بسم الله الرحمن الرحيم

PATHOLOGY

FINAL | Lecture 2

Chronic Interstitial Lung Diseases (pt.2)

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﴿ وَلَقَدْ نَعْلَمُ أَنَّكَ يَضِيقُ صَدْرُكَ بِمَا يَقُولُونَ ﴿٩٧﴾ فَسَبِّحْ بِحَمْدِ رَبِّكَ وَكُن مِّنَ السَّاجِدِينَ ﴾

سبحان الله وبحمده، سبحان الله العظيم

Chronic Interstitial Lung Diseases-2

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Table 15-5 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Connective tissue disease-associated
Pneumoconiosis
Drug reactions
Radiation pneumonitis
Granulomatous
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis-associated interstitial lung disease
Other
Langerhans cell histiocytosis
Pulmonary alveolar proteinosis
Lymphoid interstitial pneumonia

Fibrosing Diseases:

- Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
- Nonspecific interstitial pneumonia
- Cryptogenic organizing pneumonia
- Connective tissue disease-associated (Discussed Later)
- Pneumoconiosis
- Drug reactions
- Radiation pneumonitis

Idiopathic pulmonary fibrosis (Usual Interstitial Pneumonia)

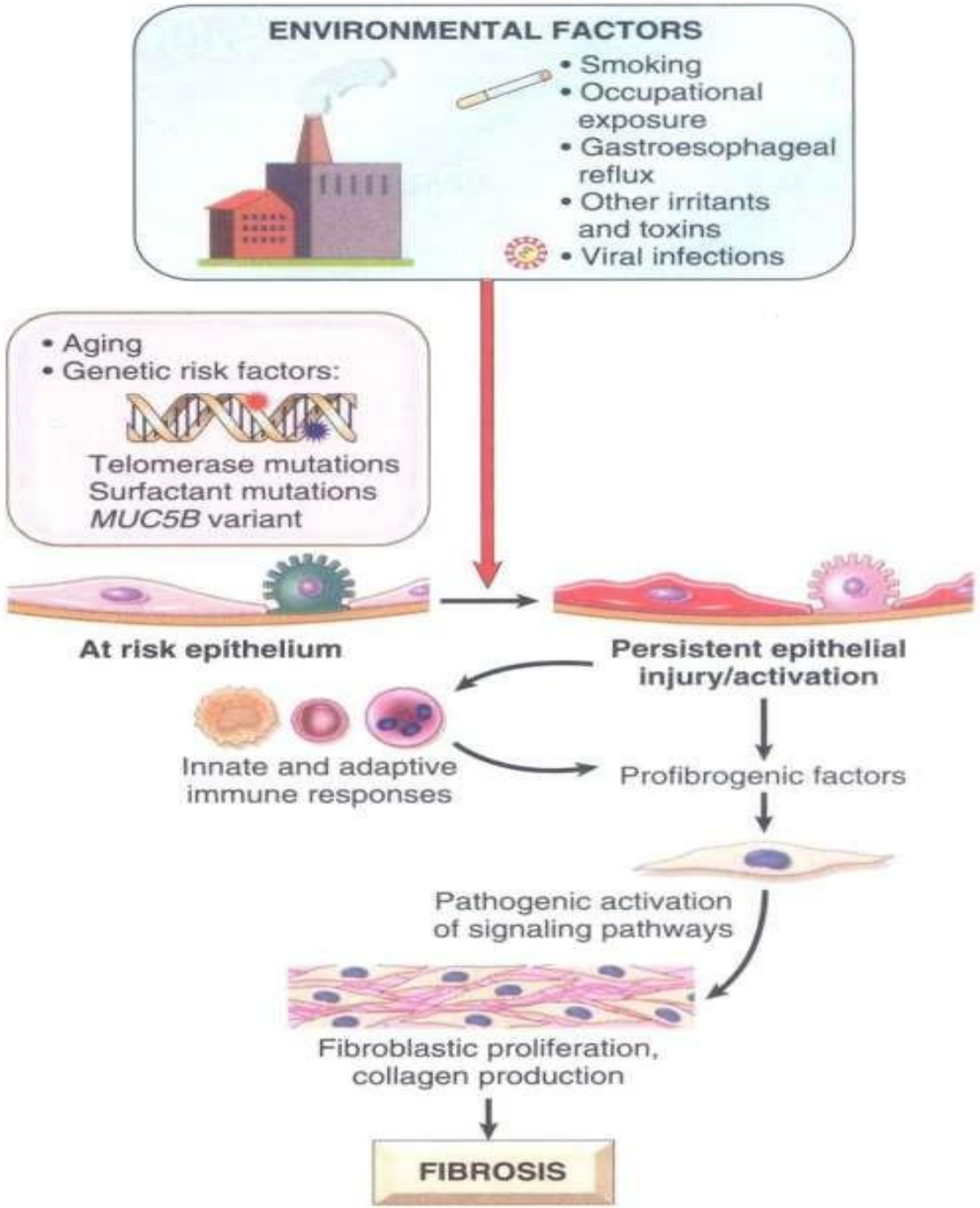
- **Unknown** etiology.
- Patchy progressive bilateral interstitial fibrosis.
- "cryptogenic Fibrosing alveolitis"
- Radiologic and histologic pattern of fibrosis (UIP pattern)
- Diagnosis of **exclusion**, which means that **all known causes of a usual interstitial pneumonia (UIP) pattern must be excluded** before **establishing the diagnosis**.
- **Males** predominant.
- **Never** occur before 50. It is a disease of aging.

UIP = Usual Interstitial Pneumonia
Underlined term is hyperlinked.

Pathogenesis

- **Repeated** injury to alveolar epithelium: Type 1 and type 2 pneumocytes.
- Defected repair mechanisms leading to fibroblastic proliferation and fibrosis.
- In **genetically predisposed** individuals.
- The cause is **obscure**.

Be sure to study this figure carefully, as the doctor went through all of its details.



