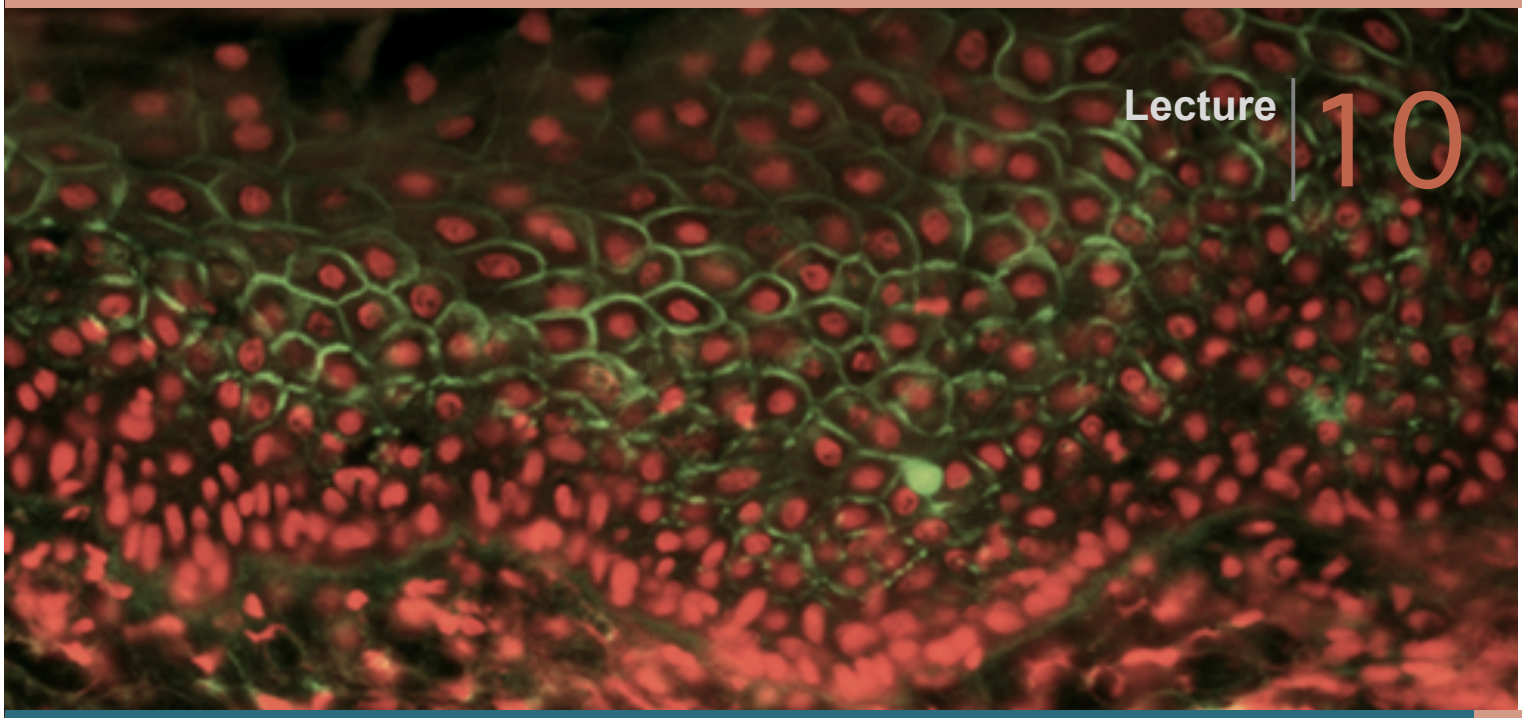


Bullous Diseases

429 Dermatology Team (F)

Sources: 1. Dr. Mona Halawani's lecture (she said it's enough for the exam)
2. Additional information from Dr. Marwan Khawaja's lecture (males' team notes)
3. Students' notes were added (notes are in *italic*)
4. Fitzpatrick Color Atlas and Synopsis of Clinical Dermatology

