Vasculitis and Mimickers

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Disclosures

- Consultant/Advisory Board for Chemocentryx, Abbvie, Novartis
- Board Member of the Vasculitis Foundation and Chicago Rheumatism Society

Why Rheumatology??


Rare diseases
C
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B
A
Y-Z
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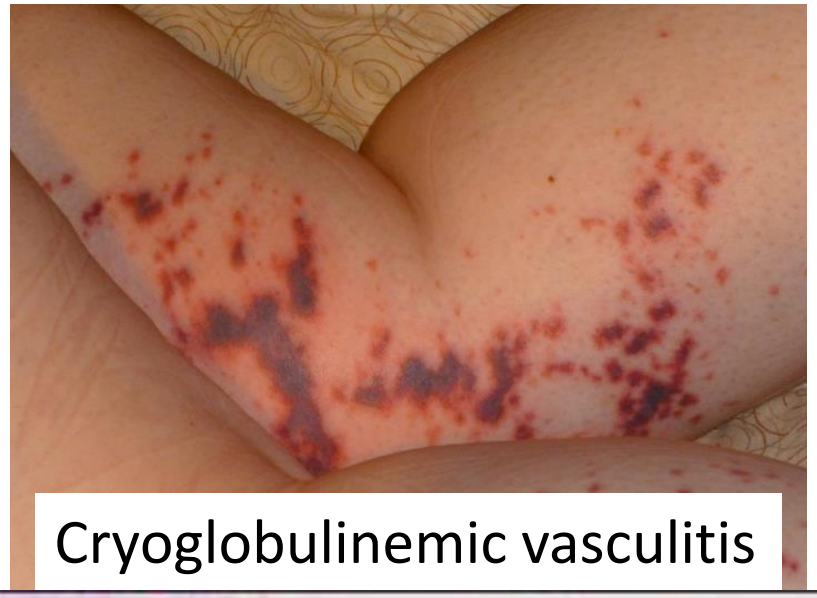
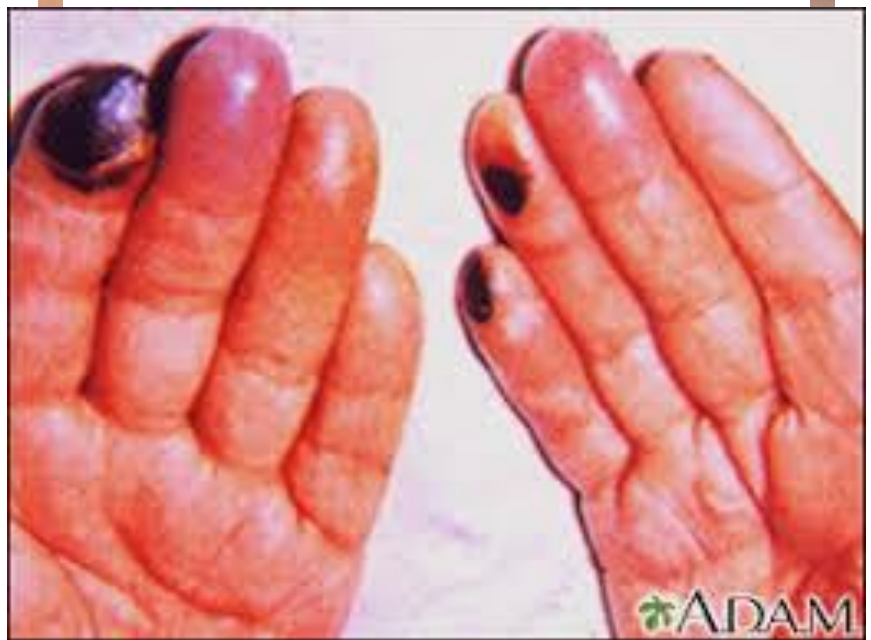
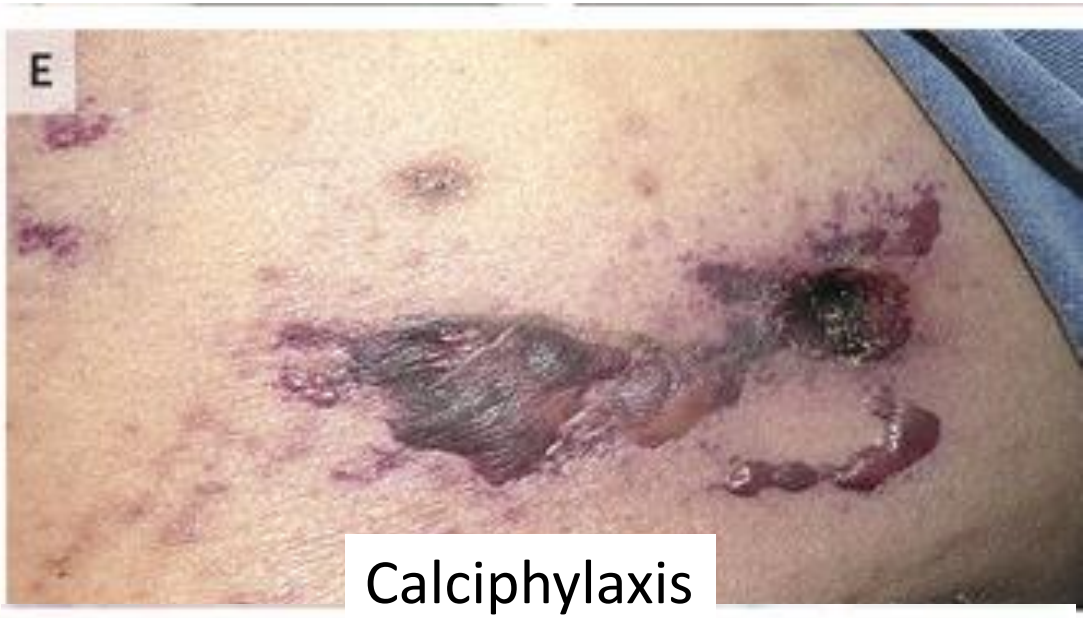
T

Low grade fevers, painful skin lesions on body and fingers



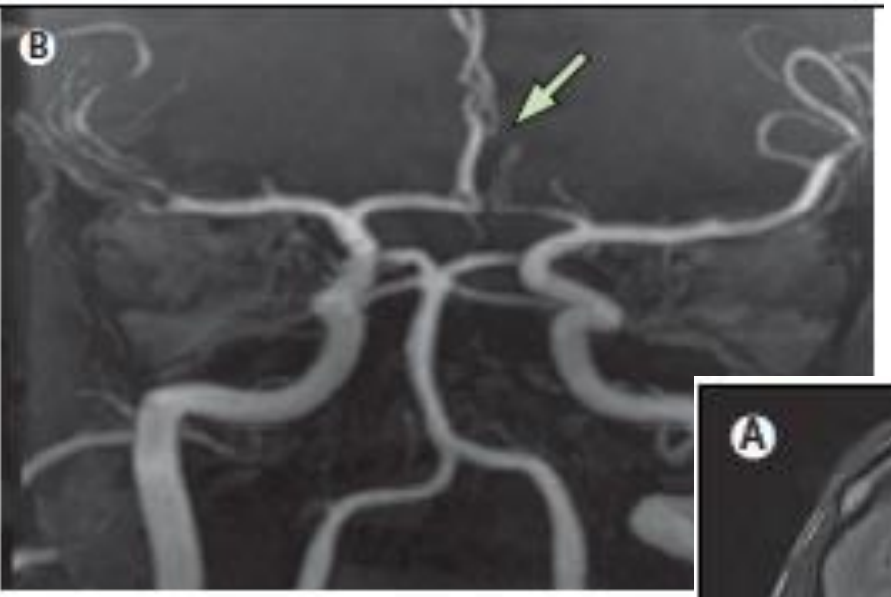
Cryoglobulinemic vasculitis

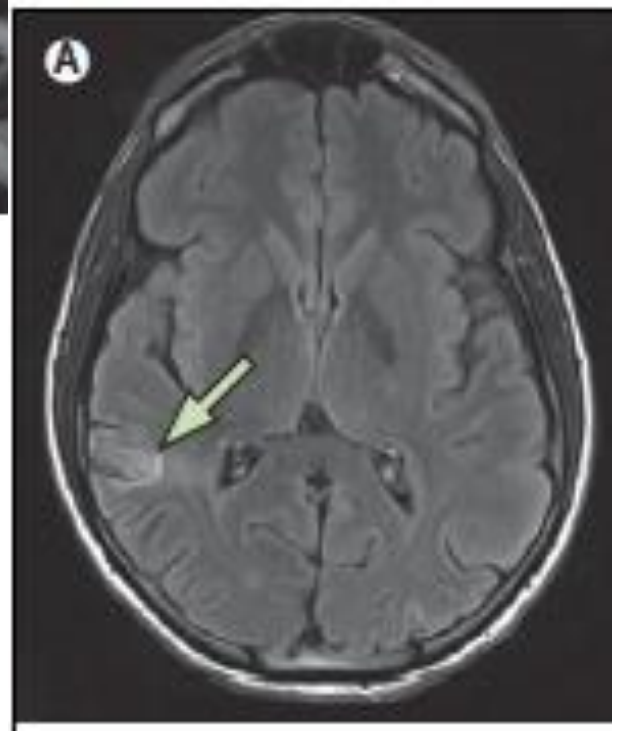




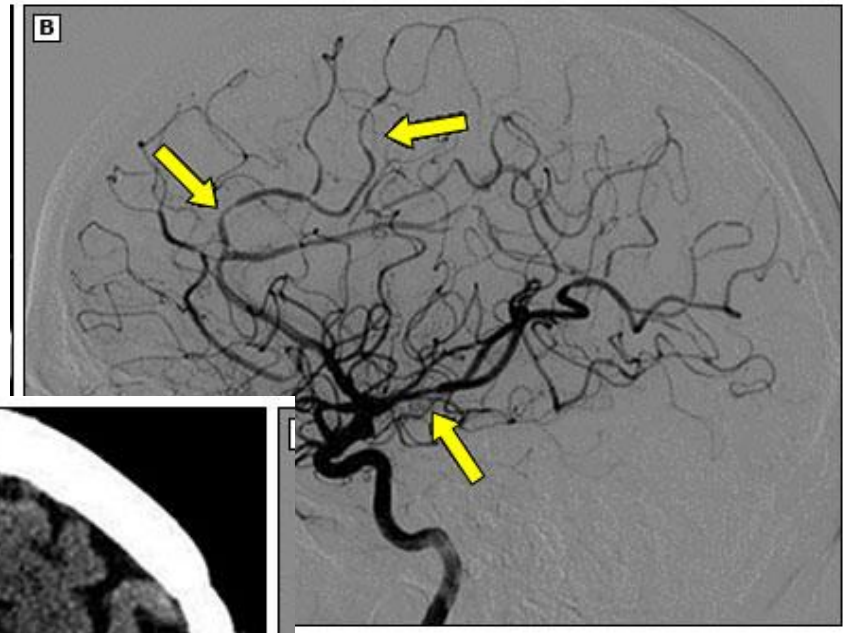
Calciphylaxis

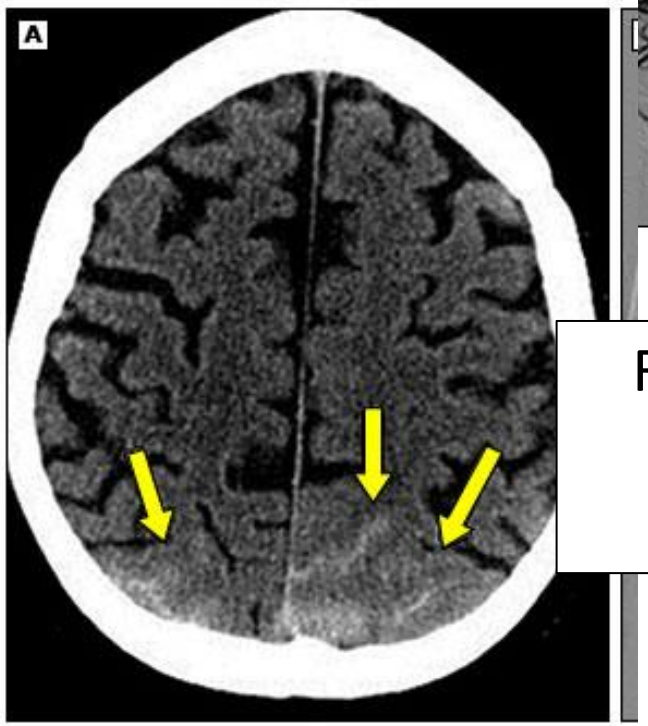
30 year old male with new onset severe headache and dizziness, found fallen down at home





