MAYO CLINIC

APPROACH TO DIFFUSE INFILTRATIVE LUNG DISEASES

UPDATE WITH CASE-BASED REVIEW

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KOPANA Spring Seminar

MAYO CLINIC

Education:

Medical School: Seoul National University College of Medicine (1976 – 1982)
Residency:
Seoul National University Hospital – AP (1983 – 1986)
Washington Hospital Center, Washington DC – AP (1987 – 1990)
University of California Irvine Medical Center – CP (1990 – 1992)

Current Position & Institution: Professor and Consultant, Mayo Clinic Rochester, School of Medicine (2006 – present)

Subspecialty area: Thoracic Pathology

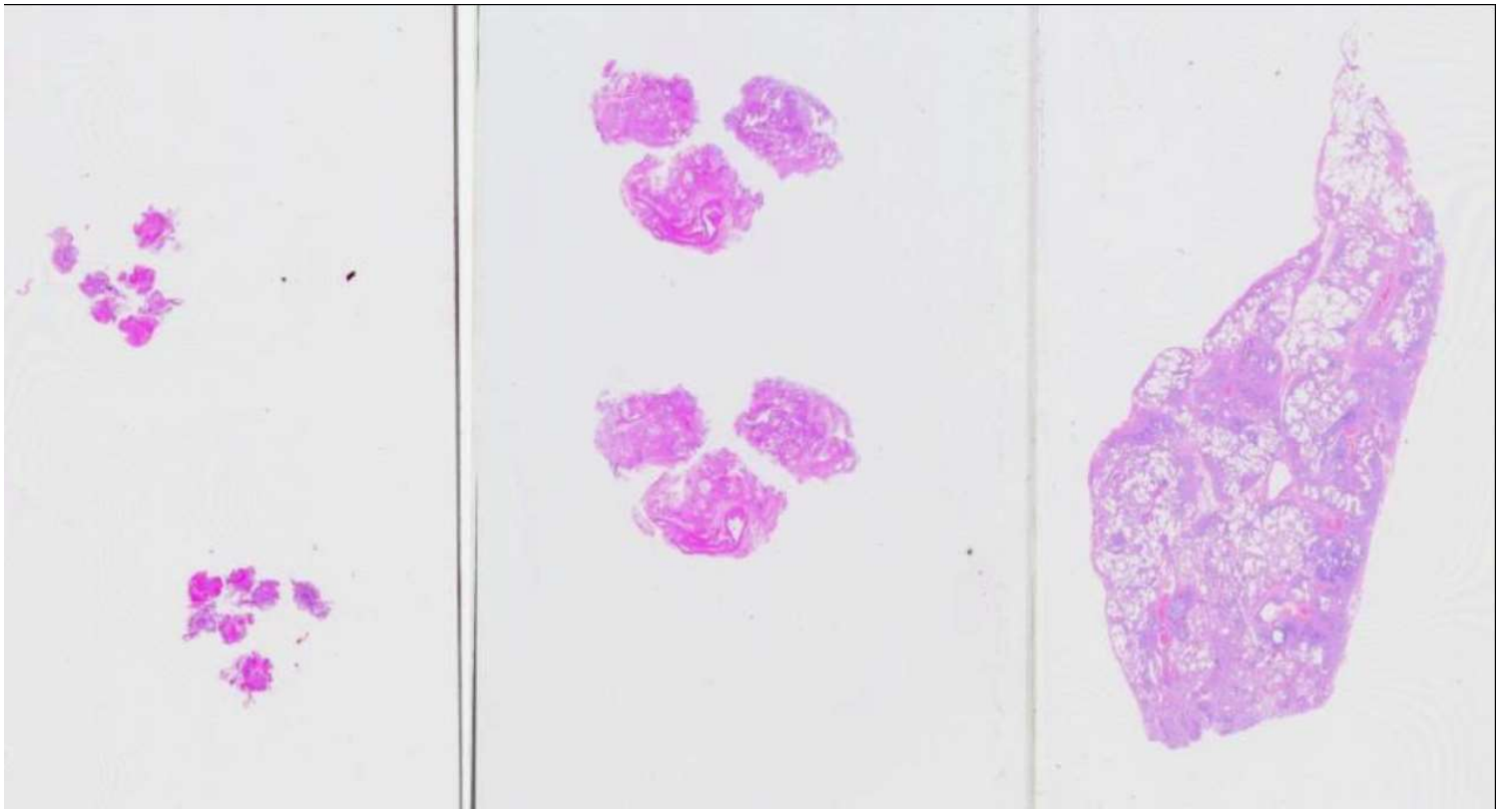
OUTLINES

- **Essentials for histopathologic dx of ILD**
  - Radiology
  - Various histopathology seen in ILDs
  - 2013 ATS classification of Idiopathic Interstitial Pneumonias (IIPs)
- **Four cases:**
  - Fibrotic hypersensitivity pneumonitis: *mimicker of UIP/IPF*
  - Familial ILD: *tales of two cousins with underlying mutation*
  - Amyloidosis: *easy to mistake as ILDs*
  - Invasive adenocarcinoma arising in ILD: *should not miss dx*
- **Take home points**

BASIC APPROACH TO ILD

- **Compile the histopathologic findings by systematic review:** Need to know the basic glossary of histopathology in ILDs
- **Correlate with clinical and radiologic findings:** Be familiar with the main clinical settings and radiologic terms
- **Put the constellation of features into an appropriate diagnostic category or disease**

SIZE OF LUNG BIOPSY SPECIMENS



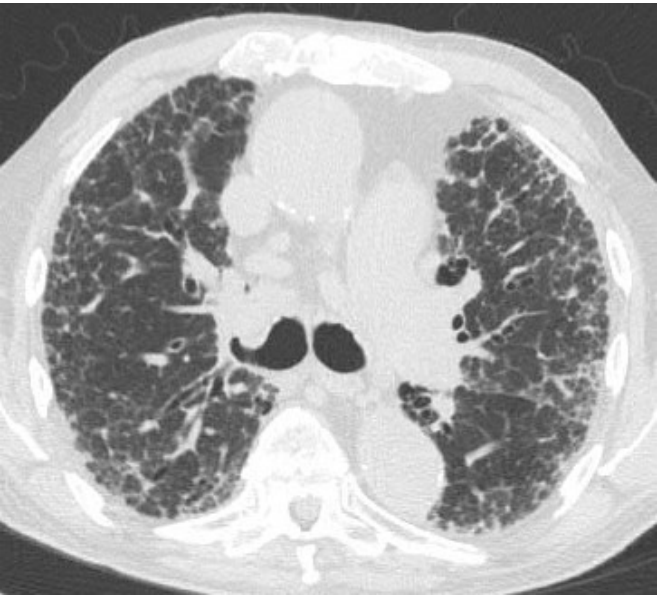
Transbronchial forcep bx **Cryobx** **Wedge bx**

(Courtesy of TV Colby)

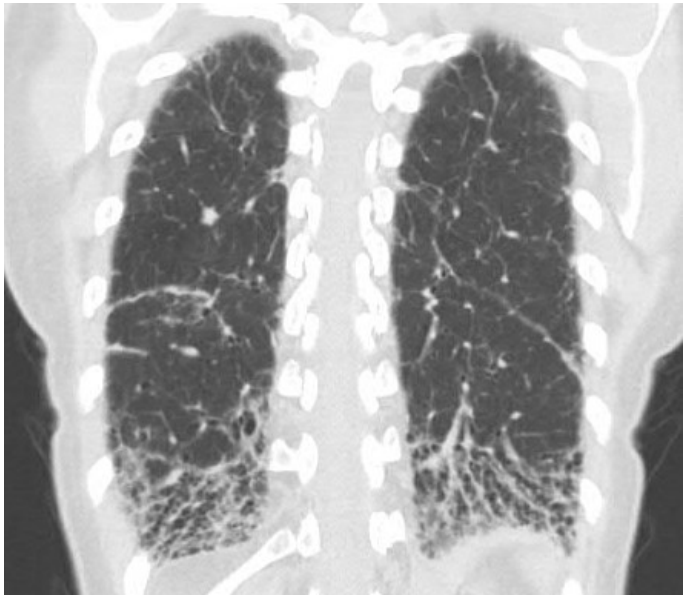
RADIOLOGY: *TERMS OFTEN USED IN HRCT*

- **Densities:**
  - Consolidation
  - Ground glass
  - Reticular
- **Distribution:**
  - Upper vs. lower
  - Centrilobular vs. peripheral, lymphangitic,etc
  - No predilection
- **Others:**
  - Honeycombing / traction bronchiectasis
  - Mosaic attenuation, air-trapping

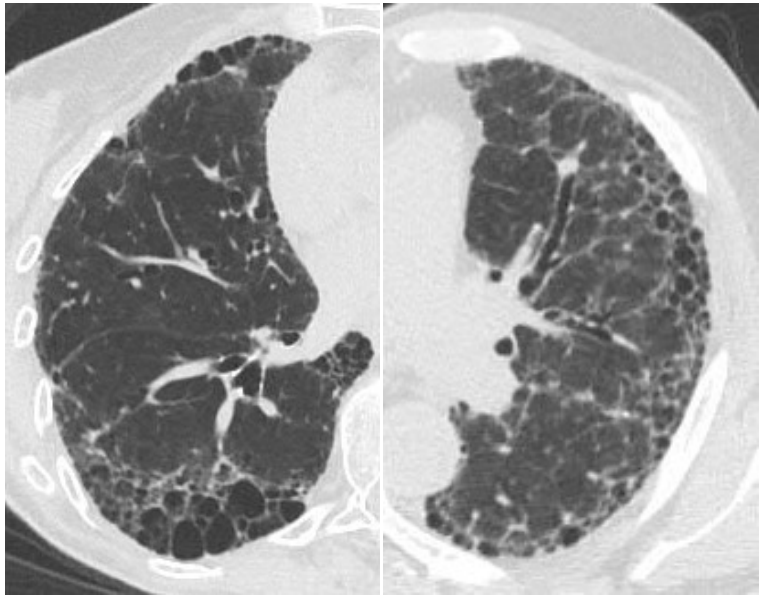
LUNGS WITH FIBROSIS AND SCARRING



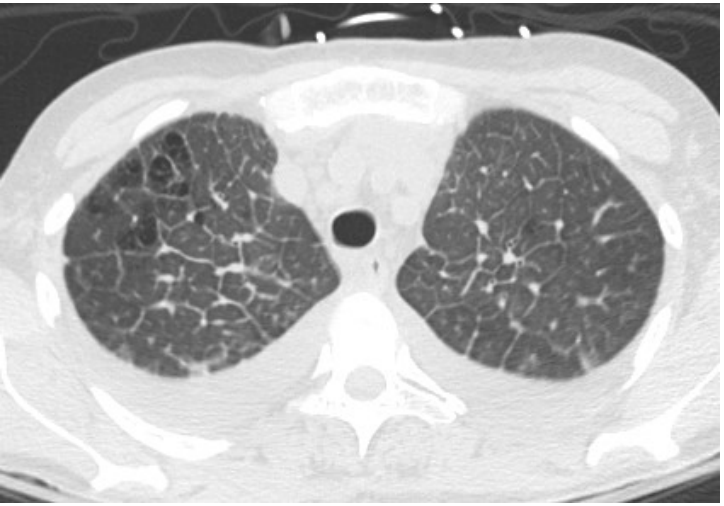
Reticulation

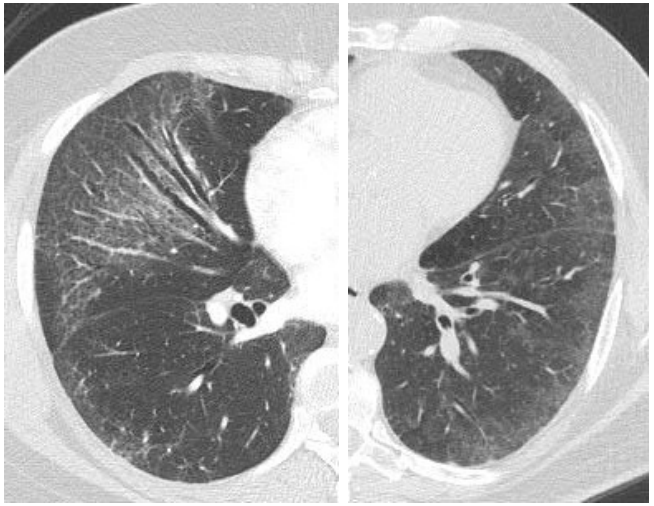


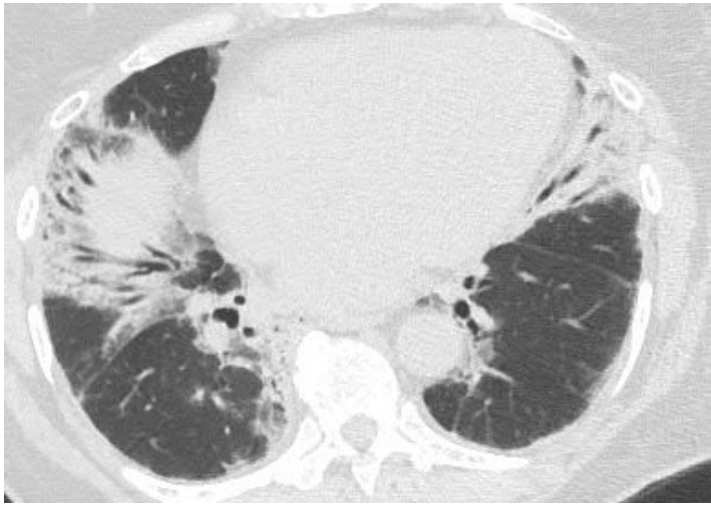
Traction bronchiectasis



Honeycombing



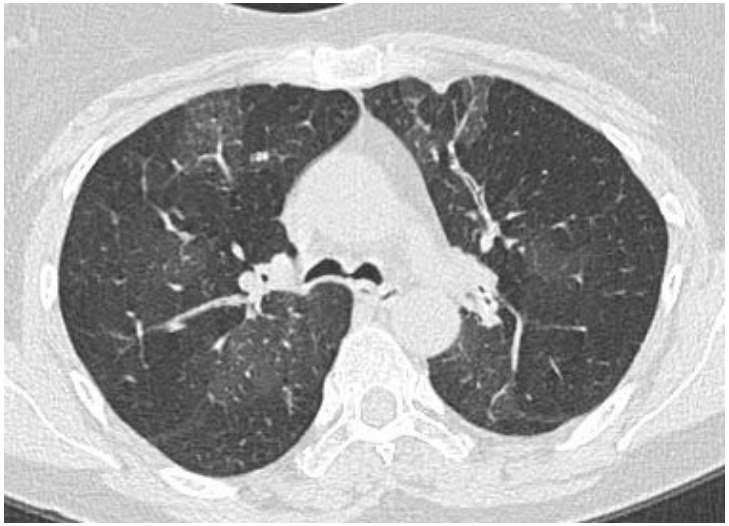




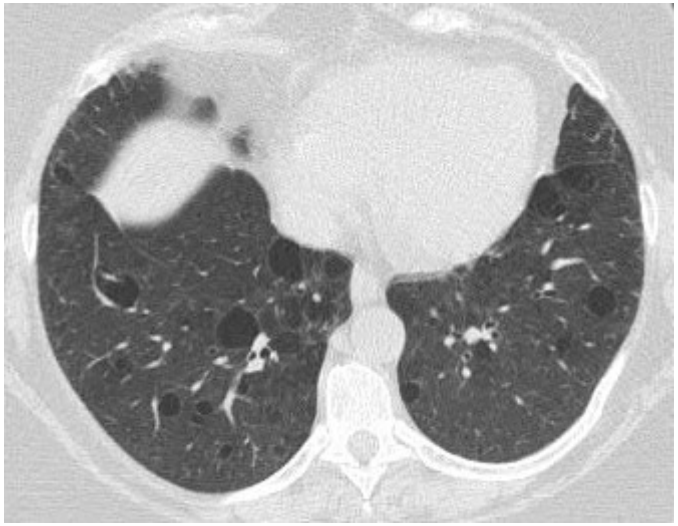
Interlobular septal thickening

Groundglass opacity

Consolidation



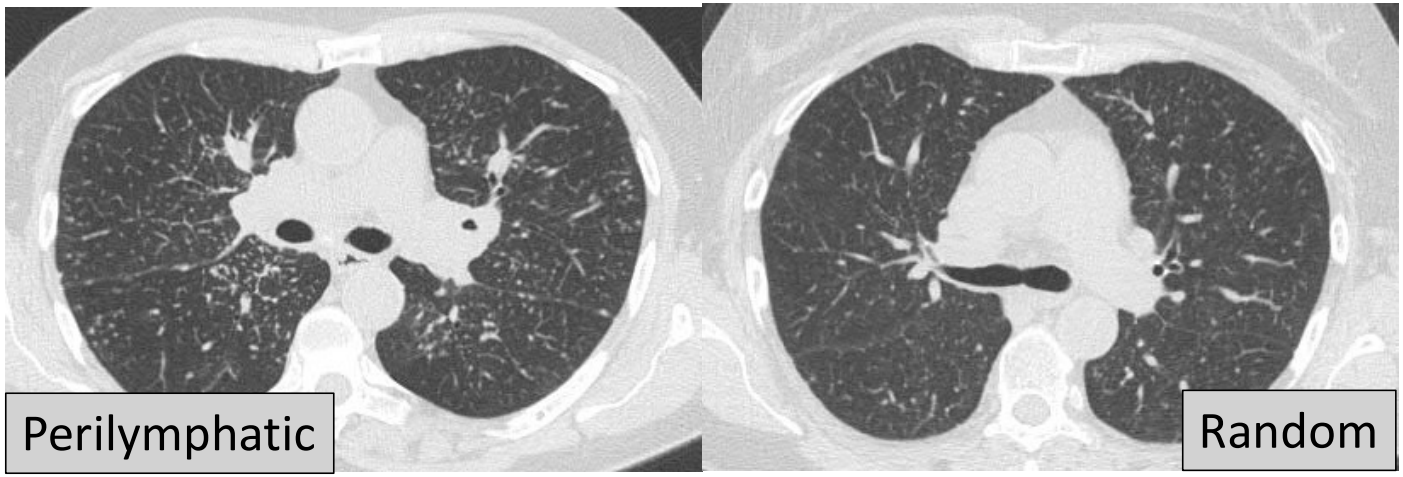
Air-trapping (expiratory scan)



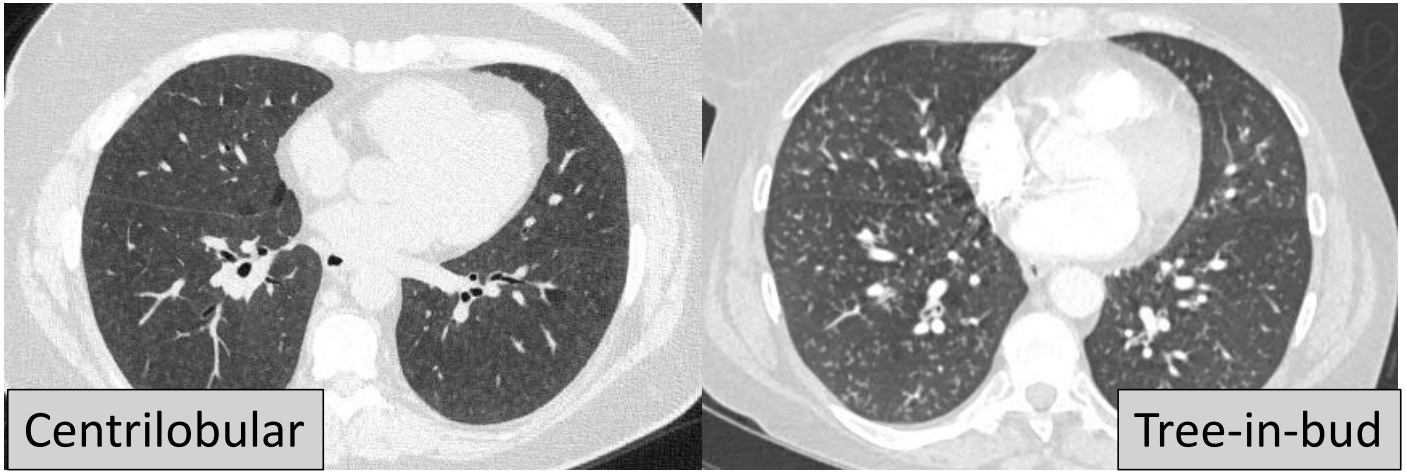
Cysts

CT PATTERNS OF INTERSTITIAL NODULARITY

(+) pleural/ fissural nodules

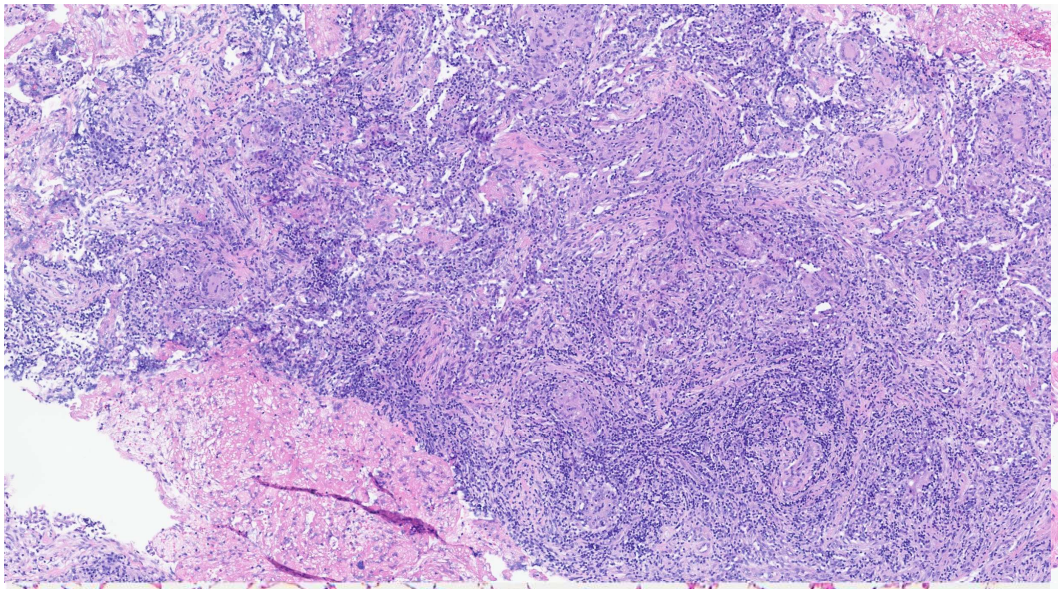


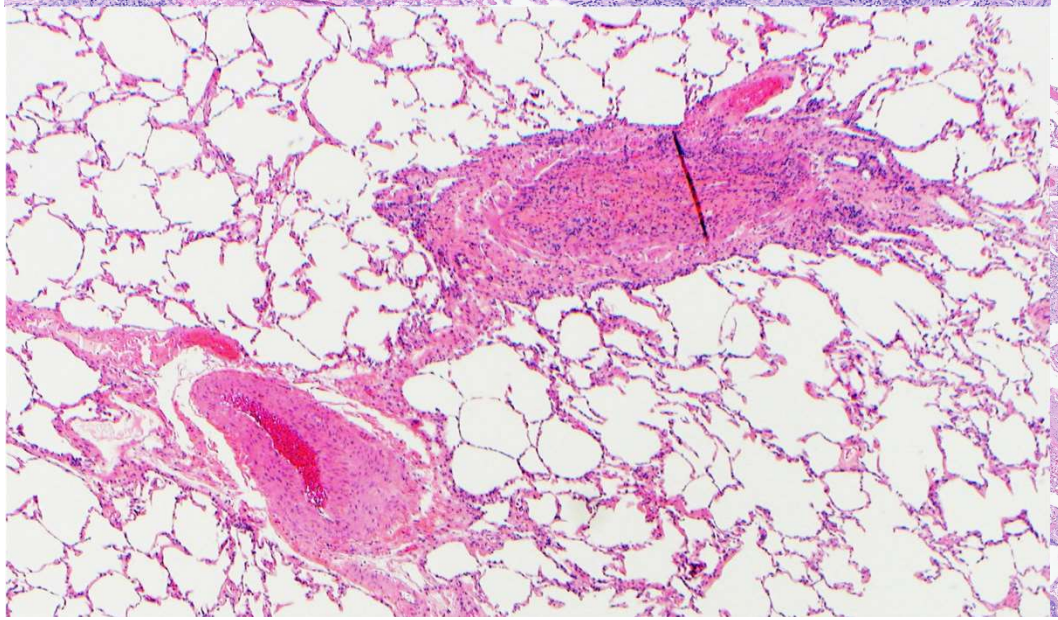
(-) pleural/ fissural nodules

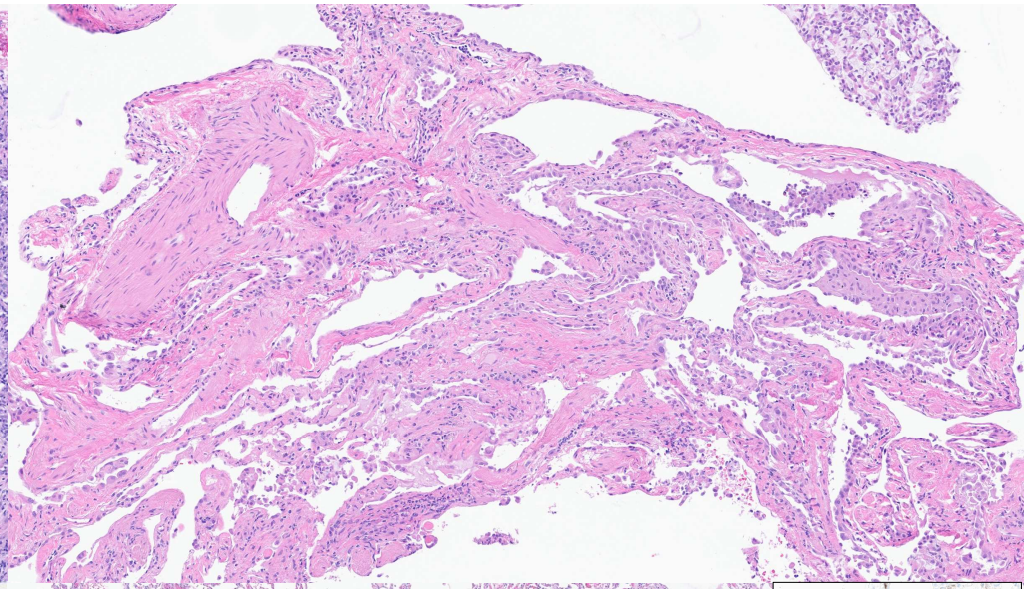


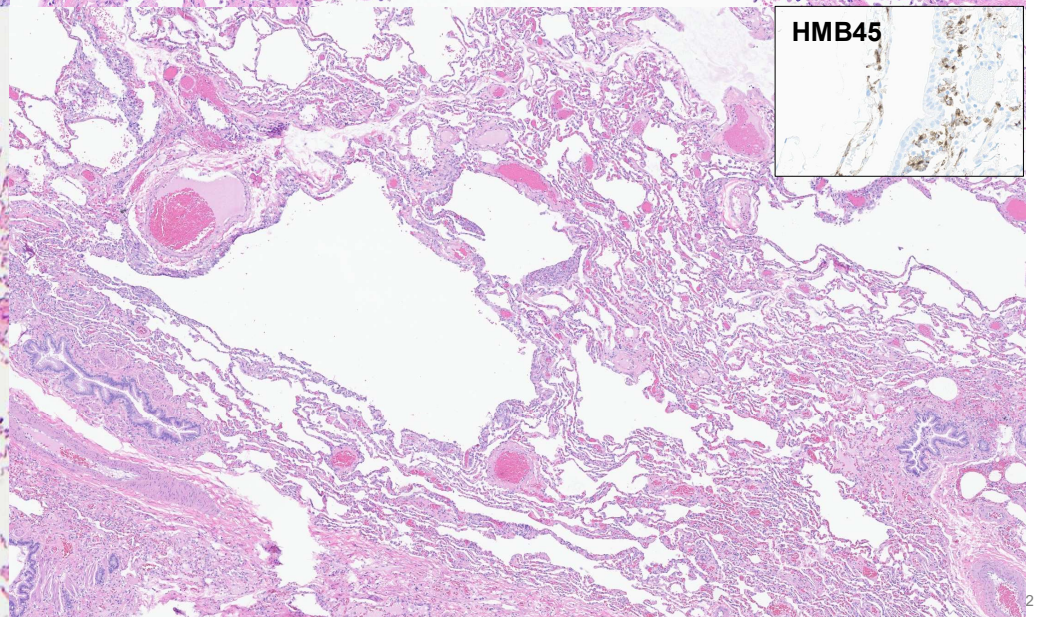
PATHOLOGY: INITIAL IMPRESSION IN MEDICAL LUNG BX

- **Inflammatory:** granulomas, types of inflammatory cells
- **Fibrosing:** distribution, scarring, honeycombing
- **Tumor (mass) – like**
- **Unremarkable:** almost look normal
  - Isolated constrictive bronchiolitis
  - Some types of pulmonary hypertension
- **Something other than ILD**








HMB45

2013 REVISED CLASSIFICATION OF IIP

MULTIDICIPLINARY DISCUSSION (MDD)

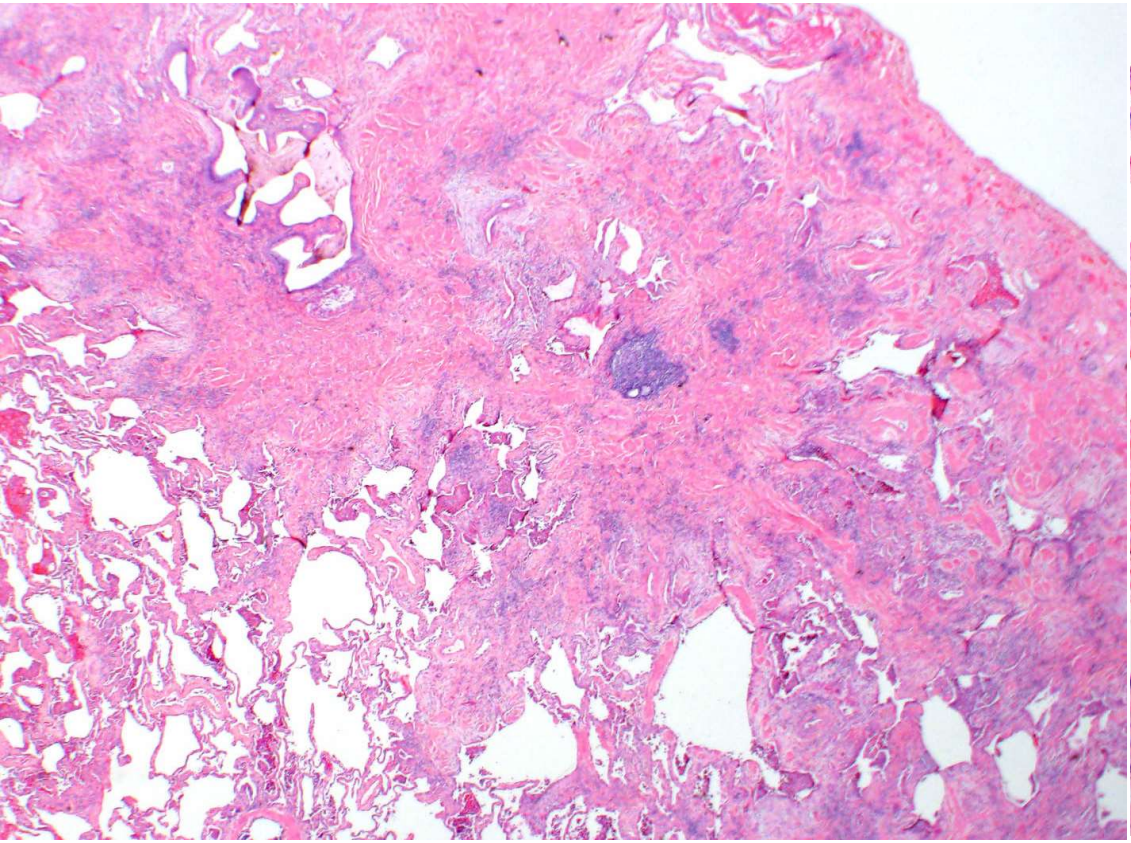
AM J CRIT CARE MED 2013;188:733-748

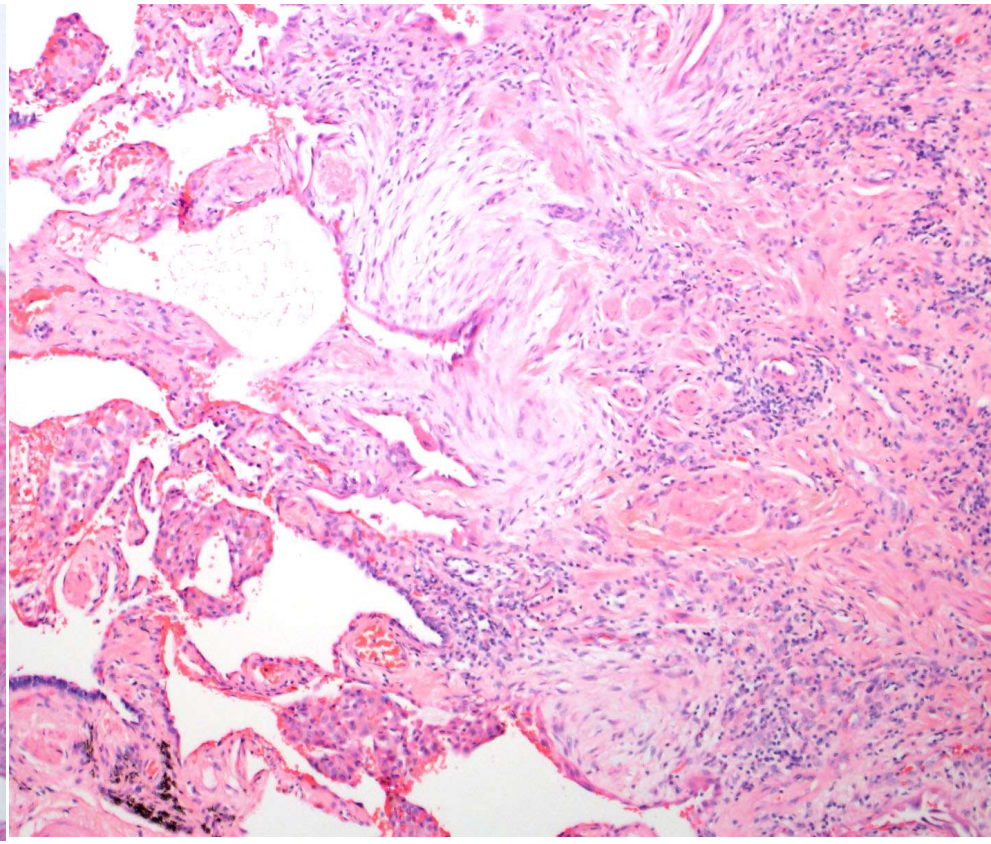
- **Major IIP MDD** - *histopathological counterpart*
  - Idiopathic pulmonary fibrosis (**IPF**) - *UIP*
  - Nonspecific interstitial pneumonia (**NSIP**) - *NSIP*
  - Cryptogenic organizing pneumonia (**COP**) - *OP*
  - Acute interstitial pneumonia (**AIP**) - *DAD*
  - Respiratory bronchiolitis interstitial pneumonia (**RB-ILD**) - *RB*
  - Desquamative interstitial pneumonia (**DIP**) - *DIP*
- **Rare IIPs:** LIP, Pleuroparenchymal fibroelastosis (PPFE)
- **Unclassifiable IIPs**

MAJOR POINTS IN 2013

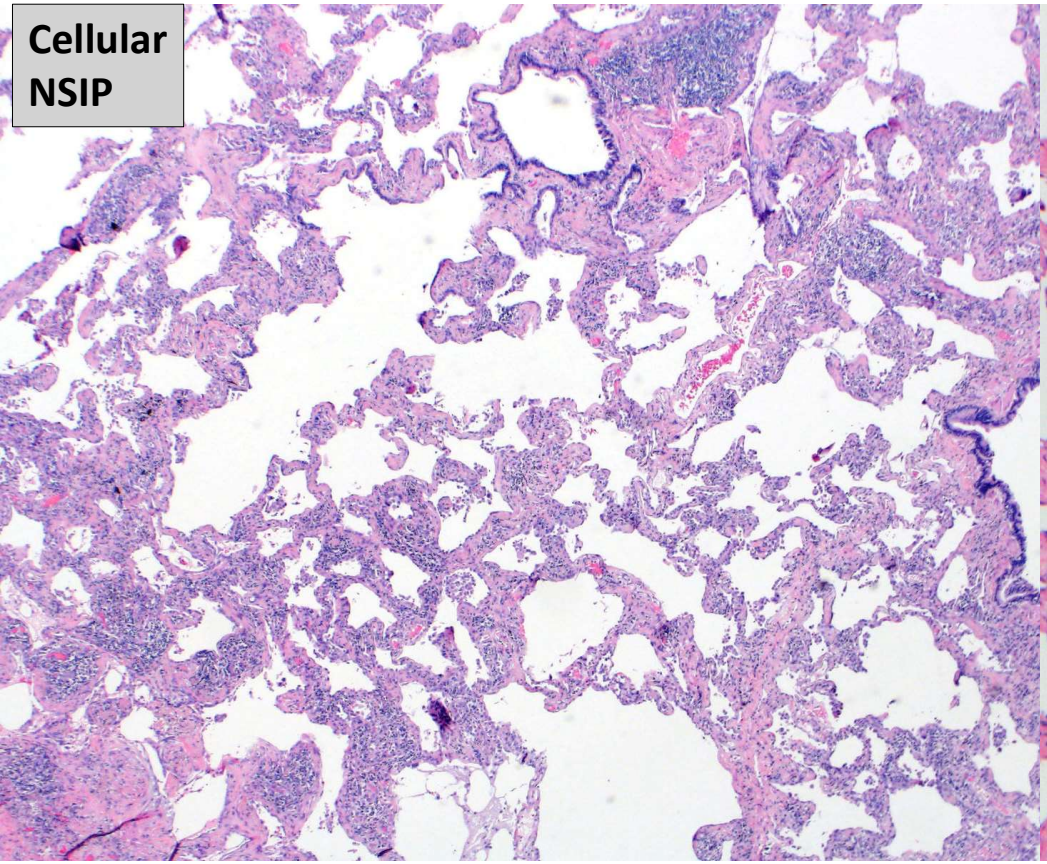
- NSIP is no longer a provisional, and accepted as a specific clinicopathologic entity of IIP
- **UIP pattern on HRCT is acceptable to render dx of IPF without Bx:** *significantly reduce the frequency of surgical lung bx!*
- PPFE and LIP as rare entities
- Unclassifiable IIP as a category: *often CTD associated with overlap of histologic patterns, or familial ILD, among others*

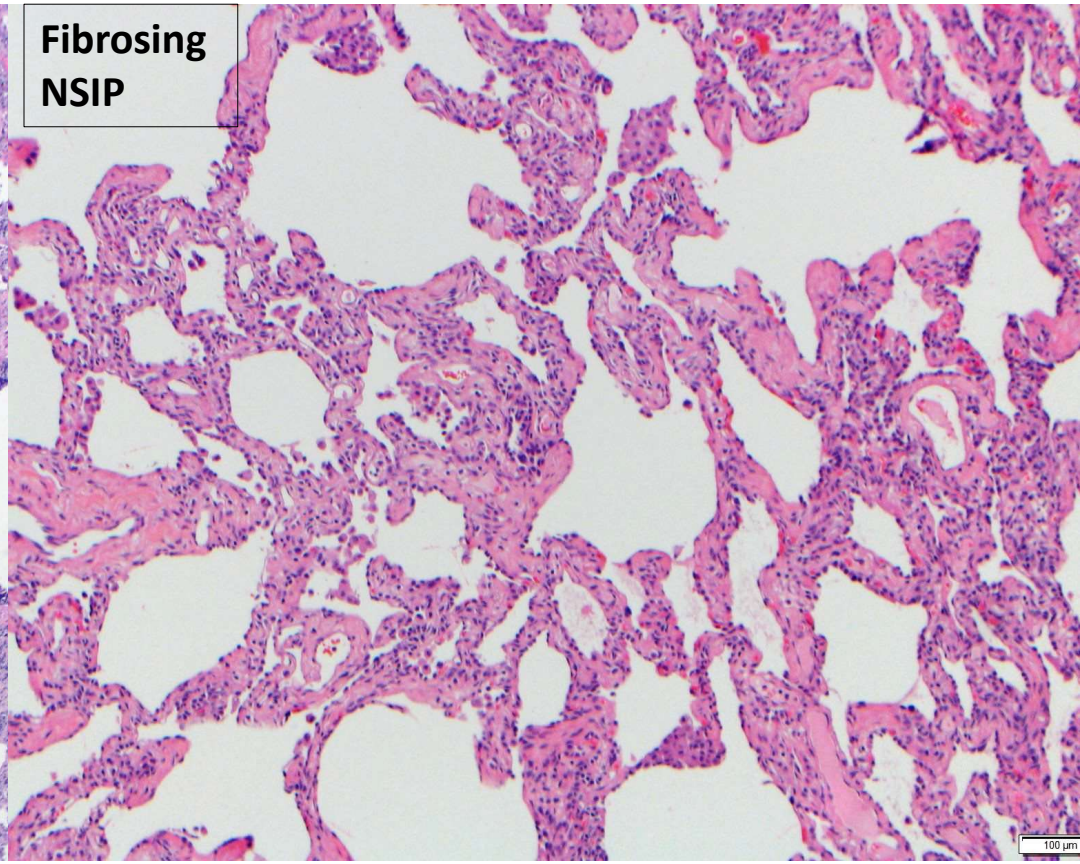
PATCHY, SCARRING, HONEYCOMB CHANGE, TEMPORAL HETEROGENEITY – UIP





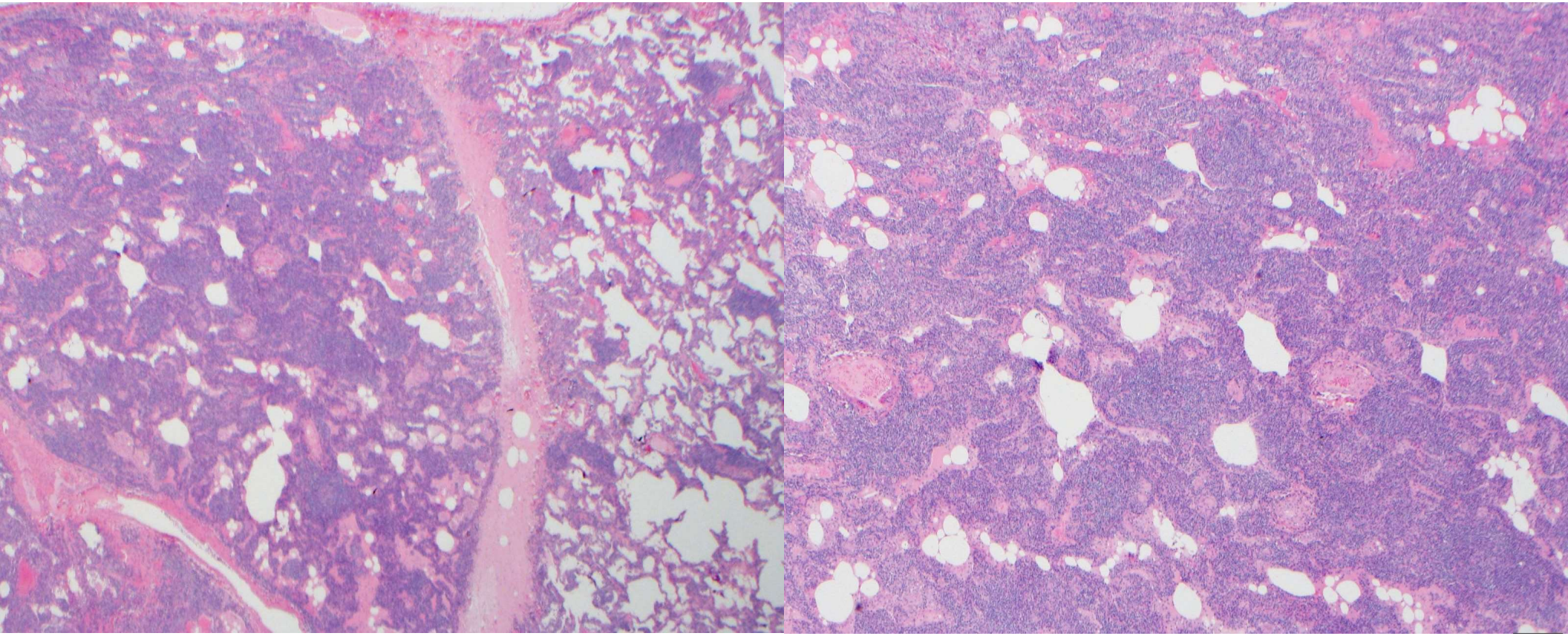
UNIFORM, PRESERVED ARCHITECTURE – NSIP



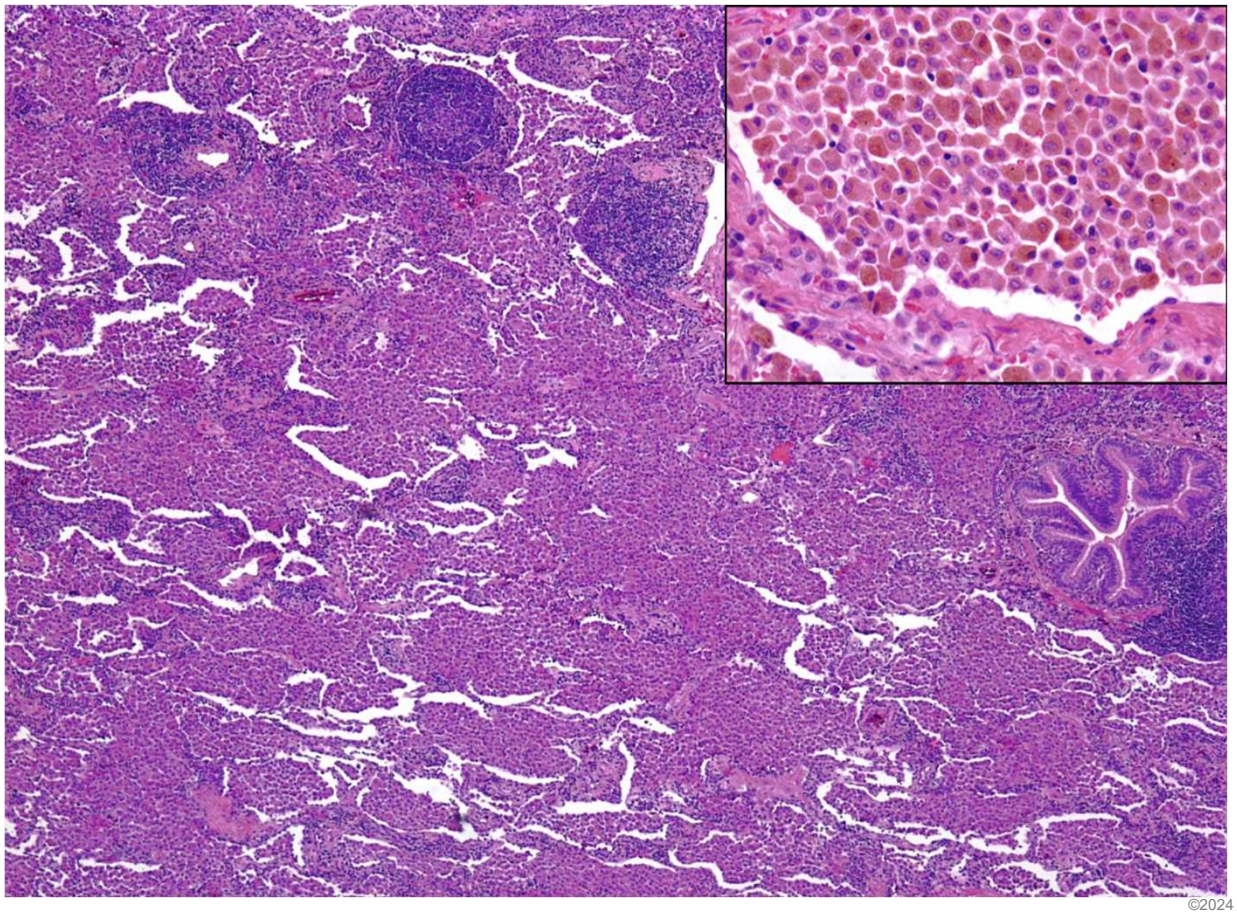


MORE CONFLUENT LYMPHOCYTIC INFILTRATES THAN C-NSIP; WORRISOME FOR LYMPHOMA – LIP

(MOSTLY SECONDARY, SUCH AS SJÖGREN'S SYNDROME)

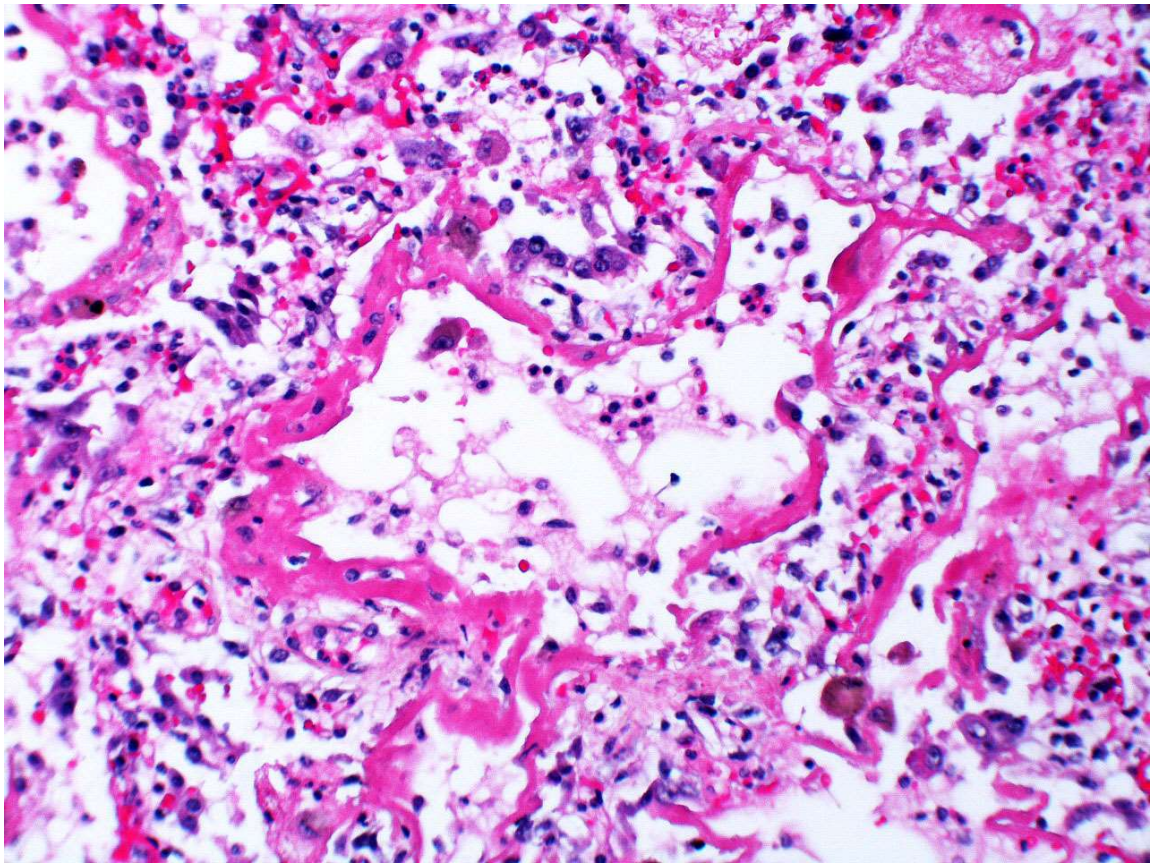


DIFFUSE ACCUMULATION OF ALVEOLAR MACROPHAGES WITH VARIABLE INTERSTITIAL FIBROSIS - DIP

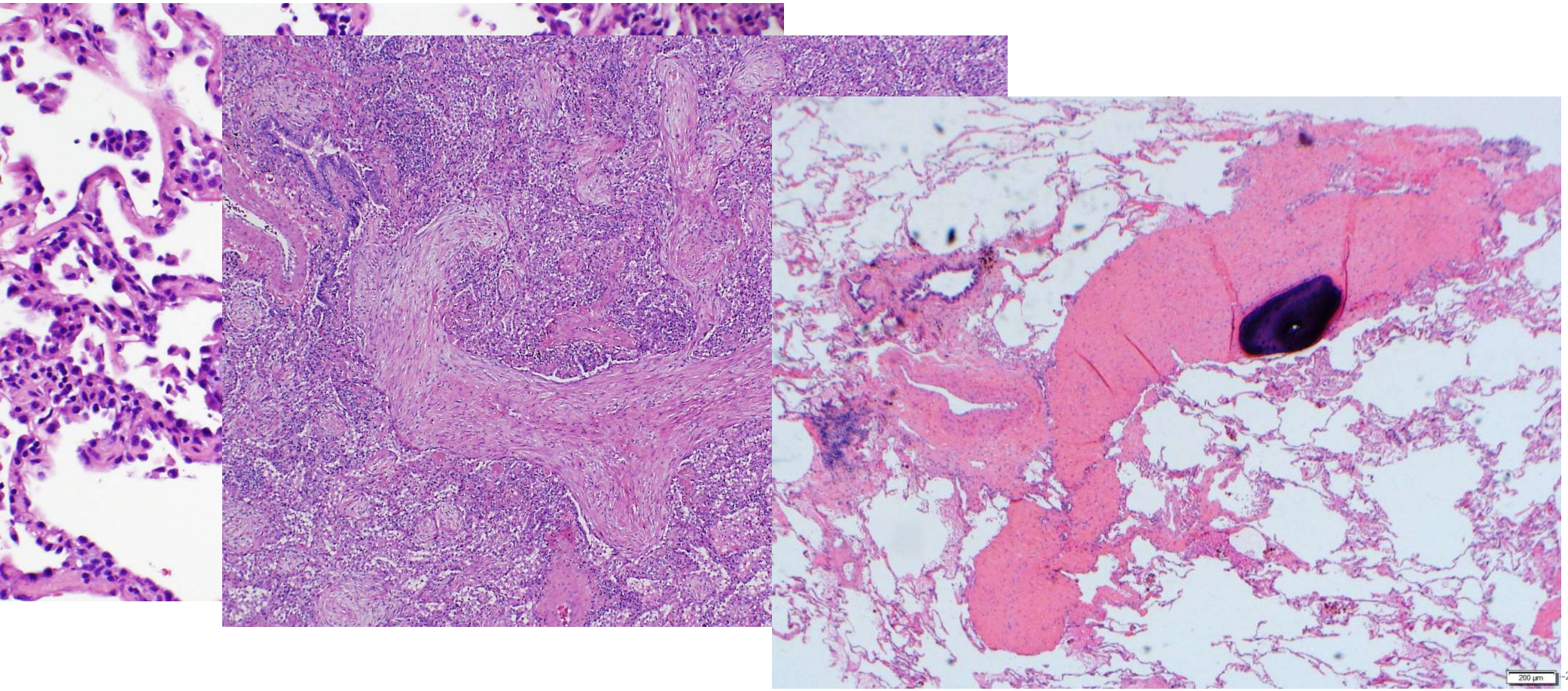


ALVEOLAR WALL THICKENING WITH FIBROBLASTIC PROLIFERATION AND HYALINE MEMBRANES – DAD

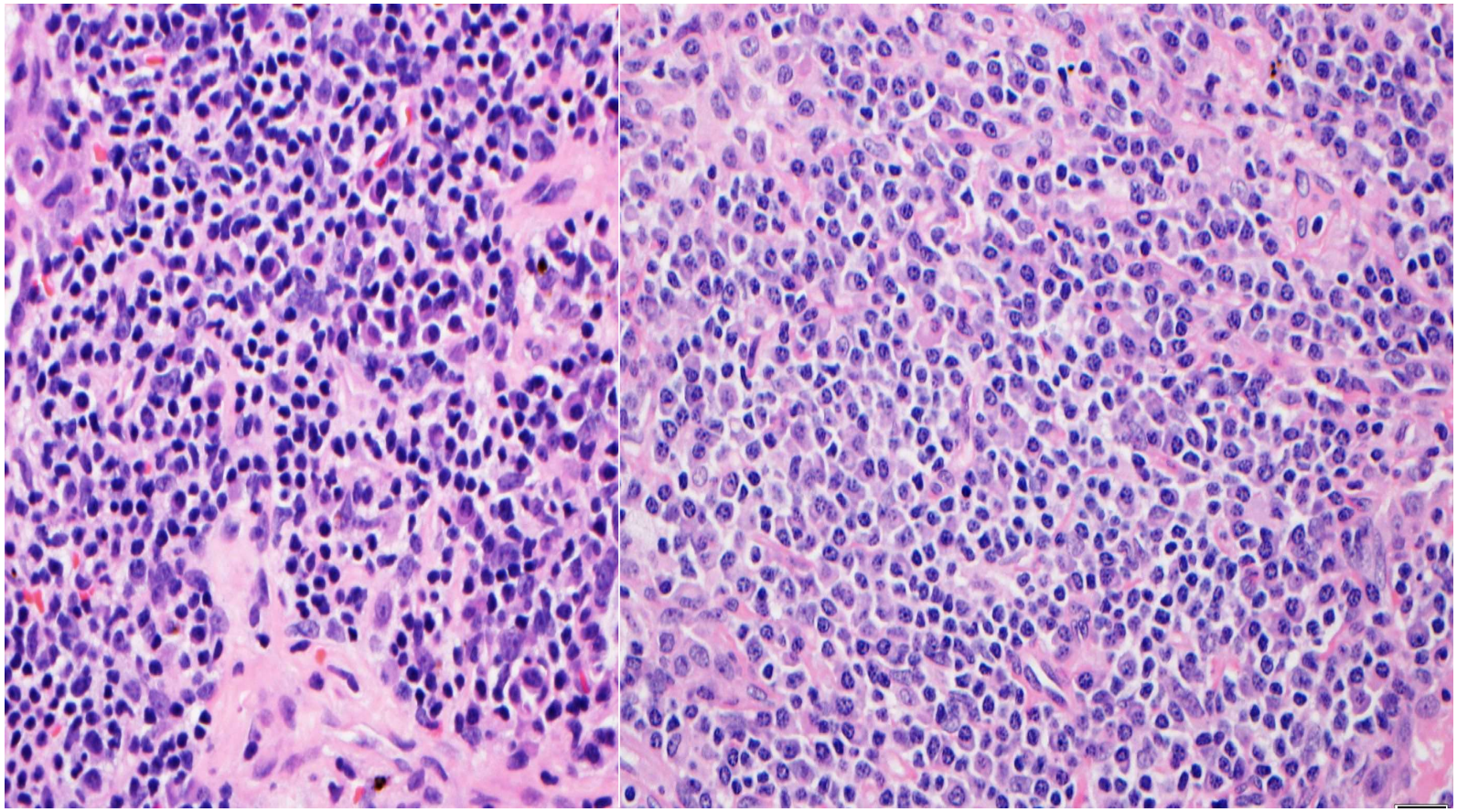
IDIOPATHIC DAD WITH FIBROSIS = AIP



INTRAALVEOLAR FIBROBLASTIC/FIBROTIC PLUGS: ORGANIZING PNEUMONIA



PLASMA CELL-RICH INFILTRATES

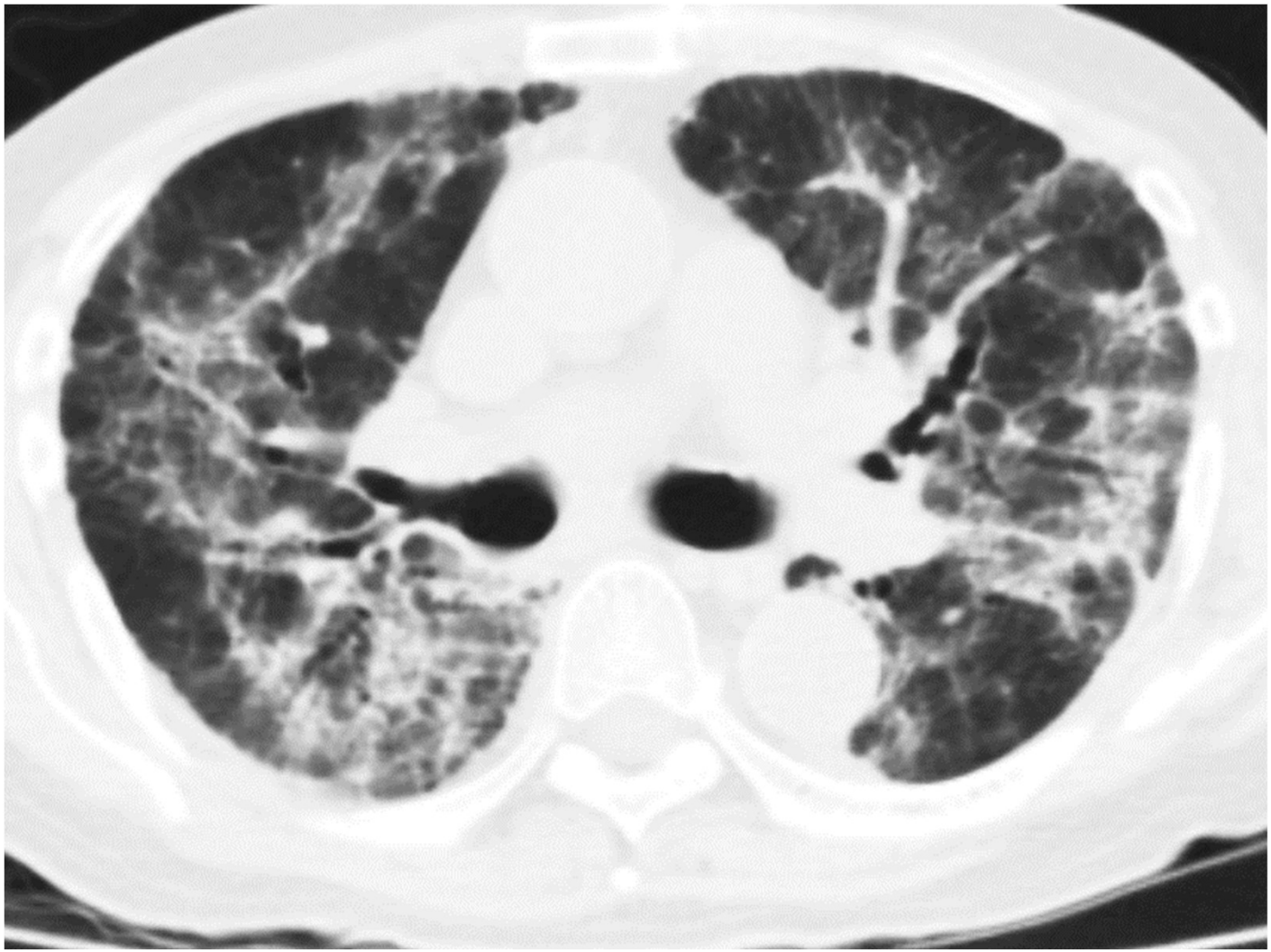


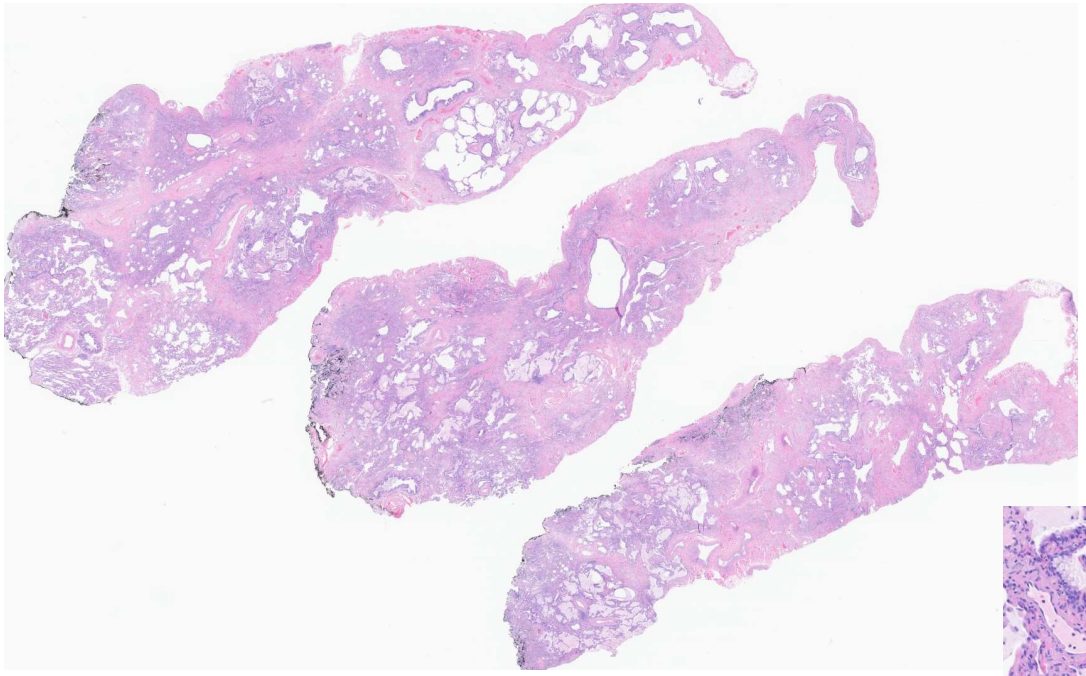
CASE 1

Fibrotic ILD with inflammatory component

CASE SUMMARY

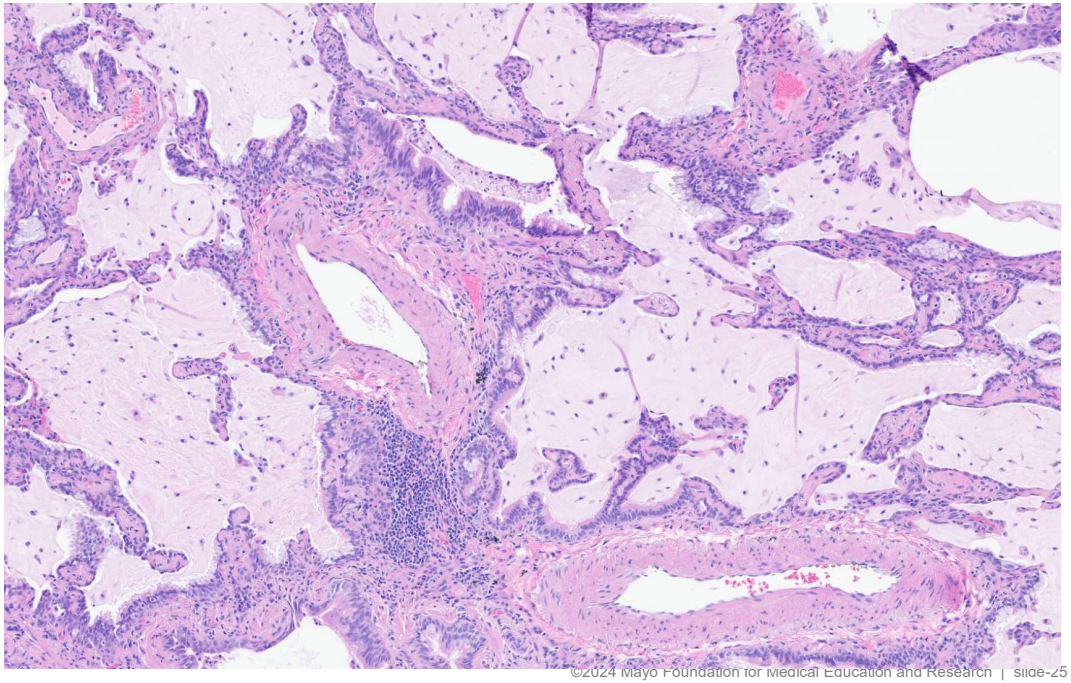
- 81M
- Worsening respiratory symptoms
- CT scan:
  - Upper lobe predominant reticular densities and ground glass opacities
  - Traction bronchiectasis, but no honeycomb change
  - Focal subpleural sparing, suggestive of NSIP
  - No mosaic attenuation or air trapping on expiratory scan

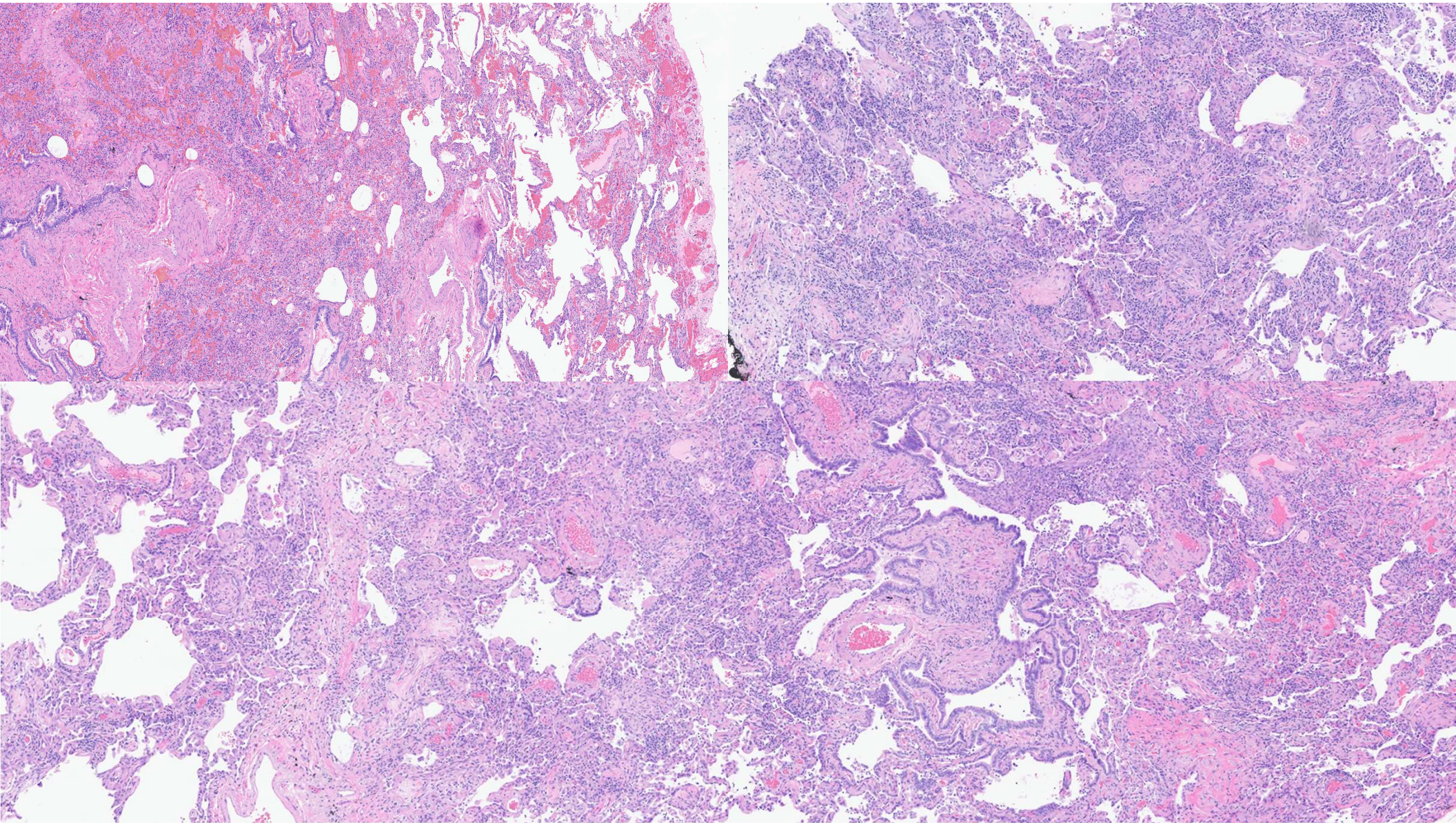




Histopathology

UIP – like features, but…..





MAYO CLINIC

Case 1: Dx

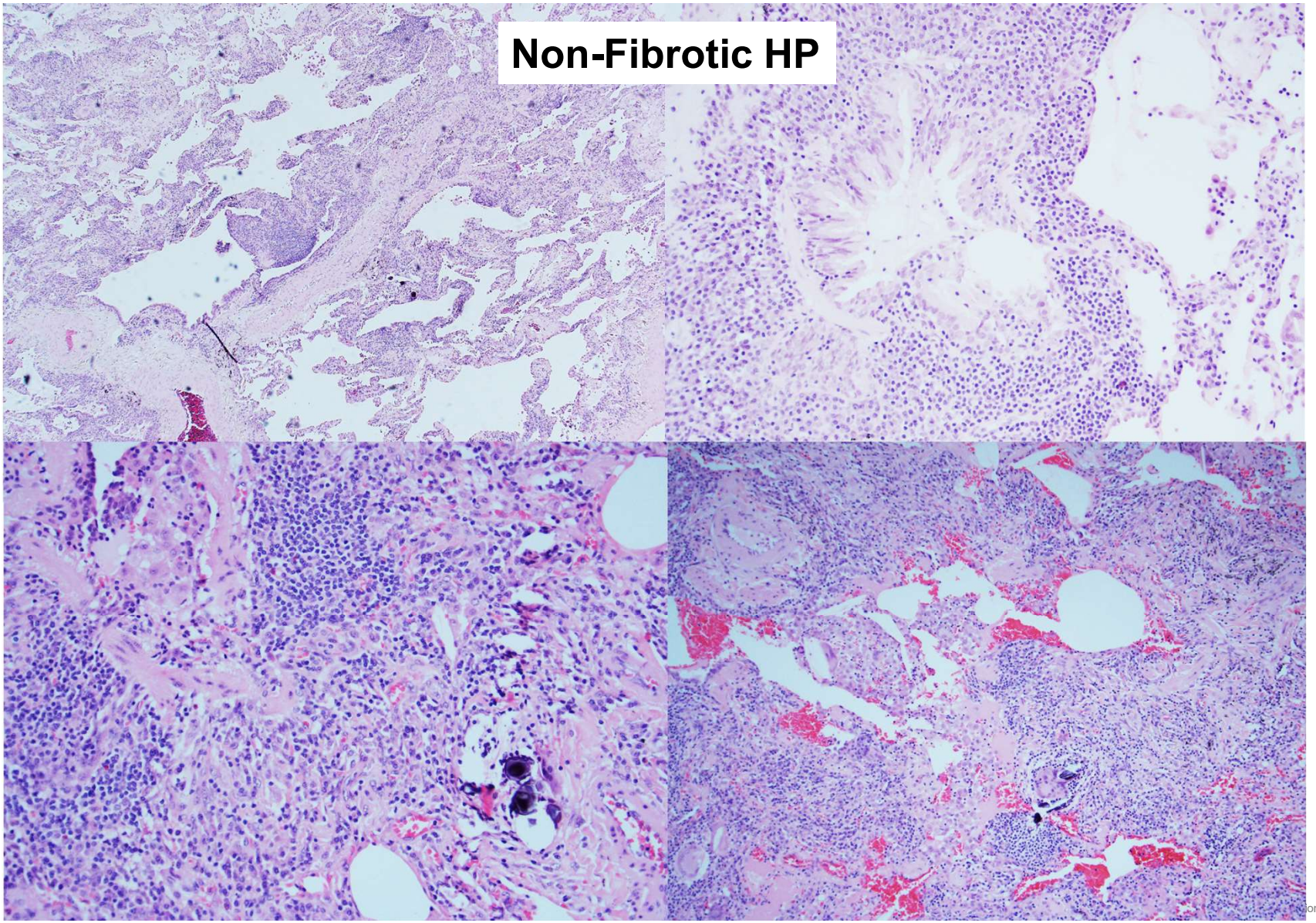
Chronic fibrosing ILD with UIP features, patchy OP and marked interstitial lymphocytic infiltrates (see comment)

Comment: Overall features are most suggestive of fibrotic HP

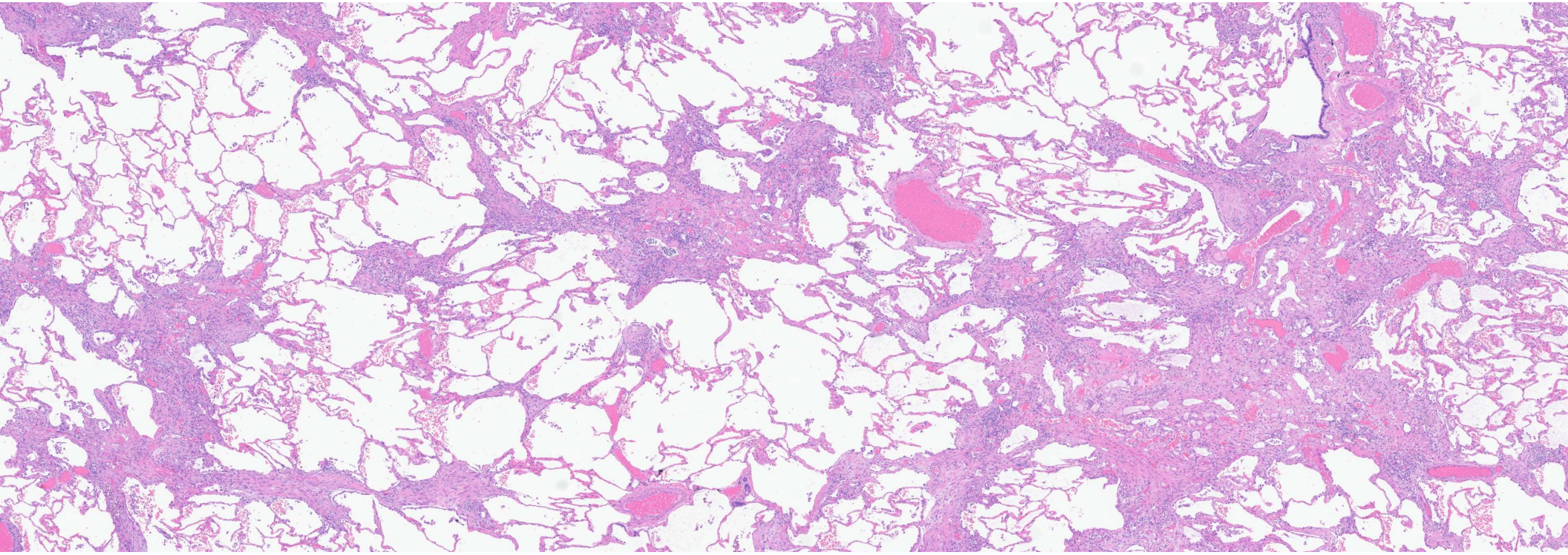
HYPERSENSITIVITY PNEUMONITIS

- Non-fibrotic (subacute) vs. Fibrotic (chronic) HP
- Non-fibrotic HP: cellular bronchiolitis, centriacinar lymphocytic infiltrate, poorly formed non-necrotizing granulomas w/wo organizing pneumonia; *Fibrotic HP tends to lose these findings…*
- Fibrotic HP may take the several forms of interstitial fibrosis:
  - Interstitial fibrosis confined to peribronchial regions
  - Fibrotic NSIP
  - Indistinguishable from UIP/IPF
- CT findings favor fibrotic HP:
  - Sparing of lung bases
  - Centrilobular nodules
  - Air-trapping or triple density sign of GGO, in a background of fibrosis

Non-Fibrotic HP



Airway–Centered Fibrosis



MAIN HISTOPATHOLOGIC DDX OF HP

Clinical and radiologic features could help in many but in not all cases

For non-fibrotic HP:

- Connective tissue disease – associated ILD
- Drug reaction: methotrexate, newer antiinflammatory drugs, and any biologic agents
- Infections: esp. viral
- CVID or other immunodeficiencies

For fibrotic HP:

- Fibrotic NSIP
- UIP/IPF – may be indistinguishable

HISTOPATHOLOGIC CRITERIA OF UIP/IPF

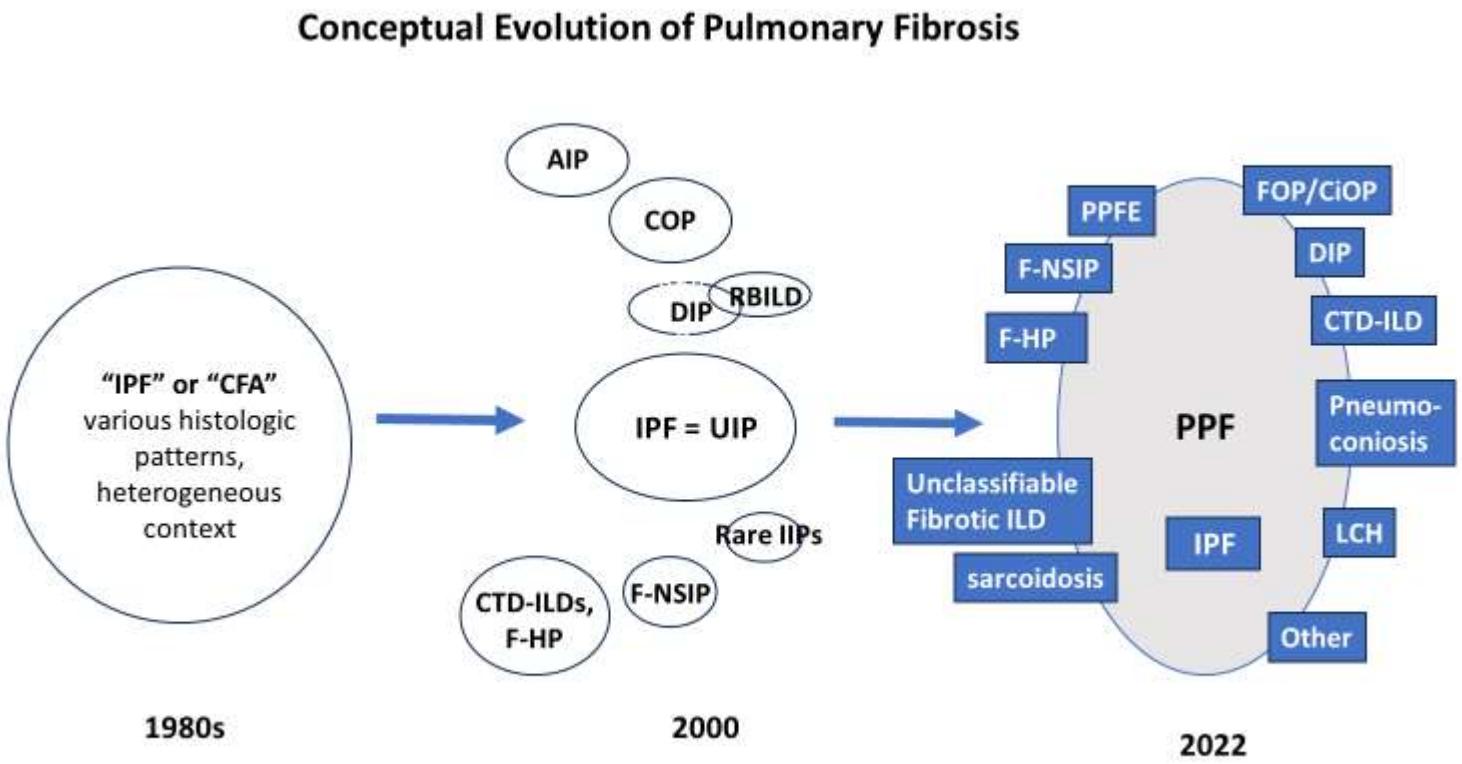
KATZENSTEIN & MYERS. AM J RESPIR CRIT CARE MED 1998;157:1301-15

1. Patchy fibrosis
2. Architectural distortion (destructive scarring, honeycombing)
3. Subpleural / paraseptal distribution
4. Temporal heterogeneity (fibroblast foci over collagen fibrosis)
5. **Absence of features suggesting an alternate diagnosis**
   - *Mainly airway-centered changes*
   - *Confluent OP*
   - *Too many granulomas*
   - *Hyaline membranes*
   - *Dense lymphocytic infiltrates*
   - *Marked chronic pleuritis*

PROGRESSIVE PULMONARY FIBROSIS (PPF)

- PPF is not a specific dx, but an entity of prognostic significance
- Many types of fibrotic lung diseases can manifest as PPF
- Definition *(**no pathology involved**):*
    1. Worsening respiratory symptoms
    2. Physiological evidence of disease progression with specific criteria
    3. Radiological evidence of disease progression with specific criteria
- Antifibrotic treatment for PPF, as for IPF
- ***Green light to lump dx*** *of fibrosing ILD, which will further decrease the frequency of lung bx*

PPF AS A PROGNOSTIC ENTITY



Yi et al. JPTM 2024;58:1-11

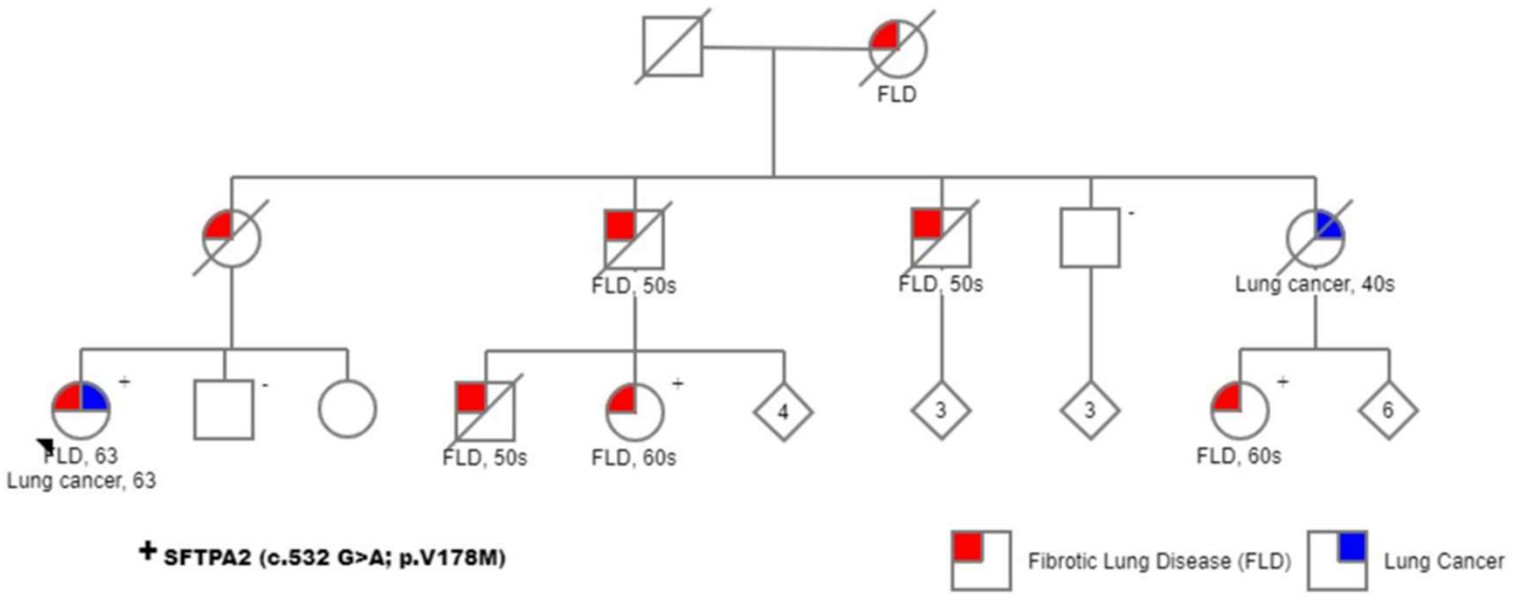
CASE 2

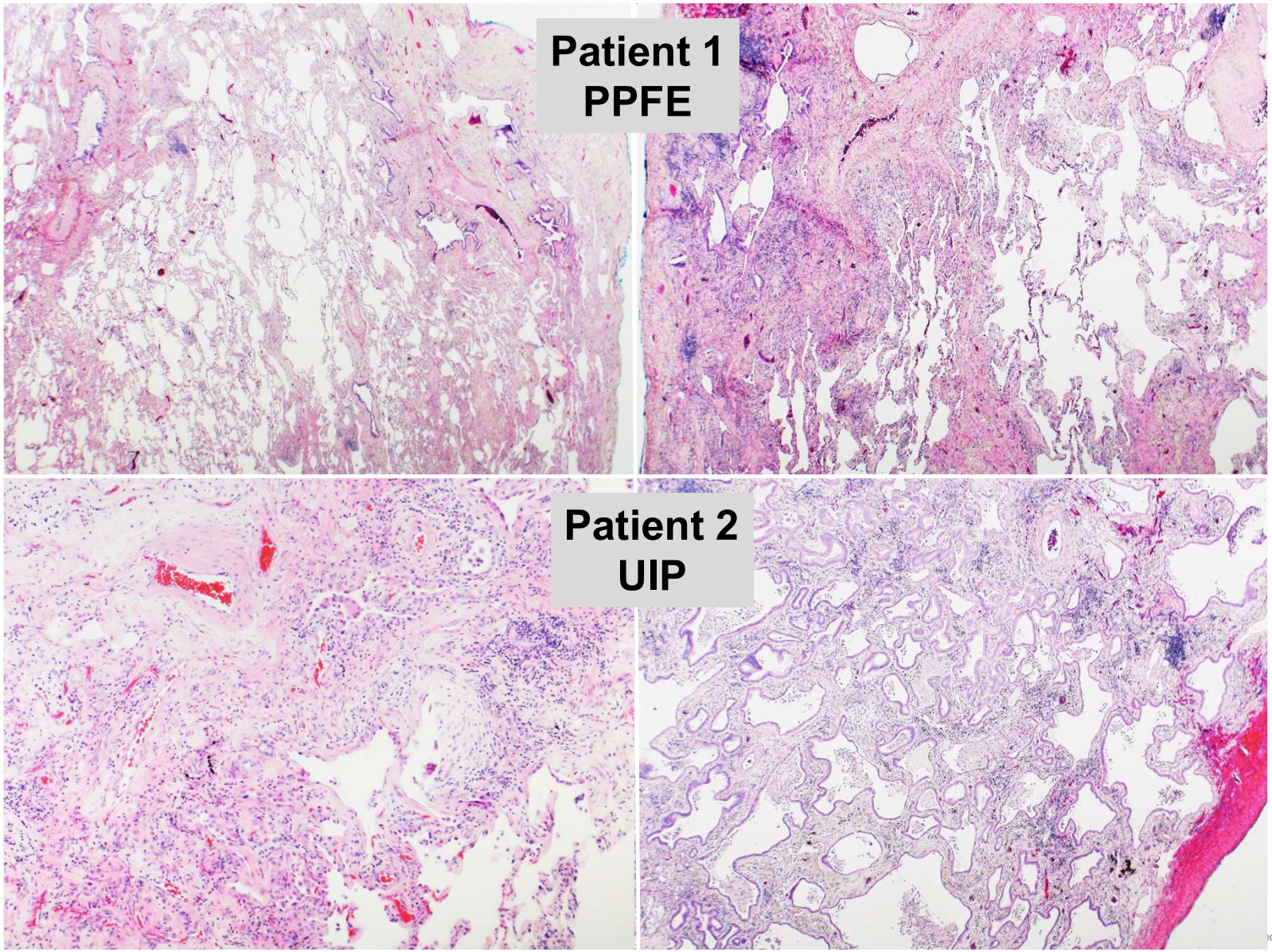
Two cousins presenting with clinical dx of ILD

CLINICAL HISTORY

- **Patient 1 (index case)**
  - 63F with fibrosing ILD and a hx of lung adenocarcinoma
  - HRCT atypical for UIP
  - Multiple family members with fibrosing ILD
  - Heterozygous *SFTPA2* variant (*c.532 G>A; p.V178Met*)

- **Patient 2**
  - 53F, maternal first cousin of Patient 1
  - HRCT atypical for UIP
  - The same *SFTPA2* mutation on genetic testing as in Patient 1
  - Double lung transplantation due to fibrosing ILD




Patient 1
PPFE
Patient 2
UIP

FAMILIAL PULMONARY FIBROSIS (FPF)

- Account for about 20% of fibrosing ILDs
- Relatives in the same family may show different types of fibrosing ILDs
- Two most frequently identified genes in FPF are associated with:
  - **Surfactant** metabolism: *SFTPC, SFTPA1/2, ABCA3*
  - **Telomere** maintenance: *TERT, TERC, RTEL-1,* etc
- Extrapulmonary systemic manifestations (e.g. BM failure, liver disease cancer, etc) in patients with telomere-related gene mutations (short telomere syndrome), *but not in those with surfactant gene mutations*
- Sporadic cases of pulmonary fibrosis also often show short telomere length compared to age matched control subjects

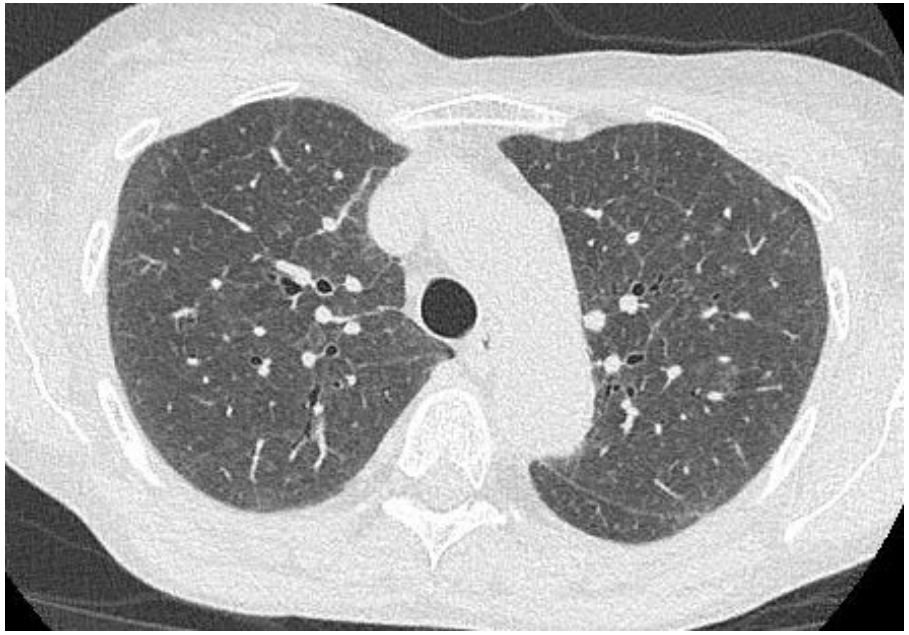
CASE 3

Unexpected finding in a lung bx for ILD

CLINICAL

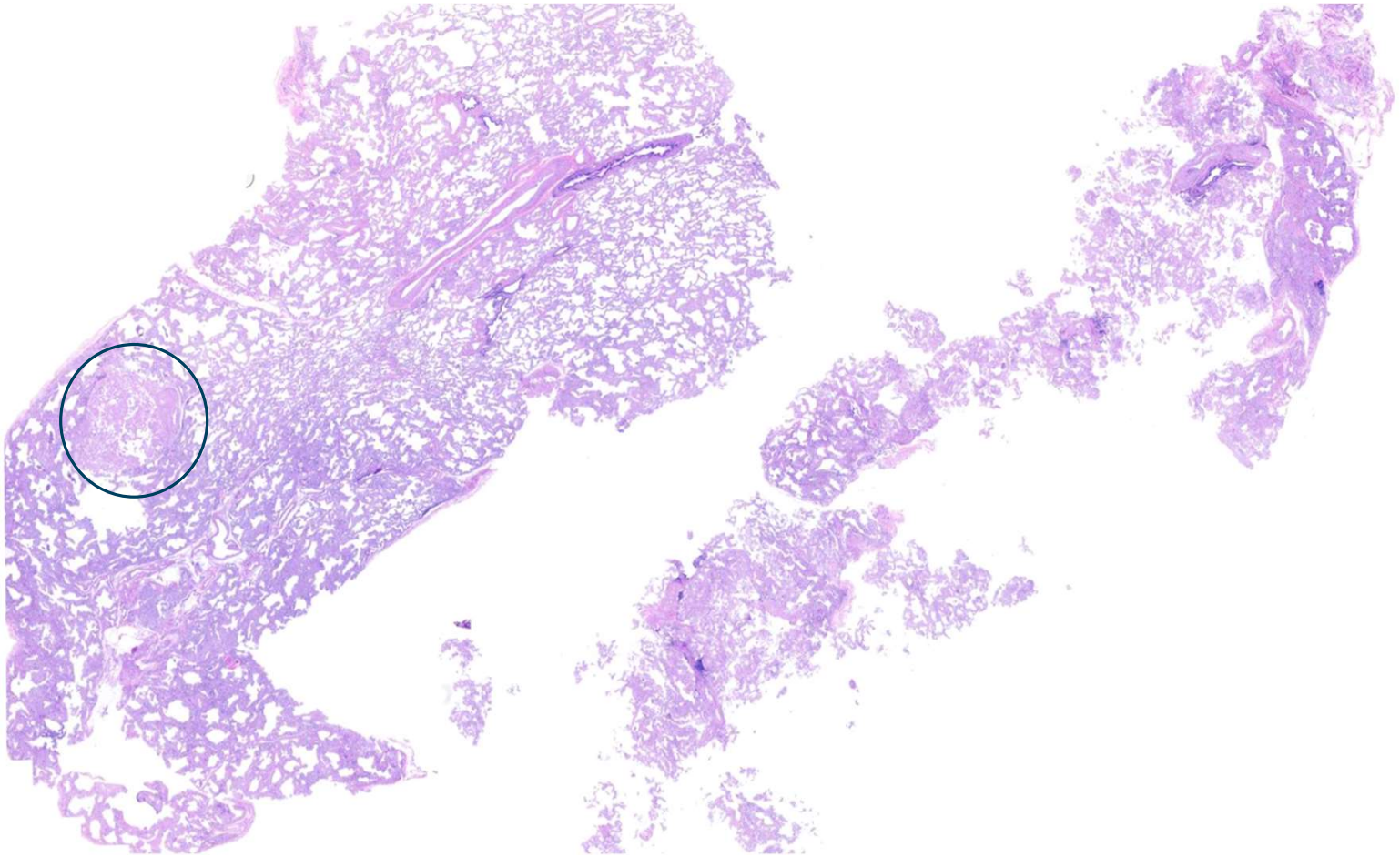
- **67F, never-smoker**
- 9 months of **dyspnea** (previous avid golfer, walker, active)
  - No fevers, cough, or infectious symptoms
  - No signs or symptoms of volume overload
  - Exertional **hypoxemia** found on cardiac stress test (into the **low 80s**, with quick recovery)
- **PMH:** CLL, migraines, kidney stones
- **SH:** down pillows, no occupational or other environmental exposures
- **FH:** none
- **Exam:** 92% on room air, clear lung sounds, normal cardiac sounds, no clubbing/cyanosis

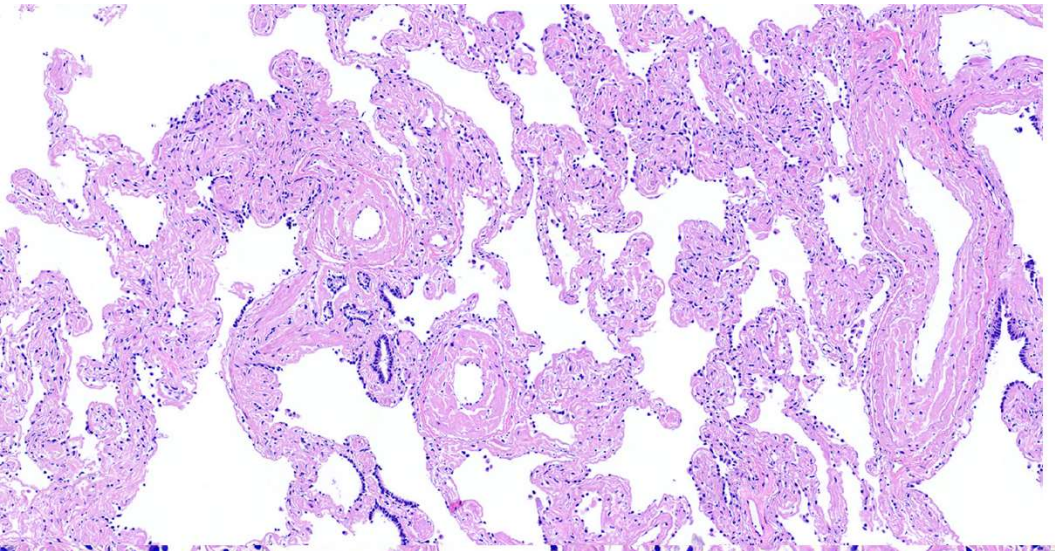
SUBACUTE/CHRONIC DIFFUSE SMOOTH INTERLOBULAR SEPTAL THICKENING + GROUNDGLASS OPACITY – DIFFERENTIAL DIAGNOSIS

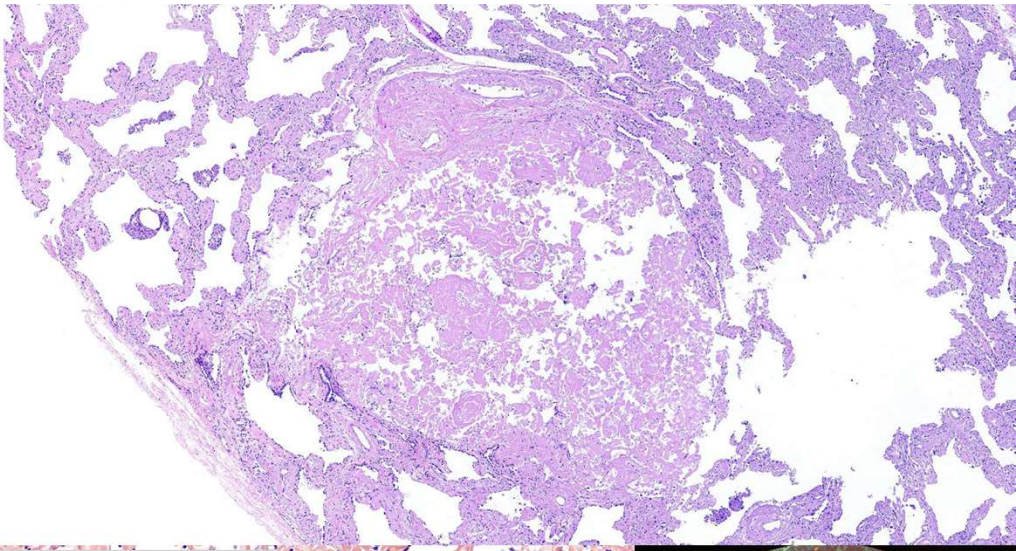


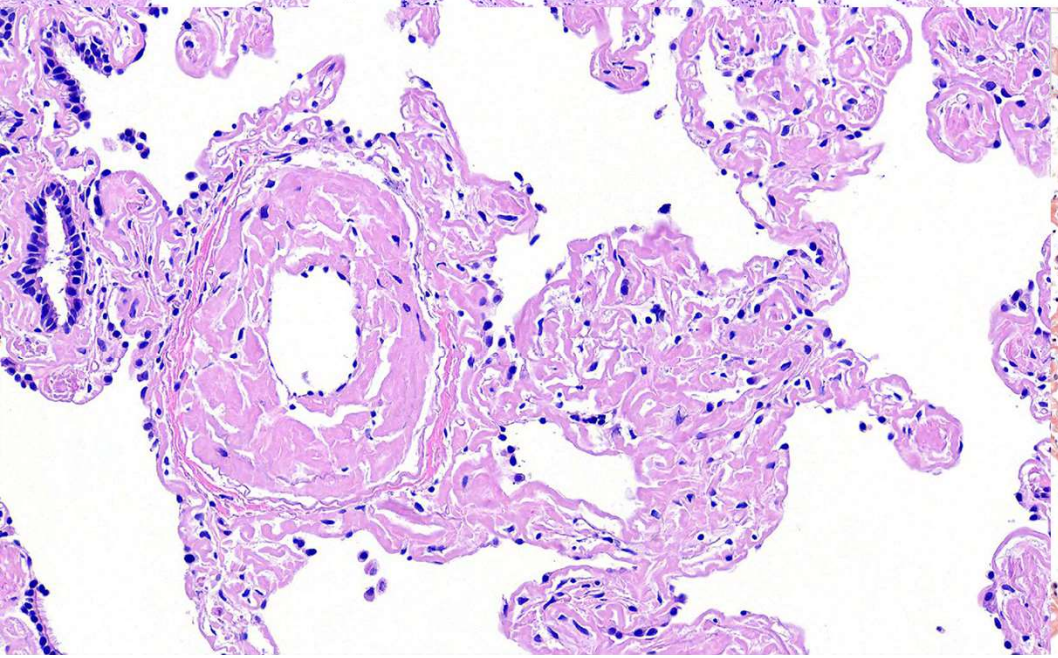
- Edema
- Resolving/recurrent diffuse pulmonary hemorrhage
- Inhalational
  - Smoking, Vaping, Hypersensitivity pneumonitis
- Drug reaction
- Pulmonary alveolar proteinosis
- Sarcoidosis
- Lymhangitic carcinomatosis
- Leukemic infiltration
- Amyloidosis
- Erdheim Chester disease
- Pulmonary venoocclusive disease
- Diffuse pulmonary lymphangiomatosis

PATHOLOGY

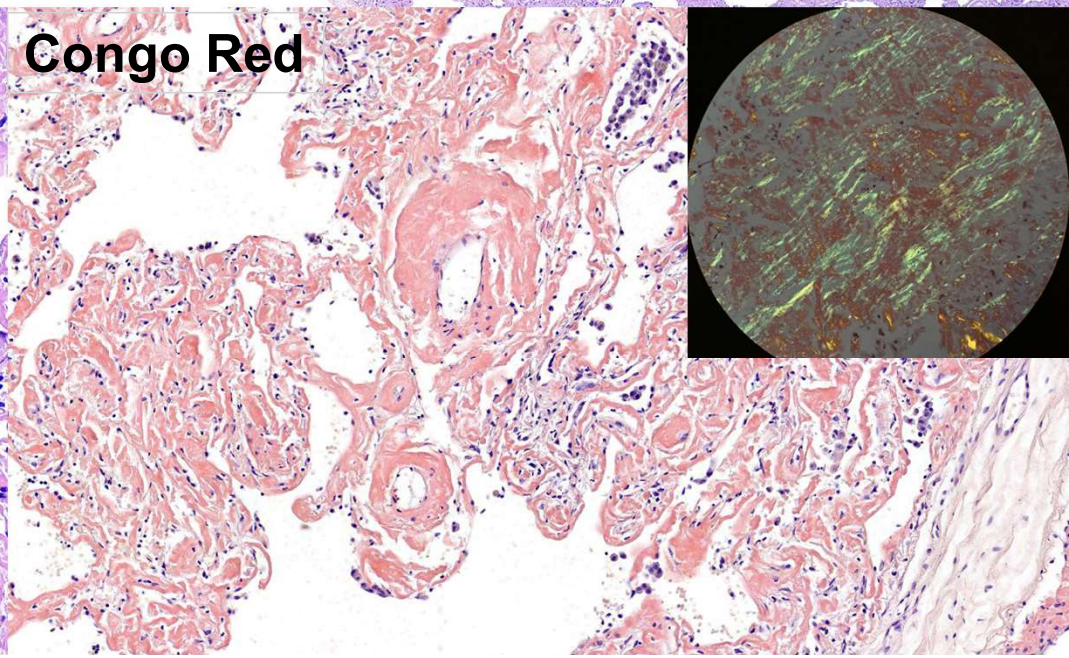


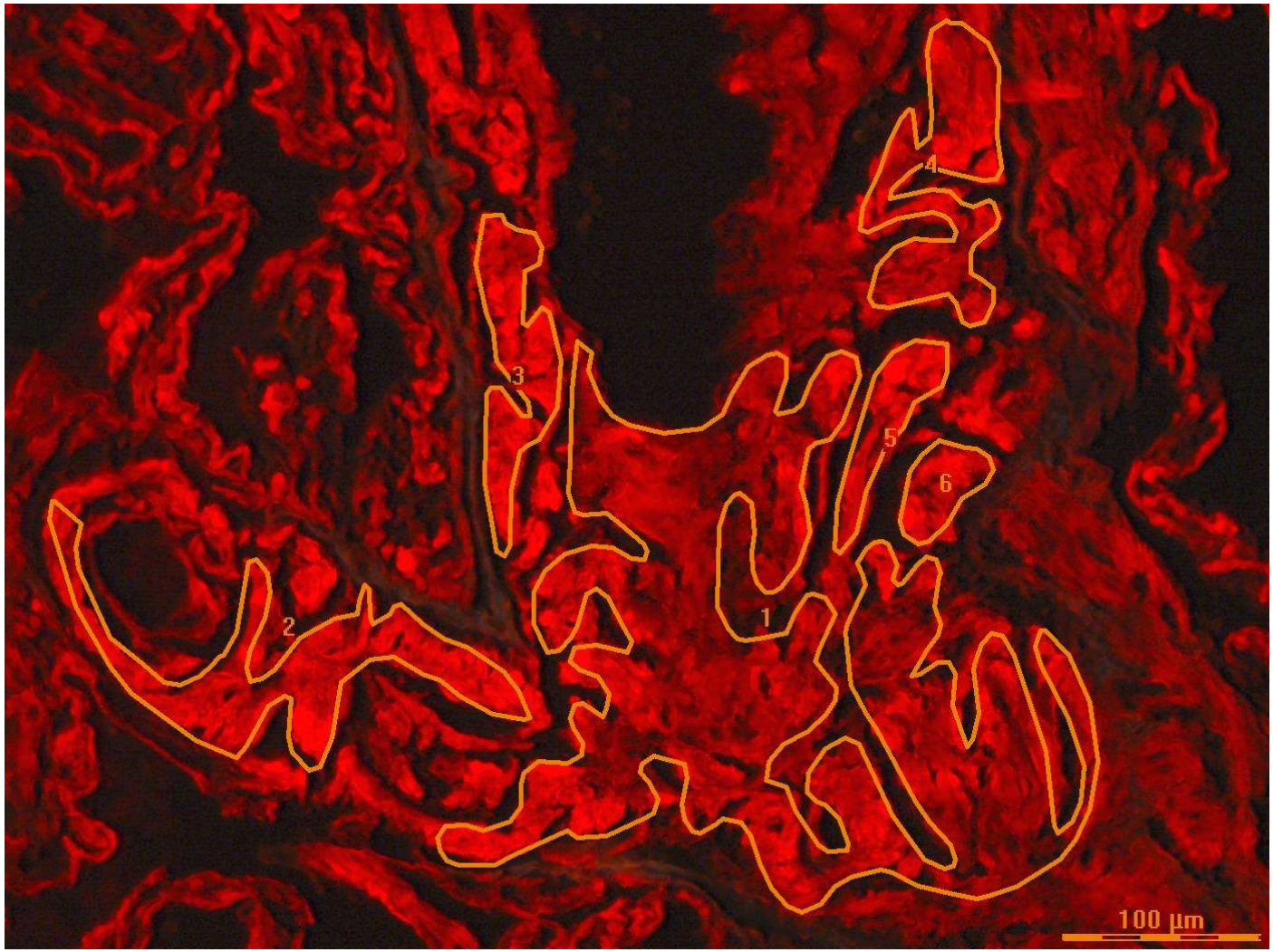




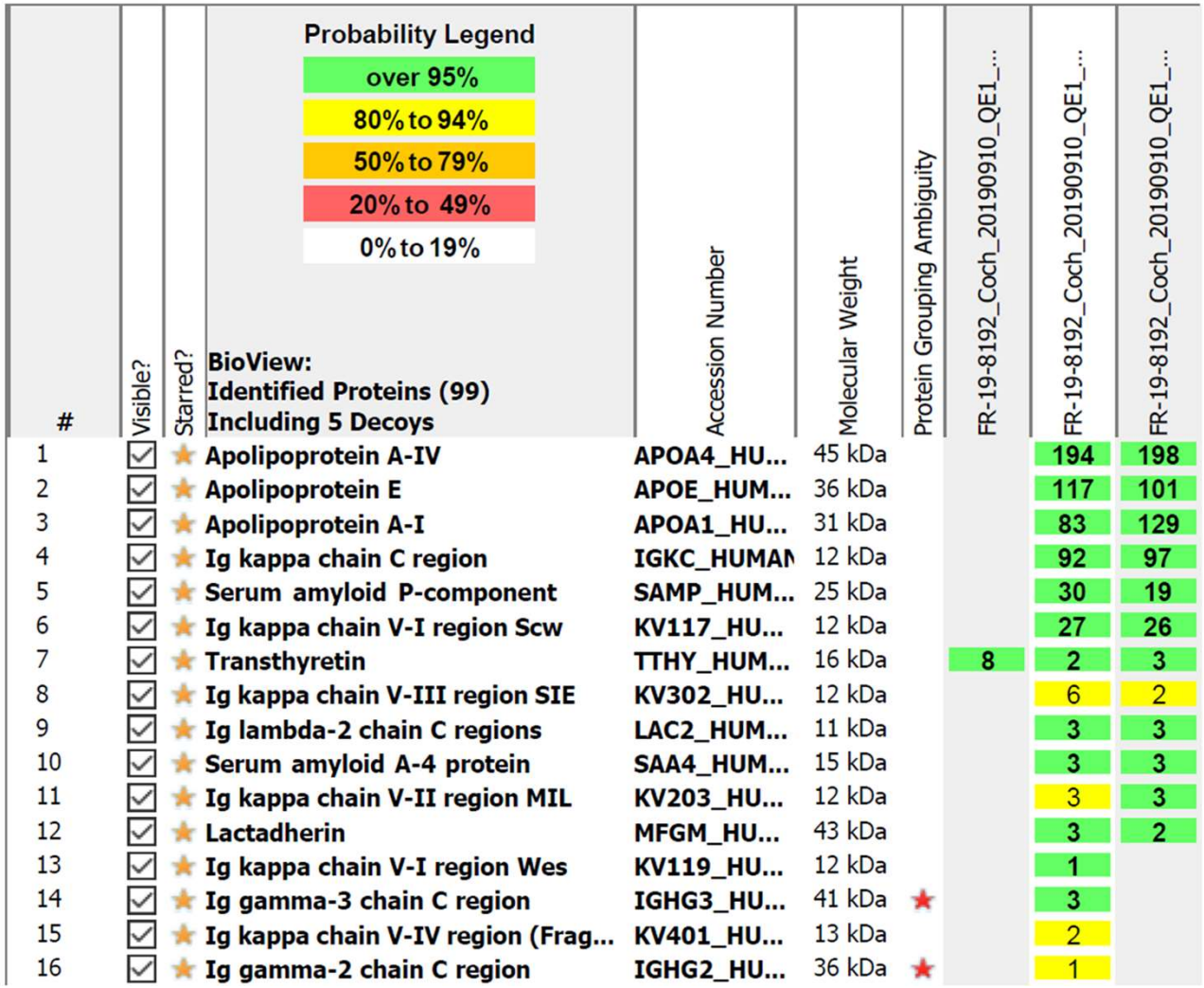


Congo Red





Liquid Chromatography Tandem Mass Spectrometry (LC MS/MS) from Congo-Red + microdissected areas of paraffin-embedded specimen



Probability Legend

over 95%

80% to 94%

50% to 79%

20% to 49%

0% to 19%

#	Visible?	Starred?	BioView: Identified Proteins (99) Including 5 Decoys	Accession Number	Molecular Weight	Protein Grouping Ambiguity	FR-19-8192_Coch_20190910_QE1_...	FR-19-8192_Coch_20190910_QE1_...	FR-19-8192_Coch_20190910_QE1_...
1	☑	★	Apolipoprotein A-IV	APOA4_HU...	45 kDa			194	198
2	☑	★	Apolipoprotein E	APOE_HUM...	36 kDa			117	101
3	☑	★	Apolipoprotein A-I	APOA1_HU...	31 kDa			83	129
4	☑	★	Ig kappa chain C region	IGKC_HUMAN	12 kDa			92	97
5	☑	★	Serum amyloid P-component	SAMP_HUM...	25 kDa			30	19
6	☑	★	Ig kappa chain V-I region Scw	KV117_HU...	12 kDa			27	26
7	☑	★	Transthyretin	TTHY_HUM...	16 kDa		8	2	3
8	☑	★	Ig kappa chain V-III region SIE	KV302_HU...	12 kDa			6	2
9	☑	★	Ig lambda-2 chain C regions	LAC2_HUM...	11 kDa			3	3
10	☑	★	Serum amyloid A-4 protein	SAA4_HUM...	15 kDa			3	3
11	☑	★	Ig kappa chain V-II region MIL	KV203_HU...	12 kDa			3	3
12	☑	★	Lactadherin	MFGM_HU...	43 kDa			3	2
13	☑	★	Ig kappa chain V-I region Wes	KV119_HU...	12 kDa			1	
14	☑	★	Ig gamma-3 chain C region	IGHG3_HU...	41 kDa	★		3	
15	☑	★	Ig kappa chain V-IV region (Frag...	KV401_HU...	13 kDa			2	
16	☑	★	Ig gamma-2 chain C region	IGHG2_HU...	36 kDa	★		1	

MAYO CLINIC

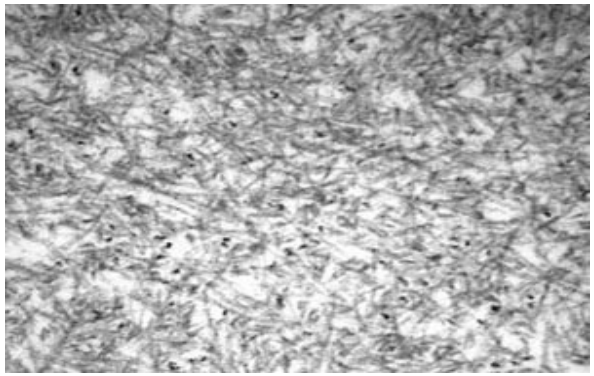
Case 3: Dx

Diffuse Septal Amyloidosis, AL (kappa) type by LC MS/MS study; No CLL in lung bx

CLL and AL (kappa) type amyloidosis in PB/BM study

AMYLOIDOSIS

- Amorphous eosinophilic deposits w/wo calcification and giant cell reaction
- Apple green birefringence on polarization of Congo Red stain
- Blue on sulfated alcian blue (SAB) stain
- EM: haphazard array of fine, non-branching, beaded fibrils, 7.5 - 10 nm in width

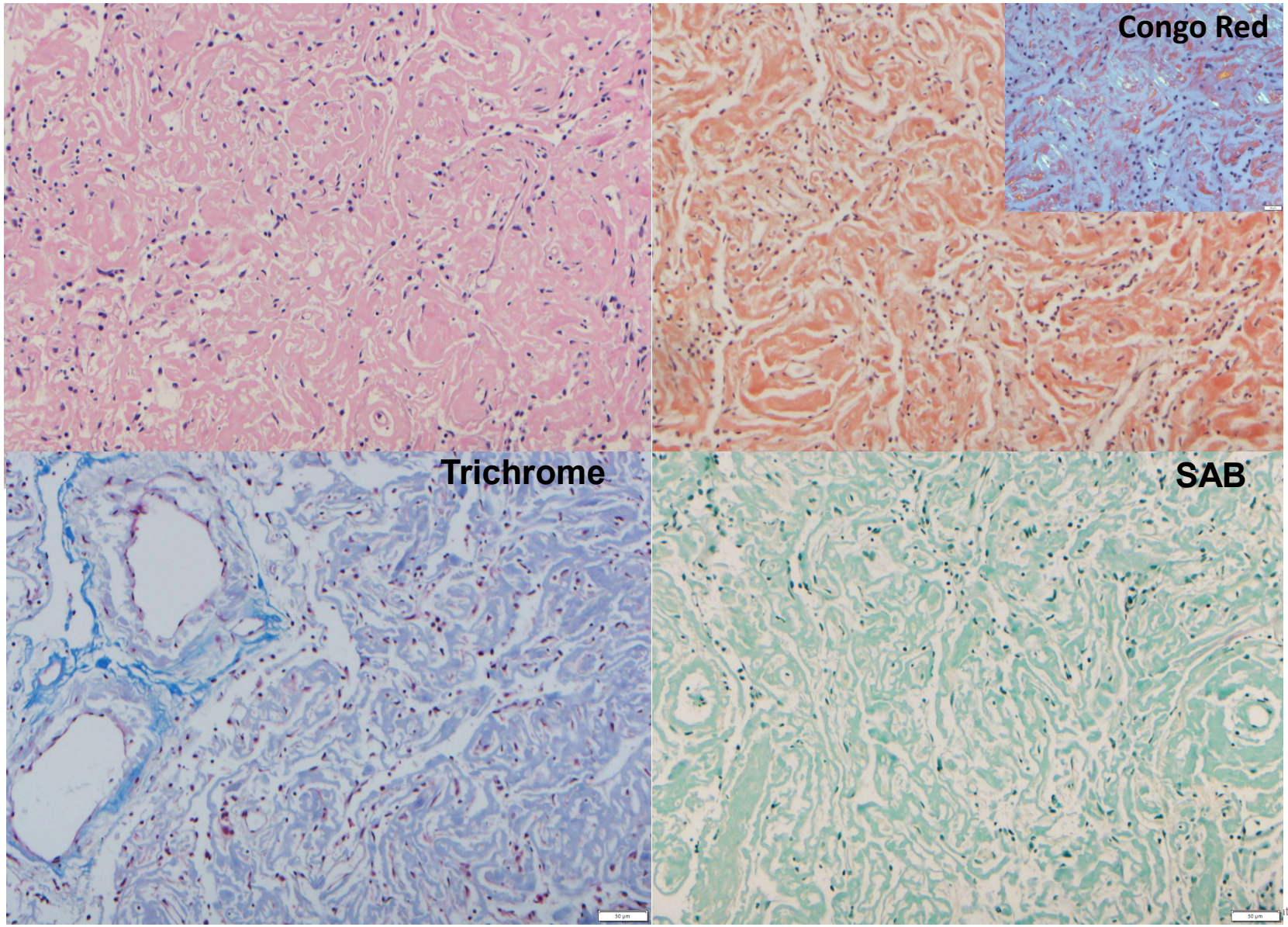


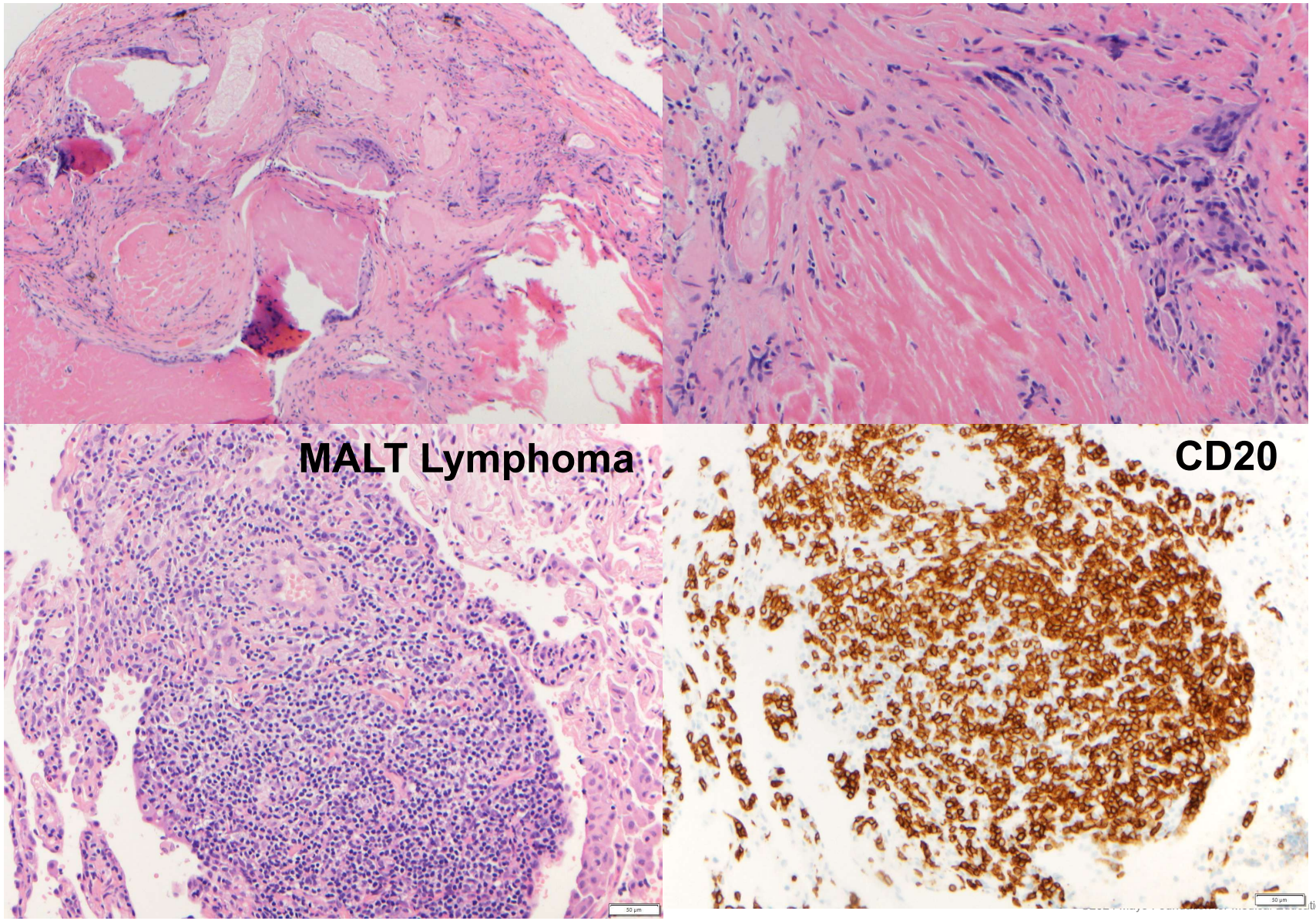
PULMONARY AMYLOIDOSIS

- **Three major patterns**
  - Diffuse alveolar septal amyloidosis
  - Nodular pulmonary amyloidosis
  - Tracheobronchial amyloidosis
- **Amyloid protein types**
  - AL, AA, ATTR, others
- **Primary vs. Secondary**
- **Localized vs. Systemic**

AMYLOID PROTEIN TYPES

- **AL:** associated with underlying lymphocytic or plasmacytic proliferative disorders
- **ATTR:** age-related (wild type) or familial/hereditary (*TTR* gene mutation)
- **AA:** secondary to chronic inflammatory conditions (e.g. RA, IBD, TB, etc.)
- **Others**


Congo Red
Trichrome
SAB


MALT Lymphoma
CD20

TYPING OF AMYLOID PROTEINS

- **Mass spectrometry**
- IHC using FFPE tissue
- IF using fresh frozen tissue
- Immunogold labelling with electron microscopy

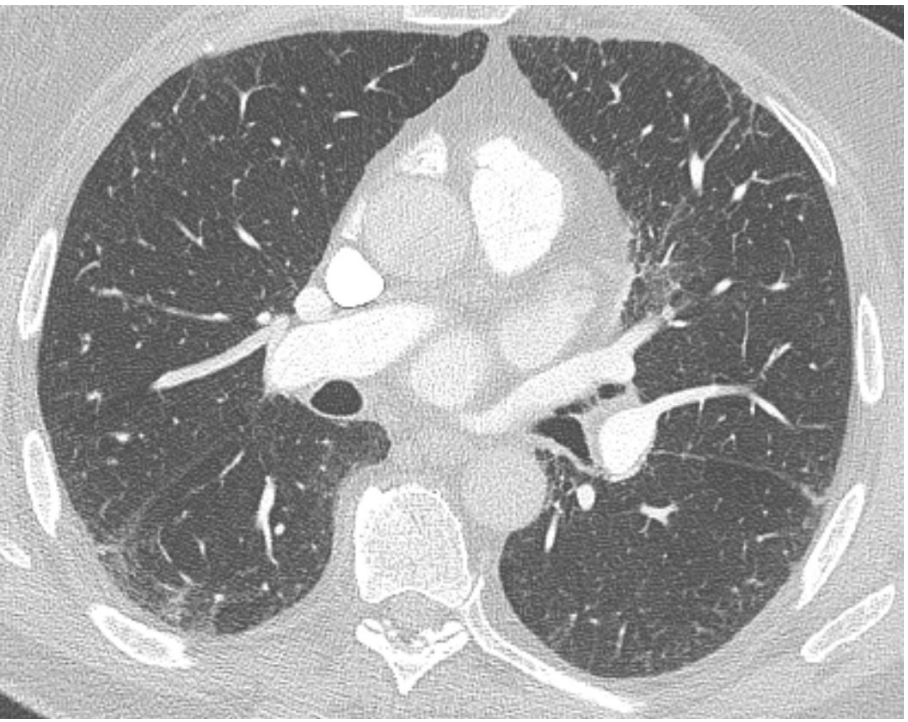
CASE 4

A patient followed up by CT scans for 4 years under the clinical dx of ILD

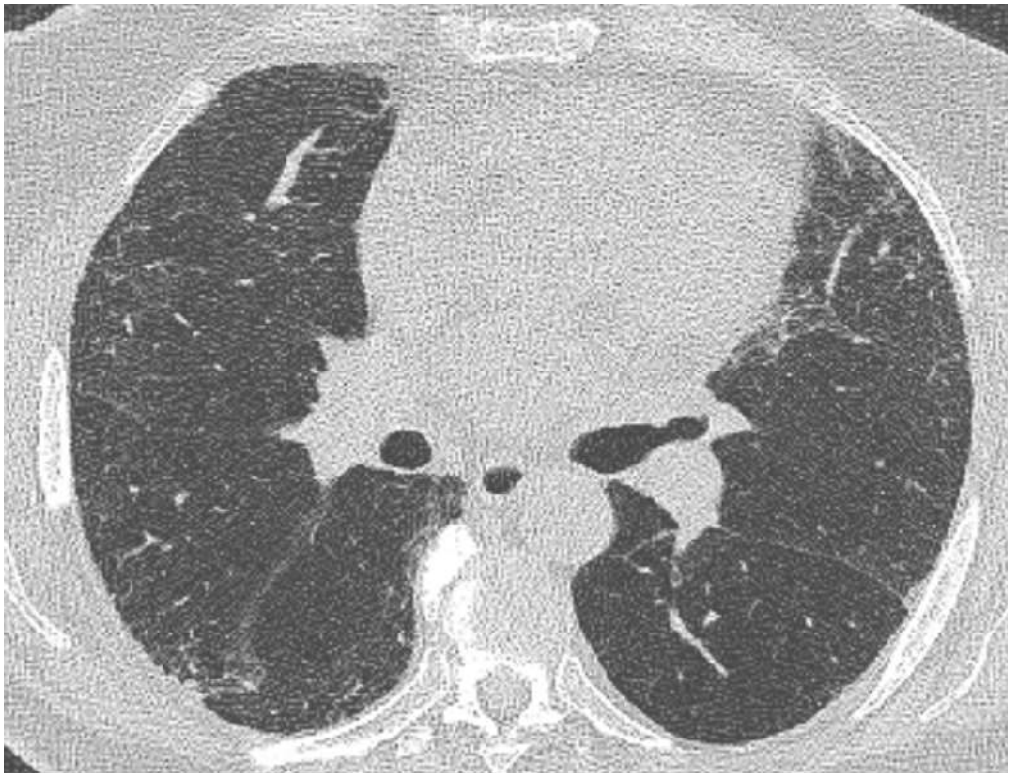
CLINICAL

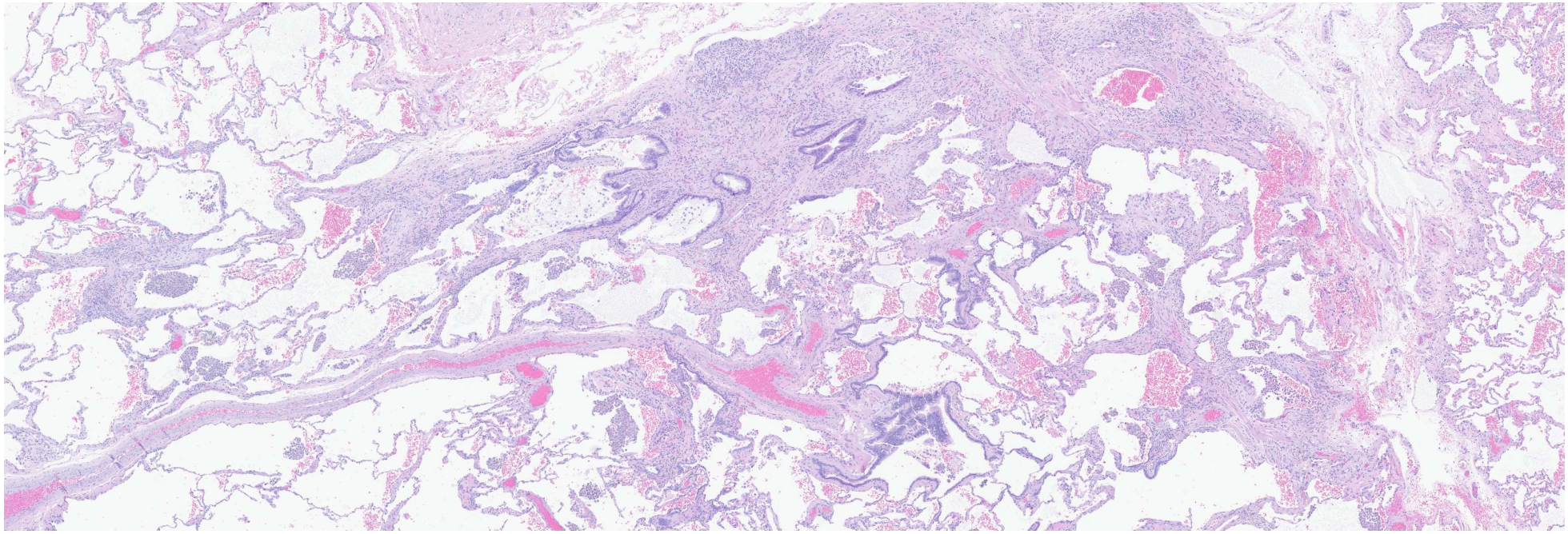
- 77M with dyspnea of exertion
- Pulmonary interstitial infiltrates since 2019
- Chest CT in October 2023: worsening subpleural reticulation, interlobular septal thickening, GGO, and traction bronchiolectasis
- Radiologic impression: fibrotic ILD, probable UIP vs. NSIP
- Wedge resection of RLL in February 2024

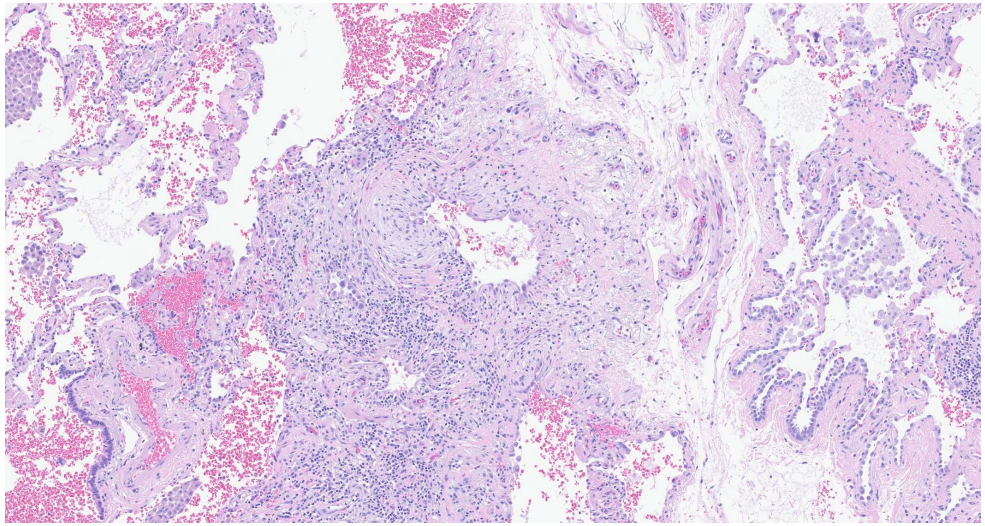
January 2019

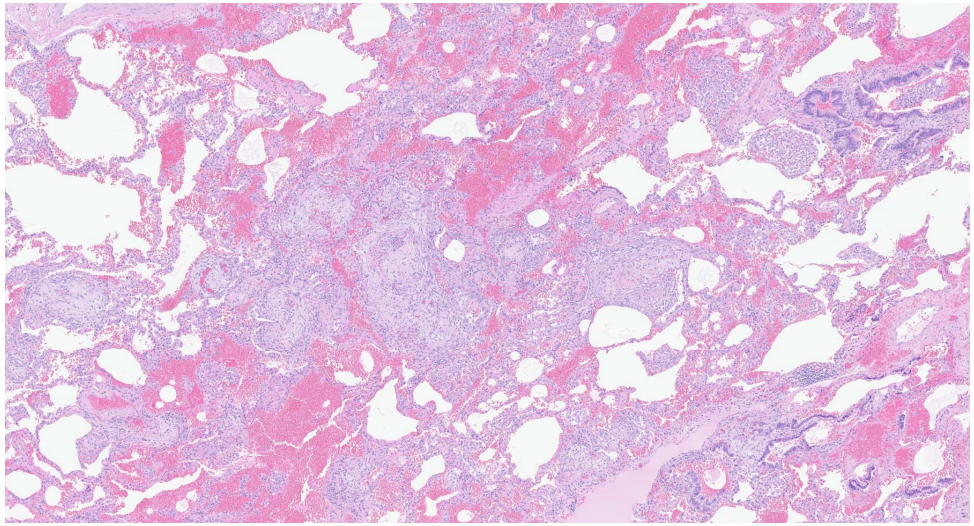


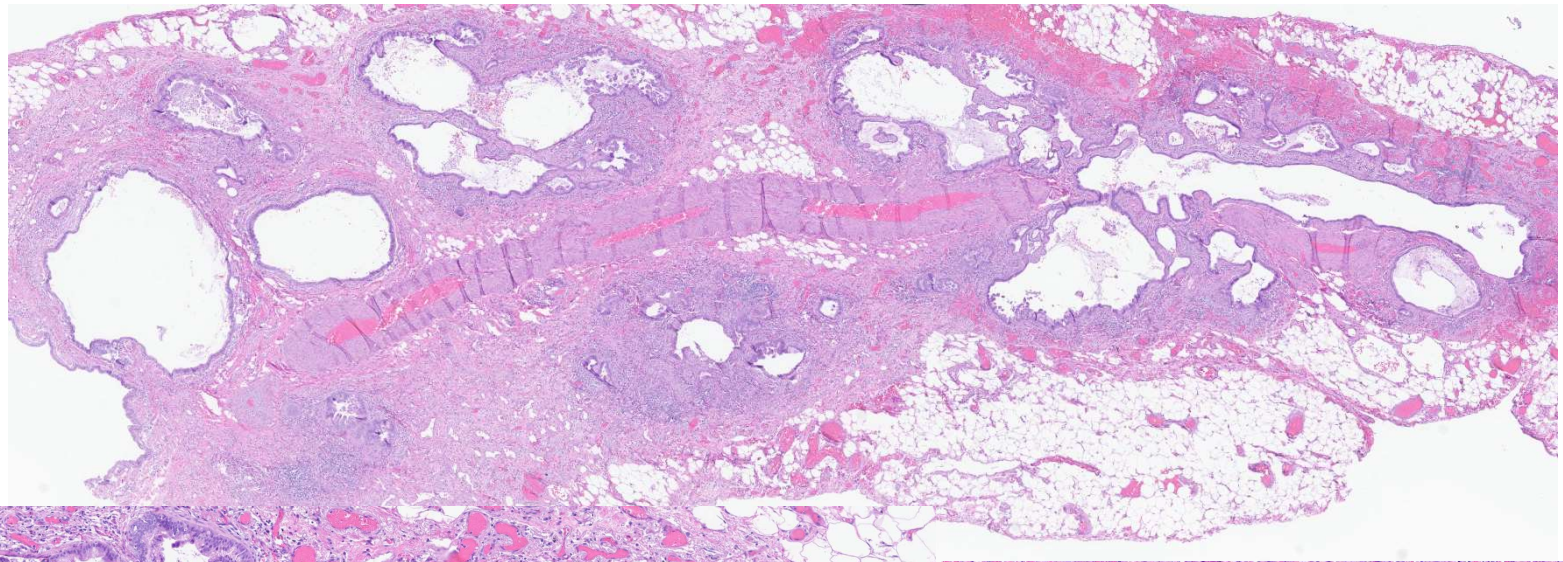
October 2023

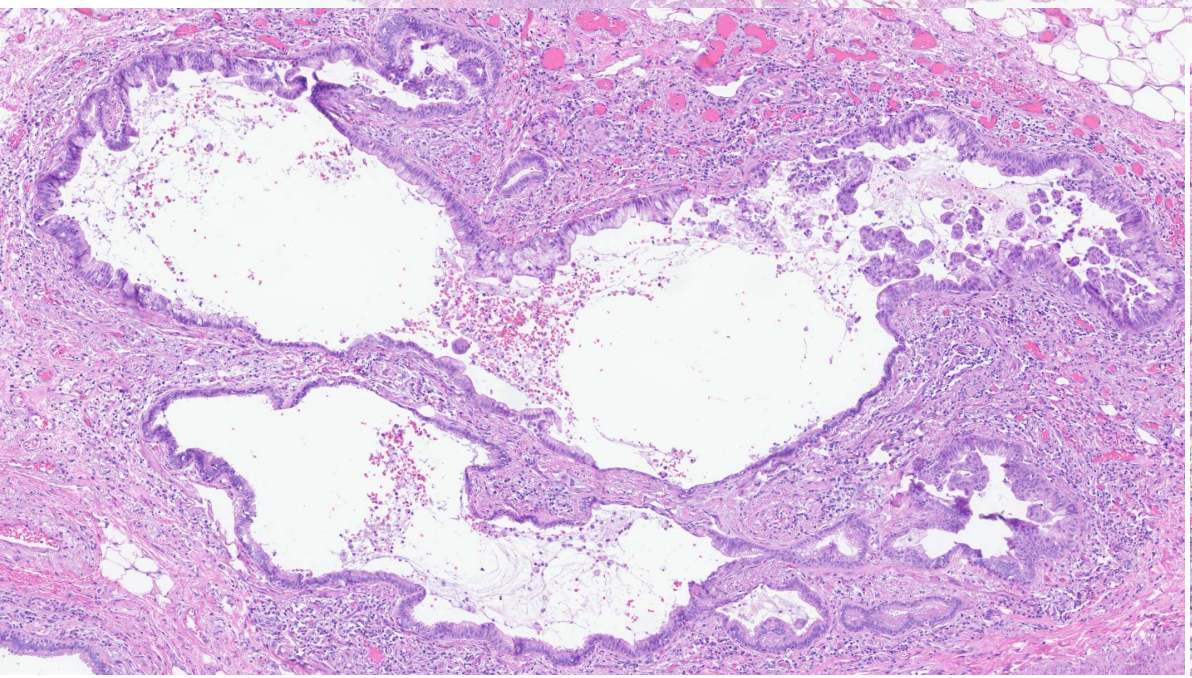


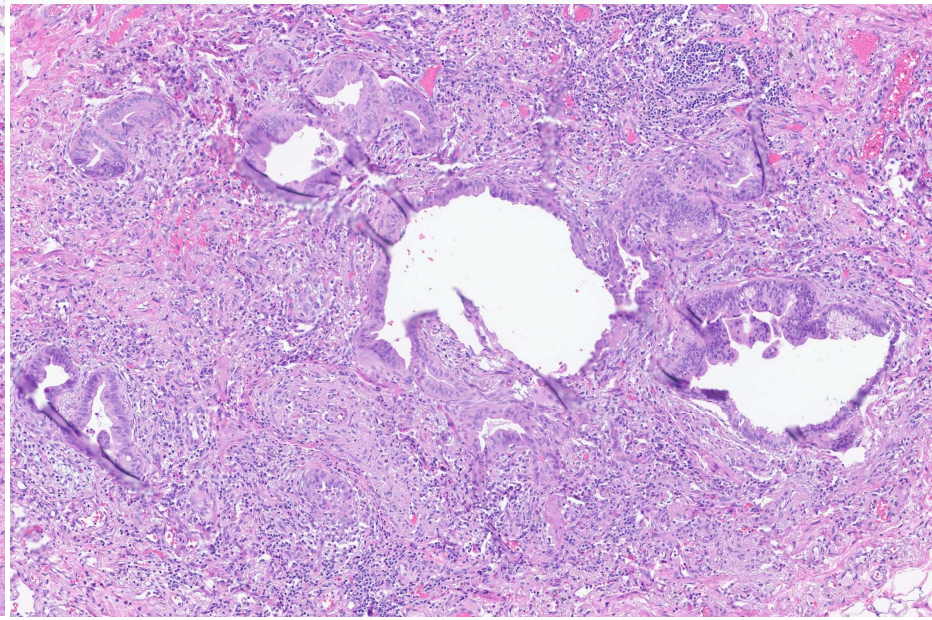


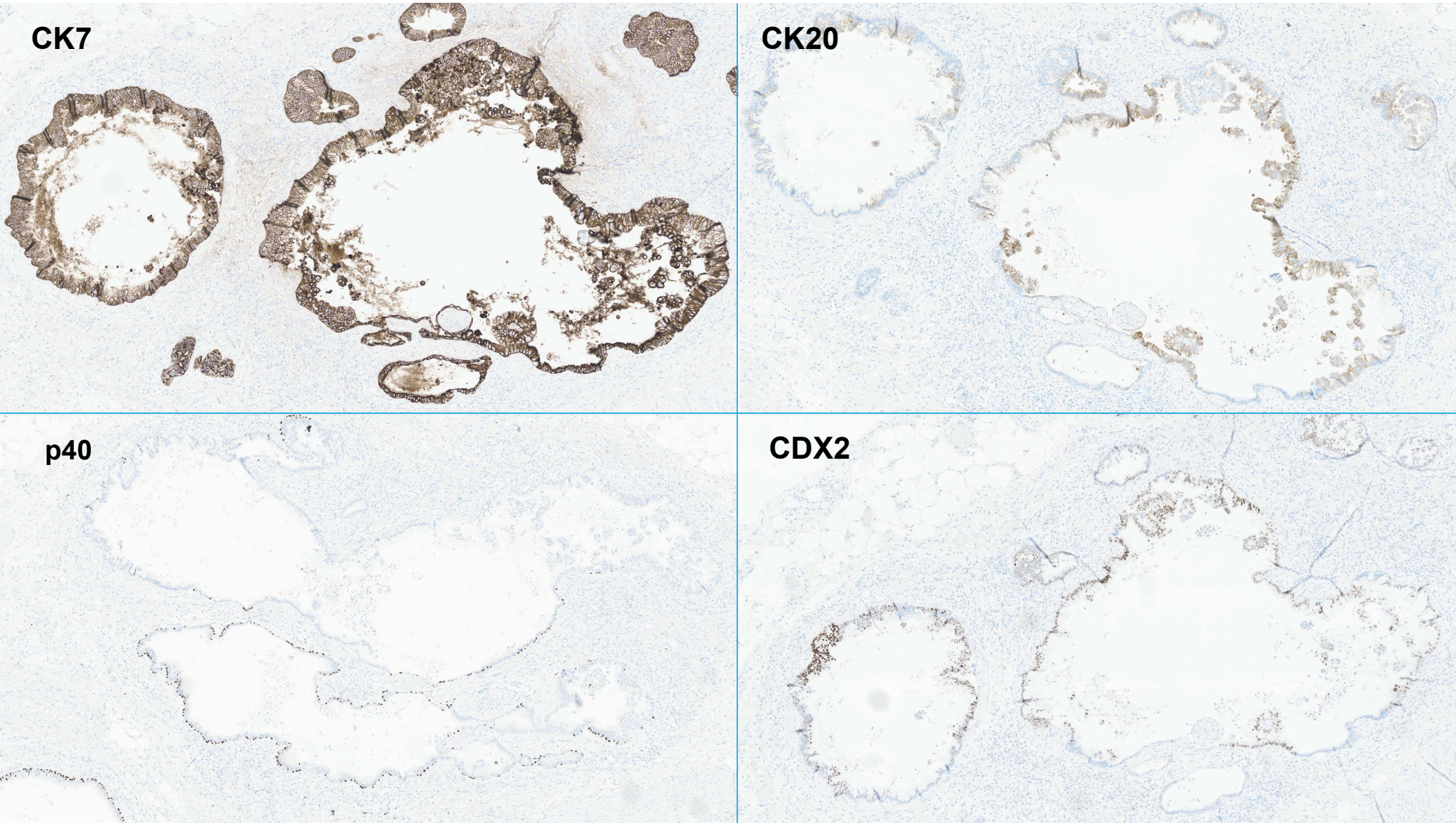










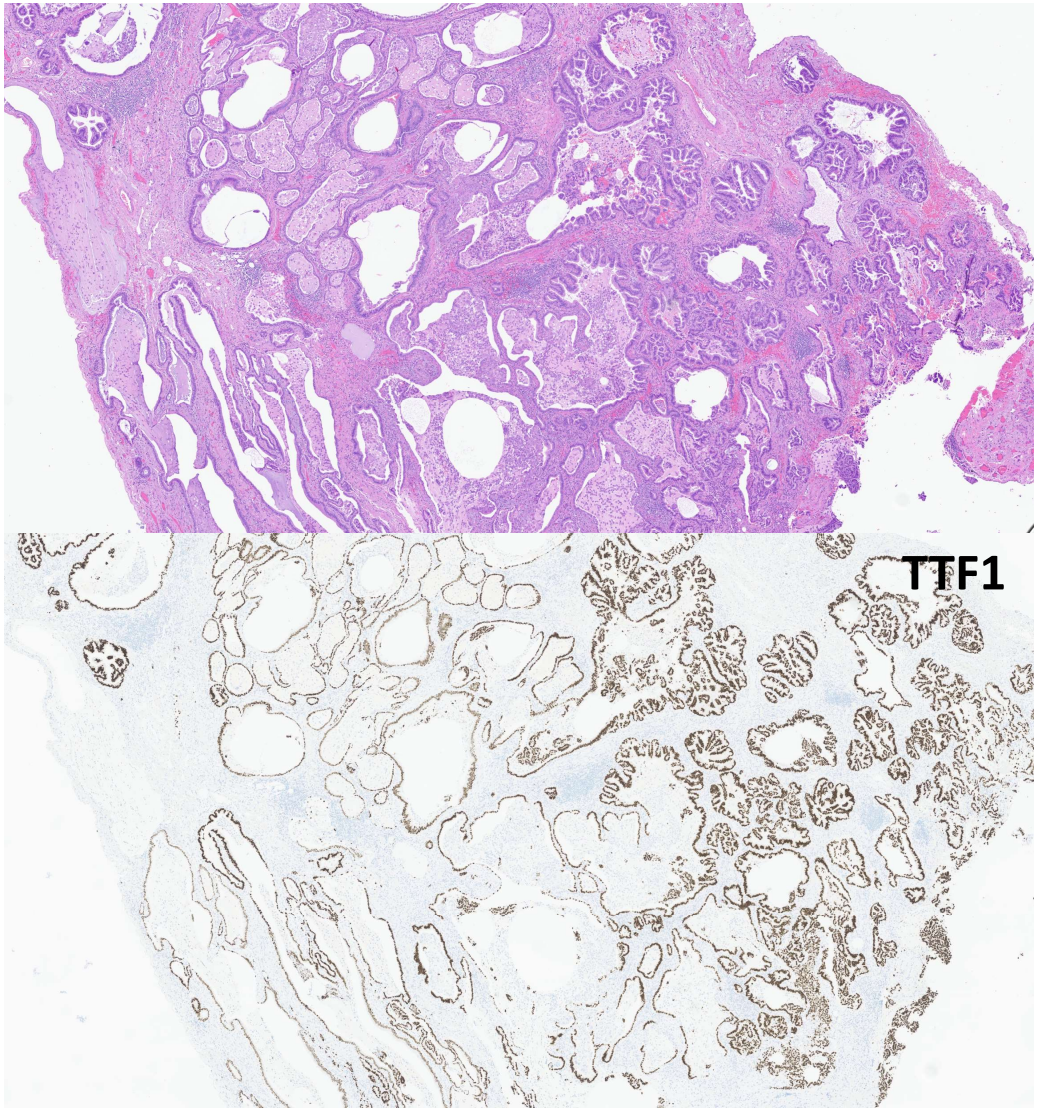

CK7
CK20
p40
CDX2

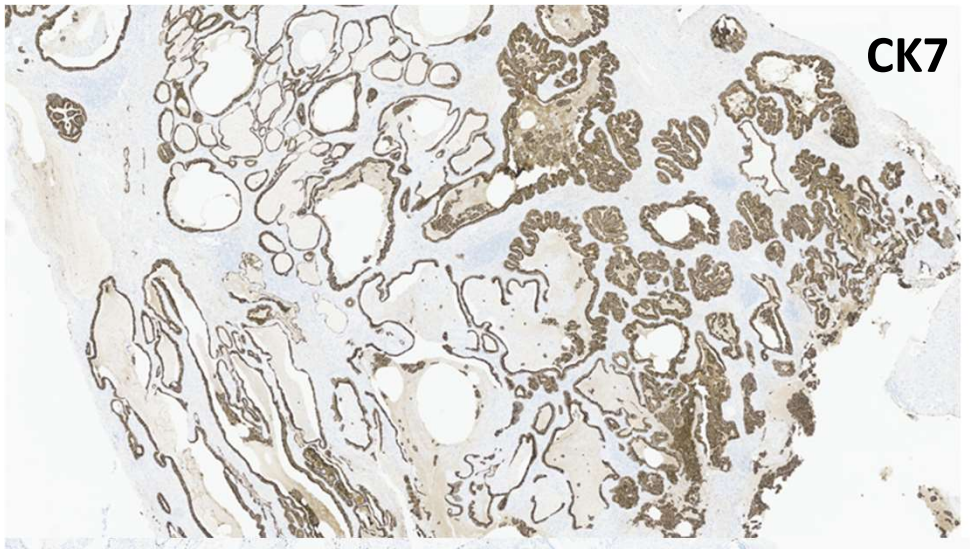
Case 4: Dx

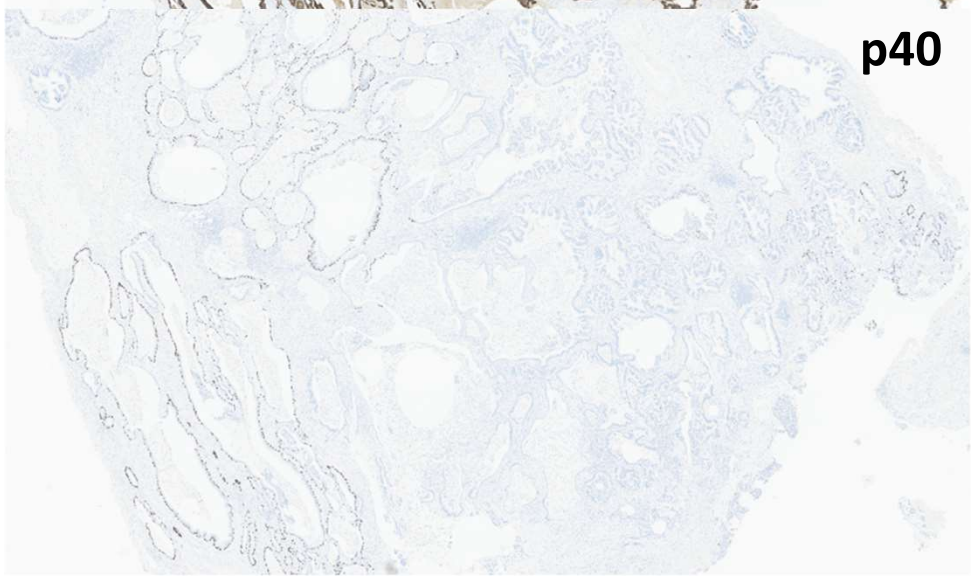
Invasive adenocarcinoma arising in a background of fibrosing ILD with UIP features

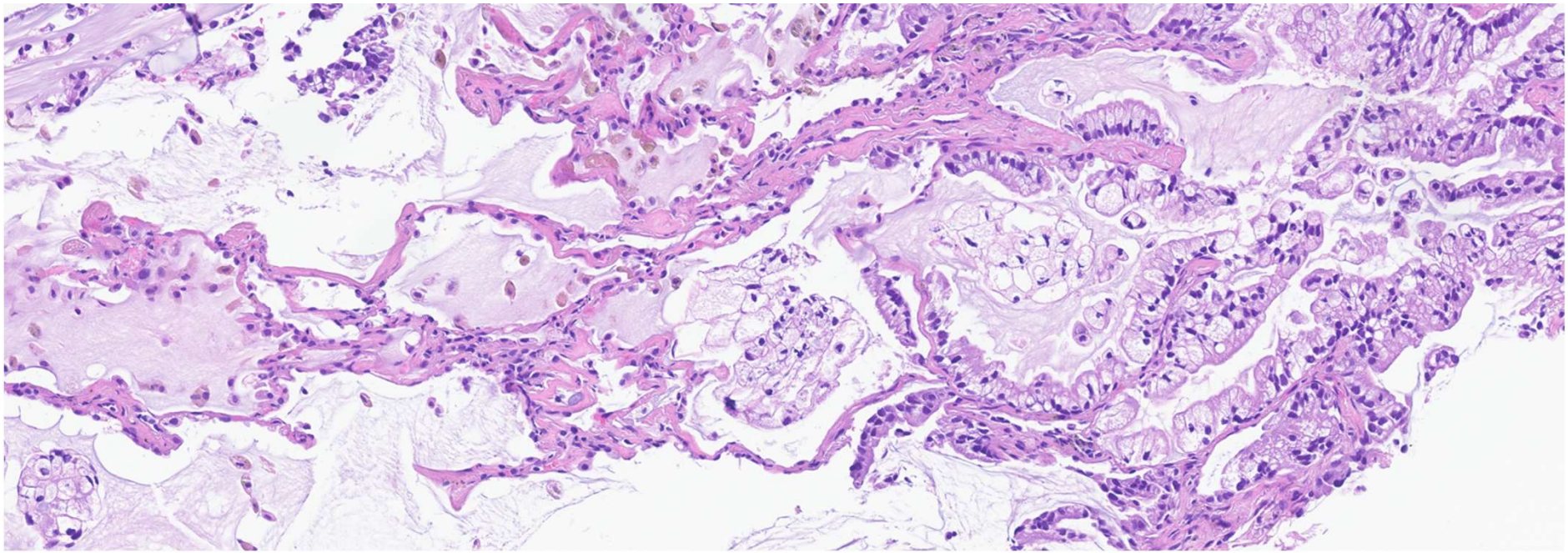
MORE OF SUCH CASES…..

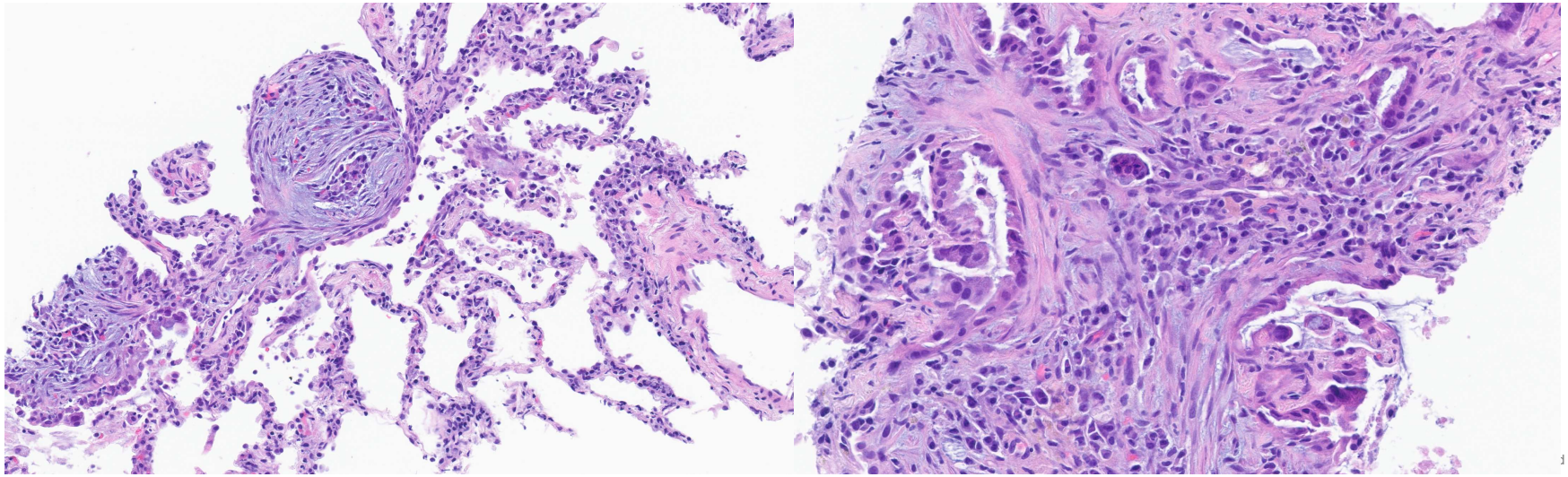
- Lung wedge biopsies for evaluation of ILDs
- Various radiologic features such as:
  - Reticular densities
  - Honeycomb changes/ traction bronchiectasis
  - Diffuse bilateral GGO/ consolidation
  - ***No apparent mass lesion***



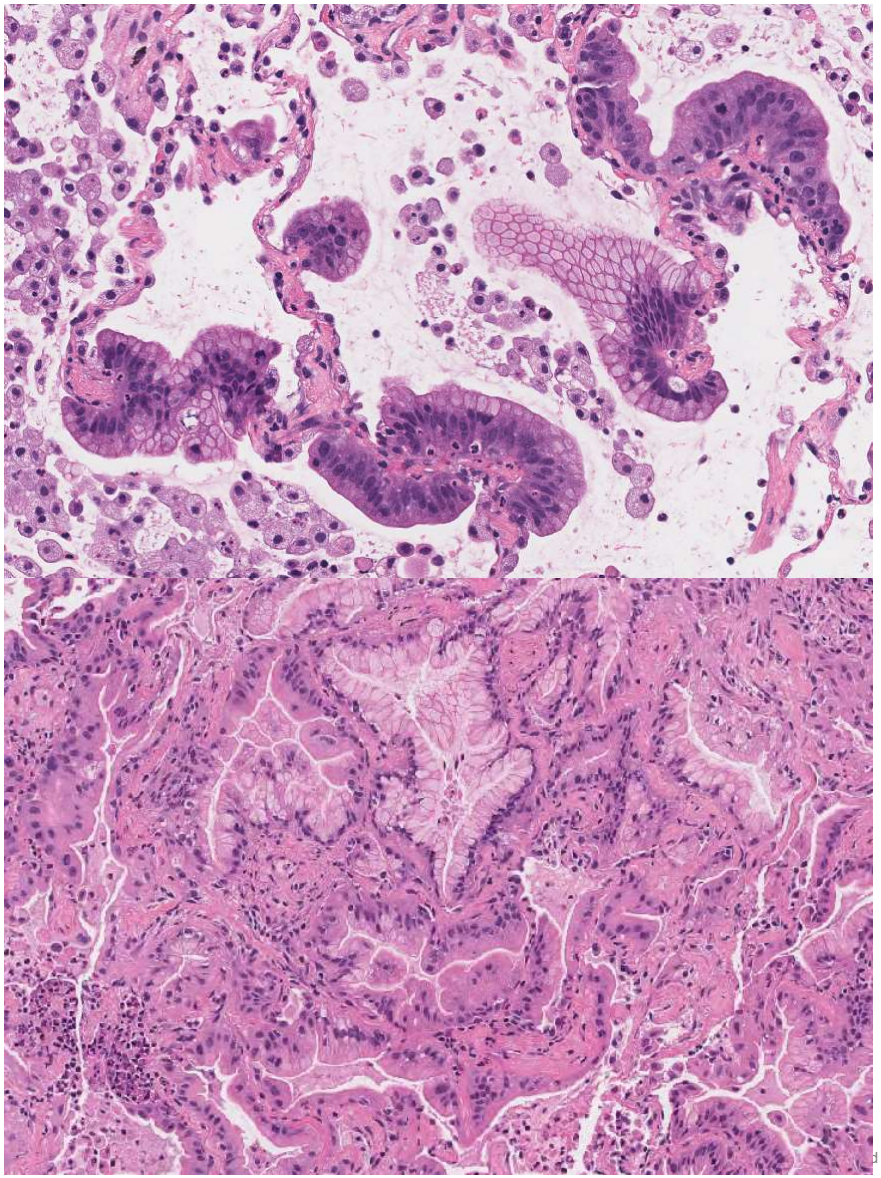








Invasive mucinous adenocarcinoma: *a mimicker of ILD*



TAKE HOME POINTS

- **Hypersensitivity pneumonitis**:
  - Non-fibrotic HP: bronchiolar/centriacinar lymphocytic infiltrates, poorly formed granulomas, w/wo OP
  - Fibrotic HP may be indistinguishable from UIP
- **Familial pulmonary fibrosis**:
  - Genes associated with surfactant and telomerase
  - ILD types may differ despite the same mutation
- **Amyloidosis**: AL and ATTR types
- **Adenocarcinoma** in a background of fibrotic ILD
  - IMA may mimic ILD/pneumonia


Thank You!
Questions?