IMAGING ATLAS OF INTERSTITIAL LUNG DISEASES

Boehringer Ingelheim

For healthcare professionals involved in the diagnosis of ILD

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse group of more than 200 heterogeneous lung disorders, mostly classified as rare or seen only infrequently in clinical practice.[1-3] Pulmonary fibrosis is an insidious threat across many ILDs, including those originating from connective tissue diseases (CTDs) such as systemic sclerosis and rheumatoid arthritis.[3-6] The heterogeneity and unpredictability of ILDs can make pulmonary fibrosis a challenge for physicians to detect, often leading to a delayed diagnosis.[4,5,7,8]

While ILDs differ, common pathogenic pathways to fibrogenesis are shared.[3,9,10]

The aim of this atlas is to help clinicians recognise lesions consistent with infiltrative lung disease and characteristic aspects of ILDs.

The CT section, while not exhaustive, illustrates the imaging approach in addressing an ILD:

- Recognition of the predominant sign
- Recognition of accessory signs
- Analysis of lesions distribution in the lung and lobule

The histopathology section presents the diagnostic process for fibrosis, as well as situations that may cause confusion. This atlas is therefore intended to assist clinicians throughout the process of diagnosing ILDs.

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1. Flaherty KR, Brown KK, Wells AU, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ Open Respir Res.* 2017;4(1):e000212.
2. Demedts M, Wells AU, Antó JM, et al. Interstitial lung diseases. An epidemiological overview. *Eur Respir J Suppl.* 2001;32:2s-16s.
3. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev.* 2018;27:180076.
4. Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. *Br J Cancer.* 2004;91(suppl 2):S3-S10.
5. Wijsenbeek M, Kreuter M, Fischer A, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. *Curr Med Res Opin.* 2019:1–10. DOI: 101080/03007995.2019.1647040.
6. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J.* 2018;51(5):1800692.
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8. Greiffo FR, Eickelberg O, Fernandez IE. Systems medicine advances in interstitial lung disease. *Eur Respir Rev.* 2017;26:170021.
9. Selman M, King TE, Pardo A, et al. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. A*nn Intern Med.* 2001;134(2):136-151.
10. Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. *Eur Respir Rev.* 2015;24(135):102-114.

CHEST CT

HISTOPATHOLOGY

* The CT elementary lesions are described based on: Hansell DM, *et al.* Fleischner society: glossary of terms for thoracic imaging. Radiology. 2008; 246: 697-722

HRCT TECHNIQUE

CT scan play a key role in the different stages of care for chronic interstitial lung diseases[1].

Its role is essential for reaching positive & aetiological diagnoses, assessing lesions, monitoring changes, screening for complications, and assessing prognosis[1].

The aetiological diagnosis is based on recognition of the elementary signs and the dominant one among them, as well as the detection of pulmonary and lobular abnormalities. The combination of these morphological and topographical data can identify CT patterns leading to a significant reduction in the number of differential diagnoses at 2 or 3, and to guide the techniques allowing, if necessary, a diagnosis of certainty (bronchoalveolar lavage; surgical lung biopsy, cryobiopsy…).

Given the importance of CT scan in diagnosing chronic ILD, high-quality CT images should be obtained[2].

The requisite conditions for conducting a chest CT scan when ILD is suspected are summarised in the table opposite[3].

Necessary conditions[2,3]	Optional conditions[2]
• CT scan **without injection of contrast** medium • **Number of acquisitions:** - Supine: inspiratory at full inspiration (volumetric acquisition) - Supine: expirwatory (volumetric or sequential acquisition) • Cross section thickness **≤ 1,5 mm** • Reconstruction field **focused** on the lungs • Acquisition in line with **European radiation standards** • **Archiving** of acquisitions in **thin-cross-sections** on CD/DVD for rereading at a later date	• **Coronal and sagittal reconstructions** if volumetric acquisitions are available • Sagittal reconstructions in **minimal intensity projection mode** (minIP) at a thickness of 5 to 8 mm • Axial/coronal/sagittal* reconstructions in **maximum intensity projection mode** (MIP) at a thickness of 5 to 8 mm • **Expiratory scans** to detect lobular air trapping

1. Brauner M, *et al.* Imagerie des pneumopathies infiltrantes diffuses. Press Med 2010 39: 73-84
2. Cottin V, *et al.* French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis - 2017 update. Full-length version. Rev Mal Respir 2017;34:900-68
3. Raghu G, *et al.* Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-e68
* Recommendations from the group of experts that wrote this atlas

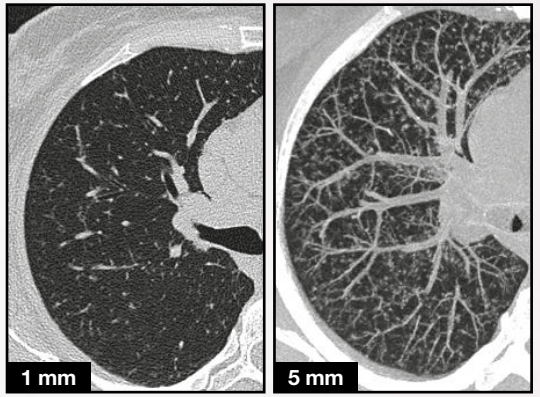
PRINCIPLE OF MIP AND MINIP RECONSTRUCTIONS

One of the optional conditions for conducting a chest CT of usual interstitial pneumonia is reconstructing images using maximum intensity projection (MIP) and minimal intensity projection (minIP) algorithms [1].

These reconstructions are used to obtain information that is not always visible on the axial cross-sections but which is useful for diagnosis[1]. These two reconstructions are based on the same principle:

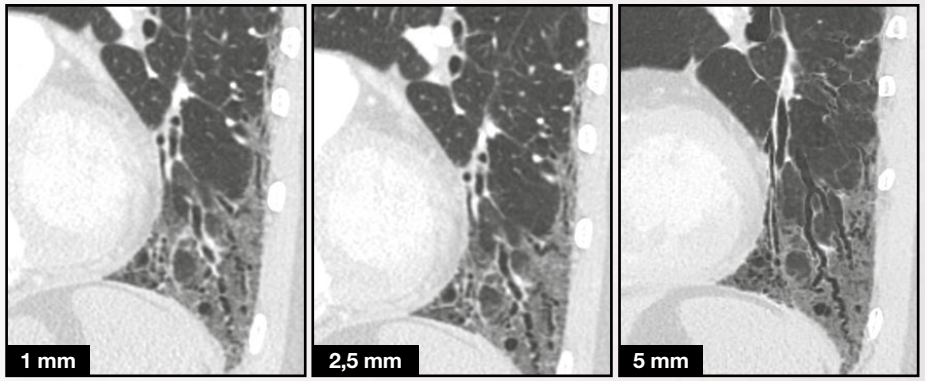
- acquisition of volumetric CT in mm-thick cross-sections
- selection of the desired orientation and thickness of the cross sections, namely 5-8 mm
- application of the MIP or minIP algorithm based on clinical needs regarding selected volume:
  - **MIP** select the densest voxels* in the selection in order to better detect dense anomalies in the lungs (for example, micronodules)
  - **minIP** select the least dense voxels* in the selection in order to better detect hypodense anomalies in the lungs (for example, cysts, emphysema, or bronchiectasis)

MIP (MAXIMUM INTENSITY PROJECTION)[1]



Application of the MIP algorithm on 1-mm and 5-mm cross-section from a patient with suspected micronodulation. The 5-mm MIP can bring together the micronodules in the 5-mm thickness, making it possible to confirm micronodulation and identify their topography within the lobule.

MINIP (MINIMAL INTENSITY PROJECTION)[1]



Application of the minIP algorithm to variable thicknesses of cross-sections between 1 and 5 mm. The minIP allows to see the air contained in the scanned area. Traction bronchiectases are therefore more visible in the minIP 5 mm CT within the ground-glass opacity.

* A voxel is a unit of graphic information that defines a point in a three-dimensional space

1. Ferretti G, Jankowski A. Tomodensitométrie volumique : reconstructions 2D et 3D. Rev Mal Respir. 2010;27:1267-74

INTERLOBULAR SEPTAL THICKENING

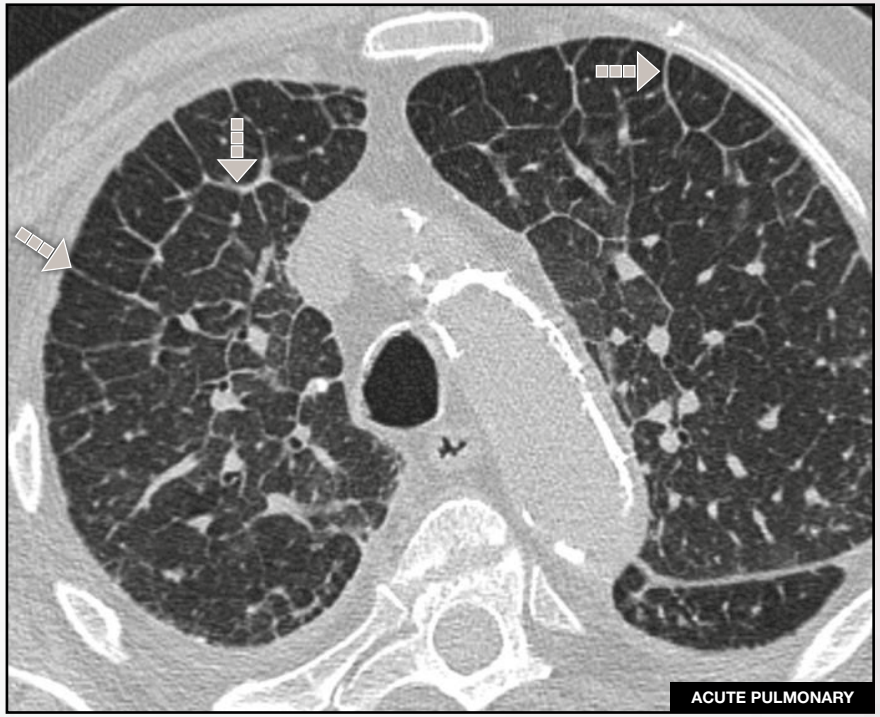
CHARACTERISTICS

- Thin linear opacities between lobules
- Length of lines: 10 - 20 mm
- Preferential location: subpleural
- Presentation: simple lines / polygons

DIAGNOSTIC ORIENTATION

- **If the septal lines are regular** (not specific)
  - pulmonary oedema, lymphangitic carcinomatosis, veno-occlusive disease, overload diseases (such as Niemann Pick disease), Erdheim-Chester disease (ECD), acute eosinophilic pneumonia
- **If the septal lines are nodular**
  - sarcoidosis, lymphangitic carcinomatosis, lymphoma, Kaposi sarcoma
- **If the septal lines are within architectural distortion**
  - fibrosis from any cause including sarcoidosis

REGULAR SEPTAL LINES



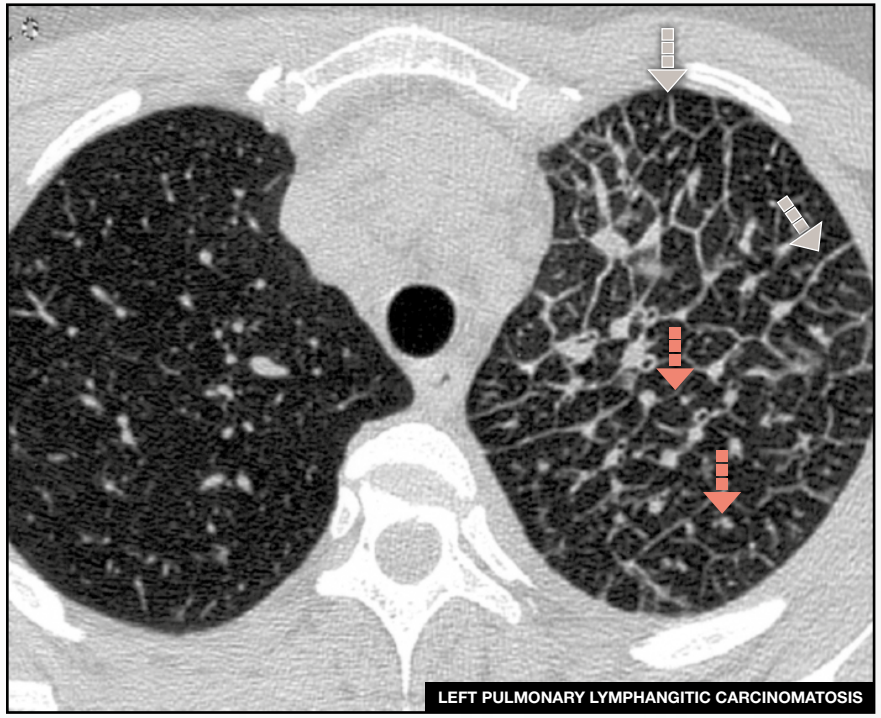
Septal thickening

Septal thickening forming polygons in the lung parenchyma.

* A voxel is a unit of graphic information that defines a point in a three-dimensional space

1. Ferretti G, Jankowski A. Tomodensitométrie volumique : reconstructions 2D et 3D. Rev Mal Respir. 2010;27:1267-74

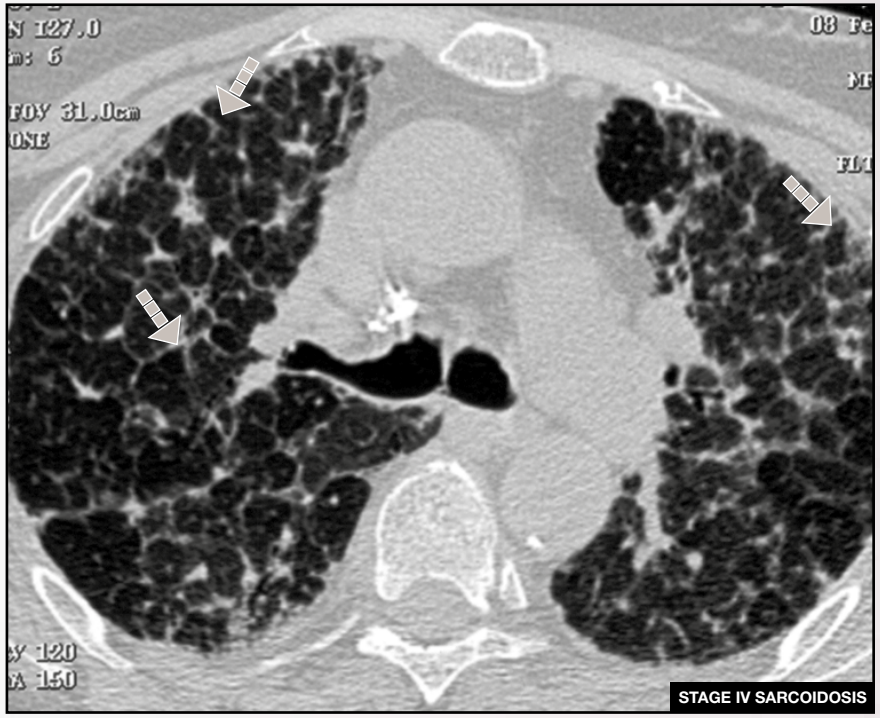
NODULAR SEPTAL LINES



Polygons Centrilobular arteries

Unilateral left septal lines forming polygons associated with a thickening of the bronchial wall and centrilobular structures (central dot) suggesting lymphangitic carcinomatosis.

SEPTAL LINES AND IRREGULAR DEFORMATION



Kerley irregular lines

Irregular bilateral septal lines in a patient with stage IV sarcoïdosis.

INTRALOBULAR RETICULATIONS (LINES)

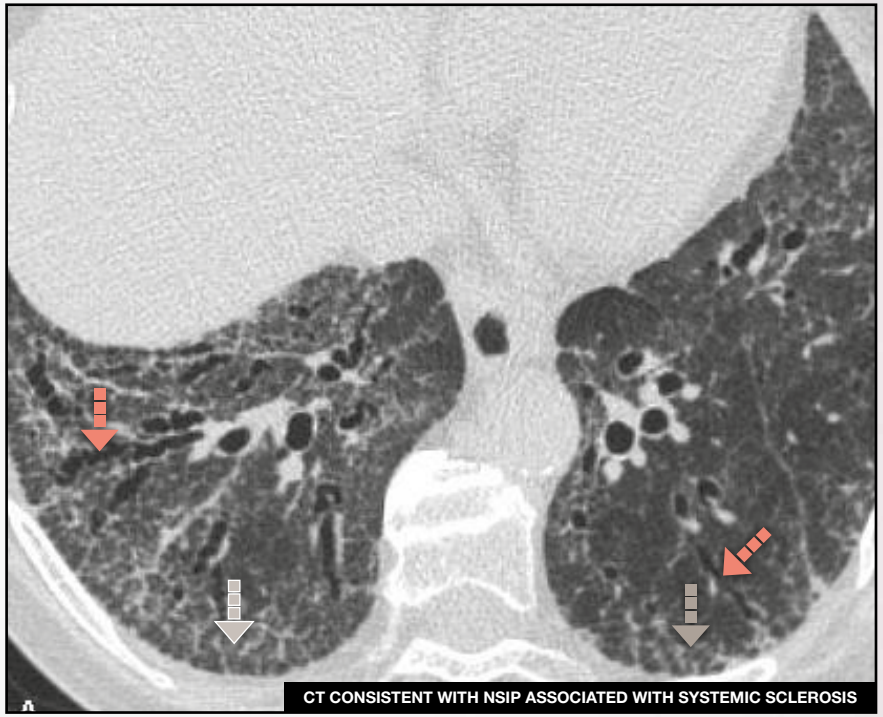
CHARACTERISTICS

- Small linear or curved intralobular opacities measuring less than 10 mm forming an irregular reticulation
- They can be isolated or associated with other signs

DIAGNOSTIC ORIENTATION

- **If the intralobular reticulations are posterior and inferior subpleural reticulations**
  - Usual interstitial pneumonia (UIP, probable UIP, indeterminate for UIP, alternative diagnosis of UIP) / Connective tissue disease (CTD)
  - Nonspecific interstitial pneumonia (NSIP)
  - Desquamative interstitial pneumonia (DIP)
- **If intralobular reticulations are associated with ground-glass opacity**
  - Hypersensitivity pneumonitis (HP), alveolar proteinosis

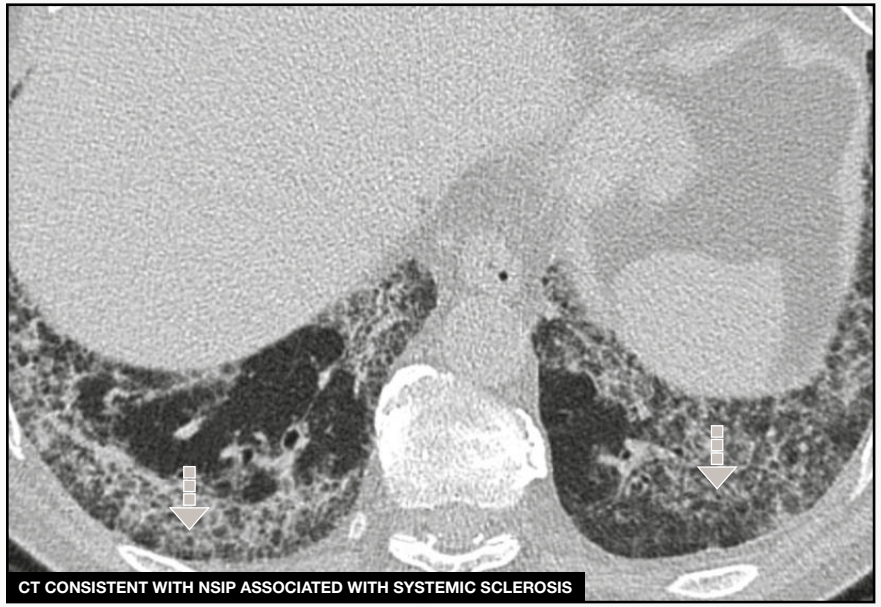
INTRALOBULAR RETICULATIONS ASSOCIATED WITH GROUND-GLASS OPACITY



Intralobular reticulations Traction bronchiectasis

Diffuse ground-glass opacities in the lower posterior lungs with intralobular reticulations and traction bronchiectasis, no honeycombing.

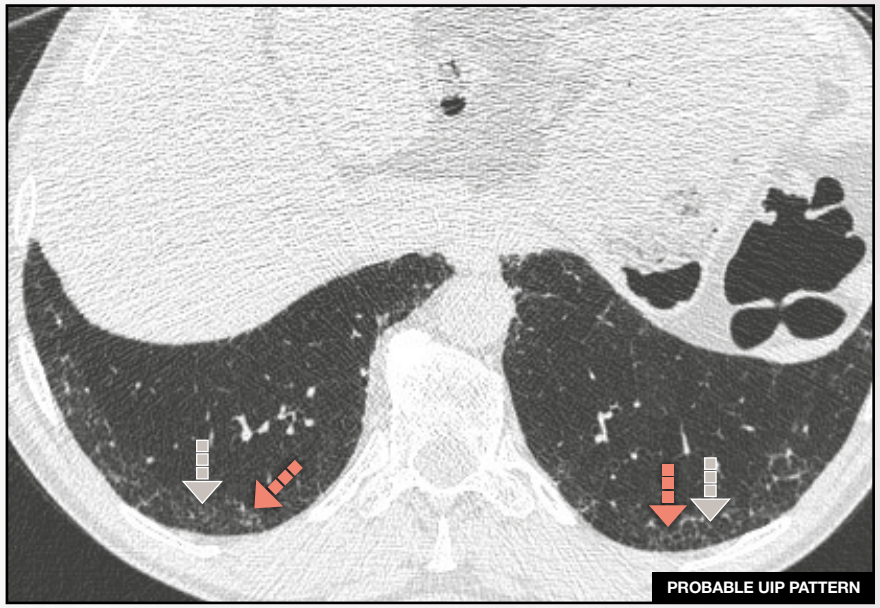
INTRALOBULAR RETICULATIONS



Intralobular reticulations

Marked intralobular reticulations in the 2 lung bases without honeycombing.
Note the relative lung savings immediately under pleura, pointing to a NSIP.

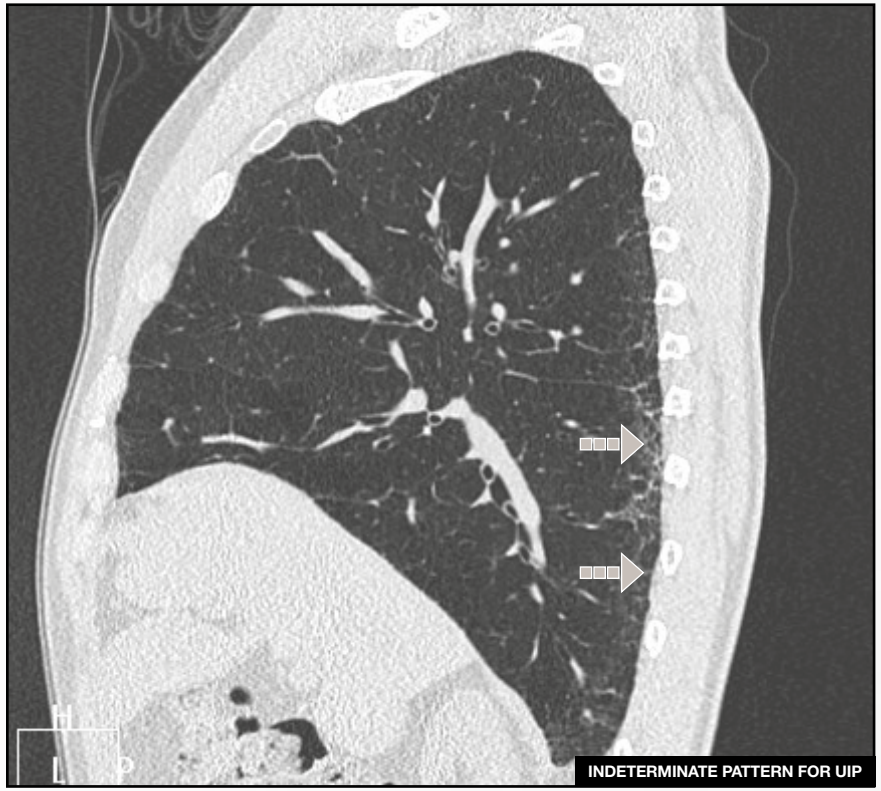
INTRALOBULAR RETICULATIONS



Intralobular reticulations Traction bronchiectasis

- Isolated and subtle subpleural intralobular reticulations and traction bronchiectasis of the 2 lower lobes.
- No ground-glass opacity or honeycombing.

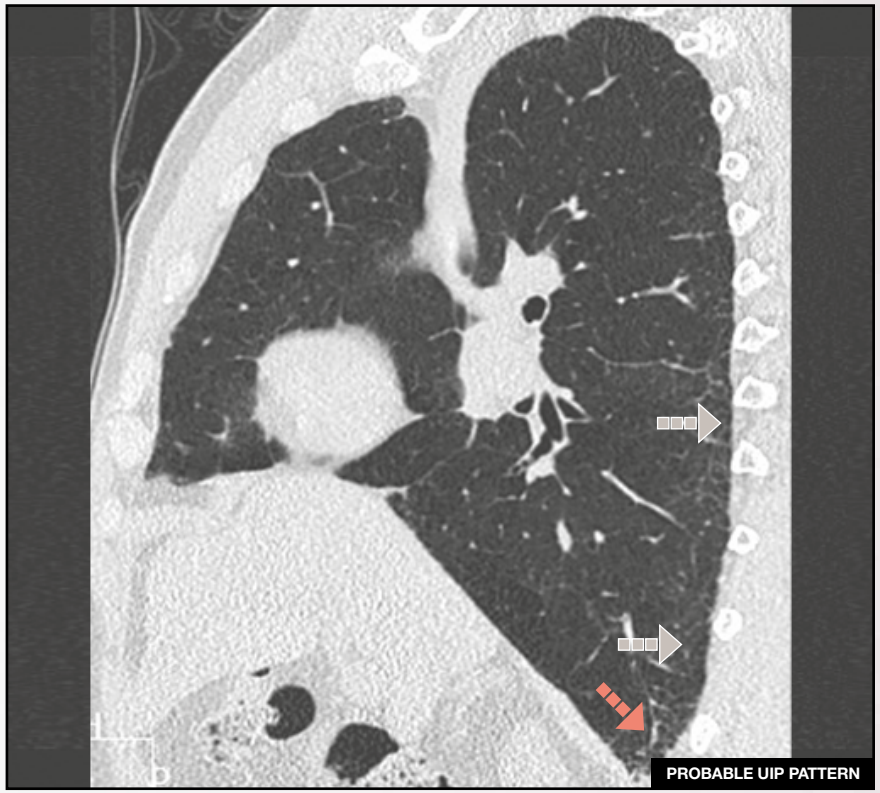
INTRALOBULAR RETICULATIONS



Intralobular reticulations

- Isolated and subtle subpleural intralobular reticulations.
- No ground-glass opacity or honeycombing or traction bronchectosis.

INTRALOBULAR RETICULATIONS



Intralobular reticulations Traction bronchiolectasis

- Isolated and subtle intralobular reticulations, with traction bronchiolectasis.
- No ground-glass opacity or honeycombing.

GROUND-GLASS OPACITY

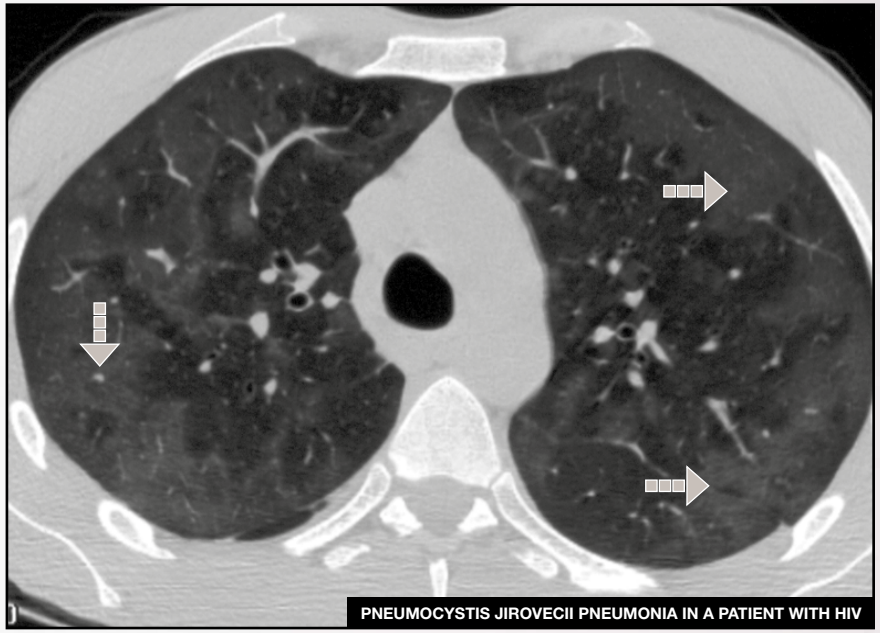
CHARACTERISTICS

- Slightly increased attenuation of lung parenchyma, with preservation of vascular and bronchial margins.

DIAGNOSTIC ORIENTATION

- Ground-glass opacity can be associated with various conditions:
  - pulmonary oedema
  - pulmonary infection: pneumocystis jirovecii pneumonia, cytomegalovirus (CMV), etc.
  - hypersensitivity pneumonitis (HP)
  - respiratory bronchiolitis
  - desquamative interstitial pneumonia (DIP)
  - acute interstitial pneumonïa (AIP)

PATCHY GROUND-GLASS OPACITY

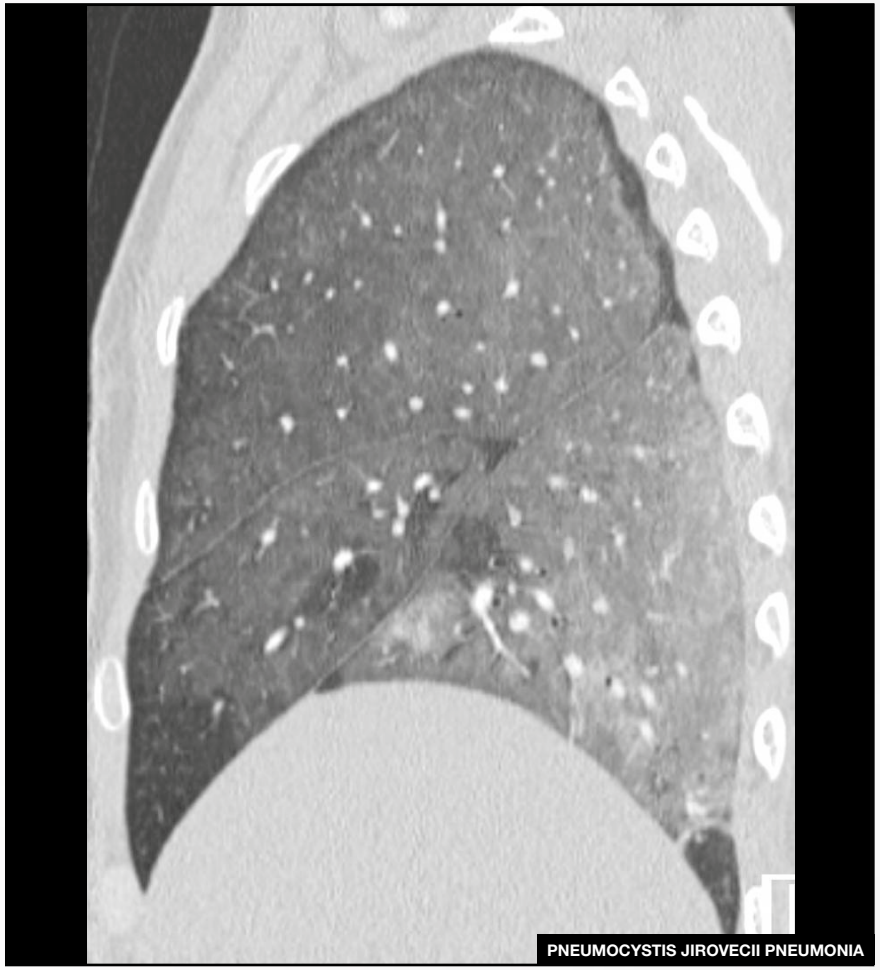


PNEUMOCYSTIS JIROVECII PNEUMONIA IN A PATIENT WITH HIV

Ground-glass opacity

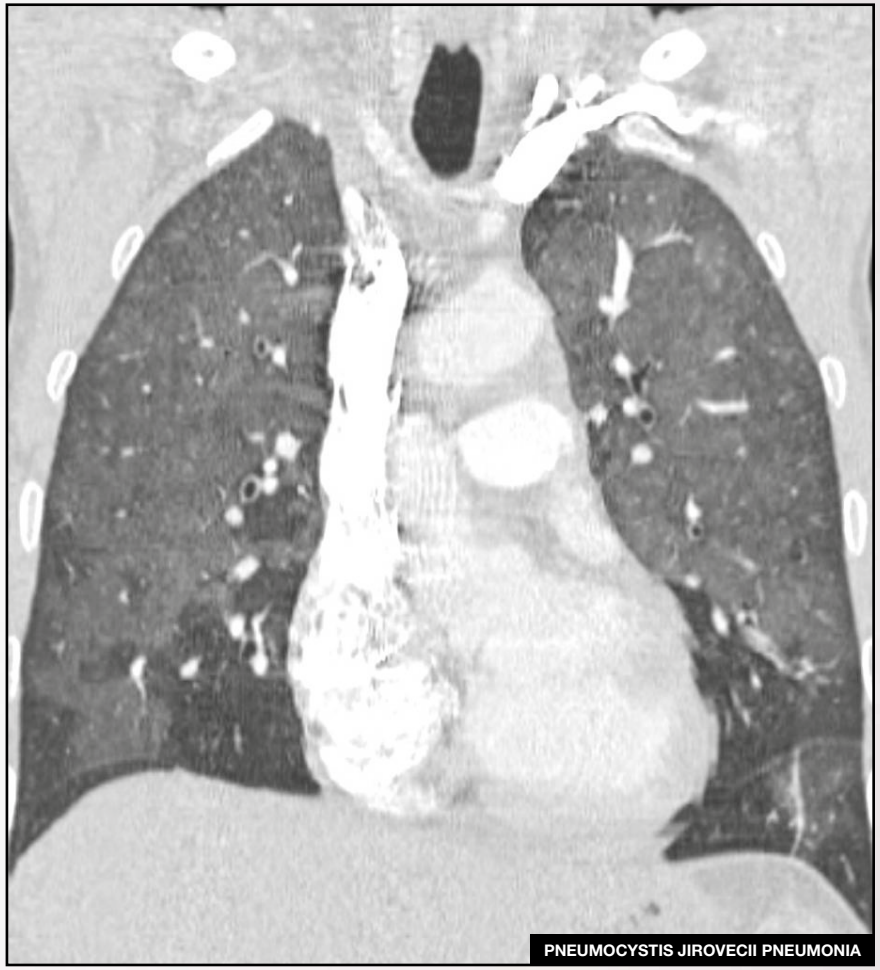
- Heterogeneous distribution of ground-glass opacity giving the appearance of a mosaic pattern.
- Note that the size of pulmonary blood vessels is identical in hypo- and hyperdense regions, suggesting alveolitis.

