VASCULITIS ACOI 2019

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Disclosures

- NONE

Learning Objectives

- Clinical features and presentations of commonly tested vasculitis
- Differentiate between different vasculitic conditions based on presentation
- Management and treatment of vasculitis

Case 1

- 71 year old female with hypertension and hyperlipidemia presents for new onset right sided throbbing headache and weight loss of 10 pounds in the past 2 weeks.
- On exam she has tenderness over the right temporal artery otherwise unremarkable
- Labs reveal ESR 87, HgB 11.3, MCHC 27
- What is the diagnosis?
  - *CVA*
  - *GCA*
  - *Migraine*
  - *Cancer*

Giant Cell Arteritis

- Granulomatous inflammatory vasculopathy that affects medium and large arteries
  - *External carotid branches (temporal and occipital arteries), ophthalmic, vertebral, distal subclavian, axillary arteries, and thoracic aorta*
- Peak incidence: 70-80 years old
- Women > men
- Incidence is highest in whites of northern European decent
- HLA-DR4 and HLA-DRB1 association

Chacko JG, Chacko JA, Salter MW. Review of Giant cell arteritis. Saudi J Ophthalmol. 2014; 29(1):48-52.
Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. N Engl J Med. 2014; 371:50-57.

Giant Cell Arteritis - Symptoms

- Headache: new esp. over temples
- Jaw claudication (most specific)
- Scalp tenderness - ask whether combing or brushing the hair hurts
- Ear pain
- Neck pain
- Intermittent low-grade fever
- Weight loss
- Malaise
- Vision loss esp. transient monocular visual loss
  - *Short posterior ciliary arteries or central retinal artery occlusion*
- Amaurosis fugax
- Diplopia
- Cranial nerve palsies; 3, 4, or 6
- Ischemic myopathy

Chacko JG, Chacko JA, Salter MW. Review of Giant cell arteritis. Saudi J Ophthalmol. 2014; 29(1):48-52.

Giant Cell Arteritis
What labs would you order?

- ESR/CRP: Elevated
- SPEP
- CBC
  - *Thrombocytosis*
  - *Mild normocytic or hypochromic*
- CMP
  - *Increased alkaline phosphatase*

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Back to the Case

- Patient was started on 60mg of prednisone daily and referred to surgery for temporal artery biopsy
- A temporal artery biopsy shows inflammation (left image), which at higher power (right image) consists of multinucleated giant cells.

