



Connective tissue disorders

- Lupus erythematosus
- Scleroderma
- Dermatomyositis, polymyositis
- Overlap syndromes

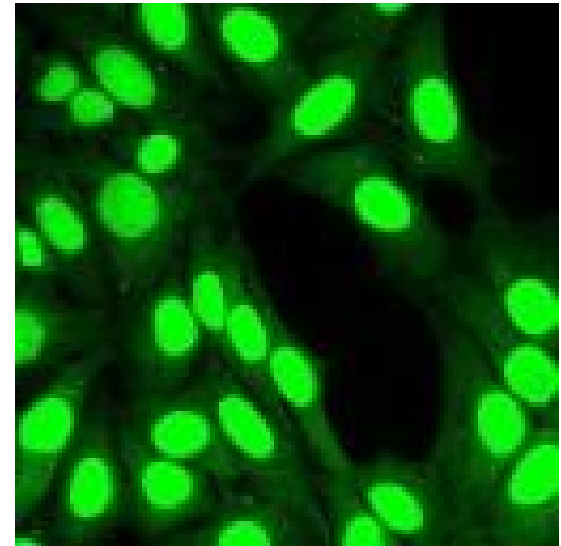
Lupus erythematosus

- ***systemic lupus erythematosus*** - SLE
- ***chronic cutaneous lupus erythematosus*** – CCLE
- ***subacute cutaneous lupus erythematosus*** – SCLE
- *neonatal LE*
- *drug induced (hydralazine, sulfonamides)*

Systemic lupus erythematosus

- SLE

- ARA criteria:
- malar rash
- discoid lesions
- photosensitivity
- oral lesions
- arthritis non-erosive
- serositis
- neurologic disorders
- lupus nephritis (proteinuria 0,5g/d)
- hematologic disorders
- immunologic disorders (LE cells, ANA ● ⊙ , anti dsDNA, Sm antigen, histones etc.)



SYSTEMIC LUPUS ERYTHEMATOSUS

SLICC Diagnostic Criteria :

CLINICAL CRITERIA	IMMUNOLOGIC
1. Acute cutaneous lupus	1. ANA
2. Chronic cutaneous lupus	2. Anti-DNA
3. Oral or nasal ulcers	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab
5. Arthritis	5. Low Complement (C3, C4, CH50)
6. Serositis	6. Direct Coombs' test
7. Renal dysfunction	
8. Neurologic dysfunction	
9. Hemolytic anaemia	
10. Leukopenia	
11. Thrombocytopenia (<100,000/mm ³)	

- Occurs after sun exposure; followed by systemic manifestations within few weeks
- Localised form: malar rash
- Generalised form: can involve whole body; systemic manifestations are present

**ACUTE
CLE**



- Subtypes include:
 1. DLE (localised or generalised)
 2. Hypertrophic DLE
 3. Lupus profundus
 4. Mucosal LE
 5. Chilblain lupus

**CHRONIC
CLE**



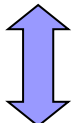
(SLICC - SLE international cooperating clinics group)



SLE



Chronic cutaneous lupus erythematosus - CCLE

- discoid lesions – CDE –scarring -lupus
 - photosensitivity – sun exposed areas
 - hypertrophic lesions –lupus tumidus - rare
 - lupus panniculitis
 - ANA low titers or none ($\leq 1:160$)
 - **no systemic disease**
- 
- **symptom of systemic disease (30%)**



Lupus panniculitis



CDE – oral and lip involvement



Subacute cutaneous lupus erythematosus - SCLE

- annular lesions
- papulosquamous lesions
- photosensitivity
- sicca syndrome secondary
- ANA, anti Ro/ SSA, La/SSB
- mild systemic disease
- neonatal LE (Ro 52 kD)







Lupus erythematosus

Therapy:

antimalarial drugs (hydroxychloroquine)

corticosteroids

immunosuppressives (cyclophosphamide, cyclosporine,
MTX, azathioprine)

