# Pathology of Autoimmune and Autoaggressive Diseases

*Semmelweis University*
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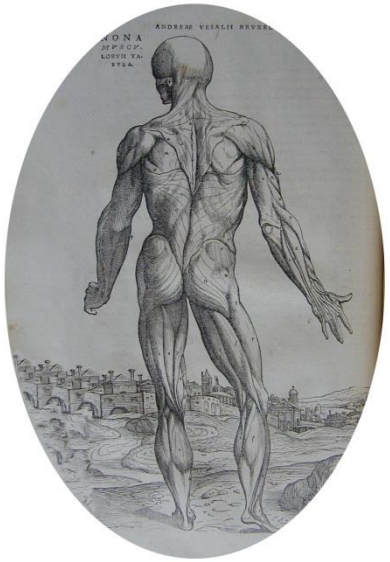

*2017/2018 – Autumn semester*
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# Pathology of Autoimmune Diseases

1. Introduction
2. Monosystemic Diseases
3. Oligo-, polysystemic Diseases

# 1.
# Introduction

# Definition

- *Autoimmune diseases*: Diseases with pathogenesis dominated by humoral and cellular immune reactions that are typically directed against body structures and/or substances
- Paul Ehrlich: „*horror autotoxicus*"
- Paul Ehrlich (1854-1915)
  - german physician and scientist in hematology, immunology and chemotherapy
  - development of Salvarsan (Arsphenamine), first drug against syphilis
  - antiserum against diphthery
  - Nobel laureate 1908

# Pathogenesis – Miscellaneous

- Normally: Immune tolerance against own structures (*autoimmune tolerance*)
- Breakage of autoimmune tolerance >> own tissue appears for the organism as pathogenic >> development of autoimmune / autoaggressive diseases
- Common clinical presentation is that of a chronic-recurring course with autoaggressive phenomena
- Pathoanatomically typical is an inflammatory tissue damage
  - chronic-fibrosing inflammatory infiltrates
  - acute exacerbations with the typical fibrinoid necrosis
- Pathogenetic mechanisms
  - type III (immune complex type) immune reactions: organ dependent appearance, cellular damage by immune complexes
  - type IV (cytotoxic, cellular type) immune reactions

# Pathogenesis – Miscellaneous

- Types of immune reactions
  - *complement binding* antibodies *against cells* (e.g. blood cells) and tissue components (e.g. basal membrane). (a) Circulating antigen-antibody complexes typically play a roll in vasculitis (deposition into vessel wall layers >> complement aktivation >> cell and tissue damage >> inflammatory reaction). (b) Non-circulating (cell-bound) antigen-antibody complexes (cell surface antigens + antibody >> complement activation >> cytolysis)
  - *non complement binding* antibodies *against cell receptors*. Antibody action on receptors can lead to cellular dysfunction, i.e. to either (a) stimulation or (b) blockage.
  - *T-effector cells* step in interaction with *cell surface antigens* >> excretion of lymphokines >> inflammation

# Pathogenesis – Miscellaneous

Types of immune reactions

– Type I. immune reaction

An immediate IgE-mediated immune reaction dependent on liberation of histamine.

– Type II. immune reaction

A membrane-bound cytotoxic immune reaction.

– Type III. immune reaction

An immune reaction activated by circulating immune complexes, tissue damage is effectuated through an accompanying inflammatory reaction >> e.g. inflammation

– Type IV. immune reaction

A cell-mediated cytotoxicity >> e.g. tbc

# Pathogenesis – Hypotheses of immune tolerance

- 1. *Clone elimination hypothesis*

  - autoaggressive antigenes must be quaranteened in the thymus as early as during embryogenesis, i.e. clones coming in early contact with body-own antigenes and therefore capable of recognising them

  - low-titres of autoaggressive antibodies in otherwise healthy individuals are explained by somatic cell mutations

- 2. *Hypothesis of suppression of autoreactive lymphocytes*

  - this theory „allows" for the existence of lymphocyte stem cells capable of recognising body-own structures, BUT these would be suppressed by T-suppressor cells through blocking autoreactive lymphocyte receptors

  - to the contrary a T-helper stimulation may favour autoreactive antibody production by B-cells

# Pathogenesis – Mechanisms of Autoagression

- 1. *Immune system derangement*

  - activity defects of T-suppressor cells >> liberation of proliferation of B-cell clones with autoreactive receptors

  - production of anti-antibodies (antiidiotypes)

  - typical in malignant lymphomas and immune defects

- 2. *Production of cross-reacting antibodies or T-cells*

  - overlapping specificity between pathogenes and a few body-own antigenes of HLA-type (molecular mimicry / antigenic mimicry)

  - e.g. γ-δ-T-lymphocytes with specificity against both body-own and pathogene dependent stress proteins

  - antigene overlaps or similarities: cytokeratin (*structural protein of own epithelial cells*) – Morbilli virus; vimentine (*structural protein of own mesenchymal cells*) – Herpes simplex virus; cardiac extracellular matrix – ß-hemolyticus-Streptococcus-A; basal membrane – gliadin (*a component in cereals*)

# Pathogenesis – Mechanisms of Autoagression

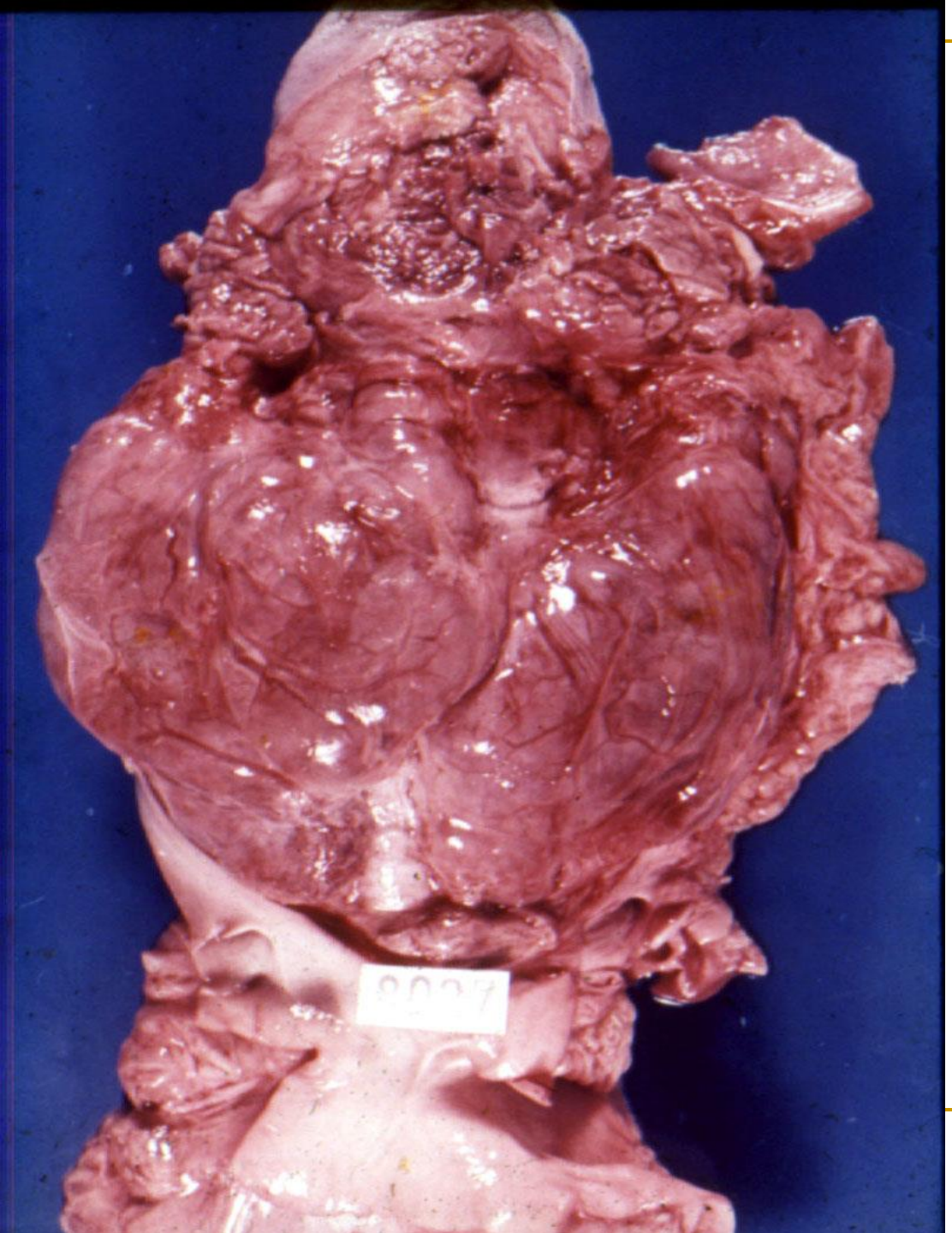
- 3. *Liberation of hidden autoantigenes*
  - mitochondrial components (AMA – *antimitochondrial antibodies*). An AMA-positivity is present in various autoimmune diseases, e.g. PBC (primary biliary cirrhosis)
  - Myosin (ASMA – *alpha smooth muscle actin*) in tissue damage
  - Retina-S-Antigen in penetrating eye injury with consecutive autoaggressive inflammation of the contralateral uninjured eye (so-called *sympathic opthalmitis*)

- 4. *Maldirection of genes (mutations)*
  - mutation of body-own HLA-antigenes
  - genetically determined autoimmune diseases
  - increased association of certain HLA-constellations with some autoimmune diseases

# 2.
# Monosystemic (organ-bound) diseases

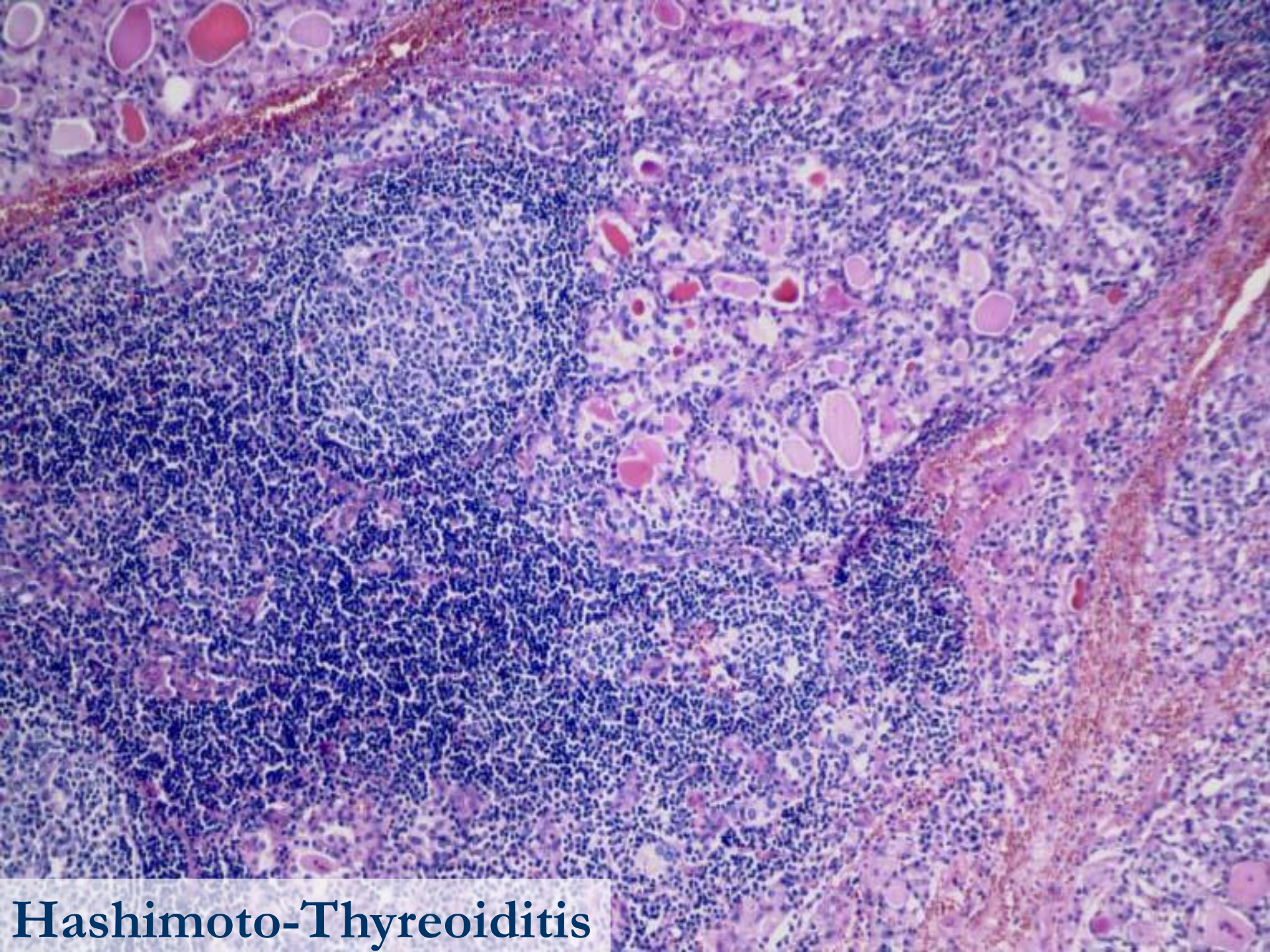
# Monosystemic (organ dependent) diseases

1. Hashimoto-Thyreoiditis
2. Autoimmune hemolytic anemia
3. Autoimmune thrombocytopenia
4. Autoimmune encephalomyelitis
5. Autoimmune orchitis
6. Primary biliary cirrhosis
7. Autoimmune hepatitis
8. Autoimmune gastritis
9. Gluten-enteropathie
10. Ulcerative Colitis
11. Goodpasture's Syndrom
12. Insulin-dependent (type I.) Diabetes mellitus (IDDM)
13. Myasthenia gravis
14. Graves Disease / Morbus Basedow
15. Multiple sclerosis



# Struma Basedowiana – Grave's disease

- Anti-TSHR-antibodies
- Hyperthyreosis, Goiter
- Nodular and diffuse struma
- Type II. hypersensitivity

