PATHOLOGY TEAM 436

Revised by
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MEDICINE
KING SAUD UNIVERSITY 436

اللهم لاسهلا إلا ماجعلته سهلًا وأنت تجعل الحزن إن شئت سهلًا

Restrictive Lung Diseases

Editing file

Objectives :

1- Understand the structure and constituents of the lung interstitium as well as the restrictive changes which occur in these diseases and lead to the development of symptoms of progressive breathlessness and cough in affected patients.

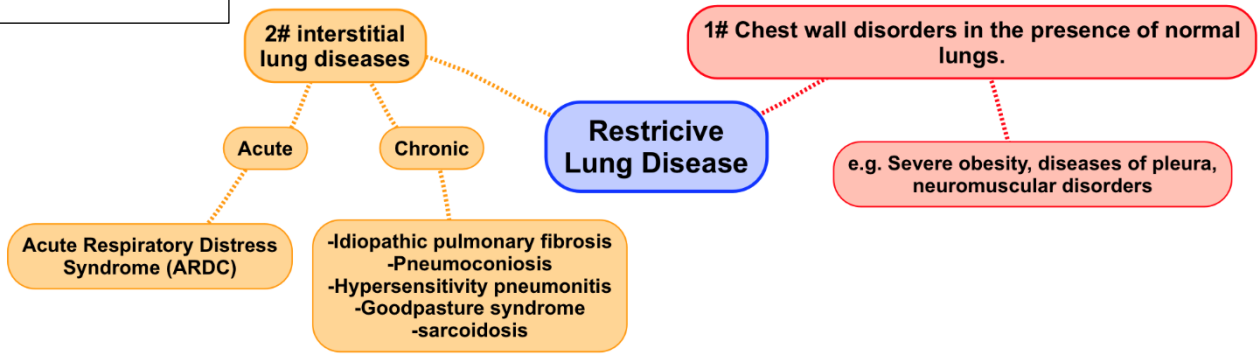
2- Appreciate the pathogenesis of interstitial lung diseases regardless of their type. This pathogenesis include the influx of inflammatory cells into the alveoli and alveolar walls, distortion of the normal structure of alveoli, release of chemical mediators and promotion of fibrosis (honey-combed lung).

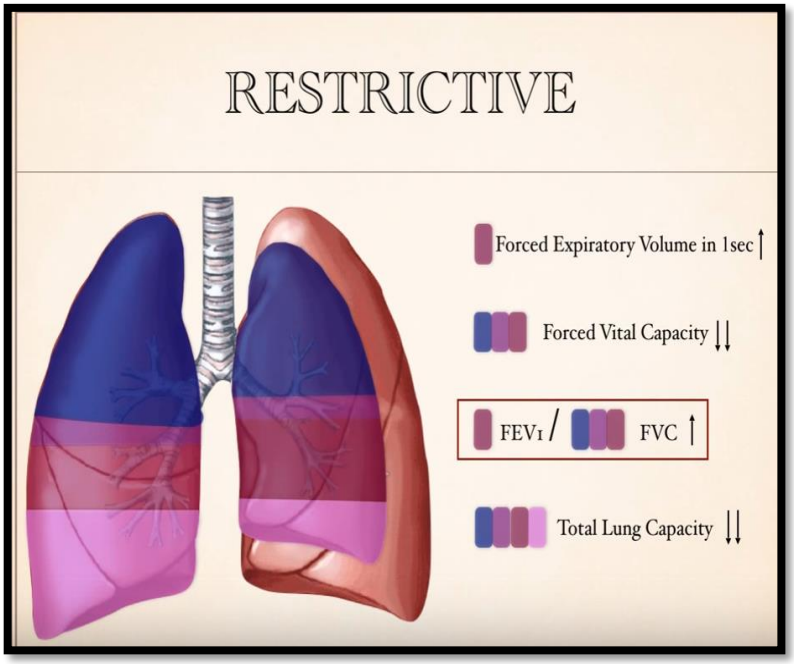
3- Become aware of the classification of interstitial lung diseases.

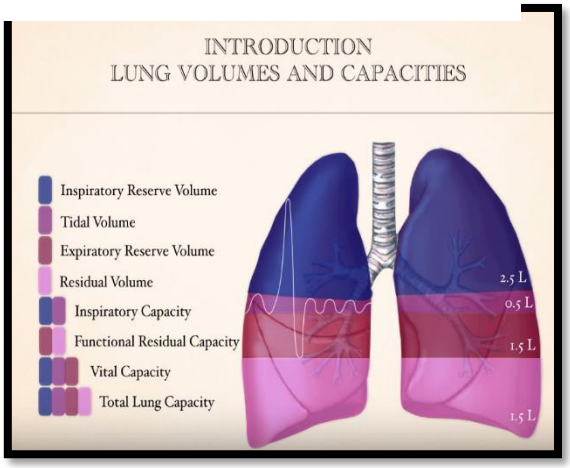
Doctor notes: green
Important : red
Extra explanation grey

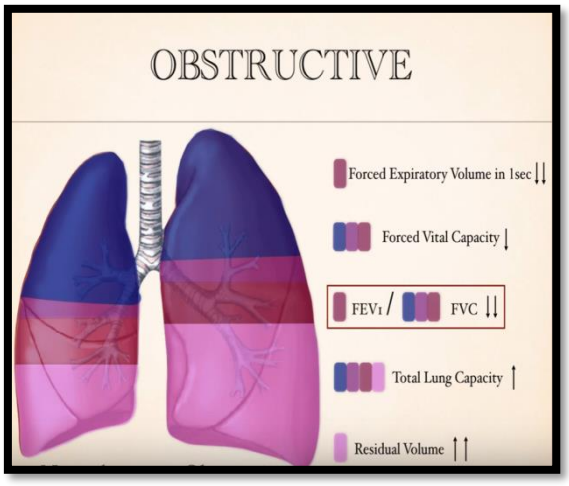
Restrictive Lung Disease

*from Robbins basic pathology









In restrictive pulmonary diseases, both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced

with normal to high FEV1/VC

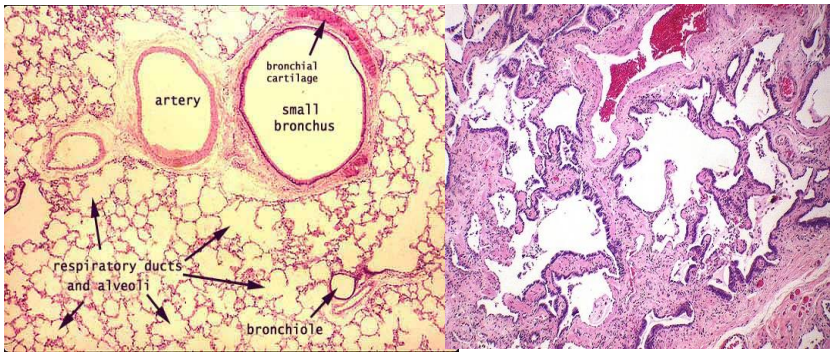
**affect the area distal to terminal bronchioles.

