Lung Manifestations of Rheumatological Diseases

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I have no conflict of interest relevant to this lecture
Objectives

1. Recognise the clinical presentations of pulmonary vasculitis in children

2. Understand the rationale behind the available treatment options for pulmonary vasculitis

3. Recognise the pulmonary presentations associated with connective tissue disease and inherited autoinflammatory disease
Why This is Important

- Pulmonologists may be the first consulted specialist
- Pulmonologists are often consulted by rheumatologists
- Lung disease can be severe, rapidly progressive and fatal
- Pulmonologists may be the primary driver of therapy (e.g. isolated pulmonary capillaritis)
Systemic Inflammatory Diseases Most Often Encountered by Pediatric Pulmonologists

Rare but Serious Pulmonary Involvement is Common

- Granulomatosis with Polyangiitis (GPA) and other vasculitides
- Scleroderma

Common but Serious Pulmonary Involvement is Rare

- Juvenile Idiopathic Arthritis (JIA)
- Systemic Lupus Erythematosus
What is Vasculitis?

• Vasculitis = inflammation of blood vessels

• Pulmonary vasculitis= rare!
  • Usually a manifestation of a recognized systemic inflammatory disease

  OR

  • Isolated pulmonary vasculitis

• Always potentially fatal
Pulmonary Involvement in Systemic Vasculitides

Ann Rheum Dis. 2006;65(7): 936-41
Kendig and Chernick’s Disorders of the Resp Tract in Child. 2018; Chapt 57:822-847
Clinical Presentations of Pulmonary Vasculitis

1. Diffuse Alveolar Hemorrhage (DAH)

2. Pulmonary Nodules or cavities

3. Tracheobronchial stenosis
Clinical Presentations of Pulmonary Vasculitis

1. Diffuse Alveolar Hemorrhage (DAH)

- Diffuse infiltrates, anemia, +/- hemoptysis
- Acute large volume hemorrhage: Hypoxia +/- respiratory failure
- Chronic insidious onset: Cough, dyspnea +/- fever
Clinical Presentations of Pulmonary Vasculitis

2. Pulmonary Nodules +/- cavities

Classic for GPA

Images courtesy of Sharon Dell, University of Toronto, Canada.

Pediatr Radiol. 2007; 37: 57-62
Clinical Presentations of Pulmonary Vasculitis

3. Tracheobronchial stenosis (specific for GPA)

Pinhole Bronchus

Tracheal Stenosis
Granulomatosis with Polyangiitis (GPA)
~Wegener’s Disease

- Most common pediatric vasculitis
  (0.5 per 100,000 per year in U.S., predominantly teens)

- Presentation: constitutional symptoms, upper airway involvement
  (sinusitis, epistaxis, nasal septal perforation) +/- renal failure

- Lower airway involvement in ~80% of cases:
  - Pulmonary nodules / cavities
  - Tracheobronchial stenosis
  - DAH

Saddle-Nose Deformity

Arthritis & Rheum. 2009; 60(11): 3413-24
Microscopic Polyangiitis (MPA)

- Rare systemic vasculitis (3-15 per million adults) and even more rare in children

- Typically presents with profound constitutional symptoms, joint involvement and renal involvement
  - Necrotizing crescenteric GN
  - Pauci-immune

- Lower airway involvement in ~30-60%
  - Classically DAH

Pediatr Nephrol. 2006; 21(1): 46-53
Eosinophilic Granulomatosis with Polyangiitis (EGPA) ~Churg-Strauss

- Exceedingly rare in children (0.15-3 million adults)

- Prodromal phase of worsening asthma, chronic rhinosinusitis and nasal polyposis

- Constitutional symptoms; eosinophilia (>10%); cardiac disease more common in children

- Lower airway involvement in ~70-90% of cases:
  - Patchy migrating pulmonary infiltrates
  - Rarely DAH

*Ann Int Med.* 2005;143: 632-8
*Ped Pulm* 2016;51:203-216
*Pediatric Pulmonology* 2018;53: 1640-1650
Isolated Pulmonary Capillaritis (IPC)

- Rare, but more common than EGPA
- Presents with isolated DAH
- +/- ANCA positivity (usually MPO)
- Frequent relapses and high mortality without treatment
- May develop extrapulmonary involvement with time

*J Pediatr.* 2005; 146(3): 376-81
Isolated Pulmonary Capillaritis (IPC)

- Classified as “single organ vasculitis” in revised Chapel Hill Consensus Criteria*

- May be misclassified as idiopathic pulmonary hemosiderosis (IPH) in cases of bland, ANCA-negative pulmonary hemorrhage

Q1. Which of the following vasculitides is least likely to have positive ANCA serology?

