How You Might Feel About ILD Pathology

Our Goal for Understanding ILD Pathology

The Alphabet Soup of Non-Infectious Lung Disease Pathology

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Acknowledgement: Alyson Van Dyke

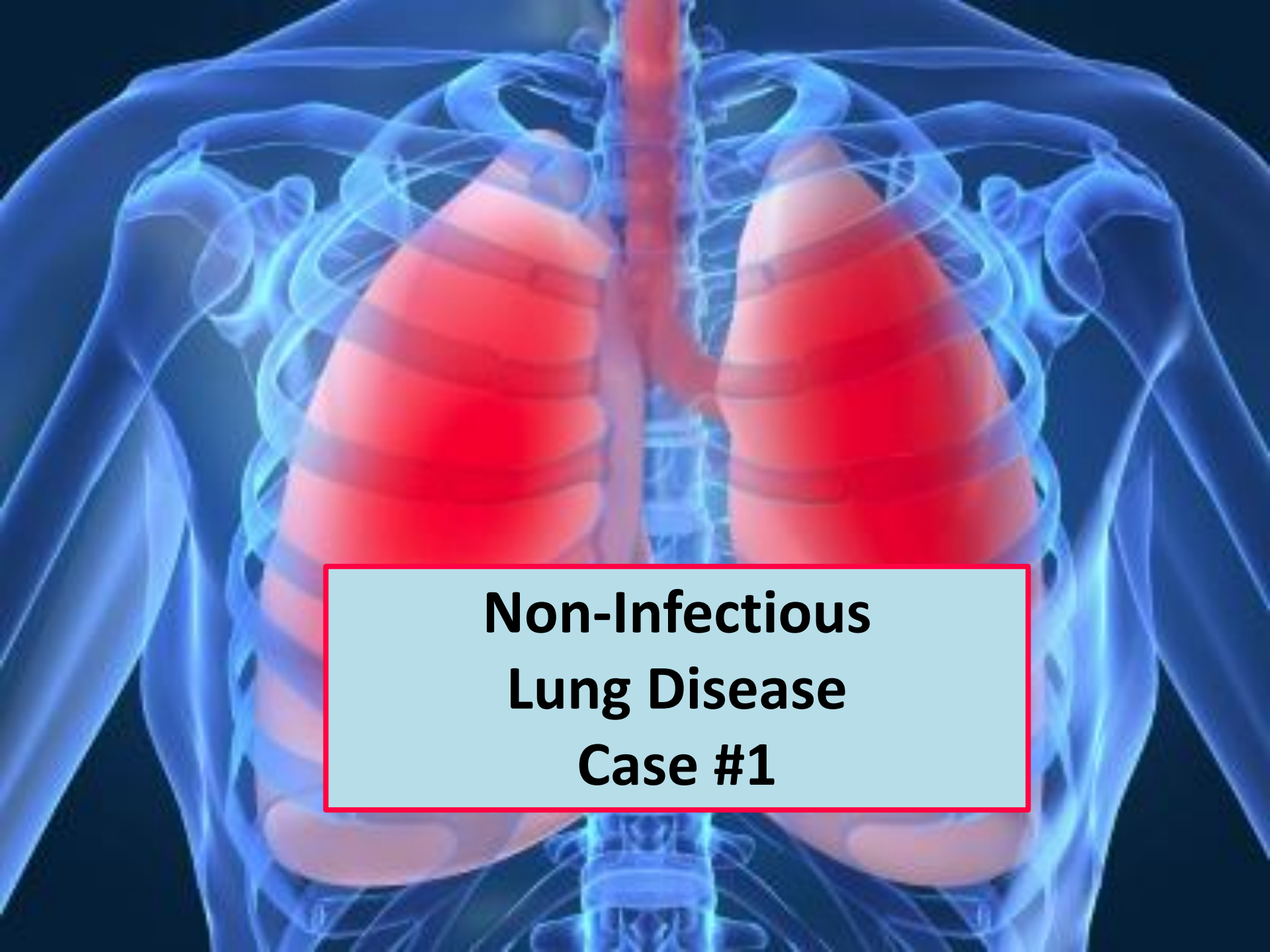
May, 15 2020

Non-Infectious Lung Disease Case Review

- Following are 5 Non-Infectious Lung Disease cases w/ associated microscopic images
- You will be presented the limited history provided to the pathologist.
- As you review each case, think about your top differential before and after reviewing the path and about what microscopic features you should see in each condition, which we will review.

Clinicopathologic Translation

Pathologic Term	Clinical Term
UIP: Usual Interstitial PNA	***IPF:*** Idiopathic Pulmonary Fibrosis
NSIP: Nonspecific Interstitial PNA	***NSIP:*** Nonspecific Interstitial PNA
RB: Respiratory Bronchiolitis	***RB-ILD:*** Respiratory Bronchiolitis-Interstitial Lung Disease
DIP: Desquamative Interstitial PNA	***DIP:*** Desquamative Interstitial PNA
DAD: Diffuse Alveolar Damage	***AIP:*** Acute Interstitial PNA
OP: Organizing PNA	***COP:*** Cryptogenic Organizing PNA
LIP: Lymphoid Interstitial PNA	***LIP:*** Lymphoid Interstitial PNA



Non-Infectious Lung Disease Case #1

History & Presentation

The Patient: 39 y.o. woman

Medical Hx: Gastroesophageal Reflux Disease

Medications: Several inhalers

HPI: Cough & Progressive SOB that's exacerbated w/ activity

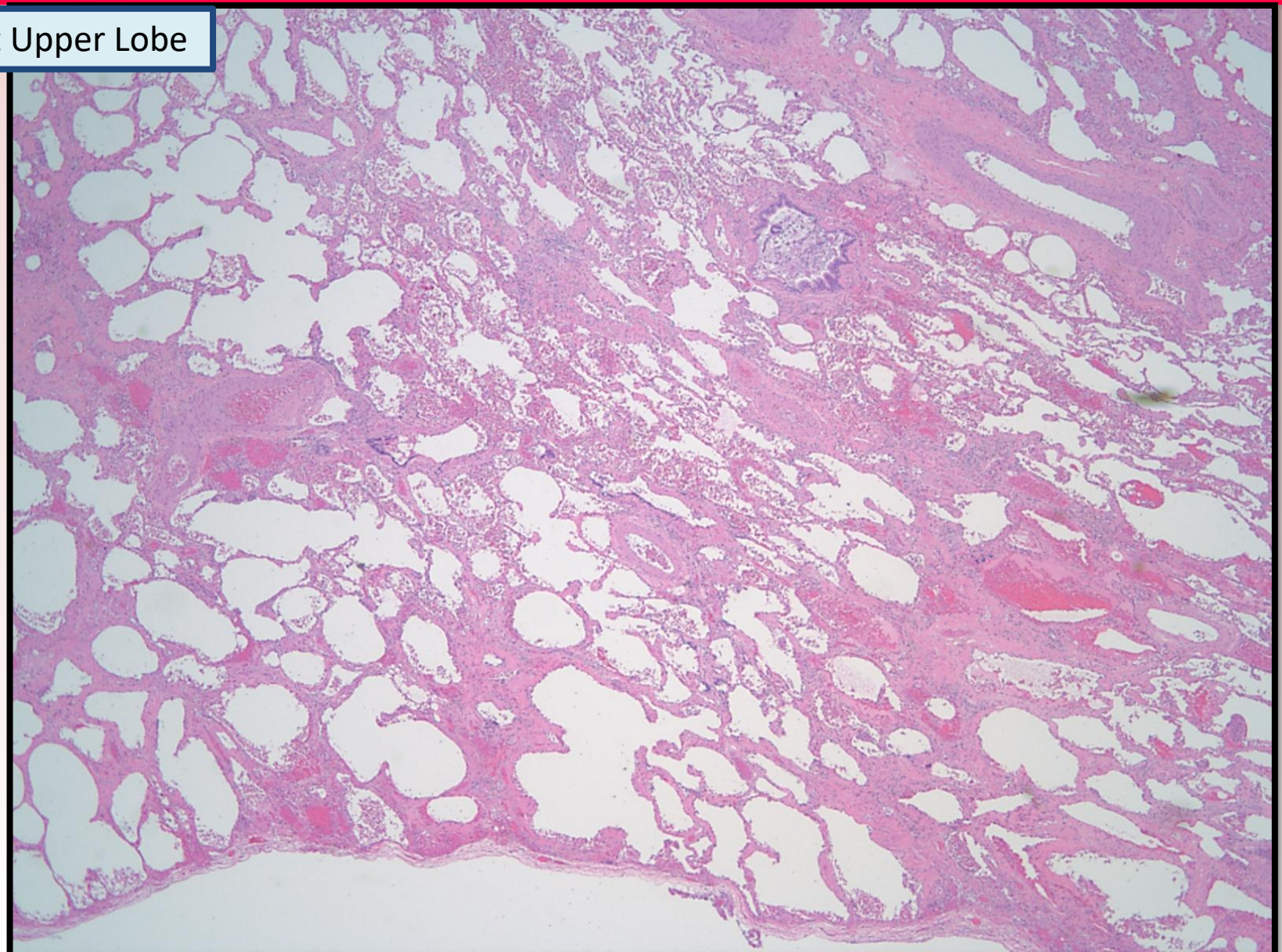
SocHx: >20 pack-yr smoking history, recently quit

Objective: -Chest CT: Small 1-3 mm subpleural zone cysts compatible w/ pulmonary fibrosis & diffuse, symmetric bilateral interstitial infiltrates

RUL, RML & RLL Wedge Biopsies Are Performed.

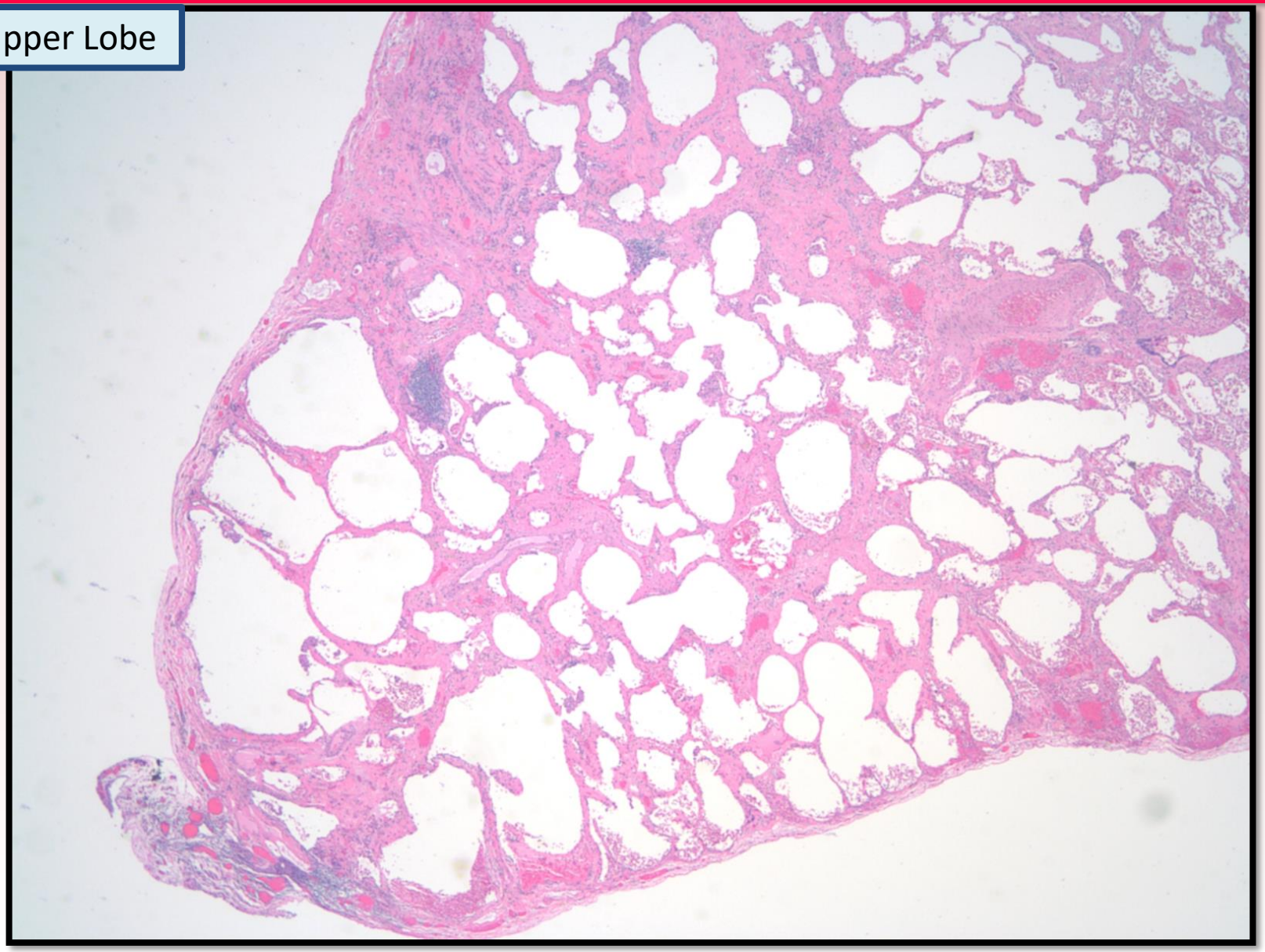
Wedge Biopsies

Right Upper Lobe



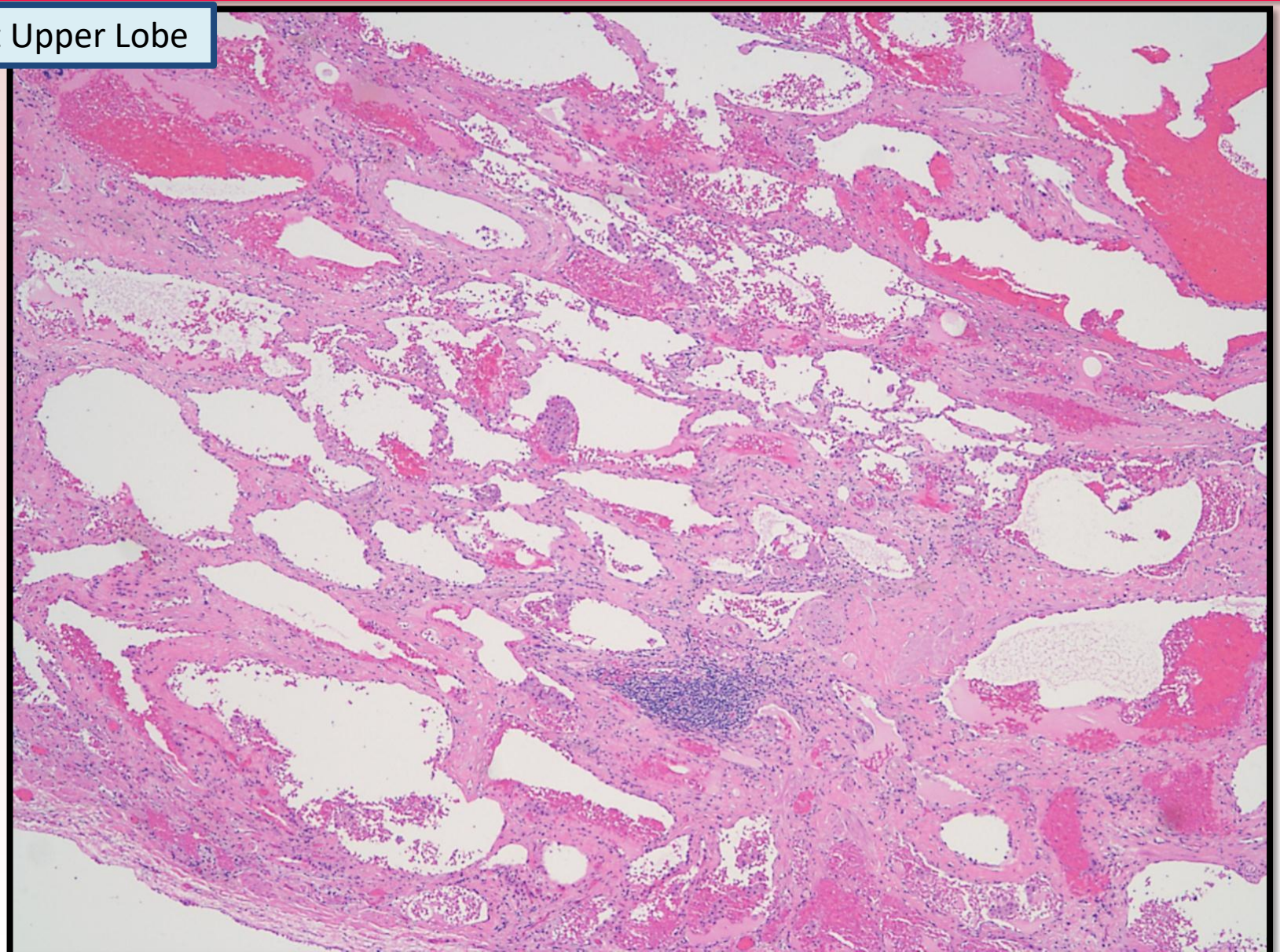
Wedge Biopsies

Right Upper Lobe



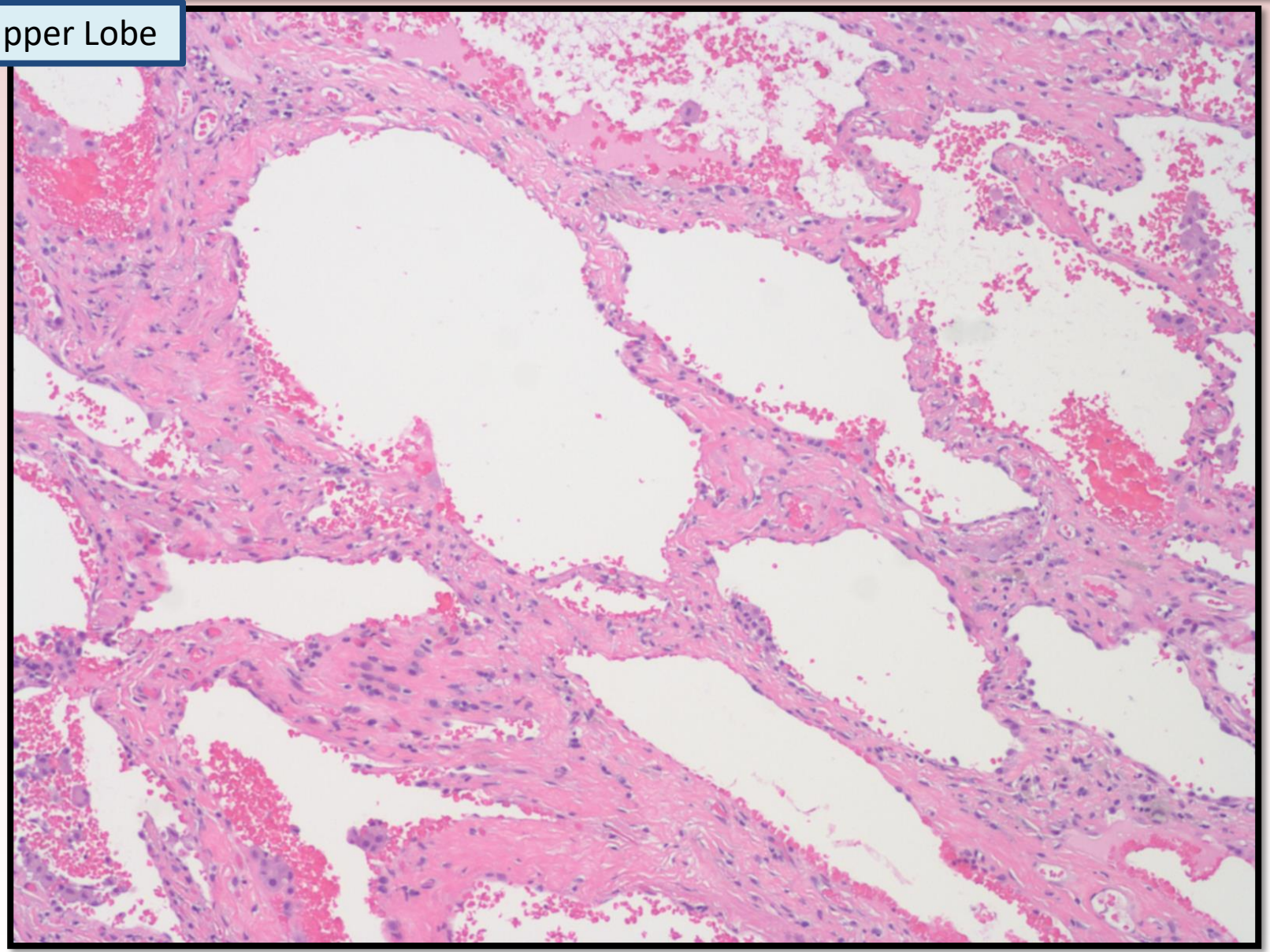
Wedge Biopsies

Right Upper Lobe



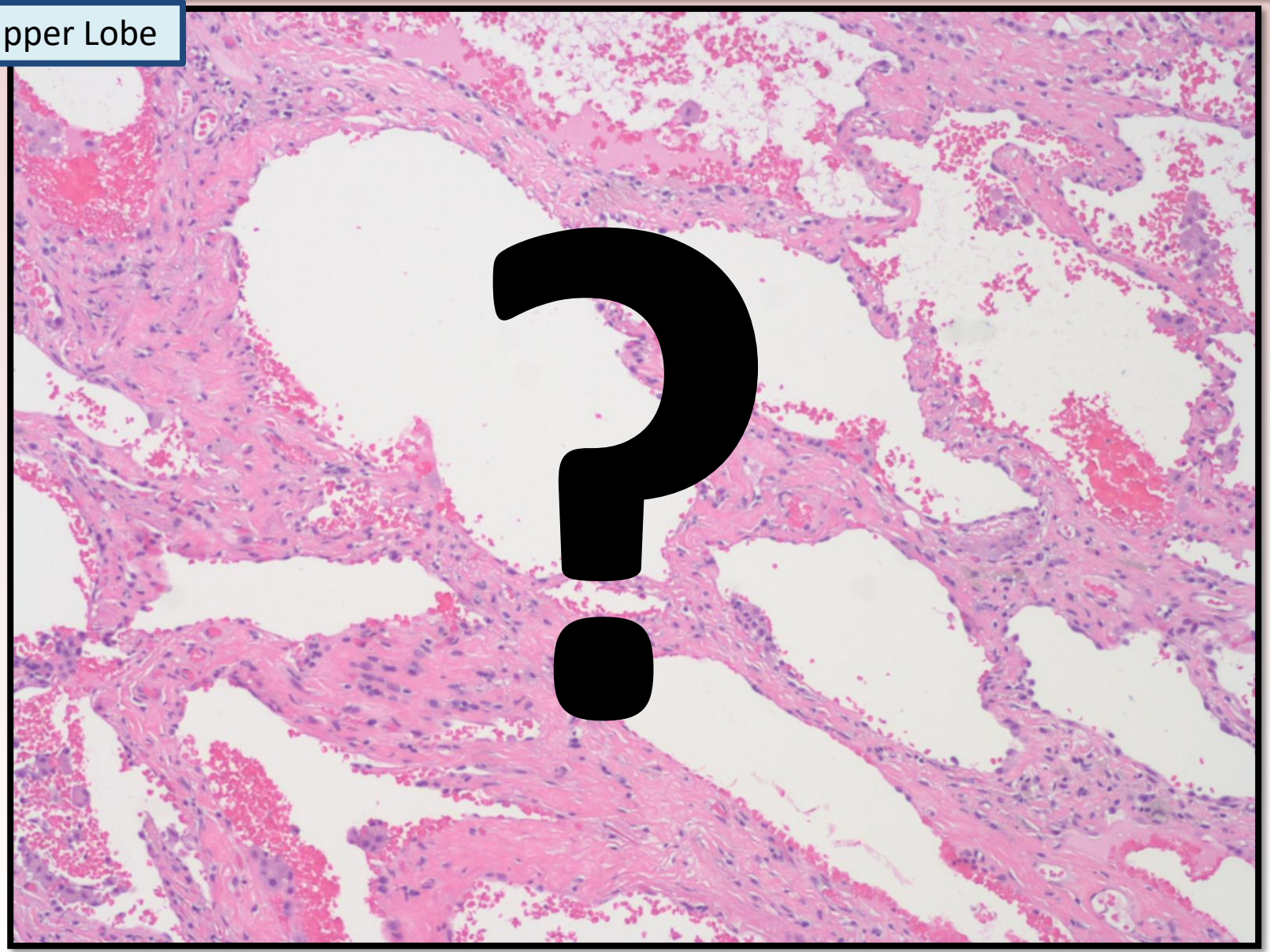
Wedge Biopsies

Right Upper Lobe



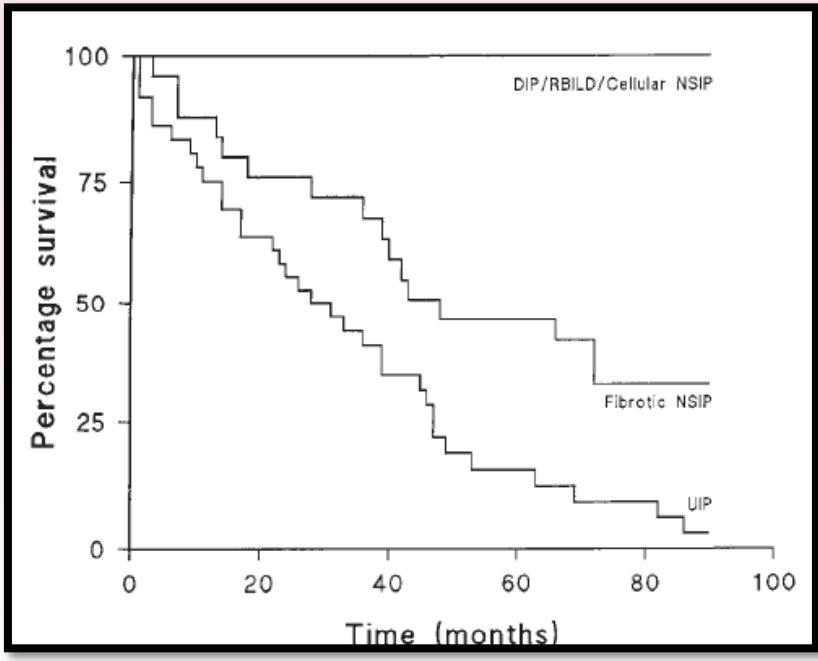
Wedge Biopsies

Right Upper Lobe



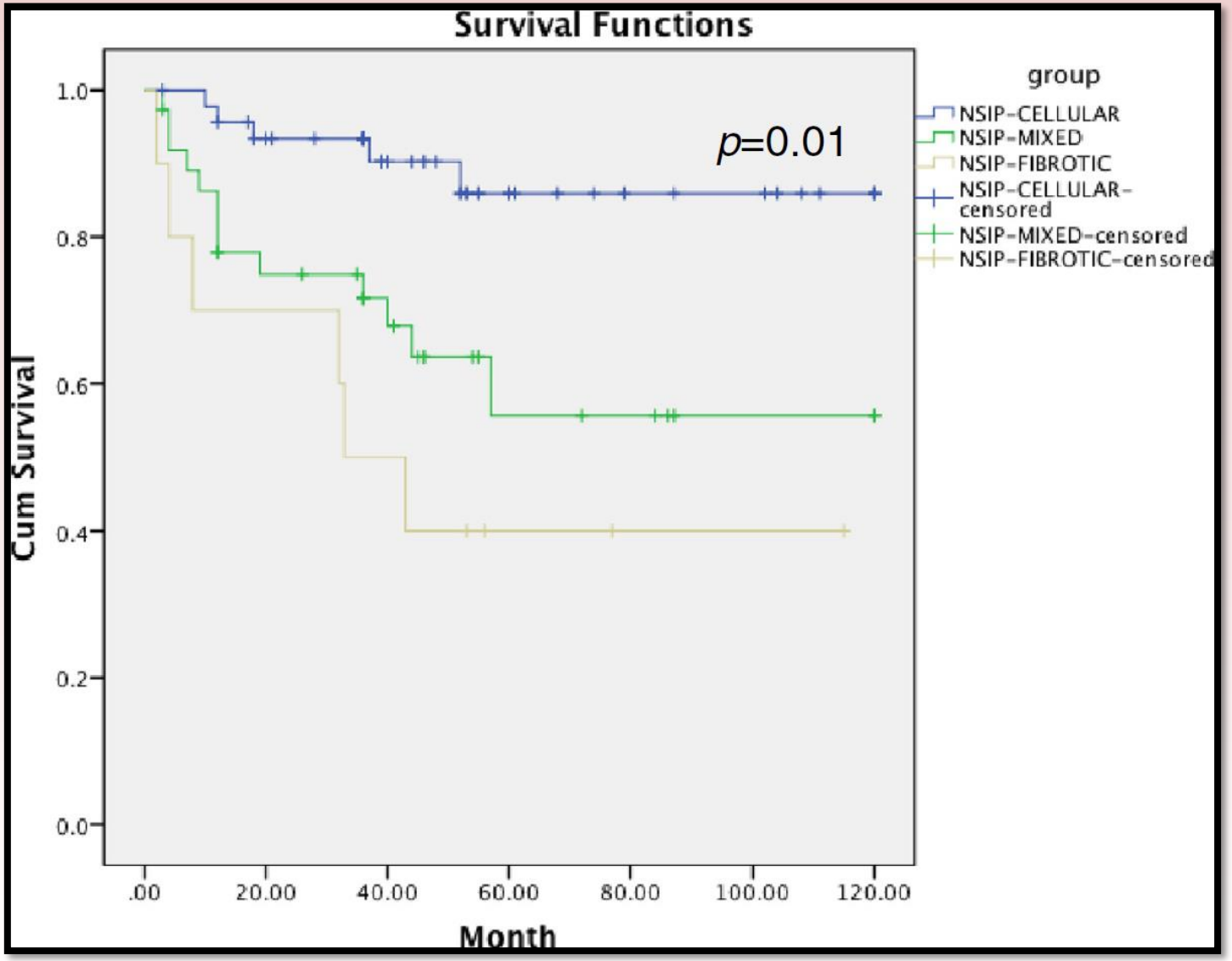
Fibrotic NSIP

- **NSIP Originally – wastebasket diagnosis**
  - NOT: UIP, DIP, RBILD, or AIP
- **Pattern:**
  - Temporal uniformity
  - Interstitial fibrosis > cellularity
- **Association w/ CT diseases**
- **Survival varies by type:**
  - *Best* – Cellular NSIP
  - *Moderate* – Mixed NSIP
  - *Worst* – Fibrotic NSIP



Nicholson *et al. AJRCCM* (2000)

Fibrotic NSIP



Xu *et al. BMC Pulm Med* (2014)

Fibrotic NSIP vs. UIP

Feature	Fibrosing NSIP	UIP
Patchwork Pattern	Absent	Characteristic
Distortion: - ***Honeycomb change*** - ***Interstitial scar***	Minimal to Absent	Characteristic
Fibroblastic Foci	Few to Absent	Characteristic

A-L. Katzenstein's *Non-Neoplastic Lung Disease* (2006)

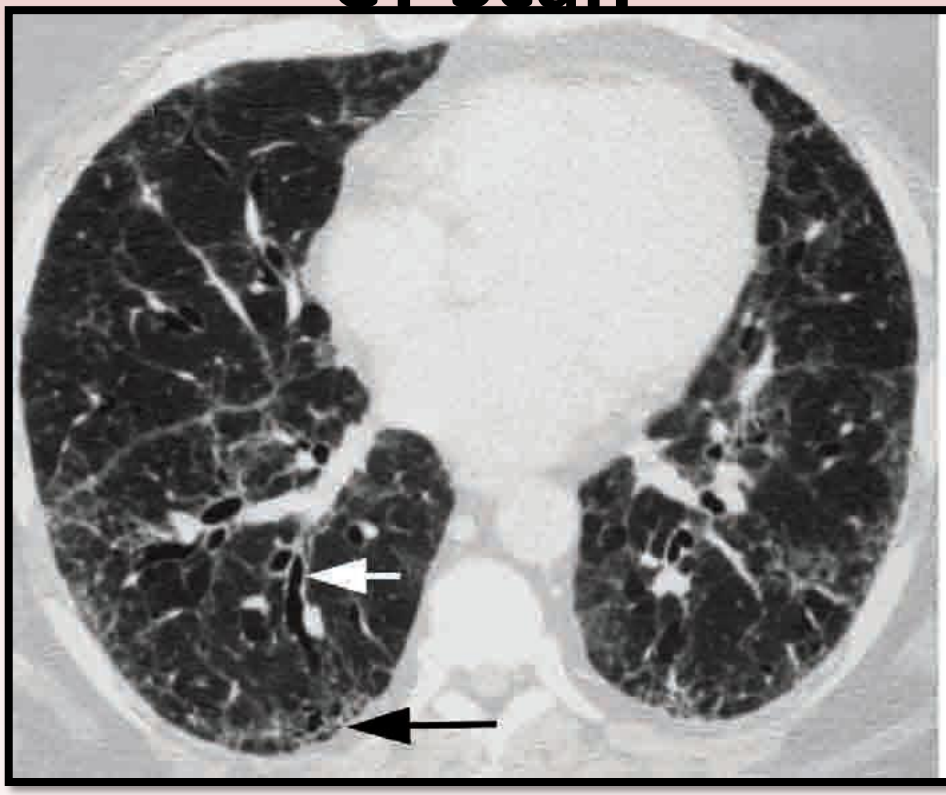
UIP: Defined Features

Term	Microscopic Findings
Spatial Variation	Patchwork Pattern of Non-uniform Fibrosis
Architectural Distortion	Honeycomb Change Interstitial Scars
Temporal Variation	*Active Fibrosis:* Fibroblastic Foci *Inactive Fibrosis:* Collagen Scar
Mild Inflammation	Fibrosis Overshadows Inflammation

A-L. Katzenstein's *Non-Neoplastic Lung Disease* (2006)

