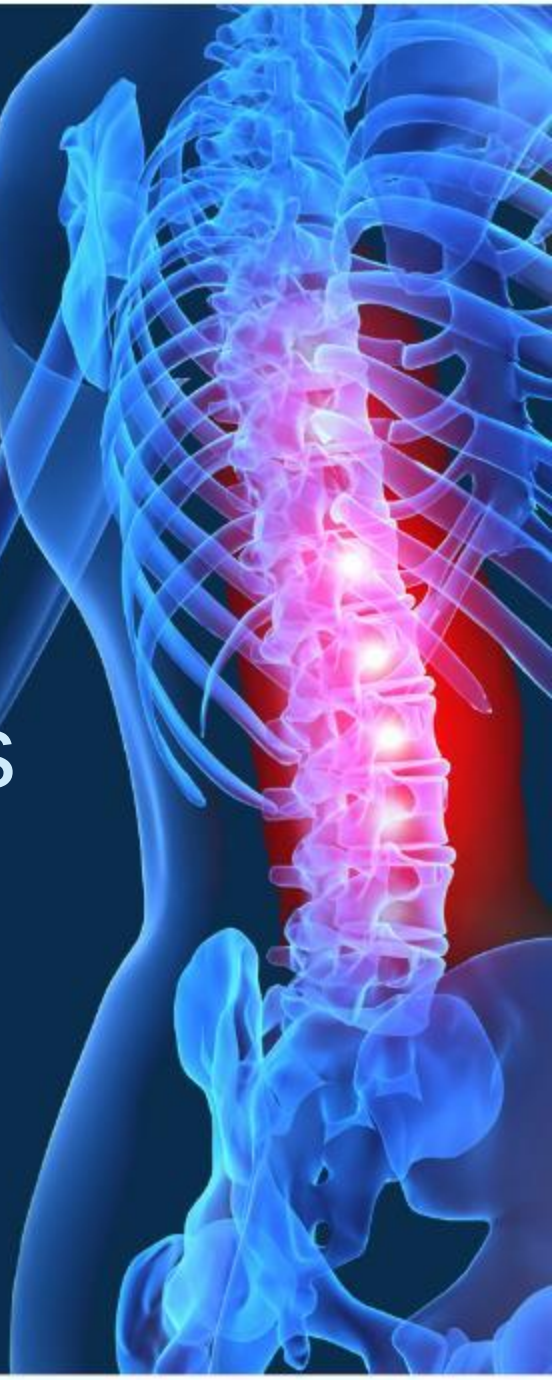
Annual Rheumatology & Therapeutics Review for Organizations & Societies



Vasculitis Pearls

Learning Objectives

- Identify significant but less recognized disease
- Features in common forms of systemic vasculitis
- Recognize important clinical mimics of vasculitis
- Apply strategies to lessen treatment risks in vasculitis

- Which of the following is NOT a feature of giant cell arteritis (GCA) ?
  - A. Cough
  - B. Increased liver function tests (LFTs)
  - C. Thrombocytopenia
  - D. None of the above – they are all features

Consider GCA in an older patient with unexplained cough

LFTs (alk phos, AST) occur in 25-35% of GCA patients

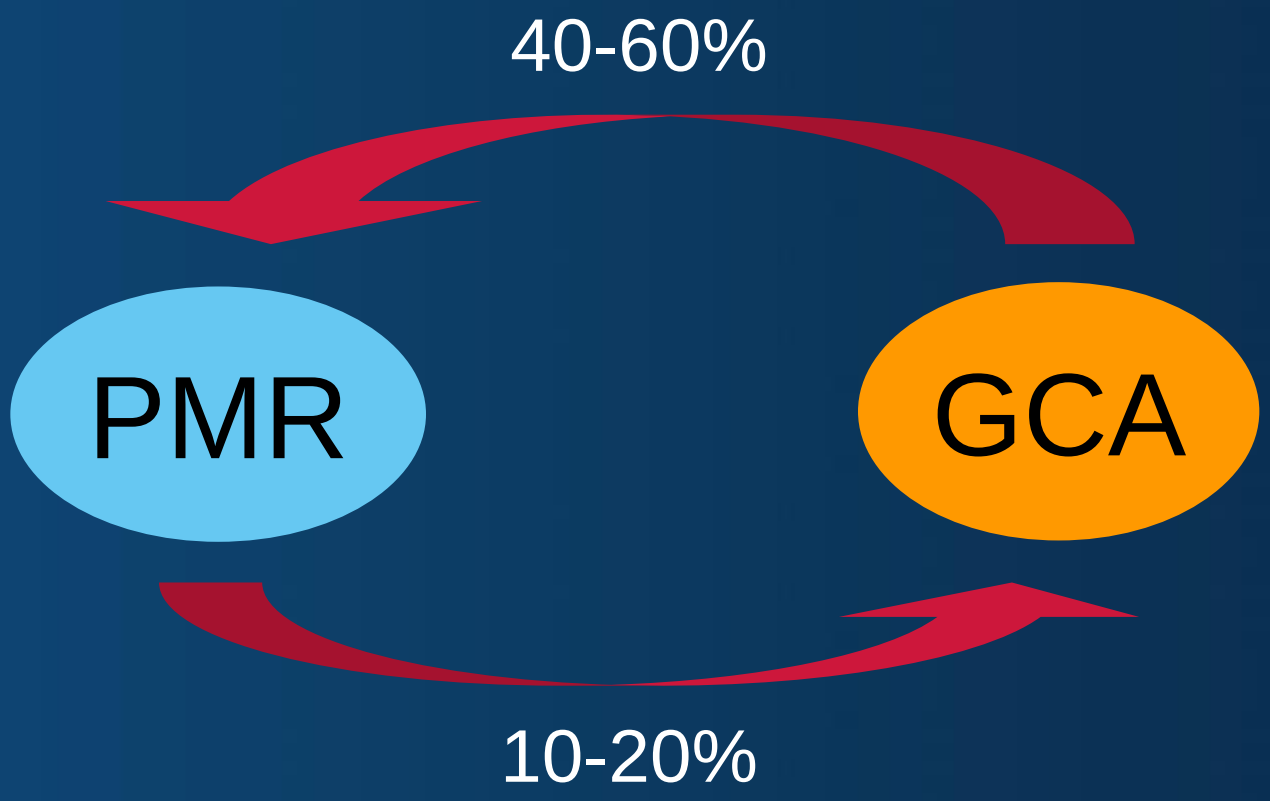
Leukopenia and thrombocytopenia are not disease-related features of a primary vasculitis

