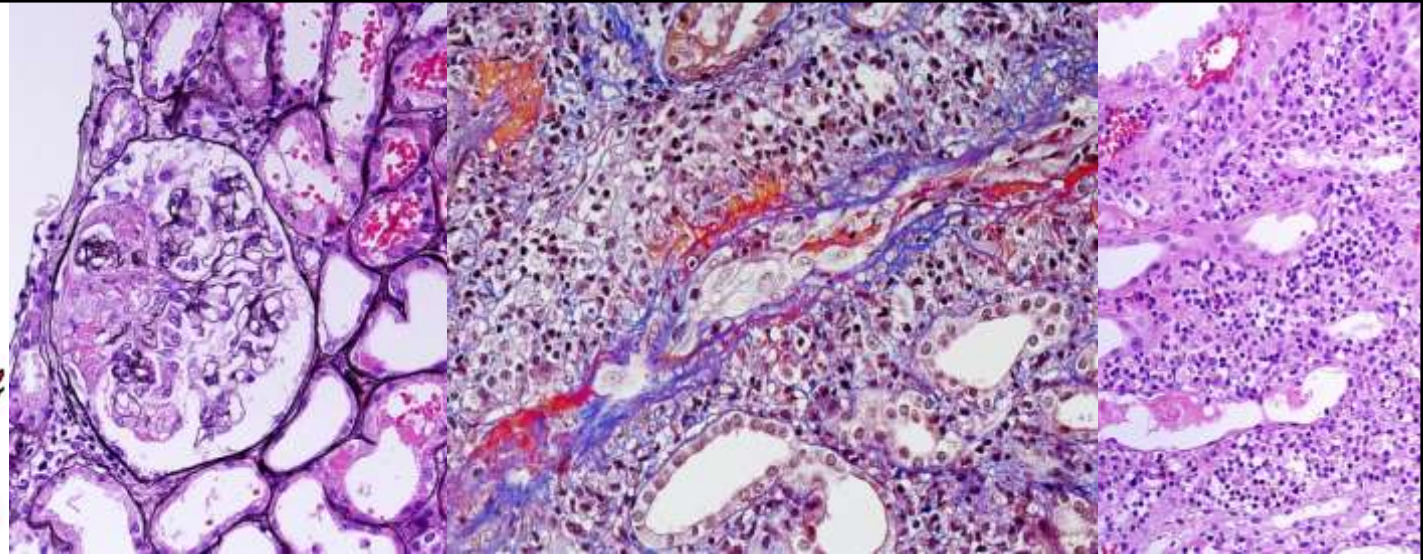


# Pathology of noninfectious vasculitides

*Eva Honsova*
Institute for Clinical and Experimental Medicine
Prague, Czech Republic
*eva.honsova@ikem.cz*

# Systemic noninfectious vasculitides

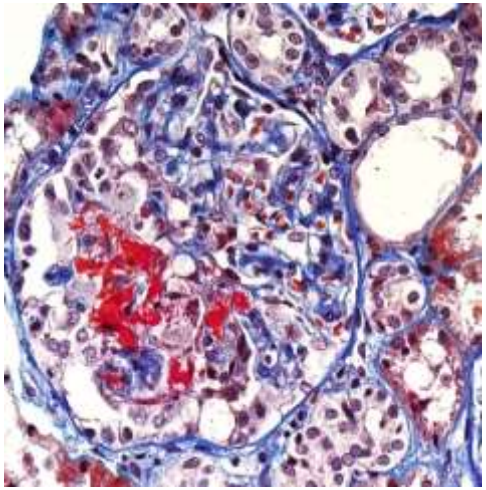
## Vasculitis = a general term for inflammation of vessel walls

Any type of vessel in all locations can be affected
in practice – overwhelming number of clinical symptoms and problems

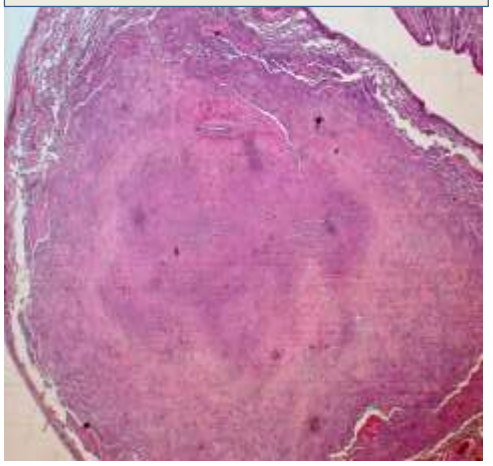
- ***Clinical manifestation:*** *very variable, the disease has attacks and spontaneous remissions*
- *the diagnosis is difficult*

The vasculitides are often serious diseases, prompt recognition and therapy.

Patients suffer from ***symptoms of systemic inflammation*** (such as fever, arthralgias, myalgias, weight loss), and can simultaneously have ***symptoms of local system involvement***. They can develop ***local mass lesion*** which can lead to the diagnosis of malignant tumor



**nodulus imitates metastasis**



# Historical development of names of vasculitides

## 1. description of necrotizing arteritis (PAN) Rokitanský (1852)

**Periarteritis nodosa (1866 Kussmaul, Maler)**

**1890 Hutchison GCA**
**1908 Takayasu**
**1934 *Horton GCA***

**1942 Rich, hypersen. a**ngiitis
**1978** Fauci, hypersen.a.
mainly skin involvement,

**1903 Osler SLE**

**1936 Wegener**
**1948-52 Zeek, hypersens. angiitis**
small vessel vasculitis
**1951 Churg- Strauss**
**1954 Godman and Churg (MPA x PAN)**
**1982 Davis, *ANCA antibodies***

**GCA**
**Takayasu**

**PAN**
**Kawasaki**

**ANCA associated** (GPA, MPO, EGPA)
**Immune complex** small vessel v.

For decades PAN was the term used for virtually any patient with necrotizing arteritis

# First description of necrotizing arteritis with aneurysmata (PAN, 1852)

## Karel Rokitanský

- Karel Rokitanský was born in Hradec Králové, started his medicine study in Prague under Purkyně.
- When Purkyně left in r. 1823 for Wroclaw Rokitanský went to Vienna.

- Aneurysmal lesions in numerous arteries in a 23-year-old shoemaker (without histology)
- Eppinger: *histological* confirmation
- 1866; Kussmaul and Maier: 27-year-old tailor; ***periarteritis nodosa*** with histology (with the involvement of gli)

Death of colleague Dr. Koletscko, who succumbed the sepsis after injury at autopsy room, has inspired Dr. Ignaz Semmelweis (a pioneer in antiseptic medical practice).

# Karl, baron von Rokitansky

## Austrian pathologist

Written by: The Editors of Encyclopædia Britannica

**Karl, baron von Rokitansky,** (born Feb. 19, 1804, Königgrätz, Austria—died July 23, 1878, Vienna), Austrian pathologist whose endeavours to establish a systematic picture of the sick organism from nearly 100,000 autopsies—30,000 of which he himself performed—helped make the study of pathological anatomy a cornerstone of modern medical practice and established the New Vienna School as a world medical centre during the latter half of the 19th century.

A professor of pathological anatomy (1844–74) at the Vienna General Hospital, he inspired the Bohemian student Ignaz Semmelweis, later a martyr to the cause of antiseptic medical practice, to take up the study of medicine (1846) and afterward supported him in his struggle to eliminate childbed fever by cleaning up Europe's maternity wards.

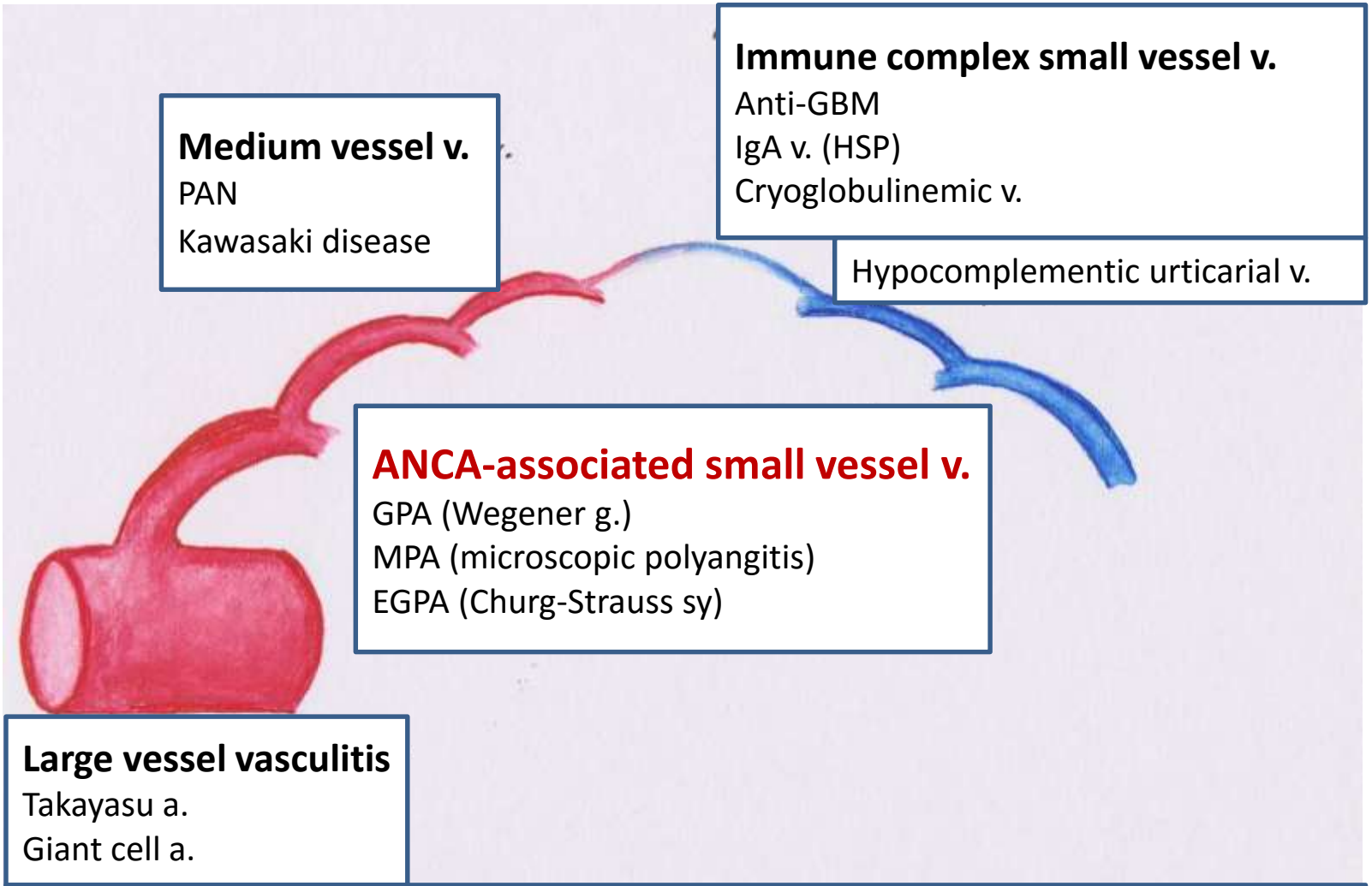
First to detect bacteria in lesions of malignant endocarditis, an often rapidly fatal inflammation of the membrane lining the inner walls of the heart, Rokitansky created the basis for a differentiation of lobar pneumonia (originating in the lower lobe of the lung) and lobular pneumonia, or bronchopneumonia (originating in the finer subdivisions of the branched bronchial tree). He made a fundamental study of acute yellow atrophy of the liver (now known as Rokitansky's disease; 1843), established the micropathology of pulmonary emphysema (a condition of the lung characterized by

Karl, baron von Rokitansky

Rokitansky, detail of an engraving

*BBC Hulton Picture Library*

# 2012 revised international CHCC nomenclature of vasculitides




According to the article: Jennette et al. Arthritis Rheum. 2013; 65:1-11.

# Nomenclature noninfectious vasculitides

**1. Large vessel vasculitis:** GCA a Takayasu

**2. Medium vessel vasculitis:** PAN a Kawasaki

**3. Small vessel vasculitis** (arteries, arterioles, venules, veins):

***a) ANCA-associated vasculitis*** (most frequent vasculitis of adults!!!)

***b) immune complex:***

IgA v.(Henoch-Schönlein), anti-GBM (ANCA : anti-GBM = 100 : 1), cryoglobulins, hypocomplementic urticarial (anti-C1q) v., serum sickness

4.

Variable vessel vasculitis (Cogan's, Behcet's, etc.)

Single organ vasculitis (cutaneous SVV, primary CNS vasculitis, etc.)

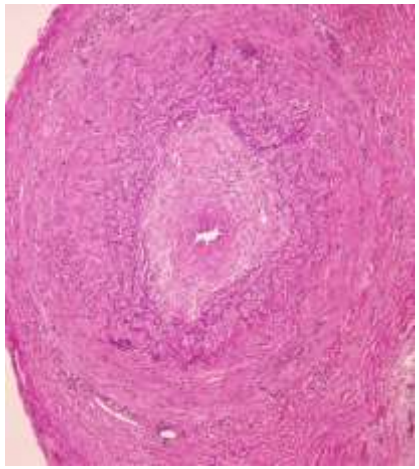
Vasculitis associated with systemic diseases (e.g. Rheumatoid, Lupus, Sarcoid, etc.)

Vasculitis associated with probable etiologies (e.g. HBV, HCV, drug, cancer, etc.)

# Large Vessel Vasculitis, 2012 CHCC definition

Vasculitis *affecting large arteries more often than other vasculitides*. Large arteries are the aorta and its major branches. Any size artery may be affected.

## 1. Takayasu arteritis



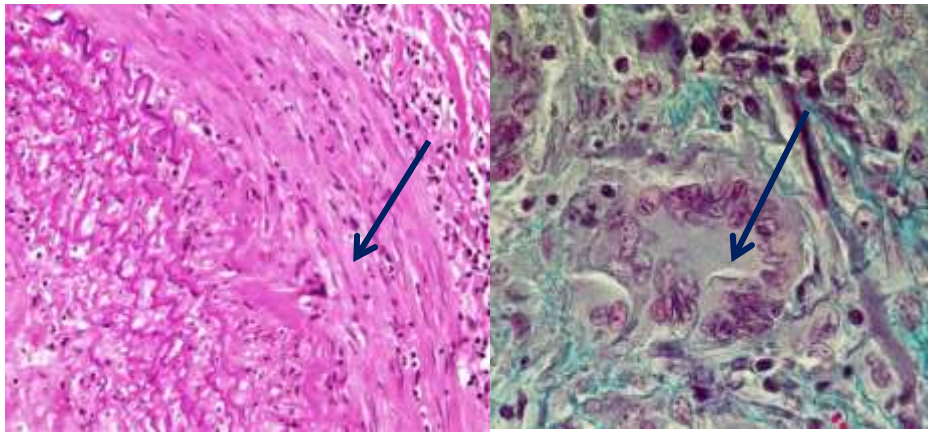
Patients: **women under 50**, rare in the Czech Rep.