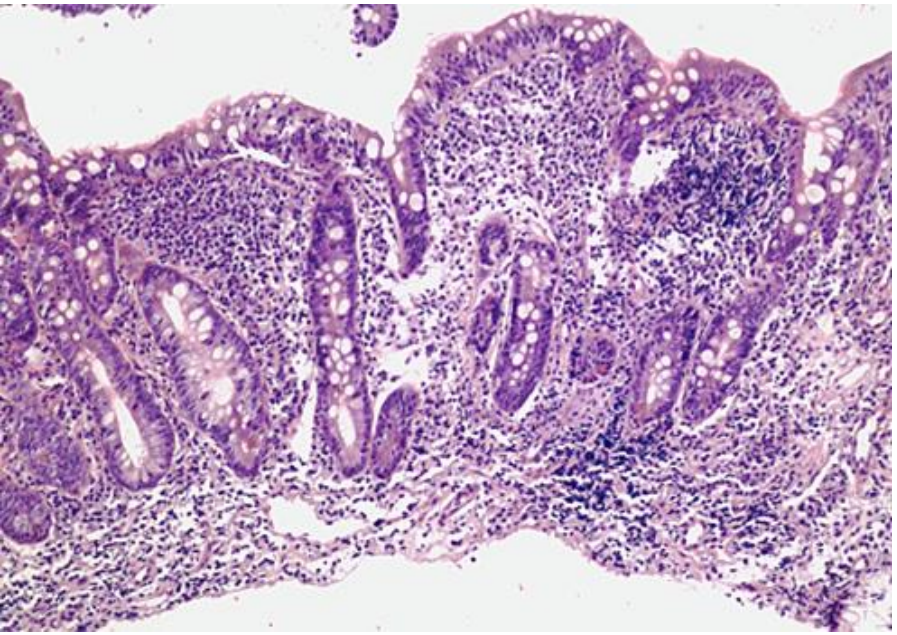


# Hashimoto-Thyreoiditis

# Autoimmune Gastritis

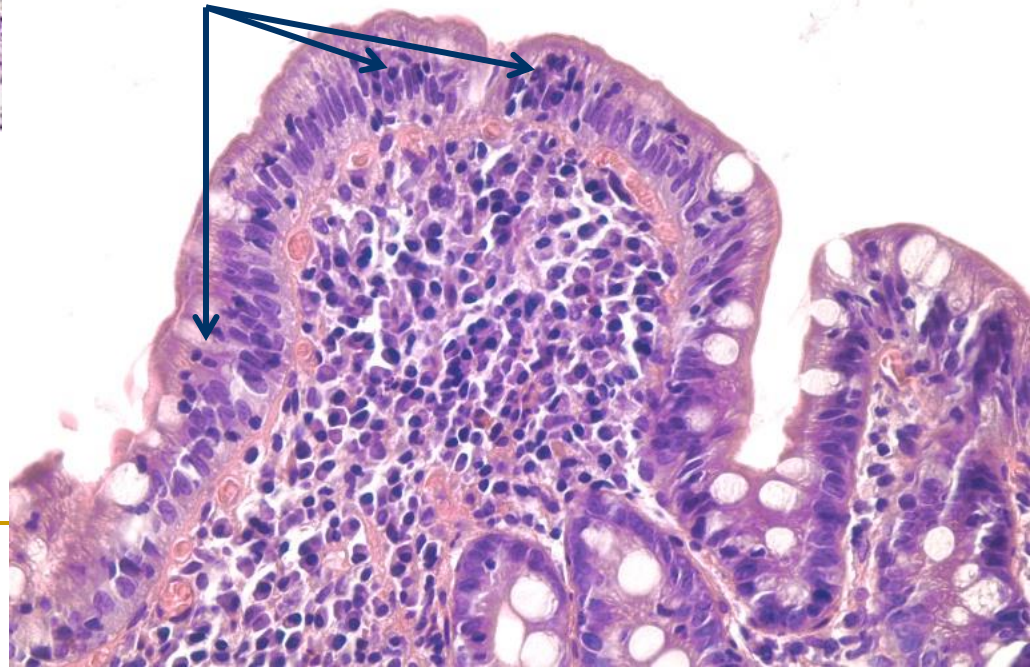
Antigene: B12-intrinsic-factor

# Glutene-sensitive enteropathy



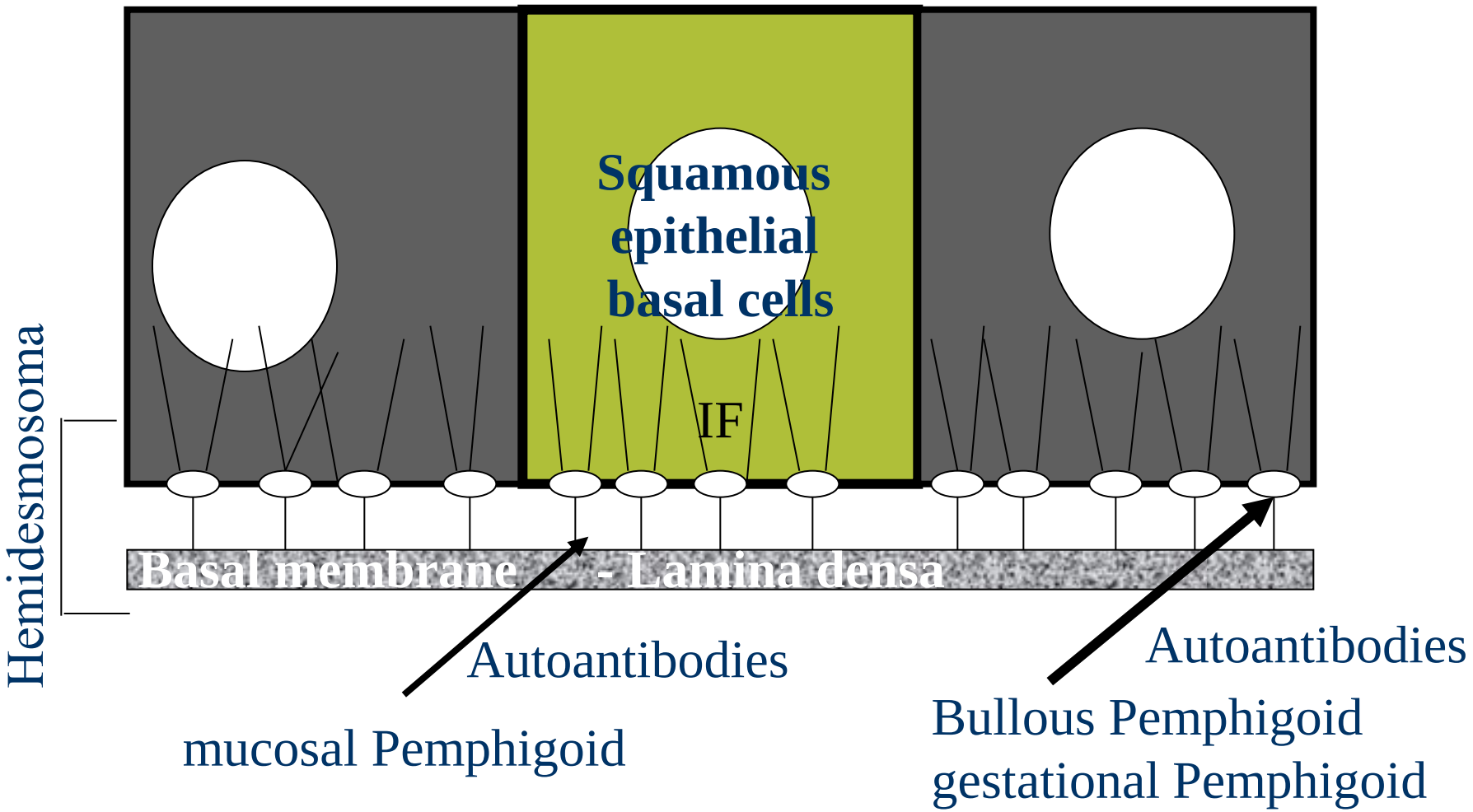
Gliadin-basal membrane overlapping
Adenoviral infektion
Chronic-superficial enteritis
Atrophic enteritis
Complete atrophy of enteral villi

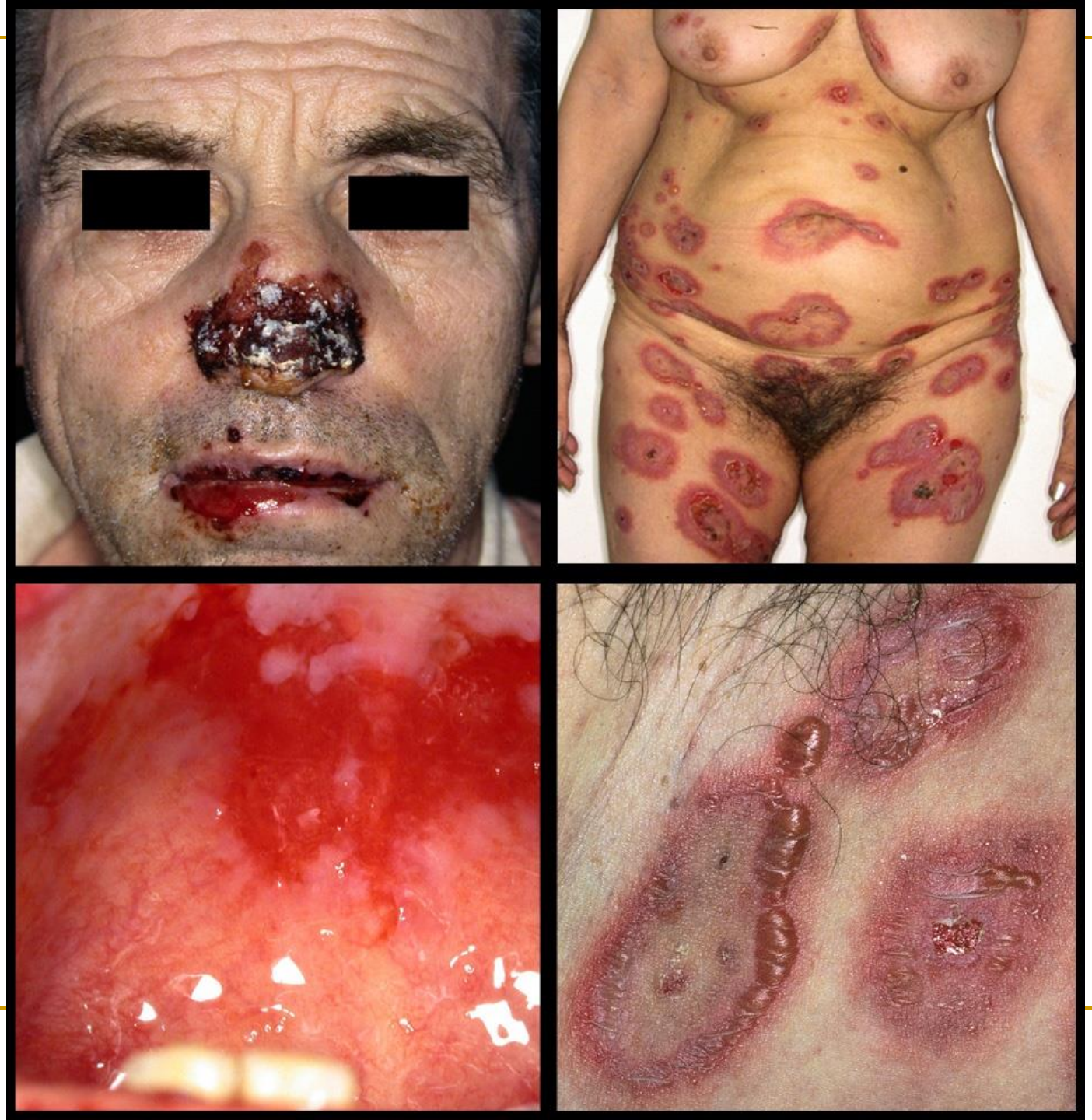
Autoaggressive intraepithelial T3-Lympho-cytes (IEL): >40/100 epithelial cells



Anti-retikulin-antibodies,
Anti-endomysium-antibodies,
Anti-gliadin-antibodies

# Bullous Pemphigoid





# Pemphigus vulgaris

# Autoimmune hepatitis (AIH)

- non-healing inflammation of the liver with
  - typical but not specific/pathognomic histological picture
  - hypergammaglobulinemia
  - **seral autoantibodies**
  - no known etiology (genetic, toxic, viral, etc.)

