ILD Collaborative

Project ECHO

Myositis-associated ILD: clinical manifestations and diagnosis

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Disclosures

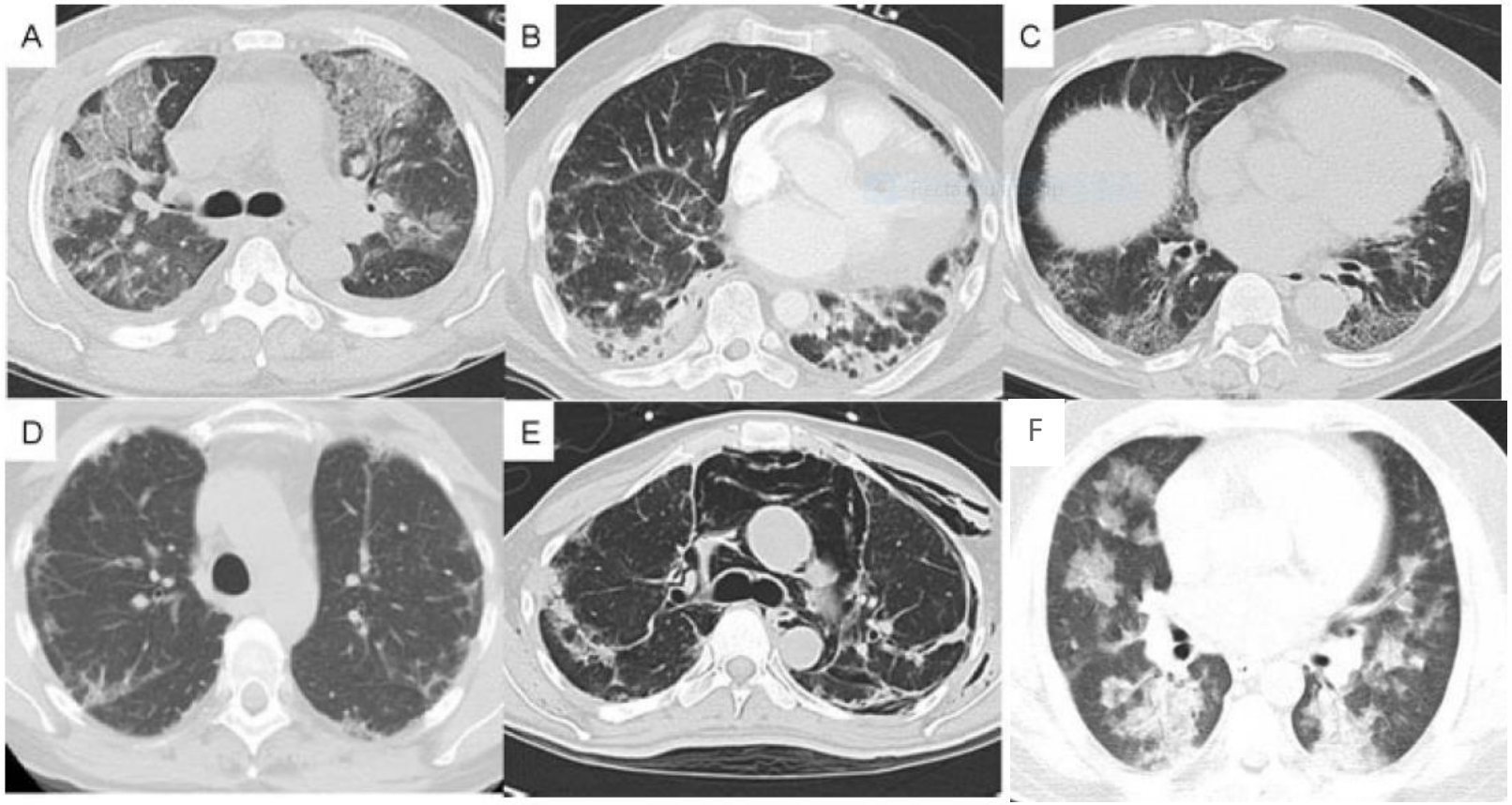
- Consulting fees from Boehringer Ingelheim, Vicore Pharma
- Research trials with Boehringer Ingelheim

ILD is common in patients with myositis

- Reported prevalence in DM/PM is 20% -78%
- Reported prevalence with anti-synthetase antibodies is 71-100%
- **ILD precedes the diagnosis of myositis in 13% to 37.5% of patients**

