Blistering Diseases

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

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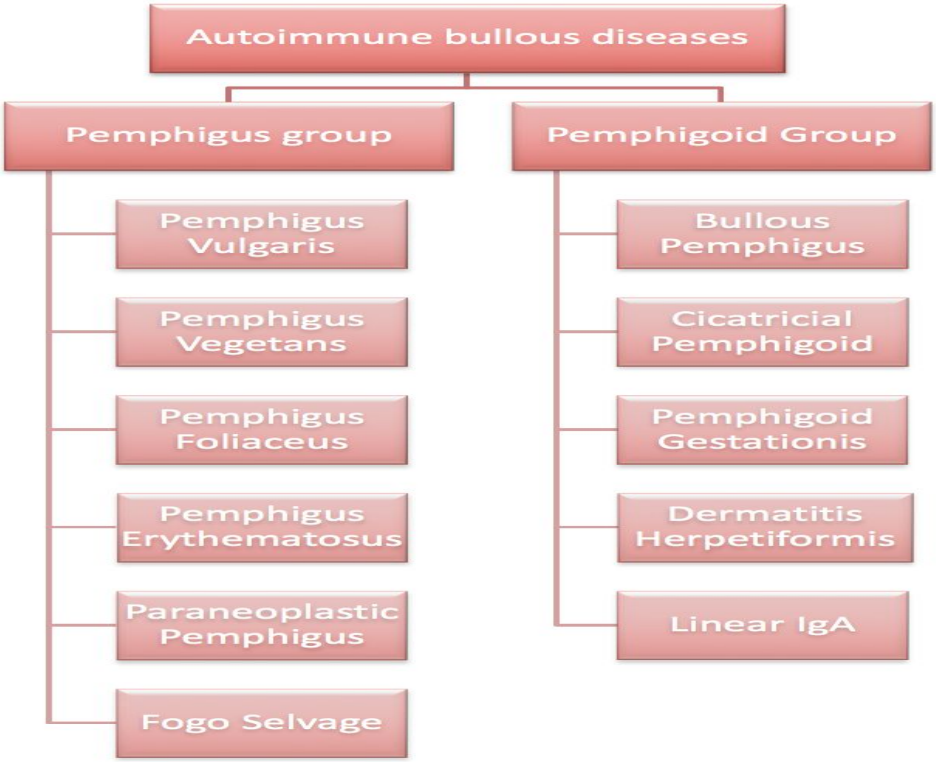
Revised by:

Sources*: FITZPATRICK color atlas +433 male + 434 + doctors slides and notes*

[Color index : Important | Notes | Extra]



Topics covered in this lecture include :

- **pemphigus group diseases**
  - Pemphigus vulgaris
  - Pemphigus vegetans
  - Pemphigus foliaceus
  - Pemphigus erythematosus
  - Paraneoplastic pemphigus
  - endemic pemphigus (fogo selvagem)
- **Pemphigoid group diseases**
  - Cicatricial pemphigoid (mucous membrane)
  - Bullous pemphigoid
  - Pemphigoid Gestationis
  - Iga dermatosis
  - Dermatitis Herpetiformis

    (the name means that it is a skin inflammation having an appearance similar to herpes)

Before we start let's revise the skin structure (will help us understand the lecture better)

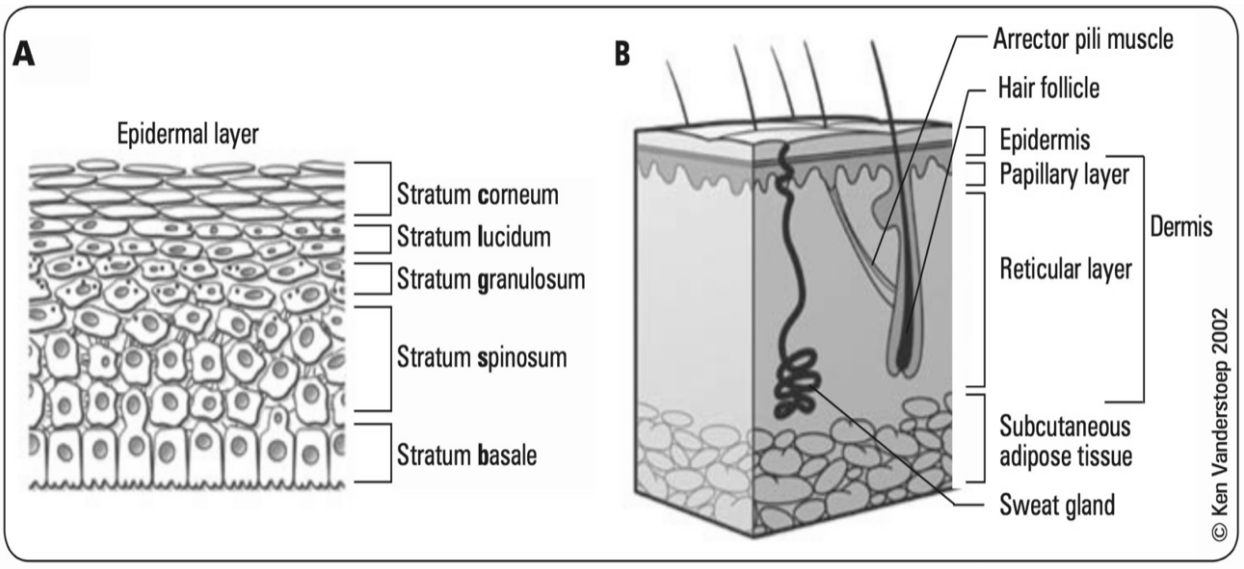
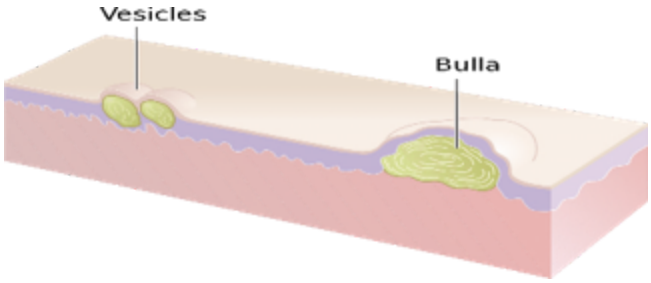


