SYSTEMIC VASCULITIS.
A REVIEW.

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OBJECTIVES

- To describe the various diagnoses of Systemic Vasculitis
- To understand and apply a systematic approach to identifying and diagnosing Systemic Vasculitis
- To address various approaches to management of Systemic Vasculitis
Inflammatory leukocytes in vessel walls

Damage to wall structures

Vessel wall integrity compromised

Bleeding / Downstream ischemia and necrosis
Immune complex small-vessel vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Hench–Schonlein)
Hypocomplementemic urticarial vasculitis
(Anti-C1q vasculitis)

Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease

Anti-GBM disease

ANCA-associated small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis

Chapel Hill Consensus Conference (CHCC) 2012
# Approach to Vasculitis

1. **Suspect the disease**
2. **Define the extent of disease**
3. **R/O mimics**
4. **Confirm the diagnosis**

### 1. No single typical presentation
- Assess demographics
- Multisystem inflammatory disease
- FUO
- Vague constitutional sx
- Ischemic s/sx / Organ infarctions
- Mononeuritis multiplex
- Skin lesions
- Rapidly progressive organ dysfunction

### 2. Assess Inflammation
- CBC with Diff
- ESR/CRP
- Albumin

### Assess Organ Involvement
- UA (protein, casts, heme)
- Renal fxn (CrCl, 24 hr protein, bx)
- CXR
- Liver fxn
- Nervous Sx: NCV/Bx, MRI
- Muscle: EMG, CK, Bx
- Cardiac: ECG, Echo
- Gut: Stool studies/Angio
- Skin: Bx
# Approach to Vasculitis

## 1. Suspect the disease
2. Define the extent of disease
3. R/O mimics
4. Confirm the diagnosis

### 3-4.

- **Serologic Tests suggesting ICs**
  - RF – should be neg. If +, think cryo or SBE
  - ANA – if + think SLE or SS
  - ACLA
  - Complements – usually nl except for cryo
  - Cryoglobulins – if +, r/o Hep C
- **Serologic Tests suggesting ANCA-related vasculitis**
  - C-ANCA
  - P-ANCA
  - OTHERS, i.e. GBM

### 3-4.

- **Differential Diagnosis**
  - Blood cultures
  - Infectious serologies (HBsAg, HCV, Parvovirus IgM, HSV, CMV)
  - TOXIIN OR MED EXPOSURES
  - SPEP
  - CSF studies
  - Echo
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Chapel Hill Consensus Conference (CHCC) (1994 to 2012)

- Eosinophilic Granulomatosis with Polyangiitis
  - Churg-Strauss Syndrome

- Granulomatosis with Polyangiitis
  - Wegener’s Granulomatosis

- IgA Vasculitis (IgAV)
  - Henoch-Schönlein Purpura

- Hypocomplementemic Urticarial Vasculitis
  - Anti-C1q Vasculitis
Chapel Hill Consensus Conference (CHCC) (1994 to 2012)

- Formally adopted ANCA-Associated Vasculitis (AAV) for the group of EGPA, GPA, MPA
- Also for Variable Vessel Vasculitis and Secondary Forms

- Not a SUBSTITUTE for CLASSIFICATION CRITERIA
  - These include clinical observations that classify a patient into a category for research
LARGE VESSEL VASCULITIS: AORTA AND MAJOR BRANCHES

TAKAYASU’S ARTERITIS
GIANT CELL ARTERITIS
IDIOPATHIC/ISOLATED SECONDARY
MEDIUM VESSEL VASCULITIS: MAIN VISCERAL ARTERIES AND BRANCHES: STENOSES AND ANEURYSMS

- Polyarteritis Nodosa
- Kawasaki Disease
SMALL VESSEL VASCULITIS: SMALL VESSELS – ARTERIOLES, CAPILLARIES, VENULES

- ANCA ASSOCIATED VASCULITIS
- GRANULOMATOSIS WITH POLYANGIITIS
- MICROSCOPIC POLYANGIITIS
- EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS
SMALL VESSEL VASCULITIS: SMALL VESSELS – ARTERIOLES, CAPILLARIES, VENULES

- IMMUNE COMPLEX VASCULITIS
- ANTI-GBM DISEASE
- CRYOGLOBULINEMIC VASCULITIS
- IGA VASCULITIS
SMALL VESSEL VASCULITIS: SMALL VESSELS – ARTERIOLES, CAPILLARIES, VENULES

SMALL VESSEL VASCULITIS

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS
VARIABLE VESSEL VASCULITIS: NO PREDOMINANT VESSEL INVOLVED – ALL ARE POSSIBLE

- BEHÇET’S DISEASE
- COGAN’S SYNDROME
OTHERS

SINGLE ORGAN VASCULITIS
• NO EVIDENCE OF AN EXTENSION OF SYSTEMIC VASCULITIS

VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE
• USE A PREFIX CATEGORIZING AND SPECIFYING DISEASE

VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY
LARGE VESSEL VASCULITIS
TAKAYASU’S ARTERITIS

- **WHO AND WHAT?**
  - UNCLEAR ETIOLOGY AFFECTING AORTA AND PRIMARY BRANCHES
  - WOMEN AFFECTED IN 80-90% CASES
  - AGE OF ONSET 10-40 Y