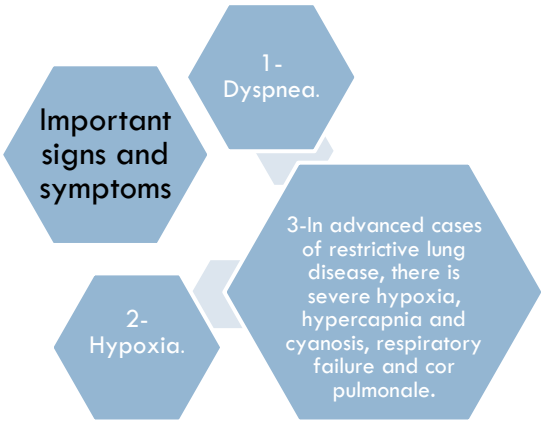
The restrictive lung diseases are divided into:	
Intrinsic lung diseases/ diseases of the lung parenchyma/primary ILD (Interstitial lung diseases):	Extrinsic disorders or extraparenchymal diseases:
The diseases cause inflammation or scarring of the lung tissue (ILD) or result in filling of the air spaces with exudate and debris (pneumonitis). They are characterized by inflammatory infiltrates in the interstitial space and the interstitium becomes thickened and fibrotic (Stiff Lung). Therefore, there is decreased oxygen-diffusing capacity. They are acute (no scars in this case) or chronic.	The chest wall, pleura, and respiratory muscles are the components of the respiratory pump, and they need to function normally for effective ventilation. Abnormalities of the chest wall include: - bony abnormalities (kyphosis or kypho-scoliosis) - massive pleural effusion, - morbid obesity - neuromuscular disease of respiratory muscles, results in respiratory muscle weakness and respiratory failure e.g. myopathy or myositis, quadriplegia, or phrenic neuropathy from infectious or metabolic causes

Intrinsic type of Restrictive lung diseases

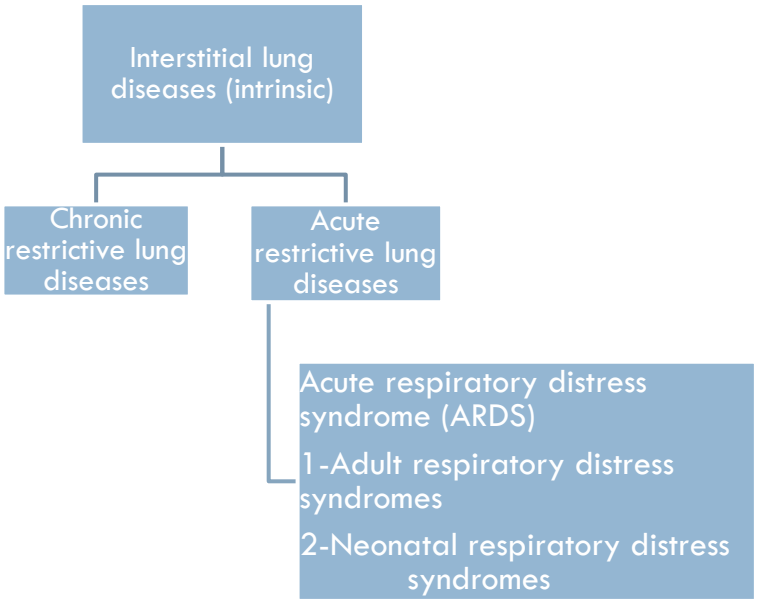
- Characterized by reduced compliance of the lung.
  -reduced expansion of lung parenchyma accompanied by decreased total lung capacity.
- The final stage of all restrictive lung disease is extensive fibrosis with honeycomb lung. The lung becomes more solid and stiff.
  *honeycomb lung refers to the fibrotic cystic change

- Honeycomb lung indicates end stage disease. In it both alveoli and bronchioles coalescence to form cysts lined with cuboidal or columnar epithelium and separated by inflammatory fibrous tissue.





*more dyspnea more fibrosis.



Adult Respiratory Distress Syndrome (ARDS): hyaline membrane disease

- ARDS is a severe form of acute lung injury with diffuse alveolar injury.
- known as shock lung/ diffuse alveolar damage/ adult respiratory failure/acute alveolar injury/ traumatic wet lung
- It is the most common cause of non- cardiogenic pulmonary edema.

Features	-Rapid acute onset progressive severe life threatening respiratory insufficiency, cyanosis, severe arterial hypoxia
Can be caused by many conditions:	-Refractory to oxygen therapy and that may progress to multi-organ failure
	-Bilateral -both lungs- pulmonary infiltrates (edema) in the absence of evidence of left sided heart failure

Direct injury to lung
-Pneumonia -Aspiration of gastric contents -Pulmonary trauma -Fat embolism -Near drowning (غرق) -Toxic inhalation injury (irritants such as chlorine, O2 toxicity) -Post lung transplant -Severe acute respiratory syndrome (SARS): The virus is a coronavirus that destroys the type II pneumocytes and causes diffuse alveolar damage
Indirect injury to lung
-Sepsis -Severe trauma (e.g. bone fractures, head injury, burns, radiation) -Shock -Cardiopulmonary bypass -Acute pancreatitis -Transfusion of blood products -Uremia -Overdose with street drugs such as heroin Therapeutic drugs such as bleomycin -Hematologic conditions e.g. multiple transfusion, coagulation disorders

Pneumonia and sepsis are the most common causes

Pathophysiology of ARDS

- ARDS is associated with diffuse alveolar damage. (DAD)
- It is initiated by injury to: give cover by eosinophilic hyaline membrane.

