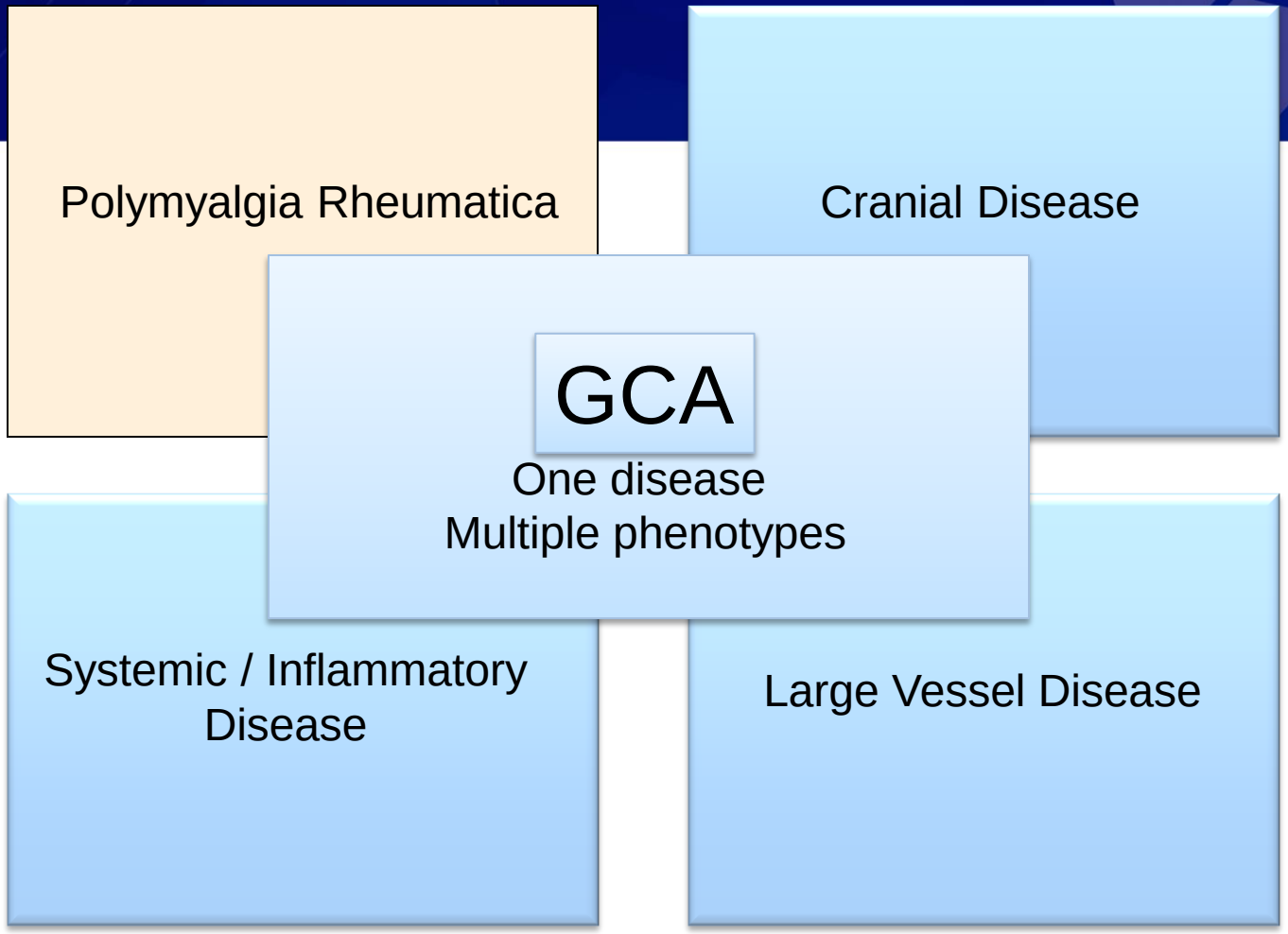
Vasculitis Pearls

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

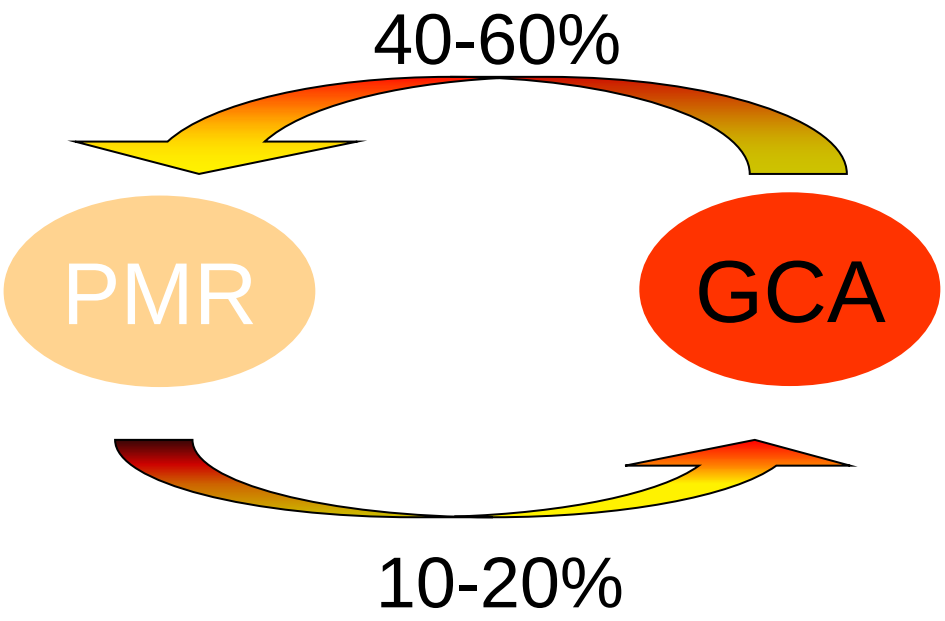
Large Vessel Vasculitides


Polymyalgia Rheumatica
Cranial Disease
GCA
One disease
Multiple phenotypes
Systemic / Inflammatory Disease
Large Vessel Disease

Risk of PMR Having/Evolving into GCA

Indicators of underlying <u>GCA in PMR</u>

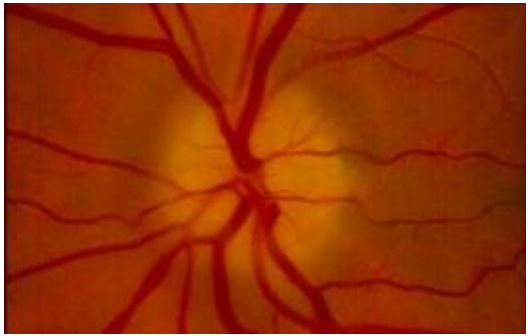
- Fever
- Failure to normalize ESR by 3-4 wks on prednisone 20mg/d
- Presence of bruits



Hernández-Rodriguez Medicine 2007;86:233

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

Greatest Concern in Giant Cell Arteritis: Cranial Ischemic Complications – Tissue Ischemia Due to Vessel Occlusion



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