- **Morphology**: shares histological features of GCA (granulomatous arteritis), *no fibrinoid necrosis*

## 2. Giant cell (temporal) arteritis (GCA)

- Patients: **over 50**, common (with polymyalgia rheumatica)

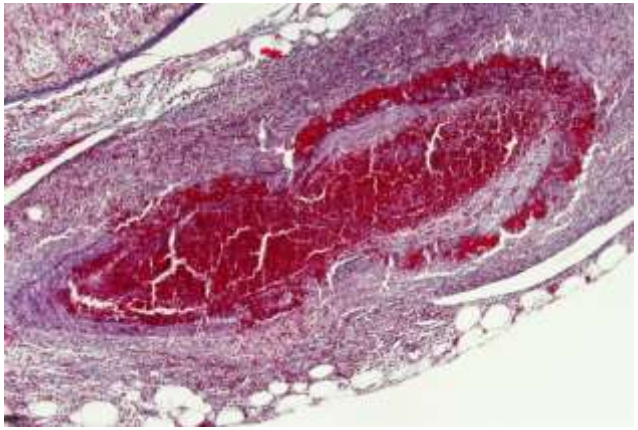
***The distinction between the two entities is made on the basis of a patient´s age!!!***

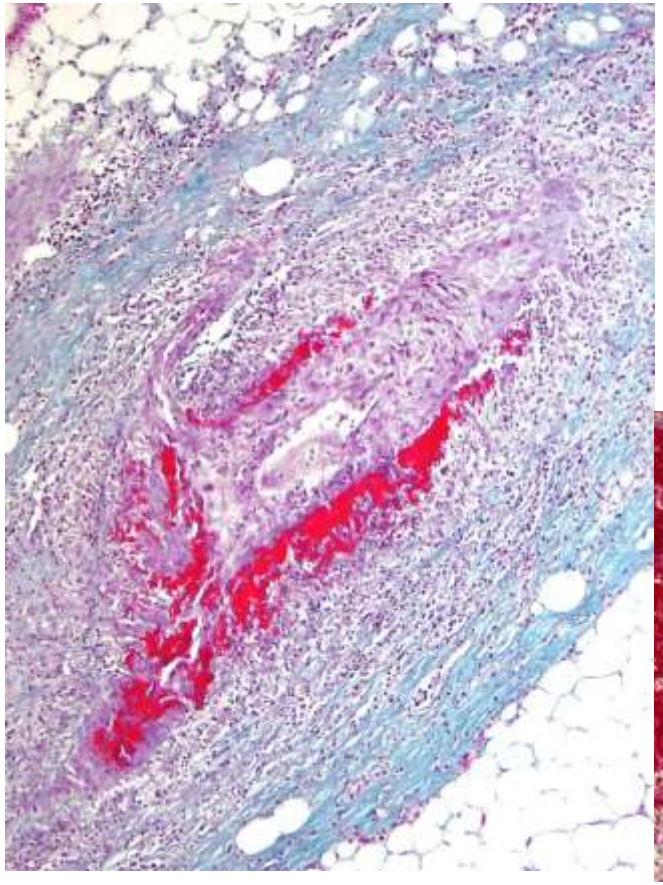


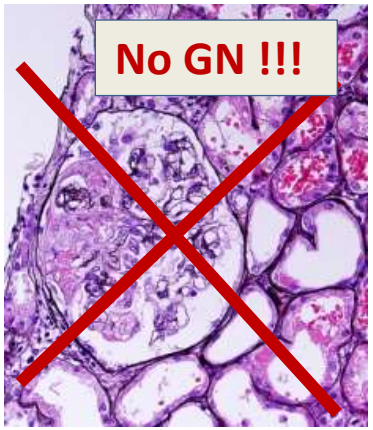
# PAN, 2012 CHCC definition

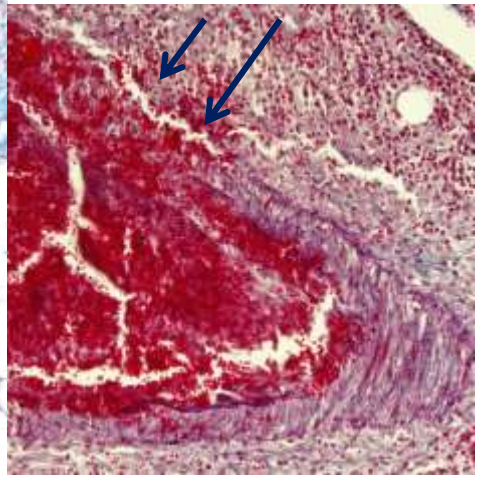
- Necrotizing arteritis of medium or small arteries ***without glomerulonephritis*** or vasculitis in arterioles, capillaries, or venules; and ***not associated with ANCA.***

- Very rare



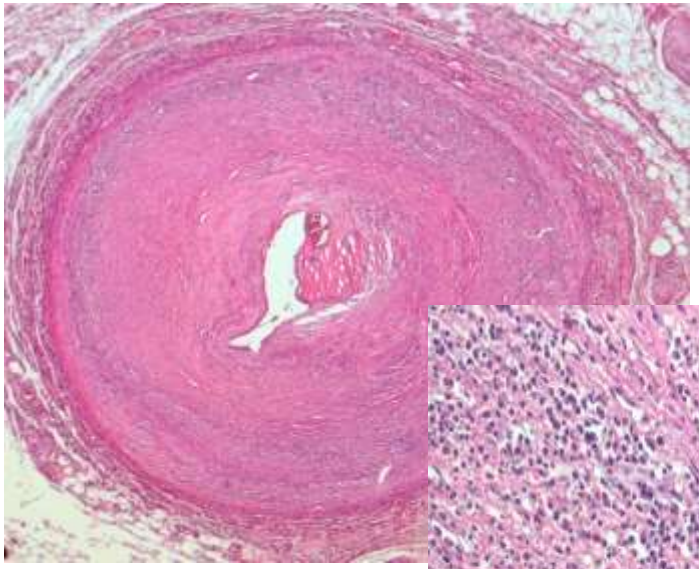


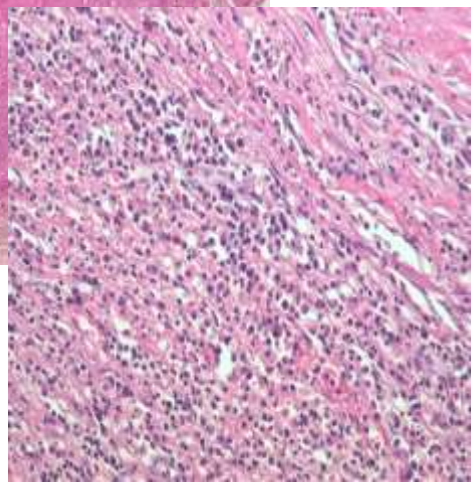


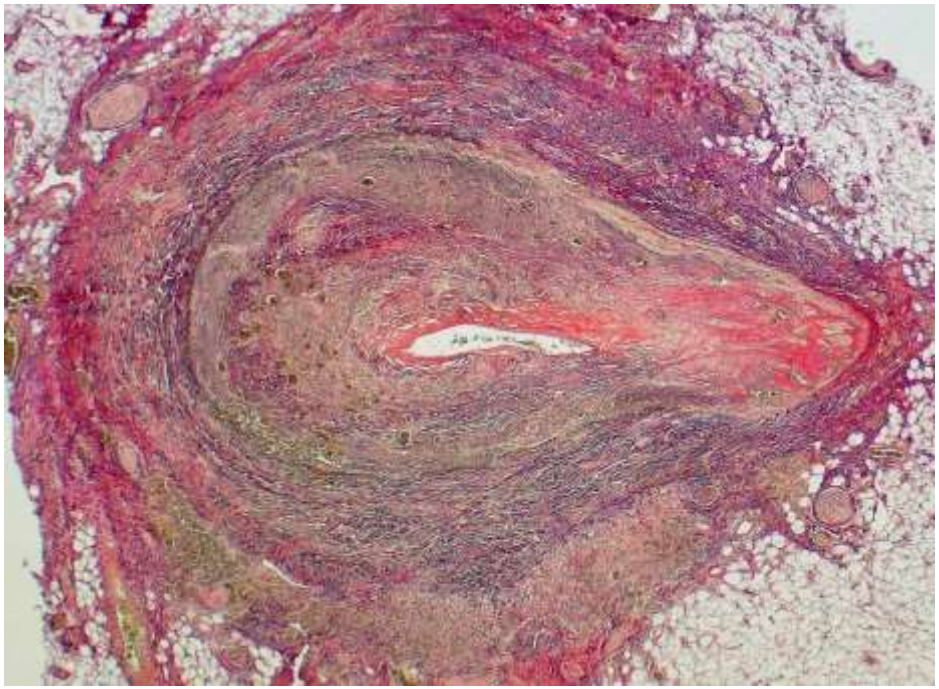



# Kawasaki disease; 2012 CHCC definition

- Arteritis associated with *the mucocutaneus lymph node syndrome*, predominantly affecting medium and small arteries.
- *Coronary arteries are often involved*. Aorta and large arteries may be involved.
- Usually occurs in infants and young children.



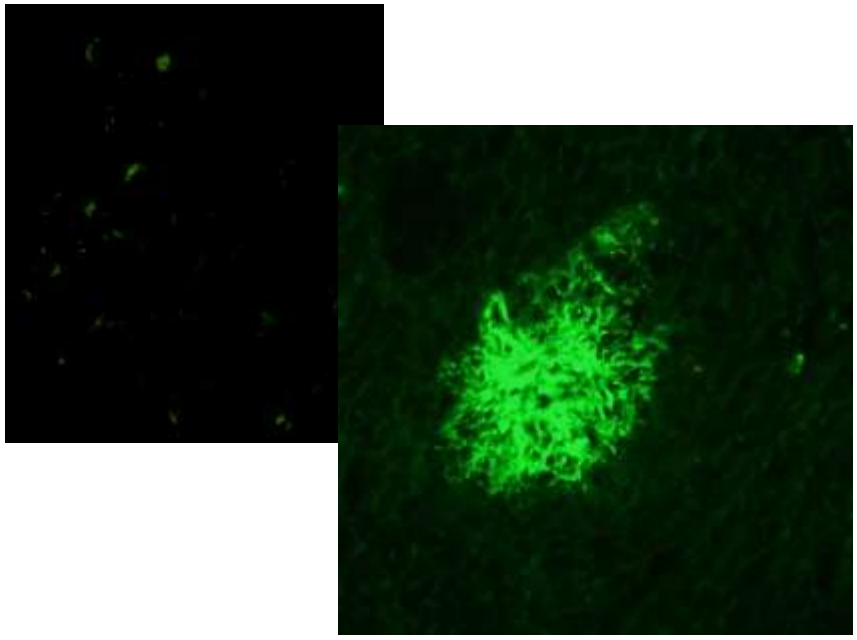




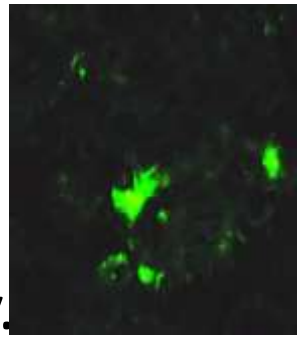
# Small vessel vasculitides

## 1. ANCA-associated small vessel v.

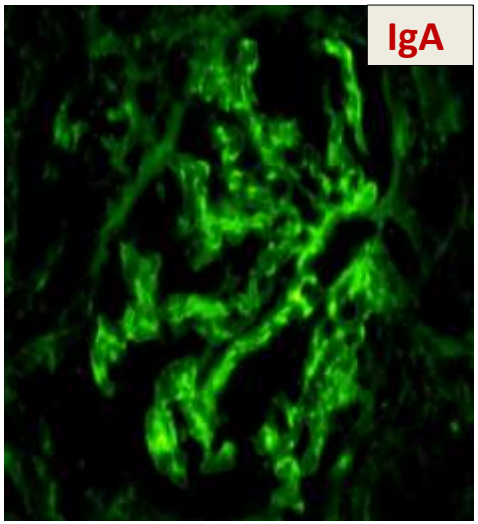
- GPA (Wegener g.)
- MPA (microscopic polyangitis)
- EGPA (Churg-Strauss sy)



## 2. Immune complex small vessel v.

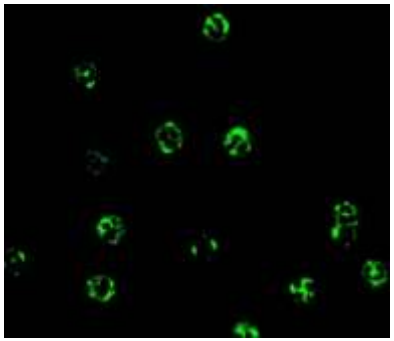


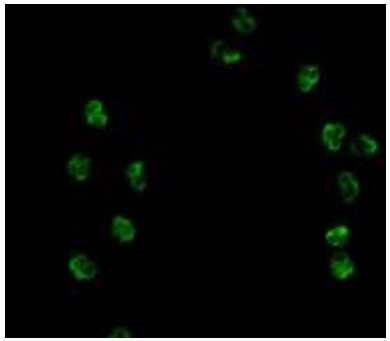
- Anti-GBM
- IgA v. (HSP)
- Cryoglobulinemic v.
- Hypocomplementic urticarial v.

# ANCA antibodies (Anti-Neutrophil Cytoplasmatic Antibody)

- ABs specific to antigens of neutrophil granules and to lysosoms of monocytes;
- **c-ANCA** (cytoplasmatic) **p-ANCA**(perinuclear)
- **Many different antigens in the group c-** or **p-** *( proteinasa 3, myeloperoxidasa-MPO, lactoferin, cathepsin G, elastasa, lysosym, azurocidin atd.)*
- **ANCA positive vasculitides:** **c-ANCA: PR3 (proteinasa 3),**





**p-ANCA: MPO (myeloperoxidasa)**

**IF determine the group** c or p

**ELISA distinguishes the precise antigens**

(PR3 or MPO) which are associated with AAV

- New methods for identification of specific epitopes (MALDI-TOF/TOF-MALDI-MS)

Epitope specificity defines pathogenicity

(Roth A. at al. Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. J Clin Invest. 2013; 123:1773-1783.)

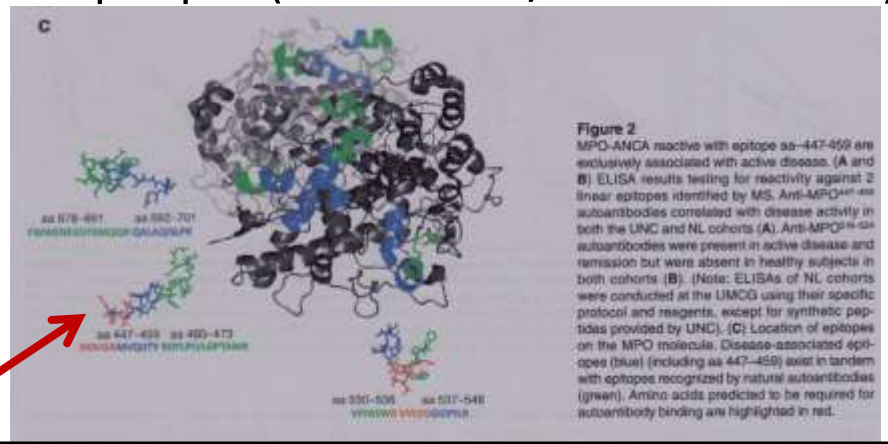



Figure 2
MPO-ANCA reactive with epitope aa 447-459 are exclusively associated with active disease. (A and B) ELISA results testing for reactivity against 2 linear epitopes identified by MS. Anti-MPO$^{447-459}$ autoantibodies correlated with disease activity in both the UNC and NL cohorts (A). Anti-MPO$^{526-534}$ autoantibodies were present in active disease and remission but were absent in healthy subjects in both cohorts (B). (Note: ELISAs of NL cohorts were conducted at the UMCG using their specific protocol and reagents, except for synthetic peptides provided by UNC). (C) Location of epitopes on the MPO molecule. Disease-associated epitopes (blue) (including aa 447–459) exist in tandem with epitopes recognized by natural autoantibodies (green). Amino acids predicted to be required for autoantibody binding are highlighted in red.