1. alveolar capillary endothelium a with resultant increase in alveolar capillary permeability
2. alveolar epithelium

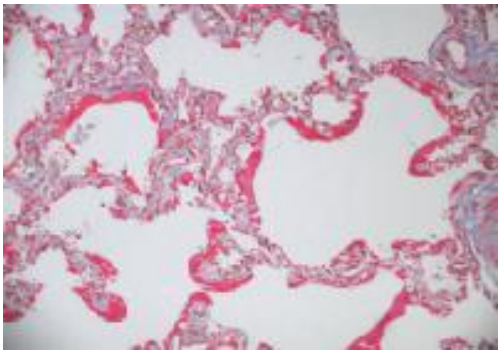
- The injury and edema is induced by the:

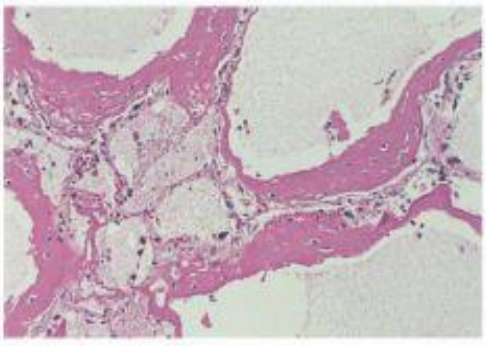
(a) Neutrophils releasing substances toxic to alveolar wall.

(b) Activation of the coagulation cascade.

(c) O2 toxicity (due to formation of free radicals).

- This causes leakage of protein-rich fluid into alveoli, formation of alveolar hyaline membrane lining the inner surface of alveoli.
- The membrane is composed of fibrin and cellular debris.
- The lungs become remarkably heavy and stiff due to inflammation and edema and later interstitial fibrosis.
- Chest x-ray: bilateral and diffuse pulmonary infiltrates





*fibrosis will result in pulmonary impairment.

Outcome of ARDS:

- Mortality was 100%
- Now 30 -40% with good ICU support
- Poor prognosis: old age, multisystem failure, high level of IL-1

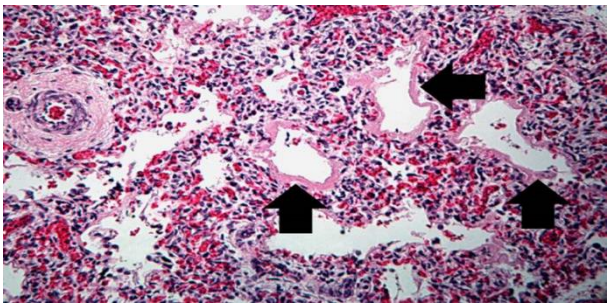
From Robbin

-The alveolar -capillary membrane is formed by 2 separate barriers: microvascular endothelium and the alveolar epithelium. In ARDS the integrity of this barrier is compromised by either endothelial or epithelial injury , or more commonly both.

-combined assault on the endothelium and epithelium perpetuates vascular leakiness and loss of surfactant that render the alveolar unit unable to expand.

Neonatal Respiratory Distress Syndrome/Hyaline membrane disease

- It is the most common cause of respiratory failure in the newborn and is the most common cause of death in premature infants.
- It is the same as ARDS except that it is caused by a deficiency of pulmonary surfactants in new born, most often as a result of immaturity.



Causes\1-prematuraty-less than 36 week- because there will be surfactant insufficiency- which is completed between 28-34 weeks. Surfactant is important for increasing tension inside the lungs so it does not collapse.

2-multible pregnancies. 3- maternal diabetes 4-caesarean section

**premature have less surfactant then hyaline formation which is composed of fibrin, edema fluid, necrotic cells (damaged pneumocyte I&II

In case of type two regeneration there will be chronic inflammation and fibrosis in the interstitum so alveolar walls are thickened (**in lower lope**).

Chronic Restrictive Lung Disease

Definition

They are a heterogeneous group of chronic interstitial diseases characterized by preventing the lung from expansion "restrict the movement of the lung".

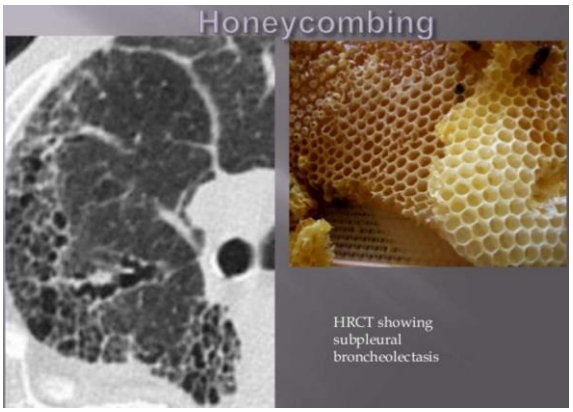
Characteristics

- Many entities are of unknown cause and pathogenesis.
- They have similar clinical signs, symptoms, radiographic alterations and pathophysiologic changes
- Affect the region **distal** to the terminal bronchioles "from respiratory bronchioles to the alveoli", Leading to Damage in alveolar epithelium and interstitial vasculature, finally reduce in the lung volume and elasticity.
  *Affecting small airways
- The hallmark of these diseases is reduced compliance.
- Account for about 15% of non-infectious lung diseases.
- End-stage: diffuse interstitial pulmonary fibrosis "honeycomp".

Main Symptoms

- **Dyspnea**
- **Dry cough**
- Hypoxia or hypoxemia

- The sever cases develop respiratory failure, pulmonary hypertension and cor pulmonale.
  *In this cases the Arterial PO_2 become 25 mmHg ; Low PO_2 , High PCO_2



Major Categories of Chronic Interstitial Lung Disease

Idiopathic Fibrosis Idiopathic pulmonary fibrosis (IPF) / Usual interstitial pneumonia (UIP) / fibrosing alveolitis / Hamman-Rich syndrome *the same names if it come in the exam	**Smoking Related** - Desquamative interstitial pneumonia - Respiratory bronchiolitis - Eosinophilic granuloma
Pneumoconiosis - Coal worker's pneumoconiosis, - Silicosis - Berylliosis - Asbestosis - Anthracosis	**Drugs** - Chemotherapy - Methotrexate - Bleomyxin toxicity
Granulomatous Diseases "Immune diseases" - Sarcoidosis - Hypersensitivity pneumonitis (allergic alveolitis) - Goodpasture syndrome - Systemic lupus erythematous - Systemic sclerosis (scleroderma) - Wegener granulomatosis	**Radiation Reactions** Occur after radiation with diffuse alveolar damage, severe atypia of hyperplastic type II cells and fibroblasts. *like if the Petain has mediastinal lymphoma; we treat him by radiation, so there will be injury and secondary fibrosis in the lung.

