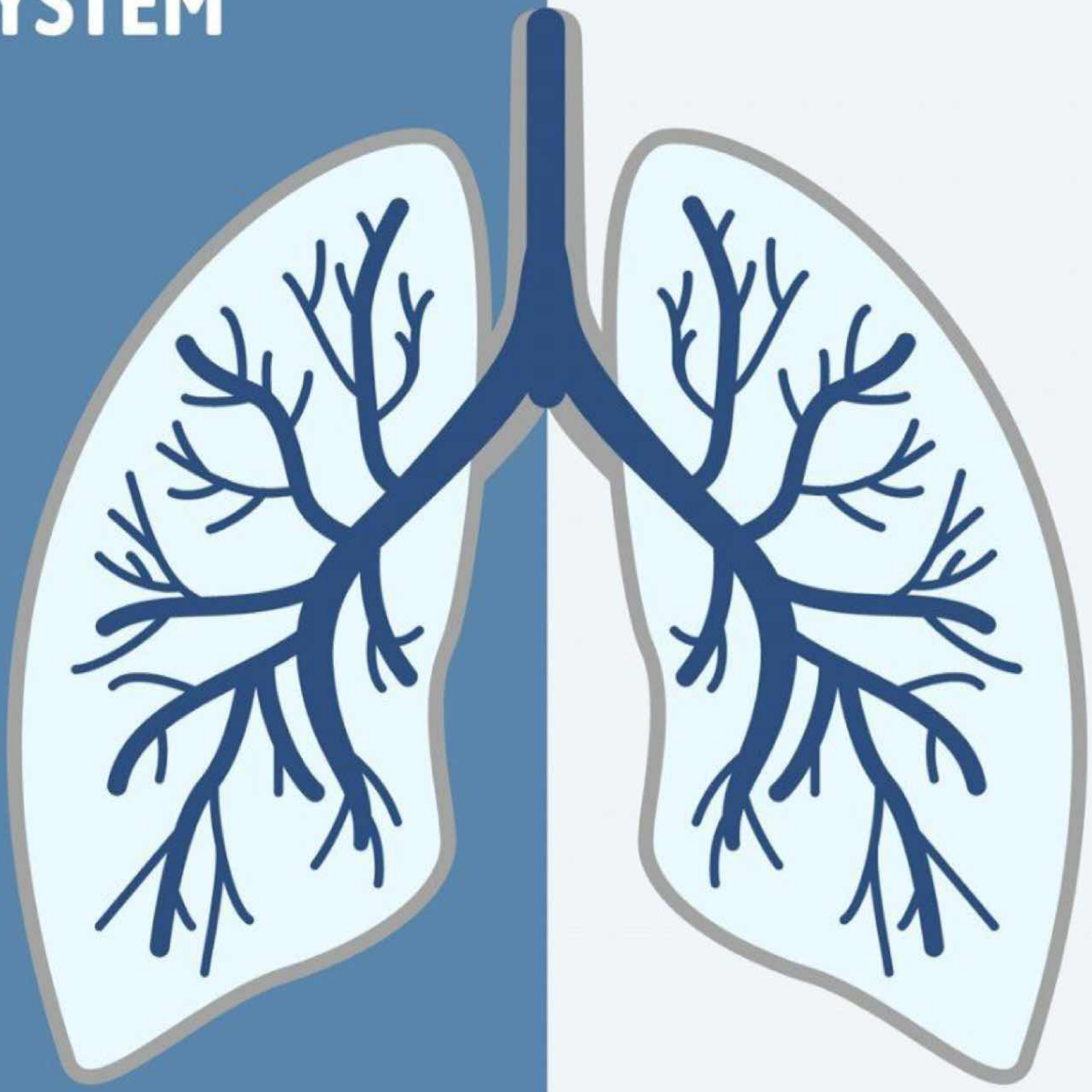
RESPIRATORY SYSTEM

PATHOLOGY



WRITER: 018 sheets

CORRECTOR: Sawsan alqeam

DOCTOR: Maram abdaljaleel

FIBROSING DISEASES

In this lecture we will continue discussing about the **restrictive lung diseases**, in the previous lecture we cover granulomatous lung diseases, now we will be discussing the majority of **fibrosing lung diseases** .

