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 GCA in PMR
- 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


Nuenninghoff et al. A & R 2003; 48:3522 and 3532

27% of GCA patients had large vessel complications

13% large-artery stenosis
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 the 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.
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

## Takayasu Arteritis

### Distribution of Vascular Lesions

<table>
<thead>
<tr>
<th>Vessel</th>
<th>USA (%)</th>
<th>India (%)</th>
<th>Symptoms / Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavian</td>
<td>69</td>
<td>59</td>
<td>Arm claudication</td>
</tr>
<tr>
<td>Carotid</td>
<td>37</td>
<td>21</td>
<td>TIA, stroke, syncope</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visual symptoms</td>
</tr>
<tr>
<td>Renal</td>
<td>16</td>
<td>53</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Iliac</td>
<td>19</td>
<td>15</td>
<td>Leg claudication</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>36</td>
<td>12</td>
<td>Abdominal angina (rare)</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>46</td>
<td>19</td>
<td>CHF</td>
</tr>
</tbody>
</table>
| 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).
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

An Abnormal Arteriogram Does Not Always = CNS Vasculitis
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*

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

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
Levamisole introduced in 1960’s as an antihelminthic agent
Since ~2004 used as a cutting agent for cocaine (found in 70-100%)
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

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
(Helper 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

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
- Post hoc analysis of Phase 3 clinical trial data using alternative definition of response
  - 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
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.
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
  

  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)

Remember in ANCA – related and really in all forms of vasculitis what looks like disease may not be
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?