Dermatology Team 441

MED441
KING SAUD UNIVERSITY

BH
Bassam Alhubaysh
REVIEWED BY

Blistering disorders

Objectives:

- To know the definition & classification of Blistering diseases
- To recognize the primary presentation of different types of main blistering diseases
- To understand the possible pathogenesis of the main types of blistering diseases
- To have an overview about managements lines of these diseases

Note: Extra text doesn't necessarily mean it's not important

Color index:

- Main text
- Important
- Dr's explanation
- Golden notes
- Extra

DERMATOLOGY TEAM 438

This lecture was originally done by both 438 & 439 teams.
So great thanks to them

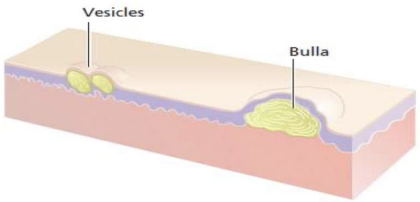
Blistering Diseases

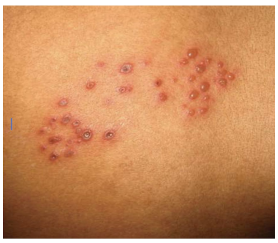
CONTENT OF THIS LECTURE:

- PEMPHIGUS VULGARIS
- BULLOUS PEMPHIGOID)
- CHRONIC BULLOUS DISEASE OF CHILDHOOD
- PARANEOPLASTIC PEMPHIGUS (Present with Cancer)

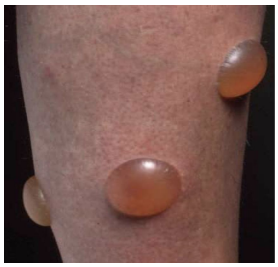
Definition:

- Vesicles and bullae are raised lesions that contain fluid.
- A **vesicle** is **less than 0.5** cm in diameter.
- A **bulla** is l**arger than 0.5** cm in diameter.



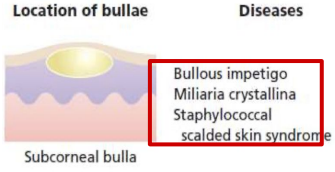
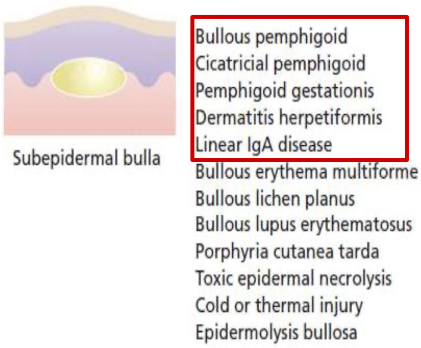


Multiple grouped vesicles on erythematous base (Vesicle is <5mm)



Multiple Bullae (> 5mm)

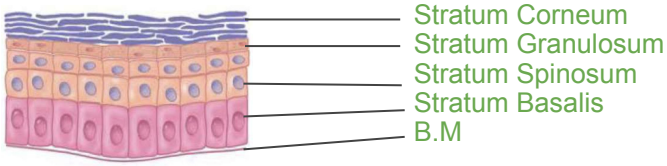
CLASSIFICATION OF VESICULOBULLOUS DISEASES:

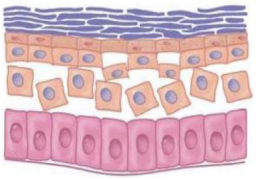
Subcorneal blister:	Intra-epidermal blister:	Subepidermal blister blister:
- Just beneath the stratum corneum. Very superficial. - Have the thinner roofs - Ruptured easily & leave an oozing denuded surface. - Not caused by autoimmune diseases. - Pathogen in subcorneal are prone to rupture so, often the presentation is Erosions not Bullae or vesicle, as is the case with Pemphigus Vulgaris in the intraepidermal Blister Group. • Bullous impetigo: Staph-Strep infection. • Miliaria crystallina: sweat duct obstruction causes prickly heat rash. • SSSS: present with peeling of the skin. SSSS: Staphylococcal scalded skin syndrome  	- within the prickle cell layer on the epidermis - Have thin roofs - Ruptured easily & leave an oozing denuded surface - Viral vesicles like: HSV, Chicken Pox virus.  	- Between the dermis and epidermis - Their roofs are relatively thick - Tend to be tense - May contain blood - Below the B.M of the epidermis, so it will present with tense bullae. 

Blistering Diseases

Dr. Note:

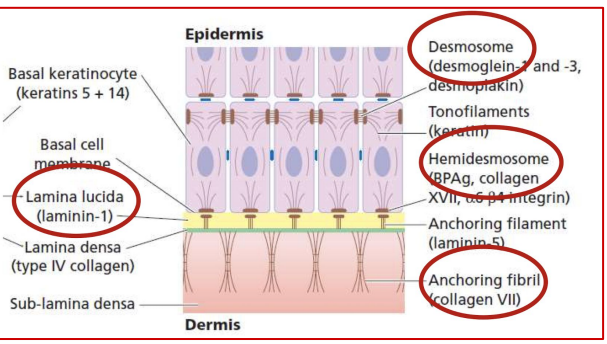
- In these autoimmune diseases, the Autoantibodies attack specific Ag in the Skin cells, the cells (layer) that are attacked, will lose the attachment and cohesion with other cells and among itself. The Cells will end up more rounded and floated.
- This process is called **Acantholysis** (totally detached) → vesicle, these cells are called acantholytic cells.

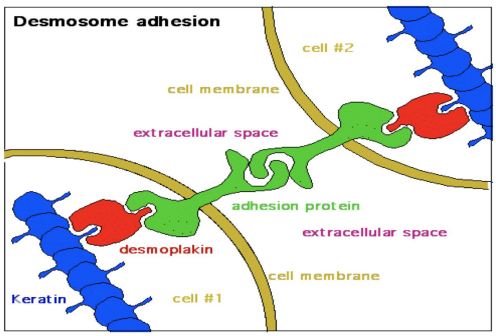




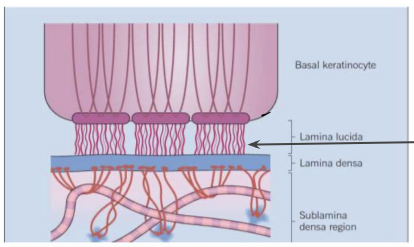
Dermo-epidermal junction: IMPORTANT

- **Desmosome**: Between the spinous layer of the epidermis, attach cells together in multiple direction, composed of **Desmoglein-1 and -3, & Desmoplakin.**
- **Hemidesmosome**: Attach cells in one direction to the B.M, (connects the epidermis to the dermis). Composed of: **BPAg** & **α6 β4 integrin** & collagen XVII.
- Lamina densa: The B.M itself.
- Anchoring fibrils: Attach the B.M to the dermis. Composed of collagen VII.
- All these structure can be affected, either genetically absent or attacked by Ab in Autoimmune.
- **Pemphigus group:** the antibodies will target **Desmoglein-1** and/or **Desmoglein -3** → level of separation is high, separation is between the basal keratinocytes themselves **(intra-epidermal)** resulting in "**flaccid** blisters" = easily ruptured.
- **Pemphigoid group:** the antibodies will target **BPAg 1 and BPAg 2** → level of separation is under the basal keratinocytes **(subepidermal)** resulting in "**tense** blisters" = hardly ruptured.
- Congenital Vesicular Blistering disease: as in the case when collagen VII absent "epidermolysis bullosa dystrophica" which is characterized by extremely fragile skin (mechanical fragility), B.m and epidermis is in surface of the blister.

