

RSM-6

**chronic interstitial (restrictive, infiltrative)
lung diseases**

Dr.Eman Kreishan,M.D.

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Chronic interstitial diseases

- ▶ Chronic interstitial diseases are a heterogeneous group of disorders characterized by bilateral, often patchy, pulmonary fibrosis mainly affecting the walls of the alveoli.
- ▶ Chronic interstitial lung diseases are categorized based on clinicopathologic features and characteristic histology

Table 13.2 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis) Nonspecific interstitial pneumonia Cryptogenic organizing pneumonia Collagen vascular disease-associated Pneumoconiosis Therapy-associated (drugs, radiation)
Granulomatous
Sarcoidosis Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome Drug allergy-related Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia Respiratory bronchiolitis

The hallmark of these disorders is

- ▶ reduced compliance (stiff lungs), which in turn necessitates increased effort to breathe (dyspnea).
- ▶ damage to the alveolar epithelium and interstitial vasculature produces abnormalities in the ventilation-perfusion ratio, leading to hypoxia.
- ▶ Chest radiographs show small nodules, irregular lines, or “ground-glass shadows.”
- ▶ With progression, patients may develop respiratory failure, pulmonary hypertension, and cor pulmonale



I. Fibrosing Diseases:

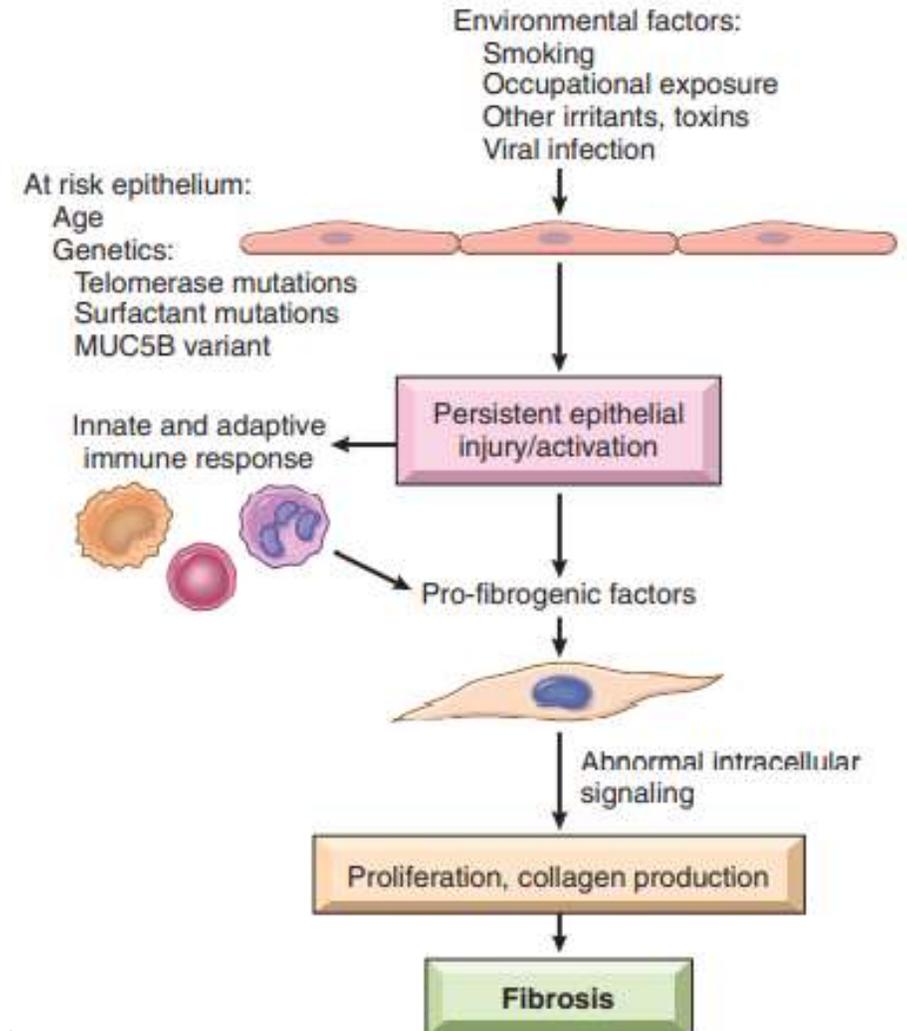
1. Idiopathic Pulmonary Fibrosis

- ▶ Idiopathic pulmonary fibrosis (IPF) refers to a pulmonary disorder of unknown etiology that is characterized by patchy, progressive bilateral interstitial fibrosis.
- ▶ it is a disease of aging, virtually never occurring before 50 years of age, mainly in males.
- ▶ The radiologic and histologic pattern of fibrosis is referred to as usual interstitial pneumonia (UIP).



Pathogenesis

► The interstitial fibrosis that characterizes IPF is believed to result from repeated injury and defective repair of alveolar epithelium, often in a genetically predisposed individual.



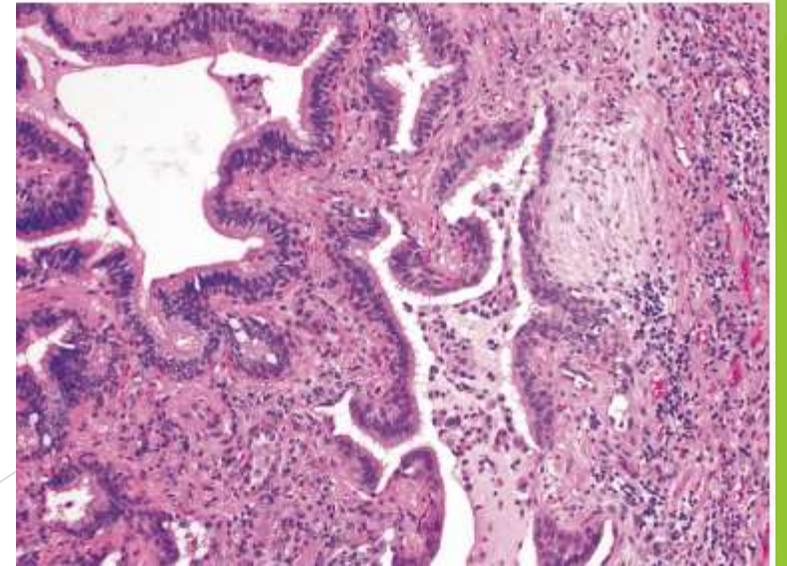
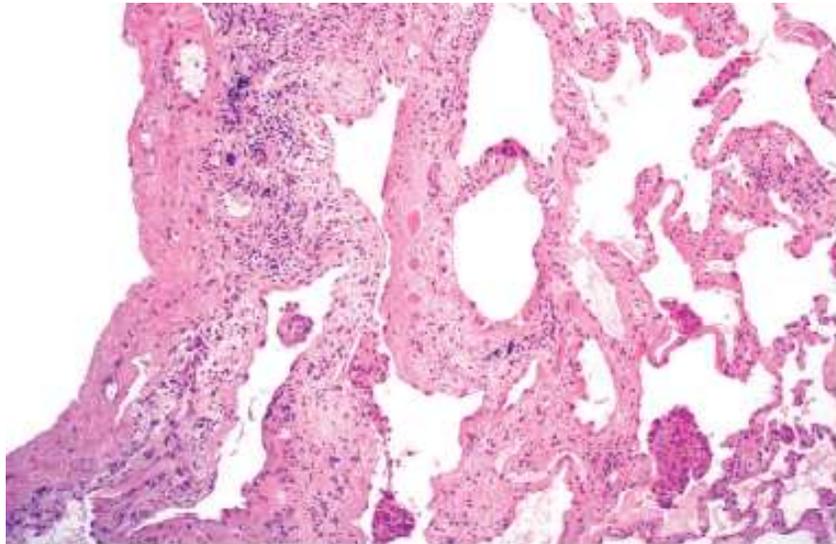
Morphology

- ▶ Grossly, the pleural surfaces of the lung are cobblestoned due to retraction of scars along the interlobular septa. The cut surface shows firm, rubbery white areas of fibrosis.



Histologically, the hallmark is patchy interstitial fibrosis.

- ▶ The earliest lesions demonstrate exuberant fibroblastic proliferation (fibroblastic foci) ,Over time these areas become more collagenous and less cellular.
- ▶ The dense fibrosis causes collapse of alveolar walls and formation of cystic spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium (honeycomb fibrosis).
- ▶ The interstitial inflammation usually is patchy and consists of an alveolar septal infiltrate of mostly lymphocytes and occasional plasma cells



Clinical Features

- ▶ gradual onset of a nonproductive cough and progressive dyspnea.
- ▶ Cyanosis, cor pulmonale, and peripheral edema may develop in later stages of the disease.
- ▶ Radiology: (subpleural and basilar fibrosis, reticular abnormalities, and “honeycombing”) often are diagnostic.
- ▶ Treatment:
 - Anti-inflammatory therapies .
 - anti-fibrotic therapies

2. Pneumoconioses

- ▶ lung disorders caused by inhalation of mineral dusts.
 - ▶ The mineral dust pneumoconioses—the three most common of which are caused by inhalation of :
 - ▶ coal dust.
 - ▶ Silica.
 - ▶ asbestos.
- stem from exposure in the workplace



Table 13.3 Mineral Dust–Induced Lung Disease

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

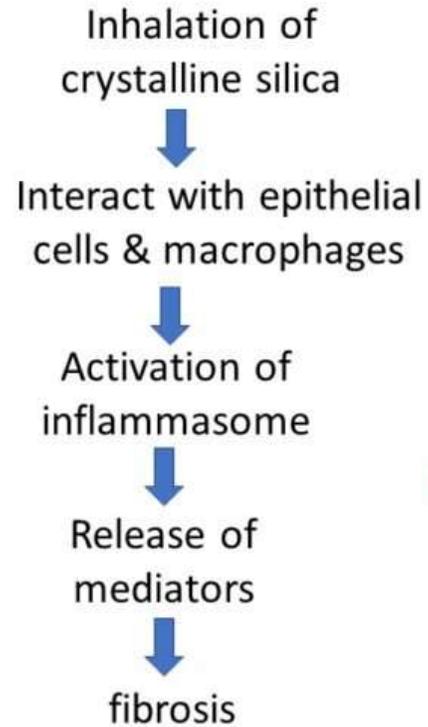
Pathogenesis

- ▶ **The reaction of the lung to mineral dusts depends on many variables, including:**
 - ✓ **size.**
 - ✓ **Shape.**
 - ✓ **solubility.**
 - ✓ **reactivity of the particles.**

- ✓ **Tobacco smoking worsens the effects of all inhaled mineral dusts, more so with asbestos than other particles.**

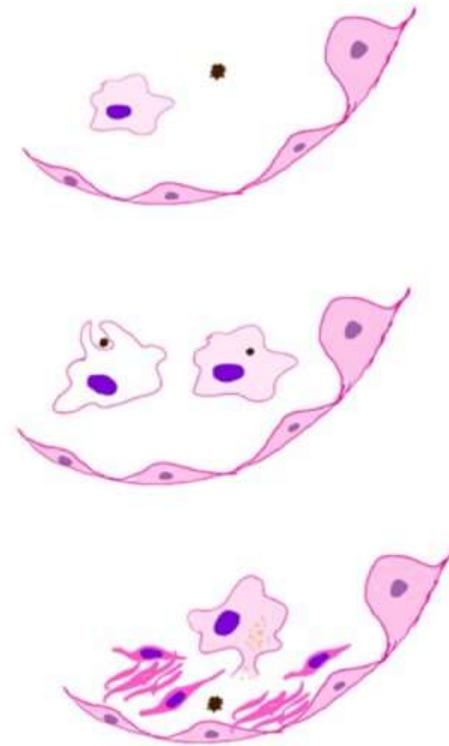
✓The pulmonary alveolar macrophage is a key cellular element in the initiation and perpetuation of inflammation, lung injury and fibrosis.