* Histopathology pictures were not included

By: Roa Alsajjan, special thanks to: AlBatool AlAmmari

BULLOUS DISEASES

1 INTRODUCTION

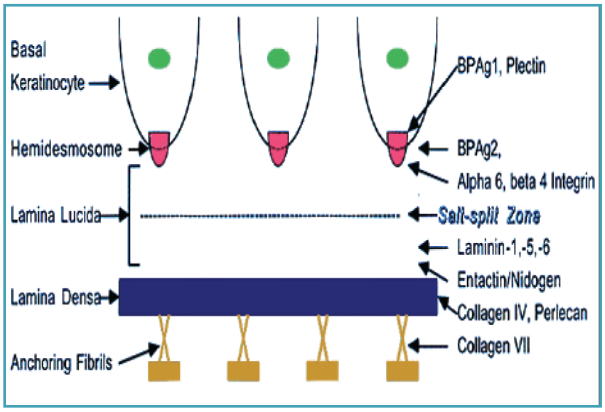
1.1 DEFINITIONS

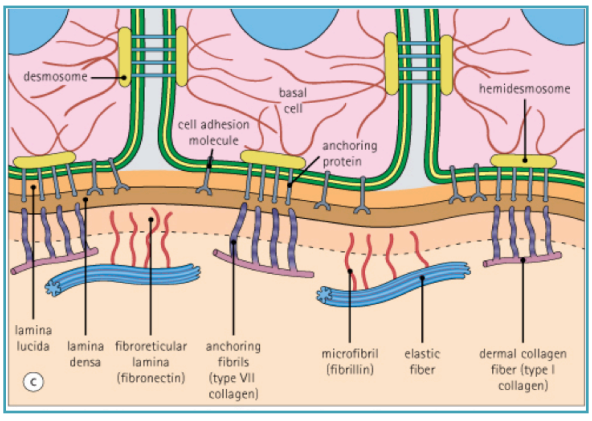
- Blister: collection of clear fluid.
- Bulla: blister >5mm diameter
- Vesicle: blister <5mm diameter
- Crust: dried exudate on skin
- Bullous skin diseases are skin conditions characterized by blister formation. Causes: congenital, acquired (infection, trauma, autoimmune) or idiopathic.

1.2 HISTOLOGY

1. Plasma membrane consisting of:
    a. Basal keratinocyte
    b. Hemi-desmosome
2. Lamina lucida
3. Lamina densa: type IV collagen
4. Anchoring fibrils: type VII collagen

- NB: Lamina densa and anchoring fibrils work as holders of the skin à if defected the blisters will be formed as the Lamina Lucida will be filled with fluid





1.3 PATHOPHYSIOLOGY

- The keratinocytes of the epidermis are tightly bound together by desmosomes.
- Beneath the epidermis lies the basement membrane zone (BMZ), which is a specialized area of cell-extracellular matrix adhesion.
- Specialized structures traversing this zone anchor the epidermis to the dermis.
- These structures (matrix) comprise polysaccharides and proteins (including collagens) linked to form macromolecules (adhesion complex).
- If any of these specialized attachments are malformed, absent or damaged, separation may occur leading to accumulation of fluid in the extracellular space and blister formation.
- The BMZ is particularly vulnerable to damage or malfunction and is a common site of blister formation.

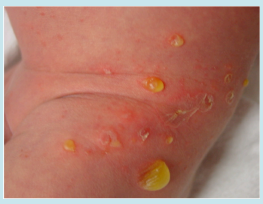
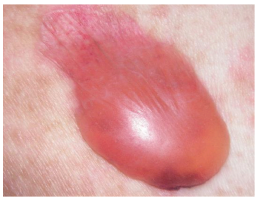
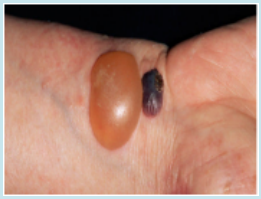
1.4 DIAGNOSIS

Box 1

- Which skin findings are helpful in evaluating a patient with blister?
    1. **Distribution**: generalized skin and oral cavity
    2. **Symmetry**
    3. **Associated** lesions
    4. **Additional** types of skin lesions e.g. urticaria
    5. **Characteristic** of blisters
    6. **Nikolsky vs Asboe-Hansen sign:**
        - Nikolsky sign: shearing stress on normal skin (sliding pressure) can cause new erosion to form
        - Asboe-Hansen sign: direct pressure on intact bulla leading to bulla-spread phenomenon
- Which tests are most useful in evaluating vesiculobullous disease?
    1. **Cultures** (bacteria, viruses, fungi)
    2. **Smears** from blisters (bacteria, dermatophytes, multinucleate giant cells of H.S)
    3. Skin **biopsy** – non infectious cause
- When are special tests necessary to diagnose blistering diseases of the skin?
    1. **Biopsy**
        - Routine histology: shows inflammatory infiltrate, and level of blister formation
        - Direct immunofluorescence (**DIF**): shows tissue-bound antibodies
    2. Indirect immunofluorescence (**IIF**): to detect circulating antibodies in the blood
    3. EM – EB.
    4. Urine porphyrin- PCT
    5. Zinc levels - ADE