What can be done to lessen this occurrence in addition to steroids?

Role of Acetylsalicylic Acid (ASA) in GCA

Nesher et al. Arthritis Rheum 2004;50:1332

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% if untreated (P=0.02)

Only 10 patients would need to be treated with ASA to prevent one CIC

Lee et al. Arthritis Rheum 2006;54:3306

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

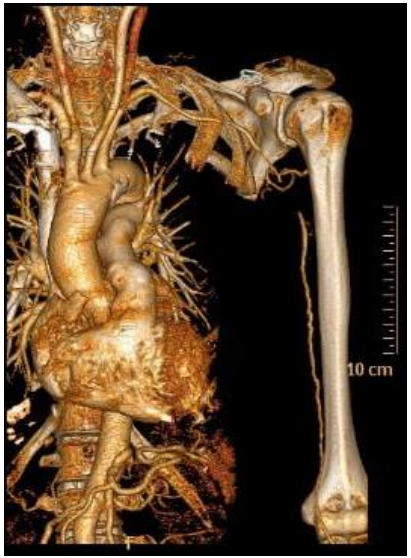
(Supportive data also in Takayasu – *de Souza et al. Circ J 2010; 74:1236)*

Large Vessel Disease Is Common in GCA

Blockmans D, et al. A&R 2006; 55:131, Prieto-Gonzalez S, et al. Ann Rheum Dis 2012; 71:1170

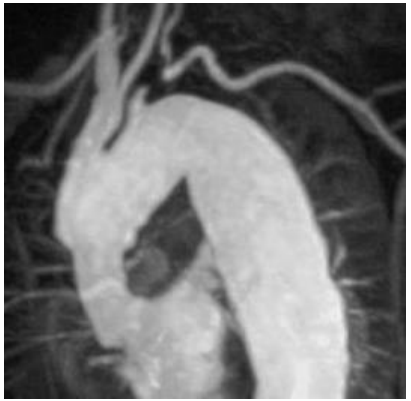
Evans et al. A & R 1994; 37:1539, Evans et al. Ann Intern Med 1995; 122:502
Nuenninghoff et al. A & R 2003; 48:3522 and 3532

