Vasculitis – A Diagnostic Dilemma for Primary Care

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Vasculitis

How to recognize it and

when to ask for help
Challenging Diagnosis for All

- Non-specific symptoms
- Overlapping syndromes
- Lack of highly specific or sensitive tests
- Absence of generally accepted diagnostic criterion
Classification criteria for different vasculitic syndromes proposed for research purposes is not useful in the clinical setting.
2012 Revised International Chapel Hill Consensus Conference on Nomenclature of Vasculitides
Diagnosis of Specific Forms of Vasculitis

Depends on recognition of particular patterns of:

- Clinical
- Radiographic
- Laboratory
- Histopathology
Vasculitis – Definition

• A general term for a group of uncommon diseases that feature inflammation of blood vessels

• Each of these diseases defined by characteristic distributions of blood vessel involvement, patterns of organ involvement and lab test abnormalities
Figure 1. Systemic Vasculitides According to Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Systemic Vasculitis\textsuperscript{2}, with AAV Shown in Blue.
Primary and Secondary Vasculitides
### Classification of Vasculitis

Some types of vasculitis previously had different, eponym-based names:

<table>
<thead>
<tr>
<th>Old Name</th>
<th>New Name</th>
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</thead>
<tbody>
<tr>
<td>Wegener’s Granulomatosis</td>
<td>Granulomatosis with Polyangiitis</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome</td>
<td>Eosinophilic Granulomatosis with Polyangiitis</td>
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<tr>
<td>Henoch-Schönlein Purpura</td>
<td>IgA Vasculitis</td>
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</tbody>
</table>
Primary

- Large Vessel Involvement
  - Giant cell arteritis
  - Takayasu’s arteritis
  - Behcet’s syndrome
Primary

- Medium and Small Vessel Involvement
  - Polyarteritis nodosa
  - Cutaneous polyarteritis
  - Granulomatosis with polyangitis
  - Eosinophilic granulomatosis with polyangitis
  - Microscopic polyangitis
  - Thromboangitis obliterans
  - Cryoglobulinemia
  - Kawasaki’s disease
  - Behcet’s syndrome
  - Primary angitis of the CNS
  - Cogan’s syndrome
Primary

- Predominately Small Vessel Involvement
  - Cutaneous leukocytoclastic vasculitis
  - Urticarial vasculitis
  - Behcet’s syndrome
  - IgA vasculitis
Evaluation of Patients Where Vasculitis is Considered

- Individually tailored
- Based on extent of organ involvement
- Tempo of the disease
- Tissue biopsy remains the gold standard for diagnosis
Initial Approach to Diagnosis of Vasculitis

- History and physical exam
- Accurately catalogue areas of disease involvement
- No single typical presentation
- Must recognize patterns of signs and symptoms
# Patterns of Symptoms / Signs

<table>
<thead>
<tr>
<th>Skin System</th>
<th>Size of Vessels</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
</tr>
<tr>
<td>Skin</td>
<td>Palpable purpura</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Mucositis GI bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Hematuria without RBC casts Proteinuria</td>
</tr>
<tr>
<td>Neuro</td>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Muscles</td>
<td>Myalgias</td>
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</tbody>
</table>
Clinical Manifestations

- Chronic fevers
- Palpable purpura
- Symptoms of tissue ischemia in unusual populations
- Neuropathy
- Rapidly progressive multisystem inflammatory disease
History

- Illicit drug use
- High risk sexual activity
- Prior thrombosis
- Miscarriages
- Travel history
- Prior malignancies
- Operations and dental procedures
- Medications and OTC supplements or herbal preparations
- Chemical exposure
GCA

- Headaches
- Scalp tenderness
- Jaw claudication
- Vision loss
- Muscle pain/stiffness
Pulmonary-Renal Syndrome

- Cough and hemoptysis
- Hematuria
- Chronic sinusitis
- Asthma
- Eosinophilia
Physical Exam

Provide clues to presence of vasculitis or its mimics

Complete vascular exam includes:

1. Palpation of arterial pulses
2. Auscultation for bruits
3. BP measurement of all extremities
Bruit

- Takayasu’s arteritis
- GCA
- Behcets syndrome
- Cogans syndrome
Loss of Pulse

- Takayasu’s arteritis
- GCA
- Thromboangitis obliterans
Polyarteritis Nodosa

- New onset hypertension
- Abdominal pain
- Mononeuritis multiplex
Laboratory Evaluation

- CBC with diff, CMP, UA, ESR, CRP, CPK, aldolase
- No specific lab test to diagnose vasculitis
- Neither ANCA or complement levels should be used as screening tests
Testing That is Suggestive of Vasculitis

- Normochromic, normocytic anemia
- Thrombocytosis (acute phase response)
- Eosinophilia
- Hematuria
- Proteinuria
- Elevated transaminases = hepatitis B and HCV
- Elevated ESR but normal does not exclude vasculitis – 24% normal ESR in GCA
- ESR elevation most also exclude malignancies and infections
ANCA – What’s the Deal?

No specific lab tests for diagnosis of vasculitis
Proposed Indications for ANCA Testing

- Cutaneous vasculitis with systemic features
- Pulmonary hemorrhage
- Glomerulonephritis (especially rapidly progressive)
- Multiple lung nodules
- Chronic destructive upper airway disease
- Longstanding sinusitis or otitis
- Subglottic or tracheal stenosis
- Peripheral neuropathy
- Retro-orbital mass
ANCA

- c ANCA (cytoplasmic staining) – generalized GPA
- p ANCA (perinuclear staining) – microscopic polyangiitis or MPA
Positive ANCA

- Does not establish a diagnosis
- Seen in diverse spectrum of disease
  - Inflammatory bowel disease
  - SLE
  - Drug induced vasculitic reactions
  - Infections
Demonstrating the presence of a circulating ANCA is NOT equivalent to diagnosing vasculitis.
What to do if ANCA Immunofluorescence Test is Positive?

- Elisa testing for PR3 and MPO
- Elisa testing vs immunofluorescence higher predictive value (83% versus 45%)
- c ANCA + PR3 highly suggestive of GPA
- p ANCA + MPO highly suggestive of MPA
- But 10-20% of patients with GPA have +p ANCA and +MPO
- Some with MPA or EGPA are c ANCA positive
Cocaine and Levamisole Associated Vasculitis

- High titer p ANCA
- Low titer MPO antibodies
- PR3 antibodies
- Human neutrophil elastase, lactoferrin, cathepsin G
• 10-50% of patients with biopsy proven vasculitis will have negative serologies

• 10% of patients with positive c ANCA and PR3 ABS with other diagnosis, i.e. malignancy, infection or other connective tissue disease

• Increased use of ANCA in patients with low clinical suspicion of vasculitis or recent changes in detection methods
ANCA Testing

• Should not replace tissue confirmation of GPA or MPA

• Unless clinical findings are classic and other causes exhaustively excluded
Complement Levels (C3 and C4)

- Decreased in lupus nephritis, cryoglobulinemia or endocarditis
- Normal in GPA or MPA
Antiglomerular Basement Membrane (GBM)

- Alveolar hemorrhage
- Normocomplementemic GN
- Pulmonary-renal syndrome
ANA and Rheumatoid Factor

- Not useful screening tests for vasculitis
- RF elevated in Sjogren’s cryoglobulinemia and subacute bacterial endocarditis
Secondary Vasculitis

- Vasculitis when documented may not be primary
- Especially the case in cutaneous small vessel vasculitis and purpura
- Leukemia, myelodysplasia, I.E., viral hepatitis, rickettsial and neisserial infections, carcinomas and systemic autoimmune disease
Secondary and Mimics

- Infections
  - Subacute bacterial endocarditis
  - Syphilis
  - Hepatitis B
  - Hepatitis C
  - Cytomegalovirus
  - Epstein-Barr virus
  - Human immunodeficiency virus
  - Meningococccemia
  - Tuberculosis
  - Brucella
  - Salmonella
  - Rocky Mountain spotted fever
Helpful Tests Useful in Excluding Some Secondary Causes of Vasculitis or Mimics