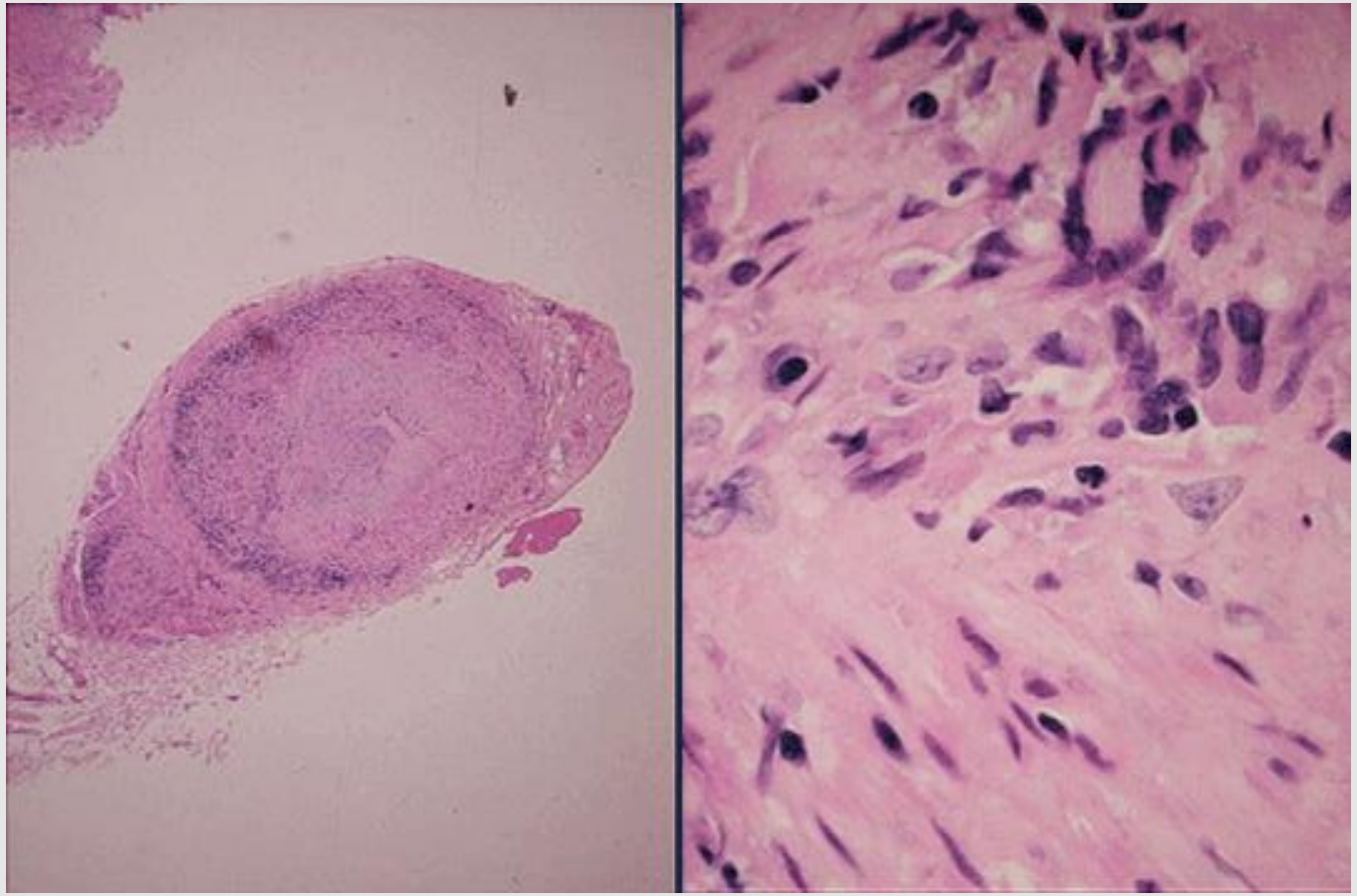

Image: Johns Hopkins medicine GCA case by John Burton

Giant Cell Arteritis – Pathology

- Temporal-artery biopsy should be 1.5 to 2.0 cm in length
- Negative biopsy finding does not rule out giant-cell arteritis; however, biopsy identifies 85 to 95% of cases
- Diagnostic sensitivity of temporal-artery biopsy remains high even after glucocorticoid therapy has been initiated
  - *Sensitivity declines after 2-6 weeks of therapy*
- Characteristic findings: panarteritis, most prominent in the media, composed of CD4+ lymphocytes and macrophages
- Positive bx: inflammation of the vessel wall (**active** arteritis) and those with post-inflammatory alterations (**healed** arteritis)

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Giant Cell Arteritis – Color Doppler ultrasound (CDUS)

