Vasculitis

"The great mimicker and undoubted diagnostic and management challenge"

Farhan Tahir M.D.

Rheumatic Disease Associates

Agenda

- Etiology and Pathogenesis
- Classification on the basis of vessel size
- Clinical spectrum

  (Skin lesions, Imaging and histological findings)
- Non immune mediated mimics
- Pulmonary Renal syndrome
- Cases of PRS and diagnostic workup
- Treatment

Etiology

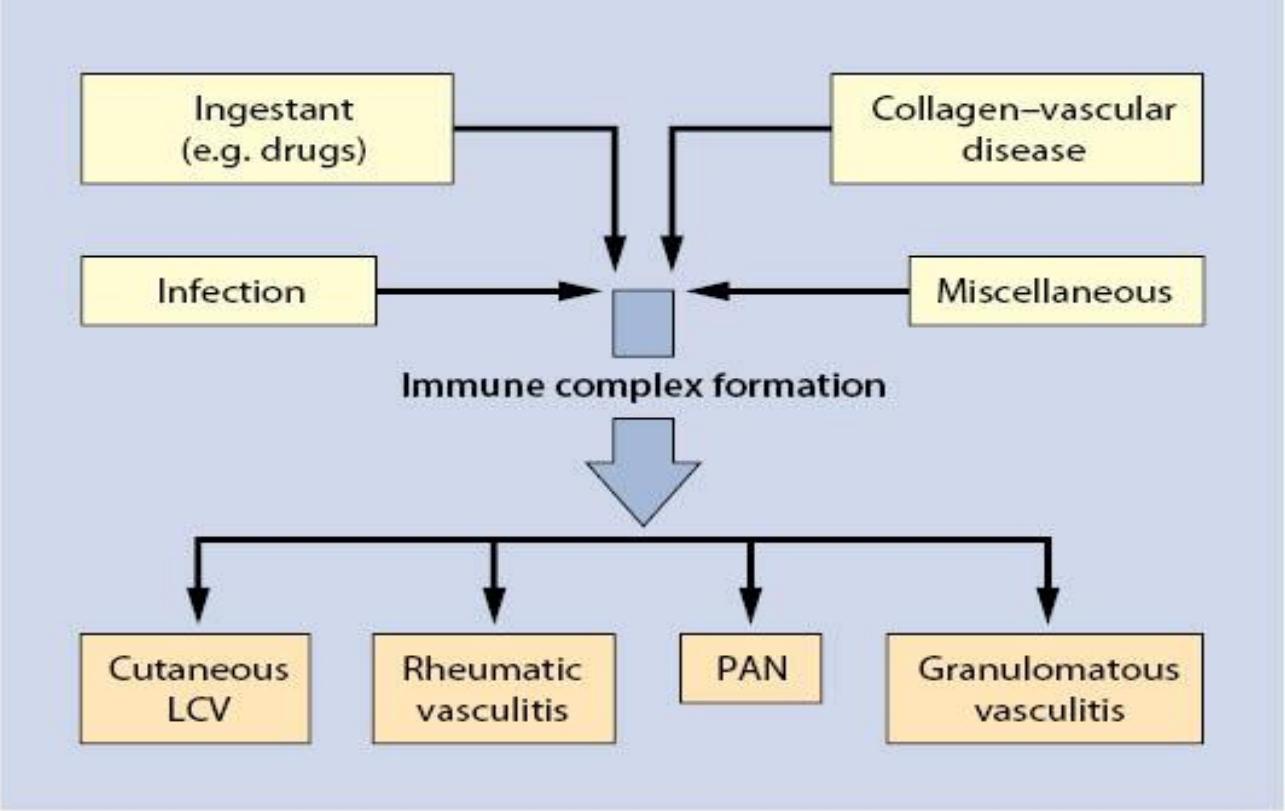
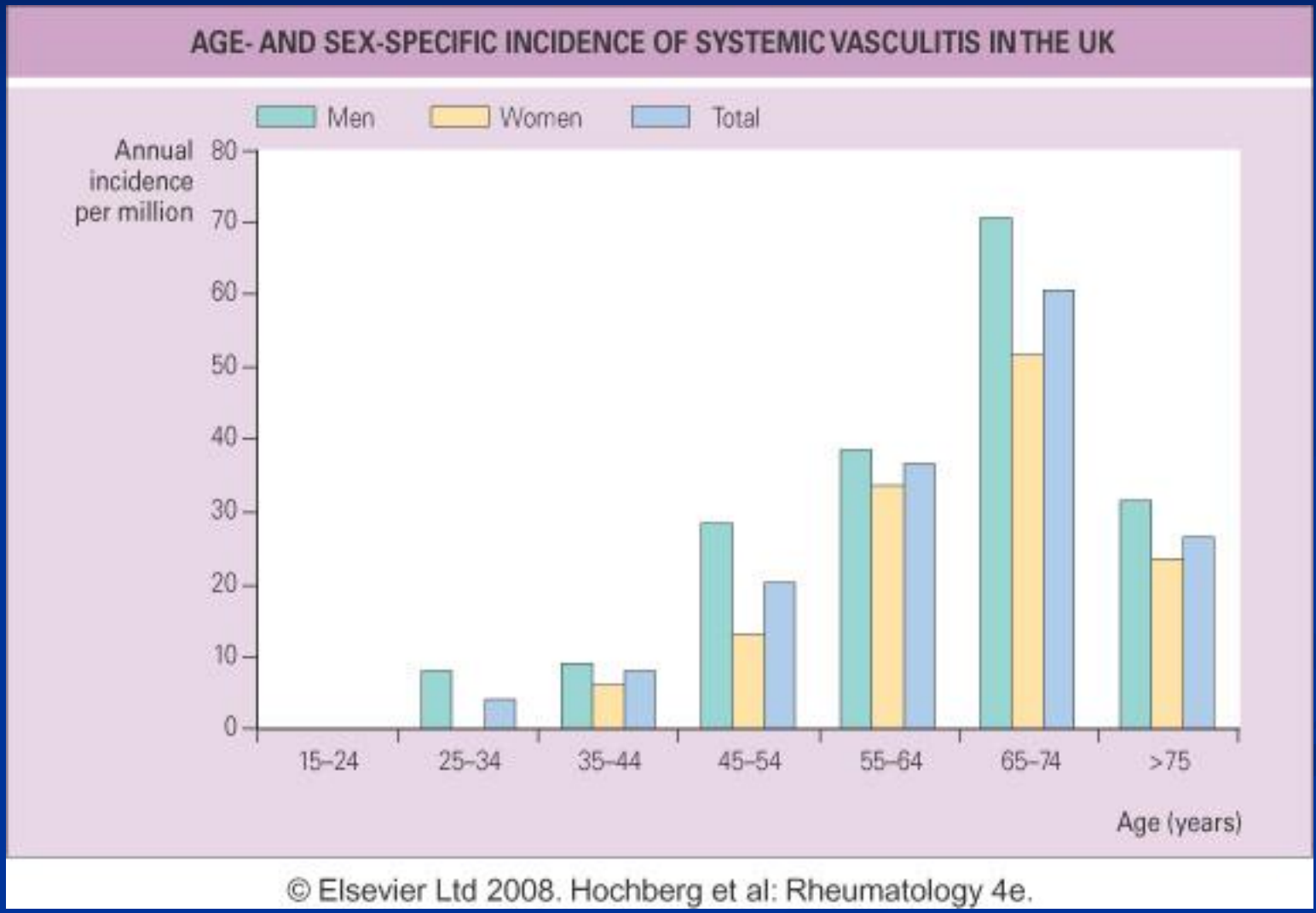
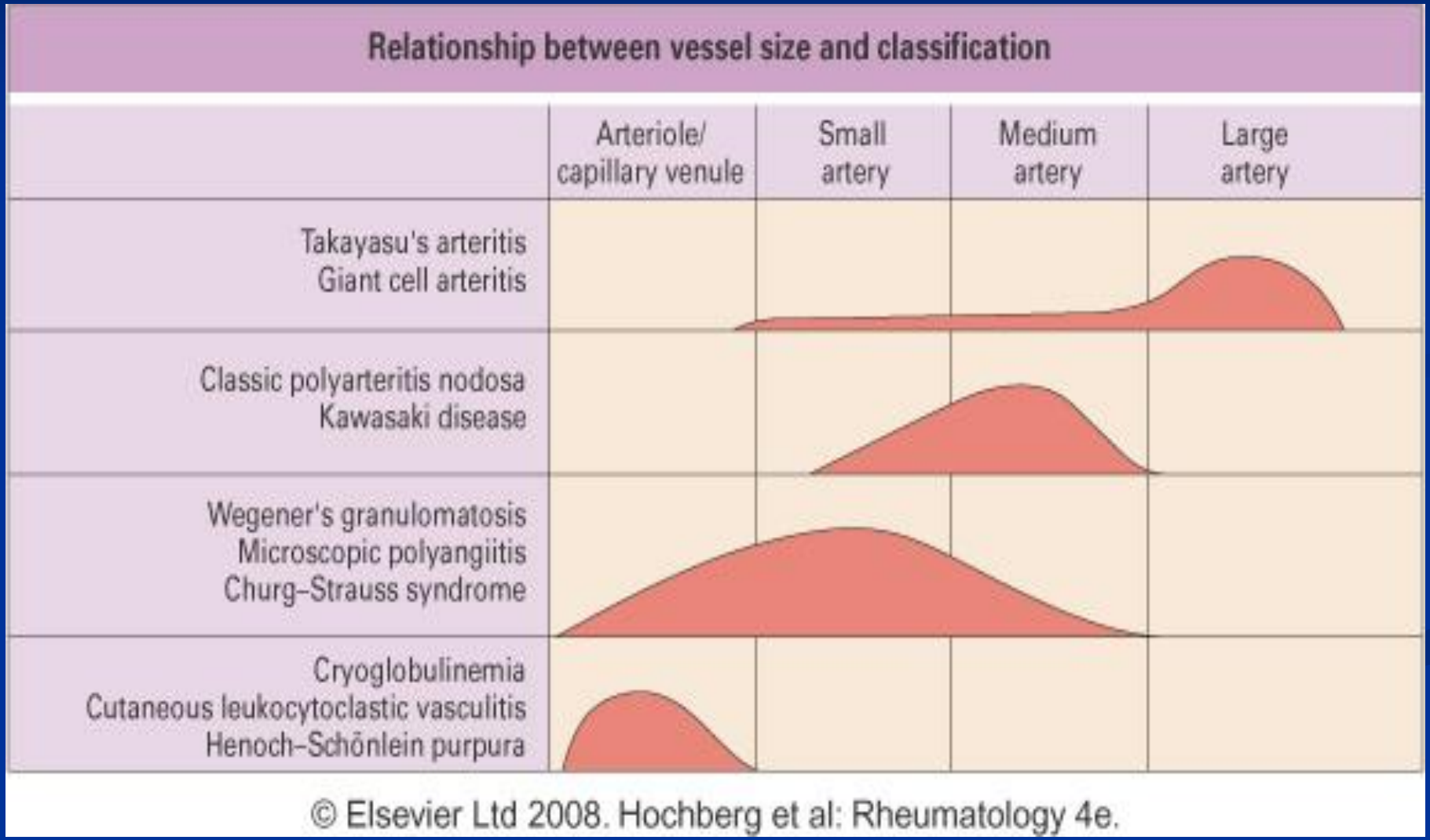


Figure 4–1 Schematic representation of multiple antigenic exposures leading, through the mechanisms of immune complex formation and deposition, to the varying manifestations of vasculitis. LCV = leukocytoclastic vasculitis; PAN = polyarteritis nodosa.

Incidence



Classification based on vessel size



Large vessel vasculitis

Takayasu's Arteritis

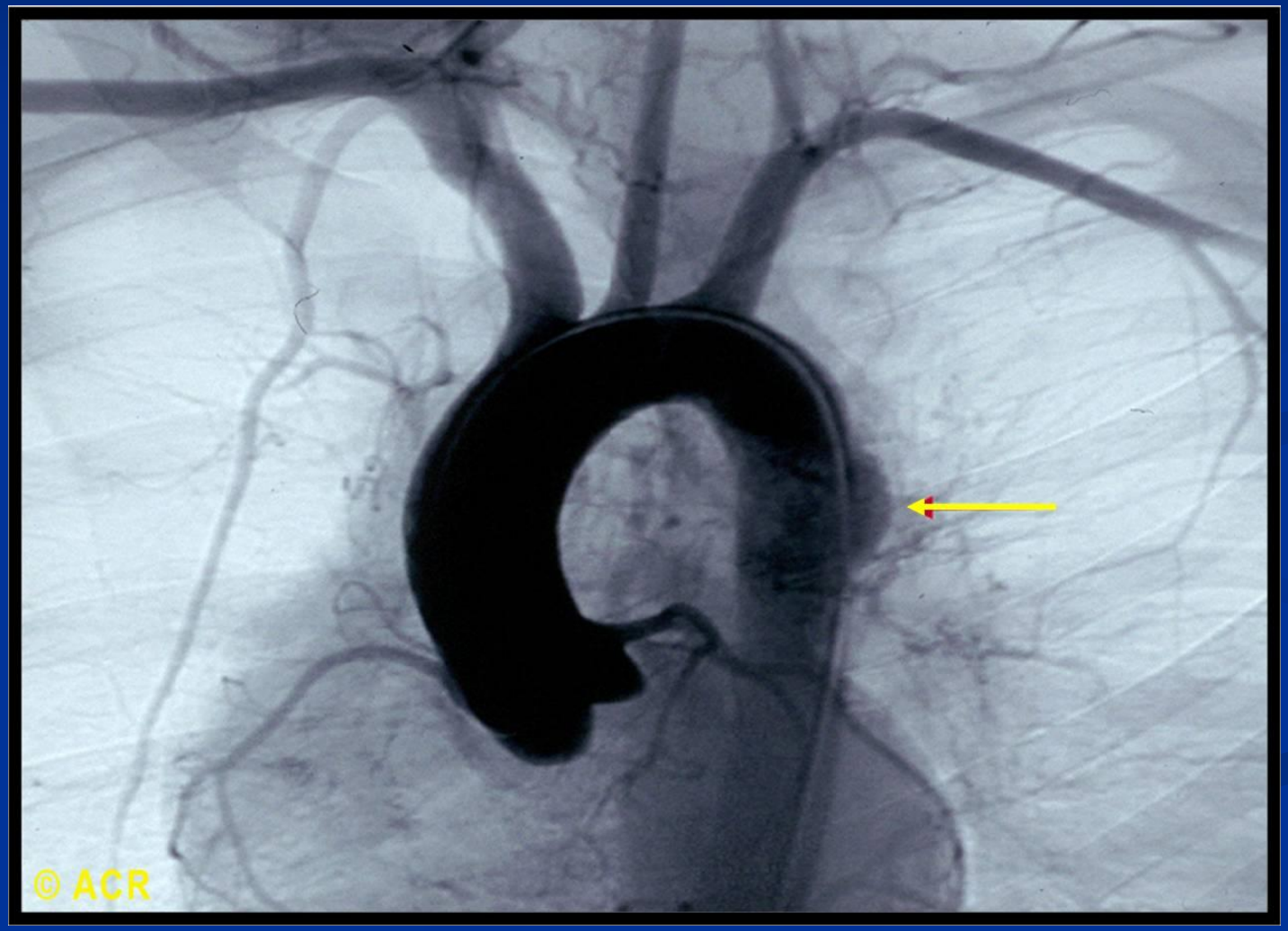
American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis

Criterion	Definition
Age at disease one ≤40 years	Development of symptoms or findings related to Takayasu arteritis at age ≤40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use, especially the upper extremities
Decreased brachial artery pressure	Decreased pulsation of one or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually foci or segmental

For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5 percent and a specificity of 97.8 percent.

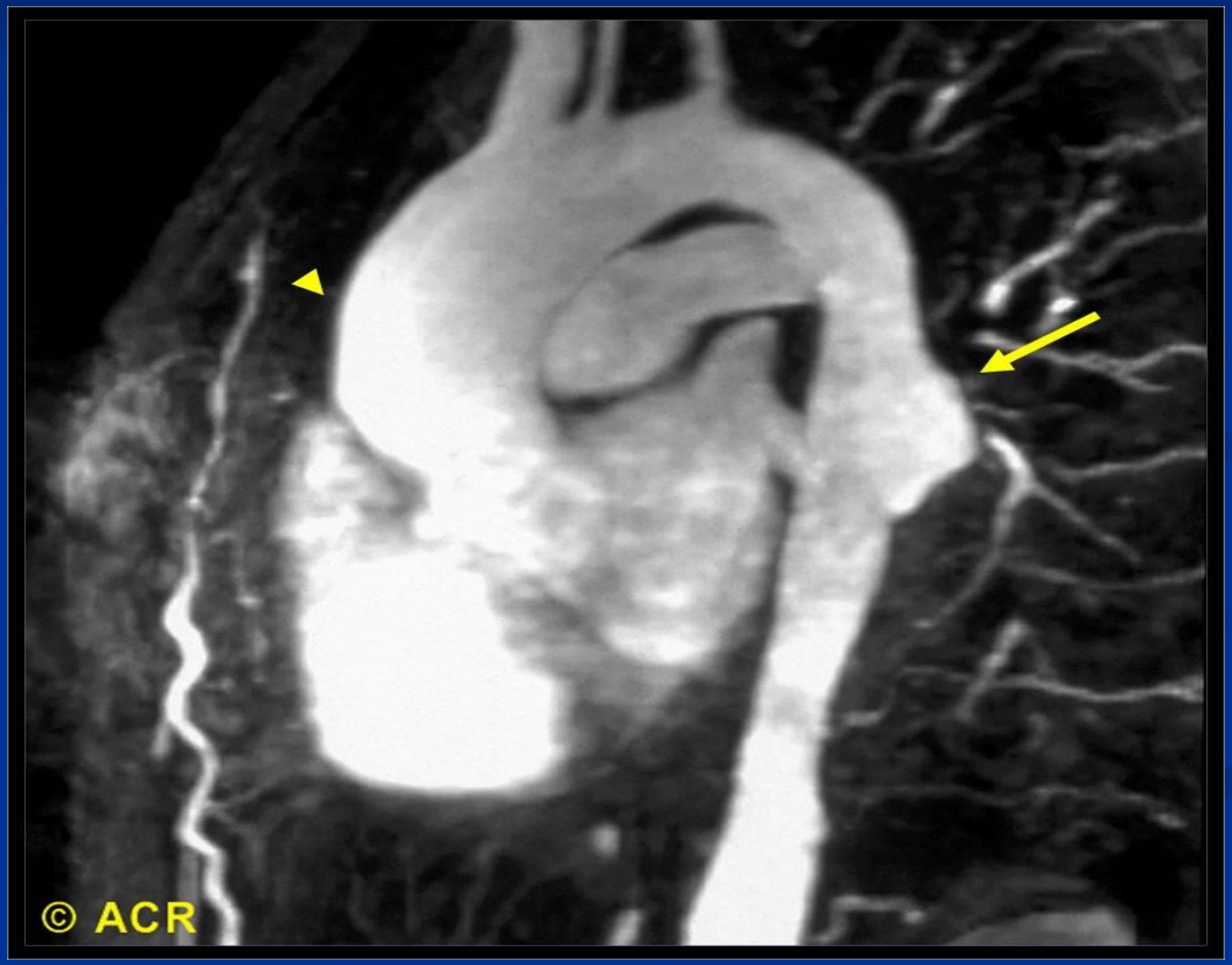
Adapted from Arend, WP, Michel, BA, Block, DA, et al, Arthritis Rheum 1990; 33:1129.

Takayasu Disease: Arteritis
Aneurysmal Dilatation

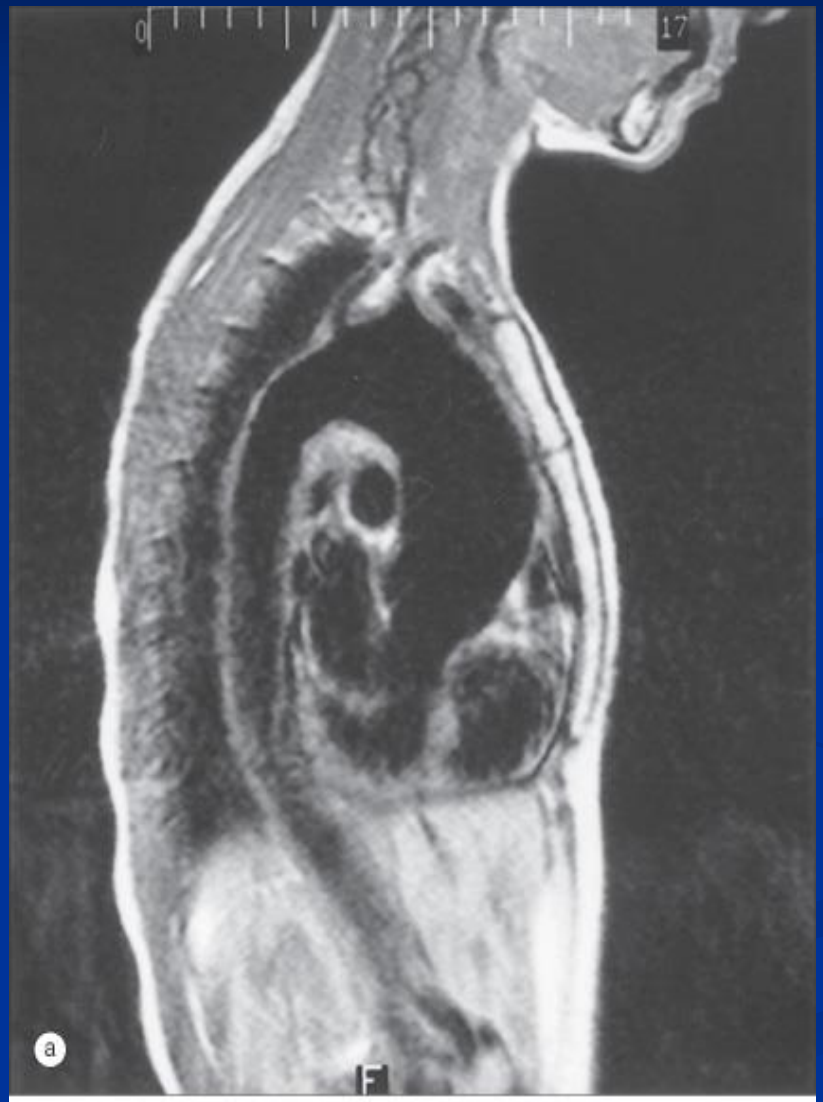


Takayasu's Arteritis

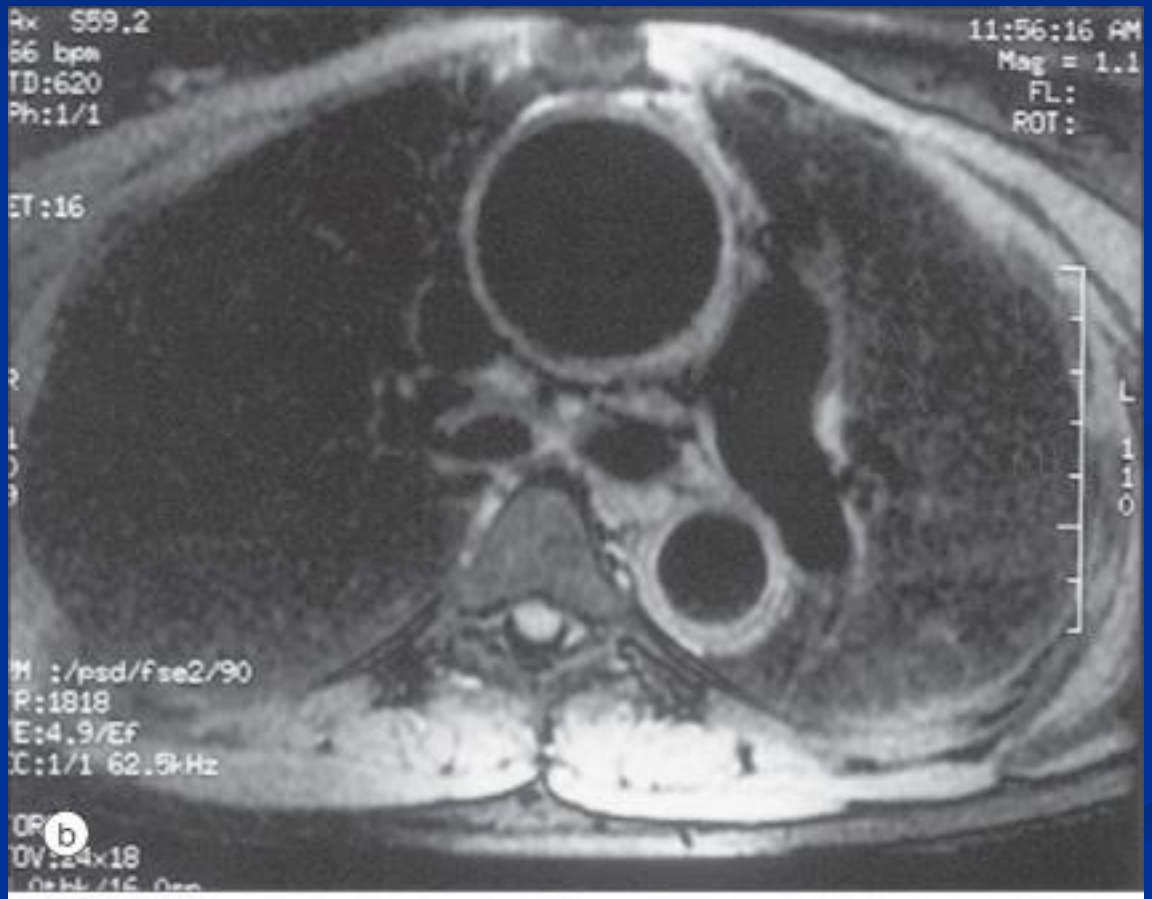
Aneurysmal dilatation of ascending and descending aorta