Marie et al. Arthritis Rheum 2011;63:3439-47.
Chen et al. Clin Rheumatol 2009;28:639-46
Yu et al. Clin Rheumatol 2011;30:1595-601
Hamaguchi et al. PLoS ONE 2013;8(4):e60442

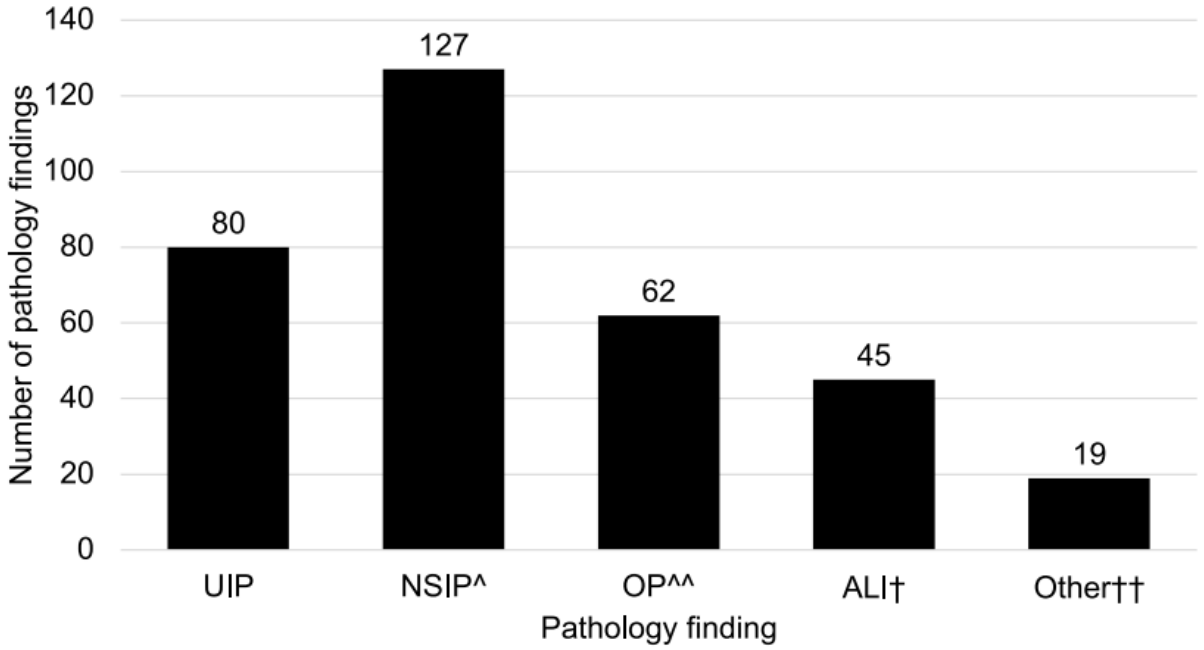
Lung manifestations of the anti-synthetase syndrome/MDA5

