Diffuse Parenchymal Lung Disease
ACOI Board Review 2019

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No Disclosures
Restrictive Lung Diseases
By Category

1. Lung Fibrosis
2. Thoracic Deformity
3. Massive effusion
4. Respiratory muscle weakness
5. Increased abdominal pressure
6. Extrinsic Compression
**ILD = Misnomer**

- Most of these diseases are not restricted to the "interstium" of the lung
- It is actually a radiographic term to differentiate it from alveolar filling diseases
- Diffuse Parenchymal Lung Disease is a better term
The interstitium is the scant space between the capillary endothelial cell and the lung epithelium. It also includes the space that airways, blood vessel, and lymphatics traverse.
Interstitial Lung Disease
Characteristics

1. Diffuse infiltrates bilaterally
2. Restrictive Physiology
3. Histologic distortion of gas exchange areas
4. Dyspnea (exercise desat) and cough
# Differential Diagnosis of DPLD

<table>
<thead>
<tr>
<th>COMMON</th>
<th>LESS COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Langerhans Cell Granulomatosis</td>
</tr>
<tr>
<td>IPF (aka cryptogenic</td>
<td>Hypersensitivity Pneumonitis</td>
</tr>
<tr>
<td>fibrosing alveolitis</td>
<td>Collagen Vascular Diseases (RA, SLE, MCTD, PSS)</td>
</tr>
<tr>
<td>BOOP/COP</td>
<td>Granulomatous vasculitis</td>
</tr>
<tr>
<td>Lymphhangetic Spread of CA</td>
<td>Goodpasture's syndrome</td>
</tr>
<tr>
<td>Pneumoconiosis</td>
<td>Alveolar proteinosis</td>
</tr>
<tr>
<td>Drug-induced</td>
<td></td>
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<tr>
<td>Chronic Eosinophilic Pneumonia</td>
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</tr>
</tbody>
</table>

**DPLD** - Diffuse Panbronchiolitis-Lipoid Disease
Pathogenesis of Interstitial Lung Diseases

Inhaled Stimulus

Blood Borne Stimulus

Alveolitis

Recruitment of Inflammatory Cells

Tissue Damage

Healing

Fibrosis
# Approach to DPLD

## Slide 1

<table>
<thead>
<tr>
<th>1. Characteristics of Presenting Illness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Symptoms</td>
<td></td>
</tr>
<tr>
<td>Rate of Progression</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
</tr>
<tr>
<td>Extrathoracic manifestations</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Exposures</th>
<th></th>
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<tbody>
<tr>
<td>Pneumoconiosis</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Drug-induced</td>
<td></td>
</tr>
<tr>
<td>Occupational</td>
<td></td>
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<tr>
<td>IV drug use</td>
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</table>
**Approach to DPLD**

**Slide 2**

<table>
<thead>
<tr>
<th>3. Physical Exam</th>
<th>Crackles</th>
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</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>Wheeze</td>
</tr>
<tr>
<td></td>
<td>Rub</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>Nodes</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Joints</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>Eyes</td>
</tr>
</tbody>
</table>
| 4. Laboratory (All) | CBC with Diff  
|                     | UA/Creatinine  
|                     | CRP, RF, ANA  
|                     | ACE level  
| If H+P Suggestive: | ANCA-c (granulomatosis with polyangitis)  
|                     | RNP (MCTD)  
|                     | Anti-GBM (Goodpasture's)  |
Serologic Tests Can Help Exclude Other Conditions

Connective tissue diseases
- CRP
- ANA
- CCP (for RA) Cyclic Citrullinated Peptide Antibody
- CK
- Aldolase
- Anti-myositis panel with Jo-1 antibody
- ENA panel
  - Scl-70 – SSc (topoisomerase I)
  - Ro (SSA) - Sjögren’s
  - La (SSB)
  - Smith -Lupus
  - RNP - MCTD

Hypersensitivity pneumonitis
- Hypersensitivity panel
  (if exposure history)

