Systemic vasculitides

Classification, pathogenesis, diagnosis, treatment

Ústav imunologie UK 2. LF a FNM, Praha

Vasculitides – definition

Vasculitides present heterogeneous group of disorders that are characterised by inflammatory destruction of blood vessels. These diseases develop various symptoms consisting both of systemic and local manifestations. Local manifestations result from impaired tissue perfusion caused by blood vessel inflammation(1).

Vasculitides - classification

- **Primary vasculitides**
- **Secondary vasculitides**

Causes of secondary vasculitides:

- external antigens (infections, allergic vasculitides, serum sickness)
- internal antigens (systemic autoimmune diseases, malignancies)
- radiation induced vasculitides, GVHD

Secondary vasculitides are usually caused by immune complexes (III. type of hypersensitivity)

Primary vasculitides - classification

- vessel size (small, medium, large vessels)
- histological classification (according to the infiltration – leukocytoclastic, lymphocytic)
- pathogenetic classification (later on)
- serological classification (ANCA+, ANCA-)
- nosologic units (later on)

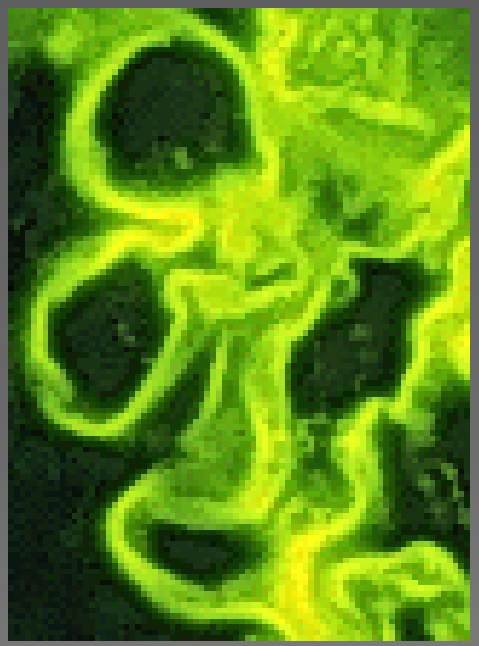
Primary vasculitides – pathogenetic classification

Hypersensitivity reactions according to Coombs and Gell classification(2)

Hypersensitivity type	Mechanism	Often mentioned disorders
I.type – immediate	IgE antibodies	Alergic rhinitis, anaphylaxis
II.type – antibody-dependent	Cytotoxic antibodies	Immune cytopenias, pemphigus
	Inhibiting or stimulating antibodies	Myasthenia gravis, pernicious anemia Graves´disease
III.type – immune complex disease	Immune complexes deposition	Systemic lupus erythematodes, serum sickness
IV.type – cell mediated hypersensitivity	Delayed hypersensitivity	Mykobacteriosis, sarcoidosis
	Cell cytotoxic reaction	Acute transplant reaction, contact dermatitis

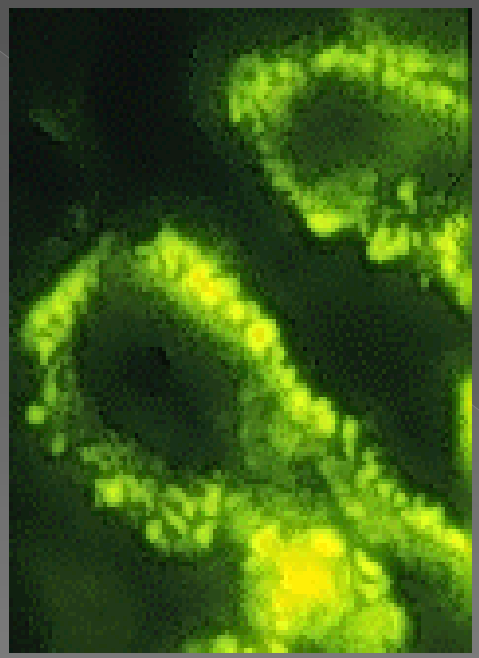
Primary vasculitides – pathogenetic classification

II. type of hypersensitivity



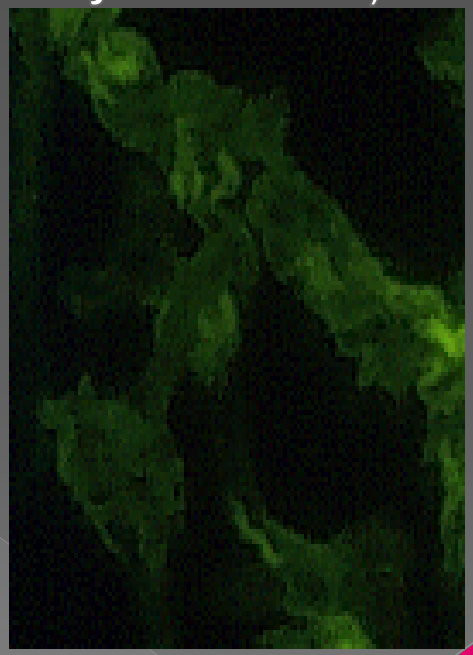
Linear type of immunofluorescence anti-GBM glomerulonephritis

III. type of hypersensitivity



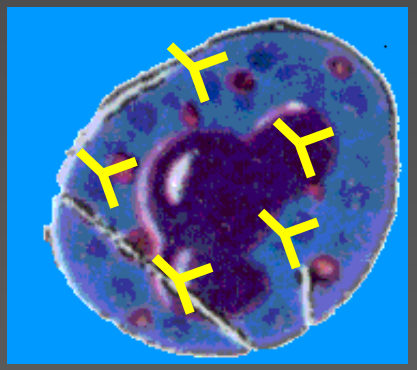
Granular type of immunofluorescence Deposits of immune complexes

option of II. type hypersensitivity reaction (stimulation of target cells by antibodies)