If present consider other causes

You have been taking care of a 76-year-old woman with polymyalgia rheumatica (PMR). She has been on the internet and is very worried about her risk of GCA and vision loss.

- True or false:
  - It is very unlikely that she would develop GCA associated with vision loss.

FALSE



Greatest Concern in Giant Cell Arteritis:

- Cranial ischemic complications - Tissue ischemia due to vessel occlusion

- Visual loss - 14% (6-42%)
- Stroke - 3-8%
- Tongue ischemia
- Scalp ischemia

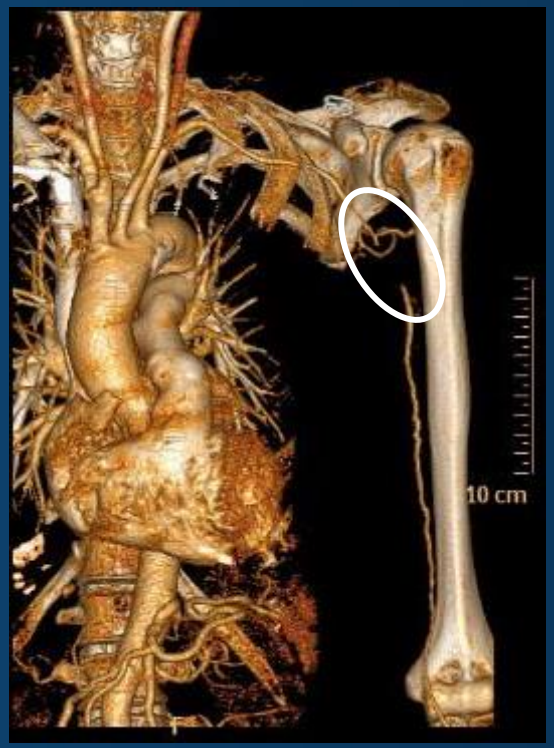
- 73 patients where PMR preceded GCA
- 20% developed ischemic complications (16 visual features, 3 stroke)

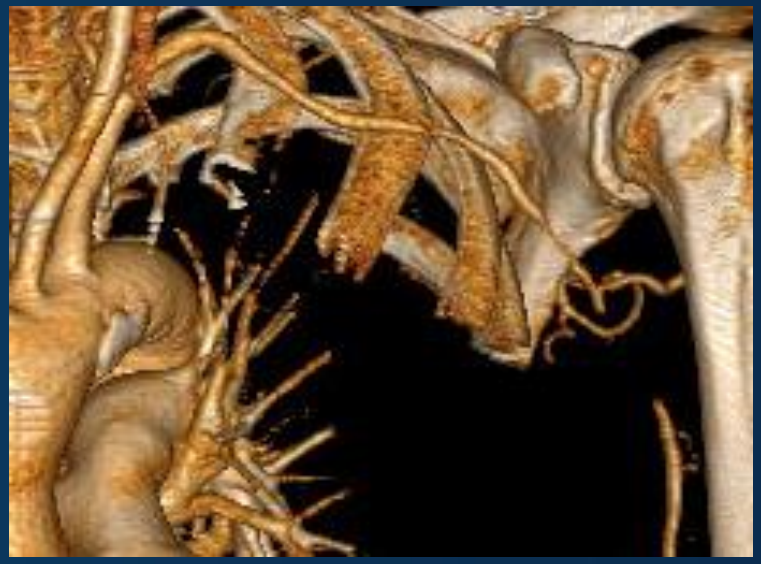
Onset of GCA can occur after PMR and may not be benign

Hernández-Rodriguez et al. Medicine 2007;86:233

You have been caring for a 73-year-old woman who you diagnosed with giant cell arteritis on the basis of prior headache, increased ESR, and jaw claudication. She did well on prednisone but now comes to see you with R arm pain on shampooing her hair. You note a decreased pulse.

CT arteriogram reveals

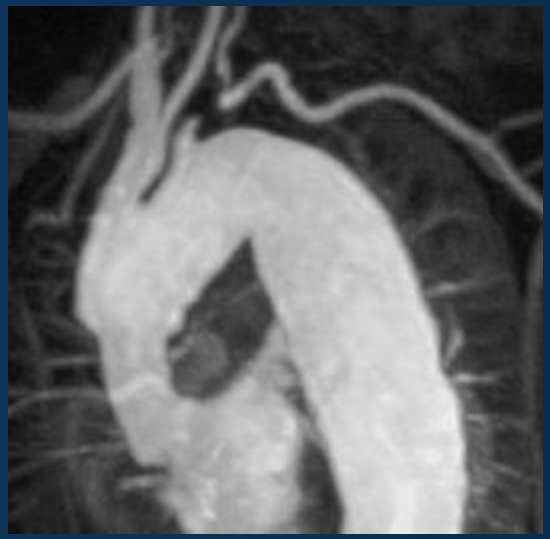




- True or false:
  - This lesion is not compatible with giant cell arteritis and she likely had Takayasu arteritis all along

