Brigham Pulmonary Board Review: Pulmonary Involvement in Rheumatic Diseases

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Disclosure

- Genentech
- FDA Advisory Board
- Up to Date

Outline

- Overview of the rheumatic diseases and clues to diagnosis
- Rheumatoid arthritis: risk factors for ILD , other lung manifestations in RA and recent trial results.
- Scleroderma: risk factors for ILD and ongoing trials
- Inflammatory myositis: risk factors for ILD and ongoing trials
- Interstitial pneumonia with autoimmune features (IPAF)
- Screening and treatment strategies in CTD-ILD

When considering a CTD diagnosis, and before you order labs, a good history and examination helps a lot!

- RA: inflammatory arthritis, pleuritis (MCP squeeze test)
- Scleroderma:Raynauds, GERD/esophageal dysmotility, limited oral aperture, calcinosis, skin thickening, dyspnea, nailfold capillary changes
- IIM: proximal muscle weakness, rash, dyspnea, diff swallowing
- Sjogrens: sicca complex, parotid swelling
- SLE: oral ulcers, pleurisy, rash, arthritis, hair loss, mostly female
- Vasculitis: like GPA/MPA/GS: DAH, GN, rash, mononeuritis,upper respiratory tract (otitis,epistaxis, sinusitis, septal perforation)

Antibodies and clinical correlation

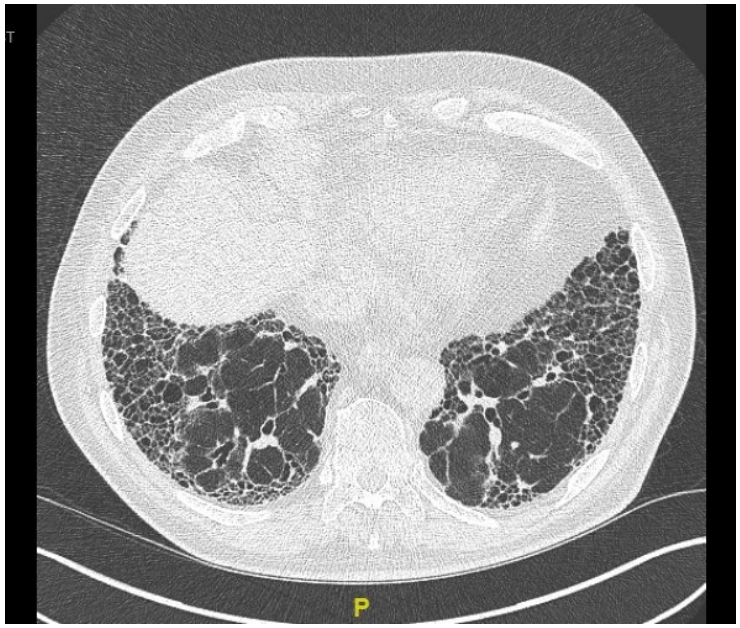
- ANA: SLE, SS, Sjogrens, viral, bacterial infection, hepatitis, false + common
- Centromere: limited scleroderma, less likely ILD, more likely PAH
- **Ro**:Sjogrens (50%),discoid lupus, scleroderma like syndromes, antisynthetase syndrome (ASSD)
- **Scl-70:** diffuse scleroderma but seen only in 20% 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
- 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

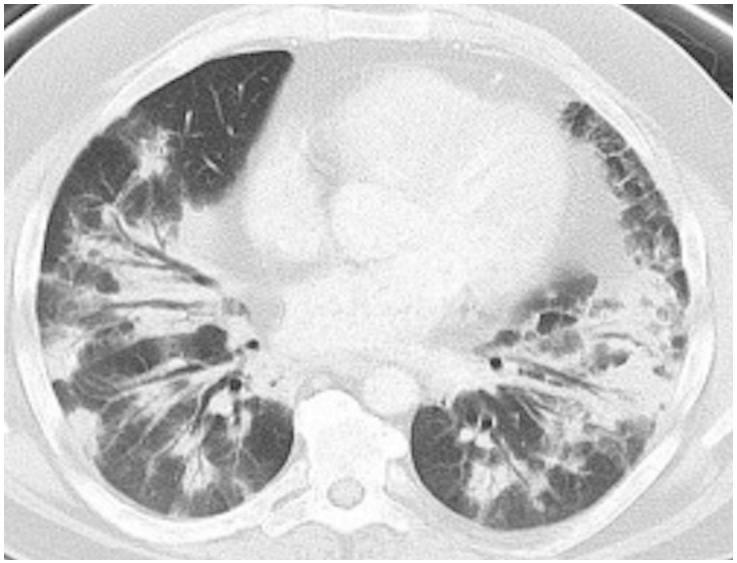
MYOSITIS PANEL				Other Antibodies	
Myositis-Specific		Myositis-Associated			
Anti-Synthetases					
JO-1	NEG	PM-SCL	NEG	P155/140	NA
PL-7	NEG	KU	NEG	RNA POL	NA
PL-12	NEG	U1RNP	NEG	TH/TO	NA
EJ	NEG	U2RNP	NEG	U3RNP	NA
OJ	NEG	RO60	IND	MJ	NA
				MDA5	NA
MI-2	NEG				
SRP	NEG			OTHER ANALYTES	NA

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)



ILD in the CTD: a new paradigm and implications for treatment

- When the predominant lung lesion is inflammatory, then anti-inflammatory therapy is indicated
- When the predominant lung lesion is fibrotic, then anti fibrotic therapies are indicated
- Will some patients benefit from both treatments?
- What are the costs ?

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%)

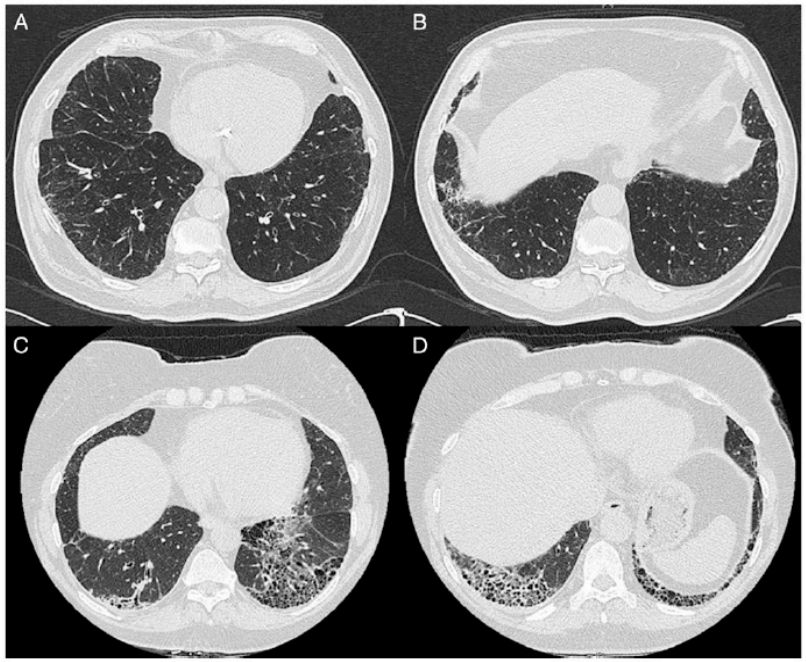
ILD in RA: A spectrum of disease

- **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**



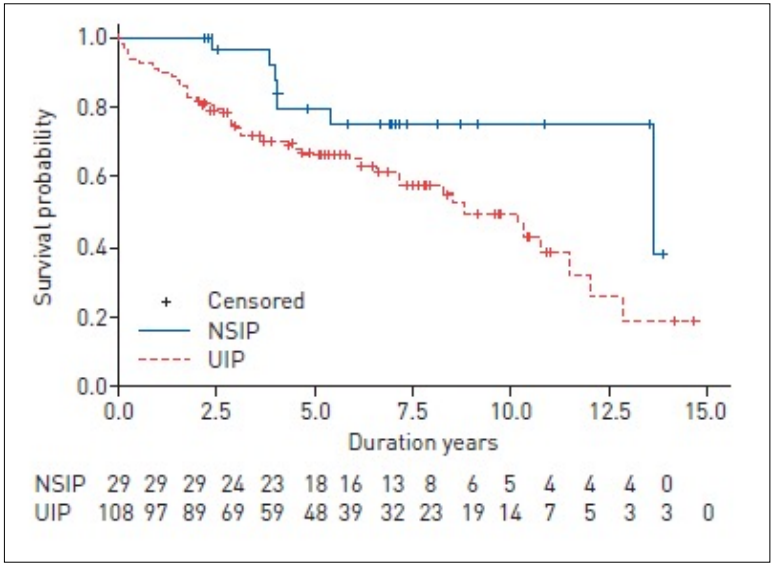
Gochuico Arch Int Med 2008
Bongartz Arth Rheum 2010
Olson AJRCCM 2011
Kim Eur Resp J 2010
Doyle Chest 2013, 2014

