CONCURRENT SESSION C 4

SECTION 3

Test Your ILD Knowledge – An Interactive Multidisciplinary Team Discussion of ILD Cases

Presenters: Dr. Margaret Kelly, Dr. Daniel Marinescu, Dr. Julie Morisset, Dr. Giang Nguyen, Dr. Alyson Wong

Moderator: Dr. Onofre Moran-Mendoza

Disclosure of Conflict of Interest (over the past 2 years)

Dr. Margaret Kelly:
Operating grants, equipment, Endowment for Chair in Pediatric Respirology: CIHR, Alberta Hospital Childrens Foundation, Canadian Foundation for Innovation, Alberta Lung Association

Dr. Daniel Marinescu:
Speaker Honoraria, Consultant: Boehringer-Ingelheim

Dr. Julie Morisset:
Speaker Honoraria: Boehringer Ingelheim and Roche
Membership on Advisory Boards: Boehringer Ingelheim and Roche

Dr. Alyson Wong:
Speaker Honoraria: Boehringer Ingelheim, AstraZeneca

Dr. Giang Nguyen: No conflicts

Disclosure of Conflict of Interest

(over the past 2 years)

Mitigating potential bias

- No discussion of off-label indications
- All comments to be based on peer-reviewed published evidence

CanMEDs Roles

This session will address the following CanMEDs roles:

- Medical Expert (the integrating role)
- Communicator
- Collaborator
- Health Advocate
- Scholar
- Professional

Learning Objectives

At the end of this session, participants will be able to:

1. Recognize the potential value of interdisciplinary discussion;
2. Understand the potential value of lung biopsy in managing ILD; and
3. Consider the less common causes of ILD.

Case 1:

Daniel Marinescu, Clinician
Giang Nguyen, Radiologist
Margaret Kelly, Pathologist

Clinical History and Findings

Incidentally discovered fibrosis during abdominal imaging for a hernia repair …

Clinical History:
- 64M
- 30py ex-smoker

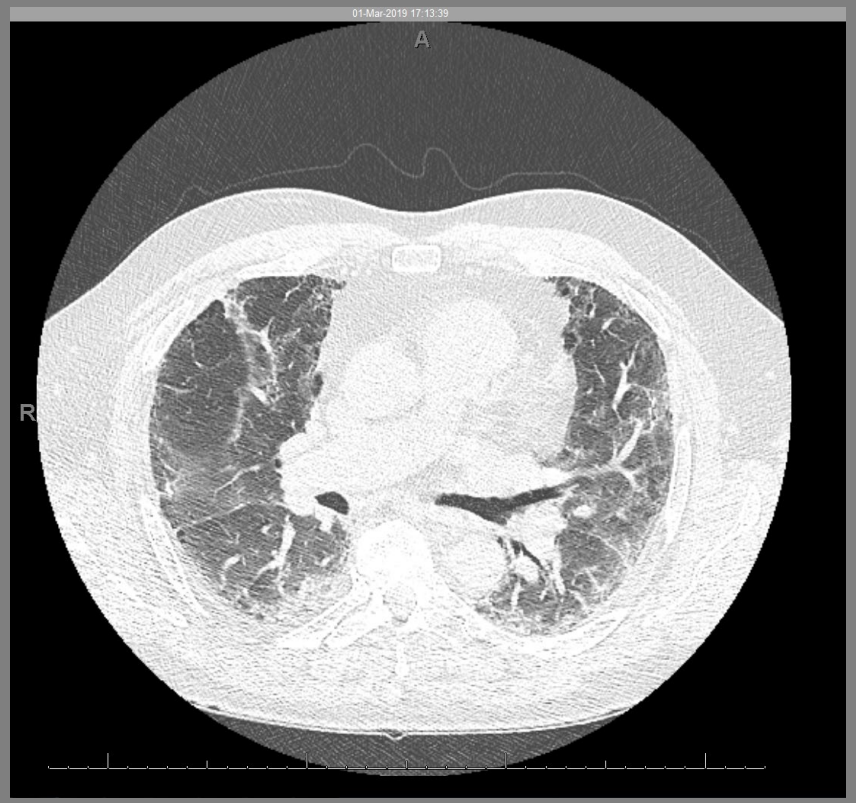
Comorbidities:
- GERD
- HTN
- DLP
- OSA

Clinical assessment for ILD:
- No family history of ILD
- No CTD symptoms or signs
- Negative basic serologies (ANA, ENA, RF, CCP)
- Possible exposure to mold 5 years ago due to flooding in home; identified and repaired
- No occupational exposures
- No drug exposures
- No history of pulmonary infections

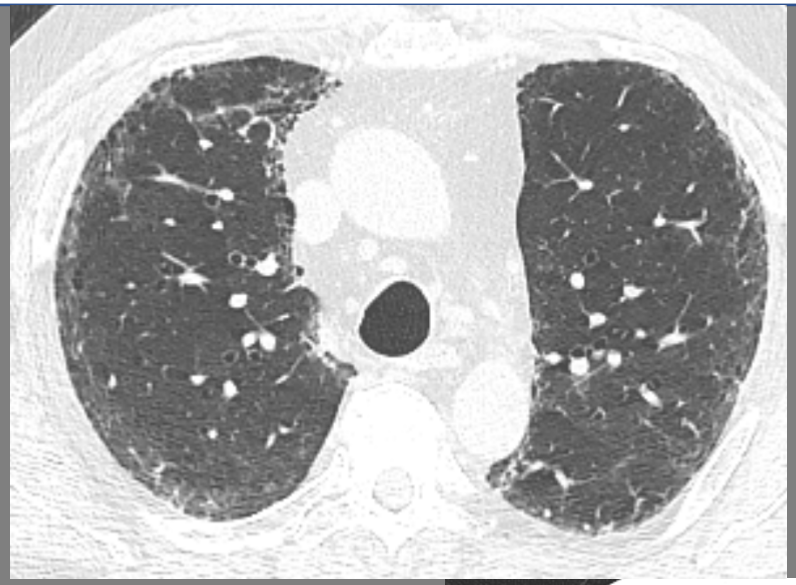
PFTs:
FVC 86%
DLCO 66%

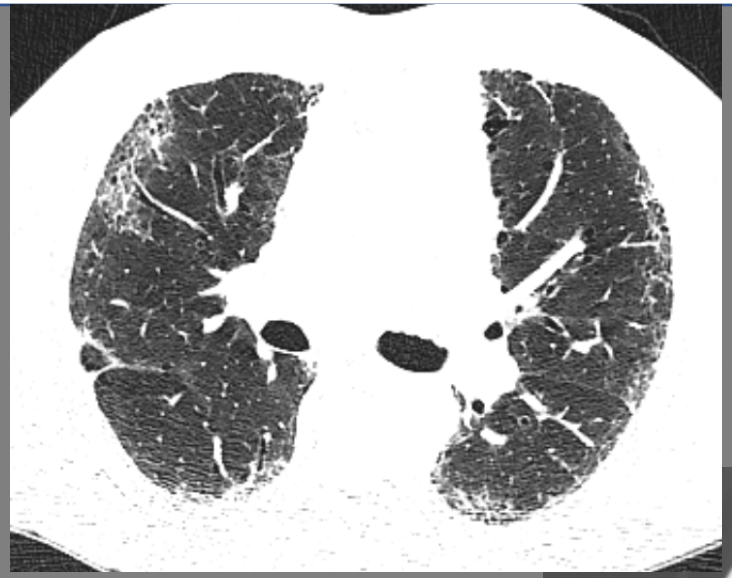
Radiology

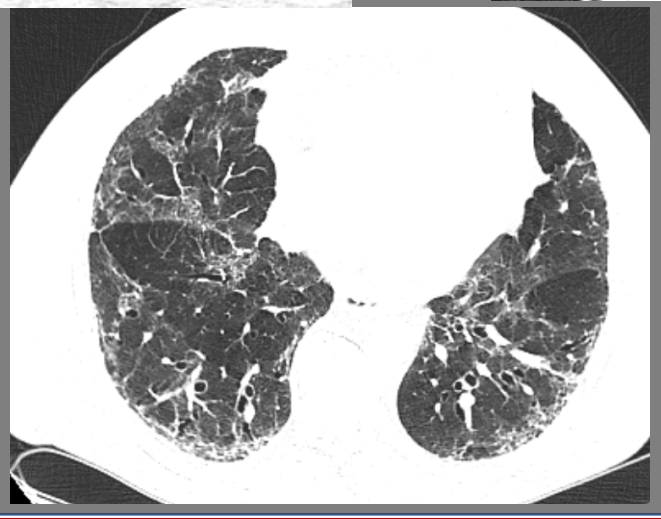
March 2019

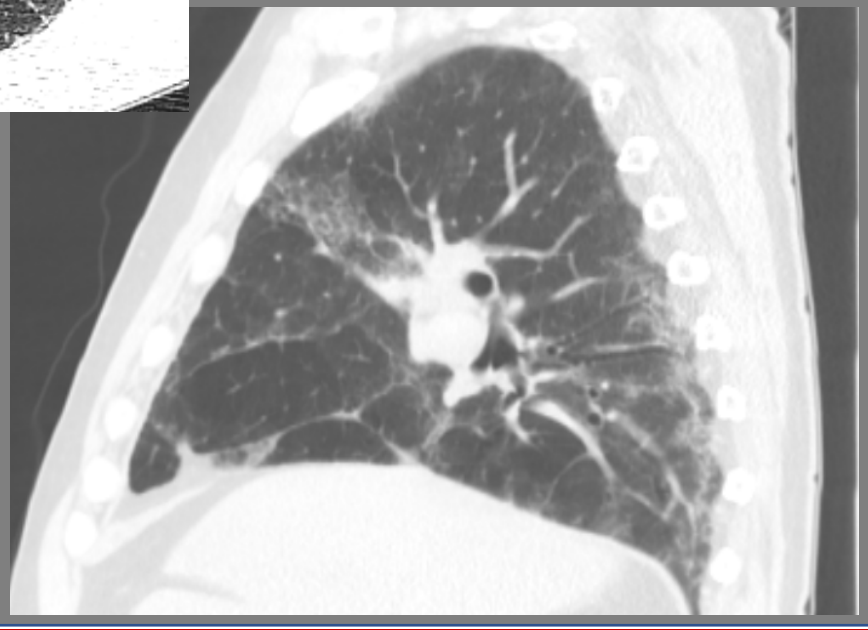


October 2020

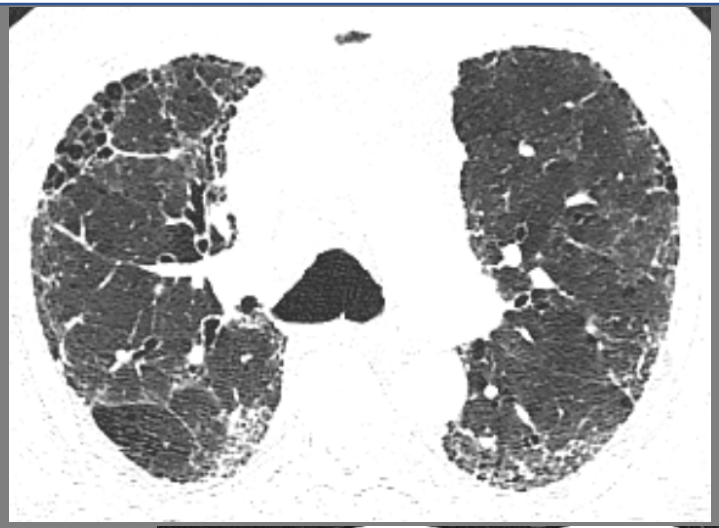


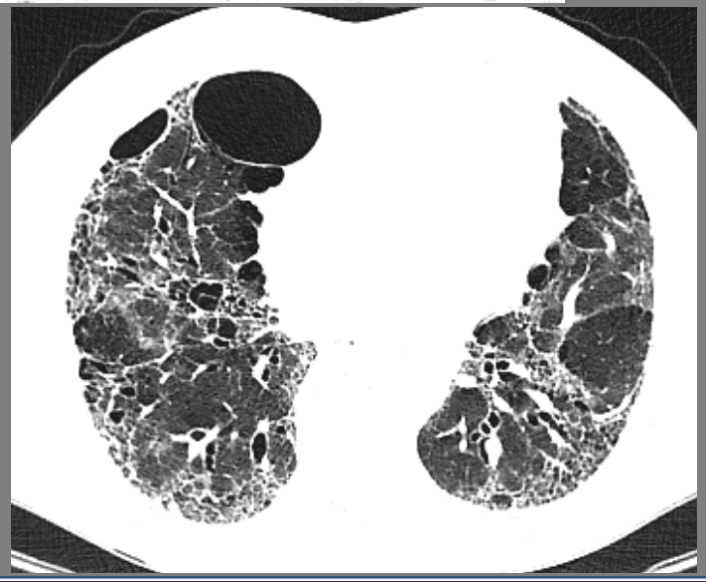


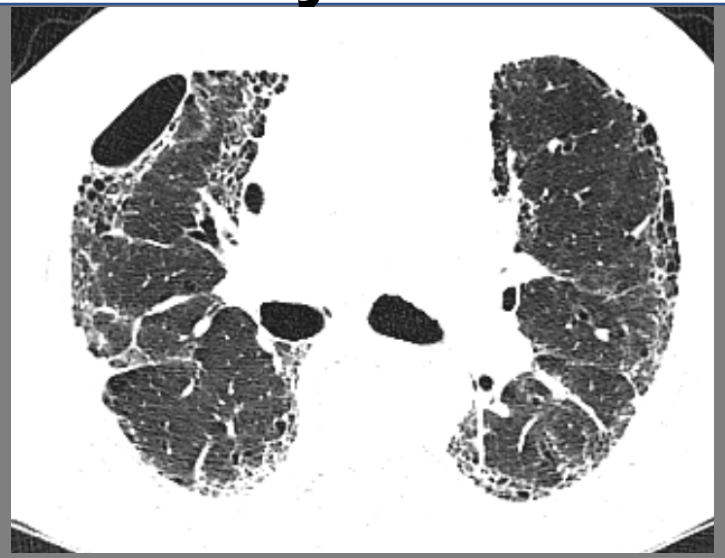


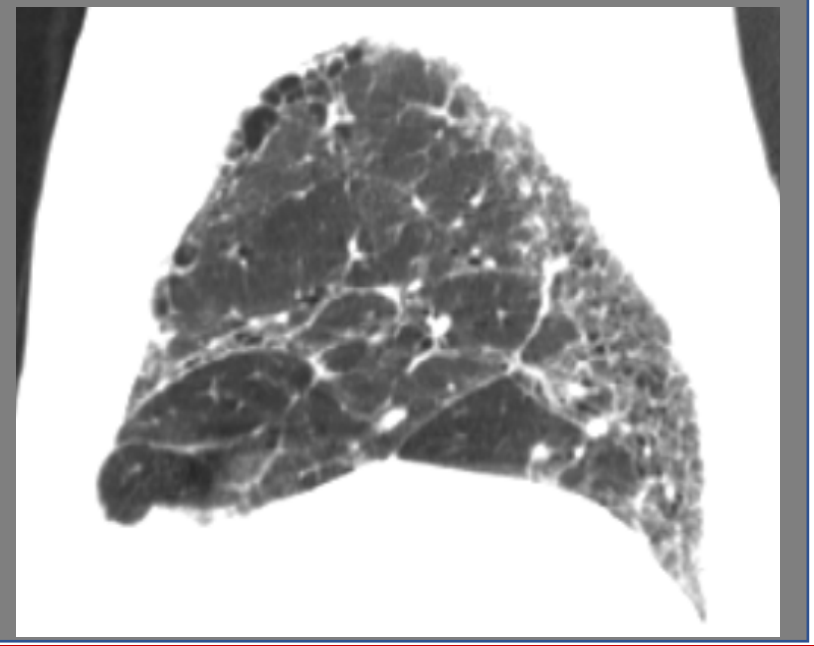


January 2022









Pathology

Wedge resections:

Right upper lobe: 7.5 x 2.3 x 1.2 cm

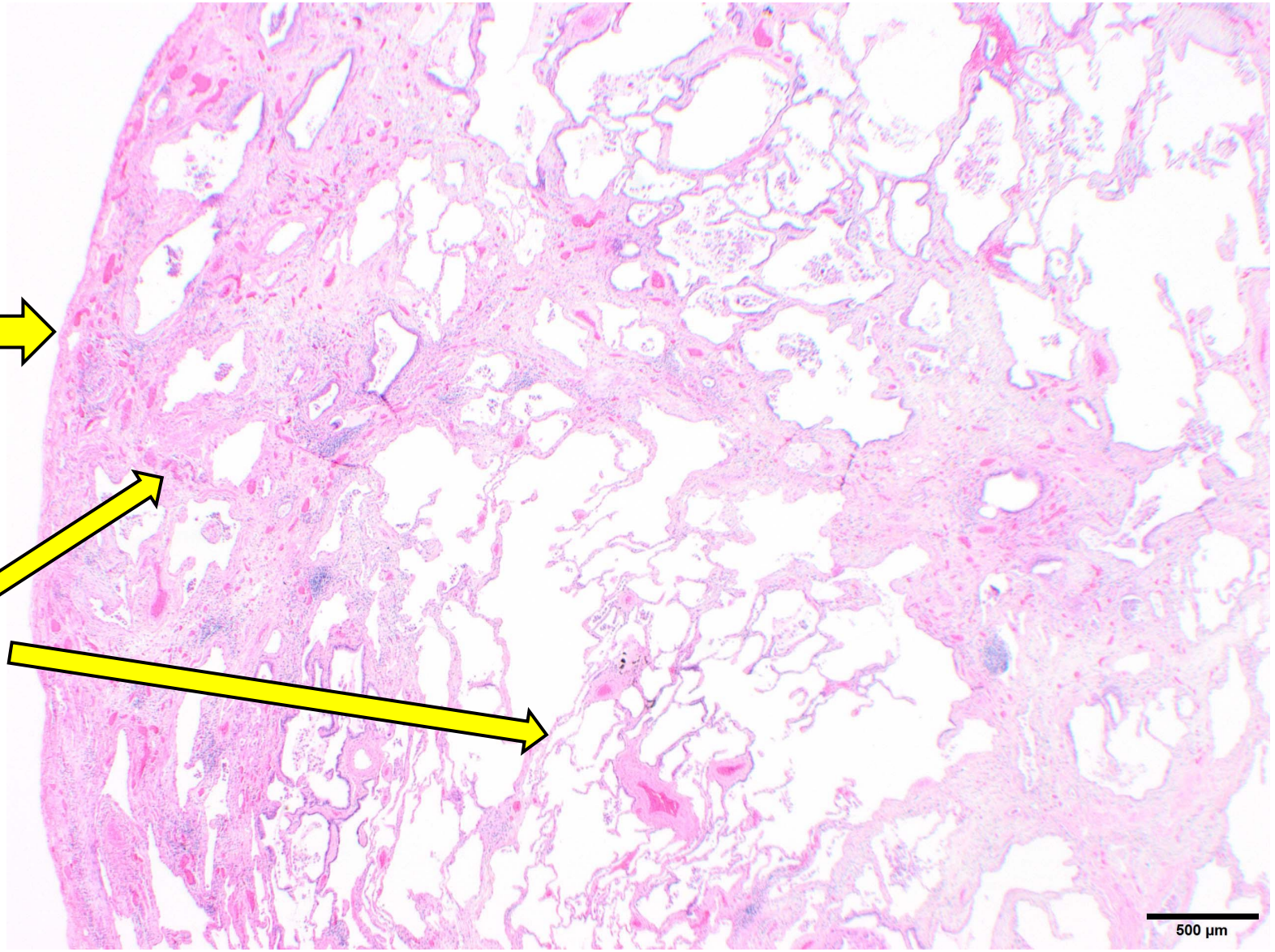
Right middle lobe: 7 x 3 x 1.5 cm

Right lower lobe; 9 x 5 x 1 cm

RUL

Subpleural fibrosis

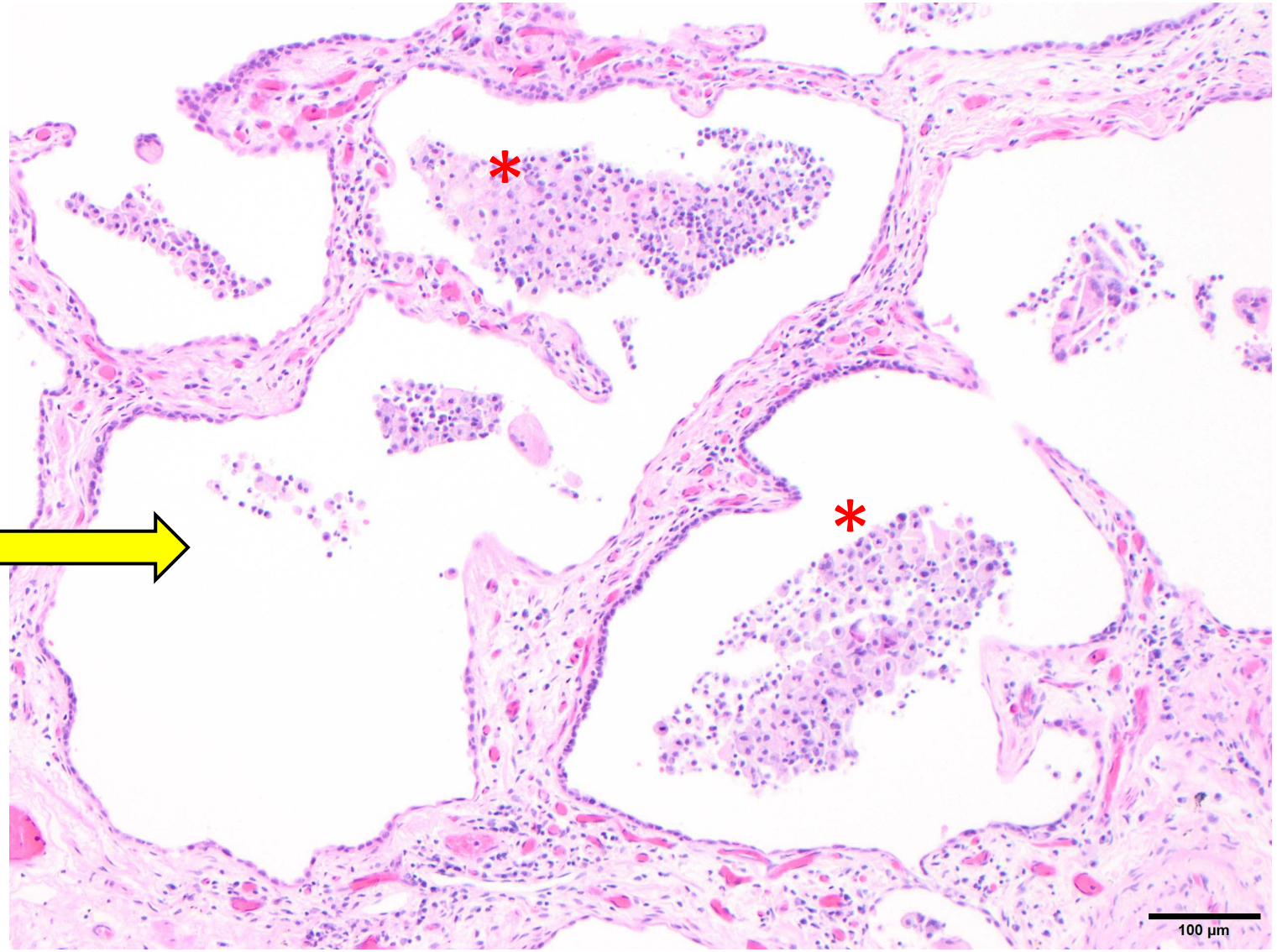
Temporal heterogeneity



RUL

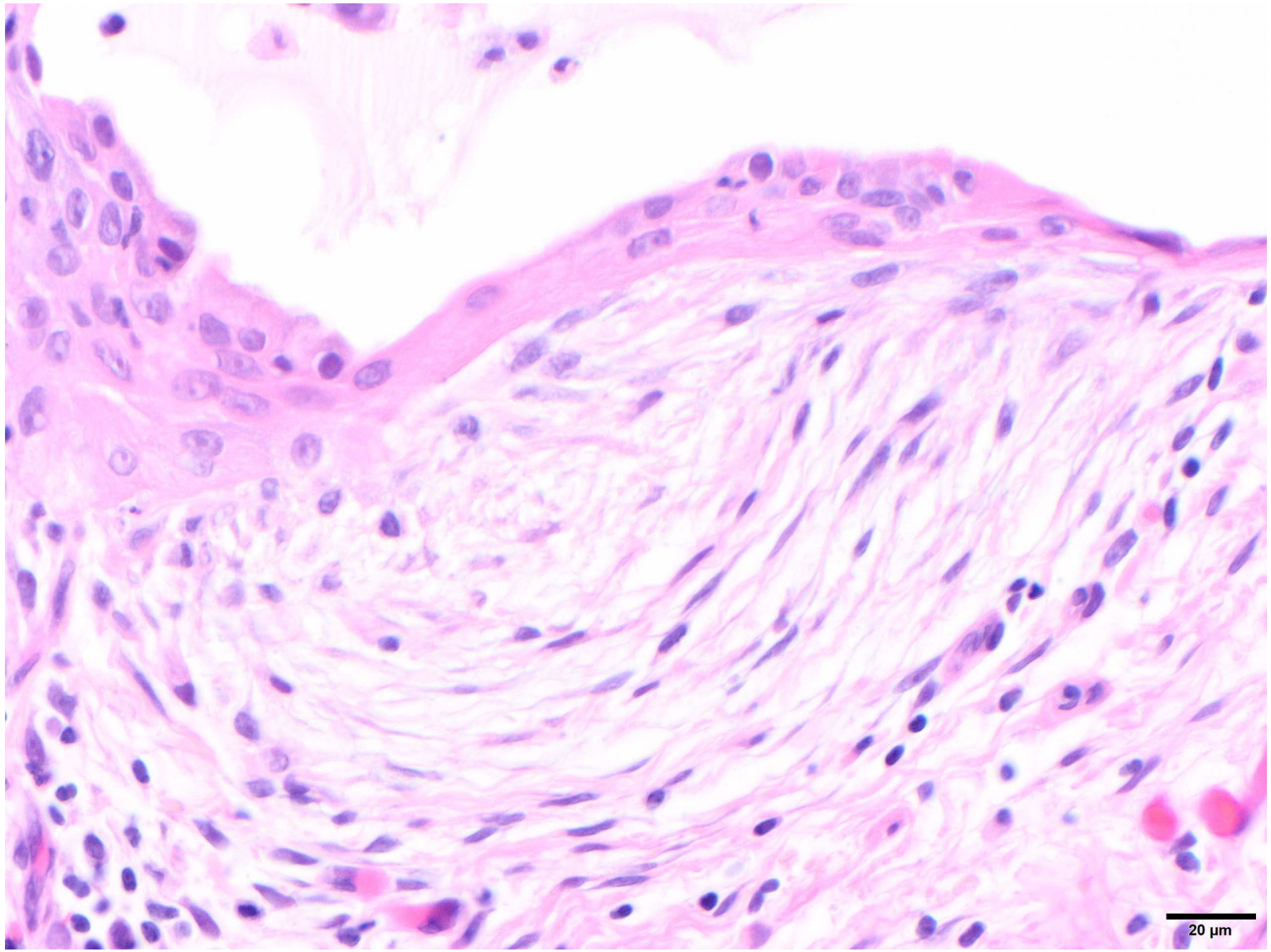
Alveolar * macrophages

Microscopic honeycomb cysts



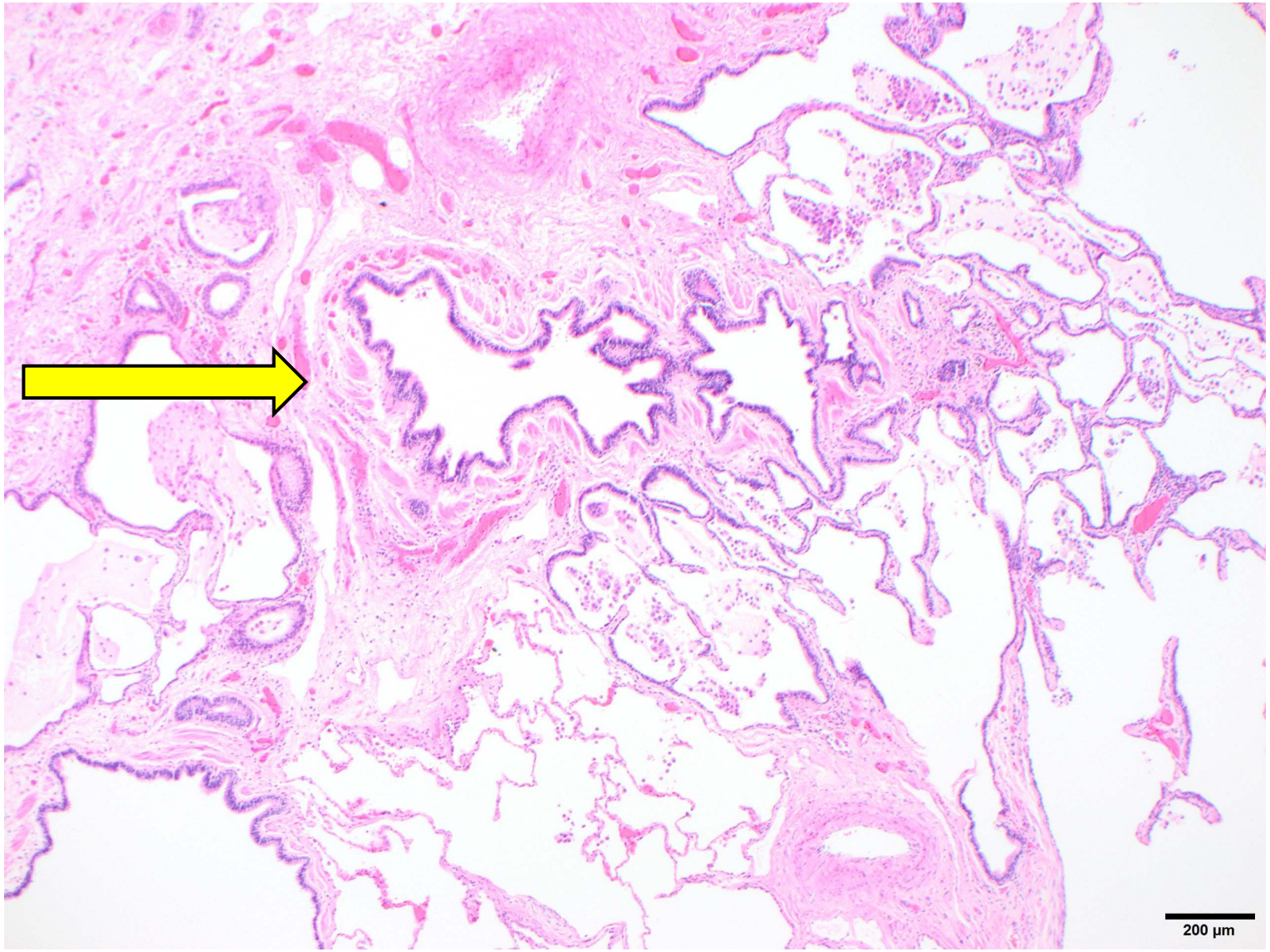
RUL

Fibroblast foci



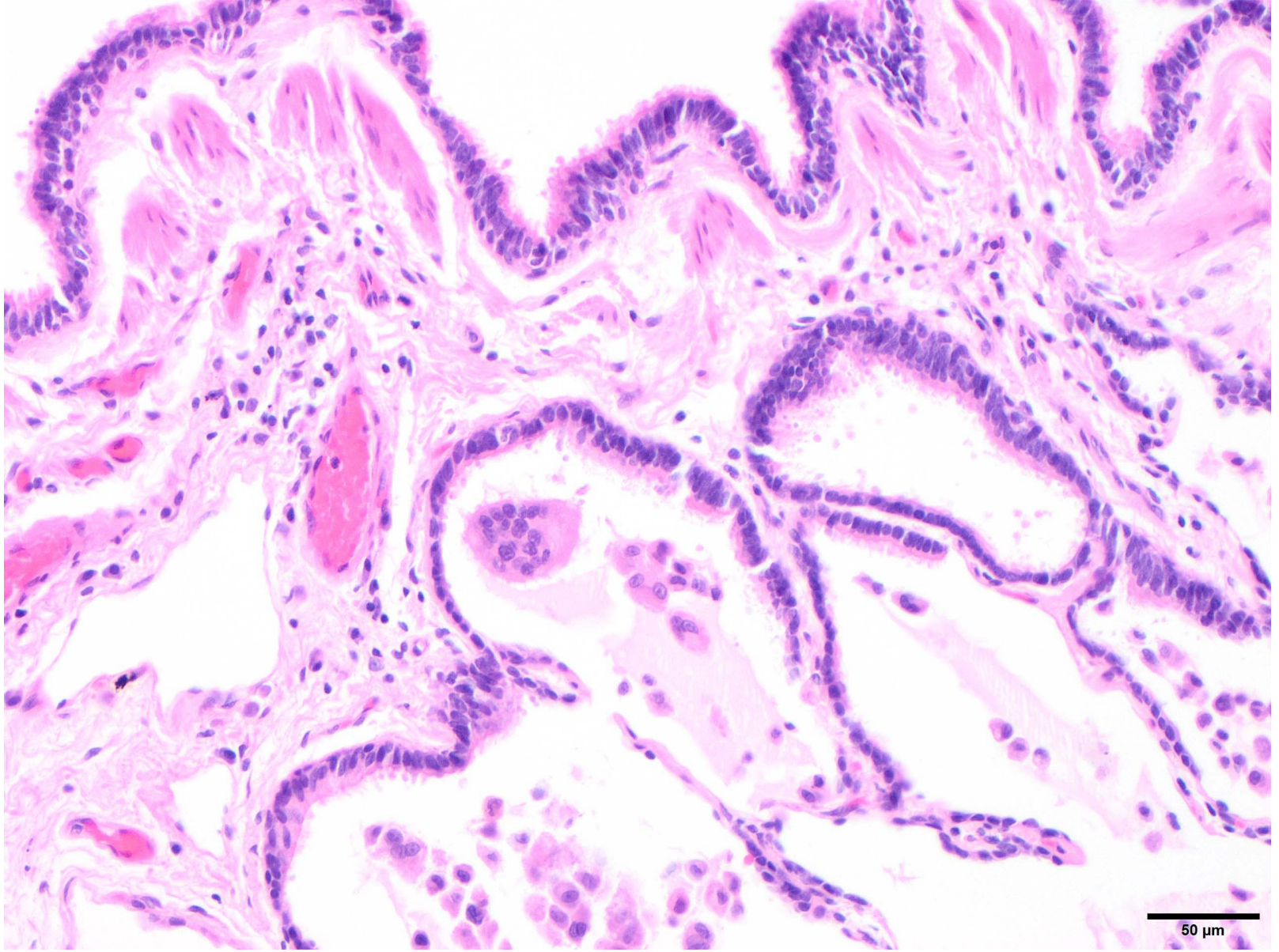
RUL

Peribronchial metaplasia



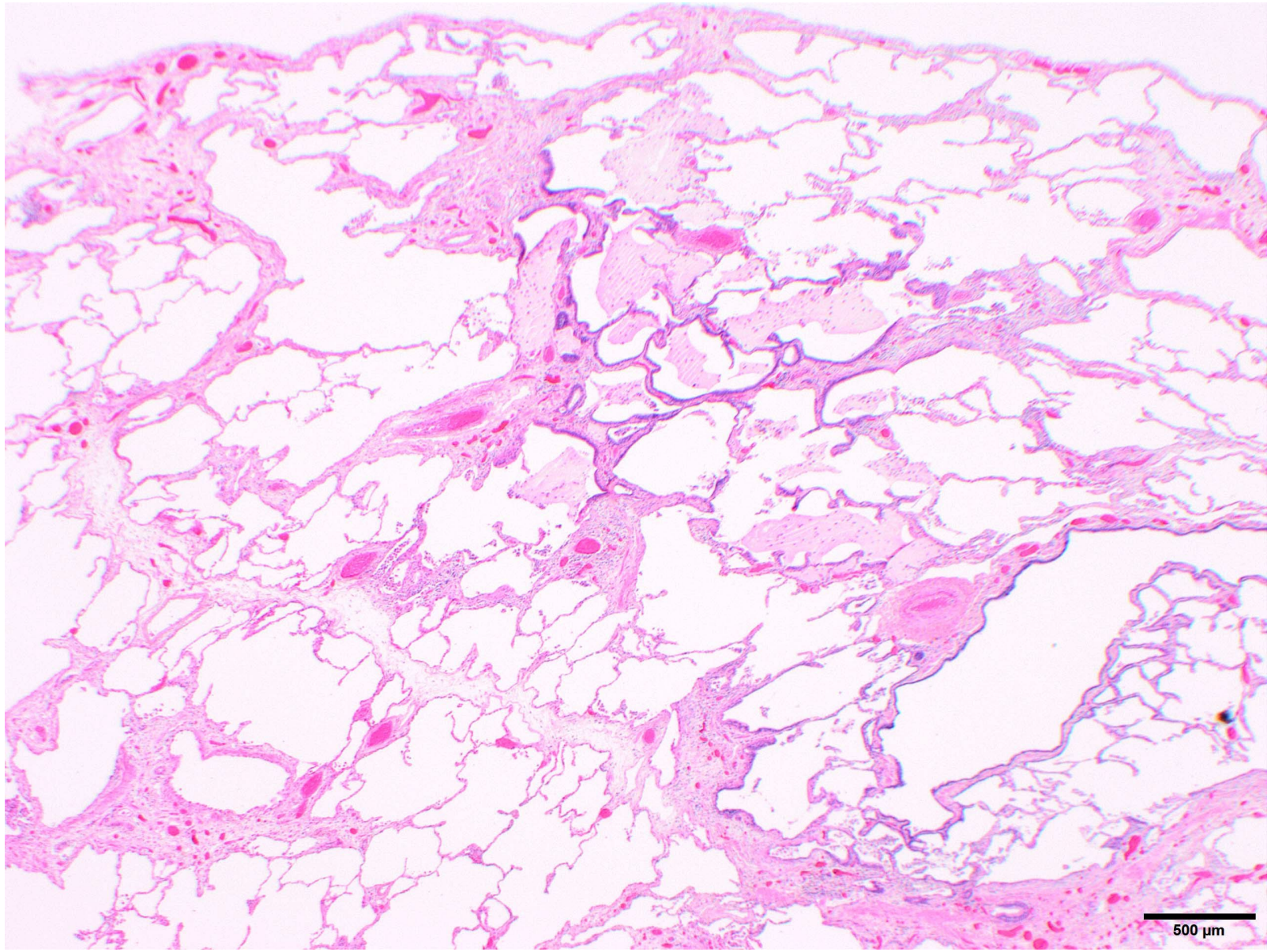
RUL

Peribronchial metaplasia



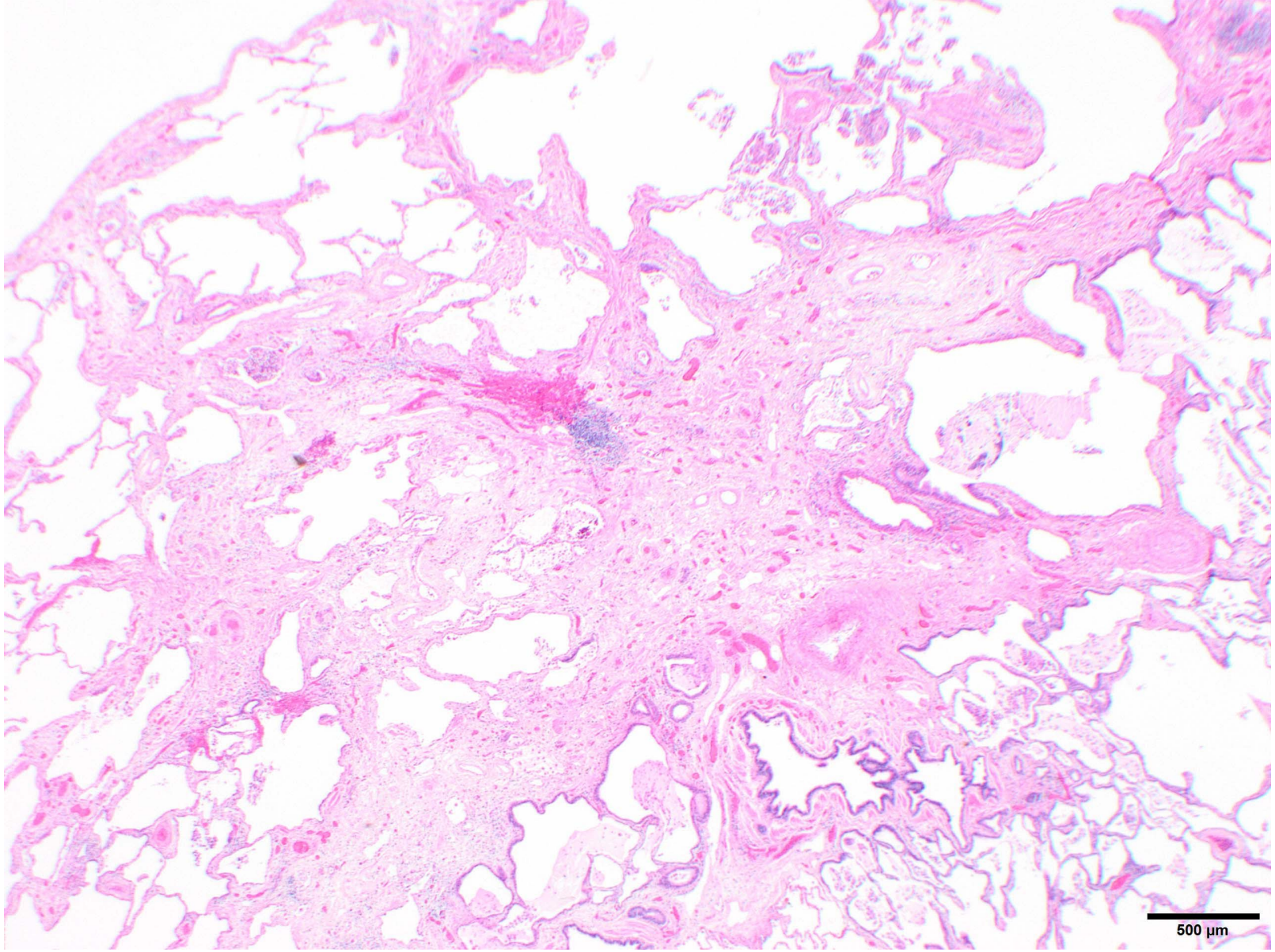
RML

No subpleural fibrosis

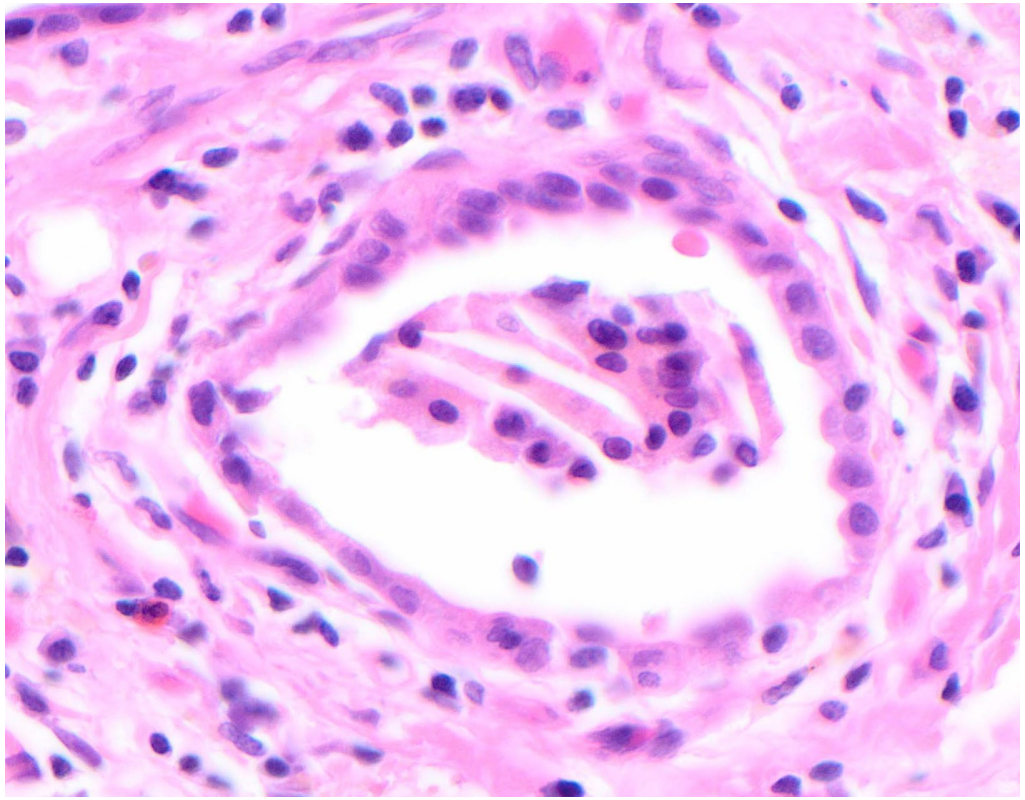


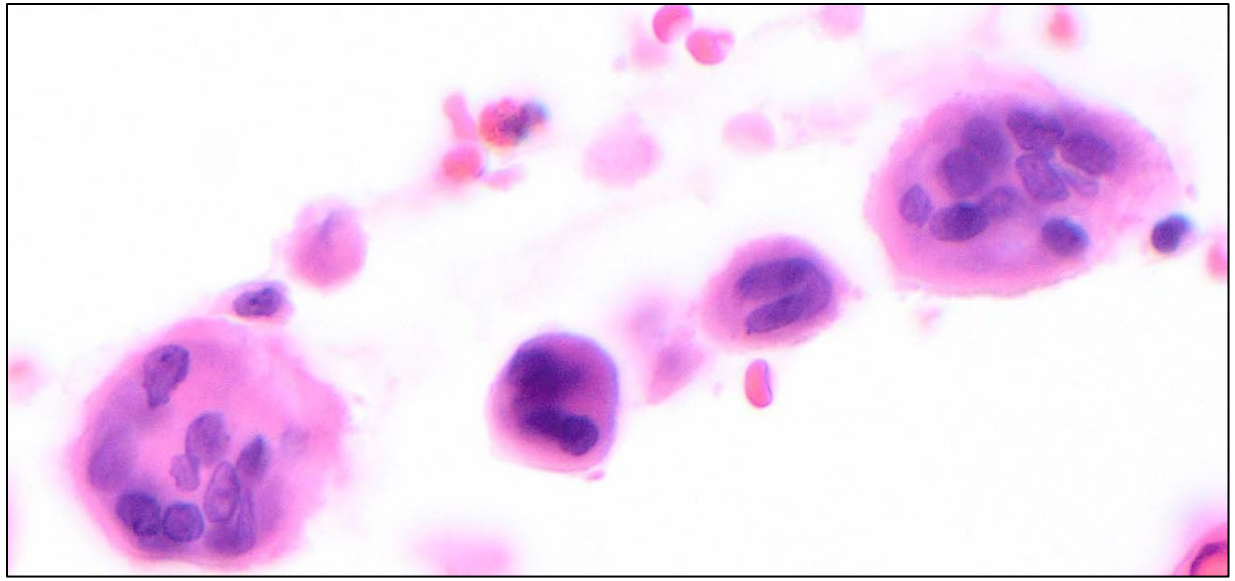
RML

Centrilobular fibrosis



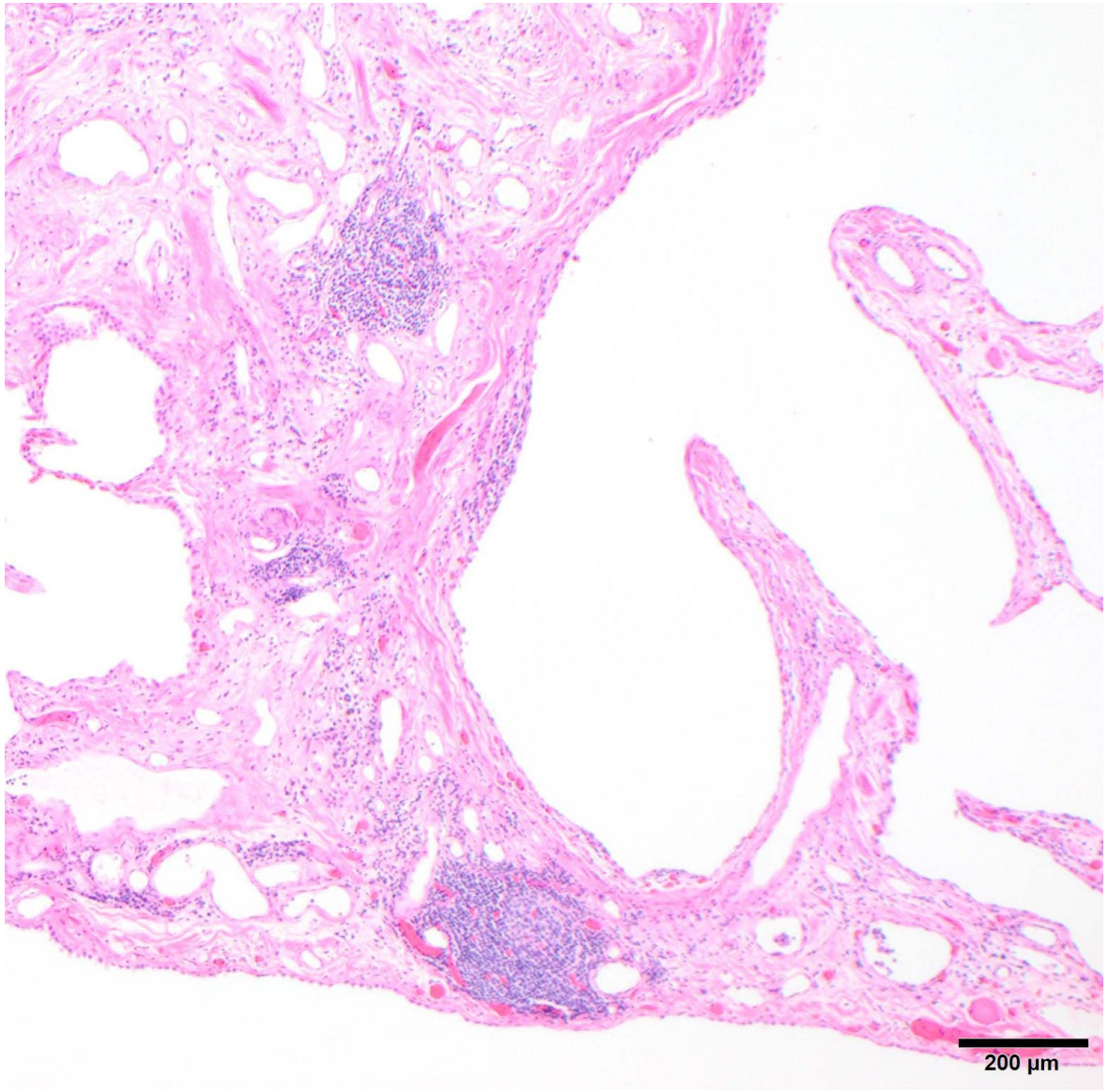
Multinuclear giant cells



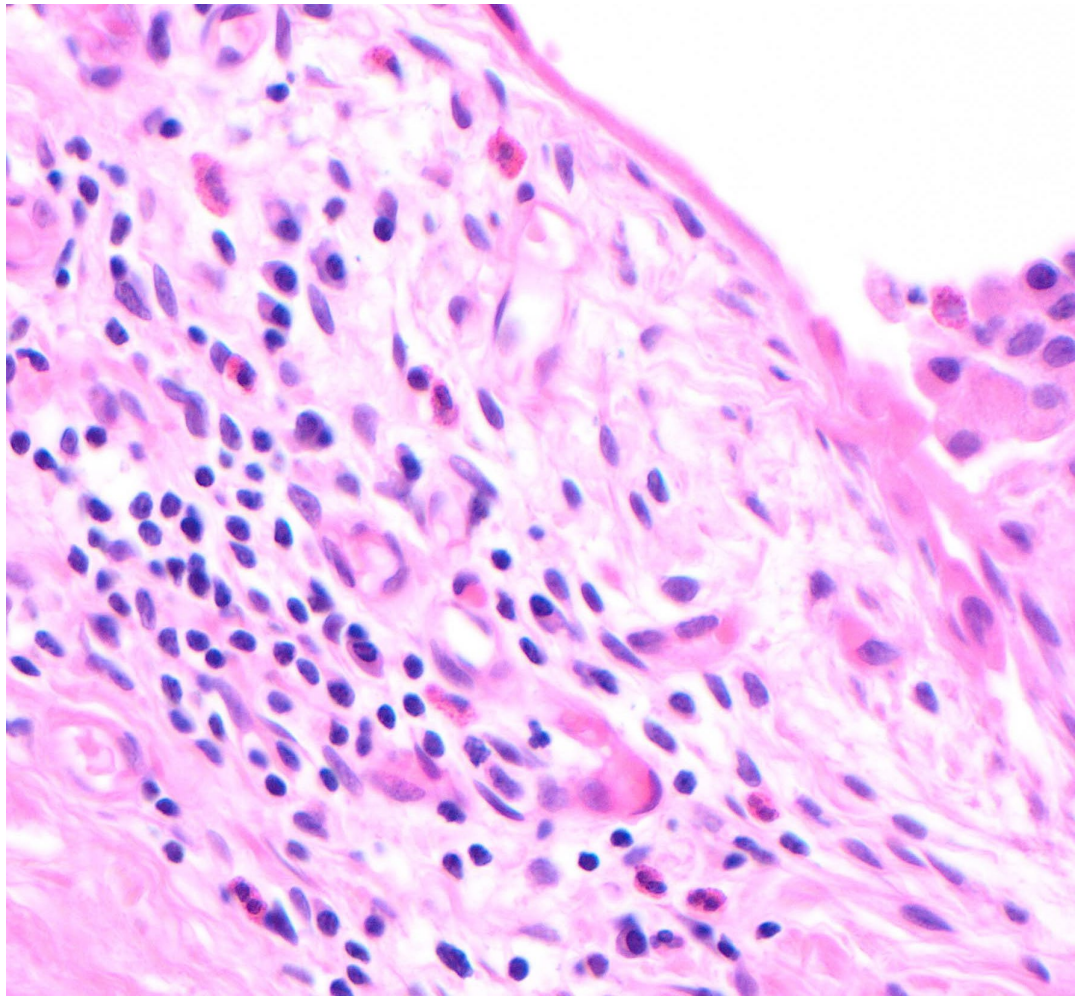


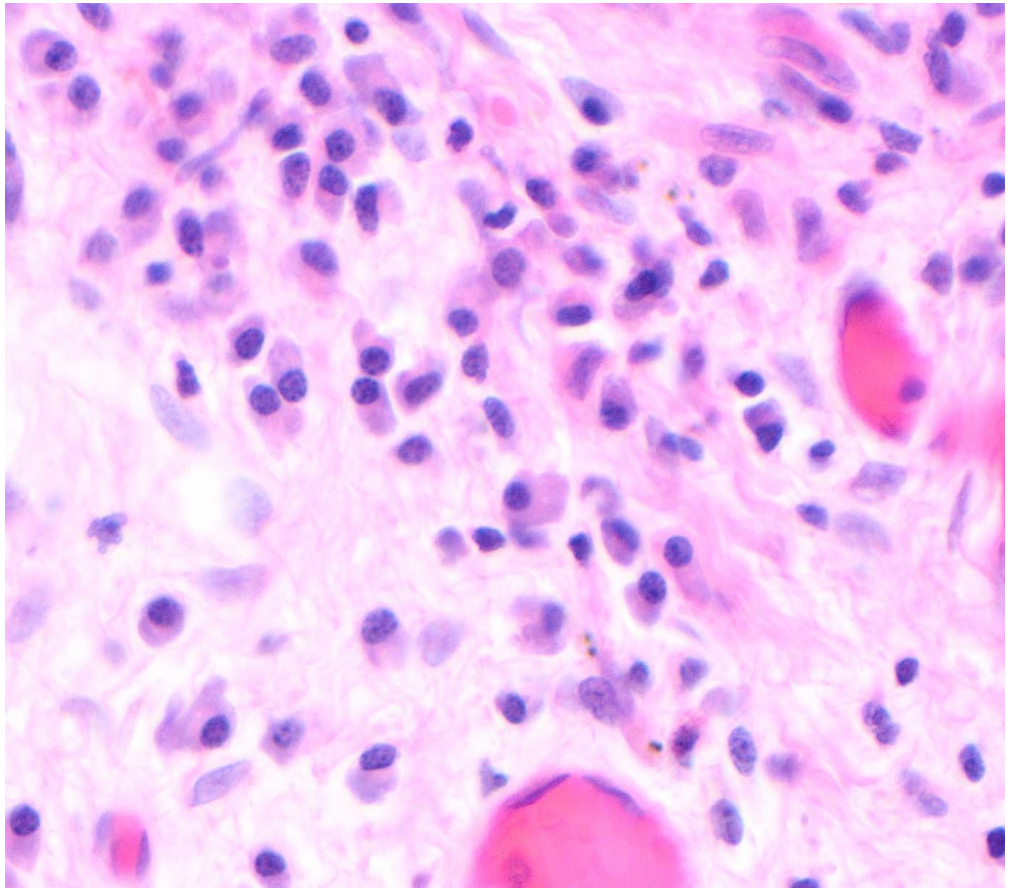
RML

Lymphoid aggregates



Occasional collections of eosinophils; plasma cells





Summary of pathology

- Temporal heterogeneity, fibroblastic foci, mHC, occasional giant cells, supleural fibrosis with some centrilobular fibrosis, peribronchial metaplasia

- Fits with a UIP pattern

Differential Diagnosis

- Idiopathic pulmonary fibrosis (IPF):
    - Less centrilobular fibrosis
    - Less peribronchial metaplasia

Differential Diagnosis

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- Connective tissue disease related
  - Lymphoid follicles with germinal centres
  - Prominent plasma cells

Differential Diagnosis

- Idiopathic pulmonary fibrosis:
  - Less centrilobular fibrosis
  - Less peribronchial metaplasia

- Connective tissue disease related
  - Lymphoid follicles with germinal centres
  - Prominent plasma cells

- Chronic hypersensitivity pneumonitis (Fibrotic HP)

A Clear Case?