antiinflammatory drugs

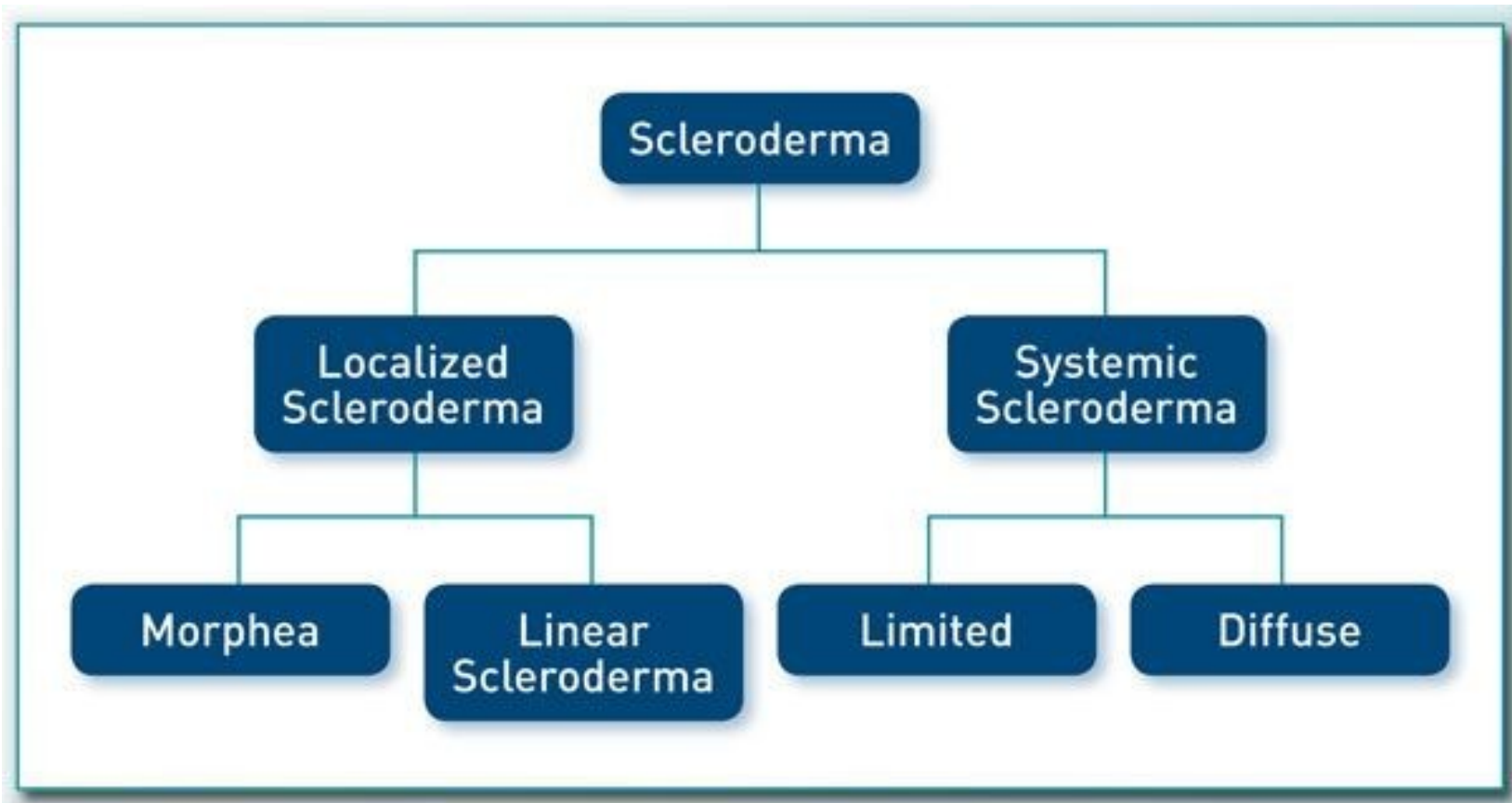
UVA, UVB sunscreens

plasmapheresis, pulse therapy etc.

Belimumab (BAFF)

Scleroderma

- vascular changes – fibroplastic factors activation
- changes in collagen synthesis
- immunological changes –
 - humoral (anti Scl70, ANA 🎱, anti centromere ACA)
 - cellular



Systemic sclerosis - scleroderma

ARA criteria:

- proximal scleroderma
- bilateral lung interstitial fibrosis
- fingertip changes DUC digital ulcerations
- sclerodactyly

other signs:

- Raynaud 's phenomenon
- esophageal changes
- renal disease
- pulmonary hypertension
- pericardial effusion



Scleroderma



CREST syndrome – limited scleroderma

- **C** alcinosis
- **R** aynaud
- **E** sophageal changes
- **S** cleroderma
- **T** eleangiectasias
- anti centromere antibody

Systemic scleroderma

Therapy:

- corticosteroids
- immunosuppressives
- antimalarials
- d-penicillamine, penicillin
- vasoactive and rheological drugs (pentoxifylline, prostavasin)
- calcium antagonists – nifedipine
- endothelin receptor antagonist – bosentan
- phosphodiesterase 5 antagonists - sildenafil
- ACE inhibitors - kidneys
- prokinetic drugs, antacids
- physiotherapy

Localized scleroderma

- morphea
- guttate
- linear
- generalized (pansclerotic morphea)
- subcutaneous – eosinophilic fasciitis
- ANA in low titers or none
- no systemic disease
- infections – late stage Lyme disease