### Approach to DPLD

**Slide 4**

<table>
<thead>
<tr>
<th>5. X-Ray Patterns</th>
<th>Adenopathy</th>
<th>Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Lobe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adenopathy**
- Silicosis
- Sarcoidosis
- Berylliosis
- Langerhans cell granulomatosis

**Nodules**
- Sarcoidosis
- Rheumatoid Arthritis
- Granulomatosis with Polyangitis
- Sjogren's
- Asbestos
- RA
- SLE
<table>
<thead>
<tr>
<th>6. PFT</th>
<th>Spirometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung volumes</td>
</tr>
<tr>
<td></td>
<td>DLCO</td>
</tr>
<tr>
<td></td>
<td>ABG</td>
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<table>
<thead>
<tr>
<th>7. Tissue</th>
<th>Transbronchial Biopsy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Thoracoscopy</td>
</tr>
<tr>
<td></td>
<td>Open lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Extrathoracic sites</td>
</tr>
</tbody>
</table>

| BAL?         | Gallium Scan?          |
## Symptom Duration in DPLD

<table>
<thead>
<tr>
<th>Chronic</th>
<th>Acute/Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF</td>
<td>BOOP/COP</td>
</tr>
<tr>
<td>Rheumatoid Lung</td>
<td>Drug-induced</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Langerhans Cell Granulomatosis</td>
<td>Chemical exposure</td>
</tr>
<tr>
<td>Pneumoconiosis</td>
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</tbody>
</table>

School of Osteopathic Medicine
**Extrathoracic Manifestations of DPLD (1)**

<table>
<thead>
<tr>
<th>Nasal symptoms</th>
<th>Wegener’s Granulomatosis</th>
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<tbody>
<tr>
<td>Arthritis</td>
<td>RA</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>CVD</td>
</tr>
<tr>
<td></td>
<td>Sjogren’s syndrome</td>
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</table>

<table>
<thead>
<tr>
<th>Skin</th>
<th>Sarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVD</td>
</tr>
<tr>
<td></td>
<td>Granulomatous vasculitis</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>PSS</td>
</tr>
</tbody>
</table>
# Extrathoracic Manifestations of DPLD (2)

<table>
<thead>
<tr>
<th>CNS</th>
<th>CVD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Lymphomatoid granulomatosis</td>
</tr>
<tr>
<td>Muscle</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
</tr>
<tr>
<td>GI</td>
<td>PSS</td>
</tr>
<tr>
<td></td>
<td>Polymyositis</td>
</tr>
<tr>
<td>Renal</td>
<td>Granulomatosis with panvasculitis</td>
</tr>
<tr>
<td></td>
<td>CVD</td>
</tr>
<tr>
<td></td>
<td>Goodpasture’s</td>
</tr>
<tr>
<td></td>
<td>PSS</td>
</tr>
</tbody>
</table>
CASE 1

- 34 y.o. black, female presents with 6 months of non-productive COUGH, and DYSPNEA with exertion
- NO MEDS or IVDA
- NO OCCUPATIONAL EXPOSURES
- NO SYSTEMIC SIGNS OR SYMPTOMS
## Sarcoidosis

### X-ray Findings at Presentation

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FINDINGS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>5</td>
</tr>
<tr>
<td>I</td>
<td>BHA</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>BHA + Lung</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>Lung Only</td>
<td>15</td>
</tr>
<tr>
<td>IV</td>
<td>Fibrosis</td>
<td></td>
</tr>
</tbody>
</table>
35 yo
male

Sarcoidosis
Stage 2 sarcoidosis
pre-tx
**Stage 2 sarcoidosis**

2 years post-tx
Adult female

Nodular Sarcoidosis

Stage 3
Sarcoidosis

- Multisystem disease of unknown etiology
  Noncaseating granuloma are characteristic
  NOT DIAGNOSTIC

- Lung is the most common organ system involved (94%)

