Interstitial Lung Disease

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Respiratory System

Causes of Disease

Structural Change

Functional Change

- Respiratory System Mechanics
- Gas Exchange
- Ventilation
- Vascular Changes
Compartments of the Lung

Courtesy Alain Borczuk, MD
Parenchymal Inflammation and Fibrosis

Normal Lung

ILD

Courtesy Alain Borczuk, MD
Overview

- Terminology and classification scheme
- Pathophysiology
- Clinical manifestations
- Pathogenesis
- Management
Alphabet Soup
Terminology

- **Diffuse parenchymal lung disease (DPLD)**
  
  A group of non-infectious, non-neoplastic lung diseases each characterized by varying degrees of inflammation and/or fibrosis of the parenchyma of both lungs.

- **Interstitial lung disease (ILD)**
  
  *Old term for DPLD – I prefer this term*

- **Idiopathic interstitial pneumonias (IIPs)**
  
  *A group of 7 ILDs of unknown cause*

- **Idiopathic pulmonary fibrosis (IPF)**
  
  *The most common IIP (full definition to follow)*

- **Pulmonary fibrosis**
  
  *Non-specific term denoting bilateral parenchymal fibrosis*
Spectrum of ILD

Interstitial Lung Diseases

- ILD of known cause
- Idiopathic interstitial pneumonias (IIPs)
- Granulomatous ILDs (e.g., sarcoidosis)
- Other forms of ILD

Known Causes of ILD

- Drugs (chemotherapy, antibiotics)
  - www.pneumotox.com

- Radiation therapy

- Connective Tissue Diseases
  - Rheumatoid arthritis
  - Systemic sclerosis (scleroderma)
  - Dermatomyositis

- Occupational/Environmental
  - Inorganic antigens (Pneumoconioses)
    - Asbestosis
    - Coal worker’s pneumoconiosis
    - Silicosis
  - Organic antigen (Hypersensitivity Pneumonitis)
### Idiopathic Interstitial Pneumonias

**Classified by histologic pattern**

<table>
<thead>
<tr>
<th>Clinical-Radiologic-Pathologic Diagnosis</th>
<th>Histologic Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
<td>Usual interstitial pneumonia (UIP)</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia (NSIP)</td>
<td>Non-specific interstitial pneumonia</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia (COP)**</td>
<td>Organizing pneumonia</td>
</tr>
<tr>
<td>Acute interstitial pneumonia (AIP)</td>
<td>Diffuse alveolar damage (DAD)</td>
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<tr>
<td>Respiratory bronchiolitis-ILD (RB-ILD)</td>
<td>Respiratory bronchiolitis</td>
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<tr>
<td>Desquamative interstitial pneumonia (DIP)</td>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia (LIP)</td>
<td>Lymphoid interstitial pneumonia</td>
</tr>
</tbody>
</table>

**Formerly known as bronchiolitis obliterans-organizing pneumonia (BOOP)**

Usual interstitial pneumonia is the histologic pattern of IPF
Fibroblastic foci are a key histological finding in UIP

Non-specific interstitial pneumonia

Cellular NSIP

Fibrotic NSIP

Cryptogenic Organizing Pneumonia

RB-ILD and DIP are *smoking related diseases*

Selected other ILDs

• Sarcoidosis
• Eosinophilic pneumonias
• Lymphangioleiomyomatosis
• Langerhan’s cell histiocytosis
Related Diseases Involving the Lung Parenchyma

- Alveolar filling diseases
  - Pulmonary edema
  - Acute respiratory distress syndrome (ARDS)
  - Alveolar proteinosis
  - Diffuse alveolar hemorrhage

- Vascular diseases
  - Lymphangitic carcinomatosis
  - Pulmonary vasculitis
Respiratory System Mechanics

Causes of Disease
Structural Change
Functional Change

Gas Exchange
Ventilation
Vascular Changes
Respiratory System Mechanics in ILD

Pressure-Volume Curves

Reduced Lung volumes

West, JB. Pulmonary Pathophysiology: The Essentials, 2008
ILD leads to a *restrictive ventilatory defect*

- Reduced lung volumes
  - Total lung capacity**
  - Forced vital capacity
  - $\text{FEV}_1$

- Typically, no airflow obstruction

**Reduced TLC = restrictive ventilatory defect**
Gas exchange in ILD

• Hypoxemia is common in ILD

• Causes of hypoxemia in ILD
  – V/Q mismatch (MAJOR)
  – Diffusion abnormality
    • Only plays a role during exercise

• Characteristics of hypoxemia in ILD
  – Worsens as the disease progresses
  – Worsens during exercise
Changes in pulmonary capillary $P_{O_2}$

West, JB. Pulmonary Pathophysiology: The Essentials, 2008
What about ventilation and vascular changes?