# ANCA associated vasculitis:

- very aggressive disease; systemic involvement (joints, skin, ENT, lungs, kidneys)
- May occur at any age, typical onset between 5th-7th decades of life
- **The most common form of systemic vasculitis in adulthood**

- Estimated incidence >**15-23/million**

  age over **65: 53/million**
- Geographical variation: *c ANCA more frequent in northern Europe,*

*p ANCA more frequent in southern Europe, Asia and Japan*

**Prognosis of untreated** GPA (c ANCA) is worse than the prognosis of the majority of tumors; and the **mortality rate at 1 year is 80%**

***Rapid dg is critical***

# Occurrence of systemic involvement

(Jennette J. N. Eng J Med: 1997; 337:1512-1523).

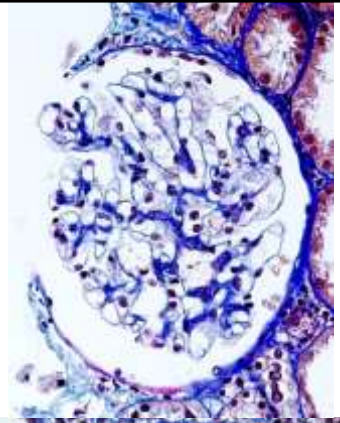
| location | HSP | cryoglob | **MPA** | **GPA** | EGPA |
|---|---|---|---|---|---|
| skin | 90% | 90% | 60% | 50 - 70% | 60% |
| **kidney** | 50% | 55% | **90%** | **80%** | 45% |
| **lung** | <5% | <5% | **50%** | **90%** | 70% |
| **ENT** | <5% | <5% | 35% | **90%** | 50% |
| joint | 75% | 70% | 60% | 60% | 50% |
| neurol. | 10% | 40% | 30% | 50% | 70% |
| **GIT** | 60% | 30% | **30%** | **50%** | 50% |

The concept that MPO- and PR3-AAV are genetically distinct diseases with phenotypic overlap and that studies and clinical practice may ***benefit from clustering according to serotype***.

Lyons P. A. et al. Genetically distinct subset within ANCA-associated vasculitis. N.Engl. J. Med. 2012; 367: 214-223.

# ANCA-associated vasculitides

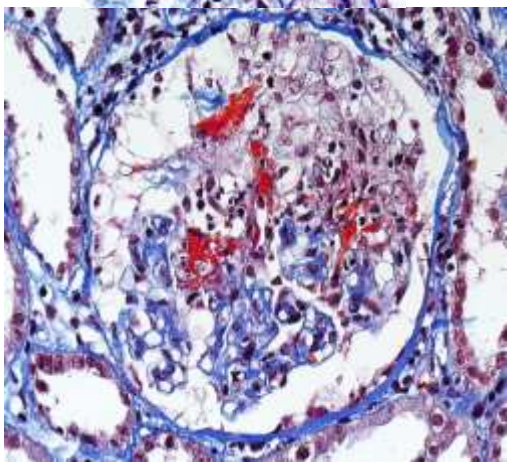
- Any organ may be afflicted (kidney, lungs, ENT...)



- **<u>Kidney involvement:</u>**

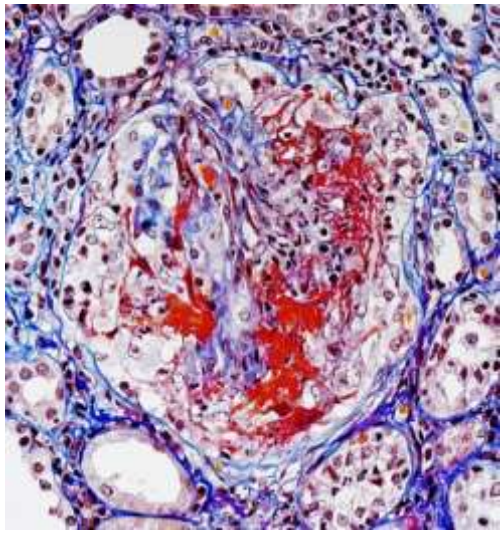
  pauciimmune necrotizing crescentic (rapidly progressive) glomerulonephritis

  *75% of patients with GN have systemic vasculitis*



- <u>Renal biopsy:</u>
  - Gold standard to confirm the diagnosis
  - To assess the prognosis
  - Not absolutely required,

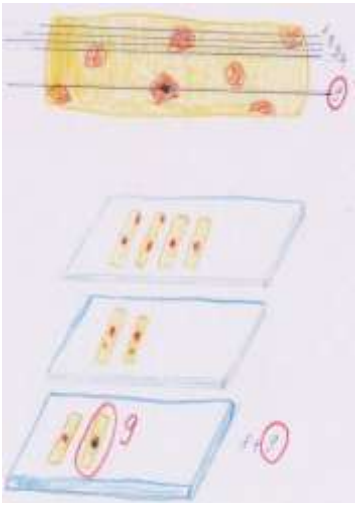
  but recommended whenever possible

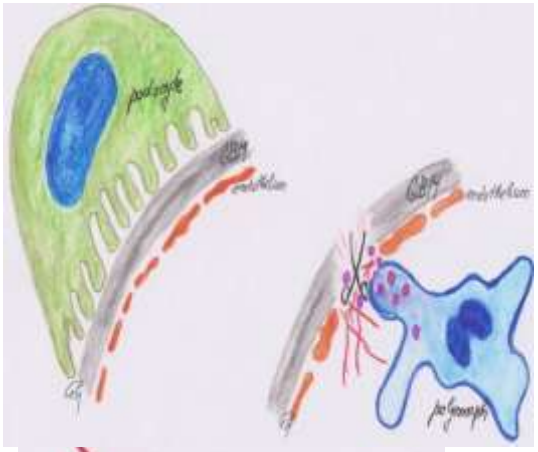


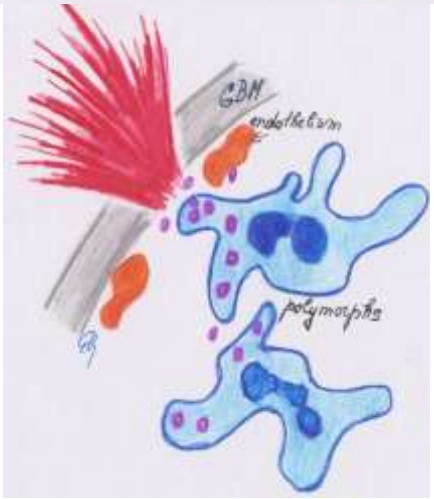
# ANCA-associated GN: morphology: gli

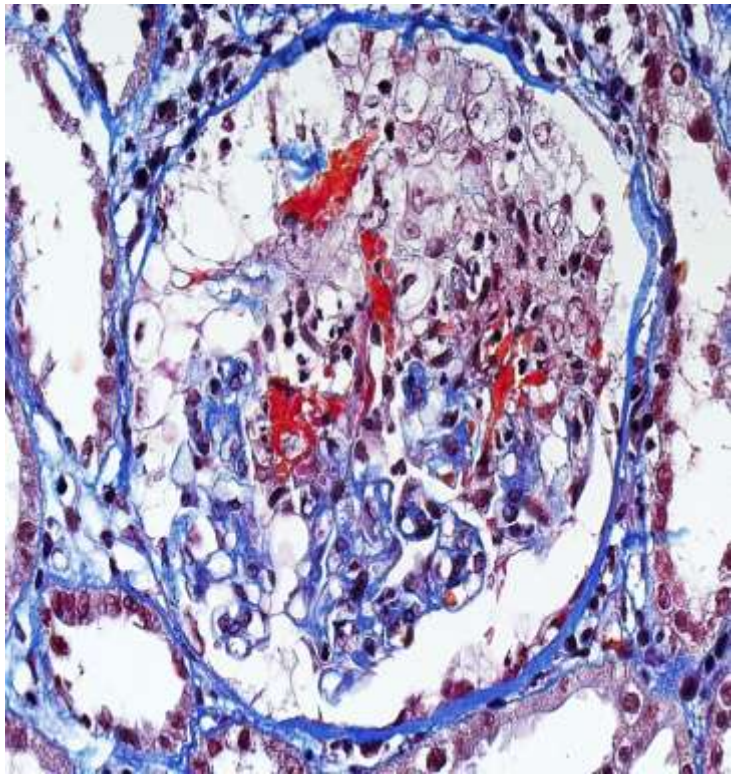
## pauciimmune necrotizing GN with crescents

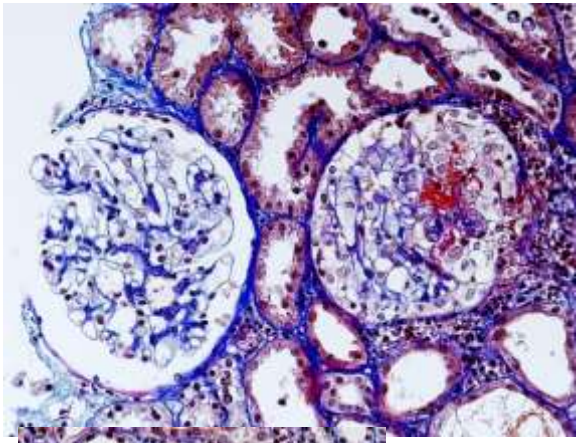
***Acute lesions:*** necrosis + crescents
***Typically scattered*** with normal gli or their parts, later with combination of acute and chronic lesions

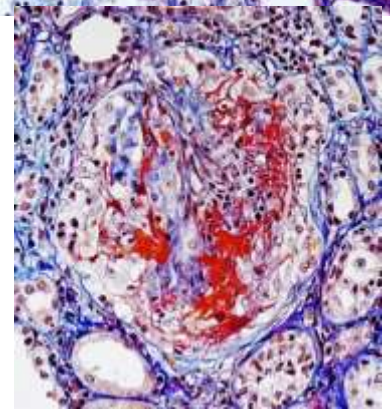




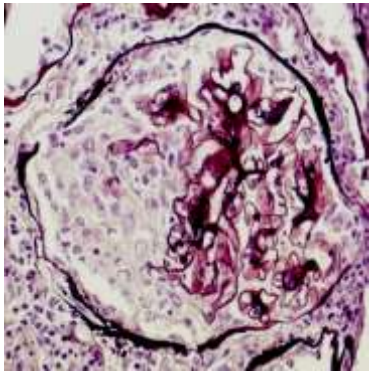



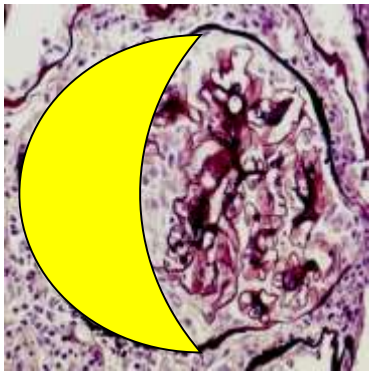


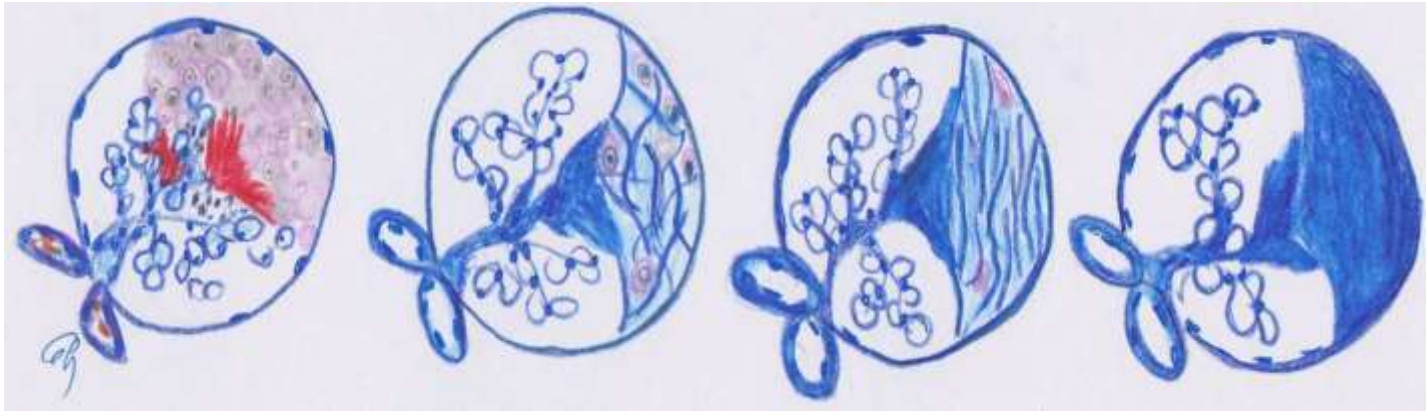


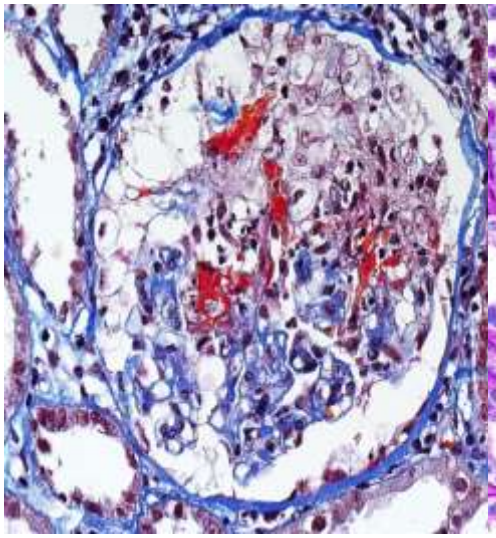
# ANCA-associated GN: morphology: gli

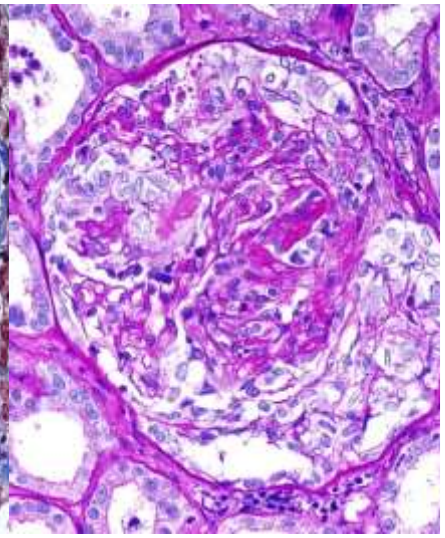
Crescents: epithelial/cellular, fibro-epithelial, fibrotic