FALSE

Large Vessel Disease is Common in GCA



- 27% of GCA patients had large vessel complications
  - 13% large-artery stenosis
  - 18% aortic aneurysm

} subclavian, carotid, iliac

Thoracic aortic aneurysms in GCA:

- 18 x more likely than the general population
- Are associated with decreased survival

Thoracic aortic aneurysms are common in GCA, they can occur late, and they are an important cause of mortality

Evans et al. A & R 1994; 37:1539, Evans et al. Ann Intern Med 1995; 122:502
Nuenninghoff et al. A & R 2003; 48:3522 and 3532

Polymyalgia Rheumatica

Cranial Disease

GCA

One disease
Multiple phenotypes

Systemic / Inflammatory Disease

Large Vessel Disease

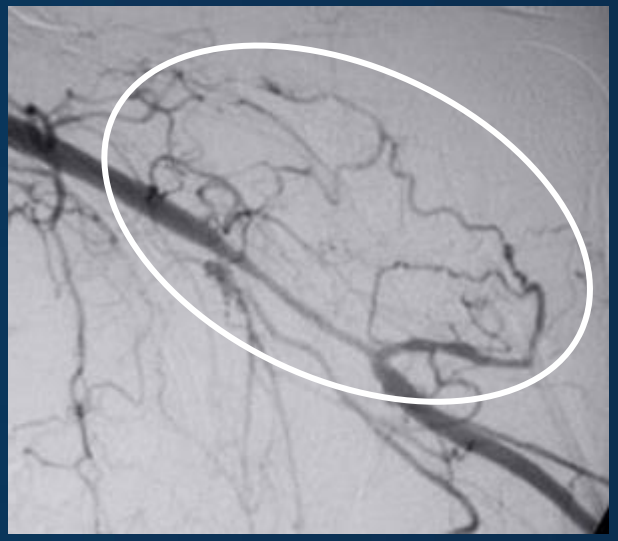
In Managing the 73-year-old Woman with GCA and Axillary Artery Stenosis

- True or false:
  - You should advise her that revascularization will be necessary in the future

FALSE

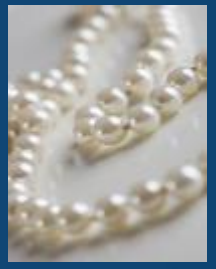
The presence of a vascular lesion should not be the sole indication for vascular intervention

Collateral vessels commonly form around upper extremity stenoses



For What Indications Is Vascular Intervention Often Considered in Large Vessel Vasculitis?

- Indications for stenotic lesions:
  - Renal artery stenosis (medically uncontrolled hypertension, renal insufficiency)
  - CNS: TIA / cerebral ischemia / stroke
  - Angina
  - Severe limb claudication affecting quality of life
  - Bowel ischemia / infarction
- Indications for aneurysmal disease:
  - Aortic aneurysm thoracic / abdominal
  - Aortic root / valve replacement



Vascular intervention for large vessel disease should be based on symptoms, signs, and location

- For which of the following medications is there evidence of benefit inpreventing cranial ischemic complications in giant cell arteritis ?
  A. Methotrexate
  B. Aspirin
  C. Infliximab
  D. Tocilizumab

Aspirin (81 mg daily) should be given to all patients with GCA who do not have a contraindication

Role of Acetylsalicylic Acid (ASA) in GCA

- 175 patients retrospectively reviewed for cranial ischemic complications (CIC)
  - ASA treated patients were 5x less likely to have CIC prior or after diagnosis
  - CIC developed in 3% of ASA-treated patients vs 13% (P=0.02)
- Only 10 patients would need to be treated with ASA to prevent one CIC

- 143 patients retrospectively reviewed for ischemic complications
  - 16% on therapy had an ischemic event compared to 40% not on therapy
  - no increase in risk of bleeding complications
- In patients without contraindications, these data support the addition of ASA 81mg daily to prednisone in GCA

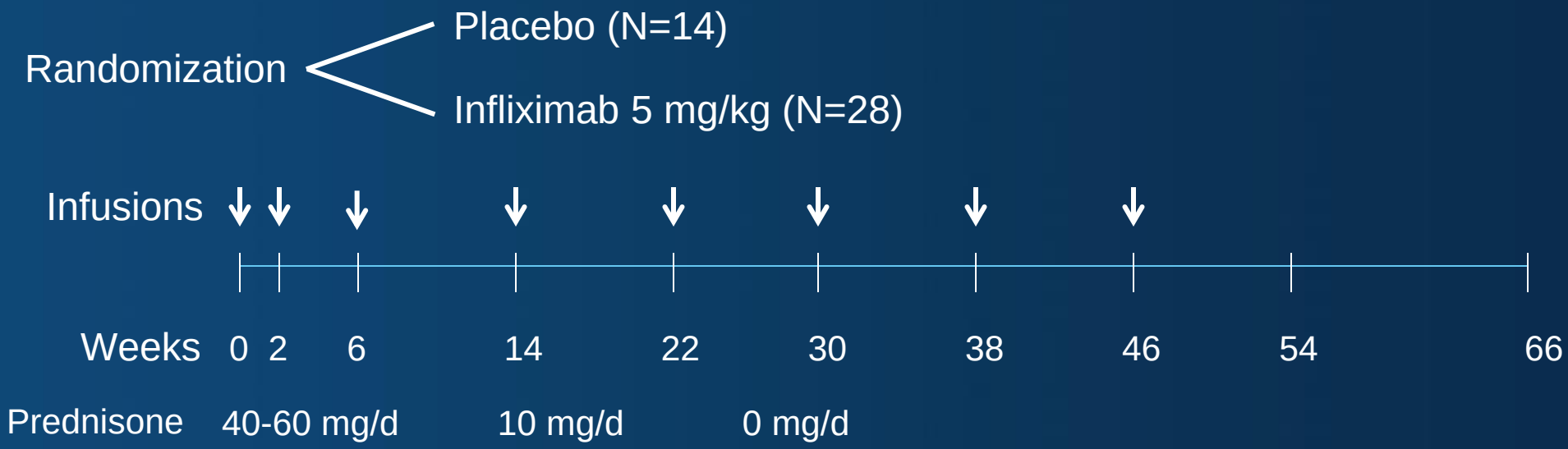
Lee et al. Arthritis Rheum 2006;54:3306
Nesher et al. Arthritis Rheum 2004;50:1332
(Supportive data also in Takayasu – de Souza et al. Circ J 2010; 74:1236)

