Pulmonary Vasculitis

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A Case!

- 34 year old female presents with hemoptysis.
- You are called as the pulmonary consultant

History

- 1-2 tablespoons of bright red blood yesterday made her come in
- Before that she had some frothy looking blood tinged sputum
- Also had some general fatigue, malaise, aches and pains x 2 months

Thoughts?

Classification of Vasculitides

- Primary Idiopathic
  - Small vessel
  - Medium vessel
  - Large vessel
- Secondary
  - Classic connective tissue diseases (SLE, RA)
  - Drug-induced (PTU)
  - Paraneoplastic
  - Infection
  - Inflammatory bowel disease

Classification of Vasculitides

- Primary Idiopathic
  - **Small vessel** → **ANCA-Associated Vasculitis (AAV)**
    - Granulomatosis with Polyangiitis (GPA)*
    - Microscopic Polyangiitis (MPA)
    - Eosinophilic Granulomatosis with Polyangiitis (EGPA)**
    - *Idiopathic Pauci-Immune Capillaritis*
  - Medium vessel
  - Large vessel

**GPA = Wegener Granulomatosis*
***EGPA = Churg-Strauss Syndrome*

Multiple classification criteria have been developed

however

The diagnosis of vasculitis rests upon the identification of particular patterns of clinical, laboratory, radiologic and pathologic features

I am what I am today because of the choices I made yesterday…

- History and physical
- Radiology
- Laboratory
- Bronchoscopy
- Biopsy something
- Treatment

History

- GEN
- HEENT
- CVS
- PULM
- GI
- RENAL
- MSK
- SKIN
- NEURO

Many historical details are not volunteered. You have to ask!

- GEN- fatigue, malaise, subjective fevers
- HEENT- bloody nasal and ear discharge, sore mouth, trouble hearing sometimes, some dull eye pain
- CVS- sharp chest pain comes and goes
- PULM- cough, hemoptysis, also hoarse voice
- GI- normal
- RENAL- one episode of “brown urine” a couple months ago
- MSK- normal
- SKIN- rash on her legs
- NEURO- foot hits the ground sometimes when she walks

Multisystem disease

ENT

GPA 75-95%

MPA 10-30%

EGPA 30-70%

Pulmonary

GPA 75-95%

MPA 10-35%

EGPA 95-100%

Renal

GPA 50-90%

MPA 95-100%

EGPA 10-50%

Neurologic

GPA 5-25%

MPA 40-60%

EGPA 50-80%

Cardiac

GPA 5-15%

MPA 10-30%

EGPA 30-60%

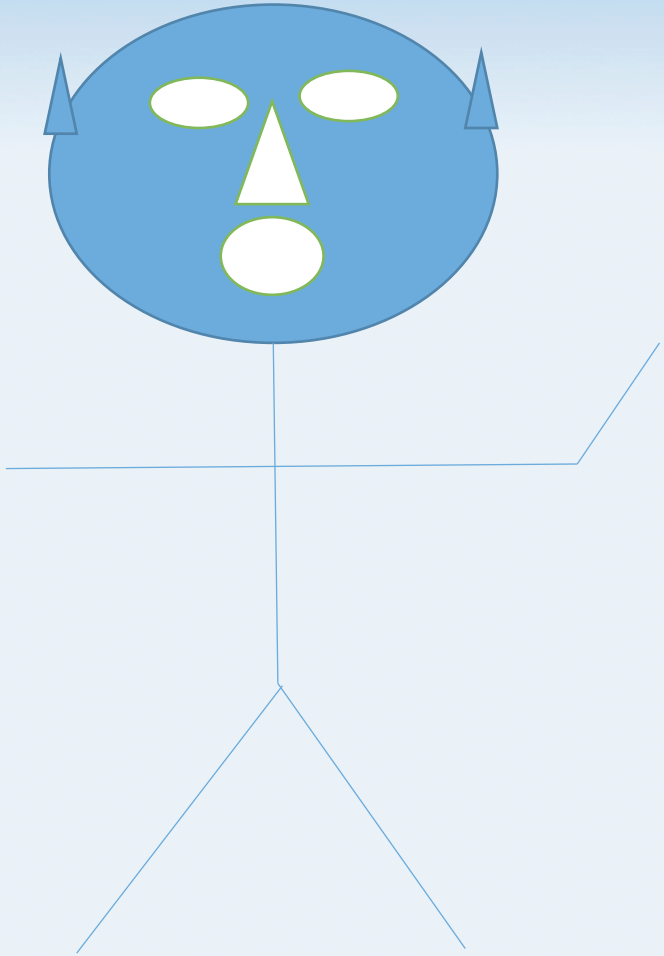
Dermatologic

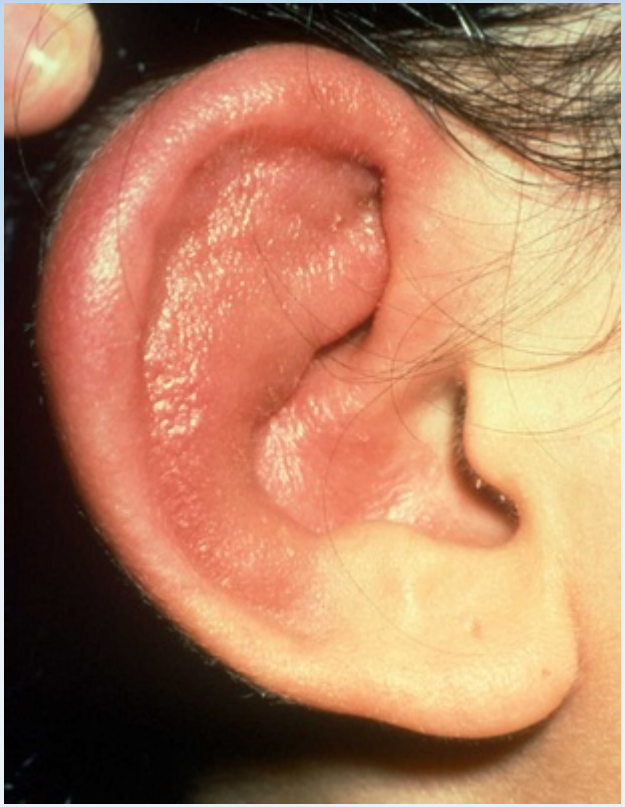
GPA 30-50%

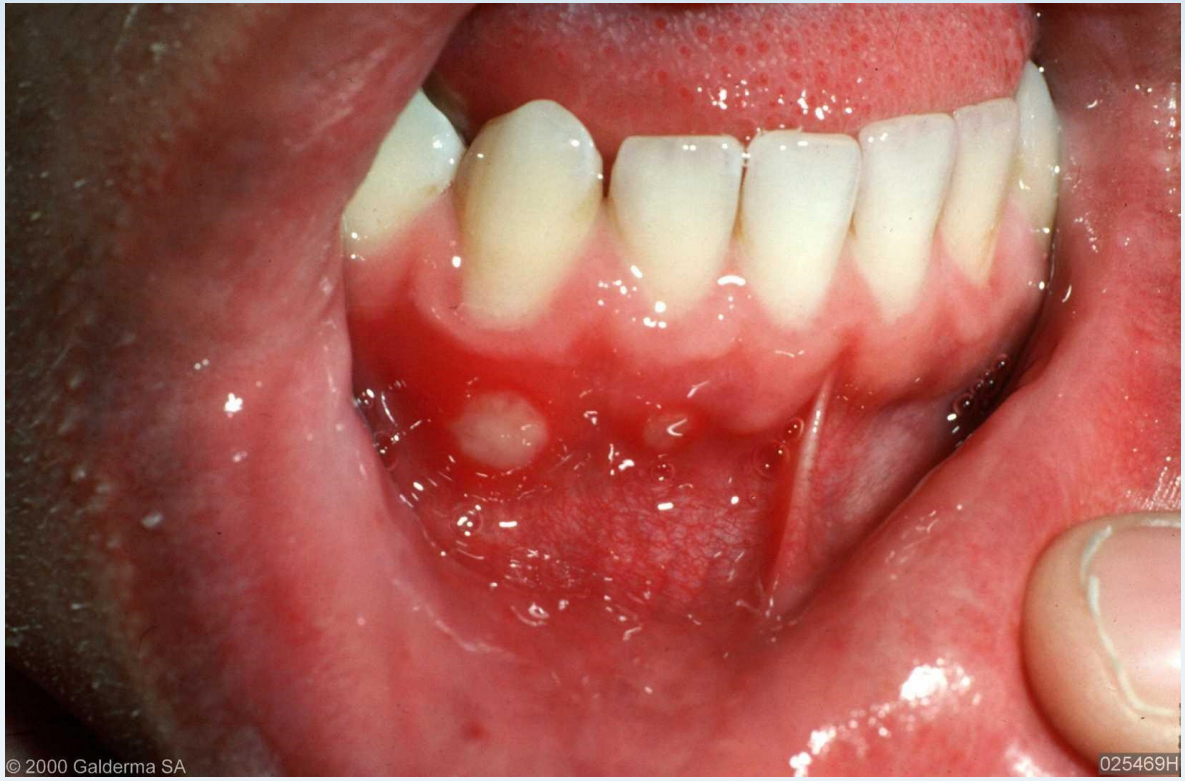
MPA 40-60%

EGPA 40-60%

Physical Exam



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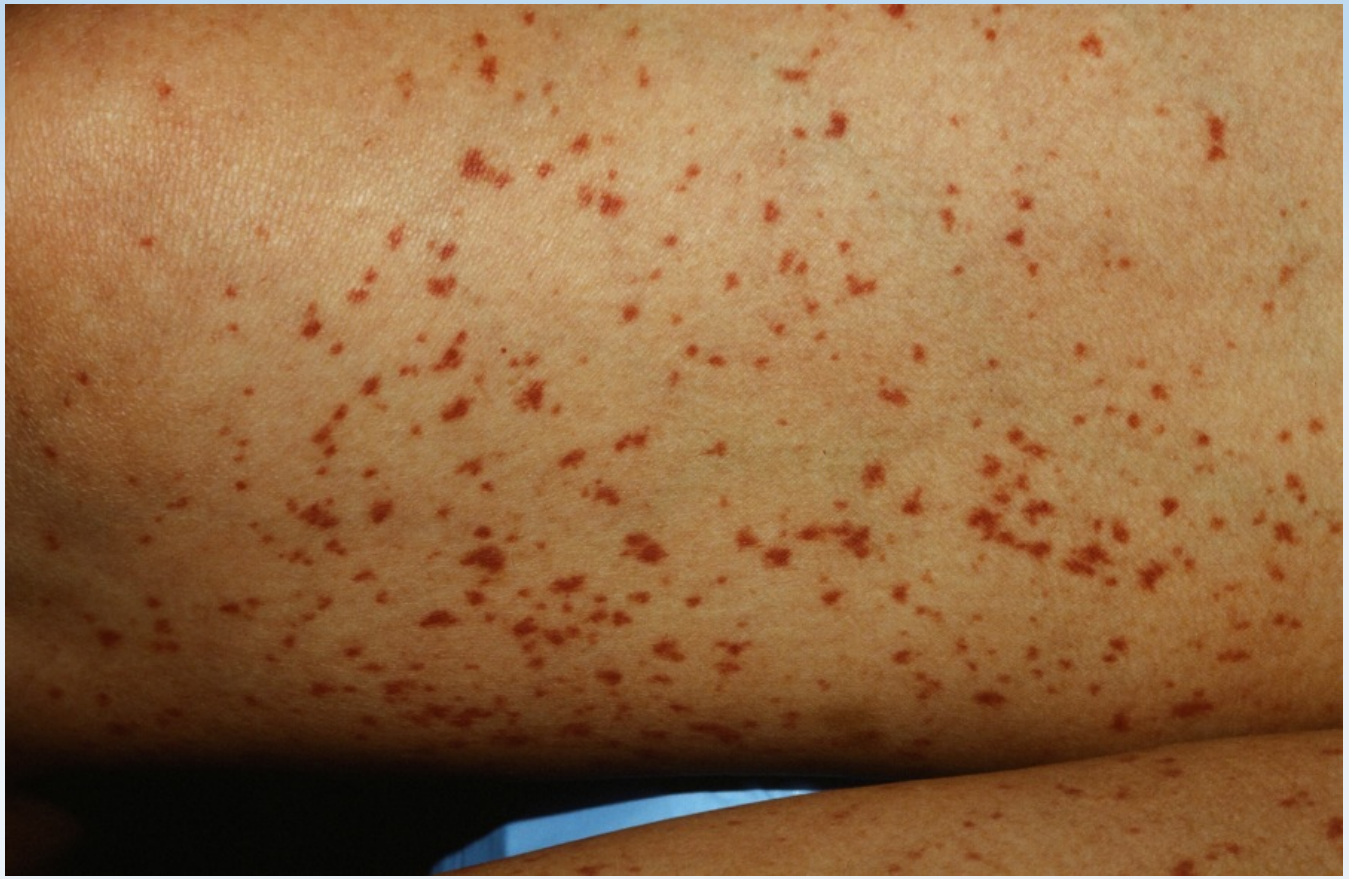

