Small vessel systemic vasculitis

Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

Large vessel vasculitis (LVV)

- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)

- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel vasculitis (SVV)

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)

- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (Wegener's) (GPA)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)

Immune complex SVV

- Anti–glomerular basement membrane (anti-GBM) disease
- Cryoglobulinemic vasculitis (CV)
- IgA vasculitis (Henoch-Schonlein) (IgAV)
- Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

Variable vessel vasculitis (VVV)

- Behcet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)

- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

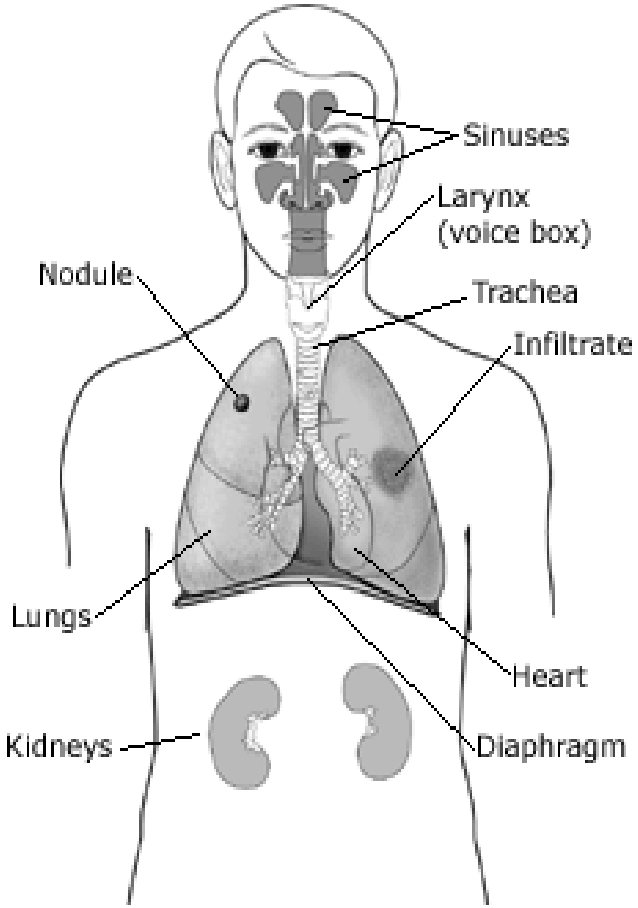
Vasculitis associated with systemic disease

- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology

- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

ANCA – Associated Vasculitis

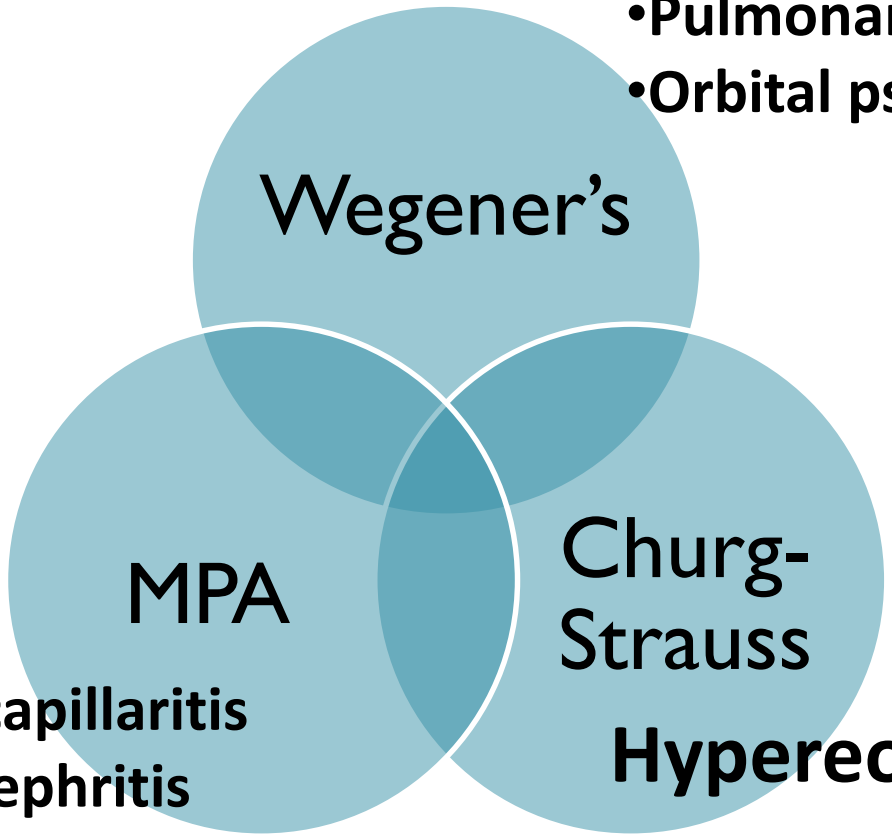


Shared Features of ANCA-Associated Vasculitides

- Microscopic polyangiitis (MPA), Granulomatosis with polyangiitis (Wegener's) (GPA), Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
- Can be considered together in view of a number of shared pathologic, clinical, and laboratory features
  - Preferentially involve small vessels (arterioles, capillaries, venules)
  - Similar glomerular lesions (crescents, focal necrosis, pauci-immune)
  - Propensity to present as lung-renal syndromes
  - Varying prevalence of ANCA positivity

Necrotizing Granuloma

- Sinusitis
- Subglottic stenosis
- Pulmonary nodules
- Orbital pseudotumor

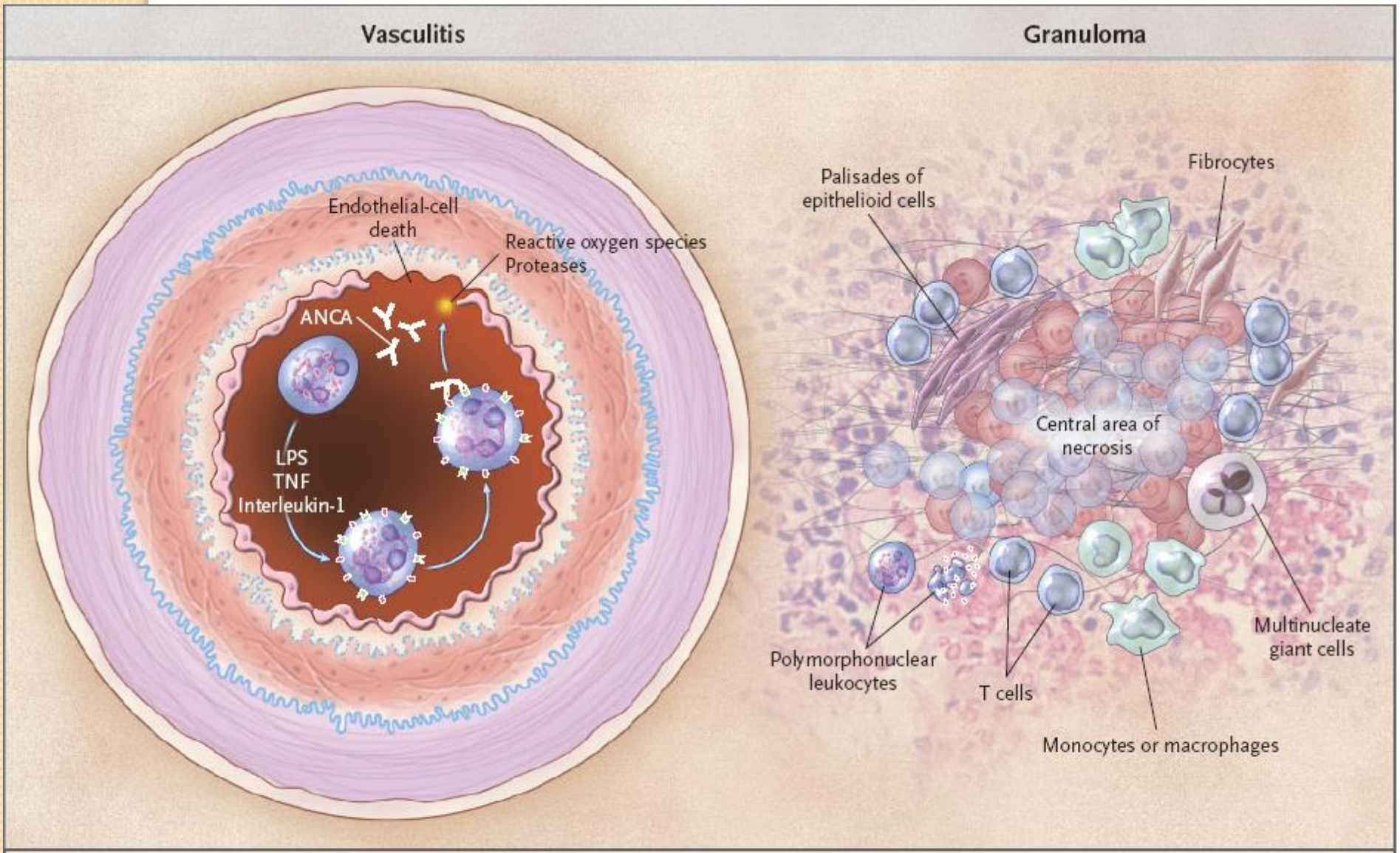


- Pulmonary capillaritis
- Glomerulonephritis
- Sensory neuropathy
- Mononeuritis multiplex

Hypereosinophilia

- Asthma
- Pulmonary infiltrates
- Myocarditis

GRANULOMATOSIS WITH POLYANGIITIS (*WEGENER'S*) (GPA)



Spectrum of Wegener's Granulomatosis.