MR Angiogram Aortic root

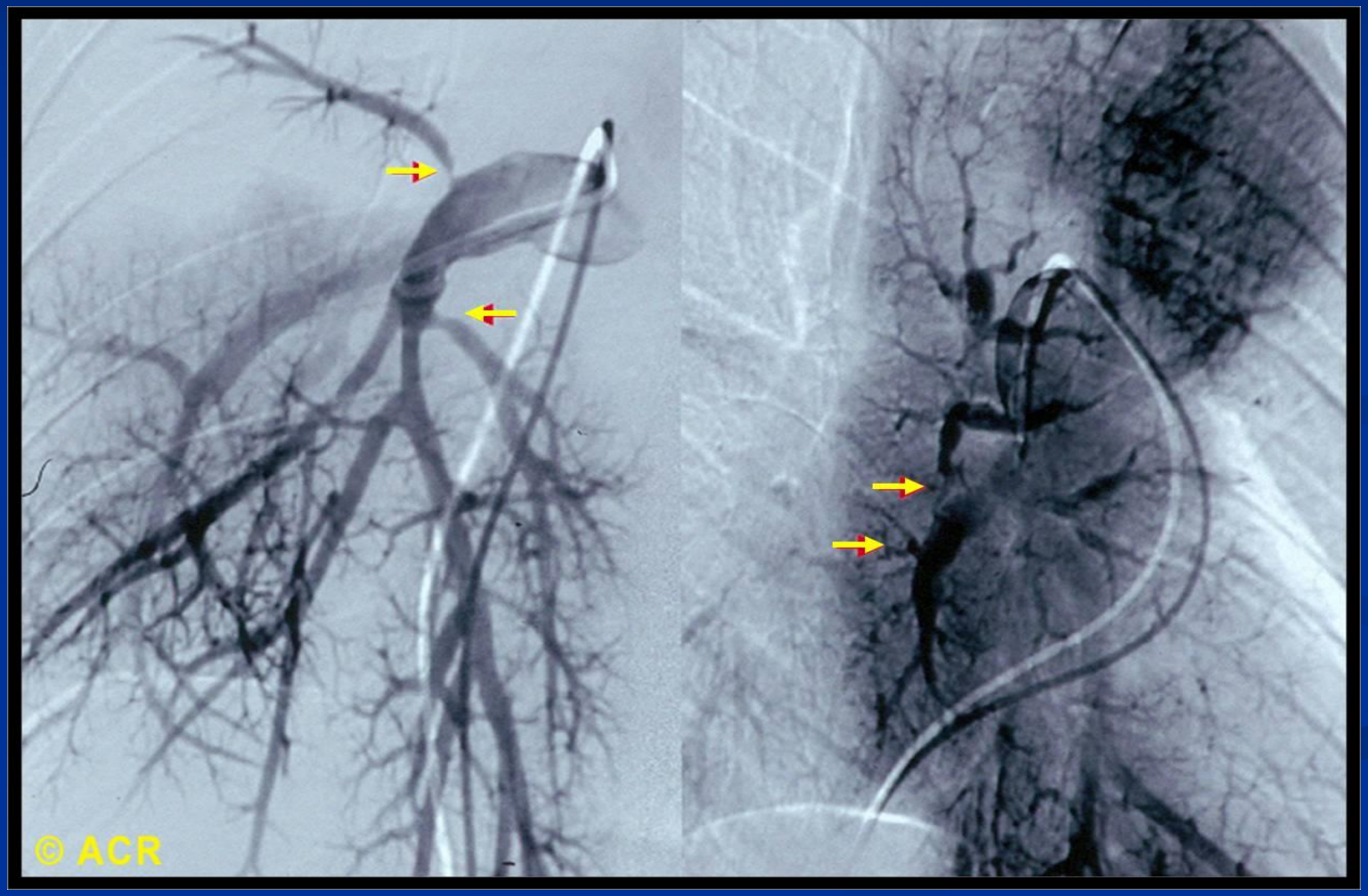


MR Angiogram Aortic root



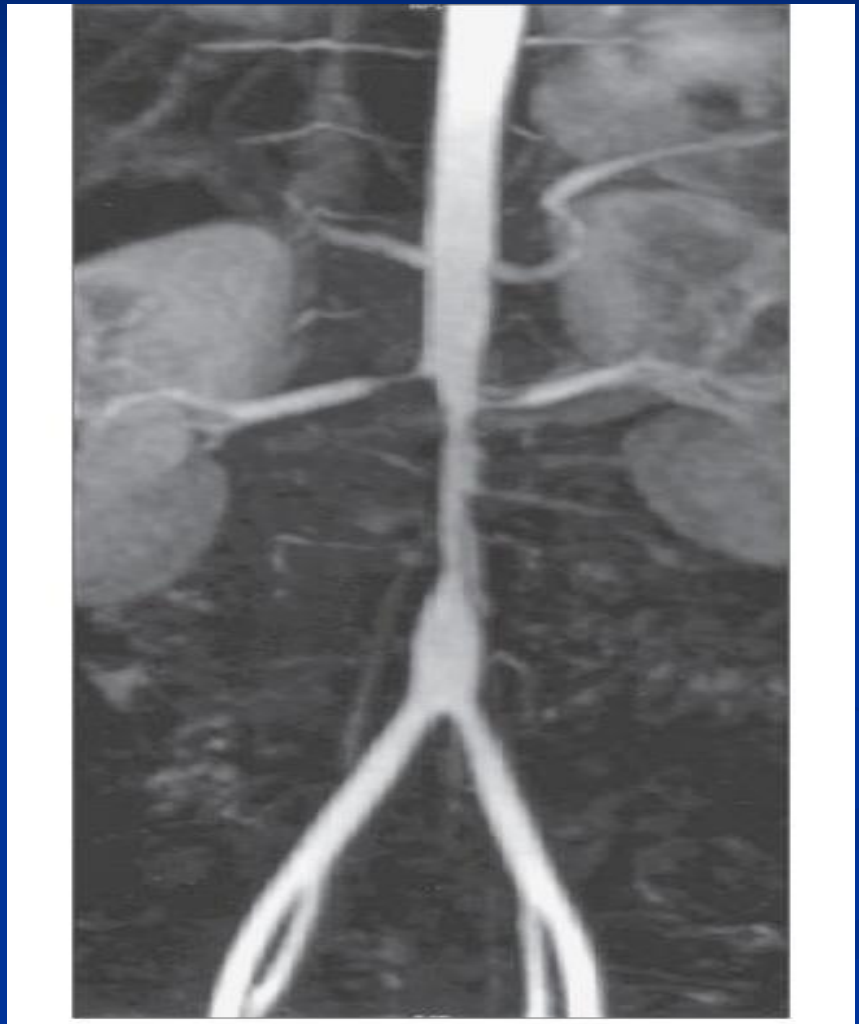
Takayasu's Arteritis

Stenosis of pulmonary arteries



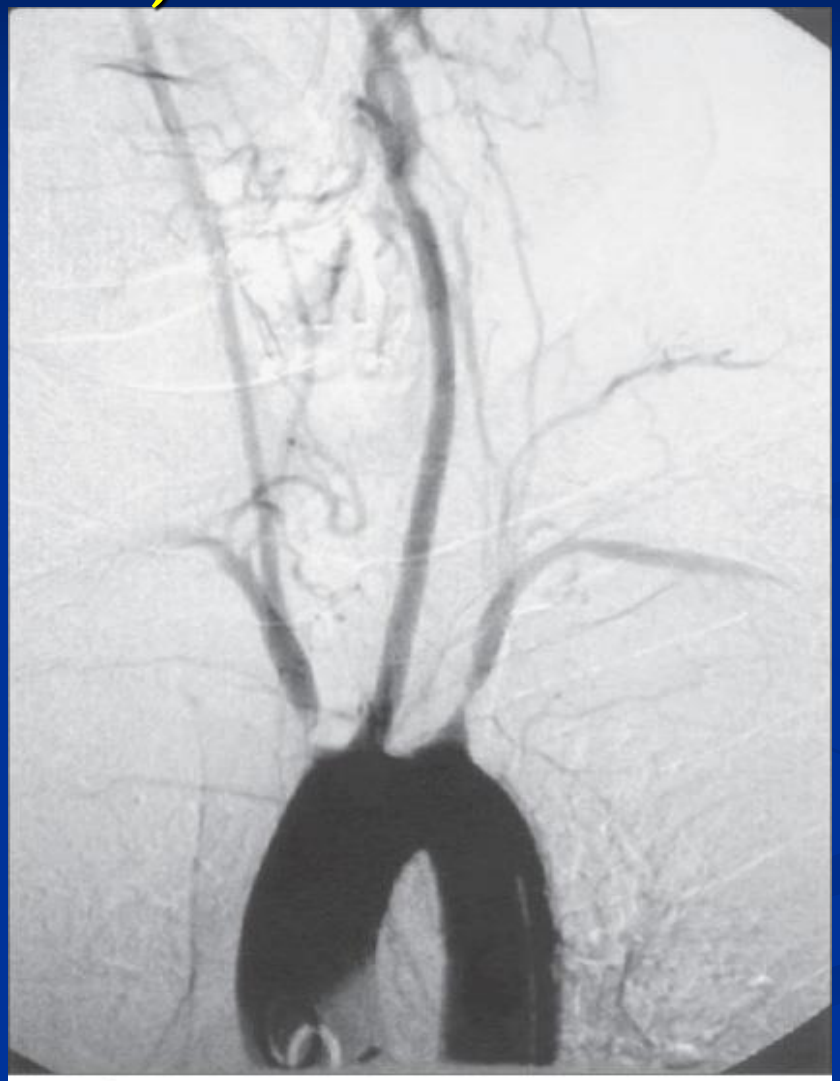
Takayasu's Arteritis

Stenosis of renal arteries



Takayasu's Arteritis

Stenosis of major branches of Aortic root

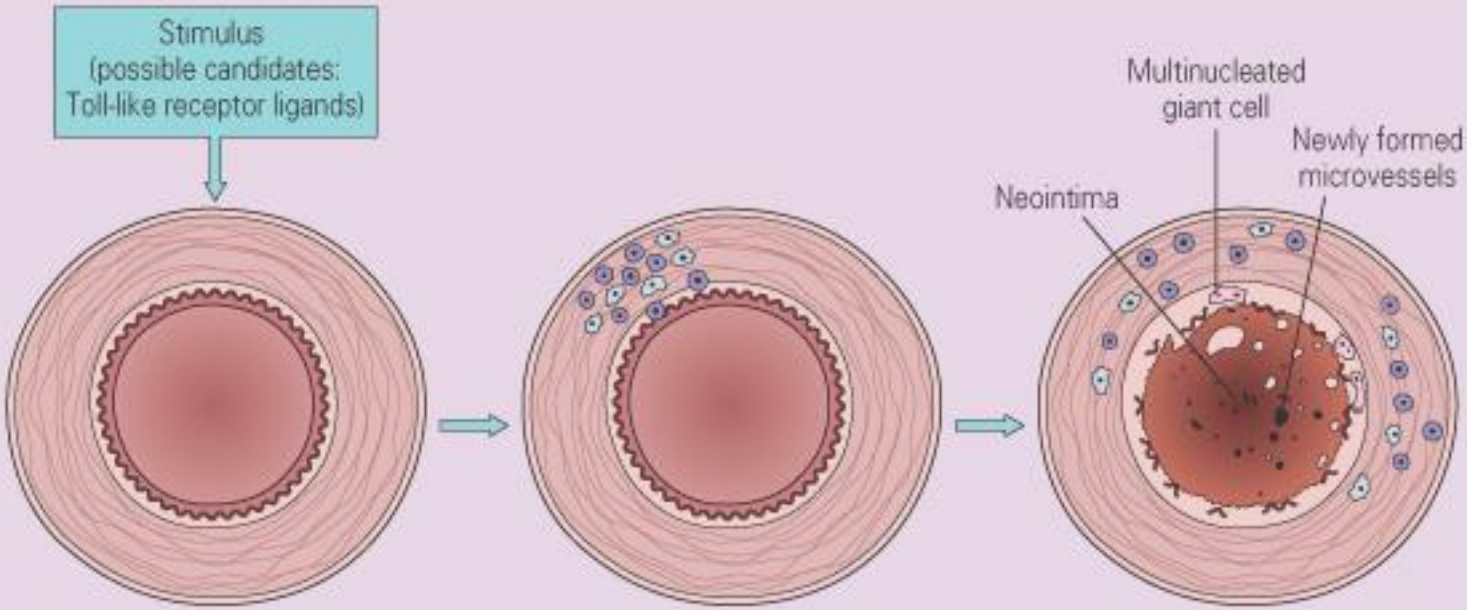


Giant cell arteritis

The ACR criteria for the classification

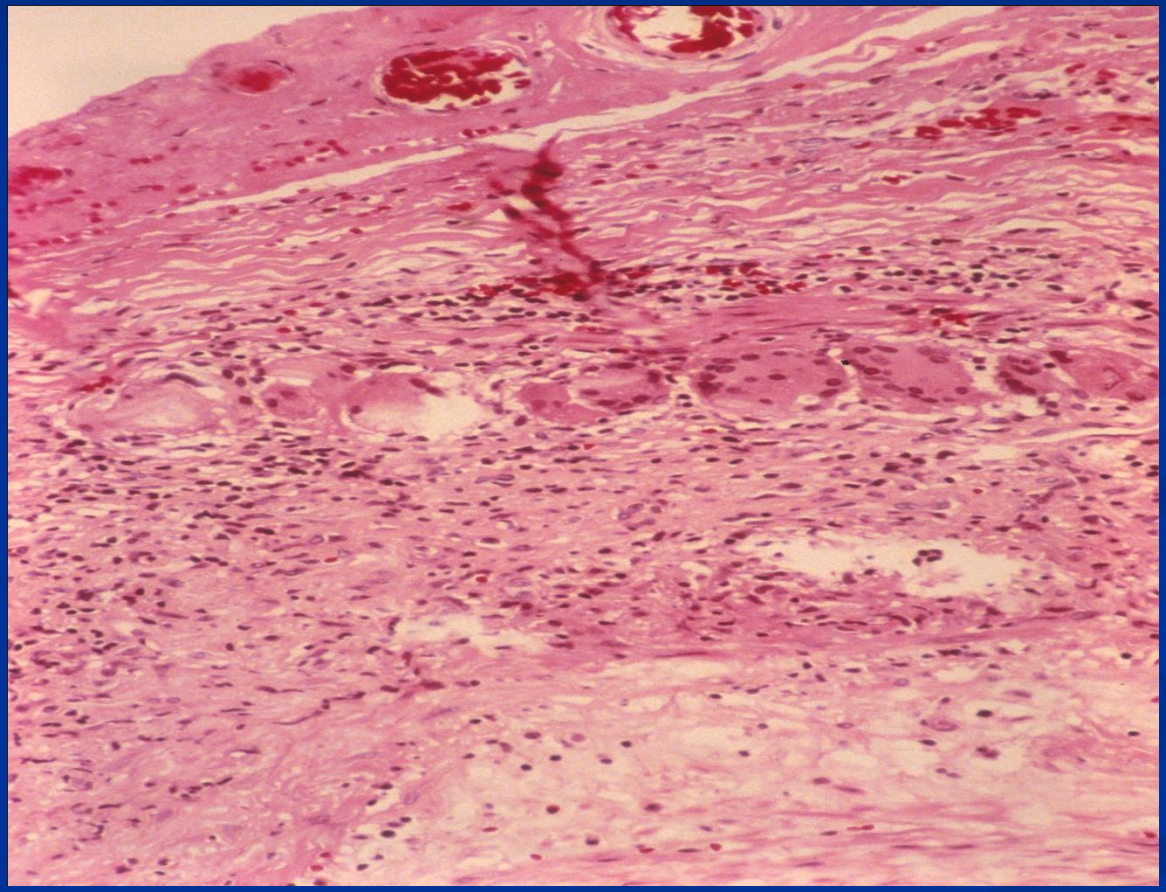
- 94 percent sensitivity and a 91 percent specificity for the diagnosis of GCA
- Age ≥ 50 years at time of disease onset
- Localized headache of new onset
- Tenderness or decreased pulse of the temporal artery
- Erythrocyte sedimentation rate (ESR) greater than 50 mm/h (Westergren)
- Biopsy of an artery; necrotizing arteritis

PATHOGENESIS OF GIANT CELL ARTERITIS



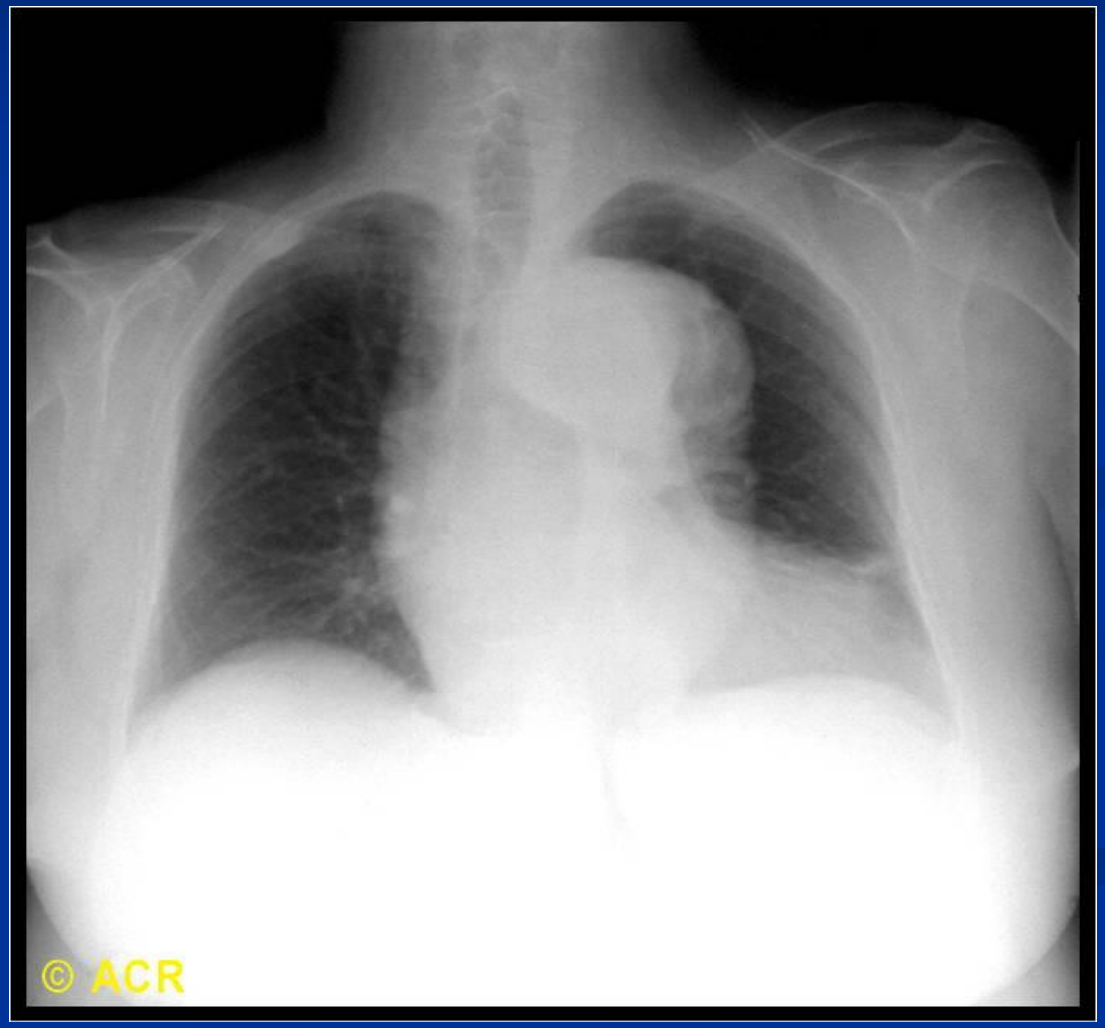
GCA

Giant cells



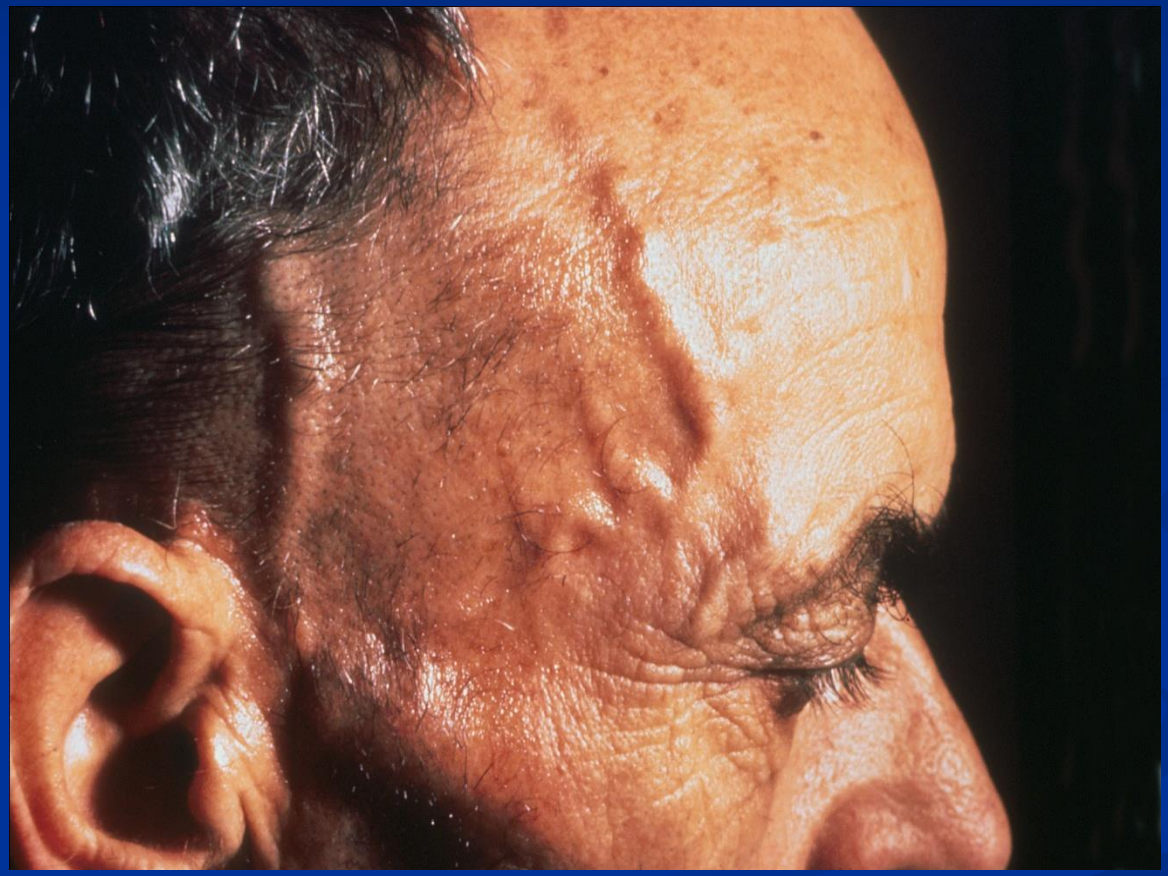
Giant Cell Arteritis

Aortic Dilatation

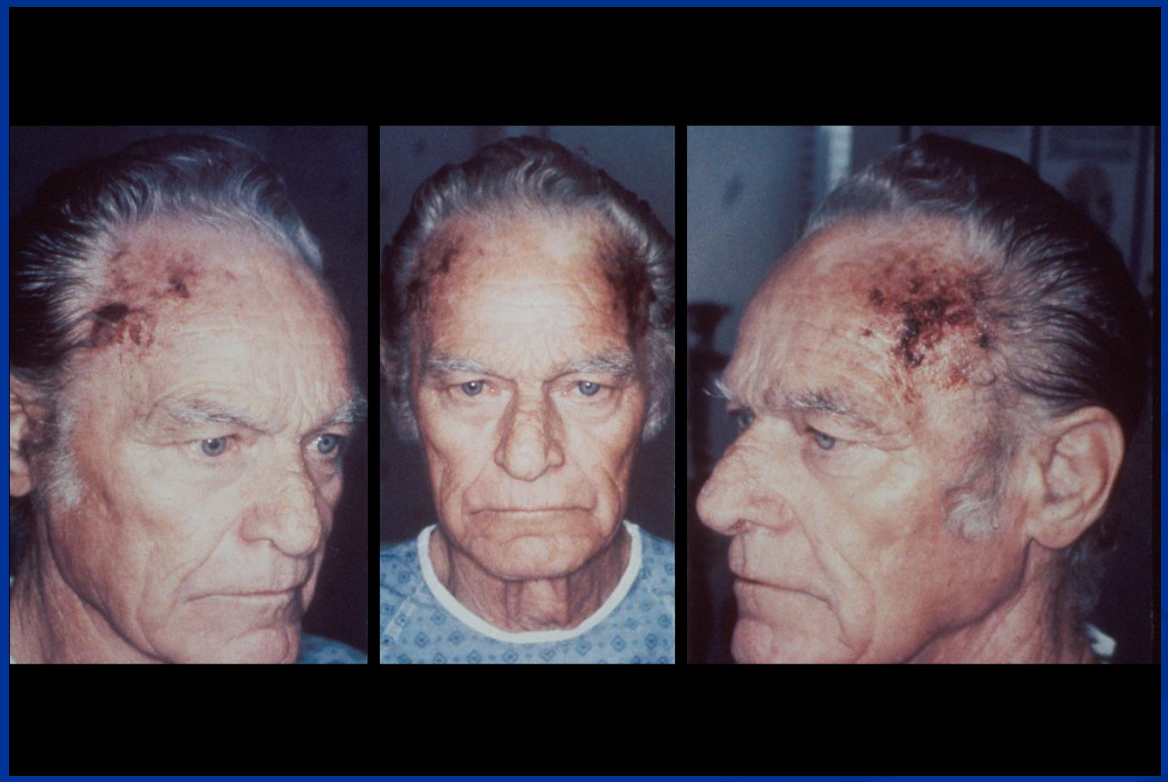


GCA

Dilated Temporal artery and branches

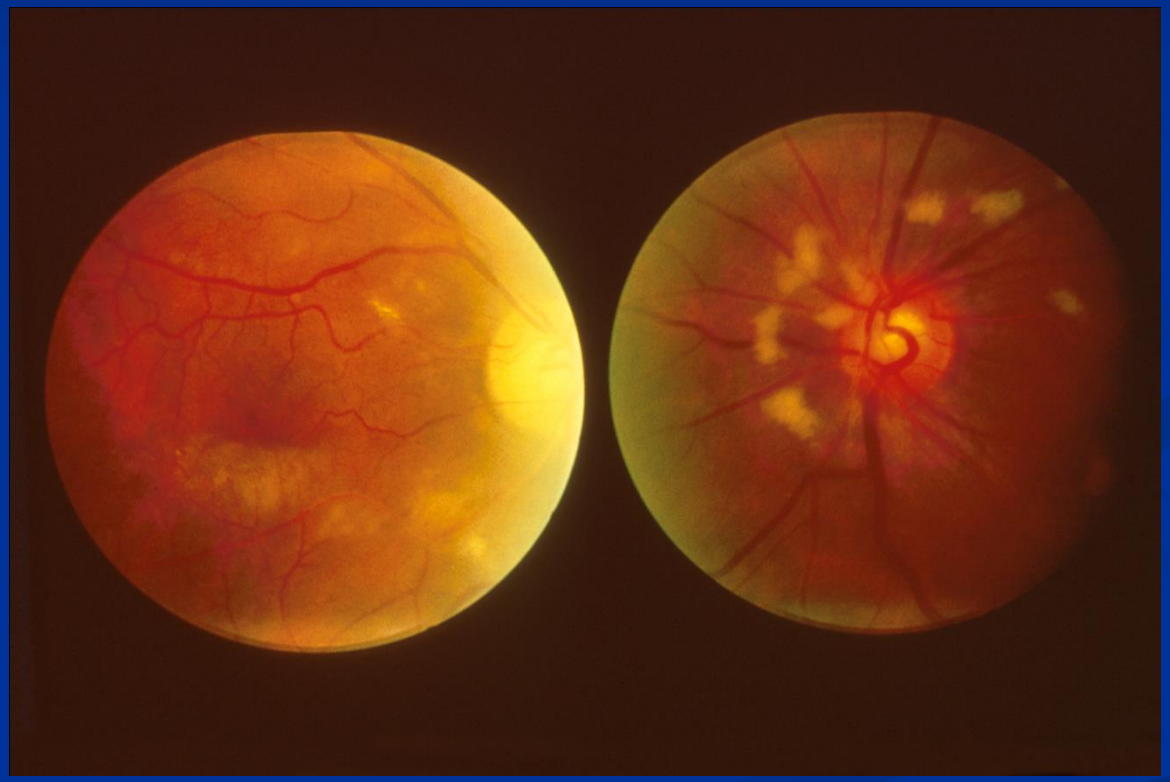


GCA
Skin necrosis



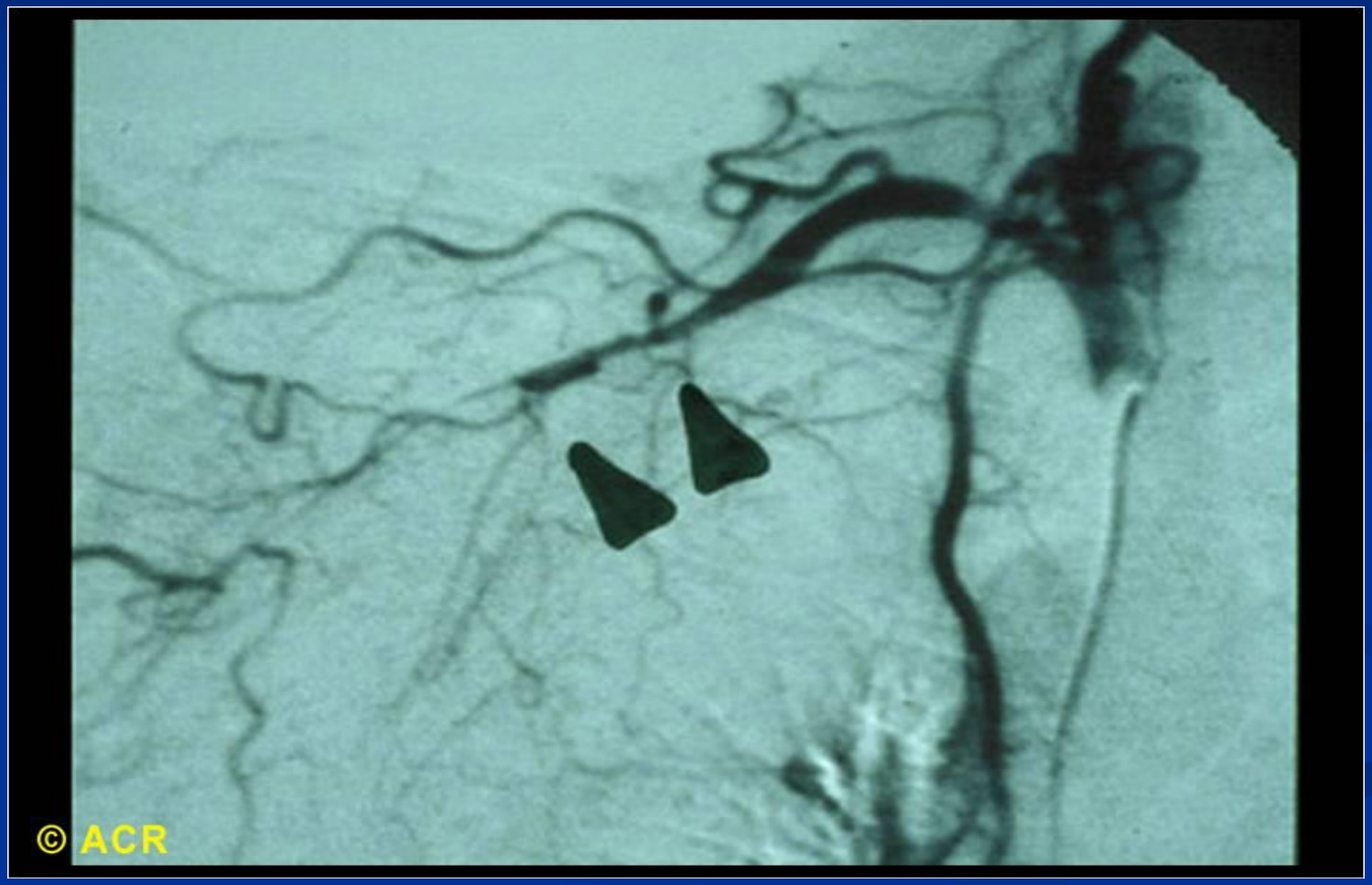
GCA

Retinal Ischmia



GCA

Subclavian artery stenosis



Differences of GCA and Takayasu's Arteritis

Distinguishing features of giant cell versus Takayasu arteritis

Finding	Giant cell arteritis	Takayasu arteritis
Female-to-male ratio	3:2	7:1
Age at onset	>50 years	<40 years
Ethnic ancestry	European	Asian
Histopathology	Granulomatous inflammation	Granulomatous inflammation
Primary vessels involved	External carotid artery branches	Aorta and branches
Renovascular hypertension	Rare	Common
HLA association	HLA-DR4	HLA-Bw52
Course	Self-limited	Chronic
Response to corticosteroids	Excellent	Excellent
Surgical intervention needed	Rare	Common

Adapted from Michel, BA, Arend, WP, Hunder, GG. Clinical differentiation between giant cell (temporal) arteritis and Takayasu's arteritis. J Rheumatol 1996; 23:106.

Large Vessel Vasculitis
Differential diagnosis

- Fibromuscular dysplasia is usually more focal in its involvement and is not associated with the systemic symptoms
- Excess ergotamine intake may cause reversible spasm of the large blood vessels
- Ehlers-Danlos syndrome may be associated with multiple aneurysms, systemic signs of inflammation are absent.
- Takayasu arteritis and giant cell arteritis. Distinction between the two disorders can usually be made based upon the age of the patient and the distribution of lesions

Medium sized vessel vasculitis

- Polyarteritis nodosa
- Kawasaki disease
- Primary central nervous system vasculitis

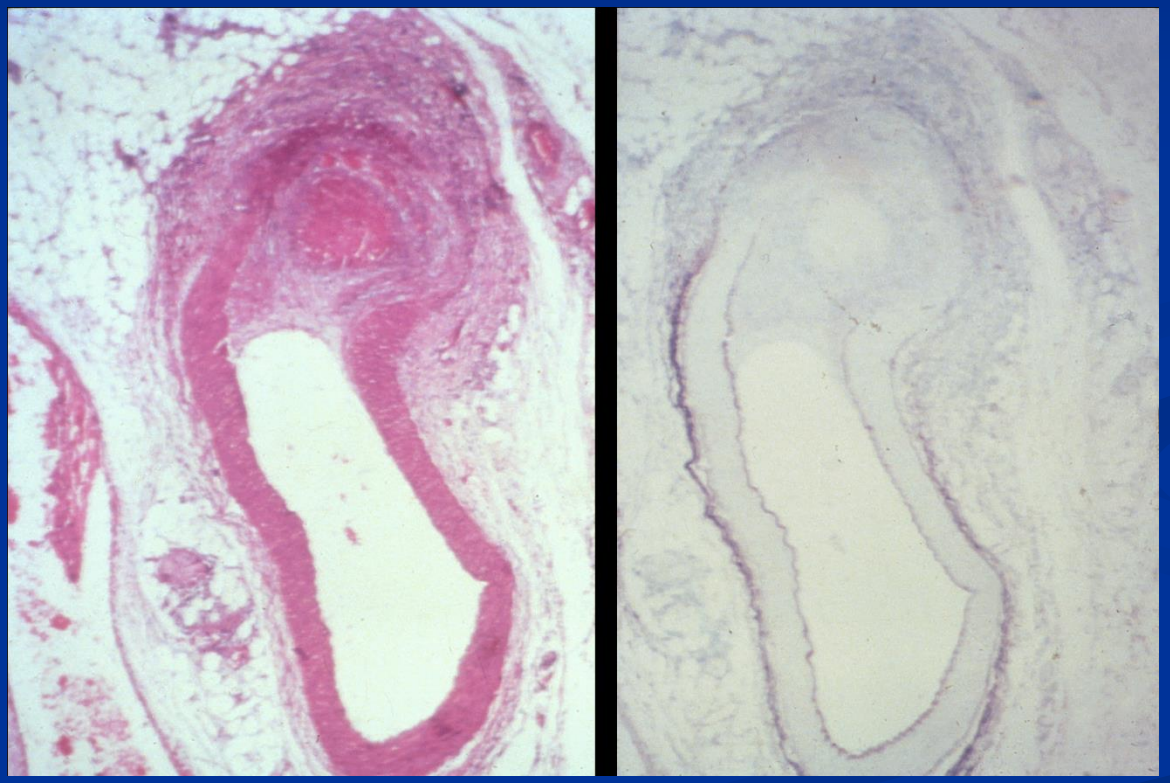
Medium Vessel vasculitis

PAN Classification criteria

- Otherwise unexplained weight loss greater than 4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias (excluding that of the shoulder and hip girdle), weakness of muscles, tenderness of leg muscles, or polyneuropathy
- Mononeuropathy or polyneuropathy
- New onset diastolic blood pressure greater than 90 mmHg
- Elevated levels of serum blood urea nitrogen (>40 mg/dL or 14.3 mmol/L) or creatinine (>1.5 mg/dL or 132 μmol/L)
- Evidence of hepatitis B virus infection via serum antibody or antigen serology
- Characteristic arteriographic abnormalities not resulting from noninflammatory disease processes
- A biopsy of small or medium-sized artery containing polymorphonuclear cells

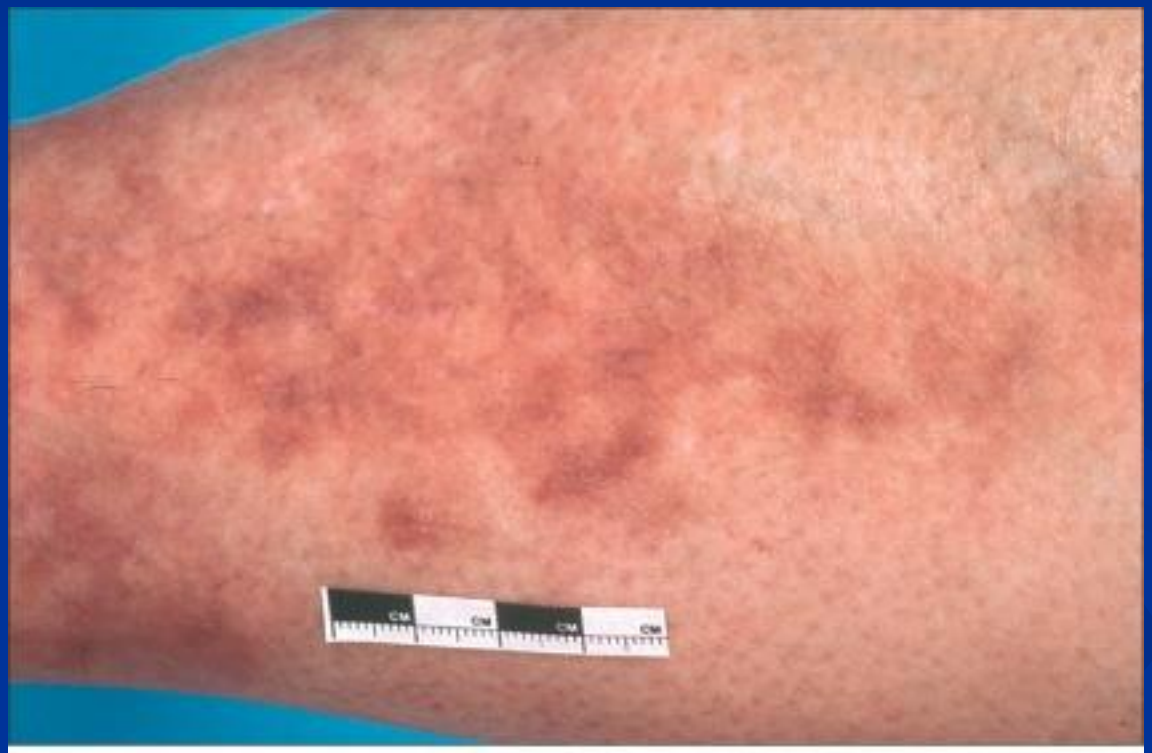
Polyarteritis Nodosa

Medium size vessel inflammation



Polyarteritis Nodosa

Livedo reticularis



Polyarteritis Nodosa

Livedo reticularis with purpuric and necrosis

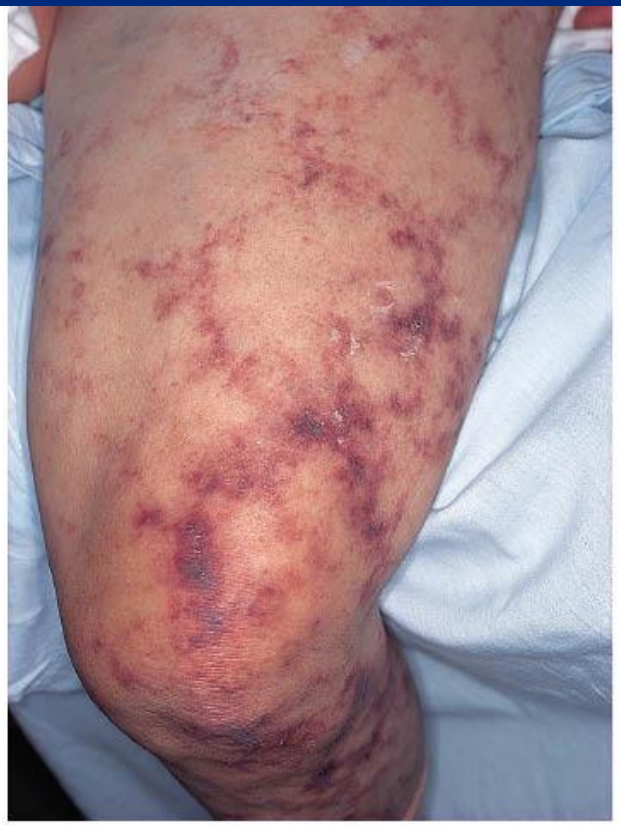
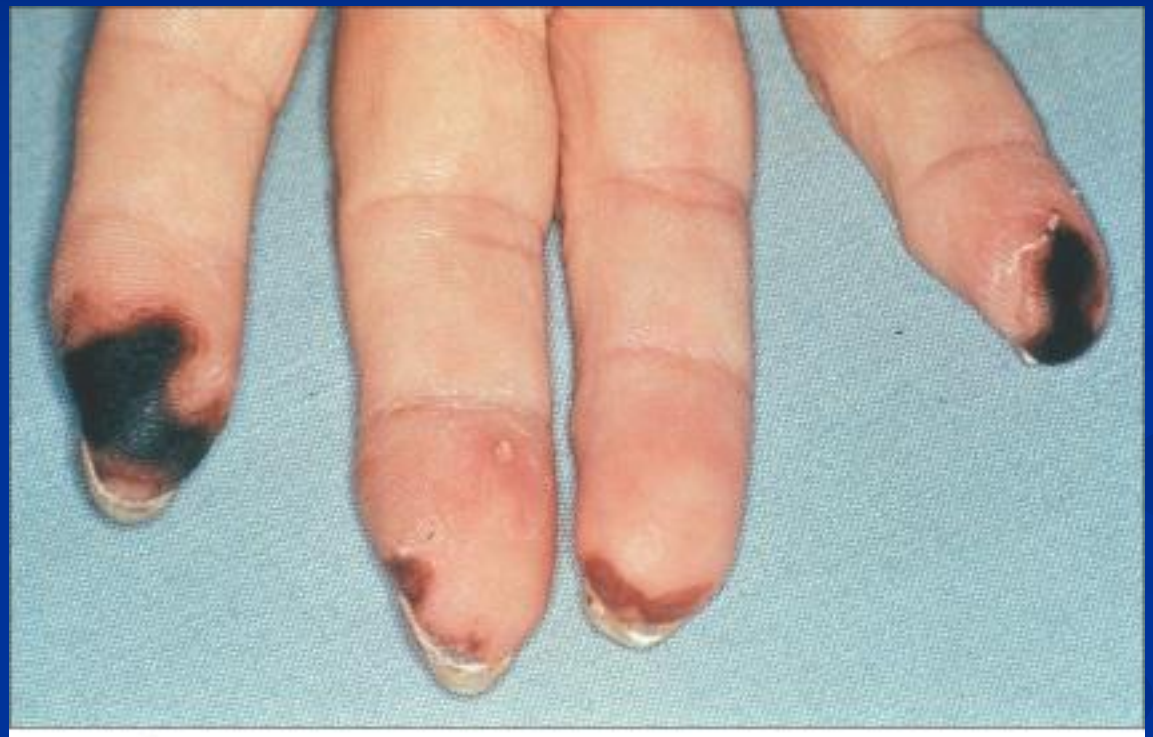


Figure 4–5 Cutaneous polyarteritis nodosa as manifested by a livedo pattern with purpuric and necrotic lesions.

Polyarteritis Nodosa



Polyarteritis Nodosa

A patient with hepatitis B

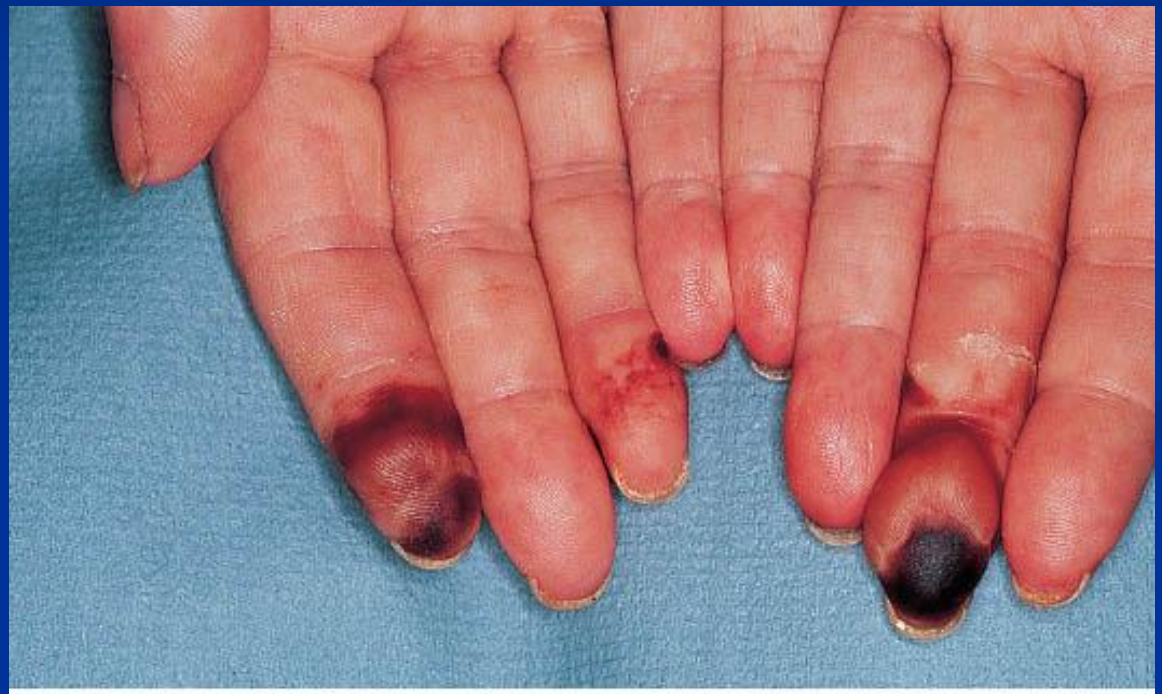
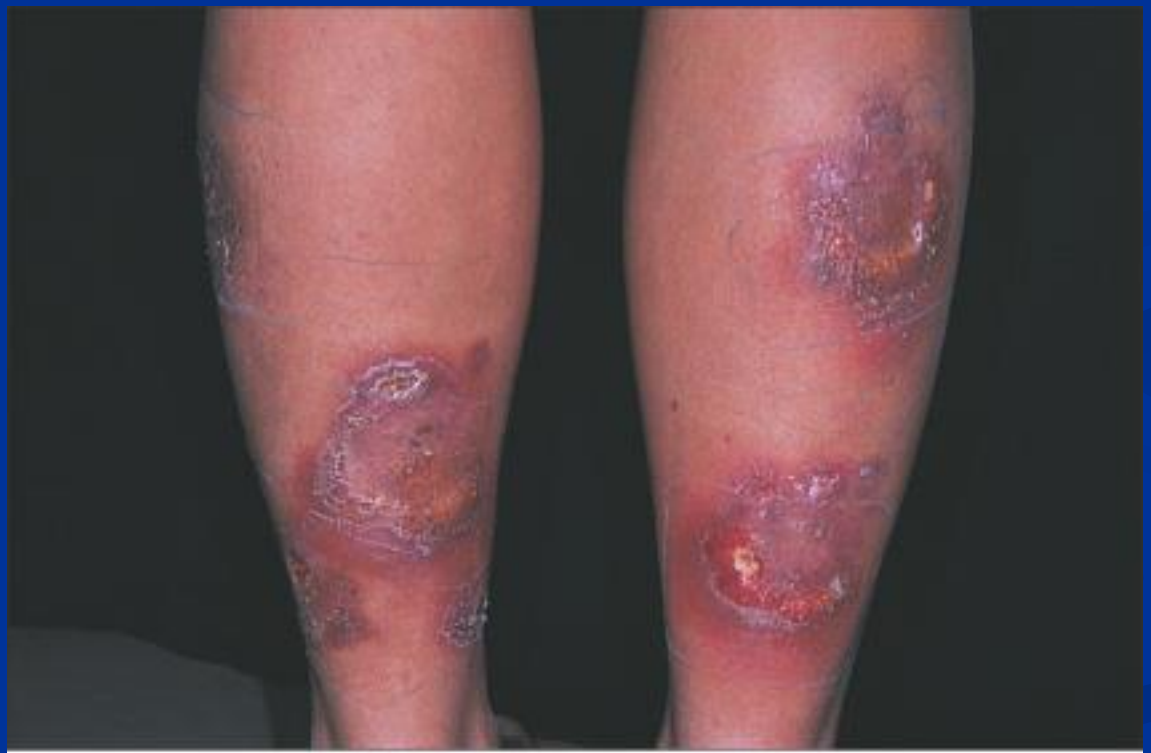


Figure 4–6 Ischemic necrosis of the fingertips in a patient with polyarteritis nodosa secondary to hepatitis B antigenemia.

(Courtesy of Dr Neil A. Fenske, Tampa, FL.)