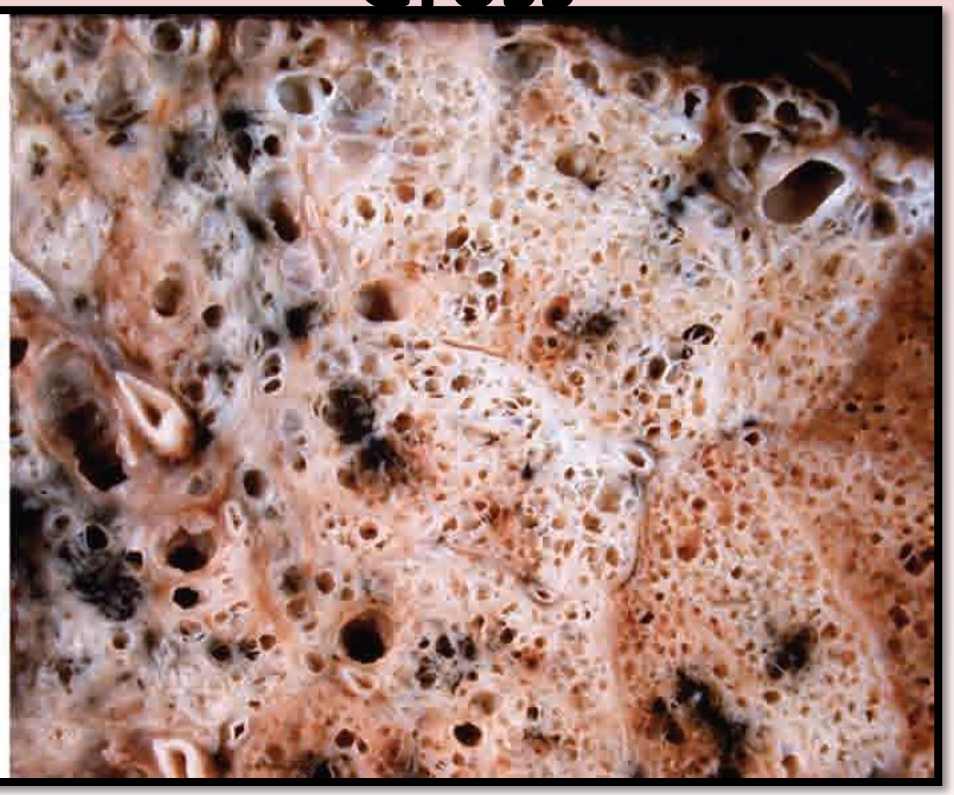
UIP Presentation

CT Scan



Subpleural Cysts
Traction Bronchiectasis

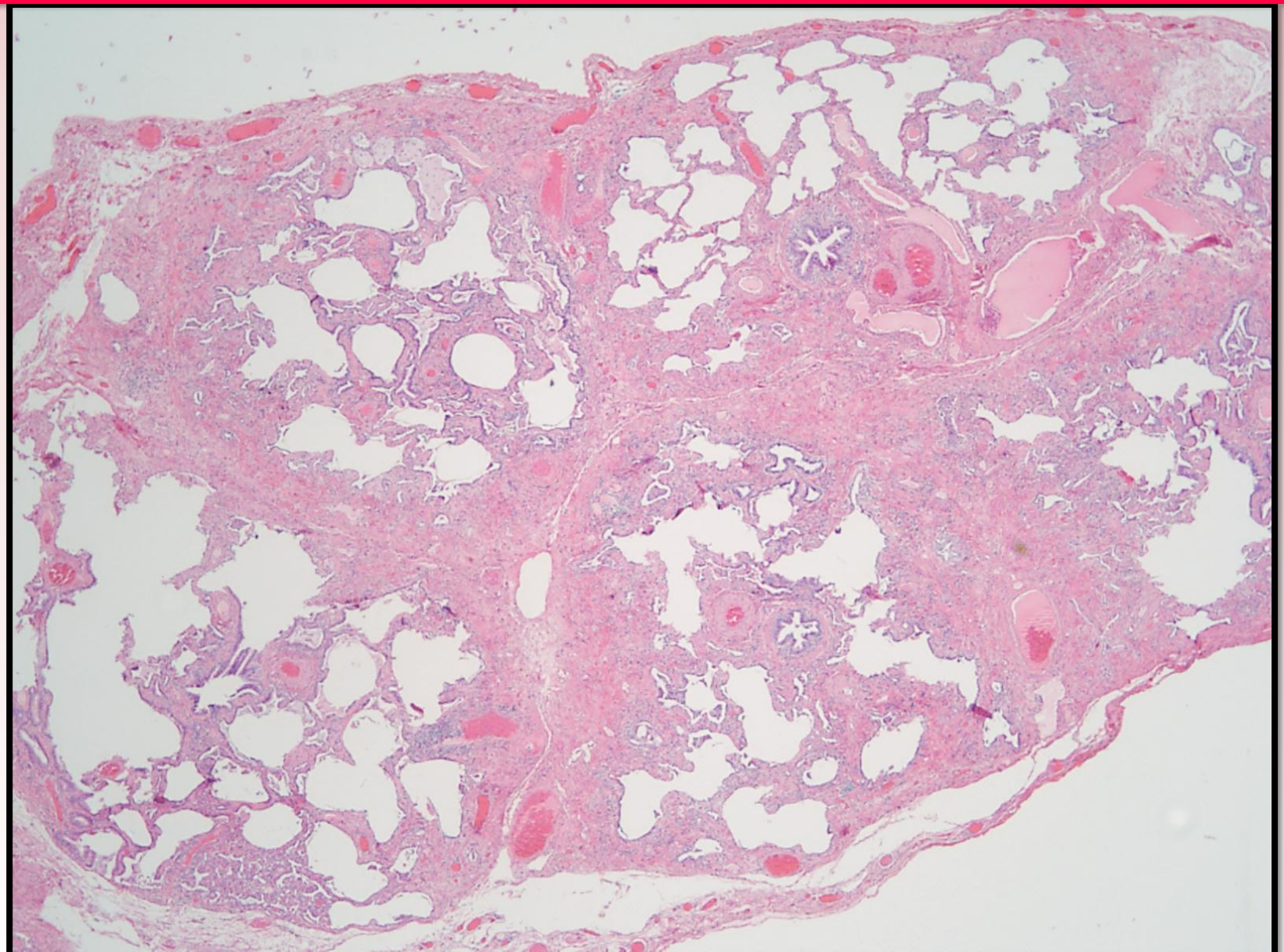
Gross



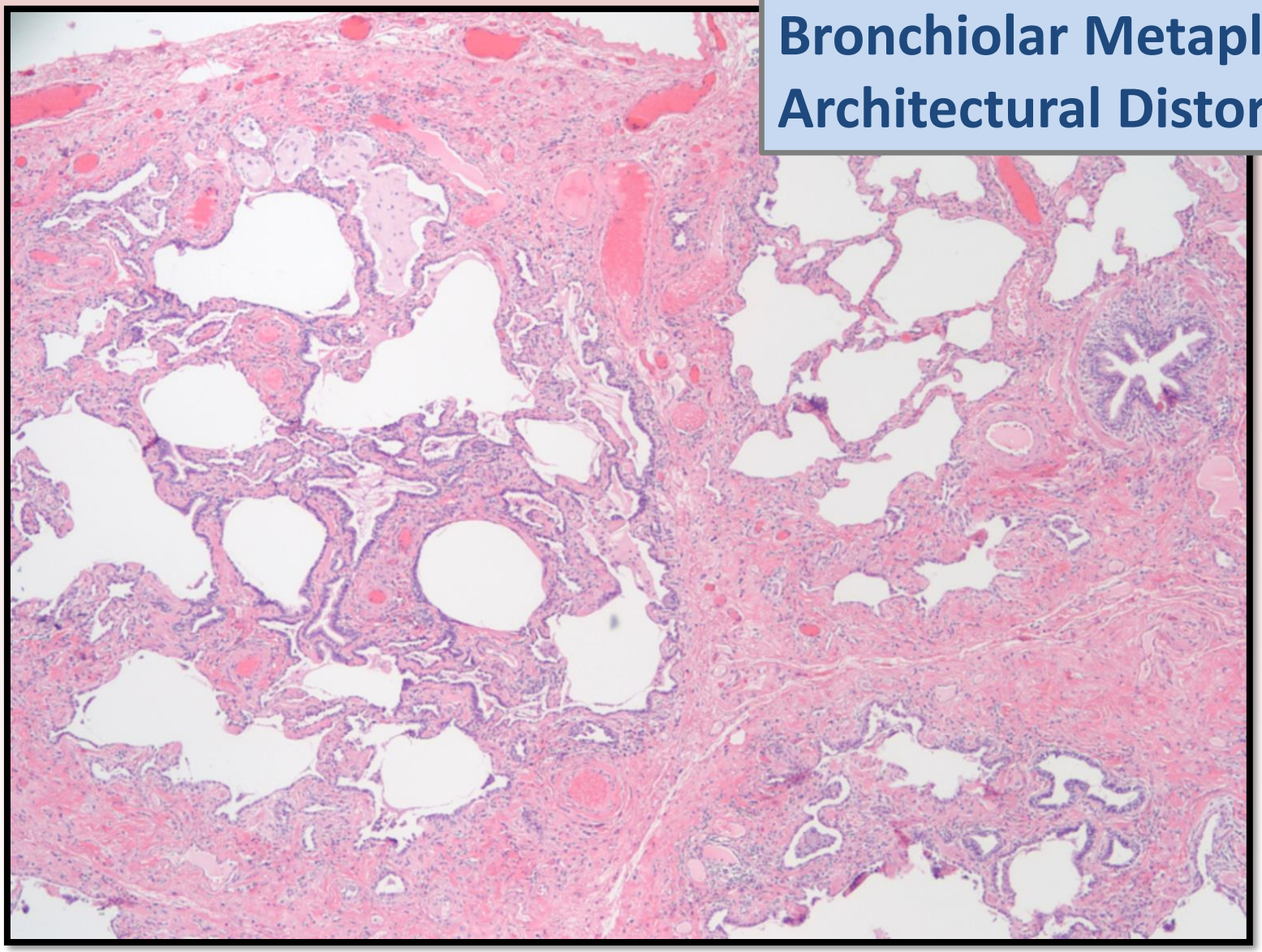
Subpleural Fibrosis &
Cysts (mm's to 1+ cm)

Leslie & Wick *Practical Pulmonary Pathology* (2011)

