Pemphigus Vulgaris and Bullous Pemphigoid of the Upper Aerodigestive Tract: A Review Article and Novel Approaches to Management

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Key Messages

- Autoimmune blistering disease is rare but potentially lethal.
- Presentation can be with ENT problems, and otolaryngologists should be aware of these conditions to ensure accurate diagnosis and timely intervention.
- The commonest cause of death in autoimmune bullous diseases is opportunistic infections, caused by prolonged immunosuppression.
- Management requires a multidisciplinary approach. Topical and systemic corticosteroids form the mainstay of treatment although new treatments are being developed to negate the potential adverse effects of long-term steroids.
- Surgical intervention is the last resort to improve the airway and oral feeding.

Keywords

Pemphigus vulgaris · Bullous pemphigoid · Disease management

Abstract

Background: Autoimmune bullous diseases are rare conditions characterized by blistering of the skin and mucous membranes. The 2 commonest forms are pemphigus vulgaris and bullous pemphigoid. The oral cavity or oropharynx may be the initial site of presentation or often the only site involved. **Summary:** These conditions are often misdiagnosed or overlooked leading to poorer patient outcomes. Due to the chronic nature of these conditions and the systemic effects of treatment, there is a significant associated morbidity and mortality. As such, an understanding of the fundamentals of autoimmune bullous diseases is vital to

those working in otolaryngology. The mainstay of management in both conditions is topical and systemic corticosteroids. There is also a role for immunomodulating and non-steroidal anti-inflammatory drugs as adjunct or alternative therapies. Surgical intervention may be required to protect the airway. Often multimodality treatment is required involving multidisciplinary input from otolaryngologists, oral surgeons, dermatologists, and rheumatologists. This review article will highlight the aetiology, pathology, clinical features, investigations, and management of both pemphigus vulgaris and bullous pemphigoid including recent advances in management.

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Introduction

Autoimmune bullous diseases affecting the upper aerodigestive tract are characterized by blistering of the skin and mucous membranes. The disease process involves pathogenic antibodies directed against keratinocyte adhesion molecules [1]. Depending on which antibodies are present and which cleavage plane within the epidermis is affected, the clinical manifestation ensues. The 2 most common forms of autoimmune bullous diseases are pemphigoid vulgaris (PV) and bullous pemphigoid (BP). In PV, the superficial cleavage plane within the epidermal layer is affected. In BP, the deeper dermal-epidermal junction is affected.

Pemphigus is derived from the Greek word “pemphix” meaning bubble. *Pemphigus vulgaris* refers to a group of uncommon but potentially lethal autoimmune conditions characterized by mucosal and cutaneous blistering. It is characterized by epithelial blistering which arises from erythematous macules or urticarial bases. It is a chronic disease of middle age with no gender predisposition. The incidence of PV is 0.7 per 100,000 person years [2].

BP usually affects more elderly patients and the incidence in the UK is 4.3 per 100,000 person years [2]. There is no geographic or racial predilection although females are affected almost twice as often as males [2]. BP is a chronic autoimmune disease of the skin and mucosal membranes with relapse and remission of vesicles, bullae, and ulcerations. Clinically, patients have blisters occupying the full thickness of epithelium taking hours to days before rupturing. This article highlights the aetiology, pathophysiology, clinical features, investigations, and management of both PV and BP including recent advances.

Aetiology

The exact aetiology of both PV and BP is not clearly understood. For PV, the aetiology is multifactorial. There is a clear genetic component as HLA (human leucocytes antigen) alleles such as HLA-DRB1*04:02 and DQB1*05:03 have a significant role in both the progression and development of the disease [3, 4]. This explains the higher incidence of PV among Ashkenazi Jews and certain Mediterranean populations [5, 6].

The association between PV and HLA was first described in the 1980s and has been demonstrated repeatedly through various studies. Despite this recognized genetic component, there remains a gap in understanding

how environmental and genetic factors trigger disease through affecting gene expression as most individuals who carry these alleles do not have the disease [4].