DIFFUSE GROUND-GLASS OPACITY

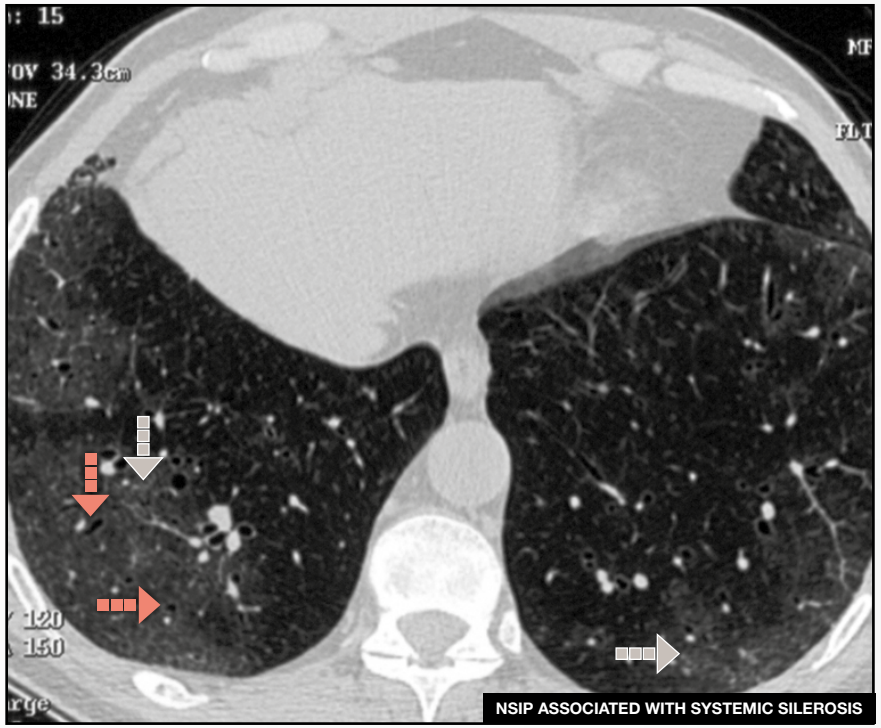


Diffuse ground-glass opacity of the lung sparing subpleural areas.

GROUND-GLASS OPACITY



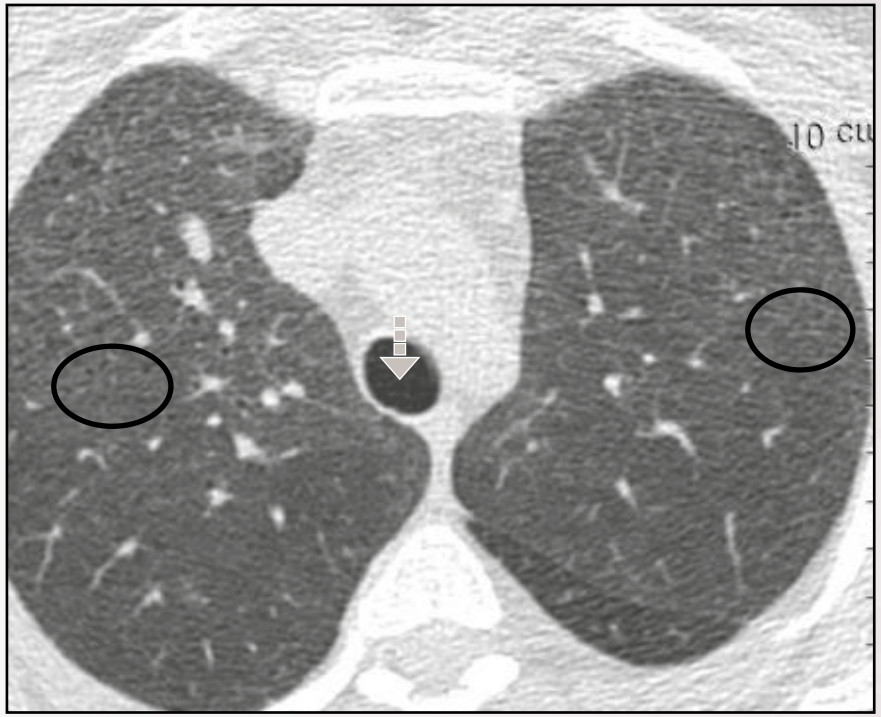
GROUND-GLASS OPACITY ASSOCIATED WITH INTRALOBULAR RETICULATIONS AND BRONCHIECTASIS



Intralobular reticulations Traction bronchiolectasis

- Radiological pattern consistent with NSIP.
- No honeycombing.

GROUND-GLASS OPACITY WITH "DARK BRONCHUS SIGN"



Intratracheal air Parenchyma

- Diagnosing diffuse ground-glass opacity can be difficult given the homogeneous increase in pulmonary density.
- Diagnosis then relies on comparisons of the intratracheal and bronchial air density (appearing black) and the parenchyma (appearing light grey).
- A gradient that is too significant compared to what is normally observed leads to identification of a dark bronchus sign, indicating a diffuse abnormal opacity of the parenchyma. Unfortunately, this assessment is qualitative, not quantitative.

GROUND-GLASS OPACITY WITH CRAZY PAVING PATTERN

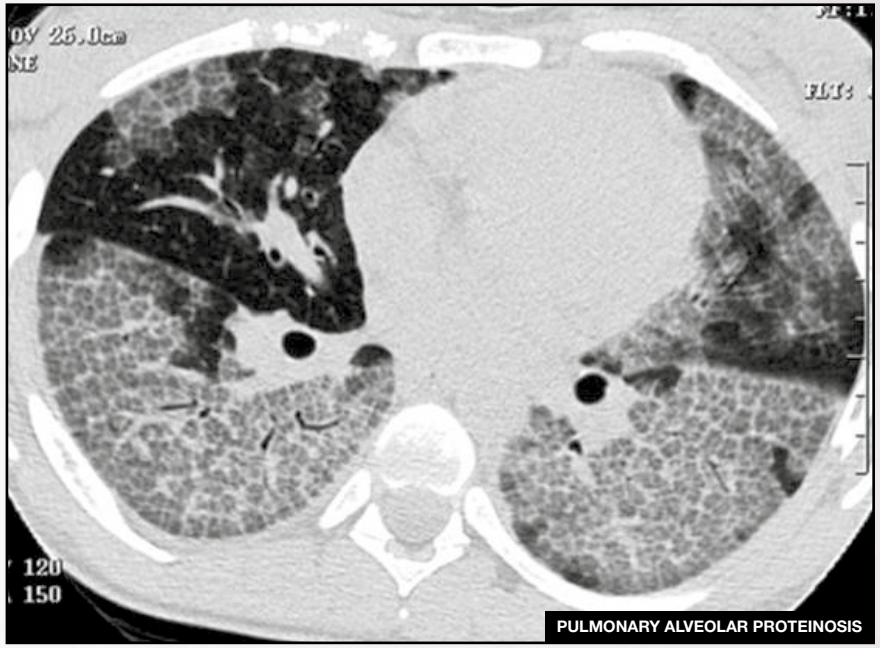
CHARACTERISTICS

- Combination of ground-glass opacity, thickened polygonal septal lines, and intralobular reticulation

DIAGNOSTIC ORIENTATION

- Ground-glass opacity with crazy paving pattern can be associated with various conditions:
  - pulmonary alveolar proteinosis ++
  - cardiogenic pulmonary oedema
  - invasive lepidic mucinous adenocarcinoma (previous denomination : bronchiolalveolar carcinoma (BAC))
  - infectious lung disease (pneumocystosis, virus)
  - drug-induced pneumonia
  - exogenous lipoid pneumonia
  - acute eosinophilic pneumonia
  - acute interstitial pneumonia
  - aspiration pneumonia
  - sarcoidosis
  - alveolar haemorrhage
  - desquamative interstitial pneumonia (DIP)
  - acute interstitial pneumonïa (AIP)

GROUND-GLASS OPACITY WITH CRAZY PAVING PATTERN



Combination of ground-glass opacity, thickened polygonal septal lines, and intralobular reticulations predominantly in the lower lobes. Note the spatial heterogeneity of lesions.

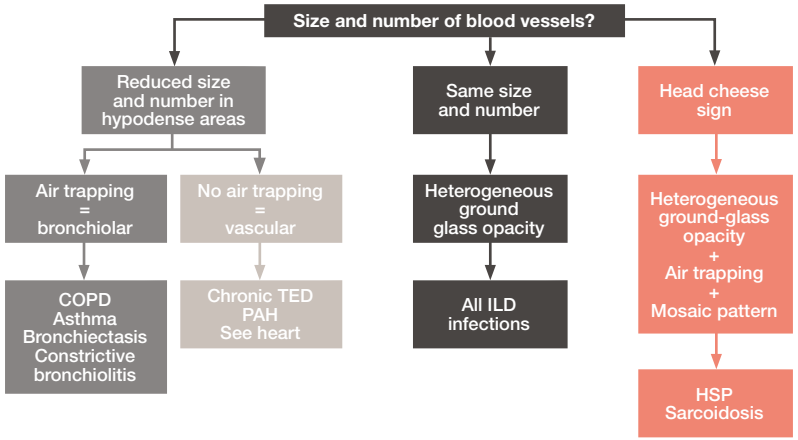
MOSAIC ATTENUATION PATTERN

CHARACTERISTICS

- Coexistence of high-density parenchymal areas (ground-glass) and normal or low-density areas of the lungs

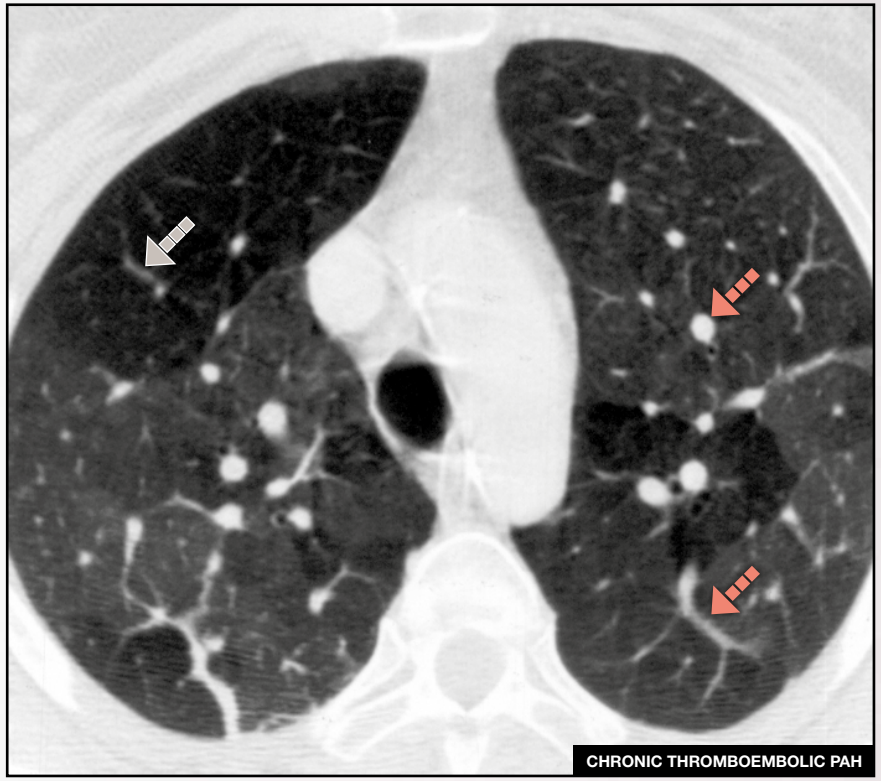
DIAGNOSTIC ORIENTATION

- Mosaic attenuation can translate into three types of anomalies that are sometimes intertwined:
  - obstructive small airways disease
  - alveolar interstitial infiltration
  - occlusive disease of the small pulmonary arteries
- The following algorithm helps recognise the nature of the mosaic attenuation based on the size of blood vessels and expiratory air trapping



COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension; HSP: hypersensitivity pneumonitis; ILD: diffuse interstitial lung disease; TED: thrombo-embolic disease

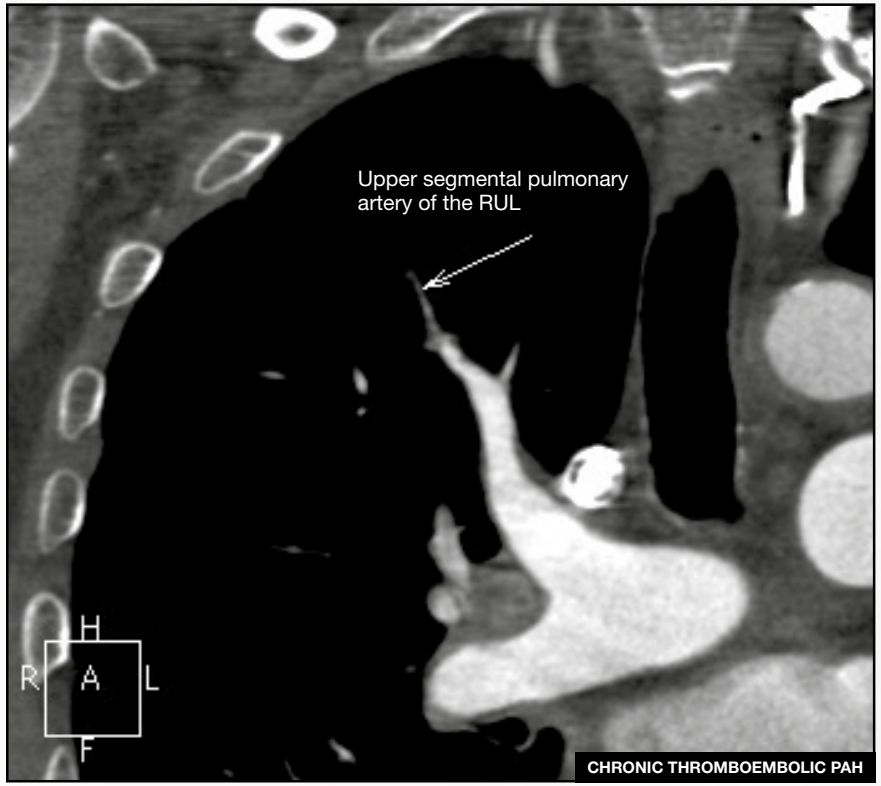
MOSAIC ATTENUATION OF THE LUNGS



Small-sized blood vessels Pulmonary arteries

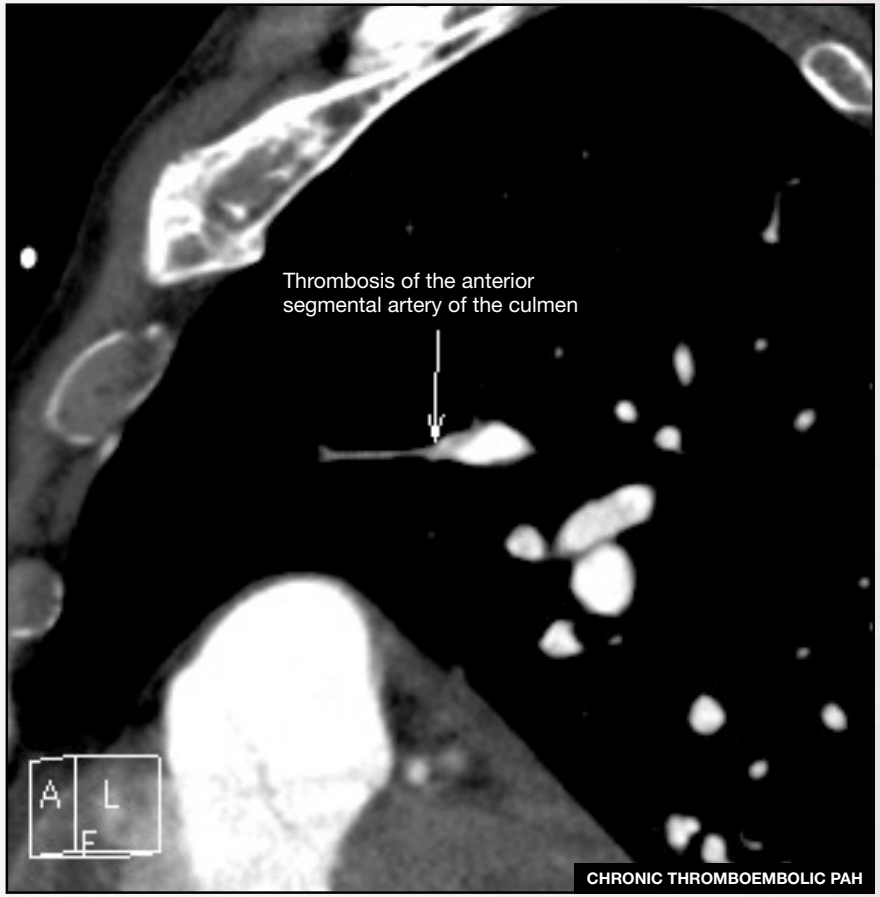
The hypodense regions of the lung contain smaller vessels, the number of which decrease while the size of the pulmonary arteries in dense regions increases corresponding to a redistribution of vascular flow to these perfused regions.
A CT scan with injection of contrast agent synchronized to opacification of the pulmonary arteries, must confirm chronic thrombosis of the pulmonary arteries.

VASCULAR MOSAIC ATTENUATION

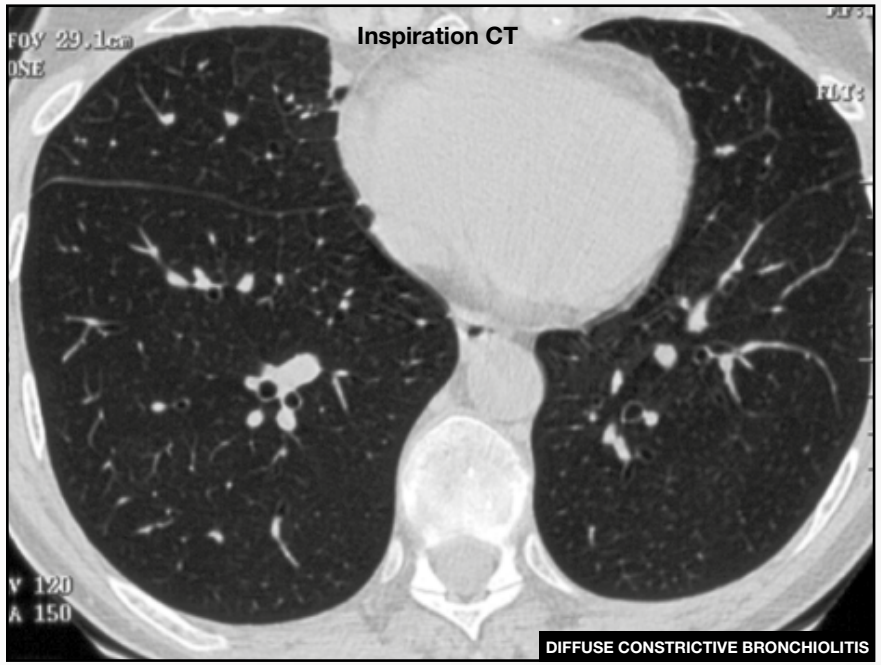


The CT scan with contrast medium injection to check for pulmonary artery obstruction shows the small size and distal thrombosis of peripheral pulmonary arteries, confirming chronic thrombosis.
Ventilation-perfusion scintigraphy is the recommended exam for screening for these anomalies.

VASCULAR MOSAIC ATTENUATION

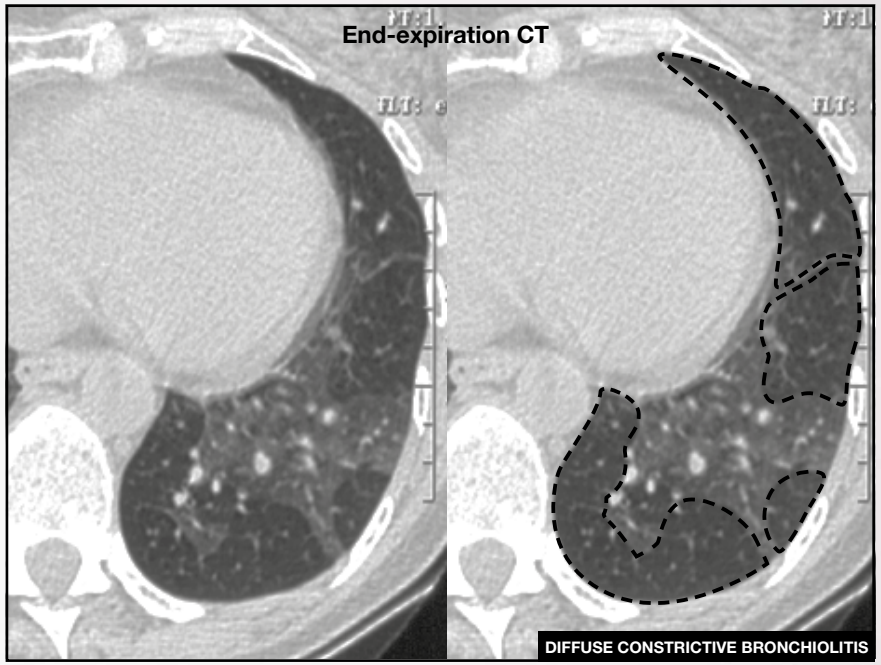


BRONCHIOLAR MOSAIC ATTENUATION



Diffuse constrictive bronchiolitis in a bone marrow transplant patient with shortness of breath and obstructive disease.
Inspiratory CT: the lung is over inflated, hypodense overall, but homogeneous.

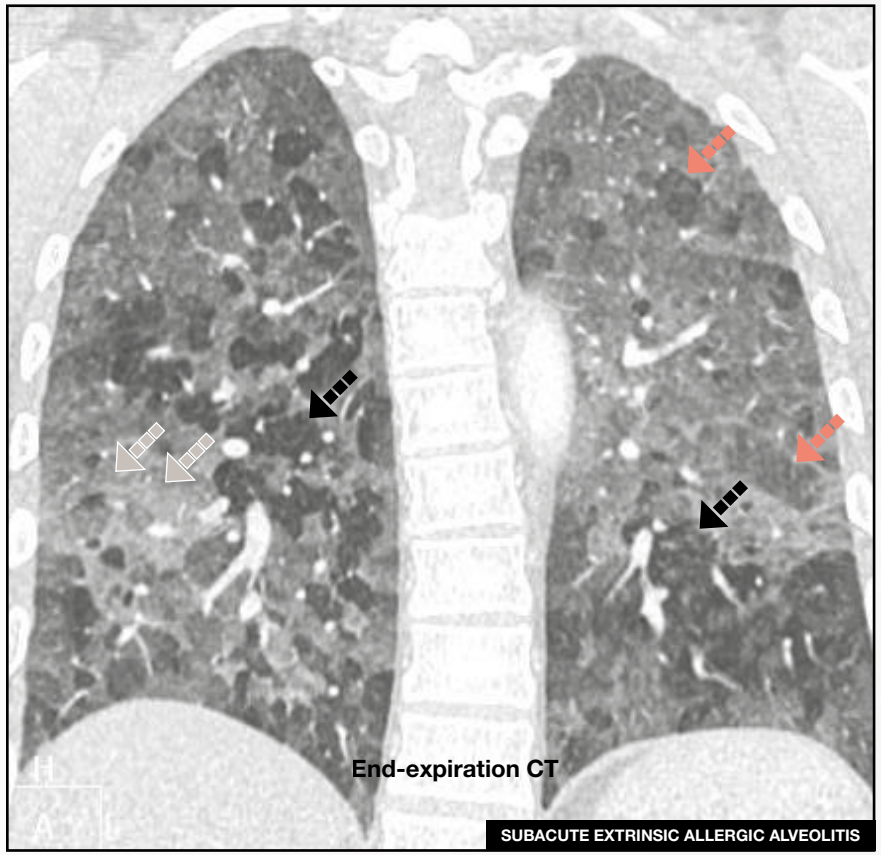
BRONCHIOLAR MOSAIC ATTENUATION



Hypodense area

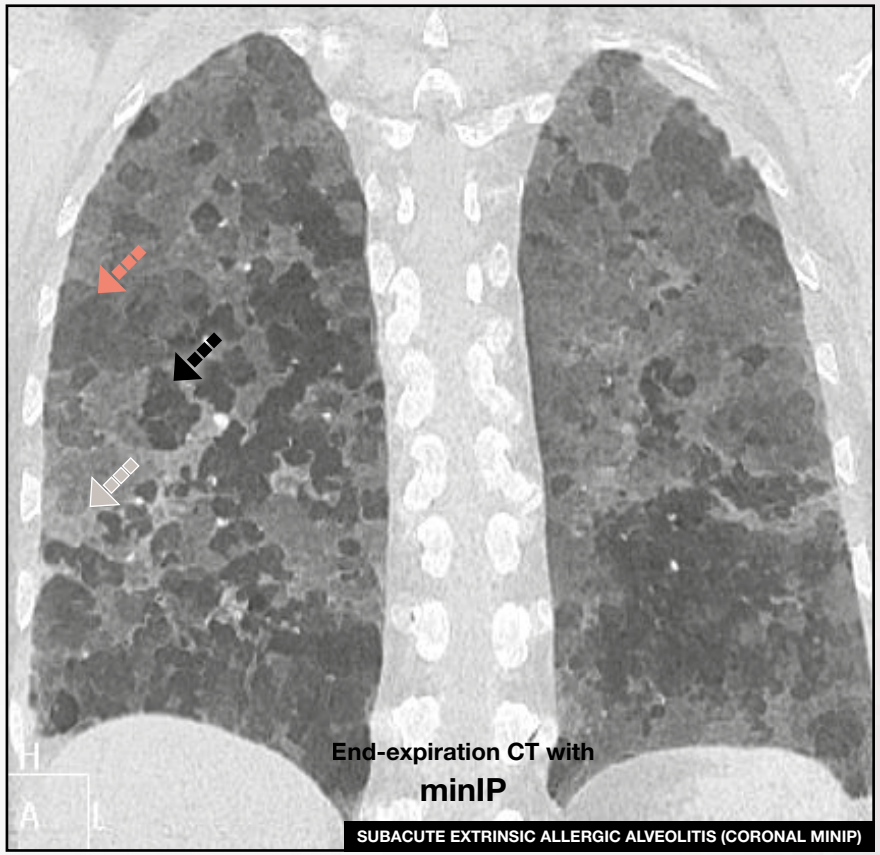
Diffuse constrictive bronchiolitis in a bone marrow transplant patient.
End-expiratory CT scan: the lung has a patchy heterogeneous mosaic attenuation alternating between normal dense areas and hypodense areas suggesting expiratory air trapping, revealing small airways disease consistent with the diagnosis of constrictive bronchiolitis.

HEAD CHEESE SIGN OF PULMONARY MOSAIC ATTENUATION



Ground-glass opacity Clear lobule Lobule with air trapping

HEAD CHEESE SIGN OF PULMONARY MOSAIC ATTENUATION



Ground-glass opacity Clear lobule Lobule with air trapping

CONSOLIDATION

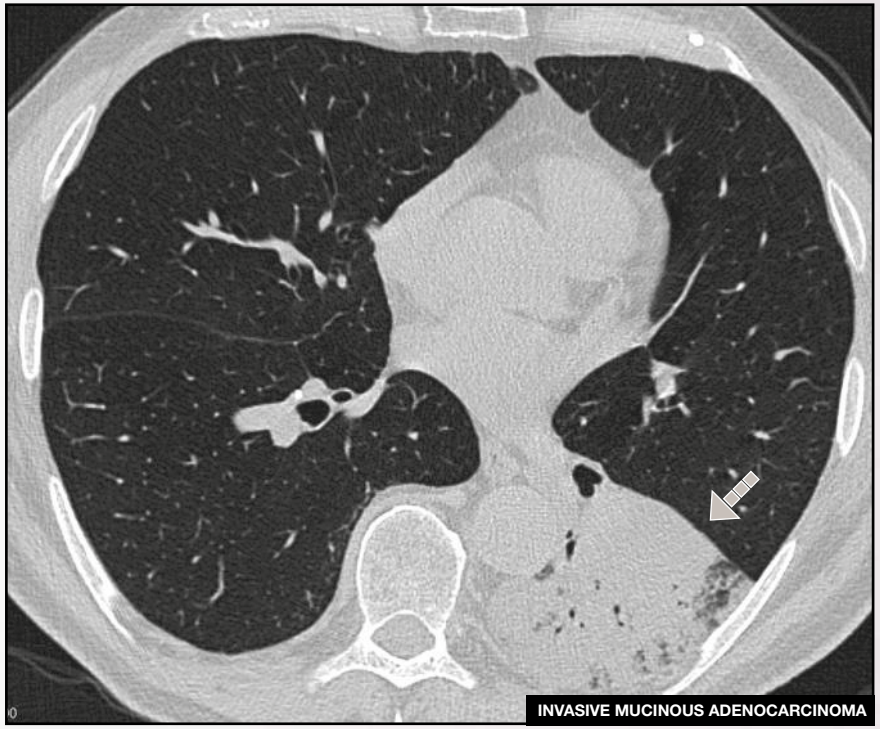
CHARACTERISTICS

- Increase in pulmonary attenuation, generally homogenous
  - Obscuration of the margins of vessels, and airway walls
  - Air bronchogram could be present
  - Little to no degree of pulmonary collapse

DIAGNOSTIC ORIENTATION

- It is useful to distinguish between acute consolidation and prolonged consolidation (> 8 weeks)
- In cases of prolonged consolidation, the following diagnoses can be considered:
  - pneumonic-type mucinous adenocarcinoma
  - pulmonary lymphoma
  - organising pneumonia (possible migration)
  - chronic eosinophilic pneumonia (possible migration)
  - exogenous lipoid pneumonia (low attenuation < -30 HU)

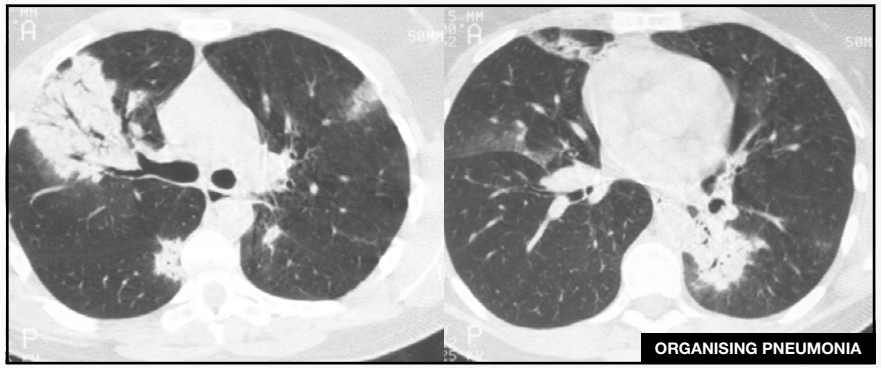
CONSOLIDATION



Consolidation of the left low lobe

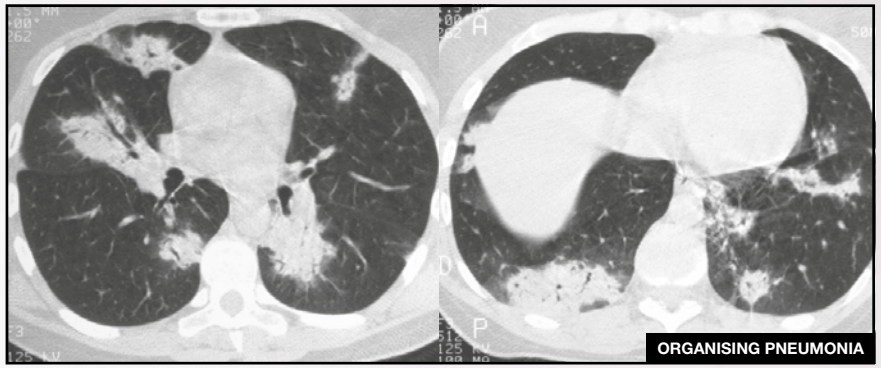
- Chronically evolving pulmonary consolidation (> 8 weeks) that is retractile with air bronchogram.
- The chronic nature of it means a fibroscopy with lavage must be performed.
- If results are negative, a transparietal lung biopsy should be suggested.