The pathogenic mechanisms of the vasculitis (left) — which are related to the role of antineutrophil cytoplasmic antibodies (ANCA) — are well established. The principal cell involved is the polymorphonuclear leukocyte. By contrast, the granuloma (right) presents a variable histologic picture involving multiple types of cells whose specific roles are not clear. LPS denotes lipopolysaccharide.

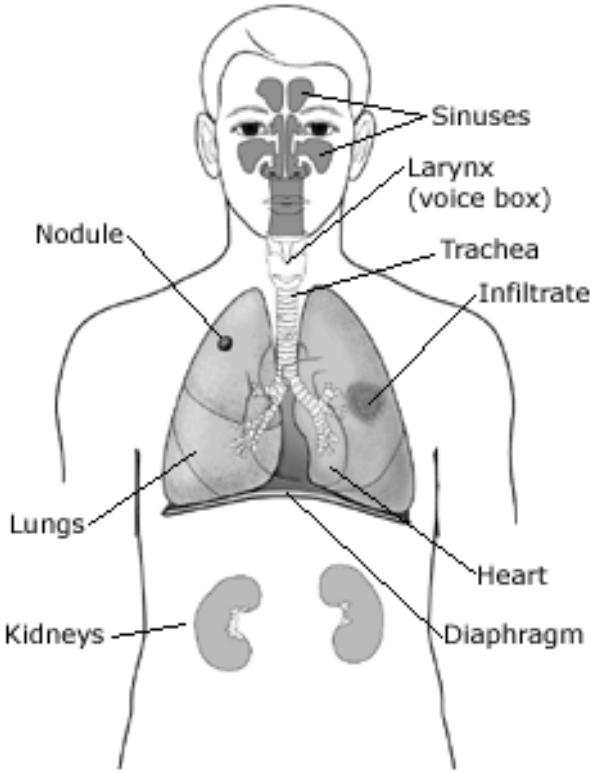
GPA: Epidemiology

- GPA affects both sexes equally
- Occurs in patients of all ages (mean age 41 years; range 9 to 78 years)
- More commonly seen in Caucasian patients (97%)
- Prevalence of GPA was estimated to approximate 3 per 100,000 persons
- It is likely that the prevalence of GPA has been underestimated

GPA: Clinical Features

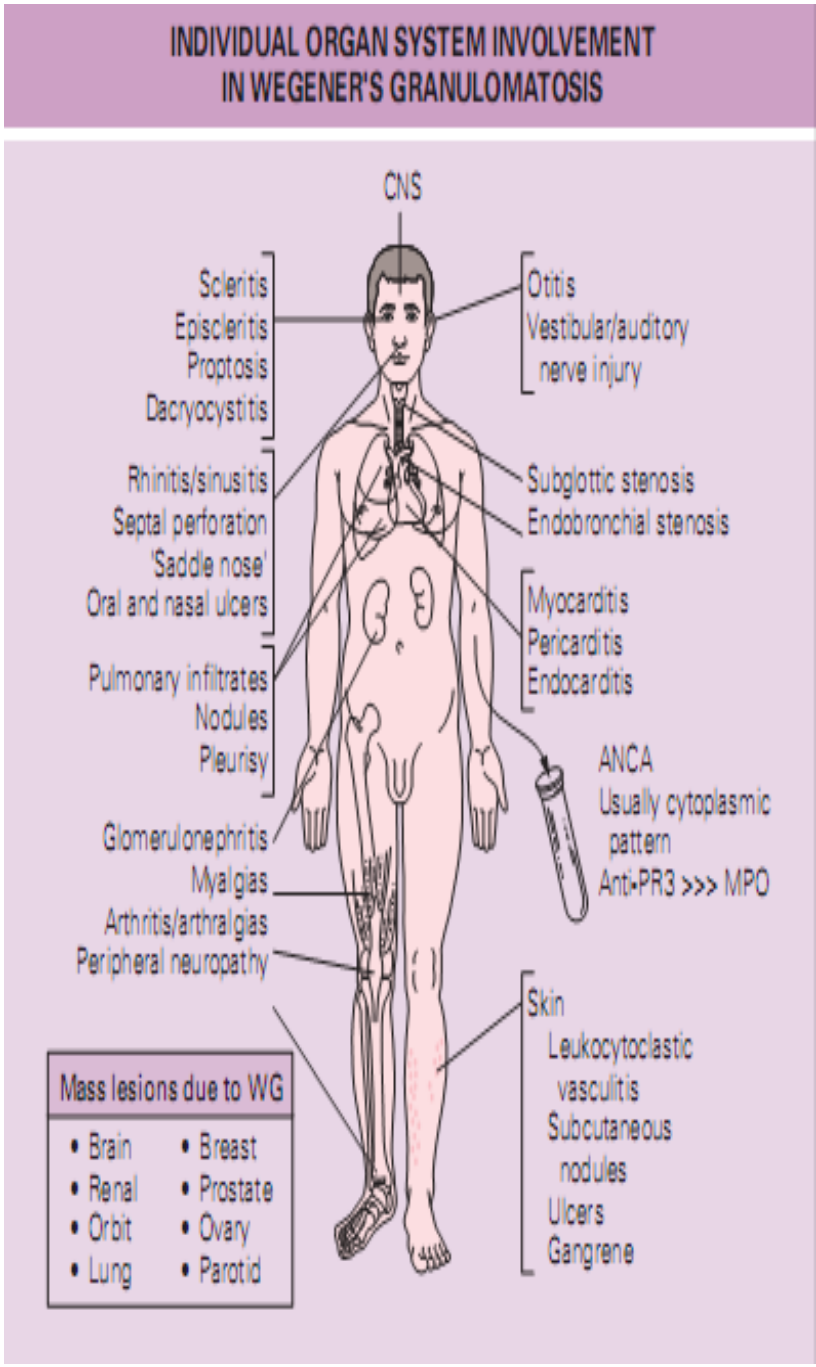
Classic Triad:

- Upper airway
- Lower respiratory tract
- Kidneys



Clinical Features

- Constitutional symptoms
- Skin
- Neurological
- Eyes
- Gastrointestinal
- Pulmonary
- Upper respiratory tract
- Renal
- Heard
- Musculoskeletal



Constitutional complaints

Patients may report the following chronic, nonspecific constitutional complaints:

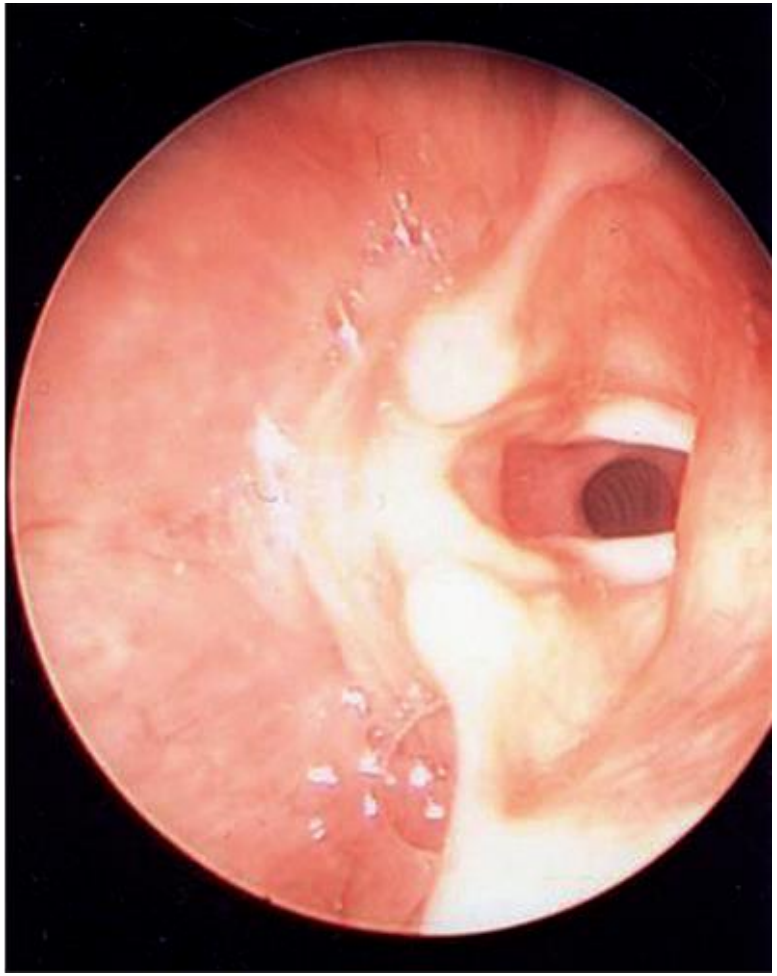
- Fevers, night sweats
- Fatigue, lethargy
- Loss of appetite
- Weight loss

Respiratory tract

- Upper
  - Purulent sinus drainage
  - Nasal mucosal ulceration with epistaxis / necrosis/perforations of nasal septum
  - Saddle nose deformity
  - Otitis media / hearing loss
  - Tracheal inflammation and sclerosis of subglotic region: stridor and airway stenosis