- **PATHOGENESIS**
  - INFLAMMATION IS LOCALIZED TO PORTION OF THORACIC/ABDOMINAL AORTA AND BRANCHES OR IS A PANARTERITIS
  - INITIAL LESIONS USUALLY IN THE LEFT MIDDLE OR PROXIMAL SUBCLAVIAN ARTERY
  - PROGRESSES TO LCC, VERTEBRAL A, BRACHIOCEPHALIC ARTERY AND AORTA
Abdominal aorta and Pulmonary artery involved in 50%
TAKAYASU’S ARTERITIS

- Age at disease onset ≤40 years
- Claudication of the extremities
- Decreased pulsation of one or both brachial arteries
- Difference of at least 10 mmHg in systolic blood pressure between the arms
- Bruit over one or both subclavian arteries or the abdominal aorta
- Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or other causes

 Patients are said to have TAK if at least three of the six criteria are present.
TAKAYASU’S ARTERITIS

- Average age: 10-30y
- F>M 8x more common
- Recurrent and chronic disease so one or all phase can present
- 10% have no sx, but incidental findings of HTN, unequal BP/P, bruits
- Phase I: Pre-pulseless inflammatory period; nonspecific systemic complaints;
- Phase II: Vessel inflammation;
- Phase III: Fibrotic stage; bruits and ischemia

Clinical Features:
- Bruits (80%)
- Claudication (70%)
- Decreased pulses (60%)
- Arthralgias (50%)
- Asymmetric BP (50%)
- Constitutional sx (40%)
- HA (40%)
- HTN (30%)
- Dizziness (30%)
- Pulmonary (25%)
- Cardiac (10%)
- E Nodosum (8%)

Aortic arch and abdominal aorta most commonly affected
TAKAYASU’S ARTERITIS (TA)

- Inflammatory processes cause thickening of walls of affected arteries.
- Narrowing, occlusion or dilation of involved degrees cause a variety of sx.
TAKAYASU’S ARTERITIS (TA) - PATHOGENESIS

ACTIVE INFLAMMATION

Destruction of the elastic lamina/muscular media can lead to aneurysmal dilatation of vessel

Progressive inflammation/dense scarring may proceed from adventitia leading to compromise of vascular lumen ..... Intimal Proliferation...
**IMMUNE INSULT IN TAKAYASU ARTERITIS**

**Cellular events**

- *Presentation of Antigen by MP*
- *Recognition of Antigen by CD4 T cells*

**Mediators**

- Proinflammatory Monokines (IL-1β, IL-6)
- INF-γ

**MMPs**

**Growth factors** (PDGF-A, PDGF-B, VEGF)

**Reactive oxygen Intermediates-lipid peroxidation**

**Nitric oxide**

**Transforming Growth Factor-β (TGF-b)**
TAKAYASU’S ARTERITIS

- Findings vary with the site and degree of vessel involvement
  - **REDUCED BP IN ONE OR BOTH ARMS**: 10 mmHg or more
  - **DIMINISHED ARTERIAL PULSES IN ARMS AND LEGS**: Often asymmetrical
  - **BRUITS**: Subclavian, brachial, carotid, abdominal
  - **MAY HAVE AORTIC REGURGITATION SIGNS
  - **HYPERTENSION**: In more than ½ cases due to narrowing of renal artery, or narrowing/decreased elasticity of aorta and branches.
    - **STENOSIS/OCCLUSION WILL MAKE IT DIFFICULT TO ASSESS BP PERIPHERALLY**
  - **SYNOVITIS**: Larger joints
Several studies analyzed different subsets of TAK to identify reliable risk predictors for development of severe complications

- Multicenter Trial (French TA Network)
  - 50% TAK patients will have relapse and vascular complication within 10 years from dx.
  - Related factors to relapse: male sex, elevated CRP, carotidynia
  - Related factors to vascular complication risk: progressive dz course at dx, thoracic aorta involvement and retinopathy

- Single Center cohort trial looking at biologic agents in presence of tapering steroids and immunosuppression

- Studies on severe ischemic complications to suggest tight control of disease activity and preventative measures such as antiplatelet agents


Imaging of major arteries usually the way to confirm dx
- TO DEFINE LOCATION AND APPEARANCE OF ARTERIAL LESION
- MEASUREMENT OF CENTRAL BP
- MAY ALLOW THERAPEUTIC INTERVENTION

Changes most pronounced in aortic arch and branches (primary and distal)
- “Smooth walled, tapered, focal, narrowed areas with some dilation”
- “Collateral circulation” because of chronicity
- DOES NOT ALLOW ARTERIAL WALL THICKENING TO BE ASSESSED
TA: ANEURYSMAL DILATATION DESCENDING AORTA
Smoothly tapered luminal narrowing accompanied by thickening of wall of vessel (CT/MRI)

In one study – 25 patients with symptoms of TA underwent both angiography and CT angiogram

- CT angio was 95% sensitive and 100% specific for dx of TA
- More specific than conventional angio for detecting mural changes

Recent study concluded that Delayed Contrast Enhanced MRI could be used to monitor disease activity in TAK

**CT/MRI**

**Edema weighted MRI**: sensitive for active disease; poor positive predictive value as edema also noted in those in remission.