27% of GCA patients had large vessel complications



13% large-artery stenosis — Subclavian (L> R), carotid, iliac

18% aortic aneurysm

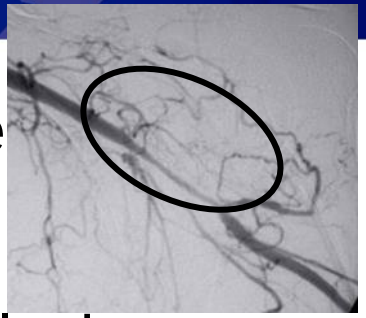


Thoracic aortic aneurysms in GCA:

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

Aortic aneurysms (thoracic > abd) are common in GCA, they can occur late, and they are an important cause of mortality

Indications for Revascularization Procedures



- The presence of a vascular lesion should not be sole indication for vascular intervention
  - Collateral vessels commonly form around upper extremity stenoses
- Indications for vascular intervention 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 (> 5 cm)
  - Aortic root / valve replacement (severe aortic regurgitation)

- Listen for AI murmur
- Listen to and palpate abdomen
- Annual CXR
- Annual abd ultrasound
- CT scans ?

Other Presentations and More Pearls

- Systemic disease and other presentations in the elderly
  - FUO: note that GCA does not cause leukocytosis
  - Unexplained cough
  - Diplopia and jaw claudication
  - Basilar/vertebral artery stroke
- Do the labs and biopsy make sense?
  - “Normal” inflammatory markers (ESR < 30mm/hr and CRP < 8 mg/L)
    - *Kermani TA et al. Semin A&R 41: 866, 2012:* Up to 10% of pts
  - Elevated alk phos/GGT in 25-35% of GCA pts
  - A low WBC or platelet count are never seen in GCA or any primary vasculitis
  - Poor man’s paraneoplastic screen: elevated LDH
  - Fibrinoid necrosis is not seen on arterial biopsies in GCA.
  - Giant cells are not always seen on arterial biopsies in GCA.

Tocilizumab in Giant Cell Arteritis

Phase 3: GiACTA RDBPCT Tocilizumab for GCA

251 patients with GCA

- 1:1:2:1 randomization: 26 wk prednisone +PCB vs. 52 week prednisone +PCB vs. TCZ 162 mg qweek +26 week prednisone vs. TCZ 162 mg q2weeks + 26 weeks prednisone
- Primary endpoint: no flares, normal CRP at week 52 with adherence to steroid taper.
- Secondary endpoint: cumulative dose of steroid

Table. Efficacy and Safety During GiACTA Part 1

	A) Short-course prednisone n = 50	B) Long-course prednisone n = 51	C) Weekly SC TCZ n = 100	D) Every other week SC TCZ n = 49
Patients in sustained remission at 52 weeks, n (%)	7 (14.0)	9 (17.6)	56 (56.0)	26 (53.1)
TCZ groups vs short-course prednisone Unadjusted difference in proportion of responders (99.5% CI)	—	—	42.0 (18.0, 66.0) $p < 0.0001$	39.1 (12.5, 65.7) $p < 0.0001$
TCZ groups vs long-course prednisone[a] Unadjusted difference in proportion of responders (99.5% CI)	—	—	38.4 (17.9, 58.8) $p < 0.0001$	35.4 (10.4, 60.4) $p = 0.0002$
Cumulative CS dose, median (min-max)	3296.00 932.0-9777.5	3817.50 822.5-10697.5	1862.00 630.0-6602.5	1862.00 295.0-9912.5
AEs Patients with event, n (%)	48 (96.0)	47 (92.2)	98 (98.8)	47 (95.9)
Withdrawals Patients withdrawn from study, n (%)	6 (12.0)	5 (9.8)	15 (15.0)	9 (18.4)
Withdrawals due to an AE, n (%)	2 (4.0)	0	7 (7.0)	3 (6.1)
SAEs Patients with event, n (%)	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
Infection SAEs Patients with event, n (%)	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)

Stone JH, et al. *N Engl J Med 377:317, 2017*

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 (Infrarenal)	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
    - Measure all 4 extremities. Legs may be most accurate
  - Treatment must balance reducing BP with flow across stenotic lesions

Large Vessel Vasculitis: Differential by Territory

- **Ascending aortic involvement**
  - Involving the arch, subclavians, and carotids
  - Inflammatory: GCA, Takayasu's, Behcet's
  - Non-inflammatory:
    - Syndromic: Marfans, Ehlers Danlos (type IV), Loeys-Dietz
    - Non-syndromic: Familial Thoracic Aortic Aneurysms
- **Isolated descending aortic involvement**
  - Takayasu's (India, Pakistan)
  - Inflammatory abdominal aortic aneurysm
  - Leriche syndrome (stenosis)
- **Isolated pulmonary artery involvement**
  - Hughes-Stovin Syndrome
- **Peri-aortitic involvement**
  - IgG4 related disease
  - Lymphoma
  - Erdheim Chester