1.5 PATHOMECHANISMS

- Epidermal edema (spongiosis: causing separation of keratinocytes) e.g. dermatitis
- Epidermal necrosis e.g. erythema multiforme
- Damage to intercellular connections e.g. pemphigus
- Basal Cell degeneration e.g. Lupus erythematosus
- Damage to basal cell membrane e.g. pemphigoid
- Dermal damage e.g. dermatitis herpetiformis

Type of Blister		Characteristics	Differential Diagnosis
	**Subcorneal**	Very thin roof; breaks easily	Impetigo, miliaria, staphylococcal scalded skin syndrome
	**Intraepidermal**	Thin roof ruptures to leave denuded area	Acute eczema, varicella, herpes simplex, pemphigus
	**Subepidermal**	Tense roof. Often remains intact.	Bullous pemphigoid, dermatitis herpetiformis, erythema multiforme, TEN, friction blisters

2 PEMPHIGUS

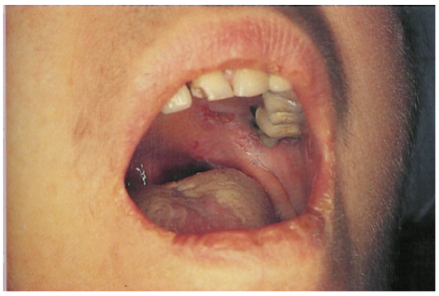
- A group of autoimmune blistering diseases of **skin and mucous membranes** ✪
- Characterized by **intra-epidermal** blisters due to **acantholysis** (loss of intracellular connections between keratinocytes resulting in their separation from each other), with bound and circulating **IgG** directed against the cell surface of keratinocytes.
- *Diagnosis by DIF. General Rx rule: do not de-roof blisters; drying agent & antibiotics + cover.*
- **Classification**:
    - Pemphigus vulgaris (the most common)
    - Pemphigus vegetans
    - Pemphigus foliaceus & pemphigus erythematosus
    - Para-neoplastic pemphigus
    - Drug-induced e.g. TEN

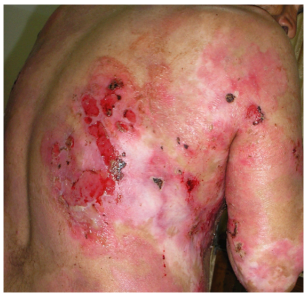
2.1 PEMPHIGUS VULGARIS

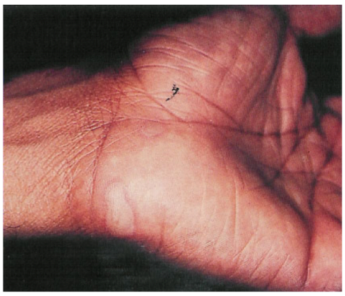
- **Epidemiology:** rare, middle age groups (40-60 years)
- **Clinical manifestations:**
    - Usually begins with **painful mouth erosions**
    - Fragile, flaccid blisters break and expand to form large erosions
    - **Positive** Nikolsky +ve
    - **FATAL** in all cases if not treated.
- Investigations:
    - Biopsy shows that vesicles are intra-epidermal with rounded keratinocytes floating freely within the blister cavity (acantholysis)
    - Direct IF of adjacent normal skin shows intercellular epidermal deposits of **IgG** and **C3**
    - Indirect IF: antibodies that bind to the desmogleins in the desmosomes of normal epidermis are found in patient's serum (**titre correlates with disease activity**)
- Treatment:
    - Supportive care
    - Systemic **corticosteroids** high dose (1st choice; to control disease process)
    - Adjuvant immunosuppressive therapy (added for lifelong maintenance)
        - **Mycophenolate mofetil** (CellCept), **azathioprine** (Imuran), **cyclophosphamide** (Cytoxan), **cyclosporine**, **gold**, **antimalarials**, or **dapsone**
    - Biological: monoclonal anti-CD20 antibody (**rituximab** "Rituxan")
    - Plasmapheresis/IVIG
    - Extracorporeal photochemotherapy