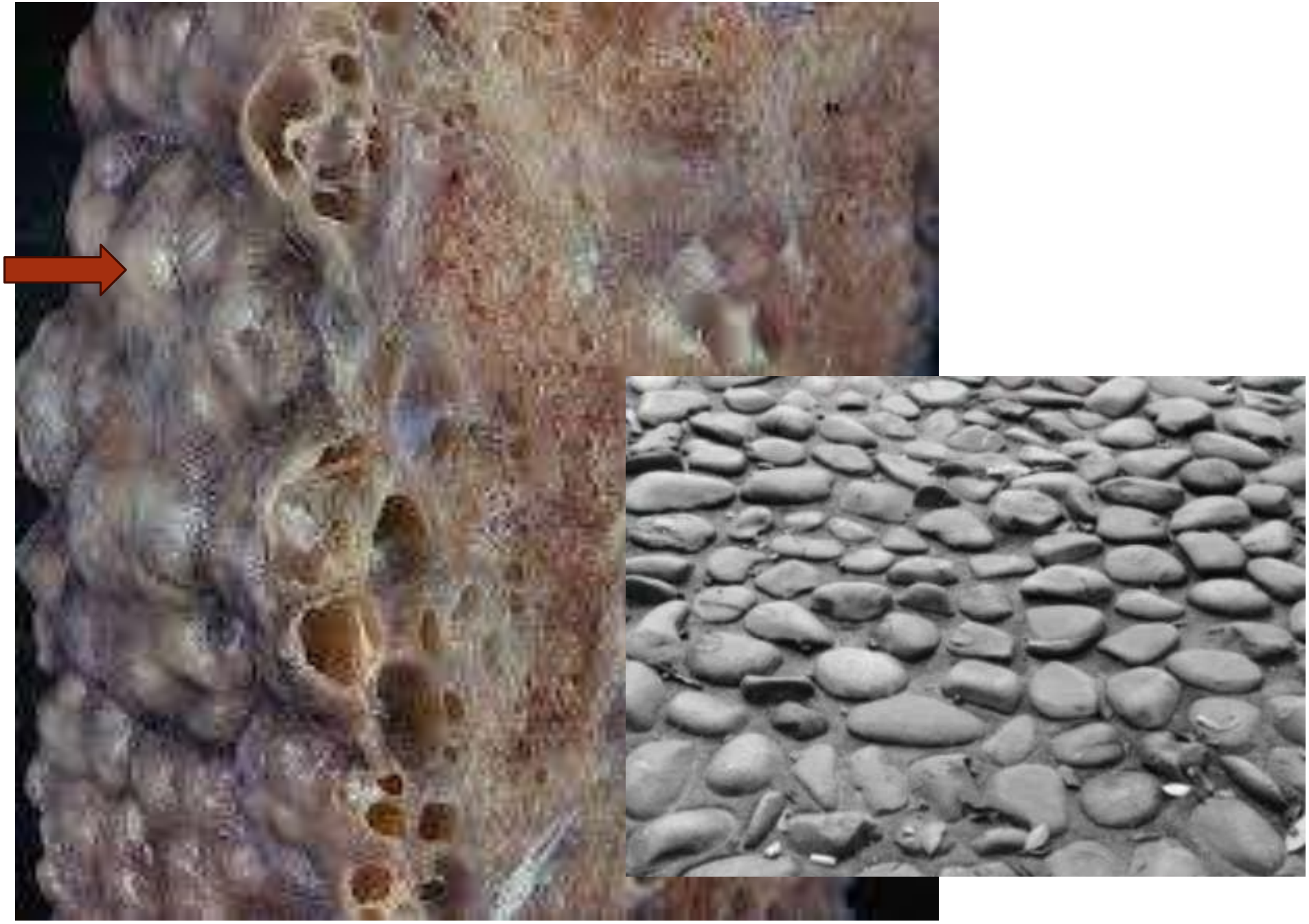
Pathogenesis of Idiopathic Pulmonary Fibrosis (IPF)

- **In genetically predisposed individuals**, exposure to **environmental risk factors** such as smoking, occupational exposures, **gastroesophageal reflux disease (GERD)**, and viral infections leads to **injury of the alveolar epithelial lining**. This injury results in **persistent and repetitive cycles of epithelial damage and abnormal repair**, triggering both **innate** and **adaptive** immune responses, which **promote the release of fibrogenic factors**. These factors cause **fibroblast activation and proliferation**, **increased collagen deposition**, and **progressive fibroblastic proliferation**, ultimately **resulting in fibrosis**.
- **The genetic factors involved include:**
  - **Germline mutations in telomerase genes**, leading to **reduced enzyme activity and cellular senescence**
  - **Mutations in MUC5B**, which **encodes mucin production**
  - **Mutations in surfactant protein genes**
- **All of these genes are expressed in the lungs**, making the **alveolar epithelium more susceptible to injury and fibrotic remodeling**.

Macroscopic Morphology

- Usually affects the subpleural area of the lung resulting in a Cobblestone appearance of pleural surface (retraction of scars along the interlobular septa)
- Cut surface shows fibrotic firm, rubbery white areas.
- Lower lobe –principally affected–, subpleural regions and along the interlobular septa are mostly affected.

Gross blips like a cobblestone appearance due to the retraction of the scars concentrated in the subpleural region

