Pulmonary Involvement in the Rheumatic Diseases: A Review

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Financial disclosures

- Up to Date (section editor, and writer)
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Summary Slide

- ILD associated with CTD (Connective tissue disease) can have a mortality that rivals IPF
- Risk factors for ILD in different CTDs are identifiable
- Inflammatory disease can be treated with anti-inflammatory agent and data suggests that fibrotic disease may be amenable to treatments employed in IPF
- Early identification of those at risk and frequent monitoring is important to assess for progression of disease and a missed opportunity for treatment, clinical trials and if needed lung transplant.

Outline

- Overview of CTD and ILD
- Rheumatoid arthritis: risk factors for ILD , other lung manifestations in RA and recent trial results.
- Scleroderma: risk factors for ILD recent clinical trials
- Inflammatory myositis: risk factors for ILD and treatment options
- Interstitial pneumonia with autoimmune features (IPAF)
- Sjogrens and ANCA related ILD (Briefly)
- Screening and treatment strategies in CTD-ILD

Clinical scenarios you will be asked to comment on:

- Patient presents with ILD, does this patient have a CTD?
- Patient with known CTD now with ILD and declining what to do?
- Patient you meet with CTD and you are wondering or asked , “ do they have ILD or are they are at higher risk for it”

Antibodies and clinical correlation

- ANA: SLE, SS, Sjogrens, viral, bacterial infection, hepatitis, false + common
- Centromere: limited scleroderma, less likely ILD, more likely PAH
- **Ro**:Sjogrens disease (50%),discoid lupus, scleroderma like syndromes, antisynthetase syndrome (ASSD)
- **Scl-70:** diffuse scleroderma but seen only in 20% SSc : **higher risk of ILD**
- **RNP;** can have different diseases, often akin to scleroderma or myositis, **high risk of ILD and PAH**
- **Ds DNA**: seen in SLE and may correlate with renal disease: we have seen false + in low titer, **rarely correlates with ILD**
- Many other ab : antisynthetase (Jo-1, pl-12 pl-7) , MDA 5 , Th/To U3 RNP. Major clinical feature with these is ILD. Cytoplasmic staining (seen in ASSD)

The value of the myositis panel in ILD assessment

MYOSITIS PANEL				Other Antibodies	
Myositis-Specific		Myositis-Associated			
Anti-Synthetases					
JO-1	NEG	PM-SCL	NEG	P155/140	NA
PL-7	NEG	KU	NEG	RNA POL	NA
PL-12	NEG	U1RNP	NEG	TH/TO	NA
EJ	NEG	U2RNP	NEG	U3RNP	NA
OJ	NEG	RO60	IND	MJ	NA
				MDA5	NA
MI-2	NEG				
SRP	NEG			OTHER ANALYTES	NA

Significance of each type is actually important ie correlation with phenotype (Robbins A et al Front Immuno 2019)

	Antibody profiles									
	Ro52 + Ro60- (*n* = 172)			Ro52 + Ro60 + (*n* = 130)			Ro52 - Ro60 + (*n* = 97)			
	n	% in the disease group	% in the Ab group	*n*	% in the disease group	% in the Ab group	*n*	% in the disease group	% in the Ab group	*p**
Auto-Immune diseases (*n* = 316)	**109**	**34.5**	**63.4**	**121**	**38.3**	**93**	**86**	**27.2**	**88.7**	$<10^{-4}$
Systemic Lupus (*n* = 122)	21	17.2	12.2	54	44.3	41.5	47	38.5	48.5	$<10^{-4}$
Sjögren disease (*n* = 76)	12	15.8	7.0	51	67.1	39.2	13	17.1	13.4	$<10^{-4}$
Systemic sclerosis (*n* = 12)	7	58.3	4.1	3	25.0	2.3	2	16.7	2.1	0.6
Inflammatory myositis (*n* = 18)	13	72.2	7.6	1	5.6	0.8	4	22.2	4.1	**0.01**
Inflammatory Rhumatism (*n* = 36)	22	61.1	12.8	4	11.1	3.1	10	27.8	10.3	0.01
Other auto-immune diseases (*n* = 52)	34	65.4	19.8	8	15.4	6.2	10	19.2	10.3	**0.01**
Malignancies (*n* = 17)	**12**	**70.6**	**7.0**	**3**	**17.6**	**2.3**	**2**	**11.8**	**2.1**	0.08
Infectious diseases (*n* = 15)	**11**	**73.3**	**6.4**	**3**	**20.0**	**2.3**	**1**	**6.7**	**1.0**	0.06
Other (*n* = 38)	**31**	**81.6**	**18.0**	**1**	**2.6**	**0.8**	**6**	**15.8**	**6.2**	$<10^{-4}$
Not classified (*n* = 13)	**9**	**69.2**	**5.2**	**2**	**15.4**	**1.5**	**2**	**15.4**	**2.0**	0.3

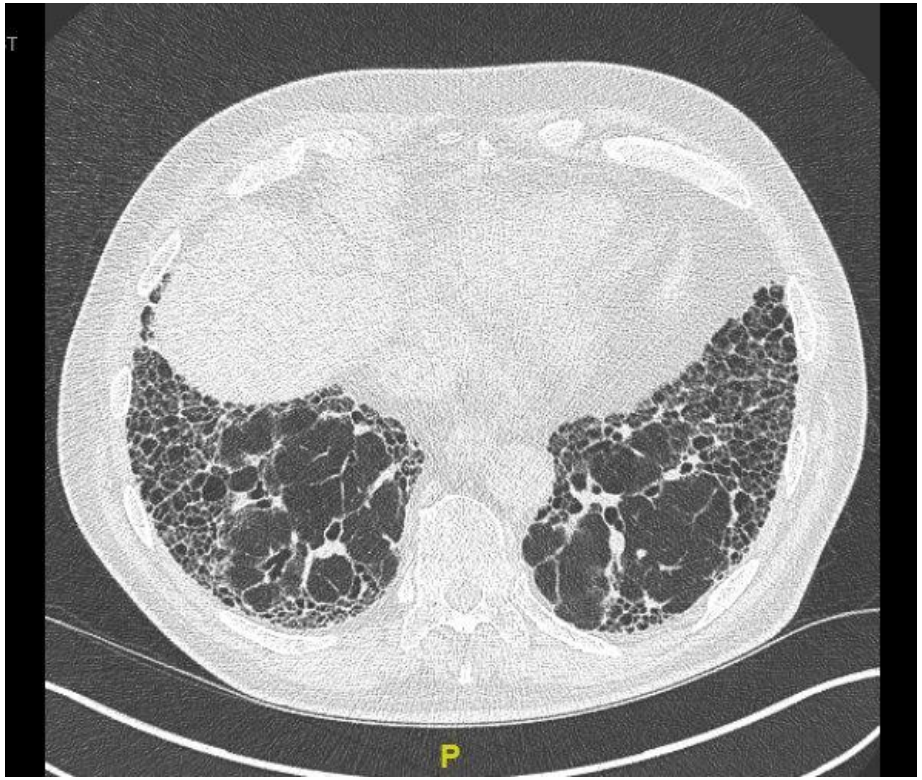
**Global p-value for comparison of each disease between each group. Ab, antibody. Results are presented as the number of patients in each category (percent of subjects in the antibodies group; percent of subjects with the clinical manifestation). For example, 21 subjects with systemic lupus were Ro52+Ro60- which represents 12.2% (21/172) of the Ro52+Ro60- patients and 17.2% (21/122) of the patients with systemic lupus. "Other" diseases were non-auto-immune, non-malignant and non-infectious diseases.*
Patients "not classified" were patients for whom no diagnosis was established; either because of missing data or because the referring physician did not conclude at last follow-up. Qualitative data were compared with chi square test or, when not possible, the Fischer exact test.
The bold values in the table represent the main diseases group.

	Ro52+Ro60- vs. Ro52+Ro60+	Ro52+Ro60- vs. Ro52-Ro60+	Ro52+Ro60+ vs. Ro52-Ro60+
OR [CI 95%], *p*			
Systemic lupus	**0.2 [0.1–0.3], $<10^{-4}$**	**0.1 [0.08–0.3], $<10^{-4}$**	0.8 [0.4–1.3], 0.3
Primary Sjögren syndrome	**0.1 [0.06–0.2], $<10^{-4}$**	0.5 [0.2–1.1], 0.09	**4.2 [2.1–8.3], $<10^{-4}$**
Systemic Sclerosis	1.8 [0.5–7.1], 0.4	2.0 [0.4–9.9], 0.3	1.1 [0.2–6.8], 0.9
Inflammatory myositis	**10.5 [1.4–81.7], 0.02**	1.9 [0.6–6.0], 0.3	0.2 [0.0–1.6], 0.1
Inflammatory rheumatism	**4.6 [1.6–13.8] 0.006**	1.3 [0.6–2.8], 0.5	**0.3 [0.1–0.9], 0.03**

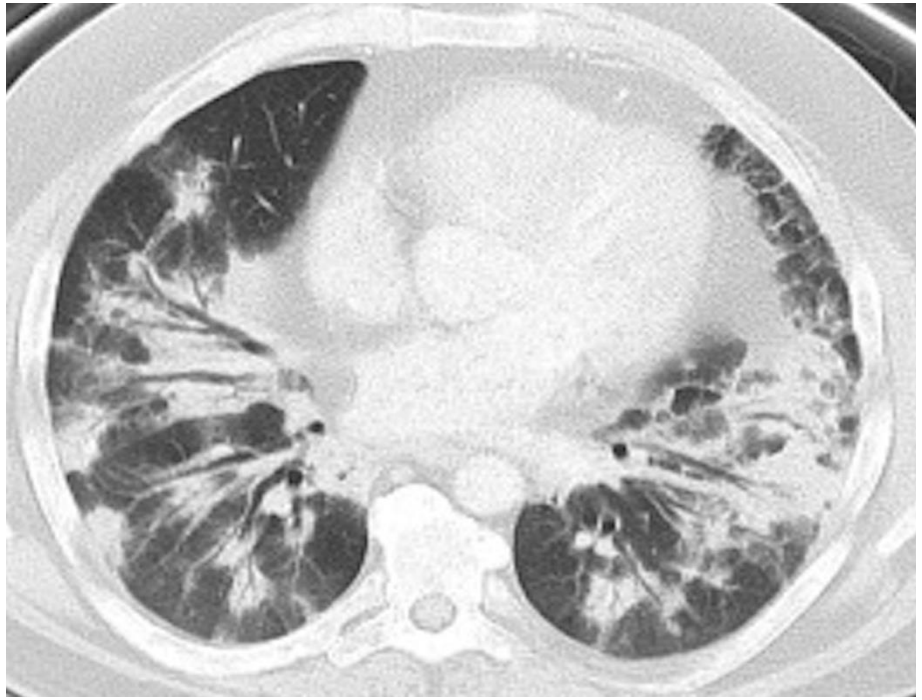
Results are presented as odds ratio with their 95% confidence interval, p-value. Qualitative data were compared with Fisher exact test. The bold values in the table represent the significant ones

CT as a guide to prognosis: Fibrotic phenotypes including UIP clearly has the highest mortality

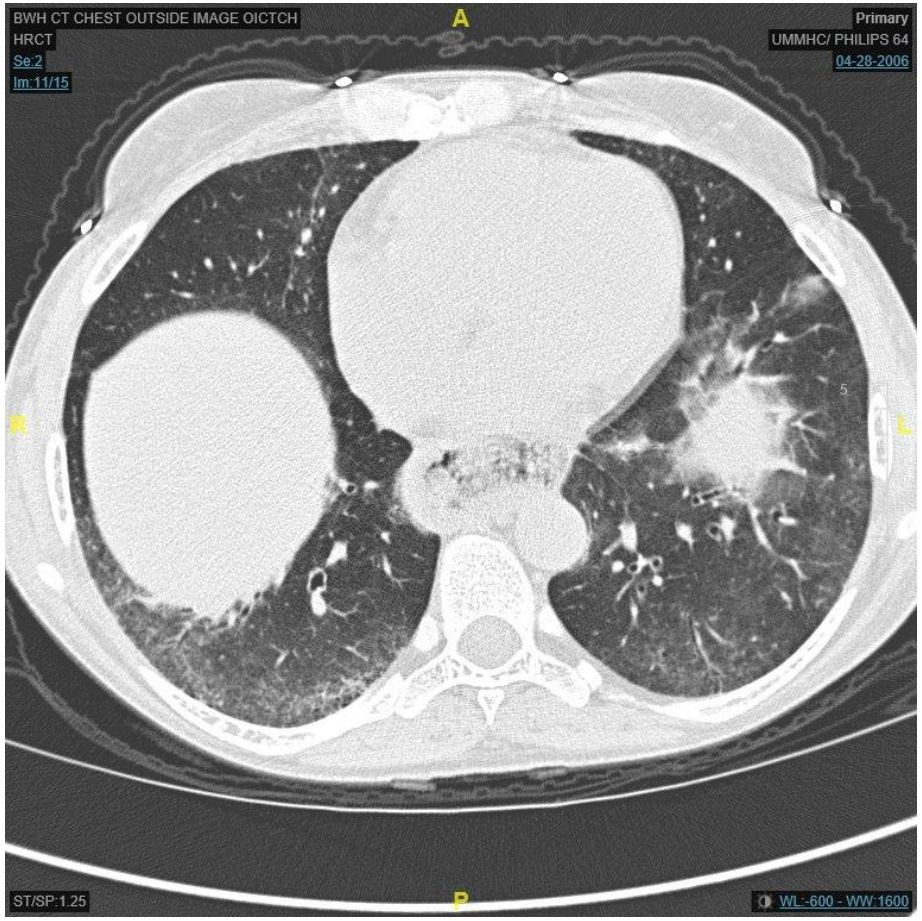
Honeycombing and traction bronchiectasis c/w UIP(specifc but not sensitive): seen in IPF and ILD-CTD and in 60% of RA-ILD, rarely in ANCA+



Consolidation and GGO most c/w inflammatory disease (like in antisynthetase syndrome or OP/NSIP in CTD)



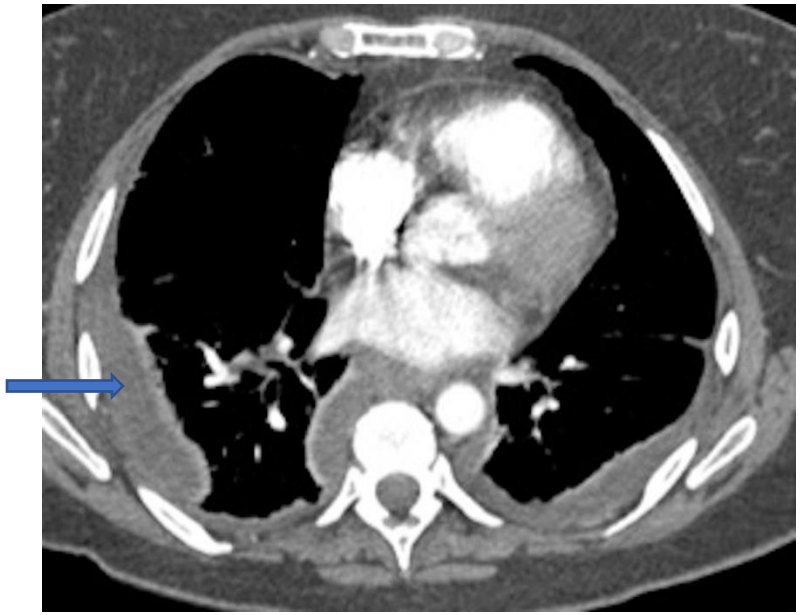
Non specific interstitial pneumonia (typically like in SSc)

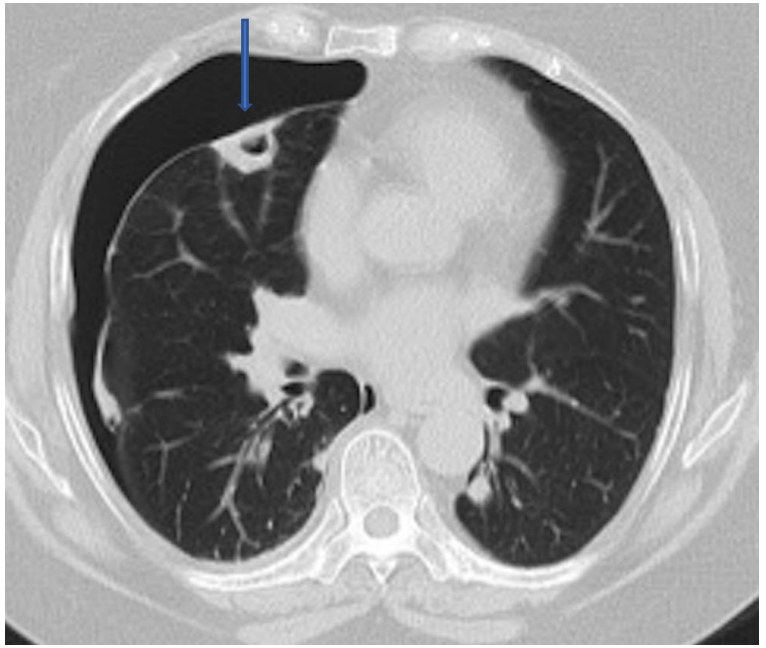


Rheumatoid Arthritis and the Lung: classic ILD CTD with multicompartmental disease

- ***Clinically significant interstitial lung disease occurs in 5-10% (UIP, NSIP, LIP).***
- Airway: Obstructive bronchiolitis (poor), Follicular bronchiolitis (better prognosis)
- Cryptogenic organizing pneumonia(better prognosis)
- Pleural effusion/sterile empyema
- Emphysema**
- Bronchiectasis
- Nodulosis
- Upper airway obstruction
- Methotrexate and other drug toxicity (.3%)

A word about Pleural disease and Rheumatoid nodules



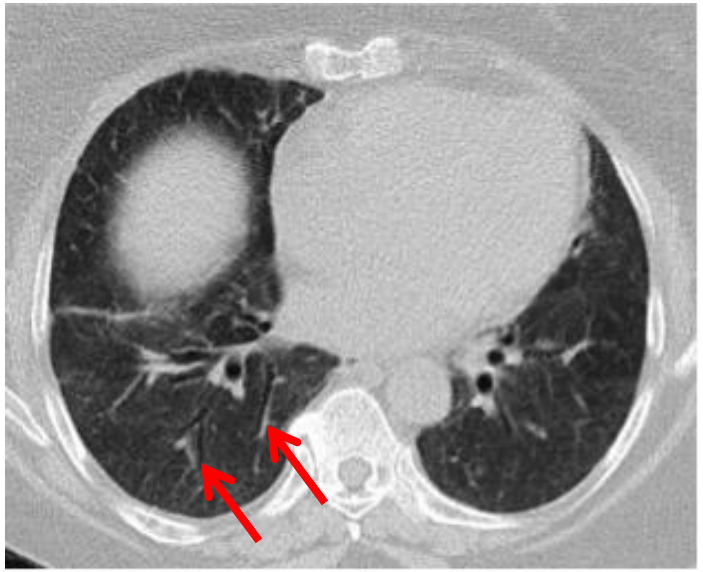


Just a word on Airway Disease in RA

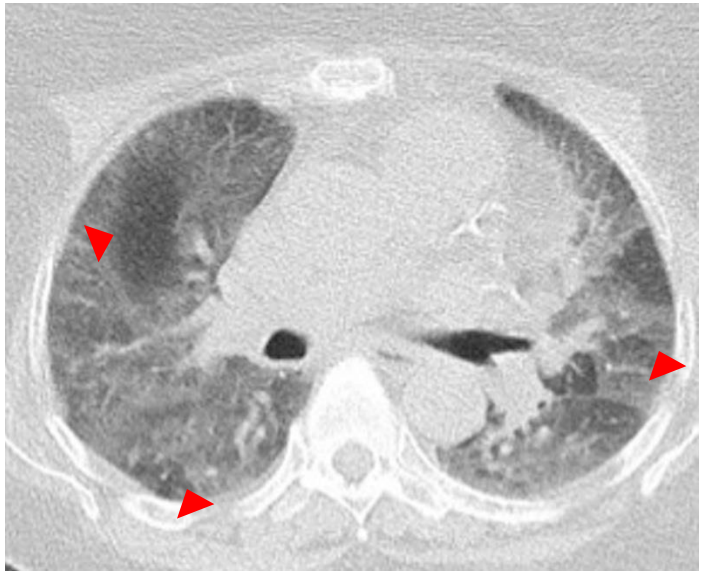
- Airway disease with predominantly obstruction on PFTs (FEV1<70%, ratio FEV1/FVC<) is not uncommon
- May mimic asthma
- mosaicism or air trapping on CT is common
- Some types of bronchiolitis are potentially treatable (like follicular bronchiolitis) though OB (obliterative bronchiolitis) is often not treatable and requires referral for transplant.
- Emphysema is common in RA, many of our pts smoke or did smoke, which can complicate attempts at treatment and clinical trials