UIP Peripheral Fibrosis

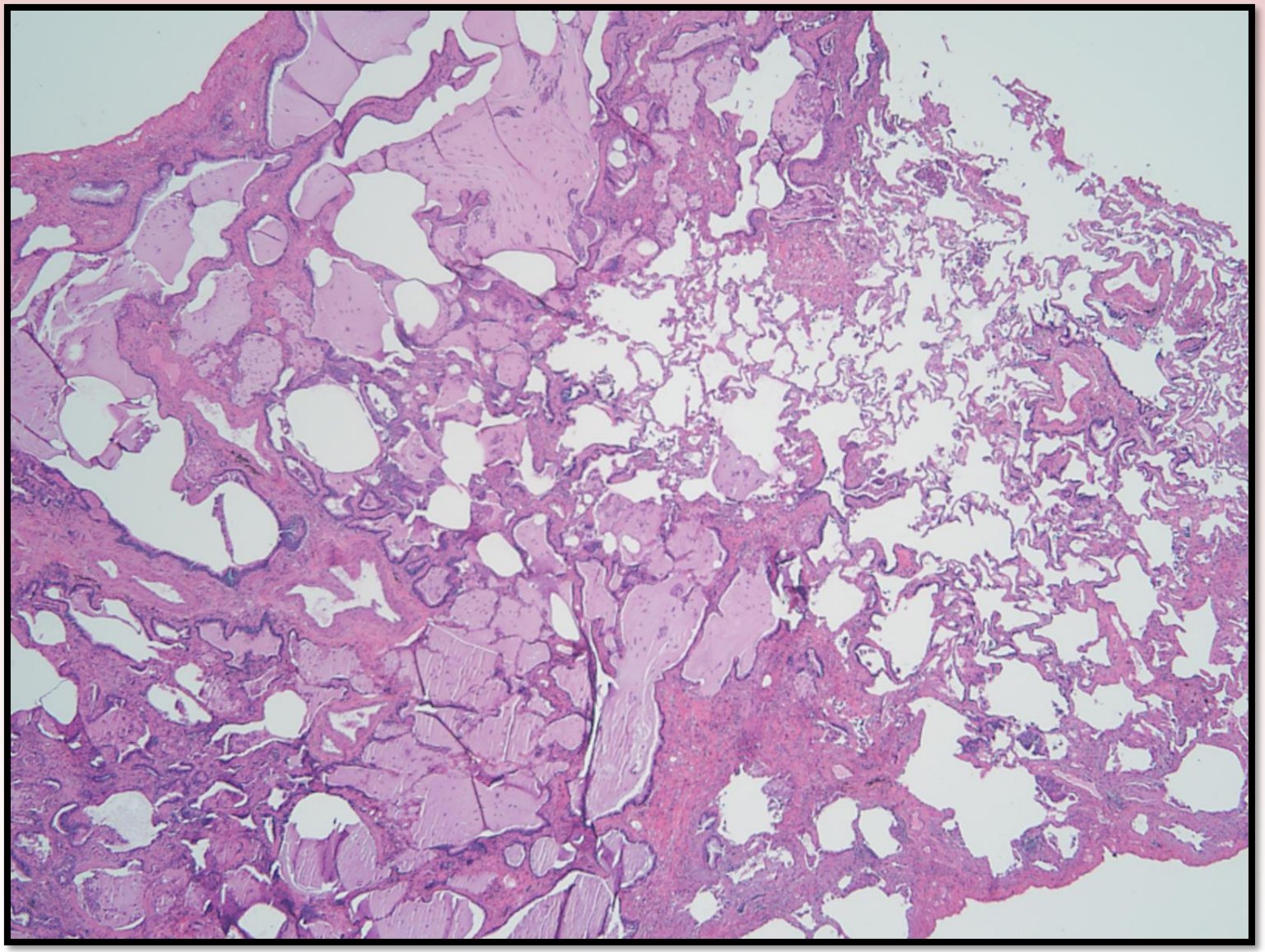


UIP Honeycombing

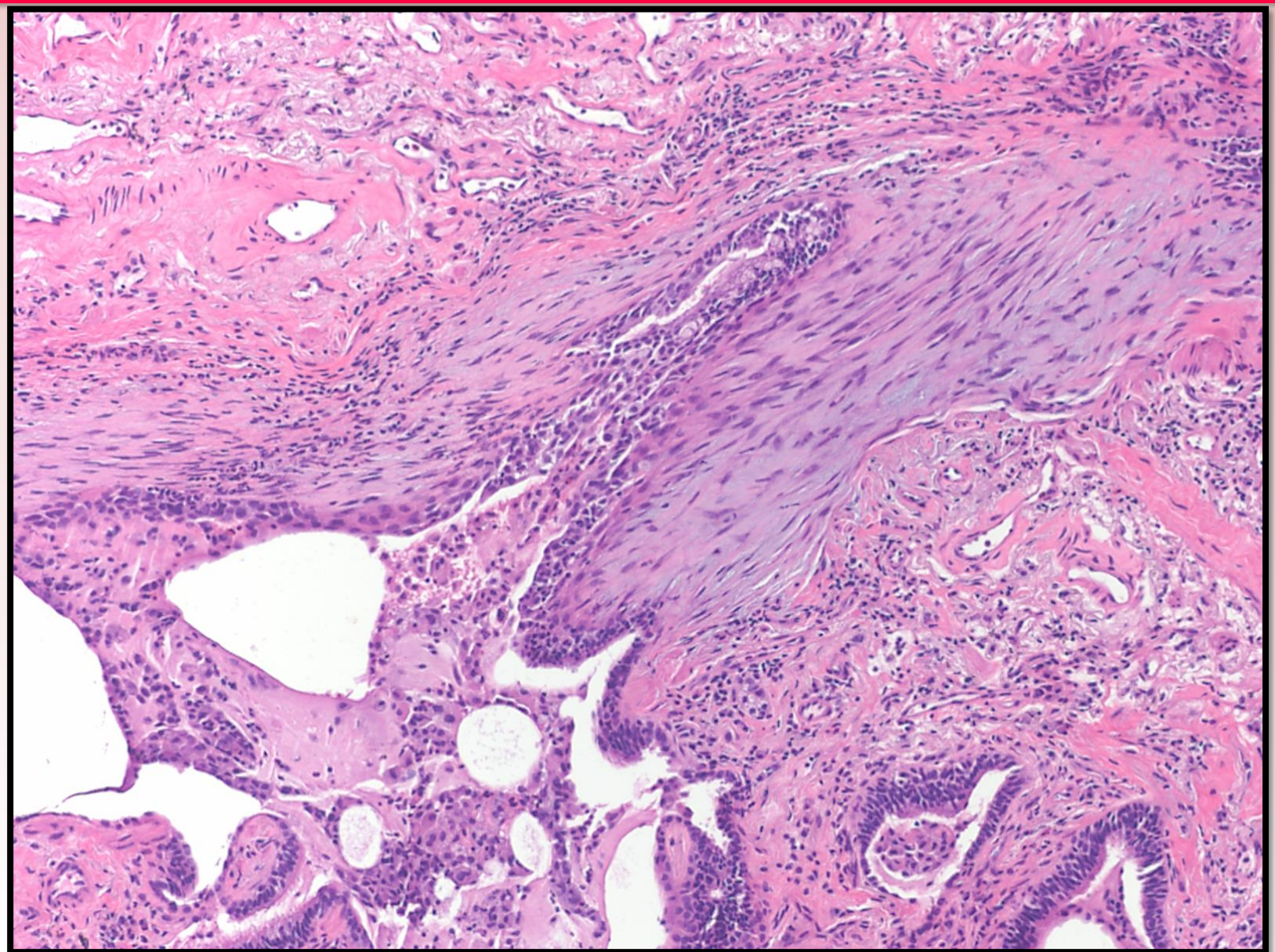


Bronchiolar Metaplasia
Architectural Distortion

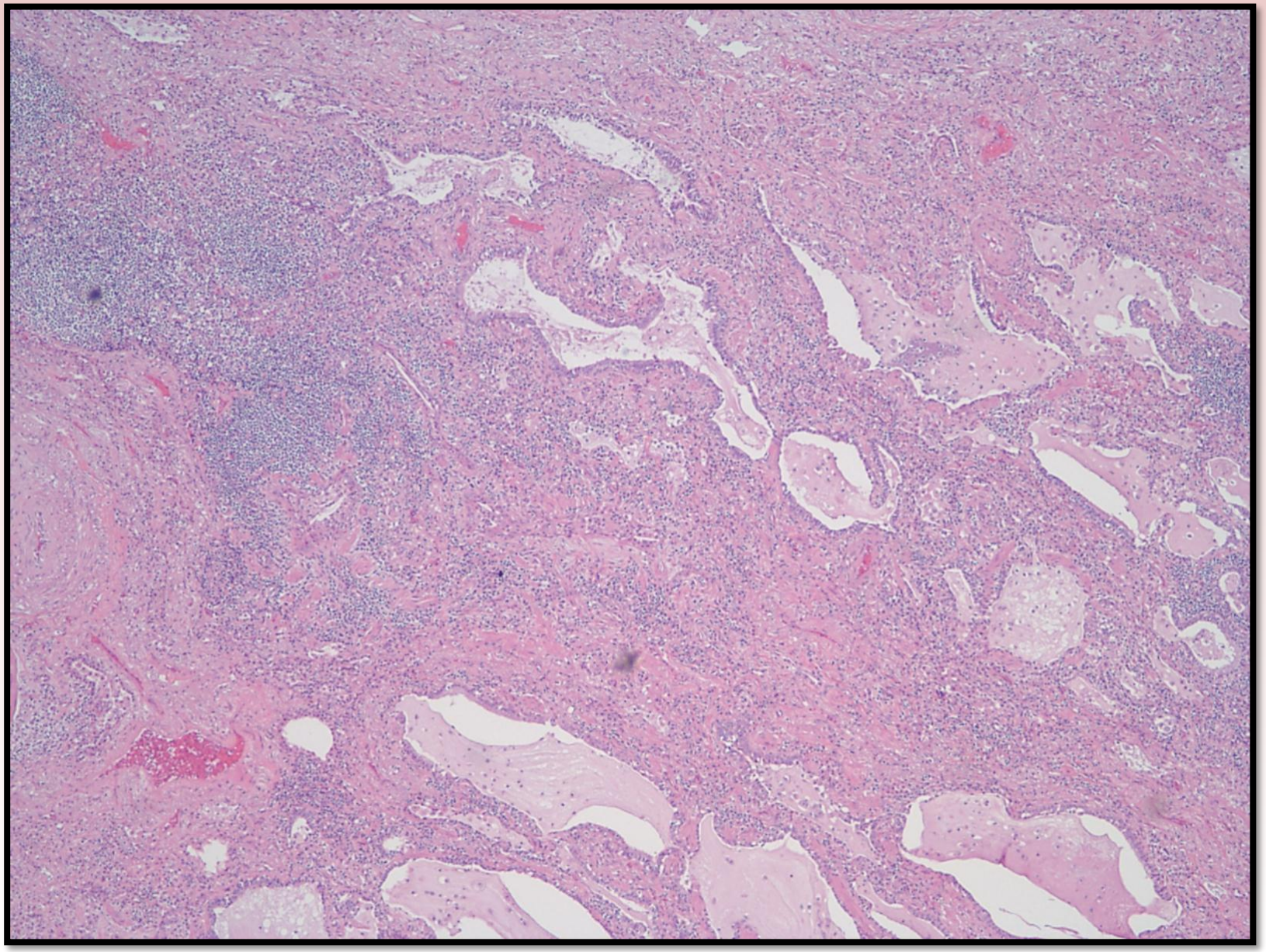
UIP - Heterogeneity



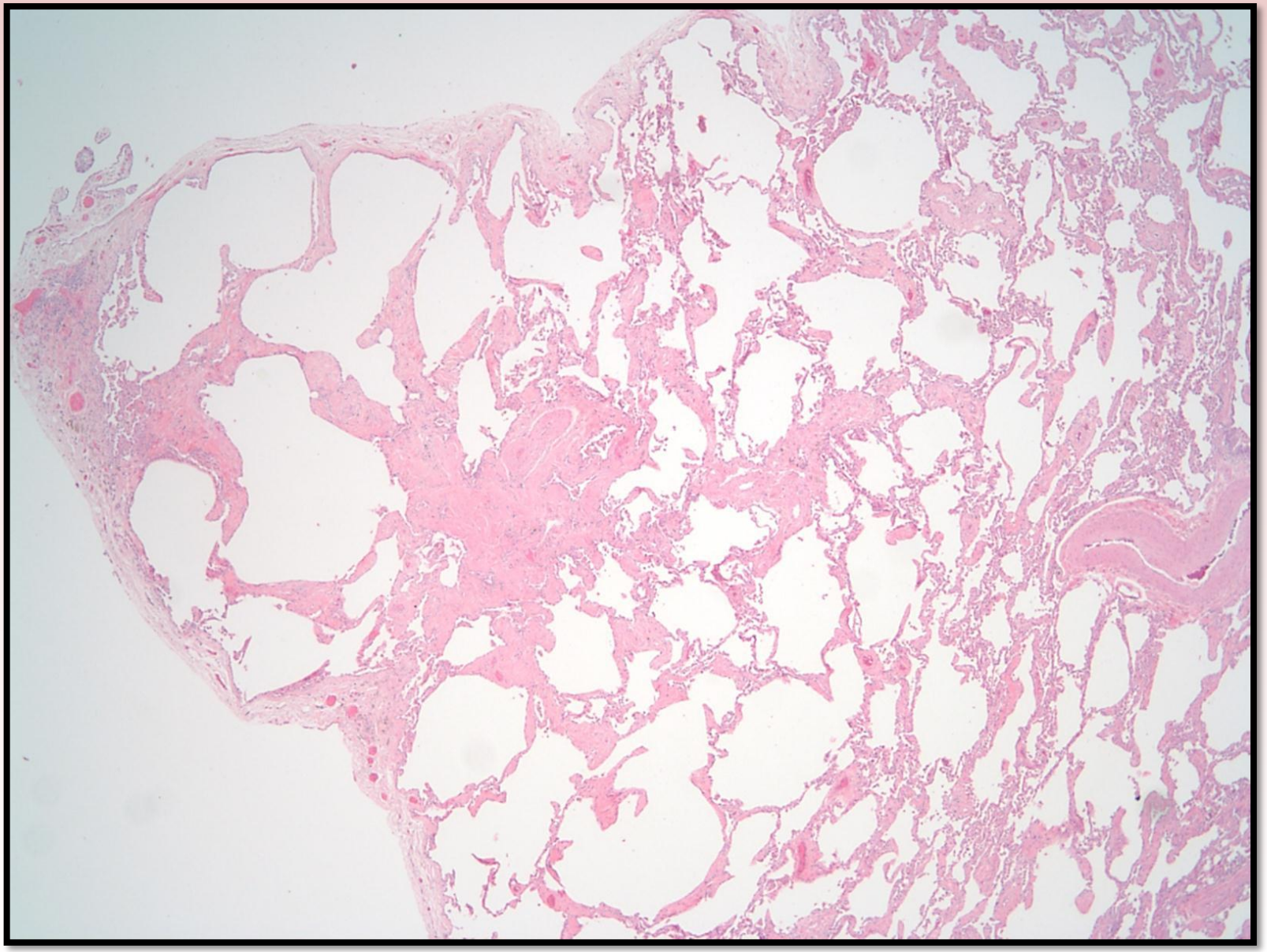
UIP: Fibroblastic Focus



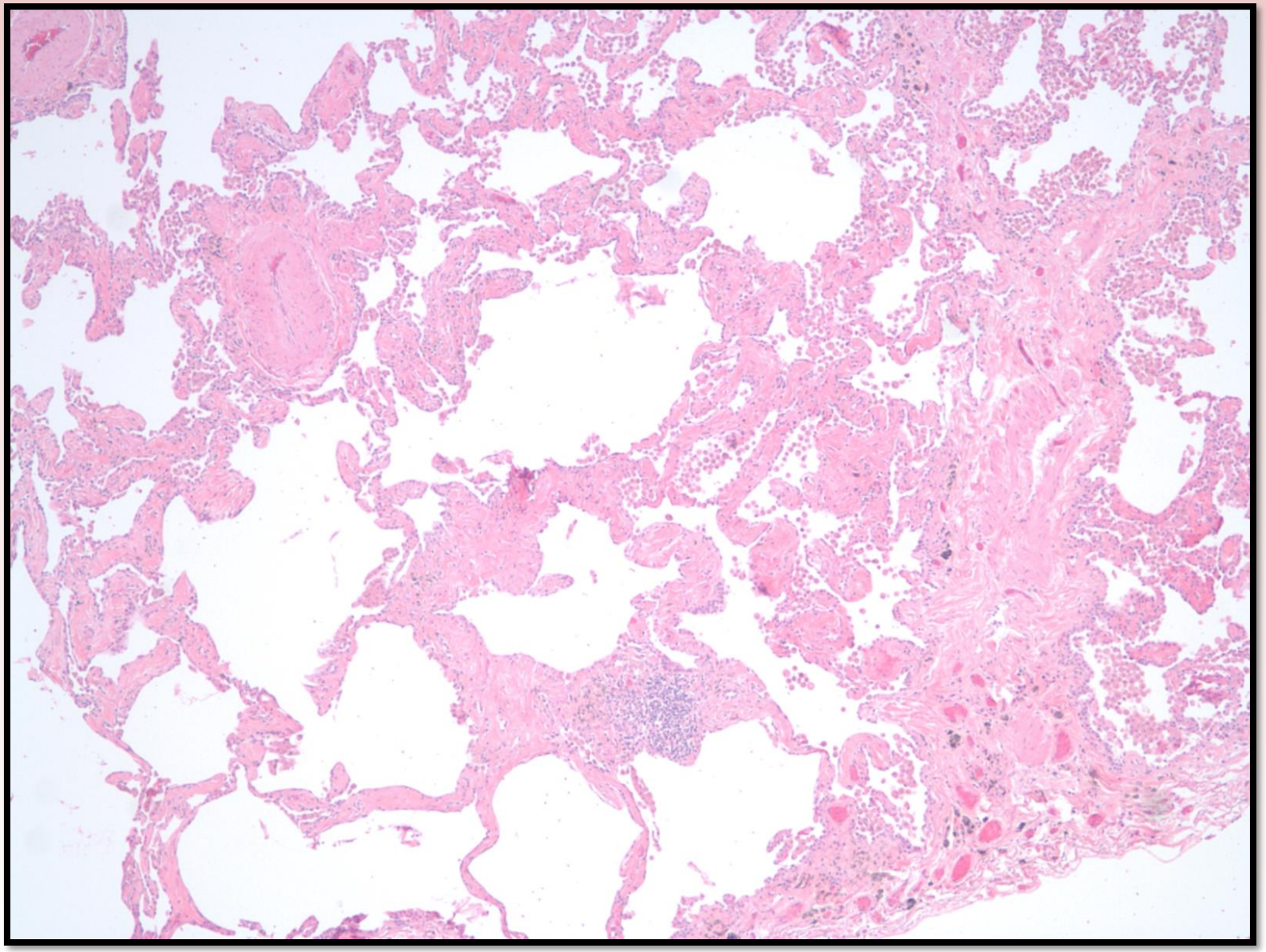
UIP with Lymphoid Aggregates



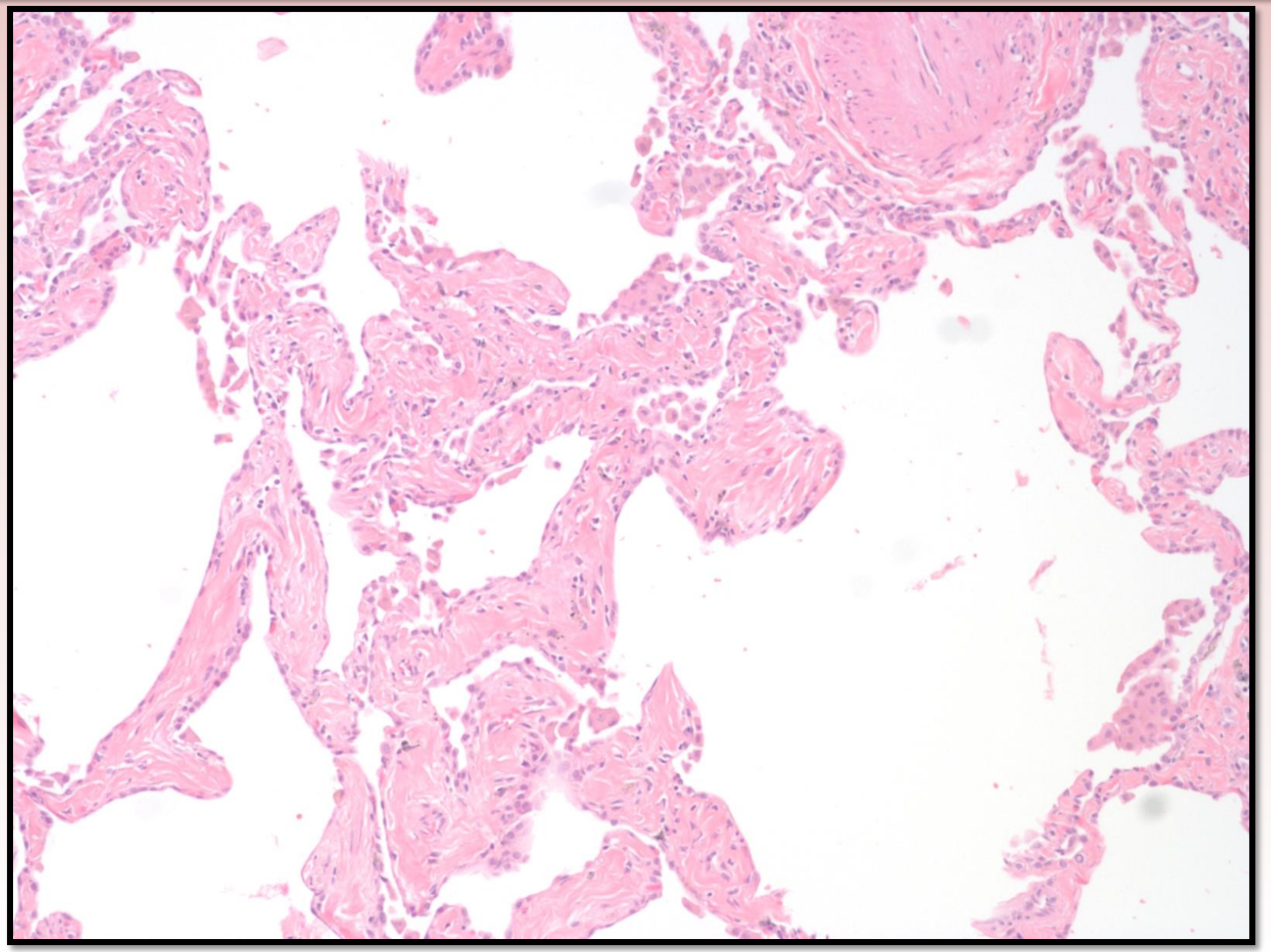
Subpleural Smoker's Fibrosis



Subpleural Smoker's Fibrosis

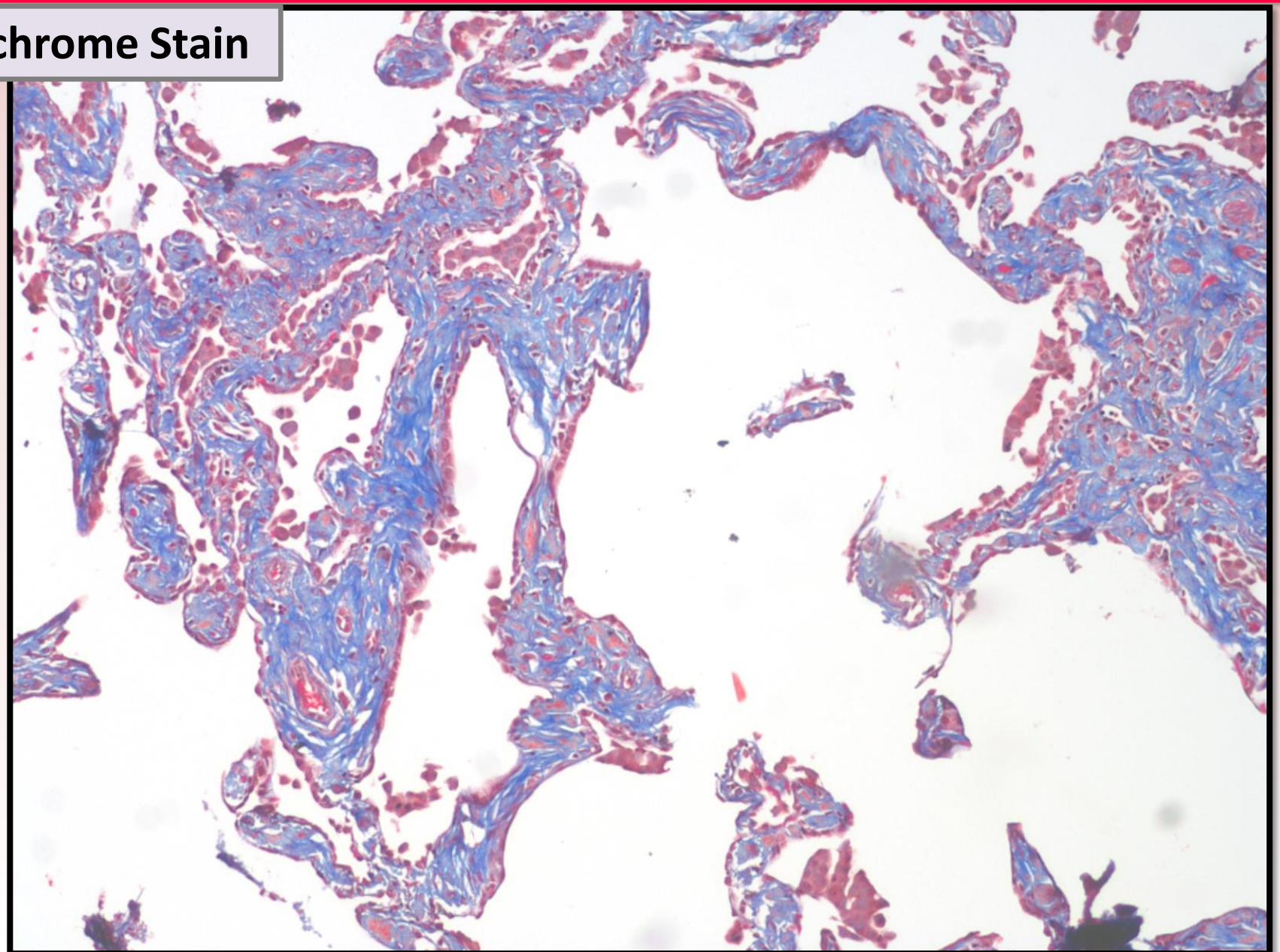


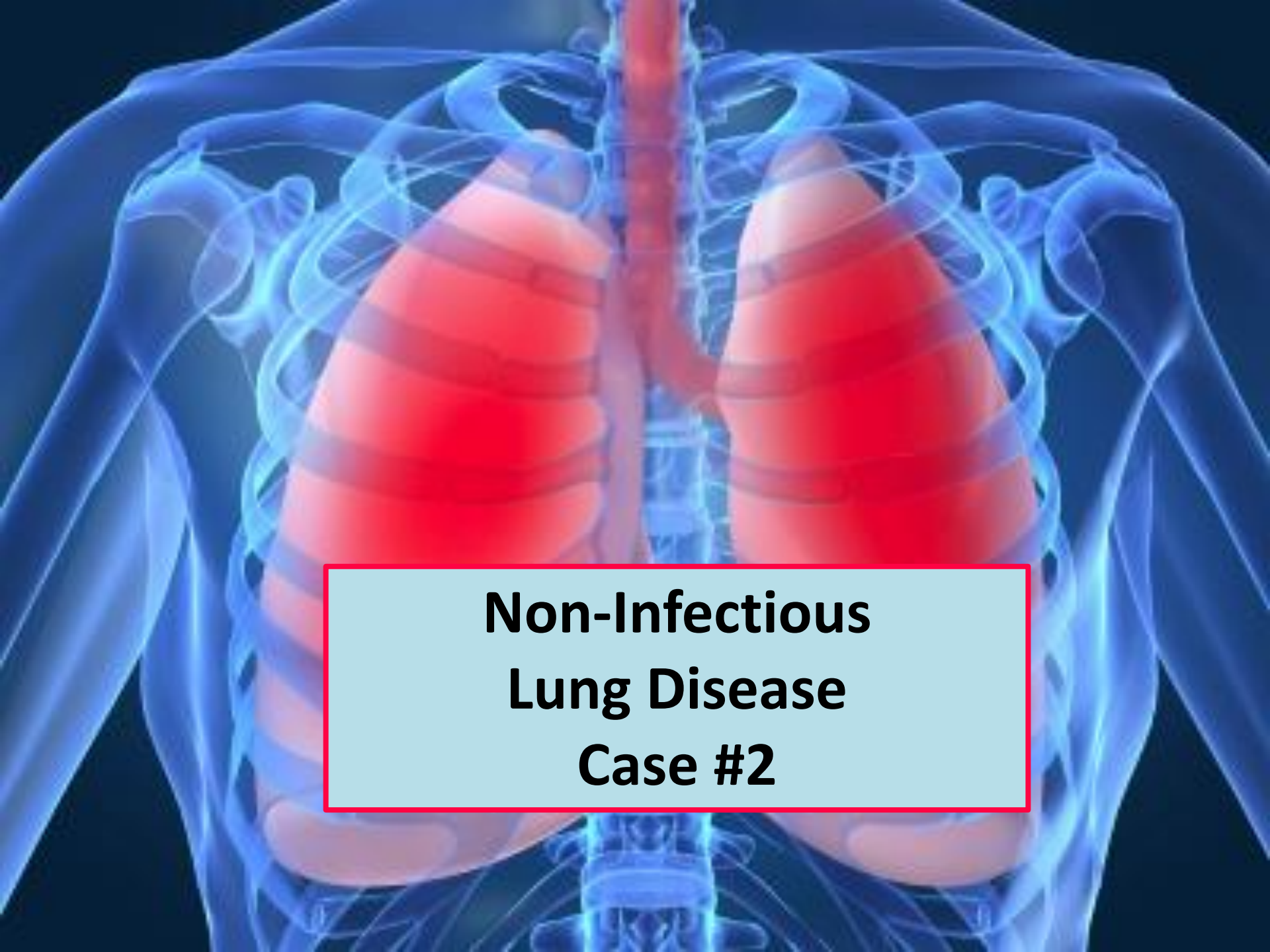
Subpleural Smoker's Fibrosis



Subpleural Smoker's Fibrosis

Trichrome Stain





Non-Infectious Lung Disease Case #2

History & Presentation

The Patient: 78 y.o. man

Medical Hx: HTN, Hepatitis C 2° to transfusion

Medications: albuterol, HCTZ

HPI: 2 mo. progressive fatigue & dyspnea; 20 pound wt loss

Social Hx: 20 pack-yr smoking history, quit 40 yrs ago

Occupational Hx: Retired from Army

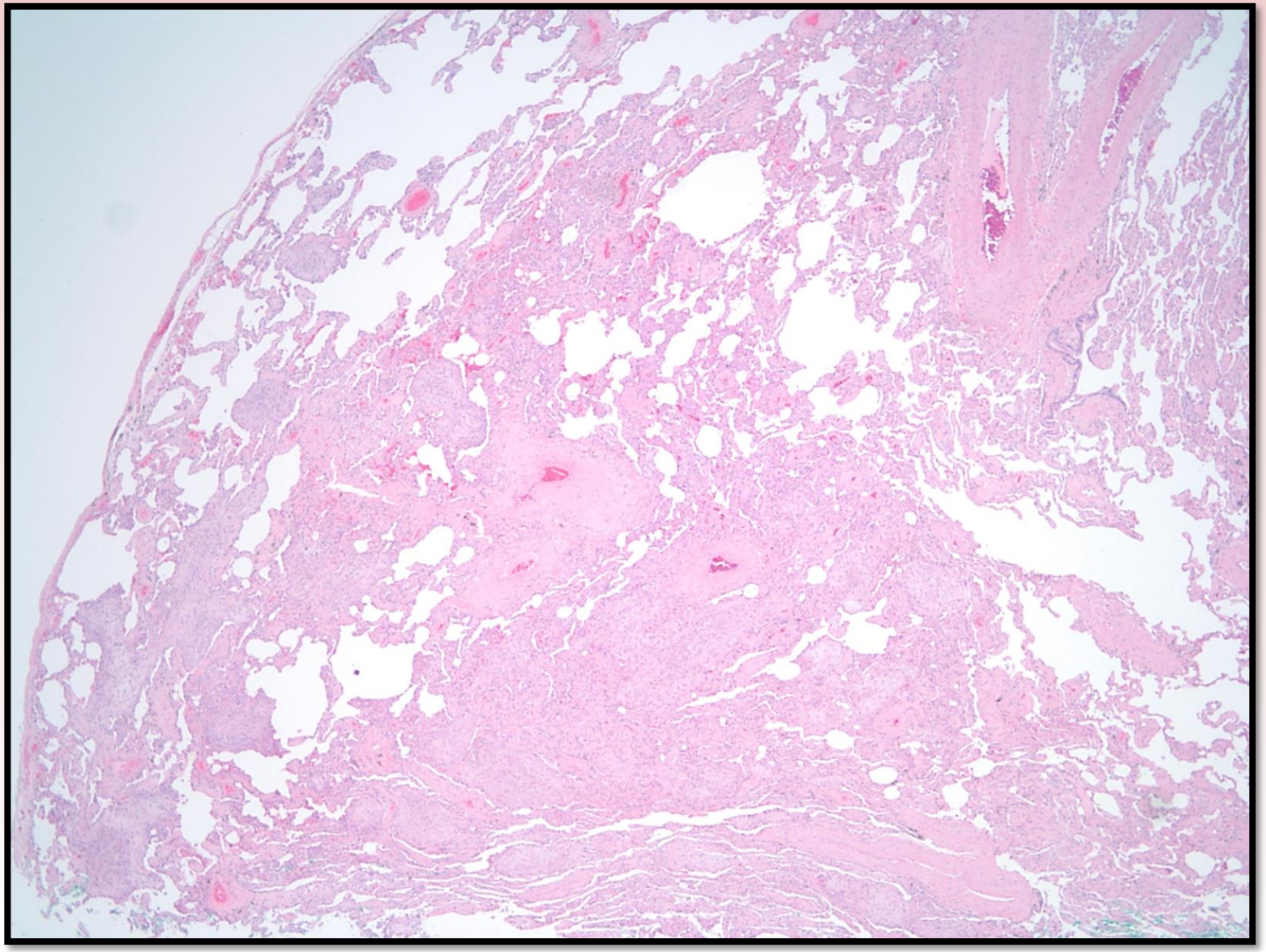
Objective: <u>CT Scan:</u> -Bilateral crazy paving GGOs R>L
upper lobe predominate
-Bilateral pleural effusions (large on L)
-RML spiculated nodule (2.1 cm)

<u>CBC & Chem Panel:</u> WNL

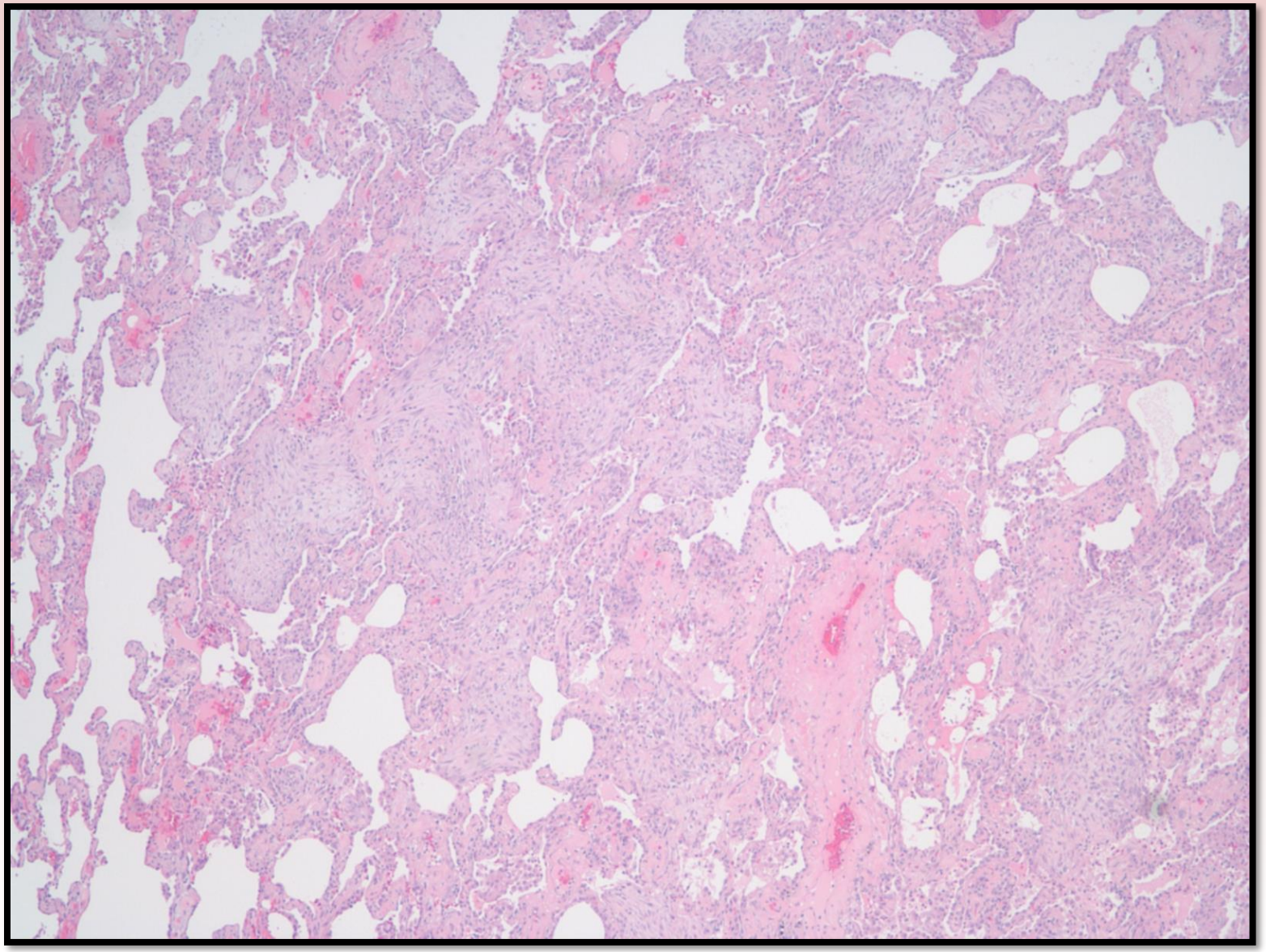
<u>Thoracentesis Cytology:</u> Results not available

LUL & LLL Wedge Biopsies Are Performed.

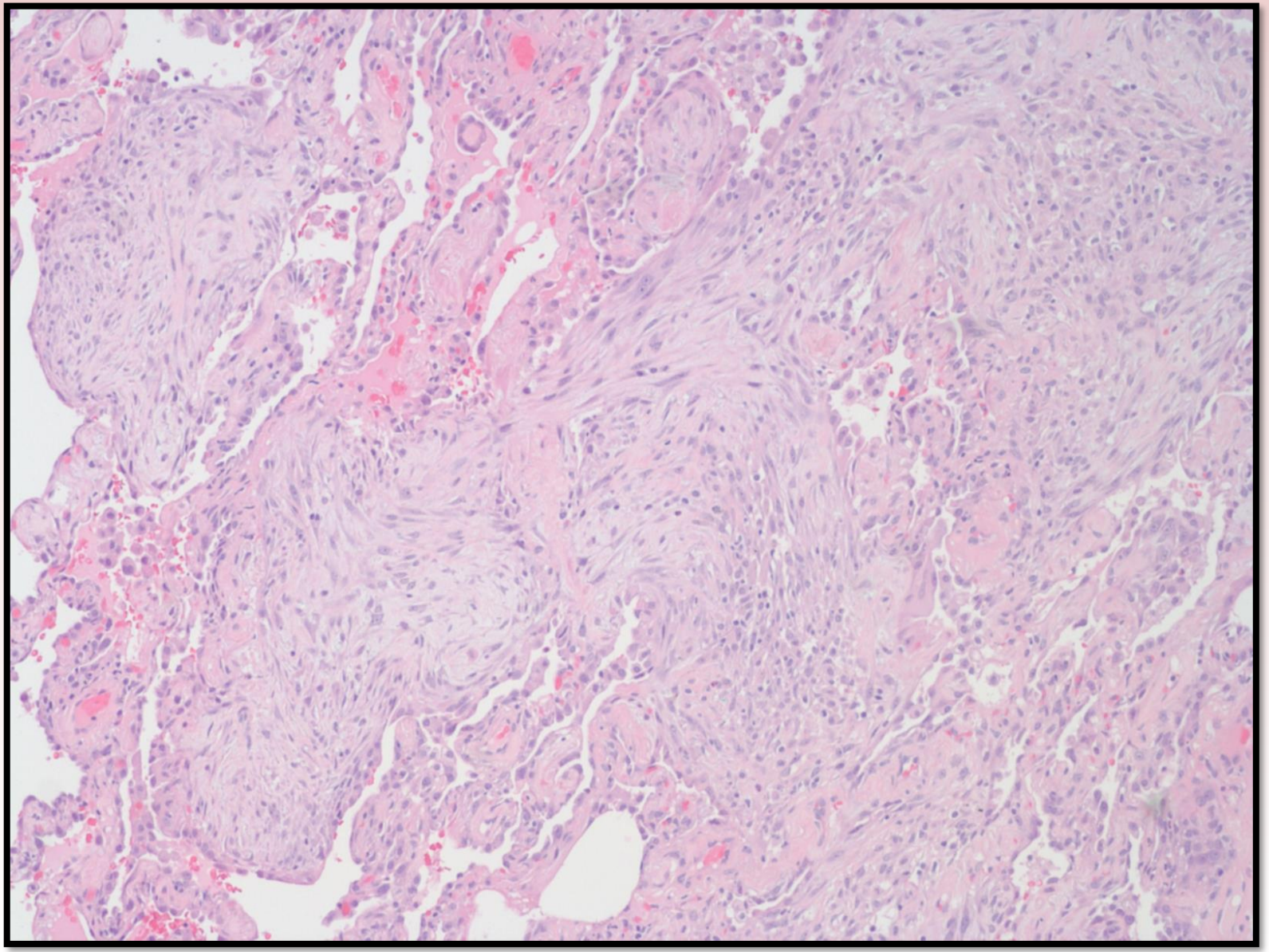
LUL Wedge Biopsy



LUL Wedge Biopsy

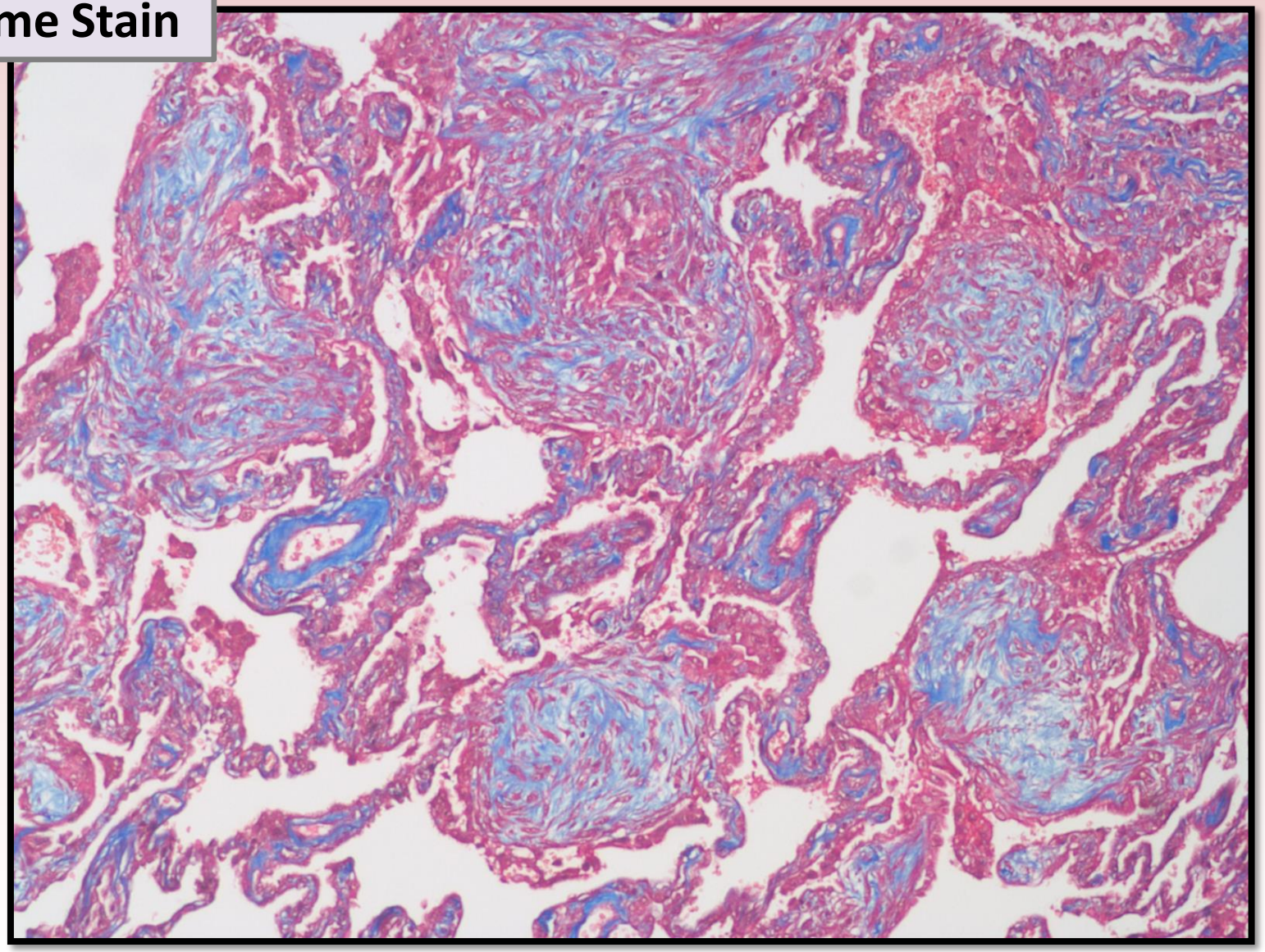


LUL Wedge Biopsy

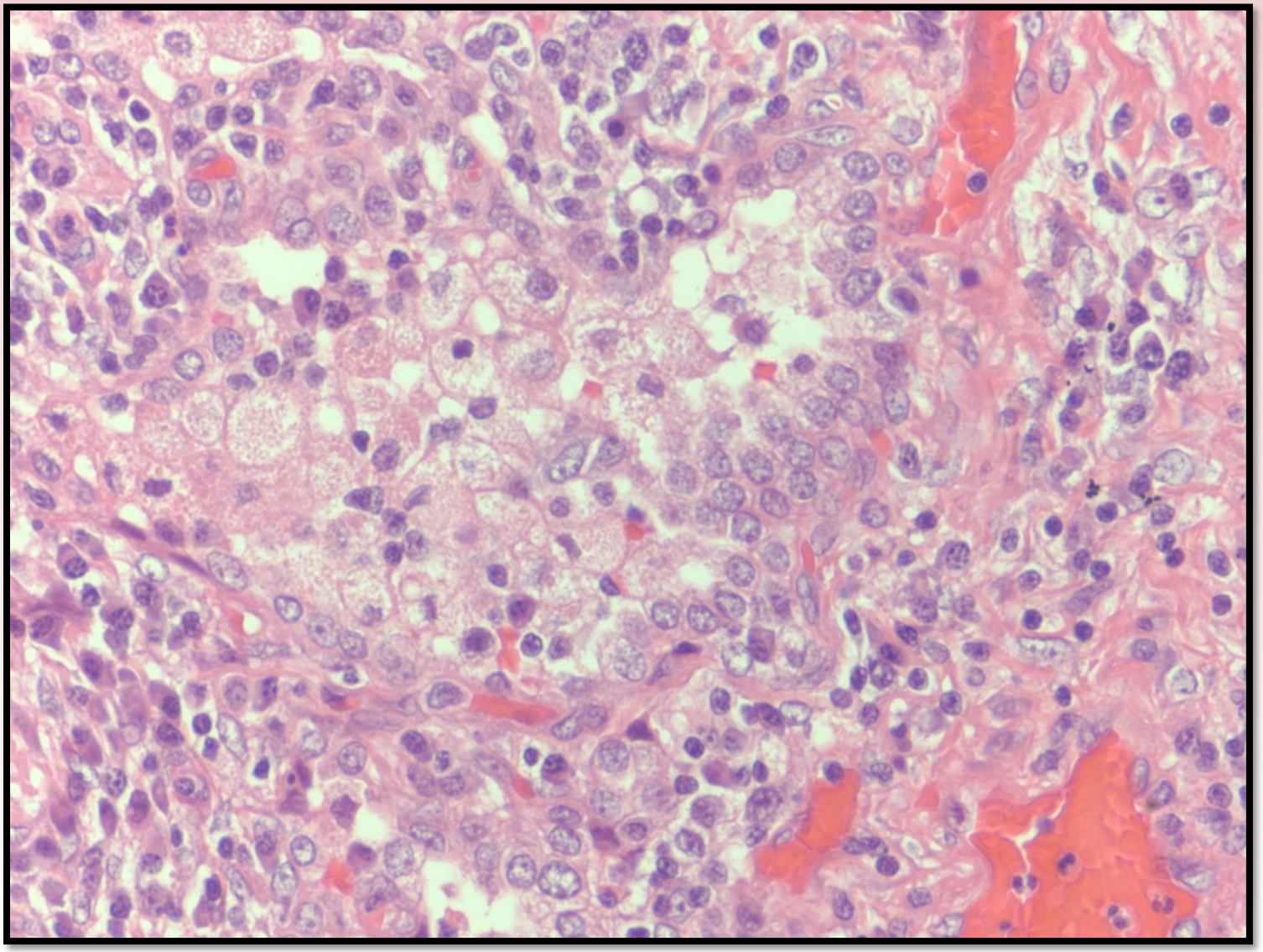


LUL Wedge Biopsy

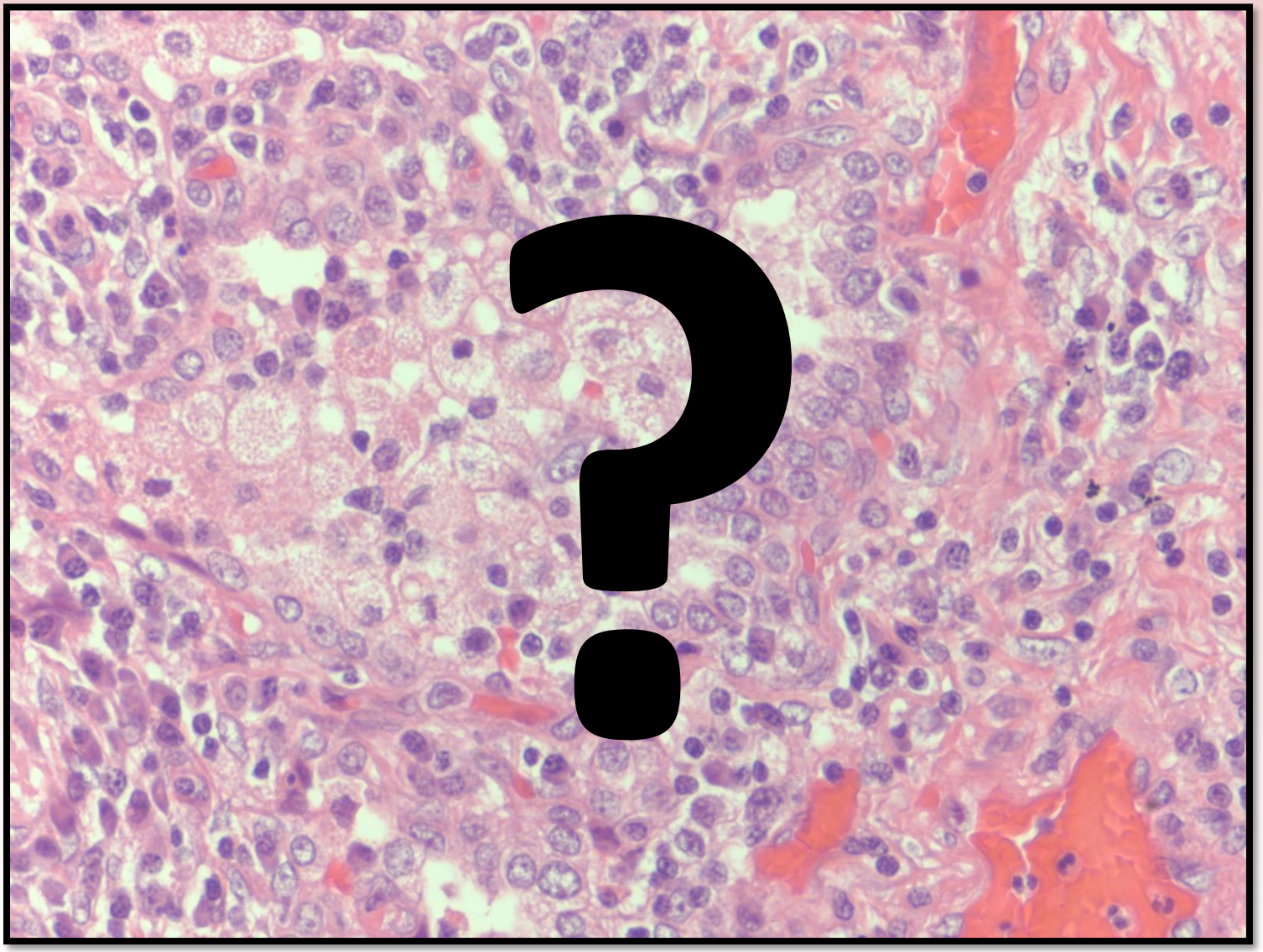
Trichrome Stain



LUL Wedge Biopsy



LUL Wedge Biopsy



Organizing PNA

- **Reaction to injury**
  - Infection, Inhaled toxins, Drugs, Radiation, Aspiration
  - Idiopathic (COP)
- **Patchy distribution of fibrosis**
  - Myofibroblastic proliferations in pale matrix
  - Airspace filling
  - Round, oval or serpiginous plugs (light pink/grey)
  - Epithelialization of plugs
- **Proteinaceous airspace exudates**
- **Post-obstructive lipoid (endogenous) PNA**
  - Foamy macrophages

Organization Differential

Finding	Acute DAD	Organizing DAD	OP	UIP
Hyaline Membranes	Extensive	Focal	No	No
Fibroblast Proliferation	No	Extensive Interstitial	Patchy Intraluminal	Yes Interstitial
Thrombi	Common	Common	No	No
Metaplasia	Yes	Yes	No	No
Peribronchiolar Distribution	No	No	Yes	No
Collagen deposition	No	No	No	Yes
Honeycomb Change	No	No	No	Yes