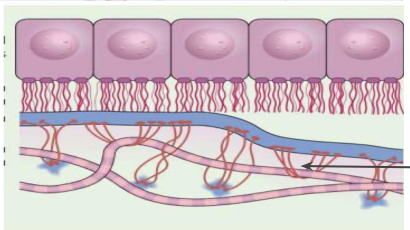




Here the adhesion molecule is desmoglein-1, -3 it is affected in Pemphigus Vulgaris



Hemidesmosome

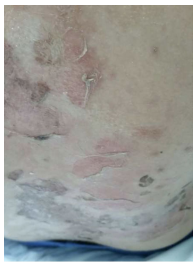
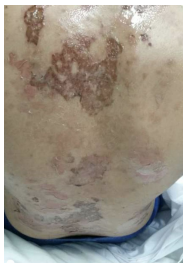


Anchoring fibrils

- Hemidesmosome: work as a strong attachment for cells, without the skin would develop blister. In Bullous pemphigoid the effect is on hemidesmosome.
- This is important clinically because we do biopsy and we check the result: if it's Bullous pemphigoid then we will not see the b.m in the surface of the bullous. But in Epidermolysis bullosa acquisita, you will see the b.m in the surface and the dermis in the floor.

Blistering Diseases

Multiple erosions with erythematous base on the back.

Since the skin is thin, then the pathology is intraepidermal (in the intra-spinosum layer). so, this is most likely is desmosome pathology. In **Pemphigus vulgaris** (you will see deeper erosion because all the epidermis is gone, unlike the bullous pemphigoid).

Blistering Disorders

- In Adults: the main group of blistering disorders is associated with autoantibody formation.
- In Children: the main cause of blistering disorders is Genodermatosis (epidermolysis bullosa):
  - Epidermolysis Bullosa is a group of mechanobullous genodermatosis. Rare, present at birth or infancy. Range from localized relatively mild trauma induced blisters to life threatening/debilitating conditions
  - Diagnosis is made based on family history, clinical examination, light and electron microscopy

Diagnostic test:

Accurate pathological diagnosis requires 2 biopsies (1 histopathology + 1 IF) of a small newly formed lesion and perilesional skin for immunopathological studies.

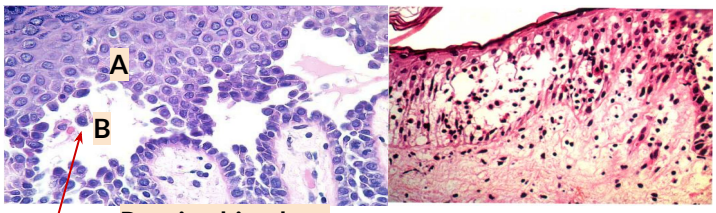
The first biopsy on the lesion to know the level of separation, while the second biopsy on the intact skin to do direct immunofluorescence.

Routine histology:

Lesional sample
(small bulla or edge of large one)

A;; The desmosomes present in the small spaces between cells

B: cell without cytoplasm, the desmosomes connect cells together will lead to stretching of cells, which is lost here



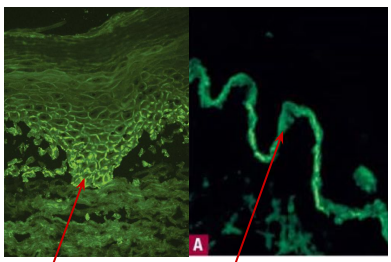
Routine histology

Acantholysis(small cytoplasm & large nucleus)

Direct immunofluorescence:

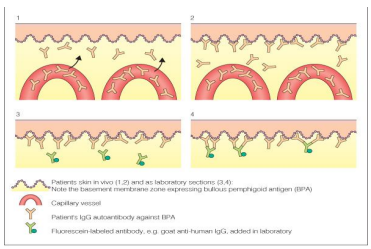
- Perilesional sample (away from inflammation).
- IgG and C3: in Pemphigus vulgaris and Bullous pemphigoid.
- IgA: in linear igA bullous Diseases.

You have to know where the cleavage is in the IF to know your DDx.



Spinosum

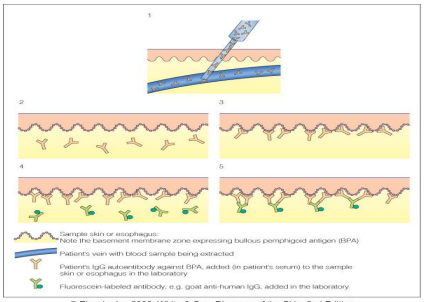
Basement membrane



Indirect immunofluorescence:

Patient's serum is added to specific substrates that express antigen of interest

mostly used in research, we don't do it usually



Electron microscopy:

Used for congenital diseases mainly

Gives you the specific place of pathology due to it's ultra structural features

Used in Genodermatosis because it's not an autoimmune disease

Blistering Diseases

Autoimmune bullous disease (438)

Loss of intraepidermal adhesion (pemphigus group)	Loss of subepidermal adhesion
I. Pemphigus vulgaris (PV): • Classic • Pemphigus vegetans	I. Pemphigoid: • Bullous pemphigoid • Cicatricial pemphigoid • Pemphigoid gestationis
II. Pemphigus foliaceus: • Classic • Fogo selvagum • Pemphigus erythematosus (Senear- Usher Syndrome)	II. Dermatitis herpatiformis
III. Drug induced pemphigus	III.linear IgA disease: • Of childhood • Adult form
IV. Paraneoplastic pemphigus	
V. IgA pemphigus	IV. Epidermolysis bullosa aquisita

Pemphigus group

Definition:

A group of disorders with loss of intraepidermal adhesion due to autoantibodies directed against proteins of the desmosomal complex that hold keratinocytes together

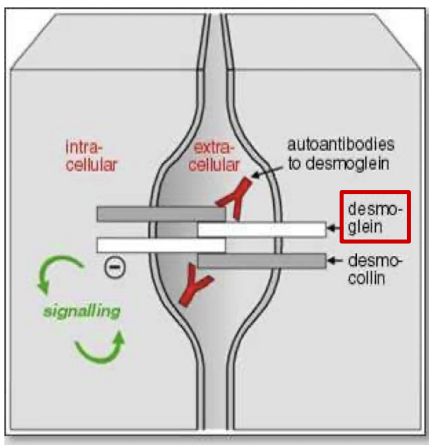
Pemphigus is a group characterized by blistering of the skin and mucous Membranes.