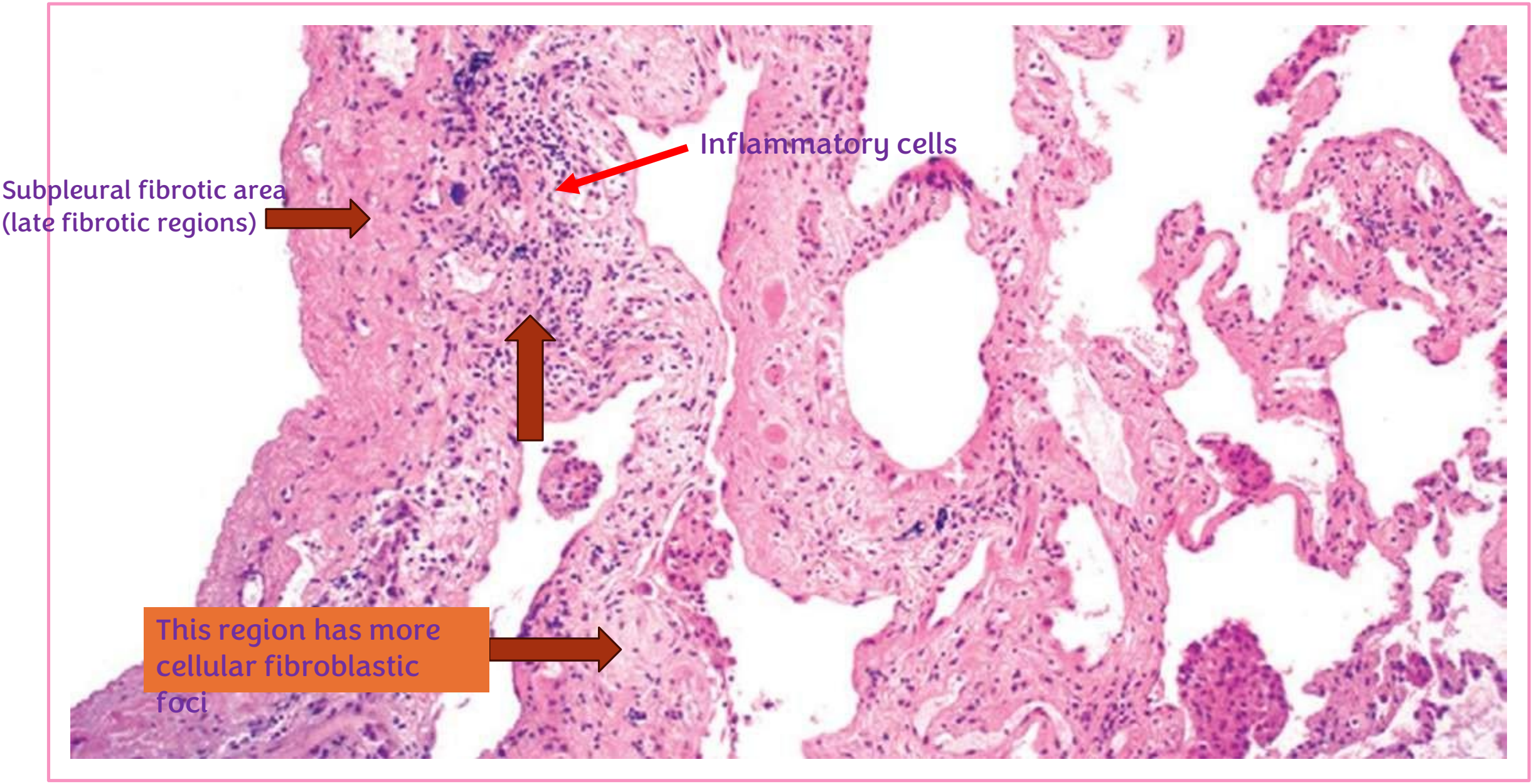


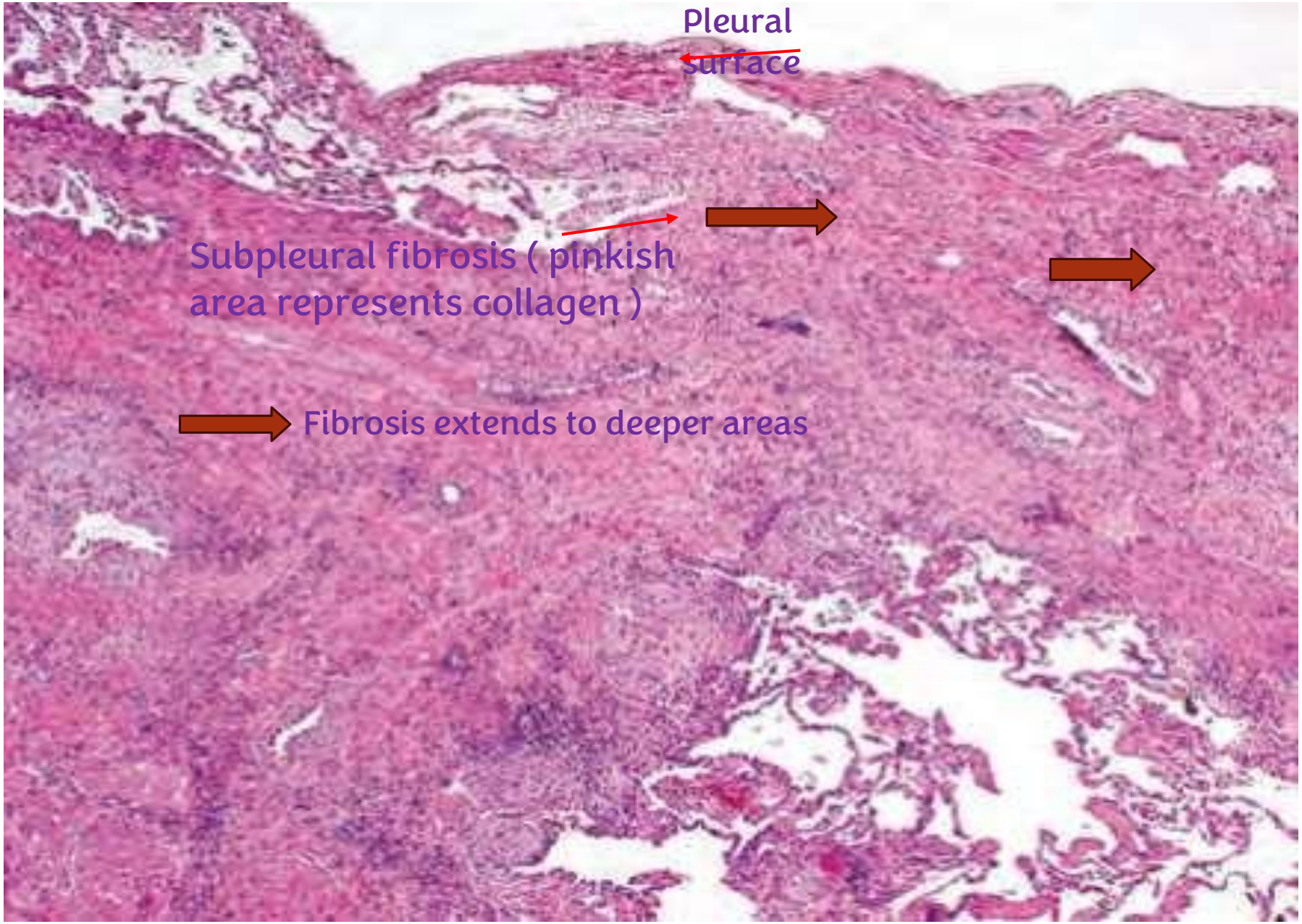
Microscopic Morphology

- Usual interstitial pneumonia (UIP) pattern of fibrosis.
- Hallmark is patchy interstitial fibrosis (varies in intensity & worsens with time).
  - This means that **some areas show marked fibrosis**, while **other areas are less fibrotic**.
- The earliest lesions: Fibroblastic foci and proliferation of fibroblast. This region is cellular.
- Later: collagenous and less cellular foci.
- Advanced: Honeycomb fibrosis.
  - This is a characteristic feature of many **interstitial lung diseases**, in general.
- Typical finding: Coexistence of early and late lesions (temporal
- heterogeneity).

