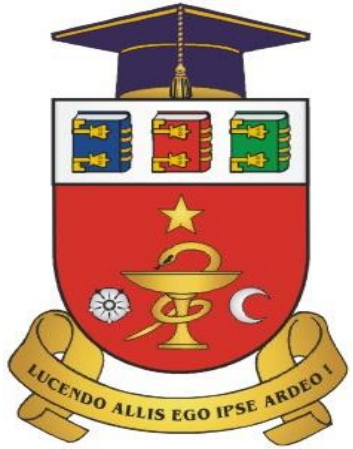


Renal impairment in systemic diseases

(secondary glomerulonephritis)

Classification

- Systemic diseases
- Dysproteinemia & paraproteinemia
- Hepatic impairment
- Infections
- Tumors
- Genetic diseases
- Drug disease
- Vaccination
- Allergic diseases
- Diverse

Renal impairment in systemic lupus erythematosus (SLE) - lupus nephritis

Incidence

- 5% of patients develop nephritis soon after SLE onset
- 95% of patients after a longer period of evolution

Etiology – still unknown

Pathogenesis – impairment of humoral immunity

- SLE is a typical model of immune complex mediated disease
- CIC - DNA & anti-DNA antibodies
- Immune Complexes could form „in situ”

Autoantibodies

- Antinuclear (ANA)
- Anti-dsDNA (double stranded)
- Anti-ssDNA
- Anti-Sm (Smith)
- Anti-Ro (SS-A)
- Anti-La (SS-B)
- Anti-ribonucleoproteine (Anti-RNP)
- Anti-histone
- Anti-eritrocitari
- Anti-lymphocytes
- Anti-platelets
- Anti-neuronal
- Anti-phospholipidic

Complement system:

-↓ C_3 correlated with disease activity

Lupic nephritis

Pathogenesis

Cellular Immunity

+ Hyperreactivity of B lymphocytes
+ ↓ number of T lymphocytes
+ ↑ activity LT-helper
+ ↓ activity of LT-suppressors
+ *mediated by IL-2 of LT production*

Genetic Mechanisms

+ Some HLA antigens: HLA B_1, HLA B_8

Lupus nephritis (LN)

Pathology

Classification ISN/RPS -2003

I. Minimal mesangial LN
II. Mesangial proliferative LN
III. Focal proliferative LN
IV. Diffuse proliferative LN
V. Membranous LN
VI. Advanced sclerosing lupus nephritis

- ≥90% of glomeruli globally sclerosed without residual activity

Immunofluorescence

- mixed appearance of immune deposits with IgG, IgA, IgM, C_3 & C_{1q}

Lupus nephritis

Pathology – minimal mesangial

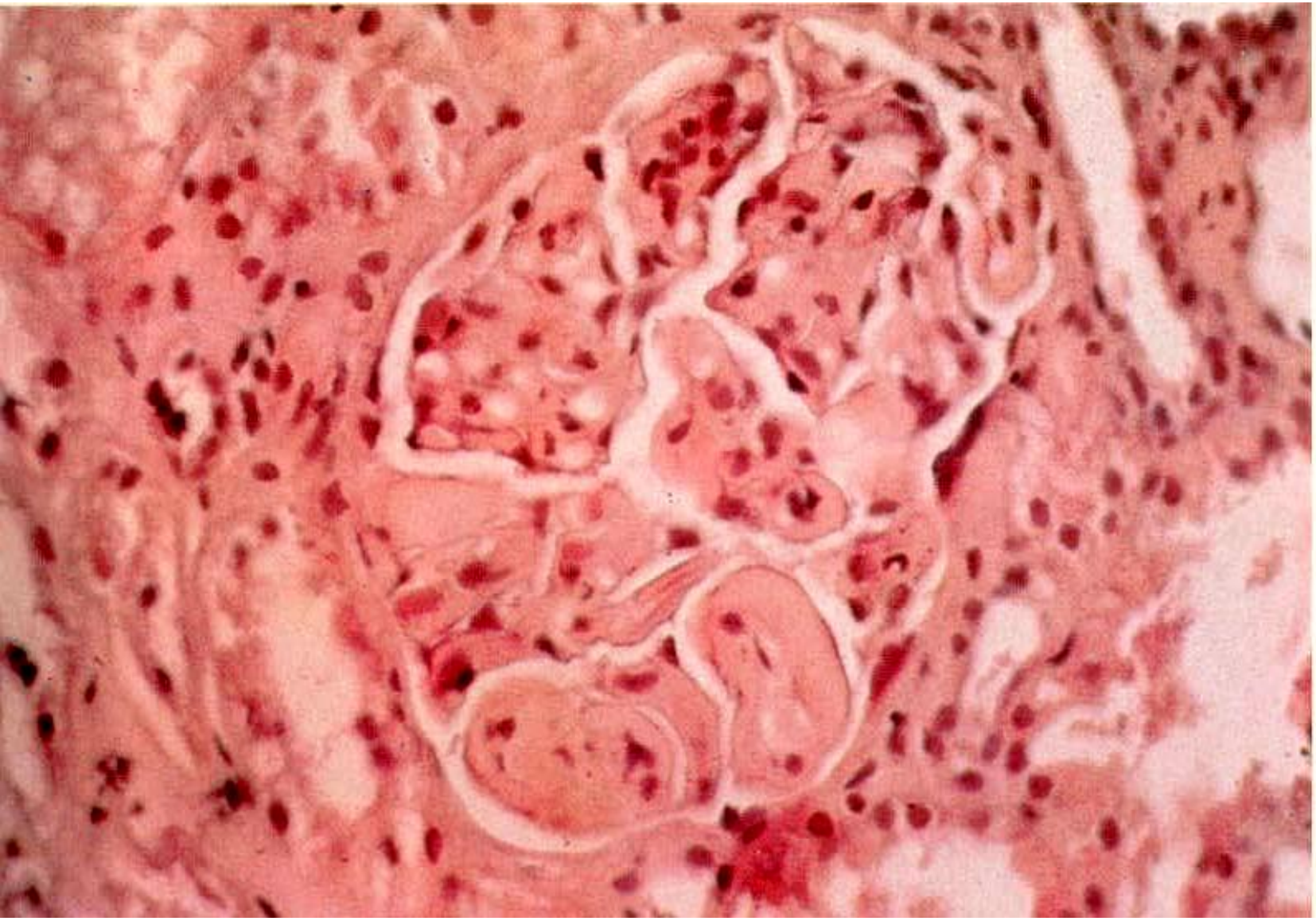
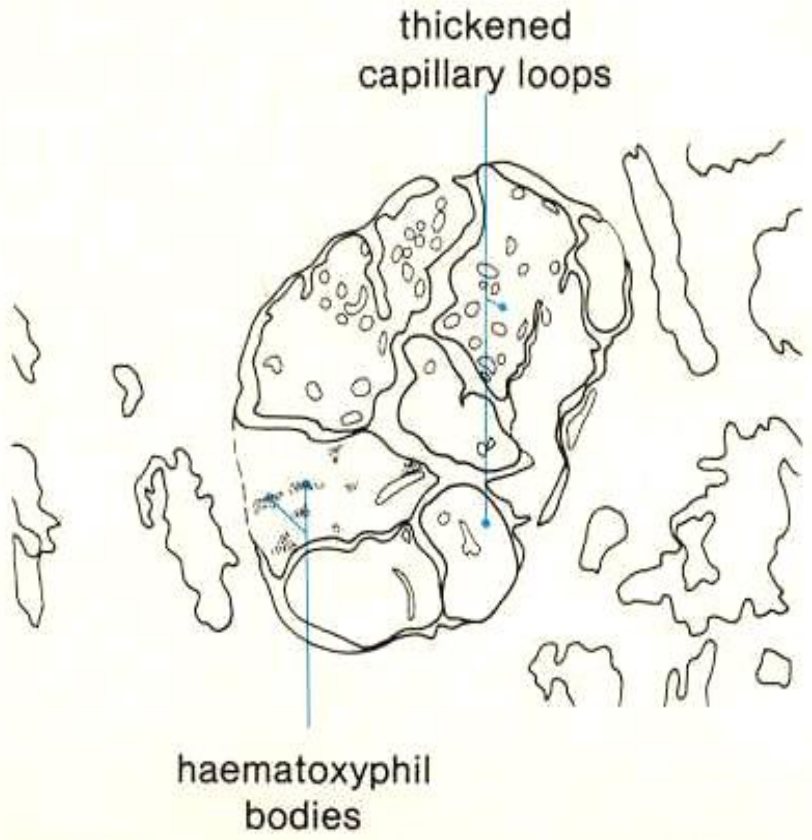
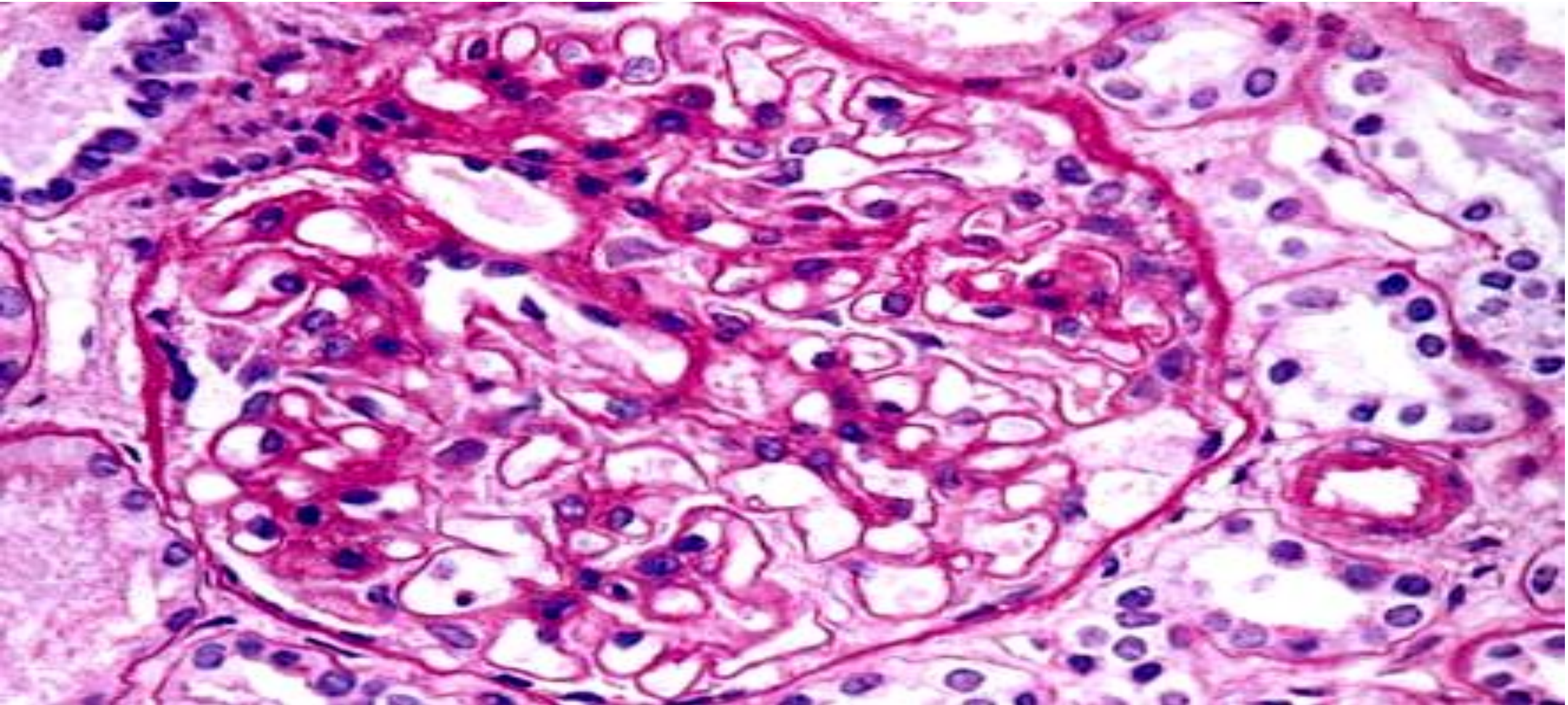


Fig. 8.7 Histological section of lupus nephritis showing diffuse thickening of the glomerular capillary loops and several haematoxyphil bodies. Haematoxylin and eosin stain.



