Pemphigus and BMZ diseases in people: presentations and management

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Autoimmune bullous diseases

Autoimmune bullous diseases are due to circulating antibodies directed against specific target antigens in the skin. The clinical presentation of the disease is usually influenced by the location of the target antigen. Antibodies directed against desmosomal proteins that anchor the keratinocytes to one another in the epidermis result in pemphigus and its variants. Due to the superficial location of the antigens, blisters are usually flaccid and often present clinically as erosions. On the other hand, antibodies directed against hemidesmosomal proteins that anchor the basal keratinocytes to the basement membrane zone (BMZ) result in pemphigoid and its variants. In this group of diseases, blistering is sub-epidermal and blisters appear tense. Diagnosis of these diseases is confirmed by histology and immunofluorescence. This review will focus on the clinical presentation of these various autoimmune blistering diseases, as well as an overview of their management.

Molecular Basis

The skin structure is maintained by secure adhesion between keratinocytes within the epidermis and between the basal keratinocytes and the underlying basement membrane. The structures that are mainly responsible for adhesion are the desmosomes between epidermal keratinocytes and the hemidesmosomes anchoring the basal keratinocytes to the basement membrane. Disruption of any of the proteins contained in these complexes leads to destabilization of the skin structure leading to blisters.1,2

A summary of the most common human autoimmune bullous diseases is set out in Table 1, along with the target antigens, antibodies, and immunofluorescence pattern seen.

Table 1. Target Antigens of Common Autoimmune Bullous Diseases

<table>
<thead>
<tr>
<th>Autoimmune Bullous Disease</th>
<th>Target Antigen</th>
<th>Location</th>
<th>Antibodies</th>
<th>DIF pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris (PV)</td>
<td>Desmoglein 3 &gt; 1</td>
<td>Desmosome</td>
<td>IgG, C3</td>
<td>Intercellular deposits around keratinocytes</td>
</tr>
<tr>
<td>Pemphigus foliaceus (PF)</td>
<td>Desmoglein 1</td>
<td>Desmosome</td>
<td>IgG</td>
<td>Intercellular deposits around keratinocytes</td>
</tr>
<tr>
<td>Paraneoplastic Pemphigus (PNP)</td>
<td>Periplakin, envoplakin, epiplakin, desmoplakin, plakoglobin, desmoglein 230-kDa BP antigen</td>
<td>Desmosome</td>
<td>IgG, C3</td>
<td>Intercellular deposits around keratinocytes and linear deposits along BMZ</td>
</tr>
<tr>
<td>Bullous pemphigoid (BP)</td>
<td>230-kDa BP antigen, Type XVII collagen</td>
<td>Hemidesmosome</td>
<td>C3, IgG</td>
<td>Linear deposits along BMZ, roof of blister in NaCl split skin</td>
</tr>
<tr>
<td>Mucous Membrane Pemphigoid (MMP)</td>
<td>Type XVII collagen, plectin, laminin 5</td>
<td>Hemidesmosome</td>
<td>IgG, C3, (IgA, IgM)</td>
<td>Linear deposits along BMZ</td>
</tr>
<tr>
<td>Pemphigoid Gestationis (PG)</td>
<td>Type XVII collagen</td>
<td>Hemidesmosome</td>
<td>C3</td>
<td>Linear deposits along BMZ</td>
</tr>
</tbody>
</table>
### Autoimmune Bullous Disease

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<tr>
<td>Linear IgA Disease (LAD)</td>
<td>Type XVII collagen (97-kDa and 120-kDa cleaved fragments)</td>
<td>Hemidesmosome</td>
<td>IgA</td>
<td>Linear deposits along BMZ, roof and floor of blister in NaCl split skin</td>
</tr>
<tr>
<td>Epidermolysis Bullosa (EBA)</td>
<td>Type VII collagen (anchoring fibrils)</td>
<td>Sub-basal layer</td>
<td>IgG, C3</td>
<td>Linear deposits along BMZ, floor of blister in NaCl split skin</td>
</tr>
<tr>
<td>Dermatitis herpetiformis (DH)</td>
<td>gliadin, reticulum, smooth muscle endomysium</td>
<td>Dermal papillae</td>
<td>IgA</td>
<td>Granular in dermal papillary tips</td>
</tr>
</tbody>
</table>