**Aneurysm of Ascending Ao. (CT)**

**Dilation of Ascending Ao. And thickening Of wall (MRI)**
TA IMAGING: US/PET

- Transthoracic ultrasound – ascending aorta
- TEE better for descending aorta

- Positron Emission Tomography – using radioactively labeled fluorodeoxyglucose (FDG) – limited availability but can be used to image great vessels.

- Areas of increased uptake of tracer correlate well with abnormal arterial segments noted by MRI
- May be more sensitive than MRI in detecting segmental arterial inflammation
- So may be able to distinguish vessel thickening due to active inflammation vs. due to scar formation
Giant Cell Arteritis (GCA)

- Most common of the systemic vasculitides
- Age over 50
- Peaks in 7th decade
- Lifetime risk 1% in women, 0.5% in men
- All ethnic groups, but most patients are Caucasian

Incidence:

- In Scandinavian Countries AND Olmstead County, MN - 17/100,000 a year
- In Southern Europe, 10/100,000 a year over age 50
- Unusual in Latinos, Asians, Arabs, and even less in AA
“The tragedies of life are largely arterial...”

- Initial manifestations
  - HA
  - PMR (50%)
  - Fever
  - Visual symptoms w/o loss
  - Weakness, malaise, fatigue
  - TA tenderness
  - Myalgias
  - Wt. Loss/anorexia
  - Jaw claudication
  - Permanent loss of vision/tongue claudication/sore throat/vasculitis on angio/stiff hands and wrists

- Clinical features which predict positive TA biopsies:
  - Jaw claudication (LR=4.2)
  - Diplopia (LR=3.4)
    - Neither are very sensitive for GCA (35%, 9%)
    - Absence does not exclude GCA
  - HA, PMR, other visual sx, constitutional sx - NOT ASSOCIATED with increased LR - “classic symptoms”

Smetana GW et al. JAMA 2002;287:92
GIANT CELL ARTERITIS

- Studies analyzing predictive models of the pretest probability of a temporal artery biopsy to minimize invasive procedures
- GCA related severe cranial ischemic events occur in 20-50% patients and include visual loss and CVA
- Nationwide cohort study:
  - HTN, DM, absence of PMR, male sex – risk factors for the development of ocular complications
- Ophthalmic complications strongly associated with GCA related CVA, (in 3-7% patients with GCA and had mortality in 1/3 patients)
- Protective effect of antiplatelet or anticoagulant agents still controversial

Consider something else...

- Adenopathy
- Pulmonary infiltrates
- Digital cyanosis, ulceration or gangrene
- Mononeuritis multiplex
- Stroke in distribution of MCA
- Evidence of glomerulonephritis or rising serum Cr
Permanent vision loss in GCA

- Most often painless and sudden, partial or complete and unilateral or bilateral
- Rarely reversible
- May be preceded by a few episodes of transient vision loss
- Estimated that within one week, further vision loss in the UNAFFECTED eye can occur in 25-50% untreated patients.
- However, if vision is intact shortly after treatment with adequate dose of steroids, risk is almost nil
Permanent vision loss in GCA

- We do not have a defined way of stratifying risk for permanent vision loss in GCA.
- Age, HTN, thrombocytosis proposed
- PRIOR TRANSIENT VISUAL LOSS IS STRONGEST PREDICTOR
Stimulus, i.e. infection → Host Risk Factors: Age/Gender/immune response genes (HLA) → IL-6 → Acute phase response

Activation of circulating Monocytes/macrophages (TLRs dictate CD4 cells invading the wall and others support the perivascular infiltrate)

Activation of vasa vasorum

Minimal vascular Immune response

Polymyalgia Rheumatica

Tissue invasion by Activated MPs – they Encounter antigen-INF-gamma production And recruitment of More MP and lymphocytes

Recognition of antigen in Adventitia:
*antigen carried in by MP
*arterial antigen

Immune insult

Injury response of arterial wall

From Inflammatory Diseases of Blood Vessels, Hoffman G et al. 2001
**Immune Insult in Giant Cell Arteritis**

**Cellular events**
- *Presentation of Antigen by MP*
- *Recognition of Antigen by CD4 T cells*
- *Differentiation of Tissue-invading MP (IFN-g-dependent)*
- *Giant Cell formation (IFN-g-dependent)*
- *Differentiation of Tissue-invading MP (matrix-dependent?)*