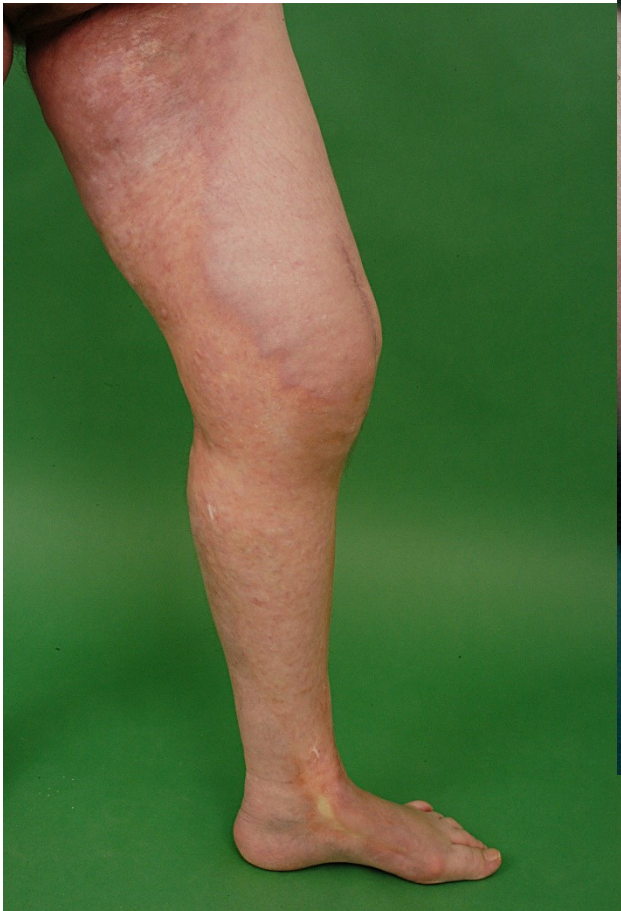
Lilac ring



Localized scleroderma



Linear scleroderma





Localized scleroderma - therapy

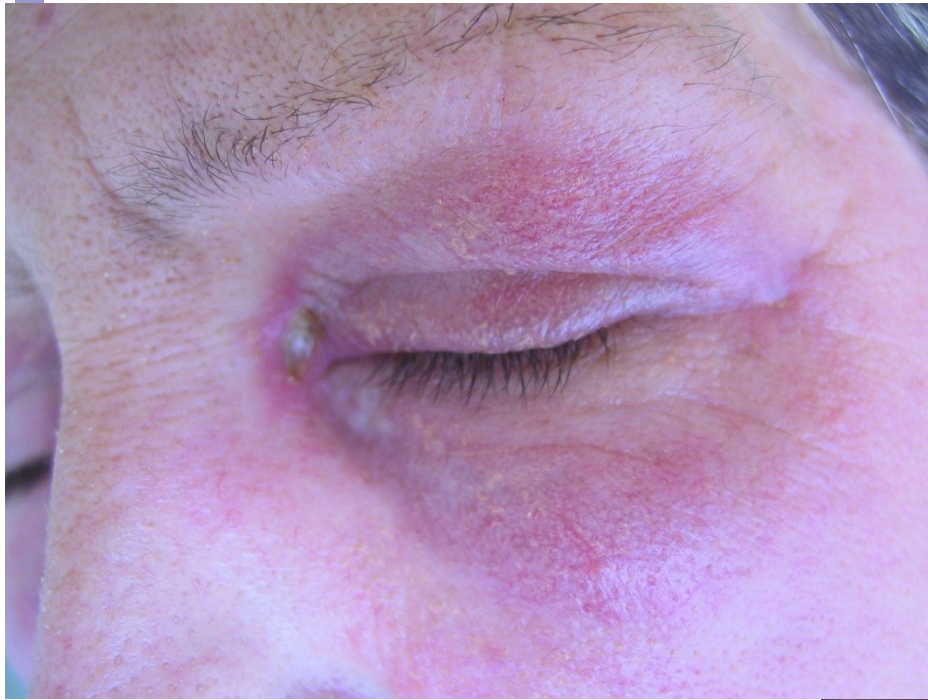
- Topical – corticosteroids, diltanoids, heparin
- Systemic- PNC
- Corticosteroids
- MTX
- Antimalarials
- UVA1

Dermatomyositis, polymyositis

- **juvenile** - association with infections
- **adult** - association with tumours (paraneoplastic)
- heliotrophic rash, Gottron's sign, poikilodermatitis, erythemas
- EMG
- ANA, anti Jo-1
- CPK, LDH, GOT, ALD, AST, ALT, myoglobin
- Histology – muscle, skin