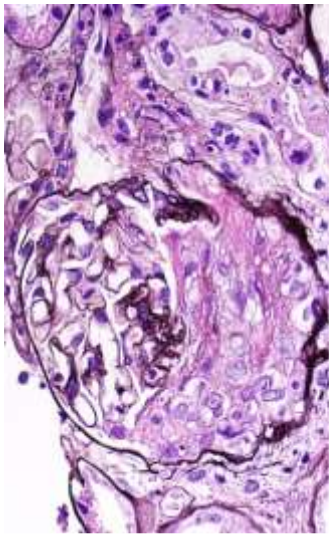


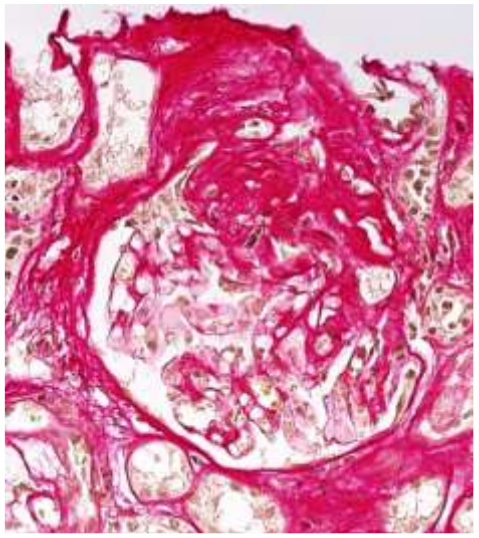






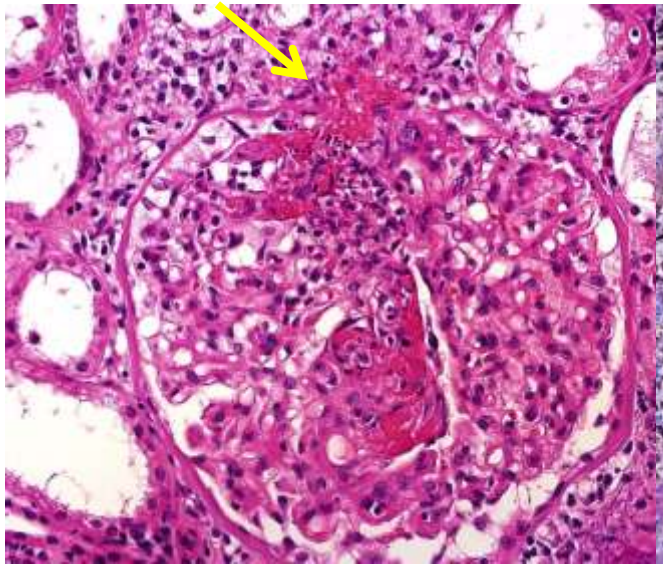


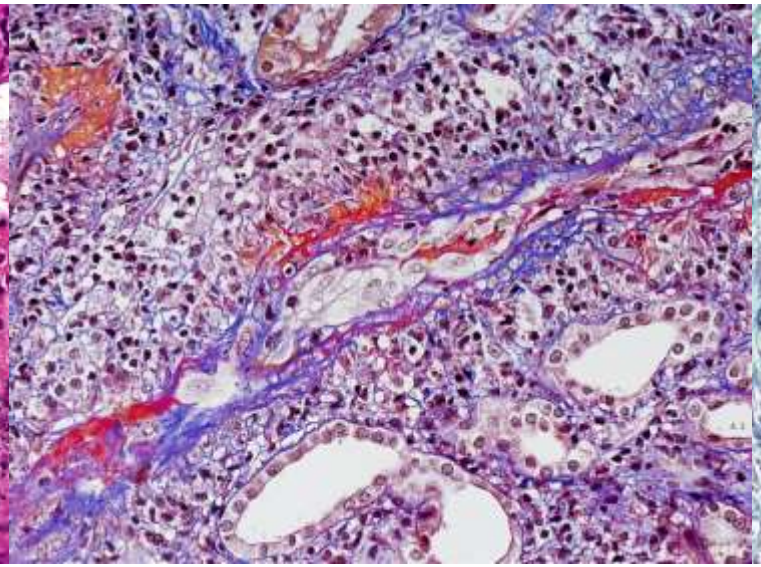


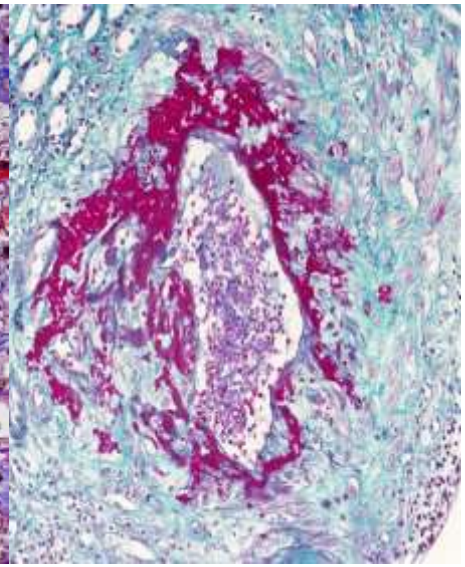


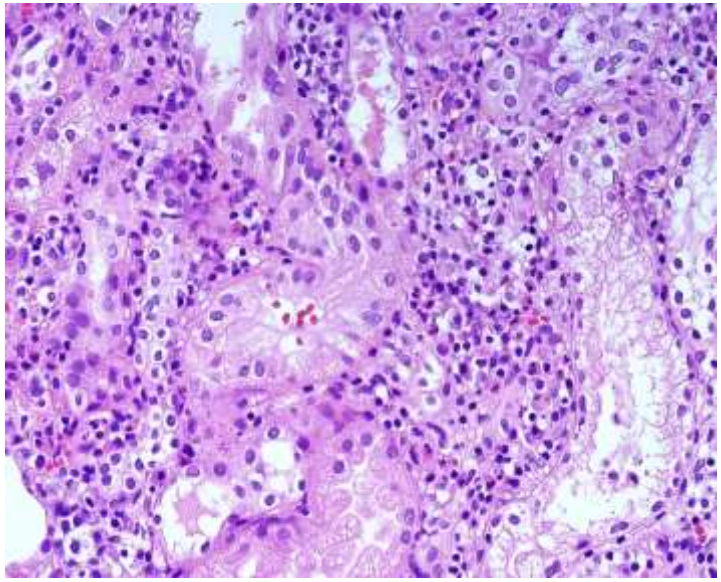
# ANCA-associated GN:morphology

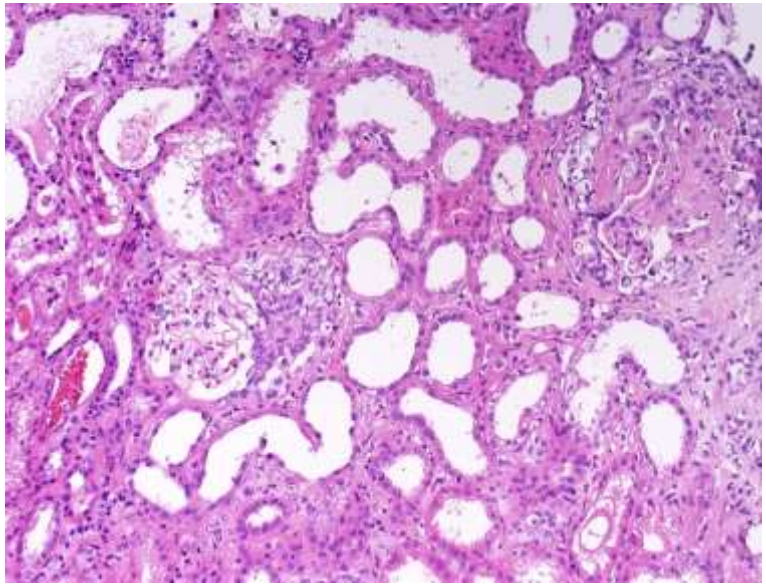
## vessels & interstitium



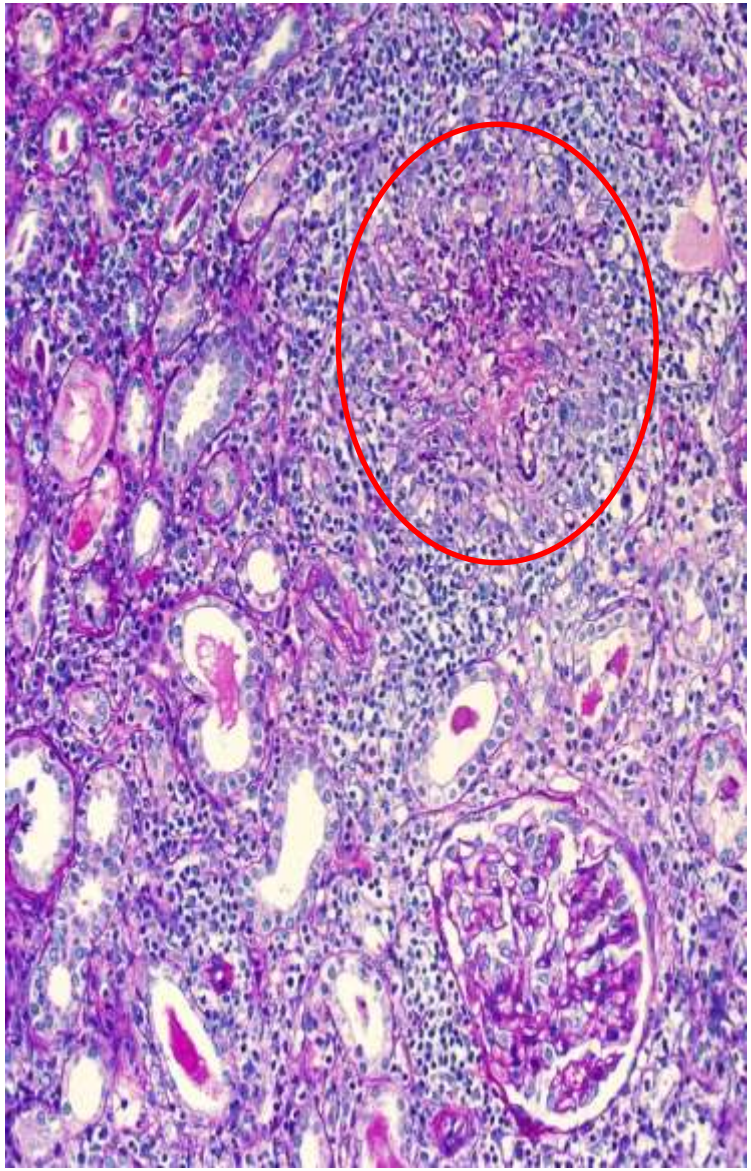


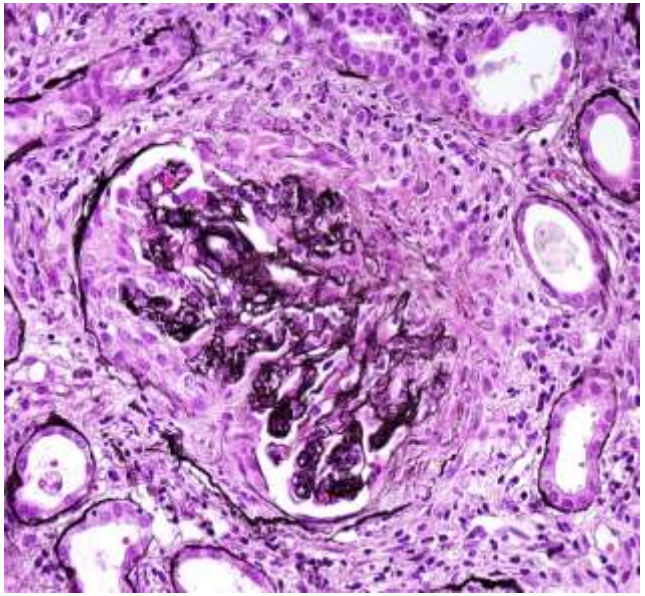


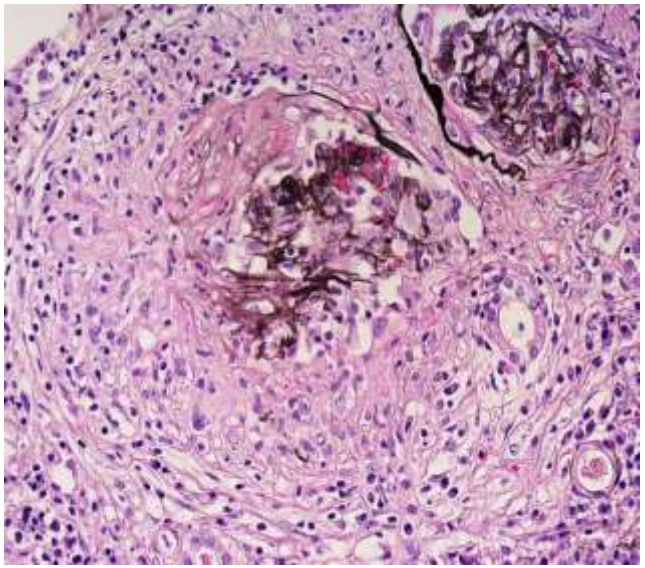


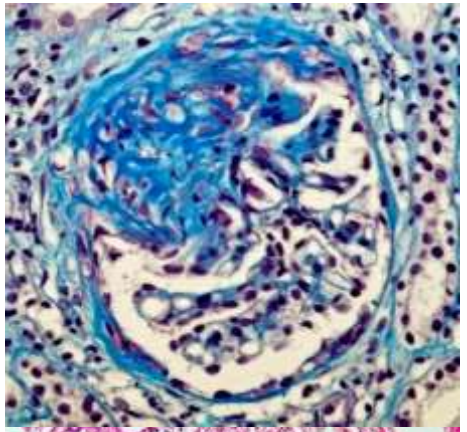


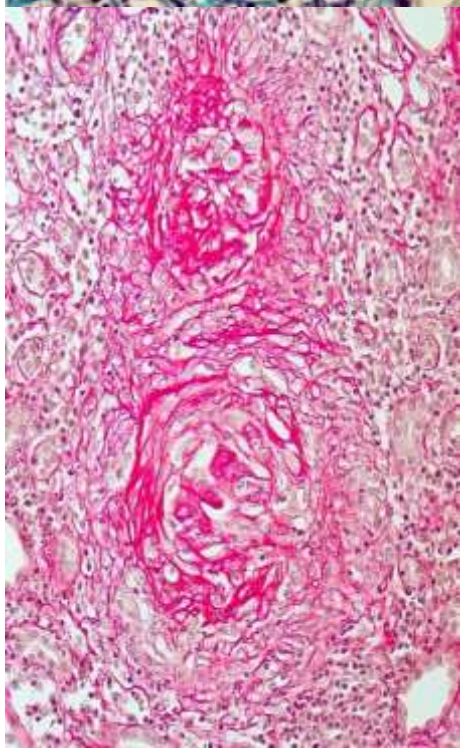
# ANCA-associated GN: morphology of advanced disease