Primary Angiitis of the CNS (CNS Vasculitis)





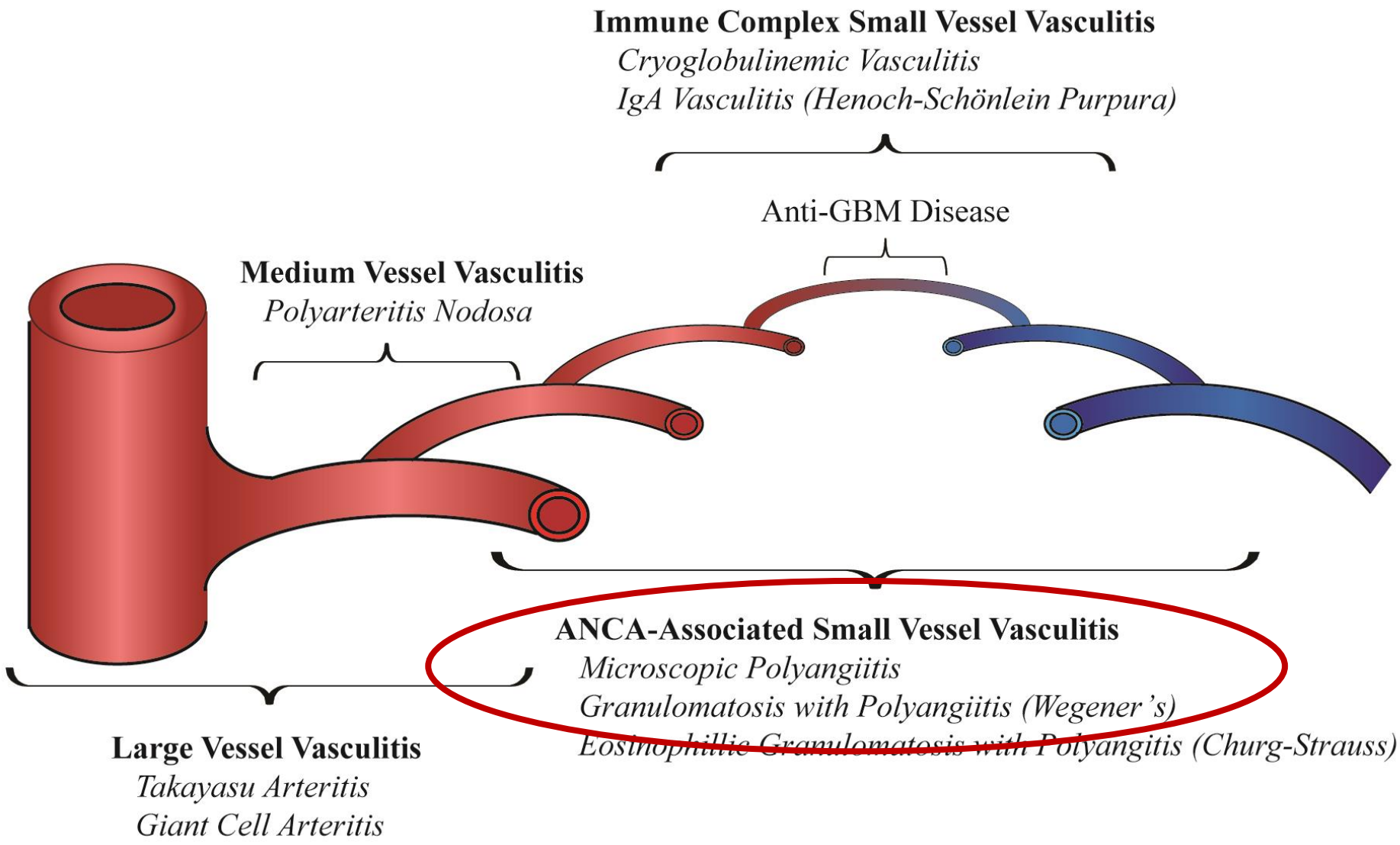
Reversible Cerebral Vasconstrictive Syndrome (RCVS)

Chapel Hill Consensus Conference 2012

Giant Cell Arteritis

Vasculitis Mimics	
Infectious causes (endocarditis, HBV, HCV, HIV, fungal, parasitic)	→ Any size
Malignancy (lymphoma, leukemia)	
Atherosclerosis	} Large→ medium
IgG4-RD, RPC, Erdheim Chester	
Hereditary disorders (Marfan's, Ehlers-Danlos)	
Vasculopathies (Fibromuscular dysplasia, Segmental Arterial Mediolysis)	→ Medium
Vasospastic disorders (RCVS, drug exposure)	} Medium→ Small
Thromboembolic disease	
Hypercoagulable states (APS, TTP, TMA, livedoid vasculopathy)	
Calciphylaxis, Drug induced	→ Small

Small vessel vasculitis: ANCA Vasculitis



ANCA Vasculitis: Background

- **Granulomatosis with Polyangiitis** (Wegener's, GPA)
  - –Northern European
  - –Annual incidence: 1.3/100,000
- **Microscopic polyangiitis (MPA)**
  - –Southern European, Asian
  - –Annual incidence: 1.6/100,000
- M=F
- Age ~ 40-60's

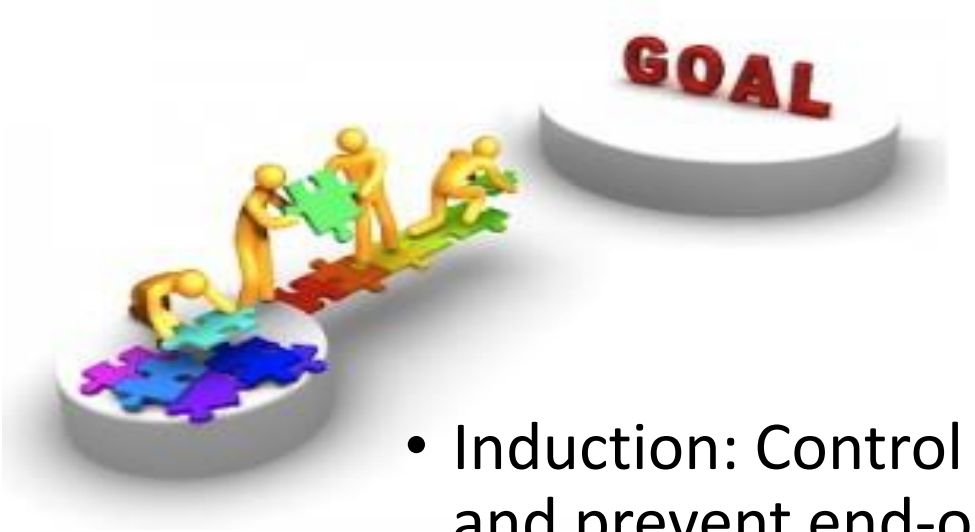
Context:

- Diabetes
  -670/100,000 adults
- Stroke
  -670 to 970 of 100,000 age 65-74
- Breast cancer
  -128.5/100,000 women

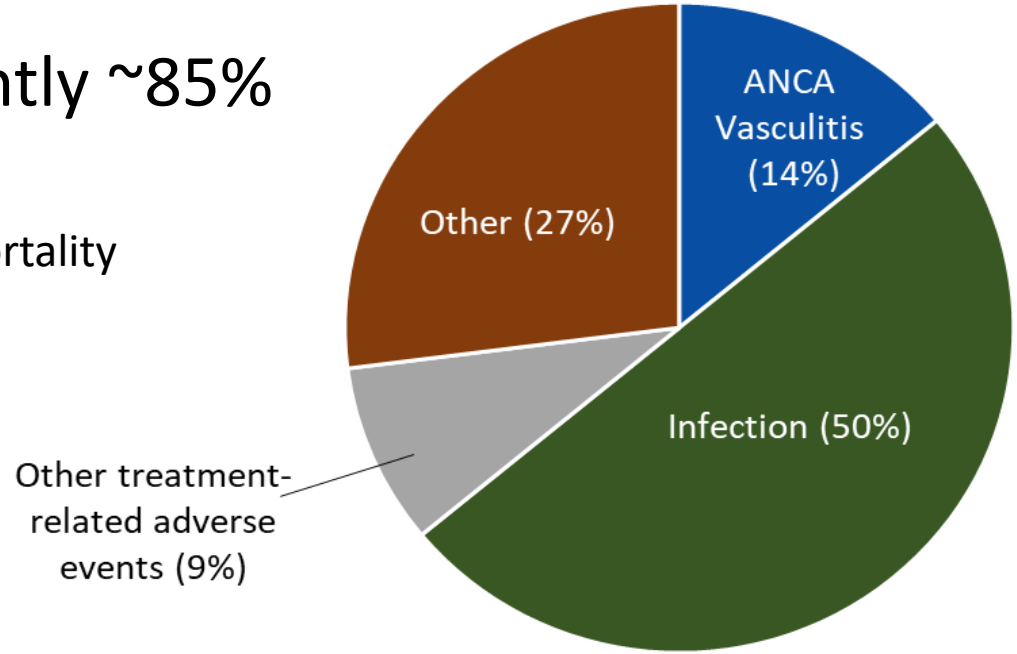
Berti Arth Rheum 2017
Kitching, Nature Reviews 2020