Airway thickening Panel A
Air trapping on expiratory views

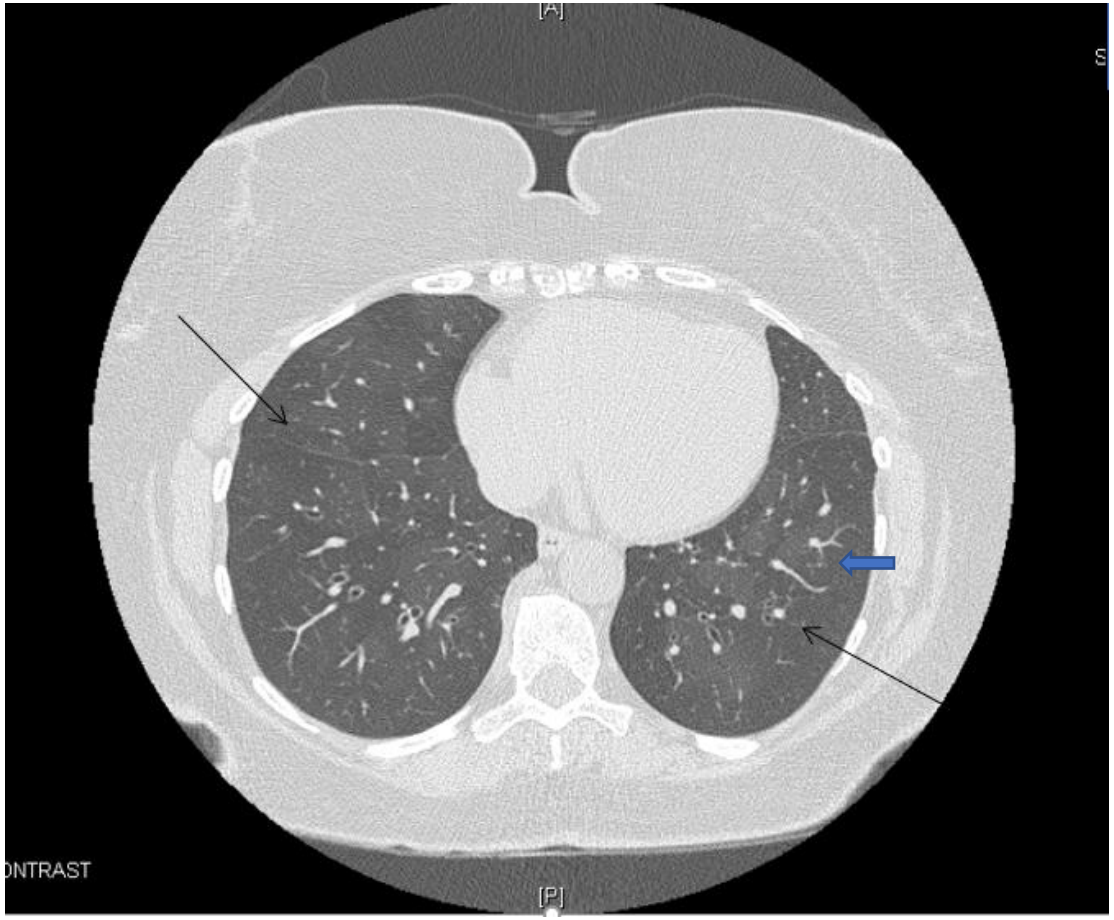
A

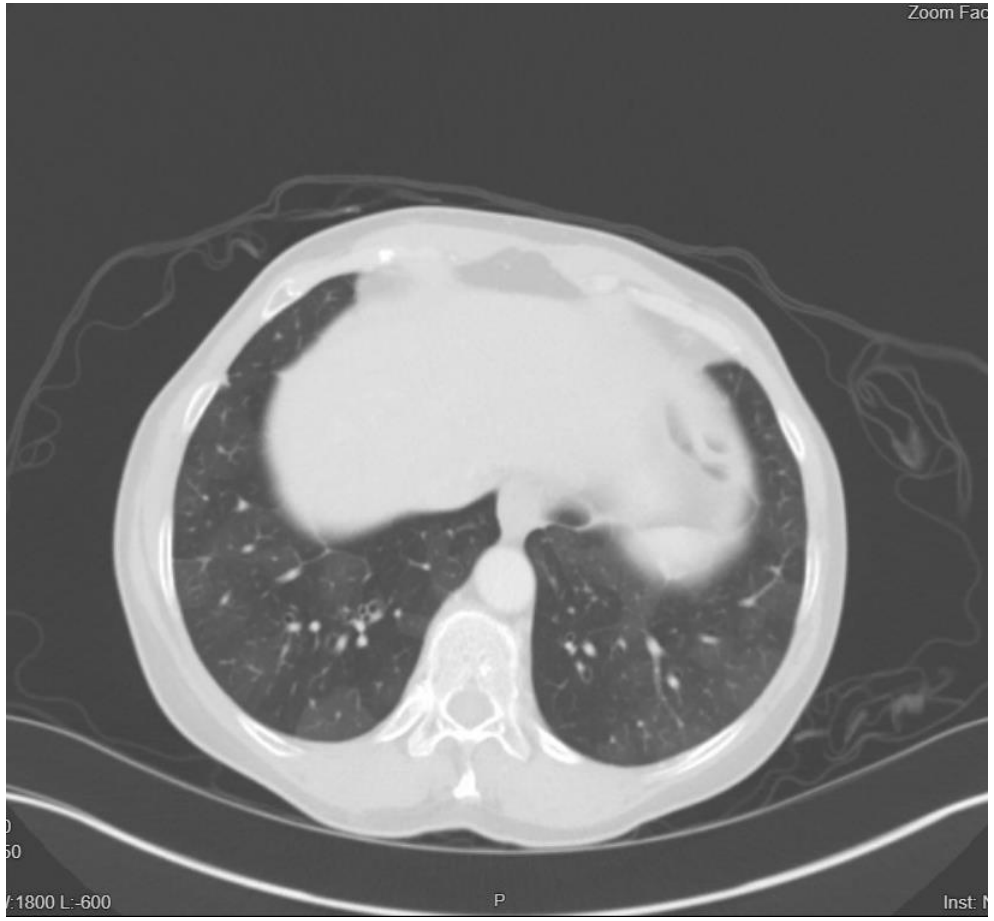


B

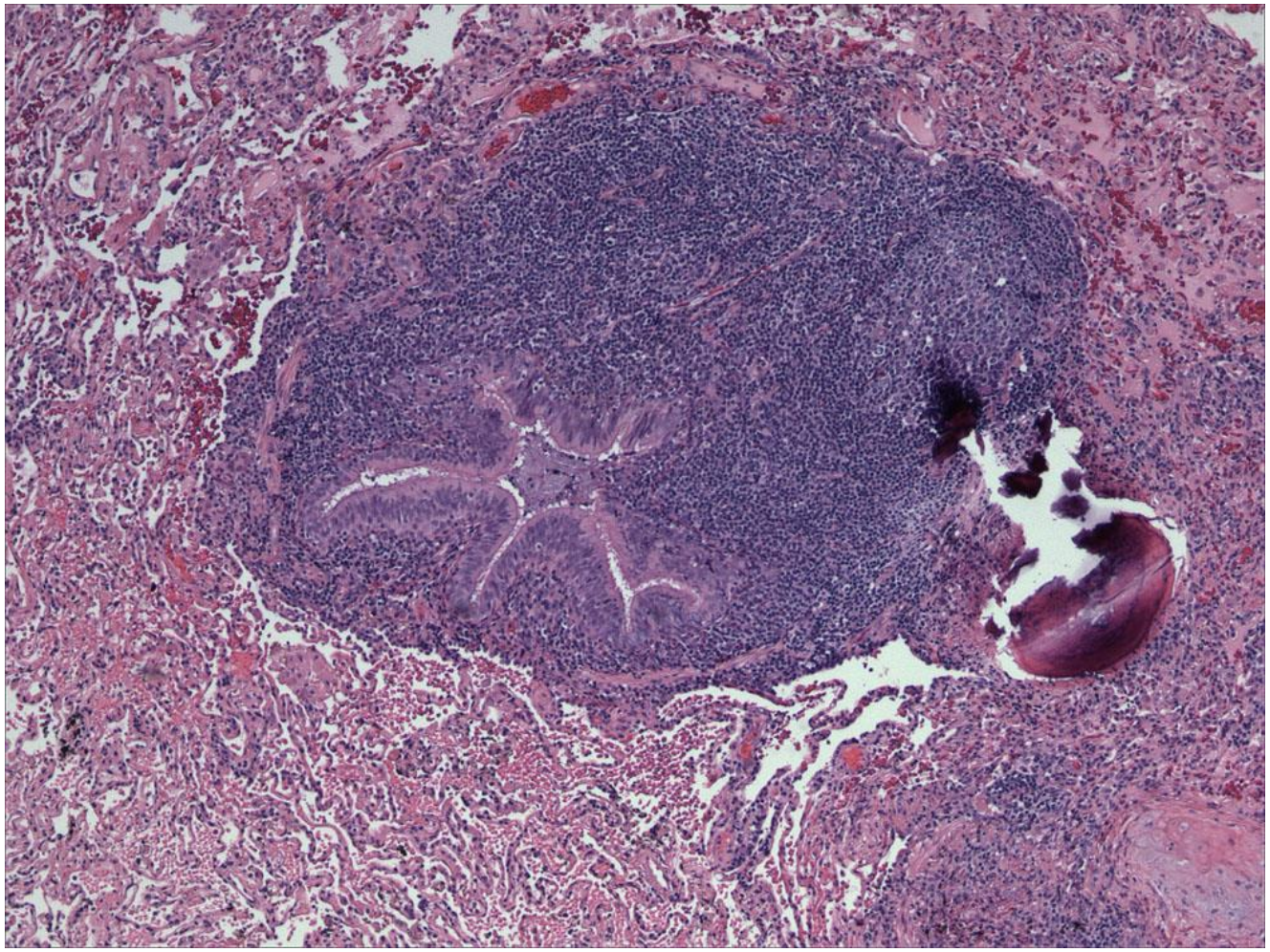


50 yo female with RA CCP + and “asthma”

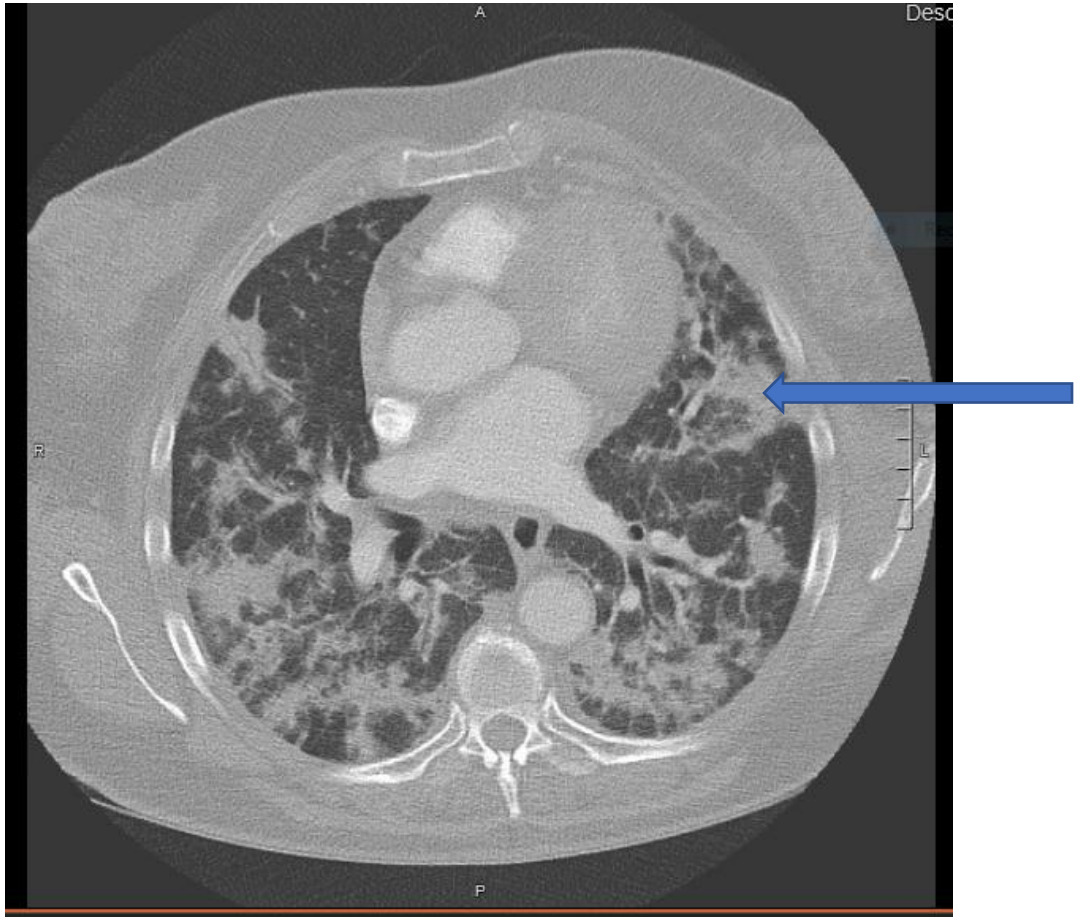




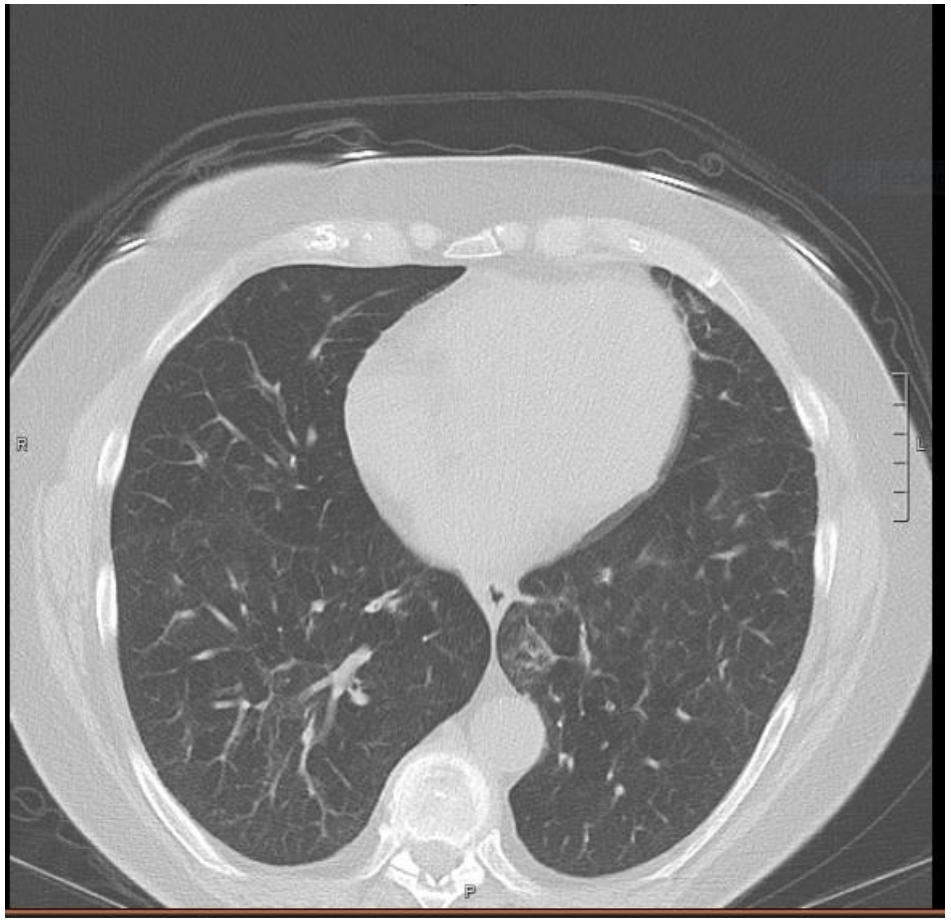
Lung biopsy dx: Follicular bronchiolitis



Case: 60 y.o. female presented to MICU with hypoxemia and new bilateral ankle pain



High Titer RF/CCP ab+. Diagnosed with RA and treated with CS and RTX with excellent result in both lung disease and arthritis



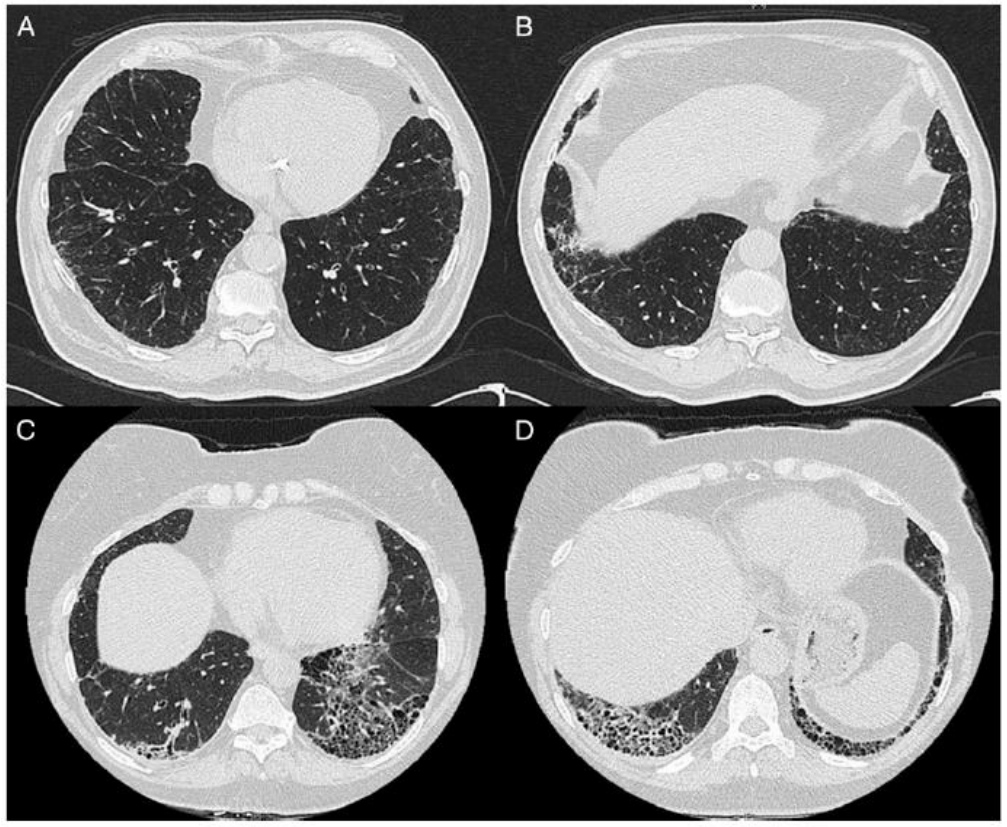
ILD in RA: A spectrum of disease

- **Most common clinical manifestation of lung involvement**

- **10% of individuals with RA have clinically-evident ILD and an additional 30% have subclinical disease**

- **Disease progression was observed in 57% of RA patients with subclinical RA-ILD after a mean length of follow-up of 1.5 years**

- **Up to 65% of individuals have UIP pattern**



Gochuico Arch Int Med 2008
Bongartz Arth Rheum 2010
Olson AJRCCM 2011
Kim Eur Resp J 2010
Doyle Chest 2013, 2014

Risk Factors for RA-ILD

- **RA-ILD is associated with:**
  - Increased age
  - Smoking history
  - Male
  - *Increased RA disease severity*
  - *Increased RF and anti-CCP levels*

Bimodal Distribution of RA-ILD

- Majority of patients with RA develop ILD >10 years after articular manifestations but when do most pts develop early ILD?
- Minority of patients develop clinically-evident ILD shortly after articular disease
- In some patients, ILD is first manifestation of RA and RA may actually ‘start’ in the lungs
  - Cohort of 74 patients with anti-CCP positivity and lung disease (~50% with ILD) in the absence of existing RA or other connective tissue disease, 3 of whom developed articular disease within 1-2 years