Medium Vessel Vasculitides

Polyarteritis Nodosa

- Must have angiographic or biopsy evidence to make the diagnosis.
- Biopsy yield
  - Biopsy a sensory nerve only if clinically involved with an abnormal EMG/NCV. Yield still only 50%.
  - Skin lesions (nodules>livedo): need excisional not punch biopsy
- Do patients with cutaneous PAN need an abdominal angiogram? Only if some clinical or lab abnormality indicating possible intra-abdominal involvement (HBP, U/A, LAEs, pain)
- PAN is a curable disease
- Mimics: fibromuscular dysplasia (stenotic), SAM (dissections)

Primary Angiitis of the CNS

- If you think the patient has PACNS they probably don't.
  - Need brain biopsy to confirm
  - Get LDH: If significantly elevated, consider intravascular B cell lymphoma. Get ANA and skin biopsy
- May or may not have abnormal angiogram: GACNS vs PACNS
- PACNS/ GACNS will always (> 95%) have an abnormal CSF analysis. If normal with an abnormal angiogram consider reversible vasoconstriction syndrome (RVCS).

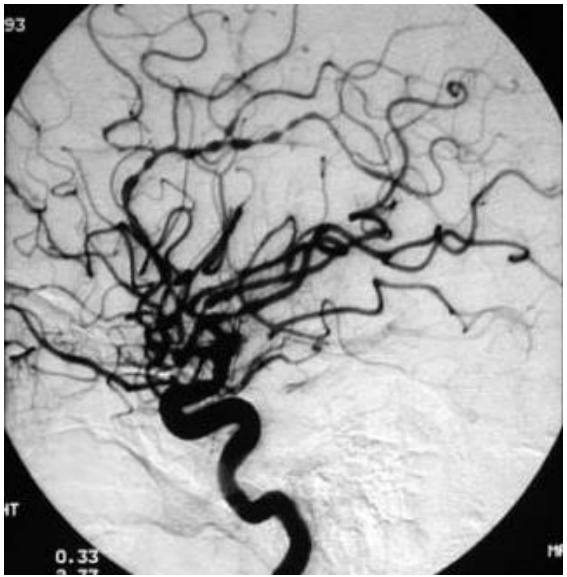
An Abnormal Arteriogram Does Not Always = CNS Vasculitis

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 Vasoconstriction Syndrome

- 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 on repeat at 4-6 weeks
- Can result in stroke or hemorrhage
- Treatment – calcium channel blockers – verapamil or nimodipine



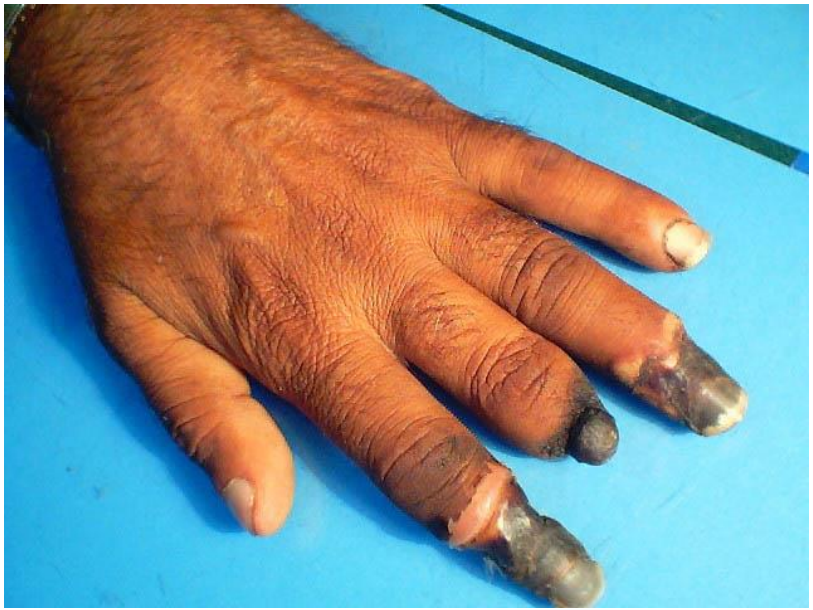
Reversible Cerebral Vasoconstriction Syndrome (RCVS)

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

	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

Thromboangiitis obliterans (TO) (Buerger disease)

- TO does not only effect one limb.
- TO does not present as Raynauds
- Migratory, recurrent thrombophlebitis is a common manifestation (40-60%)
- If a TO patient doesn’t smoke: R/O marijuana (cannabis arteritis) and chewing tobacco