• Alveolar hyperventilation
  – Hypoxemia
  – Abnormal mechanics and load

• Vascular disease is common
  – Intimal hyperplasia
  – Medial hypertrophy
  – Pulmonary hypertension is typically not severe
Clinical Manifestations of ILD
ILDs share many clinical features

**Similarities**
- Dyspnea
  - progressive
  - exertional
- Cough
  - non-productive
- Bibasilar crackles
- Restrictive ventilatory defect
- Impaired gas exchange
- Abnormal lung imaging

**Differences**
- Extrapulmonary findings
  - sarcoidosis
  - connective tissue disease
- Pattern on lung CT
- Histopathology
Case
Case

• 54 year old man comes to see you because he has been short of breath for two years
  – First, while mowing his lawn
  – Then, more dyspneic than his wife in the gym
  – Now dyspneic with most activities at home.
• Dry cough (no sputum) and occasional joint pains.
• No wheezing or hemoptysis.
• No fever or chills.
• No chest pain, orthopnea, PND, or edema.
• No rash, visual changes, Raynaud’s phenomenon, dysphagia, or heartburn
Case

- Past medical history
  - Osteoarthritis
  - Hypercholesterolemia

- Past surgical history
  - None

- Medications
  - Simvastatin, multivitamin, acetaminophen

- No known drug allergies
Case

- Family history
  - No lung disease
  - Mother 85 yo – alive and well
  - Father died at 74 with heart failure
  - Sister with ovarian cancer

- Social history
  - Smoked one pack per day for 35 years (35 packyears). Quit 3 years ago
  - No alcohol or drug use
  - No pets, humidifiers, or hot tubs
  - Real estate agent. No military or construction work
Exam

• BP 118/80 mm Hg; pulse 103; RR 28; T 99.7°

• $S_pO_2$ 92% breathing room air.

• No JVD.

• **Rapid, shallow breathing.** Chest symmetric. No accessory muscle use. **Bibasilar crackles** halfway up bilaterally. No wheezes or rhonchi.

• S1, S2 were normal. Regular rhythm. No murmur, rub, or gallop.

• No cyanosis.
New York Presbyterian Hospital
Columbia Presbyterian Medical Center
622 West 168th Street New York, NY 10032

Adult Pulmonary Diagnostic Unit

Patient:
Age:          Gender: Male
Height: 68 in (173 cm) Weight: 193 lb (87.5 kg)
Body Mass Index: 29.24

### Spirometry

<table>
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<tr>
<th></th>
<th>Ref</th>
<th>Pre</th>
<th>% Ref</th>
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<tr>
<td>FVC</td>
<td>4.55</td>
<td>2.94</td>
<td>65</td>
</tr>
<tr>
<td>FEV1</td>
<td>3.63</td>
<td>2.30</td>
<td>63</td>
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<tr>
<td>FEV1/FVC</td>
<td>80</td>
<td></td>
<td></td>
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<tr>
<td>FEF25-75%L/sec</td>
<td>3.57</td>
<td>2.18</td>
<td>61</td>
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<tr>
<td>FEF25% L/sec</td>
<td>7.79</td>
<td>6.48</td>
<td>83</td>
</tr>
<tr>
<td>FEF50% L/sec</td>
<td>4.28</td>
<td>3.38</td>
<td>79</td>
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<tr>
<td>FEF75% L/sec</td>
<td>1.62</td>
<td>0.72</td>
<td>44</td>
</tr>
<tr>
<td>PEF</td>
<td>8.31</td>
<td>7.99</td>
<td>96</td>
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<tr>
<td>MVV</td>
<td>140</td>
<td>128</td>
<td>92</td>
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<tr>
<td>PIF</td>
<td>3.85</td>
<td>5.21</td>
<td>136</td>
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<tr>
<td>FIF50%</td>
<td>4.85</td>
<td>5.08</td>
<td>105</td>
</tr>
<tr>
<td>FET100%</td>
<td></td>
<td>7.26</td>
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### Lung Volumes

