Κλινική εικόνα και εργαστηριακή προσέγγιση ρευματολογικών νοσημάτων

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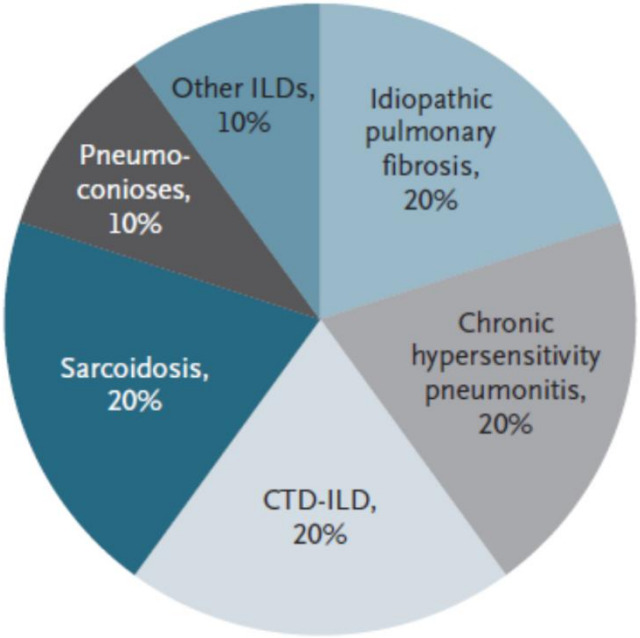
Lung involvement in CTDs

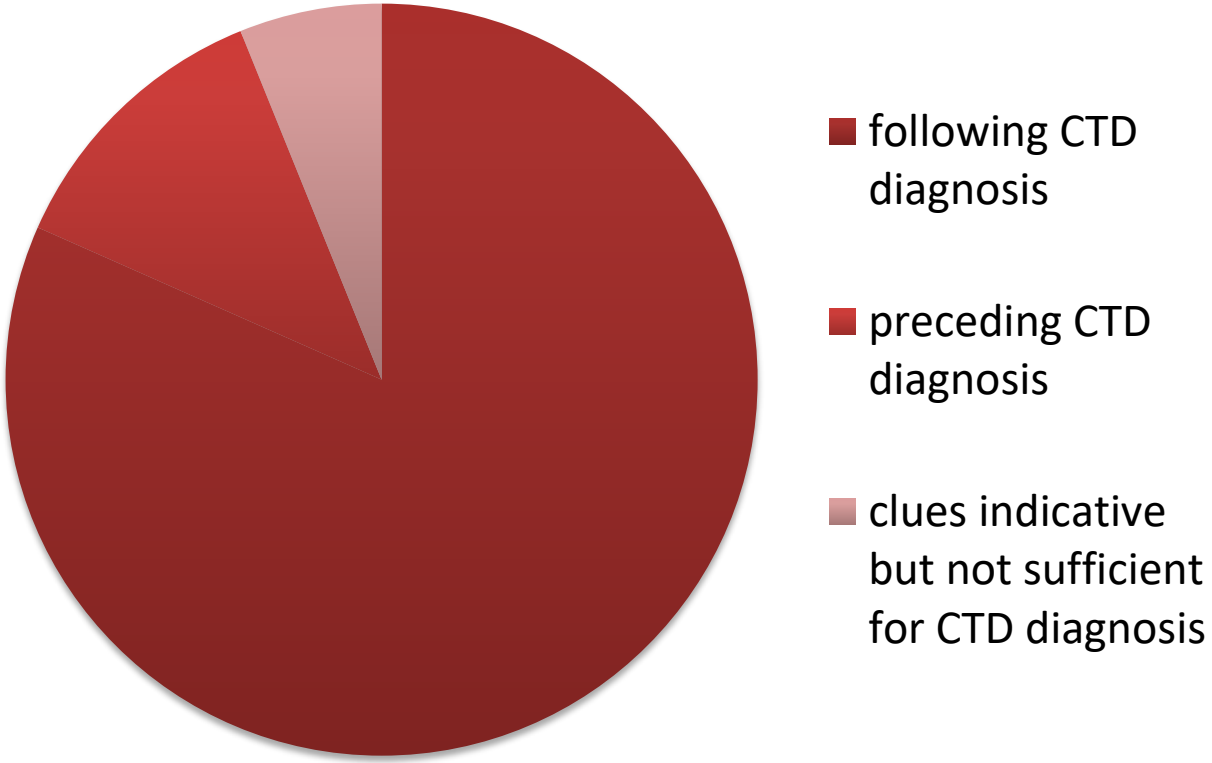


- Common
- Major determinant of morbidity and mortality
- Pleomorphic since any lung compartment may be involved

Lederer DJ, Martinez FJ. N Engl J Med 2018; 378: 1811-1823

Lung involvement in CTDs

- Any combination possible concomitantly
- Specific combinations for certain CTDs



A 'vicious' combination of

- *lung involvement*
- *lung drug toxicity*
- *lung infections*

This review will focus on the established lung manifestations for the 7 major CTDs

Rheumatoid arthritis-Lung manifestations

- Exact prevalence varies widely
- Autopsy, hospital, community-based studies
- Heterogeneous populations
- Subclinical disease common

Symptoms, structural and functional abnormalities in terms of presence, severity and change over time determine the importance of any finding and the need for intervention

RA- LUNG INVOLVEMENT

Table 1 Frequency and impact of EAM in the lung in patients with RA[a]

	Frequency	Impact if present
Pleural[21,22,30–34]		
Pleuritis	++	++
Effusion[a]	++	++
Pleural thickening	+++	+
Other—unexpandable lung, empyema, chyliform effusion,[b] pneumothorax,[b] hemothorax,[b] pyopneumothorax,[b] bronchopleural fistula[b]	+	+++
Airway[2,23,35–42]		
Upper—cricoarytenoid immobility with vocal cord abnormality, cord nodules, recurrent laryngeal, or vagus nerve vasculitis and cord paralysis	+	++
Lower		
Airflow obstruction	++	+
Obliterative bronchiolitis	+	+++
Bronchiectasis[43]	+	+

RA- LUNG INVOLVEMENT

Parenchymal[3,4,8,9,12,13,44–48]		
Interstitial lung disease	+++	+ +++
Apical fibrosis and Caplan syndrome	+	+
Nodules	+++	+
Vascular[24,49–51]		
Pulmonary hypertension	+	+++
Vasculitis	+	+++
Musculoskeletal related[3,18]		
Chest wall immobility and respiratory failure	+	+
Infection[17,52–54]		
Related to RA	+	+
Related to treatment	++	++
Treatment related[13–17,25,26]		
Pneumonitis	++	+++
Pleuritis/effusion (methotrexate, infliximab, adalimumab)	+	+
Increased risk[19,27–29]		
Lung cancer	+	+++
Pulmonary thromboembolism	+	++

RA-PLEURAL DISEASE

- Fever, pleuritic chest pain most commonly
- Dyspnea in significant effusion
- No pleuritic symptoms
- Autopsy studies 38-73% but complaints of pleurisy only 5-21%

Chronic rheumatoid pleural effusion: Typical abnormalities

Size	Small to moderate; unilateral
Appearance	Milky-green, serous, or hemorrhagic
Protein	>3 g/dL (>30 g/L), consistent with an exudate
Glucose	<29 mg/dL (<1.6 mmol/L)
Lactic dehydrogenase (LDH)	>700 U/L, consistent with an exudate
Cholesterol	>200 mg/dL (5.18 mmol/L), cholesterol crystals may be present under polarizing light
pH	<7.20
Rheumatoid factor	>240 IU/mL (>1:320)
Complement	Low
Cytology	Cell number:
	<5000/mm^3
	Cell type:
	Lymphocytes (neutrophils and eosinophils acutely)

Data from: Bouros D, Pneumatikos I, Tzouvelekis A. Pleural involvement in systemic autoimmune disorders. Respiration 2008; 75:361 and Hooper C, Lee YC, Maskell N, BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010; 65:Suppl 2:ii4.