Dermatomyositis - therapy

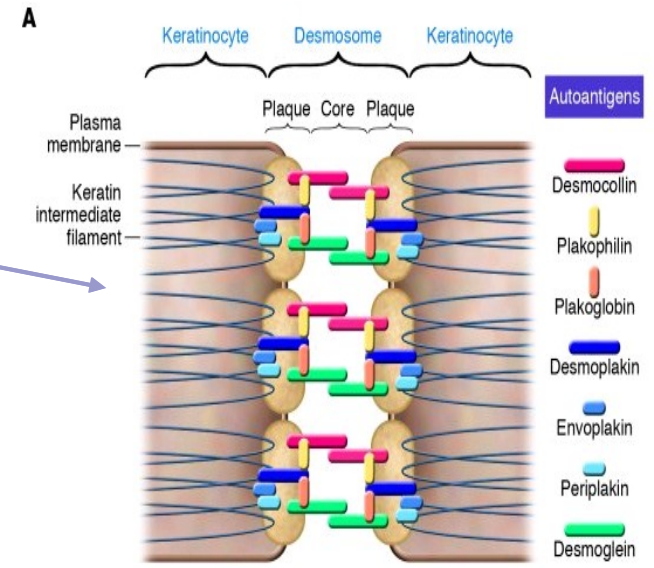
- Corticosteroids
- Immunosuppressives - MTX, azathioprine, cyclosporine
- Antimalarials
- IVIG



Autoimmune bullous diseases

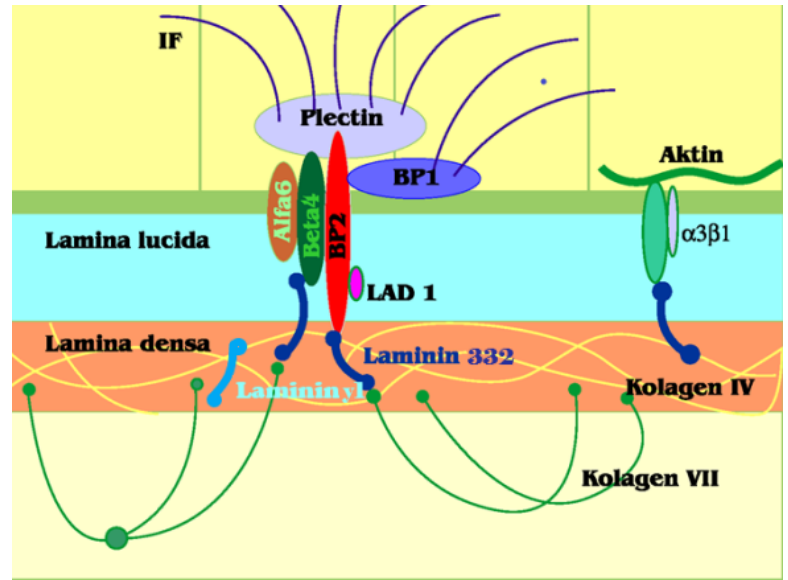
- Rare diseases, severe forms are lethal
- Skin and mucous membranes
- Two groups according to the level of cleavage
- Intraepidermal – Pemphigus and variants
- Subepidermal – pemphigoid group, DHD, EBA
- Autoantibodies IgG/IgA against antigens in the epidermis and junctional zone

Pemphigus - desmosomes



B

Pemphigoid - hemidesmosomes

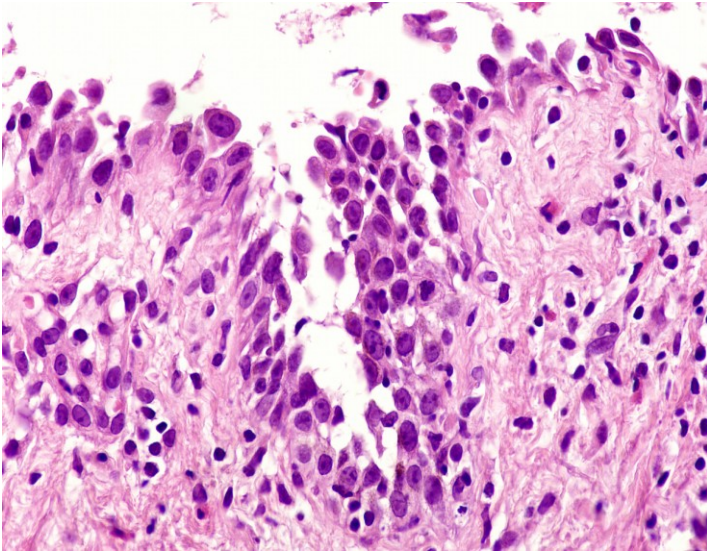


Diagnostics – Tzanck test, histology, immunofluorescence direct & indirect, ELISA, immunoblot