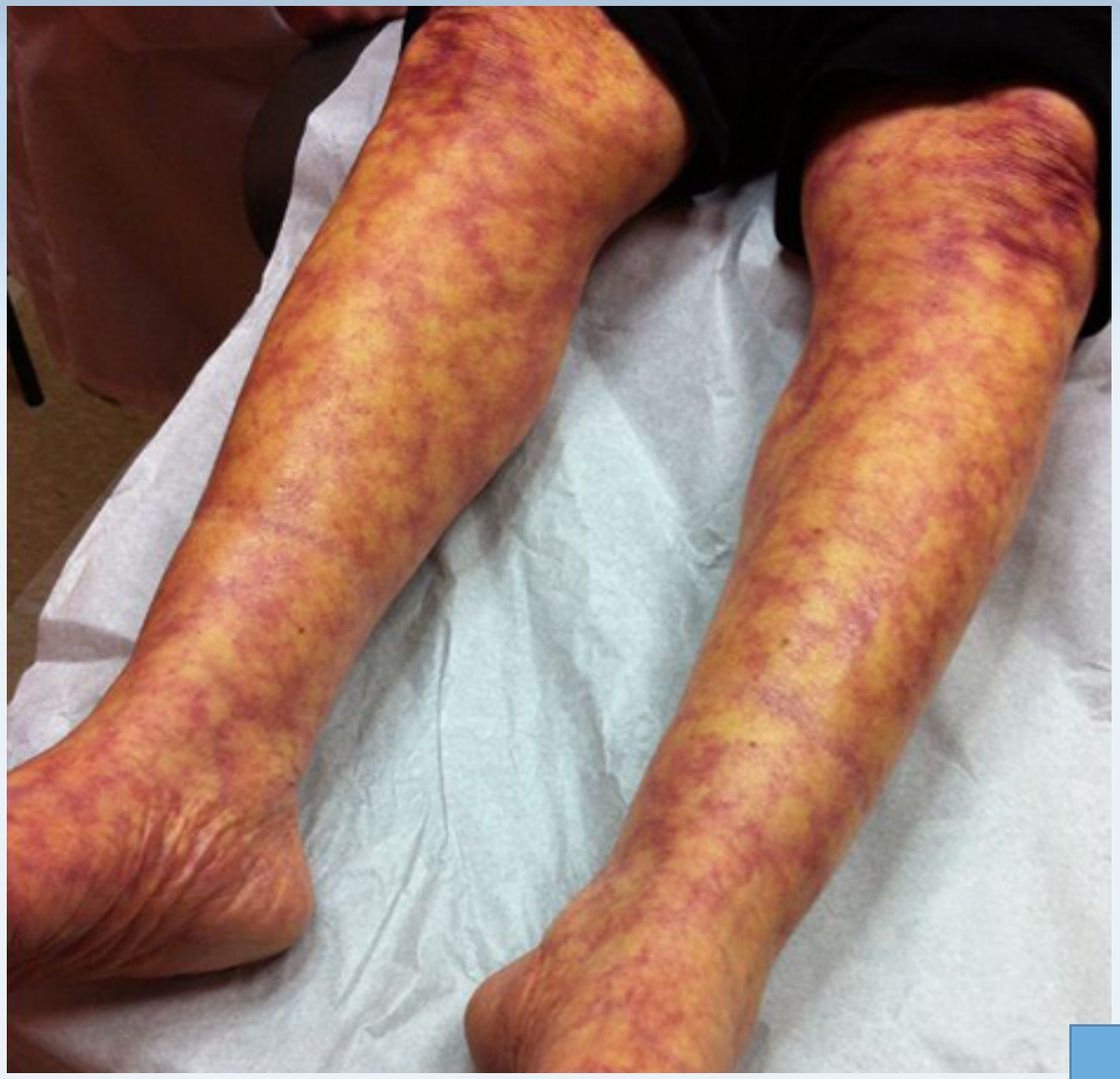

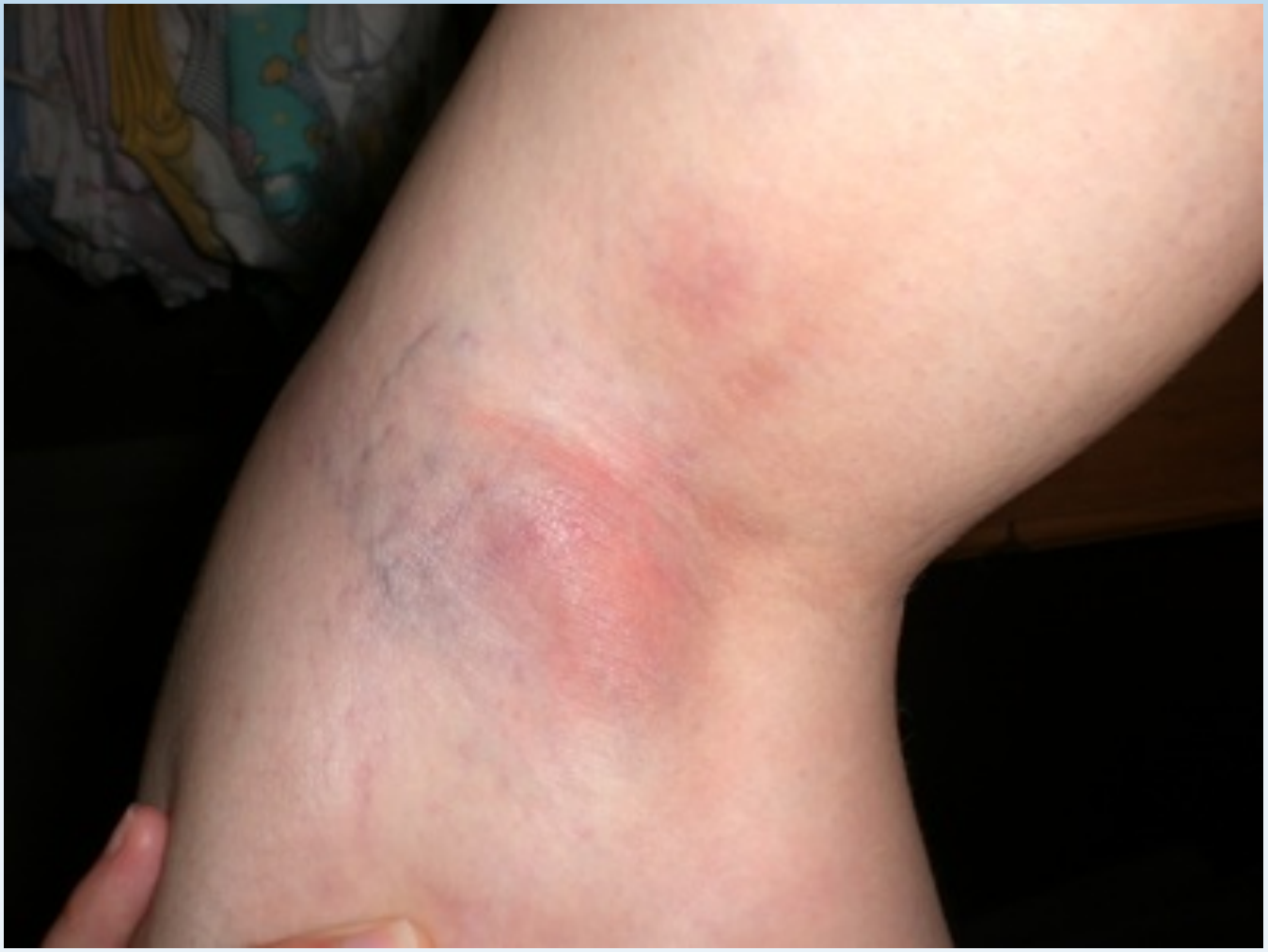

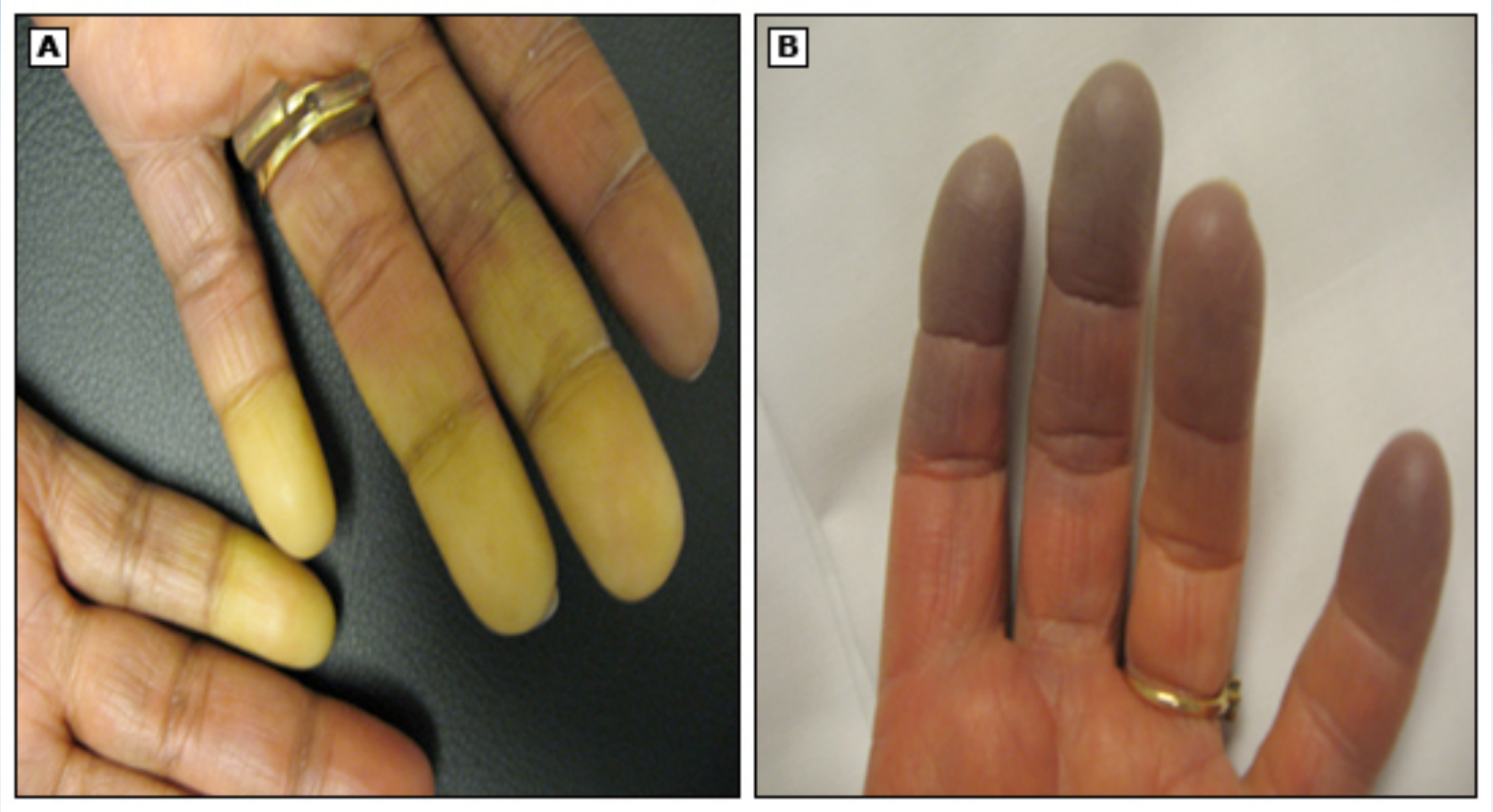
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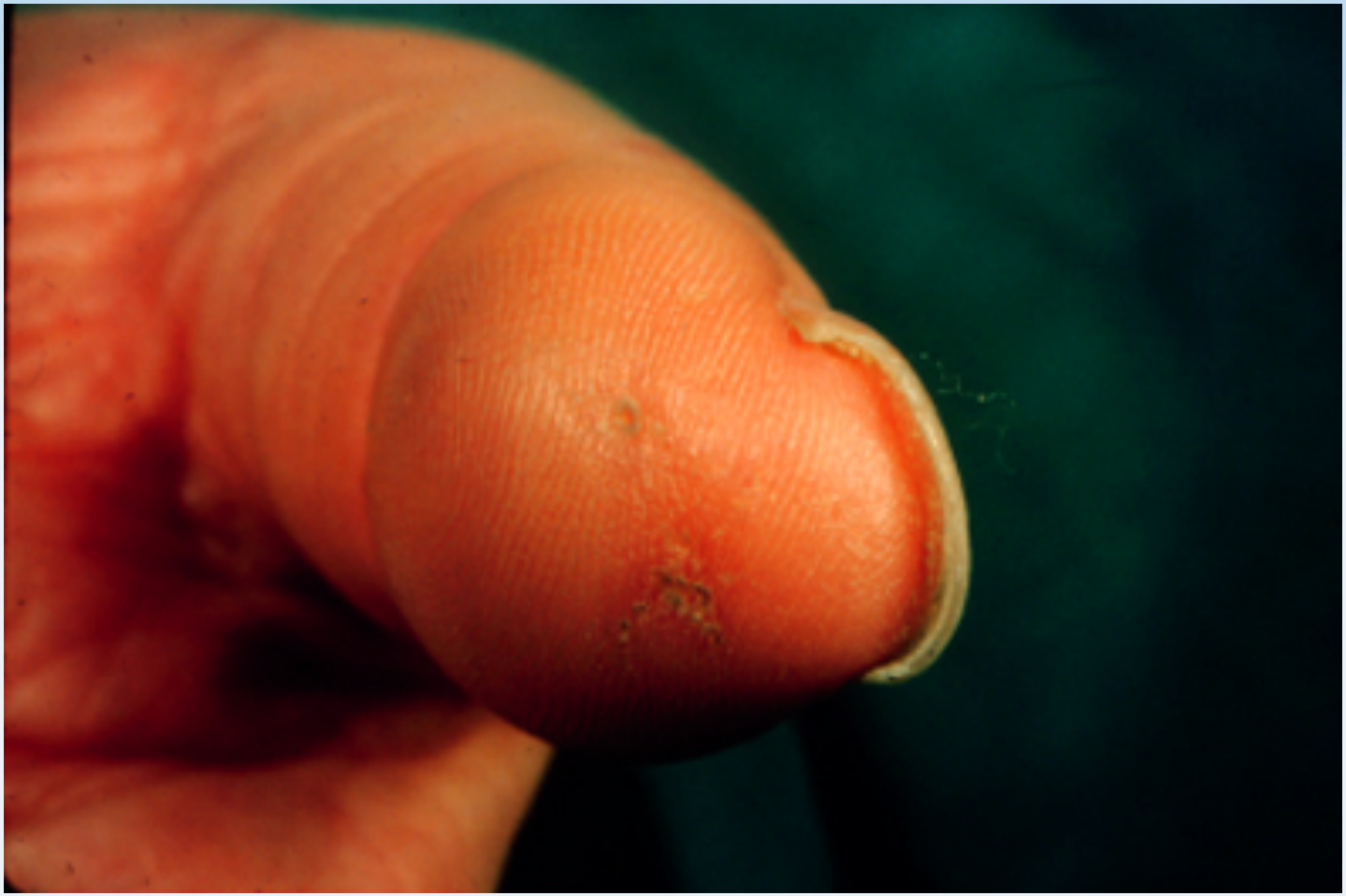
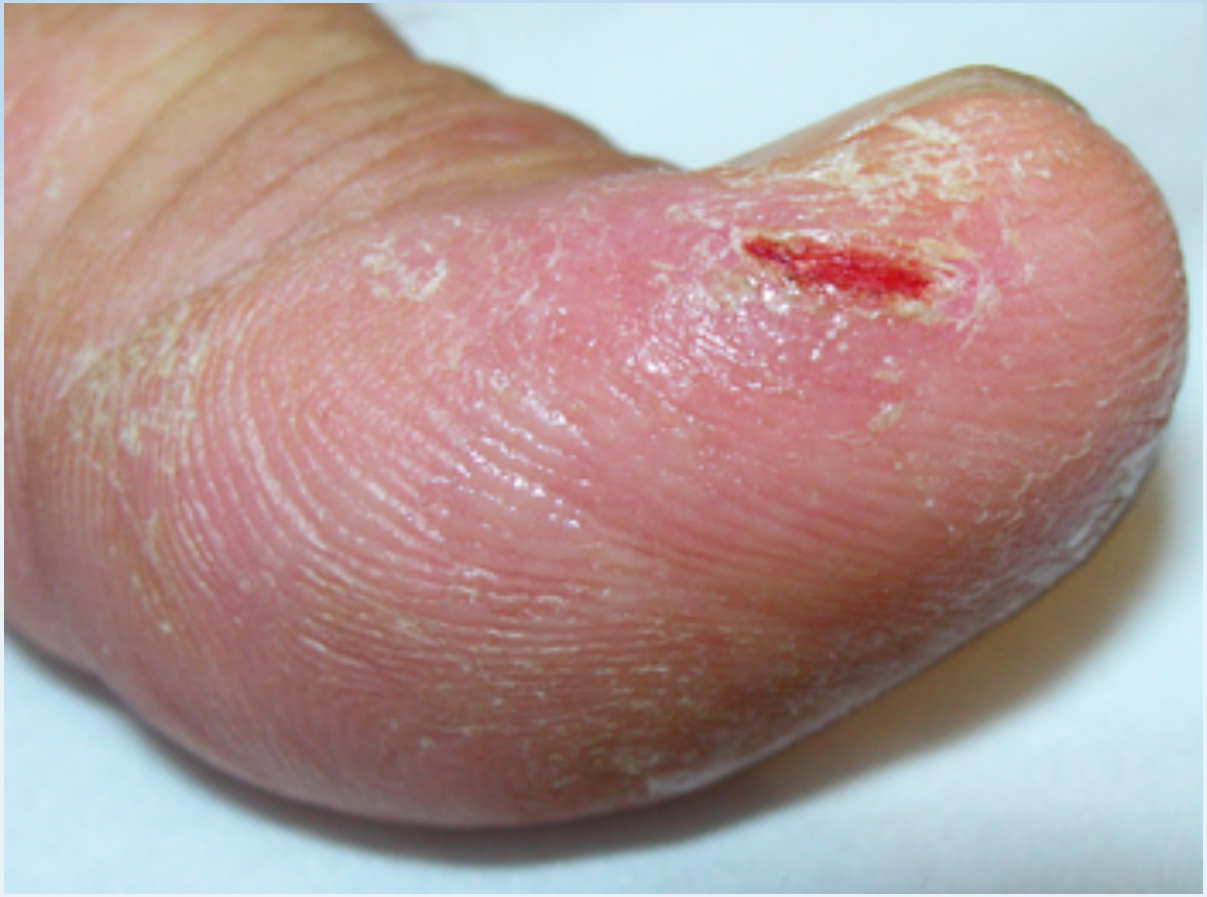
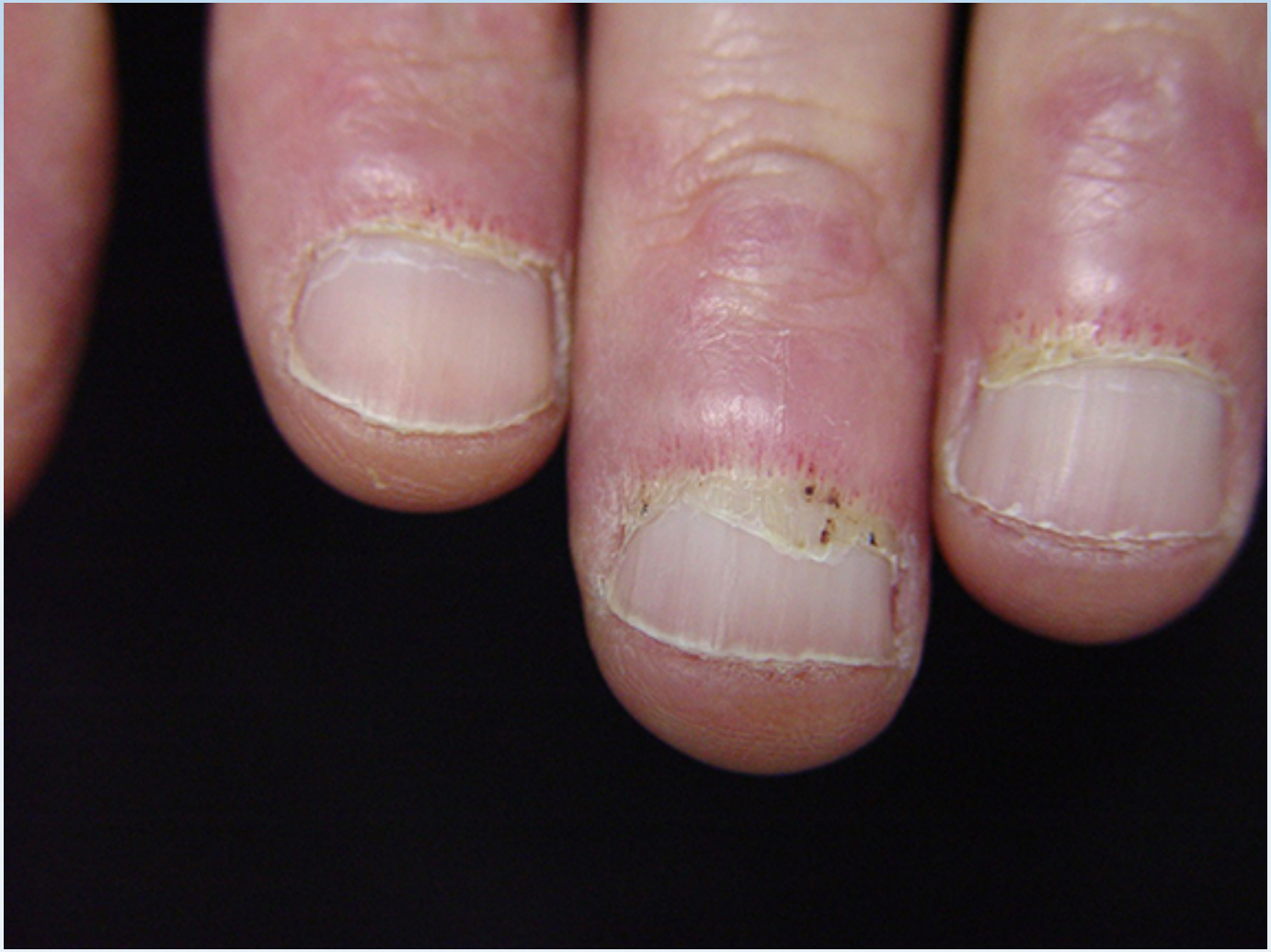
B

