PATHOLOGY

RESPIRATORY SYSTEM

SHEET NO. 6

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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES

Silica: Naturally occurring mineral.

- accounts for 59% of the earth's crust.
- two types: crystalline silica (toxic) (fibrogenic) and amorphous.
- Several processes release silica into the air such as: crushing, grinding, and blasting.

Silicosis

- **The most prevalent chronic occupational disease in the world.**
- Inhalation of crystalline silica mostly in **occupational** settings. Because the worker will be exposed to big concentrations of them for a long period of time.
- **Quartz is most implicated in silicosis.**

Quartz alone (pure) makes severe fibrogenic effect, thankfully, quartz is commonly mixed with other substances.

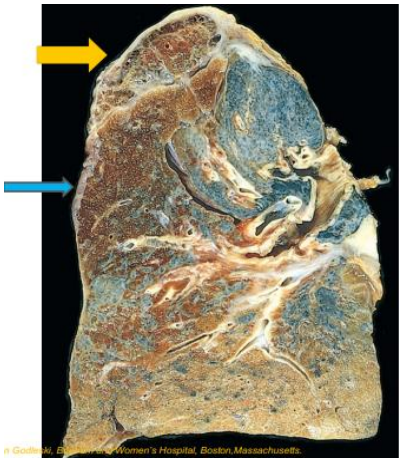
- Amorphous silica is less pathogenic.
- **Workers in sandblasting and hard-rock mining are at high risk.**

Pathogenesis

After **inhalation** of dust -that is good in size, shape, reactivity, and solubility- reaches the distal airways and get deposited at the bifurcation of the small airways(bifurcation of alveolar ducts), the particles **interact with epithelial cells and macrophages**.

- Activating the **inflammasome** and the release of **inflammatory mediators** by pulmonary macrophages.
- IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines.
- When mixed with other minerals, the fibrogenic effect of quartz is reduced.
- This fortuitous situation is commonplace, as quartz in the workplace **is rarely pure**.

Morphology, silicotic nodules:



- Macroscopically:

✓ Early stages are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules
✓ Upper zones of the lungs
✓ The dense plural thickening shown by the blue arrow.
✓ The yellow arrow shows upper lobe retraction because the scarring has contracted the upper lobe into a small dark mass.

- Microscopically:

➢ Silicotic nodules: inflammation will induce fibrogenic cytokines to release fibroblastic proliferation and collagen deposition. To get rid of the silica but some of the inflammatory hyalinized collagen will not be digested by the microphages, so the reaction against silica particles will be continuous

- Concentrically arranged hyalinized collagen fibers surrounding amorphous center.
- With "whorled" collagen fibers
- Polarized microscopy reveals weakly birefringent silica

- Nodules may coalesce into hard, collagenous scars, with eventual progression to PMF (progressive massive fibrosis: generic term that may complicate any type of pneumoconiosis that make lesions have progressive fibrosis even if the exposure is stopped), then end stage lung disease.

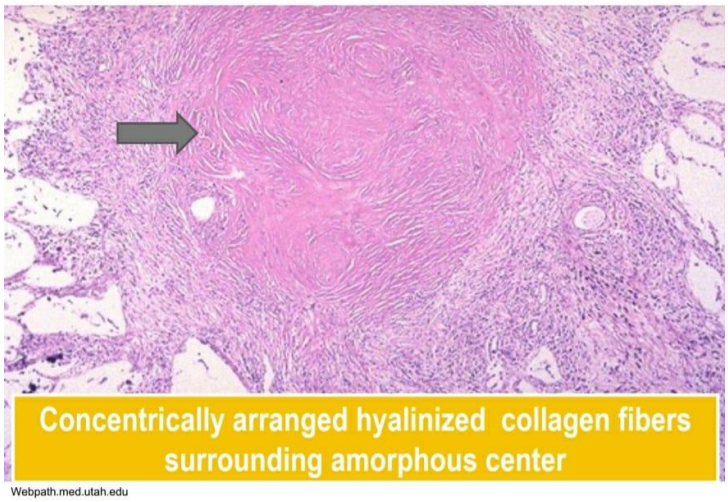
- Fibrotic lesions also may occur in hilar lymph nodes and pleura.

- The greater degree of exposure to silica and an increasing length of exposure → amount of silicotic nodule formation and the degree of restrictive lung disease.(burden of silica).

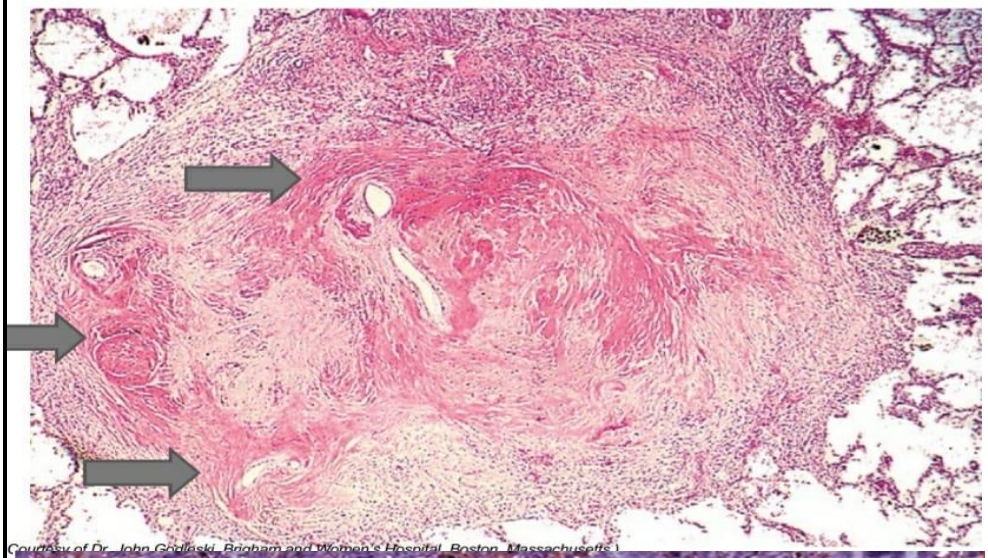
Silicotic nodule

Concentrically arranged hyalinized collagen -onion skin layers- fibers surrounding amorphous center

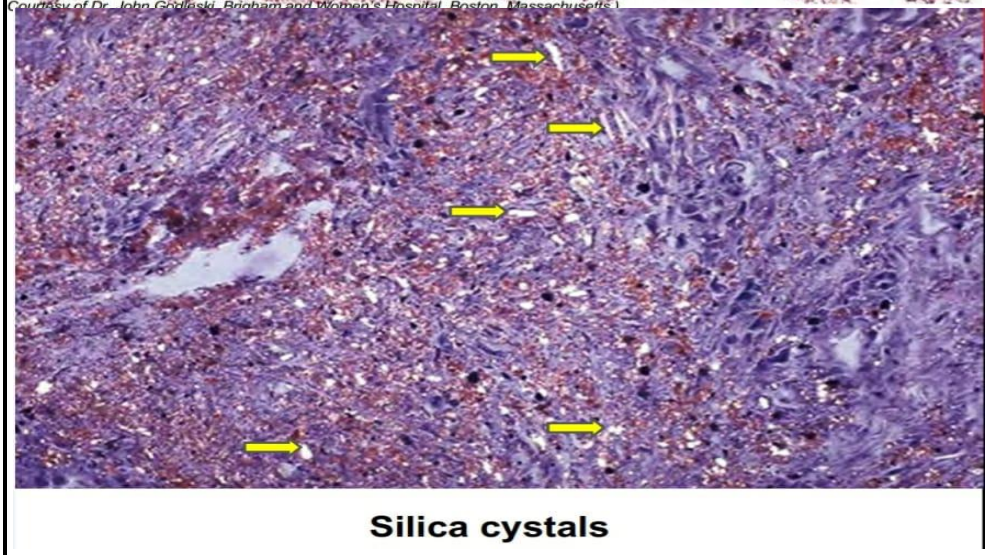
At the periphery→ patent airways.



SEVERAL COALESCENT COLLAGENOUS SILICOTIC NODULES



We can see silicotic nodules comprised of interlacing pale pink collagen with a surrounding inflammatory reaction (many inflammatory cells).



Silica cystals

Examination by polarized microscopy reveals weakly birefringent silica particles (they polarize the light) in the center of the nodules. Crystals are bright white with variable sizes

Clinical features:

• Asymptomatic: detected as fine nodularity in the upper zones of the lung on routine chest radiographs (screening is part of normal routine when applying for a job-as part of physical exam- or travelling, that's when silicosis is discovered)

• Most patients do not develop shortness of breath until late in the course. They need years and years for the disease to progress.

• After PMF: Shortness of breath, pulmonary hypertension and cor pulmonale

• The disease may continue to worsen even if the patient is no longer exposed.