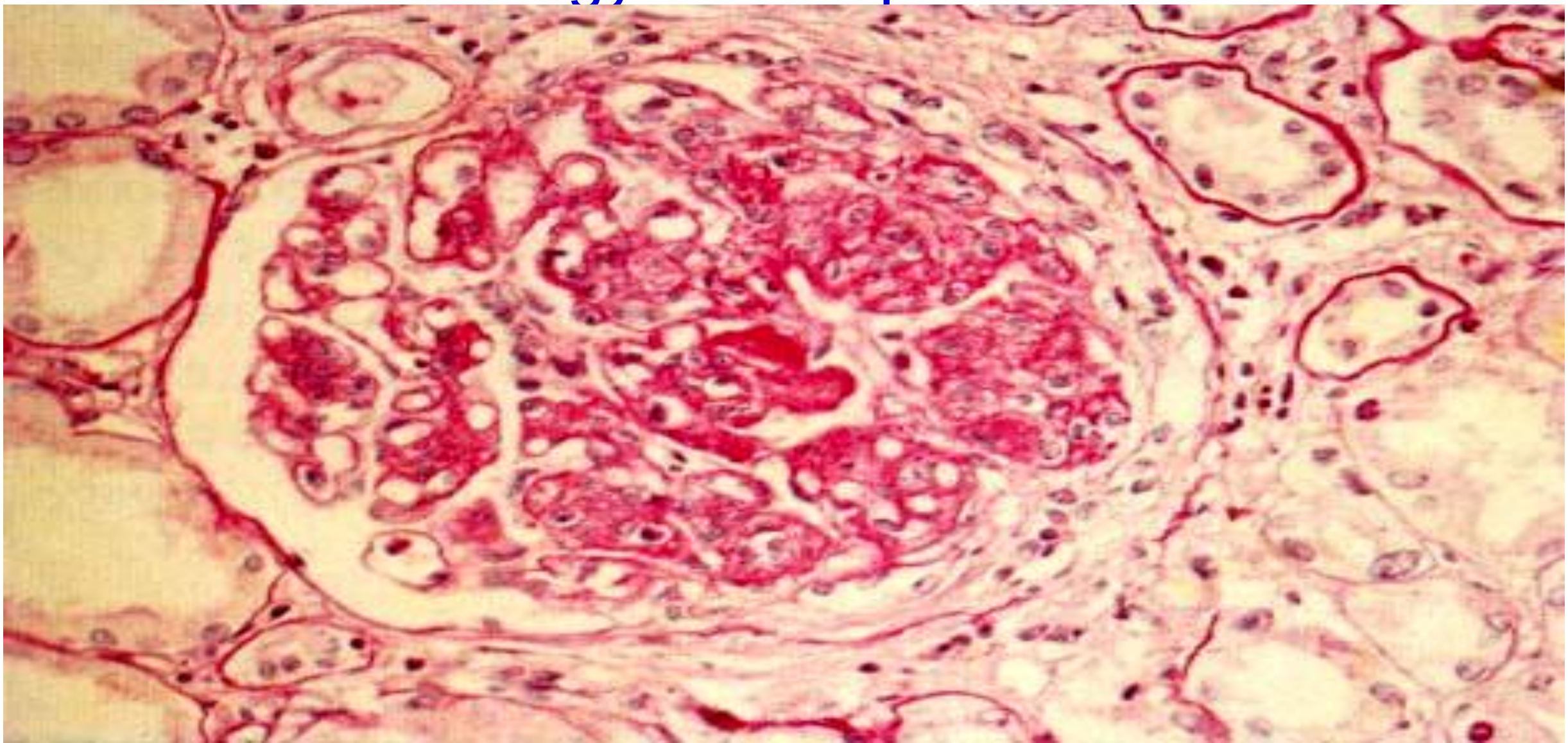
Lupus nephritis

Pathology – mesangial proliferative



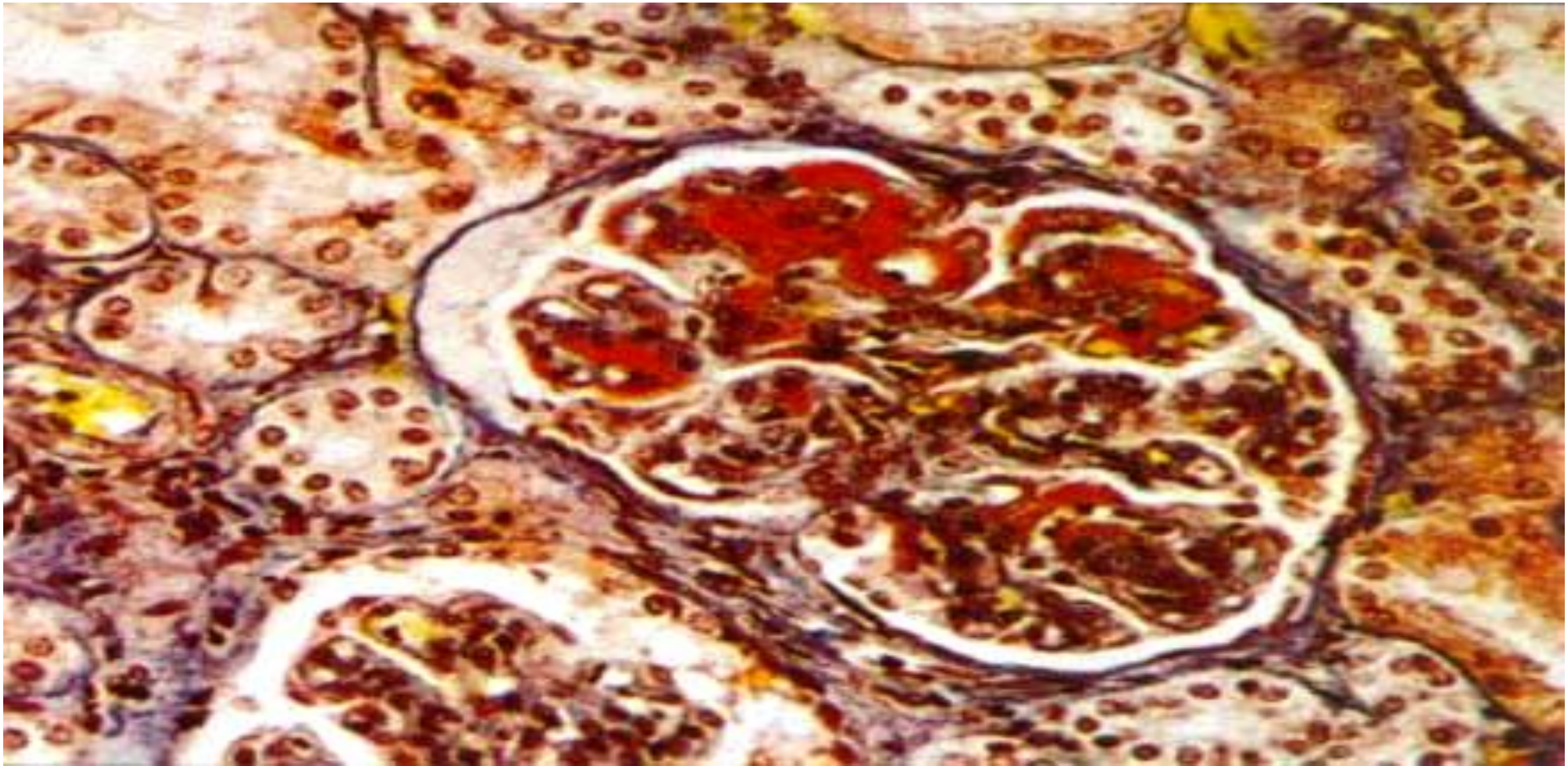
Lupus nephritis

Pathology – focal proliferative



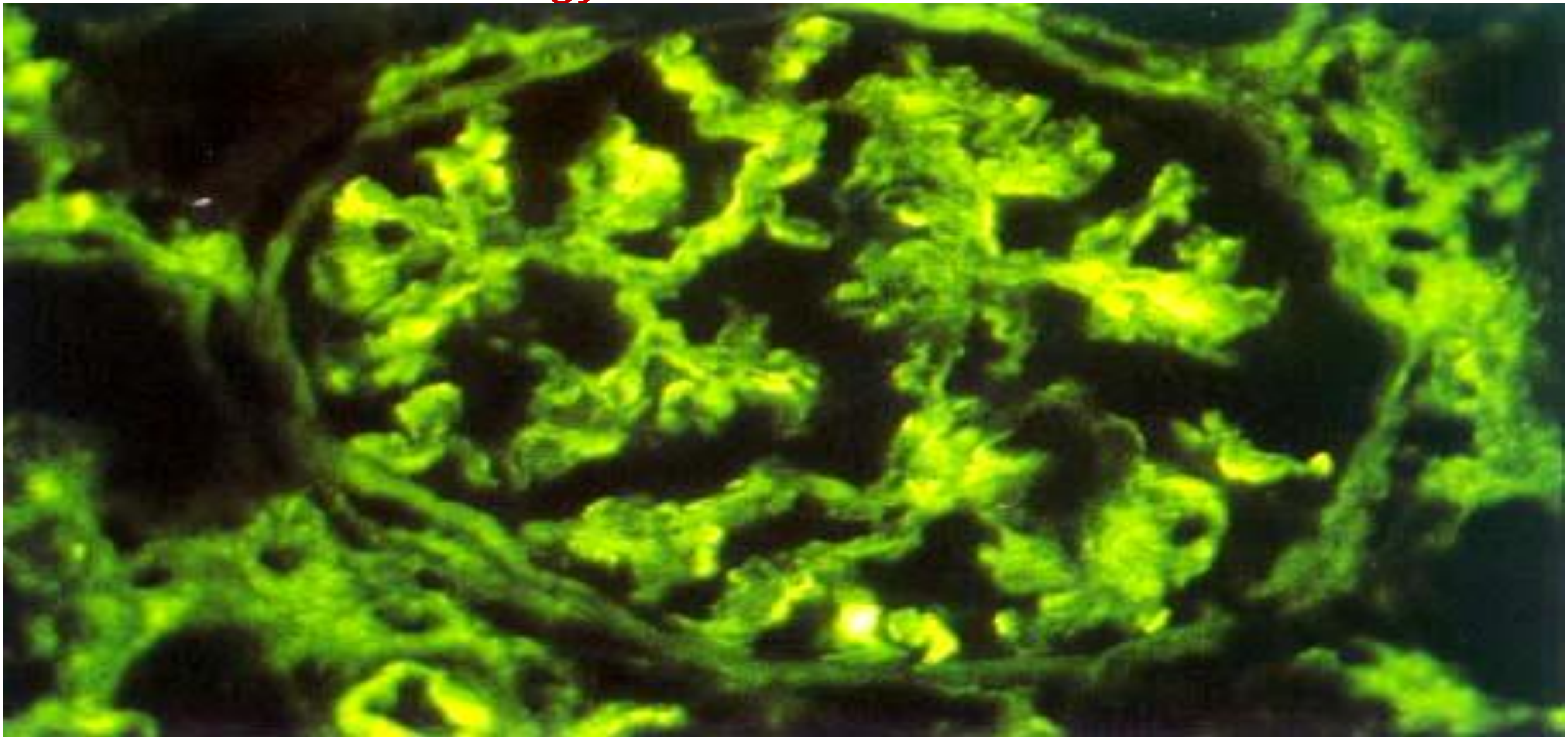
Lupus nephritis

Pathology – membranous GN



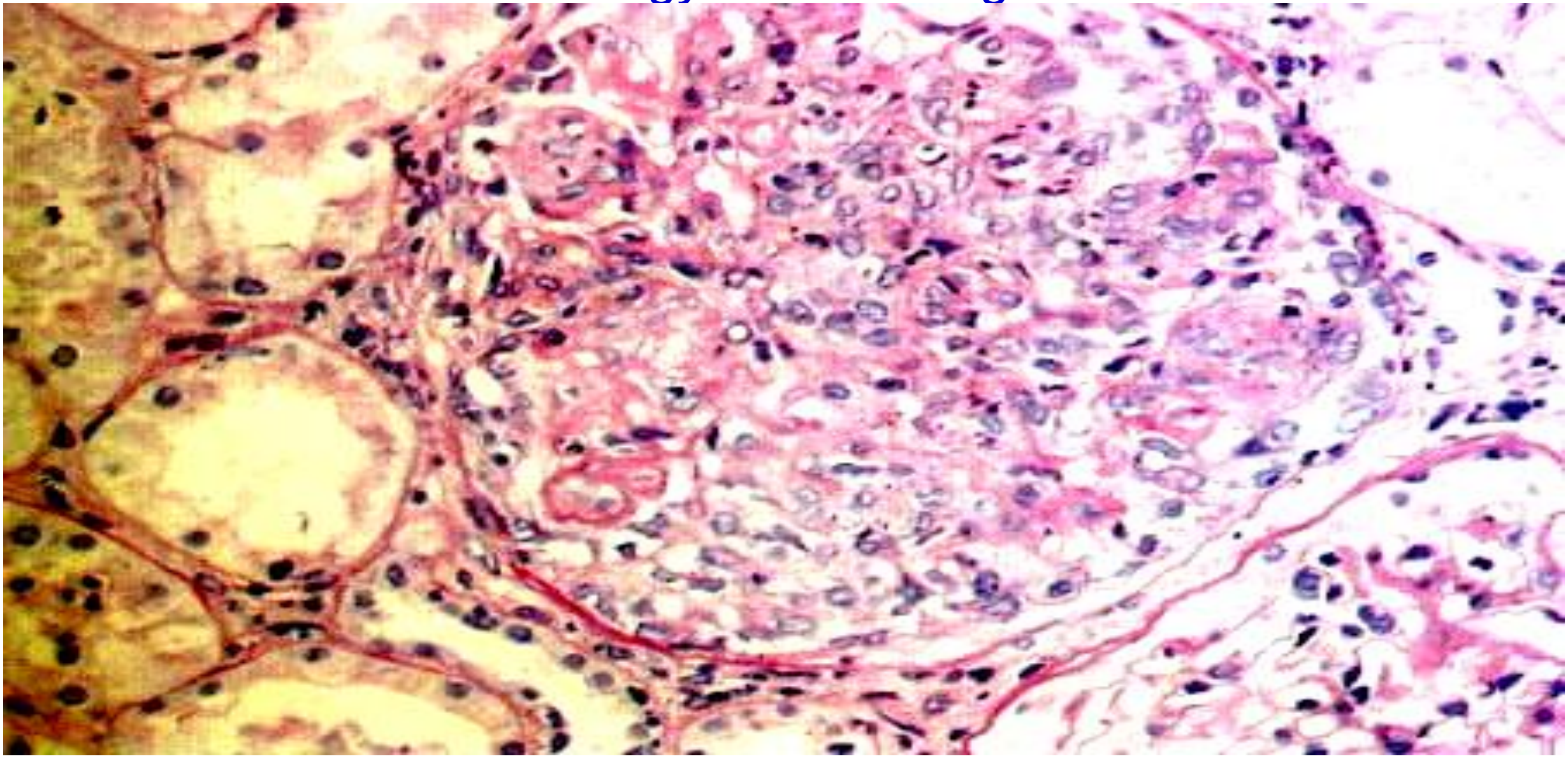
Lupus nephritis

Pathology – immunofluorescence



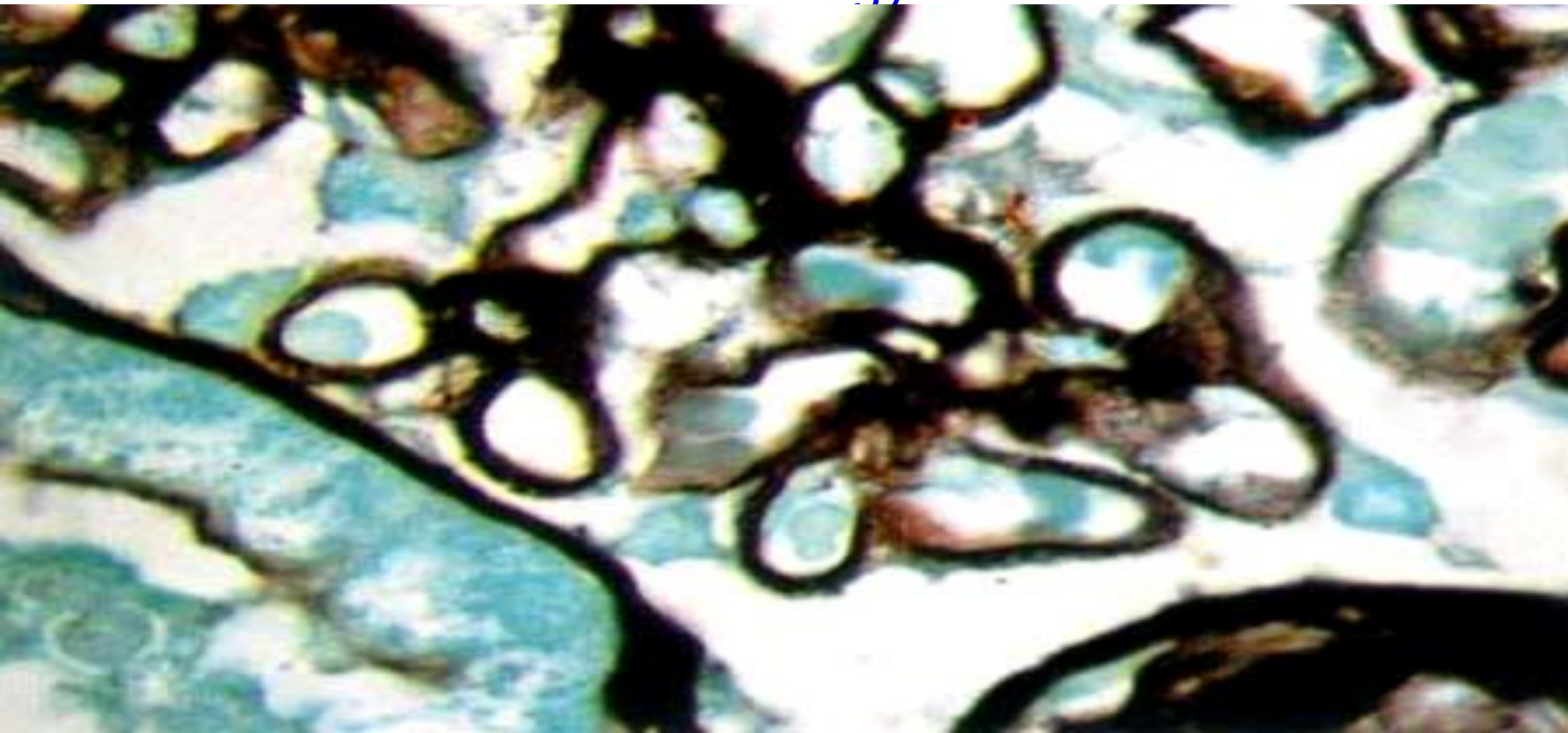
Lupus nephritis

Pathology – sclerosing GN



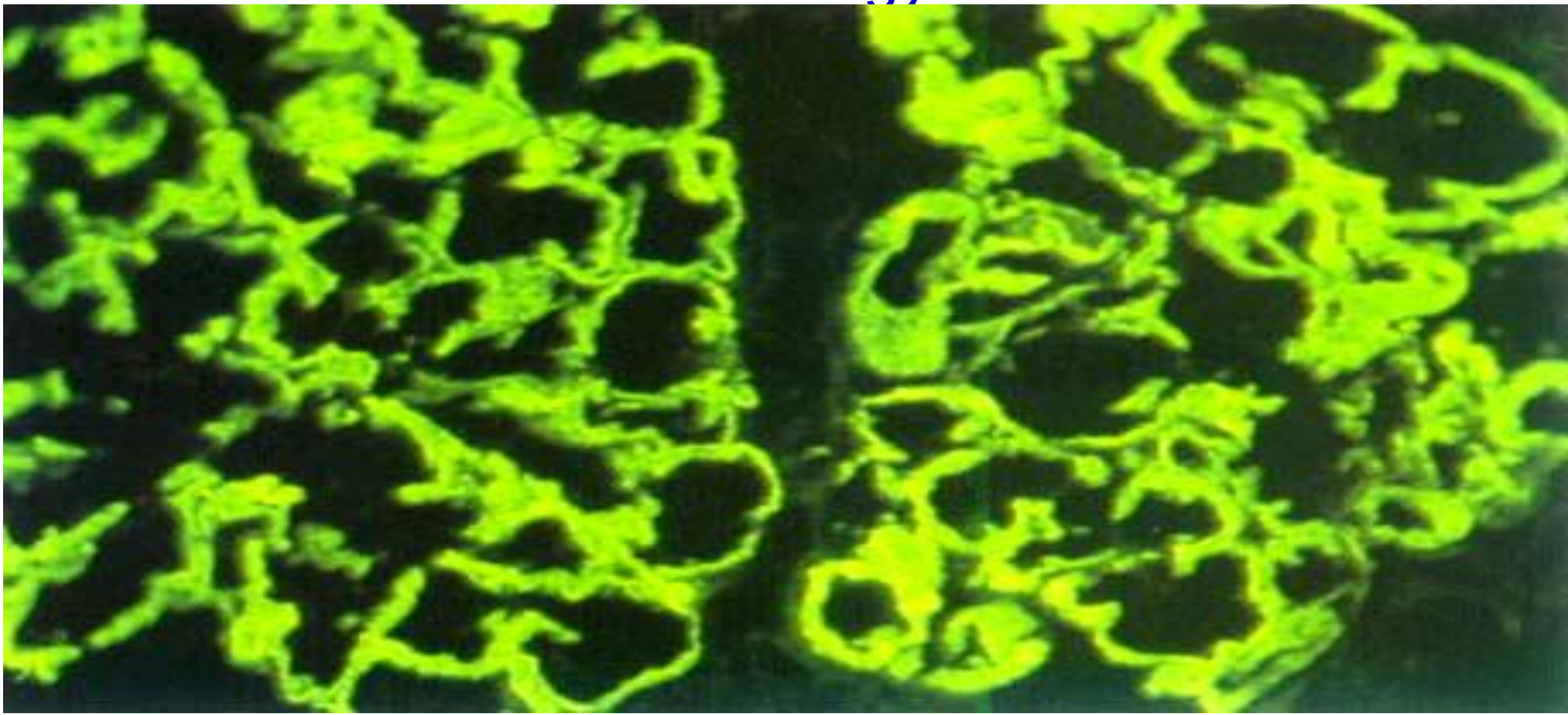
Lupus nephritis

Pathology



Lupus nephritis

Pathology

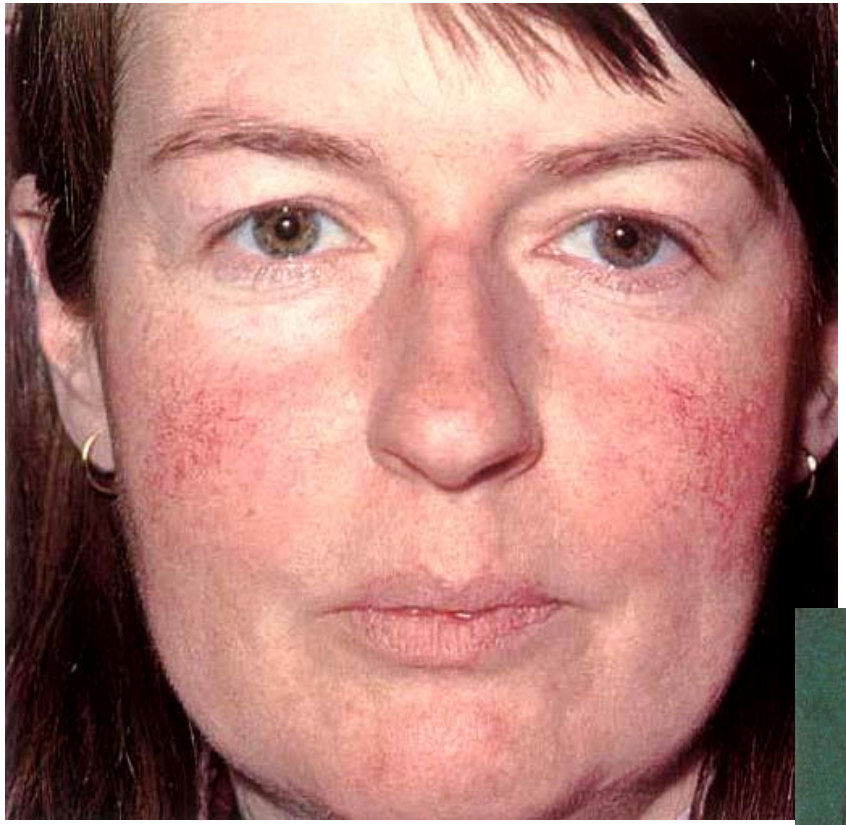


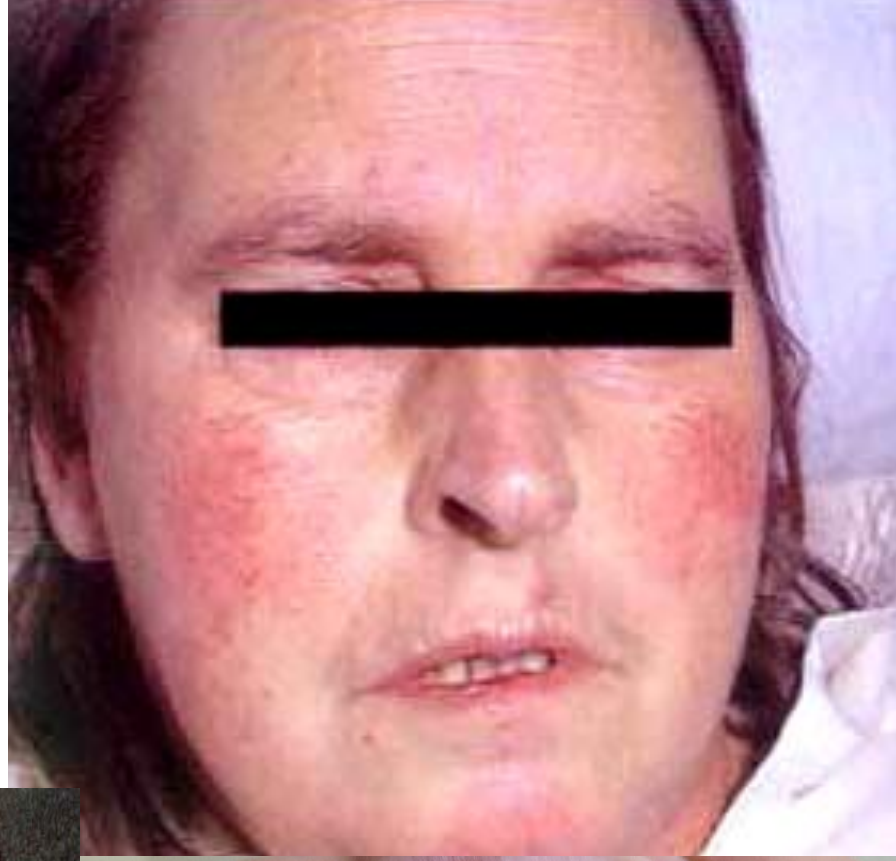
Lupus nephritis: clinical picture

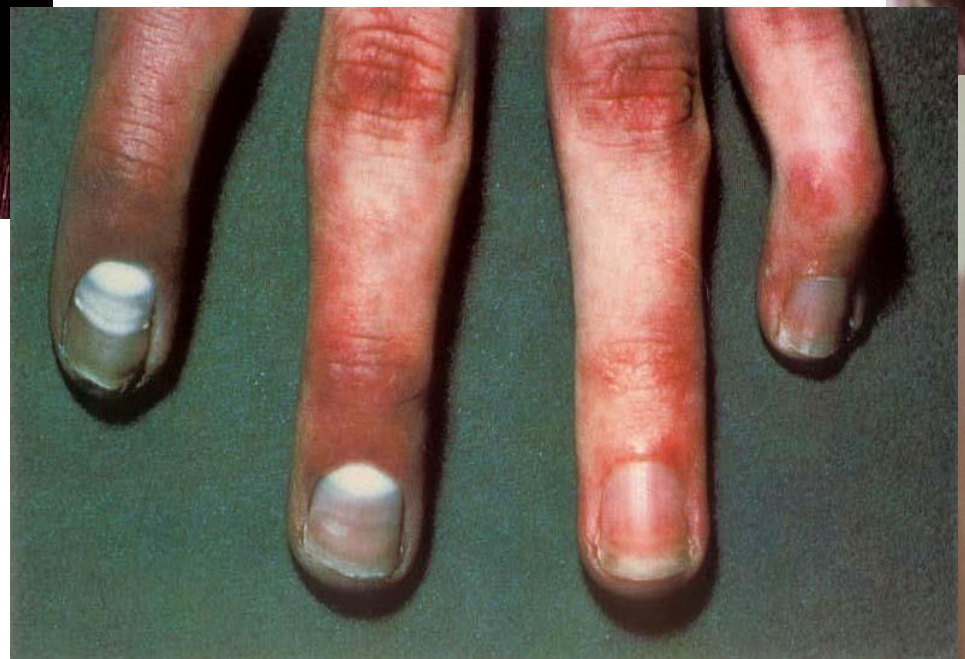
Clinical signs of SLE

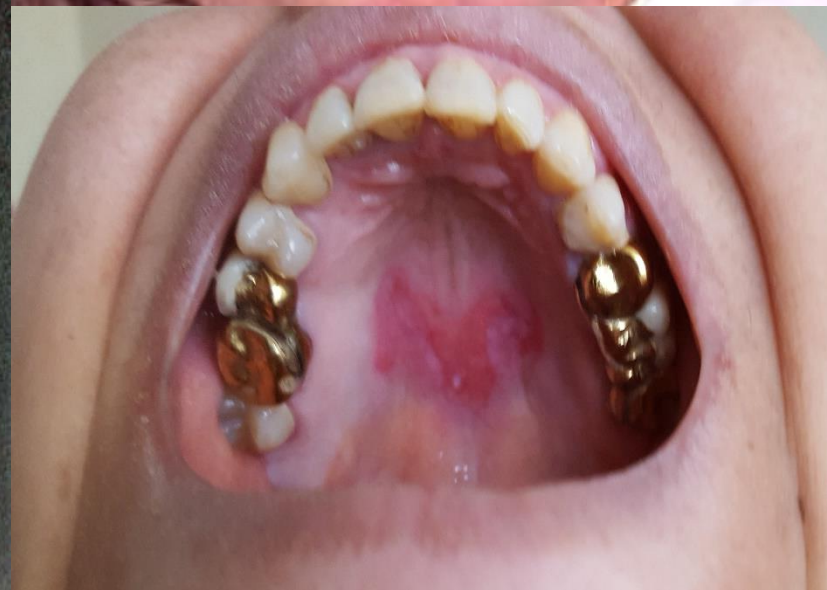
- ✓ Skin: pallor, „butterfly” facial rash (nasal & malar), discoid lupus, purpura, photosensitivity
- ✓ Mucosal lesions: mouth & nasal ulcers
- ✓ Joints: arthralgia, arthritis
- ✓ Heart: pericarditis, endocarditis, myocarditis
- ✓ Neurological signs: confusion, psychosis
- ✓ Other manifestations: adenopathy, splenomegaly, hepatomegaly, fever and livedo reticularis
- ✓ Renal impairment: edema, hypertension, oliguria, hyperchrome urine

Lupus nephritis: clinical picture









Lupus nephritis

- **Laboratory investigations**
- Hematological changes
- Inflammatory syndrome
  - ↑ ESR, ↑ fibrinogen
  - ↑ C-reactive protein
  - ↑ alfa-2 globulins
- The levels of these parameters increase with the activity of the disease.

