Connective tissue disorders

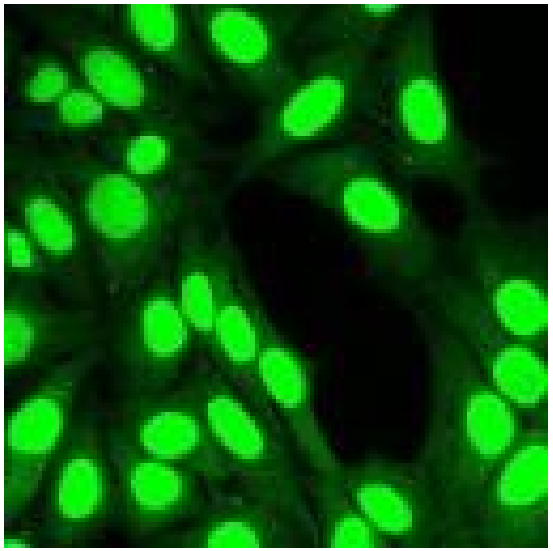
- Lupus erythematosus
- Scleroderma
- Dermatomyositis, polymyositis
- Overlap syndromes

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.)



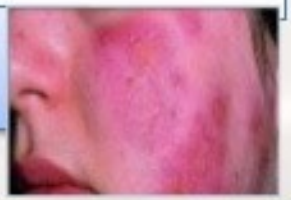
SYSTEMIC LUPUS ERYTHEMATOSUS

SLICC Diagnostic Criteria :

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

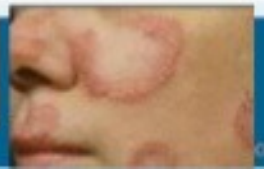
- Occurs after sun exposure; followed by systemic manifestatons within few weeks
- Localised form: malar rash
- Generalised form: can involve whole body; systemic manifestations are present

ACUTE CLE

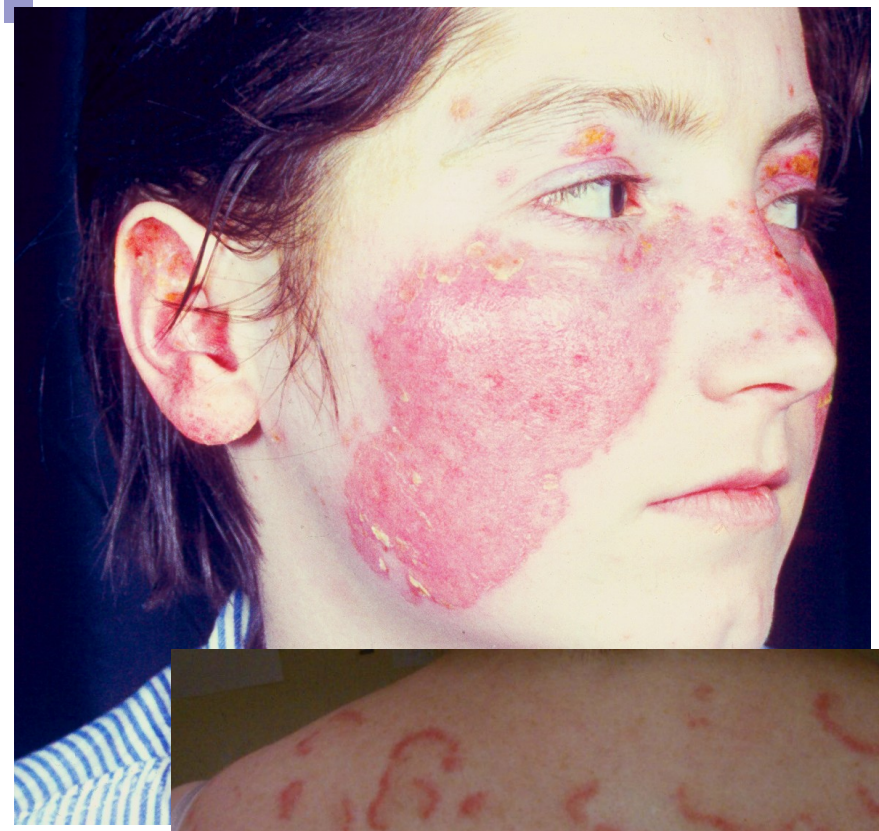


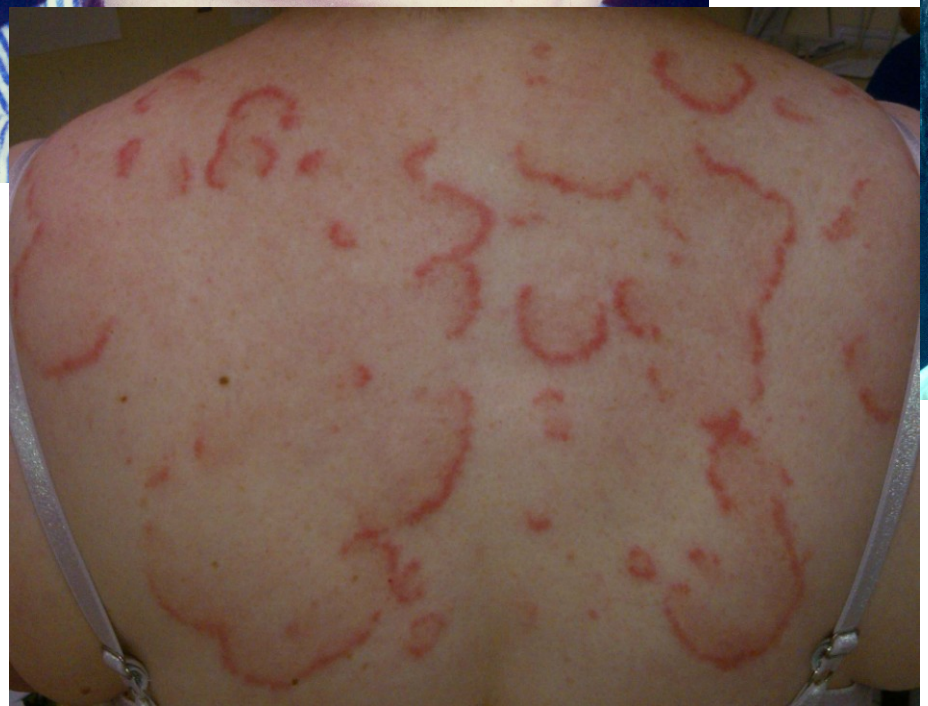
- Subtypes include:
  1.DLE(localised or generalised)
  2.Hypertrophic DLE
  3.Lupus profundus
  4.Mucosal LE
  5.Chilblain lupus

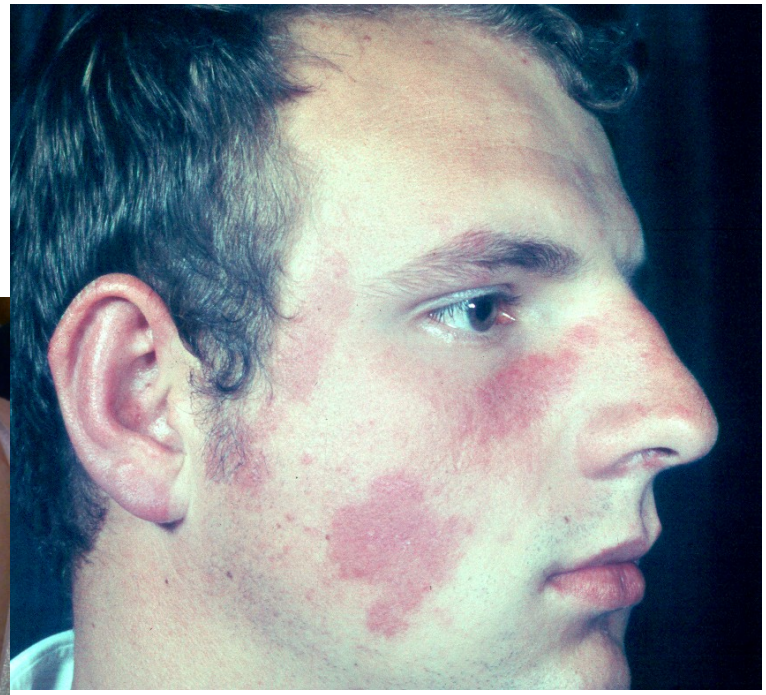
CHRONIC CLE



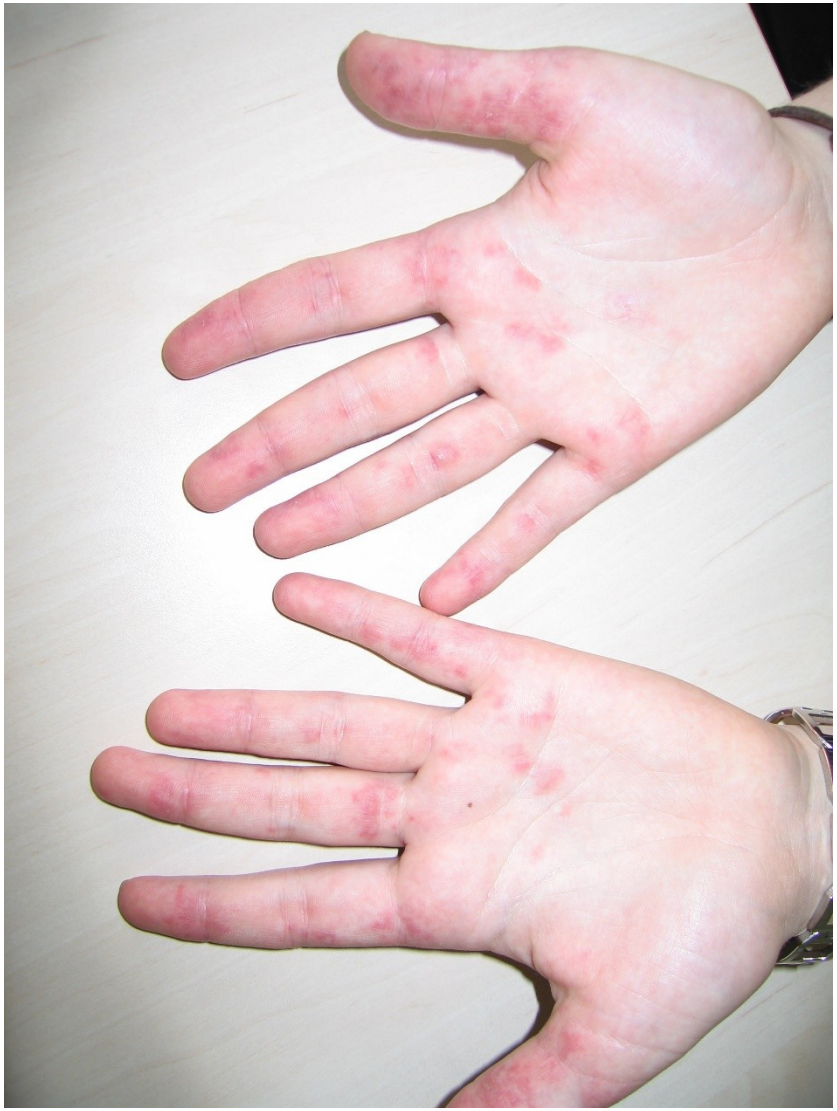
(SLICC - SLE international cooperating clinics group)

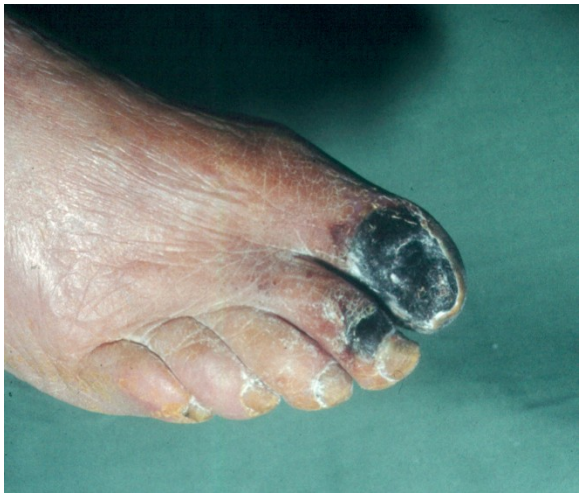


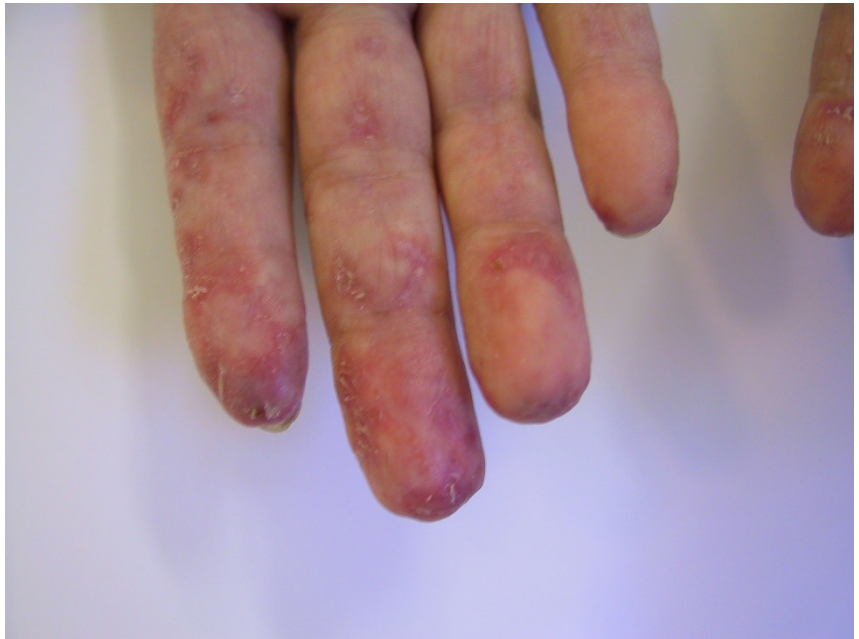




SLE

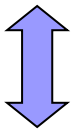




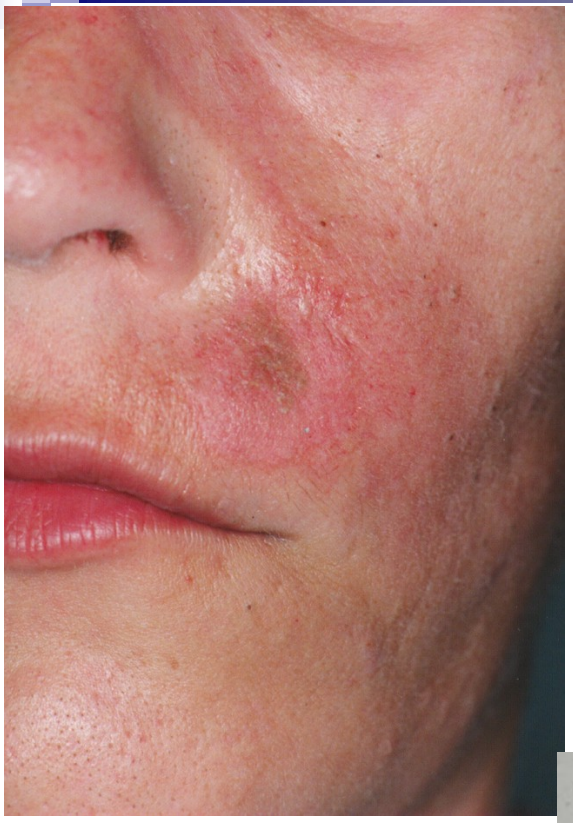


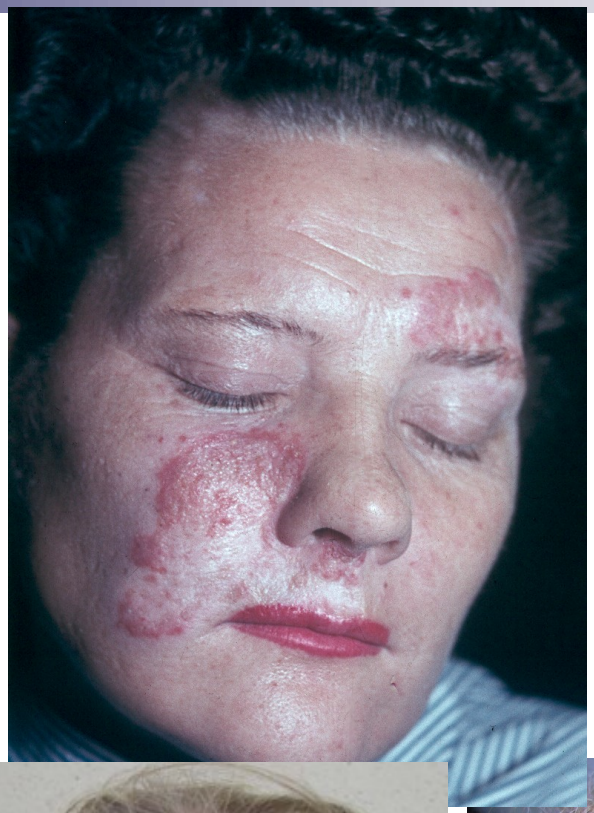
Chronic cutaneous lupus erythematosus - CCLE

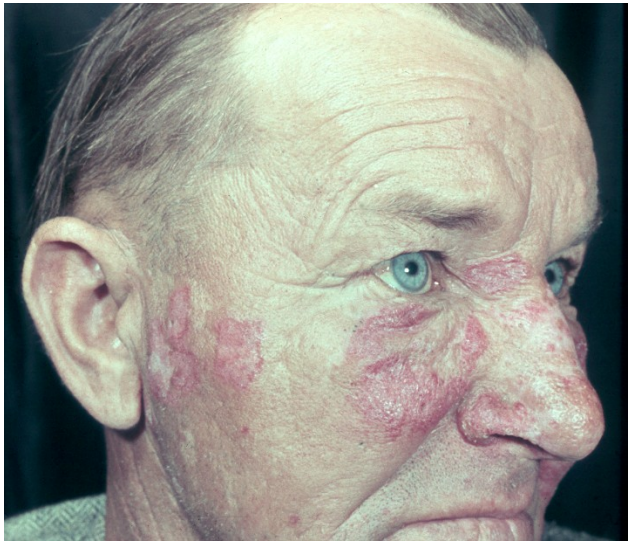
- discoid lesions – CDE –scarring -lupus
- photosensitivity – sun exposed areas
- hypertrophic lesions –lupus tumidus - rare
- lupus panniculitis
- ANA low titers or none (≤1:160)
- no systemic disease