**Mediators**
- Proinflammatory Monokines (IL-1β, IL-6)-in PMR and GCA INF-g – not in PMR
- MMPs
- Growth factors (PDGF-A, PDGF-B, VEGF)
- Reactive oxygen Intermediates-lipid peroxidation
- Nitric oxide
- TGF-b
Low power view of TA:
Intimal fibrosis, narrowed lumen, thickened Media, intact Adventitia
Skip lesions

High power view of TA:
Intimal fibrosis, infiltration of media by inflammatory cells;
Irregular disruption of media at Internal Elastic Membrane – Multinucleated GCs
NO FIBRINOID NECROSIS
GIANT CELL ARTERITIS

- Studies on cytokine profiles led to discovery of IL-6 predominance and approval of first biologic drug to treat GCA (tocilizumab)
  - IL-6 as a biomarker?
- Pathogenesis studies focused on varicella zoster virus as a trigger of inflammation
- Histopathological evidence of VZV in TA biopsies – only found in 3% of samples so conclusion that there was no correlation between the two.

GCA – LARGE VESSEL INVOLVEMENT

- Aorta and major proximal branches – to the UE
- Aneurysms and dissections of the aorta (thoracic), stenosis, occlusion and ectasia
- Subclavian arteries distal to take off on the vertebral arteries, axillary arteries and proximal brachial arteries.
  - b/l, though not symmetric and circumferential (atherosclerosis is often unilateral and eccentric involvement of the vessel wall)
GCA – LARGE VESSEL INVOLVEMENT

- Phenotypically different from cranial arteritis
  - Study of 74 patients with angiographically diagnosed subclavian or axillary involvement compared to 74 patients with biopsy proven cranial GCA.

- LV-GCA Patients:
  - Younger age of onset (66 vs 72 years)
  - Less likely to have headaches (14 vs 57%)
  - More likely to have UE claudication at presentation (51 vs. 0%)
  - Among 57 patients with LV-GCA who had TA biopsies, only 33 were positive
Large vessel involvement:

- No differences in survival compared with general population except in patients with recognized thoracic aortic dissection
- Others have reported overall shorter survival time

Who should be screened and how?

What techniques can we use to assess presence of these abnormalities?

GCA : Clinical Exam

- PULSES: LOOK FOR DIMINISHED PULSES AND DISCREPANT BLOOD PRESSURE IN ARMS
  - Palpate brachial, radial, femoral and pedal pulses
  - Measure BP in both arms
  - Listen for bruits

- TEMPORAL ARTERY ABNORMALITIES
  - Prominent or enlarged (LR of 4.3)
  - Absent pulse or tenderness (LR of 2.6-2.7)

- CARDIAC EXAM – look for signs of AAA with secondary dilatation of AV

- OCULAR EXAM

- PMR
If you suspect extracranial GCA:

- History of sx of claudication/ischemia;
- Exam of bruits, 4 extremity BP;
- Occasionally intra-op biopsy may lead to finding of aortitis

IMAGING...
TA BIOPSY

- Intermittent lesions so need a big bite
- Giant cells found in less than 50% samples so a negative specimen does not rule out disease
- GC do not alter the bx result
- Go for the abnormal side
- Do not biopsy if only extracranial
MEDIUM VESSEL VASCULITIS
POLYARTERITIS NODOSA

- Multisystem disease involving necrotizing inflammation of medium and small arteries
- Spares the smallest capillaries and venules
- Annual incidence of 5-10/1,000,000; M:F=2:1
- Average age at dx: 40s-60s

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<td>1. Weight loss &gt;4kg</td>
<td>Loss of 4kg or more body weight since illness began, not due to dieting or other factors</td>
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<td>2. Livedo reticularis</td>
<td>Mottled reticular pattern over the skin of portions of the extremities or torso</td>
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<td>3. Testicular pain or tenderness</td>
<td>Pain or tenderness of the testicles, not due to infection, trauma or other causes</td>
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<td>4. Myalgias, weakness or polyneuropathy</td>
<td>Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles</td>
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<tr>
<td>5. Mononeuropathy or polyneuropathy</td>
<td>Development of mononeuropathy, multiple mononeuropathies or polyneuropathy</td>
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<td>6. Diastolic BP &gt;90mmHg</td>
<td>Development of hypertension with diastolic BP higher than 90mmHg</td>
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<td>7. Increased BUN or creatinine</td>
<td>Increase in BUN &gt;40mg/dl (14.3 μmol/l) or creatinine &gt;1.5mg/dl (132 μmol/l), not due to dehydration or obstruction</td>
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<td>8. Hepatitis B virus</td>
<td>Presence of hepatitis B surface antigen or antibody in serum</td>
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<td>9. Arteriographic abnormality</td>
<td>Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes</td>
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<td>10. Biopsy of small or medium-sized artery containing PMN</td>
<td>Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall</td>
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POLYARTERITIS NODOSA

- Segmental transmural inflammation of muscular arteries
- Does not involve veins
- PMNs and Mononuclear cells
- Leukocytoclasia may be present
- Necrosis of arterial walls may lead to homogenous eosinophilic appearance = **FIBRINOID NECROSIS**
- Can have lesions of different ages in single sample
- Not granulomatous inflammation
Fibrinoid necrosis in PAN, periarteritis
Polyarteritis involving the celiac artery: Pleomorphic inflammatory cell infiltration / Fibrinoid necrosis.

