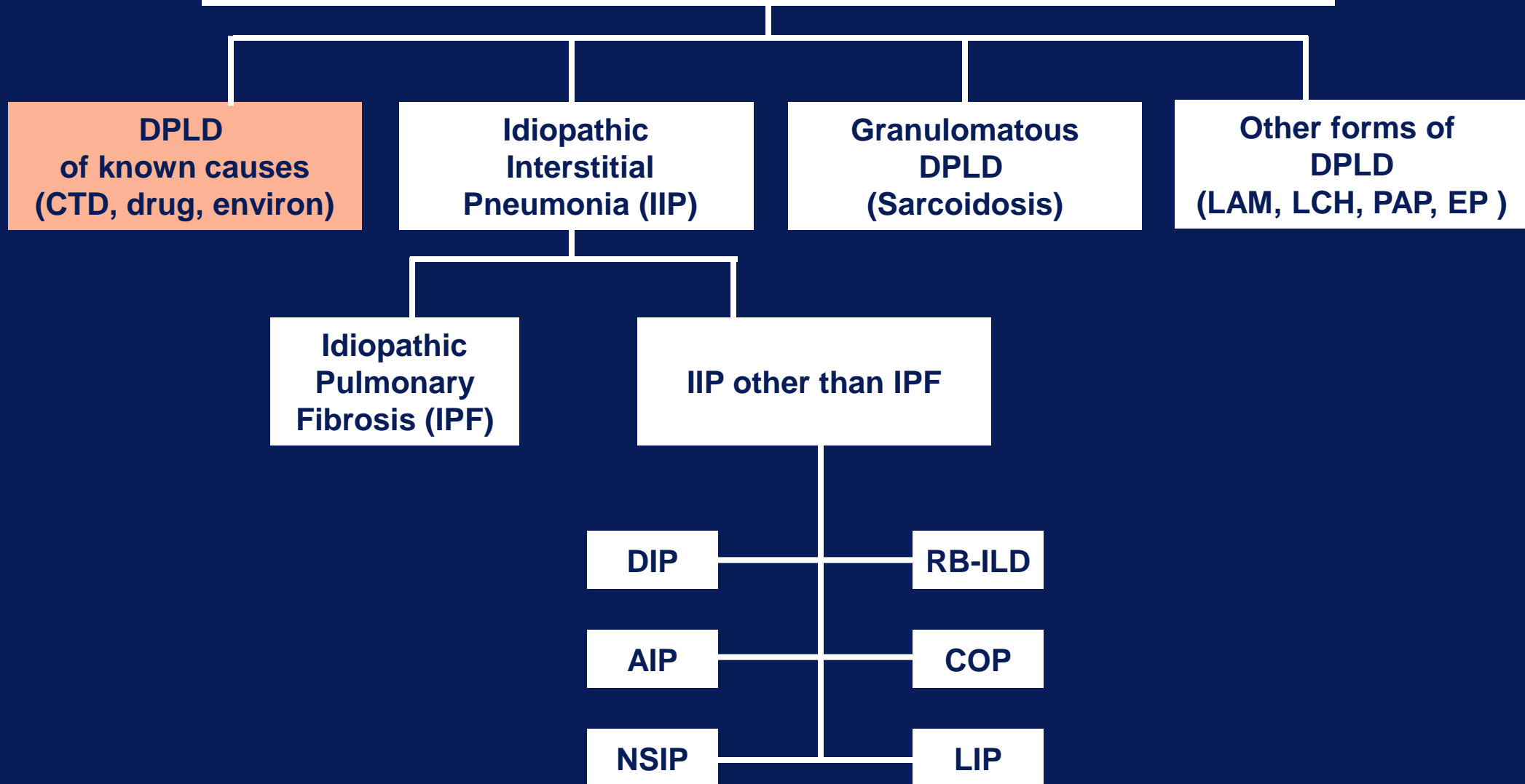


# Connective Tissue Disease-Associated Interstitial Lung Disease

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정만표

# Diffuse Parenchymal Lung Diseases



# Connective Tissue Diseases

- Systemic autoimmune diseases characterized by immune-mediated organ dysfunction

- Systemic sclerosis

Mixed CTD

Polymyositis-dermatomyositis

Rheumatoid arthritis

Primary Sjogren's syndrome

Systemic lupus erythematosus

Small vessel vasculitis,,,,,,,,,,,,,

# Common Pulmonary Manifestations in CTD

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	ILD	Airways	Pleural	Vascular	Muscle	DAH
Systemic sclerosis	+++	-	-	+++	-	-
Rheumatoid arthritis	++	++	++	+	-	-
Primary Sjogren's syndrome	++	++	+	+	-	-
Mixed CTD	++	+	+	++	+	-
Polymyositis/dermatomyositis	+++	-	-	+	++	-
SLE	+	+	+++	+	++	++

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# Interstitial Lung Disease in CTD

- The most common form of lung manifestations
- ILD in CTD; up to 15% (?)

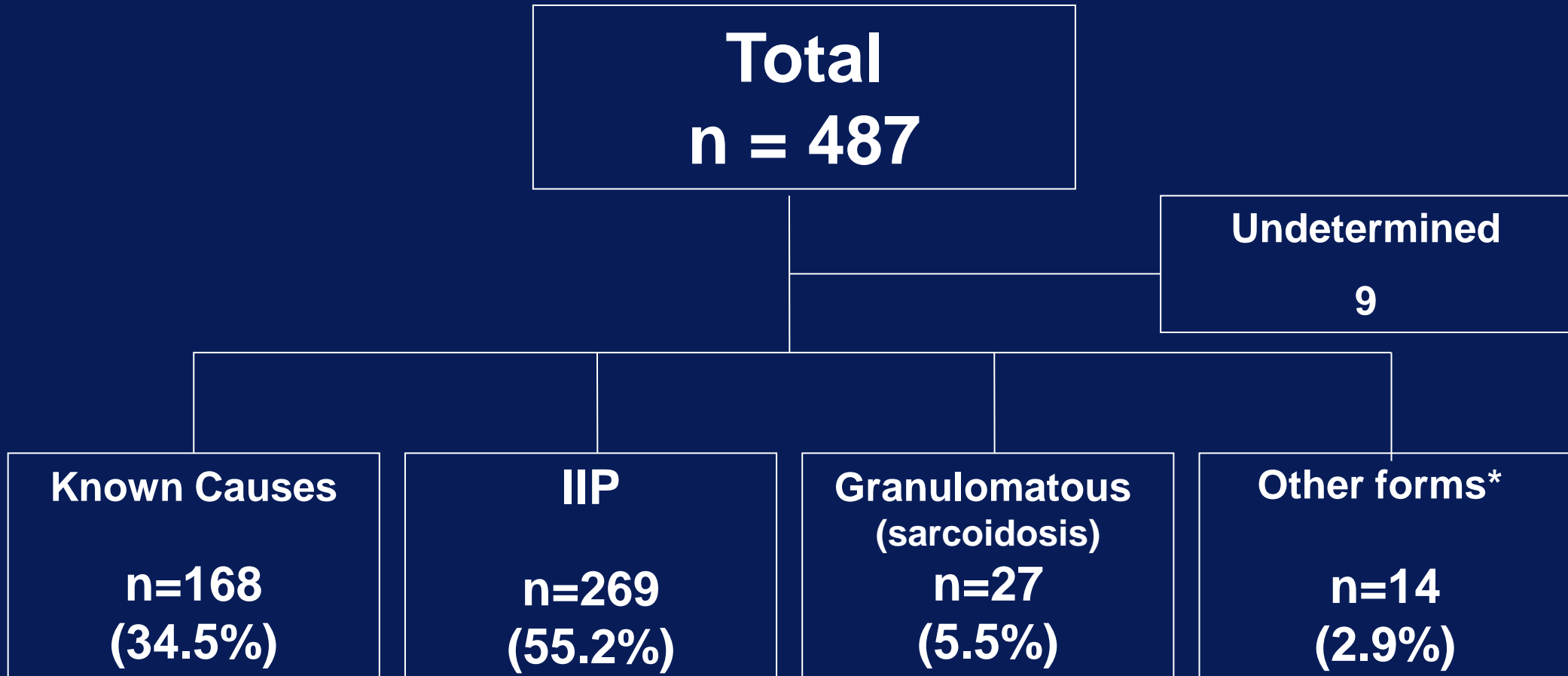
Systemic sclerosis	45~70%
Mixed CTD	20~60%
Polymyositis/dermatomyositis	20~50%
Rheumatoid arthritis	20~30%
Primary Sjogren's syndrome	up to 25%
SLE	2~8%

# Lung Disease Associated with CTD

## ? Prevalence and incidence

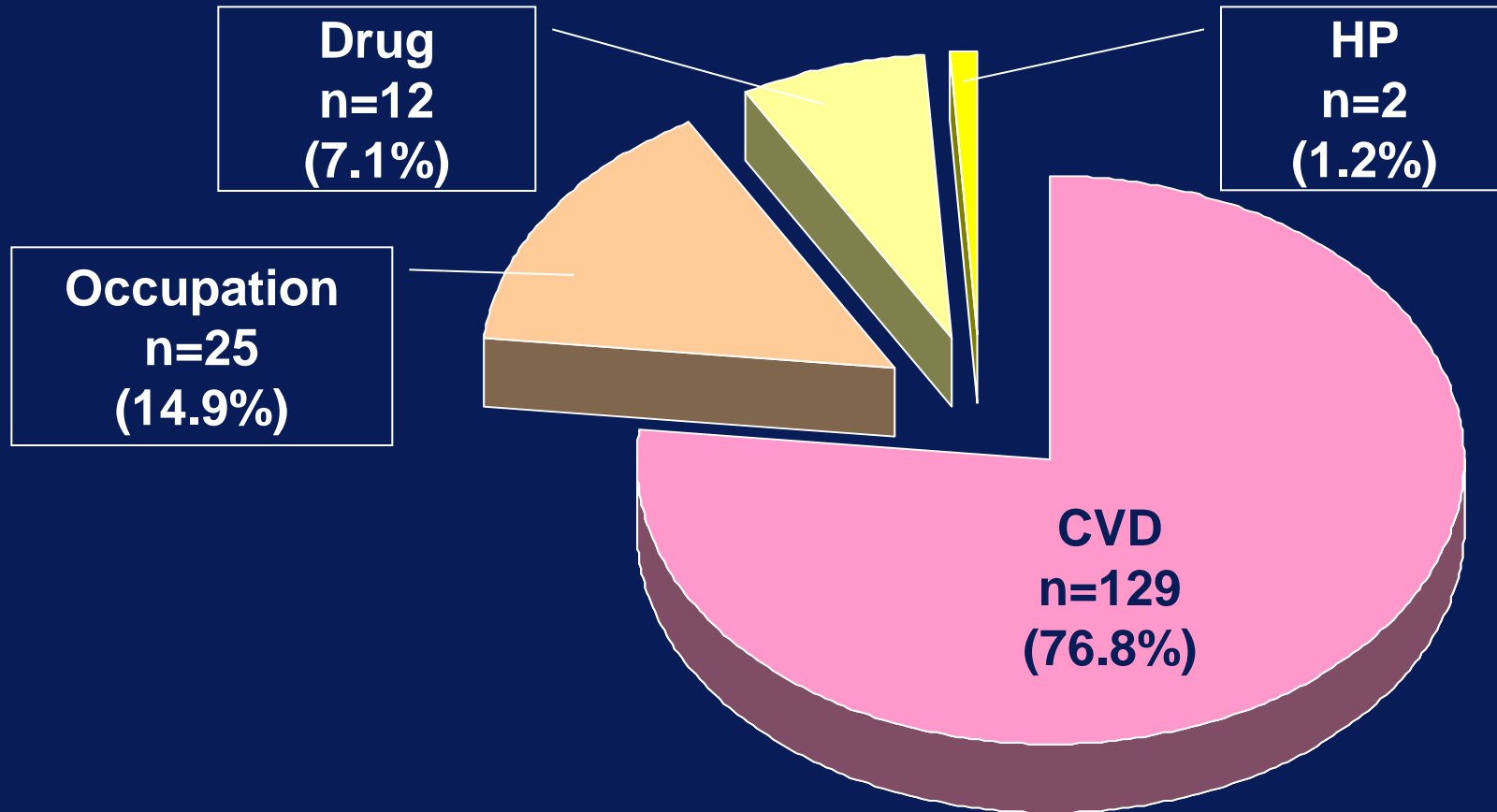
- Several manifestations → lumped as a single entity
  - interstitium, small airways, pleura, vasculature, resp muscle
- Many have subclinical ILD
- Dx methods for the investigation of ILD
- Affected by drug therapy
  - direct toxicity, opportunistic infection d/t immunosuppression
- Lung may precede extra-pulmonary evidence of CTD

# Prospective Registration of DILD



SMC data (May '02 ~ April '04)

# DILD of Known Causes (n=168)

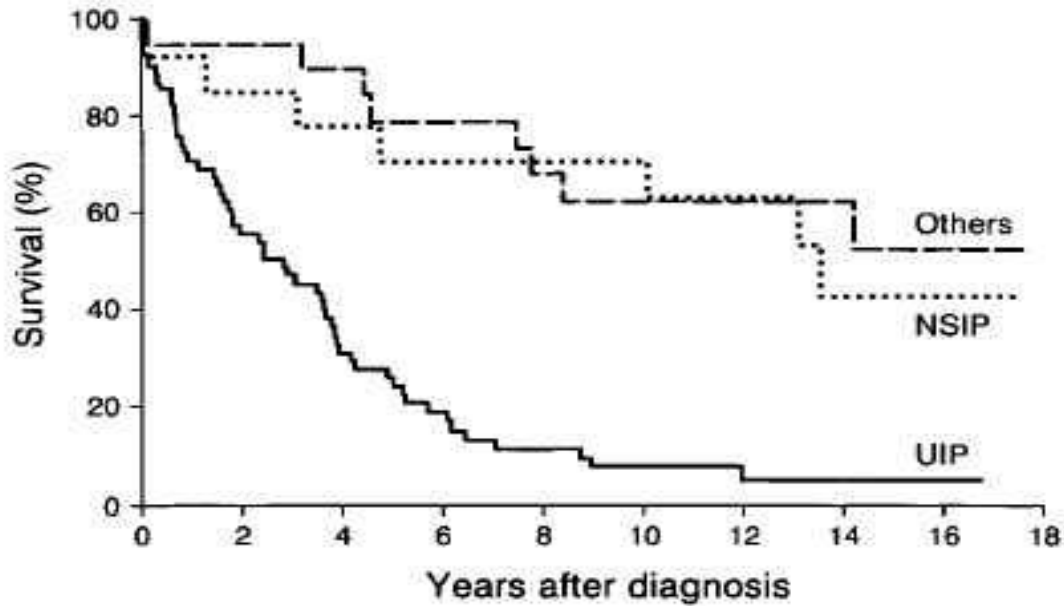


SMC data (May '02 ~ April '04)

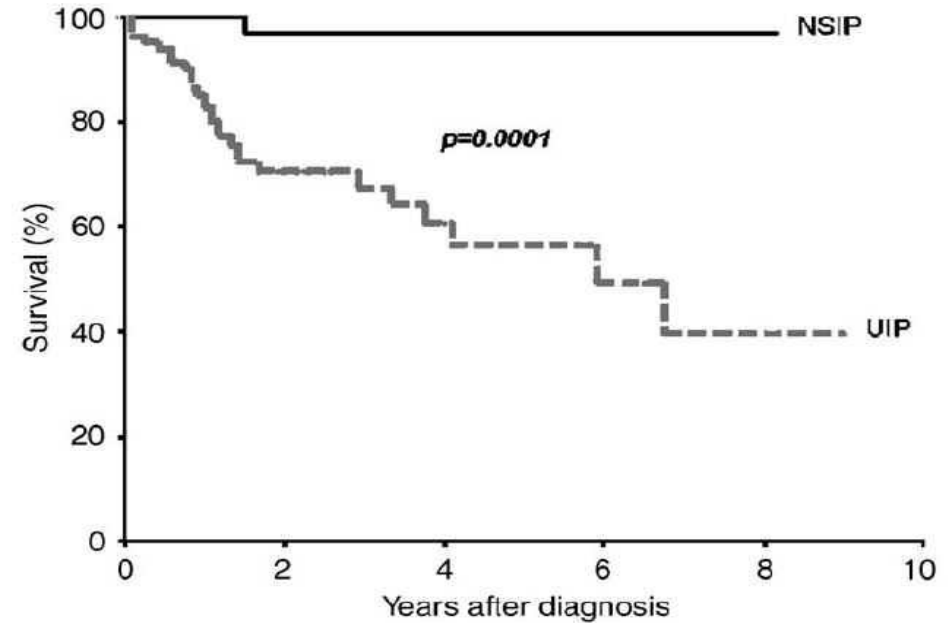
# DDx of CTD-ILD from IIP

Why so important ?

# Prognosis of Idiopathic Interstitial Pneumonia

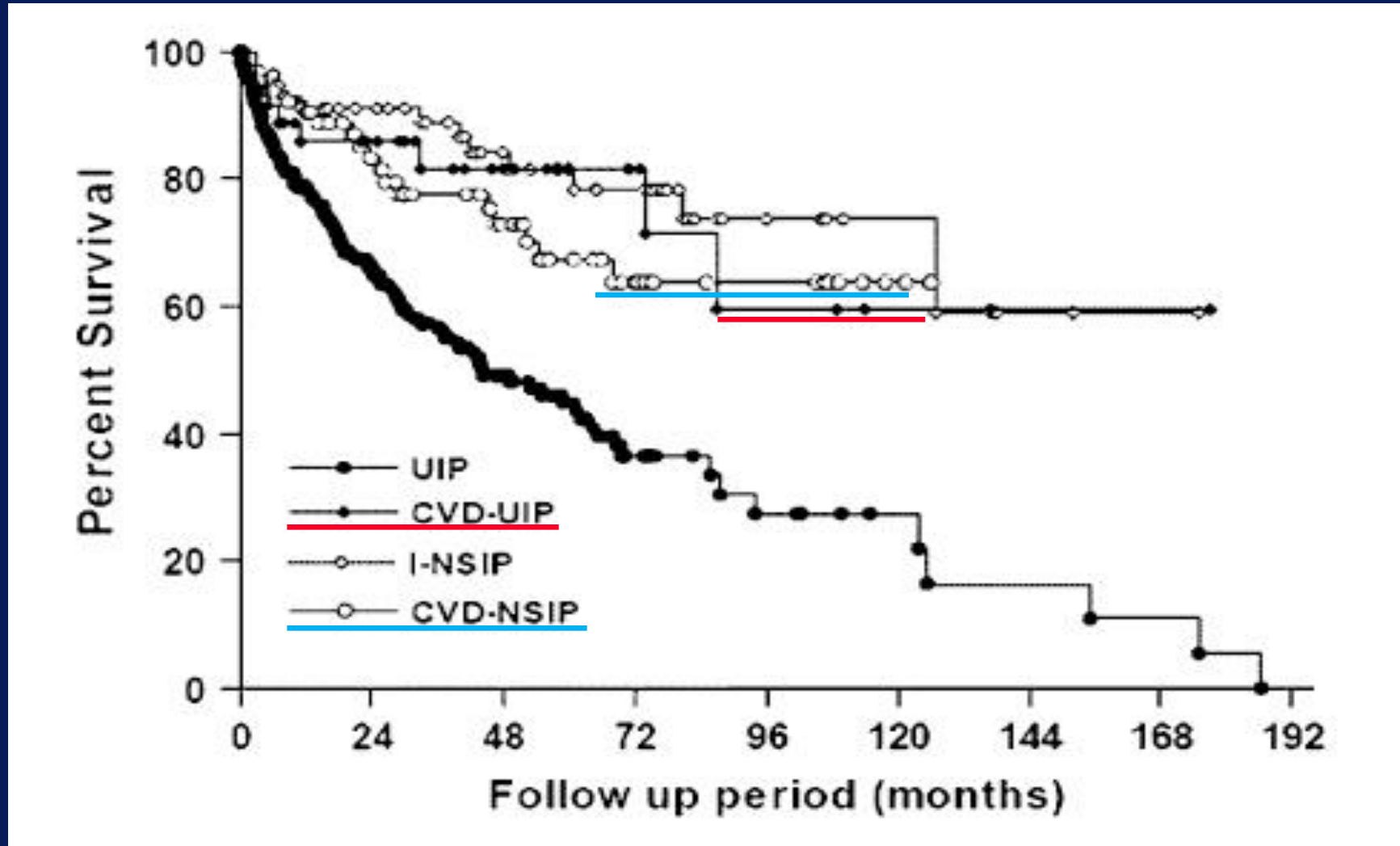


Bjoraker et al, 1998 AJRCCM



Ryu et al, 2007 Resp Med

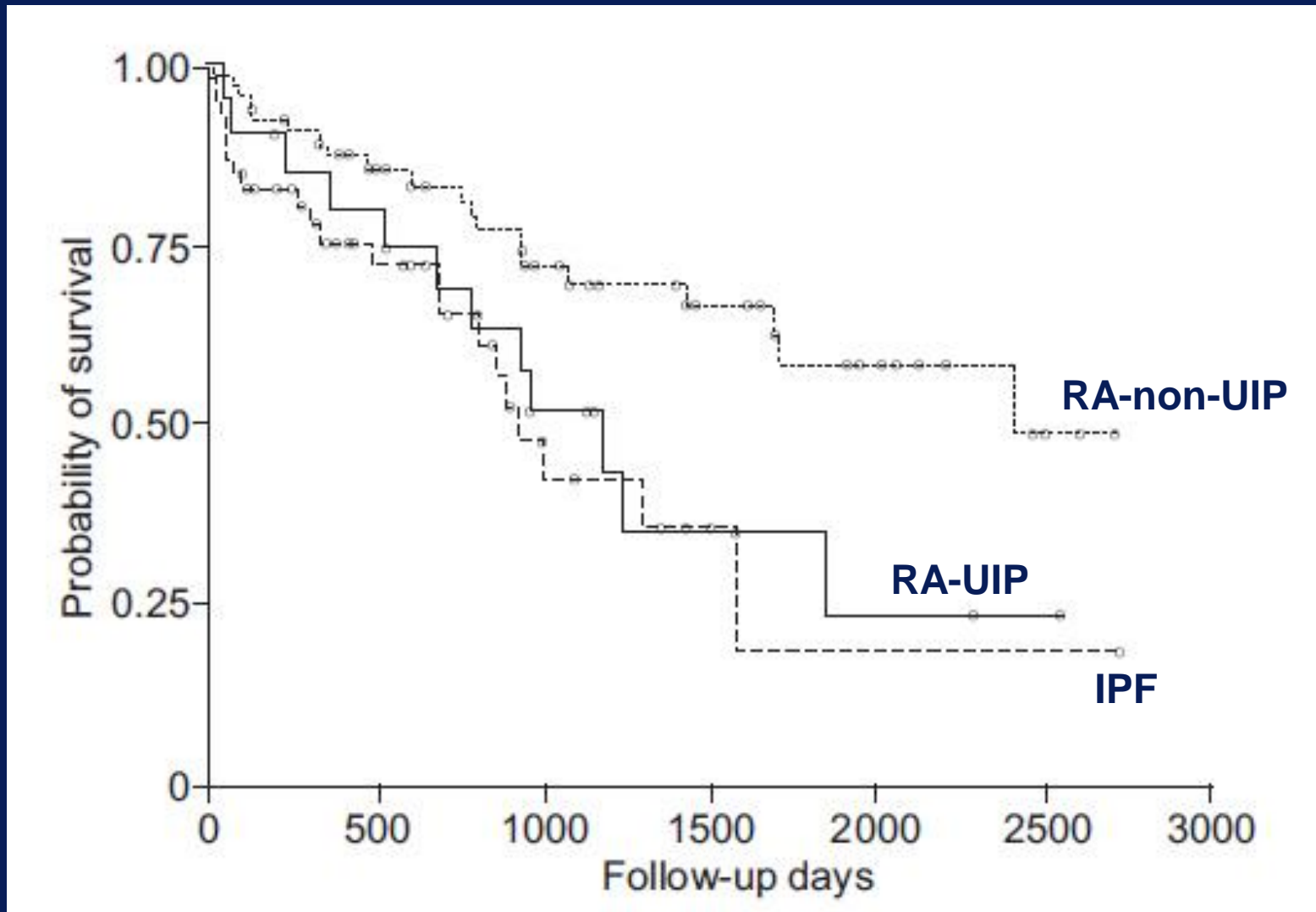
# Prognosis of UIP/NSIP Associated with CTD



# Favorable Prognosis of CTD-ILD Compared with IIP

- CTD is an immune-mediated disease
- Anti-inflammatory therapy is already given for the CTD
- Detection of ILD in subclinical or early stage
- Unclassifiable or mixed lung injury pattern on lung biopsy
- Long periods of disease stability of CTD-ILD with periods of decline

# Bad Prognosis of UIP associated with RA



# DDx of CTD-ILD from IIP

- Demographics of the patients: young age, female
- Extra-thoracic features with CTD-specific Sx and signs
- Presence of serum autoantibodies
- Chest HRCT findings suggestive of CTD
  - pleural/pericardial effusion, concomitant airway disease
  - severe pulmonary HT disproportionate to ILD
- Histopathologic findings: germinal center, NSIP, DAH
  - unclassifiable or mixed histology

# Symptoms and Signs Suggestive of CTD

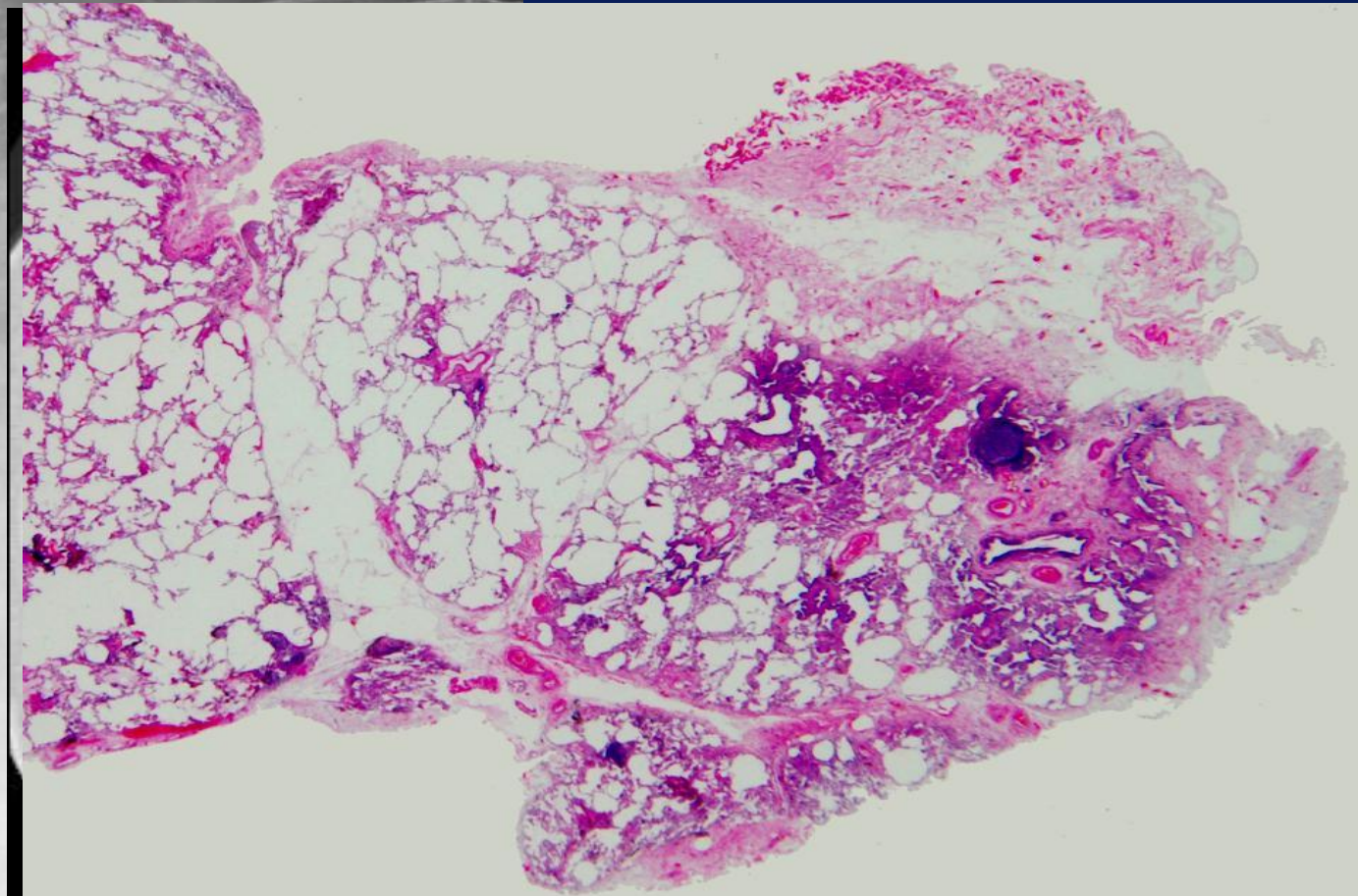
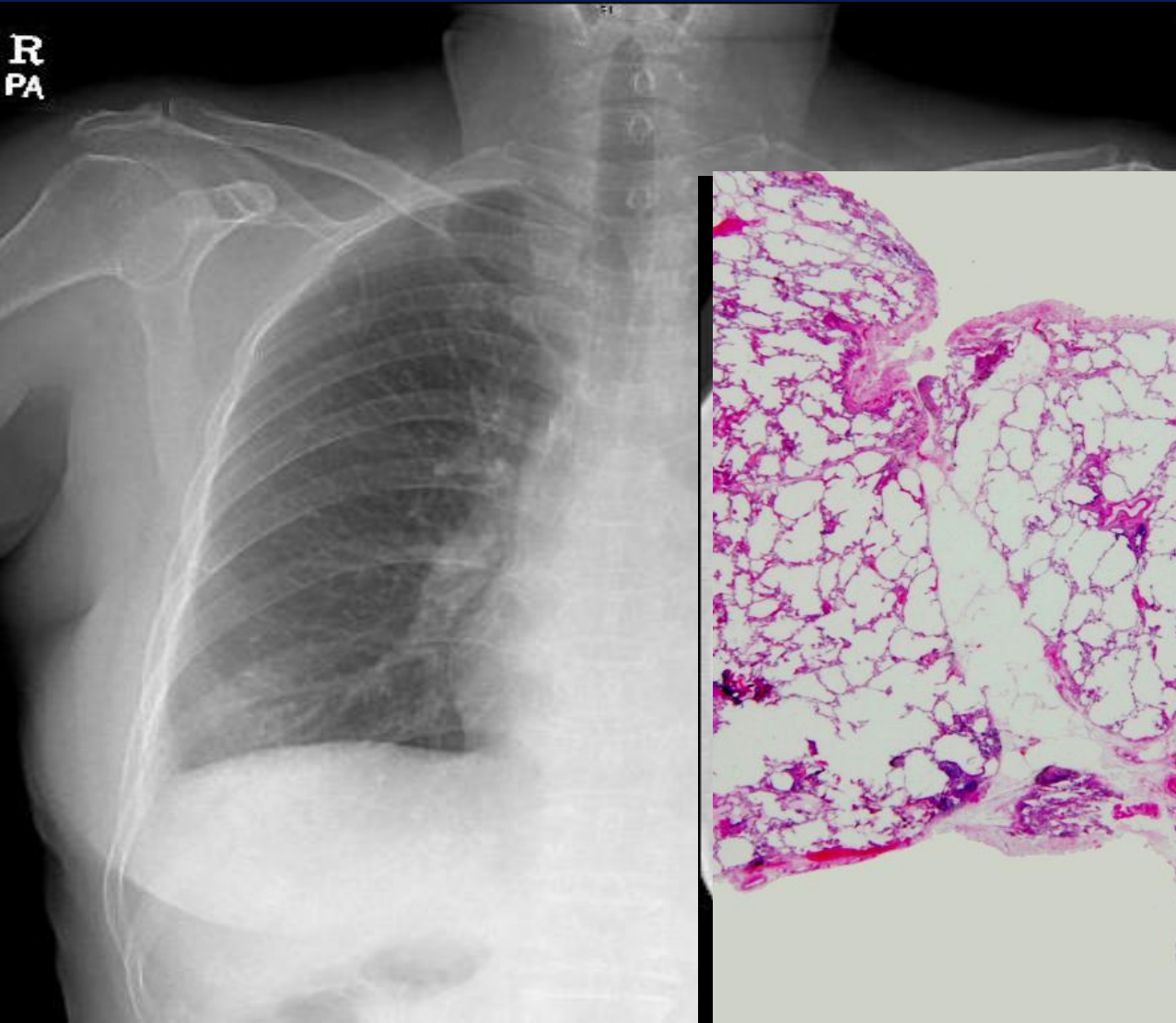
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Symptoms/Signs	Diseases
Joint pain and swelling	RA, SLE, SSc, PM/DM, Sjogren's, WG
R' phenomenon	SSc, SLE, PM/DM
Proximal muscle weakness	PM/DM
Dry eye, Dry mouth	Sjogren's syndrome, SLE, RA, SSc, PM
Dysphagia	SSc, DM/PM
Rashes, Photosensitivity	SLE
Finger ulceration	Vasculitis, SSc
Mechanic's hands	Antisynthetase syndrome
Gottron's papules	DM/PM
Neuropathy	Vasculitis, SSc
Oral ulcer, Genital ulcer	Behcet's

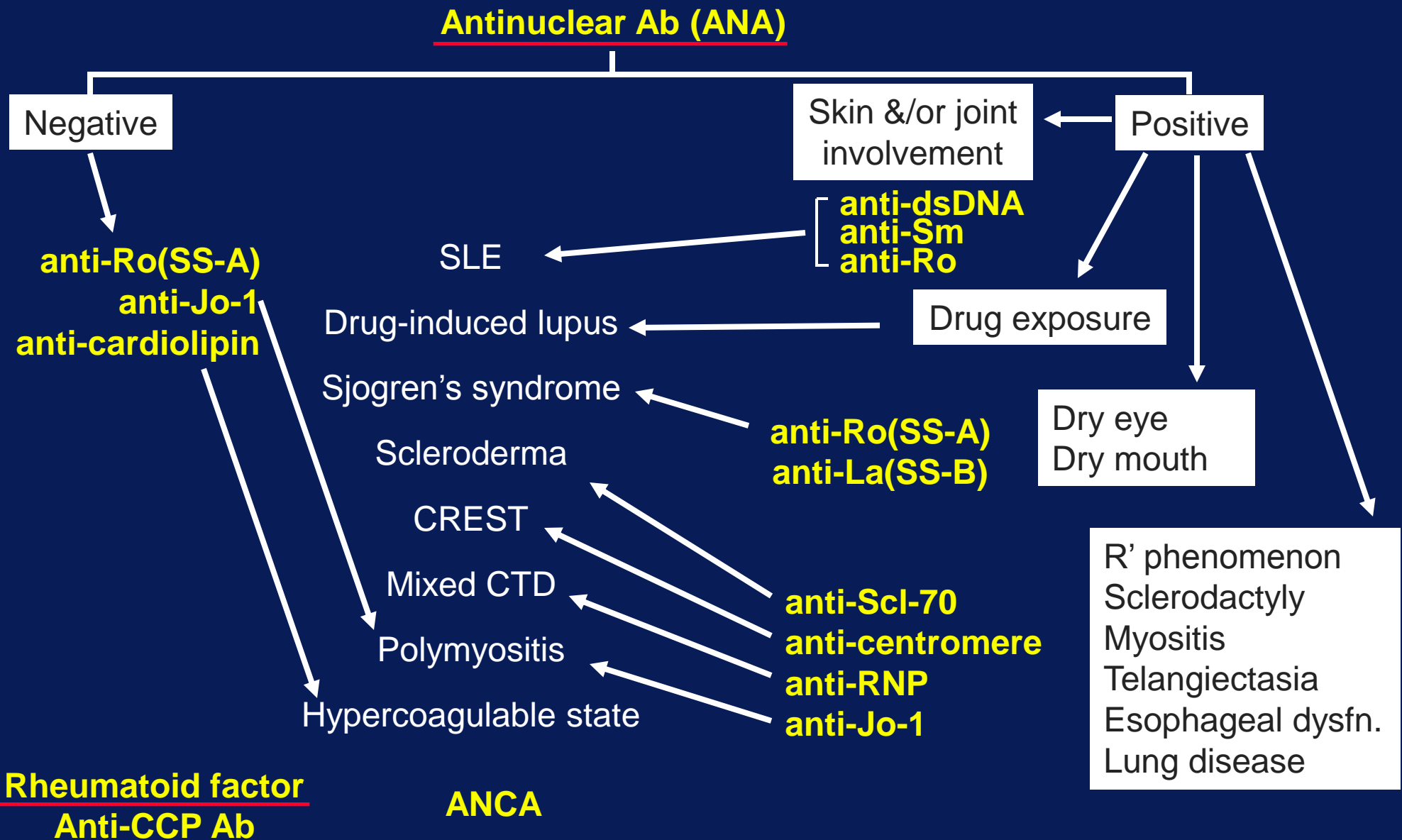
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# F/66, CXR 이상과 관절통

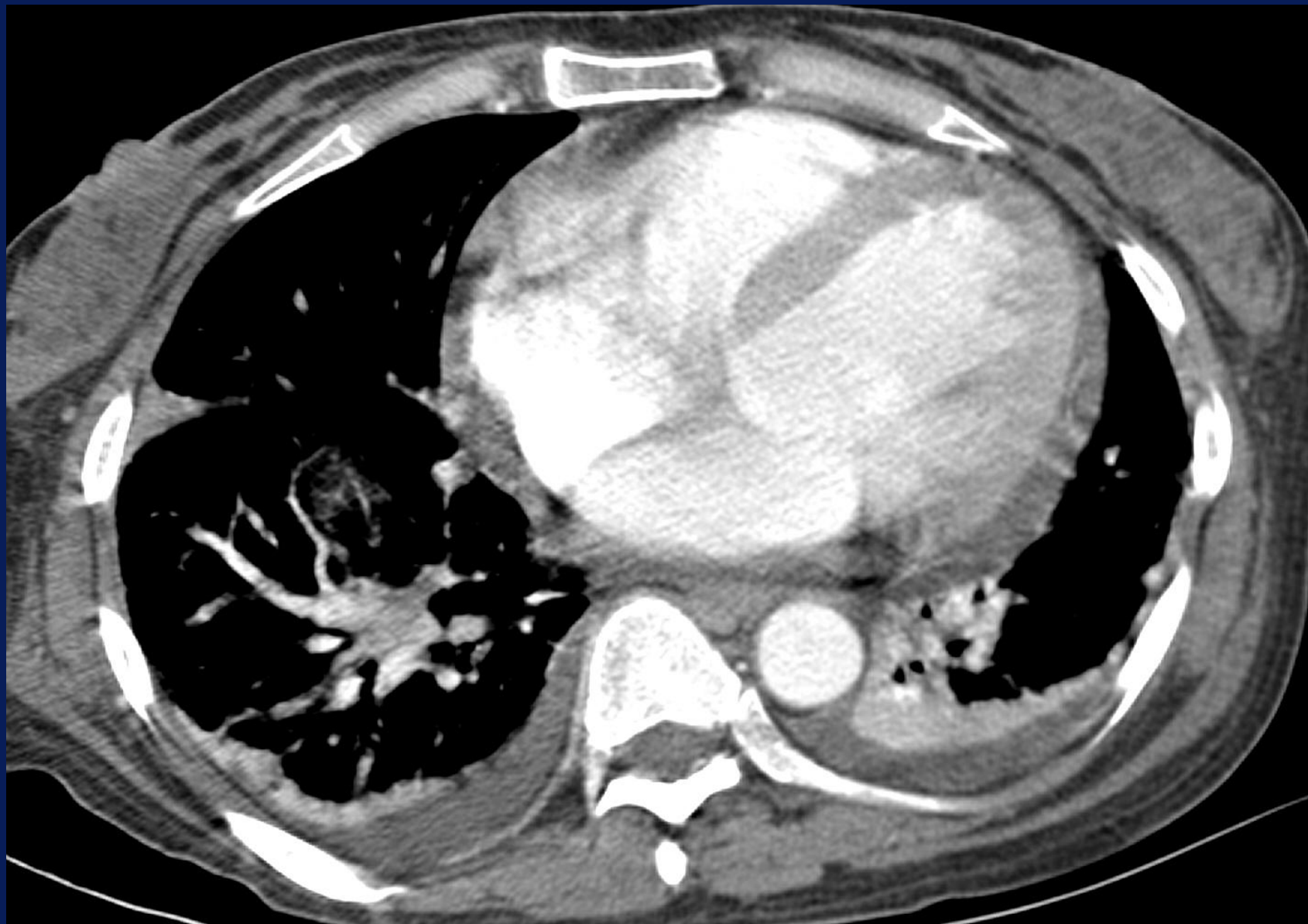
타병원 폐조직검사  
UIP



# Serologic Tests for the Diagnosis of CTD



# Pleural and Pericardial Effusion in SLE

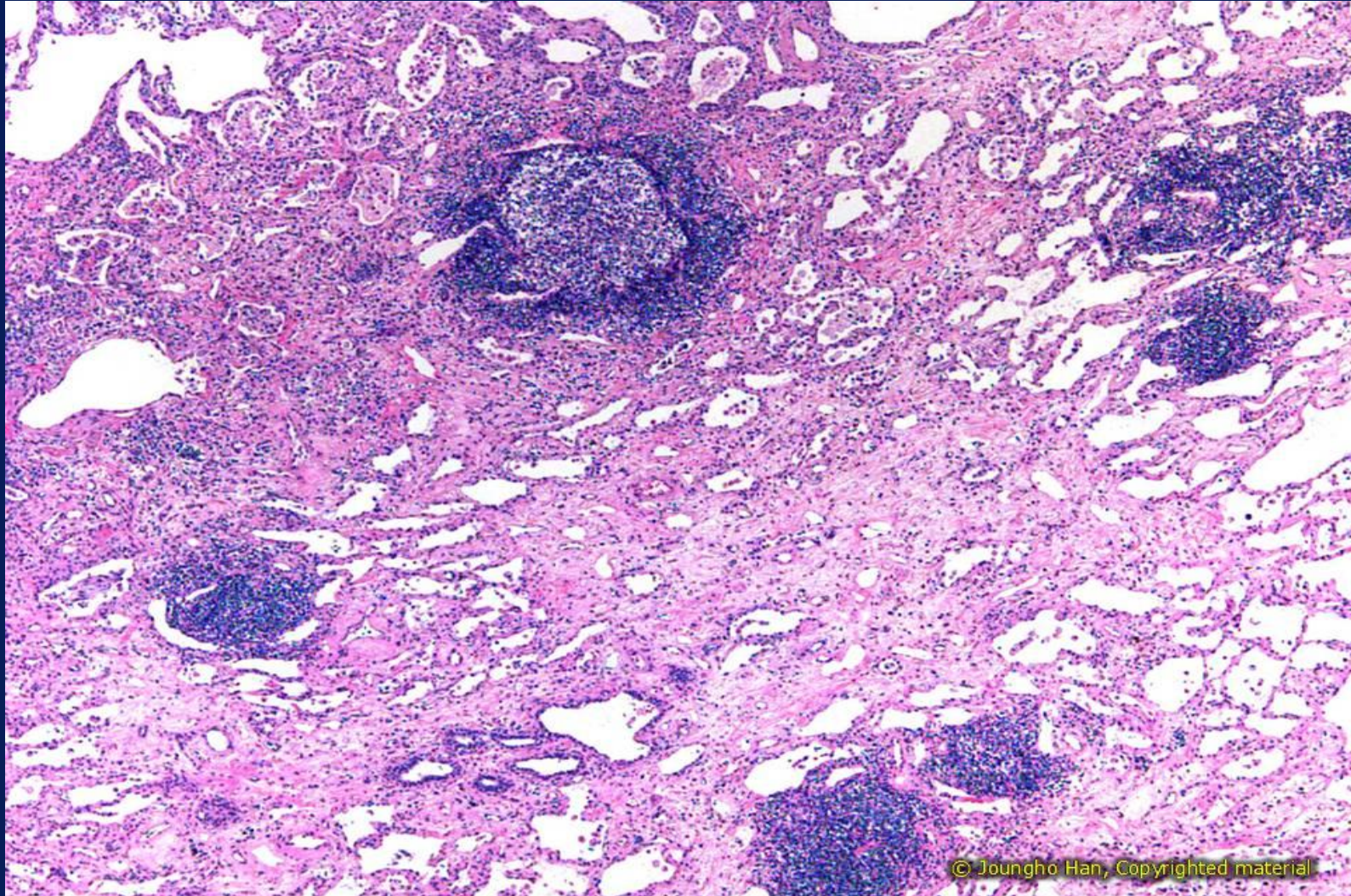


# Multiple Lung Cysts in Sjogren's Syndrome



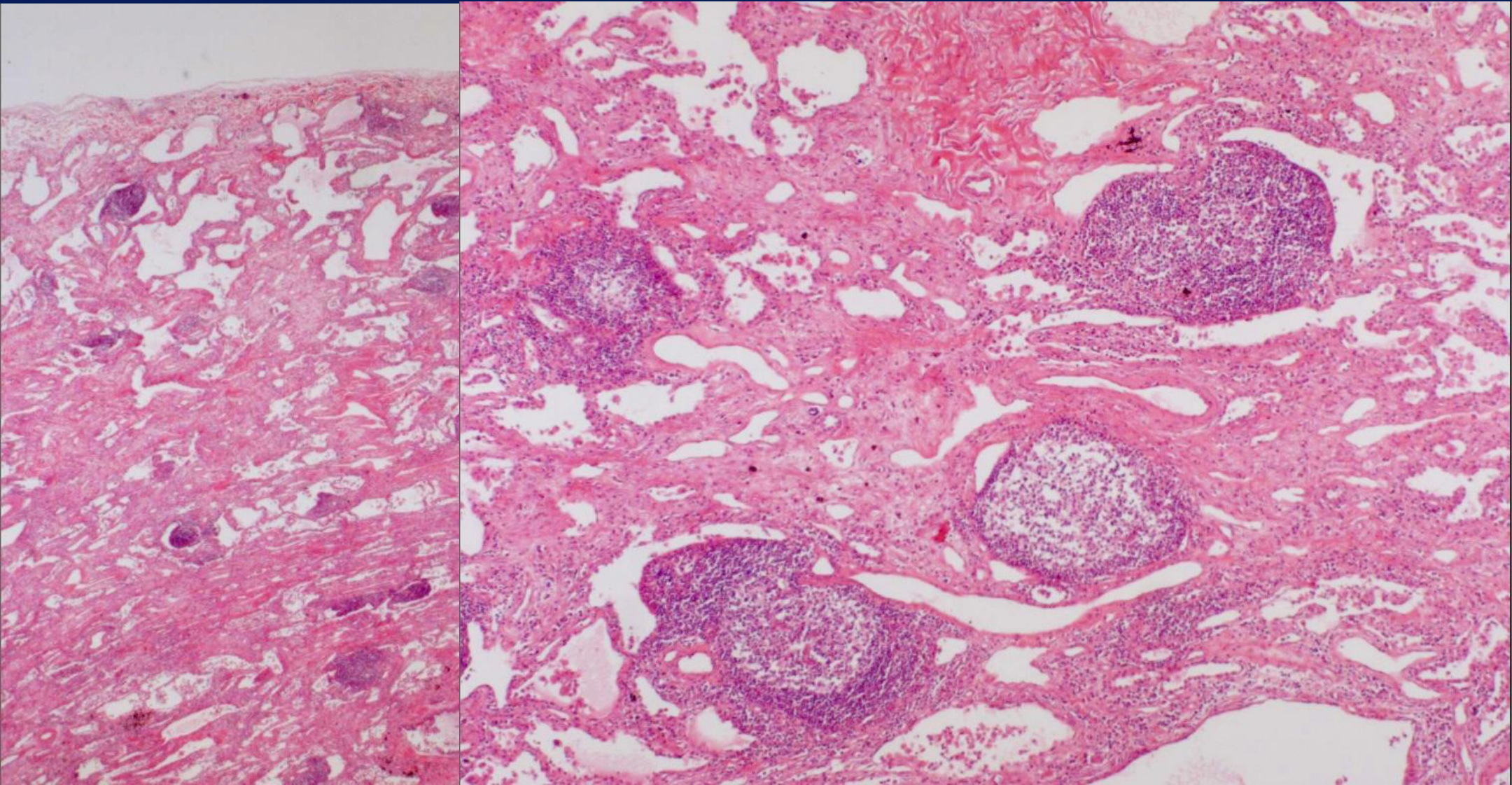
**This is not LAM !**

# Germinal Centers in CTD-ILD

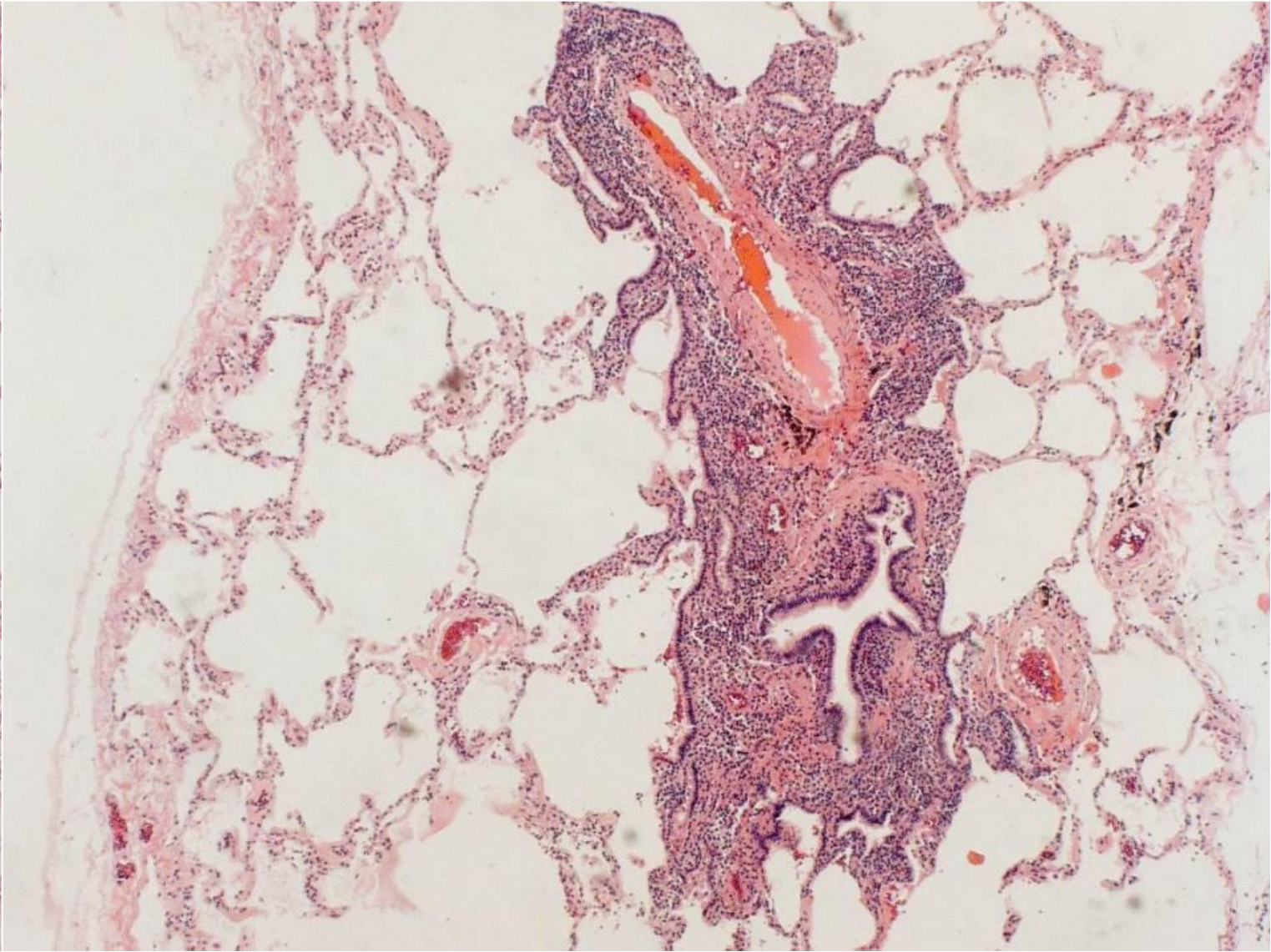
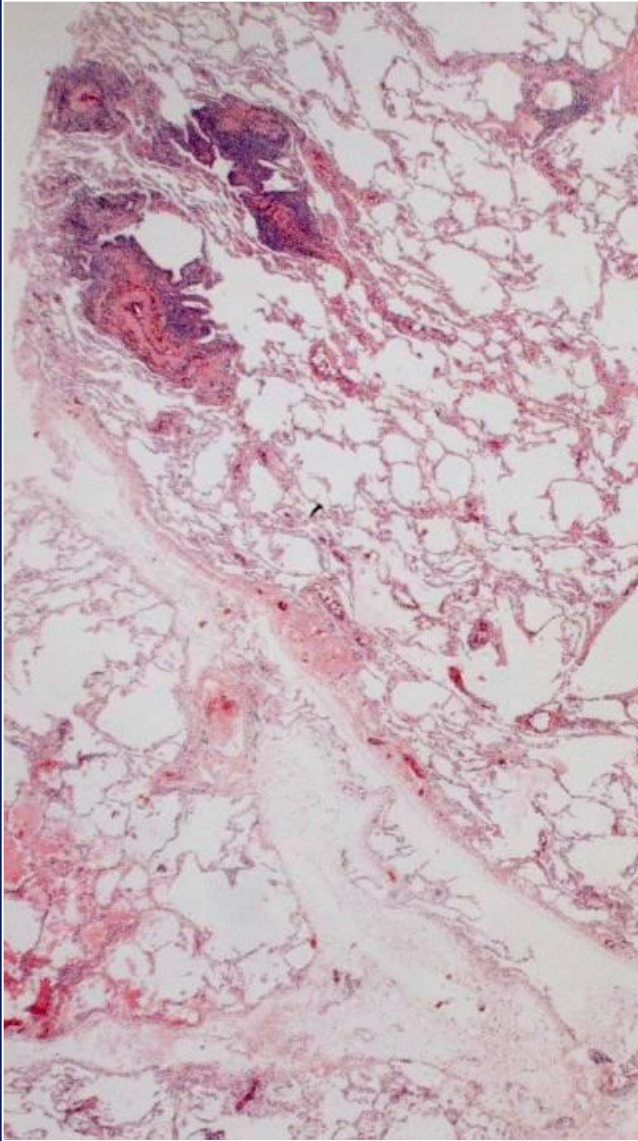


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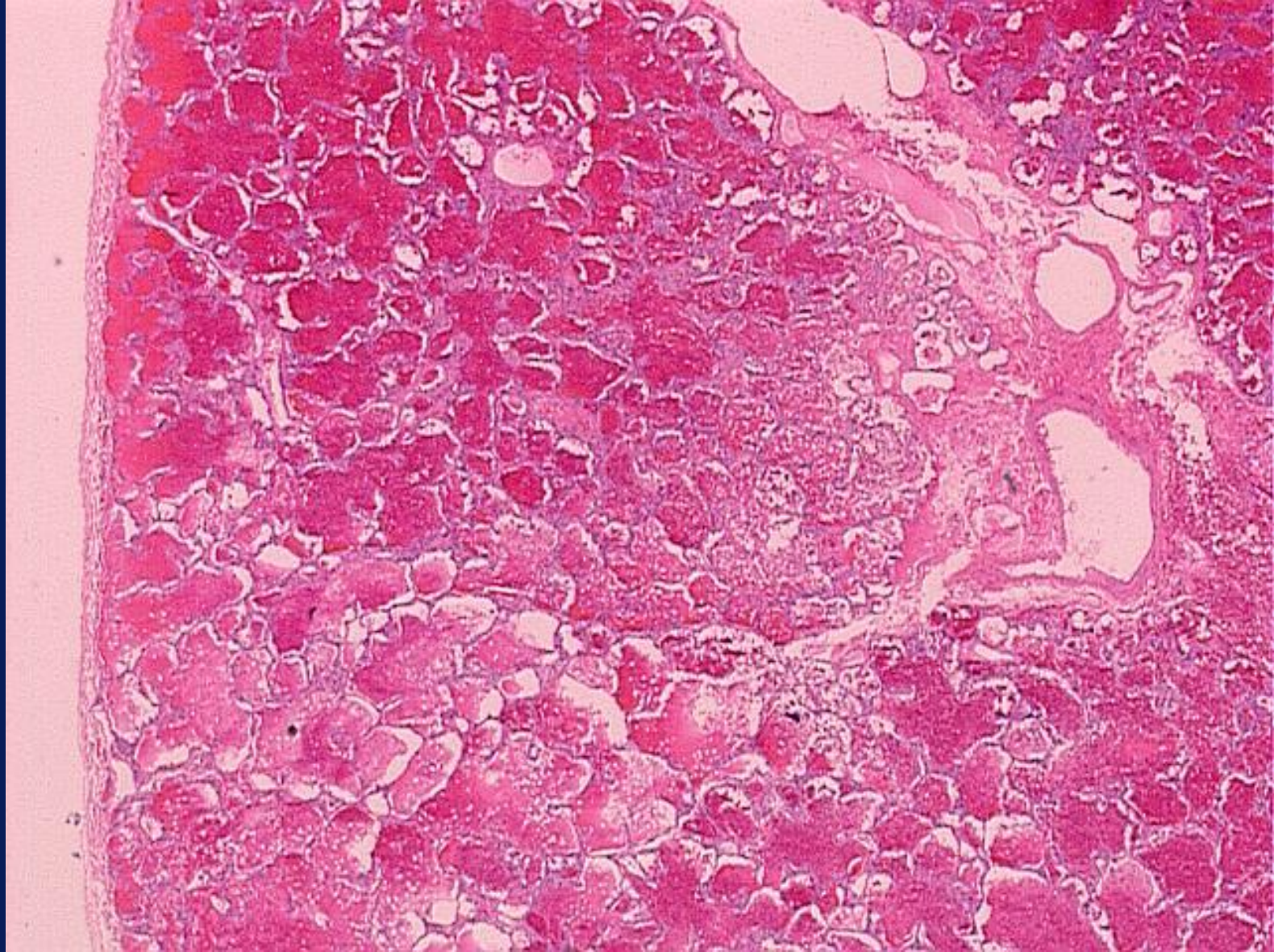
# Nonspecific Interstitial Pneumonia



# Prominent Airway Involvement



# Diffuse Alveolar Hemorrhage



# ILD Associated with CTD

## Investigations

- Thorough and comprehensive Hx taking and P/E !!!
- Serum autoantibodies
- Chest HRCT

Detection and assessment of lung disease

Pattern of HRCT

ground-glass opacity → predominantly inflammatory disease

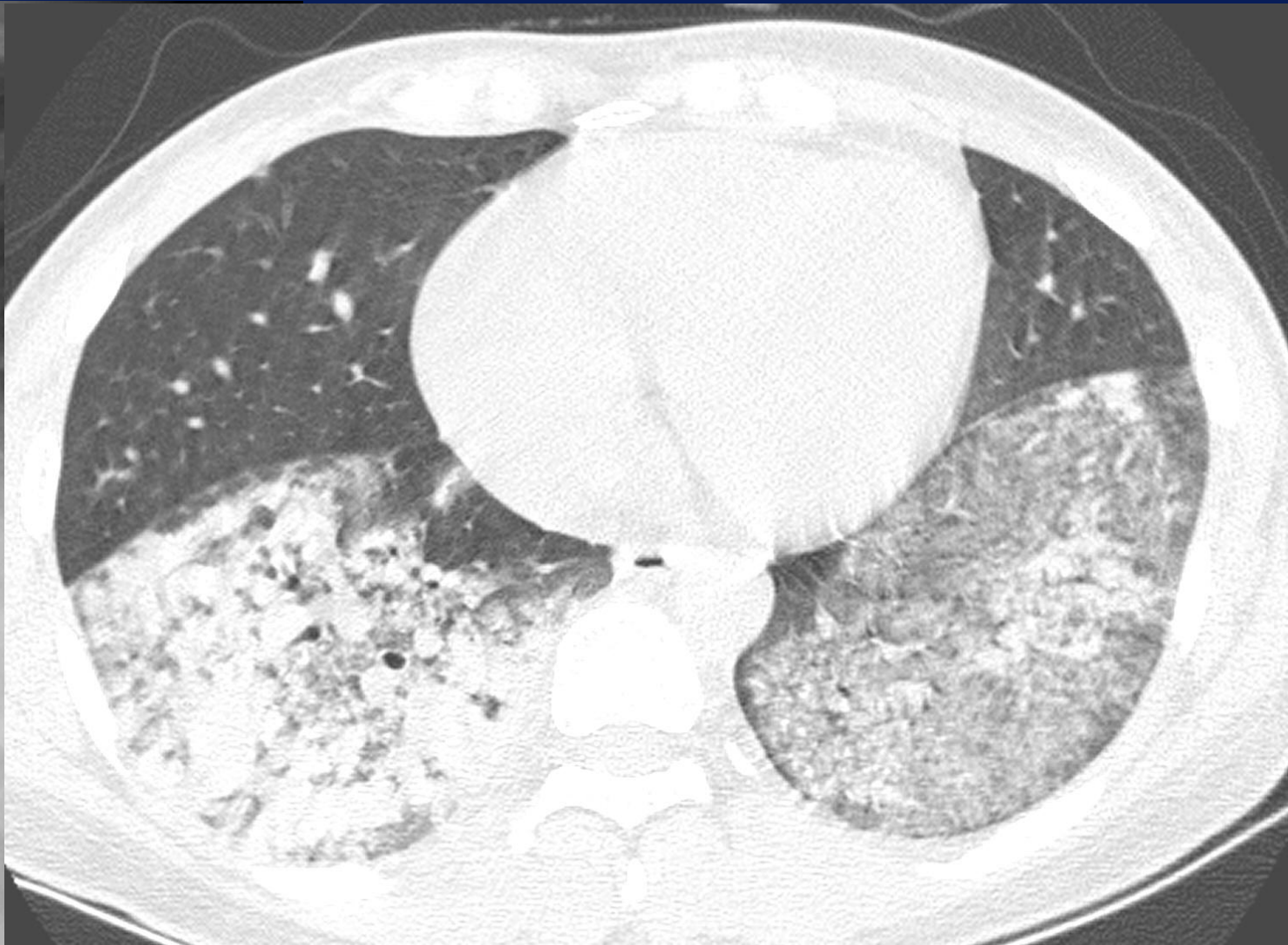
reticular pattern → predominant fibrosis

# ILD Associated with CTD

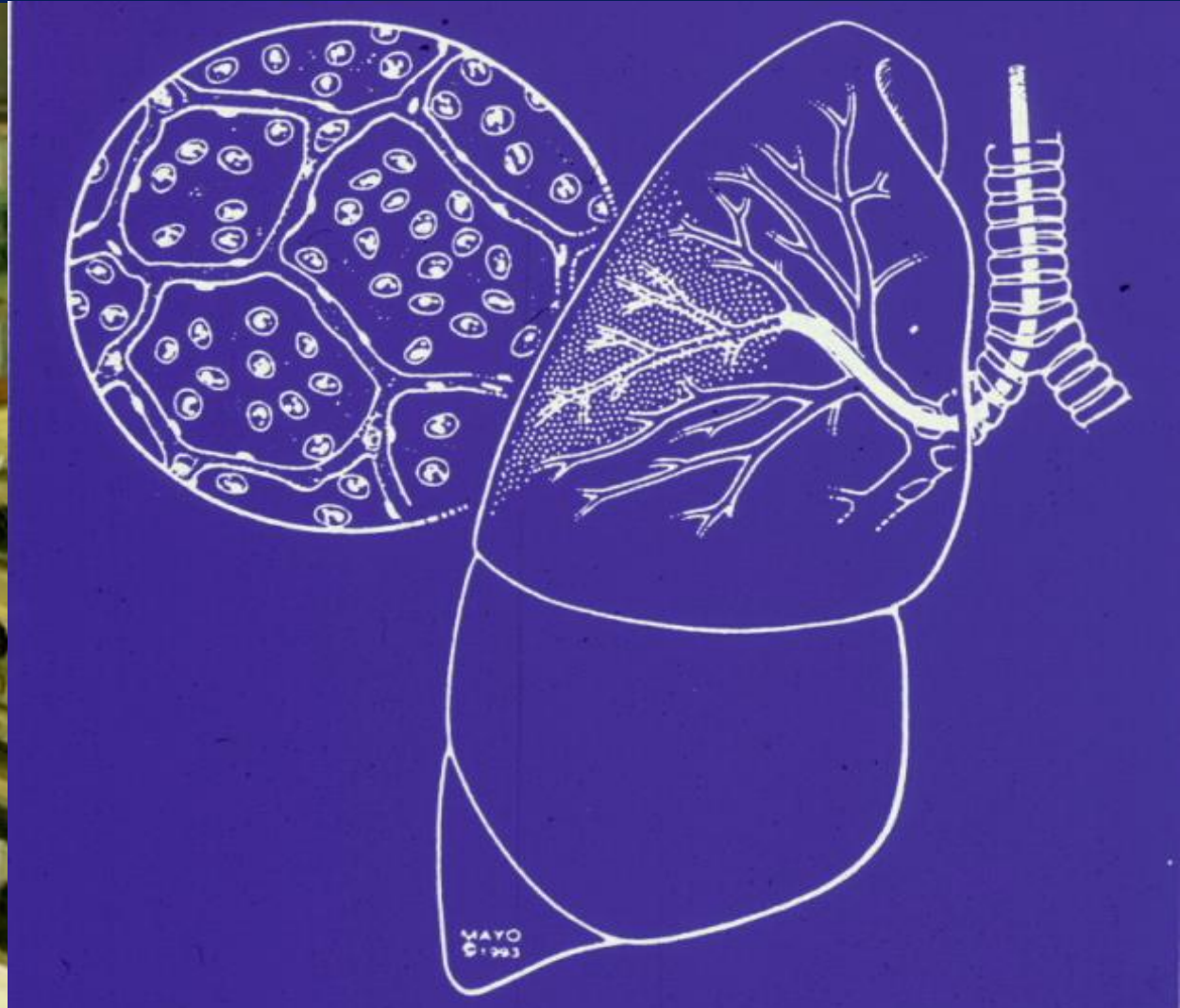
## Investigations

- Bronchoalveolar lavage (BAL)
  - Subclinical active alveolitis
  - Alveolar hemorrhage
  - R/O infection
  - Drug-induced lung disease
- Transbronchial lung biopsy (TBLBx)

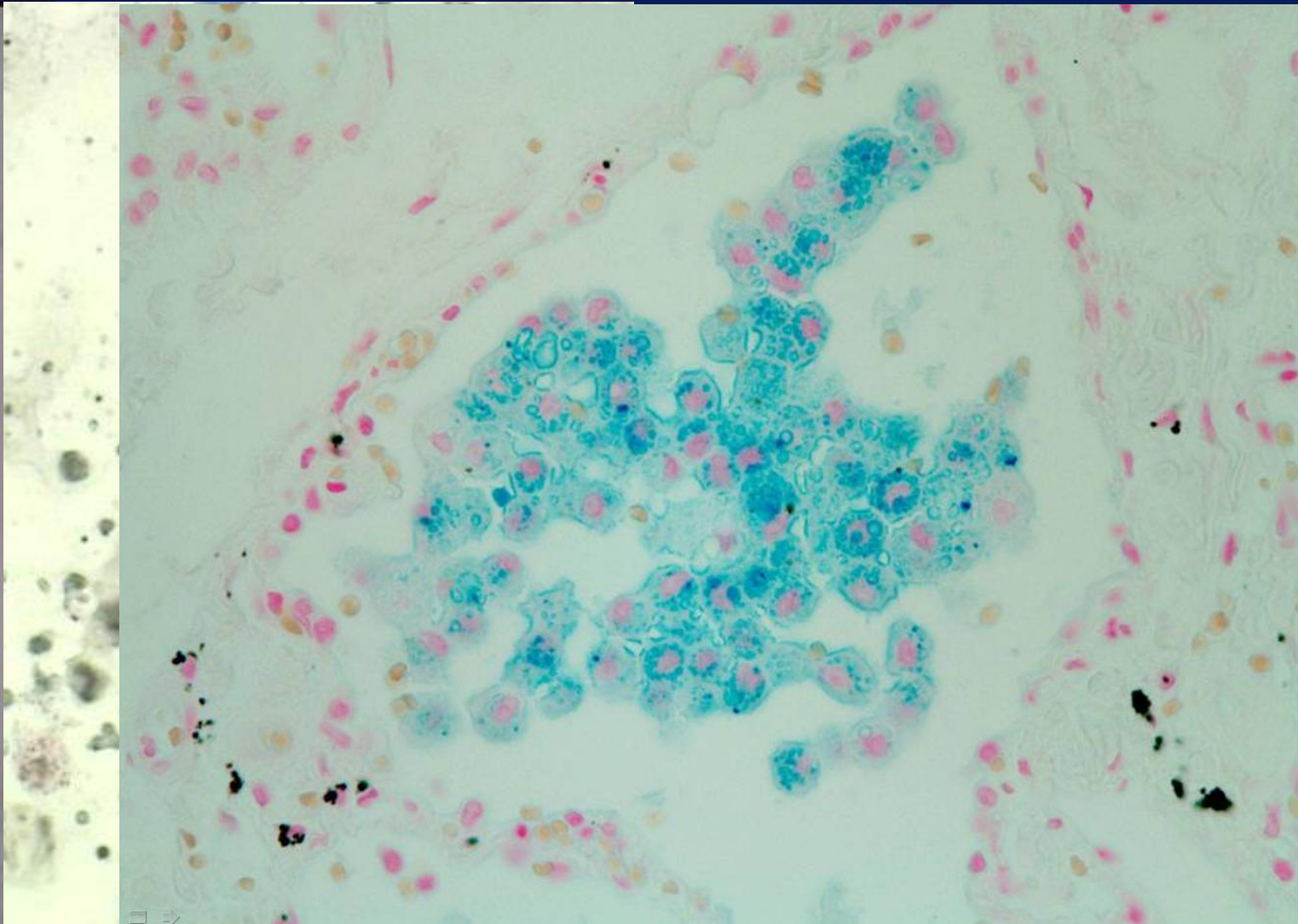
# A 32-year-old Woman with Fever and Dyspnea



# Bronchoalveolar Lavage (BAL)

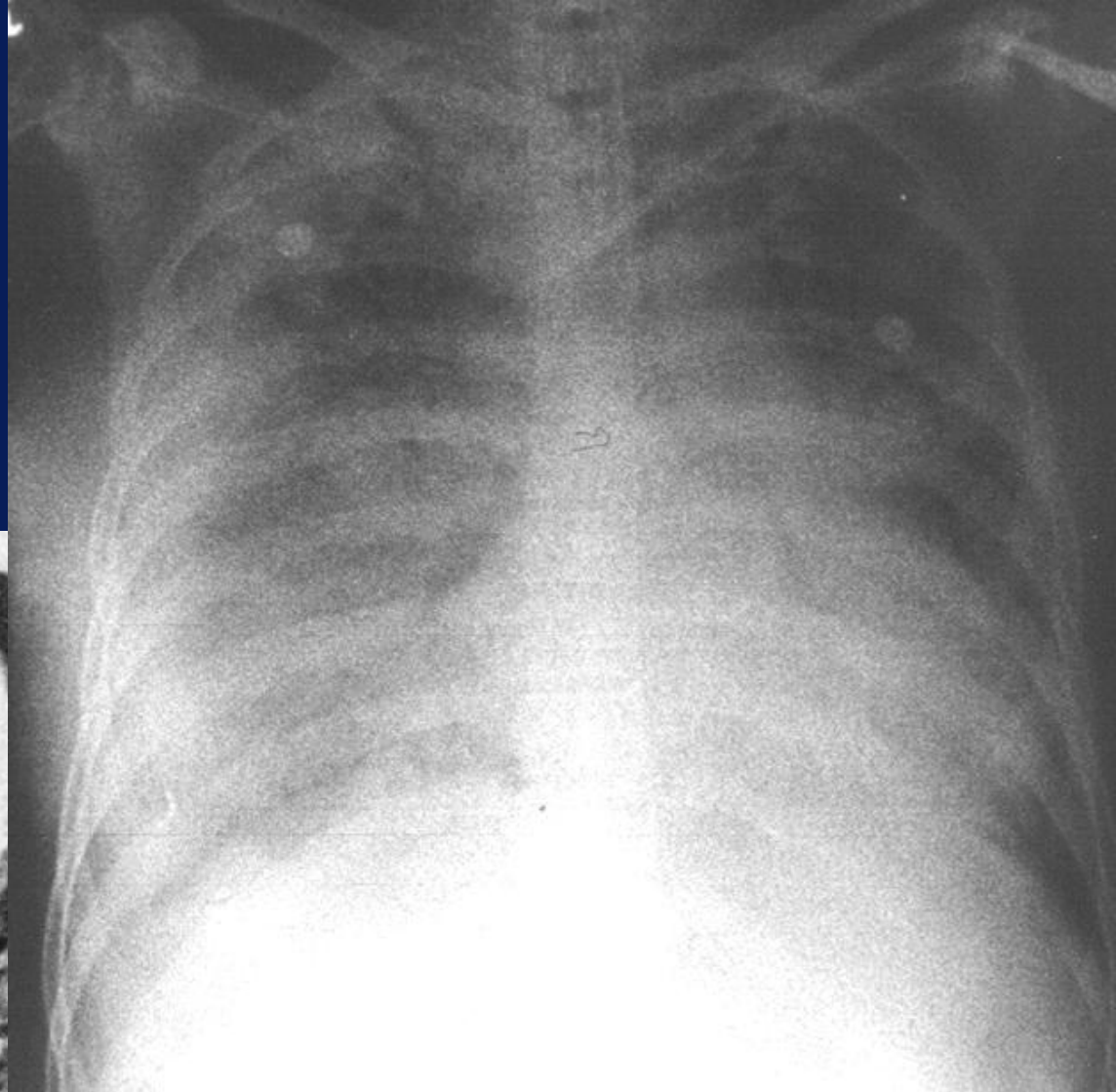
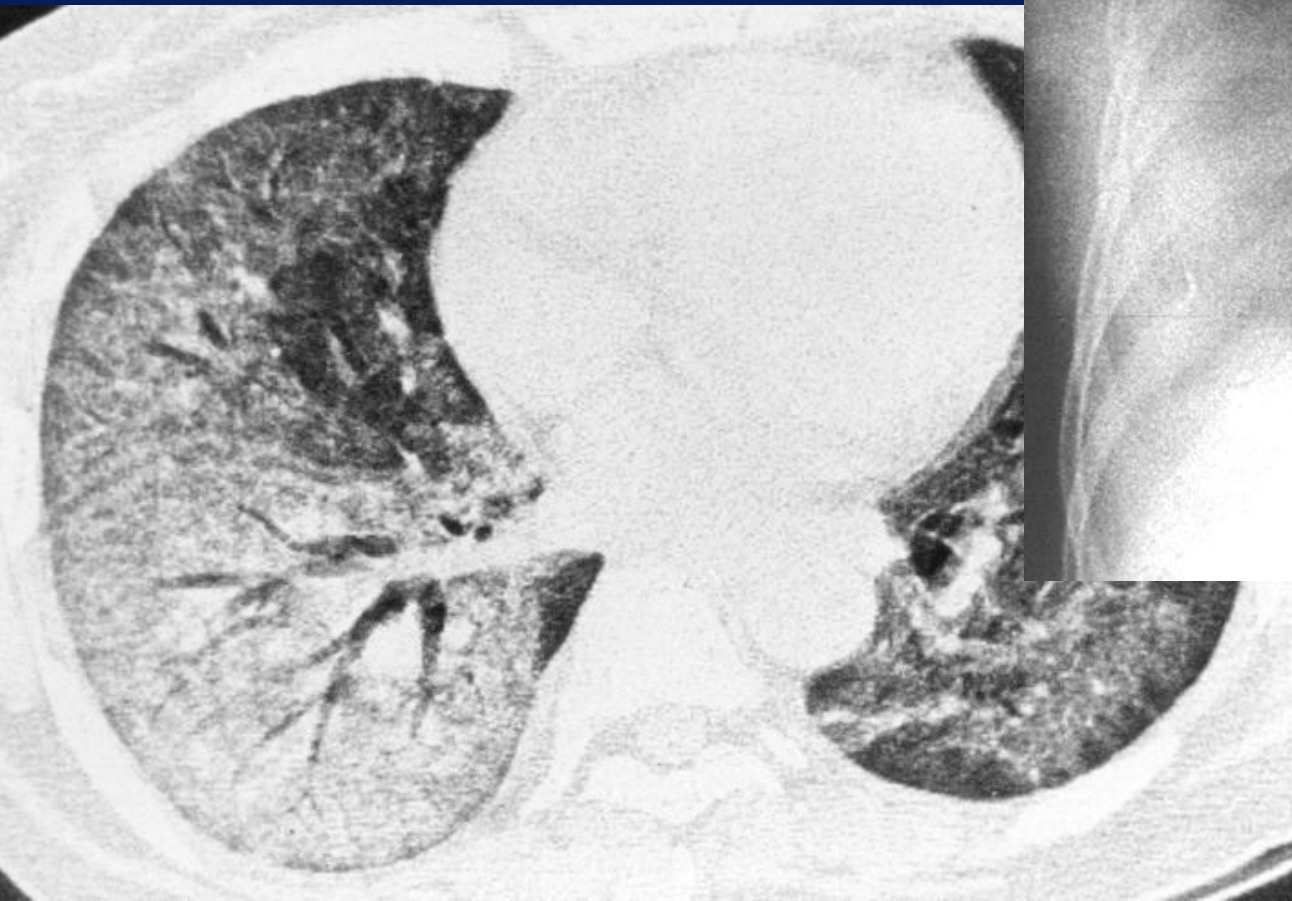


# A 32-year-old Woman with Fever and Dyspnea



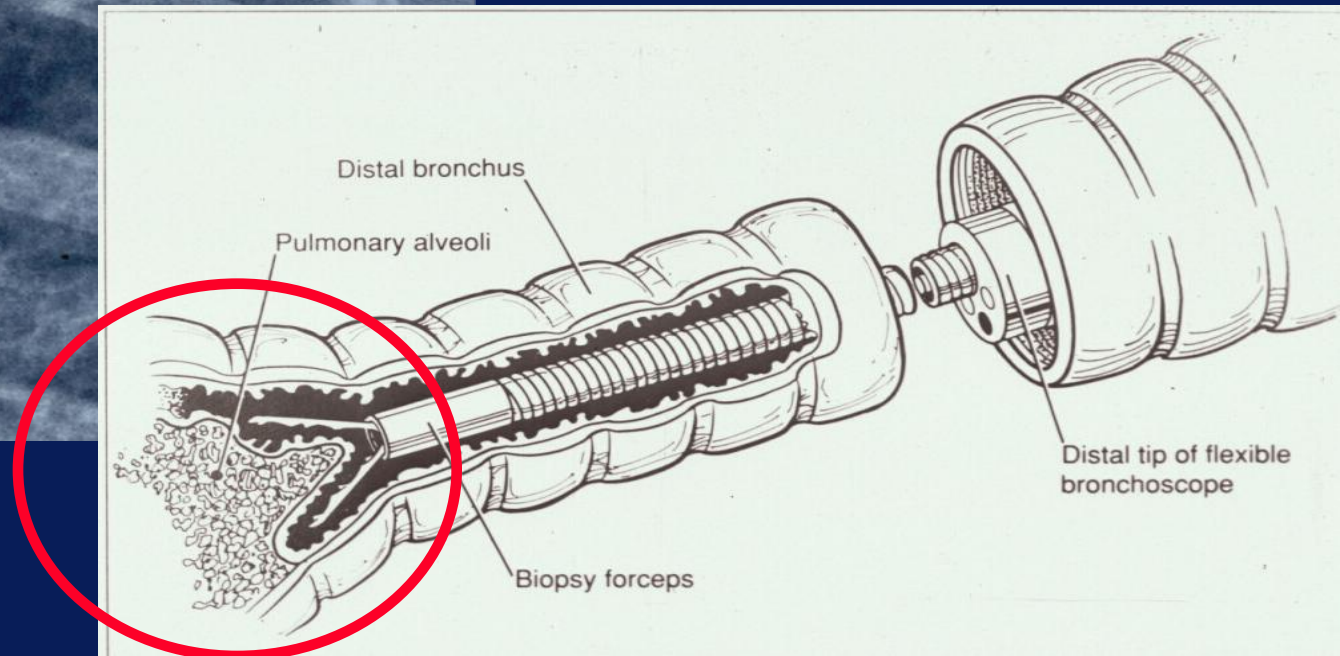
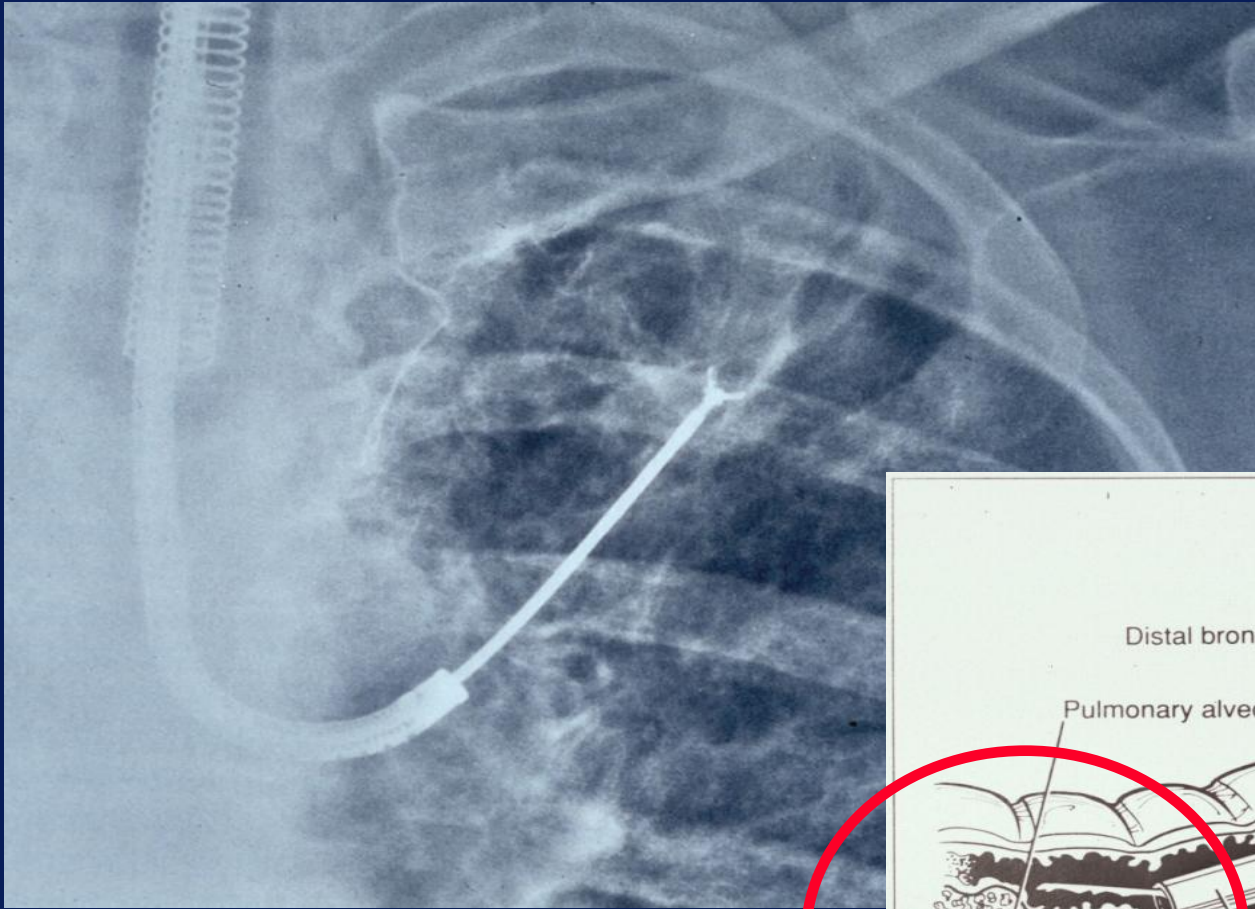
**56/F**

**SLE with CRF on steroid**



**PJ pneumonia**

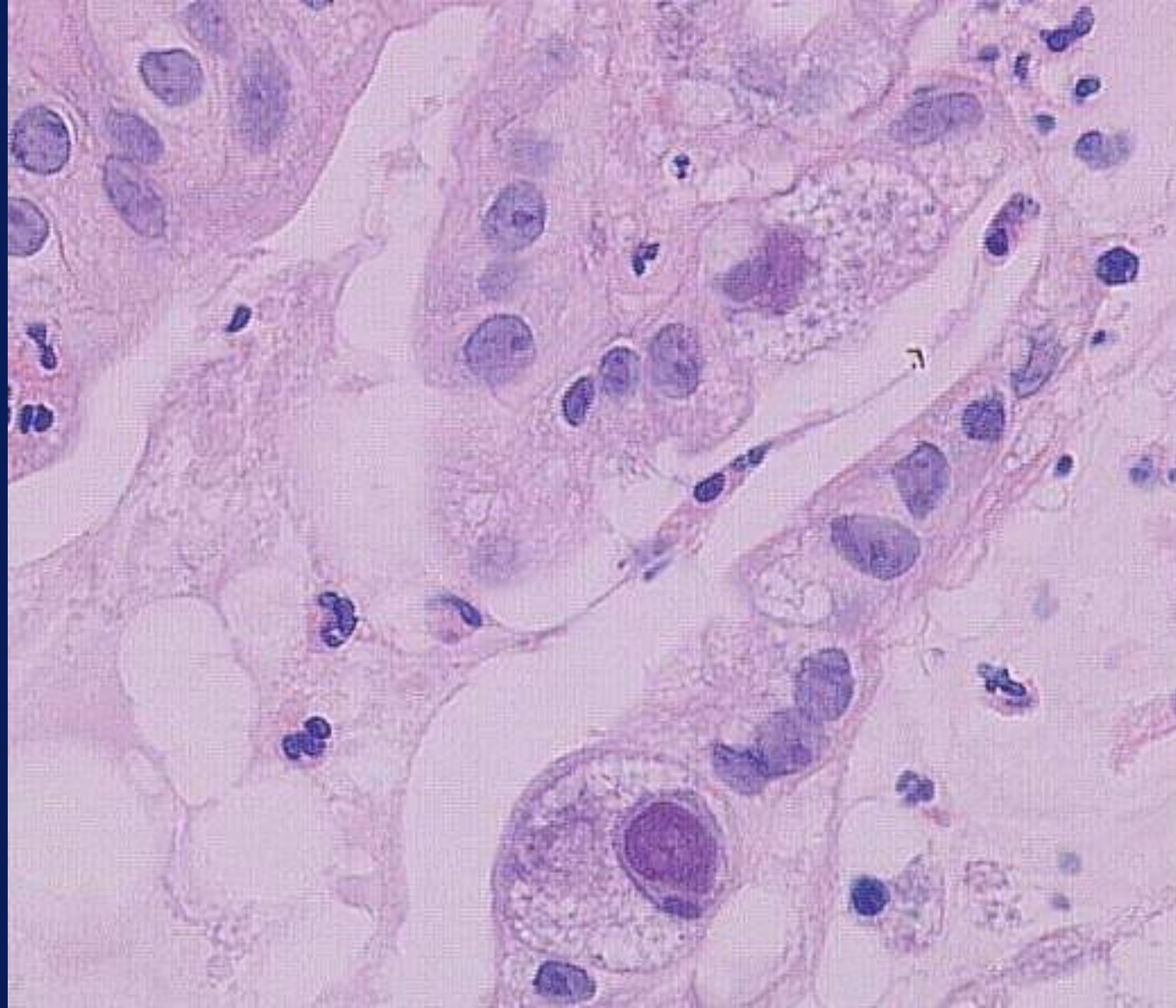
# Transbronchial Lung Biopsy (TBLBx)



# A 32-year-old Woman with DOE and Fever



# CMV Pneumonia



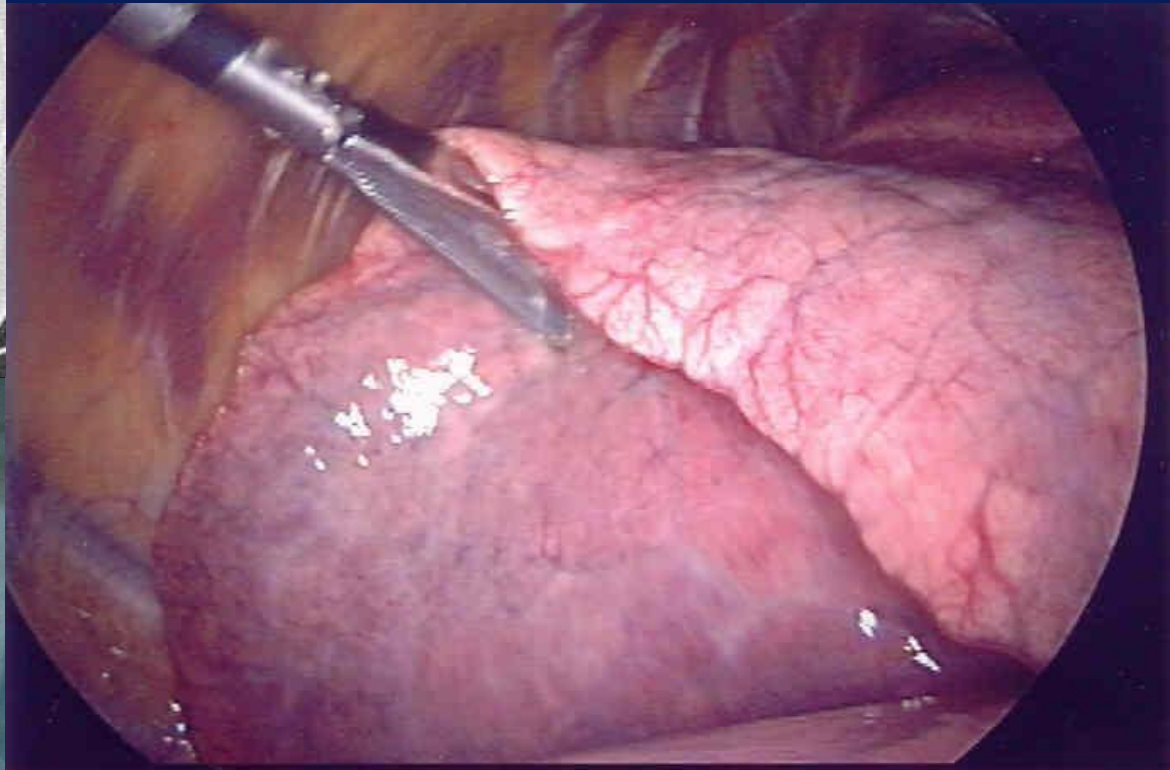
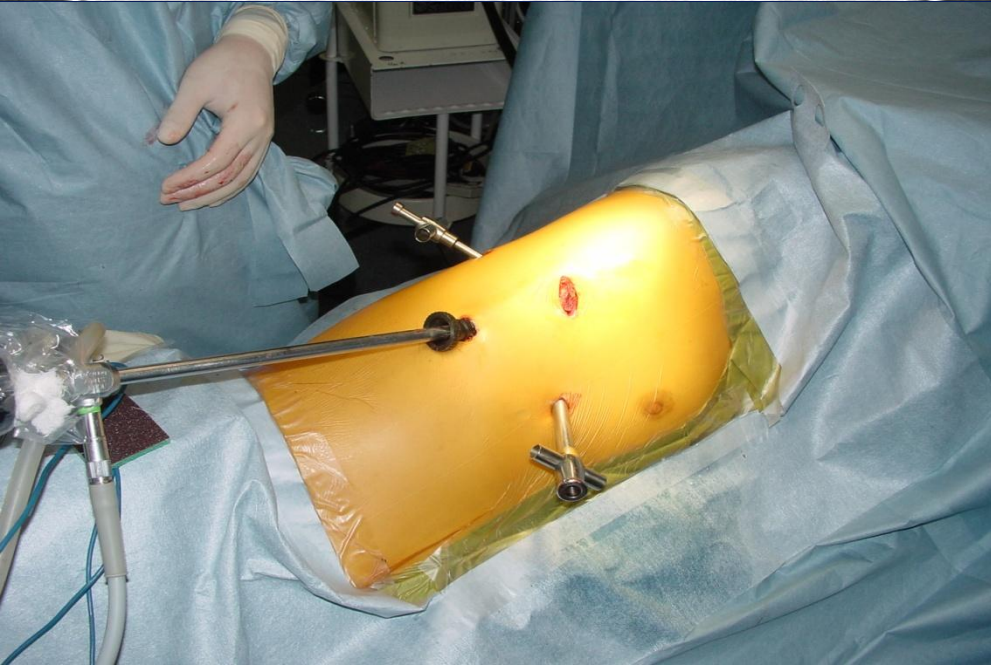
# Pneumonia and Drug Toxicity in CTD

- Superimposed pneumonia in CTD
  - decreased immunity by disease itself (SLE)
  - immunosuppressive therapy
  - aspiration pneumonia
- Drug-induced pneumonitis
  - Methotrexate, biological drugs, leflunomide

# New or Aggravated Lung infiltration in CTD

- Lung manifestation of CTD
- Infectious pneumonia
- Drug-induced pneumonitis

# VATS Lung Biopsy



# ILD Associated with CTD

	NSIP	UIP	BOOP	LIP	DAD
Systemic sclerosis	+++	+	+	-	++
Rheumatoid arthritis	++	+++	++	+	+
Primary Sjogren's syndrome	++	+	-	++	+
Mixed CTD	++	+	+	-	-
Polymyositis/dermatomyositis	+++	+	+++	-	++
SLE	++	+	+	+	++

# Diagnostic Process in DPLD

History, physical examination, chest radiograph, lung function tests

Not IIP

e.g. associated collagen vascular disease,  
environmental, drug-related, etc.

Possible IIP

HRCT

Confident CT  
diagnosis of IPF with  
consistent clinical  
features

Atypical clinical  
or CT features  
for IPF

Features diagnostic  
of another  
DPLD e.g. PLCH

Suspected  
other DPLD

TBBx or BAL?

If non-diagnostic

TBBx, BAL or  
other relevant test

Surgical lung biopsy

UIP

NSIP

RB

DIP

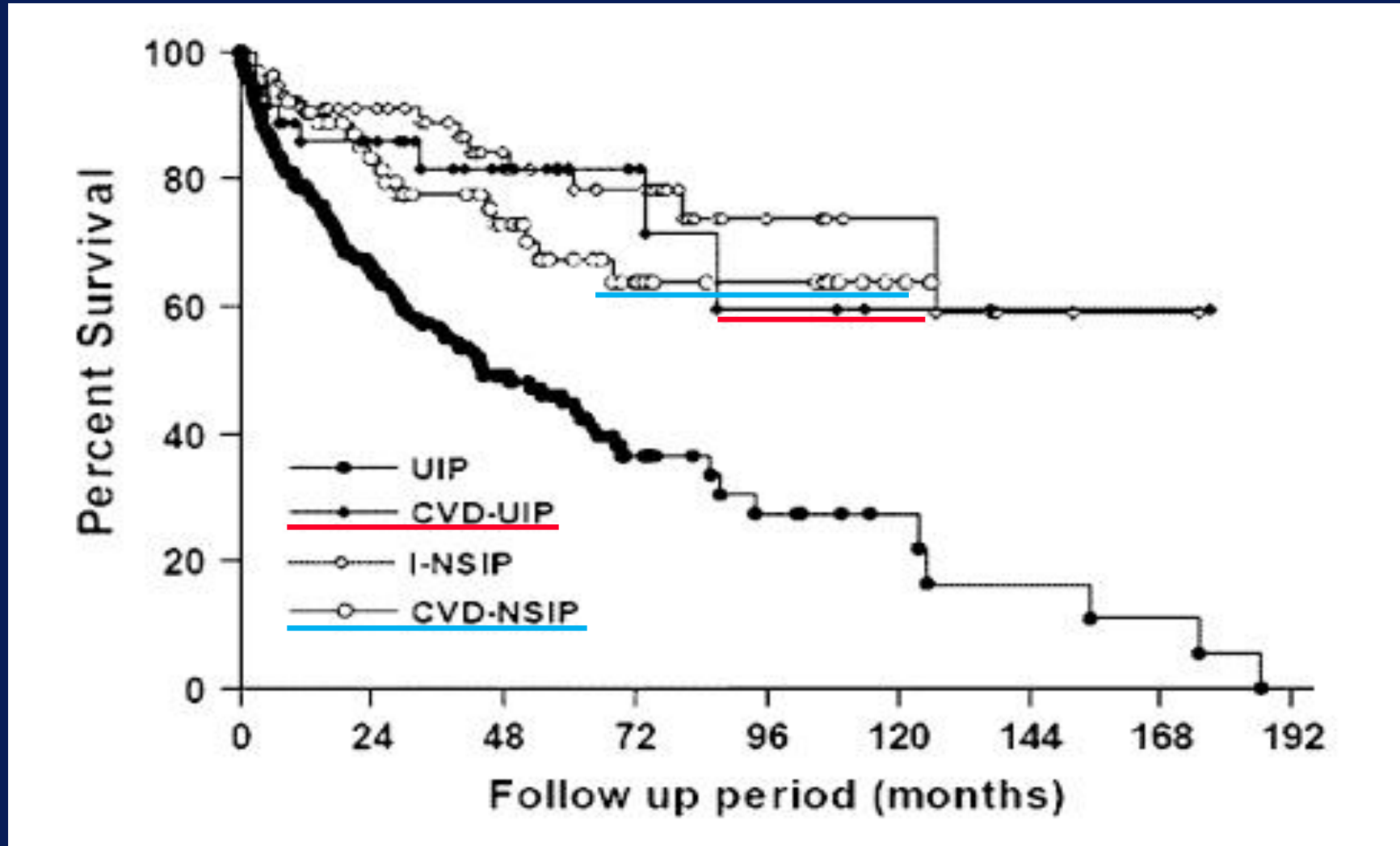
DAD

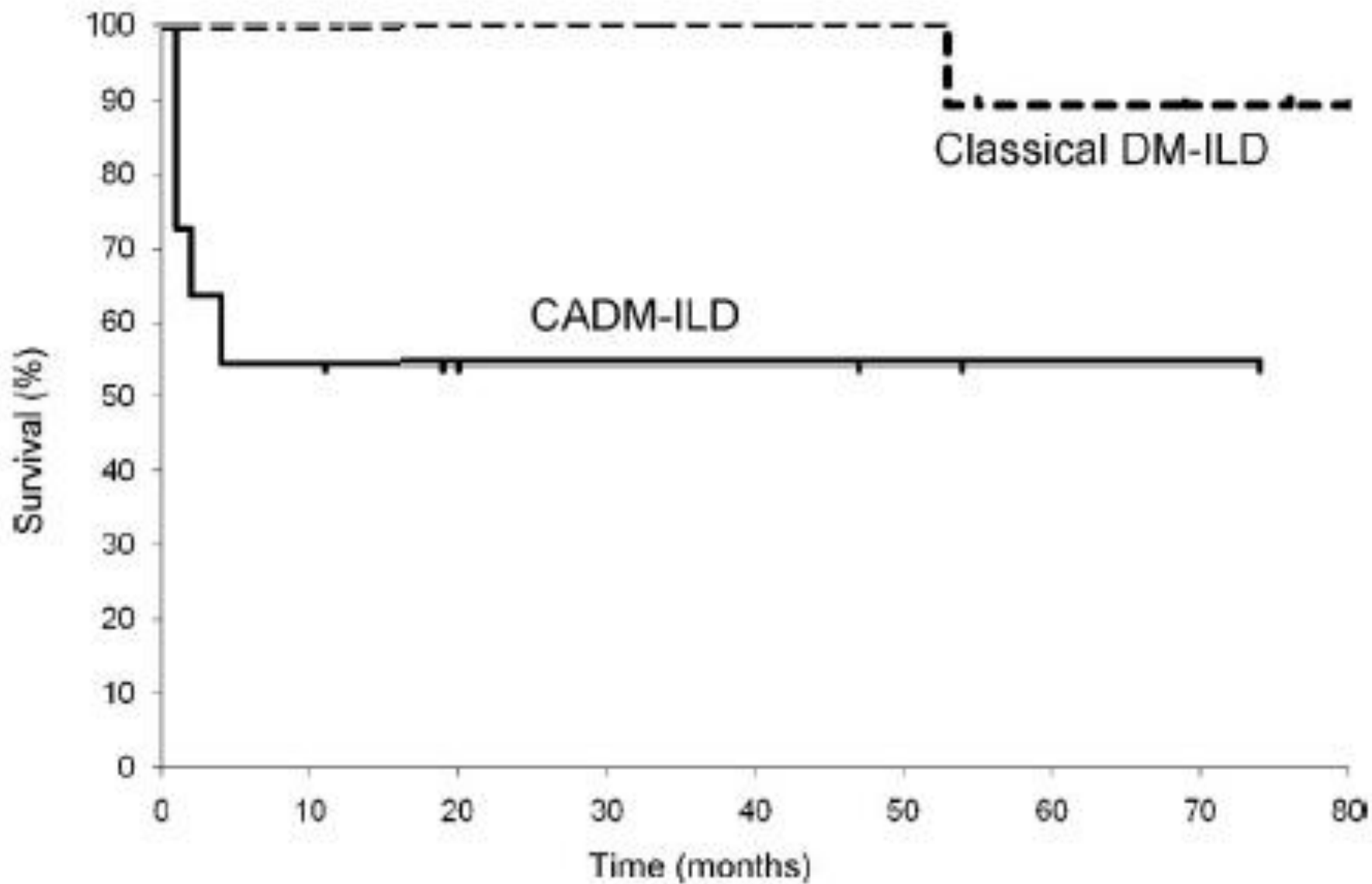
OP

LIP

Non-IIP  
confirmed

# Prognosis of UIP/NSIP Associated with CTD





# ? VATS Lung Biopsy in CTD-ILD

- No prognostic difference between UIP and NSIP (except RA)
- Unclassifiable pattern on lung biopsy
- Anti-inflammatory therapy is due for CTD
- ILD associated with dermatomyositis
  - Prognosis is dependent on clinical pattern
- Indication for VATS lung biopsy
  - DDX from infection
  - Lung-dominant CTD or undifferentiated CTD

# Undifferentiated CTD

## Lung-dominant CTD

### Autoimmune-featured ILD

#### UCTD diagnostic criteria<sup>#</sup>

At least one of: 1) Raynaud's phenomenon; 2) arthralgias/multiple joint swelling; 3) morning stiffness; 4) dry mouth or dry eyes (Sicca features); 5) proximal muscle weakness

Positive finding of at least one of: 1) ANA (high titre); 2) RF (high titre); 3) positive ENA; 4) anti-Scl70 antibody; 5) anti-RNP antibody; 6) anticentromere antibody; 7) SS-A or SS-B; 8) Jo-1 antibody

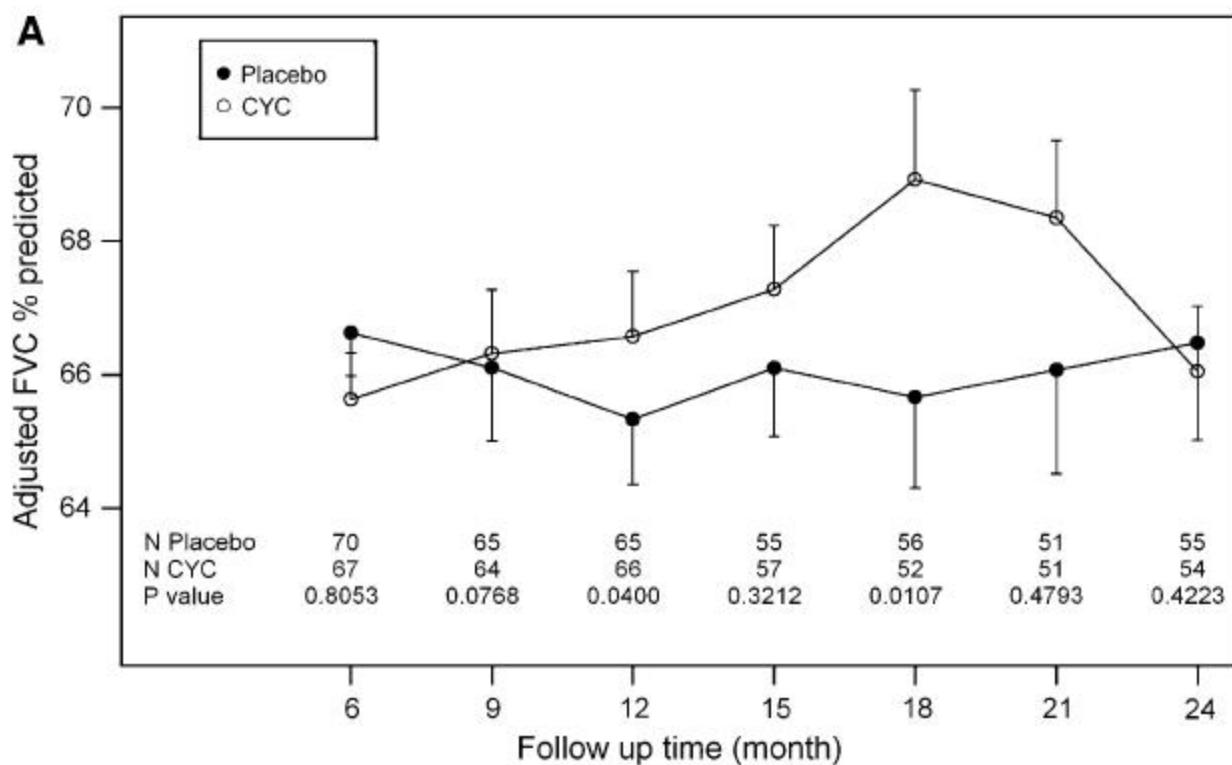
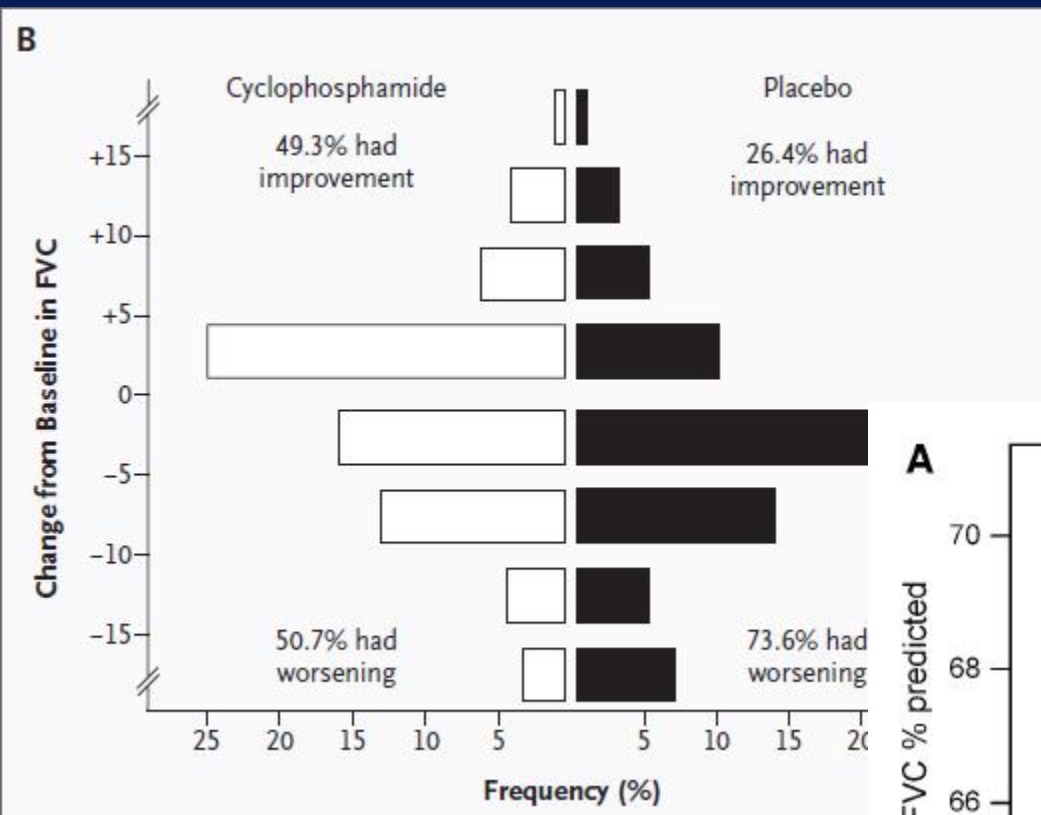
# Treatment of CTD-ILD

- Disease-modifying pharmacologic therapy
  - Corticosteroids
  - Cyclophosphamide, azathioprine
  - Mycophenolate mofetil, tacrolimus
  - Biological drugs; rituximab, infliximab, tocilizumab
- Stem cell transplantation
- No controlled clinical trial data (except PSS-ILD)

# Treatment Decision in CTD-ILD

- Likelihood of response based on chest HRCT and/or histopathologic findings
- Severity of lung disease
- Rate of disease progression
- Status of underlying CTD
- Age
- Ability to comply with toxic drugs

# Cyclophosphamide Therapy in PSS-ILD

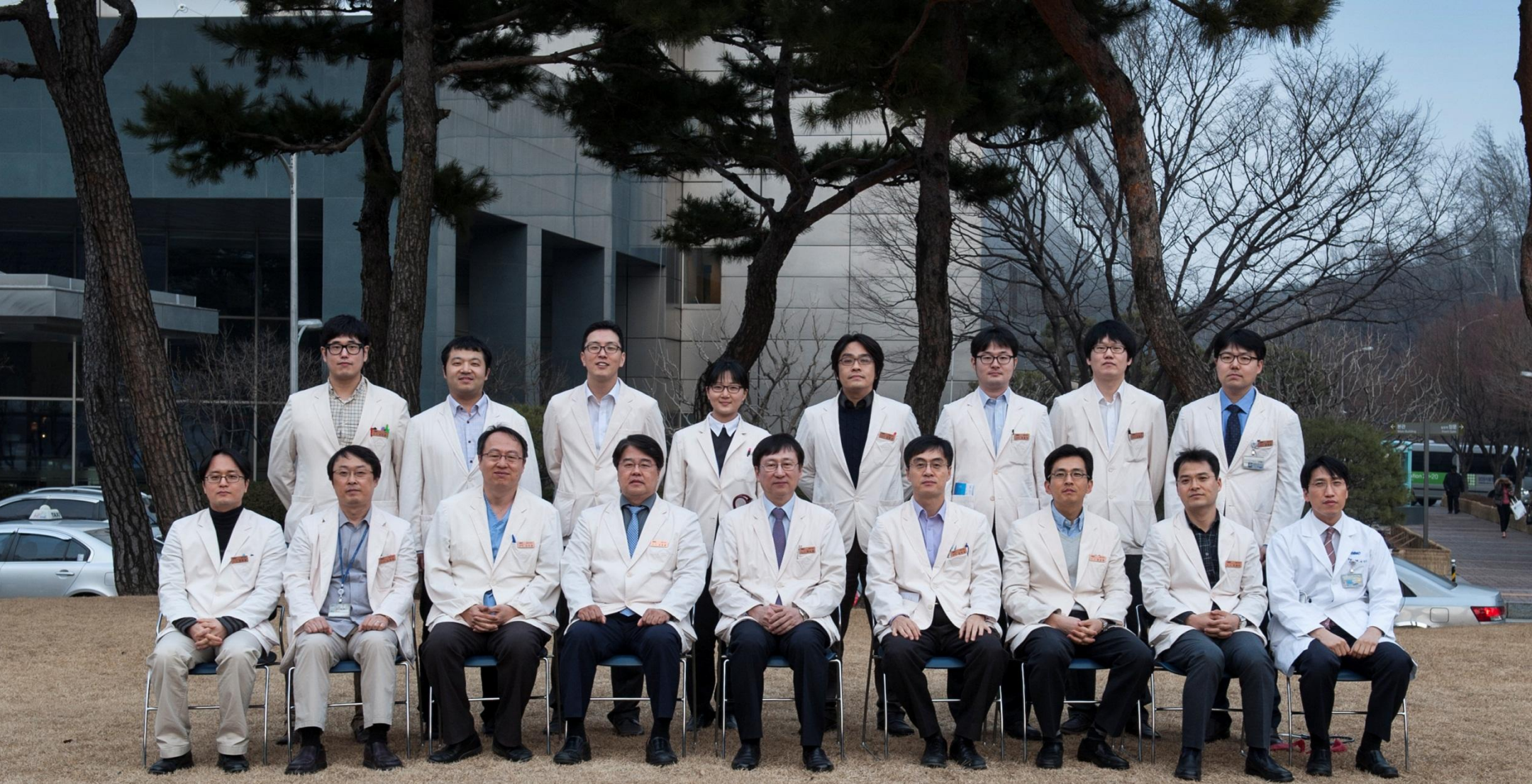


# Prognosis of CTD-ILD

- Good response in cellular NSIP and BOOP
- Prognostic factors
  - Severity of lung disease at Dx (extent of lung fibrosis on chest HRCT, FVC, DLco)
  - UIP pathology in RA
  - Rapidity of functional deterioration

# Unanswered Questions for CTD-ILD

- ? Adequate classification: ILD type? CTD type?
- ? Need of surgical lung Bx
- ? Management decision without taking into account the specific patterns of ILD
- What specific drugs for each CTD-ILD ?
- ? Cyclophosphamide for non-PSS CTD-ILD
- ? Definition and management of ILD with UCTD



감사합니다