

Pathogenesis and practical guide into the management of Bullous pemphigoid, Pemphigus Vulgaris and Linear IgA disease

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Abstract

Autoimmune blistering diseases are common dermatologic emergencies, with extensive morbidity and mortality. Vesiculobullous diseases are characterized by skin separation at a variety of levels on histopathology, and they have intersecting clinical and histological features which can cause diagnosis uncertainty. For proper treatment decision, an accurate diagnosis is pivotal and can be established by clinical, histopathology and immunofluorescence tools.

Keywords: Pemphigus vulgaris, Bullous Pemphigoids, Linear Immunoglobulin A Bullous Dermatitis, Pathogenesis.

Pemphigus Vulgaris

Background

Pemphigus vulgaris (PV) is an acquired autoimmune disease characterized by mucocutaneous blistering at the intraepithelial level, secondary to immunoglobulin G (IgG) antibodies that target desmosomal proteins. Desmoglein 3 is the major antigen targeted in PV, while desmoglein 1 is targeted by in patients with Pemphigus foliaceus (PF), however, this can additionally be targeted in 50-60% of the patients of PV [1,2].

Mucocutaneous PV have shown a higher mortality rate as compared to patients with predominantly mucosal variant; with rates ranging between (8-42%) and (1-17%) respectively [3]. This is indicated by a slow response to treatment and less likelihood to achieve remission off-treatment in patients with Mucocutaneous PV [4].

PV peak frequency is in the third to sixth decade, however, a wide age range can be affected with oral mucosa being the first site of involvement in most cases and PV may remain confined to the mucosal surfaces or subsequently, extend to involve the skin [5].

Pathogenesis and Pathology

The underlying pathogenesis is formation of IgG antibodies to desmogleins which are the transmembrane glycoproteins of the desmosomes. On histological examination PV shows an epidermal split in the form of suprabasal acantholysis [6]. The basal layer remains attached (tombstone sign) and there are intraepidermal eosinophils and sometimes neutrophils with follicular involvement. No significant dyskeratosis is noted (Figure 1A). Direct immunofluorescence (DIF) of perilesional skin biopsies is the gold-standard diagnostic investigation [6] and keratinocytes express characteristic deposition of IgG and/or complement (Figure 1B).

Although less sensitive, Indirect immunofluorescence (IIF) may be helpful if a biopsy is difficult, especially in children [7]. Commercial enzyme-linked immunosorbent assays (ELISAs) are used for direct measurement of desmoglein 1 and desmoglein 3 antibodies in the serum and considered as complementary to DIF in the process of diagnosis, but ELISA levels are related to disease activity [6].

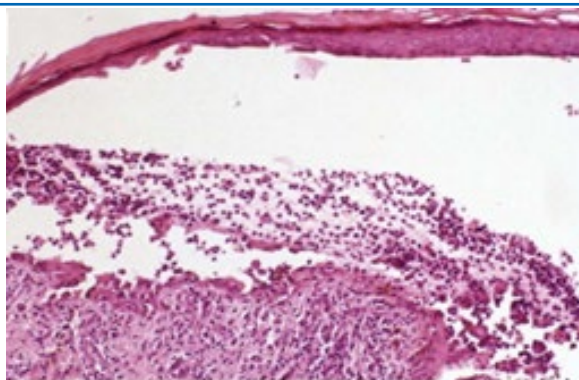


Figure 1A: Photomicrograph of pemphigus vulgaris showing a suprabasal epidermal cleft containing eosinophils mainly (H & E stain).

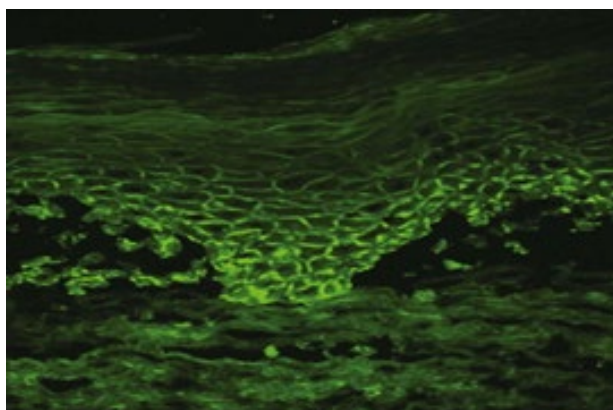


Figure 1B: Direct immunofluorescence test of pemphigus vulgaris showing IgG deposition in epidermal keratinocytes.