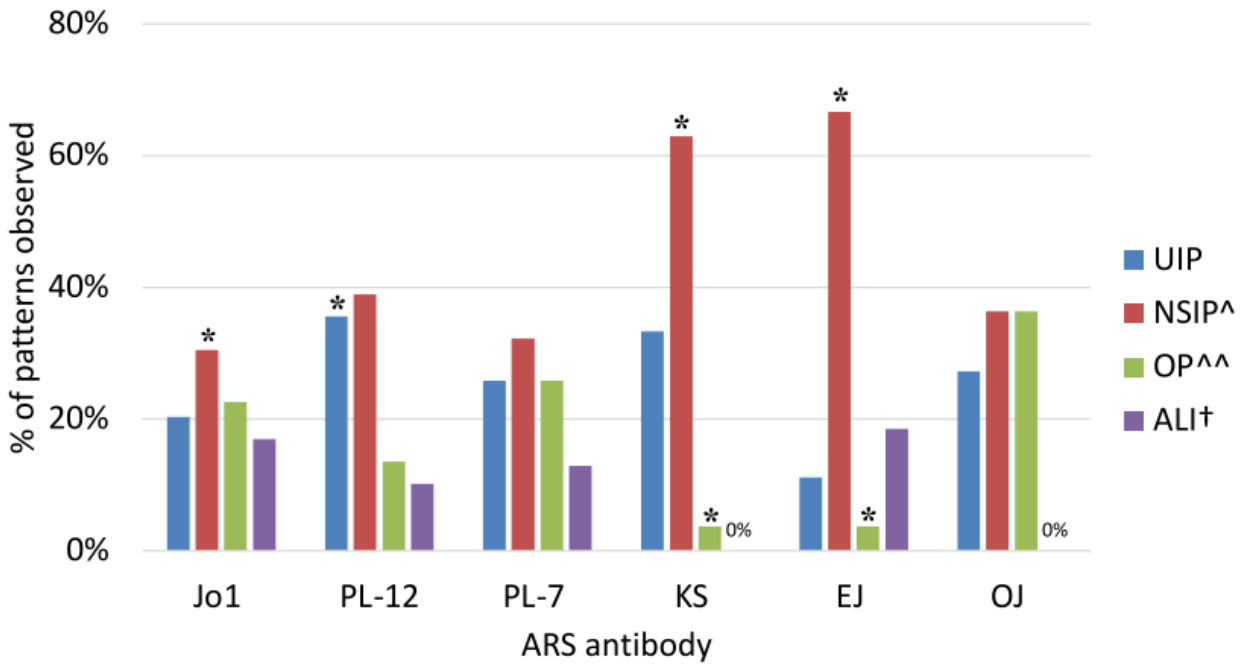


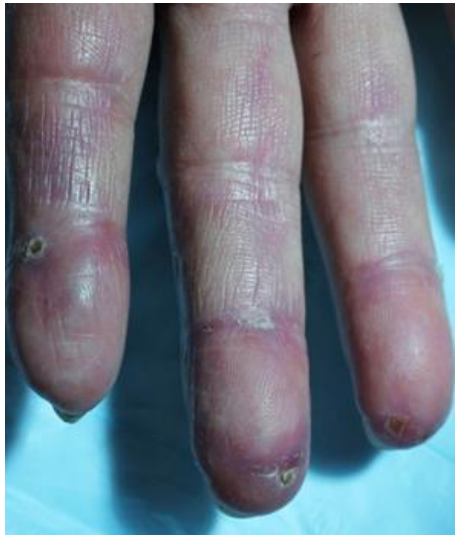
Hallowell et al. *Semin Respir Crit Care Med* 2014;35:239–248.

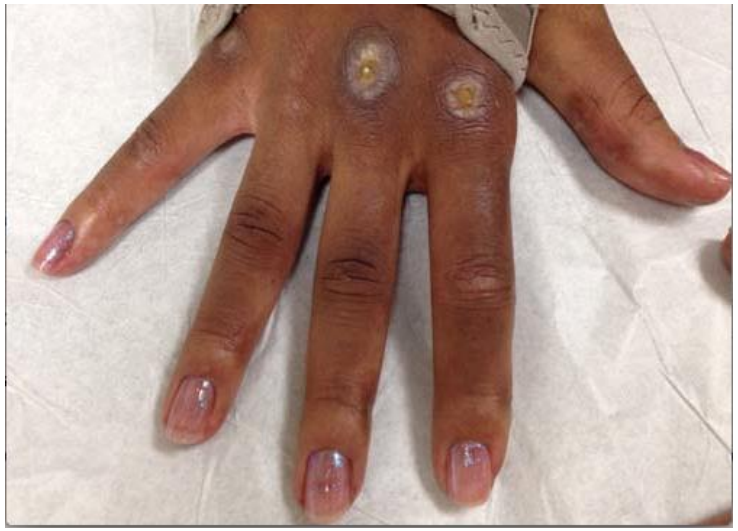
Pathology of anti-synthetase positive patients

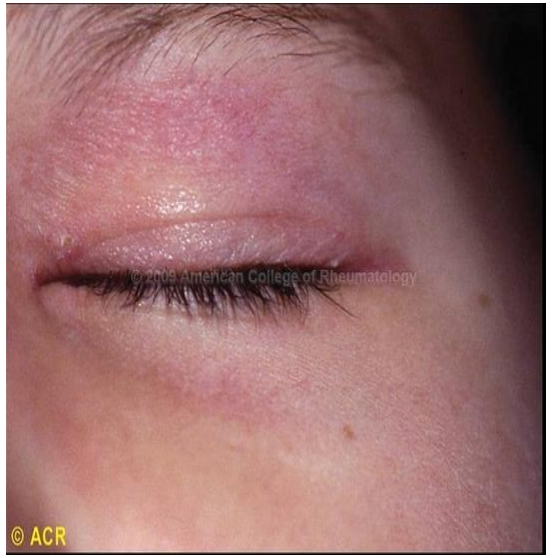
- Meta-review of the literature and BIDMC
- 310 antisynthetase-positive ILD cases and a surgical lung biopsy