Pauciimmune type of immunofluorescence ANCA-associated vasculitides

Primary vasculitides - serological classification



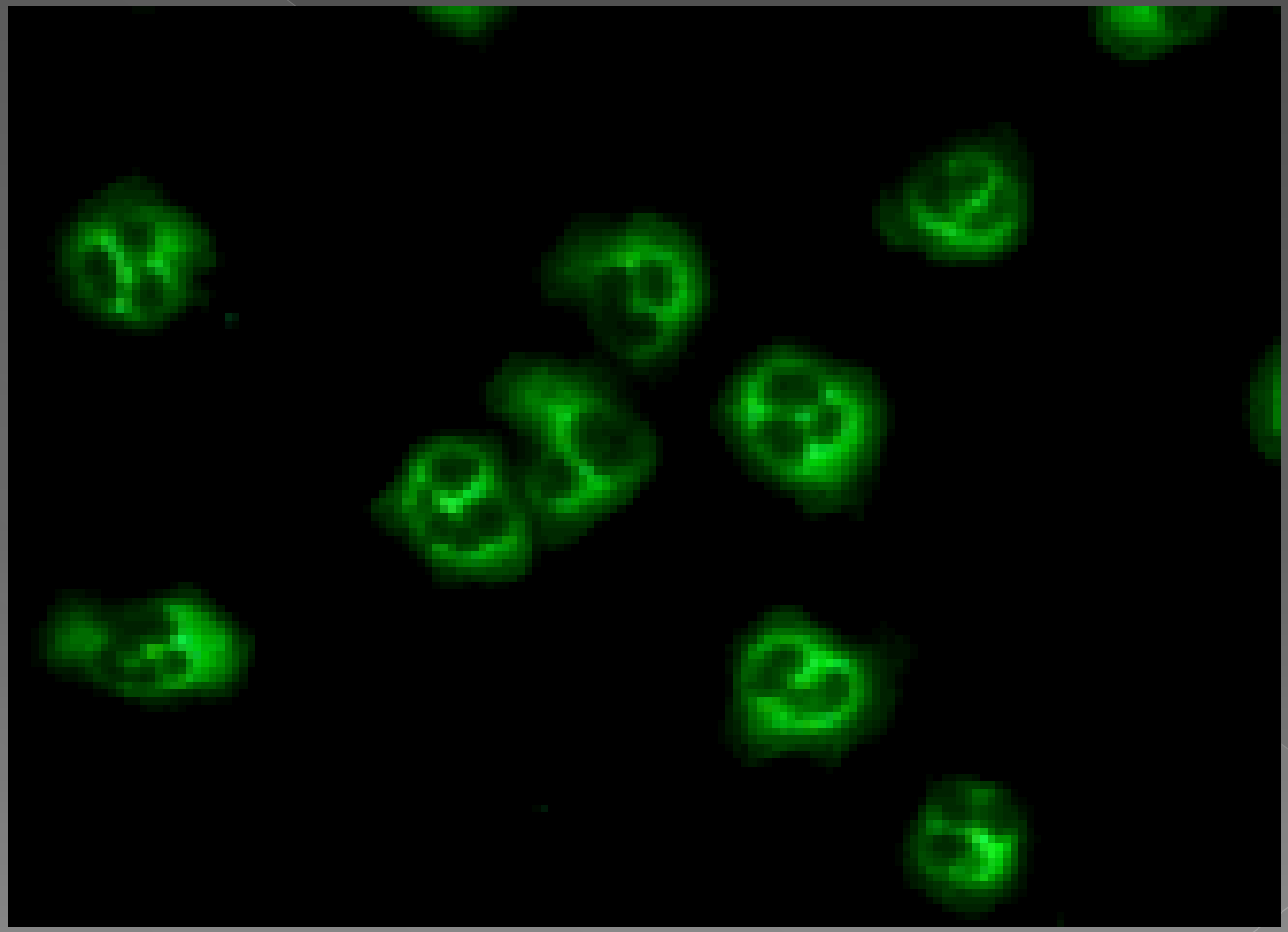
ANCA autoantibodies

Target antigens – can be found in PMN granules

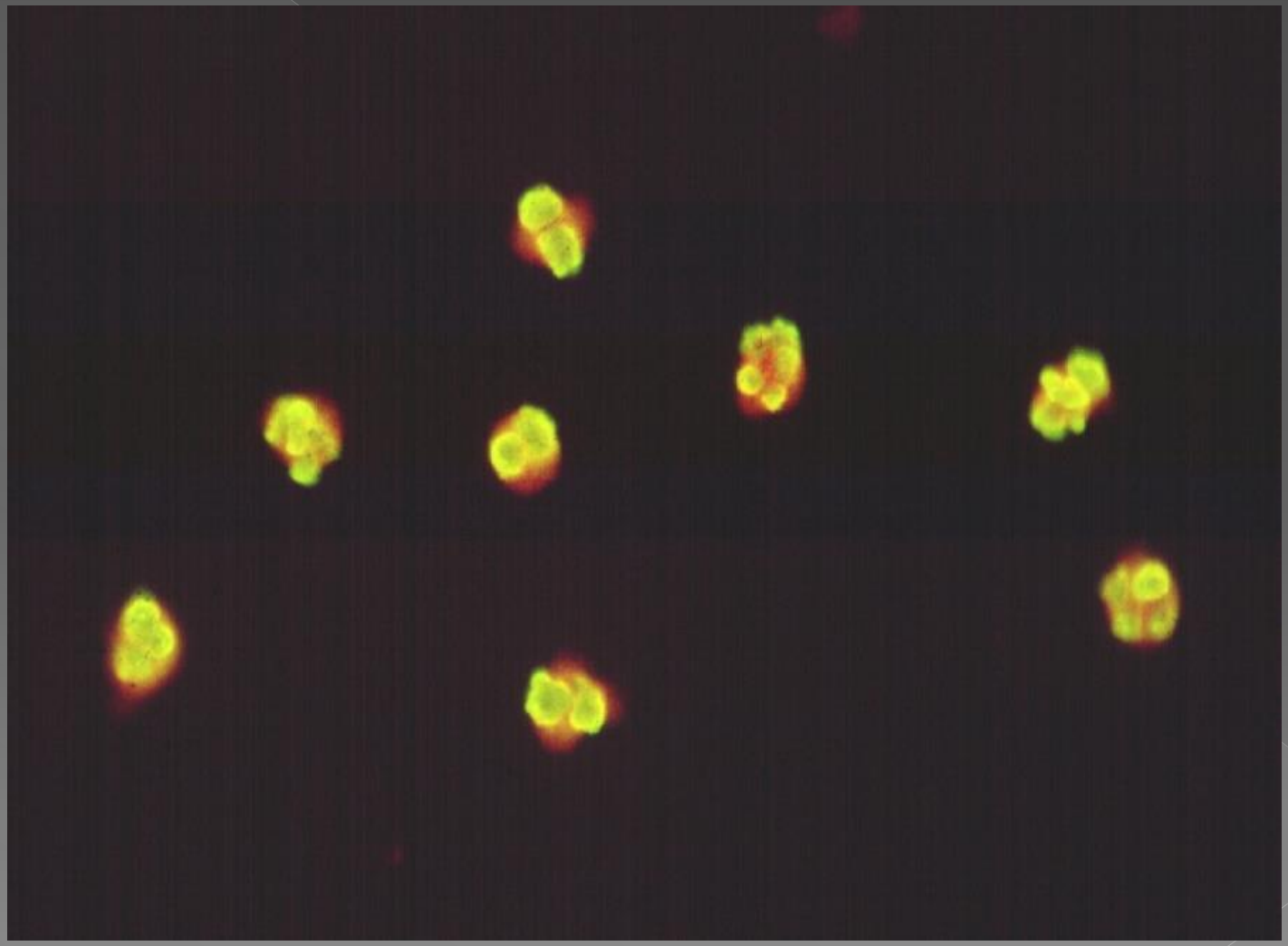
proteinase 3 (PR3)
myeloperoxidase (MPO)
Bactericidal and permeability increasing protein (BPI)
lactoferin, elastase...

C-, P-, A- ANCA

C-ANCA
cytoplasmic staining of neutrophils



P-ANCA
perinuclear staining of neutrophils



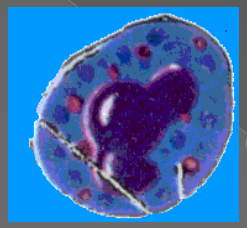
Pathogenic role of ANCA

Genetic background

External environment (infection, SiO_2, drugs)

ANCA

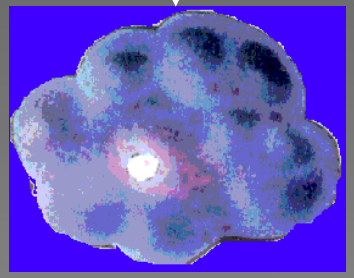
+



Anti-microbial functions inhibition

Stimulation O_2^-, degranulation

Macrophage dysfunction



Inadequate cytokine environment, TH1/TH2

Tissue injury (vessels, lungs...)

Granulomatous inflammation

Diagnostic asociations of ANCA

C-ANCA

Dg / target antigen

Wegener gr. / PR3

Cystic fibrosis / BPI

P-ANCA

Dg / target antigen

Mikroskopic polyangiitis, iRPGN / MPO

RA, JCA/ MPO, LF

C,P,A-ANCA

Dg / target antigen

UC / various

Autoimmune hepatitis/ various

ANCA POSITIVITY DOESN´T ALLWAYS MEAN ONLY DIAGNOSIS OF VASCULITIS

Primary vasculitides classification – according to the size of the vessel affected (3)

Large vessel vasculitides	Takayasu arteritis
	Giant cell (temporal) arteritis
Medium vessel vasculitides	Polyarteritis nodosa
	Kawasaki disease
Small vessel vasculitides	Wegener´s granulomatosis
	Churg-Strauss syndrome
	Mikroskopic polyangiitis
	Essential cryoglobulinaemic vasculitis
	Henoch-Schönlein purpura
	Cutaneous leucocytoclastic angiitis

Chapell Hill Consensus Conference

Large vessel vasculitides
Takayasu arteritis (1, 3, 4)

Epidemiology: mostly female under age of 50, more frequently in Asian countries (Japan, Korea, China…)

Predominantly affected vessels: aorta and its major branches

Serology: ANCA negative

Complications: renovascular hypertension, valvular heart disease, stroke, retinopathy, organ failure

Large vessel vasculitides
Giant cell (temporal) arteritis (1, 3, 4)