DAD Timeline

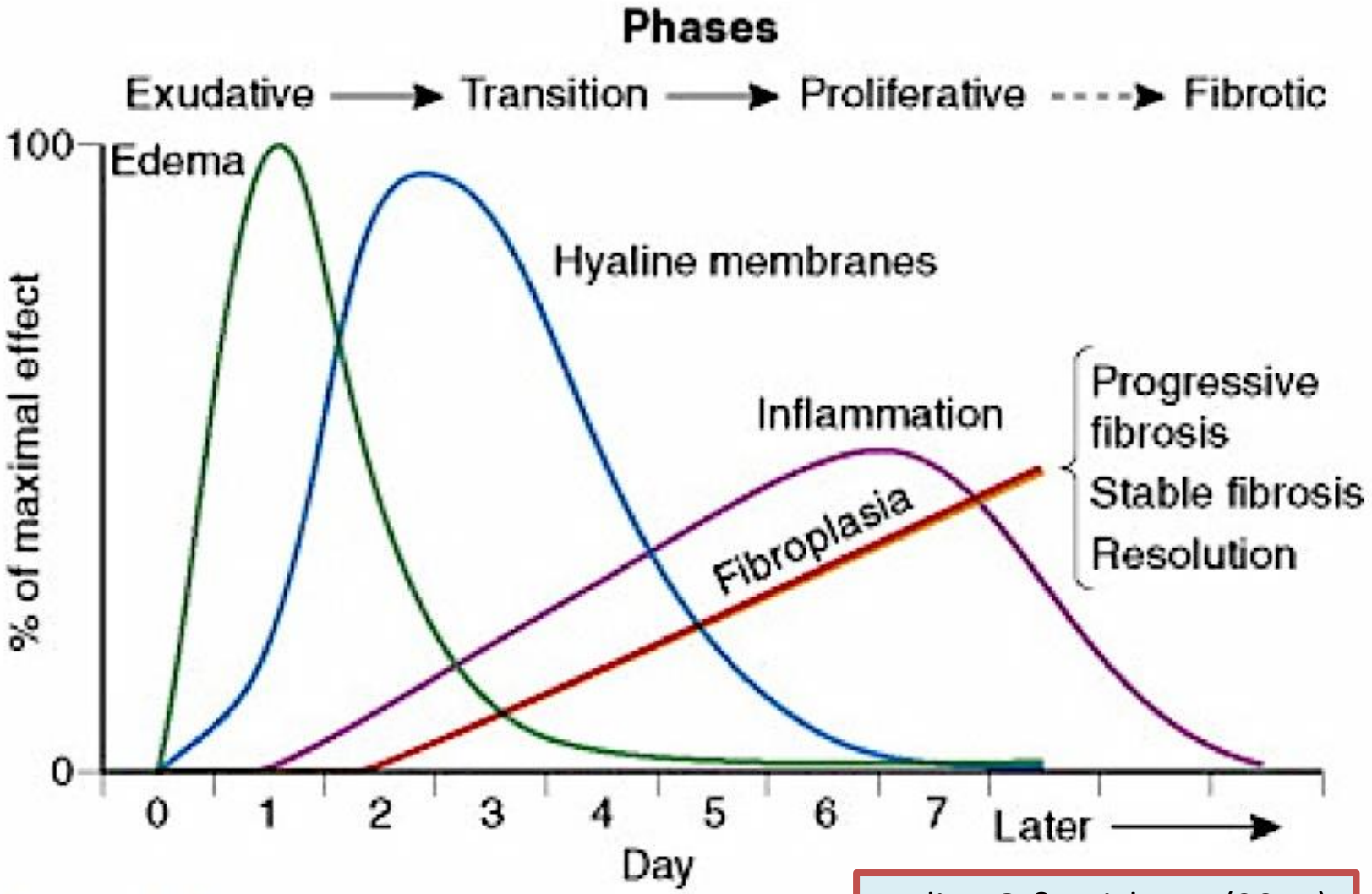
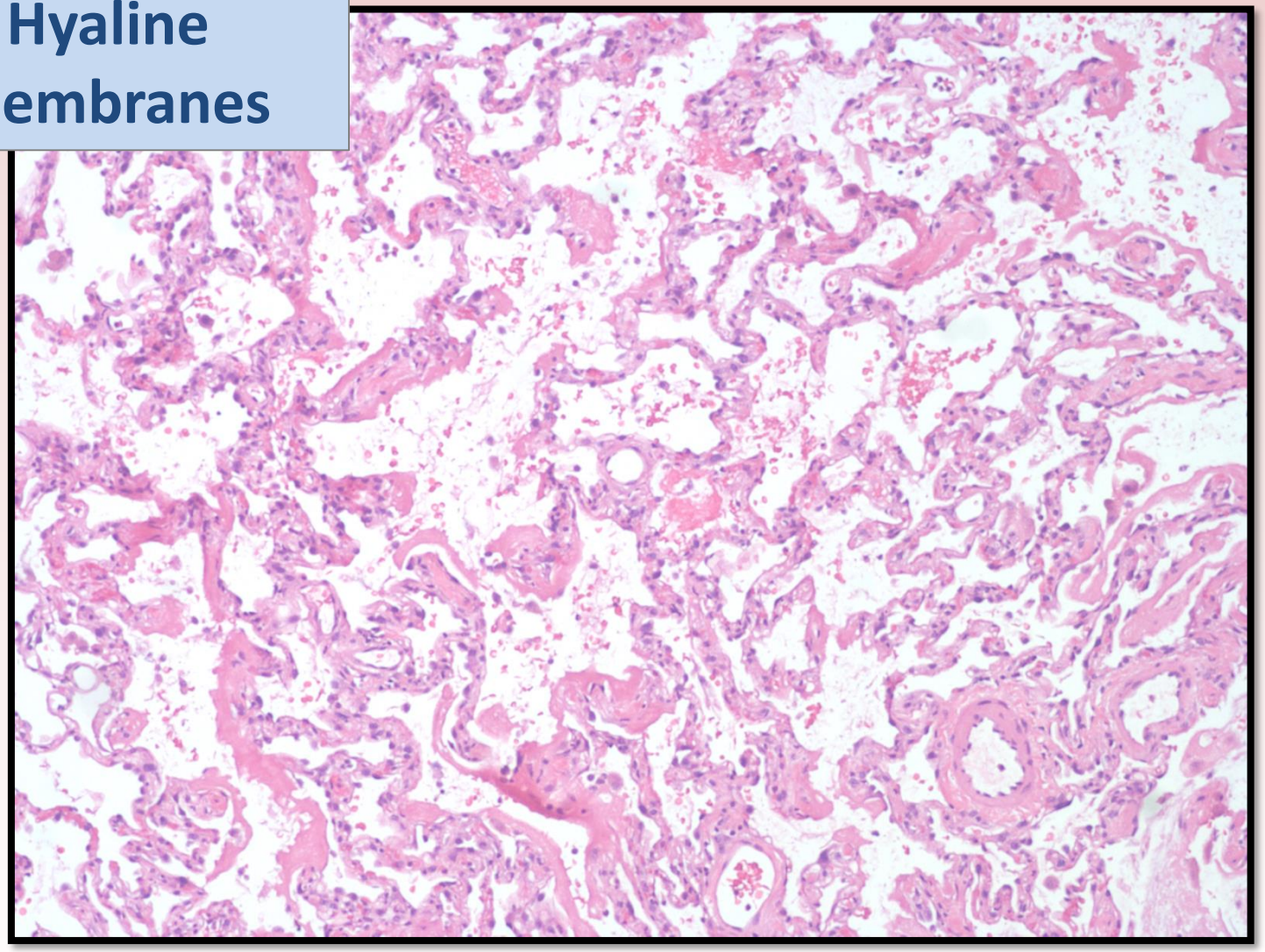


Figure 5-1

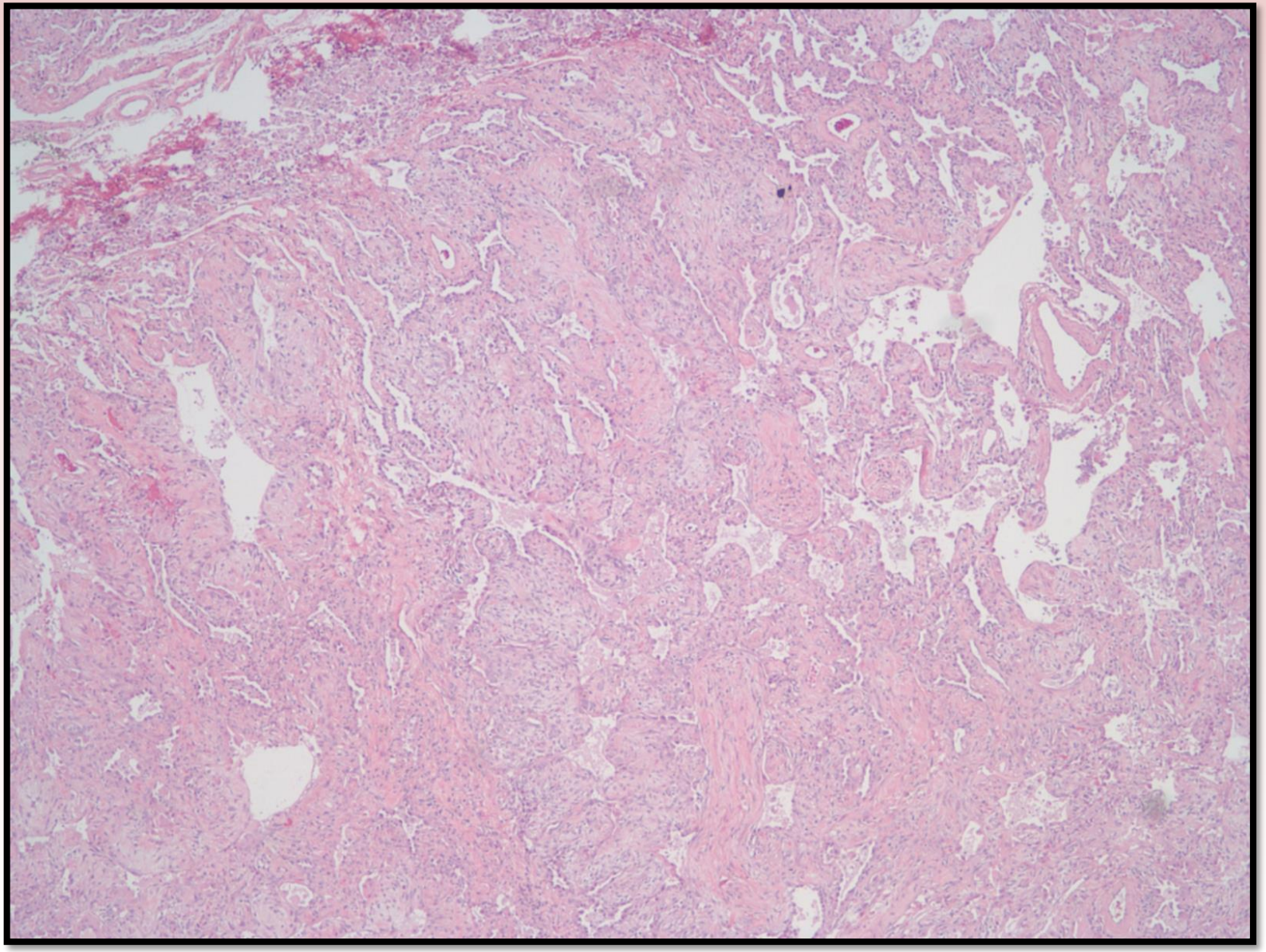
Leslie KO & Wick MR (2011)

Acute DAD

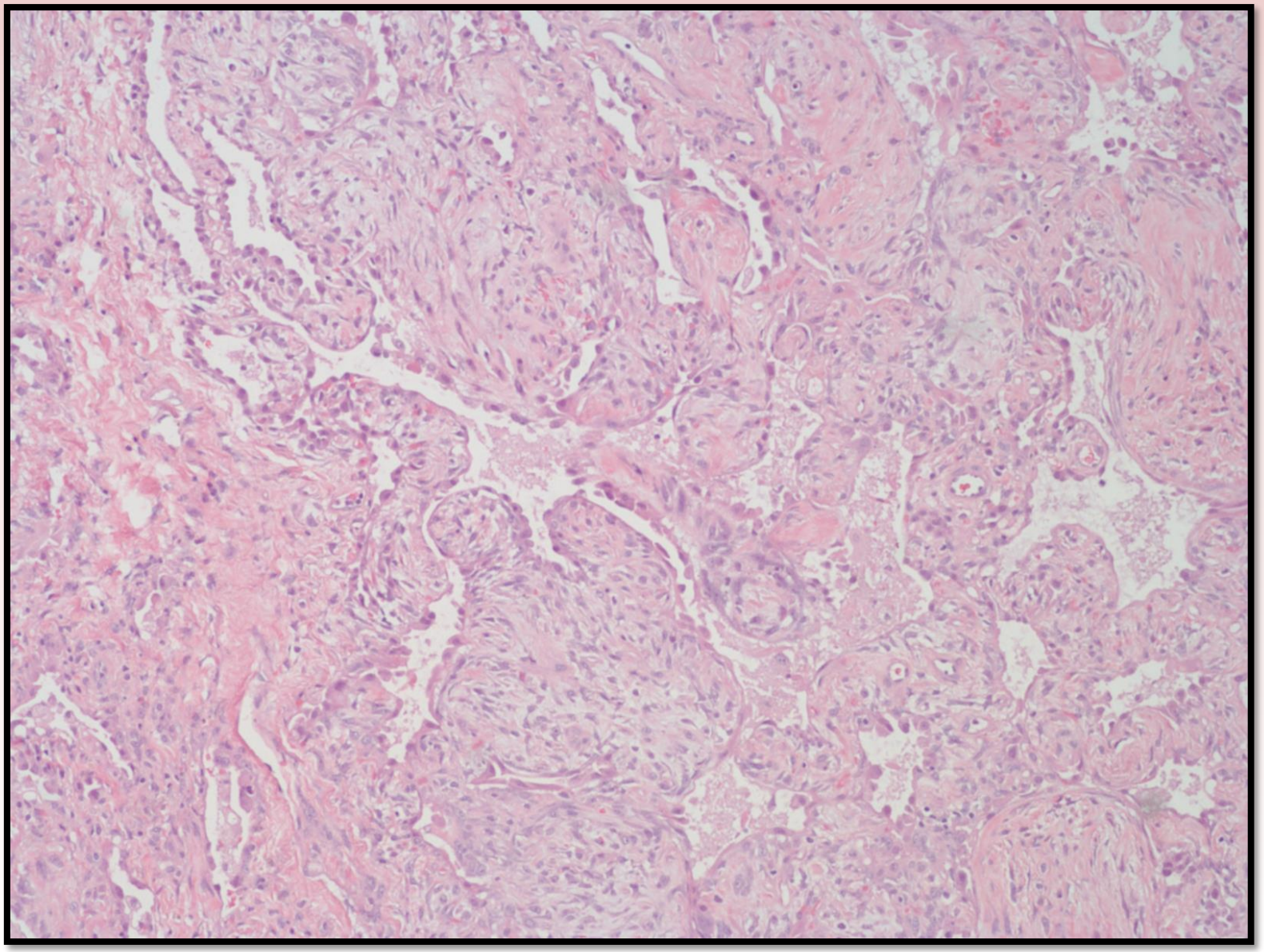
Hyaline Membranes



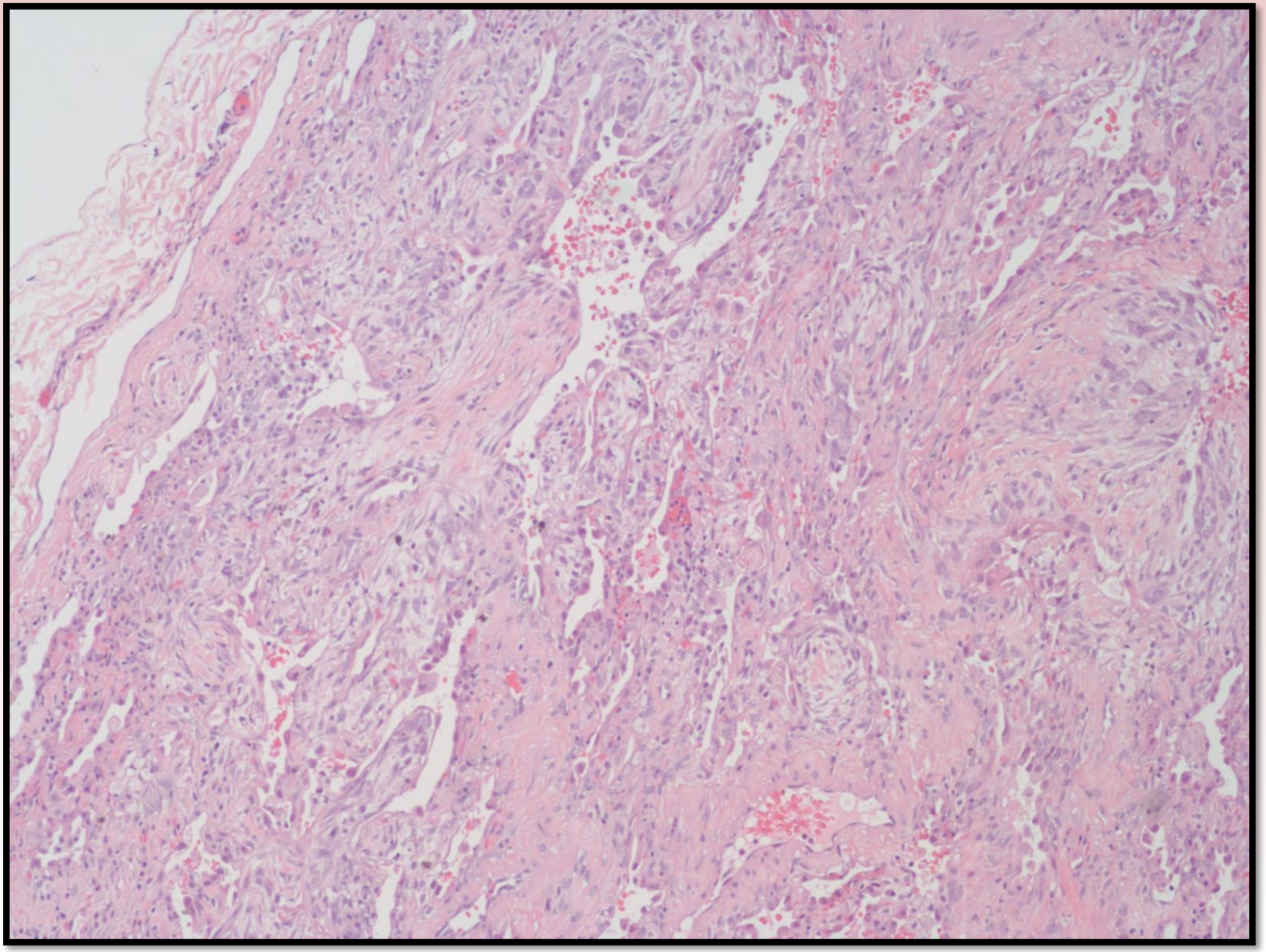
Organizing DAD



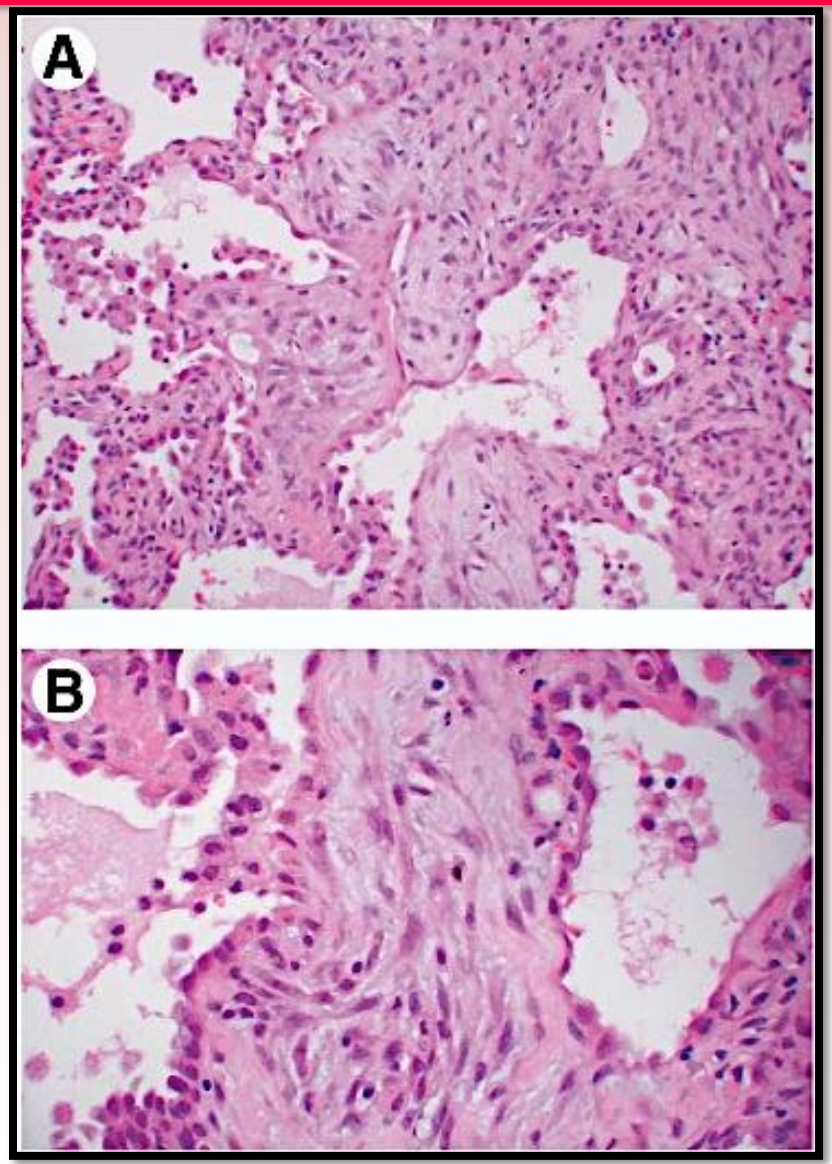
Organizing DAD



Organizing DAD



DAD: O/P Phase



EARLY PROLIFERATIVE PHASE

Incorporation of Hyaline Membranes into Septa

Epithelium Growing over Hyaline Membrane

Castro *Semin Thorac Cardiovasc Surg* (2006)

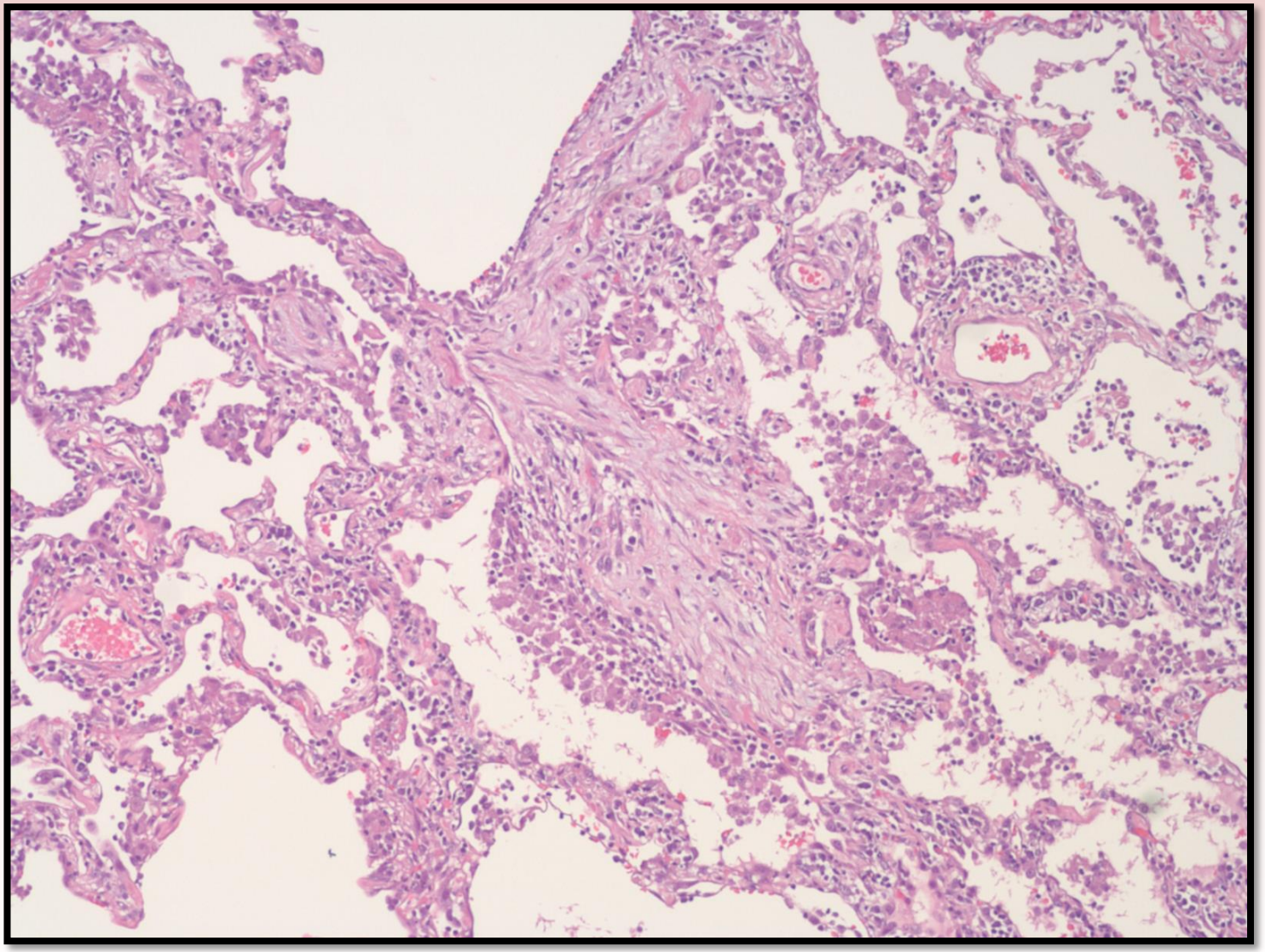
AFOP

Table 2. Histologic Features of Acute Fibrinous and Organizing Pneumonia

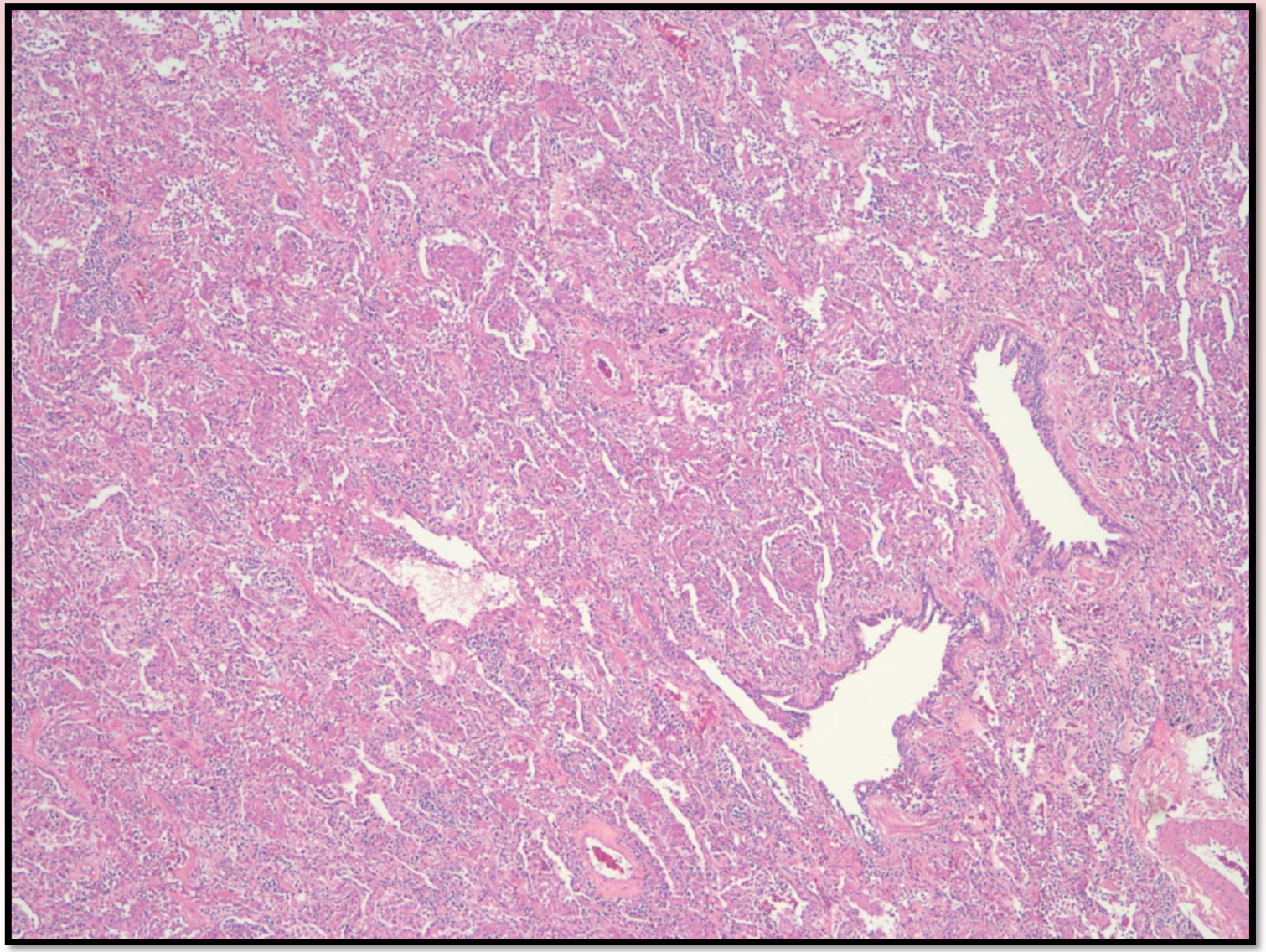
- Major features
  - ★ Dominant finding of organizing intra-alveolar fibrin
  - ★ Organizing pneumonia
  - ★ Patchy distribution
- Minor features
  - Associated interstitial changes
    - Acute and/or chronic inflammation
    - Type 2 pneumocyte hyperplasia
    - Alveolar septal expansion with myxoid connective tissue
  - Interstitial inflammation and expansion typically mild to moderate
  - Interstitial changes primarily confined to areas adjacent to intra-alveolar fibrin with the intervening lung showing only minimal changes
- Pertinent negatives
  - ★ Hyaline membranes NOT observed
  - Eosinophils inconspicuous or absent
  - Extensive bronchopneumonia and/or abscess formation absent
  - Granulomatous inflammation absent

Beasely MB et al. *Arch Pathol Lab Med* (2002)