Fibrosing diseases are one of the major categories of the **chronic interstitial lung diseases** (**restrictive lung diseases**) ,in **Fibrosing diseases** group we will discuss the following diseases: 1-Idiopathic Pulmonary Fibrosis 2-Nonspecific Interstitial Pneumonia 3-Cryptogenic Organizing Pneumonia 4-Pneumoconioses.

1.IDIOPATHIC PULMONARY FIBROSIS

- It is a pulmonary disorder of unknown etiology that is characterized by **patchy, progressive bilateral interstitial fibrosis**, and because this disorder is of an unknown etiology it is also known as **cryptogenic fibrosis alveolitis** (**Cryptogenic** refers to something of unknown origin).

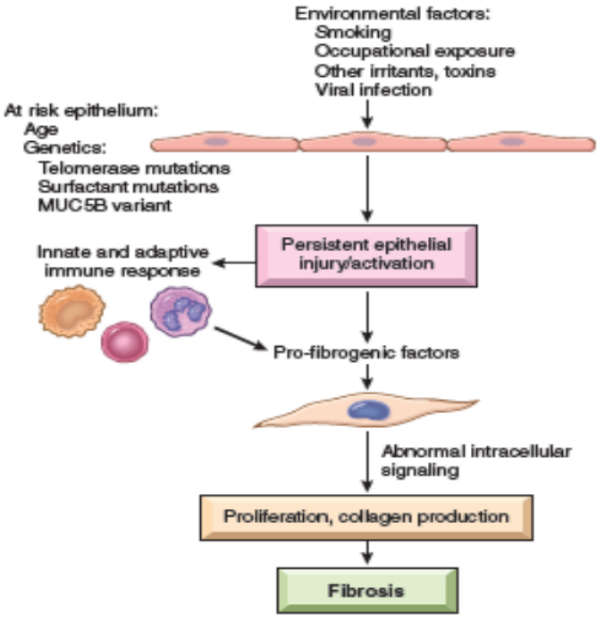
- The radiologic and histologic pattern of fibrosis in this disorder is referred to as **Usual interstitial pneumonia (UIP) pattern.**

-The disease is seen **more in males** (shows male predominance pattern),and is considered a disease of aging (never seen in patient younger than 50).

- **Diagnosis**
  THE DIAGNOSIS OF THIS disorder requires **both radiological and histological characteristic findings**. However, **the histologic findings** in the lung are **NOT** specific for this disease(it can be presented in other diseases such as asbestosis and collagen vascular diseases). Therefore, for this disease it is a **diagnosis of exclusion.**
- **PATHOGENESIS**
  As defined IPF is a disorder showing patchy progressive bilateral interstitial fibrosis, this interstitial fibrosis is believed to result from repeated cycles of epithelial activation and injury by some unidentified agents in the presence of **defective repair** of alveolar epithelium in genetically predisposed patients.
- *__GENETIC FACTORS-__ Genetic studies showed some etiologic clues, one of which is: the increased risk of IPF in cases of loss of telomerase due to germ line mutations.
  -IPF is linked to cellular aging and this is supported by the observation that it is the disorder of older adult (rarely occurring before the age of 55 years).
  -the presence of genetic variant in the **MUC5 B gene** that alters the production of mucin in 35% of the affected individuals.

*The doctor skipped this part, but you can read it as additional information

-Smaller number of patients have germ line mutations in **surfactant genes**.