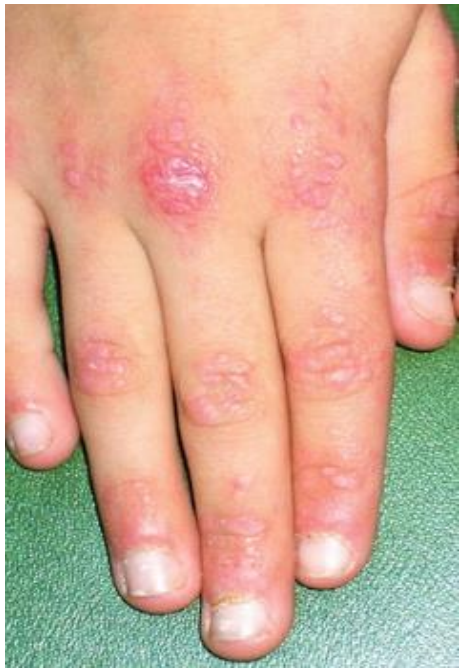


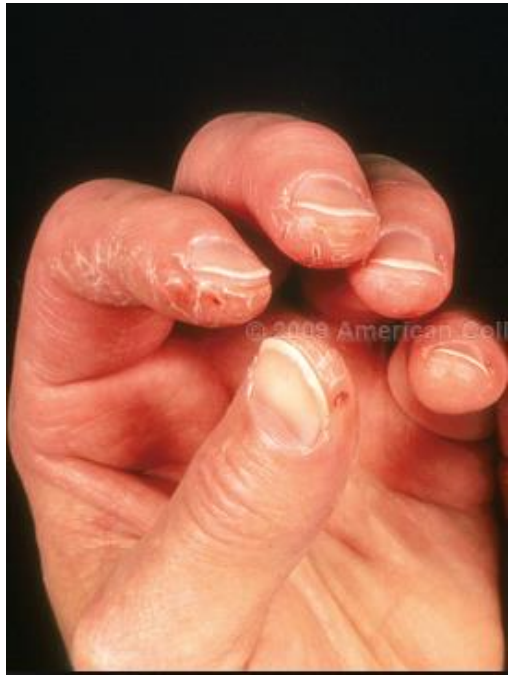


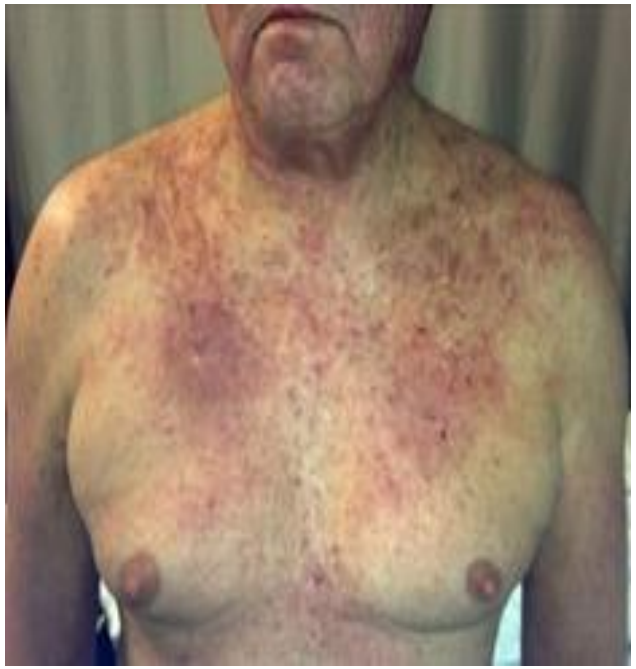












American College of Rheumatology
Garcia-Cruz, Garcia-Doval. N Engl J Med 2010; 363:e17

Bohan and Peter, NEJM 1975; 292(7)
American College of Rheumatology
http://neuromuscular.wustl.edu/lab/mantibody.html