- "Halo sign" – circumferential dark area around the vascular lumen, representing mural edema
  - *Measures 0.3 to 2.0 mm, is hypoechogenic, not anechogenic*
- Bilateral temporal artery halo signs is highly specific for GCA
- "Compression sign" – the persisting visibility of the halo during compression of the vessel lumen by the ultrasound probe
  - *Has high specificity for GCA*

UpToDate

Giant Cell Arteritis – Large Vessel Variant

- Consider large vessel involvement in patients suspected to have GCA but have negative temporal artery biopsy and/or CDUS
- Aorta and its first-order branches: carotid, subclavian and axillary
- Aortic arch syndrome-claudication of the arms, absent or asymmetrical pulses, paresthesia, digital ischemia

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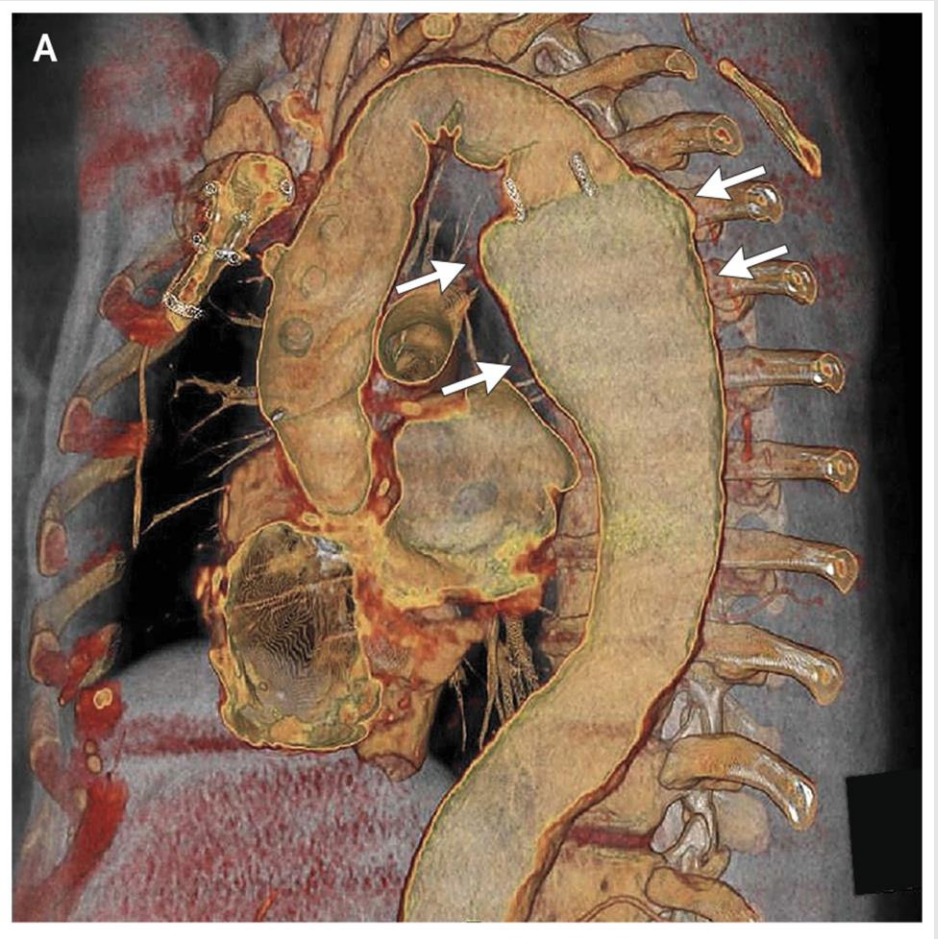
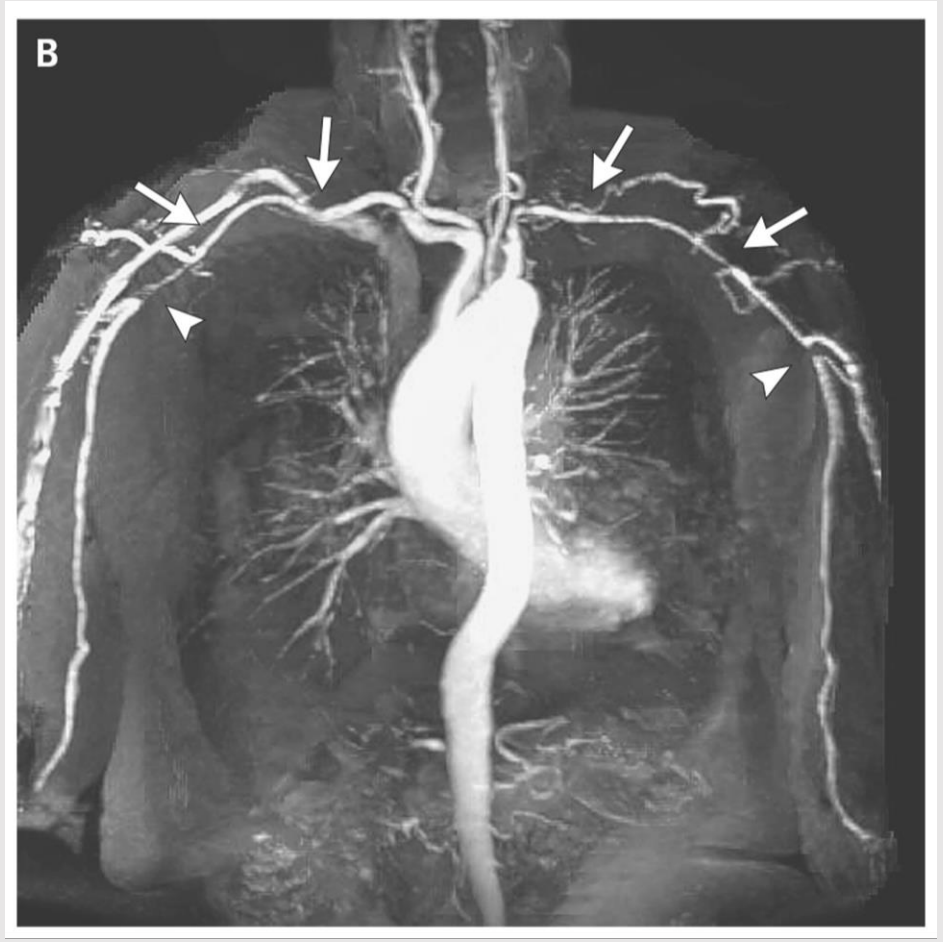
GCA– Large Vessel involvement





Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. N Engl J Med. 2014; 371:50-57.
Images courtesy of Dr. D. Fleischmann (Panel A) and Dr. F. Chan (Panel B), Department of Radiology, Stanford University.

Back to the Case

- Patient's steroids were being tapered when she developed neck, upper back and shoulder aching pain worse in the morning with associated stiffness

- What is in your differential?
  - *Steroid induced myopathy*
  - *Osteoarthritis*
  - *Polymyalgia rheumatic*
  - *Infection*

Giant Cell Arteritis – Polymyalgia Rheumatica

- PMR symptoms often appear during the taper for giant-cell arteritis
- Pain and stiffness in shoulder and pelvic girdle muscles
- Malaise, weight loss, sweats, and low-grade fever
- PMR frequency is 3-10x that of GCA
- Exclude other diagnoses but if signs of vascular insufficiency i.e. claudication, bruits over aa, and discrepant BP readings → high index of suspicion for GCA
- Very steroid responsive which may help in diagnosis

Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. N Engl J Med. 2014; 371:50-57.

Giant Cell Arteritis – Fever/Wasting Syndrome

- Fever and chills (occult presentation-GCA is cause of FUO in up to 15% elderly)
  - *Need to exclude infection, malignancy*
- Malaise, fatigue, anorexia, weight loss
- Night sweats
- Weakness
- Depression

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Giant Cell Arteritis –

Table 1. Classification Criteria for Giant-Cell Arteritis and Polymyalgia Rheumatica.*

ACR classification criteria for giant-cell arteritis, 1990[47]

At least three criteria must be met:

- Age at disease onset ≥50 yr
- New headache, either new onset or new type of localized pain in the head
- Abnormal temporal artery, with tenderness to palpation or decreased pulsation
- Elevated ESR, >50 mm/hr during first hr of testing (Westergren method)
- Biopsy evidence of vasculitis with predominance of mononuclear-cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. N Engl J Med. 2014; 371:50-57.

Giant Cell Arteritis – Treatment

- Glucocorticoids
  - *60mg of prednisone or equivalent*
  - *Pulse steroids for visual changes/loss*
  - *Relief within 12 to 48 hours*
  - *Cannot reverse intimal hyperplasia, may decrease ischemic complications by decreasing edema*
  - *Once clinically stable, decrease dose by 10% q 1-2wks*
- Tocilizumab (anti-IL6)
- ASA?

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Question

- 78 year old female with hx of biopsy proven GCA treated with glucocorticoids then tapered off was doing well for the past 2 years now presents for right sided visual loss and jaw pain with chewing. ESR is 104 What is the next best step?
  a. *Repeat temporal artery biopsy*
  b. *Start Prednisone 60mg daily*
  c. *Start pulse dose of methylprednisolone 500mg daily for 3 days*
  d. *Tocilizumab*

Answer: c. Start pulse dose steroids in the setting of vision threatening disease not 1mg/kg or 60mg daily dosing. May start Tocilizumab therapy in combination with steroids but not alone. Therapy should be initiated immediately therefore waiting for biopsy is incorrect.