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

GAP tool in RA ILD (Morisette J et al Resp Med 2017, Ley et al Ann Int Med 2012)

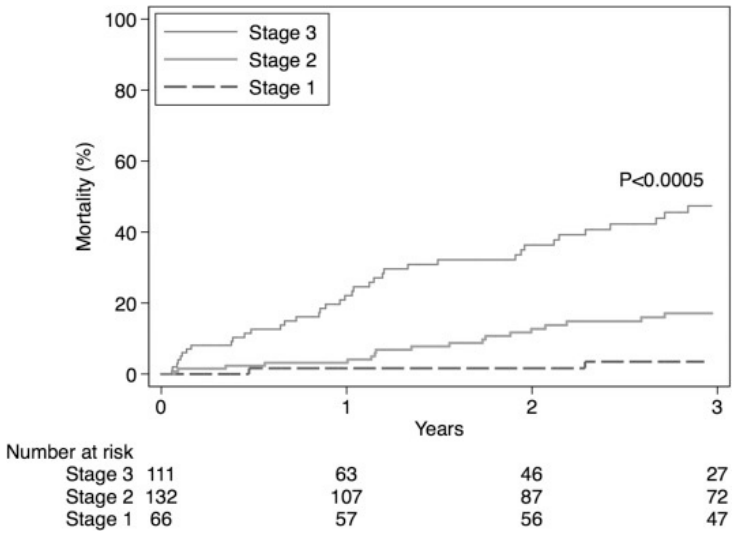
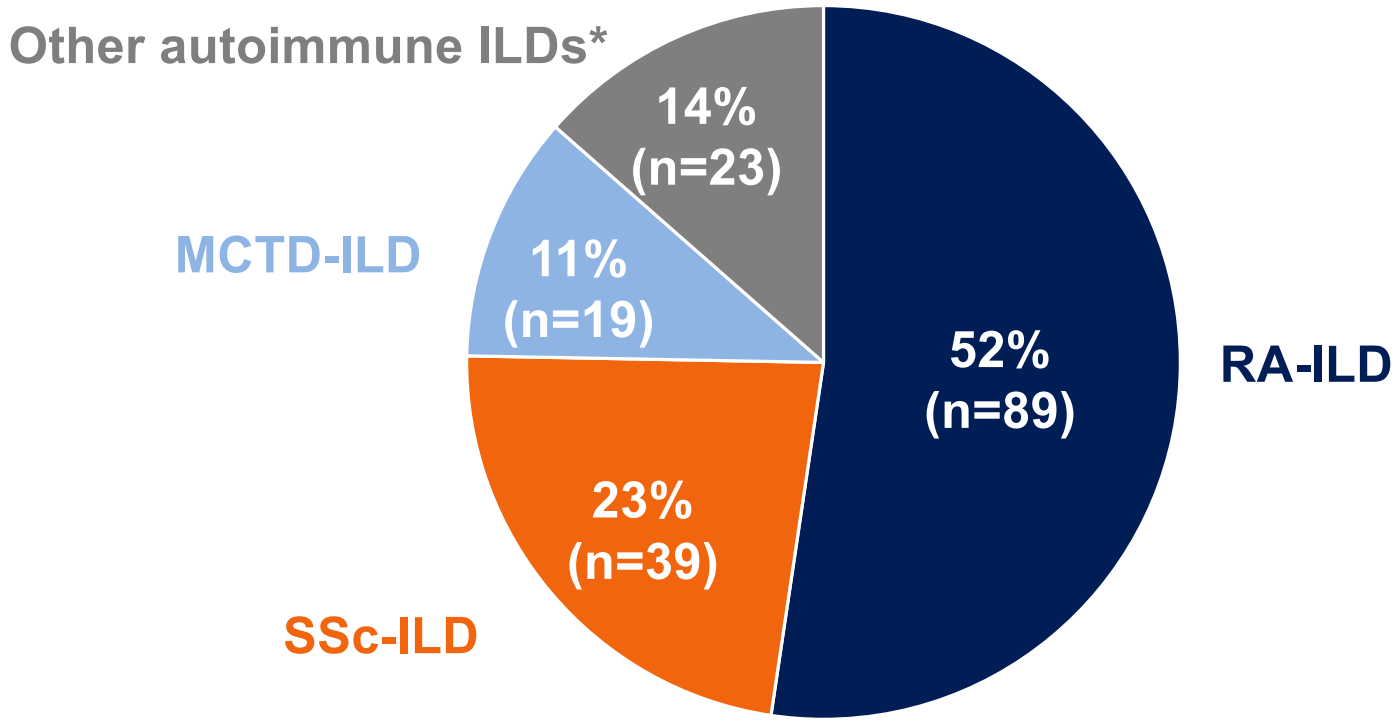


Figure 2. **The GAP index and staging system.**

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, % *predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, % *predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

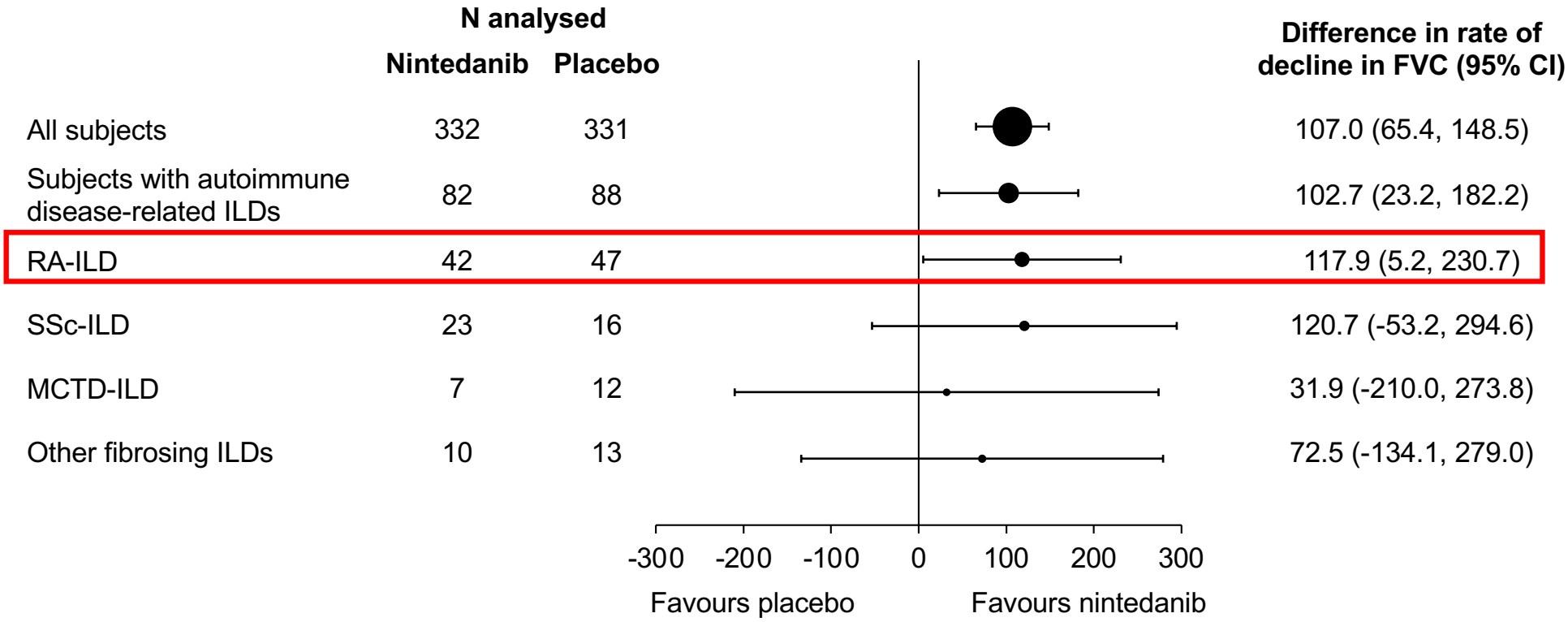
RA ILD Treatment: the INBUILD trial



*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**



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

Abatacept and RA ILD (Fernandez-Diaz C et al Rheumatology 2020)

- Observational study
- 262 patients with ILD
- All had received at least 1 dose of ABA
- UIP 40% NSIP 31%
- Over a mean 12 month follow up:
- Dyspnea worsened in 9%,
- FVC % worsened in 13%
- DLCO % worsened in 10%
- HRCT worsened in 25%

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.

