Bullous Skin Disorders (BSD)

Assist prof. Dr. Ali elethawi
Specialist dermatologist
C.A.B.D ,F.I.C.M.S
INTRODUCTION

- BSD 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.
Location of bullae

Subcorneal bulla
- Bullous impetigo
- Miliaria crystallina
- Staphylococcal scalded skin syndrome

Intra-epidermal bulla
- Acute eczema
- Viral vesicles
- Pemphigus
- Miliaria rubra
- Incontinentia pigmenti

Subepidermal bulla
- Bullous pemphigoid
- Cicatricial pemphigoid
- Pemphigoid gestationis
- Dermatitis herpetiformis
- Linear IgA disease
- Bullous erythema multiforme
- Bullous lichen planus
- Bullous lupus erythematosus
- Porphyria cutanea tarda
- Toxic epidermal necrolysis
- Cold or thermal injury
- Epidermolysis bullosa
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 basement membrane zone (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 malformation and is a common site of blister formation.
Structure of the epidermis and sites of target antigens/cleavage in bullous diseases

- **Epidermis**
  - Suprabasal cells
  - Desmosomes
  - Basal cells

- **Basement membrane**
  - Hemidesmosomes
  - Lamina lucida
  - Lamina densa
  - Collagen type IV
  - Collagen type VII
  - Sublamina densa

- **Dermis**
  - Bullous pemphigoid antigen
  - Level of split in dermatitis herpetiformis

- Pemphigus antigens
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
     - 4. Pemphigoid Gestations
     - 2. Linear IgA disease
     - 5. Epidermolysis Bullosa Acquisita
     - 3. Dermatitis Herpetiforms
IMMUNOLOGIC BULLOUS SKIN Dis.

These includes:

- Pemphigus
- Pemphigoid
- Dermatitis Herpetiformis (DH)
- 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 includes:
  - *P. vulgaris*, *vegetans*, *foliaceus*, *erythematousus*, 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 or Indian origin

• 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 (3 in PV & 1 in PF).

• Both are adhesion molecules found in the desmosomes

• The Ag-Ab reaction interferes with adhesion, causing the keratinocytes to fall apart (acantholysis)
PV: is characterized by **flaccid blisters** of the skin and mouth.

- The blisters rupture easily to leave widespread painful erosions.
- **Most** patients develop the mouth lesions first.
- **Mouth ulcers** that persists for **months** before **skin lesions** appears on the trunk, flexures and scalp.
- Shearing stress on normal skin (sliding pressure) can cause **new erosion** to form (+ve Nikolsky sign).
Mouth ulcers in PV { appear 1st in most cases }
Nikolsky Sign: Dislodging of epidermis by lateral finger pressure in the vicinity of lesions, which leads to an erosion. Shearing stresses on normal skin can cause new erosions to form.
Diagnosis

- Clinical evaluation
- Histopathologic by Light microscopy
- **Immunofluorescent examination.** is a laboratory technique for demonstrating the presence of tissue bound and circulating antibodies

- Electron microscopic examination ;(EM)  NOT routinely done
Pemphigus Vulgaris:
Dermatopathology by Light microscopy;
**skin Biopsy** from the edge of a blister

Biopsy shows that the vesicles are intra-epidermal, with rounded keratinocytes floating freely within the blister cavity (acantholysis).
Binding of Abs to the adhesion molecules → loss of cell-cell adhesion → acantholysis
Pemphigus Vulgaris; Immunofluorescence

- **A) DIF: (skin)** Note deposition of IgG around epidermal cells.
- **B) IDIF: (serum)** using monkey esophagus:
  Note binding of IgG antibodies to the epithelial cell surface.
DDx

- Other types of pemphigus
- Bullous pemphigoid
- Dermatitis herpetiformis (DH)
- Bullous impetigo
- EB or Ecthyma
- Familial benign pemphigus (Hailey-Hailey disease)

**Mouth ulcers:**

- Aphthae
- Behcet’s dis.
- Herpes simplex infection
- Bullous lichen planus
TREATMENT

Systemic steroid;
2 to 3 mg/kg of prednisolone until cessation of new blister formation and disappearance of Nikolsky sign.