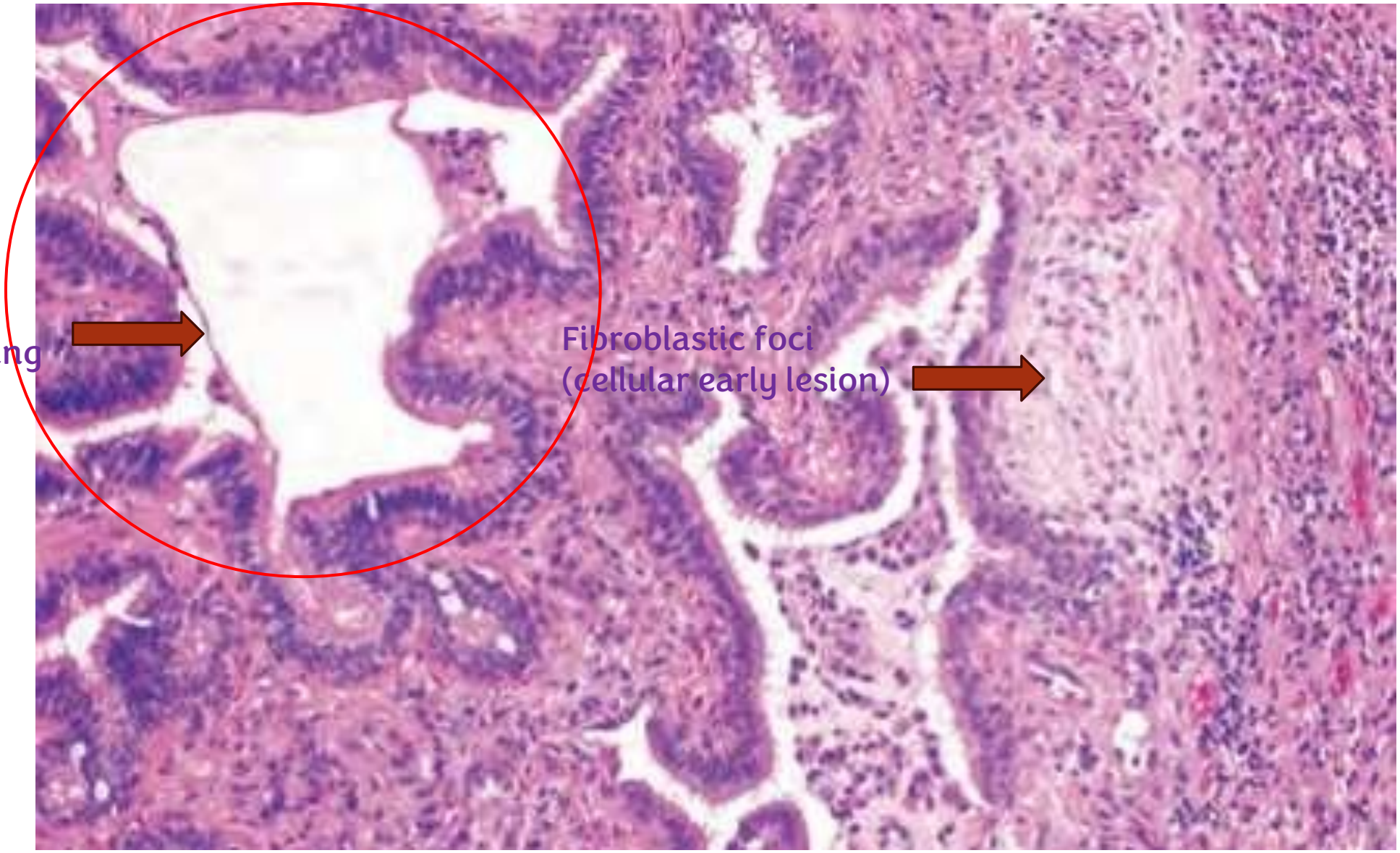
Microscopic Morphology

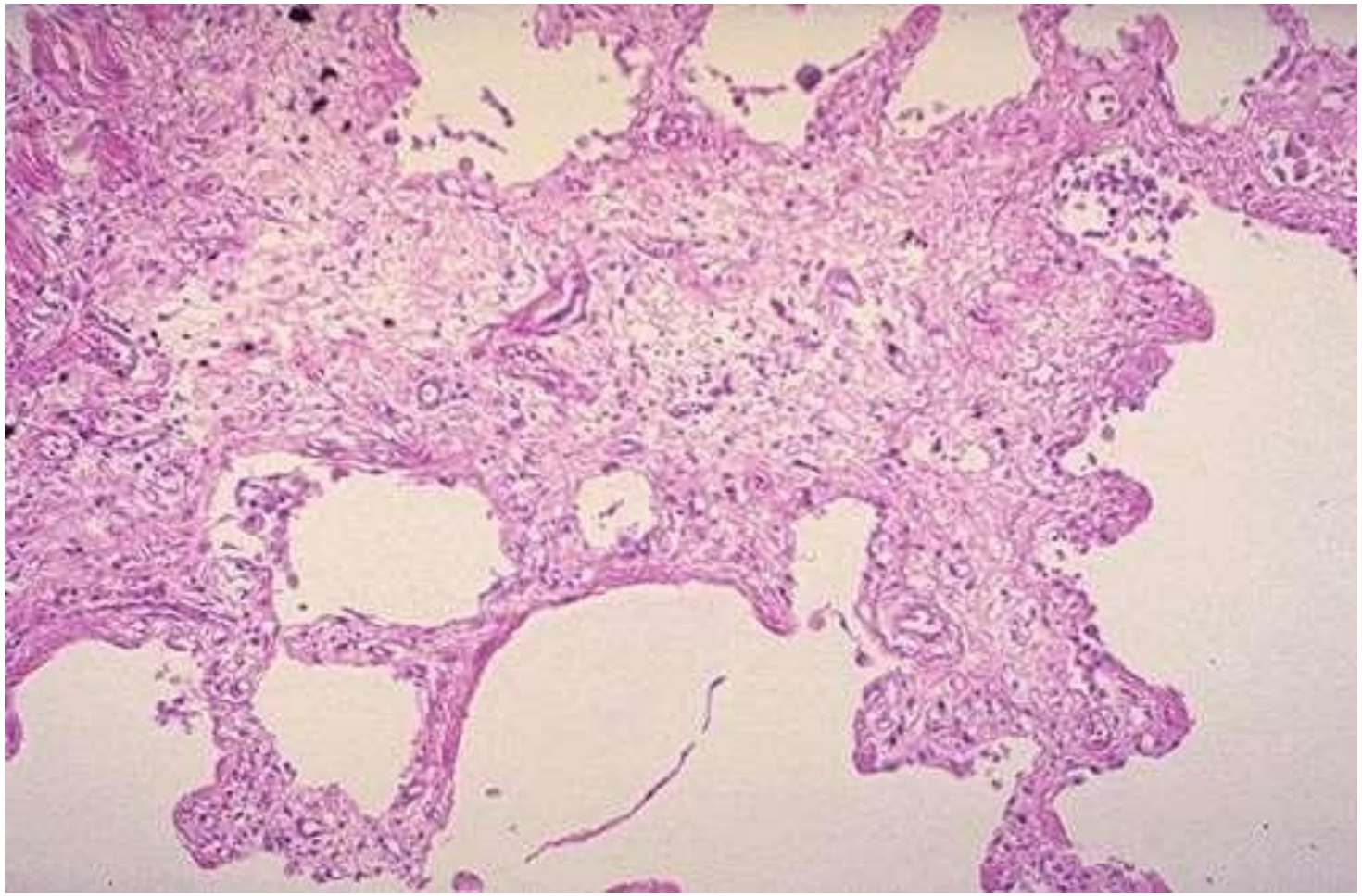
- Mild-moderate inflammation in fibrotic areas (lymphocytes, few plasma cells, neutrophils, eosinophils, and mast cells)
- Secondary pulmonary arterial hypertensive changes (intimal fibrosis and medial thickening) leading to → pulmonary hypertension and cor-pulmonale (right sided heart failure)


