Interstitial Lung Disease 2007

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ILD: Definition

1. ILD is not one disorder

2. Strictly speaking, an ILD involves the interstitium
   Anatomic structures other than the interstitium can be involved
   "alveolitis"
   "vasculitis"
   "peri-bronchial disease"
What Conditions Belong to “ILD”? 

1. Diffuse abnormalities on chest radiology 
   “Diffuse Parenchymal Lung Disease” (DPLD) is the more general and preferred term.

2. Similar clinical presentations

3. Similar physiological consequences

4. Generally, chronic non-infectious, non-neoplastic disease involving the lung parenchyma.

ILD: Thickening of the Interstitium
ILD: Thickening of the Interstitium

Slides Courtesy of Alain Borczuk, MD

ILD: Cellular and Fibrotic

Slides Courtesy of Alain Borczuk, MD
Classification of Diffuse Parenchymal Lung Disease

Systemic Disease

DPLD


Classification of Diffuse Parenchymal Lung Disease

Systemic Disease

DPLD

Known Cause & Other

Drugs
Pneumoconioses
Eosinophilic granuloma

Classification of Diffuse Parenchymal Lung Disease

Systemic Disease

DPLD

Granulomatous

Sarcoid
Chronic hypersensitivity pneumonitis

Known Cause & Other

Drugs
Pneumoconioses
EG

Idiopathic Interstitial Pneumonia (IIP)

Sarcoid
CHP

Drugs
Pneumoconioses
EG

**Classification of Diffuse Parenchymal Lung Disease**

- **DPLD**
  - **IIP**
    - **UIP (IPF)**
    - **Non-UIP**
  - **Cellular**
  - **Fibrotic**

**Survival for UIP vs NSIP**


## COMPARATIVE MORTALITY RATES

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>5-YEAR MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>85%</td>
</tr>
<tr>
<td>IPF</td>
<td>50-70%</td>
</tr>
<tr>
<td>CHF</td>
<td>50%</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>38%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>13%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>2%</td>
</tr>
</tbody>
</table>

## Prevalence of ILD

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational/Environmental</td>
<td>20.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Drug &amp; Radiation</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>7.1</td>
<td>11.6</td>
</tr>
<tr>
<td>IPF</td>
<td>20.2</td>
<td>13.2</td>
</tr>
<tr>
<td>Pulm Fibrosis (Not IPF)</td>
<td>10.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>8.3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

(Prevalence rates are per 100,000/year)

*Am J Respir Crit Care Med 1994; 150: 967-972,*
Epidemiology of IPF

Estimated 31,000 New Patients per Year in the United States

Estimated 83,000 Current Patients in the United States

ILD: CLINICAL HISTORY

• Insidious onset
• Preceding URI
• Occupational Exposure and Cigarette Smoking
• Progressive Dyspnea with Exertion (DOE)
• Paroxysmal cough

ILD: PHYSICAL FINDINGS

• Tachypnea
• Basilar crackles
• May have digital clubbing
• Low lung volume, cyanosis, tachycardia

ILD: PHYSIOLOGIC FINDINGS

• Pulmonary function
  – Restrictive ventilatory defect
    • Reduced total lung capacity (TLC) & FVC
    • Normal or increased FEV\textsubscript{1}/FVC ratio
  – Impaired gas exchange
    • Decreased DL\textsub{CO}
    • Desaturation with exercise (pulse oxymetry)
    • Decreased Pa\textsub{O\textsub{2}}
    • Increased A-a gradient

Adapted from ATS/ERS. Am J Respir Crit Care Med. 2000;161:646-664.
Pulmonary Function Testing

Examples:

<table>
<thead>
<tr>
<th></th>
<th>Obstructive</th>
<th>Restrictive</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>100%</td>
<td>50%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>FEV1</td>
<td>50%</td>
<td>50%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>43%</td>
<td>90%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>TLC</td>
<td>100%</td>
<td>65%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>RV</td>
<td>105%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>FRC</td>
<td>95%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>DlCO</td>
<td>50%</td>
<td>50%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