Graphic 77436 Version 4.0

RA-PLEURAL DISEASE

- Drug-induced pleuritis (MTX, infliximab)
- Necrosis-cavitation of a nodule ⟶

  Bronchopleural fistula ⟶ Empyema

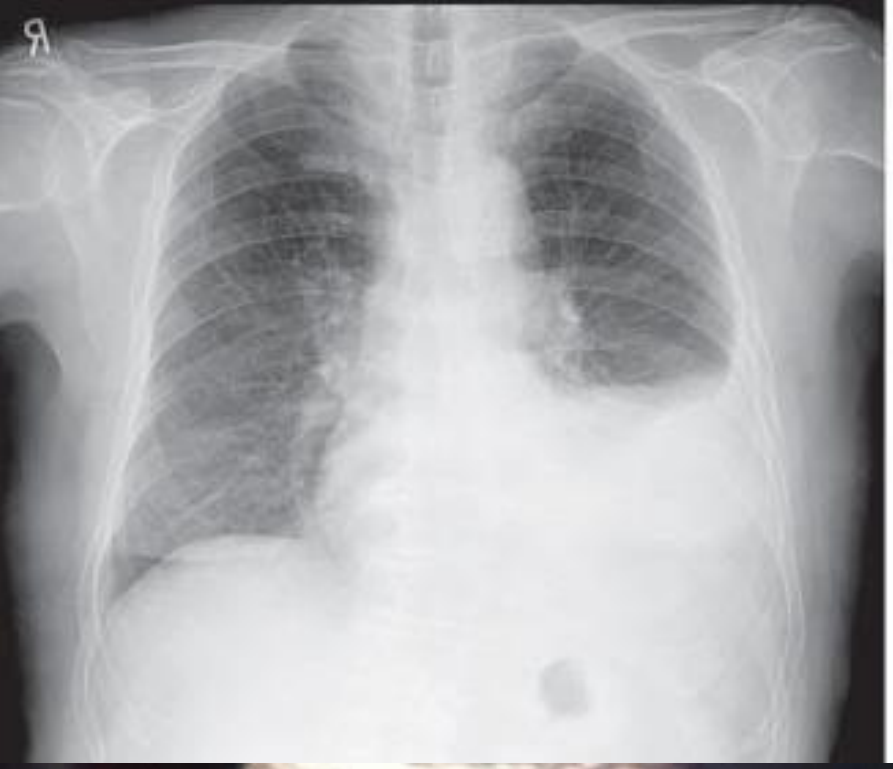
  Hemopneumothorax

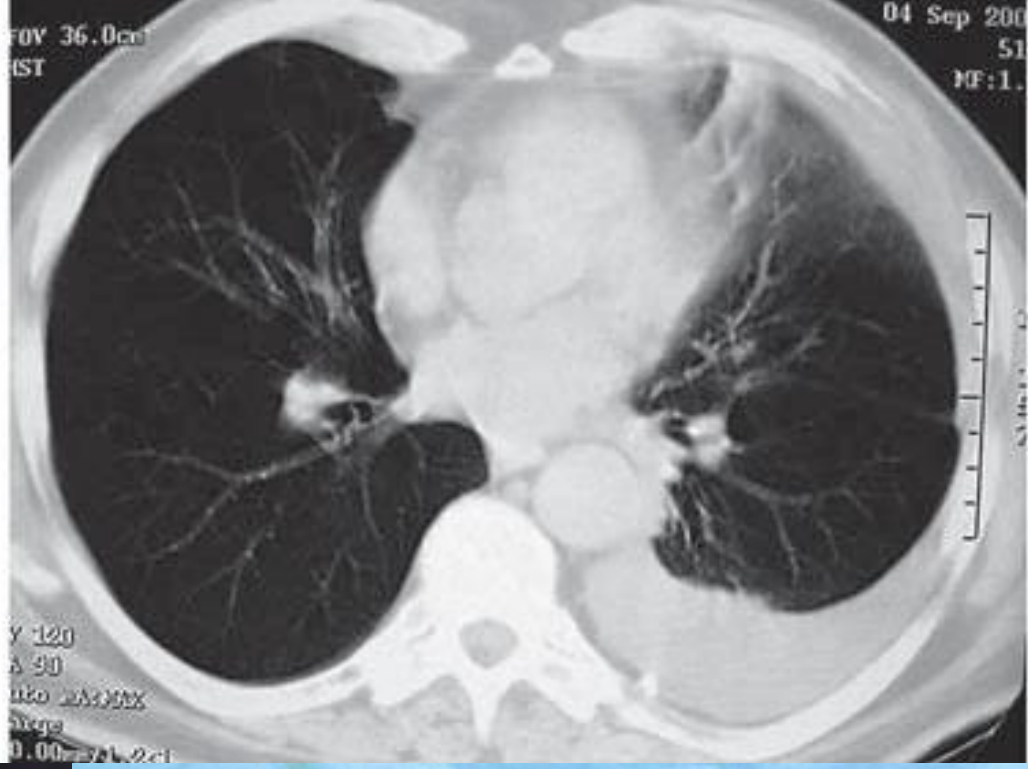
  Pyopneumothorax
- Chronic pleural inflammation ⟶

  Chyliform effusion ⟶ Trapped lung

Naylor criteria in pleural fluid

(1) Elongated macrophages
(2) Round multinucleated macrophages and
(3) Background of granular necrotic debris

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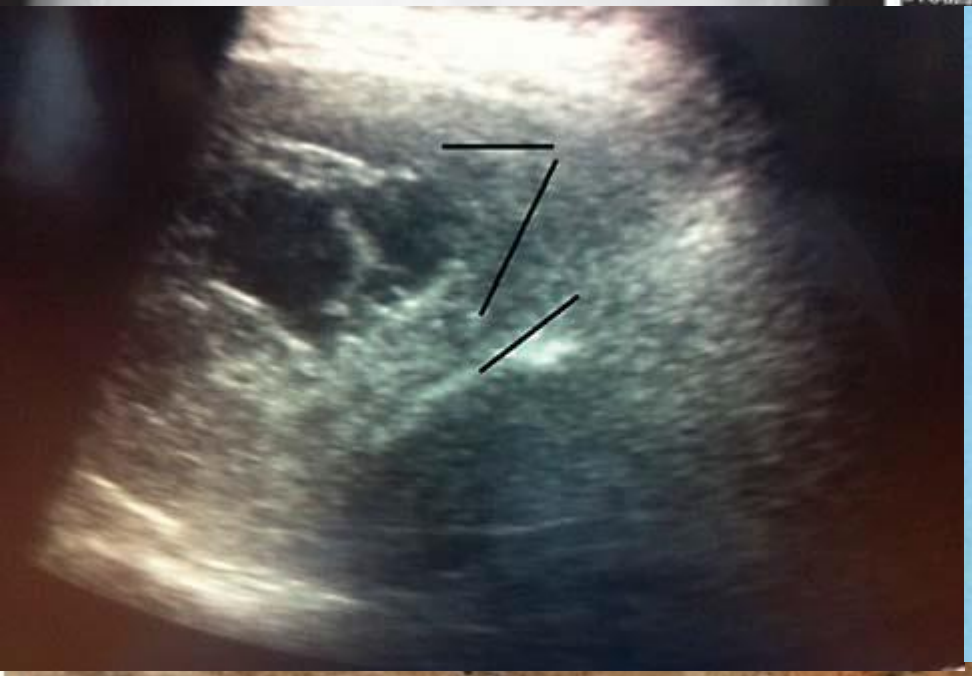
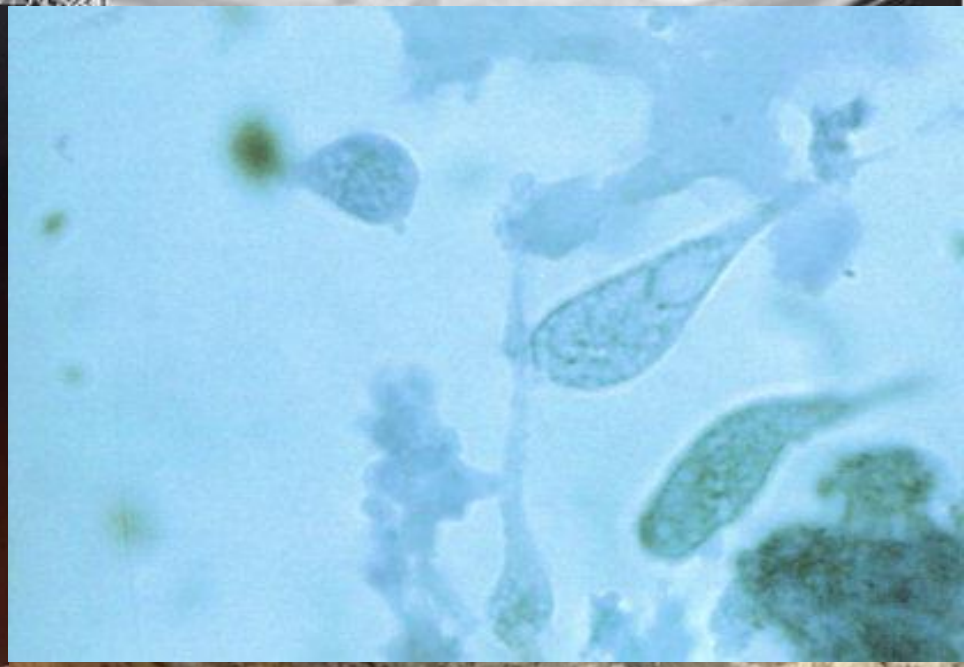




RA-pleural disease

- Pleural biopsy
  Persistent
  Sterile exudative effusion
  No classic cytology of RP
  No cholesterol effusion
  No pleural pressure of unexpandable lung

Exclude TB, malignancy, secure diagnosis RP

"gritty" appearance, numerous, small granules and nodules, similar changes in the visceral pleura

RA-ILD

- 10-50%
- UIP-type PF
- UIP pattern (HRCT): highly specific
- Surgical biopsy not necessary
- f-NSIP, DIP, COP+ CEP, LIP: biopsy may be necessary
- CPFE in smokers with RA
- No response to corticosteroids and immunosuppressants

RA-ILD

- Dyspnea, non-productive cough
- Insidious onset
- Dyspnea on exertion delayed due to exercise limitation
- PFTs