Figure 1. Histologic layers of the skin. Epidermal layer is detailed in A

Definition of blisters :

- circumscribed skin lesions containing fluid
- A vesicle is less than 0.5 cm in diameter.
- A bulla is larger than 0.5 cm in diameter



Classification Of Vesiculobullous Diseases:

Intraepidermal blisters

- Within the prickle cell layer
- Have thin roof
- Easily rupture and oozing

Types

A- Loss of intraepidermal adhesion:

1- Pemphigus vulgaris (PV) with subtypes
   a- Classic
   b- Pemphigus vegetans
2- Pemphigus foliaceus with subtypes
   a- Classic
- Fogoselvagum
- Pemphigus erythematosus(Senear-Usher)
   b- Paraneoplastic pemphigus
   c- Drug induced pemphigus

Subepidermal blisters

- Between dermis and epidermis
- Have thick roof
- Tend to be tense
- May contain blood

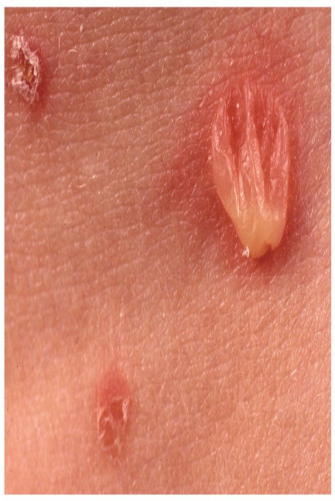
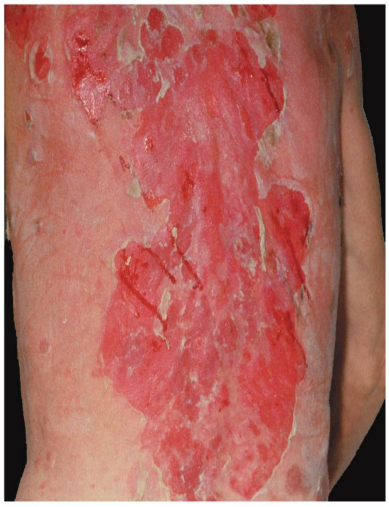
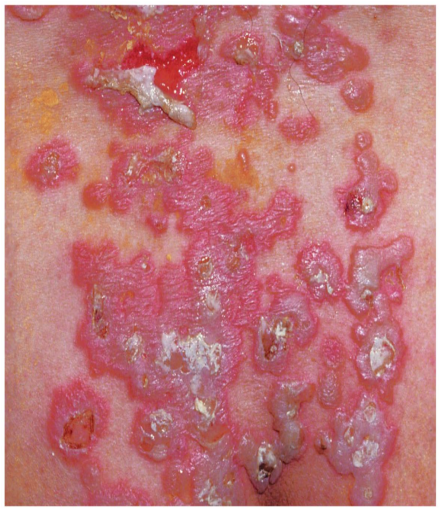
Types:

B- Loss of subepidermal adhesion :

1- Pemphigoid
   a- Bullous pemphigoid
   b- Pemphigoid gestationis
   c- Cicatricial pemphigoid
2- Linear IgA disease
   a-of childhood
   b-Adult form
3- Epidermolysis bullosa acquisita
4- dermatitis herpetiformis

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. The desmosome is a complex structure, with many of its components targets for autoantibodies.

Pemphigus Vulgaris

Definition:

severe, potentially fatal disease with **intraepidermal blister formation** on skin and **mucosa** caused by autoantibodies against **desmogleins**.

Epidemiology:

0.1-0.5/ 100000 yearly, most patients middle aged.

Pathogenesis:

- Genetic predisposition: HLA-DRQ 402- DQ0505
- Antibodies against desmoglein 3 (Dsg3) and later desmoglein 1 (Dsg1). The bound antibodies activate proteases that damage the desmosome, leading to acantholysis.
- Serum antibody titer usually correlates with severity of disease and course.

Note that dsg3 affects mainly the mucus membrane and dsg1 affects the skin

Medications That Can Cause pemphigus:

1-Agents containing sulfhydryl groups (penicillamine, captopril, piroxicam) are more likely to cause PV.

2-Those without sulfhydryl groups tend to cause PV (beta-blockers, cephalosporins, penicillins, & rifampcin

Note :drugs from either group can cause either type of pemphigus.

Clinical features:

- **Pruritus is uncommon**
- Blitersare *NOT* stable, **epidermis falls apart erosion & crusts are common we don't usually see blisters because its thin its already ruptured**
- Oral Involvement: 70%, anti-Dsg3 (Dsg3 is the main desmoglein on mucosa
- Generalized disease due to development of autoantibodies against dsg1 which is present in the skin along with dsg3
- Additional localized disease; scalp

note:always check scalp when confronted with unexplained oral erosions.