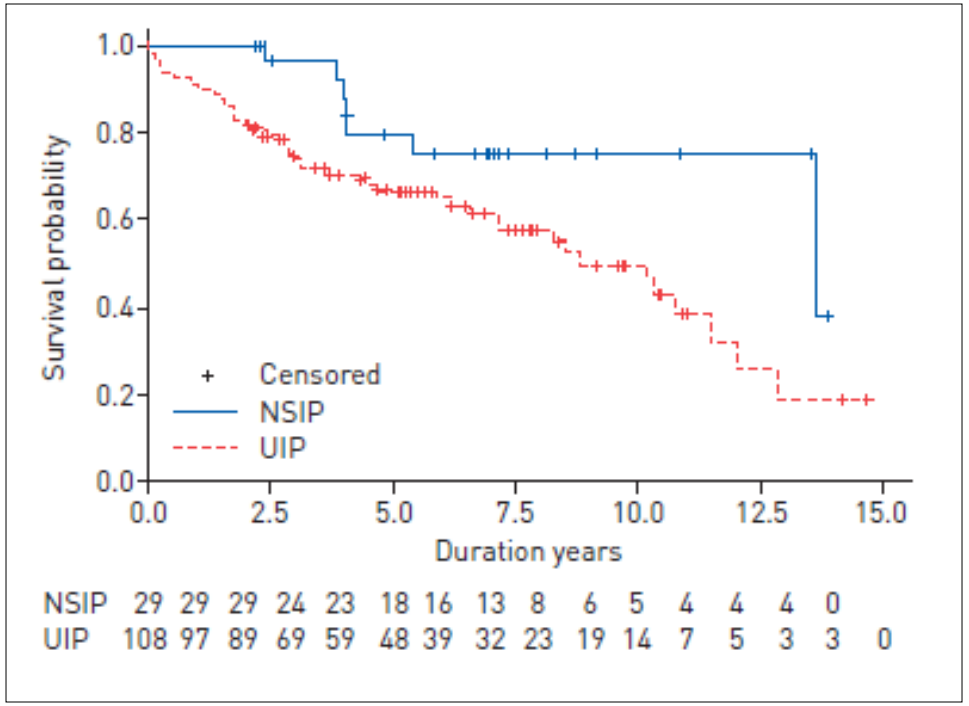
Fischer Respir Med 2012

Mortality of RA-ILD

- **While overall mortality rates for RA are declining, death from RA-ILD has increased**

- **Survival in RA-UIP resembles that of IPF**

- ***In a model controlling for age, sex, smoking and HRCT pattern, a lower baseline FVC % pred and a 10% decline in FVC % pred from baseline to any time during follow up were independently associated with an increased risk of death.***



Solomon ERJ 2016

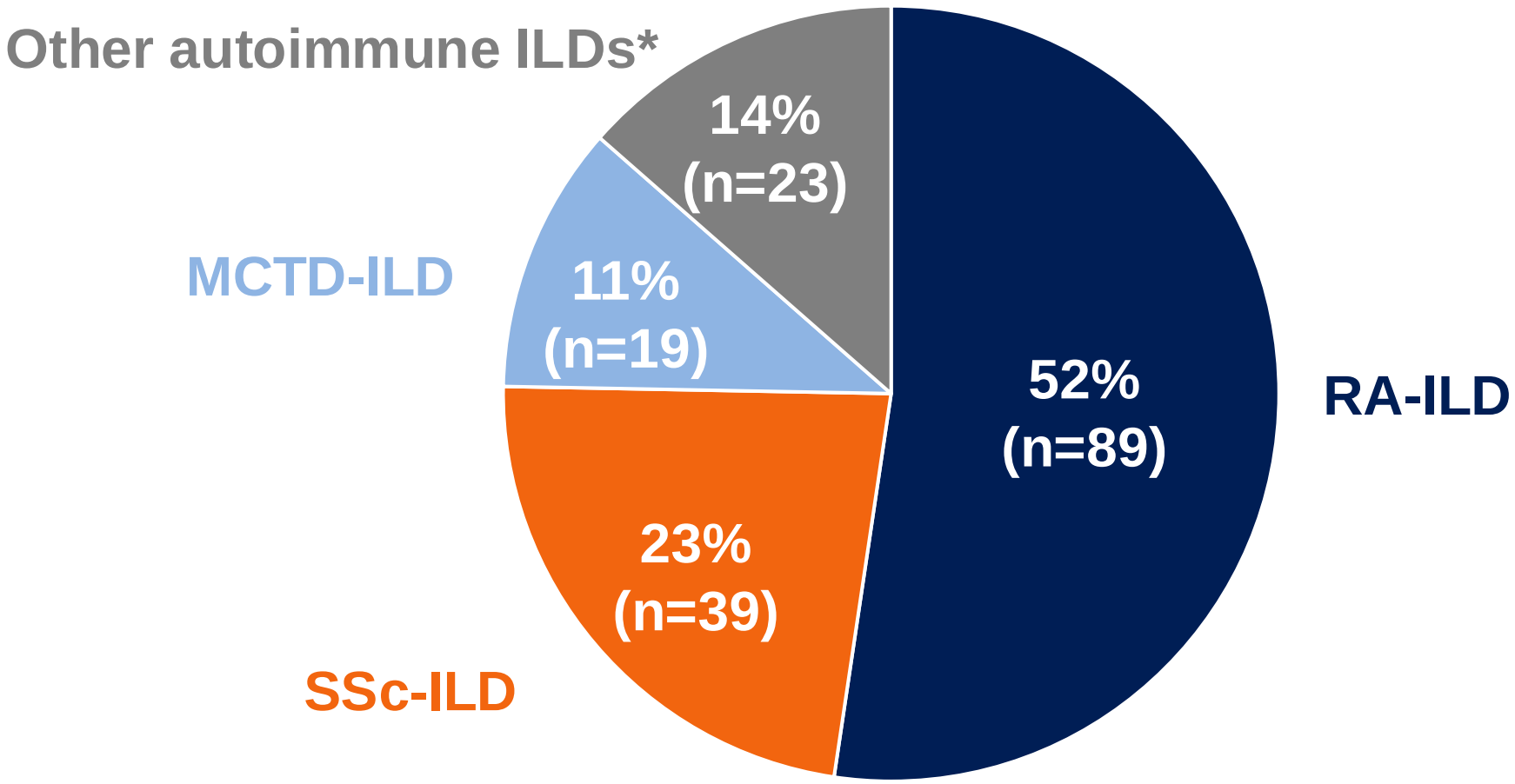
Similarities of RA UIP and UIP/IPF

- Similar demographics (male, older, smokers)
- Somewhat similar decline in lung function
- Excess of mutations in genes that were previously linked to familial interstitial pneumonia, including *TERT*, *RTEL1*, *PARN*, and *SFTPC*.
- MUC5B genetic variant in RA ILD similar to what is seen in IPF (NEJM 2019)

What about anti-fibrotic therapy in RA ILD?

- Pirfenidone
- Nintedinab
- Both FDA approved in IPF

RA ILD Treatment: the INBUILD trial (Nintedinab)

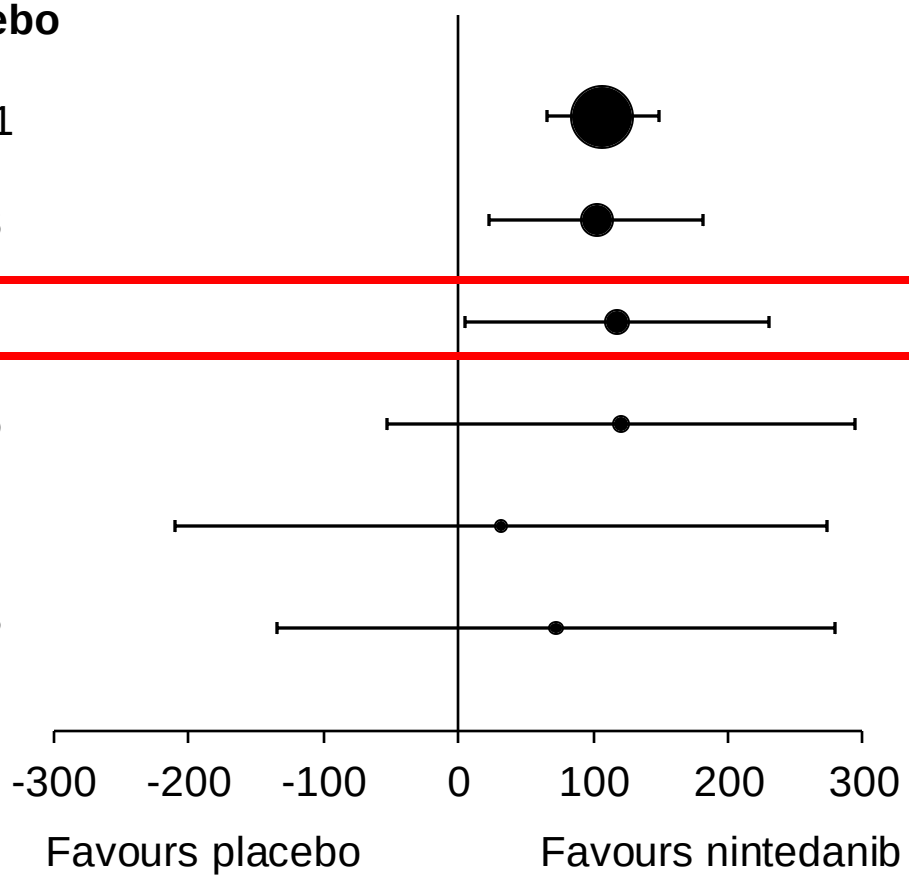


*Subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of the case report form, including Sjogren’s disease-related ILD, IPAF, and undifferentiated autoimmune disease-related ILD. IPAF, interstitial pneumonia with autoimmune features. MCTD, mixed connective tissue disease.

Matteson EL et al. Poster presented at American College of Rheumatology Convergence Conference 2020. https://www.usscicomms.com/respiratory/ACR2020/matteson

INBUILD: Difference in rate of decline in FVC (mL/year) over 52 weeks with nintedanib vs placebo by diagnosis: **similar to IPF trials**

	N analysed		Difference in rate of decline in FVC (95% CI)
	Nintedanib	Placebo	
All subjects	332	331	107.0 (65.4, 148.5)
Subjects with autoimmune disease-related ILDs	82	88	102.7 (23.2, 182.2)
RA-ILD	42	47	117.9 (5.2, 230.7)
SSc-ILD	23	16	120.7 (-53.2, 294.6)
MCTD-ILD	7	12	31.9 (-210.0, 273.8)
Other fibrosing ILDs	10	13	72.5 (-134.1, 279.0)



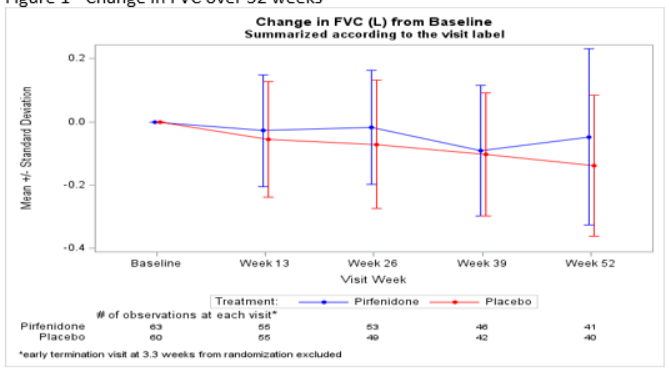
Treatment-by-subgroup-by-time interaction p=0.91

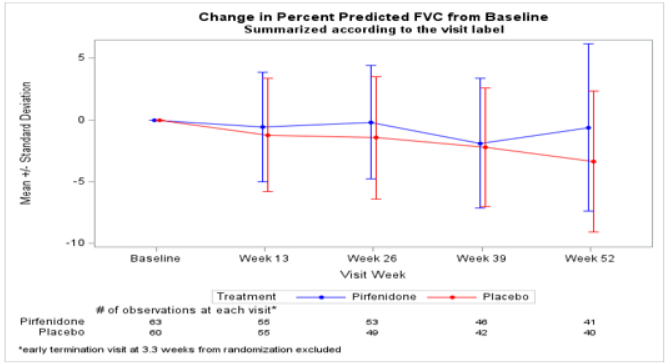
Matteson E et al. Poster presented at American College of Rheumatology/Association for Rheumatology Professionals (ACR/ARP) Annual Meeting 2019. http://ildposters2019.com/pdf/ACR_INBUILDautoimmuneILDs_Matteson.pdf

TRAIL 1:Randomized, Double-Blinded, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease (Solomon JJ et al ACR Nov 2021) CLOSED EARLY and UNDERPOWERED !!

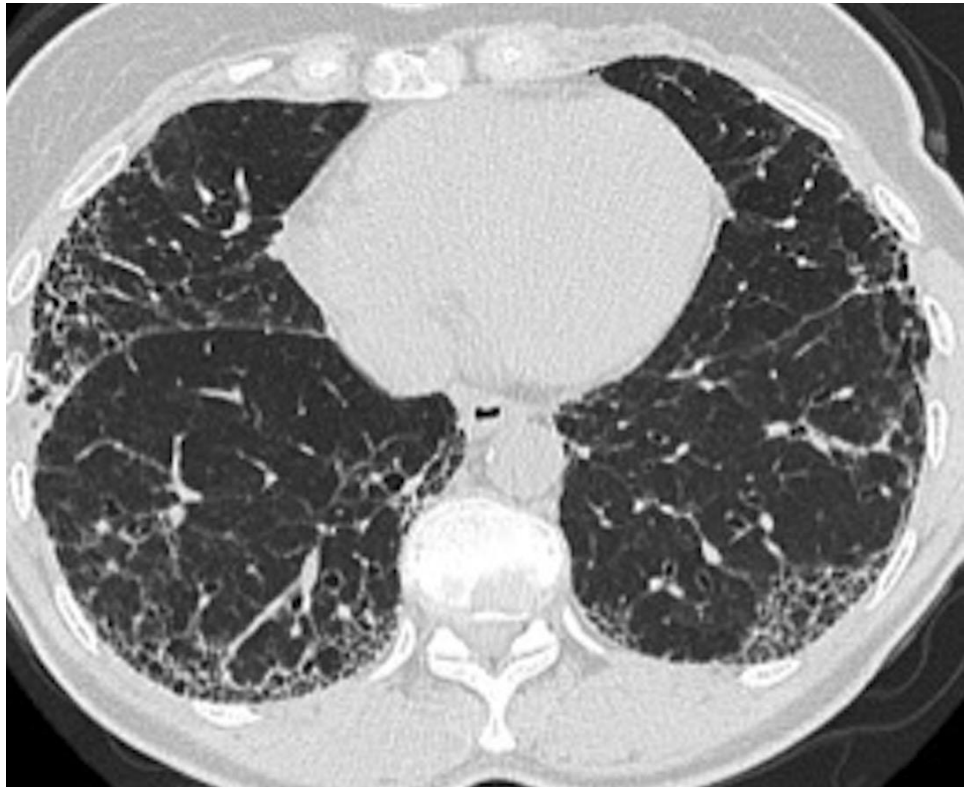
Table. Key Secondary Endpoints			
End Point	Pirfenidone (N=63)	Placebo (N=60)	P-value
Decline in FVC at 52 wk - ml/yr			
Overall Population	-66 ± 21	-146 ± 21	0.0082
Patients with UIP pattern on HRCT	-43 ± 31	-169±24	0.0014
Decline in FVC at 52 wk - % predicted			
Overall Population	-1.02 ± 0.51	-3.21 ± 0.52	0.0028
Patients with UIP pattern on HRCT	-0.2 ± 0.74	-3.81 ± 0.70	0.0002

Figure 1 - Change in FVC over 52 weeks





Fibrosis Scenario 1: 60 yo with stable RA +CCP on Abatacept: FVC 60% with progressive dyspnea for the past 6 months. Infection and heart disease are excluded. **What would you do?**



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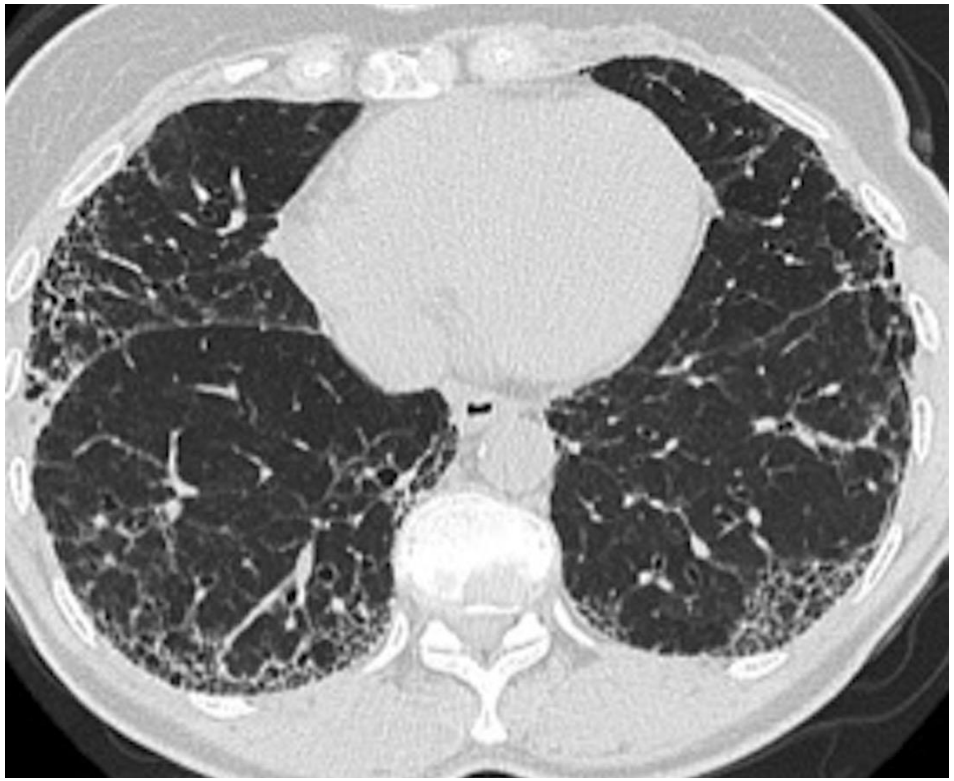
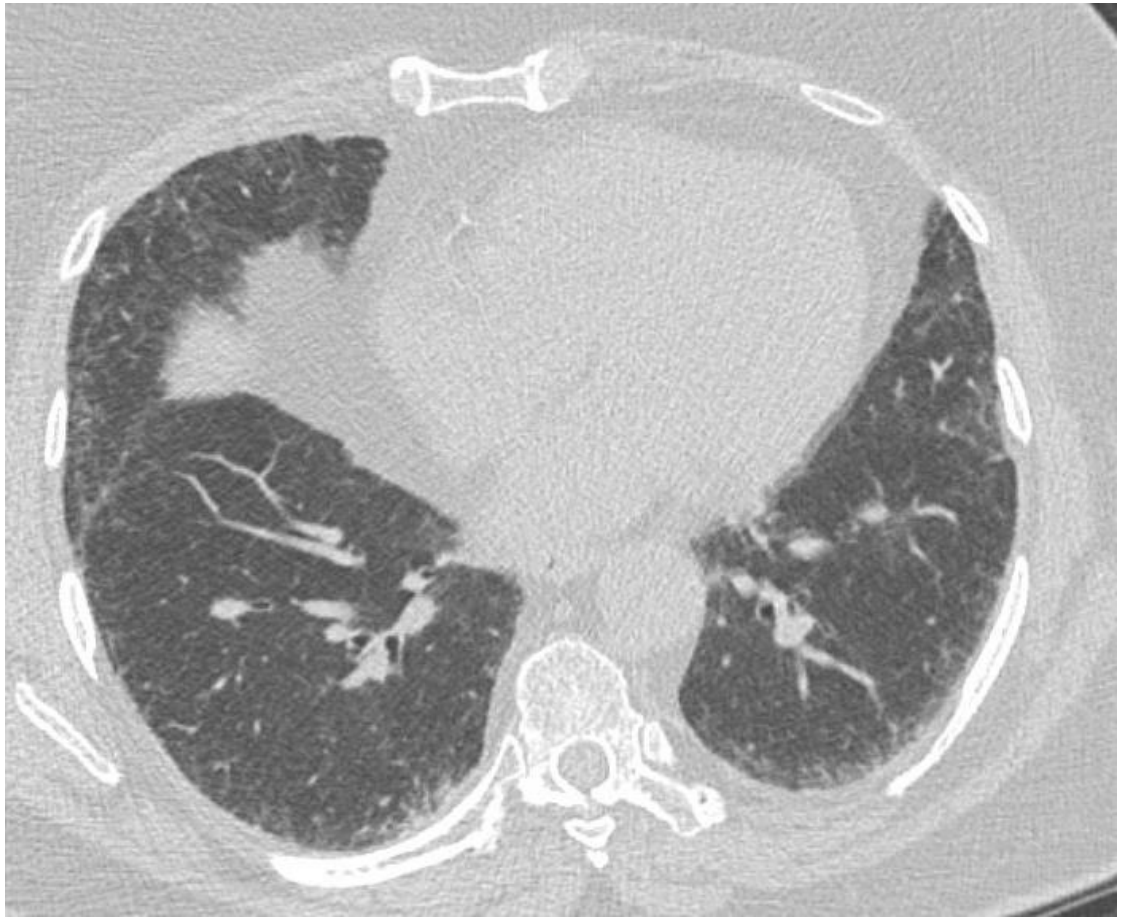


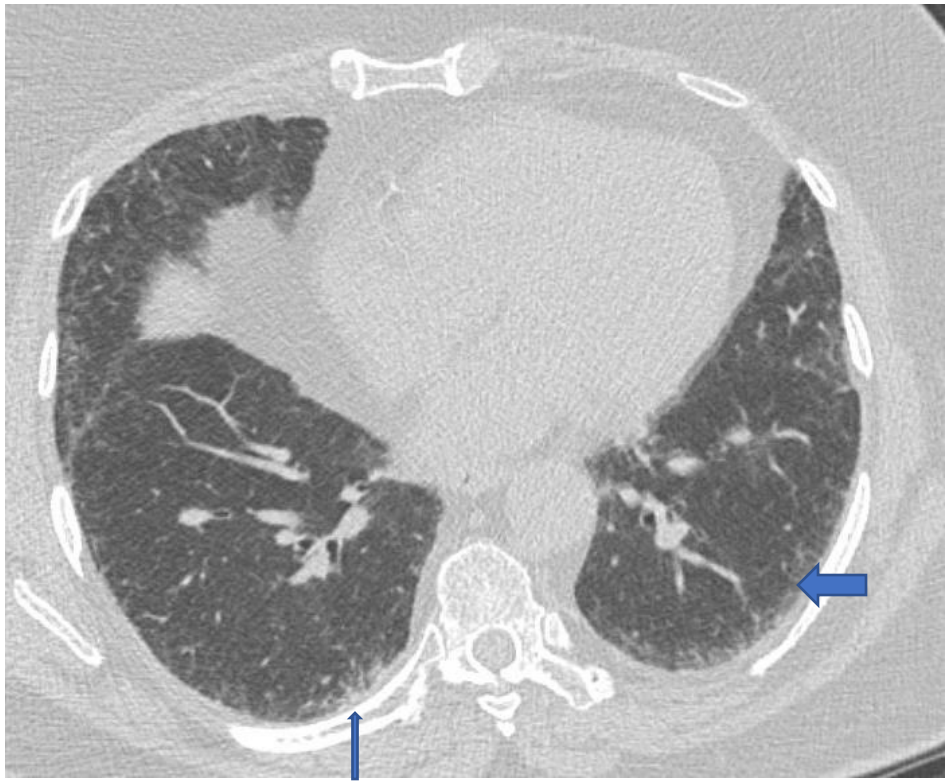
Teaching points :

- Progressive phenotype
- UIP pattern on HRCT
- ***In the year 2024, treat with anti-fibrotic therapy***
- Consider lung transplant evaluation if appropriate

Fibrosis Scenario II: 60 yo RA CCP + former smoker : low dose CT done as part of lung cancer screening, no symptoms and FVC 85% DLCO 72% (first set of PFTs): **what would you do** ?