Methotrexate (MTX) in Giant Cell Arteritis

- Methods:
  - Meta-analysis of:
    - Jover et al. Ann Internal Med 2001;134:106
    - Hoffman et al. Arthritis Rheum 2002;46:1309
    - Spiera et al. Clin Exp Rheumatol 2001;19:495
- Results:
  - Have to treat 4 patients with MTX to prevent first relapse
  - Have to treat 11 patients with MTX to prevent a cranial relapse
  - MTX use was associated with a reduction in cumulative steroid dose
  - MTX did not reduce frequency of prednisone side effects
- Limitations:
  - Very different study designs and relapse definitions
  - Does not take into account the impact of rare but life threatening MTX toxicities
- Absolute reduction in relapse by MTX is at best very modest
  Decision to use MTX must weigh risk against small margin of benefit

Mahr et al. Arthritis Rheum 2007; 56:2789

Infliximab in Giant Cell Arteritis



- Relapse-free through week 22: infliximab = placebo (p=0.651)
- Infection: infliximab (71%) > placebo (56%)

Infliximab does not reduce relapse in GCA

Hoffman et al. Ann Intern Med 2007; 146:621
Similar results also found in PMR (Salvarani et al. Ann Intern Med 2007;146:631)

Tocilizumab in Giant Cell Arteritis

Experience with tocilizumab is currently based solely on case reports

	GCA
Christidis et al. 2011	1
Seitz et al. 2011	v5
Beyer et al. 2011	2
Sciascia et al. 2011	2
Salvarani et al. 2012	2
Vinit et al. 2012	1

	GCA
Besada et al. 2012	1
Unizony et al. 2012	7
Lurati et al. 2012	1
Işik et al. 2012	1
Ashraf et al. 2013	1
Total	24

- Overall a beneficial response has been observed
- What does reduction of acute phase reactants mean with this agent ?
- 1 report of active vascular inflammation seen on histology despite treatment with tocilizumab
  - 2nd report in Takayasu arteritis patient

Efficacy of anti-IL-6 in GCA is currently unknown
A randomized trial is being conducted in GCA

www.clinicaltrials.gov
Unizony et al. AC&R 2012;64:1720
Xenitidis et al. Ann Med. 2013;45:357

A 23-year-old woman with Takayasu arteritis comes to the ER with profound dyspnea. She is frothing at the mouth and is in florid CHF. On examination: BP 100/60, P 120 regular, CV reveals a prominent S3, she has diminished B/L radial pulses, with full pulses elsewhere.

Which of the following should you do next:

A. Obtain an MRI of her aorta and great vessels
B. Check her ESR and CRP
C. Measure her BP in her lower extremities
D. Perform an echo

SBP 240

Obtain four extremity BP measurements in all patients with Takayasu arteritis (also a pearl for GCA)

Upper extremity measurement may be unreliable due to stenotic lesions

Takayasu Arteritis
Distribution of Vascular Lesions

Vessel	USA (%)	India (%)	Symptoms / Signs
Subclavian	69	59	Arm claudication
Carotid	37	21	TIA, stroke, syncope Visual symptoms
Renal	16	53	Hypertension
Iliac	19	15	Leg claudication
Mesenteric	36	12	Abdominal angina (rare)
Thoracic aorta	46	19	CHF
Abdominal Aorta	37	72	Aneurysm: No symptoms Stenosis: claudication

Hypertension is an Important Cause of Morbidity in Takayasu Arteritis

- Hypertension occurs in 32-93% of Takayasu arteritis patients
- Often secondary to renal artery stenosis
- Important cause of morbidity
  - Contributes to renal, cardiac, and cerebral injury
- Can go undetected
  - BP will not be accurate when measured distal to stenotic lesions
- Treatment must balance reducing BP with flow across stenotic lesions

Which of the following carries the worst prognosis in EGPA (Churg-Strauss) ?

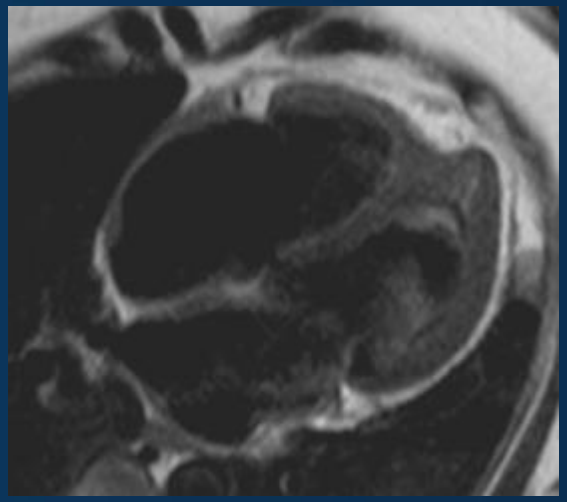
A. Glomerulonephritis
B. Eosinophilic pulmonary infiltrates
C. Cardiac involvement
D. Mononeuritis multiplex