  restrictive

  abnormal DLCO

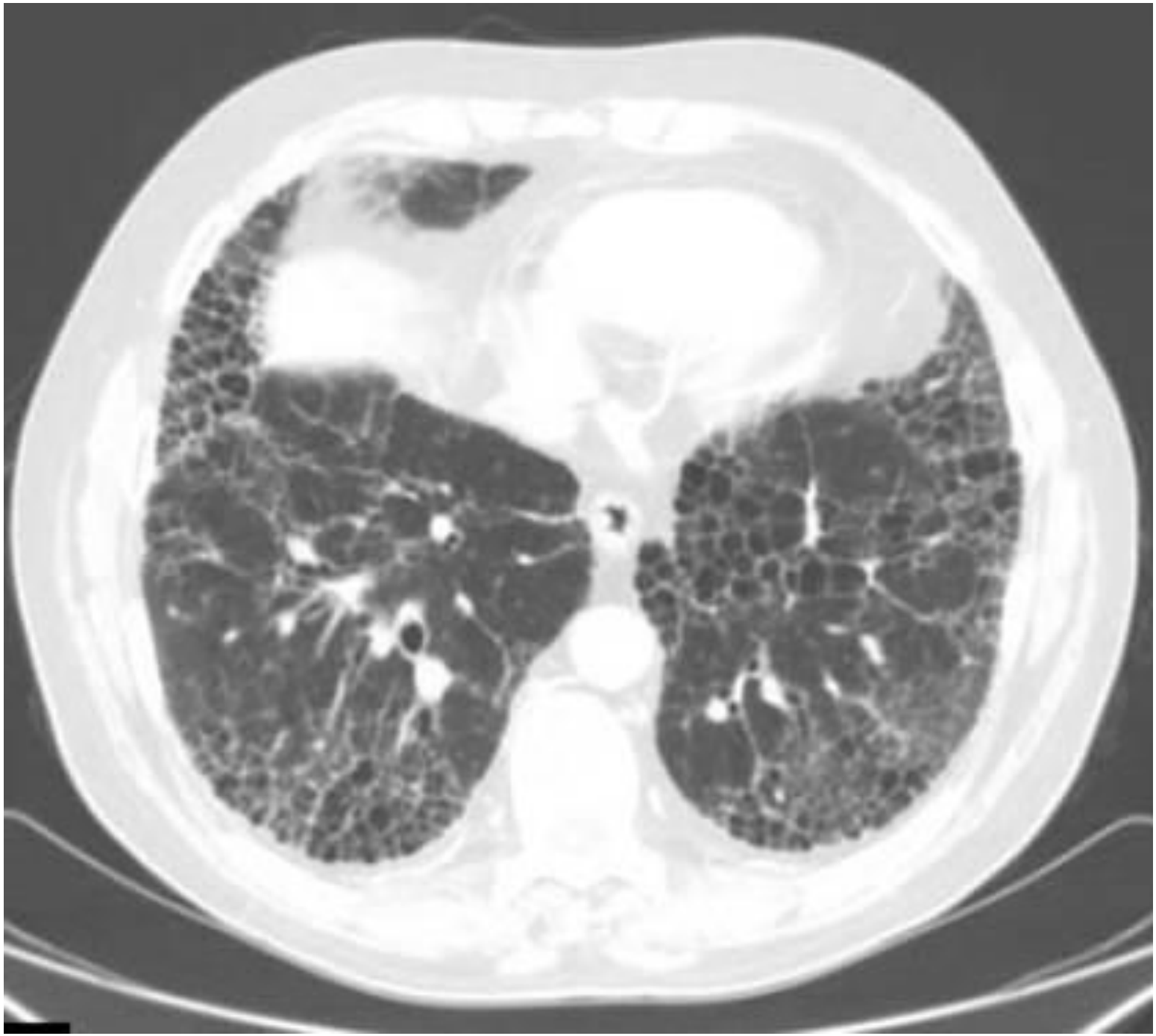
  desaturation 6MWT

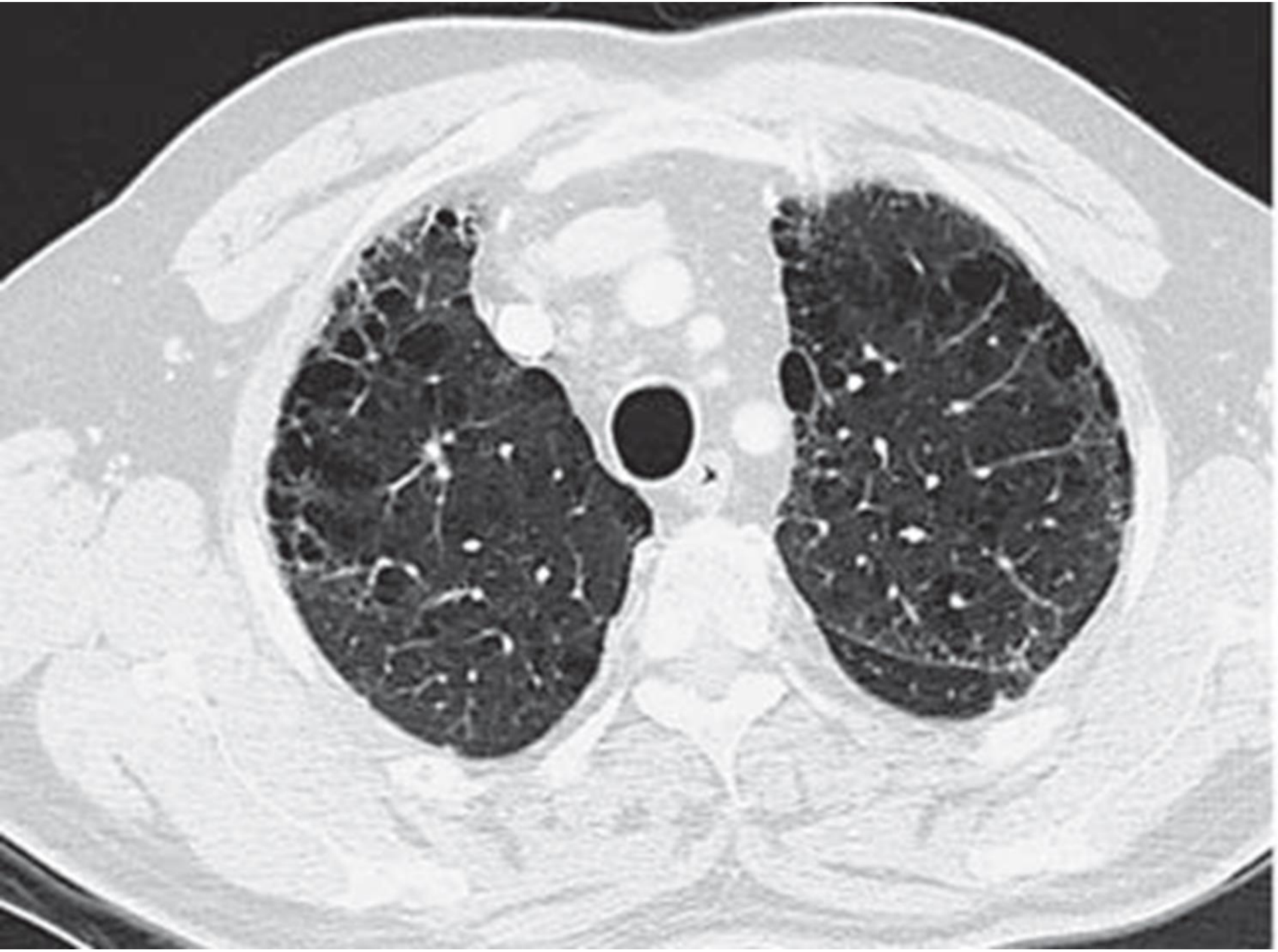
  restrictive pattern due to poor muscle strength kyphosis
- Severe RA, male, older, smoking, ACPA (subtypes)

Diagnosis of Idiopathic Pulmonary Fibrosis

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

UIP	Probable UIP
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO





Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis

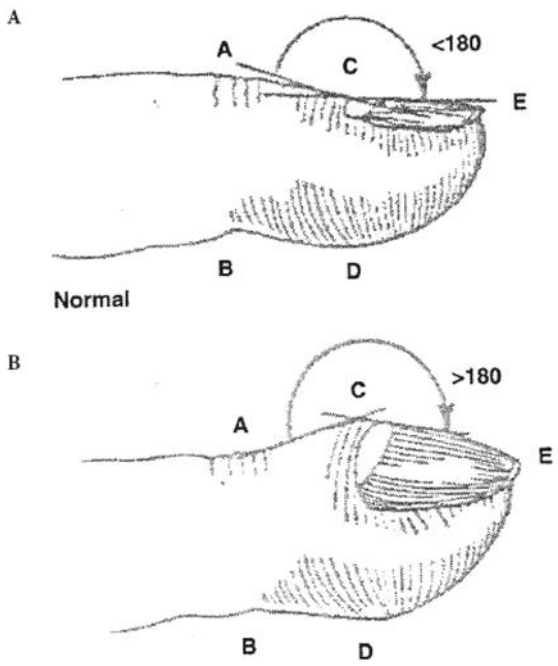
Pierre-Antoine Juge[1,2,51], Raphaël Borie[2,3,4,51], Caroline Kannengiesser[2,5,6,51], Steven Gazal[2,7,8], Patrick Revy[9,10], Lidwine Wemeau-Stervinou[11,12], Marie-Pierre Debray[2,13], Sébastien Ottaviani[1,2], Sylvain Marchand-Adam[14,15,16], Nadia Nathan[17,18,19], Gabriel Thabut[2,4,20], Christophe Richez[21,22,23], Hilario Nunes[24,25], Isabelle Callebaut[19,26], Aurélien Justet[2,3], Nicolas Leulliot[10,27], Amélie Bonnefond[12,28,29], David Salgado[30,31], Pascal Richette[2,32,33], Jean-Pierre Desvignes[30,31], Huguette Lioté[34], Philippe Froguel[12,28,35], Yannick Allanore[10,36,37], Olivier Sand[12,28,29], Claire Dromer[23,38], René-Marc Flipo[12,39], Annick Clément[17,18,19], Christophe Béroud[30,31,40], Jean Sibilia[41,42,43], Baptiste Coustet[1,2], Vincent Cottin[44,45], Marie-Christophe Boissier[25,46,47], Benoit Wallaert[11,12], Thierry Schaeverbeke[21,22,23], Florence Dastot le Moal[17,19,48], Aline Frazier[2,32], Christelle Ménard[17,18,19], Martin Soubrier[49], Nathalie Saidenberg[25,47], Dominique Valeyre[24,25], Serge Amselem[17,18,48], the FREX consortium[52], Catherine Boileau[2,5,50], Bruno Crestani[2,3,4] and Philippe Dieudé[1,2,6]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

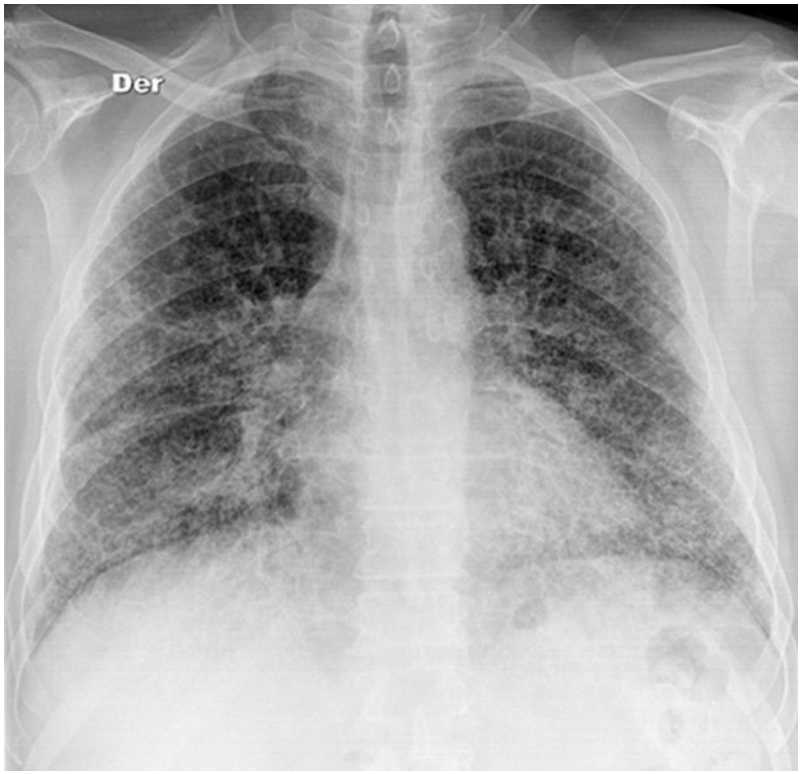
P.-A. Juge, J.S. Lee, E. Ebstein, H. Furukawa, E. Dobrinskikh, S. Gazal, C. Kannengiesser, S. Ottaviani, S. Oka, S. Tohma, N. Tsuchiya, J. Rojas-Serrano, M.I. González-Pérez, M. Mejía, I. Buendía-Roldán, R. Falfán-Valencia, E. Ambrocio-Ortiz, E. Manali, S.A. Papiris, T. Karageorgas, D. Boumpas, K. Antoniou, C.H.M. van Moorsel, J. van der Vis, Y.A. de Man, J.C. Grutters, Y. Wang, R. Borie, L. Wemeau-Stervinou, B. Wallaert, R.-M. Flipo, H. Nunes, D. Valeyre, N. Saidenberg-Kermanac'h, M.-C. Boissier, S. Marchand-Adam, A. Frazier, P. Richette, Y. Allanore, J. Sibilia, C. Dromer, C. Richez, T. Schaeverbeke, H. Lioté, G. Thabut, N. Nathan, S. Amselem, M. Soubrier, V. Cottin, A. Clément, K. Deane, A.D. Walts, T. Fingerlin, A. Fischer, J.H. Ryu, E.L. Matteson, T.B. Niewold, D. Assayag, A. Gross, P. Wolters, M.I. Schwarz, M. Holers, J. Solomon, T. Doyle, I.O. Rosas, C. Blauwendraat, M.A. Nalls, M.-P. Debray, C. Boileau, B. Crestani, D.A. Schwartz, and P. Dieudé



EDITORIAL

Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?