A. Eosinophilic granulomatosis with polyangiitis (EGPA, ~ Churg-Strauss)
B. Granulomatosis with polyangiitis (GPA, ~ Wegener’s disease)
C. Isolated pulmonary capillaritis (IPC)
D. Microscopic polyangiitis (MPA)
Q1. Which of the following vasculitides is least likely to have positive ANCA serology?

A. Eosinophilic granulomatosis with polyangiitis (EGPA, ~ Churg-Strauss)

B. Granulomatosis with polyangiitis (GPA, ~ Wegener’s disease)

C. Isolated pulmonary capillaritis (IPC)

D. Microscopic polyangiitis (MPA)
# Comparison of Small Vessel Vasculitides

<table>
<thead>
<tr>
<th></th>
<th>GPA</th>
<th>MPA</th>
<th>EGPA</th>
<th>IPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary involvement</strong></td>
<td>&gt;80%</td>
<td>~30-60%</td>
<td>70-90%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Typical pulmonary presentation</strong></td>
<td>Nodules +/- cavities, Airway stenosis, DAH</td>
<td>DAH</td>
<td>Asthma Patchy infiltrates Rarely DAH</td>
<td>DAH</td>
</tr>
<tr>
<td><strong>ANCA IF positive</strong></td>
<td>90-95%</td>
<td>70%</td>
<td>0-40% child 40-50% adult</td>
<td>0-?</td>
</tr>
<tr>
<td><strong>ANCA pattern</strong></td>
<td>c-ANCA/ anti-PR3</td>
<td>p-ANCA/ anti-MPO</td>
<td>p-ANCA/ anti-MPO</td>
<td>? p-ANCA/ anti-MPO?</td>
</tr>
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Modified from Ann Am Thorac Soc 2016: 13(6); 955-966.
Initial Workup of Pulmonary Vasculitis

• Laboratory investigations
  • CBC, coagulation profile, inflammatory biomarkers, renal studies
  • Autoantibody panel (ANCA, ANA, RF)
• Imaging
  • High resolution CT chest
  • Consider CT sinuses if clinical suspicion of sinus disease or GPA
  • Echocardiogram: r/o myocardial disease & pulmonary hypertension
• Bronchoscopy
  • To identify diffuse alveolar hemorrhage and large airway lesions
  • To rule out infection
• Tissue biopsy (eg. kidney, skin, nose, lung, bronchial lesions)
Bronchoscopy in DAH

Fresh blood in airways vs clean airways

Bloody lavage return despite clean appearing airways

Hemosideron-ladin Macrophages in BALF
Bronchoscopy in GPA with Airway Stenosis

Pinhole LMB

RMB stenosis & ulceration
Bronchoscopy in active EGPA

Images courtesy of Sharon Dell, University of Toronto, Canada

Lung Biopsy in Pulmonary Vasculitis

- Pathology
  - Transthoracic lung biopsy is gold standard for diagnosis
  - Can be difficult to interpret
    - Pre-op steroid administration
    - Patchy disease
    - Subtle findings (esp. in IPC)
Isolated Diffuse Alveolar Hemorrhage

### Idiopathic Pulmonary Capillaritis (IPC)
- Pauci-immune
- +/- Mild fibrosis
- +/- AEC2 hyperplasia
- Neutrophil infiltrate & fibrinoid necrosis of capillary walls

### Idiopathic Pulmonary Hemosiderosis (IPH)
- Pauci-immune
- +/- Mild fibrosis
- +/- AEC2 hyperplasia
- Bland alveolar hemorrhage

Images courtesy of Sharon Dell, University of Toronto, Canada

Systemic Vasculitis Treatment Options

- Rapidly fatal if untreated
  - GPA 1 year mortality 80%

- No RCTs in pediatric vasculitis; treatment options extrapolated from adult RCTs

- Modern treatment divided into “induction” and “maintenance” phases

*Ann Int Med.* 1983; *98*: 76-85
*Kendig & Chernick’s Dis of Resp Tract in Children.* 2018; Chapter 57
Therapy for Generalized Active AAVs