Polyarteritis Nodosa

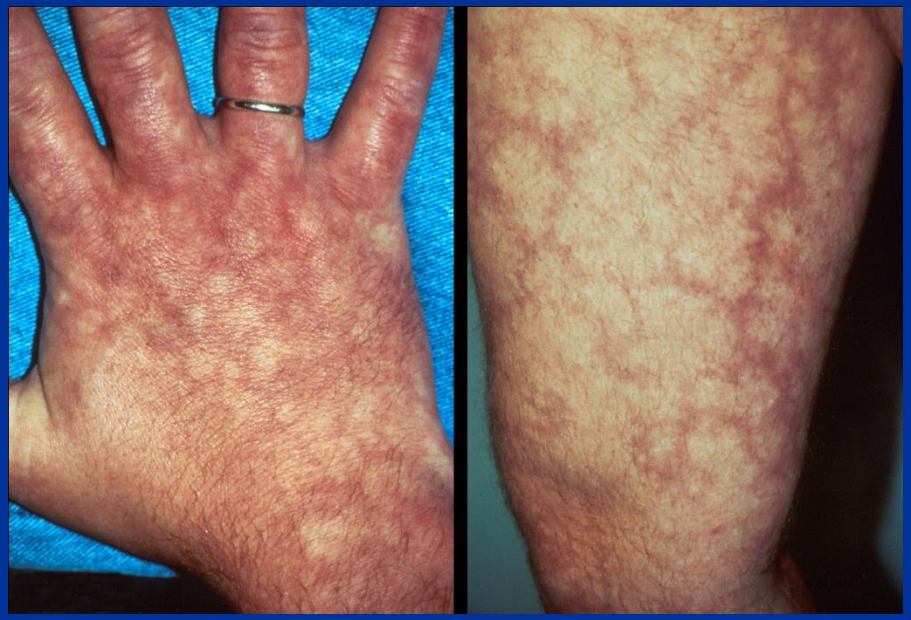
Patient with history of Crohn's disease

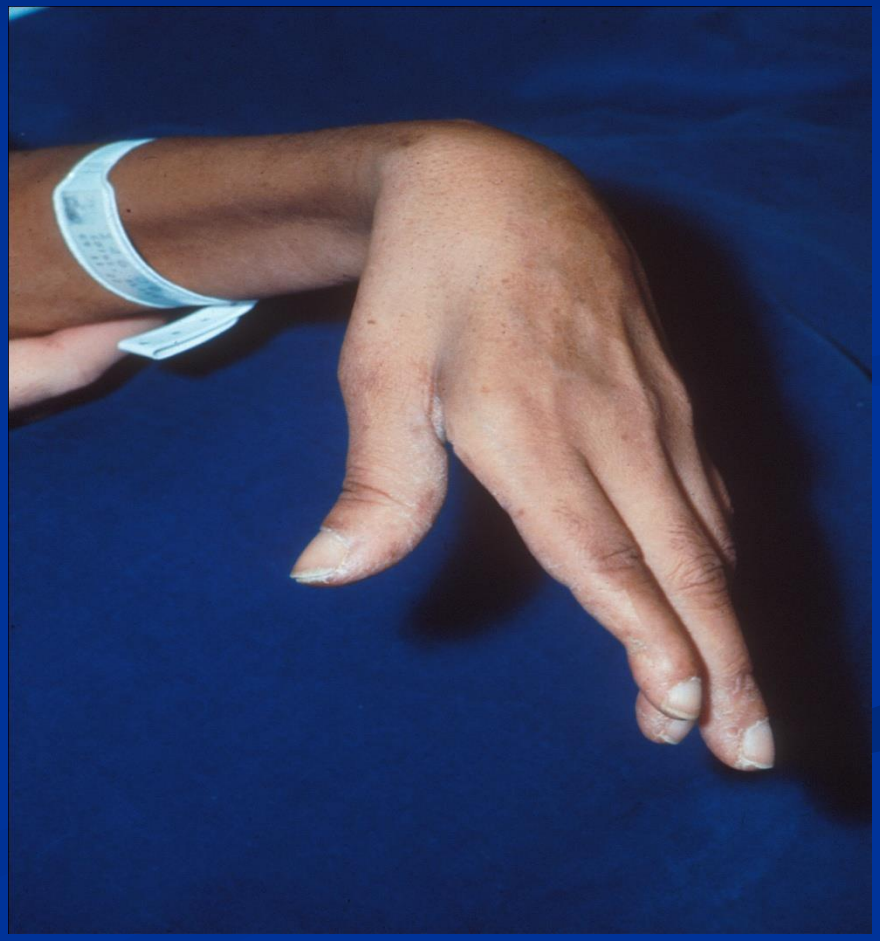


PAN

Livedo Reticularis

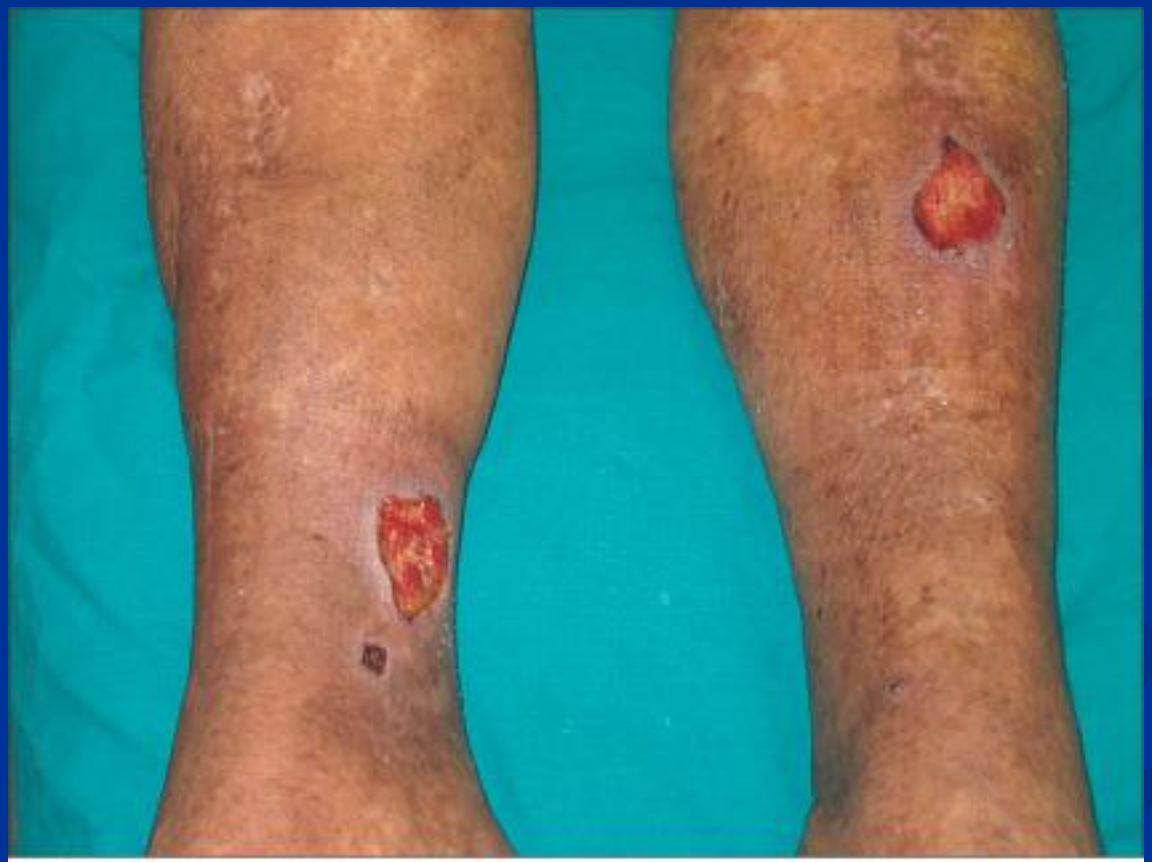
Wrist drop- Mononeuritis





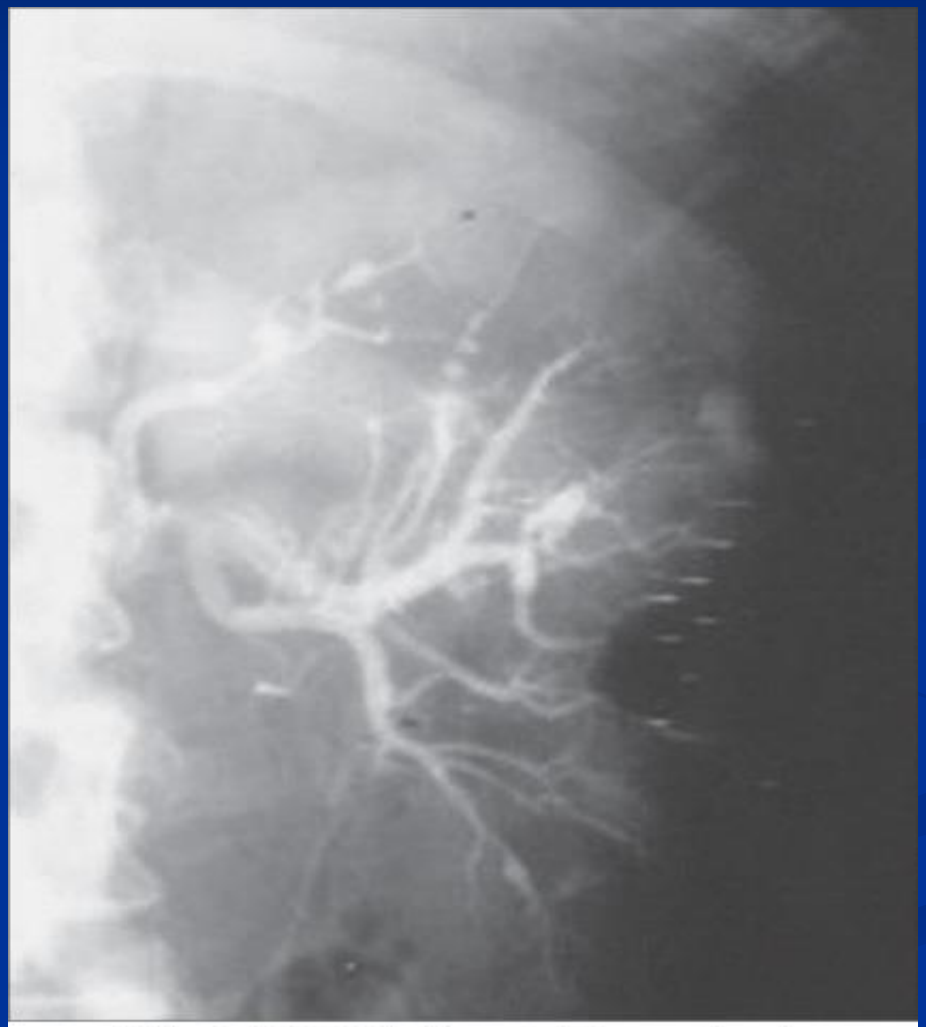
Polyarteritis Nodosa

Skin ulceration



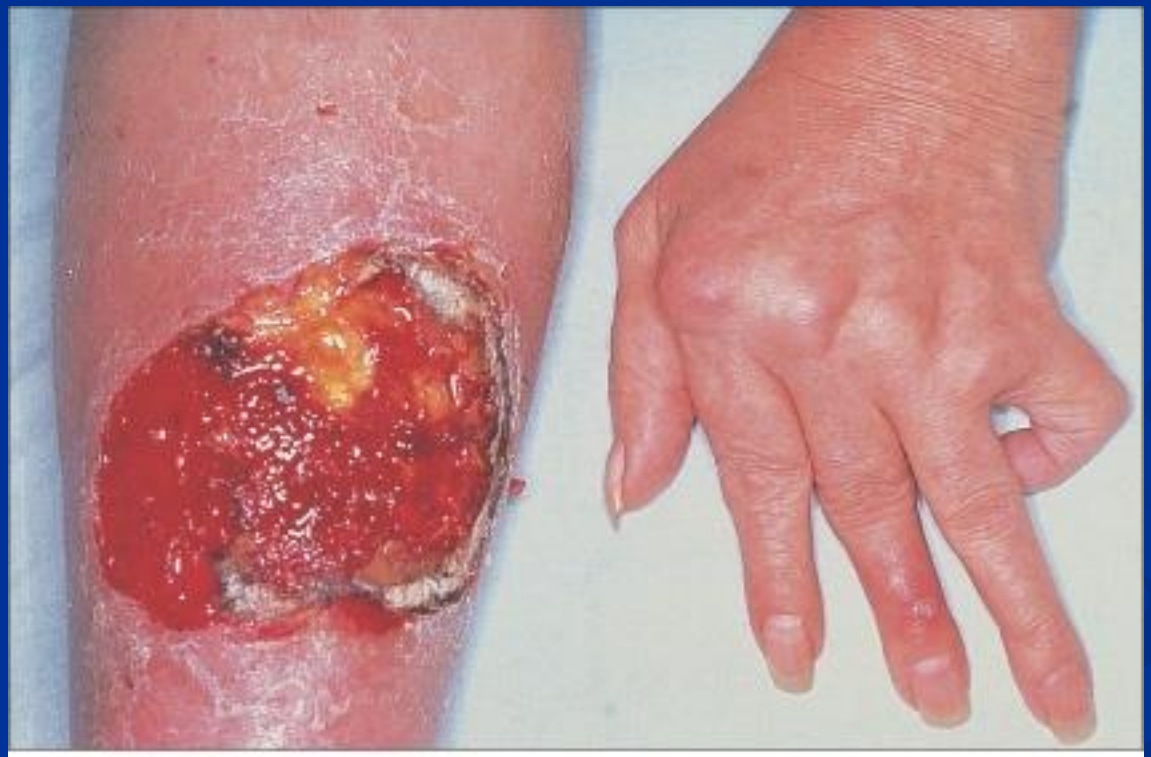
Polyarteritis Nodosa

Microaneurysms



Rheumatoid arthritis

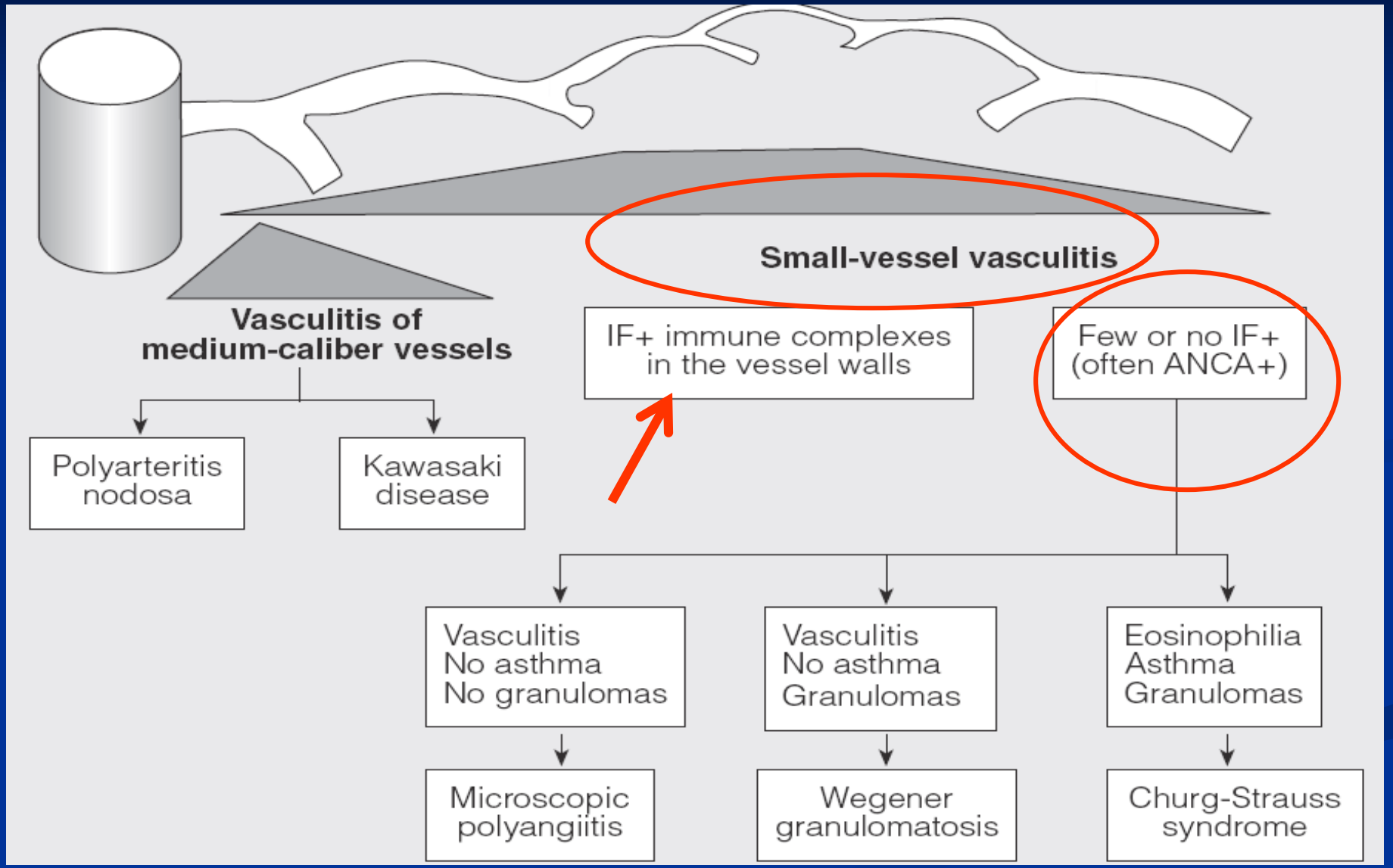
Ulcerative Vasculitis



Small Vessel Vasculitis

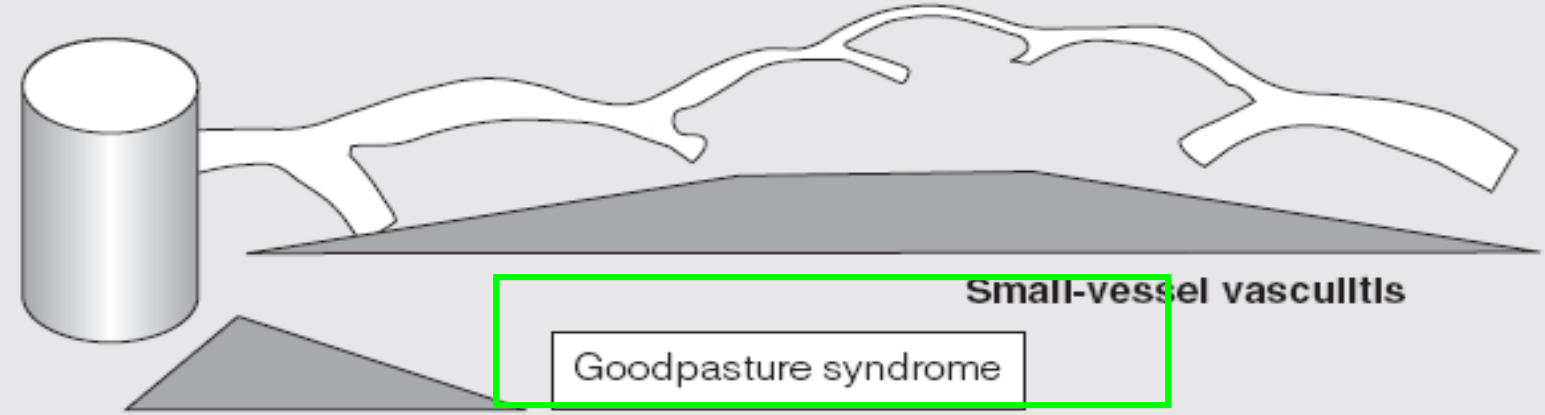
- Hypersensitivity vasculitis
- Henoch-Schönlein purpura
- Essential cryoglobulinemic vasculitis
- ANCA Associated Vasculitis
  - Churg-Strauss syndrome
  - Wegener granulomatosis
  - Microscopic polyarteritis
- Vasculitis secondary to connective tissue disorders
- Vasculitis secondary to viral infection

Small vessel vasculitis



Arch Bronconeumol. 2008;44(8):428-36

Immune Complex Deposition



Goodpasture syndrome

IF+ immune complexes in the vessel walls

Little or no IF+ (often ANCA+)

Cryoglobulins in the blood or vessel walls	IgA immune deposits in the vessel walls	Systemic lupus erythematosus	Other sources of immune complexes
Cryoglobulinemic vasculitis	Henoch-Schönlein purpura	Lupus/rheumatoid vasculitis	Other vasculitis due to immune complexes

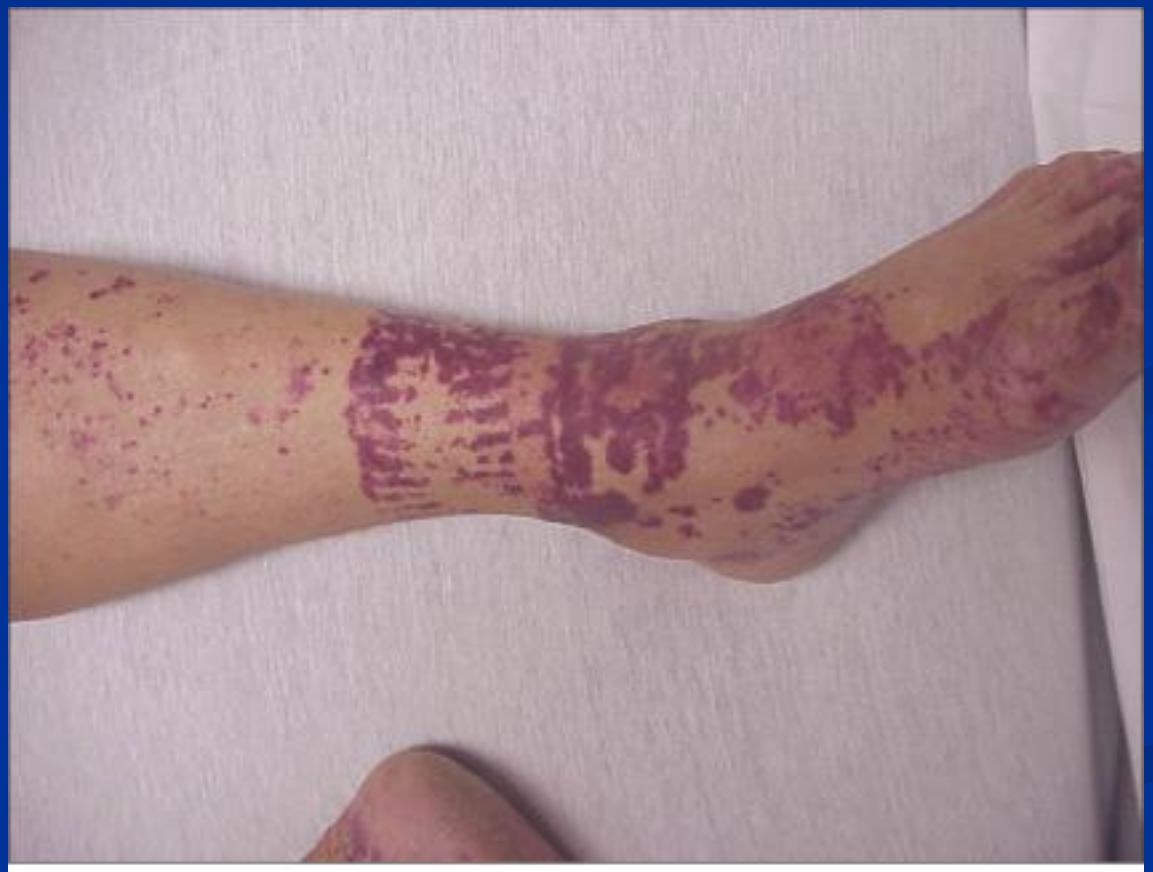
Arch Bronconeumol. 2008;44(8):428-36

Hypersensitivity vasculitis

The ACR proposed crietria

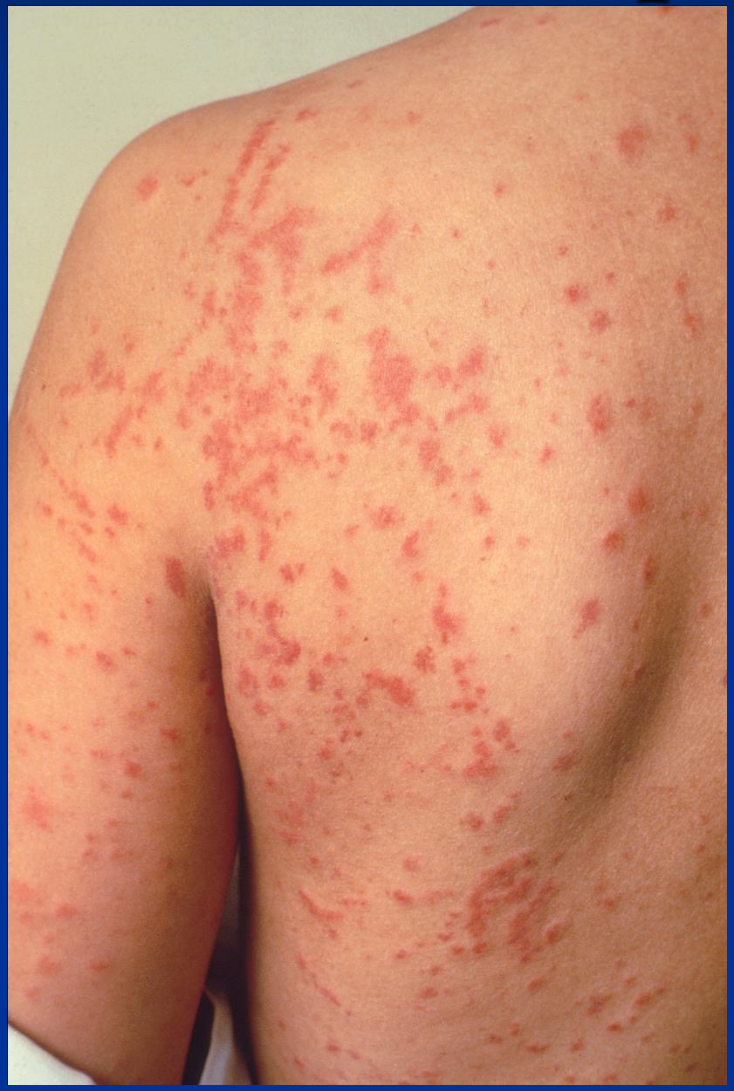
- The presence of three or more of these criteria had a sensitivity and specificity of 71 and 84 percent, respectively
  - Age >16
  - Use of a possible offending drug in temporal relation to the symptoms
  - Palpable purpura
  - Maculopapular rash
  - Biopsy of a skin lesion showing neutrophils around an arteriole or venule

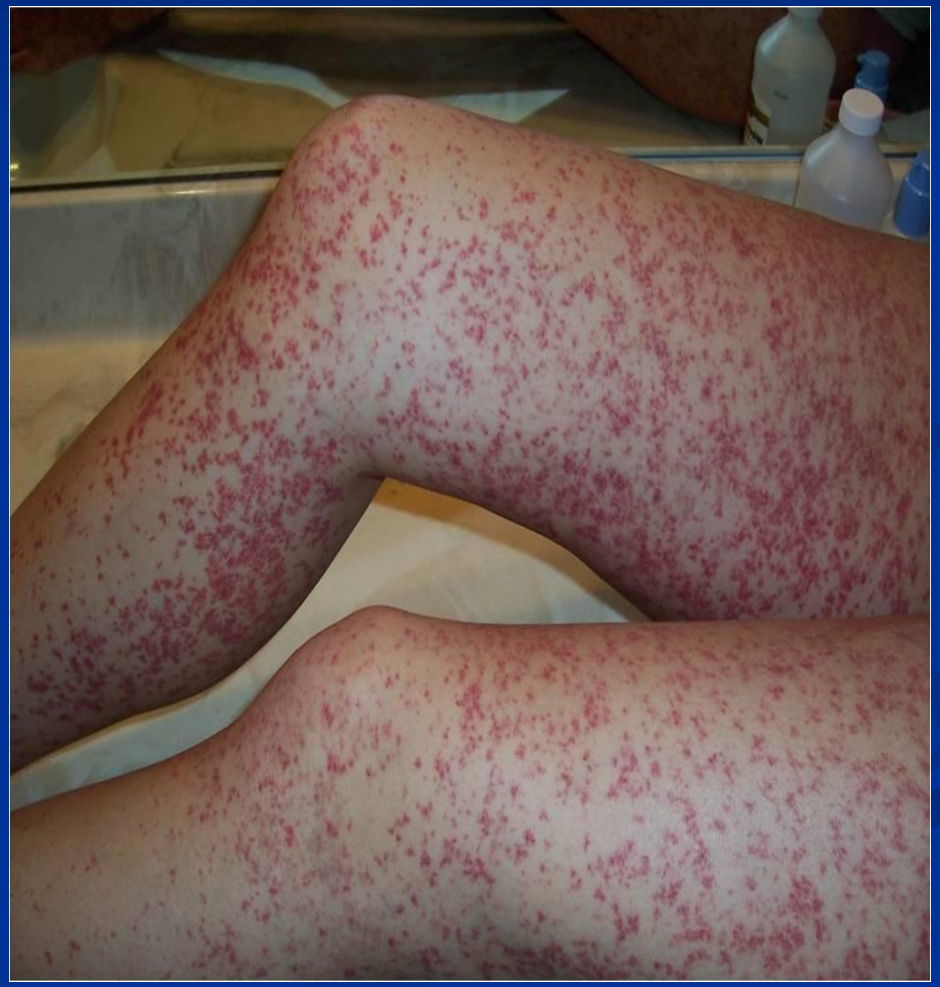
Hypersensitivity vasculitis
Purpura



Small vessel vasculitis

Palpable purpura





Hypersensitivity vasculitis

Bullous lesions

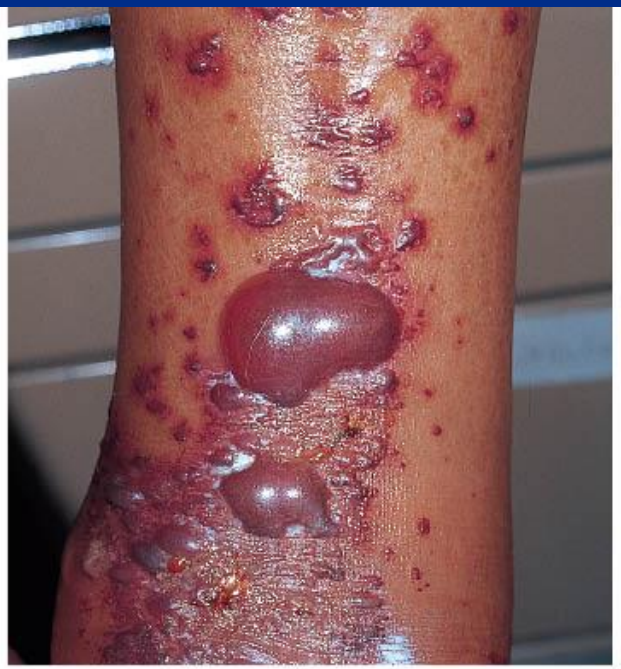


Figure 4–3 Bullous lesions exist within typical areas of palpable purpura in this patient with cutaneous small-vessel vasculitis.

Hypersensitivity vasculitis

Leucocytoclastic Vasculitis

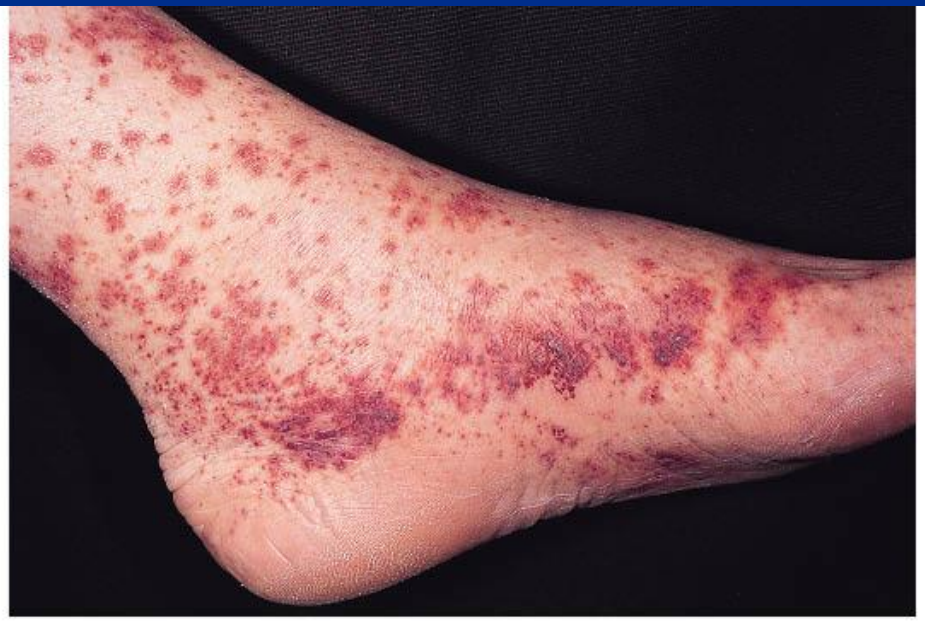
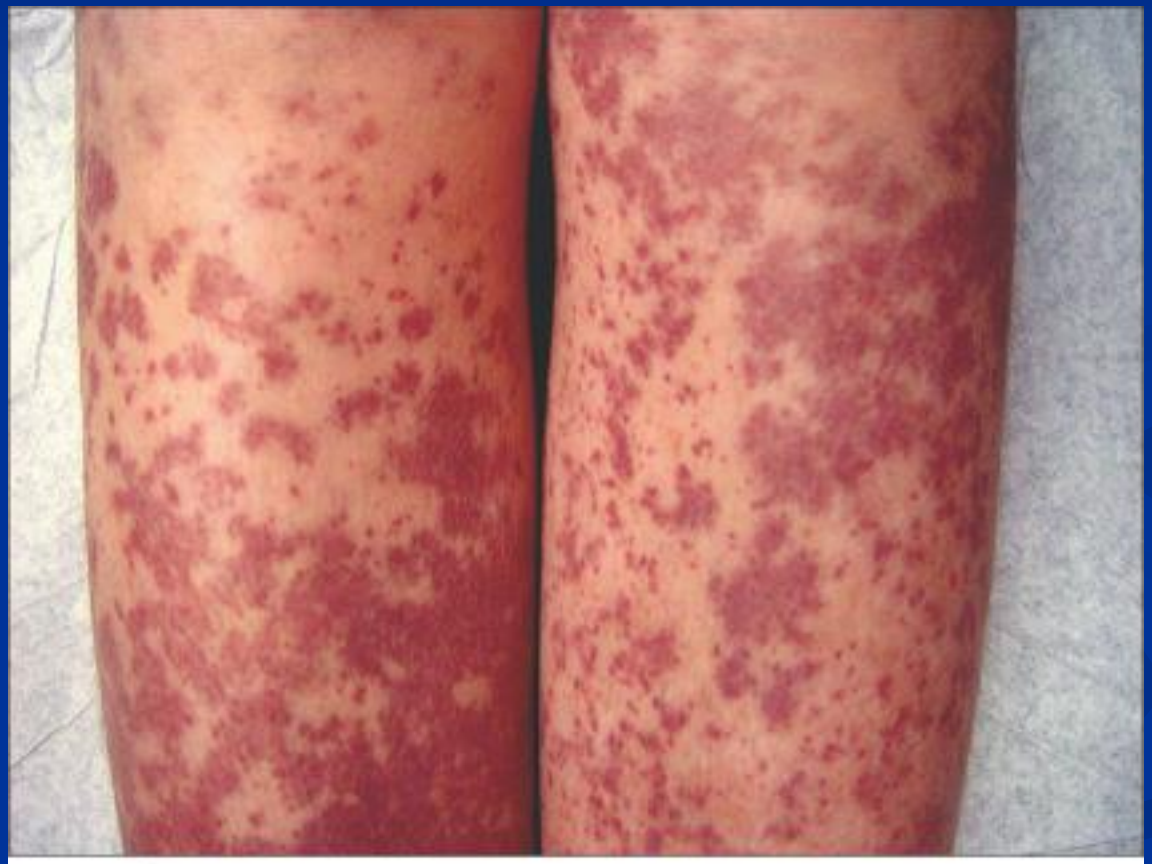


Figure 4–2 Typical palpable purpuric lesions seen in a patient with hypersensitivity vasculitis/small-vessel vasculitis.