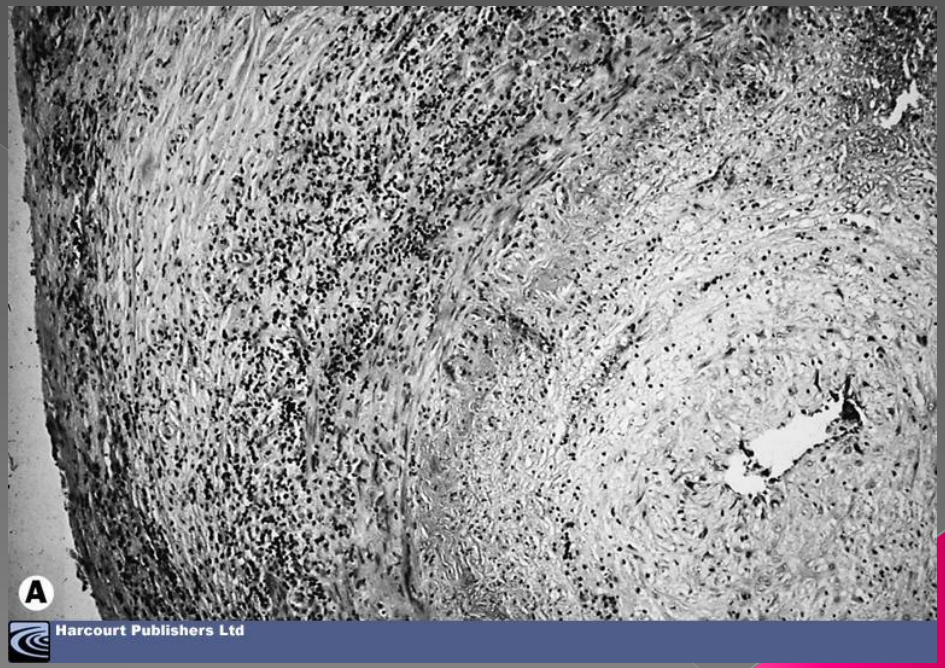
Epidemiology: mostly female older than 60 years
in 50 % patients associated with polymyalgia rheumatica

Predominantly affected vessels: external and internal carotides and its major branches

Serology: ANCA negative

Complications: blindness caused by lesion of a. ophtalmica

Takayasu and Giant cell arteritis



Medium vessel vasculitides
Kawasaki disease (1, 3, 4)

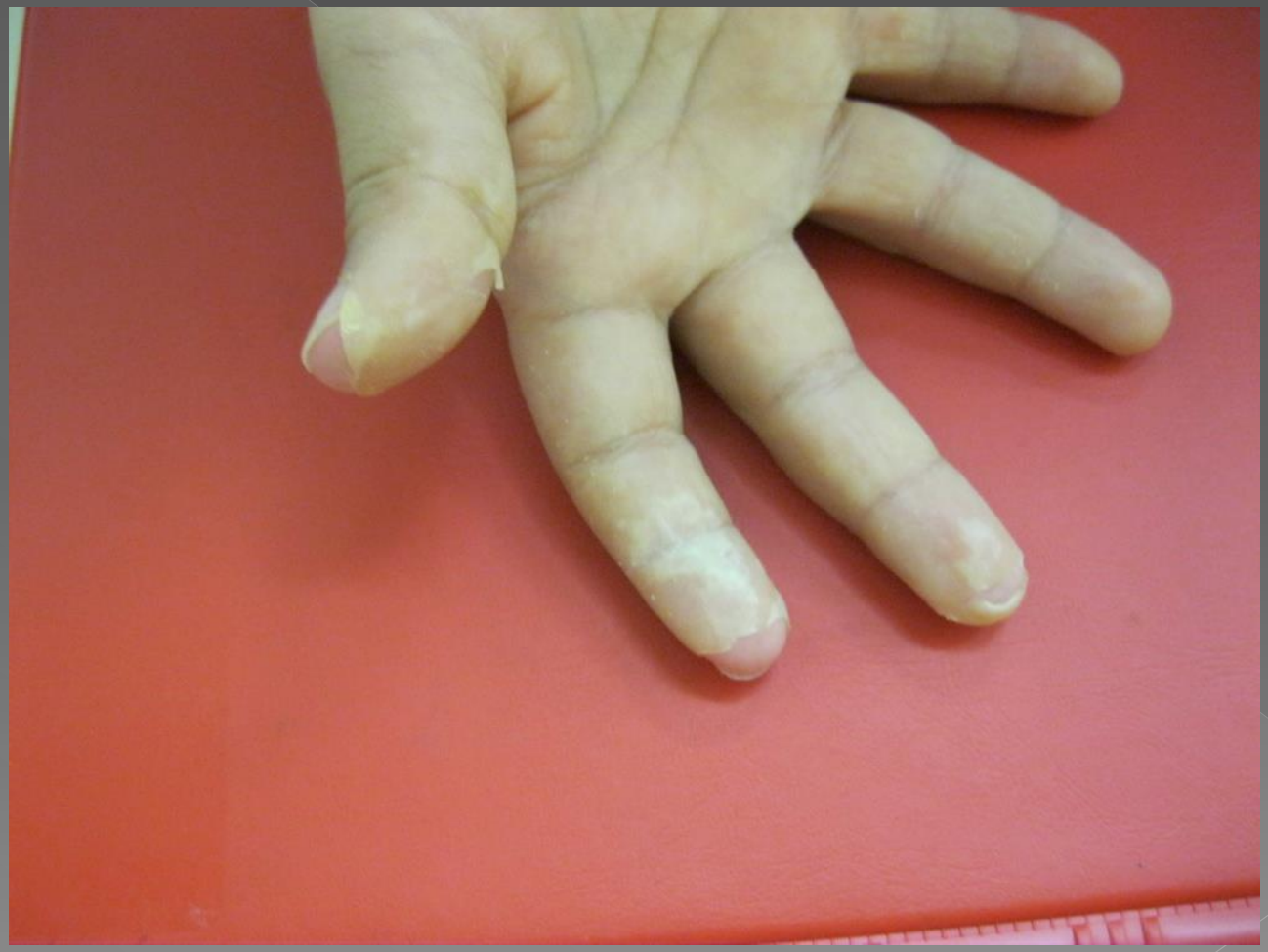
Epidemiology: children (mostly boys) younger than 5 years
more frequently in Asian countries - Japan, Korea

Predominantly affected vessels: muscular arteries (fever, lymfadenopathy, skin and mucosa manifestations)