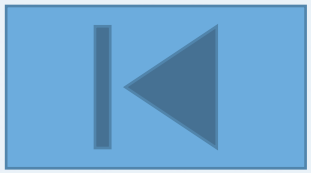


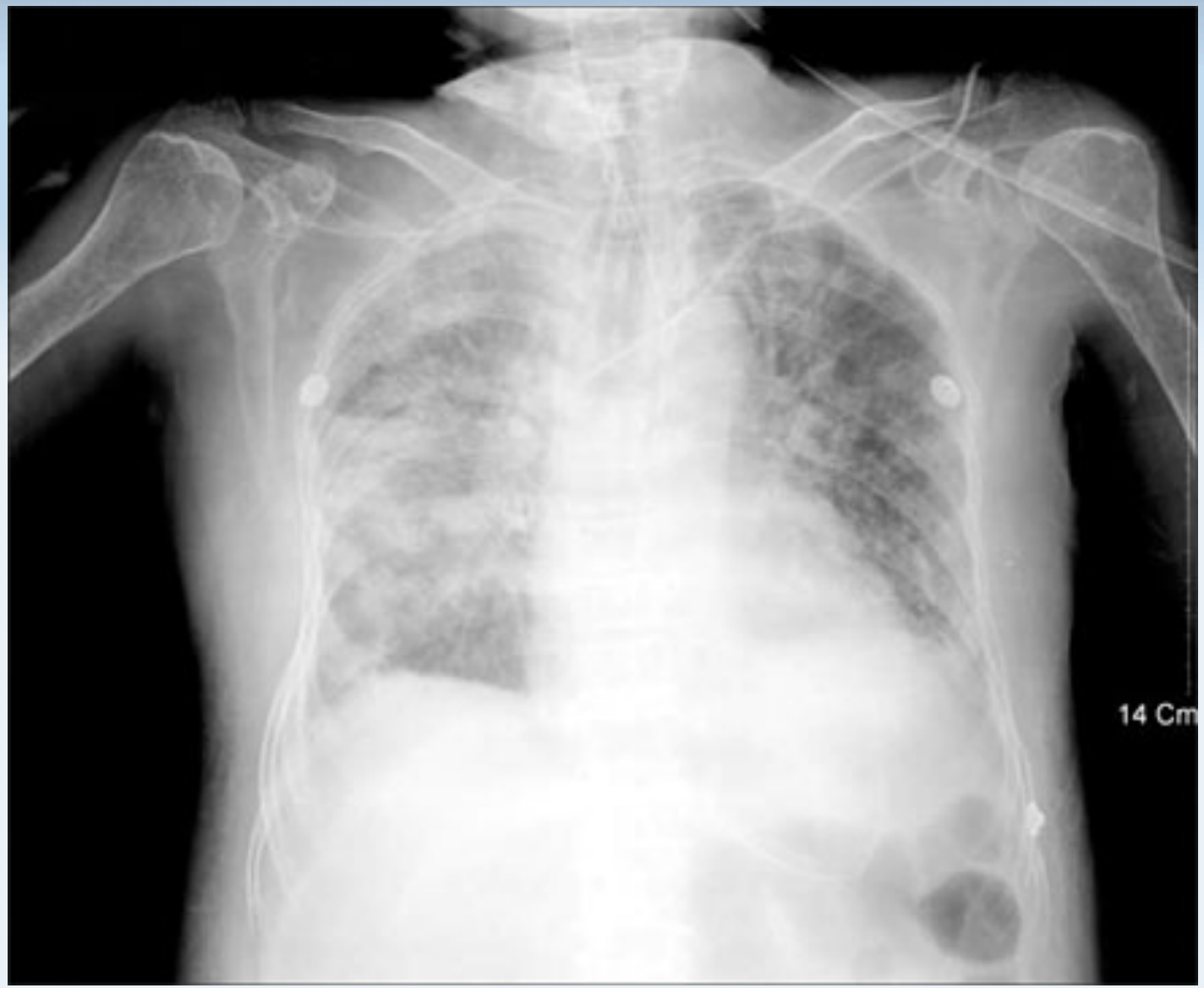




Key Point #1: Think about vasculitis when you have multisystem disease.

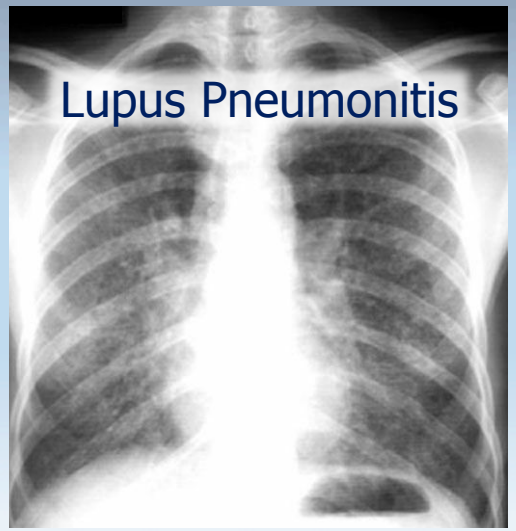
Many historical details are not volunteered. Do a thorough history and physical.



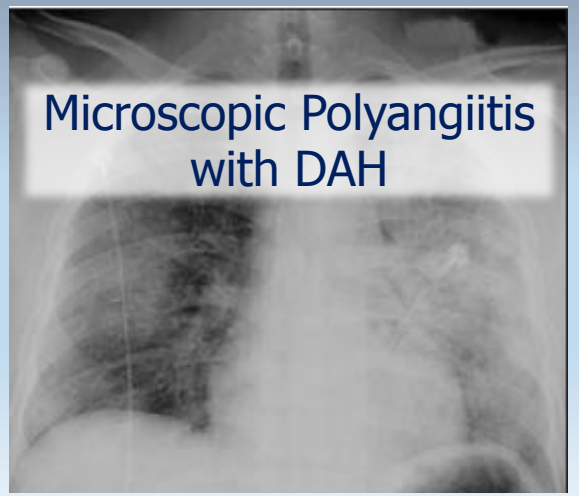

14 Cm

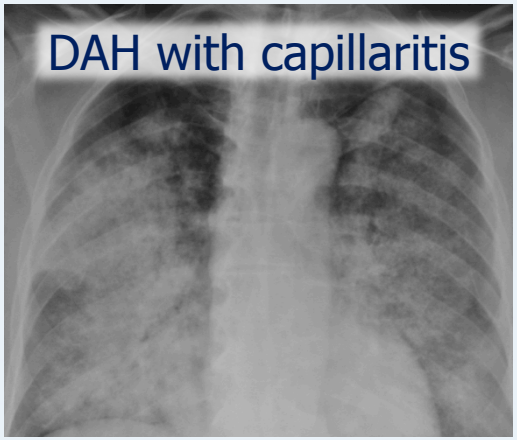
Radiographic Differential

RED (blood)	WHITE (other cells, protein)	BLUE (water)
Alveolar hemorrhage	Alveolar proteinosis	Pulmonary edema
Aspirated blood	Infection	ARDS
	Cancer	