In terms of BP, potential triggers that have been identified include trauma and certain drugs which include furosemide, antimicrobials, and non-steroidal anti-inflammatory drugs [7]. There is also an association between BP and certain neurological conditions such as multiple sclerosis and parkinsonism [8].

Pathophysiology

In both PV and BP, pathogenic antibodies are directed against keratinocyte adhesion molecules [1]. Within the epidermis, adjacent keratinocytes adhere through organelles known as desmosomes. Conversely, hemidesmosomes are the organelles responsible for dermal-epidermal junction adhesion.

Pemphigus vulgaris is characterized by circulating IgG autoantibodies against desmosomal cell adhesion proteins “desmoglein 3” (Dsg3). About 50% of the patients have “desmoglein 1” (Dsg1) autoantibodies as well. These autoantibodies cause intra-epidermal acantholysis and bulla formations as seen in early lesions. These circulating IgG autoantibodies are considered as pathogenic and correspond to the severity of disease [9].

While Dsgs are the main autoantigens identified in pemphigus, antibodies against other desmosomal cadherins, such as desmocollins (Dsc), may be found [10]. Desmocollins are a specialized calcium-dependent cadherin subfamily that, along with desmogleins, provides structure to the desmosomes [11]. Other antibodies which affect the cell adhesion of keratinocytes have also been discovered. These include several muscarinic and nicotinic acetylcholine receptor subtypes, mitochondrial proteins, HLA molecules, and thyroid peroxidase [12].

In BP, 2 basement membrane antibodies are affected: BP 180 and BP 230. These basement membranes contribute to hemidesmosome function and dermal-epidermal adhesion. The resultant inflammatory response leads to dermal-epidermal splitting and blisters which occur at the level of the stratum lucidum [13].

Clinical Presentation

In PV, patients usually present in the third to sixth decade of age with painful irregular blistering of the upper aerodigestive tract. The presenting symptoms will de-

Table 1. Differential diagnosis of bullous lesions of upper aerodigestive tract [14, 16, 17, 20–30, 32–45]

