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Vasculitis – A Diagnostic Dilemma for Primary Care

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Vasculitis

How to recognize it and

when to ask for help

Challenging Diagnosis for All

- Non-specific symptoms
- Overlapping syndromes
- Lack of highly specific or sensitive tests
- Absence of generally accepted diagnostic criteron

Classification criteria for different vasculitic syndromes proposed for research purposes is not useful in the clinical setting

2012 Revised International Chapel Hill Consensus Conference on Nomenclature of Vasculitides

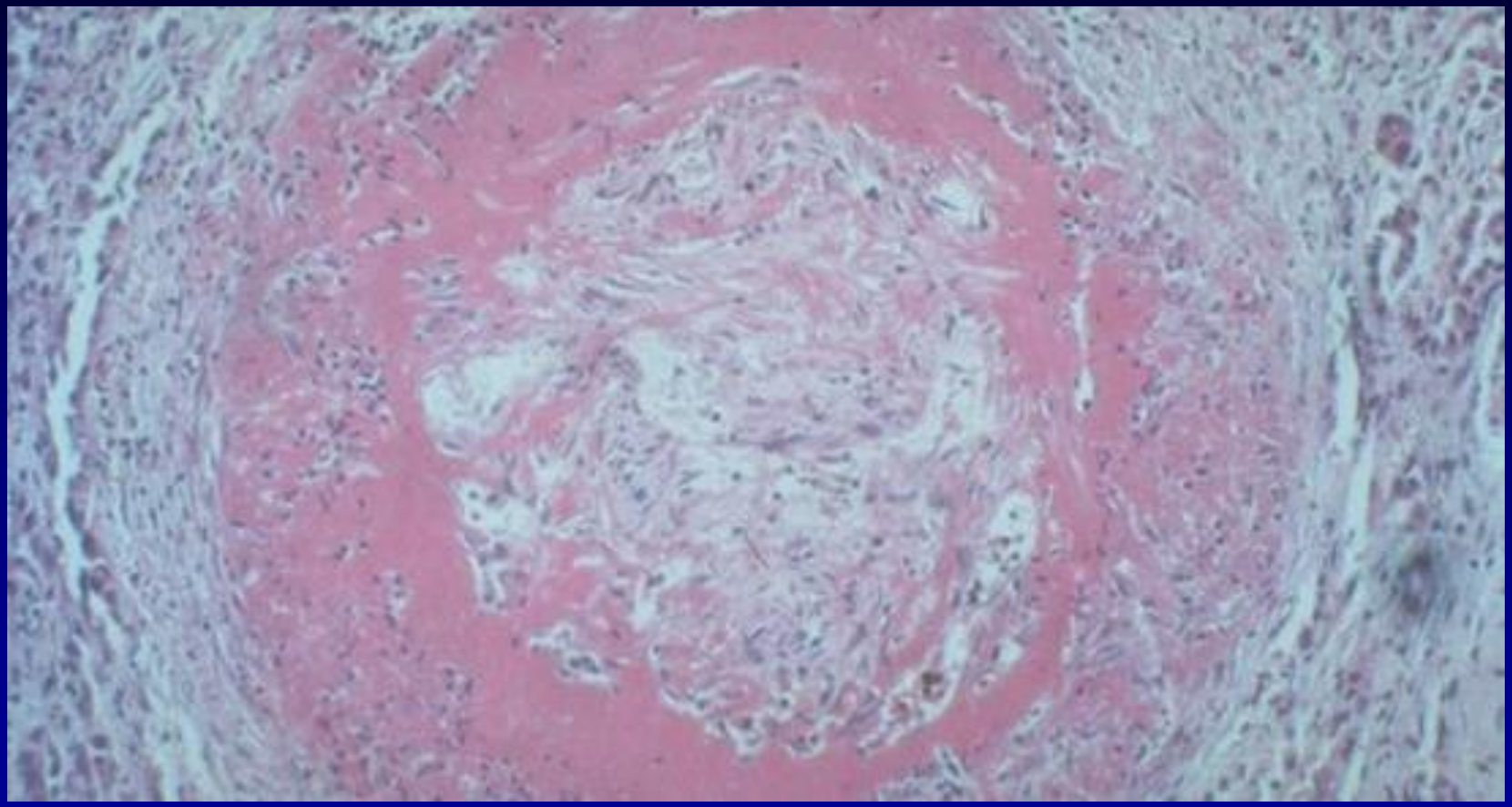
Diagnosis of Specific Forms of Vasculitis

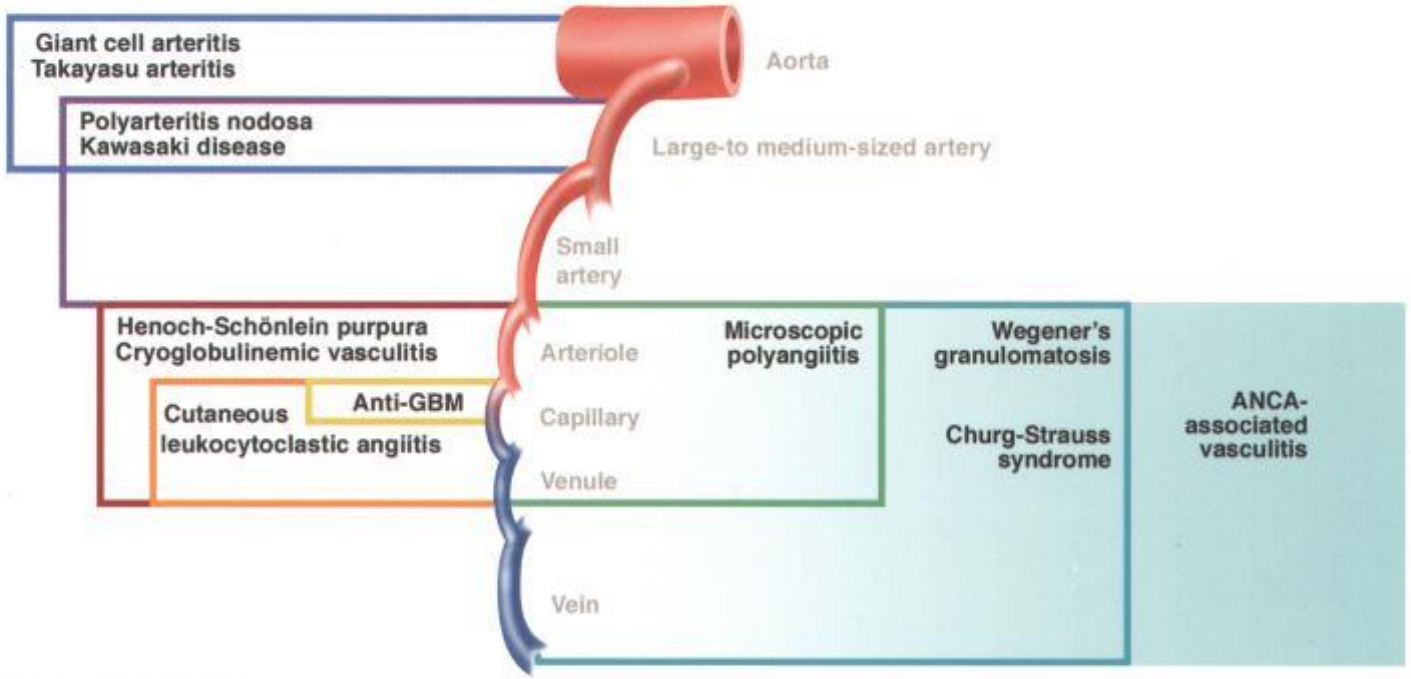
Depends on recognition of particular patterns of

- **Clinical**
- **Radiographic**
- **Laboratory**
- **Histopathology**

Vasculitis – Definition

- A general term for a group of uncommon diseases that feature inflammation of blood vessels
- Each of these diseases defined by characteristic distributions of blood vessel involvement, patterns of organ involvement and lab test abnormalities





GBM, glomerular basement membrane

Figure 1. Systemic Vasculitides According to Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Systemic Vasculitis[2], with AAV Shown in Blue

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Primary and Secondary Vasculitides

Classification of Vasculitis

Some types of vasculitis previously had different, eponym-based names:

Old Name	New Name
Wegener's Granulomatosis	Granulomatosis with Polyangiitis
Churg-Strauss Syndrome	Eosinophilic Granulomatosis with Polyangiitis
Henoch-Schönlien Purpura	IgA Vasculitis

Primary

- **Large Vessel Involvement**
  - **Giant cell arteritis**
  - **Takayasu's arteritis**
  - **Behcet's syndrome**


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Primary

- **Medium and Small Vessel Involvement**
  - **Polyarteritis nodosa**
  - **Cutaneous polyarteritis**
  - **Granulmatosis with polyangitis**
  - **Eosinophilic granulomatosis with polyangitis**
  - **Microscopic polyangitis**
  - **Thromboangitis obliterans**
  - **Cryoglobulinemia**
  - **Kawaski’s disease**
  - **Behcet’s syndrome**
  - **Primary angitis of the CNS**
  - **Cogan’s syndrome**