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

Screening strategies in RA/ILD in 2021 absent great biomarkers

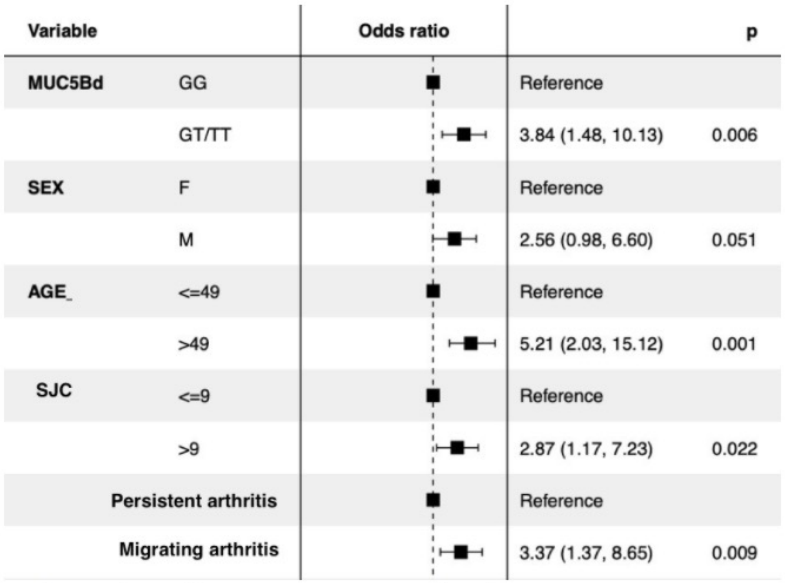
MUC5B Promoter Variant rs35705950 and Risk Stratification for Rheumatoid Arthritis – Interstitial Lung Disease

Pierre-Antoine Juge[1] et al

(ACR Nov 2020)

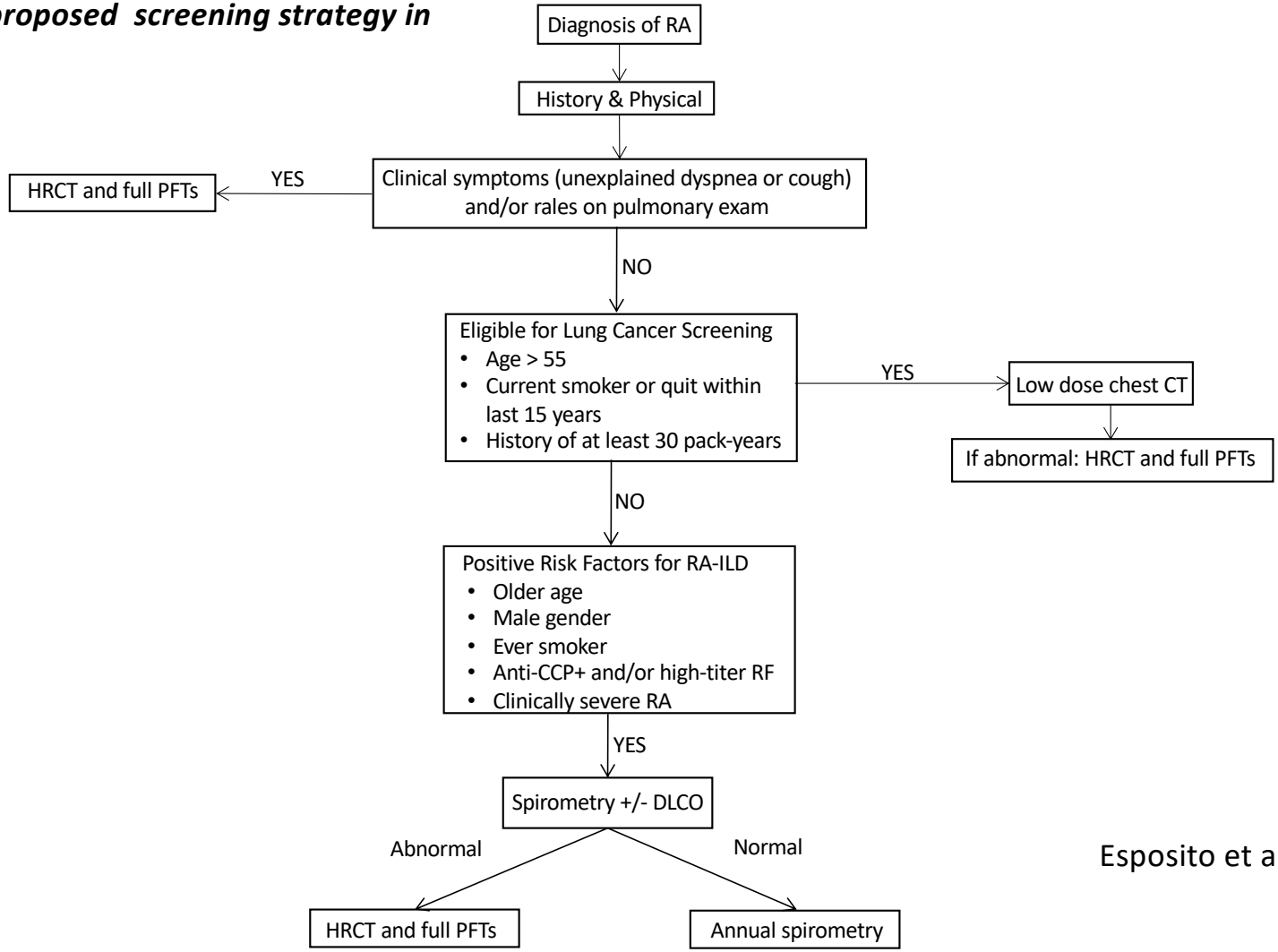
Conclusion: In RA patients, altogether with baseline clinical data, *MUC5B*rs35705950 genotyping could help to improve risk stratification for ILD occurrence at 13 years of RA duration.

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



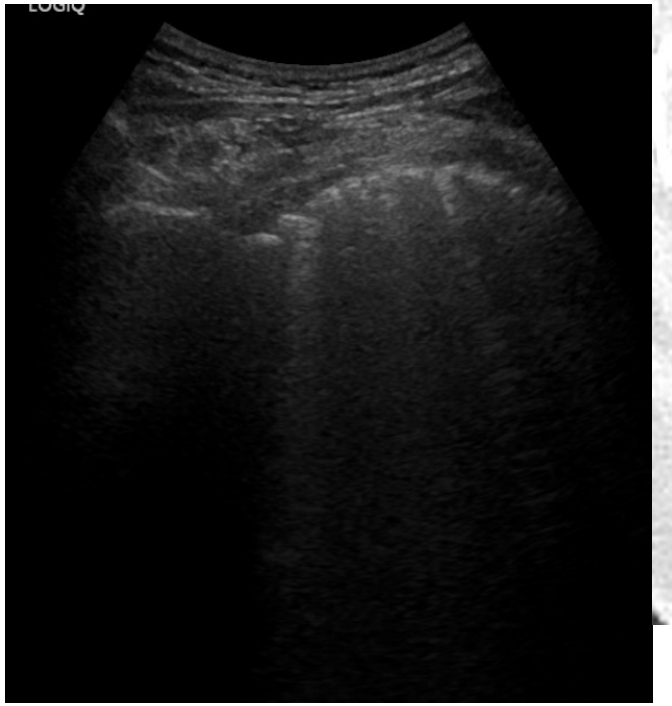
Baseline predictors of ILD occurence at 13 years of RA duration

