Vasculitis: What The Primary Care Physician Needs To Know

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Disclosures

• No financial disclosures for any of the presenters

• Rituximab and mepolizumab are the only FDA-approved medications for ANCA-associated vasculitis. Application of all other therapies constitutes off-label usage.

Objectives

• Review classification of vasculitis
• Describe organ-specific manifestations
• Discuss common clinical presentations
• Depict a logical approach to diagnosis
• Outline approach to management
• Highlight important concurrent, comorbid, and follow-up considerations

Definition & Classification of Vasculitis

• Inflammation of the walls of blood vessels
Definition & Classification of Vasculitis

- Inflammation of the walls of blood vessels


ANCA-Associated Vasculitis (AAV)

- Heterogeneous group of diseases
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (GPA)
  - Eosinophilic granulomatosis with polyangiitis (EGPA)
  - Renal-limited vasculitis (RLV)

Morbidity, mortality and organ damage are attributable to the underlying disease and to complications of immunosuppressive therapy

Multi-organ involvement, necessitating multidisciplinary care
AAV: Pathophysiology

- Role of infection
  - Frequently preceded by URI symptoms
  - Staph aureus colonization associated with risk of relapse
  - CpG stimulates ANCA production in vitro

- Role of ANCA
  - ANCA can induce neutrophil activation and degranulation
  - In mouse models, anti-MPO and anti-PR3 have produced varying degrees of inflammation, glomerulonephritis, and pulmonary hemorrhage
  - Relapse uncommon with undetectable B cells or ANCA

- Role of complement, C5a

References:
- Hurtado PR. BMC Immunology 2008;9:34.

AAV: Defining Features

- Antineutrophil cytoplasmic antibodies (ANCA)
  - Myeloperoxidase (MPO-ANCA)
  - Proteinase 3 (PR3-ANCA)

References:

Images courtesy Ulrich Specks, MD
AAV: Defining Features

- Antineutrophil cytoplasmic antibodies (ANCA)
  - Myeloperoxidase (MPO-ANCA)
    - Expressed in neutrophil cytoplasmic granules
    - Perinuclear (p-ANCA) staining pattern by indirect immunofluorescence using ethanol fixed neutrophils
  - Proteinase 3 (PR3-ANCA)
    - Expressed in neutrophil cytoplasmic granules
    - Cytoplasmic (c-ANCA) staining pattern

Images courtesy Ulrich Specks, MD

AAV: Defining Features

- Necrotizing inflammation of small blood vessels, most characteristically capillaritis
- Necrotizing granulomatous tissue inflammation in GPA, EGPA

AAV: Defining Features

- Necrotizing inflammation of small blood vessels, most characteristically capillaritis
- Necrotizing granulomatous tissue inflammation in GPA, EGPA
- Multi organ involvement (except RLV)
  - Ear, nose, and throat
  - Lungs and trachea
  - Kidneys
  - Eyes and orbit
  - Skin
  - Nervous system

- Special considerations for EGPA
  - Peripheral eosinophilia
  - Cardiomyopathy
AAV: Defining Features

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May have acute or subacute presentation, inpatient or outpatient setting

ENT and Pulmonary Manifestations of AAV

Alveolar Hemorrhage

• Capillaritis at the alveolar level
• Presentation – patients might only have one of these
  o Dyspnea
  o Hypoxemia
  o Hemoptysis
  o Anemia
  o Alveolar infiltrates on imaging
→ Can be life-threatening

De Lassence A. AJRCCM 1995;151:157

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• Presentation – patients might only have one of these
  o Dyspnea
  o Hypoxemia
  o Hemoptysis
  o Anemia
  o Alveolar infiltrates on imaging
→ Can be life-threatening
• Bronchoalveolar lavage
  o Progressive bloody return on BAL
  o >20% Hemosiderin laden macrophages
These findings are not specific for vasculitis

De Lassence A. AJRCCM 1995;151:157
ENT Features

- Sinus
  - Chronic sinusitis
  - Sinus pseudotumors
- Nasal
  - Crusting
  - Epistaxis
  - Saddle nose deformity

ENT Features

- Sinus
  - Chronic sinusitis
  - Sinus pseudotumors
- Nasal
  - Crusting
  - Epistaxis
  - Saddle nose deformity
- Hearing issues:
  - Sensorineural hearing loss
  - Recurrent otitis
  - Recurrent inner ear fluid
- Orbital pseudotumors – may impair vision

Airway Disease: “Asthma plus”

- Peripheral eosinophilia
- Steroid dependence
- Severe concurrent sinusitis
- Transient pulmonary infiltrates

→ Consider EGPA

Airway Disease: Stenosis

- Subglottic stenosis
  - Shortness of breath or cough unresponsive to albuterol
  - Stridor
  - Fixed central airway obstruction
    → blunting of both inspiratory and expiratory curves
  - Expiratory disproportion index (EDI = FEV1/PEFR) >0.5
    suggests clinically significant stenosis

Airway Disease: Stenosis

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  - Stridor
  - Fixed central airway obstruction ⇒ blunting of both inspiratory and expiratory curves
  - Expiratory disproportion index (EDI = FEV1/PEFR) >0.5 suggests clinically significant stenosis
- Large airway stenosis
  - Shortness of breath, focal wheeze
  - May yield biphasic expiratory curve or a “tail”

Pulmonary Nodules

- May be solitary or multiple
  - When following typical guidelines with serial CTs, may increase in size quickly
- May be cavitary
- May be associated with adenopathy
  ⇒ Broad differential diagnosis, including infection and malignancy. BAL and biopsies can be helpful.