**Induction**
- Steroid + Cyclophosphamide
  - Or
  - Steroid + Rituximab
- Steroid + Rituximab

**Maintenance**
- Low dose Prednisone + Azathioprine
  - Or
  - Rituximab

**Timeline**
- Dx
- 3-6 mo
- 12 mo
- 18 mo
- 24 mo

Referenced sources:
- NEJM 2010;363:221+211; Ann Rheum Dis 2015;47:1178-82
- NEJM 2014;371:1771
Plasmapheresis for Induction of Remission

- **MEPEX trial** showed reduced end stage renal disease when combined with high dose steroids*
- Ongoing **PEXIVAS trial** to determine role in AAV
  - clinicaltrials.gov NCT#00987389
- Currently used for severe acute renal failure and DAH not responding to immunosuppressive therapy


Image: *Anesthesiology*. 2013; 118(3): 722-8
Maintenance Therapy

- Necessary due to high relapse rates after cessation of therapy: 30-70% at 24-36 mo (highest for GPA and lowest for MPA)

- Minimum 18-24 months duration

- Role for continuing maintenance therapy indefinitely in select cases

- IPC misclassified as IPH and not treated with induction & maintenance is likely to be poorly controlled (expert opinion)

1. NEJM. 2003; 349: 36-44 2. NEJM. 2008; 359: 2790–803
Systemic Lupus Erythematosus

- ANA, anti-dsDNA positive
- Multi-organ: kidney, skin, brain, MS
- Pleural effusion (serositis) most common pulmonary manifestation
- Reported Lung involvement: Infection, pleural effusions, acute lupus-related pneumonitis, ILD, bronchiolitis obliterans, pulmonary hemorrhage, pulmonary hypertension, shrinking lung, thrombosis
Systemic Lupus Erythematosus

At disease presentation  

Post therapy
Thrombosis: Lupus & Vasculitis

• Antiphospholipid antibodies ↑ risk for thrombosis

• Thrombosis also associated with:
  • Adult ANCA-AV (6-30%)*
  • GPA in children (16%)**
  • Pediatric case report of IPC***

*Thrombosis Journal 2015; 13:15
**Arthritis Rheum. 2007;57(5):837-44.
Q 2. Non-specific interstitial pneumonitis (NSIP) pathology is most likely to be associated with which of the following?

A. Eosinophilic Granulomatosis with Polyangiitis
B. Juvenile Idiopathic Arthritis
C. Sarcoidosis
D. Scleroderma
E. Surfactant Protein B Deficiency
Q 2. Non-specific interstitial pneumonitis (NSIP) pathology is most likely to be associated with which of the following?

A. Eosinophilic Granulomatosis with Polyangiitis
B. Juvenile Idiopathic Arthritis
C. Sarcoidosis
D. **Scleroderma**
E. Surfactant Protein B Deficiency
ILD in Pediatric Rheumatology

**Teens**

Scleroderma

**Infants-Toddlers**

Rarely JIA, JDM, MCTD, overlap
ILD in Pediatric Rheumatology

**Teens**
- Scleroderma

**Infants-Toddlers**
- SAVI (TMEM173)
- COPA

**Rarely**
- JIA, JDM, MCTD, overlap

References:
- NEJM 2014;371:507-18
- Nat Genet 2015;47:654-60
Systemic Scleroderma

- Multisystem disease involving skin, lung, GI, MSK, kidneys
- Rare in children but pulmonary involvement common and often fatal
- ILD and pulmonary arterial hypertension
- Insidious onset of symptoms

J Clin Epi 2019
Arthritis Care Res 2012; 64(4):519-24
Rheumatology 2009; 48: 96 +119
Scleroderma - Interstitial Lung Disease

Insidious onset of symptoms: dyspnea, dry cough
PFT: restrictive pattern with low DLCO
CT: honeycombing, traction bronchiectasis
Scleroderma: NSIP Pathology

- 76% NSIP and 11% UIP pathology for adult scleroderma
- Lung biopsy usually not required & pathology not predictive of prognosis or response to therapy
- Consider aspiration and infection as causes of diffuse lung disease

Bouros D et al. AJRCCM 2002 Jun 15;165(12):1581-6
Scleroderma: Therapy

- First line: MMF +/- low dose prednisone
- Second line: Cyclophosphamide
- Refractory disease:
  - Nintedanib (anti-fibrotic) & Rituximab
  - HSCT (but not severe lung disease)