- **Auto-antibodies against DESMOSOMES in epidermis and mucosal surface.**
- Specifically Desmoglein -1, desmoglein -3. Dg-1 is usually superficial, while -3 is found in the cells of the mucous membrane and is Usually affected more hence, the prominent presentation of PV is oral erosion.

Four sub-clinical variants :

- Pemphigus Vulgaris: is the **most common** Pemphigus variant, and the form usually responsible for **oral lesions.** (Pt. Usually presents w/ dysphagia & painful oral lesions) (oral lesion seen in paraneoplastic syndrome too).

- Other types include: Folacious (superficial, affect Desmoglein -1 only, no mucous membrane involvement), vegetens (localized, no mucous membrane involvement), erythematosus (can be confused with lupus).



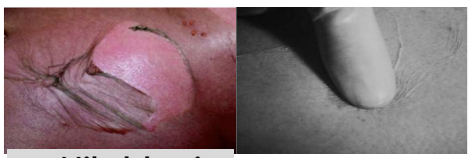
Blistering Diseases

Pemphigus group

Disease	Type of immunoglobulin	Against...
Pemphigus vulgaris (PV)	IgG	Mucosal type → desmoglein 3 Mucocutaneous type → desmoglein 3 & desmoglein 1 (PV almost always starts in the mucus membrane thus the first target is always desmoglein 3 ± desmoglein 1)
Pemphigus foliaceus (PF)	IgG	Desmoglein 1 ONLY (purely cutaneous)
paraneoplastic pemphigus	IgG	plakin molecules in addition to autoantibodies against desmogleins

1. Pemphigus Vulgaris:

- Severe, potentially fatal disease with intraepidermal blister formation of the skin and oral mucosa caused by IgG autoantibodies against "desmogleins"
- Begins with erosions on mucous membrane then other skin areas.
- **Very painful.**
- Not a self-limiting disease, it could be fetal within days
- +ve Nikolsky's sign: Twisting pressure on normal skin shears skin.
- Age: middle-age 40-60 years (in Bullous pemphigoid 65+).
- Secondary infection and disturbance of fluid and electrolyte balance are common complications.



+ve Nikolsky sign

Pathogenesis:

- Genetic predisposition: HLA-DRQ402- DQ0505
- IgG autoantibodies against desmoglein 3 (Dsg 3) and later desmoglein1(Dsg 1). The bound antibodies activate proteases that damage the desmosome, leading to acantholysis = floating cells.
- Serum antibody titer usually correlates with severity of disease and course

Clinical features:

Mucous membrane:

- lesions usually present as painful erosions

- Intact blisters are rare

- Sites: oral mucosa, vermillion lip, throat, esophagus, conjunctivae, nasal mucosa, vagina, penis, anus, labia

- Most common sites: buccal & palatine mucosa

- Vermillion lip -> thick fissured hemorrhagic crust

- throat ->hoarseness, difficulty swallowing

- 70%, anti-Dsg3 (Dsg 3 is the main desmoglein in mucosal surfaces)

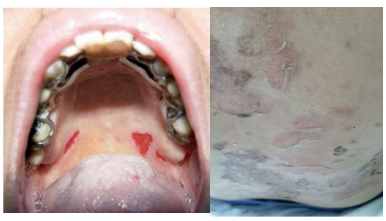
- Always check the scalp when confronted with unexplained oral erosions

1. Pemphigus Vulgaris (cont'):

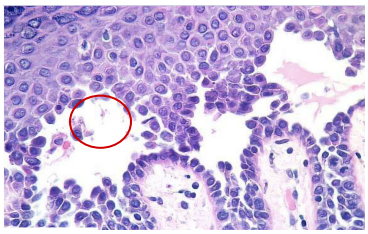
Skin

- Primary skin lesions of PV are flaccid,
- Thin-walled, easily ruptured blisters They could arise on either
- Normal-appearing skin or erythematous base
- The blisters are fragile and soon rupture to form painful erosions that ooze and
- Bleed easily, later forming crusts Can become generalized
- Lesions that heal often leave hyperpigmented patches with NO scarring
- More generalized disease due to the development of IgG autoantibodies against Dsg1 which is present in the skin along with Dsg3

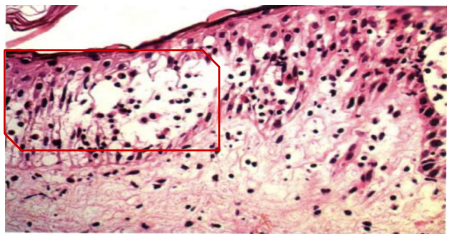
Findings:



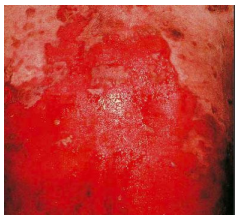
Erosion of the mucous membrane in the mouth → PV

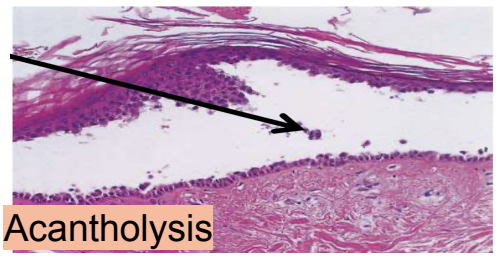


Keratocyte **acantholytic** cells, due to loss of desmosome.

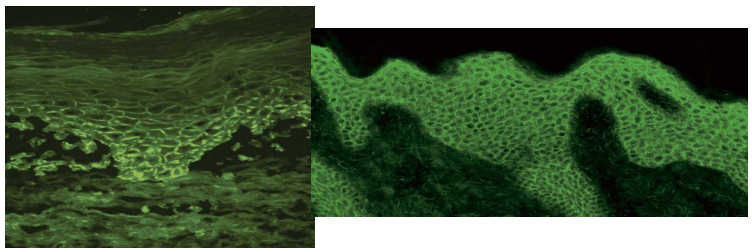


Interspinous layer with vesicle due to loss of dermosome.