*Although they differ from each other, but at the end they all causes stiff lung due to interstitial fibrosis.

*These diseases characterized by damaged in type I pneumocyte and sometimes it dead and get necrotized and it is not have the capability of generation, but type II pneumocyte have the capability of generation that's way it's hyperplastic in these diseases.

So there will be inflammation and fibrosis in interstitium and the alveolar wall very thick and infiltrated by chronic inflammatory cells, so the damage in type I pneumocyte will lead to secretion of transforming growth factor B1 (TGF-B1), So this factor will cause the fibrosis, than this fibrosis will engulf the alveolar duct and the alveoli finally create which called "honey comp".

Idiopathic Pulmonary Fibrosis (IPF)\(UIP)

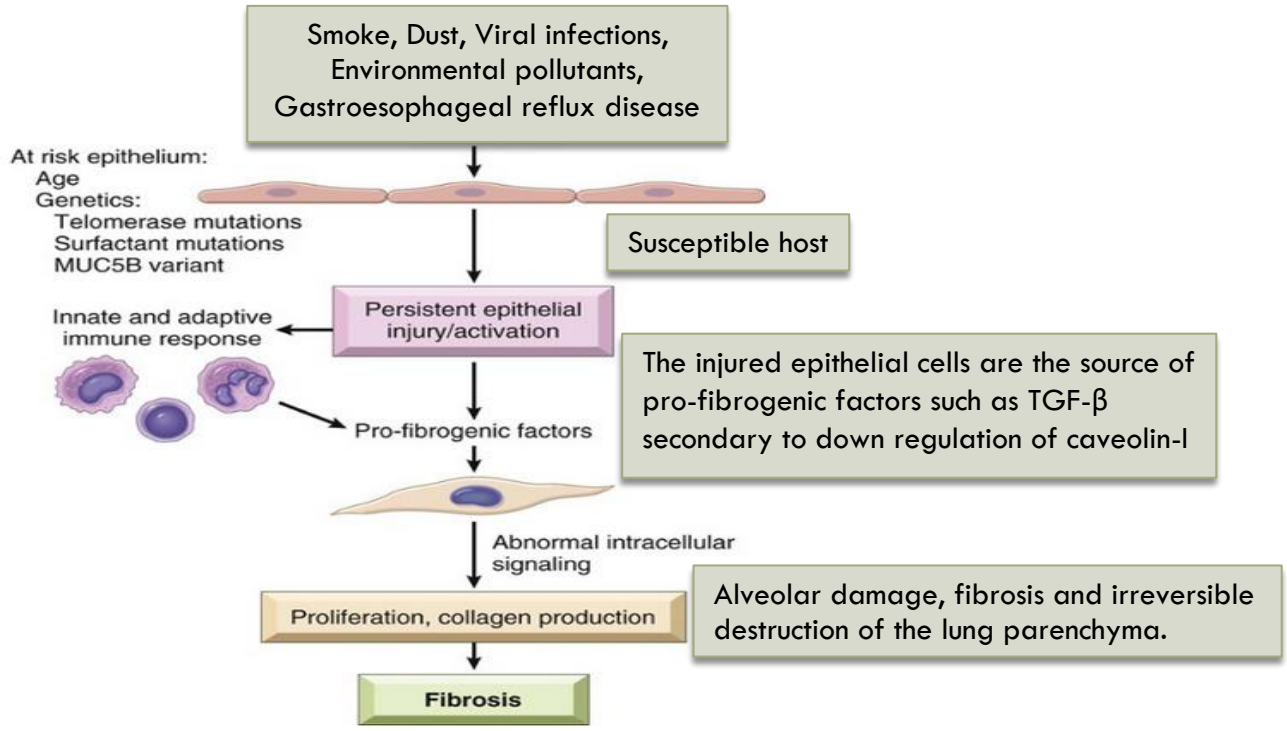
*** also know Fibrosisng alveolitis**

- UIP is progressive fibrosing disorder of unknown cause. It is an idiopathic interstitial pneumonia with diffuse interstitial fibrosis and inflammation.

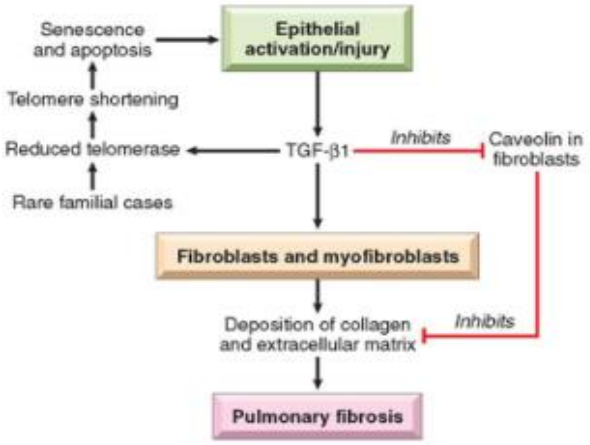
It is bilateral, which in advanced cases result in sever hypoxemia and cyanosis.

- Age group: Adults 30 to 50 years.

Pathogenesis of Idiopathic Pulmonary Fibrosis (IPF)



= Extra explanation from robbins if you still confused

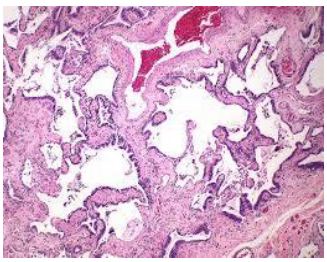


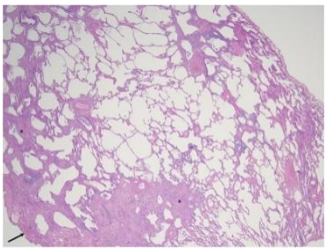
It is a 'repeated cycle' of epithelial activation\injury by undefined agent lead to damage in type I pneumocyts which will lead to secretion of transforming growth factorB1 (TGF-B1), So this factor will cause the fibrosis.

