Interstitial Lung Diseases
ACOI Board Review 2013

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UMDNJ-SOM
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 disease 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.
1. Diffuse infiltrates bilaterally
2. Restrictive Physiology
3. Histologic distortion of gas exchange areas
4. Dyspnea (exercise desat) and cough
Pathogenesis of Interstitial Lung Diseases

Inhaled Stimulus

Blood Borne Stimulus

Alveolitis

Recruitment of Inflammatory Cells

TISSUE DAMAGE

HEALING FIBROSIS
### Differential Diagnosis of ILD

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

### Slide 1

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

<table>
<thead>
<tr>
<th>2. Exposures</th>
<th>Pneumoconiosis</th>
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<tbody>
<tr>
<td></td>
<td>Hypersensitivity</td>
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<tr>
<td></td>
<td>Drug-induced</td>
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<tr>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td>IV drug use</td>
</tr>
</tbody>
</table>
### 3. Physical Exam

<table>
<thead>
<tr>
<th>Thoracic</th>
<th>Crackles</th>
<th>Wheeze</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rub</td>
<td>Normal</td>
</tr>
<tr>
<td>Extrathoracic</td>
<td>Nodes</td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Joints</td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>Eyes</td>
<td></td>
</tr>
</tbody>
</table>
| 4. Laboratory (All) | CBC with Diff  
|                     | UA/Creatinine  
|                     | CRP, RF, ANA   
|                     | ACE level      |
| If H+P Suggestive: | ANCA-c (Wegener's)  
|                     | 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) - Sjogrens
  - La (SSB)
  - Smith -Lupus
  - RNP - MCTD

Hypersensitivity pneumonitis
- Hypersensitivity panel (if exposure history)

### Approach to ILD

**Slide 4**

<table>
<thead>
<tr>
<th>5. X-Ray Patterns</th>
<th>Adenopathy</th>
<th>Nodules</th>
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</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Lobe</td>
<td>Reticular</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Reticulonodular</td>
<td>Rheumatoid Arthritis</td>
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<tr>
<td></td>
<td>Nodular</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td></td>
<td>Ground Glass</td>
<td>Wegener's</td>
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<tr>
<td></td>
<td>Silicosis</td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td>Sjogren's</td>
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<tr>
<td></td>
<td>Langerhans Cell Gran.</td>
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<tr>
<td></td>
<td>Ankylosing spondylitis</td>
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</tr>
<tr>
<td>Lower Lobe</td>
<td>IPF</td>
<td>Pleural</td>
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<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Asbestos</td>
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<tr>
<td></td>
<td>Asbestosis</td>
<td>RA</td>
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<tr>
<td></td>
<td>PSS</td>
<td>SLE</td>
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<tr>
<td></td>
<td>Sjogren's</td>
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## Approach to ILD

### Slide 5

<table>
<thead>
<tr>
<th>6. PFT</th>
<th>Spirometry</th>
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<tbody>
<tr>
<td></td>
<td>Lung volumes</td>
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<tr>
<td></td>
<td>DLCO</td>
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<td>ABG</td>
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<th>7. Tissue</th>
<th>Transbronchial Biopsy</th>
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<tbody>
<tr>
<td></td>
<td>Thoracoscopy</td>
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<tr>
<td></td>
<td>Open lung biopsy</td>
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<tr>
<td></td>
<td>Extrathoracic sites</td>
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<table>
<thead>
<tr>
<th>BAL ?</th>
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<tbody>
<tr>
<td>Gallium Scan ?</td>
</tr>
<tr>
<td>Chronic</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>IPF</td>
</tr>
<tr>
<td>Rheumatoid Lung</td>
</tr>
<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Langerhans Cell Granulomatosis</td>
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<tr>
<td>Pneumoconiosis</td>
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## Extrathoracic Manifestations of Interstitial Lung Diseases (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>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>CVD</td>
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<tr>
<td></td>
<td>Granulomatous vasculitis</td>
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<td>Sjogren's syndrome</td>
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<tr>
<td>Skin</td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>CVD</td>
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<tr>
<td></td>
<td>Granulomatous vasculitis</td>
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<tr>
<td></td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>PSS</td>
</tr>
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</table>
Extrathoracic Manifestations of *Interstitial Lung Diseases (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>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>Polymyositis</td>
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<tr>
<td>GI</td>
<td>PSS</td>
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<tr>
<td></td>
<td>Polymyositis</td>
</tr>
<tr>
<td></td>
<td>Wegener's granulomatosis</td>
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<tr>
<td></td>
<td>CVD</td>
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<tr>
<td></td>
<td>Goodpasture's</td>
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<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
<table>
<thead>
<tr>
<th>STAGE</th>
<th>FINDINGS</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</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>
BHA: Sarcoidosis
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 DIAGONOSTIC