Henoch-Schönlein purpura

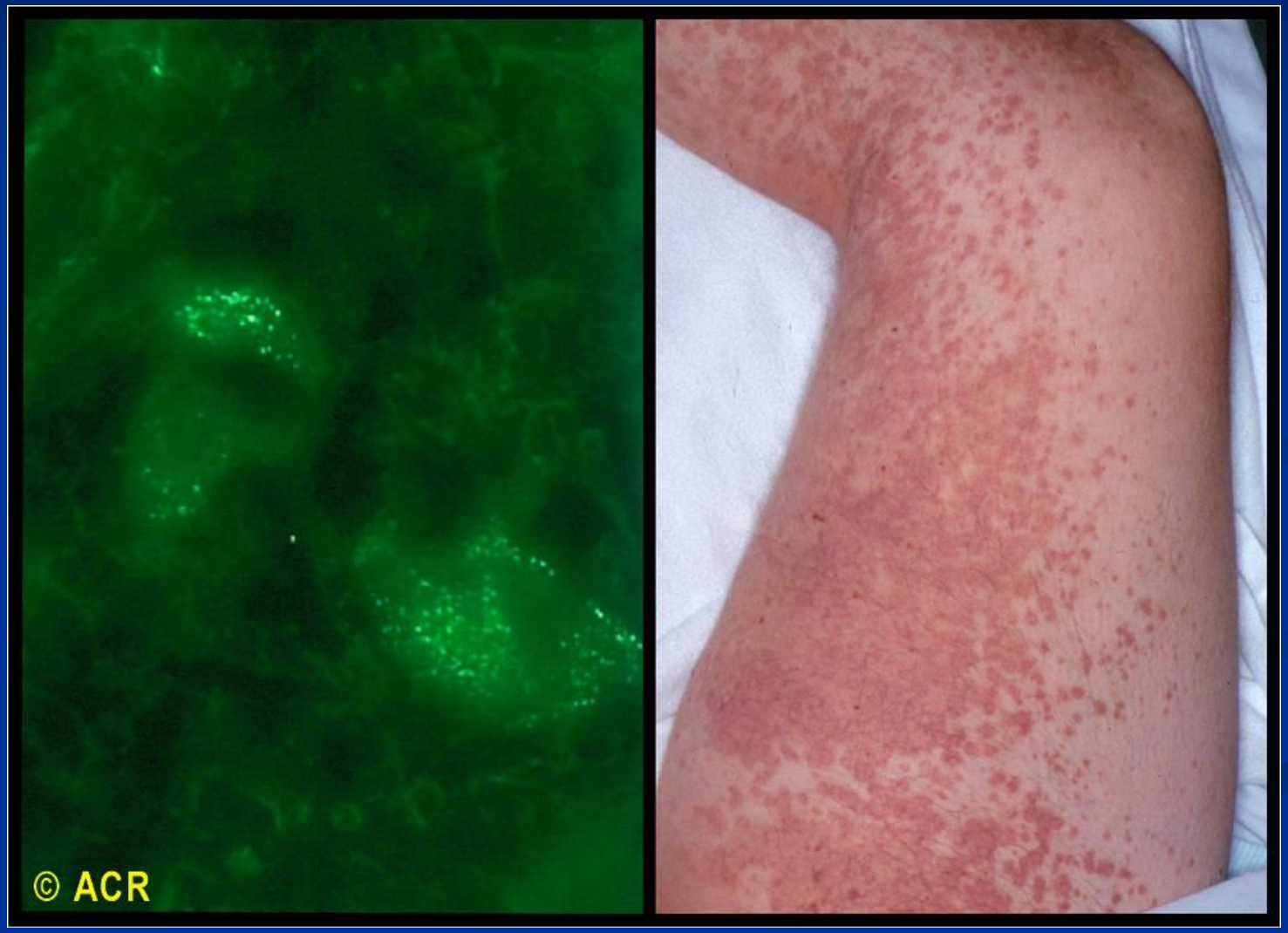
- Palpable purpura
- Bowel angina
- Gastrointestinal bleeding
- Hematuria
- Age at onset ≤20 years lesion
- No new medications

Henoch-Schönlein purpura

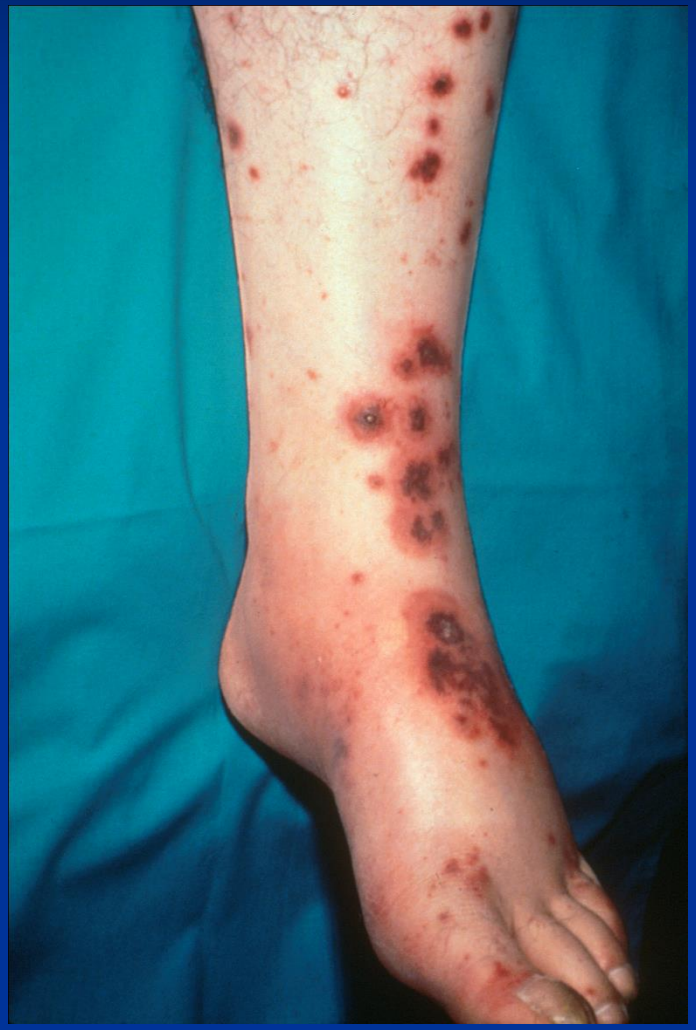


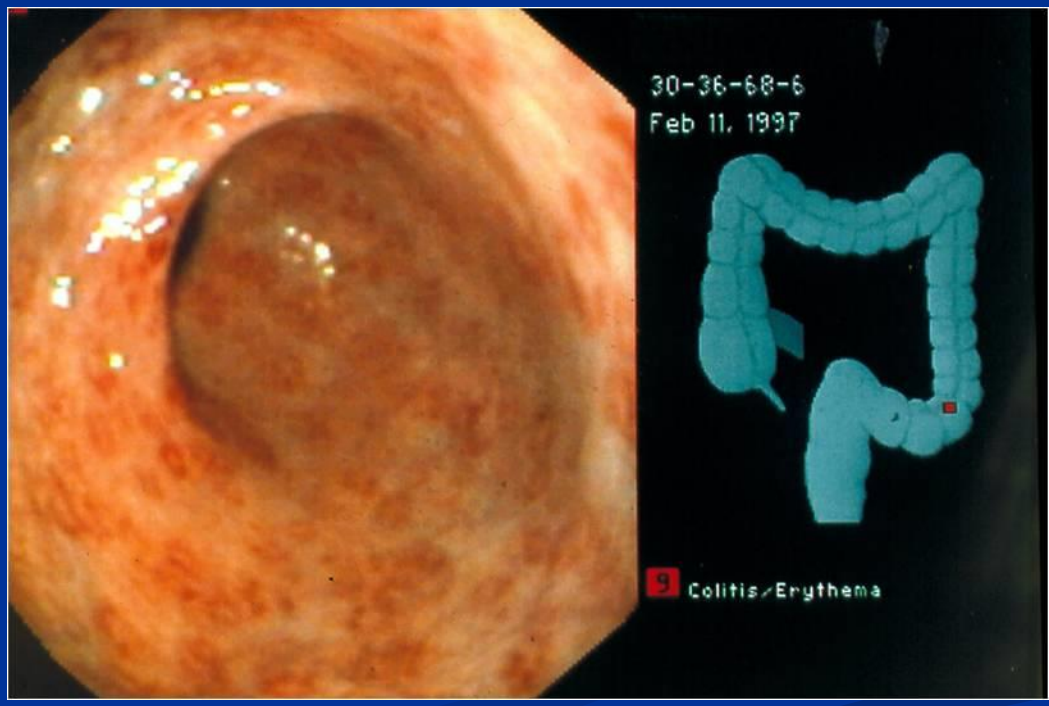
Henoch-Schönlein purpura

IgA depositis on Immunoflorence

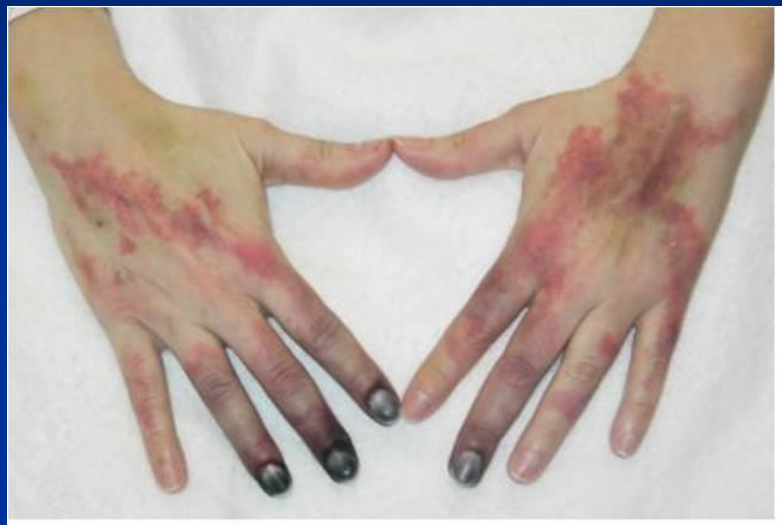


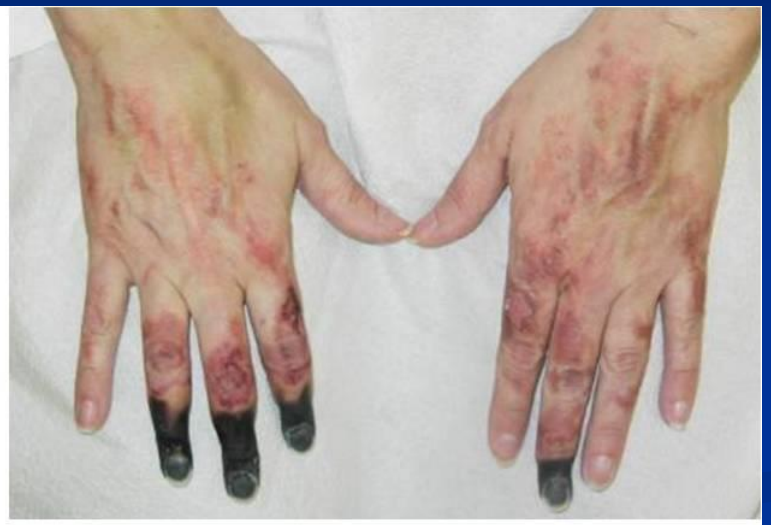
Henoch-Schönlein purpura

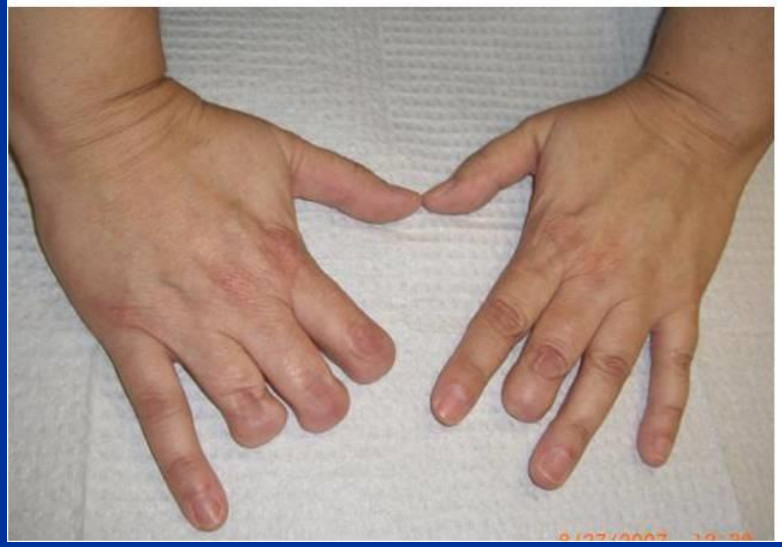




Cryoglobulinemia HCV

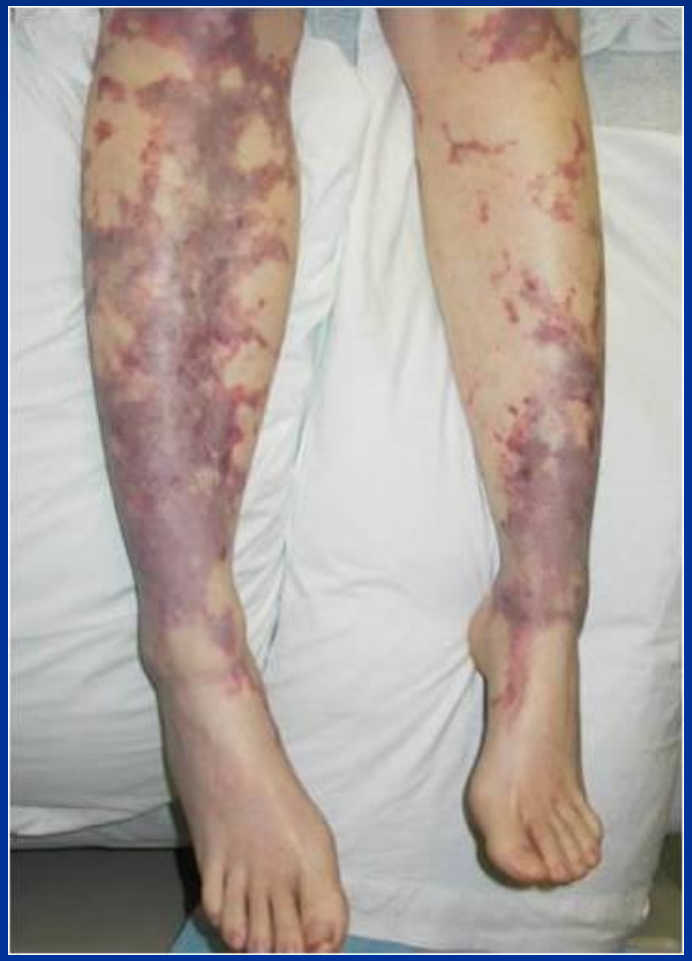


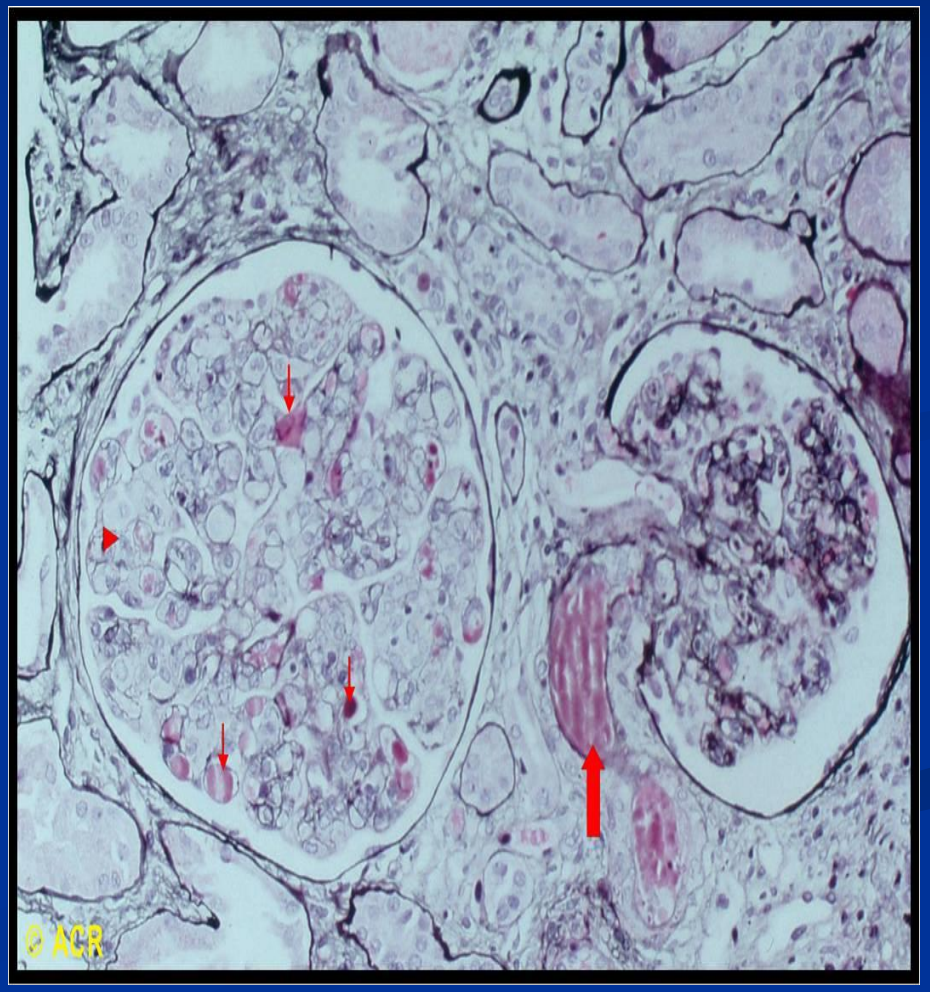




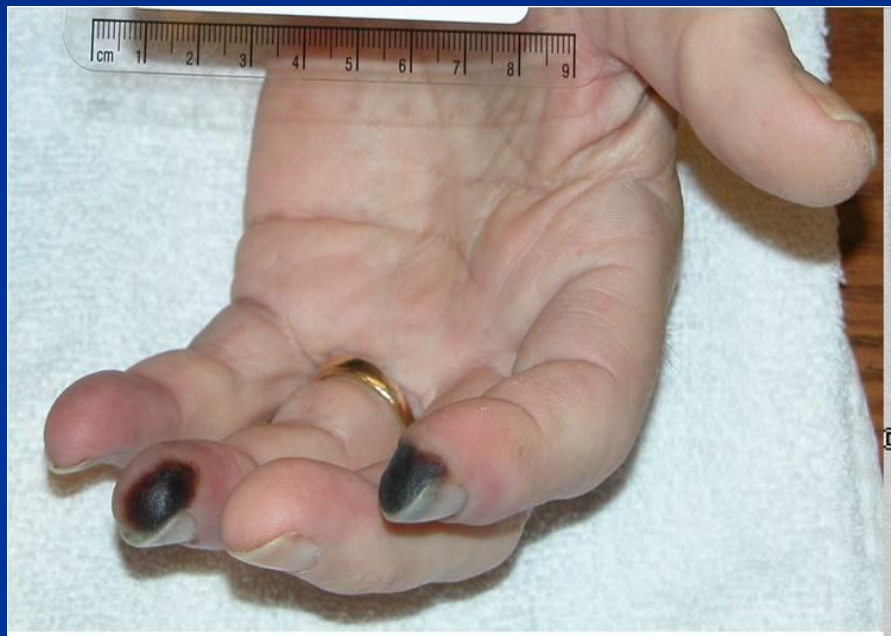
Cryoglobulinemia

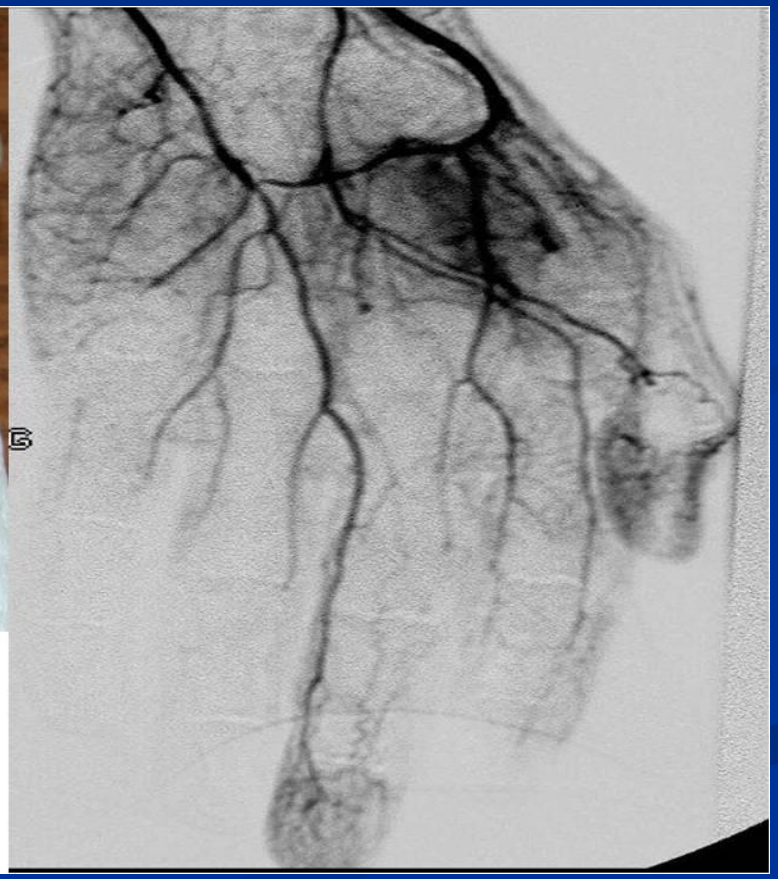
HCV Purpur and Glomerulonephritis





HCV Cryglobulinemia
Arteriogram





ANCA Vasculitis

- Role of ANCA testing
- Pulmonary Renal Syndrome

Role of ANCA in Diagnosis
Myths and Facts

- All positive for ANCA by IFA should be tested proteinase 3 (PR3) and MPO
- PR3-ANCA occur in 75% to 90% of patients with WG
- MPO-ANCAs are seen in 50% to 80% of patients with MPA
- CSS when anti-MPO ANCA are seen predominantly
- Isolated granulomatous disease of the respiratory tract may not have a positive ANCA
- The absence of a positive test does not rule out a diagnosis

Role of ANCA in monitoring vasculitis

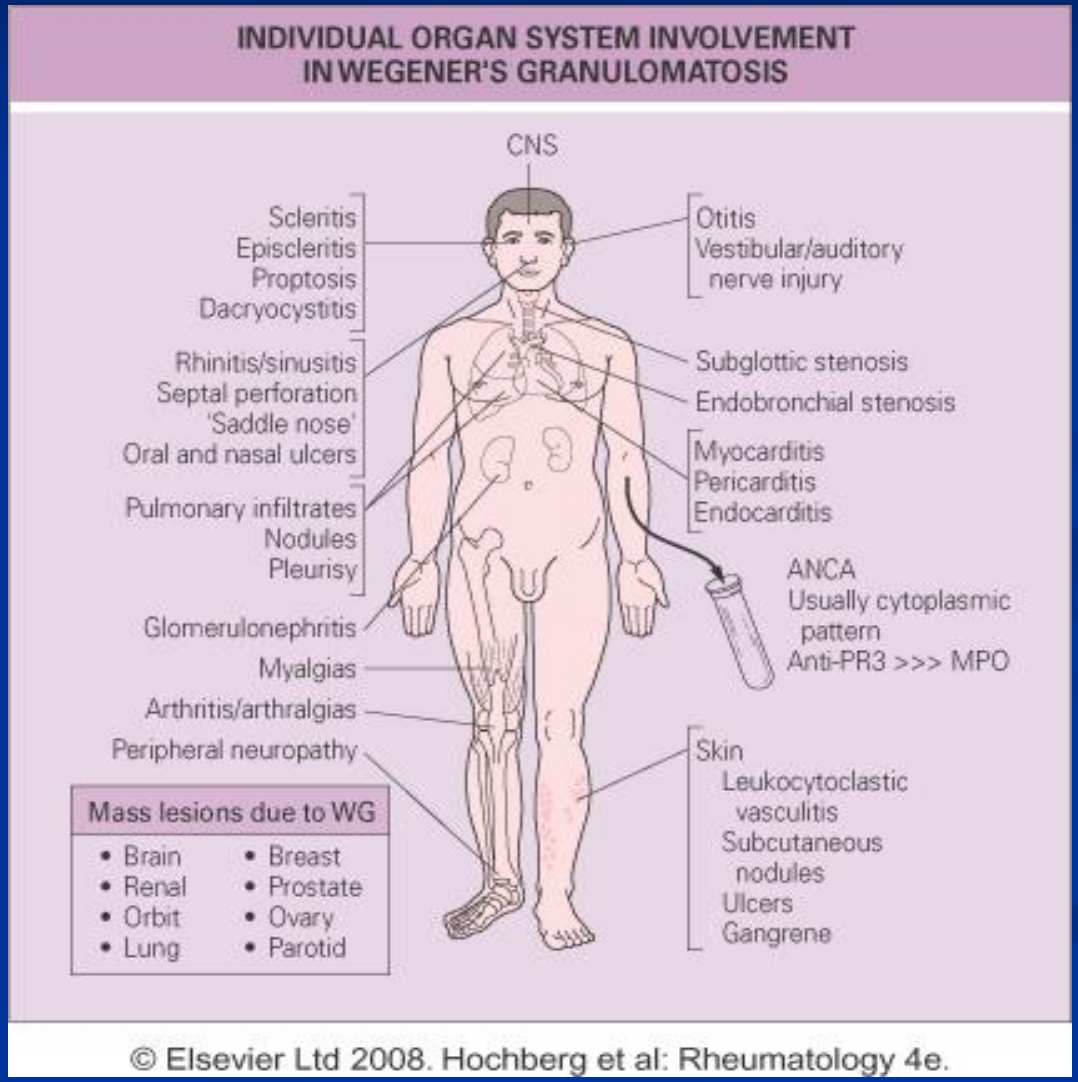
- In a prospective study increases in PR3-ANCA levels were not associated with relapse in the following year
- Serial ANCA levels should not be used to monitor disease activity or guide decisions concerning immunosuppressive treatment in ANCA-associated vasculitis.
- Biopsy with histopathologic evidence of vessel wall inflammation is the gold standard for the diagnosis of vasculitis

Wegener granulomatosis

classification of Wegener granulomatosis

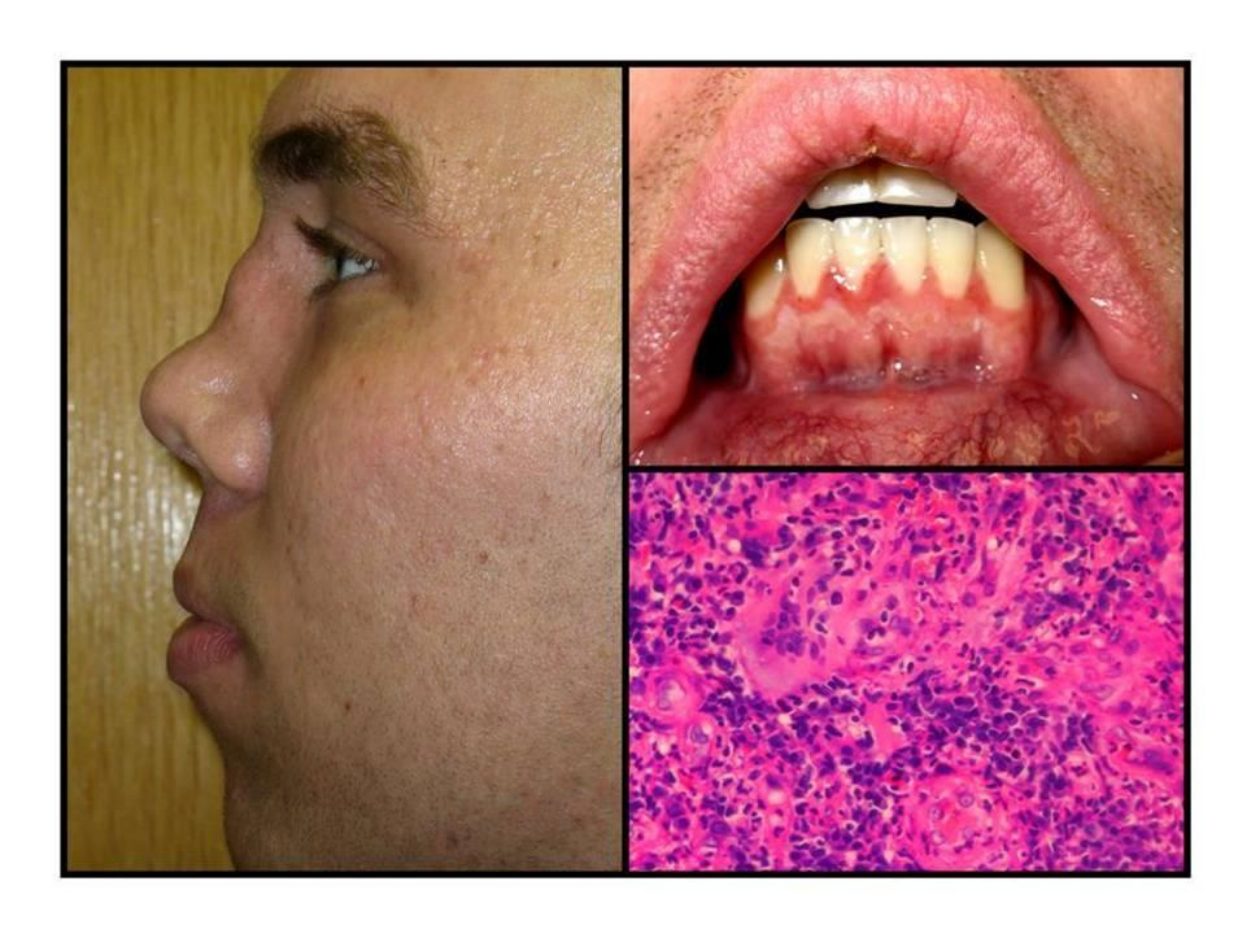
- The presence of two or more of these four criteria yielded a sensitivity of 88 percent and a specificity of 92 percent
  - Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge)
  - Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
  - Abnormal urinary sediment (microscopic hematuria or red cell casts)
  - Granulomatous inflammation on biopsy of an artery or perivascular area

