Lecture One

Restrictive Lung Diseases

432 ***Pathology*** *Team*

Done By:

Abdulrahman *Al-Aqeel ,* ***Ammar*** *Naji,* ***Nada*** *Alouda*

Revised by : ***Fahad*** *Al-Dhahiri*

Respiratory Block

NOTE: female notes are written in purple/Not important in grey

Pathology and pathogenesis of: Restrictive Lung Diseases

Restrictive lung diseases (Diffuse interstitial lung diseases)

Restrictive lung disease: are diseases that cause **restriction** or in ability of the lung to expand with reduction in the lung and pulmonary capacity

A disease in this area will be due to:

a. Inflammation

b. Fibrosis

c. Accumulation of different substance

Restrictive lung diseases are a very wide group of diseases (in chest unit of KKUH, there are chest specialists who only see patients with restrictive lung diseases!).

Causes Of Restrictive Lung Diseases:

1- Deformities of the chest wall or vertebral column

Which will lead to kyphoscoliosis resulting in lung restriction and inability to expand.

2-Neurological or neuromuscular disease

These diseases affect the muscles of the thoracic wall(intercostal muscles and the nerves which supply them) eg: poliomyelitis. diseased intercostal muscles are very weak (due to weak innervations) → limited expansion and retraction of the thorax (the chest wall) → restrictive lung disease.

3-Interstitial Lung Diseases

a heterogenous group of disorders, characterized by interstitial accumulations of cellular or non cellular material within the alveoli and alveolar walls (pulmonary interstitium**)** that restrict expansion and often interfere with gaseous exchange..

[**pulmonary interstitium (alveolar septum)**: It is the tissue between the alveoli. It is built of: Basement membrane ,type I and II pneumocytes , blood vessels and surrounding C.T].

If in the interstitium there is deposition of chronic inflammatory cells, fibrosis or exogenous substances (مواد خارجية) → interstitial lung disease.

Features of interstitial lung diseases (Which appear due to interstitial fibrosis):

- **reticular nodular shadowing (X-Ray)**

- **honey combing (gross/X-Ray/High resolution CT scan)**

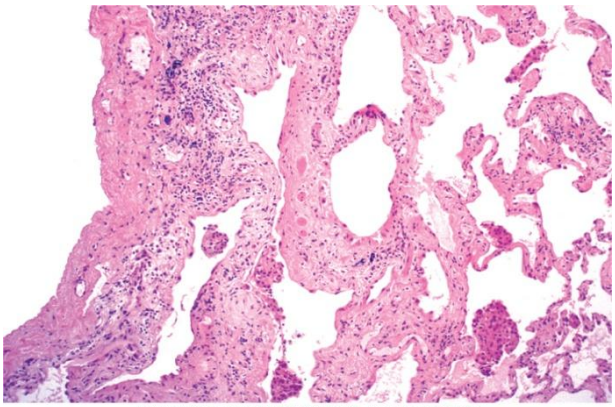
Usual interstitial pneumonitis (UIP)

Sometimes they are referred to as **idiopathic fibrosing pneumonitis**.

Pathogenesis

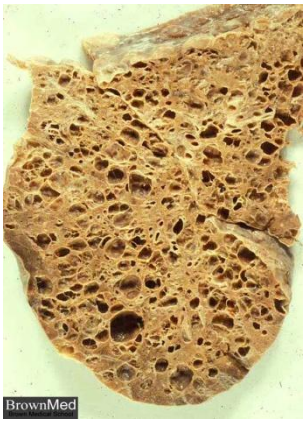
This disease is of an **unknown cause**,there must have been some injury to the interstitium, alveolar wall or pneumocytes → leading to recruitment of macrophages and T lymphocyte → secretion of interleukins (type 2, 3 and 4) →deposition of fibrosis.