ANCA Vasculitis: Background

- Untreated: 9 of 10 die at 2 years. Currently ~85% survival at 2 years



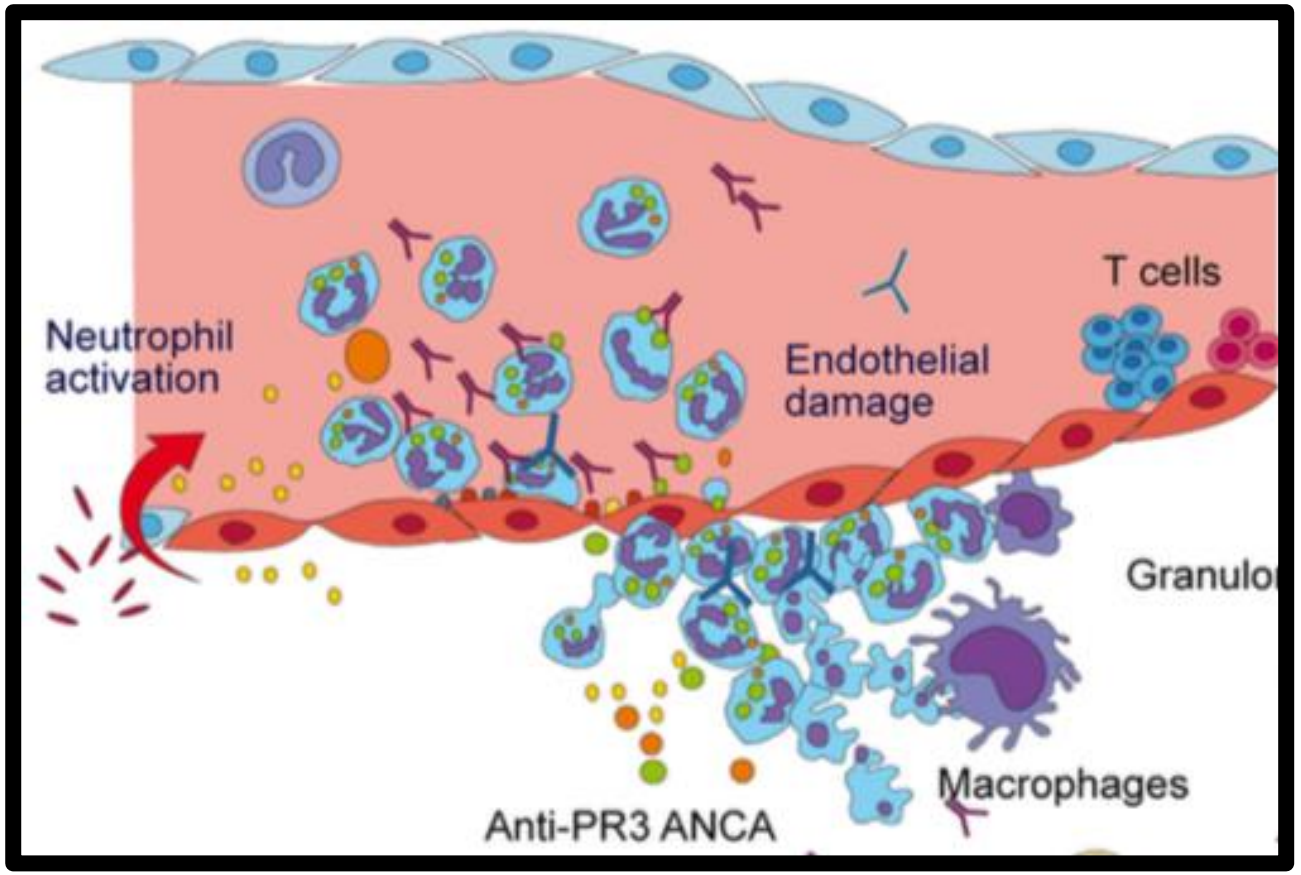
1 year mortality



- Induction: Control inflammation and prevent end-organ damage – induce remission
- Maintenance: Prevent relapses, minimize toxicity

Hunter, BMJ 2020; King, Best Prac Clin Rheum 2018

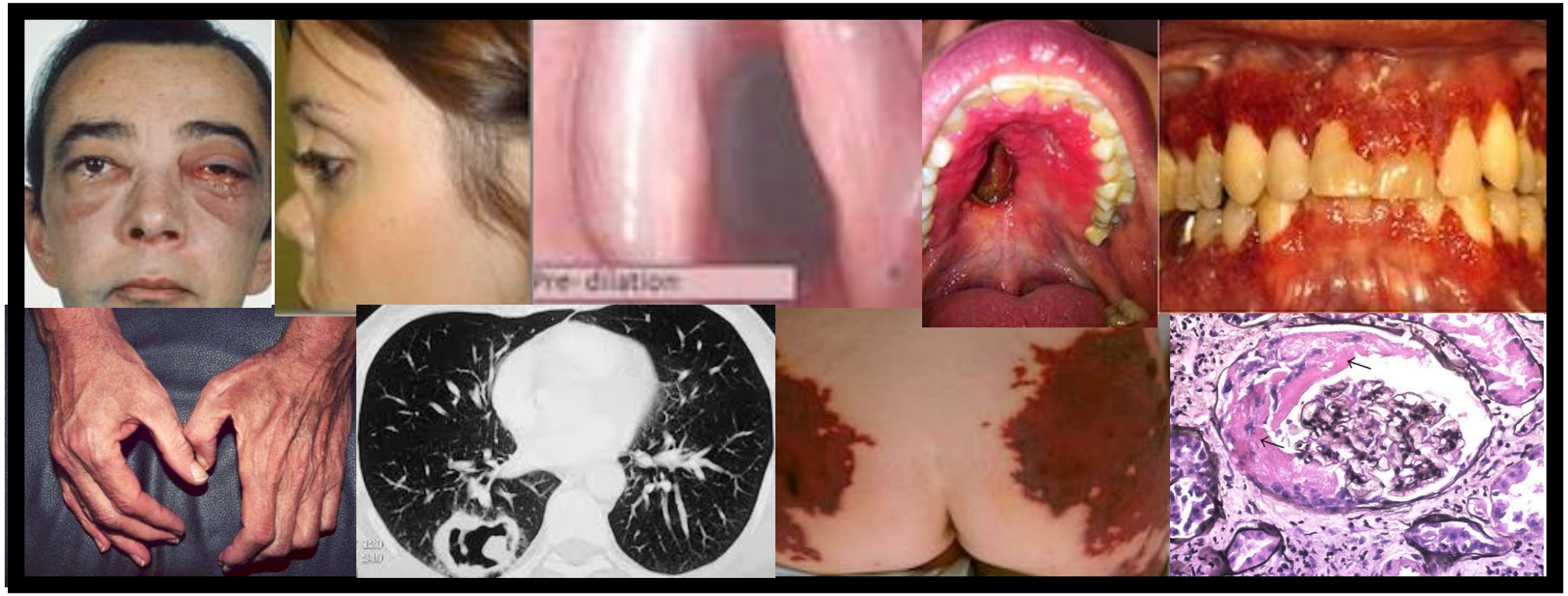
Pathogenesis



	P-ANCA (MPO)	C-ANCA (PR3)
GPA	25%	70%
MPA	60%	35%

ANCA titers do not predict disease flare

Clinical Manifestations: GPA/MPA



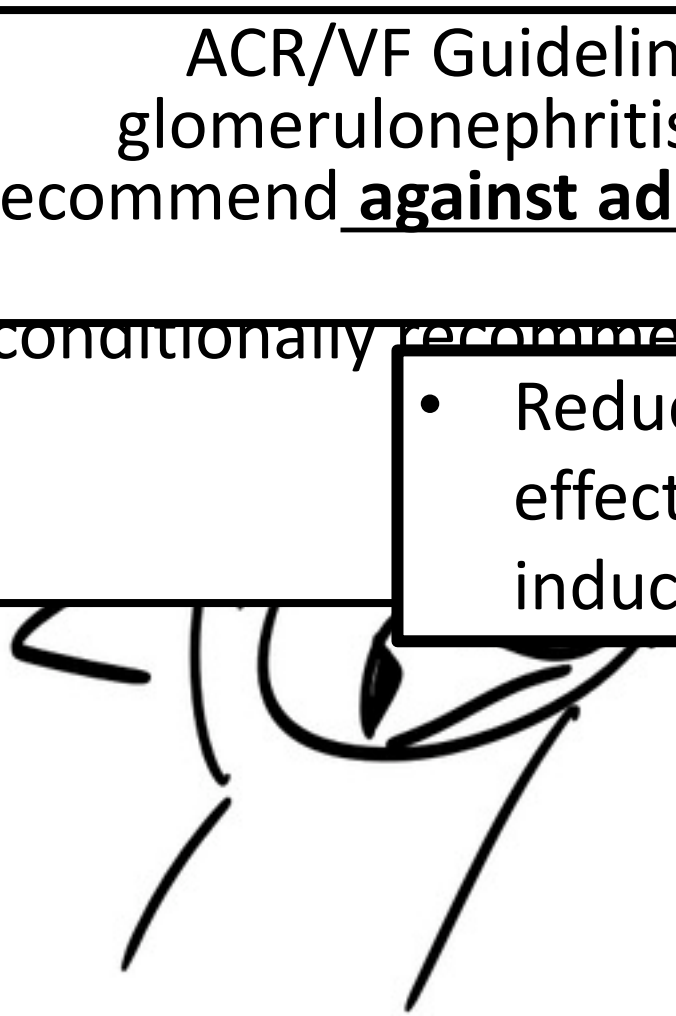
ACR Image Bank; Hopkins Vasculitis website

ACR/VF Guideline: In patients with GPA/MPA with active glomerulonephritis or alveolar hemorrhage, we conditionally recommend **against adding plasma exchange** to cyclophosphamide or rituximab

PA

conditionally recommend using rituximab over cyclophosphamide for

- Reduced dose steroid regimen was as effective as standard regimen for induction in AAV with less infections