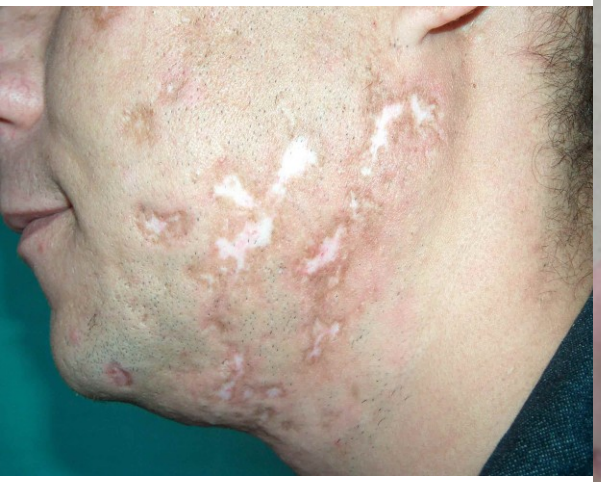


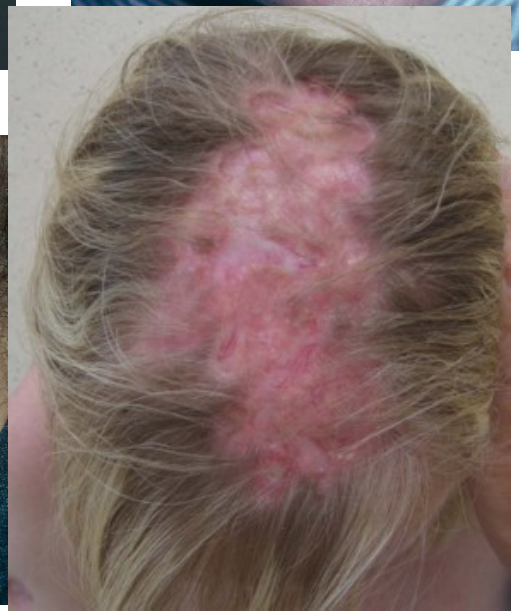
- symptom of systemic disease (30%)

