Autoimmune Connective Tissue Diseases and Vasculitides *4.4.19*

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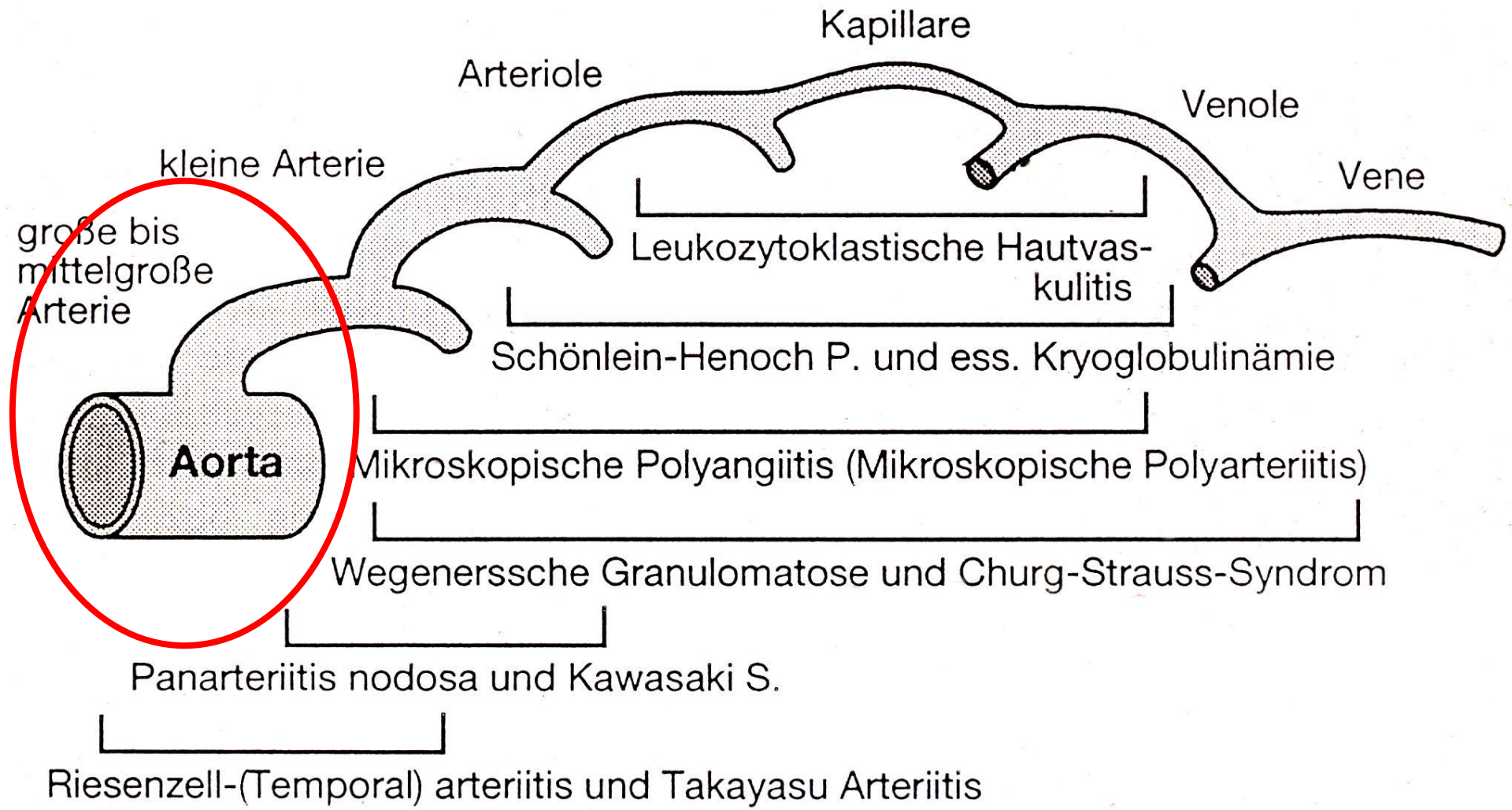
Immunologically mediated systemic vasculitides

- Giant cell arteritis (GCA)
- Panarteritis nodosa (PAN)
- ANCA-associated vasculitides (AAV)
- many others

Pattern of involved vessels



Arteritis cranialis
(sive temporalis, sive giant cell arteritis)

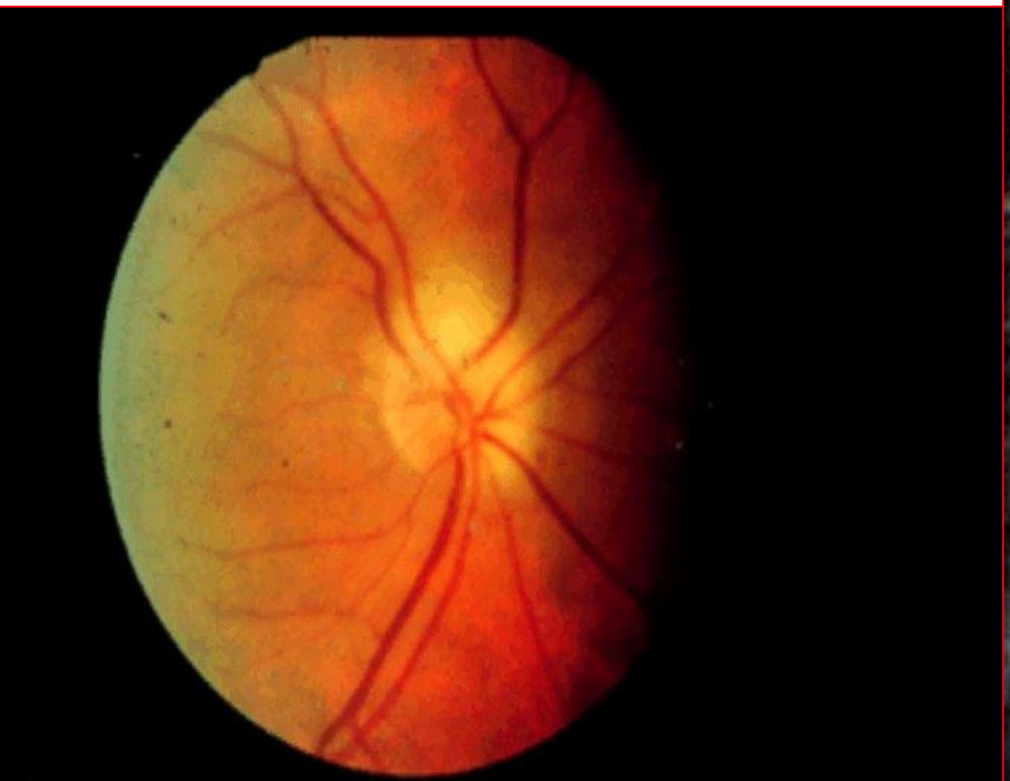
Clinical characteristics

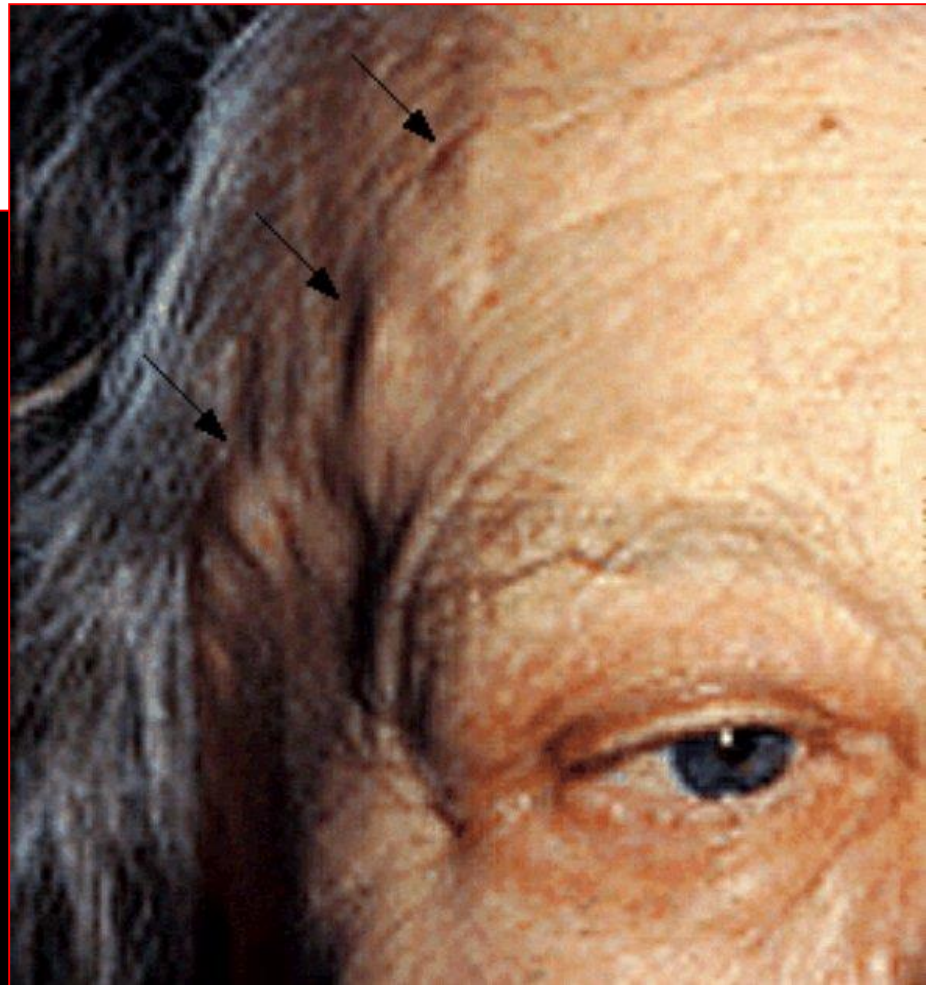
- New headache in the elderly
- Constitutional symptoms *(fever, sweat, weight loss, fatigue)*
- Jaw claudicatio
- Polymyalgia rheumatica

Laboratory features

- high erythrocyte sedimentation rate (ESR)
- thrombocytosis

Arteritis cranialis
(sive temporalis, sive giant cell arteritis)

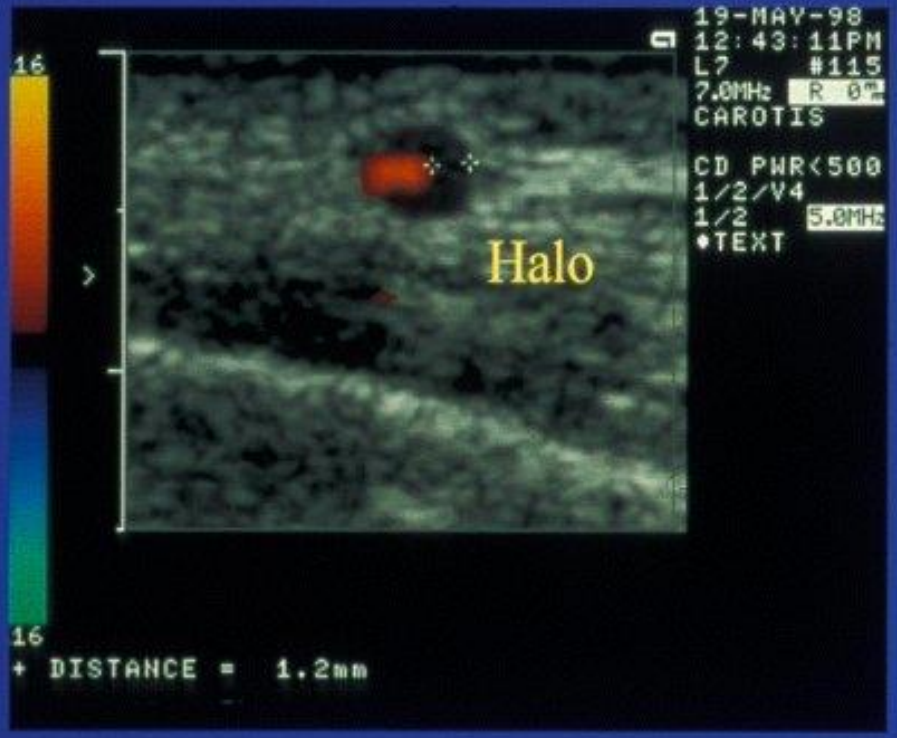




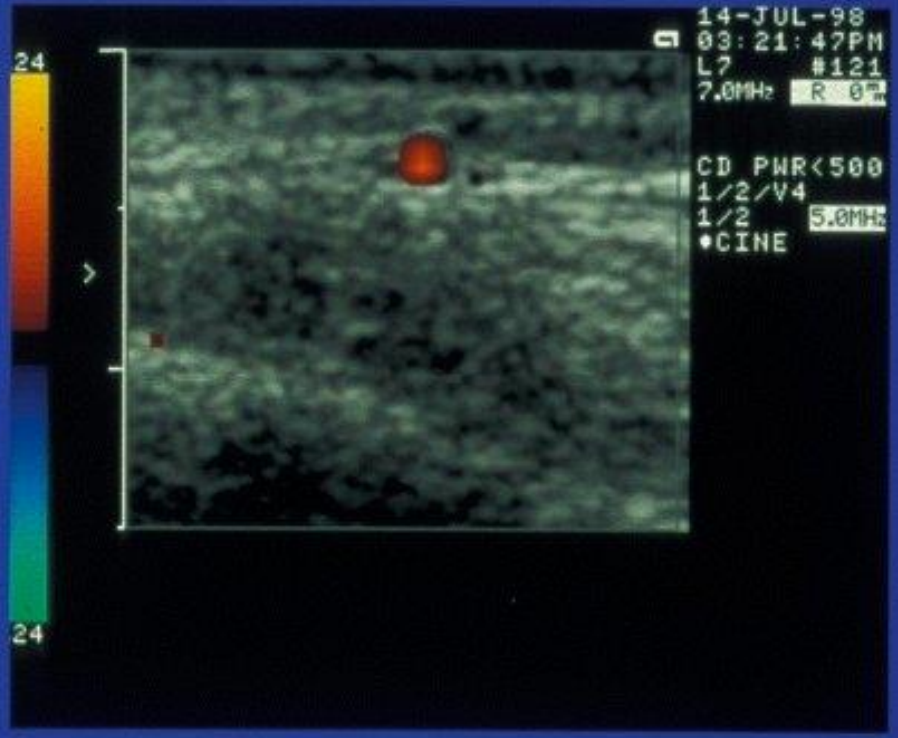
Duplexsonographie

Giant Cell Arteritis

(temporal artery)



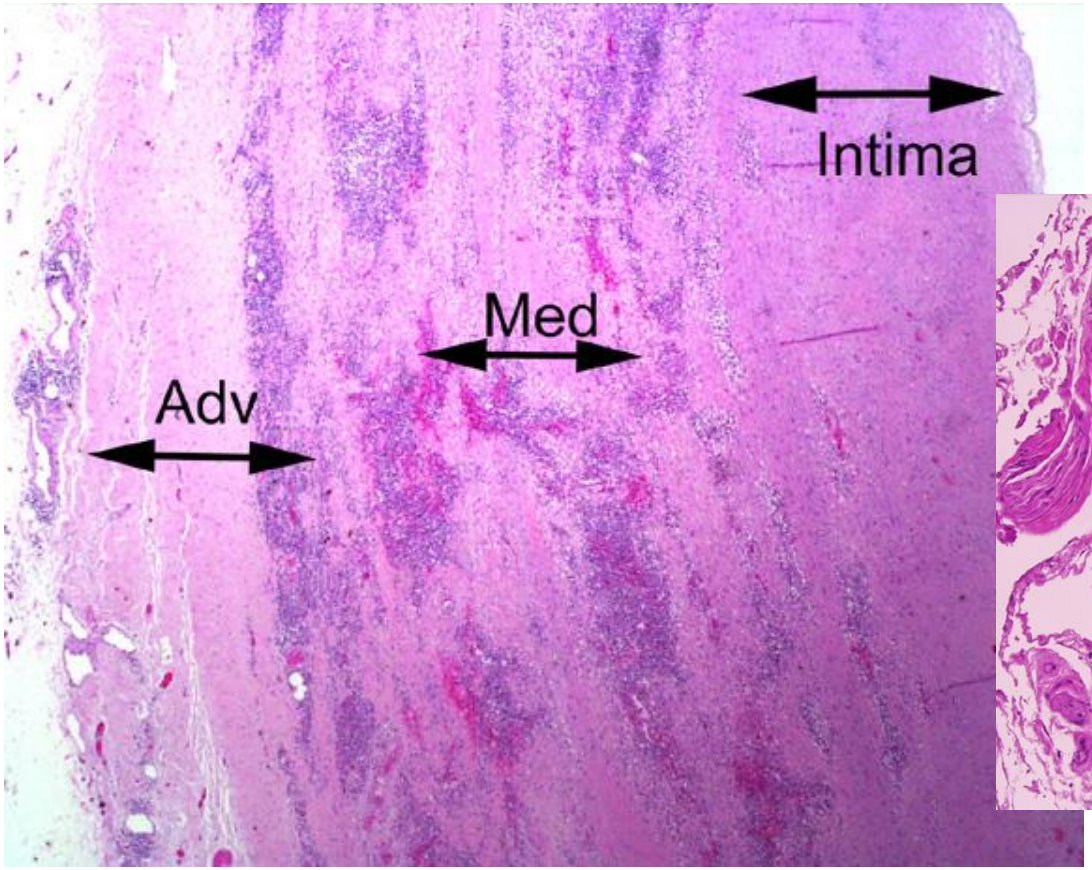
Before Tx

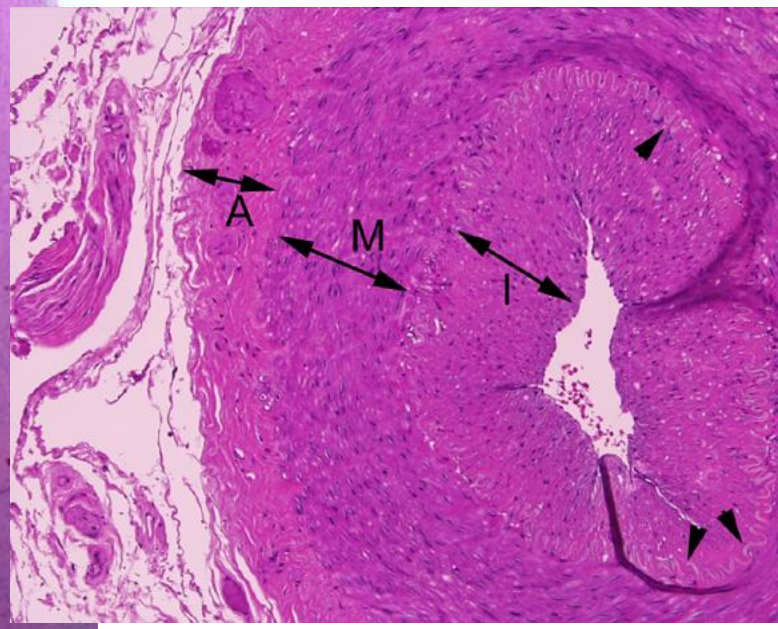


8 wks Pred. Tx

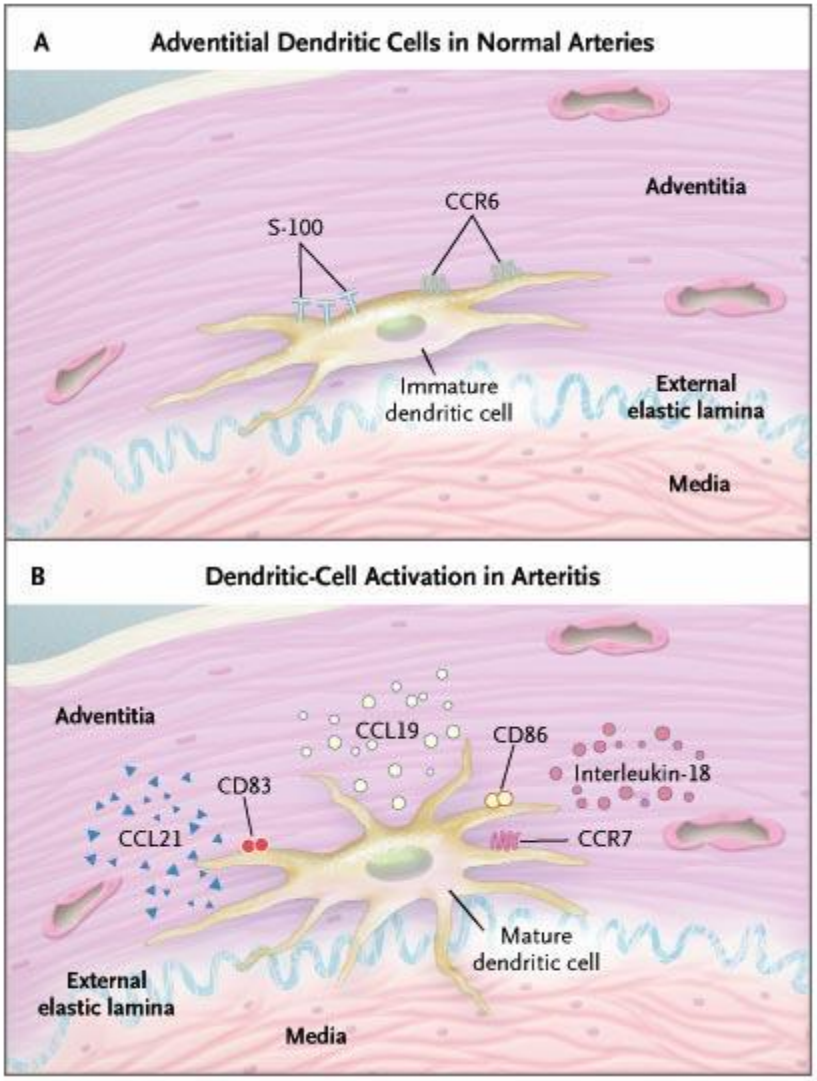
Giant cell arteritis (GCA)