Vincent Cottin and Jean-François Cordier



RA-Upper Airway disease

- Upper airway obstruction

➢ Cricoarytenoid arthritis

➢ Rheumatoid nodules on the vocal cord

➢ Vasculitis of laryngeal or vagus nerves

RA-Airway disease

- Hoarse voice
- Dysphagia
- Odynophagia
- Tenderness of the throat
- Pain on coughing or speaking
- Exertional dyspnea or acute onset respiratory failure and stridor in unsuspected disease

Diagnosis

- Limitation of inspiratory flow volume loop
- HRCT

  sclerotic foci in arytenoid and cricoid cartilages, increased spacing between them due to effusion and subluxation of the joint
- Direct laryngoscopy

  exclude mass, vocal fold edema or nodules
- Rarely EMG

  differentiate nerve from joint disease

RA-Lower airway disease

- Bronchiolectasis-bronchiectasis
  30% of patients

(a) genetic predisposition
(b) follicular bronchiolitis
  dyspnea, fever-cough
  restrictive more common
  bilateral reticular or nodular opacities
  HRCT centrilobular or peribronchial micronodules (<3mm) and branching linear structures (bronchial dilation and thickening)
  high RF
(a) repetitive infections
(b) antirheumatic drugs (‘lung microbial flora modifying drugs’)

RA-airway disease

- Obliterative bronchiolitis

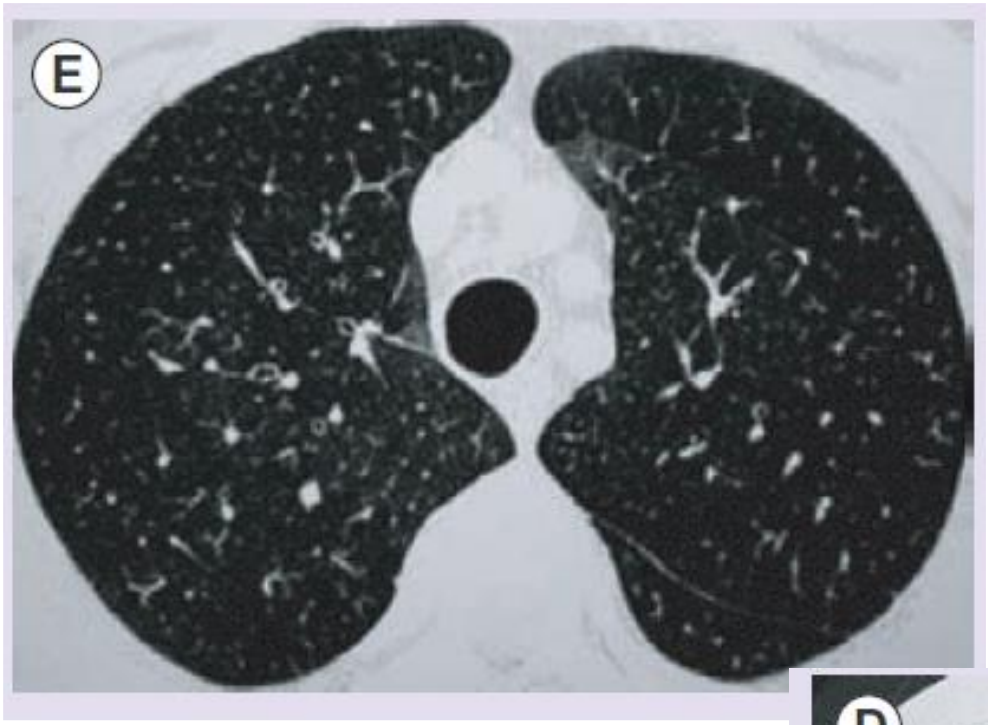
  rapid onset dyspnea and cough
  obstruction
  hypoxemia
  centrilobular emphysema
  mosaic pattern
  bronchiectasis
  young patients, women
  RF (+) or high, with no joint disease

RA-bronchiectasis

- Colonization by microbes
- MDR bacteria, atypical mycobacteria
- Therapeutic dilemmas
- Disease-modifying drugs predispose to severe lung infections
- Bronchiectasis adversely affects prognosis

RA-pulmonary necrobiotic nodules

- Characteristic and specific for RA
- Rare
- Both lungs, single or multiple, solid or cavitary, mm-cm
- Subpleural or in association with interlobular septa
- Sole DD malignancy
- PET-CT little or no uptake or (+)
- Hemoptysis-infection-rapture
- Persist, resolve or increase under treatment or spontaneously
- Caplan's syndrome occurs in association with pneumoconiosis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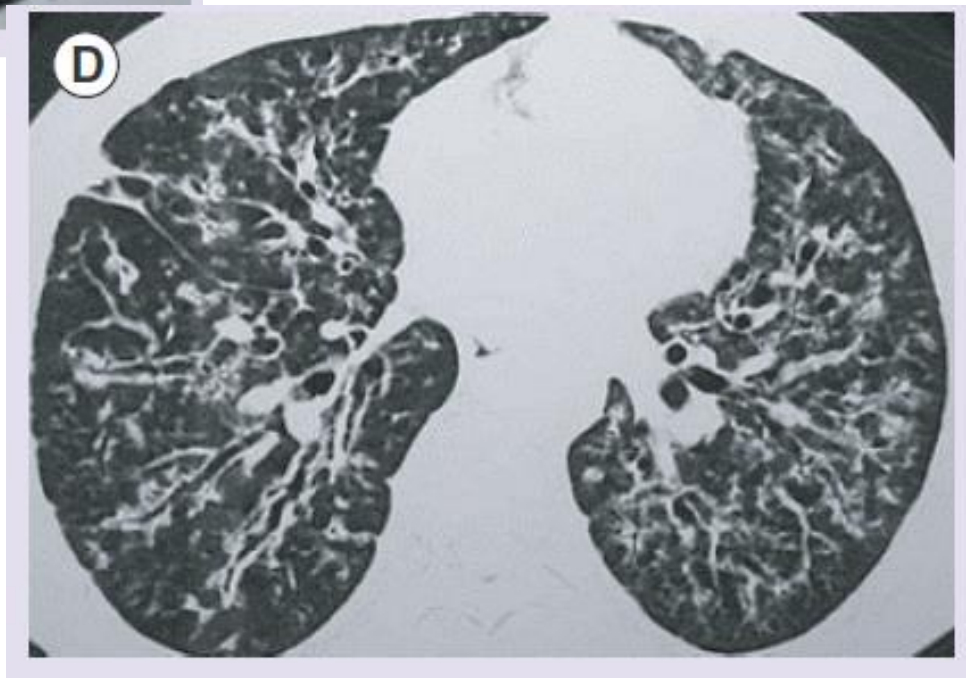
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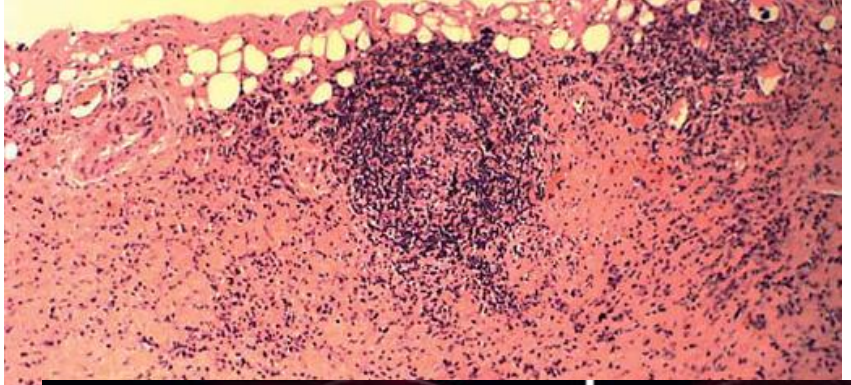