Also this factor down-regulates 'fibroblast caveolin-l' which act as an endogenous inhibitor of pulmonary fibrosis.

Morphology Of UIP

- The morphologic changes vary according to the stage of the disease





1) Early cases:

-Intra-alveolar and interstitial inflammation.

- Hyperplasia of type II pneumocytes

2) Advancing disease:

-prominent interstitial fibrosis.

-Alternating areas of fibrosis and normal tissue will be seen.

3) In the end, the lung consists of spaces lined by cuboidal or columnar epithelium separated by inflammatory fibrous tissue (honeycomb lung). It is the end stage of lung disease

Clinical Features of UIP

- Most patients present with exertional dyspnea and **a nonproductive cough.**

- Chest radiograph: x-ray will show you small nodules or irregular lines.

- Prognosis: poor.

- Respiratory and heart failure may develop within few years.

- No effective therapy is available for the treatment of idiopathic pulmonary fibrosis. Lung transplant is the only solution.

- In later stages of the disease, cyanosis, cor pulmonary and peripheral edema may developed.

- Surgical lung biopsy is needed for diagnosis in some cases.

Pneumoconiosis تغبر الرئة

- Pneumoconiosis is a group of pulmonary diseases caused by chronic exposure to inorganic mineral dust inhalation and this leads to lung damage.
- More than 40 inhaled minerals can cause lung problems.
- They include **carbon dust, silica, asbestos,** beryllium etc.

Pathophysiology:

- Alveolar macrophages ingest the particles, become activated, and release cytokines and chemotactic factors that recruit other inflammatory cells.
- The ensuing inflammation damages lung cells and also damages the interstitium of the lung by degrading the extracellular matrix glycoproteins.
- The inhaled particles also stimulate the fibroblasts to proliferate and produce collagen; fibrosis results.
- As the disease progresses the blood vessels become compromised, and ischemic necrosis ensues.

The development of pneumoconiosis is dependent on:

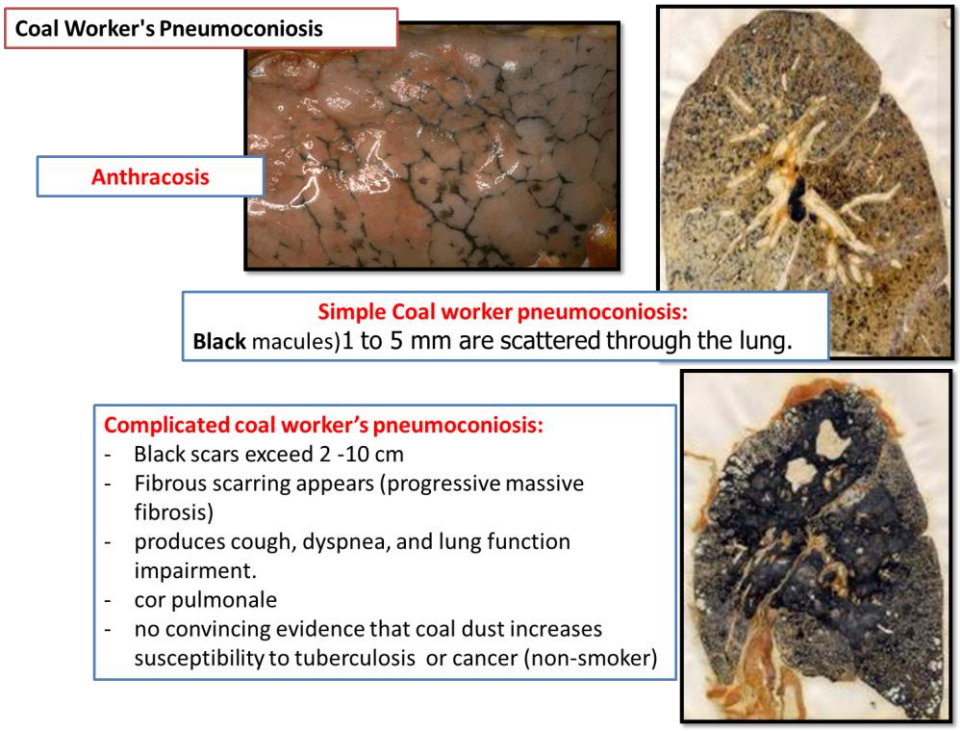
- The amount of dust retained in the lung and airways.
  - Concentration of the dust in the ambient air.
  - Duration of the exposure.
  - Effectiveness of the clearance mechanisms.
- The size (1-5μ) shape.
  - size
    - 0.5 micron ⇒ rear to cause a disease
    - More than 5 microns .⇒. rear to cause disease
    - From 1-5 microns .⇒. will develop interstitial lung disease
- Their solubility and physiochemical activity.
- The possible additional effects of other irritants, tobacco smoking.

Pneumoconiosis

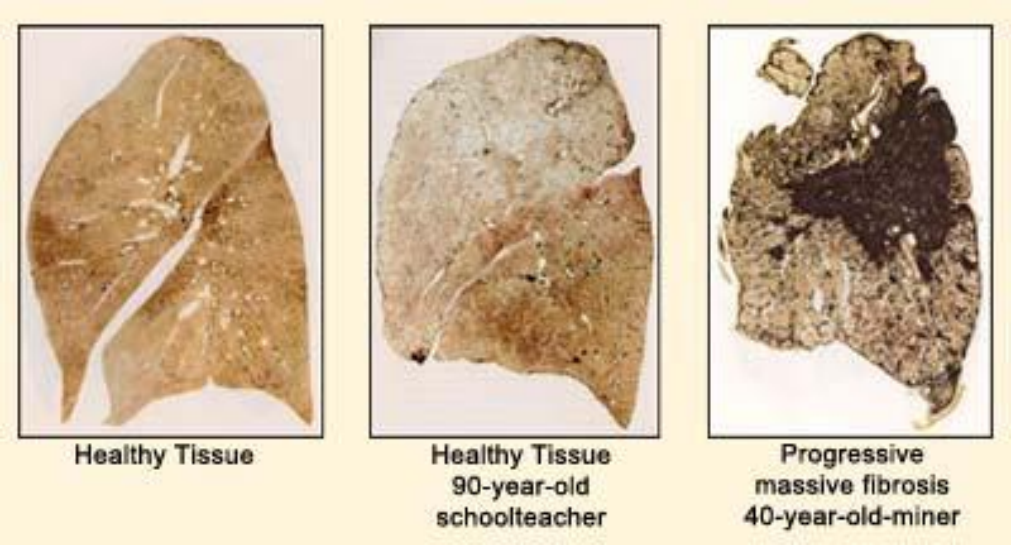
Entity	Example	Pathological features	Comment
coal worker's pneumoconi-osis	coal dust in coal miners	-Simple coal worker's -Complicated coal worker's pneumoconiosis (with rheumatoid arthritis is called Caplan syndrome)	**Anthracosis** is the accumulation of coal without consequent cellular reaction in air polution /smoker
Silicosis	**silicon dioxide**	industries: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing	-Complicated progressive massive fibrosis -Predispose to lung cancer and TB
Berylliosis	Beryllium Mining, Aerospace manufacturing	non-necrotizing granulomata distributed in the parenchyma, LN and other organs	Pedispose to lung cancer
Asbestosis	Pipes, sheets, vinyl-asbestos floor tiles, asbestos paper in filtering and insulating products	Pulmonary fibrosis Pleural fibrosis	Bronchogenic Carcinoma and Malignant Mesothelioma

