Doctor.021

no. 6

RS PATHOLOGY

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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES PART 3

Slides will be in orange, doctor's notes in black.

❖ PNEUMOCONIOSES

3 main diseases are considered under the umbrella of pneumoconiosis including:

- ✓ *Coal Worker's Pneumoconiosis (CWP)*
- ✓ *Silicosis*
- ✓ *Asbestosis and Asbestos-Related Diseases*

COAL WORKER'S PNEUMOCONIOSIS (CWP)

- ✓ lung disease caused by inhalation of coal particles and other admixed forms of dust.
- ✓ Coal is mainly carbon+/- trace metals, inorganic minerals, and crystalline silica.
- ✓ Contaminating silica in the coal dust can favour progressive disease.
- ✓ Coal workers may also develop emphysema and chronic bronchitis independent of smoking.

❖ Spectrum of changes:

- ✓ Asymptomatic anthracosis: shows pigment accumulates without a cellular reaction.
- ✓ Simple coal worker's pneumoconiosis (CWP): shows accumulations of dust laden macrophages with little to no pulmonary dysfunction.
- ✓ Complicated CWP or progressive massive fibrosis (PMF): extensive fibrosis and compromised lung function.
- ✓ less than 10% of cases of simple CWP progress to PMF.

❖PMF is generic:

- ✓ confluent fibrosing reaction in the lung.
- ✓ can be a complication of any one of the pneumoconiosis.

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

❖MORPHOLOGY

Pulmonary Anthracosis:

- ✓ Seen also in urban dwellers and tobacco smokers.
- ✓ Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages accumulate in the connective tissue along the pulmonary and pleural lymphatics and in draining lymph nodes.

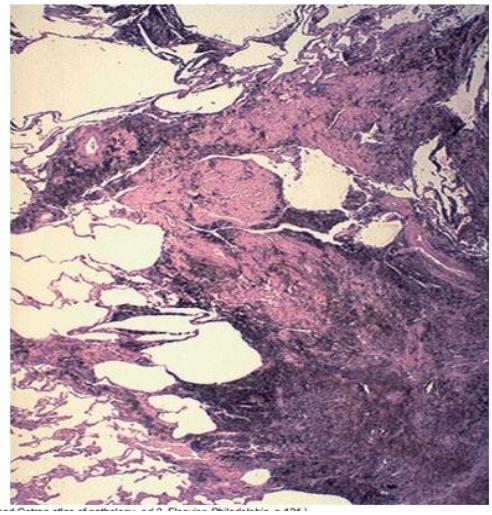
❖ Simple CWP:

- ✓ Presence of coal macules and nodules
- ✓ Coal macules (1 to 2 mm in dm): dust-laden macrophages & small amounts of collagen fibers arrayed in a delicate network.
- ✓ located primarily adjacent to respiratory bronchioles.
- ✓ centrilobular emphysema can occur.
- ✓ **Those lesions are scattered through the lung but centered mainly in** upper lobes and upper zones of the lower lobes are more heavily involved.

❖ Complicated CWP (PMF):

- ✓ **Occurs on a background of a simple CWP by** coalescence of coal nodules that develops over many years.
- ✓ **Characterized by** multiple, dark black scars >2 cm & up to 10 cm consist of dense collagen and pigment.

- **This histologic section shows progressive massive fibrosis with large amounts of black pigment and extensive fibrosis.**



❖ CLINICAL FEATURES

- ✓ CWP: benign disease that produces little effect on lung function.
  - complicated CWP:
  - The mild forms do not to affect lung function significantly.
  - 10% of complicated CWP progress to PMF: increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
  - The Progression from CWP to PMF is linked to **variety of variables including** higher coal dust exposure levels and total dust burden.
  - once established PMF has a tendency to progress even in the absence of further exposure.
  - **After taking smoking related factors into account,** no increased risk of lung carcinoma in coal miners. Distinguishes CWP from silica and asbestos exposures.