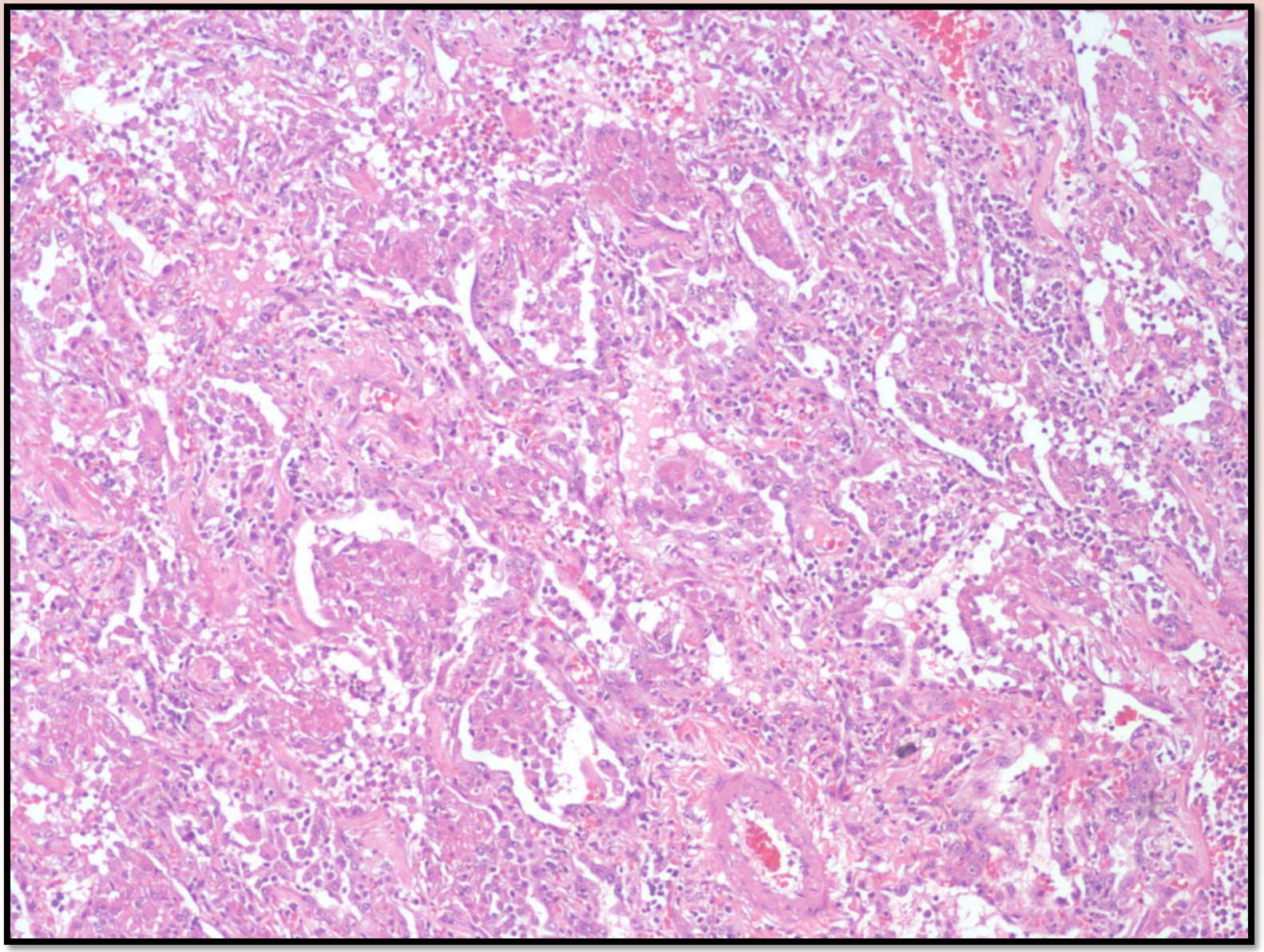
AFOP



AFOP – Fibrin Balls

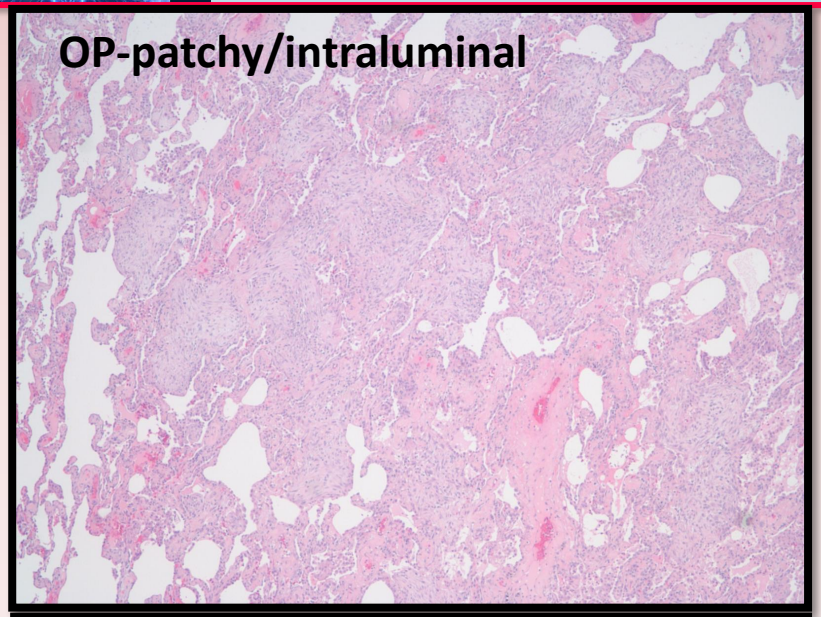


AFOP – Fibrin Balls

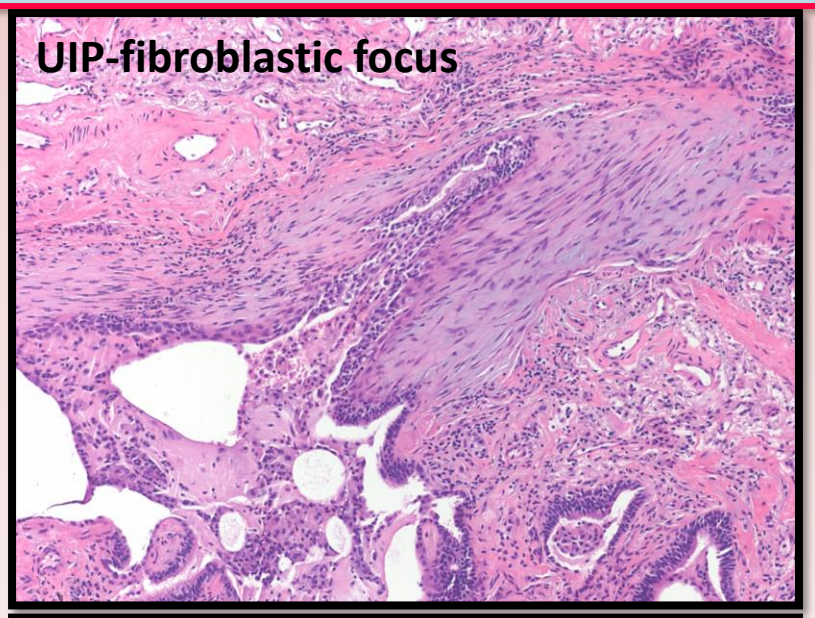


Summary

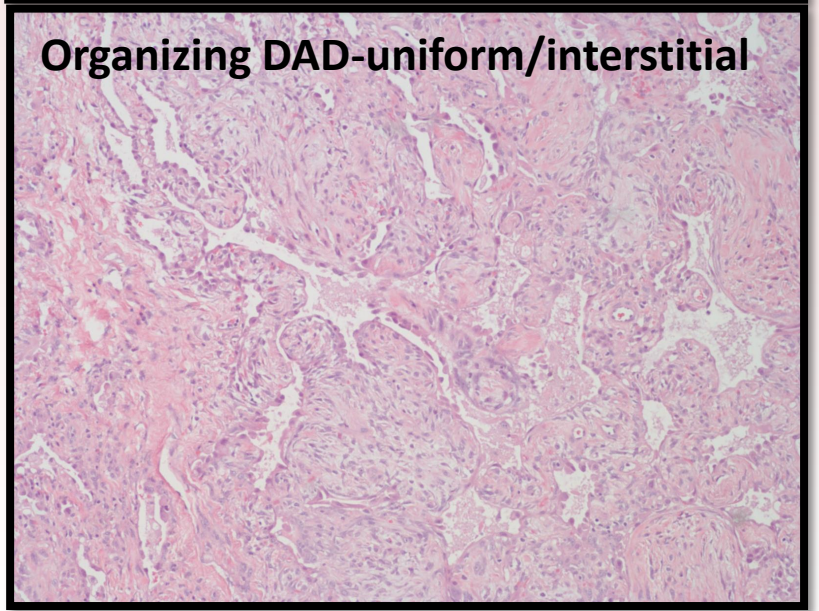
OP-patchy/intraluminal



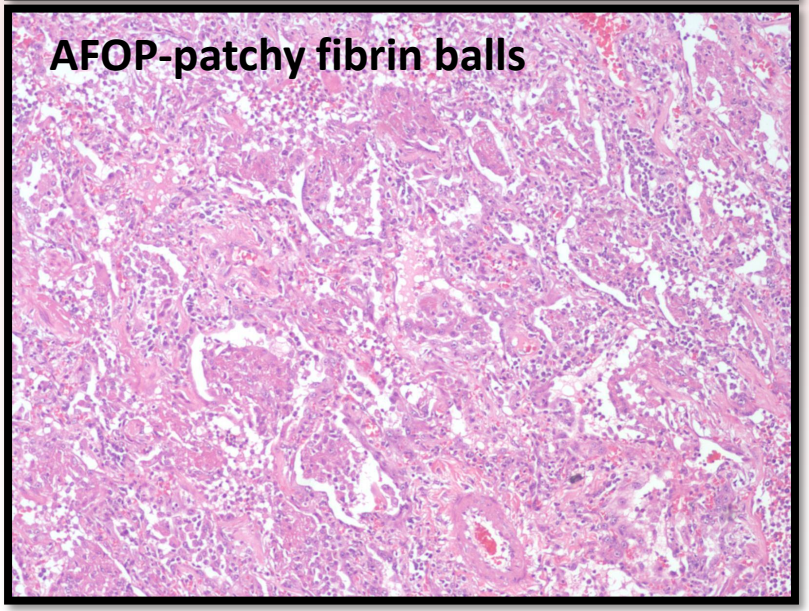
UIP-fibroblastic focus

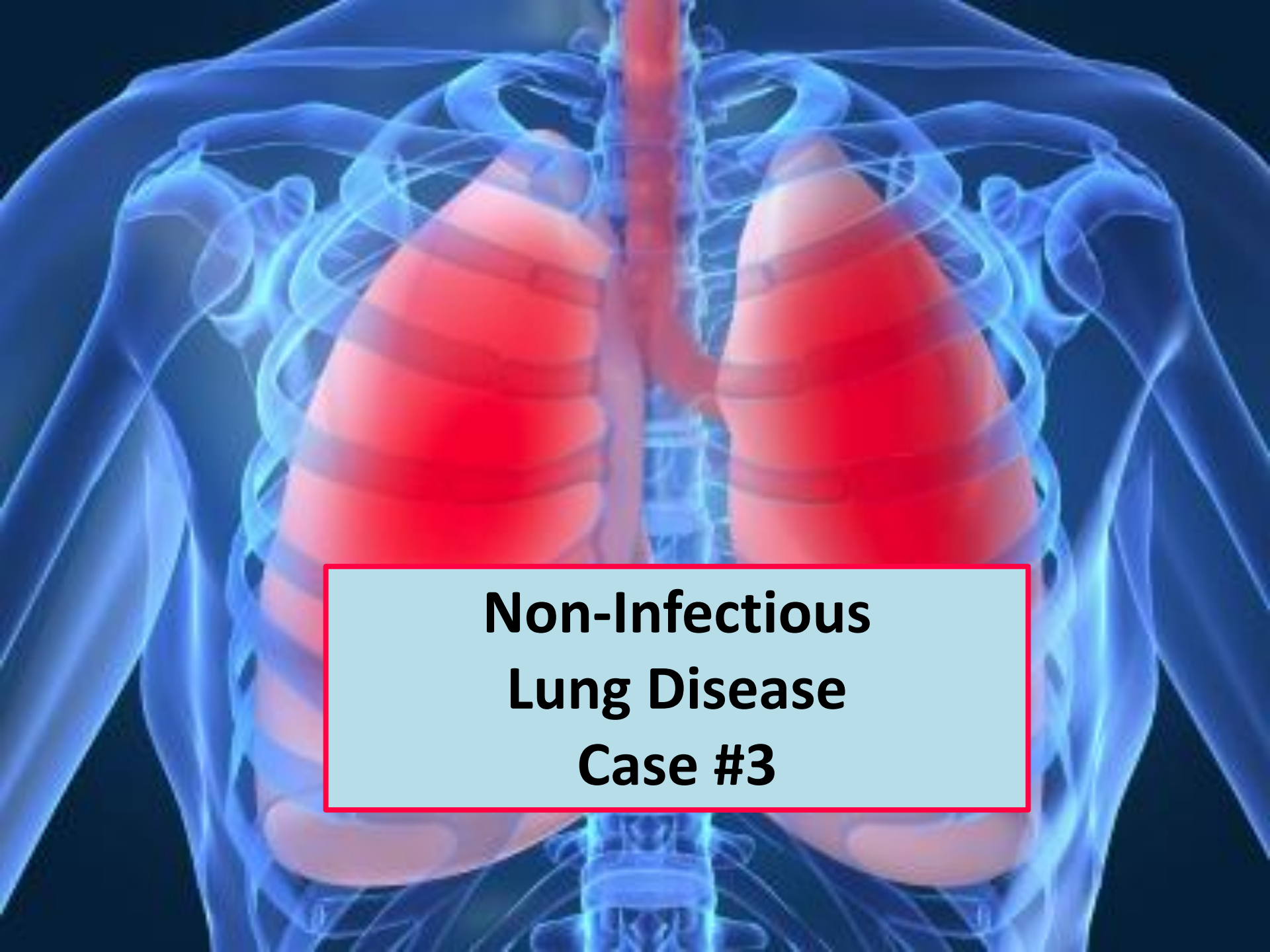


Organizing DAD-uniform/interstitial



AFOP-patchy fibrin balls





Non-Infectious Lung Disease Case #3

History & Presentation

The Patient: 59 y.o. man

Medical Hx: COPD, Metal fume fever, Occupational asthma

Medications: Inhalers

HPI: Progressive SOB & increased O_2 requirement ~2 yrs

SocHx: 3 PPD Smoker, Quit 6 yrs ago

OccHx: Unknown, Exposed to Toluene Diisocyanate & Methylene Diphenyl Diisocyanate

Objective: -Chest CT: Emphysematous changes

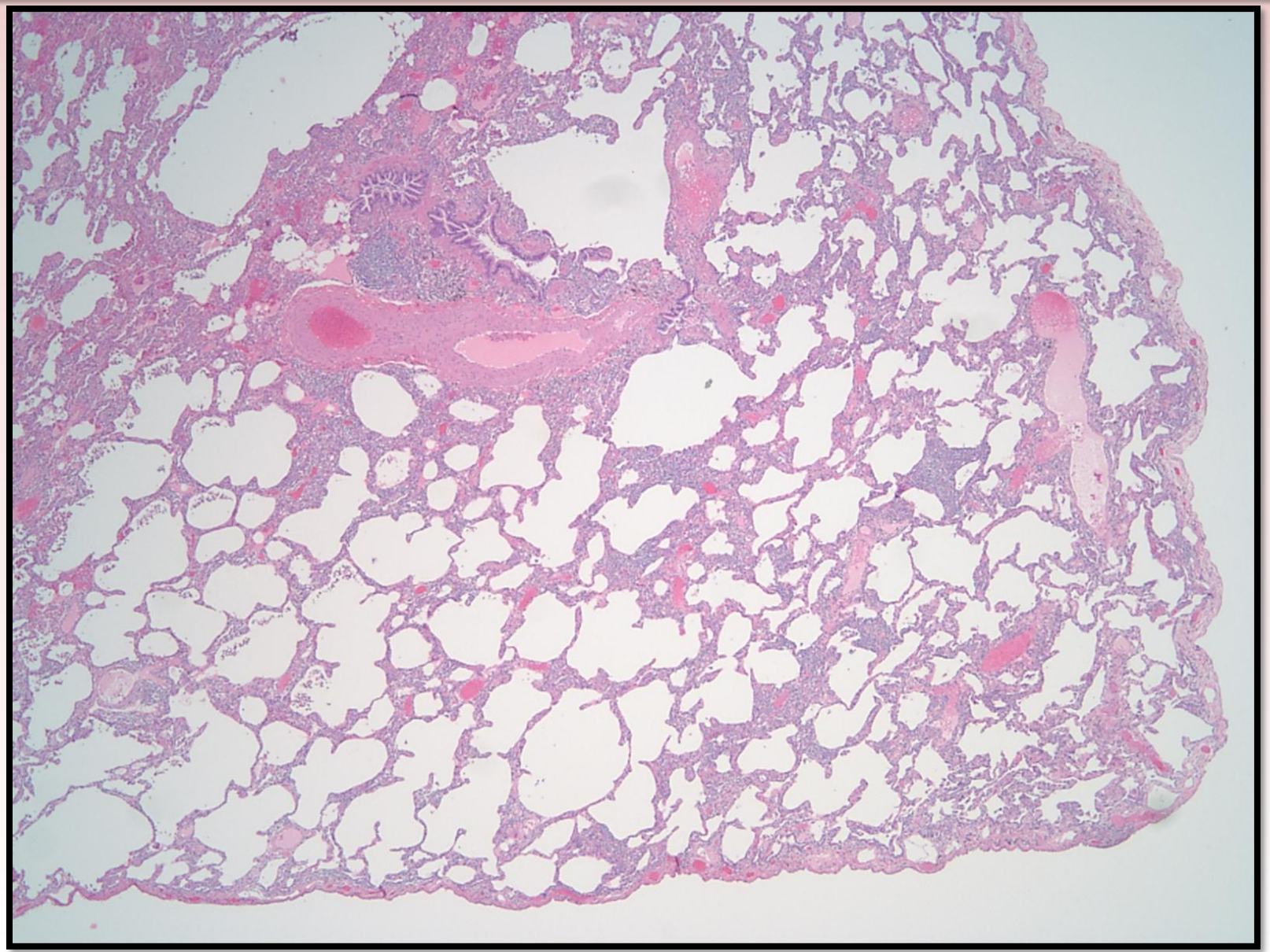
-Cardiac Catheterization: Negative

-PFTs: ↓DLCO from 63% to 54% pred.

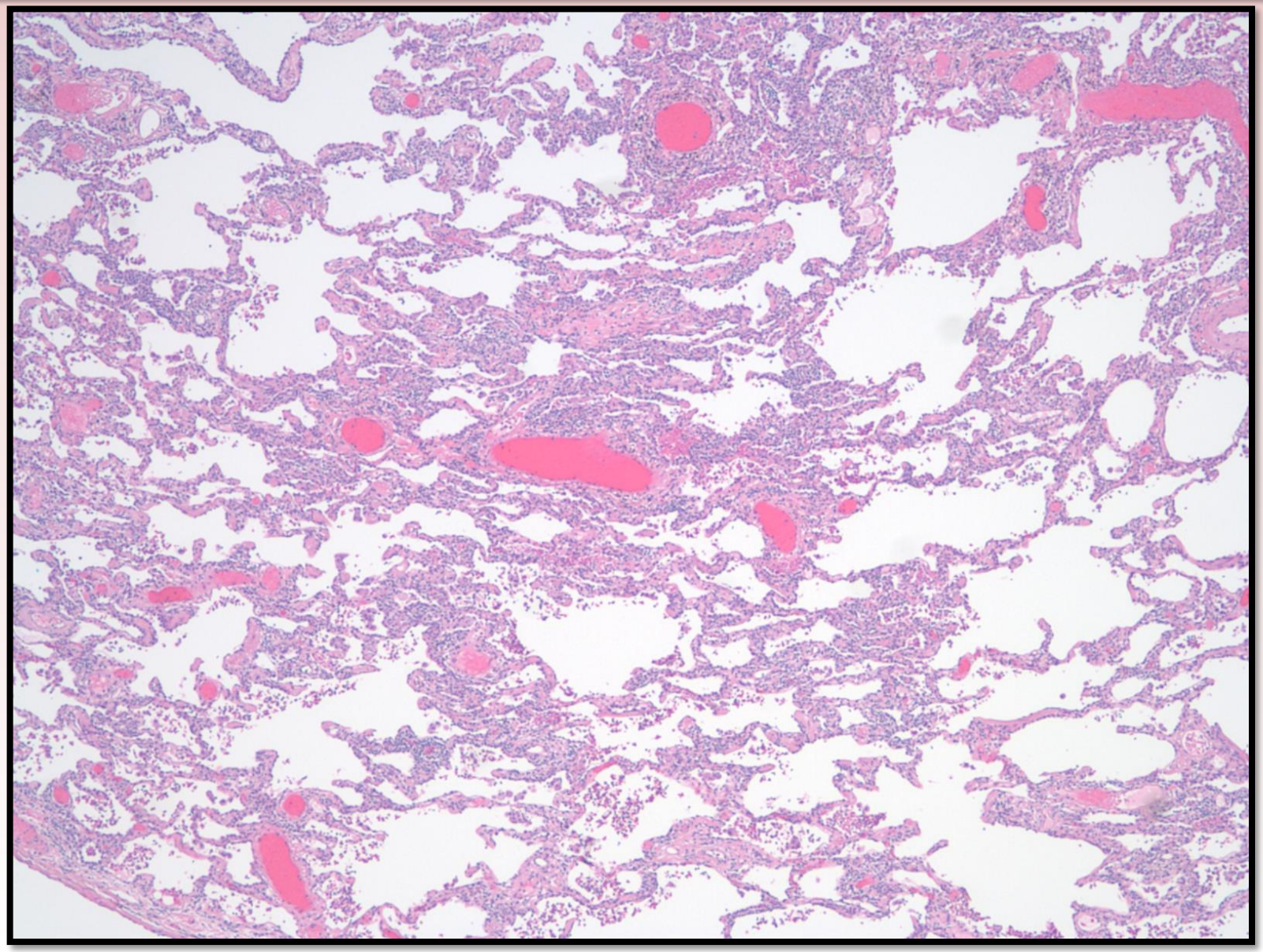
↓ TLC from 86% to 79% pred.

A RUL Wedge Biopsy Is Performed.

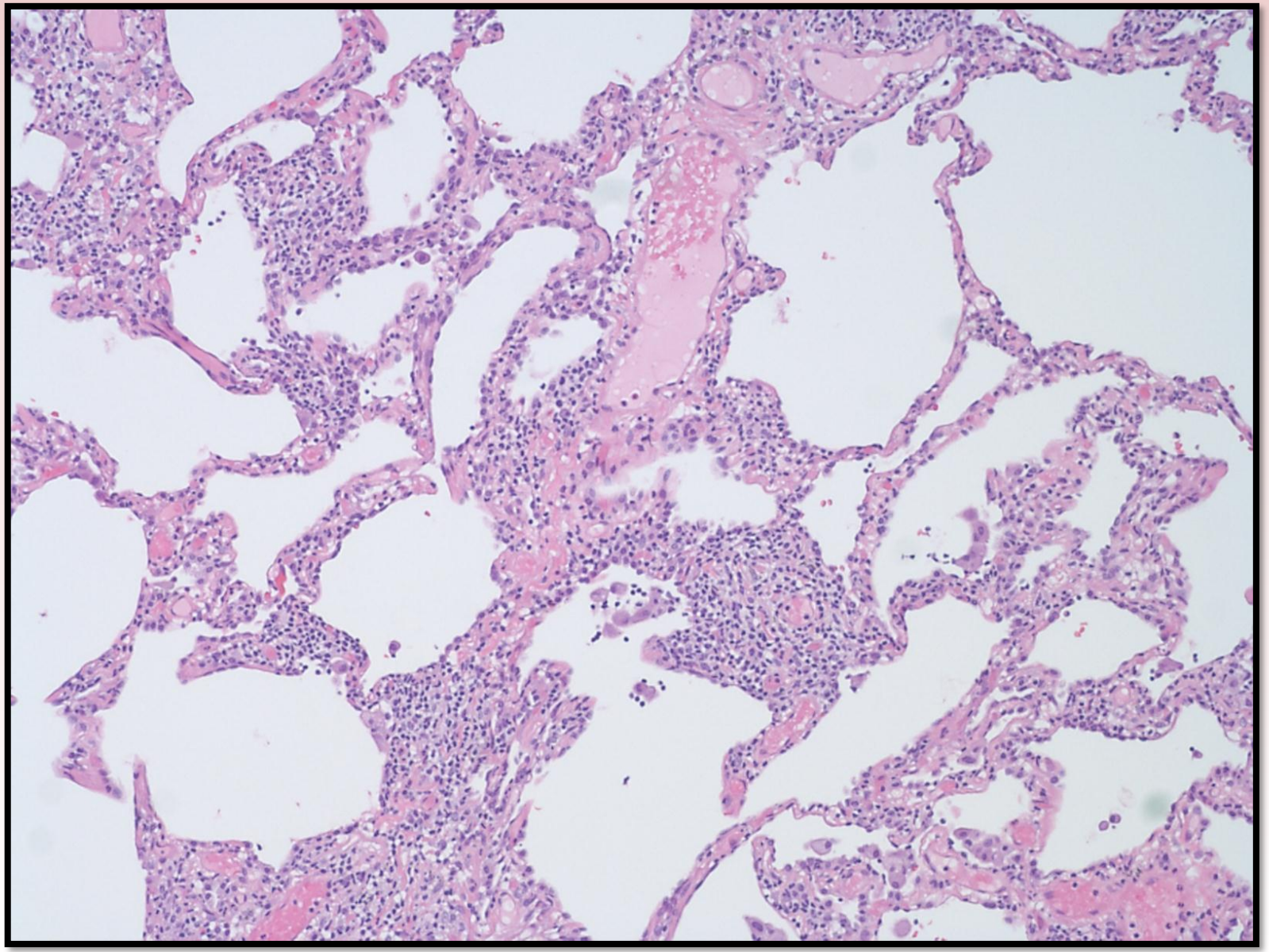
RUL Wedge Biopsy



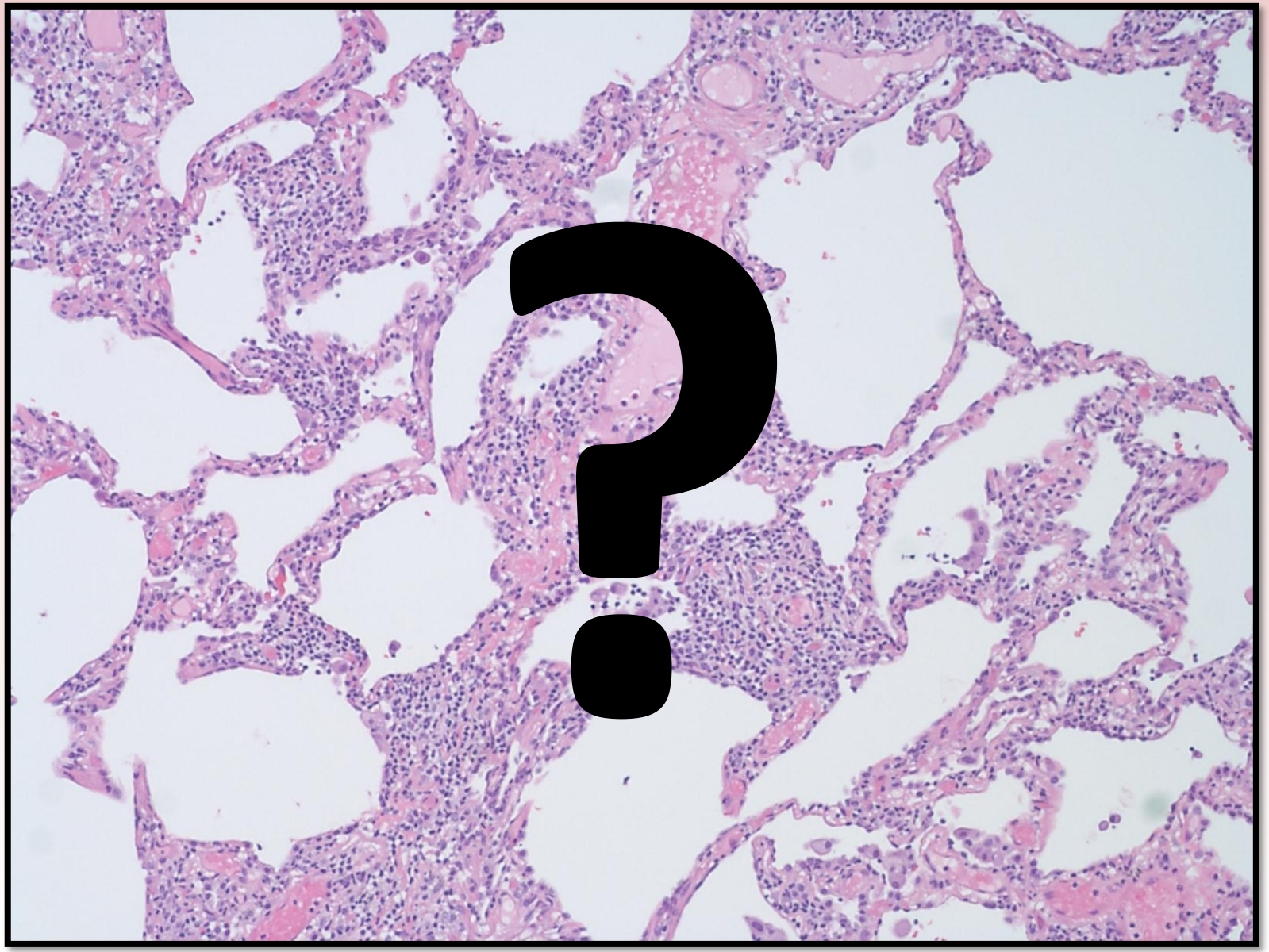
RUL Wedge Biopsy



RUL Wedge Biopsy



RUL Wedge Biopsy



Cellular NSIP

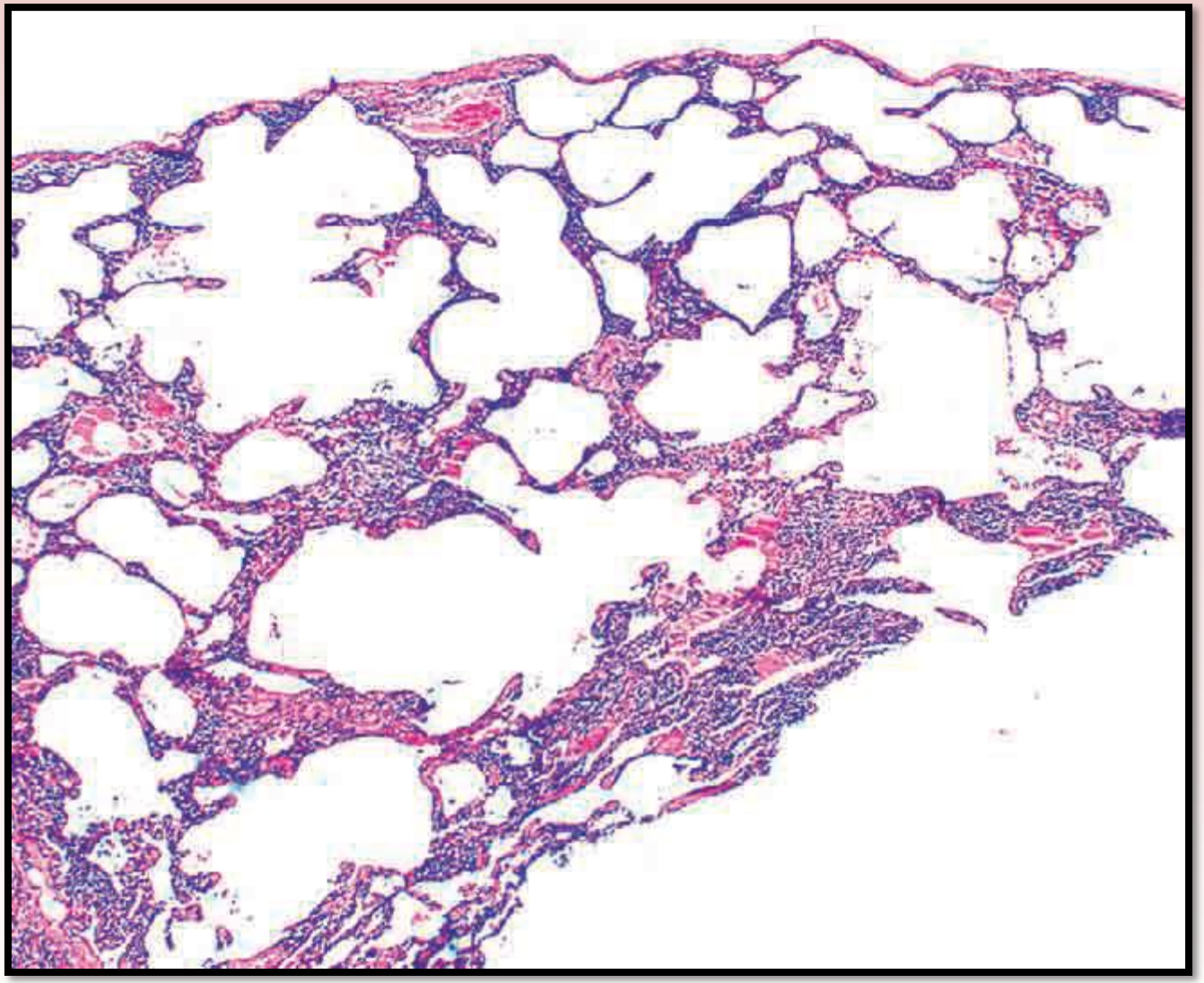
- **Clinical Outcome:** Better than Fibrotic NSIP
- **Pattern:**
  - Bilateral
  - Symmetrical
  - Often Lower Lobe Predominate
- **Uniform alveolar-septal thickening**
  - Collagen deposition
  - Prominent cellular infiltrate
- **Intraalveolar macrophages**
- **Focal proteinaceous exudate**

LIP vs. HP vs. NSIP

Feature	LIP	Cellular NSIP	HP
Dense infiltrate distorts alveolar septa	Usual	No	No
Peribronchiolar accentuation of interstitial infiltrate	No	Common	Usual
Organizing Pneumonia foci	No	Common	Common
Histiocytes/ Non-necrotizing Granulomas	Common	No	Common
Germinal centers	Usual	Uncommon	Uncommon

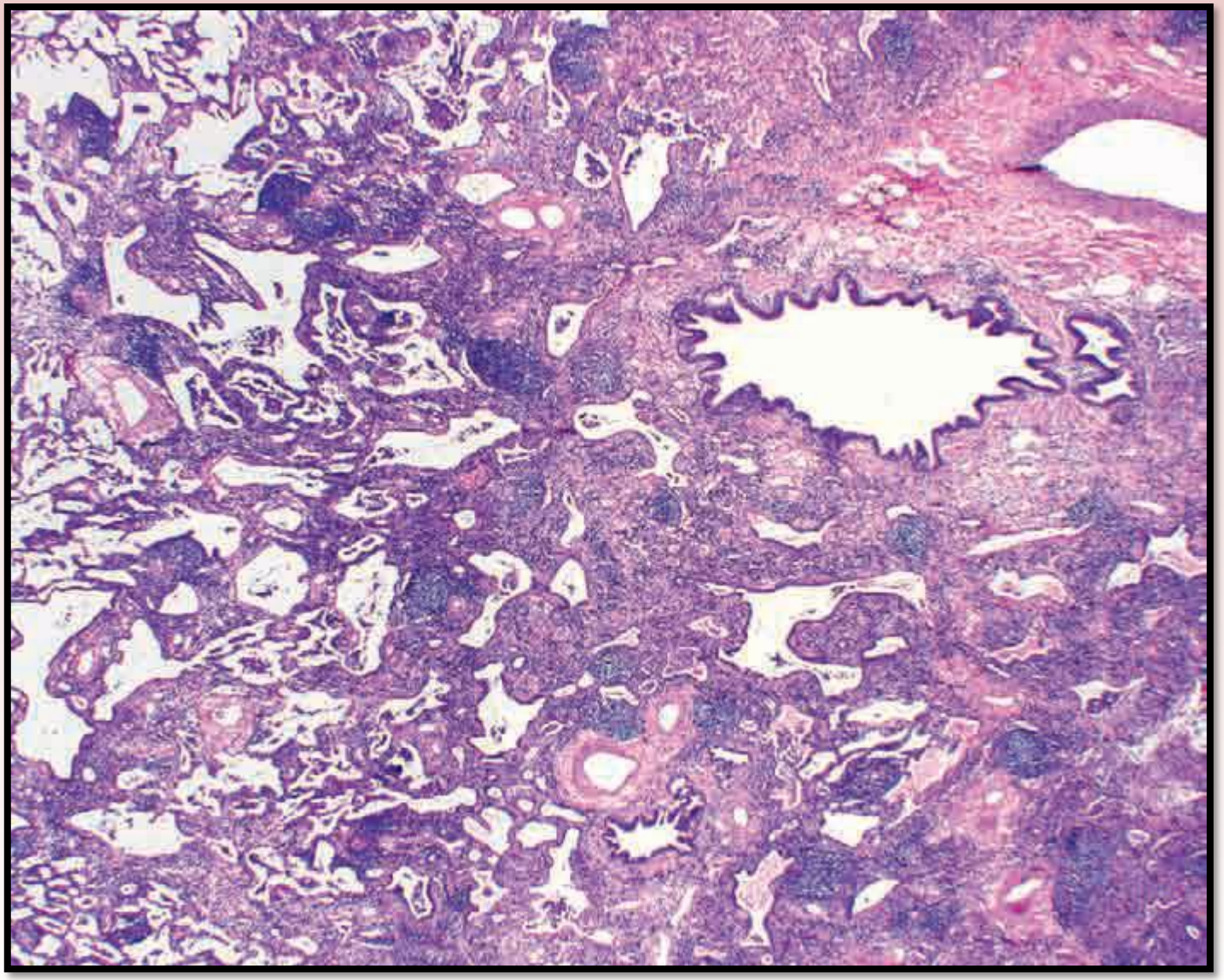
A-L. Katzenstein's *Non-Neoplastic Lung Disease* (2006)

Lymphoid Interstitial PNA



Leslie & Wick *Practical Pulmonary Pathology* (2011)

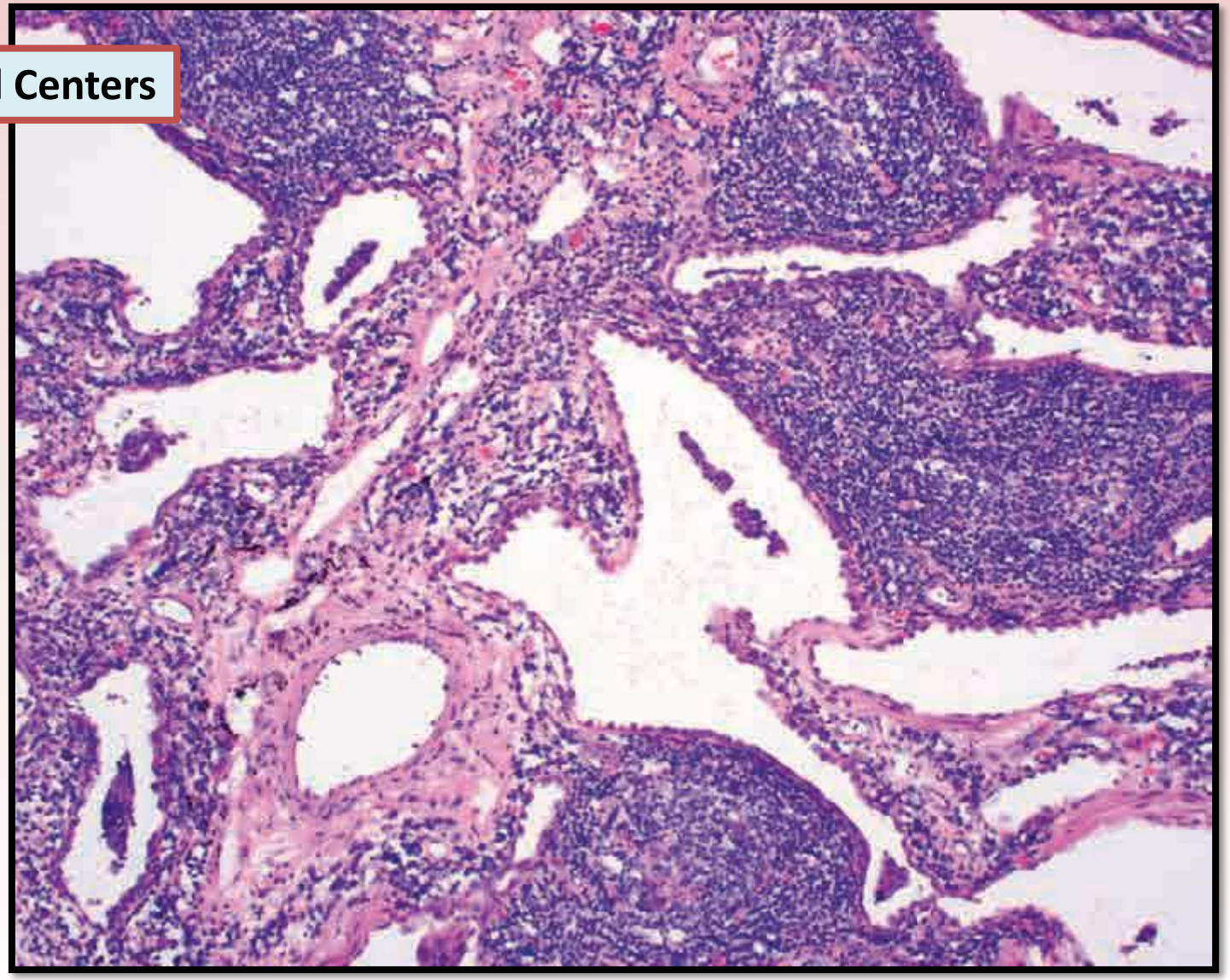
Lymphoid Interstitial PNA



Leslie & Wick *Practical Pulmonary Pathology* (2011)

