Pulmonary Vasculitides

Eduardo J. Mortani Barbosa, Jr., MD
Assistant Professor of Radiology
University of Pennsylvania

Society of Thoracic Radiology
San Antonio, TX, March 2014

Learning Objectives
1. Concise yet thoroughly updated overview of the imaging findings and diagnostic approach to the most common vasculitides involving the lungs (PV)
2. Spectrum of imaging presentations of pulmonary vasculitides, emphasizing the importance of correlation with clinical and laboratory findings, enabling a conceptual framework that allows generation of an appropriate differential diagnosis – which invariably excludes entities other than PV – and a specific set of recommendations

Strategy
1. Classification, Pathophysiology and Epidemiology
2. Imaging Patterns and Brief Discussion of Specific Entities
3. Differential Diagnosis
4. Teaching Points and Take Home Messages

DDx of Pulmonary Vasculitides

Large Vessel Vasculitides (aorta and first order branches, pulmonary arteries)
- Takayasu arteritis
- Behçet’s disease

Medium Vessel Vasculitides
- Typically do not involve the lungs! (PAN, Kawasaki’s disease, CNS vasculitides)

Small Vessel Vasculitides (ANCA-positive = AAV)
- Granulomatosis with polyangiitis (GPA = Wegener’s granulomatosis, c-ANCA)
- Eosinophilic granulomatosis with polyangiitis (EGPA = Churg-Strauss syndrome, p-ANCA)
- Capillaritis/Diffuse Alveolar Hemorrhage (DAH)
  - GPA (c-ANCA)
  - MPA (p-ANCA)
  - Systemic lupus erythematosus (SLE)
  - Anti-GBM antibody disease (Anti-GBM AD = Goodpasture’s syndrome if DAH)

ANCA = serum antineutrophil cytoplasmic antibodies
Two different patterns: perinuclear-ANCA (p-ANCA) and cytoplasmic-ANCA (c-ANCA)

Diagnosis of PV is very challenging! Why?
- Very rare diseases in the general population
  Incidence: 20-100 cases/million
  Prevalence: 150-450 cases/million
- Non-specific and protean imaging findings
- Highly variable clinical presentation, mimicked by multiple DDx
- The DDx are FAR MORE COMMON than PV (e.g. pulmonary edema, multifocal pneumonia, malignancy, connective tissue diseases)
- Oftentimes the radiologist is the FIRST to suggest a PV => Low index of suspicion!

Solution: Know the most common patterns and associations; think about PV in the proper clinical setting; interact with the referring clinician; guide them to obtain proper laboratory and pathology correlation, particularly if not a specialist; F/UP!

Clinical, laboratory and often pathology findings are crucial. Scenarios suggestive of PV:
Systemic symptoms, usually chronic AND
MF airspace disease (T, x-ray), subacute to chronic, waxing and waning AND any of the following:
- Arterial wall thickening, aneurysms (Takayasu, Behçet)
- DAH: hemoptysis (75%), anemia (Goodpasture, SLE, GPA, MPA)
- Glomerulonephritis (pulmonary-renal syndrome => Goodpasture, SLE, GPA, MPA)
- Upper airway involvement, including sinusitis (GPA)
- Multiple cranial nerves, masses (GPA)
- Eosinophilia and Asthma (EGPA)
- c-ANCA (GPA) or p-ANCA (EGPA or MPA), ANA positivity (SLE)
- Pulmonary hypertension (any)
- Palpable purpura (any)
- Mononeuritis multiplex (more often EGPA)
PV involving large/medium sized vessels cause:
- Mural thickening => Vessel stenosis with possible hypoperfusion/infarct
- Thrombosis or Thromboembolic Phenomena
- Dissection, Aneurysm, Pseudoaneurysm

PV involving small sized vessels in the lung parenchyma cause:
- Ground-Glass Opacities and Consolidation: Hemorrhage and Inflammation
- Tissue necrosis: Cavitary Nodules/Masses => GPA !
- Scarring: Tissue repair
- Thromboembolic phenomena: may lead to pulmonary infarct
- Airway/sinus involvement => more commonly in GPA

Imaging Patterns

What is the Role of Radiology ???

1) DDx based on Imaging Patterns and Temporal Evolution
2) Distribution and Severity of Disease; Monitor Treatment Response or Relapse
3) Imaging Presentations are NOT specific. PV are rarely the most common DDx of any pattern => Collaborative image interpretation is crucial
4) Serum biomarkers may be helpful (e.g. ANCA, ANA), but tissue biopsy is important (for the small vessel vasculitides) => Imaging helps to select the best site

Imaging Recommendations

CTA or MRA for suspected large vessel vasculitis
CTA or MRA for suspected large vessel vasculitis
CTA or MRA for suspected large vessel vasculitis
CTA or MRA for suspected large vessel vasculitis
CTA or MRA for suspected large vessel vasculitis

General Imaging and Clinical Features

PH + DAH + glomerulonephritis => This triad strongly suggests systemic vasculitis and should lead to appropriate work up!