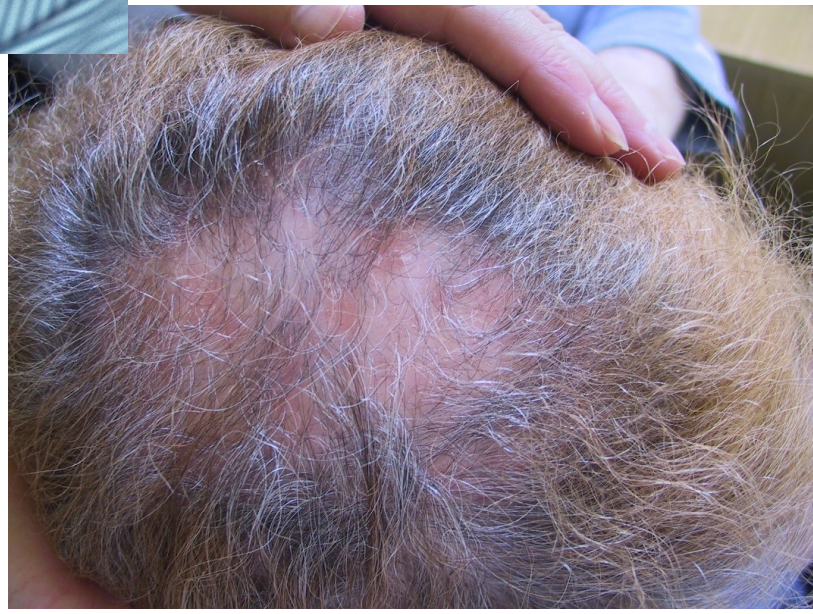




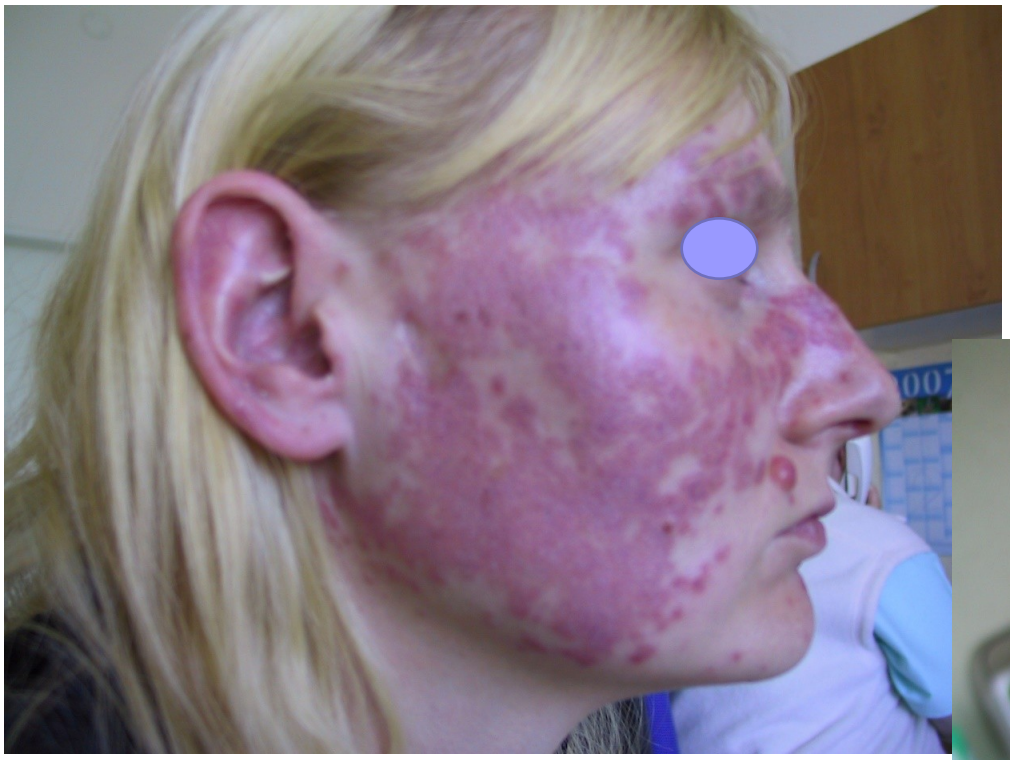


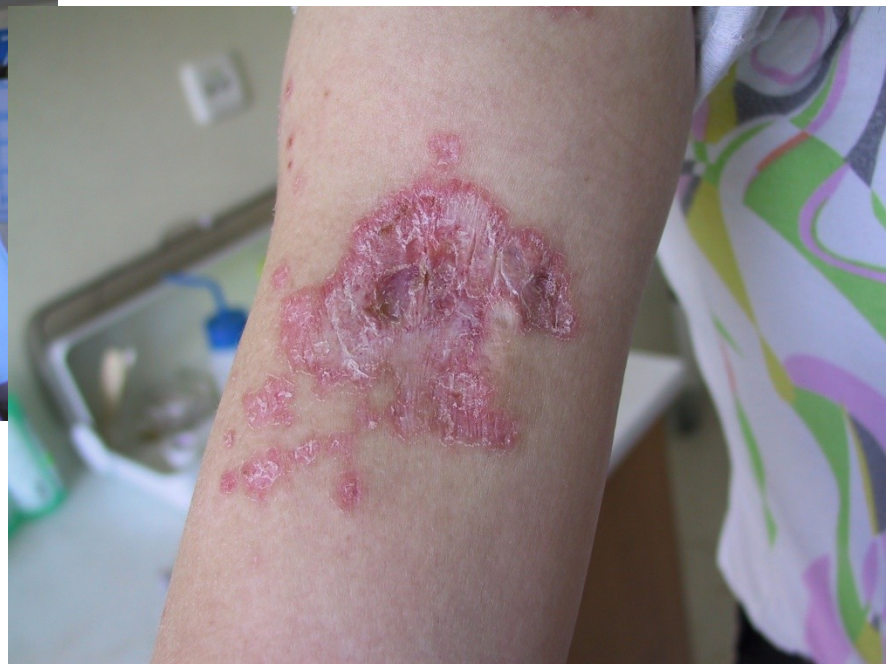




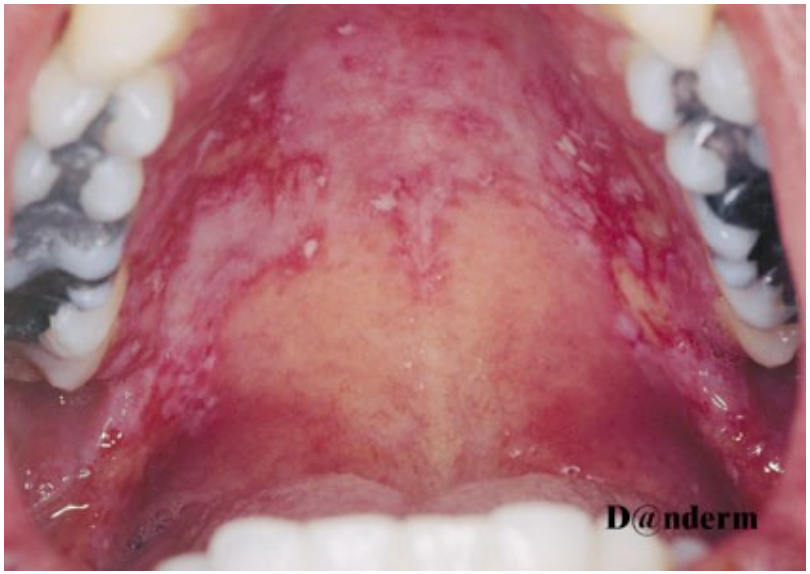


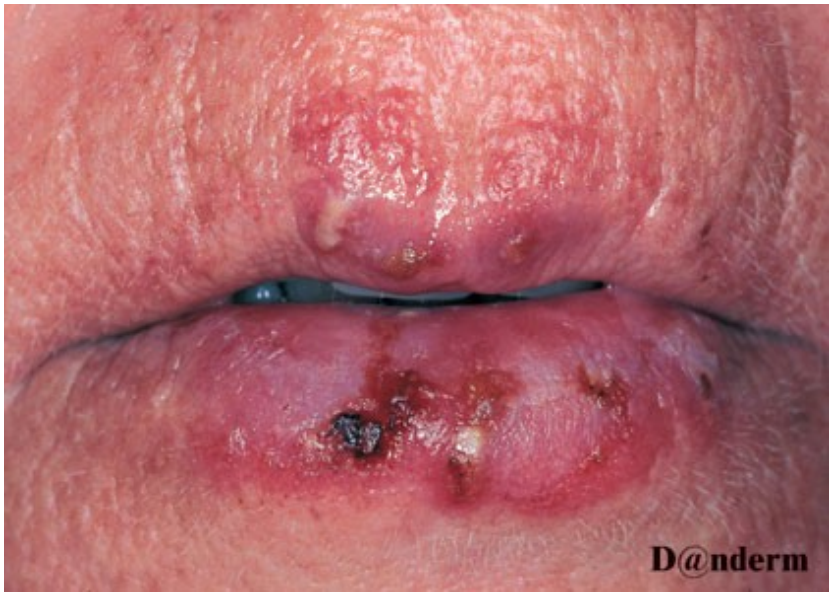
Lupus panniculitis





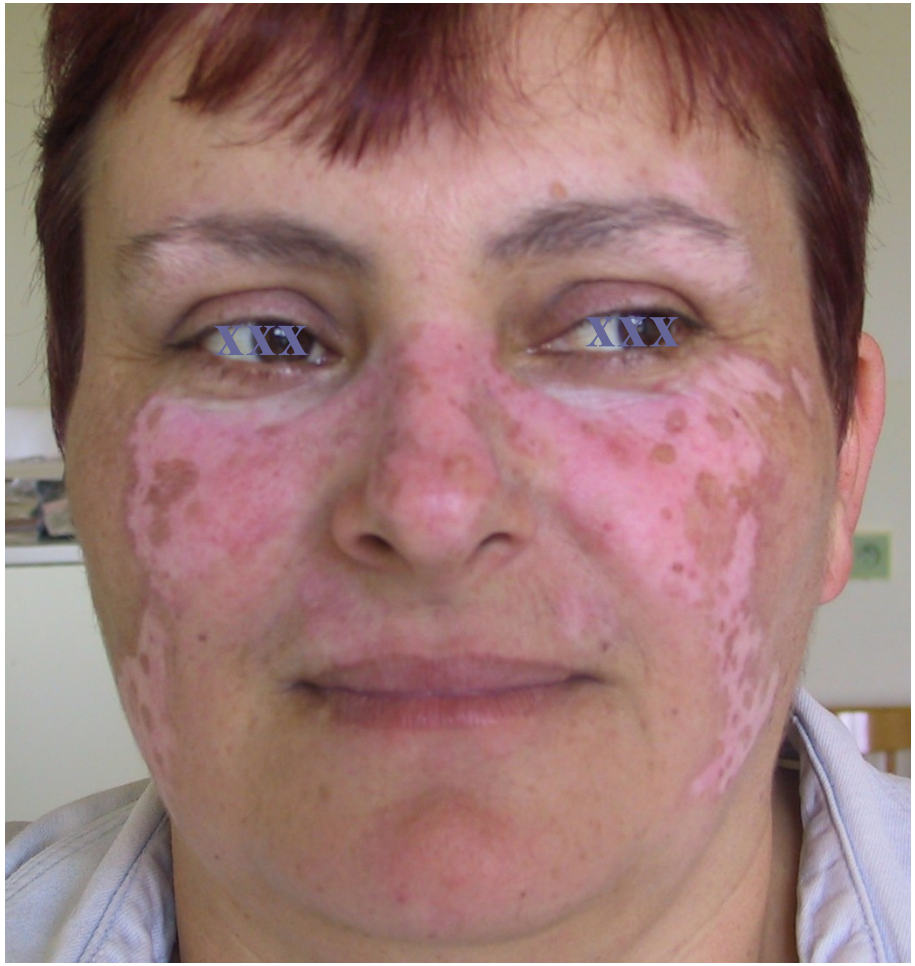
CDE – oral and lip involvement

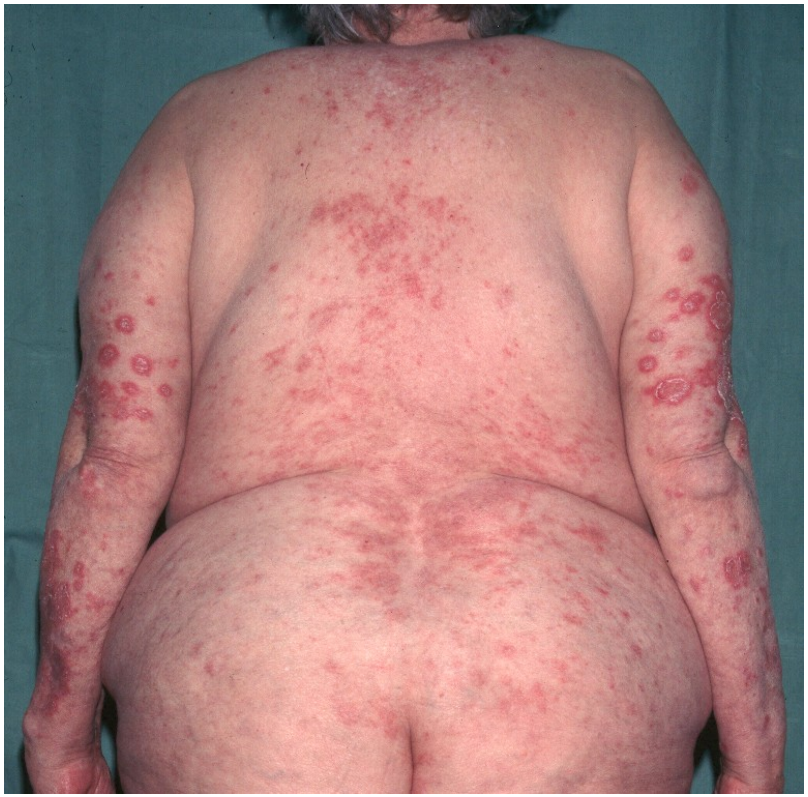


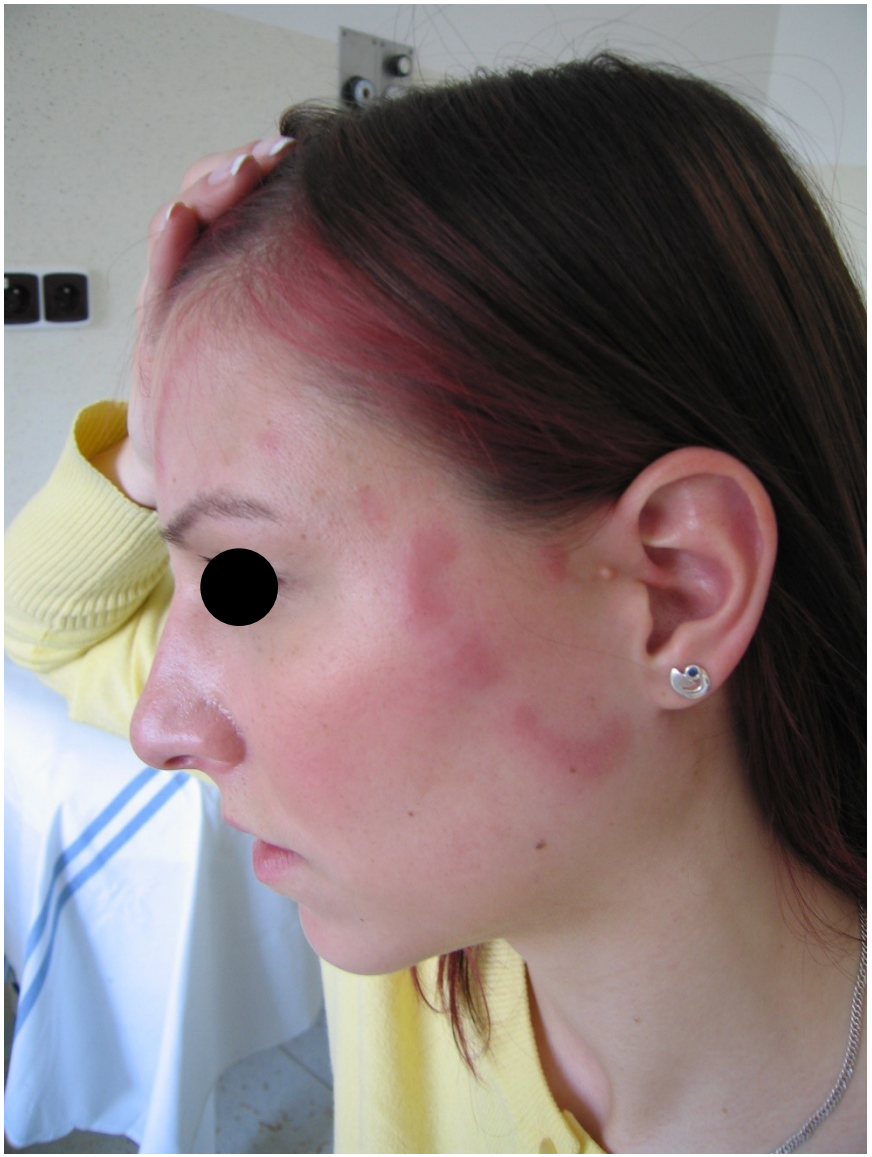


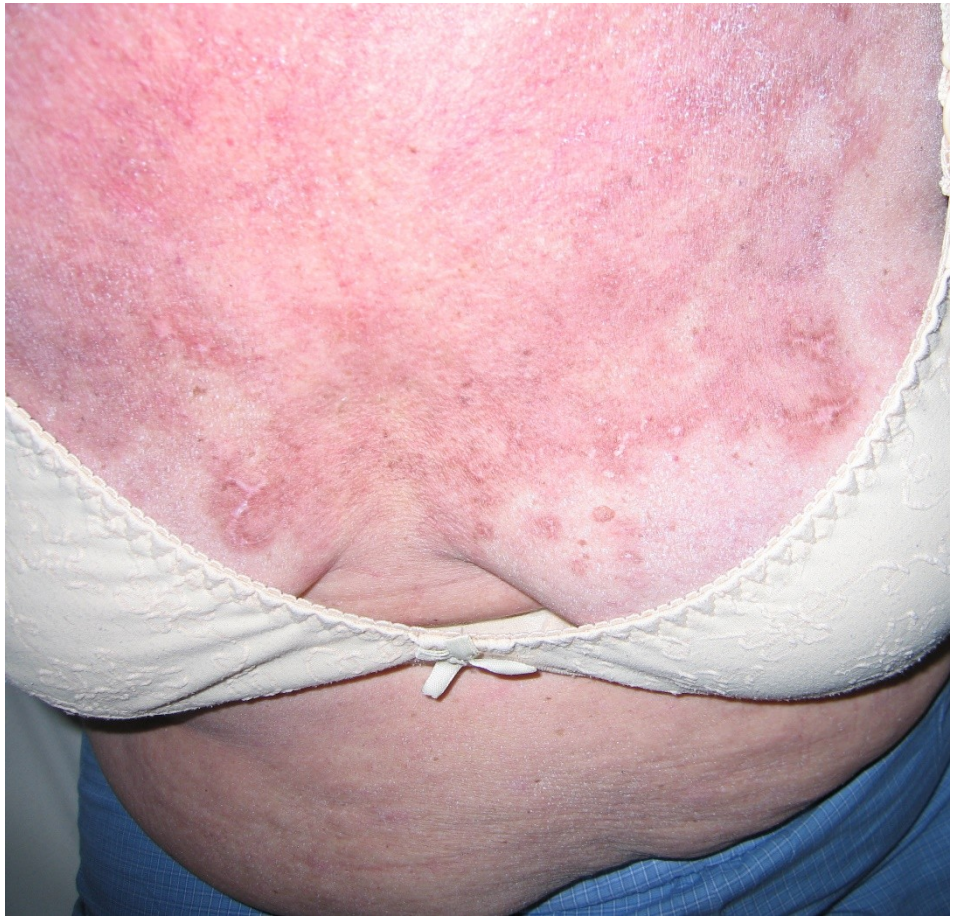
Subacute cutaneous lupus erythematosus - SCLE

- 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 (hydroxychlorochine)

corticosteroids

immunosuppresives (cyclophosphamide, cyclosporine, MTX, azathioprine)

antiinflammatory drugs

UVA, UVB sunscreens

plasmapheresis, pulse therapy etc.

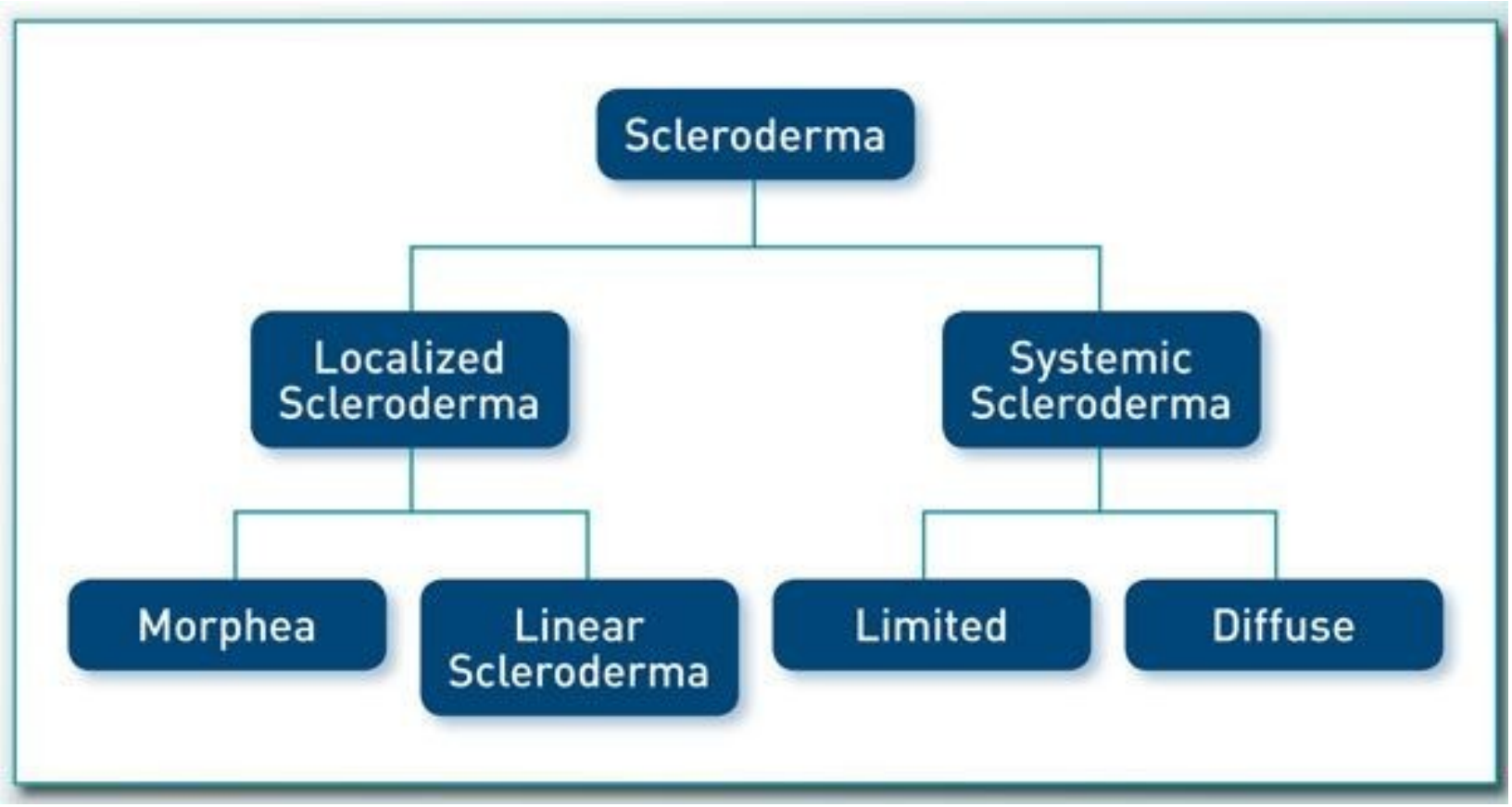
Belimumab (BAFF)

Scleroderma

- vascular changes – fibroplastic factors activation
- changes in collagen synthesis
- immunological changes –

  humoral (anti Scl70, ANA  , anti centromere ACA)

  cellular


Scleroderma
Localized Scleroderma
Systemic Scleroderma
Morphea
Linear Scleroderma
Limited
Diffuse

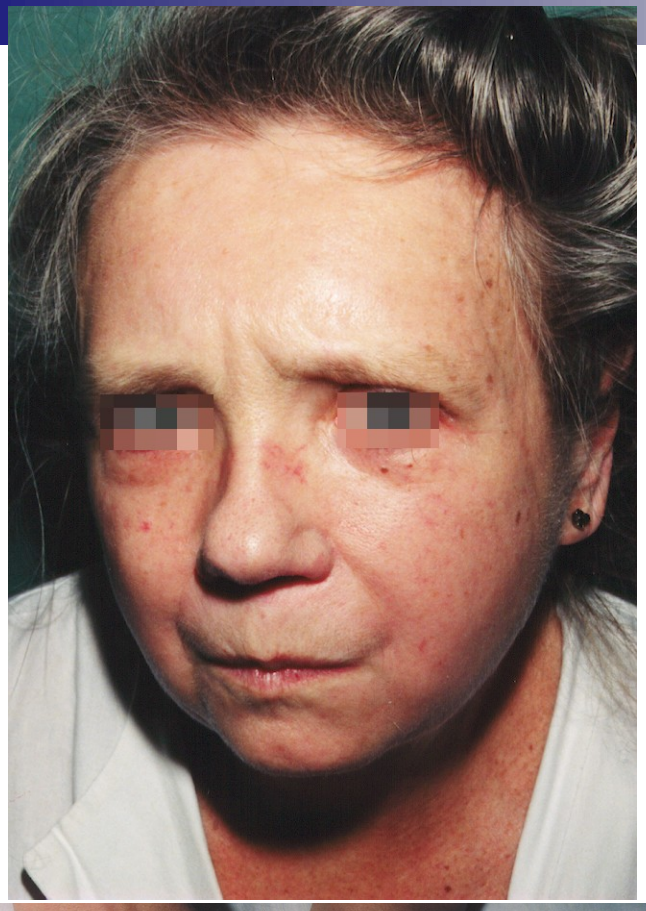
Systemic sclerosis - scleroderma

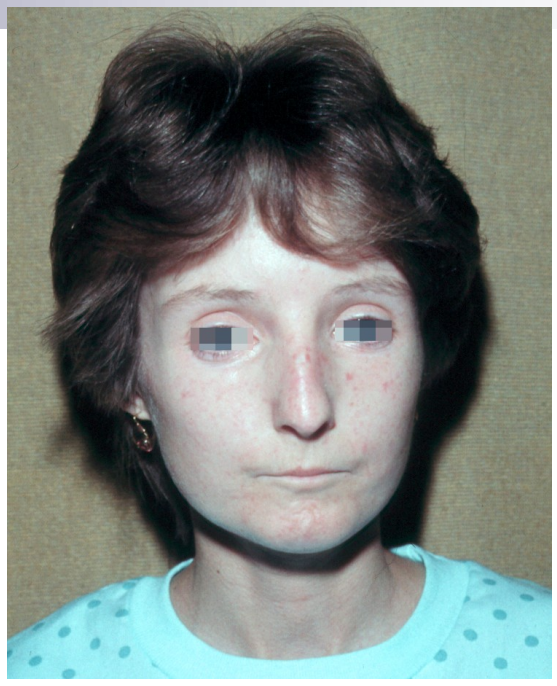
ARA criteria:

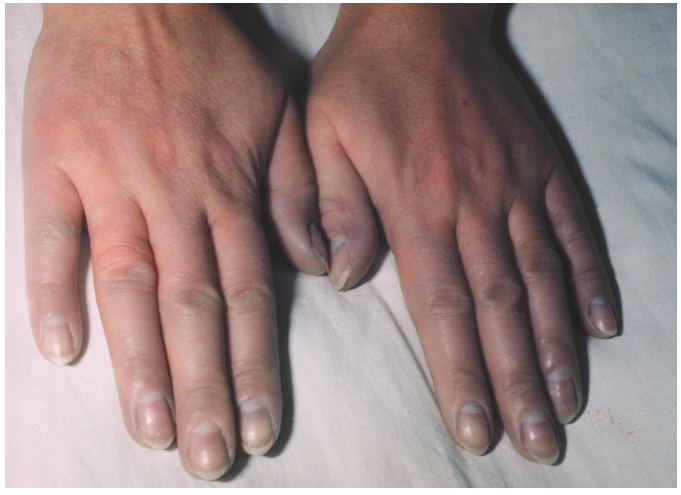
- proximal scleroderma
- bilateral lung interstitial fibrosis
- fingertip changes DUC digital ulcerations
- sclerodactyly

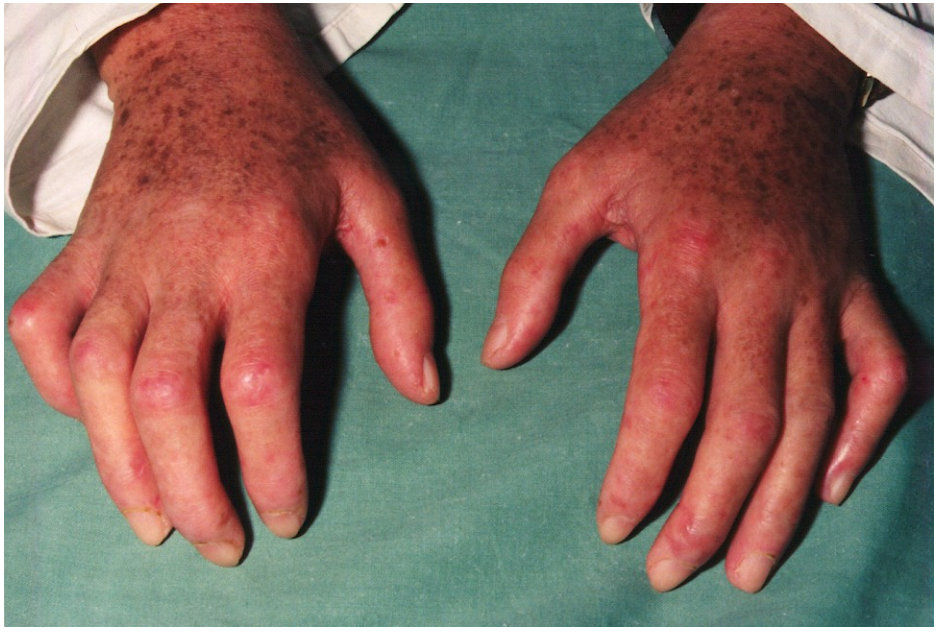
other signs:

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

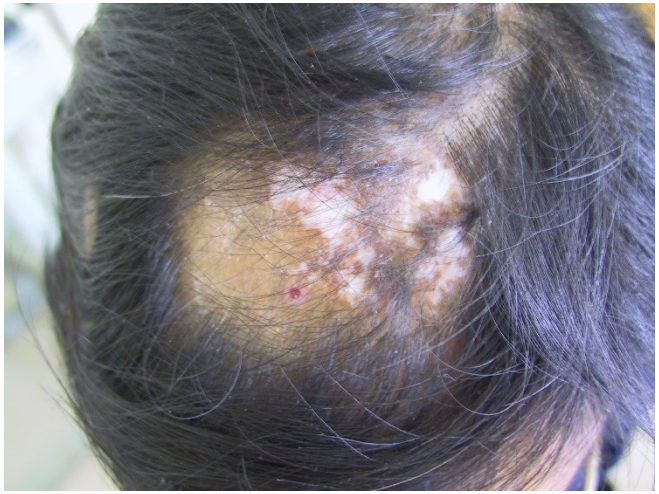


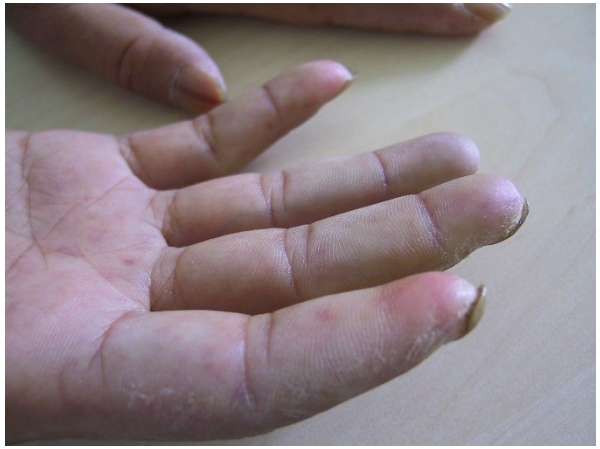


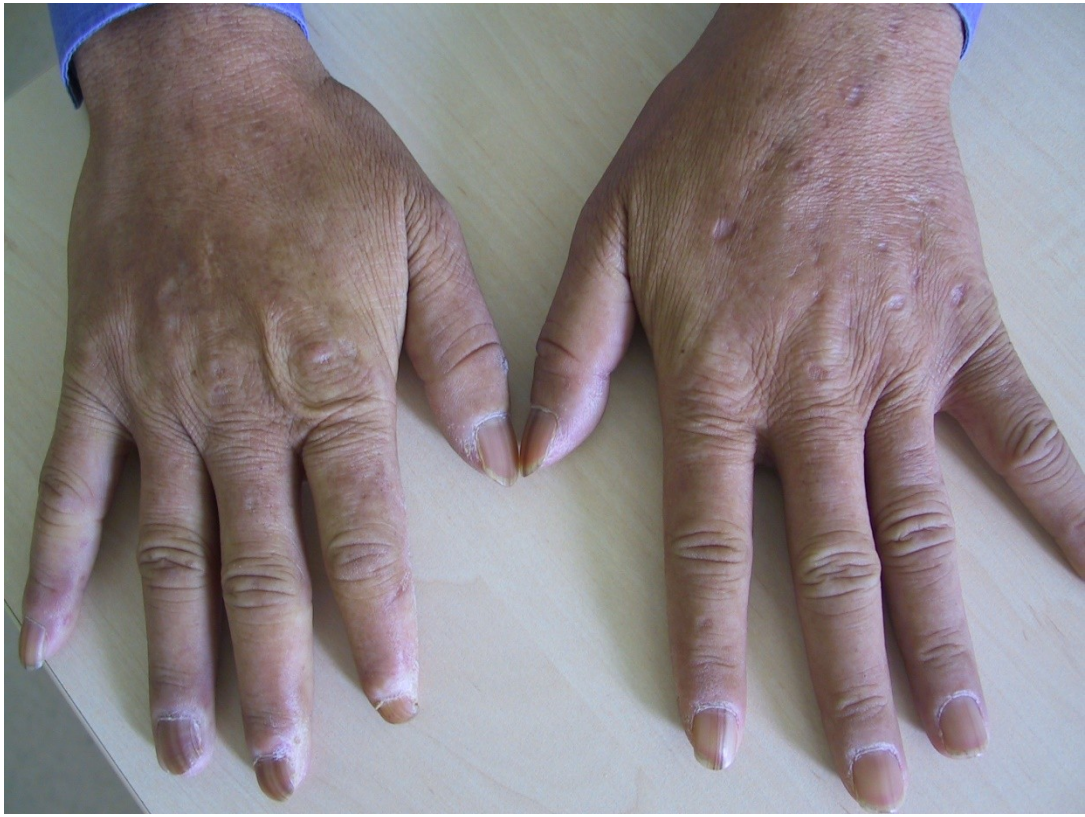




Scleroderma







CREST syndrome – limited scleroderma

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

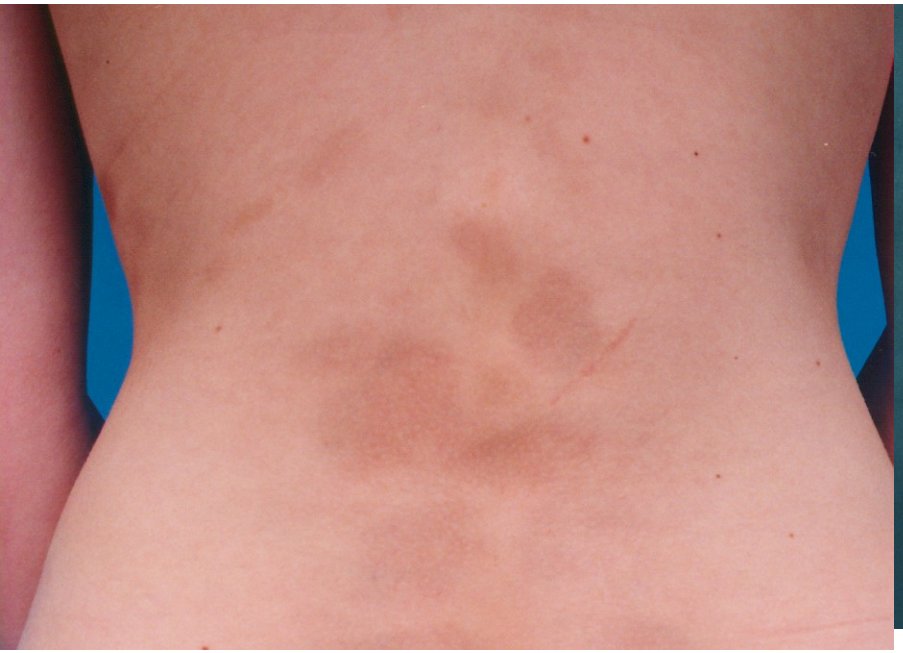
Systemic scleroderma

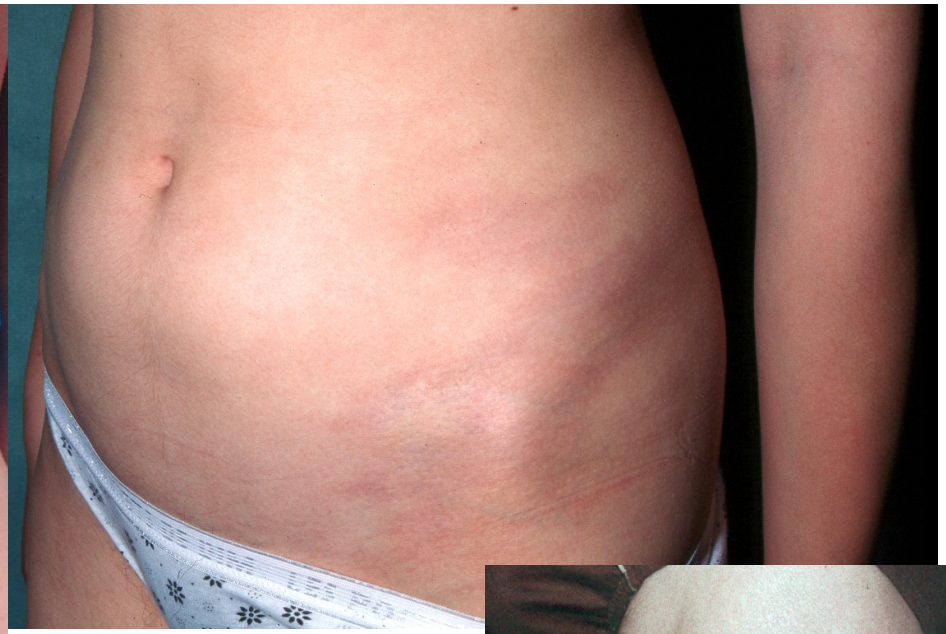
Therapy:

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

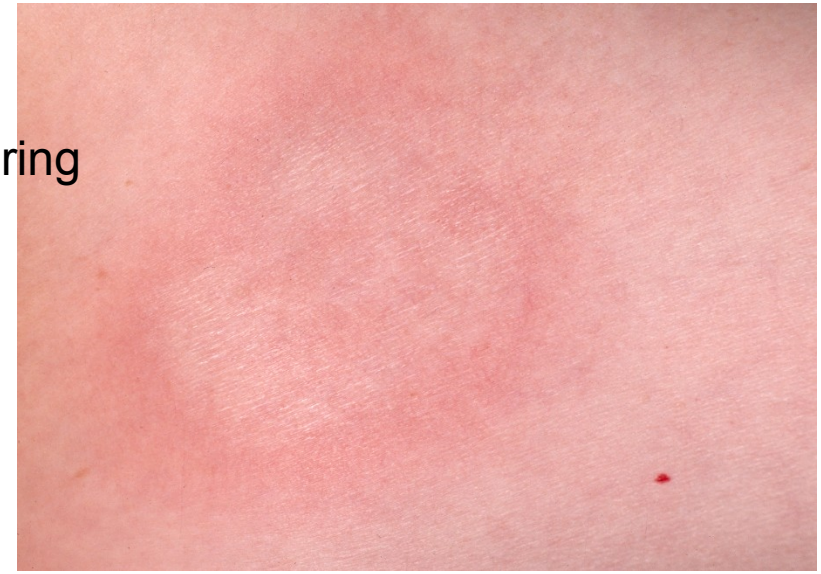
Localized scleroderma

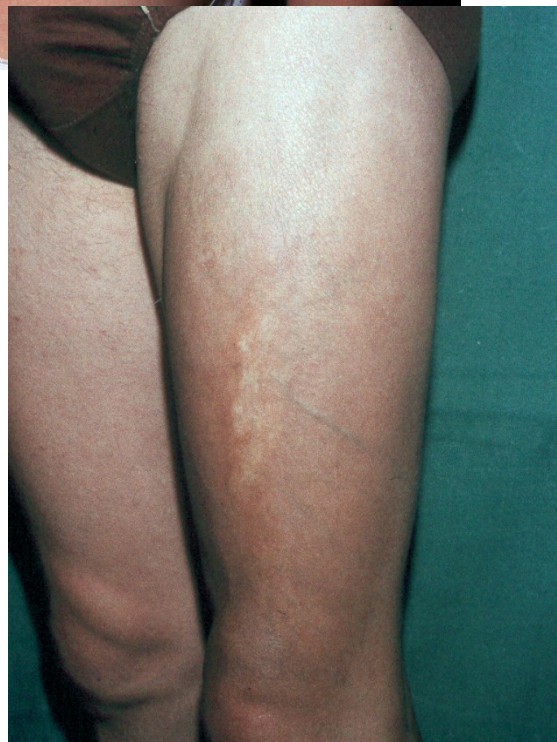
- morphea
- guttate
- linear
- generalized (pansclerotic morphea)
- subcutaneous – eosinophilic fasciitis
- ANA in low titers or none
- no systemic disease
- infections – late stage Lyme disease