Fibrosis Scenario II: 60 yo RA CCP + former smoker : low dose CT done as part of lung cancer screening, no symptoms and FVC 85% DLCO 72% (first set of PFTs)



Teaching points

- This person has ILA
- What is this? Will this progress?
- Should the person get a lung biopsy? Is this early UIP?
- Is there data to support the use of anti-fibrotics now ? (**No, but a trial in early disease might help**)
- If not, how would you follow this patient?

RA lung therapies: what type and for whom?

- For inflammatory disease like COP and cellular NSIP: corticosteroids alone or in combination with additional treatments (Rituxan , MMF, AZA, maybe Abatacept)
- Special circumstances: Rheumatoid nodulosis, bronchiolitis (Rituxan)
- Obliterative Bronchiolitis: there is no documented Rx except lung transplant but many try Rituxan.
- ILD: FDA approved and newer emerging anti-fibrotics need to be considered.
- We are not certain the role of MMF in RA ILD but many use it.

A word about MTX and RA ILD (Juge P et al Eur Resp J)

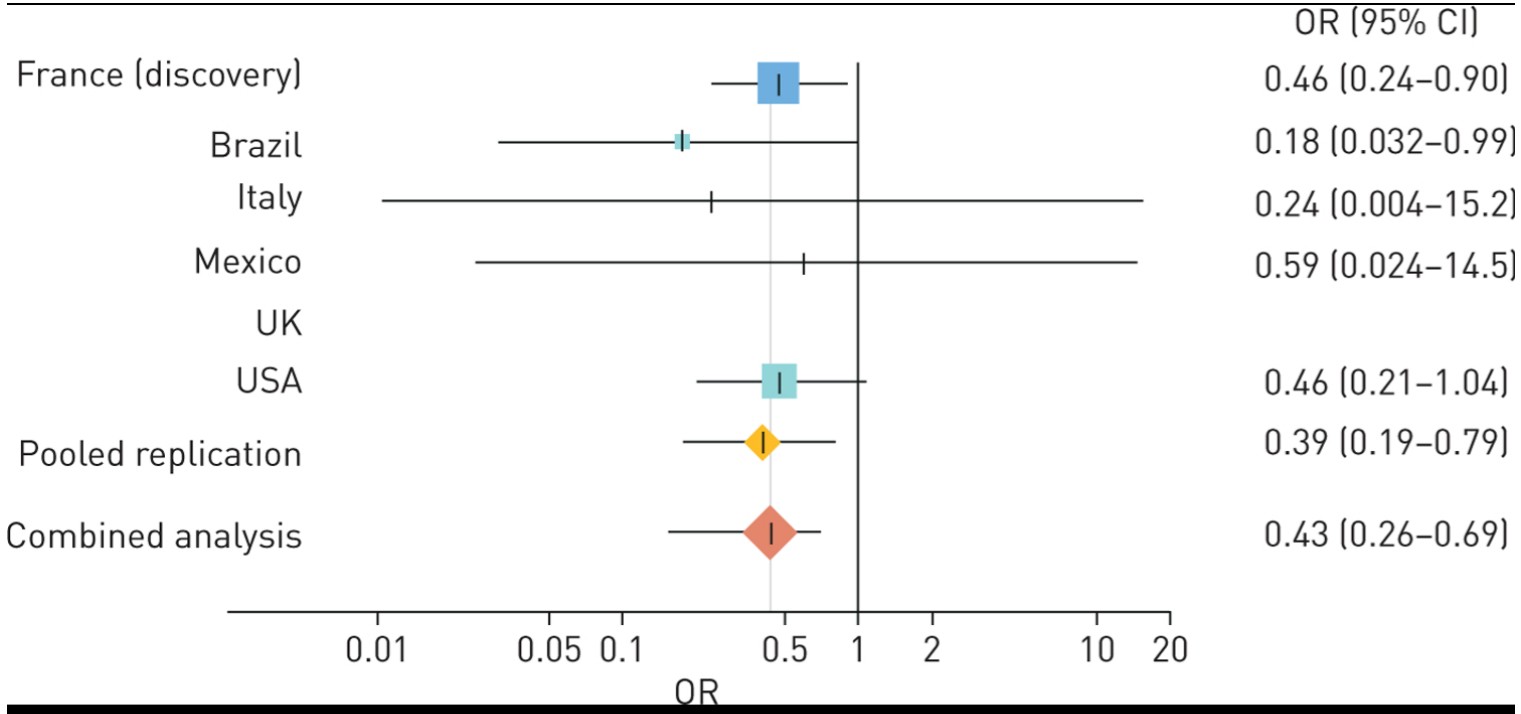
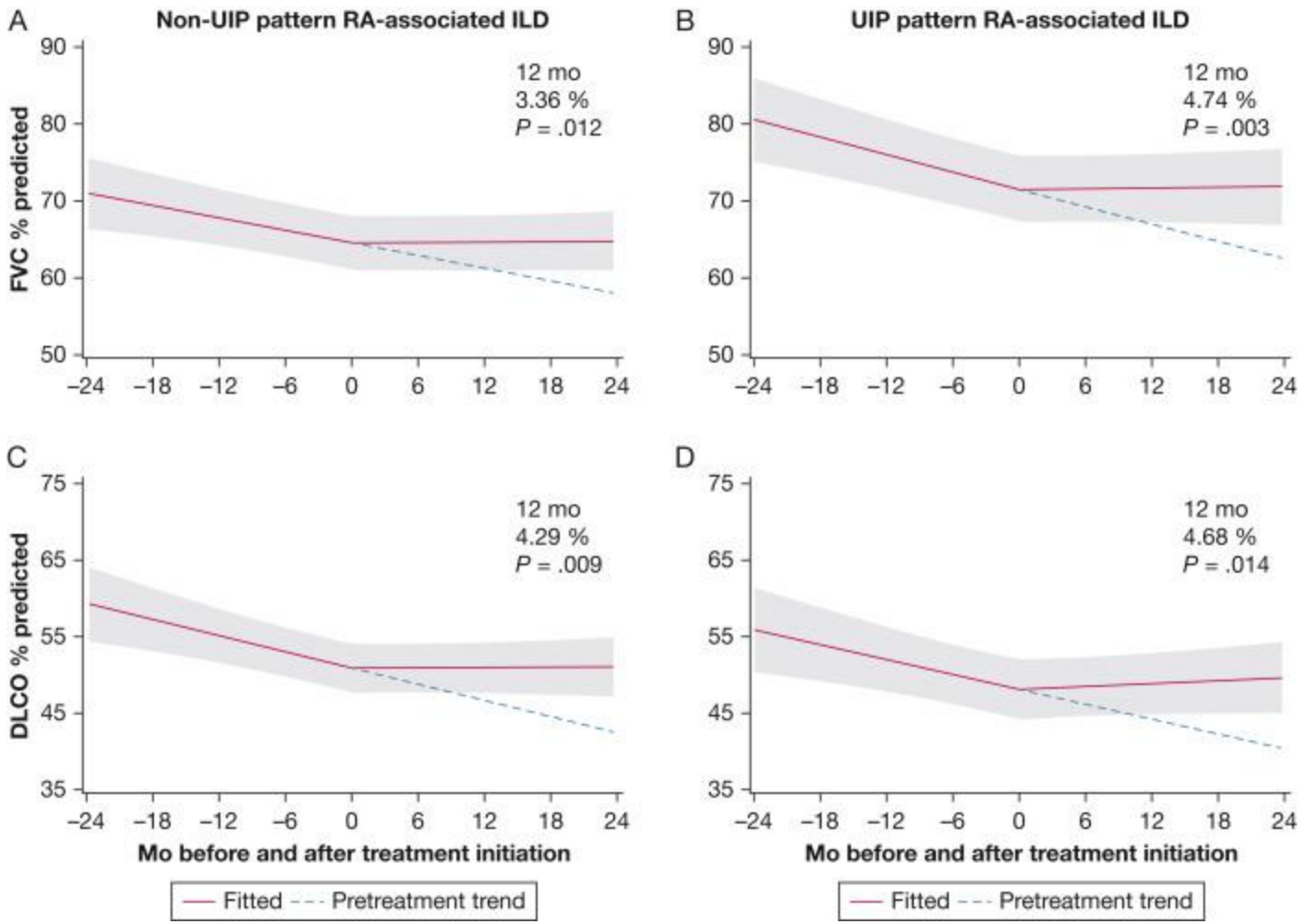


FIGURE 1 Methotrexate (MTX) ever-use and risk of rheumatoid arthritis (RA)-associated interstitial lung disease. Forest plot of odds ratios for interstitial lung disease among patients with RA according to MTX ever-use. The square boxes indicate odds ratios, and the horizontal lines indicate 95% confidence intervals for each sample. Diamonds display the pooled estimates. The black vertical line represents a mean odds ratio of 1. Odds ratios were adjusted for age at

How does immunosuppression impact pulmonary function trajectory in a multisite retrospective cohort of patients with RA-associated ILD?

- Two hundred twelve patients were included in the analysis: 92 patients (43.4%) azathioprine, 77 patients (36.3%) mycophenolate mofetil, and 43 patients (20.3%) treated with rituximab.
- In the combined analysis of all three agents, ***an improvement in FVC*** % predicted was found after 12 months of treatment compared with the potential 12-month response without treatment (þ3.90%; P # .001; 95% CI, 1.95-5.84)
- Immunosuppression was associated with an improved trajectory in FVC and DLCO compared with the pretreatment pulmonary function trajectory including AZA MMF and RTX
- Does this fly in the face of PANTHER trial ?
- (Matson S et al CHEST 2023; 163(4):861-869)


A
Non-UIP pattern RA-associated ILD
FVC % predicted
12 mo
3.36 %
P = .012
B
UIP pattern RA-associated ILD
12 mo
4.74 %
P = .003
C
DLCO % predicted
12 mo
4.29 %
P = .009
D
12 mo
4.68 %
P = .014
90
80
70
60
50
75
65
55
45
35
−24 −18 −12 −6 0 6 12 18 24
Mo before and after treatment initiation
Fitted
Pretreatment trend

So if treatment options exist in RA ILD , should we screen and if so how?

Screening strategies in RA/ILD in 2024 absent great biomarkers

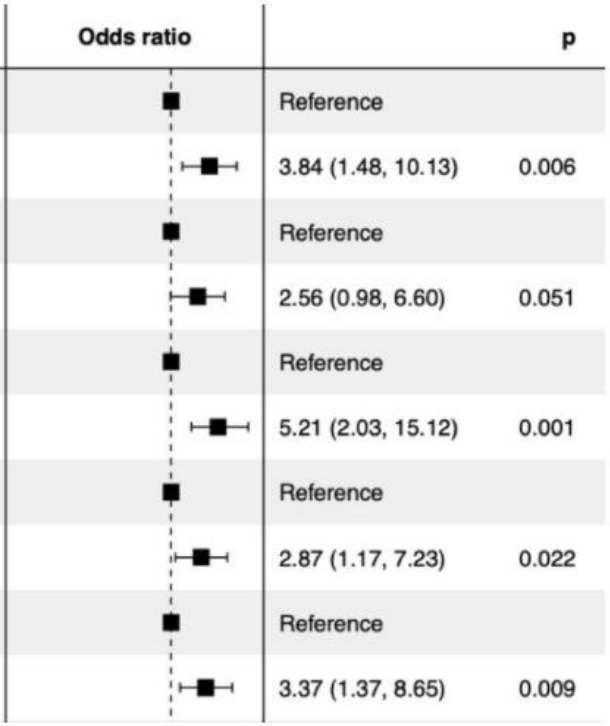
MUC5B Promoter Variant rs35705950 and Risk Stratification for Rheumatoid Arthritis – Interstitial Lung Disease

Pierre-Antoine Juge[1] et al

(ACR Nov 2020)

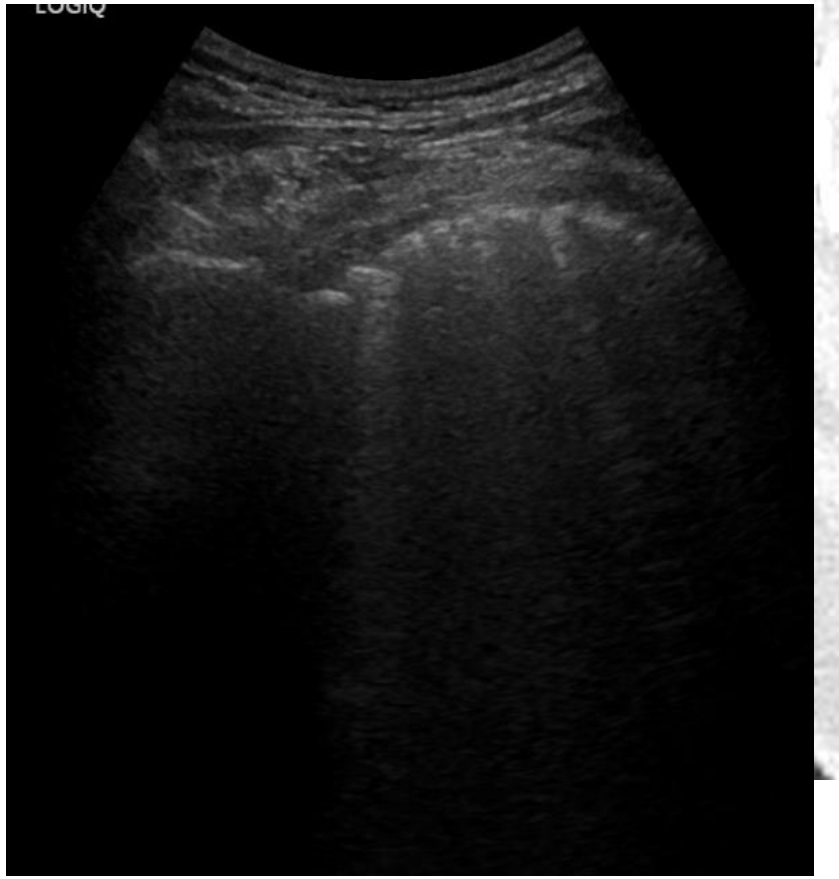
Conclusion: In RA patients, altogether with baseline clinical data, *MUC5B*rs35705950 genotyping could help to improve risk stratification for ILD occurrence at 13 years of RA duration.

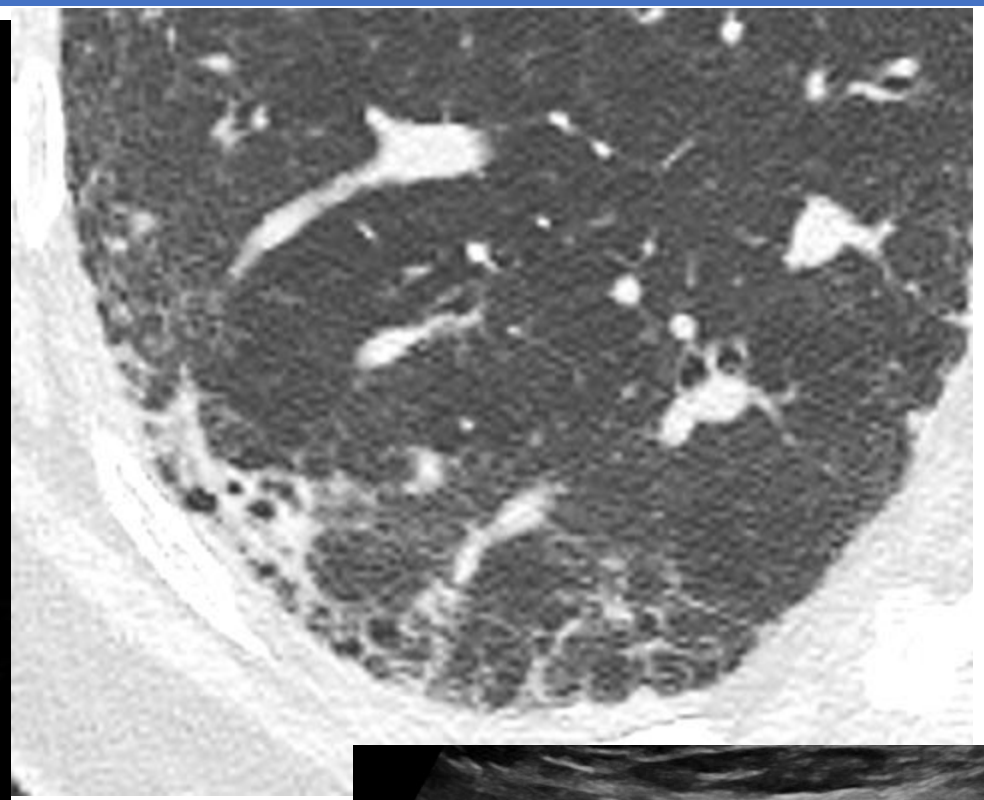
Variable		Odds ratio	p
MUC5Bd	GG	Reference	
	GT/TT	3.84 (1.48, 10.13)	0.006
SEX	F	Reference	
	M	2.56 (0.98, 6.60)	0.051
AGE_	<=49	Reference	
	>49	5.21 (2.03, 15.12)	0.001
SJC	<=9	Reference	
	>9	2.87 (1.17, 7.23)	0.022
Persistent arthritis		Reference	
Migrating arthritis		3.37 (1.37, 8.65)	0.009

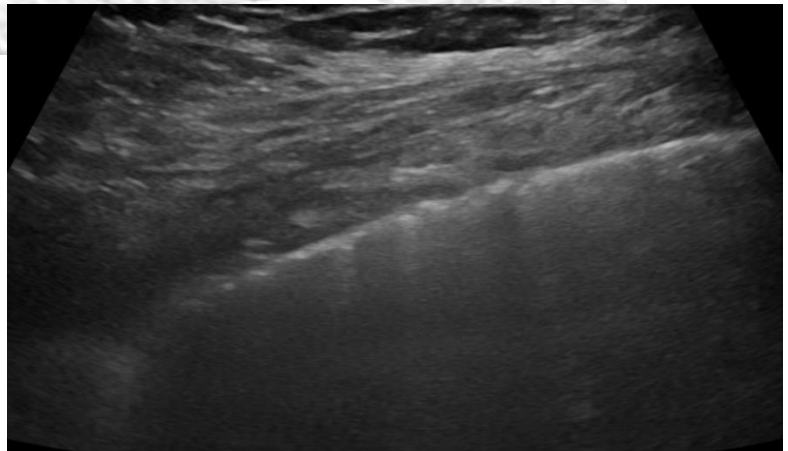


Baseline predictors of ILD occurence at 13 years of RA duration

76 yr. female, RA diag in 2014,MTX /HCQ . DAS score high for 18 months. CXR abnormal prior to biologic screening. CT scan 2017 & 2019







Courtesy of Koduri G

Screening in RA for ILD

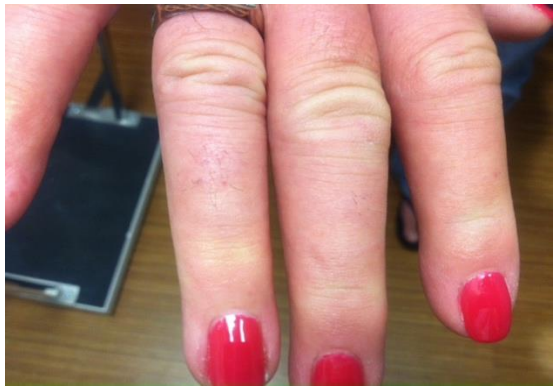
- This is a topic in flux right now
- It is controversial to screen If you don’t have a very good therapy to offer
- Should all pts be screened or should a select high risk group which is now defined mostly by demographic factors be screened.
- As we learn more and further define higher risk populations (certain citrunillated ab, genetics etc) then screening may be more targeted.