PLASMAPHERESIS

PULSE STEROIDS

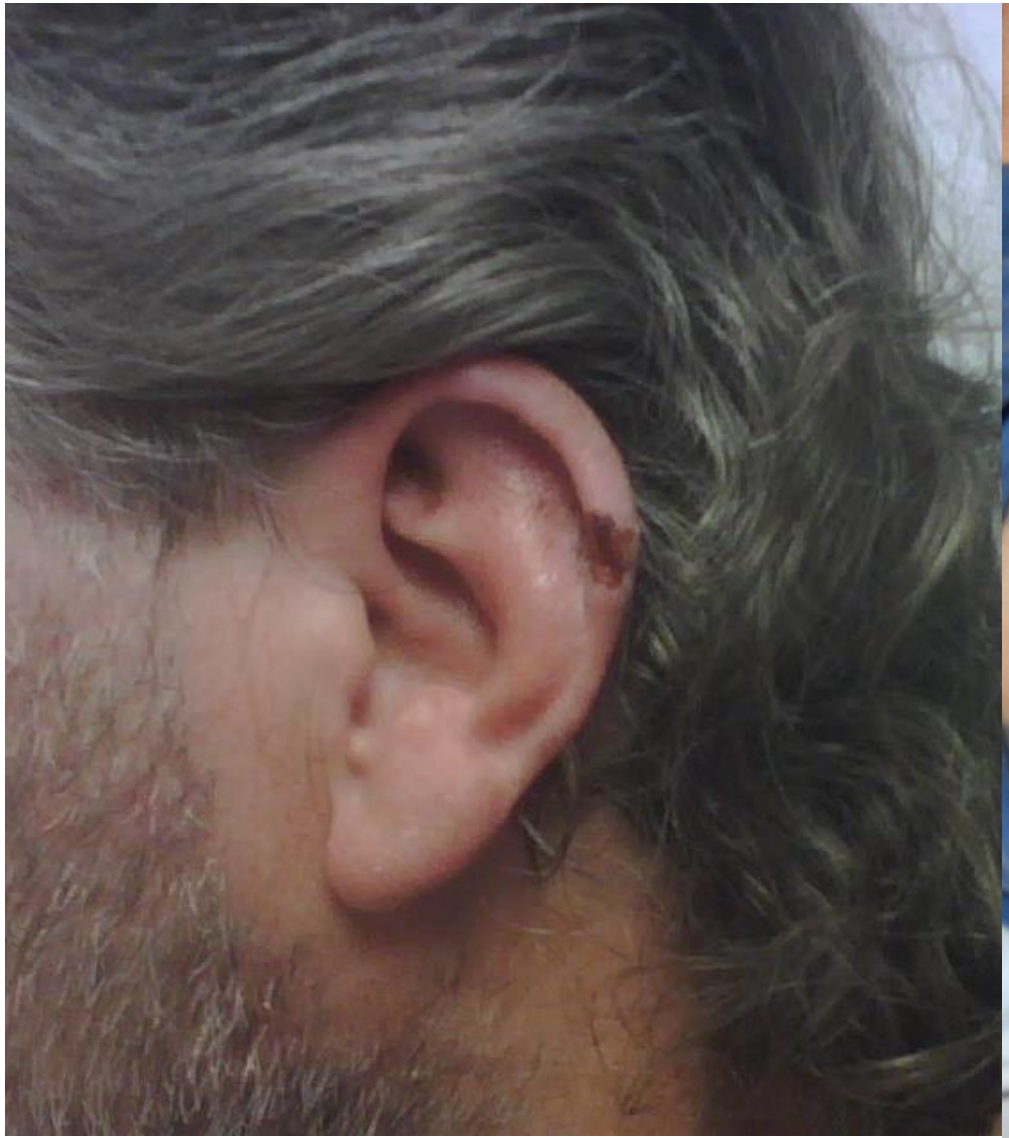
RITUXIMAB

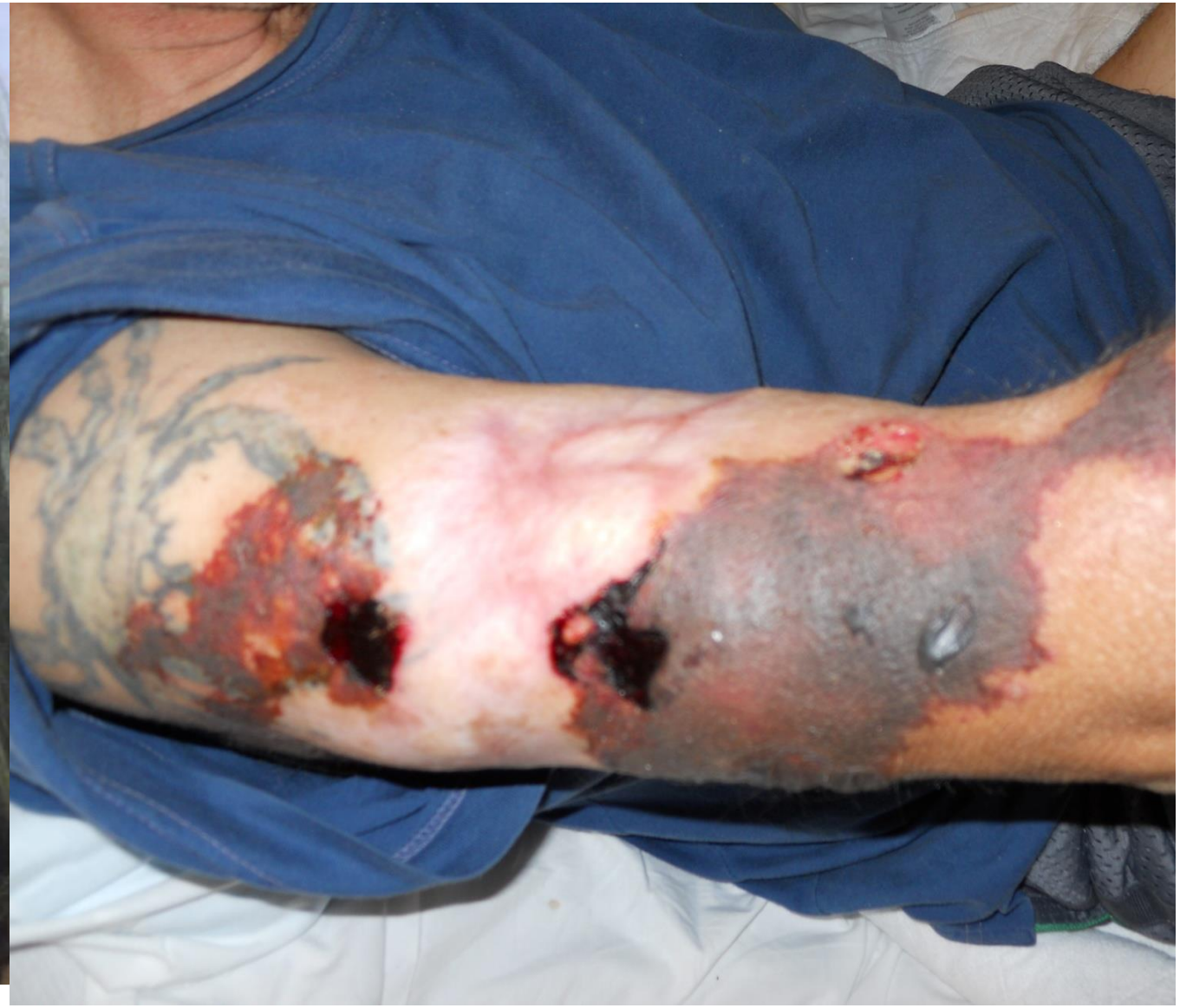
CYCLOPHOSPHAMIDE

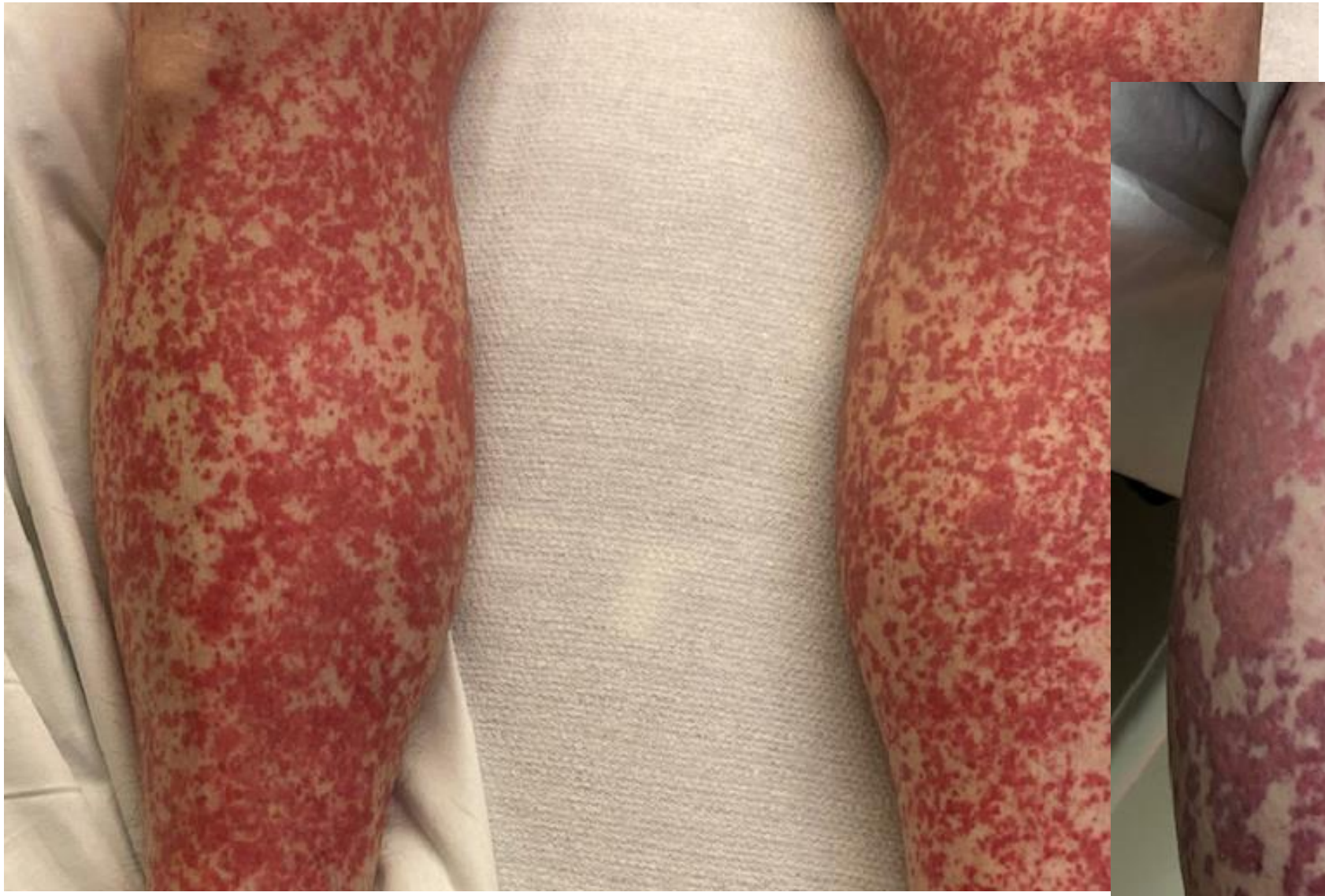
Stone, NEJM 2010; Jones, NEJM 2010; Maz, Arth Rheum 2021

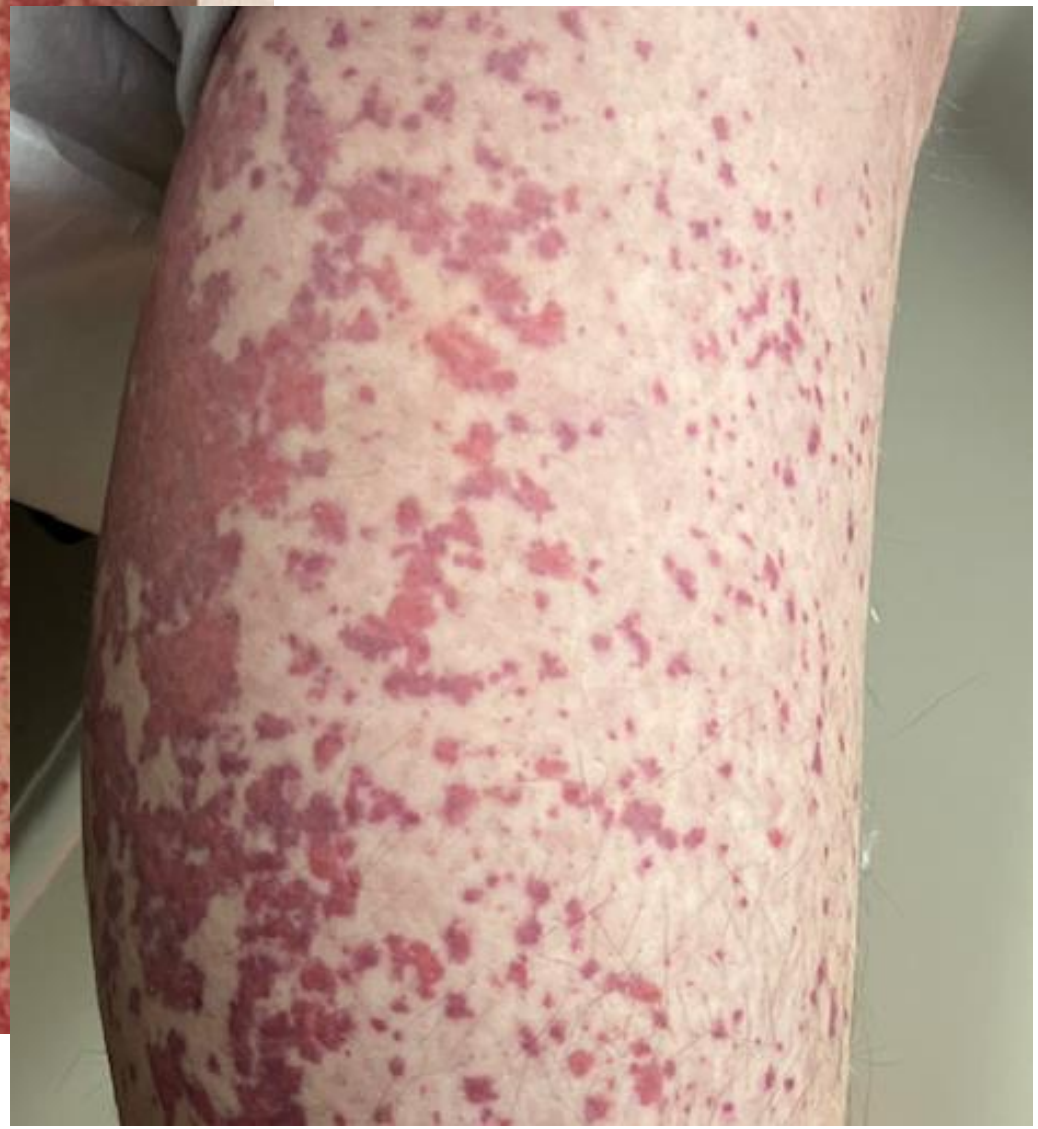
Case Presentation
Painful blistering rash and +ANCA