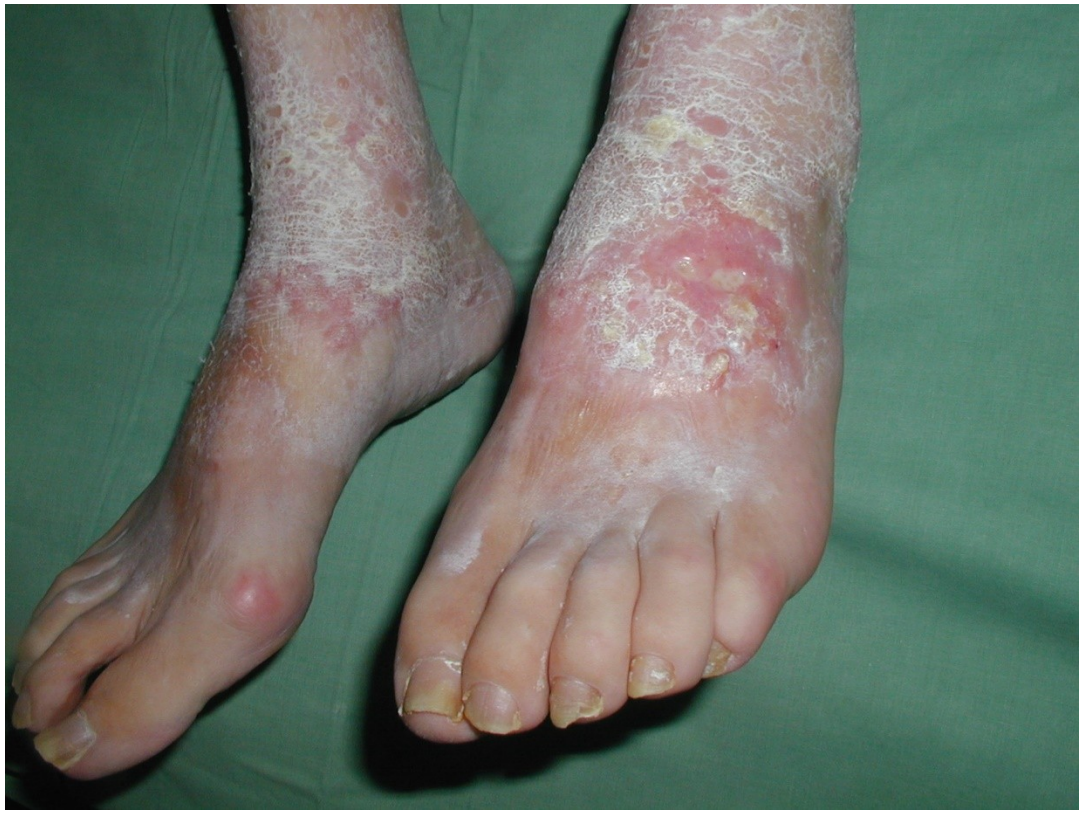


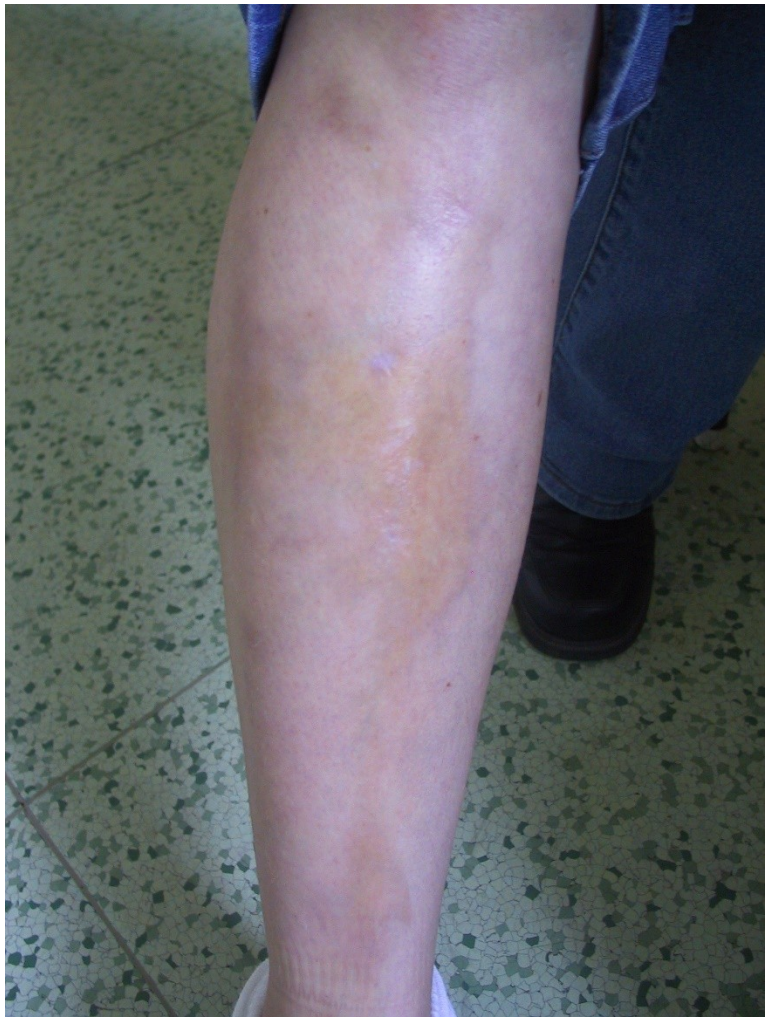
Lilac ring



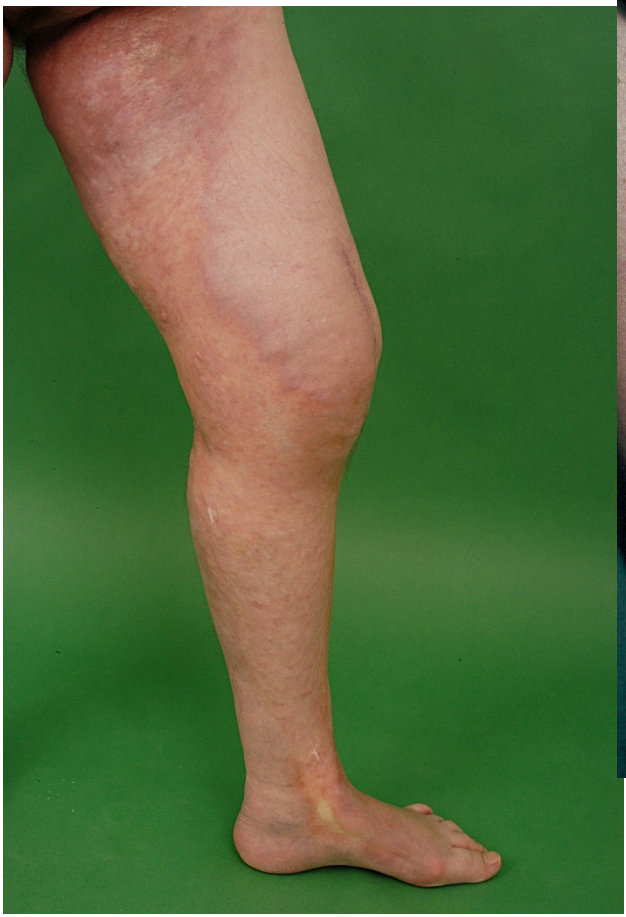


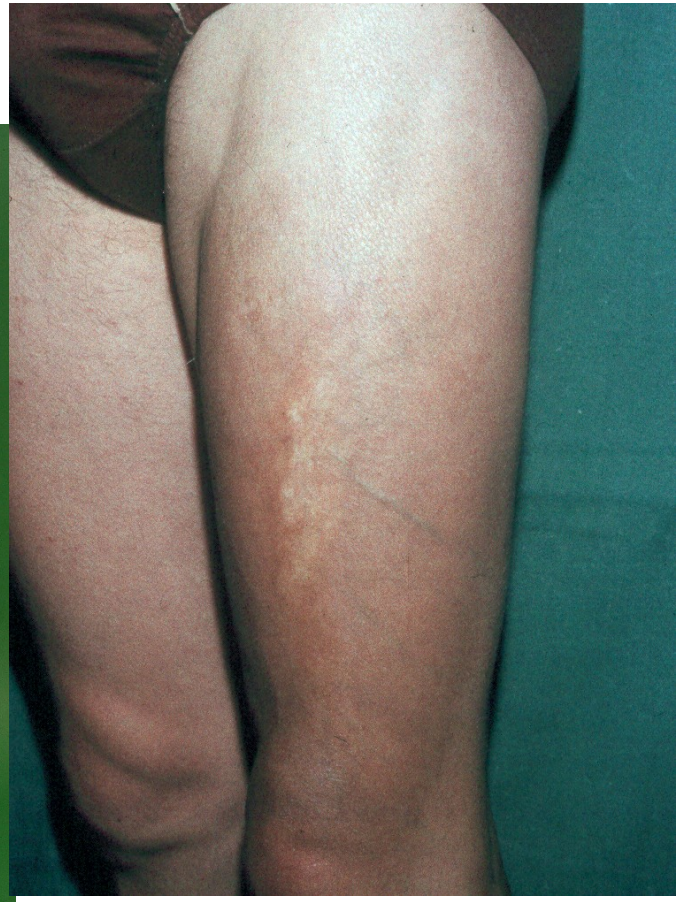
Localized scleroderma

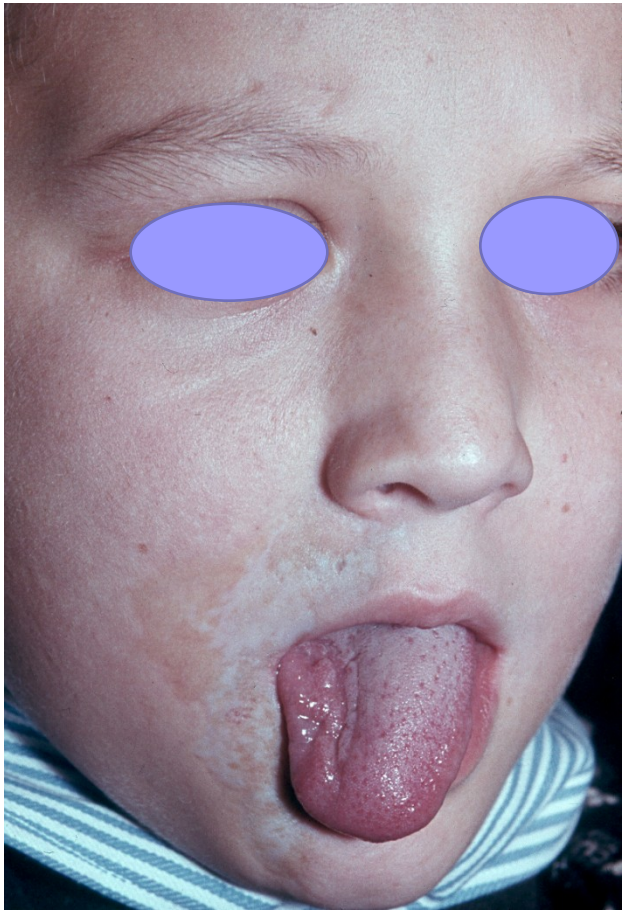




Linear scleroderma





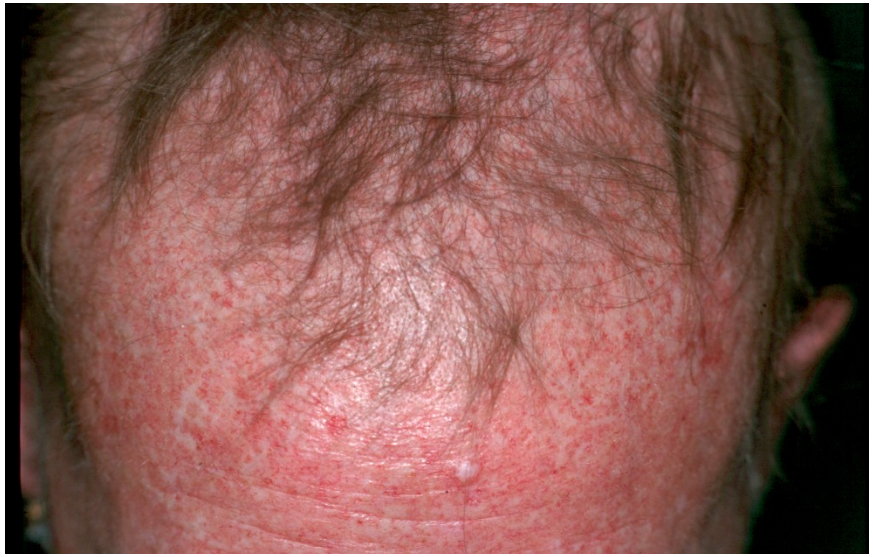


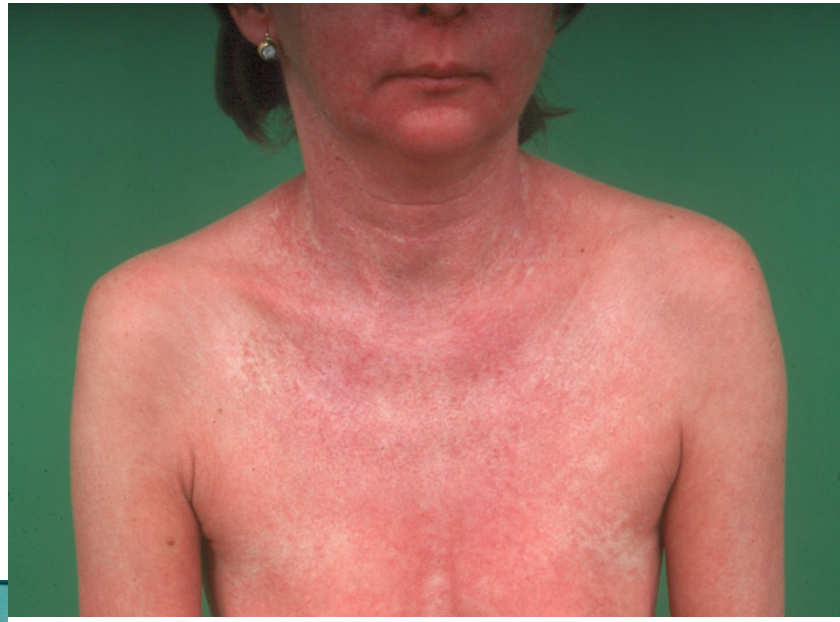
Localized scleroderma - therapy

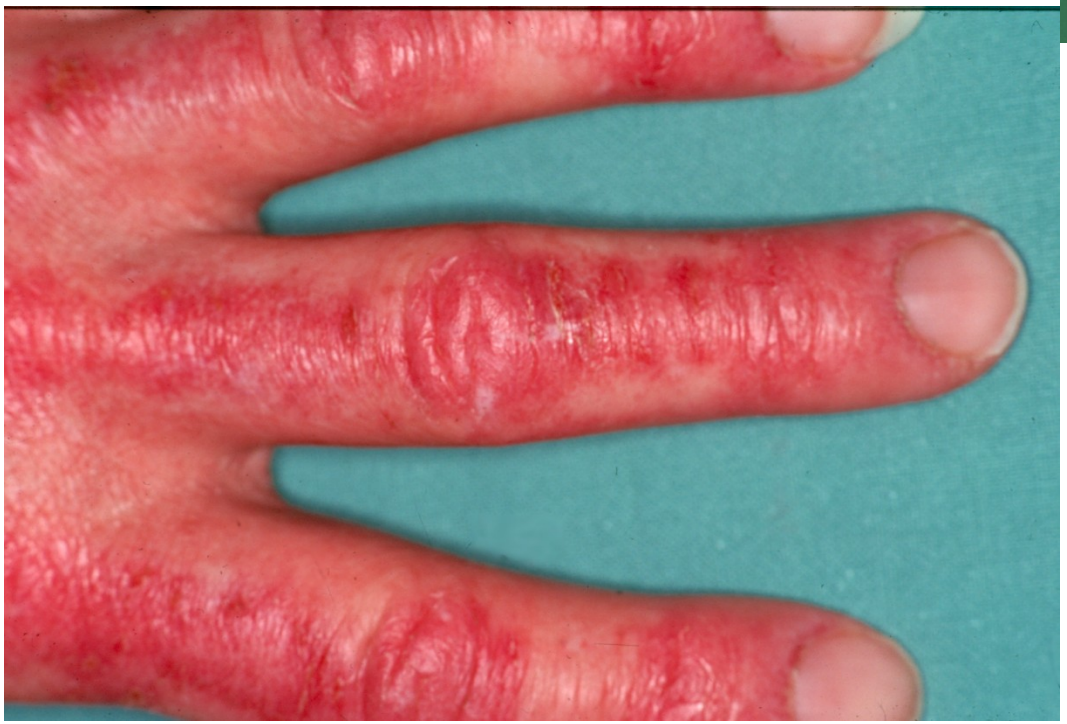
- Topical – corticosteroids, deltanoids, heparin
- Systemic- PNC
- Corticosteroids
- MTX
- Antimalarials
- UVA1

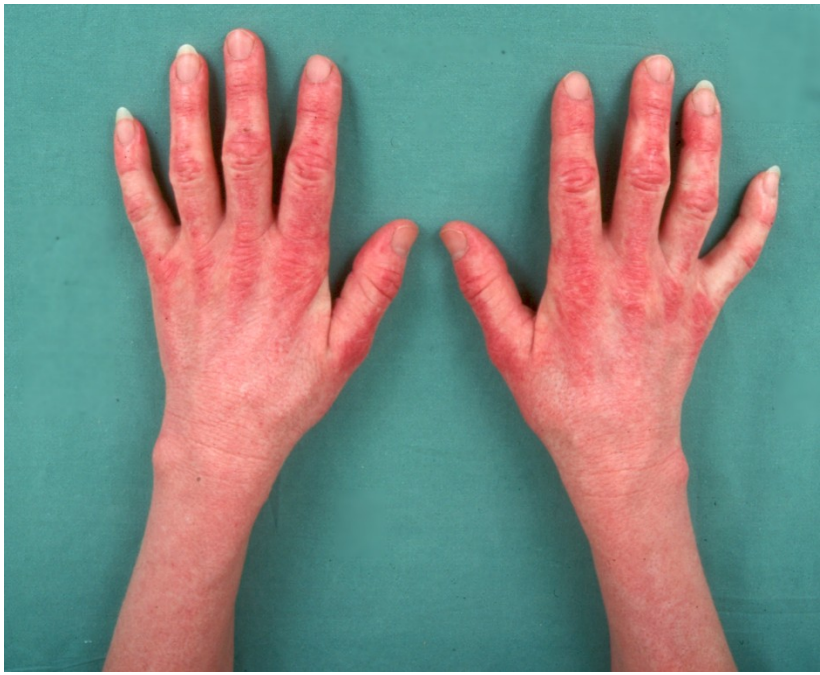
Dermatomyositis, polymyositis

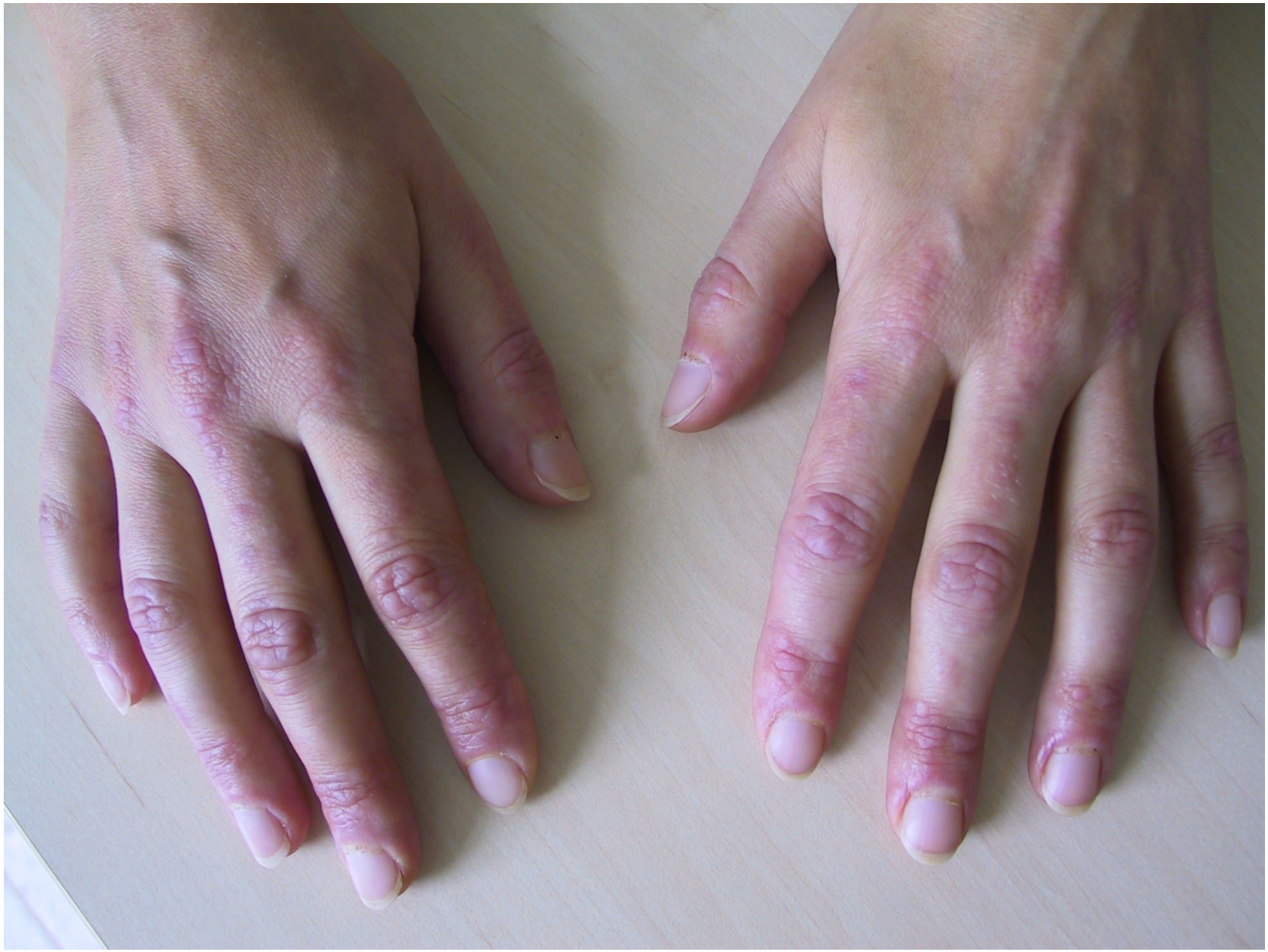
- **juvenile -** association with infections
- **adult - ** association with tumours (paraneoplastic)
- heliotrophic rash, Gottron´s sign, poikilodermatitis, erythemas
- EMG
- ANA, anti Jo-1
- CPK, LDH, GOT, ALD, AST, ALT, myoglobin
- Histology – muscle, skin

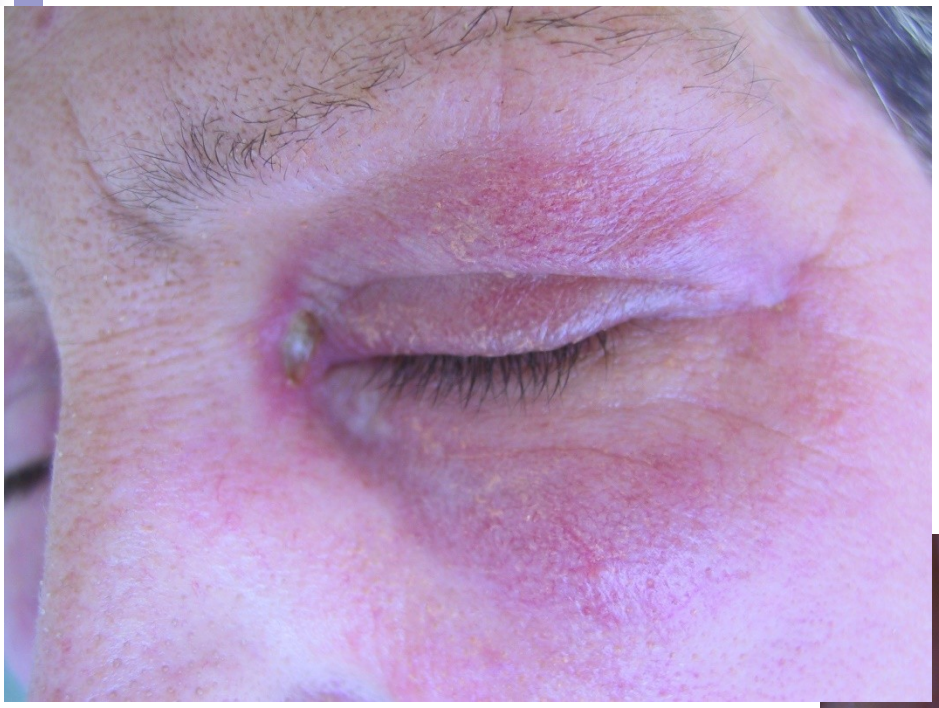


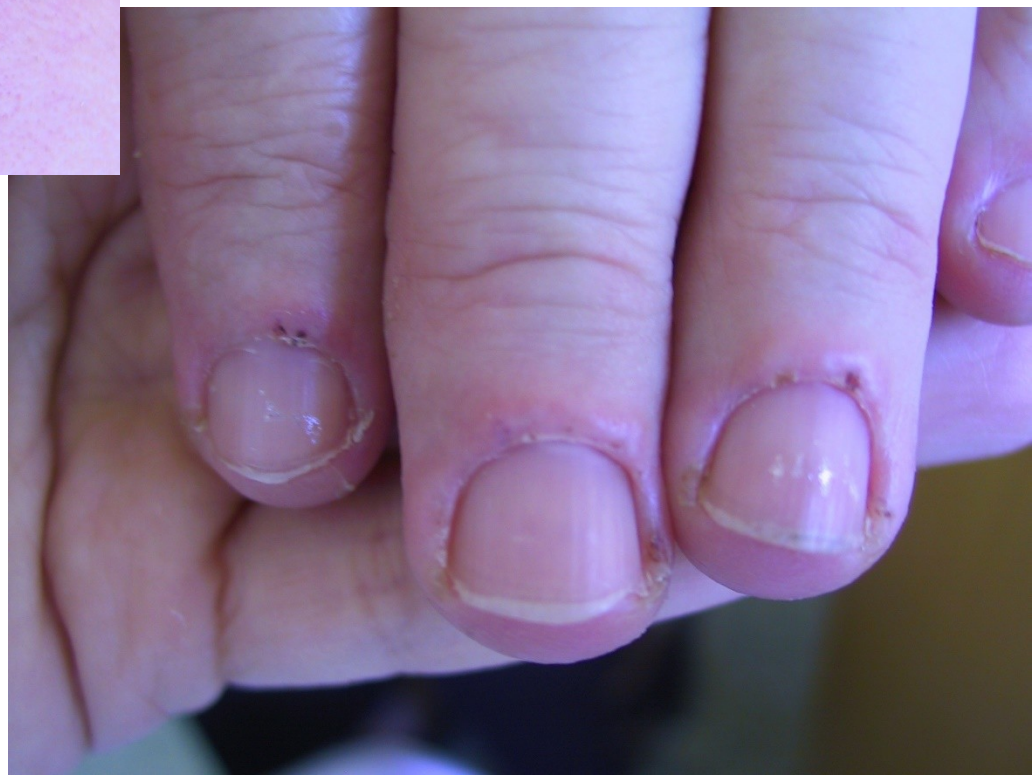












Dermatomyositis - therapy

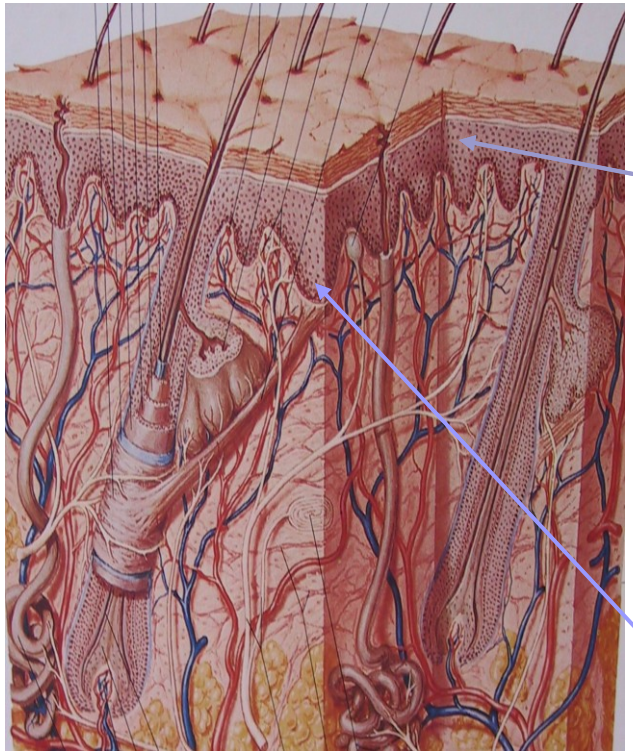
- Corticosteroids
- Immunosuppresives - MTX, azathioprine, cyclosporine
- Antimalarials
- IVIG