- 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
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.
50 % mortality at 5 years

10 % develop bronchogenic CA

Treatment is Prednisone + azathioprine, gamma interferon

10 to 20 % recover lung volume during therapy
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

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


### Minor Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50 years</td>
<td></td>
</tr>
<tr>
<td>Insidious onset of otherwise unexplained dyspnea on exertion</td>
<td></td>
</tr>
<tr>
<td>Duration of illness &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>Bibasilar, inspiratory, Velcro® crackles</td>
<td></td>
</tr>
</tbody>
</table>

- **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)**
IPF - H+E stain
IPF (trichrome stain)
CLASSIFICATION OF IIP
( IMMUNOCOMPETENT HOST )

Idiopathic interstitial pneumonia (IIP)

Idiopathic pulmonary fibrosis/Usual interstitial pneumonia (UIP)

Desquamative interstitial pneumonia (DIP)

Respiratory bronchiolitis-associated interstitial lung disease (RBILD)

Acute interstitial pneumonia (AIP)

Nonspecific interstitial pneumonia (NSIP)
## IIP Classification

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Radiology</th>
<th>Distribution</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF/UIP</td>
<td>Fibrosis, HC</td>
<td>Basilar, peripheral</td>
<td>Temporal heterog, FF, fibrotic and normal lung, microscopic HC</td>
</tr>
<tr>
<td>NSIP</td>
<td>GGO +/- fibrosis</td>
<td>Basilar, peripheral</td>
<td>Diffuse interstitial inflammation +/- fibrosis</td>
</tr>
<tr>
<td>COP</td>
<td>GGO, nodules, consolidation</td>
<td>Patchy upper lungs, small airways, alveolar</td>
<td>Granulation tissue plugs in alveolar ducts and alveoli</td>
</tr>
<tr>
<td>AIP</td>
<td>GGO, consolidation</td>
<td>Diffuse, random</td>
<td>Hyaline membranes, immature fibroblasts in alveolar spaces and interstitium to variable degree</td>
</tr>
<tr>
<td>RB-ILD</td>
<td>Bronchiectasis, GGO</td>
<td>Upper lungs, bronchocentric</td>
<td>Respiratory bronchiolitis surrounded by MΦs in alveoli</td>
</tr>
<tr>
<td>DIP</td>
<td>GGO, consolidation</td>
<td>Basilar, peripheral, alveolar</td>
<td>Alveolar MΦs in air spaces diffusely in the biopsy</td>
</tr>
<tr>
<td>LIP</td>
<td>GGO, nodules, cysts</td>
<td>Patchy</td>
<td>Lymphoid hyperplasia</td>
</tr>
</tbody>
</table>

HC, honeycombing; GGO, ground glass opacity; FF, fibrotic foci; MΦ, macrophage

Adapted from Strollo DC. *Am J Respir Cell Mol Biol.* 2003;29(3 Suppl):S10-S18.
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
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

**Oxygen**

**Illicit Drugs**
- Talc
cocaine
Collagen Vascular Diseases with ILD

- RA
- PSS
- Polymyositis/Dermatomyositis
- MCTD
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
Bronchiolitis Obliterans
Organizing Pneumonia

Diagram showing the distribution of causes, with the largest section labeled 'Idiopathic'. Other sections labeled 'Viral', 'CVD', 'Drugs', 'Gas', 'Transplant', and 'AIDS' also contribute to the overall distribution.
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
CT
BOOP

Subpleural

Ground glass infiltrates
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
56 yo
Male

Anthracosis
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
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
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
Specific Findings for LCG

- Birbeck's granules or X-bodies in the cytoplasm on EM
- Immunoperoxidase stain for S-100 protein on cell surface
- OKT-6 antibody to the CD1a antigen on the cell surface