelium, which is keratinized in areas of high friction (dorsal tongue, palate, and gingiva), with an underlying connective tissue layer (lamina propria); in the palate, buccal mucosa and labial mucosa there is an underlying submucosa. The epithelium is formed of several layers, the deepest being the layer of progenitor cells forming the stratum germinativum, adjacent to the lamina propria. Keratinocytes increase in size and flatten as they move through the stratum spinosum and stratum granulosum to the stratum corneum (in keratinized mucosa) where the desmosomes, which hold the cells together, weaken therefore allowing normal desquamation.

In addition to desmosomes, epithelial cell-cell contact occurs via occludens (tight junctions), and nexus junctions (gap junctions), with each having a complex structure. Desmosomes are small adhesion proteins (0.2 µm) which guarantee the integrity of the epidermis by linking the intermediate filaments within cells to the plasma membrane as well as adjacent cells, therefore functioning both as an adhesive complex and as a cell-surface attachment site for the keratin intermediate filaments of the cytoskeleton. Desmosomes contain a series of proteins; of particular interest with regard to bullous diseases are the desmogleins. The oral and skin epithelium both express desmoglein 3 (DSG3) and desmoglein 1 (DSG1) within desmosomes, but in the oral mucosa DSG3 is expressed at a much higher level than DSG1, which is important in disease manifestation and antibody detection for diagnosis.

Between the epithelial cell layers and the lamina propria is a complex structure linking the two layers, known as the BMZ. The 1-2µm thick BMZ (Figure 1) consists of the basal cell plasma membrane, the lamina lucida, the lamina densa, and the sub-lamina densa. On the epithelial surface of the plasma membrane of the basal keratinocytes are small electron-dense domains called hemidesmosomes. These are specialised, multiprotein complexes...

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that contribute to the attachment of epithelial cells to the underlying BMZ. A number of proteins that are implicated in the pathogenesis of subepithelial or subepidermal blistering diseases such as MMP are associated with the hemidesmosomes (such as BP230 and BP180).6

The lamina lucida consists of laminins (adhesive glycoproteins which contribute to cell adhesion as well as cell migration and organisation) and is 20–40nm thick. Anchoring filaments transverse the lamina lucida perpendicularly from the basal cell membrane to the underlying lamina densa, which contains heparin sulphate coated type IV collagen.

Mucous Membrane Pemphigoid
Pemphigoid comprises of an uncommon heterogeneous group of disorders – including MMP and linear IgA disease – characterised by subepithelial separation and deposition of autoantibodies and complement along the basement membrane zone. MMP is distinguished from skin bullous pemphigoid by its predilection for mucosal sites and the tendency to form scars, leading to oesophageal strictures, laryngeal stenosis, and blindness in extreme cases of conjunctival cicatrisation.7 Most cases are detected after the fifth decade, with a mean age of 62,8 and the disease is more frequent in women than in men.

Intraorally two variants of MMP are seen. The most common manifests as bullous lesions or, more commonly, ulceration involving much of the non-keratinized and occasionally the keratinized mucosa; these are subepithelial, may be blood-filled (Figure 2), and last longer (up to several days) than those seen in PV (see Table 1). Irregular erosions or ulcers can be seen after the bullae burst. Bullous lesions can also involve the conjunctiva, nose, larynx, pharynx, oesophagus, genitals, and anus. The oral lesions usually heal without scarring unlike those of the conjunctiva; ophthalmological assessment is therefore important in patients presenting with pemphigoid (those without ocular signs at presentation have a 22% risk of developing them over five years).9 Nasal involvement may present as bleeding or crusting, laryngeal involvement as hoarseness or dysphagia, and genital involvement as painful erosions.

The second variant presents with desquamative gingivitis and involves only the gingivae around the teeth. The gingivae are highly erythematous and hyperaemic (Figure 3), and small bullae may be formed in protected areas around the teeth. This needs to be differentiated from more common causes of desquamative gingivitis such as lichen planus. It is distinct from plaque-induced gingivitis in that it extends beyond the marginal gingivae; as it is antibody-mediated it will not resolve with improvements in oral hygiene, and these patients therefore require referral to secondary care for diagnosis and management.