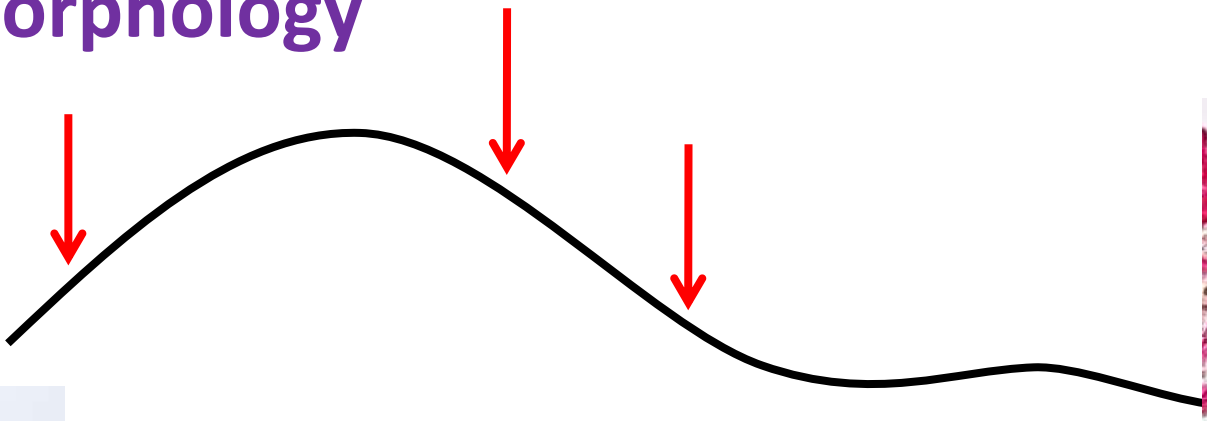


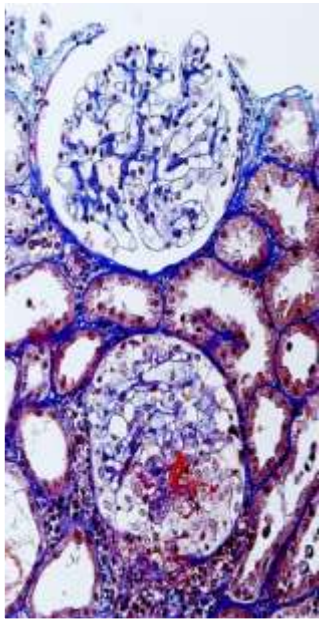


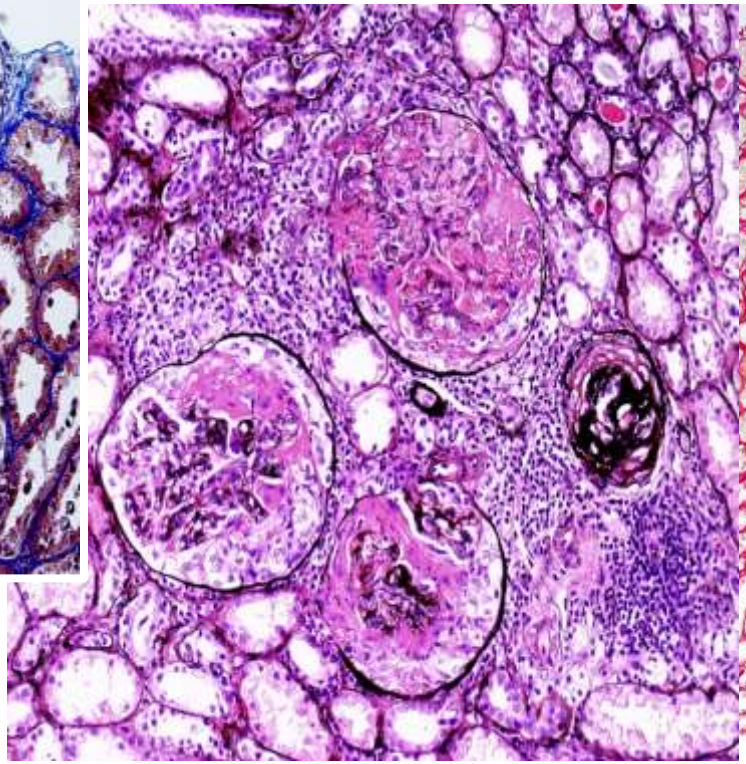


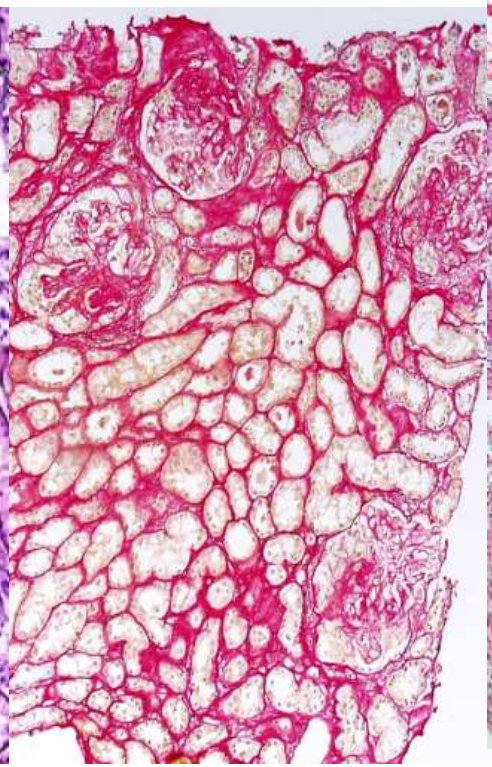


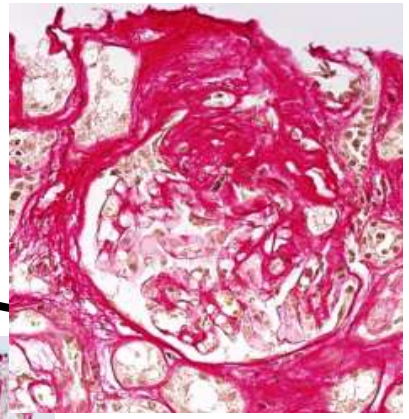
# Time period during the course of vasculitis in morphology

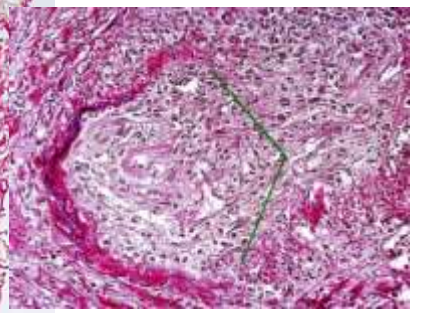


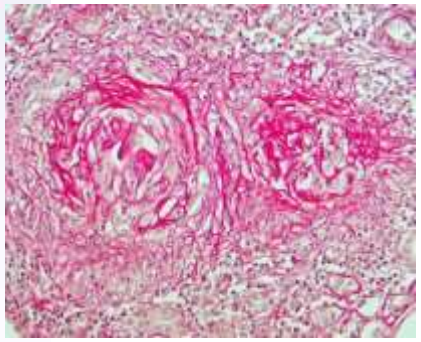












# When it is difficult to diagnosed AAV

***In a kidney biopsy:***

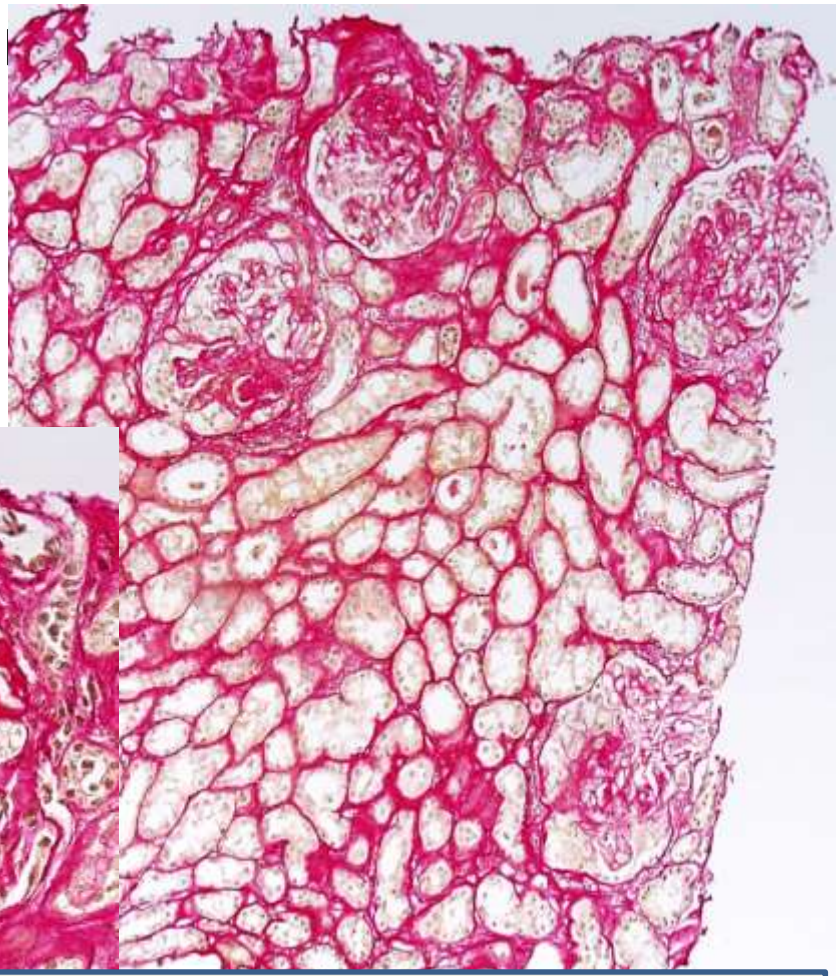
- Early acute lesion: normal morphology; sampling error
- Advanced lesion (destruction and high number of crescents)
- Chronic scaring lesions
- Combinations: with IgA and or other diseases (modify the morphological features); anti-GBM, DM, SLE: mainly MPA with slow progression with segmental sclerotic lesions

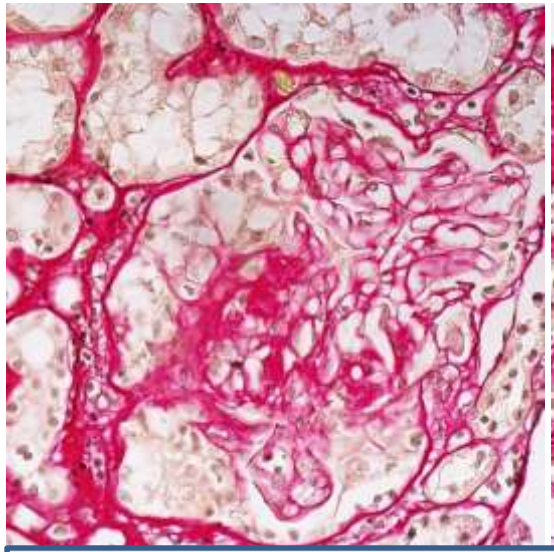
***In other locations/organs:***

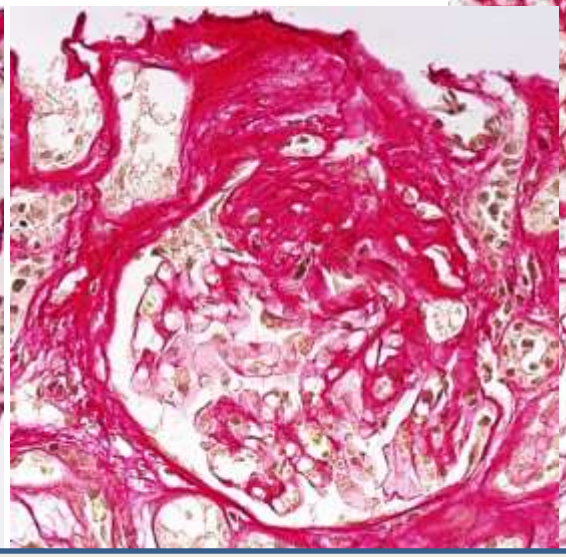
- More difficult to diagnose vasculitis (often second opinion can help)

# **Case no. 1.:** 63-year-old woman

- *Autumn* 2002 worse hearing, ENT in normal range, CT showed inflammation in the middle ear
- She visited internist in *January* next year
- She requested lungs examination, norma
- *February:* **artralgias** of small joints, susp.
- *May:* **S-Cr 197 umol/l**, microhematurie
- *June:* ***S-Cr 273 umol/l;***
- only then she is sent to nephrologist
- **Weight loss: 6 kg**



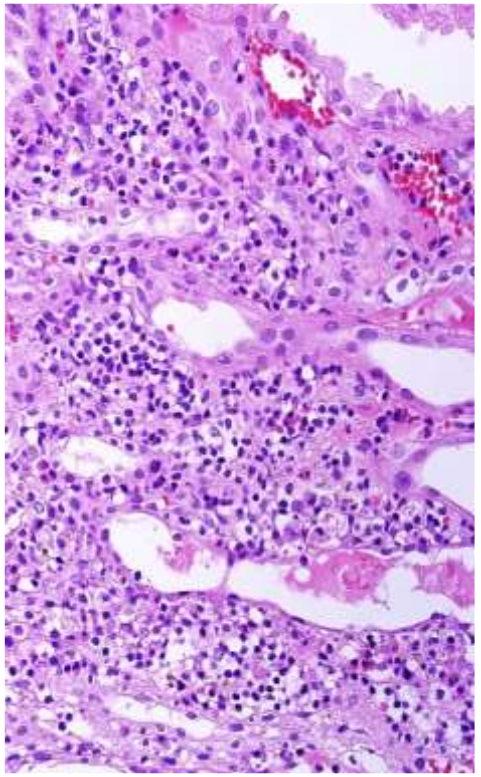


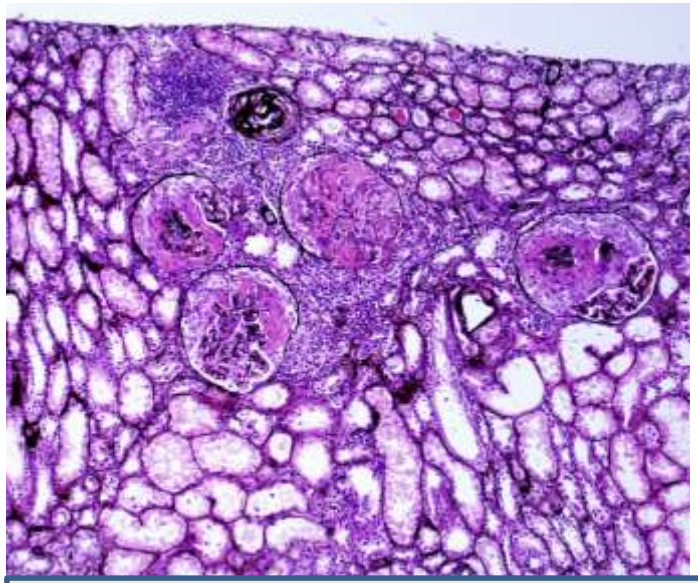


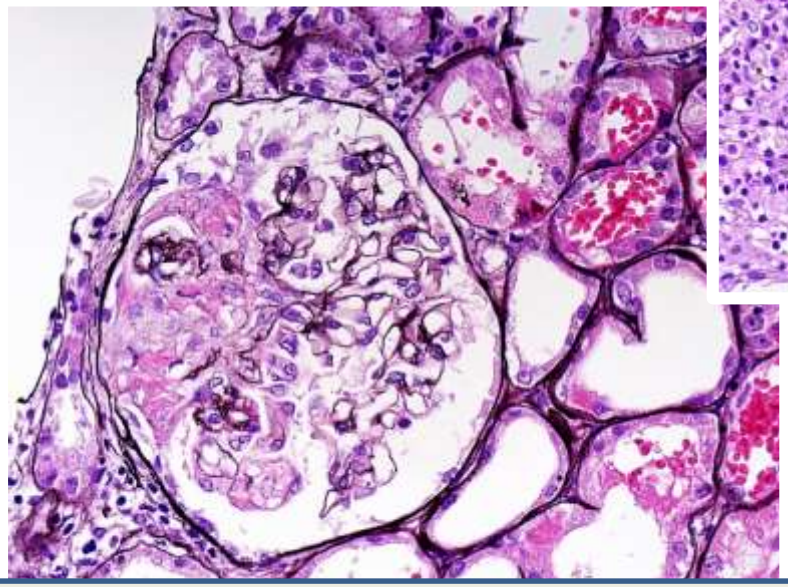
AAV advanced morphological features (MPA, p-ANCA)