- 45 year old male presents with fever, blistering painful rash on his arms, and pain with darkening/bruising of the bilateral ears
- Blood cultures, ANA and cryoglobulins negative
- Urine toxicology: + for cocaine
- p-ANCA, MPO+, PR3+
- Low WBC count





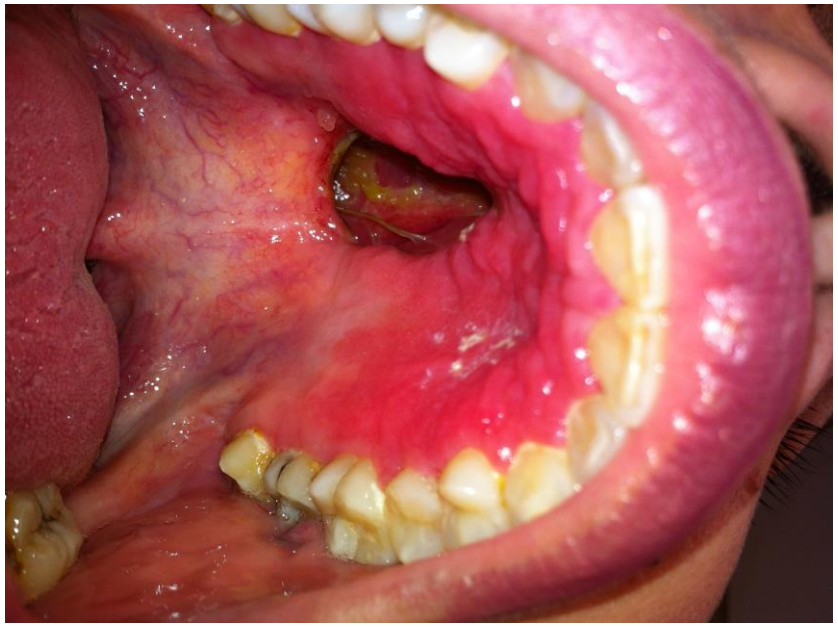




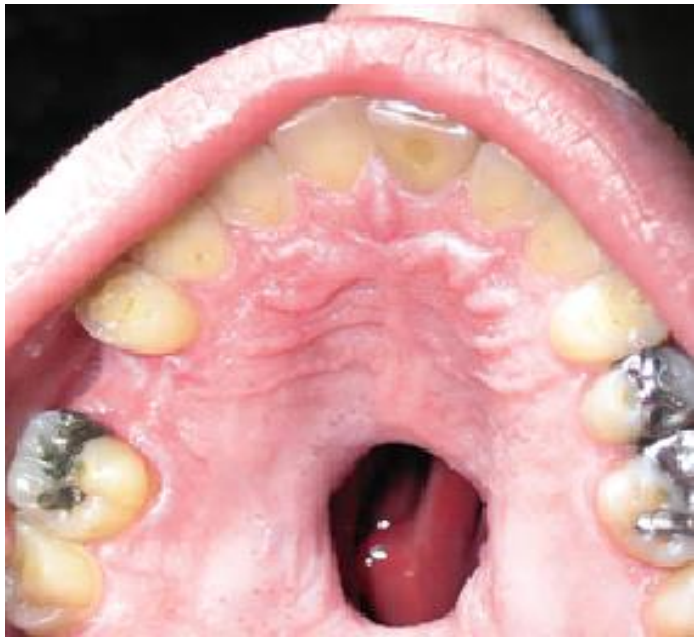
Levamisole Induced AAV

- Anti-helminthic agent used to treat parasitic worm infections
  - Withdrawn from market in 2000 because of side effects including agranulocytosis, vasculitis, leukoencophalopathy
- Adulterant in cocaine >70% of the time
- Nearly all will have a +MPO, 50% of time +PR3
- Purpuric skin lesions often involving the face and ears, lower>upper limbs
- May have constitutional sx's, myalgias, arthralgias and leukopenia
- Cocaine can be detected within 3 days of use, levamisole half life is ~5 hours
- Skin biopsy shows thrombotic vasculopathy with or without LCV

Cocaine-induced midline destructive lesions (CIMDL) or limited GPA??



GPA



CIMDL

Palate perforation

Nasal perforation

Cocaine-induced midline destructive lesions

- Mimics the limited form of granulomatosis with polyangiitis
- Associated with **more destruction than is typical of GPA**
- High-titer **PR3-ANCA**/C-ANCA positive
- Also associated with high titer atypical ANCA, caused by antibodies to elastase
- Does not respond to immunosuppression
- No other organ involvement
- Nasal biopsies in GPA are low yield—10-20% show classic necrotizing granulomatous inflammation with vasculitis

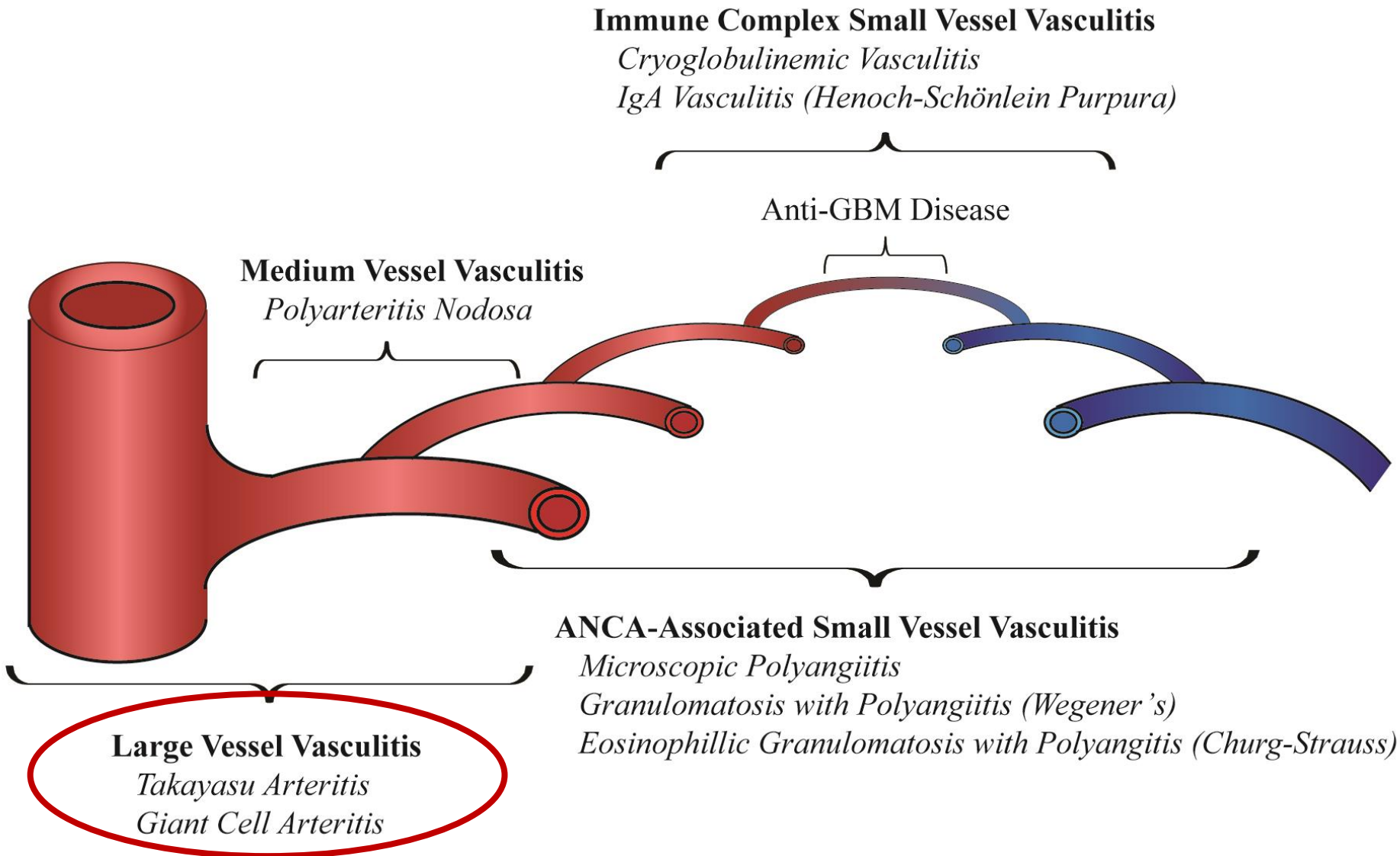
What about NOT cocaine and drug induced AAV?

- Other drugs such as hydralazine, propylthiouracil, methimazole, anti-TB drugs, anti-TNF, minocycline can cause ANCA positive vasculitis
- Usually present with palpable purpura. Reports of GN, DAH, arthralgias, myalgias
- Multiple antibodies: MPO, atypical ANCAs, lactoferrin, +APLs, +ANA
- 7% of patients exposed to propylthiouracil will become ANCA-positive (don’t switch to methimazole)
- Treatment: Stop the drug. Occasionally GC/IS therapy is used

	DAAV	CIMDL	Levamisole	GPA
ANCA	MPO	PR3	MPO	PR3
UTox	-	+ / -	+ / -	-
Purpura	+	-	+	+
Perforation	-	+	-	+
Crusting	-	+	-	+

Slide adapted from Phil Seo

Large vessel vasculitis: Giant cell arteritis



Background: GCA

granulomatous inflammation of the large blood vessels

	GCA
Age	>50
Ancestry	Scandinavian
Incidence	1-14 per 100,000
Gender	3F:1M
Clinical Presentation	Headache, jaw claudication, scalp tenderness, vision loss, constitutional symptoms
Genetics	HLA DRA, DRB1 (class1 MHC)