PMNs and monocytes

Chronic polyarteritis with intimal proliferation/Chronic fibrotic changes.
POLYARTERITIS NODOSA

Skin Disease

- Usually over LE with limb edema present
- Tender erythematous nodules
- Palpable purpura – bx would show LCV most in postcapillary venules
- Livido reticularis
- Ulcers/vesicles
- Can progress to infarction/gangrene of digits with extension into SQ tissue
  - Often reflects involvement of larger than medium size skin vessels
- Biopsy: Necrotizing vasculitis within walls of medium size arteries, in deep dermis or in subcutaneous fat
Polyarteritis Nodosa

Skin Disease

• Many of the manifestations result from vessels within the SQ tissues
• Nodules and ulcers: small 2-4 mm punch biopsies that sample only epidermis and superficial dermis may not include the muscular arteries so limited value
• Elliptical surgical skin biopsies including deeper dermis and SQ fat may be more helpful
• “medium sized” arteries in skin may actually be smaller than other medium sized arteries (coronary/mesenteric) but are still muscular and larger than the small superficial precapillary arteries associated with purpura
Renal Disease

- Most commonly involved organ
- Can lead to varying degrees of renal insufficiency and hypertension
- Aneurysms can cause perirenal hematoma
- Multiple infarctions
- Incomplete luminal narrowing leads to organ ischemia but not inflammation or necrosis so the UA will show minimal proteinuria/hematuria
- RBC casts absent
- HTN common due to renal ischemia and activation of RAS
Angiogram: Renal aneurysms in PAN
POLYARTERITIS NODOSA

Neurologic Disease

- Mononeuritis Multiplex
- Radial, ulnar, peroneal n.
- Motor and sensory deficits
- Occurs in up to 70% patients
- Asymmetric at onset but can be additive over time and lead to a more confluent symmetric polyneuropathy
- CNS involvement occurs in 5-10% patients.
Gastrointestinal Disease

- Mesenteric arteritis
- Abdominal pain, “intestinal angina”
- Weight loss
- Progressive disease can lead to bowel infarction/perforation
- N/V/melena/diarrhea/Life-threatening GI-bleed
- Perforation during colonoscopy – minimal insufflation and early termination of study
Visceral Angiogram in PAN
Gastrointestinal Disease

• Ischemia due to vasculitis of the small intestine
• Small group of patients have predominant mesenteric arterial involvement with no extraintestinal involvement
• Rare: acute cholecystitis/appendicitis (acute vasculitis of the cystic or appendiceal artery)
• Rare: Segmental pancreatic infarction/necrotizing pancreatitis
POLYARTERITIS NODOSA

Coronary Artery Disease

- Myocardial infarction rare but ischemia can occur
- Heart failure
  - Vasculitis of coronary arteries (ischemic CM)
  - Uncontrolled HTN (due to renal disease)
POLYARTERITIS NODOSA

Muscle Disease

• Myalgia
• Muscle weakness
• CK may be elevated but usually not high enough to worry about inflammatory myopathy
• Muscle pain/claudication – muscle bx has approx 50% sensitivity for PAN
POLYARTERITIS NODOSA

Other organ systems

• Orchitis with testicular tenderness (>10%)
• Ischemic retinopathy with hemorrhage and retinal detachment
• Ischemic optic neuropathy
• Breast / uterine involvement
• Bronchial arteries
  • Capillaritis or other lung parenchymal involvement by vasculitis STRONGLY suggests other systemic disease (WG, MPA, CSS)
• Splenic infarction
POLYARTERITIS NODOSA

- Clinically can suspect based on sx, PE, compatible lab results.
- **Biopsy whenever possible!**
- If no obvious site for tissue biopsy, angio can help esp in mesenteric, renal and hepatic circulation
- Arteritis consistent with PAN can occur in individual organs without evident systemic involvement
- Incidental discovery on angiography or biopsy whether during w/up for “vasculitis” or examination of a surgical specimen
- Still controversial as to whether we can call cases of MVV in a single organ as PAN
  - Always look for other potentially involved organ systems to determine activity and severity of disease
POLYARTERITIS NODOSA

- Determine what organs may be involved
- Determine other causes of PAN
- DRUG EXPOSURE: prescription/illicit drugs (i.e. amphetamines) / IV drug use
  - Associated with Hep B and C
  - **ALMOST EVERY CLASS OF DRUG HAS BEEN IMPLICATED AS A POSSIBLE CAUSE OF VASCULITIS BUT NOT ALL DRUG-INDUCED VASCULITIS FIT THE PATTERN OF PAN**
- ALTERNATIVE DX
POLYARTERITIS NODOSA