Case 2

- 43 year old male presents for shortness of breath, recurrent nosebleeds, fatigue and fever
- On exam, there is bilateral scleritis, ulcers are noted in the nares, scattered wheezes, skin exam is normal
- Labs reveal ESR 68, WBC 13.4, HgB 9.2 , Cr 2.3, with RBC casts on UA
- CXR shows multiple bilateral cavitary infiltrates

Granulomatosis with Polyangiitis (Wegener's)

- Necrotizing granulomatous vasculitis of small arteries of the upper and lower respiratory tracts and glomerulonephritis
- Prevalence: 3/100,000
- More common in people of northern European descent
- Male: female 1.5:1
- Typically present at age 35-55 years
- Rarely occurs before adolescence

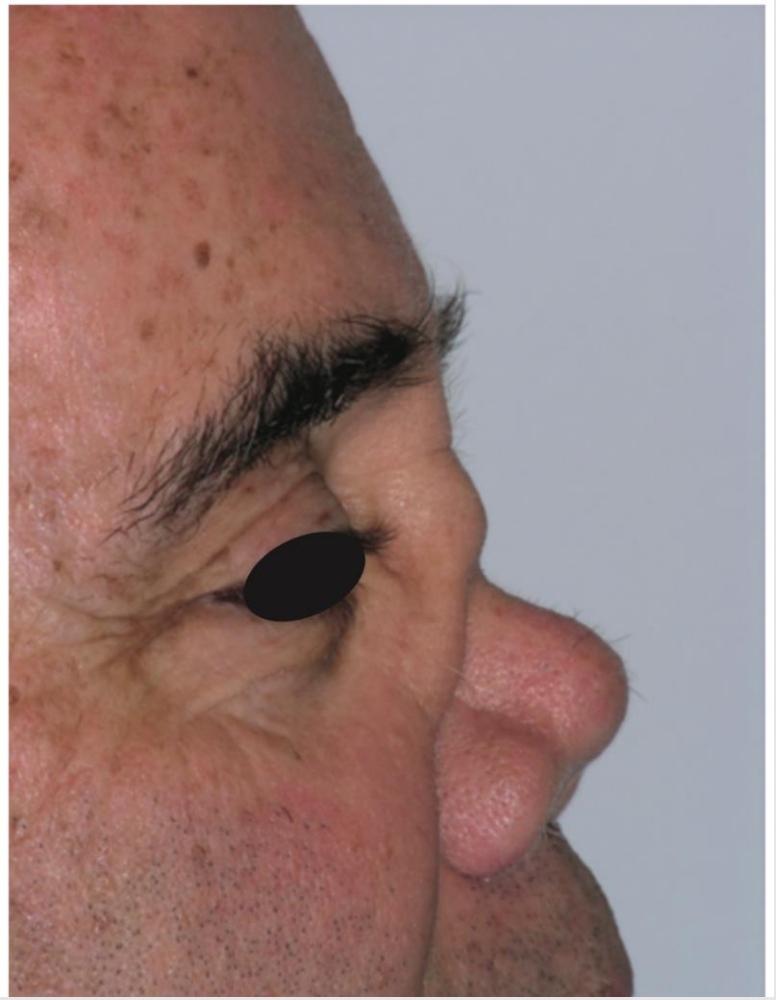
Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019

Granulomatosis with Polyangiitis Main Involvement

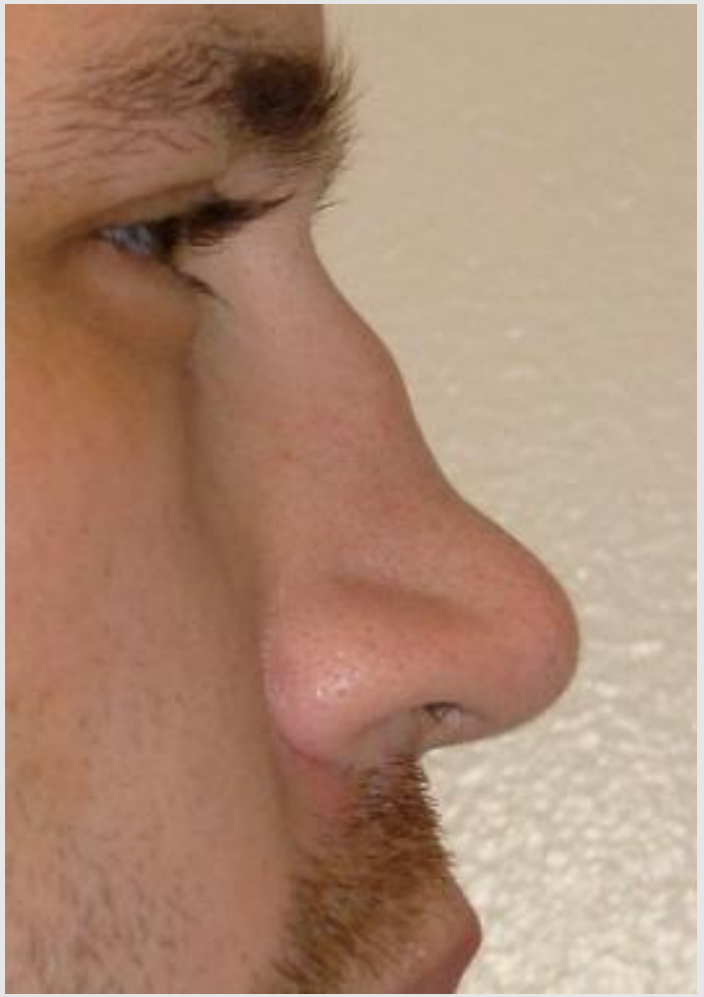
- **Lung:**
  - *Cough, hemoptysis, dyspnea, chest discomfort*
  - *Multiple bilateral nodular cavitary infiltrates*
- **Upper airway:**
  - *Paranasal sinus pain and drainage, purulent or bloody nasal discharge, nasal mucosal ulceration*
  - *Sinuses and nasopharynx reveal inflammation, necrosis, granuloma formation, with or without vasculitis*
- **Kidneys:**
  - *Proteinuria, hematuria, red blood cell casts*
  - *Focal and segmental glomerulonephritis that may evolve into rapidly progressive crescentic glomerulonephritis without immune complex deposition (Pauci-immune)*