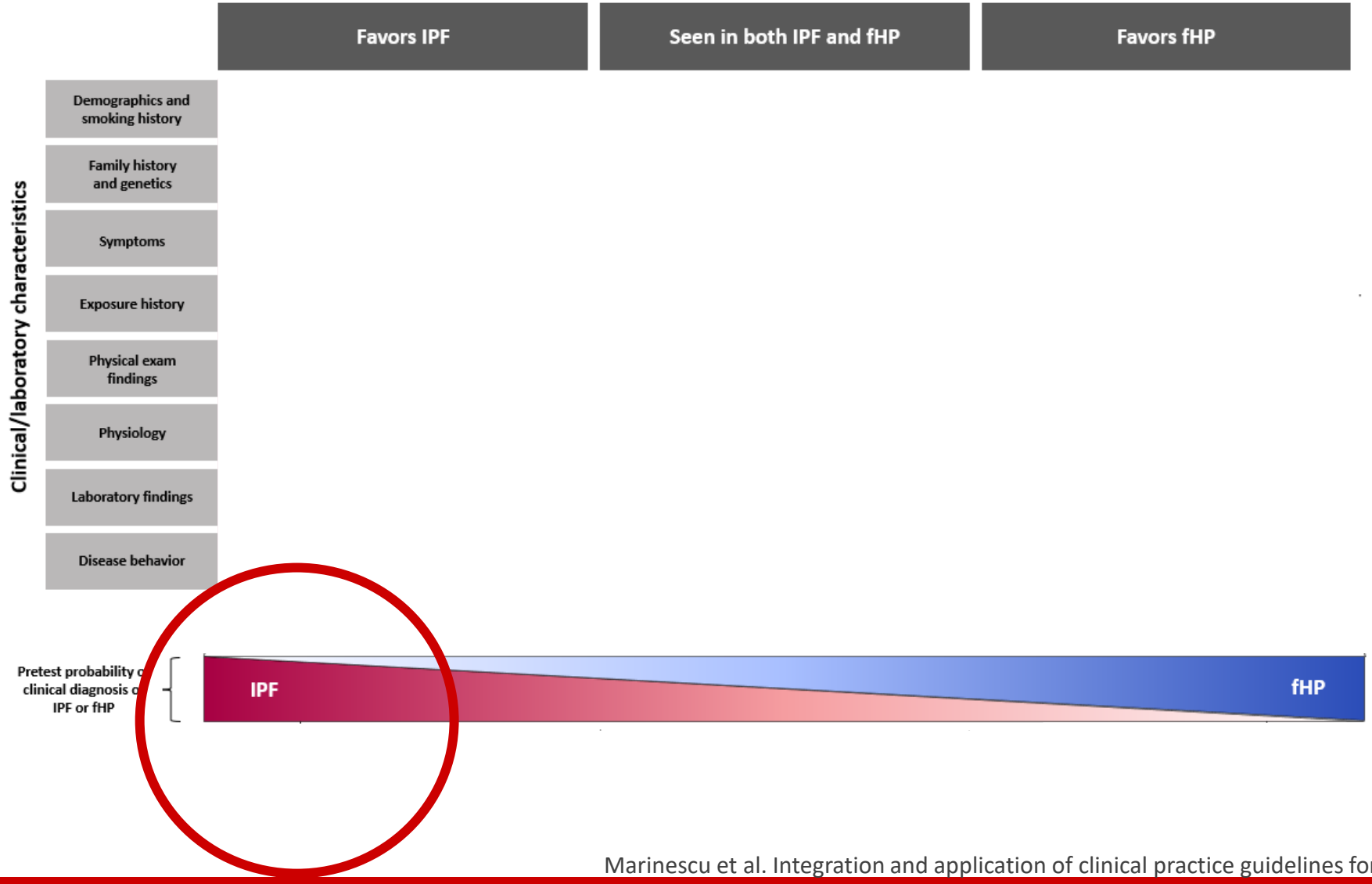
How do we synthesize the available guidelines and apply a diagnostic algorithm in patients where the primary consideration is IPF or fHP?

a) Clinical Domain
b) Radiologic Domain
c) Pathologic Domain

Integration and application of clinical practice guidelines for the diagnosis of idiopathic pulmonary fibrosis and fibrotic hypersensitivity pneumonitis

Daniel-Costin Marinescu[1,2], Ganesh Raghu[3], Martine Remy-Jardin[4], William D. Travis[5], Ayodeji Adegunsoye[6], Mary Beth Beasley[7], Jonathan H. Chung[8], Andrew Churg[9], Vincent Cottin[10], Ryoko Egashira[11], Evans R. Fernández Pérez[12], Yoshikazu Inoue[13], Kerri A. Johannson[14], Ella A. Kazerooni[15], Yet H. Khor[16,17], David A. Lynch[18], Nestor L. Müller[19], Jeffrey L. Myers[20], Andrew G. Nicholson[21], Sujeet Rajan[22], Ryoko Saito-Koyama[23], Lauren Troy[24], Simon L.F. Walsh[25], Athol U. Wells[26], Marlies S. Wijsenbeek[27], Joanne L. Wright[28], Christopher J. Ryerson[1,2]

ILD Evaluation: Clinical Assessment



Marinescu et al. Integration and application of clinical practice guidelines for the diagnosis of IPF and fHP. *In revision*.

ILD Evaluation: Clinical Assessment Pearls

Clinical profile in keeping with IPF: older, male, smoker with GERD

An inciting antigen is the most important factor in diagnosing fHP on clinical grounds but:

- A lack of exposure does not rule out fHP (approximately 50% of cases)
- A potential exposure does not necessarily equate a diagnosis of fHP
- More convinced by antigen if:
    - More strongly associated with fHP (*i.e.* birds and mold)
    - High intensity exposure (*i.e.* daily/continuous vs occasional)
    - Timing matches disease onset (*i.e.* exposure predates disease)
    - Disease activity parallels exposure
    - Antigen removal leads to stabilization (more in non-fibrotic HP)

An identified antigen does not mean fHP, and a lack of antigen does not rule out fHP!

Current clinical practice guidelines

IPF (2018)

ATS/ERS/JRS/ALAT

Radiology

- Basal, subpleural reticulation +/- honeycombing
- Lack of alternative/incompatible features

Pathology

- Patchy, subpleural/paraseptal fibrosis with fibroblastic foci
- Lack of alternative/incompatible features

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Findings suggestive of another diagnosis, including: • CT features: ° Cysts ° Marked mosaic attenuation ° Predominant GGO ° Profuse micronodules ° Centrilobular nodules ° Nodules ° Consolidation • Predominant distribution: ° Peribronchovascular ° Perilymphatic ° Upper or mid-lung • Other: ° Pleural plaques (consider asbestosis) ° Dilated esophagus (consider CTD) ° Distal clavicular erosions (consider RA) ° Extensive lymph node enlargement (consider other etiologies) ° Pleural effusions, pleural thickening (consider CTD/drugs)
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO	Subtle reticulation; may have mild GGO or distortion ("early UIP pattern") CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")	

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis	• Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF *And* • Absence of features to suggest an alternative diagnosis *Or* • Honeycombing only	• Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* • Some histologic features from column 1, but with other features suggesting an alternative diagnosis†	• Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies • Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Current clinical practice guidelines

Radiology

- Fibrosis
- Signs of airways disease:
  - (Centrilobular nodules)
  - 3-density pattern
  - Air trapping
  - Hypoattenuating lobules

Pathology

- Fibrosis
- Airway-centered disease +/-
- Granulomas

fHP (2020)

ATS/JRS/ALAT

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a*) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b*) at least one abnormality that is indicative of small airway disease	"Compatible-with-HP" patterns exist when the HRCT pattern and/or distribution of lung fibrosis varies from that of the typical HP pattern; the variant fibrosis should be accompanied by signs of small airway disease	The "indeterminate-for-HP" pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined, centrilobular nodules and/or GGOs • Mosaic attenuation, three-density pattern,* and/or air trapping (*often in a lobular distribution*)	Variant patterns of lung fibrosis: • UIP pattern: basal and subpleural distribution of honeycombing with/without traction bronchiectasis (*per 2018 diagnosis of IPF guidelines* [20]) • Extensive GGOs with superimposed subtle features of lung fibrosis Variant (predominant) distributions of lung fibrosis: • Axial: peribronchovascular, subpleural areas • Craniocaudal: upper lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined centrilobular nodules, or • Three-density pattern* and/or air trapping	Lone patterns (i.e., not accompanied by other findings suggestive of HP) of: • UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Probable UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Indeterminate pattern for UIP (*as per 2018 IPF diagnosis guidelines* [20]) • Fibrotic NSIP pattern • Organizing pneumonia–like pattern • Truly indeterminate HRCT pattern

HP	Probable HP	Indeterminate for HP
Fibrotic HP‡ Typical histopathological features of fibrotic HP; *1* or *2 and 3* in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± subpleural honeycombing • Fibrotic NSIP-like§ pattern 2. Airway-centered fibrosis • ±Peribronchiolar metaplasia • ±Bridging fibrosis‖ 3. Poorly formed nonnecrotizing granulomas† ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern ★	Both of the following features (*1* or *2* from first column) in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± subpleural honeycombing • Fibrotic NSIP-like pattern 2. Airway-centered fibrosis • ±Peribronchiolar metaplasia • ±Bridging fibrosis‖ ±Cellular interstitial pneumonia ±Organizing pneumonia pattern ±Cellular bronchiolitis ★	Either one of the following features in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± honeycombing • Fibrotic NSIP-like pattern ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern *and* ★

fHP (2021)

CHEST Guideline and Expert Panel Report

TABLE 5 | Diagnostic CT Categories of Fibrotic HP Based on CT Patterns

HRCT	Typical Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP
Features	CT signs of fibrosis with either of the following: • Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones • Inspiratory mosaic attenuation with three-density sign ***And*** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis with any of the following: • Patchy or diffuse ground-glass opacity • Patchy, nonprofuse centrilobular nodules of ground-glass attenuation • Mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP ***And*** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis without other features suggestive of HP

Typical Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP	Alternative Diagnosis
Major Features Presence of all three major features in at least one of the sampled lobe(s) of lung: 1) Regions where small airway-centered fibrosis is clearly present with or without peribronchiolar metaplasia 2) Fibrosing interstitial pneumonia affecting at least one sampled area/lobe of lung parenchyma with regions showing one or more of the following patterns a) NSIP-fibrosing pattern b) UIP-pattern c) Fibrosing pattern that is difficult to classify d) Fibrosis that is solely peribronchiolar 3) Poorly formed noncaseating granulomas ***Or*** Fibrosing interstitial pneumonia meeting only major feature #2 in at least one lobe, as well as all criteria for ***Typical Nonfibrotic HP*** in a separate lobe(s) **Minor Features** a) Organizing pneumonia, small foci b) Focal peribronchiolar metaplasia c) Foamy macrophages d) Cholesterol clefts ***Lack of*** Features of an alternative diagnosis (see column 4)	**Major Features** Presence of these two major features in at least one of the sampled lobe(s) of lung: 1) Regions where small airway-centered fibrosis is clearly present with or without widespread peribronchiolar metaplasia[a] 2) Fibrosing interstitial pneumonia affecting at least one sampled area of lung parenchyma with one or more of the following patterns a) NSIP-fibrosing pattern b) UIP-pattern c) Fibrosing pattern that is difficult to classify d) Fibrosis that is solely peribronchiolar e) Depending on the morphology this category could include some bronchiolocentric interstitial pneumonias. See Table 9. ***Or*** Fibrosing interstitial pneumonia meeting only major feature #2 in at least one lobe, as well as criteria for ***Compatible with Nonfibrotic HP*** in a separate lobe(s) **Minor Features** a) Organizing pneumonia, small foci b) Focal peribronchiolar metaplasia c) Foam cells d) Cholesterol clefts, Schaumann bodies or calcium oxalate crystals (Fig 10) ***Lack of*** a) Poorly formed non-necrotizing granulomas b) Features of an alternative diagnosis (see column 4)	Cases that show a pattern of fibrosing interstitial lung disease that does not meet the criteria for the pattern of ***Fibrotic HP, Compatible with Fibrotic HP*** or an ***Alternative Diagnosis*** **Comment:** There is uncertainty about the histologic features in these cases that raise the consideration of ***Fibrotic HP*** as well as other differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not Note: Fibrotic NSIP and UIP patterns are in this category. Depending on the morphology, this category could include some bronchiolocentric interstitial pneumonias. See Table 9.	A biopsy that shows definitive features of other interstitial lung diseases such as: • Fibrosing sarcoidosis (well-formed granulomas in a lymphatic distribution, perigranulomatous fibrosis is common,[192] inflammation is inconspicuous) • Aspiration with fibrosis (bronchiolocentric inflammation frequently with foreign material and giant cell or histiocytic reaction. However, aspiration with peribronchiolar interstitial lymphocytic infiltrates and/or fibrosis can closely resemble fibrotic HP, particularly when food or other particulate matter is not present[193,194]) • Fibrosing interstitial pneumonia in connective tissue disease,[129,195] drug-induced lung disease, or immunodeficiency[196] (prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, marked pleuritis, with or without granulomas) • Smoking-related patterns (airspace enlargement with fibrosis—which overlaps with smoking related interstitial fibrosis—which is usually accompanied by respiratory bronchiolitis and emphysema[197,198]) • Pneumoconiosis/occupational exposures (asbestos, hard metal, BADE[b])[199-201] Fibrotic pulmonary Langerhans cell istiocytosis

★ Absence of features in any biopsy site to suggest an alternative diagnosis
- Plasma cells > lymphs
- Extensive lymphoid hyperplasia
- Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas
- Aspirated particulates

ILD Evaluation: Radiologic Assessment Pearls

Distribution of UIP is basal and subpleural; distribution in fHP can encompass anything

- **Mid-upper lung and central involvement is *suggestive***
- **Basal disease does not rule out fHP (fHP can look exactly like UIP!)**

Airways disease is hallmark of fHP, detected by presence of mosaic attenuation

- 3-density pattern
- Gas trapping (requires expiratory scan)
- Hypoattenuating lobules

ILD Evaluation: Radiologic Assessment Pearls

Greater number of lobules of hypoattenuating lung/gas trapping improves confidence in fHP pattern

- More lobules increases specificity at the expense of sensitivity

Findings not clearly addressed in guidelines at lead us *away from UIP*:

- **Costophrenic angle sparing – where UIP starts and should be most prominent!**
- **A component of peribronchovascular/central disease** – may be more suggestive of fHP

Barnett J, Molyneaux PL, Rawal B, et al. Variable utility of mosaic attenuation to distinguish fibrotic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis. Eur Respir J 2019

ILD Evaluation: Pathologic Assessment Pearls

UIP pattern

- Peripheral/paraseptal
- Patchy and sharply demarcated
- Contains fibroblastic foci

fHP pattern can be very difficult to distinguish from UIP!

- **Occurs on a background of fibrosis that can look exactly like UIP**
- **Airway-centered disease and granulomas are hallmark features that distinguish from UIP**
  - Peribronchiolar fibrosis, peribronchiolar metaplasia (especially if >50% bronchioles involved), and granulomas
- **Amount of airway-centered disease/granulomas that take you from UIP to fHP is debatable and difficult to quantify**
  - Biopsy does not always give clear/definitive answer
  - Helpful to think of this as a spectrum of disease, where there may be disagreement in interpretation

MDD Integration

Clinical profile: Favors IPF
Radiologic pattern: Likely favors fHP
Pathologic pattern: Favors fHP

- **Weights given to different clinical, radiologic, and pathologic domains need to be assessed in MDD**
  - Pathology does *not* always get all the weight and may *not* be absolute

- MDD is fluid and adapting
  - In challenging cases, time is an added dimension where **disease behavior longitudinally may be integrated to help inform diagnosis**

Final diagnosis of fHP

- No culprit exposure confidently identified, which occurs in about half of fHP cases
- Started on mycophenolate and tolerated an ongoing dose of 2000mg BID
- Continued lung decline, started supplemental oxygen, and currently undergoing transplant work-up

Question 1

Which of the following is true about antigen exposure and fibrotic hypersensitivity pneumonitis (fHP)?

a) The presence of an antigen confirms a diagnosis of fHP
b) The absence of an antigen rules out fHP
c) Antigen removal leads to stabilization and improvement of fHP
d) None of the above

Question 1: Answer

Which of the following is true about antigen exposure and fibrotic hypersensitivity pneumonitis (fHP)?

a) The presence of an antigen confirms a diagnosis of fHP
b) The absence of an antigen rules out fHP
c) Antigen removal leads to stabilization and improvement of fHP
d) None of the above

Question 2

Which of the following radiological features lead away from a pattern of UIP?

a) A central/peribronchovascular component of disease
b) Sparing of the extreme costophrenic angle
c) Unilateral disease
d) All of the above

Question 2: Answer

Which of the following radiological features lead away from a pattern of UIP?

a) A central/peribronchovascular component of disease
b) Sparing of the extreme costophrenic angle
c) Unilateral disease
d) All of the above

Thank you

Questions?

Case 2:

Julie Morisset, Clinician

Giang Nguyen, Radiologist

Margaret Kelly, Pathologist

Clinical History and Findings

- 26 yo female
- Works from home (graphic designer)
- No past medical history
- No medication/ no drugs/ no vaping/ no exposure for HP
- Non smoker – no drugs

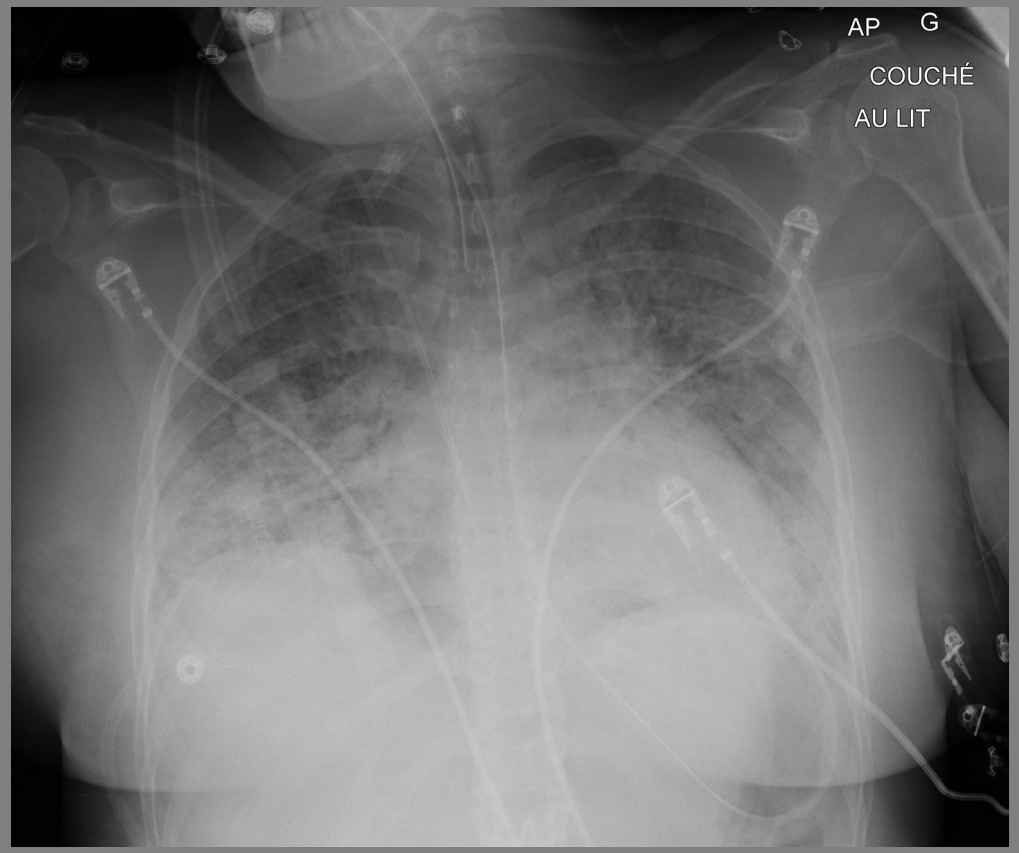
- Progressive shortness of breath in the past month
- Severe respiratory failure – required endotracheal intubation 2h after admission
- Progressive respiratory failure / persistent hypoxemia / hypercapnea despite maximal ventilator settings
- Decision to put patient on ECMO (day 1 post intubation)

Lab tests

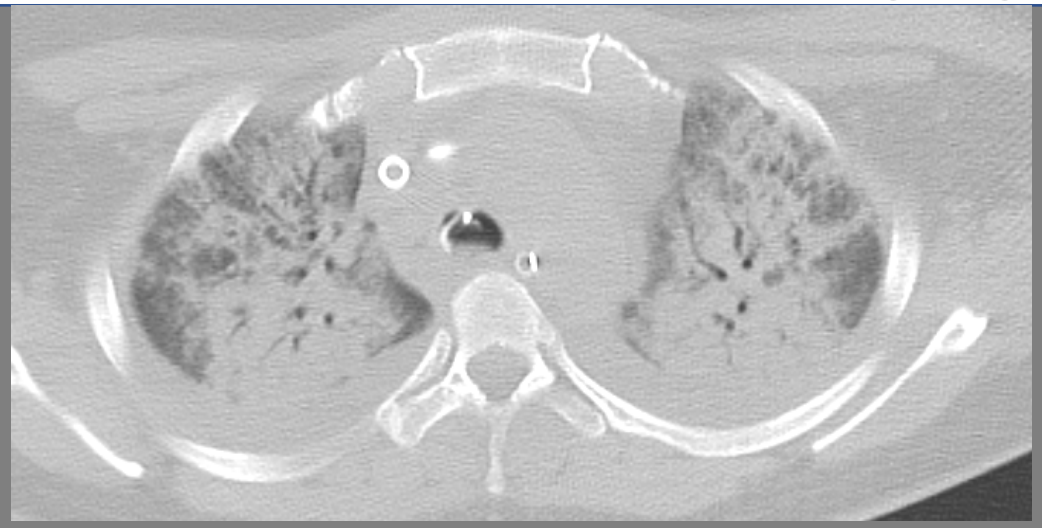
- COVID negative
- BAL: negative cultures
  70% neutrophils, 10% lymphocytes
- Negative ANA – ANCA – myositis panel – RF and CCP
- Blood work (normal CBC – kidney and liver function)