Wegener's Granulomatosis



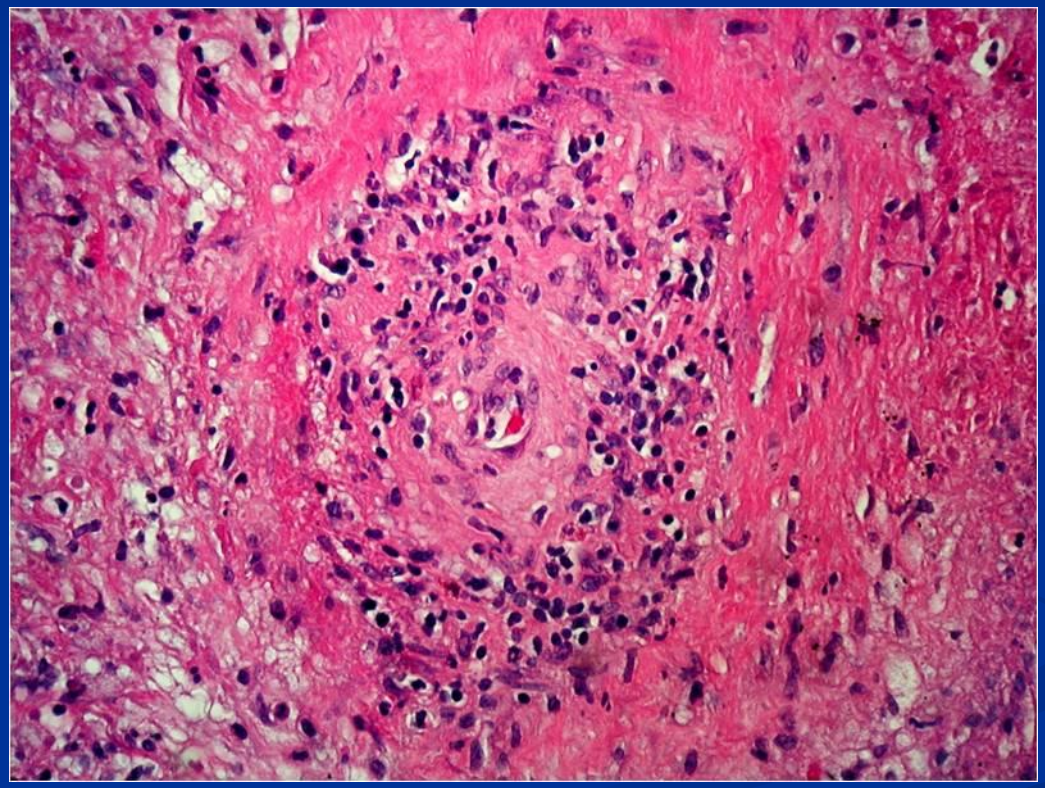
Wegener's Granulomatosis

Saddle nose, Strawberry gums and nasal biospy



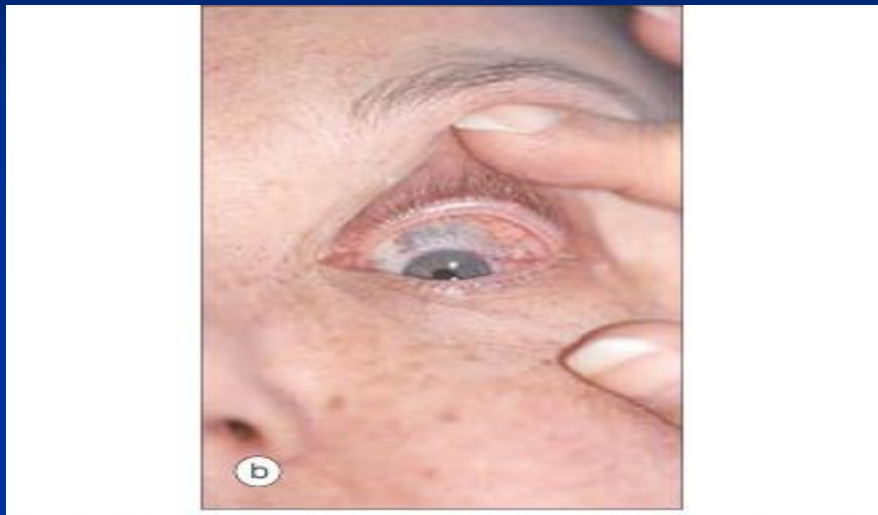
Wegener's Granulomatosis

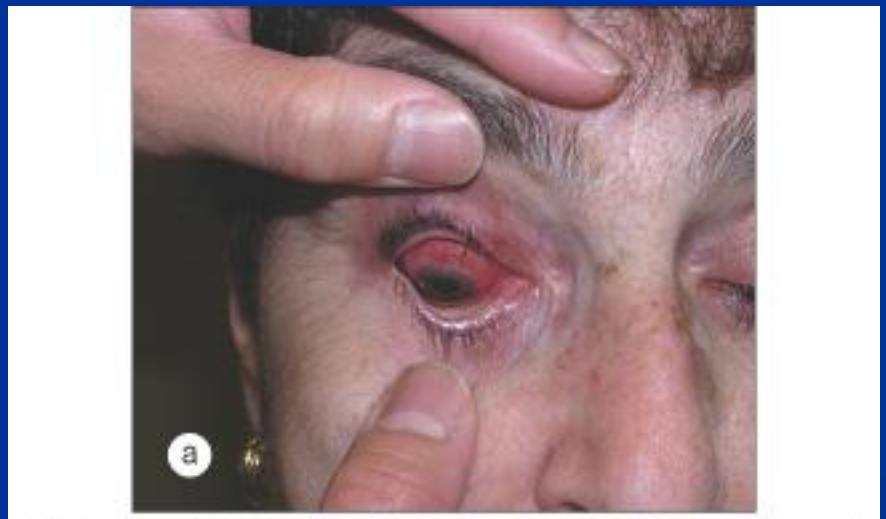
Granulomatous Necrosis



Wegener's Granulomatosis

Scleritis

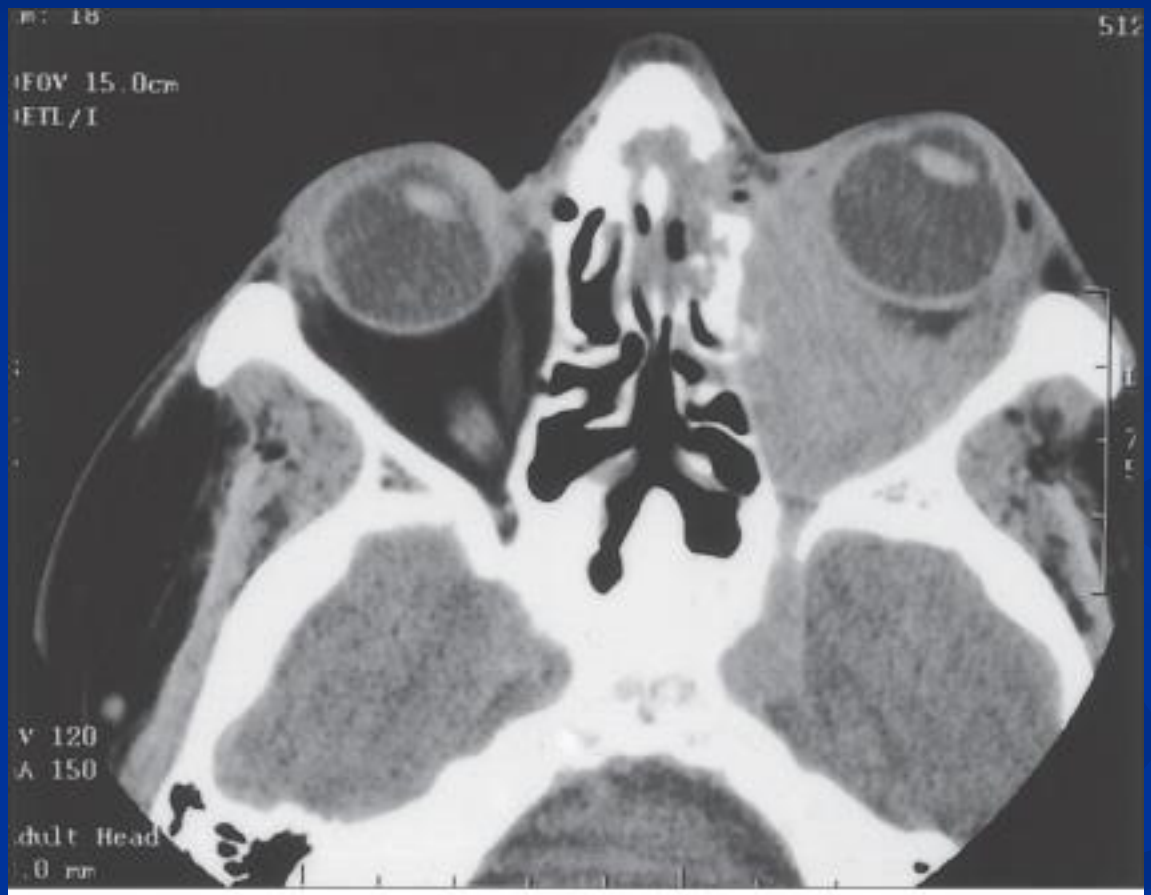




Wegener's Granulomatosis Exopthalmos, Pesudotumor

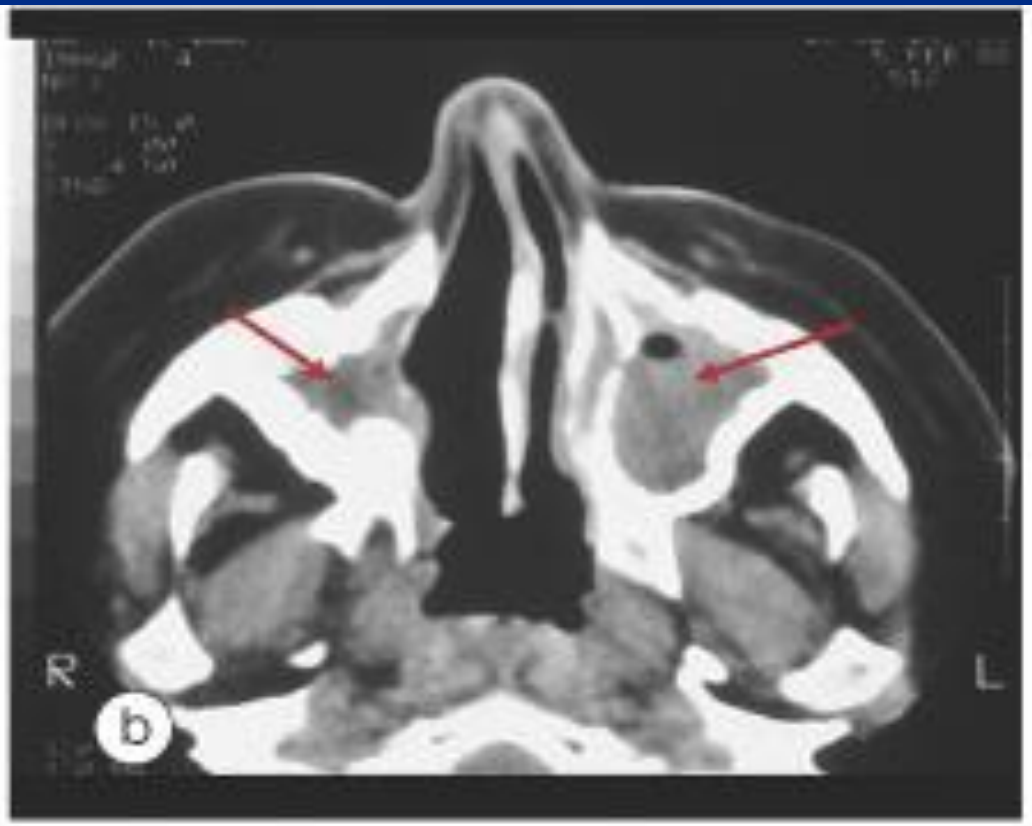
Wegener's Granulomatosis

Orbital Pseudotumor



Wegener's Granulomatosis

Sinusitis



Wegener's Granulomatosis

Skin vasculitis

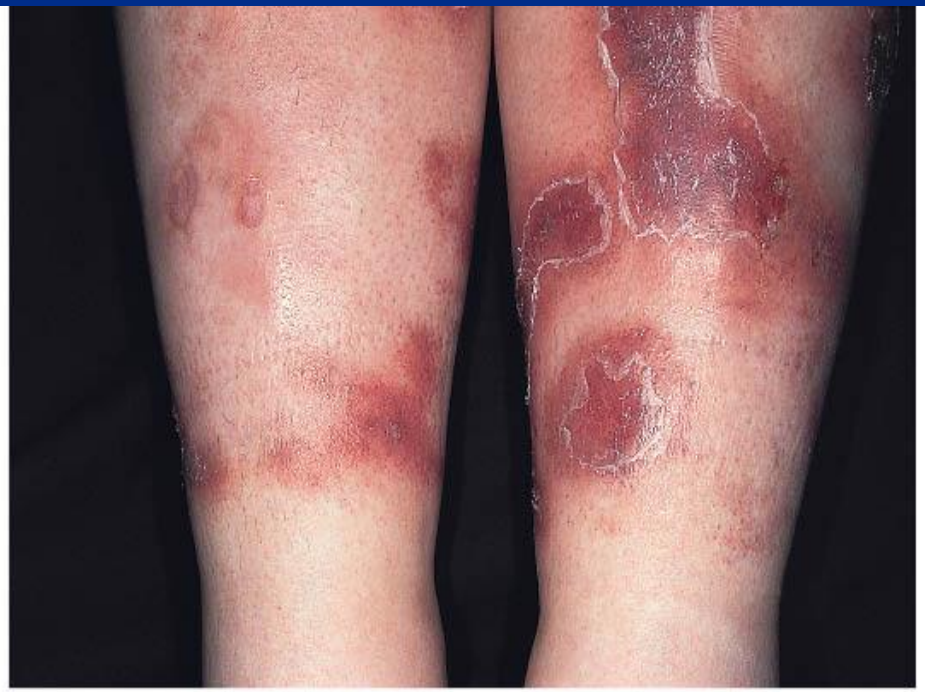


Figure 4–4 Cutaneous small-vessel vasculitis was the first evidence of recurrence in this patient with Wegener's granulomatosis.

Non immune mediated vasculitis mimics

- Cholesterol emboli
- Atrial myxoma with emboli
- **Infective endocarditis**
- **Malignancies**, such as lymphomatoid granulomatosis/polymorphic reticulosis, angioimmunoblastic T cell lymphoma, and intravascular lymphoma
- Mycotic aneurysm with embolization (predominantly with arteriole, capillary, and venule involvement)
- Bacteremia
- Rickettsial infection
- Ergotism (principally affects medium and small sized muscular arteries)
- **Thrombocytopenia** and other processes associated with purpura
- Radiation fibrosis (radiation-induced vasculopathy)
- Neurofibromatosis
- Congenital coarctation of the aorta
- Amyloidosis
- Cocaine abuse

Pulmonary Renal Syndromes

A Rheumatologic Emergency

Pattern of Immunofluorescence

Histologic and Immunofluorescence Data That Facilitate Diagnosis

Mechanism	Immunofluorescence Pattern	Terminology
Anti-GBM antibodies	Linear	Goodpasture syndromea
Immune complexes	Granular	Systemic lupus erythematosusa and other connective tissue diseases[a] Henoch-Schönlein purpura. Immunoglobulin A nephropathy. Idiopathic necrotizing glomerulonephritis with immune complexes
ANCA	Negative or pauciimmune	Wegener granulomatosisa Microscopic polyangiitis[a]. Churg-Strauss syndrome[a]. Idiopathic necrotizing glomerulonephritis without immune complexes
Unknown	Negative or pauciimmune	Idiopathic pulmonary hemorrhage[a]

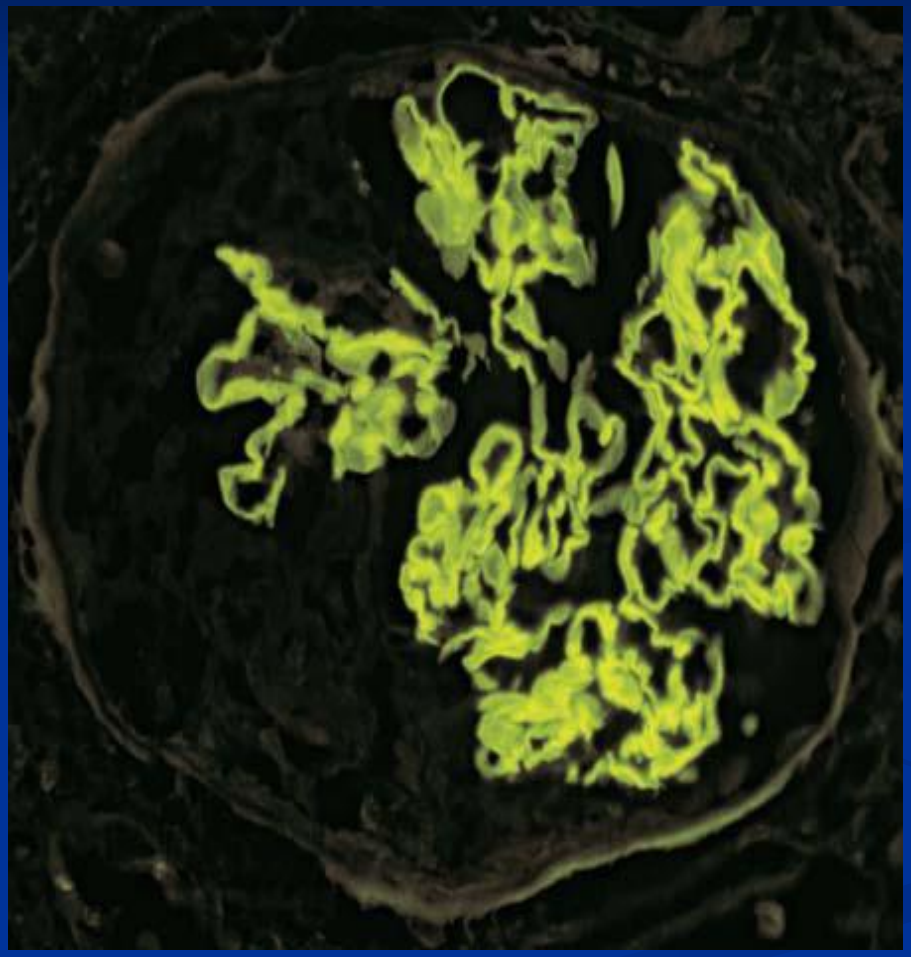
Arch Bronconeumol. 2008;44(8):428-36

Antibody mediated Vs Immune Complex Disease

SPECIFIC CAUSE	FREQUENCY	SUGGESTIVE DIAGNOSTIC FEATURES	SUGGESTIVE SEROLOGIC FEATURES
Goodpasture syndrome	20%–100% of patients develop alveolar hemorrhage (more likely in smokers and in men)	Smoking, hydrocarbon exposure, pulmonary-renal syndrome	Antiglomerular basement membrane antibody positivity Linear immunoglobulin G glomerular membrane deposits
Systemic lupus erythematosus	Up to 11% of patients have diffuse alveolar hemorrhage at onset (more commonly than any other connective tissue disorder)	Fever, arthralgia, rash	ANA positivity Anti-dsDNA antibodies Decreased C3 and C4

Arch Bronconeumol. 2008;44(8):428-36

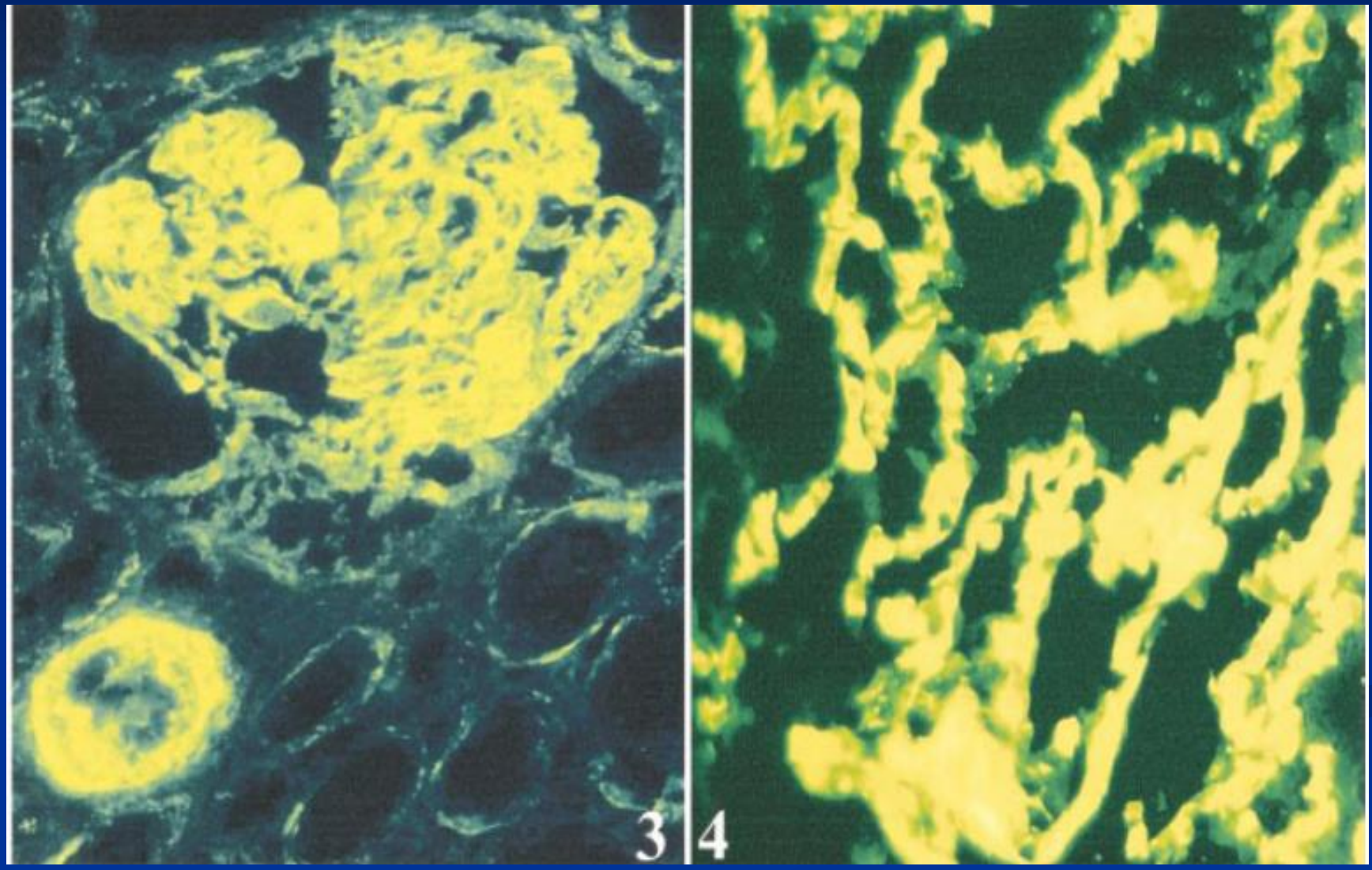
Renal Glomerulus with anti-GBM Disease



Linear staining of the GBM by direct immunofluorescence microscopy using an antibody specific for immunoglobulin G (Ig G)

Granular Immunofluorescence in SLE

Renal and Lung Immunofluorescence microscopy



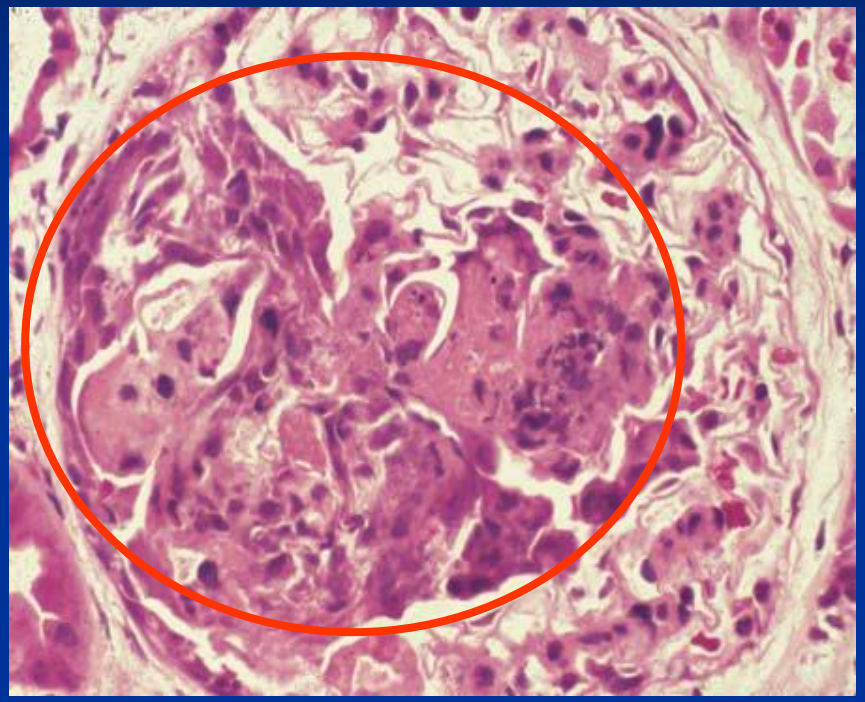
Arch Pathol Lab Med—Vol 125, April 2001

Pauci-immune Vasculitis

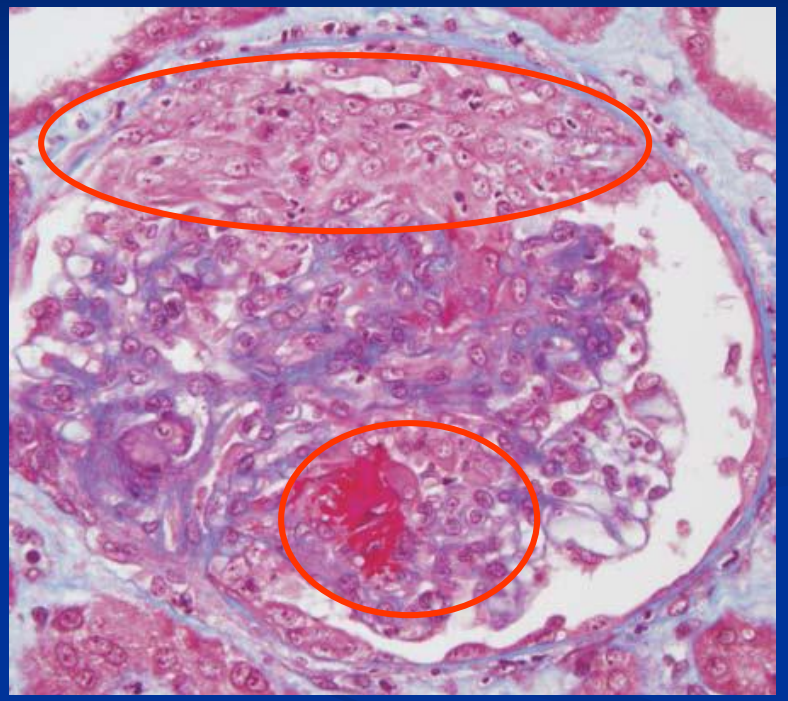
SPECIFIC CAUSE	FREQUENCY	SUGGESTIVE DIAGNOSTIC FEATURES	SUGGESTIVE SEROLOGIC FEATURES
Wegener granulomatosis	Capillaritis in about one-third of patients	Glomerulonephritis, sinusitis, multiple cavitary pulmonary infiltrates, granulomata	c-ANCA positivity
Churg-Strauss syndrome	27%–77% of patients have radiographic abnormalities, but diffuse alveolar hemorrhage is very rare	Asthma, peripheral eosinophilia, cutaneous lesions, mononeuropathy or polyneuropathy, granulomata, tissue eosinophilia	p-ANCA positivity
Microscopic polyangiitis	Half of patients with pulmonary involvement present with diffuse alveolar hemorrhage	Systematic manifestations (glomerulonephritis, fever, myalgia, arthralgia) are more common than pulmonary disease (found in 40% of cases); necrotizing vasculitis	p-ANCA positivity