# **Case no. 2.:** a 25-year-old woman

- During the last year: recurrent otitis media and sinusitis
- 5 weeks she is not feeling well, fever
- Admitted to the hospital at pulmonary department
- Dg.: pulmonary infiltrates, fever
- c-ANCA +++, treated with ATB
- S-Cr 143 µmol/l (1.61mg/dl)
- urine: numerous ery







Successful treatment, S-Cr 90umol/l, PU less than 1g/day, after 5 years: a healthy child
Now, 14 years after renal manifestation, during 2 last years: relapse in ENT and lungs location

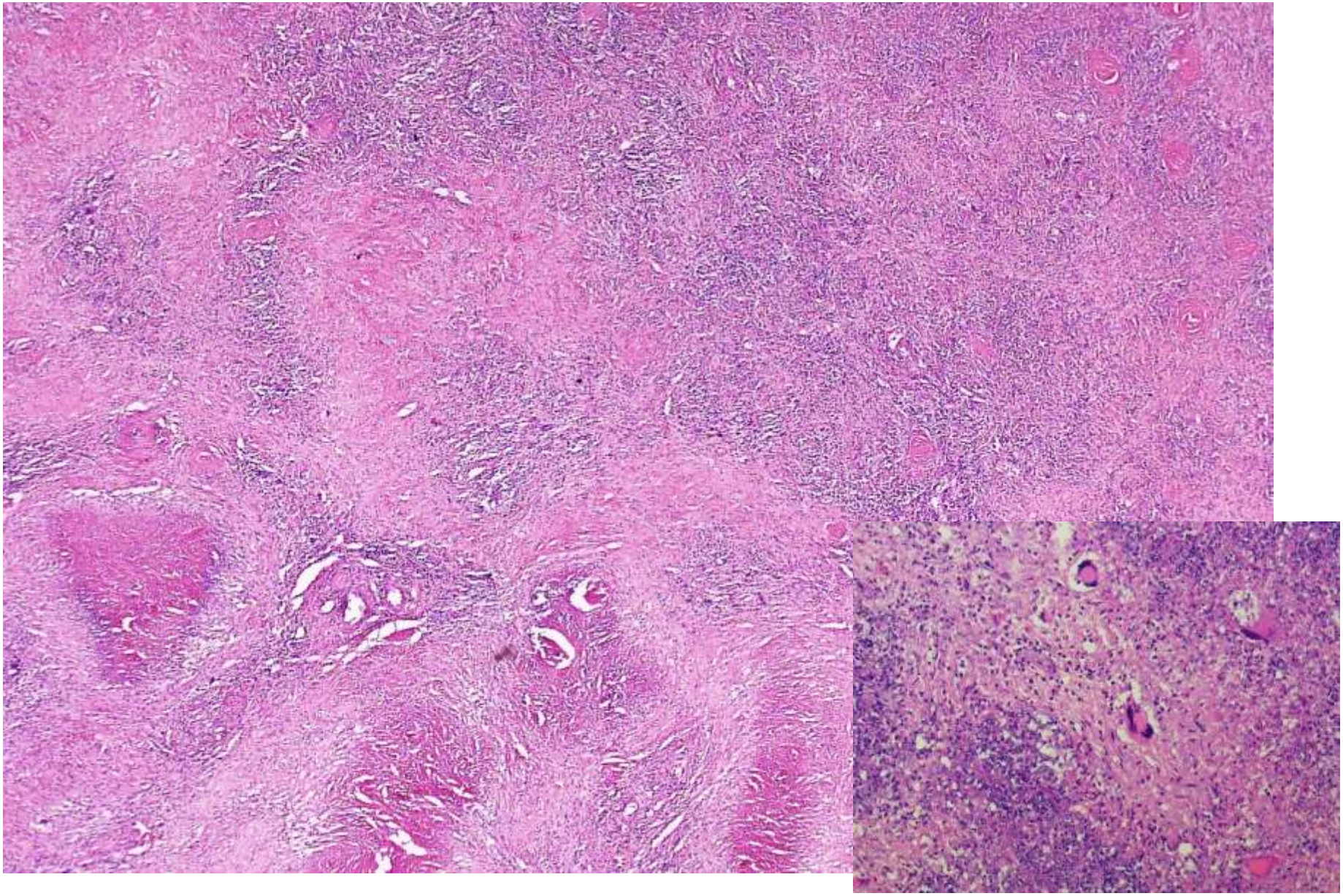
# **Case no. 3.:** 28-year-old man

- 5 mths of *non-specific symptoms*: myalgia, artralgia, unintended weight loss (10 kg)
- *chronic otitis media* with hypacusis l. sin.

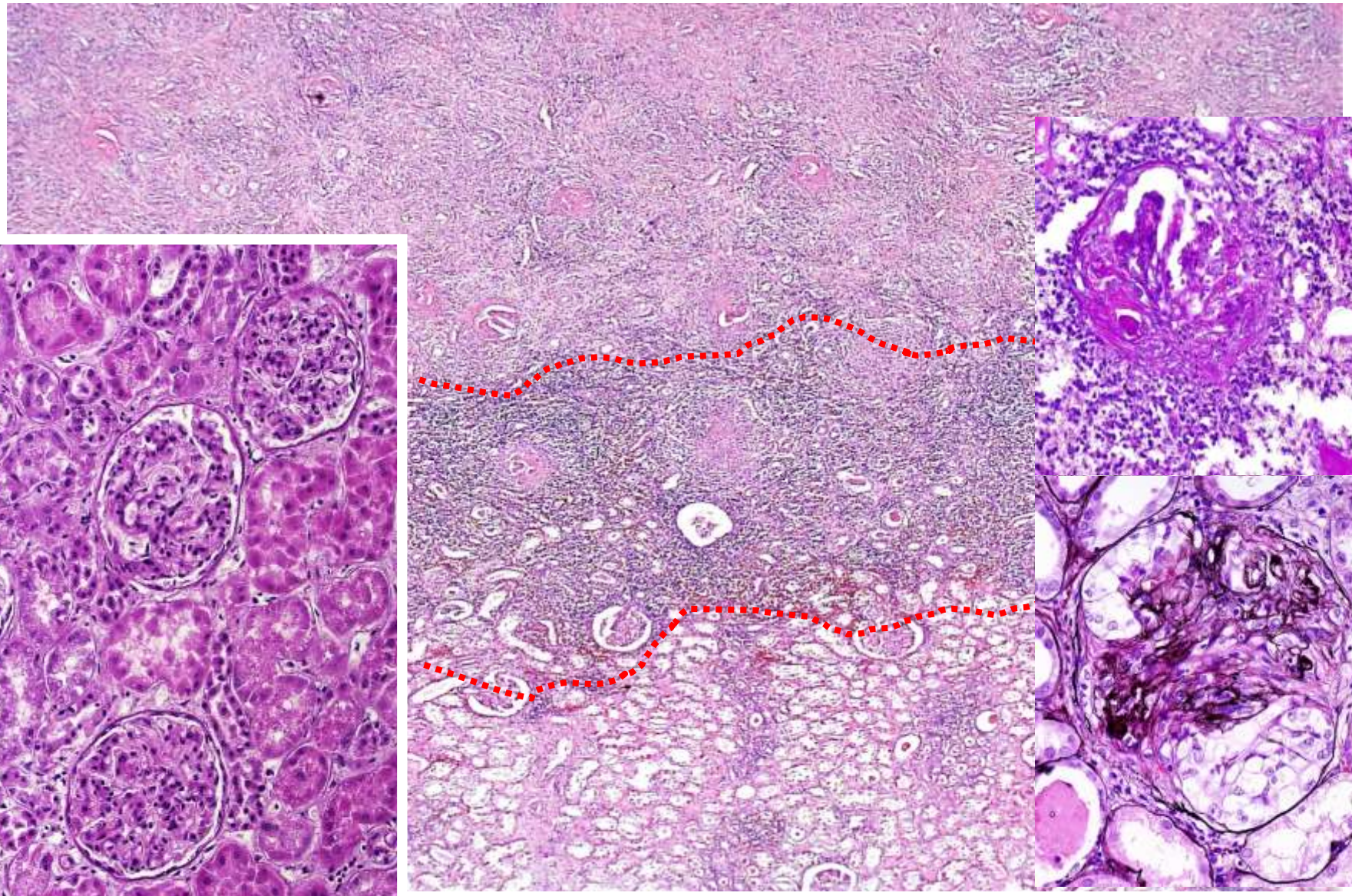
  acute polyneuropathy: hypoesthesia and paresthesia

- mild hematuria and proterinuria (1 g/day), sterile pyuria
- CRP 45 mg/dl, sCr 120µmol/l; 1.36 mg/dl, Hb 99
- US and CT: ***mass of left kidney*** – exploratory surgery
- firm and whitish appearance;
- perioperative biopsy – **no malignant cells, granulomatous inflammation**
- mass seemed malignant – nephrectomy completed