Cardiac involvement is a prominent disease feature in EGPA

Echo should be performed at diagnosis in all EGPA patients

Cardiac features of EGPA can include:

- Pericarditis
- Myocarditis
- Endocarditis
- Valvulitis
- Coronary vasculitis



Dennert et al. A&R 2010 Feb;62(2):627-34

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

- Thought of as having 3 phases
  - (Helpful conceptually but - not seen in all patients often do not occur in sequence)
- Prodromal phase: asthma, allergic rhinitis
- Eosinophilic phase: peripheral eosinophilia eosinophilic tissue infiltrates
- Vasculitic phase:
  - Nerve
  - Skin
  - Lung
  - GI tract
  - Heart

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

- Outcome
  - 96 patients with EGPA
  - Myocardial involvement was the most frequent cause of death
    - Responsible for 9 of 23 deaths (39.1%)
- Treatment strategy based upon manifestations and disease severity
  - Glucocorticoids
    - Effective alone for non-severe EGPA
    - Asthma often limits tapering
  - Cytotoxic therapy
    - Cyclophosphamide should be utilized for life-threatening disease involving the GI tract, CNS, glomerulonephritis, heart

Gayraud et al. Arthritis Rheum 2001, Guillevin et al Medicine 1999
Guillevin et al. Medicine 1999;78:26
Ribi et al. A&R 2008;58:586

A 65-year-old female with GPA (Wegener's) recently had a renal relapse. Her creatinine is normal, UA shows 2+ protein. She is ambulating normally. At her one month visit you note painless B/L symmetric lower extremity swelling with 1+ pitting. She is taking prednisone 60 mg daily and cyclophosphamide and she has been on amlodipine for hypertension.

- Which of the following should you do first:
  1. Stop amlodipine
  2. Prescribe B/L compression hose
  3. Add an ACE to reduce her proteinuria
  4. Have her get a same-day venous duplex
  5. No intervention needed as you will begin tapering the prednisone

- Patients with GPA (Wegener's) are at increased risk of venous thrombotic events (DVT and PE)
- (PS: So are MPA and EGPA)

- 180 patients in the Wegener's granulomatosis etanercept trial (WGET)
- Higher rate of DVT/PE compared to other groups
- Most were during/within 2 months of active disease

Study	DVT / PE Rate
WGET	**7.0**
General Population	0.3
JHU Lupus	1.0
RA Etanercept	0.3

- Remember DVT/PE in GPA (Wegener's)

----- also -----

- If a patient with GPA has a DVT/PE – look for active disease

Merkel P et al. Ann Intern Med 2005;142:620

A 55-year-old male with MPA has had disease of the skin, lungs, nerve, and kidneys (creatinine 2.5 mg/dL, UA 2+ protein, (-) blood). He is 4 months into treatment with cyclophosphamide and you are deciding today whether to switch him to azathioprine.

- At today's visit, chest CT is clear, creatinine 1.0 mg/dL but he has persistent:
  - Fatigue
  - Foot drop
  - Proteinuria
  - Sensory loss

- True or False:
- It is OK to switch him to azathioprine as all of his current features can be seen as a result of damage

TRUE

- Clinical features similar to active disease may be due to damage, infection, medication toxicities, or other causes

Remember - In MPA – And Really in All Forms of Vasculitis What Looks like Disease May Not Be

- New clinical features:
  - Characteristic features are NOT always indicative of activity
    - Pulmonary infiltrates (infection, MTX pneumonitis)
    - Hematuria (cyclophosphamide bladder injury)
- Always consider: infection or medication side effect
- Persistent clinical features:
  - Differentiate active disease from chronic damage
    - Renal: creatinine may not go down and proteinuria may persist
    - Nerve: persistence of motor and sensory deficits is common
    - Sinonasal: persistence of symptoms (GPA, EGPA)
    - Persistent radiographic changes: lung, orbit, sinus (GPA, MPA, EGPA)

- You are planning to treat a patient with cyclophosphamide for 3 months. You should counsel your patient that his risk of bladder cancer lasts:
  - A. Until he stops the cyclophosphamide
  - B. For 10 years
  - C. Lifelong ←

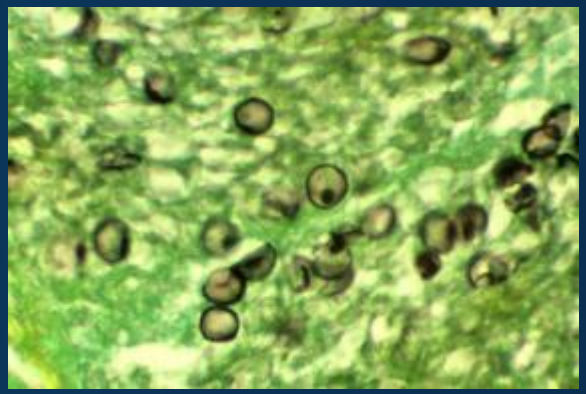
- The risk of bladder cancer in cyclophosphamide treated patients should be considered lifelong

- Which of the following is the most effective test for detecting bladder cancer in cyclophosphamide treated patients:
  - A. Urinalysis ←
  - B. Urine cytology
  - C. Bladder CT

- Urinalysis is the best test to identify CYC-treated patients at risk of developing bladder cancer

Cyclophosphamide – Strategies for Toxicity Reduction

- General - limit duration of exposure to 3-4 months
- Urothelial protection
  - Daily CYC - Take at once in the AM, fluids to maintain a dilute urine
  - Intermittent CYC – MESNA
- Bladder cancer monitoring
  - Urinalysis to detect non-glomerular hematuria and urine cytology
  - Cystoscopy for non glomerular hematuria or atypia
- Cytopenia prevention - CBC every 1-2 weeks
- *Pneumocystis* prophylaxis
  - Trimethoprim/sulfamethoxazole
  - Alternative agents:
    - Pentamidine
    - Dapsone
    - Atovaquone



True or False:

- Your patient has switched from cyclophosphamide to methotrexate, Pneumocystis prophylaxis should be continued **TRUE**
- Your patient relapses – methotrexate is stopped and rituximab is given, Pneumocystis prophylaxis should be continued **TRUE**
- Pneumocystis occurs in ~10% of vasculitis patients on prednisone + another immunosuppressive and prophylaxis should be given (Yes - Including rituximab !)