Coal Worker's Pneumoconiosis

- Coal worker's pneumoconiosis (CWP) can be defined as the accumulation of coal dust in the lungs and the tissue's reaction to its presence.
- **The disease is divided into 2 categories:**
    1. Simple coal worker's pneumoconiosis
    2. Complicated coal worker's pneumoconiosis (CCWP), or pulmonary massive fibrosis (PMF), depending on the extent of the disease.
- Pulmonary massive fibrosis in association with rheumatoid arthritis is known as Caplan syndrome.



Sometimes could be associated with emphysema and rheumatoid arthritis



Silicosis

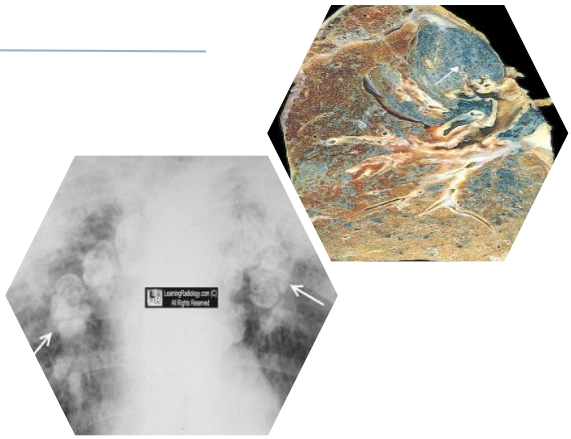
- Silicosis is a fibro-nodular lung disease caused by long term exposure to inhalation of crystalline silica particles (alpha-quartz or silicon dioxide).
- Industrial exposure: mining of gold, tin, copper and coal, sandblasting, metal grinding, ceramic manufacturing.
- Chronic forms manifest after several years of exposure
- The symptoms may be indolent or progressive: complicated progressive massive fibrosis.
- Silicosis predispose to lung cancer and tuberculosis.

Pathogenesis:

- Crystalline silica is highly fibrogenic.
- Scattered lymphocytes and macrophages are drawn rapidly with fibrosis.
- Some particles are transported to lymph nodes.

Morphology

- Tiny collagenous nodules that enlarge forming stony-hard large fibrous scars usually in the upper lobes.
- The lung parenchyma between the scars may be compressed or emphysematous.
- Calcifications may appear (eggshell calcification) .
- Similar collagenous nodules within the lymph nodes.
- Fibrous pleural plaques may develop.

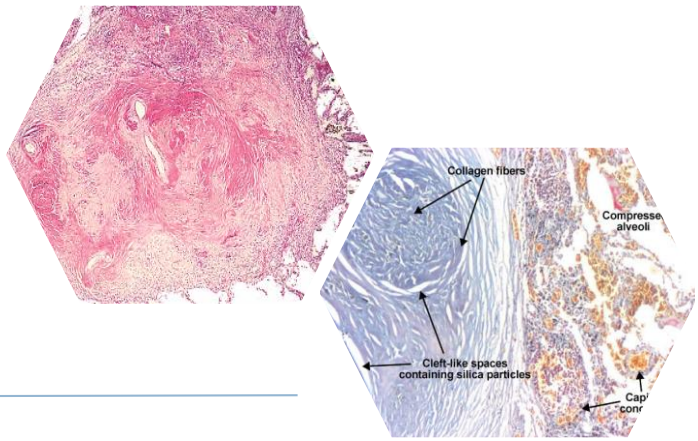


-histologically

Hyalinized collagen fiber surround an amorphous center

(fibrous nodules).

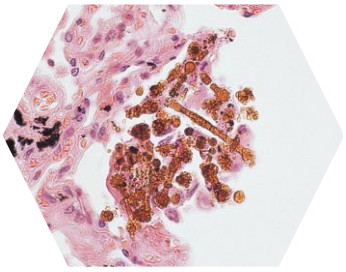
- Scarring progress to progressive massive fibrosis.



Prognosis:

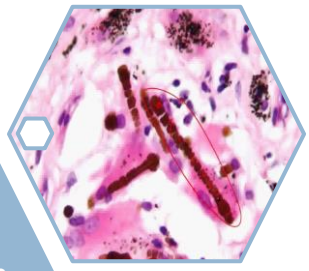
- Scarring extending and encroching the pulmonary arteries leading to Cor pulmonale.
  - Increased susceptibility to tuberculosis (crystalline silica inhibits the ability of pulmonary macrophages to kill phagocytosed mycobacteria)
  - Patients with silicosis have double the risk for developing lung cancer

Asbestosis

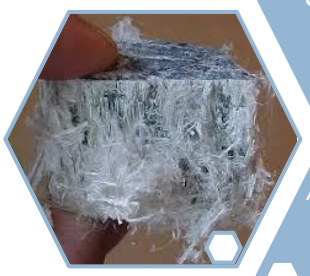


- Caused by asbestos inhalation
- Asbestos fibers are long and thin. They can curved or straight.
- All types of asbestos (crocidolite and amosite) are fibrogenic to lungs.
- **Asbestosis** occurs decades after exposure has ended.
- Characterized by scars containing asbestos bodies.
- They can **cause**
  - ➢ pleural effusion.
  - ➢ pleural adhesions.
  - ➢ parietal pleural fibrocalcific plaques
  - ➢ Some types of asbestos are carcinogenic (especially crocidolite) and prolong asbestos exposure can predisposes to bronchogenic carcinoma and malignant mesothelioma.

