INTRODUCTION

- BSDs are skin conditions characterised by blister formation.
- A blister is an accumulation of fluid between cells of the epidermis or upper dermis.
- Causes of blister could be genetic, physical, inflammatory, immunologic and as a reaction to drugs.
- BSDs are mostly autoimmune.

PATHOPHYSIOLOGY

The keratinocytes of the epidermis are tightly bound together by desmosomes and intercellular subs to form a barrier of high tensile strength and stability. Beneath the epidermis lies the BMZ, which is a specialised area of cell-extracellular matrix adhesion. Specialised structures traversing this zone anchor the epidermis to the dermis. The BMZ is particularly vulnerable to damage or malform. and is a common site of blister formation

Types:

1. Genetic Blistering Diseases:
   - A. Epidermolysis Bullosa
   - B. Hailey-Hailey disease (Benign familial pemphigus)

2. Immunobullous Diseases:
   - A. Intraepidermal Immunobullous Diseases:
     1. Pemphigus Vulgaris (PV)
     2. Pemphigus vegetans
     3. Pemphigus foliaceus
     4. Pemphigus erythematosus
     5. Paraneoplastic P
   - B. Subepidermal Immunobullous Diseases:
     1. Bullous Pemphigoid
     2. Linear IgA disease
     3. Dermatitis Herpetiforms
     4. Pemphigoid Gestations
     5. Epidermolysis Bullosa Acquisita

Structure of the epidermis and sites of target antigens/cleavage in bullous diseases:
IMMUNOLOGIC BULLOUS SKIN Dis.

These includes:

1. Pemphigus
2. Pemphigoid
3. Dermatitis Herpetiformis (DH)
4. Chronic dermatoses of childhood (linear IgA dis.)

PEMPHIGUS

- is derived from the Greek word *pemphix* meaning bubble or blister.
- A serious, acute or chronic, bullous autoimmune disease of skin and mucous membranes based on acantholysis.
- It is a severe and potentially life threatening diseases.
- Types include: P. vulgaris, vegetans, foliaceus, erythematous, and paraneoplastica

Epidemiology

- occur worldwide.
- PV incidence varies from 0.5-3.2 cases per 100,000.
- more common in Jewish and people of Mediterranean descent.
- Common in the middle age groups(40-60 yrs of life)
- men and women equally affected

AETIOLOGY

It is an autoimmune dis. in which pathogenic IgG antibodies binds to antigens within the epidermis. The main Ags are desmoglein 1 and 3. Both are adhesion molecules found in the desmosomes. The Ag-Ab reaction interferes with adhesion, causing the keratinocytes to fall apart (acantholysis)

CLINICAL FEATURES

- **Mouth ulcers** that persists for months before **skin lesions** appears on the trunk, flexures and scalp
- Blisters are superficial and flaccid, hence they rupture easily leaving a shallow erosion covered with dried serum and crust
- Shearing stress on normal skin(sliding pressure) can cause new erosion to form(+ve Nikolsky sign).
- + ve Nikolski’s Sign

Nikolsky Sign : Dislodging of epidermis by lateral finger pressure in the vicinity of lesions, which leads to an erosion. Pressure on bulla leads to lateral extension of blister.

DIAGNOSIS

1. Clinical evaluation
2. Histopathologic by Light microscopy
3. Immunofluorescent examination. is a laboratory technique for demonstrating the presence of tissue bound and circulating antibodies
4. Electron microscopic examination ;(EM) NOT routinely done
DIFFERENTIAL DIAGNOSIS

1. Other types of pemphigus
2. Bullous pemphigoid
3. Dermatitis herpetiformis (DH)
4. Bullous impetigo
5. EB or Ecthyma
6. Familial benign pemphigus (Hailey-Hailey disease)

Mouth ulcers:

1. Aphthae
2. Behcet’s dis.
3. Herpes simplex infection
4. Bullous lichen planus

TREATMENT

1. Systemic steroid; 2 to 3 mg/kg of prednisolone until cessation of new blister formation and disappearance of Nikolsky sign.
2. Concomitant Immunosuppressive Therapy (steroid sparing agents) such as Azathioprine, 2–3 mg/kg. Methotrexate, either orally or IM at doses of 25 to 35 mg/week. Cyclophosphamide or mycophenylate mofetil.
3. High-dose intravenous immunoglobulin (HIVlg); (2 g/kg every 3–4 weeks) may help gain quick control whilst waiting for other drugs to work.
4. Rituximab (Anti-CD20 monoclonal antibody) has been reported to help multidrug resistance, IV, once a week for 4 weeks.