Inflammatory cells
Subpleural fibrotic area
(late fibrotic regions)
This region has more cellular fibroblastic foci


Pleural surface
Subpleural fibrosis (pinkish area represents collagen)
Fibrosis extends to deeper areas

This area is lined by **respiratory** epithelium and **cystic** places resulting in **honeycomb** pattern

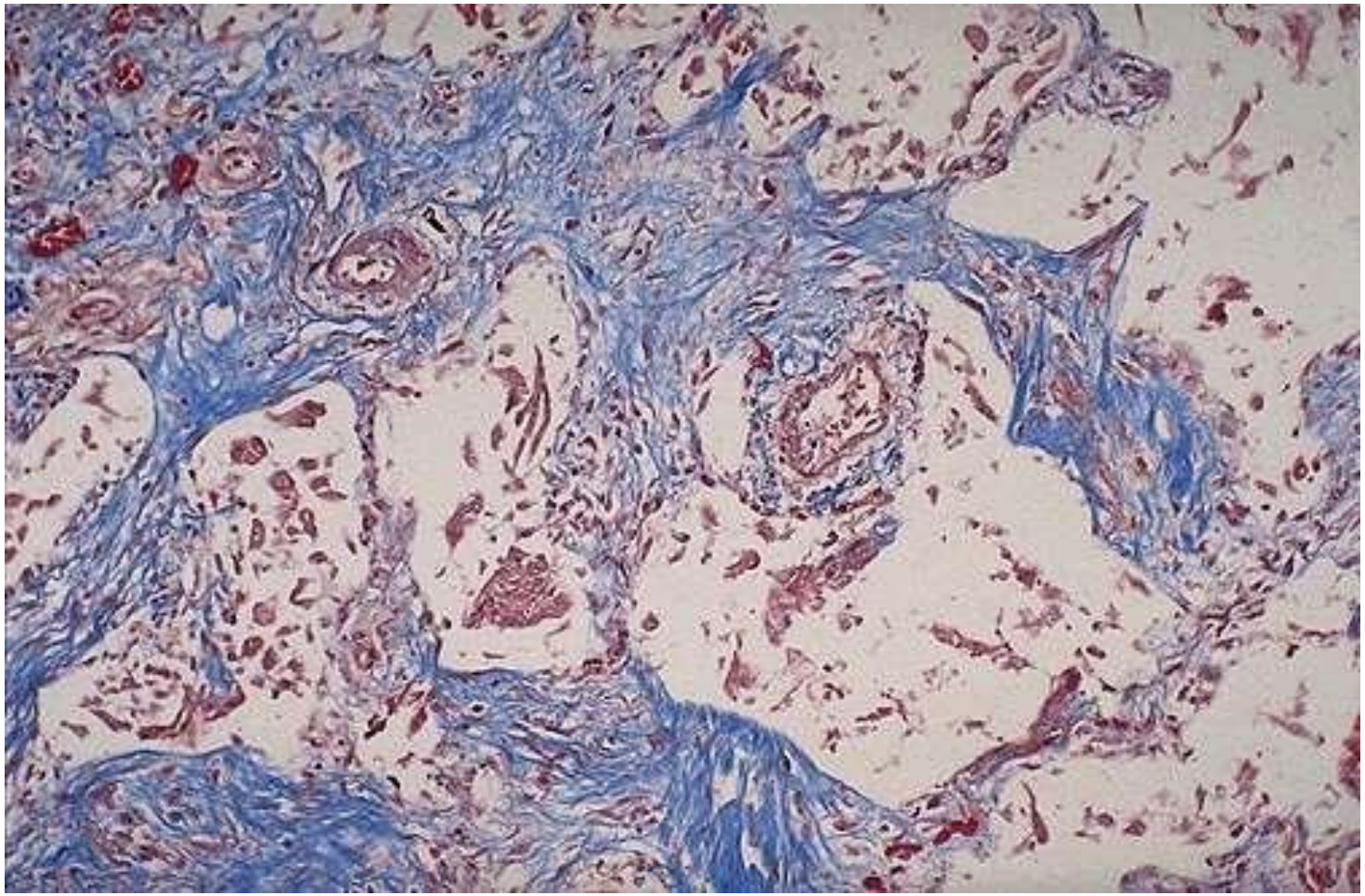




https://webpath.med.utah.edu/

Blue area = collagen

Masson trichrome special stain for fibrosis.



https://webpath.med.utah.edu/

Clinical Features

- Gradual onset of nonproductive cough and progressive dyspnea (shortness of breath; difficulty)
- Later on:
    1. **Cyanosis**, due to extensive fibrosis.
    2. The V/Q ratio would be disturbed, leading to hypoxia, cyanosis and pulmonary hypertension. Eventually leading to **Cor pulmonale**.
    3. **Peripheral edema** may develop later.
- On physicial examination (P/E): “dry” or “Velcro”-like crackles (crepitations) at the basal part of the lung during inspiration.
- CXR: subpleural and basilar fibrosis and in advanced disease “honeycombing” of the lung is seen.
- Clinical and radiologic findings often are diagnostic, but sometimes a lung biopsy is required to exclude other causes and to establish the temporal heterogeneity.

