Restrictive/Infiltrative Lung Disease (Chronic interstitial lung disease)

- Restriction = decreased total lung capacity
- Two general categories
  - Chest wall disorders
    - i.e. neuromuscular disease, obesity, kyphoscoliosis
  - Pulmonary chronic interstitial and infiltrative diseases

- Reduced lung compliance (stiff lungs)
- Dyspnea
- End inspiratory crackles
- Hypoxia
- Chest radiographs
  - Nodules, irregular lines, ground glass shadows

- Respiratory failure
  - Pulmonary HTN
  - Cor Pulmonale

- “Honeycomb lung” - end stage pathology
ILD - Miscellaneous group of disorders

Varying degree of inflammation and fibrosis of the interstitium
Categories of Chronic Interstitial Lung Disease

- **Granulomatous**
  - Sarcoidosis (20%)
  - Hypersensitivity pneumonia

- **Fibrosing**
  - Usual interstitial pneumonia (idiopathic pulmonary fibrosis) (15%)
  - Nonspecific interstitial pneumonia
  - Cryptogenic organizing pneumonia
  - Associated with collagen vascular disease (10%)
  - Pneumoconiosis (25%)
  - Therapy related (drugs, radiation)

- **Eosinophilic**

- **Smoking related**
  - Desquamative interstitial pneumonia
  - Respiratory bronchiolitis

---

**Sarcoidosis**

- Multisystem disease of unknown etiology
- Characterized by **non-caseating granulomas**
- Diagnosis of exclusion
  - For example, must rule out infections (TB, fungi) when see granulomas
Sarcoidosis

- Adults < 40
- African Americans
- Danish and Swedish

Typically disease of young adults
Tends to be upper lobe predominant
2/3 rd patients are asymptomatic
CXR abnormalities in 90% patients
- Bilateral hilar lymphadenopathy
- Lung parenchymal abnormalities
Shortness of breath, dry cough
Fever, fatigue, night sweats, weight loss, anorexia
Diffuse interstitial fibrosis; 10-15% progressive pulmonary fibrosis, cor pulmonale
Sarcoidosis – Systemic Involvement

- Heart
  - Restrictive cardiomyopathy
  - Conduction abnormalities
- Bell’s Palsy
  - CN VIII
- Eye (20-50%, pts)
  - Uveitis
- Skin (30-50%, pts)
  - Erythema nodosum: acute, nodular erythematous eruptions on the extensor aspect of LL.
  - Lupus Pernio: Chronic indurated plaques on the mid-face

Sarcoidosis

- Etiology/Pathogenesis
  - Result of both
    - Genetic susceptibility
    - Environmental trigger
      - Still unknown
    - T helper (CD4) immune response

Key Players

- CD4 T Cells
  - Dominant cell in sarcoid granulomas
- T regulatory cells
  - Suppress proliferation and cytokine production of activated T-cells
  - Downregulated in sarcoid animal models
- Interferon-γ
  - Activates macrophages
- Tumor Necrosis Factor
  - Mediator of granuloma formation

Model of the Immunopathogenesis of sarcoidosis
Morgenthau A. Chest 2011; 139: 116–132
Sarcoidosis

- Histology:
  - Non-caseating granulomas
  - Coalescent granulomas with a rim of lymphocytes (relatively thin rim), embedded in an eosinophilic collagenous stroma
  - Present along lymphatic routes: Pleura, interlobular septa and along bronchovascular bundles
  - Multinucleated giant cells with cytoplasmic inclusions: Schaumann bodies, Asteroid bodies.

Lymph node replaced by granulomas

Epithelioid histiocytes (arrowheads):
Folded, bland, "bathroom slipper/flip flop/ insole" shaped nuclei
Bronchocentric distribution of granulomas

Interstitial distribution of granulomas

Multinucleated giant cells are characteristically present in the disease, often accompanied by a variety of distinctive (but not specific) cytoplasmic inclusions: (A) upper left, asteroid body; (B) upper right, Schaumann (conchoidal) body; (C) lower left, Schaumann bodies; (D) lower right, Schaumann body in polarized light.
Diagnosis of Sarcoidosis

- Diagnosis:
  - Made on a transbronchial biopsy in 90% if 4 pieces were submitted
  - Routine AFB and GMS
  - Diagnosis of exclusion

Sarcoidosis Laboratory/Diagnostic Abnormalities

- Elevated serum angiotensin converting enzyme (ACE) level
- Hypercalcemia
- Markers to systemic immune abnormalities
  - Anergy to common skin test antigens
  - Candida, PPD
  - Polyclonal hypergammaglobulinemia
Sarcoidosis and Vitamin D Hypercalcemia