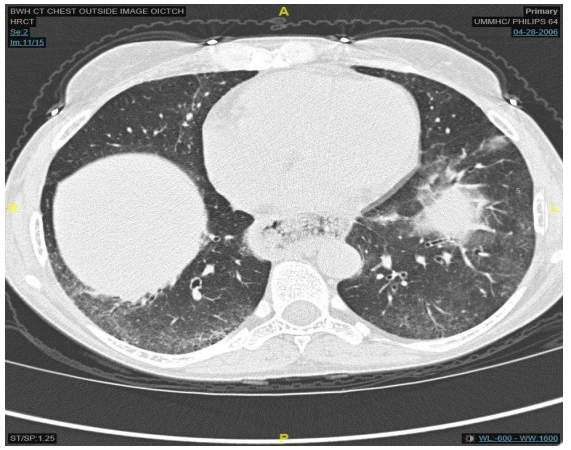
Systemic Sclerosis (SSc)

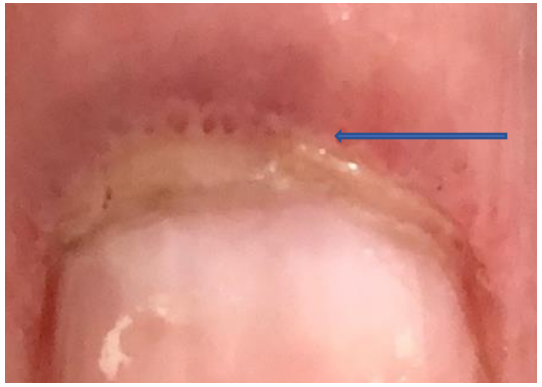
- Chronic fibrosing disorder characterized by autoimmunity vasculopathy and fibrosis

- Key clinical features:

  - Interstitial Lung Disease
  - Pulmonary Hypertension
  - Esophogeal and GI dysmotility:ASPIRATION
  - Renal crisis
  - Pericardial and myocardial disease





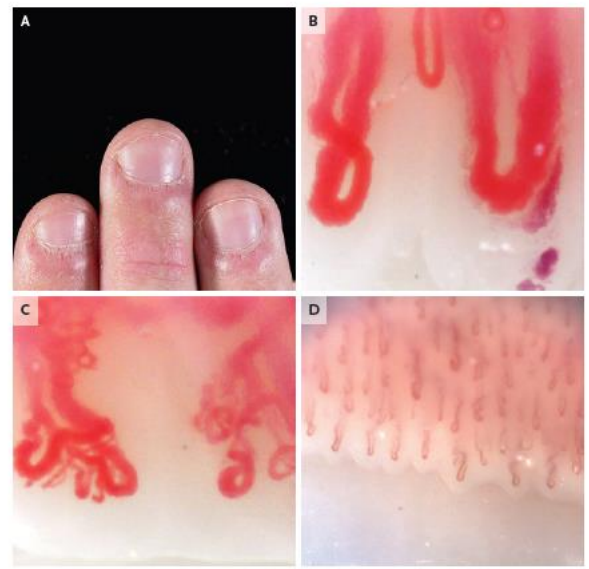


The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Stephanie V. Sherman, M.D., *Editor*

Nailfold Capillaroscopy in Rheumatic Disease



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This article was published on July 15, 2023, at NEJM.org.

A 19-YEAR-OLD MAN PRESENTED TO THE RHEUMATOLOGY CLINIC WITH A 3-YEAR HISTORY OF RAYNAUD'S phenomenon and a 1-year history of fatigue, rash on the face and hands, and pain in the finger joints. On physical examination, there were erythematous plaques on the metacarpophalangeal and interphalangeal joints, without associated synovitis. The nailbeds had periungual erythema, cuticular hypertrophy (also known as "ragged cuticles"), and prominent dilated capillary loops (Panel A). Erythema was also present on the patient's hairline, nasolabial folds, and periorbital region. The results of strength testing were normal. Nailfold capillaroscopy was performed. Nailfold capillaroscopy is a bedside assessment of nailbed microcirculation that is performed with the use of a handheld ophthalmoscope, a dermatoscope, a wide-field microscope, or a videocapillaroscopy probe. In this patient, nailfold videocapillaroscopy revealed giant nailfold capillaries with an apical diameter of more than 50 μm (reference value, <15) (Panel B), branched and bushy neovascularized capillary loops (Panel C), and markedly reduced capillary density; for comparison, Panel D shows normal findings on nailfold capillaroscopy. The patient's nailbed findings, in combination with his symptoms, were suggestive of an underlying rheumatic condition. After serologic evaluation and a skin biopsy, a diagnosis of clinically amyopathic dermatomyositis was made, and the patient's symptoms abated after immunosuppressive therapy was initiated.

DOI: 10.1056/NEJMicm2213508

ILD and Scleroderma: higher risk populations and phenotypes.

- Scl-70 ab + (newer antibodies include Th/To and U11-12)
- Diffuse skin disease, digital ulcers, arthritis, indicate higher risk
- Age (older)
- Rate of decline of FVC and DLCO decline over 2 years (Volkmann E et al Ann Rheum Dis 2018)
- African American or Native American
- Extent of disease on CT(> 20% of HRCT involved) (TA Winstone et al Chest 2014) and FVC<70%) (AJRCCM 2008)
- Composite PFTs and clinical decline (Goh et al 2018)

Loss of Lung function occurs early in SSc The First 5 years are key. (Steen et al Arthritis Rheum 1994)

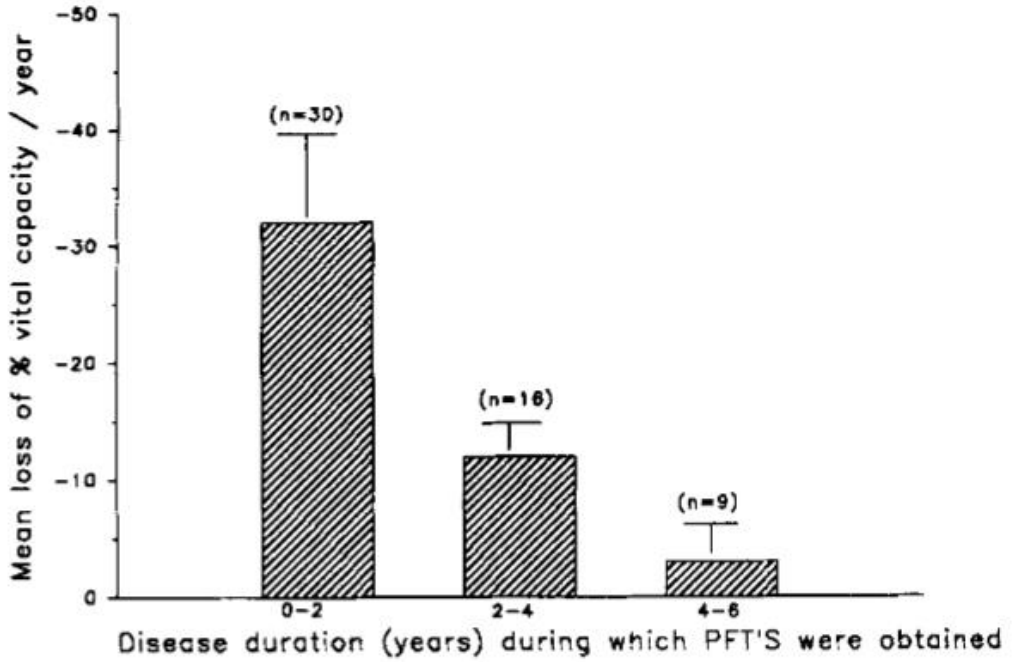
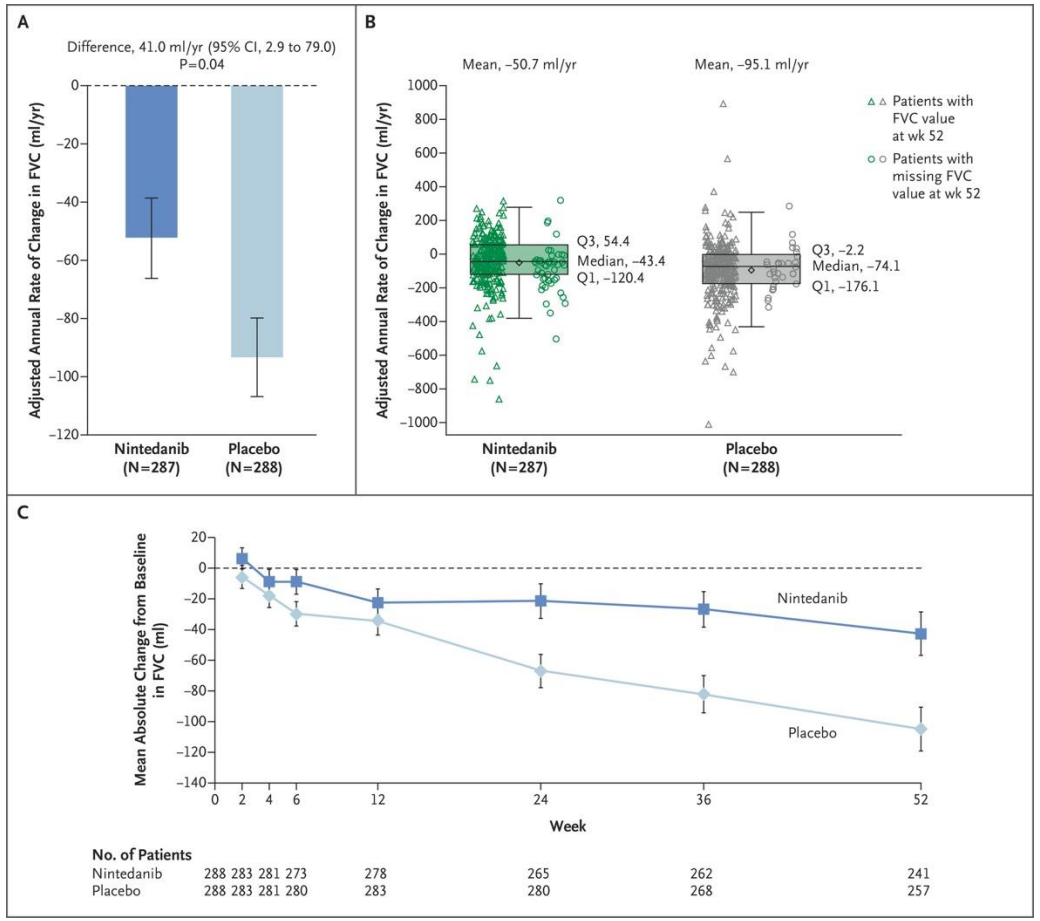
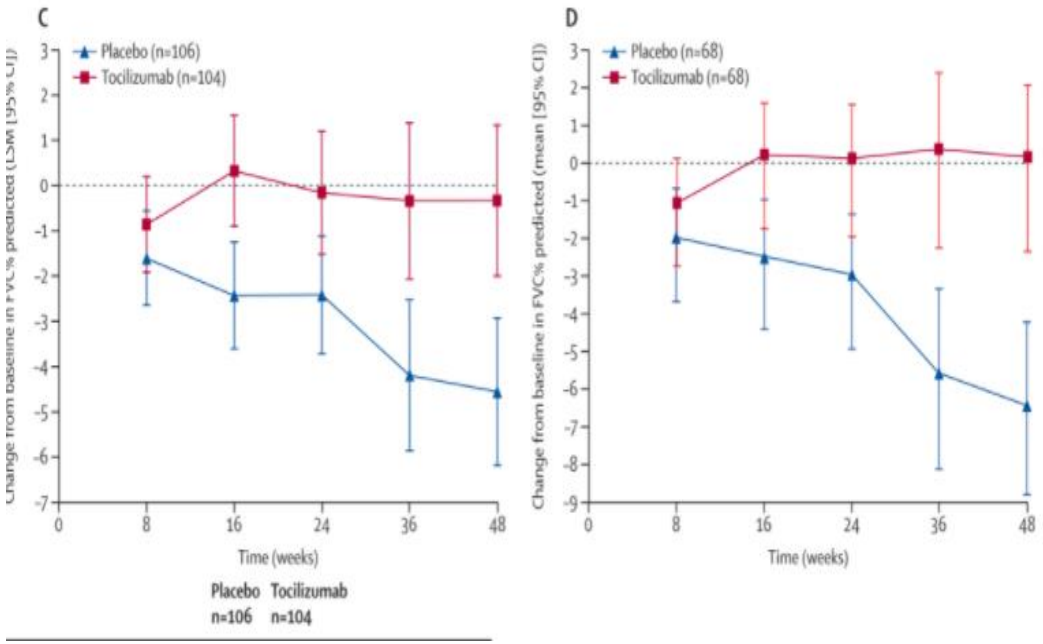


Figure 1. Mean loss of percent vital capacity occurring over 2-year time periods in 55 patients whose initial pulmonary function tests (PFT's) were performed during the first 5 years of scleroderma symptoms.

Distler O et al : SENSCIS Trial NEJM June 2019



Tocilizumab and Phase III trial (focuSSced Khanna et al Lancet Resp 2020)



- No difference in MRSS (primary end point)
- There was a difference in decline in FVC compared to placebo
- Difference in decline in FVC (LSM) was 4.2% favoring TCZ over placebo in all patients and 6.5 % in those with ILD.
- >10% decline in FVC % occurred in 17% of placebo and 5% of TCZ

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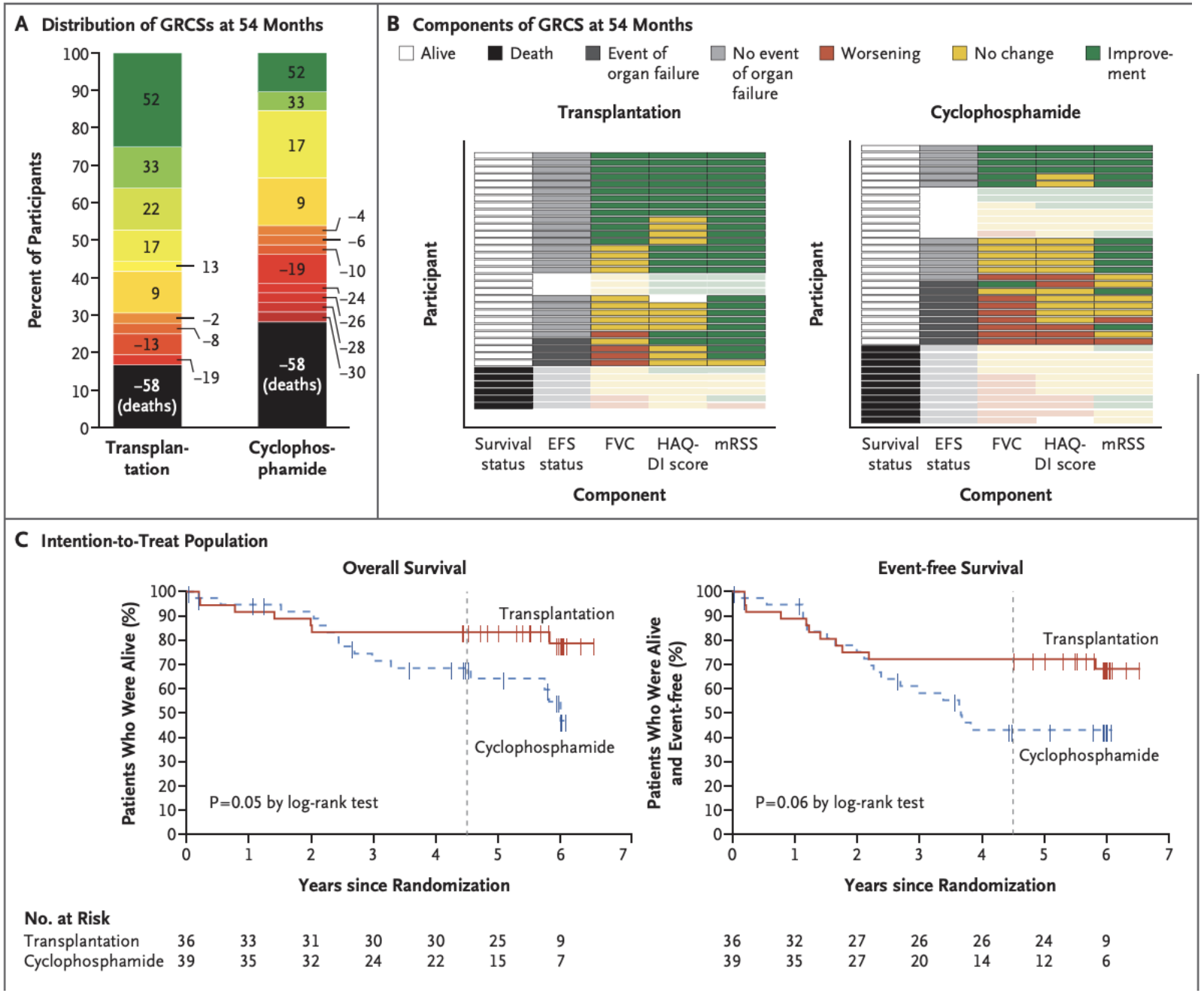
ORIGINAL ARTICLE

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*

6% treatment related mortality in SCT group at 72mo



Maher et al CYC vs RTX (Lancet Resp Med 2023)

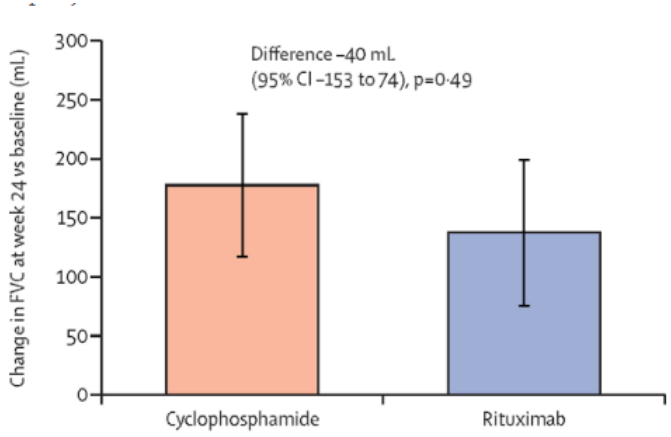


Figure 2

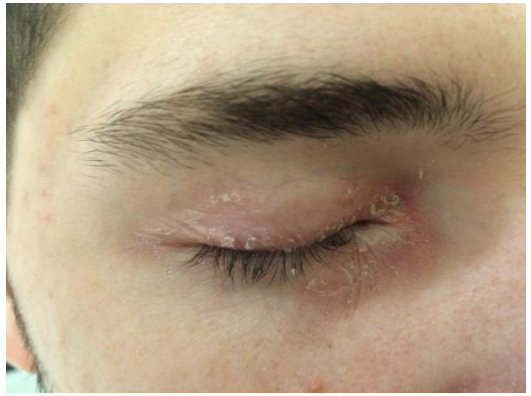
Treatment in SSc ILD Right now

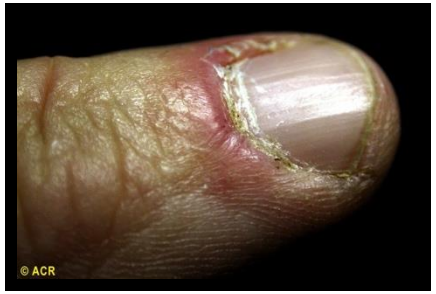
- MMF is the initial treatment of choice in most patients.
- In early disease with elevated CRP, consider IL -6 inhibitor especially if active arthritis, modest doses of steroids (20 mg or less) are a short term option for inflammatory ILD with careful attention to BP
- Consider IL-6 inhibition or RTX (Recital trial Lancet Resp Med 2023) if MMF or CYC fails.
- If progression consider adding on antifibrotics and myeloablative therapy
- What about combination therapy ?
- CART T ? Inhaled Trepostinal?