2.2 OTHER TYPES

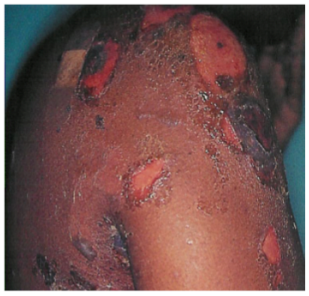
1. Pemphigus vegetans (a form of vulgaris): crusted **papillomatous** (vegetating) lesions on **scalp** and intertriginous areas (**axilla** and **groin**)
2. Pemphigus foliaceus: scaly crusted well-demarcated lesions on **face** and **upper trunk**
    a. Pemphigus erythematosus: the **most localized** form of pemphigus foliaceus (**face**)
3. Drug induced pemphigus: penicillamine, captopril, rifampin
4. Paraneoplastic pemphigus ⋆
    a. Clinical & histological features of Stevens-Johnson syndrome and pemphigus vulgaris
    b. Associated with: **Non-Hodgkin's Lymphoma**

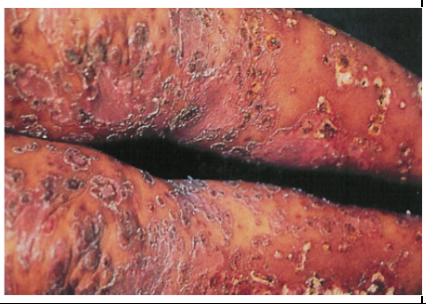


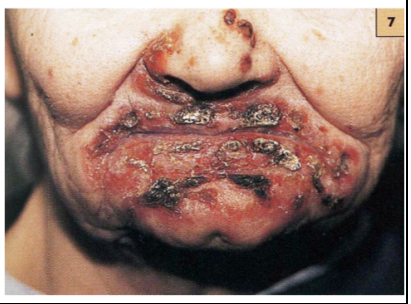


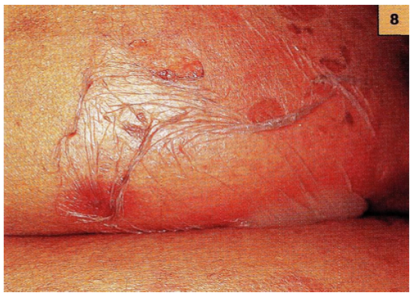


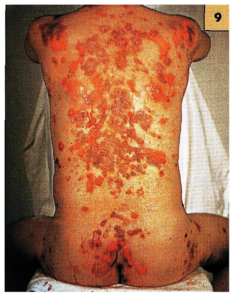
Confluent erosions that are bleeding

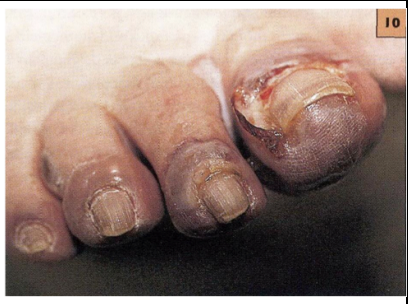






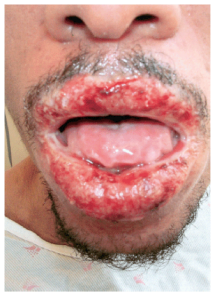


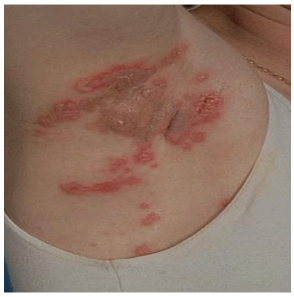


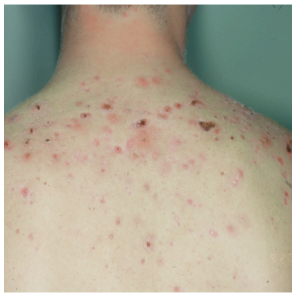


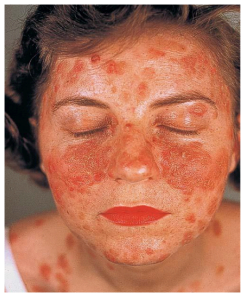
Detaching epidermis with erosions

Widespread confluent flaccid blisters w/erosions









Other types of pemphigus: vegetans, foliaceus and erythematosus

3 PEMPHIGOID

- A group of autoimmune sub-epidermal blistering diseases with circulating **IgG** and BMZ bound **IgG** and **C3**
- **Types**:
  - Bullous pemphigoid
  - Herpes gestationis
  - Cicatricial pemphigoid (affects the mucus membrane and causes scarring)
- *General Rx rule: do not de-roof blisters; drying agent & antibiotics + cover*

3.1 BULLOUS PEMPHIGOID

- **Epidemiology**: elderly males & females
- **Clinical & lab manifestations:**
  - Sub-epidermal bullae often predated by **itchy urticated** areas on limb girdles
  - Tense, large bullae on erythematous plaques or normal appearing skin lasting several days + **pruritus**
  - Site: lower abdomen, groin, flexors of arms & legs
  - **Negative** Nikolsky's sign
  - Mucosal lesions unusual, patients well
  - **Skin biopsy** shows a deeper blister (than in pemphigus) owing to a **sub-epidermal** split through the BM