Lupus nephritis

Immunological abnormalities

- ↑ Ig, especially IgG
- ↑ CIC
- Anti-nuclear antibodies (ANA)
- Anti-dsDNA
- Anti-Sm
- ↓ components of the serum complement, in particular C_3
- false positive test for syphilis
- Lupic cells

Lupus nephritis

Other anomalies

- Cryoglobulins
- ↑ Plasma fibronectin
- Abnormalities of T lymphocyte subpopulations
- Rheumatoid factor
- Anti-phospholipid antibodies
- ↓ Renal function
  - ↑ urea
  - ↑ creatinine
  - ↑ serum uric acid

Lupus nephritis

Clinical forms

- Hematuria and / or proteinuria
- Hypertension
- Acute nephritic syndrome
  - Hypertension
  - Hematuria
  - Proteinuria
  - Edema
- Nephrotic syndrome
- Acute / chronic renal failure
- Tubular acidosis

Lupus nephritis

Differential diagnosis:

- Post-streptococcal acute glomerulonephritis.
- Henoch-Schönlein Purpura.
- Primary chronic glomerulonephritis.
- Goodpasture syndrome.

Lupus nephritis

Complications

- ✓ Renal complications.
- ✓ ARF
- ✓ CRF
- ✓ Tubular anomalies
- ✓ extra-renal complications
- ✓ Infections
- ✓ Malignancies
- ✓ Vascular complications
  - ✓ Raynaud's syndrome
  - ✓ Venous thrombosis
- ✓ Atherosclerotic coronary lesions

Lupus nephritis

Prognosis.

- Positive response to corticosteroids
  - silent lupus nephritis
  - Minimal mesangial GN
  - Mesangial proliferative GN
  - Membranous GN
- Deficient response to corticosteroids
  - Diffuse proliferative GN

Lupus nephritis: treatment

- Diet
  - Reduced Na intake
  - Hypo-protein diet - up to 1g/kg/day
- Corticosteroids
  - Prednisone (Methylprednisolone) – 1-2 mg/kg/day, t.i.d.;

  alternate dose regimen
  - At least 3-6 months
  - Gradual dose tapering

Lupus nephritis: treatment

Immunosuppressors

- Cyclophosphamide - 1,5-2 mg/kg/day
- Azathioprine - 2-3 mg/kg/day
- Chlorambucil - 0,2 mg/kg/day
- Cyclosporine – 25-100 mg/day
- Mycophenolat mofetil – 2 g/day

Lupus nephritis: treatment

Combined therapies

- Corticosteroids + immunosuppressors
- More effective in lupus nephritis
- Well tolerated
- They allow to avoid the undesirable side effects of corticosteroids and cytotoxins
- Allow daily doses of each of these drugs to be lowered
- Used in maintenance schemes - 12-18 months (Azathioprine, Mycophenolate)

Lupus nephritis: treatment

- Non-steroidal anti-inflammatory drugs
- Antihypertensive agents
- Diuretics

Renal replacement therapies

- Hemodialysis
- Peritoneal dialysis

Kidney transplant

- Increased tolerance of renal graft

Goodpasture syndrome

Glomerular involvement mediated by anti-GBM antibodies, which evolves as a rapidly progressive glomerulonephritis with extracapillary proliferation and is associated with pulmonary hemorrhage

Goodpasture syndrome

Etiology - unknown

- Viral infections
- Organic solvents
- Medicines
- HLA-DRW_2
- HLA-B_8

Pathogenesis

- mediated by baseline anti-membrane antibodies → autoantibodies directed especially against GBM, but also against pulmonary BM and tubular BM

Goodpasture syndrome: clinical picture

- Preceded by respiratory infections, exposure to organic solvents or drugs
- Asthenia
- Pallor
- ***Renal symptoms***
  - Microscopic hematuria
  - Subnephrotic proteinuria
  - Hypertension
  - Progressive renal failure
- ***Respiratory symptoms***
  - Cough
  - Dyspnea
  - Recurrent episodes of hemoptysis
- Arthralgia

Goodpasture syndrome: paraclinical features

- Serum anti-GBM antibodies
- CIC absent
- C_3 normal
- ASLO normal
- Nitrogen waste retention
- Hematuria
- Proteinuria

Pulmonary X-ray

- Basal pulmonary infiltrates

Pathology

Optical microscopy

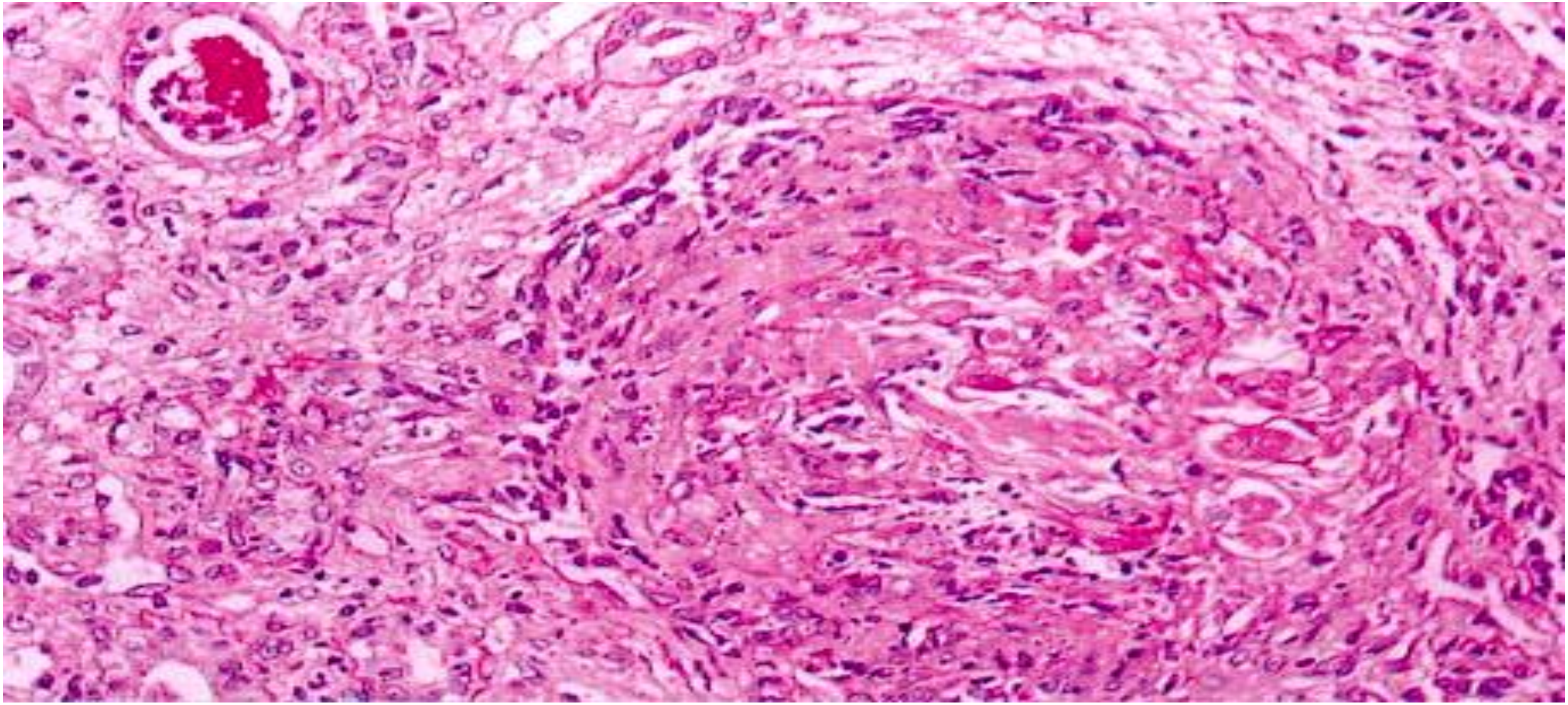
- Focal and segmental proliferative GN,
- with extracapillary proliferation,

Immunofluorescence microscopy

- linear IgG deposits corresponding to anti-GBM antibodies

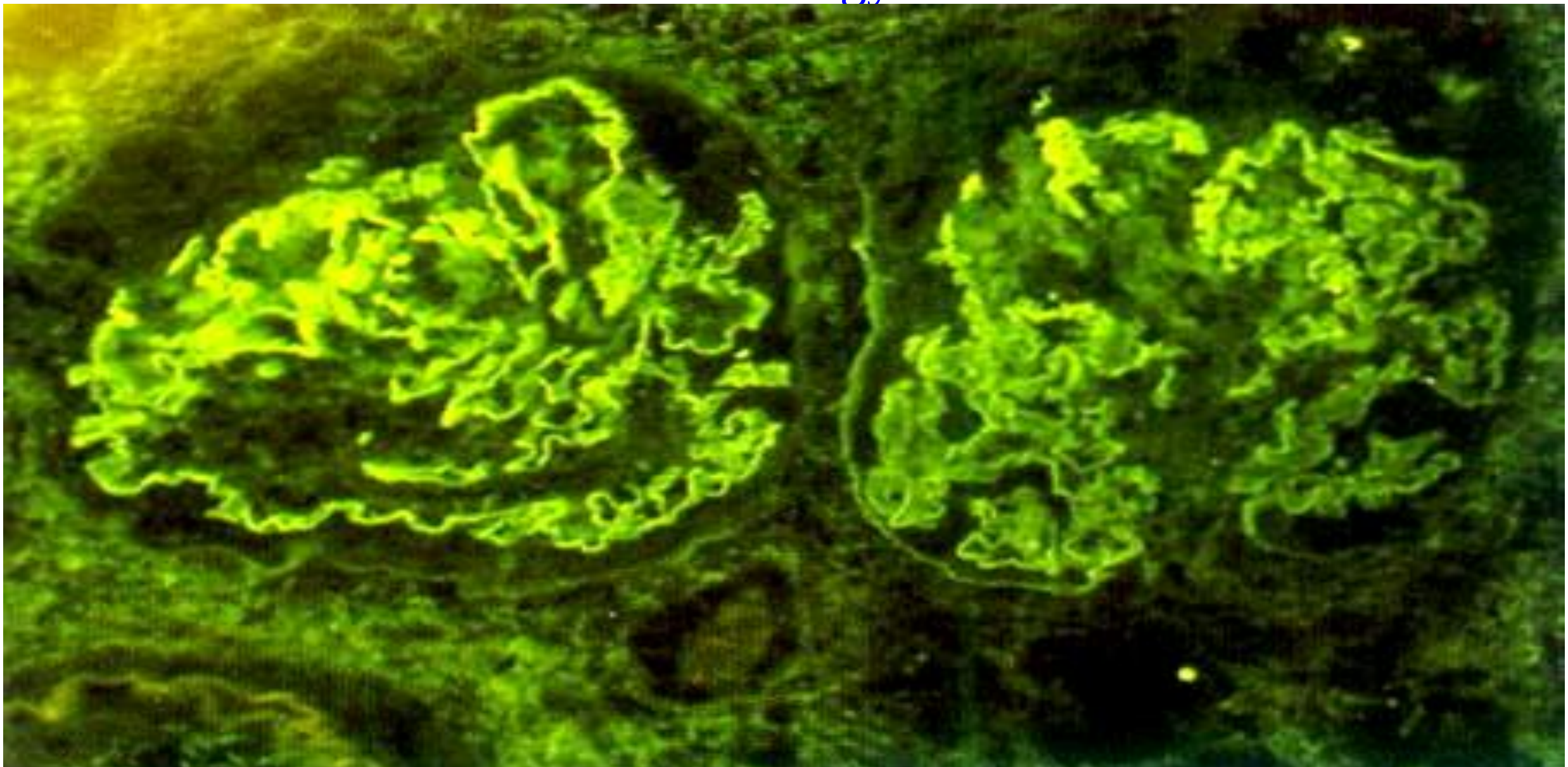
Goodpasture syndrome

Pathology



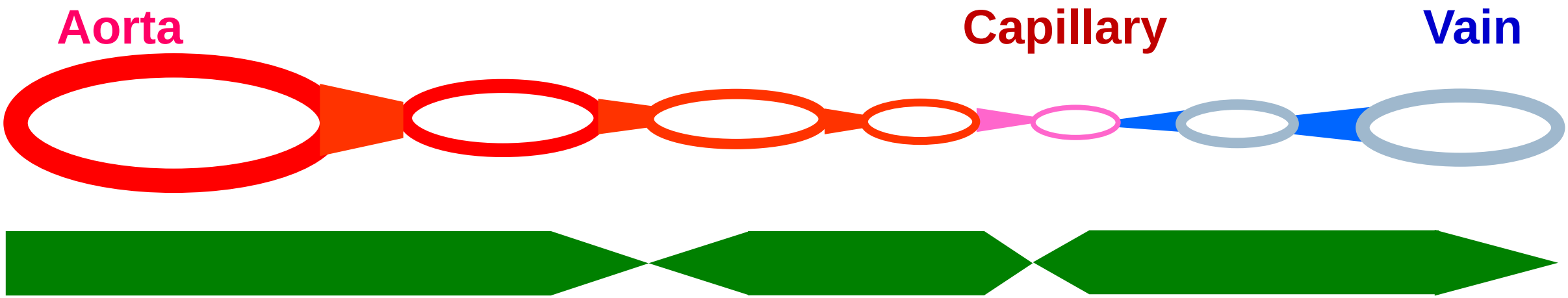
Goodpasture syndrome

Pathology



Vasculitis

- Vasculitis is a group of diseases (idiopathic or primary) characterized by inflammation of blood vessels.
- The classification is based on the size of the vessels, the histopathological manifestations, the clinical symptoms.



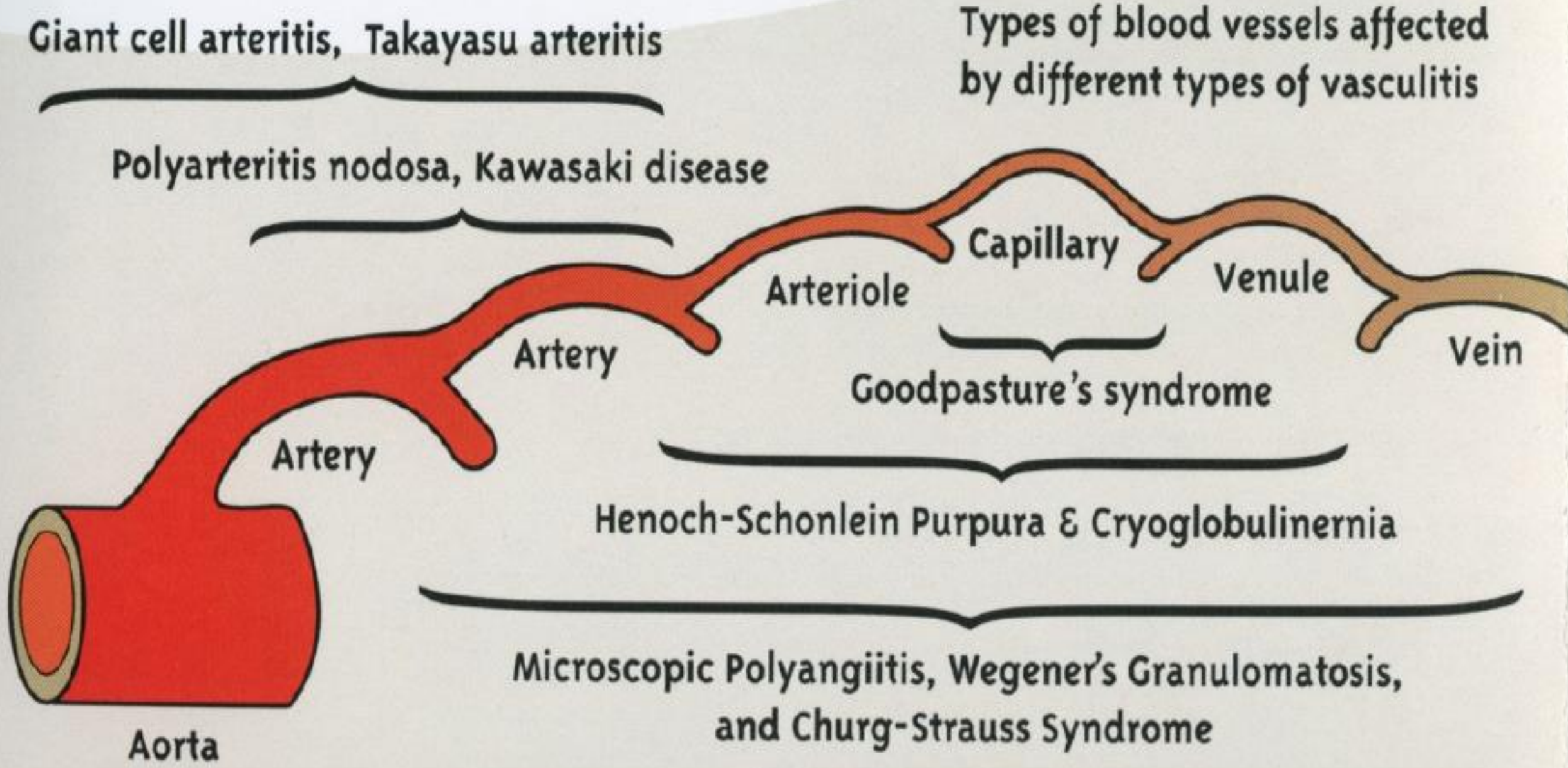
Large vessels	Medium vessels	Small vessels
Giant cell arteritis	Polyarteritis nodosa	Granulomatous polyangiitis
Takayasu arteritis	Kawasaki disease	(Wegener granulomatosis)
		Microscopic Polyangiitis
		Eosinophilic Polyangiitis
		(Churg-Strauss syndrome)
		Henoch-Schönlein Purpura
		Isolated Cutaneous Vasculitis

Vessels Caliber could determine:

Symptoms & signs

Diagnostics Metods

Types of blood vessels affected by different types of vasculitis



Vasculitis = Inflammation of blood vessels

Blood vessel lesion

Thickening of the vascular wall

Narrowing of the lumen or occlusion

Ischemia of tissue or organ

Damage to the vascular wall

Thinning of the vascular wall

Formation of aneurysm or rupture of the vascular wall with hemorrhage in the tissue

Necrotizing systemic vasculitis

A group of inflammatory and necrotizing vascular lesions affecting multiple organs

