Chronic diffuse interstitial lung disease CILD (Restrictive lung disease)

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Chronic interstitial lung disease

- A heterogeneous group of disorders

Why these are considered as a group?

- There are similarities in

    Symptoms and clinical signs

    Radiographic changes

    Pathophysiologic changes

Objectives

At the end of this lecture you should be able to

- List the causes and briefly describe the pathogenesis of chronic interstitial lung disease
- Describe the pathological changes in idiopathic pulmonary fibrosis
- List the causes of occupational lung diseases
- Describe the pathology of lung related to coal dust , silica and asbestos

Chronic interstitial lung disease

- Characteristic features

  - Chronic disorders

  - Bilateral and patchy involvement of lungs

  - Involves the most peripheral and delicate interstitium

    in the alveolar walls

Chronic interstitial lung disease

- The hall mark feature : **Reduced compliance of lungs**

  Lungs are stiff due to fibrosis

  - Needs increased effort to expand lungs causing **dyspnoea**

- Damage to the alveolar epithelium and the interstitial vasculature

  results in ventilation - perfusion mismatch causing **hypoxia**

- Later may develop **respiratory failure** often associated with

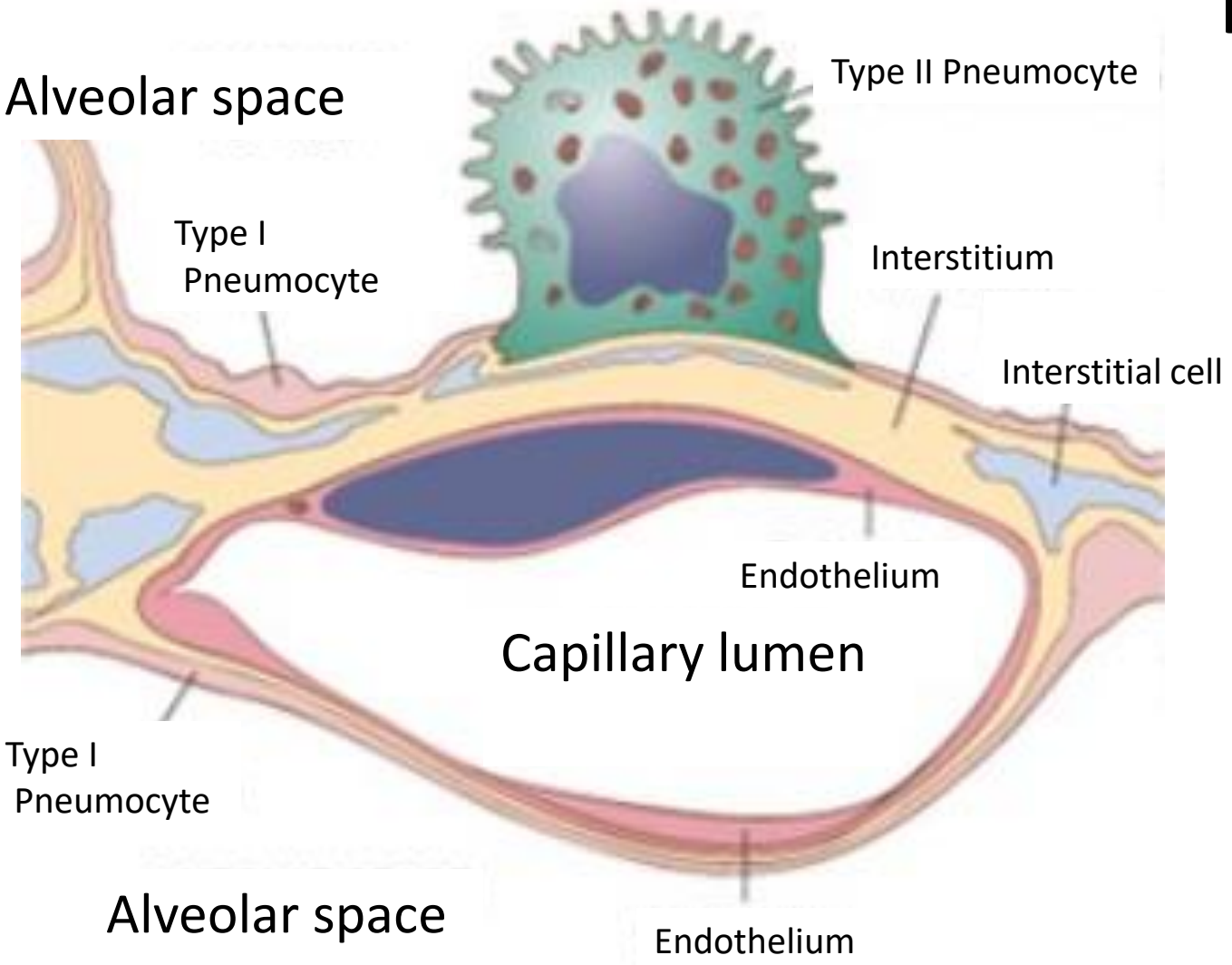
  cor pulmonale and **pulmonary hypertension**

Categories of CILD

: according to **clinicopathological features** and characteristic **histological features**

Fibrosing
Usual interstitial pneumonia - UIP (Idiopathic pulmonary fibrosis - IPF)
Nonspecific interstitial pneumonia
Cryptogenic interstitial pneumonia
Associated with collagen vascular disease
Pneumoconiosis
Associated with therapies (drugs, radiation)
Smoking related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Leoffler syndrome
Drug allergy related
Idiopathic chronic eosinophilic pneumonia



Pulmonary interstitium

- Basement membranes of
  Endothelium
  Epithelial cells
  - fused in the thinnest areas
- Collagen fibres
- Elastic fibres
- Fibroblasts
- Few mast cells
- Occasional mononuclear cells

IPF / Cryptogenic fibrosing alveolitis (CFA)

- Aetiology ?
- Patchy, progressive bilateral interstitial fibrosis
- UIP - Radiologic and histologic pattern of fibrosis

    - This feature is needed for the diagnosis of IPF

- Known causes with similar pathological changes, eg. asbestosis, collagen vascular diseases etc. should be excluded