If untreated, second eye likely to become affected within 1-2 weeks

Table 1: ACR Classification Criteria for Giant Cell Arteritis

1. Age more than 50 years;

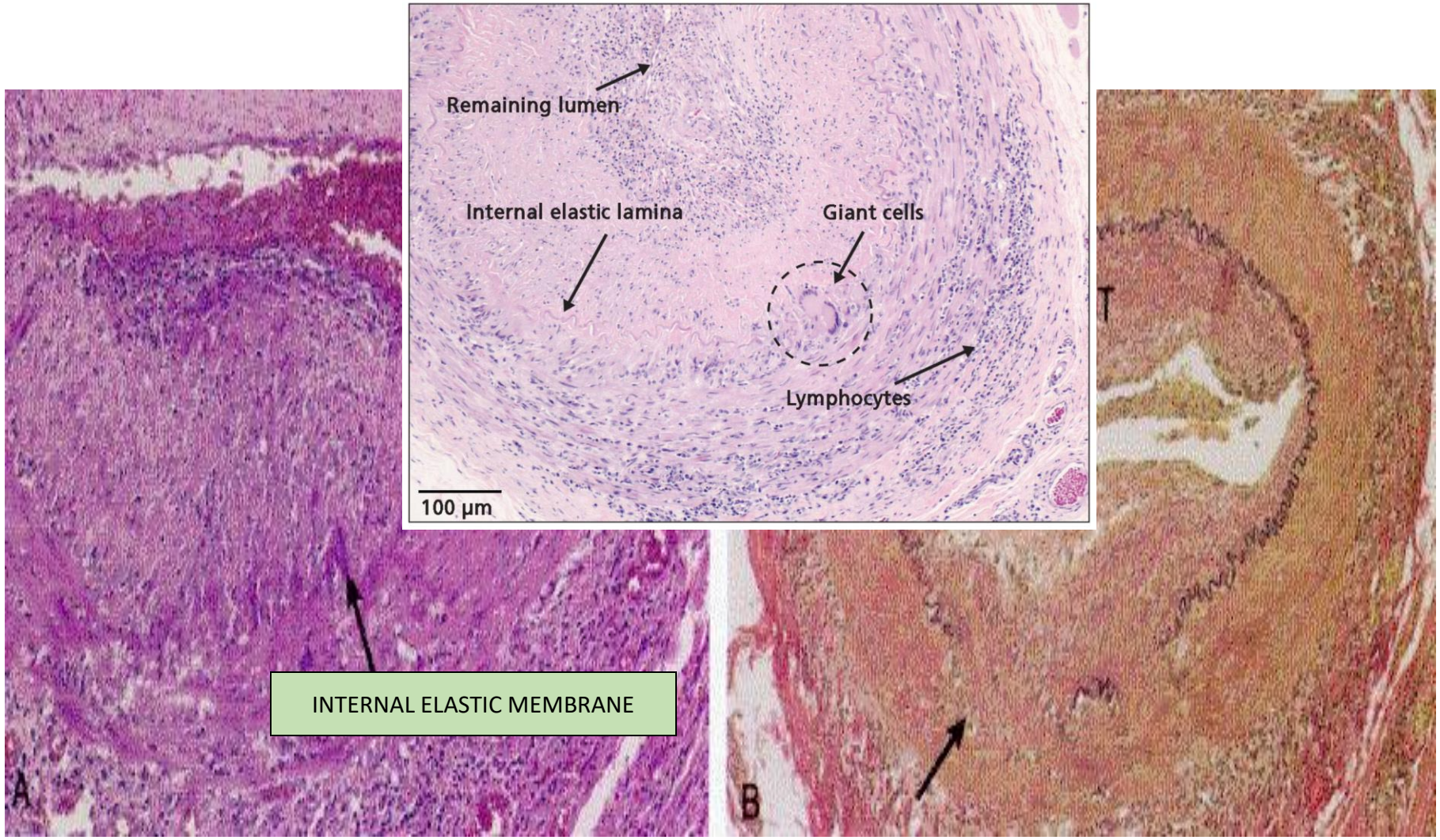
Recommendation: In patients with suspected GCA, we conditionally **recommend temporal artery biopsy** over temporal artery ultrasound for diagnosis of GCA

4. Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour; and

5. Histologic evidence of arteritis on temporal artery biopsy (e.g., mononuclear cell infiltration or granulomatous inflammation).

Three out of five criteria→93.5% sensitivity I 91.2% specificity

What are we looking for on pathology?



Muratore, J Autoimmun, 2016 ~ Ting, Clin Exp Rheum 2016

Timing: How long can I wait?

- Ca
- Le
  sm

In patients with suspected GCA, we conditionally recommend obtaining **a temporal artery biopsy** within **two weeks** of starting oral glucocorticoids over waiting longer than two weeks

Length of steroid tx	Positive biopsy
<2 weeks	35/45 (78%)
2-4 weeks	13/20 (65%)
>4 weeks	2/5 (40%)

Length of steroid tx	Positive biopsy
3 months	70%
6 months	75%
9 months	44%
12 months	44%

Achkar, Ann Intern Med, 1994 ~ Narvaez, Semin Arth Rheum, 2007 ~ Maleszewski, Mod Pathol 2017 ~ Maz, Arth Rheum 2021

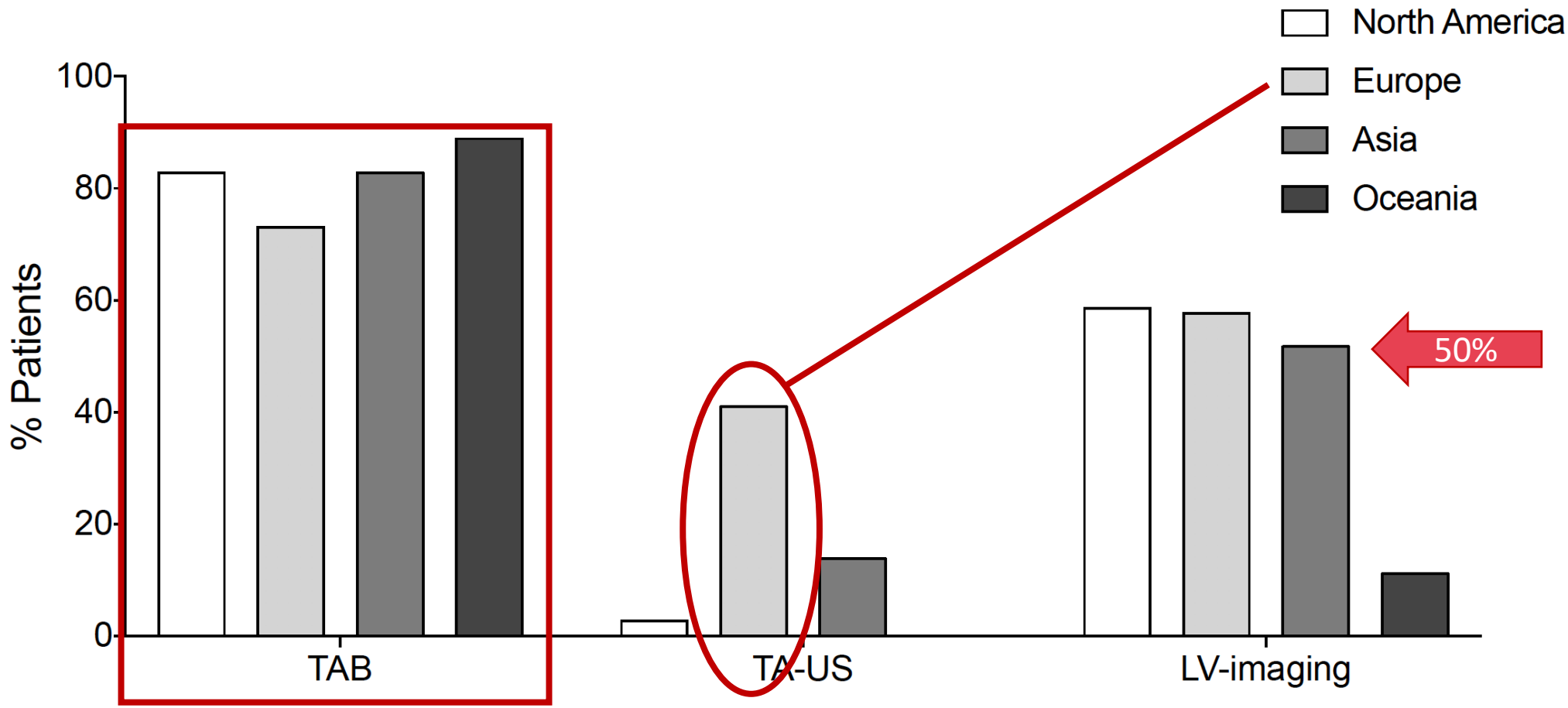
Location: Should I biopsy one or both sides?

- Yield increases 5-10% with bilateral biopsy
- 186 bilateral TAB→6 unilateral arteritis
  - These 6 were 20% of the total # of patients whose GCA was diagnosed through biopsy!
- 250 bilateral biopsies→11 unilateral arteritis
  - Rate of discordant biopsy was 4.4%

In patients with suspected GCA, we **conditionally** recommend **unilateral** over **bilateral temporal artery biopsy**

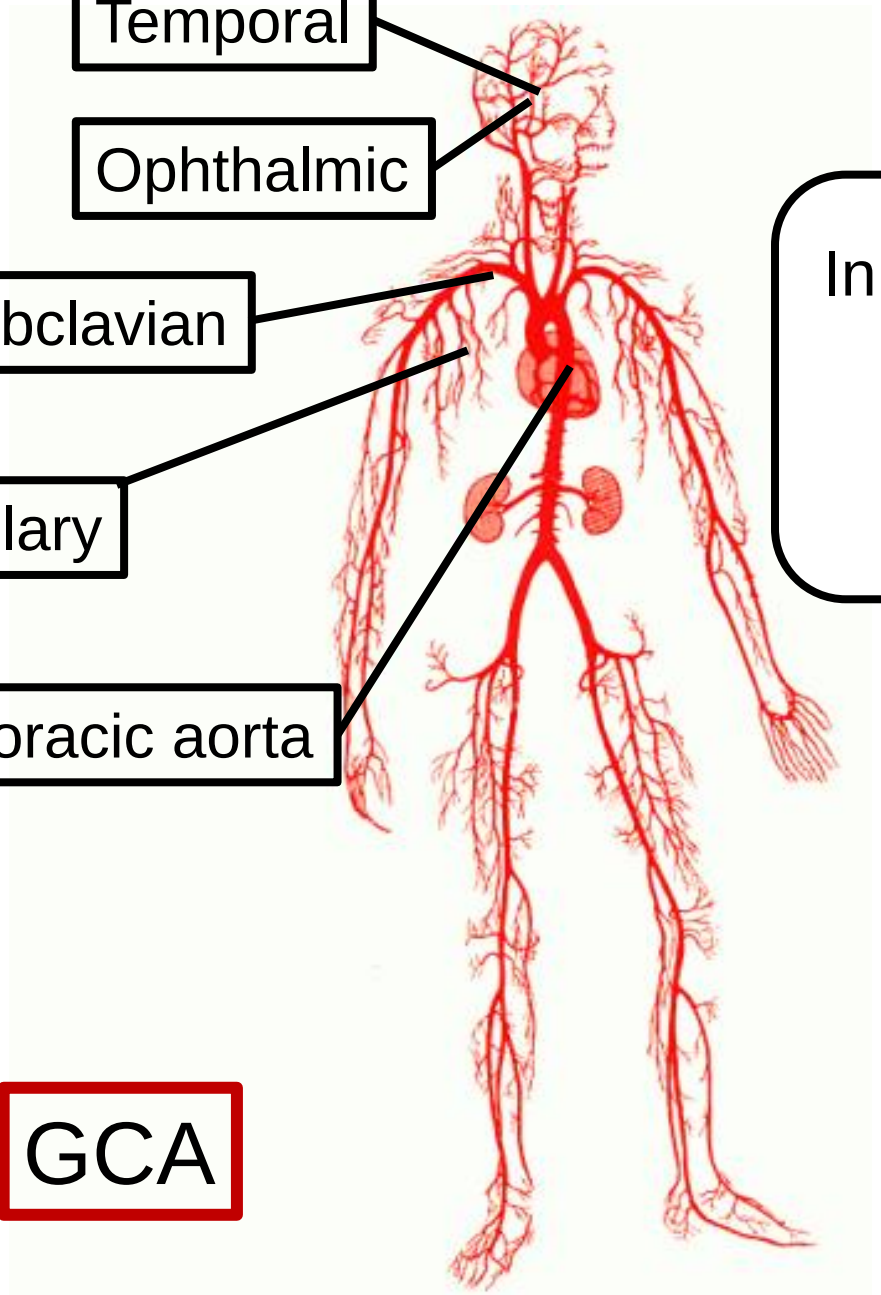
Germano, Rheumatology 2014 ~ Boyev, Am J Ophthalmol 1999 ~ Durling, Can J Ophthalmol 2014 ~ Maz, Arth Rheum 2021