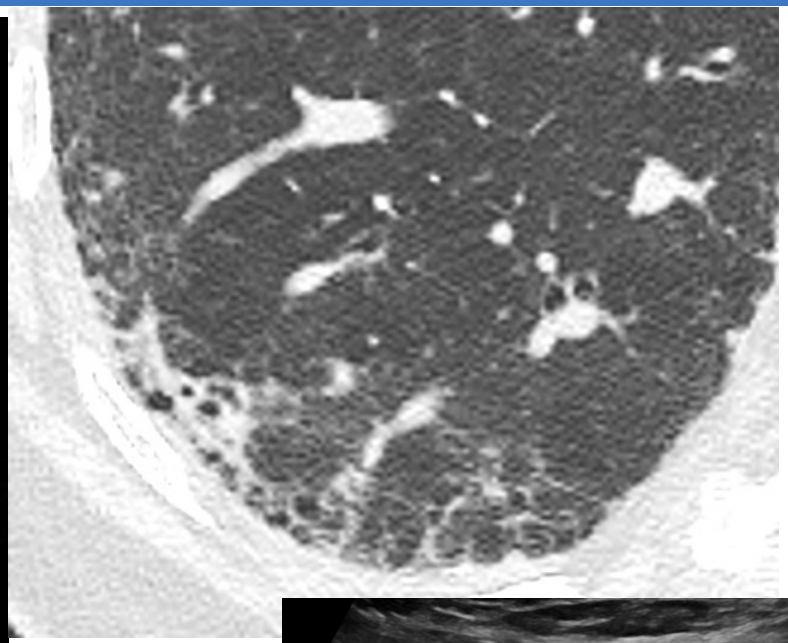
Option 1: proposed screening strategy in RA ILD

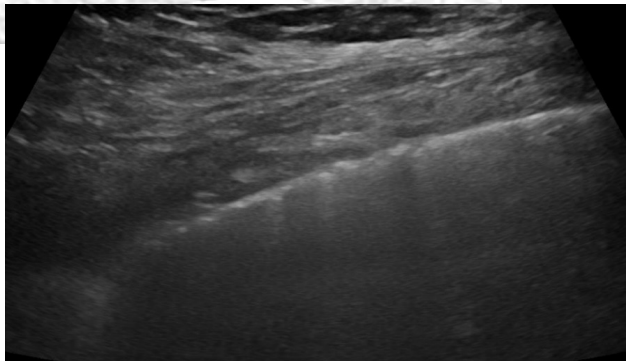


Esposito et al 2019

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





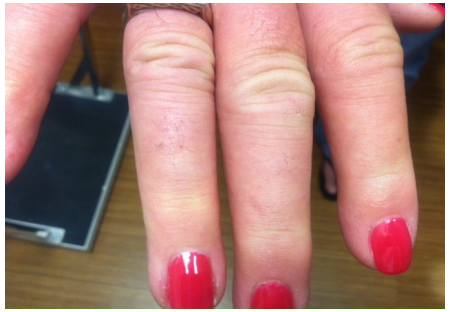


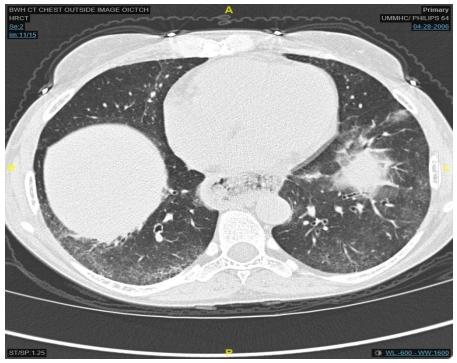
Courtesy of Koduri G

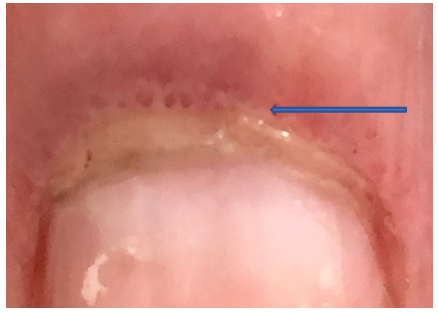
Systemic Sclerosis (SSc)

- 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







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)
- 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)
- >20% fibrosis on CT 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)

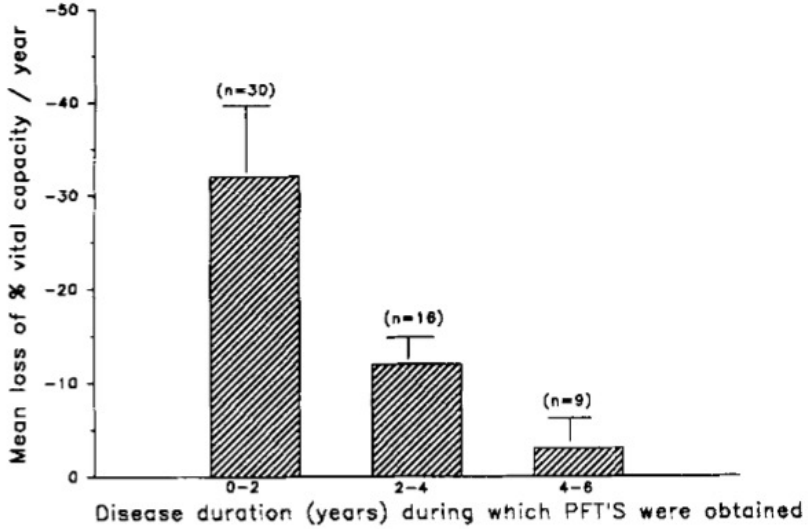
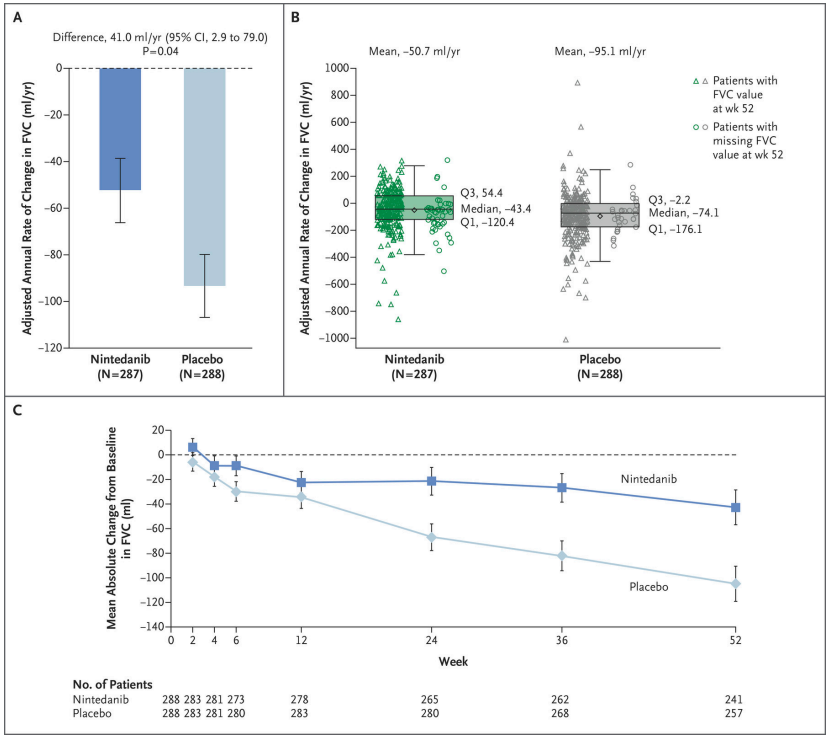


Figure 1. Mean loss of percent vital capacity occurring over 2-year time periods in 55 patients whose initial pulmonary function tests (PFT's) were performed during the first 5 years of scleroderma symptoms.