Prognosis

- Progression despite medical therapy.
- Mean survival is 3 years or less; bad prognosis.
- Lung transplantation is the only definitive therapy
- Anti-inflammatory & immunosuppressive drugs (therapy) do not stop the disease from progressing; they're of **little benefit**.
- Therefore, Antifibrotic therapy are the primary treatment (**main Tx**).

Fibrosing Diseases

- Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
- **Non-specific interstitial pneumonia**
  - By name, it might suggest a **nonspecific pattern**; however, it is characterized by **distinct clinical, radiologic, and histologic features**, and is therefore **not truly nonspecific**.
- Cryptogenic organizing pneumonia
- Connective tissue disease-associated
- Pneumoconiosis
- Drug Reactions
- Radiation Pneumonitis

Non-Specific Interstitial Pneumonia (NSIP)

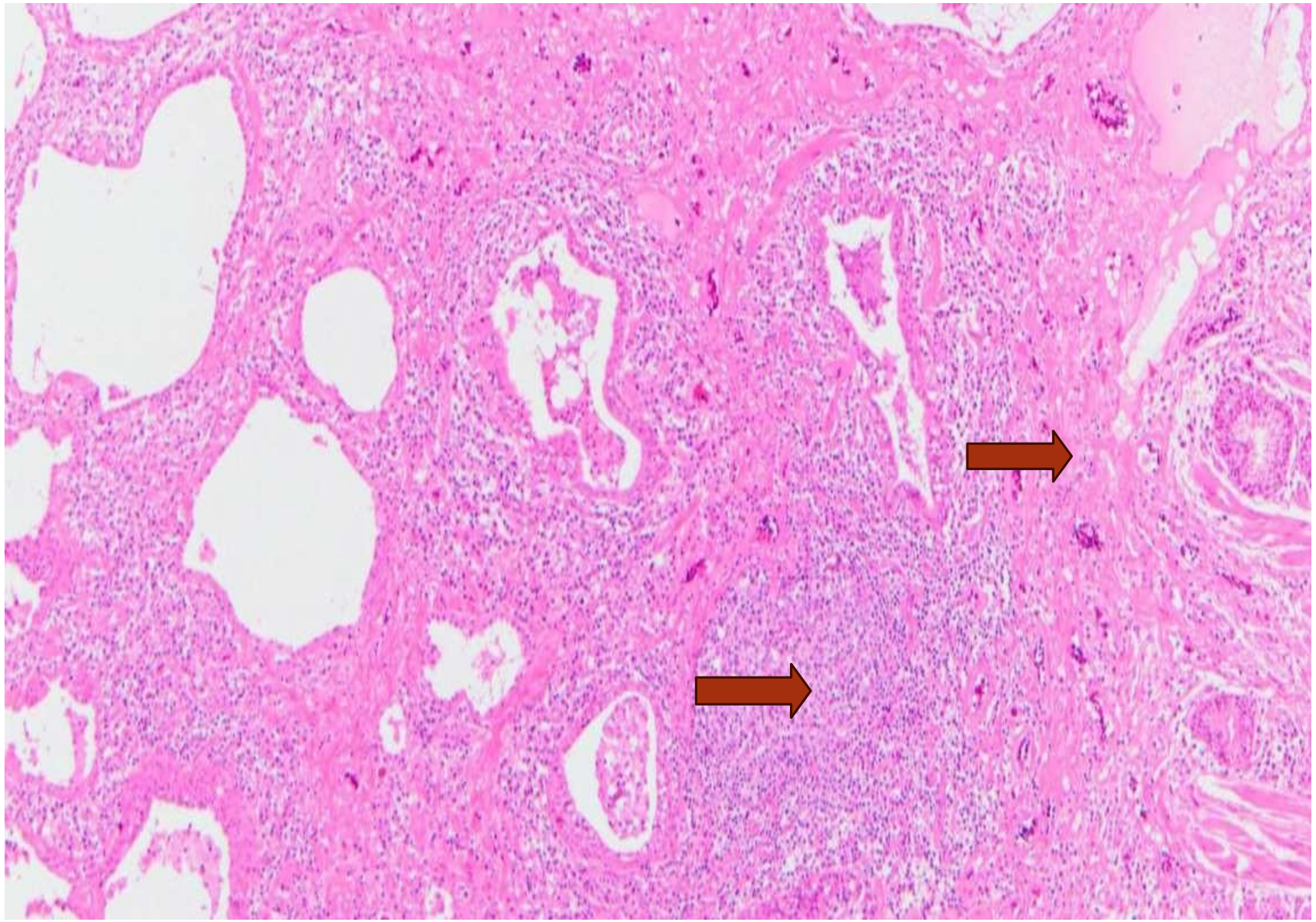
- Chronic **bilateral** interstitial lung disease
- Distinct clinical, radiologic, and histologic features.
- Idiopathic, but with Frequent association with **connective tissue diseases** (RA)
- Better prognosis than interstitial pulmonary fibrosis (IPF).
- Dyspnea and cough of several months

RA = Rheumatoid Arthritis

Microscopic Morphology

- Cellular & fibrosing patterns:
- **Cellular pattern:** mild-to-moderate chronic interstitial inflammation and infiltration (by chronic inflammatory cells such as **lymphocytes** and a few **plasma cells**) in a uniform or patchy distribution.
- **Fibrosing pattern:** diffuse or patchy interstitial fibrosis with distribution that is uniform in the areas involved
- **Temporal heterogeneity** characteristic of UIP is **ABSENT.**
- All the fibrotic foci are of the same age here, therefore, **Fibroblastic foci** typically seen in usual interstitial pneumonia are **ABSENT.**

The disease is **extensive**, involving the **subpleural regions** while also **extending diffusely beyond them**.
The **lower arrow** points to **cellular infiltrates within the lung interstitium**, indicating an **active inflammatory process**.
The **upper arrow** highlights **pink-staining areas of collagen deposition**. **Importantly, this fibrosis is temporally homogeneous**, meaning that **all the collagen appears to be of the same age**, which is a **hallmark of NSIP**.