-This figure shows the proposed pathogenic mechanism in IPF -

--The exposure of the epithelium at risk*(why at risk? remember due to cellular aging and the presence of genetic factors)* to certain environmental factors such as (*smoking , occupational exposure, other irritants ,toxins and viral infections)*will result in persistence epithelial injury and activation, this persistence injury in the presence of abnormal epithelial repair at the site of chronic injury and inflammation will result in exuberant fibroblastic or myofibroblastic proliferation mediated mainly by profibrotic factors such as TGF-B

Cobblestones appearance -> IPF

- **MORPHOLOGY, MACROSCOPIC**

  - Macroscopically a **cobblestone appearance** of the pleural surface is a characteristic of IPF, so the presence of retracted scars along the interlobular septa will result in cobblestone like appearance.

- The cut surface shows fibrosis **(firm, rubbery white areas).**

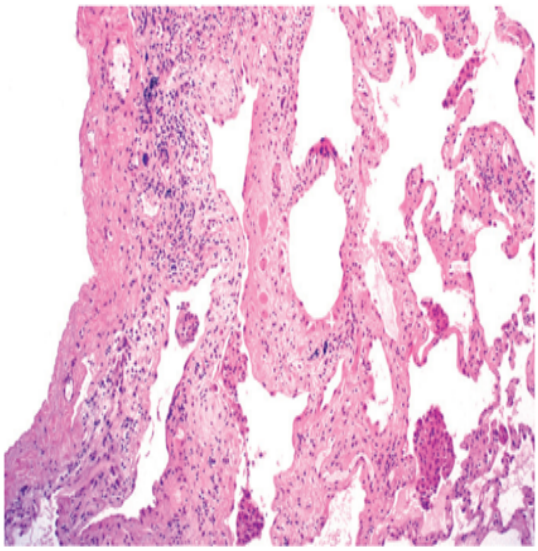
-**Lower lobes , subpleural regions and along the interlobular septa** are mostly affected.

-This pattern of fibrosis is called **Usual interstitial pneumonia (UIP) pattern of fibrosis.**

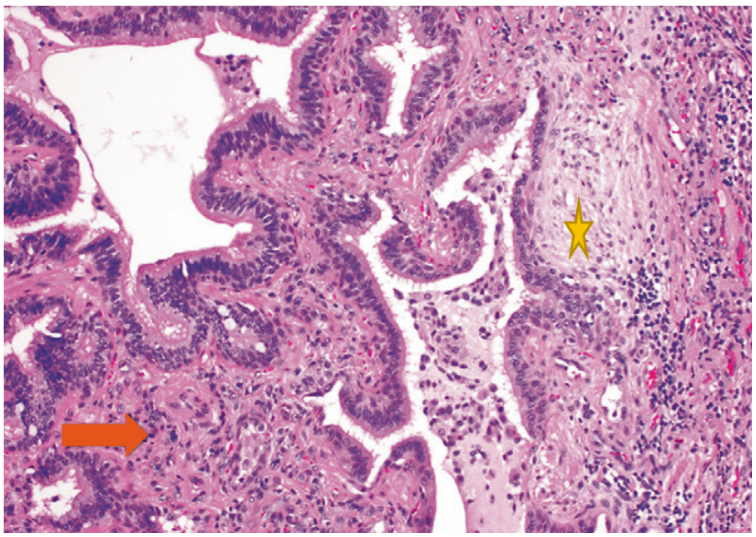
- **MORPHOLOGY, MICROSCOPIC**
- Hallmark is **patchy** interstitial fibrosis, which **varies in intensity and worsens with time**.
- You will see a patchy interstitial inflammation consisting of an alveolar infiltrate of **mostly lymphocytes** with occasional plasma cells, mast cells and eosinophils is characteristics.
- Those lesions show **Temporal heterogeneity** which means that early and late lesions coexist so you may see:

  1. Fibroblastic foci :are fibroblastic proliferations and considered the **earliest lesions**.
  2. **Late lesions** are more collagenous and less cellular and may show honeycomb fibrosis (as discussed in the previous lecture honeycomb fibrosis is a result of dense

fibrosis that causes collapse of alveolar walls and the formation of cystic spaces which is lined by hyperplastic type 2 pneumocytes or bronchiolar epithelium.