- 3 sets of blood cultures
- TEE despite negative cultures
- Serologic tests for organisms, i.e. syphilis tests in evaluation of aortitis
Bacterial Endocarditis

- Purpura
- Mesenteric arterial microaneurysms
- G.N.
- Retinal vasculitis
- Stroke
- Arthritis
- Cryoglobulins
- R.F. and PR3 + ANCA
Secondary and Mimics

- Medications
  - B-lactams
  - Sulfonamides
  - Quinolones
  - Macrolides
  - Thiazides
  - Loop diuretics
  - Beta blockers
  - Phenytoin
  - Propylthiouracil
  - Selective serotonin reuptake inhibitors

- NSAIDS
- Antitumor necrosis factor
- alpha inhibitors
- Colony stimulating factors (GM-CSF, G-GSF)
- Carbimazole
- Clopidogrel
- Montelukast
- Minocycline
Cutaneous Vasculitis

- 172 adults (Cutaneous Vasculitis -120)  
  Hypersensitivity Vasculitis - 70, HSP-39, Mixed Cryoglobulinemia-11
- 23 systemic necrotizing vasculitis (P nodosa-17, GPA-4, EGPA-2)
- 4 malignancy
- 5 systemic bacterial infection
- 20 autoimmune disease
- 80% of mixed cryoglobulinemia associated with Hep C
Secondary and Mimics

- **Drugs**
  - Cocaine + levamisole
  - Amphetamines
  - Heroin

- **Other**
  - Malignancy
  - Thrombotic thrombocytopenic purpura
  - Cardiac myxoma
  - Cholesterol emboli syndrome
  - Atherosclerosis
  - Calciphylaxis
  - Amyloidosis
  - Moyamoya disease
  - Ehlers-Danlos syndrome
  - Fibromuscular dysplasia
  - Antiphospholipid antibody syndrome
Secondary Testing

- Focus on providing supportive evidence for vasculitis
- Exclude mimics
Cancer

- Purpura
- Fever
- Mononeuritis multiplex
Peripheral Neuropathy / Myopathy

- EMG / NC
- Infection, toxin, malignancy, metabolic, inflammatory processes
- Nerve / muscle biopsy
- Direct imaging
Imaging Studies in Arteritis
Angiography

- Important in evaluation of aorta for arteritis, aneurysmal or occlusive diseases
- Angitis of CNS
- Coronary arteritis in Kawasaki disease
- Limited spatial resolution therefore small vessel vasculitis will typically not be seen
Microaneurysms

- Highly suggestive of vasculitis if seen in more than one organ
- Medium sized muscular arteries (PAN)
- Prolonged time to develop and with negative results early in disease course
- Traditional angiography only visualizes vessel lumen and misses thickening of vessel wall seen in early stenosis or aneurysms
Microaneurysms

- PAN, MPA, EGPA and Behcets
- Atrial myxoma, endocarditis, peritoneal carcinomatosis
- Severe arterial hypertension with amphetamine abuse
MRI

- More common than traditional angiography for aorta and primary branches
- Visualizes vessel lumen and demonstrates edema and thickness of vessel walls
- Can overestimate vascular occlusions
- No consistent correlation of wall edema with symptoms, acute phase reactants or new anatomic changes
• Determine areas of suspected organ involvement

• MRI for air fluid levels, mucosal inflammation, cavitary lesions, retro-ortibal involvement

• CT scans for air fluid levels, mucosal thickening, sclerosing osteitis, bone thickening, destruction
MRI in CNS Vasculitis

- Abnormal in 90% of histologically proven angitis
- Ischemia, infarcts, mass lesions and meningeal enhancement
- Normal MRI does not exclude CNS vasculitis
- Lumbar puncture, cerebral angiogram, brain biopsy
- Normal MRI and normal CSF = CNS vasculitis is rare
Pulmonary Disease

- CXR normal study does not exclude disease
- HRCT very sensitive means of detecting pulmonary abnormalities
- HRCT can differentiate between ground glass changes and fibrosis
- HRCT cannot differentiate alveolar hemorrhage from vasculitis, infection or medication
- Biopsy of lung
Ultrasound