Histology of A.temporalis



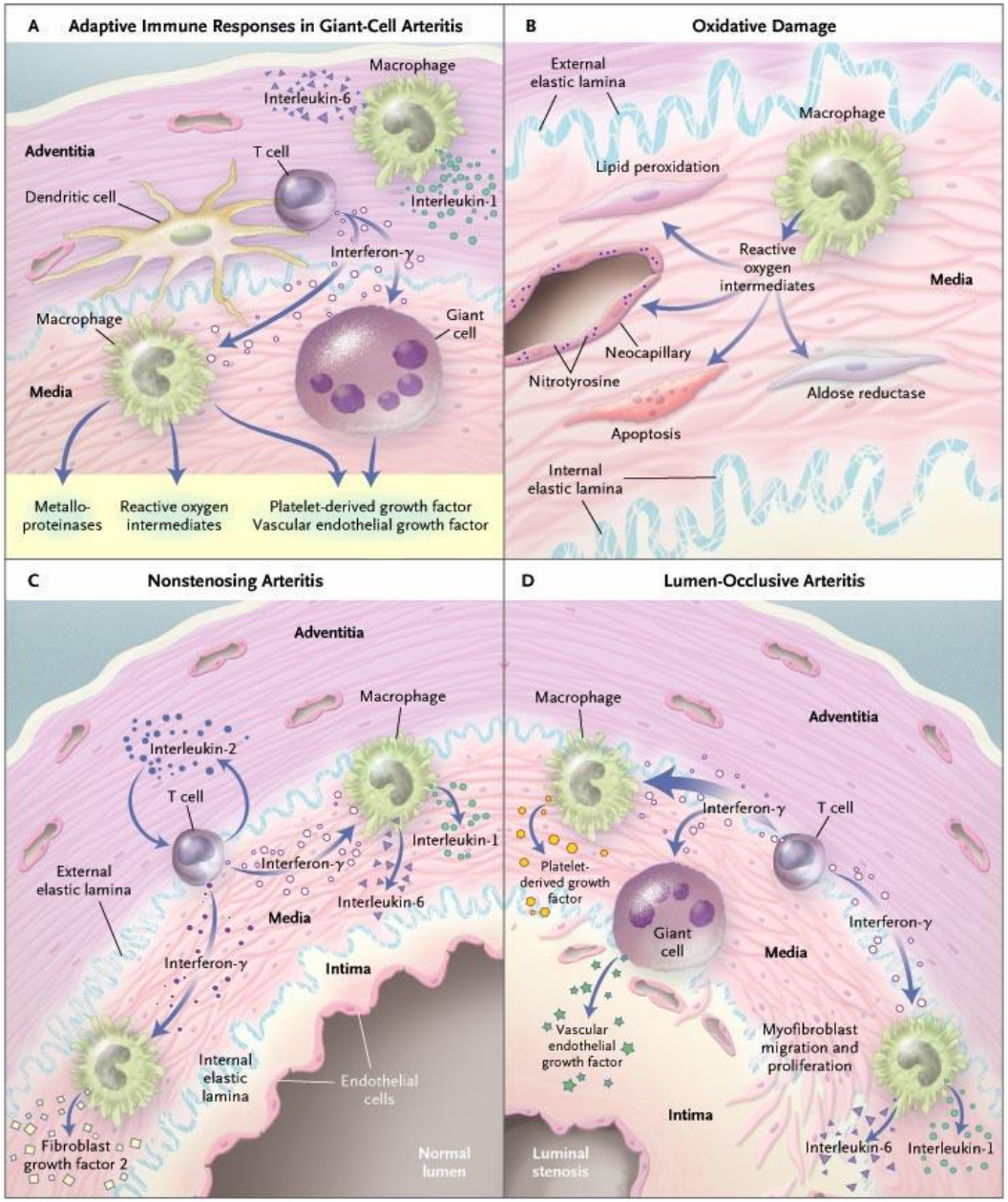


Dendritic Cells in the Arterial Adventitia



Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury

Weyand C and Goronzy J.
N Engl J Med 2003;
349:160-169



Role of T-cells in GCA ?

- implantation of bioptic material of inflamed artery in SCID-mice → depletion of tissue -T-cells → stop of inflammation

  (Brack A et al., Mol Med 1997; 3: 530-43)

- clonal expansion of CD4+ T-cells from distinct vascular lesions of the same patient → antigen-induced proliferation

  (Weyand CM et al.; J Exp Med 1994; 179: 951-60)

- distinct HLA-DRB1 alleles represent a genetic predisposition for GCA and PMR

  (Weyand CM et al., J Clin Invest 1992; 90: 2355-61)

Role of T-cells in GCA ?

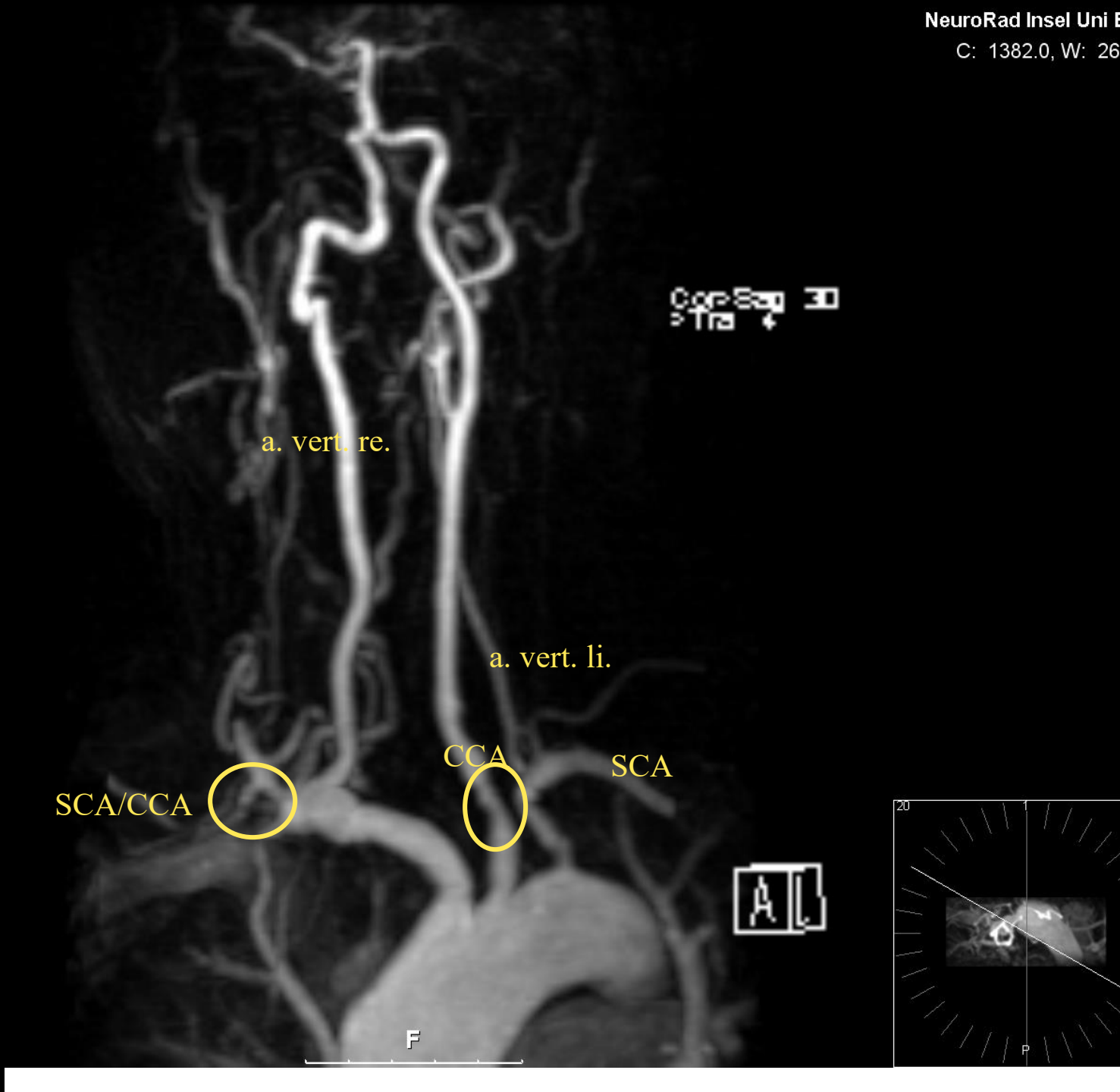
- T-cells from GCA-vessel biopsies proliferate after exposure to extracts from temporal arteries

  (Martinez-Taboada V et al., Mol Med 1996; 74: 695-703)

- relevant antigens in the arterial wall are still not identified – antigens from the Lamina elastica externa or interna ?

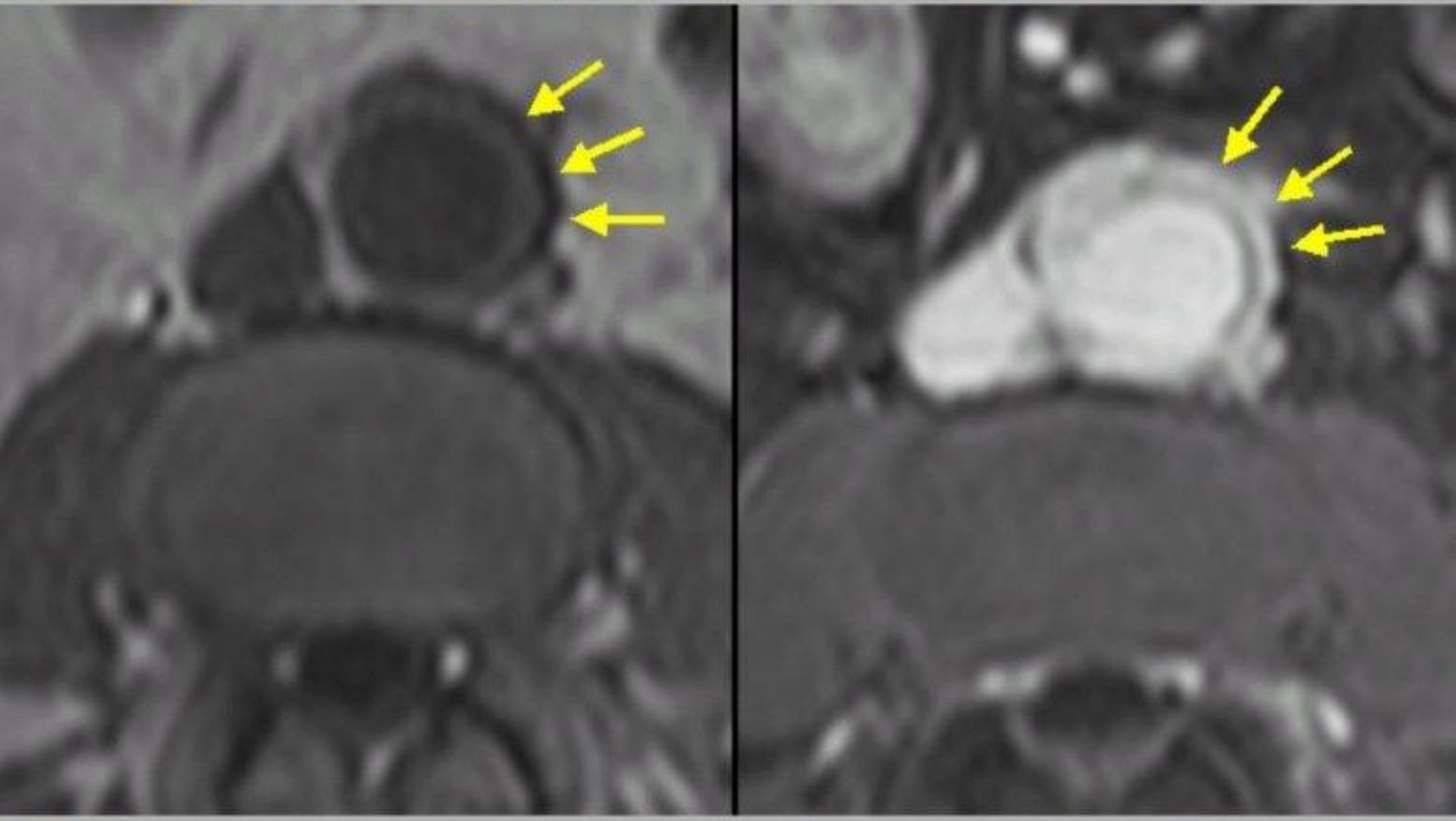
Diagnostic imaging

- Angio – MRI (magnetic resonance imaging)
- PET (positron emission tomograpy)


NeuroRad Insel Uni B
C: 1382.0, W: 26
a. vert. re.
a. vert. li.
CCA
SCA
SCA/CCA
F
20
P

MRI of abdominal aorta:

Enlargement and edema of the vessel-wall



T1 pre-contrast

T1 contrast-enhanced

When do you think of GCA ?

- new and sudden (unilaterlal) headache in the elderly
- sudden impairment of vision or blindness
- symptoms of Polymyalgia rheumatica, deterioration of general condition with or without signs of an cranial arteritis
- Fever of unknown origin (FUO) in the elderly
- high ESR ***(erythrocyte sedimentation rate of >100mm/hr)***

Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury

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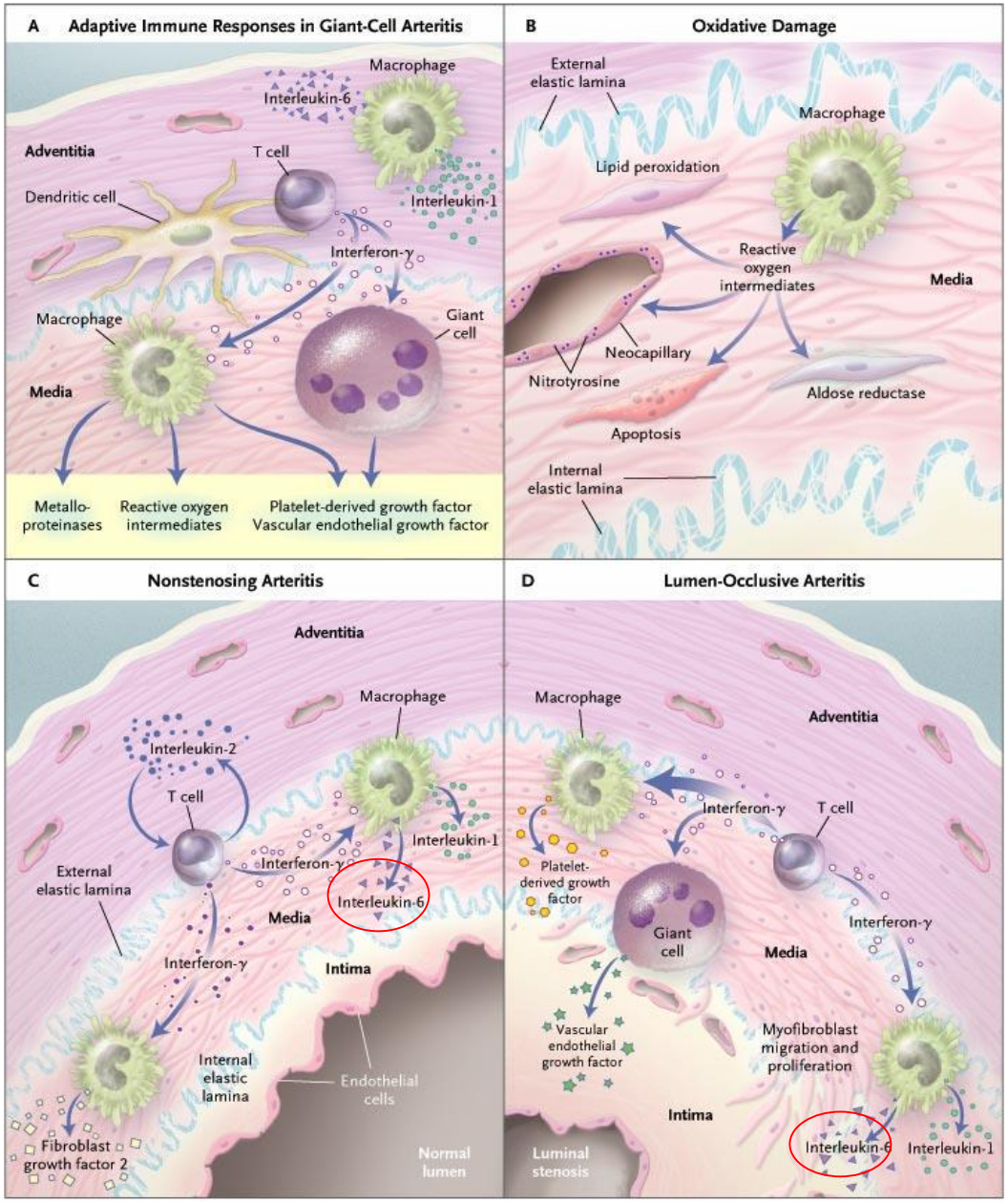
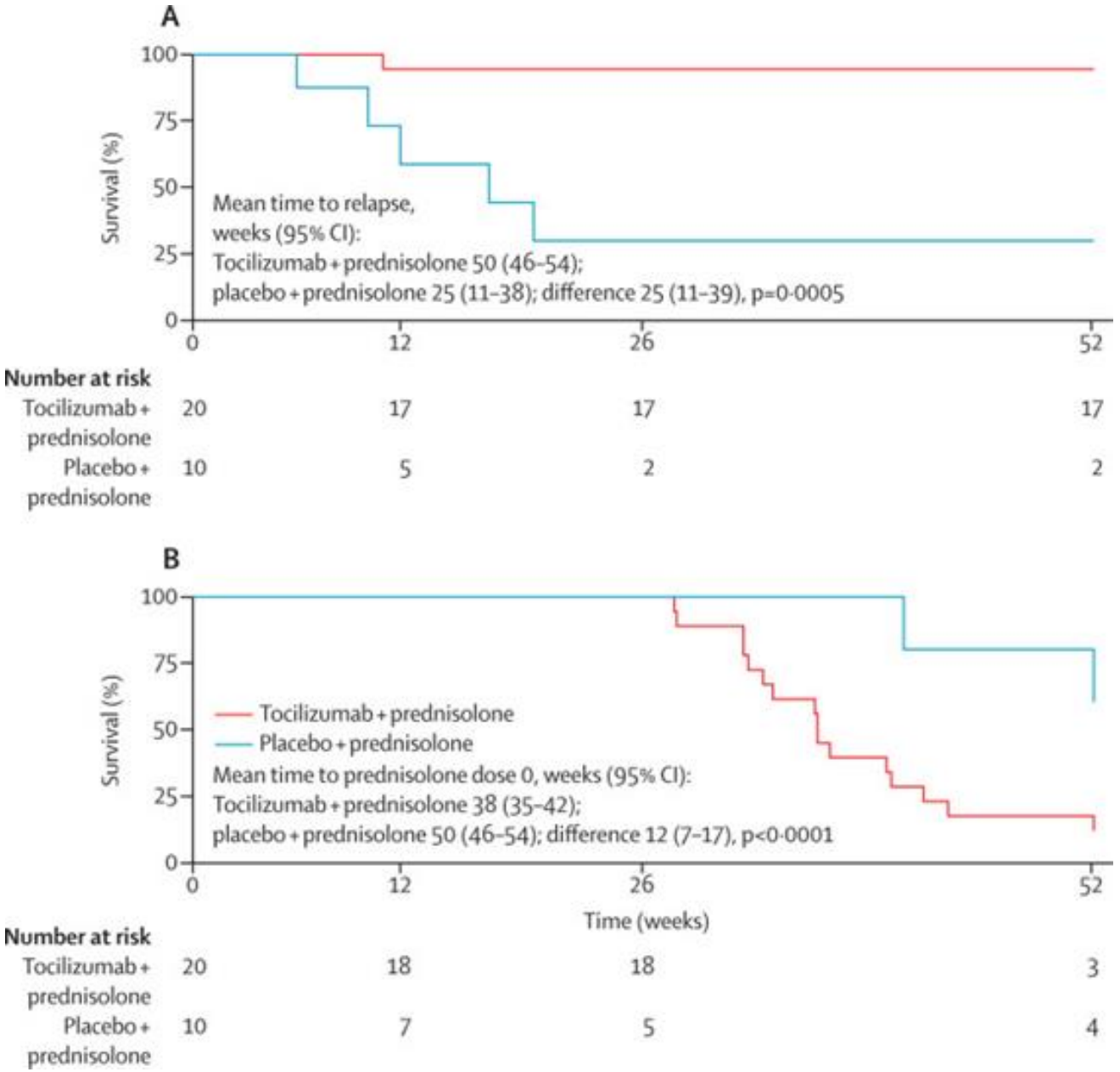
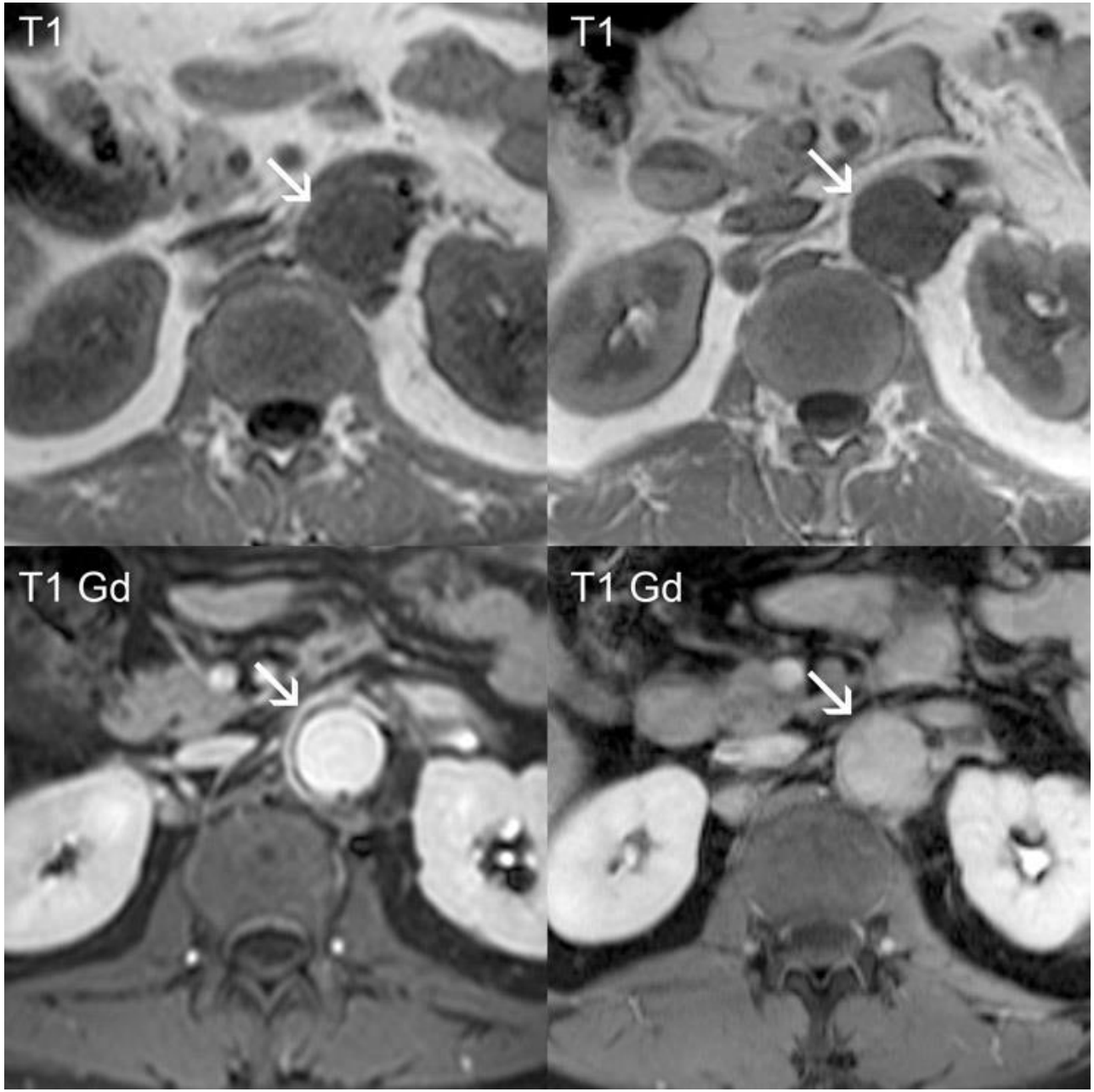


