Chronic Diffuse Interstitial (Restrictive) Diseases

By: Shefaa’ Qa’qa’
• Restrictive lung diseases, are characterized by reduced expansion of lung parenchyma (lung compliance) and decreased total lung capacity.

• Restrictive lung diseases are associated with proportionate decreases in both total lung capacity and FEV1, leading to normal FEV1/FVC ratio.
• Restrictive defects occur in two broad kinds of conditions:
  (1) chest wall disorders (e.g., severe obesity, pleural diseases, kyphoscoliosis, and neuromuscular diseases such as poliomyelitis)
  (2) chronic interstitial and infiltrative diseases, such as pneumoconioses and interstitial fibrosis.
Chronic interstitial pulmonary diseases are a heterogeneous group of disorders characterized predominantly by inflammation and fibrosis of the pulmonary interstitium.

Patients have dyspnea, tachypnea, end-inspiratory crackles, and eventual cyanosis, without wheezing or other evidence of airway obstruction.
Chest radiographs show bilateral lesions that take the form of small nodules, irregular lines, or groundglass shadows, all corresponding to areas of interstitial fibrosis.

Eventually, secondary pulmonary hypertension and right-sided heart failure associated with cor pulmonale may result.

Although the entities can often be distinguished in the early stages, the advanced forms are hard to differentiate because all result in scarring and gross destruction of the lung, often referred to as end-stage lung or honeycomb lung.
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Idiopathic Pulmonary Fibrosis

- Idiopathic pulmonary fibrosis (IPF) refers to a clinicopathologic syndrome marked by progressive interstitial pulmonary fibrosis and respiratory failure.
- The histologic pattern of fibrosis is referred to as usual interstitial pneumonia (UIP).
The UIP pattern can also be seen in other diseases, notably connective tissue diseases, chronic hypersensitivity pneumonia, and asbestosis; these must be distinguished from IPF based on other clinical, laboratory, and histological features.
• Pathogenesis:
While the cause of IPF remains unknown, it appears that the fibrosis arises in genetically predisposed individuals who are prone to aberrant repair of recurrent alveolar epithelial cell injuries caused by environmental exposures.
Environmental factors:
- Smoking
- Occupational exposure
- Other irritants, toxins
- Viral infection

At risk epithelium:
- Age
- Genetics:
  - Telomerase mutations
  - Surfactant mutations
  - MUC5B variant

Persistent epithelial injury/activation

Pro-fibrogenic factors

Abnormal intracellular signaling

Proliferation, collagen production

Fibrosis
Figure 15-15 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix. Honeycombing is present on the left.
Clinical Course:
- IPF begins insidiously with gradually increasing dyspnea on exertion and dry cough.
- Most patients are 55 to 75 years old at presentation.
- Hypoxemia, cyanosis, and clubbing occur late in the course.
- Usually there is a gradual deterioration in pulmonary status despite medical treatment with immunosuppressive drugs such as steroids, cyclophosphamide, or azathioprine.
- Other IPF patients have acute exacerbations of the underlying disease and follow a rapid downhill clinical course.
- The median survival is about 3 years after diagnosis.
- Lung transplantation is the only definitive therapy.
Pneumoconiosis

• The term pneumoconiosis, originally coined to describe the nonneoplastic lung reaction to inhalation of mineral dusts encountered in the workplace, now also includes diseases induced by organic as well as inorganic particulates and chemical fumes and vapors.
The development of a pneumoconiosis depends on:
(1) the amount of dust retained in the lung and airways;
(2) the size, shape, and buoyancy of the particles;
(3) particle solubility and physiochemical reactivity;
(4) the possible additional effects of other irritants (e.g., concomitant tobacco smoking).

- The most dangerous particles are from 1 to 5 μm in diameter, because particles of this size may reach the terminal small airways and air sacs and settle in their linings. Small particles of high solubility are more likely to cause acute lung injury.
- Larger particles are more likely to resist dissolution and may persist within the lung parenchyma for years. These tend to evoke fibrosing collagenous pneumoconioses.
Other particles may be taken up by epithelial cells or may cross the epithelial cell lining and interact directly with fibroblasts and interstitial macrophages. Some may reach the lymphatics by direct drainage or within migrating macrophages and thereby initiate an immune response to components of the particulates or to selfproteins modified by the particles or both.

The effects of inhaled particles are not confined to the lung alone, since solutes from particles can enter the blood and lung inflammation invokes systemic responses.

Any influence, such as cigarette smoking, that impairs mucociliary clearance significantly increases the accumulation of dust in the lungs.
1. Coal Workers’ Pneumoconiosis

• Coal workers’ pneumoconiosis is lung disease caused by **inhalation of coal particles** and other admixed forms of dust.