Fibrosing Diseases

- Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
- **Non-specific interstitial pneumonia**
- Cryptogenic organizing pneumonia
- Connective tissue disease-associated
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- Radiation Pneumonitis

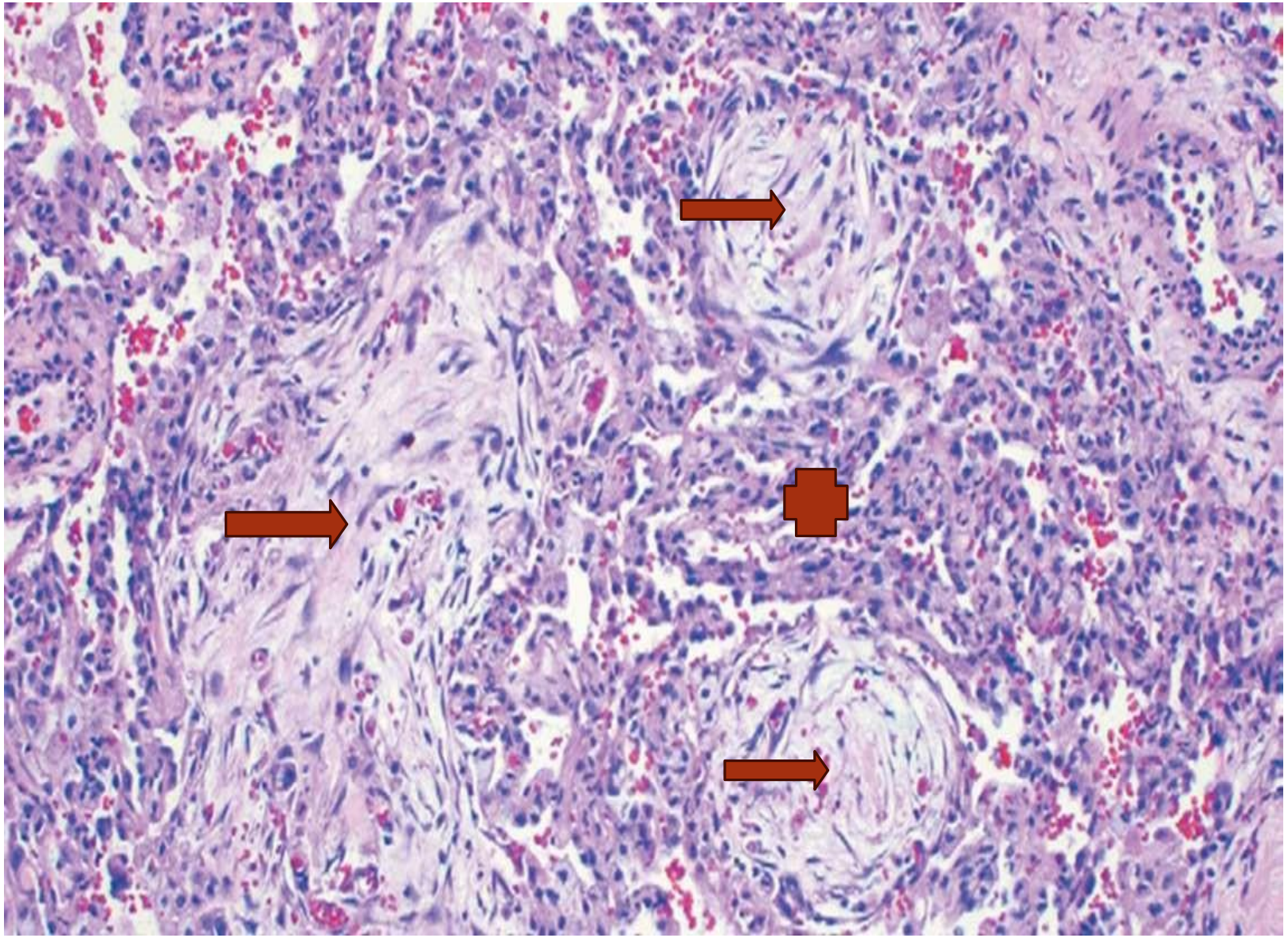
Cryptogenic Organizing Pneumonia

- Uncommon.
- Cryptogenic: Unknown etiology.
- Cough and dyspnea, like other interstitial fibrosing diseases.
- CXR: subpleural or peri bronchial patchy air space consolidation.
- The X-ray shows areas of consolidation that look very similar to typical bacterial pneumonia. The characteristic finding is patchy airspace consolidation, thereby, distinguishing it.
- Some patients recover spontaneously; however, most patients require treatment with **oral steroids** to recover.

