# Chronic Interstitial (Restrictive) Lung Disease

## Fibrosing

*Usual interstitial pneumonia (idiopathic pulmonary fibrosis)* ***IPF/UIP***

*Nonspecific interstitial pneumonia(**NSIP**)*

Cryptogenic organizing pneumonia(COP)

Connective tissue disease associated fibrosis

***Pneumoconiosis***

Drug reaction

Radiation pneumonitis

## Granulomatous

*Sarcoidosis*

*Hypersensitivity pneumonitis*

## Eosinophilic pneumonia

## Smoking related

Desquamative interstitial pneumonia (DIP)

Respiratory bronchiolitis-associated interstitial lung disease

Langerhans cell histiocytosis

## Others

Pulmonary alveolar proteinosis

Lymphoid interstitial pneumonia

# Pneumoconiosis

The term pneumoconiosis derives from **pneumon (lung) and konis (dust)**.

The term is applied to **pulmonary alterations caused by mineral dust**.

**Particle density and shape** influences the aerodynamic properties of dust. Existing airway disease also affects dust deposition.

Dust particles with **diameter in the range of 1–5 µm**, **spherical in shape** sediment out in the alveoli.

**Thin fibres over 100 µm in length may reach the alveoli.**

# Dust clearence

Inhaled dust is **removed from** the conductive airways **within a day** or two **by ciliary action**. Alveolar clearence is much slower: it takes years.

Alveolar clearance is mainly carried out by macrophages:

a. via the airways to the pharynx

b. via lymphatics to the regional lymph nodes

Long asbestos fibres present a particular problem to macrophage clearance.

Interstitial macrophages play role in the transportation of dust to the lymph nodes.

The main **tissue reaction to mineral dust is fibrosis**.

**Silica** is **highly fibrogenic** leading frequenly to pneumoconiosis.

# Pulmonary reaction to mineral dust.

| Pulmonary reaction | Examples |
|---|---|
| **Macrophage accumulation** with a little reticulin deposition | **1.Anthracosis**<br><br>**1.Coal pneumoconiosis (macules)** |
| **Nodular or massive fibrosis** | **1.Silicosis**<br>**2.Mixed-dust pneumoconiosis**<br>**3.Coal pneumoconiosis (nodules)**<br>**4. Progressive massive fibrosis** |
| **Diffuse fibrosis** | **1.Asbestosis**<br>2.Hard-metal pneumoconiosis<br>3.Aluminium pneumoconiosis |
| Epithelioid and giant cell granulomas | Chronic berylliosis |
| Alveolar lipoproteinosis | ‘Acute’ silicosis (or heavy exposure to other dusts) |

# Silicosis (≠Silicatosis)

- caused by the inhalation of silica (silicon dioxide, $SiO_2$)
- **crystalline silica is highly fibrogenic** (amorphous silica are inert).
- **silica exists in several crystalline forms:** quartz, cristobalite and tridymite. The **quartz is the least fibrogenic.**
- Nowadays silicosis still occurs in **some miners, sand blaster, tunnellers, quarrymen**, stone dressers and metal workers.

## Pathogenesis

**a)** **freshly fractured crystalline silica** is more pathogenic (sandblasting)

**b)** **uptake** of the silica **by macrophages**

c) macrophages **secrete factors that promote fibrosis** (progressive fibrosis)

**d)** **Silica particles injures the phagolysosomal membranes** (releasing of acid hydrolases).

e) the **macrophages are killed by the ingested silica**

f) It may complicate and aggravate existing immunological disease (**Rheumatoid arthritis - Caplan's syndrome**)

# Morphological alterations in silicosis

- Earliest lesion is the **cellular phase** silicosis, consist of **collections of macrophages**
- The mature **silicotic nodule is largely acellular and consists of hyaline collagen arranged in a whorled pattern**, the whole lesion being well demarcated
- Fibroblastic rim is present in the outermost part of the nodule
- Small numbers of **birefringent crystals** are generally present within the nodules (visualized with polarising filters)

## Morphological alterations in silicosis

- Silicotic nodules are occasionally found in the hilar lymph nodes in patient without occupational exposure to silica.
- large masses may undergo central necrosis and **cavitation**.
- **Cor pulmonale** develops in severe cases.