UpToDate
Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019

Granulomatosis with Polyangiitis

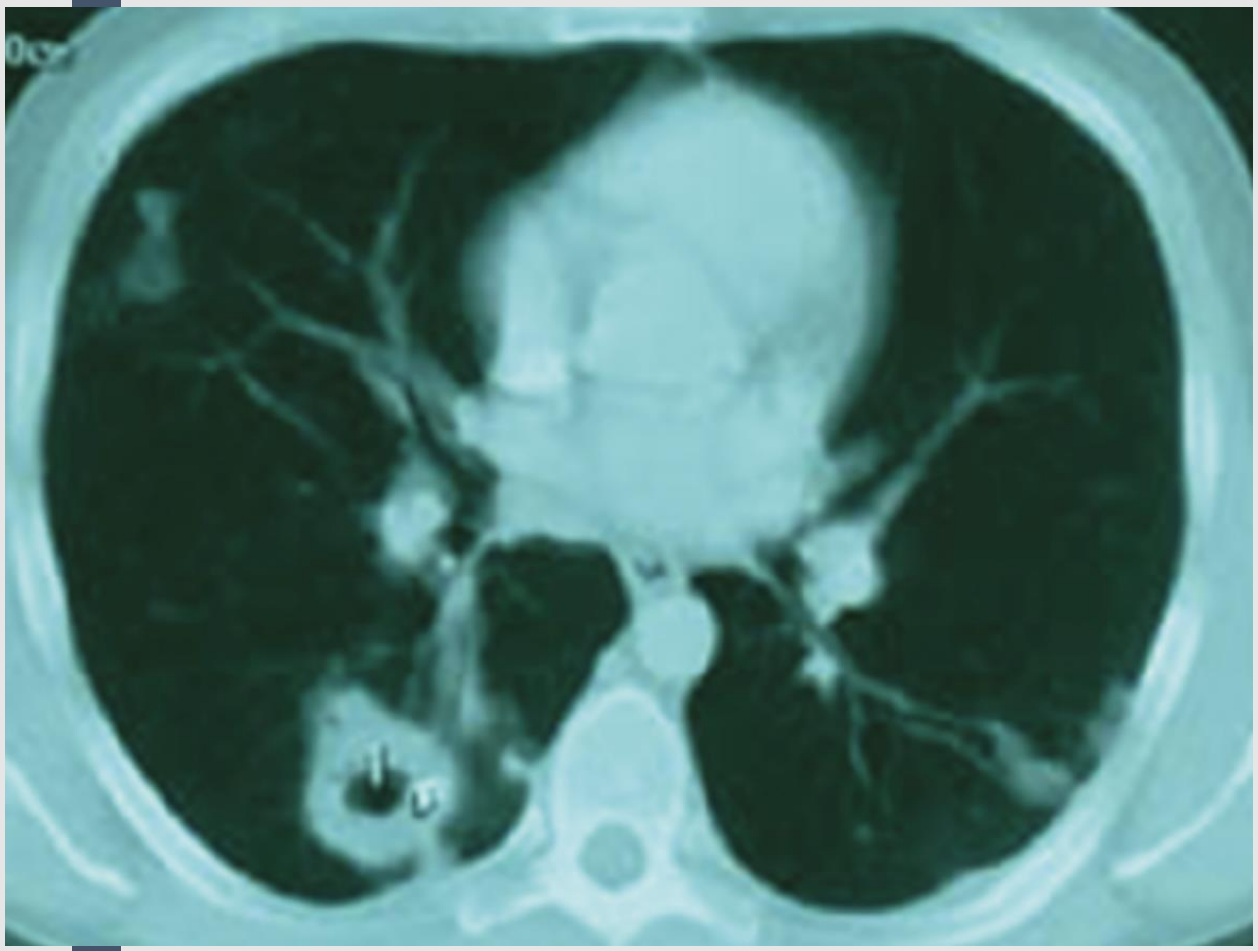


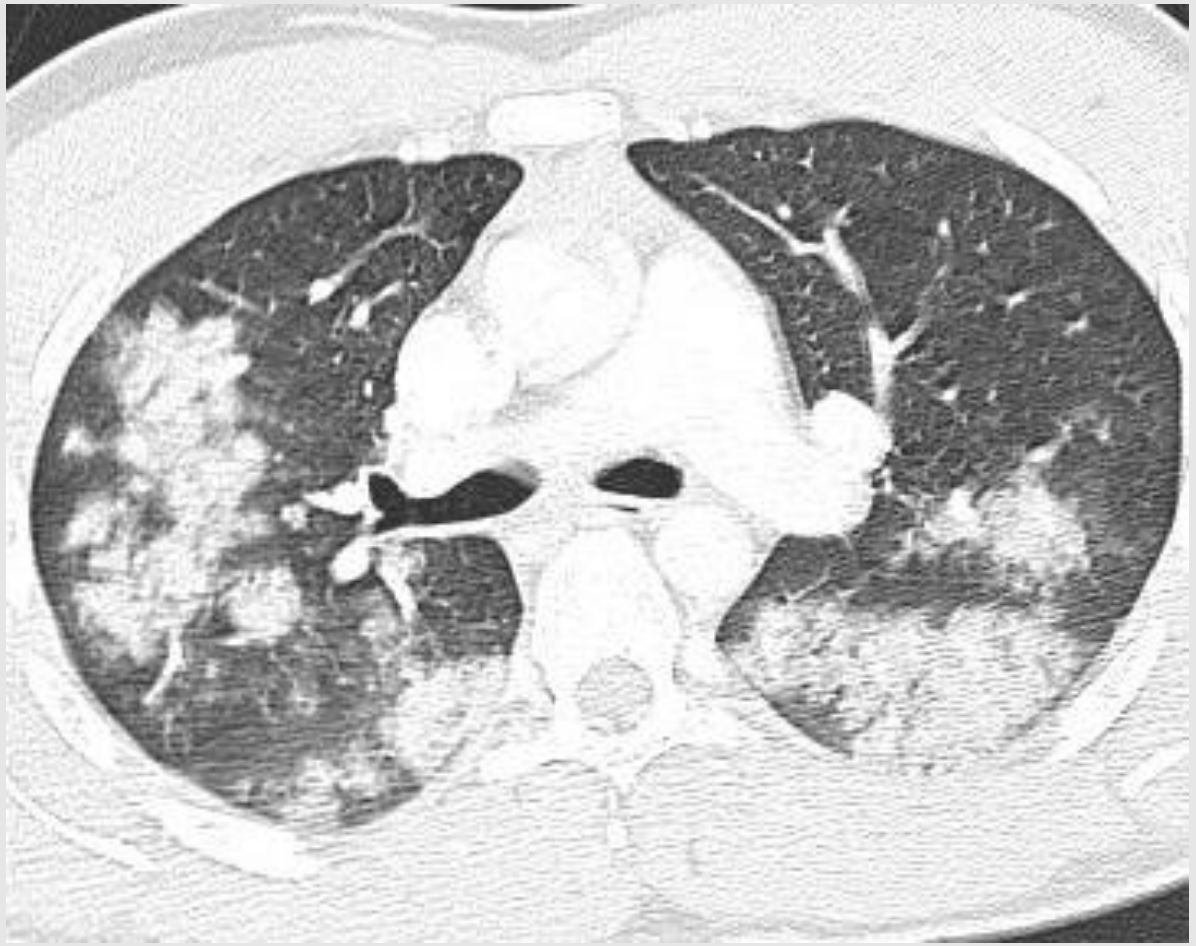
Nasal septal perforation can lead to saddle nose deformity



(Left) Primer on rheumatic diseases, 13th edition
(Right) Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019. Image courtesy of P. Papadopoulos, MD.

Granulomatosis with Polyangiitis





(Left) Primer on rheumatic diseases, 13th edition
(Right) Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019. Image courtesy of the US Government.

Granulomatosis with Polyangiitis Other Manifestations

- Skin lesions: papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules (biopsy shows vasculitis, granuloma or both)
- Cardiac involvement: pericarditis, coronary vasculitis or cardiomyopathy
- Nervous system: cranial neuritis, mononeuritis multiplex, or cerebral vasculitis and/or granuloma
- Constitutional symptoms

UpToDate
Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019

Granulomatosis with Polyangiitis
What other labs would you get?

- ANA?
- RF?
- ANCA?
- PR-3, MPO
- 90% of pts have + C-ANCA and anti-PR3
  - *But in the absence of active ds, the sensitivity drops to 60 to 70%*
  - *Correlation between titers and disease activity/flares is variable*

UpToDate
Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019

Back to the Case

- Labs returned with +C-ANCA and Anti-PR3
- Then underwent renal biopsy which showed pauci-immune crescentic glomerulonephritis
- He was started on dialysis, cyclophosphamide and high-dose steroids

Feature	GPA	MPA	EGPA
ANCA	C-ANCA	P-ANCA	P-ANCA
Antigen specificity	PR3	MPO	MPO
Histology	Leukocytoclastic vasculitis; necrotizing granulomatous inflammation	Leukocytoclastic vasculitis	Eosinophilic tissue infiltrates and vasculitis; granulomas have eosinophilic necrosis
ENT	Nasal septal perforation; saddle-nose deformity; conductive or sensorineural hearing loss; subglottic stenosis	Absent or mild	Nasal polyps; allergic rhinitis; conductive hearing loss
Lung	Nodules, infiltrates or cavitary lesions; alveolar hemorrhage	alveolar hemorrhage	Asthma; fleeting infiltrates; alveolar hemorrhage
Kidney	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis
Eosinophils	Mild eosinophilia occasionally	None	All

SOURCE: Reproduced with permission from Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med 2004;117:39–50.
ABBREVIATIONS: ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

Granulomatosis with Polyangiitis Treatment

- With proper treatment about 75% patients have complete remission
- Most effective therapy for life-threatening disease (pulmonary-renal involvement) is cyclophosphamide or rituximab with high dose glucocorticoids
  - *Cyclophosphamide-related toxicities include: cystitis (at least 30%), bladder cancer (6%), myelodysplasia (2%), high risk of infertility*
- Following induction of remission: maintenance therapy with methotrexate, azathioprine, rituximab, or Mycophenolate mofetil