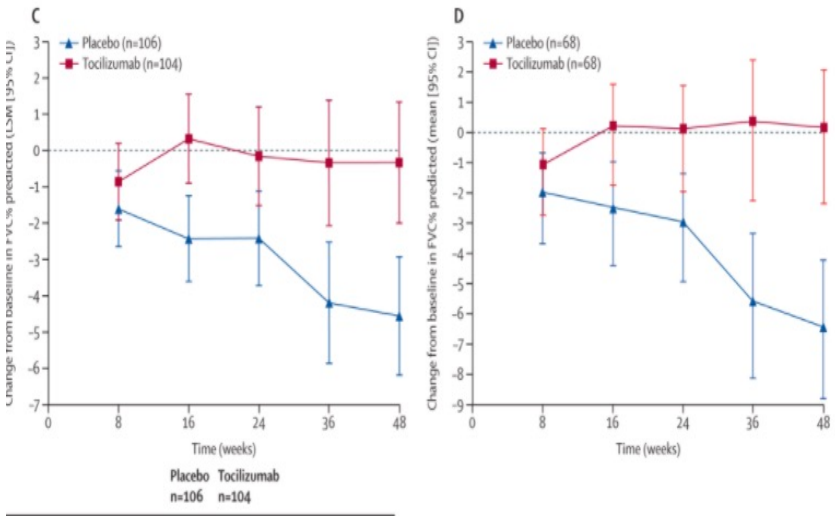
Contemporary Treatment in SSc: MMF still the cornerstone of therapy

- SLS I,II (Cyclophosphamide, **but now most of use MMF**)
- Nintedanib in SSc (SENCIS trial)
- Myeloablative therapy (NEJM 2018) :rapidly progressive ILD
- IL-6 receptor antibody (Lancet Resp Med 2020)
- SLS III: randomized trial using Pirfenidone vs SOC (stopped)
- INBUILD trial (PF- ILD non IPF) (+ trial but small number of scleroderma pts)
- Rituximab (small studies)
- Inhaled trepoprostinil in ILD? (Nathan S et el Lancet Resp 2021)

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

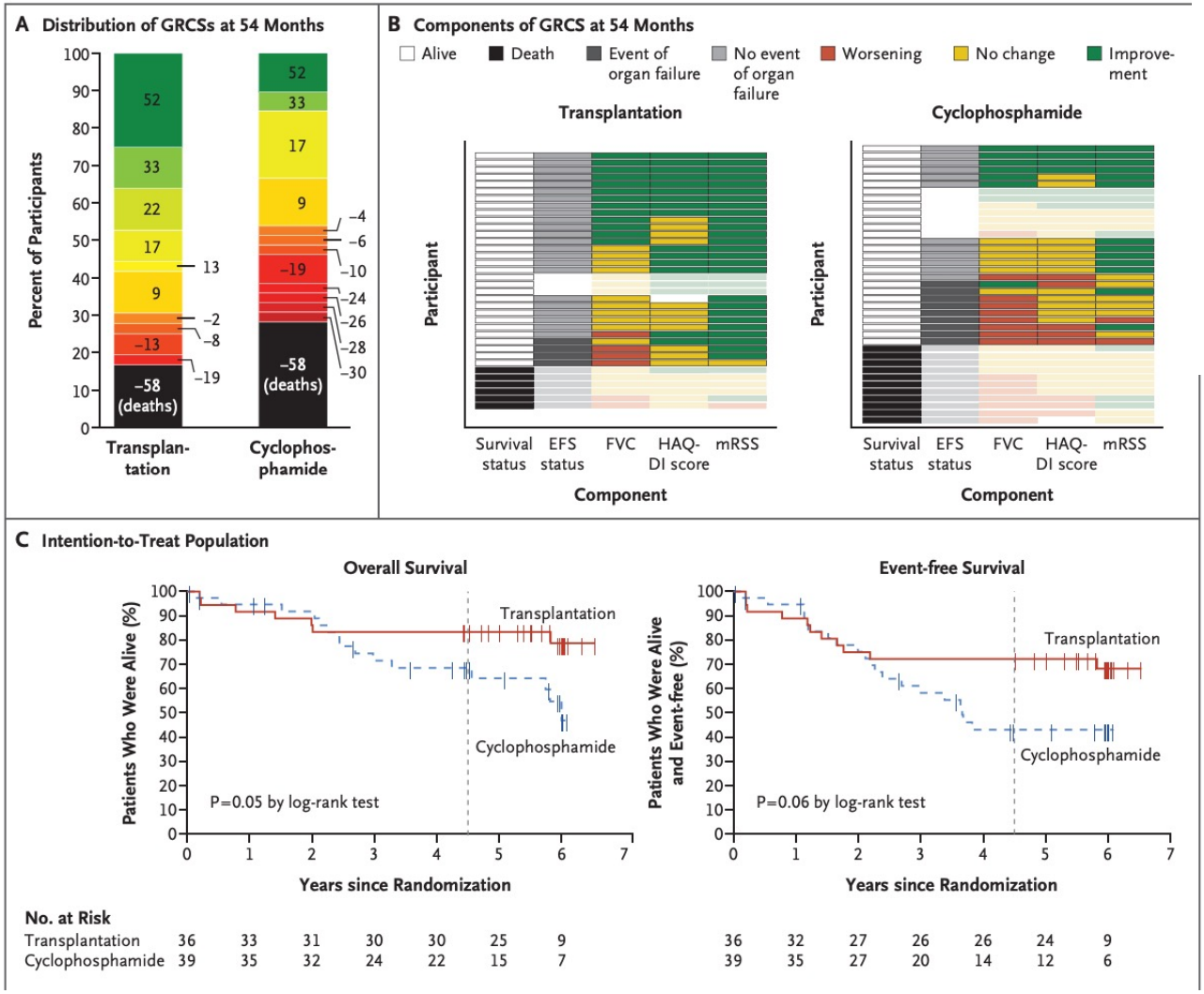
The NEW ENGLAND JOURNAL of MEDICINE

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



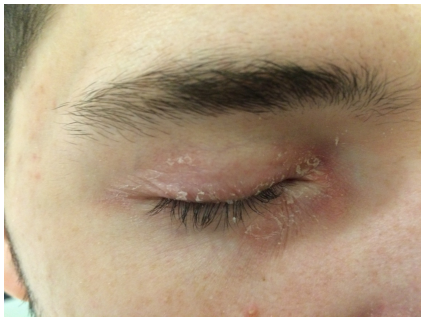
How do these trials change practice ?

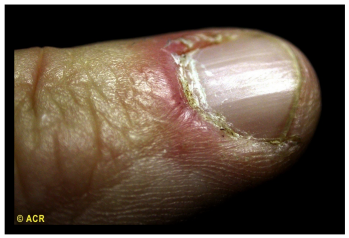
- FDA approval for antifibrotics in CTD ILD can affect the way we practice and identify and refer for ILD assessment and treatment.
- The results of the antifibrotics are modest: these drugs are not blockbusters.
- If a patient is stable on MMF and has fibrosis is there any reason to add on anti-fibrotic if lung function stable?
- If they are not stable on MMF then adding or changing to antifibrotic may be reasonable.
- In a UIP pattern patient (INBUILD phenotype), the use of antifibrotics may be considered. Can patients and society afford them?
- Therapies for ILD and fibrosis are evolving with many ongoing trials.

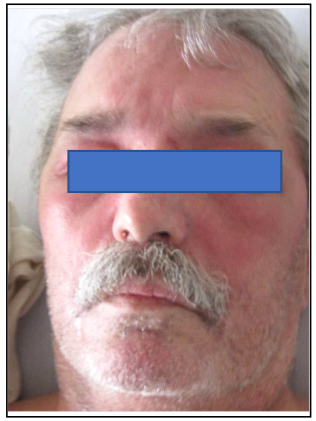
Inflammatory Myositis and the lung

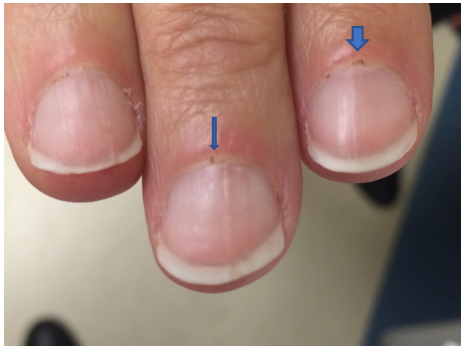
- *Interstitial lung disease* (NSIP, UIP and acute interstitial pneumonitis)
- *Organizing pneumonia (COP)*
- *Antisynthetase syndrome* (fever, Raynauds, arthritis, myositis, mechanics hands,ILD)
- MDA5
- Respiratory muscle dysfunction
- Diaphragmatic dysfunction

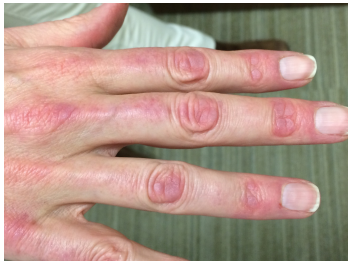
Teaching Phenotypes: how to get our Pulm/CCM colleagues to identify DM and autoimmune diseases.**Look at the hands! Look at the skin**!