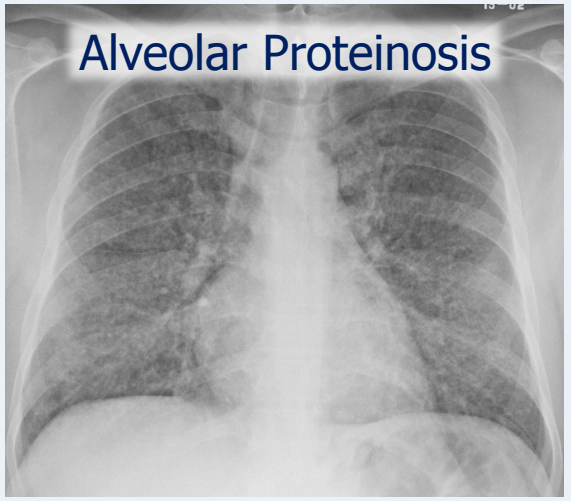

Lupus Pneumonitis

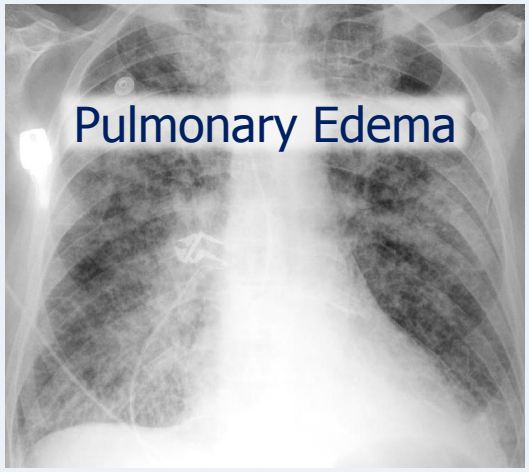

H1N1 ARDS

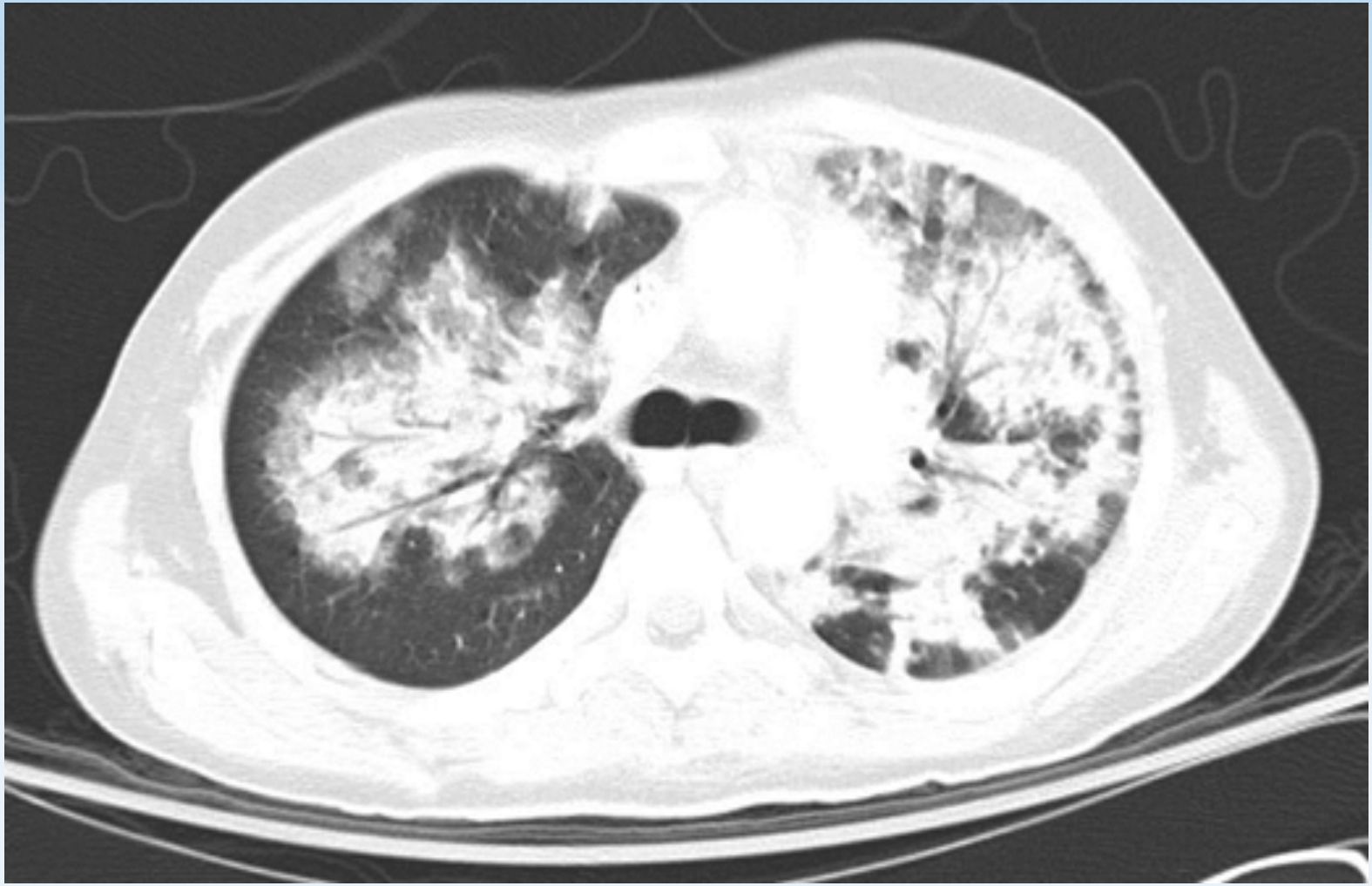

Microscopic Polyangiitis
with DAH

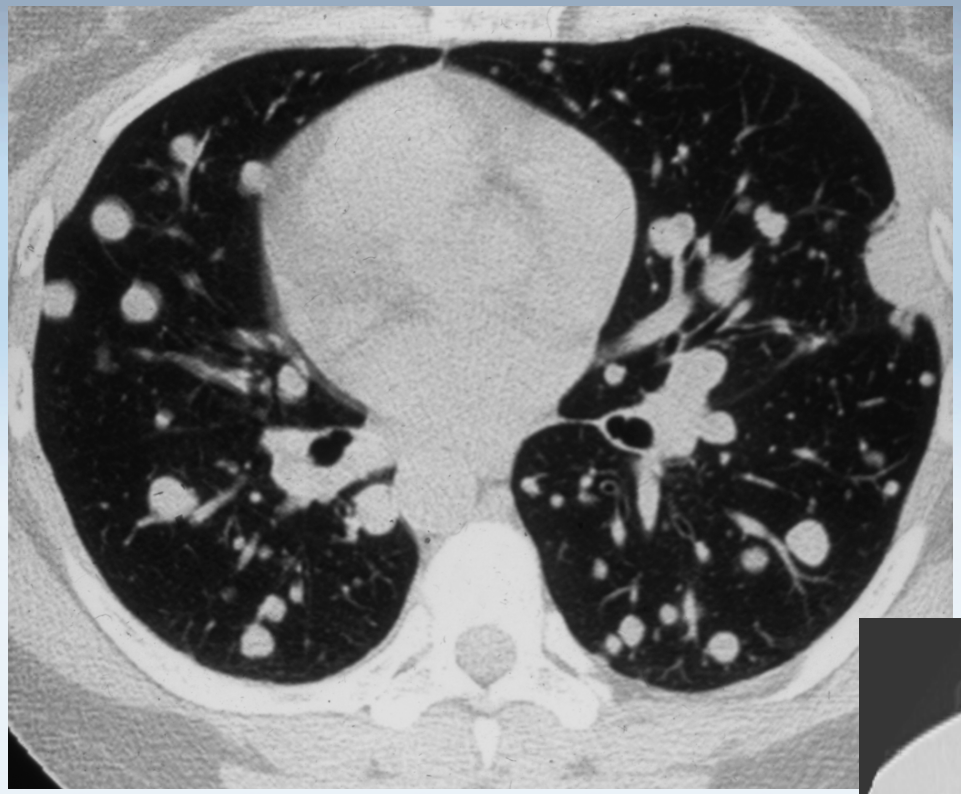

DAH with capillaritis

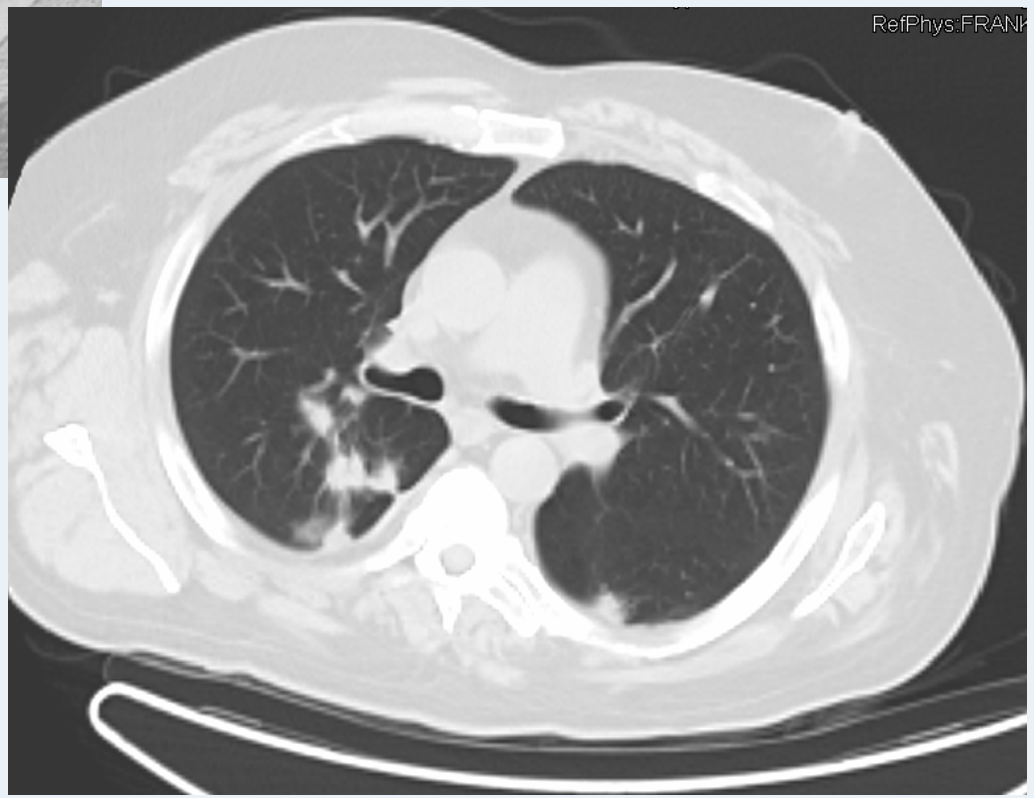

DAH from
Mitral Regurg


Alveolar Proteinosis


Pulmonary Edema



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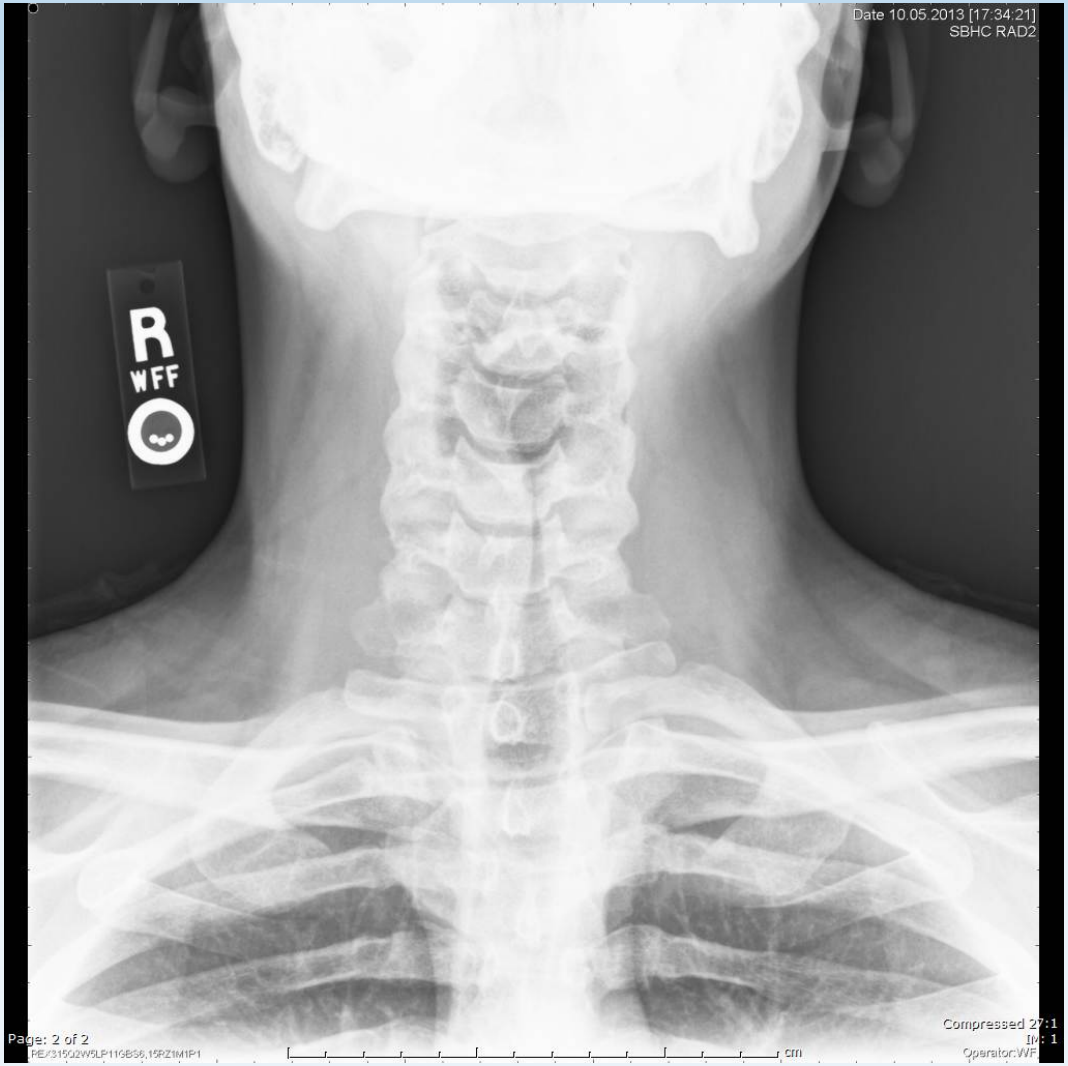
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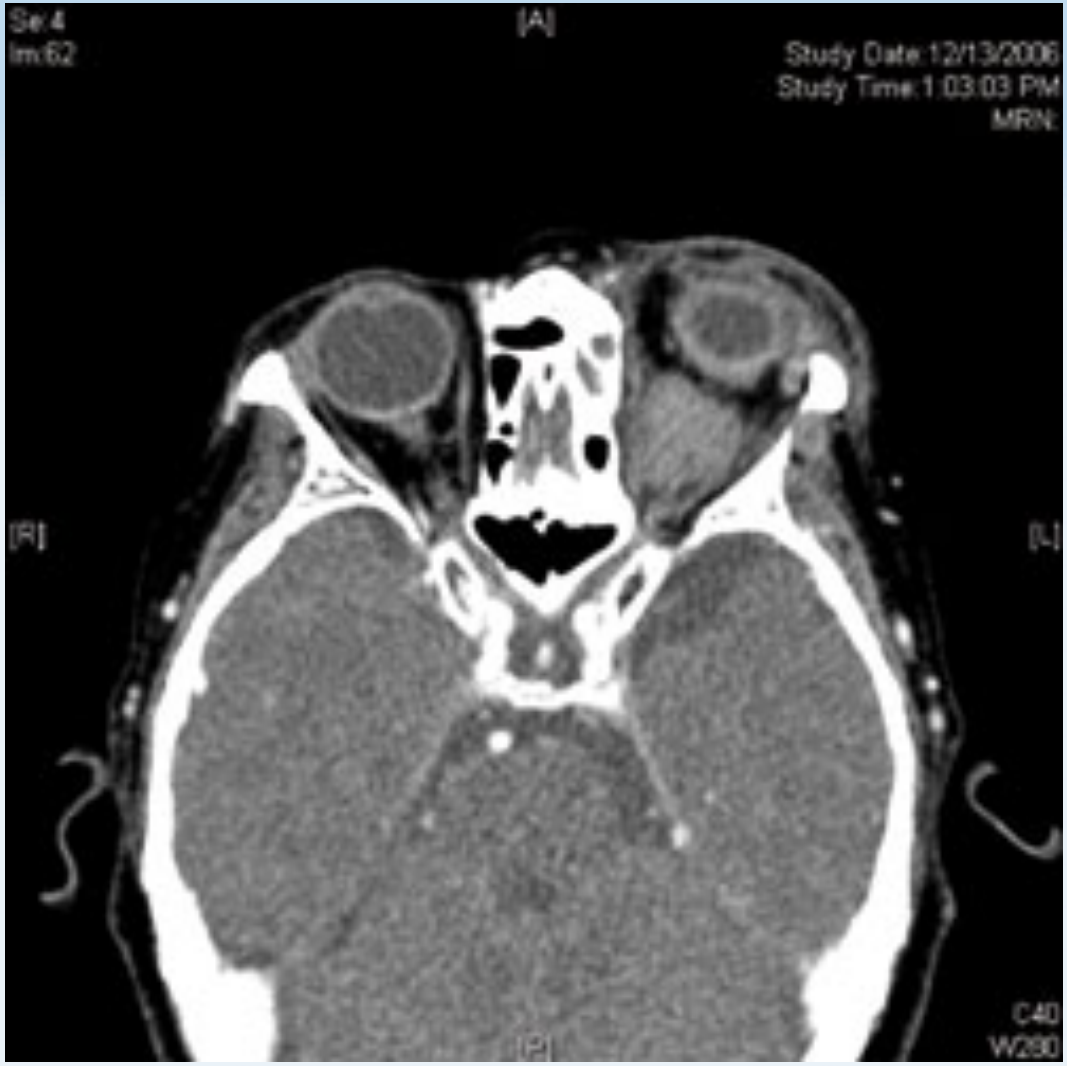
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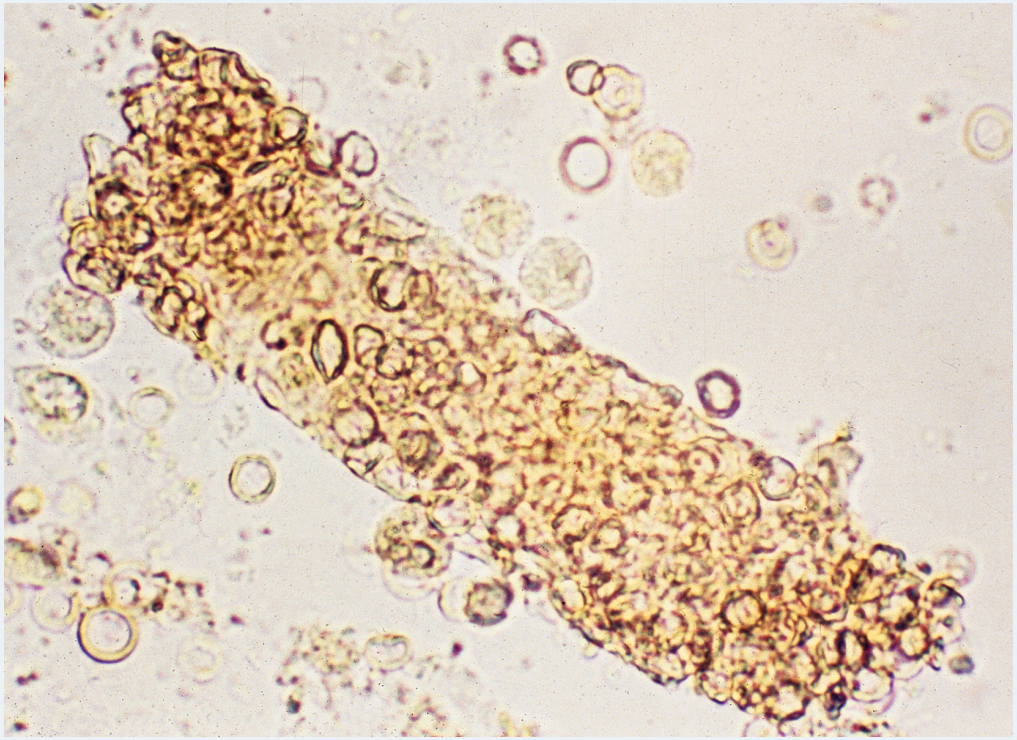
Key Point #2: Radiology is nonspecific! Most common in vasculitis is nodular and cavitary disease.