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

High-dose intravenous immunoglobulin (HIVIg);
(2 g/kg every 3–4 weeks) may help gain quick control whilst waiting for other drugs to work.

Rituximab (Anti-CD20 monoclonal antibody) has been reported to help multidrug resistance, IV, once a week for 4 weeks.

Rx is usually prolong and need regular follow up
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;

> e.g: Non-Hodgkin’s lymphoma and Chronic lymphocytic leukemia
Drug-induced PV

Drugs can induce PV

Drugs reported most significantly in association with PV are;

Penicillamine
captopril
Pemphigus vegetans in the axilla, some intact blisters can be seen
Pemphigus Vegetans
Pemphigus Vegetans
BULLOUS PEMPHIGOID

- an autoimmune blistering disorder
- Antibodies binds to normal skin at the BMZ
- It is more common than pemphigus
- Mainly affect the elderly
- Mucosal involvement is rare
PATHOGENESIS

• There is linear deposition of Igs & complements against proteins at the dermo-epidermal junction
• The IgG antibodies bind to two main antigens, 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
BULLOUS PEMPHIGOID
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

• **Skin biopsy** shows a **deeper blister** (than in pemphigus) owing to a subepidermal split through the BM

• **On direct IF**, perilesional skin shows **linear band of IgG and C3 along BMZ**

• **Indirect IF** shows IgG antibodies that reacts with the BMZ in most patients

• **Hematology Eosinophilia** (not always)
DDx

• Epidermolysis bullosa
• Bullous lupus erythematosus
• Dermatitis herpetiformis
• Bullous erythema multiforme
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**
- Acute and non **itchy**
- Seen on the trunk, flexures and scalp
- Mouth Blister is common
- Nature of blister is superficial and flaccid
- Circulating Ab is IgG to intracellular adhesion proteins
- **Serum Ab Titer** correlate with clinical disease activity.
- **Acantholysis**
- **Nikolsky sign is positive**

### Pemphigoid
- Elderly patients
- Chronic and **itchy**
- Usually **flexural**
- Mouth Blister 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**
Dermatitis Herpetiformis (DH)

- Intensely itchy, chronic **papulovesicular** eruption distributed symmetrically on **extensor surfaces**.
- It may start at **any age**, including **childhood**; however, the 2\(^{nd}\), 3\(^{rd}\), and 4\(^{th}\) decades are the most common.
- **Skin biopsy**; If a vesicle can be biopsied before it is scratched away, the histology will be that of a **subepidermal blister**, with **dermal papillary collections of neutrophils** (microabscesses).
- **DIF**; **Granular IgA** deposits in normal-appearing skin are **diagnostic** for DH.
- 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 Disease OF CHILDHOOD

- 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
Skin Biopsy will show subepidermal splits

Direct IF reveals IgA along the BM of the epidermis in a linear pattern
TREATMENTS

• Oral dapsone 50-200mg daily
• Sulphonamides and immunosuppressants
• Erythromycin
<table>
<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 flaccid 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>Intertriginous 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>Predilection 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>
<tr>
<td>Disease</td>
<td>Histopathology</td>
<td>Immunopathology/Skin</td>
<td>Serum</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>PV</td>
<td>Suprabasal acantholysis</td>
<td>IgG intercellular pattern</td>
<td>IgG AB to intercellular substance of epidermis (IIF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ELISA: AB to desmoglein 3 &gt;&gt; desmoglein 1</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 (IIF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ELISA: AB to desmoglein 1 only</td>
</tr>
<tr>
<td>P Veg</td>
<td>Acantholysis ± 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 (IIF); 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 (IIF) 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>Antiendomysial 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>
</table>