Imaging Patterns

Large vessel vasculitis
- Takayasu: Arterial wall thickening or irregularity/branching of arteries, wall may enhance with contrast administration => more elusive to arterial stenosis or aneurysms
- Behçet: Pulmonary artery aneurysms are characteristic, venous disease is common

Small vessel vasculitis
- Multifocal GGO and/or consolidation, typically admixed
- Septal thickening and GGO ("crabby pneumatic"), suggests DAH
- Multiple (sometimes cavitary) ill-defined nodules: Bilateral without zonal predominance, usually few in number (<10), may be large (up to 10 cm), cavitation suggests GPA
- Small perivascular nodules, with tree-in-bud configuration, resemble bronchiectasis

- Tracheobronchial involvement => Suggests GPA - Subglottic stenosis in 15%
- Pulmonary arterial hypertension: Enlarged central arteries with distal pruning

Specific Entities => What you need to know!

Takayasu Arteritis
- Large vessel vasculitis of aorta and first order branches
- Involves central pulmonary arteries about 50% of times, usually late manifestation
- Arterial wall thickening and vessel stenosis
- Granulomatous inflammation
- Far more common in women (8:1), younger (typically < 40 at diagnosis), Asians
- CTA, MRA are the best imaging modalities and are superior to angiography
- Miroangiographic confirmation is seldom performed
- DDx: Giant cell arteritis, Fibromuscular dysplasia, Ehlers Danlos type IV, Behçet’s disease

Behçet’s Disease
- Widespread involvement of large, medium and small vessels
- Recurrent oral and genital ulcers; cutaneous manifestations; uveitis
- More common along the ancient “silk road” – described in Turkey
- Bi is clinical flaring and waning course is typical
- Pulmonary artery involvement is characteristic, aneurysms that may cause hemoptysis
- Venous disease is common: DVT, Budd-Chiari, inferior vena cava thrombosis
- Hughes-Stovin syndrome: Variant of Behçet, does not have oral or genital ulcers

General Imaging and Clinical Features

PV involving large/medium sized vessels cause:

Serum biomarkers may be helpful (e.g. ANCA, ANA), but tissue biopsy is important (for the small vessel vasculitides) => Imaging helps to select the best site
Ear nose throat (ENT) symptoms: 75% at presentation eventually in 90% includes sinusitis, nasal stuffiness, otitis media, ear pain, oral ulcers => mucositis.
• Airway involvement is common: 70% with bronchial wall thickening, 30% with vasculitic tracheal stenosis.
• Pulmonary parenchymal involvement (ill-defined nodules, often cavitary): 50% at presentation, eventually reaching 80%.

**EGPA – Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss syndrome)**

- Very rare (0.2-100,000)
- Asthma (~90%), atopy and peripheral eosinophilia are hallmarks, and may precede systemic vasculitis by more than a decade.
- Vasculitic Phase => Multi-system involvement
- ENT / upper airway involvement => 50%, chronic rhinosinusitis, non-necrotizing.
- Cardiac: ~15-50%, major cause of mortality, includes pericarditis and myocarditis.
- Peripheral Neuropathy is common.
- Pulmonary parenchymal involvement less common than in GPA => up to 50%, may be masked by corticosteroids. Includes peribronchial thickening, small perivascular nodules, ill-defined, migratory GGO, less commonly AFM consolidation.
- p-ANCA positive 40-60%; Granulomatous Inflammation with extensive eosinophilic infiltrate.
- DDx: Eosinophilic pneumonia, ABPA, GPA.

**Goodpasture’s Syndrome**

- Rare (1/1,000,000), less common than MPA, much less common than SLE.
- Immune-complex capillaritis, often causes glomerulonephritis and DAH (pulmonary renal syndrome).
- Anti-GBM antibodies are diagnostic, bind to alveolar and glomerular capillary basement membranes, absent in SLE.
- Most common manifestation in the Thorax is DAH => GS diagnosis requires the triad of DAH, glomerulonephritis and anti-GBM antibodies.
- DDx: SLE, MPA, GPA.

**MPA – Microscopic Polyangiitis**

- Most common cause of pulmonary-renal syndrome, but VERY rare (0.3/100,000).
- Currently considered a variant of GPA (formerly thought as small vessel variant of PAN).
- Affects kidneys, peripheral nerves, skin, and lungs.
- Glomerulonephritis 80-100%.
- Pulmonary involvement in 10-30%; most commonly DAH (diffuse GGO), though also may present with multifocal GGO and small perivascular nodules.
- p-ANCA positive 40-80%.
- NON-granulomatous vasculitis (distinguishing it from GPA).
- DDx: GPA, SLE, Goodpasture.