Role of IL-6 in Giant Cell Arteritis

- induction of acute phase reaction (CRP, SAA) in the liver
- systemic inflammatory systemic response
- exciting therapeutic target for anti-IL-6 strategies
- prompt therapeutic response to tocilizumab (anti-IL-6R monoclonal antibody)

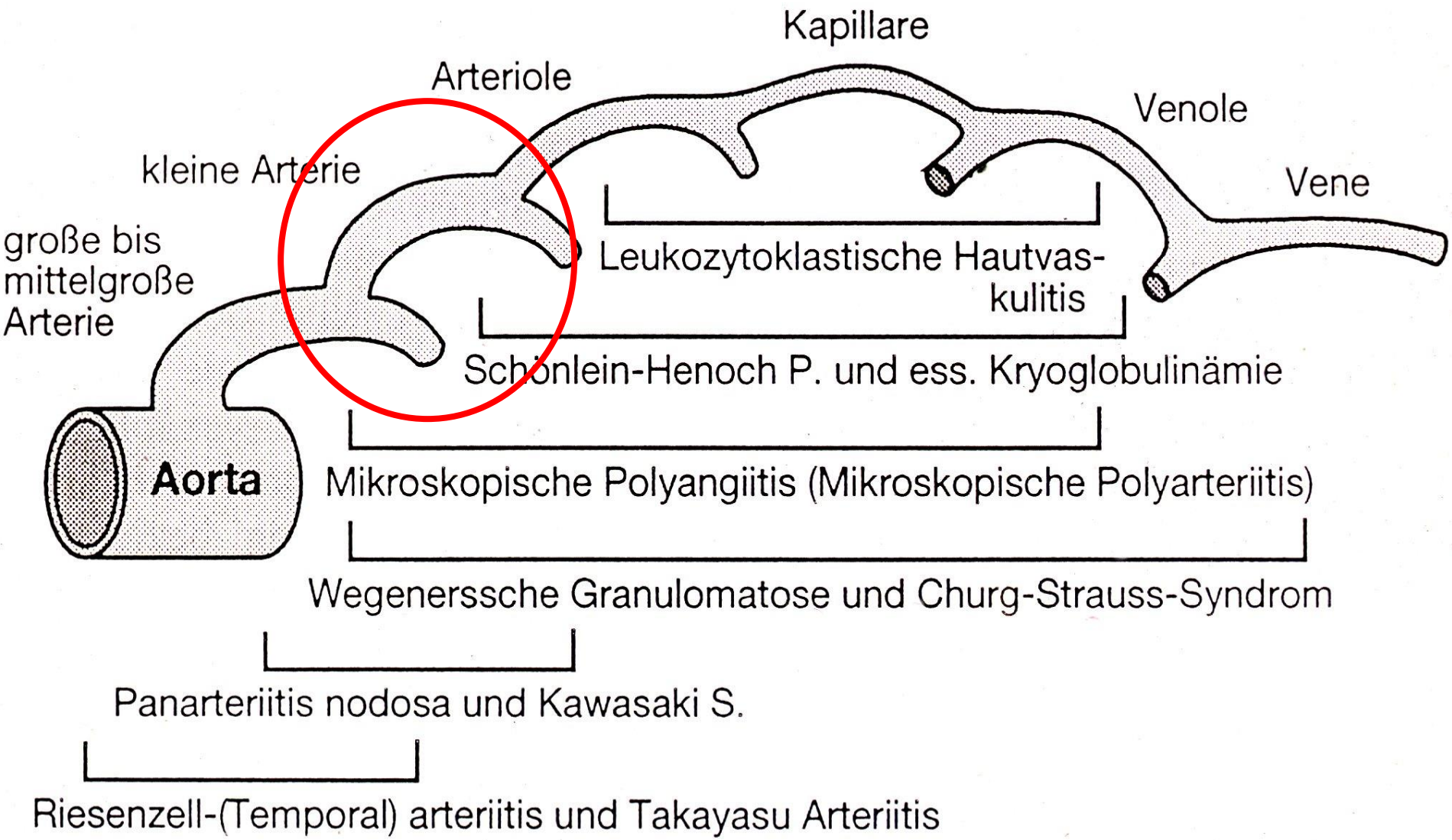


Villiger PM et al. , *Lancet 2016, published online March 4 http://dx.doi.org/10.1016/S0140-6736(16)00560-2*



Before **3 months after monthly tocilizumab**

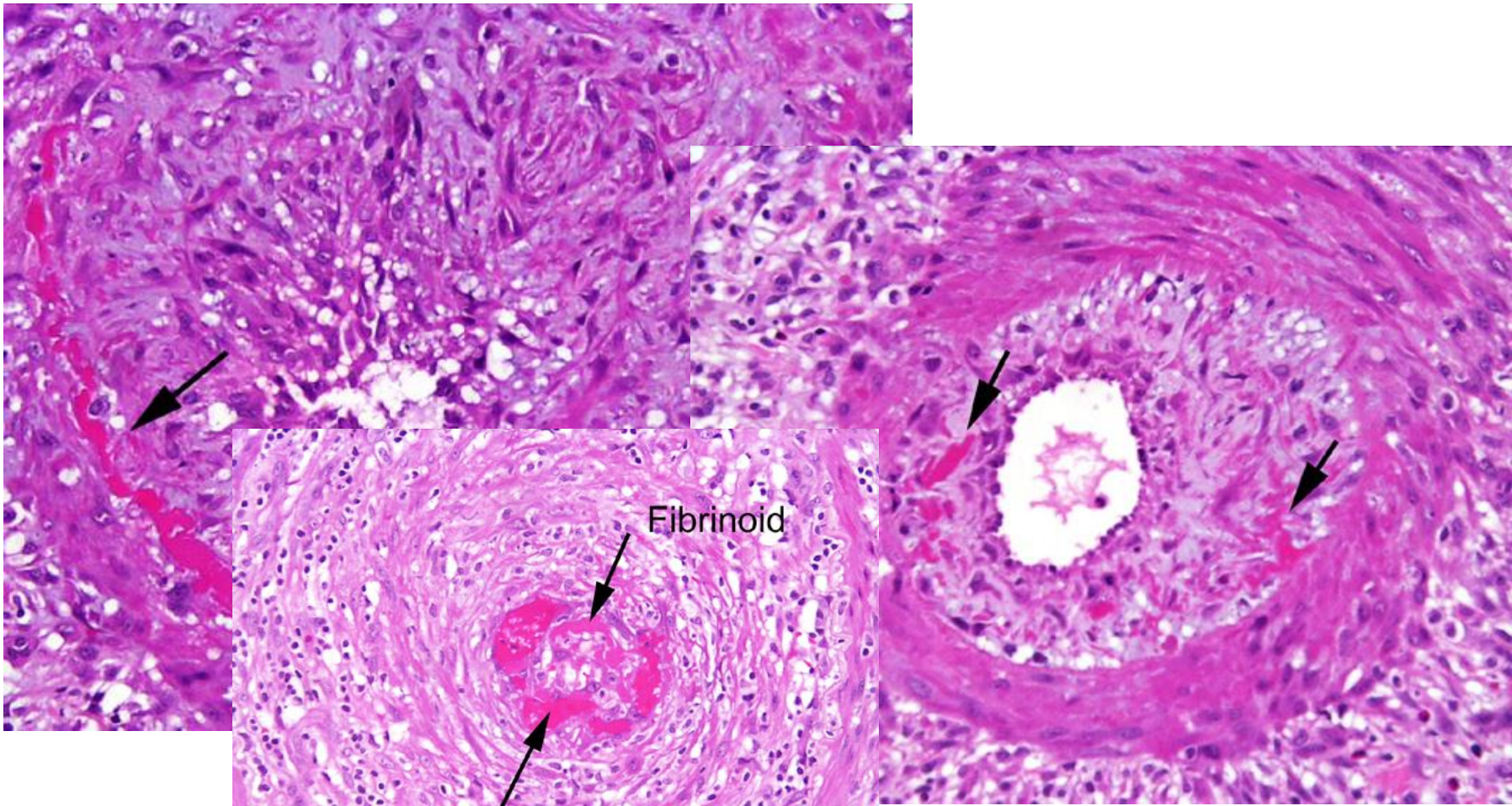
Pattern of vessels involved



Panarteritis nodosa

40 % HBV-associated

60 % Non-HBV-associated



Immunopathogenesis of PAN

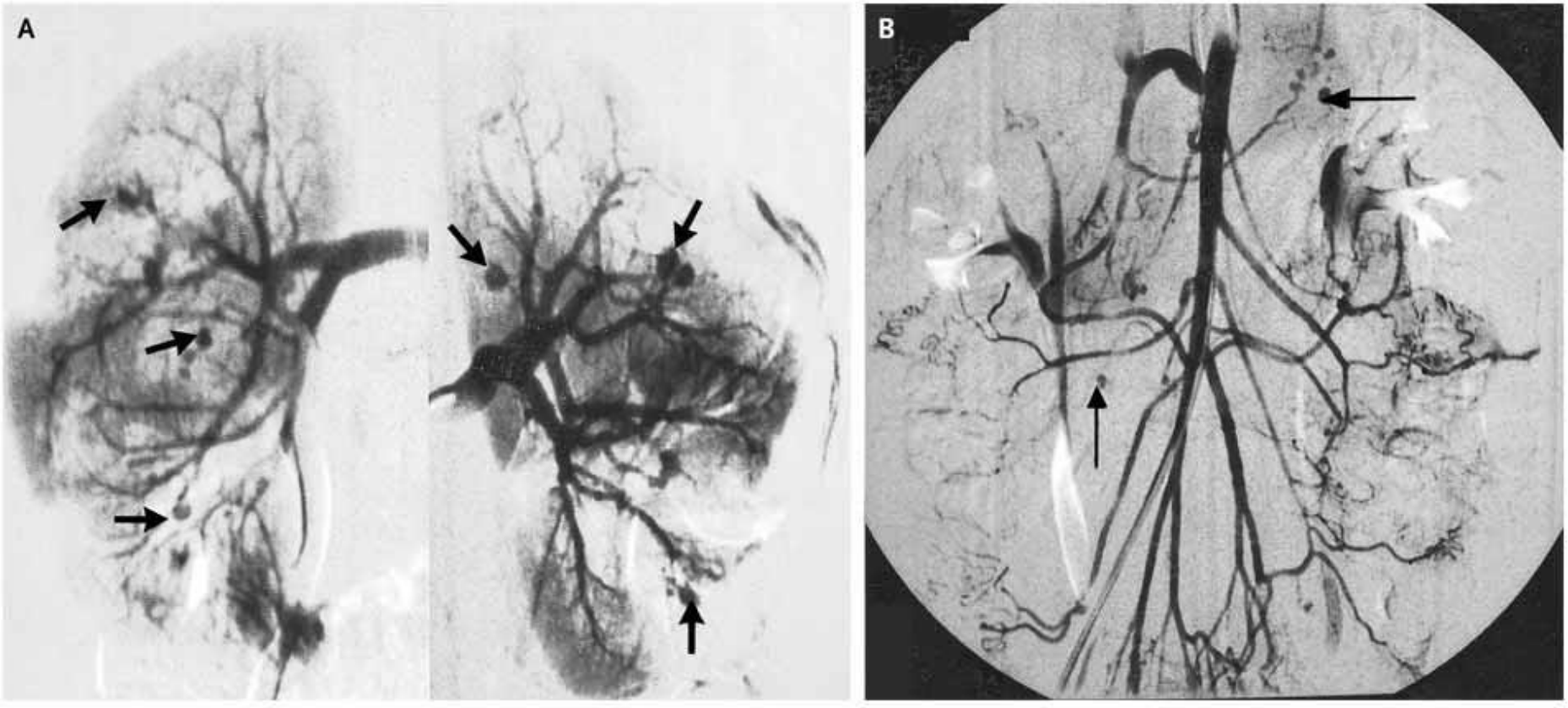
- Similar to GCA , T-cell mediated (predominant infiltrates with CD4+ T-cells)
- Association with an active chronic Hepatitis B in 40%
- *10 years-survival* identical between HBV-associated and non-HBV-associated disease

(Gayraud M et al., A&R 2001; 44: 666-75)

Vasculitis of medium-sized vessels
direct symptoms

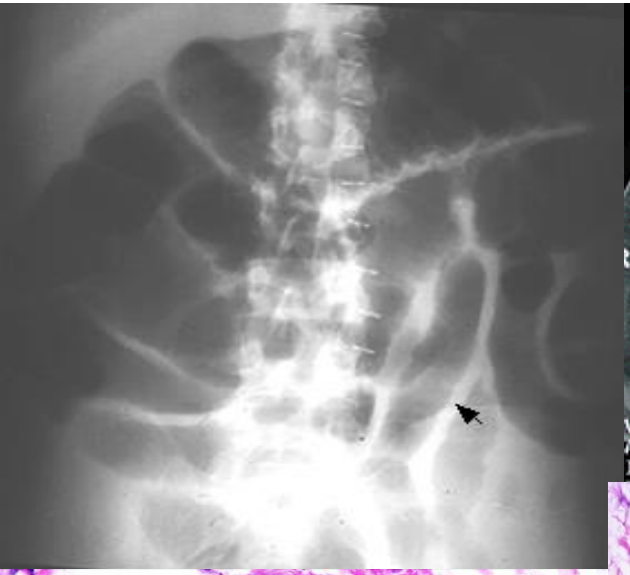
- **Insult** *(brain, heart, kidney, GIT, extremities)*
- **Bleeding** *(ruptures of microaneurysmata)*
- **Pain in testis** *(spezific for PAN)*
- **Arterial hypertension** *(recent evolution)*

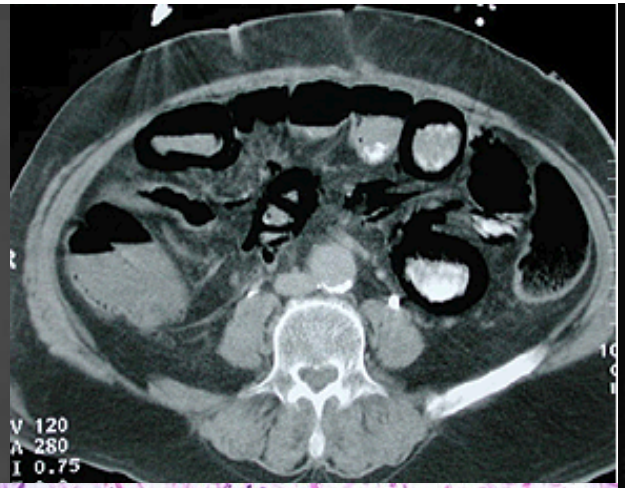
19-year-old man presented with a 10-month history of Raynaud's phenomenon, fever, abdominal pain, and hypertension

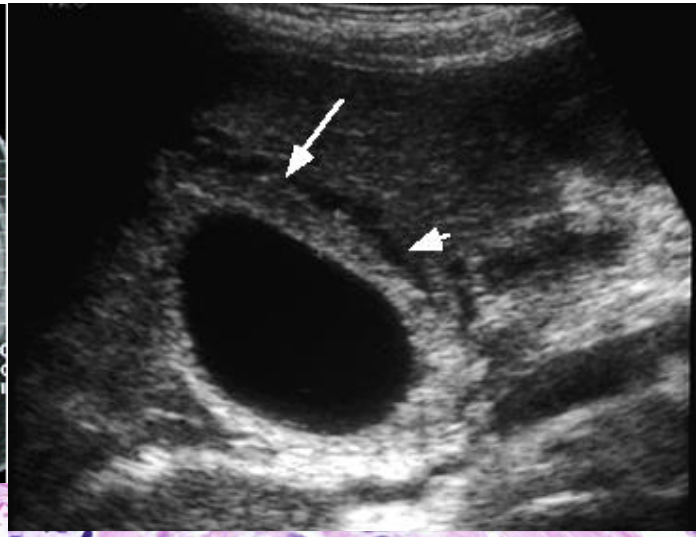


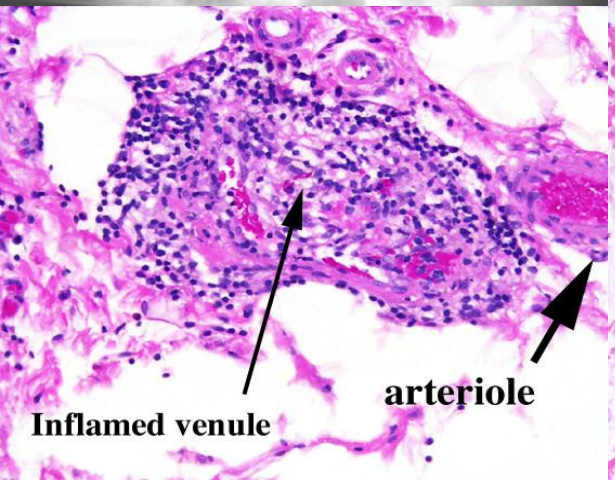
Das C and Pangtey G. N Engl J Med 2006;355:2574

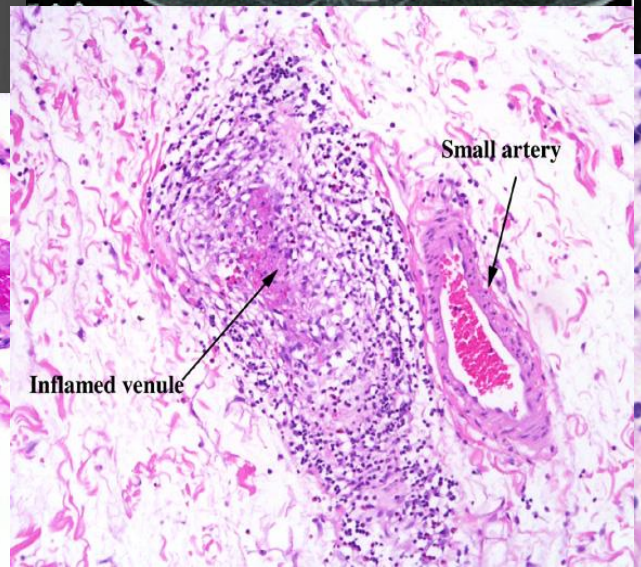
Vasculitis of medium-sized vessels
Intenstine / gall bladder