### Diagnostic Tests

A routine skin punch biopsy (3-4 mm) is taken from the edge of the blister, including a portion of normal skin and this sent for haematoxylin and eosin (H&E) staining. A biopsy is helpful in making the diagnosis since it will show the level of the split (intraepidermal for pemphigus and subepidermal for pemphigoid). It will also show the inflammatory cells which are a clue to the disease. Bullous pemphigoid, for example, has a predominantly eosinophilic infiltrate, which accounts for the pruritus associated with the disease. Linear IgA disease, on the other hand, is associated with a neutrophilic infiltrate.

While doing skin biopsies, it is also important to take a perilesional biopsy for direct immunofluorescence (DIF). This method detects antibodies deposited within the patient’s tissue. Antibodies have the fluorescent dye attached. Fluorescein-conjugated antibodies directed against complement fractions (C3, fibrinogen) and immunoglobulins (IgG, IgA, IgM) are placed on frozen sections of the tissue. A positive fluorescence (graded on intensity) in a particular pattern confirms the diagnosis. The patient’s tissue may also be incubated in 1 mol/litre NaCl prior to performing the DIF. This technique induces cleavage through the lamina lucida, and is useful in differentiating autoimmune diseases with a similar DIF pattern by observing where the IgG or C3 localizes (i.e. dermal roof pattern for BP and dermal floor pattern for EBA).

Serum may also be sent for indirect immunofluorescence (IIF) which is useful as a confirmatory test. This is used to detect circulating autoantibodies. In this setting, antibodies do not have the fluorescent dye attached. This method uses serum with fluorescein-conjugated human anti-immunoglobulin against a mucosal substrate such as monkey oesophagus or rat bladder.

### Pemphigus vulgaris

#### Clinical
- This disease involves the skin and mucous membranes
- Age 40-60 years
- HLA Associations: HLA DRB1*1454, DRB1*1401
- The oral mucosa is usually the first site of involvement, followed by the skin months later
- May be fatal if untreated
- Flaccid blisters rapidly becoming erosions
- (+) Nikolsky sign (extension of blister upon applying lateral pressure)
- Other variants: drug-induced pemphigus (penicillamine, nifedipine, captopril), pemphigus vegetans (involves skin folds)

#### Histology
- Suprabasal blister with acantholysis

*IF - see table 1*
Management
- Systemic corticosteroids are mainstay: Prednisone 1 mg/kg/day +/- other immunosuppressives
- Azathioprine, Methotrexate, Cyclophosphamide, Mycophenolate mofetil, IVIG, Rituximab, plasmapheresis

Course and prognosis
- Common cause of death is infection due to immunosuppression needed to treat the disease

Pemphigus foliaceus

Clinical
- May be localised or generalised
- Shallow, flaccid blisters rapidly becoming scaly, crusted erosions, may coalesce into large denuded areas
- Mucous membranes generally not affected
- (+) Nikolsky sign (extension of blister upon applying lateral pressure)
- Other variants: fogo selvagem (endemic PF associated with black fly Simulium nigrimanum in Brazil), pemphigus erythematosus (localised to cheeks and forehead, may have (+) ANA)

Histology
- Intraepidermal blister at the granular layer with acantholysis

IF - see table 1

Management
- Topical corticosteroids for localised PF
- Systemic corticosteroids or other immunosuppressives in recalcitrant disease

Course and prognosis
- Good if therapy instituted early

Paraneoplastic pemphigus

Clinical
- This is due to an underlying malignancy (tumour antigens evoke an immune response leading to blisters)
- Most common tumours: leukaemia, lymphoma, Waldenstrom’s macroglobulinaemia, sarcomas, thymoma, Castleman’s disease
- 100% have mucosal involvement, highly variable cutaneous lesions

Histology
- Suprabasal blister with acantholysis, basal vacuolation, dyskeratotic keratinocytes

IF - see table 1
- In addition, rat bladder transitional epithelium separates it from PV and PF as desmogleins present in stratified squamous epithelium only

Management
- Systemic corticosteroids are mainstay: Prednisone 1 mg/kg/day +/- other immunosuppressives
- Azathioprine, Methotrexate, Cyclophosphamide, Mycophenolate mofetil, IVIG, Rituximab, plasmapheresis