This histological section shows fibrosis with variable intensity , is more pronounced in the subpleural region



This histological section shows a case of usual interstitial pneumonia, the yellow star points to fibroblastic focus with fibers running parallel to the surface and bluish myxoid extracellular matrix honeycombing is presented to the left and in advanced cases you may see secondary pulmonary hypertensive changes such as intimal fibrosis and medial thickening of the pulmonary arteries

- **CLINICAL FEATURES**
- As in other restrictive lung diseases patients present with **Gradual onset of Nonproductive cough** and **progressive dyspnea**
- On physical examination**"dry" or "Velcro"-like crackles** during **inspiration.**
- Cyanosis, corpulmonale, and peripheral edema **may develop later.**
- Radiologic findings include sub pleural and basilar fibrosis, reticular abnormalities, and "honeycombing".
  So the combined clinical and radiologic findings are often diagnostic
- **OUTCOME**
- The overall prognosis remains poor.
- Survival is only from 3 to 5 years.
- Lung transplantation is the only definitive treatment.
- **MANAGEMENT:**
- **Anti-inflammatory** therapies ,although they have proven to be of **little use** since inflammation is of secondary pathogenic importance.
- **Anti-fibrotic** therapies are more important and now proved to be **used in patients with IPF.**

2. Nonspecific Interstitial Pneumonia

- Chronic bilateral interstitial lung disease of **Unknown etiology.**
- Despite its name, it has **Distinct clinical, radiologic, and histologic features,** including a frequent association with collagen vascular disorders such as rheumatoid arthritis, it is important to recognize NSIP because it has much **better prognosis** than IPF.
- **The most common presentation in those patients is dyspnea and cough of several months**.
- Characterized by **patchy but uniform** mild to moderate **interstitial chronic inflammation with or without fibrosis.**

3. Cryptogenic Organizing Pneumonia

- Another **uncommon** disease associated with fibrosis with **unknown etiology**.
-Its old name is **bronchiolitis obliterans organizing pneumonia**.
- usually patients are presented with **cough and dyspnea**
-Chest radiograph: subpleural or peribronchial patchy airspace consolidation due to the intra-alveolar plugs of loose organizing connective tissue.

- **Microscopically**

- the presence of Intra-alveolar plugs of loose organizing connective tissue.

- **Outcome**
  -the outcome is variable, some patients recover **spontaneously** while most of them require **treatment**, usually with oral steroids.

4. pneumoconioses

- Pneumoconioses is a general term given to any lung disease caused by dust that is breathed in ,and then deposited deep in the lung causing damage, so it is considered as an occupational lung disease and it includes; 1-asbestosis 2-silicosis and coal workers pneumoconiosis.

- pneumoconioses is a term originally coined to describe lung disorders caused by inhalation of mineral dust , but later the term has been broadened to include diseases induced by organic and inorganic particulates ,chemical fume and vapor, so it can develop when airborne dust – particularly the mineral dust- is inhaled at work, the dust particles remain in the lung were they can induce inflammation or fibrosis and scaring.

-The most common mineral dusts that induces pneumoconioses are **Coal dust, silica, and asbestos** and this usually stems from workplace exposure, except for Asbestos.

-In Asbestos:

• The increased risk for cancer extends to family members of asbestos workers and to individuals exposed outside the workplace, so the risk is not limited to the work place.

Table 13.3 Mineral Dust–Induced Lung Disease

Agent	Disease	Exposure
Coal dust	Simple coal worker's pneumoconiosis: macules and nodules Complicated coal worker's pneumoconiosis: PMF	Coal mining
Silica	Silicosis	Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics
Asbestos	Asbestosis, pleural effusions, pleural plaques, or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx	Mining, milling, and fabrication of ores and materials; installation and removal of insulation

PMF, Progressive massive fibrosis.