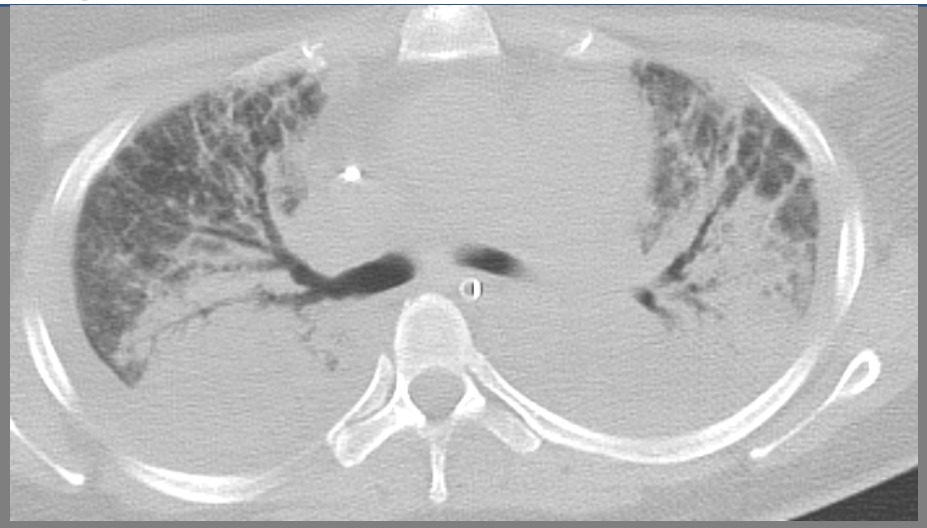
Radiology

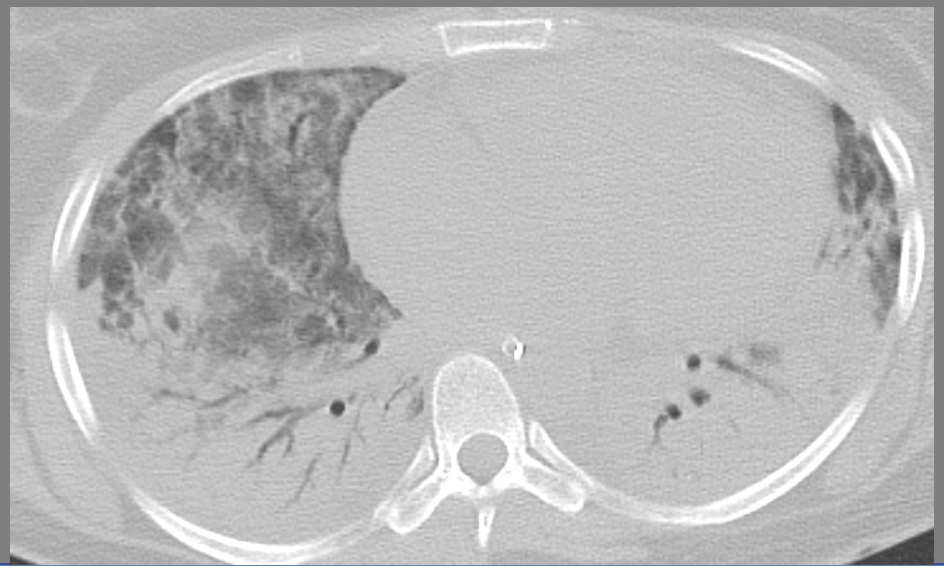
March 2021

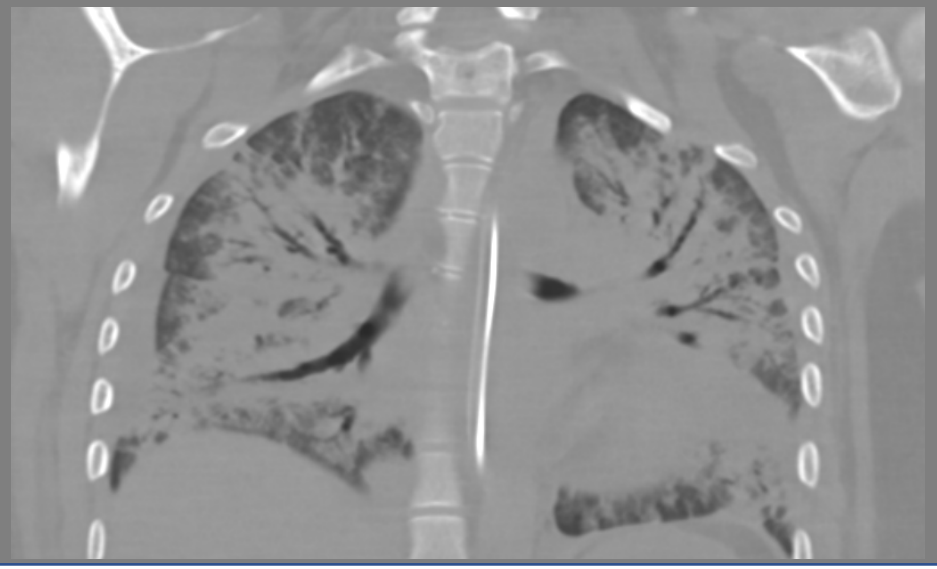


March 2021

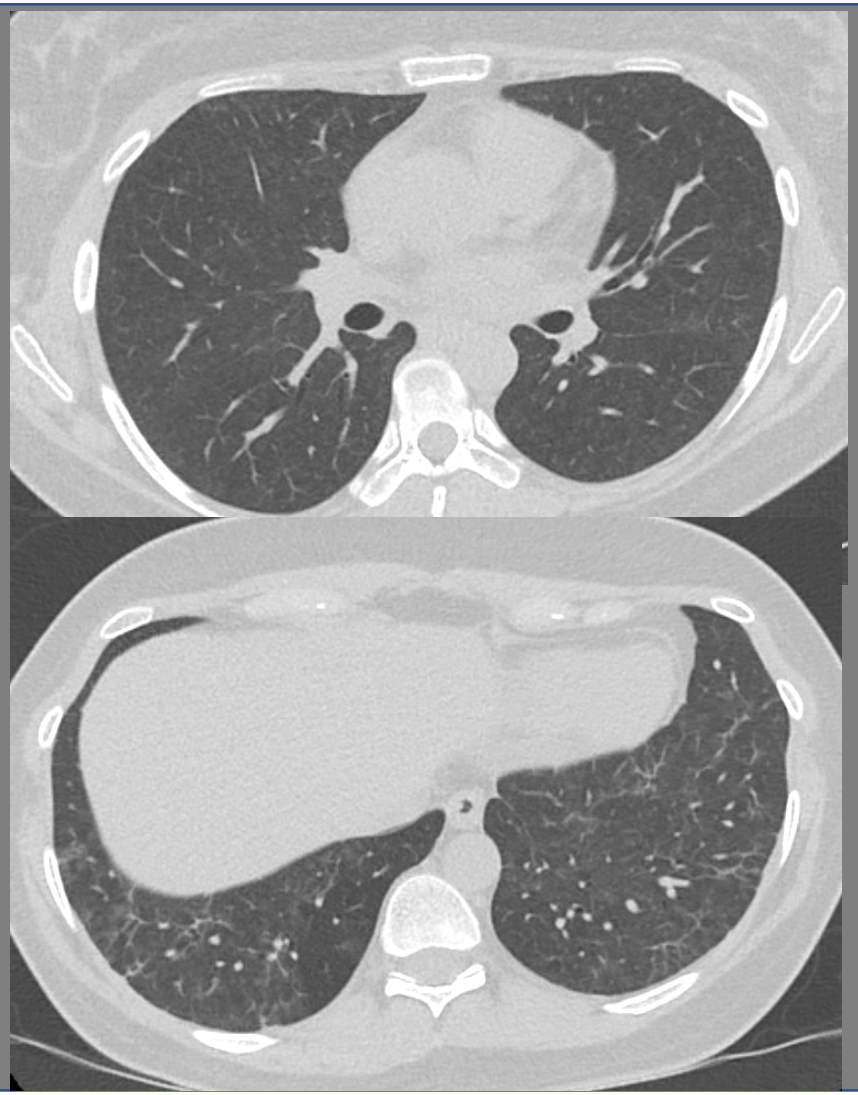


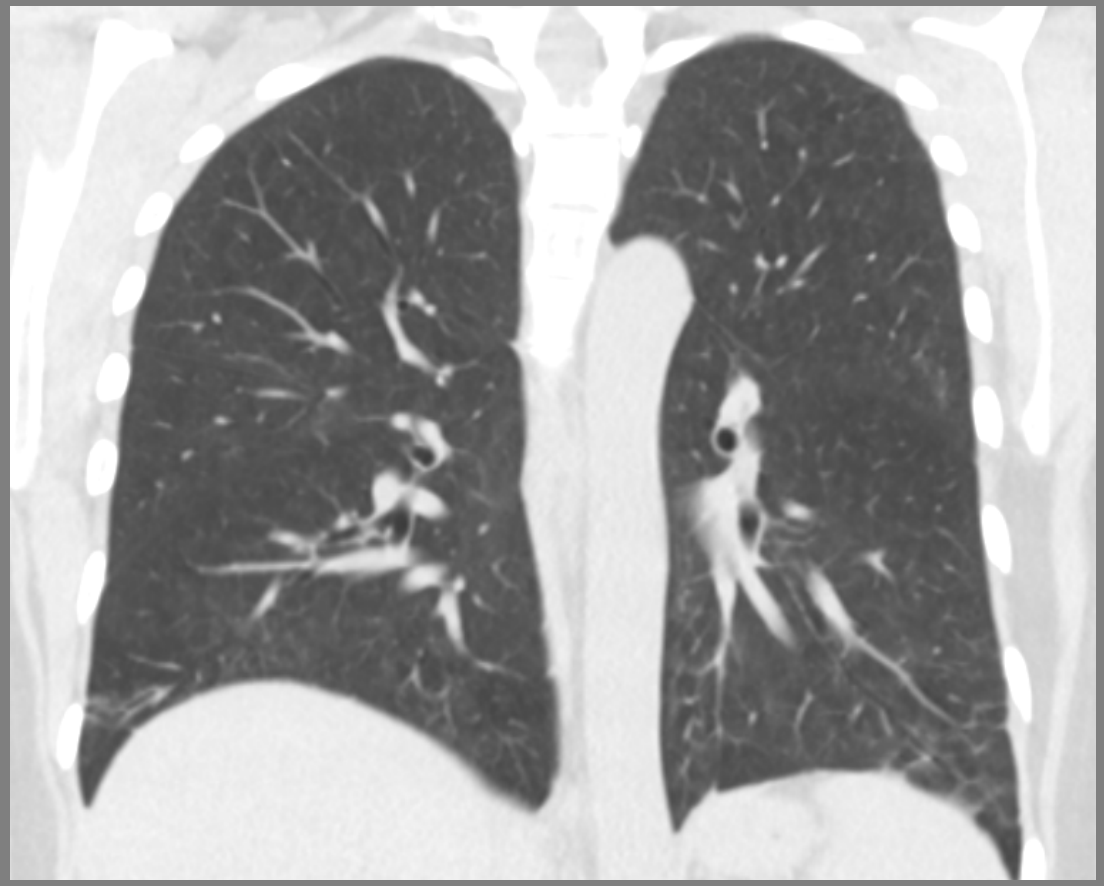






May 2021



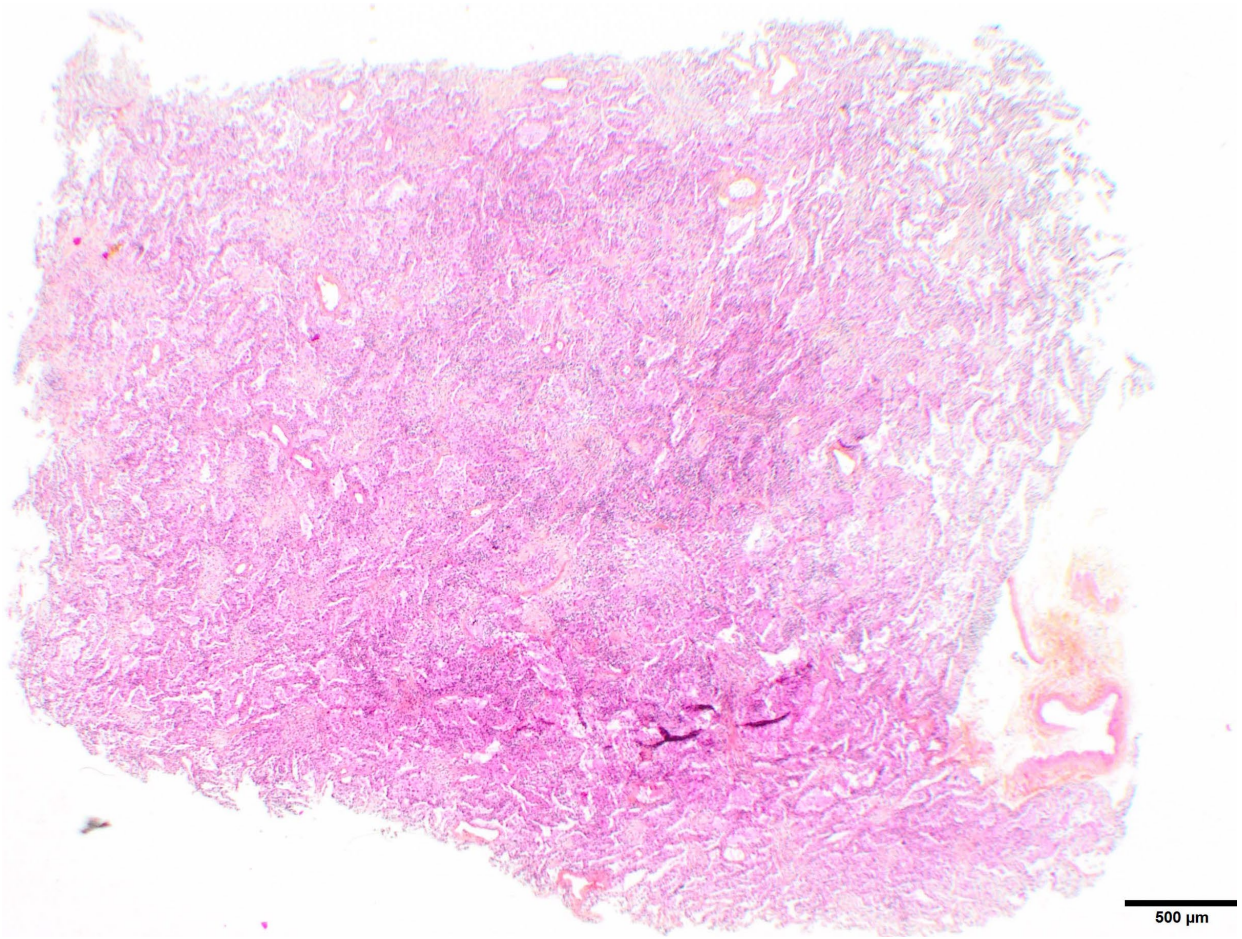


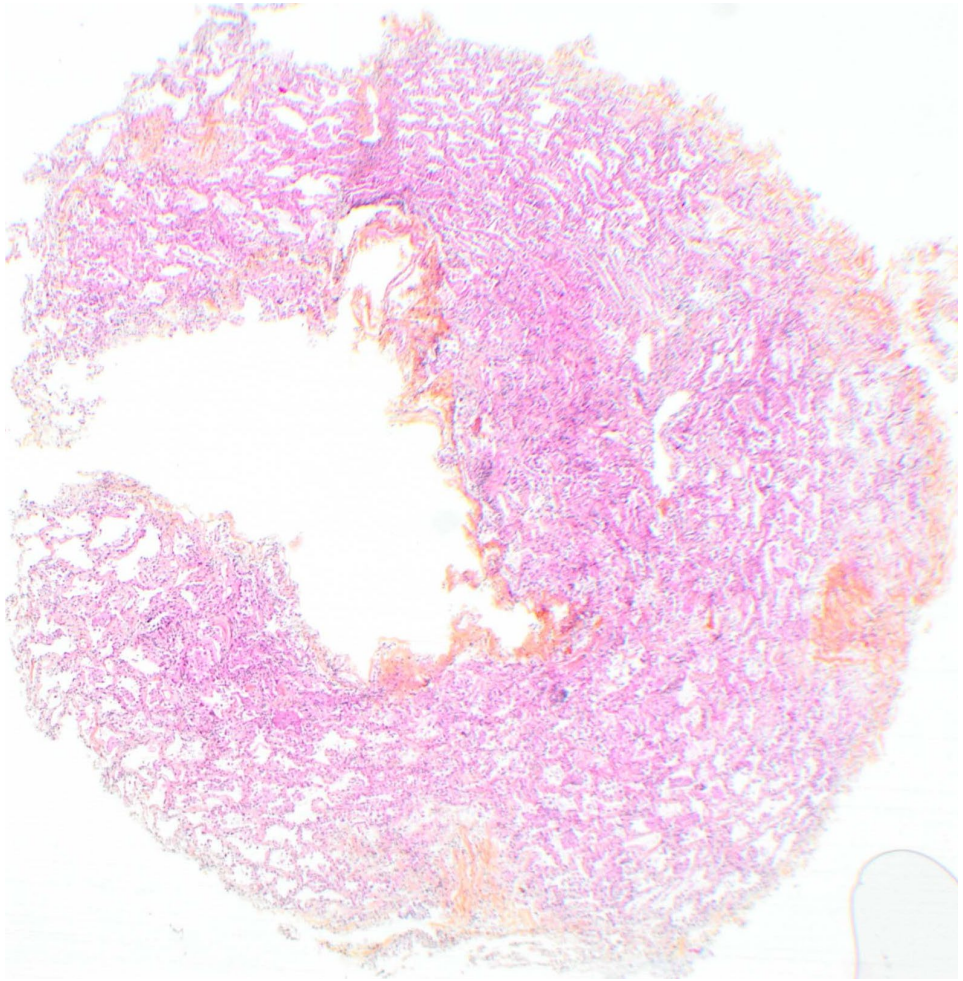
- Fulminant diffuse lung disease with severe respiratory failure in a young patient with no past medical history
- Indication for lung biopsy
- Cryo vs surgical lung biopsy?

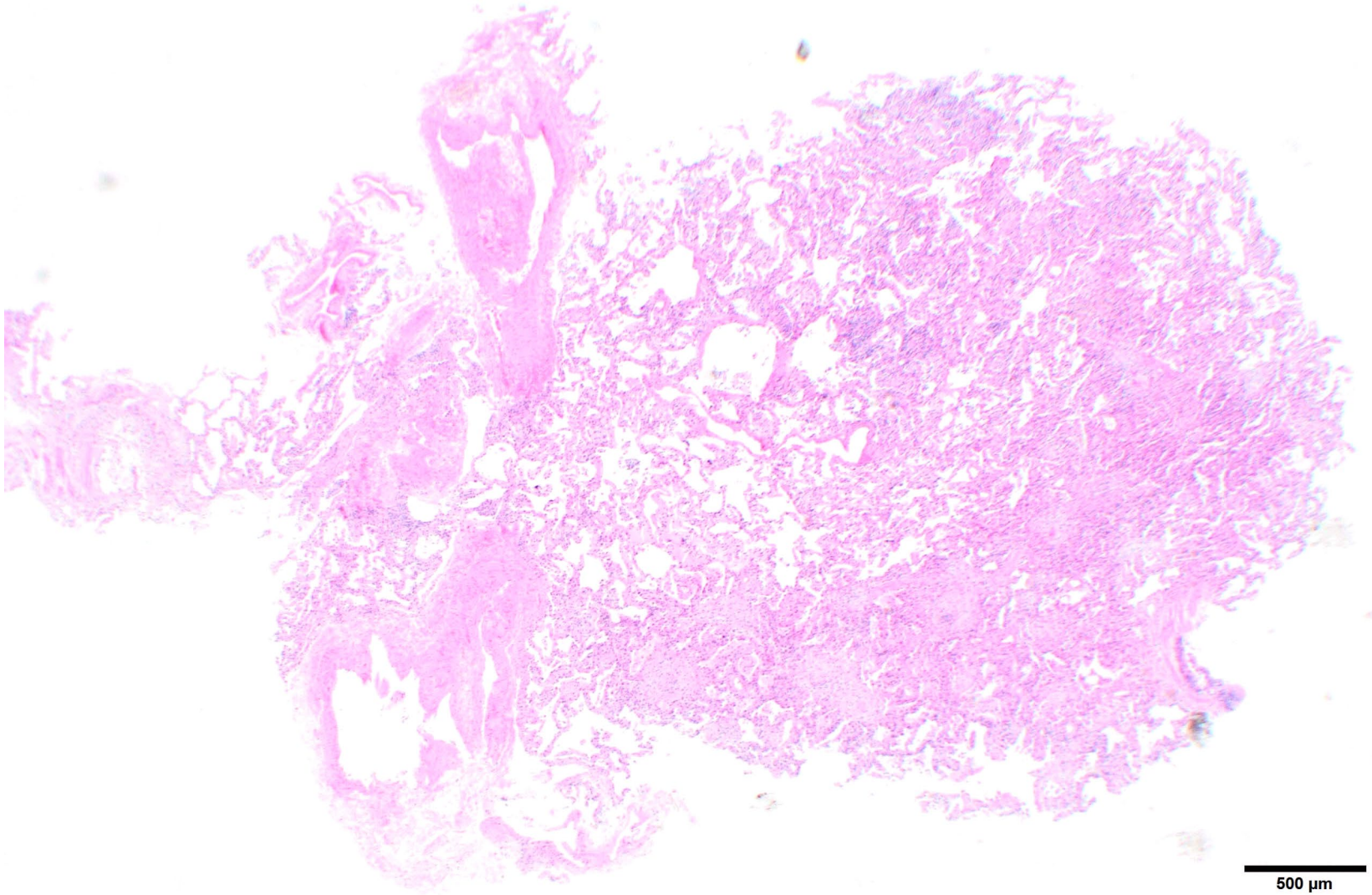
Pathology

Cryobiopsies:

Three biopsies

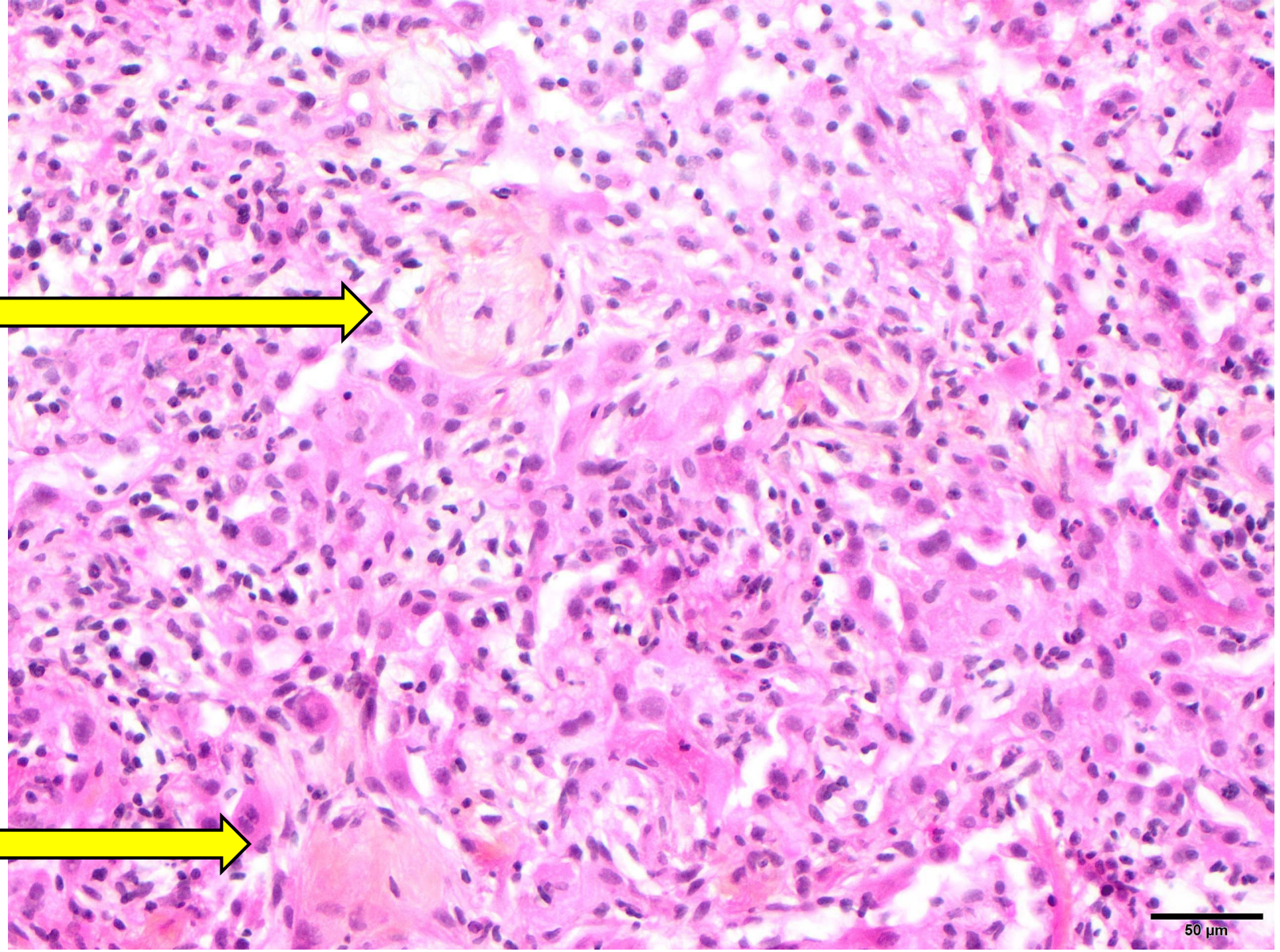

500 µm

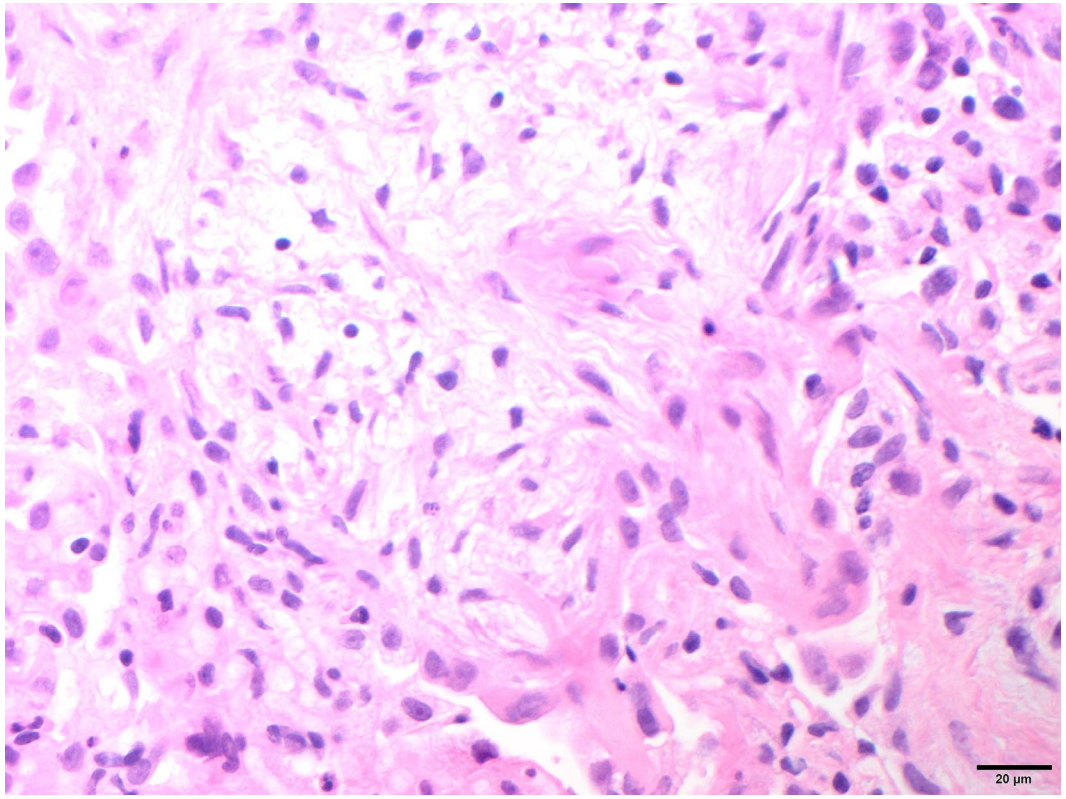


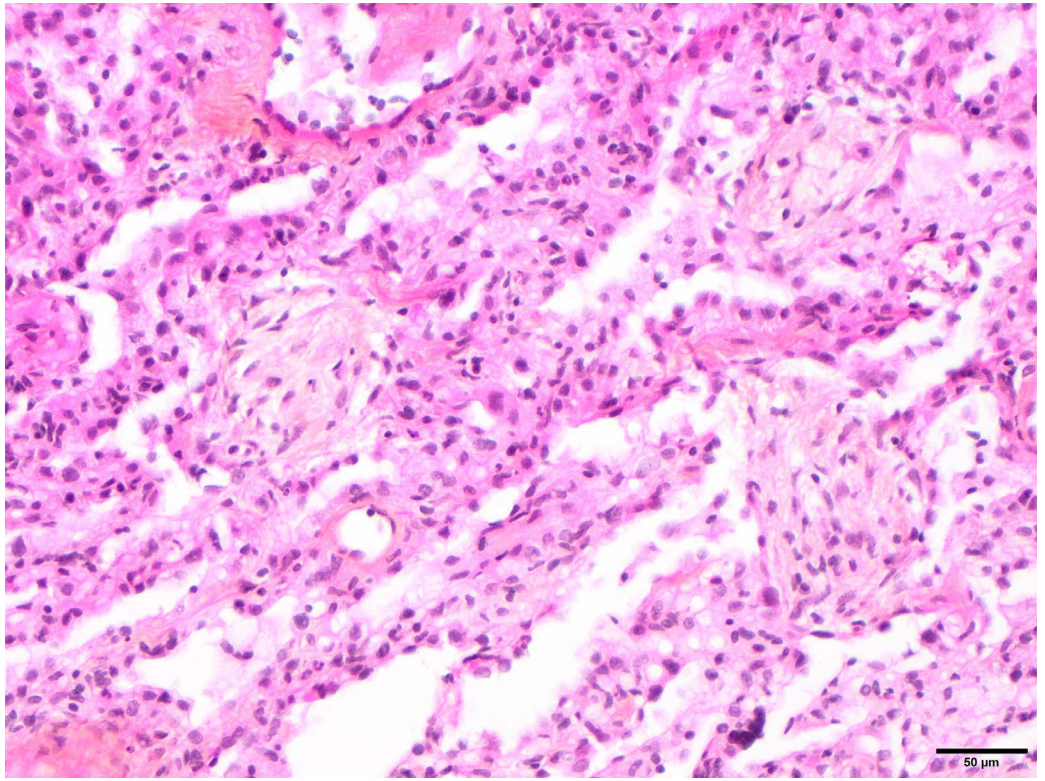

500 µm

Lungs airless

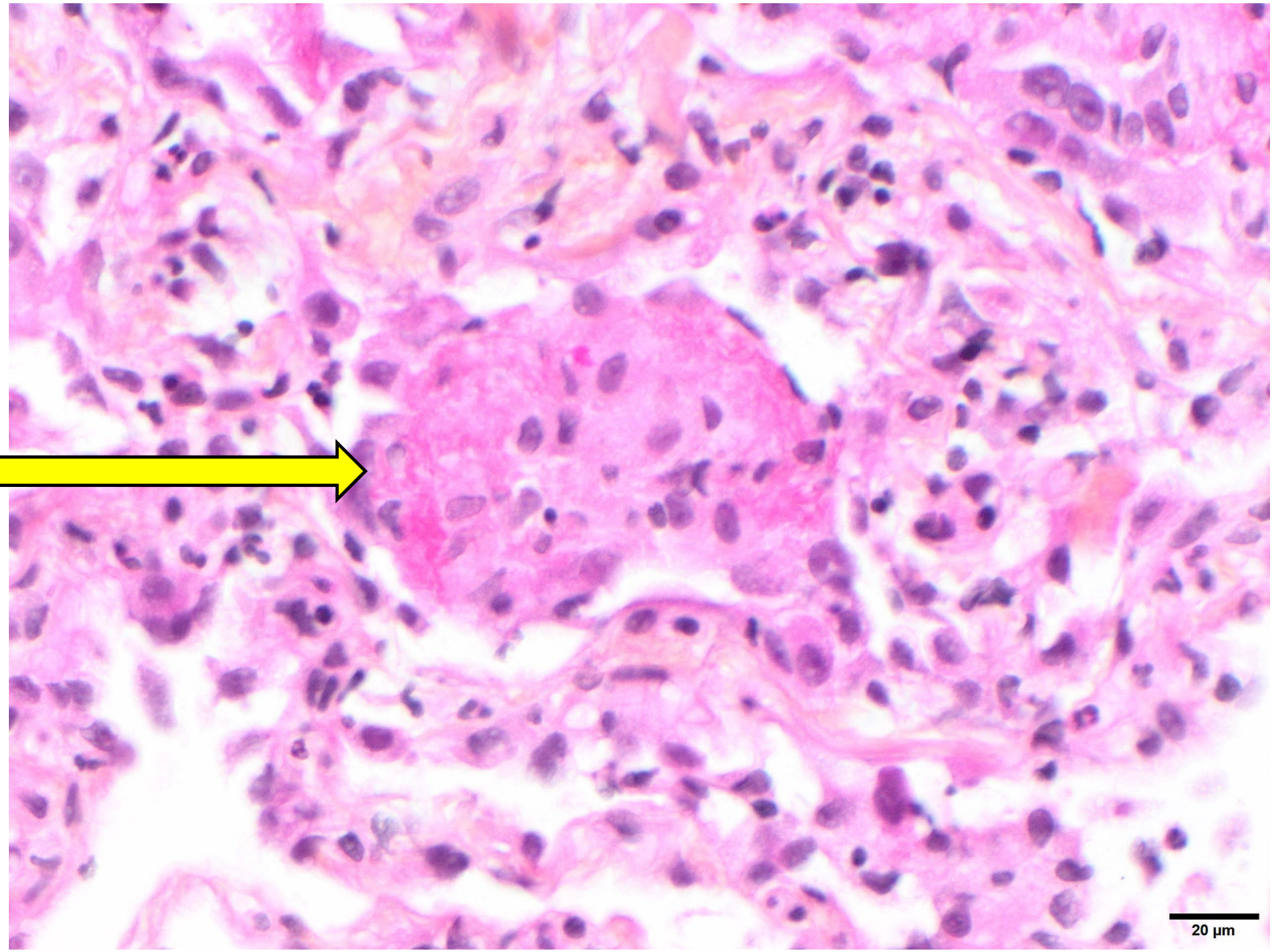
Alveoli filled with fibrous plugs: OP



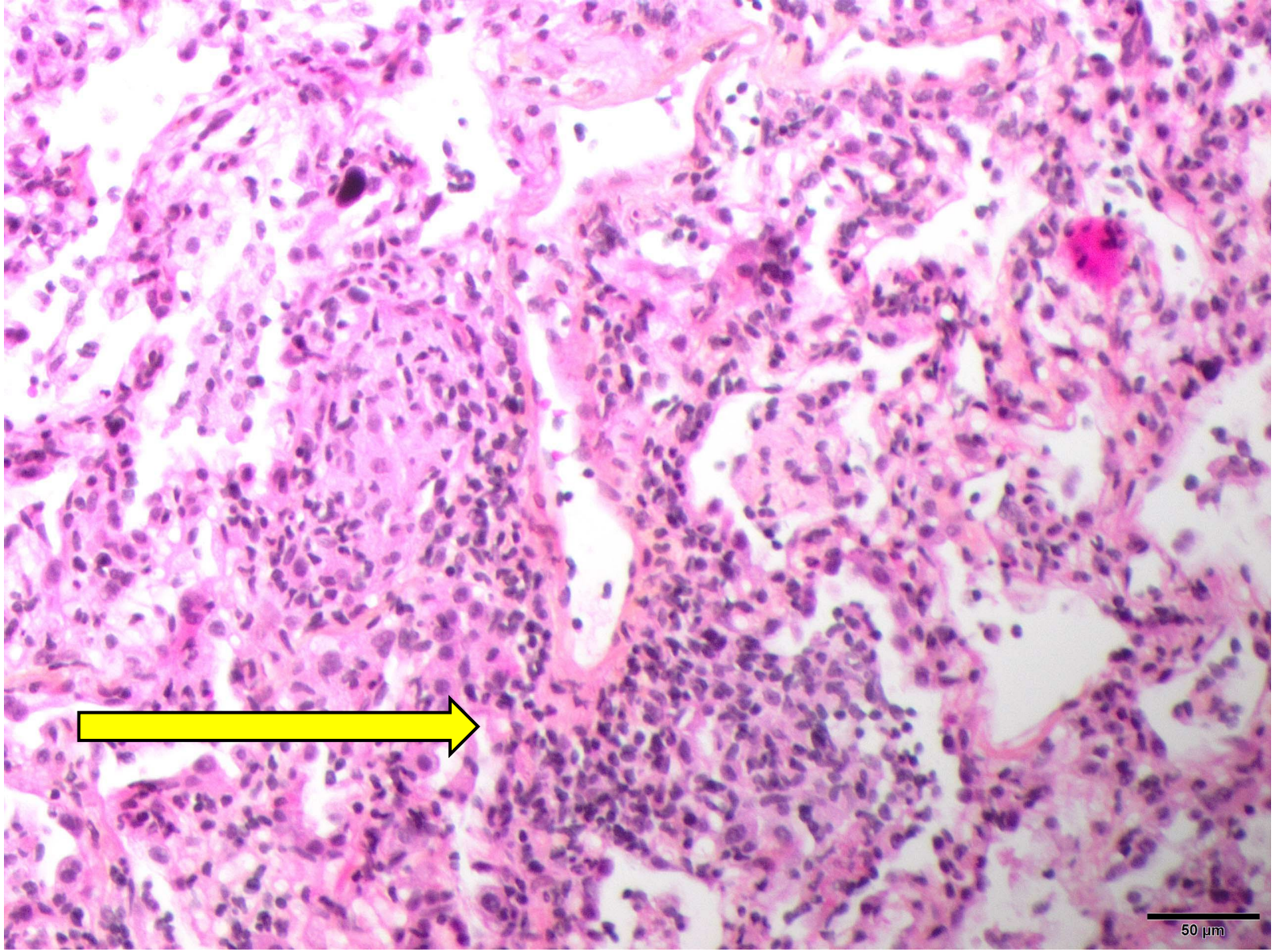

20 µm


50 µm

Intraalveolar fibrinous exudate

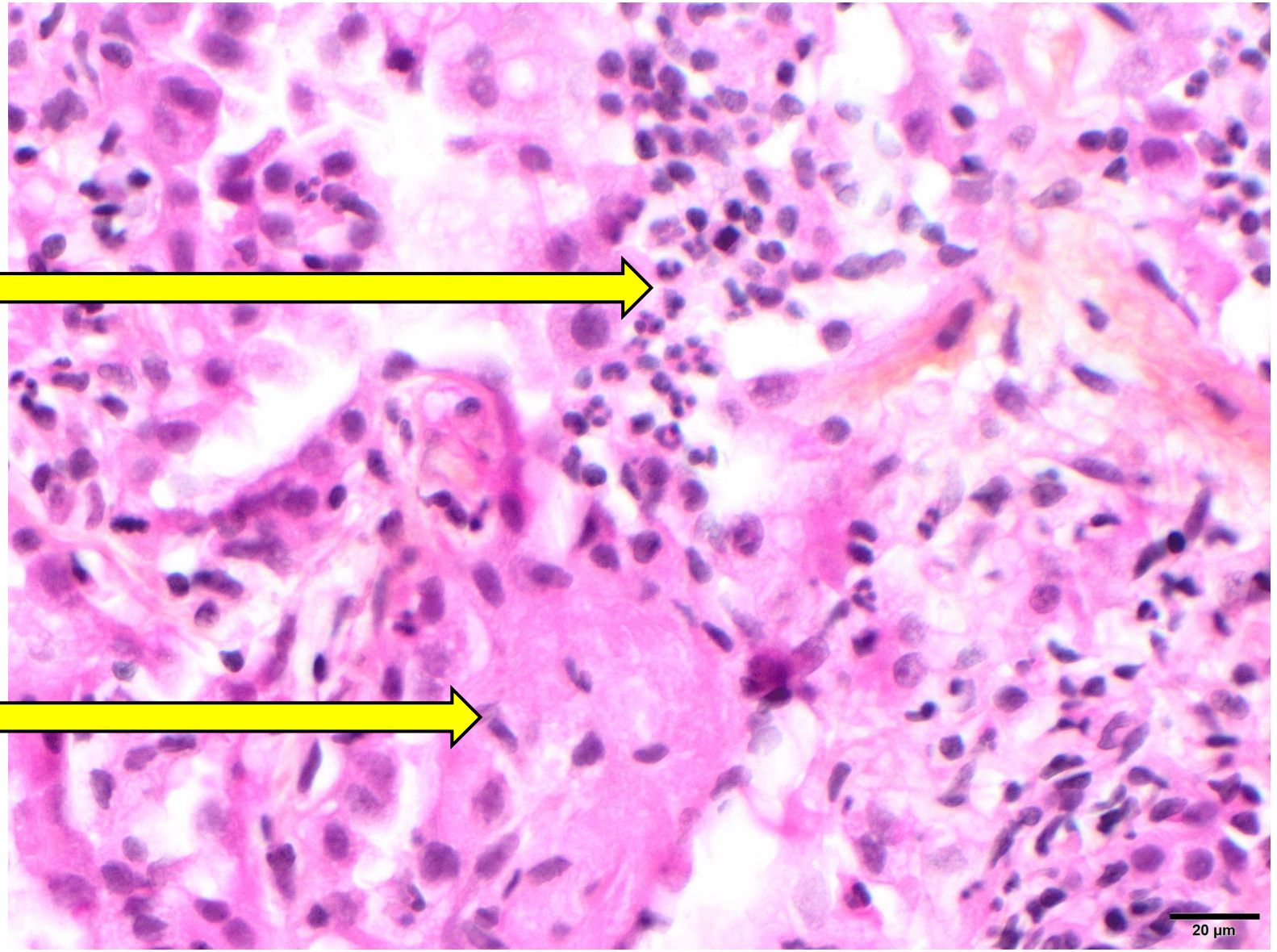


Patchy lymphoid inflammation



Patchy neutrophils

Fibrin



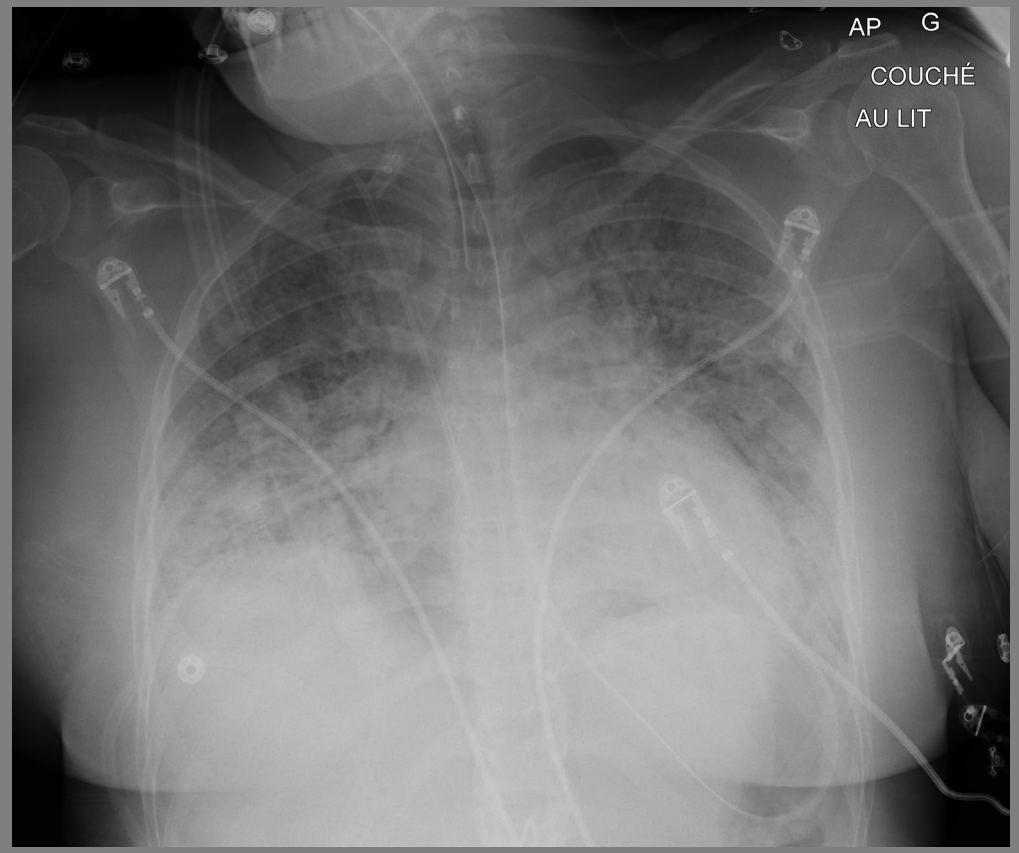
Summary of pathology

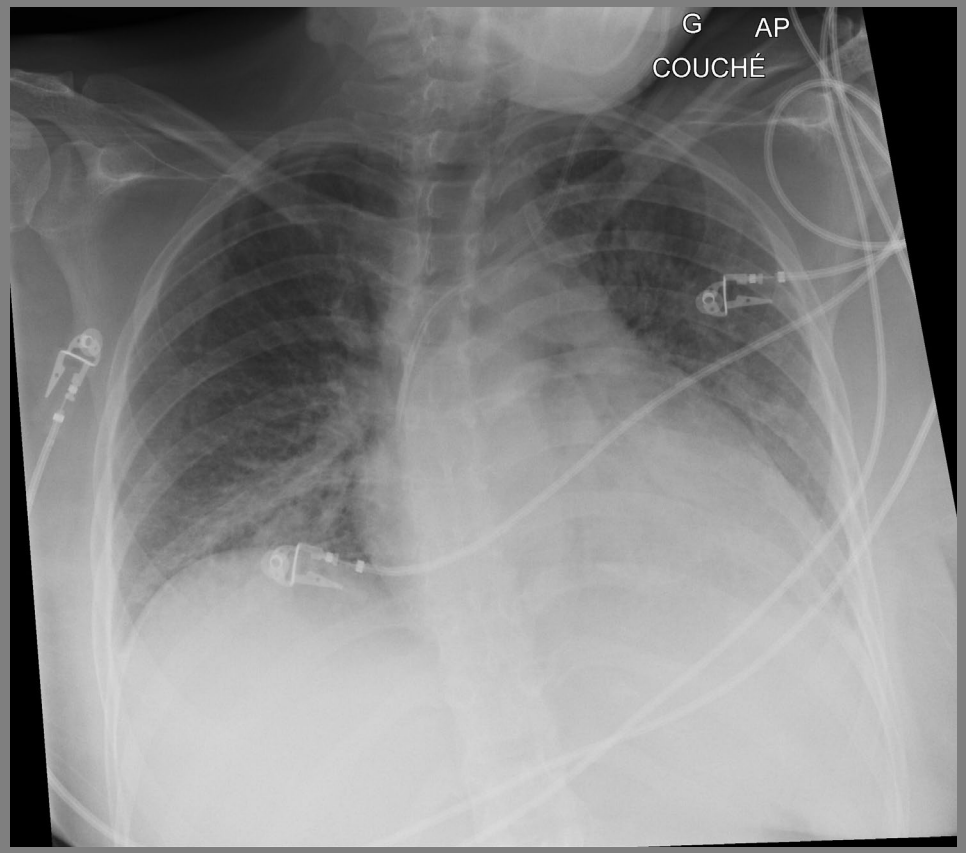
- Acute organizing lung injury

- No evidence of
  - Acute eosinophilic pneumonia
  - No evidence of alveolar hemorrhage, vasculitis, capillaritis
  - No evidence of aspiration
  - No evidence of infection
    - Negative stains for fungi
    - No viral cytopathic effect

Putting everything together

- Fulminant ILD
- Organizing pneumonia





Evolution

In summary

- Differential diagnosis of acute ILD is vast
- Considering acute ILD in patient with ARDS – respiratory failure

- Consider getting lung biopsy in patients with ARDS of unknown cause
- It may impact patient management

Question 3

In a patient presenting with acute interstitial lung disease (ILD) and respiratory failure, which diagnosis should be considered:

a) Acute exacerbation of an undiagnosed pre-existing ILD
b) Acute interstitial pneumonia
c) Cryptogenic organizing pneumonia
d) Acute eosinophilic pneumonia
e) Drug-induced ILD
f) All of the above

Question 3: Answer

In a patient presenting with acute interstitial lung disease (ILD) and respiratory failure, which diagnosis should be considered:

a) Acute exacerbation of an undiagnosed pre-existing ILD
b) Acute interstitial pneumonia
c) Cryptogenic organizing pneumonia
d) Acute eosinophilic pneumonia
e) Drug-induced ILD
f) All of the above

Question 4

In patients with acute worsening of a previously recognized ILD, what's the typical finding on a lung biopsy?

a) Organizing pneumonia

b) Diffuse alveolar damage overlying a pattern of fibrotic lung disease

c) Usual interstitial pneumonia

d) Nonspecific interstitial pneumonia

Question 4: Answer

In patients with acute worsening of a previously recognized ILD, what's the typical finding on a lung biopsy?

a) Organizing pneumonia

b) Diffuse alveolar damage overlying a pattern of fibrotic lung disease

c) Usual interstitial pneumonia

d) Nonspecific interstitial pneumonia

Thank you

Questions?

Case 3:

Alyson Wong, Clinician
Giang Nguyen, Radiologist
Margaret Kelly, Pathologist

Case: 26yo male

Past Medical History

1. Acute lymphoid leukemia 2012
    - Chemotherapy, Allogeneic bone marrow transplant (sister) in 2012, whole body radiation
2. Graft versus host disease
    - Skin, GI tract, liver, joints, ?lungs
3. Bilateral AVN of the hips, knees and humeral head (hip replacement, left shoulder arthroplasty)
4. Chronic pain
5. Hypothyroidism

Medications

Prednisone 5mg daily
Septra
Levothyroxine
Pantoprazole
Pravastatin
Gabapentin
Hydromorphone
Oxycodone

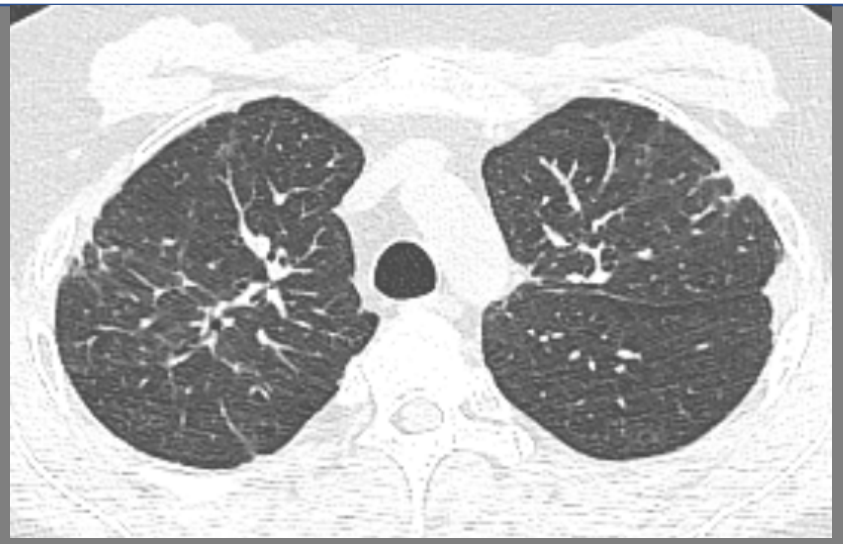
Social History

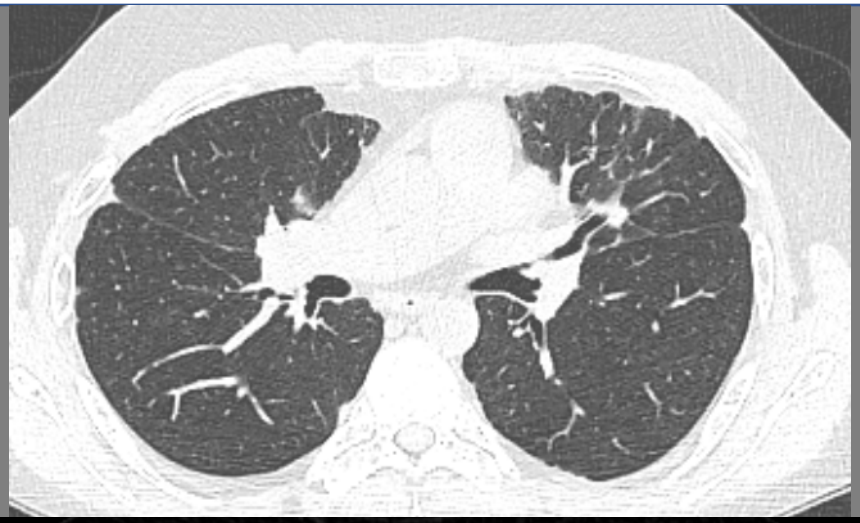
Inhaled cannabis daily

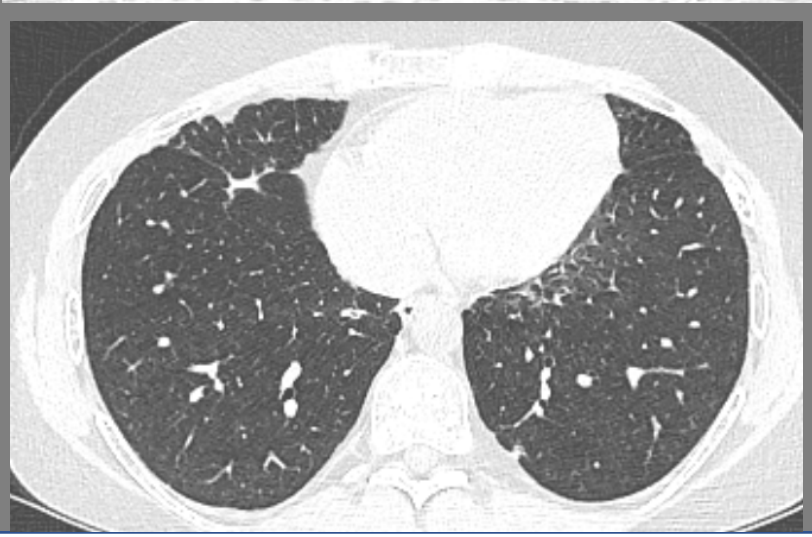
- 2012: Diagnosed with ALL and received bone marrow transplant
- 2016: Diagnosed with restrictive lung disease due to ?GVHD
- Chronic, progressive dyspnea
  - Spirometry 2021: FEV1 55% predicted, FVC 47% of predicted.
- March 2021: Admitted to hospital for left pneumothorax
  - Required VATS pleurodesis and had a surgical lung biopsy at the same time