Saddle nose deformity

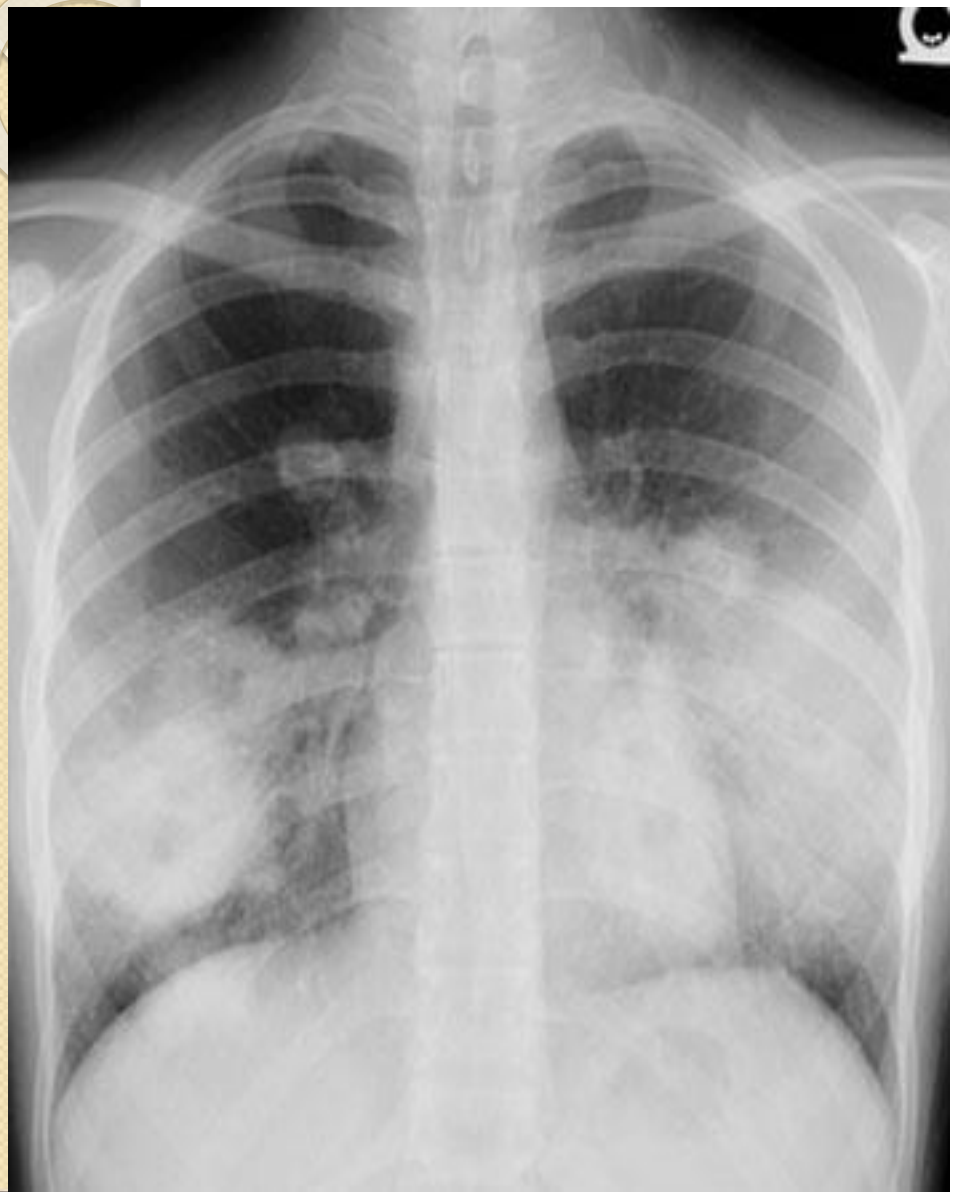
Sclerosis of subglotic region

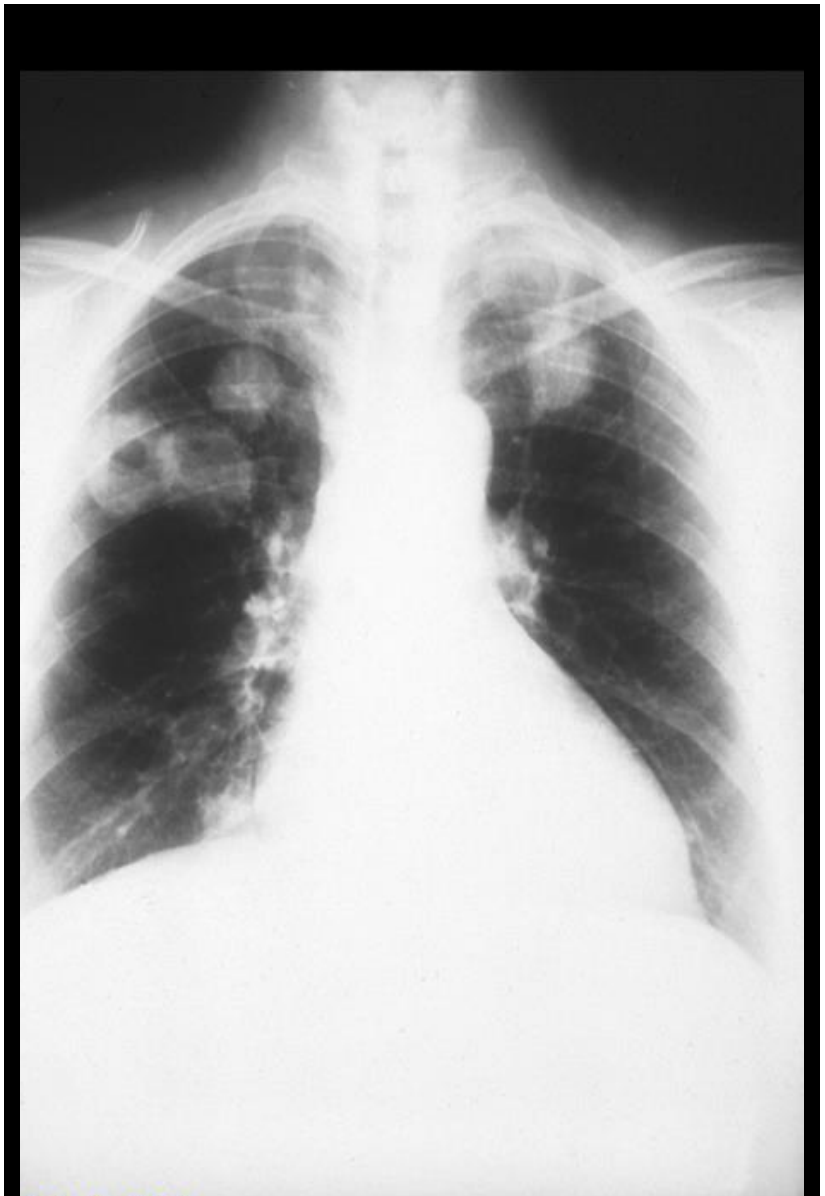


Respiratory tract

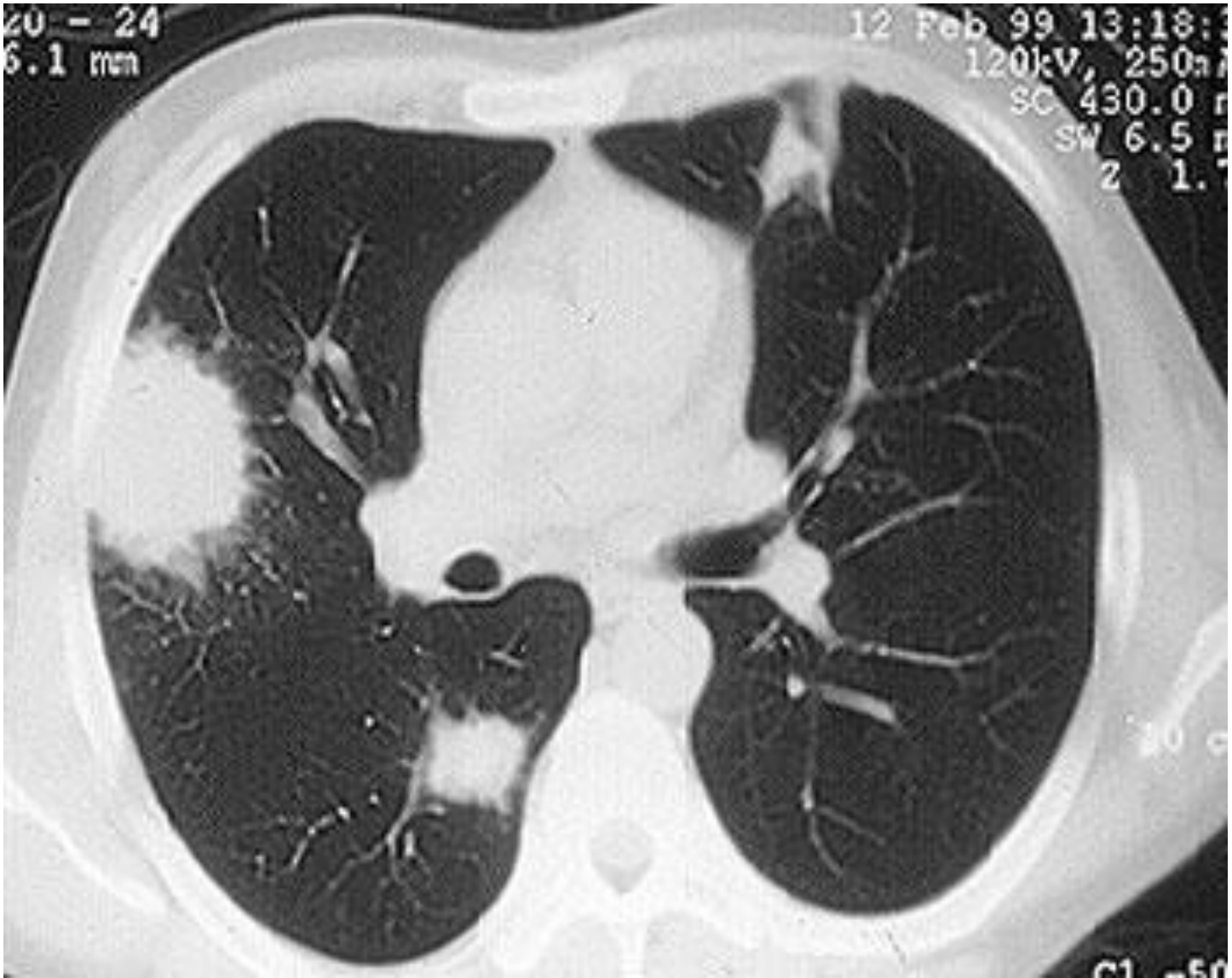
- Lower
  - Fleeting focal infiltrates, nodules
  - Cavitary lesions
  - Massive pulmonary hemorrhage and hemoptysis
    - caused by alveolar capillaritis