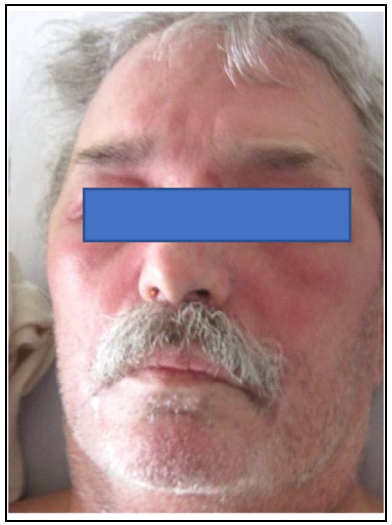
Inflammatory Myositis and the lung

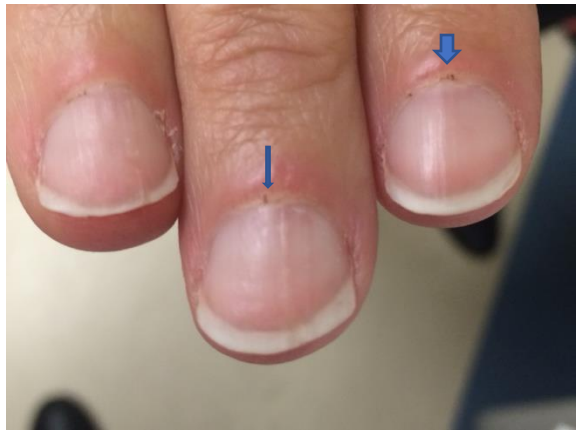
- *Interstitial lung disease* (NSIP, rarely UIP), *Organizing pneumonia (OP)*
- *Antisynthetase syndrome* (fever, Raynauds, arthritis, myositis, mechanics hands,ILD) (often NSIP or OP or both)
- MDA5 (can be associated with AIP)
- Respiratory muscle dysfunction
- Diaphragmatic dysfunction

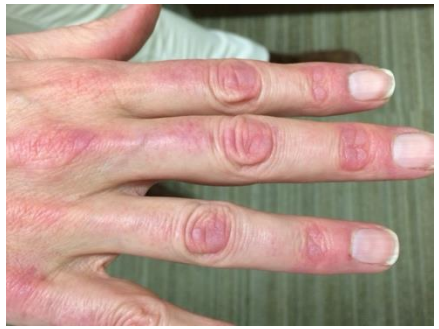
Teaching Phenotypes:**Look at the hands! Look at the skin**!







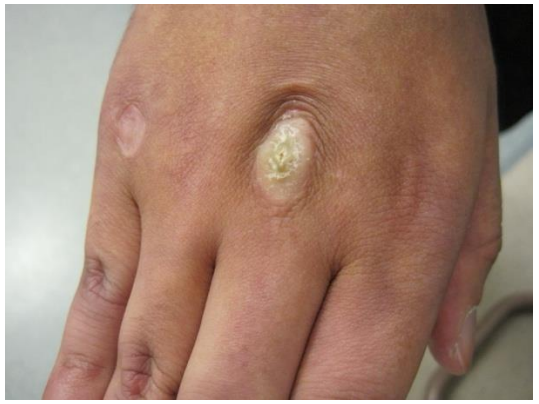


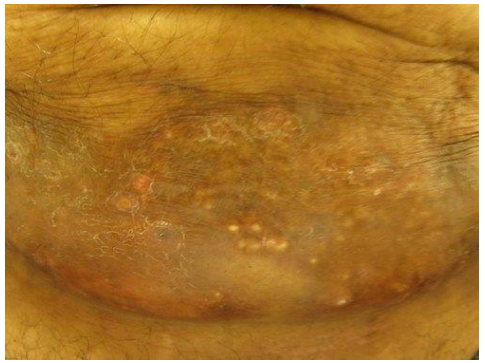


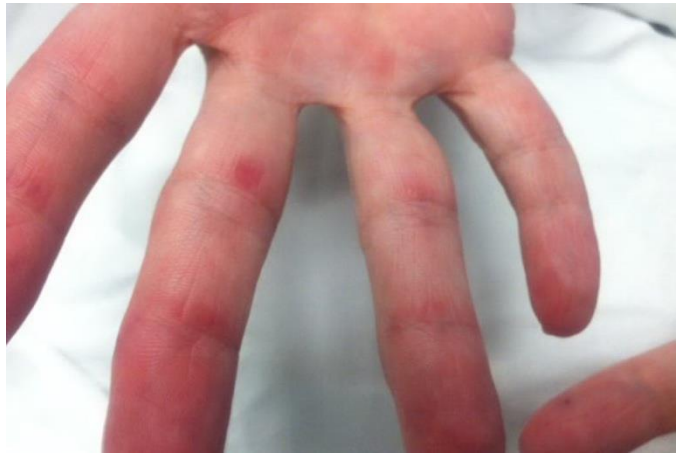
Antibodies in myositis and ILD:summary

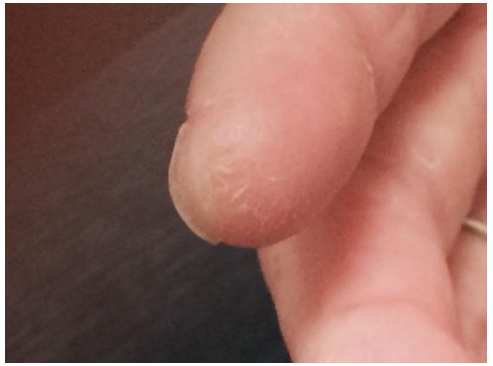
- Antisynthetase abs: Jo-1,PL-7, PL-12, EJ, OJ, KS, ZO , HA.
- Overlap antibodies: RNP, PML/Sc.
- Antibodies associated with malignancy in DM (p155/140):
- (protective for ILD)
- **Amyopathic antibodies**: **anti-MDA5, can result in rapidly progressive ILD**
- **SUMO ab: small ubiquitin-like modifier activating enzyme seen in DM/ILD**

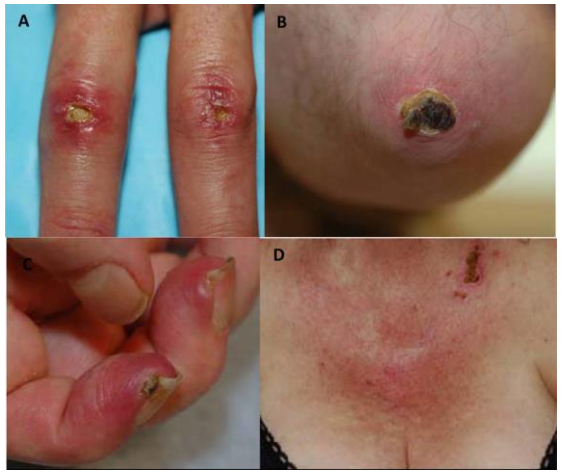
Phenotype skin MDA 5: high risk of rapidly progressive ILD inc AIP pattern





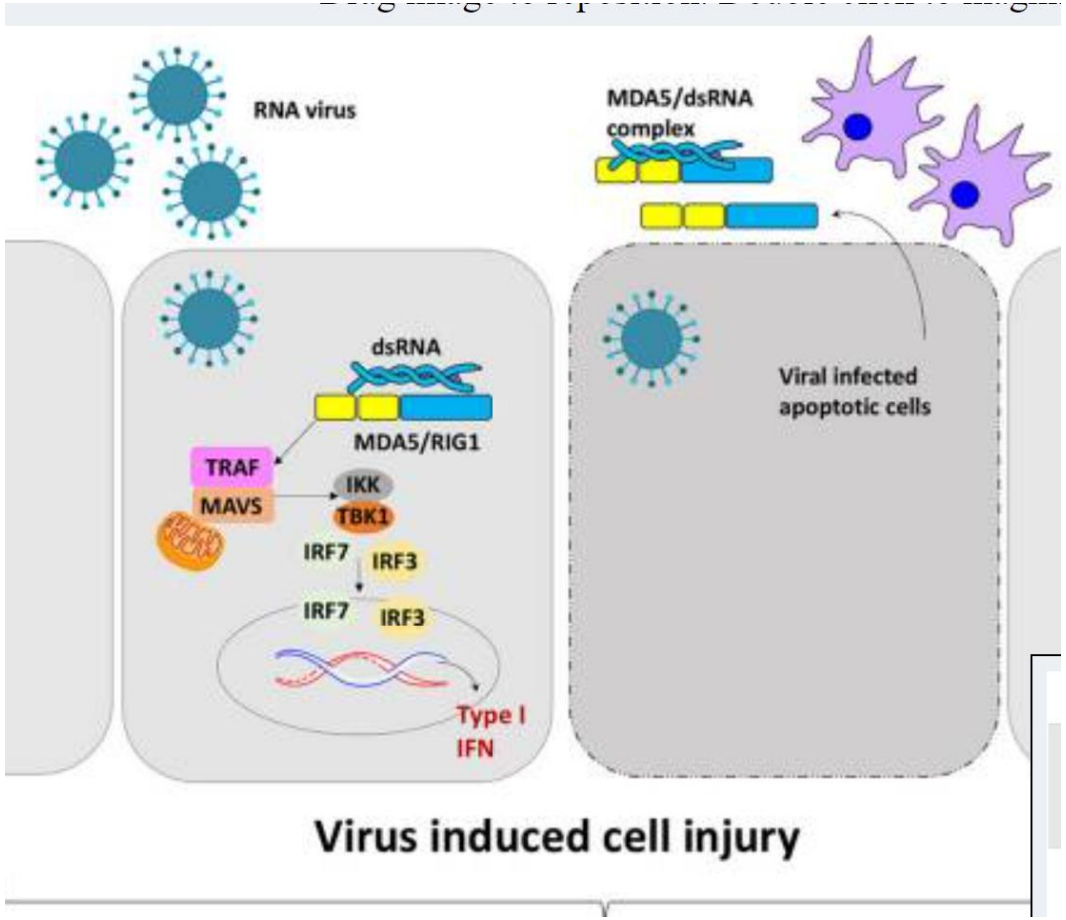




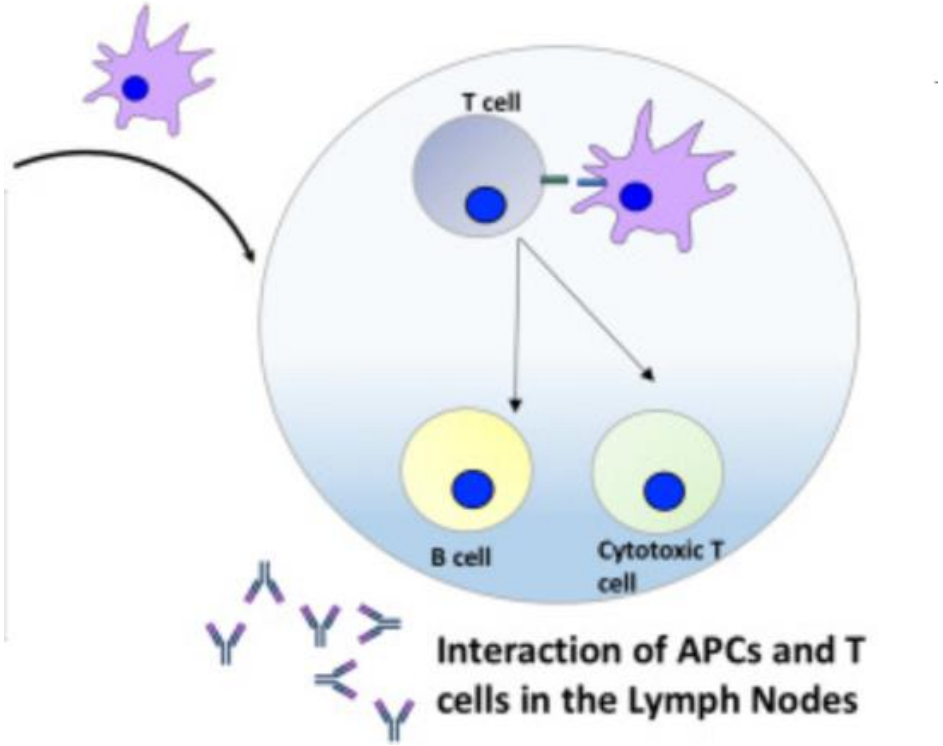


Narang et al
Arthritis Care
2015;67(5)