Labs

What do you want?

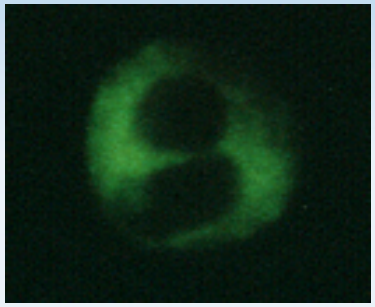
- H/H: 9/27
- WBC: 8
- Plt 95,000
- Eos 15%
- Creatinine 1.4 (baseline 0.7)
- ANA+ 1:120 nucleolar
- ANCA positive, +PR3
- Other serologies negative
- Hypercoaguable workup negative



Condition	Patients with ANAs (%)
Diseases for Which ANA Testing Is Helpful for Diagnosis	
Systemic lupus erythematosus	99-100
Systemic sclerosis	97
Polymyositis/Dermatomyositis	40-80
Sjögren's syndrome	48-96
Diseases in Which ANA Is Required for Diagnosis	
Drug-induced lupus	100
Mixed connective tissue disease	100
Autoimmune hepatitis	100
Diseases in Which ANA May Be Useful for Prognosis	
Juvenile idiopathic arthritis	20-50
Antiphospholipid antibody syndrome	40-50
Raynaud's phenomenon	20-60

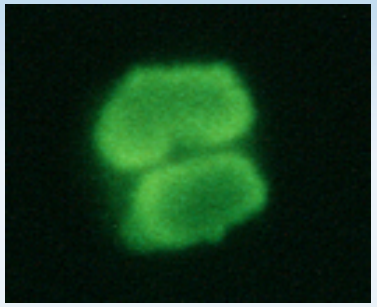
ANCA Testing

c-ANCA/PR3



- **Positive in GPA (Wegener) in 85-95% with generalized active disease**
  - 60% with organ limited disease
  - 40% in remission
- Very rare false positives, but may occur
- Rarely positive in MPA, GS

p-ANCA/MPO



- Positive in 35-70% with MPA
- Positive in 40-70% with EGPA
- **Positive in 10% of patients with GPA (Wegener)**
- Can also be positive in
  - RA
  - IBD
  - autoimmune hepatitis / PSC
  - Goodpasture Syndrome
  - CTD
  - Meds: hydralazine, propylthiouracil, D-penicillamine, minocycline

ANCA-testing: Clinical Guidelines

Clinical Indications

- Glomerulonephritis
- Alveolar hemorrhage
- Cutaneous vasculitis
- Mulitiple lung nodules
- Chronic destructive ENT disease
- Long-standing sinusitis or otitis
- Subglottic or tracheal stenosis
- Mononeuritis multiplex
- Retro-orbital mass

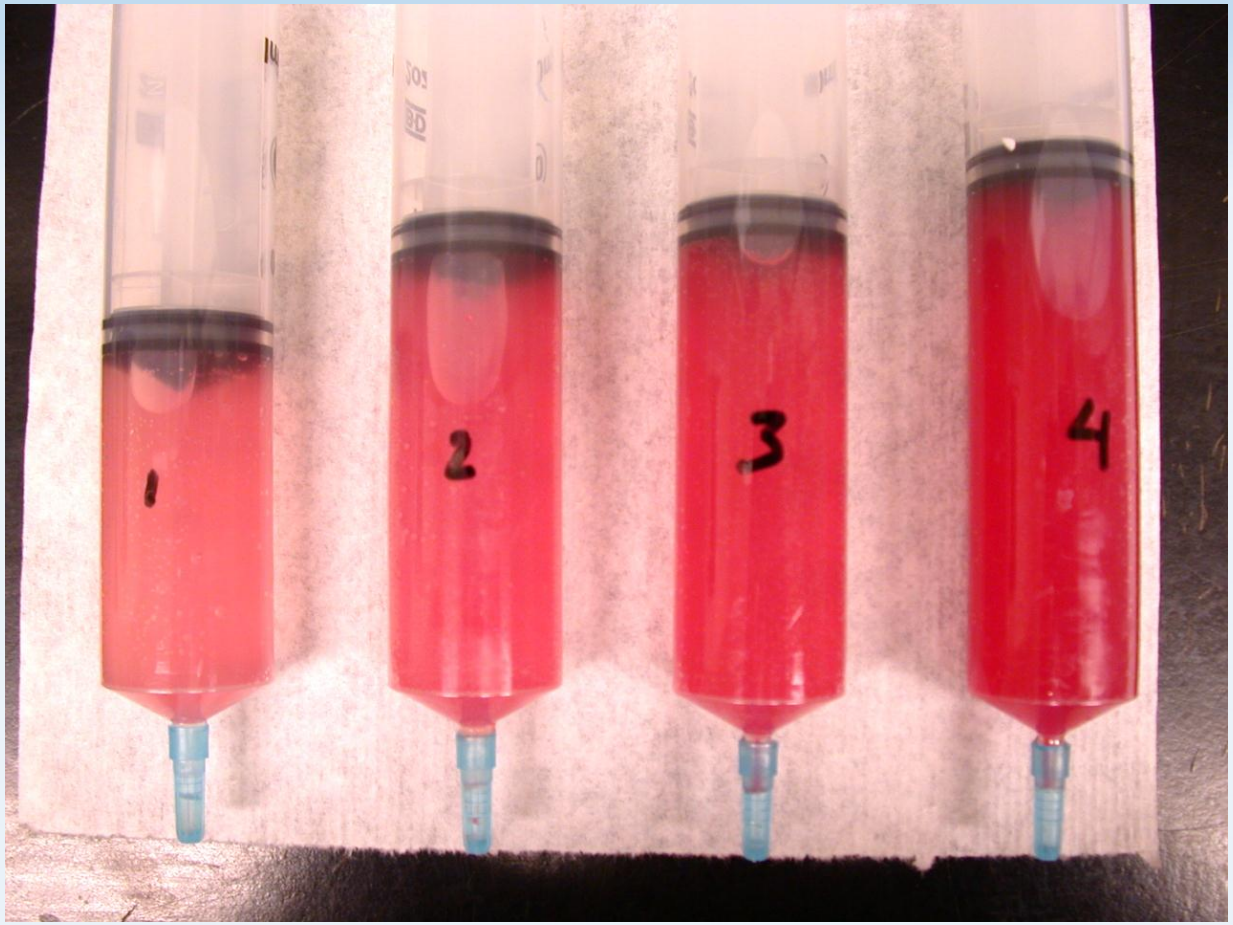
Test Performance

Sensitivity	81%	→	81%
Specificity	98%	→	98%
PPV	54%	→	62%
NPV	99%	→	99%
False +	11/497	→	8/381

Mandel et al. Arch Intern Med(2002) 162:1509

Key Point #3: Order ANCAs wisely! Have a pretest probability.

Bronchoscopy



Cytology:
hemosiderin-laden macrophages

Role of Bronchoscopy

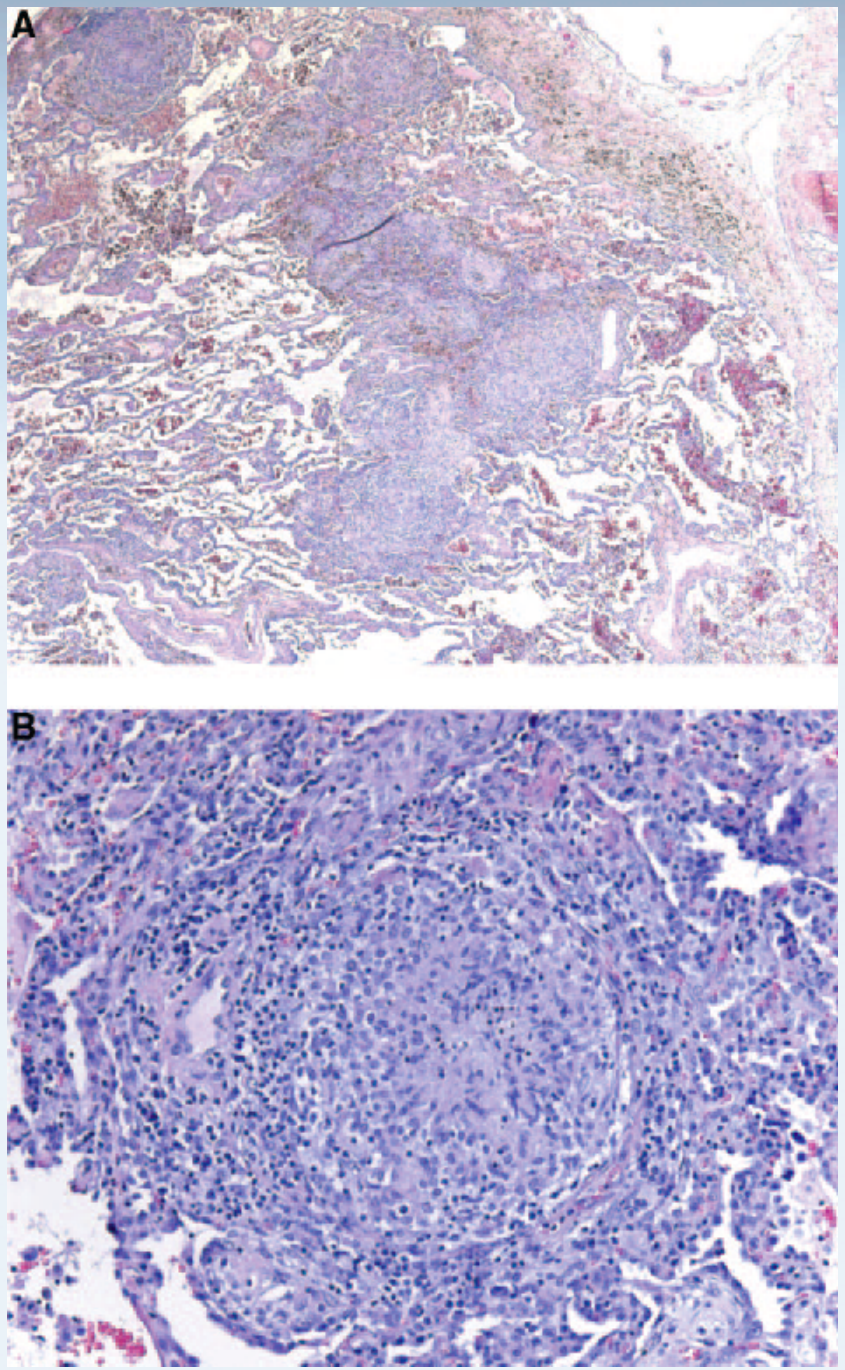
- Bronchoscopy is useful for:
  - Identifying alveolar hemorrhage
  - Assessing for infection
  - Assessing airway lesions in GPA
- Transbronchial biopsies are rarely helpful
- DAH has a differential to consider

Not all DAH is Vasculitis

DAH is associated with a number of clinical entities and several histologic subtypes

- **Pulmonary capillaritis** (vasculitis of the microcirculation)
  - Systemic vs Lung-limited
  - Vasculitis, rheumatic
  - Drugs
  - Infectious endocarditis
  - Transplant rejection
  - Ulcerative colitis
- **Bland pulmonary hemorrhage**
  - Mitral stenosis
  - Subacute bacterial endocarditis
  - Drugs (penicillamine, amiodarone, nitrofurantoin)
  - TTP, HUS, ITP
  - Goodpasture and SLE
- **Diffuse alveolar damage**
  - Drugs and inhaled toxins (crack cocaine)
  - ARDS
  - COP
  - Bone marrow transplantation

Histopathology of GPA



low-power view demonstrating patchy, "geographic" necrotizing vasculitis and granulomatous inflammation

high-power view of granulomatous inflammation

Frankel SK *et al.* (2006) Chest 129:452

Tissue is the Issue !