SILICOSIS

- **Silica:**
  - naturally occurring mineral.
  - accounts for 59% of the earth's crust.
  - two types: crystalline silica (toxic) 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
- ✓ It's caused by Inhalation of crystalline silica mostly in occupational settings.
- ✓ Silica occurs in both crystalline & amorphous forms, buy crystalline forms including quartz are more toxic and fibrogenic.
- ✓ quartz is most implicated in silicosis.
- ✓ Amorphous silica is less pathogenic so mostly, this disease is related to crystalline silica and quartz.
- ✓ Exposure is usually related to workplace, workers in sandblasting and hard-rock mining are at high risk.

❖ Pathogenesis:

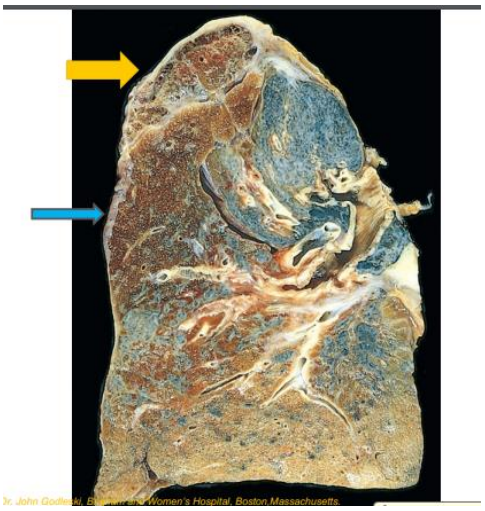
- ✓ After inhalation, the particles interact with epithelial cells and macrophages.
- ✓ Activating the inflammasome and the release of inflammatory mediators by pulmonary macrophages
- ✓ Inflammatory mediators include IL-1, TNF, fibronectin, lipid mediators, oxygen-derived free radicals, and fibrogenic cytokines.
- ✓ The characteristic inflammatory reaction with the fibrogenic effect and release of inflammatory mediators can be minimized when mixing quartz with another minerals, so the fibrogenic effect of quartz is reduced and the good thing is that quartz is rarely found pure and the common scenario is to find quartz mixed with another minerals.
- ✓ 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:**

Morphologically, lung silicosis presents as a silicotic nodules in the upper zones of the lung.

- **In early stages, silicotic nodules are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules.**
- **Upper zones of the lungs.**



➢ **This figure shows the gross appearance in the lung involved by advanced silicosis.**
Scarring has contracted the upper lobe into small dark mass (look at the yellow arrow).
Note the dense plural thickening (blue arrow).

✓ **Microscopically:**

✓ **Silicotic nodules:**

- **Concentrically arranged hyalinized collagen fibers surrounding amorphous center**
- **With "whorled" collagen fibers (this whorled appearance is characteristic)**

✓ **Examination of nodules by Polarized microscopy reveals weakly birefringent silica particles in the centre of the nodules**

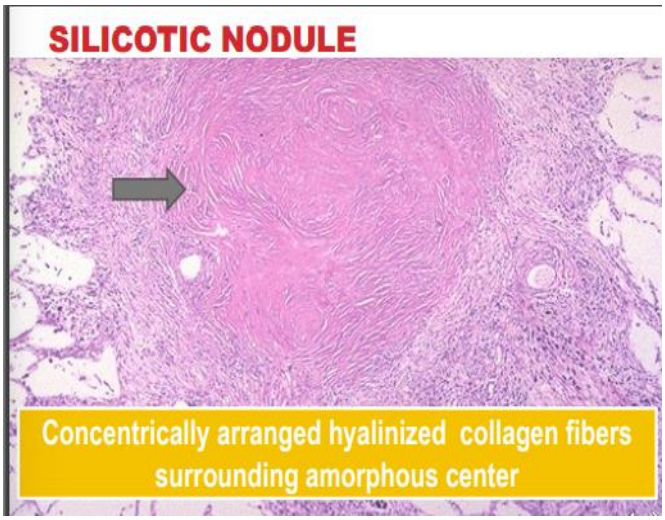
✓ **As the disease progresses, silica Nodules may coalesce into hard, collagenous scars, with eventual progression to PMF**

✓ **As you remember from the pervious lecture, PMF is associated with extensive fibrosis and deterioration in the lung function, so it's a generic term that applies to a confluent fibrosing reaction**