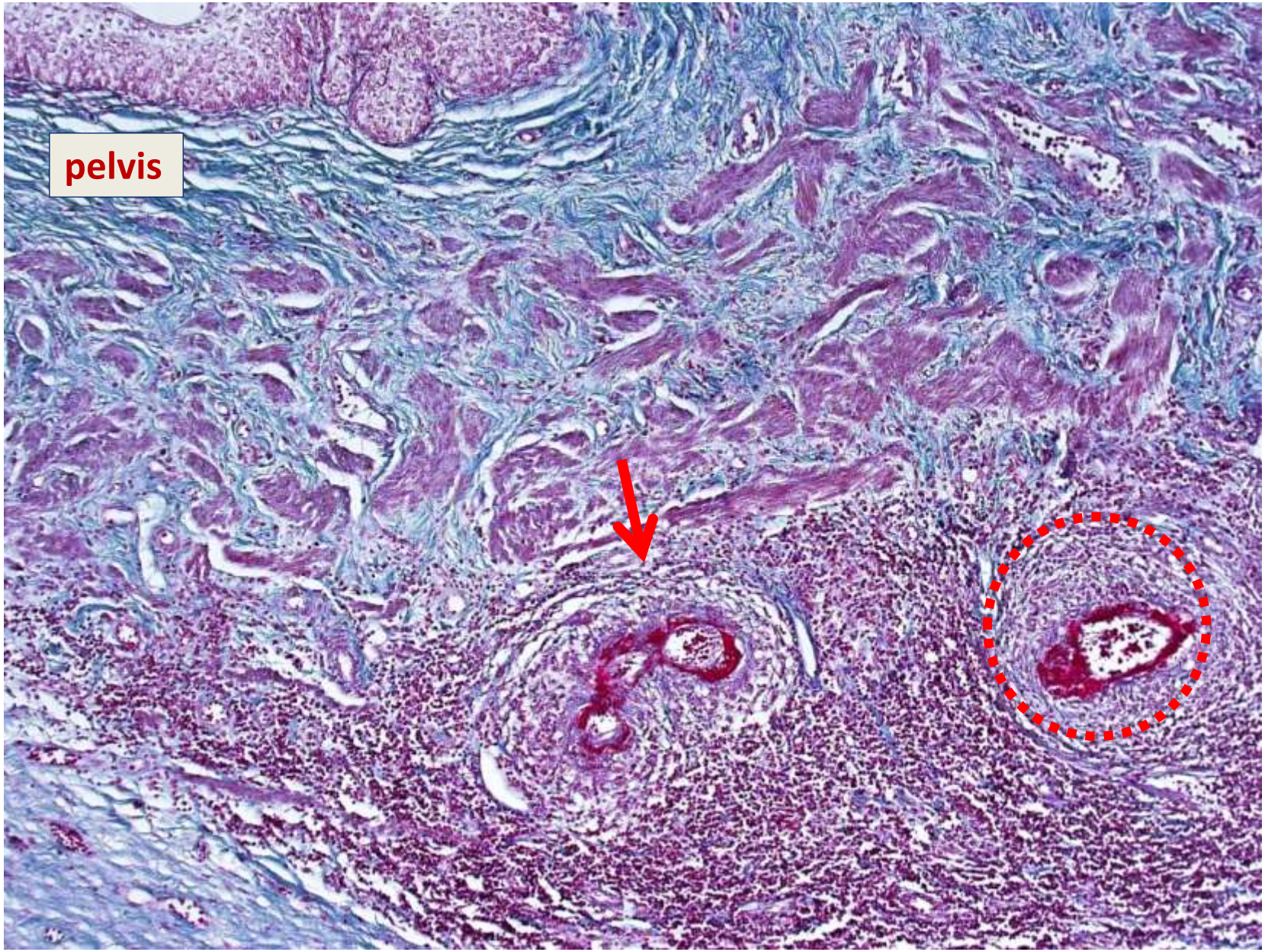
# Case no. 3.: nephrectomy specimen



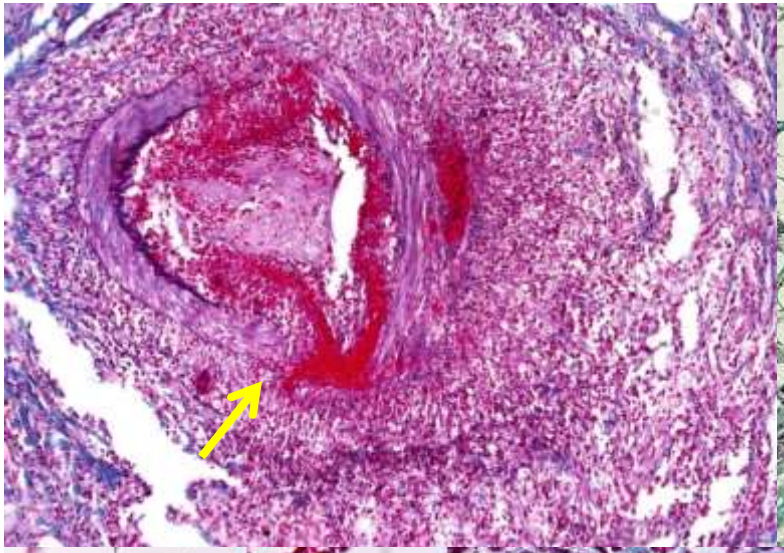
# Case no. 3.: nephrectomy specimen

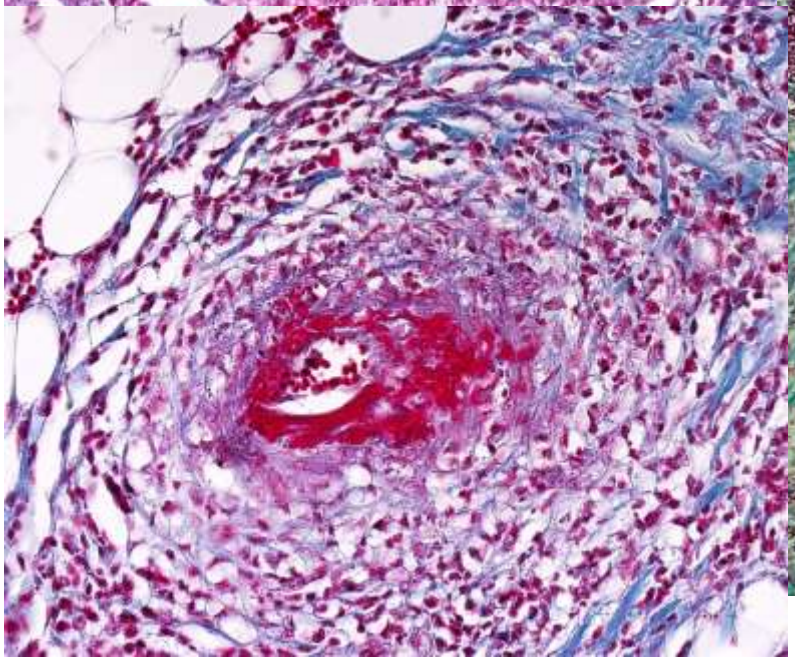


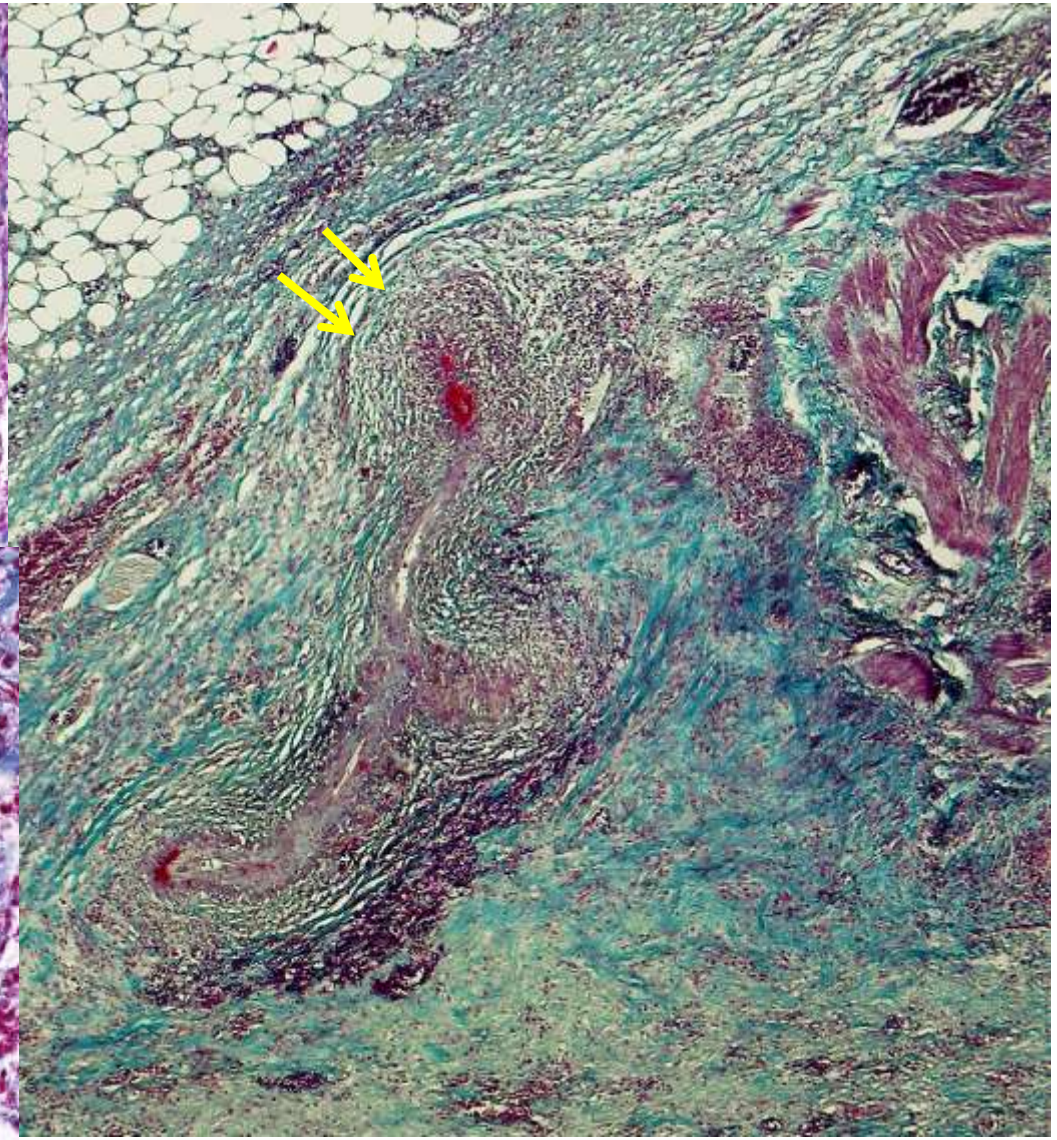
# Case no. 3.: nephrectomy specimen



# Case no. 3.: nephrectomy specimen





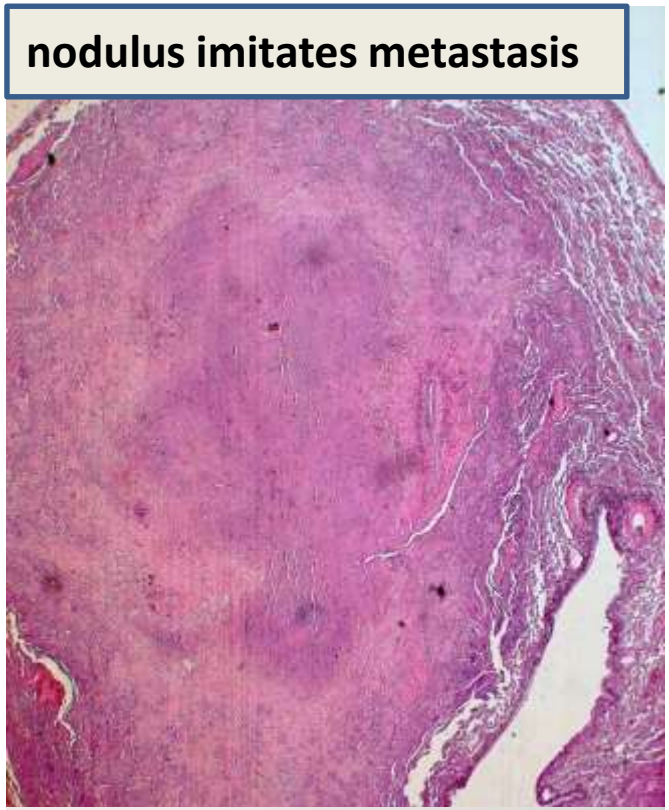


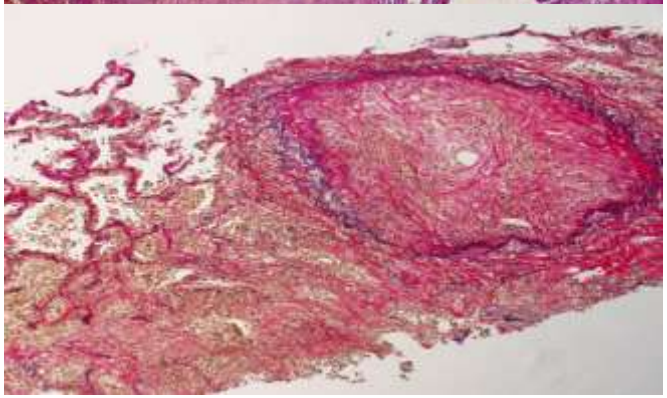
# Case no. 3.

- diagnosis of **granulomatosis with polyangiitis** confirmed by c-ANCA positive (IF and ELISA)
- treated with corticoids and cyclophosphamide until complete recovery
- remission in the ***follow-up (14 years) – normal renal function*** (S-Cr 76µmol/l; 0.86 mg/dl), ANCA negative, only mild proteinuria (0.6 g/day)
- maintainence therapy – low-dose azathioprine

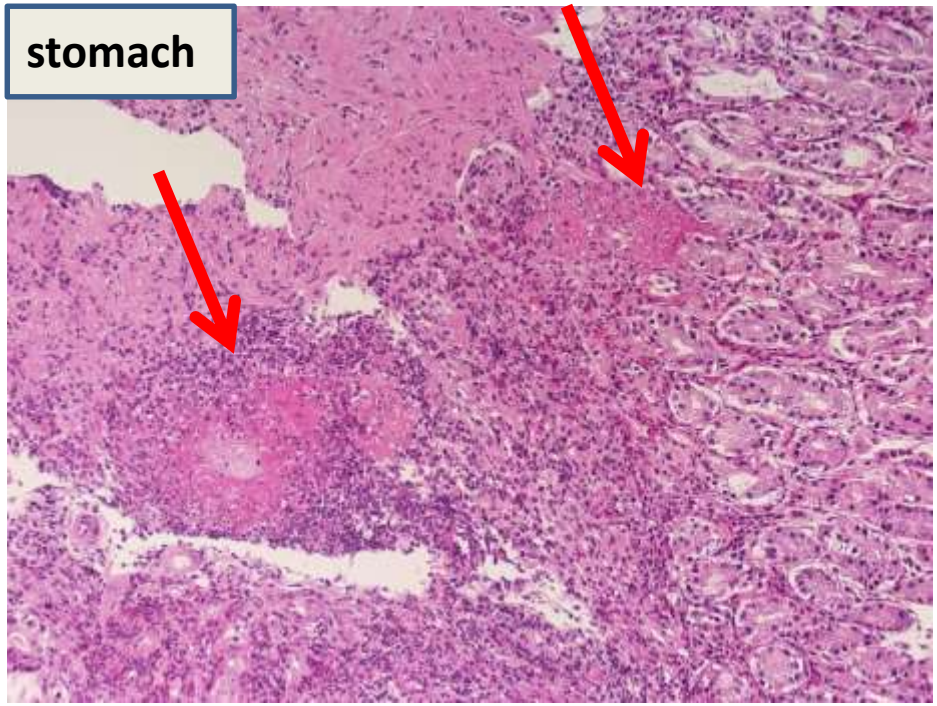
# AAV, systemic involvement

nodulus imitates metastasis

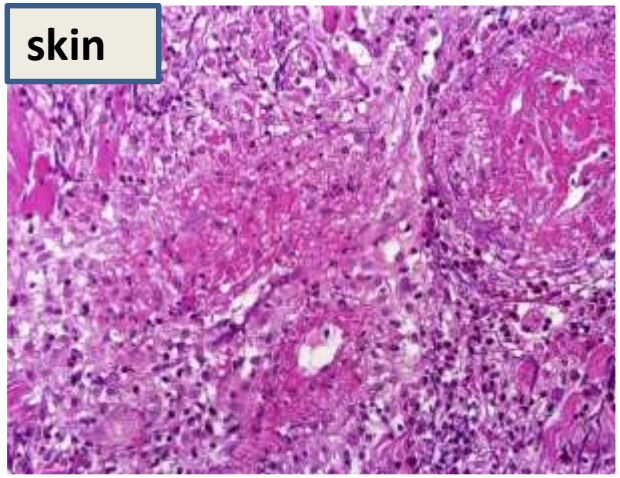


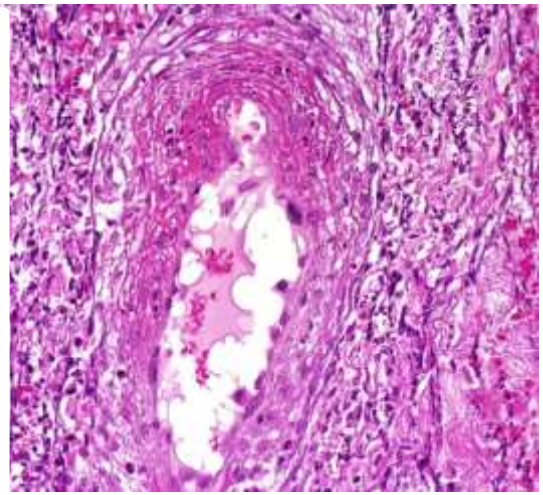


stomach



skin





# Czech Registry of ANCA-associated vasculitides (AAV)

- Local database of AAV in Prague since 1993
- National level & online data collection since 2009
- Main aims:
  - To obtain consistent epidemiologic and clinical data on patients with AAV in the Czech Republic
  - To support modern therapeutic strategies in (young and/or refractory) AAV patients