Primary

- **Predominately Small Vessel Involvement**
  - **Cutaneous leukocytoclastic vasculitis**
  - **Urticarial vasculitis**
  - **Behcet's syndrome**
  - **IgA vasculitis**

Evaluation of Patients Where Vasculitis is Considered

- Individually tailored
- Based on extent of organ involvement
- Tempo of the disease
- Tissue biopsy remains the gold standard for diagnosis

Initial Approach to Diagnosis of Vasculitis

- History and physical exam
- Accurately catalogue areas of disease involvement
- No single typical presentation
- Must recognize patterns of signs and symptoms

Patterns of Symptoms / Signs

		Size of Vessels		
		Small	Medium	Large
Skin System	Skin	Palpapable purpura	Erythema nodosum Livedo reticularis	Cyanosis Discoloration of extremities
	Gastrointestinal	Mucositis GI bleeding	Abdominal pain Bowel perforation	Bowel infarction
	Renal	Hematuria without RBC casts Proteinuria	Hematuria with RBC casts Flank pain	Hypertension No hematuria
	Neuro	Polyneuropathy	Mental status Δ's Strokes	Strokes
	Muscles	Myalgias	Myositis	Claudication

Clinical Manifestations

- Chronic fevers
- Palpable purpura
- Symptoms of tissue ischemia in unusual populations
- Neuropathy
- Rapidly progressive multisystem inflammatory disease

History

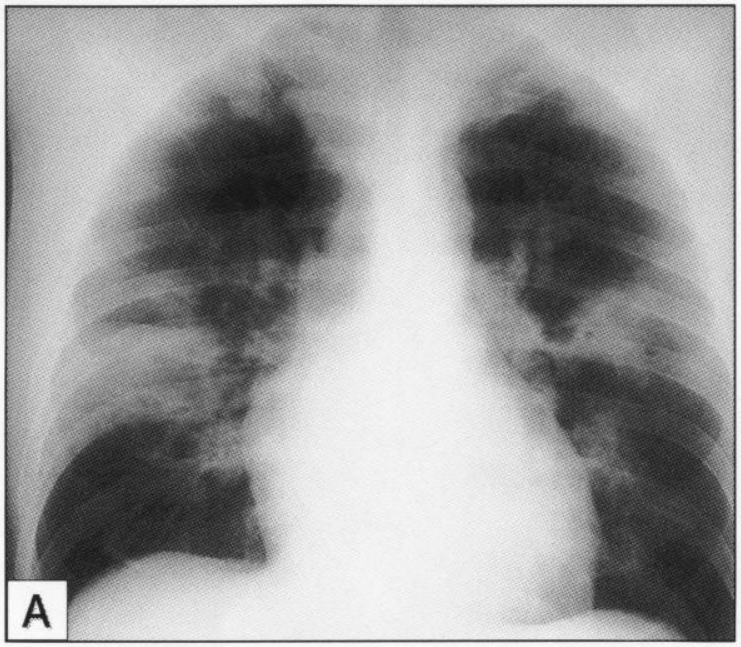
- Illicit drug use
- High risk sexual activity
- Prior thrombosis
- Miscarriages
- Travel history
- Prior malignancies
- Operations and dental procedures
- Medications and OTC supplements or herbal preparations
- Chemical exposure

GCA

- Headaches
- Scalp tenderness
- Jaw claudication
- Vision loss
- Muscle pain/stiffness

Pulmonary-Renal Syndrome

- Cough and hemoptysis
- Hematuria
- Chronic sinusitis
- Asthma
- Eosinophilia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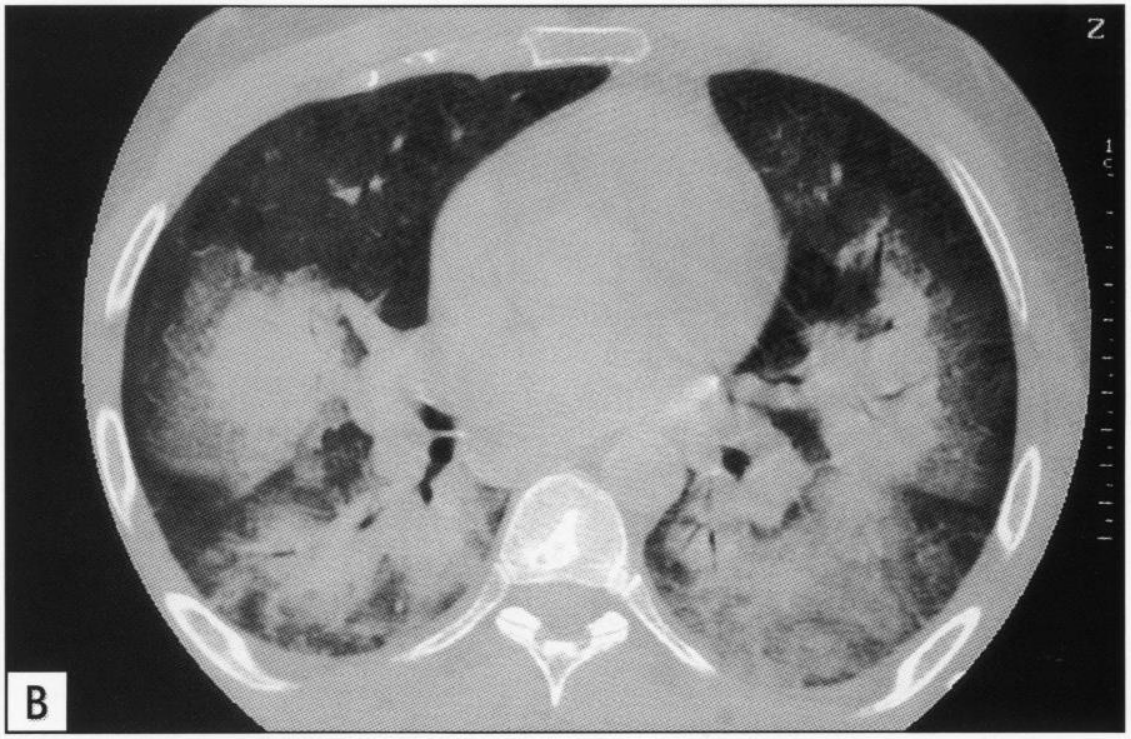
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Physical Exam

Provide clues to presence of vasculitis or its mimics

Complete vascular exam includes:

1. **Palpation of arterial pulses**
2. **Auscultation for bruits**
3. **BP measurement of all extremities**

Bruits

- Takayasu's arteritis
- GCA
- Behcets syndrome
- Cogans syndrome

Loss of Pulse

- Takayasu's arteritis
- GCA
- Thromboangitis obliterans

Polyarteritis Nodosa

- New onset hypertension
- Abdominal pain
- Mononeuritis multiplex

Laboratory Evaluation

- CBC with diff, CMP, UA, ESR, CRP, CPK, aldolase
- No specific lab test to diagnose vasculitis
- Neither ANCA or complement levels should be used as screening tests

Testing That is Suggestive of Vasculitis

- Normochromic, normocytic anemia
- Thrombocytosis (acute phase response)
- Eosinophilia
- Hematuria
- Proteinuria
- Elevated transaminases = hepatitis B and HCV
- Elevated ESR but normal does not exclude vasculitis – 24% normal ESR in GCA
- ESR elevation most also exclude malignancies and infections

ANCA – What's the Deal ?

