Diffuse Parenchymal Lung Disease

David J. Lederer, MD, MS
Irving Assistant Professor of Clinical Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University College of Physicians and Surgeons

Causes of Disease
- Structural Change
- Functional Change

Respiratory System Mechanics
- Gas Exchange
- Ventilation
- Vascular Changes

Compartments of the Lung

Parenchymal Inflammation and Fibrosis
- Normal Lung
- DPLD

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

- Diffuse Parenchymal Lung Diseases
  - DPLD of known cause
  - Idiopathic interstitial pneumonias (IIPs)
  - Granulomatous DPLDs (e.g., sarcoidosis)
  - Other forms of DPLD

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>

**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

- RB-ILD
- DIP

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

Selected other DPLDs

- Sarcoidosis
- Eosinophilic pneumonias
- Lymphangioleiomyomatosis
- Langerhan’s cell histiocytosis
Respiratory System Mechanics in DPLD

Pressure-Volume Curves

Reduced Lung volumes

West, JB. Pulmonary Pathophysiology: The Essentials, 2008

DPLD leads to a **restrictive ventilatory defect**

- Reduced lung volumes
  - Total lung capacity**
  - Forced vital capacity
  - FEV$_1$

- Typically, no airflow obstruction

**Reduced TLC = restrictive ventilatory defect

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 dyspeic 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°
- $S_o2$ 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 $S_o2$: 93%
- Exercise $S_o2$: 88%
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

Survival in IPF

Age Influences Survival in IPF

Proposed Causes of IPF

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

*PYO = patient-years of observation


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

Pathogenesis of IPF

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