IPF/CFA - Pathogenesis

Unidentified agent

↓

Repeated epithelial injury/activation

↓

TGF beta 1 released from injured type 1 pneumocytes

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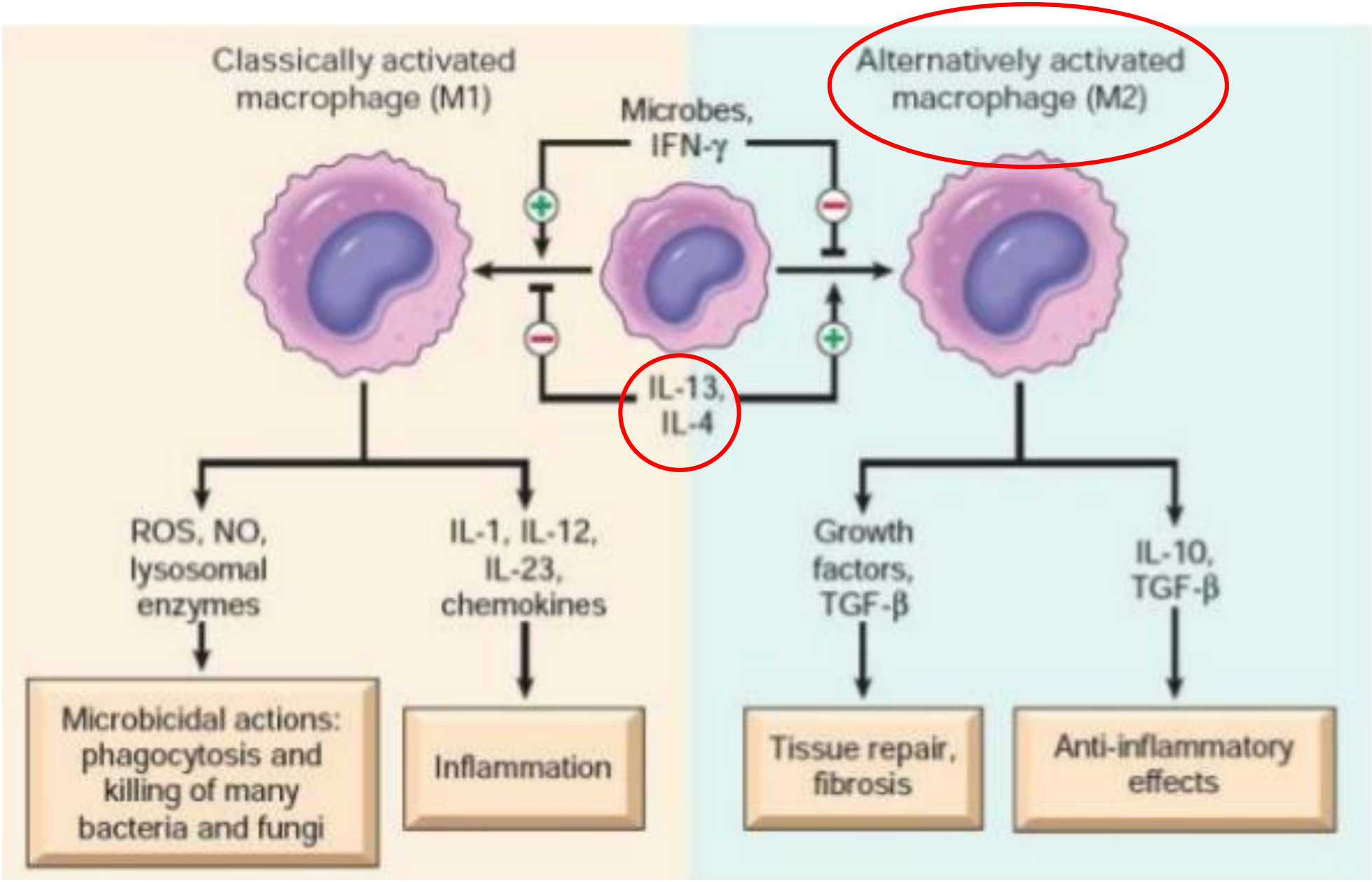
Proliferation and transformation of fibroblasts into myofibroblasts

↓

Excessive and continuing deposition of collagen and extracellular matrix

↓

Pulmonary fibrosis


Classically activated macrophage (M1)
Alternatively activated macrophage (M2)
Microbes, IFN-γ
IL-13, IL-4
ROS, NO, lysosomal enzymes
IL-1, IL-12, IL-23, chemokines
Growth factors, TGF-β
IL-10, TGF-β
Microbicidal actions: phagocytosis and killing of many bacteria and fungi
Inflammation
Tissue repair, fibrosis
Anti-inflammatory effects

IPF/CFA - Morphology

- What is the characteristic change that you expect to see?