DCVAS: Diagnosing GCA



Slide courtesy of Peter Grayson

20-80% have large vessel involvement (aorta and branches)



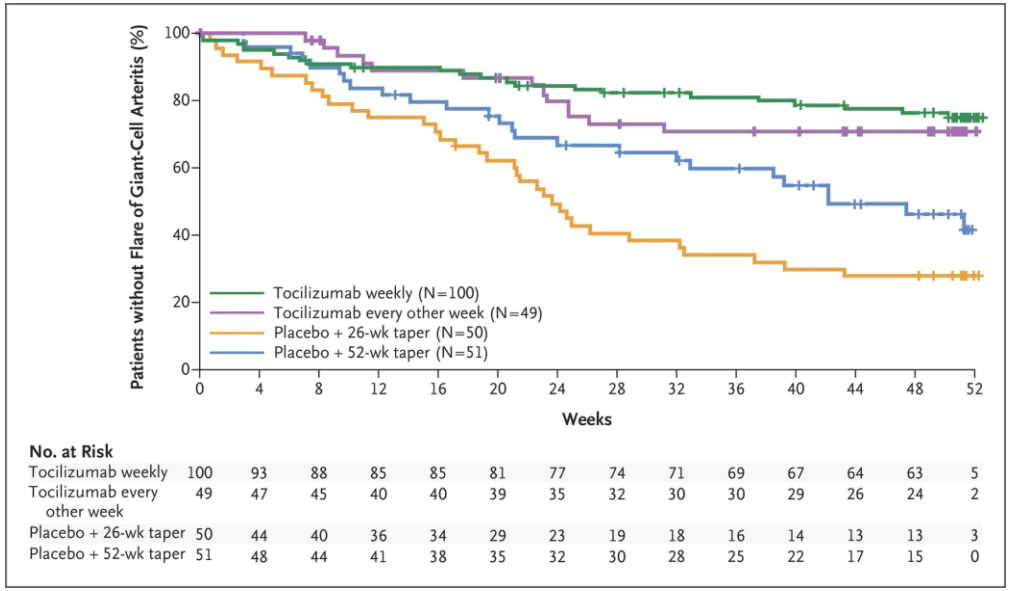
GCA

In patients with suspected GCA and negative TAB (AND) in newly diagnosed GCA, we conditionally recommend **non-invasive vascular imaging of the large vessels**

Maz, Arth Rheum 2021 ~ Koster, Rheumatology 2018

Lab Testing and Treatment

- No antibody ☹
- Utility of ESR and CRP
  - In a study of 177 biopsy proven GCA patients, elevated CRP and ESR were ~87% and 84% sensitive (respectfully) for positive results on TA biopsy
- Until 2017, high dose glucocorticoids (pulse in vision threatening disease) were mainstay of therapy
- GIACTA trial→ approval of tocilizumab (IL-6 blockade) for GCA
- Sustained remission @ 1 year 17% for prolonged pred vs 56% weekly TCA



Kermani, Semin Arth Rheum, 2012
Kermani, J Rheum, 2015

Case Presentation
Back pain and weight loss

- 58 year old custodian for a local school c/o progressive fatigue, lower back pain, and 15 lb weight loss
- Back pain: constant, 4/10, worse with use
- Denied: scalp tenderness, headache, changes in vision, jaw claudication, fevers, chills, or night sweats
- Examination: paraspinal tenderness
- Labs showed iron deficiency anemia
- C-scope normal so sent for CT C/A/P

Case Presentation

- “There is concentric thickening of the aortic wall, involving the ascending aorta, aortic arch, descending aorta, and abdominal aorta, with mild stranding and edema. Minimal atherosclerotic disease is seen. Bilateral hydronephrosis is also seen.” IMPRESSION: “These findings are suspicious for vasculitis such as giant cell arteritis
- More labs: ESR 54 mm/hr; CRP 4.0 mg/dL; ANCA-negative
- Dx: LV-GCA and started on prednisone
- 2 weeks later: c/o increasing weakness, hypomania from prednisone so MTX is added (pre-GIACTA) and prednisone is tapered rapidly over a month
- Lab tests off prednisone: ESR 90 mm/hr, CRP 8.1 mg/dL

Now what??!!!— We got another CT

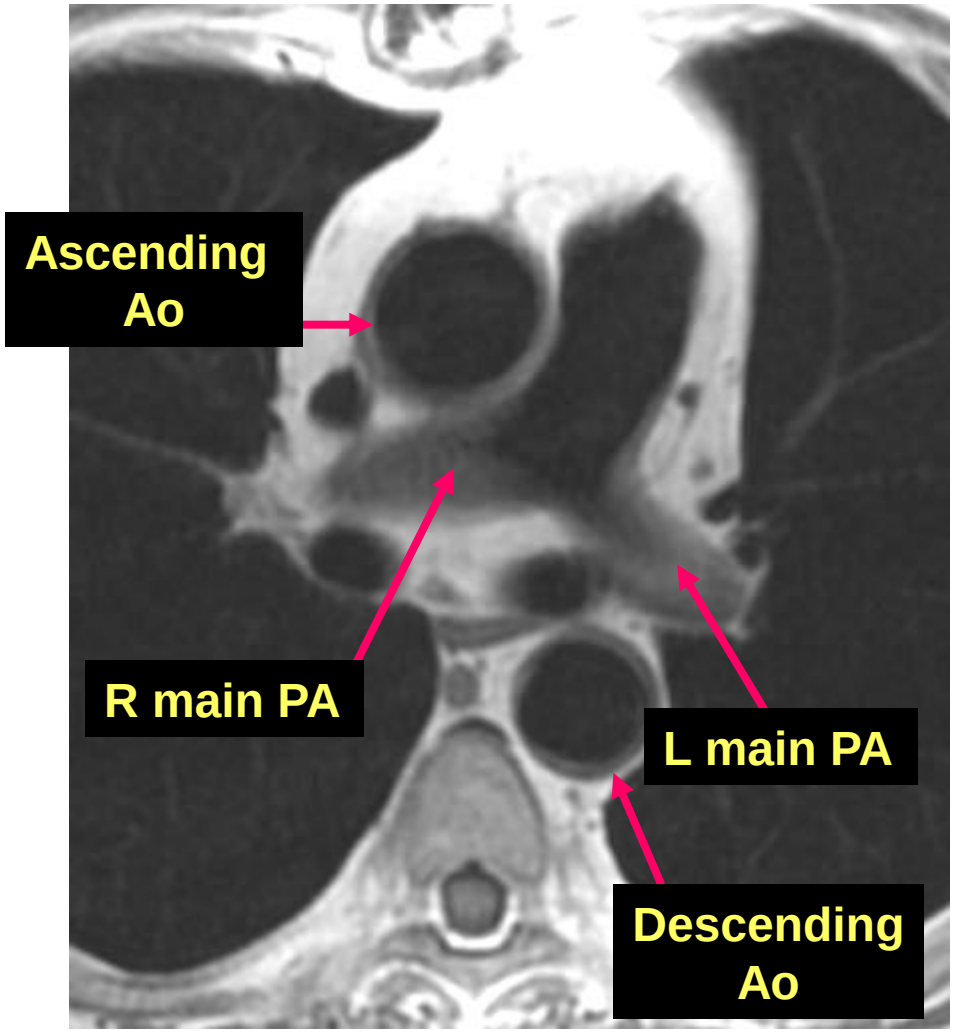
Helpful

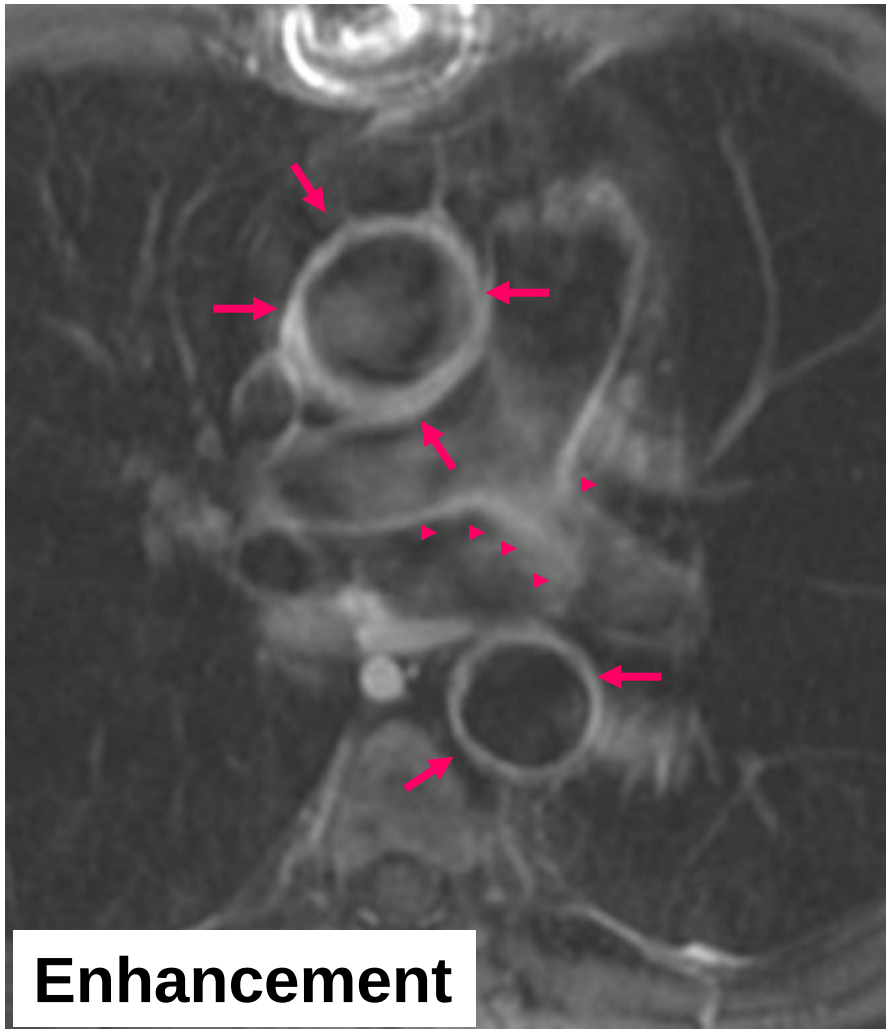
- There is wall thickening of the descending aorta and the upper abdominal aorta.
- There is fairly prominent soft tissue stranding and thickening surrounding the aorta.
- This is most prominent adjacent to the aortic arch and proximal descending aorta.
- This also surrounds the proximal neck arteries