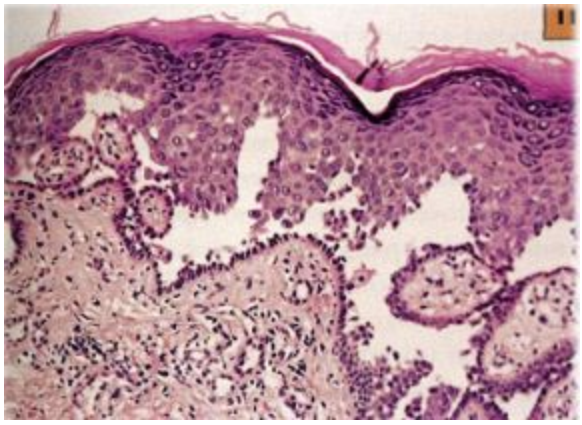
Sites include:

- oral mucosa
- Scalp
- Face
- Mechanically stressed areas
- Nailfold
- Intertriginous are

Intertriginous area : is where two skin areas may touch or rub together. Examples of intertriginous areas are the axilla of the arm

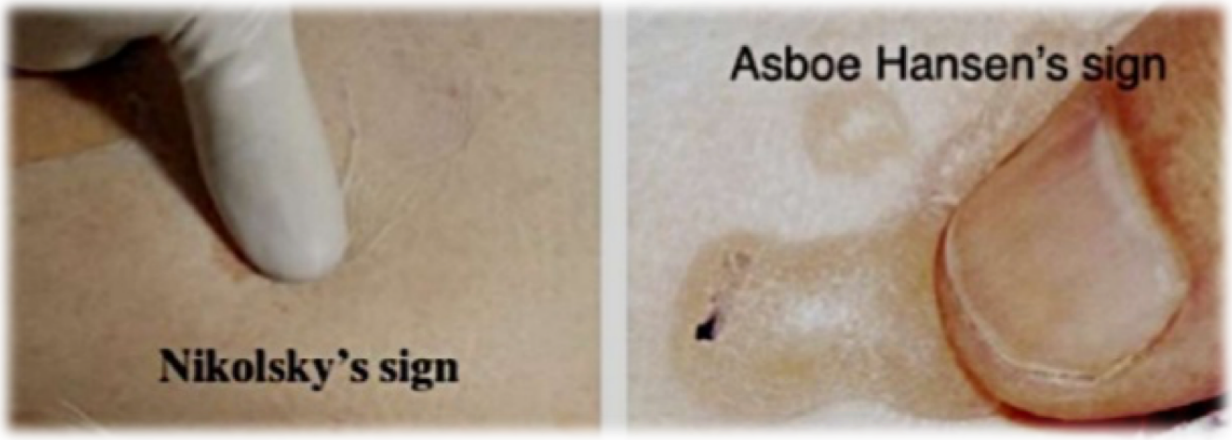
Histopathology:

- Acantholysis:loss of intracellular adhesion of epidermal cells
- mild dermal perivascular infiltrates.
- Retention of basal layer keratinocytes (tombstone effect) see pic below



Diagnostic Approach:

- Clinical Evaluation
- Nikolsky Sign
- indirect-Nikolsky Sign(Asboe-Hansen sign),less specific refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla



Histopathology:

- Direct immunofluorescence : **perilesional** (getting a sample from the border of the blister to get both normal and abnormal skin in same biopsy) shows a net-like intracellular deposition of IgG (100%), C3 (80%)
- Indirect Immunofluorescence is performed using monkey esophagus
- ELISA: to identify anti-Dsg3,Dsg1

Differential diagnosis:

- **When skin is involved:**
  - Bullous impetigo,
  - dyskeratotic acanthotic disorders(Hailey-Hailey, Grover Disease)

- **When Oral mucosa is involved:**
  - Denture Intolerance
  - Erosive Candidiasis
  - Chronic Recurrent Aphthae
  - Erythema Multiforme
  - Erosive lichen planus
  - Herpetic Gingivitis

Treatment:

- Systemic Corticosteroids
  - The main cause of morbidity & mortality in patients is CorticoSteroids side effects, have to combine with steroid-sparing agent, check for osteoporosis and latent TB
  - combination pulse therapy: prednisolone 1g + cyclophosphamide 7.5-10 mg/kg every 3-4 weeks
  - With Cyclophosphamide In interval 1-2 mg/kg daily.
  - Prednisolone- azathioprine therapy
- Alternative immunosuppressive agents: cyclosporine, mycophenolate mofetil, RITUXIMAB.
- Topical Measures: local anesthetic gels
- Therapy Resistant Course: IVIG

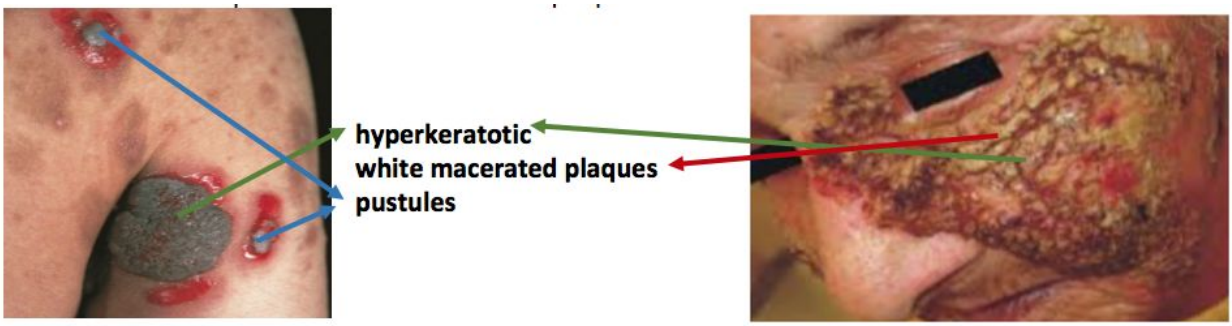
Pemphigus Vegetans

Definition:

Is Unusual Variant of Pemphigus Vulgaris with **hyperkeratotic verruciform reaction**(vegetans)

Clinical features:

- start Originally as a typical Pemphigus Vulgaris.
- then development of white macerated plaques in involved areas



pyodermite végétante : limited to intertriginous areas, starts as pustules that evolve into vegetating lesions.

Diagnostic Approach and treatment:

- same as for Pemphigus Vulgaris

DDx:

- if mild and localized **can be confused with Hailey-Hailey**

  (Hailey–Hailey disease, or amilial benign pemphigus, is a rare genodermatosis with dominant inheri- tance that is classically described as a blistering disorder but actually presents as an erythematous, erosive, oozing condition with cracks and ssures localized to the nape o the neck, axillae

Pemphigus Foliaceus

Definition:

Form Of pemphigus with superficial blisters caused by anti-Dsg1

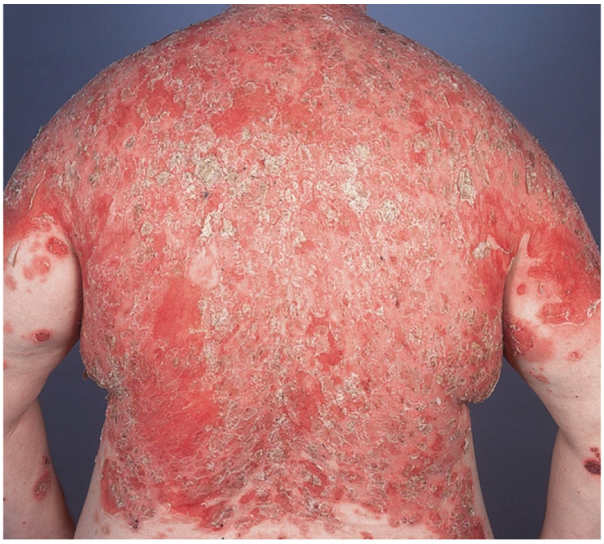
Pathogenesis:

Anti-Dsg1, the main desmoglein on the upper epidermis.

More often **drug induced** than PV,usually sulfhydryl groups : captopril, penicillamine, peroxicam

Maybe Caused By sunburn or paraneoplastic sign

Some Cases have been associated with **thymoma**



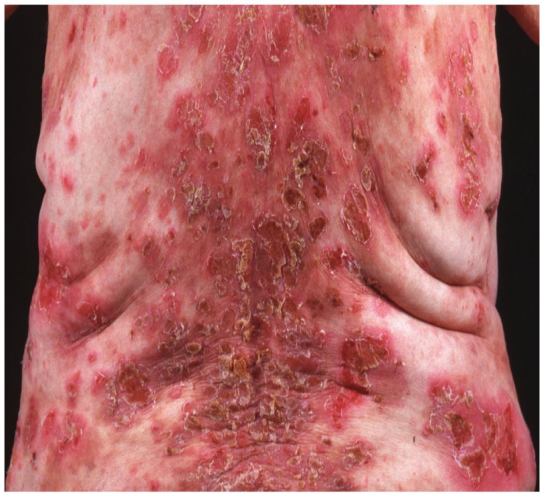


FIGURE 6-12 **Pemphigus foliaceus** The back of this patient is covered by scaly crusts and superficial erosions.

Clinical features

Scalp, face, chest and back, can progress to involve large areas with diffuse scale and erosion

PF has no mucosal lesions and starts with scaly,crusted lesions on an erythematous base

Diagnostic approach

Clinical MAINLY

Biopsy?not helpful

DIF: superficial deposition of IgG

ELISA: reveals IgG antibodies against Dsg1

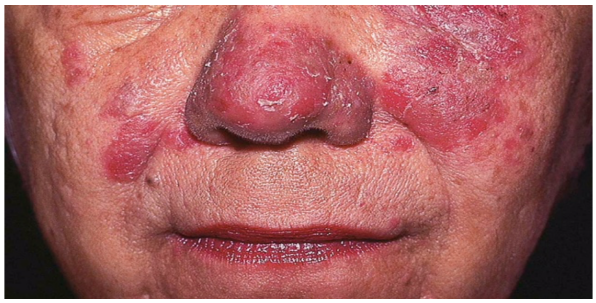
Medication history

Treatment :

- same as PV but usually more responsive to
- Dapsone might be helpful

Pemphigus Erythematosus (Senear and Usher)

- Uncommon feature of pemphigus foliaceus with additional features of **lupus erythematosus**
- More likely to be triggered by sunlight or medications than other forms of PF



Fogo Selvagem (Endemic pemphigus)

- Portuguese for (wildfire).
- Endemic Form that occurs in people living on the Amazon river .
- An observed relationship to the **bite of black fly Simulium nigrimanum.**
- Oftenly Several persons in a village may be affected in the sametime

Paraneoplastic Pemphigus

- **Most often associated with lymphoma, leukemia, thymoma, Castleman tumor.**
- **Not with SCC (small cell carcinoma) or adenocarcinoma**

Clinical:

- Severe persistent painful stomatitis extending from lips to pharynx, larynx and esophagus, so **almost always involving oral mucosa.**
- conjunctival involvement may lead to blindness.
- Cutaneous Changes are polymorphic

Note: if patient is sick and has lesions resembling erythema multiforme, lichen planus and a blistering disease, be highly suspicious of paraneoplastic pemphigus.