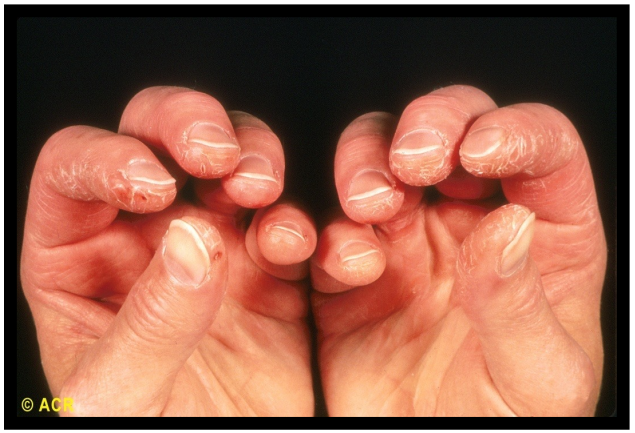


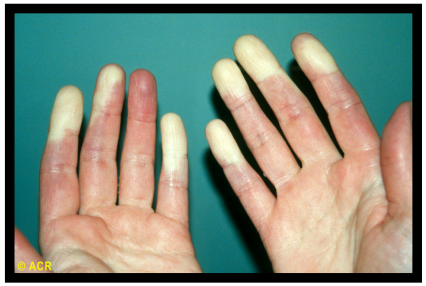


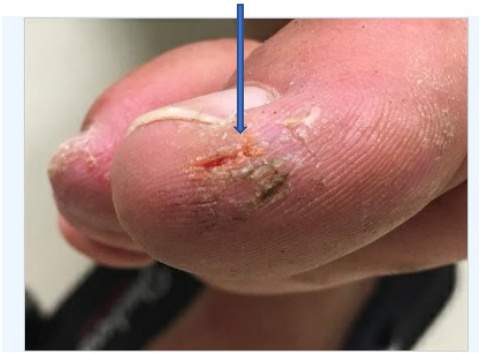




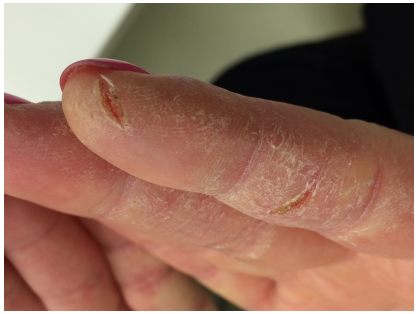
Antisynthetase Syndrome

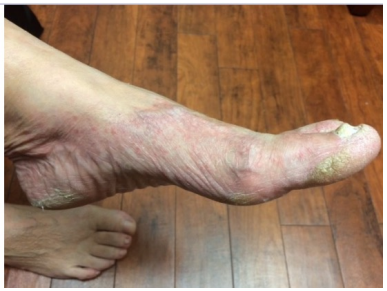






Fever
Raynaud's
Inflammatory Arthritis
Mechanics hands
ILD





Solomon et al (2011) [10]

Required: Presence of anti-aminoacyl tRNA synthetase antibody

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

Major:

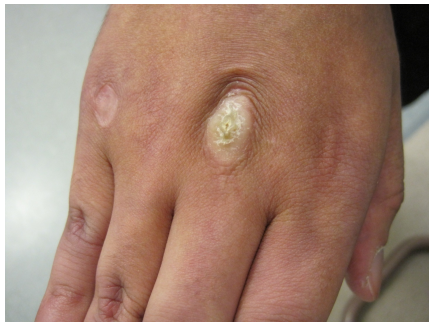
1. Interstitial Lung Disease (not attributable to another cause)
2. Polymyositis or dermatomyositis by Bohan and Peter critieria

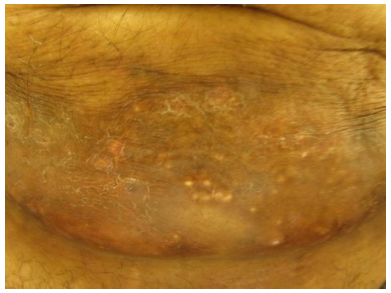
Minor:

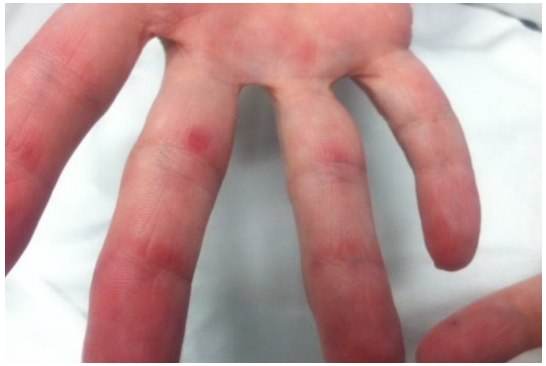
1. Arthritis
2. Raynaud's phenomenon
3. Mechanic's hands

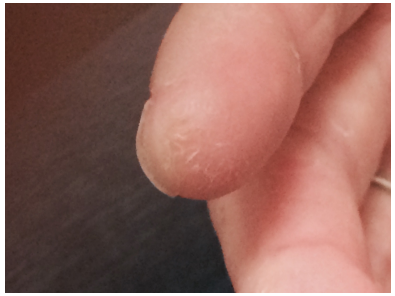
Witt LJ et al. Clin Pulm Med. 2016 Sep; 23(5): 218–226.

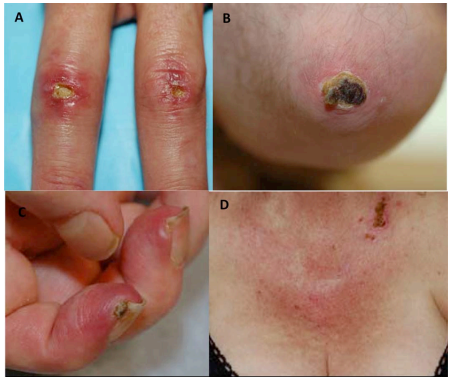
Phenotype skin MDA 5: high risk of rapidly progressive ILD inc AIP pattern









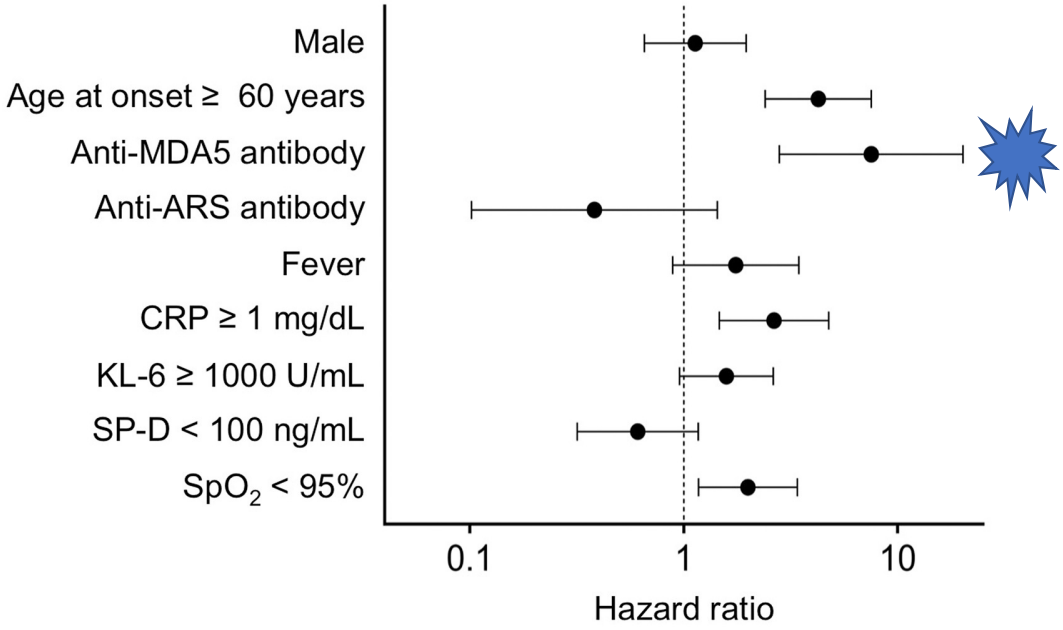


Narang et al
Arthritis Care
2015;67(5)

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**

Fig. 1 Predictive model for mortality due to respiratory insufficiency in patients with PM/DM-associated ILD
Initial ...