Management

Disease monitoring can be done by clinical observation of disease activity, which can be achieved objectively by using clinical disease scoring systems; Pemphigus Disease Area Index (PDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) (Appendix), all supplemented by immunological measures and quality-of-life scores [8].

The management of PV requires immunosuppressive medication and should be provided in the secondary care. It can be achieved in two main stages; induction of remission which is defined by ceasing new blisters and start healing in established ones, at this phase systemic corticosteroid are most effective and fast acting, in the form of oral prednisolone 1 mg/kg daily (or equivalent) in most cases, this can be raised in 50-100% increments every 5-7 days if active blisters continue to erupt, however, pulsed intravenous corticosteroids can be considered if more than 1 mg/kg oral prednisolone is required. Adjuvant drugs has limited role and rarely used alone due to limited immediate response; nevertheless, their main role is in remission maintenance, which is the second phase that is recognised as absence of new blisters and healing of the majority. At this level it is then advised to taper oral prednisolone aiming to decrease to 10 mg daily or less during which adjuvant drugs are commonly combined aiming to increasing efficacy and reducing corticosteroid doses. The risk of osteoporosis needs to be assessed immediately [2].

A well-established choice of adjuvant drug for the management of pemphigus is Azathioprine 2-3 mg/kg per day (if thiopurine methyl transferase (TPMT) is normal). Alternatively, Mycophenolate mofetil 2-3 g per day could be administered as an alternative to azathioprine in patients unresponsive to treatment or where comorbidities or baseline investigations exclude azathioprine. Rituximab is an effective modality in treatment-resistant disease. Recently a rheumatoid arthritis regimen of two infusions of rituximab 1 g, 2 weeks apart, has been effective in treatment of PV [9,10].

Third-line therapy options are considered as additional treatment based on assessment of individual patients and this requires a consensus of a multidisciplinary team. These include; Cyclophosphamide-Methotrexate as an alternative to azathioprine, pulsed cyclophosphamide and dexamethasone or methylprednisolone for severe recalcitrant PV. Other options are reserved for the treatment of patients resistant to or intolerant of other drugs. These are: Immunoabsorption, Intravenous immunoglobulin, Plasmapheresis or Plasma exchange and Extracorporeal photopheresis [2].

During remission, it is common practice to discontinue corticosteroids first to lessen their side-effects, however, adjuvant immunosuppressants are maintained at full dose, and then slowly tapered if remission persists [11,12]. Eventually, if remission has been achieved the prolonged treatment may be withdrawn. Reduced relapse has been noticed if immunofluorescence or ELISA studies are negative [13].

Topical Treatment

Topical corticosteroid preparations are frequently used as adjunctive therapy for patients with oral involvement, including mouth rinse-and-spit solutions or ointments preparation such as clobetasol 0.05% ointment mixed in 50% Orabase twice weekly applied to localized lesions on a dried mucosa. Intralesional and perilesional triamcinolone injections have obtained an acceptable compliance [14], moreover, topical tacrolimus and topical ciclosporin in a form of mouth wash were found to be effective [15,16].

Blister Care

During the active phase, PV precipitates extensive cutaneous erosions and fragility of normal skin (indicated by a positive Nikolsky sign). Hence, gentle handling of the skin is critical and is arranged by specialist dermatology nurses, or staff who are familiar with skin failure. It is also essential to consider fluid balance, thermoregulation, haemodynamic stability and prevention of infection, nutritional intake, pain control and psychological support [2].

Generally, blisters should not be ruptured or aspirated, but can be pierced at the base with a sterile needle and after cleansing with antimicrobial solution and dressed with a nonadherent dressing. Analgesia can be offered during blister piercing, the number and location of new blisters is to be documented.