Fleeting focal infiltrates, nodules, cavitary lesions

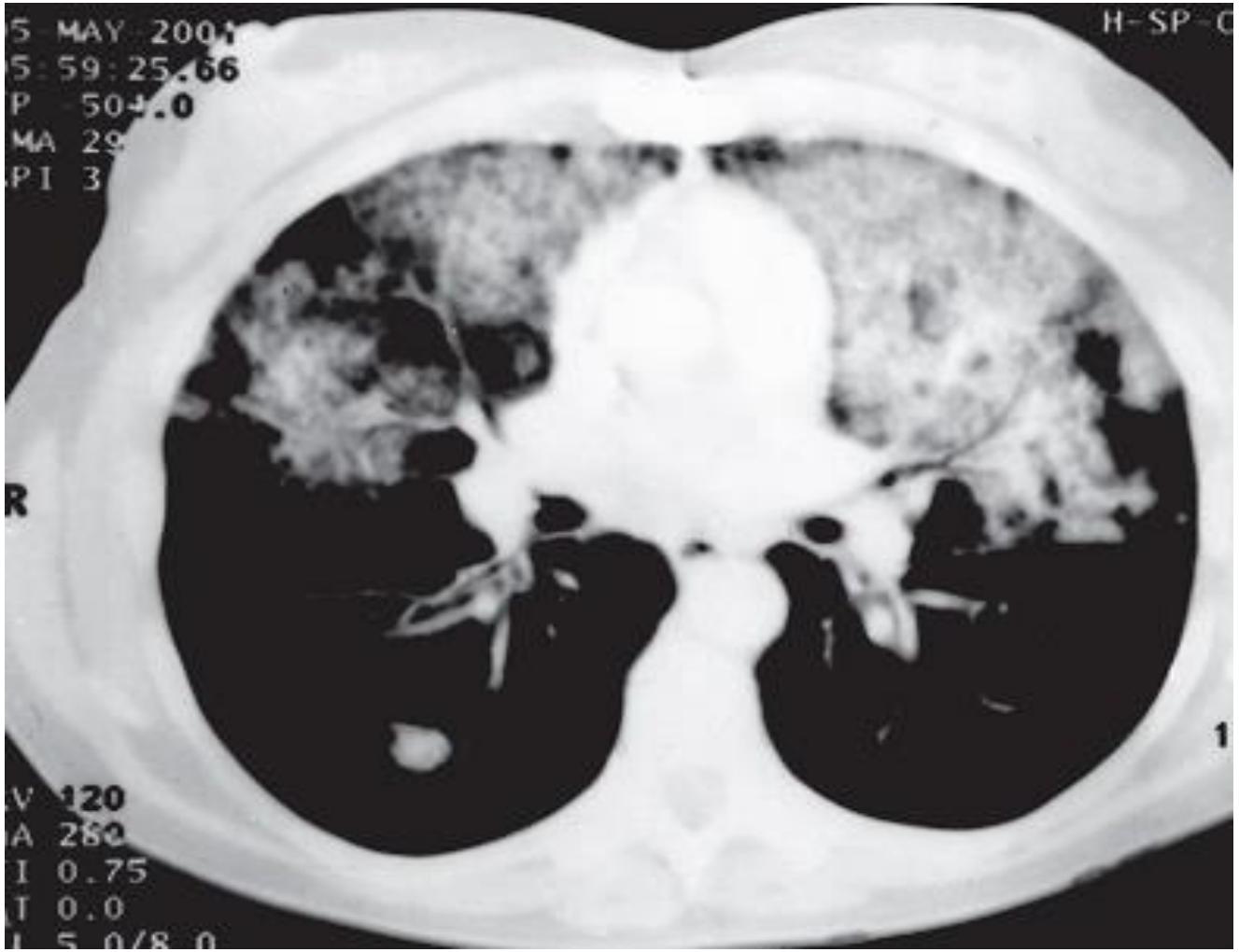




Nodules on CT



Pulmonary hemorrhage



Renal

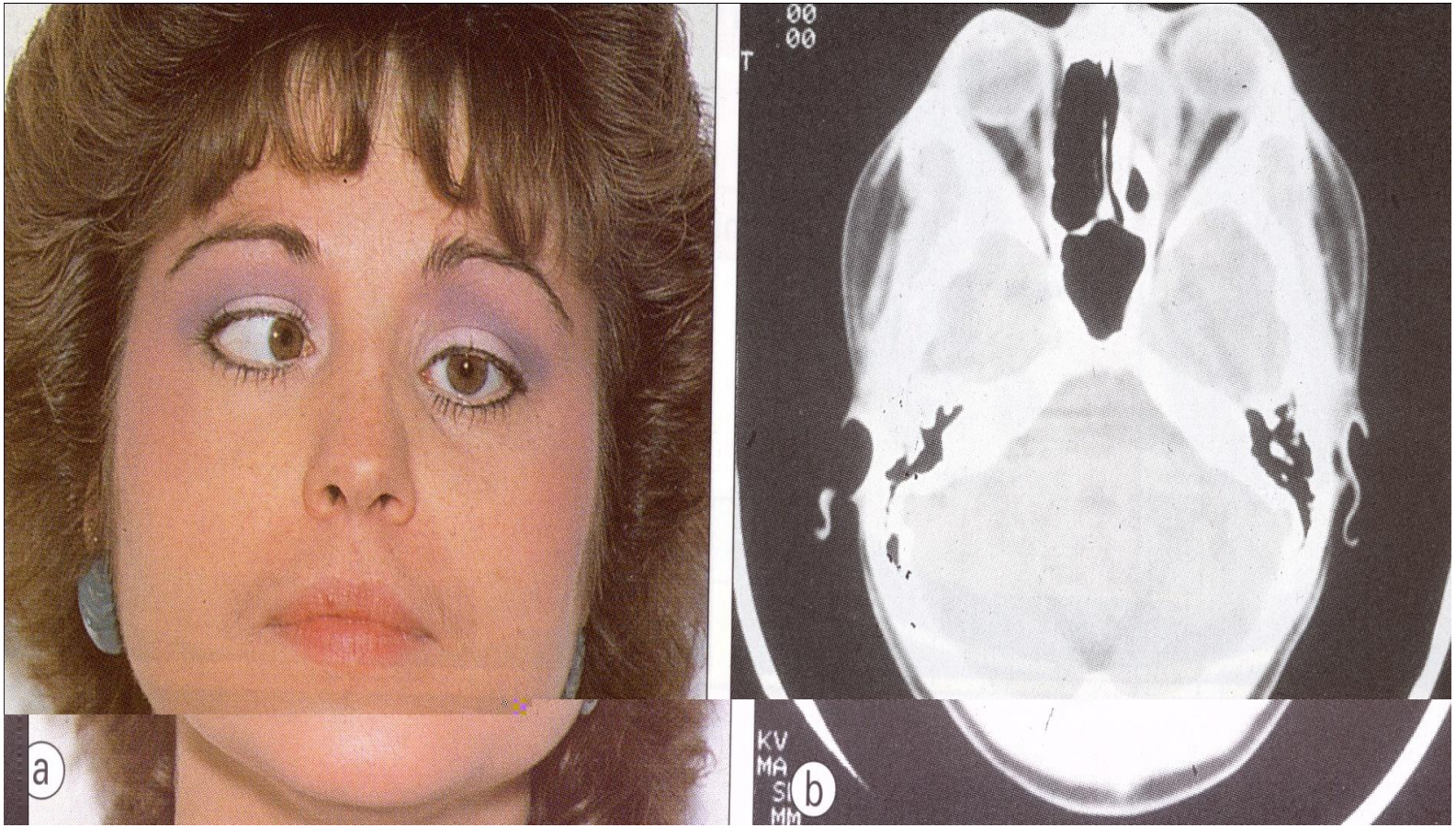
- 80% will progress to GN
- Renal disease may progress to fulminant glomerulonephritis within days or weeks, resulting in end-stage renal failure
  - Untreated, mean survival time for this subset is about 5 months
- Initial and recurrent renal damage may lead to chronic renal insufficiency in up to 42 percent of patients
- GN is characterized by
  - Focal fibrinoid necrosis
  - Crescent formation – portends rapid progression
  - Absent/paucity of Ig/C3/C4 deposits