Lymphoid Interstitial PNA

Germinal Centers



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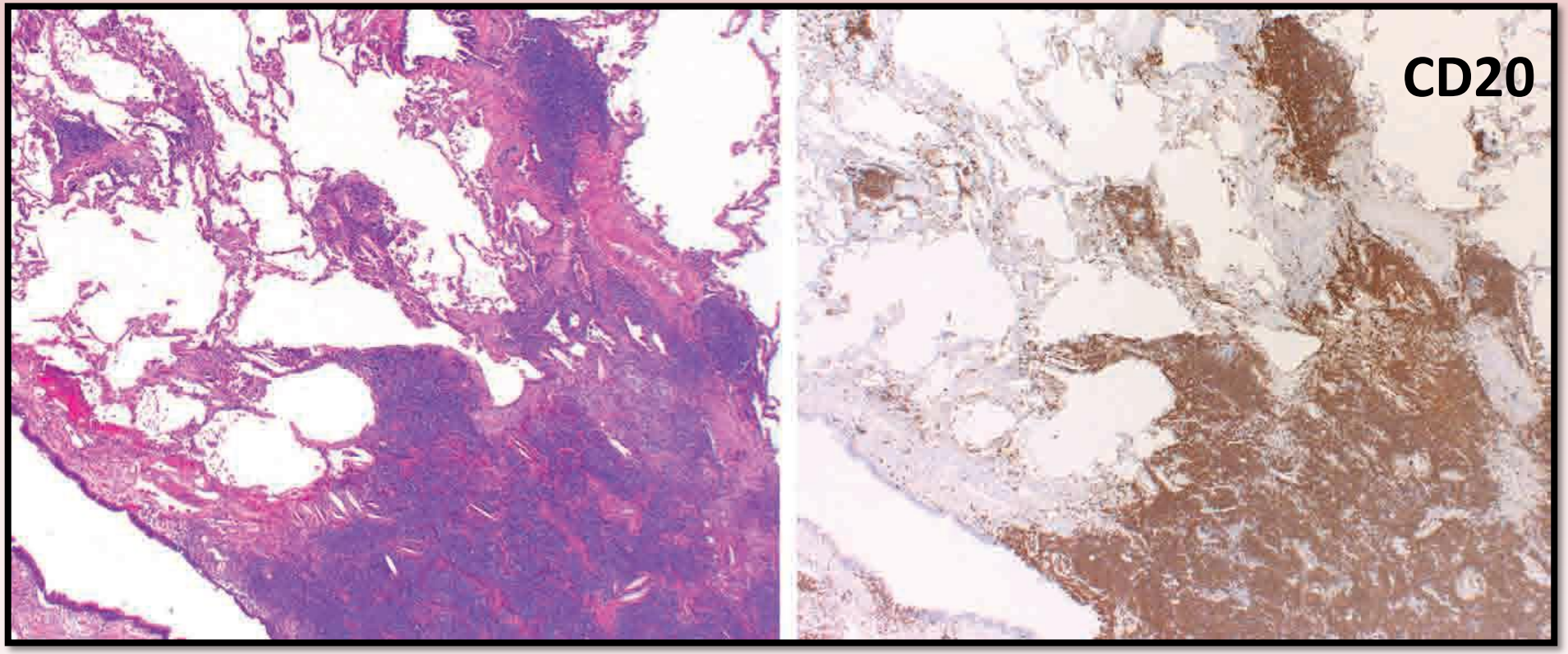
Marginal Zone Lymphoma



Low-grade B-Cell Lymphoma of MALT (Extranodal Marginal Zone B-Cell Lymphoma)

Most common 1° Lymphoma of Lung

Associated w/: Autoimmune diseases (Sjögren) & Monoclonal gammopathy

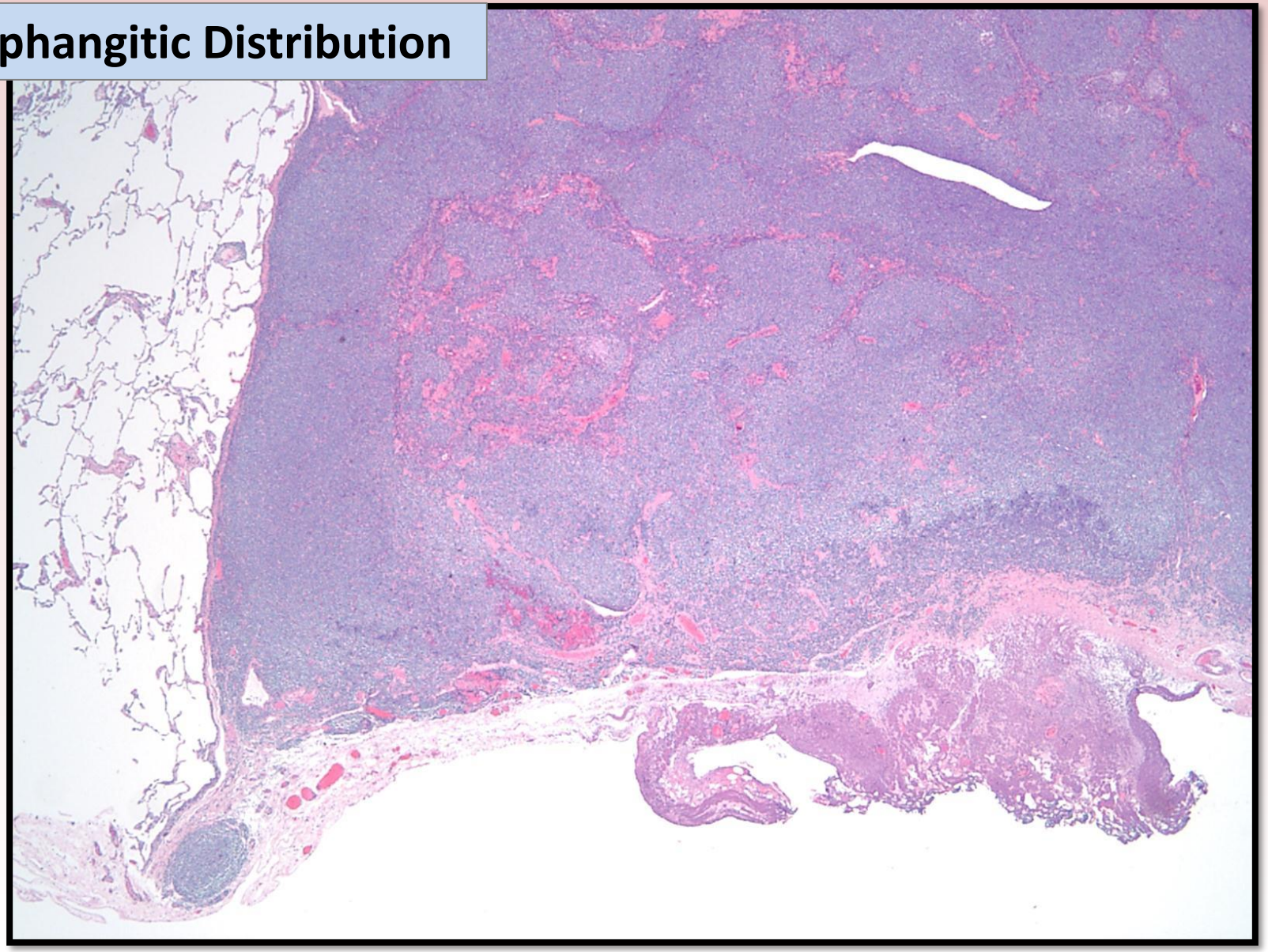
25% have multifocal nodular opacities

May transform to high-grade malignant lymphoma

Leslie & Wick *Practical Pulmonary Pathology* (2011)

Marginal Zone Lymphoma

Lymphangitic Distribution



Marginal Zone Lymphoma

Lymphoepithelial Lesion

Marginal Zone Lymphoma

"Vasculitis"

Non-Infectious Lung Disease Case #4

History & Presentation

The Patient: 65 y.o. woman

Medical Hx: "asthma" (10-20 yrs), GERD

Medications: advair, combivent, PPI

HPI: Increasing SOB & DOE, decreasing exercise tolerance w/ recent exacerbation

SocHx: Never smoker w/ exposure to 1 bird at home x2 yrs

OccHx: "Varied"

Objective: -Chest CT: Bilateral infiltrates

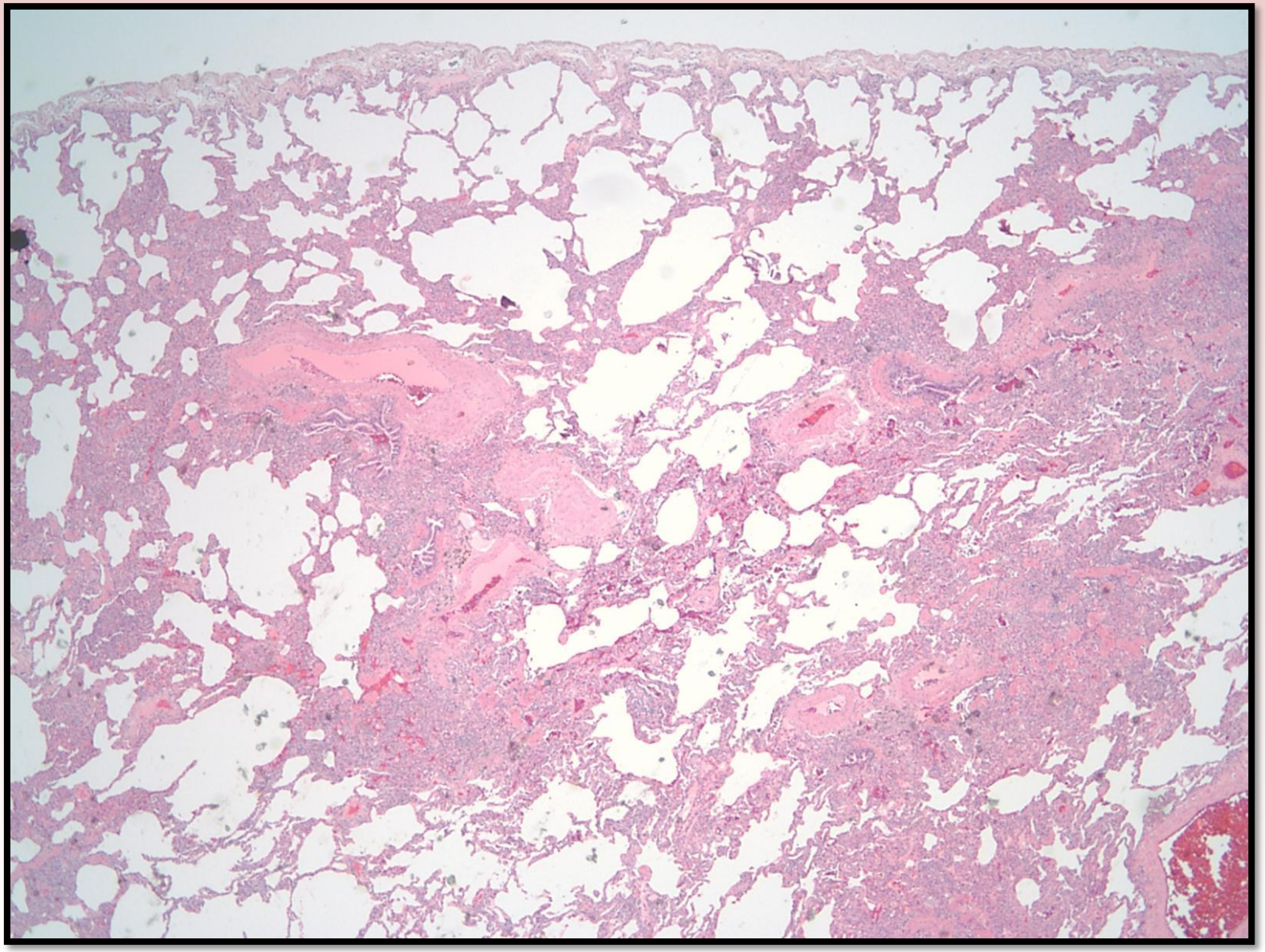
-PFTs (% predicted): FEV1 89; DLCO 62

-ECHO: Mild TR

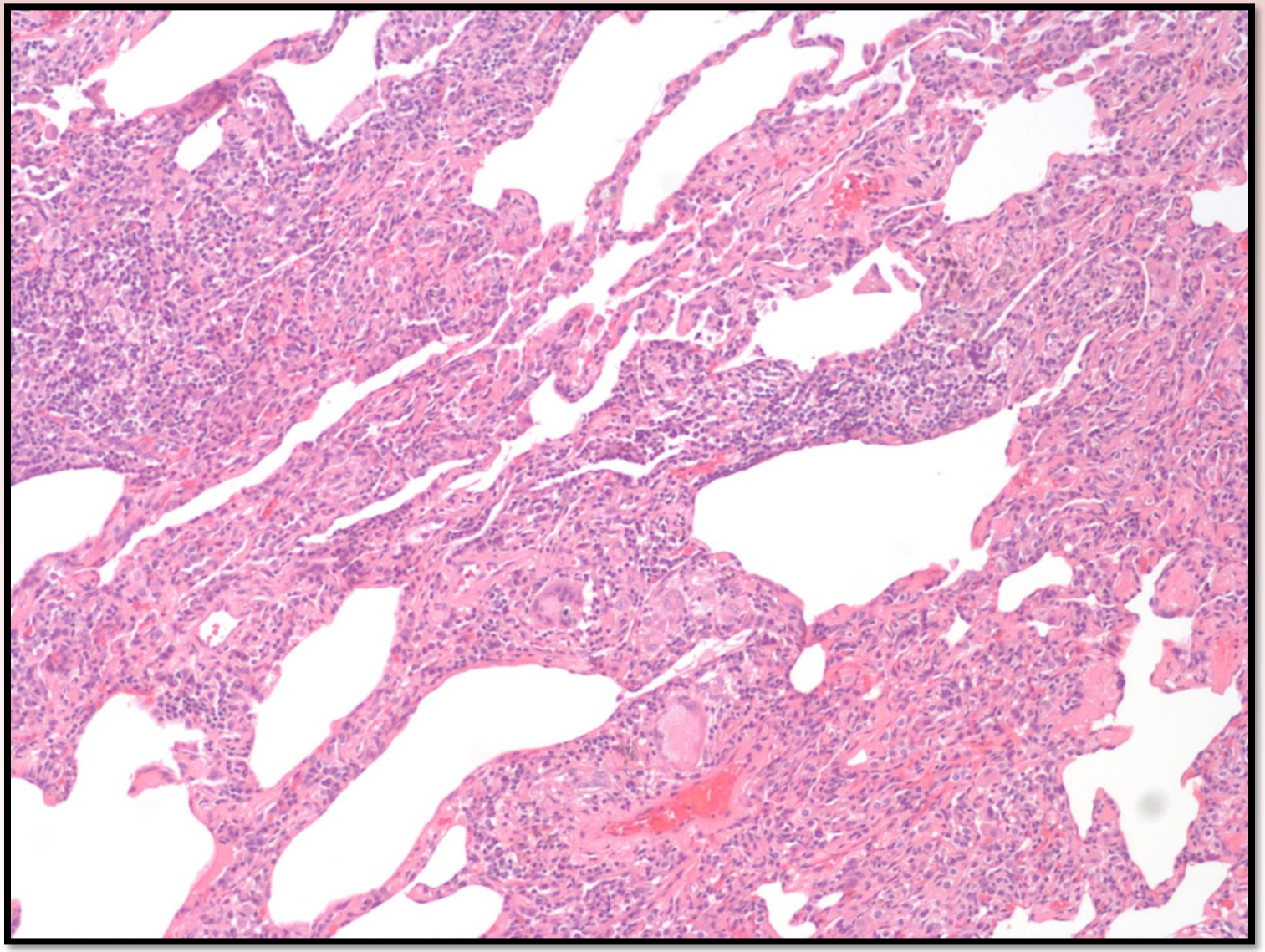
-Stress Test: Negative

RUL, RML & RLL Wedge Biopsies Are Performed.

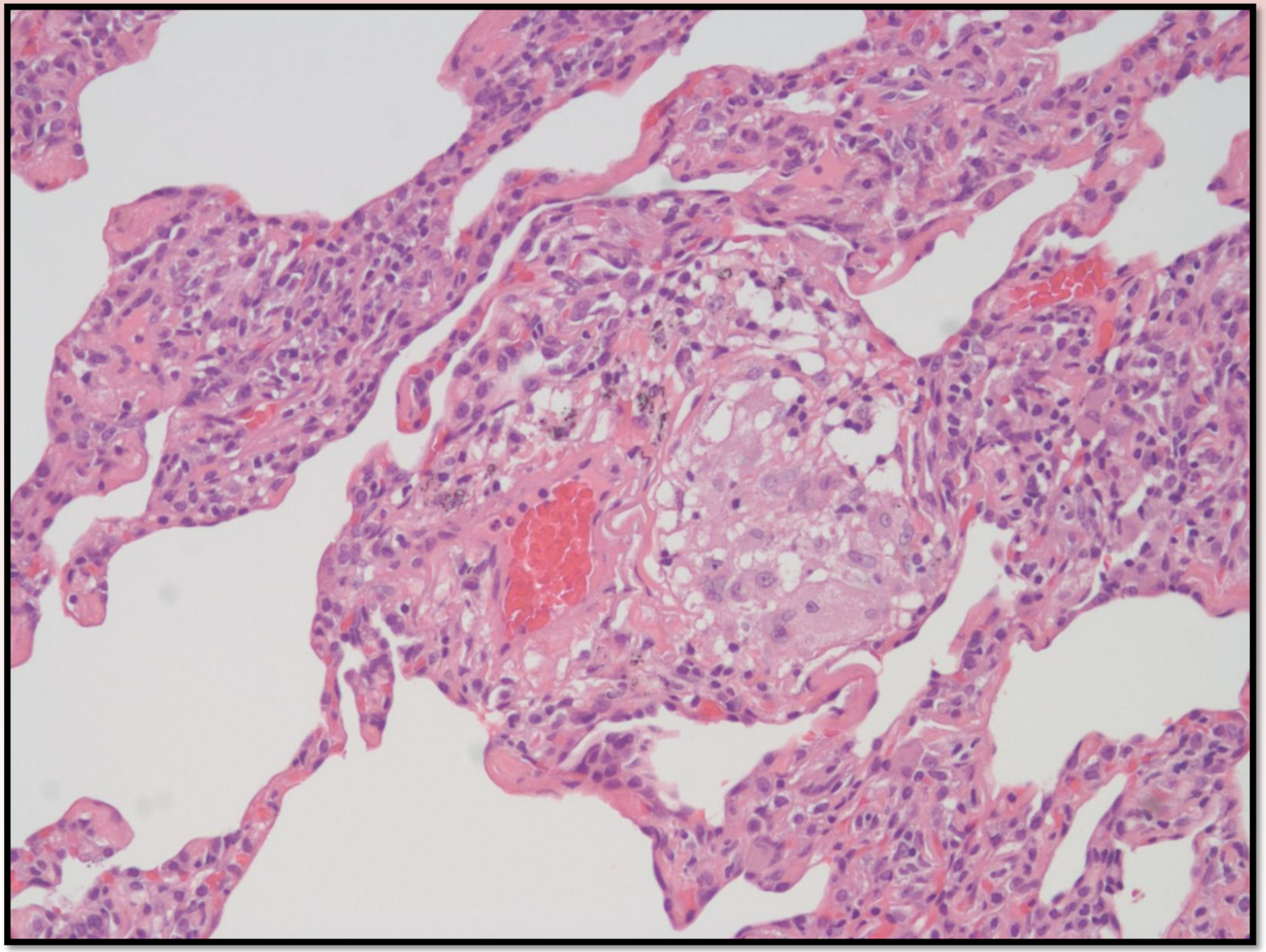
RUL Wedge Biopsy



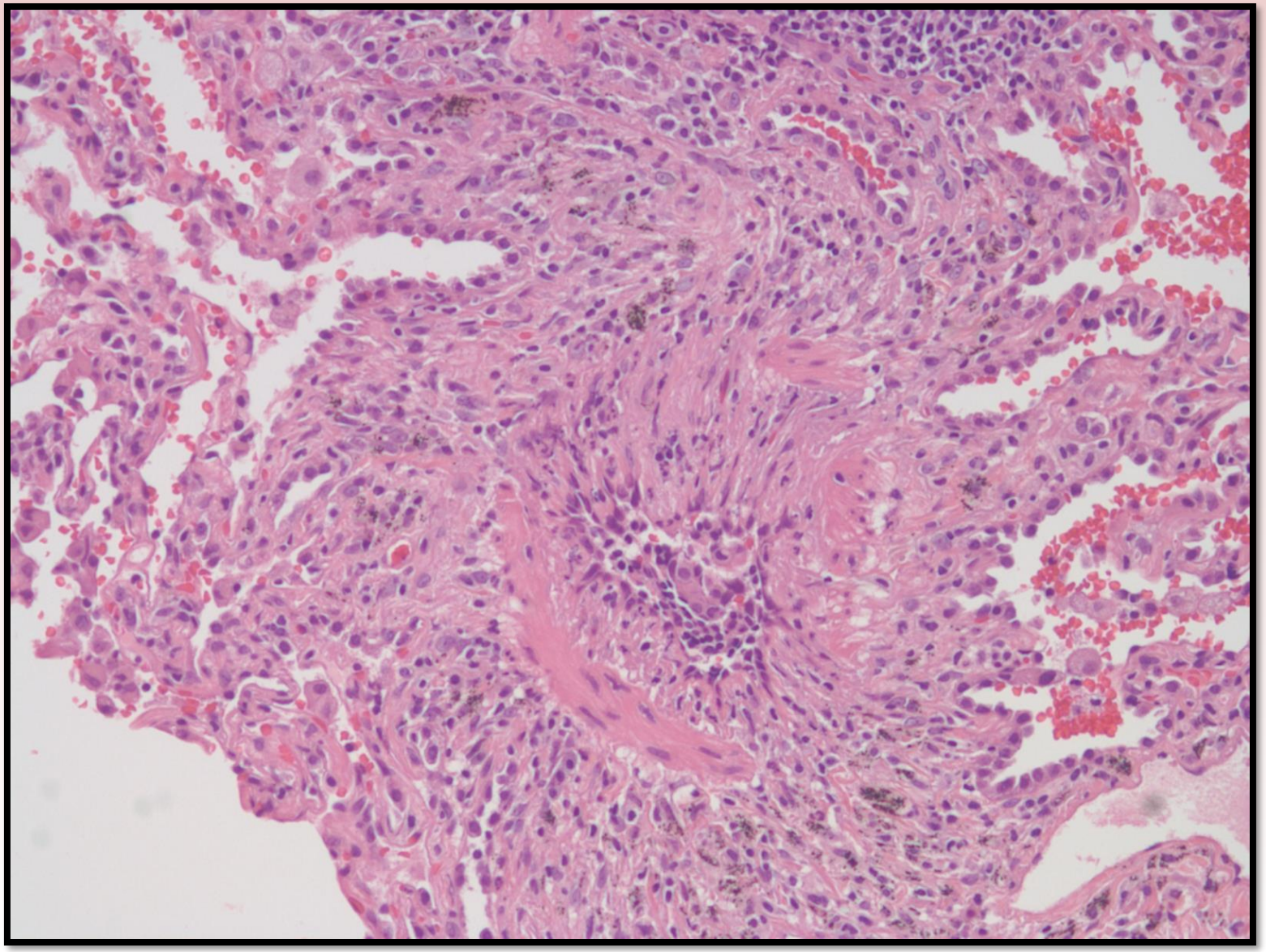
RUL Wedge Biopsy



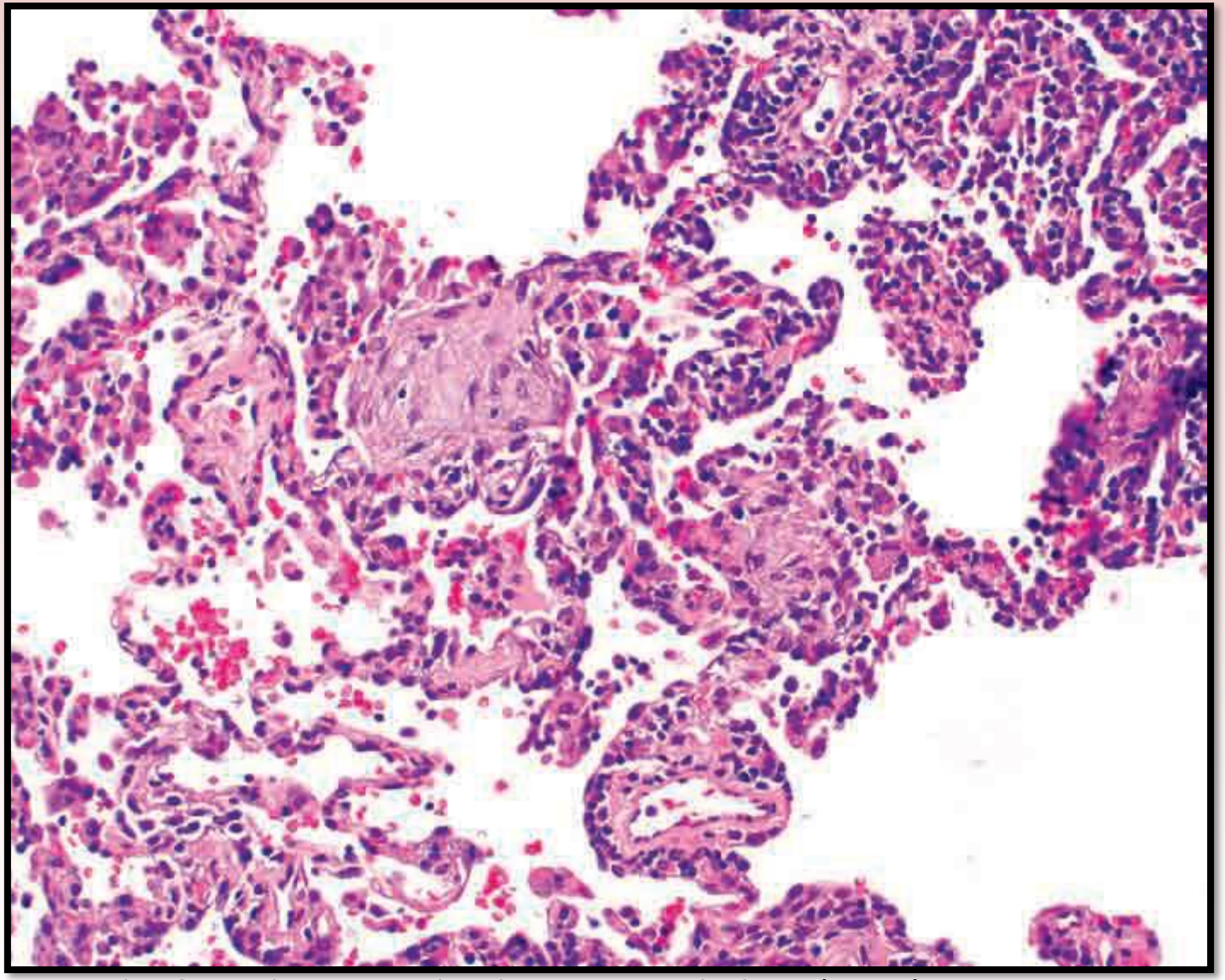
RUL Wedge Biopsy



RUL Wedge Biopsy

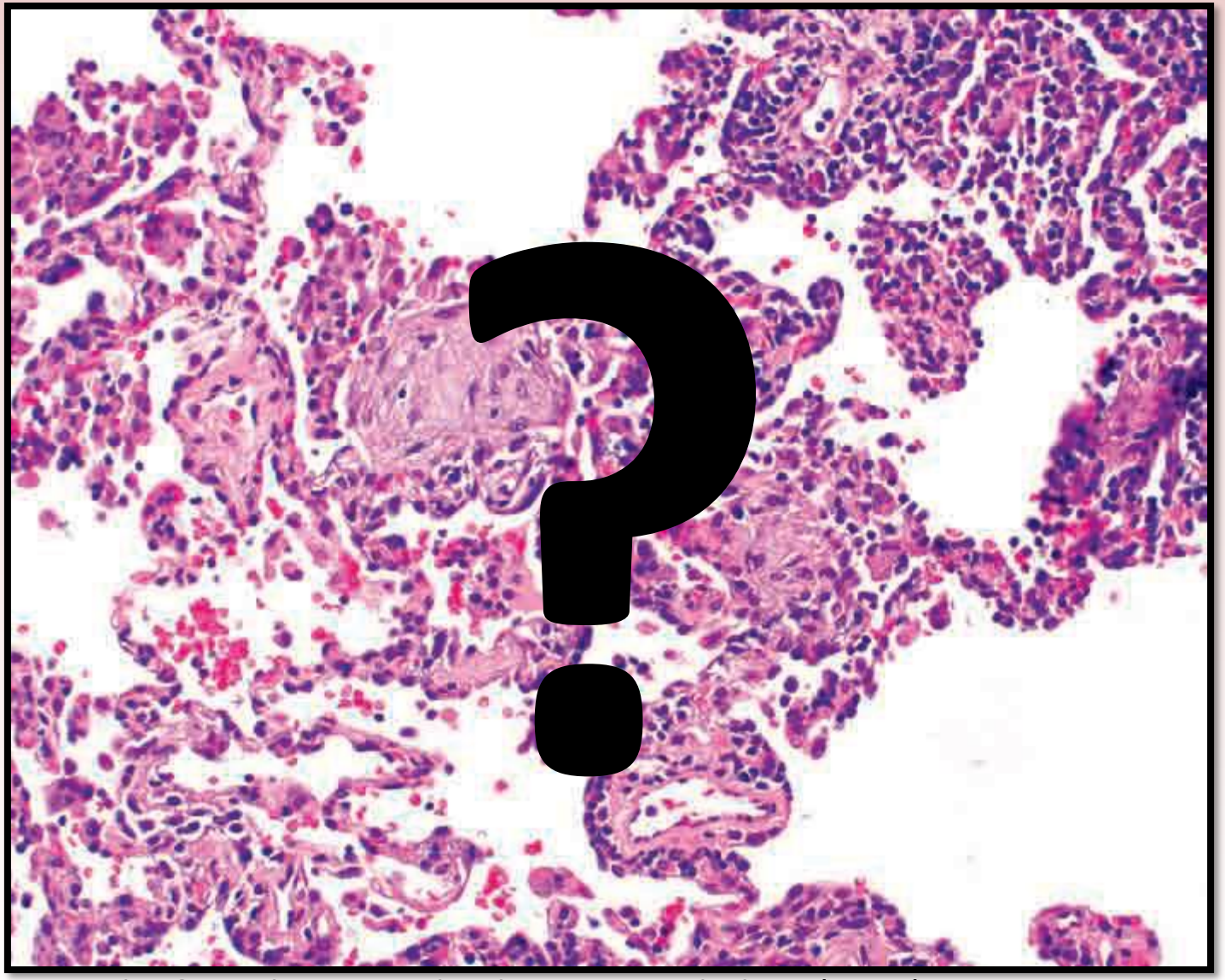


RUL Wedge Biopsy



Leslie & Wick *Practical Pulmonary Pathology* (2011)

RUL Wedge Biopsy



Leslie & Wick *Practical Pulmonary Pathology* (2011)

Chronic Hypersensitivity PNA

- AKA: **Extrinsic Allergic Alveolitis**
- **Pattern:** Bronchiolocentric
- **Granulomas:**
  - Ill-defined, Non-necrotizing, Interstitial
- **Patchy organization**
- **Foci of bronchiolitis obliterans**
- **Chronic interstitial PNA**

Noninfectious Granulomatous Disease

Noninfectious diseases

- ★ Sarcoidosis
- ★ Chronic beryllium disease
- ★ Hypersensitivity pneumonitis
- ★ Hot tub lung
- Lymphoid interstitial pneumonia
- Wegener granulomatosis
- Churg-Strauss syndrome
- ★ Aspiration pneumonia
- ★ Talc granulomatosis
- Rheumatoid nodule
- Bronchocentric granulomatosis

Mukhopadhyay & Gal (2010) *Arch Pathol Lab Med*

★ Primarily Non-necrotizing Granulomas

Key Diagnostic Questions:

1. Where are the granulomas? **Interstitium and/or Airspace**
2. Are the granulomas **Necrotizing or Non-necrotizing**?
3. Are the granulomas **Well-formed or Poorly formed**?