• Silicosis is slow to kill, but impaired pulmonary function may severely limit activity

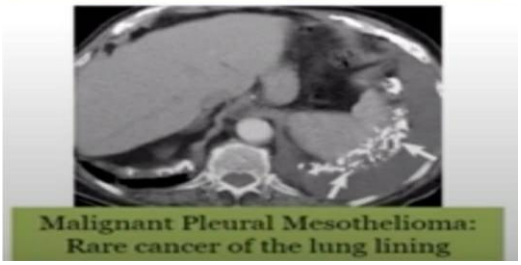
- The onset of silicosis can be:
  - *slow and insidious* (10 to 30 years after exposure; most common),
  - *accelerated* (within 10 years of exposure)
  - *rapid* (in weeks or months after intense exposure to fine dust high in silica; rare).

- Silicosis → increased susceptibility to tuberculosis.
  - crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria.
- silica and lung cancer:
- Patients with silicosis have double the risk for developing lung cancer

ASBESTOSIS AND ASBESTOSRELATED DISEASES

- Family of crystalline hydrated silicates with a fibrous geometry. الحرير الصخري

ASBESTOS ASSOCIATED WITH: from prolonged exposure
(1) parenchymal interstitial fibrosis (asbestosis);
(2) localized fibrous plaques or, rarely, diffuse pleural fibrosis.
(3) pleural effusions
(4) Lung carcinomas
(5) malignant pleural and peritoneal mesotheliomas
(6) laryngeal carcinoma



ASBESTOSIS: IS SCARRING OF THE LUNG CAUSED BY ASBESTOS EXPOSURE

Remember that asbestosis is the only one of pneumoconiosises that affects the workers and their family members – without direct exposure to it-.

Pathogenesis:

- Once phagocytosed by macrophages→asbestos fibers activate the inflammasome and damage phagolysosomal membranes →release of proinflammatory factors and fibrogenic mediators→

1. cellular and fibrotic lung reactions
2. tumor initiator and a promoter
   - mediated by the oncogenic effects of reactive free radicals generated by asbestos fibers in the distal lung near the mesothelial lining. (lower lobes)

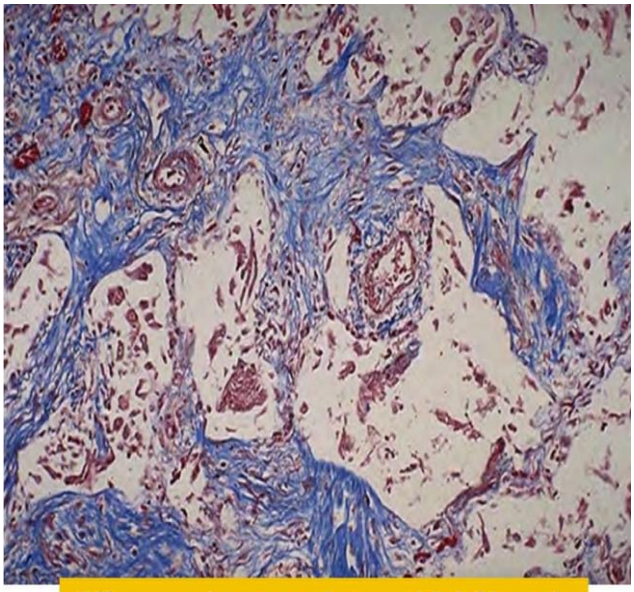
• **Asbestos and tobacco:**

• The adsorption of carcinogens in tobacco smoke onto asbestos fibers results in remarkable **synergy** between tobacco smoking and the development of lung carcinoma in asbestos workers→ Smoking enhances the effect of asbestos by interfering with the mucociliary clearance of fibers.

• asbestos workers →**fivefold increase** of lung carcinoma with asbestos exposure alone

• Asbestos exposure and smoking together →a 55-fold increase in the risk.

1. Trichrome stain highlighting collagen in blue.

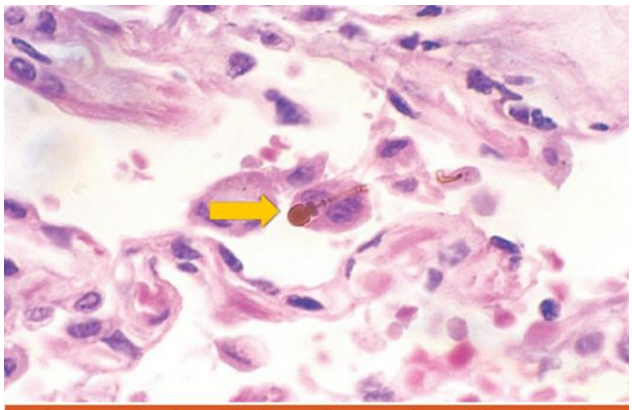


diffuse pulmonary interstitial fibrosis

Findings: Interstitium is expanded and distorted by the proliferation of fibroblasts and deposition of collagen → Diffuse Pulmonary Interstitial Fibrosis: (first characteristic feature)

- Patchy in distribution
- Associated with fibroblastic foci and the formation of cystic spaces similar to those of Usual Interstitial Pneumonia thus it's indistinguishable from other UIP.
- The extent of fibrosis actually determines the severity of the disease.
- Clinically: This is marked by a progressively worsening dyspnea.