<table>
<thead>
<tr>
<th></th>
<th>Ref</th>
<th>%</th>
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<tr>
<td>VC</td>
<td>4.55</td>
<td>68</td>
</tr>
<tr>
<td>TLC</td>
<td>6.60</td>
<td>68</td>
</tr>
<tr>
<td>RV</td>
<td>2.04</td>
<td>69</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>FRC PL</td>
<td>3.37</td>
<td></td>
</tr>
<tr>
<td>FRC N2</td>
<td>3.37</td>
<td>77</td>
</tr>
<tr>
<td>FRC He</td>
<td>3.37</td>
<td></td>
</tr>
<tr>
<td>Vtg</td>
<td></td>
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### Diffusion

<table>
<thead>
<tr>
<th></th>
<th>mL/mmHg/min</th>
<th>%</th>
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<tbody>
<tr>
<td>DLCO</td>
<td>33.6</td>
<td>10.7</td>
</tr>
<tr>
<td>DL Adj</td>
<td>33.6</td>
<td>10.6</td>
</tr>
<tr>
<td>VA</td>
<td></td>
<td>3.72</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td></td>
<td>5.21</td>
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### Arterial Blood Gases

<table>
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<tr>
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<tbody>
<tr>
<td>FIO2</td>
<td>%</td>
</tr>
<tr>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>PCO2</td>
<td>mmHg</td>
</tr>
<tr>
<td>PO2</td>
<td>mmHg</td>
</tr>
<tr>
<td>HCO3</td>
<td>meq/L</td>
</tr>
<tr>
<td>Hb</td>
<td>gm/dL</td>
</tr>
<tr>
<td>%HbCO</td>
<td>%</td>
</tr>
<tr>
<td>SaO2</td>
<td>%</td>
</tr>
<tr>
<td>P(A-a)O2</td>
<td>mmHg</td>
</tr>
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</table>
Six-minute walk test

- Distance walked: 1778 ft
- Resting SpO₂: 93%
- Exercise SpO₂: 88%
Normal chest CT
Questions

• Why does he have dyspnea?

• What are the mechanisms of hypoxemia in this patient?

• Why did oxyhemoglobin saturation decrease during exercise?

• What’s the diagnosis?
Idiopathic pulmonary fibrosis

- Most common IIP
- Prototypical form of ILD
- Histopathology:
  - usual interstitial pneumonia
- Risk factors:
  - Older age
  - Male gender
  - Cigarette smoking
  - Family history
# Epidemiology of IPF

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence rate (/100,000 PYO)*</th>
<th>Prevalence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>45-54</td>
<td>2.2</td>
<td>4.0</td>
</tr>
<tr>
<td>55-64</td>
<td>14.2</td>
<td>10.0</td>
</tr>
<tr>
<td>65-74</td>
<td>48.6</td>
<td>21.1</td>
</tr>
<tr>
<td>75+</td>
<td>101.9</td>
<td>57.0</td>
</tr>
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</table>

*PYO = patient-years of observation

Survival in IPF

Median survival following diagnosis
2.9 years (95% CI 1.9 – 4.1)

Median survival following symptom onset
6.7 years (95% CI 5.5 -7.4)

Proposed Causes of IPF

- Cigarette smoking
- Viral-induced inflammation
- Occult environmental & occupational exposures
- Gastroesophageal reflux
Pathogenesis of IPF

Selman, M. Ann Int Med. 2001
A Role for Telomere Length in IPF

Telomere length is reduced in IPF

Alder JK et.al. PNAS 2008;105:13051-13056
Cronkhite, JT. et al. AJRCCM 2008;178:729-37
Other mediators in IPF

Pathogenesis of IPF

- Inflammation oxidants
- Epithelial apoptosis
- Epithelial-mesenchymal transformation
- Coagulation
- Th2 cytokines
- Angiogenesis
- Fibroblast growth factors
- Bone marrow-derived fibroblasts
- Myofibroblasts

Noble and Homer. AJRCCM 2005:33:113-120
What about other ILDs?

• Injurious triggers
  – Autoimmune mediated inflammation
  – Drug-induced injury
  – Radiation-induced injury
  – Eosinophil degranulation
  – Hypersensitivity reaction
Management of ILD

• Biopsy often required to make a diagnosis
  – Surgical lung biopsy (gold standard)
  – Transbronchial lung biopsy (less useful)

• Oxygen therapy

• Pulmonary rehabilitation
Treatment of ILD

• Avoid lung injury
  – Inhaled agents
  – Offending drug

• Anti-inflammatory therapy
  – Treat underlying inflammatory diseases
  – Trial of corticosteroids for documented parenchymal inflammation
  – Steroid-sparing agents

• Lung transplantation