Chronic HP

Items That Reached "Important" Threshold*	Items That Reached "Unimportant" Threshold†	Items That Did Not Meet Consensus
Clinical		
Clinical improvement with antigen avoidance	Age	Absence of extrapulmonary manifestation
History of environmental exposure known to cause HP	Ethnicity	Crackles on exam
Negative CTD serology and no signs/symptoms of CTD	Sex	Hypoxemia at rest or on exertion
Presence of compatible clinical features (dyspnea, cough)	Family history	Improvement with prior steroid therapy
Reduced D_{LCO}	Symptoms for >24 wk	Inspiratory squeaks on exam
Time relation with exposure	Symptoms for >1 yr	Restriction on PFTs
	Systemic symptoms	Smoking history
	Wheezing on exam	
Radiological		
Air trapping—mosaic attenuation	Consolidation	Combination of reticulations, ground-glass and centrilobular nodules
Airway-centric disease		Peribronchovascular interstitial thickening
Centrilobular nodules		Reticular opacities
Ground-glass opacities		Upper lobe predominance
Bronchoalveolar lavage		
BAL lymphocytosis > 50%	BAL lymphocytosis > 20%	BAL lymphocytosis > 30%
BAL lymphocytosis > 40%	CD4/CD8 < 1	
Pathological		
Absence of an alternative diagnosis that could account for the pathologic findings	Fibrosis with a pattern that resembles UIP	Bronchiolitis
Airway-centered interstitial fibrosis		Fibrosis with a pattern that resembles NSIP
Chronic bronchiolocentric inflammation		Lymphocytic interstitial inflammation (pathology)
Giant cells		Organizing pneumonia
Poorly formed nonnecrotizing granulomas		
Indirect measure of exposure		
	Positive lymphocyte proliferation test	Positive precipitating antibodies
	Positive specific inhalation challenge	
Multidisciplinary discussion		
Case discussion in multidisciplinary team meeting		

At a Glance Commentary

Scientific Knowledge on the Subject: There are no widely accepted criteria or established international guidelines for the diagnosis of chronic hypersensitivity pneumonitis (cHP).

What This Study Adds to the Field: In an international modified Delphi survey, we identified 18 items that met the *a priori* definition of consensus as important for the diagnosis of cHP. We also described which combinations of diagnostic items experts feel are necessary for a confident diagnosis. This diagnostic approach may serve as an initial step toward the development of much needed international guidelines for the diagnosis of cHP.

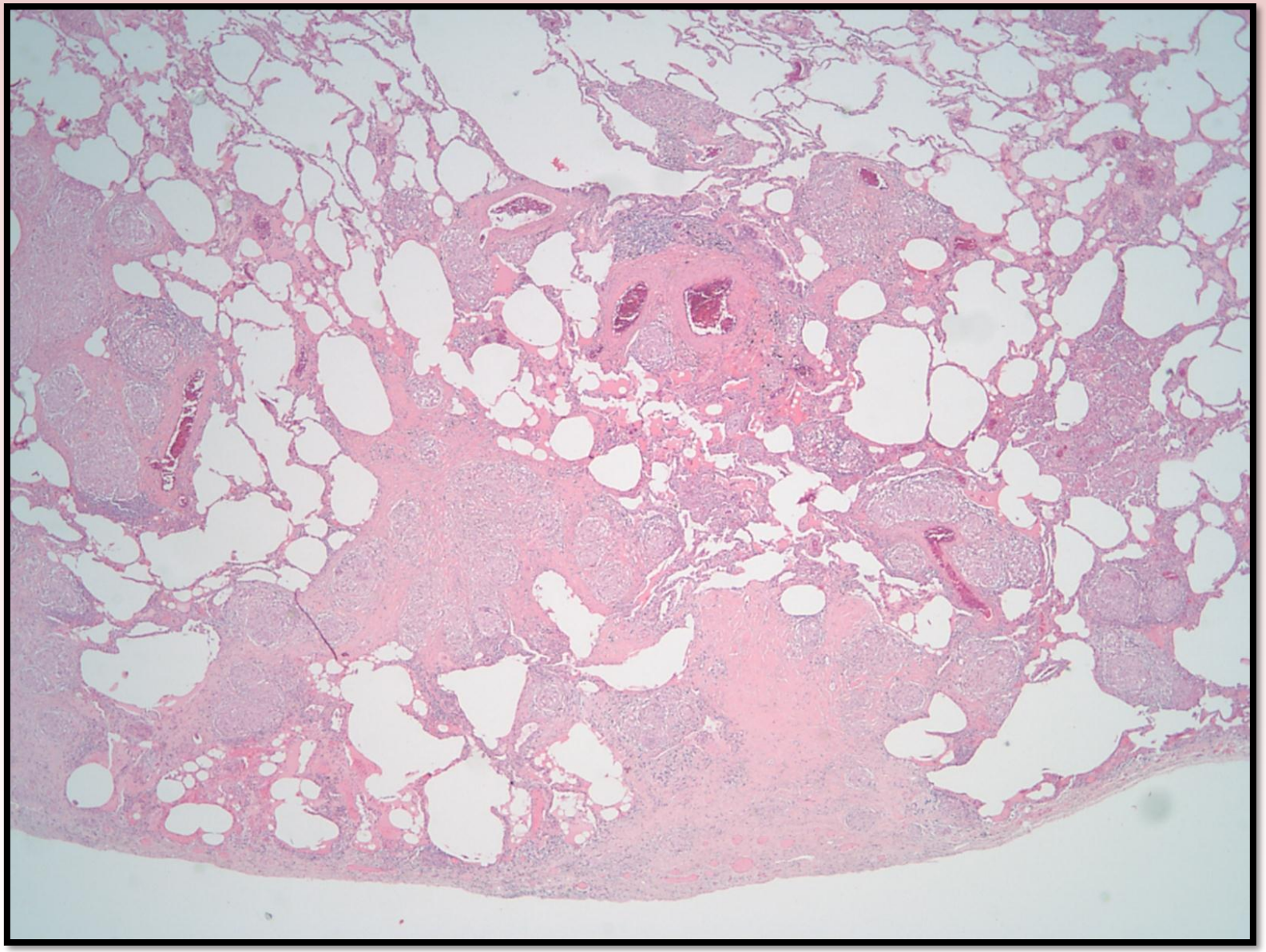
Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis

An International Modified Delphi Survey

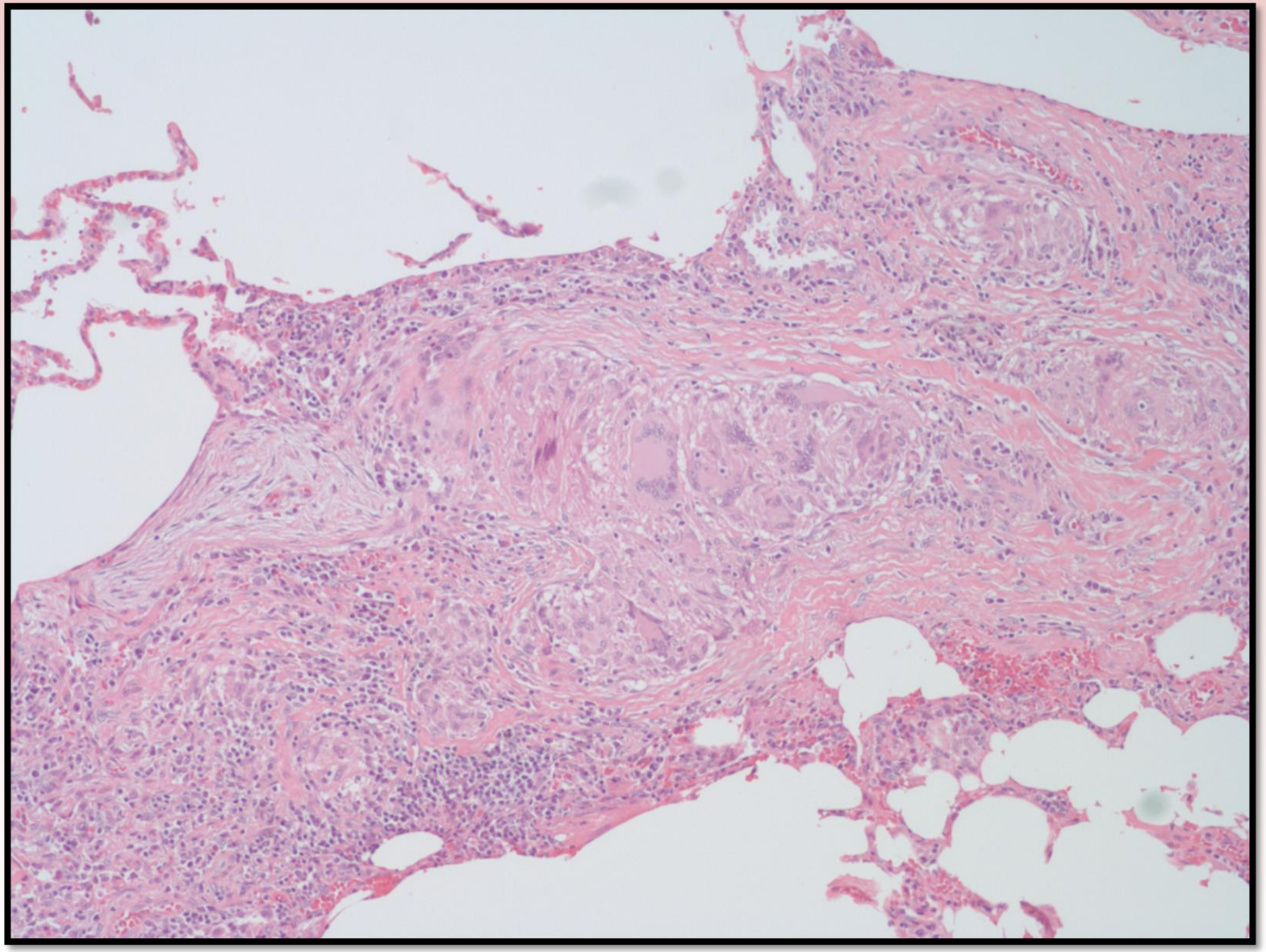
Julie Morisset[1], Kerri A. Johannson[2], Kirk D. Jones[3], Paul J. Wolters[4], Harold R. Collard[4], Simon L. F. Walsh[5], Brett Ley[4], and the HP Delphi Collaborators

[1]Département de Médecine, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; [2]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [3]Department of Pathology and [4]Department of Medicine, University of California, San Francisco, San Francisco, California; and [5]Department of Radiology, King's College, Hospital National Health Service Foundation Trust, London, United Kingdom

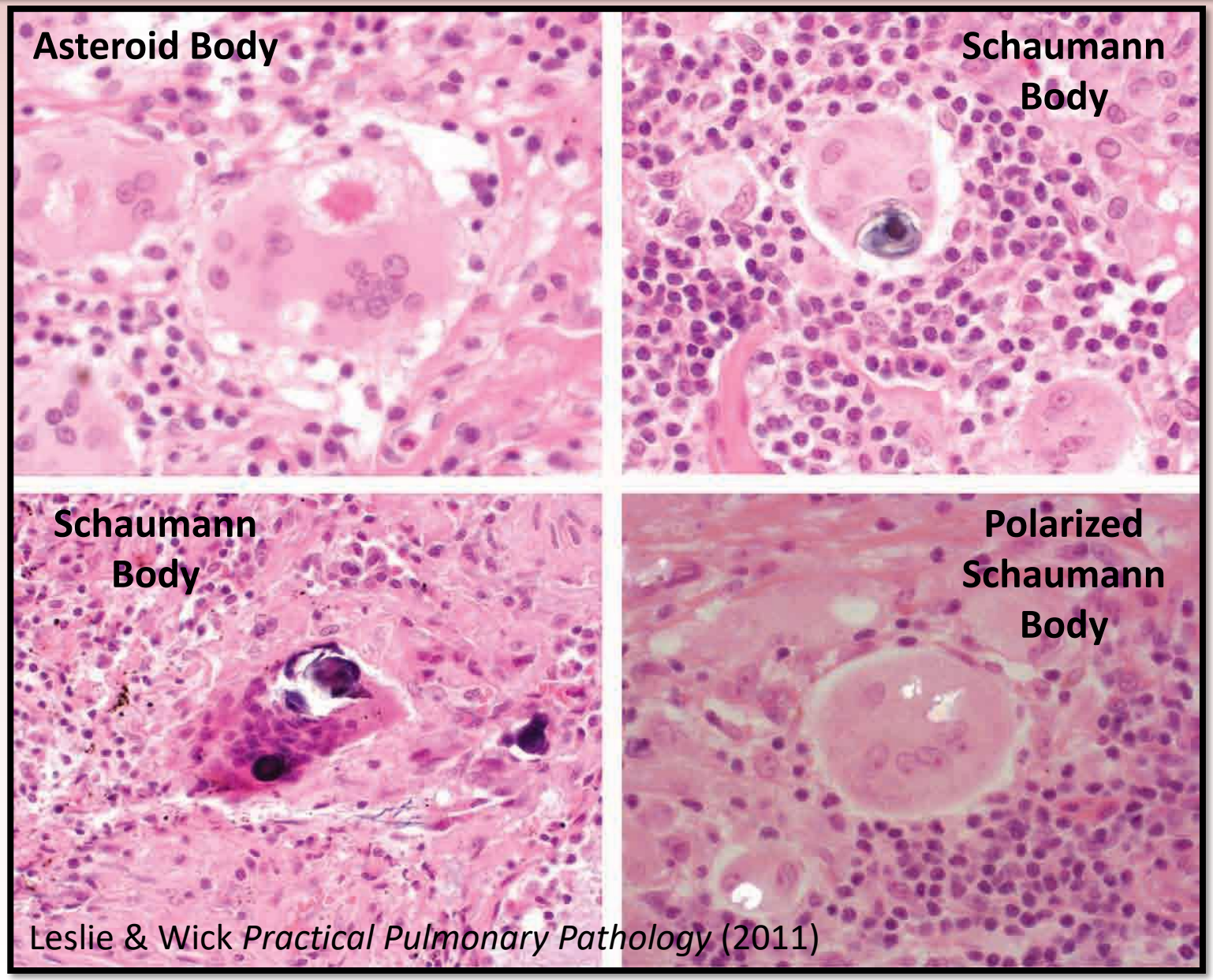
Non-necrotizing Sarcoidosis



Non-necrotizing Sarcoidosis



Non-necrotizing Sarcoidosis

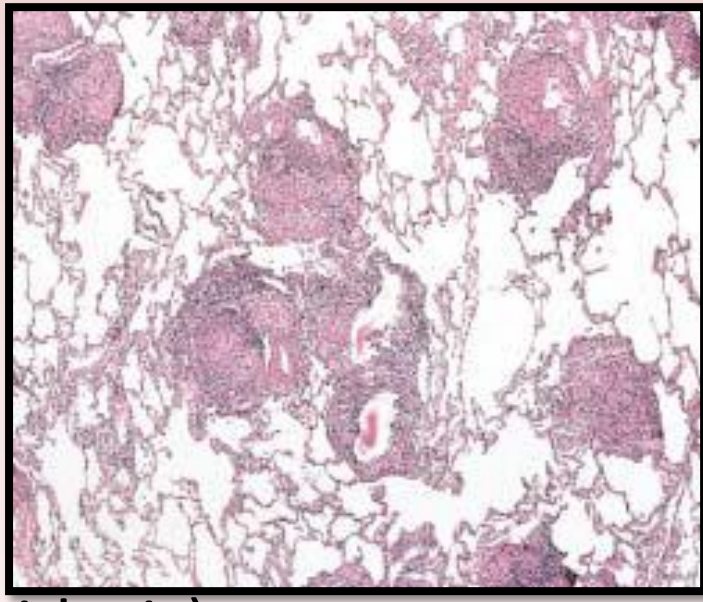


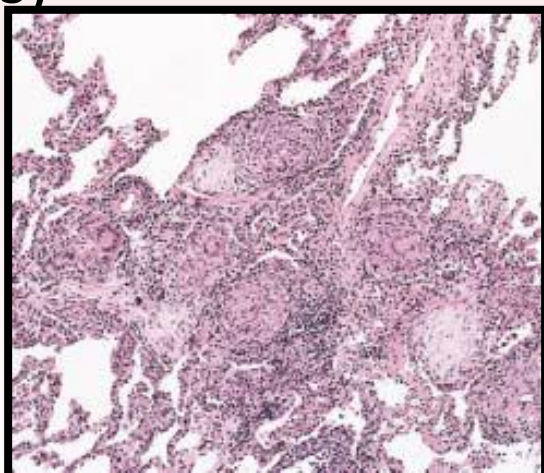
Leslie & Wick *Practical Pulmonary Pathology* (2011)

Hot Tub Lung

Khoor *et al. Anatomic Pathology* (2001)

- **True Non-Tuberculous Mycobacterial Infection vs. HP-like Reaction?**
- **Pattern:** Peribronchiolar
- **Granulomas:**
  - Non-Necrotizing
  - Well-formed & Tight (unlike HP)
  - Interstitial & Airspace (unlike Sarcoidosis)
  - Lymphocytic Rim (unlike Sarcoidosis)
- **Organizing PNA** (unlike Sarcoidosis)
- **Nonspecific chronic inflammation**





Summary: NNG Disease

Feature	Sarcoidosis	HP	Hot Tub Lung
Distribution	Lymphangitic	Bronchiolocentric	Bronchiolocentric
Granulomas	Tight, Well-formed, Naked, Confluent	Loose, ill-formed	Well-formed Lymphocytic rim
Location of Granulomas	Interstitial	Interstitial	Interstitial & Airspace
Hyalinization of Granulomas	+/-	-	-
Organizing PNA	Not seen	Present	Present
Nonspecific Chronic Interstitial Infiltrate	Not seen	Present	Present

Berylliosis

- **Systemic disease w/ beryllium exposure**
  - Aerospace, Computer, Ceramics, Electronics industries
  - Dental technicians
- **Diagnosis:**
  - Exposure history
  - Tissue analysis
- **Pathologic Findings:**
  - ***Acute:*** DAD
  - ***Chronic:*** Sarcoidosis

Non-Infectious Lung Disease Case #5

History & Presentation

The Patient: 50 y.o. Cuban man, immigrated 3 months prior

Medical Hx: None

Medications: None

HPI: Presented to ED w/ 1 wk history of SOB & left-sided pleuritic chest pain, and fever/chills at night. He denies cough & hemoptysis.

Objective:

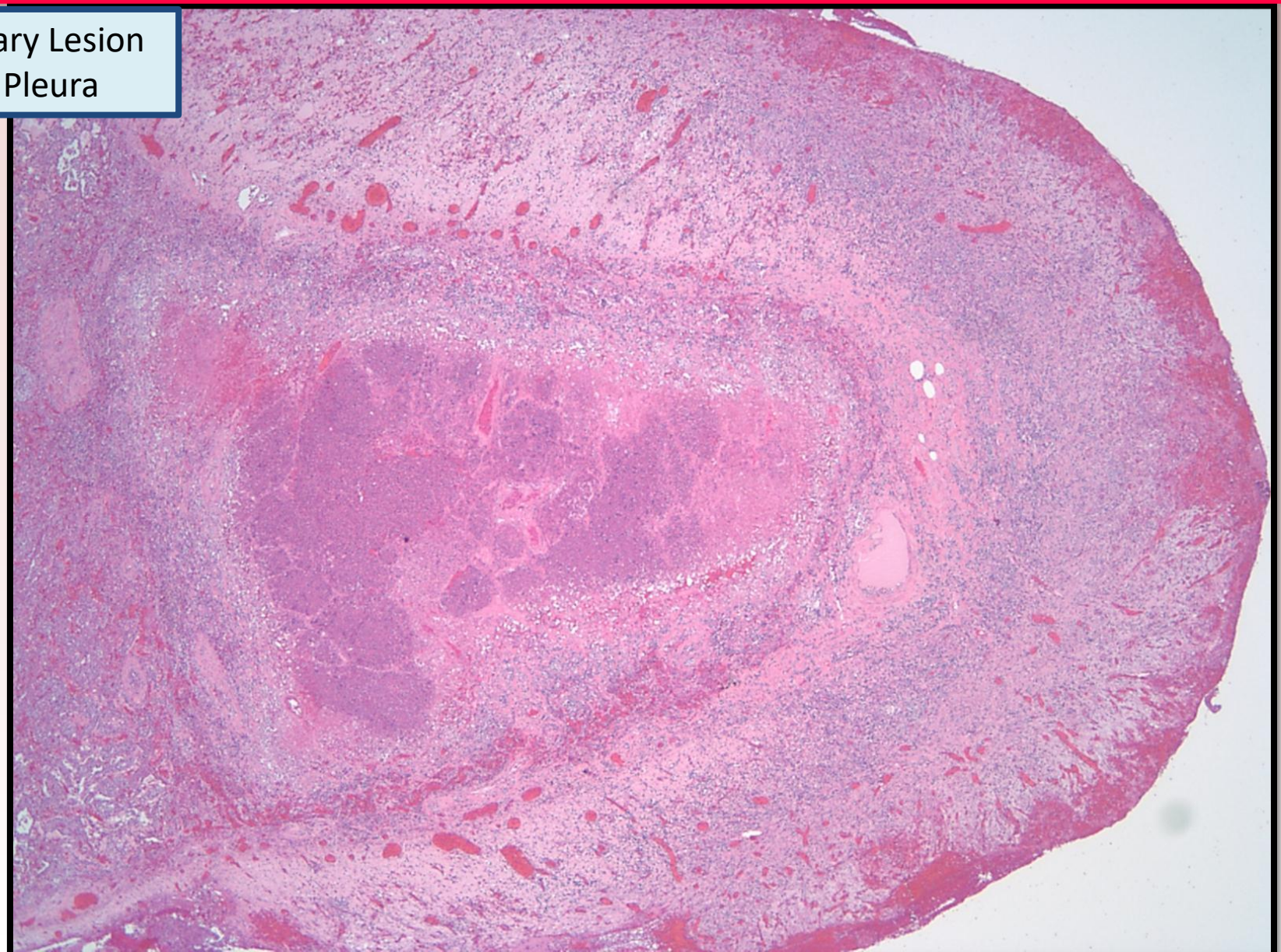
-WBC ct: 15,000 w/ 46% eosinophils

-Chest CT: Large L pleural effusion w/ compression & atelectasis of left lower lobe.

A Left Lower Lobe Lung Wedge Biopsy & Pleural Peel Are Performed.

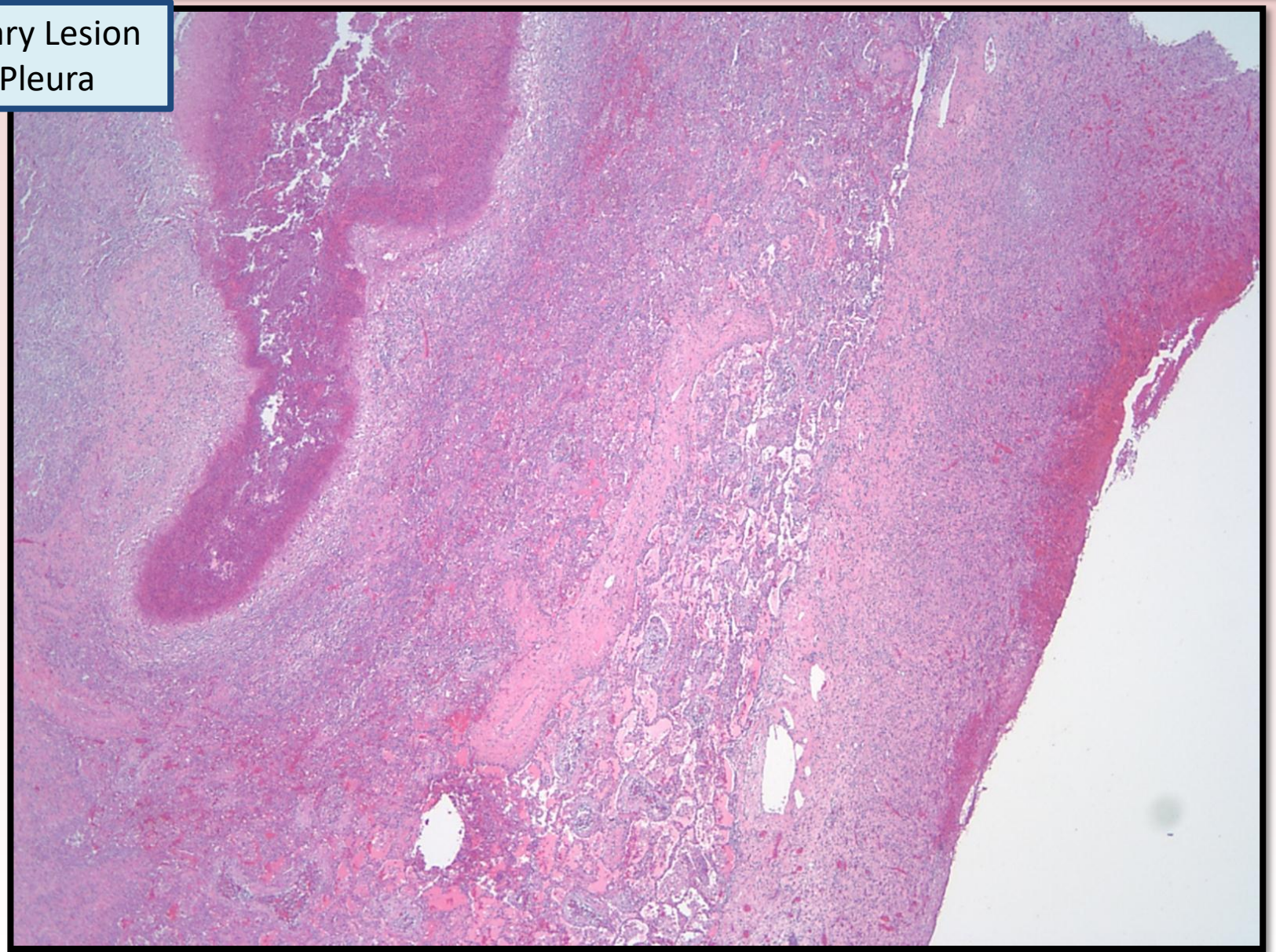
Left Lower Lobe Wedge

Cavitary Lesion to Pleura



Left Lower Lobe Wedge

Cavitary Lesion to Pleura



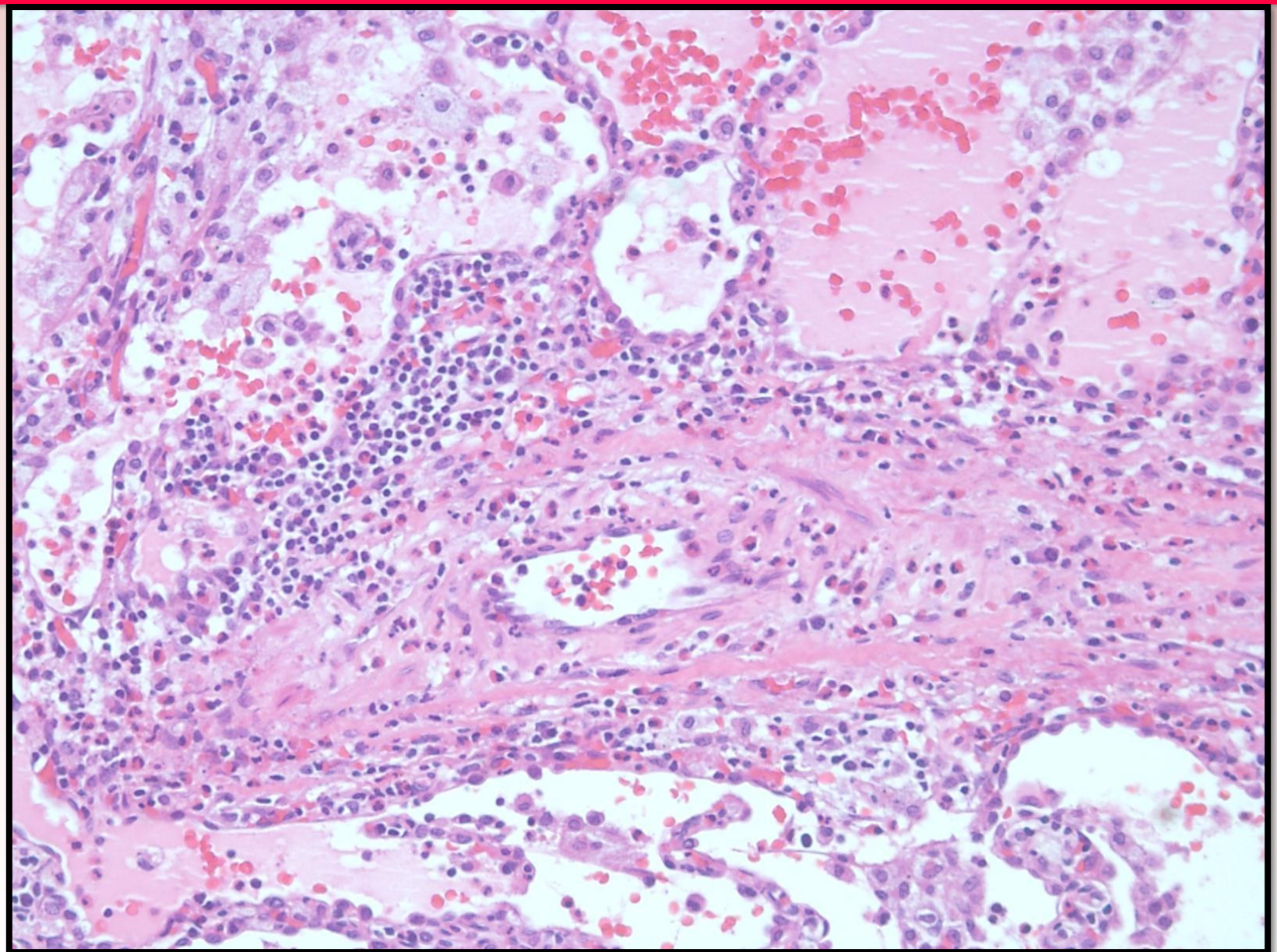
Left Lower Lobe Wedge

Edge of Cavitary Lesion

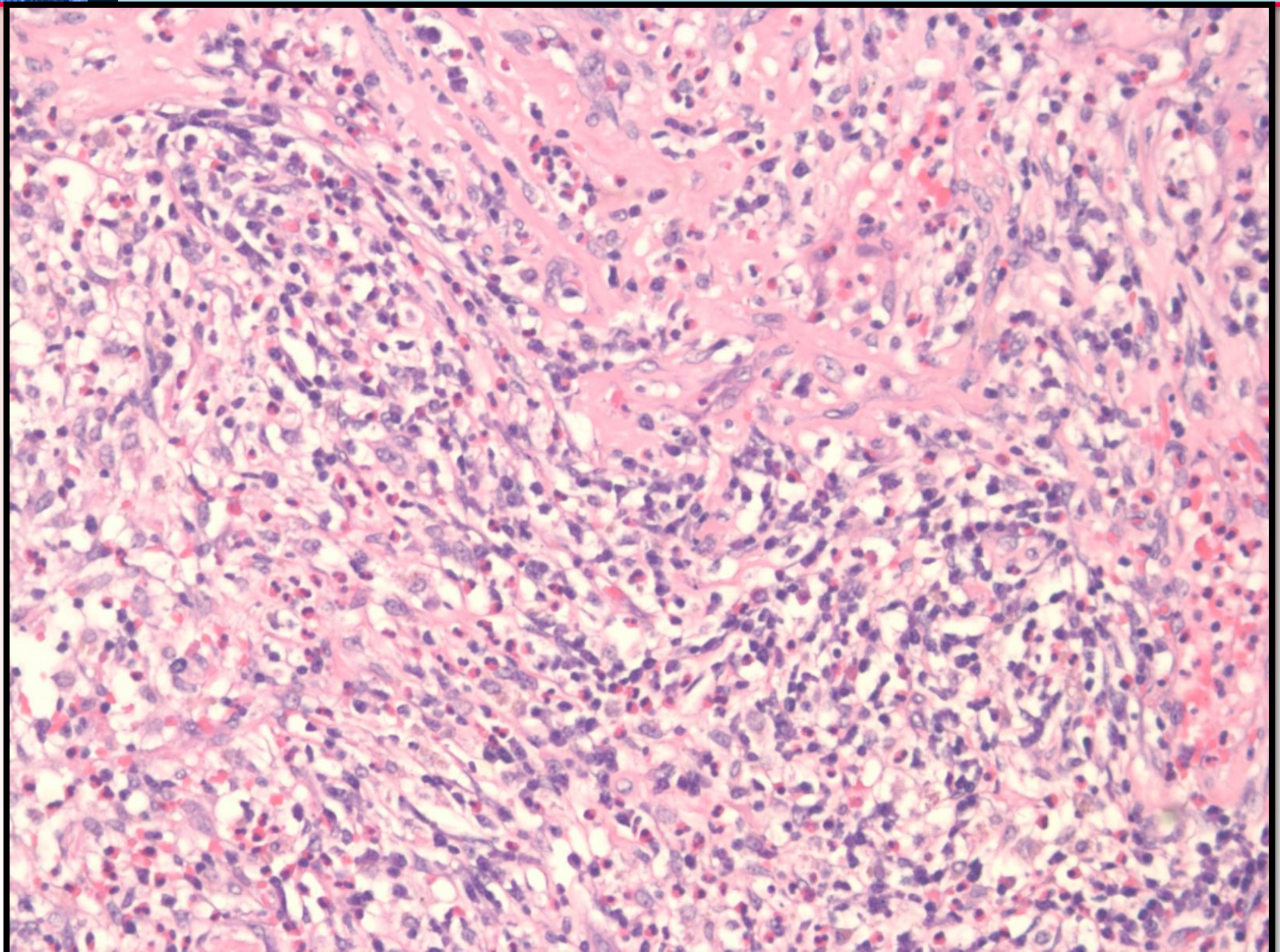
Left Lower Lobe Wedge

Middle of Cavitary Lesion

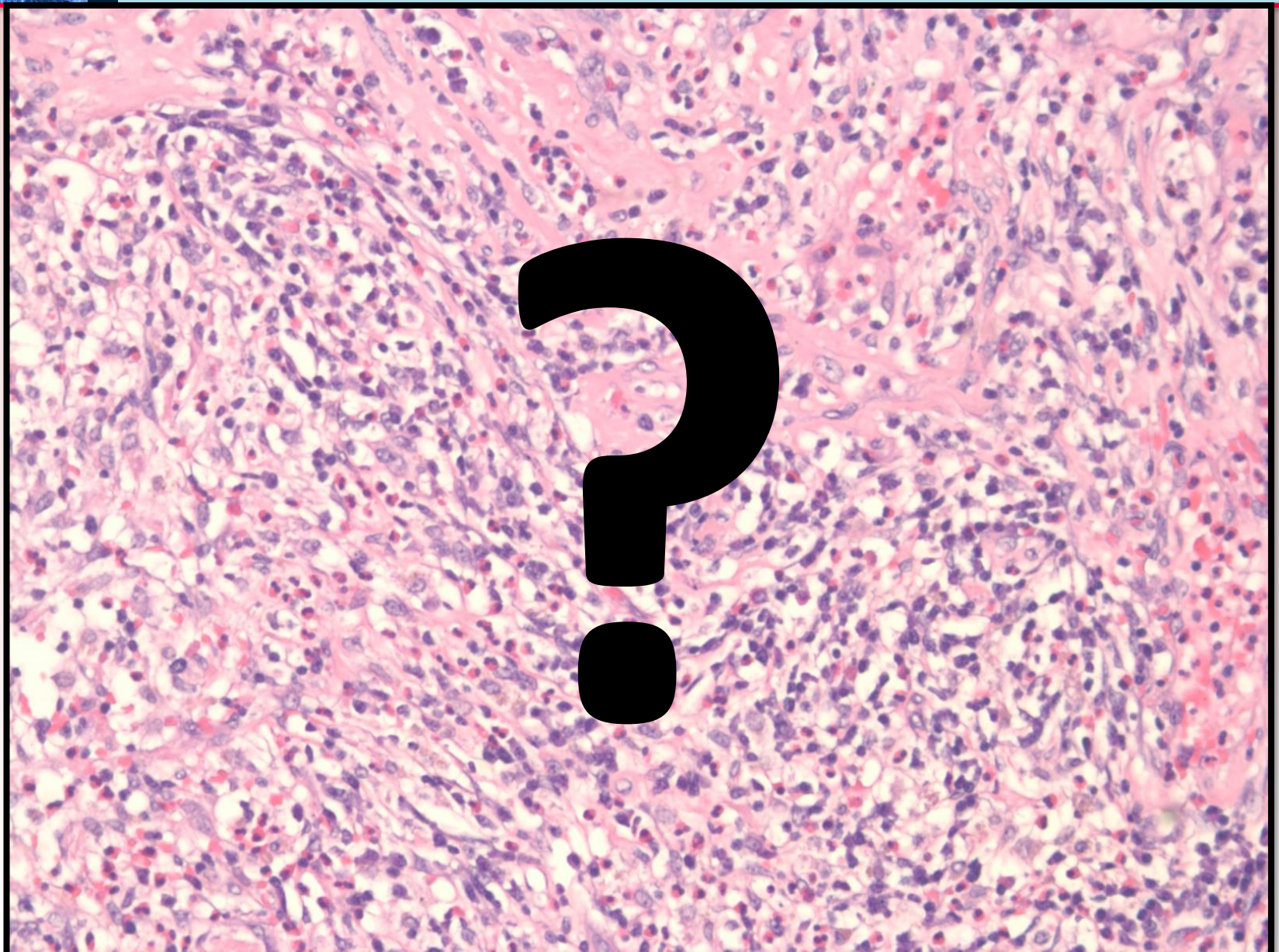
Left Lower Lobe Wedge



Left Lower Lobe Wedge



Left Lower Lobe Wedge



Eosinophilic Granulomatosis with polyangiitis (EGPA)