Interstitial Lung Disease

- Relationship less clearly defined than with other manifestations, emerging data
- High resolution chest CT pattern may be nonspecific, or suggestive of usual interstitial pneumonia (UIP)
- Findings may precede other disease manifestations
- More commonly seen with positive anti-MPO

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Renal Manifestations of AAV

Glomerulonephritis
- Present in 18% of patients at initial presentation
- Around 80% of patients develop glomerulonephritis in the first 2 years after diagnosis.
- Can be the only presenting feature (renal-limited vasculitis)
- No specific presenting symptoms for glomerulonephritis but patients often have accompanying constitutional symptoms.
- If renal involvement is severe patients can present with uremic symptoms (nausea, vomiting, malaise, confusion) and oliguria


Glomerulonephritis
- Often first detected with lab work, presentation varies in severity:
  - Rapidly progressive glomerulonephritis
    - Rapid worsening in renal function manifesting as an increase in creatinine a declining urine output
  - Mild increase in creatinine
  - Proteinuria (usually subnephrotic)
  - Hematuria

Urine sediment
- Evaluation of the urine sediment may show:
  - RBC casts
  - Acanthocytes
## Other Manifestations of AAV

<table>
<thead>
<tr>
<th>Constitutional</th>
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</thead>
<tbody>
<tr>
<td>• Fatigue</td>
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<tr>
<td>• Fever</td>
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<tr>
<td>• Arthralgias</td>
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<tr>
<td>• Weight loss</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Cutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leukocytoclastic angiitis</td>
</tr>
<tr>
<td>• Urticaria</td>
</tr>
<tr>
<td>• Livedo reticularis</td>
</tr>
<tr>
<td>• Thrombosis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological and ophthalmmic</th>
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</thead>
<tbody>
<tr>
<td>• Mononeuritis multiplex</td>
</tr>
<tr>
<td>• Sensory neuropathy</td>
</tr>
<tr>
<td>• Cranial nerve abnormalities</td>
</tr>
<tr>
<td>• Central nervous system and orbital mass lesions</td>
</tr>
<tr>
<td>• External ophthalmoplegia</td>
</tr>
<tr>
<td>• Sensorineural hearing loss</td>
</tr>
</tbody>
</table>
### Others

- **Gastrointestinal tract**
  - Peritonitis
  - Bowel perforation
  - Bowel ischemia

- **Heart**
  - Pericarditis
  - Myocarditis
  - Conduction system abnormalities

### Clinical Presentation Depends on Severity

#### Inpatient
- Often due to capillaritis manifestations, may be organ or life-threatening
- Pulmonary-renal syndrome
  - Alveolar hemorrhage, glomerulonephritis
  - “Pan-consult”
- Rapidly progressive renal failure
  - Significant rapid increase in creatinine
  - Symptoms of acute renal failure

#### Outpatient
- Often due to granulomatous features
  - Subglottic stenosis, asthma, sinusitis
  - Cough, dyspnea
  - Pulmonary nodule
  - Saddle nose deformity
  - Otitis, sensorineural hearing loss
  - Microscopic hematuria, proteinuria
  - Mononeuritis → foot drop
  - Rash
  - Fatigue
  - Arthritis

### Diagnosis - Society guidelines

- **ACR criteria** — The American College of Rheumatology (ACR) 1990 classification
  - Nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge)
  - Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
  - Abnormal urinary sediment (microscopic hematuria with or without red cell casts)
  - Granulomatous inflammation on biopsy of an artery or perivascular area
- The presence of two or more of these four criteria yielded a sensitivity of 88 percent and a specificity of 92 percent

### Diagnosis – ANCA testing

- **ANCA**
  - Indirect immunofluorescence testing
    - Sensitive, used for screening, cannot distinguish between disease based on positive ANCA
  - **p-ANCA**
  - **C-ANCA**
  - Immunoassays (ELISA, LUMINEX)
    - Specific, used for confirmation
    - Antibodies specific for antigens in neutrophil granules and monocyte lysosomes
  - **MPO-ANCA**
  - **PR3-ANCA**

<table>
<thead>
<tr>
<th></th>
<th>PR3</th>
<th>MPO</th>
</tr>
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<tbody>
<tr>
<td>C-ANCA</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>P-ANCA</td>
<td>10%</td>
<td>90%</td>
</tr>
</tbody>
</table>
### Diagnosis – ANCA testing