- Frequently biopsied sites include:
  - Kidney
  - Upper airway
  - Skin
  - Lung

- Treat empirically if clinical suspicion is high and tissue cannot be obtained in a timely manner

Biopsy Sites

Upper Airway

- Low morbidity and mortality, easy access
- Low yield ~20-40%

Renal

- Can identify glomerulonephritis
- Should see pauci-immune crecentic GN for GPA
- It is rare to find granulomas on percutaneous renal biopsy

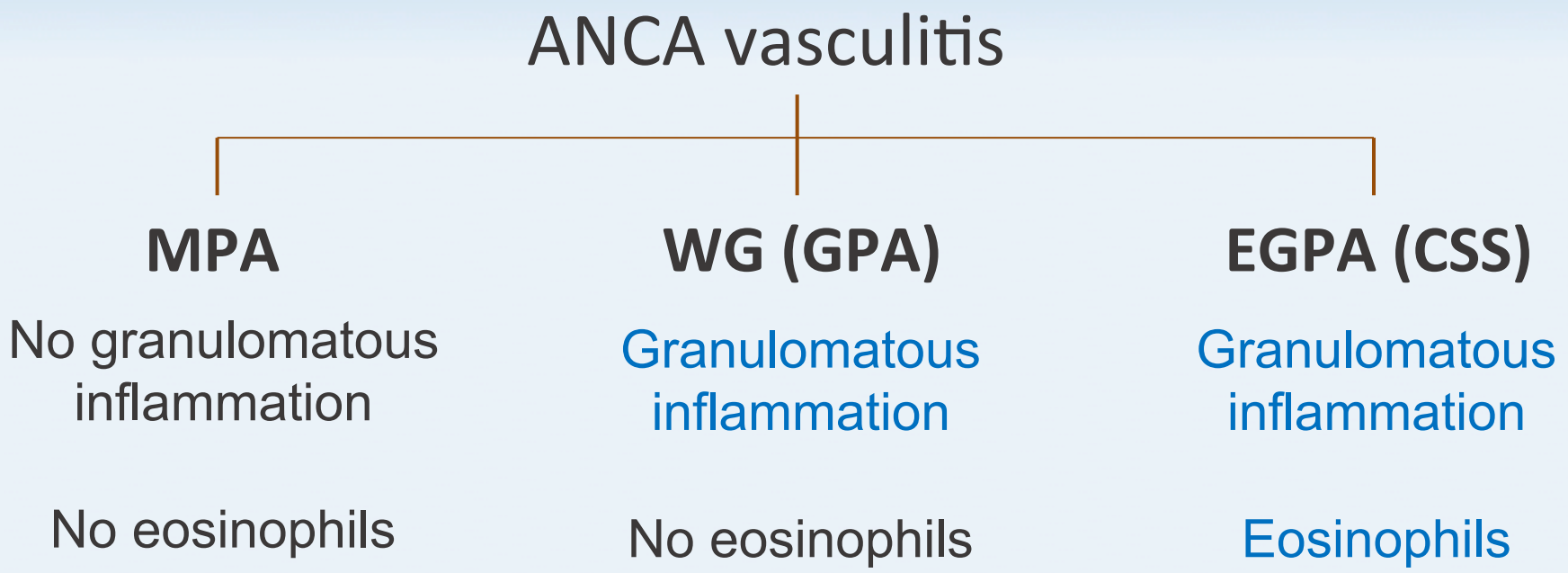
Skin

- Leukocytoclastic vasculitis

Surgical Lung Biopsy

- **When to pursue a surgical lung biopsy?**
  - DAH is associated with *negative* serology and is *not* a part of a systemic disease
- Like to see capillaritis for GPA
- granulomatous inflammation

Histologic Findings



Key Point #4: Biopsy something with active disease. Bronchoscopy has a limited role in vasculitis.

Therapeutic Approach

Mild Disease

- Glucocorticoids + methotrexate
- If no response or progressive disease → treat with either cyclophosphamide (CYC) or rituximab

Moderate to Severe Disease

- No consensus on a preferred initial immunosuppressive regimen
- Glucocorticoids + either CYC (oral or IV) or rituximab
  - Some prefer CYC-based
    - More data / experience
  - Some prefer rituximab-based
    - Less toxicity

Induction Therapy

- Methotrexate- mild disease only
- Cyclophosphamide
- Rituximab
- Plus glucocorticoids
- Usually add pheresis for severe renal disease

- Rituximab is noninferior to cyclophosphamide

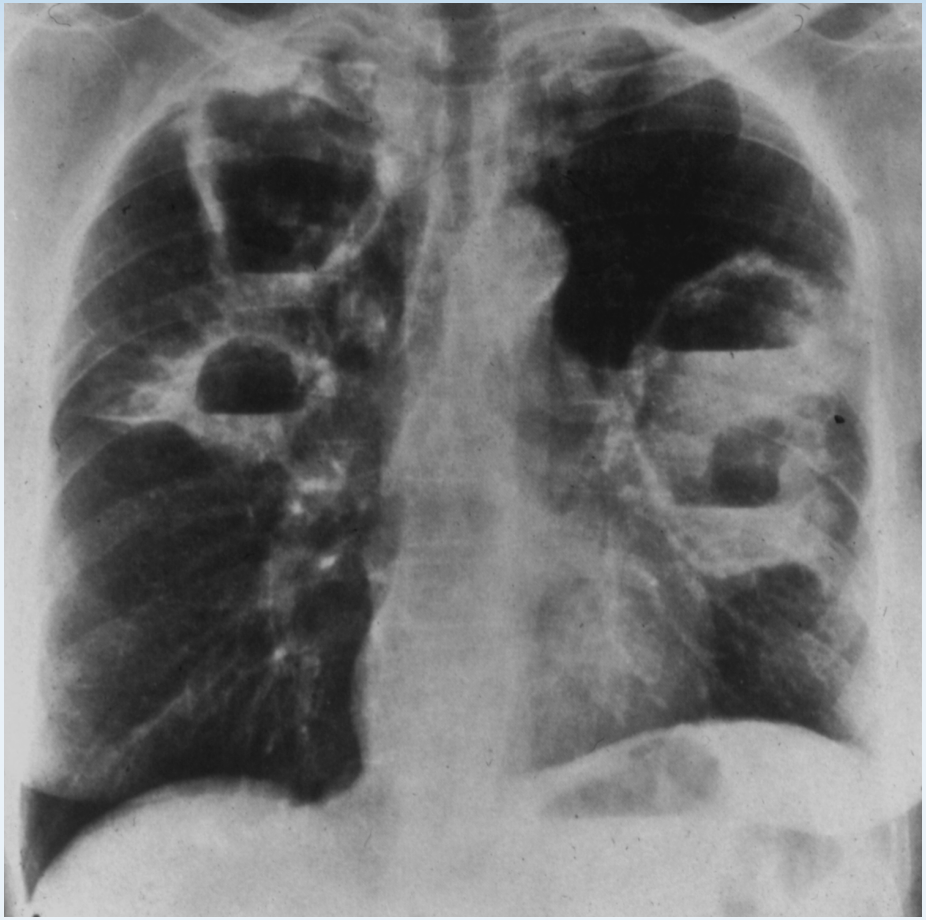
Maintenance therapy

- Azathioprine
- Rituximab
- Methotrexate

- Azathioprine in renal disease
- Rituximab may have lower relapse rates
- Duration has to do with relapse risk – increased with +PR3- 6 to 36 months or indefinitely if they've had prior relapses

Key Point #5: For patients in the hospital (and on the boards) you'll likely induce with cyclophosphamide and glucocorticoids.

Questions



Extra slides

Classification of Vasculitides

- Primary Idiopathic
  - Small vessel
  - Medium vessel
  - **Large vessel** → **Idiopathic Disease**
    - Takayasu's arteritis
    - Giant cell arteritis

Classification of Vasculitides

- Primary Idiopathic
  - Small vessel
  - **Medium vessel** → **Idiopathic Disease**
    - Kawasaki's disease
    - Polyarteritis nodosa
  - Large vessel

Classification of Vasculitides

- Primary Idiopathic
  - **Small vessel**
  - Medium vessel
  - Large vessel

Immune Complex-Mediated

ANCA-associated (AAV)

Classification of Vasculitides

- Primary Idiopathic
  - **Small vessel** → **Immune-Mediated Vasculitis**
    - Goodpasture's syndrome
    - Henoch-Schonlein purpura
    - IgA nephropathy
  - Medium vessel
  - Large vessel

Hemoptysis

Not everyone with DAH has hemoptysis, and not all hemoptysis is DAH

- Expectoration of blood originating from *below* the vocal cords
- Ranges from blood–streaked sputum to massive hemoptysis
  - No consensus on definition of massive hemoptysis – greater than 500 mL over 24 hours or 100 mL an hour are reasonable thresholds
- Must distinguish from upper airway source (epistaxis, supraglottic lesion) or hematemesis
- Causes of hemoptysis include
  - Infection (bronchitis, TB, pneumonia, abscess, mycetoma, etc.)
  - Structural lung disease (bronchiectasis)
  - Pulmonary infarction (including related to pulmonary embolism)
  - Foreign body / trauma
  - Tumor
  - Vasculitis, connective tissue disease
  - Drug-associated, including anti-coagulant therapy
  - AVM, bronchial telangectasia
  - Cardiovascular causes (LV failure, mitral stenosis, aortic aneurysm)

Multisystem disease

- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease
- Deforming/ulcerating upper airway lesions
- Palpable purpura
- Mononeuritis multiplex
- Peripheral eosinophila
- Multi-system illness
  - Fever, fatigue, weight loss, arthralgias / arthritis, myalgias

When to Think About Vasculitis

- Diffuse alveolar hemorrhage

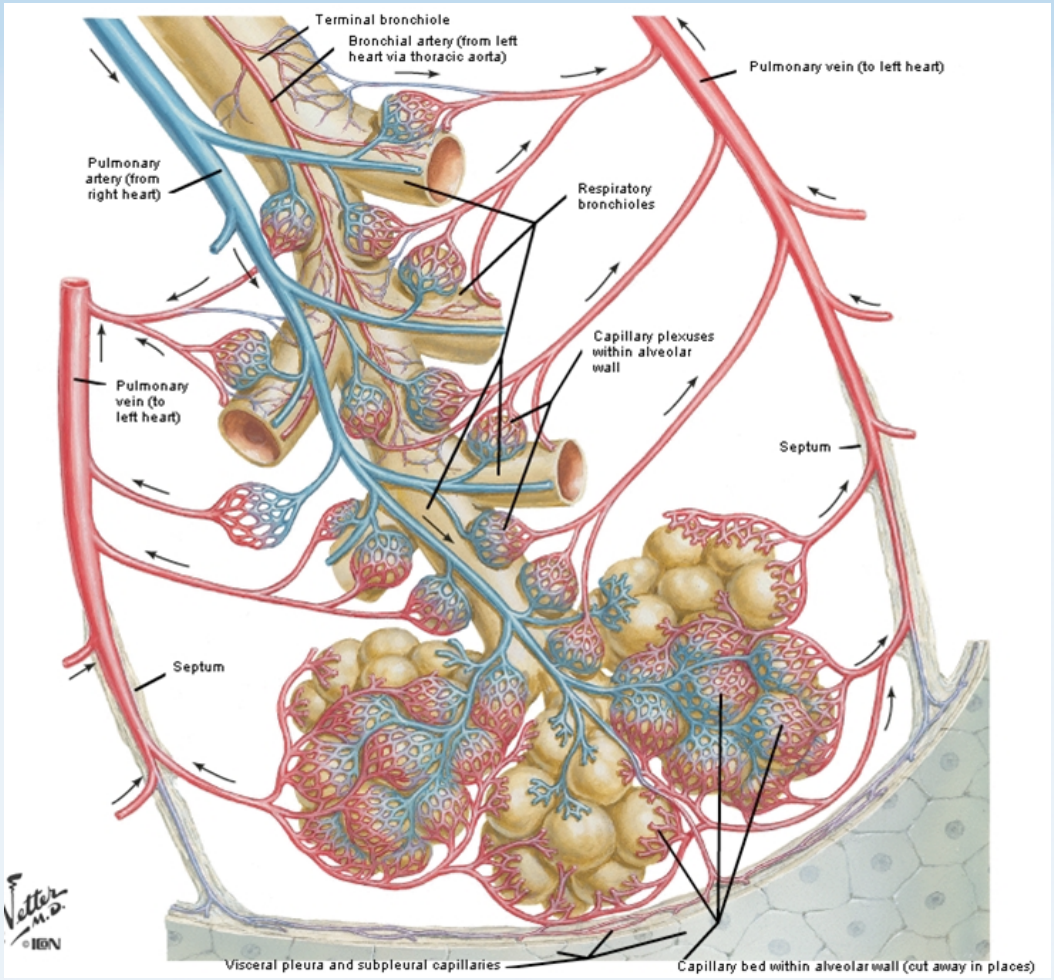
Diffuse Alveolar Hemorrhage (DAH)

- Clinicopathologic syndrome
  - Definition:
    Accumulation of intraalveolar RBCs originating from the alveolar capillaries
  - Histopathology includes
    - intraalveolar RBCs and fibrin
    - eventual accumulation of hemosiderin-laden macrophages (take up to 48-72 hours to accumulate)

- Clinical syndrome
  - **New alveolar infiltrates**
    - often rapidly evolving / resolving
    - can be localized or diffuse
  - Hemoptysis
    - absent in up to 33%
  - Anemia (drop in H&H)
  - Hypoxemic respiratory failure (spectrum of severity)

DDx: GPA(WG), MPA / IPIPC, GS, SLE

Where can bleeding from the lung originate?