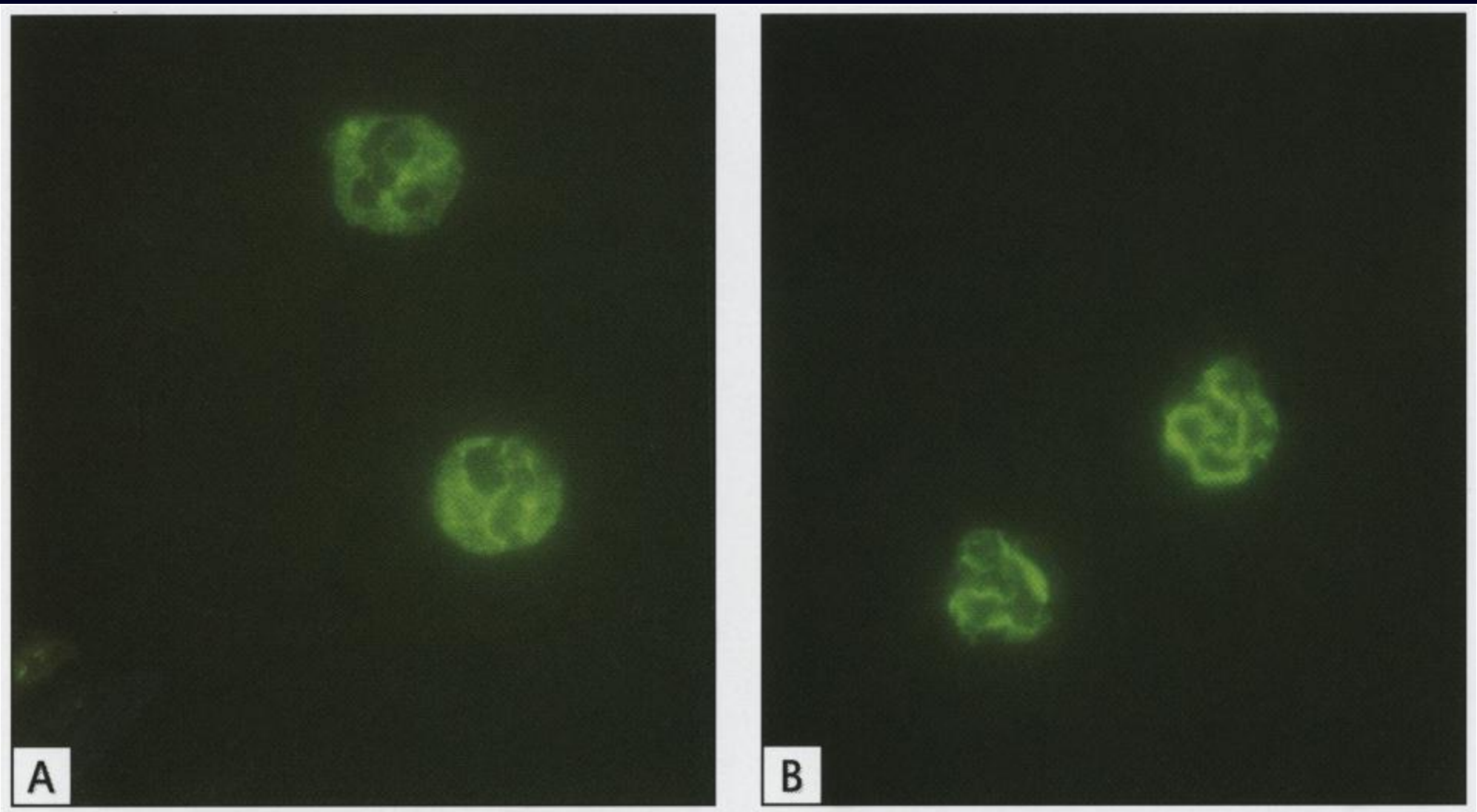
No specific lab tests for diagnosis of vasculitis

Proposed Indications for ANCA Testing

- Cutaneous vasculitis with systemic features
- Pulmonary hemorrhage
- Glomerulonephritis (especially rapidly progressive)
- Multiple lung nodules
- Chronic destructive upper airway disease
- Longstanding sinusitis or otitis
- Subglottic or tracheal stenosis
- Peripheral neuorpathy
- Retro-orbital mass

ANCA

- c ANCA (cytoplasmic staining) – generalized GPA
- p ANCA (perinuclear staining) – microscopic polyangitis or MPA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Positive ANCA

- Does not establish a diagnosis
- Seen in diverse spectrum of disease
  - Inflammatory bowel disease
  - SLE
  - Drug induced vasculitic reactions
  - Infections

Demonstrating the presence of a circulating ANCA is NOT equivalent to diagnosing vasculitis

What to do if ANCA Immunofluresence Test is Positive?

- Elisa testing for PR3 and MPO
- Elisa testing vs immunofluorescence higher predictive value (83% versus 45%)
- c ANCA + PR3 highly suggestive of GPA
- p ANCA + MPO highly suggestive of MPA
- But 10-20% of patients with GPA have +p ANCA and +MPO
- Some with MPA or EGPA are c ANCA positive

Cocaine and Levamisole Associated Vasculitis

- High titer p ANCA
- Low titer MPO antibodies
- PR3 antibodies
- Human neutrophil elastase, lactoferrin, cathepsin G

Radice and Sinico, 2005

- 10-50% of patients with biopsy proven vasculitis will have negative serologies
- 10% of patients with positive c ANCA and PR3 ABS with other diagnosis, i.e. malignancy, infection or other connective tissue disease
- Increased use of ANCA in patients with low clinical suspicion of vasculitis or recent changes in detection methods

ANCA Testing

- Should not replace tissue confirmation of GPA or MPA
- Unless clinical findings are classic and other causes exhaustively excluded

Complement Levels (C3 and C4)

- Decreased in lupus nephritis, cryoglobulinemia or endocarditis
- Normal in GPA or MPA

Antiglomerular Basement Membrane (GBM)

- Alveolar hemorrhage
- Normocomplementemic GN
- Pulmonary-renal syndrome

ANA and Rheumatoid Factor

- Not useful screening tests for vasculitis
- RF elevated in Sjogren's cryoglobulinemia and subacute bacterial endocarditis

Secondary Vasculitis

- Vasculitis when documented may not be primary
- Especially the case in cutaneous small vessel vasculitis and purpura
- Leukemia, myelodysplasia, I.E., viral hepatitis, rickettsial and neisserial infections, carcinomas and systemic autoimmune disease

Secondary and Mimics

- **Infections**
  - **Subacute bacterial endocarditis**
  - **Syphilis**
  - **Hepatitis B**
  - **Hepatitis C**
  - **Cytomegalovirus**
  - **Epstein-Barr virus**
  - **Human immunodeficiency virus**
  - **Meningococcemia**
  - **Tuberculosis**
  - **Brucella**
  - **Salmonella**
  - **Rocky Mountain spotted fever**

Helpful Tests Useful in Excluding Some Secondary Causes of Vasculitis or Mimics

- 3 sets of blood cultures
- TEE despite negative cultures
- Serologic tests for organisms, i.e. syphilis tests in evaluation of aortitis

Bacterial Endocarditis

- Purpura
- Mesenteric arterial microaneurysms
- G.N.
- Retinal vasculitis
- Stroke
- Arthritis
- Cryglobulins
- R.F. and PR3 + ANCA

Secondary and Mimics

- **Medications**
  - B-lactams
  - Sulfonamides
  - Quinolones
  - Macrolides
  - Thiazides
  - Loop diuretics
  - Beta blockers
  - Phenytoin
  - Propylthiouracil
  - Selective serotonin reuptake inhibitors
  - NSAIDS
  - Antitumor necrosis factor
  - alpha inhibitors
  - Colony stimulating factors (GM-CSF, G-GSF)
  - Carbimazole
  - Clopidogrel
  - Montelukast
  - Minocycline

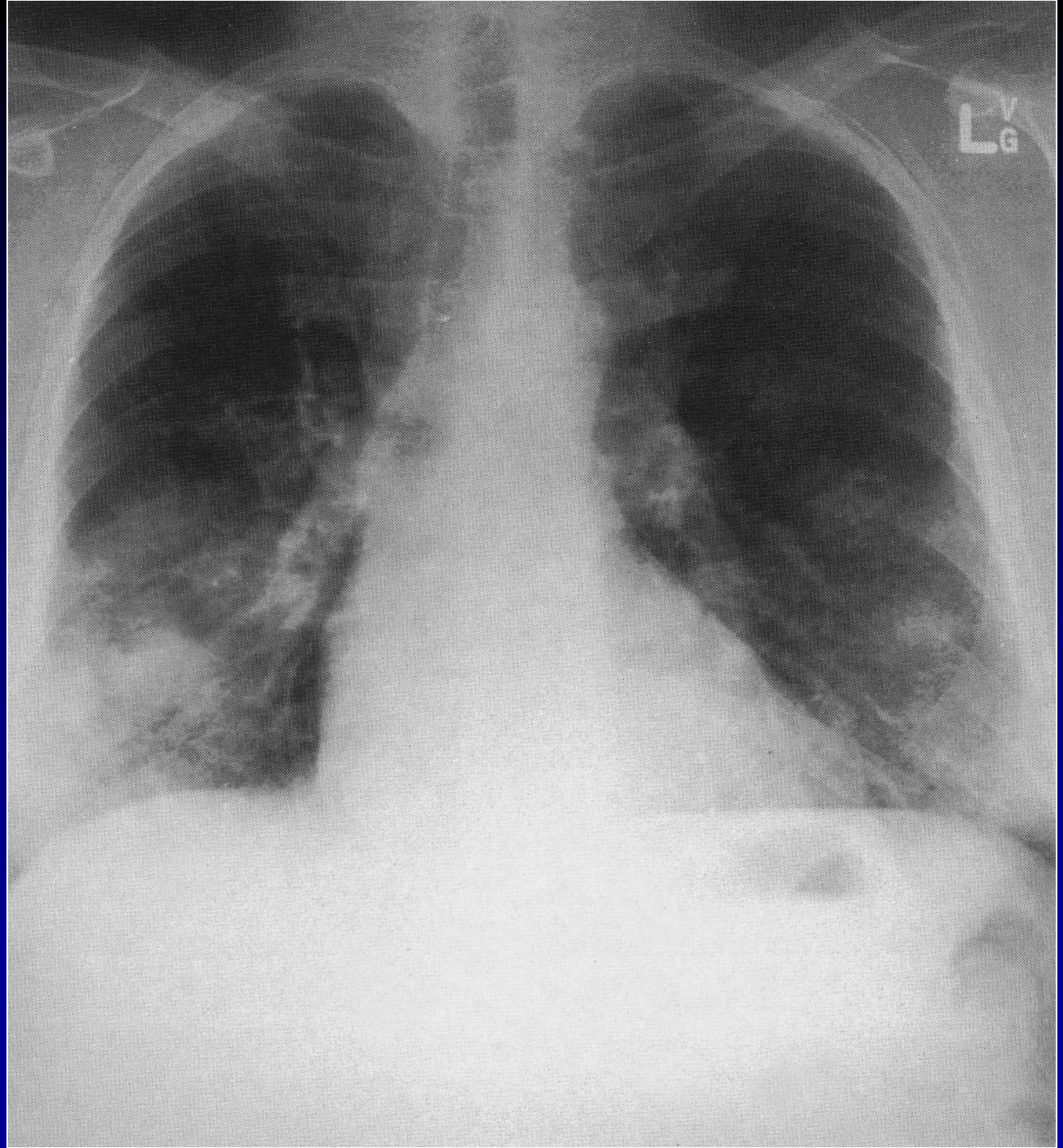
Cutaneous Vasculitis

- 172 adults (Cutaneous Vasculitis -120) Hypersensitivity Vasculitis - 70, HSP-39, Mixed Cryoglobulinemia-11
- 23 systemic necrotizing vasculitis (P nodosa-17,GPA-4, EGPA-2)
- 4 malignancy
- 5 systemic bacterial infection
- 20 autoimmune disease