Six Minute Walk Testing in ILD

Patient encouraged to walk at a maximal pace with as many stops as necessary

Oxygenation (desaturation) and symptom scores are measured

Desaturation may occur in other conditions
  - Pulmonary hypertension
  - Severe COPD
  - Heart failure
Six Minute Walk Testing in ILD

Primary end-point is distance walked

6MWT distance is used as a primary endpoint in clinical trials for ILD therapy

Degree of desaturation may have prognostic significance

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Desaturation during initial 6MWT predicts decreased survival:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Desaturation</th>
<th>4-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP (IPF)</td>
<td>Yes</td>
<td>35%</td>
</tr>
<tr>
<td>No</td>
<td>69%</td>
<td>n=83, p=0.0018</td>
</tr>
<tr>
<td>NSIP</td>
<td>Yes</td>
<td>66%</td>
</tr>
<tr>
<td>No</td>
<td>100%</td>
<td>n=22, p=0.0089</td>
</tr>
</tbody>
</table>
ILD: PLAIN CHEST X-RAY

Courtesy of David A. Lynch, MD.

ILD: Early HRCT Findings

Courtesy of David A. Lynch, MD.
ILD: HONEYCOMBING

50 year old man with “rapidly progressive IPF” transferred to CUMC 1/03

Pulm Hx: Cigarette smoking @ 1.5 ppd, teens - 45
        Pneumonia 2/02, with full recovery

PMH: Gout
     OA

Occupation: Mason
### Case Presentation: HPI

<table>
<thead>
<tr>
<th>Date</th>
<th>Event/Condition</th>
</tr>
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<tbody>
<tr>
<td>7/97-12/00</td>
<td>Subtle bibasilar infiltrates</td>
</tr>
<tr>
<td>9/02</td>
<td>Persistent cough</td>
</tr>
<tr>
<td></td>
<td>Mild DOE</td>
</tr>
<tr>
<td>11/02</td>
<td>Extensive infiltrates, Restrictive PFT’s</td>
</tr>
<tr>
<td>12/02</td>
<td>Surgical Lung Biopsy</td>
</tr>
<tr>
<td></td>
<td>(Lingula &amp; SS-LLL)</td>
</tr>
<tr>
<td>12/02</td>
<td>Predisone 60 mg/d (0.7 mg/kg/d)</td>
</tr>
<tr>
<td>12/02</td>
<td>URI, oral antibiotics</td>
</tr>
<tr>
<td></td>
<td>Acute decompensation</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 30 mg/d</td>
</tr>
</tbody>
</table>
**Case Presentation: Clinical Course**

3/03: Prednisone 25 mg/d  
Pulmonary Rehabilitation  
Less Dyspneic

4/03: Transplant Evaluation  
PA 25/13 (17)  
PCW (2)

7/03: Off Prednisone  
Full-time work  
SpO2 95 - 83% with stair climbing

**Case Presentation: PFT’s**

<table>
<thead>
<tr>
<th>DATE</th>
<th>1/03</th>
<th>3/03</th>
<th>4/03</th>
<th>7/03</th>
<th>9/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.5L (59%)</td>
<td>2.6</td>
<td>3.0</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.2L (63%)</td>
<td>2.3</td>
<td>2.7</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>F/V</td>
<td>88%</td>
<td>88%</td>
<td>90%</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>TLC</td>
<td>3.7L (61%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC</td>
<td>2.0L (65%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>7.8L (24%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 (R)</td>
<td>92%</td>
<td>89%</td>
<td>92%</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>SpO2 (EX)</td>
<td>81%</td>
<td>79%</td>
<td>83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT</td>
<td>1365’</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Case Presentation: Exercise Physiology