- diagnostic criteria of AIH
  - clinically: symptomatic (fatigue, fluctuating icterus, arthralgia, etc.) or asymptomatic
  - women > men, in younger age groups
  - **coexpression with other autoimmune diseases**
  - biochemically hypogammaglobulinemia with selective elevated IgG-levels
  - AST/ALT variably (between normal – 50x)
  - ALP variably (until slightly elevated)
  - Bilirubin (fluctuating)

# Autoimmune hepatitis (AIH)

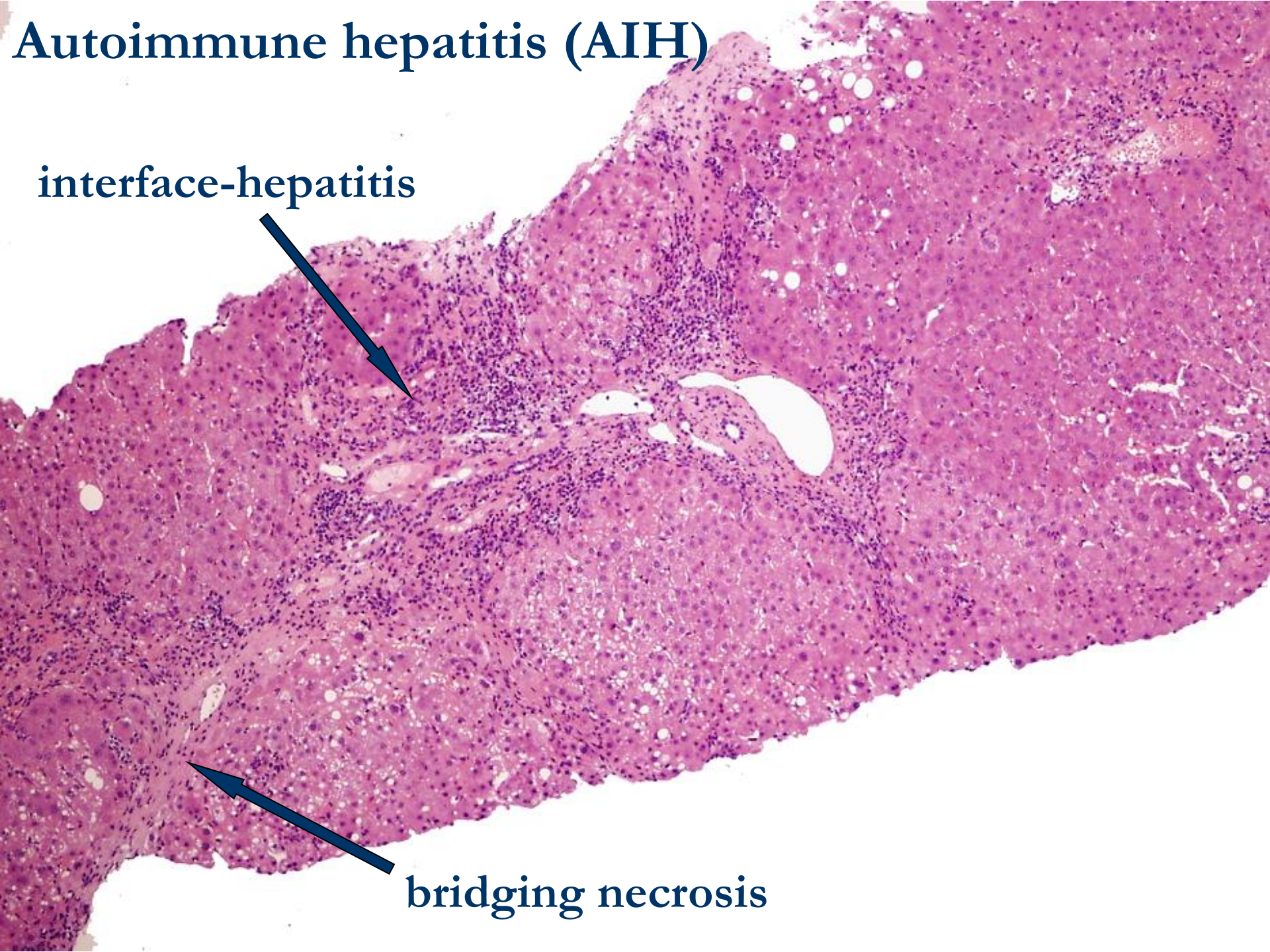
- serologic characteristics (autoantibodies)
    - **non-organ specific antibodies (Ab)**
        anti-nucleare Ab (ANA)
        anti-smooth-muscle Ab (SMA)
        anti-neutrophil-cytoplasmatic Ab (pANCA)
    - **liver-specific antibodies**
        anti-asialoglycoprotein-receptor Ab (anti-ASGPR)
        anti-solubile-liver Ab (anti SLA)
        anti-liver-pancreasantigen Ab (anti-LP)
        anti-livercytosol Ab Typ-1 (anti-LC1)
        anti-liver/kidney-microsom Ab Typ-1 (anti-LKM1)

- classification by serologic markers (*antibody profile*)
    - Typ-1: ANA/SMA positive (anti-SLA/LP positive, anti-ASSGPR, pANCA positive); frequency rate: 80%
    - Typ-2: anti-LKM1 positive (almost always severe disease of young women); frequency rate: 3-4 %
    - Typ-3: anti-SLA/LP positive (ANA/SMA positive); frequency rate: 3-4 %

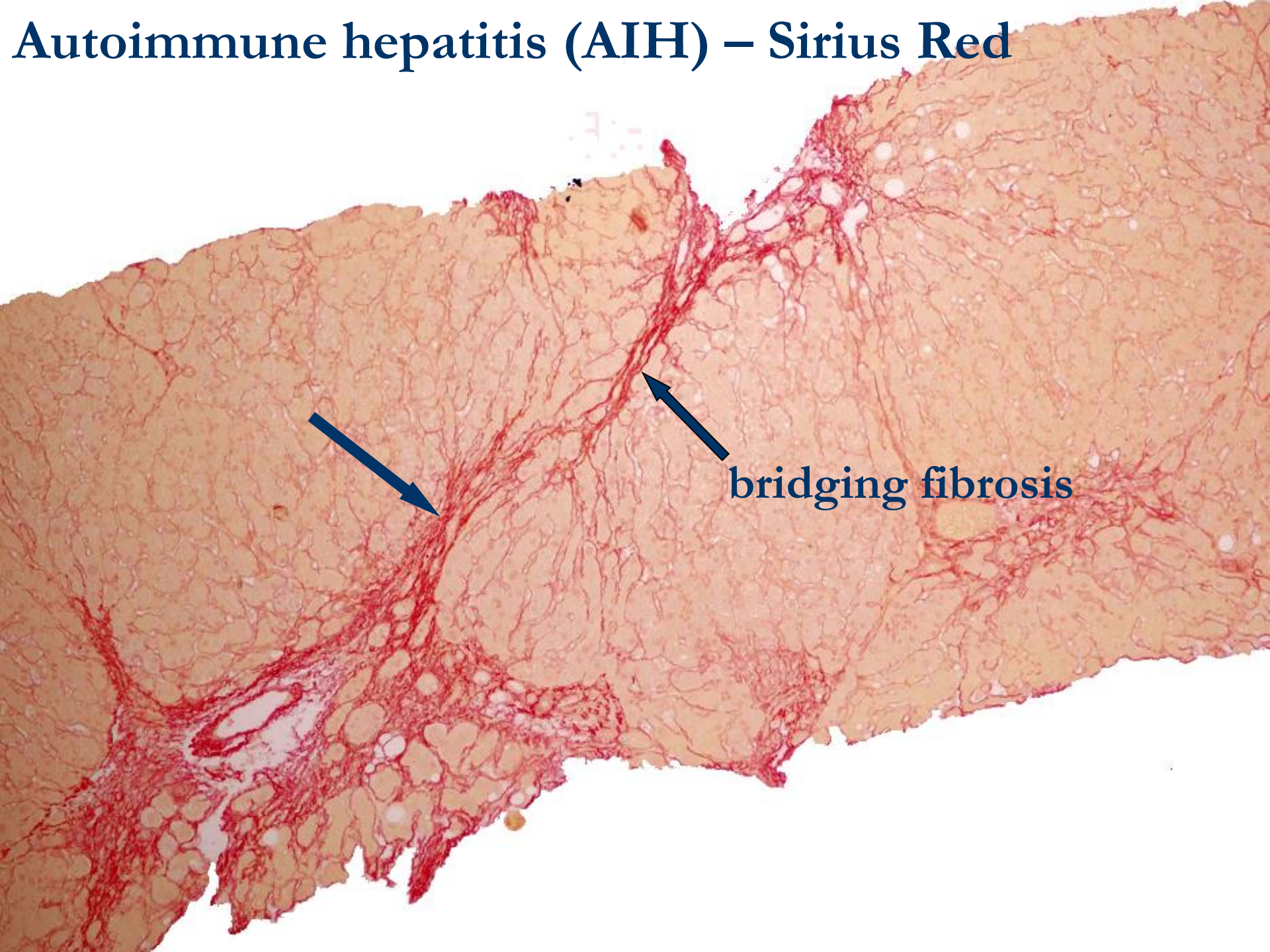
# Autoimmune hepatitis (AIH)

- histologic characteristics
    - 'Interface'- (limiting plate-) Hepatitis
        - periportal, periseptal
        - predominantly lymphoplasmacytic inflammation
    - slight to moderate acinar involvement
    - bridging necroses/-fibroses
        - porto-potal
        - centro-portal
    - rosette like arrangement of hepatocytes
    - nodular regeneration
    - no bile duct damage or granuloma
    - multinuclear hepatocellular giant cells (in children 23%)
    - cirrhosis

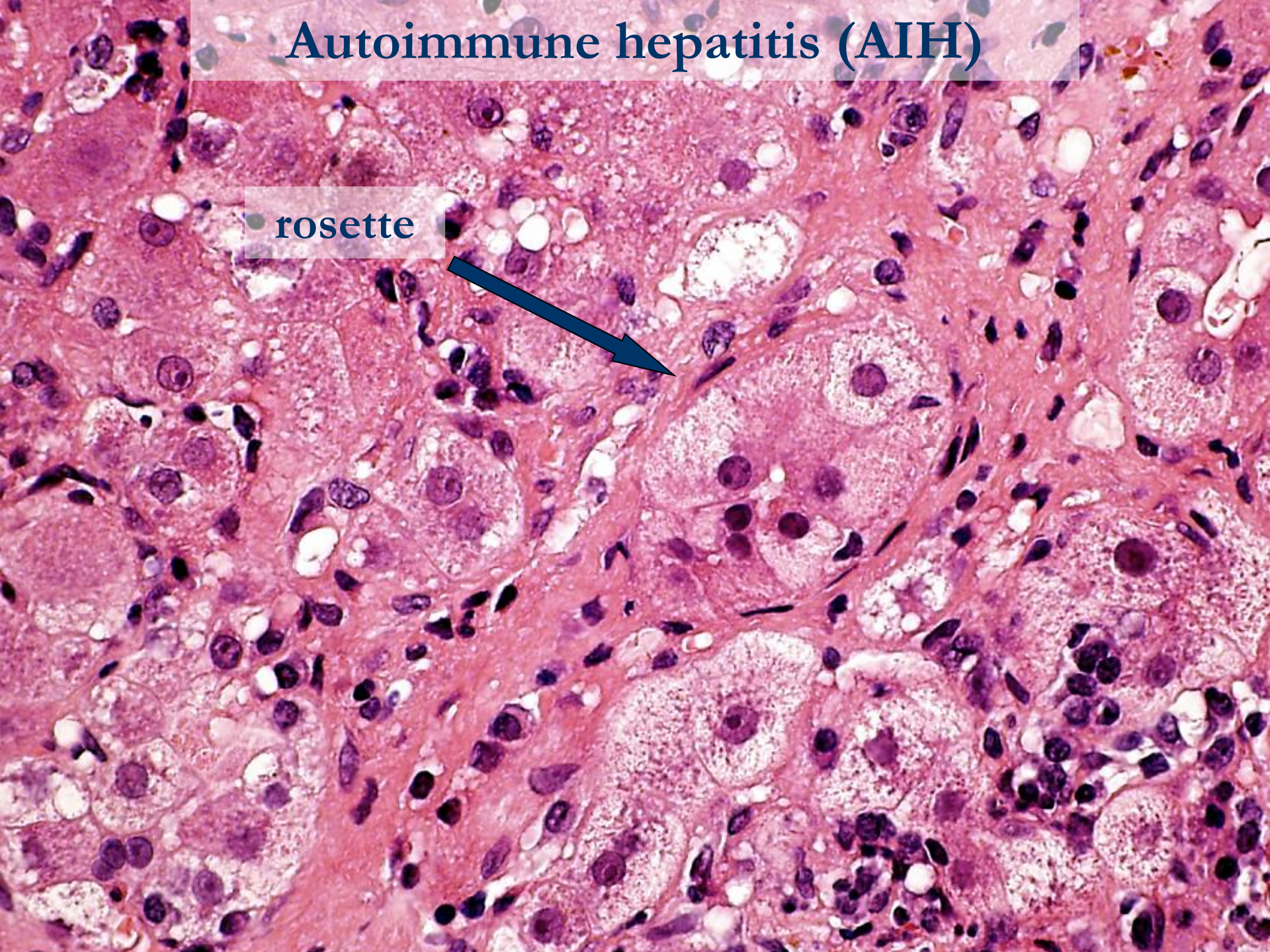
# Autoimmune hepatitis (AIH)



# Autoimmune hepatitis (AIH) – Sirius Red



# Autoimmune hepatitis (AIH)



# Autoimmune hepatitis (AIH)

- histologic scoring system of AIH

| Microscopic findings | Points |
|---|---|
| 'Interface'-Hepatitis | +3 |
| predominantly lymphoplasmacytic Infiltrates | +1 |
| rosette formation | +1 |
| none of the above | -5 |
| bile duct change | -3 |
| changes referring to other etiology | -3 |

# Autoimmune hepatitis (AIH)

- histologic scoring system of AIH: interpretation of altogether values*

| | |
|---|---|
| **Before therapy** | |
| Definitive AIH | >15 |
| Probable AIH | 10-15 |
| No AIH | <10 |
| **After therapy** | |
| Definitive AIH | >17 |
| Probable AIH | 12-17 |

** Altogether values although are quantitative, yet do not refer to severity of the disease .*

- role of histology in the diagnostics ofAIH
  - typical, yet not specific
  - important is to exclude other liver diseases
  - no diagnosis of AIH is advisible without histology

# Biliary liver cirrhosis

- damage of (smaller or larger) bile ducts >> cholestasis >> liver cell damage with necrosis >> cirrhosis (colour deep green )
- causes are (a) 'primary' o. (b) secondary:

  (a) *primary biliary cirrhosis* (PBC) and *primary sclerosing cholangitis* (PSC) are **autoimmune diseases** of the **intrahepatic** small bile ducts

  (b) *secondary biliary cirrhosis* develops following chronic progressive stenosis (e.g. intra- or extra luminar tumor, scarring stricture, lithiasis, iatrogenic-postoperative, etc.) of **extrahepatic** large bile ducts and is generally therefore of no autoimmune nature
- the (b) secondary cholestasis is often complicated by ascending cholangitis (a cholestasis of this type progresses often intermittingly and slowly over longer time >> gradual ascensus of enterobacteria from duodenum >> multiple micro-abscesses along bile-filled and dilated ducts)

# Primary biliary cirrhosis (PBC)

- Definition: a chronic progressive destructive nonsuppurative cholangitis of smaller intrahepatic (interlobular) bile ducts
- PBC is followed by scarring and cirrhotic remodelling of liver parenchyma
- **suspected autoimmune pathomechanism**
- sex distribution: female dominance of 6:1
- patients are tipically of middle aged groups
- leading clinic clinical symptoms skin itchiness, later hyperpigmentation, xanthelasmae
- **labordiagnostically**: elevated serum-phosphatase and serum-cholesterin-values, **proof of autoantibodies (v.a. AMA)**, later hyperbilirubinaemia
- in cirrhotic stage symptoms and complications are like those in cirrhoses of other etiologies
- **in PBC parallel autoimmune diseases are common**: e.g. **Sjögren-syndrome, rheumatoid Arthritis, Glomerulonephritides, Sclerodermia, Cöliakia, Raynaud-disease**