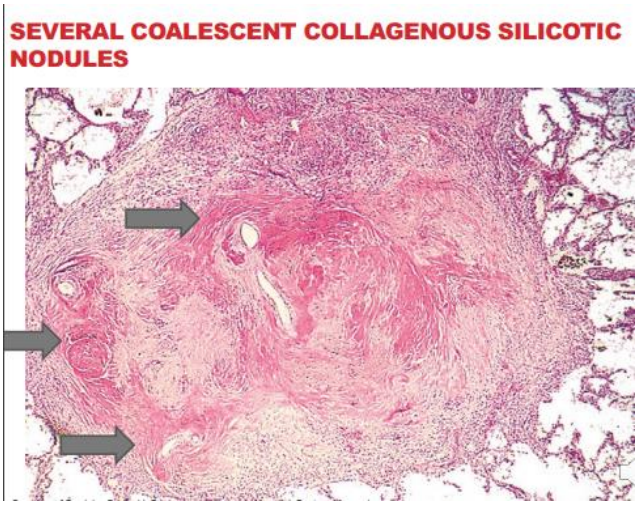
in the lung that can be a complication of any of the pneumoconiosis so due to expansion of the nodules and the progression to extensive fibrosis in some cases, the entire lung parenchyma is comprised or overexpanded which results in a honeycomb or end stage lung.

- ✓ Fibrotic lesions also may occur in hilar lymph nodes and pleura.
- ✓ The greater degree of exposure to silica and an increasing length of exposure the greater amount of silicotic nodule formation and the degree of restrictive lung disease.

- ➢ This figure shows the histologic appearance of silicotic nodule in the lung, as you can appreciate there are concentrically arranged collagen fibers surrounding an amorphous center. Alveolar spaces in periphery are still patent.

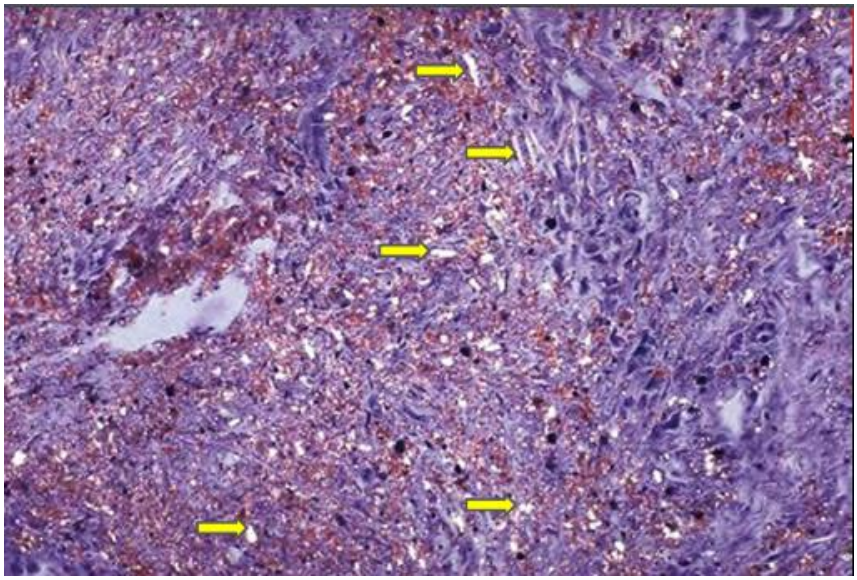


- ➢ This figure shows another silictoic nodules each is composed mainly of bundles of interlacing pale pink collagen, there is a surrounding inflammatory reaction. A greater degree of exposure to silica and



increasing length of exposure determine the amount of silicotic nodule formation and the degree of the restrictive lung disease which is progressive & irreversible.

- **This figure shows silica crystals under polarized light microscope, the crystals are bright white with variable sizes, (look at yellow arrows).**
  So, the silica crystals that are inhaled and reach the alveoli are ingested by macrophages which secrete cytokines to induce a fibrogenic response and because the inorganic matrix of crystals is never completely digested this process continues indefinity and is made worse by repeated exposure to silica.
  The result is production of many scattered nodular fossi of collagen deposition in the lung which we call the silicotic nodules and eventually restrictive lung disease progressing to cor pulmonale.