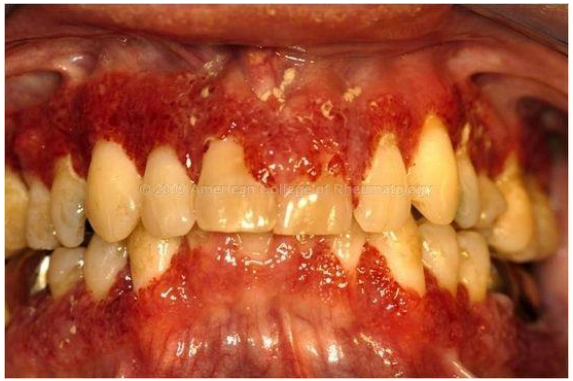
Behcet's Disease

- Without eye involvement, diagnosis is difficult
- Oral and genital ulcers: if only manifestation consider major apthous stomatitis
  - Oral ulcers: multiple, recurrent, heal without scar. R/O inflammatory bowel disease. Rare to get on palate, tonsils, and pharynx
  - Genital ulcers: labia and scrotum
  - Treatment: apremilast
- MAGIC syndrome: mouth/genital ulcers + relapsing polychondritis
- Skin: acne (arms and legs); pathergy at sites of blood draw.
- Venous thrombotic events are common whereas PE is uncommon. Treat with immunosuppression not anticoagulation.
- Pulmonary artery vasculitis with aneurysms = Behcet's; Pulmonary aneurysms with DVTs = Hughes –Stovin syndrome

ANCA-related Vasculitides

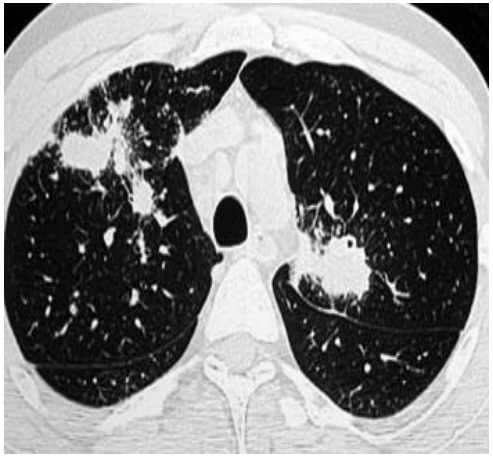
Granulomatous Polyangiitis (GPA) (Wegener's)

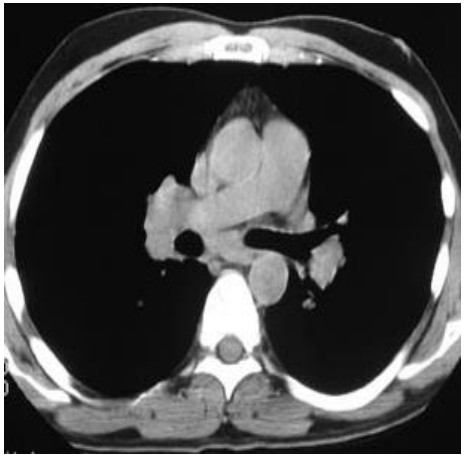
- Characteristic and less common features of GPA
  - Destructive upper airway disease: saddle nose deformity, etc
  - Subglottic stenosis: DOE/hoarseness, treat with local steroid injection/dilatation
  - Orbital pseudotumor
  - Hypertrophic pachymeningitis
  - Strawberry gums= diagnostic
  - Arthralgias/LCV are common
  - DVT/PE increased (7x) = active disease
  - Painful oral ulcers can occur
  - Episcleritis more common than scleritis



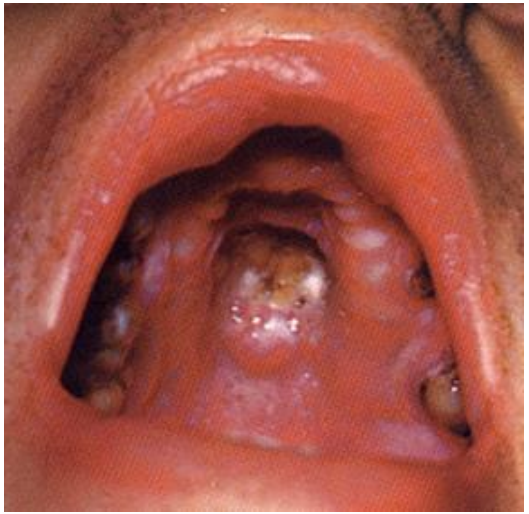
Granulomatous Polyangiitis (GPA) (Wegener's)

- How common are these manifestations in GPA?