Acantholysis pointed by the arrow, also notice how the B.M is not a part of the Bullae (below the blister). It's a Acantholysis without keratinocyte necrosis **(unlike Stevens-Johnson syndrome which has keratinocyte necrosis)**



IgG and **C3**: All are found in the interspinous area in the desmosome unlike the Bullos where discussed later.
The wide spread flaring of Abs response demonstrate the severity of PV which is more than Bullous Pemphigoid.
I.e. PV needs higher dose of steroids and often involves all the body, including: muscosa

Diagnostic approach:

History (always ask medication Hx)

Physical examination (skin, mucous membranes, nails)

- Nikolsky sign à because of an absence of cohesion within the epidermis, its upper layers easily move laterally with slight pressure or rubbing in active patients with pemphigus
- Asboe-Hansen signà " bulla- spread phenomenon" gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure

Investigation

- Skin biopsy: from lesional skin, intact vesicles if found
- DIF: from perilesional skin shows deposition of IgG (100%), C3 (80%)
- Indirect IF
- ELISA: to identify anti-Dsg3,1

Blistering Diseases

Differential Diagnosis;

When skin is involved:
- Bullous impetigo
- Dyskeratotic acantholytic disorders
- Hailey-Hailey
- Grover disease

When mucus membrane is involved:
- Denture intolerance
- Erosive candidiasis
- Chronic recurrent apothecary
- Erythema multiforme
- Erosive lichen planus
- Herpetic gingivitis

Treatment:

Nonbiological:

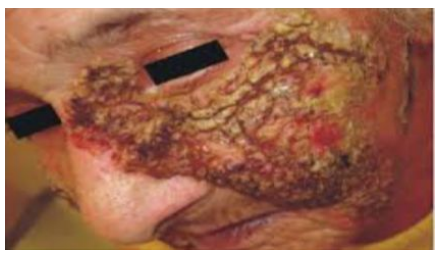
- High dose **systemic steroids 60-100 mg** of prednisolone.
- Immunosuppressive agent such as **azathioprine cyclophosphamide, Methotrexate or mycophenolate** -to decrease the uses of steroids-. (usually, Rituximab: for severe cases & mycophenolate: for mild cases.
- Patient will probably have to remain on systemic steroids for long time.
- Antibiotics; to treat superinfection only.

Biological Rx:

1. **Rituximab:** IV 86% free of disease after 3 yrs. it's an Anti-CD-20: against B-lymphocytes
2. **IVIG** (intravenous immunoglobulin).

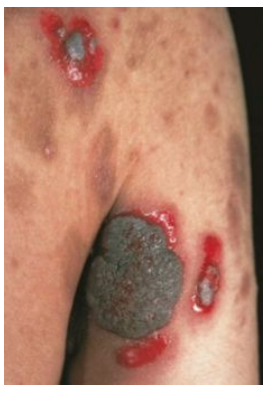
- If not treated leads to dramatic drop in QoL, like inability to speak and erosion all over the body (Poor prognosis if not treated).
- 1st line High dose steroid, then we give mycophenolate or azathioprine to decrease the steroid dose, steroid is lifelong sometimes.
- **Rituximab** is reserved for resistant cases but, **IF SEVERE**, RITUXIMAB should be given in conjunct with steroids usually gives long remission.
- **Rituximab** has 2 protocol, one for RA, and the other is Lymphoma dose (weekly) Almost always in PV we use the RA dose which is: 1000 mg twice with 2 wks apart.

2. Pemphigus vegetans:



Clinical features:

- It's a vegetative variant of pemphigus vulgaris.



- Characterized by flaccid blisters that become erosion and then form **fungoid vegetations**, especially in **intertriginous areas, the scalp and face**

- **Early lesions start as pustules (rather than vesicles)**, then they soon progress to vegetative plaques
- treatment same as pemphigus vulgaris

3. Pemphigus foliaceus:

- Is a form of pemphigus in which patients develop scaly, crusted cutaneous erosions often on an erythematous base
- Disease of middle-aged and older patients
- In this form of pemphigus they do not have mucosal involvement even with widespread disease u Lesions have a seborrheic distribution (face, scalp, and upper trunk).
- IgG autoantibodies against desmoglein 1
- More often drug induced than pemphigus vulgaris
- Patients with pemphigus foliaceus are not severely ill

Diagnostic approach:

History (always ask medication Hx)

Physical examination (skin, mucous membranes, nails)

- Nikolsky sign present

Investigation

- DIF: from perilesional skin shows superficial deposition of IgG
- ELISA: to identify IgG antibodies against Dsg 1

Treatment:

- Same as pemphigus vulgaris but usually more responsive to therapy
- Dapsone maybe helpful

4. Drug-induced PV

- Drugs can induce PV
- Drugs reported most significantly in association with PV are:
  - Penicillamine.
  - Captopril.
  - Anti-epiliptic: phenytoin and carbamazepine.

Drugs that induce pemphigus can be devided into 2 groups

Agents containing the sulfhydryl group:

- Penicillamine
- Captopril
- Piroxicam
- Penicillamine —> PF is seen more than PV, ratio 4:1
- Sulfhydryl group of these drugs interact with the sulfhydryl group of Dsg1 & Dsg 3 (acantholysis without antibody formation)

Agent without sulfhydryl group:

-Beta-blockers
- Cephalosporins
- Penicillins
- Rifampin
- Induce acantholysis via immune mechanism

Most patients with drug-induced pemphigus go into remission after the offending drug is discontinued

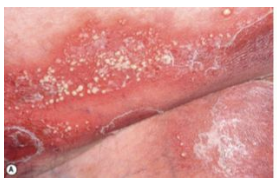
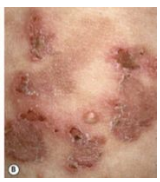
5. IgA pemphigus:

Represents a group of autoimmune intraepidermal blistering disease

Presenting with:
1- **Vesicopustular** eruption
2- **Neutrophilic** infiltration of the skin
3- Circulating **IgA** autoantibodies against the cell surface of keratinocytes, but with NO IgG autoantibodies

Two distinct types:
1- Subcorneal pustular dermatosis (SPD)
2- Intraepidermal neutrophilic type (IEN)

- Both types present with flaccid vesicles or pustules that coalesce to form an annular pattern with central crusting
- Sunflower-like configuration of pustules is a characteristic sign of the IEN type
- Most common site: axilla, groin, trunk
- NO mucous membrane involvement Pruritus is a significant symptom
- Pruritus is a significant symptom

Diagnostic approach:

History

Physical examination (skin, mucous membranes, nails)

Investigation
- DIF: **IgA** autoantibodies directed against keratinocyte cell surface (not desmoglein)

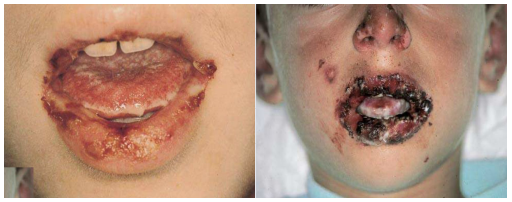
Treatment:
Most cases are responsive to dapsone, if not ,corticosteroids & other immunosuppressive agents

6. Paraneoplastic Pemphigus:

- The least common and most severe type of pemphigus is **paraneoplastic pemphigus** (PNP).
- This disorder **is a complication of** cancer usually **lymphoma,** non- Hodgkin lymphoma, Chronic lymphocytic leukemia and **Castleman's disease.**
- It may precede the diagnosis of the tumor.
- **Painful sores appear on the mouth, lips, and the esophagus.**
- Complete removal and/or cure of the tumor may improve the skin disease.
- IF you have a case of:
  - A: severe oral involvement.
  - B: IF it shows +ve for everything in serology: Anti-Desmoglein, plaqin, etc.
  - If you treat the cause (cancer) it goes away and it will be treated.

Blistering Diseases

Clinical features:



When you see this picture, the first thing you should think about is steven-johnson syndrome
but in this case it is a child so you have to think of Castleman disease.

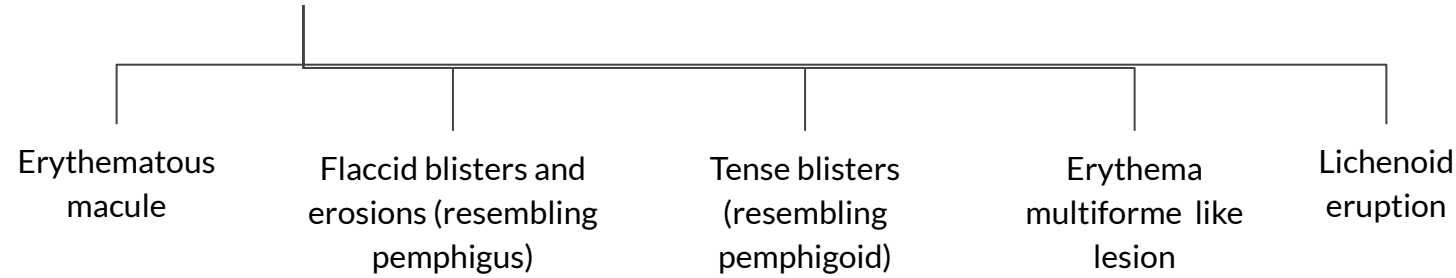
- The most constant clinical feature is the presence of intractable stomatitis

- The Stomatitis consists of erosions and ulcerations that affect all layers of the oropharynx and characteristically extend onto the Vermilion lip

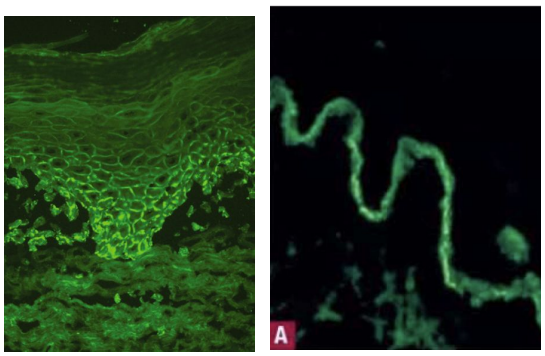
- Stomatitis is usually the earliest presenting sign and, after treatment, is the one that persists and is extremely resistant to therapy

- Pseudomembranous conjunctivitis à scarring, blindness Could also affect: esophagus, nasopharynx, vagina, labia, penis

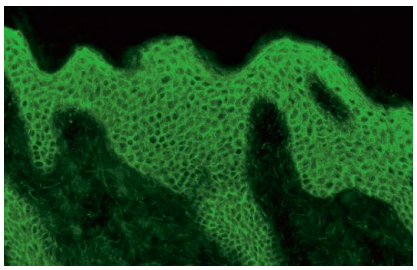
- Cutaneous findings are "polymorphic"



Findings:



- **IF** → IgG and C3 and IgA
  → linear flaring of B.M if IgG:
  Epidermolysis bullosa acquisita Bullous pemphigoid.
  → linear flaring of B.M if IgA:
  Linear IgA bullous dermatosis

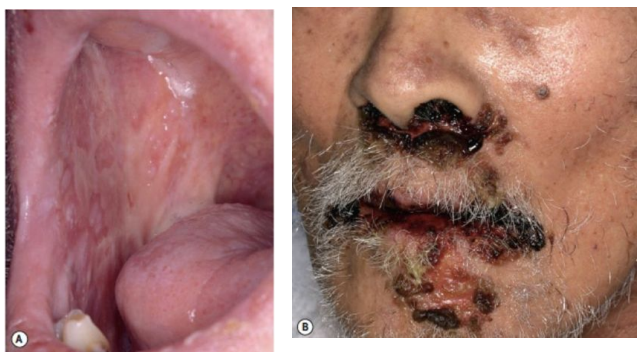


Treatment:

Treat the underlying tumor Benign tumors: it may take 6-18 months to see complete resolution of lesions after excision of benign neoplasms Malignant tumors:

1. No consensus on a standard effective therapeutic regimen
2. Cutaneous lesions respond more rapidly than the stomatitis, which is refractory to treatment

- Prognosis of paraneoplastic pemphigus is poor due to its resistant nature to treatment



Blistering Diseases

Pemphigoid group

1. Bullous Pemphigoid:

It's completely opposite to pemphigus Vulgaris

- The most common autoimmune subepidermal blistering disease, caused by autoantibodies to components of hemidesmosomes in the basement membrane zone (BMZ)
- Characterized by large blisters on an erythematous base.
- Mainly in older age group more than 60 y. **Elderly patients.**
- The **prognosis** is usually **good**.

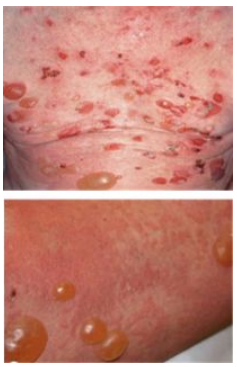
Clinical features:

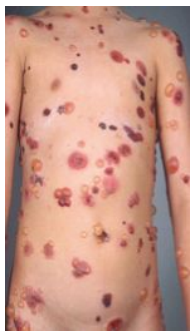
- Elderly patients
- Large **tense** blisters on upper arms and Thighs. unlike Vulgaris, which is flaccid
- Eczematous base with no clear erythema.
- Itch rather than pain. (too itchy to the point that sometimes it presents as eczema).
- Oral lesions are less frequent than pemphigus.
- Has:
  - Tense blister hard to rupture (pathology below b.m).
  - NOT Painful but Urticaria.

