Parenchymal disease – Pulmonary Interstitial Fibrosis

Learning Objectives
- Describe the etiology, pathogenesis, pathology and complications of interstitial lung diseases.
- Describe with examples how occupational dusts can lead to lung diseases.

Overview
The pulmonary interstitium consists of the connective tissues that make up the alveolar septa and tissues that support the bronchial, bronchiolar and vascular structures. Interstitial lung diseases are relatively uncommon, accounting for about 15% of non-infectious pulmonary diseases. These are a heterogeneous group of diseases caused by different etiologies. The most important pathological process is chronic inflammation, with low grade, slowly progressive damage leading to fibrosis (pulmonary interstitial fibrosis). The insult may be insidious, mild but persistent. Thus, most cases present in the late fibrotic stage and the initiating events of the disease cannot be determined (Idiopathic Pulmonary Fibrosis). A few cases may present in the earlier stages of injury (e.g. diffuse alveolar damage). The time course and outcome of the disease depend on individual cause and severity of the injury.

Although the etiologies may be different, they affect the same anatomical/structural components of the lung, lead to similar pathophysiological effects with characteristic functional impairment (restrictive lung function) and clinical features.

Etiologies of interstitial lung diseases:
1) Toxic damages - toxic fume inhalation, irradiation, cytotoxic drugs
2) Mineral dust deposition - The pneumoconioses
3) Auto-immune diseases - The lung is damaged by auto-immune reactions against self antigens of the lung. E.g. progressive systemic sclerosis (also known as scleroderma), systemic lupus erythematosis (SLE), rheumatoid arthritis.
4) Idiopathic - Idiopathic pulmonary fibrosis (also called Cryptogenic Fibrosing Alveolitis). In these cases, the cause of the initial lung damage is not known.
5) Miscellaneous - e.g. extrinsic allergic alveolitis (Hypersensitivity reaction against inhaled organic dusts deposited in the alveolar wall, such as pollens, fungal spores, animal proteins), sarcoidosis.

(Viral infections are usually self limiting and do not progress to chronic diseases, i.e., they cause interstitial pneumonia or pneumonitis but not interstitial fibrosis)

Pathological changes of pulmonary interstitial fibrosis:
a) Initial stage shows chronic inflammatory cell infiltration in the alveolar wall and interstitium, but the degree of inflammatory activity is not uniform throughout the lungs and varies from case to case. In many instances, only limited inflammatory activity may be
detected when the patient presents. In the mineral dust diseases, the initiating agent, eg. asbestos bodies, may be found.
b) Fibroblasts (stromal cells that produce fibrous tissue) in the alveolar septa and interstitial tissue proliferate and the interstitium is thickened by fibrosis. Macroscopically, the lung may show thickening of the alveolar wall.
c) End stage - Some alveolar spaces become obliterated by the fibrosis. Residual alveoli and some bronchioles become stretched and dilated to form small, round, cyst-like spaces. Macroscopically, the lung is rigid and shrunken. The pleural lining is thickened and the lung surface may have a bosselated appearance. This gross appearance is described as ‘Honeycomb Lung’.

Pathophysiological changes and complications of pulmonary interstitial fibrosis:
- Fibrosis and thickening of alveolar wall leads to decreased diffusion capacity and alveolo-capillary block. There is loss of elastic tissue leading to rigid lung and decreased pulmonary compliance. There is decreased total lung capacity with restrictive lung function.
- Fibrous obliteration of pulmonary arteries leads to a reduced vascular bed. When more than 50% of arterial bed is destroyed, the overall vascular resistance is raised and ventilation/perfusion mismatch occurs.
- Overall, gas exchange is impaired and in severe cases, leading to chronic hypoxia.

Clinical features and diagnosis of pulmonary interstitial fibrosis:
- Progressive dry cough - exudates/secrretions are not prominent in the airways or alveolar spaces
- Progressively worsening dyspnoea, tachypnoea - as lung function deteriorates, respiratory rate is increased
- Cyanosis - inadequate oxygenation of blood, ventilation/perfusion mismatch
- There is no wheezing - airflow is not obstructed
- The CXR shows coarse mottling or small nodular opacities
- In severe cases, patients die from respiratory or cardiac failure after a few years of presentation.
- There is an increased risk of lung cancer
- Diagnosis is made by finding the characteristic clinical symptoms, CXR features, and a restrictive lung function pattern. Tissue examination is helpful in assessing the relative inflammatory or fibrotic activity, and in finding the specific etiological agent (e.g. asbestos bodies) for some cases.