This table indicates the pathologic conditions associated with each mineral dust and the major industries in which the dust exposure may produce the disease.

- **PATHOGENESIS**

  -The reaction depends on the size, shape, solubility, and reactivity of the particles.

  -Regarding the size ,for example particles greater than 5 µm in diameter are unlikely to reach the distal airways while particles smaller than 0.5µm can reach the alveoli and out of them , often without deposition or injury, **but particles (1 to 5 µm in diameter) are the most dangerous** because they get lodged at the bifurcation of the distal airways.

  - regarding solubility and reactivity of the particles ,coal dust for example is relatively inert so large amounts must be deposited in the lungs before lung disease is clinically detectable ,silica asbestos and beryllium on the other hand are more reactive than coal dust, resulting in fibrotic reaction at lower concentrations.

  -Usually most inhaled dust is entrapped in the mucous blanket and rapidly removed from the lung by ciliary movement, however some of the particles become impacted at the alveolar duct bifurcation, where macrophages accumulate and engulf the trapped particles .

  So **The pulmonary alveolar macrophage is a key cellular element** in the initiation and continuity of lung injury and fibrosis. After phagocytosis, many particles activate the inflammasomes and induced the production of (IL-1) and other factors which initiate an inflammatory response leading to fibroblast proliferation and collagen deposition.

  - **Tobacco smoking** worsens the effects of all inhaled mineral dusts(more with asbestos than other particles).

Pneumoconiosis:

A. Coal Worker's Pneumoconiosis (CWP)

- A wide spectrum of lung findings are seen in coal workers, ranging from:
    1. Asymptomatic anthracosis: pigment accumulates without a cellular reaction.
    2. Simple coal worker's pneumoconiosis (CWP): accumulations of macrophages with little to no pulmonary dysfunction.
    3. Complicated CWP or progressive massive fibrosis (**PMF**): extensive fibrosis and compromised lung function.
       **PMF (Progressive massive fibrosis) is generic term that apply to confluent fibrosing reaction in the lung and can be a complication of any type of pneumoconiosis.

-Although coal is mainly carbon, coal mine dust contains a variety of trace metals, inorganic minerals and crystalline silica.

- **MORPHOLOGY**
- pulmonary anthracosis; is the most innocuous coal-induced pulmonary lesion in coal miners and is commonly seen in urban dwellers and tobacco smokers. Inhaled carbon pigments are engulfed by alveolar or interstitial macrophages. which then accumulates in the connective tissue along the pulmonary and pleural lymphatics and in draining lymph nodes.

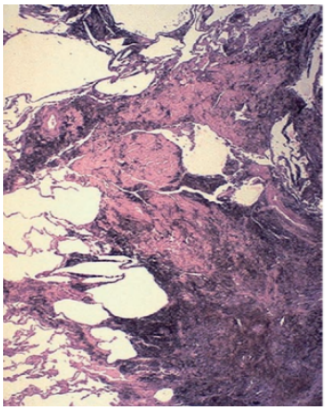
= Simple CWP

- it is characterized by the Presence of coal macules and the larger coal nodules
- macules consist of dust-laden macrophages and small amounts of collagen fibers arrayed in a delicate network, although these lesions are scattered throughout the lung, the Upper lobes and upper zones of the lower lobes are more heavily involved
- Simple CWP may be associated with **centrilobular emphysema.**

= Complicated CWP (PMF)

- occurs on a background of simple CWP by coalescence of coal nodules and generally develops over many years. It is characterized by multiple, dark black scars >2 cm & up to 10 cm consist of dense collagen and pigments.

- **CLINICAL FEATURES**
  - CWP is a benign disease that produces little effect on lung function but when progressive massive fibrosis develops there is an increased risk of pulmonary dysfunction, pulmonary hypertension, and corpulmonale.
  - The Progression from CWP to PMF has been linked to a variety of variables including higher coal dust exposure levels and total dust burden.
  - unfortunately, once established PMF it has a tendency to progress even in the absence of further exposure.
  - After taking smoking-related risk into account it is found that there is no increased frequency of lung carcinoma in coal miners, and this feature distinguishes CWP from both silica and asbestos exposures.