  Fibrosis

- What is the pattern of fibrosis

  Radiologically - UIP

  Histological hall mark of UIP

  - Patchy interstitial fibrosis of varying intensity worsens with time

IPF/CFA - Morphology

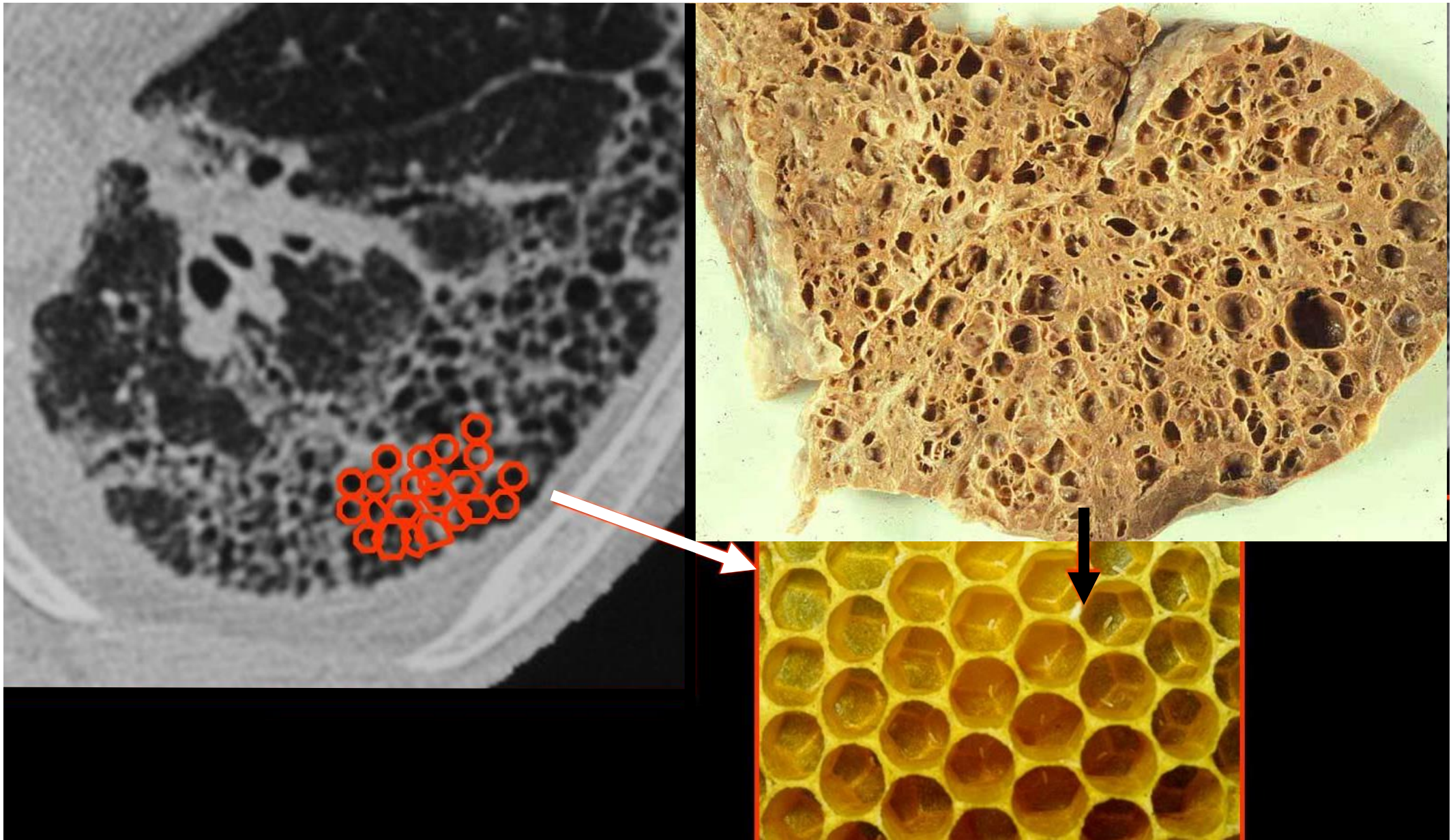
- In advanced forms

  - There is fibrosis , scarring and destruction of the lung tissue,

    resulting in “end-stage / honey comb lung”

- Difficult to differentiate different conditions at this stage

Honeycomb lung



IPF/CFA – Macroscopy of the lung

Pleural surface of the lungs: “cobblestone appearance”

-Due to retraction of the scars along the interlobular septae

Cut surface: firm , rubbery , white areas due to fibrosis

-Predominantly in lower lobes and subpleural regions and interlobular septae

A. Pleural surfaces of the lungs

B. Cut surfaces of the lungs

What are the pathological changes you observe?

IPF/CFA - Macroscopy

- Pleural surface of the lungs: “cobblestone appearance”

- Due to retraction of the scars along the interlobular septae

- Cut surface of the lungs: firm , rubbery , white areas due to fibrosis

- Predominantly in lower lobes and subpleural regions and interlobular septae

- The pattern of fibrosis : UIP

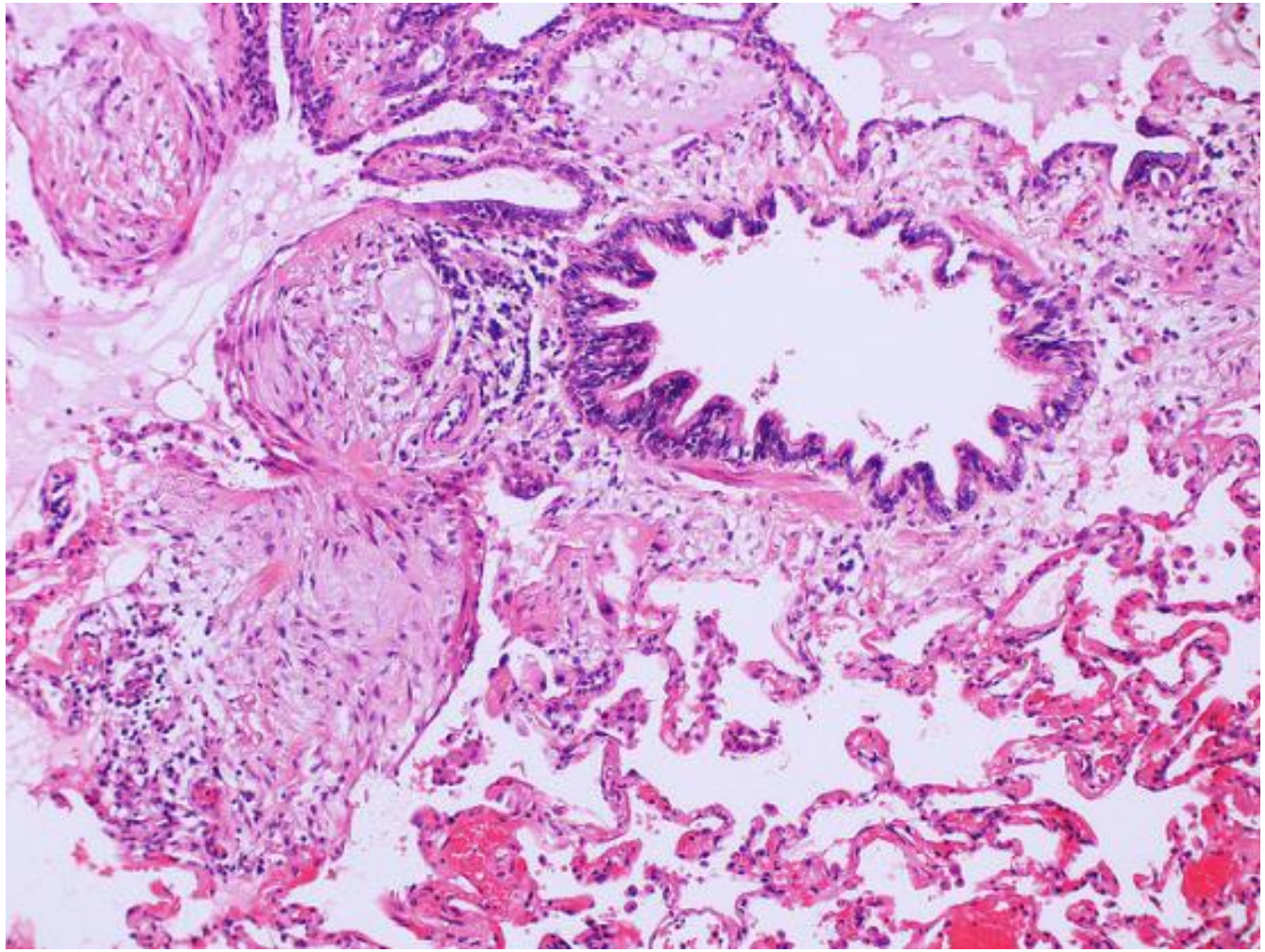
IPF/ CFA - Microscopy

- Histological hallmark of UIP : Patchy interstitial fibrosis of varying intensity worsens with time