Rx need regular follow up and is usually prolong

Dosage should be dropped only when new blisters stop appearing
COMPLICATIONS

- Side effects of treatment is the leading cause of death
- Areas of denudation become infected and smelly
- Oral ulcers makes eating painful

PARANEOPLASTIC PEMPHIGUS (PNP)

- PNP Lesions combine features of pemphigus vulgaris and erythema multiforme, clinically and histologically
- Mucous membranes primarily and most severely involved.
- Associated internal malignancy as;
  - Non-Hodgkin’s lymphoma, Chronic lymphocytic leukemia and Castleman’s disease

Drug-induced PV

- Drugs can induce PV
- Drugs reported most significantly in association with PV are; Penicillamine and captopril

BULLOUS PEMPHIGOID

- Also an autoimmune blistering disorder
- Anti bodies binds to normal skin at the BMZ
- It is more common than pemphigus
- Mainly affect the elderly
- Mucosal involvement is rare
- BULLOUS PEMPHIGOID

PATHOGENESIS

There is linear deposition of lgs which complements against proteins at the dermo-epidermal junction. The Ig antibodies binds to 2 main Ags, most commonly to BP230 and less often BP180 found in the hemidesmosome and in the lamina lucida. Complement is then activated, starting an inflammatory cascade. Eosinophils often participate in the process, causing the epidermis to separate from the dermis.

CLINICAL FEATURES

- Pemphigoid is a chronic, usually itchy, blistering disease, mainly affecting the elderly
- Early stages of the dis. is characterised by pruritus
- Bullae may be centered on erythematous and urticated base.
- Large tense bullae found anywhere on the skin
- The flexures are often affected; inner aspect of the thigh, flexure surface of forearms, axillae, groin and lower abdomen
- The mucous membranes usually are not.
- The Nikolsky test is negative.

INVESTIGATIONS

1. Skin biopsy shows a deeper blister (than in pemphigus) owing to a subepidermal split through the BM
2. On direct IF, perilesional skin shows linear band of IgG and C3 along BMZ
3. Indirect IF shows IgG antibodies that reacts with the BMZ in most patients
4. Hematology Eosinophilia (not always)
DDx

- Epidermolysis bullosa
- Bullous lupus erythematosus
- Dermatitis herpetiformis
- Bullous erythema multiforme

TREATMENT

- In acute phase, **prednisolone** 40-60mg daily is usually needed to control the eruption
- **Immunosuppressive agents** may also be required
- **Dosage** should be reduced as soon as possible to low maintenance, taken on alternate days until treatment is stopped.
- In **very mild cases** and for **local recurrences**, topical glucocorticoid or topical tacrolimus therapy may be beneficial.
- **Tetracycline ± nicotinamide** has been reported to be effective in some cases.
- Treatment can often be withdrawn after 2-3yrs

COMPLICATIONS

- Complications of systemic steroids and immunosuppressive agents if used on the long term
- Loss of fluid from ruptured bullae

DIFF BTW PEMPHIGUS AND PEMPHIGOID

**Pemphigus**

- Usually affects the middle age
- Seen on the trunk, flexures and scalp
- Blister in the mouth is common
- Nature of blister is superficial and flaccid
- Circulating Ab is IgG to intracellular adhesion proteins. Serum Ab Titer correlate with disease activity.
- Acantholysis
- Nikolsky sign is positive
- Acute and non-itchy

**Pemphigoid**

- Elderly patients
- Usually flexural
Mouth bister is rare
Blister is tense and bloody
IgG to BM region. Serum Ab Titer does not correlate with clinical disease activity.
No acantholysis
Nikolsky sign is negative
Chronic and itchy

Dermatitis Herpetiformis (DH)
Intensely itchy, chronic papulovesicular eruption distributed symmetrically on extensor surfaces.
It may start at any age, including childhood; however, the second, third, and fourth decades are the most common.

Skin biopsy; Characterized histologically by dermal papillary collections of neutrophils (microabscesses).

DIF; Granular IgA deposits in normal-appearing skin are diagnostic for dermatitis herpetiformis.

Most, if not all, DH patients have an associated gluten-sensitive enteropathy.