Serology: ANCA negative, sometimes AECA positivity

Complications: coronary arteries involvement (20 - 25 % untreated children)

Kawasaki disease
skin manifestations on hand



Medium vessel vasculitides
Polyarteriitis nodosa (1, 4)

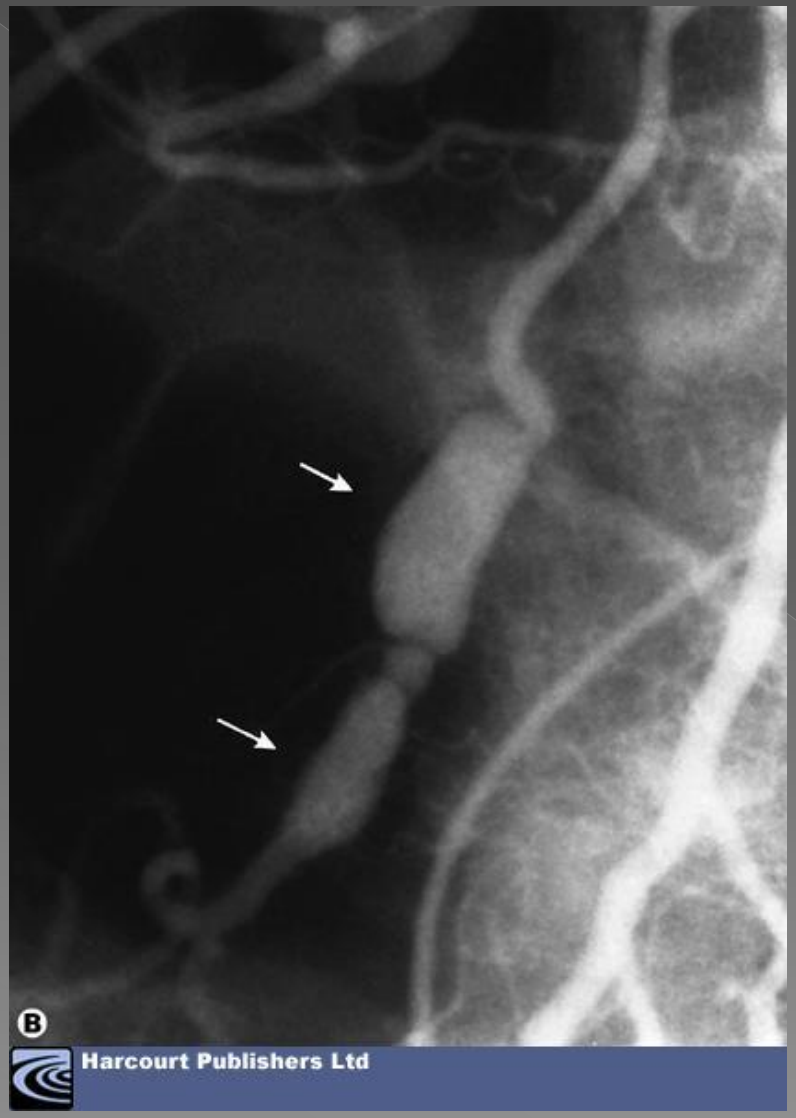
Epidemiology: mostly men, age 45 – 65
More frequently in Asian countries - Japan, Korea
Associated with viral infections (HVB, HVC, HIV)

Predominantly affected vessels: small and medium sized vessel bifurcations in various tissues and organs

Serology: sometimes P-ANCA positivity

Complications: neuropathy, hypertension, renal or heart failure, gastrointestinal bleeding…

Polyarteriitis nodosa



Small vessel vasculitides
Wegener granulomatosis (1, 4)

Epidemiology: slightly more common in men aged 35 – 55 years
More frequent in northern Europe

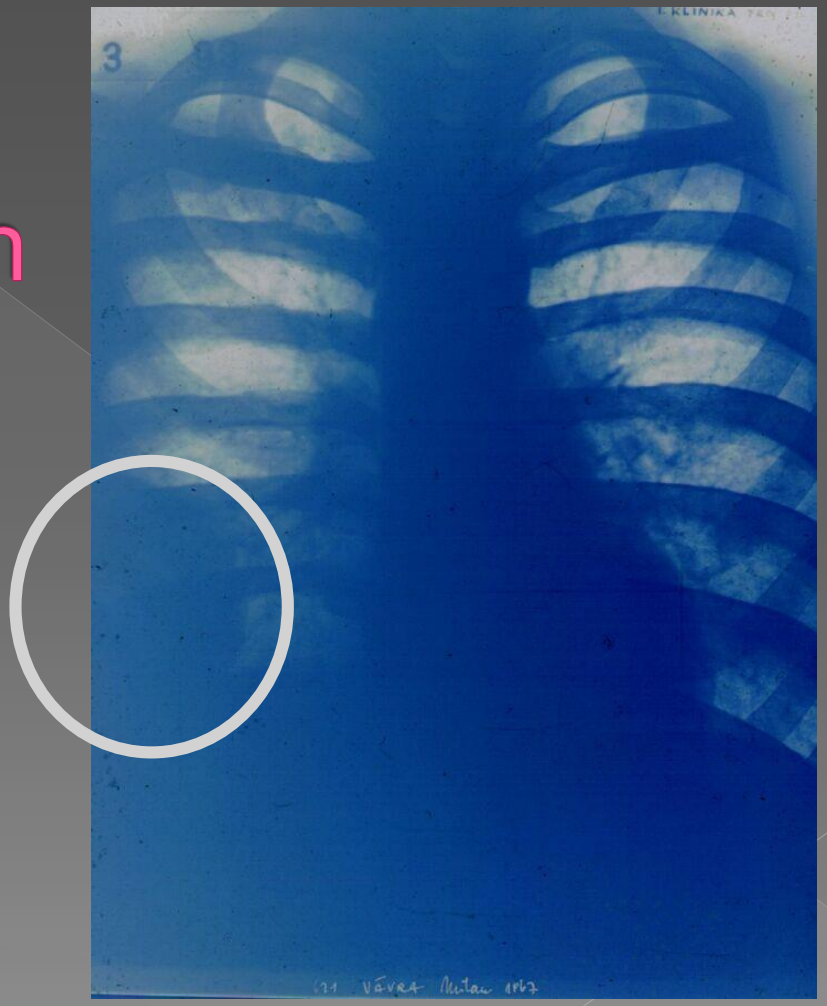
Predominantly affected vessels:
ENT regions, lungs, kidneys