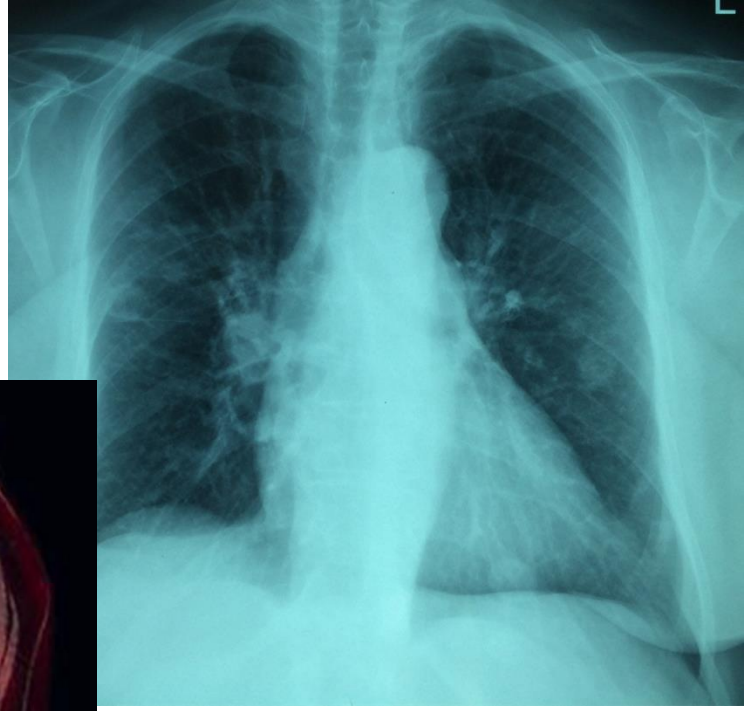

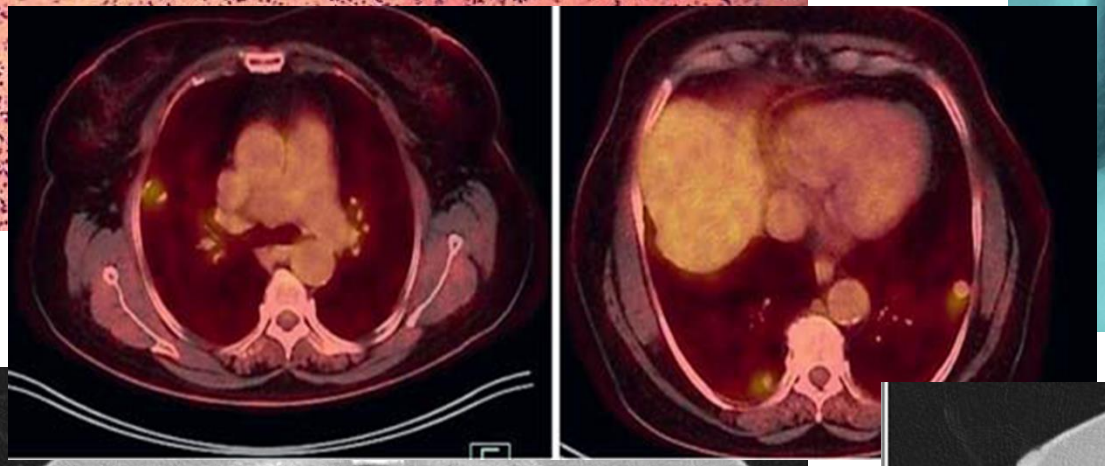

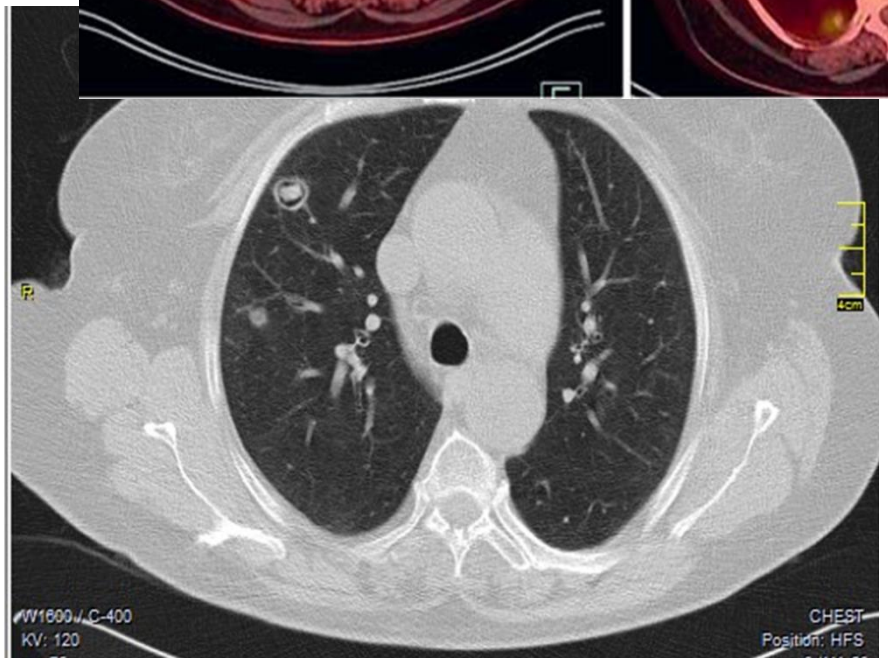
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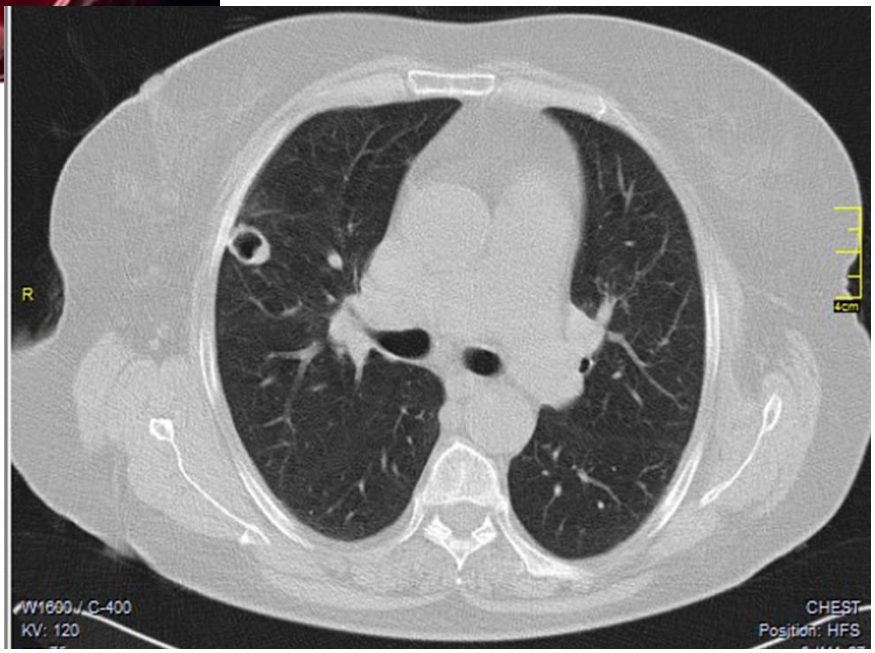
KV: 120
CHEST
Position: HFS


R
4cm
W1600/C-400
KV: 120
CHEST
Position: HFS

Pulmonary complications from drugs for rheumatoid arthritis

Pneumonitis
Anakinra
Azathioprine
Cyclophosphamide
Methotrexate"
Leflunomide
NSAID¶
Rituximab
TNF inhibitors$^{\Delta}$
Tocilizumab
Sulfasalazine
Chlorambucil
Gold"
d-Penicillamine
Fibrosis
Methotrexate
Gold
Cyclophosphamide
Chlorambucil
Azathioprine
Sulfasalazine
Obliterative bronchiolitis
d-Penicillamine
Gold
Sulfasalazine
Infection
TNF inhibitors$^{\Delta}$"
IL-1 inhibitors$^{\circ}$
Methotrexate"
Glucocorticoids"
Cyclophosphamide
Abatacept
Rituximab
Noncardiogenic pulmonary edema
Aspirin (high doses)
NSAID¶
Methotrexate
Cyclophosphamide
Colchicine (overdose)
Rituximab
Tocilizumab
Pulmonary renal syndrome
Pulmonary hemorrhage
d-Penicillamine
Drug-induced lupus
d-Penicillamine
TNF inhibitors$^{\Delta}$
Sulfasalazine
Bronchospasm
Aspirin
NSAID¶
Methotrexate
Air trapping
? Methotrexate

" Most common reactions reported.
¶ Nonsteroidal anti-inflammatory medications.
Δ Tumor necrosis factor modifying agents (infliximab, etanercept, adalimumab).
○ Interleukin-1 blocking agents (anakinra).

Systemic Sclerosis

- > 80%
- Poorer prognosis

- Limited cutaneous SS
  lungs 25%
  ACA (+) SS-PAH
  a subset ILD

- Diffuse cutaneous SS
  lungs 50%
  anti-Scl-70 (+) f-NSIP
  less UIP

SS-lung manifestations

- pulmonary thromboembolic disease
  (increased risk)
- pleural disease
- aspiration pneumonitis
  esophageal dysmotility and GERD
  fibrosis and worsening of ILD
- airways disease
- drug-induced pneumonitis
- lung cancer (especially in ILD)

Table 3. Respiratory manifestations in Systemic Sclerosis
Pleural disease
Pleural effusions
Pleural fibrosis
Pneumothorax
Airways involvement
Bronchiolitis
Bronchiolectasis - Bronchiectasis
Parenchymal involvement
Usual interstitial pneumonia
Non-specific interstitial pneumonia
Organizing pneumonia
Lymphocytic interstitial pneumonia
Desquamative interstitial pneumonia
CPFE
DAD-ARDS
Lung cancer
Aspiration pneumonia
Pulmonary vascular disease
Pulmonary arterial hypertension
Diffuse alveolar hemorrhage / Capillaritis
Vasculitis
Pulmonary thromboembolism - CTEPH
Other
Shrinking lung syndrome

SS-ILD

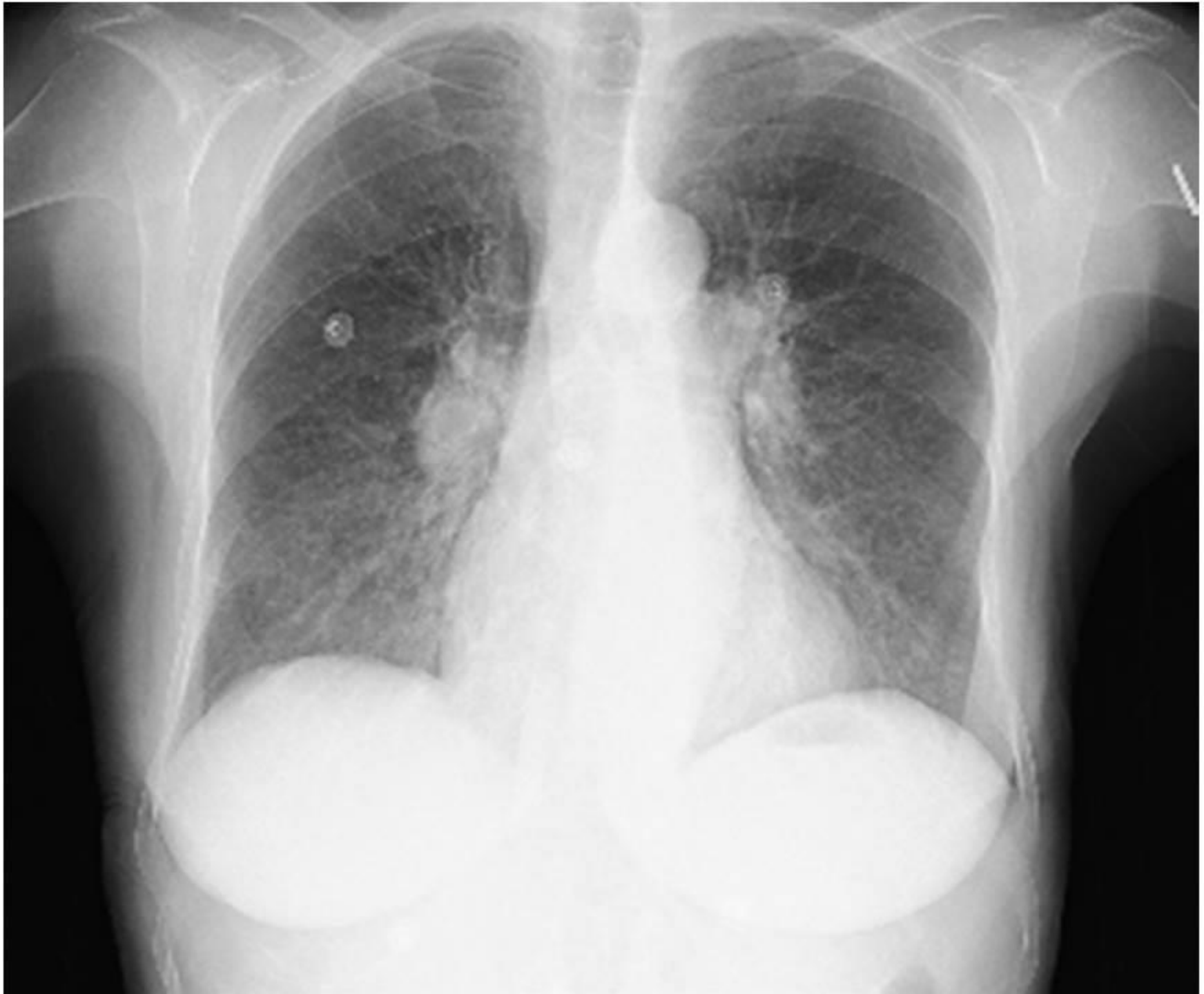
- At the time or soon after the diagnosis
  rarely precedes
- Evaluation for ILD and PH in new diagnosis
- Subacute dyspnea on exertion
  Nonproductive cough
- CPFE (smoking)
- Velcro sounds, digital clubbing (-)
- Restrictive pattern, low DLCO
  and desaturation 6MWT

SS-PAH

- 10-15%
- Mainly group 1 PAH
- Long-standing SSc at greatest risk

- Dyspnea on exertion
- Chest pain
- Near-syncope or syncope on exertion

- NT-PRO-BNP, BNP ⬆ - DLCO ⬇ with normal lung volumes
- PASP > 35-40 mmHg Doppler Echo= RHC
- FVC/DLCO % pred >1.6 = pulmonary hypertension



Subsequent monitoring

3-6 m	1 y	1-2 y	Every 2 years	HRCT
Symptoms and physical examination	PFTs 6MWT	NT-pro-BNP BNP Doppler Echo	• Long-standing SS > 5y with a normal DLCO • no dyspnea or exercise intolerance • unchanged PFTs > 3y	• new symptoms or signs develop • decline in lung volumes or DLCO

SLE-lung manifestations

Respiratory manifestations occur commonly in SLE, mainly infective pneumonias, pleural disease and pulmonary thromboembolism.