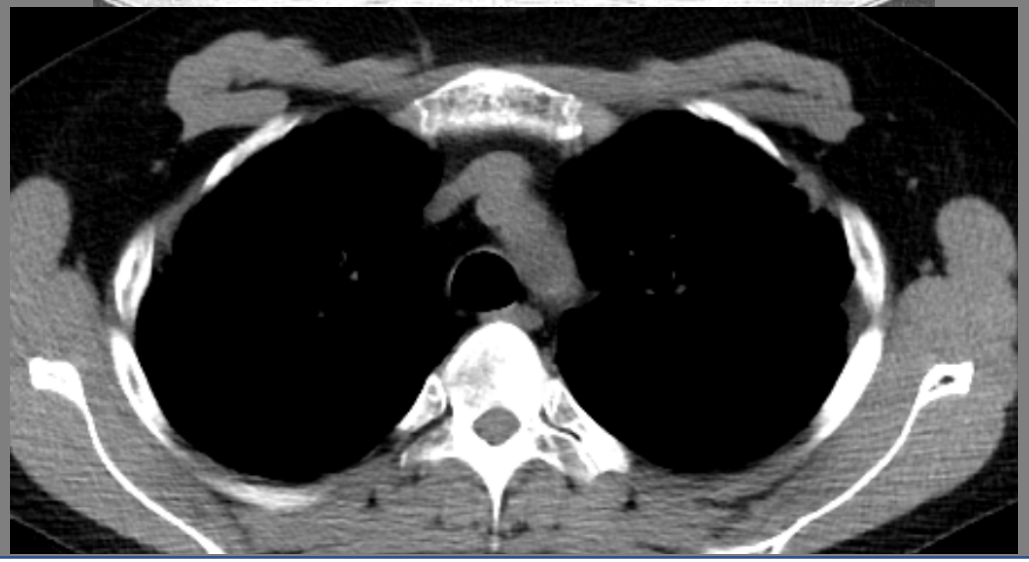
Radiology

February 2019 - baseline

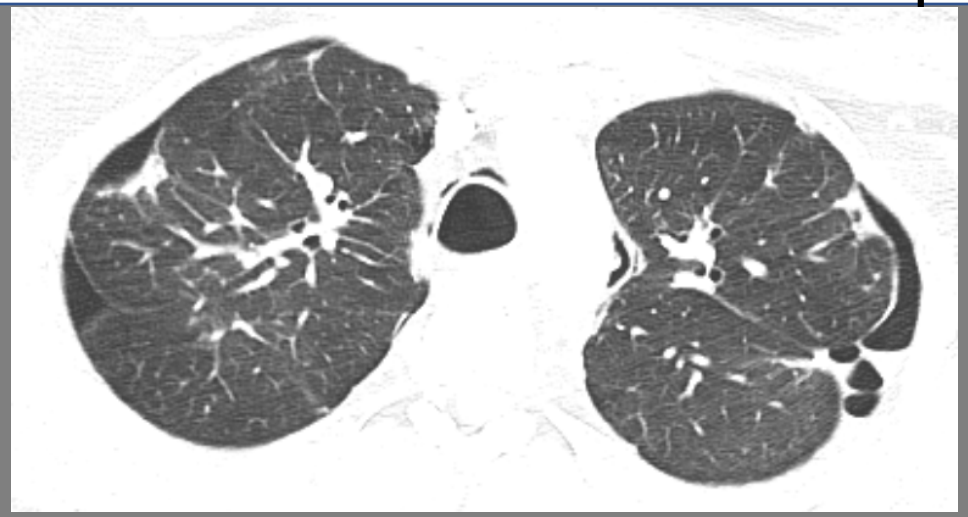


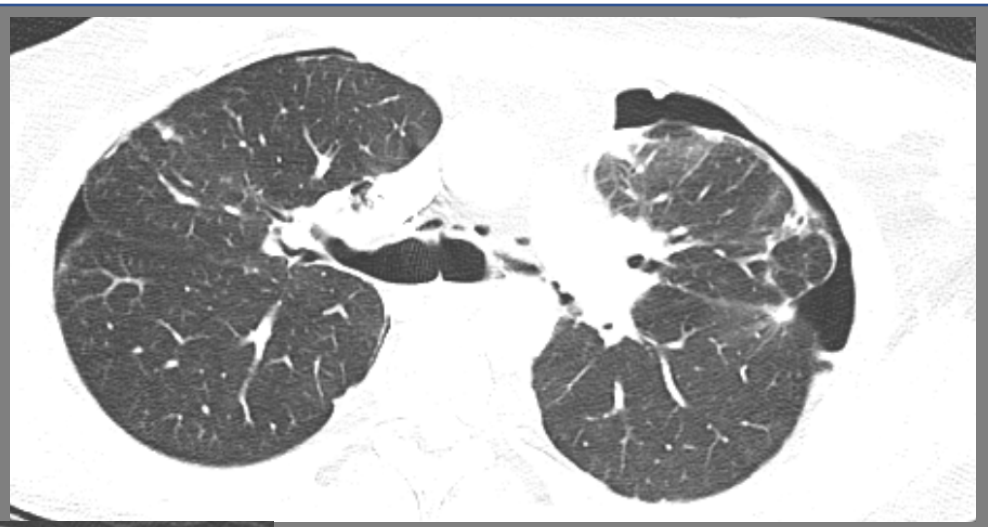


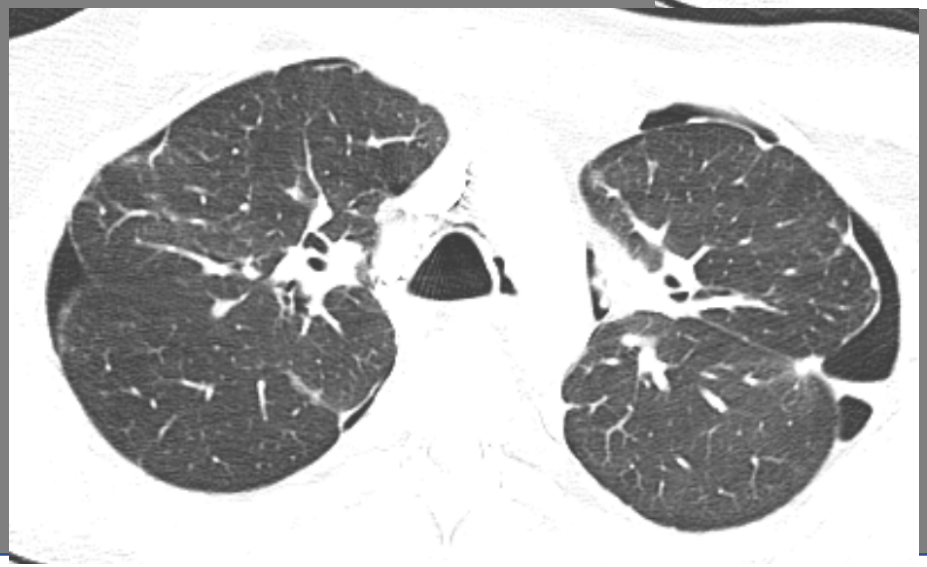




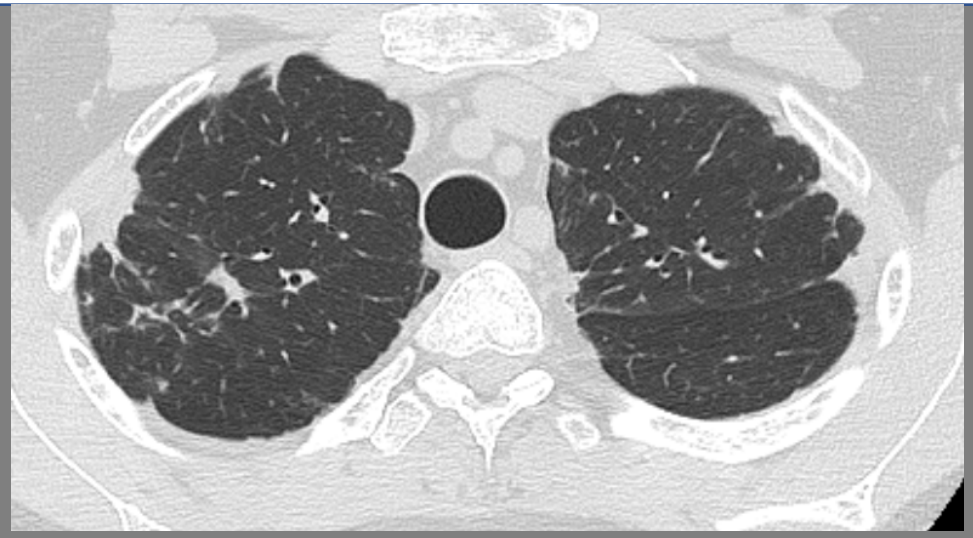
April 2021

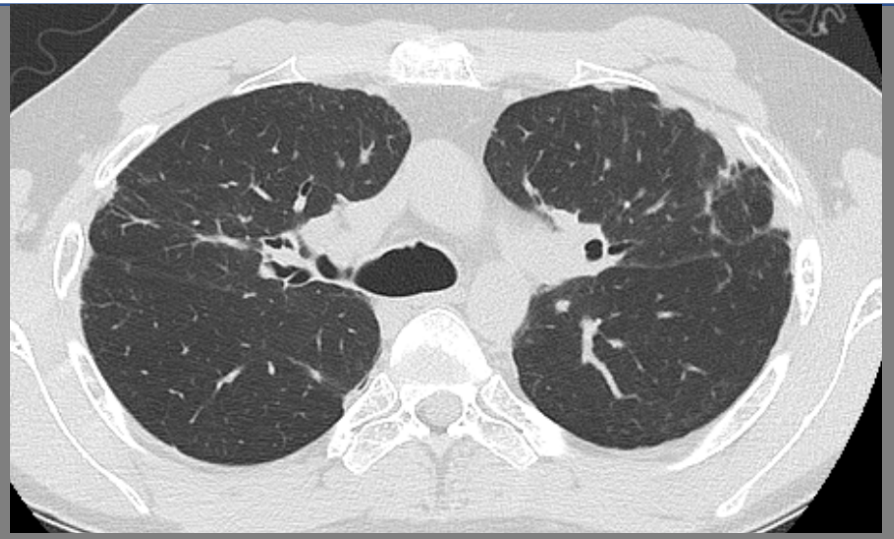


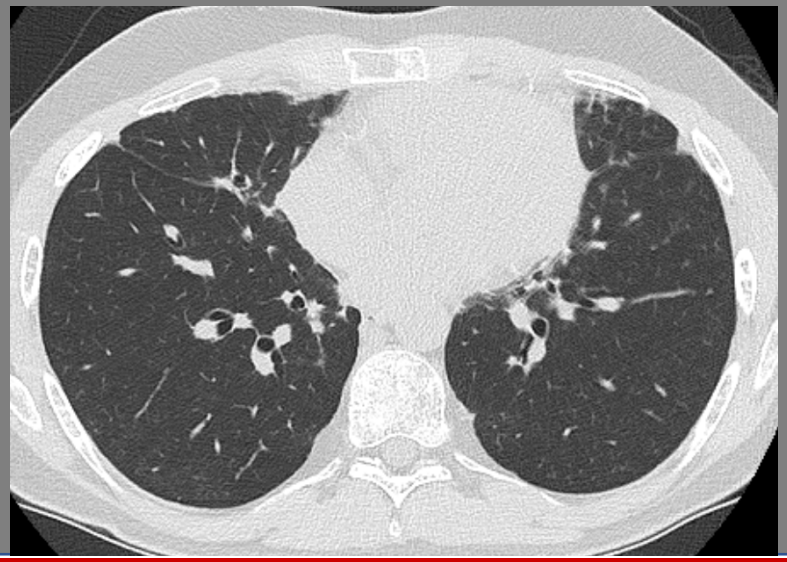




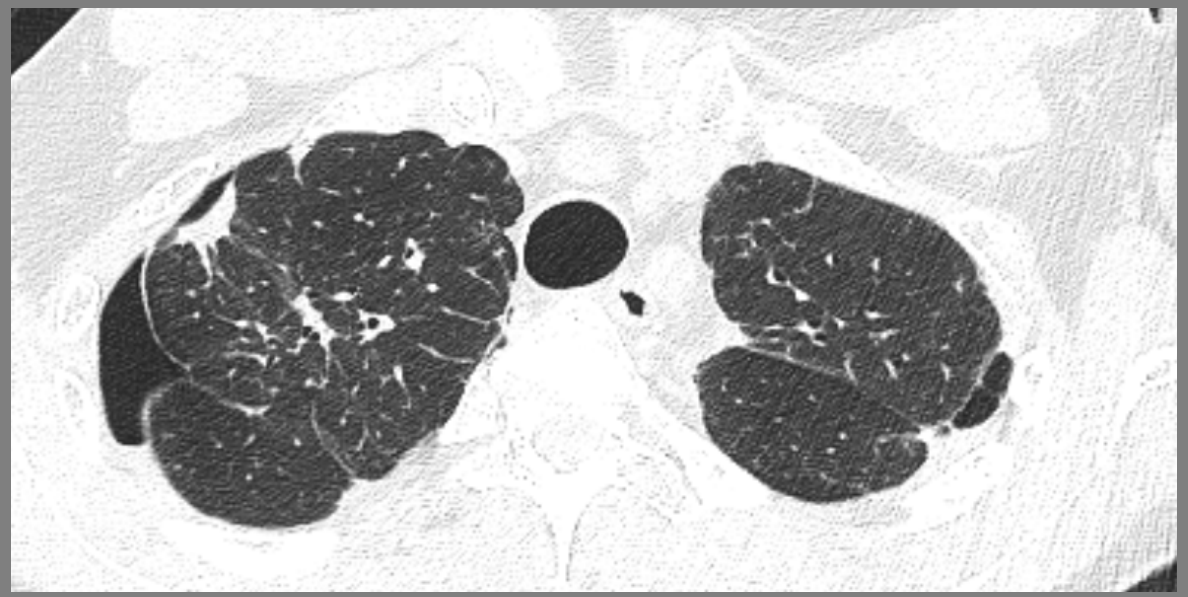
January 2022

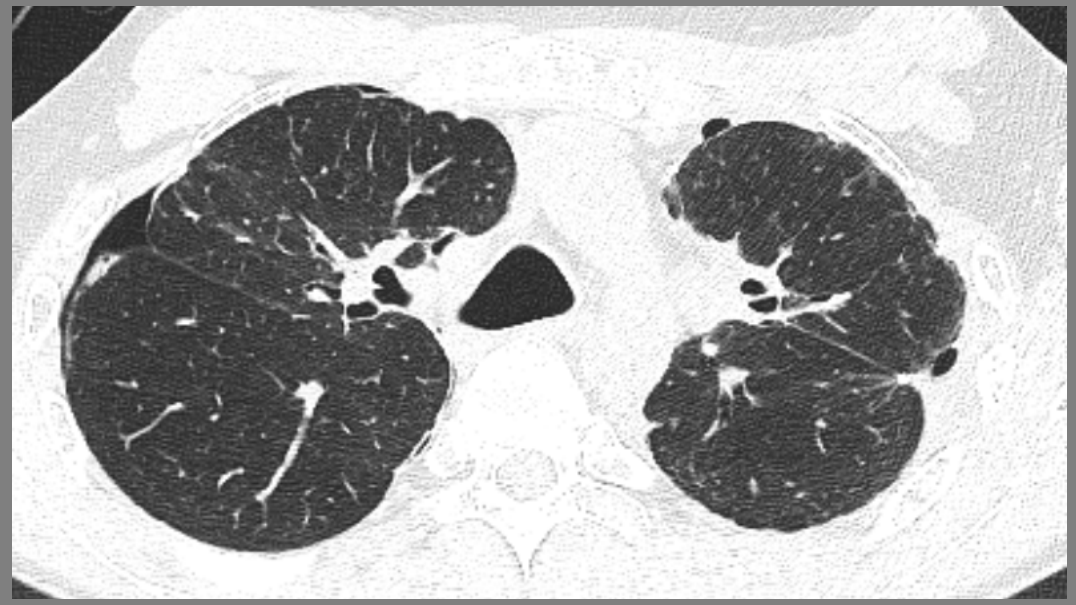






Mar 2022





Pathology

Wedge resections:

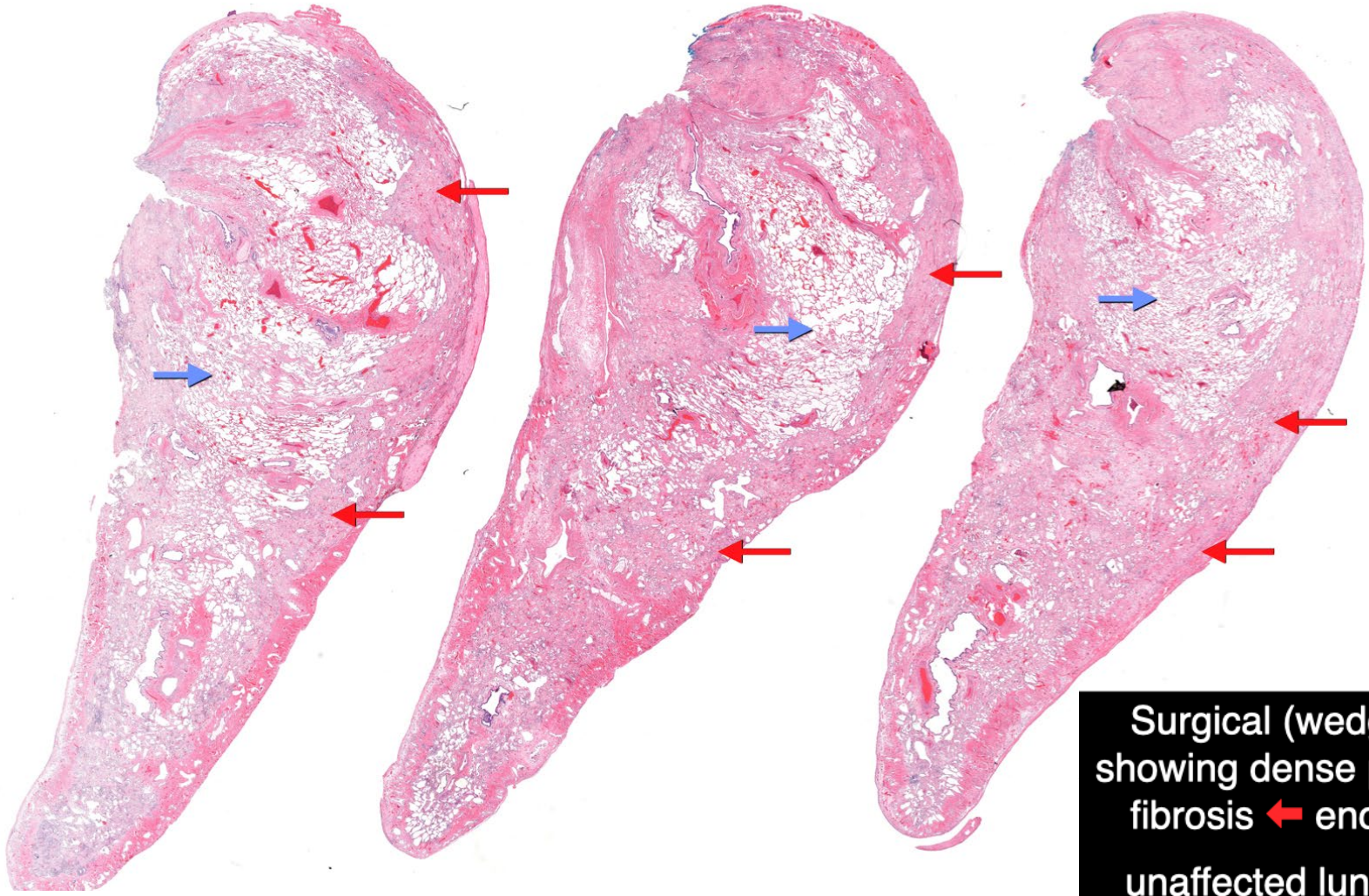
LUL

Left upper lobe: 6 x 2.2 x 0.8 cm

Left lower lobe: 4.8 x 1.0 x 0.4 cm

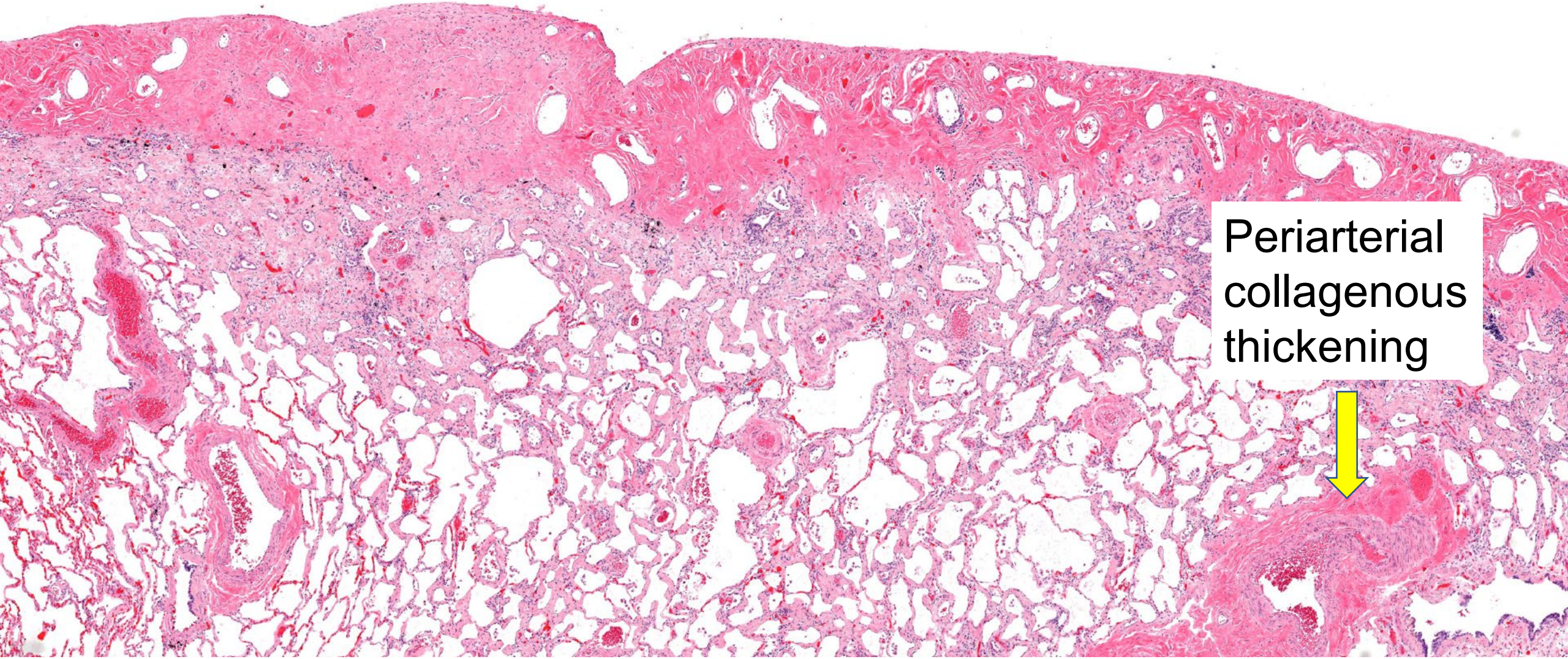
Left lower lobe: 3 x 1.2 x 0.4 cm

LUL



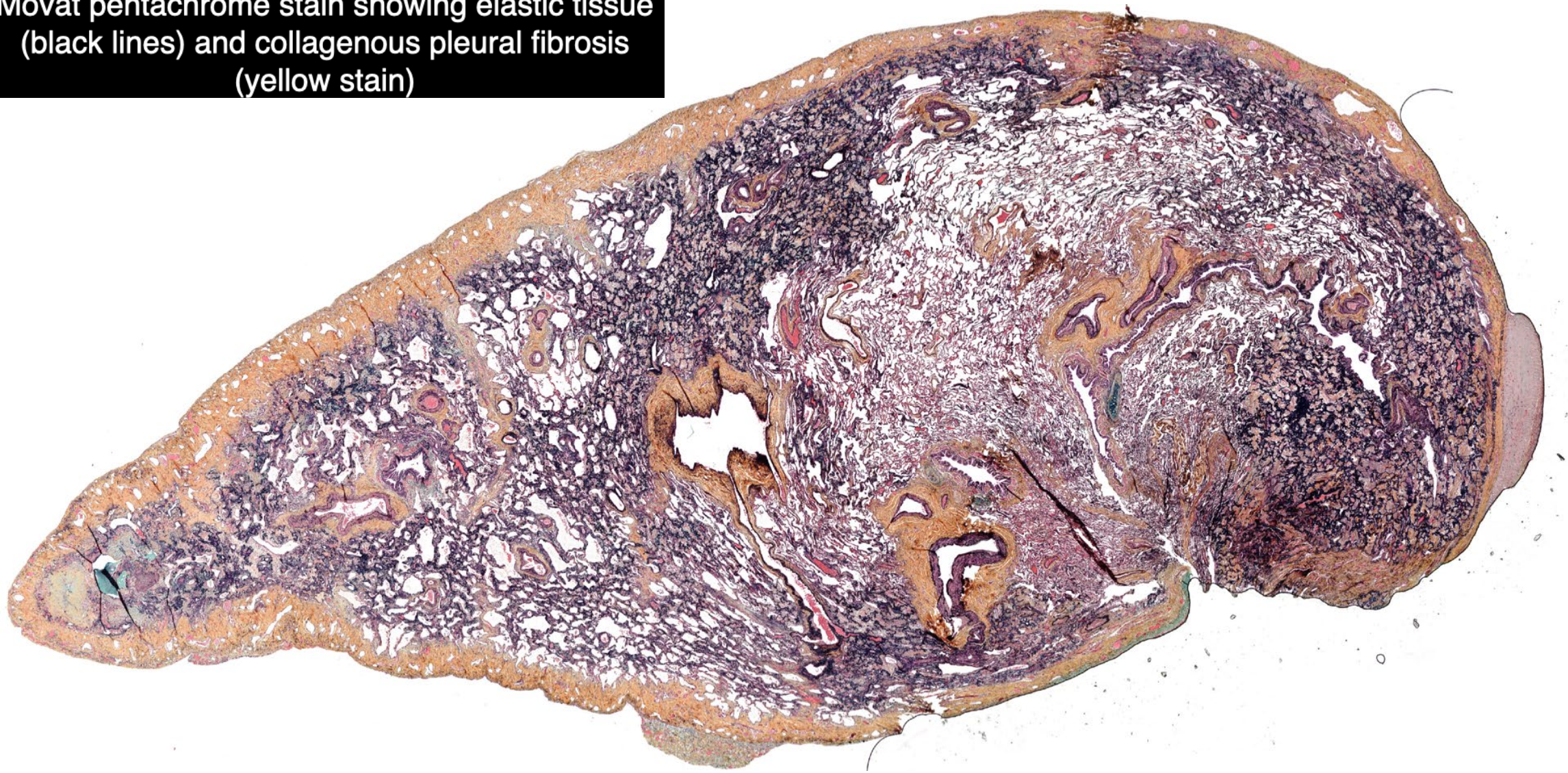
Surgical (wedge) lung biopsies showing dense pleural / subpleural fibrosis ← enclosing regions of unaffected lung parenchyma ←

LUL

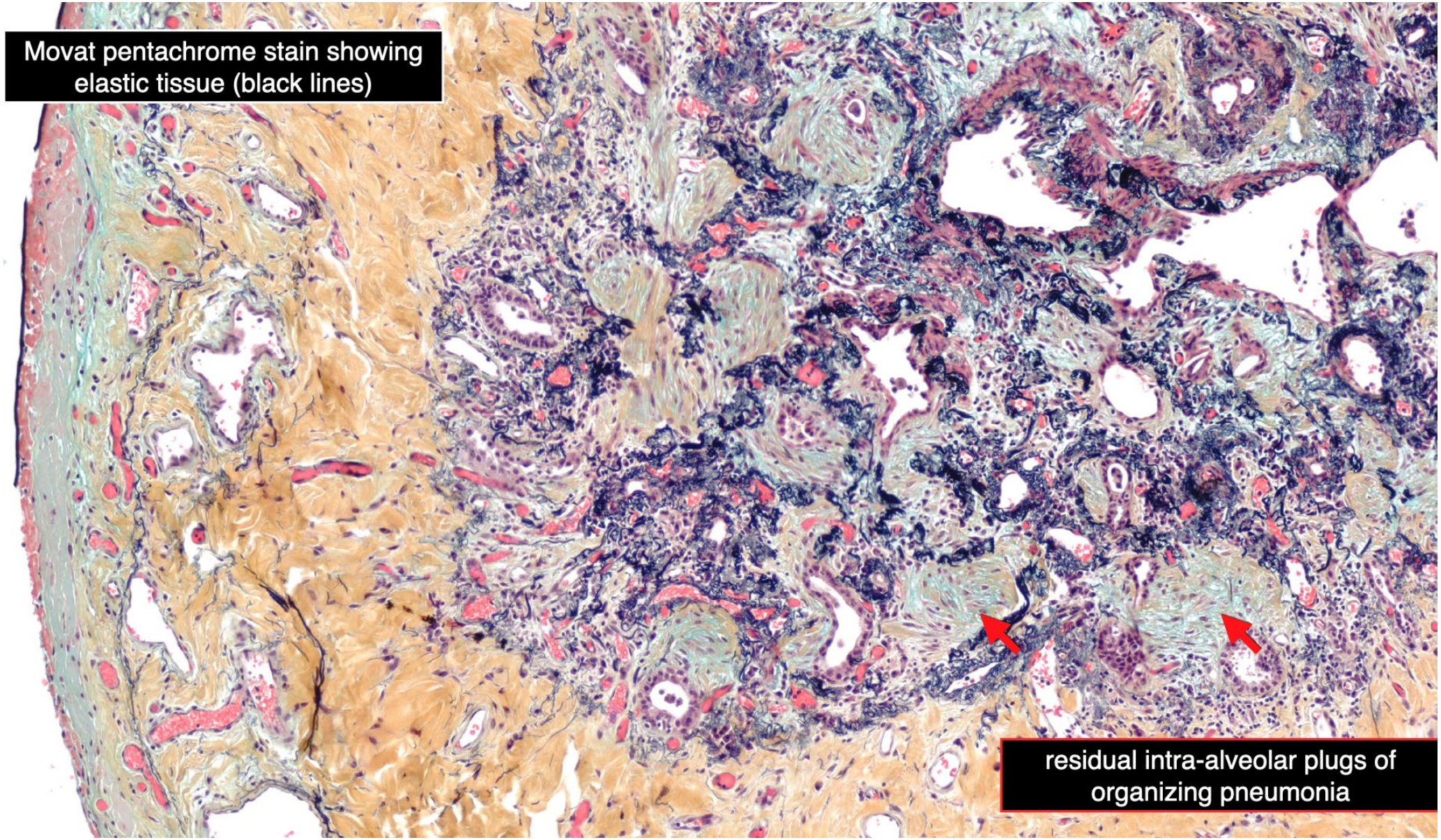


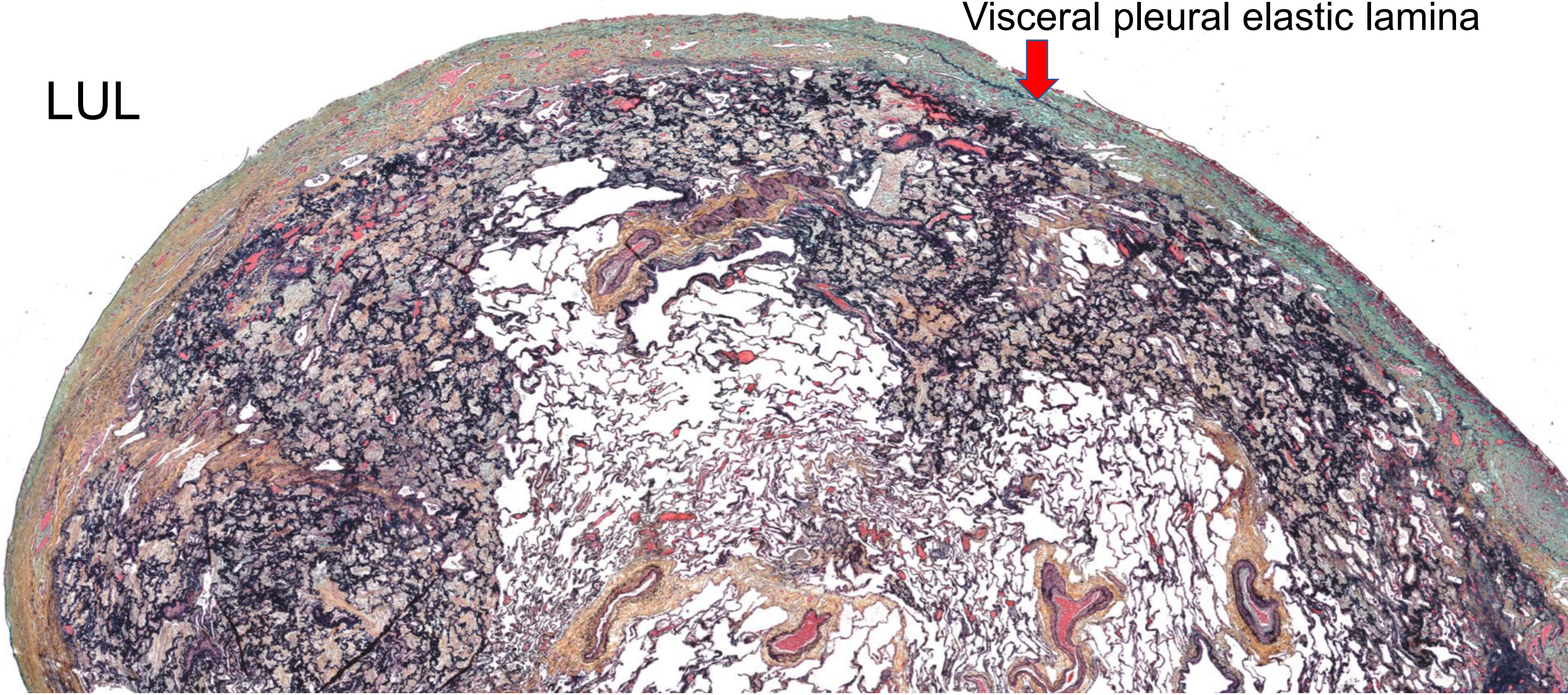
Movat pentachrome stain showing elastic tissue (black lines) and collagenous pleural fibrosis (yellow stain)

LUL



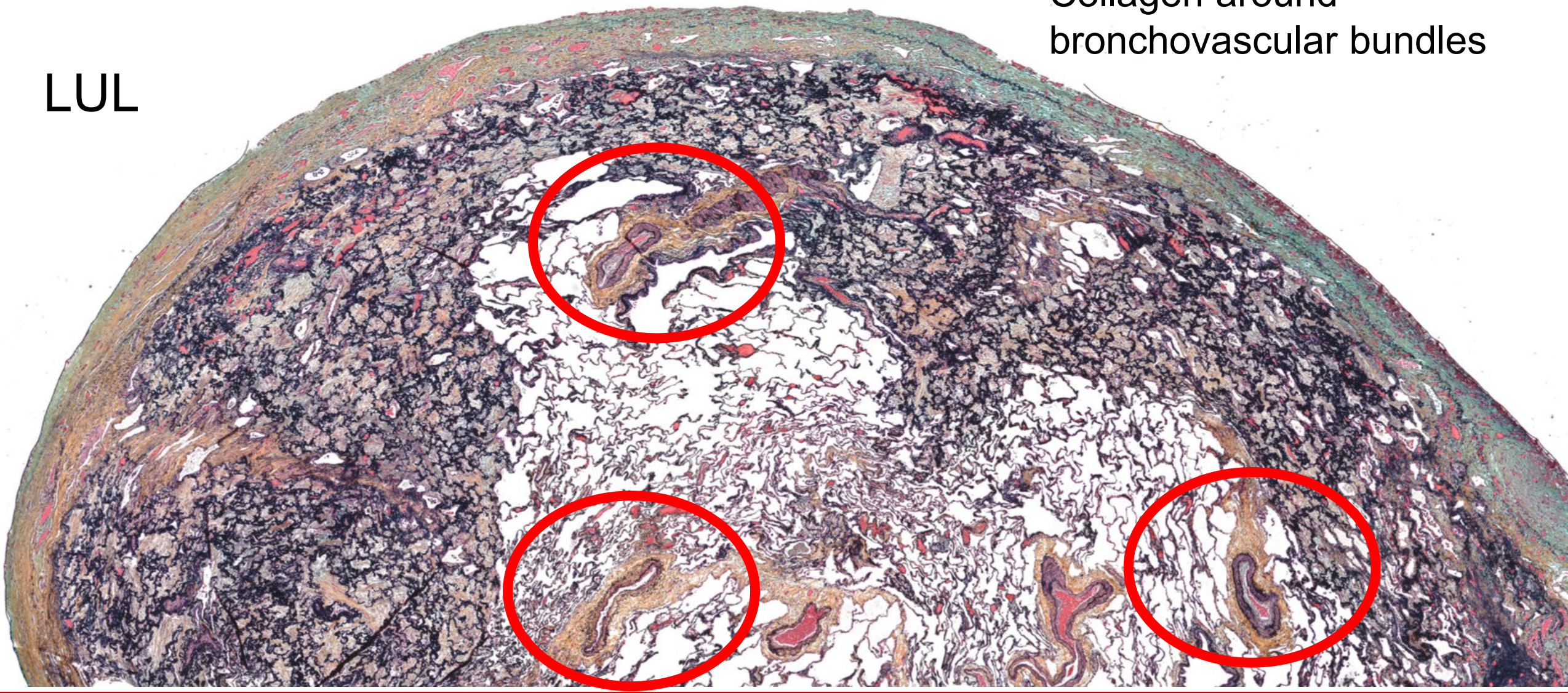
LUL


Movat pentachrome stain showing elastic tissue (black lines)
residual intra-alveolar plugs of organizing pneumonia