PATHOGENESIS



@VijayPatho

IL-1, IL-18 TNF,
fibronectin,
lipid mediators,
oxygen-derived free
radicals, and
fibrogenic cytokines



A. Coal Worker's Pneumoconiosis

- ▶ The spectrum of lung findings in coal workers is wide, ranging from :
 - ❖ asymptomatic anthracosis, in which pigment deposits without a perceptible cellular reaction.
 - ❖ simple coal worker's pneumoconiosis (CWP), in which macrophages accumulate with little to no pulmonary dysfunction.
 - ❖ complicated CWP or progressive massive fibrosis (PMF), in which fibrosis is extensive and lung function is compromised

Asymptomatic anthracosis



Simple CWP with little to no pulmonary dysfunction



Complicated CWP, or progressive massive fibrosis (PMF), in which lung function is compromised



▶ Pulmonary anthracosis:

❖ inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue along the pulmonary and pleural lymphatics and in draining lymph nodes.

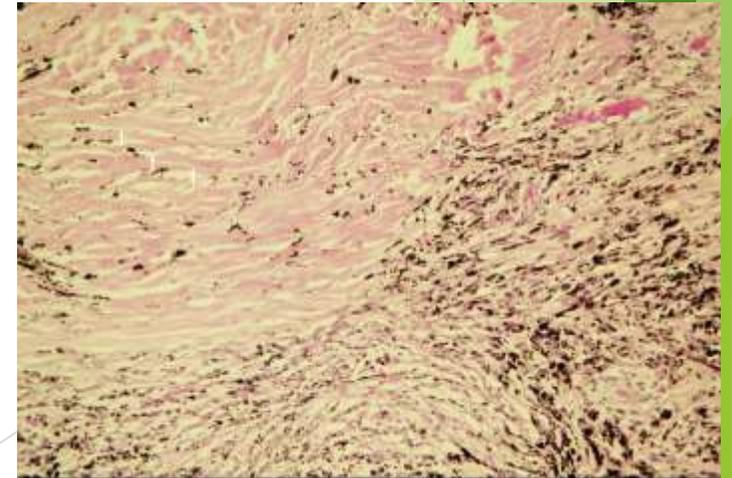
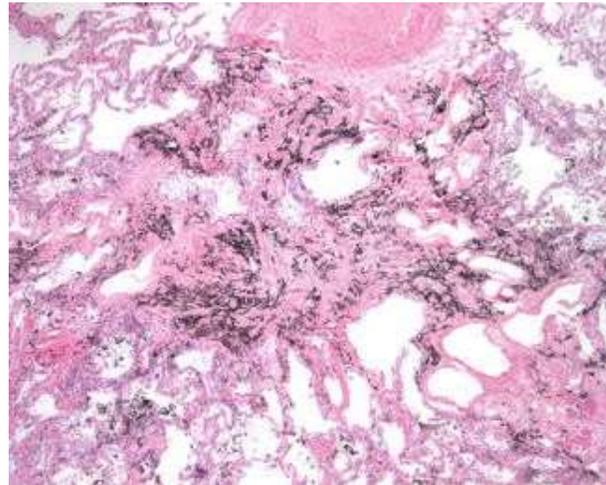
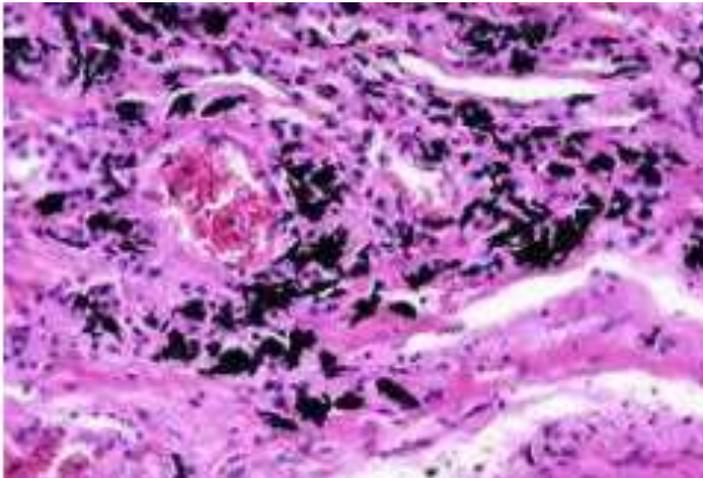
▶ Simple CWP is characterized by the presence of :