Histology

- Histopathology is rarely helpful.
- IIF testing with rat bladder.

Treatment :

- treat the underlying tumour, prognosis correlates with the response
- No consensus on what immunosuppressive regimen. Good success with anti-CD20 (rituximab)

Bullous pemphigoid

Definition:

- Subepidermal blistering disease caused by autoantibodies to components of hemidesmosomes in the basement membrane zone (BMZ).
- Most common autoiummune bullous disease, 1/100000,
- favours elderly male<female.

Pathogenesis:

- Autoantibodies Directed Against 2 hemidesmosomal proteins
  - BP 230
  - BP 180

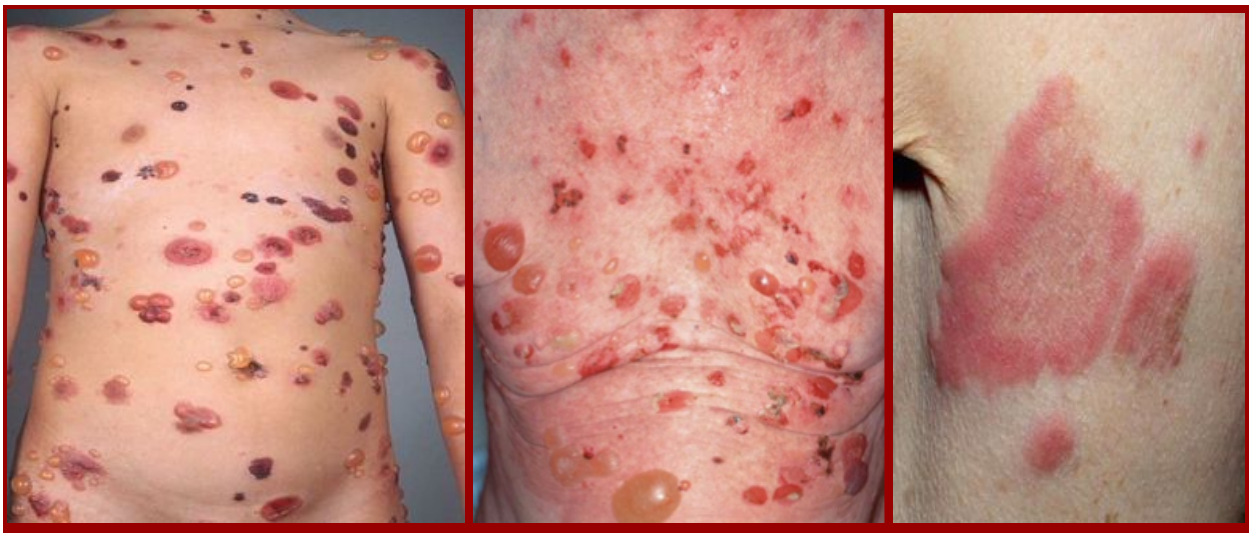
BP 180 is most likely to be more involved in the initial immune response, sinceitistrans membranous.

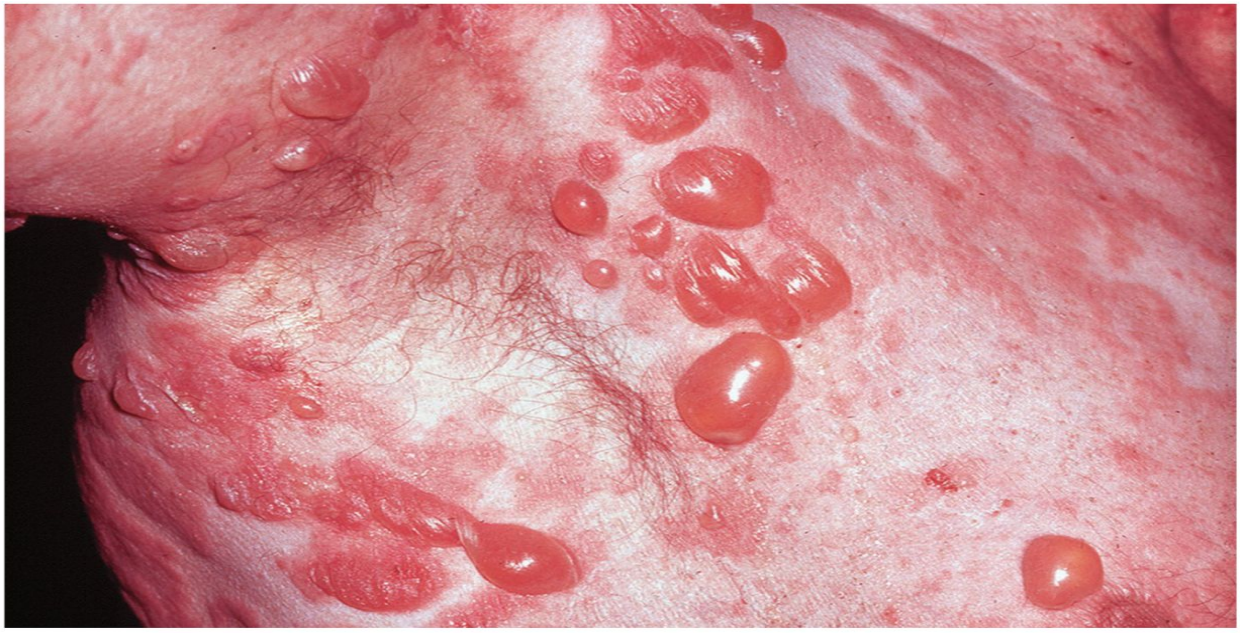
- Less common causes include drugs (benzodiazepine, furosemide, penicillin, sulfasalazine), sunlight, and ionizing radiation.