**16 centres in 7 cities**:

***9x Nephrology***

4x Rheumatology

2x Immunology

1x Pediatrics

# Results

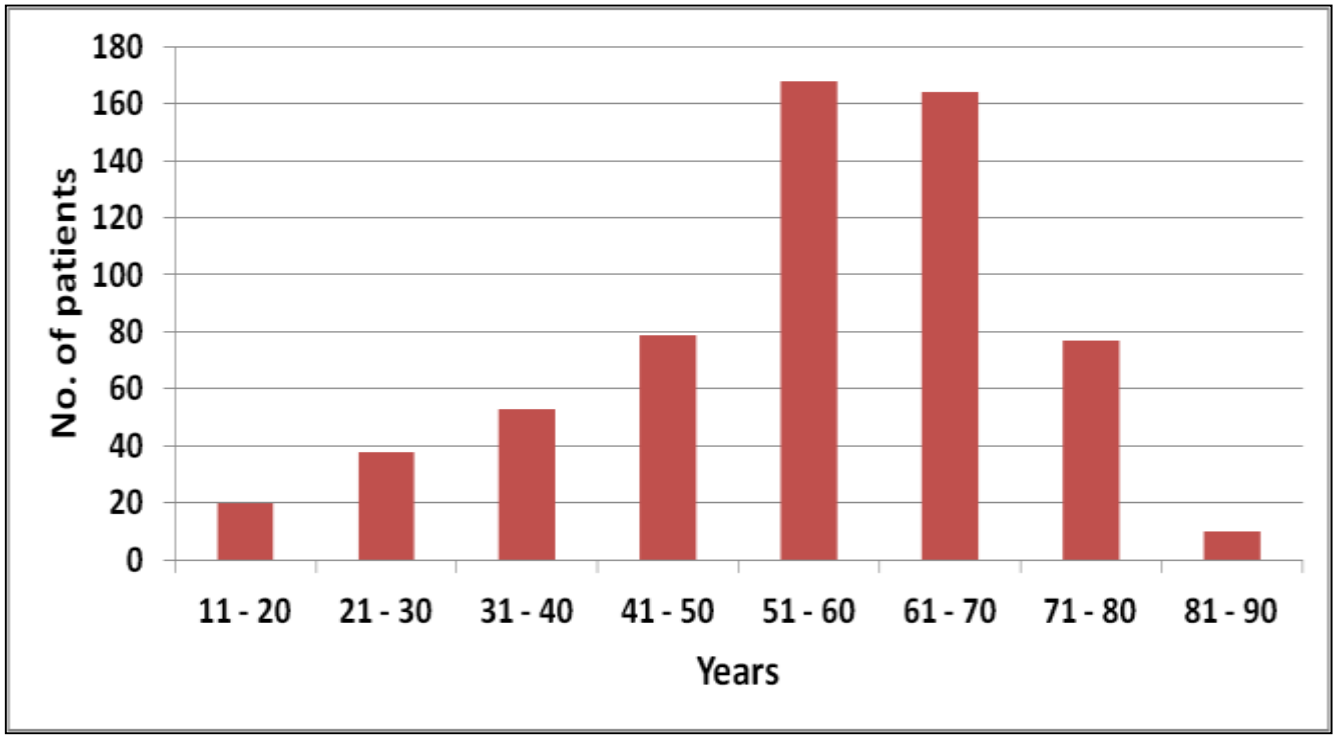
**n = 689 patients:**

Male/Female: 330/359 (48/52%)

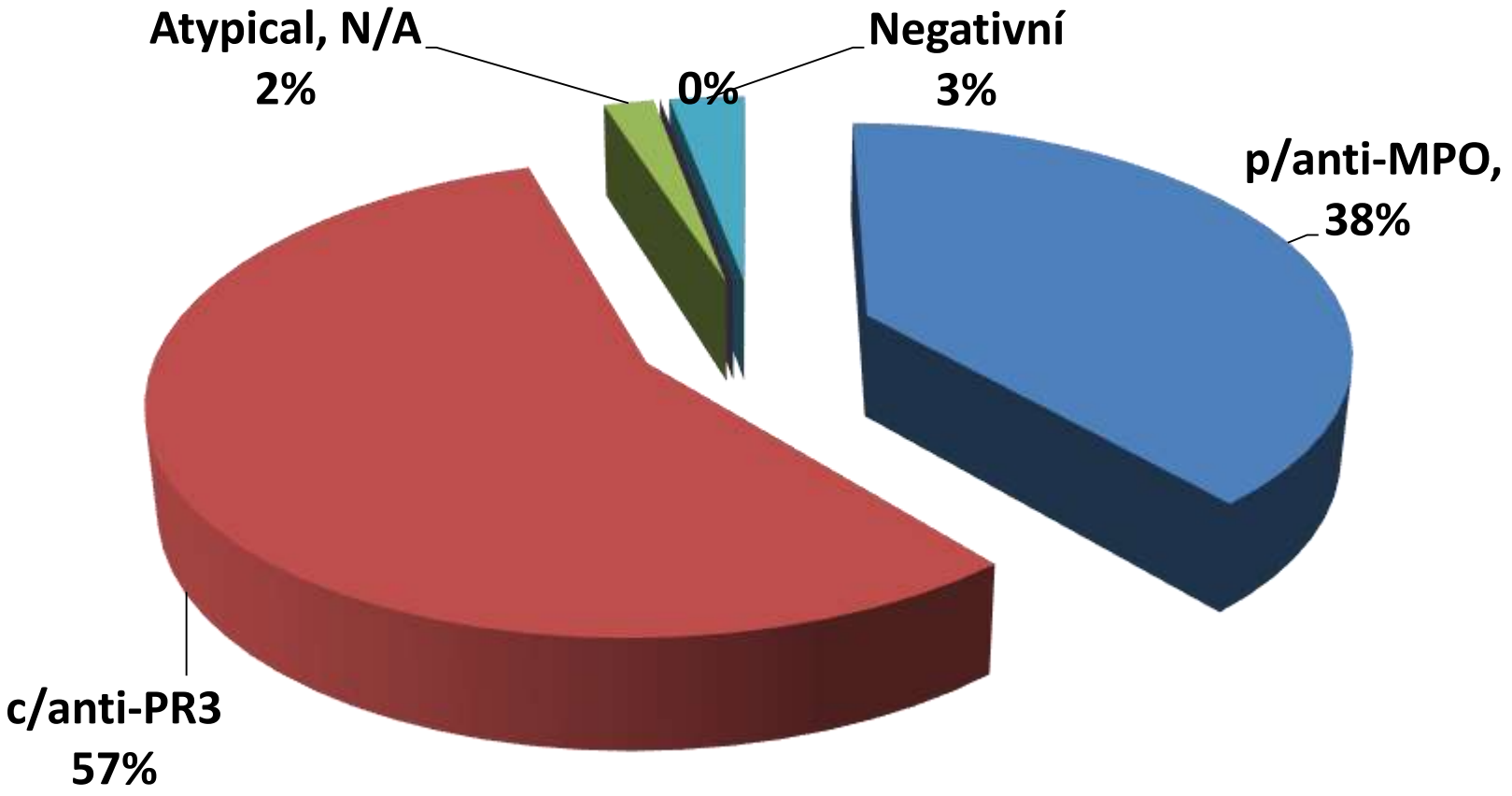
Median age at dg: 58 (range 11 – 89) years

No of patients alive: 510 ; → Prevalence 48.5 pmp

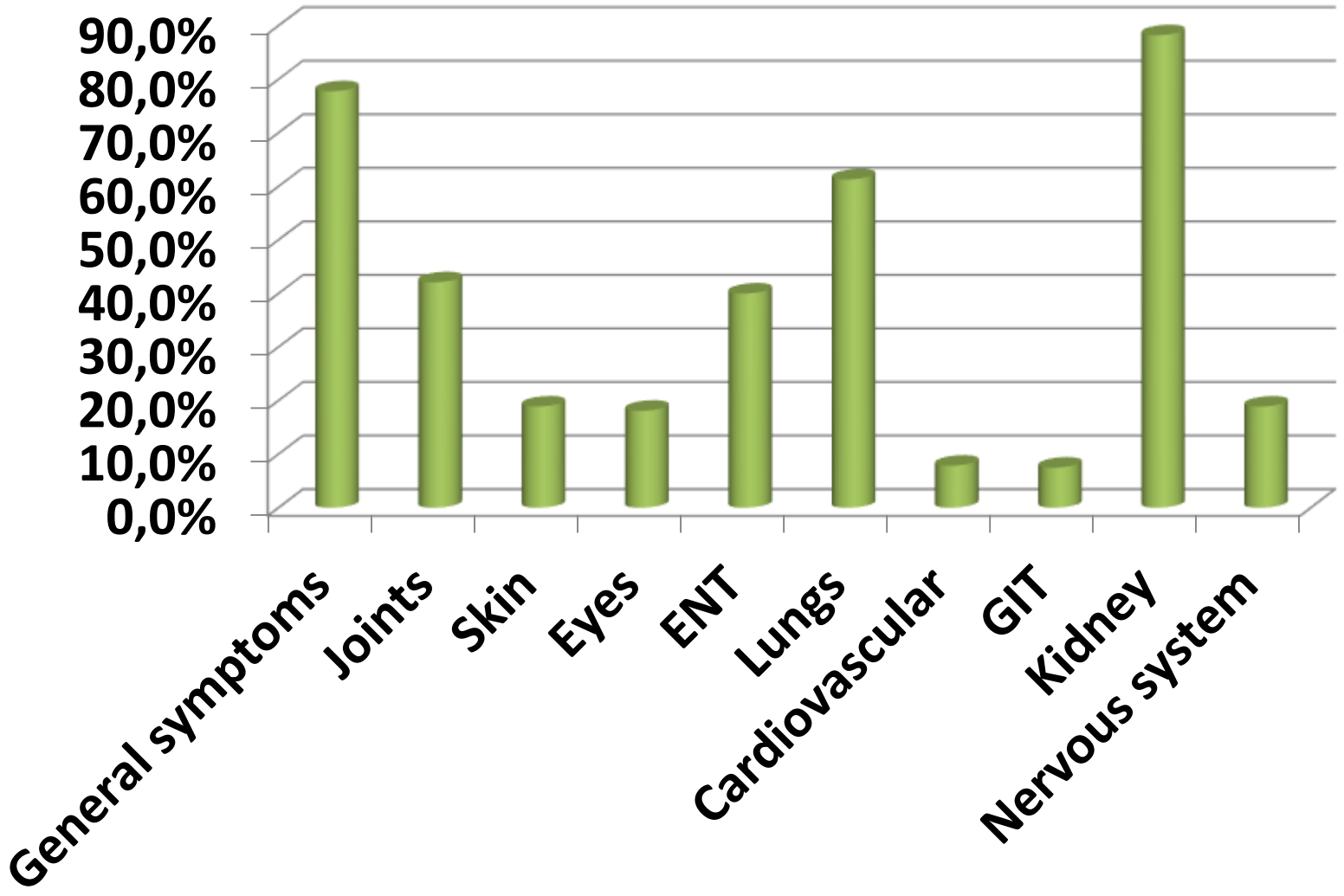
Age distribution:



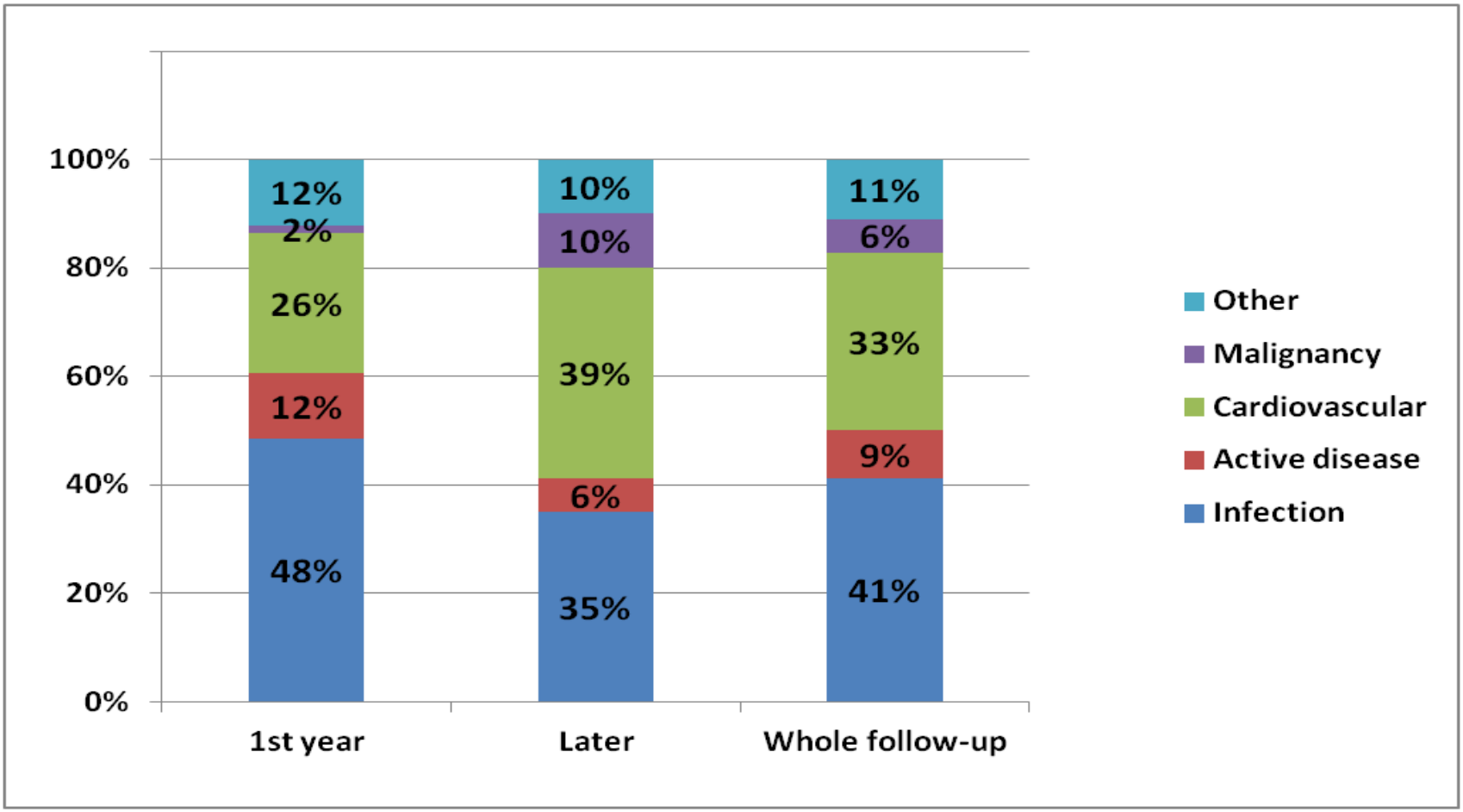
# ANCA type (ever) ELISA and/or IIF



# Cumulative organ involvement (n: 689)



# Causes of death




2.9x increased risk of death due to cardiovascular cause,
in patients aged 15-64 years: 10x increased risk of mortality (all causes)

## In *morphological point of view, ANCA vasculitis should be considered when* :

- ***Chronic inflammation in ear and/or repeated sinusitis***
- Skin vasculitic lesions: painful
- ***Ischemic ulcers in GIT***
- Pauciimmune necrotizing GN
- Lungs: ***hemoptysis and changing infiltrates*** („GPA“ can imitate **tumor** and older patients are sometimes treated with cytostatic drugs)
- **Unexplained chronic inflammatory disease**

**Rare:** PAN, Kawasaki, Takayasu

**„More frequent“:** GCA, drugs associated vasculitis (mainly skin lesions)

**ANCA associated vasculitis is the most common form of systemic vasculitis of adults.**

16th Prague Postgraduate Training Course in Nephrology and ERA-EDTA CME Course (**22. – 23. 1. 2016**)

Organized by CNS, ERA- EDTA immunonephrology WG, RPS, and Nephropath®

# *Nephropathology for the nephrologists*

Introduction to renal pathology and approach to diagnosis (clinic-pathology correlations)

When to add *molecular pathology* to the diagnosis of kidney diseases (*Helen Liapis, US*)

Clinical up-data of membranous nephropathy: *Is it time to change the guidelines?* (*Pierre Ronco*)

Should the patients with a clear diagnosis of AAV be biopsied? (*V. Tesař*)

***How I treat*** a patient with AAV (3 case reports)

Interpretation of renal allograft biopsies: an algorithmic approach with up-grade of Banff classification system (*A. Perkowska-Ptasińská*)