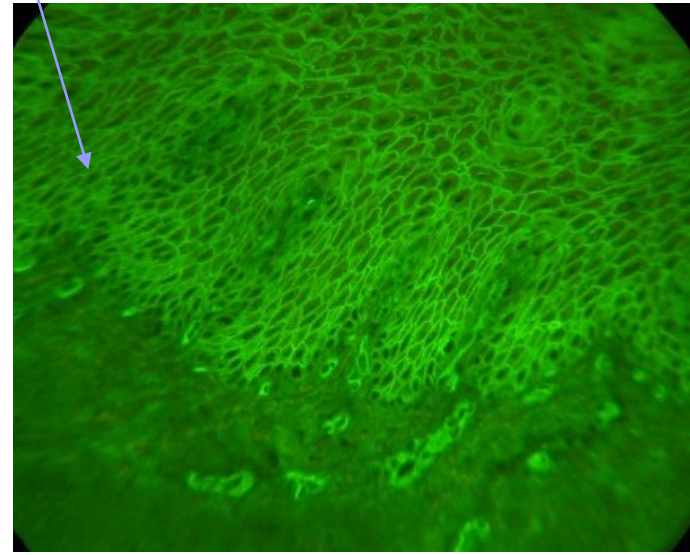
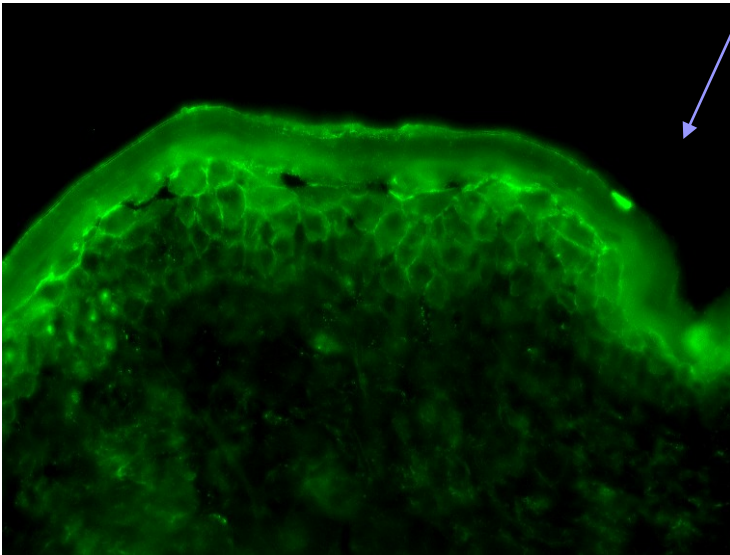
Pemphigus

- **Suprabasal** (Dsg 3,1, IgG)
 - pemphigus vulgaris
 - vegetans
- **Superficial** (Dsg 1, IgG)
 - pemphigus foliaceus
 - fogo selvagem (Brazil)
 - drug induced (thiols, phenols, penicilamin, captopril)
 - pemphigus erythematosus Senear Usher –
 - fotosensitivity, ANA antibodies
- **Paraneoplastic Pemphigus** – lichenoid, EEM features, bronchiolitis
- **IgA pemphigus**

Pemphigus

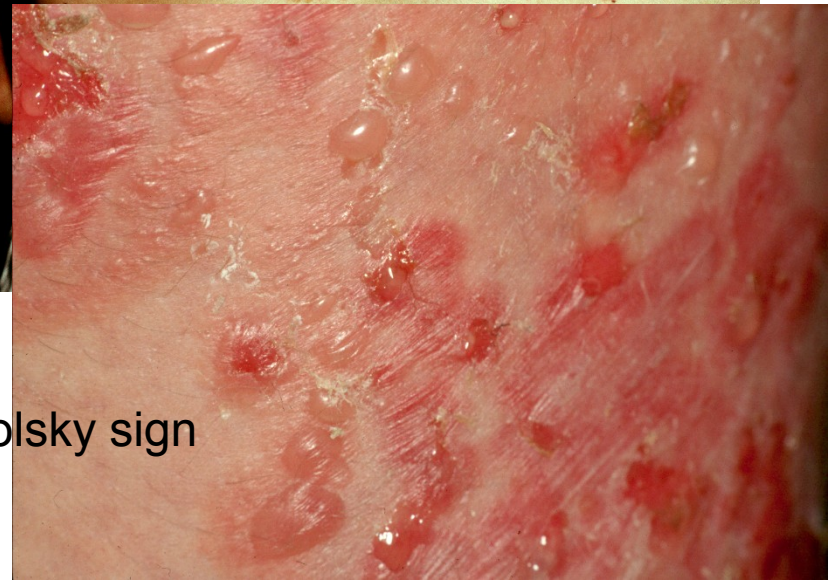


- Suprabasal acantholysis H+E
- Direct IF – pemphigus foliaceus
- Anti IgG/C3
- Indirect IF – monkey esophagus
- ICS anti IgG



Pemphigus vulgaris

- Rare bullous disorder with autoantibody-induced intraepidermal blisters (desmosomes - acantholysis)
- Incidence 5/ 1 million inhabitants
- Chronic disease, can be lethal
- Average age 30-60 years
- Etiopathogenesis
- Genetic factors (HLADR4)
- Drug induced, infections, phenols
- Antibodies against desmoglein 1,3