Bullous Pemphigoid

Background

Bullous Pemphigoids (BP) is an autoimmune subepidermal blistering disease in which IgG autoantibodies (and less commonly IgA, IgM and IgE) attack the basement membrane zone (BMZ)

and result in subepidermal blistering. The main autoantigens are BP230 (BPAG1) and BP180 (BPAG2, collagen XVII) [17]. BP affects the elderly, however, can rarely present in children and younger adults. In the UK the reported incidence is 43 per million per year [18]. The mean age of onset is around 80 years. Neurological disease such as multiple sclerosis, dementia, Parkinson disease, and cerebrovascular disease has been recently shown to be associated with BP [19,20]. Clinically, BP is presents as widespread or localised tense blisters, which are often seen on erythematous or normal-looking skin. BP can also present with pruritus alone or in association with erythema and/or urticated plaques which occur weeks to months before the formation of blisters. Mucosal surfaces can be involved.

Pathogenesis and Pathology

The pathogenesis is production of IgG autoantibodies against hemidesmosomal proteins BPAG1 and BPAG2. On histopathology, the skin from a fresh blister shows subepidermal splitting and an eosinophil rich inflammatory infiltrate (Figure 2A).

Eosinophils may line up along the the dermo epidermal junction and extend into the epidermis with eosinophilic spongiosis and pseudovacuolar interface change [6]. Uncommonly, neutrophil rich and cell poor infiltrates are noted. Immunofluorescence (IF) studies continue to be the gold standard for diagnosis [6]. This shows linear deposits of C3 and IgG at basement membrane zone (BMZ) (Figure 2B).

Recently, Serum levels of antibodies to both BP180 and BP230 can be quantified with enzyme-linked immunosorbent assay (ELISA) kits [16].

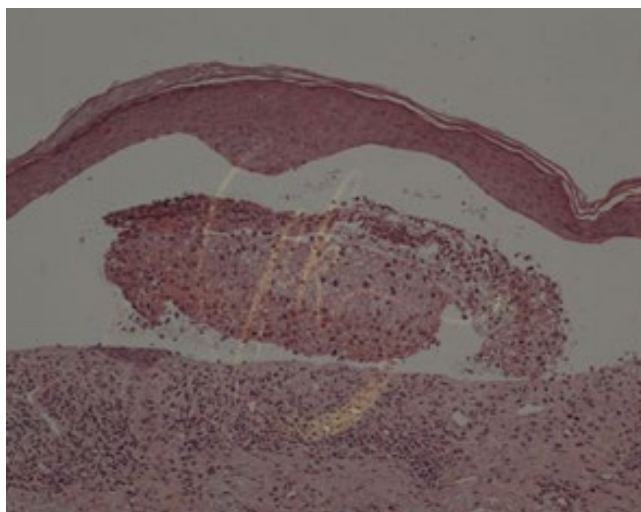


Figure 2A: Photomicrograph of bullous pemphigoid showing a subepidermal cleft containing eosinophils mainly (H & E stain).

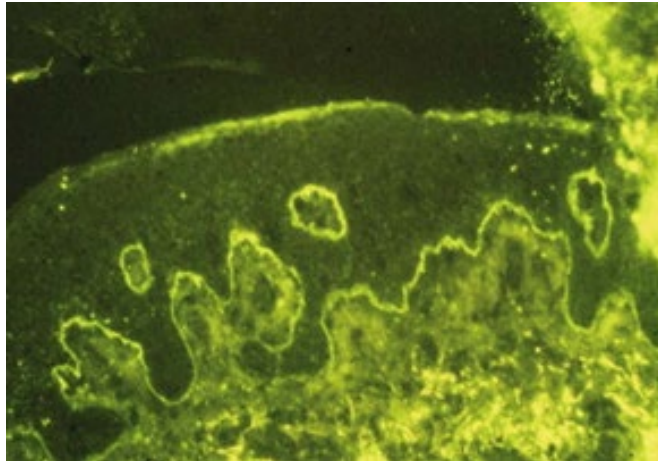


Figure 2B: Direct immunofluorescence test of bullous pemphigoid showing linear IgG deposits in the basement membrane zone (BMZ).