# Primary biliary cirrhosis (PBC)

- histologically 4 stages are defined
- *Stage I.*: chronic destructive non-suppurative cholangitis – around small interlobular bile ducts intensive lymphocytic infiltrates and frequent formation of granulomas. Within hepatocytes often proof of copper-protein-complexes. No cholestasis at this stage.
- *Stages II. and III.*: progressive proliferation and scarring of bile ducts with cholestasis
- *Stage IV.*: classic cirrhosis and severe cholestasis

# Primary sclerosing cholangitis (PSC)

- disease of the middle and large sized (intra- and extrahepatic) bile ducts with inflammation fibrosis and progressive stenosis
- radiologically typical picture: varyingly and irregularly stenosed and dilated bile ducts
- **suspicion for autoimmune etiology**
- male dominance: M/W - 2:1
- **coexpression with ulcerative colitis to 70% (!)** of PSC-patients
- leading clinical symptoms: fatigue, itching (*pruritus*), progressive icterus
- labordiagnostically: elevated se-alk. phosphatase-values
- transmission to a cholangiocarcinoma is possible
- therapeutically liver transplantation
- histomorphology fibrosing progressive cholangitis with onion skin-like concentric collagenic fibres and dense lymphocytic infiltrates around diseased bile ducts >> stenosis and obliteration of ducts with destruction of epithelial lining >> dilation and cholestasis of the prestenotic ducts >> end stage: biliary cirrhosis

# 3.
# Oligo-, polysystemic (systemic) diseases

# Oligo-, polysystemic (systemic) diseases

1. SLE (discoid, subacute-cutanous, chronic, connatal, drug-induced)
2. Sjögren-Syndrome („Sicca-Syndrome")
3. Sclerodermia (systemic sclerosis)
4. Rheumatoid arthritis
5. Idiopathic inflammatoric Myopathy (Dermatomyositis, Polymyositis)
6. Reiter-Syndrome

# Systemic lupus erythematosus – SLE

– *Definition*: a disease with chronic-periodic course of immunologic damages to peripheral small arteries (immune vasculitis) creating a compound clinical picture with changes in various organs.

– variants in namings and forms

- *Lupus erythematosus disseminatus* – synonym for *SLE*, a generalised Form
- *Lupus sine lupo* – a visceral variant without the typical butterfly shaped facial skin appearances (70-80% of SLE cases appear with skin eruptions)
- *Discoide lupus erythematosus* (DLE) – a chronic photosensitive skin eruption typically within the confines of sun-exposed areas like the cheeks, nose, ear, nuchae, hands, later followed by pigmentation, atrophy, scarring, alopecia

– histologically swelling/thickening of collagen fibers and fibrinoid degeneration with leukocyte and lymphoplasmacellular infiltrates primarily within walls of small arteries

# SLE – Etiology and pathogenesis

– Viral: EBV (?)

– Sexual hormones

- 90% of patients are females between 20-30 years of age
- disease progression on oestrogenic therapy
- androgenes act against the disease

– Genetic factors

- HLA-DR2, HLA-DR3
- C3b
- Immuncomplex-elimination

– Possibly associated immunologic anomalies and diseases

- chronic autoimmune hepatitis (AIH)
- Crohn's disease
- rheumatoid arthritis
- Sjögren-syndrome
- Hashimoto-thyreoiditis

# SLE – Clinical presentation

– Typically multiorgan changes with active phases and remissions often starting acutely with a high and irregular course of long-term fever, polyarthritis and the typical butterfly shaped bilateral facial erythema

– *General symptoms*: bad general feeling, loss of appetite, tiredness, weight loss, fever

– *Joints*: painful polyarthritis later with deformities

– *Skin*: facial butterfly shaped exanthemas, lilac to red efflorescences upon light-exposed areas and extensor sides of extremities

– *Kidneys*: focal or diffuse glomerulonephritis (so-called wireloop- or lupus-nephritis) clinically presenting with nephrosis syndrome, finally uraemia

– *Cardiovascular*: Liebman-Sacks endocarditis, myocarditis and stenosing coronary vasculitis, thrombophlebitides, Raynaud-syndrome

– *Respiratory organs*: serous pleuritis (together with pericarditis and peritonitis: polyserositis), callous formation, interstitial pneumonia (pneumonitis)

– GI-tract: hepatosplenomegaly, ‚lupoid' hepatitis, ulcerative colitis

# SLE – Antibodies

– against serum proteins: complement and hemostatic proteins

– against antigenes of circulating blood cells: erythrocytes, thrombocytes, leukocytes, lymphocytes

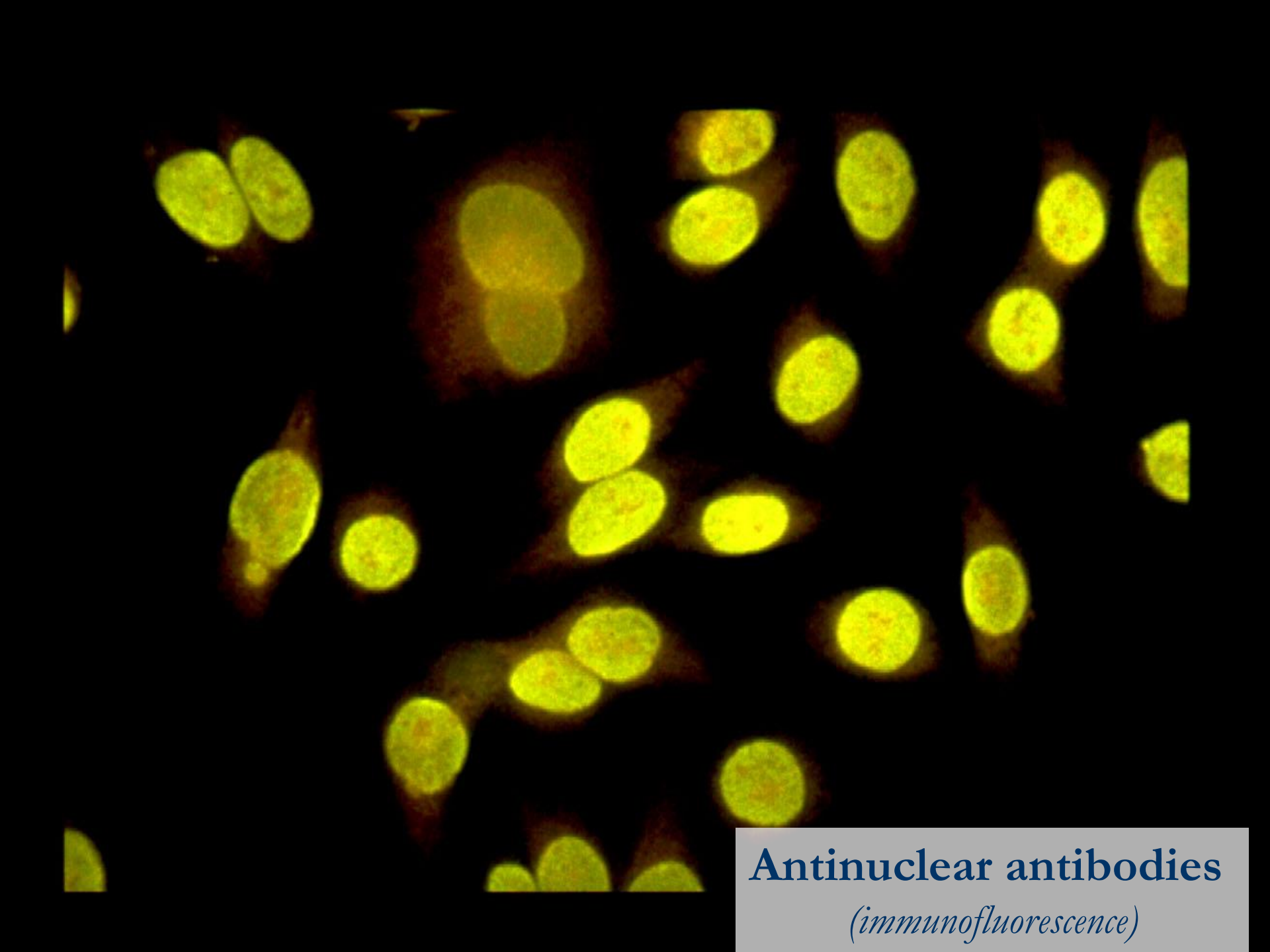
- against cytoplasmatic proteins: microfilaments, microtubuli, lysosomal, ribosomal proteins

– against nuclear antigenes: anti-dsDNS, Sm/RNP (*Smith extractable nuclear Ab+Ribonucleoprotein extractable nuclear Ab*): a pathognomic immunologic change

# SLE – Diagnosis

1. Butterfly facial erythema (Dermatitis)
2. Discoid Lupus
3. Photosensitivity
4. Mucosal ulceration
5. Arthritis
6. Pleuritis, Pericarditis
7. Glomerulonephritis
8. CNS-changes
9. Hemopoietic system
    - 9.1. Hemolytic Anemie
    - 9.2. Leukopenia
    - 9.3. Lymphopenia
    - 9.4. Thrombocytopenia
10. Immunologic changes
    - 10.1. anti-DNA AK
    - 10.2. anti-Sm AK
    - 10.3. Fas-positive VDRL test *or* positive anti-cardiolipin Ab-test
11. Antinuclear Ab

**For diagnosis at least 4/11 positivities needed**



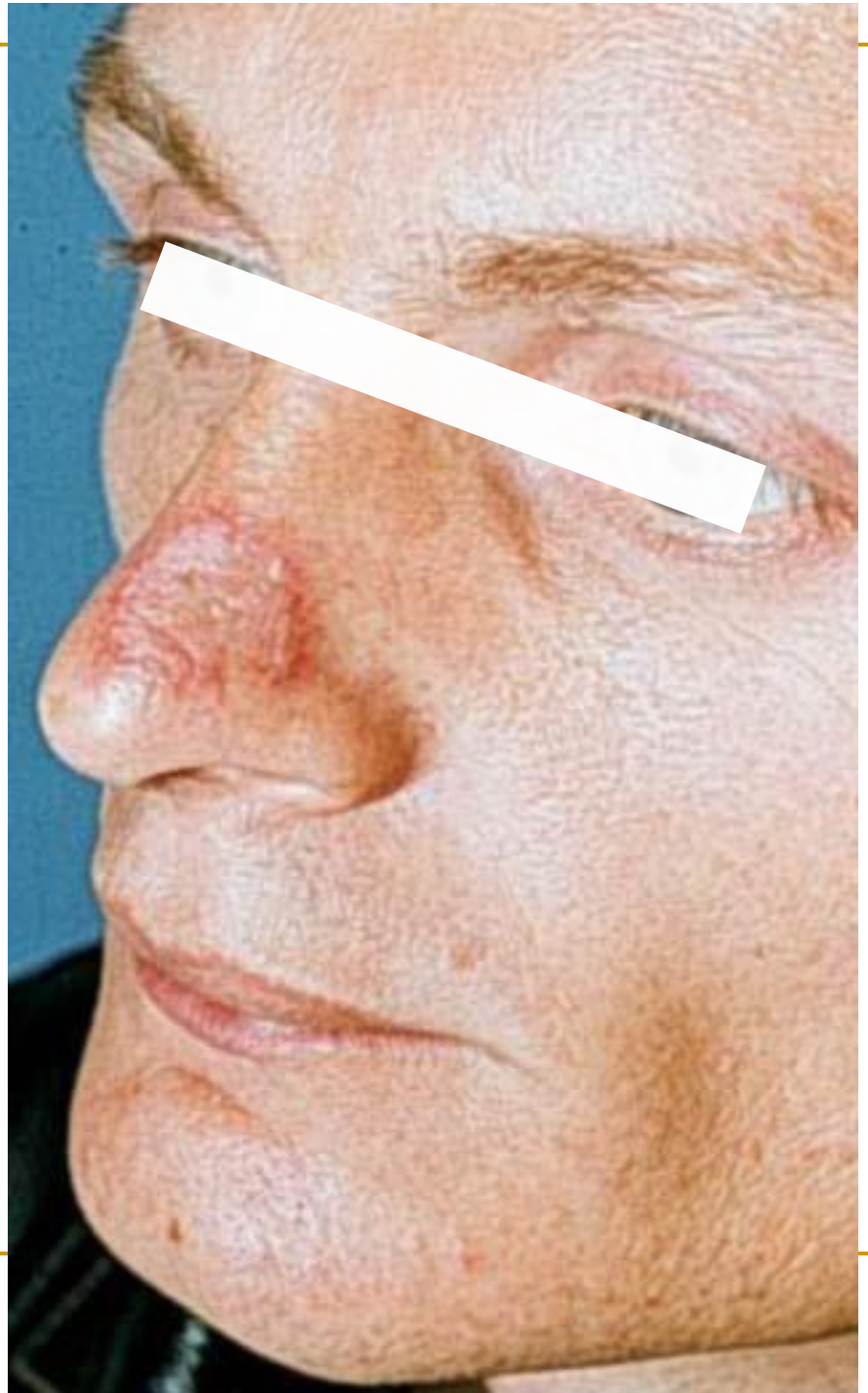
**Antinuclear antibodies**

*(immunofluorescence)*

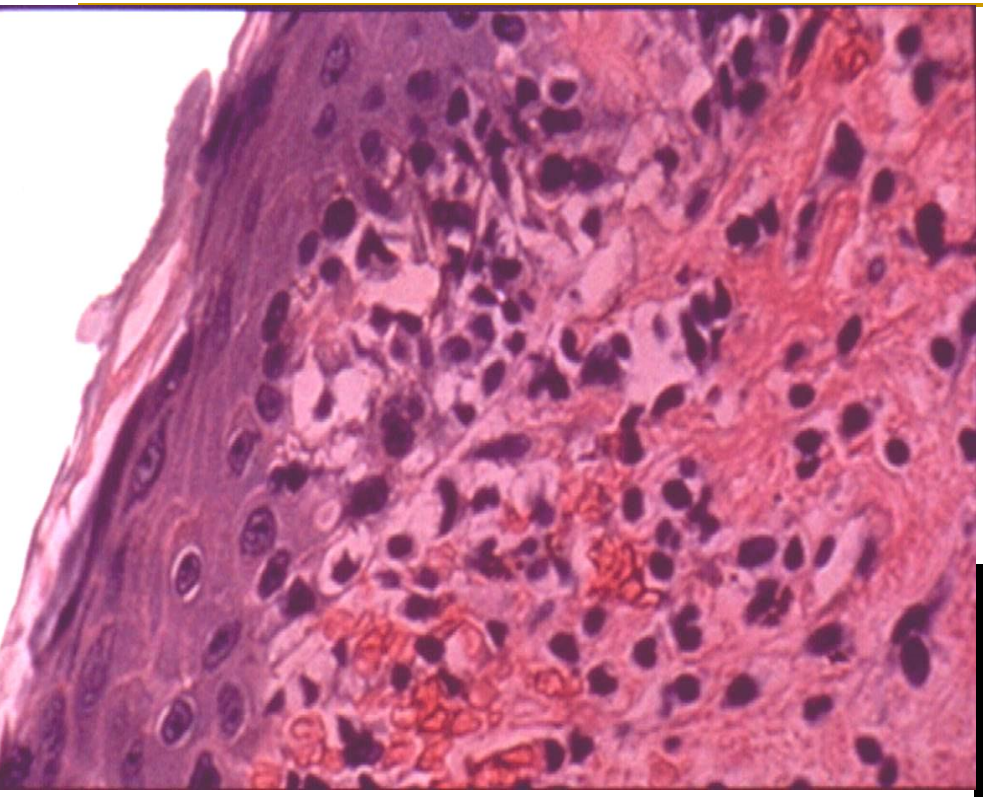
# Antinuclear antibodies in autoimmune diseases