Mediastinal/hilar lymphadenopathyl

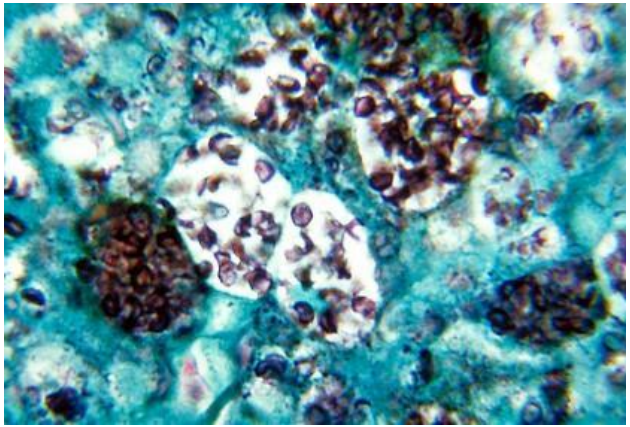


Hard palate erosions

These Manifestations are Rarely, if Ever, Seen in GPA

Mediastinal/hilar adenopathy

- Lymphoma
- Infections (TB, Histo)
- Sarcoidosis

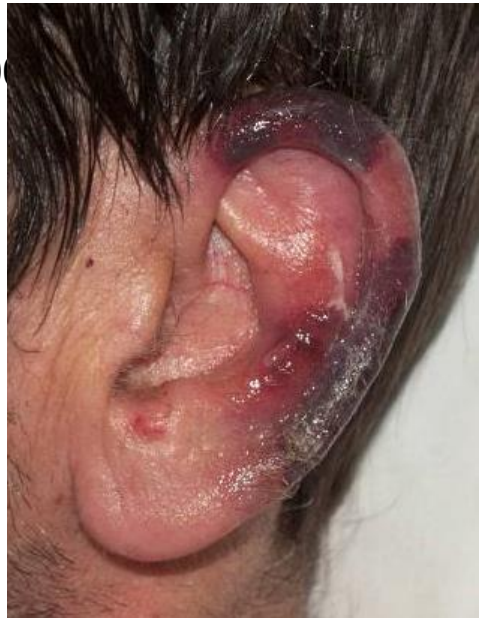


Hard palate erosions

- Lymphoma (extranodal NK/T cell)
- Invasive infections (fungus, others)
- Cocaine

Cocaine (Levamisole-Induced) Cutaneous Necrosis

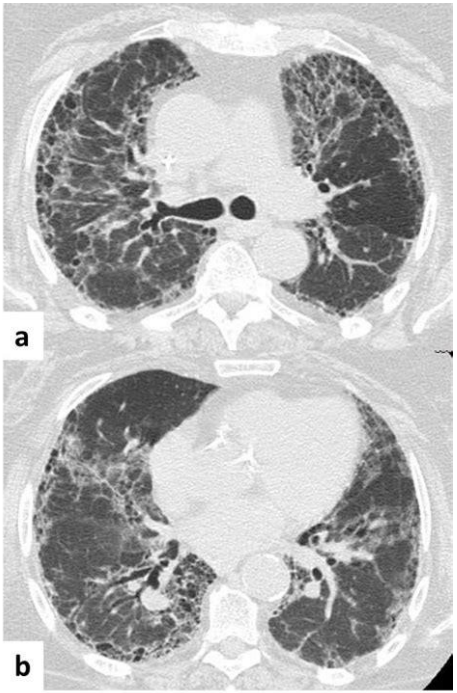
- Levamisole introduced in 1960's as an antihelminthic agent
- Since ~2004 used as a cutting agent for cocaine (found in 70-10
- Suggestive findings
  - Leukopenia and specifically agranulocytosis
  - Cutaneous necrosis
    - Vasculitis/thrombotic vasculopathy
    - Predilection for the earlobe (> 50%)
  - Autoantibodies: pANCA, LAC, ACL
    - 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*)
  - 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

Microscopic Polyangiitis (MPA)

- Characteristic features
  - Acute pulmonary-renal syndrome
  - pANCA (MPO) > cANCA (PR3)
  - Less likely to relapse than GPA
- Unique disease feature:
  - Interstitial pulmonary fibrosis
    - Resembles UIP on HRCT scan
    - pANCA (MPO) positive
    - Often have kidney involvement
    - Responsive to glucocorticoids



Get an ANCA and urinalysis in all patients presenting with IPF

Acute ANCA-related Pulmonary-renal syndromes

- Most common in microscopic polyangiitis (MPA) and GPA.