- 80% of mixed cryoglobulinemia associated with Hep C

Secondary and Mimics

- Drugs
  - Cocaine + levamisole
  - Amphetamines
  - Heroin
- Other
  - Malignancy
  - Thrombotic thrombocytopenic purpura
  - Cardiac myxoma
  - Cholesterol emboli syndrome
  - Atherosclerosis
  - Calciphylaxis
  - Amyloidosis
  - Moyamoya disease
  - Ehlers-Danlos syndrome
  - Fibromuscular dysplasia
  - Antiphospholipid antibody syndrome



Secondary Testing

- Focus on providing supportive evidence for vasculitis
- Exclude mimics

Cancer

- Purpura
- Fever
- Mononeuritis multiplex

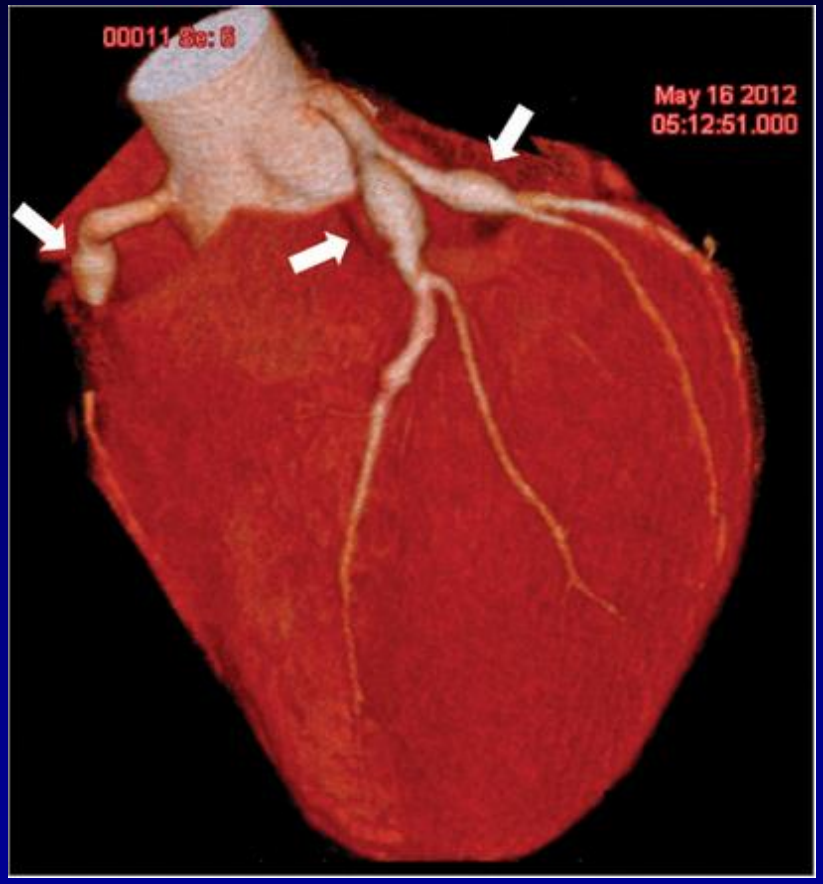
Peripheral Neuropathy / Myopathy

- EMG / NC
- Infection, toxin, malignancy, metabolic, inflammatory processes
- Nerve / muscle biopsy
- Direct imaging

Imaging Studies in Arteritis

Angiography

- Important in evaluation of aorta for arteritis, aneurysmal or occlusive diseases
- Angitis of CNS
- Coronary arteritis in Kawasaki disease
- Limited spatial resolution therefore small vessel vasculitis will typically not be seen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Microaneurysms

- Highly suggestive of vasculitis if seen in more than one organ
- Medium sized muscular arteries (PAN)
- Prolonged time to develop and with negative results early in disease course
- Traditional angiography only visualizes vessel lumen and misses thickening of vessel wall seen in early stenosis or aneurysms

Microaneurysms

- PAN, MPA, EGPA and Behcets
- Atrial myxoma, endocarditis, peritoneal carcinomatosis
- Severe arterial hypertension with amphetamine abuse

MRI

- More common than traditional angiography for aorta and primary branches
- Visualizes vessel lumen and demonstrates edema and thickness of vessel walls
- Can overestimate vascular occlusions
- No consistent correlation of wall edema with symptoms, acute phase reactants or new anatomic changes

CT or MRI Studies

- Determine areas of suspected organ involvement
- MRI for air fluid levels, mucosal inflammation, cavitary lesions, retro-ortibal involvement
- CT scans for air fluid levels, mucosal thickening, sclerosing osteitis, bone thickening, destruction