| Antigen | Anti-bodies | SLE | Diffuse SSC | Limited SSC | Sjögren-syndrome | PM |
|---|---|---|---|---|---|---|
| Native DNS | Antidouble-lined DNS | ++ | – | – | – | – |
| RNP (Smith-Ag) | Anti-Sm | + | – | – | – | – |
| RNP | SS-A (Ro) | + | – | – | ++ | – |
| RNP | SS-B (La) | + | – | – | ++ | – |
| Topoiso-merase | Scl-70 | – | ++ | + | – | – |
| Centromer | Anti-Centromer | – | + | ++ | – | – |
| Histidil-tRNS-Syntetase | Jo-1 | – | – | – | – | + |

# SLE – Skin

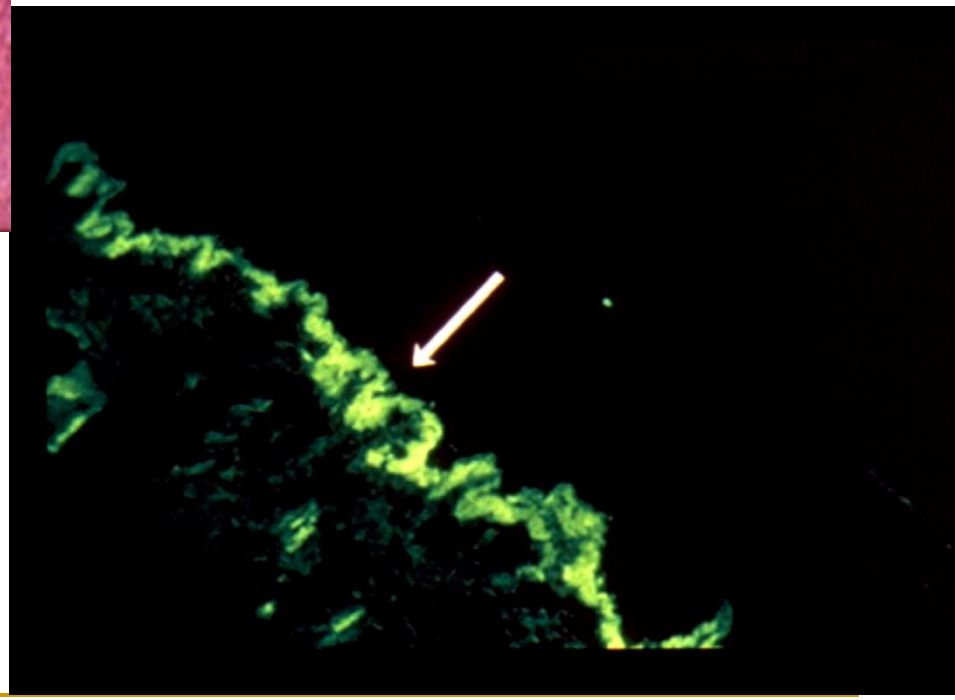


# SLE

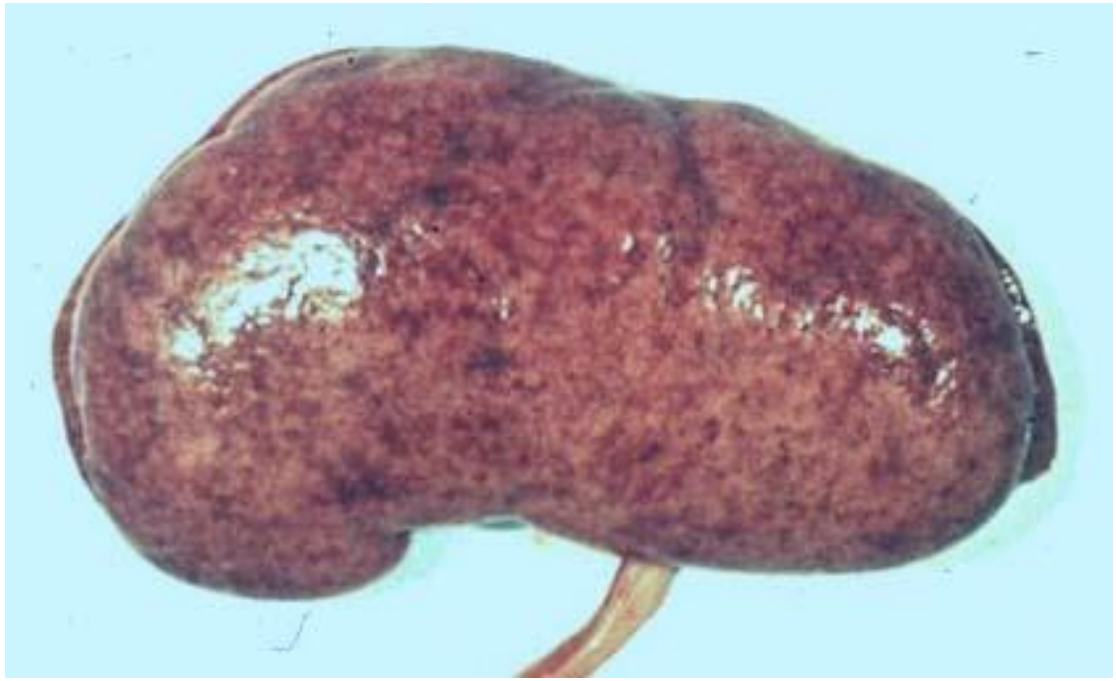


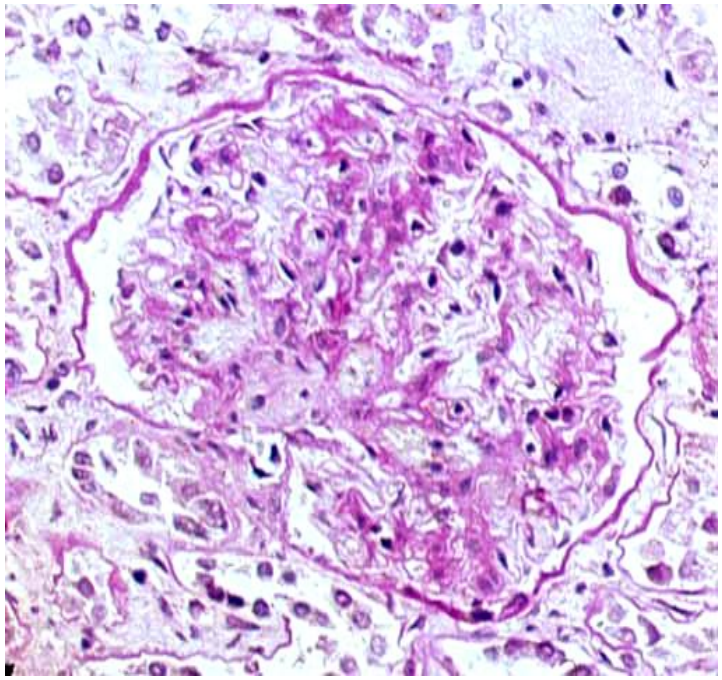
H&E: Lysis of basal cells in the epidermis

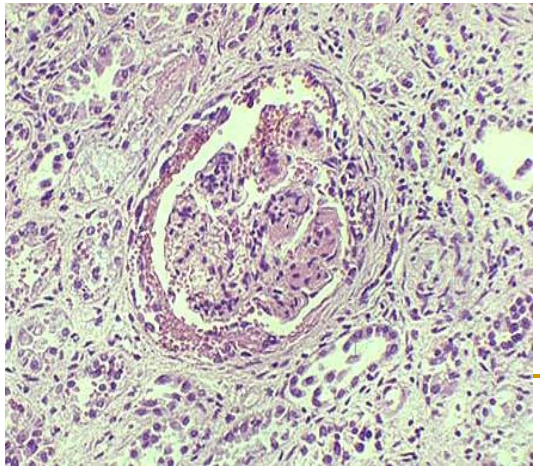
Granular immundeposits along the dermo-epidermal junction