2. presence of asbestos bodies



Asbestos body with beading and knobbed ends

- Golden brown, fusiform or beaded rods with a translucent center.
- Formed by asbestos fibers coated with an ironcontaining proteinaceous material derived from phagocyted ferritin.

• Begins in the lower lobes and subpleurally

Usual Interstitial Pneumonia is caused by:

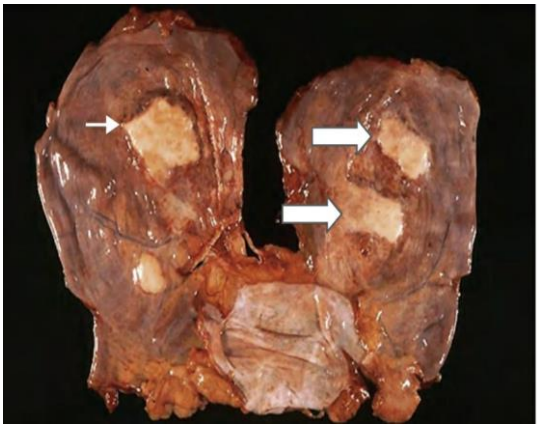
1- Asbestosis
2- Hypersensitivity pneumonitis
3- Idiopathic pulmonary fibrosis
4- Some connective tissue diseases

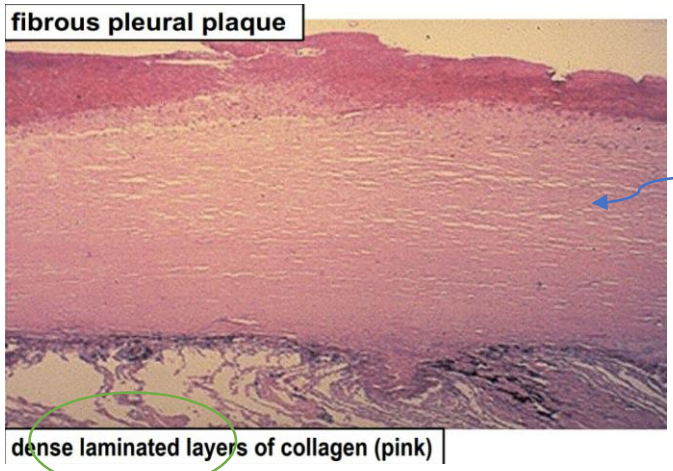
• Pleural plaques:

• the most common manifestation of asbestos exposure

• well-circumscribed plaques of dense collagen containing calcium

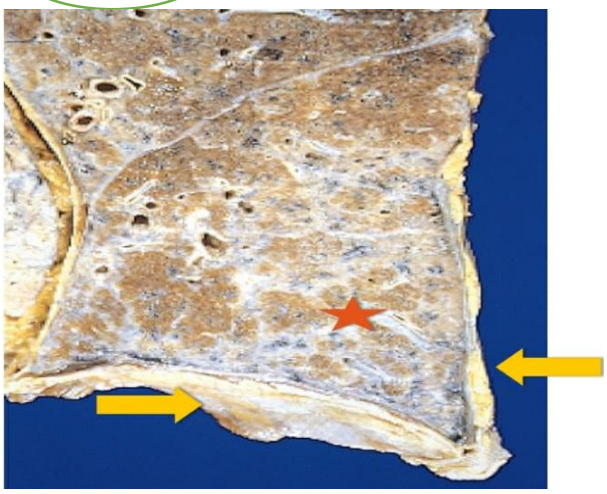
• anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm.





➢ Dense laminated collagen with or without calcium

➢ The circle is (patent airways)



Yellow: Markedly thickened area of visceral pleura on the lateral and diaphragmatic aspects of the lung.

Red star: Severe interstitial fibrosis affecting the lower lung.

CLINICAL FEATURES:

• Progressively worsening dyspnea at least after 10 years after first exposure. (typically, after 20-30 years after exposure).

• Dyspnea is the first manifestation (by exertion, but later at rest).

• cough and production of sputum (due to smoking mainly).

• static or progress to honeycomb lung, congestive heart failure, cor pulmonale, and death.

• Pleural plaques are usually asymptomatic, the most common manifestation of this disease.