❖ coal macules: consists of dust-laden macrophages and small amounts of collagen fibers .

❖ larger coal nodules:

▶ Complicated CWP (PMF) :

❖ Caused by coalescence of coal nodules. consist of dense collagen and pigment



Clinical Features

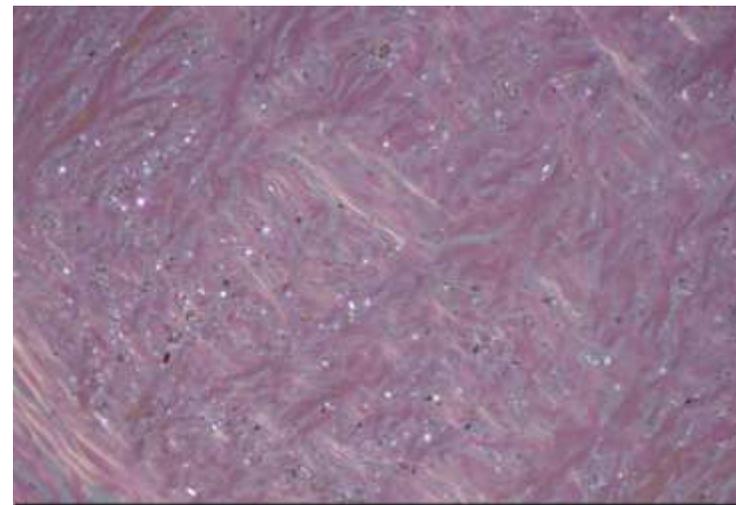
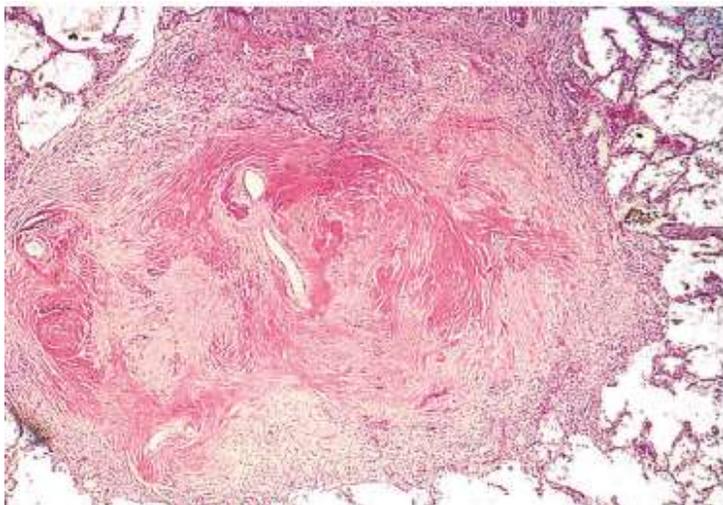
- ▶ CWP usually is a benign disease that produces little defect in lung function.
- ▶ If PMF develops, there is increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale.
- ▶ there is no increased frequency of lung carcinoma in coal miners, a feature that distinguishes CWP from both silica and asbestos exposures