Autoimmune bullous diseases

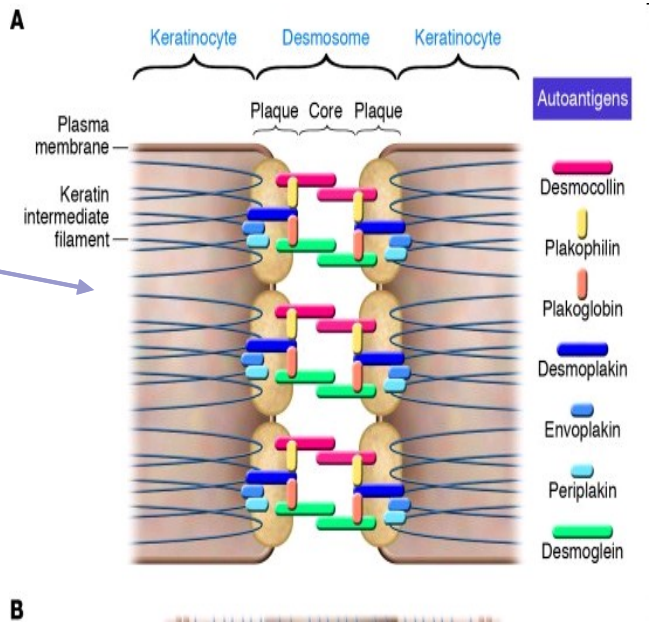
- Rare diseases, severe forms are lethal
- Skin and mucous membranes

- Two groups according to the level of cleavage
- Intraepidermal – Pemphigus and variants
- Subepidermal – pemphigoid group, DHD, EBA

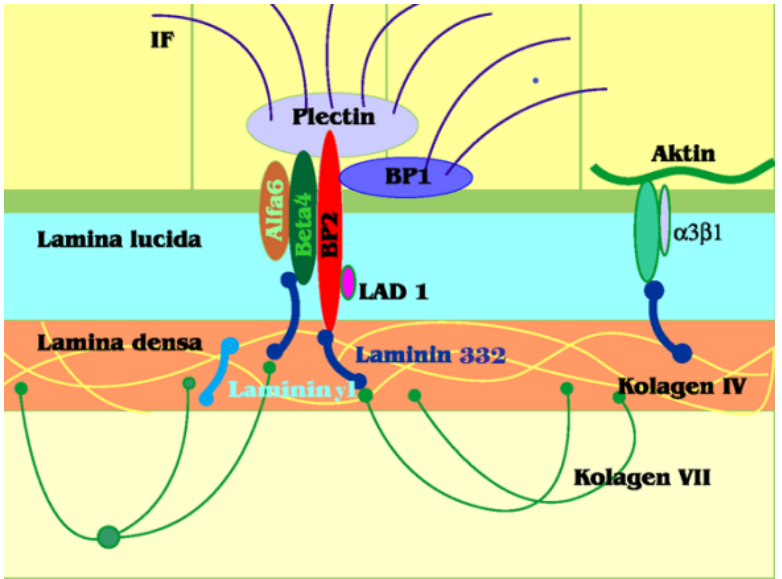
- Autoantibodies IgG/IgA against antigens in the epidermis and junctional zone



Pemphigus - desmosomes



Pemphigoid - hemidesmosomes

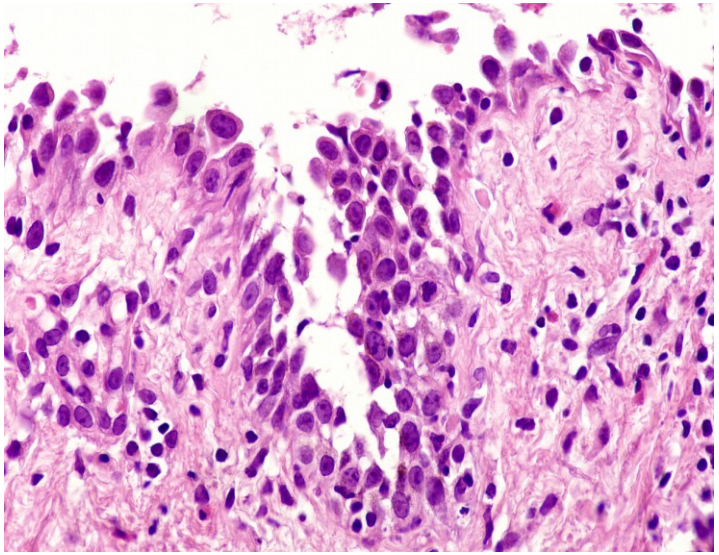


Diagnostics – Tzanck test, histology, immunofluorescence direct & indirect, ELISA, immunoblot

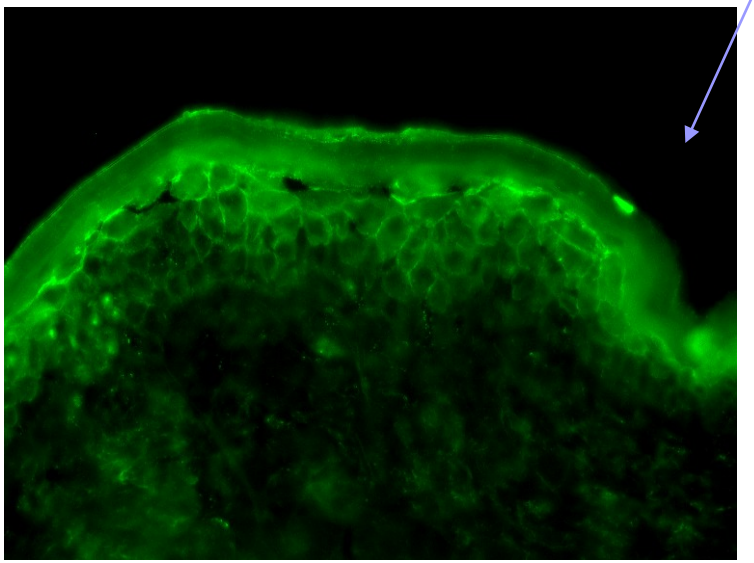
Pemphigus

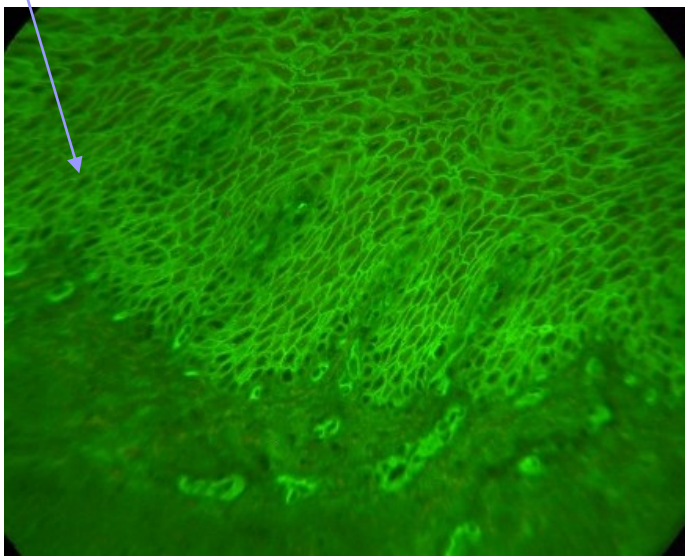
- Suprabasal (Dsg 3,1, IgG)
- pemphigus vulgaris
  vegetans
- Superficial (Dsg 1, IgG)
- pemphigus foliaceus
  fogo selvagem (Brazil)
  drug induced (thiols, phenols, penicilamin, captopril)
  pemphigus erythematosus Senear Usher – fotosensitivity, ANA antibodies
- Paraneoplastic Pemphigus – lichenoid,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

Pemphigus



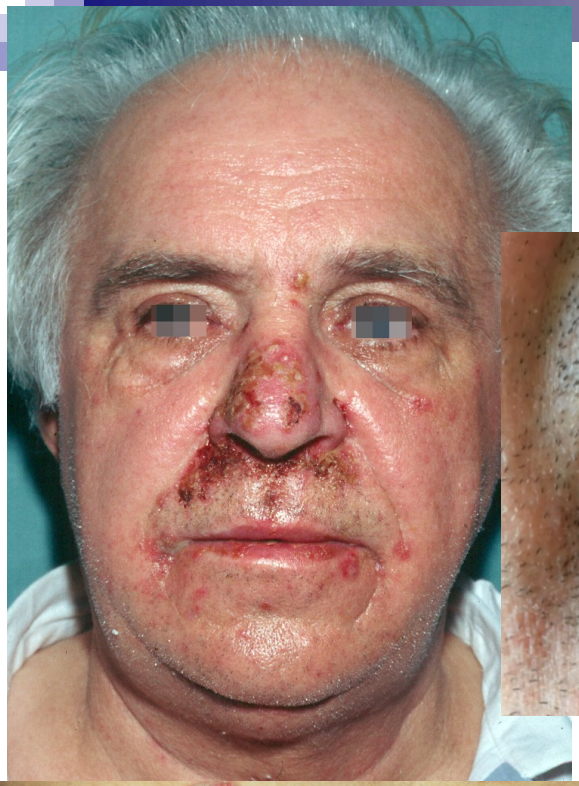
- Suprabasal acantholysis H+E
- Direct IF – pemphigus foliaceus
- Anti IgG/C3
- Indirect IF – monkey esophagus
- ICS anti IgG

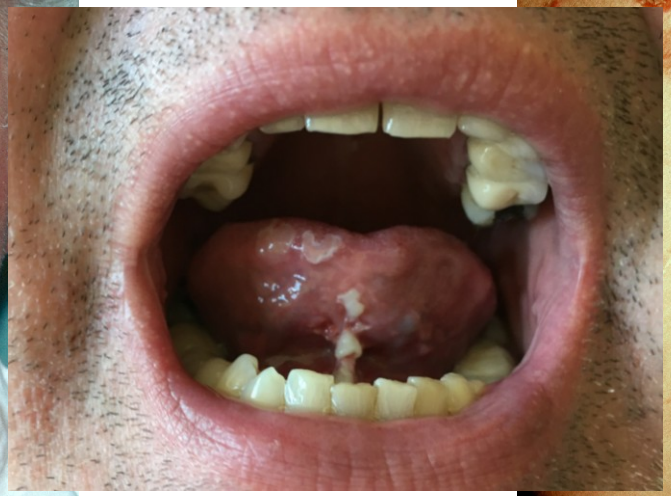


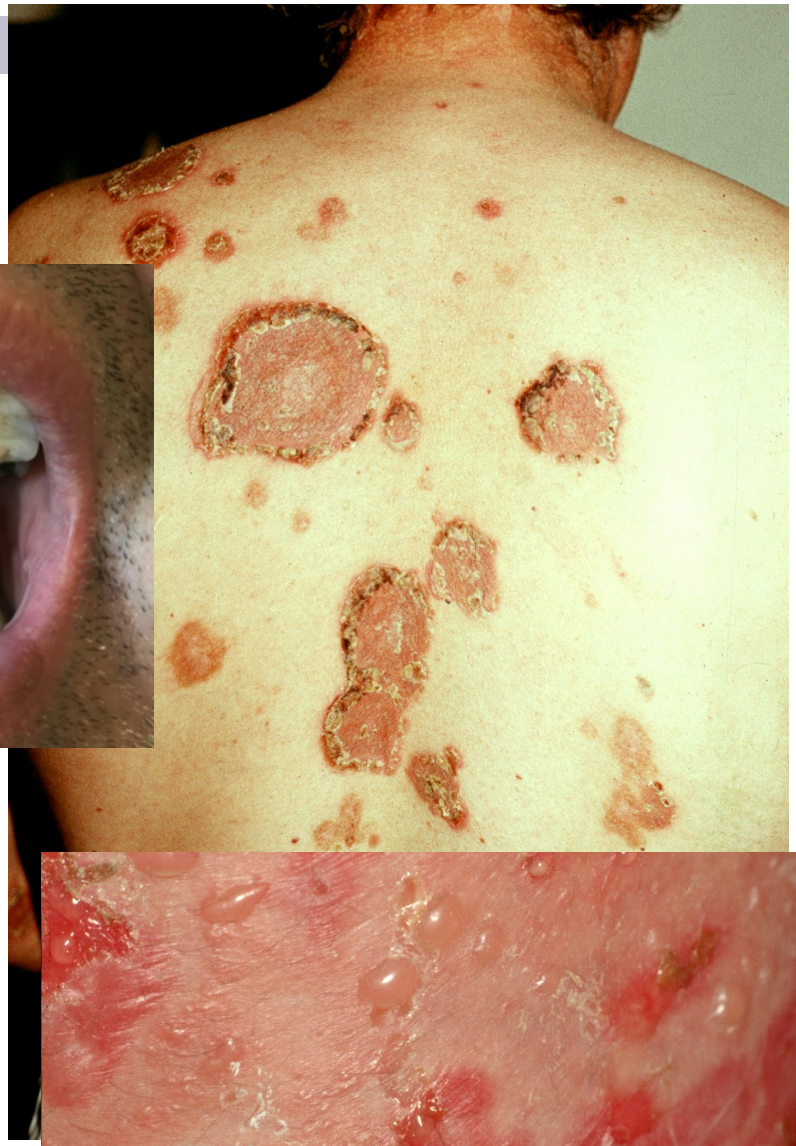


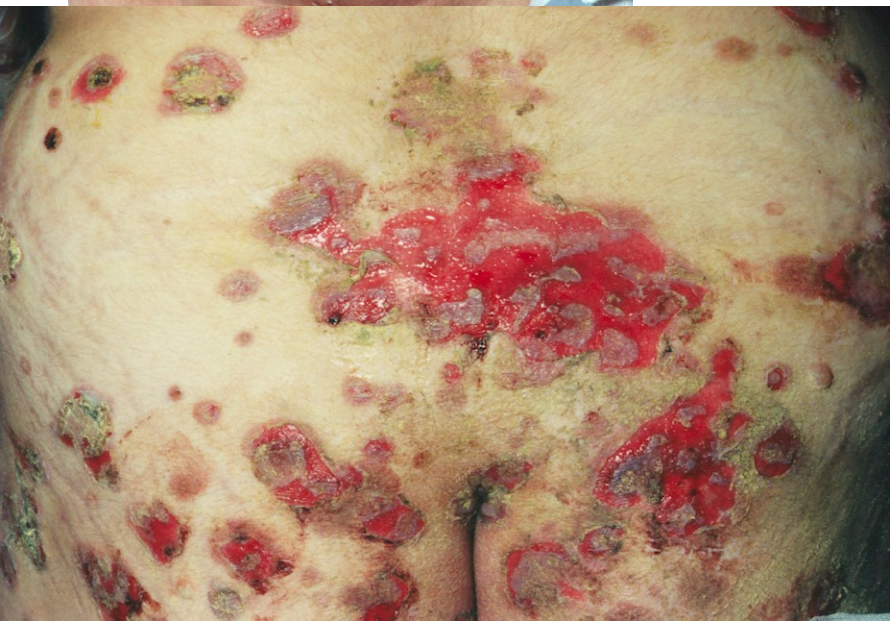
Pemphigus vulgaris

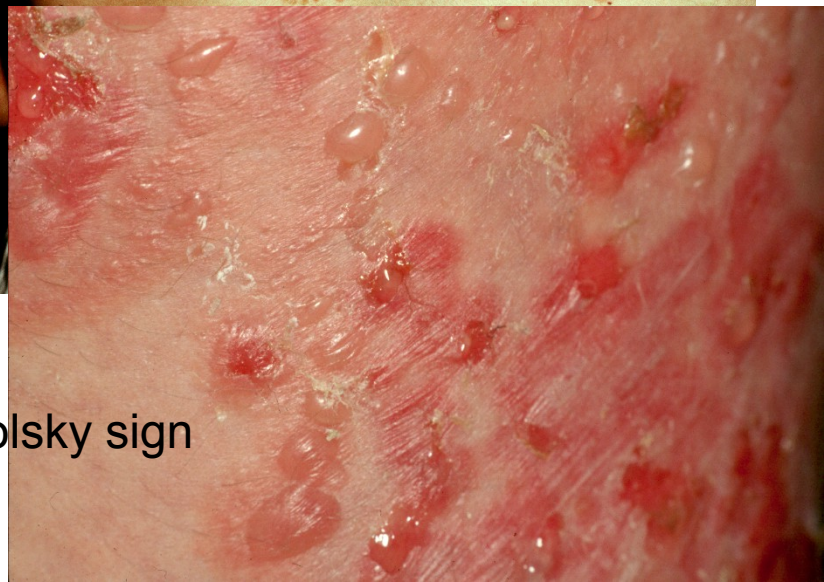
- Rare bullous disorder with autoantibody-induced intraepidermal blisters (desmosomes - acantholysis)
- Incidence 5/ 1 million inhabitants
- Chronic disease, can be lethal
- Average age 30-60 years
- Etiopathogenesis
- Genetic factors (HLADR4)
- Drug induced, infections, phenols
- Antibodies against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