ALVEOLAR CONSOLIDATION



Bilateral subpleural alveolar consolidation with air bronchogram, in a patient with chronic cough.
- Note whether the foci migrate between the two scans, strengthening the argument for organising pneumonia.

ALVEOLAR CONSOLIDATION



MICRONODULATION

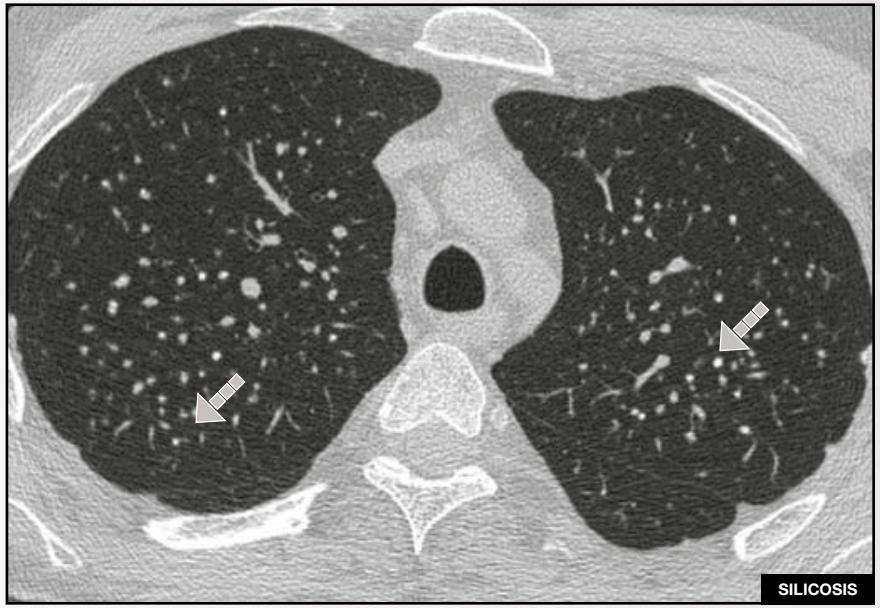
CHARACTERISTICS

- Focal rounded opacities < 3 mm presenting the following characteristics:
  - Attenuation: ground glass opacity or tissular or even calcified
  - Borders: blurry to clear

DIAGNOSTIC ORIENTATION

- The location of micronodulations helps guide the diagnosis:
  - within the lungs
  - within the secondary pulmonary lobule: key to diagnosis
- The CT scans helps categorise diffuse micronodulations based on three types of lobular distribution, thereby significantly reducing the differential diagnosis:
  - random micronodulation
  - centrilobular micronodulation
  - perilymphatic micronodulation

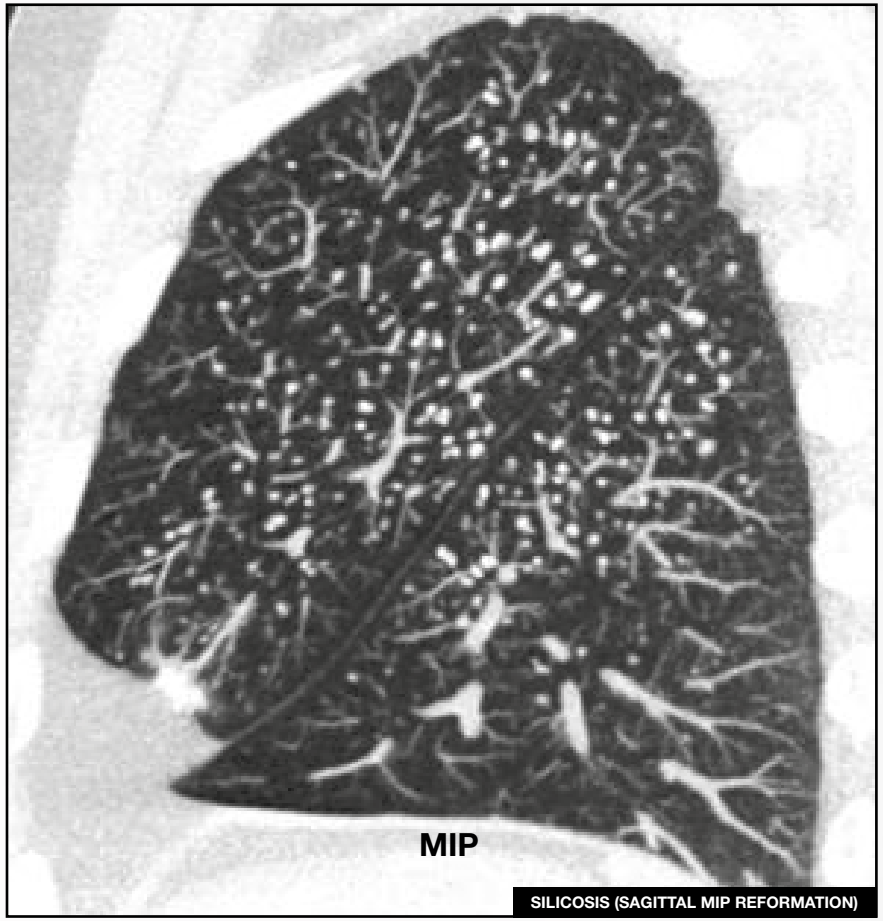
MICRONODULATION, PERILYMPHATIC DISTRIBUTION



Micronodules

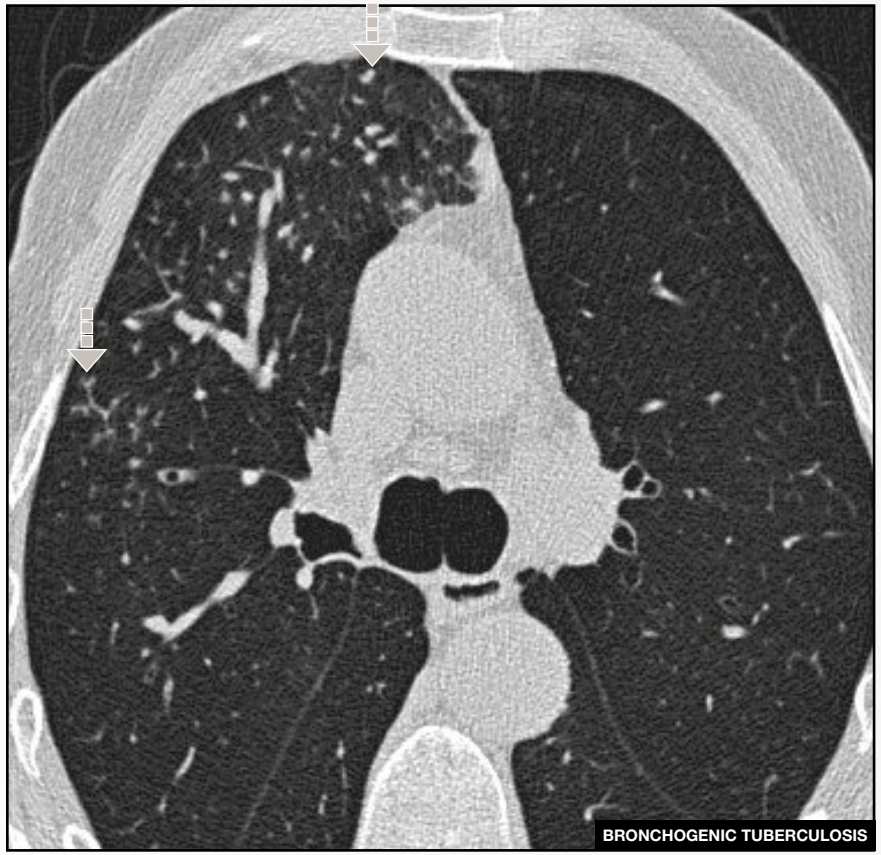
- Coal workers' pneumoconiosis.
- Extensive micronodulation with a perilymphatic distribution. Micronodules have an apical and posterior predominance.

MICRONODULATION



Centrilobular and perilymphatic micronodulation.

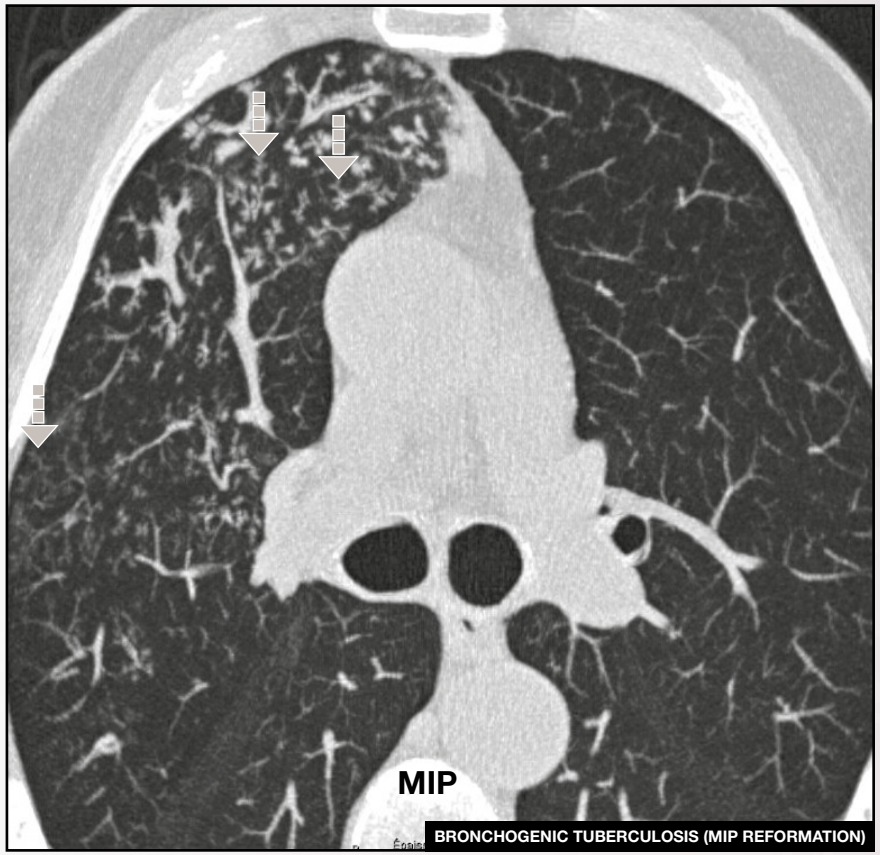
MICRONODULATION, CENTRILOBULAR DISTRIBUTION



Micronodulation

Micronodulation in the ventral segment of the right upper lobe sparing the subpleural part of the lung.

MICRONODULATION, CENTRILOBULAR DISTRIBUTION



Micronodulation

Micronodulation in the ventral segment of the right upper lobe forming the tree-in-bud pattern indicative of cellular bronchiolitis (***M. tuberculosis*** infection).

RANDOM MICRONODULATION

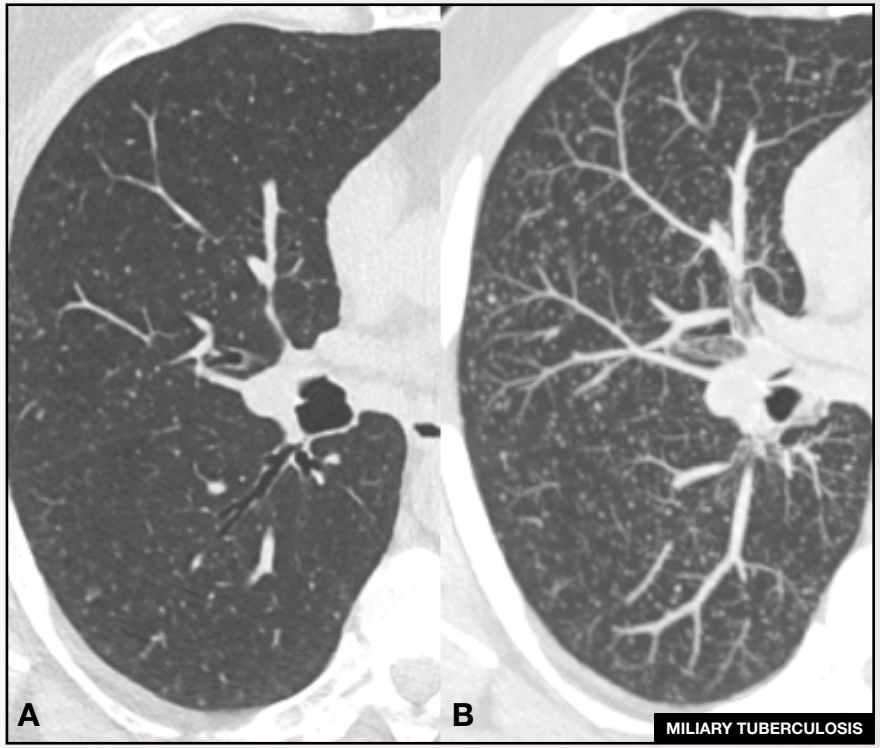
CHARACTERISTICS

- Micronodules with identical diameters spread at regular intervals across the two pulmonary areas without any predominance of topographical elements compared to the pleural surface, fissures, bronchovascular elements, and boundaries of the lobule

DIAGNOSTIC ORIENTATION

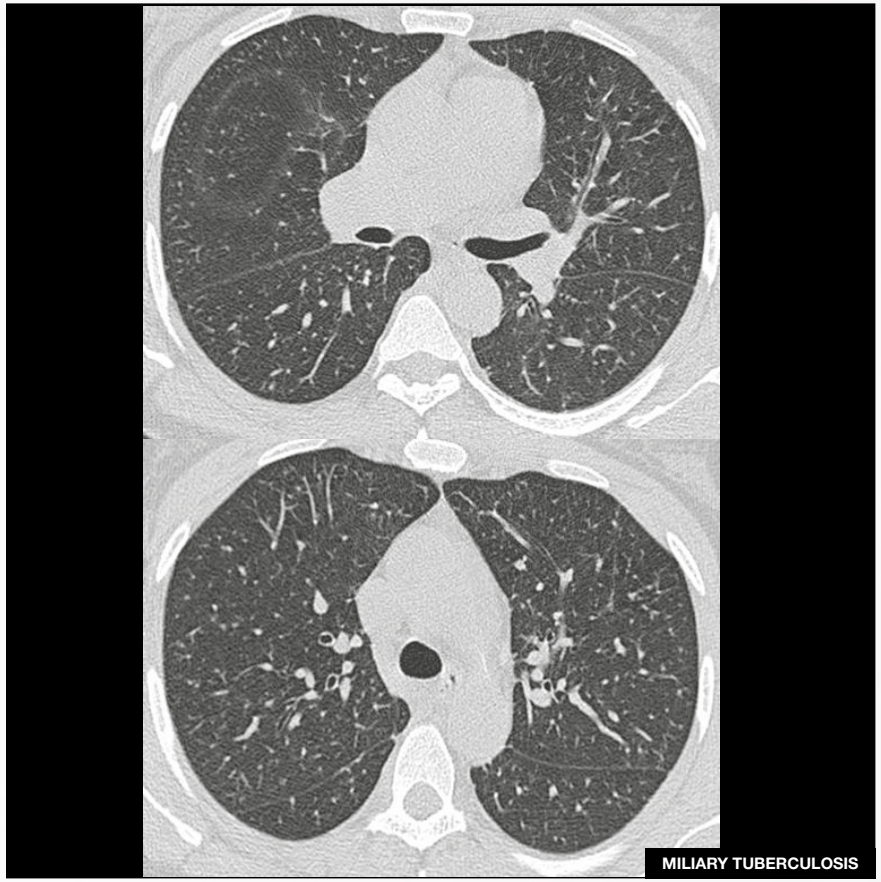
- Random micronodulations can be associated with different conditions:
  - miliary (haematogenous) tuberculosis
  - miliary (haematogenous) metastases
  - miliary mycosis (aspergillosis, candidosis)
  - virosis (herpes, Cytomegalovirus)

RANDOM MICRONODULATION



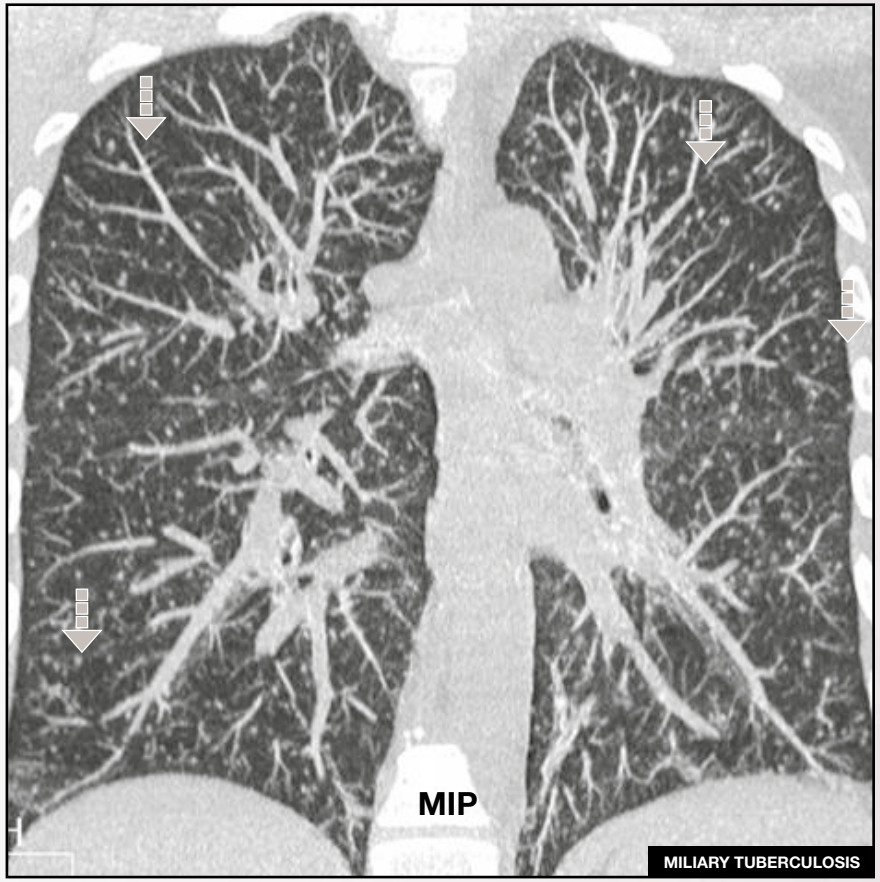
Multitude of dense micronodules spread bilaterally and ubiquitously on HRCT (A); MIP reformation (B) helps the detection of micronodules and allows to assert their random distribution.

RANDOM MICRONODULATION



Random micronodulation in an inflammatory context suggesting miliary tuberculosis.

RANDOM MICRONODULATION



Micronodules

MIP reformation helps confirming random micronodulation.

CENTRILOBULAR MICRONODULATION

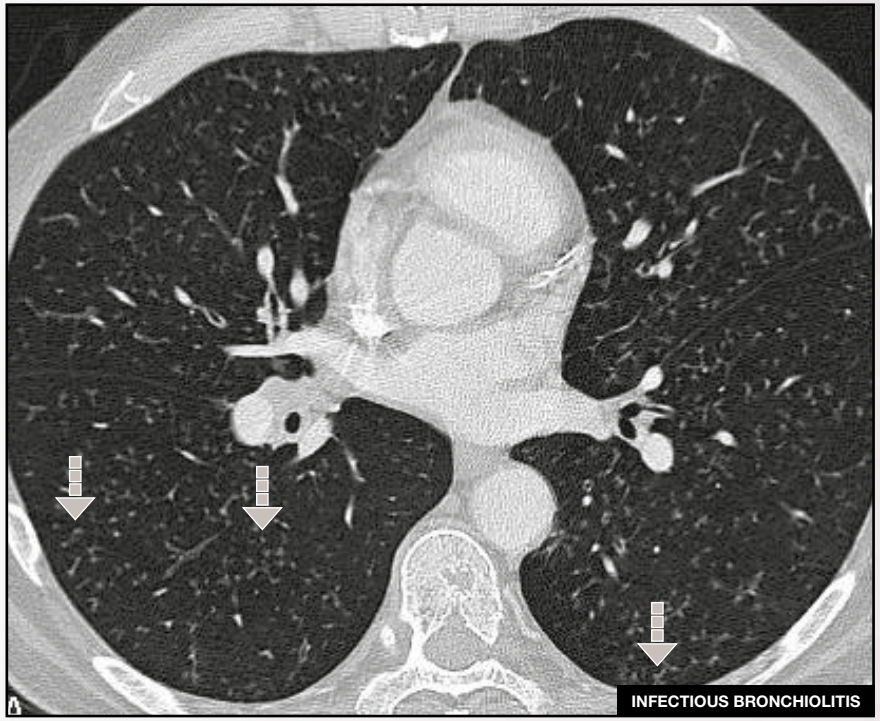
BRANCHING CENTRILOBULAR MICRONODULATIONS (TREE-IN-BUD PATTERN) OF BRONCHIOLAR ORIGIN ARE ASSOCIATED WITH DIFFERENT CONDITIONS

- Infectious bronchiolitis
  - tuberculosis, atypical mycobacteria, cytomegalovirus, Aspergillus, Candida, and other bacteria
- Aspiration, inhalation (gas, smoke)
- Follicular bronchiolitis
  - Sjögren's syndrome, rheumatoid arthritis, immune system deficiencies
- Bronchiectasis, cystic fibrosis, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis, panbrochiolitis, constrictive bronchiolitis

CENTRILOBULAR MICRONODULES CAN ALSO BE ASSOCIATED WITH VASCULAR AND PERIVASCULAR DISEASES

- Vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis)
- Endovascular metastases
- Pulmonary haemorrhage
  - miliary mycosis (aspergillosis, candidosis)
  - virosis (herpes, Cytomegalovirus)

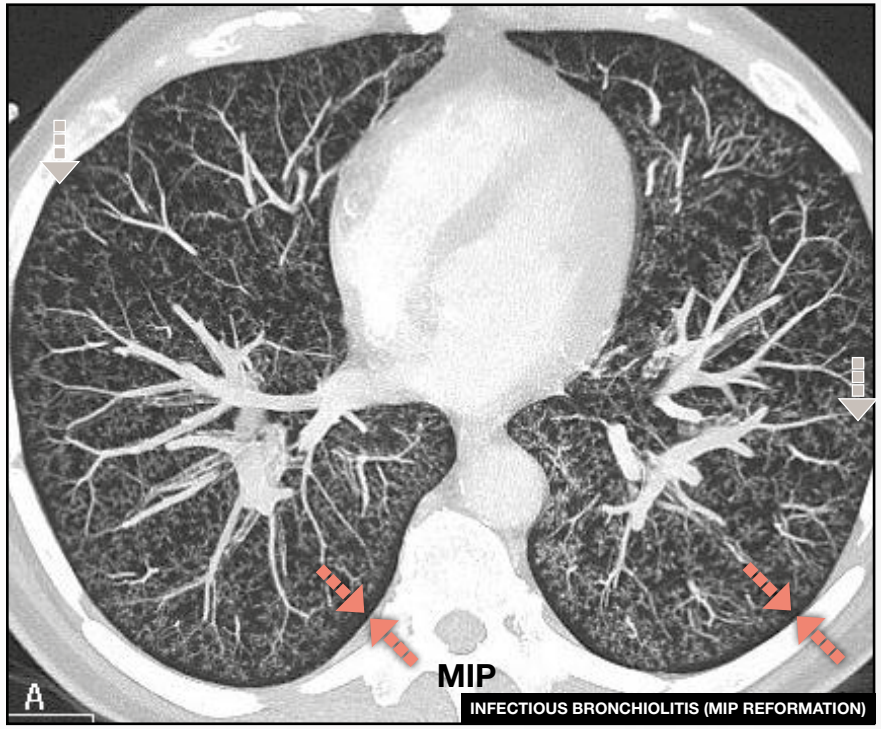
CENTRILOBULAR MICRONODULATION



Micronodules

- Bilateral micronodules sparing the subpleural lung.

CENTRILOBULAR MICRONODULATION



Tree-in-bud sign Subpleural lung intact

Axial MIP image shows tree-in-bud pattern in a bilateral distribution.

SIMPLE CENTRILOBULAR MICRONODULATION

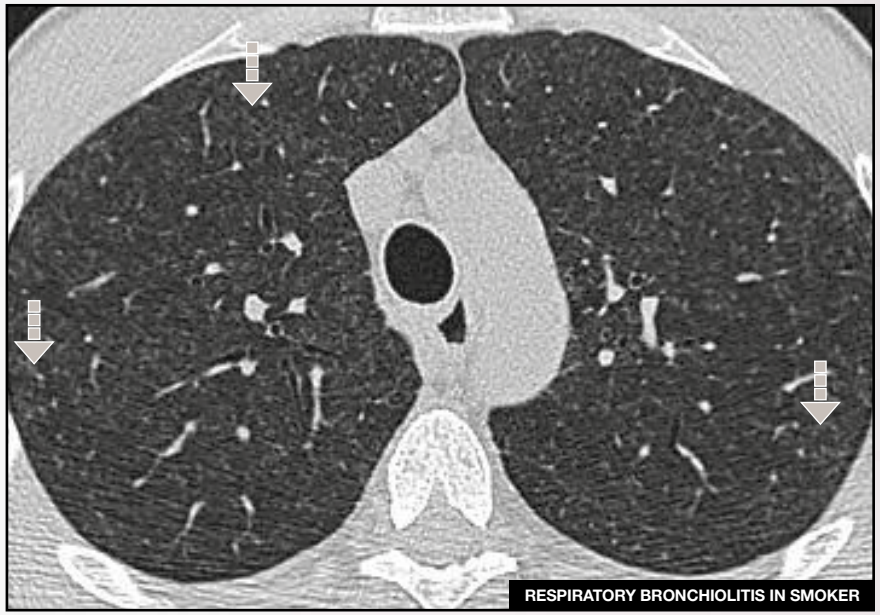
SIMPLE CENTRILOBULAR MICRONODULATIONS ARE PRIMARILY ASSOCIATED WITH SMALL AIRWAYS DISEASES

- Bronchiolar inflammation
  - Hypersensitivity pneumonitis, respiratory bronchiolitis, histiocytosis, asthma, allergic bronchopulmonary aspergillosis, follicular bronchiolitis (connective tissues), pneumoconiosis
- Lepidic adenocarcinoma
- Infectious bronchiolitis
  - Tuberculosis, atypical mycobacteria, bronchopneumonia

THIS LESION CAN ALSO BE FOUND

- In angiocentric conditions: pulmonary oedema, vasculitis, talcosis, pulmonary haemorrhage, haemosiderosis, metastatic calcifications, pulmonary arterial hypertension, metastases
- In perilymphatic conditions, the centrilobular nodules are rarely isolated

SIMPLE CENTRILOBULAR MICRONODULATION



Micronodules

Poorly defined and low attenuation micronodules within the upper lobes in an active smoker.

PERILYMPHATIC MICRONODULATION

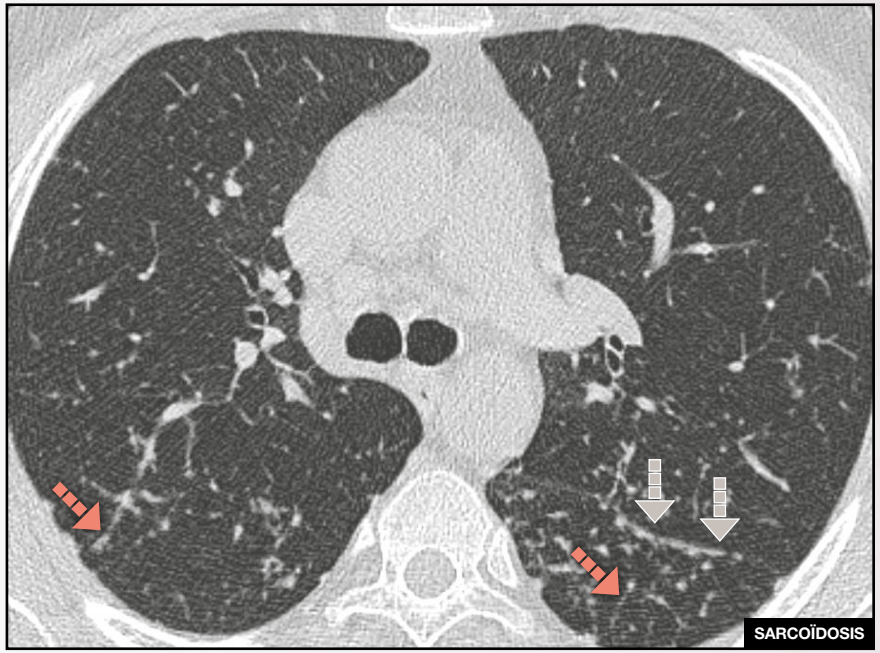
CHARACTERISTICS

- Perilymphatic micronodules are well defined nodules < 3 mm
- Their distribution is along the lymphatic vessels:
  - the fissures and the pleura
  - the interlobular septa
  - the vascular and bronchial routes
  - in the center of the lobule

DIAGNOSTIC ORIENTATION

- Perilymphatic micronodulations can be associated with different conditions:
  - sarcoidosis
  - lymphangitic carcinomatosis
  - silicosis
  - berylliosis
  - diffuse amyloidosis
  - primary pulmonary lymphoma
  - lymphoid interstitial pneumonia (Sjögren's syndrome, autoimmune diseases, HIV)

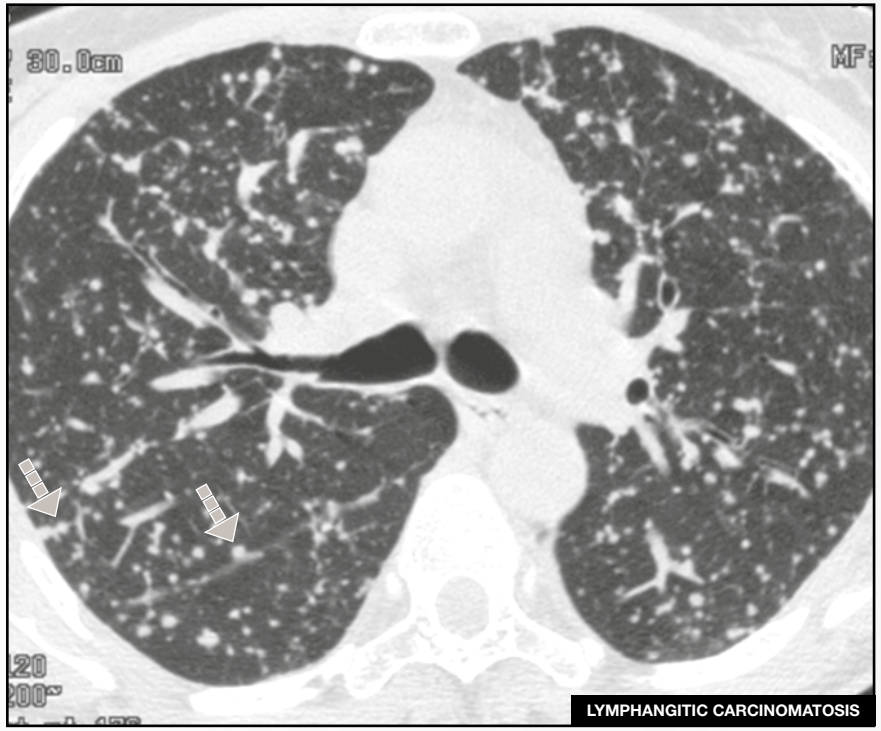
PERILYMPHATIC MICRONODULATION



Fissures Intralobular septa

Micronodules with clear outlines & high densities distributed along fissures, peripheral pleura, and intralobular septa.