Disease	Age of onset	Pathophysiology	Clinical features	Involvement of oral mucosa	Extra-oral upper aerodigestive tract involvement	Other sites involved	Management
Pemphigus vulgaris	30–60	Autoimmune Main antigen: Desmoglein III	Mucous membrane erosions Skin flaccid blisters/erosions	60–90% [16] Often first site of disease [20] Gingiva, buccal mucosa, palate, tongue, and floor of mouth can be affected	Pharyngolaryngeal involvement previously considered rare Studies on PV patients have cited laryngeal lesions in 40–88% of cases [14, 21, 22] Oesophageal involvement rare; can present with odynophagia, dysphagia, and upper GI bleeding [23]	Cutaneous lesions in most cases (>50%) Urogenital tract, anus rarely affected	Immunosuppression through corticosteroid Anti-CD20 antibodies Nutritional supplementation and vit D, calcium
Paraneoplastic pemphigus	45–70*	Autoimmune Always associated with an underlying neoplasm (most commonly non-Hodgkin lymphoma in adults)	Painful mucosal and skin eruptions in the presence of confirmed/occult malignancy	100% of reported cases [24] Oral lesions as initial presentation in 45% of cases [25], usually erosions and shallow ulcerations	Rare [26] Involvement of tonsils, nasopharynx, and oesophagus reported but limited to case reports [27, 28]	Skin lesions usually appear after mucosal involvement (commonly head and neck and dorsum) [30, 31] Pulmonary involvement in 93% [30, 31]	First line is high dose corticosteroids [32]
BP	60–80	Autoimmune Main antigen: BP 180 BP 230	Tense bullae arising from skin surface with predilection for flexural areas	10–30% [17]	In 50% of cases of oral pemphigoid, disease progresses to extra-oral sites: eye, larynx, pharynx, and oesophagus [33] Laryngeal involvement in <5% [34] Oesophageal involvement limited to case report Can present with upper GI bleeding [35]	Rarely conjunctival, anogenital [17]	Immunosuppression through corticosteroid Topical corticosteroids Nutritional supplementation and vit D, calcium
Mucous membrane pemphigoid (cicatrical pemphigoid)	50–60 Female predilection	Autoimmune Autoantibodies to components of the basement membrane autoantigens [36]	Mucosal lesions Oral lesions alone or with ocular/other mucosal/systemic involvement Characterized by scarring of mucous membranes (hence name cicatrical)	100% Oral mucosa almost always affected with vesiculobullous lesions	Nasal involvement in <10% of cases Oesophageal involvement in <5% [37]	Ocular involvement in up to 60% [37] Skin, urogenital tract	Systemic corticosteroids Local pain control (emollient mouthwash)
Erythema multiforme	30	Type IV hypersensitivity reaction Multiple triggers: bacterial, viral or chemical triggers	Characteristic target-shaped lesions Affects skin and mucosal membranes and manifested by papular, bullous, and necrotic lesions	Up to 10% Mucosal lesions usually in mouth Initially bullous but rapidly turn into painful erosions [38]	Oesophageal involvement rare Can present with odynophagia with oesophagitis findings on endoscopy [39]	Lesions measure <3 cm and are typically found in acral skin Extensive skin involvement may lead to dehydration	Antiseptic topical treatment for bullous lesions Antiseptic mouthwashes and topical anaesthetic agents
SLE	50 Female predilection	Autoimmune Antibodies to nuclear and cytoplasmic antigens Affects connective tissue	Multisystemic involvement with highly variable presentation and course Classic triad of fever, arthralgia and rash in woman of childbearing age	Reported in up to 45% of cases [40]	Up to 70% of patients with SLE have oesophageal motility disorder Infectious oesophagitis can result from immunosuppression [41] Bullous SLE with oesophagitis limited to case reports [42]	As well as vesiculobullous lesions, oral manifestations include ulceration, purpura, petechiae, and cheilitis Can also affect brain, lungs, kidneys, heart, and blood vessels	Depends on disease manifestations Antimalarials (hydroxychloroquine) NSAIDs Glucocorticoids Immunosuppressive agents
OLP	50 Female predilection	Autoimmune Aetiology not fully understood Chronic T-cell mediated – apoptosis of epithelial cells	Striae or plaques affecting oral mucosa/gingiva May be accompanied by blisters and erosions	100% Lesions may appear as white striae (wickham striae), bullae, white plaques, white papules and ulcers	Extra-oral upper aerodigestive tract involvement extremely rare [43, 44]	Rare	Topical corticosteroids Oral rinses (triamcinolone, dexamethasone, clobetasol)

OLP, oral lichen planus; PV, pemphigoid vulgaris; BP, bullous pemphigoid; SLP, systemic lupus erythematosus; NSAID, non-steroidal anti-inflammatory drugs. * Children can be affected where paraneoplastic pemphigus is associated with Castleman's disease [45].

pend on the site involved; larynx (hoarseness), pharynx (odynophagia), oesophagus (dysphagia), and nasal mucosa (crusting and epistaxis) [14]. Pemphigus vulgaris should be suspected in anyone presenting with blisters or mucocutaneous erosions.

Often, the oral cavity is the first site of involvement [15]. Oral lesions are initially vesiculobullous and present in 60–90% of patients [16]. They are usually found in areas of friction in the oral cavity. Lesions readily rupture leaving tender raw areas. New bullae develop as the older bullae rupture and ulcerate. Bullae are relatively large and flaccid. Cutaneous lesions are seen in 50% of patients, and systemic features of fevers and weight loss are common. Diagnostic delay is much more common if the disease is confined to the oral mucosa [15].

In BP, presentation is usually with tense blisters. This can be either localized or widespread. The bullae or erosions may initially present in the oral mucosa with the oral cavity being involved in 10–30% of cases [17]. Patients can suffer from desquamation and bleeding of the upper aerodigestive tract mucosa. A typical example would be chronic desquamative gingivitis. During the later stages of disease, the skin becomes extensively involved. Pruritus and/or erythema may precede bullae formation by weeks or even months [18].