- lung
- heart
- pancreas
- central nervous system
- skin
- kidney (glomeruli)

Polyarteritis nodosa

Medium vessels

Extrarenal manifestations

- ✓fever
- ✓various skin lesions
- ✓polyarthralgia
- ✓gastrointestinal symptoms
- ✓peripheral neuritis

Polyarteritis nodosa

Renal manifestations

- Malignant hypertension
- Proteinuria
- Hematuria
- Alteration of renal function

Prognosis

the condition is severe - frequent vascular complications in the affected organs

Polyarteritis nodosa

Biological data

- leukocytosis
- eosinophilia
- ↑ ESR
- ↑ C-reactive protein
- ↑ CIC
- ↓ C_3
- Viral markers (HBV)
- ↑ ANCA

Pathology

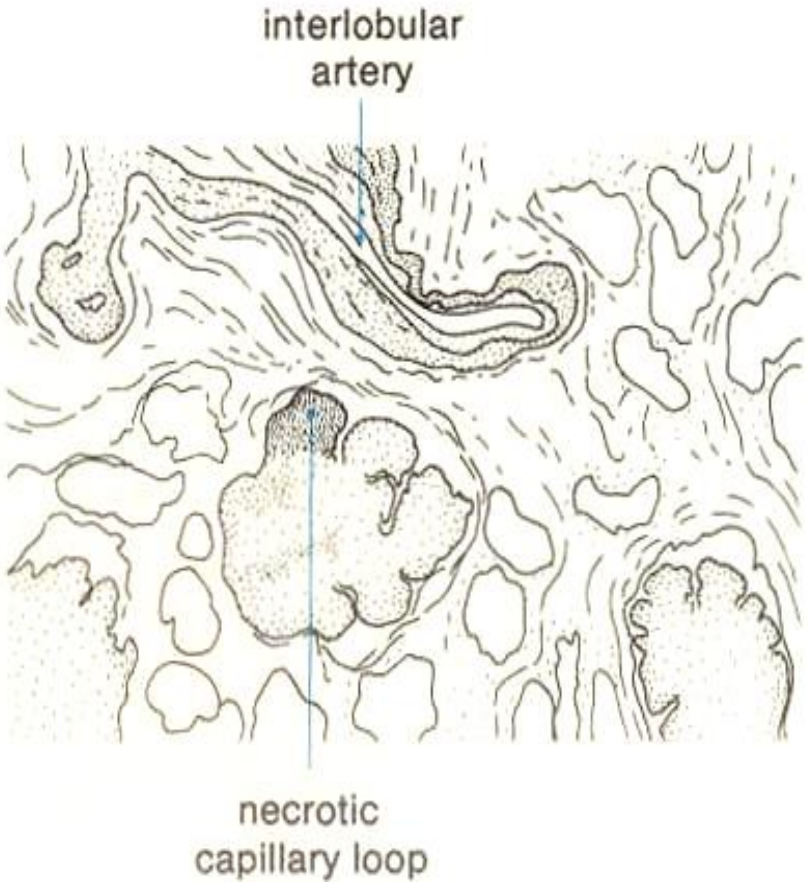
- Necrotizing GN, with extra-capillary proliferation
- Proliferative segmental or diffuse GN
- Fibrinoid necrosis of the interlobular and arcuate arteries

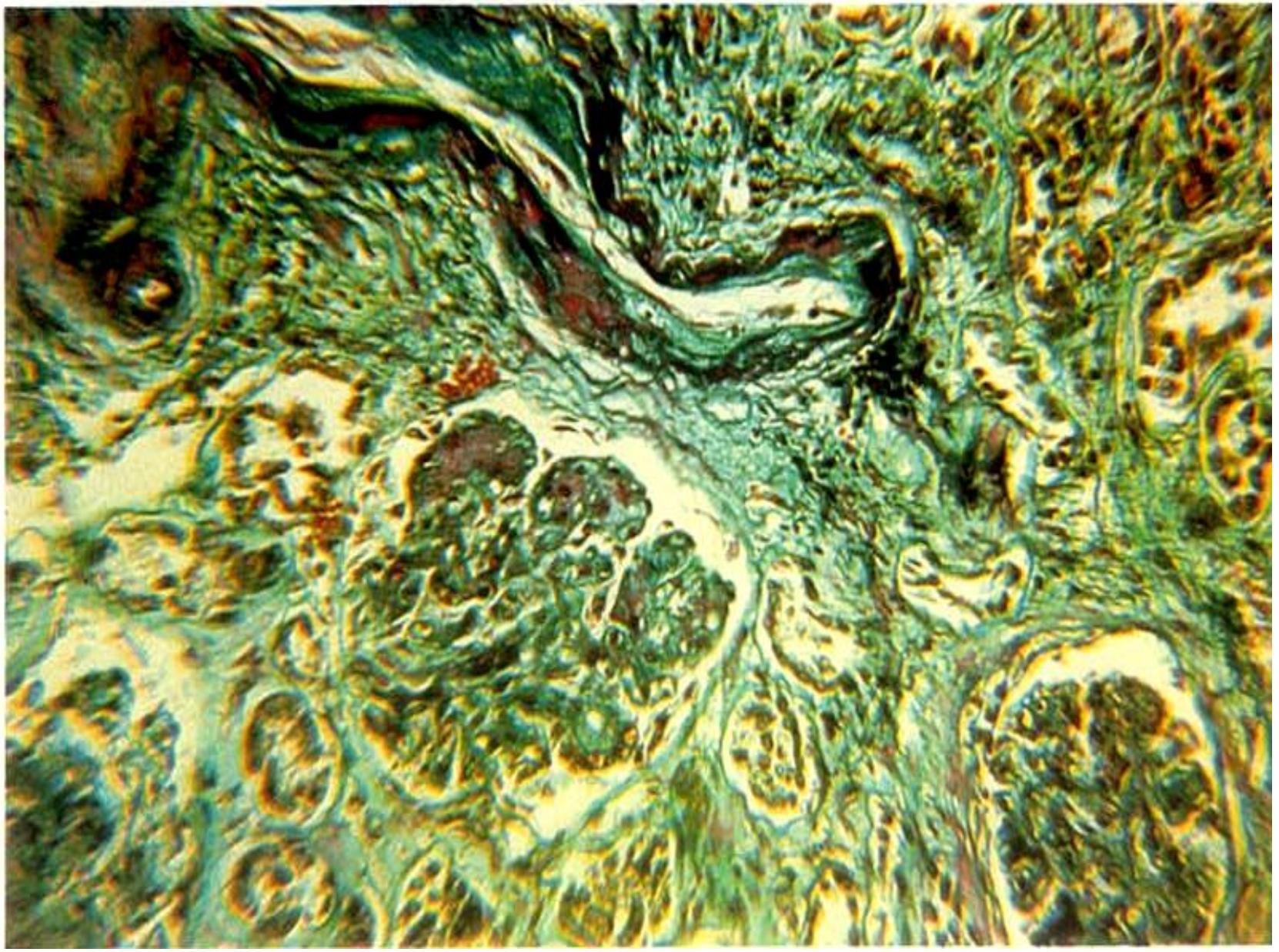
Angiography

- microaneurysms of renal vessels

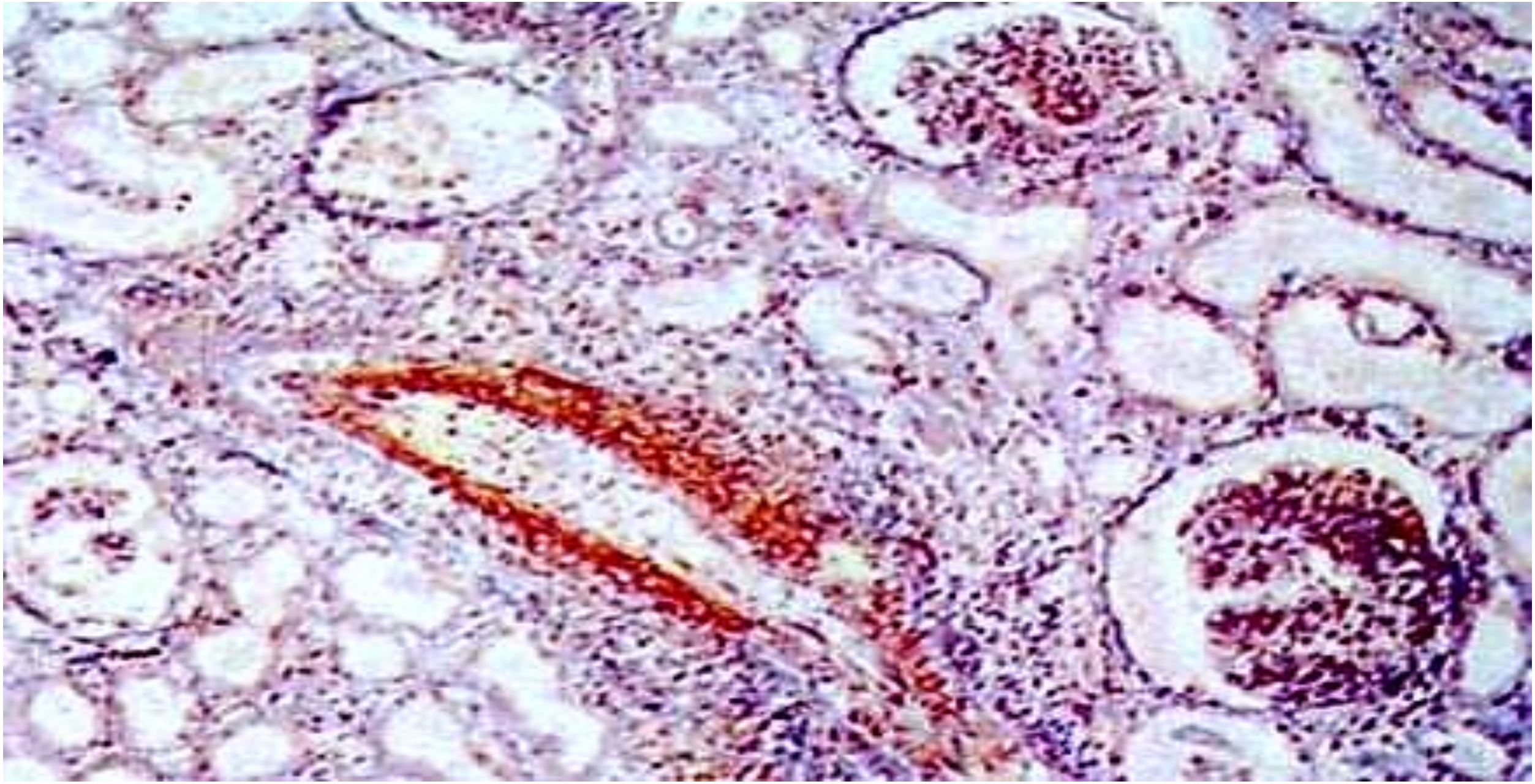
Polyarteritis nodosa

Fig. 8.14 Histological section of kidney in polyarteritis nodosa showing a major interlobular vessel with evidence of arteritis in its wall. Note focal glomerulonephritis. Masson trichrome stain, light-green counterstain.

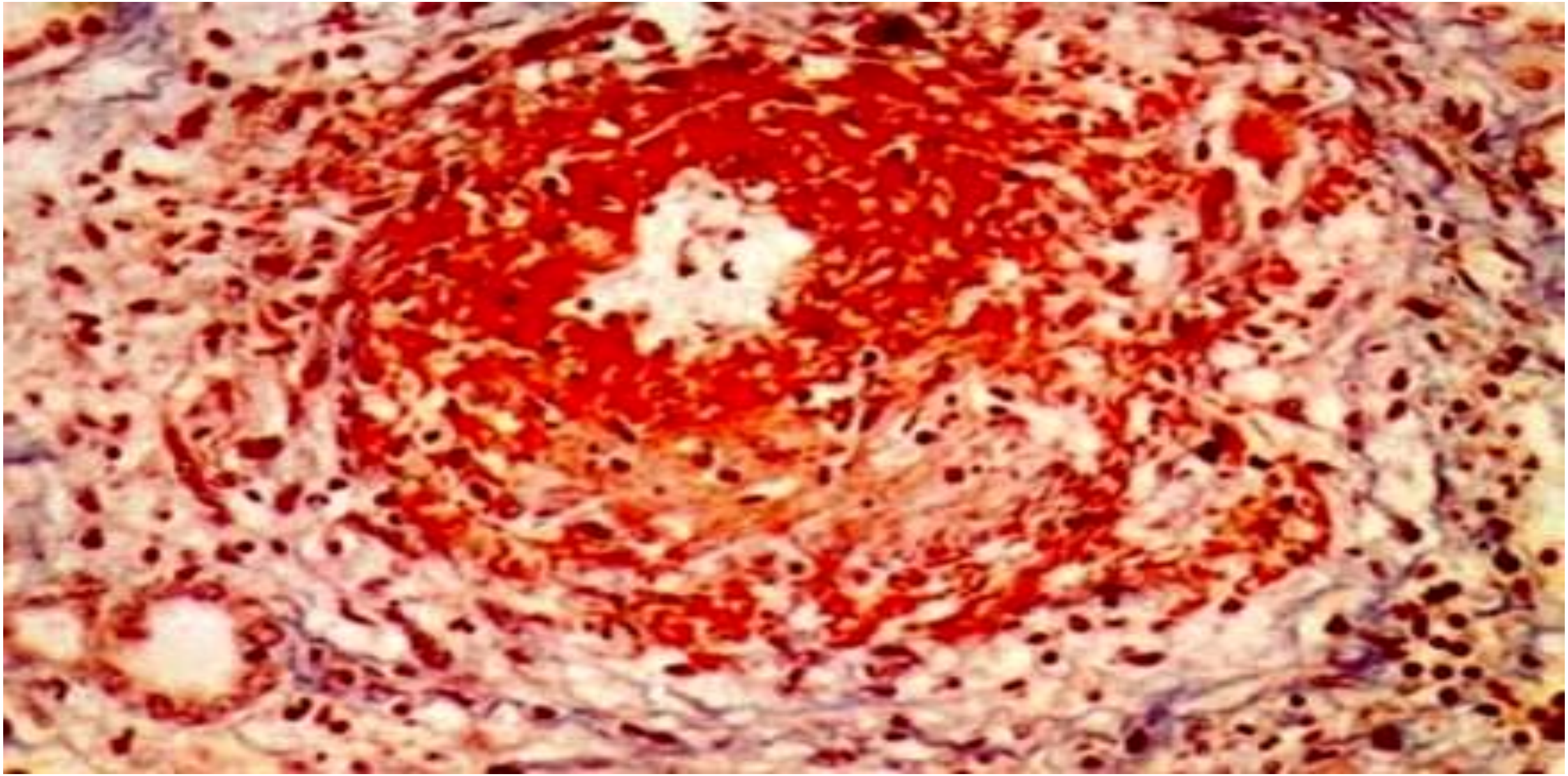




Polyarteritis nodosa



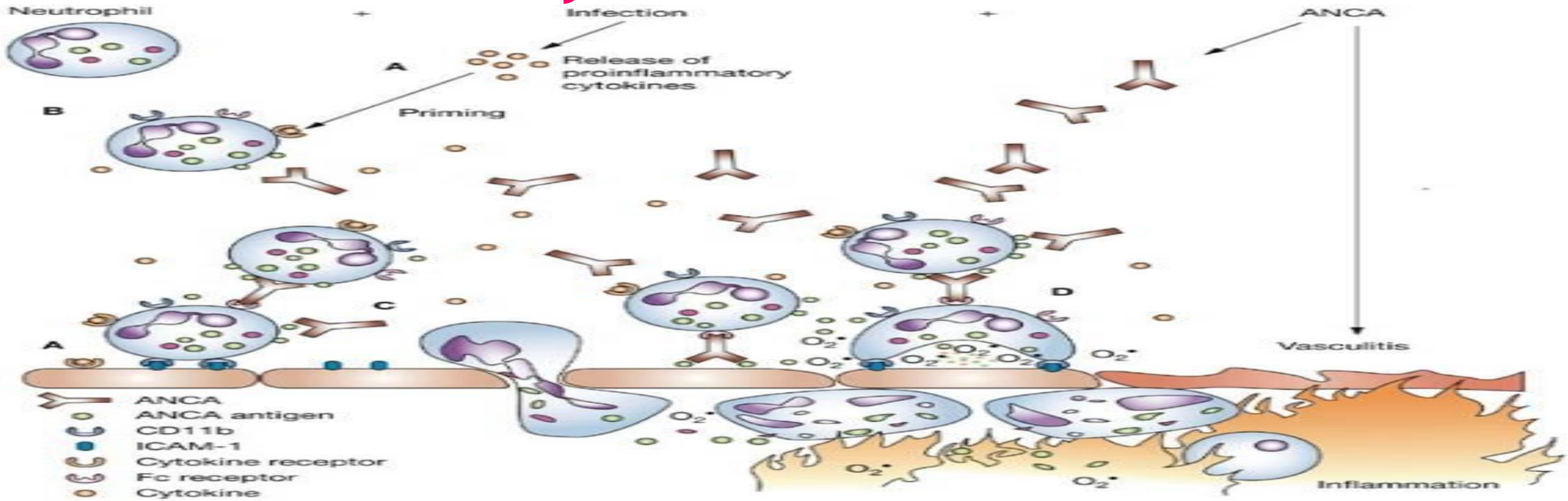
Polyarteritis nodosa



ANCA-associated vasculitis

- Wegener granulomatosis
- Microscopic polyangiitis
- Renal limited vasculitis
- Churg-Strauss Syndrome

- Histological similarities
- ANCA's contribution to their pathogenesis
- Similar response to immunosuppressive treatment



Nat Clin Rheumatol 2006; 2: 661-670

Microscopic polyangiitis

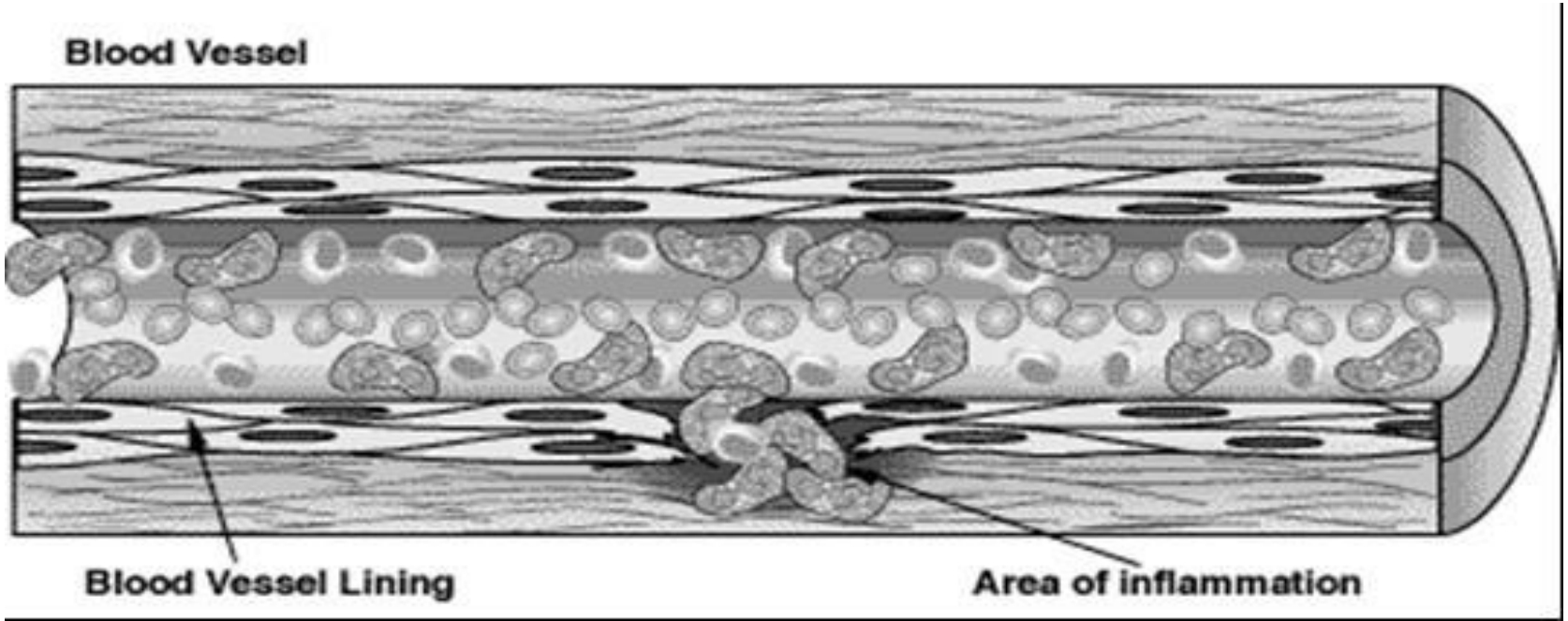
- MPA - granulomatous necrosis systemic vasculitis, with reduced deposits of immunoglobulins (pauci-immune), which electively interest microscopic caliber vessels - arterioles, capillaries, venules, but with possible interest of small and medium caliber arteries.
- It leads to glomerulonephritis and renal failure