Arch Bronconeumol. 2008;44(8):428-36

Crescentic Glomerulonephritis in Pauci immune Vasculitis

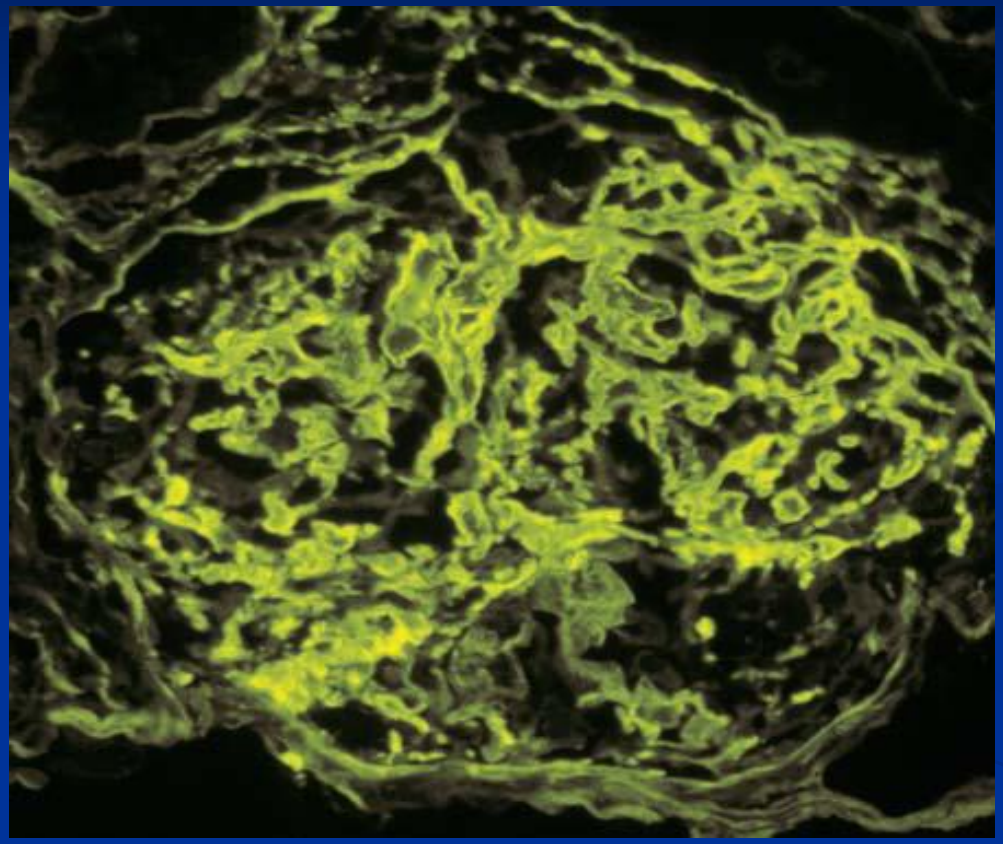


WG segmental fibrinoid necrosis and cellular crescent



MPA: cellular crescent at the top of the image and a small irregular (red) focus of fibrinoid necrosis

Direct immunofluorescence of ANCA Crescentic GN



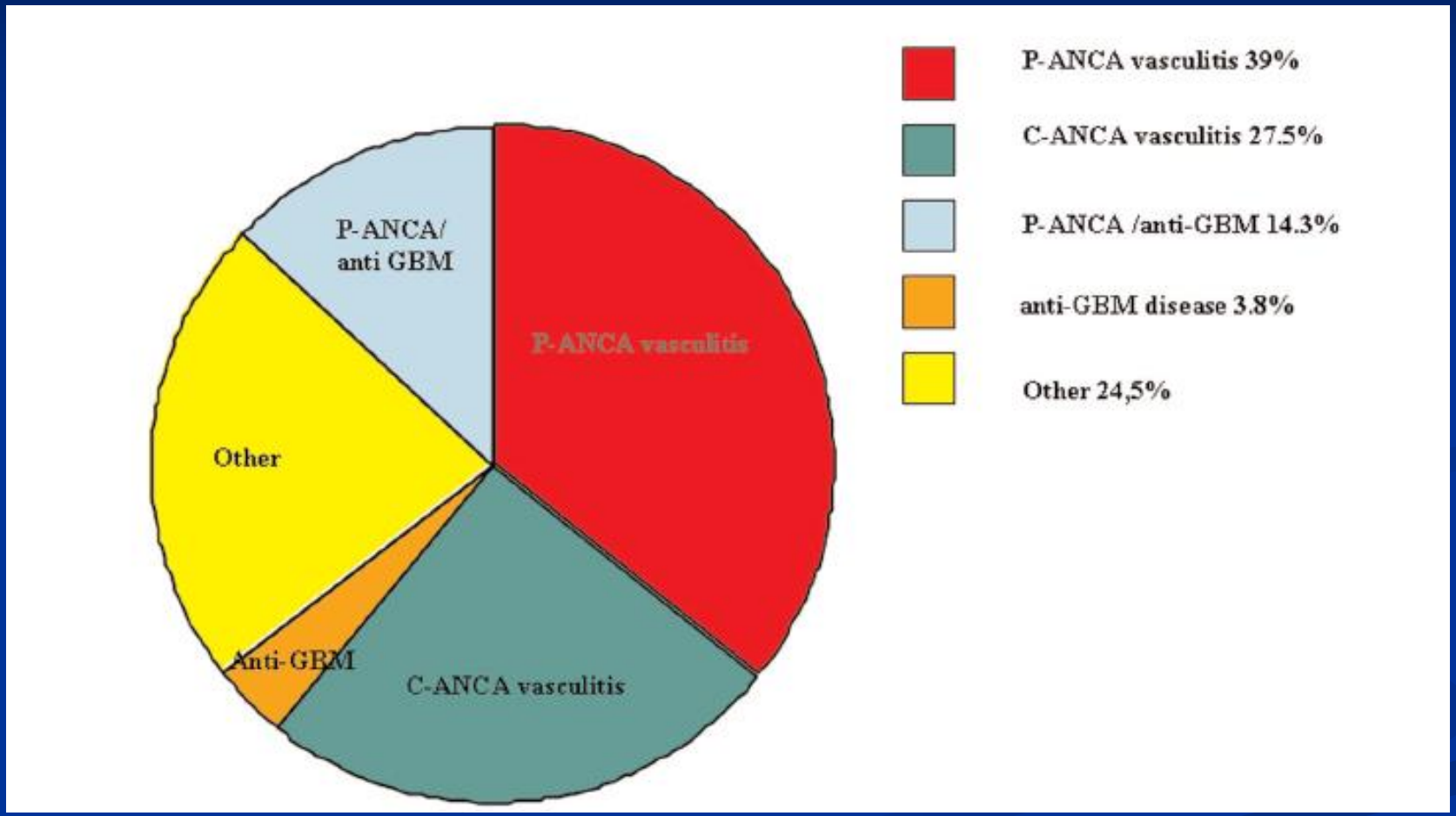
Irregular staining of a large crescent by IF microscopy using an antibody specific for fibrin

Pulmonary Renal Syndromes

- Pulmonary–renal syndrome in drug-associated ANCA-positive vasculitis
  - Propylthiouracil
  - D-Penicillamine
  - Hydralazine
  - Allopurinol
  - Sulfasalazine
- Pulmonary–renal syndrome in anti-GBM-postive and ANCA-positive patients
- Pulmonary–renal syndrome in autoimmune rheumatic diseases (immune complexes and/or ANCA mediated)
  - Systemic lupus erythematosus
  - Scleroderma (ANCA?)
  - Polymyositis
  - Rheumatoid arthritis
  - Mixed collagen vascular disease
- Pulmonary–renal syndrome in thrombotic microangiopathy
  - Antiphospholipid syndrome
  - Thrombotic thrombocytopenic purpura
  - Infections
  - Neoplasms
- Diffuse alveolar haemorrhage complicating idiopathic pauci-immune glomerulonephritis

Critical Care Vol 11 No 3 Papiris *et al.*

Relative Frequencies of Vasculitis



Critical Care Vol 11 No 3 Papiris *et al.*

Profiles of selected conditions that cause diffuse alveolar hemorrhage

	WEGENER GRANULOMATOSIS	MICROSCOPIC POLYANGIITIS	CHURG-STRAUSS SYNDROME	GOODPASTURE SYNDROME	SYSTEMIC LUPUS ERYTHEMATOSUS	IDIOPATHIC PULMONARY HEMOSIDEROSIS
Incidence (millions per year)[12–19]	8.5–10.3	6.8–8.9	0.5–3.7	3.0–4.0	60–350	0.2–1.2
Laboratory findings[20–24]						
Anti-GBM	No	No	No	Yes	No	No
c-ANCA	Yes	Possible	Possible	No	No	No
p-ANCA	Possible	Yes	Possible	No	No	No
ANA	No	No	No	No	Yes (99%)	No
Eosinophilia	Rare, mild	Rare, mild	Often, severe	Rare, mild	Possible	Possible
Organ involvement[20–24]						
Lungs	55%–90%[25–29]	25%–50%[36,37]	40%[42]	60%–94%[19,38,44]	50%–70%[45–49]	Always[52,53]
Diffuse hemorrhage	17%–50%[25,30,31]	10%–50%[38–40]	Rare[42,43]	80%–94%[19,38,43]	4%–20%[48,50]	Always[52,53]
Diffuse infiltrates	>15%[32]	>50%[32]	30%–70%[42,43]	80%–94%[19,38,43]	50%–70%[51]	Possible[52,53]
Kidney	70%–85%[26–29,33–35]	80%–90%[41]	25%	41%–71%[19,38]	Often	No
Other organs	Often	Often	Yes	No	Possible	No
Asthma[20]	Rare	Rare	Often	No	No	No
Prognosis[40,48,54–62]						
2-year survival	35%–37%	25%	20%–50%	33%–50%	50%–90%	25%
5-year survival	50%	35%–40%	20%–30%	80%	80%	5%–15%

Reaching Diagnosis in Challenging Cases

Hemoptysis and renal failure is not equivalent to pulmonary renal syndrome

Evaluating PAH and Hematuria

Are you dealing with a systemic vasculitis	Y/N
Is there evidence of oral and nasal inflammation	Y/N
Any history of Asthma, eosinophila or paranasal sinus disease	Y/N
Is there palpable purpra, arthritis or/and abdominal pain	Y/N
Does patient has bilateral pulmonary infiltrates + bronchoscopy with hemorrhagic BAL	Y/N
Oral and genital ulceration, uveitis and skin lesions	Y/N
Is there history of D-penicillamine or PTU use or BMT	Y/N
Risk factors for pneumonia with renal failure, in an immunosuppressed host (bacterial/viral or PCP)	Y/N
Is there new congestive heart failure with prior hx renal disease	Y/N

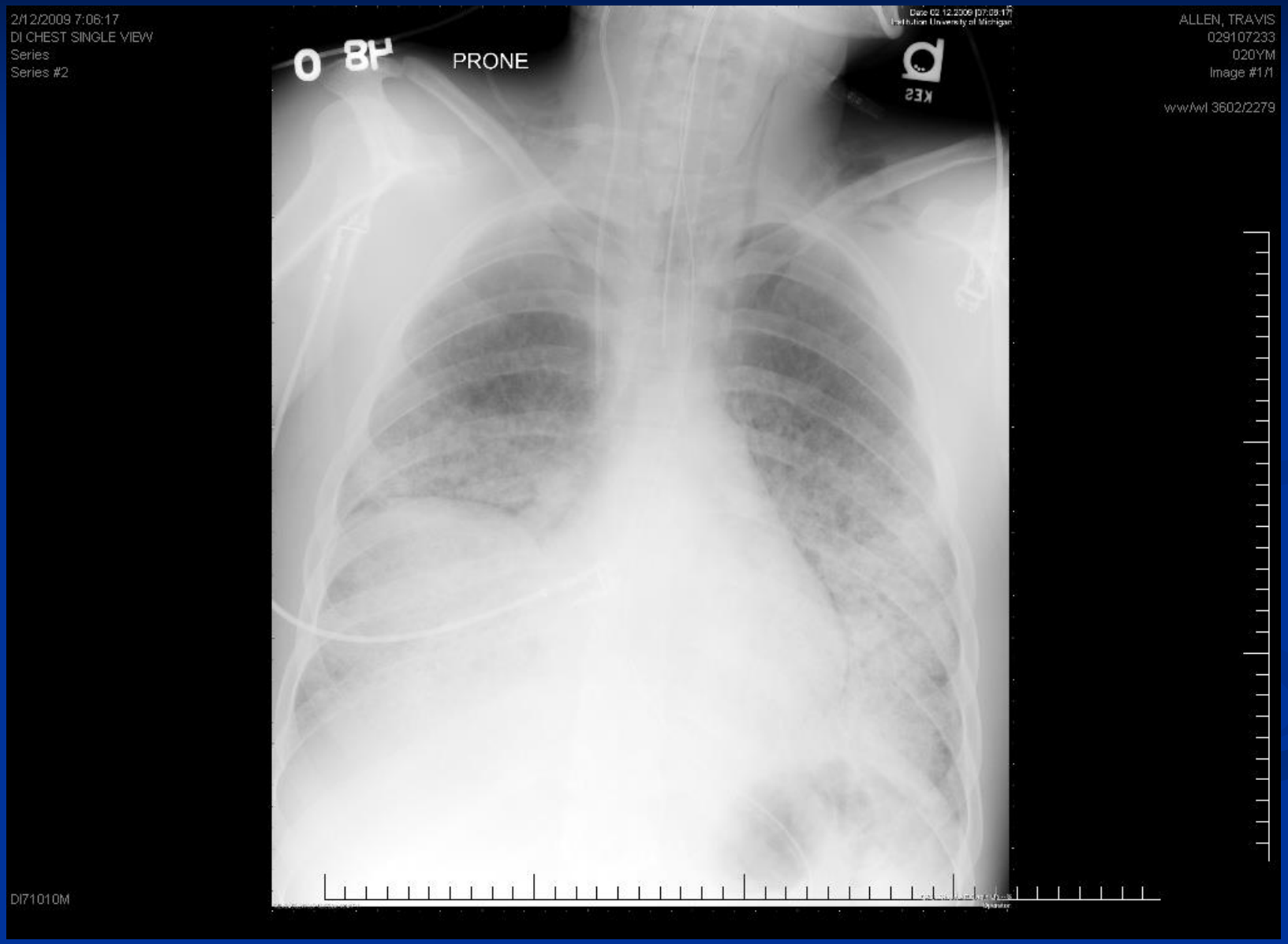
Evaluating PAH and Hematuria

Any evidence of MAHA (HUS/TTP): HPT, LDH, DAT, Peripheral smear, Low PLT	Y/N
Possibility of a bleeding diathesis: DIC , Coags, coumadin	Y/N
Is there nephrotic proteinuria → Pulmonary Embolism	Y/N
Serologies Lupus: ANA, ENA, DsDNA, C3,C4 Pauci-Immune: ANCA, Pr3, MPO, AGBM Immune complex Vasculitis: Cryo, RF, viral hepatitis Antiphospholipid syndrome: DRVVT,CAB, B2GP1	Y/N
Tissue biopsy showing necrosis, vasculitis, granulomatous inflammation	

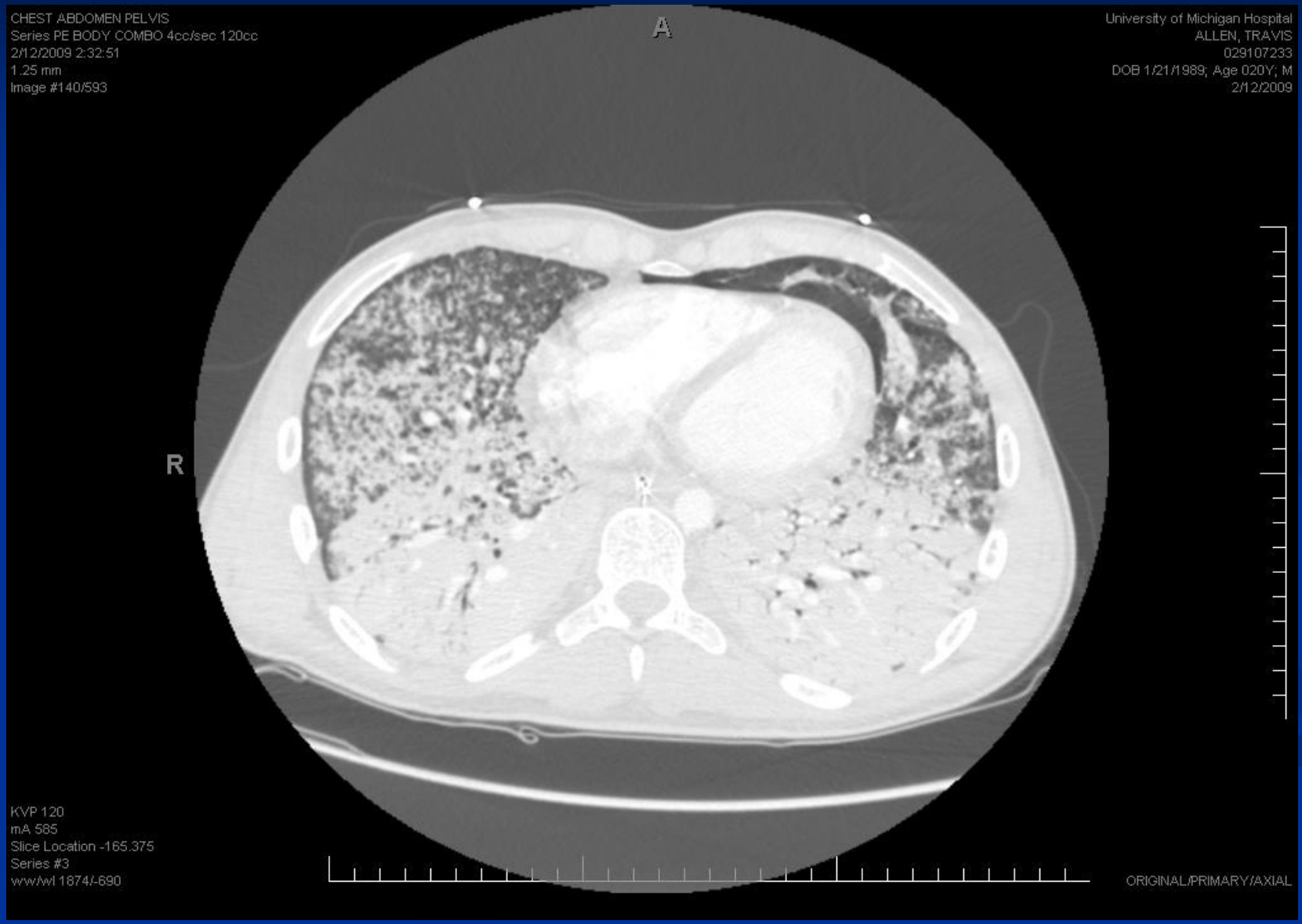
Case-1

Age/Sex	20 Male
Prior Hx	Neurofibromatosis
Presentation	Fevers, Respiratory distress, Hemoptysis
Laboratory	Wbc 15, hb 8, plt 395, creat 0.8, Ur: rbc5, no cast, pr30mg
COAGS	Normal ptt, inr, hpt, ldh
Chest X-ray	Pulmonary edema, pneumonia, pl eff
Chest CT	Bilateral opacities multilobar infection, ARDS. No PE
BAL/Bronch	sub segmental blood clots, no fresh blood
Microbiology	Legionalla and mycoplasma (neg), BAL : GS, Tb and fungal negative
ECHO	Not done
Immunology	Negative NAB, NCAB,CAB. Positive AGBM
Biopsy	Not done

DAH in a 20 year old male



DAH in a 20 year old male



Differential Diagnosis and Treatment

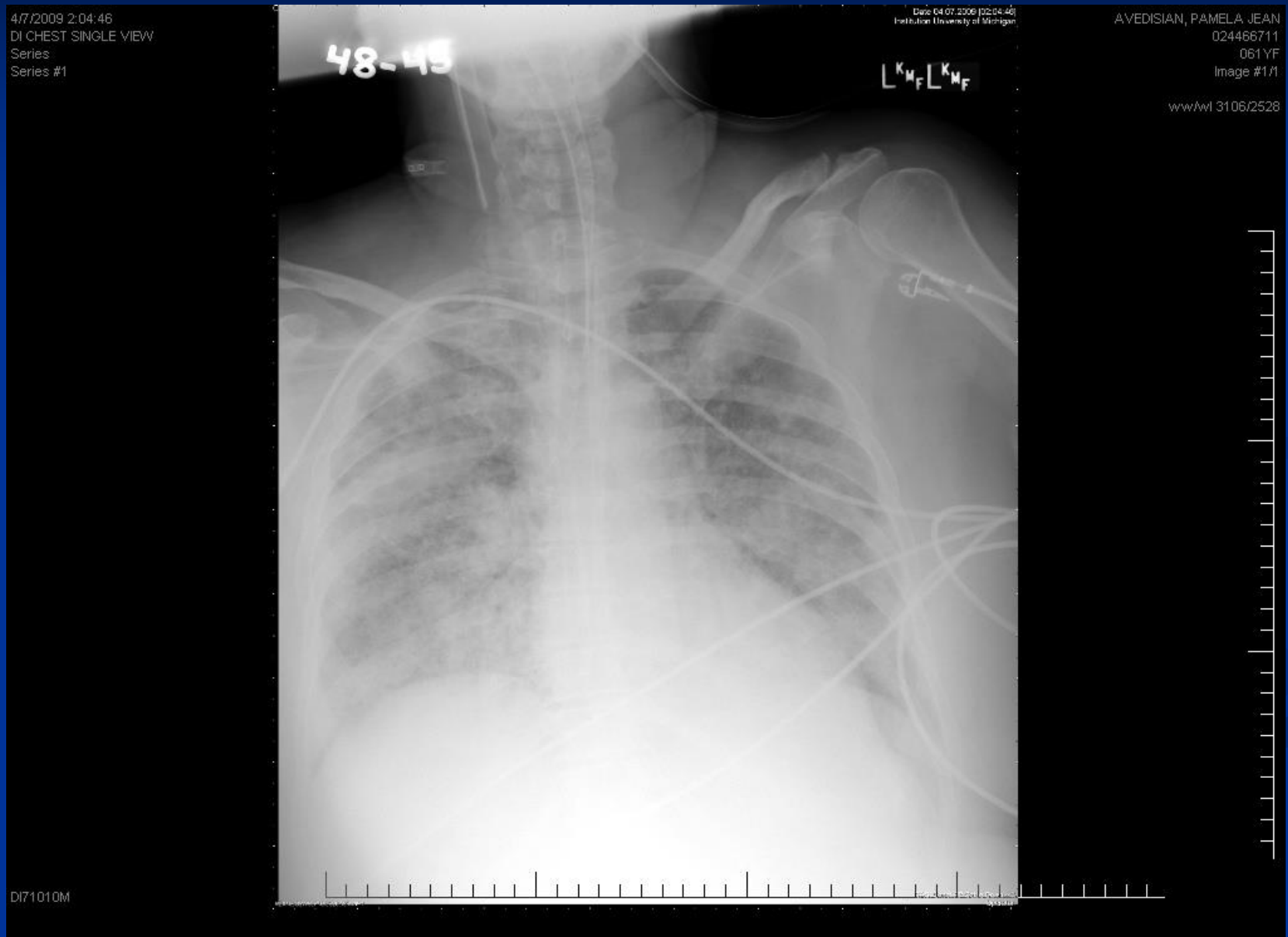
- Goodpastures's disease
- Infection

- Pulse dose steroids x3
- Plasmapheresis
- IV Cytoxan
- Broad spectrum antibiotics pending cultures
- IVIG for hypogammaglobulinemia
- Resulted in favorable outcome

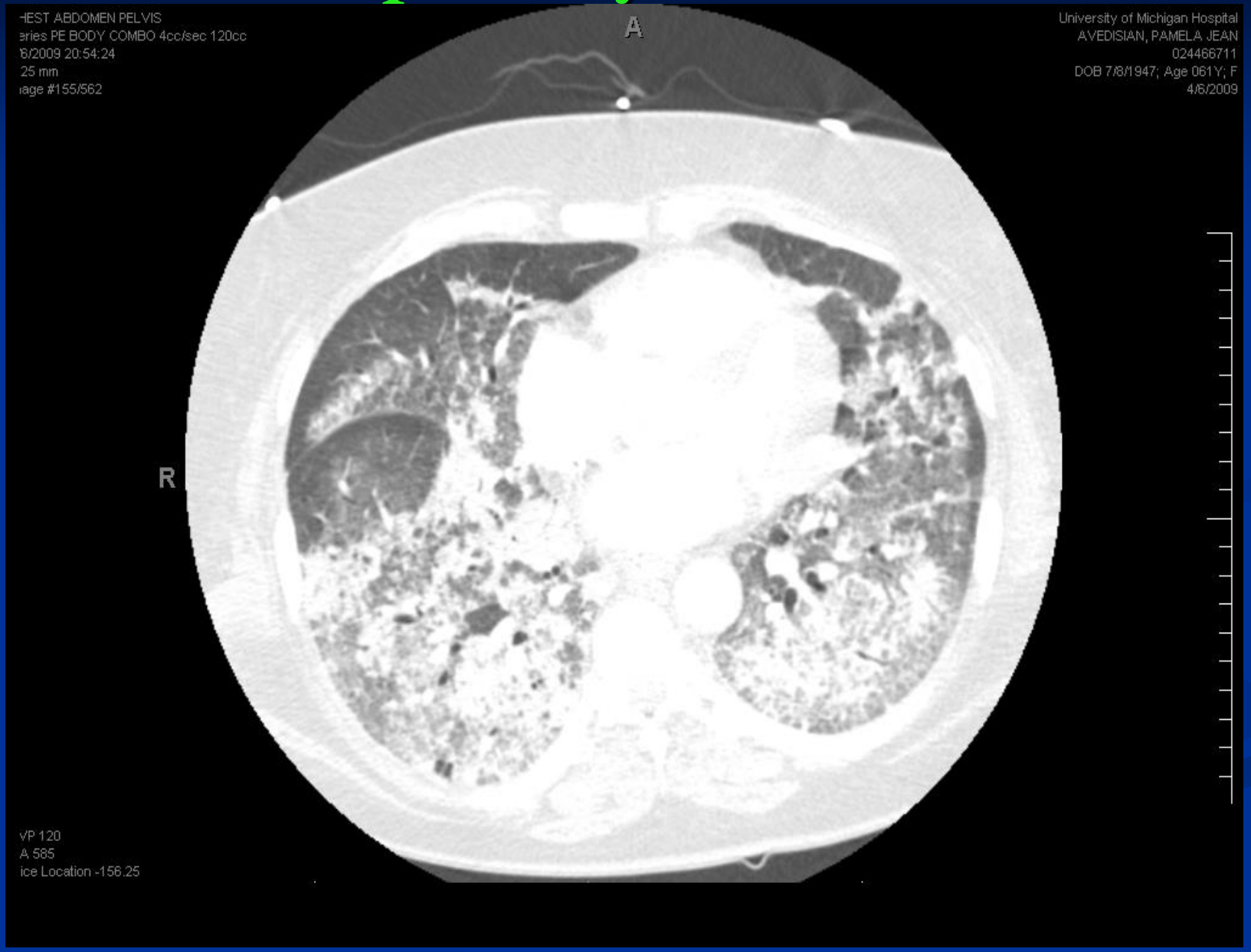
Case-2

Age/Sex	61 F recent travel to Mexico
Prior Hx	Hypertension, Dyslipedemia, Bronchitis
Presentation	Acute dyspnea, Fatigue and dry cough
Laboratory	Wbc 8.1, hb 9, plt 212, creat 0.9, Ur: rbc 100, no cast, pr
COAGS	Normal ptt, inr. (Hpt, LDH, DAT not done)
Chest X-ray	Pulm edema/ARDS and/or multifocal pneumonia
Chest CT	B/L consolidations and ground glass opacities, No PE
BAL/Bronch	Moderate amount of blood
Microbiology	Legionnella (neg), BAL : G.S,Tb and fungal negative
Echo	LVH, EF 60%
Immunology	Pos: P-anca, +MPO, Negative NAB,CAB,AGBM
Biopsy	Renal: Moderate to severe arteriolosclerosis; diffuse tubular injury/focal tubular necrosis