## Tuberculosis complicating silicosis (silicotuberculosis)

- **the prognosis rapidly worsens** after mycobacterial infection.
- The tubercle bacilli proliferate easily as a result of suppressed macrophage activity

## Alveolar lipoproteinosis in response to heavy dust exposure

- heavy exposure to silica and other dusts provokes hypersecretion of alveolar surfactant
- the normal clearance mechanism is unable to remove surfactant.
- The alveoli are filled by macrophages which are enlarged due to ingested surfactant. It has the appearances of endogenous lipid pneumonia.

# Coal workers' pneumoconiosis

- The term '**anthracosis**' is applied to the common **carbon pigmentation of city dwellers' lungs**
- Massive, dense pigmentation is seen in coalminers (lungs have black or slate-grey colour at autopsy)
- Black colour is the most spectacular in the visceral pleura along the lines of the lymphatics
- **Macules** consist of closely dust particles free or within macrophages
- **Nodules** contain large amounts of **collagen**

# Progressive massive fibrosis

- **caused by heavy dust burden**
- characterised by **large (over 1 cm) black masses**
- compromised lung function

# Asbestosis

- **diffuse** interstitial fibrosis (fairly large dust burdens)
- Asbestos is used mainly for **fireproofing**, in heat and sound **insulation**.
- After reaching alveoli the sharp **asbestos fibres become coated with a film of protein which is rich in iron**: **asbestos bodies**
- Asbestos exposure **predisposes to carcinoma of the lung** and **mesothelioma of the pleura** and peritoneum. The risk of malignancy increases with dose.

## Morphology of asbestosis:

- pleural fibrosis,
- fine subpleural fibrosis,
- lower lobes earlier involved
- widespread interstitial fibrosis
- asbestos bodies are numerous

# Usual interstital pneumonia (UIP)/ **Idiopathic** pulmonary fibrosis (IPF)

- **UIP is a morphological pattern of fibrosis**, which is most frequently associated with idiopathic pulmonary fibrosis (IPF).
- **UIP pattern** can develop on the ground other pulmonary diseases (drug reactions, autoimmun diseases, hypersensitivity pneumonia etc.)
- IPF develops in **old age** (mean age at diagnosis: 71 years).
- Prevalence is 5 per 100 000 population
- breathlessness on exertion, dry cough and loss of weight
- Functional studies show a **restrictive respiratory defect**, the **lungs being small and stiff**.
- On high-resolution computed tomography (HRCT) **‘honeycombing’ and ‘traction bronchiectasis’ present in advance cases**

# Etiology and pathogenesis

- The initiating cause remains unknown
- **Injury of alveolar epithelium is followed by dysregulated repair and eventual fibrosis**
- **regenerating epithelial cells produce cytokines**: TGF-β, IL-10, etc.
- delayed or defective re-epithelialisation → fibroblast recruitment, activation and sustained proliferation

# Clinical course of IPF:

- 3 years median survival
- **steady, predictable decline**, some patients experience more rapid, episodical deterioration (**acute exacerbations**).
- **cyanosis and dyspnoea at rest** in the late stage of disease
- death caused by **respiratory failure**, **cor pulmonale** or lung cancer
- new therapeutic approach: downregulation of growth factors and procollagens
- Standard therapy: **oxygen therapy and transplantation**

# Gross morphology:

- lungs are **shrunken and firm**
- the lower lobes are most severely affected, the **pleura has a finely nodular 'cobblestone' pattern**
- the cut surface shows fibrosis and '**honeycombing**', which is most pronounced beneath the pleura
- the contracted fibrous tissue **prevents the lungs from expanding**

# Histological findings

**The cardinal features of UIP**:

i. **subpleural** (lower lobe mainly)

ii. **patchy** parenchymal involvement (**spatial heterogenity**)

iii. **fibroblastic foci**

iv. **collagenous fibrosis** leading to loss of architecture (‘honeycombing’)

v. Variation in the age of the fibrosis is described as ‘**temporal heterogeneity**’

# Non-specific interstitial pneumonia (NSIP)

- NSIP may be idiopathic or a morphologic presentation of connective tissue diseases
- NSIP shows a **good response to steroid** therapy and have a good prognosis
- functional examination shows restrictive impairment.
- HRCT shows **ground-glass opacities** and reticular changes

## Histology

- **Expansion of the interstitium caused by chronic inflammation and fibrosis**
- **The distribution is diffuse**
- Fibrosis is collagenous or fibroblastic: **temporally homogeneous**
- **Preserved alveolar architecture** - no honeycombing

- Chronic inflammation is mainly composed of lymphocytes
- Cellular and fibrotic phase can be distinguished
- developed fibrosis means worse prognosis.