**GPA – Granulomatosis with Polyangiitis (Wegener’s)**

- Rare (3/100,000), but the most common vasculitis to affect the lungs.
- Ear nose throat (ENT) symptoms: 75% at presentation, eventually in 90%, includes sinusitis, nasal stuffiness, otitis media, ear pain, oral ulcers => mucositis.
- Airway involvement is common: 70% with bronchial wall thickening, 30% with vasculitic tracheal stenosis.
- Pulmonary parenchymal involvement (ill-defined nodules, often cavitary): 50% at presentation, eventually 85-90%. Can cause GGO/consolidation, albeit less frequently.
- Glomerulonephritis 20% at presentation, eventually reaching 80%.
- Hallmark is granulomatous vasculitis => biopsy any site of active disease to confirm.
- c-ANCA + in 80-90% of patients with GPA.

**Systemic Lupus Erythematosus (SLE)**

- Immune-complex capillaritis, causes glomerulonephritis and DAH (pulmonary renal syndrome).
- Infrequent manifestation of SLE (2% of patients); however, carries 70-90% mortality.
- 2 mechanisms: capillaritis with immune complex deposition and bland hemorrhage, usually co-exist.
- Most often, SLE causes serositis (pericardial and pleural inflammation with associated exsudative effusions) in the thorax.
- Pulmonary hypertension in 10-15% of patients.
- ANA is sensitive, high titers correlate with disease activity; anti-dsDNA and anti-sm antibodies are highly specific.

**Cardiogenic Pulmonary Edema**

- Cardiomegaly, bilateral, symmetric gravity-dependent GGO and/or consolidations, septal thickening and pleural effusion.
- Resolves rapidly with therapy (+ inotropes, diuretics).

**Extensive Pulmonary Infection [Multifocal Pneumonia]**

- Fever, chills, productive cough and elevated white blood cell count are common.
- Requires culture, stains and/or molecular studies to exclude.

**Remember that the DDx are numerous and generally FAR more common than Vasculitides**

**Very Common!**

- Extensive Pulmonary Infection [Multifocal Pneumonia]:
  - Fever, chills, productive cough and elevated white blood cell count are common.
  - Requires culture, stains and/or molecular studies to exclude.

**Goodpasture’s Syndrome**

- Very rare (1/1,000,000), less common than MPA, much less common than SLE.
- Immune-complex capillaritis, often causes glomerulonephritis and DAH (pulmonary renal syndrome).
- Anti-GBM antibodies are diagnostic, bind to alveolar and glomerular capillary basement membranes, absent in SLE.
- Most common manifestation in the Thorax is DAH => GS diagnosis requires the triad of DAH, glomerulonephritis and anti-GBM antibodies.
- DDx: SLE, MPA, GPA.
Still more common than PV!

Chronic Thromboembolic Pulmonary Hypertension
- Pulmonary artery hypertension; mural perfusion
- Central pulmonary artery walls thickened by chronic thrombus, usually much thicker than thickened vessel walls from vasculitis
- No systemic symptoms

Cryptogenic Organizing Pneumonia
- Peripheral rounded opacities, GGO and/or consolidations
- Peripheral rounded opacities, GGO and/or consolidations
- Opacities may be migratory, waxing and waning pattern
- Chronic (>1 month); responds to steroids

Non-Cardiogenic Pulmonary Edema (ARDS)
- Septal thickening uncommon, diffuse GGO and consolidation common
- Usually no cardiomegaly, pleural effusions less common
- Usually severely hypoxemic, requiring mechanical ventilation

PAU and intramural hematoma => Vessel wall thickening, luminal outpouchings (DDx for Takayasu, typically in older patients with severe atherosclerosis)

Septic Embolism and Cavitary Metastases (SCC)
- Cavitary Nodules/Masses (DDx for GPA)

RARER than PV!

Angiosarcoma and Intimal Sarcoma => Vessel wall thickening and aneurysms, typically large masses and enhancement

Genetic Vasculopathies (Marfan, Ehlers-Danlos) => Aneurysms, dissection, specific mutations

Teaching Points – Take Home Messages
1. Understanding the pathogenesis, clinical and laboratory findings is crucial to effective image interpretation of PV => Collaborative image interpretation!
2. Always begin by excluding the most common DDx: infection, pulmonary edema, malignancy, drug use/abuse
3. Think about PV when: DDx have been excluded, clinical presentation is chronic, waxing and waning, relapsing; the patient is younger; multi-systemic disease
4. Consider the proper clinical and imaging questions:
   - Large vessel disease (CTA/MRA)? => Takayasu (stenosis), Behçet (aneurysm)
   - MF cavitory consolidations + renal and/or airway involvement? => GPA
   - MF, GGO, migratory + asthma and eosinophilia? => EGPA
   - Signs/symptoms of DAH => MPA, SLE, Goodpasture’s
   - ANCA positivity => GPA (c-ANCA) sensitive and specific, MPA and EGPA (p-ANCA)

In summary => with proper correlation with clinical features and laboratory findings, as well as interaction with the referring clinician, the radiologist is often able to either reach a specific diagnosis of PV or at least suggest the correct diagnosis, which may require tissue sampling for ultimate confirmation

Thank you for your attention!

Selected References