- Varying severity, varying sites involved
- Steroid therapy
- Progressive multisystem disease or remissions and flares
- 65-70% recover with minimal manifestations
- 20% permanent loss of lung or vision function
- Deaths
  - 10-15% cardiac or CNS complications
  - Majority progressive pulmonary fibrosis and cor pulmonale

Sarcoidosis Course

- Varying severity, varying sites involved
- Steroid therapy
- Progressive multisystem disease or remissions and flares
- 65-70% recover with minimal manifestations
- 20% permanent loss of lung or vision function
- Deaths
  - 10-15% cardiac or CNS complications
  - Majority progressive pulmonary fibrosis and cor pulmonale

Categories of Chronic Interstitial Lung Disease

- Granulomatous
  - Sarcoidosis (20%)
  - Hypersensitivity pneumonia
- Fibrosing
  - Usual interstitial pneumonia (idiopathic pulmonary fibrosis) (15%)
  - Nonspecific interstitial pneumonia
  - Cryptogenic organizing pneumonia
  - Associated with collagen vascular disease (10%)
  - Pneumoconiosis (25%)
  - Therapy related (drugs, radiation)
- Eosinophilic
- Smoker related
  - Desquamative interstitial pneumonia
  - Respiratory bronchiolitis
Idiopathic Pulmonary Fibrosis

- AKA cryptogenic fibrosing alveolitis, usual interstitial pneumonia (histologic pattern)
- Pathogenesis
  - Repeated cycles of epithelial activation/injury by some unidentified agent
  - Abnormal epithelial repair
  - Fibroblastic proliferation

Pathogenesis

Summary

- “Repeated cycles of lung injury and wound healing with increased collagen”
- Idiopathic Pulmonary Fibrosis: Clinical term; Usual Interstitial Pneumonia (UIP): Pathology term
Idiopathic Pulmonary Fibrosis
Morphology

- Pleural surface scarring ("cobblestoned")
- Firm, rubbery white cut surface - fibrosis
- Patchy interstitial fibrosis
  - Non-uniform pattern fibrosis
  - Fibrosis varies in intensity and age
  - Early finding - "exuberant" fibroblastic proliferation (fibroblastic focus)
- Dense fibrosis destroys alveolar architecture
  - Cystic spaces
  - Lined by hyperplastic (type II) pneumocytes or bronchiolar epithelium
  - "Honeycomb fibrosis"

https://grosspathology-sites.uchicago.edu/page/lung-explant
Varying fibrosis, some zones are spared

Usual interstitial pneumonia

Extensive fibrosis

Trichrome stain: Area of fibrosis stains blue

Source - UTAH Web Path
Idiopathic Pulmonary Fibrosis

- Clinicopathologic Correlation
  - 40-70 years
  - Men>women
  - Dyspnea on exertion
  - Dry cough
  - Velcro crackles
  - Deterioration
  - Mean survival less than 3 years
  - Lung transplant only definitive tx; anti-fibrosis drugs can prevent progression of the disease

Categories of Chronic Interstitial Lung Disease

- Fibrosing
  - Usual interstitial pneumonia (idiopathic pulmonary fibrosis) (15%)
  - Non-specific interstitial pneumonia
  - Cryptogenic organizing pneumonia
  - Associated with collagen vascular disease (10%)
  - Pneumoconiosis (25%)
    - Therapy-related (drugs, radiation)
  - Granulomatous
    - Sarcoidosis (20%)
    - Hypersensitivity pneumonia
  - Eosinophilic
  - Smoking related
    - Desquamative interstitial pneumonia
    - Respiratory bronchiolitis

Pneumoconioses

- Miscellaneous group of disorders characterized by the accumulation of dust in the lungs and the tissue reaction to its presence
  - Particulate, chemical fume, vapor-induced non-neoplastic lung diseases
Mineral Dust Pneumoconioses

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Industry</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coal dust</td>
<td>Coal mining</td>
<td>Anthracosis, Progressive Massive Fibrosis</td>
</tr>
<tr>
<td>Silica</td>
<td>Sandblasting</td>
<td>Silicosis</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Roof building</td>
<td>Asbestosis</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Mining, fabrication</td>
<td>Berylliosis</td>
</tr>
<tr>
<td>Iron Oxide</td>
<td>Welding</td>
<td>Siderosis</td>
</tr>
<tr>
<td>Barium sulfate</td>
<td>Mining</td>
<td>Baritosis</td>
</tr>
<tr>
<td>Tin Oxide</td>
<td>Mining</td>
<td>Stannosis</td>
</tr>
</tbody>
</table>