- Bronchial vessels
  - Bleeding is usually a result of bronchiectasis or endobronchial malignancy
- Pulmonary arteries and veins
- Microcirculation of the lung

Pulmonary Vascular Anatomy
Two Circulations in the Lung

- Bronchial circulation
  - Bronchial arteries arise from the aorta
  - Part of the systemic circulation
  - Receives ~ 1-3% of the left ventricular output
  - High Pressure, Low Flow circulation
- Pulmonary circulation
  - Arises from the right ventricle
  - **Receives 100% of cardiac output**
  - Pulmonary arteries, pulmonary veins and microcirculation (capillaries, arterioles, venules)
  - Low Pressure, High Flow circulation

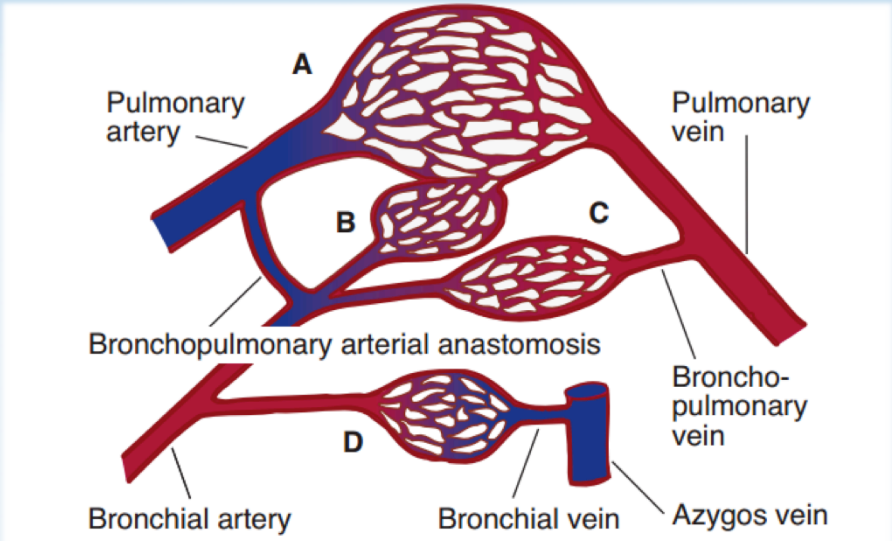
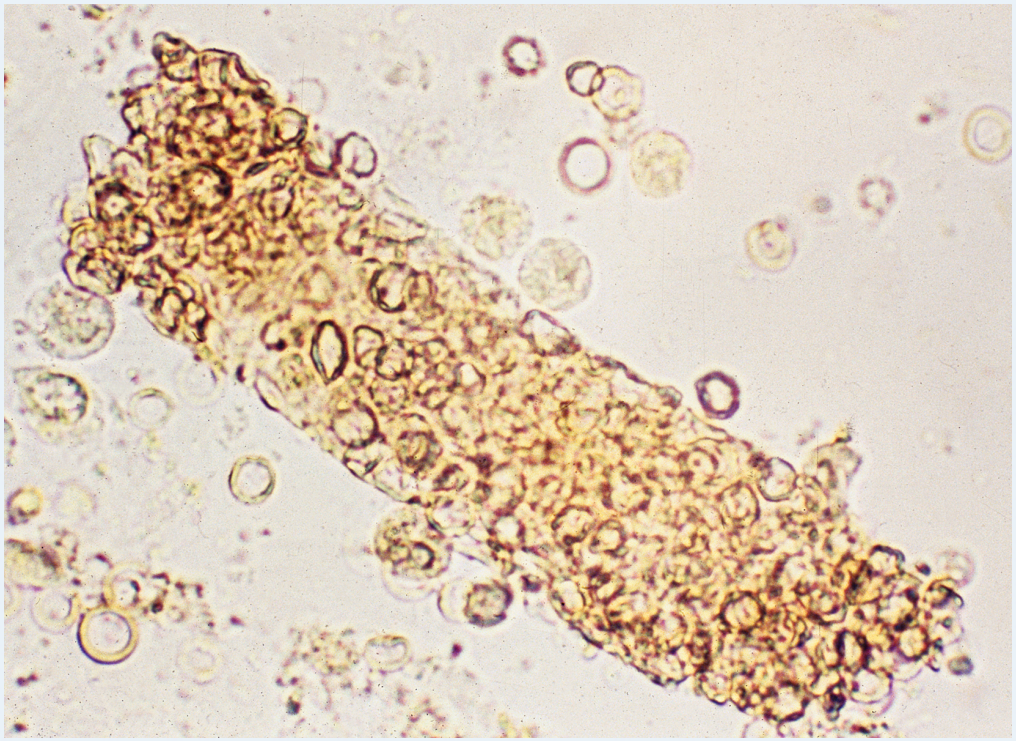


FIGURE 35–5 **Relationship between the bronchial and pulmonary circulations.** The pulmonary artery supplies pulmonary capillary network **A.** The bronchial artery supplies capillary networks **B, C,** and **D.** Blue-colored areas represent blood of low O_2 content. (Reproduced with permission from Murray JF: *The Normal Lung.* Saunders, 1986.)

Ganong's Review of Medical Physiology, 23rd Edition

When to Think About Vasculitis

- Diffuse alveolar hemorrhage
- Glomerulonephritis



Courtesy of Scott Lucia, MD, Department of Pathology, University of Colorado Health Sciences Center (Denver, CO)

When to Think About Vasculitis

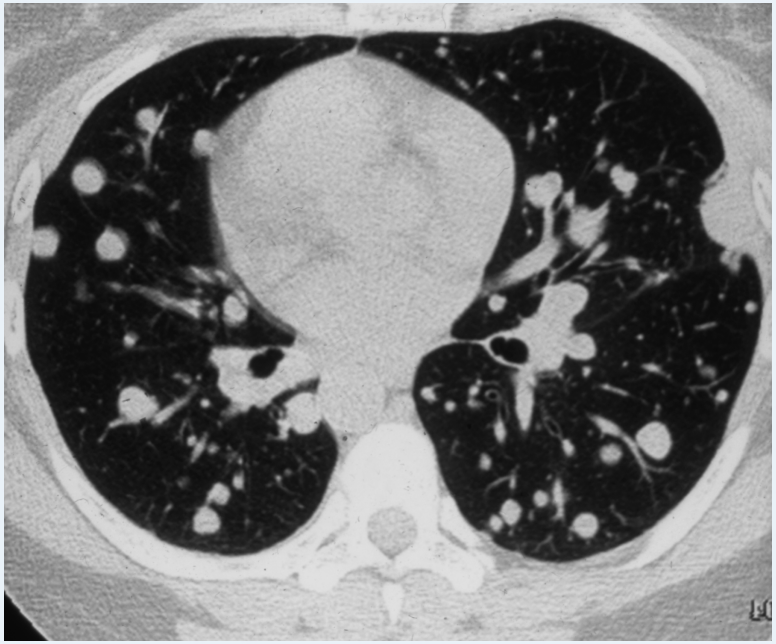
- Diffuse alveolar hemorrhage
- Glomerulonephritis
  - Rapidly progressive glomerulonephritis (RPGN) represents ~5% of ARF
  - Active urinary sediment: proteinuria, hematuria, red cell casts
  - Three categories:

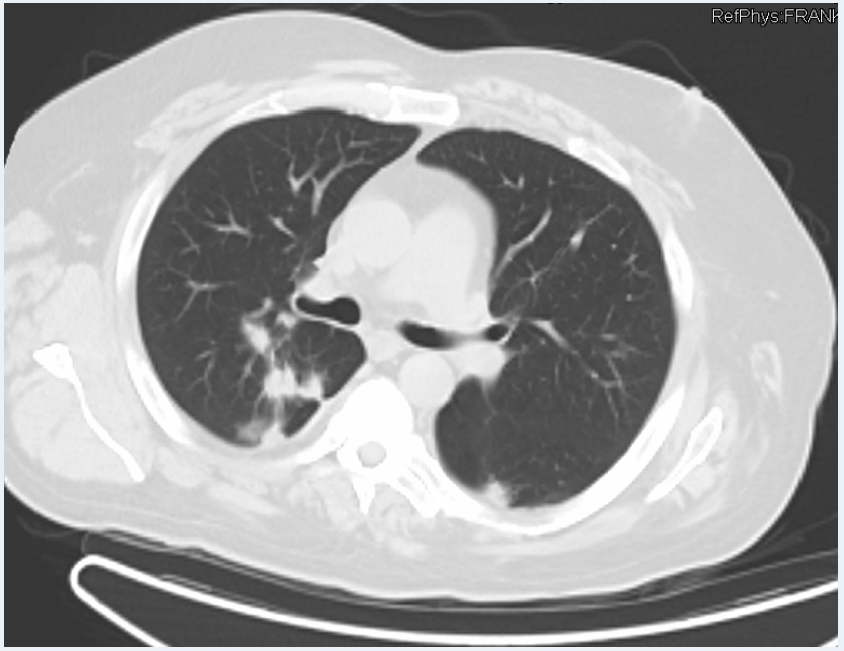
RPGN

Anti-GBM Ab	Immune Complex	Pauci-immune
• Goodpasture syndrome (lung and kidney involvement) • Anti-GBM disease (only kidney involvement) Note: 10-40% of patients may be ANCA positive	• Postinfectious (staphylococci/streptococci) • Collagen-vascular disease • Lupus nephritis • Henoch-Schönlein purpura (immunoglobulin A and systemic vasculitis) • Immunoglobulin A nephropathy (no vasculitis) • Mixed cryoglobulinemia • Primary renal disease • Membranoproliferative glomerulonephritis • Fibrillary glomerulonephritis • Idiopathic Note: Of all patients with crescentic immune complex GN, 25% are ANCA positive; however, less than 5% of patients with non-crescentic immune complex glomerulonephritis are ANCA positive	• Granulomatosis with polyangiitis (Wegener granulomatosis) • Microscopic polyangiitis (MPA) • Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) • Renal-limited necrotizing crescentic glomerulonephritis (NCGN) Note: 80-90% of patients are ANCA positive

When to Think About Vasculitis

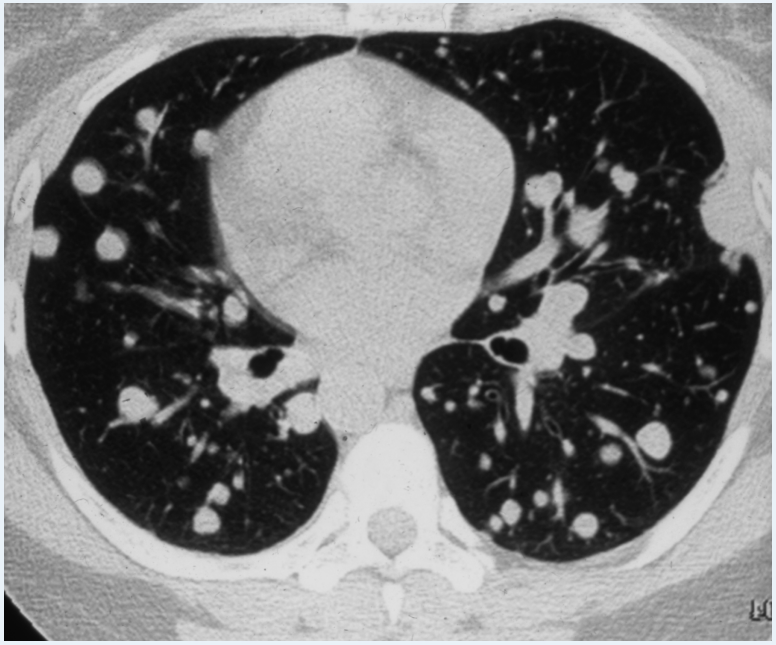
- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease

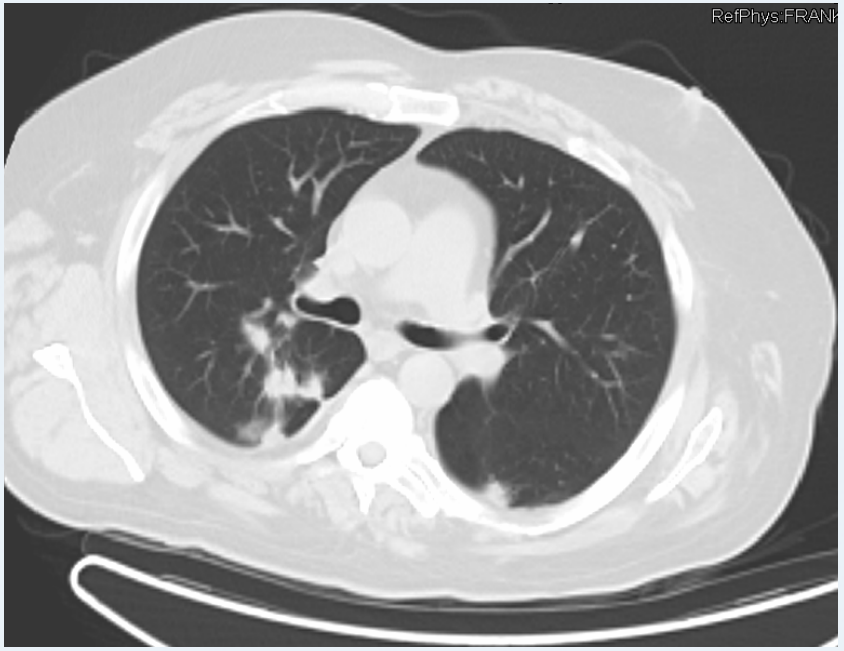




Cavitary / Nodular Lung Disease

- Among individuals with GPA (Wegener)
  - 55-70% will have nodular disease
  - 35-50% will have cavitary disease
- DDx: **malignancy, infections, embolic phenomena**, sarcoidosis, lymphocytic interstitial pneumonia, connective tissue disease





DAH: Radiology

Findings depend upon chronicity and are non-specific

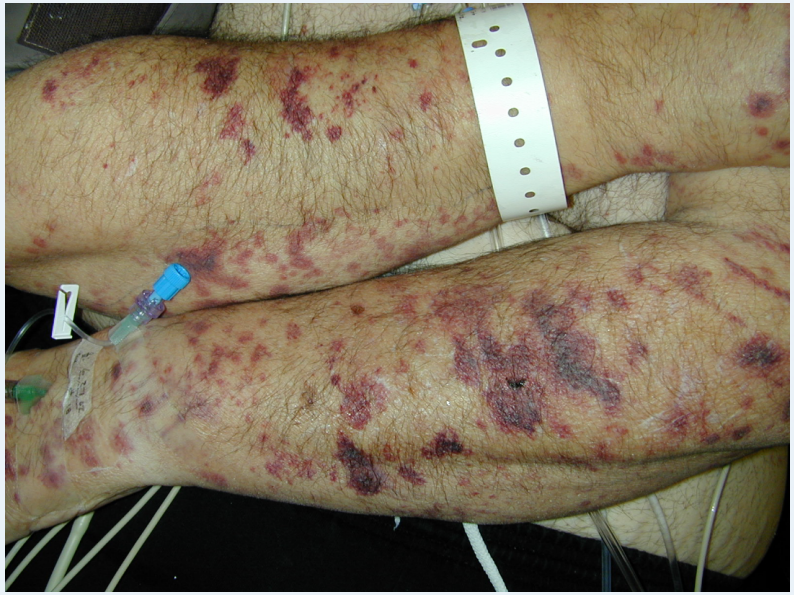
- Patchy or diffuse alveolar infiltrates
  - Ground glass opacities (subtotal alveolar filling) or consolidation with air bronchograms
  - May start in a focal, unilateral pattern and become more diffuse with time
  - Often with apical and peripheral sparing
- May see interlobular septal thickening
- May see ill-defined centrilobular nodules
- May see features of interstitial fibrosis
  (endogenous pneumoconiosis seen with recurrent / chronic episodes of hemorrhage)
- Kerley B lines suggestive of pulmonary veno-occlusive disease, mitral stenosis
- Nodules, cavities suggestive of GPA (Wegener), Rheumatoid Arthritis