*NEJM 2019; 380:2518-28
NEJM 2018; 378:35-47
AnnRheumDis 2017; 76(8): 1327-1339

SENSCIS Trial*
Scleroderma - Importance of early detection of lung disease

- Pulmonary fibrosis is now main cause of death, may start in childhood
- Initially disease is asymptomatic
- Lung disease seems to respond to therapy
- Controversy: should mild lung disease be treated?
Juvenile Idiopathic Arthritis (JIA)

- Minor pulmonary function abnormalities common but symptomatic or progressive lung disease is rare

- **Pleuritis** very common with systemic JIA onset-limited course

- Severe progressive interstitial lung disease is rare but can be fatal and occurs almost exclusively with systemic onset disease

ILD in Systemic JIA

Pulmonary Interstitial Cholesterol Granulomas (PICG)
Epidemiology of sJIA ILD

- Also called “PICG”: Progressive Pulmonary Interstitial and Intra-alveolar Cholesterol Granulomas

- 4 published Case Reports PICG 1996-2010
  - No IL1 or IL6 therapy

1. First retrospective case series (n=25, 68% dead)
   2013 Kimura et al

2. 2nd Cincinnati cohort 2010-2019 (n=18, alive)
   - Median follow-up one year (0.5-13) after LD
   - Detailed mechanistic work of tissue/BALF

3. 3rd case series+ (n=61, 45 unique, 36% dead)
   - Identified in 37 international centers
   - Multi-D review of history, imaging, pathology +/- WES

1. 2013 ACR 2013;65:745-52
   3. 2019 AnnRheumDis 2019; 0:1-10
sJIA Interstitial Lung Disease
A novel inflammatory lung disease with distinct clinical and immunological features

- Insidious onset: clubbing, dyspnea, cough

- HRCT: patchy but extensive disease, subpleural & interlobular septal thickening, GGO, lymphadenopathy, “crazy paving”

- Pathology: patchy lymphoplasmocytic infiltrates, features of PAP & ELP, vasculopathy

- Immunology: increased MAS & serum IL-18, reactions to tocalizumab, BALF neutrophilia with IFNγ signature

ArthRheum 2019; 71:1943-1954
CanRespJ 2010; 17 (3): e42-44
Prognosis of sJIA ILD

1. Cincinnati cohort (n=18, 1 yr f-u):
   • ~ half stable over time
   • ~ quarter worsen
   • ~ quarter improve (no MAS)

2. Saper-Mellins case series (n=61 LD)
   • 42% survival at 5 years
   • Hypoxia and BAL neutrophilia (>40%) associated with worse prognosis

2. 2019 AnnRheumDis 2019; 0:1-10
Juvenile Dermatomyositis (JDM)

- Characterized by myopathy with vasculitis involving skin and muscles
- Lung involvement rare in JDM but common in adult onset DM- associated with anti-Jo-1 autoantibodies
- Case reports of ILD in childhood: COP, fatal interstitial pneumonitis with air leak*

ILD (COP) as Initial Presentation of Juvenile Dermatomyositis
Lungs & Inherited Autoinflammatory Disease

**FMF & TRAPS**
- Familial Mediterranean Fever
- Onset in infancy, fevers, vasculitic rash, ILD
- Pleuritis is common x 1-3 days
- SAVI*
- COPA**

Pulmonology vs Rheumatology:
Synergy in Management Approaches

- Physiologic versus immunologic based specialty\(^1\)
- Differences in medication prescriptions\(^1\):
  - Pulse steroid therapy approach
  - High dose hydroxychloroquine approach
- Multicenter networks for rare lung disease are at infancy stage (except for cystic fibrosis)\(^2,3\)

PEARLS to Recognize and Manage Lung Manifestations of Rheumatological Disease *

- Pulmonary vasculitis presents as DAH, pulmonary nodules or tracheo-bronchial stenosis +/- renal and other symptoms

- Pulmonary vasculitis usually associated with ANCA +ve small vessel vasculitis (except IPC)

- Thrombosis is associated with lupus and vasculitis

*Dell’s PEARLS based on published case reports, case series and personal anecdotes*
PEARLS to Recognize and Manage Lung Manifestations of Rheumatological Disease *

• NSIP histopathology should prompt work up for CTD

• sJIA and JDM associated ILD can be rapidly fatal

• Consider genetic testing for autoinflammatory disease in patients with ILD associated with vasculitic rash, “atypical” lupus or JIA, especially if familial disease or consanguinity

• Talk to your rheumatologists for therapy choices in the induction and maintenance phases!

* Dell’s PEARLS based on published case reports, case series and personal anecdotes
Acknowledgements

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Pediatric Vasculitis Team

CHILD Network