❖ CLINICAL FEATURES:

- ✓ Asymptomatic: detected as fine nodularity in the upper zones of the lung on routine chest radiographs
- ✓ Most patients do not develop shortness of breath until late in the course.
- ✓ After development of PMF: patients start to experience 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 (this happens because silicosis is associated with depressed immunity).
    - 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 (this topic is still controversial).

Asbestosis and Asbestos-Related Diseases

❖ Asbestos:

• Family of crystalline hydrated silicates with a fibrous geometry.

It can cause pneumoconiosis for silica and coil; exposure mainly happens in workplace. But it's not the case for asbestos.

For this mineral, the increased risk for cancer extends to the family members of asbestos workers and family individuals who are exposed to asbestos outside workplace.

So, the risk for asbestos is increased in any patient who is exposed to the mineral in workplace or outside the workplace in addition to family members of asbestos workers.

❖ ASSOCIATED WITH:

On the basis of epidemiologic studies, occupational exposure to asbestos is linked to:

(1) parenchymal interstitial fibrosis (asbestosis)
(2) localized fibrous plaques or, rarely, diffuse pleural fibrosis.
(3) pleural effusions
(4) Lung carcinoma
(5) malignant pleural and peritoneal mesothelioma
(6) laryngeal carcinoma

❖ ASBESTOSIS: IS SCARRING OF THE LUNG CAUSED BY ASBESTOS EXPOSURE

❖ Pathogenesis:

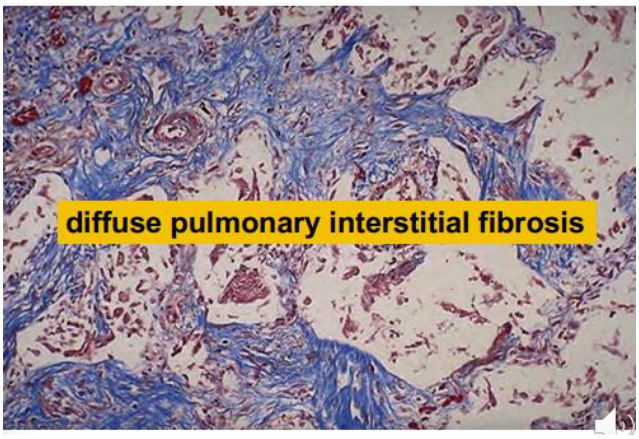
As for silica crystals, the pulmonary macrophages are the key cellular elements in inflammation.

- ✓ **Inflammatory response leads to fibroblast proliferation and collagen deposition.**
- ✓ **once phagocytosed by macrophages, asbestos fibers activate the inflammasome and damage phagolysosomal membranes which release of proinflammatory factors and fibrogenic mediators including:**
  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.**
       - **Why mesothelium? Because asbestos fibers are usually localized in distal lung close to the mesothelial layer.**
- ✓ **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.**
  - **The relationship between asbestos and smoking is interesting, in general, adsorption of potentially toxic chemicals into the asbestos fibers increases its pathogenicity.**
  - **Tobacco smoking is considered no.1 risk factor for developing lung cancer.**

- ✓ **asbestos workers: fivefold increase of lung carcinoma with asbestos exposure alone**
- ✓ **Asbestos exposure and smoking together: a 55-fold increase in the risk.**
- ✓ **Tobacco smoking worsens the effects of all inhaled mineral dusts.**