Pathogenesis

- Inhaled dusts largely entrapped in mucous, removed by ciliary movement
- 1-5 μm particles most dangerous
  - Reach terminal small airways, air sacs, settle in linings
- Shape, buoyancy, solubility
- Host factors
  - Tobacco
  - Genetics

Pneumoconioses

- Macrophages
  - Endocytose trapped particles
  - Reactive particles trigger release of inflammatory mediators from macrophages
  - Interleukins, TNF
  - Fibrogenesis
  - Collagen deposition
Coal Worker’s Pneumoconiosis

- Anthracosis
- Simple coal worker's pneumoconiosis
- Progressive massive fibrosis
- Caplan syndrome
- Clinical course will depend on extent of fibrosis

Anthracosis

- Smokers, urban dwellers, coal miners
- Inhaled carbon pigment engulfed by alveolar/interstitial macrophages
  - Accumulate in connective tissue, pleural lymphatics, lymph nodes
- No sequelae
Simple Coal Workers Pneumoconiosis
- Coal macules, nodules
  - Accumulations of dust-laden macrophages
  - Fibrosis

Progressive Massive Fibrosis
- Coalescence of coal nodules, large scars
- Fibrotic, bulky, heavily pigmented black tissue masses
- “Black Lung”

Caplan Syndrome
- “Rheumatoid pneumoconiosis”
- Form of Coal Worker Pneumoconiosis associated with rheumatoid arthritis
- Suggestion that presence of rheumatoid arthritis is a host factor that modifies response of an individual to coal mine dust exposure
- Radiology - the nodules may cavitate

Asbestos Controversies
- Mass legal actions
- Public health policy
  - Asbestos removal in old buildings?
- Continued use in underdeveloped countries
Asbestos

- Smallest naturally occurring fiber
- Cheap, Durable, heat resistant
- Mining, milling, fabrication of ores and materials, installation and removal of insulation
- Indirect exposure

Asbestos

- Fibrotic lung reaction
- Lung interstitial fibrosis
- Pleural plaques
- Tumor initiator and promoter
- Lung cancers
- Mesothelioma
- Free radicals generated by asbestos fibers localize in distal lung, close to mesothelial layers

Asbestos - Plethora of Effects

- Interstitial fibrosis (asbestosis)
- Localized fibrous plaques
  - Diffuse fibrosis of pleura
- Pleural effusions
- Bronchogenic carcinoma
- Malignant mesothelioma
- Laryngeal carcinoma
Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).

Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).

Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).

Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).

Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).

Asbestos bodies can be found in the pleura and lung, in areas of fibrosis. Can be seen in sputum, BAL. The central core of the fiber gets coated with iron and calcium (which imparts a blue color on the Prussian blue stain). The arrow points to an uncoated segment of asbestos fiber in this ferruginous body (H&E stain).
Silicosis

- Foundries, sandblasting, mines
- Most prevalent chronic world occupational disease
- Inhalation of crystalline silica
  - Within macrophages causes activation, release of mediators
  - Fibrogenic

Silicosis

- Nodules
  - Concentric hyalinized collagen
  - Whorled appearance
- Coalescence of nodules
- Progressive massive fibrosis
- Fibrotic lesions in hilar lymph nodes, pleura

Silica crystals
Under polarized light
Web Path
“Eggshell” calcification of lymph nodes

Silicosis

- Incidental finding on CXR
- PMF - dyspnea, pulm HTN, cor pulmonale
- Increase susceptibility to tuberculosis
  - Silica depresses cell-mediated immunity
  - Pulmonary macrophage phagocytosis impaired
- Carcinogenic - lung cancer
  - Still under debate

See Table 1 in Handout for summary of Pneumococcosis

Kumar: Robbins and Cotran: Pathologic Basis of Disease, 7th ed.
A 66-year-old man has had increasing dyspnea for the past year. He is a smoker. He is retired from the construction business. There are some rales auscultated in both lungs on physical examination. A chest radiograph reveals bilateral diaphragmatic pleural plaques with focal calcification as well as diffuse interstitial lung disease. A BAL cytology shows Ferruginous bodies. Pulmonary function studies reveal a low FVC and a normal FEV1/FVC ratio. These findings are most likely to suggest prior exposure to which of the following environmental agents?

A  Cotton fibers
B  Silica dust
C  Fumes with iron particles
D  Asbestos crystals
E  Beryllium

Thank you! Questions!