Ophthalmic manifestations

- Conjunctivitis
- Episcleritis, sleritis
- Uveitis
- Optic nerve vasculitis
- Retinal artery occlusion
- Nasolacrimal duct occlusion
- Proptosis

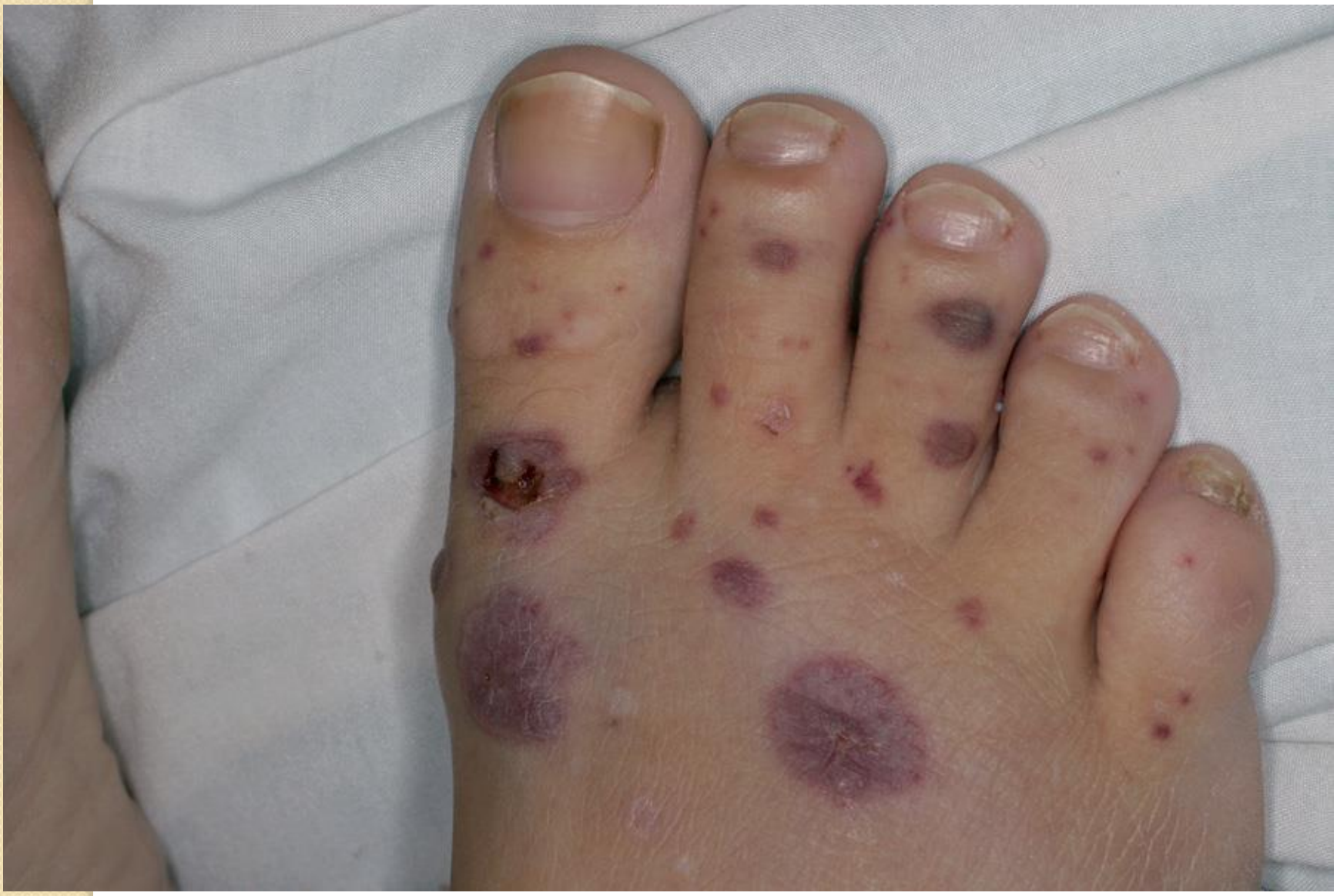
Scleritis

Proptosis



Cutaneous manifestations

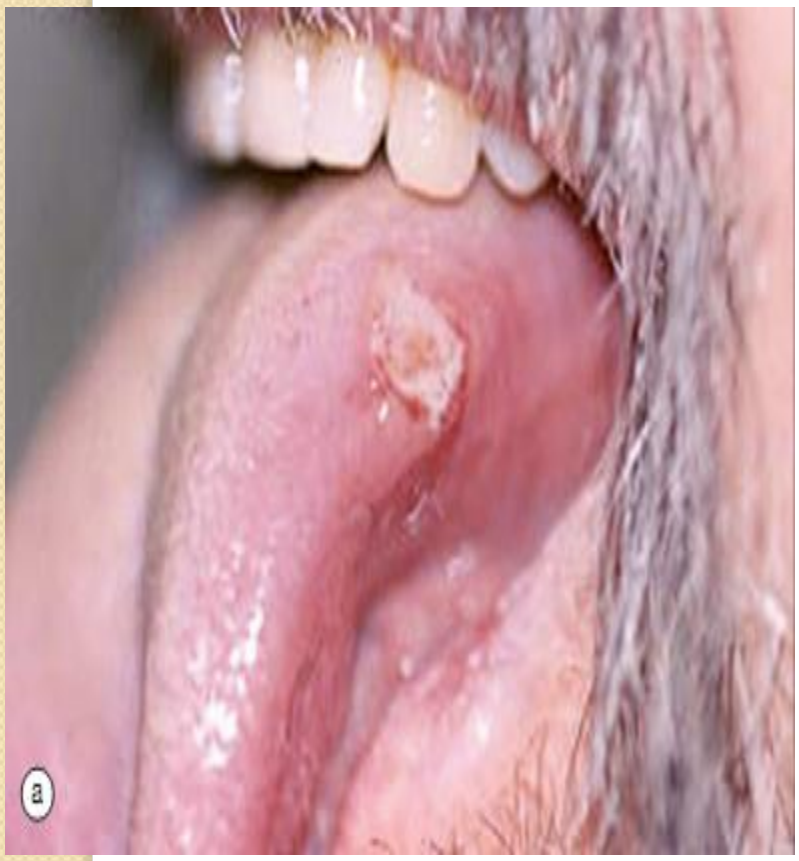
- Cutaneous findings are variable and nonspecific and usually affect the lower extremities
- Palpable purpura or skin ulcers (45%); ulcerations may resemble pyoderma gangrenosum
- Petechiae, vesicles, pustules, hemorrhagic bullae, livedo reticularis, digital necrosis, subungual splinter hemorrhages, and genital ulcers resembling squamous cell carcinoma have been reported

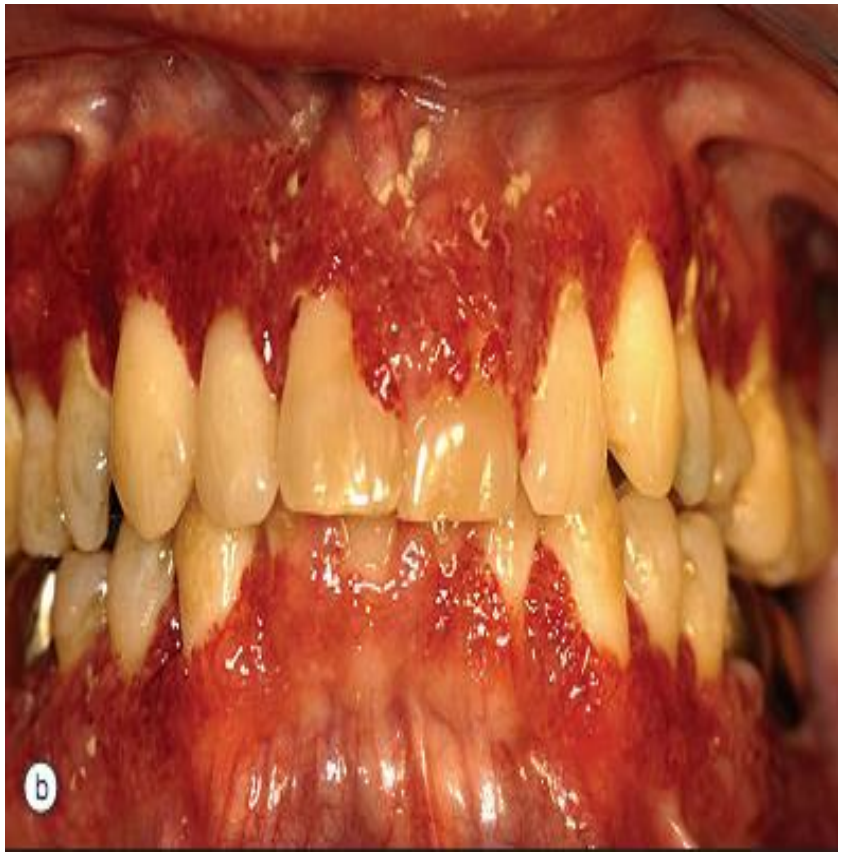


Oral manifestations:

a) painful tongue ulcer

b) strawbery gums due to gingival inflamation





- Neurological
  - Mononeuritis multiplex caused by inflammation of small epineural arterioles resulting in neural ischemeia
  - Sensorimotor polyneuropathy
  - Cranial nerve palsies