- AKA: **Allergic Angiitis & Granulomatosis**
- **Clinical Criteria:**
  - Asthma
  - Peripheral Eosinophilia
  - Extrapulmonary vasculitis (2+ sites)
- **Histologic Features:**
  - Eosinophilic pneumonia filling airspaces
  - Palisaded necrotizing granulomatous inflammation (+/-)
  - Necrotizing vasculitis

Lung ANCA Vasculitides

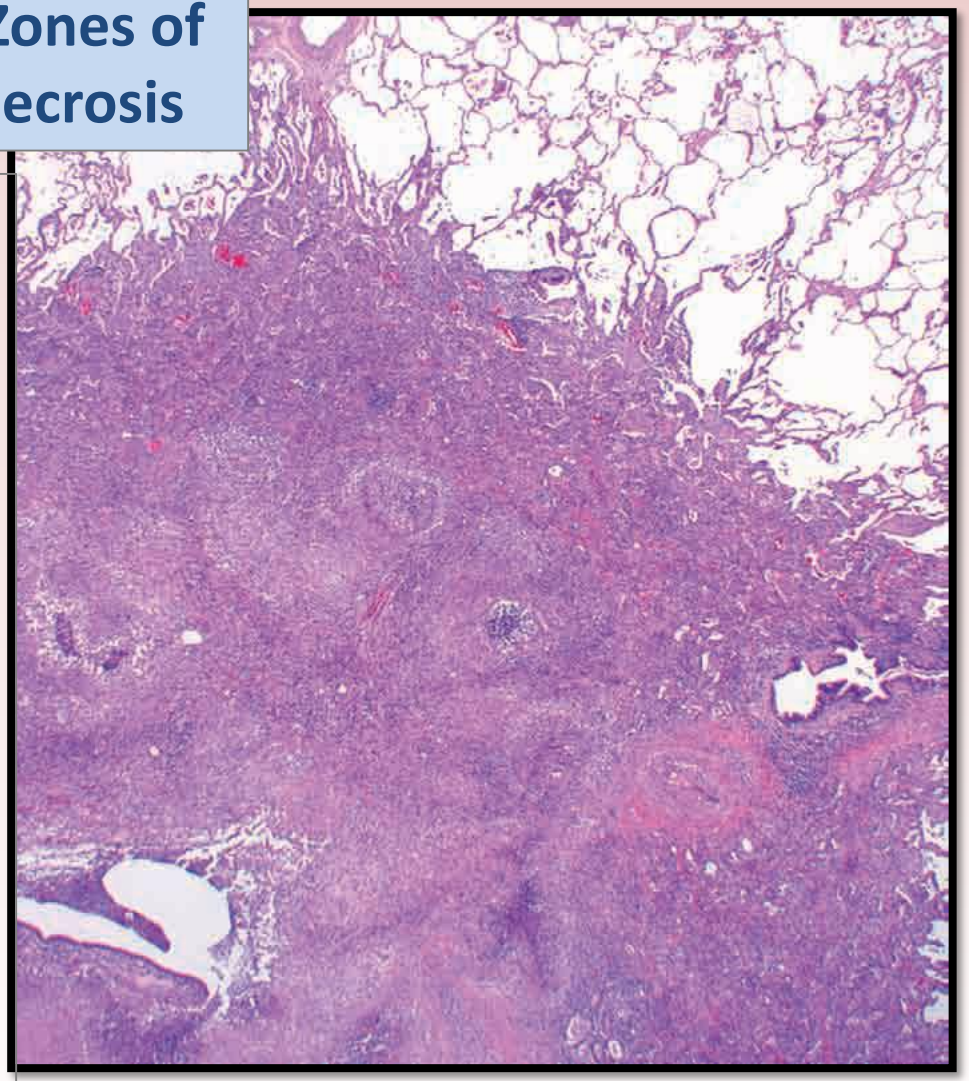
Feature	EGPA	Granulomatosis w/ Polyangiitis	Microscopic Polyangiitis
Asthma	Yes	No	No
Eosinophilia	Yes, high	Usually not	No
ANCA (usual type)	50-70% (P-ANCA)	60-95% (C-ANCA)	70-80% (P-ANCA)
Necrotizing Granulomas	Classically - yes Often – no	Yes	No
Necrotizing Vasculitis	Yes	Yes	Yes (capillaritis only)
Tissue Eosinophilia	Yes	Rare	No

A-L. Katzenstein's *Non-Neoplastic Lung Disease* (2006)

Granulomatosis w/ Polyangiitis

Serpiginous Zones of Basophilic Necrosis

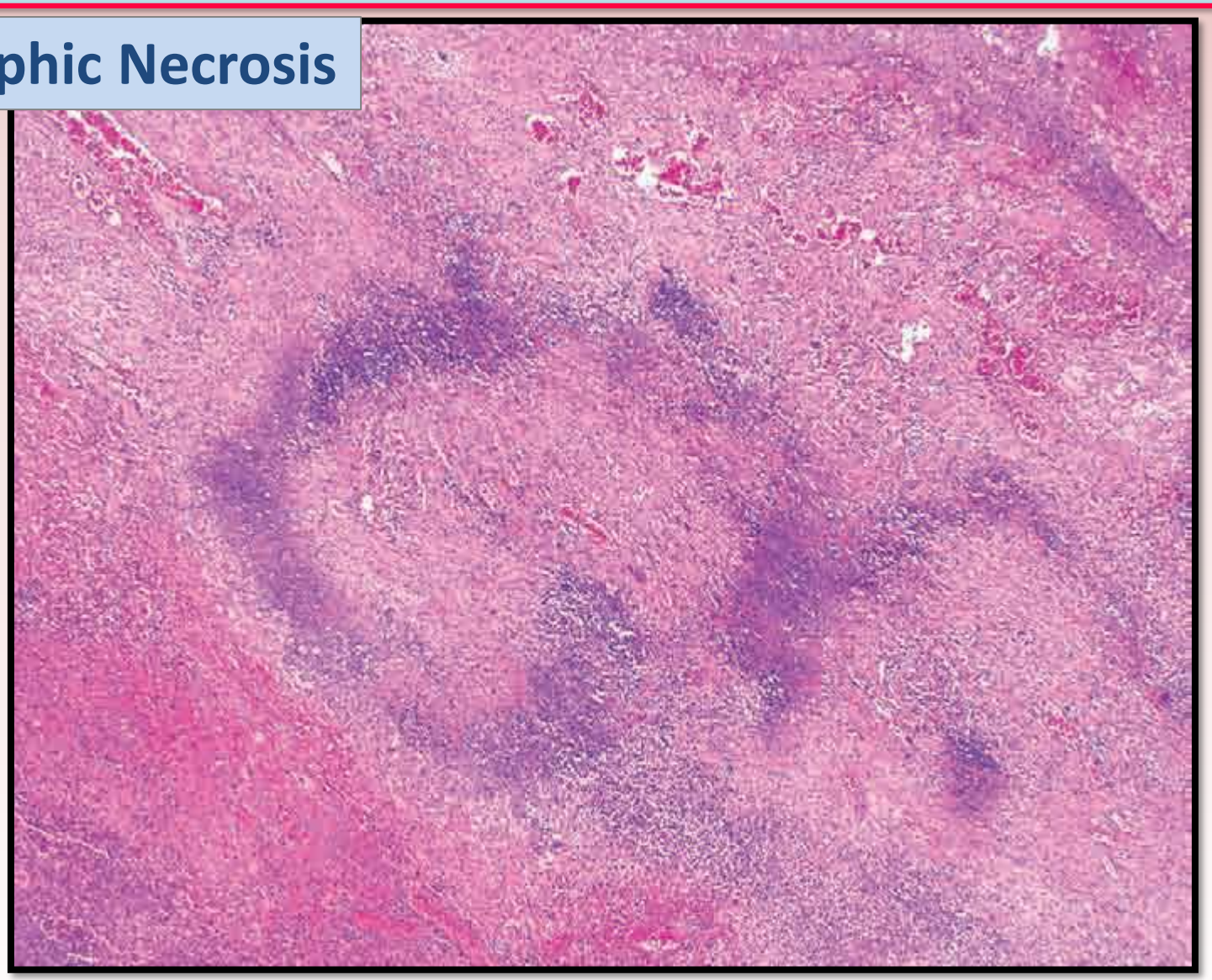
- **Classic Type**
  - Necrotizing granulomas
  - Geographic necrosis
  - Necrotizing vasculitis
  - Lack of Non-Necrotizing Granulomas
- **Subtypes:**
  - Eosinophilic variant
  - Bronchocentric variant
  - BOOP-like variant



Leslie & Wick *Practical Pulmonary Pathology* (2011)

Granulomatosis w/ Polyangiitis

Geographic Necrosis



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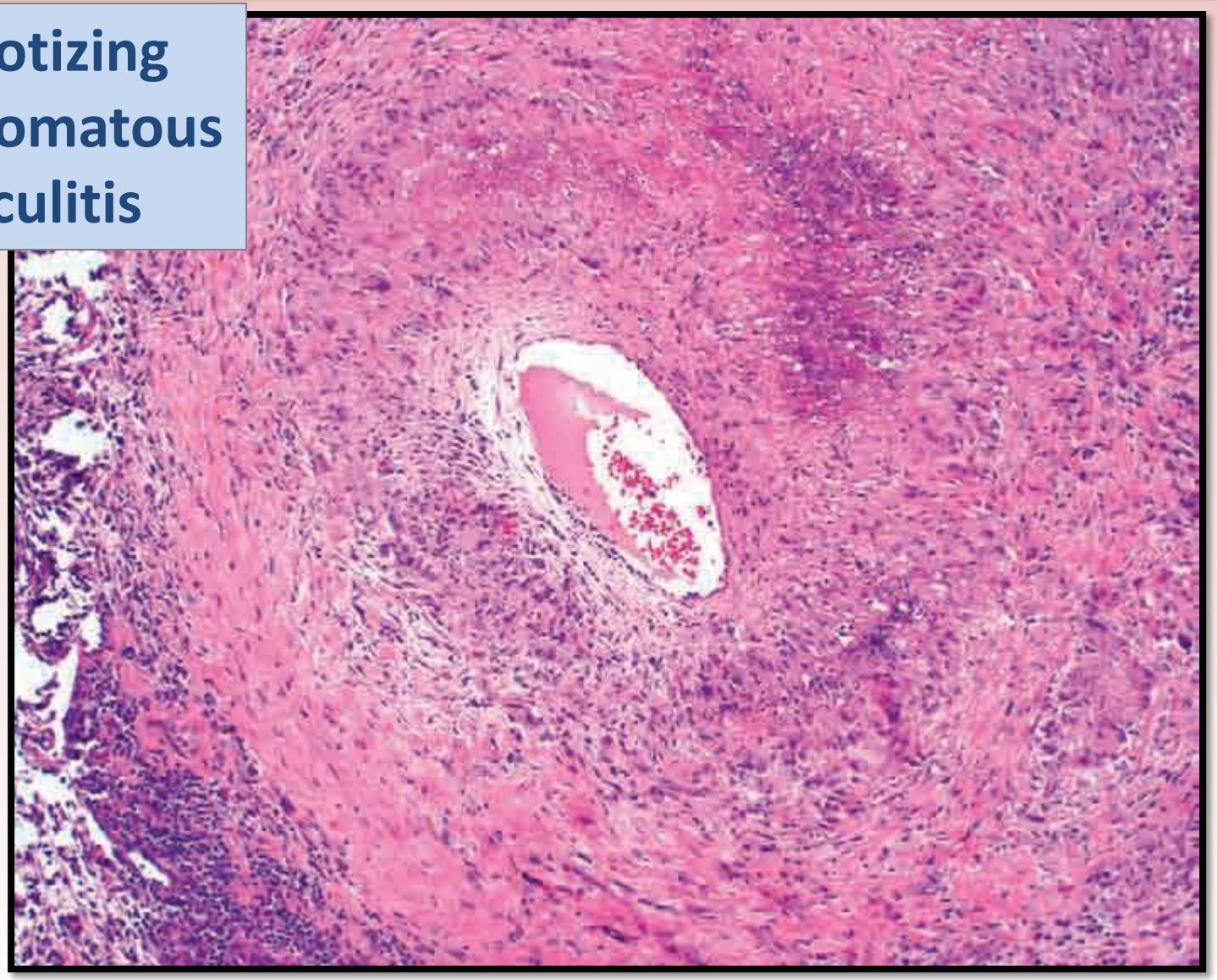
Granulomatosis w/ Polyangiitis

Necrotizing Granulomatous Vasculitis



Leslie & Wick *Practical Pulmonary Pathology* (2011)

Necrotizing Sarcoidosis

RARE

W>M

Pleural Effusions common

Histologic Features

Large areas of
Parenchymal Necrosis

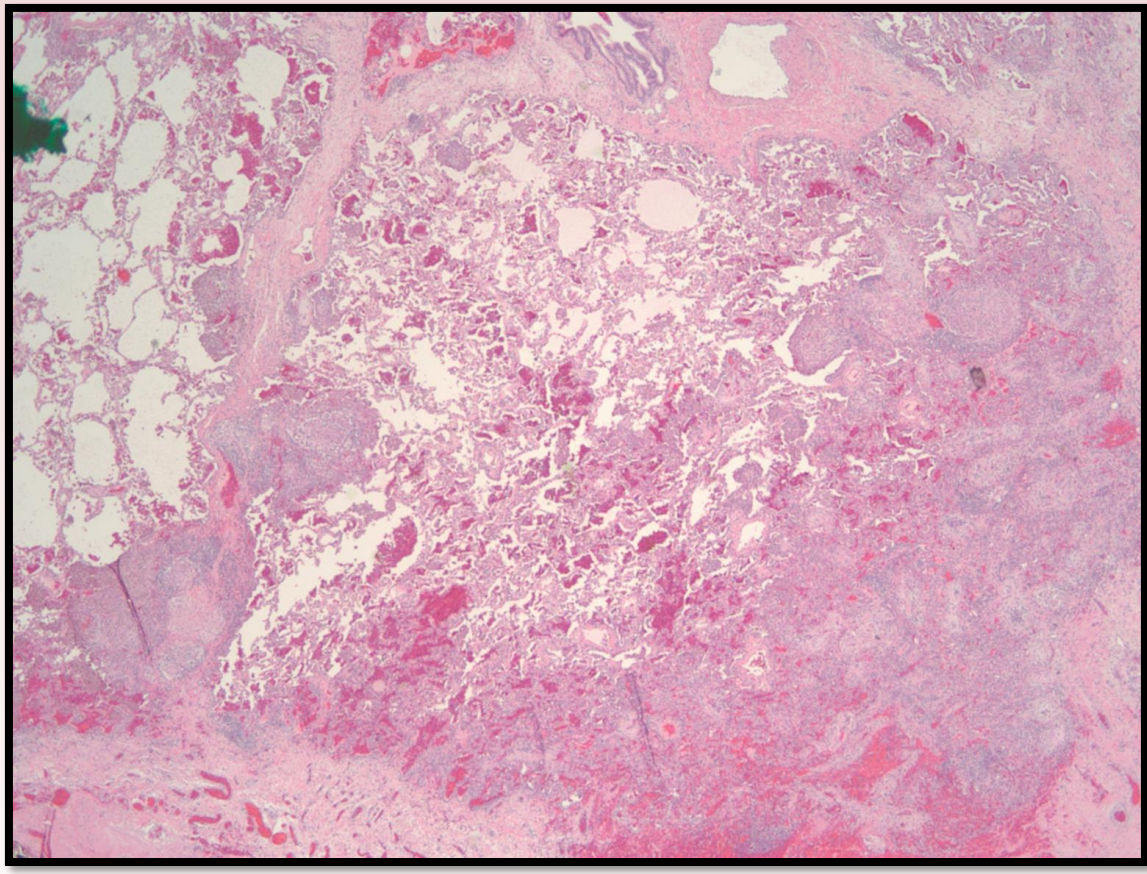
Background Granulomas

-Confluent

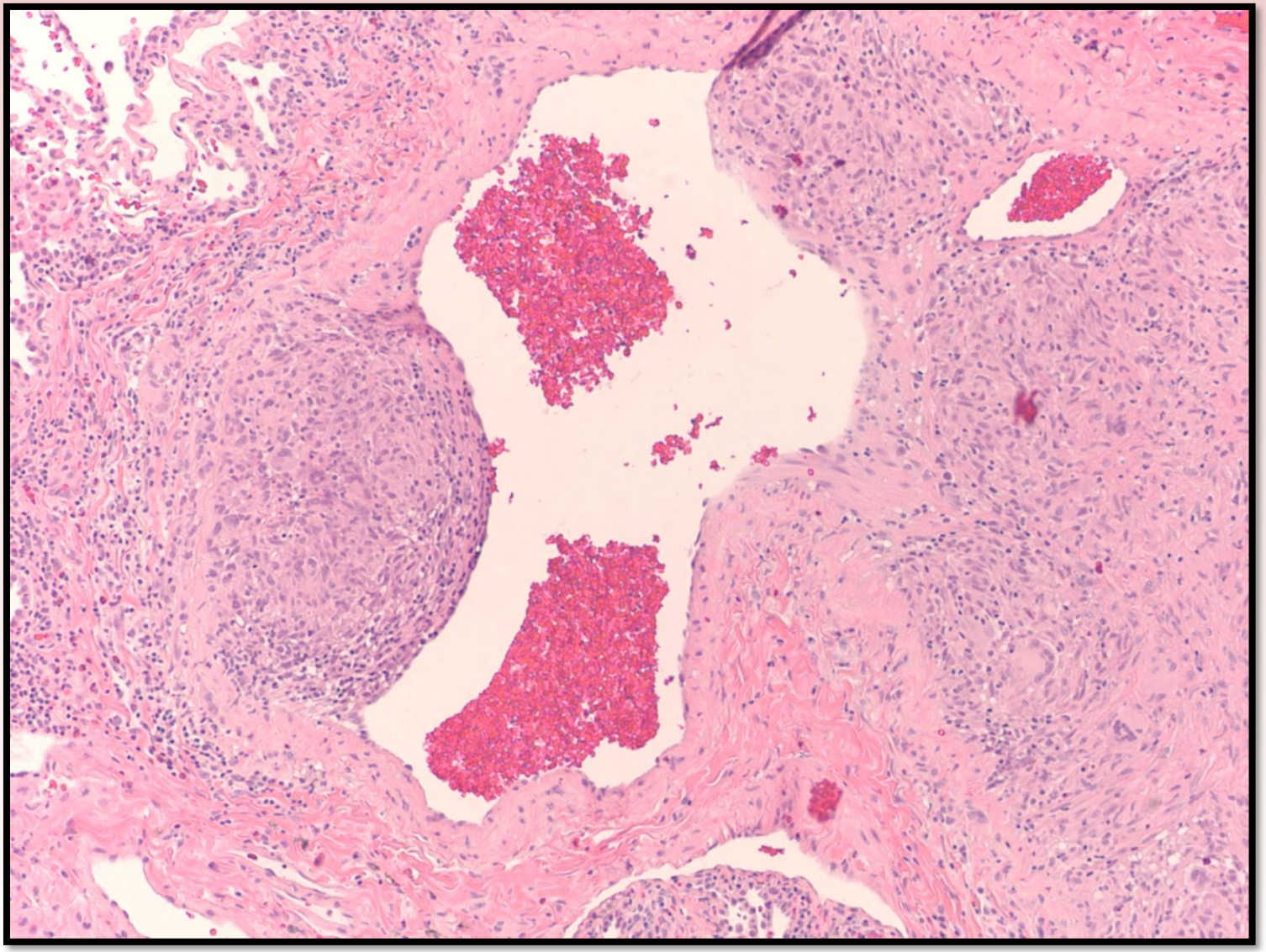
-Non-Necrotizing

-“Sarcoid Like”

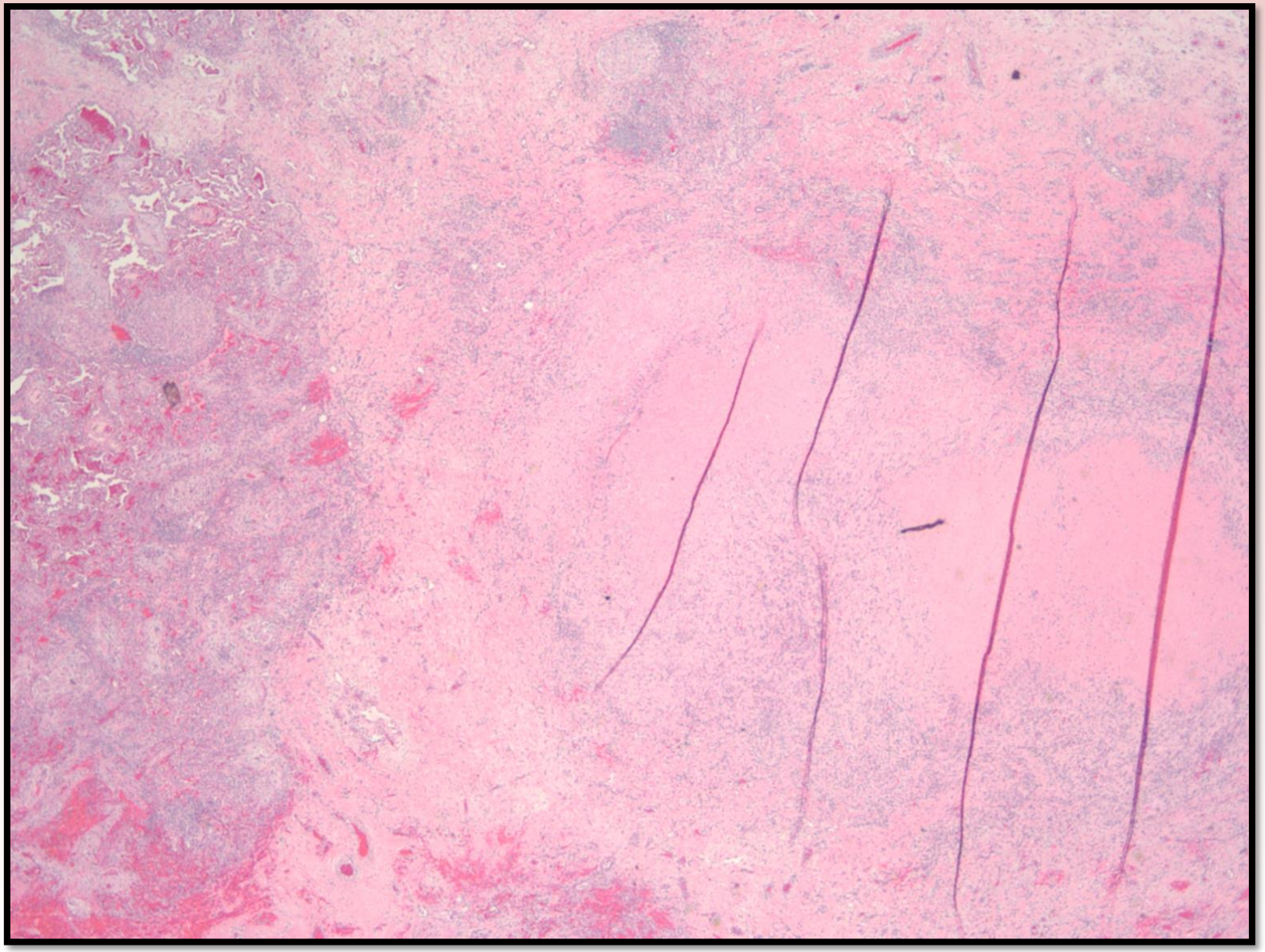
Granulomatous vasculitis



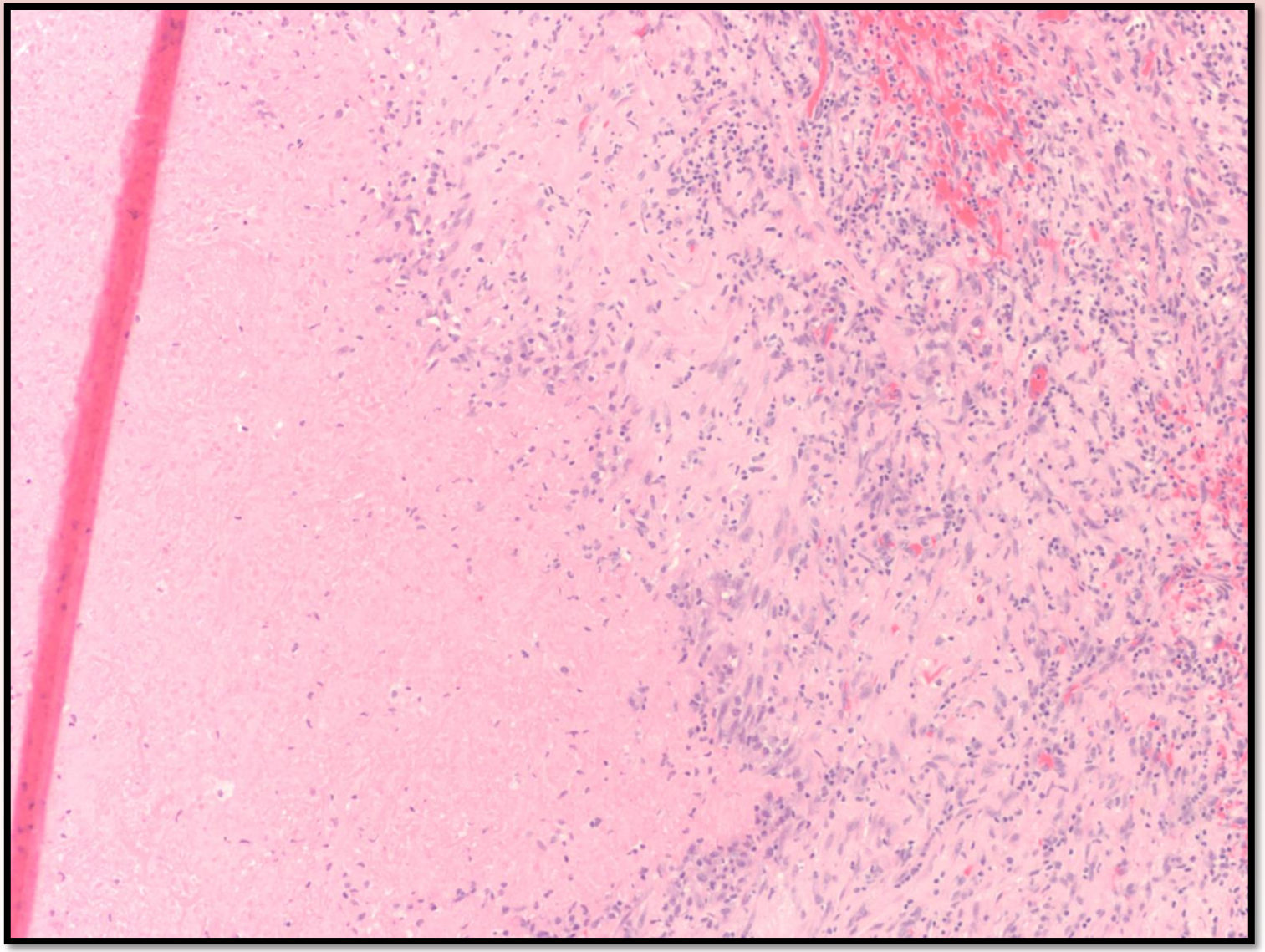
Necrotizing Sarcoidosis

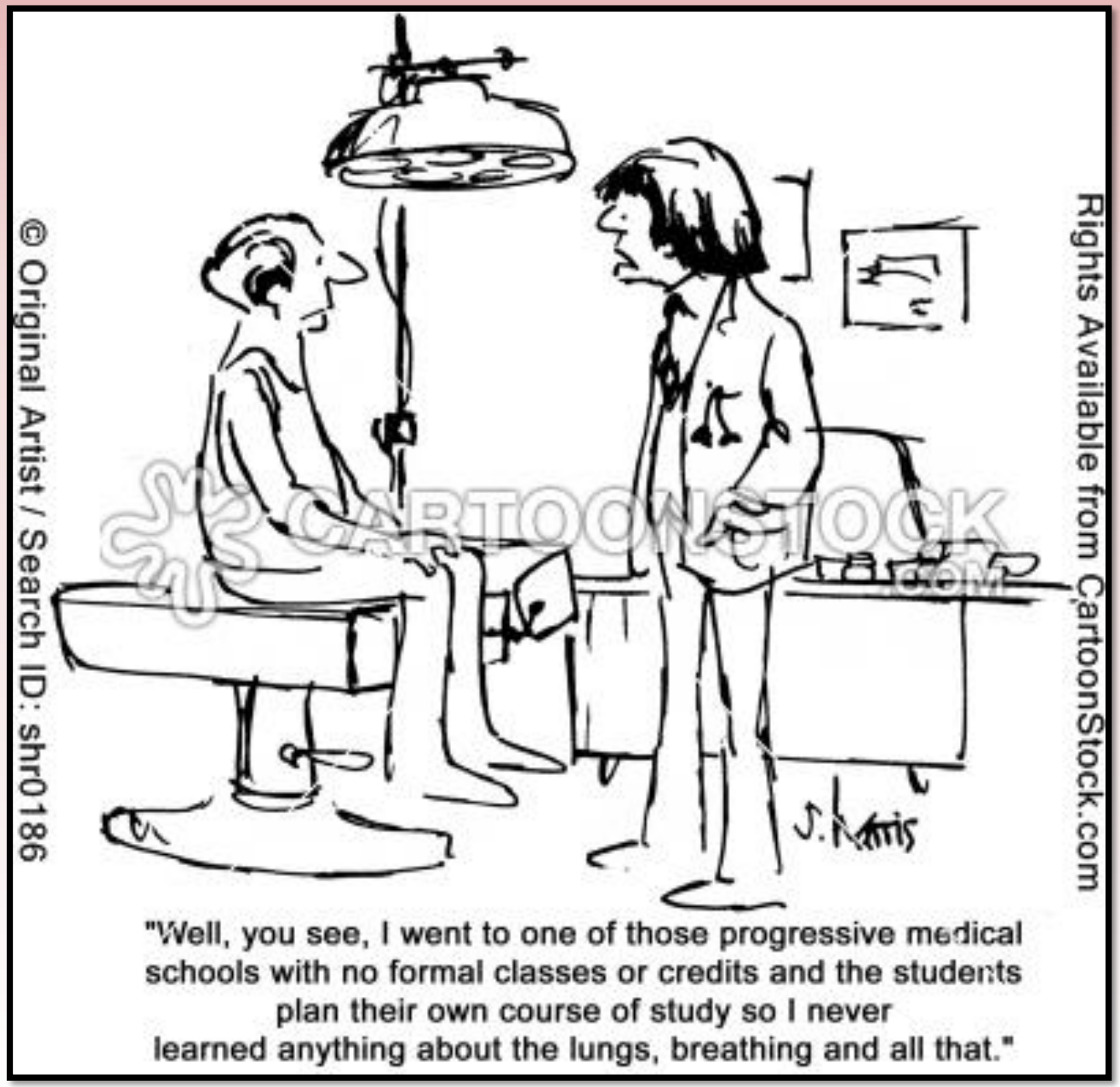


Necrotizing Sarcoidosis



Necrotizing Sarcoidosis




"Well, you see, I went to one of those progressive medical schools with no formal classes or credits and the students plan their own course of study so I never learned anything about the lungs, breathing and all that."
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