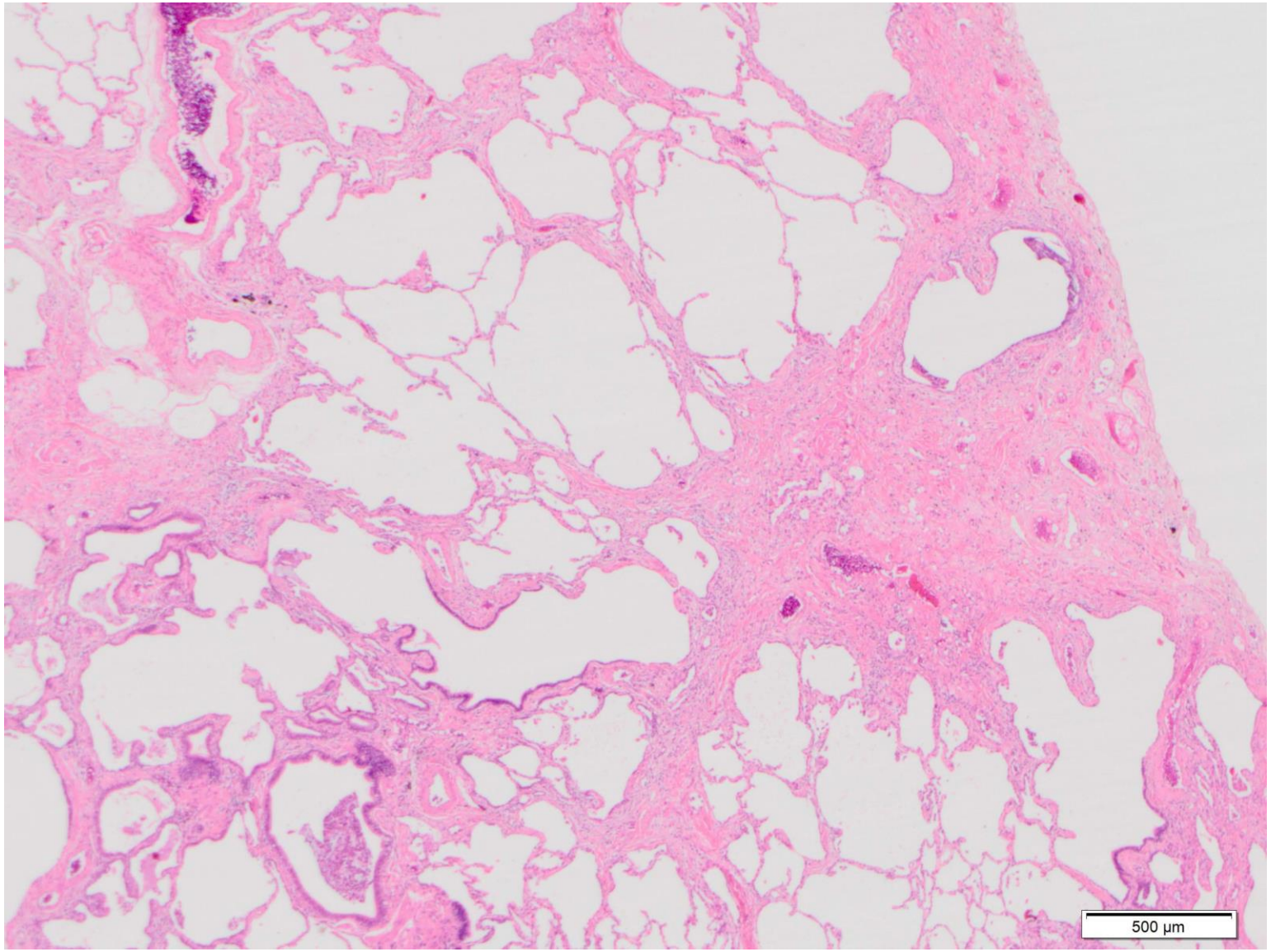
- Early lesions : Fibroblastic foci with marked fibroblastic proliferation
- Late lesions : More collagenous and less cellular
- “temporal heterogeneity” - Both early and late lesions occur together
- Dense fibrosis results in collapse of alveolar septae forming cystic spaces lined by hyperplastic type 2 pneumocytes or bronchiolar epithelium

  - “honeycomb fibrosis”