Pauci-immune necrotizing vasculitis (MPA)

- Presence of autoantibodies to the neutrophil cytoplasmic constituents
- ANCA: Anti-neutrophil cytoplasmic antibodies
- Neutrophils are the main effector cells of MPA lesions

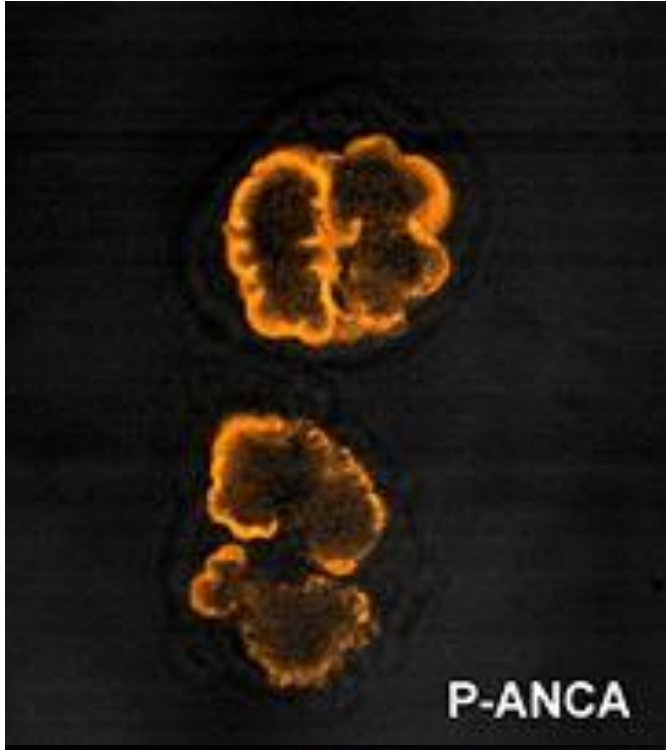
Pathogenetic Mechanisms

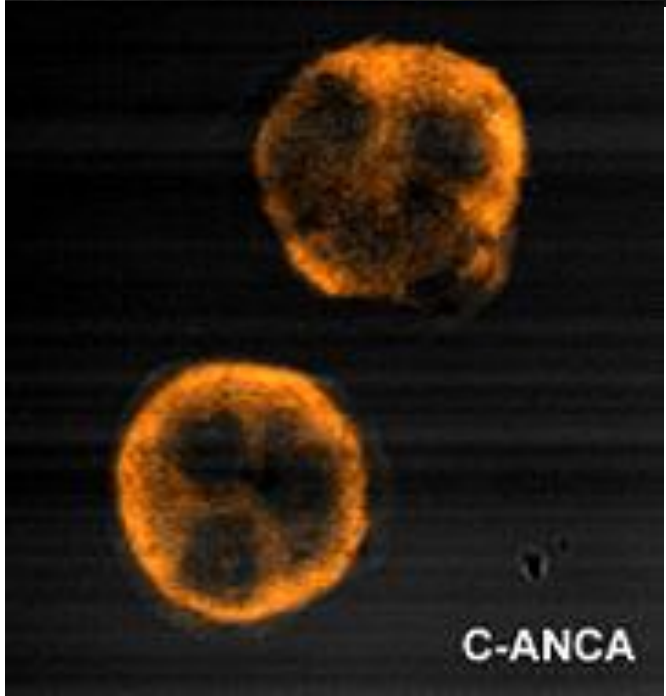
- PR-3 and MPO are mobilized on the surface of PMN and monocytes activated by TNF-α or IL-1
- They react with ANCA circulating through the blood
- The PMN degranulate and induce local inflammation
- The way in which ANCA are initially produced is less known



ANCA

- Anti-neutrophil cytoplasmic antibodies directed against neutrophils and monocytes
- The P-ANCA target (*perinuclear stai*ning) is MPO myeloperoxidase (MPA)
- The C-ANCA target (*cytoplasmic staining*) is PR3 proteinase 3 (WG)
- ANCA attachment may induce neutrophil activation resulting in endothelial cell damage.





ANCA

- **MPA:**
  - 60% positive with MPO-ANCA
  - 30% positive with PR3-ANCA
- **Wegener Granulomatosis:**
  - 70-80% positive with PR3-ANCA
  - 10% positive with MPO-ANCA
- **Few are ANCA negative**

Clinical manifestations of MPA

- Cardinal sites - lungs and kidneys
- Lack of granulomatous component but with clinical manifestations similar to WG
- There are no formal ACR criteria
- The classic pulmonary presentation is diffuse alveolar hemorrhage

MPA: clinical signs

- Prodromal phase of several months with constitutional symptoms, including polymyalgia
- Macroscopic hematuria, edema, oliguria (symptoms of glomerulonephritis)
- Renal involvement >80%
- Body weight loss >70%
- Skin lesions >60%
  - *Palpable purpura 41% & Livedo reticularis 12%*
- Neurologic involvement 60%
- Fever 55%
- Myalgia 50%
- Hemoptysis - 11%

MPA: clinical signs

The onset of the disease may be insidious, but it is often acute.

- glomerulonephritis (80%) may be rapidly progressive → renal failure;
- hemoptysis may be the first symptom of alveolar hemorrhage (12%);
- mononeuritis multiplex;
- Gastrointestinal vasculitis;
- Cutaneous vasculitis.
- the upper airways are not affected and no pulmonary nodules appear. If such manifestations occur, the diagnosis is probably Wegener's granulomatosis.
- features of systemic inflammation.

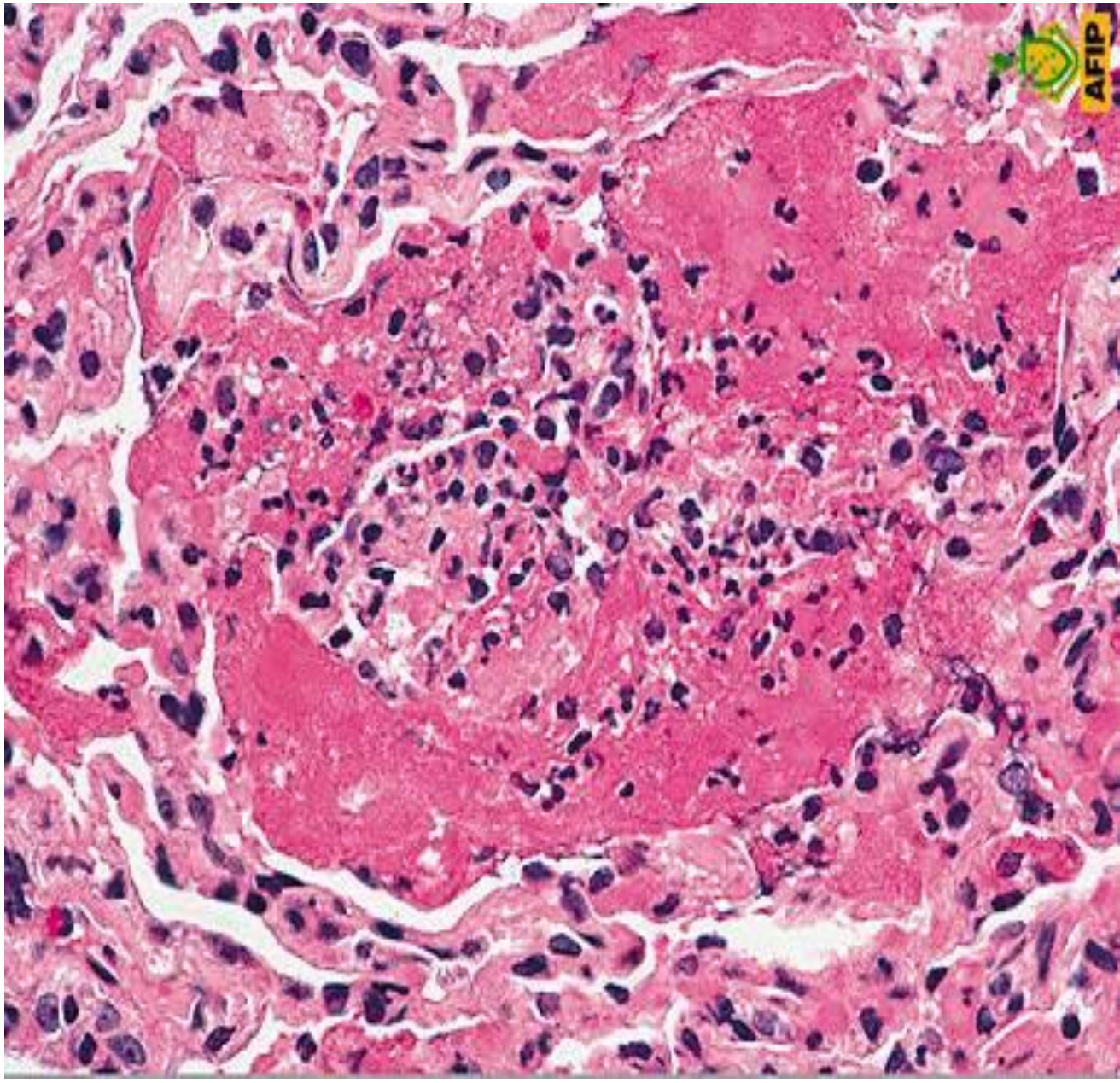
All patients develop rapidly progressive renal failure, with most cases progressing to end-stage renal failure.

Pulmonary impairment: manifests as hemoptysis ranging from blood striations to expectoration with pure blood, dyspnea to severe hypoxemia and anemia.

MPA

Pathology:

Pulmonary hemorrhage (erythrocytes, fibrin in alveolar spaces), neutrophilic capillaritis, polypoid fibrosis slices in the organization.



Evaluation of vasculitis

History

- Complex physical examination
- Drugs: inclusive OTC, supplements etc.

Physical exam

- Provides data on organ involvement, manifestations of some background disease

Laboratory

All cases

Urine - RBC (+), check creatininemia immediately)
Biochemistry (includes creatinine and liver tests)
Hemogram with ESR, CRP

Additional laboratory tests in the presence of manifestations:

Systemic vasculitis
connective tissue disease
Infection
Tumors

Evaluation of vasculitis

Imagistic

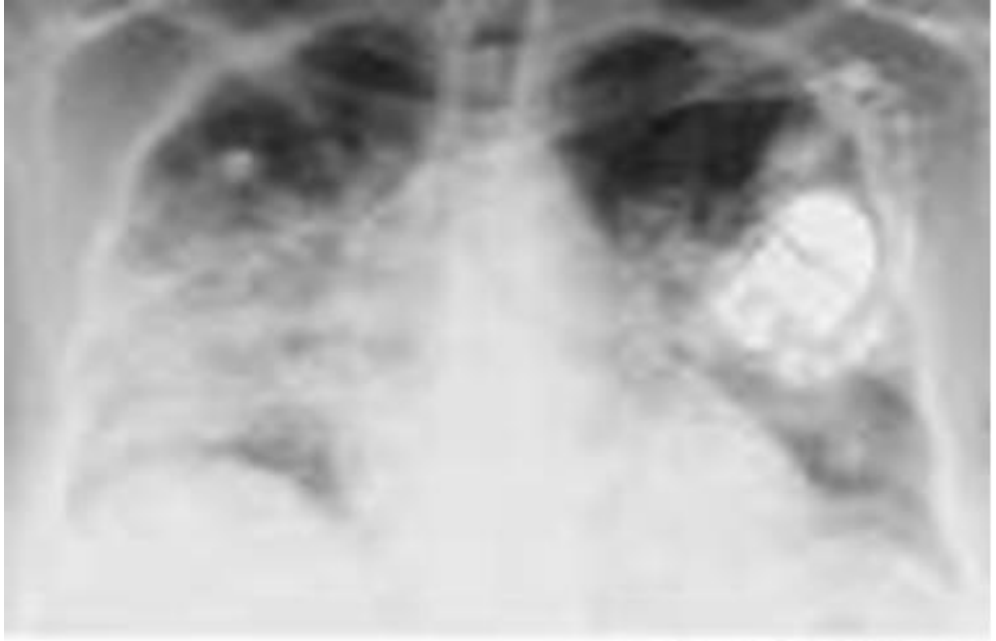
Thorax
(Rg-gr, CT)

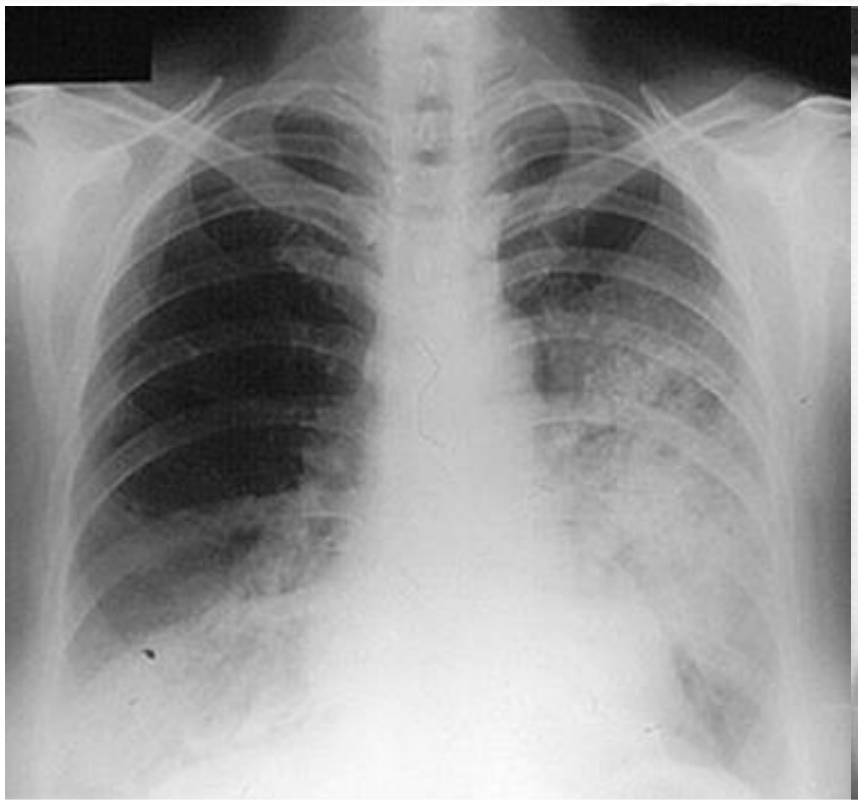
- Performed in all patients with pulmonary symptoms
- In the absence of pulmonary symptoms: if there are other manifestations that suggest systemic vasculitis of small vessels

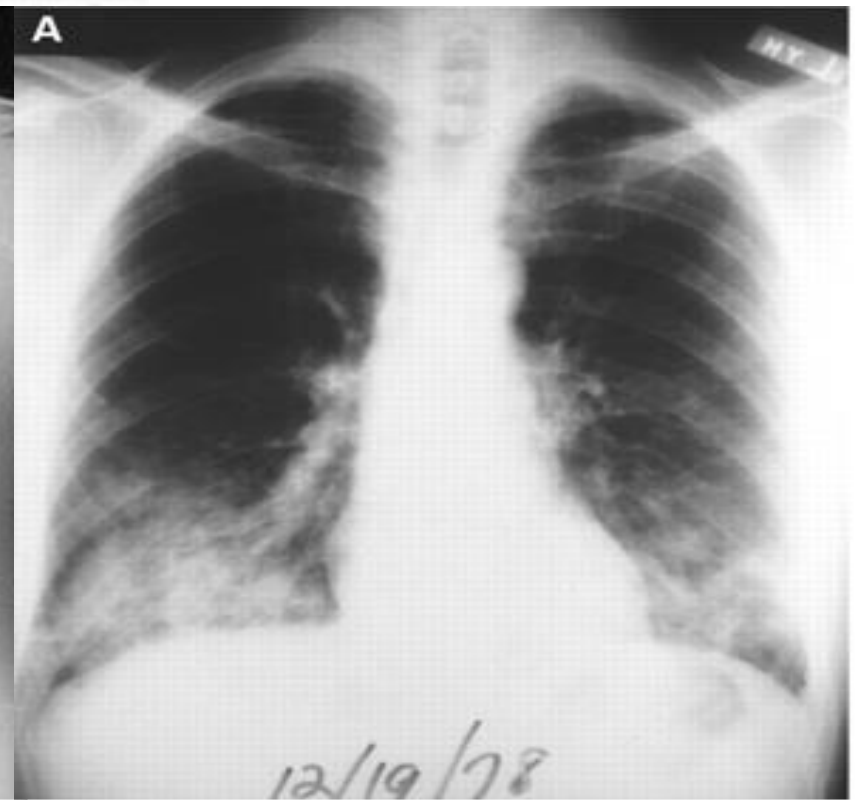
CT, MRI, arteriography of other regions if clinical indications

Biopsy

- Lesions characteristic of vasculitis may be absent
- The skin is usually the best location for biopsy to confirm vasculitis (in the presence of skin lesions)