SLE-Pleural disease

- Up to 93% in autopsy studies
- Inflammation of the pleura with no effusion
- Pericarditis
- Chest pain, fever
- 50% bilateral
- Exudate, normal Glu and pH, lymphomononuclear cells

SLE-Pleural disease

- Rule out
  infection
  embolism
  malignancy
  heart failure

- Pleuritis and/or pleuropericarditis ensue before SLE diagnosis

- Pharmacologic lupus: pleuritis, histone antibodies

- Don't test for ANA, LE and complement in fluid

  - ANA, anti-ds-DNA, anti-SM, anti-RNP, anti-Ro/SSA, anti-La/SSB
    if diagnosis of SLE not firm

SLE-pulmonary infections

- Per se an SLE manifestation
- Major determinant of morbidity and mortality
- Bacterial, mycobacterial, viral, fungal
- Pre-existing lung damage + immunosuppression

opportunistic microbes and severe infections

SLE-pulmonary infections

Lupus "paradox"

severely impaired cellular and humoral immune responses to external agents

though they present B lymphocyte hyperactivity, high levels of gammaglobulins including high antibody titers against viruses and other pathogens and a high ability to attack self-tissues

SLE-pulmonary thromboembolism

- Lupus-associated antiphospholipid antibody syndrome
- Vascular thrombosis and/or pregnancy morbidity
- Lupus anticoagulant, anticardiolipin antibodies and anti-β2-glycoprotein I antibodies

- **One clinical and one laboratory criterion**

- Rule out PE
- CTEPH less than 5% of PTE pts
- Lupus-related PAH

- Catastrophic antiphospolipid syndrome < 1% of pts

SLE-PAH

- Pulmonary arterial hypertension

  (similar to idiopathic PAH)
- Severe symptomatic PH

  rare complication of SLE
- Pulmonary hypertension in a patient with a well-established diagnosis of SLE is likely to be due to SLE itself
- Consider other causes of secondary PH (advanced ILD, CTEPH, PVOD, LHF)

SLE-ILD

- Uncommon 3-9%
- In overlap autoimmune syndromes
- f-NSIP
- COP
- LIP
- exclude
  environmental causes of ILD
  drug toxicity
  heart failure
  infection

SLE-shrinking lung syndrome

- Lupus patient with worsening dyspnea, diaphragmatic elevations, episodes of pleuritic chest pain and clear lung fields

- Restrictive pattern

  Decreased DLCO

  Decreased maximal expiratory and inspiratory pressures

- Absence of pleural and parenchymal disease

diaphragmatic inflammatory myositis or myopathy and/or phrenic neuropathy, chronic pleural inflammation may impair deep inspiration and subsequently lead to parenchymal reorganization that impairs lung compliance

SLE-acute pneumonitis

- Lupus patient with fever and infiltrates
- Clinical presentation similar to acute interstitial pneumonia
- Tachypnea, tachycardia, inspiratory crackles, hypoxemia
- diffuse or patchy opacities- lower lung zones

DD INCLUDES infection, organizing pneumonia, pulmonary embolism, drug toxicity, diffuse alveolar hemorrhage, pulmonary infarcts

SLE-pulmonary-renal syndrome

Acute pulmonary capillaritis or bland pulmonary hemorrhage as DAH

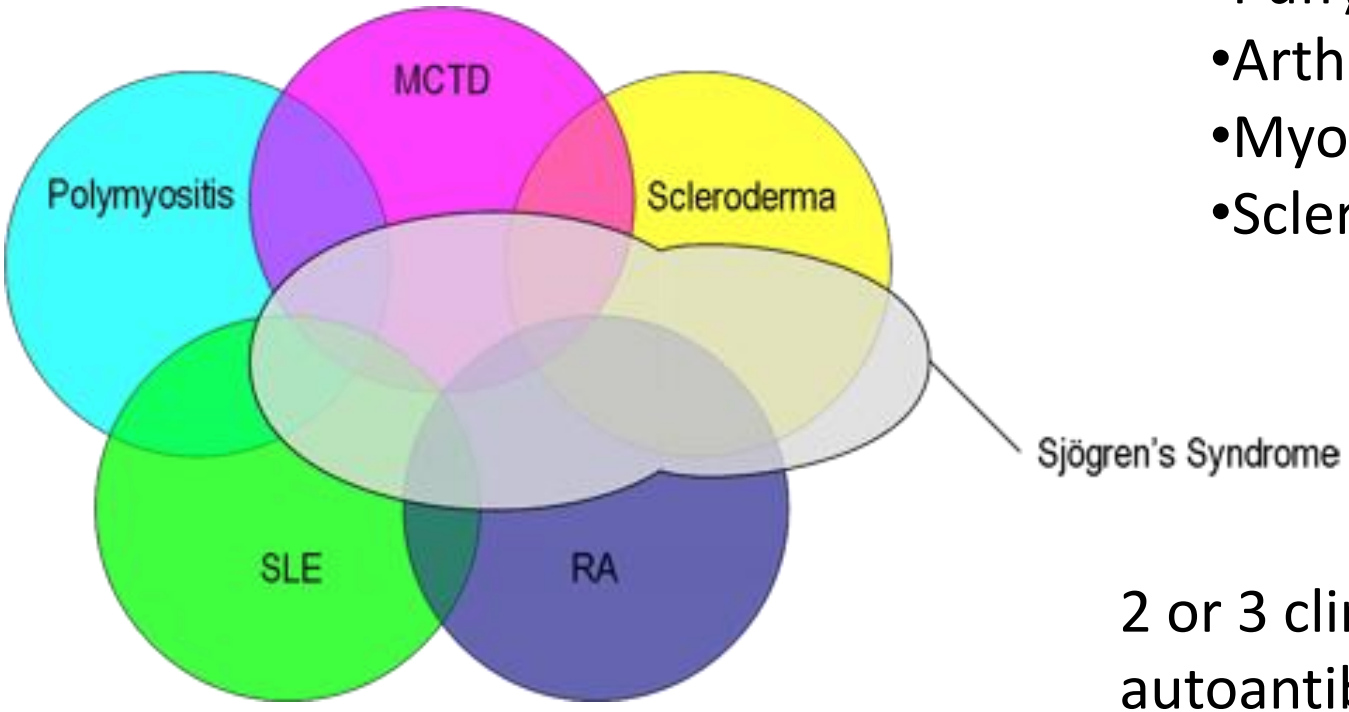
+

Rapidly progressing glomerulonephritis

- acutely ill with dyspnea, cough, hemoptysis, fever, anemia

- ❑ bilateral opacities
- ❑ anticardiolipin antibodies and anti-beta2-glycoprotein I, lupus anticoagulant test
- ❑ Hemorrhagic BAL

Mixed connective tissue disease



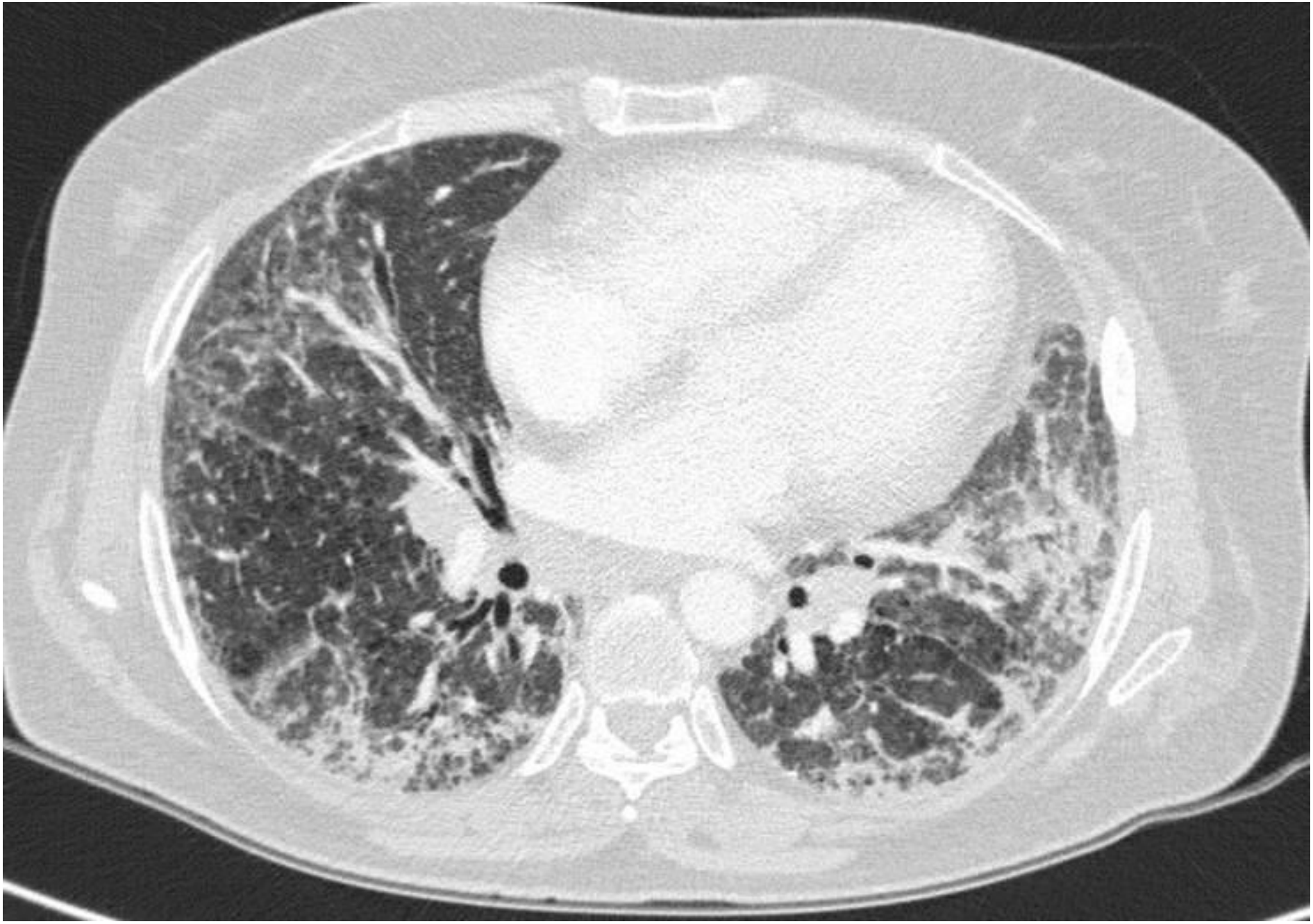
- Raynaud's
- Puffy hands
- Arthralgia-arthritis
- Myositis
- Sclerodactyly

2 or 3 clinical + autoantibodies (anti-U1-ribonucleoprotein)

Pulmonary manifestations common and pleomorphic

- f-NSIP
- Serositis
- PAH

Table 6. Main Respiratory manifestations of Mixed Connective Tissue Disease
Pleural disease
Pleural effusions
Pneumothorax
Airways involvement
Bronchiolitis
Parenchymal involvement
Non-specific interstitial pneumonia
Usual interstitial pneumonia
Lymphocytic interstitial pneumonia
Desquamative interstitial pneumonia
Organizing pneumonia
CPFE
DAD-ARDS
Aspiration pneumonia
Pulmonary vascular disease
Pulmonary arterial hypertension
Diffuse alveolar hemorrhage / Capillaritis
Vasculitis
Respiratory muscle dysfunction



Ankylosing spondylitis

- Axial skeleton and pelvic sarcoiliac joints
- RA (-) spondyloarthropathy
- more than 90% of Caucasians HLA-B27 antigen
- After longstanding disease pulmonary compromise due to restrictive changes