Clinical features:

- ***Pruritus, start first***
- **Urticarial Lesion**s (second appear)
- blisters tend to develop in wheal.
- Blisters are stable and tense.
- Oral mucosal involvement in <20%.

Note:always keep BP in mindwhenconfrontedwithan elderly patient with persistent « urticaria ».





Histopathology:

- Prebullous lesions: presence of unexpected eosinophils is a good clue.
- Later subepidermal blister formation

Diagnostic Approach:

- **Labs:**
  - Elevated ESR
  - eosinophils,
  - increased IgE in 60%.
- **DIF**: best taken from erythematous area at periphery, not blister itself; band of IgG & C3 along Basement Membrne Zone.
- **Indirect IF**: using NaCL split skin
- **ELISA**: identifies antibodies against both BP 230 & 180 in 60-80% of pts.

Treatment:

1-Steroids??:
(Argumental point) some say we can use systemic steroids and others say we shouldnt Mainly due to the harmful effect of systemic steroid in old patient as pemphigiod affect mainly elderly +recent researchs say that topical steroids have the same effect **So we give topical steroids**
2-methotrexate 15-20 mg weekly
3-steroid-sparing agents Mostly widely used, azathiporine & mycophenolate mofetil.

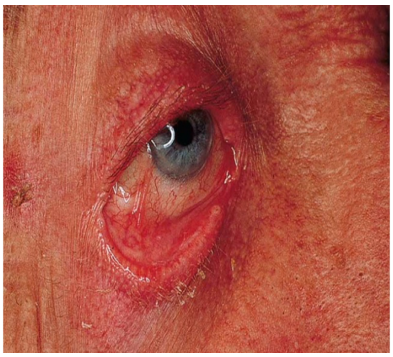
Cicatricial pemphigoid

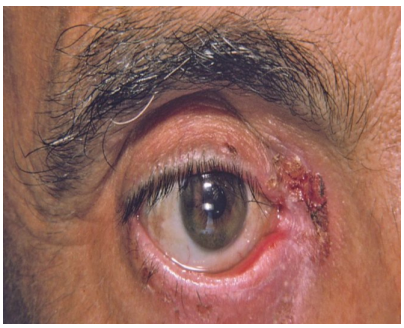
Definition:

- Chronic subepidermal blistering disease favoring mucus membrane especially ***mouth and eyes.***
- Patients > 65 years.Women> men

Clinical Features:

- **Conjunctiva Affected In 75% of cases**
  - Starts Unilaterally
  - within 2 years usually
  - bilateral.
  - Adhesions, ectropion, corneal damage
- **Oral mucosa:**
  - much less painful than PV**.**
- **Esophagus And larynx**
  - develop strictures, requiring surgery.
- **Genitalia**:
  - narrowing of vaginal orifice;
  - Adhesions between glans & foreskin.
- **Skin**:
  - only involvedin 25%





Diagnostic approach :

DIF and Indirect If

Treatment :

Ocular: topical or systemic corticosteroids, OPH consultation

Mucosal: topicals

Widespread: Pred+azathioprine pred+ cyclophosphamide pulse therapy

IVIG

Another type (Variant) is called Brunsting-Perry Characterized by the Lack of mucosal involvement
Occurs on the head, neck and scalp of older men. consists of erosion that heal with scarring.

Pemphigoid gestationis

Definition:

- Is a Form of BP occuring during pregnancy.
- Occurin 1/10000-40000 pregnancies.
- No maternal risk, no increase in birth defects (worsen in next pregnancy)
- Infants born to affected mothers may develop lesions as well(10% of cases).

Pathogenesis:

- **Mothers** often HLA-88, -DR3, -DR4,
- **Father** often HLA-DR2. possible that mothers are sensitized against placental antigens. Target antigens are BP 180
- 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 recur with menses or ingestion of OCP, tends to be worse in next pregnancy.
- The antibodies cross the placenta, that's why the newborn have blisters for a few weeks.

Diagnostic Approach: Labs: eosinophilia, DIF, IIF

Treatment :

•Systemic Potent steroids: For blisters, avoid the systemic in the 1st trimester (topicals)
•Skin care : to prevent infections
•Antihistamines: For pruritis.
Usually no need for treatment it resolves by itself but sometimes it leaves a hyperpigmented lesions

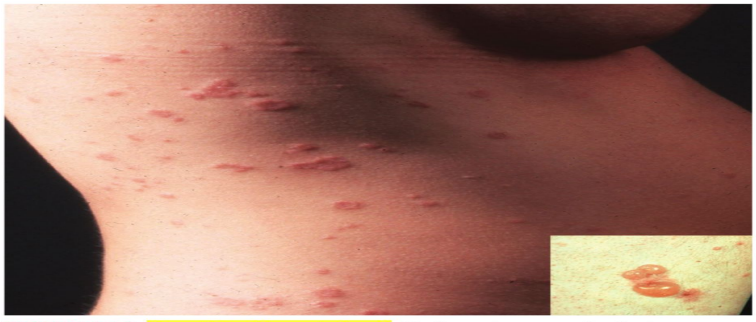


FIGURE 6-16 **Pemphigoid gestationis** Erythematous papules that were

Dermatitis Herpetiformis

Definition:

- Is a lifelong Pruritic vesicular disease caused by IgA antibodies directed against epidermal transglutaminase & presenting with granular pattern in papillary dermis.
- M>F 1:2, disease of young adults.
- DH & gluten-sensitive enteropathy are closely related (i.e. celiac disease).
- Grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations.

sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp .

Spontaneous remissions may occur, **but disease often lifelong.**

Histopathology:

•Neutrophilic Microabscesses In the papillary dermis are the hallmark

Diagnostic Approach:

- Skin biopsy
- DIF: **granular deposits of IgA** in **dermal papillae**
- Indirect IF
- ELISA: identifies IgA antibodies against transglutaminase in at least 80%
- Jejunal biopsy: flattening of villi

Treatment:

•Gluten free diet.

•Dapsone: amazingly effective

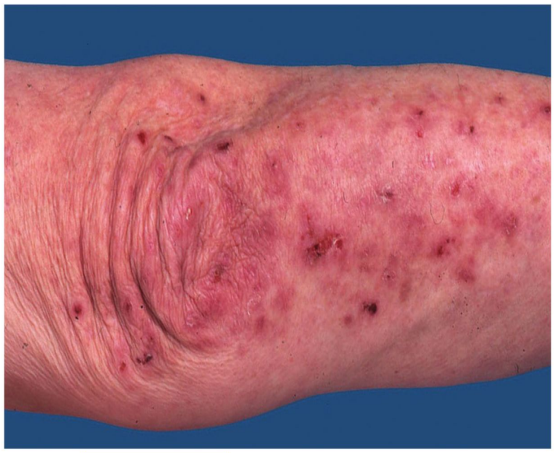


FIGURE 6-17 Dermatitis herpetiformis These are the classic early lesions. Papules, urticarial plaques

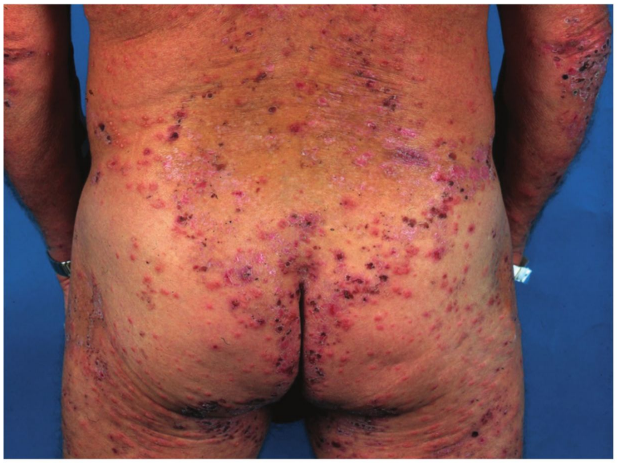


FIGURE 6-18 Dermatitis herpetiformis A 56-year-old male patient with a generalized highly pru-

Linear iga disease

Adult form

- Subepidermal blistering disease caused by depositsof IgA along Basement membrane zone.
- Maybe identical to Dermatitis herpitiformis but **without GI involvement**, or resembleBullous Pemphigoid.
- Over 50% have mucosal involvement

Child form:

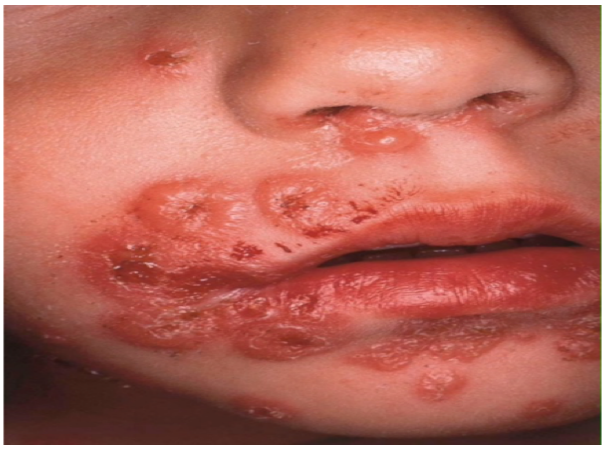
Before 5 years of age and resolves spontaneously
Large tense blisters arranged in a rosette fashion, predilection of abdomen, groin , axilla and face **mucosal disease very common 90% approx. GI disease extremely rare.**

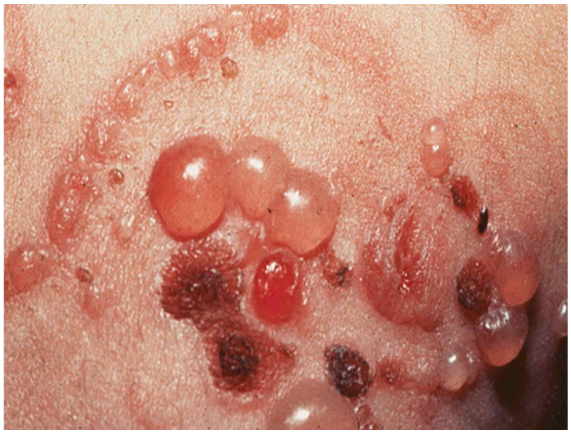
Diagnostic Approach:

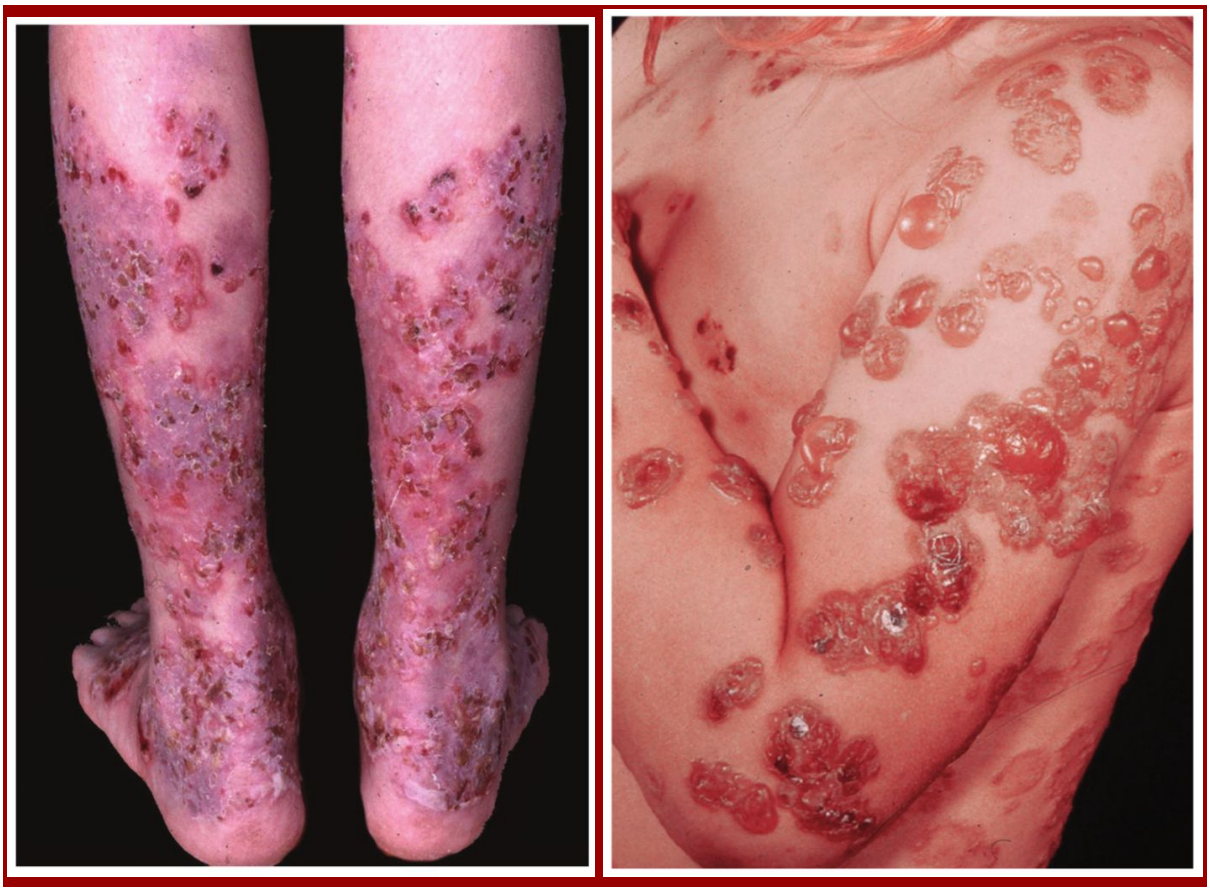
DIF: IgA deposits
IIF: IgA
OPH,
to exclude celiac (jejunalbiopsy..)

Treatment:

- **Adult treatment**
  - CORTICOSTEROIDS
  - Dapsone
- **Child treatment**
  - Dapsone, sulfapyridine
  - If ContraIndicated or failure: then use Corticosteroids





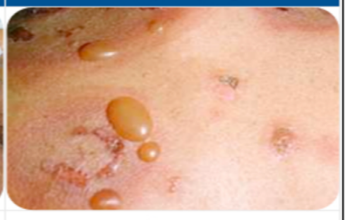


Summery:

Table 9.1 Distinguishing features of the three main immunobullous diseases.

	Age	Site of blisters	General health	Blisters in mouth
Pemphigus	Middle age	Trunk, flexures and scalp	Poor	Common
Bullous pemphigoid	Old	Often flexural	Good	Rare
Dermatitis herpetiformis	Primarily adults	Elbows, knees, upper back, buttocks	Itchy	Rare

	Nature of blisters	Circulating antibodies	Fixed antibodies	Treatment
Pemphigus	Superficial and flaccid	IgG to intercellular adhesion proteins	IgG in intercellular space	Steroids Immunosuppressives
Bullous pemphigoid	Tense and blood-filled	IgG to basement membrane region	IgG at basement membrane	Steroids Immunosuppressives
Dermatitis herpetiformis	Small, excoriated and grouped	IgG to endomysium and transglutaminase	IgA granular deposits in papillary dermis	Gluten-free diet Dapsone Sulfapyridine

	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger	Older
Mucous membrane involvement	Yes	Rare
Autoantibodies	Against desmoglein 3	Against hemidesmosomes
Blister location	Intraepidermal (superficial)	Subepidermal (deep)
Blister quality	Flaccid, rupture easily	Tense and firm
Nikolsky's sign	Nikolsky **positive**	Nikolsky **negative**
Prognosis	Poor	Favorable