- Determine extent of vascular lesions
- Determine distribution of affected organs
- Presence of additional disease
- Look for skin manifestations and objective evidence of motor or sensory loss
- Full vascular exam
- Positive test for occult blood may suggest mesenteric enteritis
KAWASAKI DISEASE

- Mucocutaneous LN syndrome
- Childhood vasculitis
- Self limiting with fever and acute inflammatory manifestations lasting about 12-14 days
- Clinical findings can occur at different times so must be vigilant
- Can have an atypical “incomplete” KD
- Can have complications such as coronary artery aneurysms, depressed myocardial contractility, heart failure, premature MI, arrhythmia
Must have fever lasting at least 5 days without any other explanation PLUS 4/5 of below:

- B/L bulbar conjunctival injection
- Oral mucous membrane changes (injected or fissured lips, injected pharynx, strawberry tongue)
- Peripheral extremity changes (erythema of palms and soles, edema of hands/feet, periungual desquamation)
- Polymorphous rash
- Cervical LA
KAWASAKI DISEASE
Indurated edema of the dorsum of the hands as seen in Kawasaki disease (acute phase)

The erythema overlying the metacarpophalangeal and proximal interphalangeal joints is indicative of arthritis of the small joints of the hand.

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SMALL VESSEL VASCULITIS
GRANULOMATOSIS WITH POLYANGIITIS

- Extravascular granulomatous vasculitis, SVV
- Strong association with C-ANCA, anti-PR-3
- Limited vs Generalized – renal involvement
- ACR criteria:
  - Nasal/Oral inflammation (ulcers or purulent/bloody nasal d/c)
  - Abn CXR with nodules, cavities or fixed infiltrates
  - Abn urinary sediment with microhematuria or RBC casts
  - Granulomatous inflammation in vessel wall on bx
Saddle Nose:
Can also be seen in Relapsing Polychondritis and Syphilis
Uveitis
Proptosis
Extraocular Muscle Involvement in GPA
Pulmonary Manifestations: Nodules and masses

- Centrilobular distribution
- Can mimic TB, viral, bacterial or fungal pneumonia
- R/O metastases, abscess or septic infarcts

49 y.o. with active WG and epistaxis

Ananthakrishnan L. et al. AJR 2009; 192:676-682
Pulmonary Manifestations: Nodules and masses

35 y.o on chronic immunosuppression and WG – found to have superimposed Aspergillus Fumigatus superinfection

Ananthakrishnan L. et al. AJR 2009; 192:676-682
Pulmonary Manifestations: Alveolar Hemorrhage

61 y.o. with HTN, dyspnea and RI
Elevated C-ANCA /PR-3
Ground glass opacity/consolidation
Subpleural sparing

63-year-old man who presented in respiratory distress.
Ground-glass opacity with interlobular septal thickening and patchy consolidation

Ananthakrishnan L. et al. AJR 2009; 192:676-682
46-year-old man with WG presenting with dyspnea and stridor. Transverse and sagittal CT images show eccentric narrowing of subglottic trachea (arrows).

-15-25% may develop progressive stridor
-Dx may occur in absence of other features
-May occur during immunosuppressive treatment
-Treatment with Steroid injection and dilation

Renal manifestations

Segmental necrotizing glomerulonephritis with crescent formation – classic in WG:

Immunofluorescence studies in this disease show a paucity of immunoglobulin and complement deposition.

Poor renal outcome determined by:

- Severe RD at presentation
- Lack of response to initial treatment
- Renal relapse
- Age > 65 y
- Prominent fibrotic changes on renal biopsy

Renal involvement does not preclude induction of remission

Induced in 72% of 240 patients with GFR < 30 ml/min

Subungal and Digital infarcts
Deep Vein Thrombosis

- WECLOT (Wegener's Clinical Occurrence of Thrombosis Study)
  - Measured the incidence of VTE in 180 WG pts
  - Prospective observational study/multicenter randomized trial to look at incidence rates of DVT/PE – time to first VTE.
  - 228 patient years: 16 VTE in 167 pts without h/o prior VTE
  - Incidence 7.0/100 person yrs (higher than compared to SLE/RA)
  - May be due to endothelial change and hypercoagulability

The ANCA story

- Immunofluorescence assay more sensitive than the ELISA.
- ELISA more specific.
  - Perform both if available and ELISA to detect antibodies against the vasculitis specific target antigen (PR3 or MPO)
  - PR3 and MPO located in azurophilic granules of neutrophils and peroxidase + lysosomes of monocytes
  - PR3-ANCA, MPO-ANCA (antibodies with the target specificities identified)
- When sera of patients with AAV are incubated with ethanol-fixed human neutrophils, two major patterns observed.
  - C-ANCA / P-ANCA
  - NEED BETTER SENS/SPEC.
  - USE IN DIAGNOSIS VS. MEASUREMENT OF DISEASE ACTIVITY
  - "DUAL POSITIVITY" IN LEVAMISOLE EXPOSURE (50% COCAINE IN US IS CONTAMINATED WITH THIS)
The ANCA story

- Little role in disease management
- Once diagnosis is established, neither presence of ANCA or a rise reliably predicts flare
- If patient ANCA + in active disease, then Neg. ANCA may be considered consistent with remission but should not lead to change in therapy

Interplay of inflammatory event and immune response directed against epitopes of neutrophil granule proteins = production of ANCA

That ANCA directs against antigens in the neutrophil primed by Th1 cytokines and tissue damage produced via interactions with endothelial cells and the primed neutrophils.