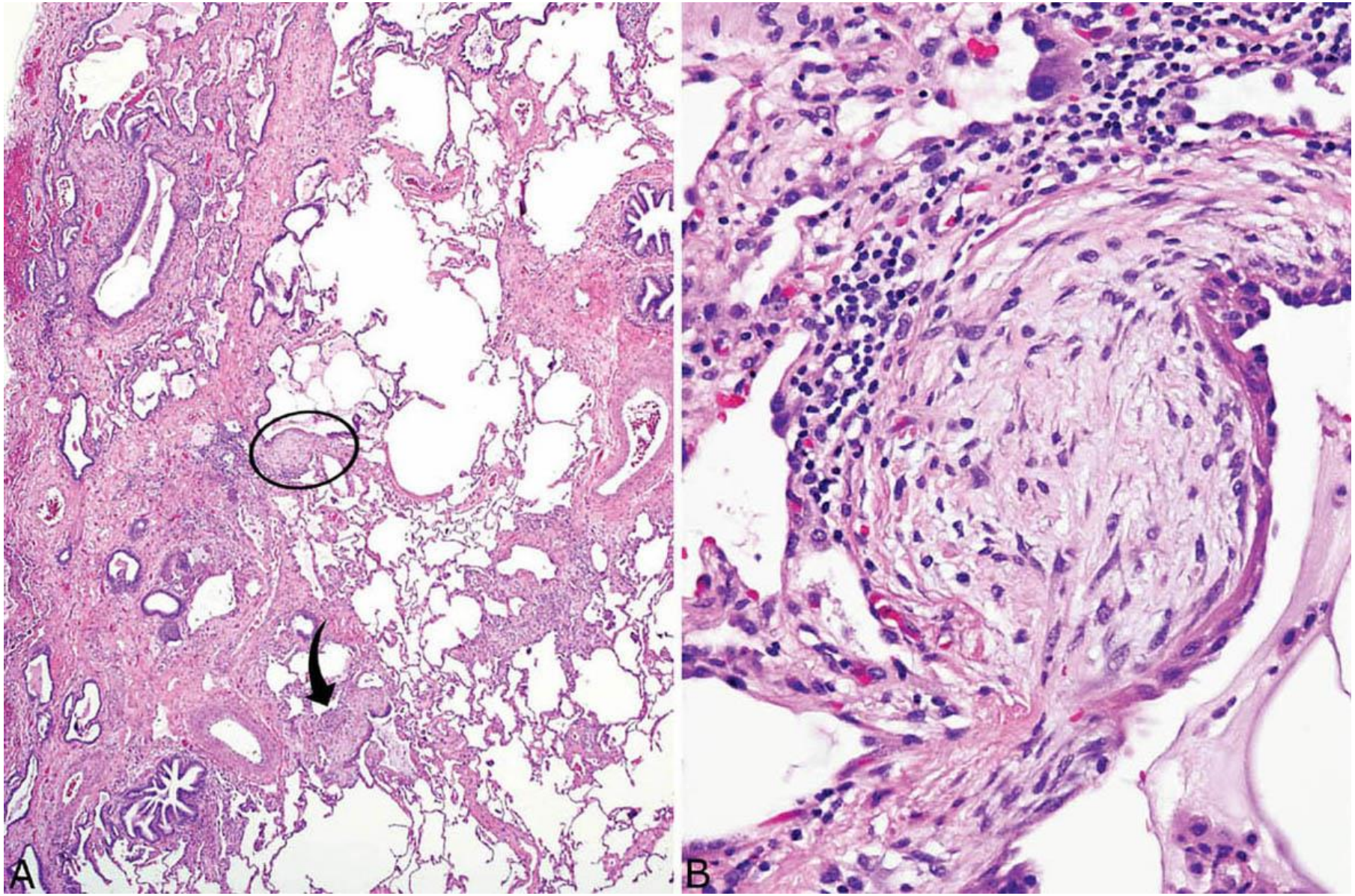
Fibroblastic foci



Honey comb lung



Fibroblastic foci in honeycomb lung



IPF/ CFA - Microscopy

- Patchy interstitial inflammation

  - Alveolar septae infiltrated predominantly by lymphocytes

    occasionally plasma cells , mast cells and eosinophils are present

- Later stages: Secondary pulmonary hypertensive changes in blood vessels

Major categories of CILD

Fibrosing	Granulomatous
Usual interstitial pneumonia (Idiopathic pulmonary fibrosis)	Sarcoidosis
Nonspecific interstitial pneumonia	Hypersensitivity pneumonia
Cryptogenic interstitial pneumonia	**Eosinophilic**
Associated with collagen vascular disease	Leoffler syndrome
Pneumoconiosis	Drug allergy related
Associated with therapies (drugs, radiation)	Idiopathic chronic eosinophilic pneumonia
Smoking related	
Desquamative interstitial pneumonia	
Respiratory bronchiolitis	

List the possible pulmonary changes that can occur in collagen vascular diseases

Pneumoconeosis

- Non-neoplastic lung diseases induced by

    - mineral dusts

    - organic and inorganic particles

    - chemical fume and vapour

Mineral dust pneumoconiosis : coal dust, silica, asbestos

Pneumoconeosis - Pathogenesis

- Variable factors decide the reaction of the lung to mineral dust

  Size, shape, solubility and reactivity of the particles

  eg. size: 1 to 5 micrometers , lodged at the bifurcation of distal airway

  coal dust - less reactive , large amounts must be deposited

  silica, asbestos, beryllium - more reactive , even lower

  concentrations result in fibrotic reactions

  amphibole form of asbestose - straight , stiff and brittle

  less soluble, delivered deeper into the lung

  more reactive

Pneumoconeosis - Pathogenesis

- Entrapped particles are engulfed by pulmonary alveolar macrophages
- These particles activate the macrophage and induce production of IL-1 and trigger inflammation
- More reactive particles trigger macrophages to release mediators that initiate fibroblast proliferation and collagen deposition
- Some particles reach the lymphatics and initiate an immune response

  - amplify and extend the local reaction

- Tobacco smoking worsens the effects of all inhaled mineral dusts

Coal worker’s pneumoconiosis (CWP)