Course; The condition typically lasts for decades unless patients avoid gluten entirely.
Differential diagnosis: scabies, an excoriated eczema, insect bites or neurodermatitis.

RX; The rash responds rapidly to dapsone therapy gluten-free diet works very slowly. Combine the two at the start and slowly reduce the dapsone

CHRONIC BULLOUS DIS. OF CHILDHOOD (linear IgA dis.)
Chronic blistering dis. which occur in children, usually starts before the age of 5yrs
Small and large blisters appears predominantly on the lower trunk, genital area, and thighs
May also affects the scalp and around the mouth
New blisters form around healing old blisters forming a CLUSTER OF JEWELS
Course is chronic and spontaneous remission usually occurs after an average of 3-4 yrs

IgA autoantibodies binds to the BM proteins such as ladinin and laminin in linear form

CLINICAL FEATURES
• Circular clusters of large blisters like the type seen in pemphigoid
• It involves the perioral area, lower trunk, inner thighs and genitalia
• Blistering may spread all over the body

INVESTIGATION
1. Skin Biopsy will show subepidermal splits
2. Direct IF reveals IgA along the BM of the epidermis in a linear pattern
TREATMENTS

1. Oral dapsone 50-200mg daily
2. Sulphonamides and immunosuppressants
3. Erythromycin

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<th>Histopathology</th>
<th>Immunopathology/Skin</th>
<th>Serum</th>
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<tr>
<td>PV</td>
<td>Suprabasal acantholysis</td>
<td>IgG intercellular pattern</td>
<td>IgG AB to intercellular substance of epidermis (IF) ELSA: AB to desmoglein 3/3 desmoglein 1/1 only</td>
</tr>
<tr>
<td>PF</td>
<td>Acantholysis in granular layer</td>
<td>IgG, intracellular pattern</td>
<td>IgG AB to intercellular substance of epidermis (IF) ELSA: AB to desmoglein 1 only</td>
</tr>
<tr>
<td>PVeg</td>
<td>Acantholysis in intraepidermal neutrophilic abscesses, epidermal hyperplasia</td>
<td>As in PV</td>
<td>As in PV</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Subepidermal blister</td>
<td>IgG and C3 linear at BMZ</td>
<td>IgG AB to BMZ (IF); directed to BPAG1 and BPAG2</td>
</tr>
<tr>
<td>EBA</td>
<td>Subepidermal blister</td>
<td>Linear IgG at BMZ</td>
<td>IgG AB to BMZ (IF) directed to type VII collagen (ELISA, Western blot)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Papillary microabscesses, subepidermal vesicle</td>
<td>Granular IgA in tips of papillae</td>
<td>Antinuclear antibodies</td>
</tr>
<tr>
<td>Linear IgA dermatosis</td>
<td>Subepidermal blister with neutrophils</td>
<td>Linear IgA at BMZ</td>
<td>Low titers of IgA AB against BMZ</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Disease</th>
<th>Skin Lesions</th>
<th>Mucous Membranes</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>Flaccid bullae on normal skin, erosions</td>
<td>Almost always involved, erosions</td>
<td>Anywhere, localized or generalized</td>
</tr>
<tr>
<td>PF</td>
<td>Crusted erosions, occasionally illiacal vesicles</td>
<td>Rarely involved</td>
<td>Exposed, seborrheic regions or generalized</td>
</tr>
<tr>
<td>PVeg</td>
<td>Granulating plaques, occasionally vesicles at margin</td>
<td>As in PV</td>
<td>Intriginous regions, scalp</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Tense bullae on normal and erythematous skin; urticarial plaques and papules</td>
<td>Mouth involved in 10-35%</td>
<td>Anywhere, localized or generalized</td>
</tr>
<tr>
<td>EBA</td>
<td>Tense bullae and erosions, noninflammatory or BP, DH- or LAD-like presentation</td>
<td>May be severely involved (oral esophagus, vagina)</td>
<td>Traumatized regions or random</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Grouped papules, vesicles, urticarial plaques, crusted</td>
<td>None</td>
<td>Prolific sites: elbows, knees, gluteal, sacral, and scapular areas</td>
</tr>
<tr>
<td>Linear IgA dermatosis</td>
<td>Annular, grouped papules, vesicles, and bullae</td>
<td>Oral erosions and ulcers, conjunctival erosions and scarring</td>
<td>Anywhere</td>
</tr>
</tbody>
</table>