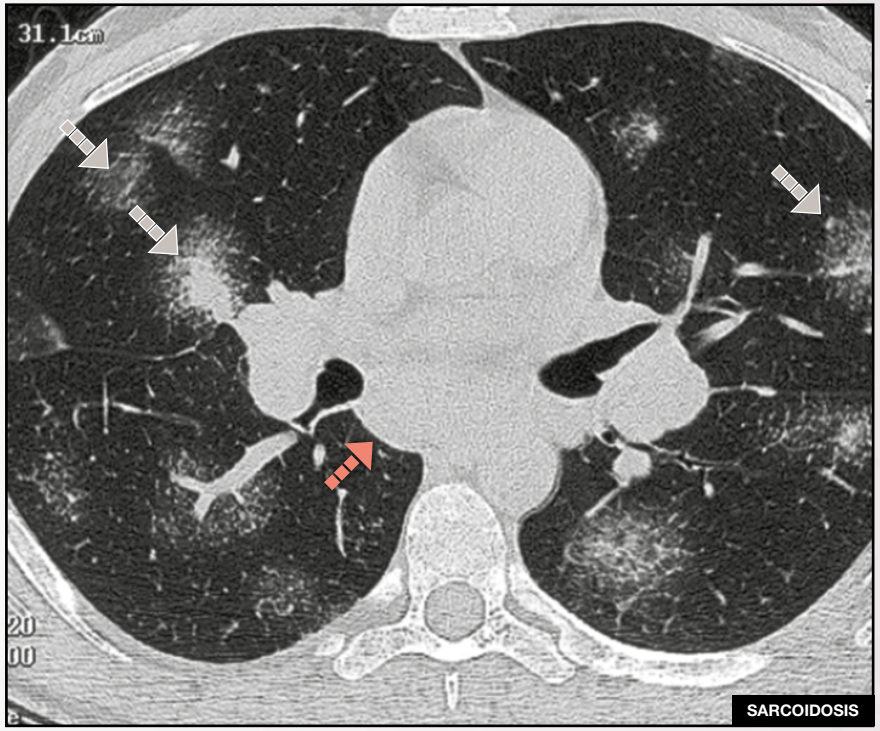
PERILYMPHATIC MICRONODULATION



Perilymphatic micronodulation

Patient presenting an adenocarcinoma in the stomach and micronodulation of the lung with a perilymphatic distribution related to lymphangitic carcinomatosis.

GALAXY SIGN



Grouped micronodules Subcarinal space

HRCT shows large sarcoid nodules resembling galaxies associated with enlarged sub carinal lymphnodes.

CYSTS

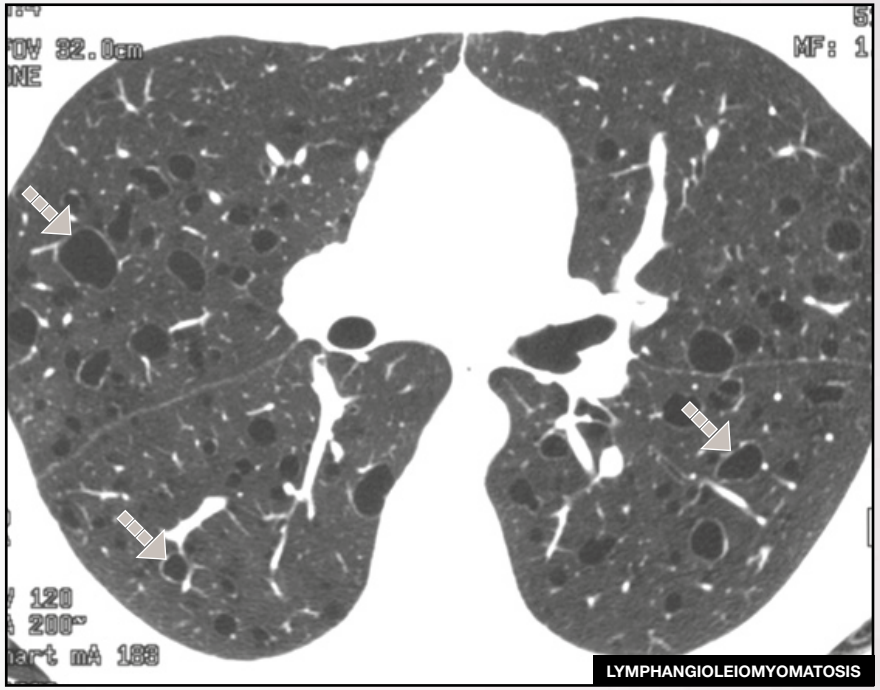
CHARACTERISTICS

- A cyst appears as a well-defined round or oval-shaped parenchymal lucency bordered by a thin, regular wall (< 2 mm)
- The adjacent pulmonary parenchyma can be strictly normal or present associated lesions: nodules, ground-glass opacities, septal thickening, or reticular CT pattern

DIAGNOSTIC ORIENTATION

- Emphysema, bronchiectasis
- To establish the diagnosis, it is important to check for associated signs: renal tumour, lymphangioma, chylothorax

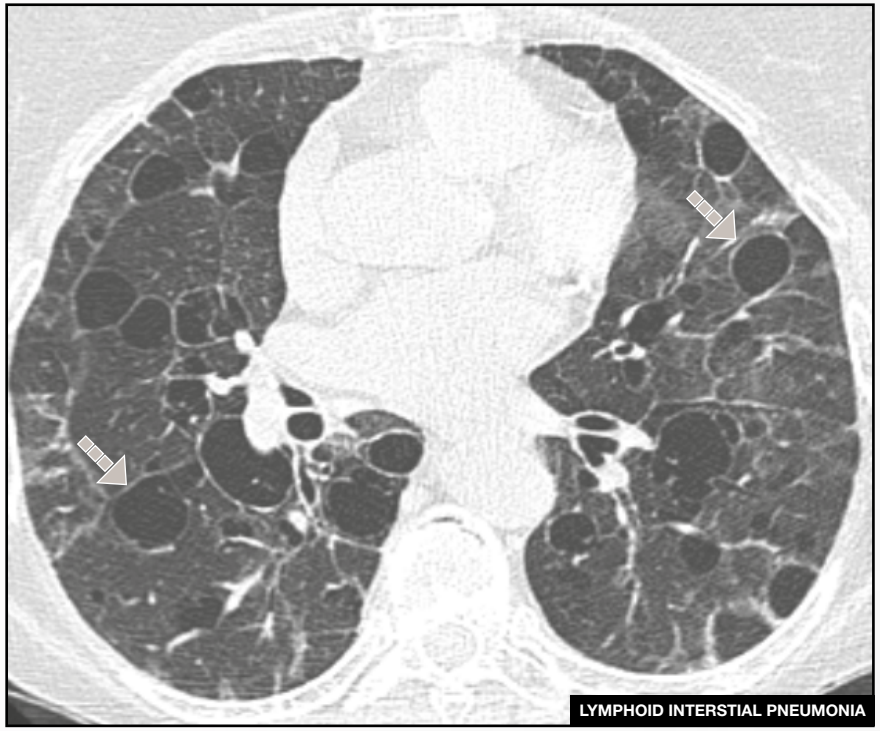
CYSTS



Cysts

HRCT shows multiple cysts throughout the lung parenchyma in a young female patient. Note that the adjacent lung is unremarkable.

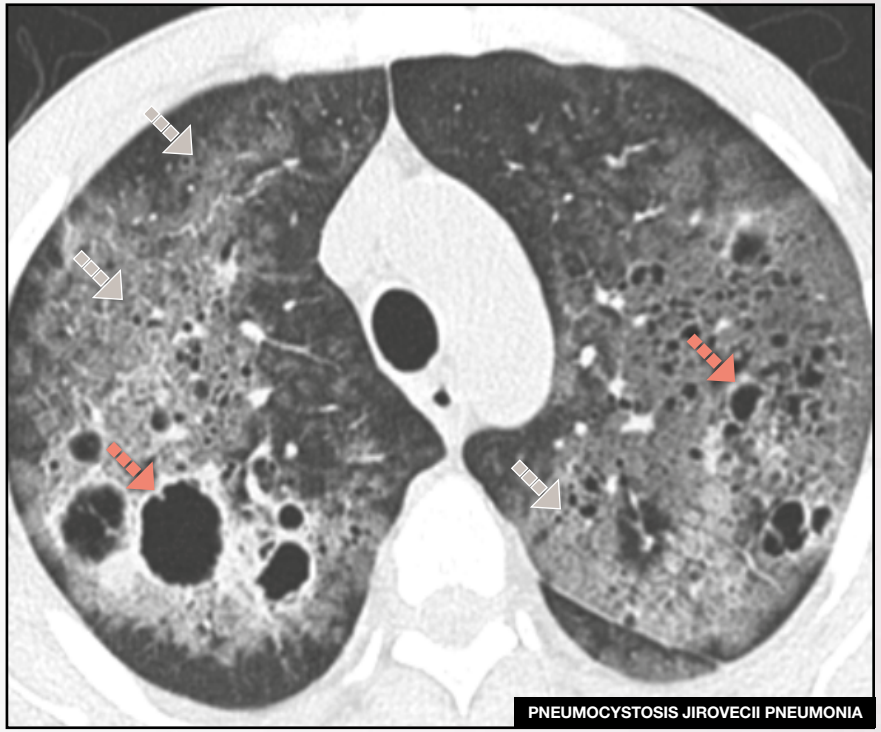
CYST



Cysts

72-year-old woman with Sjögren's syndrome and lymphoid interstitial pneumonia. HRCT shows bilateral ground-glass opacities and multiple thin-walled cysts.

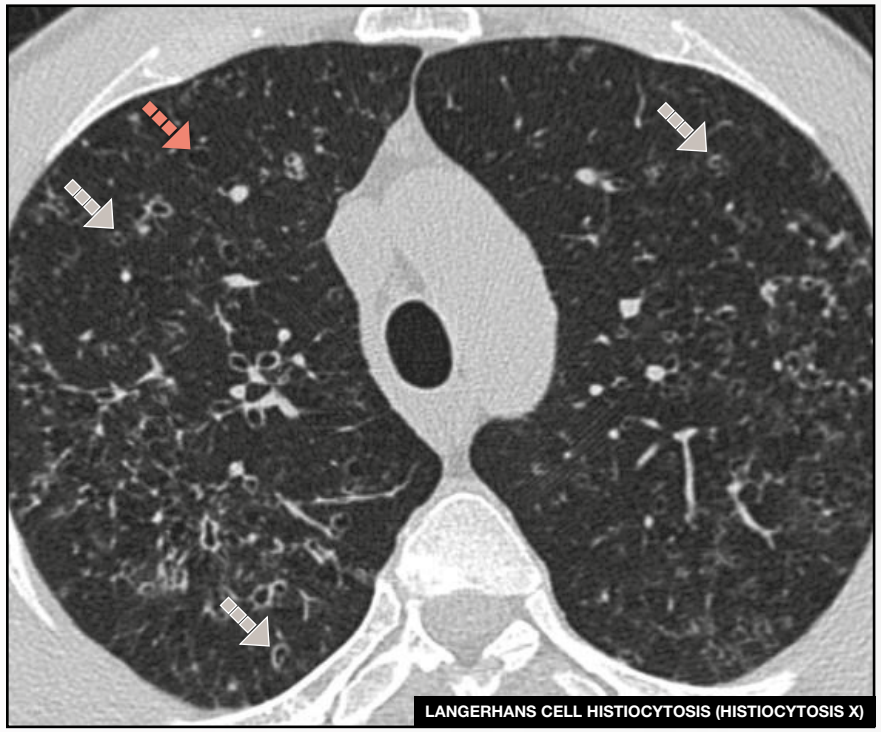
CYST - GROUND-GLASS OPACITIES



Ground-glass opacities Cysts

34-year-old man, HIV positive at AIDS stage. Progressive dyspnea for 1 month. The HRCT shows diffuse ground-glass opacification with cysts of variable size. Diagnosis of pulmonary jirovecii pneumonia was done on bronchoalveolar lavage.

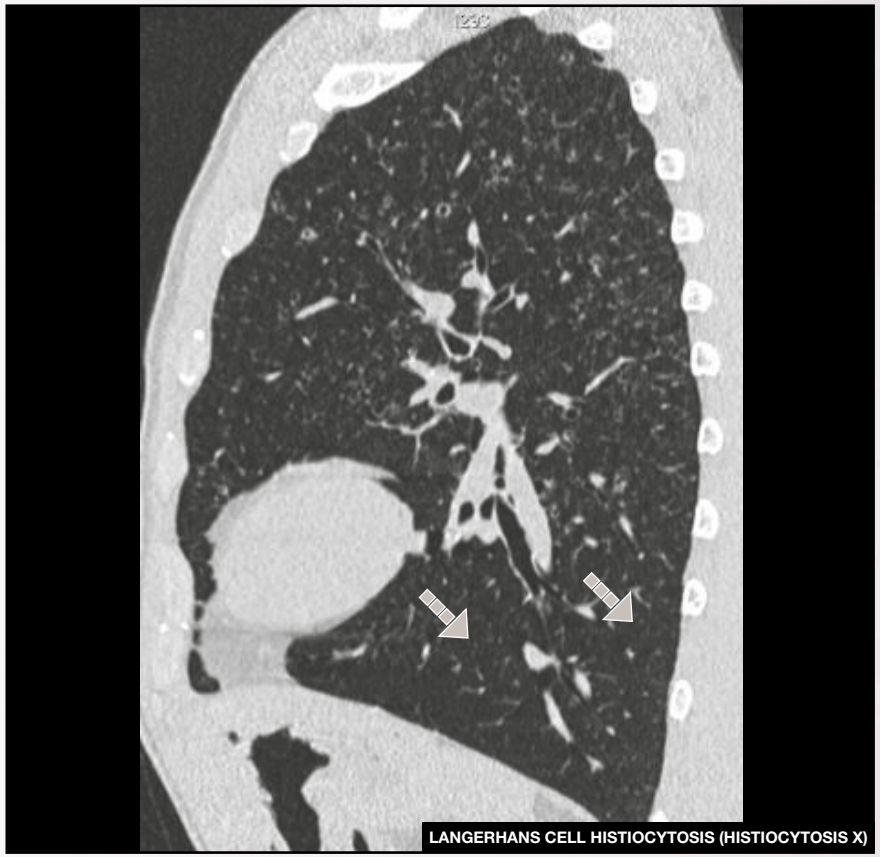
CYST - NODULE



Cavitary nodules Cysts

HRCT at the level of the upper lobes shows numerous micronodules, cavitated nodules, and cysts in a 32-year-old man curent smoker who developped langerhans cell histiocytosis.

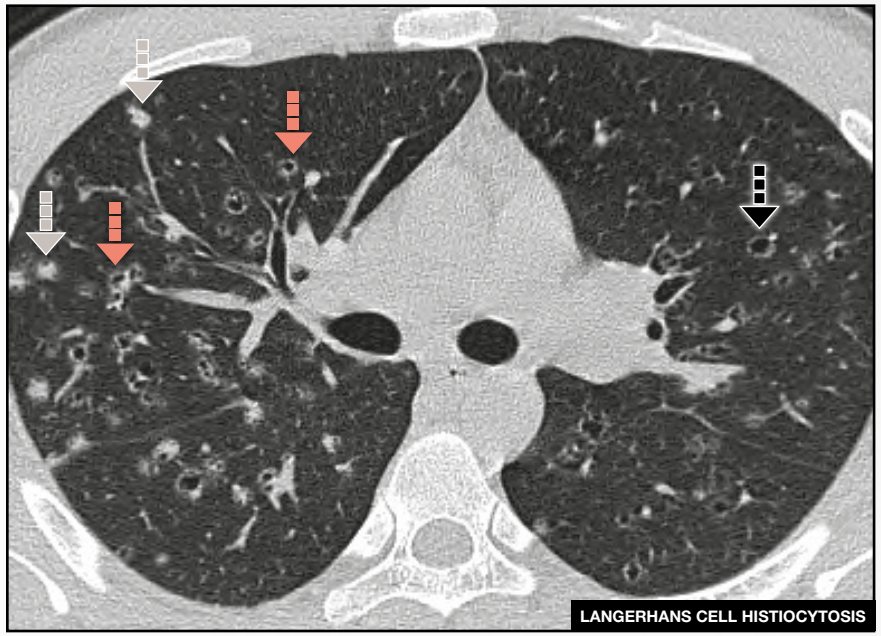
CYST - NODULE



Lower portion spared

Sagittal reformation in the same patient shows the upper lobe distribution of parenchymal abnormalities.

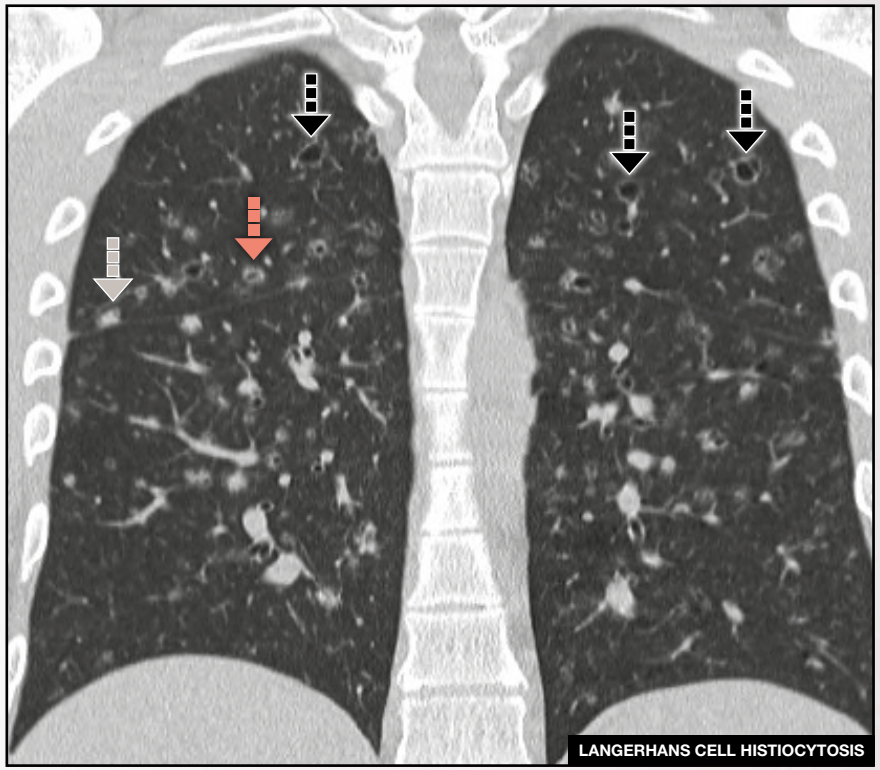
CYST - NODULE



Nodules Cavitary nodules Cysts

The patient is a 28-year-old male, smoker, with langerhans cell histiocytosis.
HRCT at the level of middle zone shows bilateral and symetrical abnormalities of the lung parenclyma consisting in nodules, cavitated nodules, and cysts.

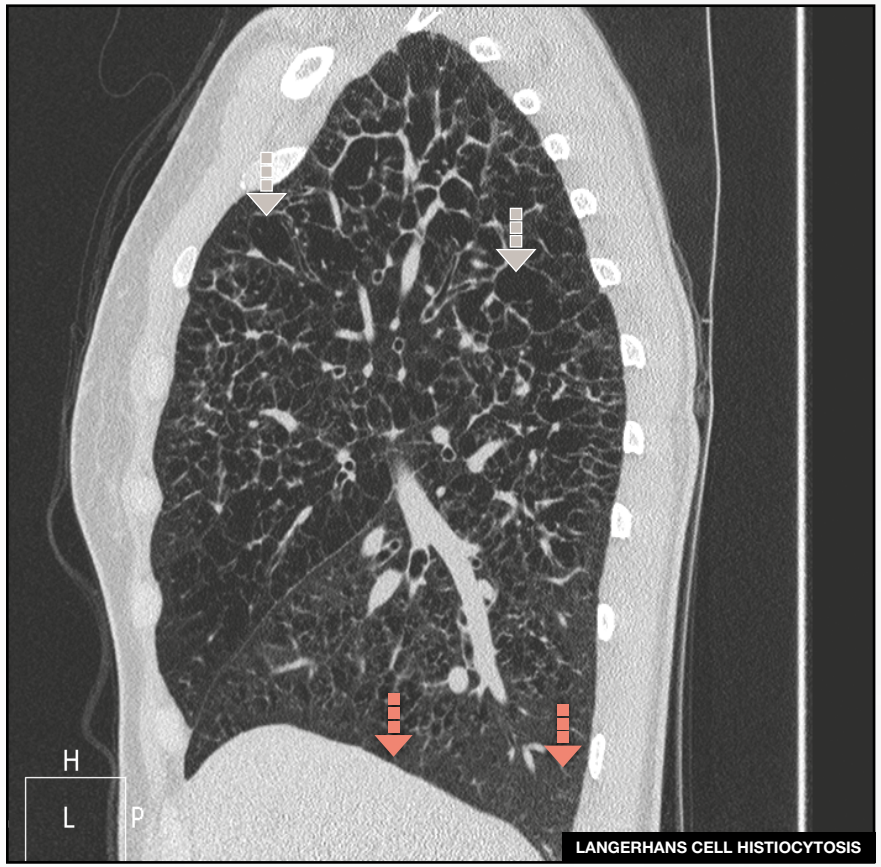
CYST - NODULE



Nodules Cavitary nodules Cysts

Same patient - coronal reformation shows that the abnormalities are predominating in the upper lungs.

CYSTS WITH "BIZARRE SHAPE"



Irregular pulmonary cysts Lower pulmonary strips spared

Sagittal reformation in a 58-year-old patient who was a former smoker and developped langerhans cell histiocytosis. HRCT shows large cysts with bizarre shapes.

DIAGNOSTIC ORIENTATIONS

Pulmonary cysts

Cysts + normal lung	Cysts + nodules	Cysts + ground-glass opacity
- Lymphangioleio myomatosis (women) - Histiocytosis X (Tobacco ?) - Birt-Hogg-Dubé - Metastasis	- Histiocytosis X (Tobacco ?) - Metastasis - Lymphocytic interstitial pneumonia (LIP) + amyloidosis - Respiratory bronchiolitis-ILD - Papillamatosis	- Pneumocystis jirovecii pneumonia - Subacute Hypersensitivity pneumonia - LIP - Nieman Pick disease - Light chains disease

Pulmonary cysts

With renal tumor	With known extra-renal tumor	Family history of pneumothorax
- LLMM - Birt-Hogg-Dubé	- Cystic metastases (bladder, ENT, uterus, sarcoma, thyroid...)	- LLMM - Birt-Hogg-Dubé - Marfan syndrome - Ehlers-Danlos

HONEYCOMBING

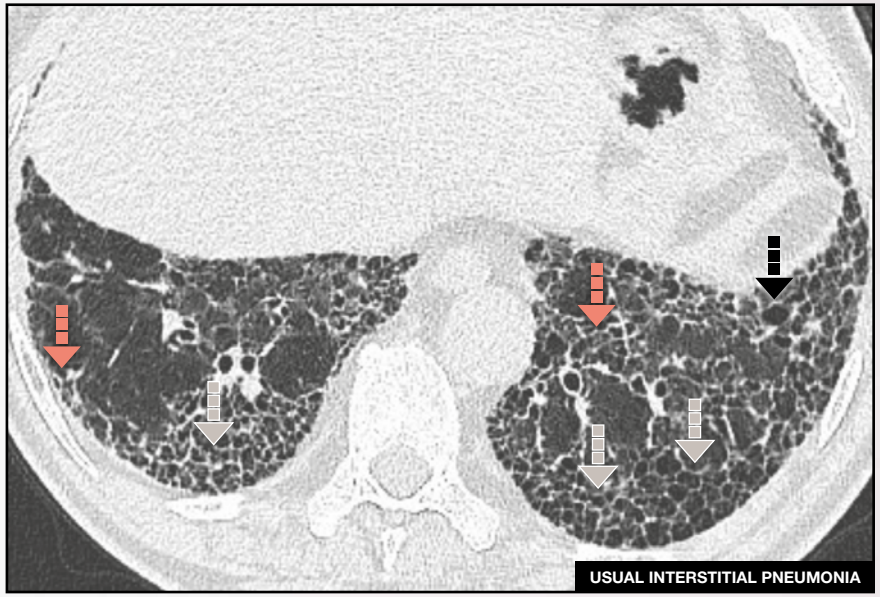
CHARACTERISTICS

- Clustered cystic airspaces with well defined walls, measuring 2-10 mm in diameter, sometimes reaching 25 mm, usually in subpleural regions

ASSOCIATED SIGNS WITH HONEYCOMBING

- Intralobular reticulation
- Traction bronchiectasis and bronchiolectasis
- Loss of lobar volume
- Fissured distortion

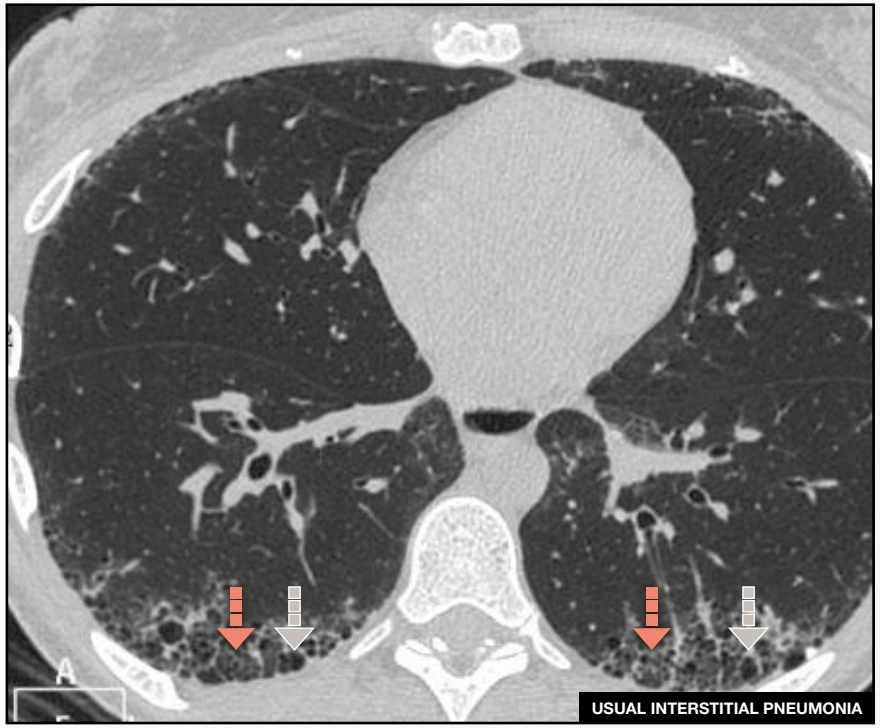
HONEYCOMBING



Honeycombing Intralobular reticulations of the lower sections Traction bronchiectasis

Subpleural honeycombing forming several layers of cysts in a 73-year-old man with usual interstitial pneumonia.

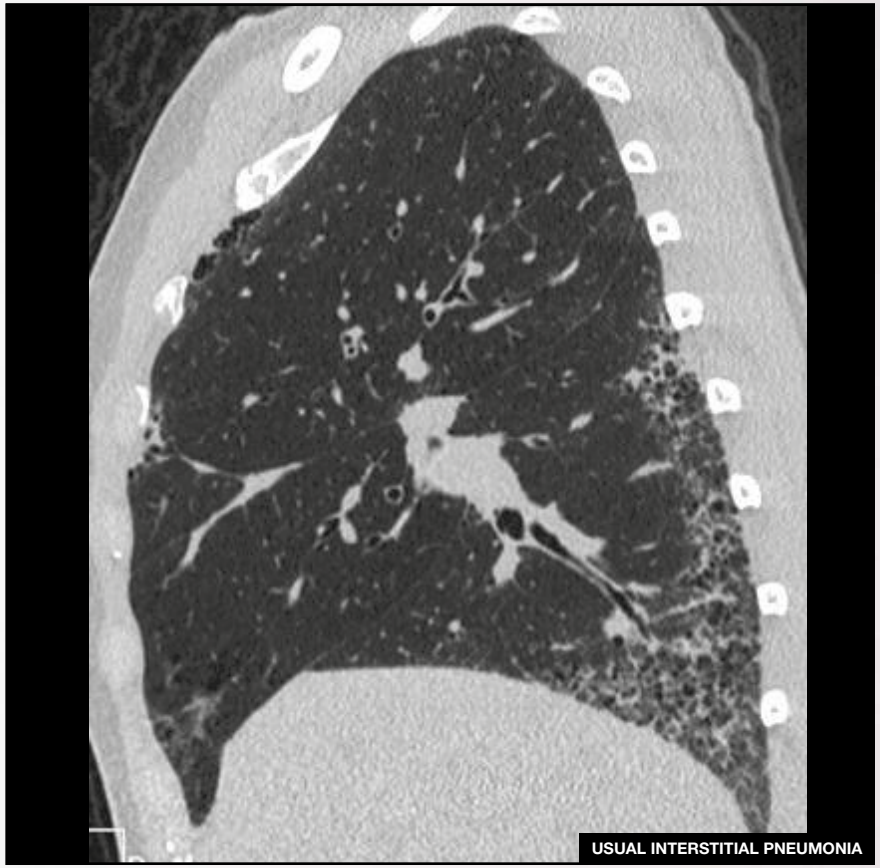
HONEYCOMBING



Subpleural honeycombing Intralobular reticulations

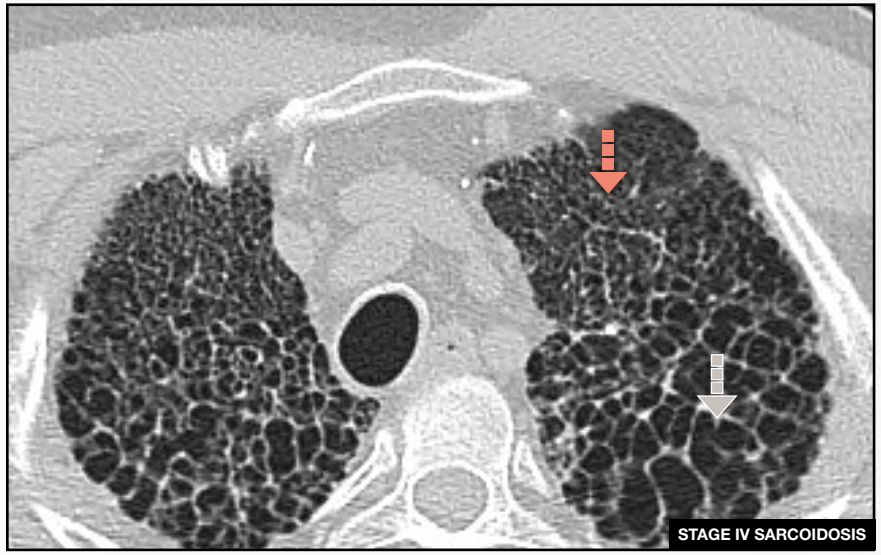
69-year-old man with usual interstitial pneumonia. Subpleural honey combing is associated with reticular pattern.

HONEYCOMBING



Sagittal reformation in the same patient showing the preferential subpleural and basal distribution.