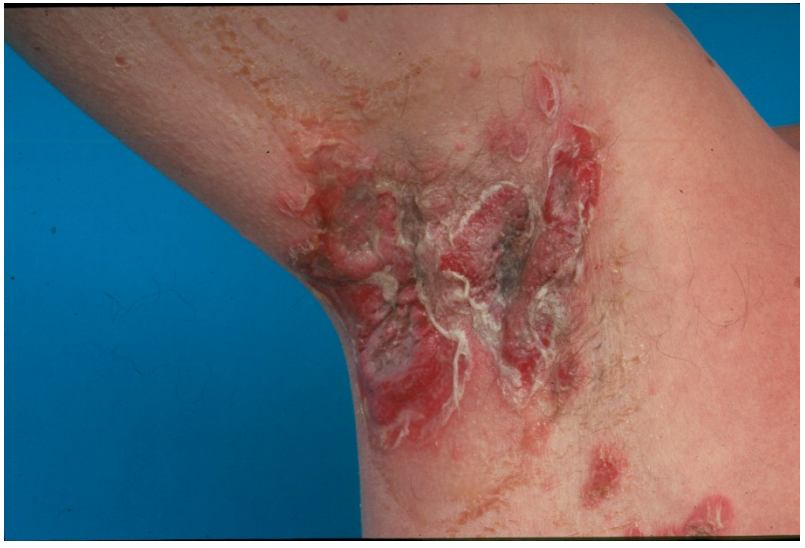


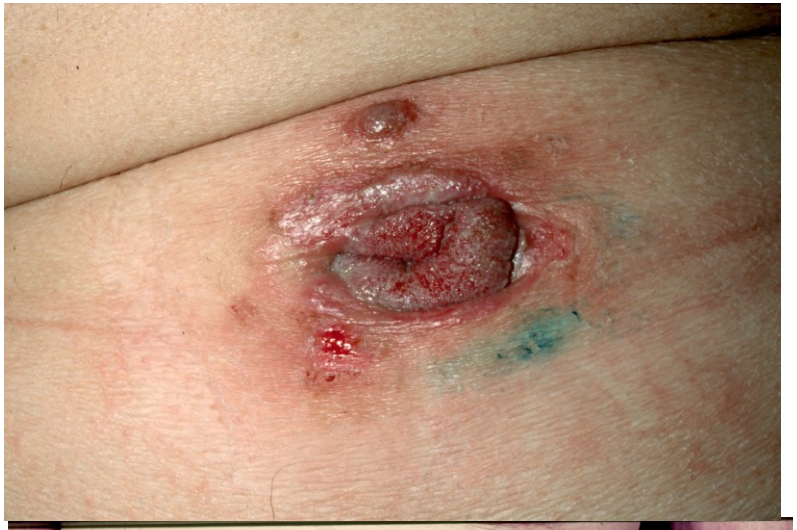


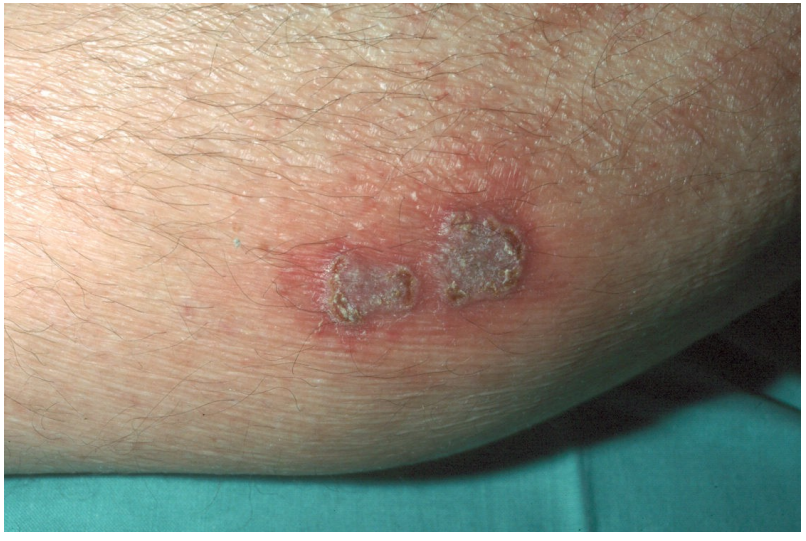


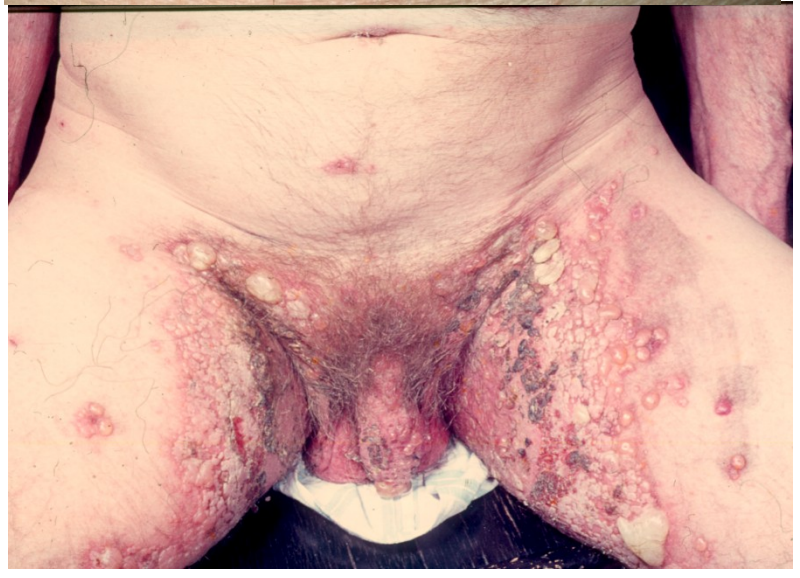
Nikolsky sign

Pemphigus vegetans

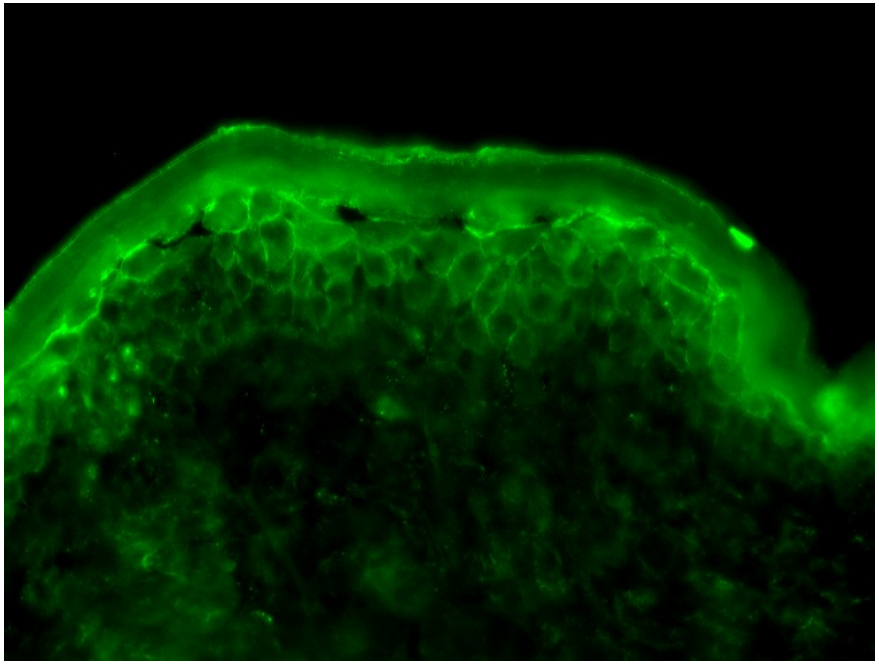


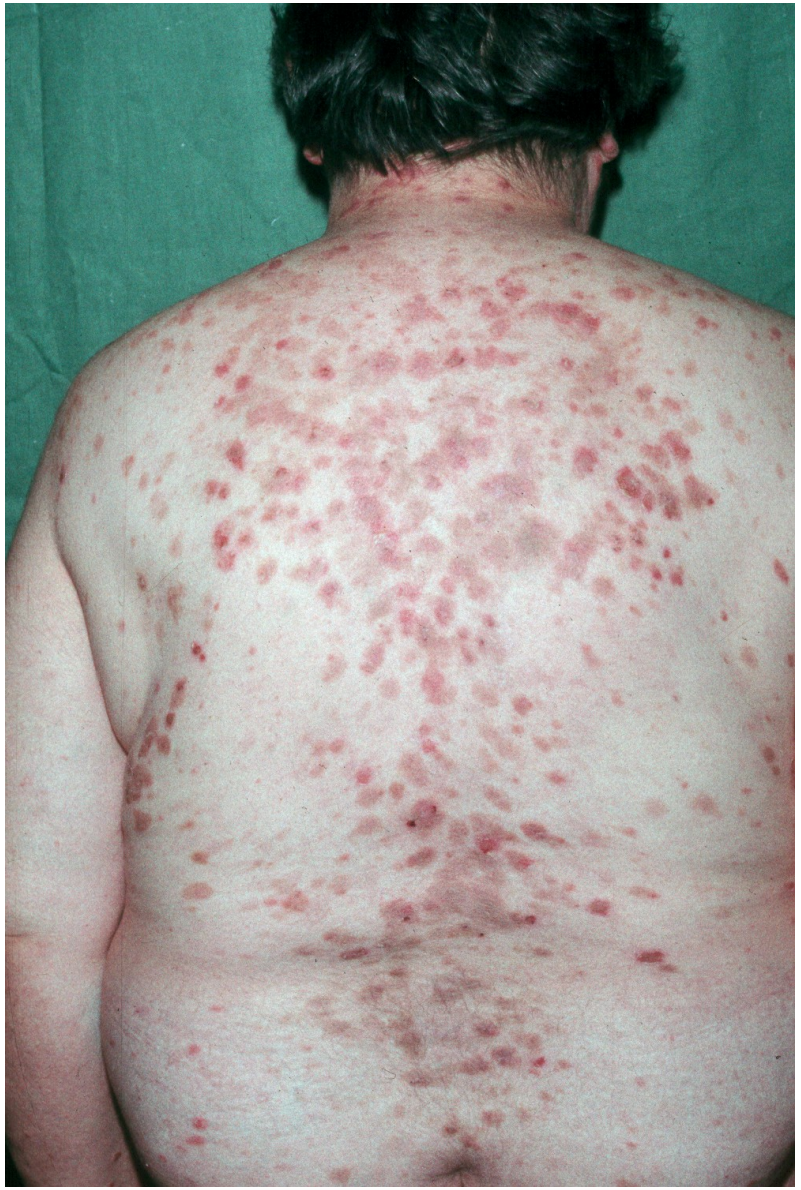






Pemphigus foliaceus





Pemphigus therapy

- Corticosteroids (Prednisone 1-1,5mg/kg/d)
- ...taper to 15 -20 mg/d
- Immunosuppresives - corticosteroid sparing agents
- Mycophenolate mofetil 2g/d
- Azathioprine – cave TPMT deficiency
- MTX 10-20mg per week

(Cyclophosphamide – toxic)

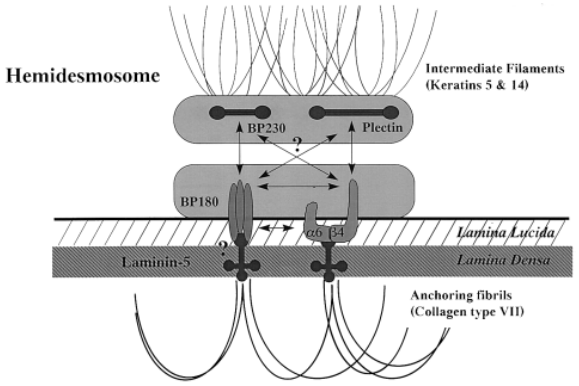
-

- Rituximab anti CD20 antibody –risk of infections
- Dapsone
- IVIG 1-2g/kg pulse every 6 weeks
- Immunoadsorption IgG
- Long term therapy, 2 years minimum, often life long

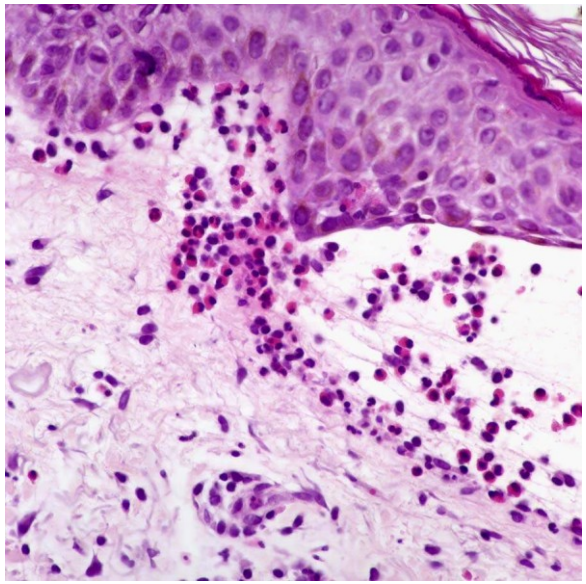
Subepidermal autoimmune bullous dermatoses

- Rare disorders with autoantibody-induced subepidermal blisters (basement membrane – hemidesmosomes)

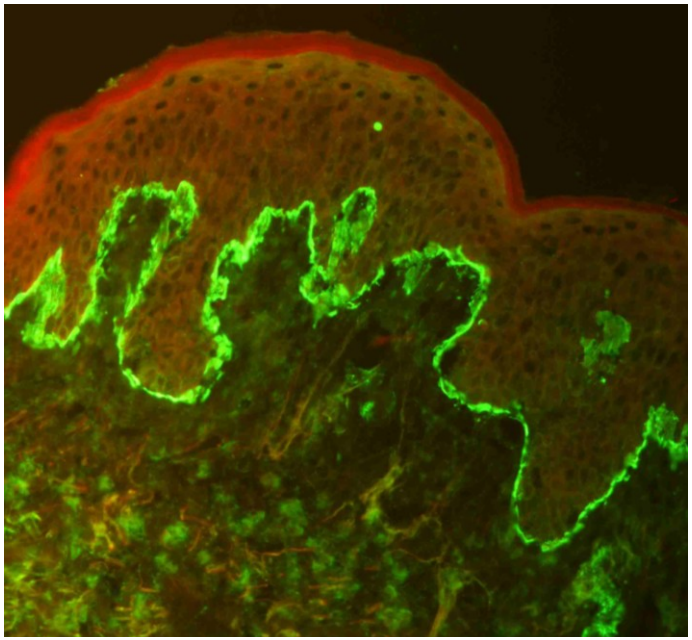
- Bullous Pemphigoid - BP
- Pemphigoid gestations (variant of BP)
- Cicatricial Pemphigoid – mucous membrane pemphigoid
- Epidermolysis bullosa acquisita (association diabetes, bowel disease)
- IgA linear dermatosis – typically childhood, in adults drug induced – vankomycin
- Dermatitis herpetiformis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



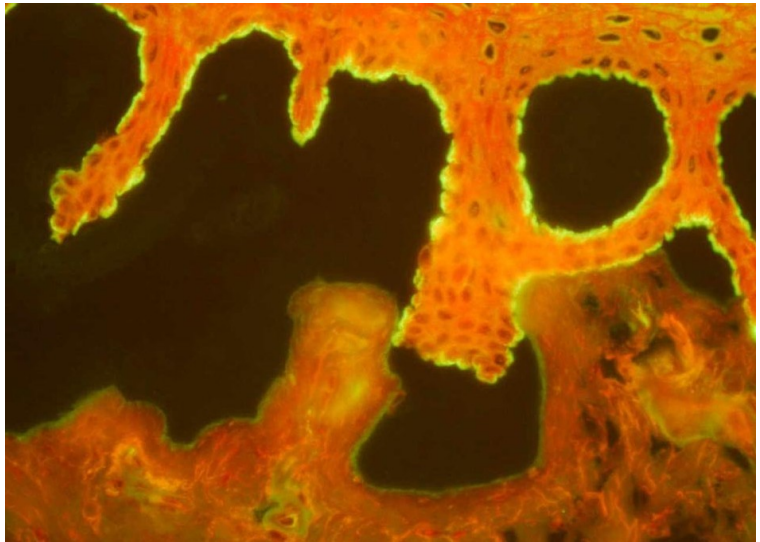
BP – subepidermal blister - eosinophils

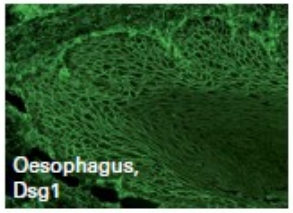


Direct IF line on BM IgG/C3



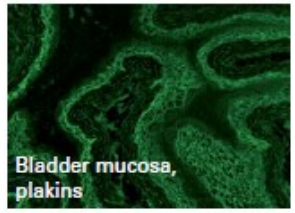
Salt split skin blister roof in BP



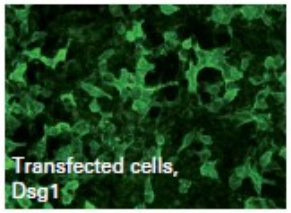


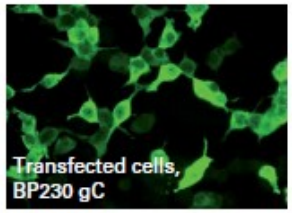
Oesophagus: detection of antibodies against **prickle-cell desmosomes** (pemphigus) and **basal lamina** (pemphigoid).

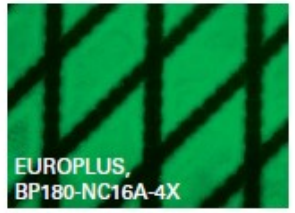
Salt-split skin: differentiation of autoantibodies against antigens of the epidermal (**BP180, BP230**) and dermal (**collagen type VII, laminin 332, p200**) sides of the skin.