• The spectrum of lung findings in coal workers is wide, varying from **asymptomatic anthracosis**, to **simple coal workers’ pneumoconiosis** with little to no pulmonary dysfunction, to **complicated coal workers’ pneumoconiosis**, or progressive massive fibrosis, in which lung function is compromised.
**Anthracosis**: is the most innocuous coal-induced pulmonary lesion in coal miners and is also seen to some degree in urban dwellers and tobacco smokers. *Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages*, which then accumulate in the connective tissue along the lymphatics, or in organized lymphoid tissue along the bronchi or in the lung hilus.

**Simple coal workers’ pneumoconiosis**: is characterized by coal macules (1 to 2 mm in diameter) and somewhat larger coal nodules. Coal macules consist of carbon-laden macrophages; nodules also contain a delicate network of collagen fibers. The upper lobes are more heavily involved. centrilobular emphysema.

**Complicated coal workers’ pneumoconiosis** (progressive massive fibrosis): occurs on a background of simple disease and generally requires many years to develop. It is characterized by intensely blackened scars 1 cm or larger. lesions consist of dense collagen and pigment. The center of the lesion is often necrotic, most likely due to local ischemia.
Clinical Course:
- Coal workers’ pneumoconiosis is usually benign, causing little decrement in lung function.
- In a minority of cases (fewer than 10%), progressive massive fibrosis develops, leading to increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- Once progressive massive fibrosis develops, it may continue to worsen even if further exposure to dust is prevented.
2. Silicosis

- Silicosis is a common lung disease caused by inhalation of proinflammatory crystalline silicon dioxide (silica) that usually presents after decades of exposure as slowly progressing, nodular, fibrosing pneumoconiosis.

- Currently, silicosis is the most prevalent chronic occupational disease in the world.
• workers in a large number of occupations are at risk, including individuals involved with the repair, rehabilitation or demolition of **concrete structures** such as buildings and roads.

• Less commonly, the disease occurs in workers producing stressed denim by sandblasting, stone carvers, and jewelers using chalk molds.

• Silica occurs in both **crystalline and amorphous forms**, but crystalline forms (including quartz, cristobalite, and tridymite) are much more fibrogenic. Of these, **quartz** is most commonly implicated.
After inhalation, the particles are phagocytosed by macrophages. The phagocytosed silica crystals activate the inflammasome, leading to the release of inflammatory mediators, particularly IL-1 and IL-18.

The relatively benign response to silica in coal and hematite miners is thought to be due to coating of silica with other minerals, especially clay components, which render the silica less toxic.
• Silicosis is characterized grossly in its early stages by tiny, barely palpable, discrete pale to blackened (if coal dust is also present) nodules in the hilar lymph nodes and upper zones of the lungs.
• Nodules coalesce into hard, collagenous scars.
• Some nodules may undergo central softening and cavitation due to superimposed tuberculosis or to ischemia.
• Sometimes, thin sheets of calcification occur in the lymph nodes and are seen radiographically as eggshell calcification.
• Progressive massive fibrosis.
Figure 15-19 Several coalescent collagenous silicotic nodules. (Courtesy Dr. John Godleski, Brigham and Women's Hospital, Boston, Mass.)
• Clinical Course:
- Pulmonary functions are either normal or only moderately affected early in the course, and most patients do not develop shortness of breath until **progressive massive fibrosis** supervenes.
- It is associated with an increased susceptibility to **tuberculosis**. This may be because crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria.
- The onset of silicosis may be slow and insidious (10 to 30 years after exposure; most common), accelerated (within 10 years of exposure) or rapid (in weeks or months after intense exposure to fine dust high in silica; rare). Patients with silicosis have double the risk for developing **lung cancer**.
3. Asbestos-Related Diseases

- Asbestos is a family of proinflammatory crystalline hydrated silicates that are associated with pulmonary fibrosis, carcinoma, mesothelioma, and other cancers.

- Asbestos-related diseases include:
  - Localized fibrous pleural plaques (the most common manifestation of asbestos exposure)
  - Rarely, diffuse pleural fibrosis
  - Pleural effusions, recurrent
  - Parenchymal interstitial fibrosis (asbestosis)
  - Lung carcinoma
  - Mesotheliomas
  - Laryngeal, ovarian and perhaps other extrapulmonary neoplasms, including colon carcinomas; increased risk for systemic autoimmune diseases and cardiovascular disease has been proposed
Asbestos occurs in two distinct geometric forms, serpentine and amphibole. Amphiboles, even though less prevalent, are more pathogenic, particularly with respect to induction of mesothelioma, a malignant tumor derived from the lining cells of pleural surfaces.