# Cryptogenic organizing pneumonia

- Unknown etiology
- Obsolete term: bronchiolitis obliterans organizing pneumonia (BOOP)
- Polypoid plugs of loose organizing connective tissue present in small airways and alveolar spaces (Masson bodies)
- No interstitial fibrosis: preserved architecture
- Spontaneous recovery is possible

# Organizing pneumonia

<u>Intraalveolar fibrosis</u>

- Viral or bacterial pneumonia
- Inhaled toxins, drugs
- Connective tissue diseases

# Extrinsic allergic alveolitis (hypersensitivity pneumonia)

- **granulomatous disease**
- The **inhalation** of **organic substances** may lead to local hypersensitivity reaction (**Avian proteins** are responsible for 1/3 of cases (pigeon breader)
- The clinical course can be acute, subacute and chronic (dose of allergen)
- Patients may suffer from slowly progressive breathlessness

## Morphology

- **poorly formed non-necrotising granulomas** (smaller and less frequent than those seen in sarcoidosis)
- widespread thickening of the alveolar walls by a diffuse **lymphocytic infiltrate**
- peribronchiolar inflammatory process
- giant cells with cytoplasmic clefts are characteristic but not specific
- the hilar lymph nodes are unaffected
- Fibrosis is bronchocentric in distribution contrasted to subpleural fibrosis in UIP (fibrosis develops in chronic disease)

# Sarcoidosis

- multisystem granulomatous disease developing in young/middle age person (<40 women affected most frequenly)
- unknown cause
- characterised by anomalous immunological reactions (CD4+ T helper cells present in large number)
- Lymph nodes, the lungs, liver, spleen, skin and eyes are the organs most commonly affected
- Spontaneous resolution in a part of the cases
- In 15-20% of cases significant pulmonary fibrosis evolves, pulmonary dysfunction persists
- The mediastinal lymph nodes often form large masses detectable by chest x-ray
- In case of the disease progresses to irreversible pulmonary fibrosis pulmonary hypertension develops
- Serum levels of calcium is often elevated

# Pathomorphology of sarcoidosis

- Epithelioid cells and multinucleate giant cells of Langhans or foreign-body type are found in the centres of the non-necrotizing granulomas.
- The giant cells often contain Schaumann and asteroid bodies
- most numerous along the lymphatics
- A part of the cases results in significant interstitial fibrosis
- lung involvement is not necessarily preceded by hilar lymphadenopathy

# SMOKING RELATED DISEASES

## Desquamative Interstitial Pneuomia (DIP)

In middle age cigarette smokers, reduced diffusing capacity
'Ground-glass' opacification on chest radiograph
Good prognosis after cessation of smoking – spontaneous improvement
**Morphology:**
Excess of macrophages → alveolar spaces filled with macrophages, associated with mild degree of chronic interstitial inflammation

## Langerhans cell histocytosis

Synonyms: pulmonary histiocytosis x, eosinophilic granuloma of the lung
Lung involvement either in isolated (more frequent) or in disseminated disease.
**Morphology:**
Focal interstitial infiltrate of Langerhans cells mixed with eosinophils
Small cavities develop in the centre of the lesion
Electron microscopy: Birbeck granule (pentalaminar structure with regularly spaced cross-striations)

# Diffuse Eosinophilic lung disease

## *Acute eosinophilic pneumonia (cryptogenic)*

- bronchoalveolar lavage fluid contains more than 25% eosinophils
- histology shows interstitial infiltrate and a lesser alveolar exudate of eosinophils, diffuse alveolar damage
- there is a prompt response to corticosteroids

## *Secondary eosinophilia*

- parasitic, fungal, and bacterial infections
- allergic bronchopulmonary aspergillosis, or vasculitis (Churg-Strauss syndrome), asthma

## *Idiopathic chronic eosinophilic pneumonia*

- heavy aggregates of lymphocytes and eosinophils within both the septal walls and the alveolar spaces.
- interstitial fibrosis and organizing pneumonia are often present
- Patient's condition improves to corticosteroid therapy