Histopathology :



Biopsy Picture in sever UIP:

1- the interstitium is dilated
2- many areas of entrapped air
3- alveoli and respiratory bronchioles in some places are dilated.
4- the alveolar septum is very wide, expanded and there is a lot of chronic inflammatory cells.



Gross: When we see the lung, we see honey combe lung (عش النحل)(interstitial fibrosis with entrapment of air in alveoli and bronchioles)

Why is it occurring? Why does it look like this?

Clinical presentation:

1. Severe dyspnea during effort (or even at rest in very severe cases).
2. Hypoxemia (low PO2, high PCO2).
3. Pulmonary hypertension and cor pulmonale.
4. Dry irritating persisting cough.

Note dyspnea is the most important symptoms of restrictive lung diseases

Complication

1- Lung failure.

2- Cor pulmonale

SUMMARY:

unknown cause → recruitment of macrophages and T lymphocyte → secretion of interleukins (type 2, 3 and 4) →deposition of fibrosis in the interstitium→ the interstitium is widened → fibrosis surrounds the alveoli and respiratory bronchiole → it entraps and restricts them→ we have interstitial lung disease → Restrictive lung disease → may lead to lung failure or cor pulmonale

A-RESPIRATORY DISTRESS SYNDROMS (RDS)

Respiratory distress syndromes cause **acute interstitial pneumonitis which consist of two stages** :

Stage I:

1- The cause of the syndrome results in infiltration of edema and exudates to the alveolar space.

2- Formation of hyaline membrane

Stage II:

1- Regeneration

2- Fibrosis:

a. Mild fibrosis → Recovery

b. Severe fibrosis → Respiratory failure

A.ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) (acute medical emergency) → **Injury to alveolar wall**

(ARDS): acute medical emergency. Sometimes surgical and anesthetic emergency. Usually those patients have damage to alveolar wall.

NOTE : It is also called defuse alveolar damage (DAD).

Causes:

1. Severe road traffic accident or trauma.
2. Severe burn.
3. Certain toxins (oxygen toxicity produce free radicals → free radicals are toxic to the cells).
4. Drug addiction (eg. heroine inhalation).
5. Certain drugs.
6. Major surgery (eg. removal of a large part of the bowel)
7. People with septicemia,
8. Shocks
9. Aspiration of gastric fluid after anesthesia (especially long anesthesia and major surgery) → **that's why surgeons ask their patient not to eat 24 hrs before surgery**

   Note: aspiration (the entry of secretion or foreign materials into the trachea and lung, eg: gastric secretion and amniotic fluid.

Pathogenesis

STAGE I :

ARDS is initiated by a damage to alveolar capillary endothelium and alveolar epithelium , and it is influenced by the following pathogenetic factors:

(a)**Neutrophils** release substances toxic to the alveolar wall.

(b)**Activation of the coagulation cascade** is suggested by the presence of micro emboli.

(c)**Oxygen toxicity** is mediated by the formation of oxygen-derived free radicals.

These factors cause → interstitial edema & proteinaceous exudate fill the lumen → severe shortness of breath.

#The exudate is full protein → Proteins form membranes (hyaline membrane like) cover the alveoli from inside

STAGE II:

1- Regeneration by Type II pneumocytes → minimal fibrosis → respiratory function improves gradually → full recovery

2- Regeneration by Type II pneumocytes → Fibrosis → honeycombed lung → Severe chronic respiratory impairment → death

Treatment

1- Admit the patient to the intensive care unit (ICU)

2- give him oxygen .

3- Treat the cause. (If he has an infection it should be treated with antibiotics).

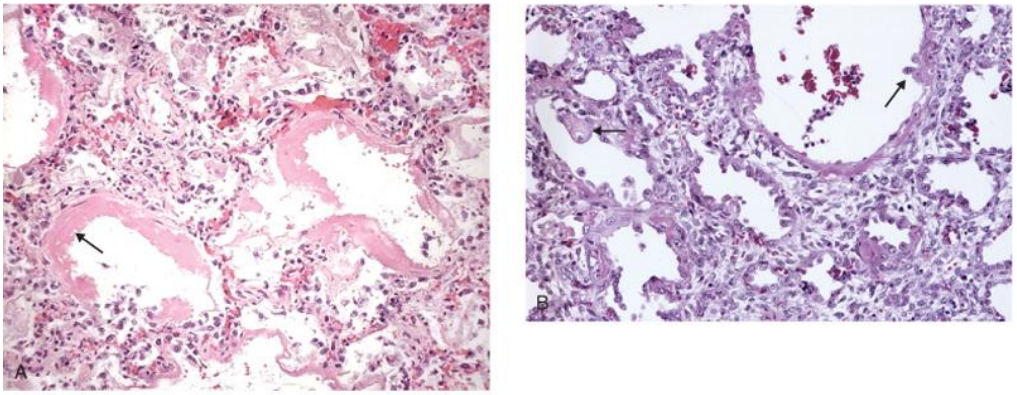
4- We intubate (نعمل له تمديد) him

5- He should be looked out by an anesthetist and an intensivist.

Histopathology

In the interstisium , there is leak of blood, proteins and fluids due to the damage of the alveolar wall.

PICTURE:



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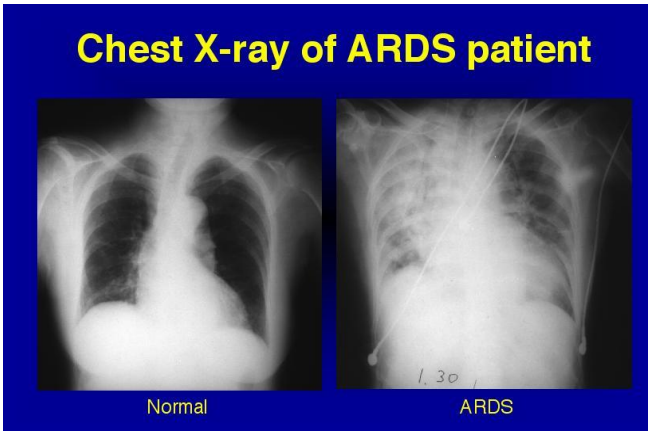
A, Diffuse alveolar damage in acute lung injury and ARDS. Some alveoli are collapsed; others are distended. Many are lined by bright pink hyaline membranes *(arrow).*

B, In the healing stage there is resorption of hyaline membranes with thickened alveolar septa containing inflammatory cells, fibroblasts, and collagen. Numerous atypical type II pneumocytes are seen at this stage *(arrows),* associated with regeneration and repair.

X_ray

Lungs appear white in the X-ray because of the exudates of the fluid and fibrin into the alveolar wall and the reaction occur in type 2 pneumocytes.



SUMMARY:

ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, and diffuse pulmonary infections.There is an imbalance of pro- and anti-inflammatory mediators causing acute inflammatory injury to the alveolar epithelium and capillary endothelium. Neutrophils and their products have a crucial role in the pathogenesis of ARDS.The characteristic histologic picture is that of alveolar edema, epithelial necrosis, accumulation of neutrophils, and presence of hyaline membranes lining the alveolar ducts.

B.NEONATAL RESPIRATORY DISTRESS SYNDROME (NRDS)_ (HYALINE MEMBRANE DISEASE)(acute phase disease): → **Surfactant deficiency**

NRDS is the **most common** cause of respiratory failure in the **newborn** and is the most common cause of death in premature infants.

Causes:

1. Prematurity (less than 36 weeks) → (low level of surfactant)
2. Multiple pregnancy.
3. Maternal diabetes mellitus
4. Delivery by cesarean section
5. Aspiration of amniotic fluids

Signs:

This syndrome's signs are marked shortly after birth, most often as a result of immaturity :

1. Dyspnea

2. cyanosis
3. Tachypnea سرعة في التنفس

Pathogenesis:

Stage I :

The neonate aspires the amniotic fluid → he becomes cyanosed (bluish)→ decrease in PO2 → difficulty in breathing → he starts vomiting → as a result to the aspiration there will be damage to type II pneumocytes (which secrete the surfactant) → low level of surfactant → alveolar collapse → hypoxemia → The neonate will go into series of damages (pulmonary vasoconstriction, endothelial cell damage, alveolar cell damage) → inflammatory reaction → fibrin and exudates go into the alveoli → The exudate is full protein → Protiens form membranes (hyaline membrane like) covering the alveoli from inside

Stage II:

1- Regeneration
2- Fibrosis:
   a. Mild fibrosis → Recovery
   b. Severe fibrosis → Respiratory failure

Treatment:

In this case:

1- we give him oxygen
2- Put him in the incubator
3- He will need a lot of attention!

SUMMAR:

Neonatal respiratory distress syndrome is caused mainly by low surfactant caused by an injury to type2 pneumocytes as a result of the causes.

B-Pneumoconiosis (تغبر الرئة)

This group of diseases is caused by inhalation of **dust particles** which usually come from the environment or the occupation (profession). But, not all dust particles cause them, you need to have the correct size. These diseases are industrial diseases, and they usually affect workers because of their occupation and environment.

Size of dust particles:

Dust is measured by micron (micro meter µm) = $1x10^{-6}$ m .

1- If the dust particles are very small ≥0.5µm they will not deposit, but instead fly away with air in inspiration and expiration and they will not cause a disease.
2- On the other hand, big dust particles between 5-10 µm will get trapped by the cilia and be rid of.
3- **So, for pneumoconiosis to occur dust particles should be between 1-5 µm** .

NOTE: The person needs to be exposed to dust continuously for years to develop the disease not just for short period of time.

Those diseases are:

A.Coal worker's pneumoconiosis

Coal worker's pneumoconiosis is caused by inhalation of coal dust, which contains both carbon and silica. It is divided to three types :

i. **Anthracosis** (or anthracotic alveolar microphages)
   - In which inhaled carbon dust accumulate in the alveolar macrophages without causing cell reaction. It is endemic in urban areas and causes no harm (*asymptomatic*) .
   - Characterized by carbon-carrying macrophages, it results in irregular black patches visible on gross inspection. It will not cause any damage to the interstitium.

ii. Simple coal worker's pneumoconiosis(SCWP)

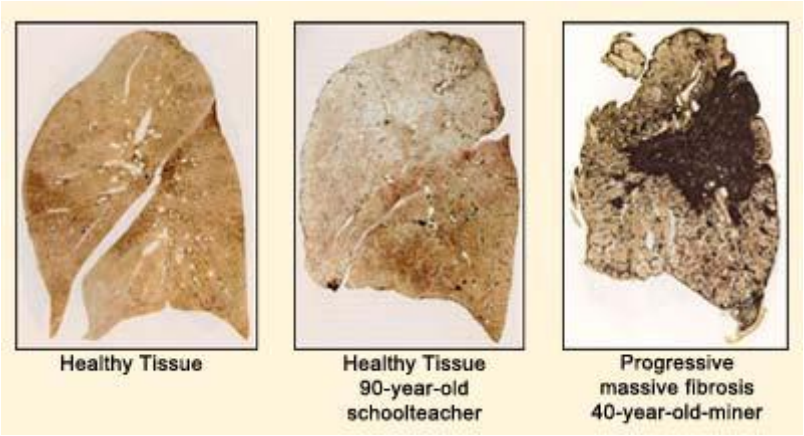
in which accumulations of macrophages occur with little to **no pulmonary dysfunction**. It is marked by **coal macules** around the bronchioles, formed by ingestion of coal dust particles by macrophages. In most cases, it is inconsequential and produces no disability. Morphologically it cause patches of black soot in the lung **no fibrosis** and the rest of the lung is ok. So, it does not cause symptoms.

iii. Progressive massive fibrosis (PMF)

It's usually happens in people who work in coal mines (مناجم الفحم). It's Worldwide but mostly (Europe, America and South Africa).
It is **marked by fibrotic nodules** filled with necrotic black fluid.

Picture:

Progressive massive fibrosis superimposed on coal workers' pneumoconiosis. The large blackened scars are principally in the upper lobe. Note the extensions of scars into surrounding parenchyma and retraction of adjacent pleura.



Clinical presentation

- Sever dyspnea
- Dry cough
- May be associated with hypoxemia

Pathogenesis

The coal dust reaches to the alveoli → macrophages engulf them → They slowly go to the circulation → they accumulate in the interstisum → alveolar septum become thick → inflammatory reaction → fibrosis → Dyspnea and other symptoms

Complications

PMF can result in:

- Bronchiectasis
- pulmonary hypertension
- death from respiratory failure or right-sided heartfailure.

B.Silicosis

The most common type of Pneumoconioses In the world

It's usually happen with Construction workers (sand blasters, glass manufacturers, stone cutter, marble cutters…etc.)
Also, it could be due to inhalation of sand.

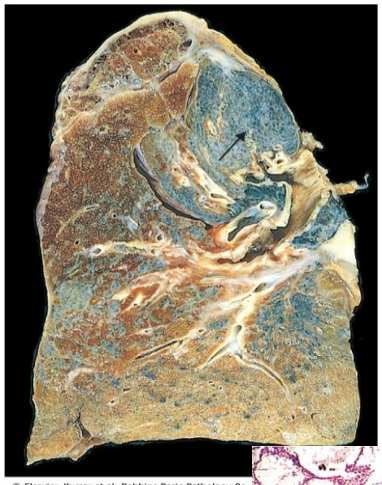
Pathogenesis

Silicosis is mainly caused by exposure to sand dust, which contain silica particles/crystals **(mainly quartz)** → inhaled particles accumulate in the alveoli → They interact with epithelial cells and macrophages → Ingested silica particles cause activation and release of mediators by macrophages → Formation of silicotic nodules sometimes associated with calcification, surrounded by reactive fibrosis →Pneumoconioses → respiratory failure

Note ;
1-silicotic nodules (nodules of collagen fibrosis silica particles and inflammatory reaction)
2-Silicotic patients have increased risk to get TB. Also, the frequent concurrence is referred to as silicotuberculosis.

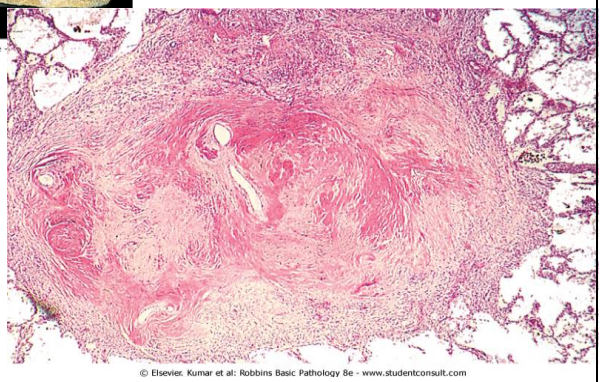
Picture:

Advanced silicosis seen on transection of lung. Scarring has contracted the upper lobe into a small dark mass *(arrow).* Note the dense pleural thickening.



Picture:

Several silicotic nodules (nodules of collagen, fibrosis, silica particles and inflammatory reaction)



C.Asbestosis (not common now a days)

A fibroblastic response which usually affects insulation workers who were exposed to asbestos. It is characterized by the presence of **ferruginous bodies (asbestos bodies)** in the alveoli and alveolar wall. These bodies are yellow-brown, rod-shaped bodies with clubbed ends **that stain positively with Prussian blue.**

These bodies when phagocytosed by macrophages cause the release of fibroblast-stimulation growth factors by macrophages, thus, leads to **diffuse interstitial fibrosis mainly in the lower lobes.** Dense hyalinized fibrocalcific plaques of the parietal pleura are also present.

The main problem with asbestosis is that it's symptoms appear after a long period of time (years to decades!) and **can be very aggressive**.

Pathogenesis

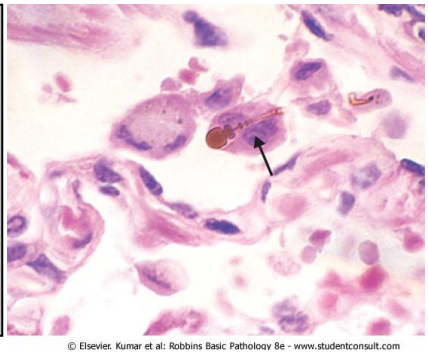
Inhalation of asbestos fibers (amphibole needles) → they enter the alveoli and alveolar wall → they get coated with hemosiderin and become yellow → Phagocytoses → Release of chemical mediators → inflammation → fibrosis.

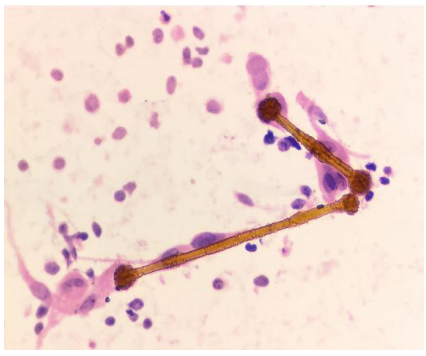
NOTE:

In addition to cellular and fibrotic lung reactions, asbestos probably also functions as both a tumor initiator and a promoter.

Pictures:

1- High-power detail of an asbestos body, revealing the typical beading and knobbed ends
2- Typical dumbbell shaped ferruginous rod-shaped bodies with clubbed ends .





Complication

1- Tumors
   a) **Bronchogenic carcinoma** cancer of the bronchi
   b) **lung cancer**
   c) **Malignant mesothelioma** (cancer of the pleura) Has no treatment
   d) **laryngeal cancer**
2- **Parenchymal** interstitial **fibrosis** *(asbestosis)*
3- **Pleural effusions**

4- localized **fibrous plaque** or, rarely, diffuse pleural fibrosis
NOTE: **Cigarette smoking** increases the risk of lung cancer in the setting of asbestos exposure

SUMMARY:

Pneumoconioses: Pneumoconioses encompass a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.

Pulmonary alveolar macrophages play a central role in the pathogenesis of lung injury by promoting inflammation and producing reactive oxygen species and fibrogenic cytokines.

Coal dust-induced disease varies from *asymptomatic anthracosis,* to *simple coal workers pneumoconiosis* (coal macules or nodules, and centrilobular emphysema), to progressive massive fibrosis (PMF), manifested by increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.

Silicosis is the most common pneumoconiosis in the world, and crystalline silica (e.g., quartz) is the usual suspect.The manifestations of silicosis can range from asymptomatic silicotic nodules to PMF; individuals with silicosis also have an increased susceptibility to tuberculosis. The relationship between silica exposure and subsequent lung cancer is controversial.

Asbestos fibers come in two forms: the stiff *amphiboles* have a greater fibrogenic and carcinogenic potential than the serpentile *chrysotiles.*Asbestos exposure is linked with six disease processes: (1) parenchymal interstitial fibrosis *(asbestosis);* (2) localized fibrous plaques or, rarely, diffuse pleural fibrosis; (3) pleural effusions; (4) lung cancer; (5) malignant pleural and peritoneal mesotheliomas; and (6) laryngeal cancer.Cigarette smoking increases the risk of lung cancer in the setting of asbestos exposure; moreover, even family members of workers exposed to asbestos are at increased risk for cancer.