B. Silicosis

- ▶ **Silicosis is currently the most prevalent chronic occupational disease in the world.**
- ▶
- ▶ **It is caused by inhalation of crystalline silica, mostly in occupational settings.**
- ▶ **Silica occurs in both crystalline and amorphous forms, but crystalline forms (including quartz) are by far the most toxic and fibrogenic**

MORPHOLOGY

- ▶ Silicotic nodules in their early stages are tiny, barely palpable, discrete, pale-to-black (if coal dust is present) nodules in the upper zones of the lungs.
- ▶ Microscopically:
 - ❖ the silicotic nodule demonstrates concentrically arranged hyalinized collagen fibers surrounding an amorphous center.
 - ❖ The “whorled” appearance of the collagen fibers is quite distinctive for silicosis.
 - ❖ Examination of the nodules by polarized microscopy reveals weakly birefringent silica particles.



Clinical Features

- ▶ Silicosis usually is detected in asymptomatic workers on routine chest radiographs, which typically show a fine nodularity in the upper zones of the lung.
- ▶ Most patients do not develop shortness of breath until late in the course.
- ▶ patients with PMF develop pulmonary hypertension and cor pulmonale as a result of chronic hypoxia-induced vasoconstriction and parenchymal destruction.
- ▶ Silicosis is associated with an increased susceptibility to tuberculosis

c. Asbestosis and Asbestos-Related Diseases

- ▶ Asbestos is a family of crystalline hydrated silicates with a fibrous geometry. On the basis of epidemiologic studies.
- occupational exposure to asbestos is linked to:
 - ❖ parenchymal interstitial fibrosis (asbestosis).
 - ❖ localized fibrous plaques.
 - ❖ pleural effusions.
 - ❖ lung carcinoma.
 - ❖ malignant pleural and peritoneal mesothelioma.
 - ❖ laryngeal carcinoma.

Pathogenesis

- ▶ As with silica crystals, once phagocytosed by macrophages.
 - ▶ asbestos fibers activate the inflammasome.
 - ▶ damage phagolysosomal membranes.
- ▶ stimulating the release of proinflammatory factors and fibrogenic mediators.

MORPHOLOGY

▶ Asbestosis is marked by diffuse pulmonary interstitial fibrosis, characterized by the presence of asbestos bodies, which are seen as golden brown, fusiform or beaded rods with a translucent center.

▶ Asbestos bodies apparently are formed when macrophages attempt to phagocytose asbestos fibers; the iron “crust” is derived from phagocyte ferritin.

▶ asbestosis begins in the lower lobes and subpleurally, spreading to the middle and upper lobes of the lungs as the fibrosis progresses.

▶ Contraction of the fibrous tissue distorts the normal architecture, creating enlarged air spaces enclosed within thick fibrous walls; eventually, the affected regions become honeycombed



- ▶ Pleural plaques are the most common manifestation of asbestos exposure and are well-circumscribed plaques of dense collagen often containing calcium.



Clinical Features

- ▶ Progressively worsening dyspnea appears 10 to 20 years after exposure.
- ▶ cough and production of sputum.
- ▶ The disease may remain static or progress to congestive heart failure, cor pulmonale, and death.
- ▶ Both lung carcinoma and malignant mesothelioma develop in workers exposed to asbestos

II. Granulomatous Diseases

Sarcoidosis

- ▶ Sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granulomatous inflammation in many tissues and organs.
- ▶ can manifest in many different ways:
 - ❖ bilateral hilar lymphadenopathy or lung involvement (or both), visible on chest radiographs, is the major finding at presentation in most cases.
 - ❖ Eye and skin involvement each occurs in about 25%