Diagnosis
Diagnosis is confirmed with a biopsy and immunofluorescence. Histologically, subepithelial bullae are seen, with no acantholytic cells, and the epithelium tends to detach itself from the underlying lamina propria.
IgG antibodies bind to normal mucosa. Around 90% of patients with mucosal disease alone have IgG antibodies that bind to the dermal side of salt-split skin and recognise laminin 5.

**Treatment**

If the disease is confined to the mouth and with a low severity score, topical corticosteroids are often adequate to control the lesions. In more severe cases, however, and if there is involvement of other sites, systemic corticosteroids may be needed. In order to keep the steroid dose to a minimum and reduce steroid-related side effects, such as increased susceptibility to infections, diabetes, osteoporosis and hypertension, an immunosuppressant such as azathioprine or dapsone can also be used. MMp is a chronic disease, which persists, often with exacerbations and remissions, over many years. Disease severity as well as response to therapy can be monitored by oral disease severity scoring, a system which is helpful in both indicating whether local or systemic therapy is needed as well as monitoring therapeutic responses. Active vesicobullous conditions can make maintenance of good oral hygiene more challenging for the patient at home, due to discomfort with brushing. However, it is vital that oral hygiene is maintained, with assistance from their general dental practitioners, to prevent caries and periodontal disease developing.

**Pemphigus vulgaris**

PV is a potentially lethal, chronic, bullous disease of the stratified squamous mucosa and skin, which commonly affects the oral mucosa and may initially present orally. More than 90% of patients may have oral lesions at some stage of the disease. In the UK it occurs mainly in adults with a median age of 71 at presentation; it is rarely observed in children and adolescents.

Clinically, PV can present as painful, fragile, fluid-filled blisters, which may appear on any areas of the oral mucosa and burst within a few hours; as a result, clinical examination often only reveals shallow ulcers or erosions (Figure 4). Clinically there should be little difficulty in differentiating lesions from recurrent aphthous ulcers as they are large and erythematous with irregular outlines and are persistent ulcers, not recurrent with onset in middle age rather than in teens as with recurrent aphthous stomatitis (RAS). These persist for weeks or months, but new lesions recur throughout the disease process. Only occasionally is the Nikolsky sign helpful – rubbing the mucosa to induce a bulla – as this is also seen in other bullous conditions such as MMp. Oral manifestations of the disease may persist for many months, without overt ill health, but skin lesions (often found on the chest, face or back), malaise, and loss of weight may occur at a later stage.

In view of the serious and potentially fatal nature of PV, due to dehydration or infection, if not treated, it must be diagnosed correctly and treated in an appropriate setting. Diagnosis is again via mucosal biopsy and IMF. Histologically there is acantholysis (separation and rounding of the keratinocytes owing to disruption of the cell-cell adhesion molecules such as desmosomes) with intraepithelial bulla formation, as well as a leucocytic infiltrate in the lamina propria (Figure 5). Serum IgG, IgM, or sometimes IgA autoantibodies to desmogleins in skin and mucosa are found in nearly all cases of pemphigus on indirect IMF, and IgG bound to intercellular areas of the
epithelium on direct IMF. Antibodies against DSG3 are found in oral disease, whereas antibodies against DSG1 are predominant in skin disease. The autoantibody titre is generally correlated with the severity of pemphigus, and as the lesions heal with treatment, circulating antibodies usually decrease. Antibodies to pemphigus antigens can also be detected in saliva, although at present this is not routinely tested for. PV has a genetic background with HLA class II allele associations found with HLA-DR4 (DRB1*0402) and DQB1*0503. These HLA class II alleles appear critical to T lymphocyte recognition of DSG3 peptides and antibody production.