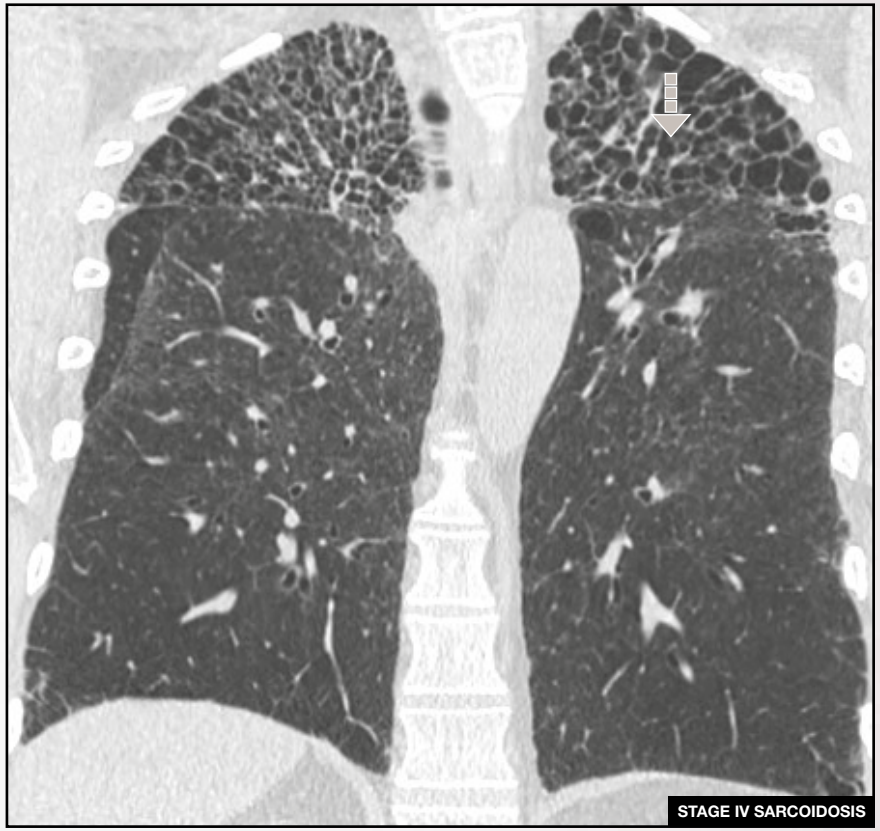
HONEYCOMBING



Honeycombing Reticulations of biapical distribution

56-year-old man with history of sarcoidosis. Typical honeycombing in a upper lobe distribution.

HONEYCOMBING



Honeycombing

- Coronal reformation in the same patient shows the association of honeycombing and reticulation in lung apices.
- Distribution of fibrosis to apices makes this fibrosis incompatible with UIP.

TRACTION BRONCHIECTASIS/ BRONCHIOLECTASIS

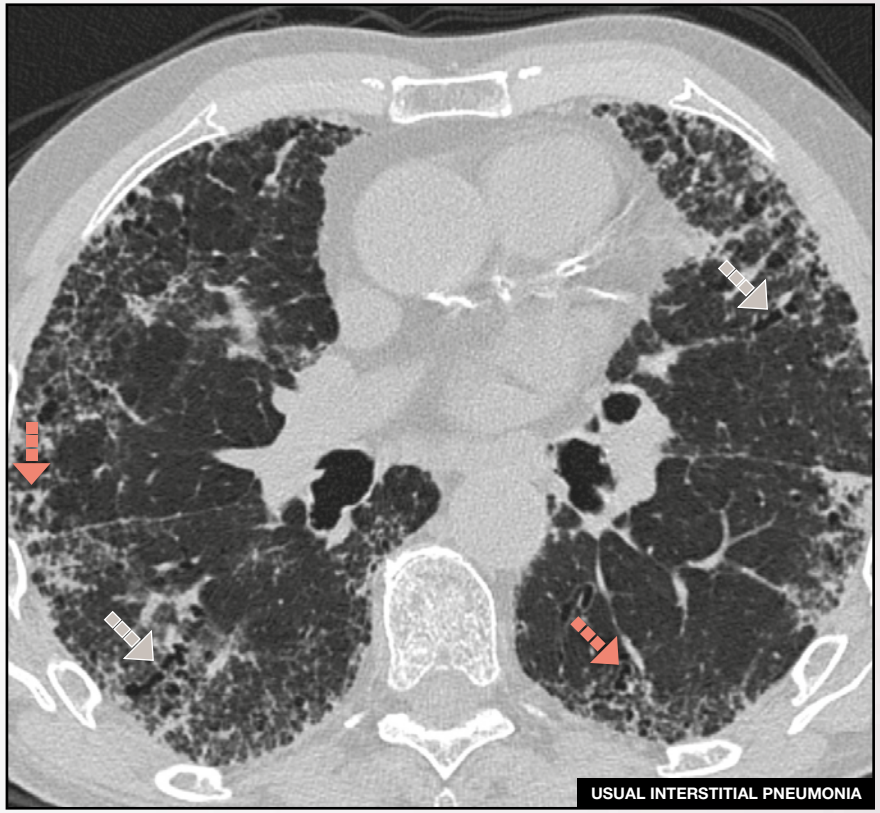
CHARACTERISTICS

- Abnormal and irregular dilation of the bronchi/bronchioles due to respiratory tract inflammation (sometimes reversible) or pulmonary fibrosis
- On a high-resolution CT scan, it appears as an increase in the calibre of the distal respiratory tract (no reduction in the diameter peripherally, visibility in the subpleural lung at least 20 mm from the pleura)
- On the scan, they present as tubular or cystic air spaces depending on the orientation of the bronchi in the cross-section
- Differentiating between traction bronchiectasis and honeycomb is sometimes difficult on axial cross-sections. Sagittal or coronal cross-sections and the minIP are useful

DIAGNOSTIC ORIENTATION

- Traction bronchiectasis are associated with signs of fibrosis

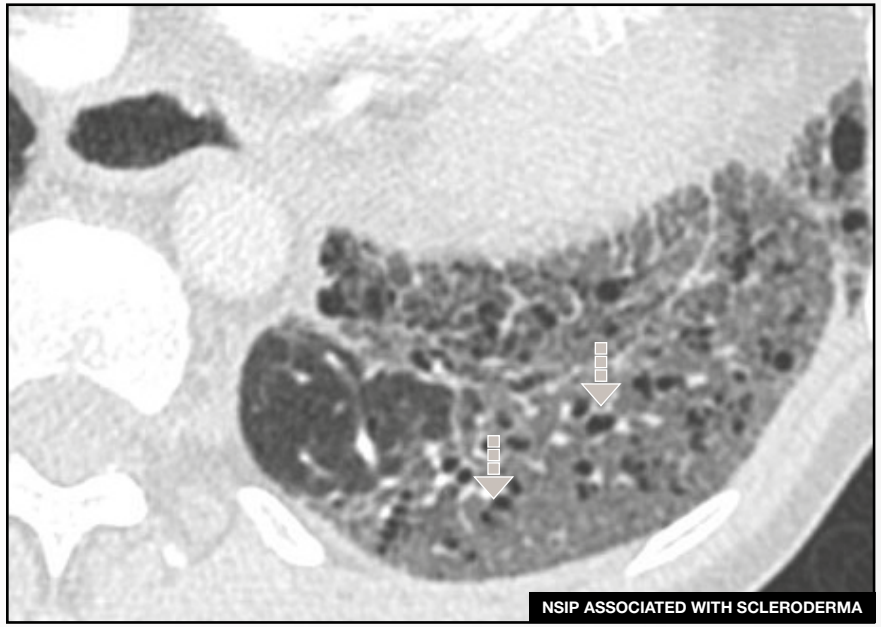
TRACTION BRONCHIECTASIS



Traction bronchiectasis Traction bronchiolectasis

72-year-old man with usual interstitial pneumonia. HRCT shows diffuse reticulations, and traction bronchiectasis and bronchiolectasis.

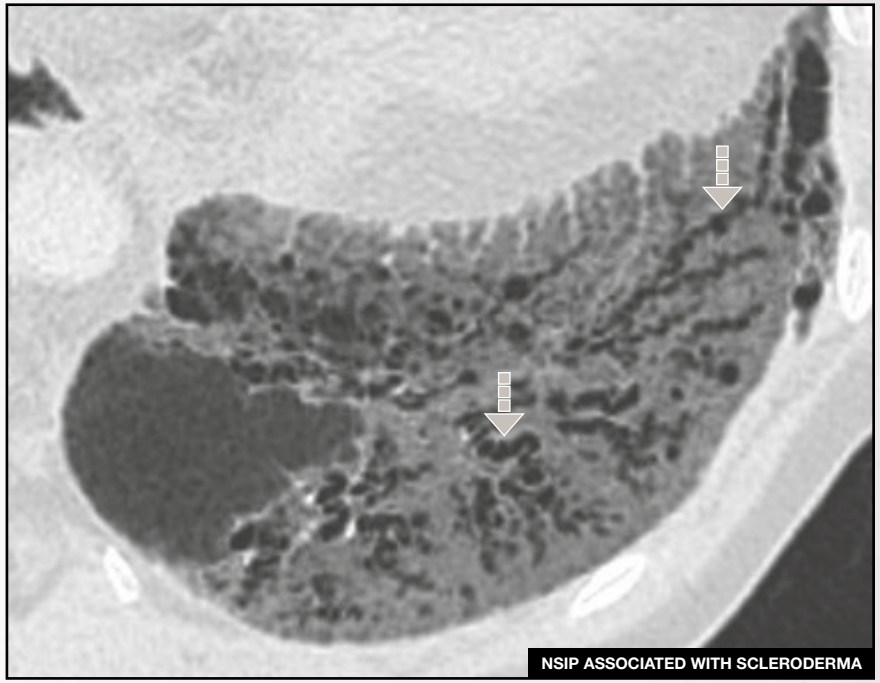
TRACTION BRONCHIECTASIS



Dilated bronchiolar lumina

42-year-old woman with systemic sclerosis and non specific interstitial pneumonia. HRCT shows extensive ground-glass opacities containing traction bronchiectasis and bronchiolectasis.

TRACTION BRONCHIECTASIS



Dilated and irregular bronchiolar lumina

Some patient minIP reformation 6-mm thick better demonstrates ectatic bronchioles within the ground-glass opacities.

CT DIAGNOSTIC CRITERIA FOR UIP

Thoracic high resolution CT scan is the **first line test** for diagnosing ILD and idiopathic pulmonary fibrosis (IPF).

In about 50% of cases, the thoracic HRCT shows a characteristic **usual interstitial pneumonia** (UIP) pattern, supporting the IPF diagnosis without performing lung biopsy in an appropriate clinical context.

For a CT to suggest UIP, a certain number of CT criteria must be met according to an official ATS/ERS/JRS/ALAT clinical pratice guideline.[1]

UIP	**Subpleural and basal predominance of anomalies** Distribution is often heterogeneous *Variants of distribution: occasionally diffuse, may be asymmetrical* **Honeycombing** with or without traction bronchiectasis or bronchiolectasis *Possibly superimposed mild ground-glass opacities, reticular pattern, pulmonary ossification*	
Probale UIP	**Subpleural and basal predominance of anomalies** Distribution is often heterogeneous **Reticular pattern with peripheral** traction bronchiectasis or bronchiolectasis *May have mild ground-glass opacities*	
Indeterminate for UIP	**Subpleural and basal predominant** **Subtle reticulation** may have mild ground-glass opacities or distortion **("early UIP pattern")** **CT features and/or distribution of lung fibrosis that do not suggest** any specific etiology **("truly indeterminate")"**	
Alternative diagnosis	**Predominant distribution** • **Peribronchovascular** • **Perilymphatic** • **Upper or mid-lung** CT features: • Cysts • Marked mosaic attenuation - Predominant GGO - Profuse micronodules - Centrilobular nodules - Nodules - Consolidation	**Orientation to a secondary pulmonary fibrose** • Pleural plaques (asbestosis) - Dilated esophagus (CTD) - Distal clavicular erosions (RA) - Extensive lymph node enlargement - Pleural effusions, pleural thickening (CTD/drugs)

1. Raghu G, *et al.* Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-e68.

VIDEO-ASSISTED SURGERY LUNG BIOPSY TECHNIQUE

Surgery Lung Biopsy (SLB) is indicated when the **scan does not show a typical appearance of IPF**.

The decision to suggest a video-assisted surgery lung biopsy is on **the discretion of the clinician following the multidisciplinary discussion** involving pulmonologists, radiologists, and pathologists involved in ILD. This decision must take into account:

- assessment of potential risks of the biopsy
- age
- comorbidities
- stage of the disease
- pulmonary function testing
- how the interstitial lung disease evolves

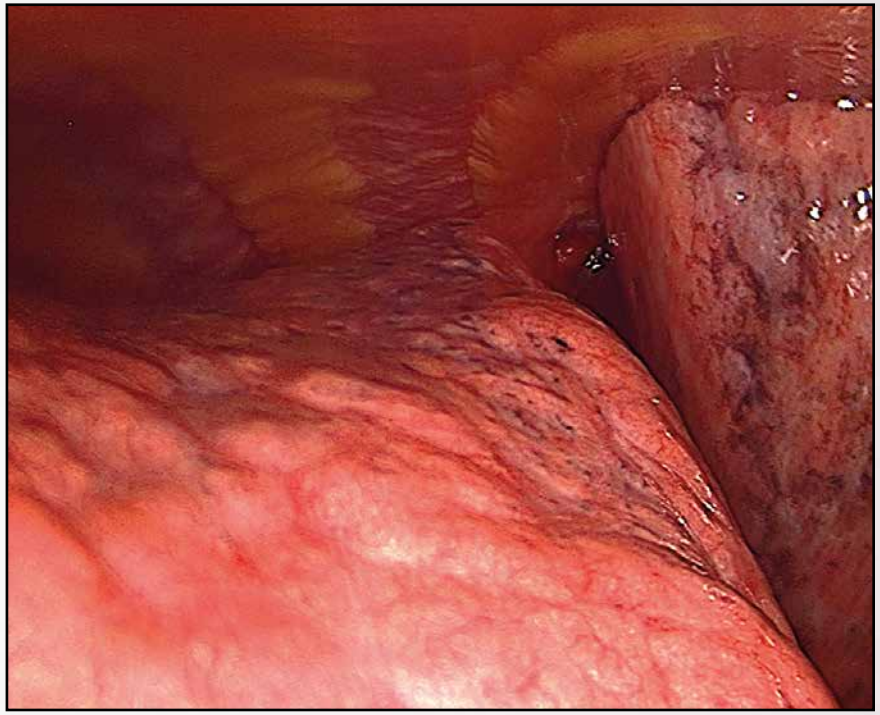
SLB TECHNIQUE

Videothoracoscopic lung biopsy is a relatively simple surgical technique, but it requires specific involvement of the surgeon to obtain a diagnosis in the majority of cases. Morbidity associated with the operation is estimated at 7% and mortality is under 1%. Morbidity is reportedly higher in patients with IPF.

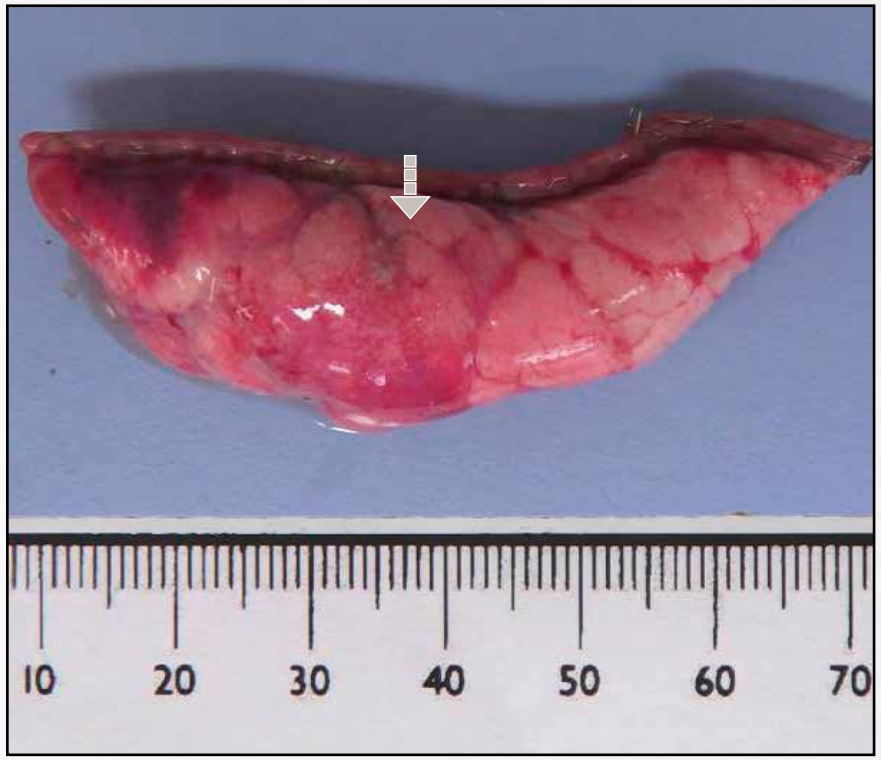
It is recommended to:

- **select** the site that will be biopsied using the **pre-op scan**
- biopsy at least **2 different lobes**
- make the biopsies around **3 cm**
- take the biopsy from the **bases of upper lobes** (posterior section of the fissure) and **lower lobes** (diaphragm section)
- not crush the parenchyma: **“No touch technic”**

THORACOSCOPY: MICRONODULAR PATTERN OF LUNG FIBROSIS



SURGICAL LUNG BIOPSY INFLATED WITH FORMALIN



Staple line

SURGICAL LUNG BIOPSY FIXED IN FORMALIN

PATCHWORK PATTERN

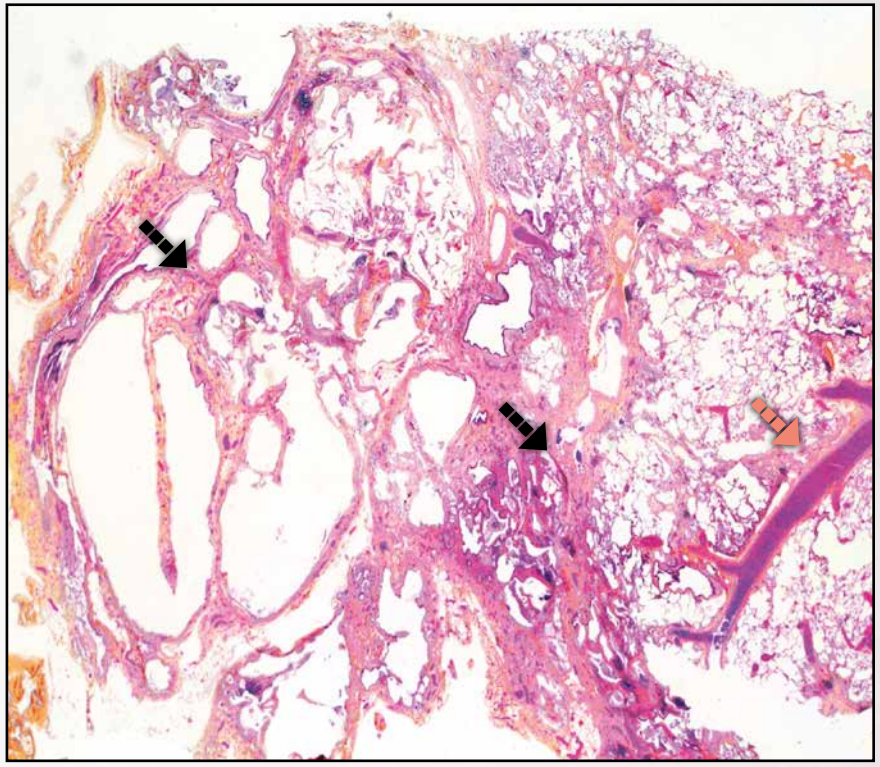
CHARACTERISTICS

- **Disseminated, non uniform patchwork pattern of interstitial fibrosis**
- Non-uniform, heterogeneous appearance with alternation between abnormal fibrotic areas and apparently normal lung parenchyma at low-magnification.
- The juxtaposition of abnormal areas and normal areas resembles a patchwork, hence the term “patchy”.

DIAGNOSTIC ORIENTATION

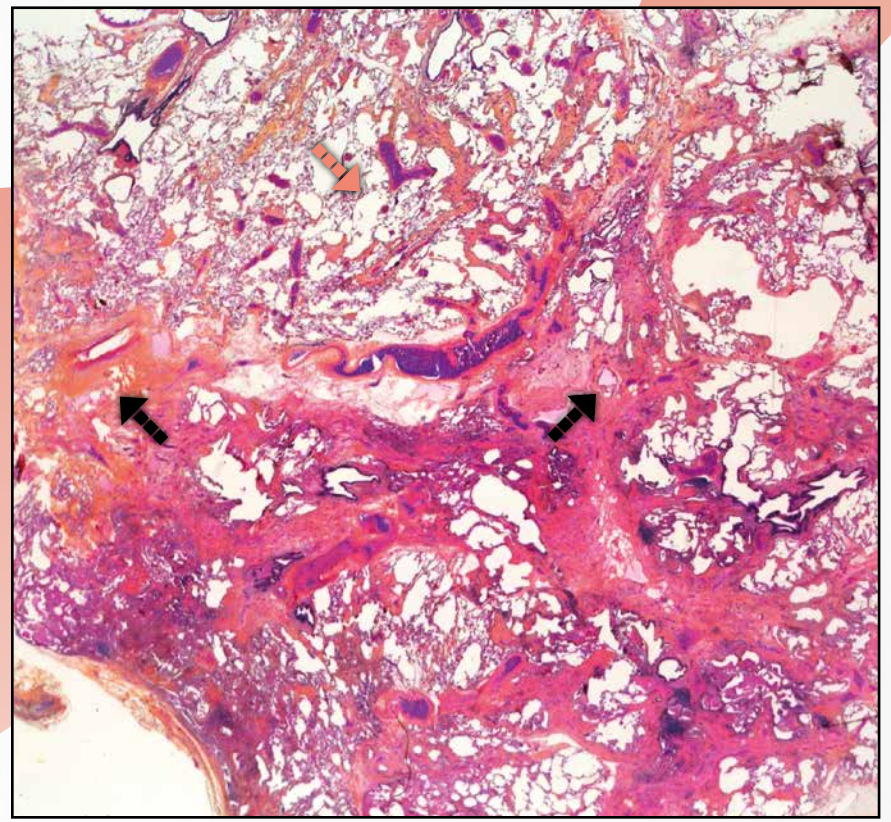
- **Topographic diagnosis at low-magnification**
- **Fibrosis**
  - easily identifiable by the saffron in HES (Hemalum-Eosin-Saffron)
  - on special staining like trichrome

PATCHWORK PATTERN



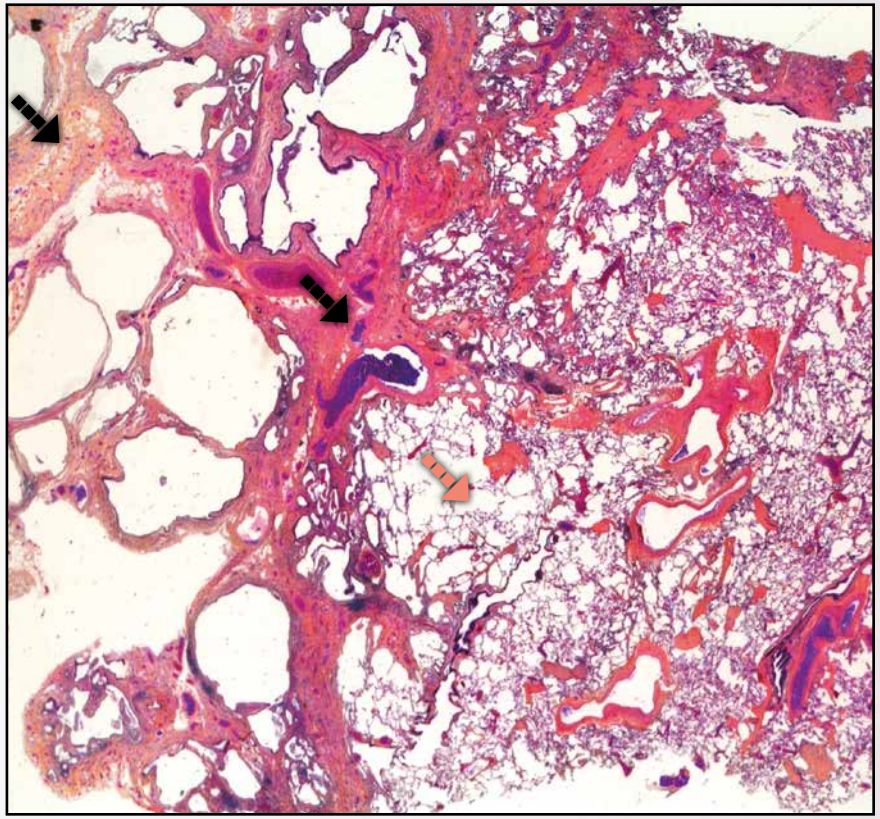
Normal lung parenchyma Abnormal fibrous areas

CHARACTERISTIC PATCHWORK PATTERN



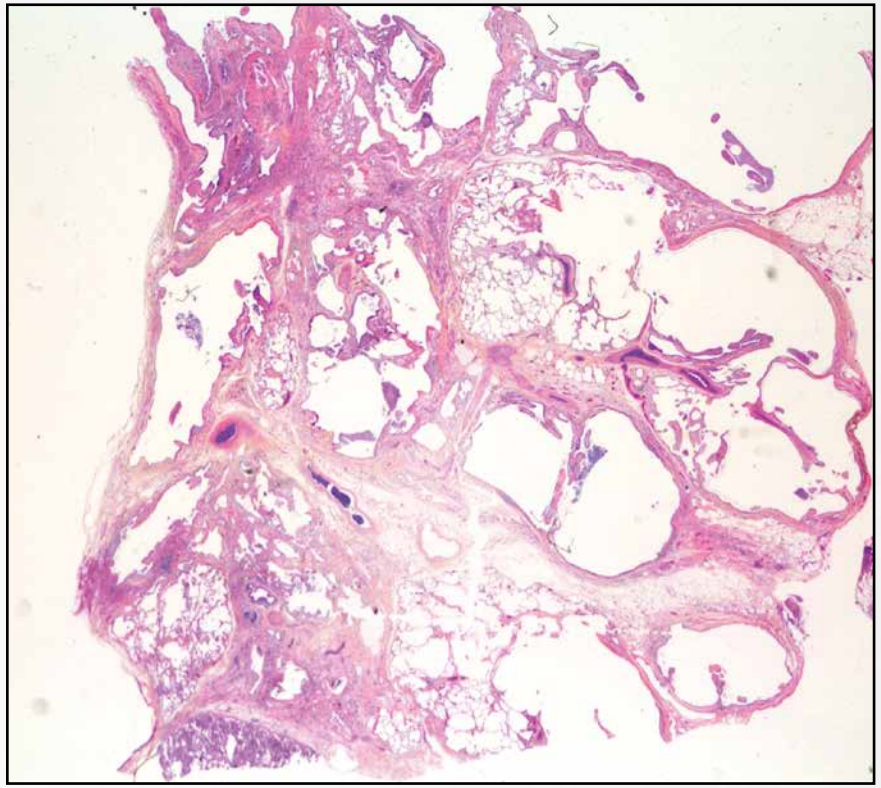
Normal lung parenchyma Abnormal fibrotic areas

CHARACTERISTIC PATCHWORK PATTERN

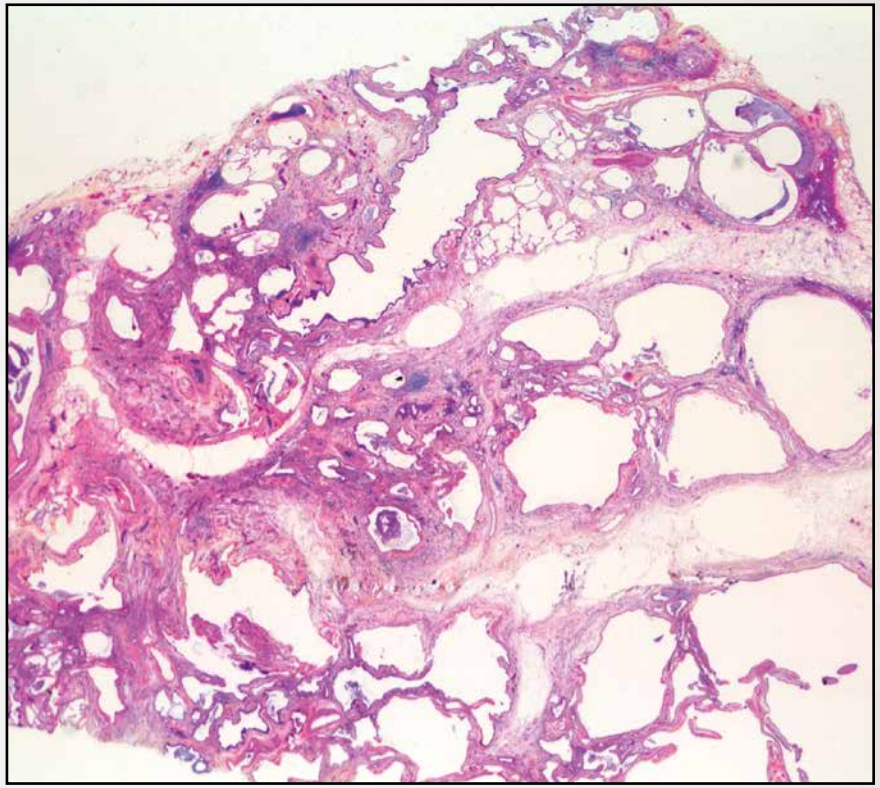


Normal lung parenchyma Abnormal fibrotic areas

LESS TYPICAL DISTRIBUTION OF FIBROSIS: ABSENCE OF NORMAL NON-FIBROTIC PARENCHYMA



LESS TYPICAL DISTRIBUTION OF FIBROSIS: ABSENCE OF NORMAL NON-FIBROTIC PARENCHYMA



ARCHITECTURAL DISTORTION

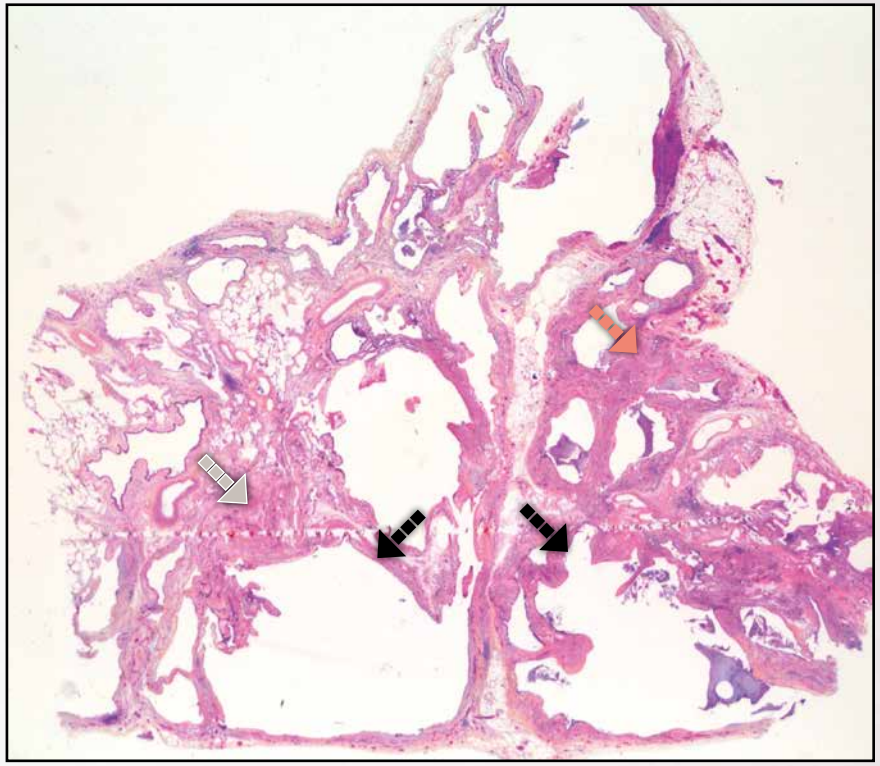
CHARACTERISTICS

- Destruction of the normal lung architecture and its replacement by fibrotic areas, fibrous scars and honeycombing cysts, sometimes both at the same time

DIAGNOSTIC ORIENTATION

- Association of several histological features of architectural distortion
  - **honeycombing cysts**
  - **fibrous scars**
  - **smooth muscle hyperplasia**
- The honeycombing cysts are practically always present and most often with fibrotic areas
- In a few cases, the honeycombing cysts are absent and the fibrotic scars are the only sign of architectural distortion

ARCHITECTURAL DISTORTION



Fibrosis Honeycombing cysts Smooth muscle hyperplasia

HONEYCOMB CHANGE

DEFINITION

- Irreversible terminal destruction of the lung (end stage)