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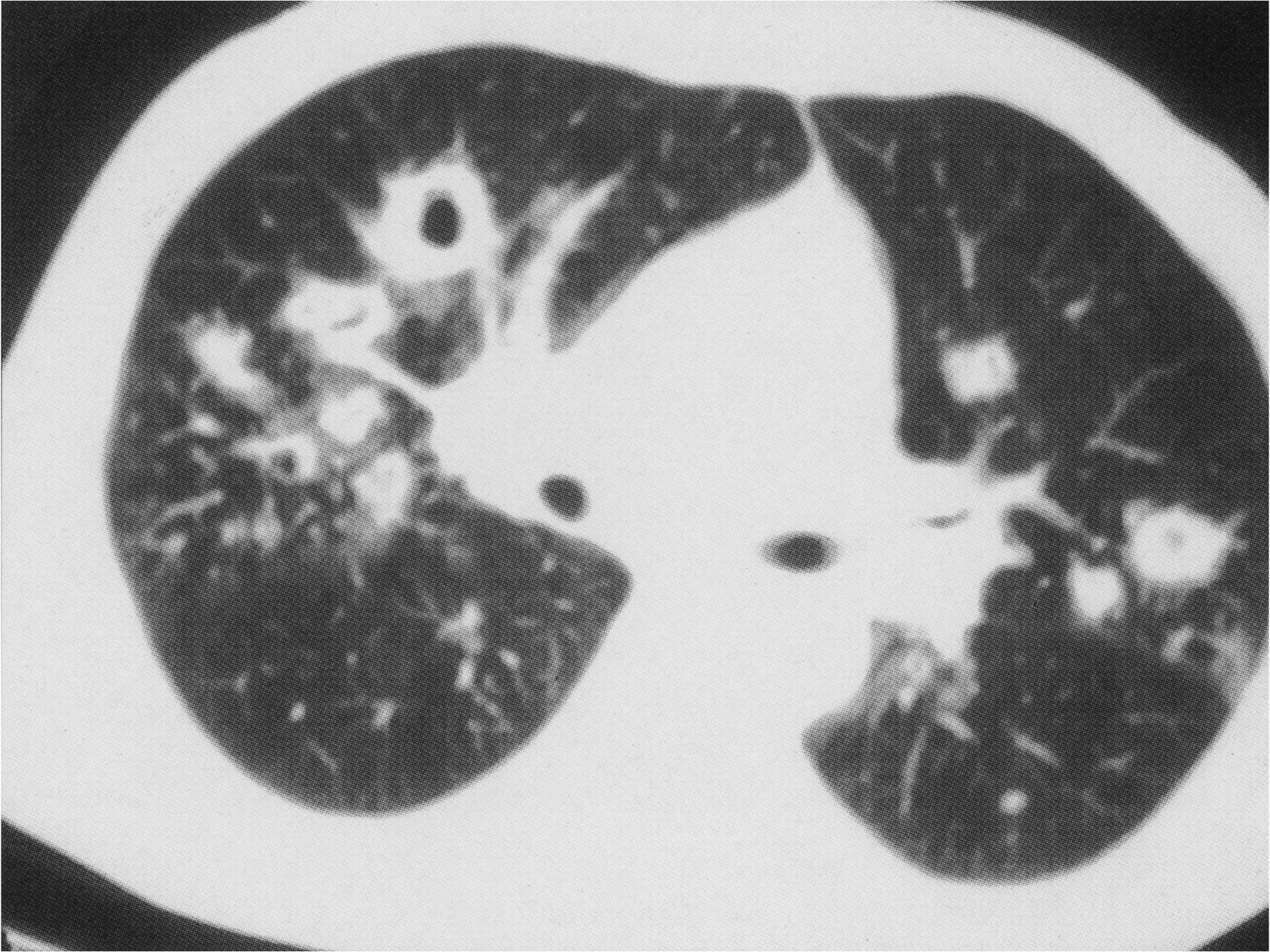
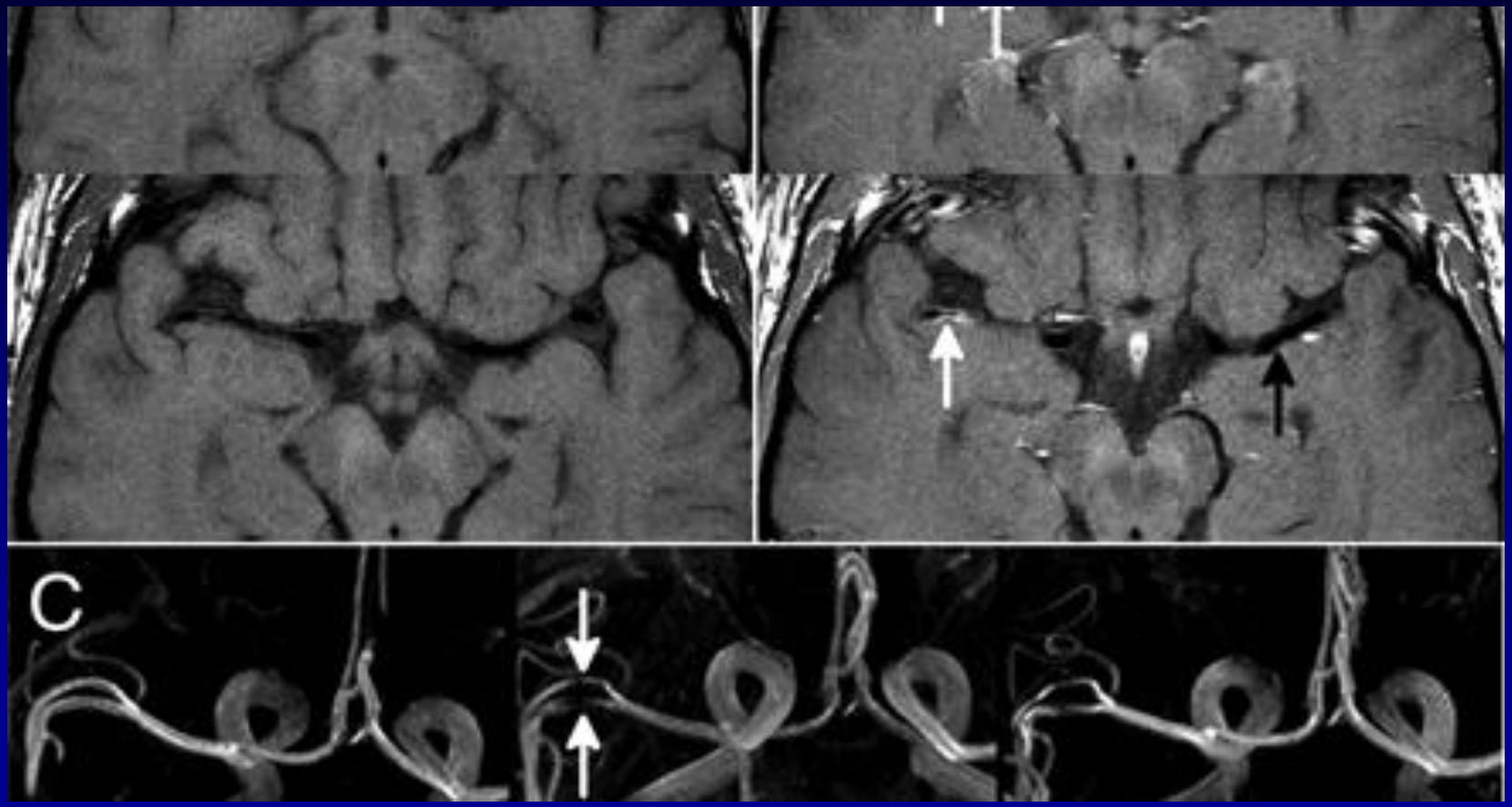


MRI in CNS Vasculitis

- Abnormal in 90% of histologically proven angitis
- Ischemia, infarcts, mass lesions and meningeal enhancement
- Normal MRI does not exclude CNS vasculitis
- Lumbar puncture, cerebral angiogram, brain biopsy
- Normal MRI and normal CSF = CNS vasculitis is rare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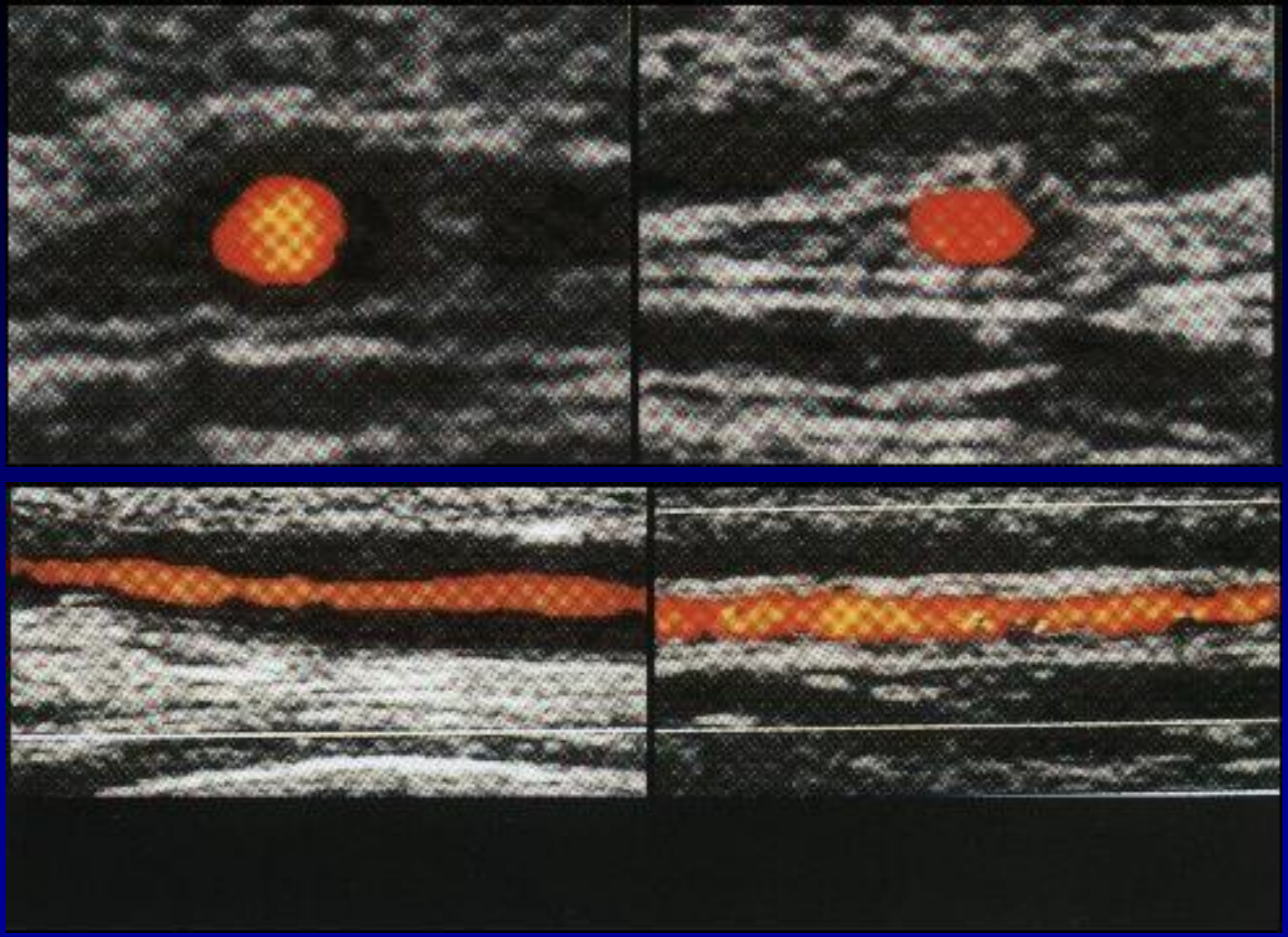
Pulmonary Disease

- CXR normal study does not exclude disease
- HRCT very sensitive means of detecting pulmonary abnormalities
- HRCT can differentiate between ground glass changes and fibrosis
- HRCT cannot differentiate alveolar hemorrhage from vasculitis, infection or medication
- Biopsy of lung