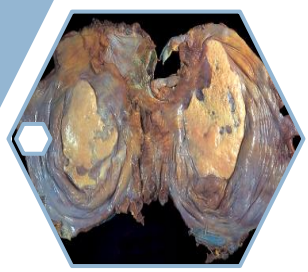
- cause
- ➢ Cause interstitial lung disease
- ➢ Laryngeal carcinoma
- ➢ Fibrous thickening
- ➢ Fibers block in thee pleura
- ➢ hemorrhage



scarring containing asbestos bodies (ferruginous bodies).

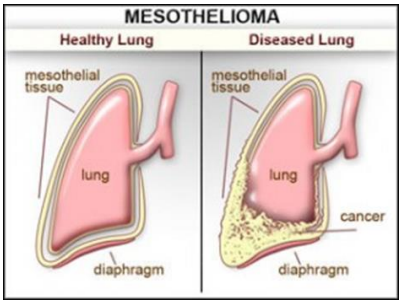


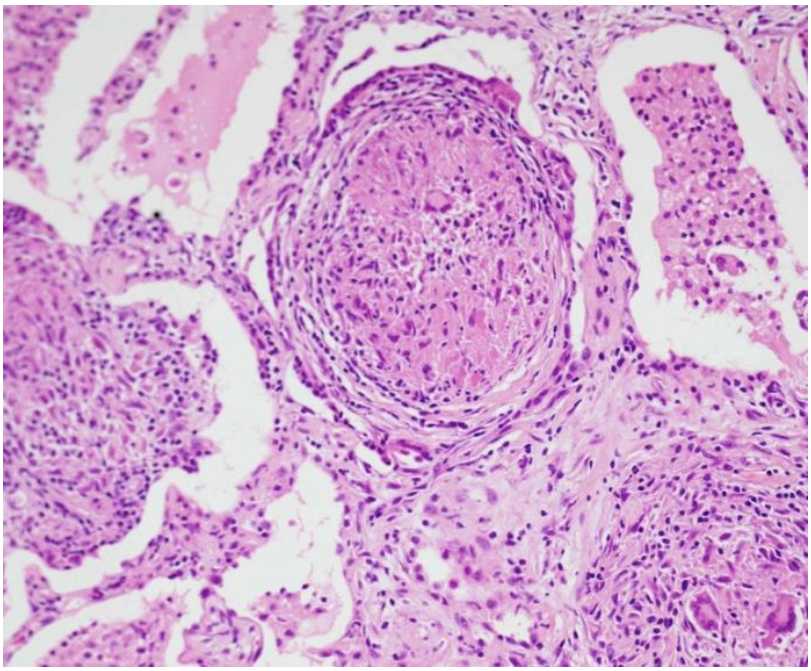
parietal pleural fibrocalcific plaques



Asbestos bodies are long, thin asbestos fibers coated with hemosiderin and protein to form brown filaments with a beaded or drumstick pattern.

- Both bronchogenic carcinoma and mesothelioma develop in workers exposed to asbestos.
-
- The risk of bronchogenic carcinoma is fivefold and for mesothelioma is 1000 fold greater





People who are exposed to beryllium :where people work in nuclear reactors or florescent light industries

Hypersensitivity pneumonitis (interstitial lung debase –granulomatous) Robbins P.480

Prolonged exposure → (To inhaled) Organic antigen → (Such as) dairy and grain products[1], animal droppings

→ (Lead to) Hypersensitivity type 3 , 4 → (In) Alveoli

Definition

Immunologically mediated disorder affecting alveoli , airways and interstitium.

Site

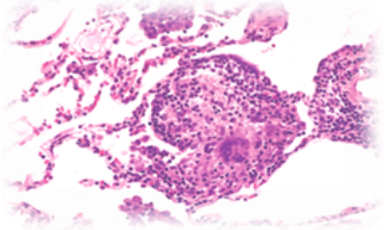
It primarily affects the alveoli and is therefore often called allergic alveolitis , later it will cause bronchiolitis, interstitial pneumonitis, and diffuse interstitial fibrosis.

Classifications

*It is an occupational restrictive disease.(it is important to take occupational history)
*Hypersensitivity pneumonitis can present as acute, subacute (intermittent) or chronic progressive.
*clinical course is variable

Morphology

noncaseating interstitial granulomas (small undefined poorly formed granuloma) (IV hypersensitivity reaction), bronchiolitis, interstitial pneumonitis, and diffuse interstitial fibrosis.



Symptoms and characteristics

Dyspnea – chronic inflammation –fibrosis – small granuloma

Etiology:-

Source

These dusts come from sources such as dairy and grain products, animal droppings and feathers and animal proteins etc. Poultry and other bird handlers are commonly exposed to droppings, feathers, and serum proteins of pigeons etc.

Common antigens

The most common antigens are thermophilic *Actinomycetes* species and avian proteins , Sugarcane bagasse ,agar culture , pigeon droppings (most common) petrochemicals , bakhoor

common diseases

1-farmer's lung[2]

2-bird fancier's[3](Pigeon breeder's)

3-Bagassosis [4]

4-Air-condition lung , (caused by Thermophilic bacteria)

5-handler's lung

The main deference between asthma and Hypersensitivity pneumonitis that , in asthma the pathology in mainly , related to the airway (bronchi and bronchioles) but , Hypersensitivity pneumonitis , the pathology mainly starts with alveoli (**team 434**)

1* منتجات الألبان والحبوب

2* is a hypersensitivity pneumonitis induced by the inhalation of biologic dusts coming from hay dust or mold spores Thermophilic actinomycetes in hay

3* is a type of hypersensitivity pneumonitis caused by bird droppings .

4* Bagassosis, an interstitial lung disease , is a type of hypersensitivity pneumonitis attributed to exposure to Sugarcane bagasse.