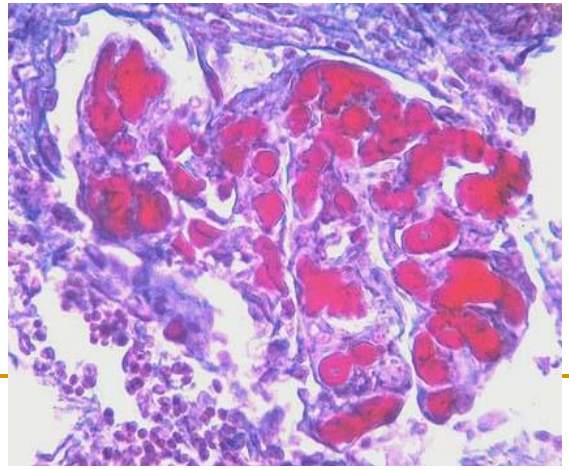


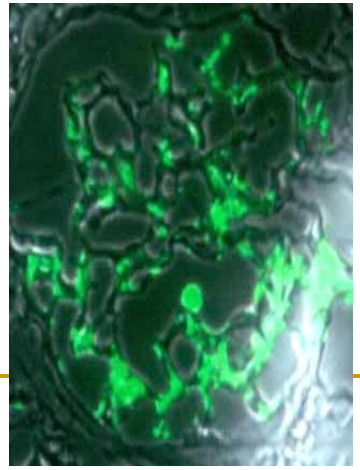
# SLE – Kidney

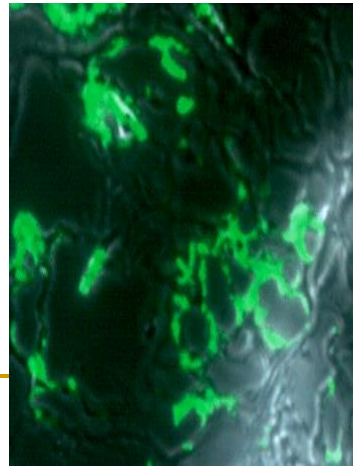


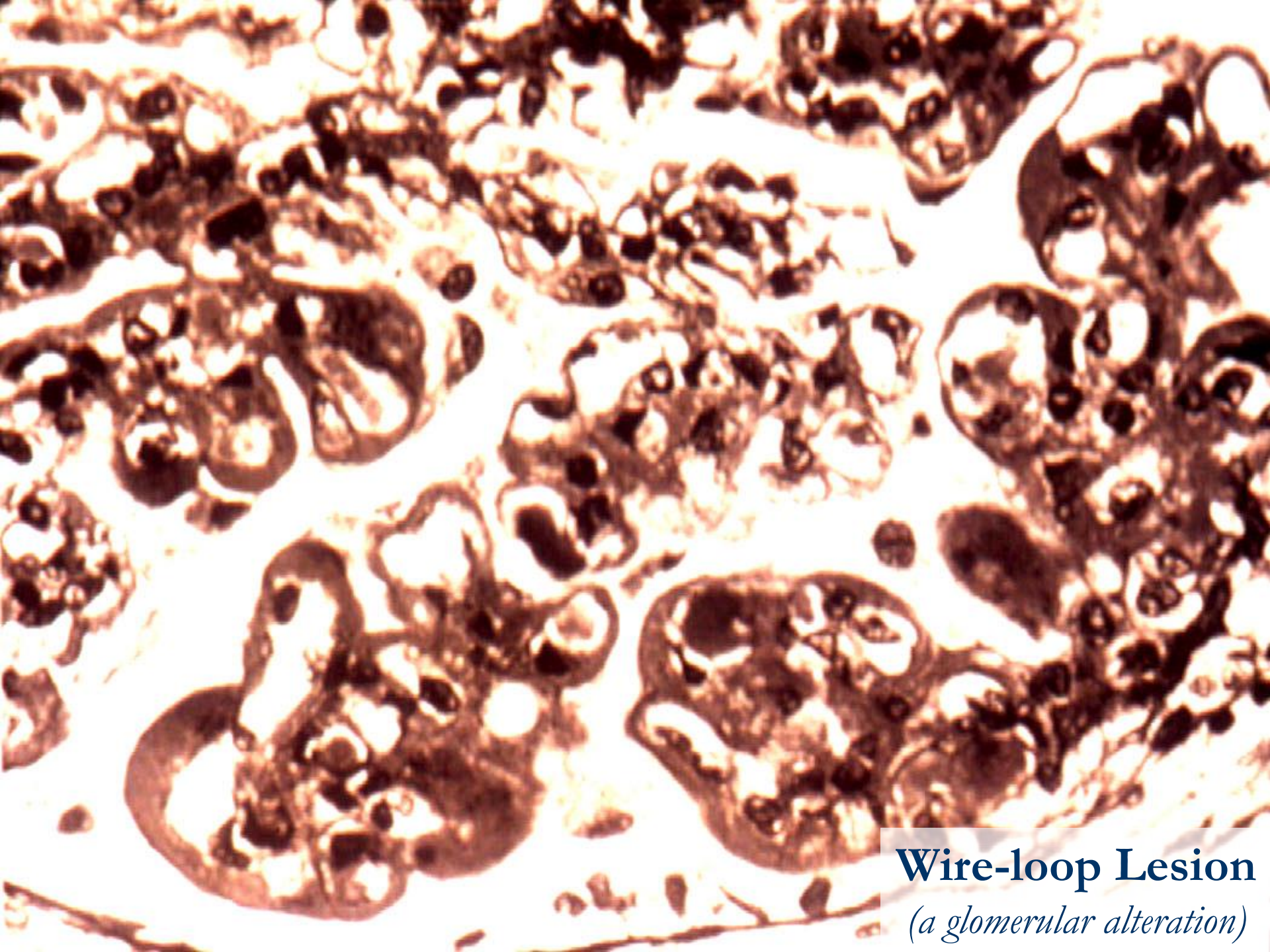










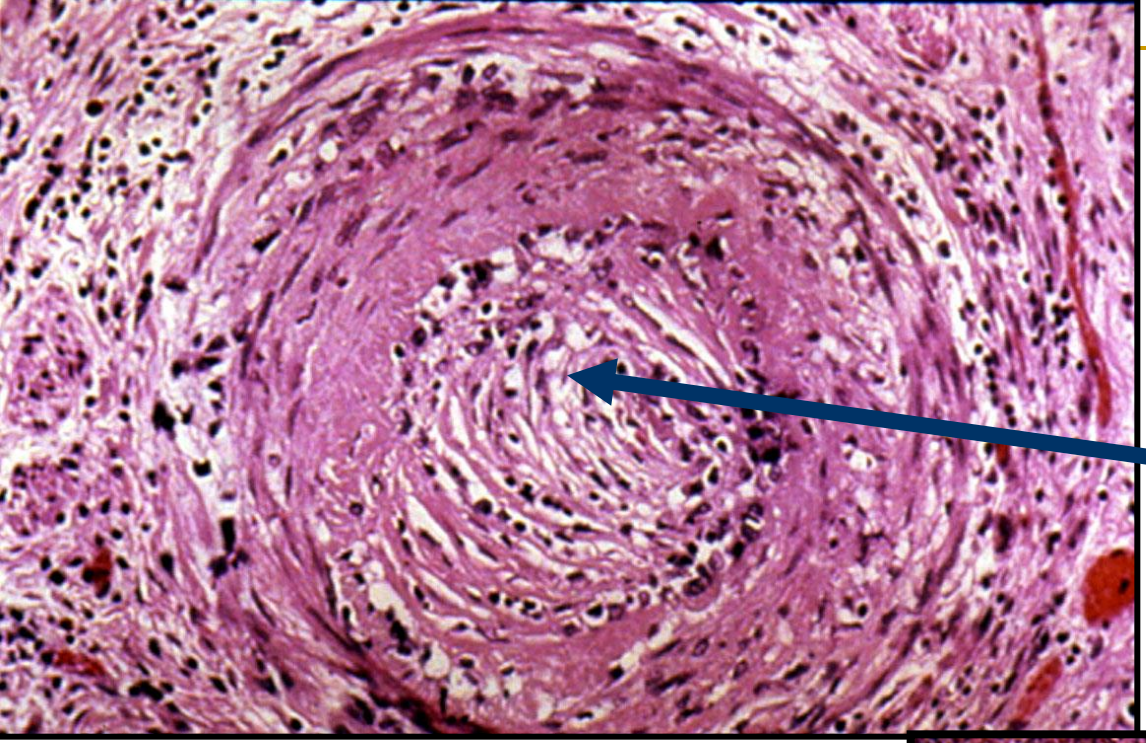


**Wire-loop Lesion**

*(a glomerular alteration)*

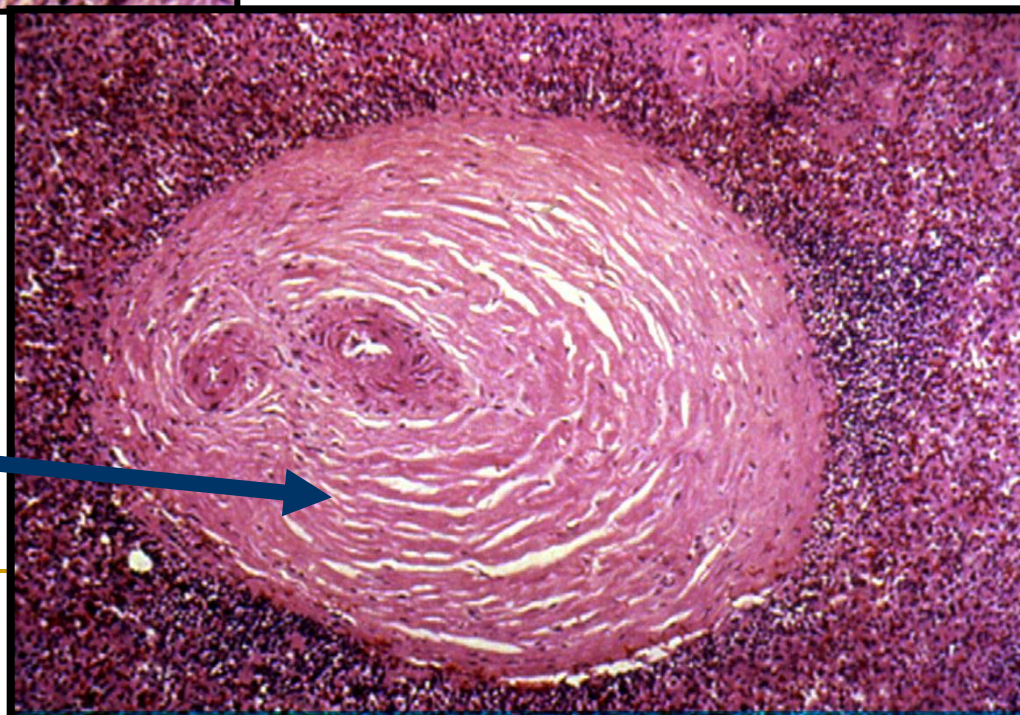
# Libman-Sacks endocarditis in SLE

# SLE – Vasculitis



Occlusion of vascular lumina

Perivascular fibrosis (onion skin lesion) in the spleen

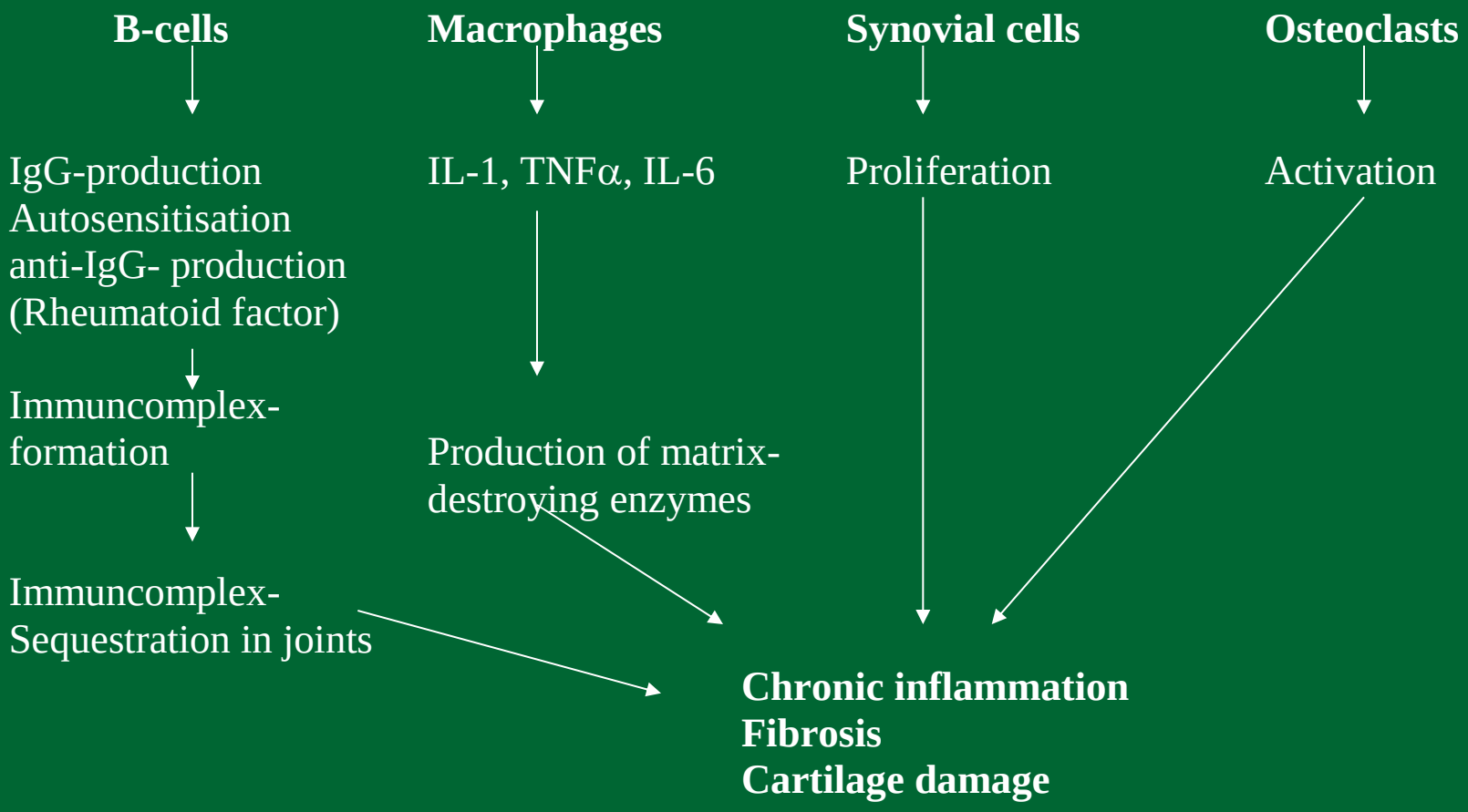


# Rheumatoid arthritis (RA)

# RA – Pathomechanism

**New AG on synoviale surfaces + genetic predisposition**

CD4+ T-cell activation
(IL-2, IFNγ, TNFα, GM-CSF, IL-6)



# RA – Pathomechanism

- Derangement of the humoral immune system: Rh-factor

- Derangement of the cellular immune system : T-helper-activation

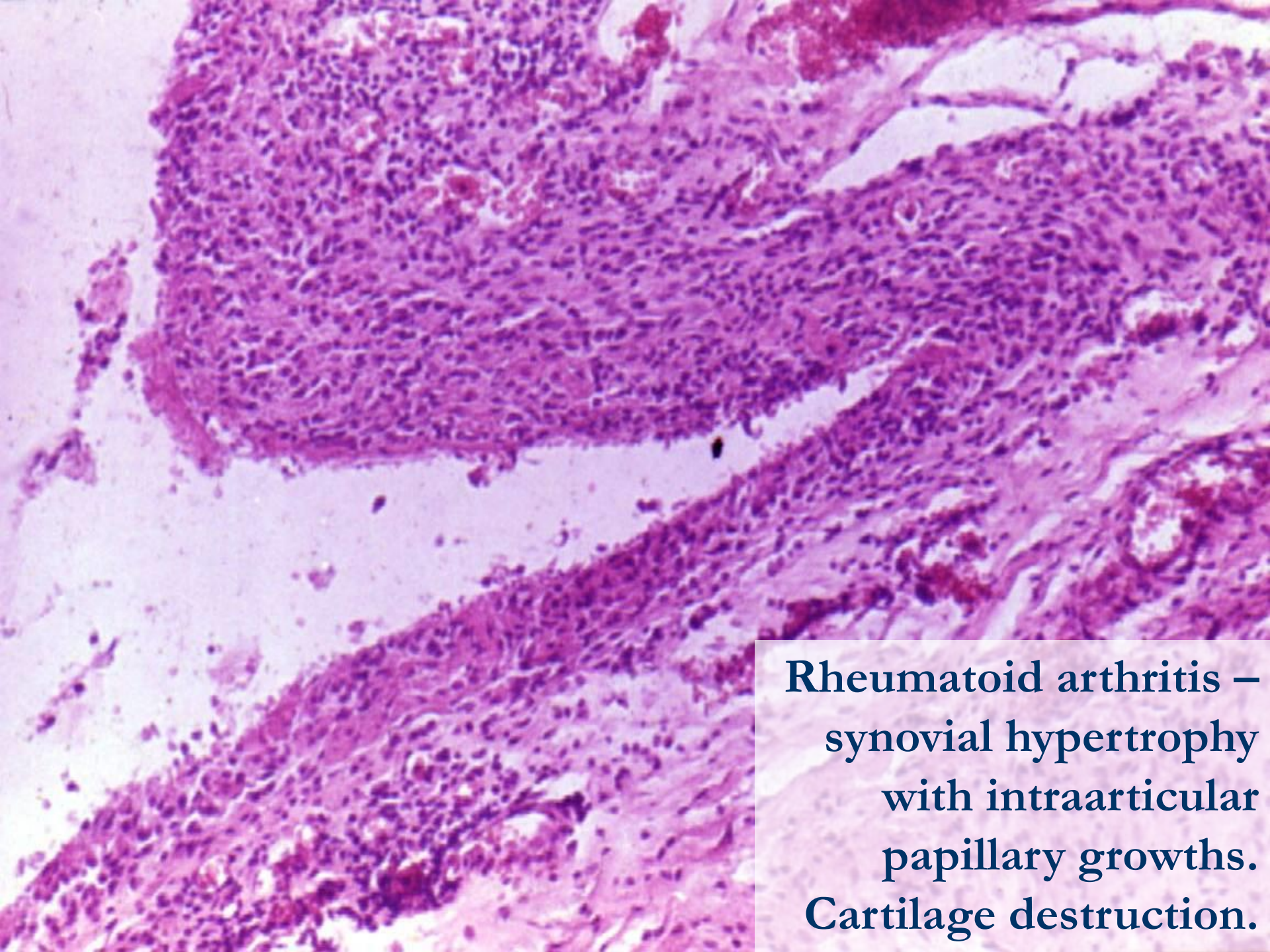
- Possible role of infections (??): EBV, Parvovirus, Mycoplasma, Mycobacterium