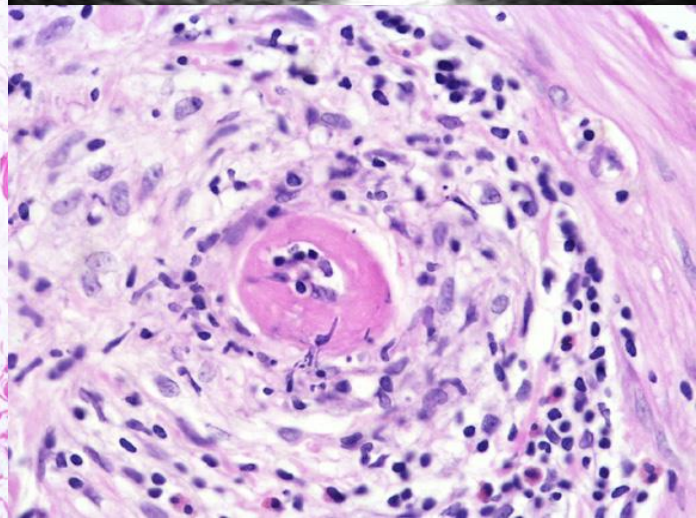




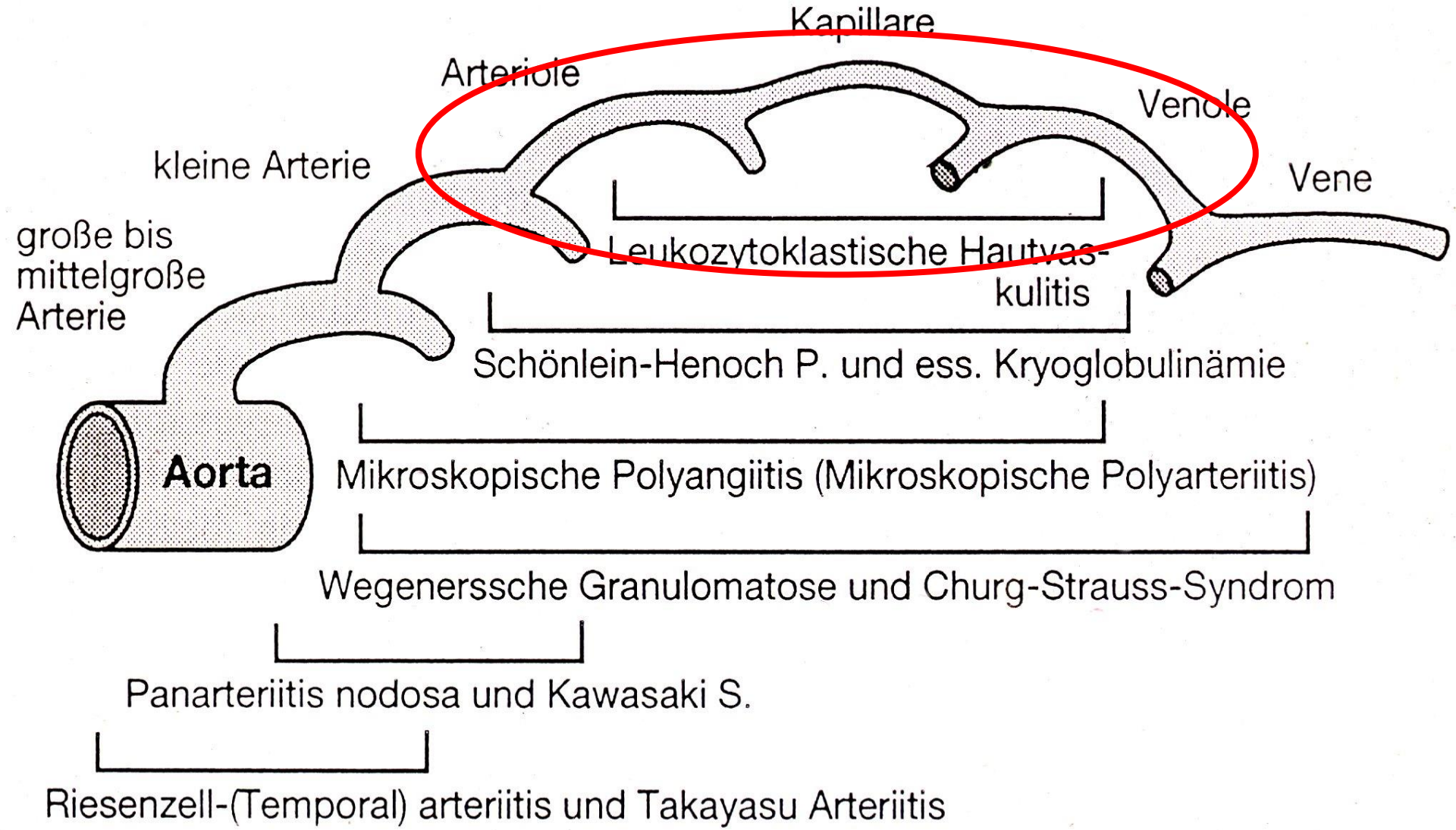






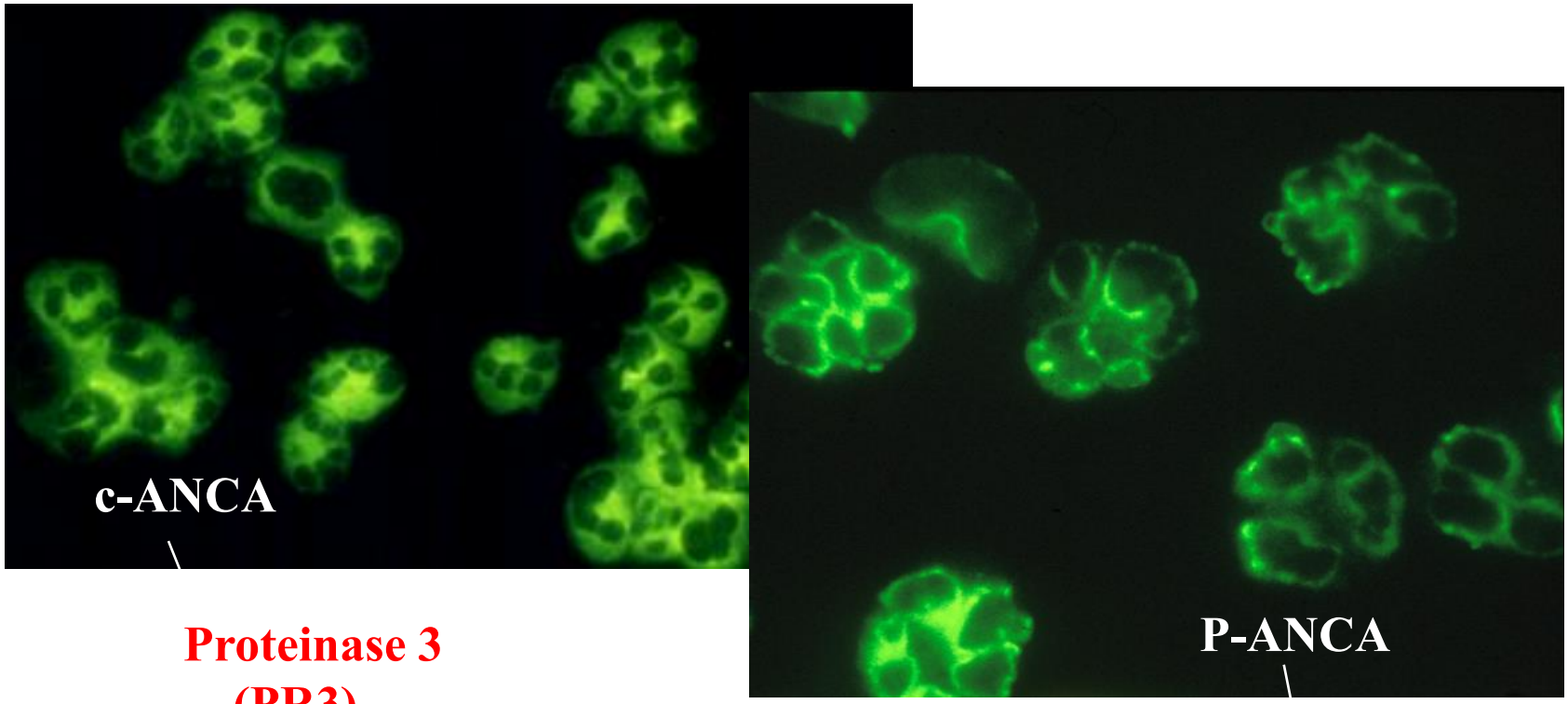


Pattern of involved vessels



AASV = ANCA-associated small vessel vasculitis

ANCA (Antineutrophil cytoplasmic antibodies)

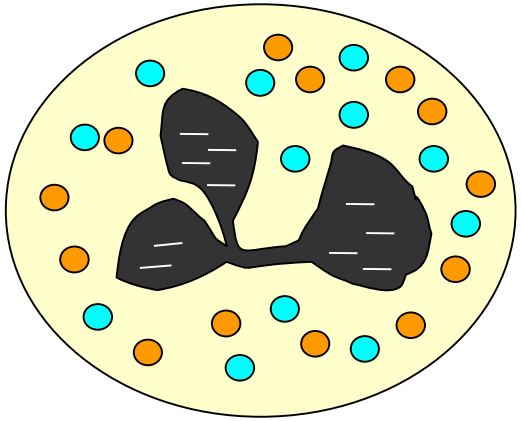


Proteinase 3
(PR3)

Myeloperoxidase

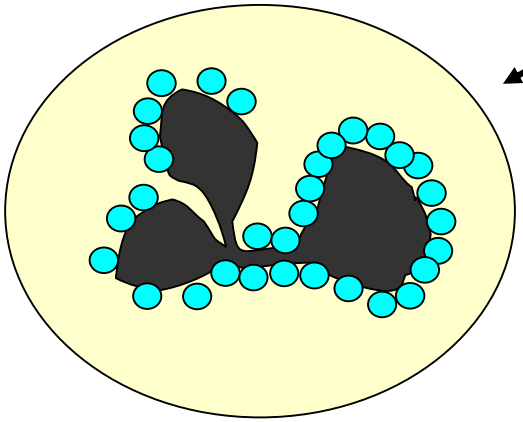
ANCA: IIF-Pattern

ANCA

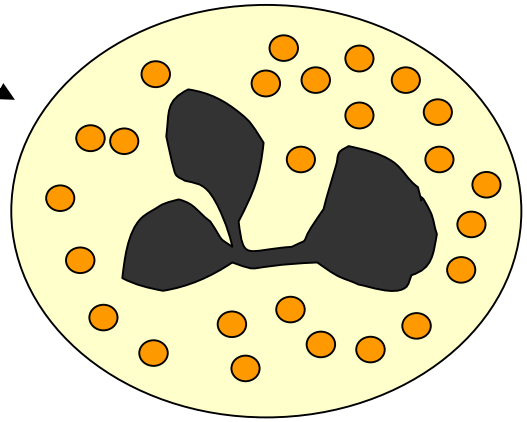


+ Ladung

neutral



pANCA



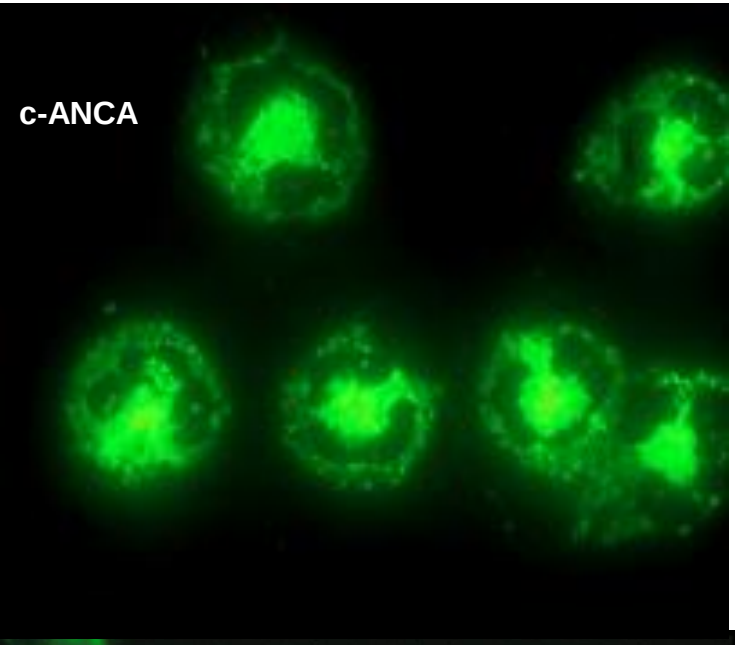
cANCA

ANCAs

Fluorescence pattern

associated antigens

disease association



Major antigen:

Proteinase 3 (PR3)

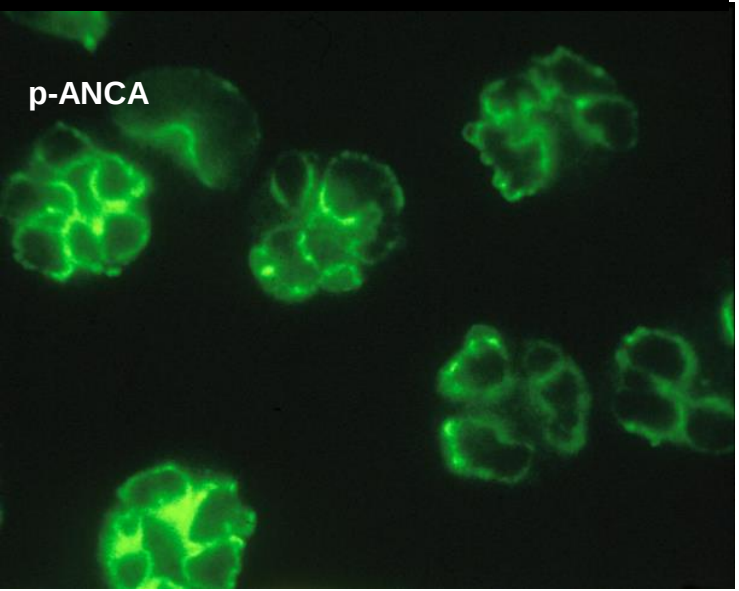
M. Wegener:

Sensitivity: 73 %

Specificity: 99 %

other associations:

infections: i.e. endocarditis,
Medi: Propylthiouracil, etc.



Major antigen:

Myeloperoxidase (MPO)

other antigens:

Elastase, Lactoferrin, Kathepsin G, andere ?

Microscop. Polyangiitis:

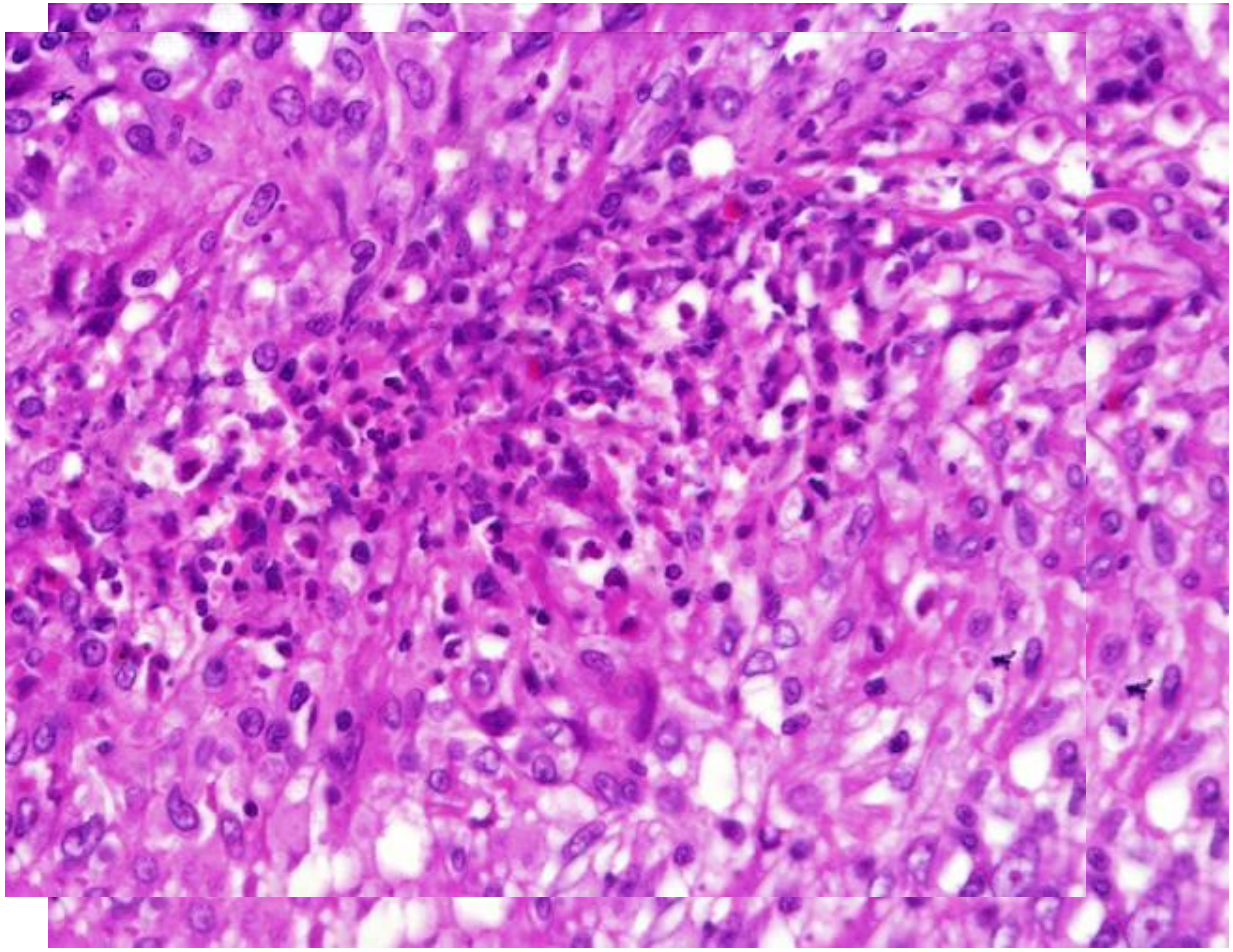
Sensitivity: 67 %

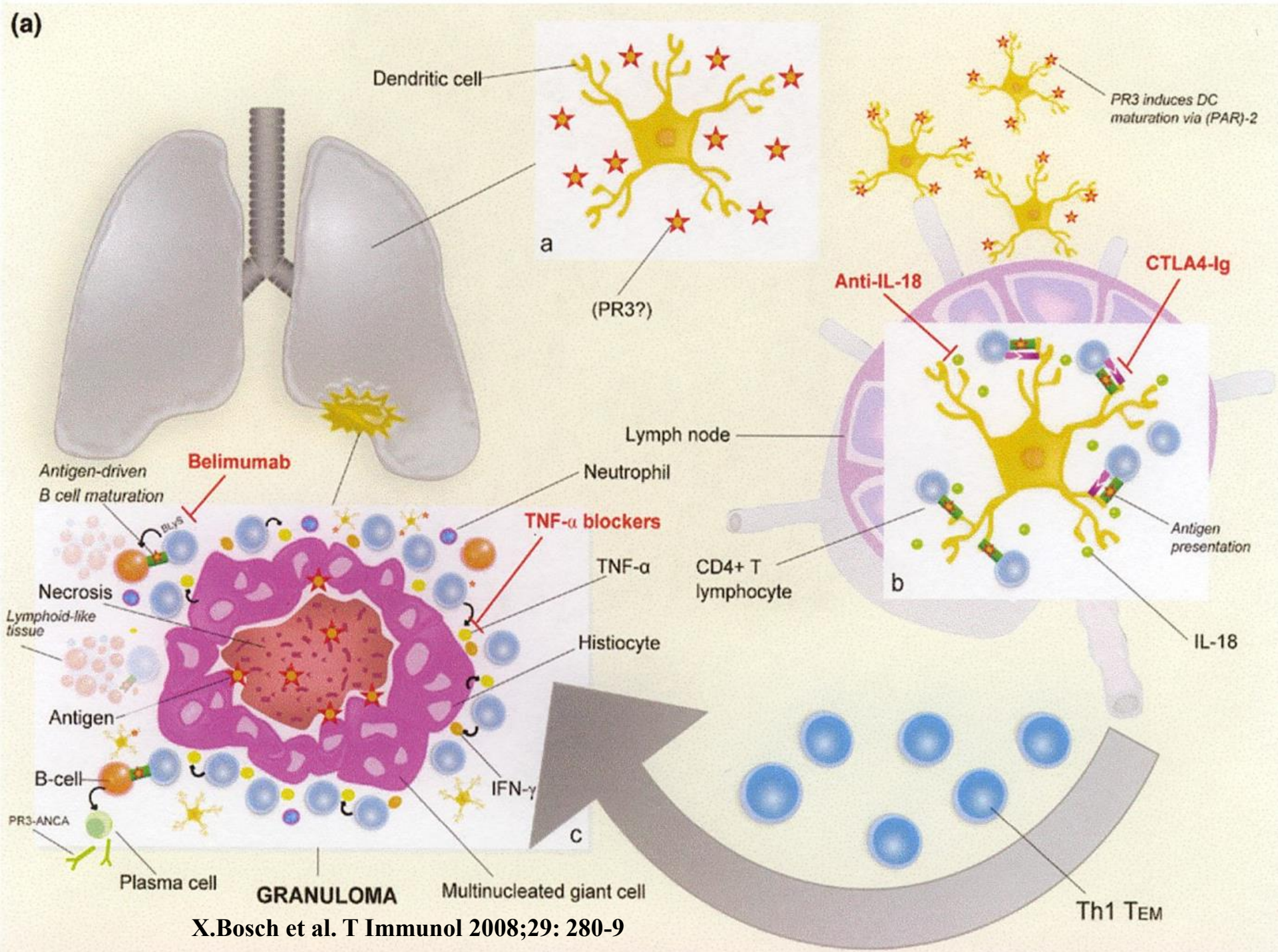
Spezificity: 99 %

other associations:

IBD, rheumatoid arthritis, others
Medi: Propylthiouracil, etc

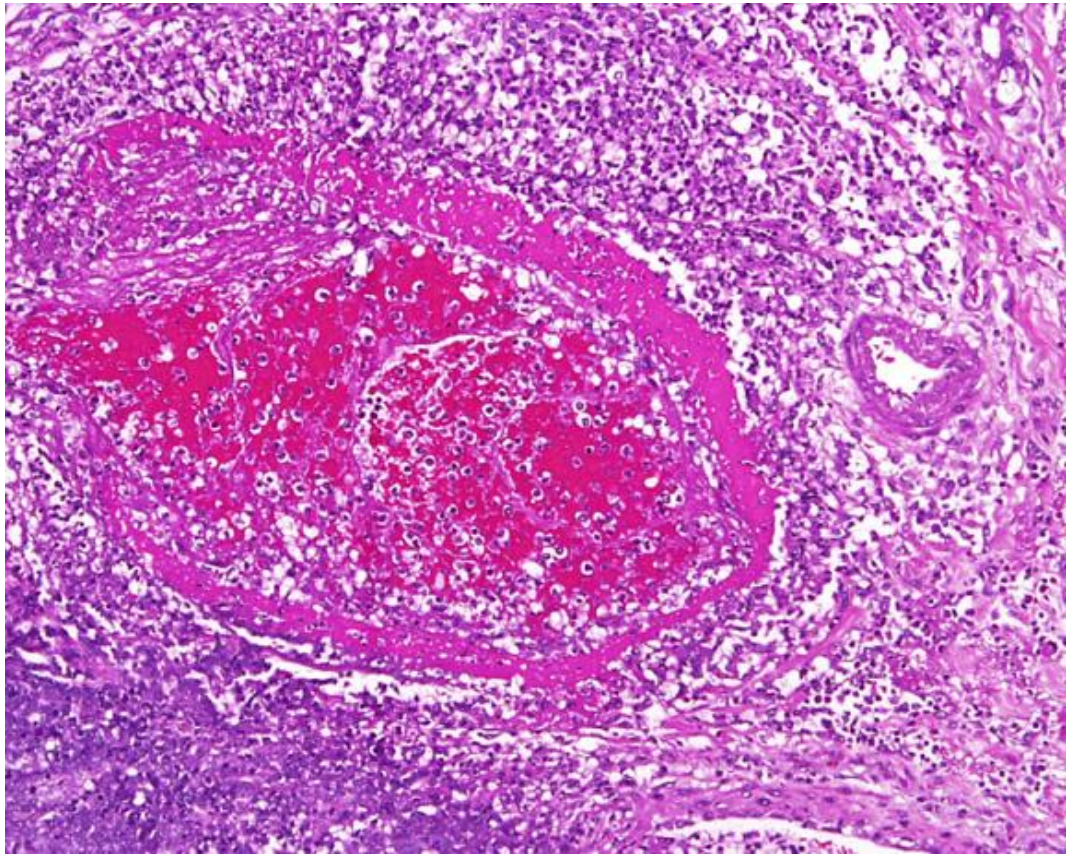
Pathogenesis of granuloma formation in Wegener‘s Disease

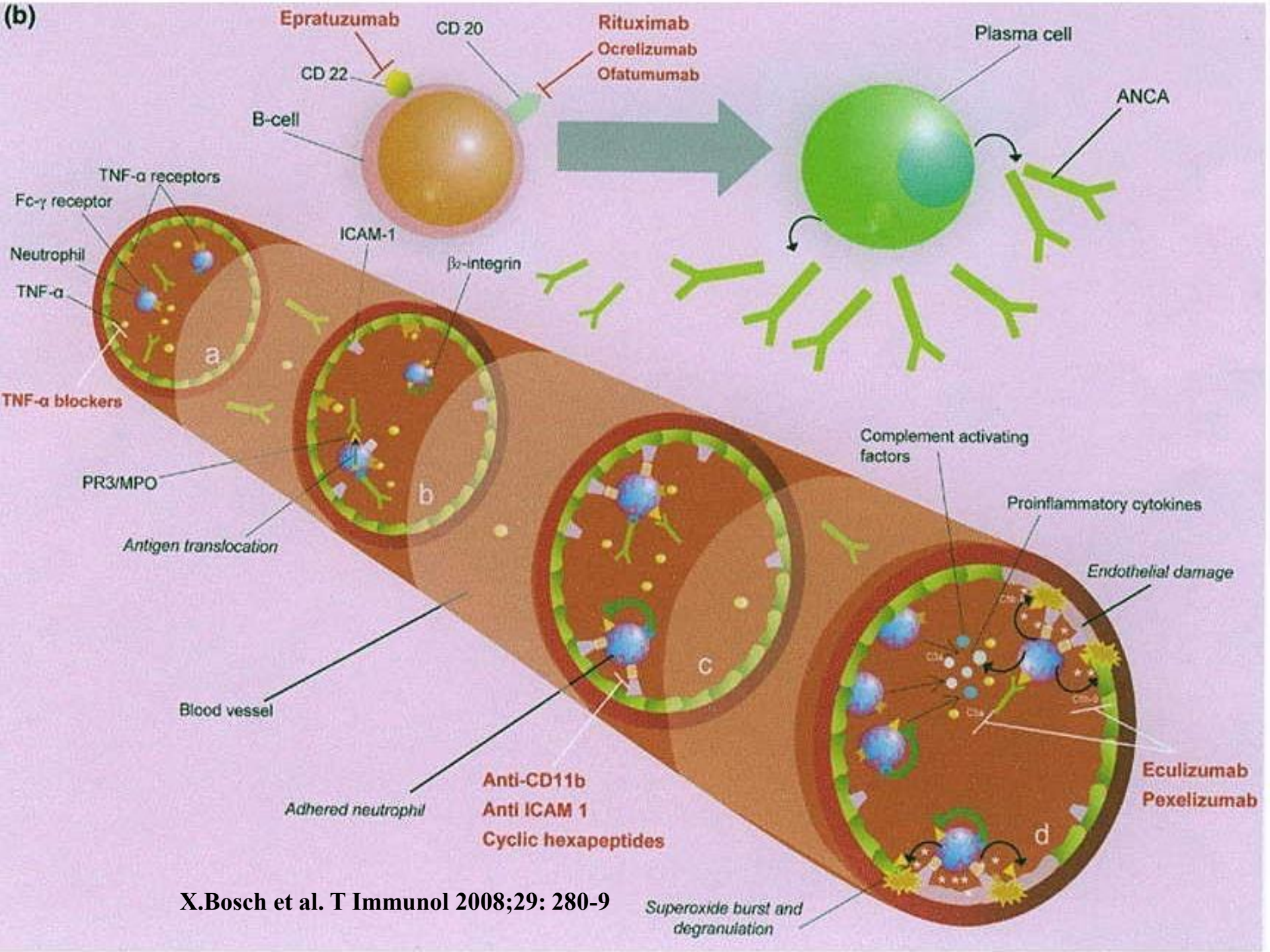




X.Bosch et al. T Immunol 2008;29: 280-9

Pathogenesis of vasculitis in Wegener‘s Disease





X.Bosch et al. T Immunol 2008;29: 280-9

Direct Symptoms *(sma*
vasculitis)

- episcleritis, scleritis, keratitis, u
- hearing loss, dizziness, chronic … tis
- chronic rhinitis, sinusitis
- hemoptysis, dyspnoe
- palpable purpura , skin ulcera …
  healing, after simple injury, ur
- microhematuria, proteinuria *(*
- mononeuritis multiplex *(sens*
  progressive pareses)
- perimyocarditis

Target Organs:

Eye

Nose

Ear

Lung

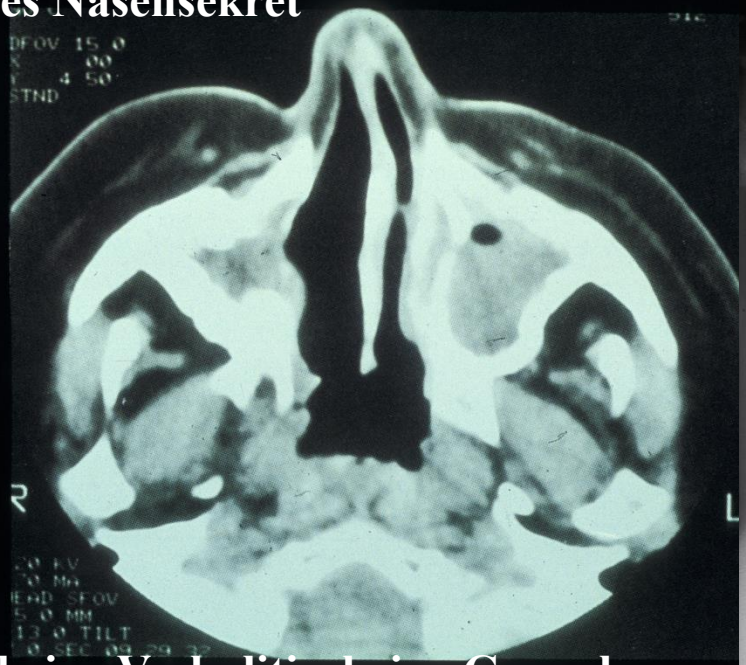
Skin

Kidney

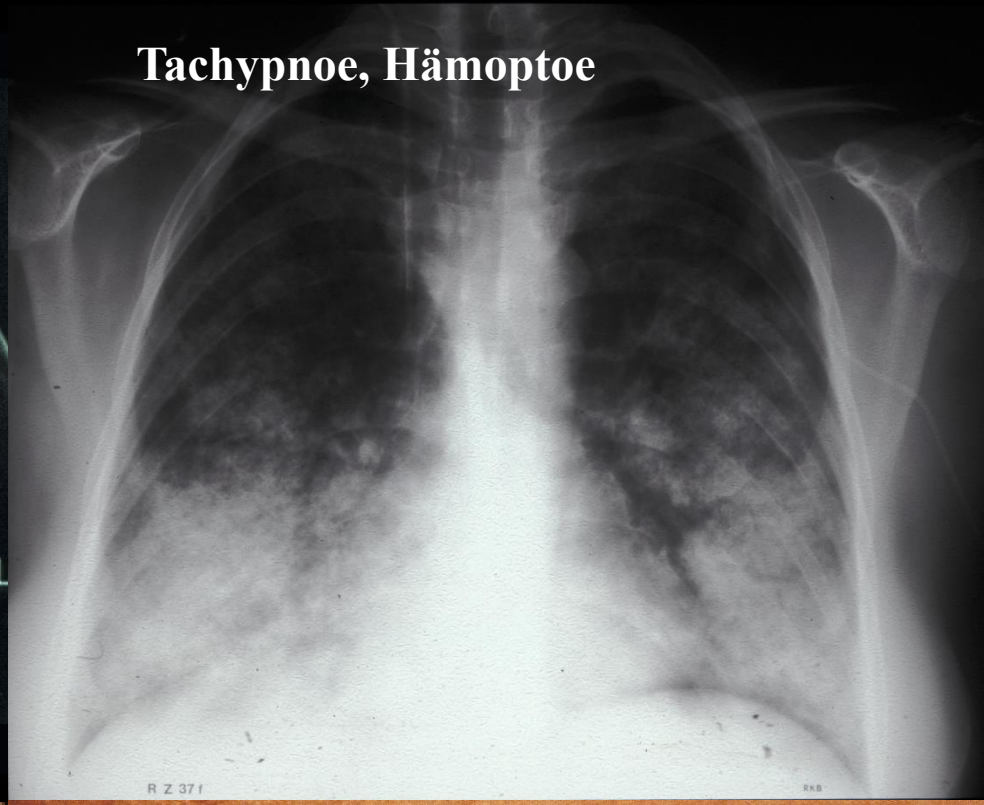
Nerves

Heart

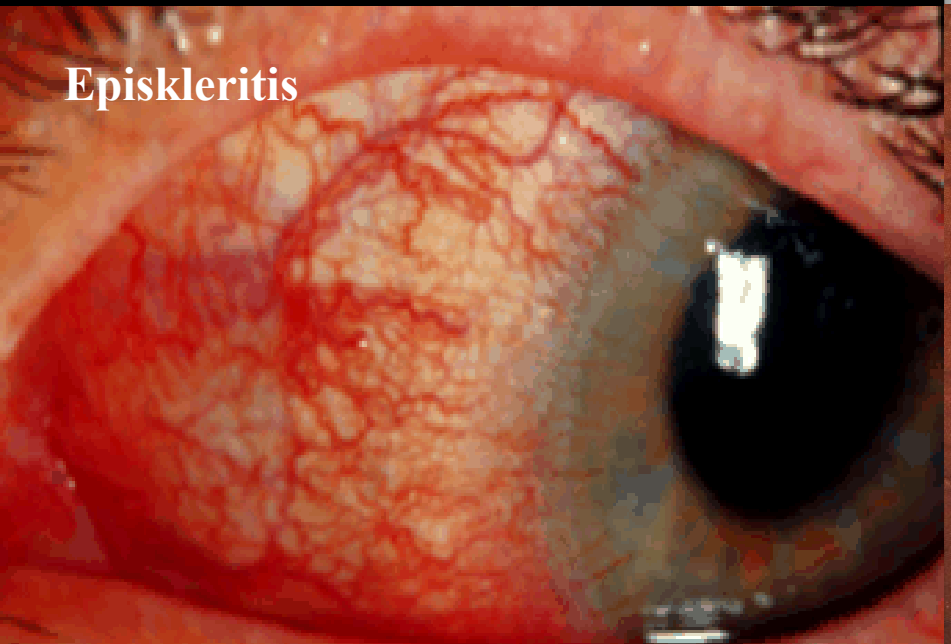
Blutiges Nasensekret



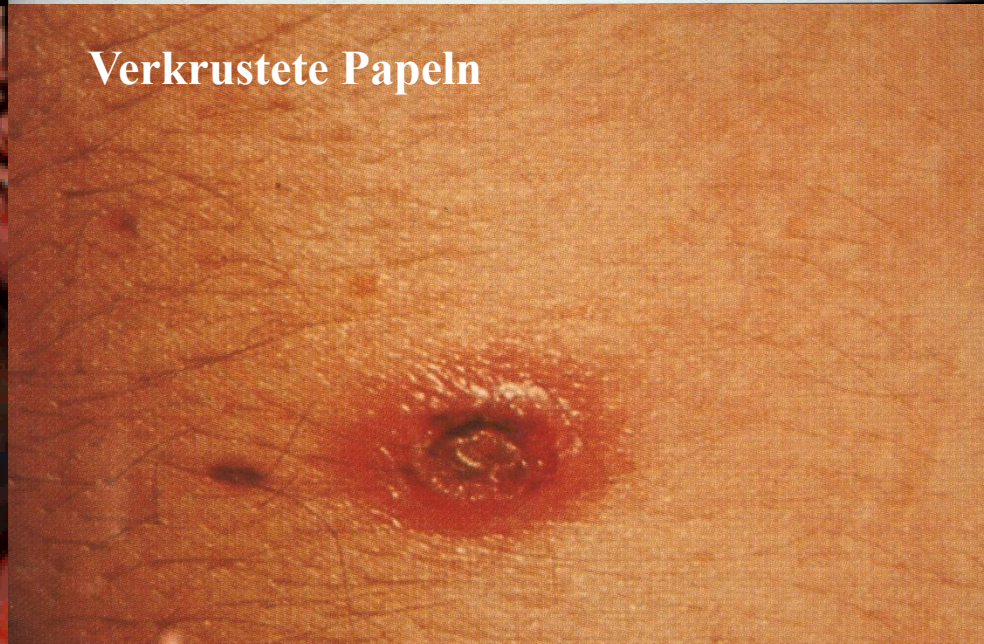
Tachypnoe, Hämoptoe



Histo: keine Vaskulitis, keine Granulome



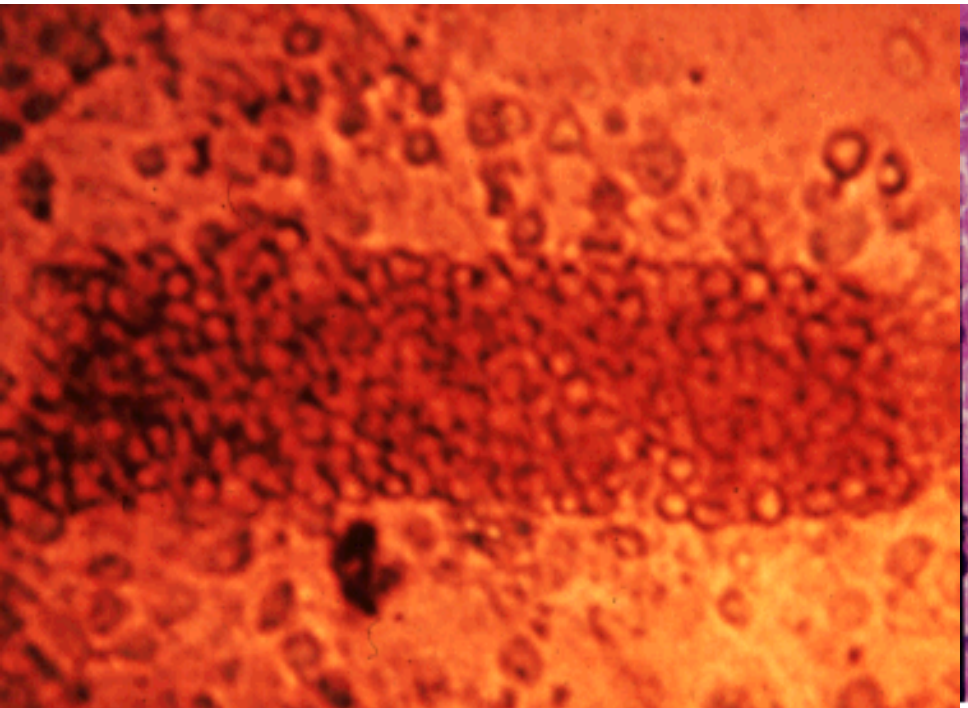
Episkleritis



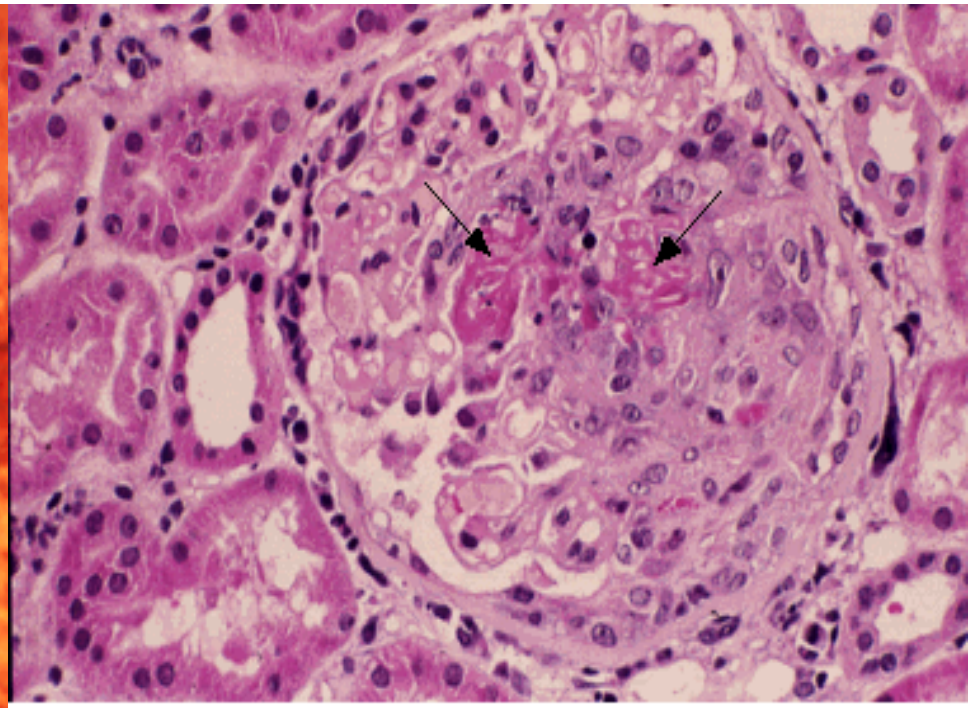
Verkrustete Papeln

AASV

erythrocyte zylinders



necrotizing GN



Vasculitis - Treatment principles

For remission induction and maintenance

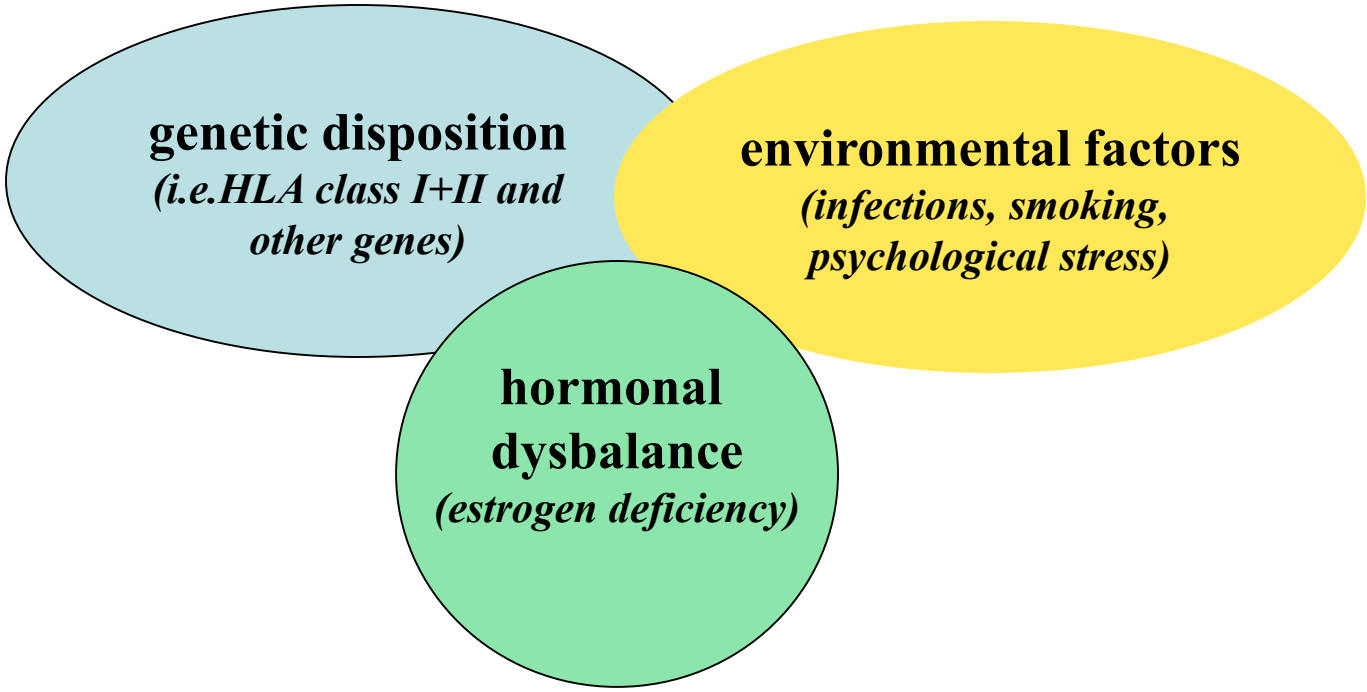
- *systemic glucocorticoids*
- *+/- immunosuppressants (i.e. Methotrexate, Leflunomide, Cyclophosphamide)*
- *+/- biologics (i.e. rituximab in ANCA-associated vasculitides)*
- *Prophylaxis of infections (vaccination, co-trim)*
- *Prophylaxis of osteoporosis (Ca, VitD, bisphosponates) and CVI's (ASS in GCA)*
- *Treatment(adjustment) of diabetes*