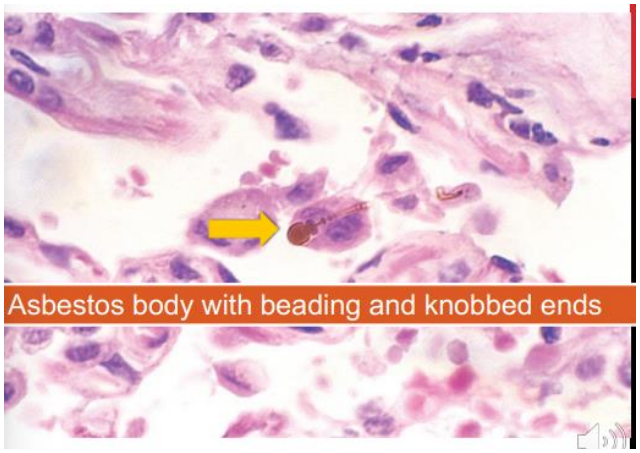
❖ MORPHOLOGY:

- **This figure shows the 1st characteristic feature of asbestosis, the tissue section is stained by trichrome stain.**

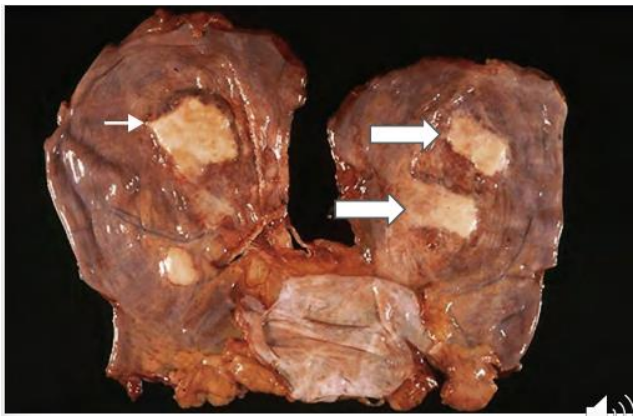


This stain highlights collagen in blue, so all the blue areas of the interstitium are expanded and stored by fibroblastic proliferation & collagen deposition which is called pulmonary interstitial fribrosis.
The extent of fibrosis determines the severity of the disease, this is marked by progressively worsening dyspnea clinically.
So, the 1st characteristic feature is the presence of diffused pulmonary interstitial fibrosis.

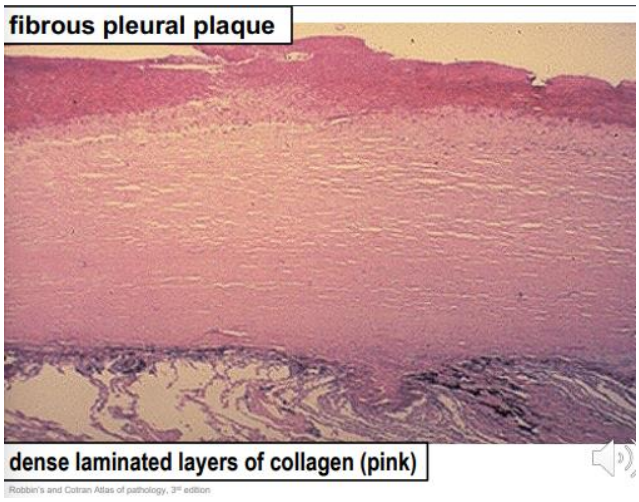
- **Another characteristic is presence of asbestos bodies, they are golden brown, fusiform, or beaded rods with translucent center.**
  As you can see, at the center of this figure there is a golden rounded beaded rod with the translucent center, and this is called asbestos body.



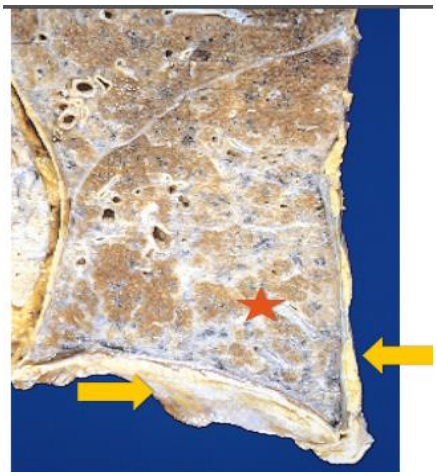
- **The most common manifestation of asbestos exposure is the plural plaques. (white arrows)**
  These plaques develop most frequently on the anterior and posterolateral aspects of the parietal pleura and over the dome of the diaphragm.