- Gastrointestinal
  - Ischemic ulceration
  - Perforation
  - Intussusception
  - Pancreatitis

Musculoskeletal manifestations

- Myalgias
- Arthralgias, usually polyarticular and symmetrical, affecting small and medium joints
- Arthritis, typically affecting large joints, but rarely deforming

Wegener's Emergencies

- Pulmonary hemorrhage
- Rapidly progressive kidney failure
- CNS disease – stroke, meningitis
- Bad eye inflammation / retro-orbital pseudotumor
- Subglotic stenosis
- Gangrene

Diagnosis

Criteria for Classification (ACR,1990)

- **Nasal or oral inflammation**
  - Development of painful or painless oral ulcers or purulent or bloody nasal discharge
- **Abnormal chest radiograph**
  - Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
- **Abnormal urinary sediment**
  - Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
- **Granulomatous inflammation on biopsy**
  - Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

Investigation of vasculitis

Assessing inflammation

- Blood count and differential (total white cell count, eosinophils)
- Acute - phase response (erythrocyte sedimentation rate, C - reactive protein)
- Liver function

Assessment of organ involment

- Urine analysis (proteinuria, haematuria, protein excretion)
- Renal function (creatinine clearance, 24 - hour protein excretion, urine protein/creatinine ratio, biopsy)
- Chest radiograph
- Liver function
- Nervous system (nerve - conduction studies, biopsy)
- Cardiac function (electrocardiography, echocardiography)
- Gut (angiography)

Immunological tests

- Antineutrophil cytoplasmic antibodies (including proteinase 3 and myeloperoxidase antibodies)
- Other autoantibodies (rheumatoid factor, antinuclear antibodies, anticardiolipin antibodies)
- Complement
- Cryoglobulins

Differential diagnosis

- Blood cultures
- Viral serology
- Echocardiography

Diagnosis

Routine laboratory tests are nonspecific in GPA. Results may include the following:

- Abnormal kidney function tests and urinalysis in patients with renal involvement
- Rheumatoid factor is positive in a low titer in two thirds of patients
- CBC: Mild normochromic normocytic anemia is present in 50% of patients; leukocytosis is common, with a neutrophil predominance
- Elevated inflammatory markers (ESR, CRP)

Antineutrophil cytoplasmic antibody (ANCA) testing

- Cytoplasmic antineutrophil antibody (c-ANCA) directed against proteinase-3 (PR3) is most specific for GPA
- Some patients with GPA express perinuclear-staining ANCA (p-ANCA) specific for myeloperoxidase (MPO)
- Combining immunofluorescence and ELISA enhances the sensitivity and specificity of a diagnosis of an ANCA-associated vasculitis to 96% and 98.5%, respectively

Diagnosis

- Biopsy specimens showing the triad of vasculitis, granuloma and large areas of necrosis
  - Sinuses
  - Nose
  - Skin - leukocytoclastic vasculitis with little or no complement and immunoglobulin on immunofluorescence
  - Kidney - segmental necrotizing glomerulonephritis that is usually pauci-immune on immunofluorescence / EM
  - Lung-vasculitis and granulomatous inflammation

    (Only large sections of lung tissue obtained via thoracoscopic or open lung biopsy are likely to show all of the histologic features)
- Seropositivity for C-ANCAs

MICROSCOPIC POLYANGIITIS (MPA)

Microscopic Polyangiitis (MPA)

- MPA was first recognized as a distinct entity by Davson and colleagues in 1948
  - described as a subgroup of polyarteritis nodosa, distinguished by the presence of segmental necrotizing glomerulonephritis.
- The Chapel Hill International Consensus Criteria defined MPA as
  - a necrotizing vasculitis (with few or no deposits) affecting small vessels (i.e., capillaries, venules, or arterioles)
  - It was noted that MPA is frequently associated with necrotizing glomerulonephritis and pulmonary capillaritis

MPA: Clinical Features

Clinical Feature	Percentage
Constitutional symptoms	76-79
Fever	50-72
Renal Disease	80-100
Arthralgia	28-65
Purpura	40-44
Pulmonary Disease	50
Neurologic Disease	28
ENT	32

MPA: Renal Disease

- Renal involvement is seen in 80-100% of patients with MPA.
- The classic presentation of renal disease in MPA is a rapidly progressive glomerulonephritis
- Some patients, however, have renal deterioration that progresses more slowly, over many months.

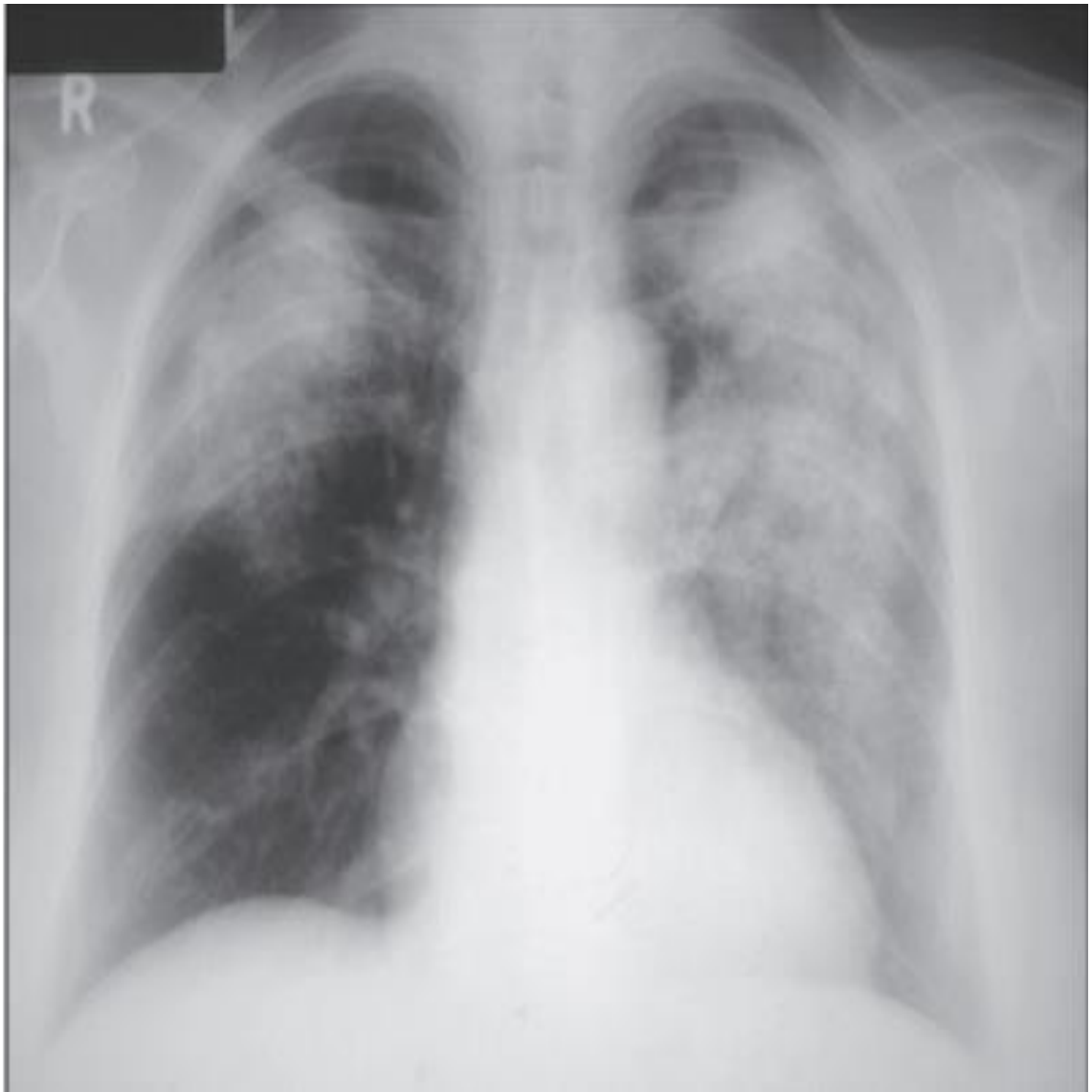
MPA: Renal Disease

- The pathologic features of renal disease in MPA are indistinguishable from other forms of pauci-immune glomerulonephritis—namely, a necrotizing, crescentic lesion
- Compared with biopsies from patients with ANCA directed against proteinase 3, those with MPO-ANCA have a more chronic pattern of renal injury, with more glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

MPA: Pulmonary Disease

- Lung involvement is common in MPA and is present in more than half of reported cases
- Diffuse alveolar hemorrhage (DAH) is the most serious form of lung involvement
- The clinical manifestations range from mild dyspnea and anemia without any hemoptysis to massive hemorrhage and bleeding with profound hypoxia with acute onset in most patients
- The radiographic features of DAH are nonspecific, demonstrating patchy or diffuse alveolar infiltration
- The characteristic histopathology of MPA is that of pulmonary capillaritis

Pulmonary hemorrhage in MPA



MPA: Pulmonary Disease

- Interstitial fibrosis and pleuritis occur in some patients with MPA.
- Pulmonary fibrosis that resembles usual interstitial pneumonitis in clinical presentation is increasingly recognized as a disease manifestation of MPA.
- Many cases of pulmonary fibrosis are associated with previous alveolar hemorrhage, but the precise relationship between alveolar hemorrhage and fibrosis is not clear.