WG patients in remission often experience flares after bacterial or viral infections – could be due to increased priming and sets off cascade.

ANCA also increases rate of release of chemo-attractants and O2 free radicals and degranulation of primed neutrophils.
EOSINOPHILIC GRANULOMATOsis WITH POLYANGIITIS

- Multisystem disease characterized by:
  - Chronic rhinosinusitis
  - Asthma – (>95%) usually precedes the vasculitis phase by 8-10 years
  - Peripheral neuropathy/Mononeuritis multiplex in up to 75%
  - CNS manifestations – subarachnoid and cerebral hemorrhages, cerebral infarction, cranial nerve palsies, loss of visual acuity
  - Skin (palpable purpura to SQ nodules) – need bx
  - Cardiac – (cause of ½ deaths in EGPA)
  - Peripheral eosinophilia (>= 1500 cells/microL and/or >10% eosinophils on CBC Diff)
  - MPO-ANCA in 30-60% patients
  - Looking for characteristic changes on HRCT – patchy parenchymal consolidation / GGO, nodules
The presence of four or more of these criteria had a sensitivity of 85 percent and a specificity of 99.7 percent for EGPA:

- Asthma (a history of wheezing or the finding of diffuse high pitched wheezes on expiration)
- Greater than 10 percent eosinophils on the differential leukocyte count
- Mononeuropathy (including multiplex) or polyneuropathy
- Migratory or transient pulmonary opacities detected radiographically
- Paranasal sinus abnormality
- Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Cutaneous ulceration on the elbow of a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

Courtesy of Talmadge E King, Jr, MD.
Histopathology of eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Small artery in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) showing intimal fibrinoid necrosis and mural infiltration by histiocytes consistent with a necrotizing granulomatous vasculitis. There is marked extravascular eosinophilia.
# Cryoglobulinemic Vasculitis

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
<th>CLINICAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – 6%</td>
<td>MONOCLONAL IGM OR IGG</td>
<td>ASSOCIATED WITH MULTIPLE MYELOMA OR WALDENSTROM’S MACROGLOBULINEMIA/ASYMPTOMATIC</td>
</tr>
<tr>
<td>II (MIXED) – MOST COMMON 62%</td>
<td>POLYCLONAL IGG AND MONOCLONAL RF AGAINST IGG</td>
<td>ASSOCIATED WITH CHRONIC HCV</td>
</tr>
<tr>
<td>III (MIXED) – 32%</td>
<td>POLYCLONAL IGG AND IGM RF</td>
<td>CHRONIC INFLAMMATORY DISEASE/AUTOIMMUNE DISEASE OR LYMPHOPROLIFERATIVE DISEASE</td>
</tr>
</tbody>
</table>
CRYOglobulinemic Vasculitis

- Palpable Purpura
- Arthralgia
- Lymphadenopathy
- Peripheral Neuropathy
- Low C3, C4
- Renal disease (20-60%) - Hematuria, Renal Insufficiency, CKD, Nephrotic Syndrome
- Rare – Cardiovascular, Thrombooses, GI Symptoms
Membranoproliferative pattern in mixed cryoglobulinemia

Light micrograph in mixed cryoglobulinemia showing a membranoproliferative pattern with increased cellularity and thickening of the glomerular capillary walls. The pathognomonic finding is PAS-positive microthrombi composed of precipitated cryoglobulins that are occluding some of the capillary loops (arrows).

PAS: periodic acid Schiff.

Courtesy of Helmut Rennke, MD.
Cutaneous vasculitis most often presents as palpable purpura that is typically a manifestation of benign, localized, self-limited cutaneous disease, often triggered by preceding infection or drug ingestion. Histologically, it is identified by a neutrophilic infiltrate surrounding and disrupting small vessels (postcapillary venules) associated with fibrin deposits and nuclear debris (leukocytoclasia). Extravasated red blood cells, purpura, will be found in the adjacent dermis.