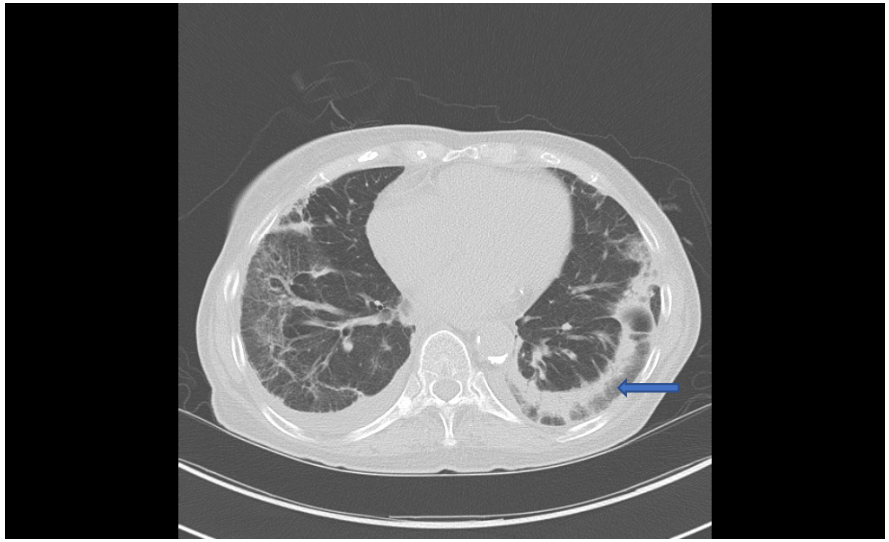


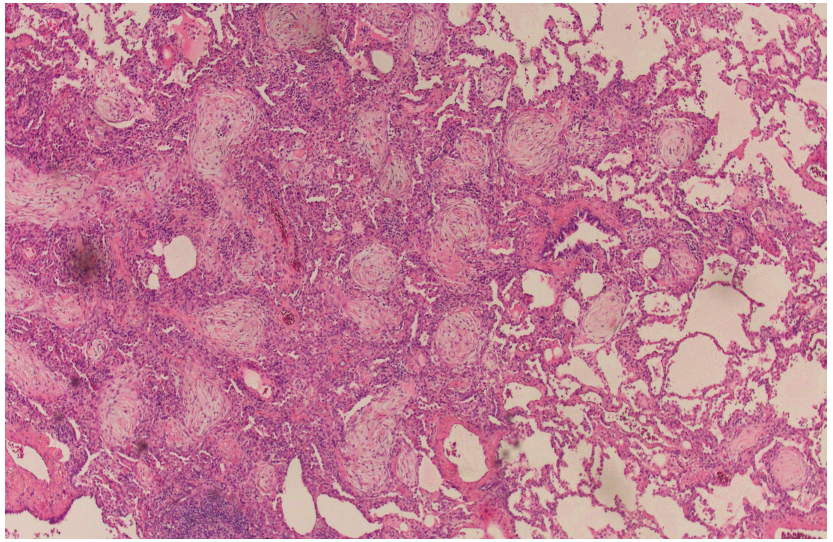
Rheumatology, Volume 57, Issue 7, July 2018, Pages 1212–1221, https://doi.org/10.1093/rheumatology/key060

ILD in Inflammatory Myositis : predictors of poorer outcomes

- Acute/subacute form*
- Older age onset *
- Lower level of FVC,DLCO at onset* (Fujisawa 2017 Respir Med 55(2):130)
- African American and pl-12 and PL-7* Pinal-Hernandez I et al Rheumatology 2017:56(6)
- GAP Model scoring (sex, age, physiology)
- Ro 52, *MDA5*

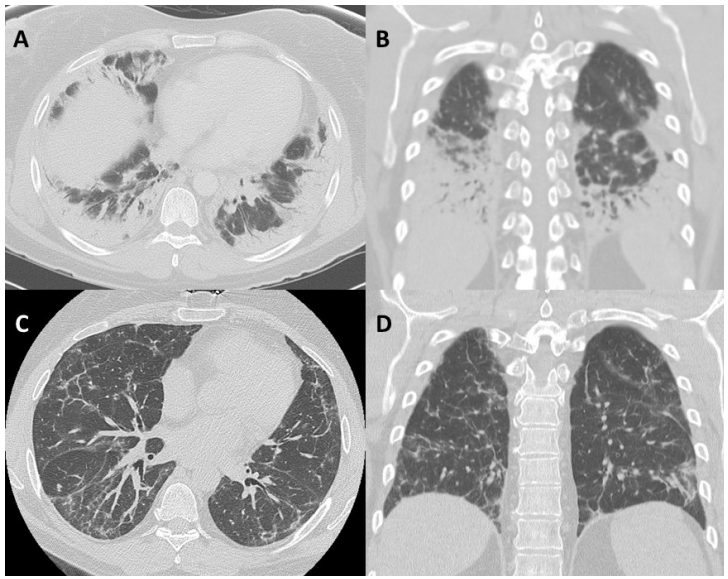
Typical CT finding in antisynthetase ILD:39 yo female with weakness, dyspnea and elevated CK : Jo-1+. What pathology does this CT suggest? Note the Atoll sign on CT, which correlates with organizing pneumonia



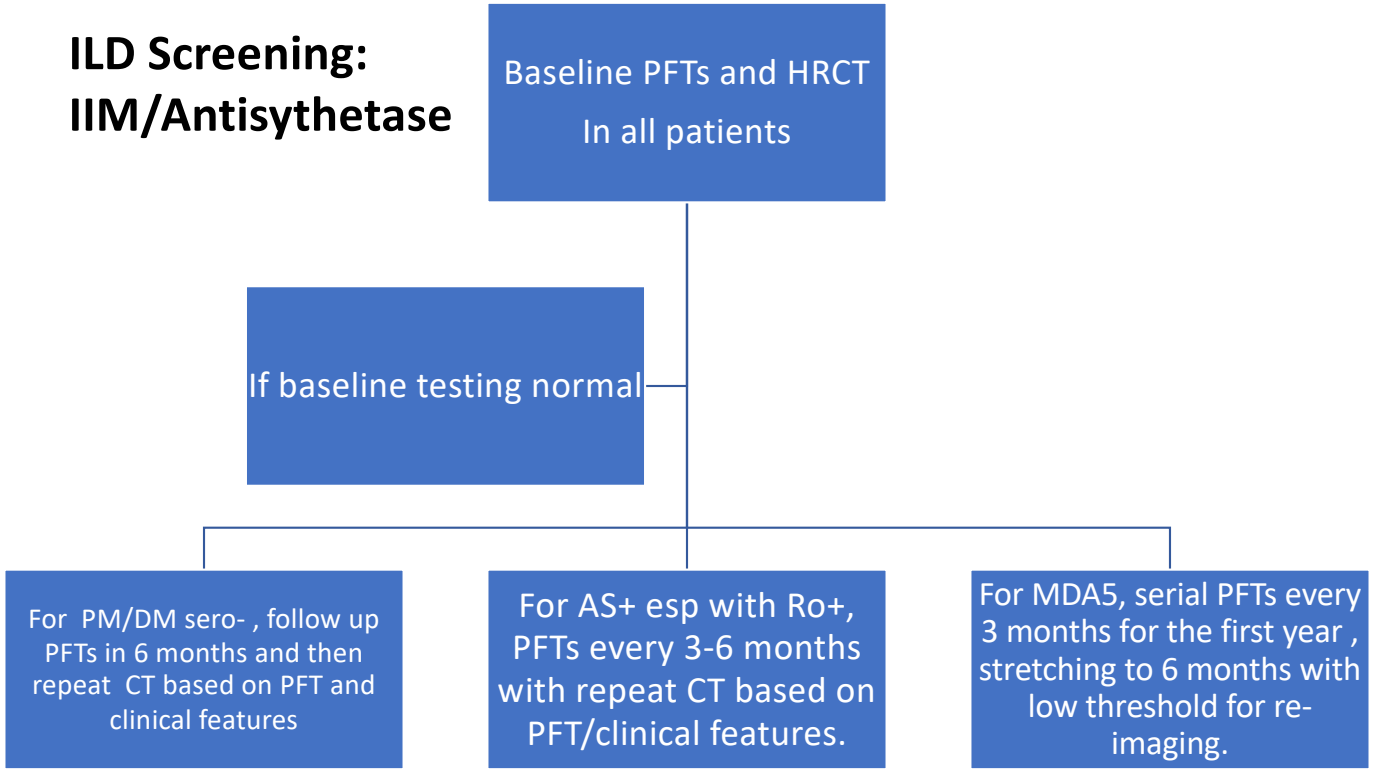


Path showed Organizing pneumonia(OP) and NSIP:Initially treated with CS and MMF, prednisone, incomplete response (muscle and lung) so Rituxan added with success. **FVC 100% DLCO 72%.**