<table>
<thead>
<tr>
<th>CPET</th>
<th>1/8/03</th>
<th>10/7/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME</td>
<td>7 min</td>
<td>8 min</td>
</tr>
<tr>
<td>MAX WORK</td>
<td>65 watts</td>
<td>60 watts (32%)</td>
</tr>
<tr>
<td>VO2-max</td>
<td>12.2 ml/min/kg (37%)</td>
<td>11.1 (34%)</td>
</tr>
<tr>
<td>VE/VCO2</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>MVV</td>
<td>86 L/min (58%)</td>
<td>124 (85%)</td>
</tr>
</tbody>
</table>

### Progression of IPF: Acute Exacerbation vs Slow Decline

**Traditional View of UIP/IPF Progression**

- **Acute Exacerbation**
- **Slow Decline**

**FVC =** forced vital capacity.
**Progression of IPF:**

*Acute Exacerbation vs Slow Decline*

**Step Theory of UIP/IPF Progression**

![Graph showing progression of IPF with indicators for acute exacerbation and slow decline](Am J Respir Cell Mol Biol. 2003;29(3 suppl):S1-S105.)

**Pathological Sections Demonstrating UIP**

- Peripheral accentuation of the disease
- Transition into uninvolved lung
- Low power pathology
- High power image of fibroblastic focus

*Courtesy of Kevin O. Leslie, MD.*
Multiple Hypotheses for the Pathogenesis of IPF

• Inflammation causes fibrosis
• Noninflammatory (multiple hit) hypothesis: fibrosis results from epithelial injury and abnormal wound healing in the absence of chronic inflammation
• Vascular remodeling: aberrant vascular remodeling supports fibrosis, and may contribute to increased shunt and hypoxemia
• Abnormalities in host defense.

**Inflammatory Hypothesis**

- *Inflammation causes fibrosis*
  - Inflammatory concept was dominant in the 1970s and 1980s
    - IPF resulted from unremitting inflammatory response to injury culminating in progressive fibrosis
  - Role of inflammation remains controversial
    - Lack of efficacy of corticosteroids

**Noninflammatory (multiple hit) Hypothesis**

- Recurrent pulmonary injury
  - Epithelial/endothelial injury and apoptosis
    - Loss of basement membrane
      - Failure of re-epithelialization/re-endothelialization
        - Fibroblast proliferation
          - ECM deposition
            - Release of profibrotic growth factors (TGF-β, PDGF, IGF-1)
              - Progressive fibrosis with loss of lung architecture

Vascular Remodeling Hypothesis

- Aberrant vascular remodeling supports fibrosis and may contribute to increased shunt and hypoxemia
  - Increased angiogenesis results from imbalance of pro-angiogenic chemokines (IL-8, ENA-78) and anti-angiogenic, IFN-inducible chemokines (IP-10)
  - Vascular remodeling leads to anastomoses between the systemic/pulmonary microvasculature, increasing right-to-left shunt, contributing to hypoxemia

Defects in Host Defense Mechanisms May Contribute to Fibrosis

- Defects in endogenous host defense mechanisms (eg, IFN-γ, PGE2 production) that limit fibrosis after acute lung injury may contribute to progressive fibrosis
Center for Interstitial Lung Disease

A multi-disciplinary group at NY-Presbyterian Hospital, based in the Jo-Ann LeBuhn Center for Chest Disease

Goals:
• Diagnosis
• Monitoring disease progression
• Coordination of therapy
• Clinical trials
• Investigative research

Composition of the multi-disciplinary group

Pulmonologists
Lung pathologists
Chest radiologists
Exercise Physiologists
Rheumatologists
Transplant physicians
Basic researchers

Clinical coordinators
Physical therapists
Respiratory techs.
Outside consultants
Cardiologists
Thoracic surgeons
(Medical Informatics)
Center for Interstitial Lung Disease

Potential system-wide goals & projects:

Data base
  Diagnosis, natural history, pathogenesis
Diagnosis
  Central review of cases, clinical conferences
Coordination of care
  Clinical trials, transplant/tertiary care
Basic research