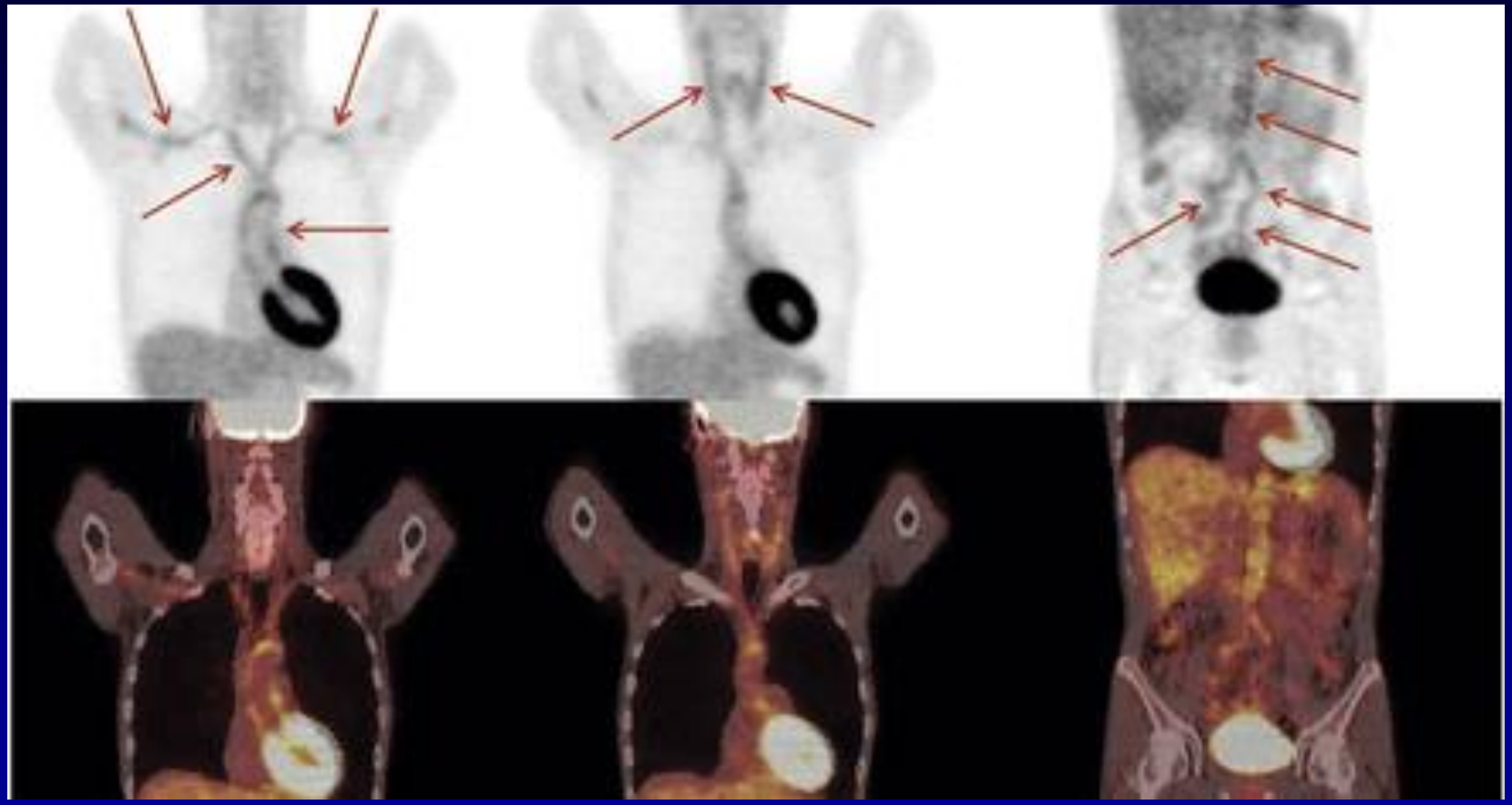
Ultrasound

- Better for medium sized peripheral arteries
- Halo sign – hypoechoic dark wall swelling
- Sensitivity 69%, specificity 82% compared to temporal artery biopsy
- Much less effective in detecting recurrent disease



PET Scanning

- Useful in diagnosis and follow up of large vessel vasculitis
- PET signal strong for branches extending from aorta
- Evaluation of atypical presentation of vasculitis, FUO, increased ESR or CRP
- PET/CT upper respiratory tract and lung lesions in G.P.A. and vascular lesions in Behcet’s



What Should I Biopsy?

Biopsy Location

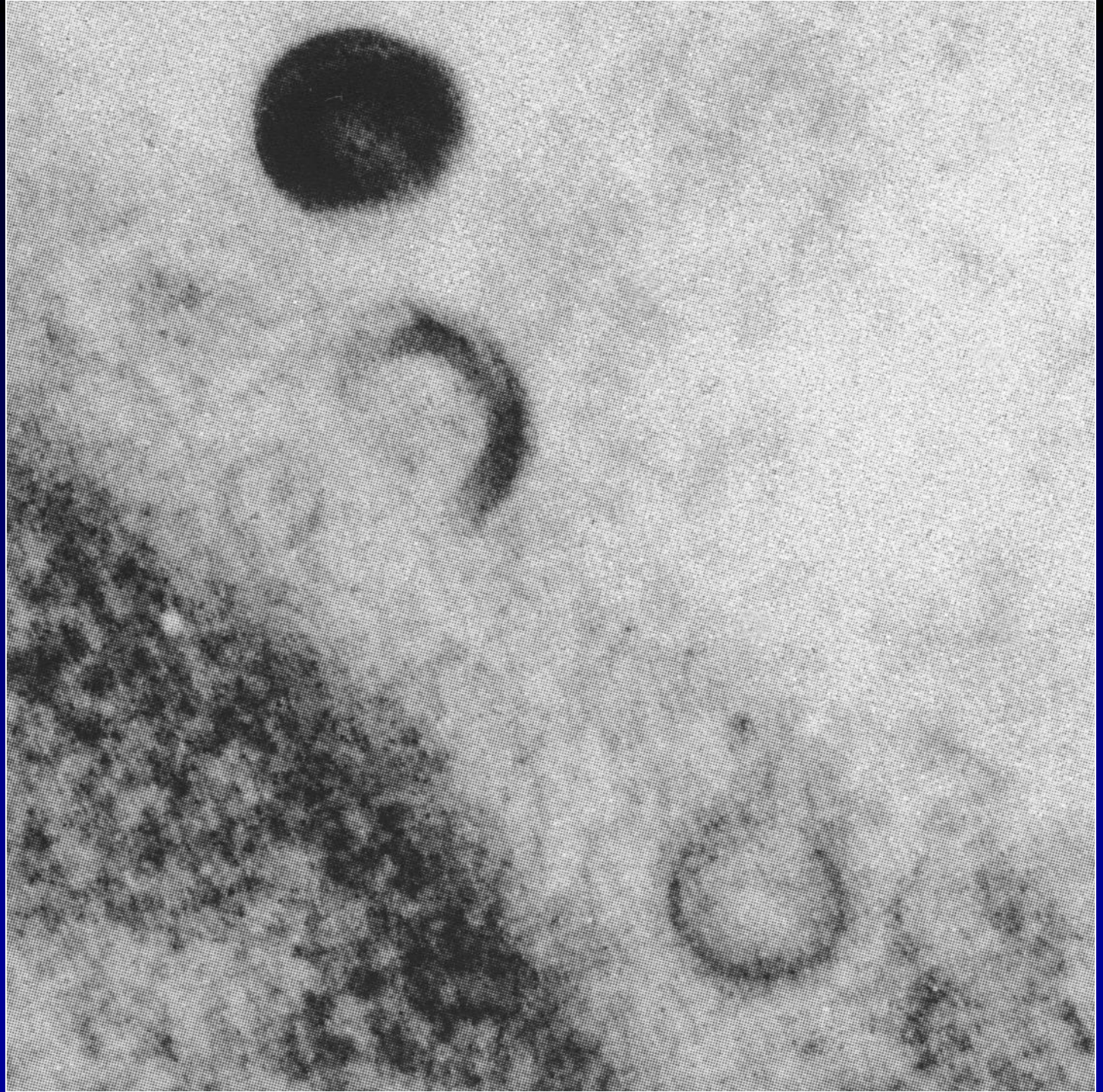
- Suspicion of clinical involvement
- Accessibility of tissue
- Several organ systems involved biopsy site determined by morbidity and amount of disease specific data

Skin Biopsy

- Small vessel vasculitis of involved skin easily demonstrated but not specific
- IgA vasculitis with IgA deposits Henoch-Schonlein purpura

Sample Size

- Vasculitis may not equally effect all portions of organ/vessel
- Skip areas of vasculitic involvement not unique to GCA
- Lung, nasal and sinus biopsies in GPA
- Muscle and nerve in small/medium sized vessels
- Blind biopsy of non-involved tissue low yield (19%-nerve, 29%-muscle)