OUTCOMES:

• The risk for developing lung carcinoma is increased 5-fold for asbestos workers
• the relative risk for mesothelioma is more than 1000 times greater than the risk for lung cancer
• Concomitant cigarette smoking increases the risk for lung carcinoma but not for mesothelioma.
• Lung or pleural cancer associated with asbestos exposure carries a poor prognosis.

PULMONARY EOSINOPHILIA PULMONARY EOSINOPHILIA

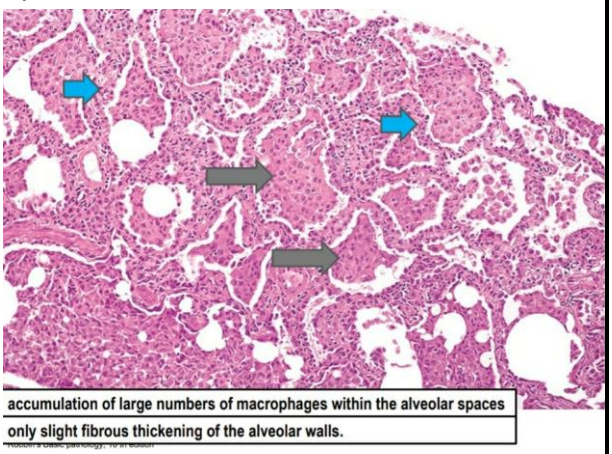
• number of disorders of immunologic origin, characterized by pulmonary infiltrates rich in eosinophils. Only the definition is required. ☺

SMOKING-RELATED INTERSTITIAL DISEASES

• Desquamative interstitial pneumonia (DIP)
• Respiratory bronchiolitis- Associated interstitial lung disease

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

• The most striking histologic feature of DIP is the accumulation of large numbers of macrophages containing dusty-brown pigment (smoker's macrophages) in the air spaces
• Sparse inflammation in alveolar septa (lymphocytes, plasma cells and eosinophils)
• +/- mild Interstitial fibrosis +/- emphysema



- Grey arrows: Collections of smoker's macrophages (pigmented MPhs) within the alveolar spaces.
- Blue arrows: Mildly expanded alveolar septa by lymphocytes and mild fibrosis.

CLINCAL PRESENTATION AND OUTCOME:

• Male= females, 4th-5th decade, all are smokers
• Insidious onset of dyspnea and dry cough over weeks or months
• PFT→ mild restrictive abnormality
• good prognosis
• excellent response to steroids and smoking cessation, however, some patients progress despite therapy.

RESPIRATORY BRONCHIOLITIS – ASSOCIATED INTERSTITIAL LUNG DISEASE

- common lesion in smokers
- Histology:
- presence of pigmented intraluminal macrophages akin to those in DIP, but in a "bronchiolocentric" distribution (first- and second-order respiratory bronchioles).
- Aggregates of smokers' macrophages: Respiratory bronchioles, alveolar ducts, and peribronchiolar spaces
- Mild peribronchiolar fibrosis.
- Centrilobular emphysema is common but not severe • Desquamative interstitial pneumonia is often found in different parts of the same lung.
- Symptoms are usually mild→ gradual onset of dyspnea and cough in 4th to 5th decade smokers with average exposures of over 30 pack-years of cigarette smoking.
- Cessation of smoking usually results in improvement.

Pack-years: #of cigarettes in a day × years of smoking

- The term respiratory bronchiolitis-associated interstitial lung disease is used for patients who develop significant pulmonary symptoms, abnormal pulmonary function, and imaging abnormalities.

Cases:

1-A 60-year-old gentleman had progressively worsening dyspnea over the past 12 years. He has noticed a 7-kg weight loss in the past 2 years. He has a chronic cough with minimal sputum production and no chest pain. On physical examination, he is afebrile and normotensive. A chest radiograph shows extensive interstitial disease. Pulmonary function tests show diminished lung volumes and capacities. Increased exposure to which of the following pollutants is most likely to produce these findings?

A. Carbon monoxide
B. Silica
C. Tobacco smoke
D. Wood dust

Ans:B

2- A 42 year old lady had a low-grade fever and worsening non productive cough and dyspnea for the past 2 years. On examination, she has breath sounds in all lung fields. A chest CT scan shows reticulonodular pattern of infiltrate. An arterial blood gas show mild hypoxemia and normal CO_2. Pulmonary function tests show decreased lung capacities and volumes. Her pulmonary compliance is reduced. What is the most likely diagnosis?

A. α1-Antitrypsin deficiency
B. Diffuse alveolar damage
C. Nonatopic asthma
D. Sarcoidosis

Ans: D

Good luck ")