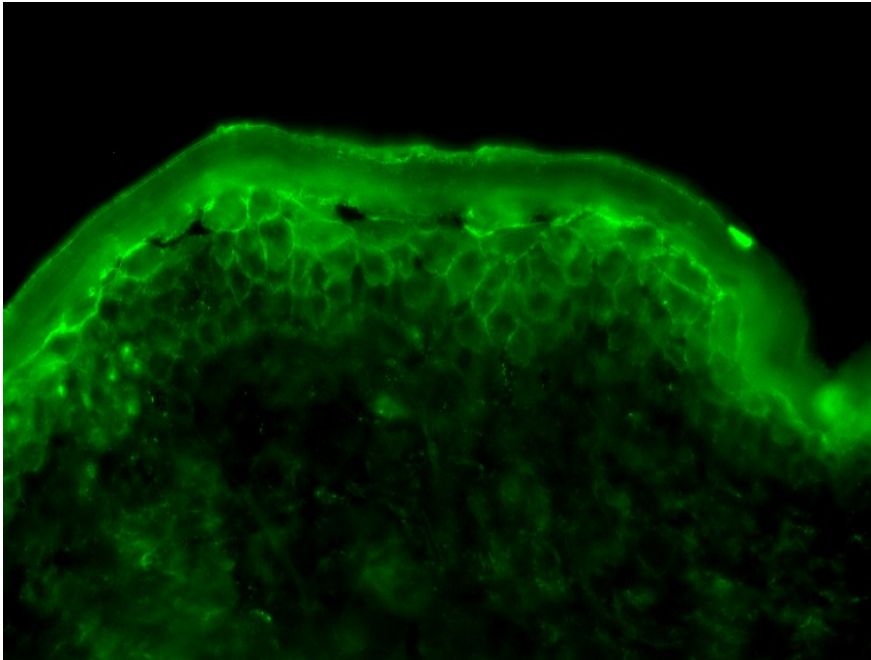


Nikolsky sign

Pemphigus vegetans



Pemphigus foliaceus

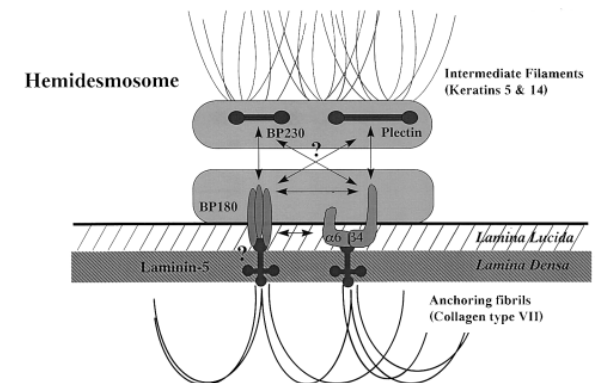


Pemphigus therapy

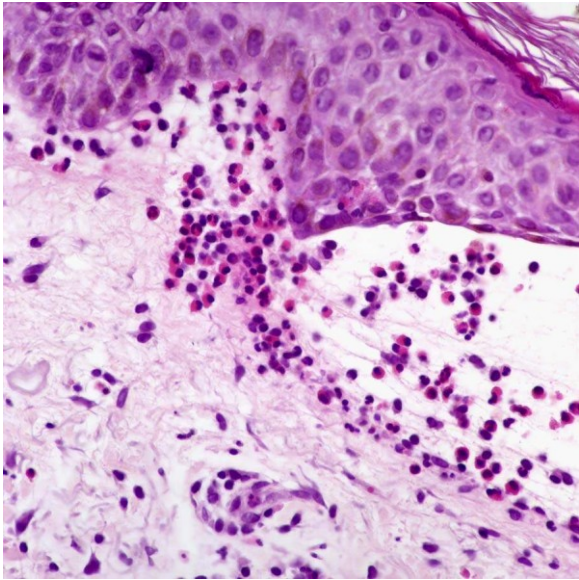
- Corticosteroids (Prednisone 1-1,5mg/kg/d)
- ...taper to 15 -20 mg/d
- Immunosuppressives - corticosteroid sparing agents
- Mycophenolate mofetil 2g/d
- Azathioprine – cave TPMT deficiency
- MTX 10-20mg per week
(Cyclophosphamide – toxic)
-
- Rituximab anti CD20 antibody –risk of infections
- Dapsone
- IVIG 1-2g/kg pulse every 6 weeks
- Immunoabsorption IgG
- Long term therapy, 2 years minimum, often life long