- **This figure shows the histologic appearance of the plural plaques. As you can see, pleural plaques are made of dense laminated layers of collagen.**



- **This figure shows gross appearance of two important findings, the yellow arrows point to markedly thickened area of the visceral pleura covering the lateral and the diaphragmatic surface of the lung. The area under the red star shows severe interstitial fibrosis affecting the lower lobe.**



❖ MORPHOLOGY

- ✓ **Asbestos is characterized by Diffuse pulmonary interstitial fibrosis which is usually patchy in distribution associated with fibroblastic foci and the formation of cystic spaces, a pattern that it's known histologically as usual interstitial pneumonia,indistinguishable from UIP.**
- ✓ **Asbestos bodies:**
    - **golden brown, fusiform or beaded rods with a translucent centre.**
    - **Formed of asbestos fibres coated with an iron-containing proteinaceous material**
    - **Generally asbestos bodies are formed when macrophages try to phagocytose asbestos fibers, the iron coat (outer cryst) is derived from the phagocytosed ferritin.**

- ✓ **Begins in the lower lobes and suprapleurally, spreading to the middle & upper lobes of the lung as the fibrosis progresses (opposite to what happens in silicosis and coal workers pneumoconiosis).**

- ✓ **Pleural plaques:**
    - **the most common manifestation of asbestos exposure**
    - **characterized by well-circumscribed plaques of dense collagen containing calcium**
    - **they develop most frequently on the anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm**

❖ Clinical features:

Clinical findings in asbestosis are similar to those related to another chronic interstitial lung diseases:

- ✓ Progressively worsening dyspnea appears 10 to 20 years after first exposure. (typically, after 20-30 years after exposure).
- ✓ Dyspnea is the first manifestation (by exertion, but later at rest).
- ✓ Usually associated with cough and production of sputum (due to smoking mainly).
- ✓ The course of disease is variable, it may remain static in some patients or progress to honeycomb lung, congestive heart failure, cor pulmonale, and death.
- ✓ Pleural plaques are usually asymptomatic and detected on radiograph as circumscribed densities.

❖ Outcomes:

Both lung carcinoma and malignant mesothelioma can develop in workers exposed to asbestos.

- ✓ The risk for developing lung carcinoma is increased 5-fold for asbestos workers, while the relative risk for mesothelioma (a very rare tumor) is more than 1000 times greater.
- ✓ Furthermore, the risk for lung carcinoma is greatly increased in patients who are tobacco smokers and exposed to asbestos. However, tobacco smoking doesn't increase the risk for mesothelioma in asbestos workers. So, although smoking increases risk for developing asbestos related to lung carcinoma it doesn't increase risk for mesothelioma, because mesothelioma development is highly related to asbestos exposure not to tobacco smoking.

يعني باختصار التدخين مع التعرض للأسبستوس بزيد احتمالية الإصابة بسرطان الرئة بينما ما بزيد خطر الإصابة بال**mesothelioma**

- ✓ 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.

- ✓ Tobacco smoking worsen the symptoms of mesothelioma and reduces the body ability to heal.

❖ Main features on pneumoconiosis (highlight)

Our discussion included coal workers, silicosis, and asbestos pneumoconiosis. All are occupational diseases (related to workplace exposure).

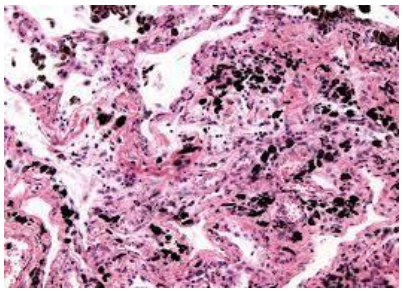
- Coal workers pneumoconiosis caused by long term exposure to coal dust, and this may happen in coal miners, urban dwellers & tobacco smokers.
- Silicosis is caused by inhalation of crystalline silica dust, risky occupations include hard rock mining and sandblasting (cleaning of the surface with a get of sand and this is usually driven by compressed air or stem).
- Asbestosis is related to asbestos fibers inhalation; risky occupations include constriction painters and miners.