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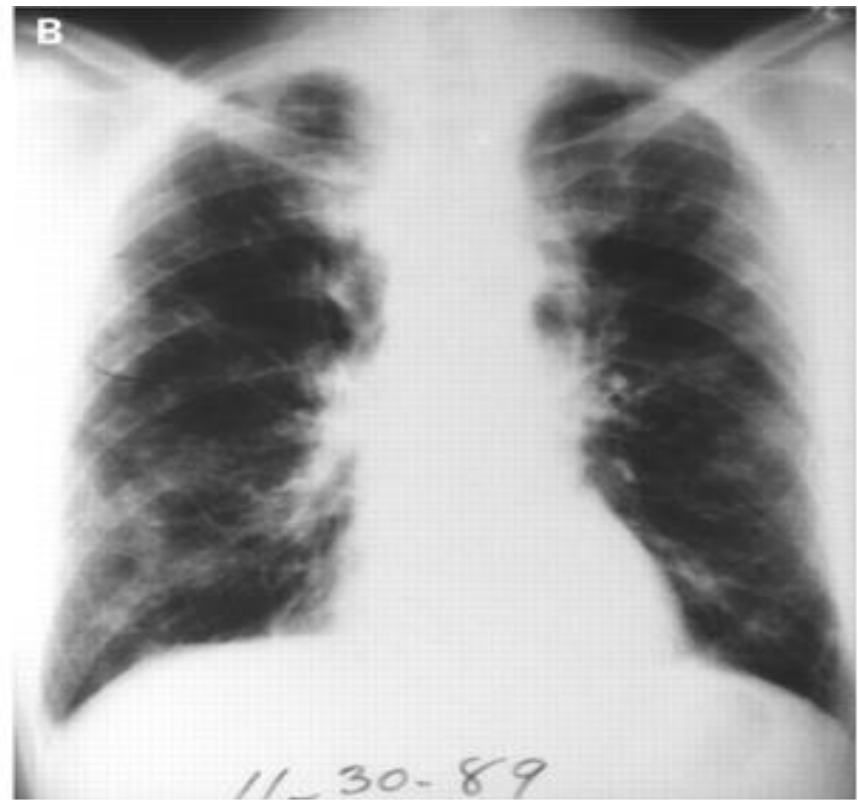
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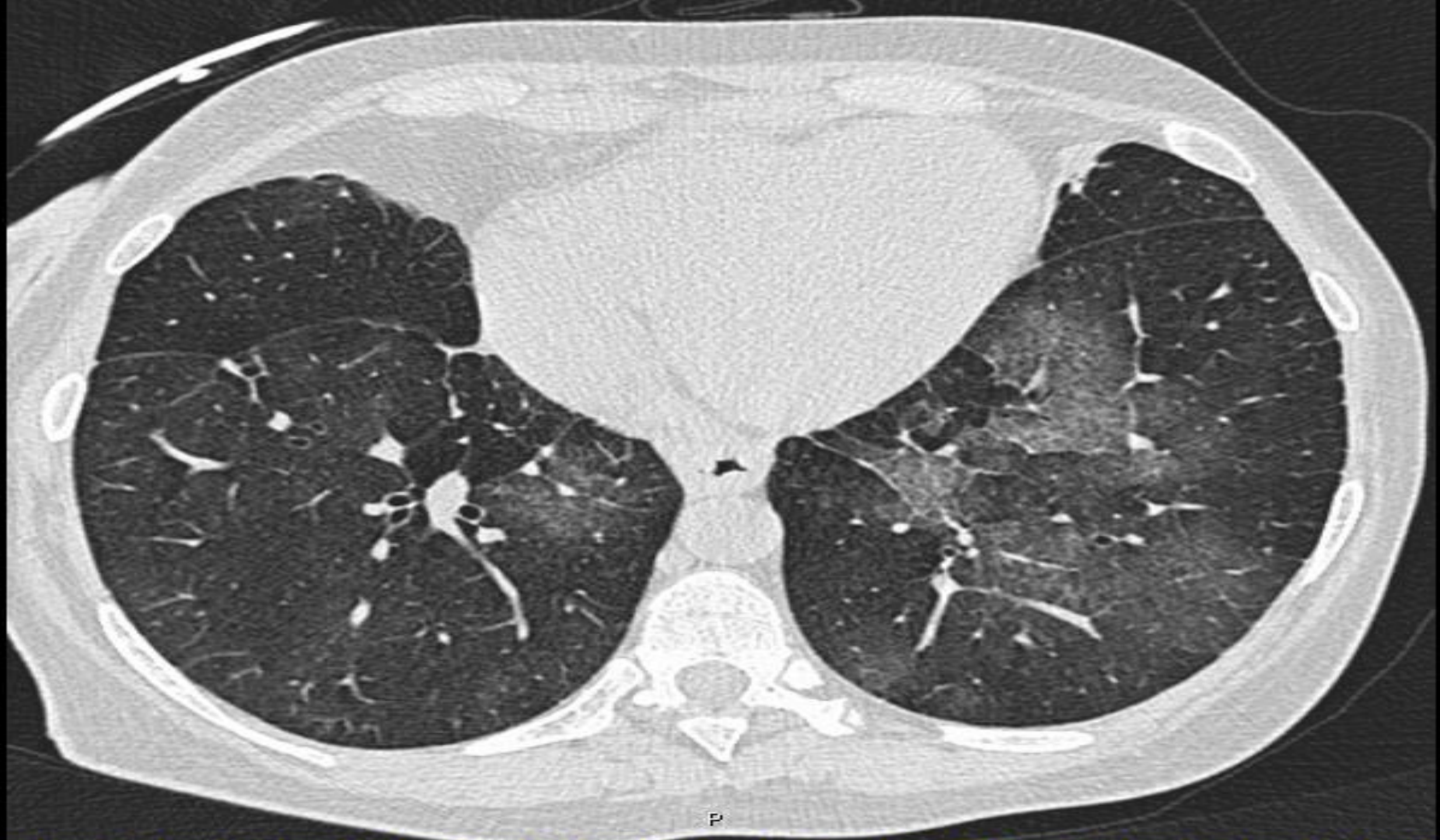
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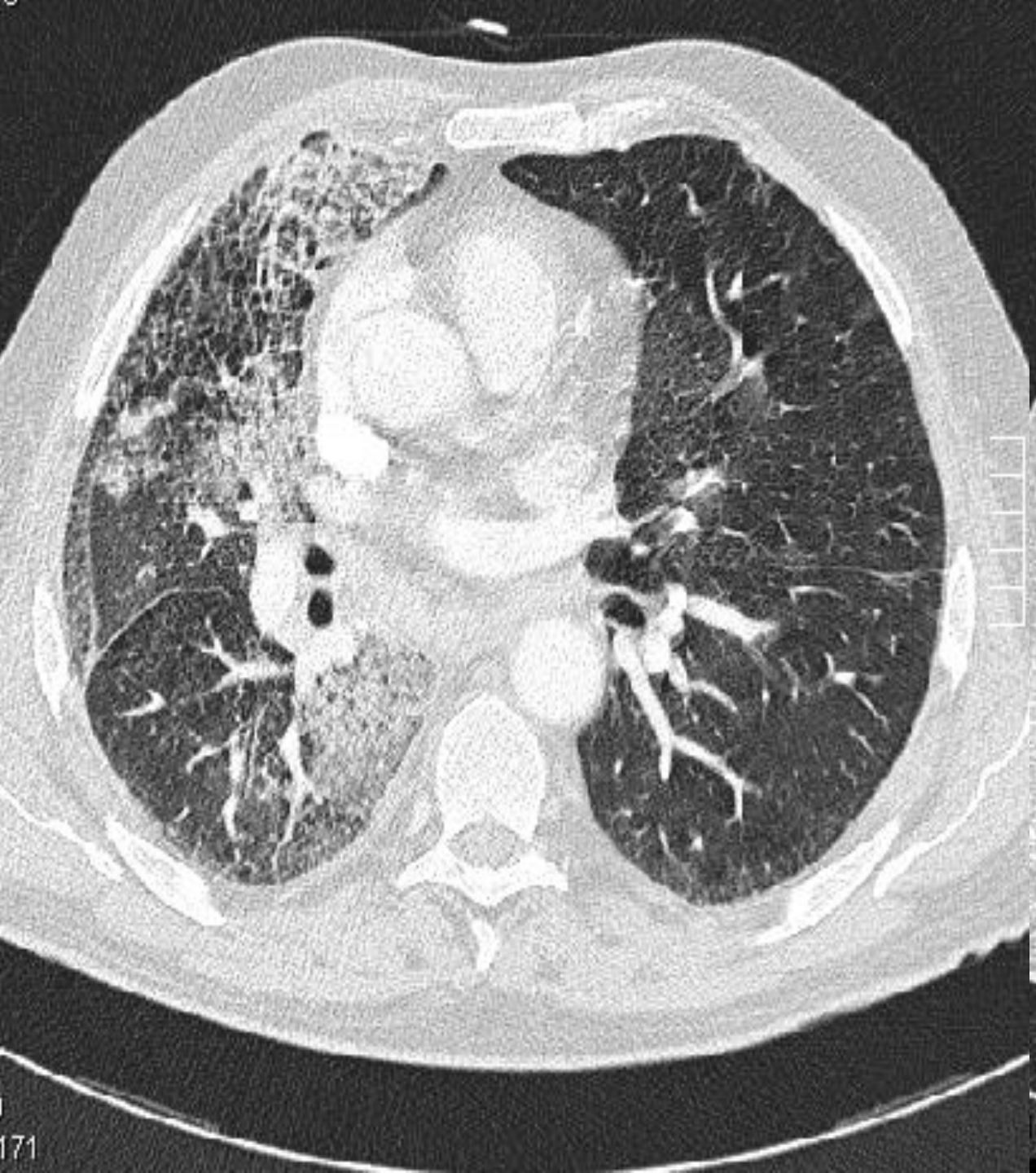
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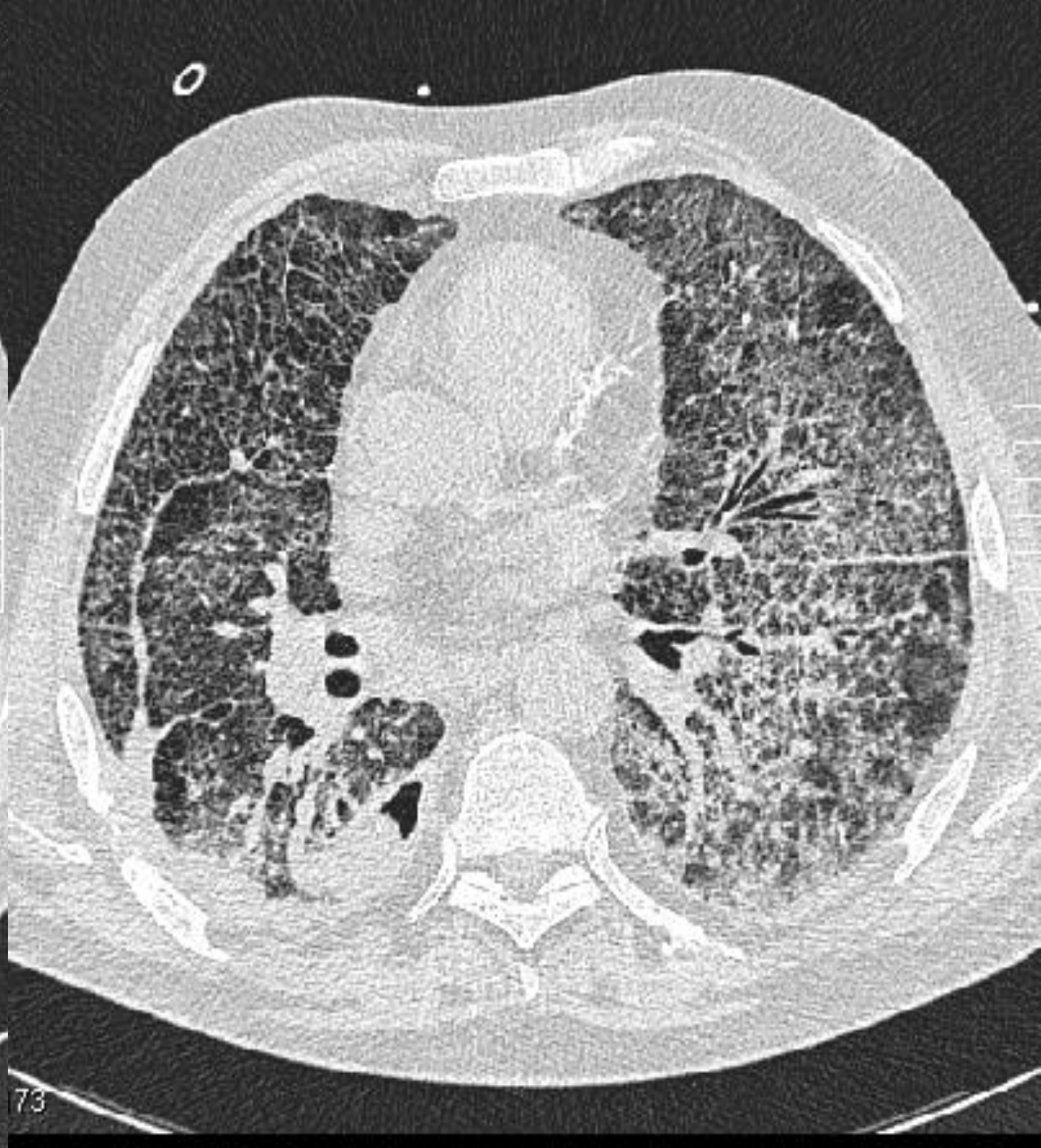
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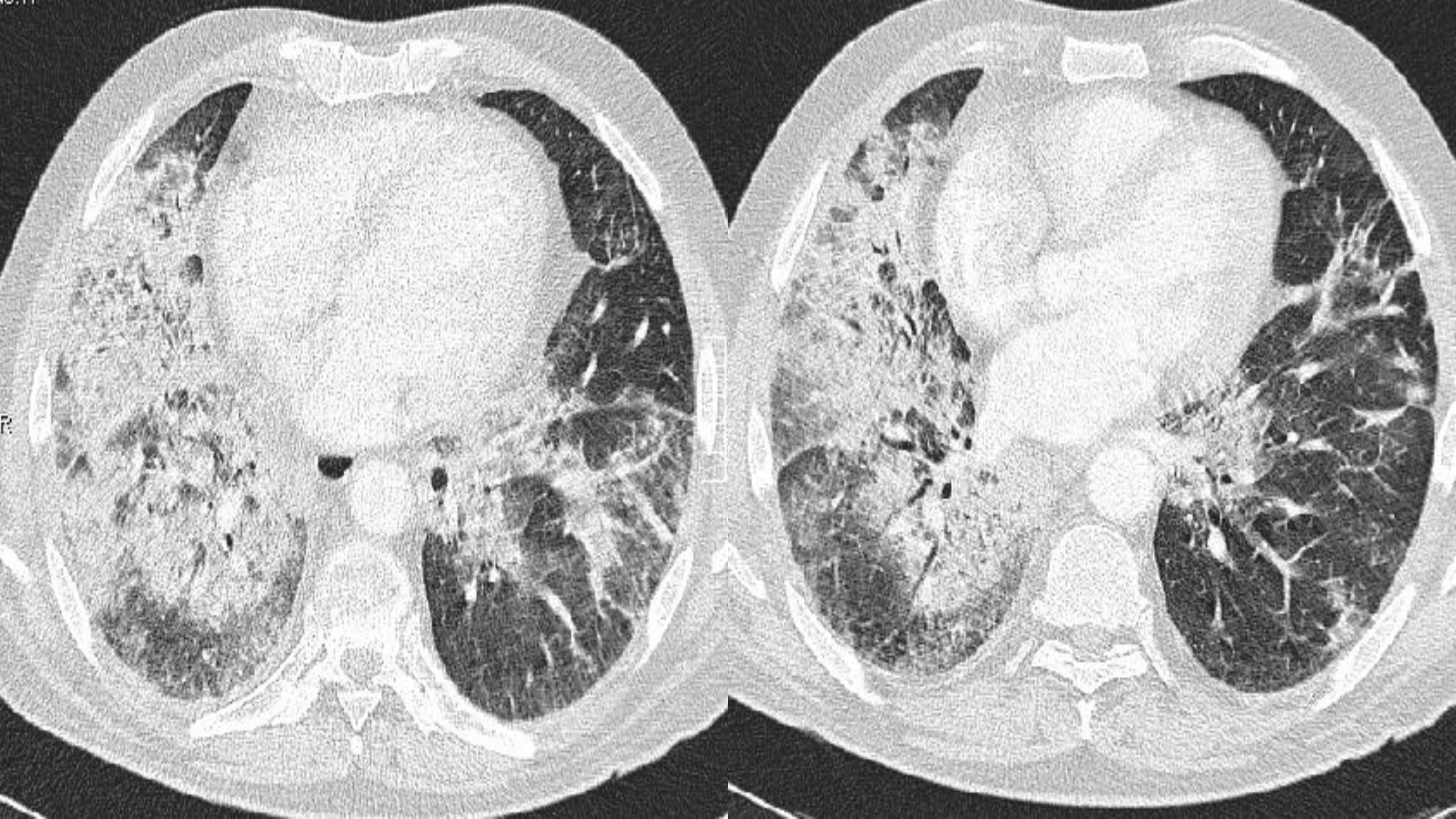


Vasculitis recognition: Suspicion is important

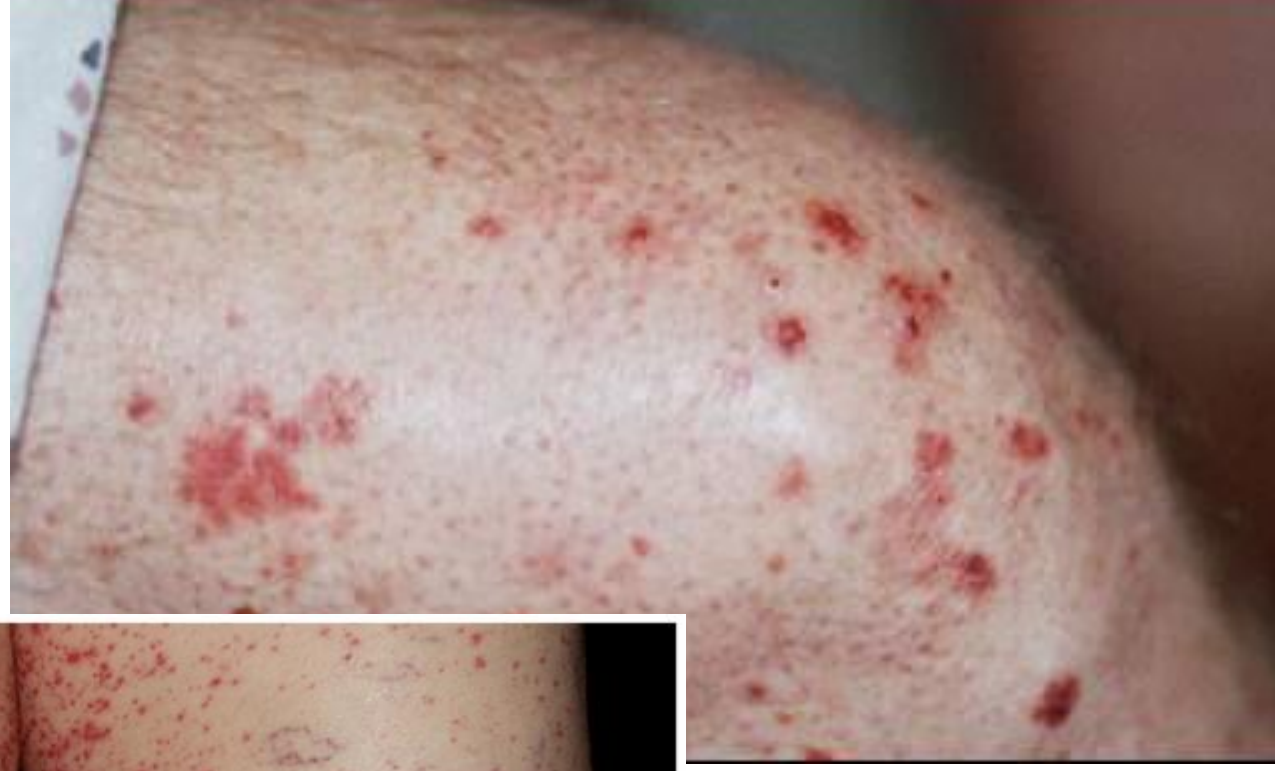
Any manifestations of:

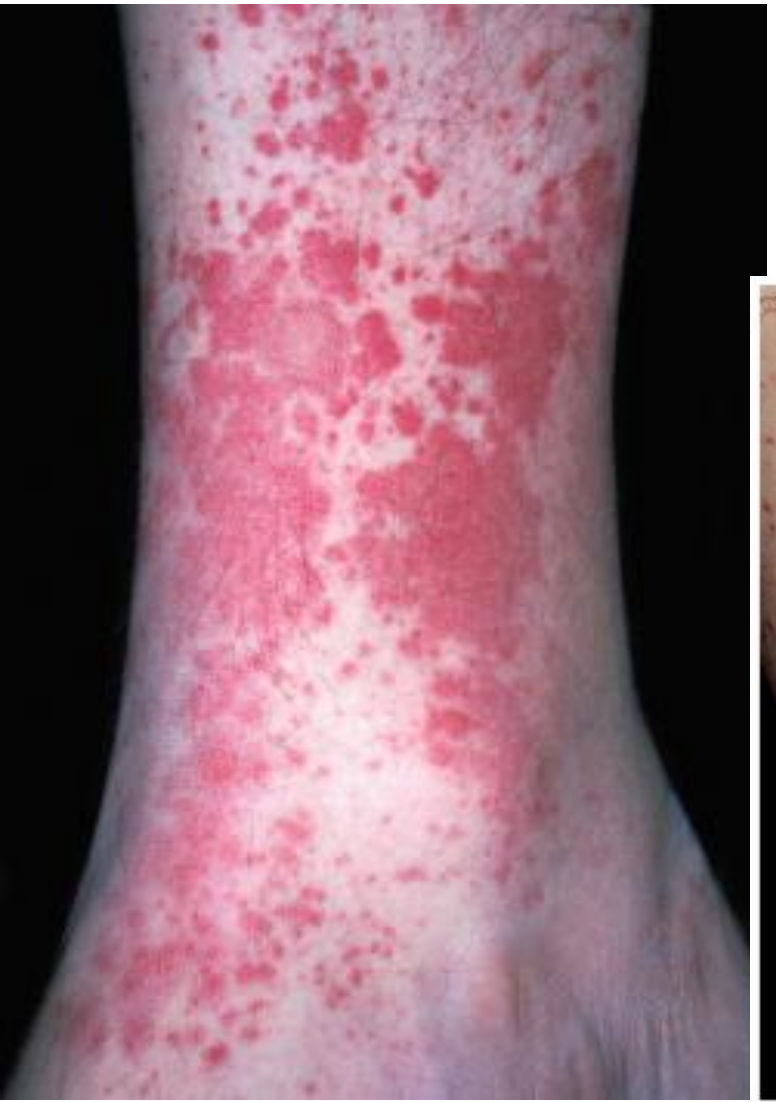
- Palpable purpura
- Pulmonary hemorrhage
- Glomerulonephritis
- Digital ischemia
- Mononeuritis multiplex (hands or plants)