MPA: Nervous system

- Vasculitic neuropathy is a potentially devastating complication of MPA.
- The nerve involvement typically occurs in the pattern of a distal, asymmetric, axonal polyneuropathy (mononeuritis multiplex).
- The first symptoms of vasculitic neuropathy are usually sensory, with numbness, tingling, and dysesthesias.
- Muscle weakness and wasting follow the infarction of motor nerves.

MPA: Nervous system

- Because the named peripheral nerves are usually mixed nerves, bearing both sensory and motor fibers, patients with vasculitic neuropathy typically have both sensory and motor symptoms.
- Recovery from vasculitic neuropathy may take months; some patients have residual nerve damage after the disease is controlled.
- Although peripheral nerve lesions tend to dominate the neurologic features of MPA, central nervous system involvement by vasculitis is also described in this disease.

MPA: Head, eyes, ears, nose, and throat

- Some vasculitis experts regard the presence of any upper respiratory tract involvement as evidence that the diagnosis is GPA, not MPA.
- Thus, HEENT involvement in MPA is limited generally to rhinitis or mild cases of nondestructive sinusitis.
- Serous otitis media may occur in MPA, but unlike in GPA, granulomatous inflammation is absent.
- Inflammatory ocular lesions in MPA have been reported, but are less common and less severe than in GPA.

MPA:Musculoskeletal system

- Nonspecific arthralgias and frank arthritis usually present early in the course of MPA and respond quickly to therapy.
- Musculoskeletal symptoms may also herald disease flares.
- The arthritis of MPA is migratory in nature and can assume a variety of joint patterns, from a pauci-articular syndrome of large joints to a polyarthritis of small joints.
- Destructive joint lesions do not occur in MPA.

MPA: Diagnosis

Test	Typical Result
Complete blood cell count	• Normochromic, normocytic anemia; acute, severe anemias possible in alveolar hemorrhage • Mild to moderate leukocytosis common, usually not exceeding 18 ×10 9/L • Moderate to pronounced thrombocytosis typical, ranging from platelet counts of 400 ×109/L to occasionally >1000 ×109/L
Electrolytes	Hyperkalemia in the setting of advanced renal dysfunction
Liver function tests	Hepatic involvement unusual in MPA When present, there can be elevations of transaminases (AST/ALT) in excess of 1000 mg/dL

MPA: Diagnosis

Test	Typical Result
Urinalysis with microscopy	• Hematuria (ranging from mild to so high that red blood cells are too numerous to count) • Red blood cell casts • Proteinuria (nephritic range proteinuria in a small minority)
Erythrocyte Sedimentation rate/C-reactive protein	• Dramatic elevations of acute phase reactants are typical, generally with good correlation to disease activity
ANA	Positive < 20%
Rheumatoid factor	Positive in 40–50% of patients, often leading to diagnostic confusion with rheumatoid arthritis

MPA: Diagnosis

Test	Typical Result
C3, C4	Usually normal (or increased, because complement proteins are acute phase reactants)
ANCA (antiMPO)	Positive in 70% of patients with MPA (and probably a higher percentage of patients with generalized disease)
Anti-GBM	A small number of patients have both ANCA and antiGBM antibodies

MPA: Diagnosis

- Problems in diagnosis
  - Variable clinical presentation
  - Histologic findings not specific
  - Imperfect association with p-ANCA (anti-MPO)
  - c-ANCA (anti-PR3) can be positive in MPA
  - Differentiation from GPA may at times be difficult
    - granulomas are not always found in GPA
    - Prominent involvement of the upper respiratory tract or the presence of c-ANCA should seriously raise the possibility of GPA

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS) (EGPA)

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)

- The syndrome defined by Churg and Strauss in 1951 has undergone several redefinitions, but is still characterized by three histopathologic features:
  - necrotizing vasculitis
  - infiltration by eosinophils
  - extravascular granulomas

EGPA: Clinical Features

EGPA is characterized by **3 distinct phases**:

- The **prodrome** phaseis characterized by the presence of allergic disease (typically asthma or allergic rhinitis). This phase often lasts for several years.
- During the **eosinophilia/tissue infiltration** phase, striking peripheral eosinophilia may occur. Tissue infiltration by eosinophils is observed in the heart, lung, gastrointestinal tract, and other tissues.
- In the third phase, **vasculitis**, systemic necrotizing vasculitis affects a wide range of organs, ranging from the heart and lungs to the peripheral nerves and skin.

EGPA: Nose and sinuses

- Upper airway disease in EGPA usually takes the form of nasal polyps or allergic rhinitis.
- A surprisingly high percentage of patients with EGPA have histories of nasal polypectomies, usually long before suspicion of an underlying disease is raised.
- Although pansinusitis occurs frequently, destructive upper airway disease is not characteristic of EGPA.

EGPA: Ears

- Middle ear granulation tissue with eosinophilic infiltrates occurs in some patients, leading to conductive hearing loss.
- Cases of sensorineural hearing loss have also been reported.

EGPA: Lungs

- More than 90% of patients with EGPA have histories of asthma.
- Typically, the asthma represents either adult-onset reactive airway disease or, less commonly, a significant worsening of long-standing disease.
- Upon encroachment of the vasculitic phase of EGPA, patients' asthma may improve substantially, even before therapy for vasculitis has begun.

EGPA: Lungs

- Following successful treatment of the vasculitic phase, however, glucocorticoid-dependent asthma persists in many patients.
- The pathologic features of lung disease in EGPA vary according to the disease phase.
- In the early phases, there may be extensive eosinophilic infiltration of the alveoli and interstitium.
- During the vasculitic phase, necrotizing vasculitis and granuloma may be evident.

EGPA: Kidneys

- EGPA is less likely to cause end-stage renal disease than are other forms of ANCA-associated vasculitis.
- Acute kidney injury may be caused by an eosinophil- mediated interstitial nephritis.
- When glomerulonephritis does occur (15-20% of patients), however, the histopathologic findings are often indistinguishable from those of other forms of pauciimmune vasculitis (eg, granulomatosis with polyangiitis, microscopic polyangiitis, and renal-limited vasculitis).

EGPA:Peripheral nerves

- Mononeuritis multiplex occurs with a remarkable frequency in EGPA, with often devastating effects.
- Vasculitic neuropathy was evident in 50-75% of patients.
- Clinically, nerve infarctions are heralded by the abrupt occurrence of a foot drop, wrist drop, or some other focal nerve lesion.
- Muscle wasting secondary to nerve infarctions may continue to appear for weeks after the disease has been brought under control.

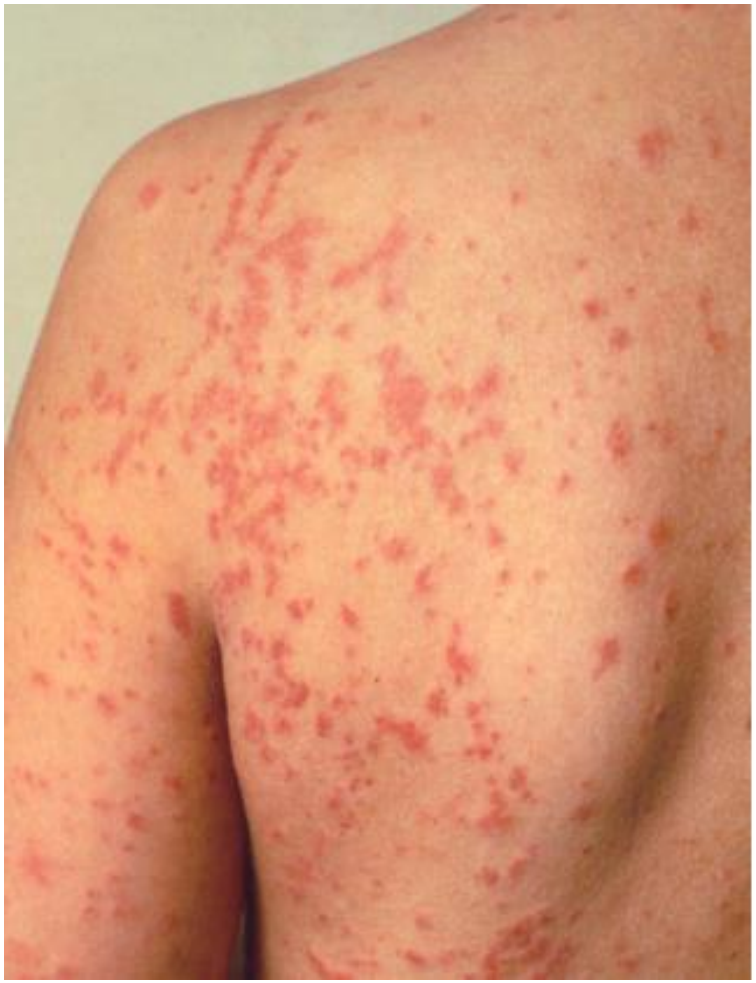
EGPA: Heart

- Cardiac involvement also occurs with a disproportionate frequency in EGPA, and is a common cause of death.
- Congestive heart failure is the most common cardiac manifestation, although coronary arteritis and valvular abnormalities have also been reported.