Serology: C-ANCA (anti-PR3) detectable almost at 100 % patients with active generalized disease

Complications: renal or lung failure, hearing loss, blindness, upper-airway deformities (subglotic stenosis)

Wegener granulomatosis with pulmonary involvement

23 years old man



Small vessel vasculitides
Mikroskopic polyangiitis (1, 4)

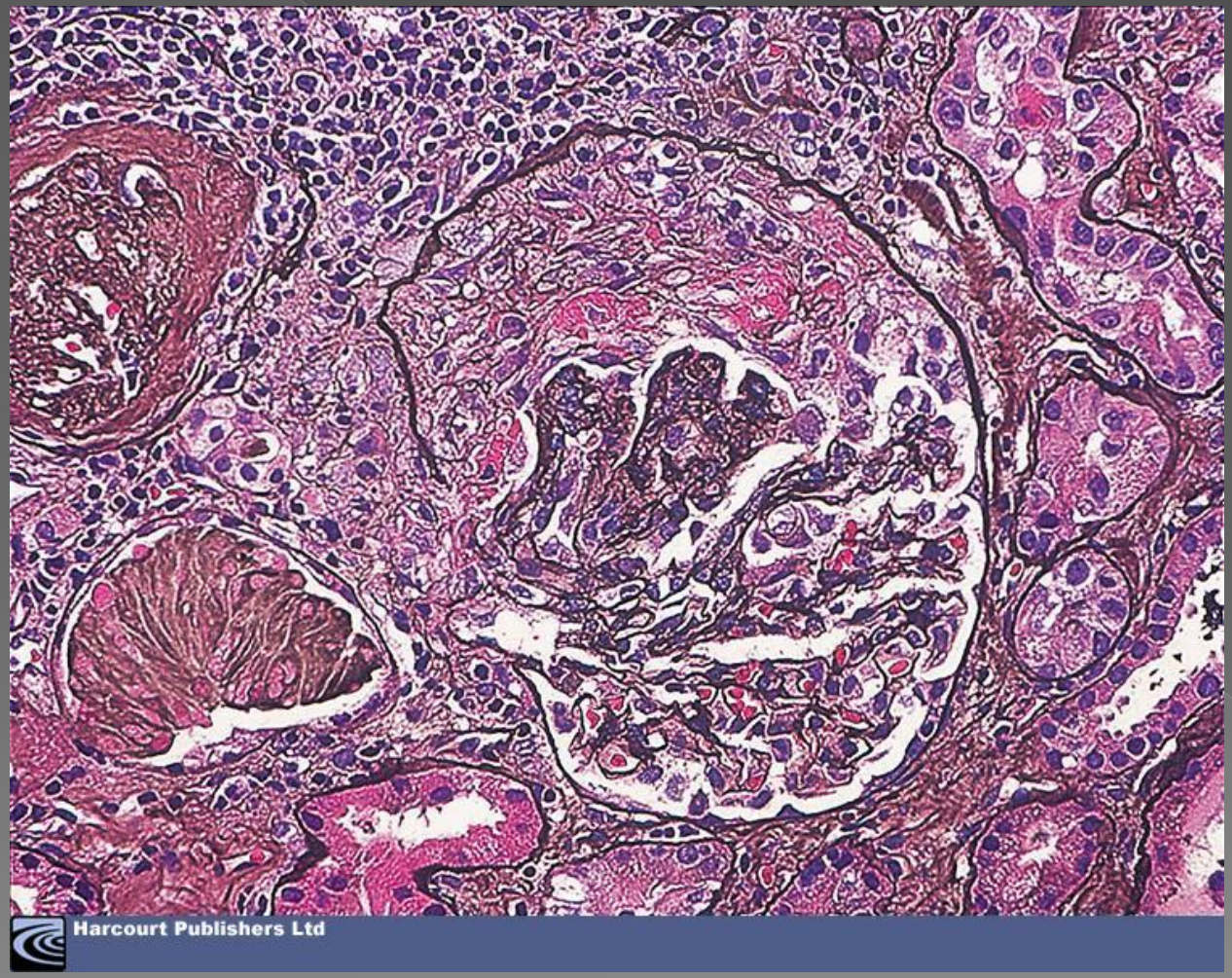
Epidemiologiy: slightly more often in men 50 years old and older
More frequent in white population

Predominantly affected vessels: small vessels in kidneys (lungs, skin, central and peripheral nervous system)

Serology: ANCA (80 % patients)
P-ANCA, anti-MPO(60 %)
C-ANCA, anti-PR3 (40 %)

Complications: renal failure

Rapidly progressive glomerulonephritis (crescentic glomerulonephritis)



Small vessel vasculitides
Churg-Strauss syndrome (1, 4)