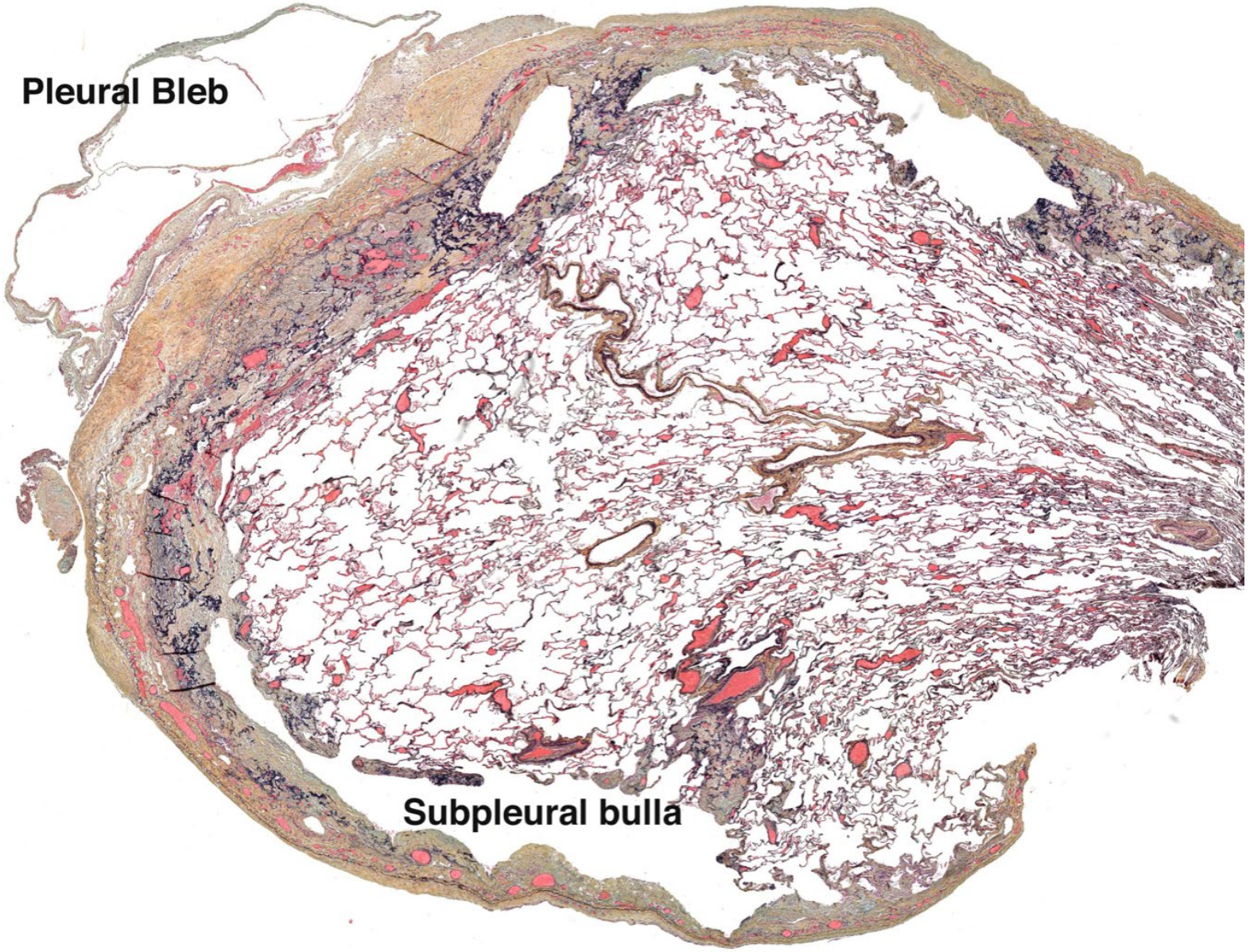

Visceral pleural elastic lamina
LUL

LUL

Collagen around bronchovascular bundles



LLL



Summary of pathology:

Collagenous thickening of apical visceral pleura; alveolar fibroelastosis, upper lobe dominant, typical of pleuropulmonary fibroelastosis (PPFE)

Pleural blebs and bullae in lower lobe considered non-specific

Negative for evidence of Graft Versus Host Disease including bronchial obliterans

Negative for evidence of infection, no granulomas

Differential Diagnosis of pathology:

Apical ‘cap’: similar alveolar fibroelastosis; non-progressive, less volume loss

UIP: No pleural fibrosis, doesn’t have preserved alveolar outlines

Radiation induced lung injury, pulmonary paraquat toxicity

Pleuroparenchymal fibroelastosis (PPFE)

- 1980s: PPFE first acknowledged (“pulmonary upper lobe fibrosis”)
- 2003: First case series (shared a pattern of chronic interstitial and pleural fibrosis that did not fit other types of idiopathic interstitial pneumonias [IIPs])
- 2013: PPFE included as a rare IIP in guidelines

Chua et al. Annals ATS (2019).16:11: 1351-1359

Pathogenesis

- Acute lung injury → diffuse alveolar damage → exuberant interstitial inflammation
- Unknown why such injuries lead to chronic well-demarcated and predominantly subpleural fibrotic abnormalities

Question 5

Which of the following are considered risk factors for PPFE?

a. Connective tissue diseases
b. Bone marrow transplant
c. Chemotherapy
d. All of the above

Question 5: Answer

Which of the following are considered risk factors for PPFE?

a. Connective tissue diseases
b. Bone marrow transplant
c. Chemotherapy
d. All of the above

Risk factors and/or associated diseases

Type of PPFE
Idiopathic PPFE
Nonidiopathic PPFE
As a form of restrictive allograft syndrome complicating lung, bone marrow, and hematopoietic stem cell transplant (also known as “restrictive chronic allograft dysfunction”)
Fibrotic interstitial lung disease (e.g., usual interstitial pneumonia, hypersensitivity pneumonitis)
Chronic or recurrent bronchopulmonary infection (e.g., *Aspergillus*, nontuberculous mycobacteria)
Autoimmune or connective tissue disease (e.g., scleroderma, rheumatoid arthritis, inflammatory bowel disease)
Familial history of pulmonary fibrosis
Short telomere lengths resulting from mutations of genes encoding the telomerase complex
Anticancer/cytotoxic chemotherapy (e.g., cyclophosphamide and carmustine) and radiation therapy
Occupational dust inhalation (e.g., asbestos and aluminum)

→ UIP 25-50% of PPFE cases

Chua et al. Annals ATS 2019;16.

Question 6

Which of the following is *not* a typical clinical or radiologic finding of PPFE?

a) Deepening of suprasternal notch

b) Pleural thickening with subpleural fibrosis

c) Honeycombing

d) Fibrosis is concentrated in the upper lobes

Question 6: Answer

Which of the following is *not* a typical clinical or radiologic finding of PPFE?

a) Deepening of suprasternal notch

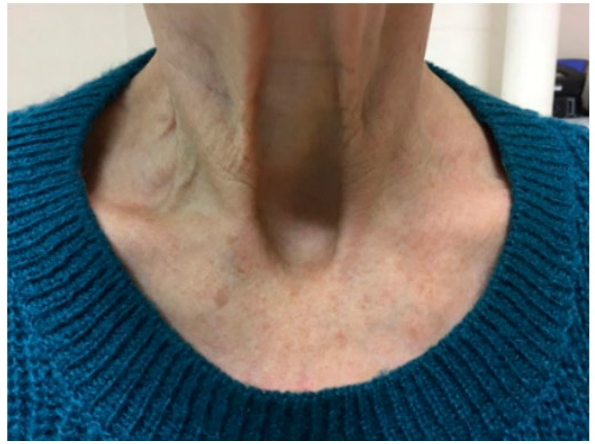
b) Pleural thickening with subpleural fibrosis

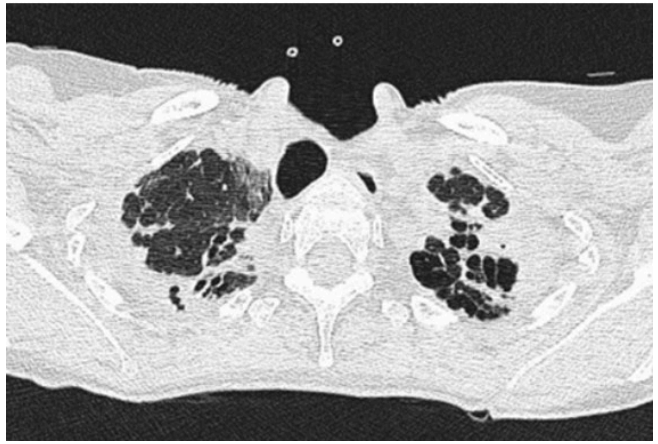
c) Honeycombing

d) Fibrosis is concentrated in the upper lobes

Clinical Features

- Most patients present between age 40-70 years
- Progressive dyspnea, cough, nonspecific chest discomfort
- Weight loss
- Auscultation may be normal, unless PPFE has extended outside upper zones or coexistent fibrosis elsewhere
- Platythorax (flat chest and reduced AP diameter)
  - Due to upper lobe volume contraction and reduced chest wall bulk from weight loss
  - Suprasternal notch deepens and can become noticeable clinically and radiologically





Diagnosis

- Differential diagnosis: HP, sarcoidosis, IIP with extension of disease to the upper zones, atypical infection, post–lung injury remodeling, pneumoconiosis, malignancy, and apical pleural cap
- Diagnostic criteria first proposed in 2012

Category	Histopathology	High-Resolution Computed Tomography
Definite PPFE	Upper zone pleural fibrosis with subjacent intraalveolar fibrosis accompanied by alveolar septal elastosis	Pleural thickening with associated subpleural fibrosis concentrated in the upper lobes with less marked or no lower lobe involvement
Consistent with PPFE	Intraalveolar fibrosis present but *1*) not accompanied by significant pleural fibrosis, *2*) not predominantly subpleural, or *3*) not present in an upper lobe biopsy	Upper lobe pleural thickening with associated subpleural fibrosis but *1*) distribution not concentrated in the upper lobes or *2*) with features of coexistent disease elsewhere
Inconsistent with PPFE	Absence of features in "definite PPFE" and "consistent with PPFE" categories	Absence of features in "definite PPFE" and "consistent with PPFE" categories

Reddy et al. Eur Respir J 2012;40.

Work-up

- History
  - Transplant
  - Autoimmune diseases
  - Family history of ILD
  - Exposures
- Autoimmune serologies
  - ANA, ENA, RF, anti-CCP, dsDNA, ANC
- Aspergillosis, NTM, TB
- Bronchoscopy on case-by-case bas
- Avoid surgical lung biopsy

Type of PPFE
Idiopathic PPFE
Nonidiopathic PPFE
As a form of restrictive allograft syndrome complicating lung, bone marrow, and hematopoietic stem cell transplant (also known as “restrictive chronic allograft dysfunction”)
Fibrotic interstitial lung disease (e.g., usual interstitial pneumonia, hypersensitivity pneumonitis)
Chronic or recurrent bronchopulmonary infection (e.g., *Aspergillus*, nontuberculous mycobacteria)
Autoimmune or connective tissue disease (e.g., scleroderma, rheumatoid arthritis, inflammatory bowel disease)
Familial history of pulmonary fibrosis
Short telomere lengths resulting from mutations of genes encoding the telomerase complex
Anticancer/cytotoxic chemotherapy (e.g., cyclophosphamide and carmustine) and radiation therapy
Occupational dust inhalation (e.g., asbestos and aluminum)

Management

- Oxygen assessment, nutritional input, pulmonary rehabilitation
- ?Lung transplantation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

- Double-blind, placebo-controlled trial
- Progressive fibrosing ILD (PF-ILD)
- Nintedanib vs placebo
- Nintedanib slows rate of FVC decline in PF-ILD

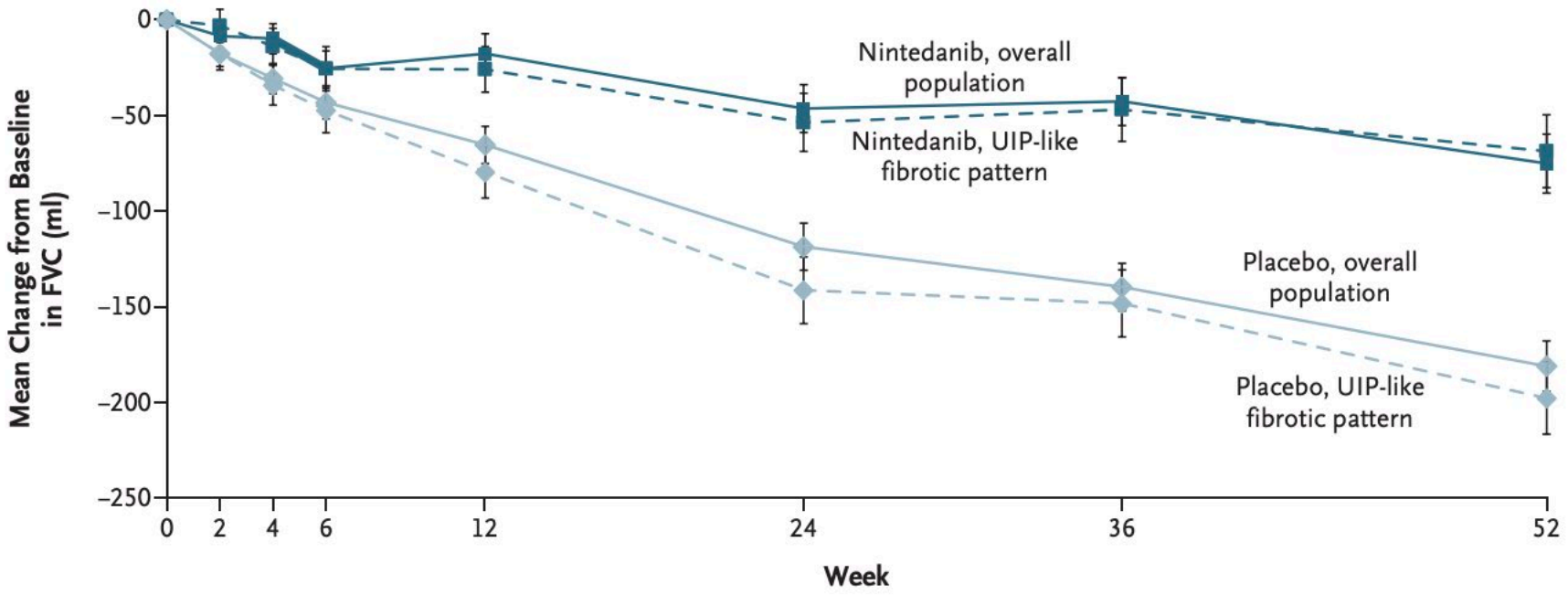


Table S2: Clinical ILD diagnoses (grouped) in the overall population

	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in “Other fibrosing ILDs”.

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RESEARCH Open Access

Nintedanib in idiopathic and secondary pleuroparenchymal fibroelastosis

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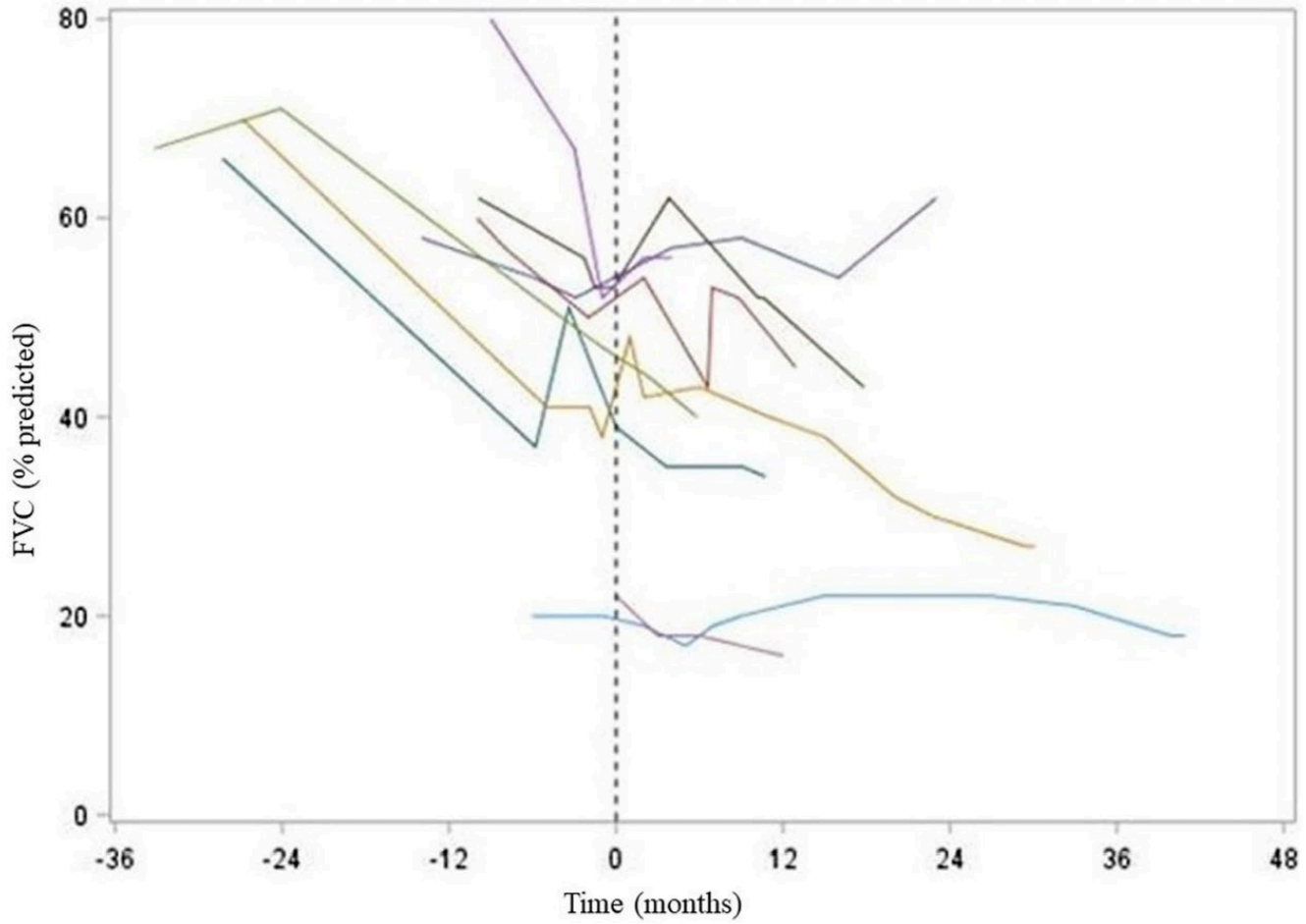
- Retrospective study of patients with PPFE 2010-2019
- 21 patients total (nintedanib 9, other treatment 6, surveillance 6)
- Compared FVC trajectory before and after treatment

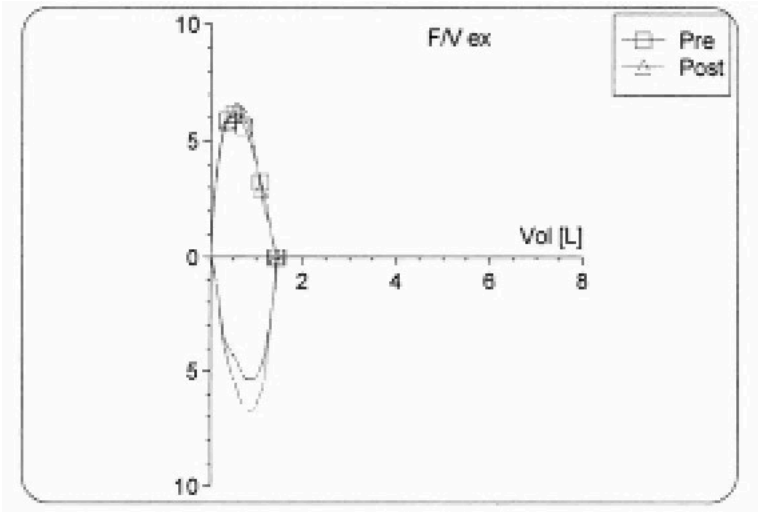
Nintedanib may slow lung function decline in PPFE



	Nintedanib group (N = 9)			Non-nintedanib group (N = 6)			Non-treated group (N = 6)
	Pre-treatment	On treatment	P value	Pre-treatment	On treatment	P value	At diagnosis
Follow-up duration (days)	376 ± 370	530 ± 382	–	1904 ± 2296	593 ± 389	–	1526 ± 1291
Δ FVC (mL)	− 274 ± 188	− 169 ± 214	0.023*	− 193 ± 463	− 275 ± 607	NS	− 50 ± 144

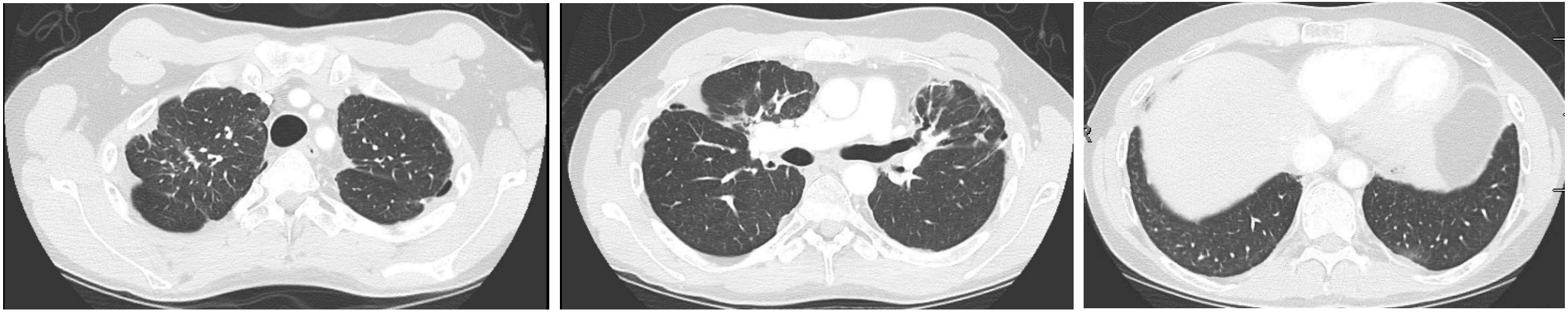
Case summary

Spirometry								
FVC	5.28	1.44	27	1.44	27	-0	4.26	6.30
FEV 1	4.41	1.42	32	1.42	32	0	3.55	5.25
FEV 1 % FVC	84.08	98.23	117	98.80	118	1	72.66	93.52
MEF50	5.44	5.60	103	6.05	111	8	2.77	8.11
MMEF 75/25	4.64	5.16	111	5.14	111	-0	2.94	6.72
PEF	9.50	6.18	65	6.36	67	3	5.62	13.38
FVC IN		1.43		1.41		-2		
Plethysmography								
VC	5.55	1.44	26				4.57	6.52
IC	3.69	0.84	23				2.43	4.95
ERV	1.80	0.61	34				0.83	2.77
RV	1.59	1.71	108				0.82	2.37
FRCpl	3.39	2.32	68				2.22	4.57
TLC	7.09	3.16	45				5.74	8.43
RV % TLC	22.48	54.26	241				21.42	23.54
Diffusion SB								
DLCO Single...	31.72	18.95	60				25.05	39.38



Case summary

December 2021



Non-idiopathic PPFE

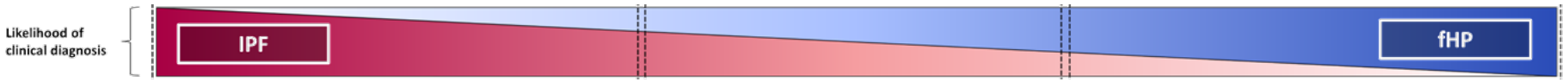
- Risk factors: bone marrow transplant, chemotherapies, radiation
- Applied for antifibrotic – declined
- Supportive care and anticipate will need lung transplant

Thank you

Questions?

Bonus Slides

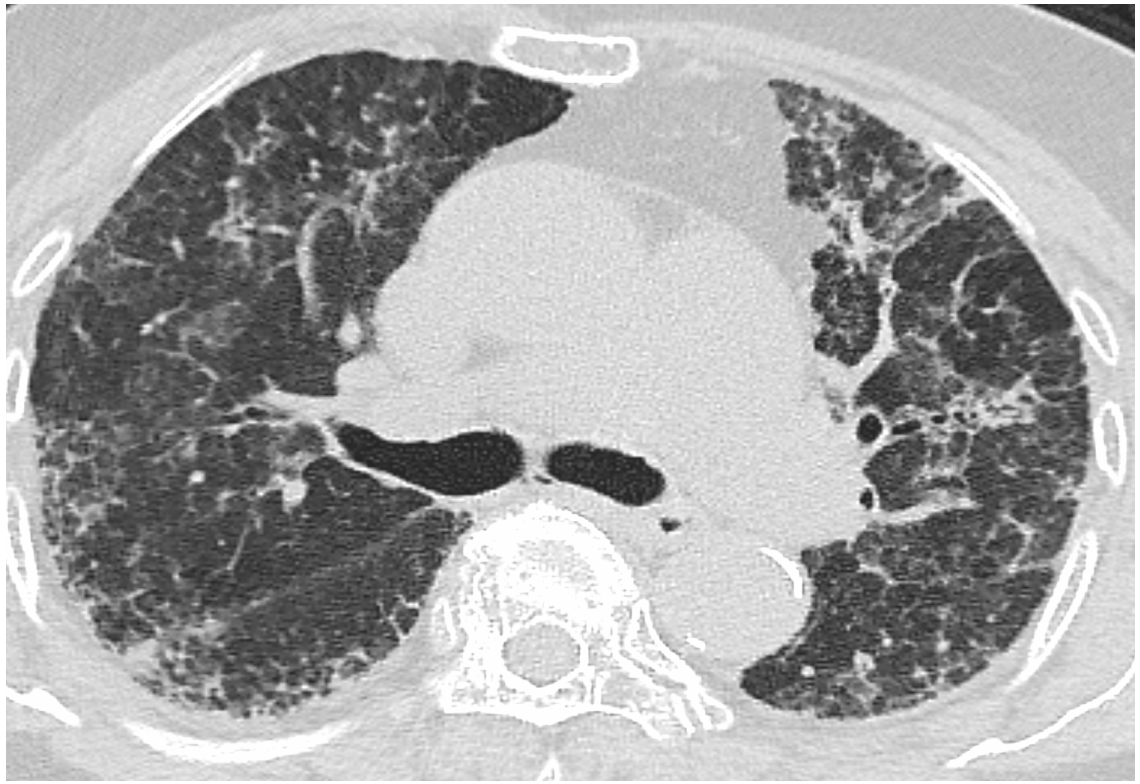
ILD Evaluation: Radiologic Assessment



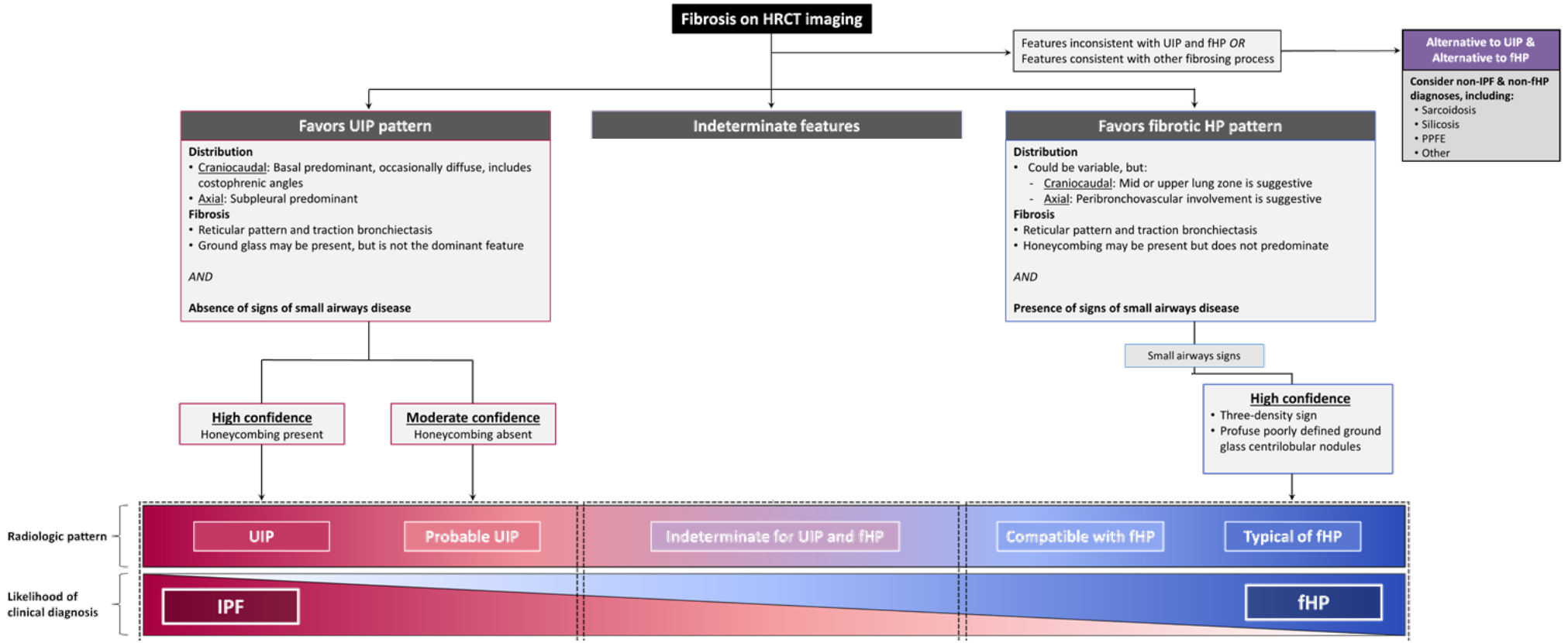
Marinescu et al. Integration and application of clinical practice guidelines for the diagnosis of IPF and fHP. *In revision*.