Get an anti-GBM antibody

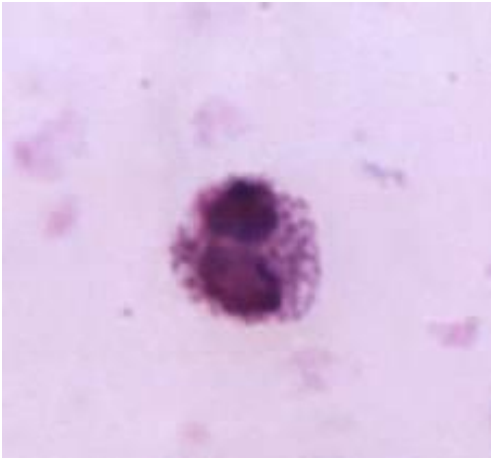
- Up to 10% of MPA/GPA can be anti-GBM positive
- Plasmapharesis in addition to immunosuppression is treatment of choice

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)

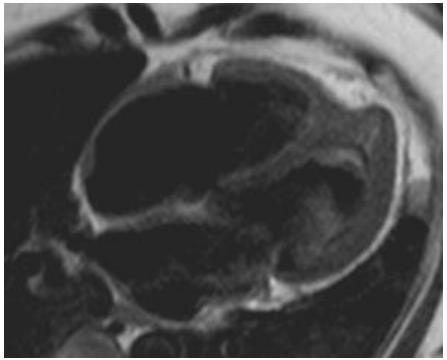
Prodromal phase: asthma, allergic rhinitis



Eosinophilic phase: peripheral eosinophilia
eosinophilic tissue infiltrates

Vasculitic phase:
Nerve: mononeuritis multiplex
skin
Lung: may have lymphadenopathy
GI tract
Heart: pericarditis, myocarditis, coronary vasculitis, valvulitis, endocarditis

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss) Outcome and Treatment



Outcome - *Guillevin et al. Medicine 1999;78:26*

- 96 patients with EGPA
- Myocardial involvement was the most frequent cause of death
  responsible for 9 of 23 deaths (39.1%)

Get an echo on all patients with EGPA

Treatment strategy based upon manifestations and disease severity

Glucocorticoids

effective alone for non-severe EGPA (*Ribi et al. A&R 2008;58:586)*
asthma often limits tapering

Cytotoxic therapy

(Gayraud et al. Arthritis Rheum 2001, Guillevin et al Medicine 1999)

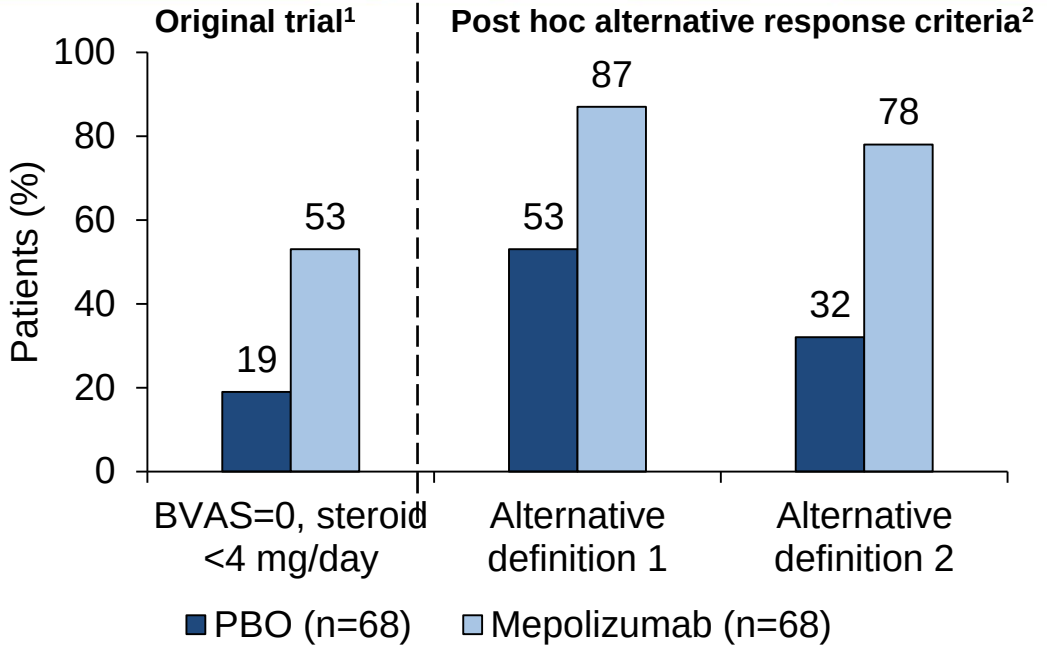
Cyclophosphamide should be utilized for life-threatening disease involving the GI tract, CNS, glomerulonephritis, heart

What About RTX and Mepolizumab in EGPA?