- **ANCA positivity**
  - GPA: 90% (80-90% of which is PR3-ANCA)
  - GPA without renal involvement: 60%
  - MPA: 90% (vast majority MPO-ANCA)
  - RLV: 75%
  - EGPA: 50% (70% of which is MPO-ANCA)


- **Other diseases with positive ANCA:**
  - Drug-induced vasculitis (hydralazine, propylthiouracil, methimazole, carbimazole, minocycline, and levamisole)
  - Other rheumatologic diseases:
    - Rheumatoid arthritis,
    - Systemic lupus erythematosus (SLE),
    - Sjögren’s syndrome, inflammatory myopathies
  - Gastrointestinal disorders:
    - Ulcerative colitis
    - Primary sclerosing cholangitis
  - Cystic fibrosis
  - Infection-associated glomerulonephritis (around 25%)
Large cellular crescent

Unremarkable glomerular ultrastructure. No deposits were seen.
Diagnosis – Other biopsies

- Sinus, airway, lung, skin
- Pathologic features, key terms
  - Necrosis
  - Giant cells
  - Vasculitis
  - Capillary formation
  - Granulomatous inflammation
  - Palisading histiocytes


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Treatment GPA & MPA

- Initial therapy depends on severity of presentation
  - Severe disease = organ or life-threatening, often includes a capillaritis manifestation
  - Nonsevere disease = none of the above
- Phases of therapy
  - Remission induction
  - Maintenance of remission


Treatment GPA & MPA – Remission Induction

<table>
<thead>
<tr>
<th>Phase</th>
<th>Nonsevere</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction agent</td>
<td>Methotrexate MPA</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Prednisone 0.5 mg/kg tapered over 6 months</td>
<td>Methylprednisolone 1g IV x 1-3 doses,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisone 0.5-1mg/kg tapered over 6 months</td>
</tr>
<tr>
<td>Other</td>
<td>Directed therapies</td>
<td>Plasma Exchange</td>
</tr>
</tbody>
</table>

*The only FDA approved medication is Rituximab
Treatment GPA & MPA – Maintenance

• Azathioprine
• Mycophenolate
• Rituximab, evolving data
• Prednisone

Treatment of EGPA

• If there are true “vasculitic” manifestations, same agents are typically used for remission induction
• Mepolizumab (anti-IL-5) recently approved by the FDA
  – Depletes eosinophils
  – Subcutaneous injection, monthly
  – 300mg dose vs. 100mg dose for eosinophilic asthma
• Continue to aggressively treat asthma, triggers

Outcomes of Treatment GPA, EGPA, MPA

• Good news: Remission is achieved in approximately 90% of patients
• Bad news: More than half of patients with severe disease go on to experience relapse

Predictors of Relapse

<table>
<thead>
<tr>
<th>Consistent Predictors of Relapse</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-ANCA/PR3</td>
<td>1.8 (1.1,2.9)</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>2.2 (1.4,3.6)</td>
</tr>
<tr>
<td>Upper respiratory involvement</td>
<td>1.6 (1.1,2.5)</td>
</tr>
<tr>
<td>All of the above</td>
<td>3.4 (2.1,5.7)</td>
</tr>
<tr>
<td>Any one of the above</td>
<td>1.8 (1.0,3.5)</td>
</tr>
</tbody>
</table>

Hogan et al. Annals Int Med. 2005 Nov 1;143(9):621-312005
**Treatment: Nonpharmacologic Interventions**

- ENT
  - Sinus surgery, particularly with EGPA
  - Laryngoscopy
  - Airway laser
- Interventional Pulmonary
  - Stent placement
  - Balloon dilatation
  - Role in active disease vs. “damage” related to prior inflammation

**Contraception:**

- Risks for vasculitis patients and benefits need to be considered
  - IUD: increased risk of upper genital infections
  - Oral contraceptive pill containing estrogen:
    - Increased risk of thrombosis
  - Depo-provera injections and progestin-only pills are available

**Bone Health**

- Treatment and prevention of osteoporosis is problematic for vasculitis patients on chronic corticosteroids
  - Calcium and vitamin D
- Long term effects of bisphosphonates on future fetal growth are unknown
- Use of estrogen is associated with increased risk of flares in some studies

**Diet and Exercise**

- Heart healthy diet
- Moderate exercise has significant beneficial effect
### Infection prevention/monitoring

- Vigilance in evaluating suspected infectious processes
- Vaccination
  - Live virus vaccines: may be contraindicated depending on the medications the patient is on
- Vigilance with screening studies
- Use prophylaxis while on aggressive immunosuppressive regimen
  - Pneumocystis prophylaxis
  - Important to note that rituximab may remain active/present for >6 months, and may not always be captured on patient's EMR medication list

### Autoimmune Diseases at a Glance

- Spectrum of diseases that vary from organ specific to systemic
- Almost every organ can be involved
- Autoimmune diseases' clinical manifestations can evolve over time
- A patient may have multiple autoimmune diagnoses

### Autoimmune Diseases at a Glance

- Therapy is only partially driven by data and the guidelines are largely consensus based
- Comorbidities are multiple and require vigilance