Differential Diagnosis

The differential diagnosis of blistering mucosal disease is outlined in Table 1. An important differential to consider in adults is paraneoplastic pemphigus (PNP), a fatal autoimmune blistering disease which is accompanied by either benign or malignant neoplasms. This rare condition was first described in 1990, and unlike other forms of pemphigus, it can affect the epithelia of the gastrointestinal or respiratory tract. The prognosis is often poor, both because of progression of tumour and the complications of aggressive immunosuppression [19].

Investigations

The diagnosis of both PV and BP can be challenging. Diagnosis is based on a combination of clinical findings, histopathological characteristics, direct immunofluorescence (DIF), and occasionally antibody testing.

For PV, in patients with isolated oral disease, a perilesional biopsy should be taken for histology. In addition, a DIF sample should be taken from an uninvolved area,

such as the buccal mucosa [46]. The characteristic deposition of IgG and/or complement on the epithelial keratinocyte surfaces confirms diagnosis. Indirect Immunofluorescence is less sensitive than DIF but can be a useful alternative if the biopsy is difficult, such as in a child or uncooperative adult.

For BP, the gold standard is also immunofluorescence studies. A biopsy for DIF is taken 1 cm away from a blister from unaffected skin. The classical picture in BP is deposition of IgG and/or C3 along the basement membrane zone. Recently, as with PV, ELISA has emerged as an additional diagnostic tool. Serum levels of antibodies to BP 180 and BP 230 can also be measured [15].

Management

The mainstay of treatment for both PV and BP is immunosuppression through corticosteroids. The British Association of Dermatologists has published guidelines for the management of PV [15] and BP [18].

The management of PV is divided into induction of remission and remission maintenance. Induction of remission is defined as a clinical state in which new lesions no longer form and established lesions start healing [47]. Corticosteroids are the mainstay of treatment for induction of remission, and a median of 3 weeks is required to reach this stage [48]. The end of the disease control phase is accomplished when 80% of lesions have healed, and no new lesions have formed for 2 weeks [15].

During the remission maintenance phase, treatment is tapered to minimize adverse effects. The end goal is to maintain remission on a daily dose of ≤ 10 mg of prednisolone. Around one-third of patients require more than 10 years of treatment, reiterating the chronicity of PV. Corticosteroids are also the mainstay treatment for maintenance of remission. Adjuvant drugs azathioprine and cyclophosphamide reduce the relapse risk by almost a third [49].

In BP, systemic corticosteroid therapy has been the mainstay of treatment since the 1950s. Suppression of blistering is usually achieved within 4 weeks after which the dose is reduced. The initial dose is dependent on severity of disease. Success of treatment within 4 weeks can be measured by the absence of new blistered or inflammatory lesions [18].

There is a strong evidence base for the use of topical steroids in bullous pemphigus. A Cochrane review found that topical steroids are both effective and safe for the treatment of bullous pemphigus. Potent topical steroids

such as clobetasol propionate are often used as first-line treatment in localized disease. They are associated with less adverse effects when compared to high dose oral steroids (1 mg kg^{-1}) [50].

Tetracycline anti-inflammatory antibiotics are widely used in the management of BP despite a small evidence base for efficacy [18]. Drugs such as azathioprine, chlorambucil, dapsone, and methotrexate have all been shown to be effective in the treatment of BP, but the evidence is limited. There is insufficient evidence of a steroid sparing effect with any of these drugs [18]. A summary of the work-up from presentation to management of both PV and BP is displayed in Figures 1 and 2.

Prognosis

The average mortality of PV was 75% before the introduction of corticosteroids [51]. Pemphigus vulgaris is a chronic condition, with few patients achieving complete remission. Mucosal PV still carries a mortality reported as high as 17% and mucocutaneous PV as high as 42% [15].

In contrast, bullous pemphigus is usually a self-limiting condition. Despite this, during the active phase of the disease, BP can carry a high morbidity and even mortality. This is usually associated with the adverse effects of high dose corticosteroids.

Novel Approaches to Management

The chronicity of autoimmune bullous diseases often necessitates long-term steroid treatment. Potential adverse effects include hypertension, osteoporosis, diabetes mellitus, gastrointestinal ulcers, and infections secondary to immunosuppression [52]. This section will outline some of the novel treatments being trialled in the treatment of autoimmune bullous diseases.

Anti-CD20 Antibodies

Rituximab is a human chimaeric IgG1 monoclonal antibody which targets B-cell surface markers CD20. Through targeting CD20, Rituximab has the effect of B-cell depletion. A multi-centre single arm study of 21 patients with refractory pemphigus in France showed that 18/21 (86%) achieved complete remission with a single cycle regimen of rituximab. At a median follow-up of 34 months, 18 of 21 patients (86%) had maintained complete remission [53].

A subsequent prospective randomized trial compared oral prednisolone alone to oral prednisolone with rituximab. The study concluded that rituximab with lower doses of prednisolone is safer and more effective than prednisolone alone in the first-line treatment of pemphigus [54]. There are also multiple case reports which have demonstrated rituximab to be effective as a second- or third-line therapy [55–57].

While the use of rituximab is well documented in pemphigus, the evidence for use in pemphigoid is scarce. Reported complete remission rates for rituximab in BP have been reported as 60–70% [58]. A phase 3 trial has been conducted looking at the efficacy and safety of rituximab in BP. The results are yet to be published (NCT00525616).

B-Cell Therapies Other than Rituximab

There are potential limitations to rituximab. The murine component of the drug is responsible for the appearance of human anti-chimeric antibodies (HACAT), which can limit drug efficacy [59]. Recently, different anti-CD20 monoclonal antibodies (anti-CD20 mAb) have been developed. Ofatumumab is a type 1 anti-CD20 mAb which has demonstrated efficacy in a patient suffering from PV, in whom rituximab was no longer effective, presumably due to the emergence of HACAT [31, 60].

Anti-Neonatal Fc Receptor (FcRn)

Fc receptor has an important role in the regulation of host IgG levels, protecting it from intracellular digestion. This is important for host defence but also means that Fc receptor maintains the concentration of pathogenic IgG in numerous autoimmune diseases, including autoimmune bullous diseases. Anti-FcRn treatments have shown promise in mice, and FcRn inhibition is in fact thought to be a potential mode of action for intravenous immunoglobulin therapy in autoimmune bullous diseases [58].

PRN1008

Bruton's tyrosine kinase (BTK) has an essential role in both development and function of B-cells [61]. It has therefore been targeted in the treatment of autoimmune conditions. Ibrutinib, a BTK inhibitor, has been successfully used in a case of paraneoplastic pemphigus [62]. A recent phase 2 trial of 27 patients with PV and pemphigus foliaceus showed promising results using PRN1008, another BTK inhibitor. More than half of the patients achieved disease control within 4 weeks without the need of prednisolone doses $>0.5 \text{ mg/kg/day}$ [63].

Fig. 1. Diagnosis and management of pemphigus vulgaris (based on British Association of Dermatology Guidelines) [15]. *Taken from perilesional mucosa. **Sample taken from uninvolved area (ideally buccal mucosa). ***Management is split into induction of remission and remission maintenance. DIF, direct immunofluorescence.

Ixekizumab

TH17 cells, by virtue of production of interleukin 17 (IL-17), have an important role in inflammation and autoimmunity. Studies have demonstrated that TH17 cells contribute to the pathogenesis of BP and autoimmune bullous diseases in general [64]. IL-17A expression in both serum and lesioned skin is higher among BP patients than healthy individuals, making it a target for BP treatment [65]. Ixekizumab is a humanized antibody which targets IL-17 and has been used for the treatment of psoriasis. The efficacy of Ixekizumab is being determined in a phase 2 clinical trial (NCT03099538).

Other Considerations

Nutritional and Dietary Factors

In PV, aggressive nutritional support is often required to minimize protein losses during the healing phase of cutaneous lesions. In cases where mucosal lesions affect oral intake, a nasogastric tube may be required. A high protein diet (2-3 g/kg body weight) is recommended [66]. Hospital admission may be required in acute flare ups to improve nutrition and optimize fluid and electrolyte balance. In both PV and BP, where long-term corticosteroids are needed, calcium, vitamin D supplementation, and bisphosphonates should be commenced to preserve bone density [18].

While no dietary factors have been implicated in the aetiology of BP, numerous substances (including tanins) present in various foods are believed to have a role in precipitating PV in genetically predisposed individuals. There are case reports of garlic and leek consumption (contains tanins), worsening pemphigus symptoms [67].

Airway Management

Laryngeal involvement has previously been considered rare in PV. There are 3 studies, however, which counter this notion. They report laryngeal lesions in 40%, 57%, and even 88% of cases of PV [14, 21, 22]. Laryngeal involvement is usually limited to manifestations of pain and tenderness in the throat, dysphonia, and odynophagia.

The laryngeal lesions in PV are usually not bullous lesions, but rather superficial ulcerations of the mucosa with an occasional white fibrinous exudative membrane. Lesions may encompass the entire larynx or may be limited to the arytenoids or epiglottis [68]. If left untreated, laryngeal lesions can result in fibrous adhesions and glottic stenosis which may cause airway compromise and necessitate tracheostomy [68]. Intubation is avoided as the mucosa of the larynx is friable and may be prone to significant injury [69].

Laryngeal mucosal involvement in BP was previously considered very rare and restricted to anecdotal case re-

Fig. 2. Diagnosis and management of BP (based on British Association of Dermatology Guidelines) [18]. *0.75–1 mg kg⁻¹ daily prednisolone is effective within 4 weeks in 60–90% of patients. **Can be used as first line in topical or moderate disease. BP, bullous pemphigoid; DIF, direct immunofluorescence.

ports [34, 70]. A recent study of 328 patients with BP found laryngeal involvement in 16 patients (4.9%). The most common finding was erosions on the laryngeal surface of the epiglottis. Patients with laryngeal mucosal involvement did not necessarily present with clinical manifestations. However, identification of mucosal involvement is important as these patients are treated with higher doses of corticosteroids [34].

Mucous membrane pemphigoid (MMP), unlike BP, can present with acute airway compromise. Also known as cicatricial pemphigoid, it is a vesiculobullous condition which primarily affects the oral cavity and eyes. Although rare, there are reported cases in the literature of MMP, causing epiglottic ulceration and oedema [71] or even as a large laryngeal mass encasing the glottis [72]. In both cases, an emergency tracheostomy was performed. There is some evidence of use of topical mitomycin in preventing laryngotracheal stenosis in cicatricial pemphigoid [71, 73].

Conclusion

Pemphigus vulgaris and BP are rare but potentially devastating conditions. They may present with ENT problems, and a high index of suspicion and immunopathological investigations are required to reach at a diagnosis and to start appropriate and timely treatment.

Treatment depends on disease severity, and it requires a multidisciplinary approach. The mainstay of treatment

remains topical and systemic corticosteroids although new treatments are being developed to negate the potential adverse effects of long-term steroids. Surgical intervention is usually reserved for cases of airway compromise which may necessitate emergent procedures such as a surgical tracheostomy.

Learning Points

1. Autoimmune blistering disease is rare but potentially lethal.
2. Presentation can be with ENT problems, and otolaryngologists should be aware of these conditions to ensure accurate diagnosis and timely intervention.
3. The commonest cause of death in autoimmune bullous diseases is opportunistic infections, caused by prolonged immunosuppression.
4. Management requires a multidisciplinary approach. Topical and systemic corticosteroids form the mainstay of treatment although new treatments are being developed to negate the potential adverse effects of long-term steroids.
5. Surgical intervention is usually reserved for cases of airway compromise.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Mohammed Hassan Hussain: drafting of manuscript and acquisition of data. Faiz Tanweer: drafting of manuscript and acquisition of data. Georgios Sakagiannis: manuscript revision. Manish Mair: manuscript revision. Sara Mahmood: manuscript revision. Sithamparappillai Ashokkumar: conception of idea and manuscript revision.

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