Ankylosing spondylitis

- Thoracic cage: chest wall restriction

- Parenchymal involvement: apical fibrobullous disease

  NSIP, UIP

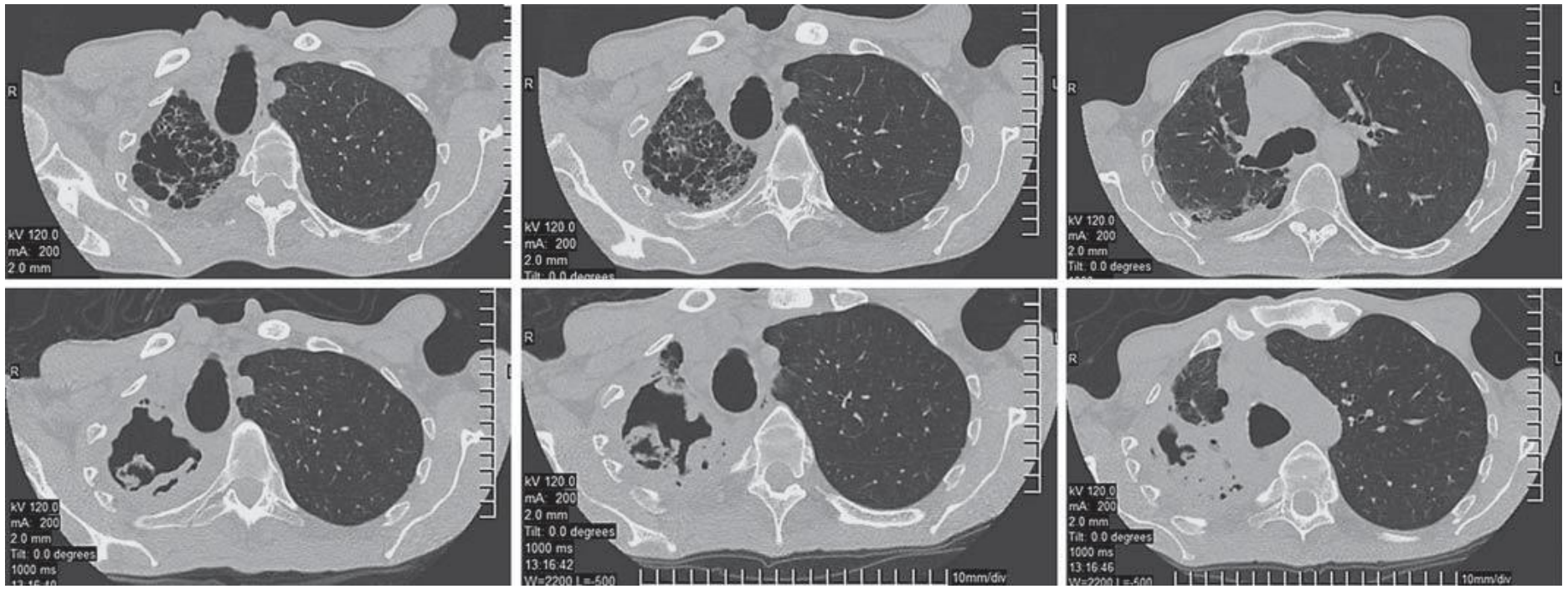
  disordered ventilation, perfusion of the upper lung segments

  altered upper lung mechanical stress

  recurrent upper lobe infections

  complicated by spontaneous pneumothorax and superinfection of cysts with fungi and mycobacteria

- Obstructive sleep apnea syndrome



fibrobullous involvement of the right upper lobe associated with pleural thickening and traction of the trachea
Aspergillus fumigatus later in the course of the disease

DM-PM

- 75% lung manifestations
- Overlap with other CTDs or cancer-associated
- PET mandatory
- 20% precedes diagnosis DM-PM

Table 4. Respiratory manifestations in Dermatomyositis/Polymyositis
Parenchymal involvement
Non-specific interstitial pneumonia
Usual interstitial pneumonia
Organizing pneumonia
DAD/ARDS
Acute interstitial pneumonia
Acute fibrinous and organizing pneumonia
Lymphocytic interstitial pneumonia
Diffuse alveolar hemorrhage
Chronic eosinophilic pneumonia
Aspiration pneumonia
Lung cancer
Pulmonary vascular disease
Pulmonary hypertension
Thoracic cage involvement
Myositis of the respiratory muscles
Other
Pneumomediastinum
Pneumothorax

ANTISYNTHETASE SYNDROME

coexistence of autoantibodies to aminoacyl-tRNA synthetases, highly specific for myositis, and

one or more of the following clinical features:

ILD, inflammatory myopathy, arthritis or arthralgias, Raynaud's phenomenon, mechanic's hands and fever

ANTISYNTHETASE SYNDROME

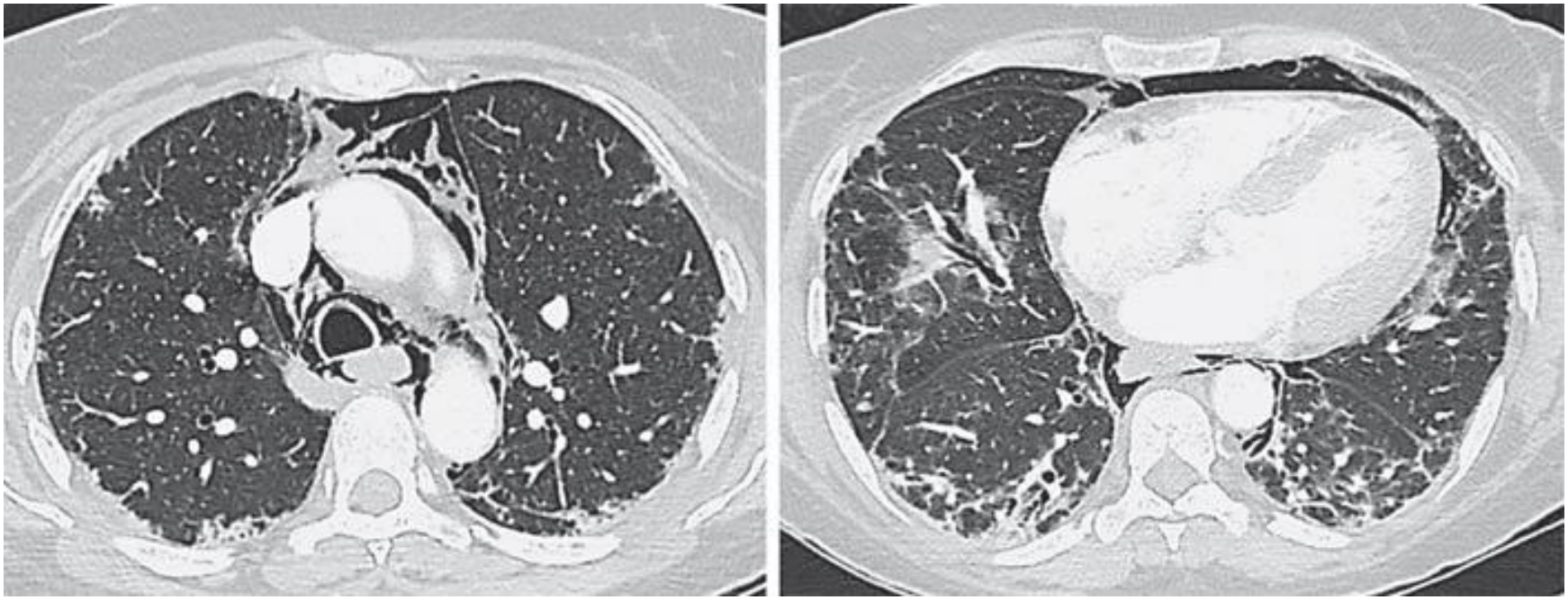
- Jo-1 which is encountered in 20–30% of DM-PM patients
- The PL-7, PL-12, EJ and OJ antibodies are encountered in less than 5%
- The KS, Zo and YRS antibodies in less than 1% of DM-PM patients

- Overall, ILD in AS is present in nearly 90% of cases, reaching even 100% in cases of anti-PL-7, anti-OK, anti- EJ or anti-Zo positivity

Amyopathic dermatomyositis (CADM)

Shares the same characteristics as DM (cutaneous manifestations) with minimal or absent muscle involvement

Complicated by ILD in up to 75% and associated with poor prognosis especially in cases of rapidly deteriorating ILD may in some patients be the first manifestation of lung involvement in DM (DAD upon normal or ILD lungs) allowing a 6-month survival in only 40% of patients



positivity for anti-melanoma differentiation-associated protein 5 antibodies

DM-PM and secondary lung complications

- Pulmonary hypertension
- Aspiration pneumonia
- Hypercapnic respiratory failure
- Carcinoma

DM-PM and serum biomarkers

- Anti-TNF-a
- IL-6
- IL-8
- IL-10
- Serum ferritin

Associated with the development of ILD

OR

Characterize a more severe ILD phenotype

Primary Sjögren's Syndrome

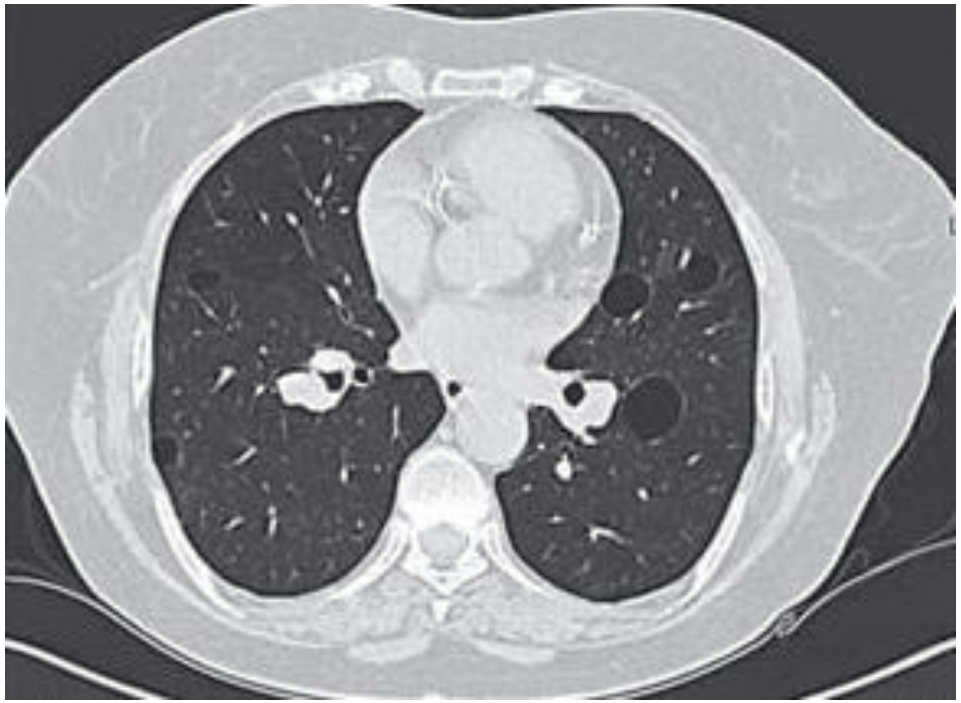
- Ro(SSA) and La(SSB) ribonucleoproteins and RF, and lymphocytic infiltration of the exocrine glands, mainly the ocular and salivary ones
- Lymphocytic infiltrations at the level of the submucosal tracheobronchial exocrine glands
- In 30% of patients in association with another CTD