2017 EULAR/ACR Classification Criteria

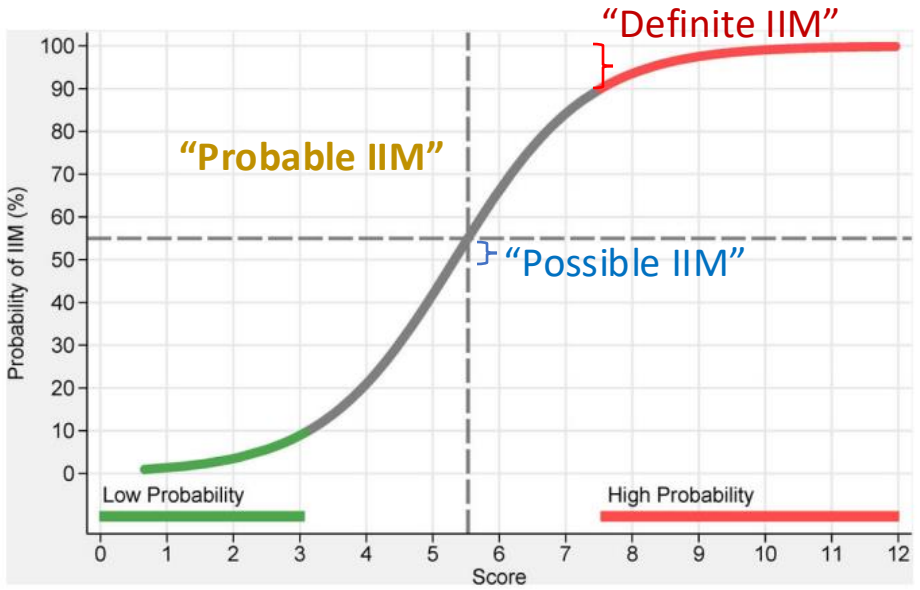
Table 1 Score points for the European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies to be used when no better explanation for the symptoms or signs exists[1]

Variable	Score points	
	No biopsy	Biopsy
Age of onset of first related symptoms		
18–40	1.3	1.5
≥40	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo-1 (anti-histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LDH)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4
Muscle biopsy features		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

*Serum levels above upper limit of normal.

- Cutoff for IIM classification is the 55% probability mark (scores of 5.5, 6.7)

With biopsy	Without biopsy
Sensitivity: 93%	Sensitivity: 87%
Specificity: 88%	Specificity: 82%



Bottai et al. *RMD Open* 2017;3:e000507
Lundberg et al. *Ann Rheum Dis*. 2017 December ; 76(12): 1955–1964.

The Anti-synthetase Antibodies

Anti-synthetase antibody	Target tRNA synthetase	Prevalence in myopathy	% of ARS Abs detected	Clinical features
anti-Jo-1	Histidyl-	8-18%	36-88%	**Myositis**, Joint dz
anti-EJ	Glycyl-	5-10%	7-23%	Classic DM, CADM
anti-PL-7	Threonyl-	5%	9-25%	Classic DM, **Worse ILD**
anti-OJ	Isoleucyl-	3%	5-8%	**Isolated ILD**
anti-PL-12	Alanyl-	1%	2-11%	**Isolated ILD, Worse ILD**, CADM
anti-KS	Asparaginyl-	1%	4-8%	**Isolated ILD**
anti-Zo	Phenylalanyl-	< 1%	< 1%	
anti-YRS	Tyrosyl-	< 1%	< 1%	

Additional Myositis antibodies

Antibody	Target antigen	Prevalence In Myositis	Clinical features
anti-MDA-5	MDA-5 RNA helicase	20-25%	Skin ulceration; CADM; Rapidly progressing ILD
anti-Ro-52	Extractable Nuclear Antigen (Ro-52)	13-26%	More severe ILD; worse outcomes
anti-PM-Scl	Complex of proteins in the nucleolus	5-24%	Scleroderma; PM/DM
anti-Ku	70-80 kDa proteins in the nuclei and nucleoli	3-23%	Increased risk of ILD
anti-155/140 (anti-TIF-1γ)	155/140-kDa polypeptides	7-16%	Malignancy; Lower risk of ILD
anti-SRP	Cytoplasmic **S**ignal **R**ecognition **P**article	5-6%	Severe myopathy; Malignancy
anti-SAE1	**S**mall ubiquitin-like modifier-1 **A**ctivating **E**nzyme	1.5-8%	Increased risk of ILD; Malignancy

Jia et al. Clin Rheumatol. 2019 Apr 27.
Cavazzana et al. Lupus (2008) 17, 727–732
Rietveld *et al. Pract Neurol* 2019;0:1–11
Arthrit and Rheum Vol. 35, No. 10 (Oct 1992)