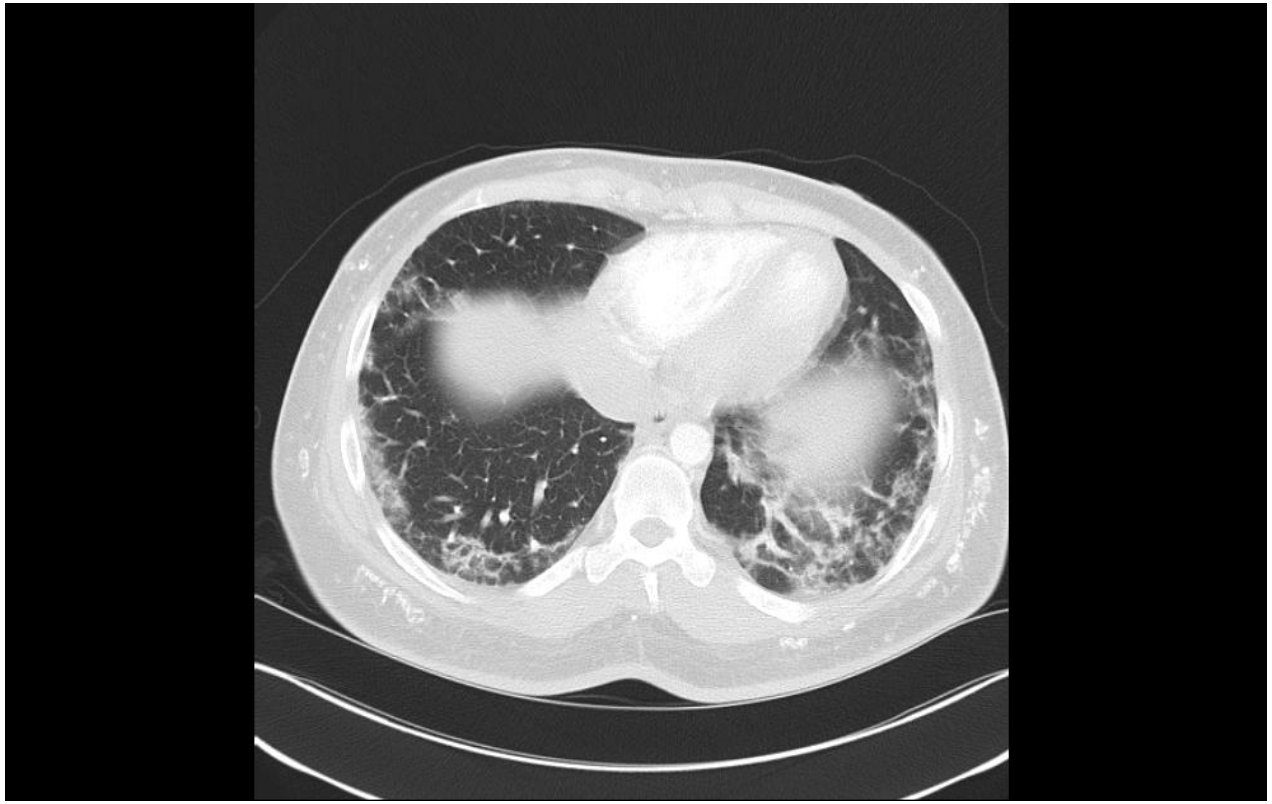
MDA5

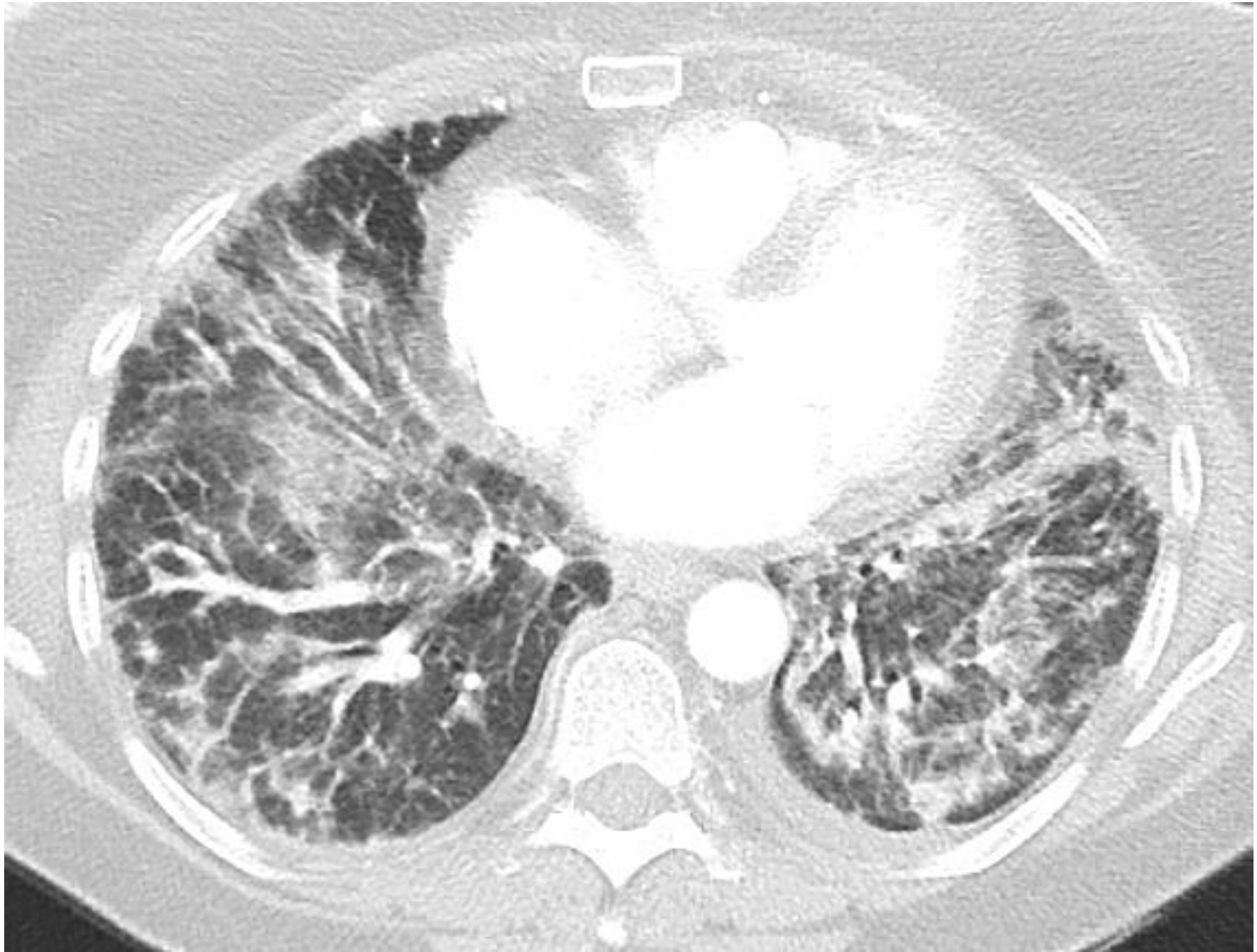


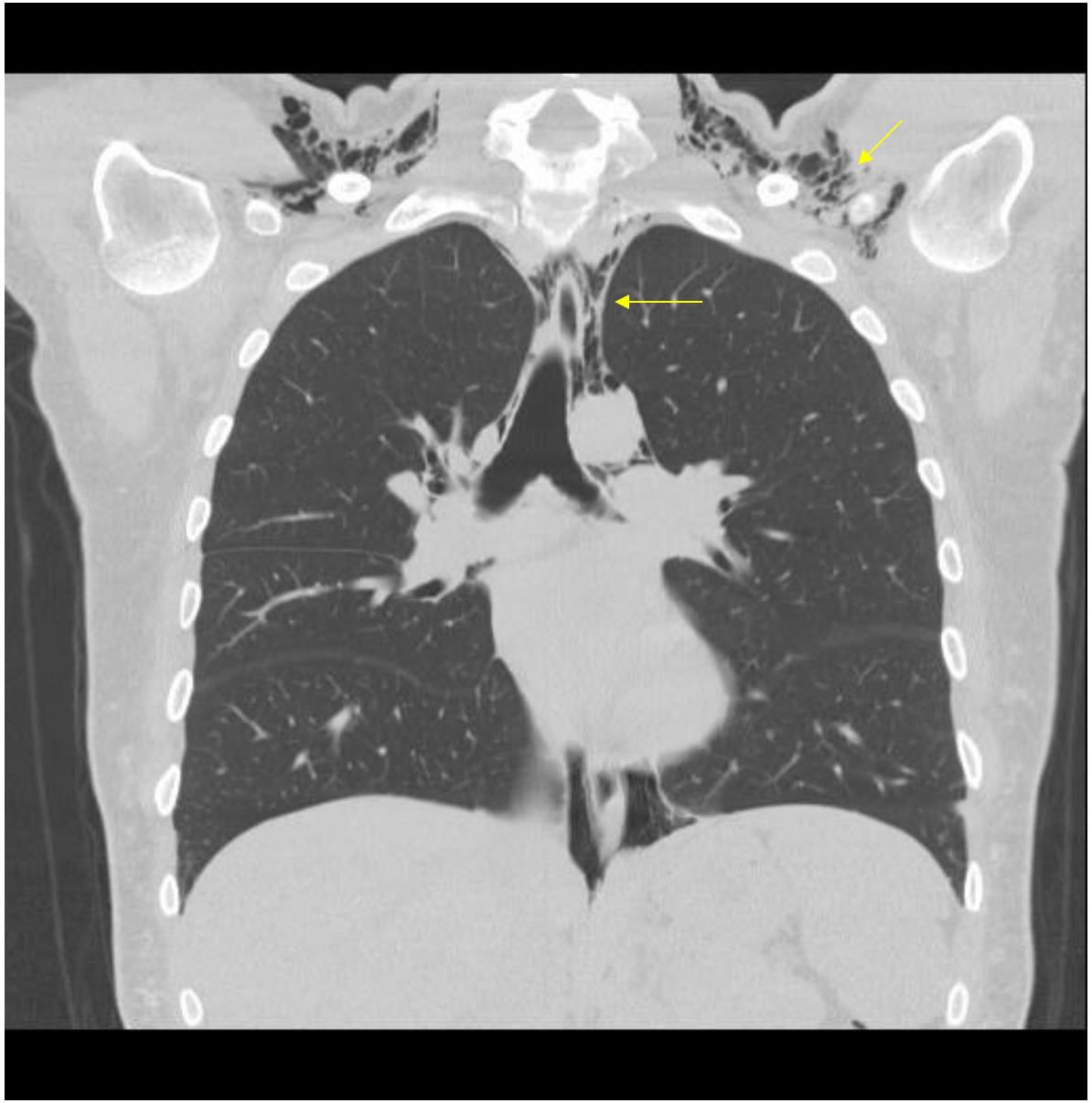
Mehta P et al Rheum Int 2021



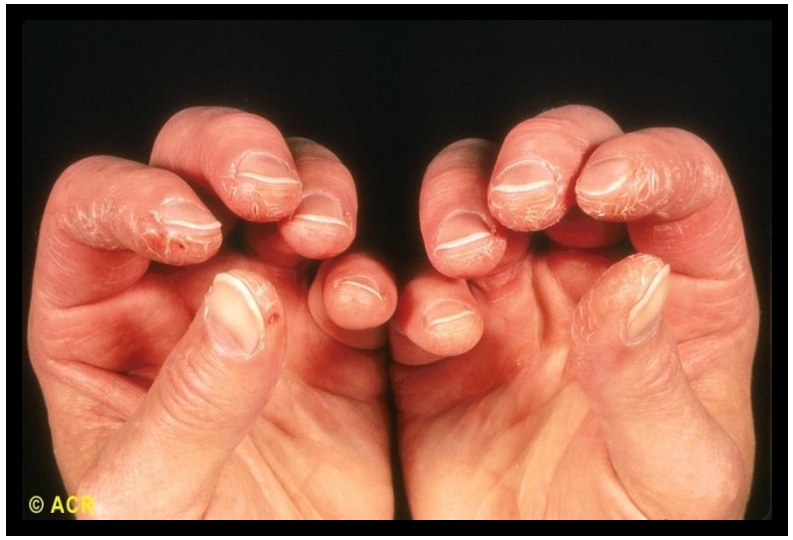
Lung Phenotype: ILD can include OP, AIP (diffuse alveolar damage) and pneumomediastinum

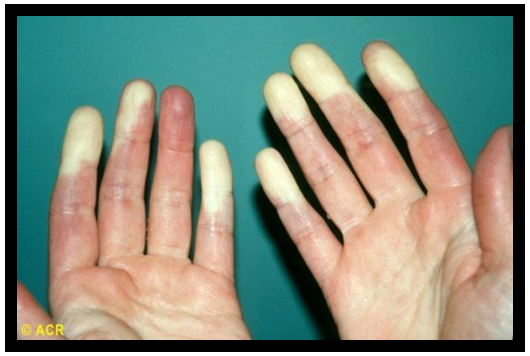


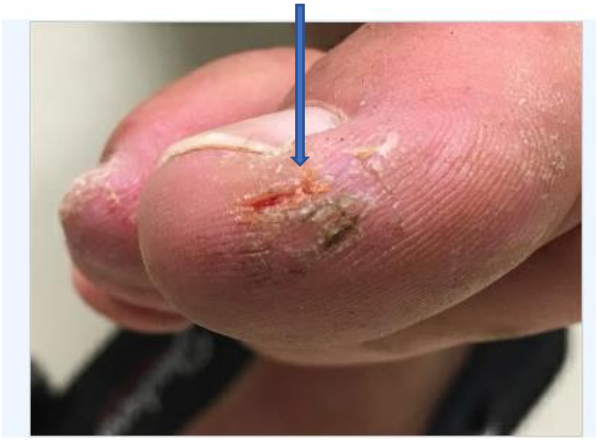




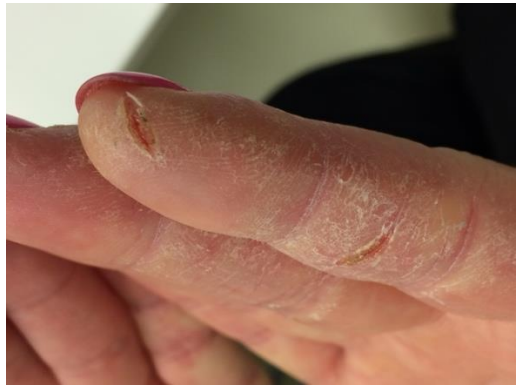
Antisynthetase Syndrome

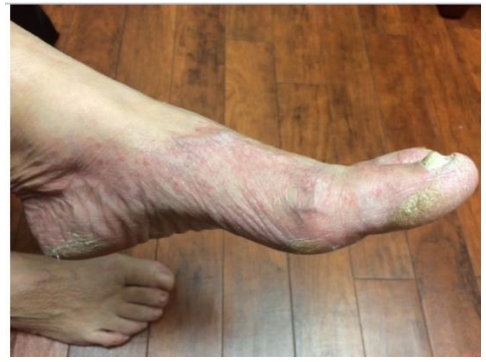






Fever
Raynaud's
Inflammatory Arthritis
Mechanics hands
ILD





Solomon et al (2011) [10]

Required: Presence of anti-aminoacyl tRNA synthetase antibody

PLUS *two major* or *one major and two minor criteria*:

Major:

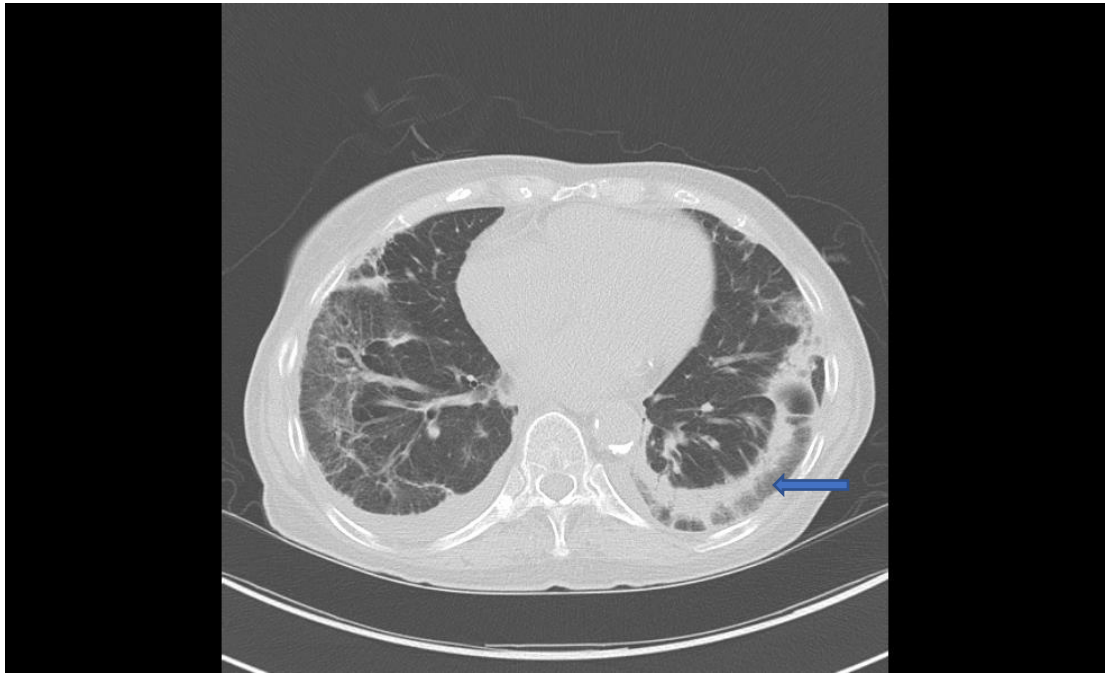
1. Interstitial Lung Disease (not attributable to another cause)
2. Polymyositis or dermatomyositis by Bohan and Peter critieria

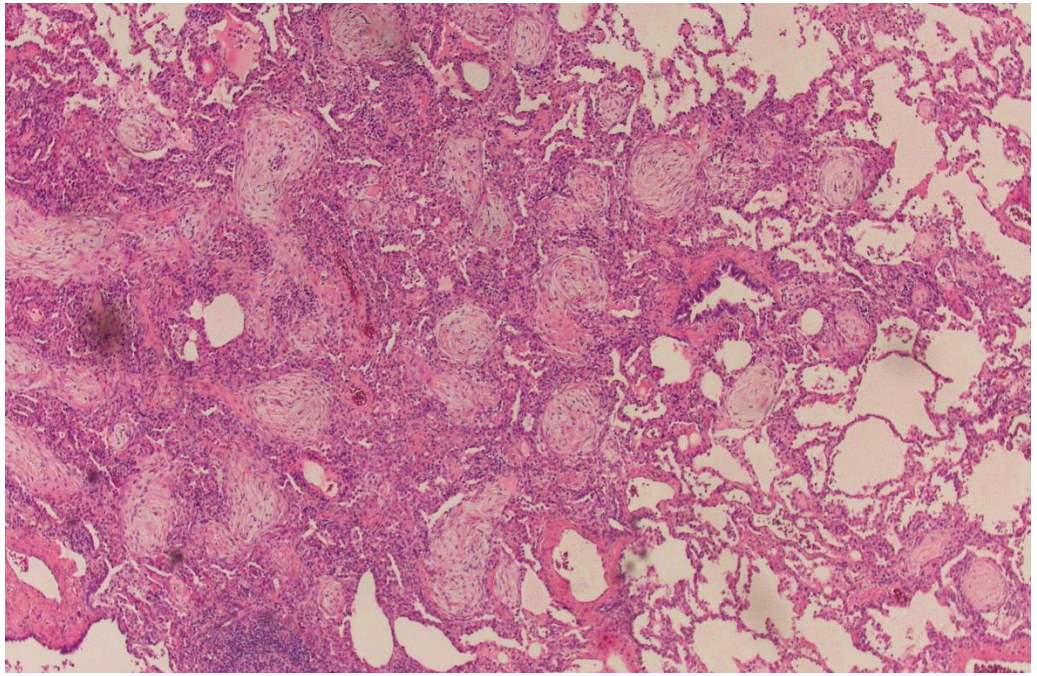
Minor:

1. Arthritis
2. Raynaud's phenomenon
3. Mechanic's hands

Witt LJ et al. Clin Pulm Med. 2016 Sep; 23(5): 218–226.

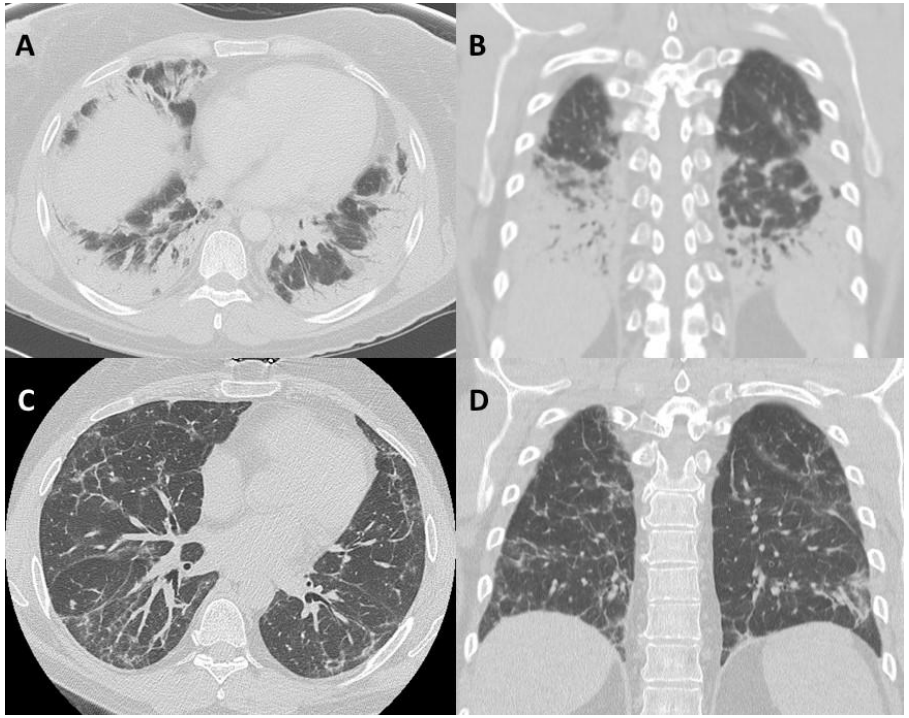
Case: Typical CT finding in antisynthetase ILD:39 yo female with weakness, dyspnea and elevated CK : Jo-1+. What pathology does this CT suggest? Note the Atoll sign on CT, which correlates with organizing pneumonia



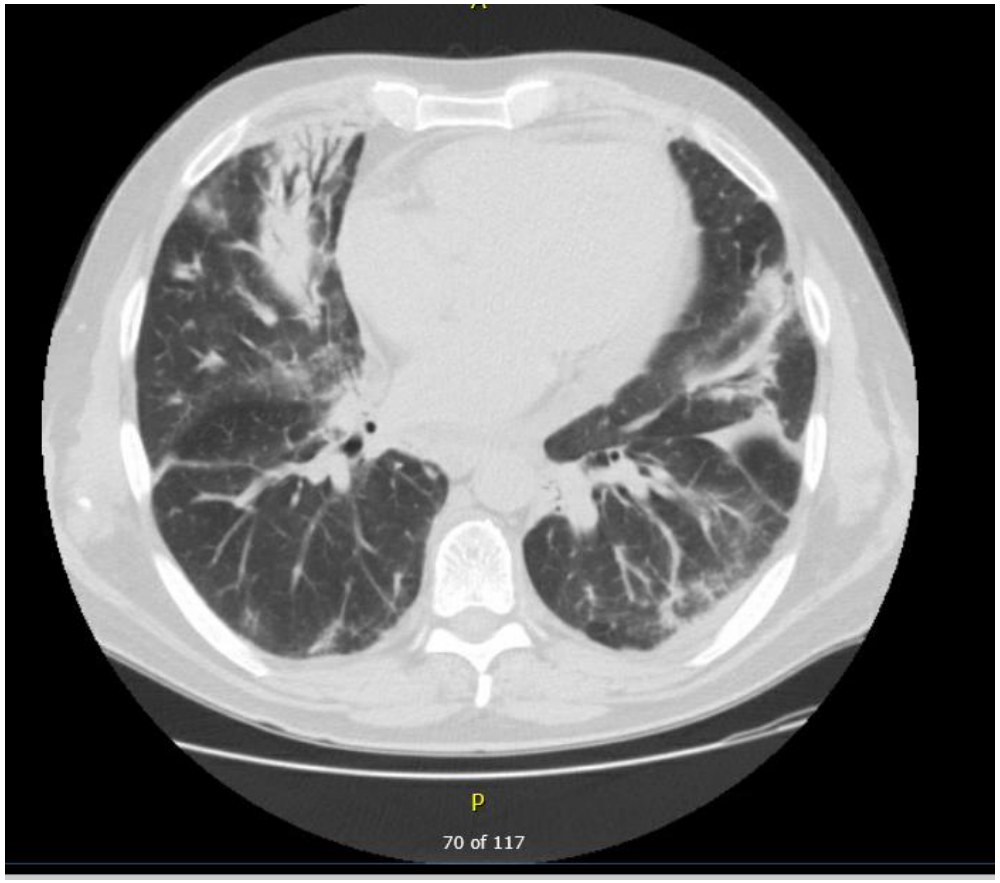


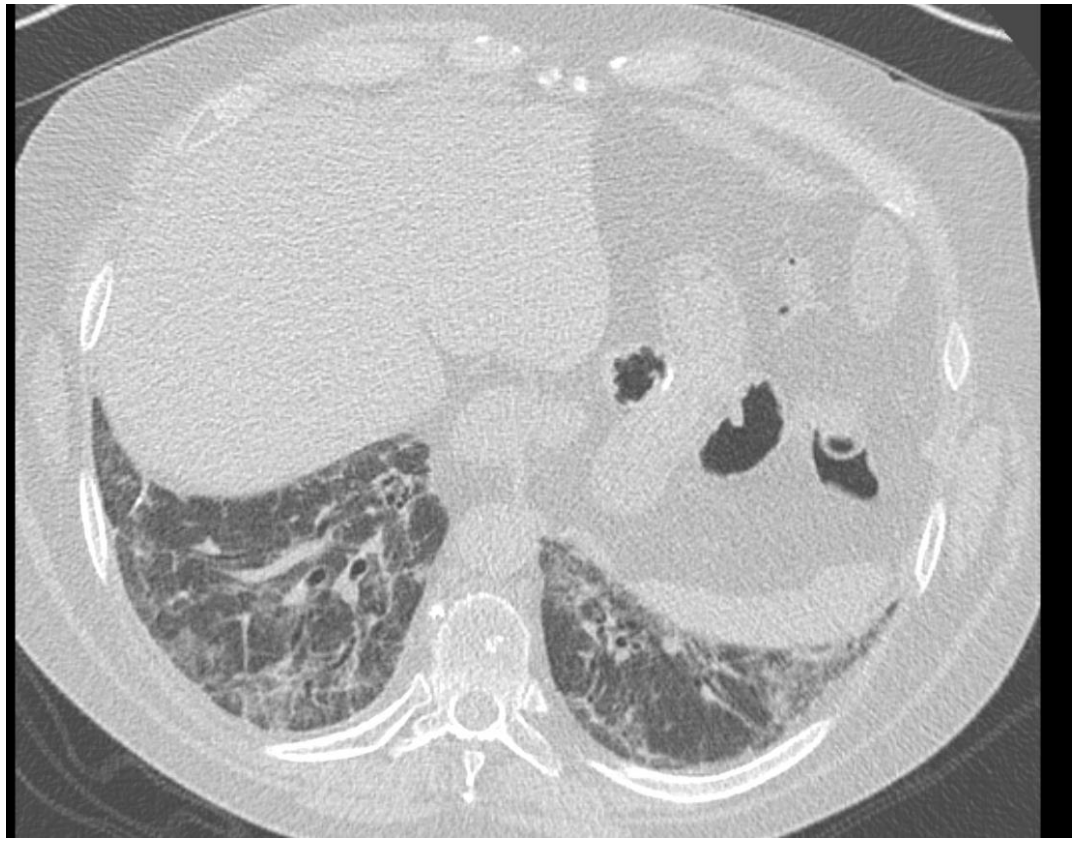
Path showed Organizing pneumonia(OP) and NSIP:Initially treated with CS and MMF, prednisone, incomplete response (muscle and lung) so Rituxan added with success. **FVC 100% DLCO 72%.**

Anti-inflammatory therapy can work for this group of patients



Caution!: Inflammatory disease can evolve to fibrotic phenotype (Jo-1+ 2014 and then 2019)