Pathology:

- **Sub epidermal between epidermis and dermis the epidermis forms the roof of the blister.**
- Immunoglobulin and complement are deposited in the lamina lucida of the basement membrane in a linear band.
- Antigens identified are BP 1 "BP230' and BP 2 "BP180" which is most likely to be more involved in the

- Drug-induced bullous pemphigoid:
  1. Diuretics (furosemide)
  2. D-penicillamine
  3. Antibiotics (amoxicillin, ciprofloxacin)
  4. Potassium iodide





Clinical features:

BP is an **intensely pruritic** eruption with widespread blister formation

In early stages and atypical variant: excoriated, eczematous, urticarial lesions

Blisters are stable and tense

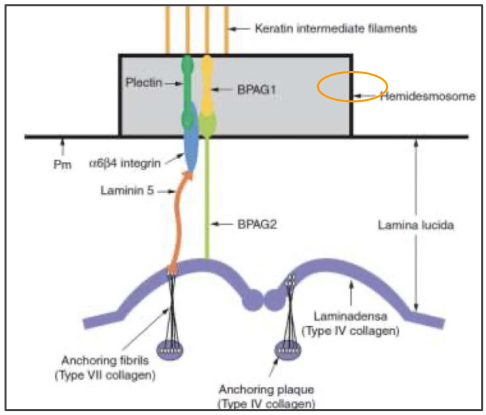
Mucosal involvement in < 20 %

Non-bullous phase: cutaneous manifestations are non-specific & polymorphic (pruritus, excoriations, eczematous, urticarial lesions)

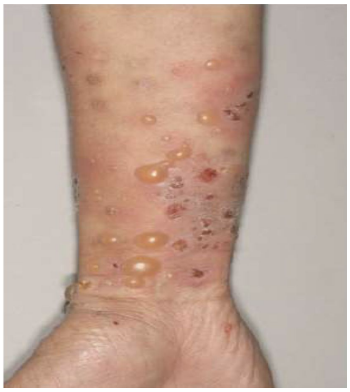
Bullous phase: characterized by the development of vesicles and bullae on normal or erythematous skin along with urticarial lesions

- Bullae predominate on the flexural aspects of the limbs and the lower trunk

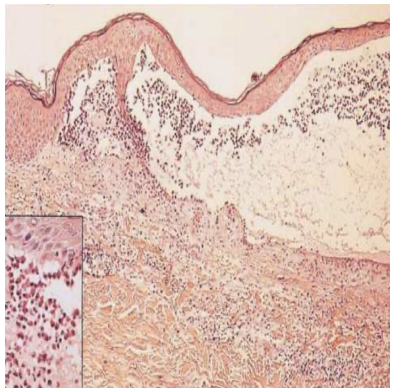
Blistering Diseases



BPAG1: Intracellular binds BPAG2 to hemidesmosome.
BPAG2: Extracellular attach hemidesmosome to the papillary dermis.
Pm, lamnin, a6B4 integrin: all target for congenital diseases



Extensive erythema and deeper erosion and the blister are most tense and often present with blisters



Eosinophils

Diagnostic approach:

The diagnosis of BP is based upon the clinical presentation, histologic features, and positive findings on direct and indirect immunofluorescence

History

Physical examination

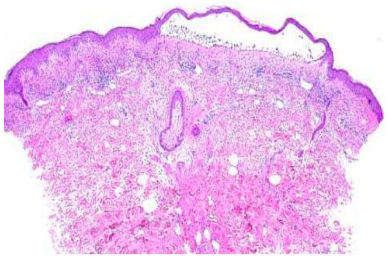
Investigation

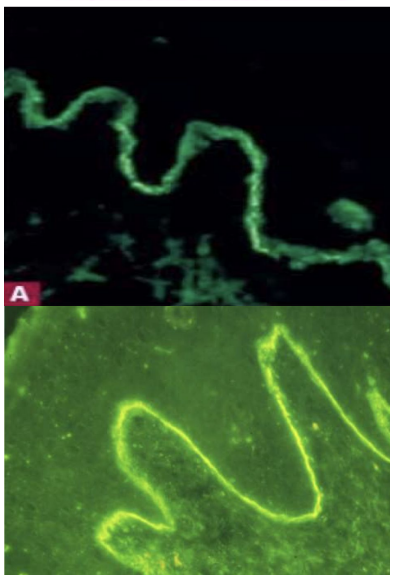
- CBC & Differential —> ↑eosinophils
- ESR↑
- IgE ↑ eosinophils, ESR & IgE are elevated in 60% of patients with BP
- Skin Biopsy:

• Non-bullous phase → non- specific, eosinophilic inflammatory infiltrate

• Bullous phase → subepidermal blister, accompanied by a dermal inflammatory infiltrate composed of eosinophils

- DIF → from perilesional, uninvolved skin, linear, continuous deposits of IgG and C3 along the epidermal basement membrane





In Bullous pemphigoid the IF shows **linear** band.

Treatment:

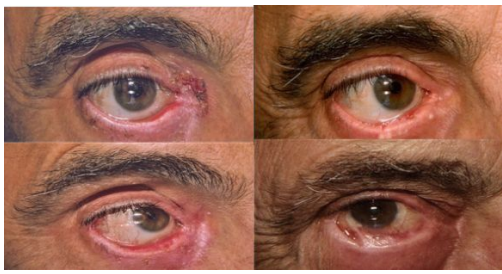
- Mild may also respond very well to potent or moderately potent topical steroids alone.
- Severe pemphigoid :Systemic steroids , but unlike pemphigus, it may be possible to discontinue.
- The addition of either azathioprine enable the oral steroid dose to be reduced more rapidly.
- Potent steroid moderate dose is enough… Even if severe topical high potency steroid is enough.
- So, the good thing here you don't use orals steroids and you don't get the complications especially for the elderly, but it's hard because it need to be topically applied for the whole body, if oral 1/2 mg of dose is enough we add azathioprine if not recovered enough.
- Some physician use doxycycline and niacinamide and say they have anti-inflammatory effect.