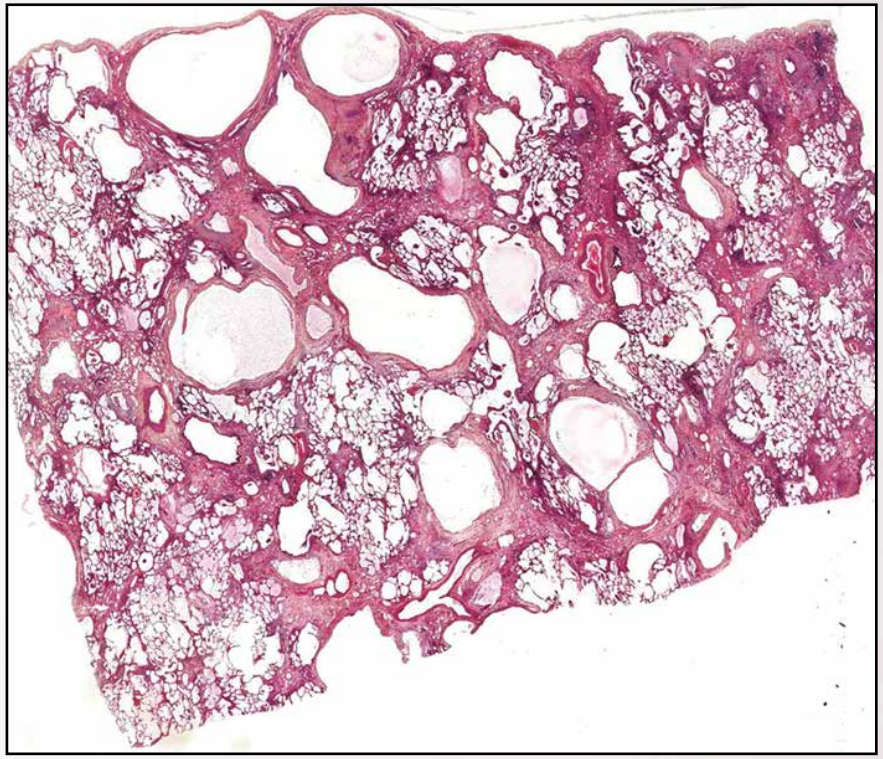
CHARACTERISTICS

- Enlarged pulmonary alveolar cavities: clustered cystic airspaces
- Thick, fibrous walls
- At least partially lined by bronchiolar epithelium
- Contents: mucin and/or inflammatory cells: neutrophils, macrophages, and lymphocytes

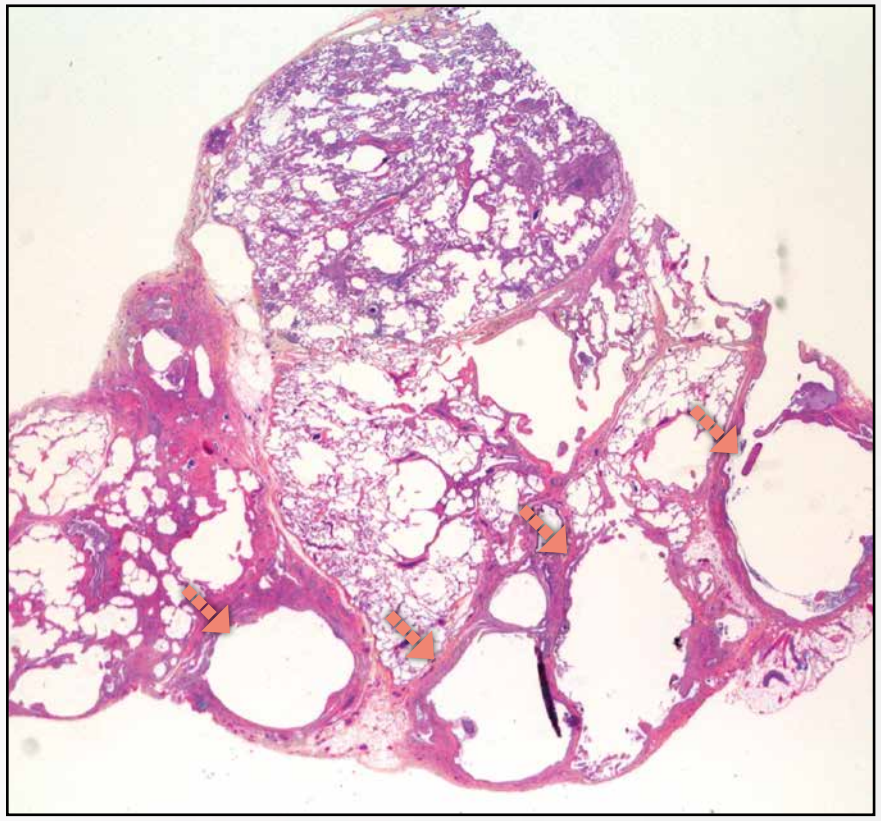
DIAGNOSTIC ORIENTATION

- **Location**
  - lower lobes
- **Alveolar epithelium**
  - absent
  - sometimes replaced by bronchiolar epithelium when the adjacent bronchiolar lining slides in. This process is known as bronchial epithelial metaplasia.

HONEYCOMB CHANGE

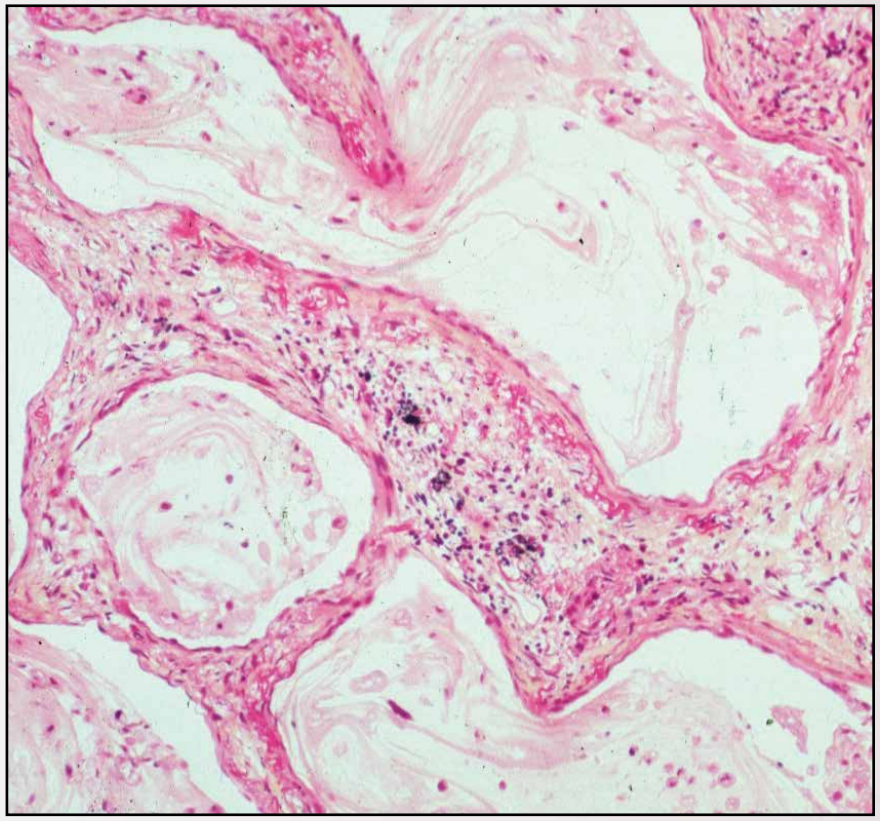


SUBPLEURAL HONEYCOMBING CYSTS

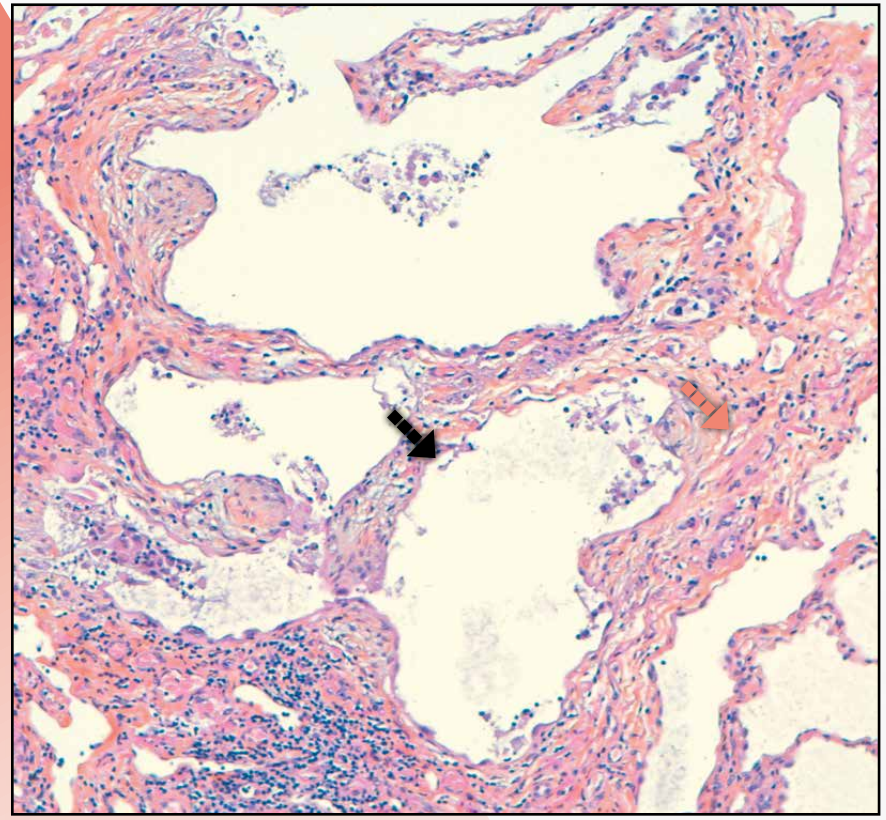


Pulmonary alveolar cysts

MUCIN FILLED ALVEOLAR CYSTS DELIMINATED BY THICK FIBROTIC WALLS

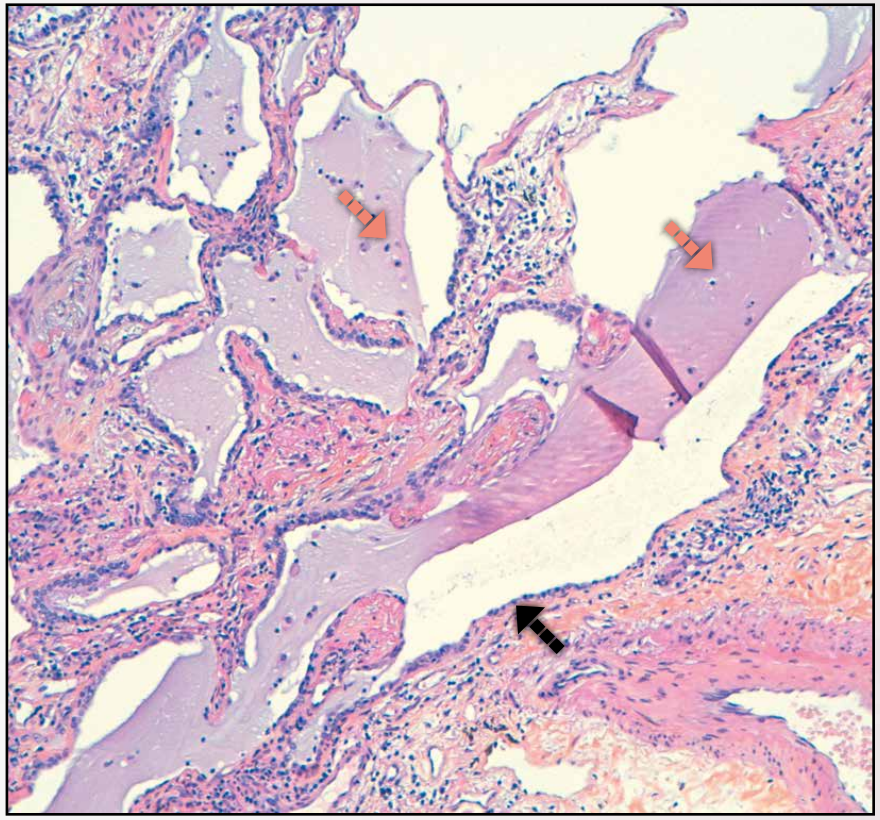


ALVEOLAR CYSTS WITH THICK FIBROTIC WALLS



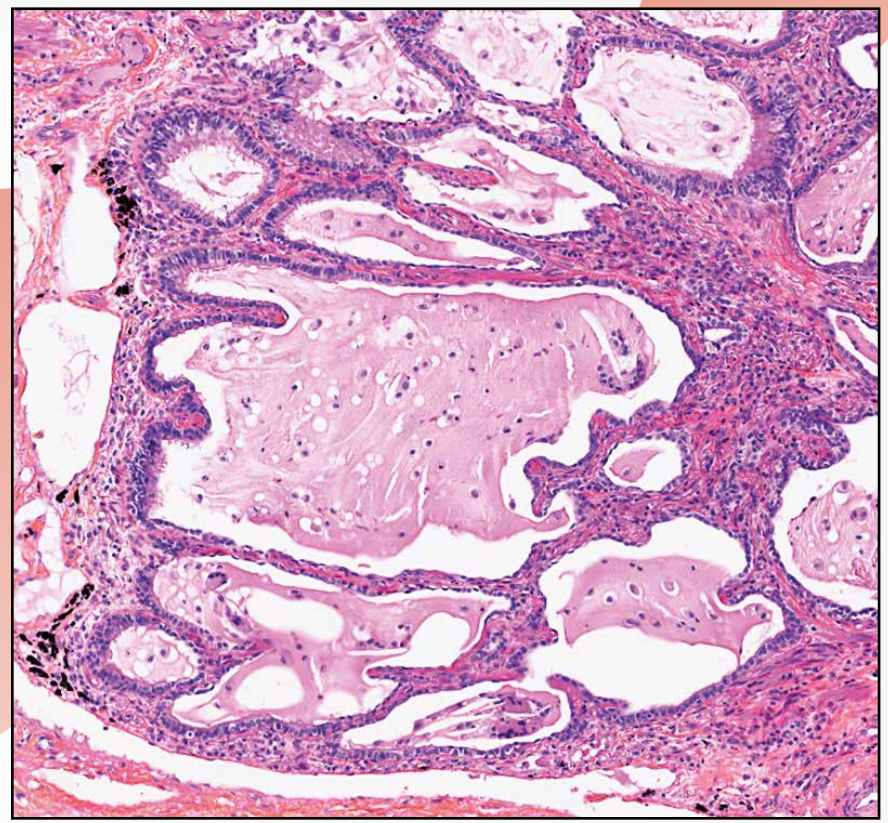
Thick fibrotic walls Pulmonary alveolar cyst

MUCIN FILLED ALVEOLAR CYSTS



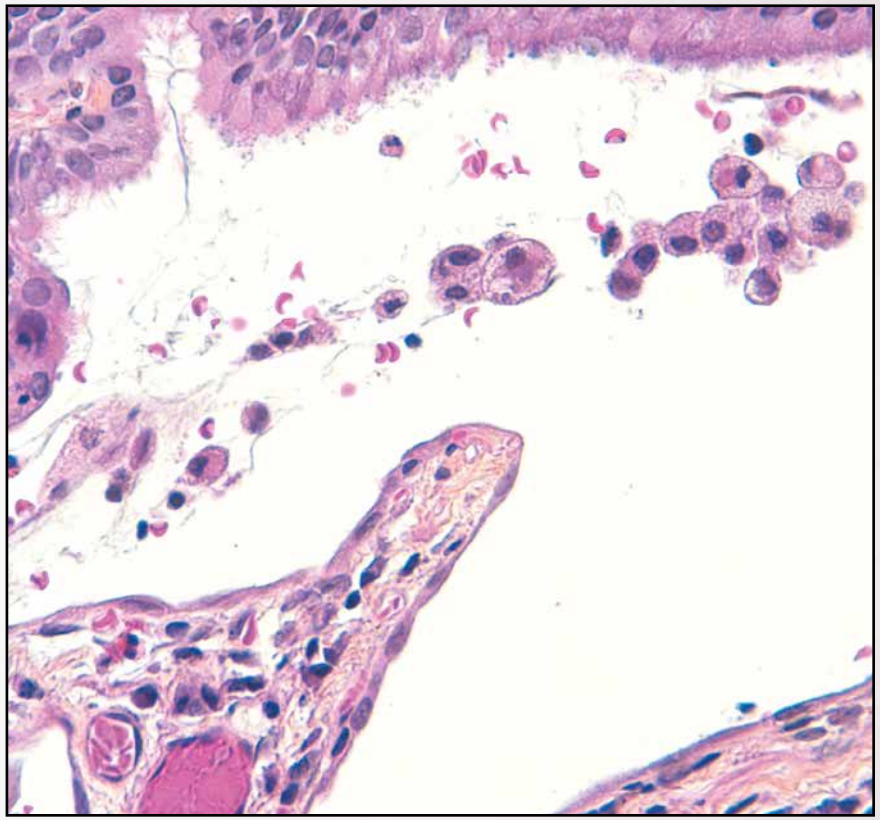
Containing mucous Pulmonary alveolar cysts

HONEYCOMBING CYSTS



Intraluminal mucin containing inflammatory cells.
Chronic lymphocytic inflammation in the alveolar walls.

ALVEOLAR CYSTS



Pulmonary alveolar cyst partially lined by pseudo-stratified, ciliated respiratory epithelium.

BRONCHIAL EPITHELIAL METAPLASIA

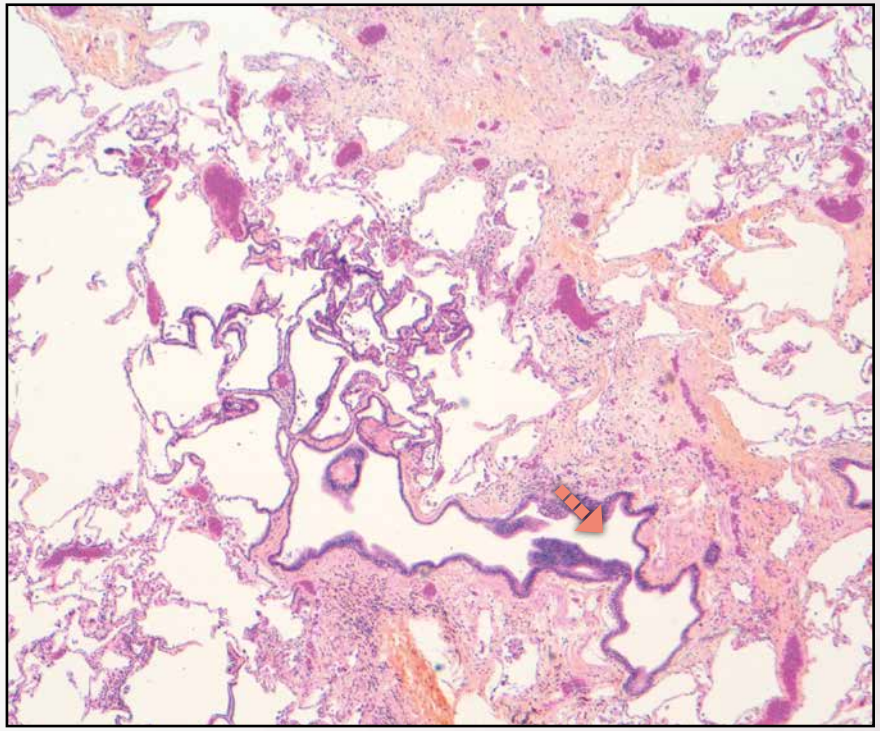
CHARACTERISTICS

- Re-epithelialisation of pulmonary alveolar cysts through slippage of the bronchiolar lining
- Passage through the “Lambert channels”: continuity solution between respiratory bronchioles and adjacent alveoli
- Secondary to bronchiolectasis

DIAGNOSTIC ORIENTATION

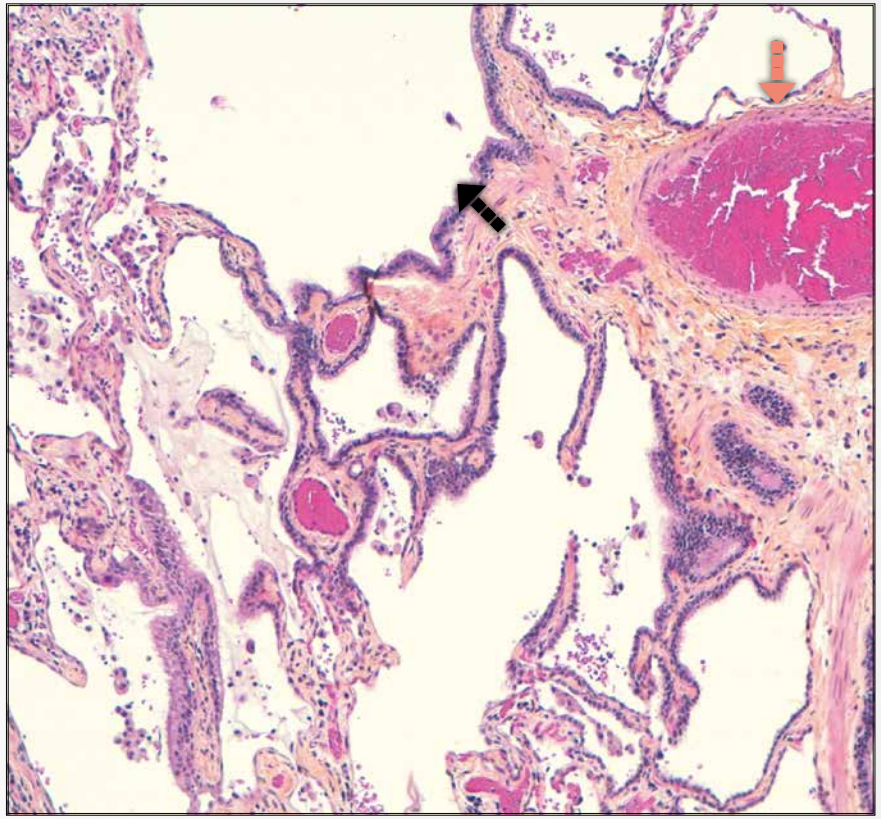
- **Bronchiolectasis**
  - dilatation of the bronchioles’ by traction of the fibrosis on the bronchiolar wall
  - opening of the bronchiole in the next alveolus
- **Cylindrical bronchiolar epithelium**
  - ciliated and mucous-secreting
- **Bronchiolar wall**
  - site of muscular cells

BRONCHIAL EPITHELIAL METAPLASIA



Residual bronchiole in a fibrosis focus

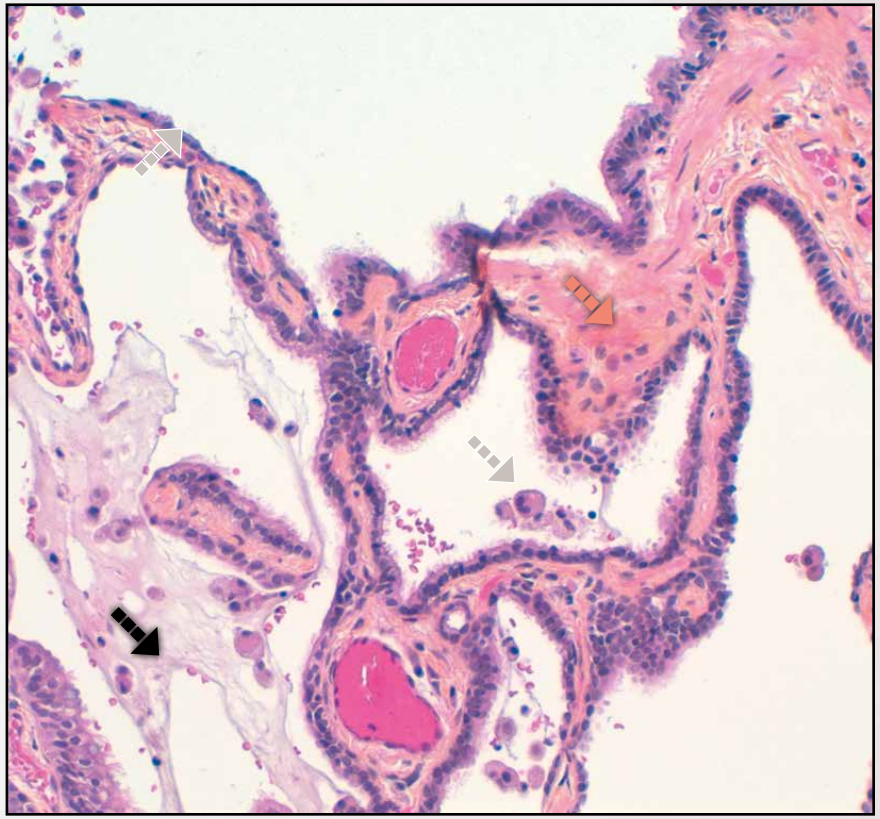
BRONCHIAL EPITHELIAL METAPLASIA



Root arteriole Bronchiole

Residual distended bronchioles in fibrotic area.

BRONCHIAL EPITHELIAL METAPLASIA



Fibrosis Mucous content Pulmonary alveolar cyst

Sliding of the bronchiole lining into adjacent alveolar cavities.

FIBROSIS

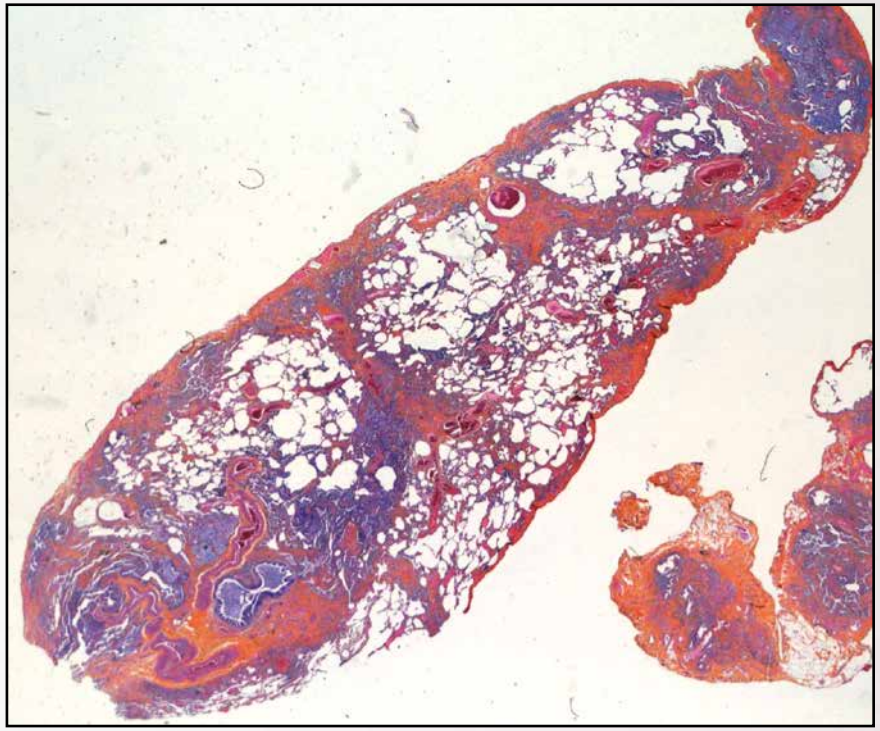
CHARACTERISTICS

- Large quantities of dense connective tissue with few cells, related to inactive chronic fibrosis rich in collagen tissue
- Pleural, subpleural, paraseptal and peri-bronchiolar topography
- Disseminated over time: juxtaposition of dense connective tissue with few cells with fibroblast focus

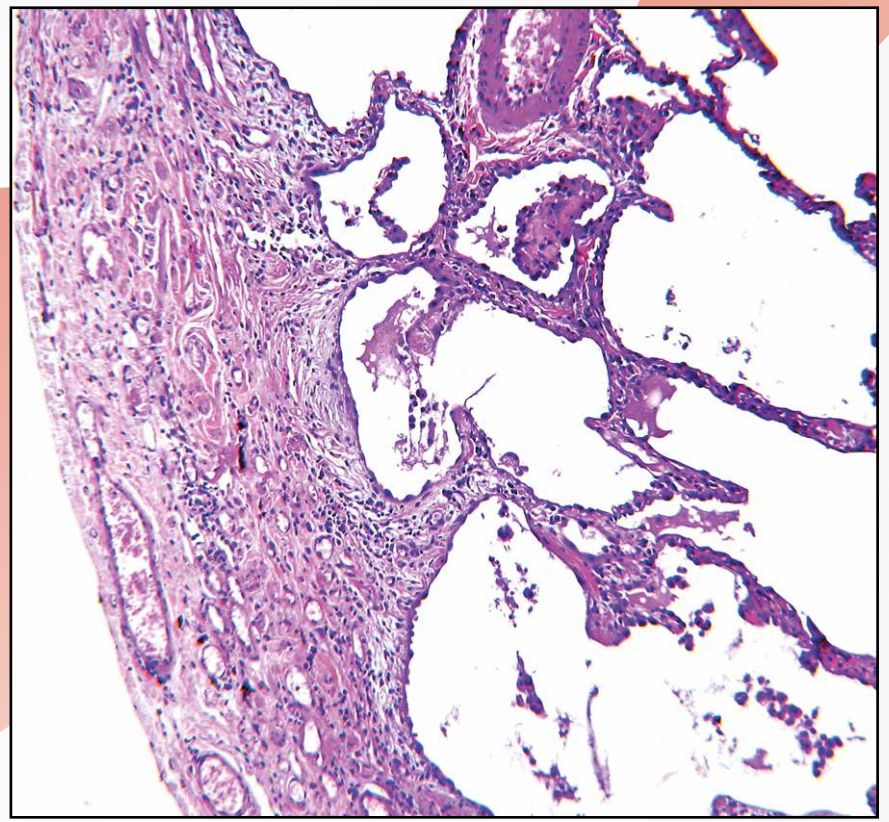
DIAGNOSTIC ORIENTATION

- Fibrosis is characterised by expanses of collagen tissue without bronchiolar remnants or restructured alveolar cavities
- It replaces the normal pulmonary parenchyma
- It can contain lymphocyte infiltrates which are characteristic of chronic inflammation and small blood vessels
- This scarring fibrosis is different from ordinary interstitial fibrosis with thickening of the pulmonary alveolar septa, but preserves the same alveolar architecture

FIBROSIS

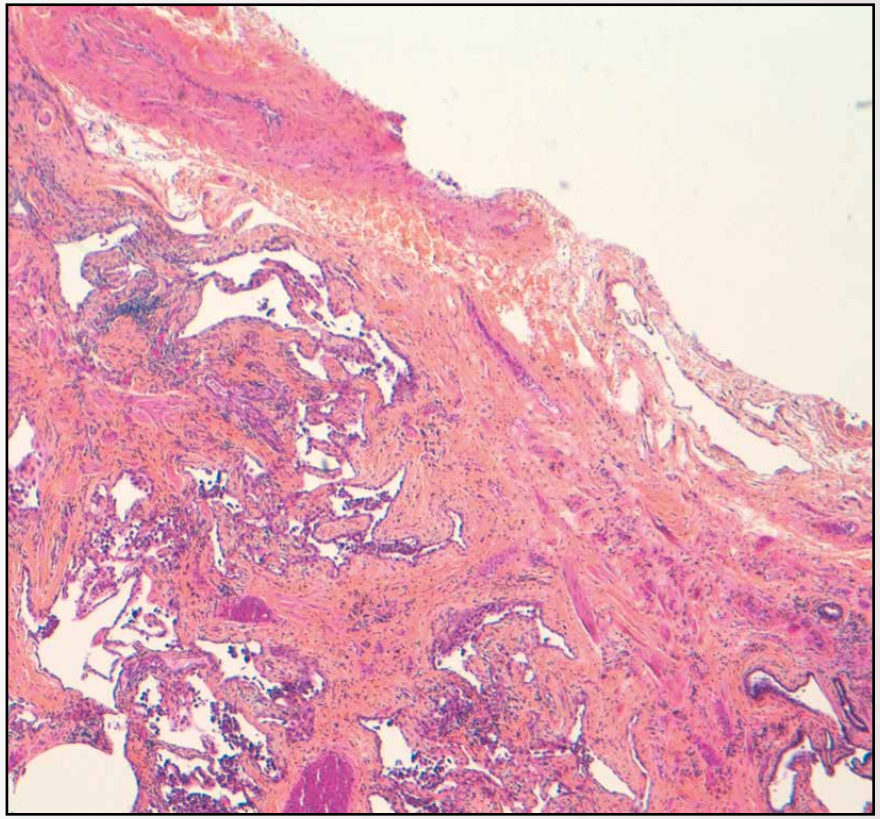


SUBPLEURAL FIBROSIS



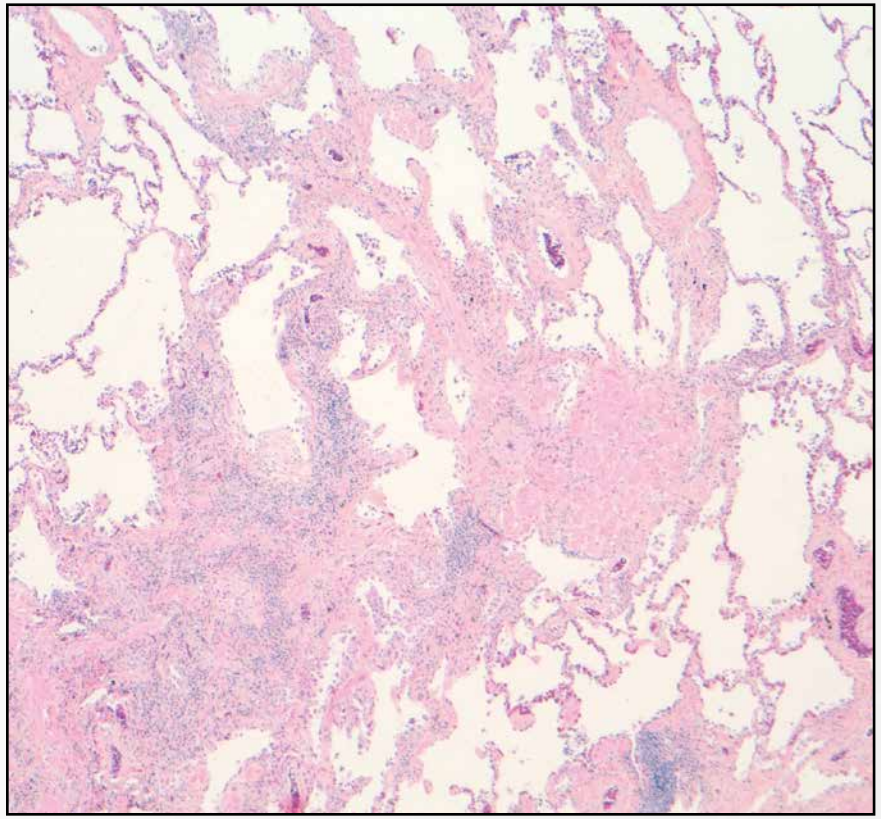
Thickening of the visceral pleura with a dense fibrous tissue.