# RA – Variants in appearances

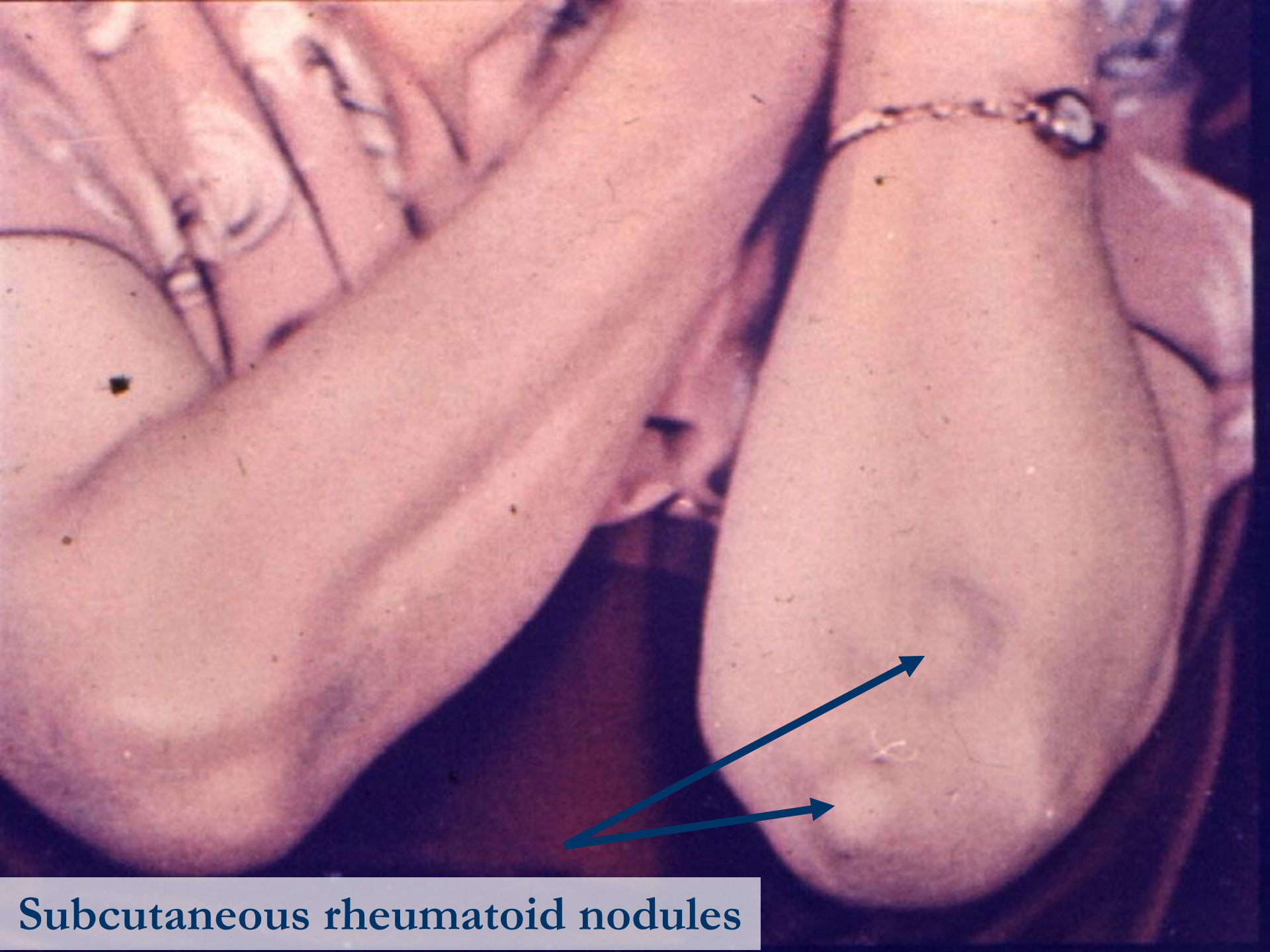
| | |
|---|---|
| **Joints** | Arthritis |
| **Skin** | rheumatoid nodules, vasculitis |
| **Eyes** | episcleritis, uveitis, retinitis, glaucoma, cataract |
| **Lung** | pleuritis, interstitial fibrose |
| **Heart** | pericarditis, myocarditis, coronary-arteritis, endocarditis |
| **CNS** | multiple neuritides |

# RA – Morphology

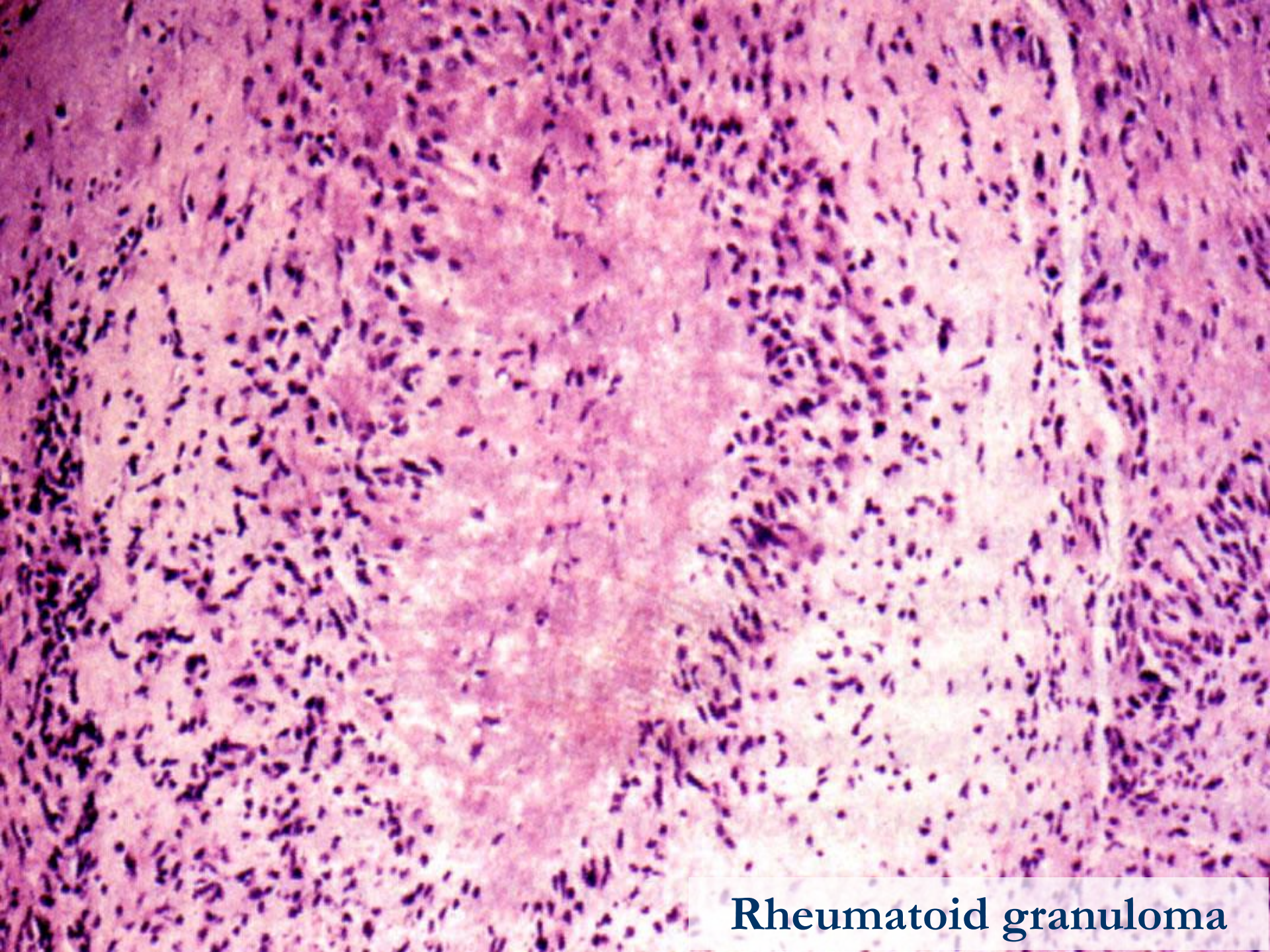
- synovial hypertrophy, villus fomation
- cartilage damaging
- pannus formation
- rheumatid granuloma
- vasculitis



Rheumatoid arthritis – synovial hypertrophy with intraarticular papillary growths. Cartilage destruction.



Subcutaneous rheumatoid nodules


Rheumatoid granuloma

# Progressive systemic sclerosis – PSS

– Definition: a chronic stiffening, fibrosis, sclerosis and shrinkage/retraction of cutaneous, subcutaneous and visceral connective tissues

– above all in females between 35-50 years of age

– Synonyms

- *Systemic sclerosis* –
- *Sclerodermia* –
- *Progressive Systemic Sclerosis* (PSS) –

– histologically in the periphery of sclerosing a predominantly lymphoplasmahistiocytic, fibroblastic infiltration, obliterating arteriitis and intimal proliferation

# Sclerodermia
# (progressive systemic sclerosis)

- Diffus sclerodermia (systemic sclerosis)

fibrosis of the skin gastrointestinal tract lungs kidneys and heart

- Limited sclerodermia : sog. CREST-sy.

C - *calcinosis cutis*

R - *Raynaud sy.*

E - *esophageal dismotility*

S - *sclerodactylia*

T - *teleangiectasia*

# PSS – Clinical presentation

– general symptoms : general weakness, weight loss, muscle and joint pains, fever, accelerated blood sedimentation. Long-term prognosis bad with uncontrolled progression and death because of cardiac pulmonary or renal disease

– *Skin*: through scarring of connective tissue framework shrinkage of the cutaneous surfaces, narrowing, atrophy, later necrosis and ulceration of acral parts (above all fingertips). Finger movements becomes limited (*Sklerodaktylie*), the palm of the hand is contracted, the face is stretched with poor in mimics, the nose is pointed and narrow, the oral opening is slimmed and little movable surrounded by radially wrinkled skin, the lips are slim and retracted so the teeth are visible, limitation of neck movements because of skin stretching

– *Soft tissues*: Extensive calcifications (*calcinosis*)

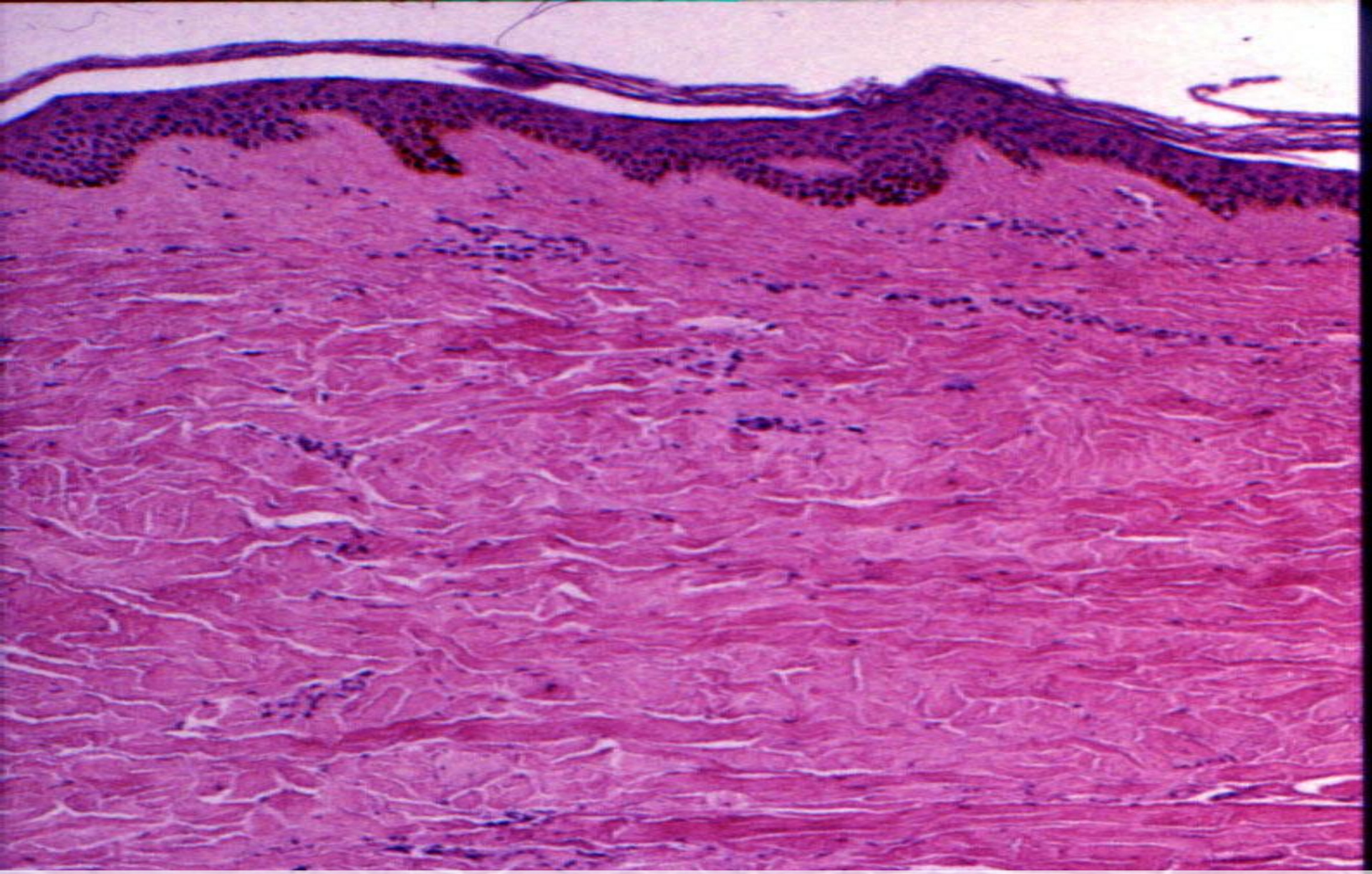
– *GI-tract*: limited esophageal and gastric movements the esophagitis becomes a narrowed stiff tube causing problems of swallowing and esophagitis and ulceration