When to Think About Vasculitis

- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease
- Deforming/ulcerating upper airway lesions

When to Think About Vasculitis

- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease
- Deforming/ulcerating upper airway lesions
- Palpable purpura

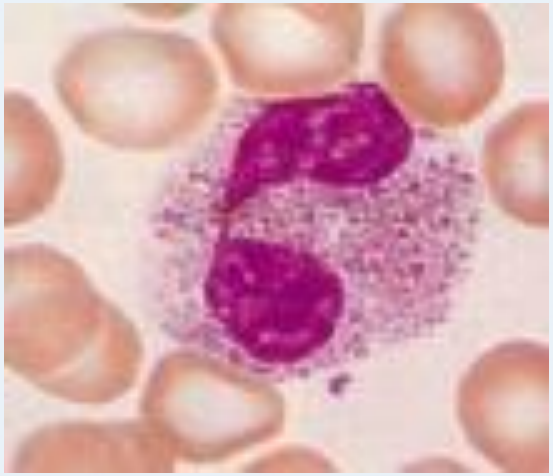


When to Think About Vasculitis

- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease
- Deforming/ulcerating upper airway lesions
- Palpable purpura
- Mononeuritis multiplex
  - Motor or sensory deficit in two or more peripheral nerve distributions, typically in unrelated portions of the body. Asymmetric and temporally distinct
  - Need to ASK about this, patients don't usually volunteer this on history or ROS

When to Think About Vasculitis

- Diffuse alveolar hemorrhage
- Glomerulonephritis
- Cavitary or nodular disease
- Deforming/ulcerating upper airway lesions
- Palpable purpura
- Mononeuritis multiplex
- Peripheral eosinophila



Clinical Evaluation

- Detailed history with careful ROS
- Detailed examination
- Laboratories / ANCA testing
- Imaging studies
- Invasive testing

Diagnostic Studies

- CBC
- Renal function and urinalysis
- Serologies
  - classic primary connective tissue diseases
  - ANA with profile (SSA, SSB, RNP, dsDNA, anti-centromere, Scl-70), CPK/ aldolase, anti-cardiolipin antibodies
  - ANCA / PR3, MPO
  - Anti-GBM
- EKG and ECHO

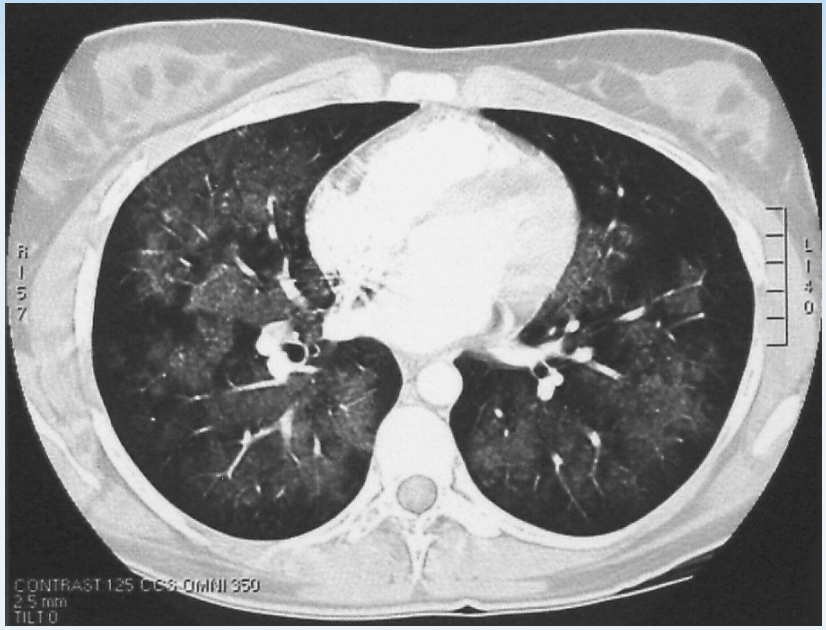
ANCA-testing: Clinical Guidelines

When guidelines were applied:

- ✓ test ordering reduced by **23%**
- ✓ false positives reduced by **27%**
- ✓ **no** reduction in sensitivity or specificity
- ✓ increased PPV

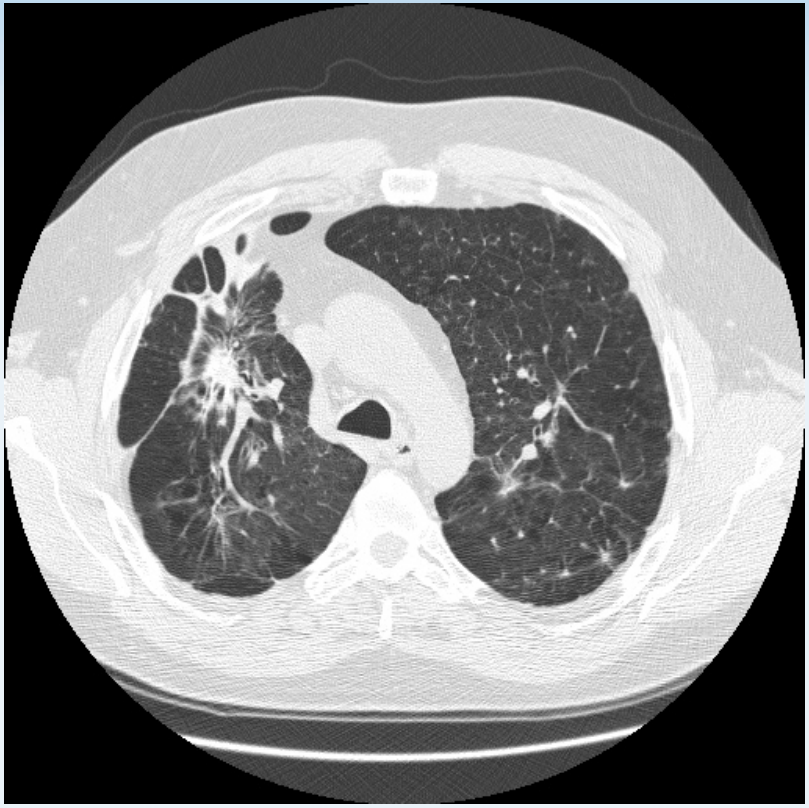
Mandel et al. Arch Intern Med(2002) 162:1509

Imaging Studies



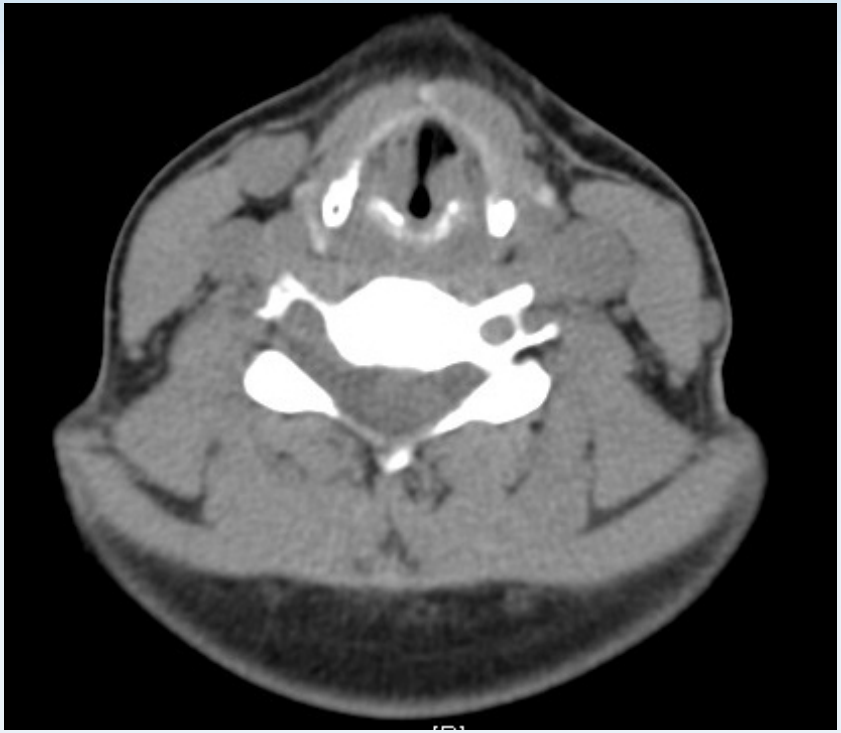
- CXR may identify disease or complications
- HRCT of the chest is sensitive for both detection and characterization of lung involvement
- 85-90% of GPA (Wegener) patients have CT chest abnormalities
- Up to 70% of EGPA (CSS) patients will have CT chest abnormalities

Chest Imaging Patterns



- Alveolar filling pattern
- Diffuse infiltrates
- Migratory infiltrates
- Multiple nodules
- Solitary nodule
- Cavities
- Airways disease
- Pleural disease
- Lobar collapse

Additional Imaging Studies



- CT sinus
- CT abdomen
- MRI head
- Angiography

Tissue is the Issue !

- Histopathologic diagnosis is often necessary to make the clinical diagnosis

Tissue is the Issue !

- Histopathologic diagnosis is often necessary to make the clinical diagnosis
- Choosing biopsy site
  - Organ involvement
  - Accessibility
  - Morbidity
  - Likelihood of diagnostic tissue

Mortality in Vasculitis

- Early deaths often due to the active disease
- Late deaths may be due to complications of therapy

Villa-Forte *et al.* (2010) Curr Opin Rheumatol 22:49

Principles of Therapy

- Titrate the intensity of the immunosuppression to disease activity
- Three components
  - Remission induction
  - Remission maintenance
  - Monitoring
    - Disease activity
    - Drug toxicity / adverse events
    - Superimposed infections
    - Disease recurrence after achieving drug-free remission
    - Disease complications (e.g., tracheal stenosis in GPA)

Principles of Therapy

Example: GPA (Wegener)

Overall Approach

- How severe is the disease?

Mild Disease	**Moderate to Severe Disease**
• No evidence for “active” glomerulonephritis • No organ-threatening or life-threatening manifestations	

- Which organ systems are involved?
- Remember appropriate monitoring and prophylaxis (e.g., for Pneumocystis)

Limiting Glucocorticoid Exposure

- No consensus on initial glucocorticoid dosing
  - Pulse methylprednisolone (7-15 mg/kg to a maximum dose of 500-1000 mg/day for three days) in all patients versus only those with more severe disease
- Oral glucocorticoid therapy from day 1 or 4 (if pulse-dose given) generally 1 mg/kg/day (maximum 60-80 mg/day) of oral prednisone or equivalent
- Various tapering schemes have been used
  - Initial dose for 2-4 weeks and if improvement observed, taper slowly
  - Goal is 20 mg/day by the end of two months
  - Total duration of prednisone therapy generally 6-9 months unless needed for control of persistent systemic symptoms
  - Use of glucocorticoids beyond 6 months is associated with significantly higher incidence of infections but is **NOT** associated with reduced risk of relapse

Severe Disease

Indication for plasma exchange or plasmapheresis?

"Randomized controlled trials of PLEX in renal vasculitis suggest a reduction in the risk of development of ESRD with adjunctive PLEX, although the data are not sufficiently strong to make firm recommendations and there are no controlled trials in alveolar haemorrhage."

Casian & Jayne (2011) Curr Opin Rheumatol 23:12

Maintenance Therapy

- Assessment of Disease Activity
  - GPA (WG) Birmingham Vasculitis Activity Score (BVAS)
  - Monitoring serum ANCA titers
    - Alone is NOT helpful
    - May provide some useful information when used along with changes in ESR and CRP levels

Maintenance Therapy

- Assessment of Disease Activity
- AVOID excess immunosuppression in *irreversible* disease
  - Is disease *active* or this is *irreversible damage* (e.g., scarring of vessels) in the setting of remission?
  - Patients who progress to ESRD and are on chronic RRT have a substantially lower rate of relapse AND are at increased risk of infections while on maintenance therapy

Maintenance Therapy

- Assessment of Disease Activity
- AVOID excess immunosuppression in *irreversible* disease

- Initiation of maintenance therapy
  - Generally continue CYC induction therapy 1-2 months after first documentation of remission
  - Start maintenance therapy AFTER cyclophosphamide has been discontinued
    - Timing depends upon whether oral or IV CYC was administered and recovery of WBC / ANC

Maintenance Therapy

- Assessment of Disease Activity
- AVOID excess immunosuppression in *irreversible* disease
- Initiation of maintenance therapy

- Duration of maintenance therapy
  - Usually 12-18 months after stable remission induced
  - Must also consider risk of relapse
  - No randomized trials

Maintenance Therapy after CYC

Glucocorticoids

- Initially continued at low dose in most patients receiving maintenance therapy
- Tapering should begin once there is significant response to initial immunosuppressive therapy
- Goal: attain minimum dose required for control of systemic symptoms
- Once asymptomatic: slowly taper OFF
  - Rec: At 5 mg/day, taper down by 1 mg/day every 4 weeks
- May require longer term low dose maintenance therapy in patients who have had multiple relapses

Induction of Remission: Glucocorticoids + Cyclophosphamide

- Combination of cyclophosphamide (CYC) for at least 3-4 months and high-dose glucocorticoids induces remission in 85-90% of patients
- Approximately 75% experience complete remission
- Toxicity often limits duration of cyclophosphamide therapy

Induction of Remission: Cyclophosphamide *vs* Methotrexate

NORAM trial (2005)

- 95 patients: 89 with WG(GPA), 6 with MPA
- *No difference* between methotrexate and CYC for induction of remission in early, generalized ANCA-associated vasculitis
- Methotrexate is *less effective* at maintaining remission in patients who were not initially treated with CYC
  - 70 versus 47 percent relapse rate at 18 months

Induction of Remission: Cyclophosphamide *vs* Rituximab

- Two randomized trials (RAVE, RITUXVAS)
  - Both found equivalent efficacy and tolerability
  - Short duration of follow-up

- In 2011 the FDA approved use of rituximab as an alternative to cyclophosphamide

Not all DAH is Vasculitis

DAH is associated with a number of clinical entities and several histologic subtypes

- **Pulmonary capillaritis** (vasculitis of the microcirculation)
  - Systemic vs Lung-limited
  - Vasculitis, rheumatic
  - Drugs
  - Infectious endocarditis
  - Transplant rejection
  - Ulcerative colitis
- **Bland pulmonary hemorrhage**
  - Mitral stenosis
  - Subacute bacterial endocarditis
  - Drugs (penicillamine, amiodarone, nitrofurantoin)
  - TTP, HUS, ITP
  - Goodpasture and SLE
- **Diffuse alveolar damage**
  - Drugs and inhaled toxins (crack cocaine)
  - ARDS
  - COP
  - Bone marrow transplantation