- What about the risk of combining trimethoprim sulfa (T/S) and methotrexate ?

OK Dose to prevent Pneumocystis

T/S DS three times a week
T/S SS once a day

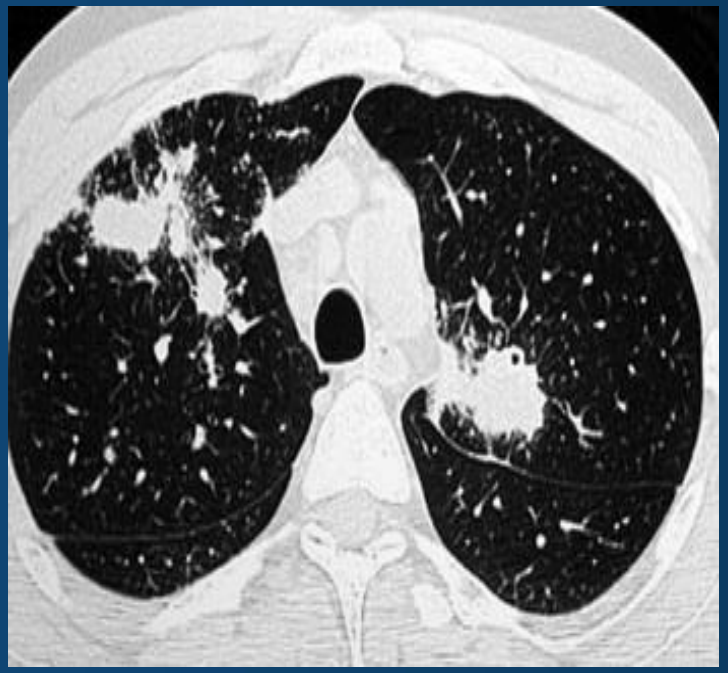
Can be combined with MTX with monitoring

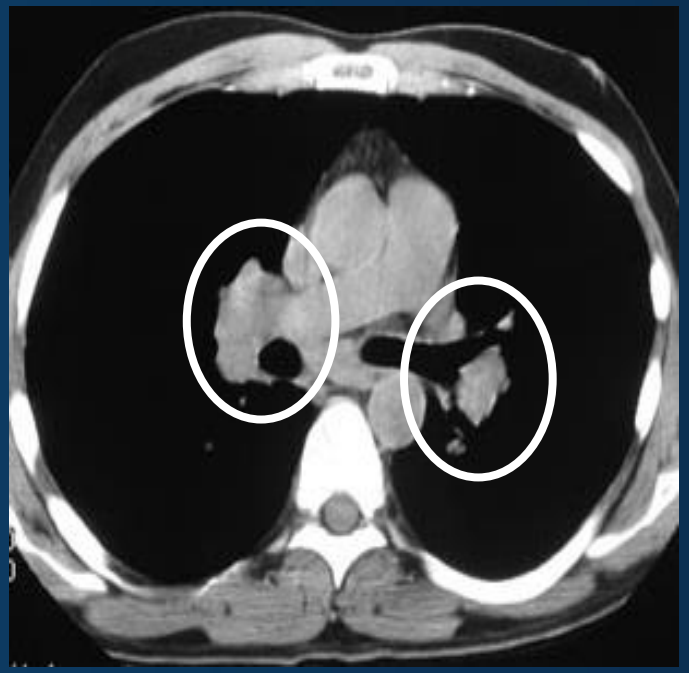
Dose to treat infection (UTI)

T/S DS BID

Reports of fatal pancytopenia

45-year-old male presents with 3 month history of cough. Otherwise feels well - no sinus symptoms, fevers, arthralgias, rash, weight loss.
Examination completely unremarkable
Labs: CBC, chemistries, LFT, UA all normal, pANCA (+)
Chest CT:





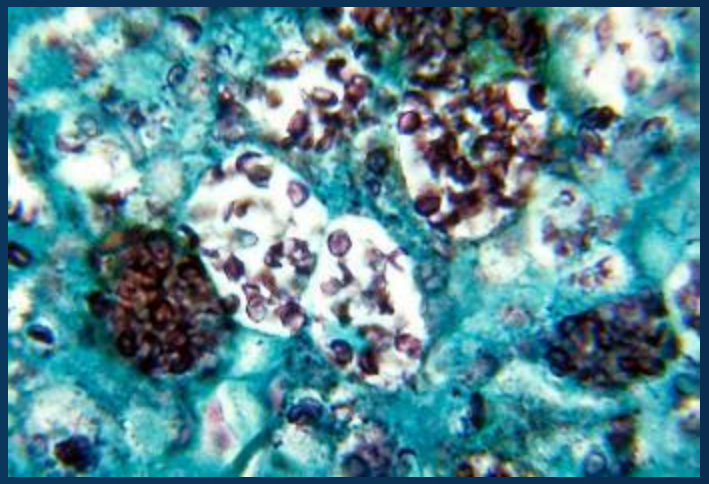
- True or False:
  - There is a high likelihood that this patient has granulomatosis with polyangiitis (Wegener's)