Confusing

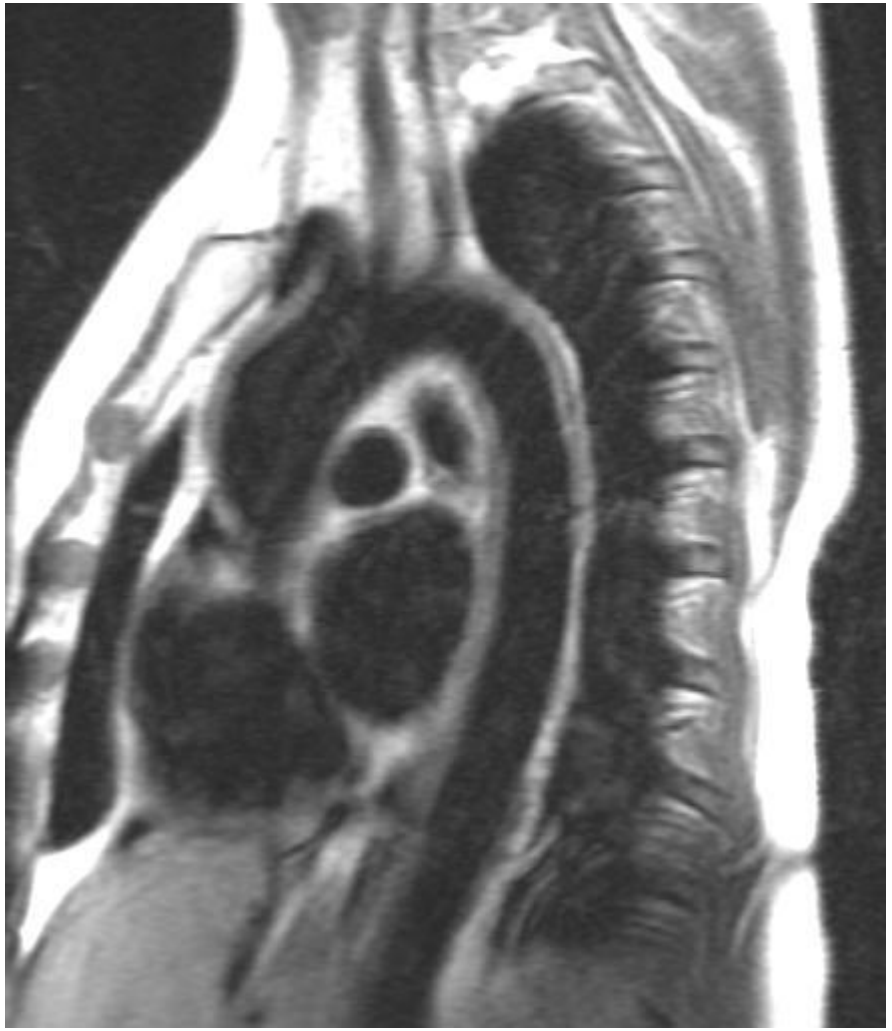
- Moderate pericardial effusion
- Bilateral pleural effusions
- Diffuse soft tissue surrounding both kidneys, in the subcapsular and perinephric space.

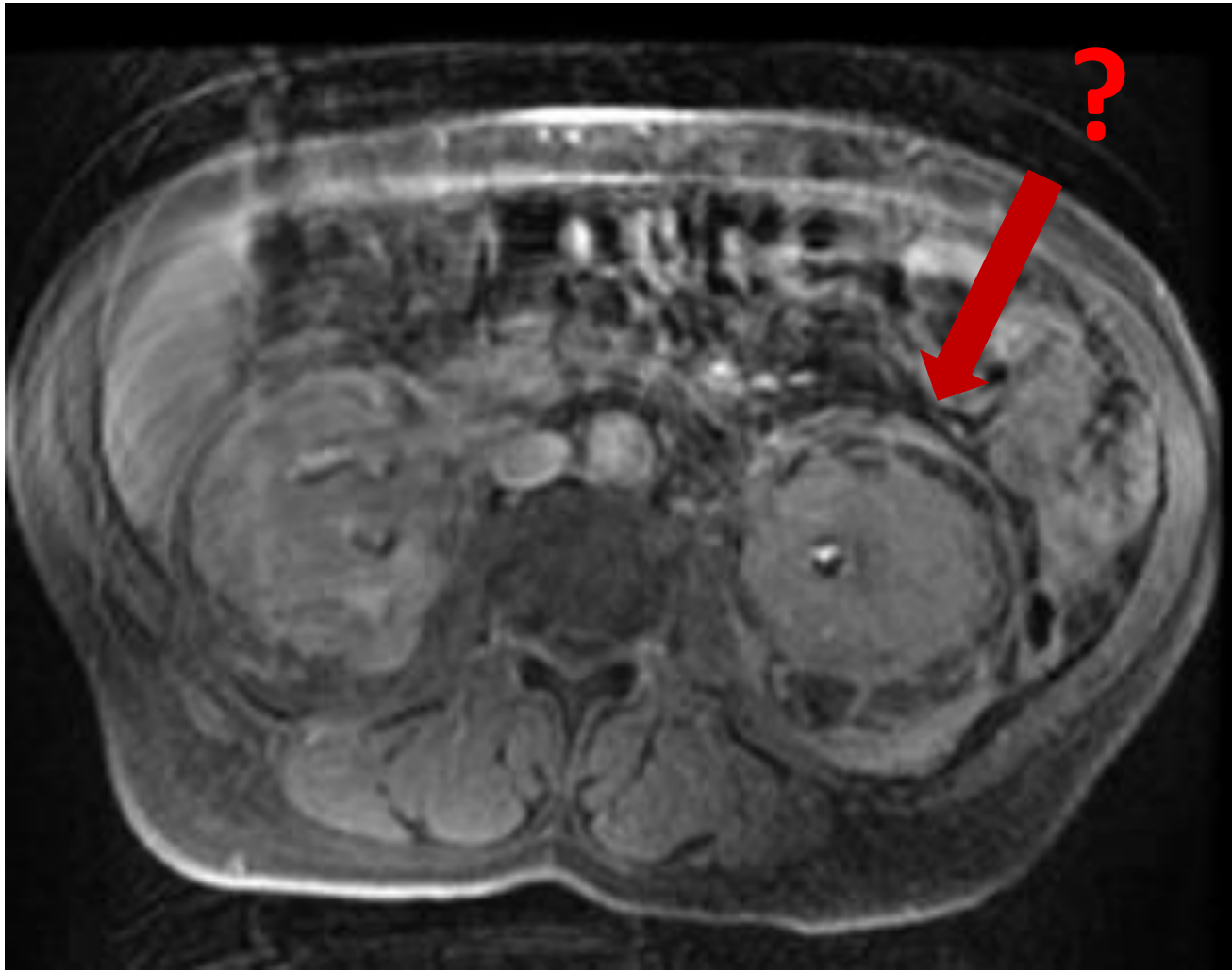
Large Vessel Vasculitis: Contrast MRI





Thickening of thoracic aortic wall





Images courtesy of Phil Seo

Erdheim-Chester Disease: Clinical Manifestations

- **Bone** (95%): Mild, persistent juxta-articular pain, particularly in the lower extremities
- **Cardiac** (57%): Valvular abnormalities, peri-aortic fibrosis, pericardial thickening/effusion
- **Pulmonary** (46%%): Pleural thickening/effusion, ground glass opacities, lung cysts
- **Retroperitoneum**: Rind-like lesion surrounding the kidneys (“Hairy Kidney Sign”)
- **CNS**: exophthalmos, xanthoma, pituitary, cognitive impairment

Erdheim Chester Disease: Fast Facts

- An abnormality of histiocytes, now classified as a malignancy
- Disease manifestations are caused by infiltration of histiocytes into specific organ systems
- The most common presenting symptom is bone pain
- Can be associated with fibrosis around the aorta, pleura, and pericardium.
- V600E BRAF mutation may be diagnostic in 50% of patients
- Vemurafenib for patients with the BRAF mutation; interferon-α for patients without the mutation

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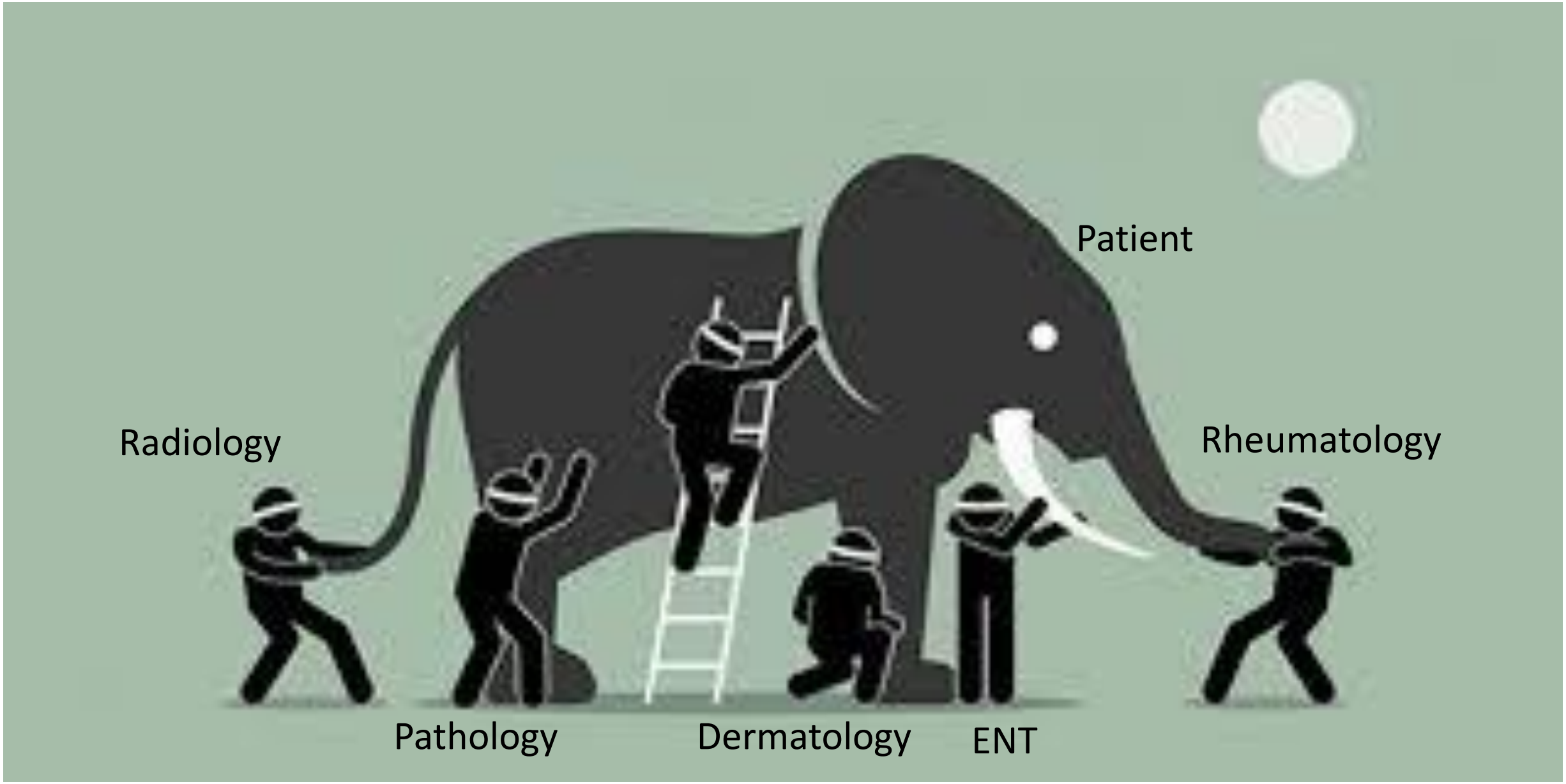
Patient
Radiology
Rheumatology
Pathology
Dermatology
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QUESTIONS/ACKNOWLEDGEMENTS

- MY FELLOWS
- MY PATIENTS
- MY MENTORS

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