EGPA: Skin

- Skin disease in EGPA takes many forms, none of which is specific: palpable purpura, papules, ulcers, and vesiculobullous lesions are common.
- Nodular skin lesions are usually "Churg-Strauss granuloma" (cutaneous extravascular necrotizing granuloma). These tend to occur on the extensor surfaces of the elbows and other pressure points.
- Skin biopsy specimens in EGPA reveal eosinophilic infiltration of blood vessel walls.
- Splinter hemorrhages, digital ischemia, and gangrene associated with inflammation in medium-sized digital arteries are often present at the time of diagnosis.

Palpable purpura in EGPA



EGPA: Joints

- Nonspecific arthralgias and frank arthritis often occur early in the course of EGPA.
- The arthritis of EGPA is migratory in nature and may assume a variety of joint patterns, from a pauciarticular syndrome of lower extremity joints to a polyarthritis of the small joints of the hands.

EGPA: Laboratory Findings

- Eosinophilia (before treatment) is a *sine qua non* of EGPA.
- Eosinophil counts may comprise as much as 60% of the total white blood cell count.
- Eosinophil counts are usually sensitive markers of disease flares, but generally respond very quickly to treatment with high doses of glucocorticoids.
- Most patients with EGPA also have elevated serum IgE levels.

EGPA: Laboratory Findings

- Serum complement levels are usually normal.
- Immune complexes are not believed to play a primary role in this disease.
- The erythrocyte sedimentation rate, serum C-reactive protein level, and eosinophil count can be useful in the longitudinal evaluation of disease activity.

EGPA: Laboratory Findings

- The reported percentages of EGPA patients with ANCA are variable, with most figures in the literature in the range of 50%.
- Antibodies to either proteinase-3 or MPO (but not to both) may be found.
- Of the two vasculitis-specific ANCAs, those to MPO are more common in EGPA.
- Patients who are ANCA negative tend to have more cardiopulmonary complications, while patients who are ANCA-positive tend to have more of the classic vasculitic manifestations of this disease, although there is considerable overlap between these two groups.

EGPA: Imaging Studies

- Pulmonary infiltrates are evident in approximately one third of patients with EGPA.
- These lesions are usually migratory infiltrates that occur bilaterally.
- Pulmonary hemorrhage is unusual, but has been reported.
- Nodular or cavitary lesions suggest the alternative diagnoses of granulomatosis with polyangiitis, infection, or malignancy.
- Among patients with cardiac involvement, echocardiography or cardiac MRI may confirm poor cardiac function consistent with cardiomyopathy or demonstrate findings compatible with regional myocardial fibrosis.

American College of Rheumatology (ACR) classification criteria, 1990

- Asthma
- Blood eosinophilia (>10% on white cell count)
- Mono- or polyneuropathy
- Pulmonary infiltrates, non-fixed
- Paranasal sinus abnormality
- Extravascular eosinophils in biopsy.

At least 4 criteria must be present.

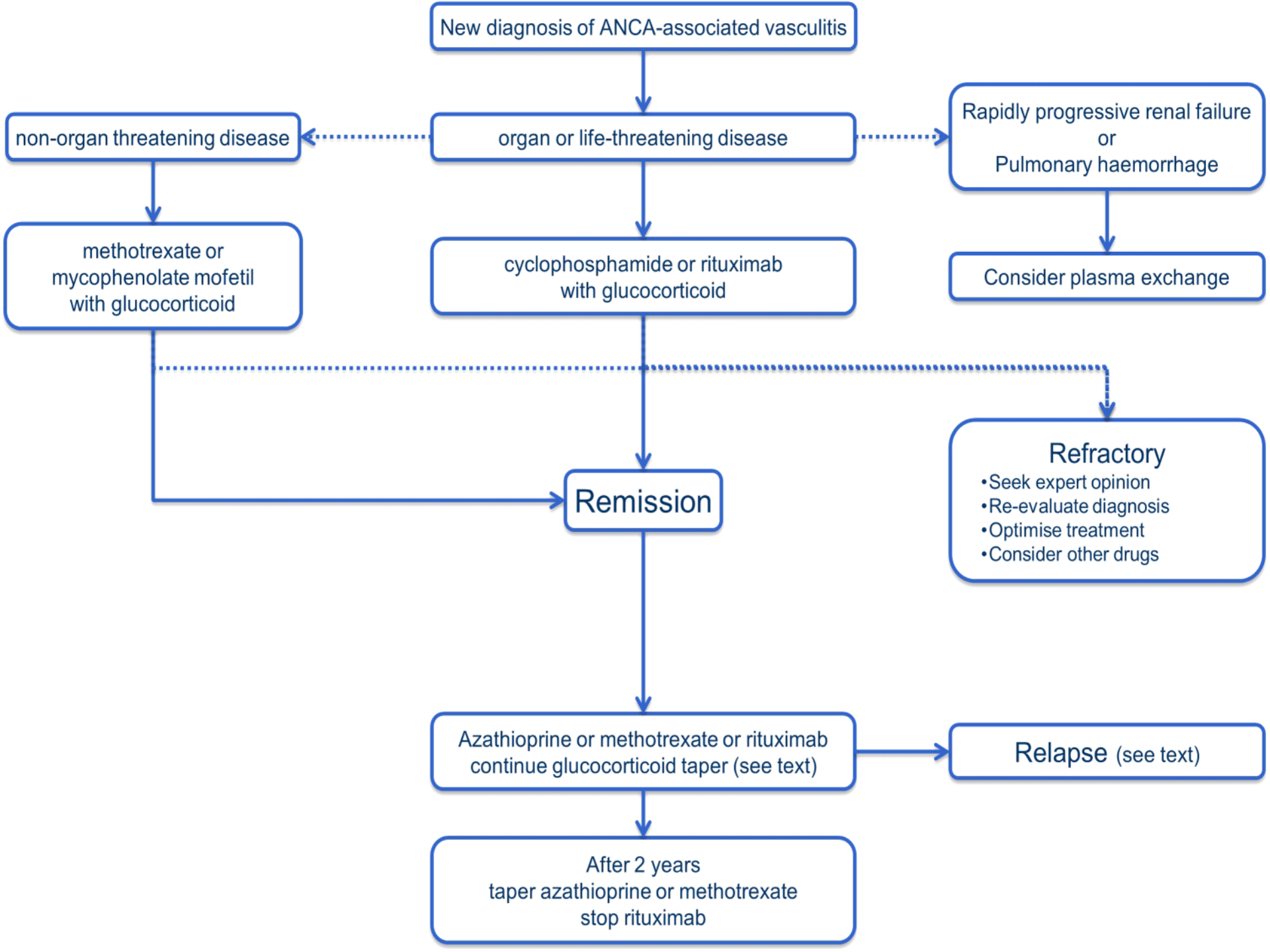
TABLE IV. Clinical features of the medium- and small-vessel vasculitides

	WG	MPA	CSS	PAN
Sinus disease	+++	−	++	−
Subglottic stenosis	++	−	−	−
Asthma	−	−	+++	−
Pulmonary nodules	+++	+	+	−
Cavitary lung disease	++	−	−	−
Alveolar hemorrhage	++	++	+	−
Glomerulonephritis	+++	+++	+	−
Renal artery involvement	−	−	−	++
Neuropathy	+	+	++	+++
Cardiac involvement	+	+	++	+
Granuloma formation	+++	−	++	−
Eosinophilia	−	−	+++	−
ANCA positivity	+++	+++	+	−
Microaneurysm formation	−	−	−	++

Update on vasculitis: J Allergy Clin Immunol 2009

Treatment of ANCA vasculitis

- Untreated carries a very poor prognosis
  - Median survival of 5 months
  - Primarily due to ESRF
- Three phases
  - Induction of remission
  - Maintenance of remission
  - Treatment of relapse


New diagnosis of ANCA-associated vasculitis
non-organ threatening disease
organ or life-threatening disease
Rapidly progressive renal failure
or
Pulmonary haemorrhage
methotrexate or
mycophenolate mofetil
with glucocorticoid
cyclophosphamide or rituximab
with glucocorticoid
Consider plasma exchange
Refractory
•Seek expert opinion
•Re-evaluate diagnosis
•Optimise treatment
•Consider other drugs
Remission
Azathioprine or methotrexate or rituximab
continue glucocorticoid taper (see text)
Relapse (see text)
After 2 years
taper azathioprine or methotrexate
stop rituximab

Treatment

- **Remission induction**:
  - Cyclophosphamide 2mg/kg po qd x 3-6 months
    [or 15 mg/kg IV q 2 wk x3 then q 3 weeks x 6-12 months]
    Or Rituximab 375mg/m2, once a week, for four infusion
  - Prednisone 1mg/kg po qd
- **Remission maintenance** (minimum 2 years)
  - **Methotrexate** 20-25 mg po q week + folate
  - Azathioprine 2mg/kg po qd
  - **Mycophenolate mofetil** 1.5 g po BID
  - Leflunomide 20-30 mg po BID

Summary

- ANCA-associated vasculitides are still rare, but life-threatening disorders
- ANCA-associated vasculitides may present with lung-renal syndromes often with neurologic, ocular or cutaneous manifestations
- MPA and GPA may be hard to separate when the clinical presentation is incomplete
- EGPA appears to be a more distinctive disorder
- The treatment approach is similar and largely successful
- Relapse and long-term morbidity are still serious issues

Diagnostic Approach to Small Vessel Vasculitis