- Peak onset 2nd and 3rd decades

- 10 to 17 times more prevalent in blacks
Sarcoidosis

- Gallium scan does NOT correlate with need for or response to TX.
- LAB: ACE, LFT's, Calcium, UA hypergammaglobulinemia (68 %)
- Anergy (43 to 66 %)
- Dx: Transbronchial lung biopsy (TBLBx) is adequate for Dx 80 to 90 %. BAL - lymphocytic
- Tx: Steroids
Noncaseating Granulomas
Diagnosis of Sarcoidosis
THREE ELEMENTS

1. Compatible clinical picture
2. Noncaseating granulomas in tissue
3. Negative culture/stains for AFB and fungi
**CASE 2**

- 60 y.o. white, male severe exertional dyspnea over 3 to 4 years. Non-productive cough is noted.

- Viral prodrome prior to initial symptoms.

- Nonsmoker, no meds, no occupational exposures, No high risk behaviors

- EXAM - Crackles, digital clubbing
Idiopathic Pulmonary Fibrosis
AKA Cryptogenic Fibrosing Alveolitis

- Older age (> 60 Y.O.), M sl > F
- Slow progression over 2 or more years.
- Non-productive cough, dyspnea
- Clubbing 50-90% of patients
US Demographics of IPF

- Incidence: > 30,000 patients/year
- Prevalence: > 80,000 current patients
- Age of onset: most 40–70 years
- Two-thirds > 60 years old at presentation
- Males > females

Idiopathic Pulmonary Fibrosis

IPF
The surface of the lung of an IPF patient showing advanced honeycombing.
Tx for IPF

50 % mortality at 5 years

10 % develop bronchogenic CA

Nintedanib, (OFEV) a receptor blocker for multiple tyrosine kinases that mediate elaboration of fibrogenic growth factors

Pirfenidone (Espiert) is an antifibrotic agent that inhibits transforming growth factor beta (TGF-b)-stimulated collagen synthesis, decreases the extracellular matrix, and blocks fibroblast proliferation in vitro

Transplant
Idiopathic Pulmonary Fibrosis

Diagnosis

- X-ray shows bilateral reticular or reticulonodular infiltrates with lower lobe distribution
- HRCT - subpleural septal thickening
- Lab: non-specific
- Classically Open lung biopsy is required for definitive diagnosis
Current Definition of IPF

- Distinct chronic fibrosing interstitial pneumonia
- Unknown cause
- Limited to the lungs
- Has typical HRCT findings
- Associated with a histologic pattern of UIP

# Diagnostic Criteria for IPF Without a Surgical Lung Biopsy

## Major Criteria

- Exclusion of other known causes of ILD
- Evidence of restriction and/or impaired gas exchange
- HRCT: bibasilar reticular abnormalities with minimal ground-glass opacities (honeycombing is characteristic*)
- TBB or BAL that does not support an alternative diagnosis

## Minor Criteria

- Age > 50 years
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness > 3 months
- Bibasilar, inspiratory, Velcro® crackles

- All major criteria and at least 3 minor criteria must be present to increase the likelihood of an IPF diagnosis
- Criteria currently under revision (2009)

*Not included in current guidelines
IPF - H+E stain
IPF (trichrome stain)
CASE 3

- 43 y.o. white female presented with 2 months of fever, cough, dyspnea, and 12 lbs wt loss
- No meds, 20 P-Y smoker
- No occupational exposures
- No high risk behavior
- Exam: 100 temp, crackles upper lobes
Chronic Eosinophilic Pneumonia
Chronic Eosinophilic Pneumonia
Chronic Eosinophilic Pneumonia

http://www.mevis-research.de/~hhj/Lunge/ima/inf_eos_thb99.JPG
Chronic Eosinophilic Pneumonia

- Peak 3rd decade, 2:1 F:M
- Subacute presentation over months cough, fever, dyspnea, wt loss
- X-ray - bilateral upper lobe infiltrates PERIPHERAL distribution (esp HRCT)
- Blood, biopsy, BAL all with eosinophilia
- Dramatic improvement with steroids (maintain for 6 months)
Drug-induced Interstitial Lung Disease