– *Lung*: interstitial fibrosis with cor pulmonale chronicum

– *Heart*: myocardial fibrosis and low output syndrome arrhythmias

# Sclerodermia (PSS) – Pathomechanism

- unknown extracellular matrix-antigen
- immune activity changes (IL-4, TGFb…)
- endothelial damage
- vascular proliferation

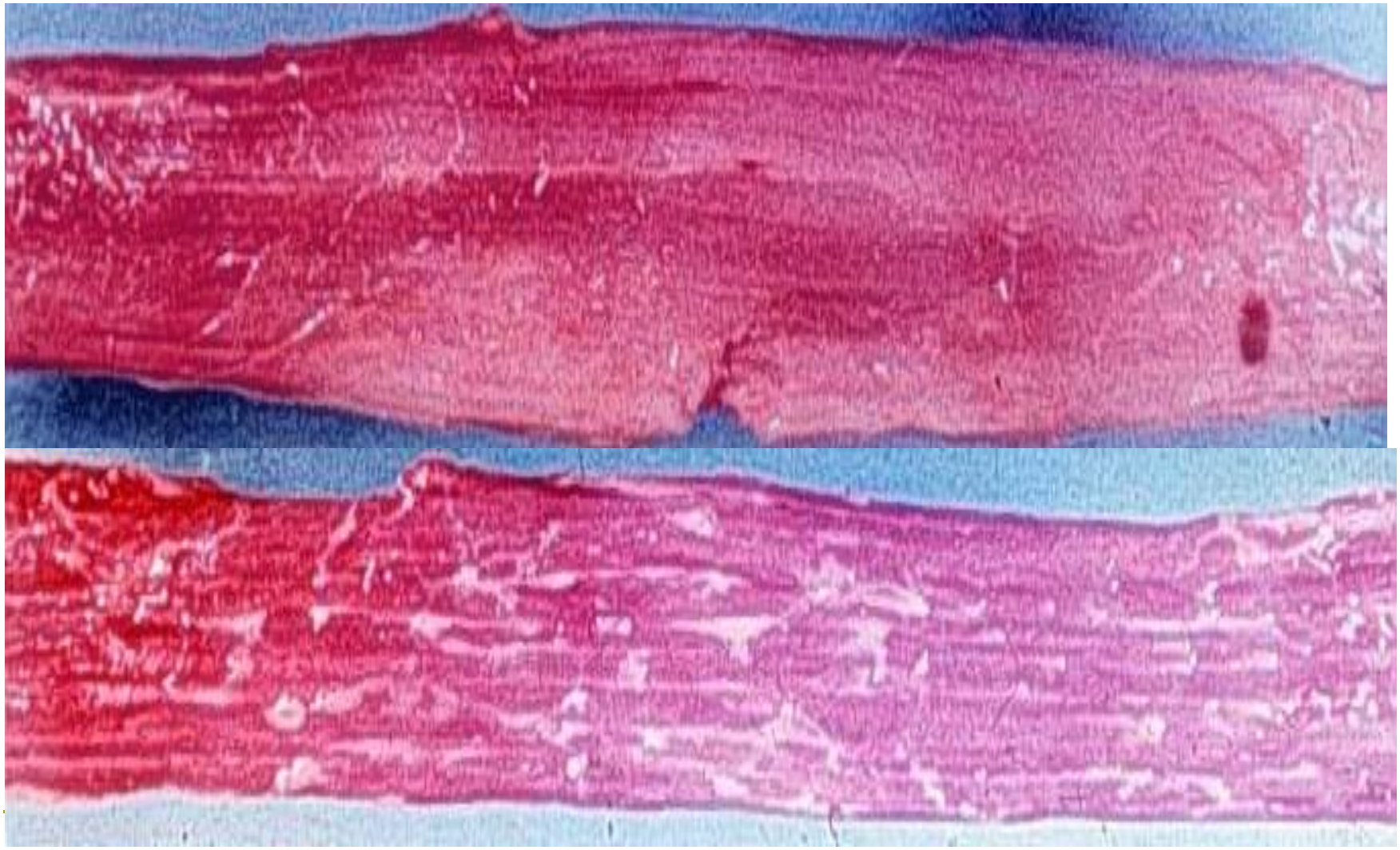


Extensive dermal deposition of thick collagene fibers, complete abscence of dermal appendiges

# Antinuclear antibodies in autoimmune diseases

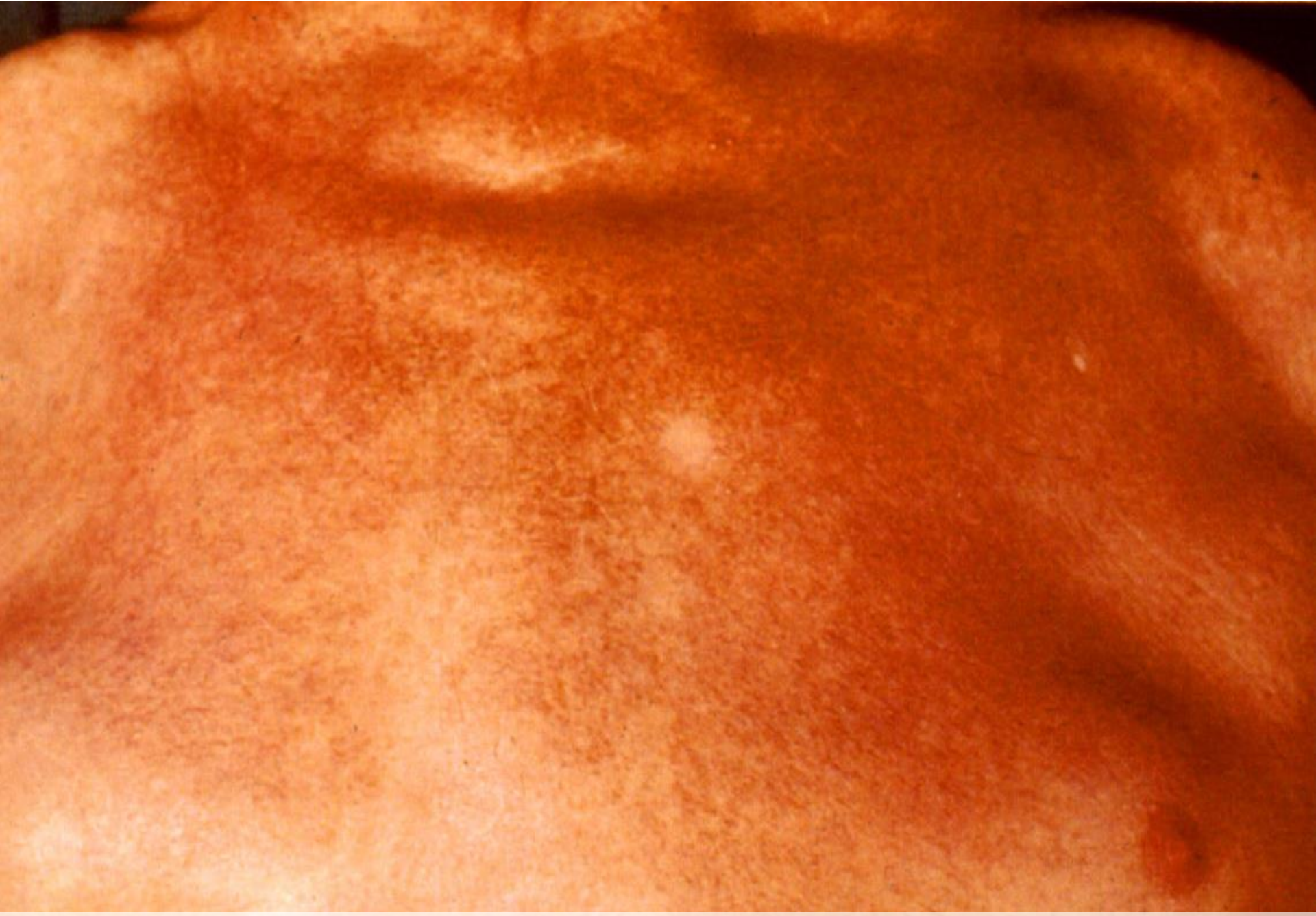
| Antigen | Anti-bodies | SLE | Diffuse SSC | Limited SSC | Sjögren-syndrome | PM |
|---|---|---|---|---|---|---|
| Native DNS | Antidouble-lined DNS | ++ | – | – | – | – |
| RNP (Smith-Ag) | Anti-Sm | + | – | – | – | – |
| RNP | SS-A (Ro) | + | – | – | ++ | – |
| RNP | SS-B (La) | + | – | – | ++ | – |
| Topoiso-merase | Scl-70 | – | ++ | + | – | – |
| Centromer | Anti-Centromer | – | + | ++ | – | – |
| Histidil-tRNS-Syntetase | Jo-1 | – | – | – | – | + |

# Idiopathic inflammatory Myopathy (IMP): Dermatomyositis, Polymyositis



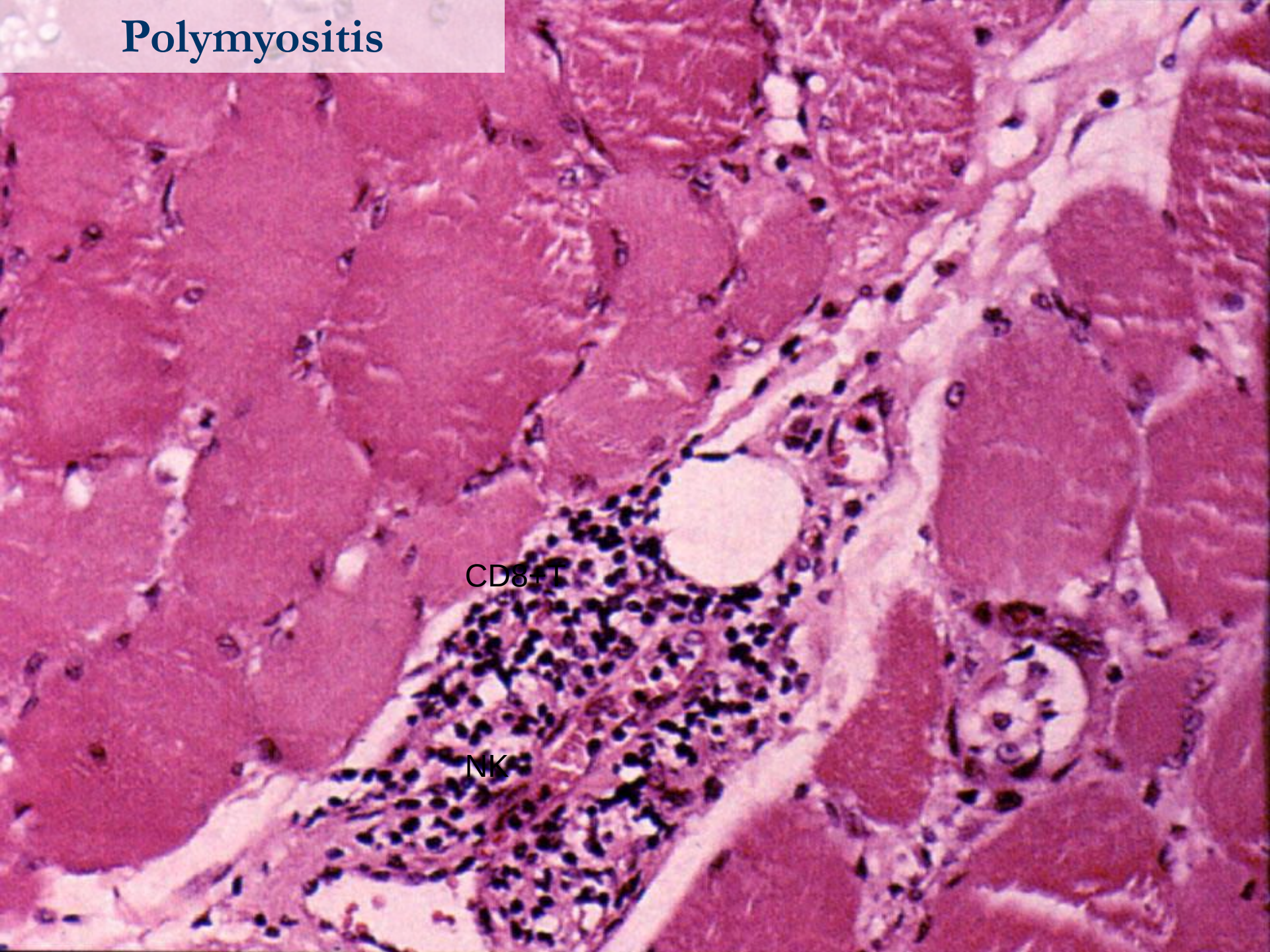
# IMP – Clinical presentation

– *Definition*: generalised inflammatory disease of striated muscles and the surrounding skin (*Dermatomyositis*). Muscular inflammation without cutaneous component is possible (*Polymyositis*).
– *General symptoms*: initially fever, general weakness, gait, dysphagia, speech derangements, diffuse or localised erythema, dermatitis, oedema, later Raynaud-syndrome. In about 20% of the cases there is in the background an evolving or already existing malignancy.
– *Epidemiology*: typical disease of elderly women
– *Pathogenesis*: can follow an acute or chronic course
– *Serology*: elevation of alpha- and gammaglobulins antinuclear antibodies
– *Joints*: painful arthritis
– *Prognosis*: will be defined by the severity of the accompanying visceral components as well as by the development of the background malignancy



Dermatomyositis (skin lesions)

# Polymyositis



# Antinuclear antibodies in autoimmune diseases

| Antigen | Anti-körper | SLE | Diffuse SSC | Limitierte SSC | Sjögren-Syndrom | PM |
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| Native DNS | Antidoppel-läufige DNS | ++ | – | – | – | – |
| RNP (Smith-Ag) | Anti-Sm | + | – | – | – | – |
| RNP | SS-A (Ro) | + | – | – | ++ | – |
| RNP | SS-B (La) | + | – | – | ++ | – |
| Topoiso-merase | Scl-70 | – | ++ | + | – | – |
| Zentromer | Anti-Zentromer | – | + | ++ | – | – |
| Histidil-tRNS-Syntetase | Jo-1 | – | – | – | – | + |