The greater pathogenicity of amphiboles is apparently related to their aerodynamic properties and solubility (less soluble).

The straight, stiff amphiboles may align themselves in the airstream and thus be delivered deeper into the lungs, where they can penetrate epithelial cells and reach the interstitium.
• Some of its oncogenic effects are mediated by **reactive free radicals** generated by asbestos fibers, which preferentially localize in the distal lung, close to the mesothelial layers.

• **Toxic chemicals adsorbed** onto the asbestos fibers also likely contribute to the oncogenicity of the fibers. One study of asbestos workers found a fivefold increase of lung carcinoma with asbestos exposure alone, while asbestos exposure and smoking together led to a 55-fold increase in the risk.

• Smoking also enhances the effect of asbestos by interfering with the mucociliary clearance of fibers.

• As with silica crystals, once phagocytosed by macrophages asbestos fibers activate the inflammasome and stimulate the release of proinflammatory factors and fibrogenic mediators.
• Asbestosis is marked by **diffuse pulmonary interstitial fibrosis** (similar to UIP), and presence of multiple **asbestos bodies** (asbestos fibers coated with an iron-containing proteinaceous material, arise when macrophages phagocytose asbestos fibers).

• In contrast to coal workers’ pneumoconiosis and silicosis, asbestosis begins in the **lower lobes** and subpleurally.

• The scarring may trap and narrow pulmonary arteries and arterioles, causing pulmonary hypertension and cor pulmonale.

• Pleural plaques, the most common manifestation of asbestos exposure. They develop most frequently on the anterior and posterolateral aspects of the **parietal pleura**.
• Clinical Course:
The clinical findings in asbestosis are very similar to those caused by other diffuse interstitial lung diseases. These rarely appear fewer than 10 years after first exposure and are more common after 20 to 30 years.

Dyspnea
Pleural plaques are usually asymptomatic and are detected on radiographs as circumscribed densities.

The disease may remain static or progress to respiratory failure, cor pulmonale, and death.
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<thead>
<tr>
<th>Organic Dusts That Induce Hypersensitivity Pneumonitis</th>
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<td>Moldy hay</td>
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<td>Bagasse</td>
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<tr>
<td>Bird droppings</td>
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<td>Farmer’s lung</td>
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<td>Bagassosis</td>
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<tr>
<td>Farming</td>
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<tr>
<td>Manufacturing wallboard, paper</td>
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<td>Bird handling</td>
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Sarcoidosis

- Sarcoidosis is a **systemic granulomatous** disease of unknown cause that may involve many different tissues and organs.
• Sarcoidosis presents in many clinical patterns, but bilateral hilar lymphadenopathy or lung involvement is most common, occurring 90% of cases.
• Eye and skin lesions are next in frequency.
• Since other diseases, including mycobacterial and fungal infections and berylliosis, can also produce noncaseating granulomas, the diagnosis is one of exclusion.
• Sarcoidosis usually occurs in adults younger than 40 years of age, but can affect any age group.
• The prevalence is higher in women but varies widely in different countries and populations.
• In the United States the rates are highest in the Southeast and are 10 times higher in blacks than in whites.
• In contrast, the disease is rare among Chinese and Southeast Asians.
• Pathogenesis:
  - Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed individuals. It is not clear whether exposure to any environmental or infectious agent has a role in its pathogenesis.
  - There are several immunologic abnormalities in the local milieu of sarcoid granulomas that suggest the involvement of a cell-mediated immune response to an unidentified antigen.
    accumulation of CD4+ T cells
    Increased levels of T cell-derived TH1 cytokines such as IL-2 and IFN-γ
    Increased levels of several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein 1α)
  TNF concentration in the bronchoalveolar fluid is a marker of disease activity.
Additionally, there are systemic immunologic abnormalities in individuals with sarcoidosis:

- **Anergy** to common skin test antigens such as Candida or tuberculosis purified protein derivative (PPD).
- Polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation.
• Virtually every organ in the body has been described as being affected by sarcoidosis, at least on rare occasions. Regardless of the tissue, involved tissues contain well-formed nonnecrotizing granulomas composed of aggregates of tightly clustered epithelioid macrophages, often with giant cells.
• Clinical Course:
- Because of its varying severity and inconstant tissue distribution, sarcoidosis may present with diverse features.
- It may be discovered unexpectedly on routine chest films as bilateral hilar adenopathy or may present with peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly.
- Shortness of breath, cough, chest pain, hemoptysis or of constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats).
- Sarcoidosis follows an unpredictable course.