Myositis antibodies are lurking in our ILD patients

Retrospective study of 165 patients with “idiopathic” ILD

(36% of those with a MSA referred with a presumed diagnosis of IPF)

ANA, RF, CCP negative in 61.4% of patients with a MSA+

14 patients (8.5%) had a change in diagnosis as a result of the testing

Myositis antibodies	*n* (%)
Any antibody	44 (26.7)
Ro-52	18 (10.9)
PM/Scl75	8 (4.8)
Jo-1	5 (3.0)
PL-7	5 (3.0)
PL-12	4 (2.4)
PM/Scl100	4 (2.4)
SRP	4 (2.4)
Ku	3 (1.8)
MDA-5	2 (1.2)
Mi-2β	2 (1.2)
TIF-1γ	2 (1.2)
NXP2	1 (0.6)
EJ	1 (0.6)
Mi-2α	1 (0.6)
Mi-2	0 (0.0)
OJ	0 (0.0)

Fidler et al. *Lung*. 2019 Mar 5 (Epub)

Myositis-specific antibodies are frequently associated with lung-dominant disease

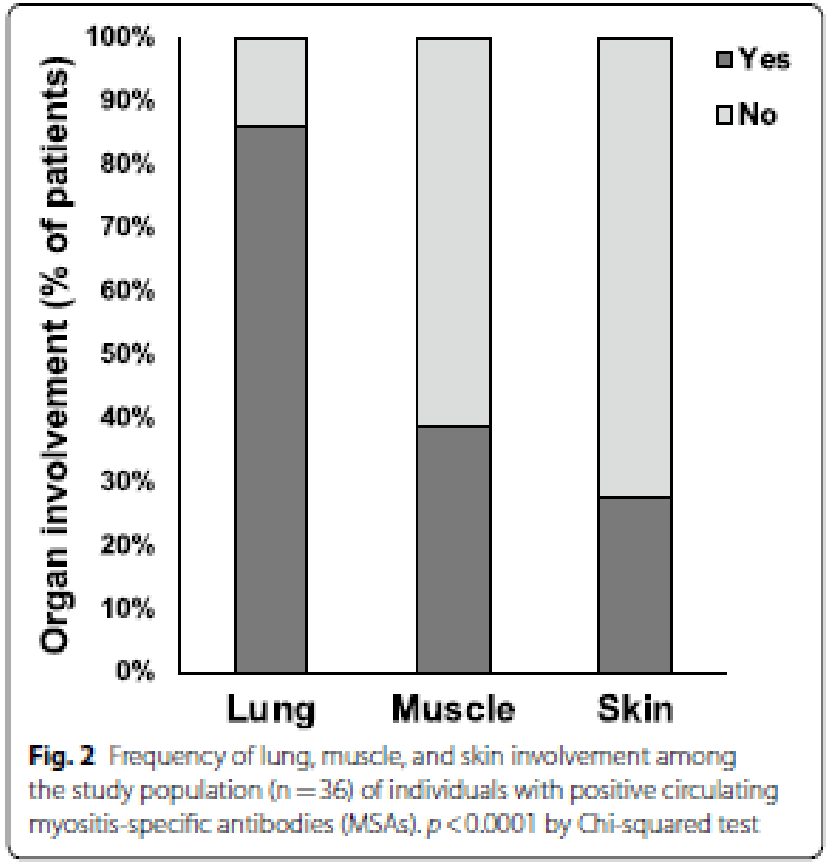


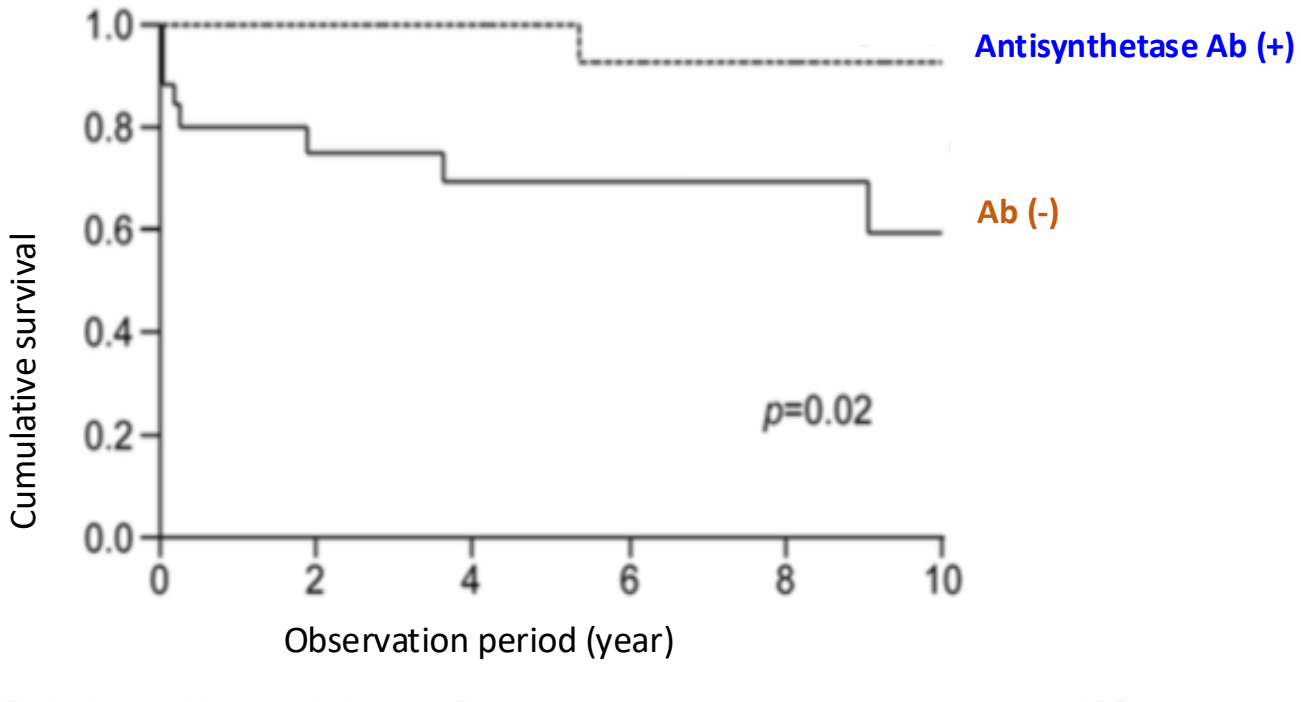
Fig. 2 Frequency of lung, muscle, and skin involvement among the study population (n = 36) of individuals with positive circulating myositis-specific antibodies (MSAs). $p < 0.0001$ by Chi-squared test

Chart review of 3078 tested patients

2631 tested for Jo-1

447 tested with a myositis panel

Anti-synthetase antibodies are associated with improved prognosis in myositis-ILD