Sarcoidosis Robbins P.478

(interstitial lung debase –granulomatous)

Definition

Sarcoidosis is a **multisystem(systematic) granulomatous** inflammatory disease

Etiology

unknown cause

characteristics

non- caseating / non-necrotizing granulomas in affected organ tissues

Sex and age group

*affecting all races
*affecting both sexes equally
* Common beyond African American people

site

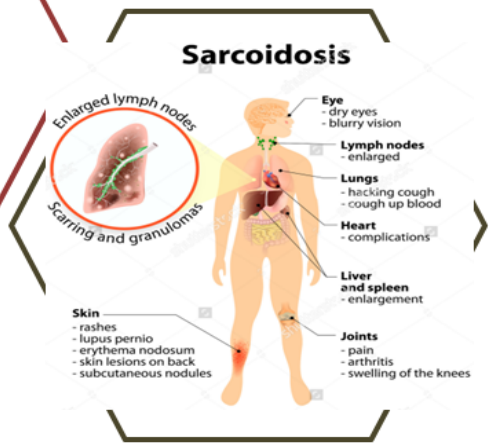
that predominantly affects the lungs and intrathoracic lymph nodes

Also, can affect mainly:

eyes, skin, liver, spleen and bone marrow

Occasionally:

kidney, heart, CNS and endocrine organs may be involved.



Examinations :

*X-ray : hilar lymphadenopathy (the hilar lymph node in the hilum of the lung becomes enlarged .
* ACE (angiotensin-converting enzyme) will be increased (angiotensin hormone causes vasoconstriction)

Clinical features

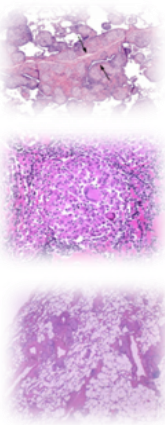
Clinically the patient may present with fever, anorexia, and arthralgias, dyspnea on exertion, cough and chest pain, chest tightness. Depending on the organs involved the patient can have dermatological, occular, cardiac or neural(rare) manifestations.

Progression

- The prognosis of sarcoidosis is unpredictable. It can progressive and chronic. It may present as episodes of activity. Majority of the patients respond well to treatment. A small percentage of patients may die of the complications of sarcoidosis.

Morphology

Sarcoidosis noncaseating granulomas in the lung



*Can cause prebronchial and prealveolar noncaseating granuloma.
*the granuloma shows Schumann bodies (calcified structures inside giant cells) and asteroid bodies (crystals like materials inside giant cells) (you can find that by taking transbronchial biopsy .
*fibrosis and inflammation.
* The major deference between Sarcoidosis and TB usually has caseating necrosis in the middle of granuloma (team 434) دائم يشتبه تشخيصه بتشخيص TB

Goodpasture Syndrome: (Anti GBM disease)

Dr notes: only the kidney and the lungs are affected

Hemorrhagic pneumonitis and glomerulonephritis caused by antibodies directed against glomerular basement membranes . **because the lung and the kidney have a thick basement membrane that's why these antibodies are directed to them

A rare disease which is a triad of:

- Diffuse pulmonary hemorrhage. *these patient have a rapture alveoli which will accumulate hemosiderin in the alveolar microphage leading to pulmonary hemorrhage .
- Glomerulonephritis.
- Circulating antialveolar and antiglomerular basement membrane (antiGBM) antibodies

Also called antiGBM disease and it is an autoimmune disorder. The antiGBM antibody can usually be found in serum.

Clinical presentation : Most of the patients have:

1. Pulmonary symptoms:

Hemoptysis Dyspnea

2. Renal symptoms (which occur later):

Hematuria. Proteinuria. Red cell casts. Renal failure. Progressing to uremia(blood in urine) and death.

3. Arthralgias.

The lung will show features of acute necrotizing alveolitis with marked hemorrhage.

Kidney may show rapidly progressive glomerulonephritis that may lead to renal failure. Immunofluorescence of renal biopsy staining for IgG in a linear patternin patient with antiglomerular basement membrane (antiGBM) disease

Eosinophilic Granuloma:

pulmonary histiocytosis X / pulmonary Langerhan cell histiocytosis X

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

- An uncommon interstitial lung disease in which there is accumulation of Langerhans cells in the lungs.
- It is considered as a form of smokingrelated interstitial lung disease.
- Some patients recover completely after they stop smoking, but others develop longterm complications such as pulmonary fibrosis and pulmonary hypertension.
- It chiefly affects young adults in the third or fourth decades of life.
- It is a localized form of Langerhan cell histiocytosis.
- It commonly involves the lungs. Other organ systems like bone, skin and lymph nodes may also be affected.
- In pulmonary Langerhans cell histiocytosis X there is infiltration of the lungs by activated Langerhans cells and eosinophils. They form nodules around the bronchioles, causing destruction of the airway walls. In late stages of the disease, fibrotic stellate scarring happens.
- They may be identified by immunohistochemical staining with CD1a or by the presence of rod like Birbeck granules via electron microscopy.

*eosinophilic granuloma is seen mainly in the lung, Although some studies show that there are monoclunel proliferation of langerhans cell in neoplastic cell

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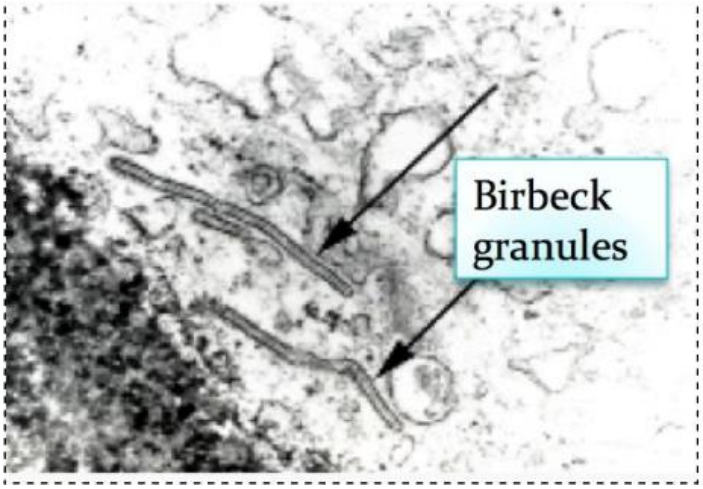

Thank you

اللهم إني استودعتك ما قرأت وما حفظت فرده إلى وقت حاجتي

Girls

Leader:

Munirah aldofyan

Members :

1- **Rawan Alwadee**
2- **Do'aa Abdulfattah**
3-**Fatima Alangari**
4- **Raneem Alghamdi**
5- **wejdan alzaid**

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