**Treatment**

This is usually with systemic corticosteroids such as prednisolone in doses of 40-60 mg/day initially, and is gradually reduced to the minimal dose that will prevent formation of new lesions; again immunosuppressant may also be used to control the disease and reduce the required steroid dose. Treatment with corticosteroids has completely changed the prognosis of the disease. Steroids may need to be maintained for life, but clinical improvement, along with reduction in circulating antibody titre, allows the dose to be reduced to minimal levels. Patients rarely die now from the disease but they may develop the side effects of steroid therapy (such as adrenal suppression, impaired glucose metabolism, osteoporosis, and glaucoma).

Immunosuppressive therapy using azathioprine is usually effective and allows lower doses of systemic steroids to be used. Local therapy with steroid mouthwashes (e.g., Betnesol) is usually a helpful adjunct therapy, and especially useful when the clinical disease is under control and the circulating antibody titre has dropped. Oral disease severity scores are helpful in assessing both the presenting disease severity and the response to treatment.

**Other forms of pemphigus**

Another important form of pemphigus affecting the oral mucosa is...
paraneoplastic pemphigus (most commonly associated with haematological malignancies), as oral lesions have been seen in all reported cases of paraneoplastic pemphigus and may be the first or sole manifestation. Paraneoplastic pemphigus should be suspected if assumed PV does not respond to therapy. This form usually improves with treatment of the underlying malignancy. Other types of pemphigus such as pemphigus foliaceus rarely affect the oral mucosa as the target antigen is DSG1. In pemphigus vegetans, vegetation type lesions may be found on the oral mucosa and lips, and histological examination shows intraepithelial abscesses containing numerous eosinophils.

Erythema multiforme

Erythema multiforme (EM) is an uncommon, mucocutaneous disease characterised by symmetrical skin target lesions, particularly of the extremities, with oral or other mucosal involvement in some cases, and a marked tendency to recur. Mucosal involvement may precede or follow skin lesions and is commonly found without skin lesions. The condition mainly affects young adult men and it is most commonly found in the mild form, but more severe and potentially fatal forms can occur (erythema multiforme major).

The aetiology of oral EM has not been established, but many agents have been implicated including drugs (allopurinol, antibiotics, anticonvulsants, and NSAIDs) and viruses (particularly herpes type 1 and 2, and Mycoplasma pneumoniae). Recurrent EM is almost always associated with herpes simplex virus (HSV), although it is not usually isolated from the lesions or demonstrable in biopsy specimens.

Diagnosis is based on clinical signs and histology; there are degenerative changes at the dermoepidermal junction and acanthosis, with either subepithelial or intraepithelial bullae. The degenerating oral epithelium is strikingly eosinophilic, and there is a lymphohistiocytic infiltration in the lamina propria.

There is no specific treatment for EM, although corticosteroids are often used, either topically in mild disease or systemically in more severe disease, as well as supportive management such as intravenous fluids and analgesia. In recurrent EM, antivirals such as acyclovir may be used to suppress disease recurrence.

Summary

The wide variety of vesicobullous diseases, with their associated morbidity and mortality mean that early diagnosis at a specialised centre (such as oral medicine or dermatology) is vital, if potential sequelae are to be avoided. As most of these conditions present initially with oral lesions, it is imperative that general dental practitioners refer all suspected cases for further investigation.

Epidermolysis bullosa

Epidermolysis bullosa represents a group of bullous diseases, which can be either inherited or the acquired autoimmune form (epidermolysis bullosa acquisita). It predominantly affects the skin, but there may also be mucosal involvement. The inherited form may also show dental abnormalities such as pitting hypoplasia or thin enamel. Clinical presentation can vary, with bullae at the intraepithelial level, BMZ, or subepithelial depending on the type. The subepithelial forms result in scarring, which can result in stricture formation, ankyloglossia and microstomia. Treatment of epidermolysis bullosa acquisita is traditionally with immunosuppression or, more recently, with intravenous immunoglobulins.