FALSE

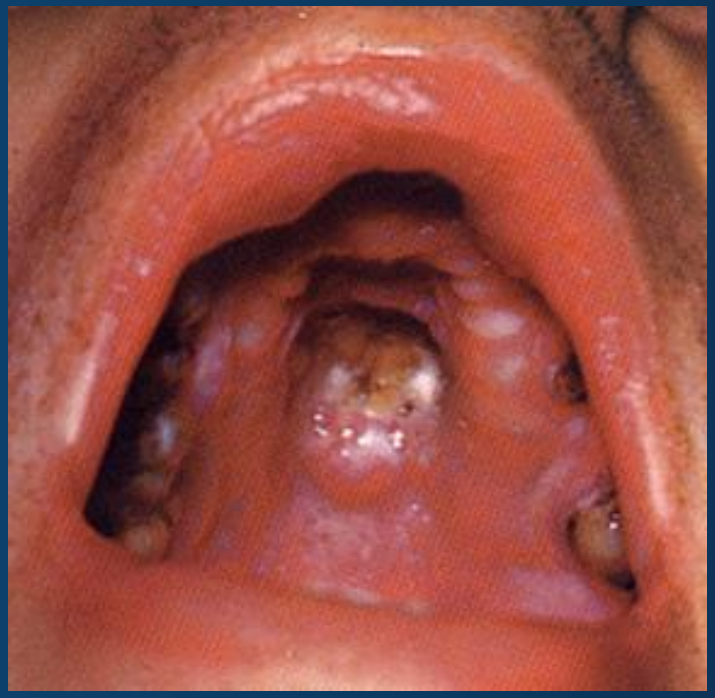
Lymphadenopathy is Uncommon in GPA (Wegener's)

- Lymphadenopathy should raise concern for:
  - Lymphoma
  - Infections (mycobacteria, histoplasmosis)
  - Sarcoid

- So what did the patient have ?
- Histoplasma capsulatum



A patient is referred to you from ENT for the question of GPA (Wegener's). There are no other features other than the lesion pictured below. Labs are notable only for (+) PR3-cANCA.



- True or False:
  - This patient is likely to have GPA (Wegener's)

FALSE

Erosive Lesions of the Hard Palate are Exceedingly Rare in GPA (Wegener's)

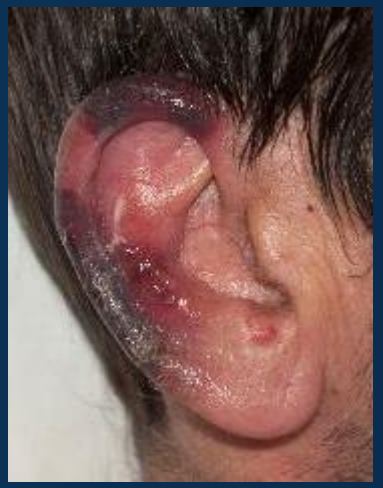
- Hard palate erosions should raise concern for:
  - Lymphoma (extranodal NK / T-cell lymphoma)
  - Invasive infections (fungus, leishmaniasis)
  - Cocaine
- ANCA can be found in cocaine-induced midline destructive lesions
- Reacts to human neutrophil elastase, a serine protease which is structurally and functionally related to PR3, such that (+) PR3-ANCA can be seen

Weisner et al. A & R 2004; 50: 2954

This Same Patient Now Comes Into the ER 2 Months Later with this Lesion

- True or False:
  - You should now conclude this patient has GPA (Wegener's)