  - **Direct IF**: skin shows linear bands of **IgG** and **C3** at dermo-epidermal junction
  - **Indirect IF**: shows IgG antibodies against basement membrane in most patients. It does not correlate with the severity of the disease (≠ pemphigus)
  - **CBC**: eosinophilia (in 50%), serology: high IgE (in 70%)
- **Course & prognosis:** Good; relatively benign (≠ pemphigus); variable course, spontaneous remission possible
- **Treatment**:
  - Topical (if localized) or systemic **steroid** (if severe)
  - **Antibiotics:** tetracycline, minocin
  - **Dapsone**
  - Immunosuppressive: azathioprine, mycophenolate mofetil

3.2 CICATRICAL PEMPHIGOID

Not mentioned in Dr. Halawani's lecture

- Clinical & lab manifestations:
  - Tense blisters & erosions of **mucous membranes**; oral cavity, eyes, nose, pharynx
  - Skin occasionally involved – 25% (serious condition)
  - Pronounced tendency to scarring and stricture formation
  - Histology: sub-epidermal blister
  - DIF: **IgG**, **IgA**, **C3** in basement membrane zone
- **Complications**:
  - Pharyngeal, laryngeal, esophageal strictures
  - Ocular involvement ➔ blindness ⋆
- **Treatment**
  - Steroids (topical, intralesional, systemic)
  - For ocular disease: **dapsone** (1st choice)
  - Immunosuppressives: **cyclophosphamide**, **azathioprine,** IVIG
  - Surgical therapy (*for strictures*)

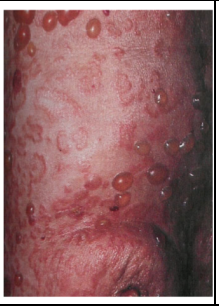
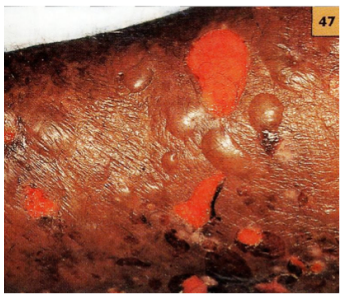
3.3 PEMPHIGOID (HERPES) GESTATIONIS

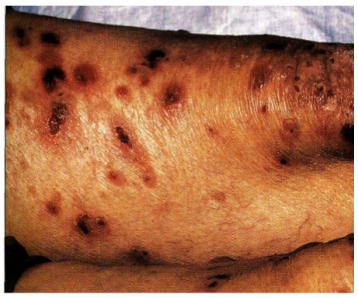
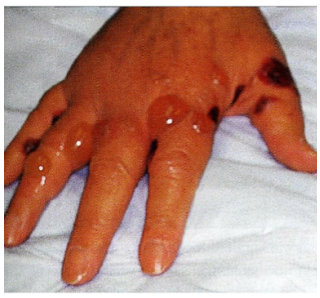
- 2nd & 3rd trimesters (every pregnancy), flares at post partum, and w/OC
- Erythematous **urticarial plaques/*targetoid lesion*** ± papules, vesicles, bullous, erosions
- Mostly on abdomen and proximal extremities
- Intense **pruritus**
- Histology: Sub-epidermal blister
- DIF: **C3 more than IgG** at BMZ. **IFF**: human gastonal factor in patient's serum
- ***Complications****: premature birth*
- **Treatment**: steroids (topical or systemic) *& antihistamines; can't be given during 1st trimester*