- Both are used as steroid-sparing agents during maintenance phase of treatment, not as induction therapy for life-threatening manifestations that should be treated with cyclophosphamide.
- RTX: Is ANCA pathogenic? Present in only 50% of pts
- Mepolizumab: anti-IL-5 therapy takes time to affect the eosinophil and 50-80% effective

Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis (EGPA)

- Anti-IL-5 therapy is promising for the treatment of EGPA[1]
- Post hoc analysis of Phase 3 clinical trial data using alternative definition of response[2]
  - Original trial: BVAS=0, steroid <4 mg/day
  - Post hoc analysis
    1. BVAS=0, steroid <7.5 mg/day (EULAR definition)
    2. Original definition and/or 50% reduction in baseline steroid dose and/or no relapses through Week 52



Relaxing response criteria results in higher response rates to mepolizumab in EGPA

BVAS, Birmingham Vasculitis Activity Score

1. Wechsler ME, et al. N Engl J Med 2017;376:1921–32; 2. Steinfeld J, et al. ACR 2017, San Diego, #1884

ANCA (GPA, MPA) Vasculitis Treatment

- CYC for severe disease (FS ≥ 2), RTX for moderate disease, AZA > MMF for maintenance of mild disease or RTX intolerant
  - Get IgG levels before RTX infusions. IgG < 300-500 mg/dL = IVIG
- GPA
  - Subglottic stenosis: treat with local steroid injections, topical mitomycin C, and dilatation
- MPA
  - Maintenance therapy with azathioprine for mild disease is effective
- Plasmapharesis: if anti-GBM+, diffuse alveolar hemorrhage, ? other
- Don’t stop treatment if ANCA positive. Otherwise consider stopping therapy after 3 years of quiescent disease.

Remember in ANCA – related 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)
- Hemoptysis: Deep venous thrombosis/PE increased 7x

(Merkel P, etal. Ann Int Med 142: 620, 2005)

Always consider: infection, clot, 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)

Small Vessel Vasculitides

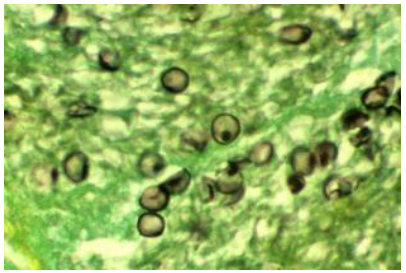
Small Vessel Vasculitis Pearls

- Immune complex vasculitis causes more extensive skin lesions than ANCA-vasculitis.
  - If you are going to do a skin biopsy, make sure they will do immunofluorescence for IgA vasculitis.
- Henoch-Schonlein purpura
  - Scrotal swelling in children
  - Refractory disease: R/O IgA monoclonal gammopathy
- Cryoglobulinemia
  - Poor man’s cryo (type II, III) test: + RF, low C4

Treatment Pearls

Cyclophosphamide – Strategies for Toxicity Reduction

- General - limit duration of exposure to 3-4 months
- Fertility preservation: infertility unlikely if < age 30 and receive < 6 months IV CYC.
  Lupron (women), testosterone (men)
- Urothelial protection
  - Daily CYC - Take at once in the AM, fluids to maintain a dilute urine
  - Intermittent CYC – MESNA
- Bladder cancer monitoring (risk may be lifelong)
  - Urinalysis to detect non-glomerular hematuria and urine cytology
  - Cystoscopy for non glomerular hematuria or atypia
- Cytopenia prevention - CBC every 1-2 weeks if on oral cyclophosphamide
- *Pneumocystis* prophylaxis
  - Trimethoprim/sulfamethoxazole (DS)
  - Alternative agents:
    - pentamidine; dapsone; atovaquone



Pneumocystis Jiroveci Pneumonia (PJP) Prophylaxis

Pneumocystis occurs in ~10% of vasculitis patients on prednisone + another immunosuppressive and prophylaxis should be given

- Prophylaxis if use prednisone > 15-20 mg/d for ≥ 4 wks
- Recommendations for stopping prophylaxis
  - If no additional risk factors, stop PJP prophylaxis after 3 weeks on prednisone 15mg/d or less.
  - If ≥ 2 additional risk factors continue PJP prophylaxis even on prednisone < 15mg/d if have underlying lung injury (vasculitis, myositis).

- Additional risk factors:
  - Elderly
  - Underlying lung dz (esp GPA, MPA, DM/antisynthetase syndrome)
  - Initial prednisone dose > 60mg/d,
  - Lymphopenia (< 1000/uL)
  - Low CD4 count (< 250uL),
  - Cyclophosphamide use, anti-TNF use, or rituximab use. What about MTX/MMF/AZA/calcineurin inhib?