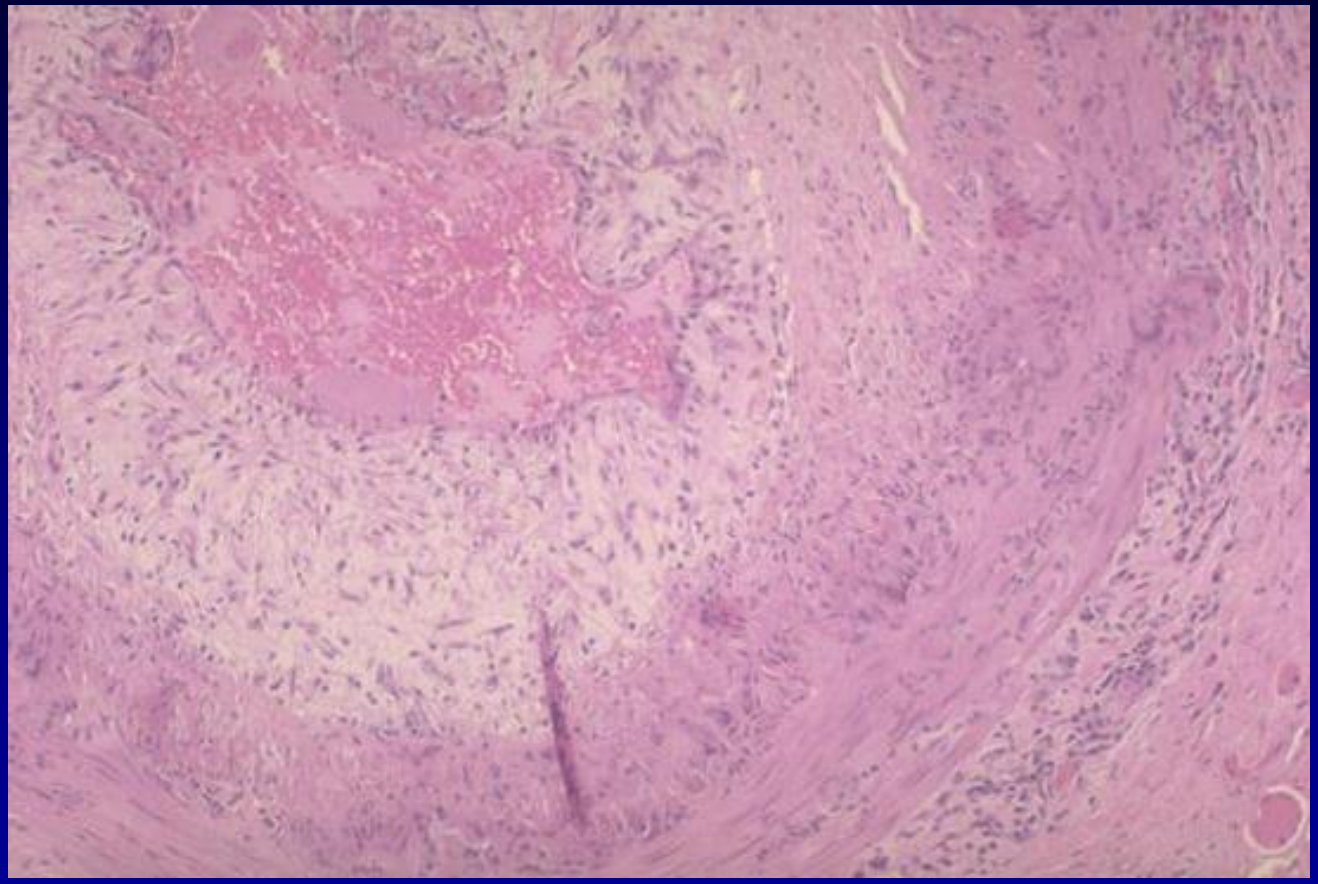


Demonstration of Vasculitis on Biopsy

- Not a final diagnosis
- Is a sign of underlying condition to be evaluated in the context of clinical, serologic and imaging to establish final diagnosis

GCA

- Vague signs and symptoms, fevers, myalgia and anemia without headache or jaw claudication
- 65-year-old patients or older diagnosed in 16% of all patients with FUO
- Biopsy considered in all with FUO with malignancy and infections excluded
- Unilateral versus bilateral TA biopsy
- Specimen .5 cm in length positive in 19%
- Specimen >2 cm in length positive in 89%
- 10% with clinical diagnosis of GCA have normal biopsies



Lung Biopsy

- Transbronchial – low diagnostic return in vasculitis
- Helpful for infection, malignancy and hemorrhage
- VATS low morbidity and mortality compared to open lung with high sensitivity and specificity

Nasal and Sinus Biopsy

- For GPA and EGPA low diagnostic yield
- Vasculitis or granulomas rarely seen

Renal Biopsy

- Arteritis or granulomas rarely seen
- Generalized GPA biopsy site of choice is lung
- Proteinuria, increased CR, casts in setting of multisystem disease

General Steps to Diagnosing a Vasculitis

- Identify a collection of clinical findings (symptoms, signs) which either suggest a vasculitis in general, or optimally, a specific vasculitis
- Check routine labs (including coags, UA), and consider checking imaging studies (e.g. CTA, MRA) and/or ANCAs
  - Narrow down differential diagnosis to 1-2 specific vasculitides
  - Search for an associated systemic illness (e.g. malignancy, infection, connective tissue disease, etc…)
  - Rule out mimics
- Confirm diagnosis with biopsy (usually preferred) and/or angiography

VASCULITIS TREATMENT APPROACH

- **REMISSION INDUCTION**
  - **Medium to high dose corticosteroids**
  - **Immunosuppressive agents disease specific**
  - **Failure of disease recognition associated with significant morbidity and mortality**

REMISSION MAINTENANCE

- Corticosteroid dose steadily tapered to reduce toxicity
- Immunosuppressive/Corticosteroid treatment continued for a period of time-disease specific and protocol based
- Goals
  - Control of disease activity
  - Prevent recurrence
  - Minimize drug toxicity

MONITORING

- Active treatment phase-disease activity and drug toxicity
- Disease recurrence in drug free remission

DISEASE SPECIFIC THERAPY

- Based on specific diagnosis
- Severity of disease
- Vessel size does not determine which medication or treatment regime effectiveness or type of monitoring required

TREATMENT

- Randomized Trials
- Observational Studies
- Large Cohort Studies

PROGNOSIS

- Good outcomes for many
- Highly dependent on diagnosis
- Acute remission induction and subsequent maintenance phase of treatment
- Adverse drug effects and infections