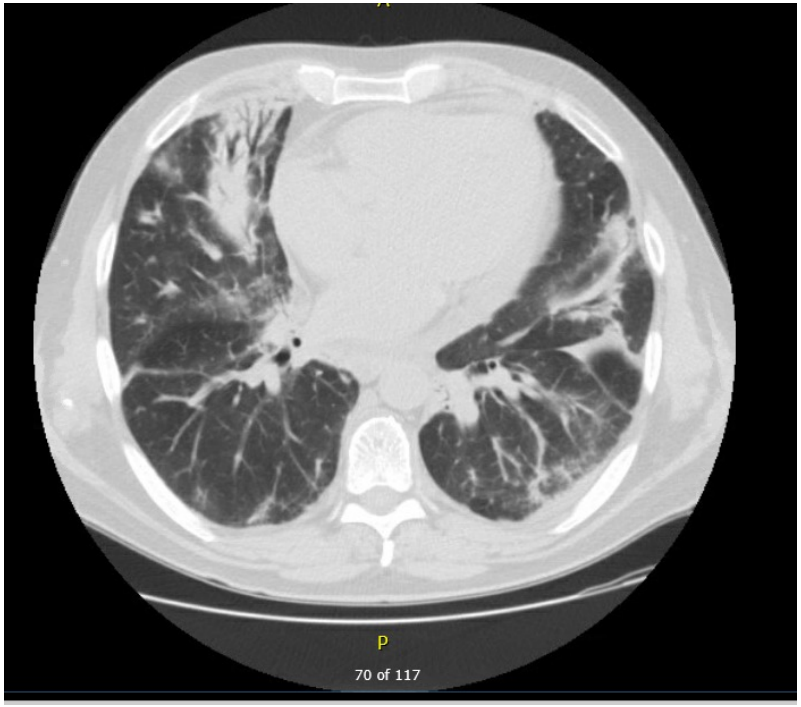
Anti-inflammatory therapy can work for this group of patients

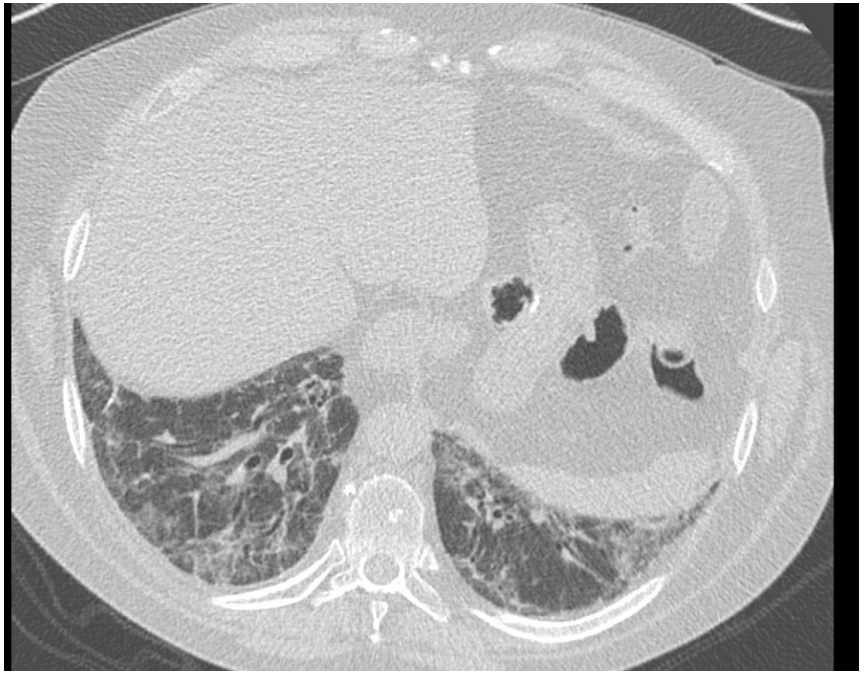


ILD Screening:
IIM/Antisythetase



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



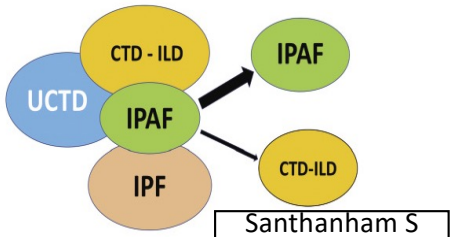


Treatment in ILD/IIM

Corticosteroids almost always in combination with another agent
MMF
AZA
Tacrolimus
Rituxan
Cyclophosphamide (used initially and with severe disease)
JAK inhibitors (some data on MDA5)
IVIG in cases where muscle involvement
Will some of these pts need antifibrotic therapy?
Ongoing Trial: ATTACK MY ILD: Abatacept in antisynthetase 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 i. Anti-Smith i. Anti-topoisomerase (Scl-70) 0. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; thers are: EJ, OJ, KS, Zo, tRS) 1. Anti-PM-Scl 2. 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



Santhanham S 2020

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

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.

Summary: How aggressive to screen in CTD for ILD and whom?

- **Scleroderma**:CT in most pts, 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 and especially in antisynthetase patients/MDA5.
- **RA**: probably a risk factor analysis in combination with a functional test 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.
- **What about the use of Ultrasound?**

Review Question 1

- Which of the following antibodies is associated with ILD in the rheumatic diseases?
- A Scl-70
- B Ro antibody
- C PL-12
- D MDA 5 antibody
- D A, C and D
- E all of the above

The correct answer is E

- Scl-70 or topoisomerase antibody positive patients are at highest risk for ILD in systemic sclerosis
- Ro antibody can be seen in those patients with scleroderma like syndromes with ILD, Sjogren with ILD and also Ro antibody + in association with antisynthetase antibodies.
- PL-12 antibody is seen in the antisynthetase syndrome. PL-12 + patients have a high risk for ILD
- MDA 5 anibody is part of a clinical syndrome involving the skin, sometimes inflammatory myositis and potentially rapidly progressive ILD.

Review Question 2

- A 30 year old healthy female presents with progressive dyspnea, low grade fever, and fatigue over the prior 3 months. She has normal skin, muscle and joint examination. A HRCT shows features suggesting organizing pneumonia and NSIP. Which of the antibodies listed is *least likely* to be associated with this clinical syndrome?
- A Jo-1
- B. PL-7
- C Ro antibody
- D centromere antibody

The correct answer is D

- This clinical scenario is most consistent with the antisynthetase syndrome. Jo-1 is the most common antibody identified in this syndrome but others include Pl-7,PL-12 amongst others. A portion of such patients will also be Ro antibody positive as well. If this pt is antisynthetase ab + we would in most cases not do a lung biopsy.
- Anti centromere antibody is seen in systemic sclerosis of the limited variant and is most associated with the long term development of pulmonary hypertension and very infrequently with ILD.

Summary/Take Home Slide

- ILD associated with CTD can have a mortality that rivals IPF
- Risk factors for ILD in different population of CTD are identifiable
- Inflammatory lung disease like in dermatomyositis can be treated with anti-inflammatory agent and emerging 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 limit progression of disease and avoid a missed opportunity for treatment, clinical trials and if needed lung transplant.
- A multidisciplinary approach can aid in optimizing diagnosis and treatment.

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