UpToDate
Primer on rheumatic diseases, 13th edition
Tracy, CL et. al. Granulomatosis with Polyangiitis. Medscape. 2019

Granulomatosis with Polyangiitis Treatment Considerations

- **For mild ds:** methotrexate
- **For pulmonary hemorrhage:** plasma exchange
- **For subglottic stenosis:** intralesional injection of glucocorticoids in combination with endoscopic dilation may avoid the need for more invasive surgical procedures
- TMP-SMX for Pneumocystis jiroveci pneumonia prophylaxis and also to prevent upper respiratory relapse

UpToDate
Primer on rheumatic diseases, 13th edition
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Question

What medication would be a good option for maintenance therapy for our patient?

a. *Low dose cyclophosphamide*
b. *Azathioprine*
c. *Prednisone*
d. *Methotrexate*

Answer: b. Azathioprine; recent guidelines can use rituximab as maintenance therapy. Methotrexate is used as maintenance therapy but should be avoided if CrCl<10. Prednisone and cyclophosphamide are used for induction therapy.

Case 3

- 62 year old male with diabetes, hypertension, hyperlipidemia, coronary artery disease on metformin, lisinopril, hydralazine, metoprolol, aspirin and atorvastatin admitted to the hospital for renal failure
- On exam vitals are stable, lungs are clear, heart RRR, no murmur, 2+ lower extremity edema with macular, purpuric rash on the LEs
- Labs reveal Cr increase from 1.1 to 3.5 over the past month, Hgb 10.5, ESR 113, urinalysis shows RBC and WBC's with casts
- What is in your differential?
  - *Diabetic nephropathy*
  - *Medication induced AKI*
  - *Systemic Lupus Erythematosus*
  - *ANCA Vasculitis*

Drug-Induced ANCA Vasculitis

- Antineutrophil cytoplasmic autoantibodies are directed against certain proteins in the cytoplasmic azurophilic granules of neutrophils and monocytes
- Two testing methods: immunofluorescence assay (sensitive) and ELISA (specific)
- Two patterns of ANCA:
  - *Cytoplasmic (C-ANCA)*
    - Major target is Proteinaise-3 (PR-3)
  - *Perinuclear (P-ANCA)*
    - Major target is the enzyme myeloperoxidase (MPO)

Choi HK et. al. Drug-induced ANCA-Positive Vasculitis. Arthritis &Rheumatism. 2000; 43(2):405-413
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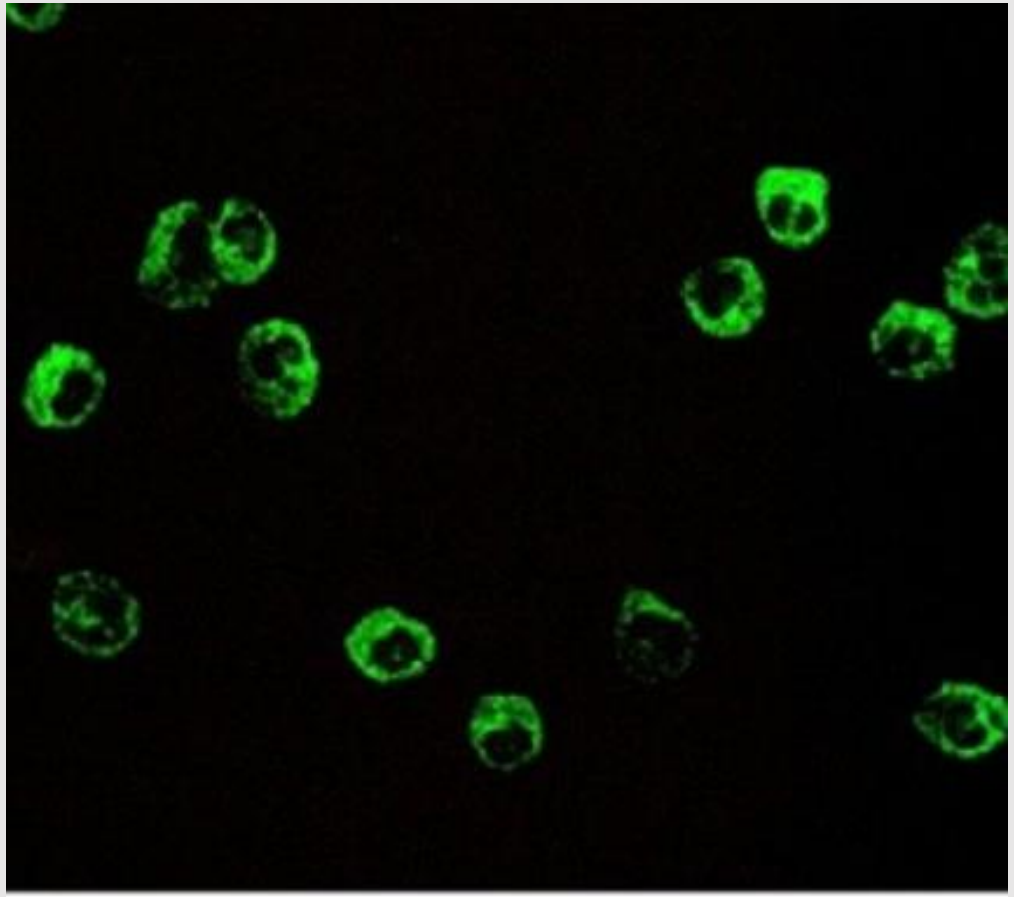
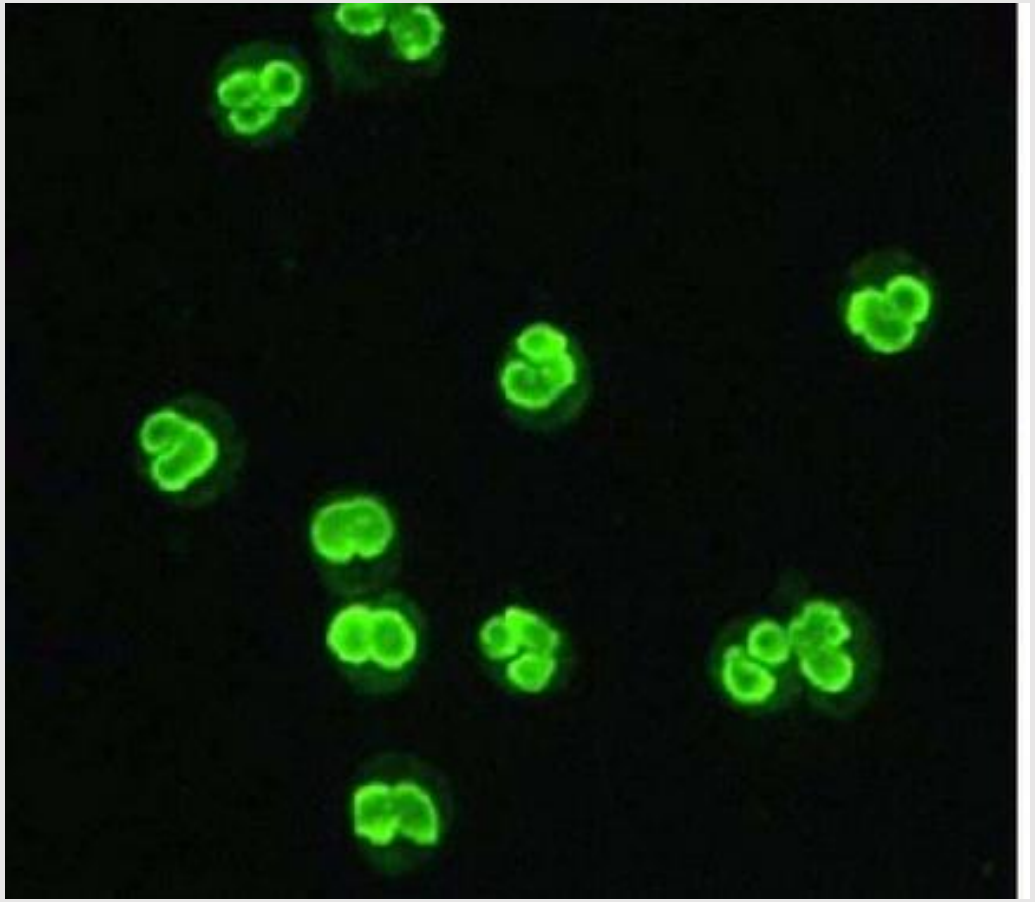
C-ANCA