- ➢ **The reaction of the lung to mineral dusts depends on the size of the particles, particles > 5 – 10 µm are unlike to reach the distal airways and usually cleared out by the cilia in large airways. Wherase particles smaller than 0.5 µm move into and out of the alveoli with gas exchange without causing any injury.**

- ➢ **So, the most dangerous particles are the ones between 1 µm to 5 µm in diameters because these can be lodged at the bifurcation of the distal airways. And they are considered small to be detected by the cilia of the large air ways and large to move through alveoli in gas exchange.**

- ➢ **The main player in the reaction to mineral dusts exposure are the macrophages.**

- **Anthracosis develops gradually over many years of exposure, and it's characterized by <u>black spotting</u> of the lung grossly.**



- **Histologically, alveolar macrophages are seen engulfing the coal dusts, over many years of exposure and with more accumulation in macrophages, those macrophages eventually release inflammatory mediators that results in fibrosis and may eventually result in PMF.**

- **After inhalation of silica particles, they are engulfed by pulmonary macrophages, and this results in release of inflammatory mediators that will stimulate the cell mediated immune reaction. However, silica particles decrease macrophage's phagolysosmal capacity with time. This explains why patients with silicosis are at higher risk of developing TB.**

- **Microscopically, silicotic nodules show an amorphous center containing silica particles and macrophages surrounded by multiple concentric layers of arranged hyalinized collagen fibers.**

- **In asbestosis, once the fibers are phagocytosed by the macrophages, they activate the inflammasomes damaging phagolysosmal membranes resulting in cellular and fibrotic lung reactions. Those reactions also work as tumor initiators & promoters (go up and see histologic pictures related to asbestosis).**

- **Regarding lung involvement:**

  - **Lung involvement in coal dusts and silicosis affect the upper zones of the lung.**
  - **Asbestos is centered in the lower zones.**

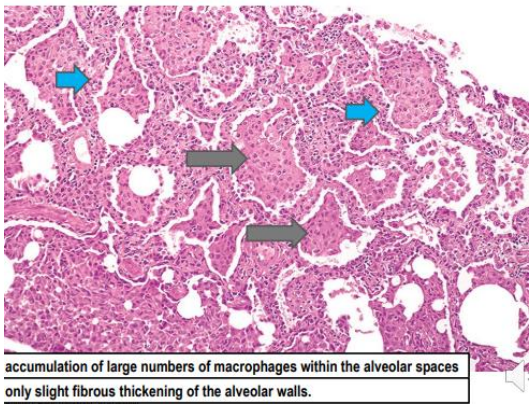
❖ Smoking related interstitial diseases include:

1. Desquamative interstitial pneumonia (DIP)
2. respiratory bronchiolitis

❖ Desquamative interstitial pneumonia (DIP)

- **the most striking histologic feature of DIP is accumulation of large numbers of macrophages containing dusty-brown pigments in the air spaces, these pigmented macrophages are called (smoker's macrophages).**
- **the alveolar septa are thickened by spars lymphocytes and sometimes fibrosis.**
- **When the interstitial fibrosis related to DIP is present it's considered mild.**

- **the grey arrows point to the collections of smoker's macrophages (pigmented macrophages) within the alveolar spaces.**
- **The blue arrows point to mildly expanded alveolar septa by lymphocytes and mild fibrosis.**



- **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 like those in DIP, but in a "bronchiolocentric" distribution (first- and second-order respiratory bronchioles). **(remember in DIP there were collections of pigmented macrophages within alveolar spaces, so what's the difference now? <u>The distribution is different</u> because here they are presented in <u>brochiolocentric distribution which means that the pigmented macrophages are presented within the lumen of 1st and 2nd order respiratory bronchioles instead of being in alveolar spaces like DIP</u>)**
  - Aggregates of smokers' macrophages: Respiratory bronchioles, alveolar ducts, and peribronchiolar spaces
  - Mild peribronchiolar fibrosis **can be also seen in those cases.**
  - Centrilobular emphysema is common but not severe.
  - Desquamative interstitial pneumonia is often found in different parts of the same lung.

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

V2

Page 11, the highlighted sentences