Diffuse Parenchymal Lung Disease

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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  DPLD

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*

• **Idiopathic interstitial pneumonias (IIPs)**
  
  A group of 7 DPLDs 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 DPLD

![Diagram showing the spectrum of DPLD](ATS/ERS Guidelines for IIP. AJRCCM 2002;165:277-304.)
Known Causes of DPLD

- Drugs (chemotherapy, antibiotics)
  - www.pneumotox.com
- Radiation
- Connective Tissue Diseases
- Occupational/Environmental
  - Inorganic antigens (Pneumoconioses)
  - 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>
</tr>
<tr>
<td>Respiratory bronchiolitis-ILD (RB-ILD)</td>
<td>Respiratory bronchiolitis</td>
</tr>
<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>

**Previously 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 DPLDs

- 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 in DPLD

Pressure-Volume Curves

Reduced Lung volumes

DPLD leads to a restrictive ventilatory defect

- Reduced lung volumes
  - Total lung capacity**
  - Forced vital capacity
  - FEV₁

- Typically, no airflow obstruction

**Reduced TLC = restrictive ventilatory defect

West, JB. Pulmonary Pathophysiology: The Essentials, 2008
Gas exchange in DPLD

Changes in pulmonary capillary PO$_2$

West, JB. Pulmonary Pathophysiology: The Essentials, 2008
DPLD leads to *impaired gas exchange*

- V/Q mismatch
- Diffusion impairment *only with exercise*
- Shunt does *not* play a role

*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 DPLD

DPLDs 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

- 54 year old man comes to see you because of two years of dyspnea
  - 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.
**Six-minute walk test**

- Distance walked: 1778 ft
- Resting $S_pO_2$: 93%
- Exercise $S_pO_2$: 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 DPLD

• Usual interstitial pneumonia

• Risk factors
  – Older age
  – Male gender
  – Cigarette smoking
  – Family history
Epidemiology of IPF

Incidence rate (/100,000 PYO)*

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Prevalence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>2.2</td>
<td>4.0</td>
<td>8.7</td>
</tr>
<tr>
<td>55-64</td>
<td>14.2</td>
<td>10.0</td>
<td>28.4</td>
</tr>
<tr>
<td>65-74</td>
<td>48.6</td>
<td>21.1</td>
<td>104.6</td>
</tr>
<tr>
<td>75+</td>
<td>101.9</td>
<td>57.0</td>
<td>174.7</td>
</tr>
</tbody>
</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)

Age Influences Survival in IPF


Proposed Causes of IPF

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

A Role for Telomere Length in IPF
Telomere Length Decreases with Age


Telomeres and cellular senescence

Telomerase mutations are associated with pulmonary fibrosis

Telomerase mutations in familial 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

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

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

Management of DPLD

• Biopsy often required to make a diagnosis
  – Surgical lung biopsy
  – Transbronchial lung biopsy (less useful)
• Oxygen therapy
• Pulmonary rehabilitation
Treatment of DPLD

• Injury avoidance
  – Inhaled agents
  – Offending drug

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

• Lung transplantation