There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive.

P-ANCA



Staining is limited to the perinuclear region and the cytoplasm is nonreactive.

Schulte-Pelkum J et. al. Novel Clinical and Diagnostic Aspects of ANCAs. J Immunology Research. 2014; 185416.

Drug-Induced ANCA Vasculitis – P-ANCA

- P-ANCA can be associated w/ medications (drug-induced) including:
  - *Hydralazine, propylthiouracil, minocycline, penicillamine, allopurinol, methimazole, carbimazole, isoniazid, sulfasalazine, procainamide, thiamazole, clozapine, phenytoin, rifampicin, cefotaxime, and indomethacin*
- Typically P-ANCA pattern associated with anti-MPO antibody on ELISA if present is helpful and more suggestive of true vasculitis
- Atypical ANCA pattern may be confused with P-ANCA pattern however MPO and PR3 testing is negative
  - *Connective tissue disorders, inflammatory bowel disease, and autoimmune hepatitis*

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UpToDate

Back to Case

- Labs returned with positive P-ANCA and MPO
- Hydralazine was discontinued and systemic steroids were initiated
- Patients renal function continued to decline requiring initiation of hemodialysis
- Renal biopsy was obtained and showed pauci-immune necrotizing and crescentic glomerulonephritis
- Cyclophosphamide was added to his therapy
- Patient eventually had return of his renal function

Drug-Induced ANCA Vasculitis – Digression on Hydralazine

- Hydralazine is one of the most common drugs for treatment of HTN
- Associated with drug-induced lupus and ANCA associated vasculitis (AAV)
- One review of high titer MPO AAV showed 9/10 cases of hydralazine ANCA vasculitis had renal involvement
  - *Second common presentation was skin involvement*
  - *Most patients had both*
- Atypical ANCAs are associated with drug induced ANCA vasculitis

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Short AK, Lockwood CM. Antigen specificity in hydralazine associated ANCA positive systemic vasculitis. QJM. 1995;88(11):775.

Question

- What drug is not associated with drug induced ANCA vasculitis?
  a. *Propylthiouracil*
  b. *Methimazole*
  c. *Minocycline*
  d. *Levaquin*
  e. *Isoniazid*

Answer: d. Levaquin. PTU, Methimazole, Minocycline and Isoniazid are associated with drug induced ANCA vasculitis.

References

- UpToDate
- Chacko JG, Chacko JA, Salter MW. Review of Giant cell arteritis. Saudi J Ophthalmol. 2014; 29(1):48-52.
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