Different lung pathologies: Anthracosis, simple CWP, complicated CWP

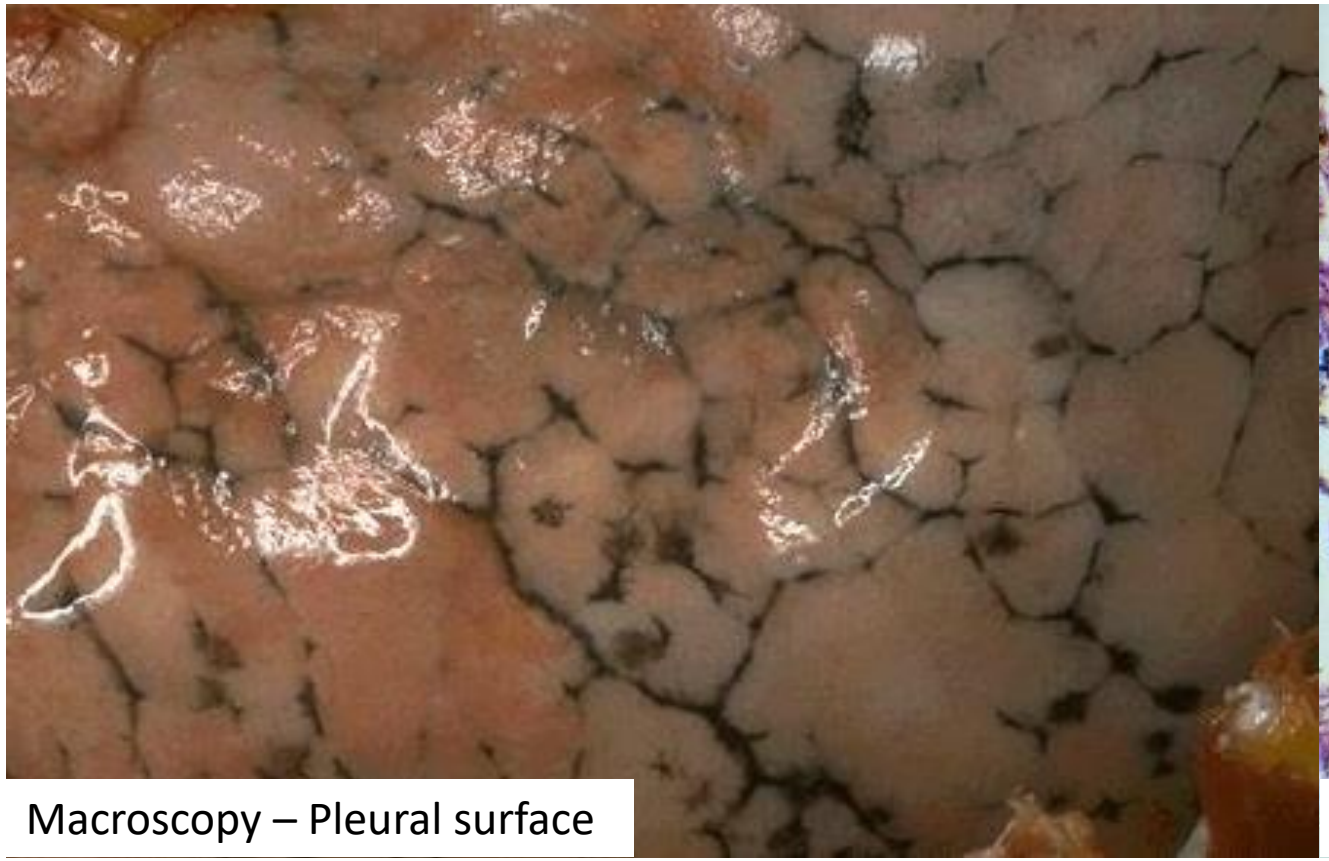
- Anthracosis - asymptomatic

  - In all urban dwellers and tobacco smokers

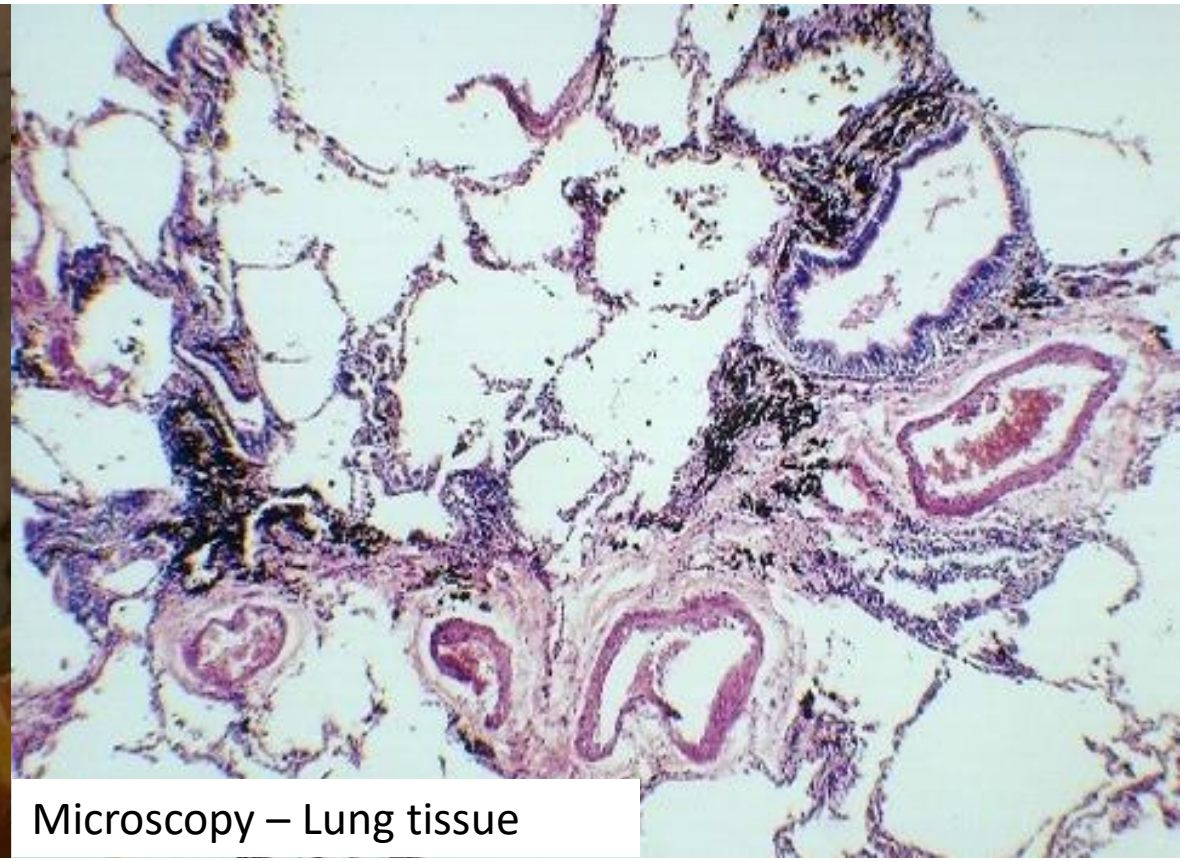
  - Pigment is engulfed by macrophages and accumulates in the connective tissue, along the pleural lymphatics and in lymph nodes

  - There is no significant cellular reaction

Anthracosis



Macroscopy – Pleural surface



Microscopy – Lung tissue

Note the black colour pigment

CWP

- Simple CWP: Coal macules and coal nodules

  - Coal macules contain pigment laden macrophages (PLM)

  - Coal nodules are larger than macules

    In addition to PLM, contain small amount of collagen fibres

    Scattered throughout the lung (ULs and upper zones of LLs are heavily involved)

CWP

- Complicated CWP / progressive massive fibrosis (PMF)

  - Occurs in the background of simple CWP

  - Coalescence of coal nodules

Macroscopy : Multiple intensely black scars , > 2 cm up to 10 cm

Microscopy: Fibrosis with deposition of dense collagen and pigment

PMF can be a complication of any of the pneumoconeosis

Silicosis

- Caused by inhalation of crystalline silica
- Which then interact with the epithelial cells
- Pulmonary macrophages engulf the particles which then get activated and release chemical mediators (IL-1, TNF, fibronectin, lipid mediators , oxygen derived free radicals and fibrogenic cytokines)

Silicosis

Early lesions : Silicotic nodules

- Macroscopy - tiny, pale to blackened nodules in the upper zones

  Microscopy - an amorphous centre surrounded by concentrically arranged hyalinized collagen fibres

  Polarized microscopy – weakly birefringent silica particles in the centre

Late stages : Hard collagenous scars , may progress to PMF

Intervening lung parenchyma - compresses or overexpanded – “honeycomb lung”

Fibrotic lesions may also occur in pleura and LNs (+/- calcification)

Asbestosis

- Two distinct forms of asbestos fibres – serpentine and amphibole

  Both can produce asbestosis, lung cancer and mesothelioma

- Pathogenesis of asbestosis

  - Like other pneumoconiosis , causes fibrosis

  - Probably function as both a tumour initiator and a promoter

  - Some oncogenic effects on mesothelioma are mediated by

    reactive free radicals

Asbestosis

- Diffuse pulmonary interstitial fibrosis

  Indistinguishable from UIP, except for the presence of **asbestos bodies**

  asbestos fibres coated with an iron- containing proteinaceous material

  (golden- brown fusiform or beaded rods with translucent centre)

- Begins in the LLs subpleurally (unlike in CWP and silicosis) later involves the middle and the upper lobes

- Contraction of the fibrous tissue distorts the normal architecture, creating enlarged air spaced surrounded by thick fibrous walls – “honey comb lung”