Treatment in ILD/IIM

Corticosteroids nearly always in combination with another agent typically MMF or AZA

CNIs: (Tacrolimus) embraced more now, esp in MDA 5

Rituxan or Cyclophosphamide (often for severe disease)

JAK inhibitors (limited data MDA5 but mechanistically plausible)

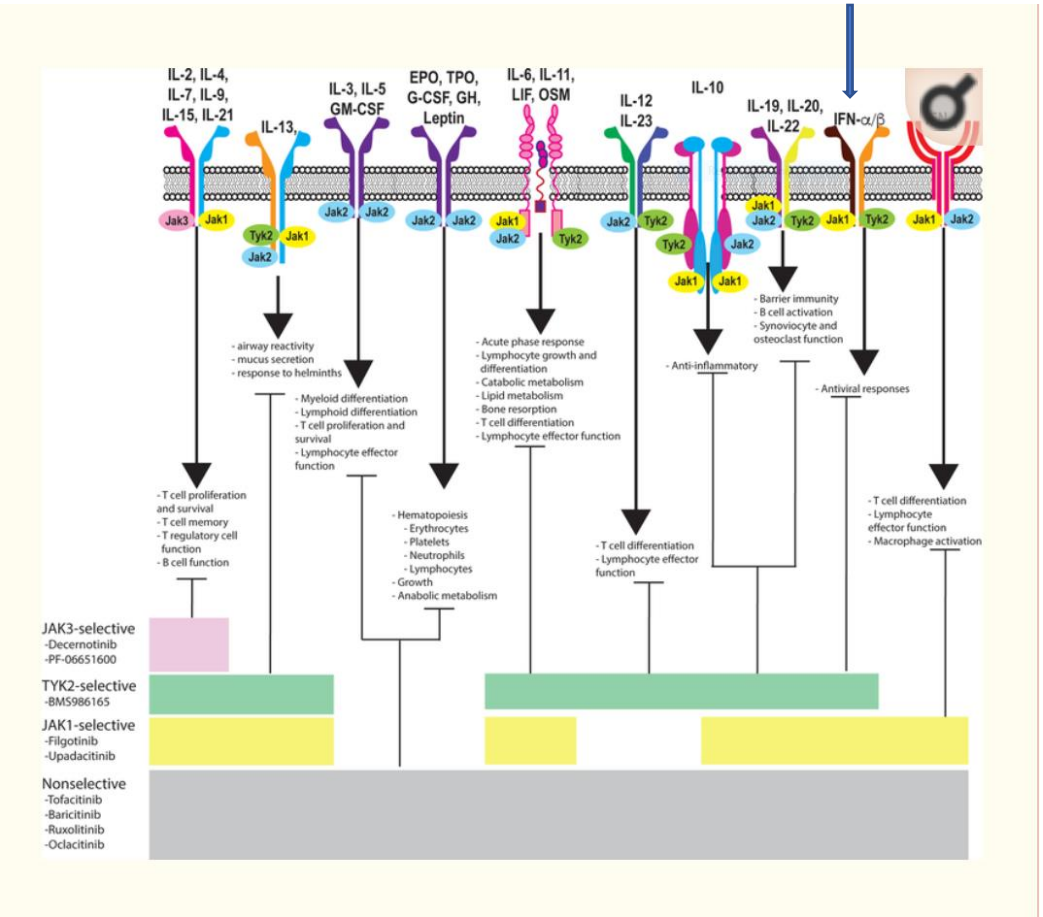
IVIG often in cases that fail to respond to CS/MMF or AZA (Huapaya et al Resp Med 2019) though IVIG has become popular given low toxicity

Will some of these pts need antifibrotic therapy? Probably

Abatacept in antisynthetase ILD *

CD 19 targeted chimeric antigen therapy (CAR) T case reports (Muller Lancet 2023, Pecher JAMA 2023)

- If MDA 5 and other DM ILD has **an interferon signature**, is there a role for JAK inhibitor here?



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Long-term treatment with human immunoglobulin for antisynthetase syndrome-associated interstitial lung disease

J.A. Huapaya[a,b,1], R. Hallowell[c], L. Silhan[d], I. Pinal-Fernandez[e], M. Casal-Dominguez[e,f,g], C. Johnson[h], J. Albayda[g], J.J. Paik[g], C.T. Lin[i], A. Hussien[i], A.L. Mammen[e,f,g], L. Christopher-Stine[f,g,1], S.K. Danoff[a,*,1]

[a] Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, United States
[b] Division of Internal Medicine, MedStar Georgetown University Hospital, Washington, DC, 20007, United States
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ABSTRACT

Background: Interstitial lung disease-associated antisynthetase syndrome (AS-ILD) carries significant morbidity and mortality. Corticosteroids and immunosuppressive drugs are the mainstay of treatment. Human immunoglobulin (IVIg), an immunomodulator without immunosuppressive properties, is effective in myositis but the evidence supporting its use in ILD is scarce.

Objective: To describe clinical outcomes of AS-ILD patients receiving IVIg.

Methods: Retrospective analysis of AS-ILD patients. Linear mixed models using restricted maximum likelihood estimation was used to estimate the change in lung function and corticosteroid dose over time.

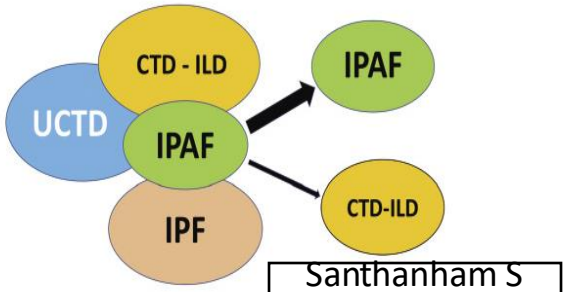
Results: Data from 17 patients was analyzed. Median follow-up was 24.6 months. Fourteen patients had refractory disease. The mean percent-predicted forced vital capacity (FVC%) ($p = 0.048$) and percent-predicted diffusing capacity of the lung for carbon monoxide (DLCO%) ($p = 0.0223$) increased over time, while the mean prednisone dose ($p < 0.001$) decreased over time. Seven patients achieved a > 10% increase in FVC%, including two who used IVIg as initial treatment. Five patients showed a > 10% increase in DLCO% and TLC%. Nine (53%) patients experienced side effects.

Conclusions: IVIg may be a useful complementary therapy in active progressive AS-ILD but is associated with potential side effects. Fssssurther investigation is required to determine the value of IVIg as an initial treatment in AS-ILD.

IPAF designation (Fischer A et al EJR 2015)

A. Clinical domain	B. Serologic domain	C. Morphologic domain
1. Distal digital fissuring (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)	1. ANA ≥1: 320 titer, diffuse, speckled, homogeneous patterns or a) ANA nucleolar pattern (any titer) or b) ANA centromere pattern (any titer) 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	1. Suggestive radiology patterns by high-resolution computed tomography (HRCT): 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 centers 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 d) Unexplained pulmonary vasculopathy

ANA, antinuclear antibody; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune features; LIP, lymphoid interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function testing.



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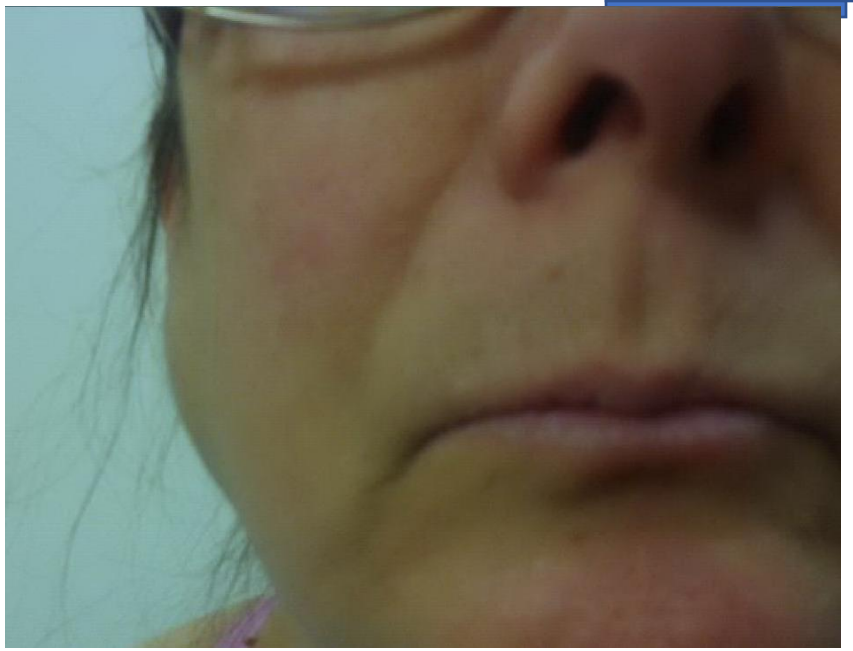
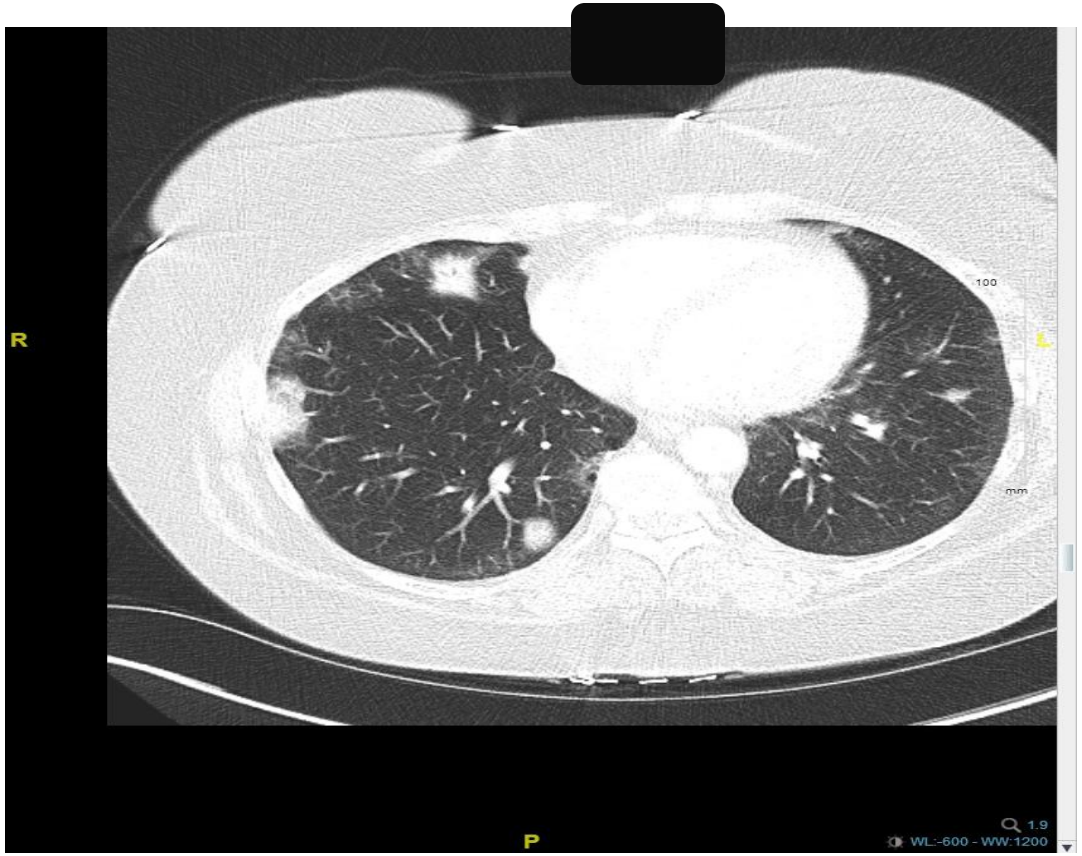
UCTD – Undifferentiated connective tissue disease; IPAF – Interstitial pneumonia with autoimmune features; IPF – Idiopathic pulmonary fibrosis; CTD – ILD – Connective tissue disorder associated interstitial lung disease

Lung disease and Sjogren's disease

- All forms of ILD (9%) are described though severe disease is not common
- Patients cough a lot partly due to xerostomia/trachea
- NSIP, UIP, LIP,OP.
- Bronchiolitis also common
- Thin walled cysts commonly seen
- ***Male, smokers, older, antibody positivity are at higher risk for ILD***
- Functional deterioration is unusual but has been described.
- **Major concern is where there is a focal nodular lesion, which could represent lymphoma and in rare cases amyloidosis.**

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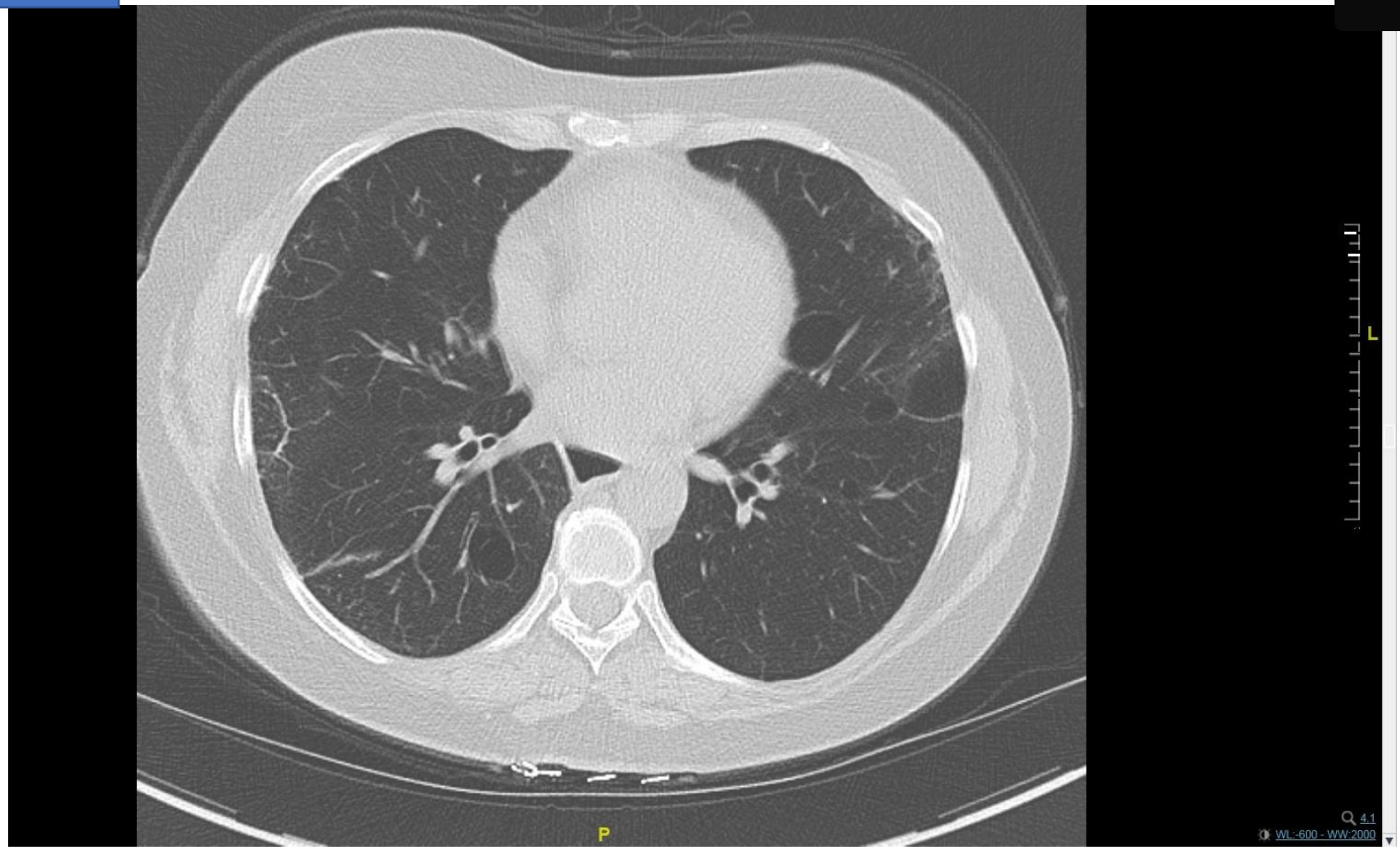
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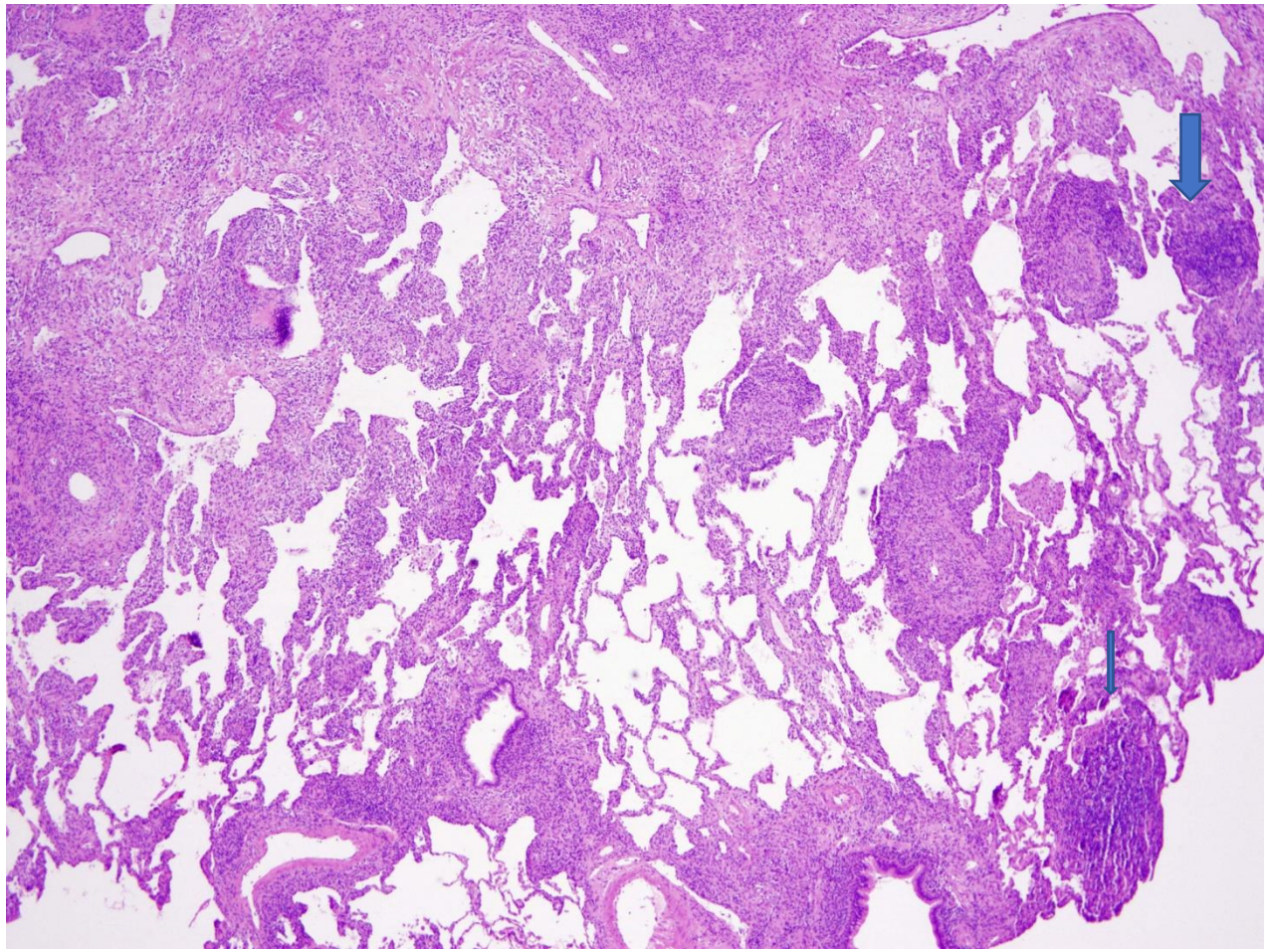
Lung bx 9/2014:lymphcytic interstitial pneumonia (LIP)



How aggressive to screen in CTD for ILD and whom?

- **Scleroderma**:HRCT at baseline, and Echo/PFTs baseline then PFT yearly (>10% decline in FVC or composite FVC/DLCO decline with assessment of extent fibrosis on CT)
- **IIM**: Baseline PFT/CT ,especially in antisynthetase patients/MDA5
- Malignancy guidelines in IIM now published
- **MDA 5** : baseline CT and frequent PFTs q 3-6 months esp the first 1-2 years
- **RA**: probably a risk factor analysis in combination with a functional test and emerging genetic and other biomarkers will determine who gets PFT/CT scanning or screen using a low dose CT in those who qualify for lung cancer screening. Many active efforts at numerous institutions to find these patients.

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