- Better for medium sized peripheral arteries
- Halo sign – hypoechoic dark wall swelling
- Sensitivity 69%, specificity 82% compared to temporal artery biopsy
- Much less effective in detecting recurrent disease
PET Scanning

- Useful in diagnosis and follow up of large vessel vasculitis
- PET signal strong for branches extending from aorta
- Evaluation of atypical presentation of vasculitis, FUO, increased ESR or CRP
- PET/CT upper respiratory tract and lung lesions in G.P.A. and vascular lesions in Behcet’s
What Should I Biopsy?
Biopsy Location

• Suspicion of clinical involvement
• Accessibility of tissue
• Several organ systems involved biopsy site determined by morbidity and amount of disease specific data
Skin Biopsy

- Small vessel vasculitis of involved skin easily demonstrated but not specific
- IgA vasculitis with IgA deposits
  Henoch-Schonlein purpura
Sample Size

- Vasculitis may not equally effect all portions of organ/vessel
- Skip areas of vasculitic involvement not unique to GCA
- Lung, nasal and sinus biopsies in GPA
- Muscle and nerve in small/medium sized vessels
- Blind biopsy of non-involved tissue low yield (19%-nerve, 29%-muscle)
Demonstration of Vasculitis on Biopsy

- Not a final diagnosis
- Is a sign of underlying condition to be evaluated in the context of clinical, serologic and imaging to establish final diagnosis
GCA

- Vague signs and symptoms, fevers, myalgia and anemia without headache or jaw claudication
- 65-year-old patients or older diagnosed in 16% of all patients with FUO
- Biopsy considered in all with FUO with malignancy and infections excluded
- Unilateral versus bilateral TA biopsy
- Specimen .5 cm in length positive in 19%
- Specimen >2 cm in length positive in 89%
- 10% with clinical diagnosis of GCA have normal biopsies
Lung Biopsy

- Transbronchial – low diagnostic return in vasculitis
- Helpful for infection, malignancy and hemorrhage
- VATS low morbidity and mortality compared to open lung with high sensitivity and specificity
Nasal and Sinus Biopsy

- For GPA and EGPA low diagnostic yield
- Vasculitis or granulomas rarely seen
Renal Biopsy

- Arteritis or granulomas rarely seen
- Generalized GPA biopsy site of choice is lung
- Proteinuria, increased CR, casts in setting of multisystem disease
General Steps to Diagnosing a Vasculitis

• Identify a collection of clinical findings (symptoms, signs) which either suggest a vasculitis in general, or optimally, a specific vasculitis
• Check routine labs (including coags, UA), and consider checking imaging studies (e.g. CTA, MRA) and/or ANCAs
  - Narrow down differential diagnosis to 1-2 specific vasculitides
  - Search for an associated systemic illness (e.g. malignancy, infection, connective tissue disease, etc…)
  - Rule out mimics
• Confirm diagnosis with biopsy (usually preferred) and/or angiography
VASCULITIS TREATMENT APPROACH

• REMISSION INDUCTION
  - Medium to high dose corticosteroids
  - Immunosuppressive agents disease specific
  - Failure of disease recognition associated with significant morbidity and mortality
REMISSION MAINTENANCE

• Corticosteroid dose steadily tapered to reduce toxicity
• Immunosuppressive/Corticosteroid treatment continued for a period of time - disease specific and protocol based
• Goals
  - Control of disease activity
  - Prevent recurrence
  - Minimize drug toxicity
MONITORING

- Active treatment phase-disease activity and drug toxicity
- Disease recurrence in drug free remission
DISEASE SPECIFIC THERAPY

• Based on specific diagnosis
• Severity of disease
• Vessel size does not determine which medication or treatment regime effectiveness or type of monitoring required
TREATMENT

- Randomized Trials
- Observational Studies
- Large Cohort Studies
PROGNOSIS

• Good outcomes for many
• Highly dependent on diagnosis
• Acute remission induction and subsequent maintenance phase of treatment
• Adverse drug effects and infections
Cleveland Clinic

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