Course and prognosis
- High mortality (75-80%) due to underlying neoplasm and medications required to treat this

Bullous Pemphigoid

Clinical
- Subepidermal blistering disease
- Age > 60 years
- May start as an urticarial eruption (very pruritic)
- Tense blisters, common locations: abdomen, flexor surfaces of forearms, inner thighs
- (-) Nikolsky sign

Histology
- Subepidermal blister with prominent eosinophilic infiltration

IF - see table 1

Management
- Topical steroids or systemic corticosteroids +/- other immunosuppressives
- Tetracycline +/- Nicotinamide, Azathioprine, Mycophenolate mofetil, Methotrexate, Cyclophosphamide

Course and prognosis
- Self-limited with good prognosis
- 50% enter remission within 2-6 years

Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)

Clinical
- Erosive lesions of skin and mucous membranes
- Skin involvement in 1/3 of patients, mostly mucosal
- Heals with scarring (i.e. conjunctival scarring)
- Eye involvement may lead to blindness
- Mucosal involvement may lead to dysphagia or even oesophageal stenosis requiring dilatation
- (-) Nikolsky sign

Histology
- Subepidermal blister with mixed inflammatory cell infiltration

IF - see table 1

In addition, antiepiligrin cicatricial pemphigoid circulating autoantibodies bind to dermal side of salt-split skin

Management
- Topical steroids or systemic corticosteroids +/- other immunosuppressives
- Tetracycline +/- Nicotinamide, Azathioprine, Mycophenolate mofetil, Methotrexate, Cyclophosphamide

Course and prognosis
- Chronic, progressive

Pemphigoid Gestationis (Herpes gestationis)

Clinical
- Rare, autoimmune disease of pregnancy
- Extremely pruritic, polymorphic bullous dermatosis with urticarial plaques
- Usually starts on the abdomen spreading peripherally sparing the face, palms, soles, mucous membranes
- Exacerbations after delivery common
- Babies born to these mothers may have transient blistering after delivery
- Heals with scarring (i.e. conjunctival scarring)

Histology
- Subepidermal blister with eosinophilic infiltration

IF - see table 1
Management
• Topical steroids or systemic corticosteroids if required

Course and prognosis
• Maternal mortality rate is unaffected
• Regresses without scarring a few days to weeks after delivery
• May recur in subsequent pregnancies

Linear IgA Disease (Chronic Bullous Disease of Childhood)
Clinical
• Often in patients > 30 years; <5 years in children
• Abrupt onset of tense bullae on an inflamed, erythematous base
• Blisters often occur in collarettes or rosettes as new blisters arise in periphery of old blisters
• Oral ulcers in 50%
• Drugs implicated: vancomycin, lithium, diclofenac

Histology
• Subepidermal blister with neutrophilic infiltration

IF - see table 1

Management
• Dapsone or sulfapyridine

Course and prognosis
• Variable and unpredictable
• May remit spontaneously after 2 years

Epidermolysis Bullosa Acquisita
Clinical
• Chronic bullous disease primarily involving skin, but may also affect mucous membranes
• Common sites: trauma-prone areas of the skin - extensor surfaces of elbows, knees, ankles, buttocks
• Nail destruction and hair loss seen

Histology
• Subepidermal blister with mixed inflammatory cell infiltration

IF - see table 1

Management
• Systemic corticosteroids +/- other immunosuppressives

Course and prognosis
• Chronic disease with periods of partial remissions and exacerbations

Dermatitis Herpetiformis
Clinical
• Associated with HLA B8-DR3-DQ2
• Intensely pruritic, chronic skin disease
• Age 20-40 years
• Intensely pruritic, chronic, grouped papules and vesicles symmetrically distributed on extensor surfaces, buttocks, hairline
• Associated with gluten-sensitive enteropathy

Histology
• Subepidermal blister at level of lamina lucida
• Neutrophilic microabscesses in dermal papillae

IF - see table 1

Management
• Dapsone or sulfapyridine
• Gluten-free diet
• Avoid iodine and NSAIDs

Course and prognosis
• Persists indefinitely
• Waxes and wanes

References