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

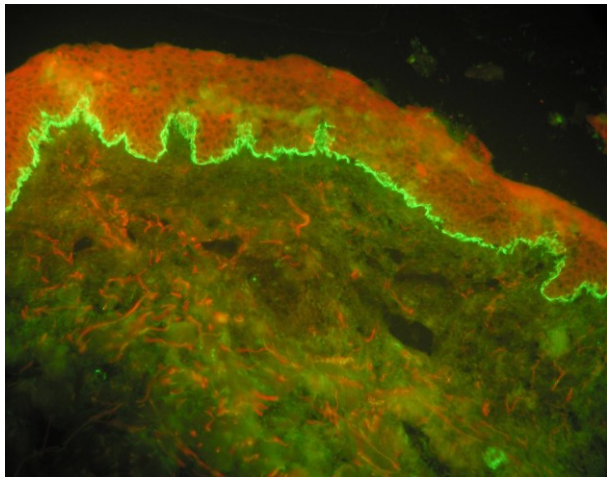




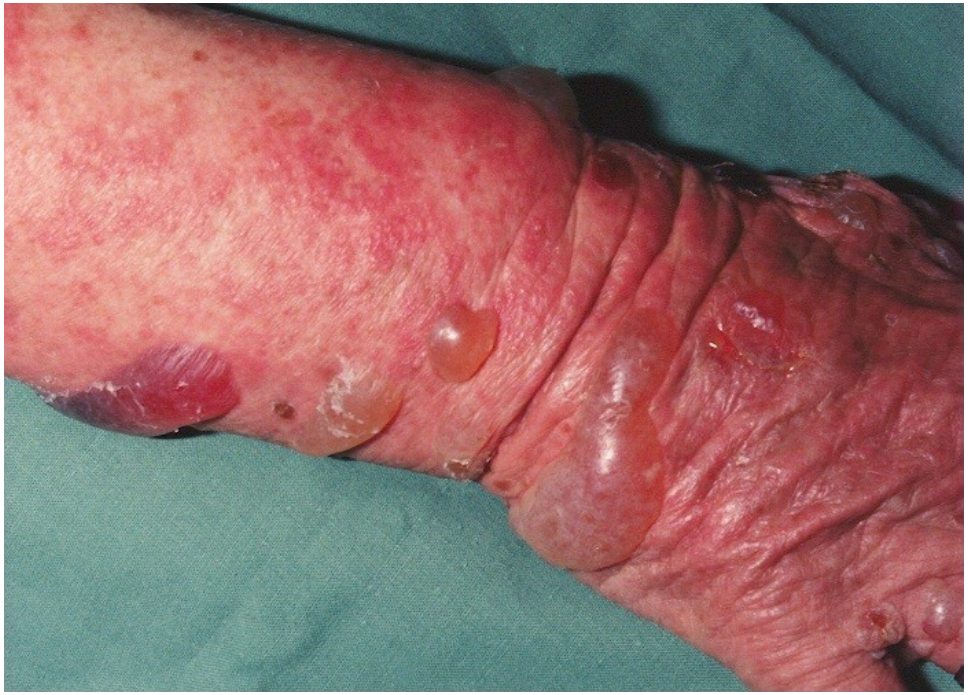


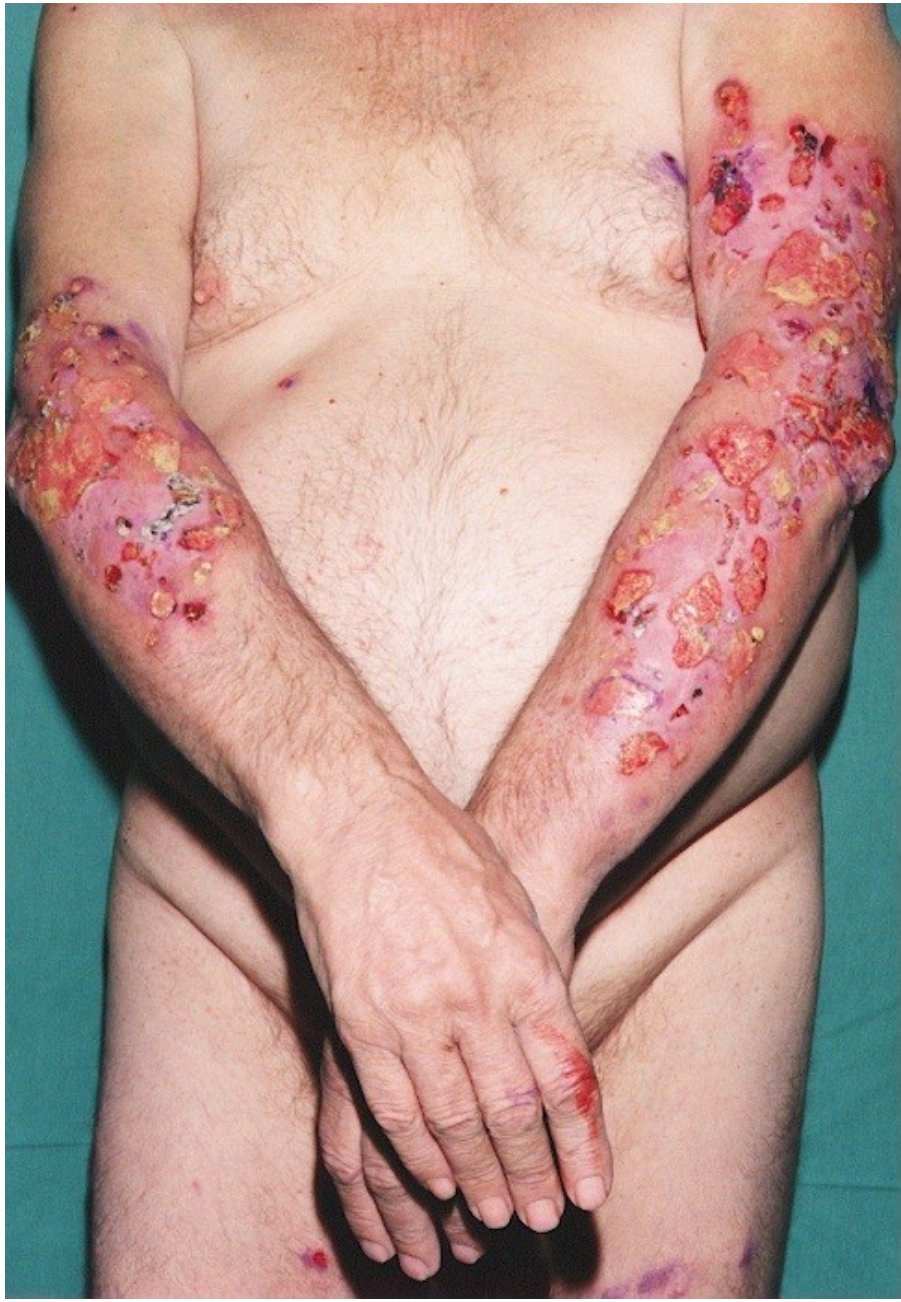
Pemphigoid bullosus

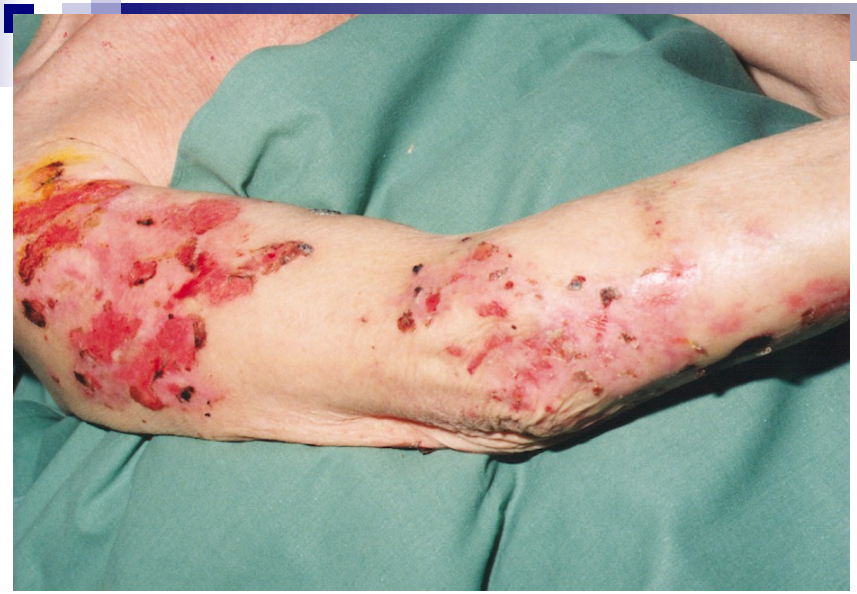
- Elder people – over 70 years
- Many concomitant diseases
- Paraneoplastic disease (13%) prostate, breast cancer
- Drug induced (PNC, enalapril, furosemid, gliptins)
- Neurodegenerative diseases!
- Cerebral stroke + paresis, Parkinson disease, dementia
- (BP expression in neuronal tissue)
- 1 year survival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

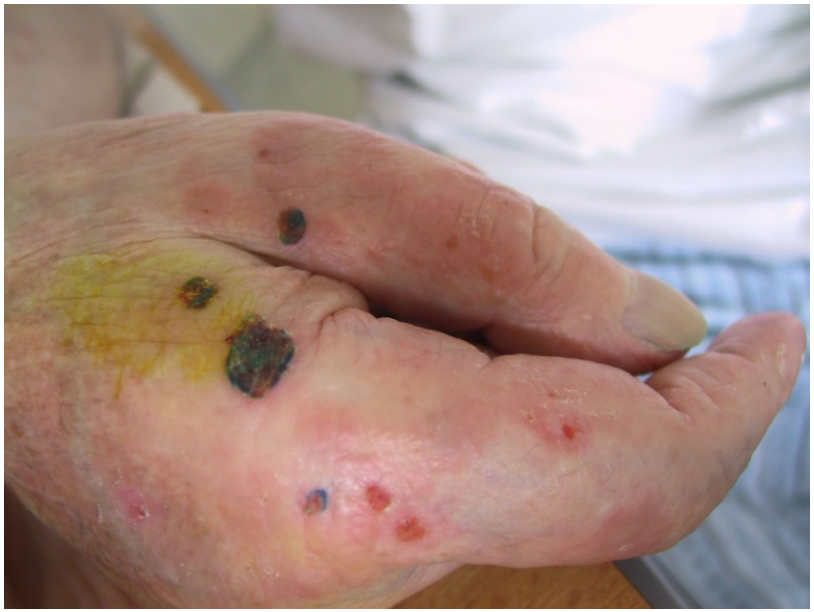


BP tense hemorrhagic blisters, infiltrated skin
Tissue and blood eosinophilia, strong pruritus

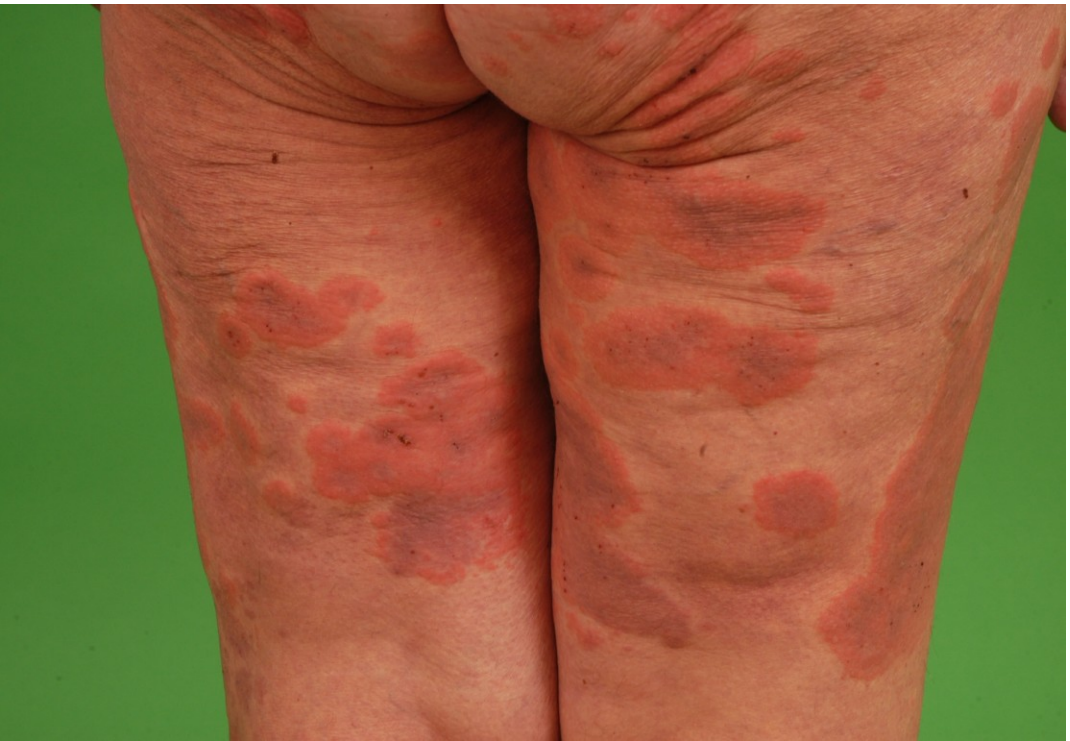








BP in paretic limb



Urticarial lesions in BP

Pemphigoid bullosus therapy

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

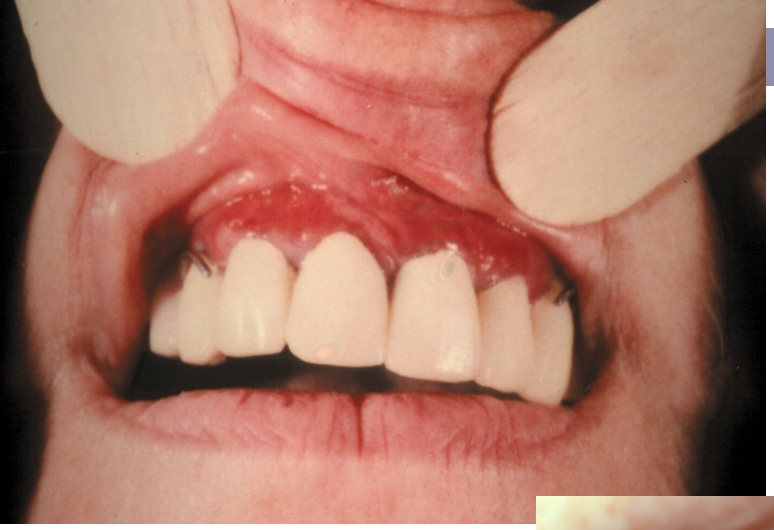
or

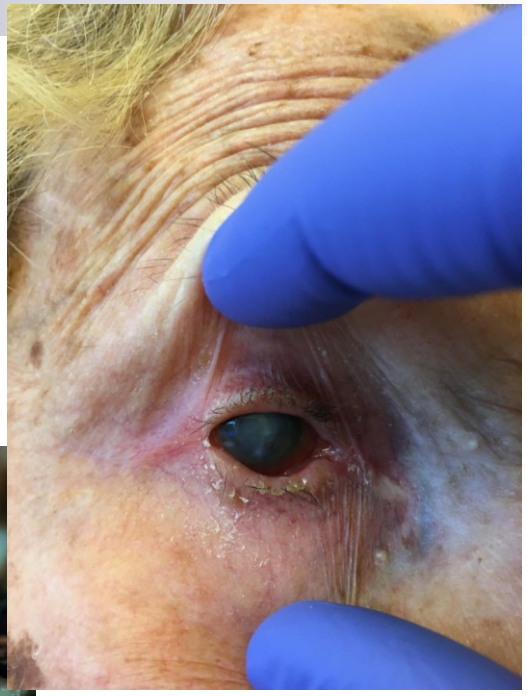
- Potent topical corticosteroids (clobetasol)
- Immunosuppresives (azathioprine, methotrexate, mycophenolate)
- Dapsone
- TTC – antiinflammatory effect

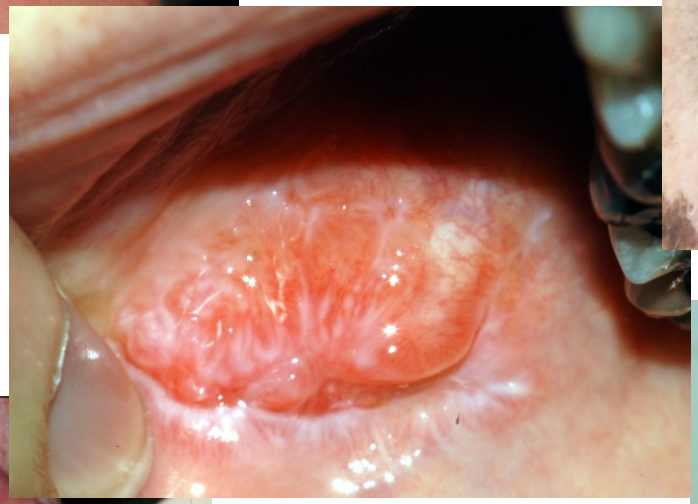
Cicatricial Pemphigoid MMP

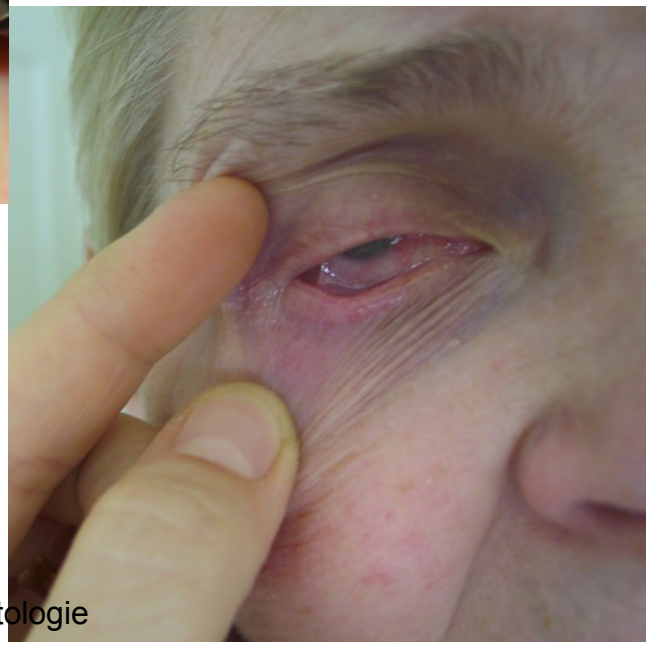
- Incidence 1/million inhabitants
- 60 years of age
- Paraneoplasia (stomach cancer), topicals for glaucoma
- Mucose membranes ⟶ stenosis, scarring
- Conjunctiva - entropion, symblepharon, trichiasis ⟶ blindness
- Pharynx, larynx,
- Genital area
- Skin – minor disease Brunsting Perry Pemphigoid

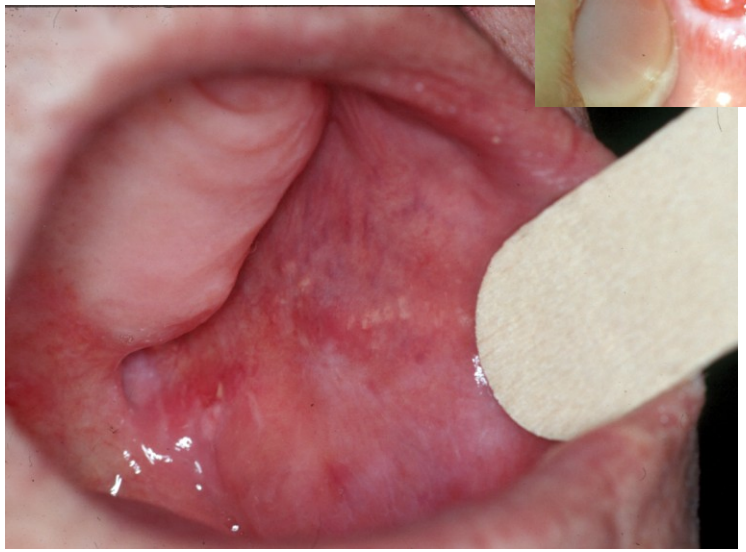
- Therapy – as in pemphigus







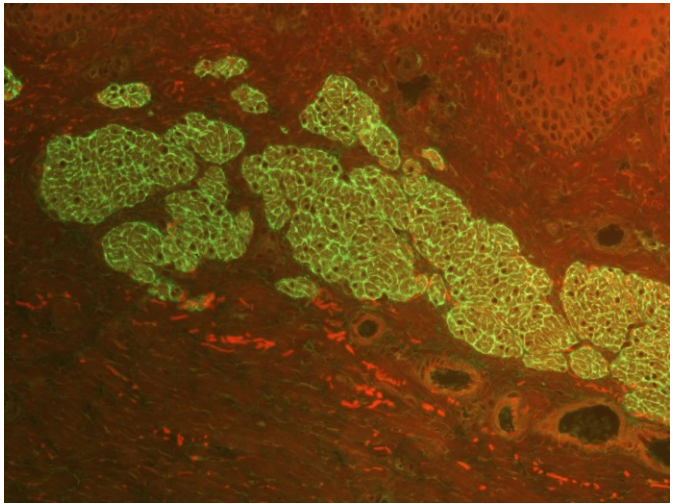




Pictures from Praktická dermatologie

Dermatitis herpetiformis Duhring

- rare disease – incidence 3/1 million inhabitants
- gluten sensitive entheropathy – coeliakia
- IgA antibodies against endomysium (tissue transglutaminase)
- cross reaction with eTG on reticulin fibers in dermal papilae
- 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