Complications of chronic hypoxia:
- Any cause of chronic hypoxia (e.g. pulmonary interstitial fibrosis, COPD) may give rise to a series of common changes.
- Chronic hypoxia induces constriction of the pulmonary arteries. In early mild cases, the constriction is reversible. In chronic cases, irreversible structural changes occur with thickening of the vessel wall and reduction of vascular lumen. In severe cases, the arterial wall may become necrotic and obliterated. (The changes are similar to those in systemic hypertension which you would be learning about in the CVS module)
- With reduction in the vascular channels, there is increased vascular resistance to blood flow and pulmonary hypertension occurs (a systolic blood pressure in the pulmonary circulation exceeding 30 mmHg; normal pulmonary blood pressure is 25/8).
- Cor pulmonale occurs - This is right ventricular hypertrophy and dilatation resulting from primary pulmonary diseases affecting the function and/or structure of the lungs and its
vessels. By definition, right ventricular changes secondarily resulting from left heart diseases and congenital heart diseases are not counted as cor pulmonale.

- In the late phase, systemic venous congestion of the liver, spleen, kidneys and peripheral oedema occur. (You would learn about blood pressure, cardiac changes and systemic venous congestion in the CVS module)
- Increased circulatory RBC (polycythaemia) leading to raised blood viscosity and predisposition to venous thrombosis.

### PNEUMOCONIOSES (Dust Diseases)

- Pneumoconiosis is a term initially used to describe a group of lung diseases resulting from the inhalation of inorganic/mineral dusts that cause widespread lung destruction and fibrosis.
- Pulmonary fibrosis results from chronic inflammatory reactions induced by the engulfed dust particles, with release of fibrogenic enzymes by alveolar macrophages and inducing fibroblasts proliferation.
- The type of lung disease varies according to the nature, size, physical state, chemical composition and concentration of the inhaled dusts. The duration of exposure and coexistence of other lung diseases are also important.
- Pneumoconioses are occupational diseases and compensation may be claimed. The Pneumoconiosis Compensation Board is the official organization responsible for assessment of these cases.

### SILICOSIS (Pulmonary fibrosis due to silica deposition)

Silica (SiO₂) is the major component of the crust of the earth. Silicosis develops after prolonged exposure (often more than 20 yrs.) to dusts containing a high percentage of free silica (usually quartz). Workers involved in cutting rocks, mining industry, glass-making, pottery, and sand-blasting industry are at risk.

Inhaled silica particles are deposited in the alveolar and bronchiolar wall and they are highly fibrogenic, i.e. stimulate active fibroblasts proliferation.

There are two forms of disease. Simple silicosis - The lung forms small, well circumscribed, greyish-black, fibrotic nodules up to 5 mm in diameter. Progressive massive fibrosis (PMF) - the lung forms large masses of fibrous tissue from coalescence of simple nodules. Simple silicosis may progress to the massive form even after exposure stops. In advanced cases, honeycomb lung may develop. The hilar lymph nodes may also become enlarged and fibrotic with silicotic nodules. An important complication is tuberculosis which occurs in more than 50% of patients.

### ASBESTOSIS

Asbestos is a general term for a number of fibrous magnesium silicates. Asbestos is fire-resistant and is a good acoustic and thermal insulator. The widest exposure occurs in shipyards and in the building industry in the manufacture of floor tiles, brake linings and plastics.

All forms of asbestos are long thin fibres and when inhaled can pass deep into the lung, into the alveolar ducts and respiratory bronchioles of the lower lobes. The longer fibres are covered by a film of protein impregnated with haemosiderin, producing long beaded yellowish asbestos bodies, some of which are engulfed by macrophages.

Asbestosis is the diffuse interstitial fibrosis that develops in lungs exposed to inhaled asbestos dust. The most important factor in the development of diffuse fibrosis is the amount and
type of dust inhaled. Heavy exposure for a few years or exposure to low levels over many years is equally likely to result in asbestosis. The lungs show diffuse interstitial fibrosis and honeycomb lung at a late stage. Asbestos fibres and asbestos bodies are found in the areas of scarring.

Asbestos exposure is associated with increased risk of two types of malignancies:

- Lung cancer - Asbestos exposure by itself, even without accompanying asbestosis (i.e. diffuse fibrosis) increases the risk. The risk is even higher in cigarette smokers.
- Malignant mesotheliomas - These tumours may arise in the mesothelium of either the pleura or peritoneum. They are highly malignant tumours which are difficult to remove or treat with a high mortality rate.

References: