Nonspecific Interstitial Pneumonia and Connective Tissue Disease

American College of Radiology™

We Have No Relevant Disclosures

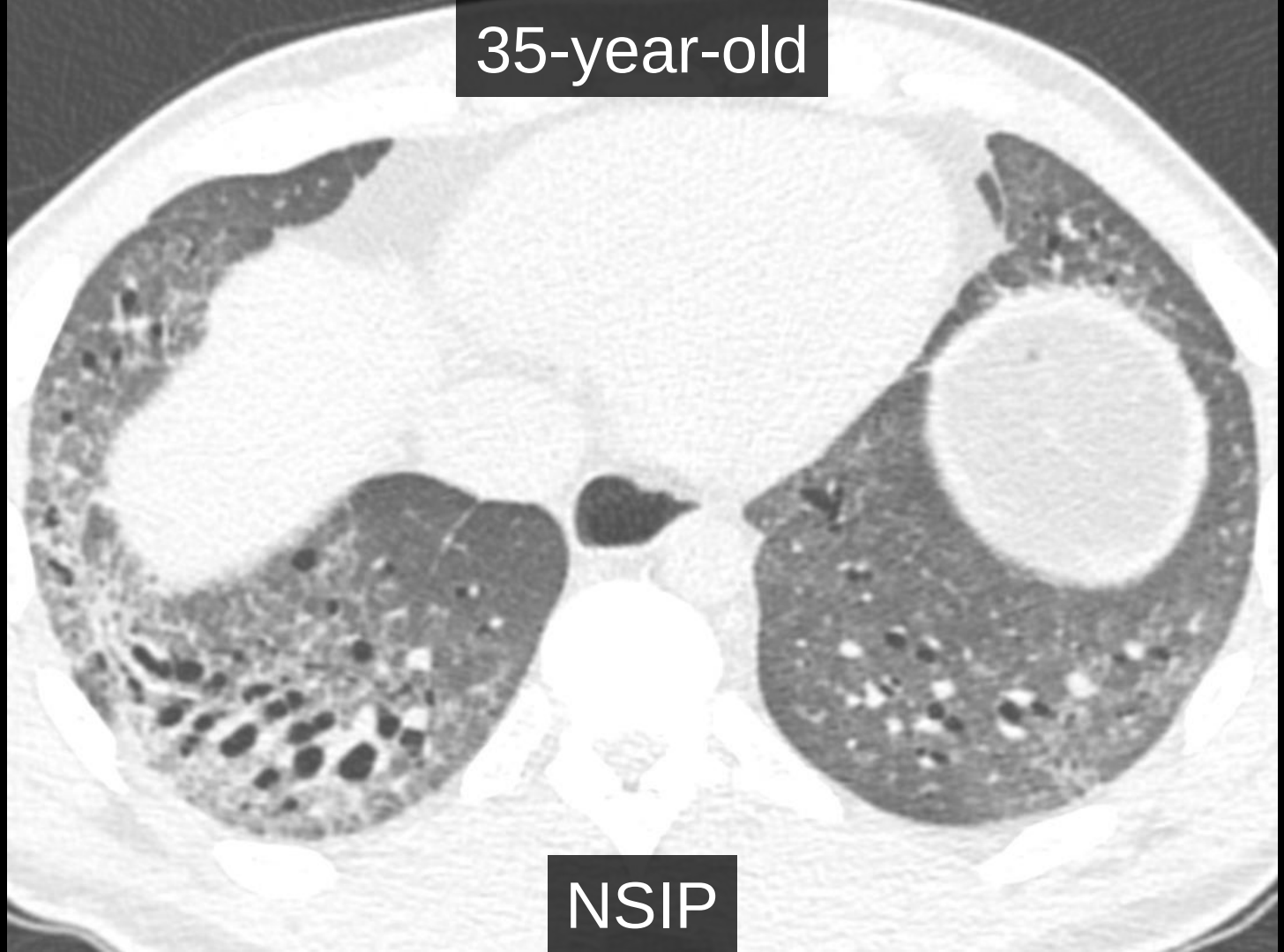
Table 3. High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis

	HRCT Pattern			
	UIP Pattern	**Probable UIP Pattern**	**Indeterminate for UIP**	**CT Findings Suggestive of an Alternative Diagnosis**
Level of confidence for UIP histology	Confident (>90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (≤50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • Occasionally diffuse • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribronchovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking-related IP)

CT features	• Honeycombing with or without traction bronchiectasis/ bronchiolectasis
	• Presence of irregular thickening of interlobular septa
	• Usually superimposed with a reticular pattern, mild GGO
	• May have pulmonary ossification
		• Reticular pattern with traction bronchiectasis/ bronchiolectasis
		• May have mild GGO
		• Absence of subpleural sparing
			• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings
				  ○ Cysts (consider LAM, PLCH, LIP, and DIP)
				  ○ Mosaic attenuation or three-density sign (consider HP)
				  ○ Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis)
				  ○ Profuse centrilobular micronodules (consider HP or smoking-related disease)
				  ○ Nodules (consider sarcoidosis)
				  ○ Consolidation (consider organizing pneumonia, etc.)
				• Mediastinal findings
				  ○ Pleural plaques (consider asbestosis)
				  ○ Dilated esophagus (consider CTD)

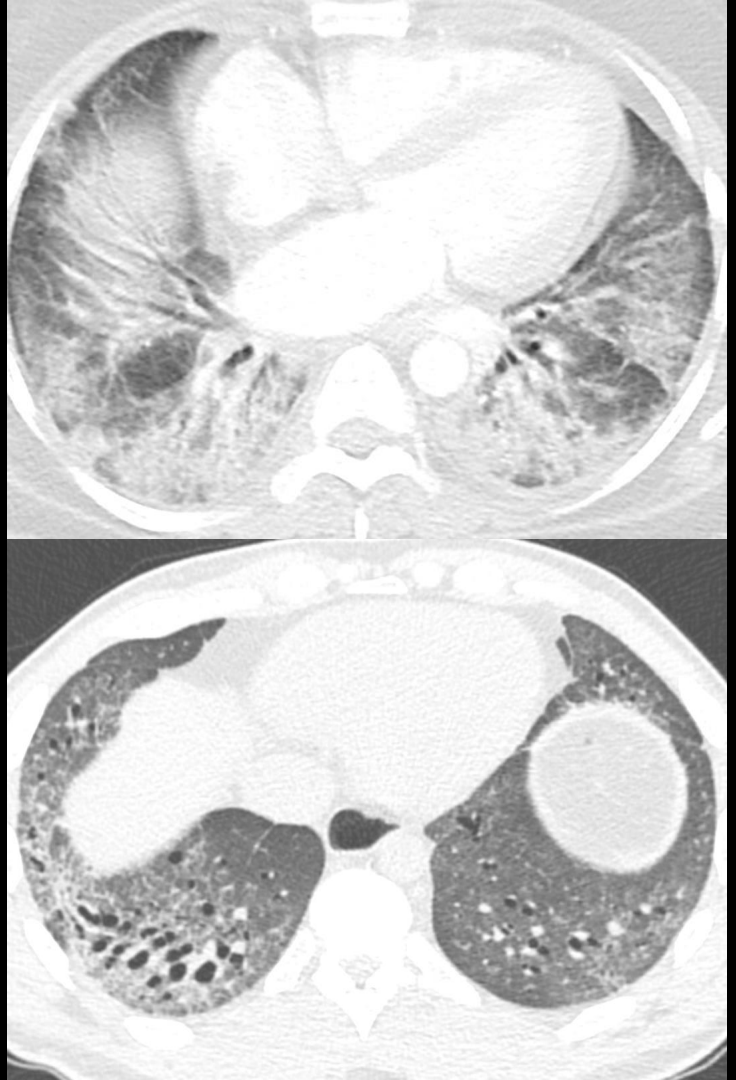
Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IP = interstitial pneumonia; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; UIP = usual interstitial pneumonia.
The previous term, "early UIP pattern," has been eliminated to avoid confusion with "interstitial lung abnormalities" described in the text. The term "indeterminate for UIP" has been retained for situations in which the HRCT features do not meet UIP or probable UIP criteria and do not explicitly suggest an alternative diagnosis. Adapted from Reference 3.

ATS/ERS/JRS/ALAT Clinical Practice Guideline


35-year-old
NSIP

Nonspecific Interstitial Pneumonia (NSIP)

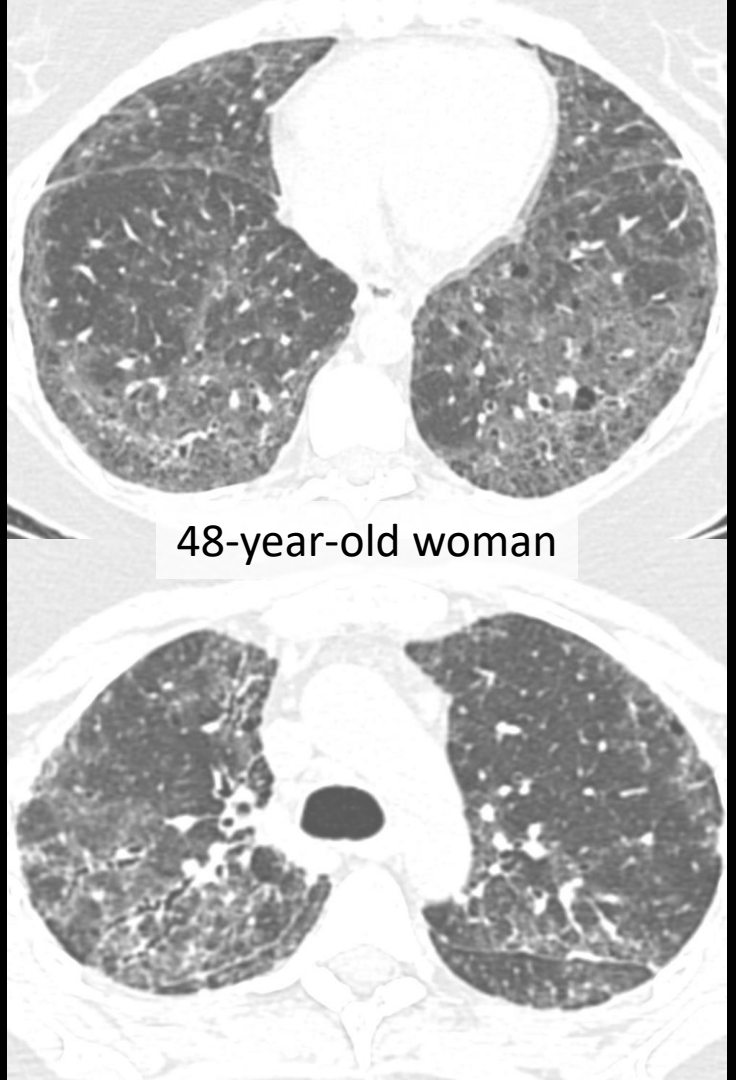
- Variable imaging appearance
  - Inflammation → fibrosis
- Association:
  - Connective tissue disease >>> medications, HP, others

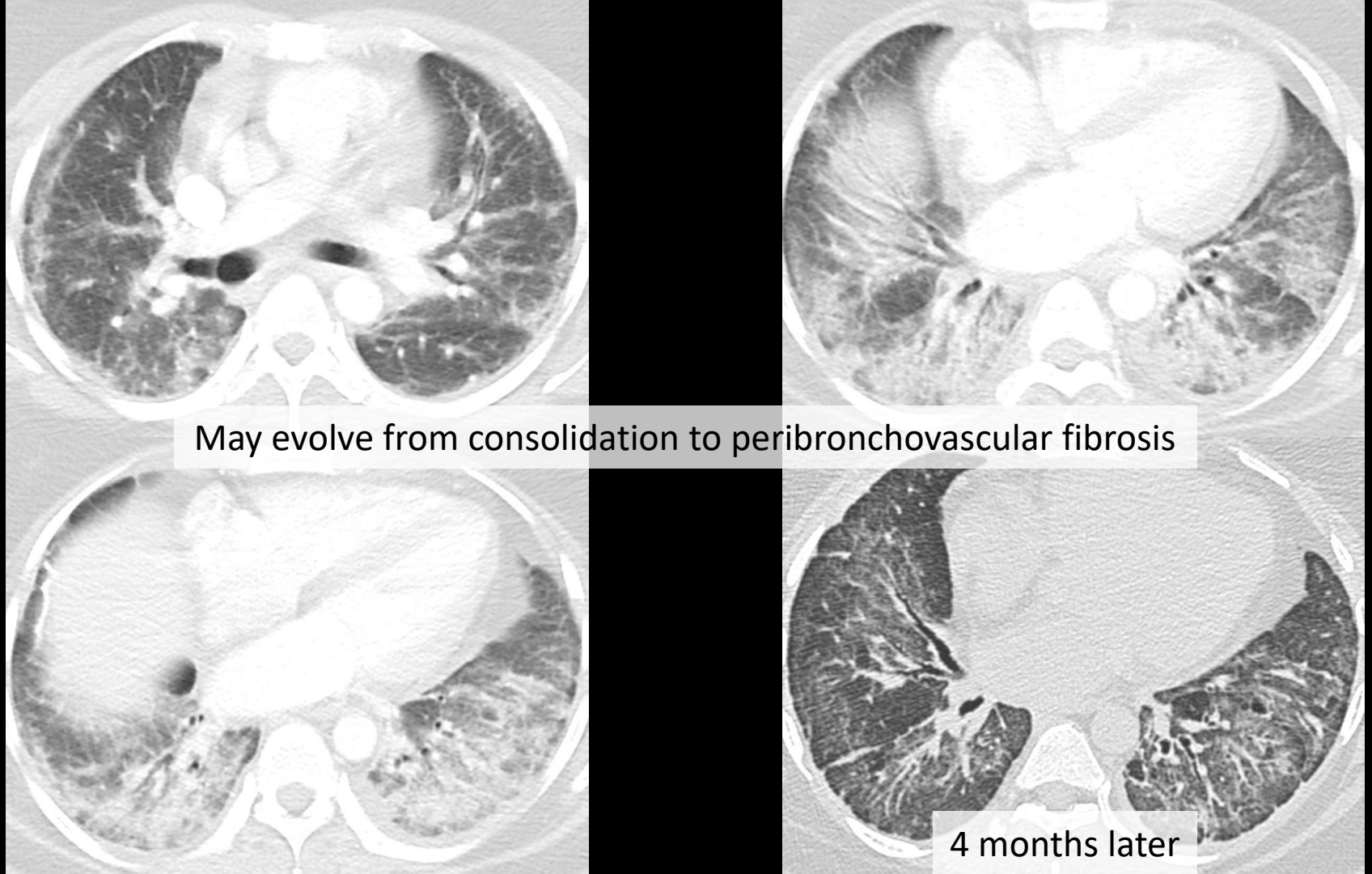


Imaging of NSIP:

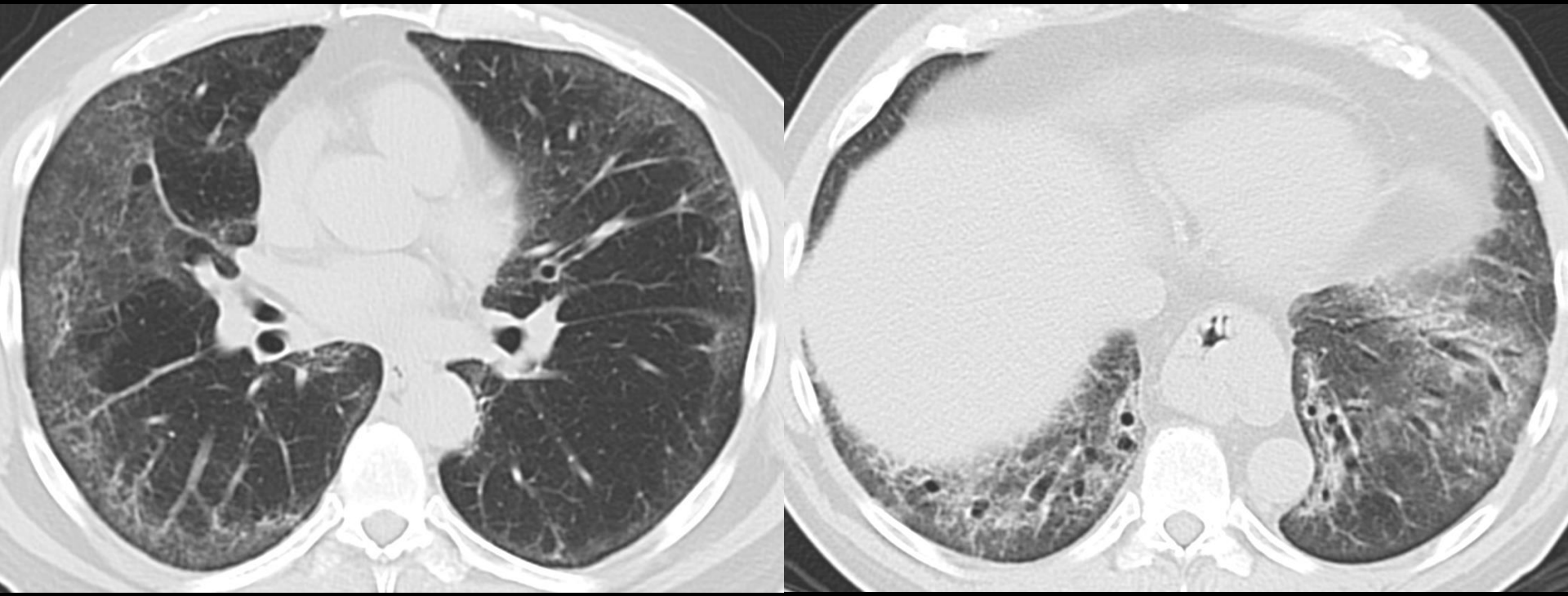
- More uniform than UIP

- Spectrum:
  - Infiltration (GGO/consolidation)
  - Fibrosis (reticulation/traction)

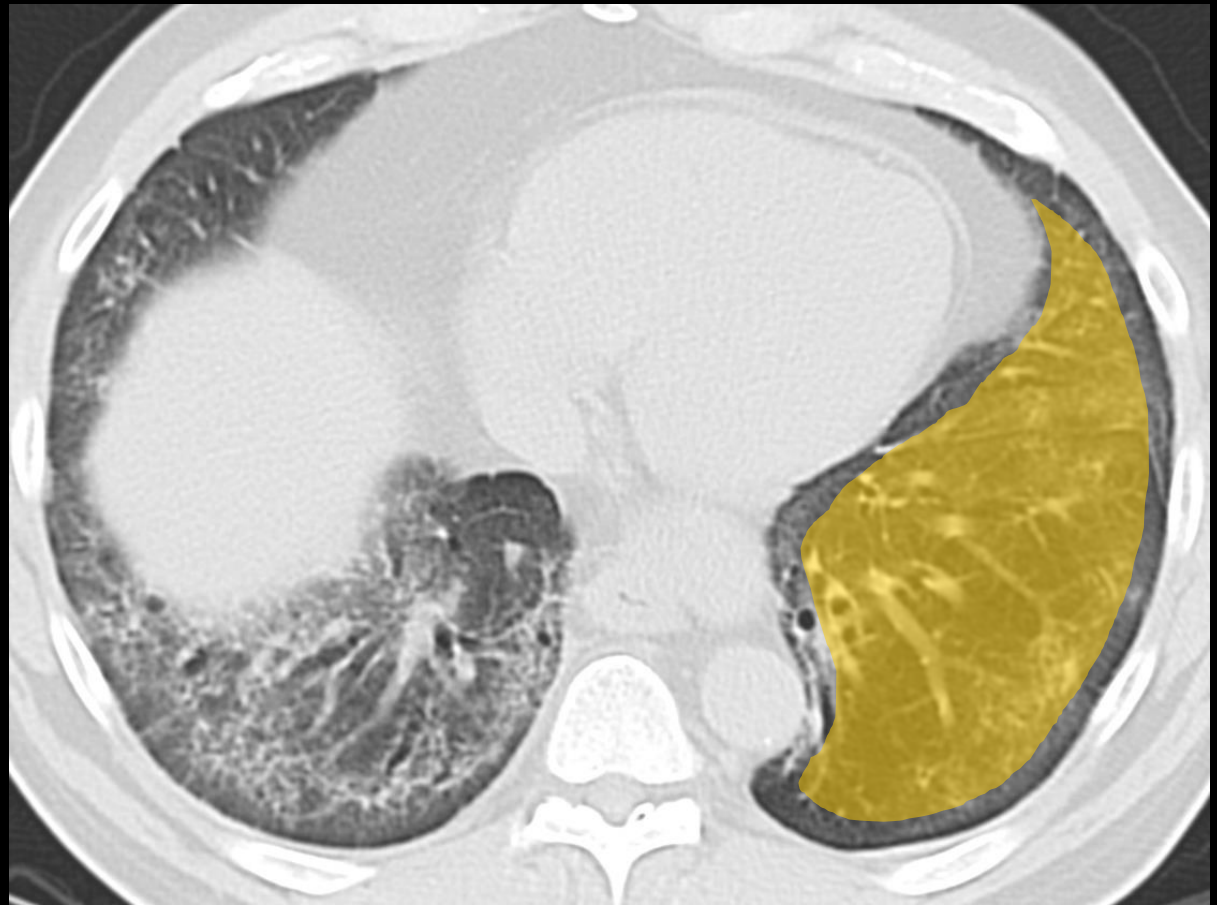



May evolve from consolidation to peribronchovascular fibrosis
4 months later

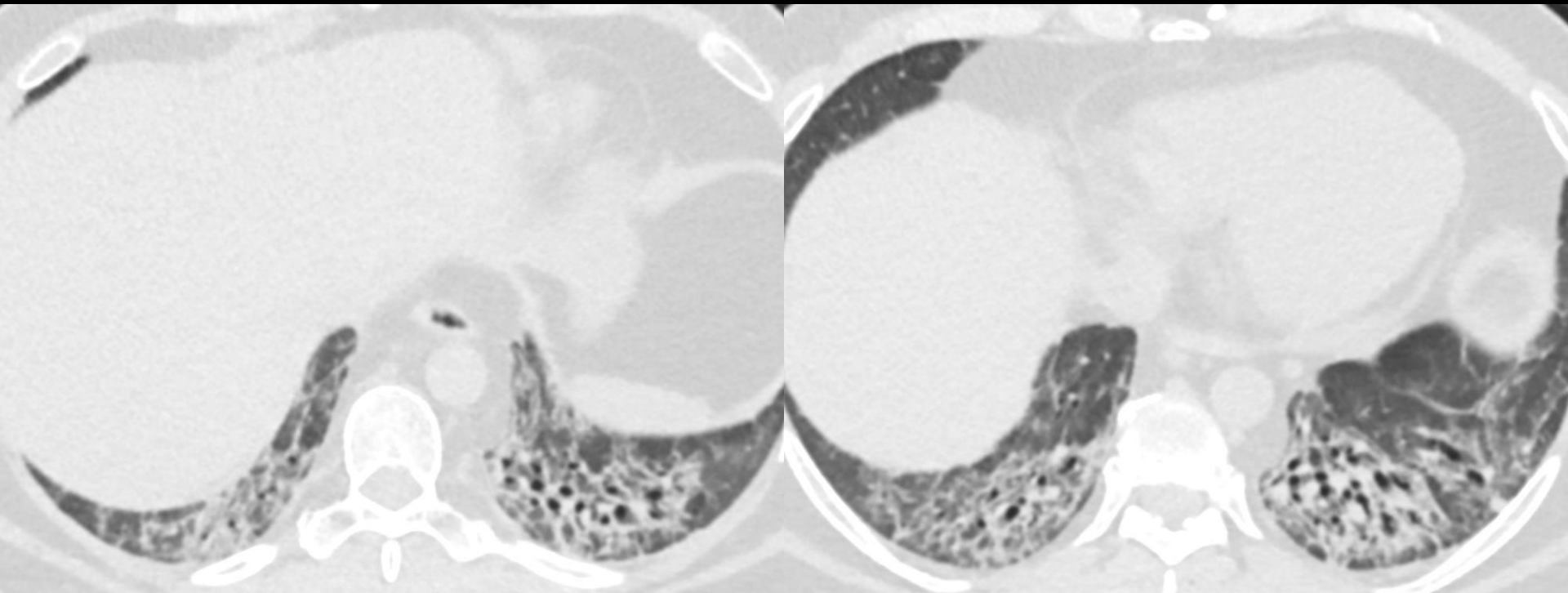
55-year-old male with NSIP (RA)



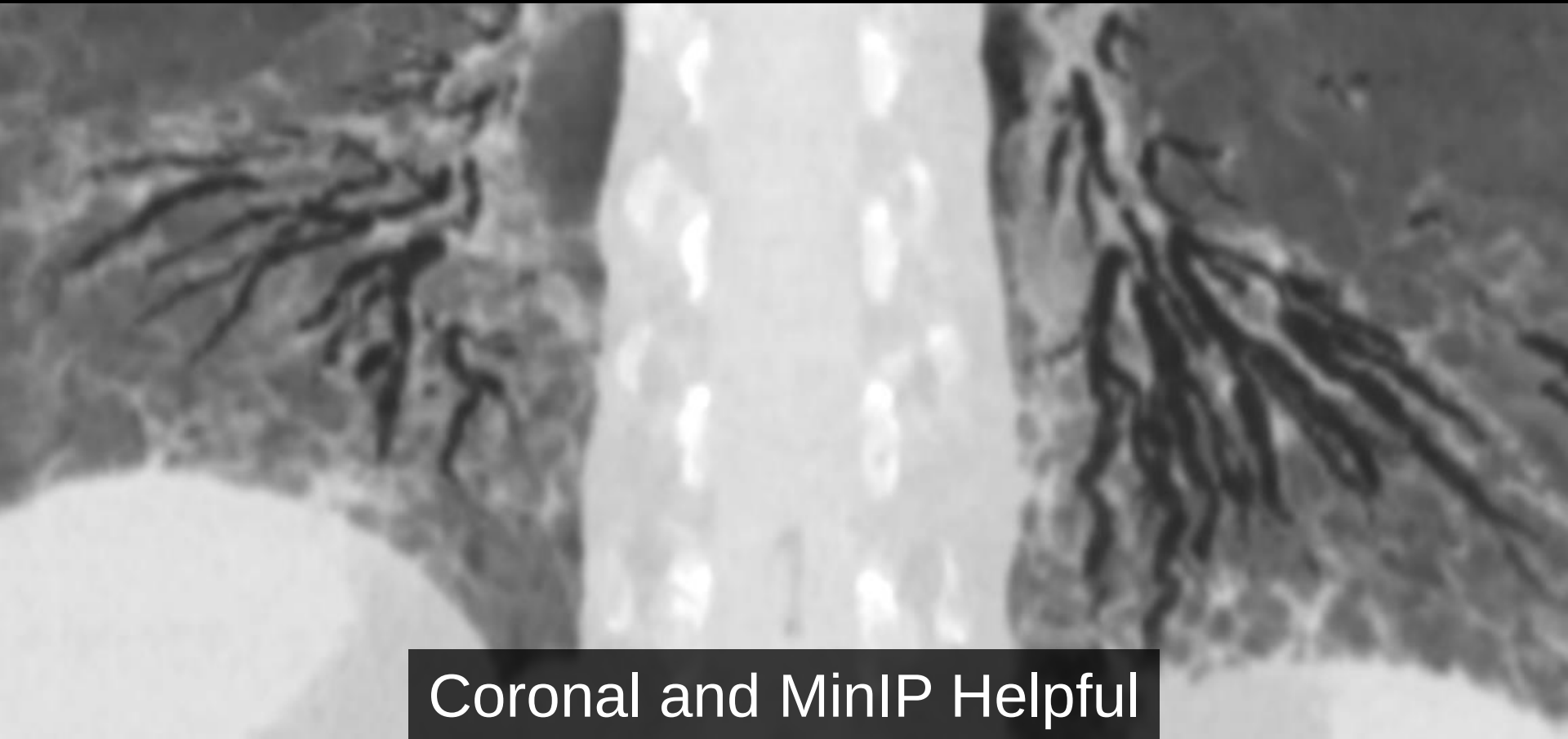
Subpleural Sparing



Traction Bronchiectasis

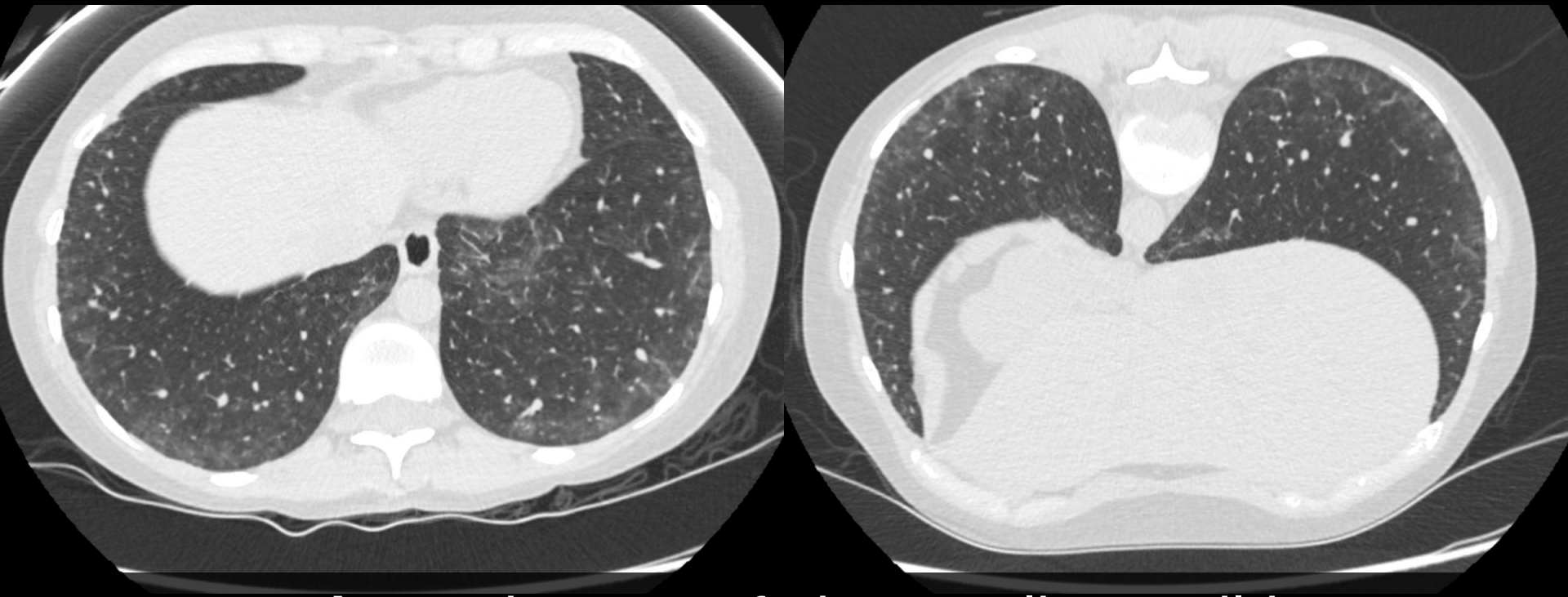


Traction Bronchiectasis



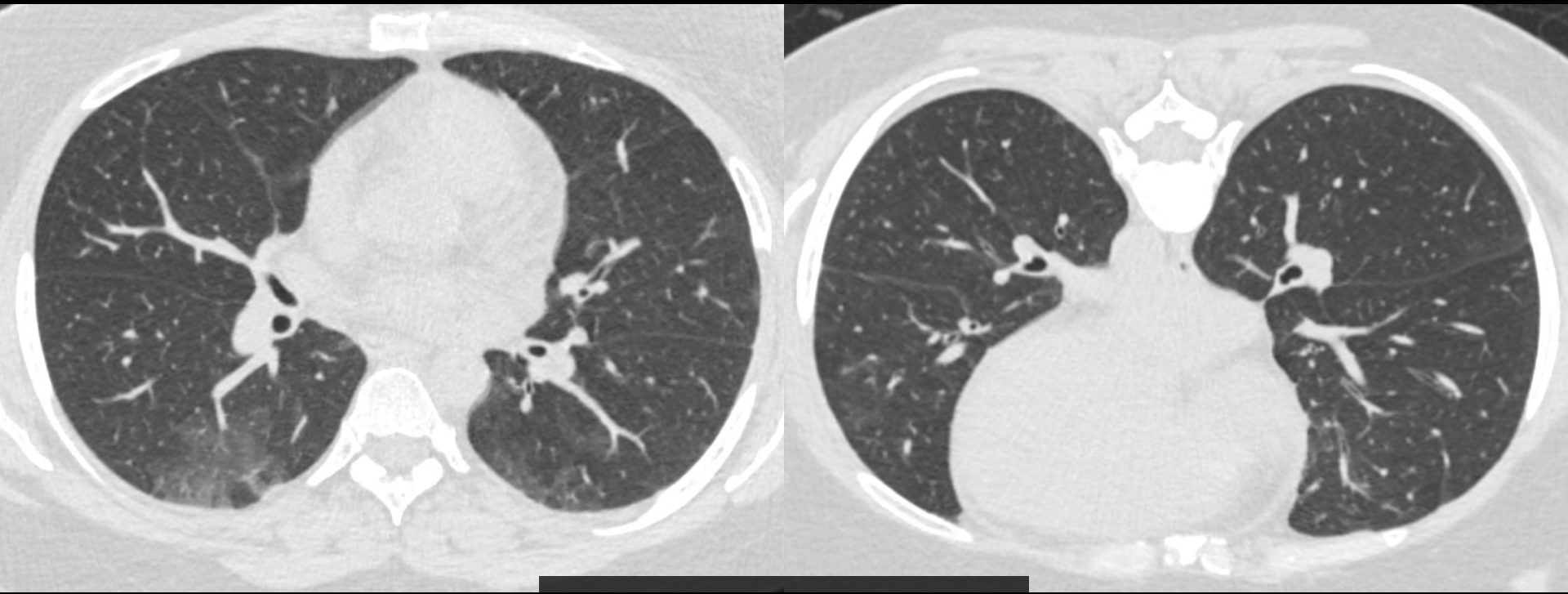
Coronal and MinIP Helpful

35-year-old with CTD, evaluate for ILD



Prone → persistence of abnormality = mild NSIP

35-year-old with dyspnea



Prone → Normal

Connective Tissue Disease

- Rheumatoid arthritis
- Systemic sclerosis
- Mixed connective tissue disease (MCTD)
- Myositis and antisynthetase syndrome
- Systemic lupus erythematosus
- Sjögren disease
- Interstitial pneumonia with autoimmune features (IPAF)

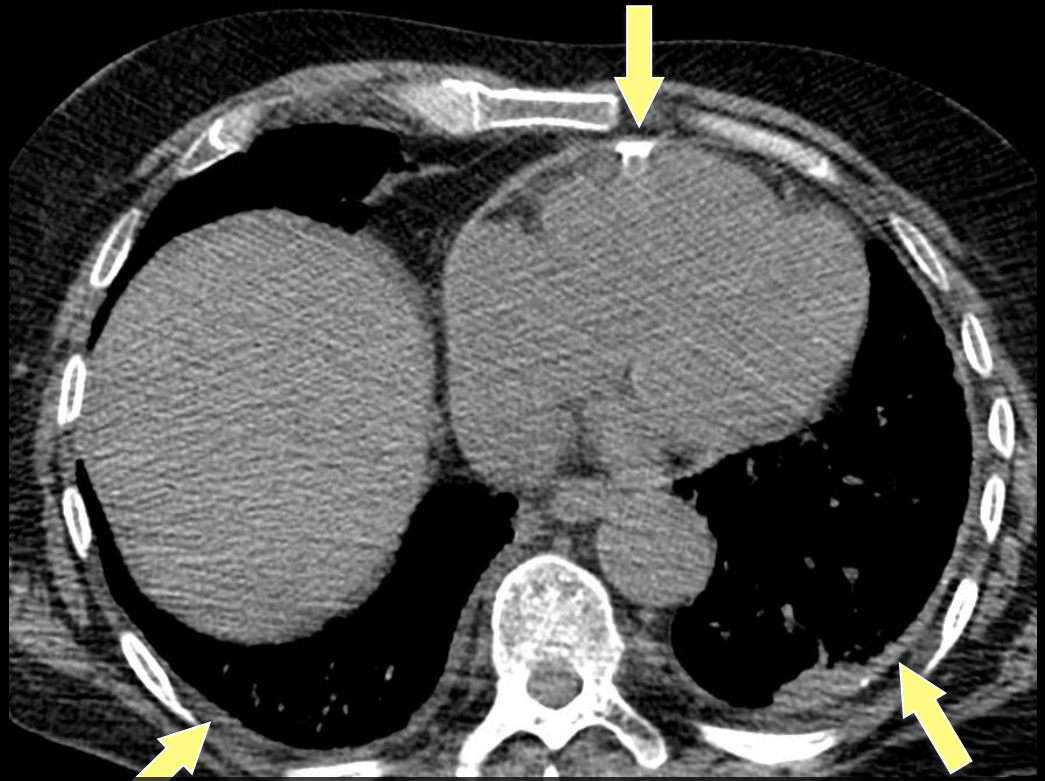
Rheumatoid Arthritis

- Most patients have abnormalities on CT
  - Often asymptomatic
- Airways may be the earliest affected structure
  - Air trapping
  - Bronchiectasis (mild)

Rheumatoid Arthritis

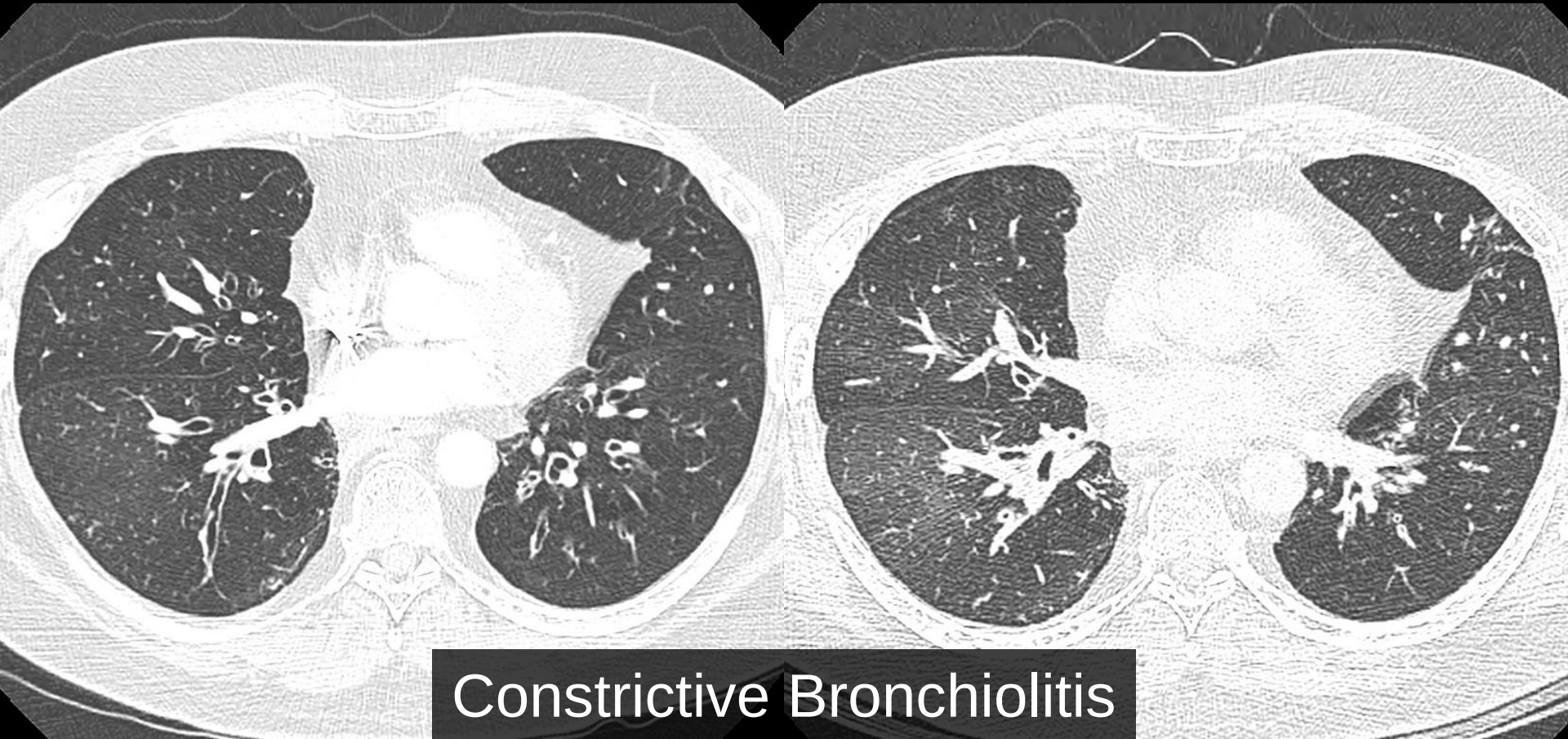
Compartment	Pattern of Injury
Parenchyma	Usual interstitial pneumonia
	Nonspecific interstitial pneumonia
	Organizing pneumonia
	Necrobiotic nodules
Vascular	Pulmonary hypertension
Airways	Follicular bronchiolitis
	Constrictive bronchiolitis
	Bronchiectasis
Pleura	Effusion
	Thickening

Rheumatoid Arthritis



Pleural and Pericardial Thickening

Rheumatoid Arthritis

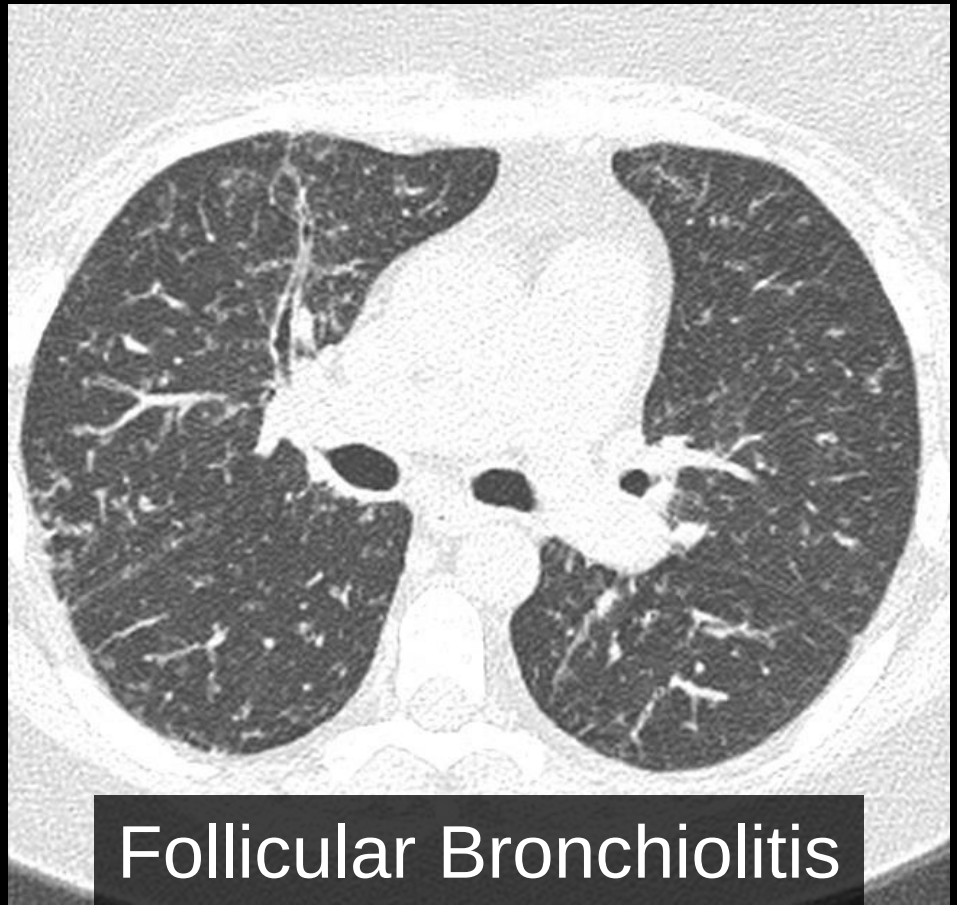


Constrictive Bronchiolitis

Rheumatoid Arthritis

- Follicular bronchiolitis
  - Lymphoid aggregates
  - +/- germinal centers
  - Walls of small airways
- CT
  - Centrilobular and peribronchial nodules
  - Ground-glass opacity

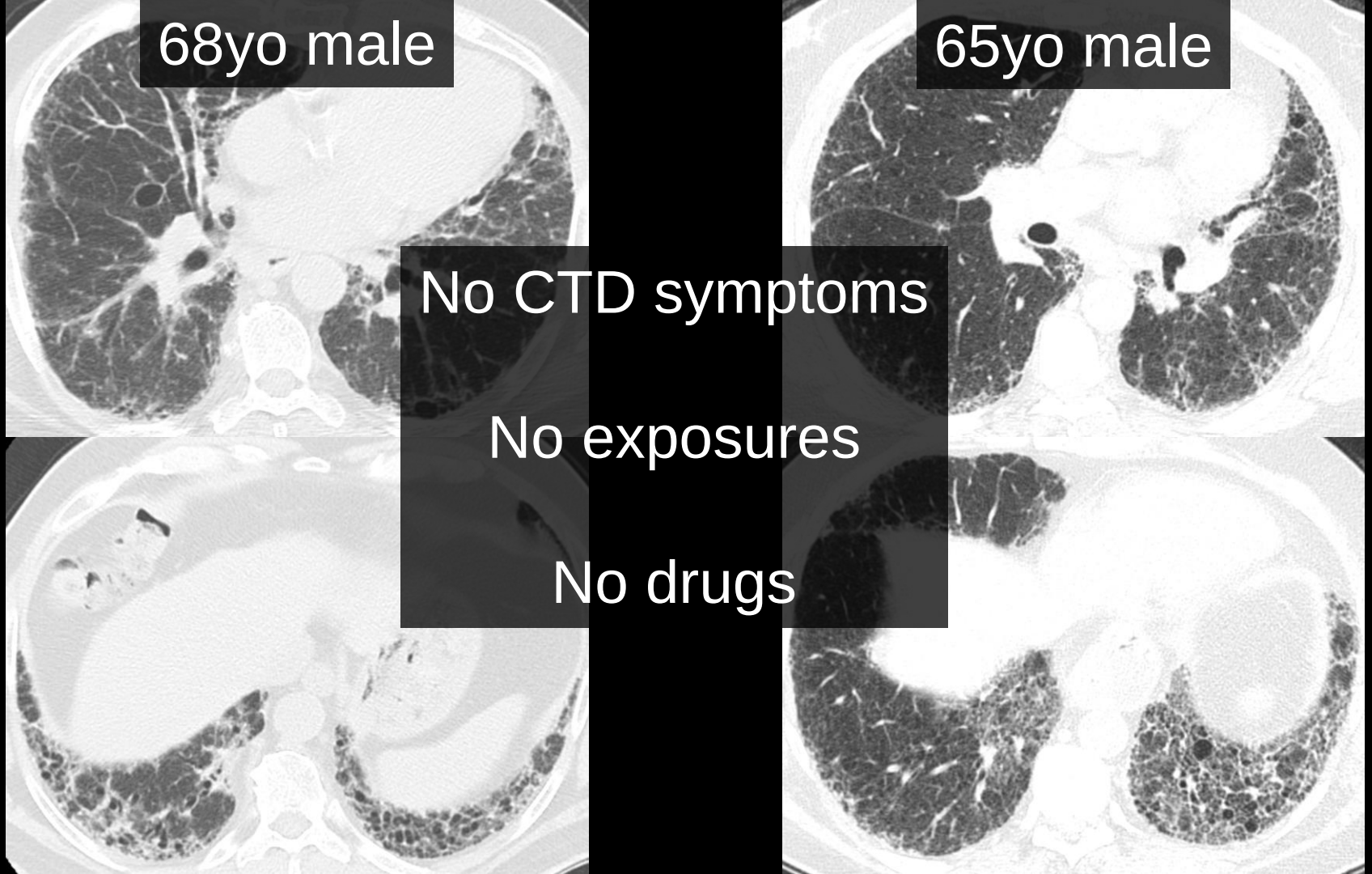
Rheumatoid Arthritis

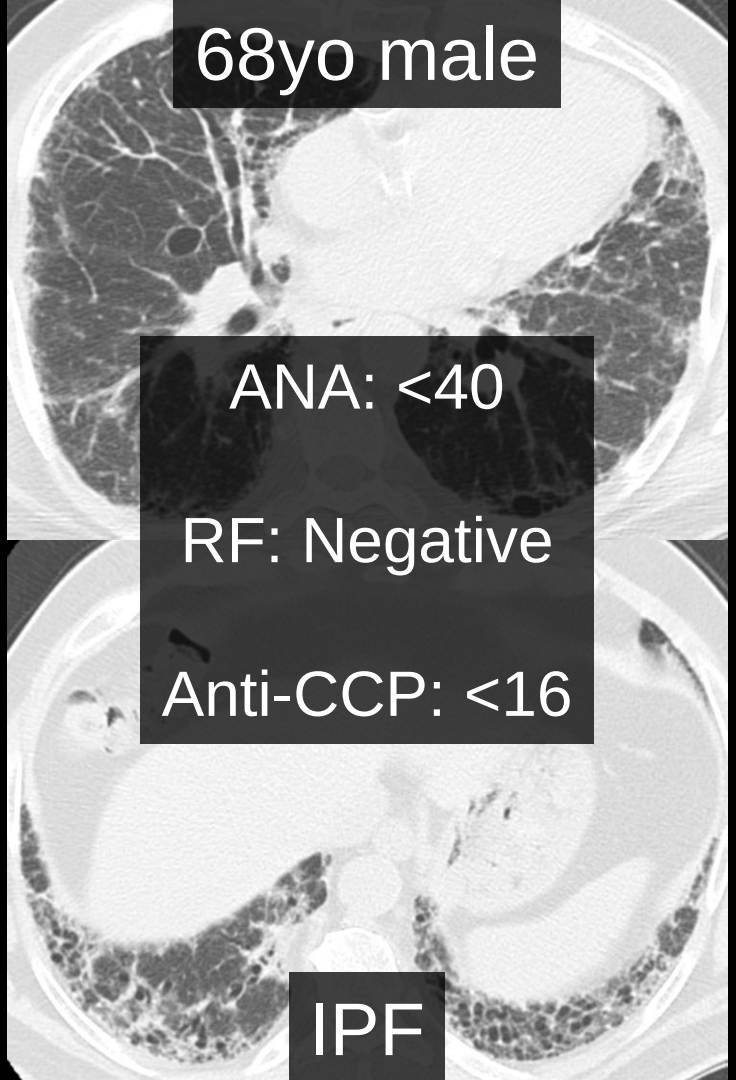


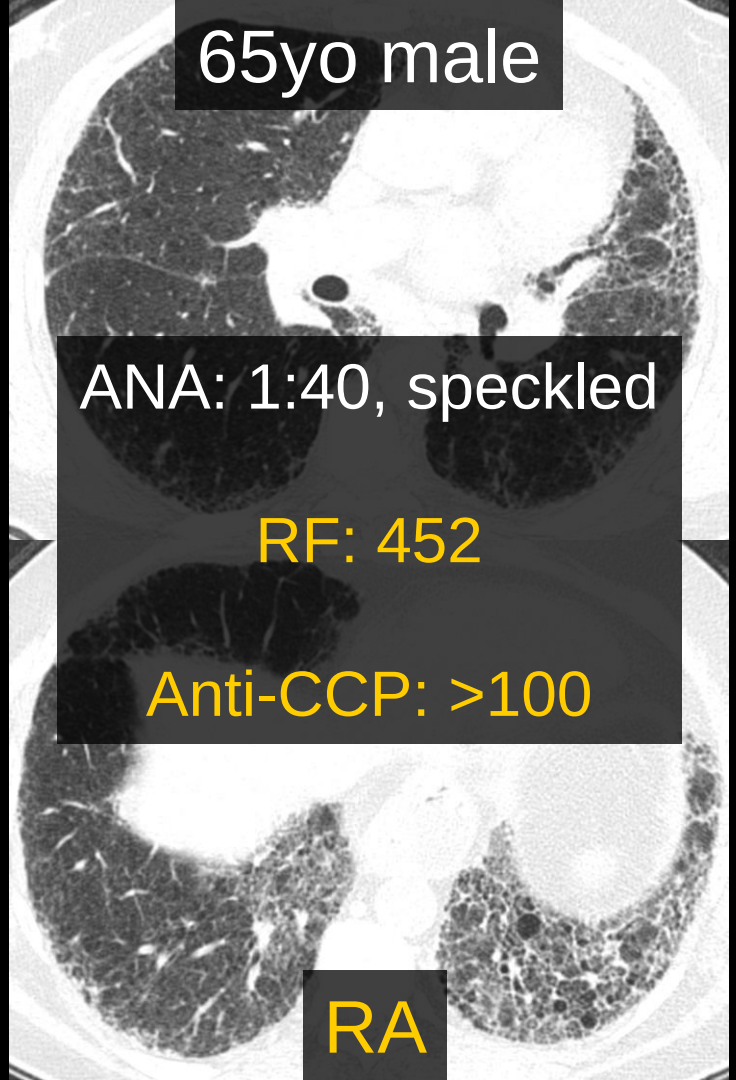
Follicular Bronchiolitis

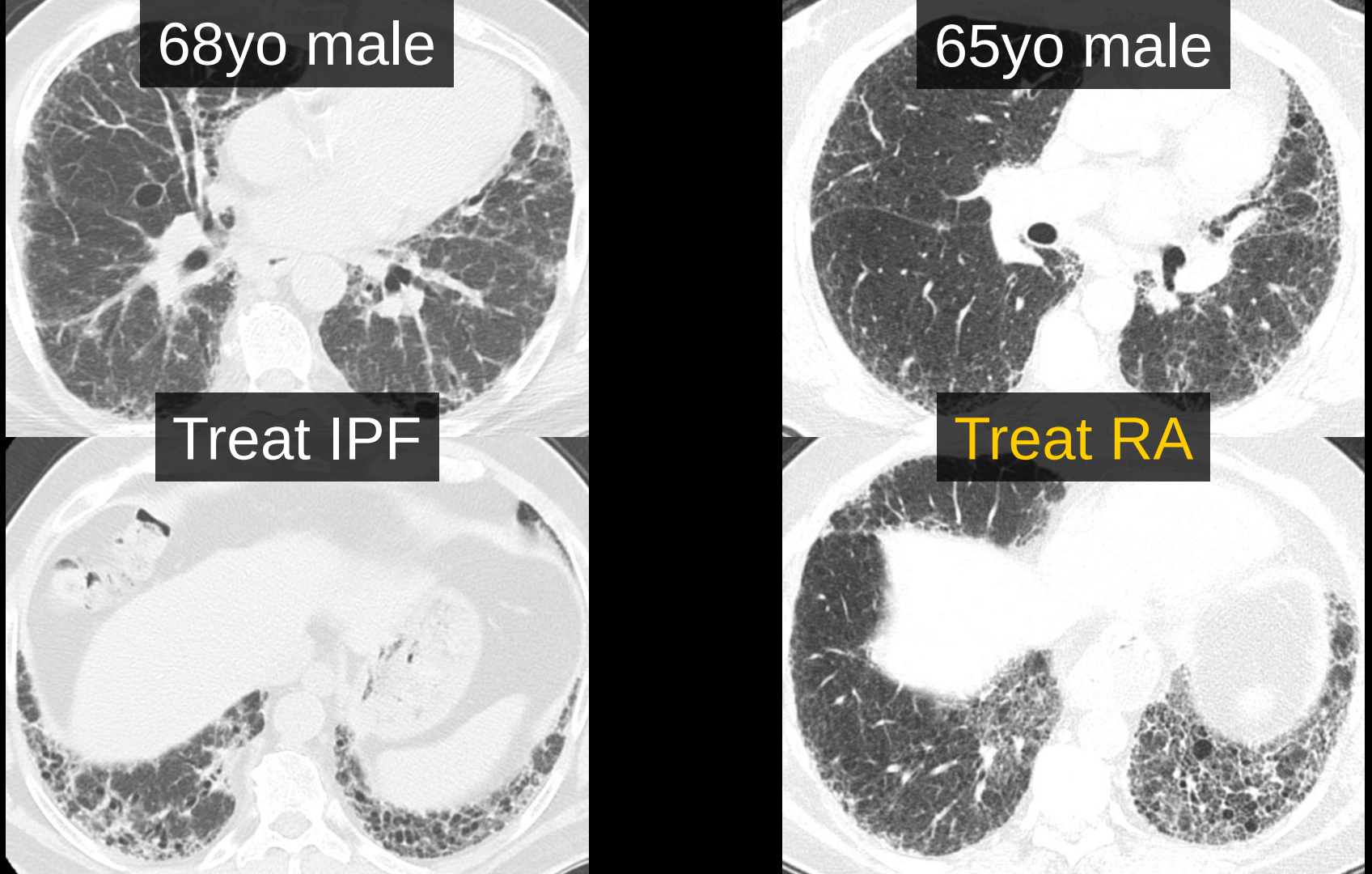
Rheumatoid Arthritis

- Fibrosis more common in men
- Strong association with cigarette smoking
- Usual interstitial pneumonia pattern most common


68yo male
65yo male
No CTD symptoms
No exposures
No drugs


68yo male
ANA: <40
RF: Negative
Anti-CCP: <16
IPF

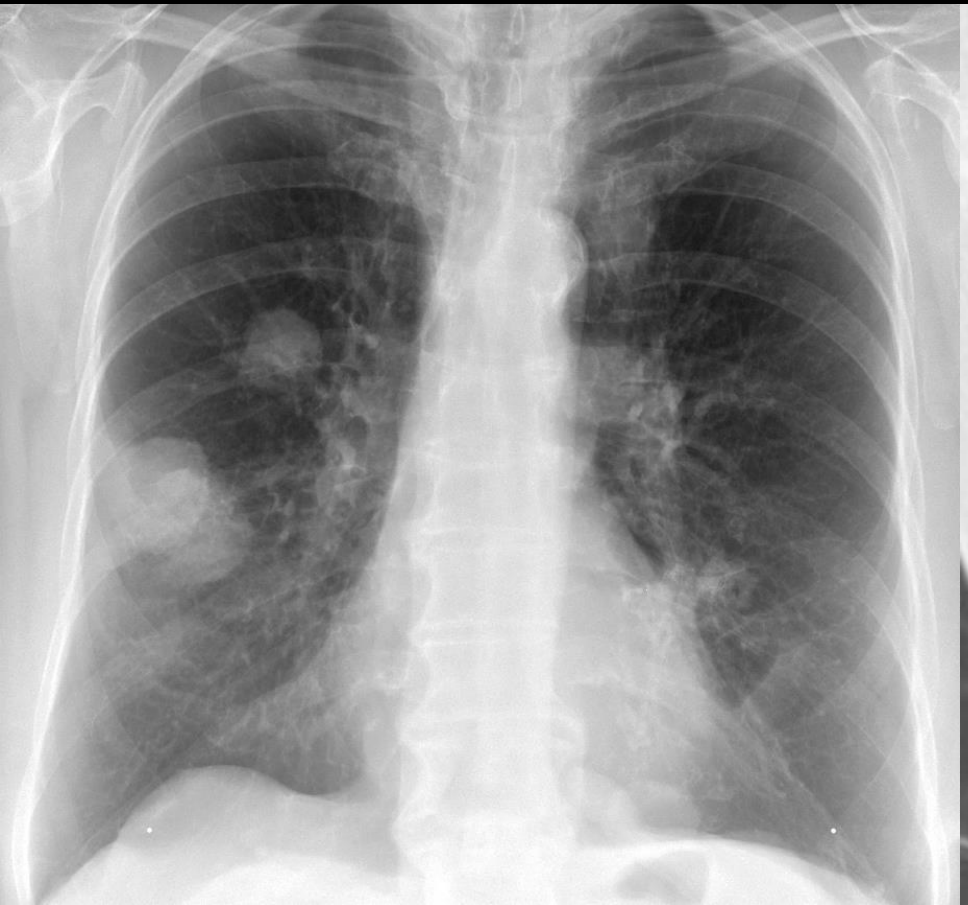

65yo male
ANA: 1:40, speckled
RF: 452
Anti-CCP: >100
RA

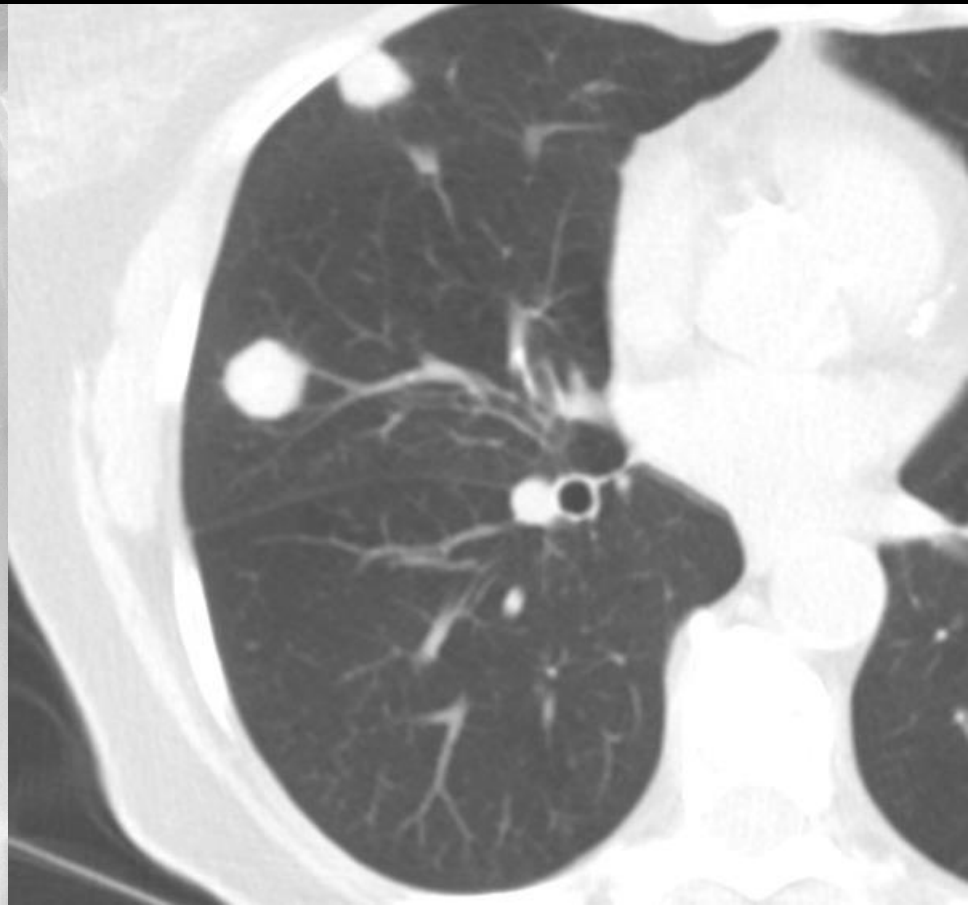

68yo male
65yo male
Treat IPF
Treat RA

Rheumatoid Arthritis

- Rheumatoid necrobiotic nodules
  - Similar to subcutaneous nodules
  - Well defined, round +/- cavitation
- Caplan syndrome
  - Coal miners with large nodules + RA
  - Extremely rare
  - Primarily Welsh miners (reported cases)

RA – Necrobiotic Nodules





Rheumatoid Arthritis

Pathology	**RA**
UIP	+++
NSIP	++
OP	+
Diffuse alveolar damage	
LIP	
Alveolar hemorrhage	
Constrictive bronchiolitis	++
Bronchiectasis	++
Follicular bronchiolitis	+++
Aspiration	
Pulmonary hypertension	+
Pleural effusion	++

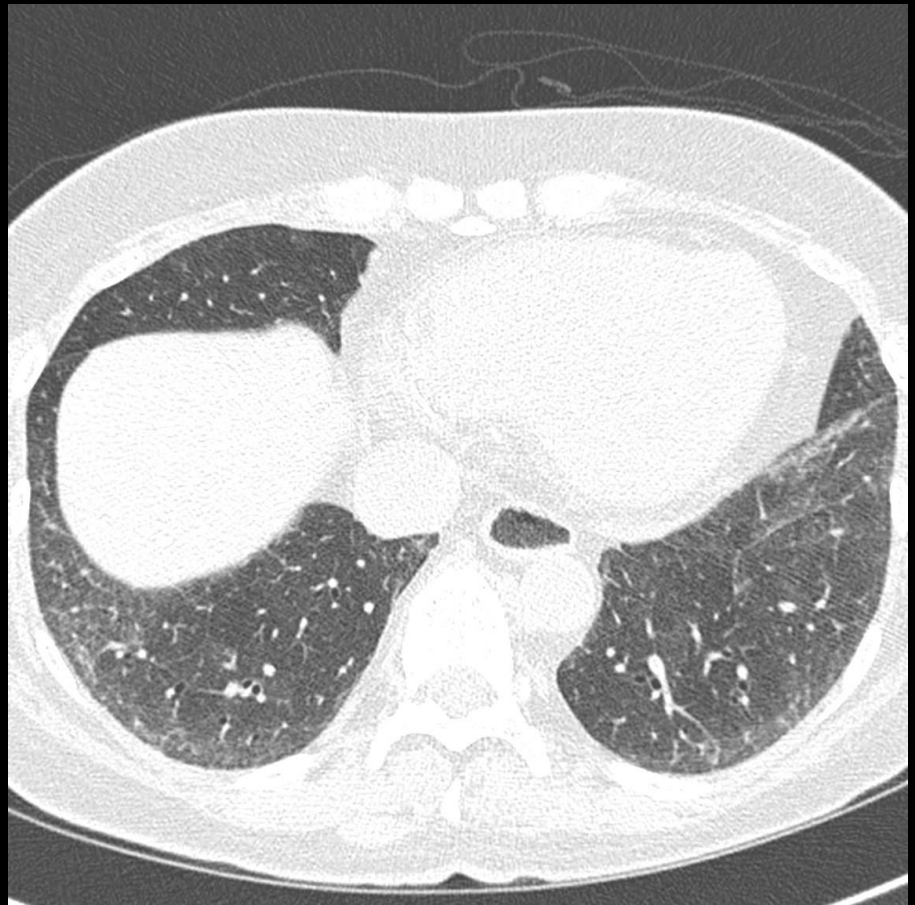
Systemic Sclerosis

Compartment	**Injury**
Parenchyma	Nonspecific interstitial pneumonia
	Usual interstitial pneumonia
	Organizing pneumonia
Vascular	Pulmonary hypertension
Airways	Aspiration

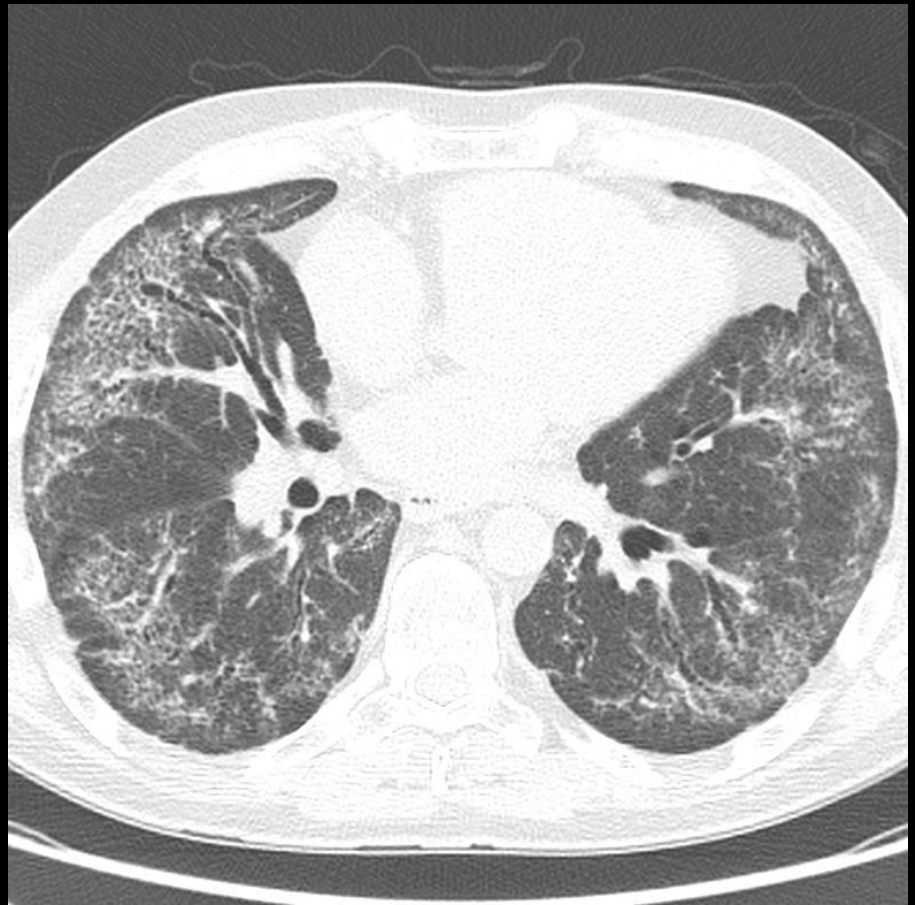
Systemic Sclerosis

- Lung involvement very common
  - At least 80% on autopsy series
- Fibrosis most common
  - NSIP >> UIP
- CT (reflects NSIP)
  - Ground-glass opacity
  - Reticulation
  - Peribronchial distribution
- Esophageal dilation (80%)

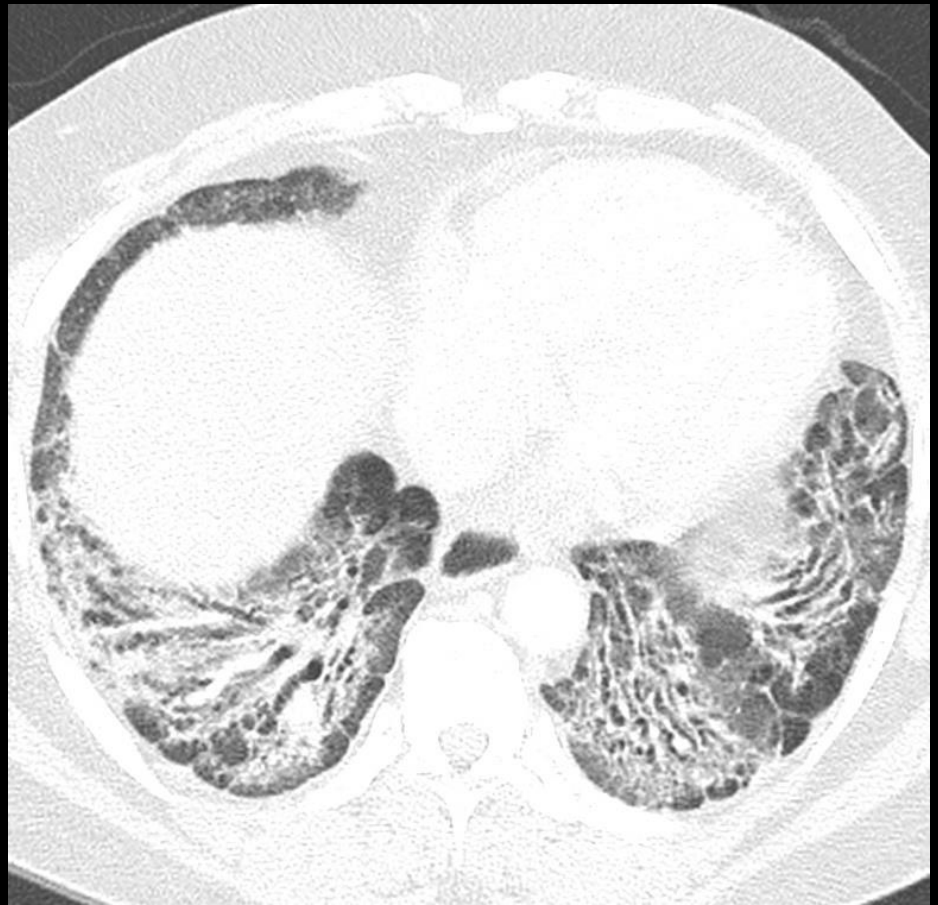
Systemic Sclerosis - NSIP



Systemic Sclerosis - NSIP



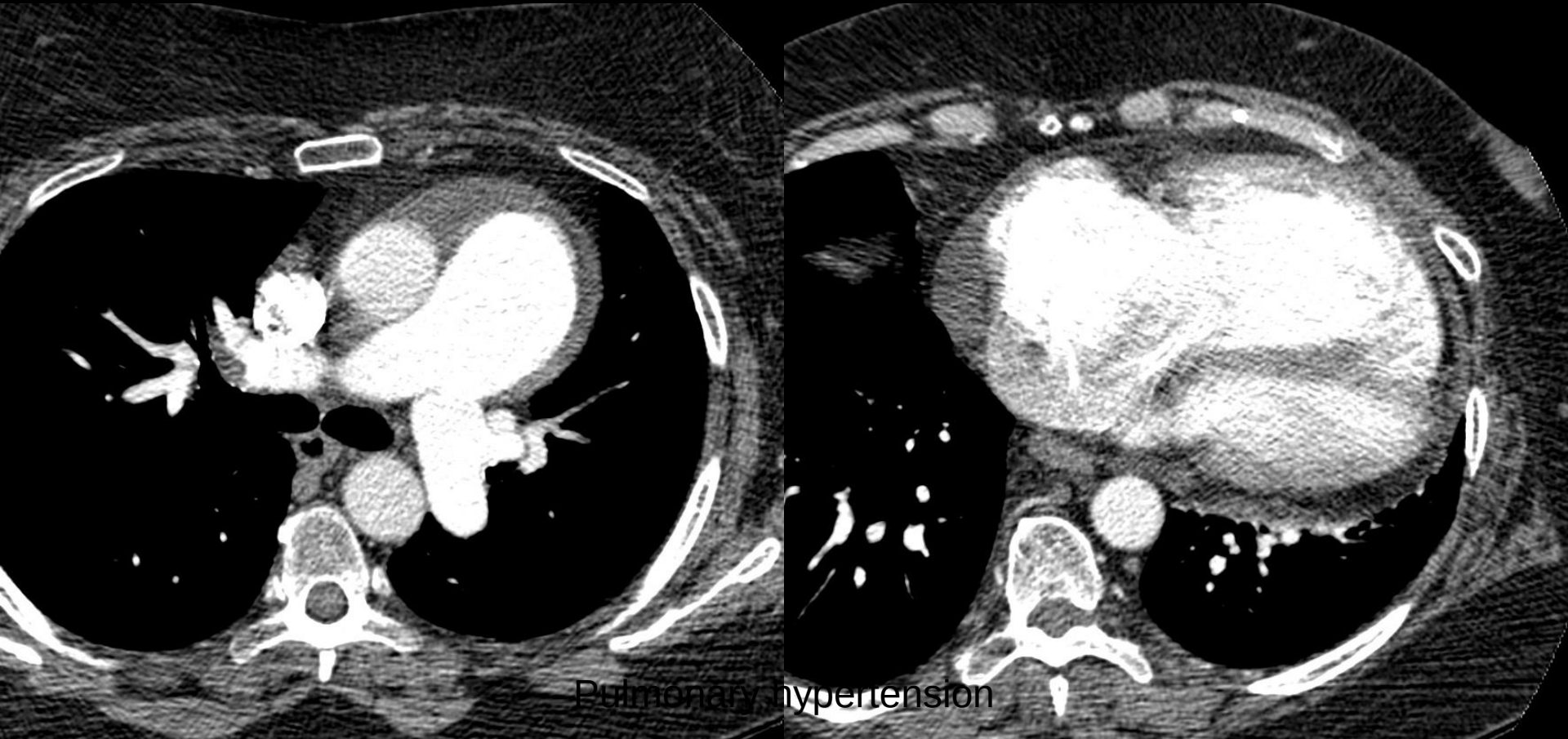
Systemic Sclerosis - NSIP



Systemic Sclerosis

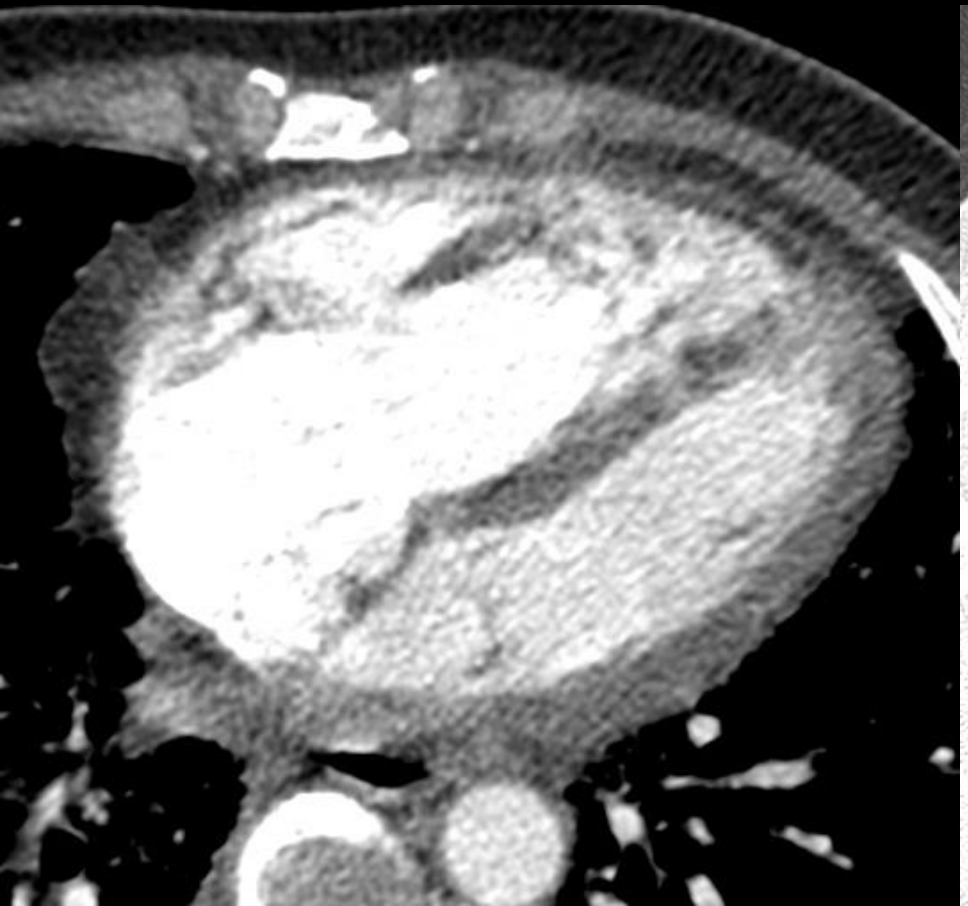
- Pulmonary hypertension
  - Isolated (arteriopathy)
  - In conjunction with fibrosis
- Central pulmonary arteries may or may not be enlarged
- Pericardial effusion or thickening predictive of PH in SSc

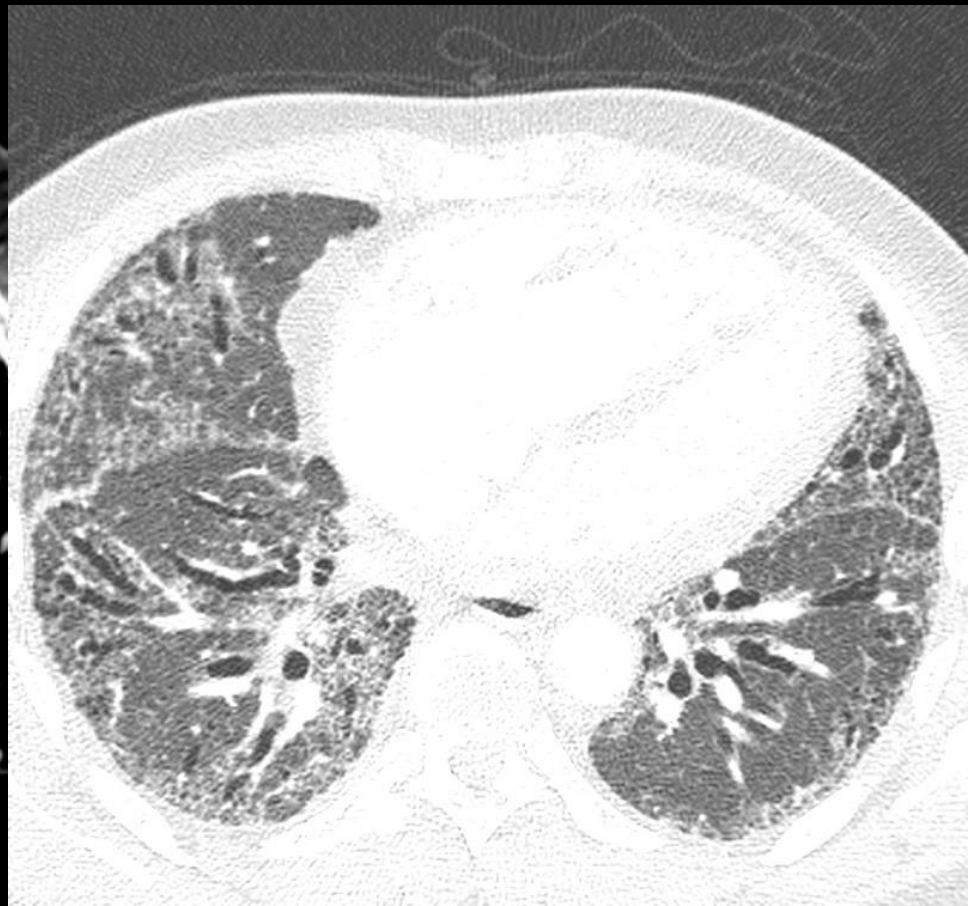
Systemic Sclerosis - PH



Pulmonary hypertension

Systemic Sclerosis - PH

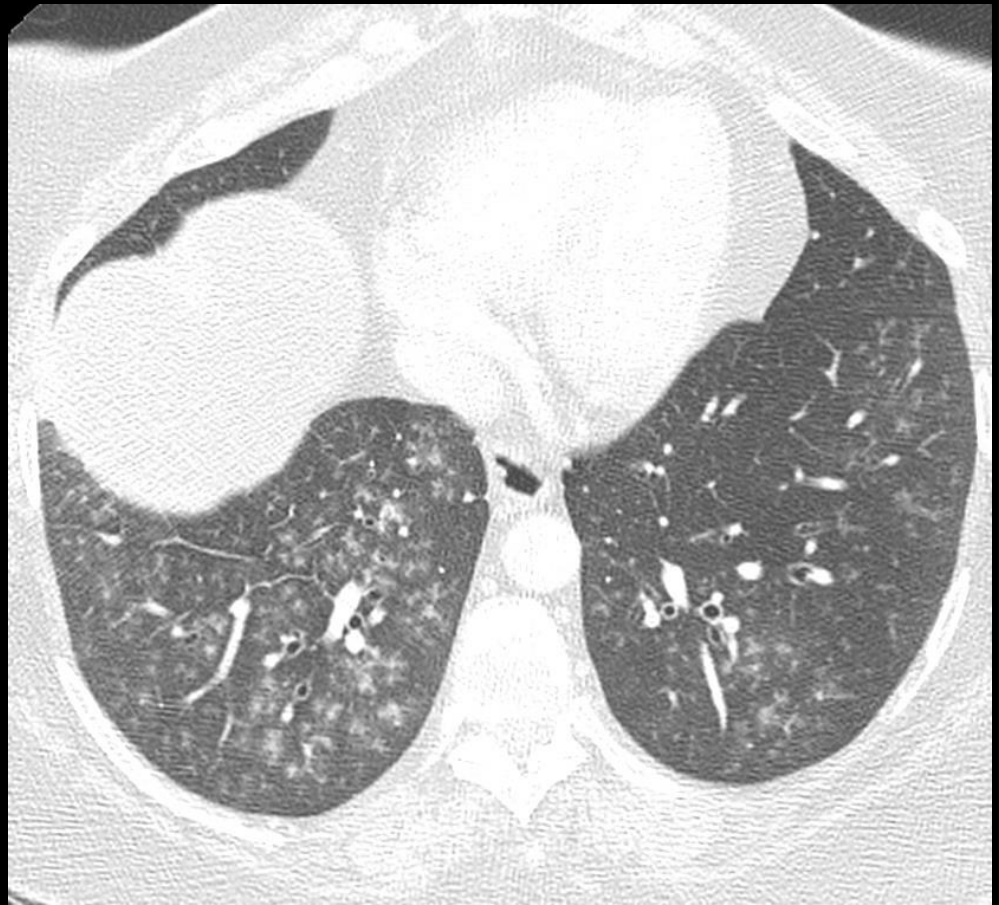




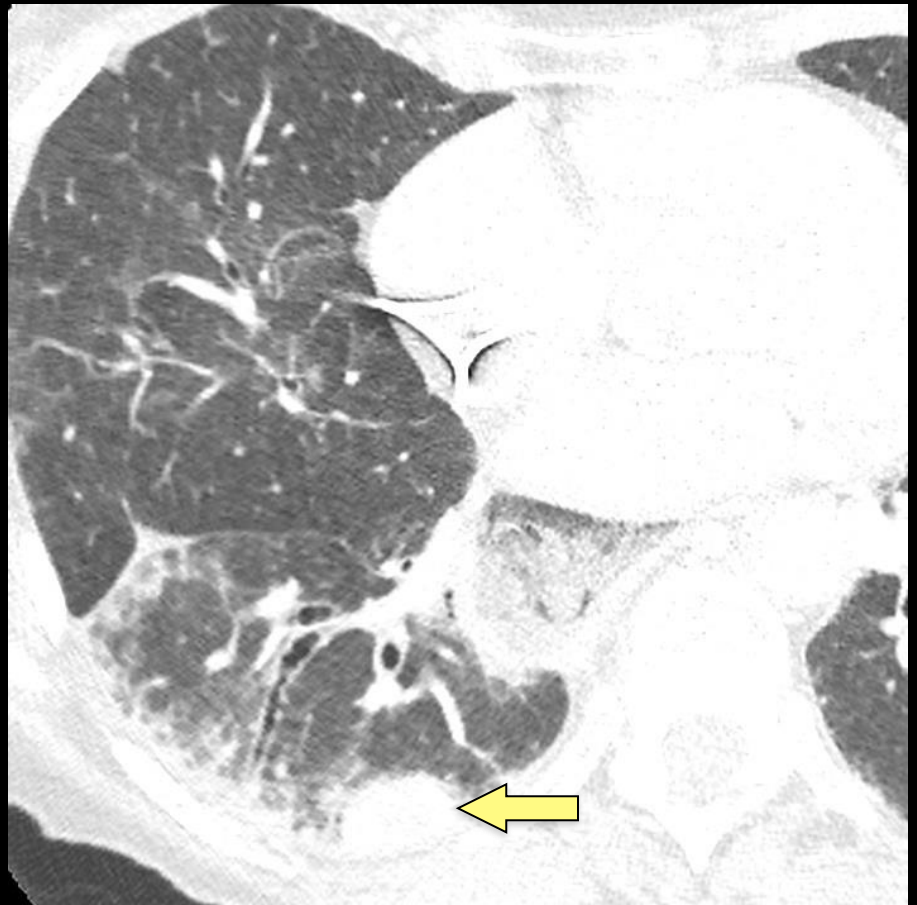
Systemic Sclerosis

- Other complications
  - Aspiration
  - Lung cancer
    - 1.8 – 6.5 relative risk
    - Most often occurs in setting of fibrosis

Systemic Sclerosis - Aspiration



Systemic Sclerosis – Lung Cancer



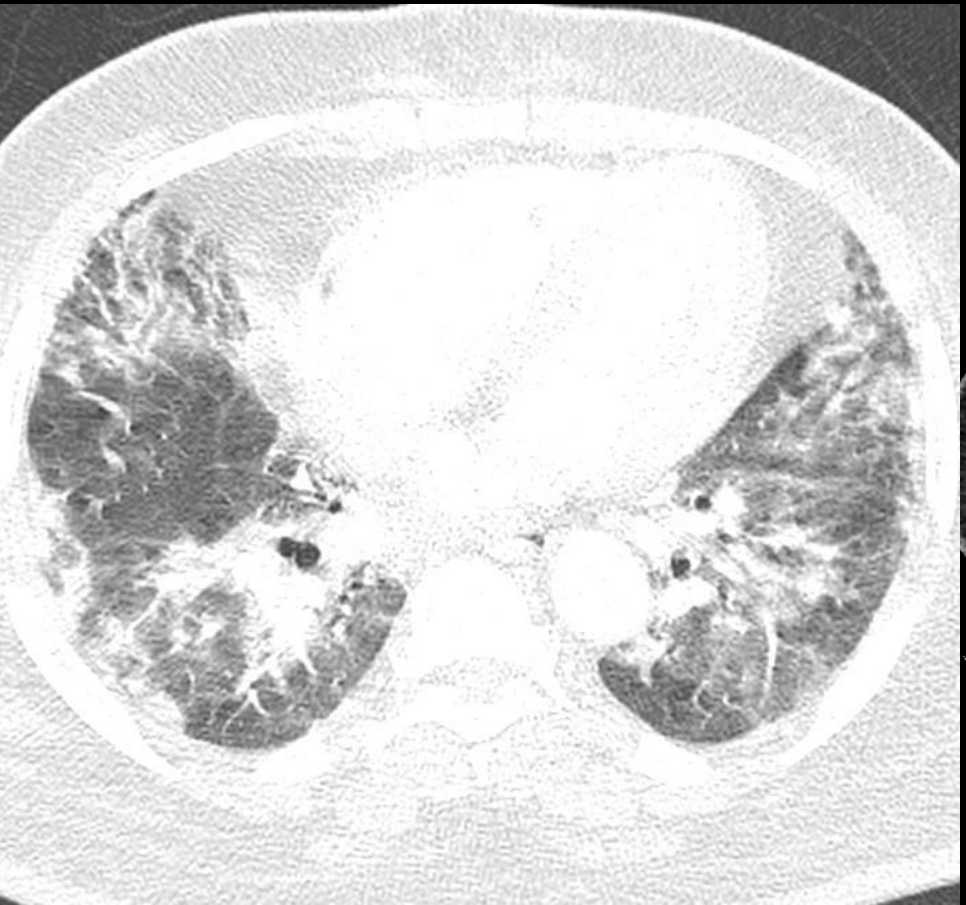
Systemic Sclerosis

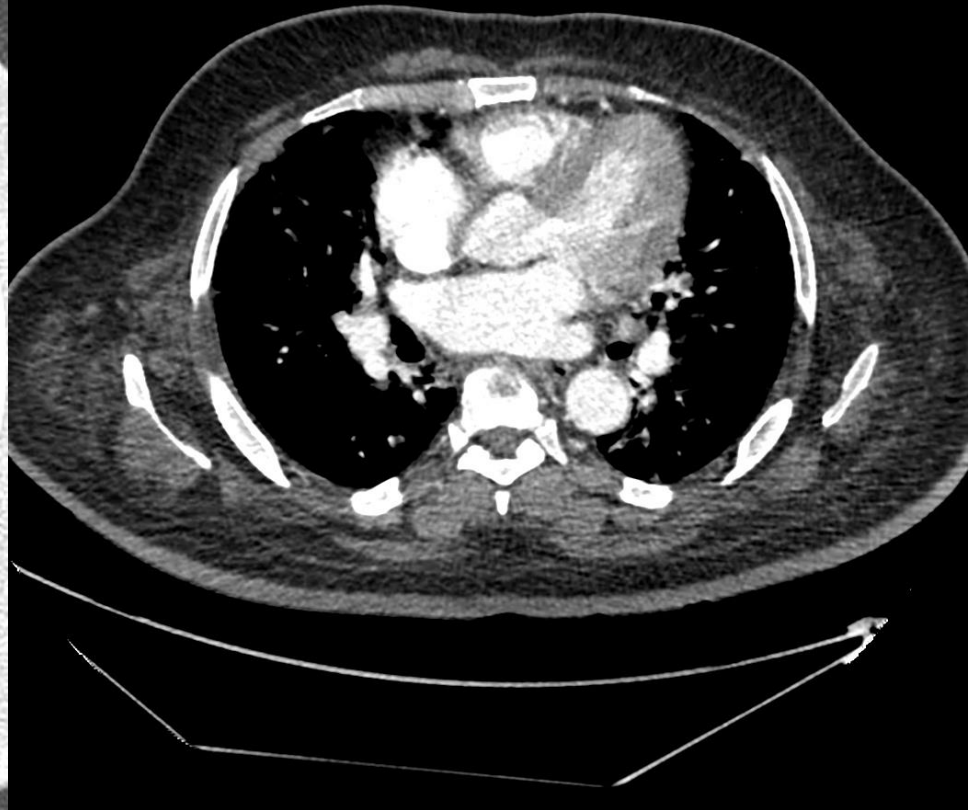
Pathology	RA	SSc
UIP	+++	+
NSIP	++	+++
OP	+	+
Diffuse alveolar damage		
LIP		
Alveolar hemorrhage		
Constrictive bronchiolitis	++	
Bronchiectasis	++	
Follicular bronchiolitis	+++	
Aspiration		+
Pulmonary hypertension	+	+++
Pleural effusion	++	

Myositis and Antisynthetase Syndrome

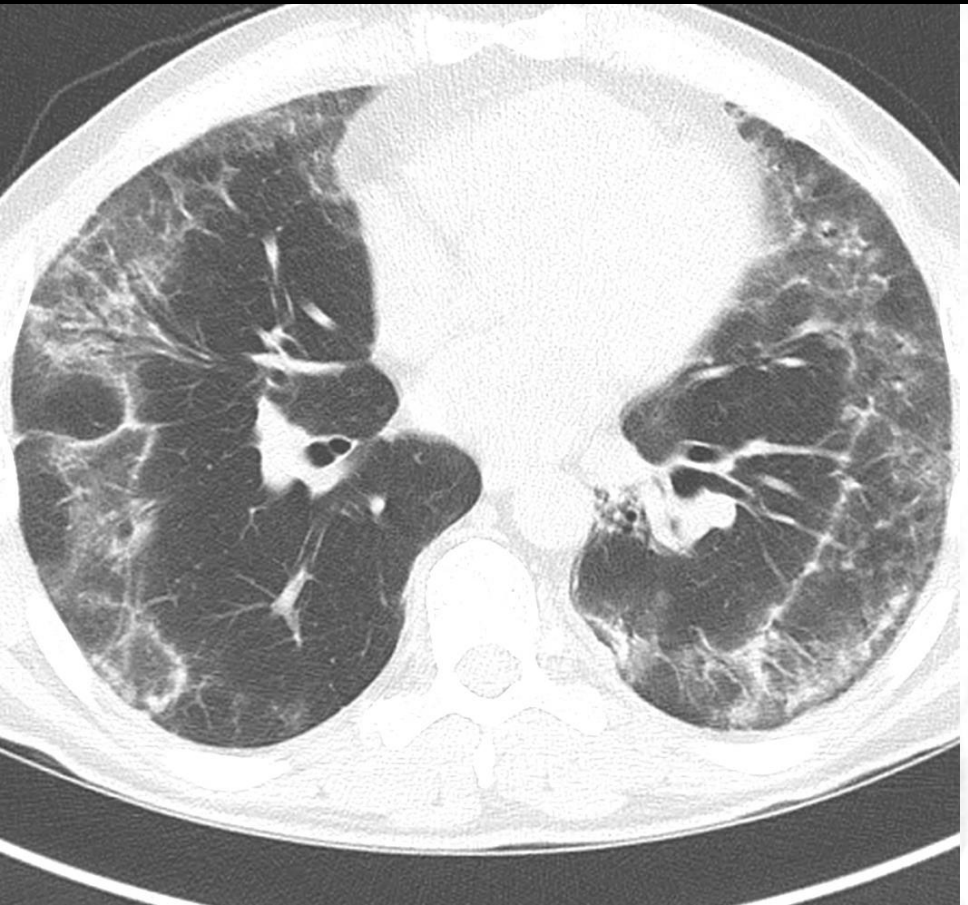
- ILD highly correlates with presence of anti-Jo-1 antibody (anti-synthetase syndrome)
  - 70% of patients with anti-Jo-1 have ILD
  - 10% of patients without anti-Jo-1 have ILD
- NSIP and OP most common
  - Frequently occur together
- Diffuse alveolar damage
  - Can be an acute presentation

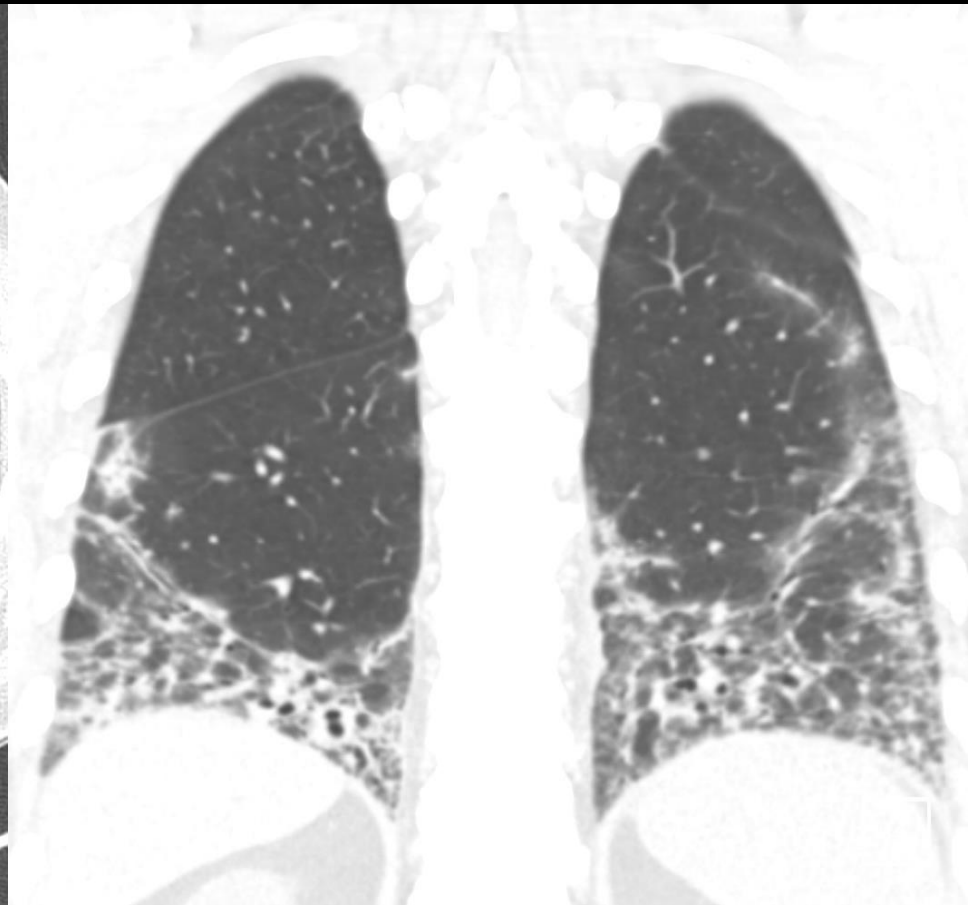
Polymyositis - OP



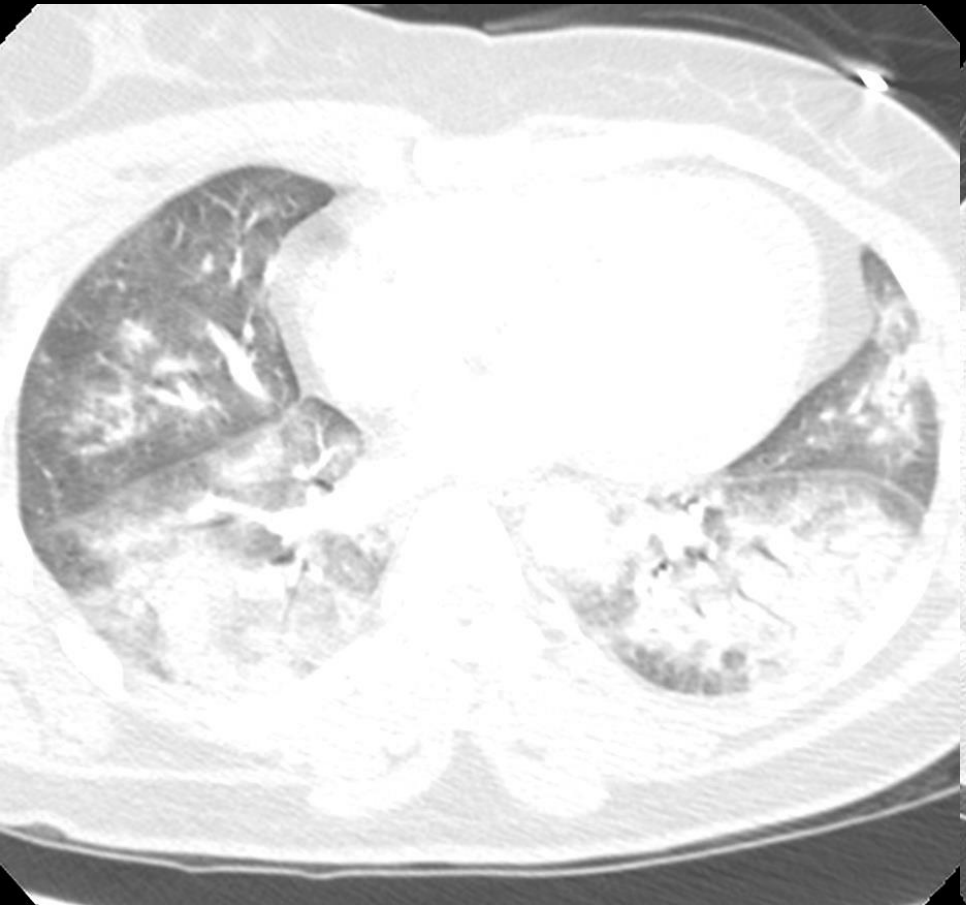


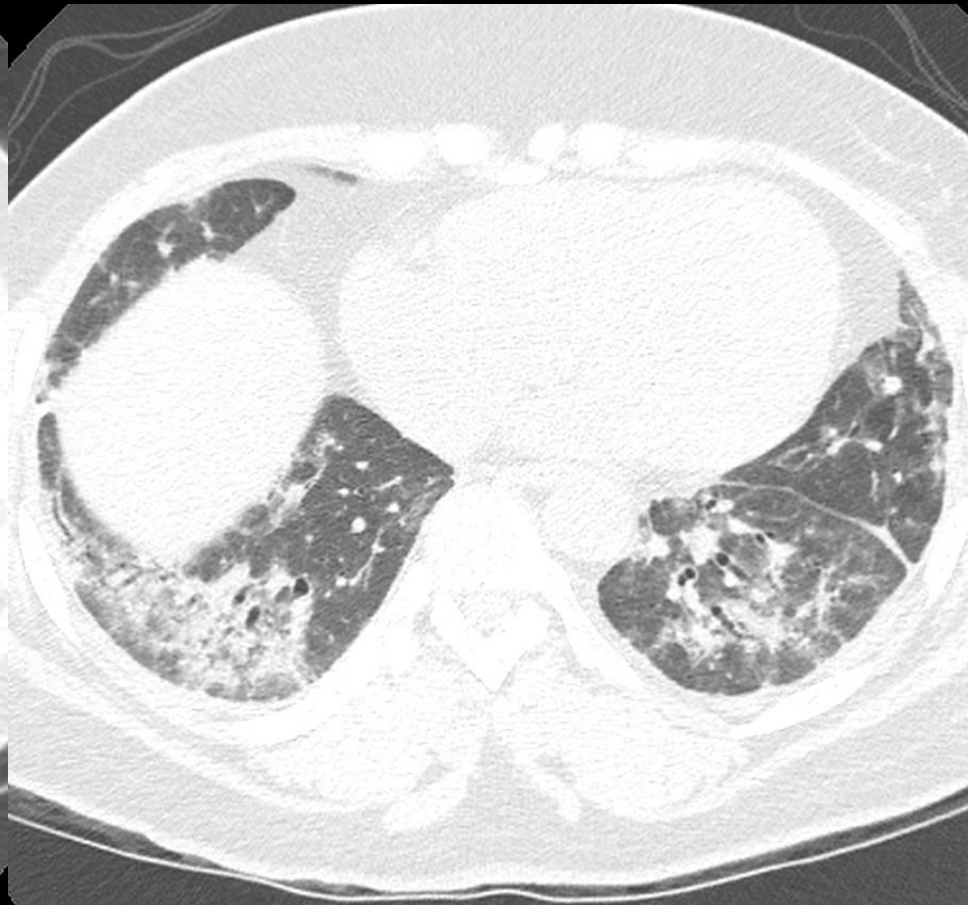
Dermatomyositis – Mixed OP/NSIP





Dermatomyositis – DAD → Fibrosis





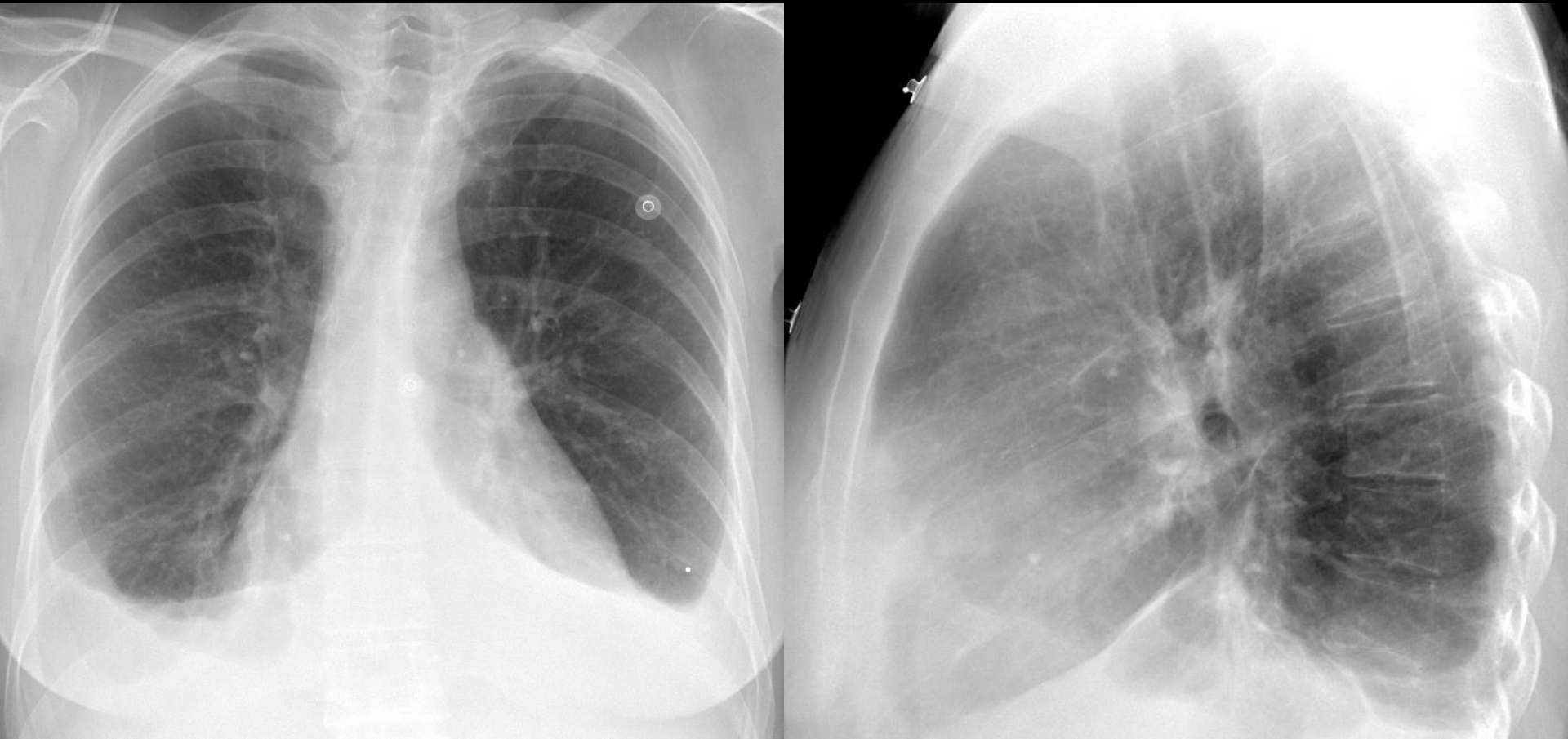
Myositis and Antisynthetase Syndrome

Pathology	RA	SSc	Myositis
UIP	+++	+	+
NSIP	++	+++	+++
OP	+	+	+++
Diffuse alveolar damage			++
LIP			
Alveolar hemorrhage			
Constrictive bronchiolitis	++		
Bronchiectasis	++		
Follicular bronchiolitis	+++		
Aspiration		+	++
Pulmonary hypertension	+	+++	
Pleural effusion	++		

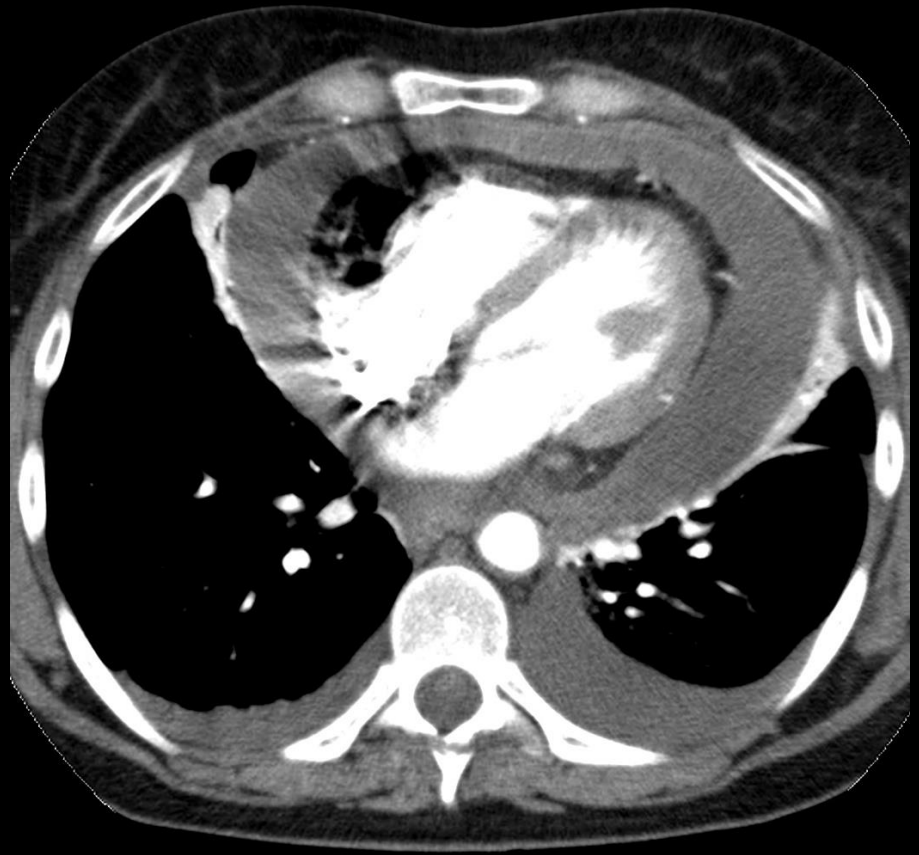
Systemic Lupus Erythematosus

- Pleuritis most common
  - (40% - 60%)
  - +/- effusion
- Pericarditis
  - +/ - effusion

SLE – Serositis



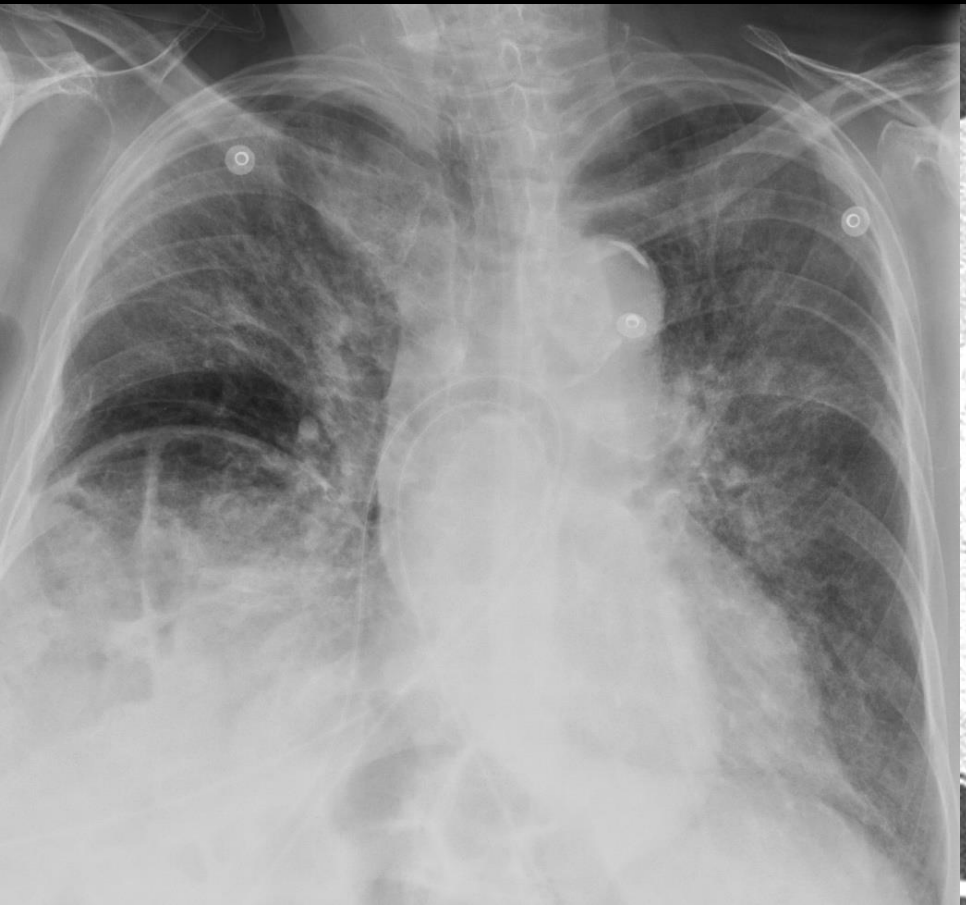
SLE - Serositis

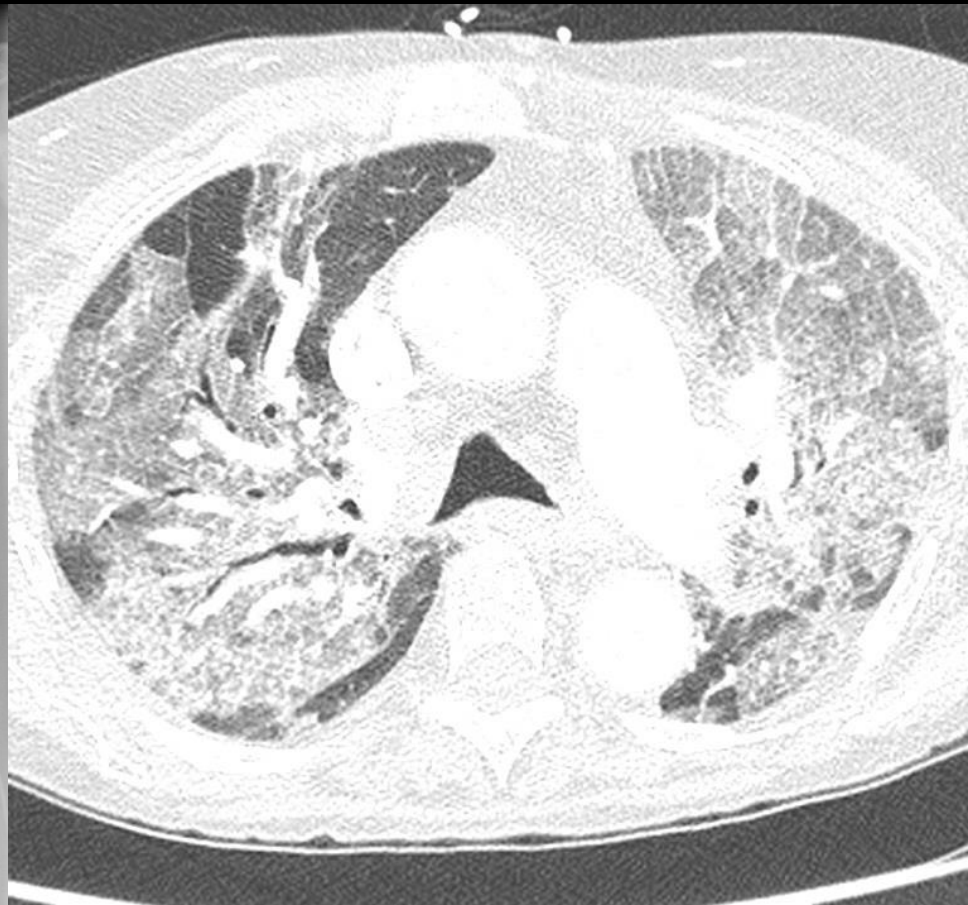


Systemic Lupus Erythematosus

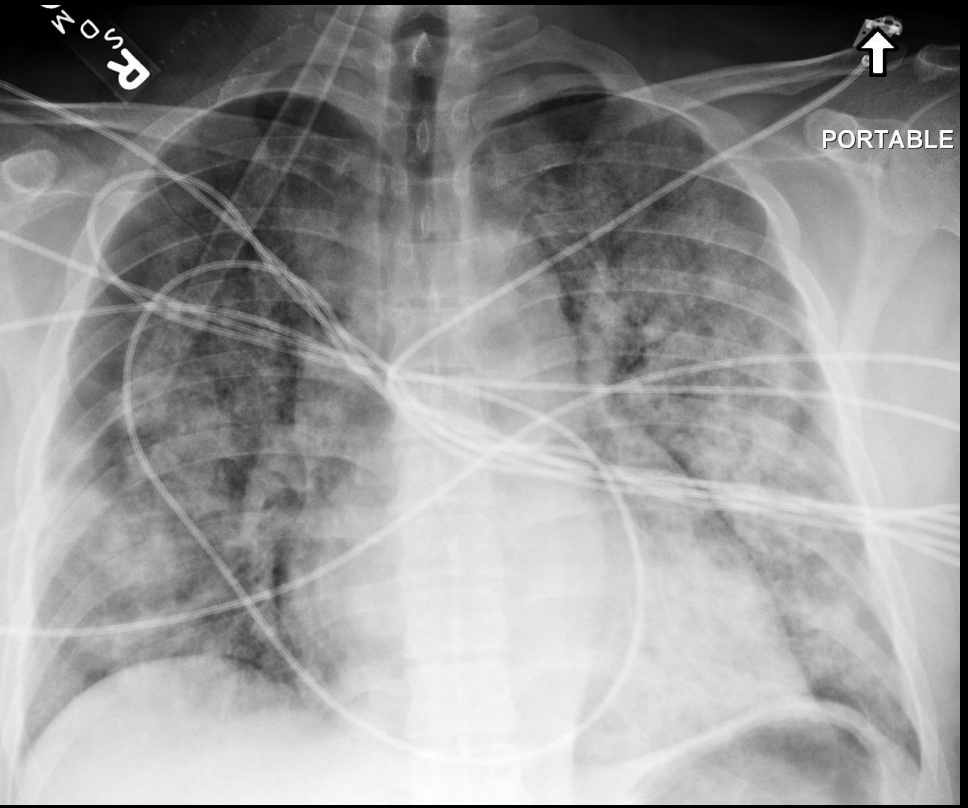
- Infection
  - Most common cause of acute respiratory disease
- Diffuse alveolar hemorrhage
  - Acute dyspnea, hypoxia, +/- hemoptysis
- Acute lupus pneumonitis
  - Up to 6% of hospitalized SLE patients
  - Most cases acute interstitial pneumonia
    - +/- alveolar hemorrhage

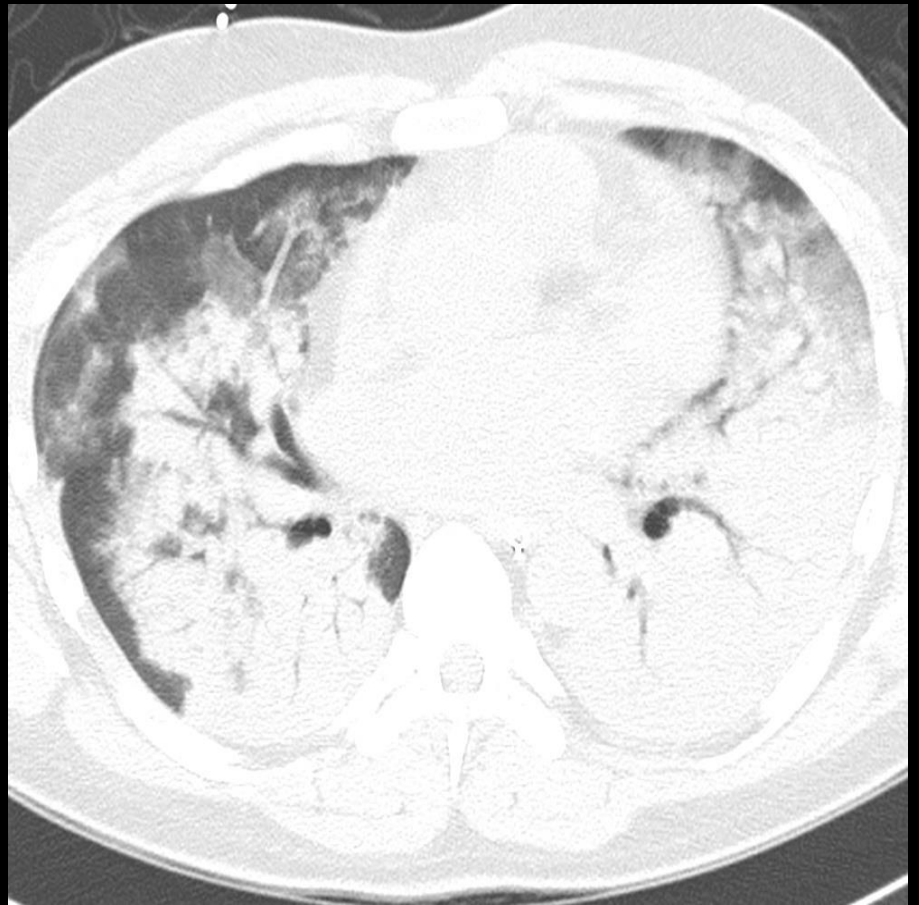
SLE – Infection (PJP)



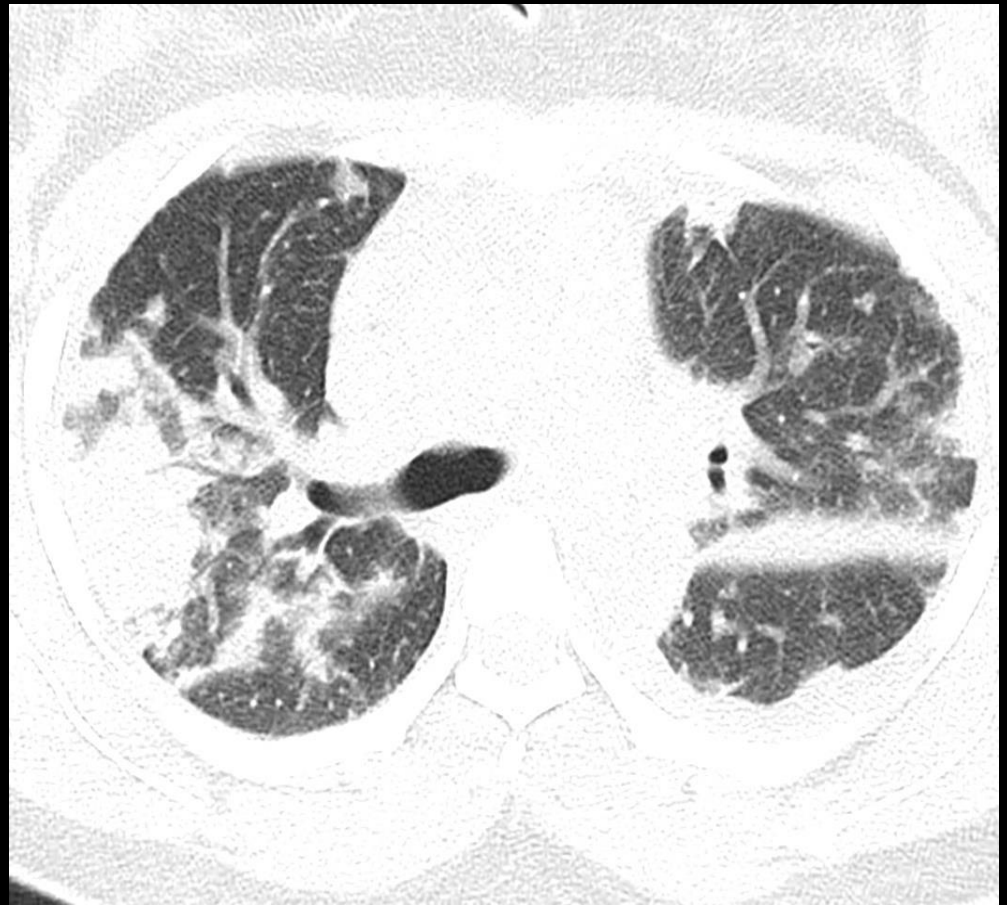


SLE – DAH





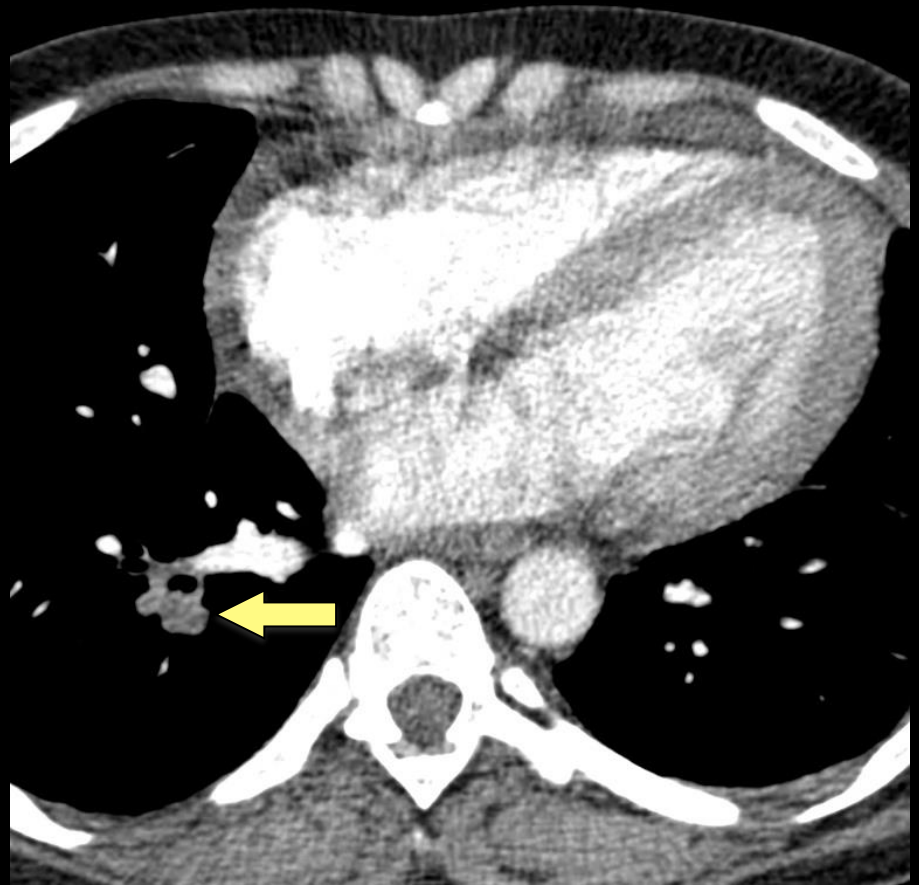
SLE – Acute Lupus Pneumonitis



Systemic Lupus Erythematosus

- Pulmonary embolism
  - Anticardiolipin antibodies commonly found in patients with SLE
  - Lupus anticoagulant
  - Association with antiphospholipid antibody syndrome (up to 20%)

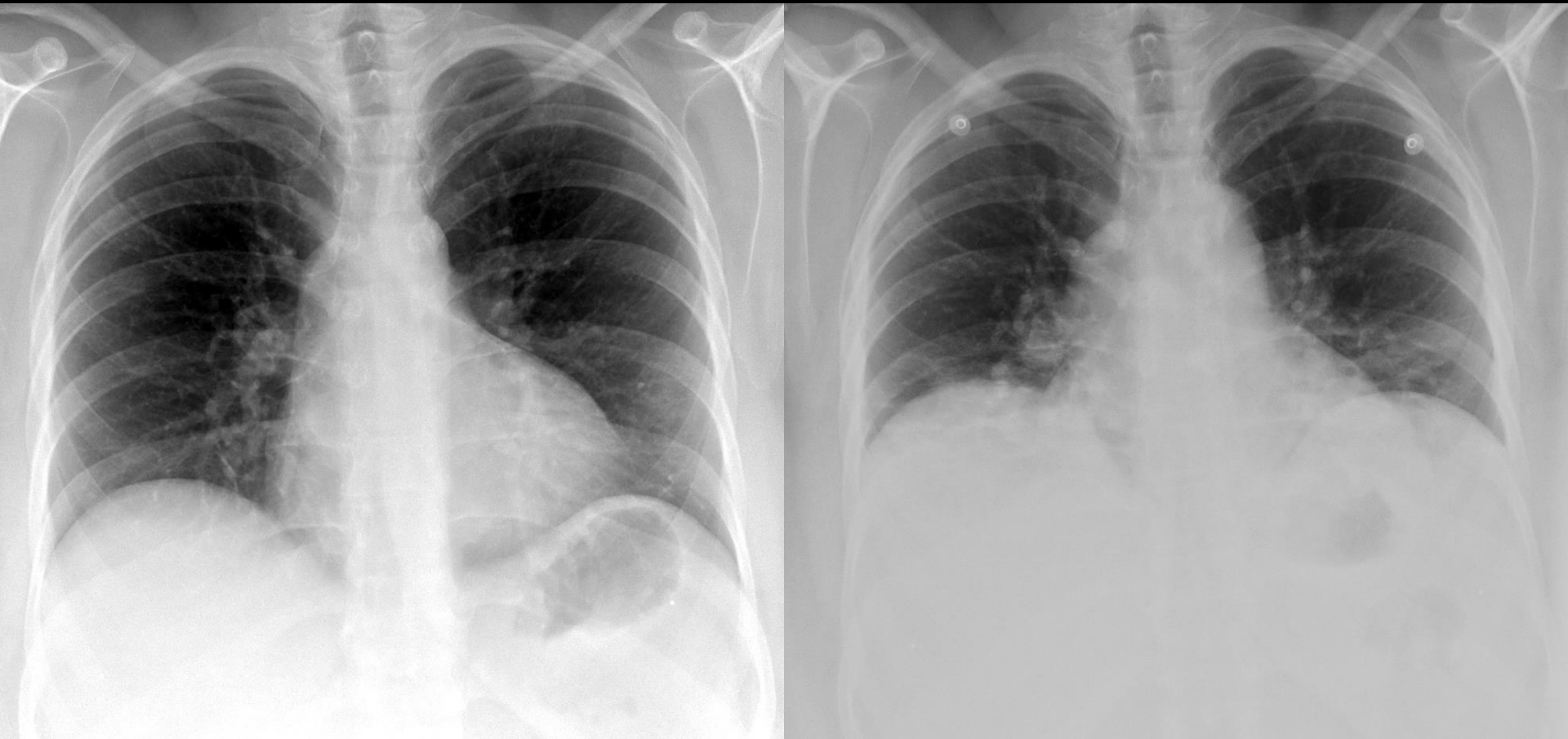
SLE – PE and Pericarditis



Systemic Lupus Erythematosus

- Diaphragm dysfunction
  - Manifests as progressive reduced lung volume (“shrinking lung”)
  - Believed to result from phrenic myopathy

SLE – Shrinking Lung Syndrome



Systemic Lupus Erythematosus

Pathology	RA	SSc	Myositis	SLE
UIP	+++	+	+	
NSIP	++	+++	+++	+
OP	+	+	+++	
Diffuse alveolar damage			++	++
LIP				
Alveolar hemorrhage				++
Constrictive bronchiolitis	++			
Bronchiectasis	++			
Follicular bronchiolitis	+++			
Aspiration		+	++	
Pulmonary hypertension	+	+++		
Pleural effusion	++			++

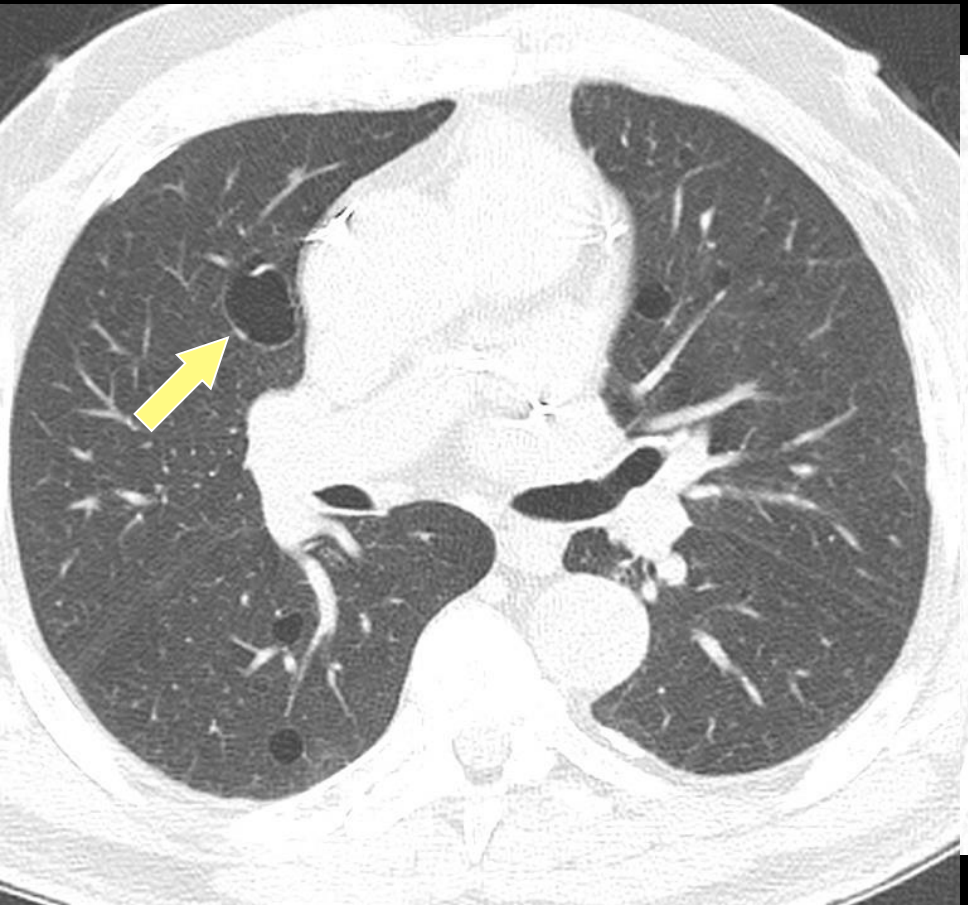
Sjögren Disease

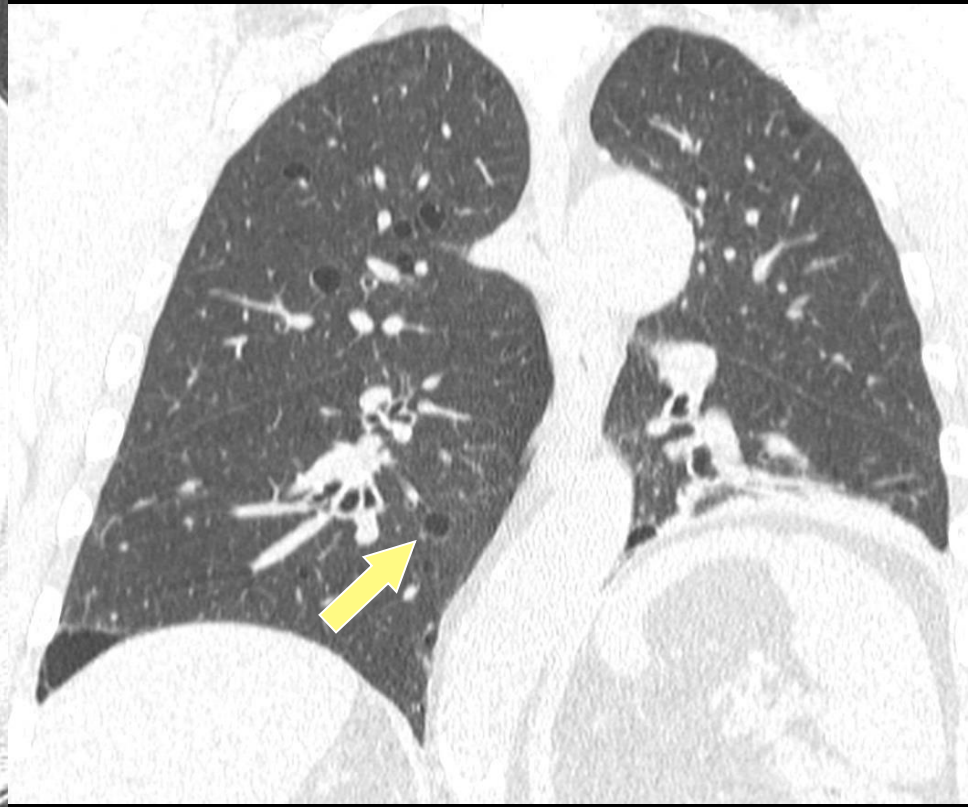
Compartment	Injury
Parenchyma	Lymphoid interstitial pneumonia (radiologic) NSIP
Airways	Follicular bronchiolitis
Other	Lymphoproliferative

Sjögren Disease

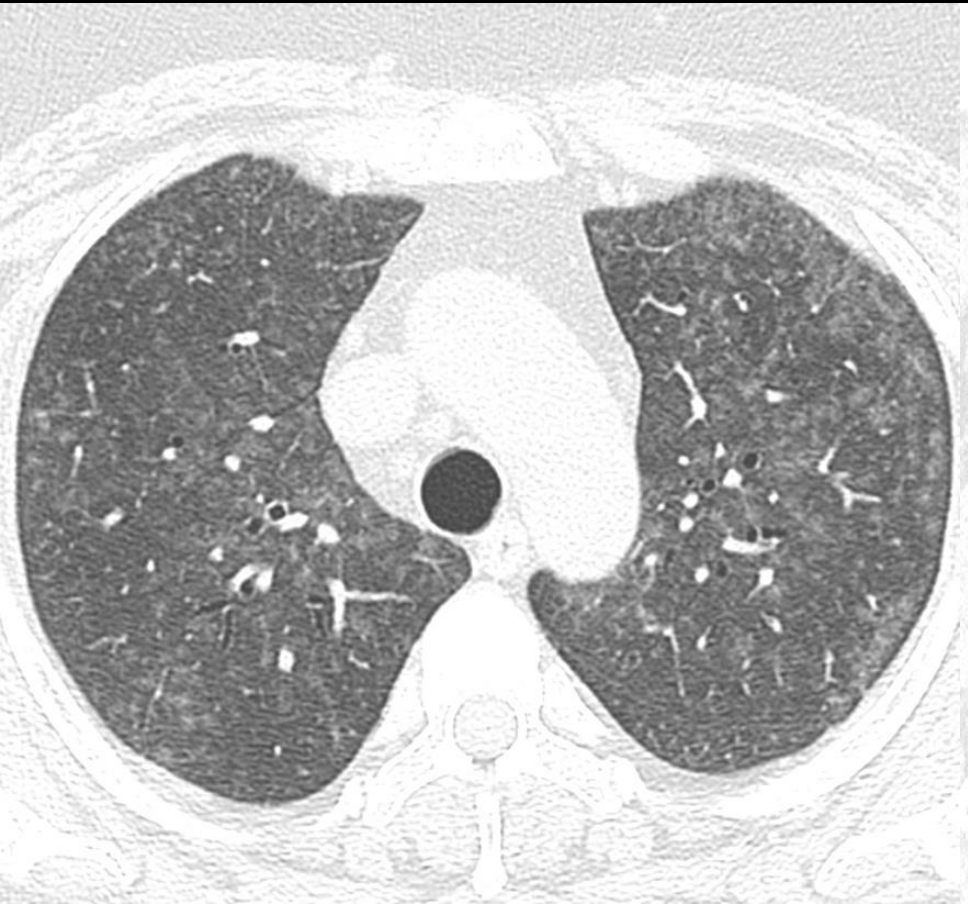
- 10% of patients with primary Sjögren disease have lung involvement
  - Lymphoid interstitial pneumonia (radiologic) most common
  - Follicular bronchiolitis
  - Nonspecific interstitial pneumonia

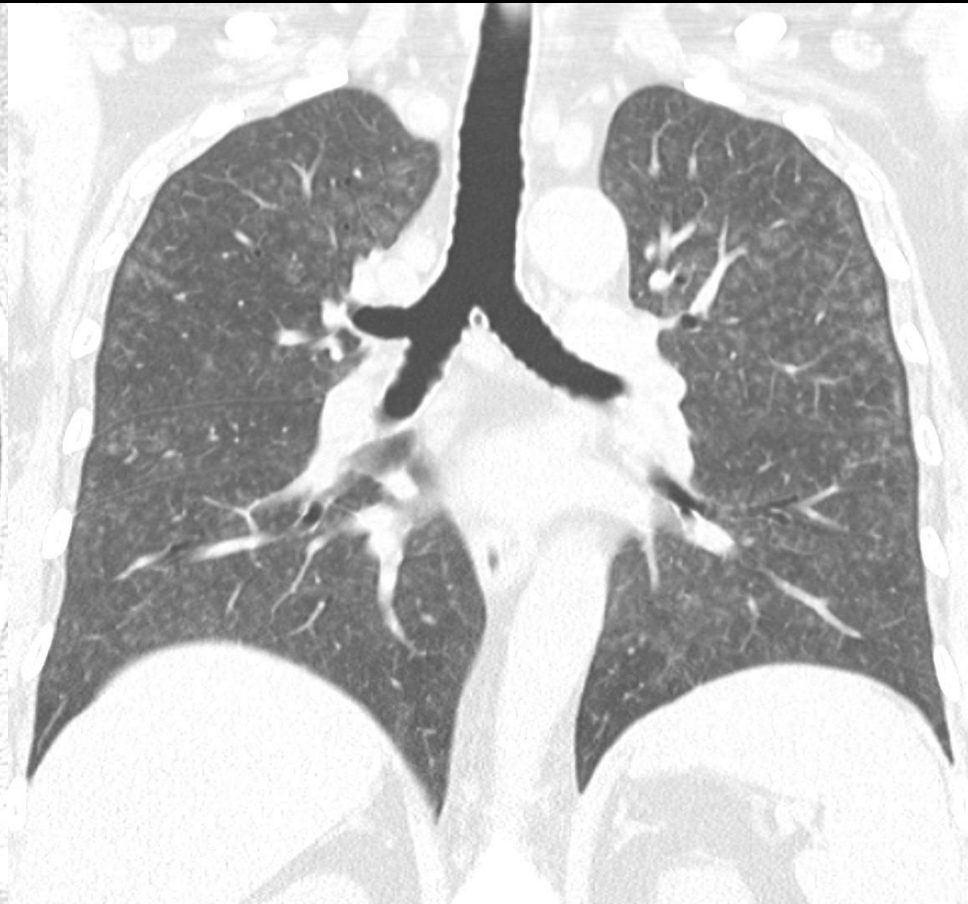
Sjögren Disease - LIP



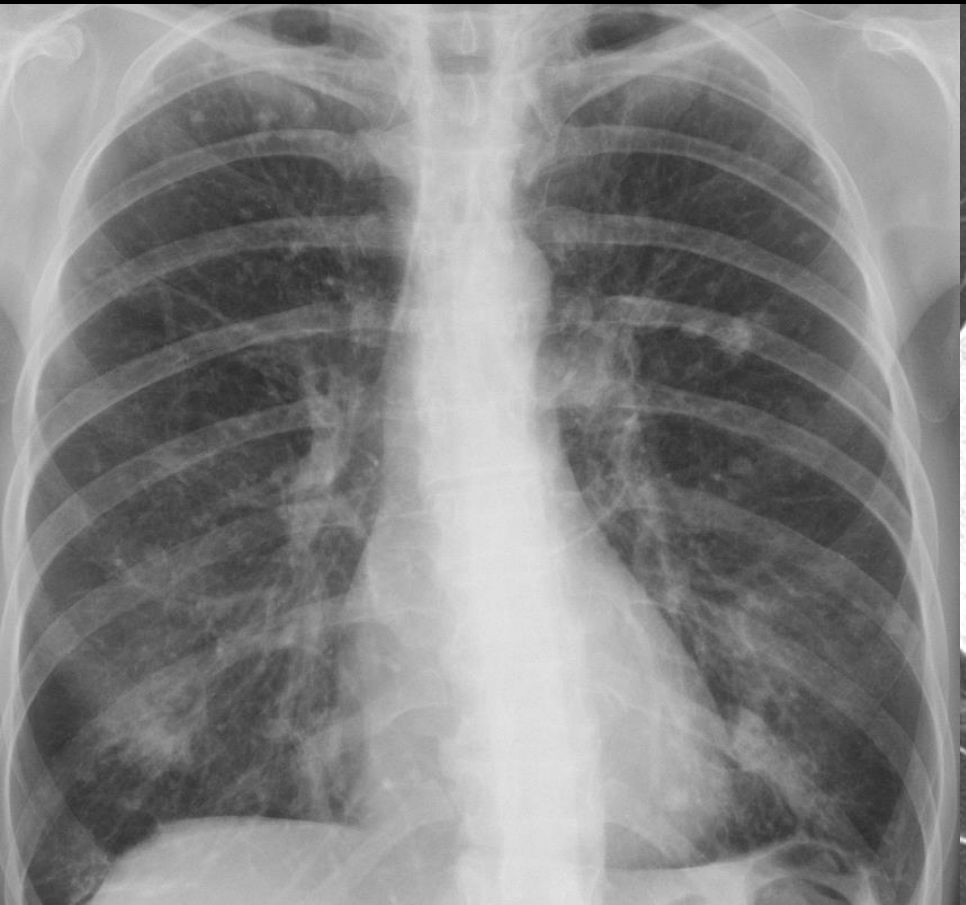


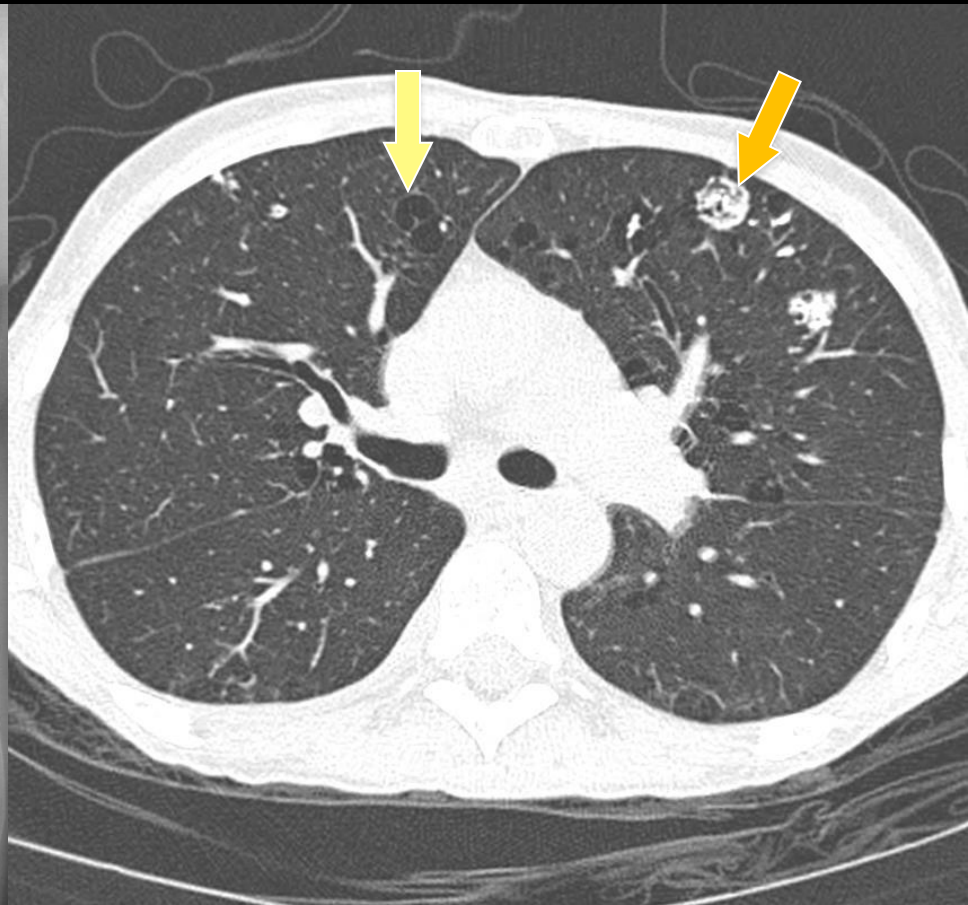
Sjögren Disease - LIP



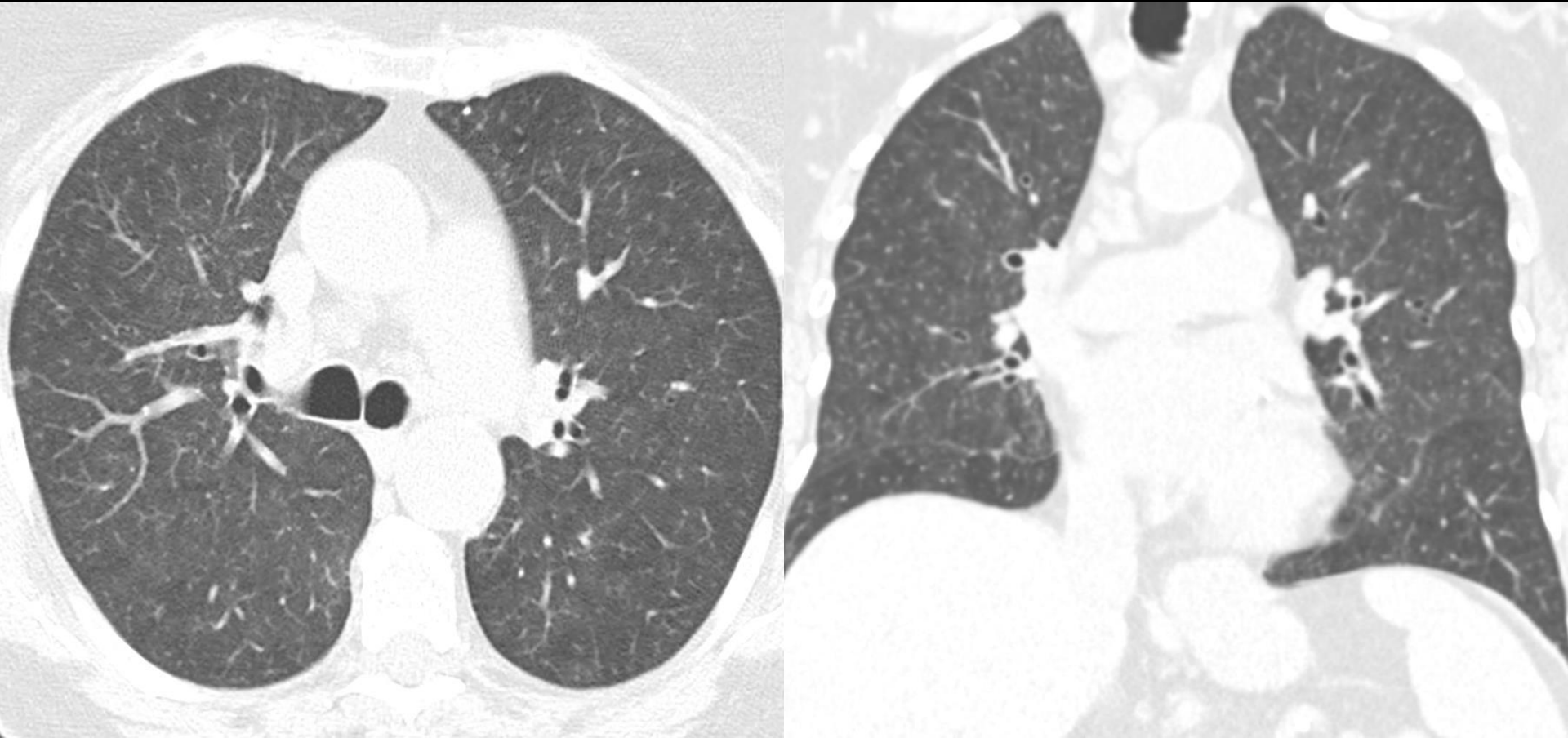


Sjögren Disease - LIP

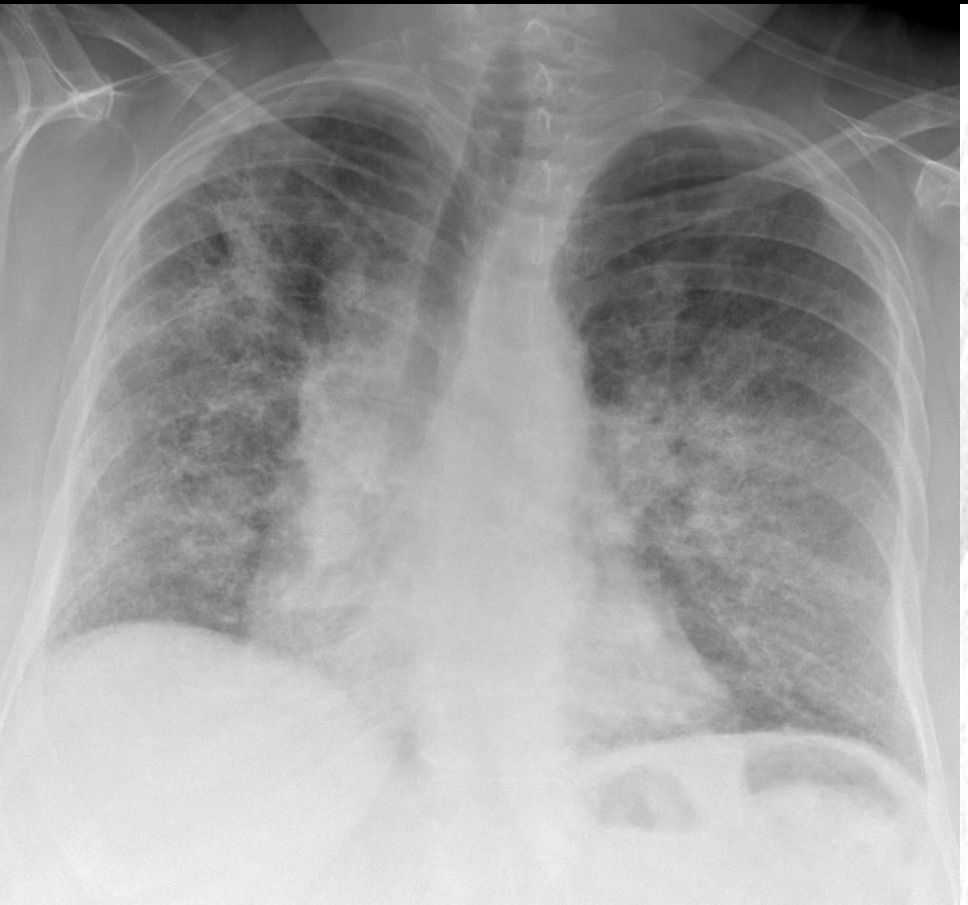


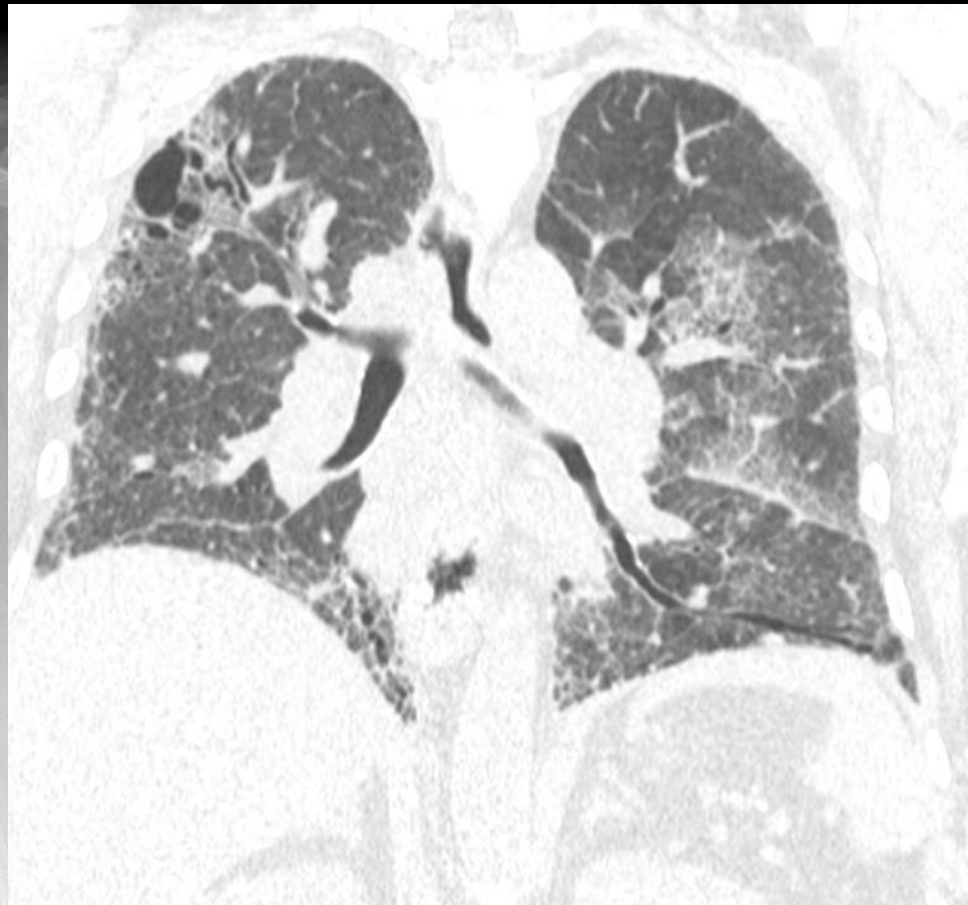


Sjögren Disease – Follicular Bronchiolitis



Sjögren Disease – Fibrosis

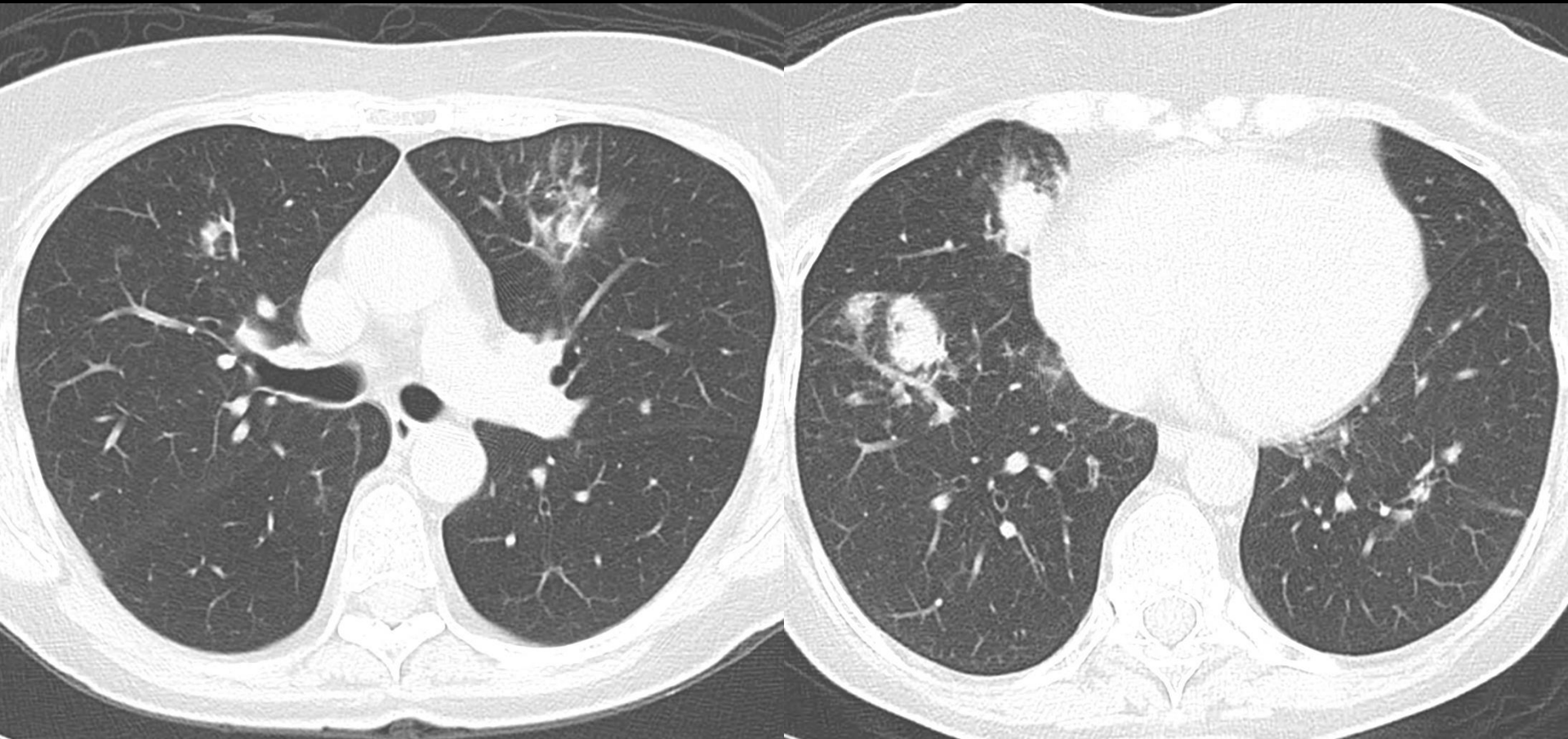




Sjögren Disease

- 44-fold increased risk of developing non-Hodgkin lymphoma
- Primary pulmonary lymphoma rare
  - Localized consolidation with air bronchograms
  - Lymphangitic infiltration (less common)
- Nonpulmonary lymphoma
  - Mediastinal and hilar lymphadenopathy

Sjögren Syndrome - Lymphoma



Sjögren Disease

Pathology	RA	SSc	Myositis	SLE	SD
UIP	+++	+	+		
NSIP	++	+++	+++	+	+
OP	+	+	+++		
Diffuse alveolar damage			++	++	
LIP					+++
Alveolar hemorrhage				++	
Constrictive bronchiolitis	++				
Bronchiectasis	++				
Follicular bronchiolitis	+++				++
Aspiration		+	++		
Pulmonary hypertension	+	+++			
Pleural effusion	++			++	

Interstitial Pneumonia with Autoimmune Features (IPAF)

- Patients suspected of having a CTD but don’t meet strict clinical criteria
- Previously referred to as:
  - Undifferentiated CTD
  - Lung-dominant CTD
  - Autoimmune-featured CTD
- Originally proposed for research purposes, now gaining clinical acceptance

IPAF Criteria

- Presence of ILD (HRCT or surgical lung biopsy)
- Does not meet strict CTD definition
- Other etiologies for lung disease excluded
- Requires features from 2 of 3 “domains”
  - Clinical
  - Serologic
  - Morphologic

IPAF – Diagnostic Criteria

A. Clinical domain

1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

Fischer - *Eur Respir J* 2015; 46: 976–987

IPAF – Diagnostic Criteria

C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

HRCT: high-resolution computed tomography; ANA: antinuclear antibody; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function testing. [#]: includes airflow obstruction, bronchiolitis or bronchiectasis.

**Patients with UIP pattern can still have IPAF, they just don't get "credit" for it*

Fischer - *Eur Respir J* 2015; 46: 976–987

Summary

Pathology	RA	SSc	Myositis	SLE	SD
UIP	+++	+	+		
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OP	+	+	+++		
Diffuse alveolar damage			++	++	
LIP					+++
Alveolar hemorrhage				++	
Constrictive bronchiolitis	++				
Bronchiectasis	++				
Follicular bronchiolitis	+++				++
Aspiration		+	++		
Pulmonary hypertension	+	+++			
Pleural effusion	++			++	

Summary

- Lung disease is a common manifestation of connective tissue disease
- CTD may first present with pulmonary pathology
- Recognizing patterns of lung involvement can help the radiologist suggest the diagnosis of CTD