C- Hypersensitivity pneumonitis (extrinsic allergic alveolitis)

A.Pigeons Breeder disease (مرض مربي الحمام) :

Related to Pigeon's dropping فضلات الحمام

Pigeon dropping contain proteins → Those proteins get inhaled→Susceptible people develop **Hypersensitivity reaction** (not all people)→ **hyper sensitivity pneumonitis**

Note (whatever the medication you give it will not help unless you diagnose the cause)

B.Birds fancier disease (مرض محب الطيور)

Similar to pigeons breeder disease but related to other birds.

C.Farmers lung disease

Here, the cause is mold hay

D.Psittacosis - Ornitosis(داء الببغاء)

Here, the cause is **chlamydia in parrot's dropping** .

Interstitial noncaseating granulomas are present in more than two-thirds of hypersensitivity pneumonitis cases

D- Sarcoidosis (Granulomatous Diseases)

Clinical presentation

- Dyspnea
- Hypoxemia
- Fever
- enlarged lymph nodes,
- loss of Wight
- systemic symptoms. ie: skin manifestation

Pathogenesis

-Idiopathic

-It usually affects the black Americans

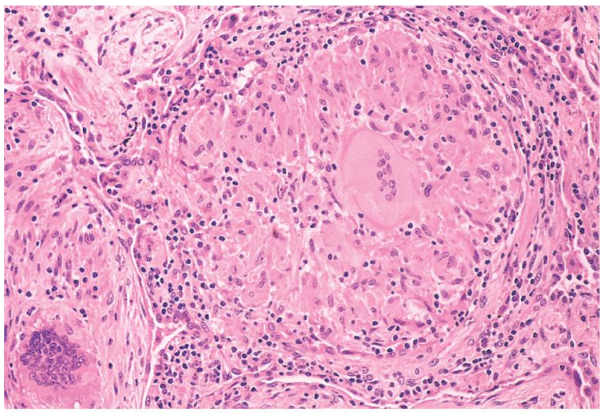
-It is thought that some sort of allergin causes the disease

-There is presence of non- caseating granuloma in the mediastinum

-It was found that affected people have hyperimmunoglobulinimea and high numbers of T-lymphocyte

Picture:

Characteristic sarcoid noncaseating granulomas in lung with many giant cells.



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Diagnosis

-**We use angiotensin-converting enzyme**

E-Goodpasture's syndrome (respiratory and renal disease) (acute phase disease)

Note: It affects young people

Clinical presentation

- Severe hemoptysis
- Hematuria (دم في البول)
- Dyspnea
- Hypoxemia

When you look to the lung you will see the following:

- **reticular nodular shadowing (X-Ray)**

- **honey combing (gross)**

Pathogenesis

Its autoimmune disease → anti basement membrane Antibodies act on the basement membrane of alveolar wall and the basement membrane of the glomeruli → proliferative glomerulonephritis and interstitial pneumonitis Note: It's hard to treat

Eosinophilic granuloma
Proliferationa of histiocytic cells related to Langerhan's cells of the skin.

Other interstitial lung diseases

1- Paganosis
It comes to the farmers working with Sugar-cane (قصب السكر)

2- Borreliosis: allergy to borreleom.

3- Viral pneumonitis

5- mycoplasmic pneumonitis

SUMMARY:

Diseases that cause interstitial lung disease:

1-Deformities of the chest wall

2-Neuromuscular diseases affecting intercostals muscles and/or there nerves

3-Idiopathic disease (UIP and Sarcoidosis)

4-Pneumoconiosis

- Coal workers pneumoconiosis
- Silicosis
- Asbestosis

5- Good pastures syndrome

6- hypersensitivity pneumonitis

7- Respiratory distress syndromes (ACUTE)

*432 **Pathology** Team*

*Good Luck ^_^*