This histologic section shows PMF with large amount of black pigment and extensive fibrosis

case

A 59 year old lady works as electrical engineer and nonsmoker, has a 4-month history of increasing dyspnea. On examination she is afebrile and normotensive. Chest CT shows lower lobe reticular opacities. A transbronchial biopsy is performed and microscopically shows patchy interstitial inflammation with lymphocytes and plasma cells. No organisms are identified. Her condition slowly worsens over the next 10 years. Which of the following is the most likely diagnosis?

A) Desquamative interstitial pneumonitis

B) Hypersensitivity pneumonitis

C) Idiopathic interstitial fibrosis

D) Nonatopic bronchial asthma

E) Nonspecific interstitial pneumonia

-The patient is a nonsmoker

- typical for restrictive lung disease

-The disease is not episodic and characterized by gradual progression

- slowly progressing course

(e)Nonspecific interstitial pneumonia is characterized by both cellular and fibrosing patterns in transbronchial biopsies.

Desquamative interstitial pneumonitis (DIP) is smoking related disease (as we will discuss in next lecture).

Hypersensitivity pneumonitis mostly relates to episodic inhaled allergens and rarely progresses to marked interstitial disease.

Idiopathic pulmonary fibrosis tends to have a more rapid course and involve more of the lungs.

Nonatopic asthma is typically episodic and rarely progresses to extensive interstitial disease

AMBOSS

Idiopathic pulmonary fibrosis (IPF)

- **Definition**: most common type ILD, characterized by irreversible pulmonary fibrosis and impaired pulmonary function
- **Epidemiology**
  - Incidence: 10:100,000 cases per year [2]
  - Affects mostly men 50–70 years of age
- **Diagnosis** [3]
  - Requires the absence of other known causes of interstitial lung disease (e.g., medication, environmental exposures, connective tissue disease)
  - Presence of usual interstitial pneumonia (UIP) pattern on HRCT or histopathological studies
    - Honeycomb appearance with or without traction bronchiectasis
    - Ground-glass opacification with superimposed reticular abnormalities
    - Bibasal subpleural distribution
- **Prognosis**: Respiratory failure usually occurs within 3–7 years.

Cryptogenic organizing pneumonia (COP)

- **Definition**: a rare, type of ILD characterized by inflammation of the bronchioles, alveolar ducts, and alveolar walls
- **Epidemiology**
  - Incidence: 1–3 per 100,000 hospital admissions [4]
  - Affects mostly individuals 40–50 years of age
- **Diagnostics**: histologically characterized by the presence of **Masson bodies** (granulation tissue buds made of foamy macrophages, mononuclear cells, and fibrous tissue) and chronic patchy interstitial inflammation without fibrosis

Nonspecific interstitial pneumonia (NSIP)

- **Definition**: a type of ILD characterized by a mild to moderate chronic interstitial inflammation, without specific histopathologic findings that characterize UIP
- **Epidemiology**: affects nonsmoker women 50–60 years of age
- **Etiology**: associated with connective tissue diseases (e.g., systemic sclerosis), HIV infection, and hypersensitivity pneumonitis
- **Diagnostics**
  - Immediate subpleural sparing on imaging studies is considered specific for NSIP.
  - Histological findings include interstitial thickening due to fibrosis and/or inflammatory cells

Coal workers' pneumoconiosis [15][16]	• Prolonged exposure to large amounts of coal dust
	• Inflammation and fibrosis induced by carbon-laden macrophages
			• A more severe form of anthracosis
			• Complications
			  ◦ **Chronic bronchitis** that progresses to progressive **massive pulmonary fibrosis**
			  ◦ ↑ Risk of Caplan syndrome
				• Fine nodular opacifications (**< 1 cm**) in **upper** lung zone

THE END