4 DERMATITIS HERPETIFORMIS

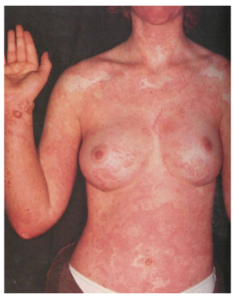
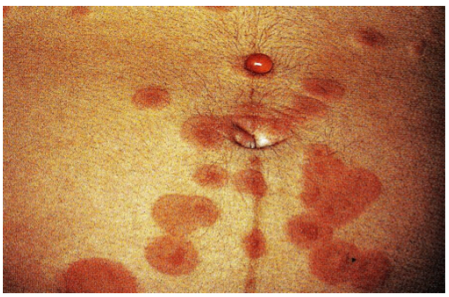
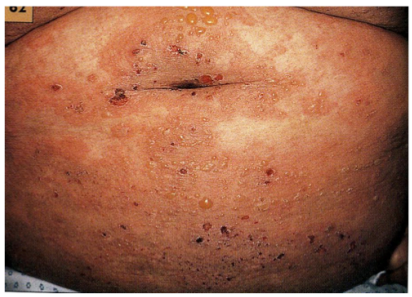
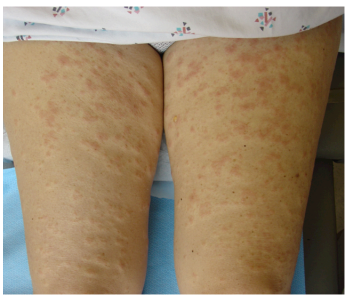
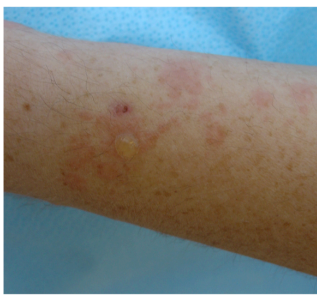
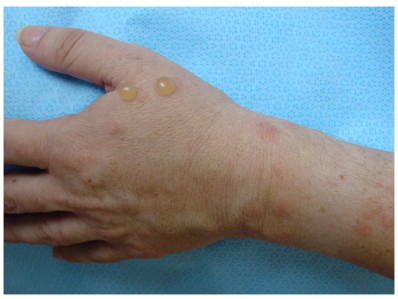
- Age: any ages late 2nd Early 4th decades
- Rare
- **Clinical & lab manifestations:**
  - Small grouped papules, vesicles, blisters, and **<u>erosions</u>** on erythematous plaques
    - *Presents with erosions more than blisters*
  - Intense **pruritus**
  - **Extensors** of large joints (knees, elbows, buttock, neck shoulders, frontal hairline, scalp)
  - Histology: papillary microabscesses; neutrophilic infiltrate, sub-epidermal split
  - DIF: **IgA** (granular, at BMZ, pronounced in **dermal papillae)**
  - Iodides may induce flares
- Associated with: Gluten sensitive enteropathy +/- clinical features of celiac disease
- **Treatment**:
  - Dietary measures: gluten free diet
  - **Dapsone** (1st line)
  - Sulfapyridine
  - Tetracycline and nicotinamide

Bullous pemphigoid: Bullae: large, tense, firm-topped, oval or round; may arise in normal, erythematous, or urticarial skin and contain serous or hemorrhagic fluid. Can erode and form crusts.

Pemphigoid Gestationis: Urticarial plaques and small vescicles and blisters

Dermatitis Herpetiformis: erythematous papules or wheal-like plaques; tiny firm-topped grouped vesicles, sometimes hemorrhagic. Excoriations and crusts due to scratching. Post-inflammatory hyper or hypopigmentation.