Antirheumatics
- Gold
- Penicillamine
- Methotrexate

Antineoplastics
- Bleomycin
- Cyclophosphamide
- Mitomycin

Antiarrhythmics
- Amiodarone

Radiation

Oxygen

Illicit Drugs
- Talc
- cocaine
Collagen Vascular Diseases with ILD

- RA
- PSS
- Polymyositis/Dermatomyositis
- MCTD
- LUPUS
pulmonary fibrosis due to RA
CASE 4

- 47 y.o. homosexual male with 11 month Hx of non-productive cough, fever, sweats, wheezing
- Also 35 lbs wt loss over 6 months
- EXAM: fever, basilar crackles
  No clubbing
CT
BOOP/COP
Subpleural
Ground glass infiltrates
Bronchiolitis Obliterans
Organizing Pneumonia/COP
Bronchiolitis Obliterans-Organizing Pneumonia
AKA Cryptogenic Organizing Pneumonia

- Patient with patchy alveolar infiltrates who does not improve following antibiotics
- 4th to 6th decade - subacute 2 -10 wk present
- Fever, dry cough, following flu-like illness
  Myalgia, headache, malaise are common
- X-ray shows bilateral infiltrates, 10 % reticular
  Peripheral distribution on HRCT
Bronchiolitis Obliterans-Organizing Pneumonia (COP)

- **Pathology**
  Intraluminal fibrosis with connective tissue plugs in the respiratory bronchioles, alveolar ducts, and alveoli

- **Open lung Bx** - NOT NECESSARY
  TBLBx and BAL are adequate

- **Steroid Responsive**
  3 to 6 months Tx
  Recurrence common if Tx stopped too early
CASE 5

53 y.o. white male progressive dyspnea over 1 year. Some cough with yellow sputum

Heavy Smoker

Occupation: tombstones engraver

EXAM: decreased breath sounds digital clubbing
56 yo Male

Anthracosis PMF
56 yo
Male

Anthracosis
PMF
Silicosis, PMF, Cavitation
Egg shell calcification
Pneumoconiosis
Inhaled Inorganic Dusts

1. Big Three
   Asbestosis, Anthracosis, Silicosis

2. Long gap between exposure and symptoms from ILD

3. Asbestos - Lower lobe reticular changes
   Parietal pleural plaques

4. Anthracosis - Upper lobe nodules - PMF

5. Silicosis - Upper lobe nodules - PMF
   Hilar adenopathy
   Egg shell calcification
Asbestos plaques
Asbestos plaques
Hypersensitivity Pneumonitis

* Caused by repeated inhalation of an ORGANIC dust or chemical - leads to sensitization

* Symptoms may be acute or chronic

* Fever, cough, dyspnea, and infiltrates occur 4 to 6 hrs post exposure
  Repeated exposure leads to fibrosis

* Dx: depends on history and specific precipitating antibodies to the antigen
Hypersensitivity Pneumonitis

* Type III - immune complex injury and Type IV - delayed hypersensitivity is involved in pathology

* Acute pathology shows PMN infiltrate. 3 days later the infiltrate becomes lymphocytic and loose granulomas form. FOAMY histiocytes and bronchiolitis obliterans may be noted.
Hypersensitivity Pneumonitis
Langerhans Cell Granulomatosis
EG, HSC, and LS

All 3 disorders share a common pathology
Aggregations of abnormal histiocytes (Langerhan's cells)

Lung and bone are most often affected with UNIFOCAL disease

Multifocal disease - worse prognosis
26 yo male

Langerhans Cell

Granulomatosis

Histiocytosis X
26 yo
male
LCG
Langerhans Cell Granulomatosis
LCG

CLINICAL FEATURES

- 10 to 40 Y.O. M=F
- Present with cough, fever, dyspnea, chest pain
- 10% present with pneumothorax
- X-ray - upper lobe cystic and reticulonodular changes
  NO VOLUME LOSS