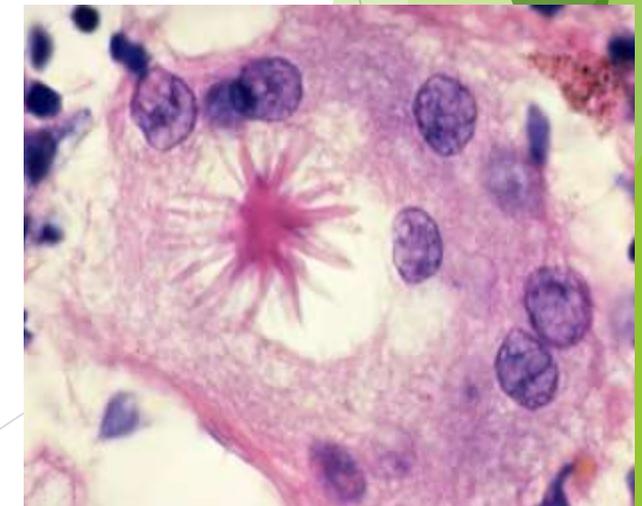
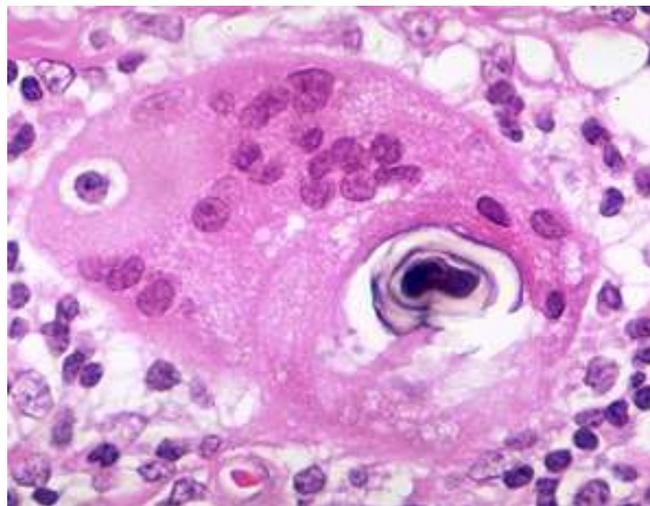
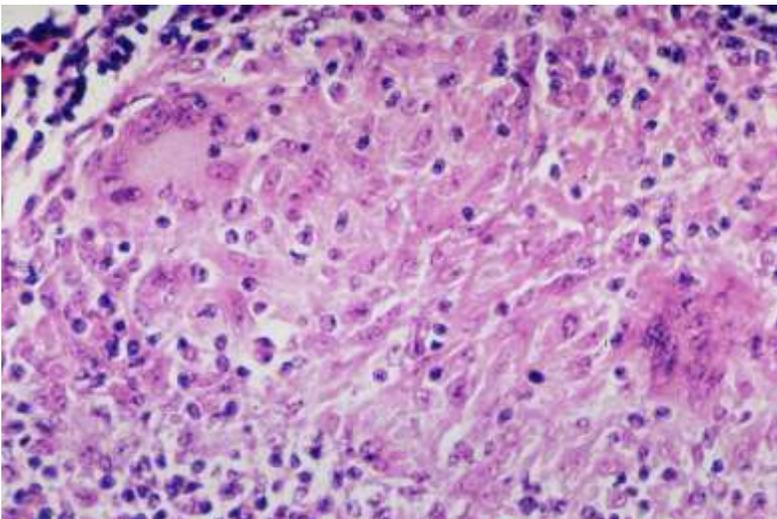
Etiology and Pathogenesis

- ▶ it is a disease of disordered immune regulation in genetically predisposed individuals exposed to certain environmental agents.
- ▶ Several immunologic abnormalities in sarcoidosis suggest the development of a cell-mediated response to an unidentified antigen. The process is driven by CD4+ helper T cells:....clues:
 - ▶ Intraalveolar and interstitial accumulation of CD4+ TH1 cells, with peripheral T cell cytopenia.
 - ▶ Increases in TH1 cytokines such as IL-2 and IFN- γ , resulting in T cell proliferation and macrophage activation, respectively.