Subepidermal autoimmune bullous dermatoses

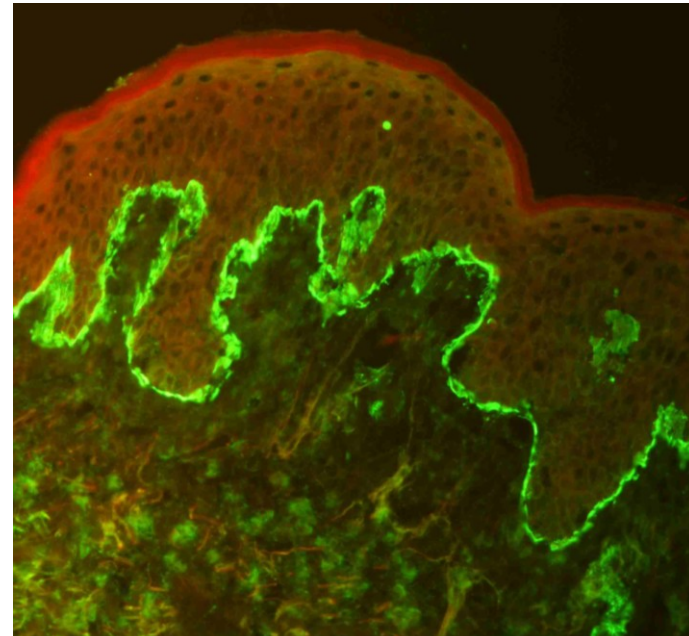
- Rare disorders with autoantibody-induced subepidermal blisters (basement membrane – hemidesmosomes)
- Bullous Pemphigoid - BP
- Pemphigoid gestations (variant of BP)
- Cicatricial Pemphigoid – mucous membrane pemphigoid
- Epidermolysis bullosa acquisita (association diabetes, bowel disease)
- IgA linear dermatosis – typically childhood, in adults drug induced – vankomycin
- Dermatitis herpetiformis Duhring



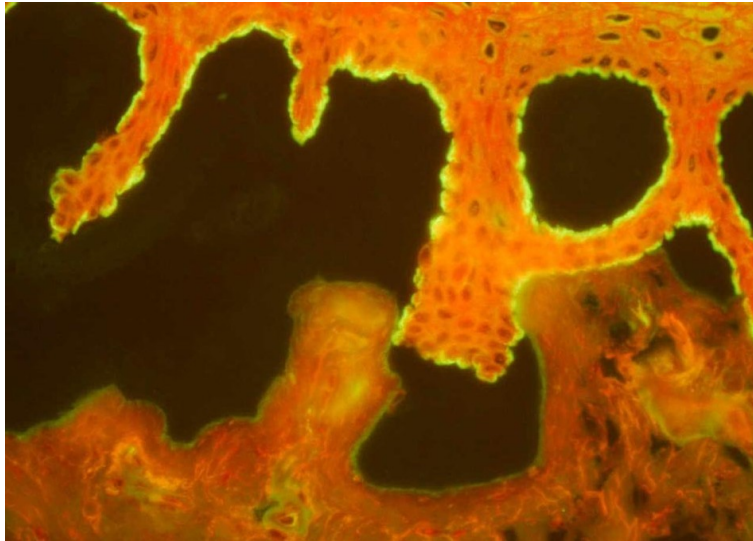
BP – subepidermal blister - eosinophils



Direct IF line on BM IgG/C3



Salt split skin blister roof in BP



Oesophagus,
Dsg1

Oesophagus: detection of antibodies against prickle-cell desmosomes (pemphigus) and basal lamina (pemphigoid).



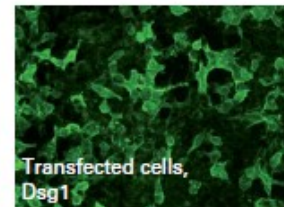
Salt-split skin,
BP180

Salt-split skin: differentiation of autoantibodies against antigens of the epidermal (BP180, BP230) and dermal (collagen type VII, laminin 332, p200) sides of the skin.

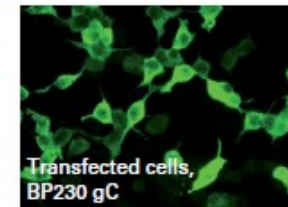


Bladder mucosa,
plakins

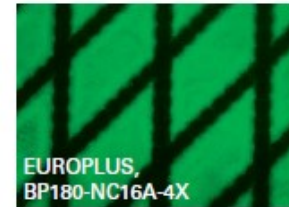
Bladder mucosa: detection of autoantibodies against plakins (paraneoplastic pemphigus).