FALSE

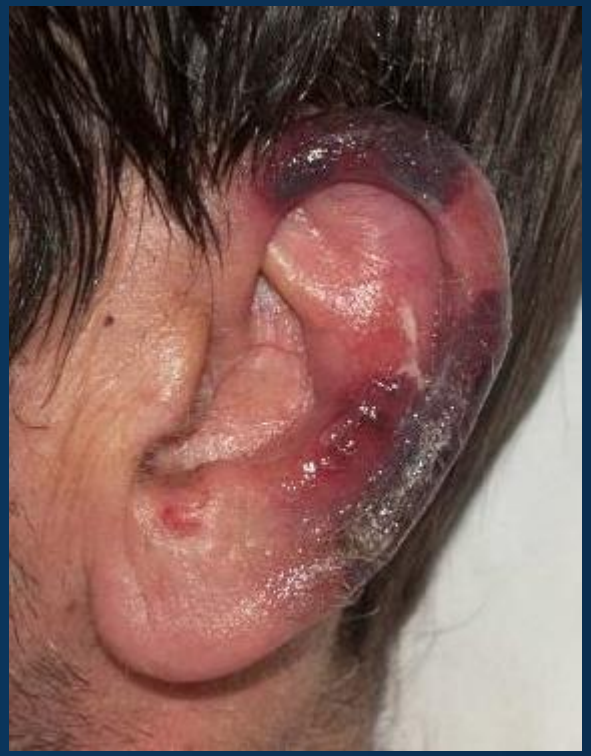


What does he have ? → Levamisole-induced cutaneous necrosis

Levamisole induced disease is an important mimic of vasculitis

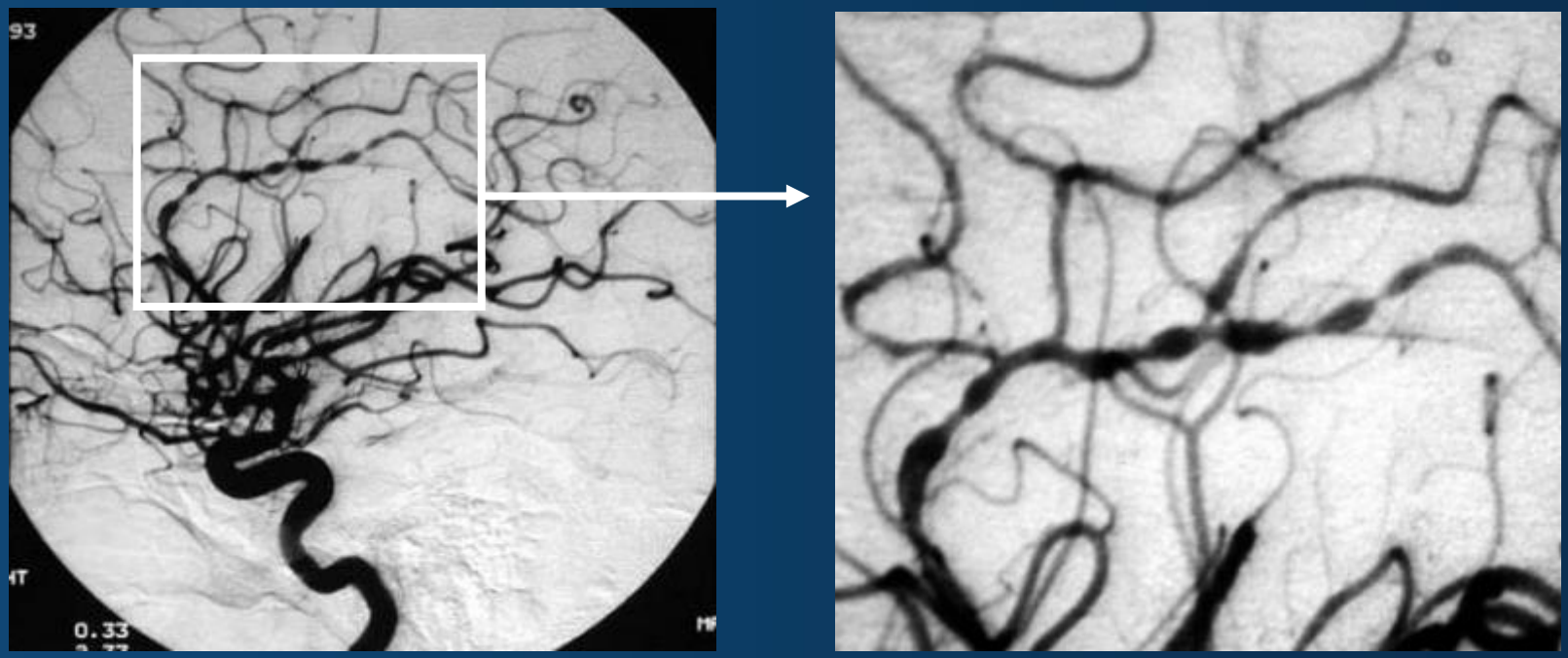
Levamisole-Induced Cutaneous Necrosis

- Introduced in 1960's as an antihelminthic agent
- Found to have immunomodulatory properties
  - Studied in RA, colon CA
- Since ~2004 used as a cutting agent for cocaine (found in 70-100%)
- Linked findings
  - Leukopenia and specifically agranulocytosis
  - Cutaneous necrosis
    - vasculitis/thrombotic vasculopathy
    - predilection for the earlobe (> 50%)
  - Autoantibodies: pANCA, LAC, ACL
  - Features of cocaine use



Zhu et al. Ann Intern Med 2009; 150:287
Farhat et al. Arch Derm 2010;146:1320
Gross et al. Clin Rheumatol 2011;30:1385

A 26-year-old non-pregnant woman was well until she developed sudden onset of a severe headache. She was exercising when this began. She is on no medications and denies recreational drug use. Her examination is non focal. Spinal fluid reveals 0 wbc, protein 31 (normal). Brain MRI is normal but MRA is abnormal. Dye arteriogram reveals:



- True or False:
  - This patient is very likely to have Primary CNS vasculitis

FALSE

LP is Almost Always Abnormal in CNS Vasculitis (>95%)

- What diagnosis does she most likely have ?

- Reversible Cerebral Vasoconstriction Syndrome (RCVS)
  - Women > Men
  - Sudden onset of severe “thunderclap” headache
  - Associated conditions
    - Pregnancy
    - Drugs: pseudoephedrine, cocaine, amphetamines
    - Misc: exercise, intercourse
  - Normal LP
  - Abnormal arteriogram that demonstrates reversibility
  - Can result in stroke or hemorrhage
  - Treatment – calcium channel blockers - verapamil

An Abnormal Arteriogram Does Not Always = CNS Vasculitis

Settings Where an Abnormal CNS Arteriogram has been Reported

- RCVS
- Malignant hypertension
- Subarachnoid hemorrhage
- Childbirth
- Other causes of vasospasm
- Sarcoidosis
- Cholesterol emboli
- Myxoma
- TTP
- Moyamoya
- Anticardiolipin antibody
- Fibromuscular dysplasia
- Neurofibromatosis
- Pseudoxanthoma elasticum
- Atherosclerosis
- (Infections)
- (Drugs)
  - Amphetamines
  - Ephedrine
  - Cocaine
  - Allopurinol
  - Ergotamines

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

	RCVS	PACNS
Sex	F>M 2-3:1	F=M
Onset	Acute (seconds to minutes)	Subacute to chronic
Headache	Acute and severe Thunderclap	Insidious, dull progressive
CSF	Normal or near-normal	Abnormal 88-95% (wbc, protein)
CT/MRI	Normal, watershed infarcts Small SAH	Abnormal 90% Infarct gray, white matter
Angiogram	Multiple areas of stenosis and dilation - reversible	Often normal Cutoffs, irregularities Changes like RCVS

Calabrese et al. Ann Intern Med 2007;146:34