Management

Options are generally involving anti-inflammatory, immunomodulating, immunosuppressive medications. So far, systemic steroids are the best-established treatment for BP. In severe involvement, doses of 0.75-1 mg/kg/day of prednisolone are effective within 1-4 weeks in about 60-90% of cases. For moderate disease dose can be effective at 0.5 mg/kg/day and to lower extent in localised or mild involvement (as low as 0.3 mg/kg/day). Side effects whether immunosuppressive or metabolic are dose dependent [16]. It has been recommended that calcium and vitamin D supplementation and a bisphosphonate are initiated from the start to preserve bone density in patients with immunobullous diseases [21].

In the absence of new blisters or inflammatory lesions within 4 weeks, the treatment can be considered as successful, and the dose should be gradually reduced. It is suggested that reduction is in fortnightly intervals, as one-third or one-quarter lowering of the prednisolone dose reaching 15 mg daily, then by 2.5 mg decrements down to 10 mg daily. The dose could then be reduced by 1 mg each month. During the dose-reduction period, relapse can occur, indicating that the previous dose is expected to be the minimal effective dose for that patient [16].

Topical steroids in the form of clobetasol propionate 0.05% is used successfully as a first-line treatment for both localized and moderate disease. While for moderate to severe disease; systemic steroids are started with or without topical potent steroid [22].

For patients with widespread BP who do not respond or who relapse on high doses, other options, alone or in combination with the systemic steroid, may be superior to higher doses of steroids.

Azathioprine is a commonly used drug in BP with doses of up to 2.5 mg/kg. On the other hand; antibiotics with anti-inflammatory effects are used widely in the treat BP (Doxycycline 200 mg/day, Lymecycline 408 mg twice daily Minocycline 100 mg/day, Oxytetracycline 1 g/day, Erythromycin 1-2 g/day). A survey in the UK showed that 80% of dermatologists use antibiotics as part of their management [23].

More options are available for patients who are not responding to existing treatment, or who relapse on high doses of ongoing treatment. These are; anti-inflammatory antibiotics with or without nicotinamide 500-2500 mg daily, Azathioprine 1-2.5 mg/kg daily, Methotrexate 5-15 mg weekly, Dapsone 50-200 mg daily, and Chlorambucil 0.05-0.1 mg/kg daily [16].

If response is not achieved with all of the above, other modalities to be considered in special circumstances including; Mycophenolate mofetil 0.5-1 g twice daily, IVIg, Cyclophosphamide and Plasmapheresis.

Skin Care in Bullous Pemphigoid

It is advisable that blisters are to be left intact to avoid contamination and secondary bacterial infection, however, piercing with a sterile needle to release the fluid and keeping the blister roof is recommended if the blister is large or interferes with function due to blister location such as on the sole of the foot. Painful eroded areas can be covered with a low-adhesion dressing. Antiseptics and topical steroid are to be applied on this area [16].

Linear IgA Bullous Dermatitis

Background

Linear immunoglobulin A (IgA) bullous dermatosis (LABD), is clinically a pruritic immunobullous disease presenting as erosions vesicles, and bullae, symmetrically distributed on extensor surfaces, with mucous membrane involvement in 8% of patients. The peak age of incidence is 60-65 years with a slight female predominance [24]. LABD is mostly precipitated by medications and Vancomycin is frequently.

Pathogenesis and Pathology

Aetiology is unclear and the target antigen of IgA autoantibodies is 120 kd secretory portion of BP180 antigen, but other antigens have also been reported. Aetiology has been linked to the administration of antibiotics, nonsteroidal anti-inflammatory agents, diuretics and rarely interferon alpha-2A. Histology is characterised by the presence of a subepidermal vesicle with a primarily neutrophilic infiltrate identical to dermatitis herpetiformis [6] (Figure 3A) and DIF of perilesional skin shows presence of linear

deposition of BMZ-specific IgA antibody in the absence of other immunoglobulins [25] (Figure 3B).