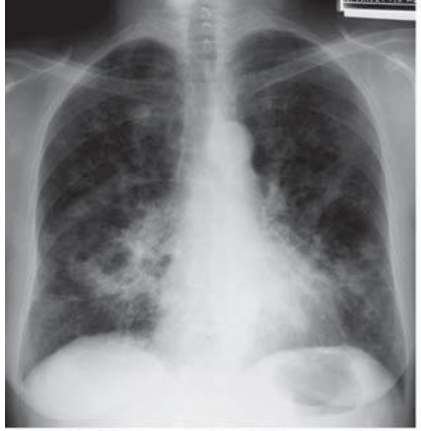
Table 5. Respiratory manifestations in Sjogren's Syndrome
Upper airways disease
Rhina sicca
Xerostomia
Lower airways disease
Xerotrachea - sicca cough
Lymphocytic bronchitis / bronchiolitis
Bronchial hyperresponsiveness
Lymphoproliferative disorders
Diffuse lymphoid hyperplasia of the lungs
Follicular bronchiolitis
Lymphoid interstitial pneumonia
Pseudolymphoma
Lymphomatoid granulomatosis
B cell non-Hodgkin's lymphoma (mainly extranodal marginal zone B cell lymphomas of the bronchus-associated lymphoid tissue)
High-grade malignant B cell non-Hodgkin's lymphoma
Other diffuse interstitial pneumonias
Nonspecific interstitial pneumonia
Usual interstitial pneumonia
Cryptogenic organizing pneumonia
Diffuse panbronchiolitis
Multiple lung cysts or bullae
Vasculitis and primary pulmonary hypertension
Pulmonary amyloidosis
Pleural disease (mainly in the secondary Sjogren's syndrome)

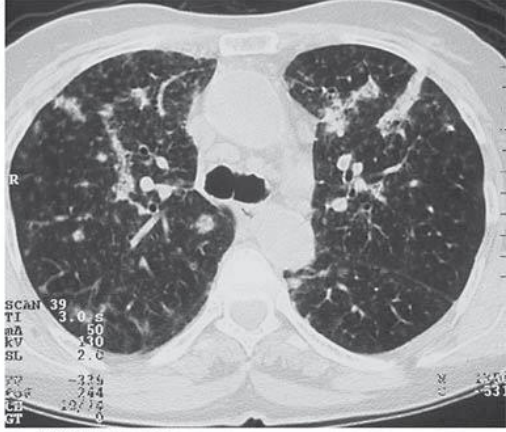
pSS – Airway manifestations

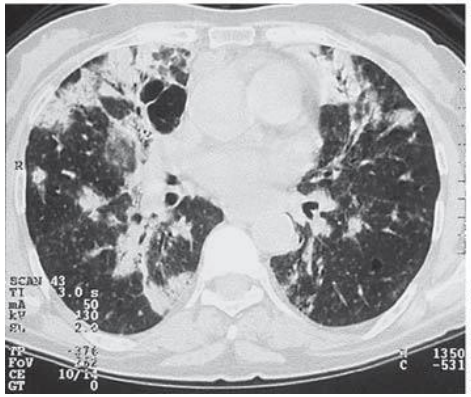
- ‘Rhina sicca’
- ‘xerostomia’
- ‘xerotrachea’
- ‘xerobronchitis’: lymphocytic bronchitis
- ‘sicca cough’ 50% of pts: lymphocytic bronchiolitis

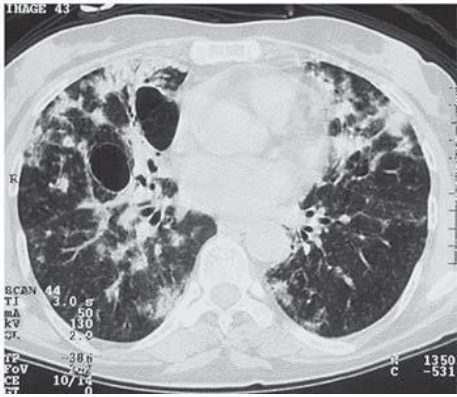
- hyperplasia of the BALT
  persistence of the unknown antigenic stimulation
  mild, degree of small airway obstruction
  occasional formation of a limited number of bullae

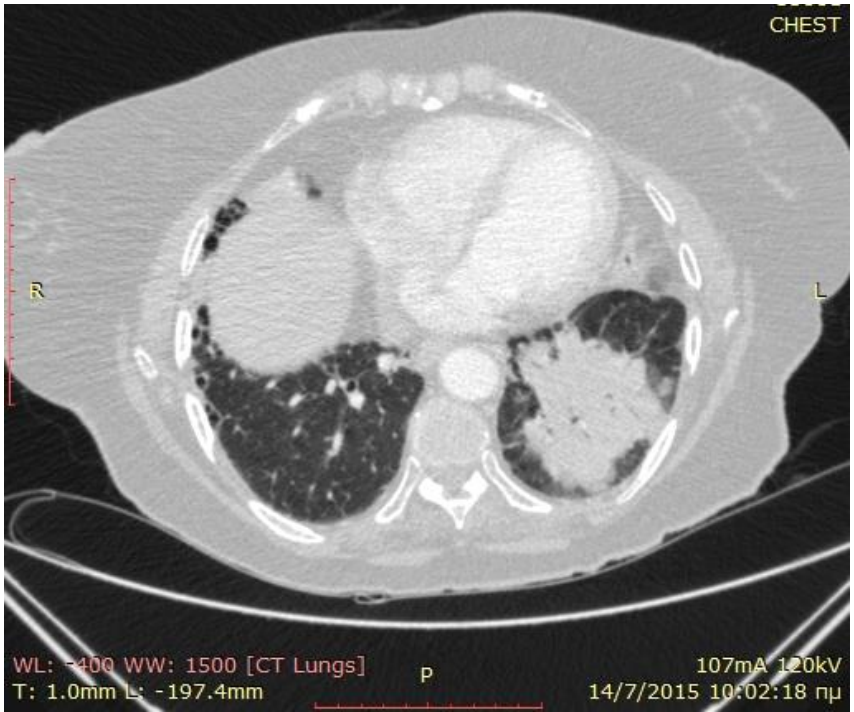








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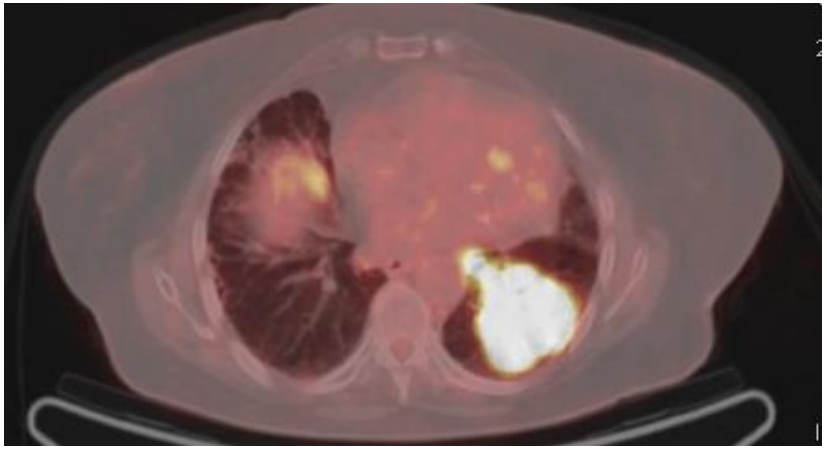

pSS-Lymphoproliferative Manifestations and interstitial disease

- from peribronchiolar BALT hyperplasia (follicular bronchiolitis) **TO**
- diffuse alveolar interstitial LIP characterized by the alveolar tissue infiltration of a polyclonal population of B lymphocytes **AND FINALLY**
- monoclonal B lymphocytic population (marginal zone B-cell non-Hodgkin's lymphoma or more aggressive)
- F-NSIP mainly, UIP, COP, lung amyloidosis
- coexistence of a second CTD not yet fulfilling diagnostic criteria

Conclusions

- CTD diagnosis requires the fulfilment of clearly defined clinical and laboratory criteria including in most cases positivity for autoantibodies
- Lung disease has become a major cause of morbidity and mortality of patients with CTDs
- “Vicious” combination of lung involvement, lung drug toxicity and lung infections
- Exertional dyspnea, cough, hemoptysis, chest pain, fever, syncope, systemic symptoms
- Velcro sounds, finger clubbing
- PFTs, HRCT, Doppler Echo, BNP, RHC
- Bronchoscopy: exclude infection and secure PAH

Table 1. Immunofluorescence nuclear pattern, specific nuclear antigens and nonantinuclear autoantibodies in CTDs and their relation with pulmonary involvement

	RA	SLE	Scleroderma	DM-PM	Sjögren's syndrome	MCTD
Immunofluorescence nuclear pattern						
Homogeneous		+				
Speckled		+	+	+	+	+
Peripheral		+	+			
Nucleolar			+	+		
Specific nuclear antigens targeted in CTDs						
dsDNA		+				
ssDNA		+				
Histones		+				
Sm		+				
U1-RNP		+	+ (PH)			
U3-RNP			+ (ILD, PH)			
U11-RNP			+ (ILD)			
U12-RNP			+ (ILD)			
rRNP		+				
RNP	+	+	+			+
SSA/Ro		+ (ILD)		+ (ILD)	+	
SSB/La		+			+	
Ku		+	+	+ (PH)		
Ki		+				
Scl-70			+ (ILD)			
CENP A-E			+ (PH)			
Th/To			+ (ILD, PH)			
RNA-pol-1			+			
RNA-pol-2			+			
RNA-pol-3			+			
Jo-1 (cytoplasmic)				+ (ILD)		
EJ (cytoplasmic)				+ (ILD)		
OJ (cytoplasmic)				+ (ILD)		
PL-7 (cytoplasmic)				+ (ILD)		
PL-12 (cytoplasmic)				+ (ILD)		
KS (cytoplasmic)				+ (ILD)		
Zo (cytoplasmic)				+ (ILD)		
YRS (cytoplasmic)				+ (ILD)		
Mi-2 (cytoplasmic)				+		
SRP				+		
CADM-140 (MDA5)				+ (AIP)		
PM-Scl			+	+		
Non-ANA autoantibodies						
ANCA						
RF	+					
ACPA	+ (↑ILD)					

Table 1. Acute respiratory events in CTDs

Manifestation	RA	SLE	SSc	DM-PM	pSS	MCTD	AS
ILD 'acute exacerbation'	+	–	+	++	–	?	–
OP	+	+	+	++	–	+	–
AFOP	±	±	±	±	–	–	–
DAH	±	+	±	±	–	–	–
Venous thromboembolism	±	++	–	–	–	±	–
Catastrophic APS	–	+	–	–	–	–	–
Bronchiectasis exacerbation	++	–	–	–	±	–	–
PNX-pneumomediastinum	±	–	–	+	±	–	±
Aspiration pneumonia	–	–	++	++	–	±	–
Hypercapnic respiratory failure	–	±	–	++	–	–	–
Pericarditis	±	++	±	±	±	±	–
Pulmonary infections	+	+++	+	+	+	+	+
Drug toxicity	++	+++	++	++	+	++	+

SSc = Scleroderma; pSS = primary Sjögren's syndrome; MCTD = mixed CTD; AS = ankylosing spondylitis; APS = antiphospholipid syndrome; PNX = pneumothorax.