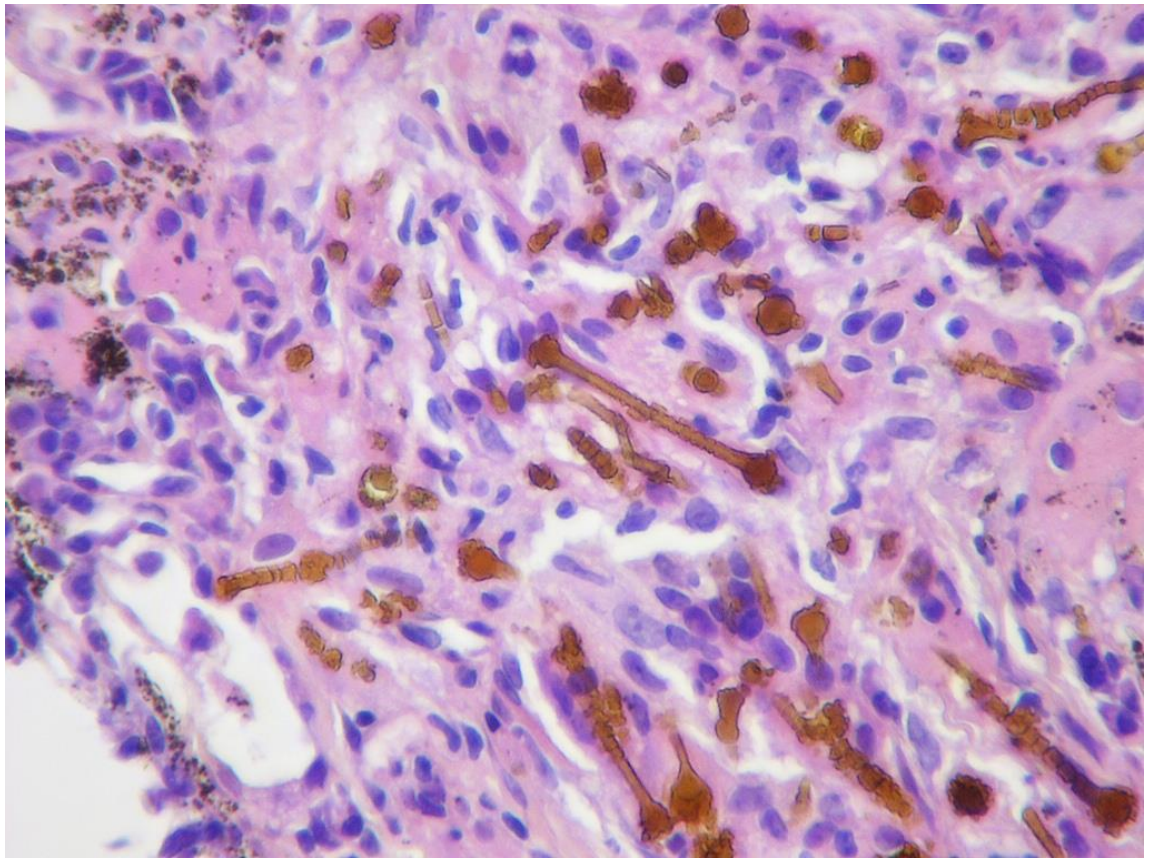
Asbestosis

- Fibrosis also develops in the visceral pleura

  Cause adhesions between the lungs and the chest wall

- Scarring may trap/narrow the pulmonary arteries and arterioles

  Results in pulmonary hypertension and cor pulmonale



Asbestos bodies

Asbestosis

Pleural plaques - Usually asymptomatic

- Anterior and posterolateral aspects of the parietal pleura and over the domes of the diaphragm
- Well circumscribed dense collagen containing calcium
- Do not contain asbestos bodies

Rarely cause pleural effusion and diffuse pleural fibrosis

Pleural plaques

Drug and radiation induced Pulmonary diseases

- Read

Granulomatous diseases

- Sarcoidosis

  - Unknown aetiology

  - Multisystem disease

    Bilateral hilar LN or lung involvement (or even both) is the major presenting manifestation in most cases

  - Eye and skin involvement may occasionally be the presenting feature

  - A disease with a higher prevalence in non-smokers

Sarcoidosis

Pathogenesis

- Disordered immune regulation (cell mediated immune reaction) in genetically predisposed individuals exposed to unidentified environmental agents

Microscopy

Non-caseating epitheioid granulomas in the interstitium of the lungs

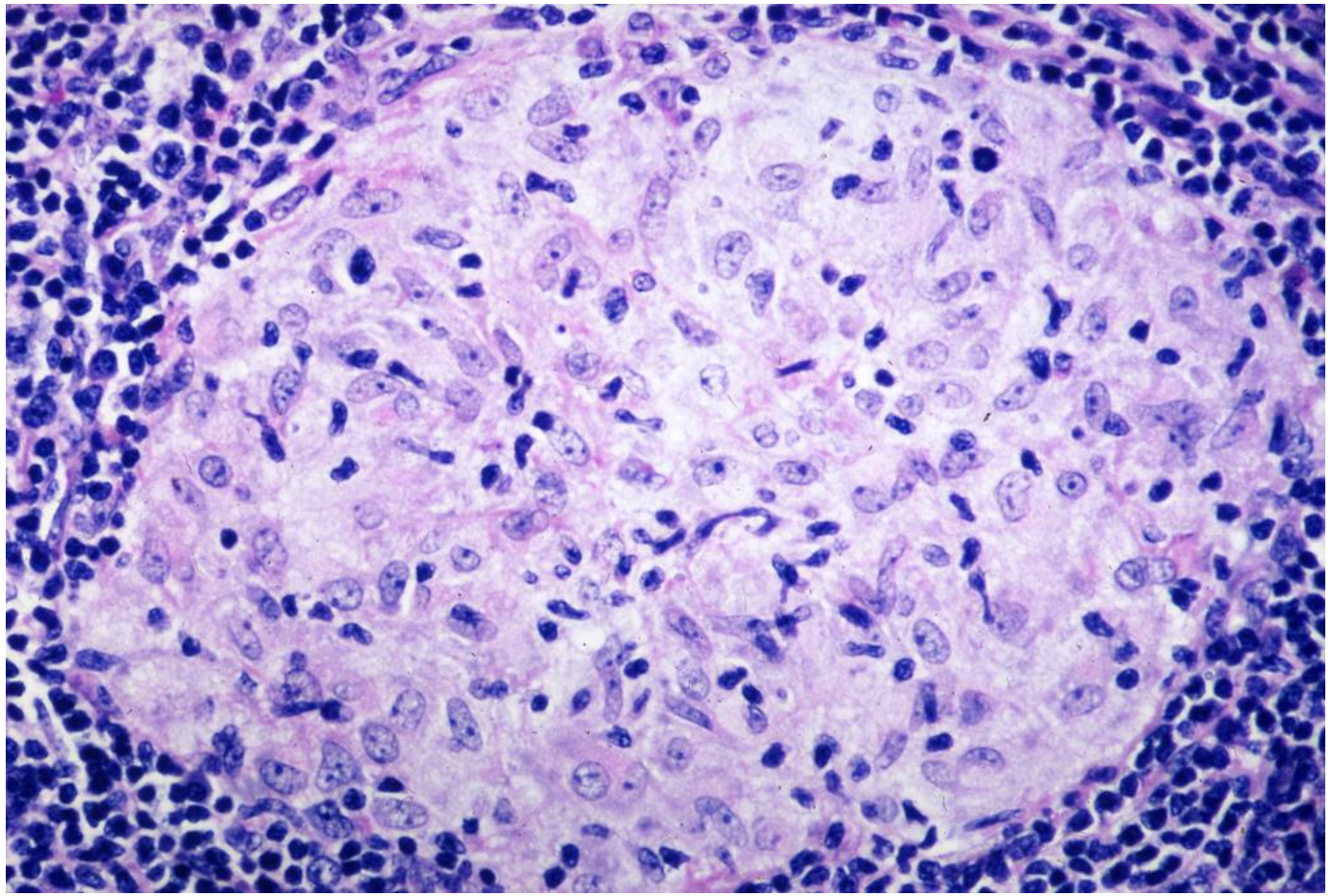
- Characteristic features are sometimes seen in granulomas