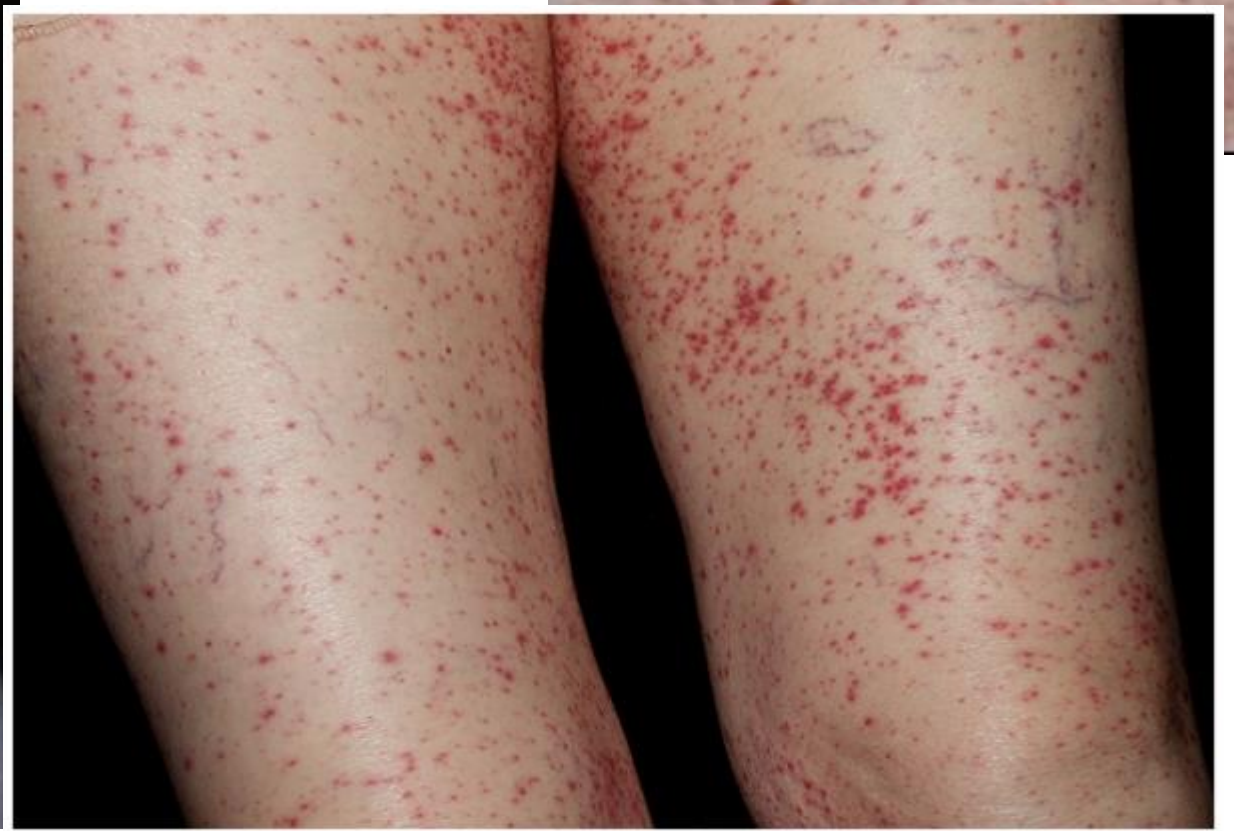
Also to be considered:

- Worsening of sinus symptoms without response to treatment
- Unexplained multisystemic disease
- Unexplained pulmonary infiltrates
- Major progressive major organ dysfunction

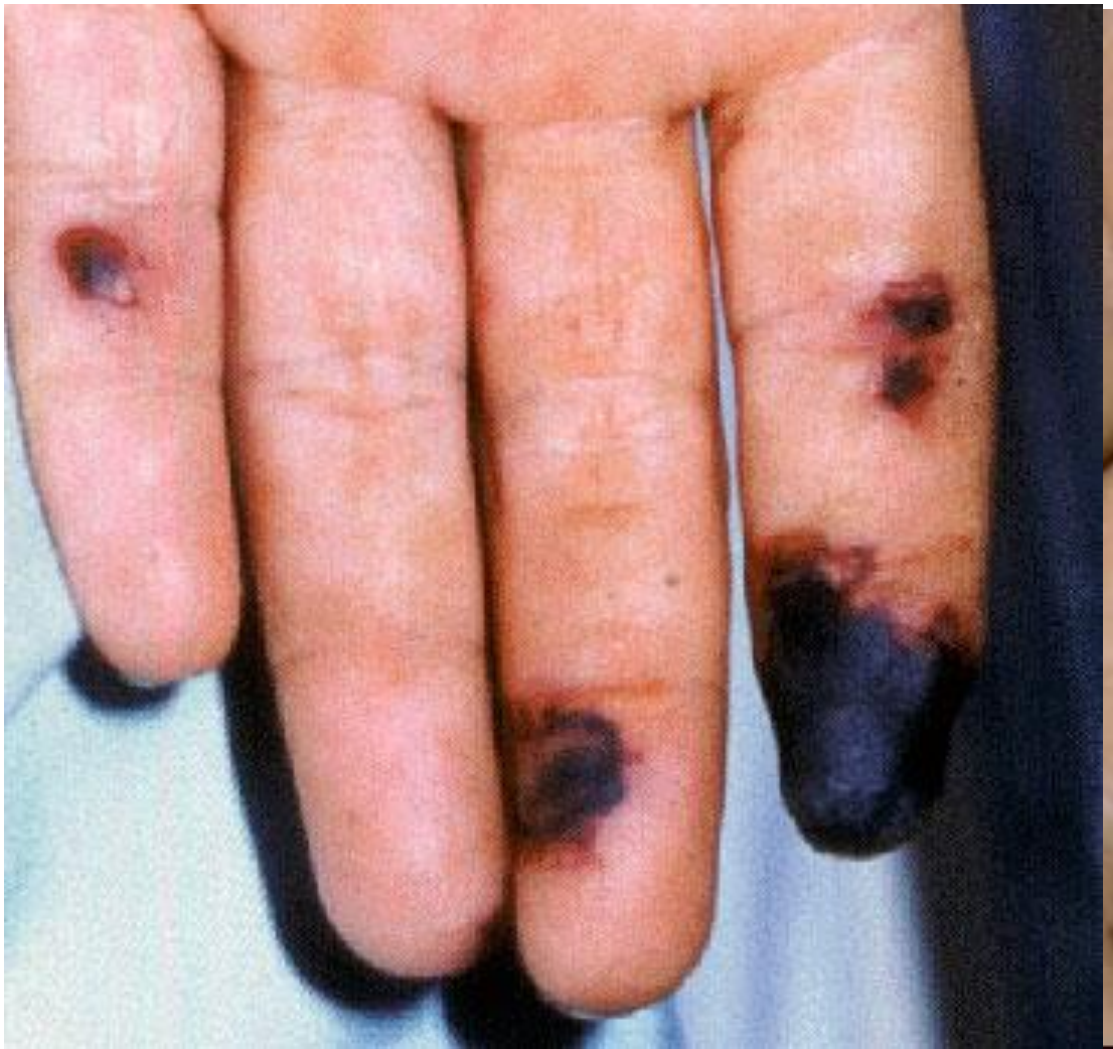
Palpable purpura

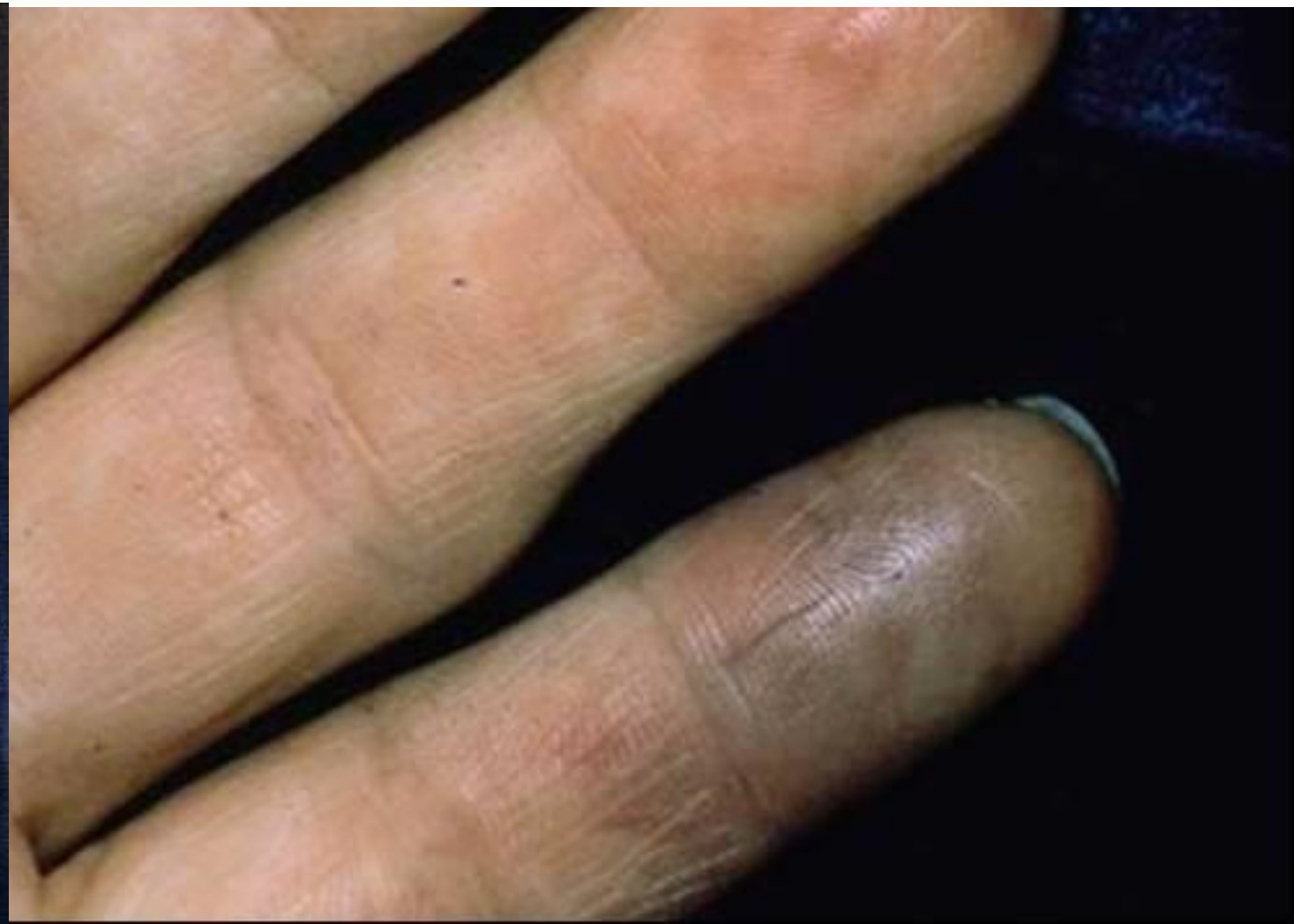






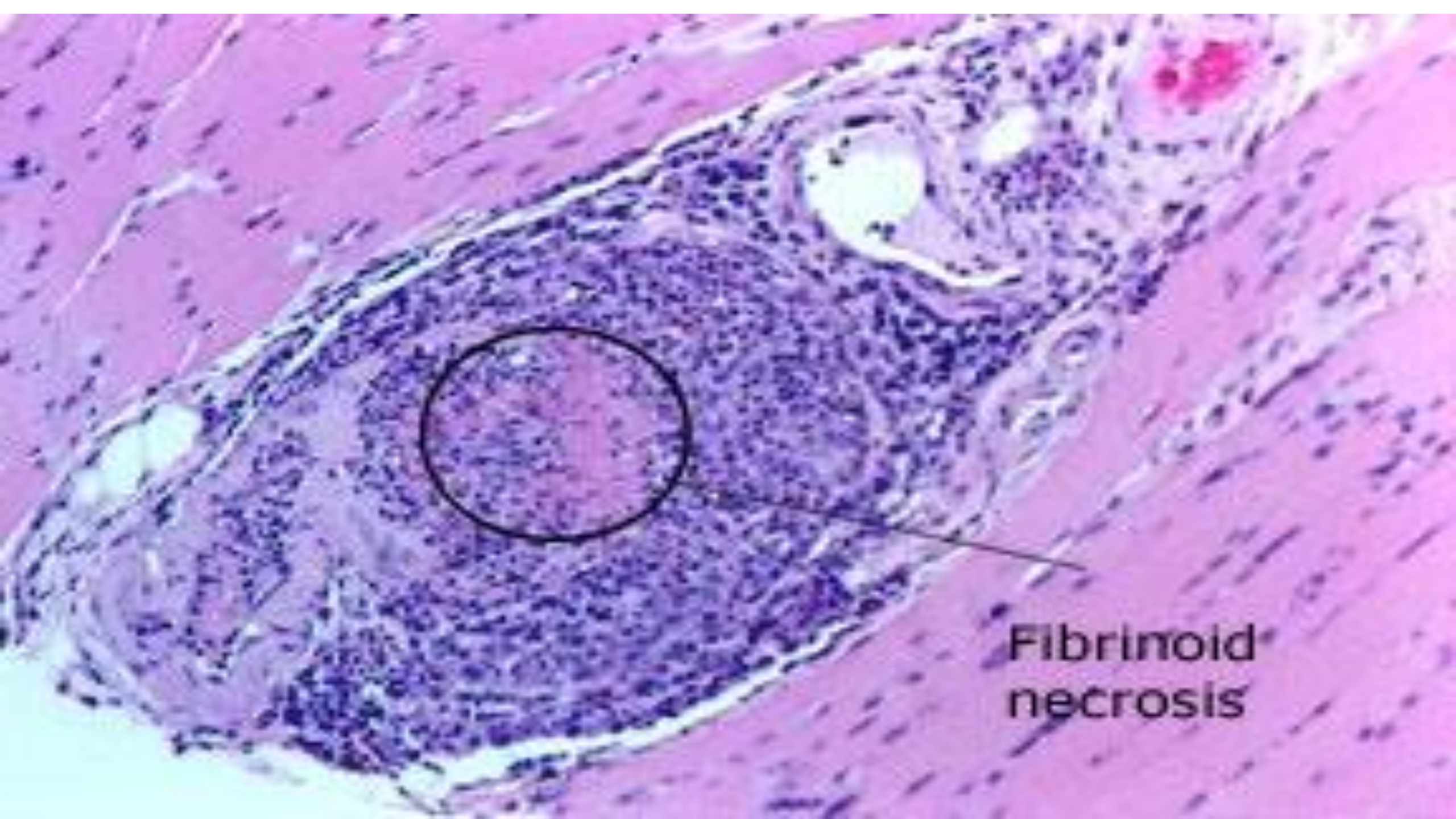
Digital ischemia

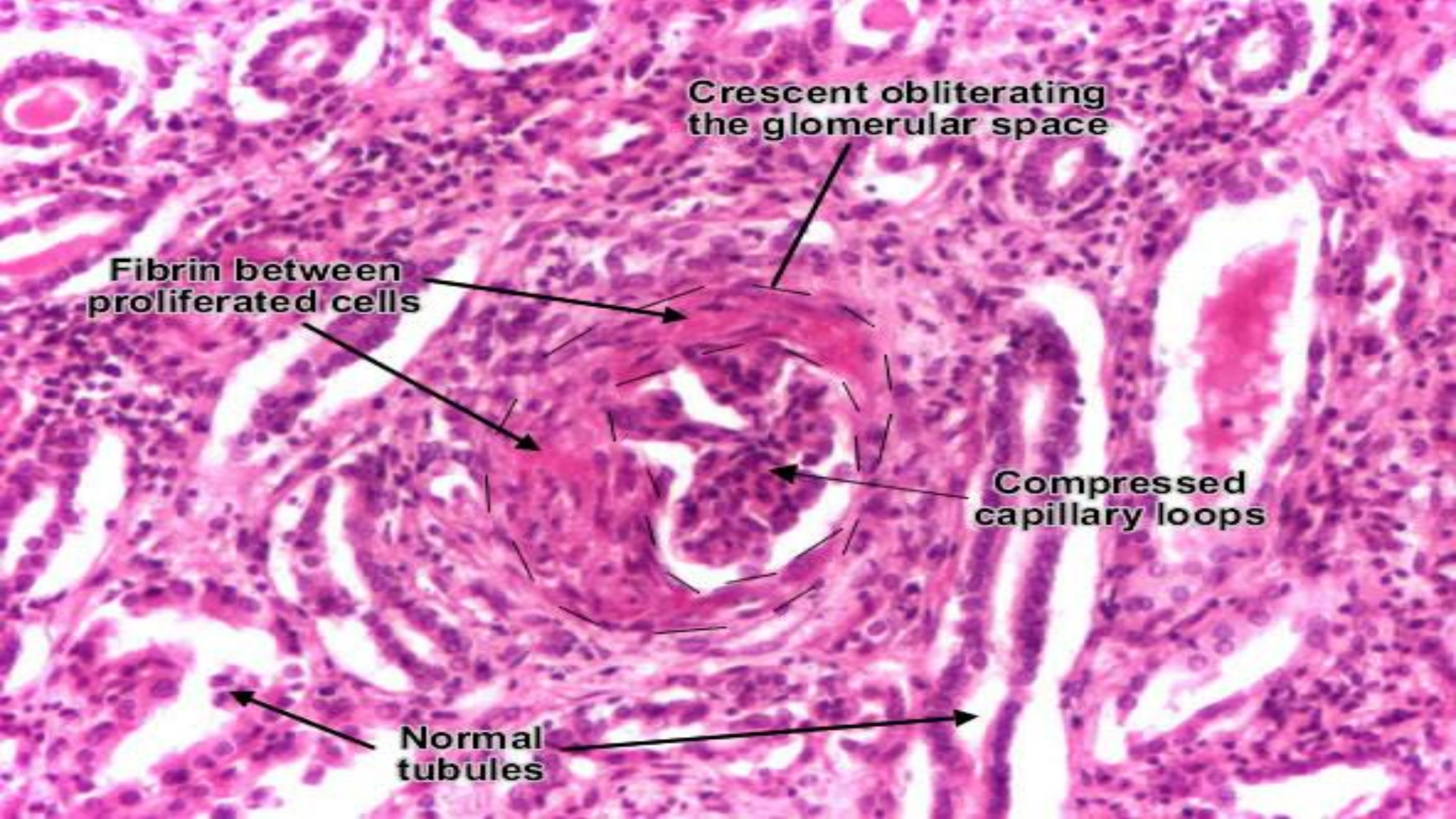


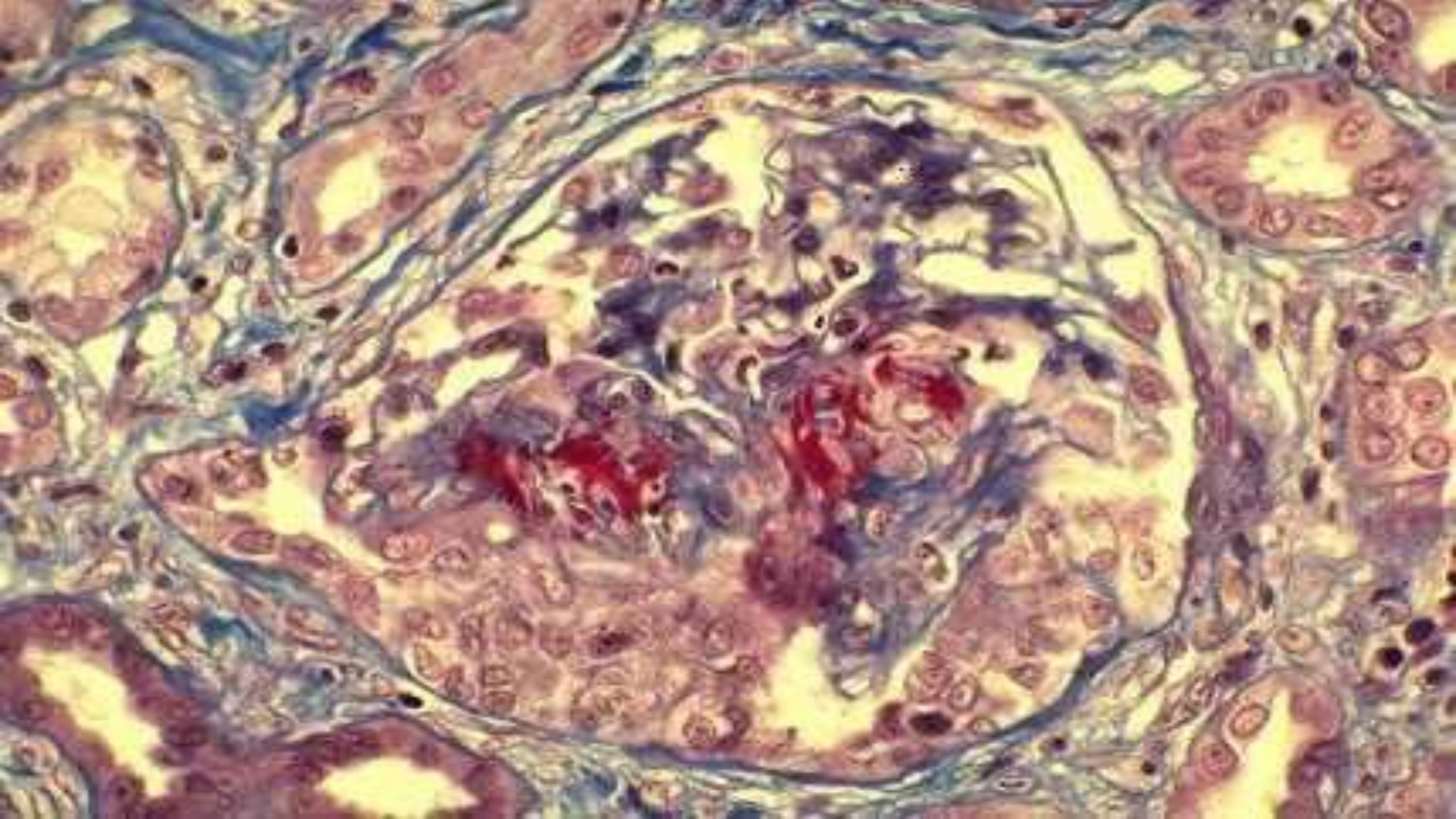


Histopathological examination

- Renal biopsy is the most used; characteristic is the inflammatory lesion that affects the glomerular vessels and less the arterioles and inter-lobular arteries. The histopathological picture is characterized by segmental thrombosis and extra-capillary glomerulonephritis (with crescents in various stages of evolution: cellular and sclerotic), non-cystic (fibrinoid necrosis).
- The poverty of the immunoglobulin deposits and components of the complement system at the glomeruli level defined the pauci-immune character of inflammation.