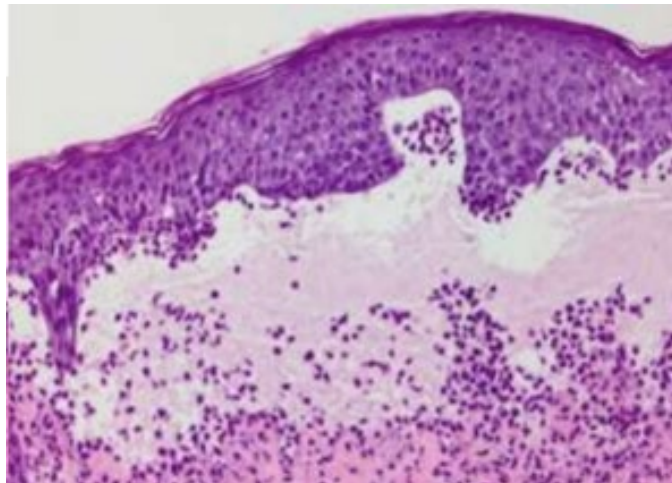


Figure 3A: Photomicrograph of linear IgA bullous dermatosis showing a subepidermal cleft containing neutrophils mainly (H & E stain).

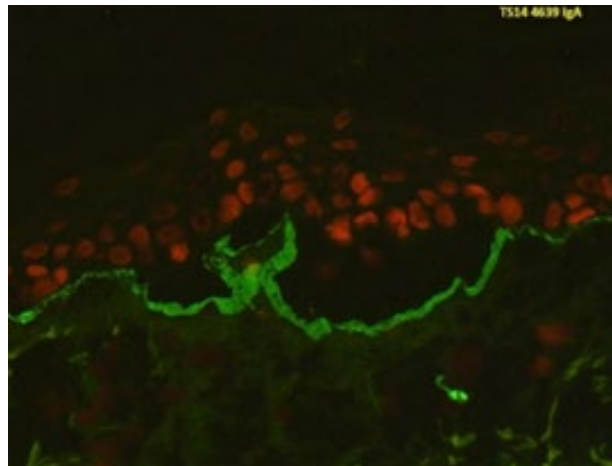


Figure 3B: Direct immunofluorescence test of linear IgA bullous dermatosis showing only IgA deposition in the BMZ.

Management

Treatment is dapsone (25 mg/day in adults, 6.25 mg/day in children) and increased gradually to be maintained (100-200 mg/day in adults, 25-50 mg/day in children). Haemolysis and Methemoglobinemia are common side effects, patients should

be counselled about cyanosis and haemolytic anaemia. Hence, close monitoring is essential. Patients should undergo frequent laboratory tests. Sulphapyridine might be used if the is intolerant to dapsone. The dose is 1.0-1.5 g/day [25].

ABSIS SCORING SHEET

Date:
Patient's weight (kg):

Legend for weighing factor (most dominant appearance of skin lesions):

1.5	<i>Erosive, exudative lesions</i>
1	<i>Erosive, dry lesions</i>
0.5	<i>Reepithelialized lesions (incl post inflamm erythema &/or hyperpigmentation)</i>

Skin Involvement (Max BSA)	Patient's BSA	Weighting factor
Head & neck (9%):		
L Arm including hand (9%):		
R Arm including hand (9%):		
Trunk (front & back) (36%):		
L Leg (18%):		
R Leg (18%):		
Genitals (1%):		

(Skin involvement total score: % BSA x weighing factor = 0–150 points) - will be calculated by the program

Oral Involvement:

I. Extent (enter 1 for presence of lesions, 0 absence of any lesion):

Upper gingival mucosa		Tongue	
Lower gingival mucosa		Floor of the mouth	
Upper lip mucosa		Hard palate	
Lower lip mucosa		Soft palate	
Left buccal mucosa		Pharynx	
Right buccal mucosa			

(Total score ranges from 0–11)

Severity (discomfort during eating/drinking)

Food	Level	Factor of Discomfort	Severity score
Water	1		
Soup	2		
Yogurt	3		
Custard	4		
Mashed potatoes/ scrambled egg	5		
Baked fish	6		
White bread	7		
Apple/ raw carrot	8		
Fried steak/ whole-grain bread	9		

(Severity score= Level multiplied by the factor of discomfort= 0–45 points)

<i>Legend for factor of discomfort</i>	
1	<i>Pain/bleeding occurred always</i>
0.5	<i>Pain/bleeding occurred sometimes</i>
0	<i>Never experienced problems</i>

Appendix: Bullous skin disorder intensity score (ABSIS) in pemphigus [26].

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