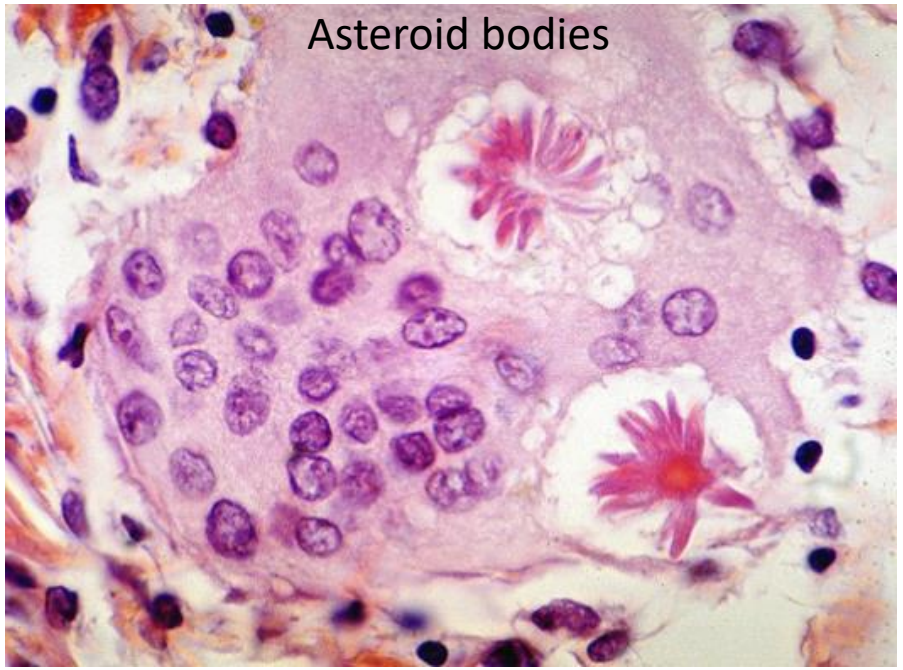
Schaumann bodies- laminated concretions of calcium and proteins

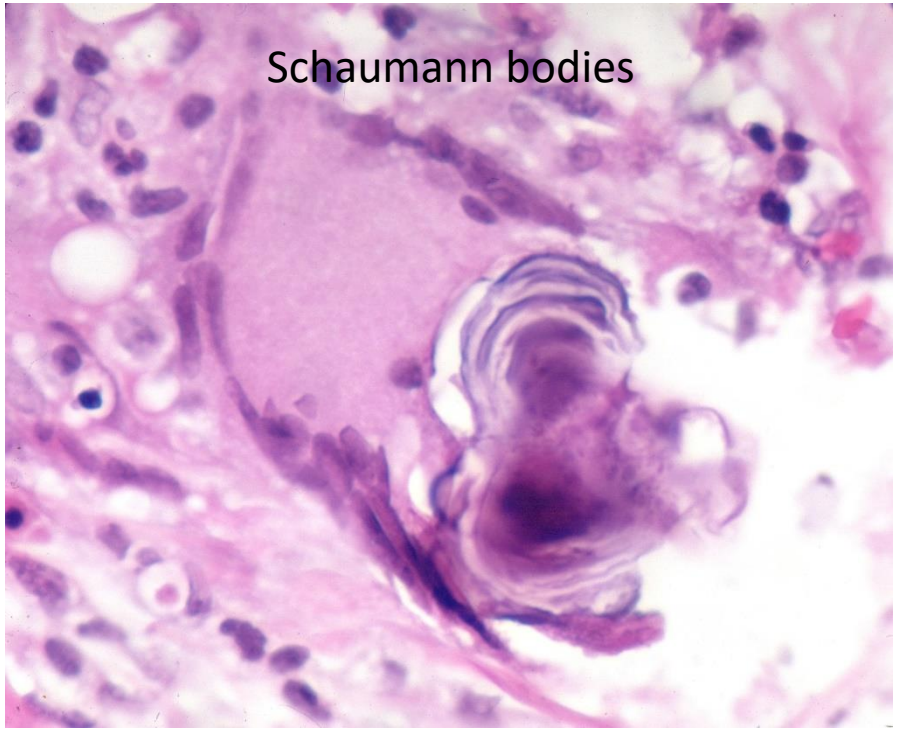
Asteroid bodies - Stellate inclusions enclosed within giant cells

However these features are not diagnostic of sarcoidosis

Sarcoid granulomas







Sarcoidosis - Microscopy

- Other causes of granulomatous inflammation should be excluded before diagnosing sarcoidosis in lung
- Granulomas predominantly involve the interstitium rather than air spaces
- Granulomas tend to localize around bronchioles, pulmonary venules and in the pleura – “lymphangitic distribution”
- Late stages : granulomas are replaced by diffuse interstitial fibrosis resulting in “honeycomb lung”

Sarcoidosis

- Hilar and paratacheal LN are enlarged in about 75% - 90 % of patients
- I/3 present with peripheral lymphadenopathy
- LNs - Painless, firm and rubbery
  - Non-matted/non-adherent
  - Do not ulcerate

Skin lesions - present in about 25% of patients

Hall mark of acute sarcoidosis – Erythema nodosum

Sarcoid granulomas are uncommon in these lesions

Discrete painless subcutaneous nodules – contain non-caseating granulomas

Sarcoidosis

Eye and lacrimal gland lesions – 1/5 – ½ of patients

Occular involvement: Iritis, iridocyclitis,

- corneal opacities, glaucoma, loss of vision

Posterior uveal tract: choroiditis, retinitis, optic nerve involvement

Inflammation in the lacrimal glands

- Suppression of lacrimation (sicca syndrome)

Parotid glands – parototis eith painful enlargement of the parotid glands

Xerostomia

Other organs - Spleen , liver (granulomas in portal tracts), bone marrow

Miculicz syndrome (read)

Other features – hypercalcaemia, hypercalciuria **(read)**

Hypersensitivity pneumonitis

- Immunologically mediated inflammatory lung disease
- Primarily affects **alveoli** (therefore also known as allergic alveolitis)

*In **bronchial asthma** the immunologically mediated injury is at the level of bronchi*

- Predominantly a restrictive type of lung disease with reduced diffusion capacity , lung compliance and total lung volume

Microscopy :Mononuclear infiltrate in pulmonary interstitium (lymphocytes, plasma cells)

Characteristic peri-bronchiolar distribution

2/3 have non-caseating granulomas

<u>Advanced stages</u> : diffuse interstitial fibrosis

List the causes hypersensitivity pneumonitis

Summary

Now you should able to

- List the causes and briefly describe the pathogenesis of chronic interstitial lung disease
- Describe the pathological changes in idiopathic pulmonary fibrosis
- List the causes of occupational lung diseases
- Describe the pathology of lung related to coal dust , silica and asbestos

Assignment

- Correlate the pathogenesis and pathological changes of these disease entities with the symptoms and signs