Transfected cells,
Dsg1



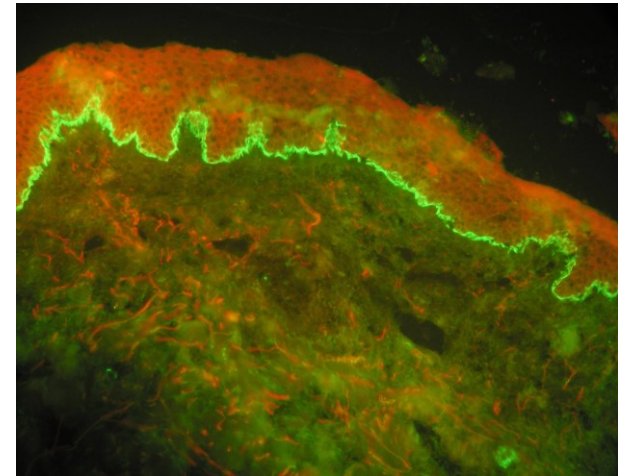
Transfected cells,
BP230 gC



EUROPLUS,
BP180-NC16A-4X

Pemphigoid bullosus

- Elder people – over 70 years
- Many concomitant diseases
- Paraneoplastic disease (13%) prostate, breast cancer
- Drug induced (PNC, enalapril, furosemid, gliptins)
- Neurodegenerative diseases!
- Cerebral stroke + paresis, Parkinson disease, dementia
- (BP expression in neuronal tissue)
- 1 year survival 60% patients



BP tense hemorrhagic blisters, infiltrated skin
Tissue and blood eosinophilia, strong pruritus





BP in paretic limb

Urticarial lesions in BP



Pemphigoid bullosus therapy

- Corticosteroids (Prednisone 0,5-0,7mg/kg)

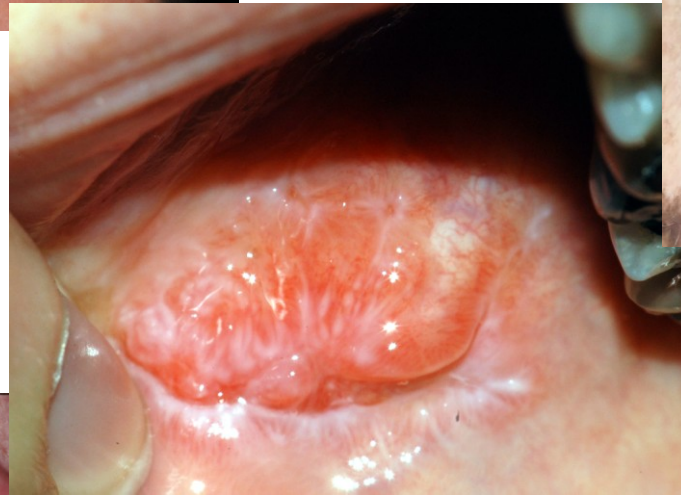
or

- Potent topical corticosteroids (clobetasol)
- Immunosuppressives (azathioprine, methotrexate, mycophenolate)
- Dapsone
- TTC – antiinflammatory effect

Cicatricial Pemphigoid MMP

- Incidence 1/million inhabitants
- 60 years of age
- Paraneoplasia (stomach cancer), topicals for glaucoma
- Mucose membranes —————> stenosis, scarring
- Conjunctiva - entropion, symblepharon, trichiasis —————>
blindness
- Pharynx, larynx,
- Genital area
- Skin – minor disease Brunsting Perry Pemphigoid

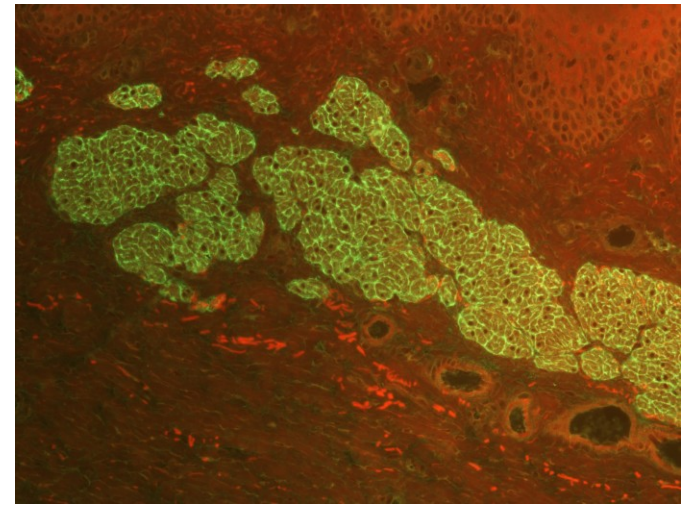
- Therapy – as in pemphigus



Pictures from Praktická dermatologie

Dermatitis herpetiformis Duhring

- rare disease – incidence 3/1 million inhabitants
- gluten sensitive enteropathy – coeliacia
- IgA antibodies against endomysium (tissue transglutaminase)
- cross reaction with eTG on reticulin fibers in dermal papillae
- sensitivity to gluten, iodine



Dermatitis herpetiformis Duhring

- Children rarely
- Young adults
- HLA DQ2, DQ8 association
- Predilection sites – elbows, knees, sacrum, hairline

Therapy

- Gluten free diet
- Dapsone
- Topical corticosteroids