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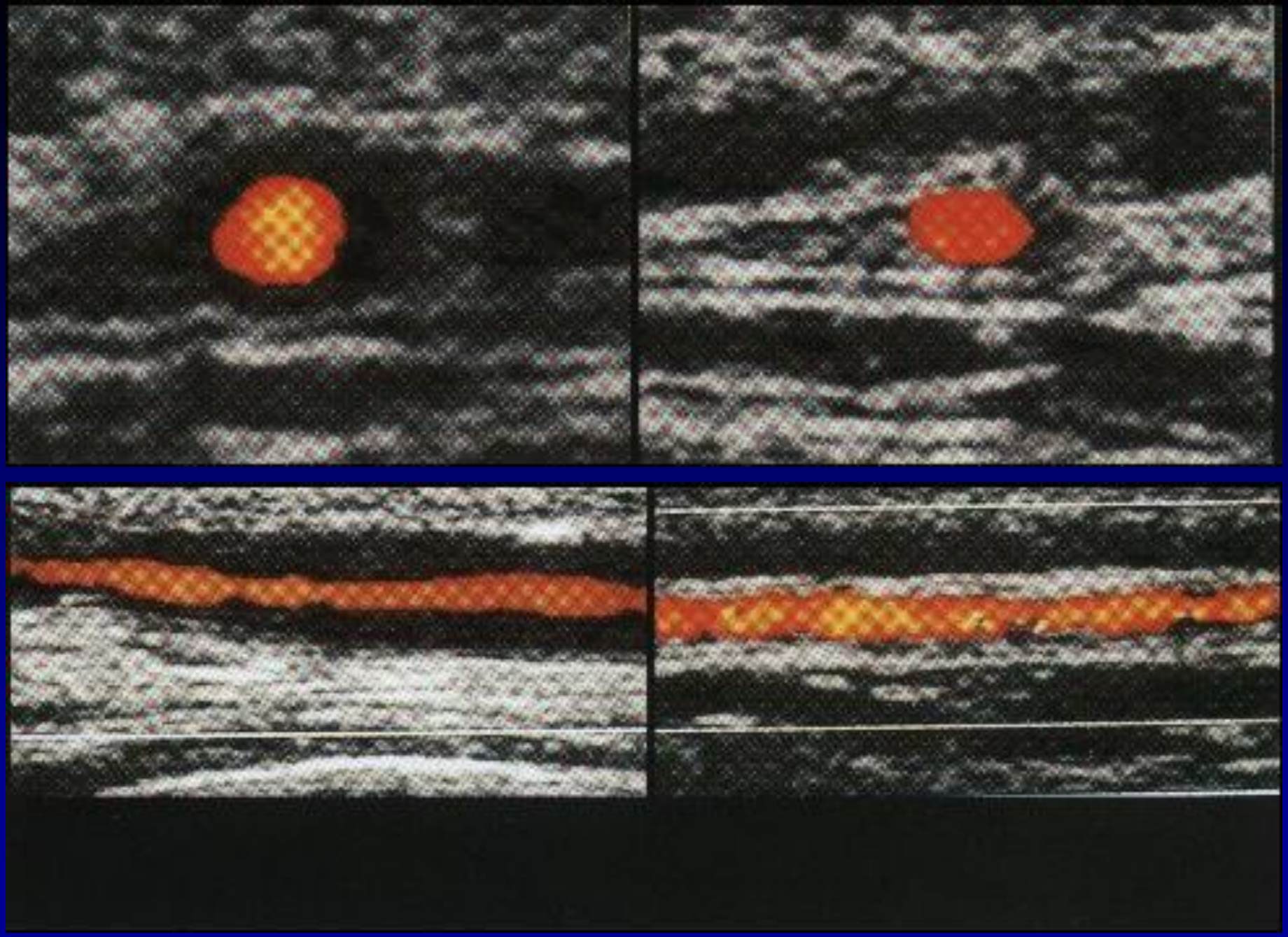
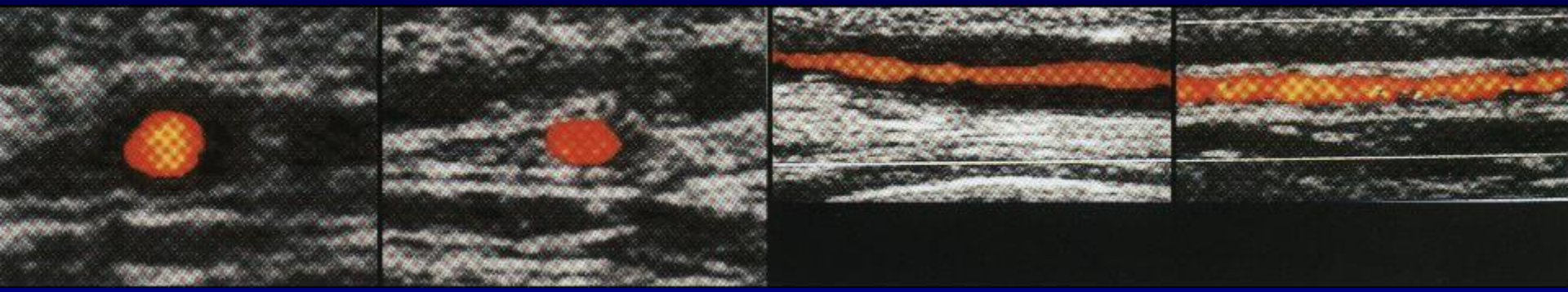
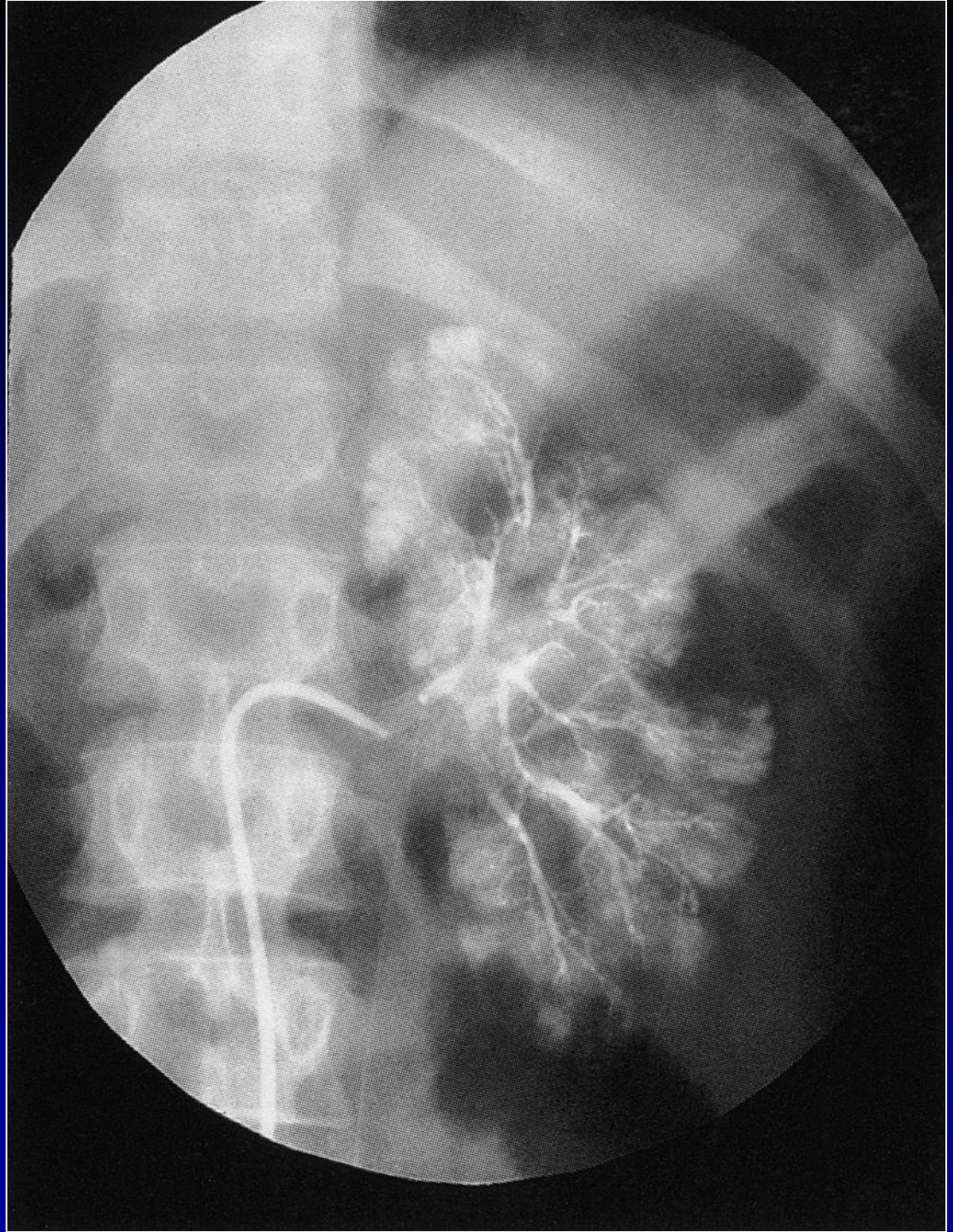
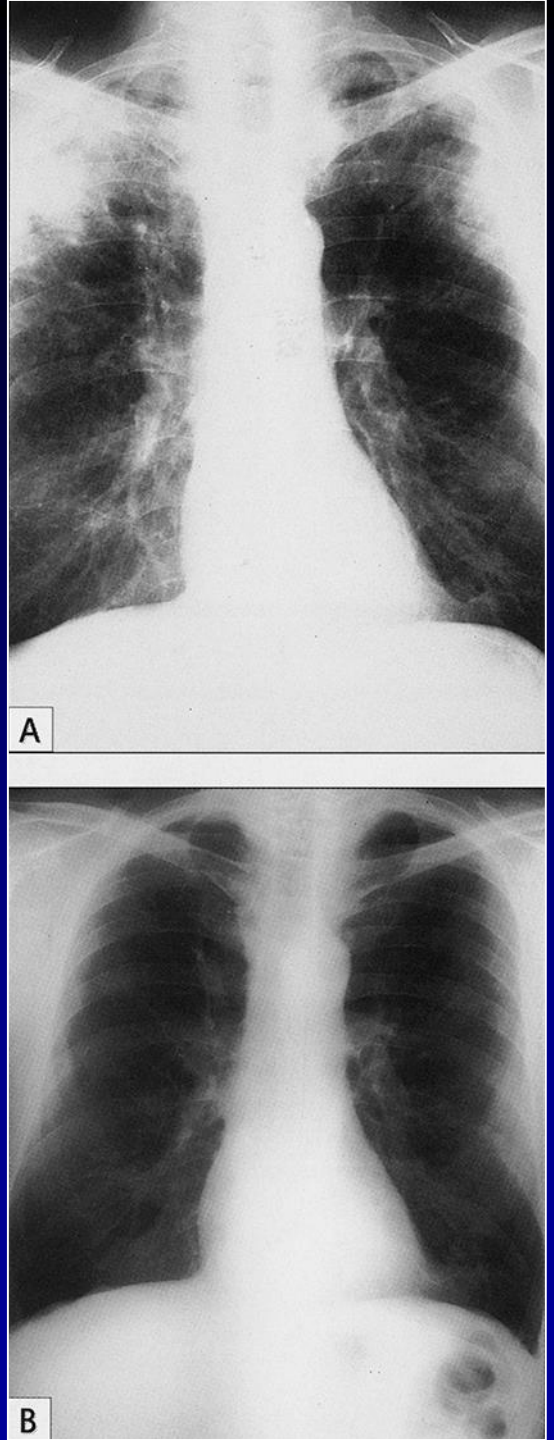
Every life deserves world class care.





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