- ▶ Increases in several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein-1 α) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas.
- ▶ Anergy to common skin test antigens such as Candida or purified protein derivative (PPD).
- ▶ Polyclonal hypergammaglobulinemia.
- ▶ Familial and racial clustering of cases, suggesting the involvement of genetic factors

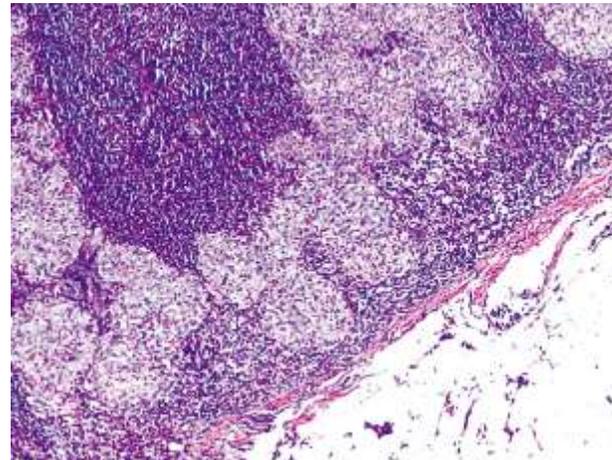
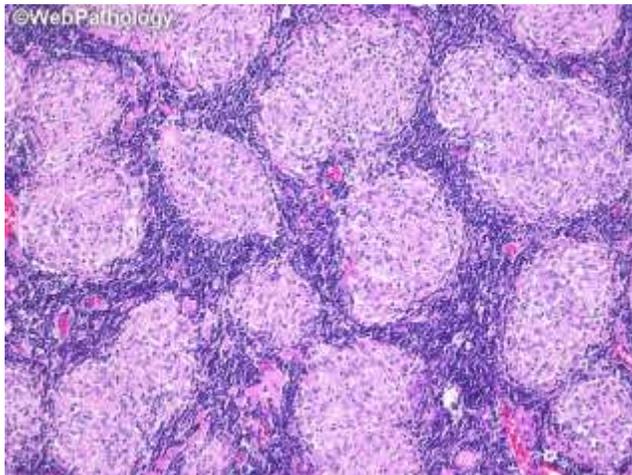
Morphology

- ▶ The cardinal histopathologic feature of sarcoidosis, irrespective of the organ involved, is the nonnecrotizing epithelioid granuloma.
- ▶ Schaumann bodies: laminated concretions composed of calcium and proteins.
- ▶ asteroid bodies: stellate inclusions enclosed within giant cells



Which organs?????

- ▶ 1. lung:
 - ❖ The granulomas predominantly involve the interstitium rather than air spaces,
 - ❖ The bronchoalveolar lavage fluid contains abundant CD4+ T cells.
 - ❖ The granulomas eventually are replaced by diffuse interstitial fibrosis, resulting in a so-called “honeycomb lung”.
- 2. Intrathoracic hilar and paratracheal lymph nodes:
 - ❖ They are enlarged, painless and have a firm, rubbery texture.



▶ 3. skin:

- ❖ Erythema nodosum, the hallmark of acute sarcoidosis, consists of raised, red, tender nodules on the anterior aspects of the legs.

▶ 4. eye and lacrimal glands:

- ❖ optic nerve involvement and total vision loss.
- ❖ Unilateral or bilateral parotitis with painful enlargement of the parotid glands.

- ❖ 5. spleen, liver and bone marrow.



Clinical Features

- ▶ asymptomatic, discovered on routine chest films as bilateral hilar adenopathy or as an incidental finding at autopsy.
- ▶ peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly.
- ▶ respiratory symptoms (shortness of breath, dry cough, or vague substernal discomfort).
- ▶ definitive diagnostic test for sarcoidosis does not exist, and establishing a diagnosis requires the presence of clinical and radiologic findings.
- ▶ Sarcoidosis follows an unpredictable course characterized by either progressive chronicity or periods of activity interspersed with remissions