ILD Evaluation: Radiologic Assessment

3-density pattern



ILD Evaluation: Radiologic Assessment



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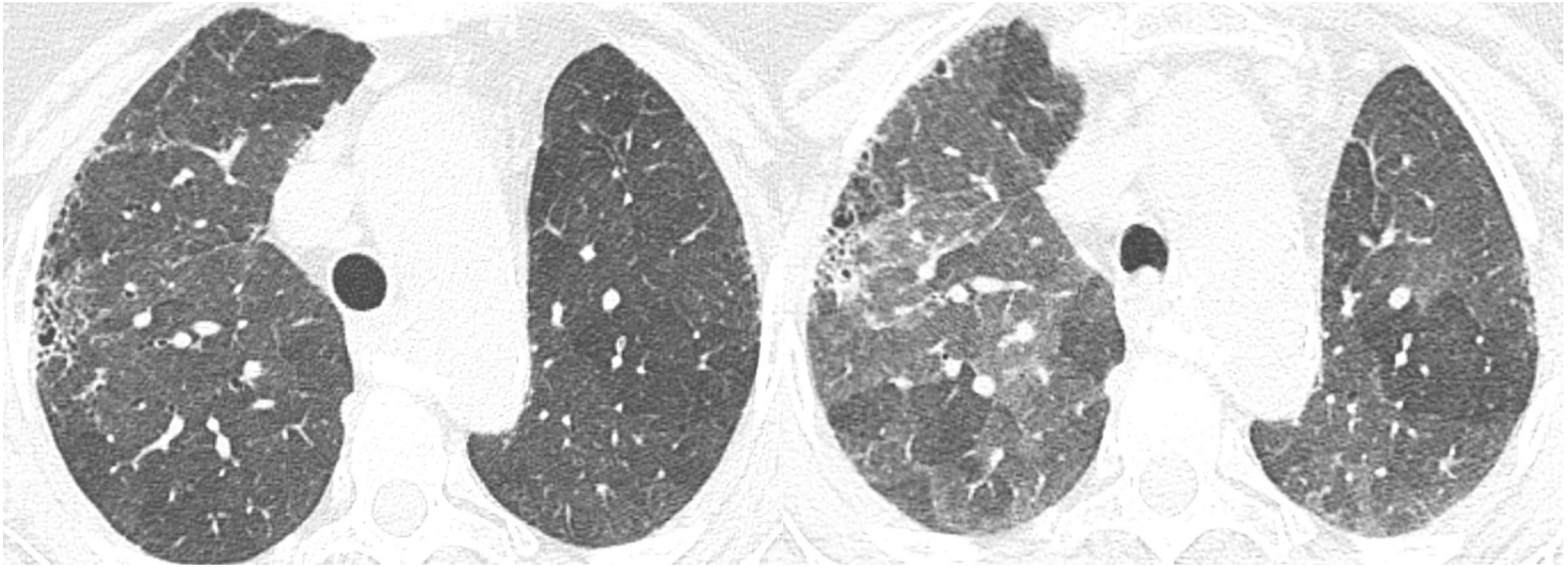
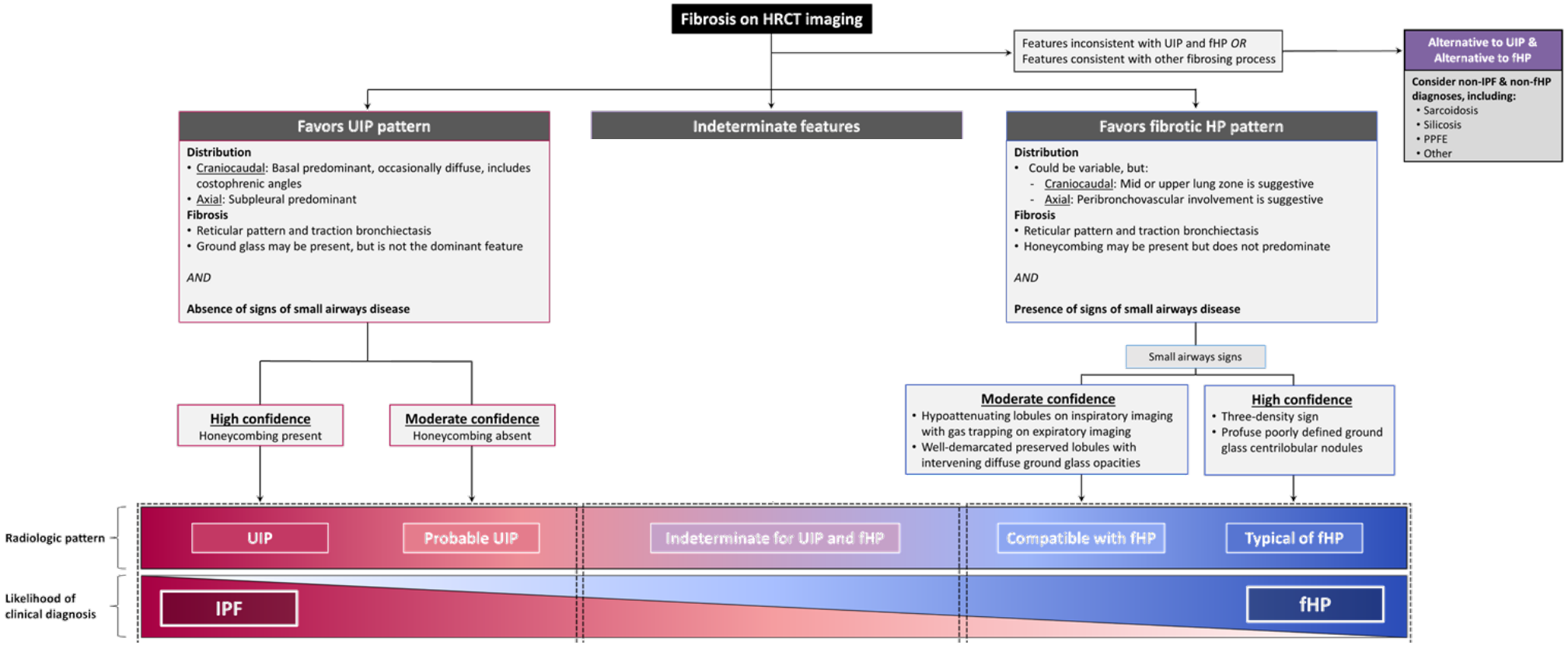
ILD Evaluation: Radiologic Assessment

Gas trapping



ILD Evaluation: Radiologic Assessment



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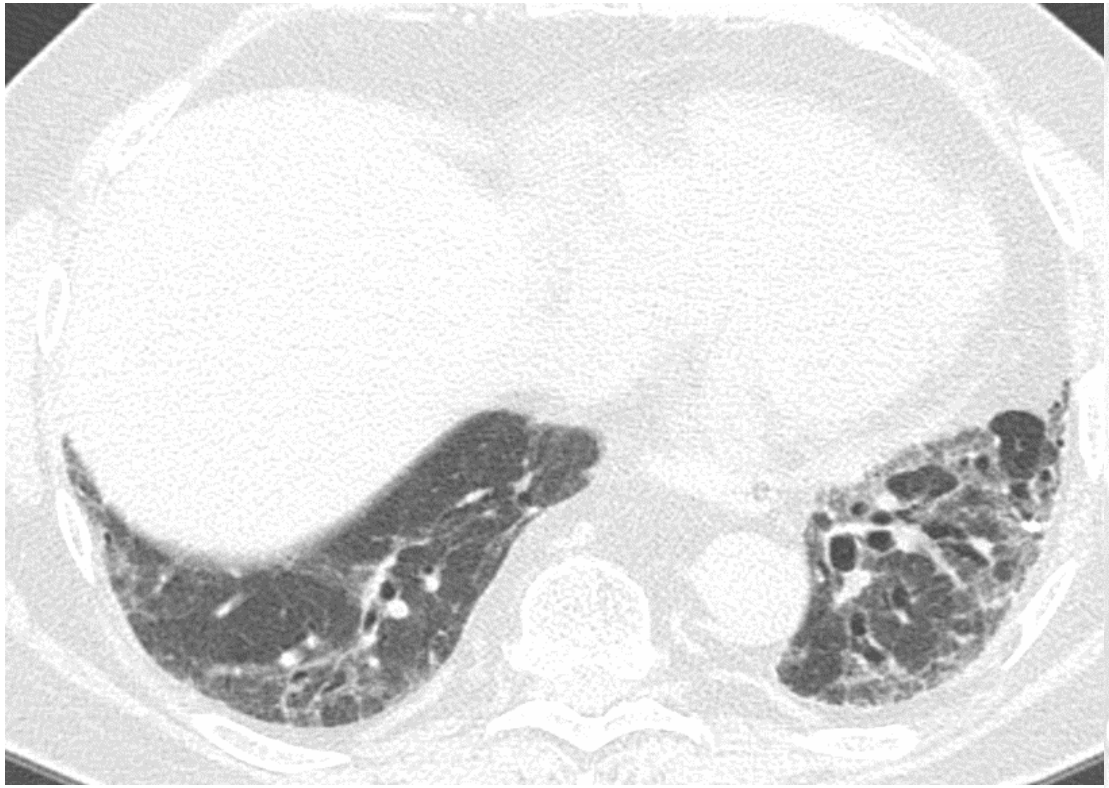
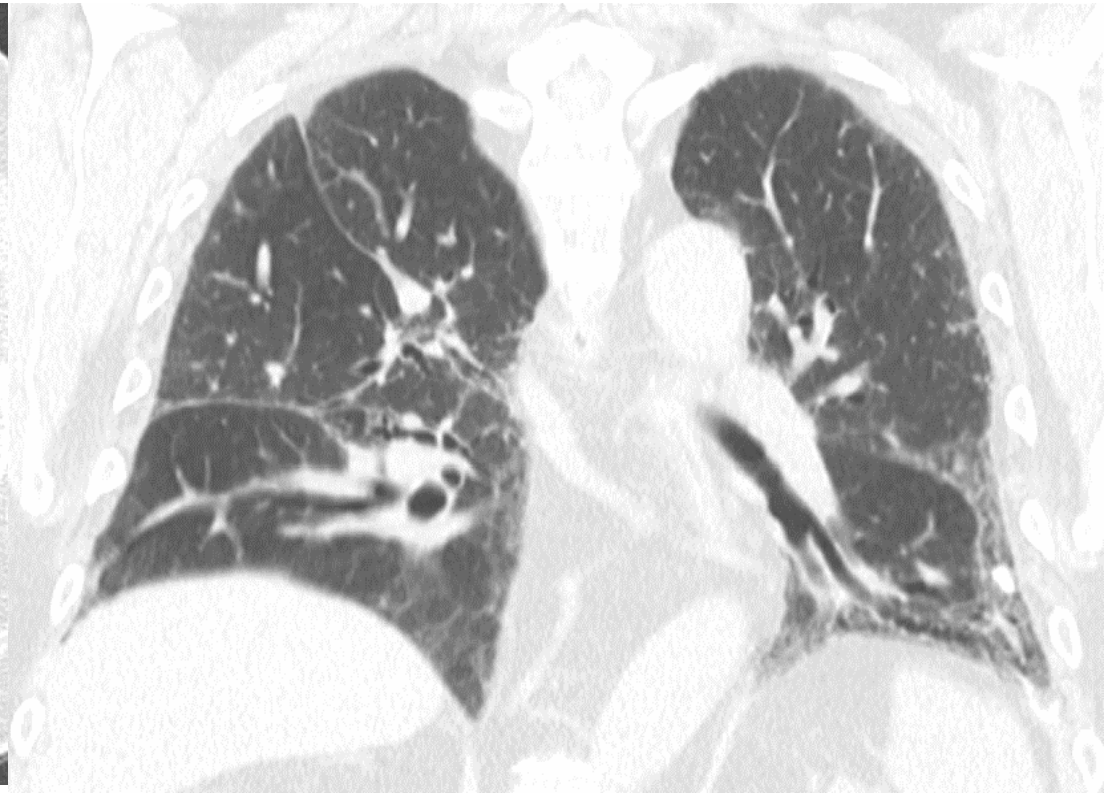
ILD Evaluation: Radiologic Assessment

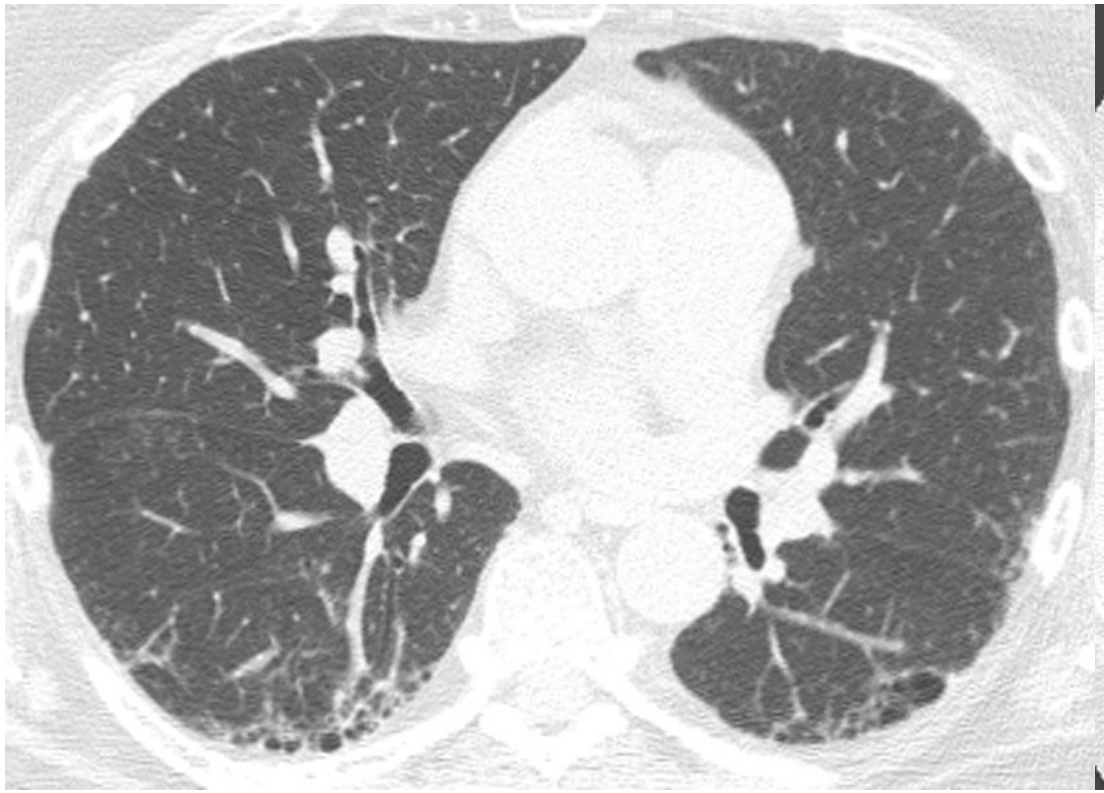
Minor peribronchiolar component

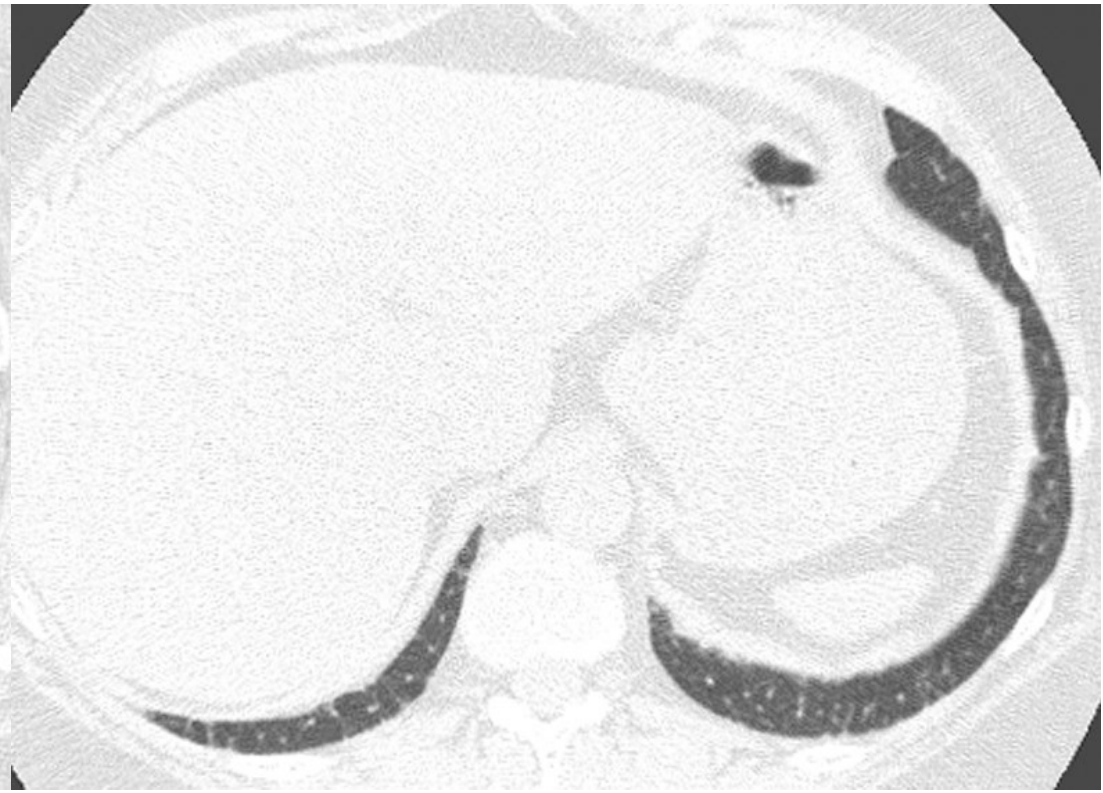




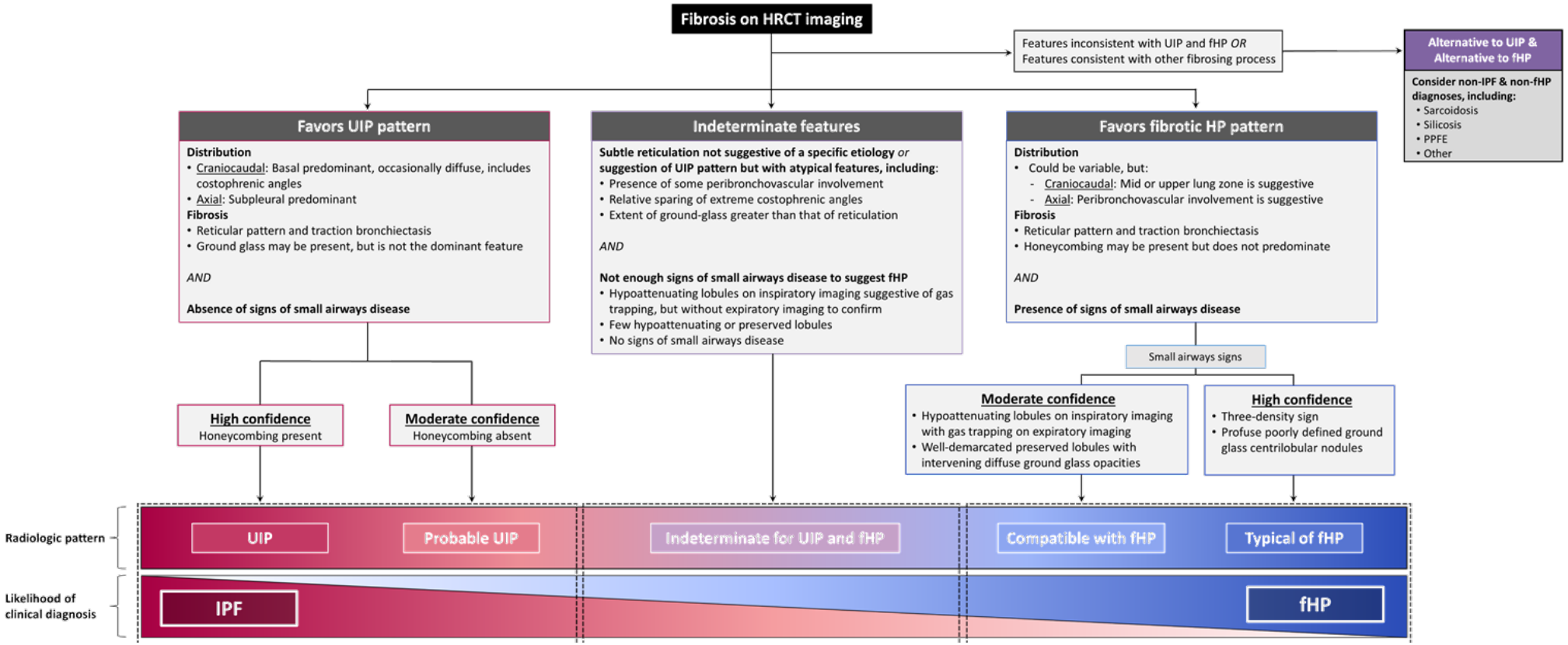
ILD Evaluation: Radiologic Assessment

Costophrenic angle sparing





ILD Evaluation: Radiologic Assessment



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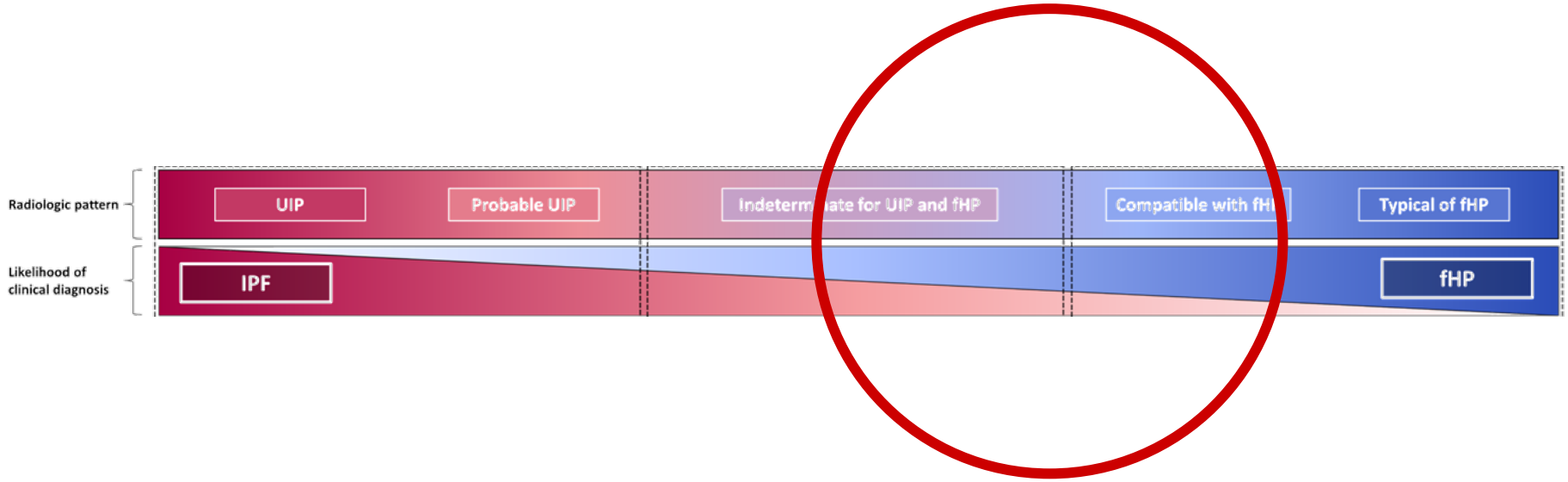
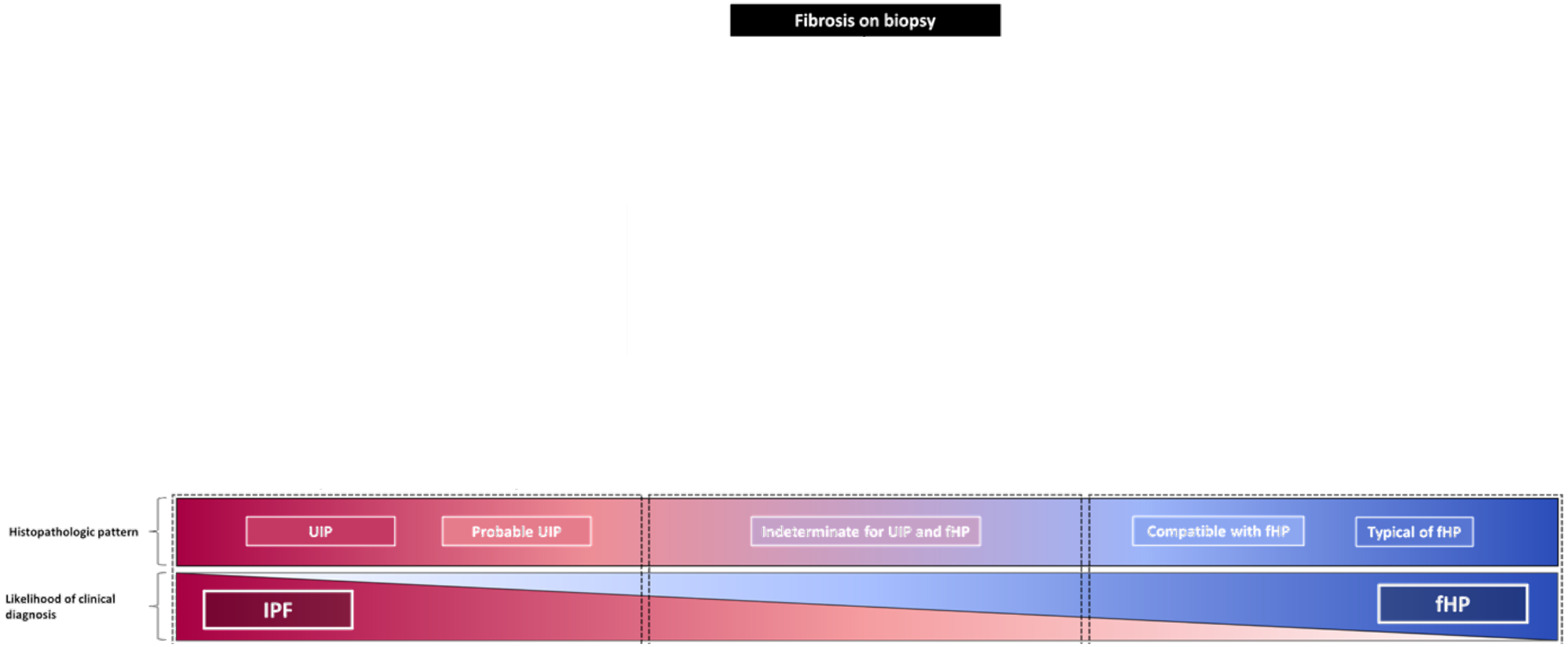
ILD Evaluation: Radiologic Assessment In Our Case

Subpleural distribution with reticulation but:

- Hypoattenuating lobules suggestive of airways disease (no expiratory)
- Costophrenic angle sparing



ILD Evaluation: Pathologic Assessment



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ILD Evaluation: Pathologic Assessment In Our Case