Epidemiology: slightly more frequent in men, age 15 – 70 years

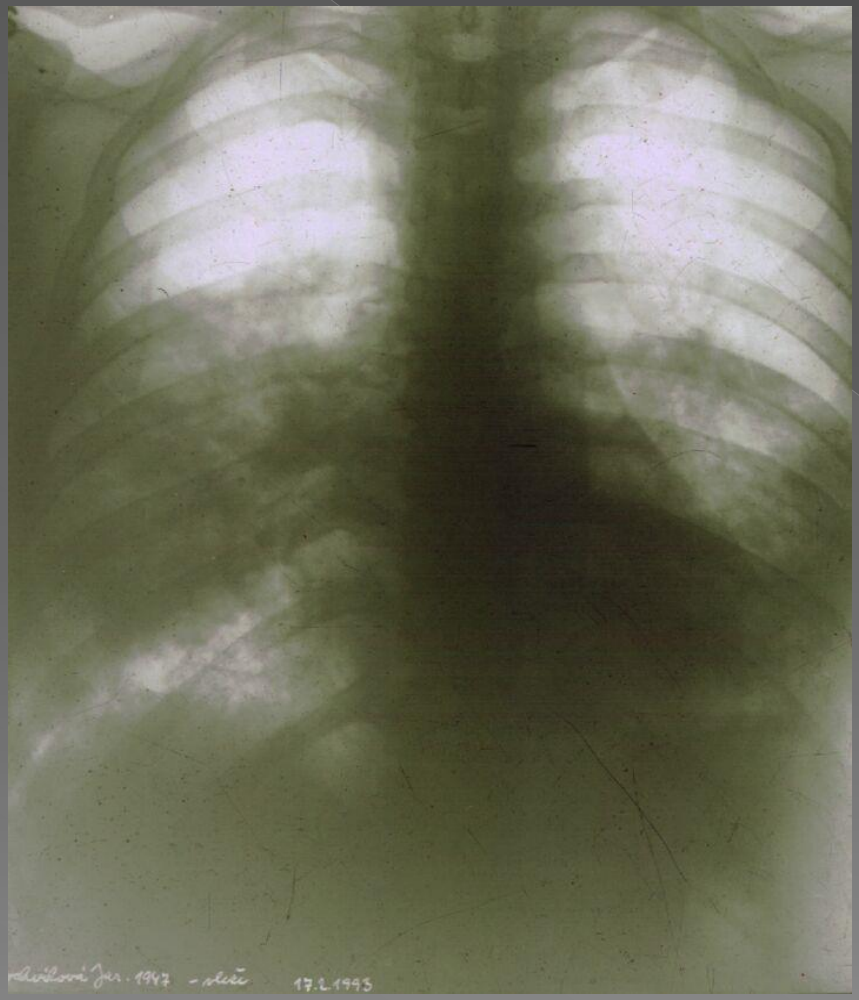
Predominantly affected vessels: small vessels mostly in ENT regions and lungs (mononeuritis multiplex, skin, gastrointestinal system)

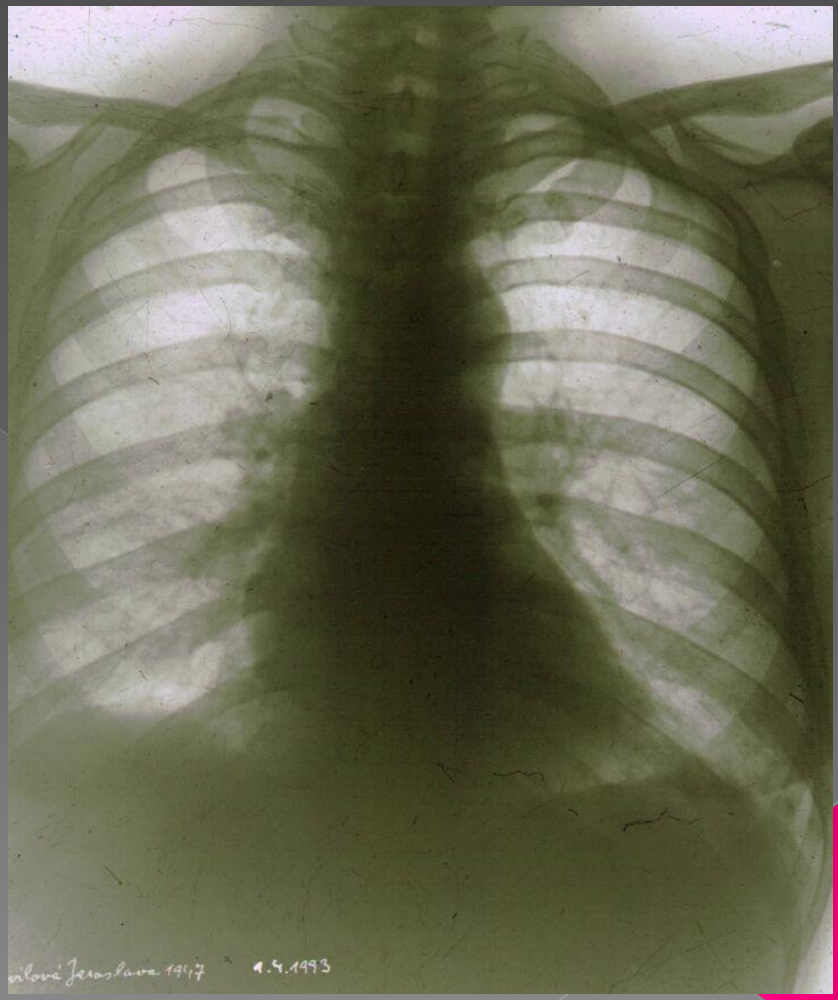
Alergic rhinitis and asthma → eosinophil infiltration → granulomatous vasculitis

Serology: ANCA (40 % patients)
P-ANCA, anti-MPO

Complications: coronary arteries involvement (myocarditis, heart attack)

Churg-Strauss syndrome before and after treatment





Small vessel vasculitides
Henoch-Schönlein purpura (1, 4)