SUBPLEURAL FIBROSIS

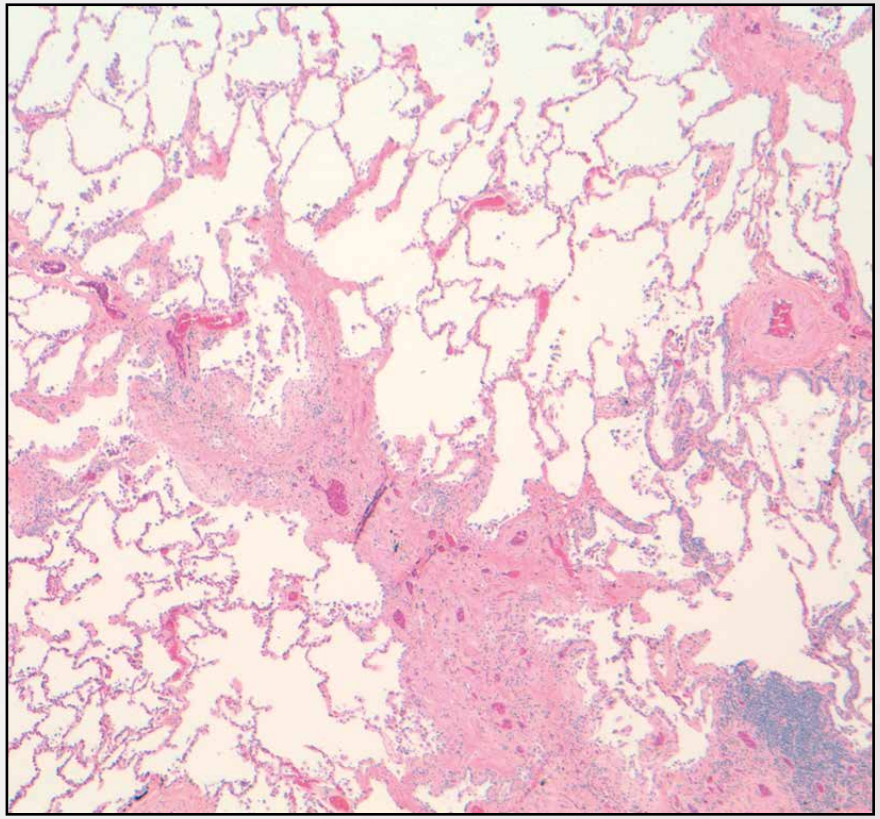


Subpleural thickening with fibrosis penetrating the underlying pulmonary parenchyma.

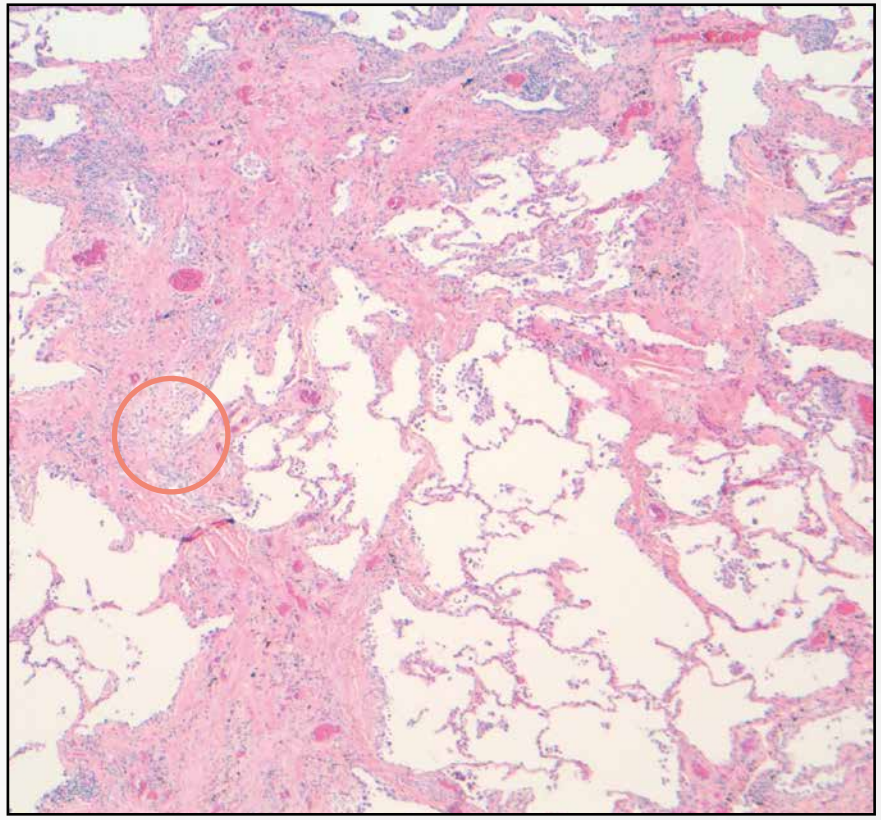
PARASEPTAL FIBROSIS



PARASEPTAL FIBROSIS



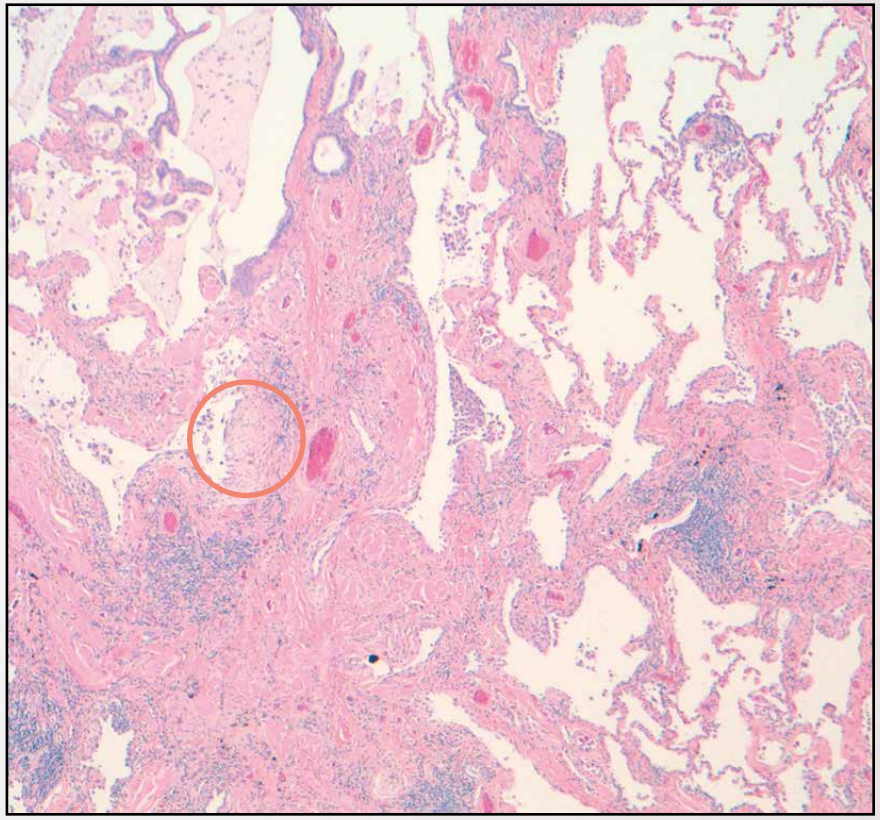
PARASEPTAL AND PERIBRONCHIOLAR FIBROSIS



Fibroblast focus at low-magnification

Some airspaces are replaced by an irregular patchwork of fibrous scars.

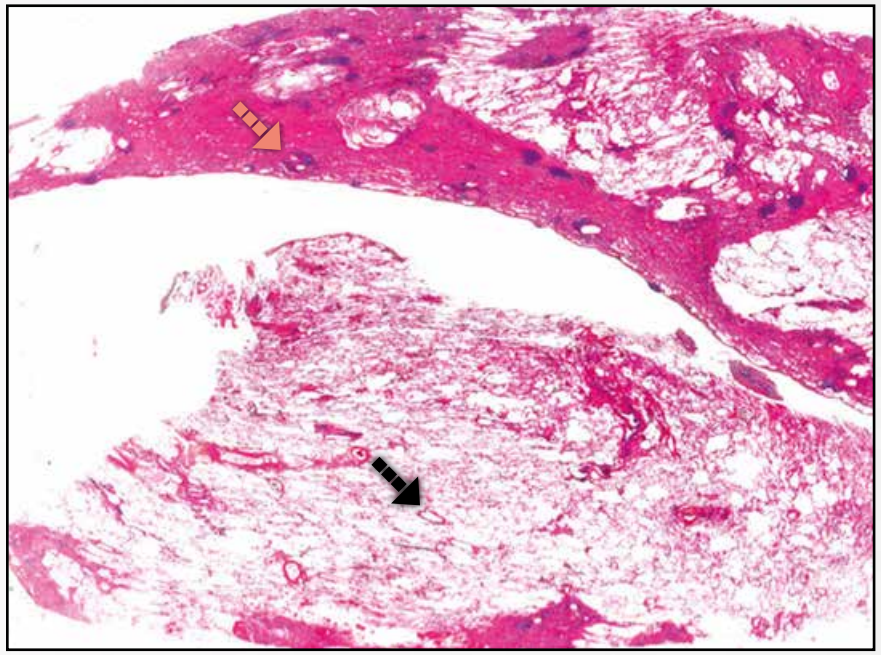
FIBROUS SCARRING



Fibroblast focus at low-magnification

Fibrous scar of dense connective tissue with some dispersed lymphocyte infiltrates.

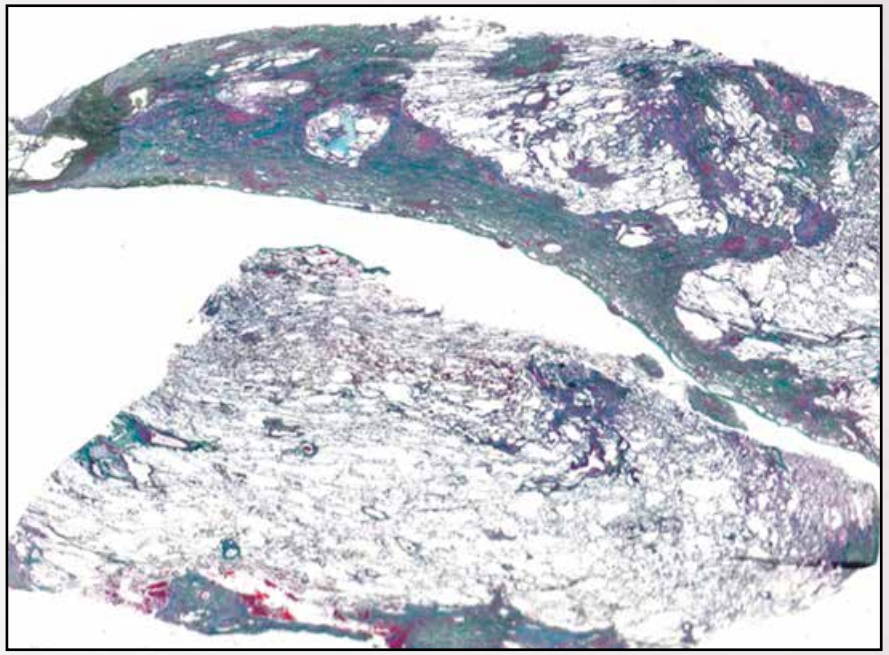
FIBROSIS



Fibrosis Normal pulmonary parenchyma

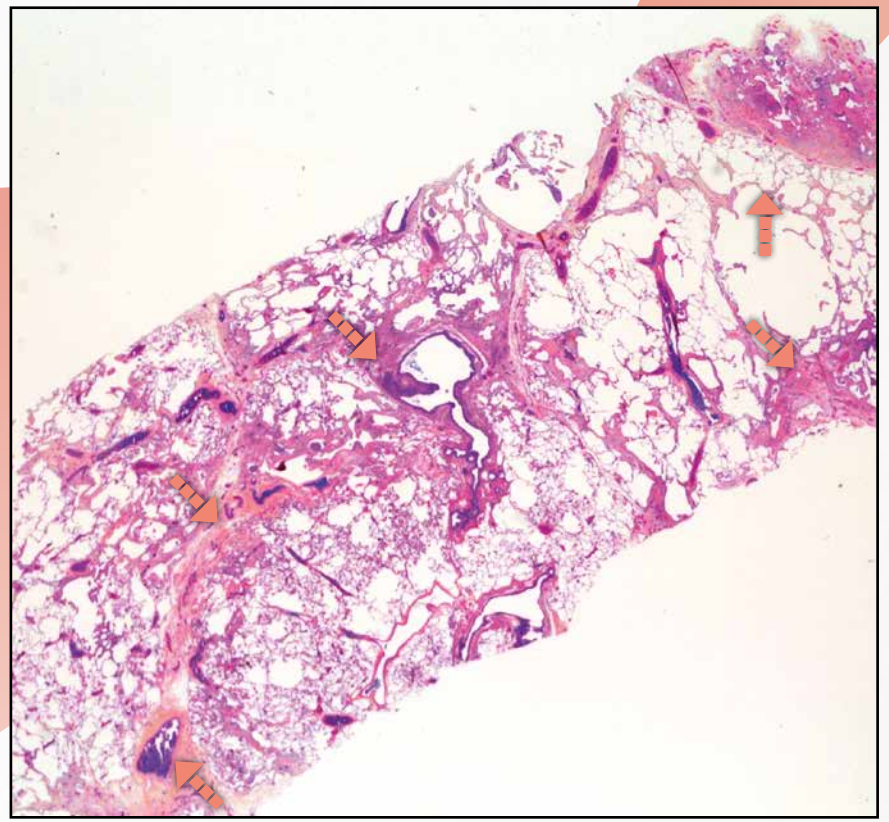
Less typical pattern: fibrosis without honeycombing cysts.

FIBROSIS



Masson's trichrome staning: fibrosis appears green.

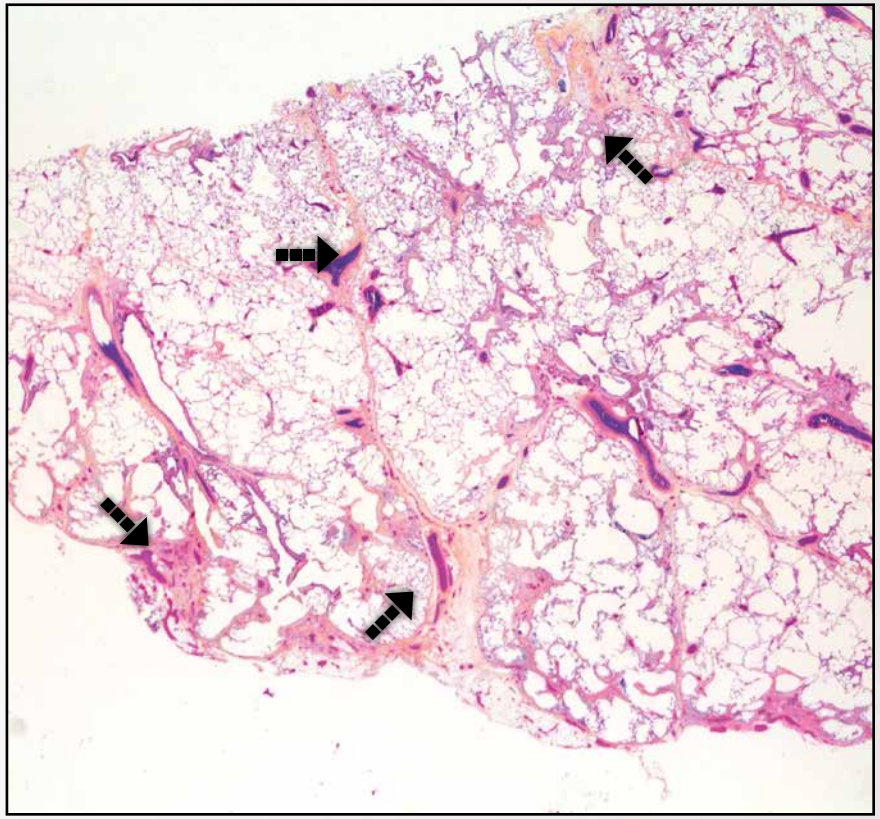
FIBROSIS



Fibrosis

Less typical appearance: fibrosis without honeycombing cysts.

FIBROSIS



Fibrosis

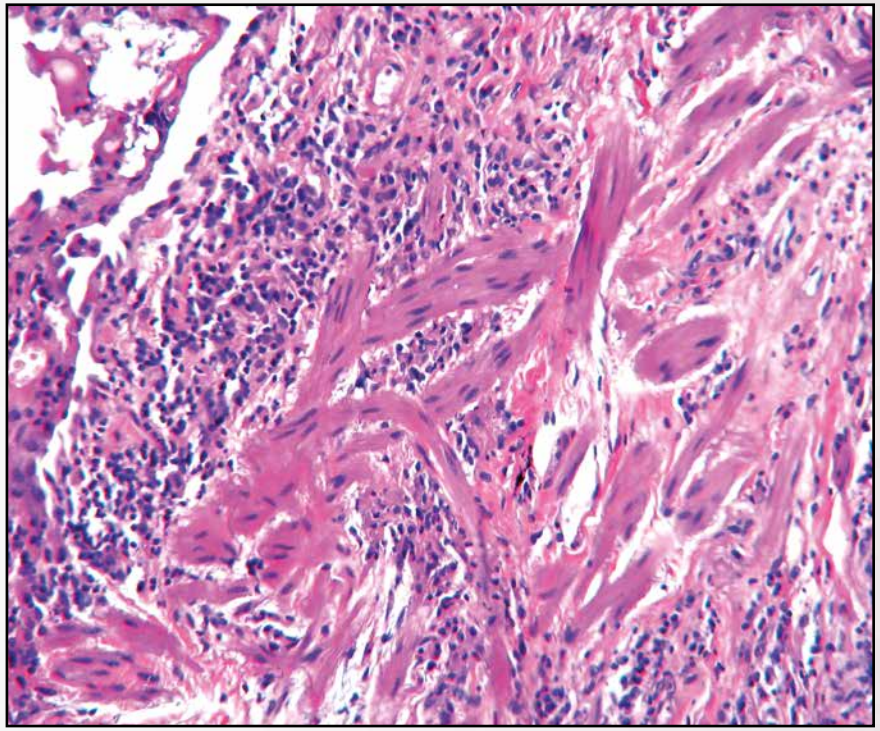
Fibrosis without honeycombing cysts.

SMOOTH MUSCLE HYPERPLASIA

CHARACTERISTICS

- Bundles of hyperplastic smooth muscles
- Synonyms: “myomatosis”, “muscular cirrhosis”
- Destruction of the normal alveolar structure by fibrosis

“MYOMATOSIS”

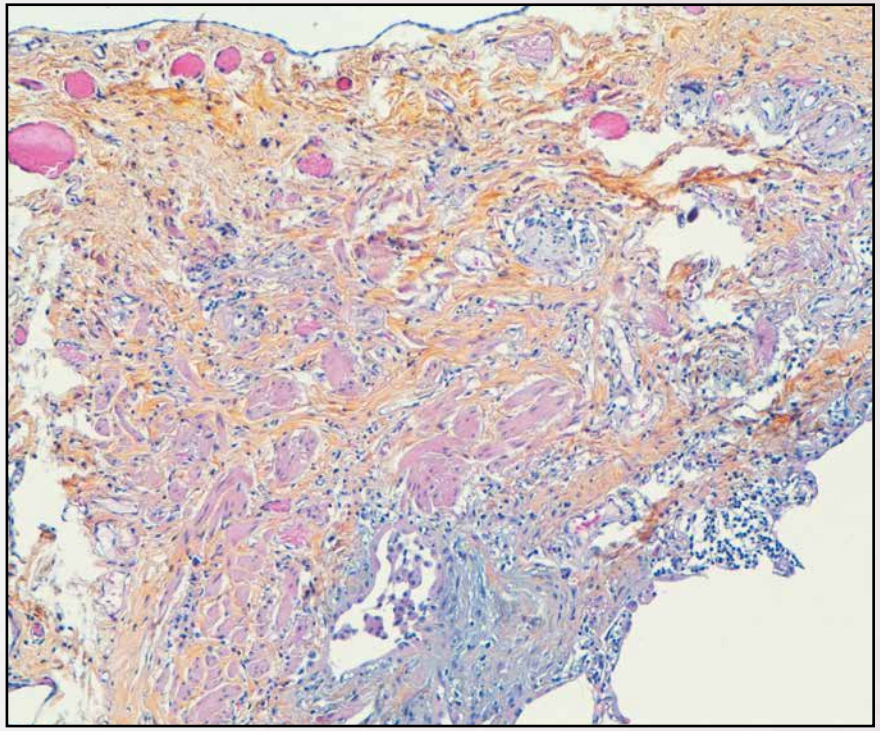


SMOOTH MUSCLE HYPERPLASIA

CHARACTERISTICS

- Hyperplastic smooth muscle bundles within subpleural fibrosis

SMOOTH MUSCLE HYPERPLASIA

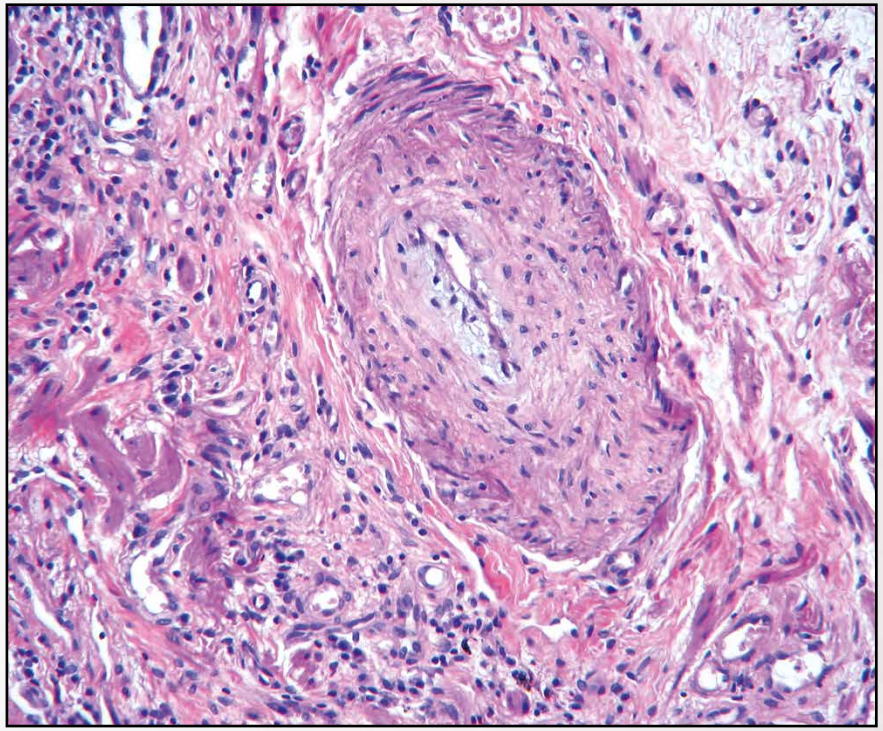


VASCULAR CHANGES

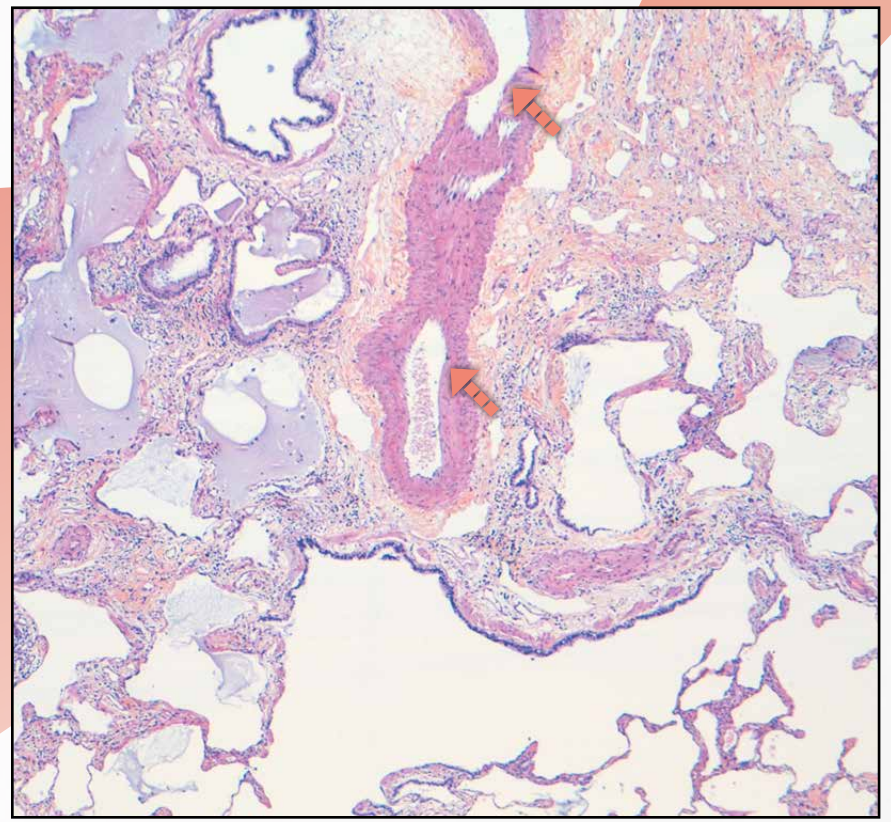
CHARACTERISTICS

- Reductions of the vascular lumen
- Marked intimal and medial hyperplasia in this artery
- Sometimes complete luminal occlusion

VASCULAR CHANGES



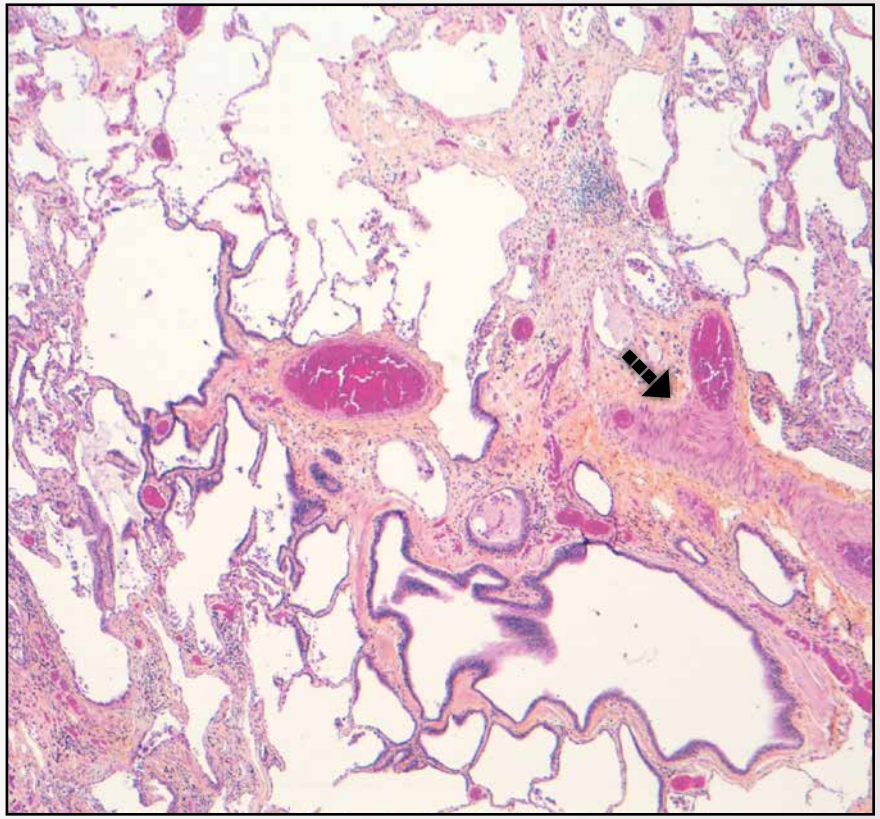
VASCULAR CHANGES



Arterial lesion

Hypertensive arterial lesion.

VASCULAR CHANGES



Fibrosis

Reduction of the vascular lumen in fibrotics area.