Autoimmune connective tissue diseases

- **Systemic lupus erythematosus (SLE)**
- Mixed connective tissue disease (MCTD)
- Sjögren‘s syndrome
- Systemic sclerosis (SSc)
- Dermato/Polymyositis (DM/PM)
- Undifferentiated connective tissue disease (UCTD)
- Overlap syndrome (combination of two or more co-existing autoimmune connective tissue diseases)

Autoimmune Diseases

- Multifactorial etiology



Basic mechanisms of autoimmunity

- Break of central and/or peripheral tolerance
- Genetic predisposition (individual pattern of HLA class I and II genes)
- Gender specific factors (hormones)

Genetic factors in SLE

- concordance of 14-57% in monozygotic twins
- no single gene polymorphisms/alteration
- HLA-B8; HLA-DR2; HLA-DR3; DQW1; HLA-DMA*O401; C2 deficiency (C2D); C1q deficiency; C4 (especially C4A) deficiency (C4D); C3 polymorphisms
- and many others
- Epigenetics with alterations in methylation and acetylation of DNA

Hormonal factors in SLE

- little evidence of an association between disease severity and sex hormone concentration in plasma
- use of estrogen-containing contraceptive agents is associated with an 50 percent increase in risk
- lupus flares have been associated with hyperprolactinemia

Immunopathogenesis of SLE

- SLE is primarily a disease with abnormalities in immune regulation.These abnormalities are thought to be secondary to a loss of self-tolerance
- autoantibodies and immune complexes they form with autoantigens
- Autoantigens that are recognized are presented primarily on cell surfaces, particularly by cells that are activated or undergoing apoptosis

Immunopathogenesis of SLE

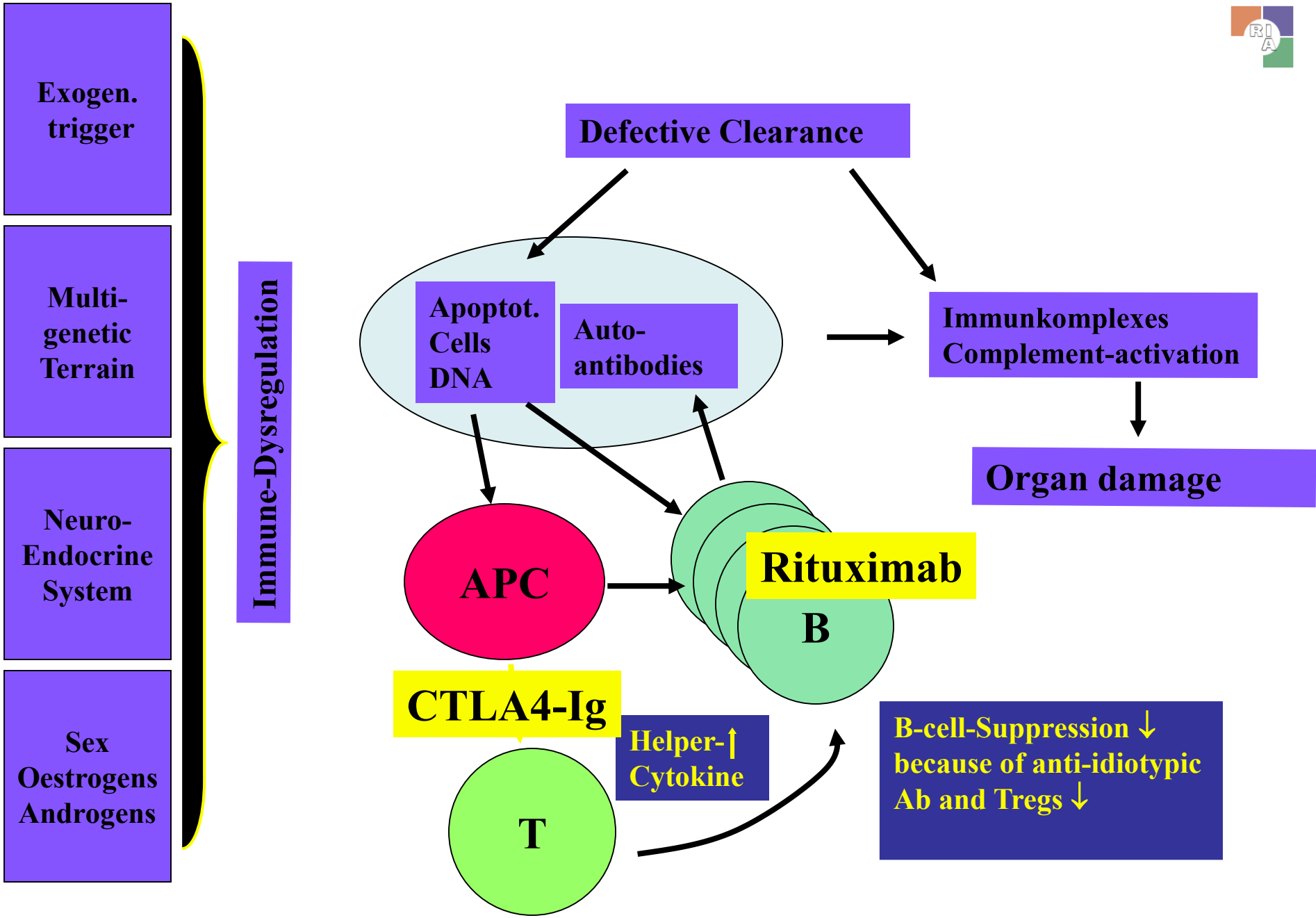
- Phagocytosis and clearing of immune complexes, of apoptotic cells, and of necrotic cell-derived material are defective in SLE, allowing persistence of antigen and immune complexes
- B cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by BlyS (BAFF) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10.

Immunopathogenesis of SLE

- This increased autoantibody persistence is not downregulated appropriately by anti-idiotypic antibodies, or by CD4+CD25hi-Foxp3+ regulatory T cells, or by CD8+ suppressor T cells.
- Some antibody/antigen complexes, particularly those containing CpGDNA or RNA/proteins, activate the innate immune system via TLR-9 or TLR-7, respectively.

Immunopathogenesis of SLE

- Thus dendritic cells are activated and release type 1 interferons and TNFalpha, T cells release IFNgamma, IL6, IL10, while NK and T cells fail to release adequate quantities of TGFbeta. These cytokine patterns favor continued autoantibody formation.


Exogen. trigger
Multi-genetic Terrain
Neuro-Endocrine System
Sex Oestrogens Androgens
Immune-Dysregulation
Defective Clearance
Apoptot. Cells DNA
Auto-antibodies
Immunkomplexes Complement-activation
Organ damage
APC
Rituximab
B
CTLA4-Ig
Helper-↑ Cytokine
T
B-cell-Suppression ↓ because of anti-idiotypic Ab and Tregs ↓


Systemic Lupus
erythematosus

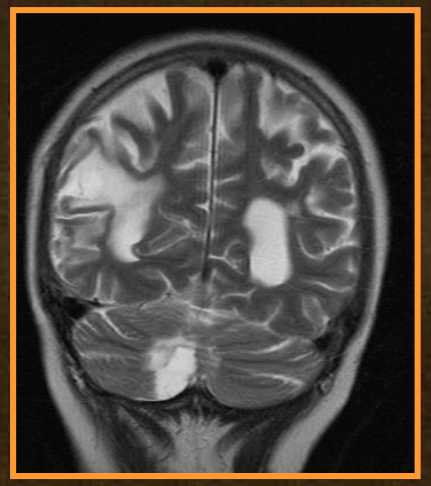
Diagnostic Criteria of Lupus erythematodes

1. butterfly erythema
2. discoid skin lesions
3. photosensitivity
4. orale ulcerations
5. arthritis
6. serositis
7. renale disturbances
   -proteinurie
   -cellular zylinders
8. neurological symptoms
   - seizures, psychosis
9. hematological disturbances
   -hemolytic anemia
   -leukopenia
   -lymphopenia
   -thrombozytopenia
10. immunological disturbances
    -anti-dsDNA
    -anti-Sm, anti-C1q
11. antinuclear antibodies (ANA)

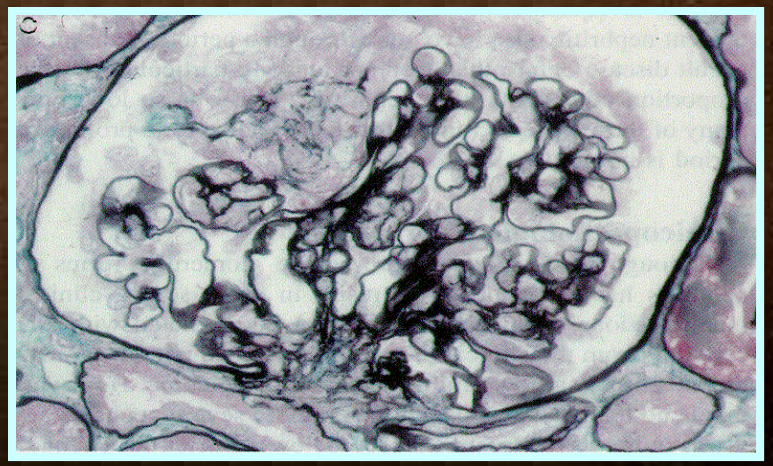
Systemischer Lupus erythematodes

Arthralgien >90%
Jaccoud Arthritis 10%

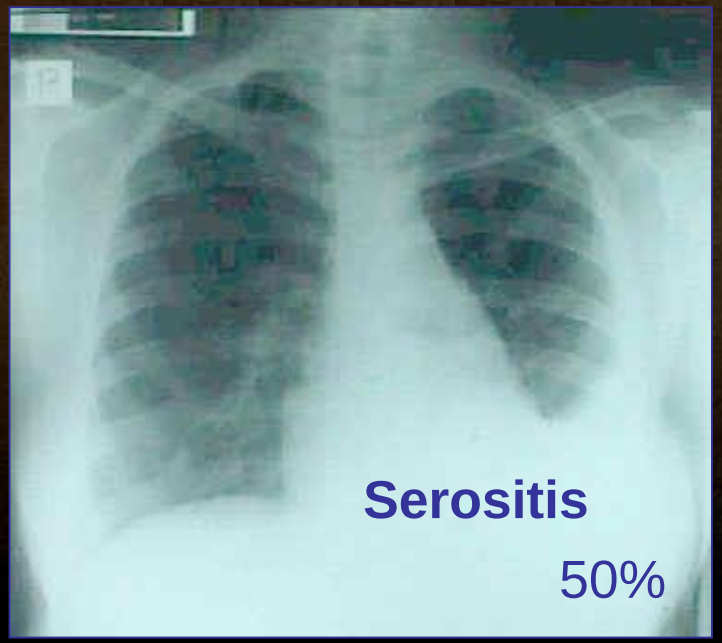
>90%



ZNS-Beteiligung 40%



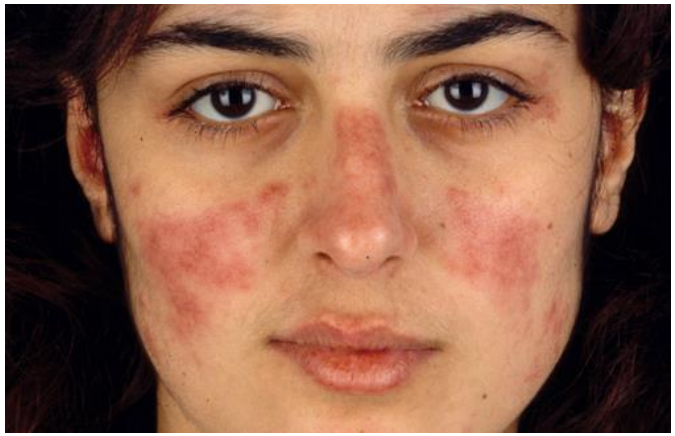
Nierenbeteiligung 50%



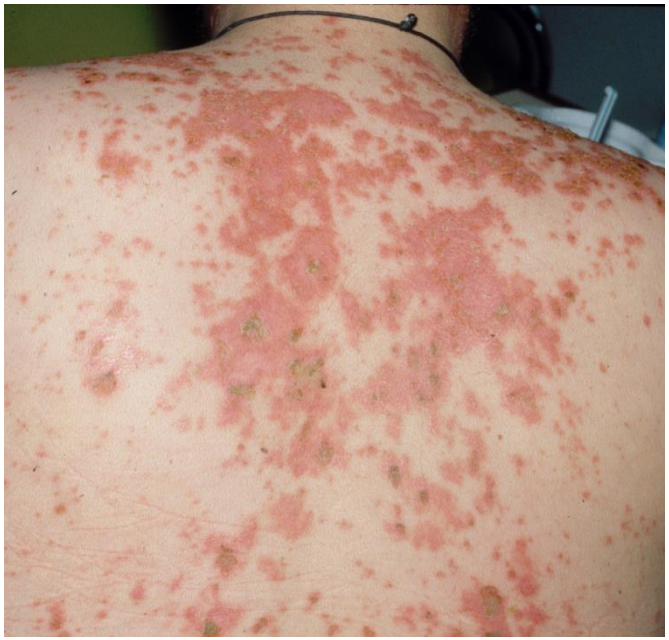
Serositis

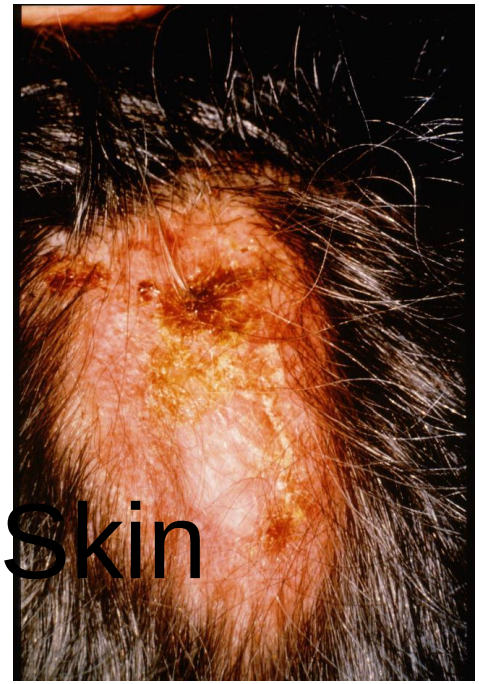
50%

„Faces“ of Lupus erythematosus

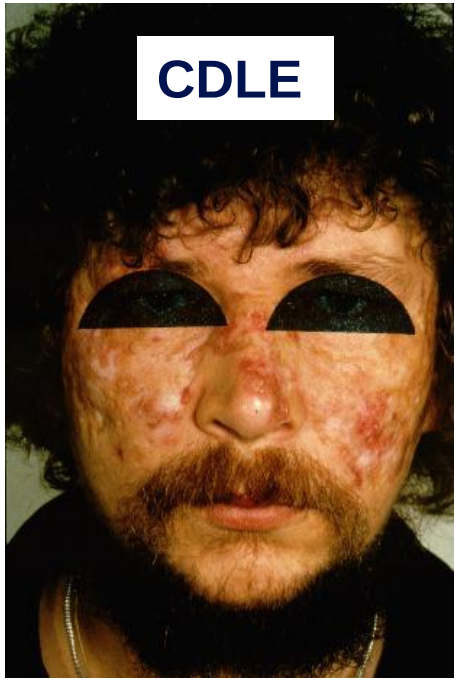


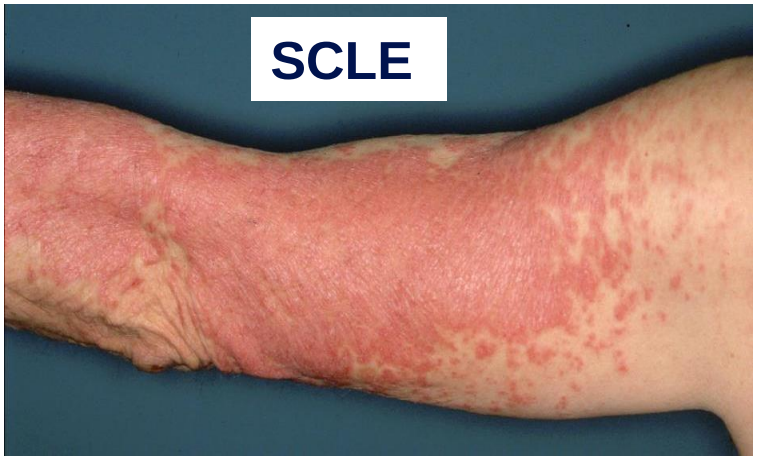
‚Butterfly‘ erythema

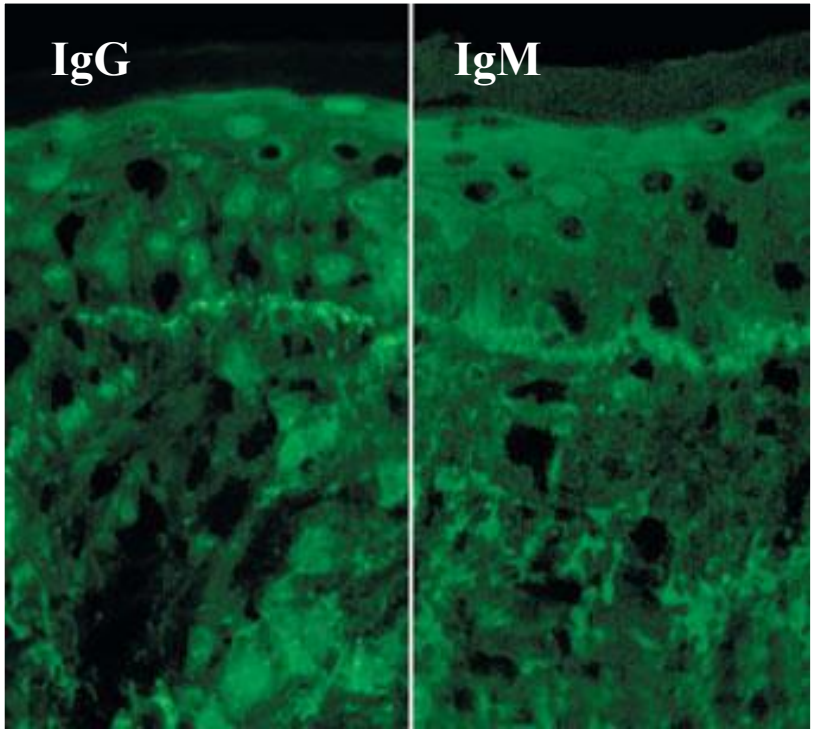




Skin







Granular deposits of IgG and IgM at the basal membrane of the skin

Lunge: Symptome: Dyspnoe, Husten, atemabhängige Schmerzen

Pleuritis (50%)

Pneumonit

Pulmonale

Pulmonale

Pulm

Diagnostik:

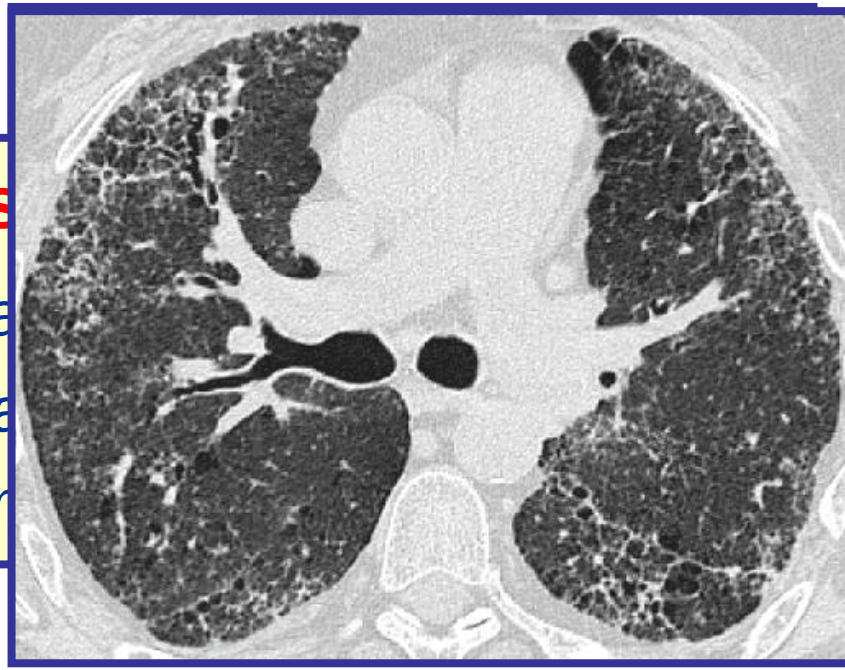
Therapie:

Sons

Ba

Ka

Ar



Diagnostik: ANA: oft antiRo pos.
HRCT, Lungenfunktion, BAL, Biopsie
DD: Medikamenten induzierter SLE, MCTD, SSc, Overlap-Syndrome.
Therapie: Immunsuppression

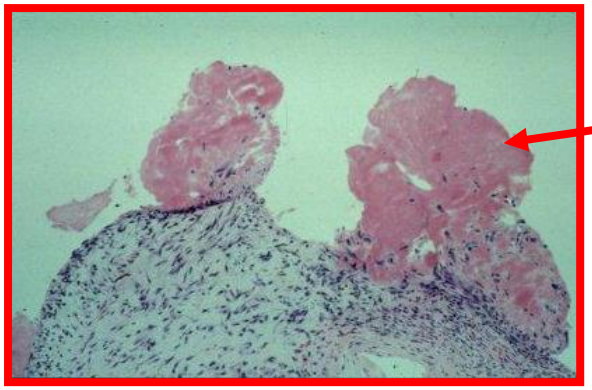
nostik: Herzecho
genfunktion, CT, Angio
apie: Immunsuppression

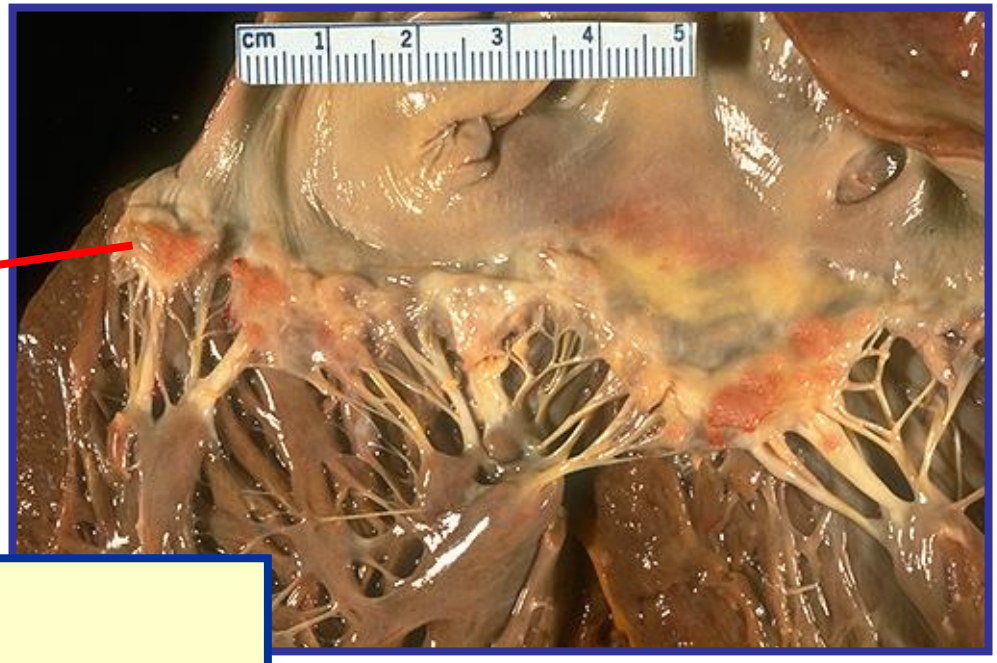
Heart

Pericarditis (20-30%)

Libman Sachs Endocarditis

(15-60% postmortem)





clinics: - often undetected,

diagnostics: - echocardiography

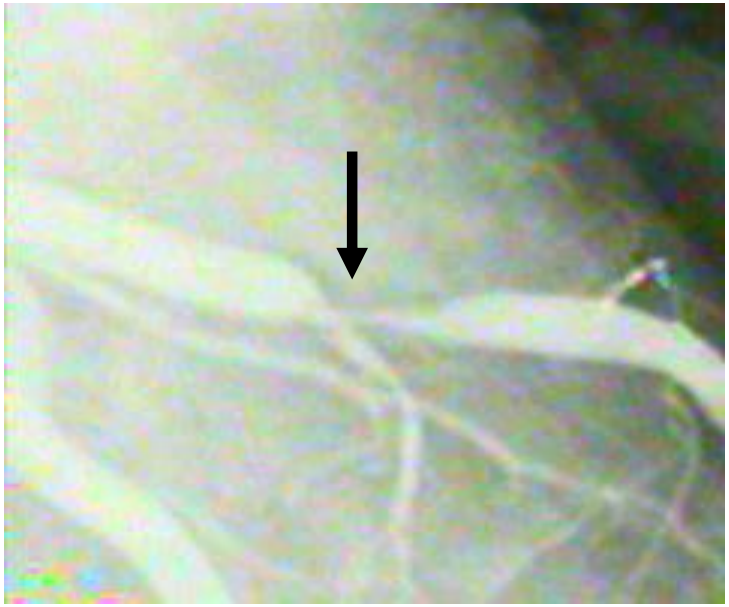
therapy: - rarely replacement of valves

- endocarditis prophylaxis!!

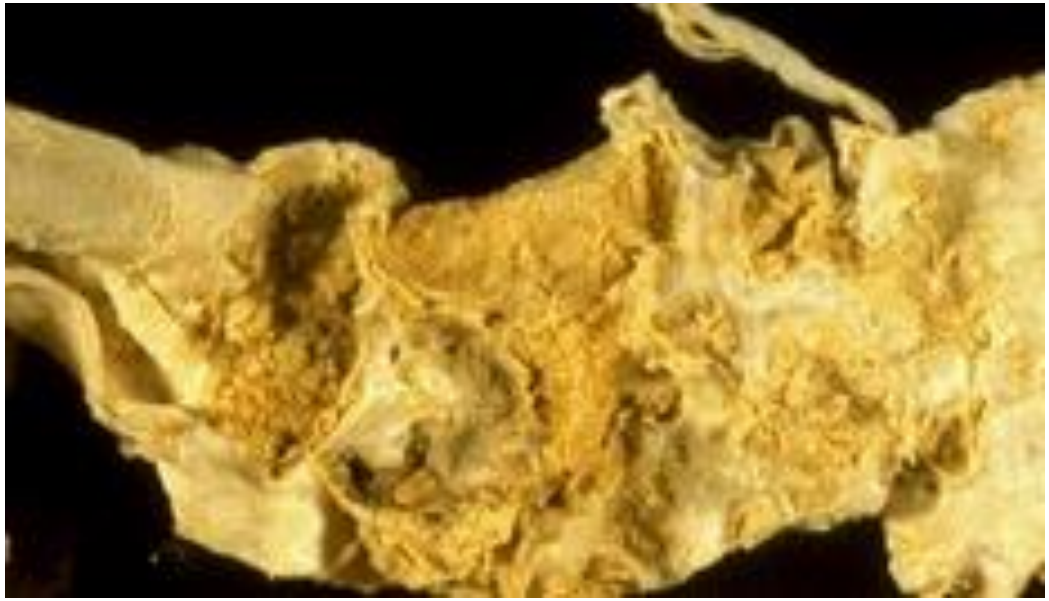
Prognostic factors
Accelerated Arteriosclerosis

Causes:

- **Chronic Inflammation**
- **Immunekomplexe-Vasculitis**
- **Anti Phospholipid-Antibodies**
- **Lipid levels high(i.e. steroid - induced)**
- **renal failure, arterialhypertension**



Koronare Herzkrankheit



Carotisplaques 40%

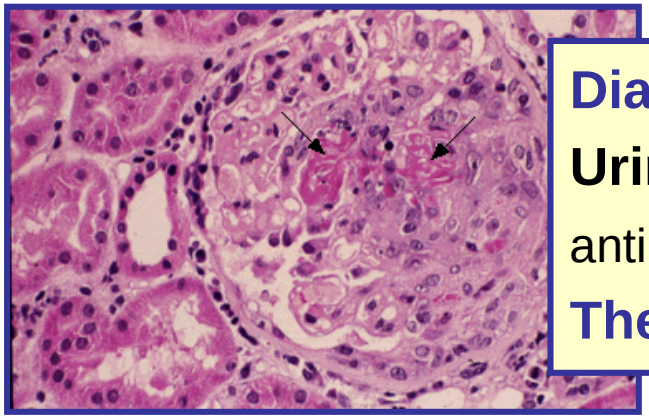
Kidney

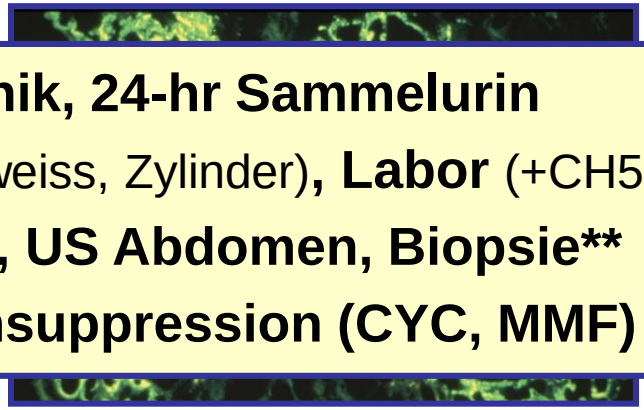
Lupus Nephritis (WHO Classifikation)

I. Minimal mesangial lesion
II. Mesangial hypercellularity /GN
III. Focal proliferative GN
IV. Diffuse proliferative GN
V. Membraneous GN
VI. Advanced Sklerosing GN 1-2%

- interstitial Nephritis in 50%

	Immunosuppr.
1%	none
26%	steroids (0.5-1mg/kgKG)
18%	steroids +/- MMF
38%	steroids + CYC Bolus
16%	steroids + CSA

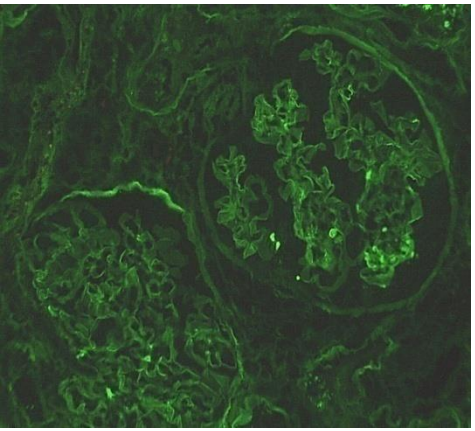


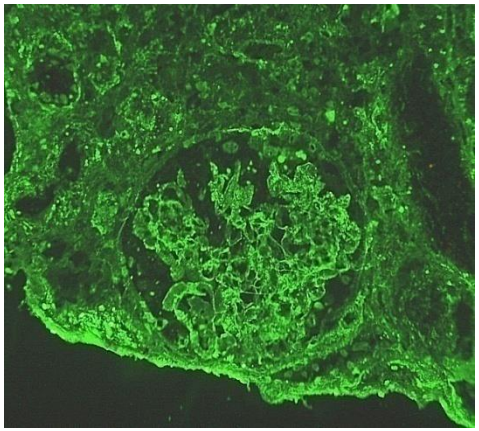


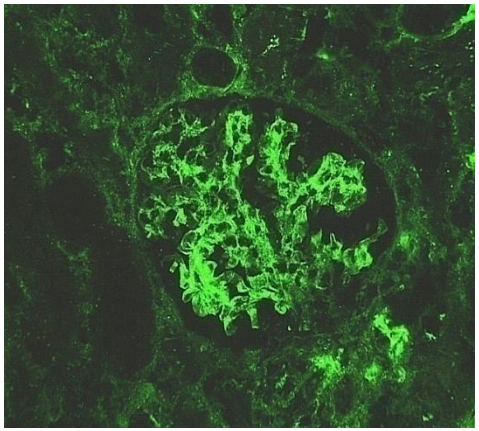
Diagnostik: **Klinik, 24-hr Sammelurin Urinstatus** (Blut, Eiweiss, Zylinder)**, Labor** (+CH50, anti dsDNA, anti C1q)**, US Abdomen, Biopsie****

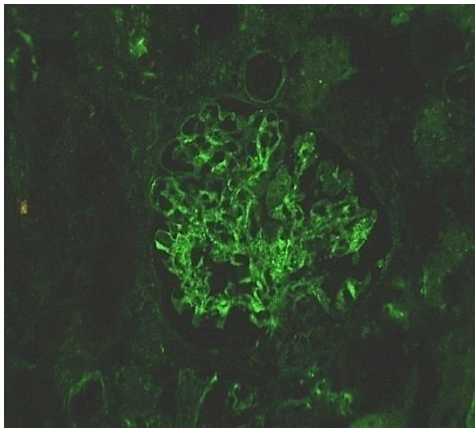
Therapie: **Immunsuppression (CYC, MMF)**

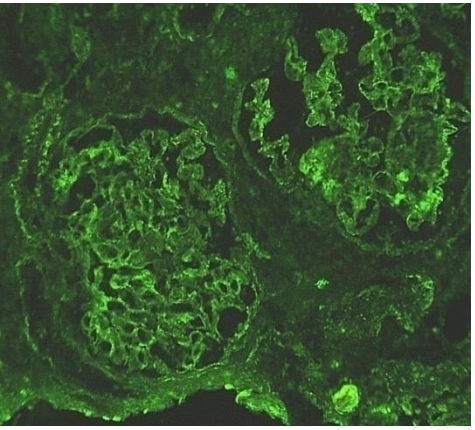
Immunfluoreszenz Lupus GN



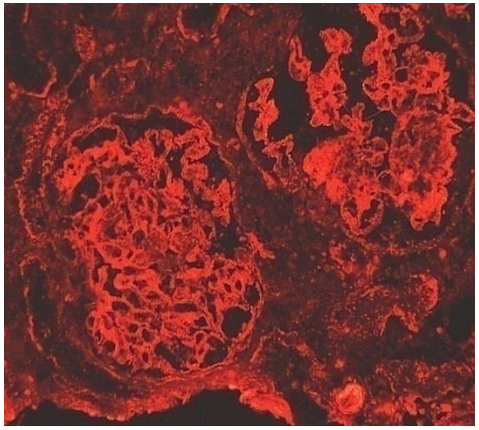




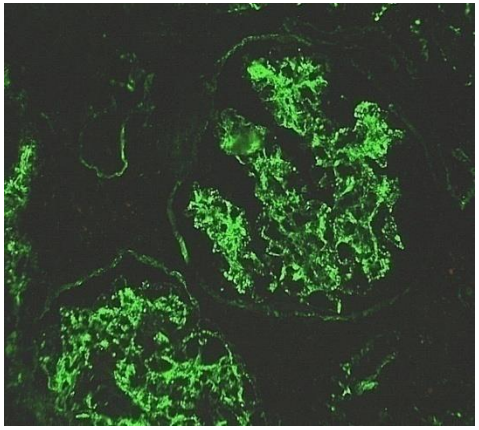




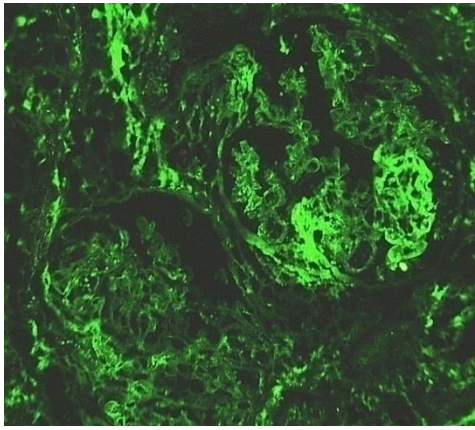
leichte Immunglobulin-Kette kappa



leichte Immunglobulin-Kette lambda



C5b-9



Fibrinogen

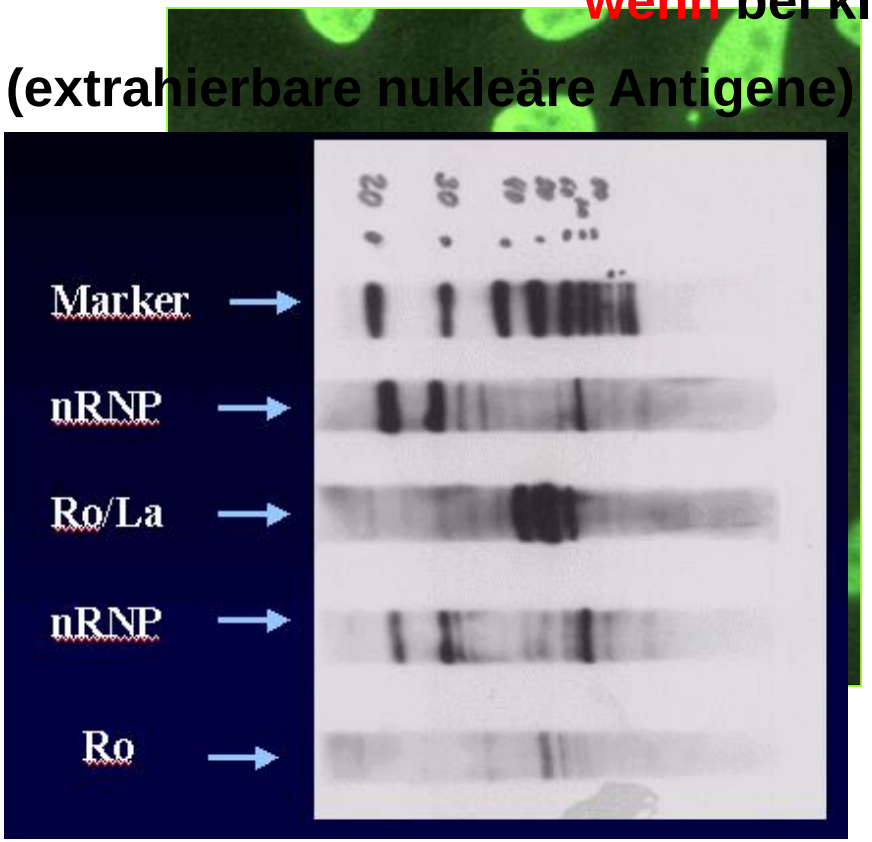
Labordiagnostik 1

Primärdiagnostik:

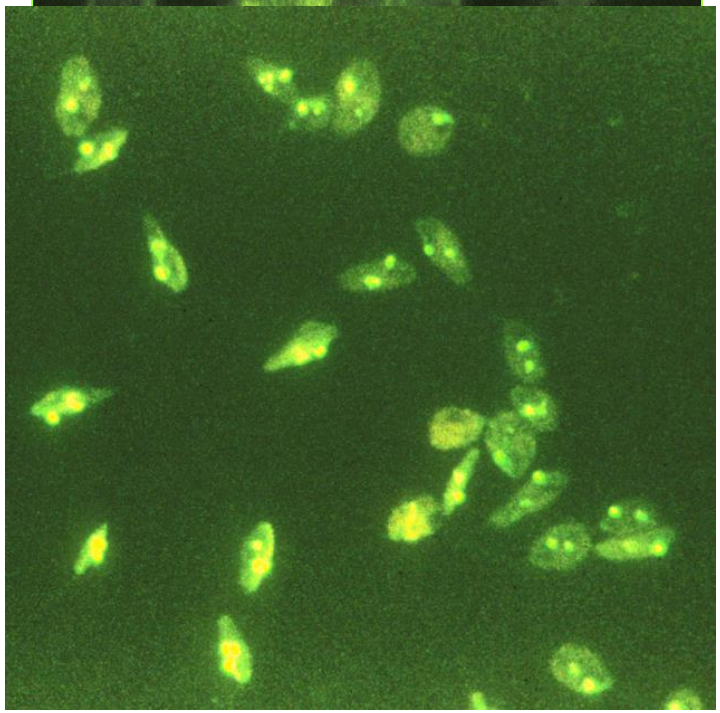
Diagnose: **ANA (antinukleäre Antikörper)**

wenn bei klinischem V.a. SLE positiv, dann

ENA (extrahierbare nukleäre Antigene)



anti dsDNA AK (Crithidien)