Epidemiology: children 2 – 11 years old, more frequently boys
75 % of patients report antecedent upper-respiratory or GI infections

Predominantly affected vessels: small vessels of skin, kidneys, GI tract and joints

Serology: ANCA extremely rare

Deposits containing immune complexes with IgA

Complications: end-stage renal disease (5 % patients), GI complications (bleeding, perforation)

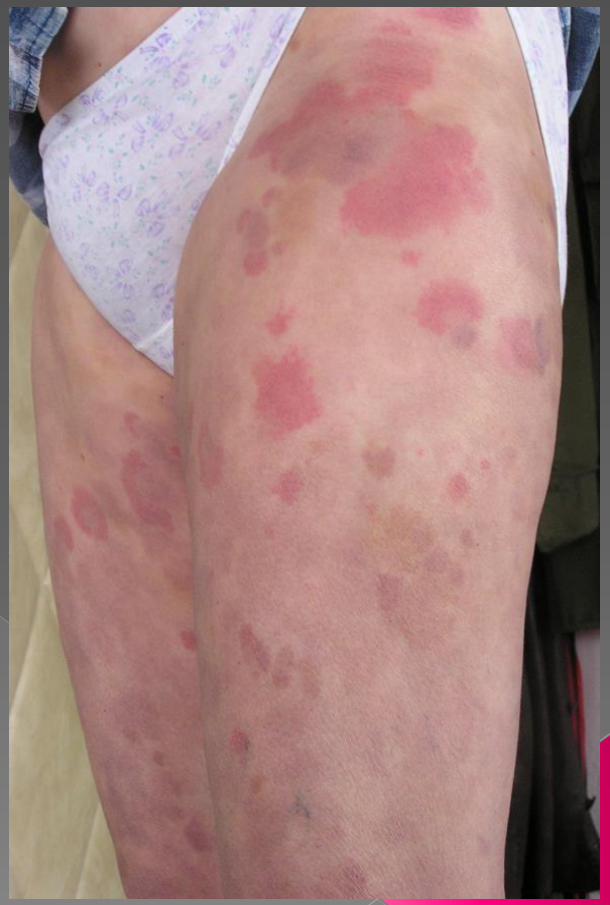
Small vessel vasculitides
Cutaneous leucocytoclastic angiitis (1, 4)

Epidemiology: men and women in any age, slightly more often in white population
Cause is identified in up to 50 % of patients with this condition (drugs, infections, malignancies, other autoimmunities)

Predominantly affected vessels: small vessels mostly in skin (kidneys, joints, GI tract)

Serology: sometimes ANCA and RF

Complications: good prognosis



Small vessel vasculitides

Essential cryoglobulinaemic vasculitis (1, 3, 4)

Epidemiology: more frequently female, age 52 – 62 years

Secondary forms are more often (lymphoproliferations, infections, autoimmunities)

Predominantly affected vessels: vessels in skin, kidneys, lungs, nervous system and musculoskeletal system

Serology: cryoglobulins (I., II. or III. type)

Complications: renal failure

Other vasculitides: Goodpasture syndrome (disease) (1, 4)

Epidemiology: more frequently in men (smokers), age 20 – 40 and 60 – 70 years, more common in certain ethnic groups (Maoris in New Zealand)

Predominantly affected vessels: vessels in lungs and kidneys

Serology: anti-GBM antibodies (type IV collagen)

Complications: renal failure, high mortality without treatment

Other vasculitides: Behçet's disease (1, 4)

Epidemiology: The sexual prevalence varies by country (in Asian countries more common in men, in USA in female), age 20 – 40 years, highest prevalence in Middle-East and Japanese persons

Predominantly affected regions: oral and genital ulcerations, uveitis (CNS, GIT, joints, kidneys)

Serology: occasionally P-ANCA

Complications: CNS and coronary arteries involvement, blindness

Other vasculitides: Buerger disease (thromboangiitis obliterans) (1, 4)

Epidemiology: more common in men 20 – 45 years old
Exposure to tobacco is essential for both initiation and progression of the disease

Predominantly affected vessels: small and middle-sized vessels of upper and lower extremities

Migrating thrombophlebities → claudication → trophic defects

Serology: no specific findings

Complications: gangrene, amputations

Vasculitides - diagnosis

- History and physical findings
- Laboratory findings
- Imaging studies
- Histologic findings

- Constitutional and organ symptomatology
- Non/specific
- RTG, angiography,MR, CT, UZ
- regular histology immunohistochemistry

Therapy (1, 4, 5)

INDUCTION TREATMENT

- corticosteroids – pulse, classical
- immunosuppressive agents (CFA)
- plasmapheresis
- intravenous immunoglobulins
- biological treatment (rituximab - anti-CD-20)
- acetylsalicylic acid at Kawasaki disease

MAINTENANCE THERAPY

- corticosteroids (classical, alternative)
- immunosuppressive agents (azathioprin, MTX)
- TMP/SMX

Prognosis (1)

Primary vasculitides are potentially life-threatening disorders with uncertain prognosis.

- early complications (renal failure, lung hemorhagia)
- late complications – atherosclerosis, immune deficiency due to the immunosuppression

Prognosis is dependent on early diagnosis.

Laboratory diagnosis is possible only at AAV.

Not every ANCA positivity means vasculitis (not even PR3-ANCA).

References:

1/ Imunologie a alergologie, Bartůňková J., Vernerová E.,Triton, Praha 2002, str. 52-59.

2/ Základy imunologie, Hořejší V., Bartůňková J., Triton, Praha 2009, str. 208-217

3/ Klinická revmatologie, Pavelka K a kol., Galén, Praha 2003, str. 293-302

4/ www.emedicine.com

5/ www.vasculitis.org