Acute Respiratory Distress in 61 F



Acute Respiratory Distress in 61 F



Differential Diagnosis and Treatment

- Microscopic polyangitis
- Churg-Strauss Syndrome
- Pneumonia

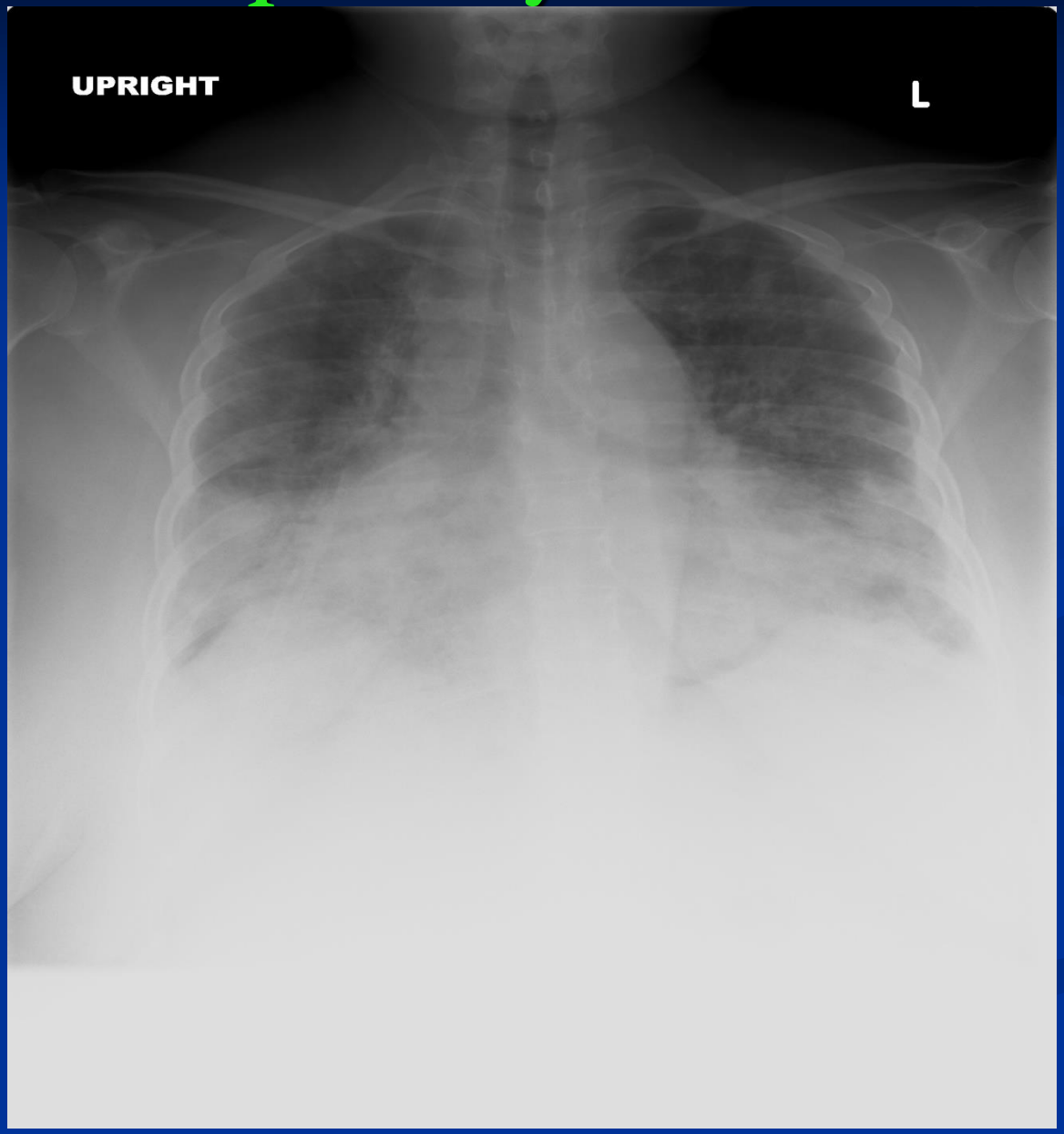
  Legionalla or PCP, Nosocomial infection

- Pulse dose steroids x3
- Plasmapheresis
- Hold Cytoxan concern for infection-pending cultures
- Broad spectrum antibiotics
- IV Cytoxan started after Renal biopsy
- Resulted in favorable outcome

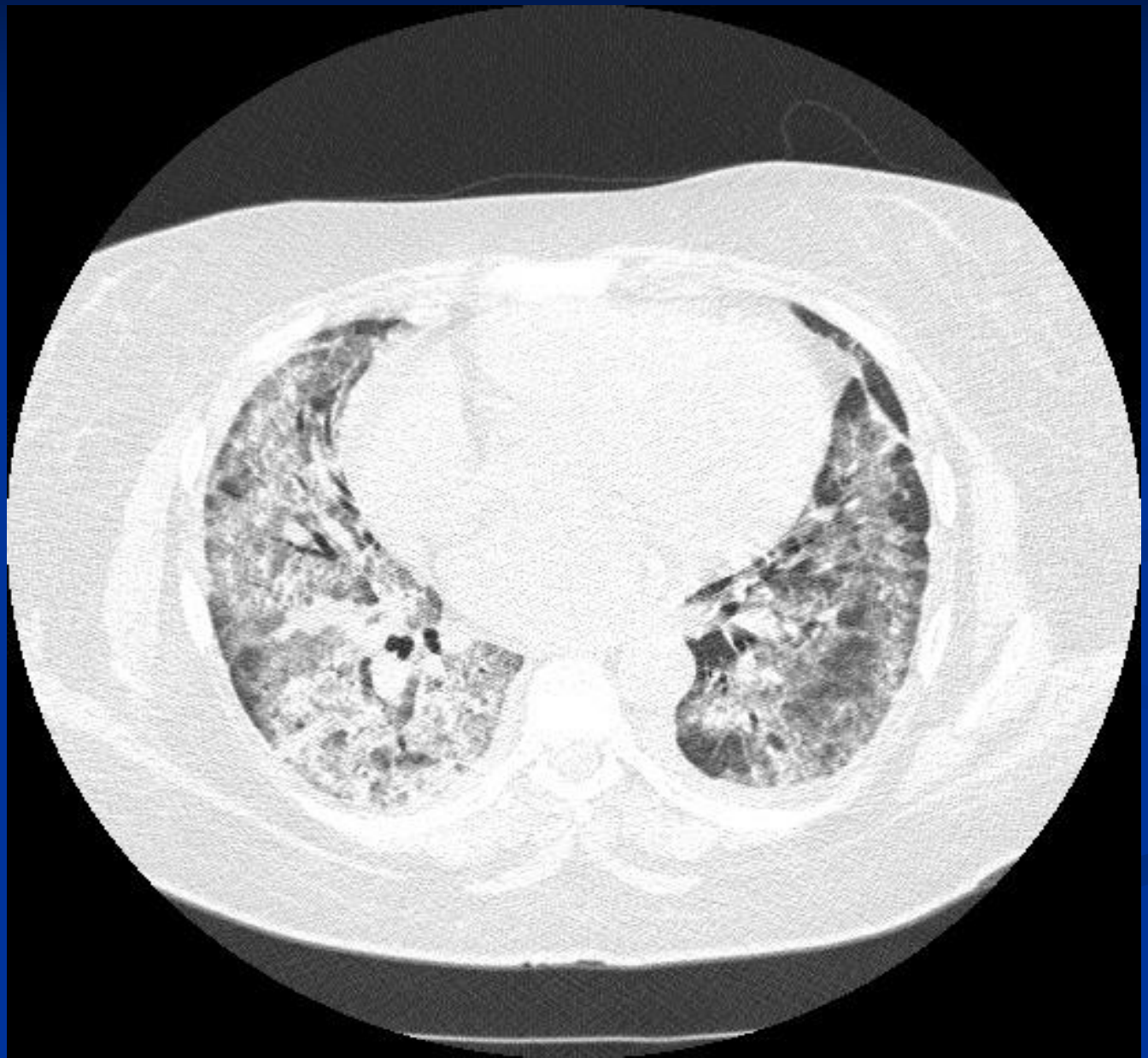
Case-3

Age/Sex	38/F
Prior Hx	Lupus
Presentation	SOB, cough with streaks of blood, not frank hemoptysis
Laboratory	Wbc 15, Hb 8->6.5 , Plt 155->85, Creat 1.5->2.6, Pr/cr : 12 g, Ur: 10rbc , smear 1-3 schitiocytes
COAGS	Normal PTT , INR, HPT 3, LDH 1415, DAT neg
Chest X-ray	Airspace opacities bilaterally, pulmonary edema, pneumonia and pulmonary hemorrhage
Chest CT	Pulmonary hemorrhage or pneumonitis
BAL/Bronch	RBC 147,000, WBC 1197
Microbiology	BAL(9/9) NEG, BAL 9/20: + Staph; neg AFB, FNG
Echo	Globally hypokinetic left ventricle , LVEF 40%
Immunology	NAB, DsDNA, Low C3,C4. Neg PR3,MPO,AGBM
Biopsy	Membranous focal necrotizing and proliferative GN

Acute Respiratory Distress in 38 F



Acute Respiratory Distress in 38 F



Differential Diagnosis and Treatment

- Lupus nephritis flare with pulmonary hemorrhage
- TTP or HUS
- End-stage renal disease with congestive heart failure
- Legionalla pneumonia
- Nephrotic syndrome with hypercoagulable state causing a pulmonary embolus

- Pulse steroids
- Plasmapheresis
- Broad spectrum antibiotics
- IVIG
- Cytoxan
- Rituxan
- IVIG
- Cellcept

Diagnostic Workup

- It is a life threatening condition which requires early intervention to prevent high mortality
- Concurrent infection, severe anemia and long mechanical dependence are poor prognostic markers
- Aim for an early bronchoscopy to document hemorrhage and exclude infection
- Biopsy (open lung or renal with IF) can be extremely helpful and reassuring

Review of Treatment

- Use of Immunosuppression and Plasma Exchange in PRS - 13 case series and 1 RCT
  - Goodpastures's Syndrome
  - Small Vessel Vasculitis
  - SLE
  - Antiphospholipid Syndrome
- Non Immunosuppressive Treatment Modalities in DAH

Long-Term Outcome of Anti–Glomerular Basement Membrane Antibody Disease Treated with Plasma Exchange and Immunosuppression

Jeremy B. Levy, MA, PhD, MRCP; A. Neil Turner, PhD, FRCP; Andrew J. Rees, MSc, FRCP, FMedSci; and Charles D. Pusey, MSc, FRCP, FRCPath

- 71 patients with positive anti GBM antibody disease presented who with pulmonary hemorrhage and rapidly progressive GN
- Followed in three categories based on renal function at presentation
  - Creatinine <5.6mg/dl (<500mgUmol/l), n=19
  - Creatinine >5.6mg/dl(>500mgUmol/l) but no dialysis dependent, n=13
  - Dialysis dependent with in 72 hours, n=39
- All treated with IS including oral prednisone 1mg/kg(or 60mg max), Cytoxan (2-3mg/kg/day) for 2-3 months, No Pulse steroids
- Plasma exchange (50ml/kg or 4L)daily for at least 14days

Ann Intern Med. 2001;134:1033-1042.

Survival at 1 Year

Renal Function at Presentation	Patients	Median Creatinine Concentration	Median Proportion of Crescents (Range)	1-Year Patient Survival
	n	*μmol/L*	%	←
Creatinine concentration < 500 μmol/L	19	207 (53–475)	28 (0–87)	19 (100)
Creatinine concentration ≥ 500 μmol/L	13	700 (505–955)	55 (38–100)	11 (83)
Dialysis dependent	39	NA	100 (62–100)	26 (65)
Total	71	317 (53–955)	41 (0–100)	55 (77)

Long-Term Survival

Renal Function at Presentation	Patients	Median Follow-Up	5-Year Patient Survival*	Current Survival	Median Time to Death (Range)
	n	*mo*	*n (%)*		*mo*
Creatinine concentration < 500 μmol/L	19	120 (12–280)	16 (94)	16 (84)	267 (12–280)
Creatinine concentration ≥ 500 μmol/L	13	96 (1–265)	8 (80)	8 (62)	96 (1–120)
Dialysis dependent	39	22 (0.2–289)	16 (44)	14 (36)	5 (0.2–237)
Total	71	90 (0.2–289)	40 (63)	38 (54)	9 (0.2–280)

Renal Function at Presentation	Patients	Median Time to Death (Range)	Surviving Patients with Independent Renal Function	
			At 5 Years†	At Death or Last Follow-Up
	n	*mo*	*n (%)*	
Creatinine concentration < 500 μmol/L	19	267 (12–280)	15 (94)	14 (74)
Creatinine concentration ≥ 500 μmol/L	13	96 (1–120)	4 (50)	9 (69)
Dialysis dependent	39	5 (0.2–237)	2 (13)	2 (5)
Total	71	9 (0.2–280)	21 (53)	25 (35)

Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients With Small-Vessel Vasculitis

Philip J. Klemmer, MD, W. Chalermskulrat, MD, Michael S. Reif, MD, Susan L. Hogan, PhD, David C. Henke, MD, and Ronald J. Falk, MD

- 20 pts with DAH and confirmed Pauci-immune SVV
- 17MPA, 2 WG,1 CSS at UNC
- Treated with pulse dose steroids x3 days, 18/20 received intravenous cytoxan (0.5g/m2) and plasmapheresis daily until DAH improved, Mean number of apheresis 6(range 4-9)
- Average time to admission and first exchange was 2 days
- DAH had 100% response rate
- 14/20 (70%) had abnormal renal function on admission
- Creatinine (4.5+/- 4.5)at baseline and on discharge 2.4=/- 0.8.

Clinical Parameters in SVV

Patient No.	Sex	Race	Admission Age (y)	Diagnosis	ANCA Pattern	Admission Hematocrit (units)	Admission Serum Creatinine (mg/dL)	Ventilator Required	Days on Ventilator	Apheresis Treatments	Lung Symptom Outcome
1	F	C	61	MPA	C	24.0	0.8	Yes	5	6	Resolved
2	M	C	49	MPA	C	24.0	16.6	No	NA	4	Resolved
3	M	C	72	MPA	C	25.0	0.7	No	NA	8	Resolved
4	F	AA	92	MPA	P	19.0	3.9	Yes	2	5	Resolved
5	F	C	75	MPA	P	19.0	7.8	Yes	6	6	Resolved
6	F	C	72	WG	P	23.0	1.2	Yes	10	7	Resolved*
7	M	C	50	CS	C	34.0	0.9	No	NA	6	Resolved
8	M	C	65	MPA	P	20.0	7.0	No	NA	6	Resolved
9	F	C	68	MPA	P	22.6	4.6	Yes	7	6	Resolved
10	F	AA	71	MPA	Negative	23.0	10.5	Yes	12	7	Resolved
11	M	AA	70	MPA	P	18.6	9.7	Yes	3	9	Resolved
12	M	H	43	MPA	C	28.0	1.0	No	NA	4	Resolved
13	F	C	60	MPA	P	17.0	2.5	No	NA	5	Resolved
14	M	C	70	MPA	P	20.0	7.2	No	NA	4	Resolved
15	M	C	60	MPA	P	18.9	3.4	Yes	6	6	Resolved
16	F	C	58	MPA	P	19.7	1.8	Yes	26	9	Resolved
17	F	C	77	MPA	P	24.0	5.8	No	NA	6	Resolved
18	M	AA	41	WG	C	45.0	1.6	No	NA	6	Resolved
19	F	C	59	MPA	P	30.9	0.8	No	NA	6	Resolved
20	M	C	78	MPA	P	24.0	9.7	No	NA	7	Resolved
Total	10 F,	15 C,	63 ± 11	1 CS,	6 C,	24.0 ± 6.5	4.7 ± 4.0	9/20	8.5 ± 7.2;	6.15 ± 1.42	100%

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Clinical Nephrology, Vol. 54 – No. 4/2000 (282-288)

Diffuse alveolar hemorrhage in lupus nephritis

J.G. Lee[1], K.W. Joo[2], W.K. Chung[2], Y.C. Jung[3], S.H. Zheung[2], H.J. Yoon[2], Y.S. Kim[2], C. Ahn[2], J.S. Han[2], S. Kim[2], J.S. Lee[2]

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- 7 lupus nephritis - 9 episodes DAH
- Serologic evidence of flare and lung biopsy c/w IC deposits
- Treated pulse dose steroids and IV Cytoxan (3/9) and oral 1mg/kg Cytoxan in 6/9 with no plasma exchange
- Mortality 57%, higher mortality associated with infections PCP and actinobacter, severe anemia at presentation and longer duration of mechanical ventilation

Mortality Associated with Pulmonary Vasculitis

Prognostic Factors for Hospital Mortality and ICU Admission in Patients With ANCA-Related Pulmonary Vasculitis

FERNANDO HOLGUIN, MD, MPH; BASSEL RAMADAN, MD; ANTHONY A. GAL, MD; JESSE ROMAN, MD

Poor Prognostic Factors

Variable	P value
Mean Age - 60y	<0.05
Mean BUN - 53	<0.05
Low Hemoglobin -9.8%	=0.05
Elevated WBC count -15.4	=0.05
Fio2 54%	<0.05
ICU length of stay – 16days	<0.05
Mech. Ventilator use	<0.0001
Need for Blood transfusion	<0.0002
Secondary infection	<0.005

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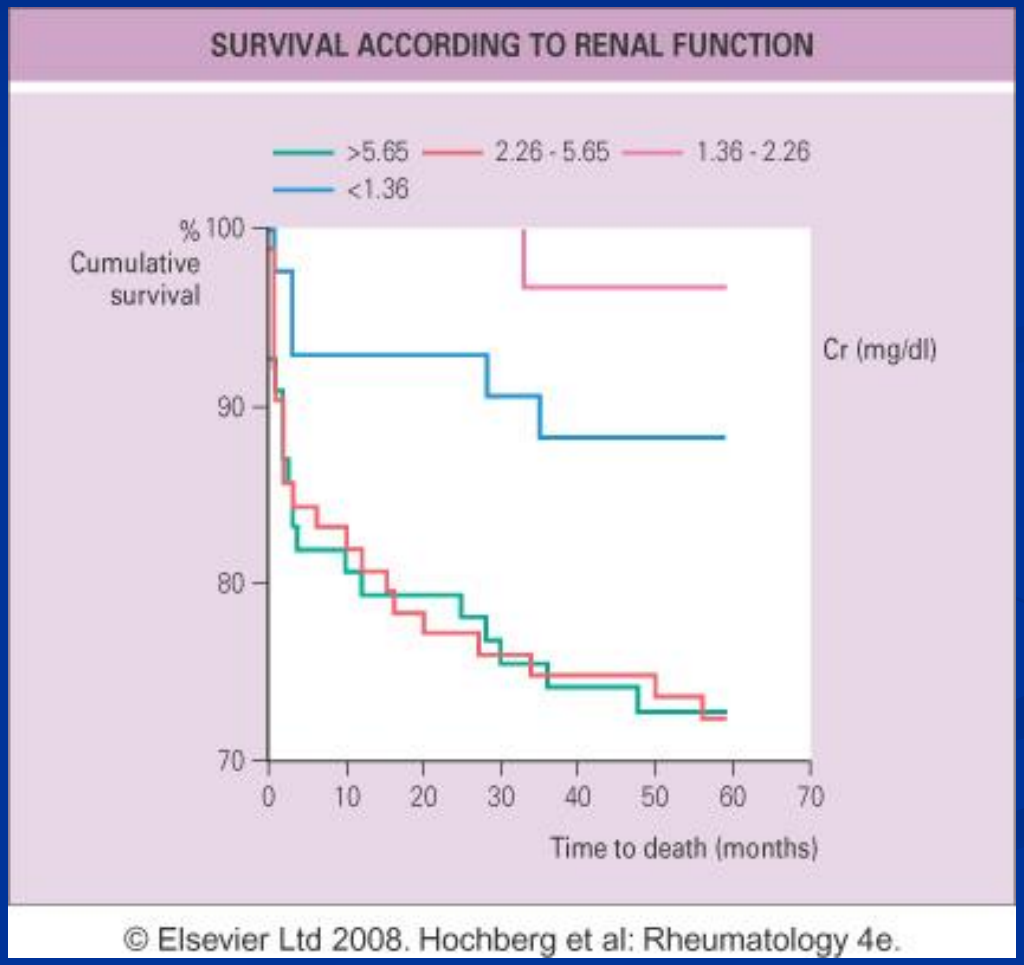
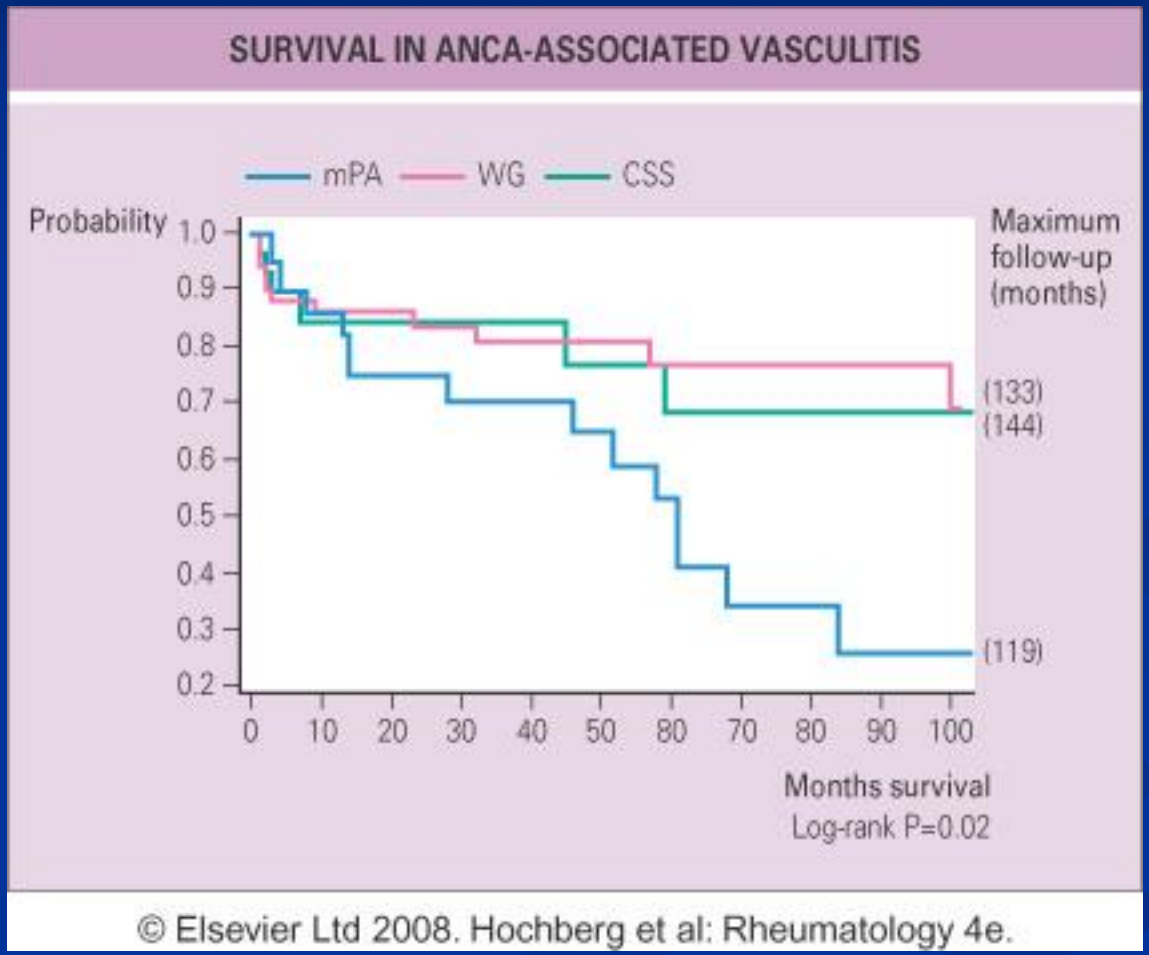
Renal failure
poor prognostic factor



Survival estimates

ANCA vasculitis



Summary of Treatment

- Common practice to use of Pulse dose steroids and Cytoxan in life threatening renal and pulmonary involvement
- There is good data early use of plasma exchange followed by IVIG in life threatening and treatment resistant cases
- Plasma exchange has been helpful in situations with concomitant need for anticoagulation

RAVE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Rituximab versus Cyclophosphamide for ANCA-associated vasculitis

- Design: US based multicenter, randomized, double blinded, non inferiority trial, 197 pts
- Methods: Rituximab 375mg/m2 once a week for 4 weeks, control group (oral cyclophosphamide 2mg/kg), 1-3 pulse solumedrol followed by prednisone 1mg/kg
- Primary end point was remission of disease without prednisone at 6 months
- Results: 64% patients in Rituximab arm and 53% in control arm reached primary end point and met criteria of non inferiority P<0.001

Stone JH - *N Engl J Med* - 15-JUL-2010; 363(3): 221-32

RAVE

- Safety: No significant differences in adverse effects
- Conclusion: Rituximab was non inferior
- More effective is inducing remission for refractory relapsing disease, 67% (34/51) vs. 42% (21/50) in control group
- Same efficacy as cyclophosphamide in major renal disease or alveolar hemorrhage

Stone JH - *N Engl J Med* - 15-JUL-2010; 363(3): 221-32

RITUXVAS

The NEW ENGLAND JOURNAL of MEDICINE

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Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

Rituximab versus Cyclophosphamide in ANCA-associated RENAL vasculitis

- Design: Open label, 3:1 ratio randomized trial, 44 patients, 8 centers in European and Australia
- ANCA vasculitis with renal involvement (Necrotizing GN or active urinary sediment)
- Methods: Plasma exchange or 1-2 Pulse steroids
- Randomized: Rituximab 375 mg/m2 per week for 4 weeks with two intravenous Cyclophosphamide pulses (33 patients)
- I/V Cyclophosphamide for 3 to 6 months followed by Azathioprine (11 patient)
- Primary end point sustained remission rates at 12 months and absence of severe adverse events

Jones RB - *N Engl J Med* - 15-JUL-2010; 363(3): 211-20

RITUXVAS trial

- Results 25 patients in the Rituximab group (76%) and 9 patients in the control group (82%) had a sustained remission (P=0.68)
- Safety: Non significant but more severe adverse events in Rituximab 42% vs. 36% control group (P=0.77), 18% died in both group
- Conclusion: Rituximab-based regimen was not superior to standard intravenous Cyclophosphamide and Rituximab-based regimen was not associated with reductions in early severe adverse events
- Discussion: Open label study with CYC used in both groups

Jones RB - *N Engl J Med* - 15-JUL-2010; 363(3): 211-20

Take home message

- Rituximab was efficacious in inducing remission particularly for refractory relapsing cases
- Adverse effect profile is a consideration, risk of PML infection
- Candidate for induction of refractory cases
- Long term data of RAVE trial will be provide insight
- Azathioprine appears to be reasonable choice for maintenance