Labordiagnostik 2

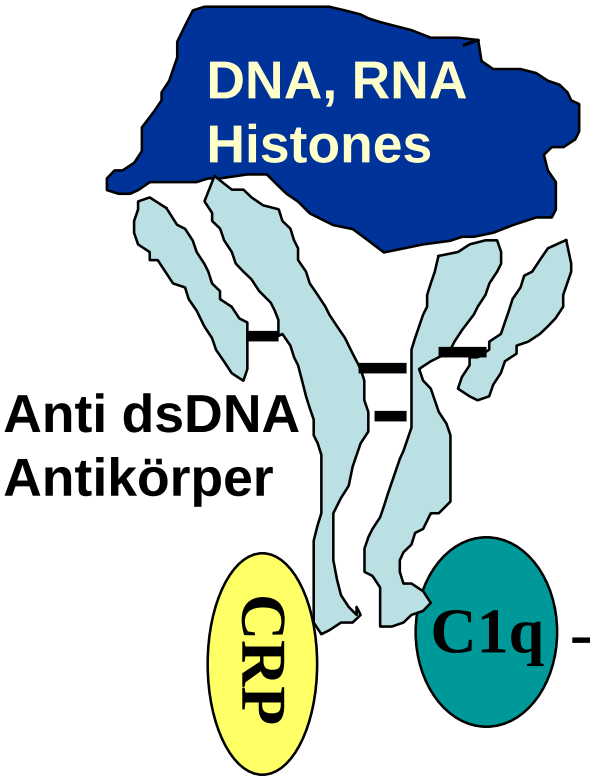
Primärdiagnostik:

Aktivität:

BSG nicht sicher verwertbar

(CRP) meist normal DD: Infekt/Serositis

Komplement (CH50/C3d)



C4 C2 → C3 → C3a

C3 → C3b → **C3d**

Klassische Komplementaktivierung

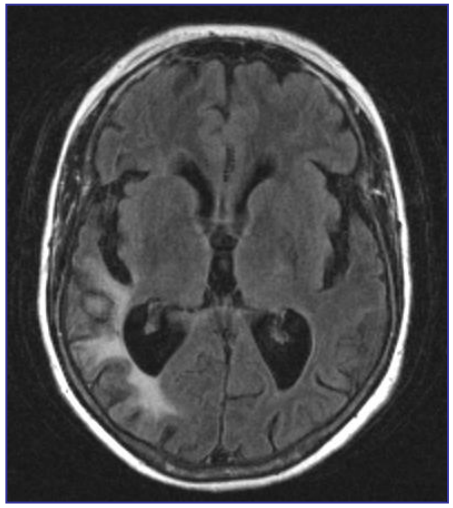
Bei aktivem SLE:

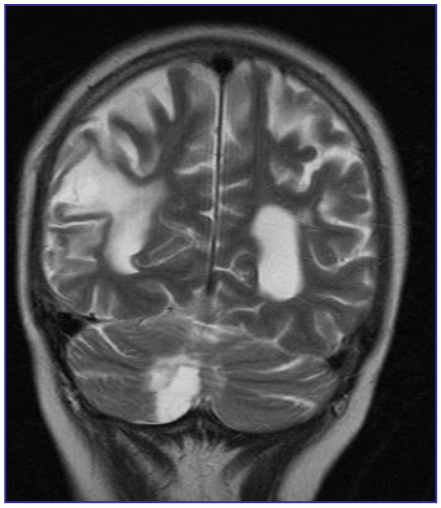
CH50 ⇓, (C4 ⇓, C3 ⇓) **C3d ⇑**

Neuropsychiatrischer SLE

Diagnostik:

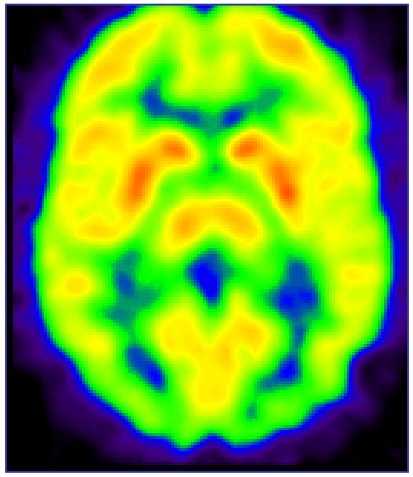
NMR





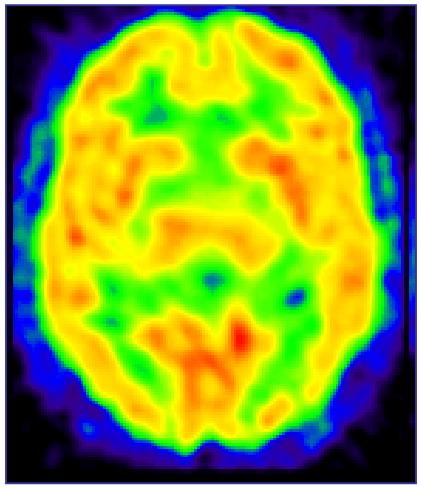
Marklager Hyperintensitäten Territoreale Infarkte

PET



Immun-

Suppression



Hämatologische Beteiligung

Anämie

DD: Autoimmunhämolytisch, renal, Med. toxisch

Therapie: Steroide +/- AZA, CYC, Plasmapherese (bei TTP)

Leukopenie/ Lymphopenie

DD: SLE bedingt: 2.500-4000/µl
unter 1.500/µl: z.T. Medikamenten bedingt,

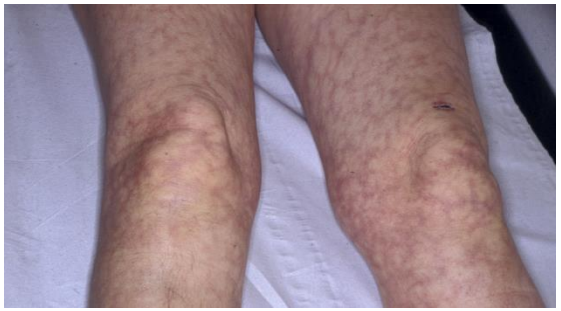
Therapie: Meist nicht notwendig, evtl.G-CSF

Thrombopenie

DD: AITP, TTP, Med toxisch

Therapie: Steroide +/- AZA
Danazol, ivIg, anti CD20
Plasmapherese
Splenektomie

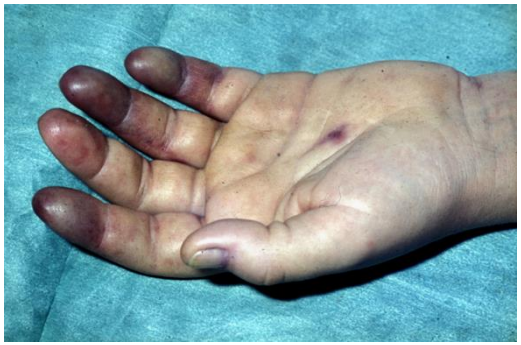
Anti-Phospholipid Syndrom



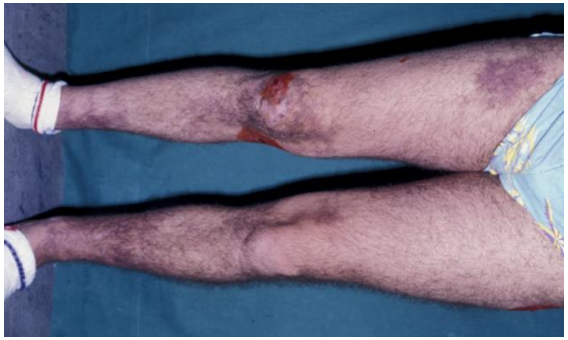
Livedo reticularis

Laborkonstellation

- Phospholipid AK
- Cardiolipin-AK
- ß2GPI AK
- PTT Verlängerung
- Lupus Antikoagulans



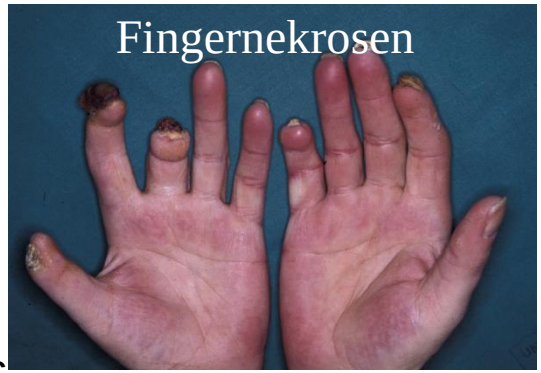
Arterielle Thromboembolie

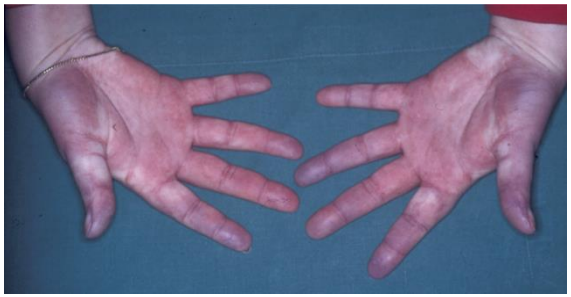


Livedo racemosa

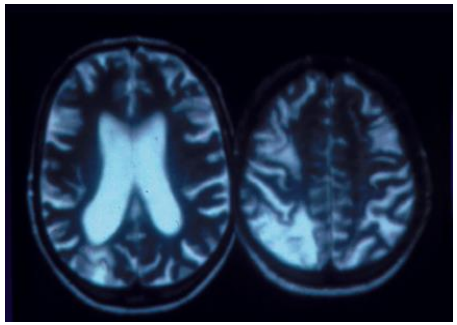
Plus klinische Symptome

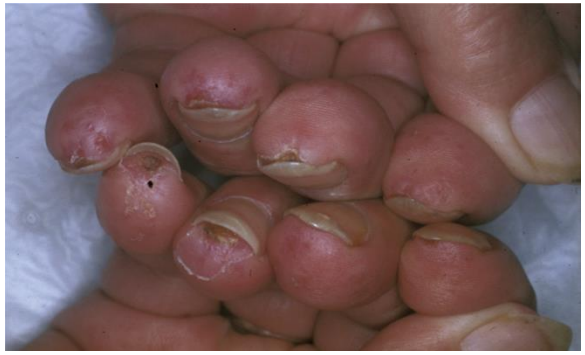
- Thrombozytopenie
- wiederholte Aborte
- Thromboembolie
- Schlaganfälle
- Libman Sacks Endocarditis





Raynaud Phänomen





Apoplexia capillaris

Diagnostic autoantibodies and autoimmune diseases

- ANA — Screening
- ds-DNA — SLE
- Sm — SLE
- Ro, La — Sjögren Syndrome, SLE
- cm — limited systemic sclerosis
- Scl-70 — diffuse systemic sclerosis
- U1-RNP — mixed connective tissue disease
- Jo-1 — polymyositis/anti-synthetase syndrome

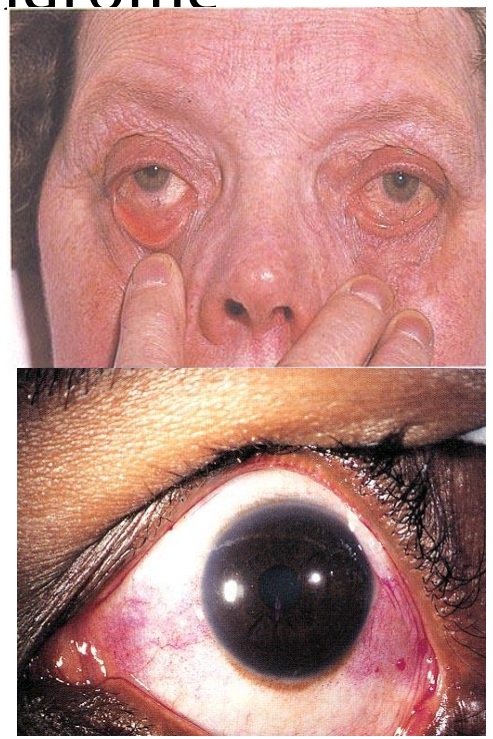
Other Autoimmune Connectivitides

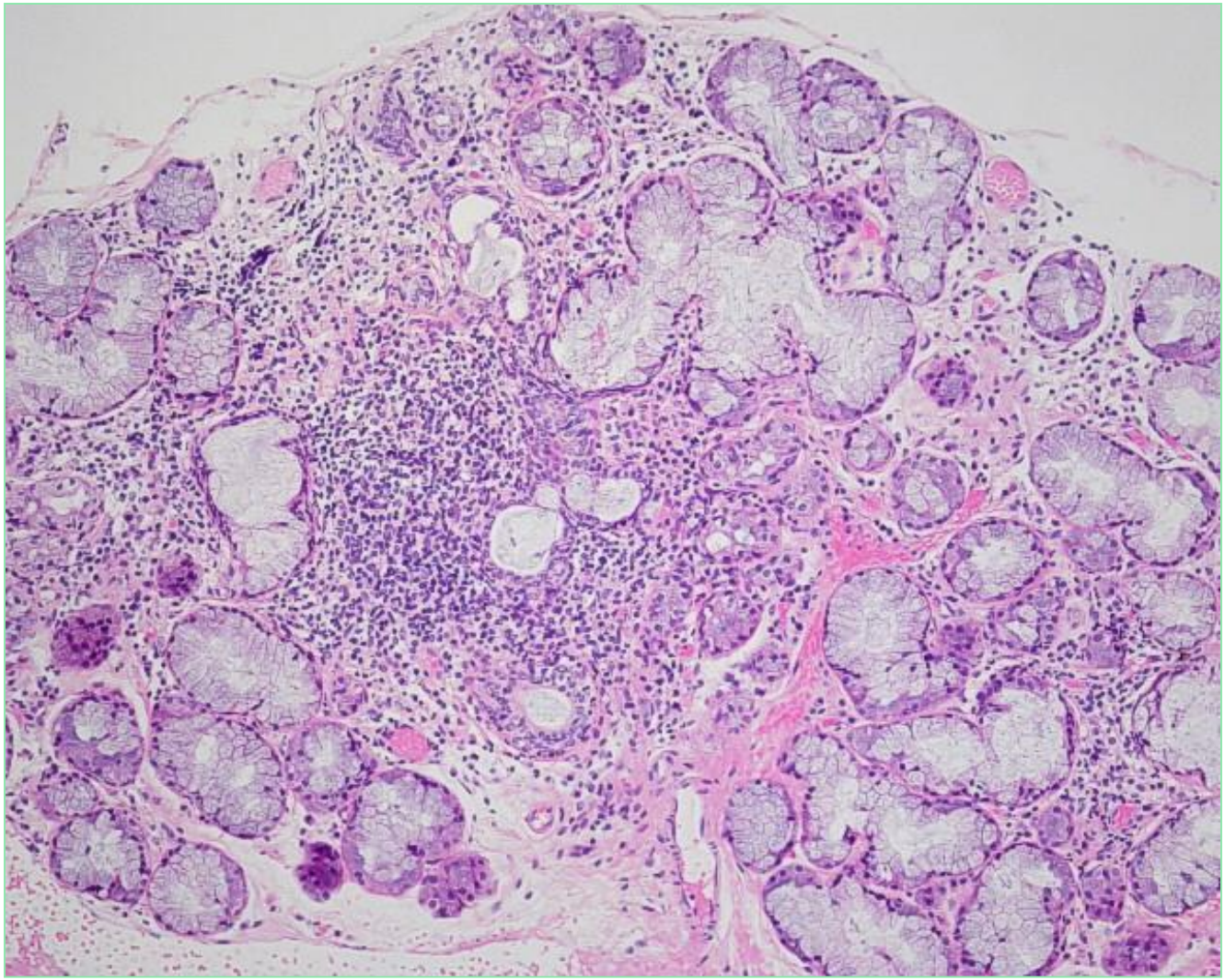
- Sjögren‘s syndrome
- Systemic sclerosis
- Mixed connective tissue diease (MCTD)
- Dermato/polymyositis
- Autoimmune hepatitis
- Undifferentiated connective tissue disease (UCTD)
- Overlap syndromes

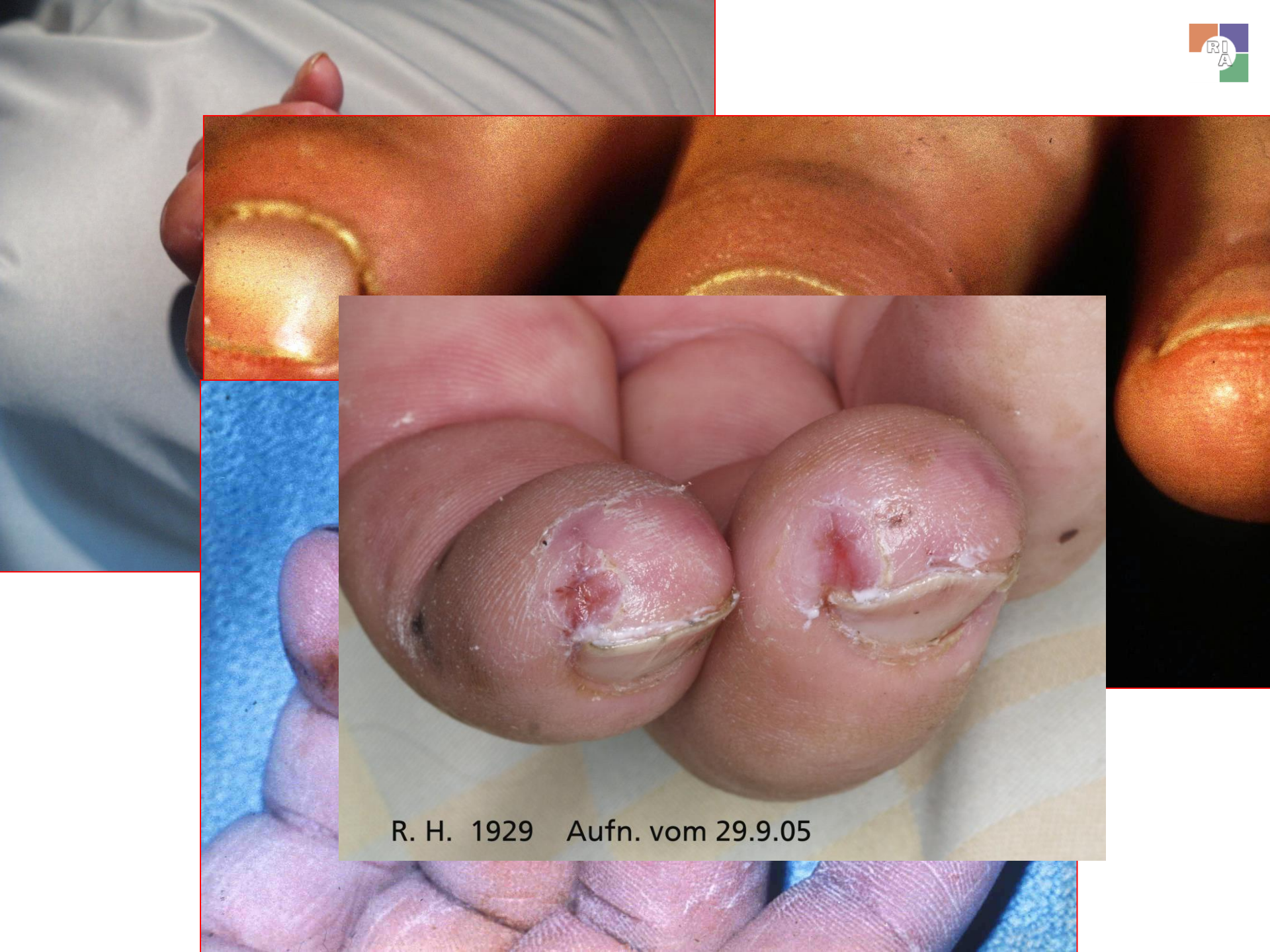
Sjögren‘s Syndrome

Sjogren’s Syndrome

- eye complaints
  - dryness, burning, itching, foreign body sensation
- keratoconjunctivitis sicca
  - corneal abrasions - rose bengal staining






R. H. 1929 Aufn. vom 29.9.05

Autoimmune connective tissue diseases

Common features

- Raynaud phenomenon
- Sicca syndrome (xerophthalmia, xerostomia)
- Serositis (pleuritis, pericarditis)
- Constîtutional symptoms (fever, weight loss, sweating during night)
- Arthralgia, arthritis
- ANA positivity

Autoimmune connective tissue diseases

Discriminating features

- SLE : discoid skin lesions, skin rash (butterfly), renal insufficiency due to glomerulonephriits, CNS involvement, ds-DNA Ab, C-consumption
- SyScl : skin induration, sclerodaktyly, interstitial lung disease, pulmonary hypertension, acral skin ulcers, malabsorption, cm or Scl-70 Ab
- DM/PM : muscle weakness, skin rash, heart failure, Jo-1 Ab in the minority of cases

Autoimmune connective tissue diseases

Discriminating features

- Sjögren's syndrome: severe autoimmune sialadenitis, SS-A and SS-B Ab
- MCTD : high titers of RNP Ab, on clincial terms much similarity to SLE, however much less renal involvement

Treatment principles in autoimmune connectivitides

- antiinflammatory drugs *(NSAIDs, glucocorticoids)*
- antimalarial drugs *(background drug, skin, joints)*
- antimetabolites *(methotrexate, azathioprine)*
- alkylating agents *(cyclophosphamide for severe renal and CNS disease)*
- T-cell inhibitors *(ciclosporine A , mycophenolate mofetil)*
- biologics *(B-cell depletion by rituximab/anti-CD20 and inhibition of T-cell co-stimulation by CTLA4-Ig)*

Treatment principles in autoimmune connectivitides

- artificial lacrimal and salivary fluid *(Sicca-syndrome)*
- skin protection *(dryness, akral lesions)*
- infection prophylaxis upon immunosuppression *(antibiotics, vaccination)*
- active physiotherapy *(against joint contractures, loss of muscle strength, joint deviation)*
- lymphdrainage *(against lymphedema)*
- connective tissue massage *(against cutaneous fibrosis/induration and fibrosing tendovaginitis)*