Fibrinoid
necrosis


Crescent obliterating the glomerular space
Fibrin between proliferated cells
Compressed capillary loops
Normal tubules



Wegener granulomatosis

- ✓ Chronic destructive inflammation of the upper and lower respiratory tract
- ✓ Necrotizing glomerulonephritis and with crescents
- ✓ Granulomatous inflammation
- ✓ Necrotizing vasculitis - small vessels
- ✓ Renal impairment
  - ✓ segmental focal necrotizing glomerulonephritis
  - ✓ extra-capillary proliferation
  - ✓ rapidly progressive glomerulonephritis
- ✓ ANCA test positive at the onset of a suspected vasculitis has increased significance for the diagnosis of Wegener granulomatosis

Wegener granulomatosis

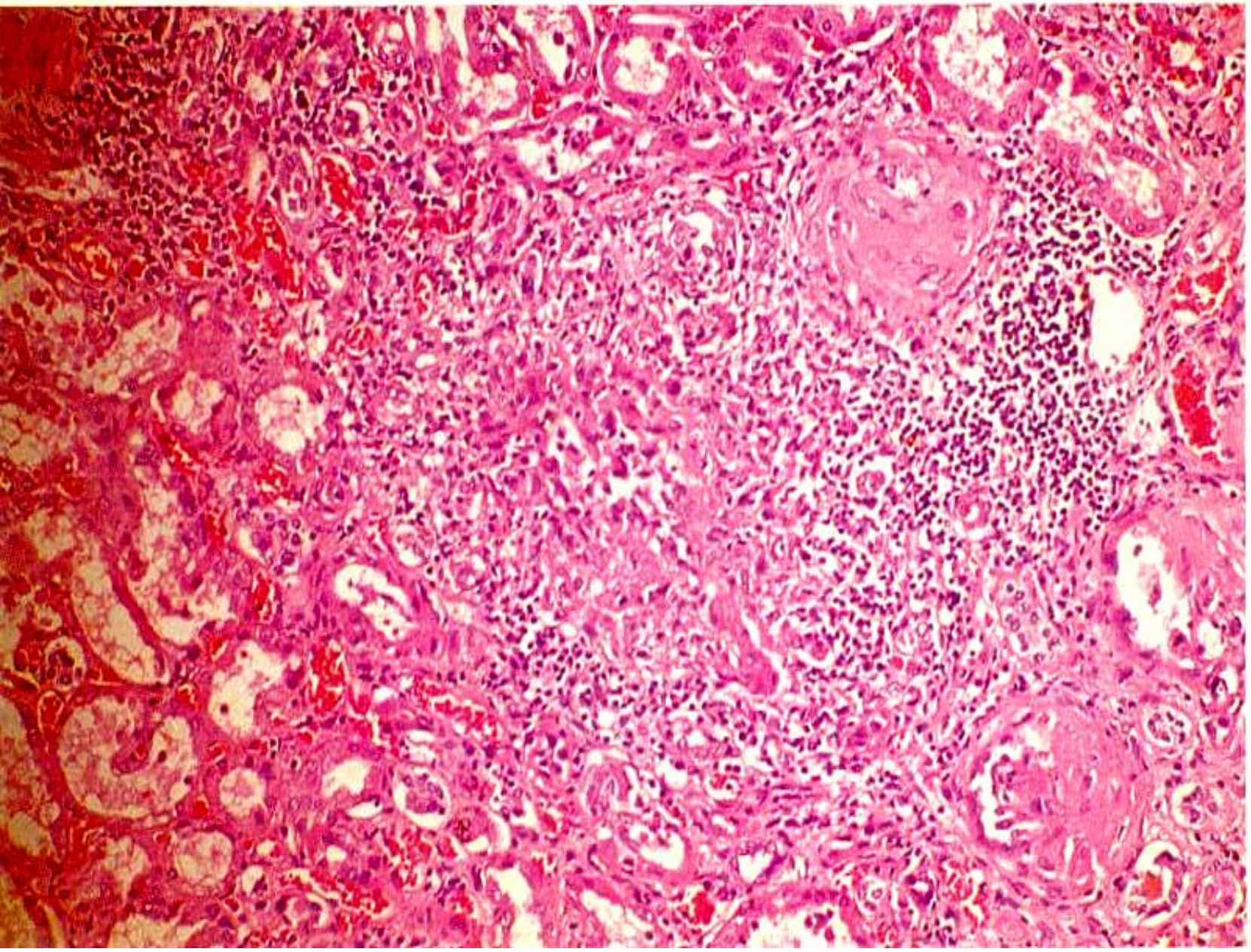
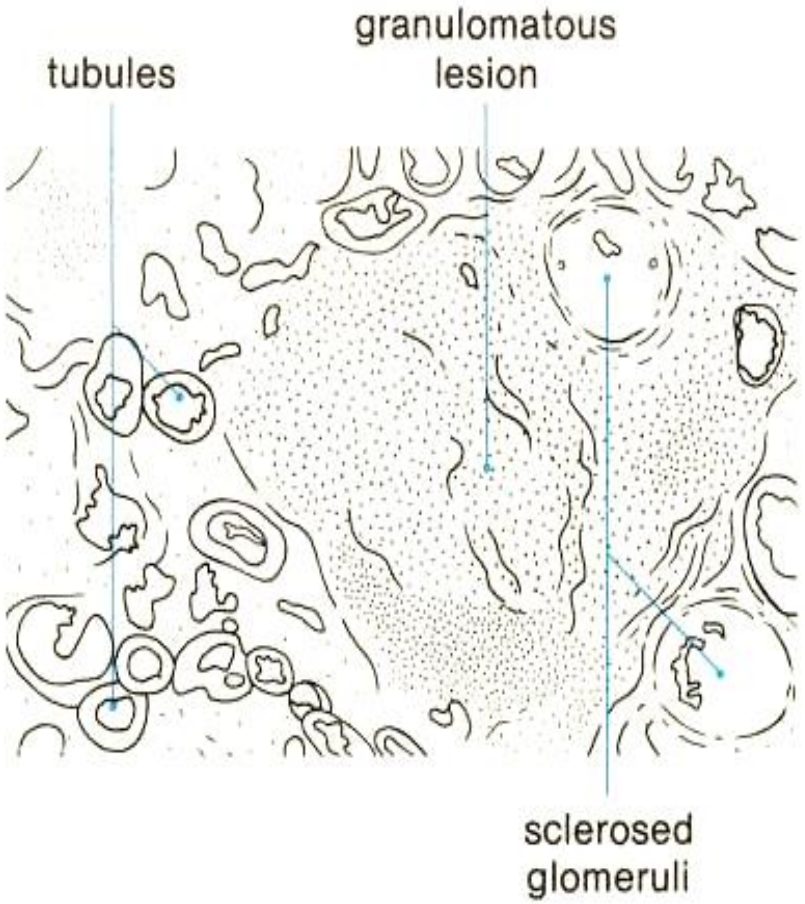
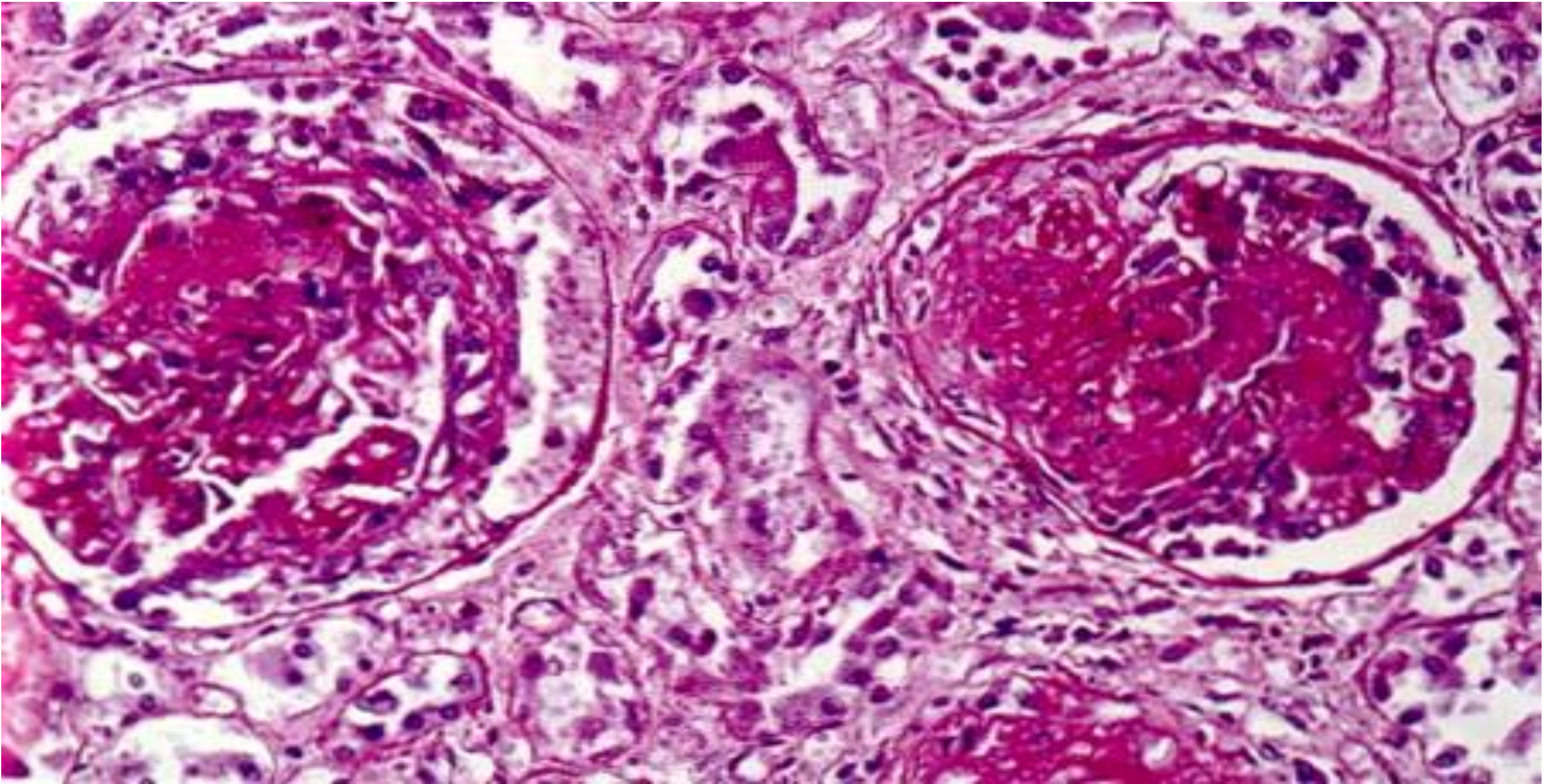


Fig. 8.16 Histological section of kidney in Wegener's granulomatosis showing a non-caseating granuloma with epithelioid giant cells and round cell infiltration. Haematoxylin and eosin stain. By courtesy of Prof. D.J. Evans.



Wegener granulomatosis



Treatment of systemic vasculitis

- corticosteroids
- immunosuppressants
- plasmapheresis

Henoch-Schönlein Purpura

Vasculitis affecting small / medium vessels in the skin, gastrointestinal tract, kidneys and joints

Henoch-Schönlein Purpura

Etiology - unknown

- Streptococcal infection
- other infections
- Food allergens
- Drugs
- HLA BW_{35}

It mainly affects children

Henoch-Schönlein Purpura

Pathogenesis

- immune mediated via CIC
- IgA (IgA antibodies anti-α galactosil)
- the complement system

Henoch-Schönlein Purpura: clinical picture

The onset is preceded by infection

Acute phase

- fever
- asthenia
- purpura
- arthralgia or arthritis of the large joints
- epistaxis
- hemoptysis

Gastrointestinal symptoms

- nausea
- vomiting
- abdominal pain
- melaena
- haematemesis

Henoch-Schönlein Purpura

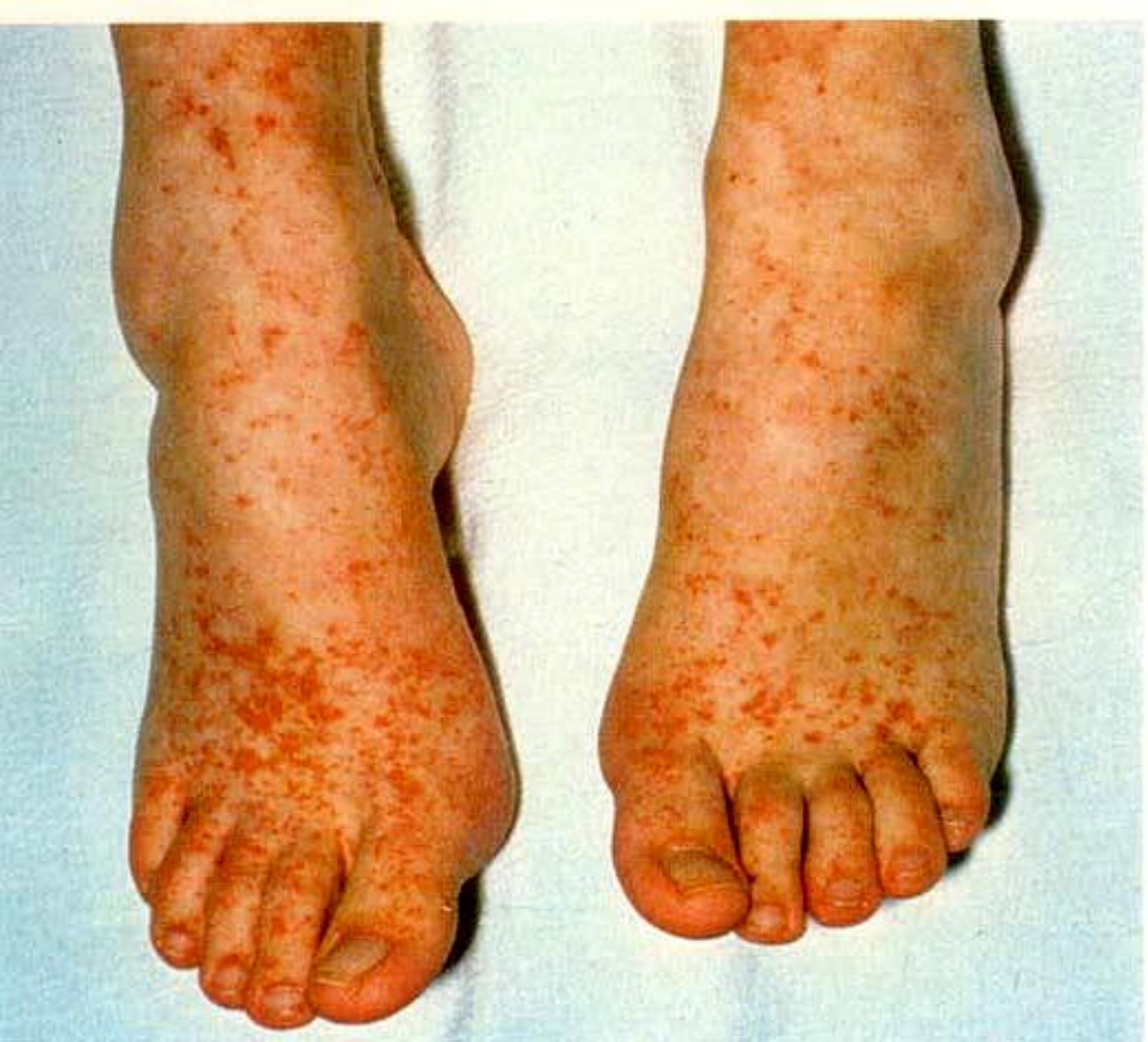


Fig. 8.20 Clinical appearance of Henoch-Schönlein purpura. The typical rash occurs over the lower limbs and the buttocks.

Henoch-Schönlein Purpura: lab investigations

- ↑ ESR
- ↑ CIC
- ↑ serum IgA
- cryoglobulins
- Rheumatoid factor
- Anti-α-galactosyl antibodies
- ANCA-type IgA antibodies

- +/- signs of streptococcal infection
- (pharyngeal exudate, ASLO)
- +/-↓C_3
- hematuria
- proteinuria
- hypertension
- ARF
- CKD

Henoch-Schönlein Purpura

Pathology

Optical microscopy

- Proliferative mesangial GN
- Proliferative extracapillary GN
- Minimal lesions

Immunofluorescence microscopy

- granular deposits of IgA in the mesangium and capillary walls
- C_3
- fibrin deposits

Henoch-Schönlein Purpura

Differential diagnosis

- Acute glomerulonephritis
- glomerular nephropathy with mesangial IgA deposits
- Lupus nephritis

Prognosis

- Minimal lesions
- proliferative mesangial GN
- extracapillary proliferation - **unfavorable prognosis**

good prognosis

Henoch-Schönlein Purpura

Treatment

- antibiotics – streptococcal infection
- corticosteroids - Prednisone
- immunosuppressive medication - Azathioprine
- plasmapheresis
- hemodialysis in ARF or CKF

Rheumatoid Polyarthritis

- Microscopic hematuria
- Proteinuria

Pathology

❖ ***Optical microscopy***

- **Proliferative focal GN**
- **Proliferative diffuse GN**
- **Interstitial nephritis**

Rheumatoid Polyarthritis

Renal impairment

- Rheumatoid nephritis
- secondary amyloidosis
- treatment with gold salts or D-penicillamine
  - microscopic hematuria
  - Nephritic / nephrotic proteinuria

Pathology

- Membranous GN
- Mesangial proliferative GN
- Necrotizing GN

Ankylosing spondylitis

- IgA-Nephropathy
- Secondary amyloidosis

Scleroderma renal crisis

50% of patients with renal dysfunction - moderate proteinuria, hypercretininemia and urinary sediment

- Pathological - intimal hyperplasia interlobular arteries, fibrinoid necrosis, GBM thickening

Appears in the first 5 years

- Risk Factors:
  - Diffuse skin disease
  - Glucocorticoids use
  - Presence of anti-RNA polymerase
  - Anti-centromer

Characteristics:

- HTN de novo > 150/85 mmHg (RAAS activation)
- Decreased renal function with increased creatinine
- Thrombocytopenia
- Hypertensive retinopathy
- Proteinuria / hematuria de novo
- Pulmonary edema
- Oliguria or progressive anuria
- CNS involvement - seizures

Essential mixed cryoglobulinemia

- the clinical and biological data of a systemic disease are absent
- cryoglobulin (IgM-IgG) - IgM acts as an antibody against IgG
- Cold precipitating CIC (+4°C)
- mediated by CIC that precipitates in vessels of various organs, including glomeruli
- associated with the hepatic C virus - possible triggering factor of the disease

Essential mixed cryoglobulinemia

Clinical picture

General symptoms

- fever

Extrarenal manifestations

- arthralgia
- purpura
- Raynaud syndrome
- necrotic skin lesions
- urticaria
- neuritis
- splenomegaly
- neuritis
- hemoptysis

Renal manifestations

Chronic

- proteinuria
- microscopic hematuria
- hypertension
- Nephrotic syndrome - rare

Pathology

- ***Optical microscopy***
  - Membranoproliferative GN
- ***Electron microscopy***
  - electron-dense deposits in the glomerular capillaries, with crystalloid structure
- ***Immunofluorescence microscopy***
  - deposits of IgG, IgM, C_3, C_{1q} și C_4 in capillary walls

Essential mixed cryoglobulinemia

Treatment

- corticosteroids
- immunosuppressive agents
- hemodialysis
- plasmapheresis
- Antiviral agents

Prognosis

- remission
- CKD