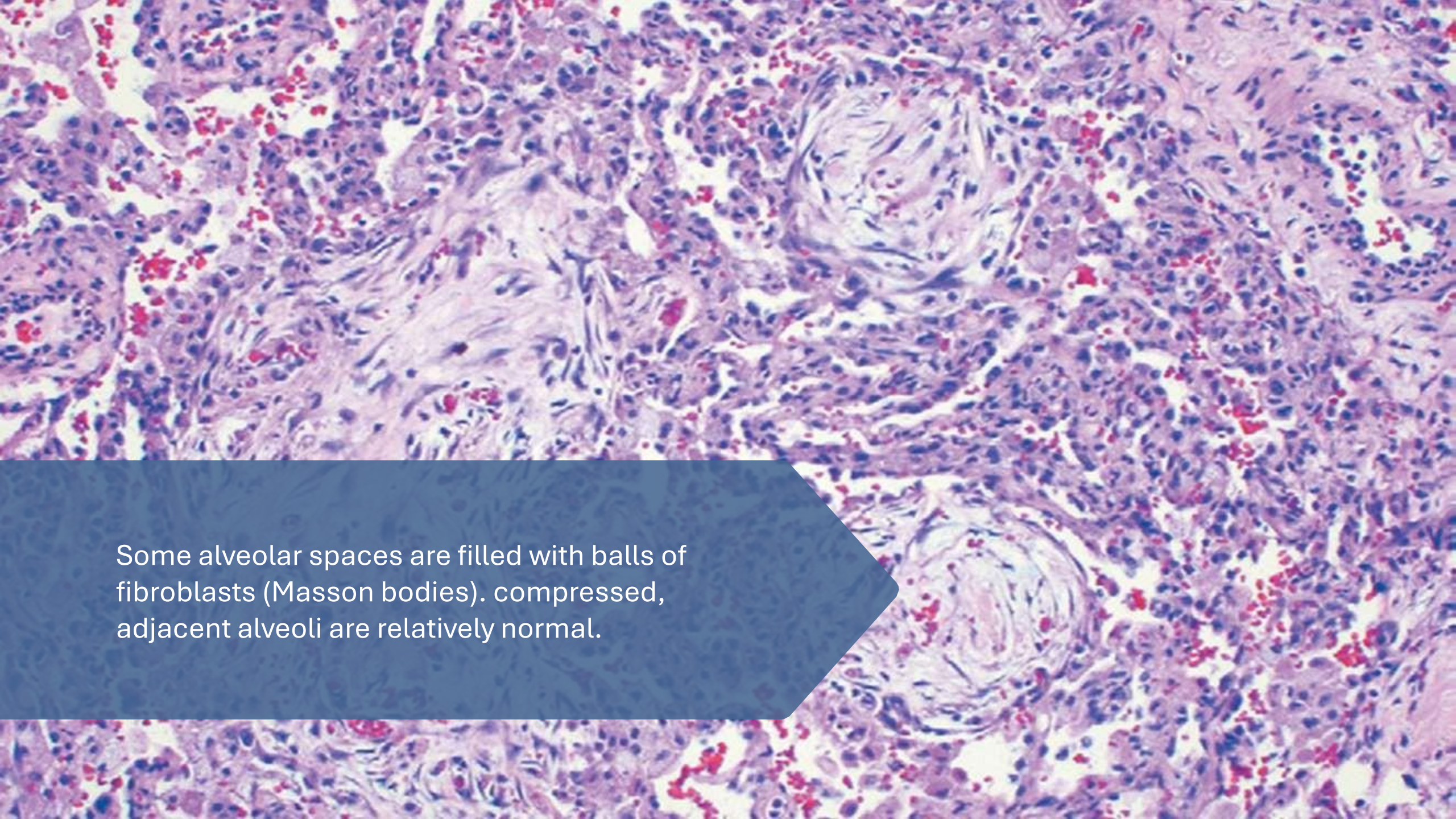
Microscopic Morphology

- Polypoid plugs of loose organizing connective tissue within alveolar ducts, alveoli, and bronchioles (Masson bodies).
- Connective tissue is all the same age, so temporal heterogeneity is not present.
- Underlying lung architecture between involved areas is **normal**.
- **No** interstitial fibrosis or honeycomb lung.

- This section shows **fibroblastic foci**, also known as **Masson bodies** (arrows).
- The key difference between these and the foci seen in Usual Interstitial Pneumonia (UIP) is that these are located within the **alveolar spaces** or **terminal bronchioles**.
- Additionally, the lung architecture between these foci remains **normal**, with **no evidence of fibrosis** (plus sign).



Masson bodies are not “fibroblastic foci”. Do your own research.



Some alveolar spaces are filled with balls of fibroblasts (Masson bodies). compressed, adjacent alveoli are relatively normal.

Microscopic Morphology

- Similar changes are seen in infections (e.g., pneumonia) or inflammatory injury (e.g., collagen vascular disease, transplantation injury) , in this case not “cryptogenic”.
- Therefore, to diagnose a cryptogenic organizing pneumonia it is needed to exclude all these underlying causes.

Fibrosing Diseases

- Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
- **Non-specific interstitial pneumonia**
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Pneumoconiosis

- Lung reaction to inhalation of mineral dusts, organic and inorganic particulates, chemical fumes and vapor.
- Coal dust, silica, and asbestos are most common mineral dust.
- Nearly always result from occupational exposure.
- However, in asbestos the increased risk of cancer **extends to family members** of asbestos workers.

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

PMF, Progressive massive fibrosis.

Pneumoconiosis

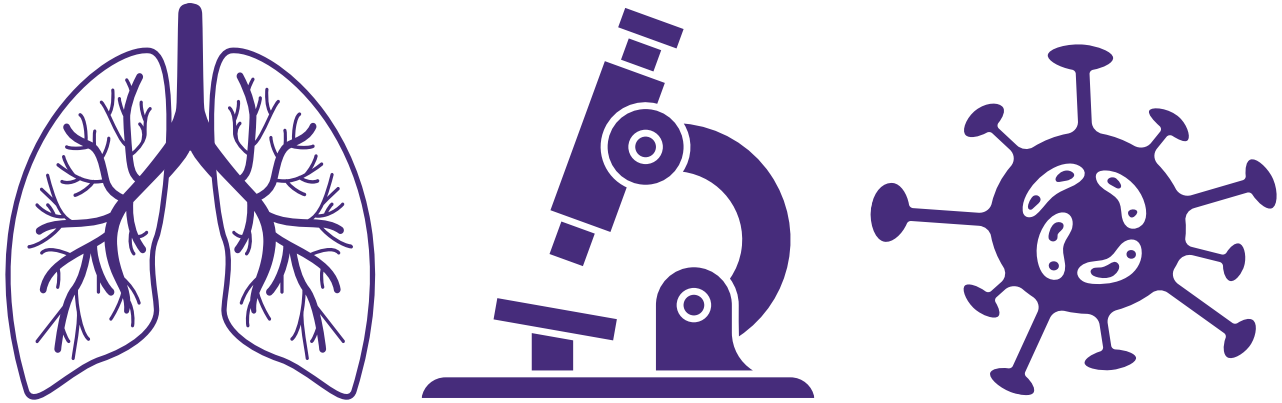
- There are **three major diseases associated with mineral dust exposure**:
- **Coal dust:**
  - Exposure leads to **coal workers' pneumoconiosis**. **Individuals working in coal mining** are at **higher risk**.
- **Silica:**
  - Exposure leads to **silicosis**, and **individuals working in sandblasting and stone cutting** are at **increased risk**.
- **Asbestos:**
  - Exposure can lead to **asbestosis**, **pleural effusions**, and **pleural plaques**.
  - It also **significantly increases the risk of malignancy**, particularly **mesothelioma and lung carcinoma**.
  - **Individuals involved in mining, construction, and material fabrication** are at **higher risk**.

Pathogenesis

- Reaction of lung to mineral dust depends on:
- **Amount** of dust retained in the airways & lung; more dust, more risk.
- **Size and Shape:**
  - Particles that are 1 to 5 μm in diameter are the most dangerous because **they are small enough to reach the deep lung**, lodging in the **distal airways and alveolar spaces**. In contrast, **larger dust particles** are **trapped in the larger airways** and **cannot reach the peripheral or distal parts of the lung**.
- **Solubility of particles**
  - Soluble particles produce acute lung injury, while insoluble may produce chronic lung injury.
- **Proinflammatory properties**
  - Coal dust is inert, silica and asbestos provoke greater immune response, resulting in more damage.

Pathogenesis

- The pulmonary alveolar macrophage is a key cellular element in the initiation and perpetuation of lung injury and progression to fibrosis.
- Tobacco smoking worsens the effects of all inhaled mineral dusts, more so with asbestos. The **combination of smoking and asbestos exposure** leads to **much worse clinical outcomes**, including a **markedly increased risk of lung cancer**, compared with **asbestos exposure alone**.



PATHOLOGY QUIZ LECTURE #1

External Resources

رسالة من الفريق العلمي

Additional sources:

1. cryptogenic Fibrosing alveolitis, slide 5

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			