2. Cicatricial Pemphigoid:

Is a chronic, autoimmune, subepithelial blistering disorder characterized by a predominant involvement of the external mucosal surfaces (mainly oral & conjunctival mucosa, but it could affect any mucosal site) and a tendency for **scarring**

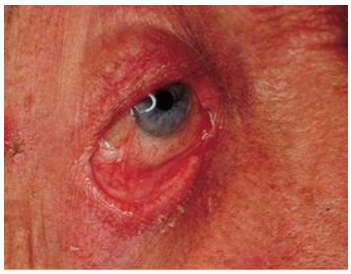
- Patients > 65 years

Clinical features:



Oral mucosa → lesions less painful than PV

Conjunctiva:
- affected in 75% of cases.
- Starts unilaterally, within 2 years becomes bilateral
- adhesions, ectropion, corneal damage



Esophagus & larynx → can develop strictures that may require surgery

Genitalia → narrowing of vaginal orifice, adhesions between glans & foreskin

Skin: only involved in 25% , face, scalp and upper trunk, atrophic scarring

Diagnostic approach:

History

Physical examination

Investigation
- DIF → IgG autoantibodies directed against the basement membrane of mucosa and/or skin
- Indirect IF → salt-split skin

Treatment:

- Local therapy such as potent topical corticosteroids is crucial and, in some cases, maybe sufficient
- Oral lesions → topical steroids (mouthwash, topical preparations),
- Nasal, pharyngeal, esophageal disease → steroid sprays/ inhalers
- Ocular → topical / systemic cortecosteroids, ophthalmology referral
- Severe disease: Oral corticosteroids, Dapsone, Cyclophosphamide, Azathioprine, Surgical therapy

3. Pemphigoid Gestationis:

- Synonym: « herpes gestationis » was previously termed herpes gestationis because the morphology of the blisters was similar to that of herpes, however it's not herpetic.
- A form of BP occuring during pregnancy
- Occurs in 1/10000-40000 pregnancies
- No maternal risk, no increase in birth defects. However, pregnancy complications and fetal death occurs in 15-30%
- Erythematous urticarial plaques, alone or with papules, vesicles, blisters in sub-epidermal area, erosions
- Intense pruritus
- Sites: abdomen, proximal extremities
- Rarely appears postpartum, resolve within 3 months
- Occasionally recurs with menses or ingestion of OCP, tends to be worse in next pregnancy
- The antibodies cross the placenta, the newborn can have blisters for a few weeks

Diagnostic approach:

History

Physical examination

Investigation

- Cbc & differential eosinophilia
- DIF & indirect IF

Treatment:

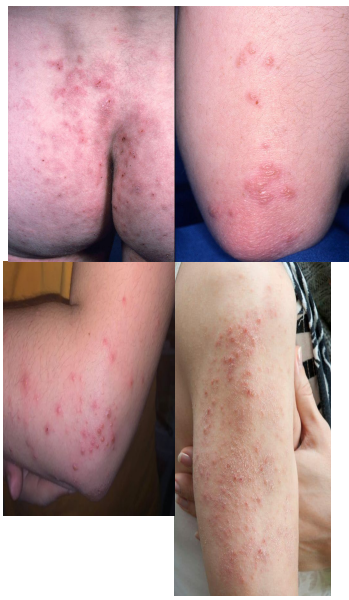
Topical steroids

- Systemic steroids: avoid in 1st trimester
- Skin care to prevent infection
- Antihistamines for tx of pruritus

4. Dermatitis Herpetiformis

Herpetiformis means "herpes-like lesion", which is a group of vesicles

- A chronic, **recurrent intensely pruritic** Although, they're tense, pts. Remove'em due to their itchiness
- 30-40 year old
- Grouped vesicles, papules on extremities and buttocks
- Associated with Gluten sensitive enteropathy
- **IgA autoantibodies against transglutaminase**
- **Exacerbated by Iodide and Gluten ingestion**
- DH is a cutaneous manifestation of celiac disease and is associated with gluten sensitivity in virtually all cases
- DH and celiac disease are genetic disorders strongly associated with HLA-DQ2 genotype, in which IgA antiendomysial antibodies are directed against tissue transglutaminases (in the skin → epidermal transglutaminase)



Clinical features:

Sites : extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Grouped 'herpetiform' papules/vesicles/urticarial wheals over an erythematous base, associated with intense pruritus, burning, stinging and **excoriations**

Spontaneous remissions may occur, but disease often lifelong

DH other symptoms include Malabsroption, Iron deficiency anemia, Steatorrhea

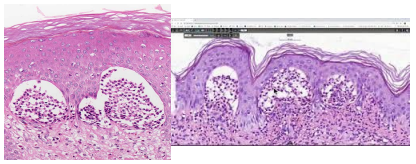
Diagnostic approach:

History

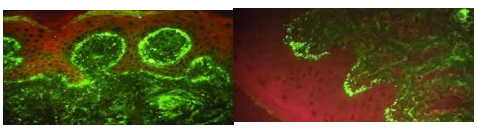
Physical examination

Investigation

Skin biopsy: **subepidermal blister, with neutrophilic microabscesses in the papillary dermis is the hallmark of the disease**



- DIF → **Granular deposits of IgA in the dermal papillae** (Confirmatory test)

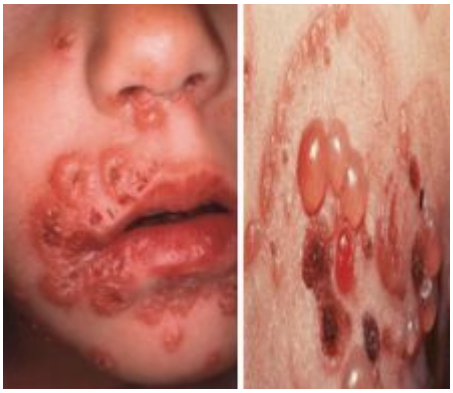


- Indirect IF
- ELISA identifies IgA against transglutaminase in 80% of cases
- Jejunal Biopsy flattening of the villi

Treatment:

- **Dapsone** 100-150 mg/d works by inhibiting the adhesion between neutrophils and IgA
  - **Quick** response within hours
  - It can precipitate G6PD or methemoglobin
- Sulfapyridine 1-1.5 grams/d if dapsone not tolerated. Monitor kidney function
- **Gluten free diet is slow, and usually not enough** but can lower doses of medications

5. Linear IgA Disease:



- Subepidermal blistering disease caused by deposits of IgA along BMZ
- Linear IgA disease is characterized by on linear IgA deposition at the basement membrane
- Maybe identical to DH but WITHOUT GI involvement , or resemble BP
- Over 50% have mucosal involvement

Diagnostic approach:

History

Physical examination

Investigation

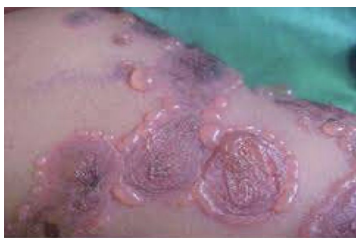
- DIF → linear IgA deposits along the basement membrane
- Indirect IF

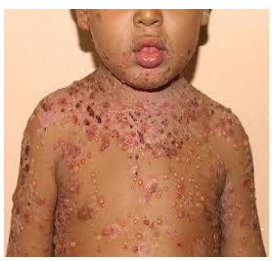
Treatment:

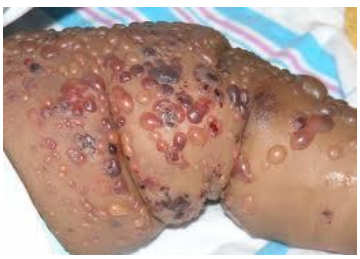
- Dapsone
- Sulfapyridine
- Antibiotics: tetracycline, erythromycin, dicloxacillin
- Antibiotics are a good treatment for the childhood form, and were found to be better than dapsone in this age group

6. childhood form "Chronic bullous disease of childhood":

Clinical Feature:







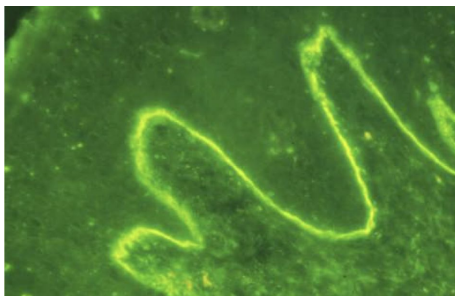
- Occurs in children "preschool", and resolves spontaneously
- **Circular clusters of large blisters like the type seen in pemphigoid (cluster of jewels).**

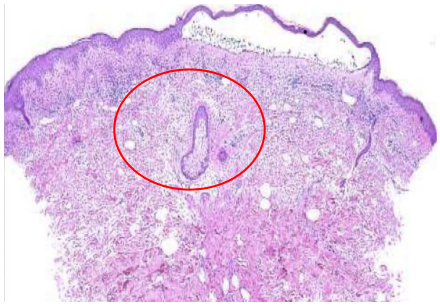
  (similar target of Bullous pemphigoid).
- It involves the perioral area, lower trunk, inner thighs and genitalia.
- Blistering may spread all over the body.

Blistering Diseases

Investigations:

- Skin Biopsy will show subepidermal splits
- Direct IF reveals IgA along the BM of the epidermis in a linear pattern (similar to BP except in BP it's IgG).





Neutrophils unlike BP which is eosinophils

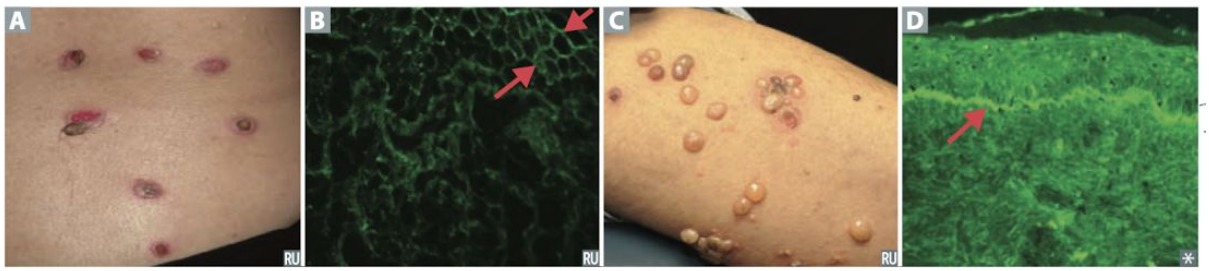
Treatment:

- Oral **dapsone** 50-200 mg daily (Ad/E) (dapsone works greatly on Neutrophils).
- Sulphonamides and immunosuppressants.
- Erythromycin. (in case of sulfa allergy)
- **Flucloxacillin** : 7 cases reported excellent response from KKUH.
- We can use steroid but as last option

Summary regarding the differences between P. Vulgaris & Bullous P. "Dr slides"

Autoimmune blistering skin disorders

	Pemphigus vulgaris	Bullous pemphigoid
PATHOPHYSIOLOGY	Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum).	Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are "bullow" the epidermis).
GROSS MORPHOLOGY	Flaccid intraepidermal bullae A caused by acantholysis (separation of keratinocytes, "row of tombstones" on H&E stain); oral mucosa is involved. Nikolsky sign ⊕.	Tense blisters C containing eosinophils; oral mucosa spared. Nikolsky sign ⊖.
IMMUNOFLUORESCENCE	Reticular pattern around epidermal cells B.	Linear pattern at epidermal-dermal junction D.



Nikolsky sign: is a skin finding in which the top layers of the skin slip away from the lower layers when rubbed.

Quiz!

1- 30-year-old male present s with erosion and crust on lips. He was diagnosed with lymphoma a month ago. What is the most likely diagnosis?

A) Scurvy
B) Pemphigus vulgaris
C) Herpes labialis.
D) Paraneoplastic pemphigus

2- Pt with erosions and vesicles, DIF was done and showes IgG & C3 deposition in the epidermis pattern, what's most likely diagnosis

A) Rosacea
B) Bullous pemphigoid
C) Dermatitis herpetiformis
D) Pemphigus vulgaris

3- A pregnant female with papulovesicular eruption involving abdomen and extremities, suspected to have herpes gestationis. Which of the following is a feature of Pemphigoid gestationis?

A) It's a viral disease
B) It's non itchy eruption
C) It starts in first trimester
D) It relapses with contraceptive pills

4- 12-year-old boy presented with vesicles and erosion look like cluster of jewels, what's the most likely diagnosis?

A) Linear IgA dermatosis
B) Bullous pemphigoid
C) Pemphigus vulgaris
D) Impetigo

5- patient with pruritus, his skin biopsy shows neutrophilic microabscesses in the papillary dermis What's the management?

A) Topical steroid
B) Systemic steroid
C) Dapsone
D) A diet containing wheat.

6- 21 year old male complaining of grouped itchy vesicles at his extensors, immunofluorescent shows positive granular IgA deposition in dermal papilla. Which of the following is the most likely diagnosis?

A) Rosacea
B) Dermatitis herpetiformis
C) Pemphigus vulgaris.
D) Bullous pemphigus

7- Direct immunofluorescence of skin biopsy from 54 years old patient with blistering disease revealed intracellular deposit of IgG and C3. In which one of the following blistering diseases this immunopathology finding is seen?

A) Bullous pemphigoid
B) Pemphigus vulgaris
C) Cicatricial pemphigoid
D) Dermatitis herpetiformis

Answers:
1:D, 2:D, 3:D, 4:A, 5:C, 6:B, 7:B

DERMATOLOGY TEAM 438

Dermatology Team 439

438 Team leader:
Mohsen Almutairi

439 Team leader:
Mohammed Albabtain

438 Done by:
Faisal Alkoblan

439 Done by:
Mohammed Albabtain

438 Academic leader
Saud Bin Queid

439 Academic leader
Hamad Almousa

This lecture was updated by: 441 Academic Leader *Bassam Al Hubaysh*

Dermatology Team 441

MED441
KING SAUD UNIVERSITY

BH
Bassam Alhubaysh
REVIEWED BY