FIBROBLAST FOCUS
TEMPORAL VARIABILITY OF FIBROSIS

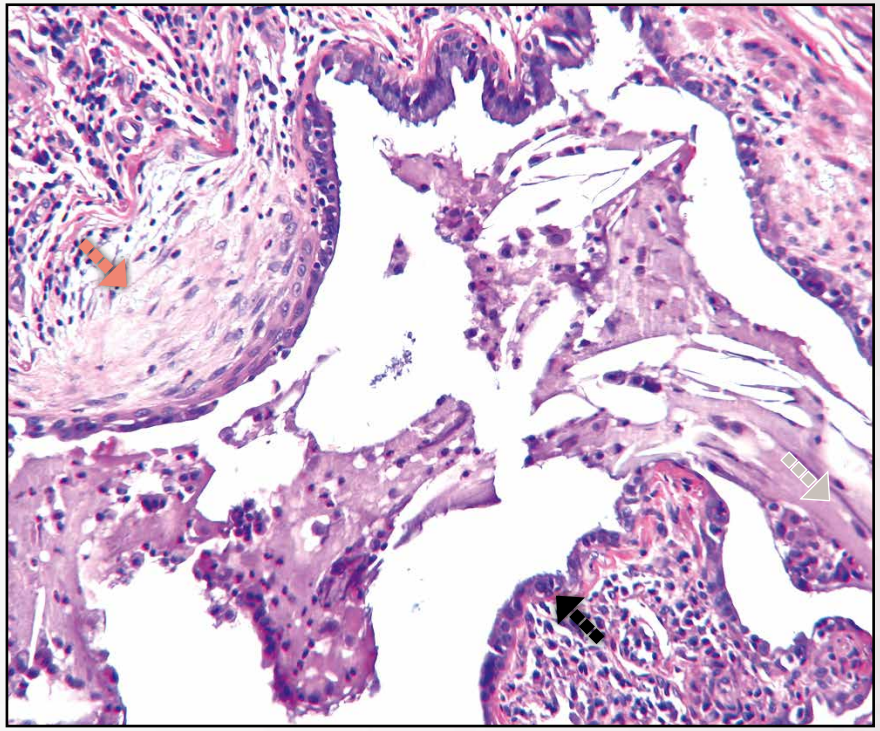
CHARACTERISTICS

- Localised focus of active, ongoing fibrosis
- Stretched out elongated structure of active fibrosis rich in myofibroblasts embedded within myxoid stroma
- Characteristic of usual interstitial pneumonia. Helps confirm the diagnosis

CHARACTERISTICS

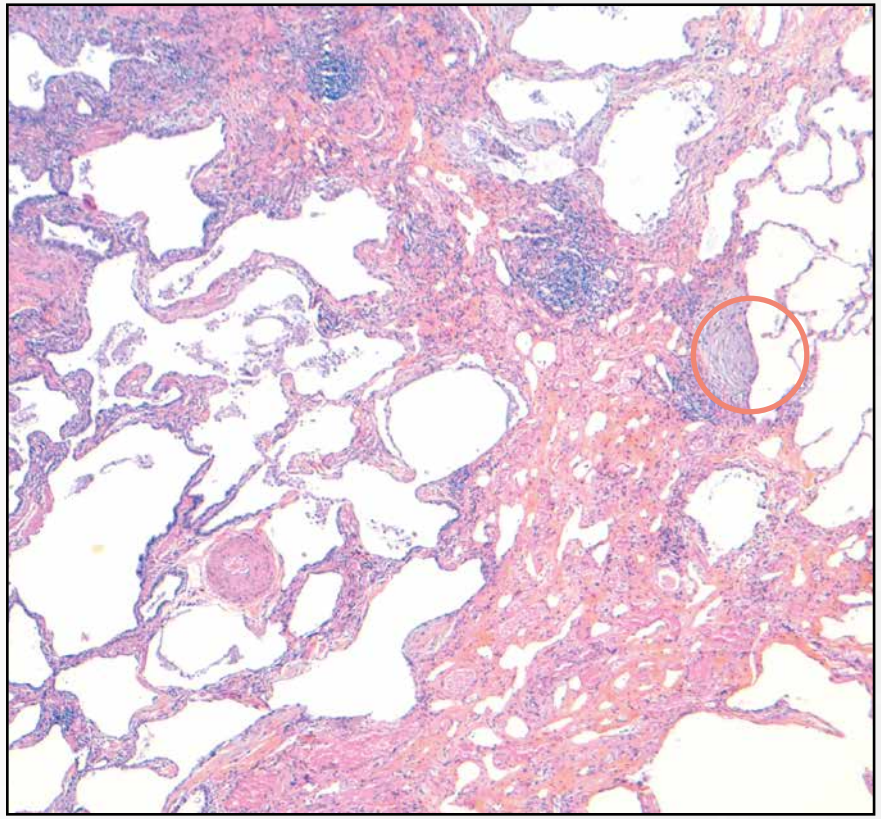
- **Localis**
  - At the expanding front of the fibrosis between the apparently normal lung and the established areas of fibrosis
- **Orientation**
  - Parallel to the surface of the alveolar cavity
  - Protrudes into the alveolar lumen

FIBROBLAST FOCUS



Fibroblast focus Pulmonary alveolar cyst Mucous content

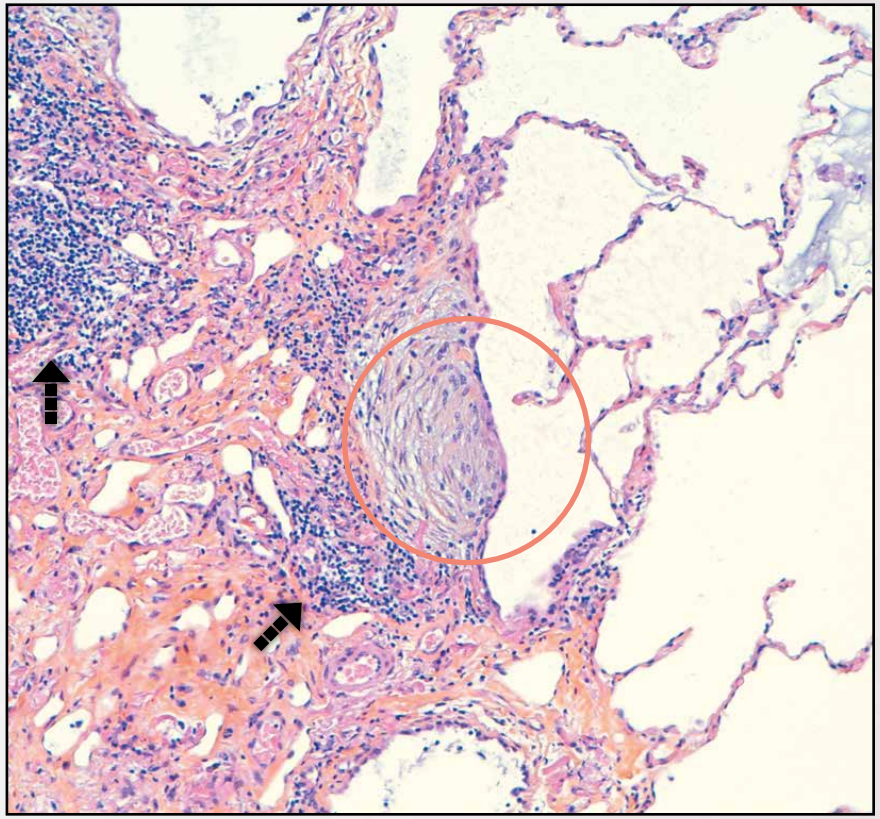
FIBROBLAST FOCUS



Fibroblast focus

Collagen dense scar tissue, with a fibroblast focus stand out at low magnification.

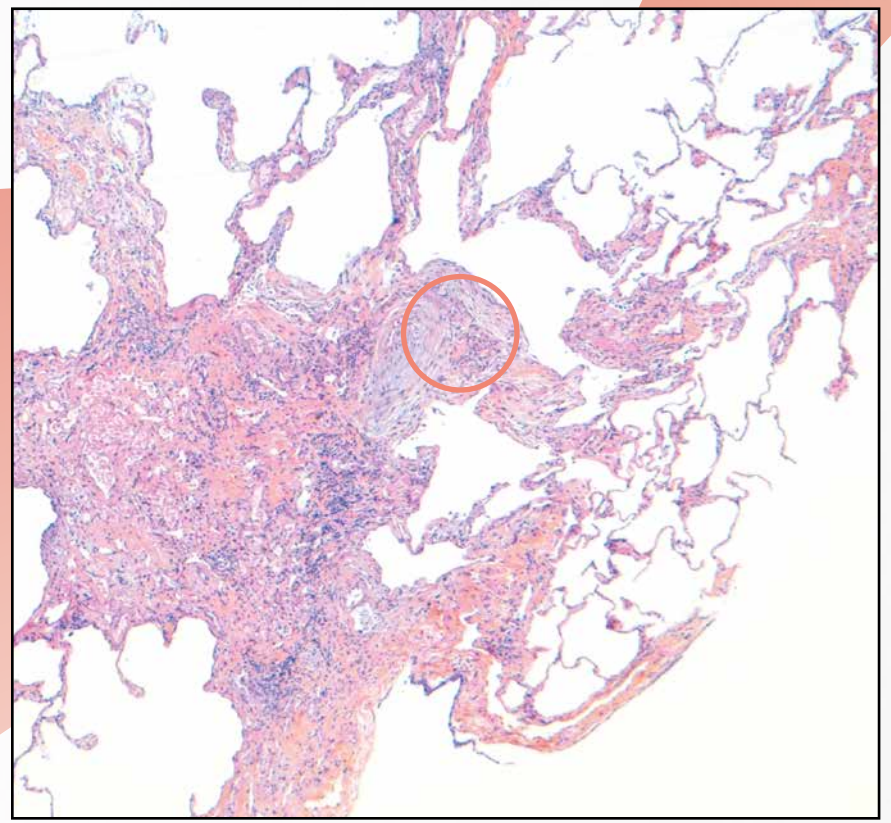
FIBROBLAST FOCUS



Lymphocytic infiltrate Fibroblast focus

Mature inactive collagen disposition showing mild associated chronic lymphocytic infiltrate and typical fibroblast focus.

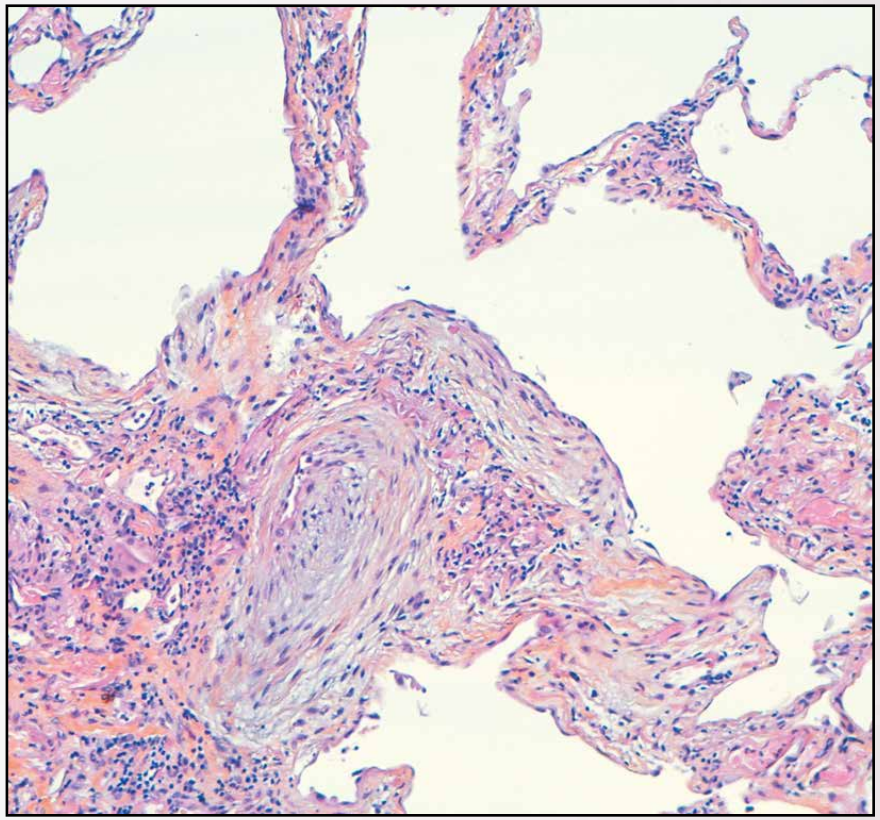
FIBROBLAST FOCUS



Fibroblast focus

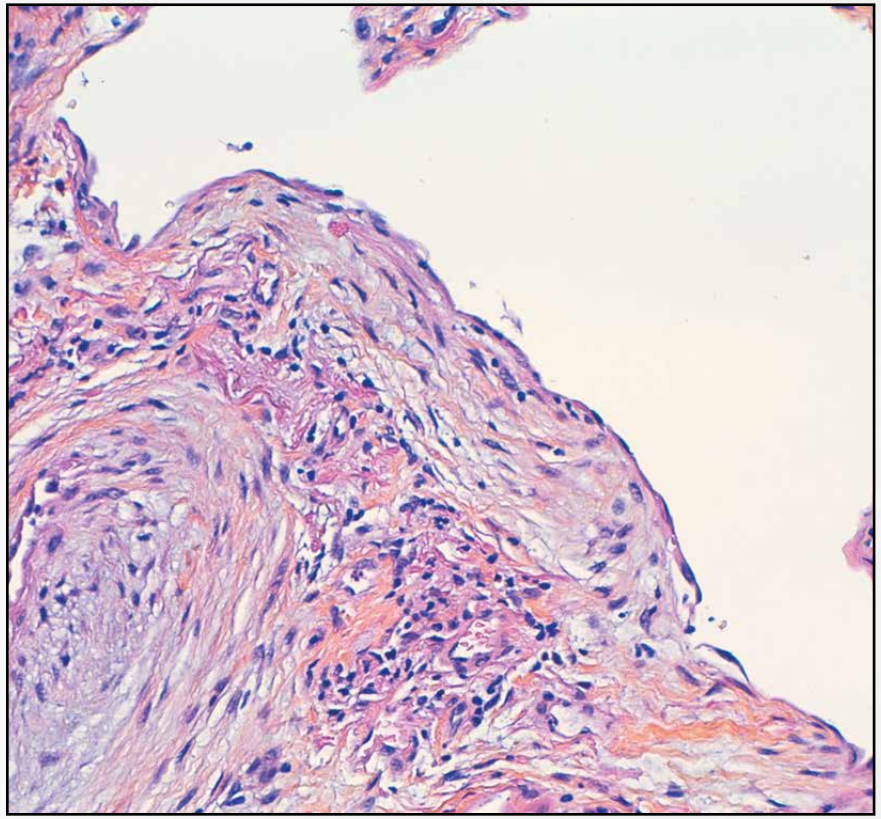
Collagen fibrous scar with fibroblast focus protruding into the alveolar lumen at the expanding front of the fibrosis.

FIBROBLAST FOCUS



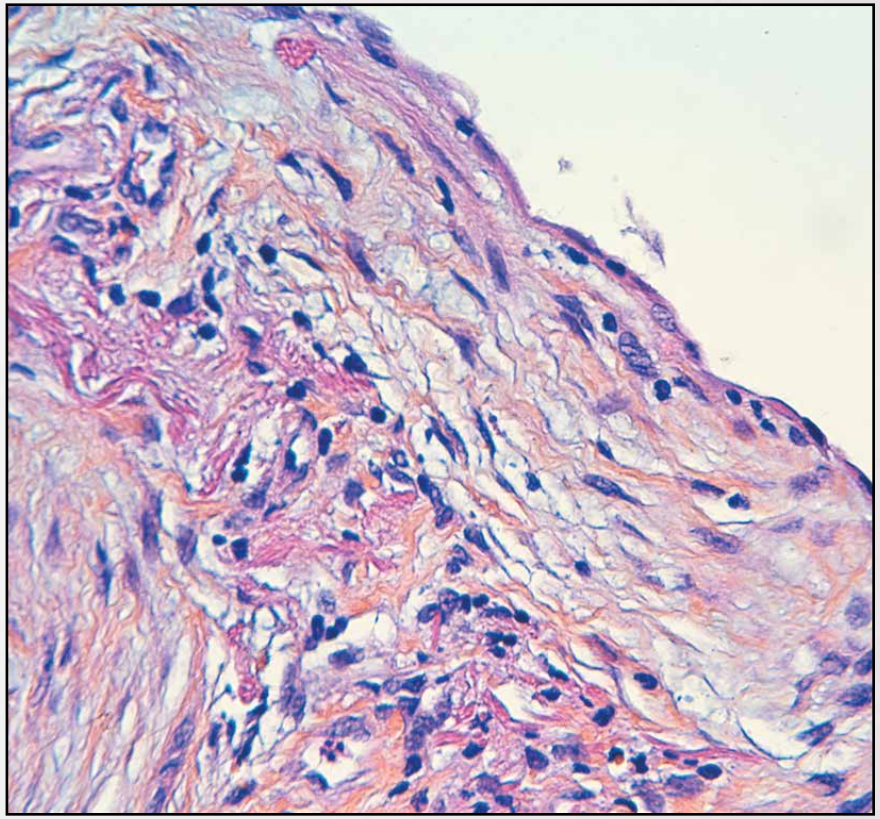
Fibroblast focus protruding into the alveolar lumen.

FIBROBLAST FOCUS



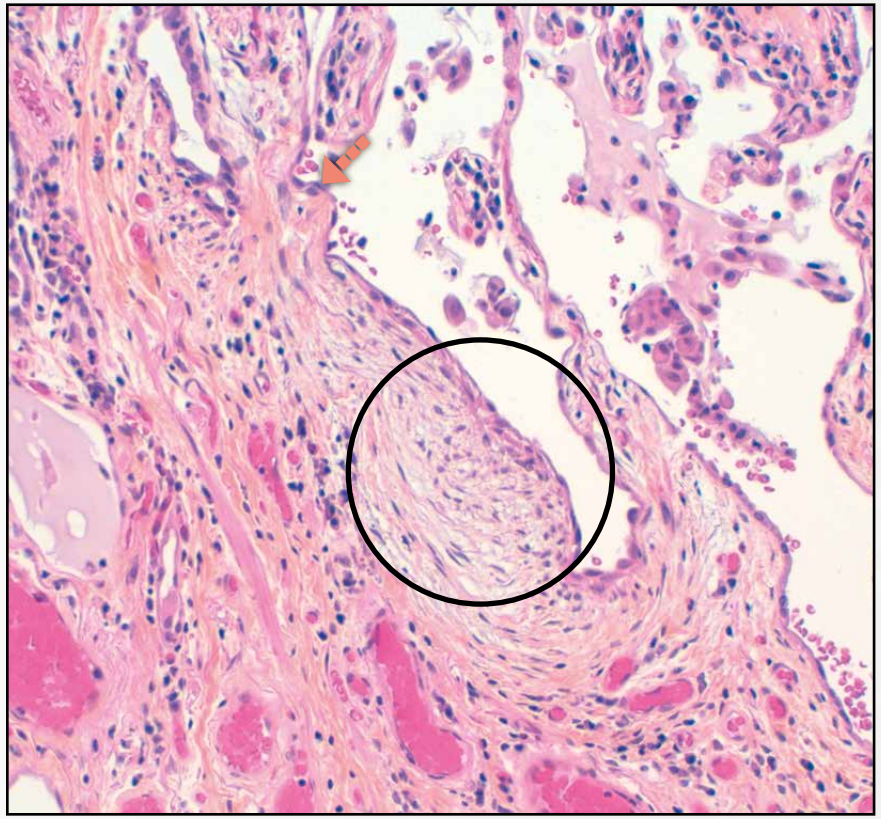
Fibroblast focus: myofibroblasts stretched out on loose collagen tissue.

FIBROBLAST FOCUS



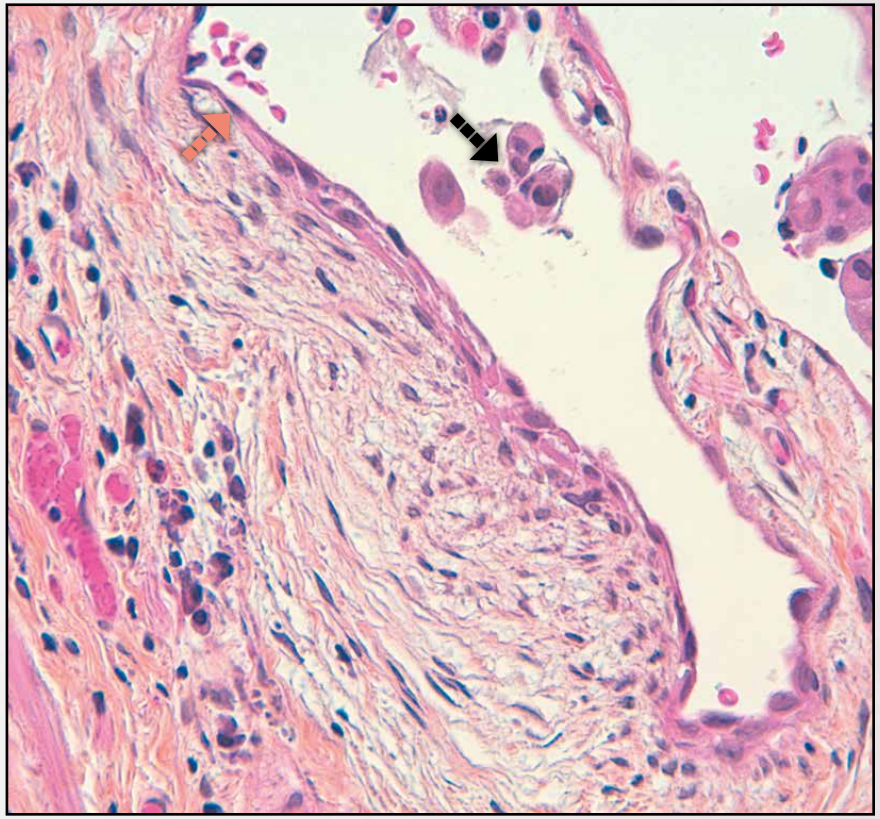
The fibroblast focus is covered by base of flattened alveolar cells.

FIBROBLAST FOCUS



Pulmonary alveolar cyst Possible fibroblast focus

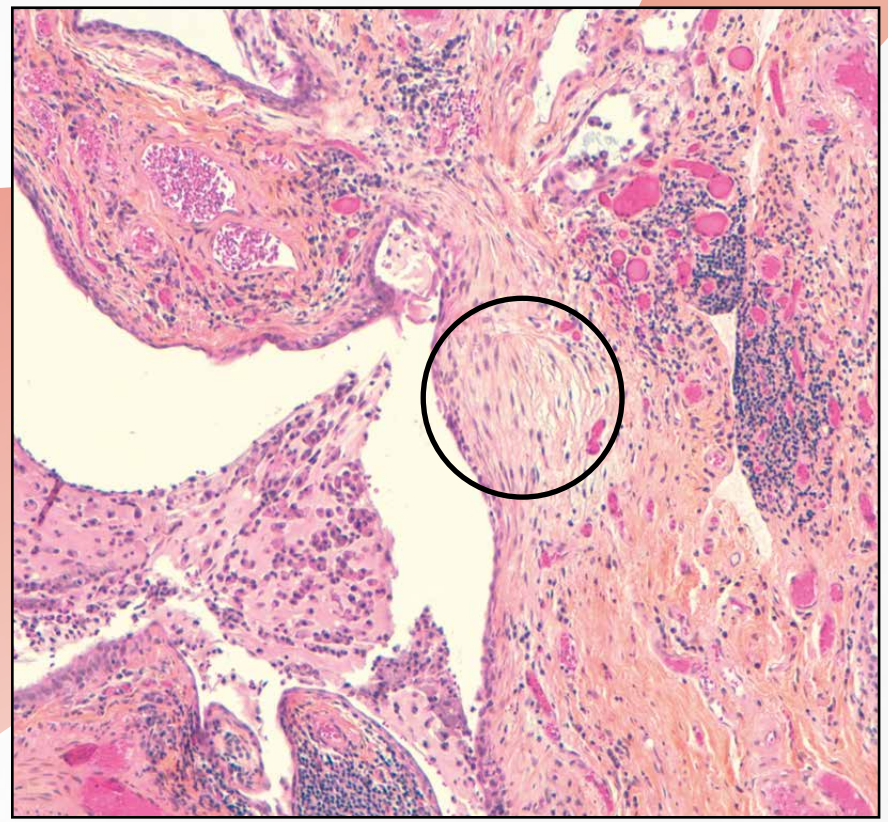
FIBROBLAST FOCUS



Pulmonary alveolar cyst Macrophages

Fibroblast focus protruding into the alveolar cavity containing macrophages.

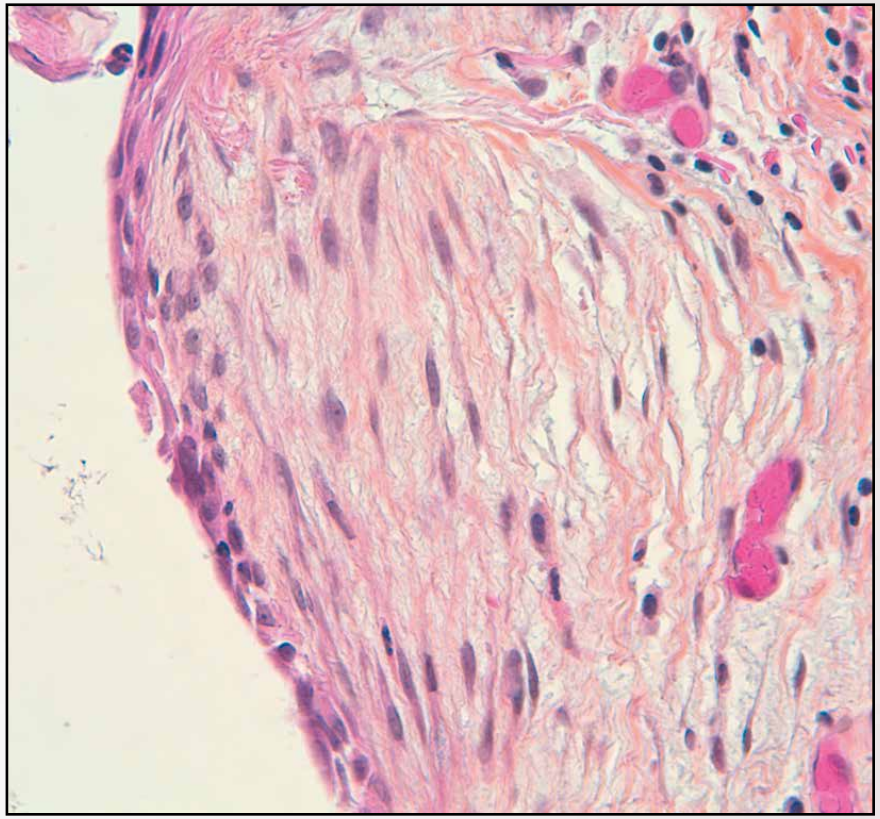
FIBROBLAST FOCUS



Possible fibroblast focus

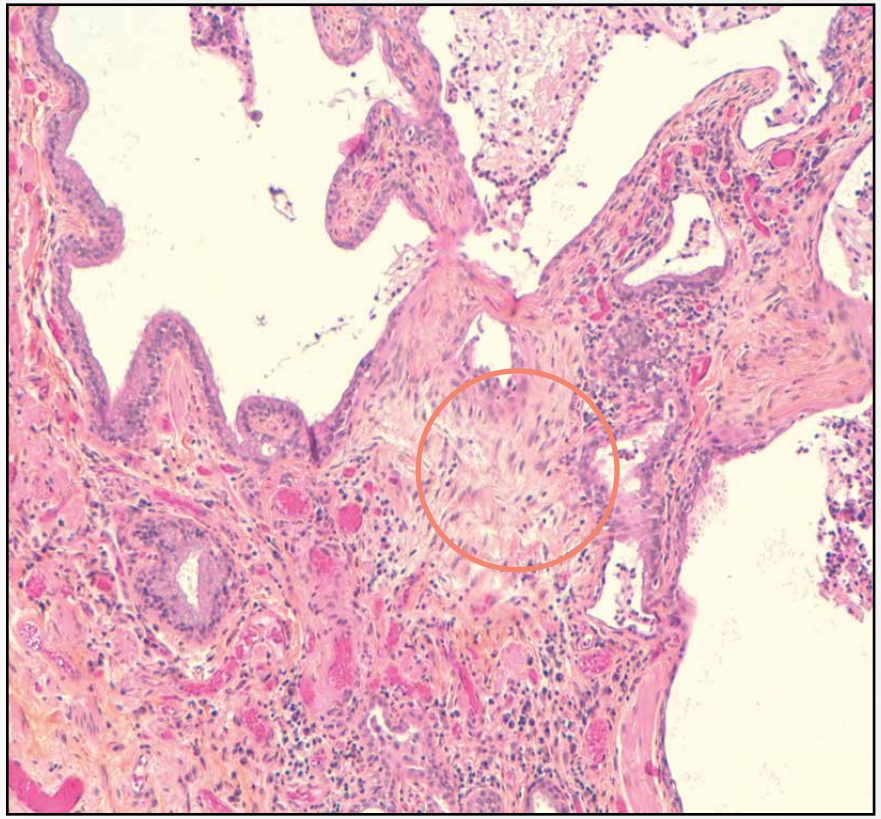
Possible fibroblast focus on the front of a pulmonary alveolar cyst containing inflammatory cells.

FIBROBLAST FOCUS



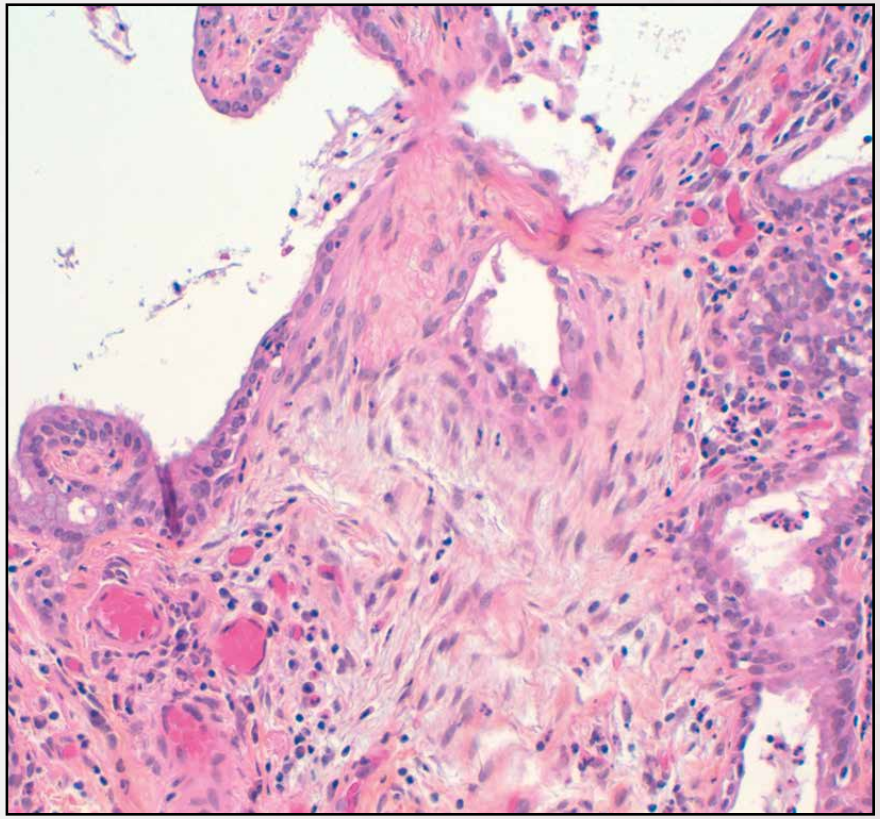
Fibroblast focus covered by a flattened alveolar lining.

FIBROBLAST FOCUS



Atypical fibroblast focus

FIBROBLAST FOCUS



Looser collagen tissue yet which does not protrude into the alveolar lumen.

HISTOPATHOLOGICAL DIAGNOSTIC CRITERIA FOR UIP[1]

The pulmonary biopsy helps obtain a definitive diagnosis in **80 to 95%** of cases of diffuse interstitial lung diseases (DILD).

The pulmonary biopsy plays a central but second line role in diagnosing cases of DILD.

Definite UIP-IPF	**Dense fibrosis** causing architecture remodelling **with frequent honeycombing** **Patchy lung** involvement by fibrosis **Subpleural** or **paraseptal** distribution or both Fibroblast foci at the edge of dense scars
Probable UIP-IPF	**Honeycomb fibrosis only** Or **Dense fibrosis** causing architecture remodelling **with frequent honeycombing** **Patchy lung** involvement by fibrosis **Subpleural** or **paraseptal** distribution or both Fibroblast foci at the edge of dense scars may or may not be present
Indeterminate for UIP-IPF	**Patients have less compelling histological changes than those classified by the final column** (eg, occasional foci of centrilobular injury of scarring, rare granulomas or giant celles, only a minor degree of lymphoid hyperplasia or diffuse homogeneous fibrosis favouring fibrotic non specific interstitial pneumonia) These features and the differential diagnoses they call to mind, become part of the multidisciplinary diagnosis of IPF, or not
Features most consistent with an alternative diagnosis	**Non-UIP pattern** Patients with features of other fibrotic disorders-eg, fibrotic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, fibrosing organising pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans cell histiocytosis, or smoking-related interstitial fibrosis **UIP pattern with ancillary features strongly suggesting an alternative diagnosis** Eg, prominent diffuse alveolar damage or organising pneumonia (consider acute exacerbation of UIP), granulomas (consider hypersensitivity pneumonitis, sarcoid, infection), marked interstital inflammatory cell infiltrate away from areas of UIP (consider hypersensitivity pneumonia)

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NOTES

SUMMARY

- A common threat across a wide range of ILDs, pulmonary fibrosis can become a key driver of irreversible harm and early mortality that warrants urgent identification and intervention.[1-4]
- For at-risk patients, high resolution CT (HRCT) should be evaluated at the first suspicion of ILD involvement—if possible at baseline diagnosis—and repeated upon worsening of either pulmonary function test (PFT) scores or respiratory symptoms.[5,6]
- Demonstrate a healthy suspicion: identifying pulmonary fibrosis in your patients as early as possible may help to improve their burden of disease, slow decline in daily functioning and quality of life, and reduce the risk of early mortality.[5,7-9]

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