FINALIZING THE DIAGNOSIS

- Biopsy:
  - Skin may be most accessible
  - Vasculature is ideal but not always practical

- Non-invasive testing:
  - MRI/MRA/CTA/Vascular US/PET Scan – may all help to detect large artery lesions and are standard of care
  - No findings are specific but can be helpful in supporting a dx
  - Some vessels below the resolution of angiogram

- Invasive angiography helpful in anatomy as well as measurement of central pressures
APPROACHING THE TREATMENT: GENERAL PRINCIPLES

- Specific treatment depends on the organ involvement and the severity of disease.
- “What is the severity? What is the activity?”
- Induce remission
- Maintain remission
- Reduce short and long term adverse effects
APPROACHING THE TREATMENT: INDUCE REMISSION

- **MEDIUM-HIGH DOSE STEROIDS**
  - Systemic Vasculitis has a rapid onset and can be rapidly progressive
  - Flares can often be more severe than the initial presenting symptoms

- **STEROID SPARING AGENT**
  - Allows for reduction of glucocorticoid as tolerated
  - Continue both until enough time for the DMARD to take effect and then reduce steroid slowly
  - Goals: maintain control of disease activity, improve symptoms, prevent relapse and recurrence, minimize drug toxicities
APPROACHING THE TREATMENT: INDUCE REMISSION

- CONVENTIONAL THERAPY OF HIGH DOSE STEROIDS AND CYCLOPHOSPHAMIDE
  - Efficacy of steroids is there but risk of complications is high.
  - Study ongoing to compare regimens with high standard dosing with lower.
  - Induction with CYC, Mycophenolate Mofetil, Methotrexate, Rituximab
  - Daily oral CYC vs Pulsed IV regimen. (those who received daily were older and had renal disease so likely poorer outcome)
  - Similar results to other trials – PO and IV CYC equally effective but PO had more side effects i.e. neutropenia and infections / death

Treatment regimens are based upon specific diagnosis and severity and extent of the disease.

Size of vessel does not determine which treatment regimen is most effective or what monitoring is required.

**EXAMPLE:**

- AAV (high dose glucocorticoids and immunosuppressive agents) VS. NSAIDs or steroids for symptoms but neither alter the self limited course of disease.

- **DRUG INDUCED VASCULITIS:** removal of offending agent may not be enough and if persistent, consider GC, immunosuppression.
APPROACHING THE TREATMENT: MAINTENANCE OF REMISSION

- Studies looking at length of time on maintenance medication.
- Longer time on maintenance therapy beyond standard 24 month course
  - 48 months had more severe adverse effects but less chance of relapse and better renal outcome in AAV
  - Other studies showed the opposite
  - Controversial in terms of practical application
- Looking at inhibition of the complement system growing as a novel treatment (C5a)
- REFRACTORY EGPA: Mepolizumab (il-5 monoclonal ab that binds to il-5 and prevents the interaction with the receptor on the eosinophil surface
  - MORE WEEKS IN REMISSION AND REDUCED GC USE AT WEEK 36 AND 48

APPROACHING THE TREATMENT

USE OF METHOTREXATE IN GCA AND TAKAYASU’S ARTERITIS:
- CAN USE IN MAX DOSE OF 25MG/WEEK
- DECREASED RECURRENCE OF DISEASE IN GCA
- INEFFECTICITY RELATED TO YOUNGER AGE, BASELINE CV DISEASE, HIGH DOSE STEROIDS EARLY AND LOW DOSE MTX.
- REMISSION IN 75% WITH MTX

USE OF TOCILIZUMAB IN GCA (IL-6 RECEPTOR ALPHA INHIBITOR)
- WEEKLY TOCI WITH 26 WEEK TAPER OF PRED WAS SUPERIOR TO LONGER TAPERING AND PLACEBO IN TERMS OF REMISSION


APPROACHING THE TREATMENT: MONITORING

- CLOSE CLINICAL FOLLOW UP
- MONITOR VITAL ORGAN FUNCTION – even for manifestations that have not been previously experienced
- MAY NEED TO REIMAGE CERTAIN AREAS
- MRA may be helpful
- MAY NEED REPEAT BIOPSY

- Flares can occur even after successful remission induction and maintenance
- May need standardized measures of activity (i.e. BVAS)
APPROACHING THE TREATMENT: MONITORING

- Even after remission, vascular injury during acute phase can lead to scarring and narrowing of affected BV.
- Ischemia that does not reflect active inflammation of the disease
- Diagnosis and symptom improvement may take time.
- Monitor for comorbidities of the disease or treatment – HTN, accelerated atherosclerosis, anemia, infertility, premature ovarian failure, GC complications
Questions:

1. The clinical feature in Giant Cell Arteritis that is associated with the highest likelihood ratio of a positive temporal artery biopsy is:
   - A. Scalp Tenderness
   - B. Shoulder and Hip Girdle pain
   - C. Jaw Claudication
   - D. Fever

   (Answer: C. Jaw Claudication)
Questions:

2. Complications of Kawasaki Disease include all of the below except:
   - A. Myocardial infarctions
   - B. Anterior Uveitis
   - C. Glomerulonephritis
   - D. Congestive heart failure

(Answer: C. Glomerulonephritis)
3. The role of invasive angiography in large vessel vasculitis includes:
   - A. Measurement of central pressures
   - B. Treatment with intralesional steroids
   - C. Measurement of vessel wall thickness

(Answer: A. Measurement of Central Pressures)