48 patients with DM/PM-ILD

23 with antibodies

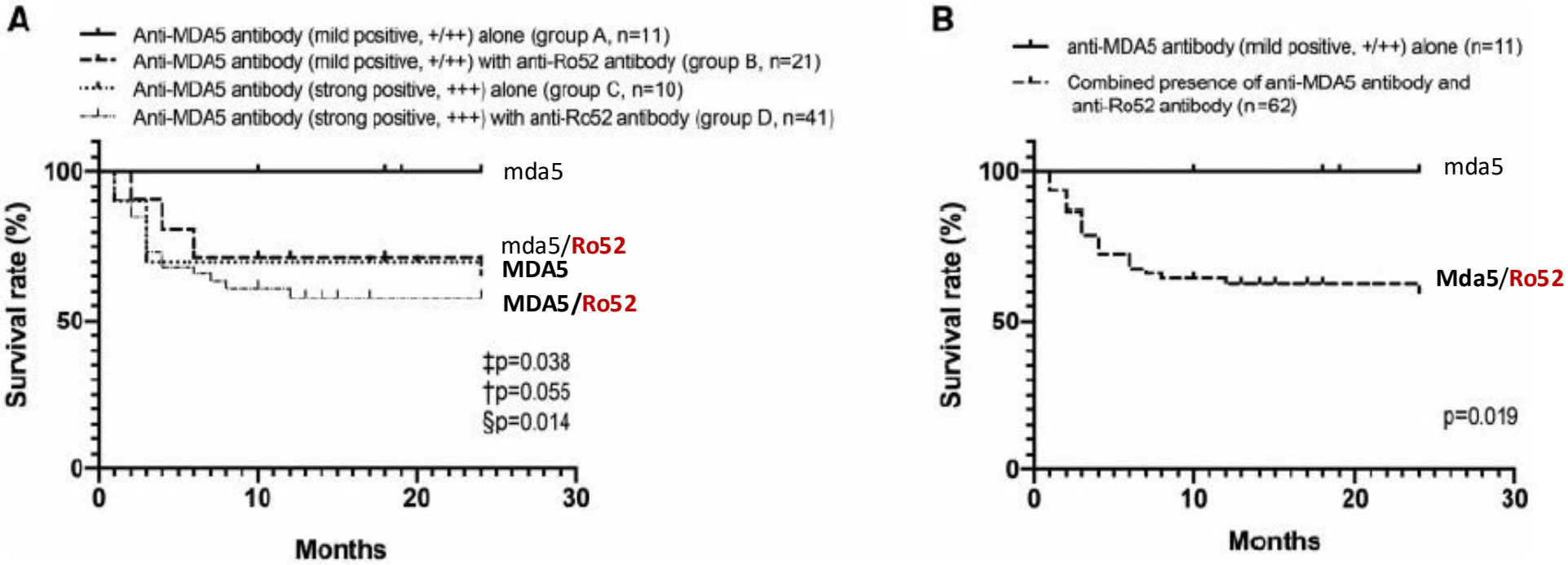
25 without antibodies

HR of mortality = 0.34 with antisynthetase antibodies

Mortality rate = 4% vs 32%

anti-MDA5 levels and the presence of anti-Ro52 influence prognosis

83 consecutive patients with CADM-ILD, anti-MDA5 +
-- 74% also had anti-Ro52



Anti-Ro52 associated with RP-ILD, 54.5% vs 23.8% (p = 0.014)
Anti-Ro52 associated with cutaneous ulcerations, 27.4% vs 4.8% (p = 0.033)

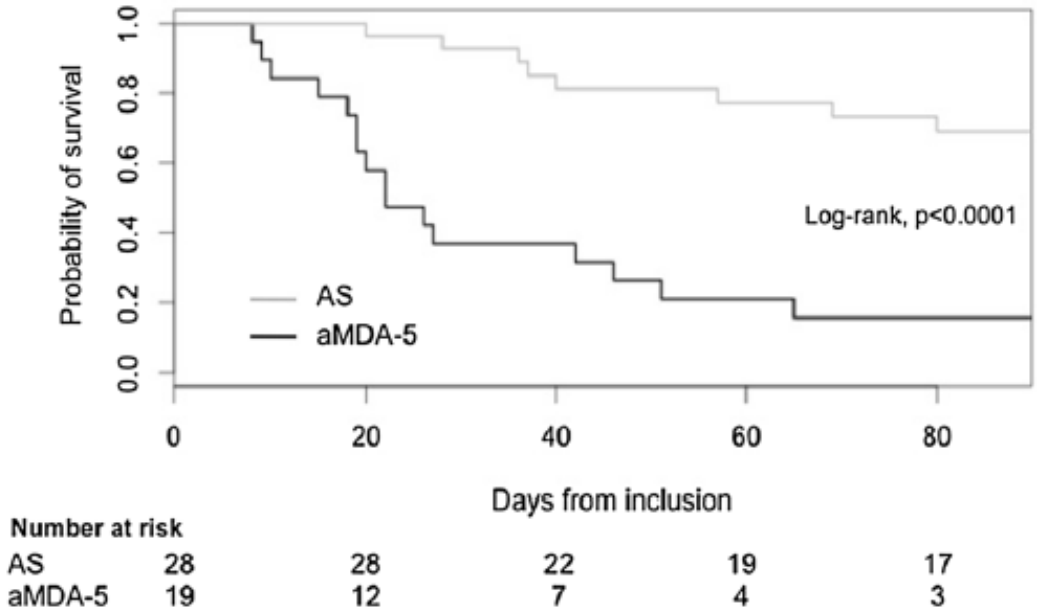
Xu et al. *Rheumatology* 2021;60:3343–3351

Dermato-pulmonary syndromes masquerading as ARDS

- 47 patients with acute respiratory failure and no risk factors for ARDS
- Myositis panel ordered during hospitalization

- Muscular manifestations (23%)
- Articular manifestations (30%)
- Cutaneous manifestations (43%)

- **No extrapulmonary manifestations (36%)**



How do we define patients with ILD and myositis-specific antibodies in the absence of a defined CTD?

Undifferentiated CTD-associated ILD

Autoimmune-featured ILD

Lung-dominant CTD

Idiopathic pneumonia with autoimmune features (IPAF)

Idiopathic pneumonia with autoimmune features (IPAF)

TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

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

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

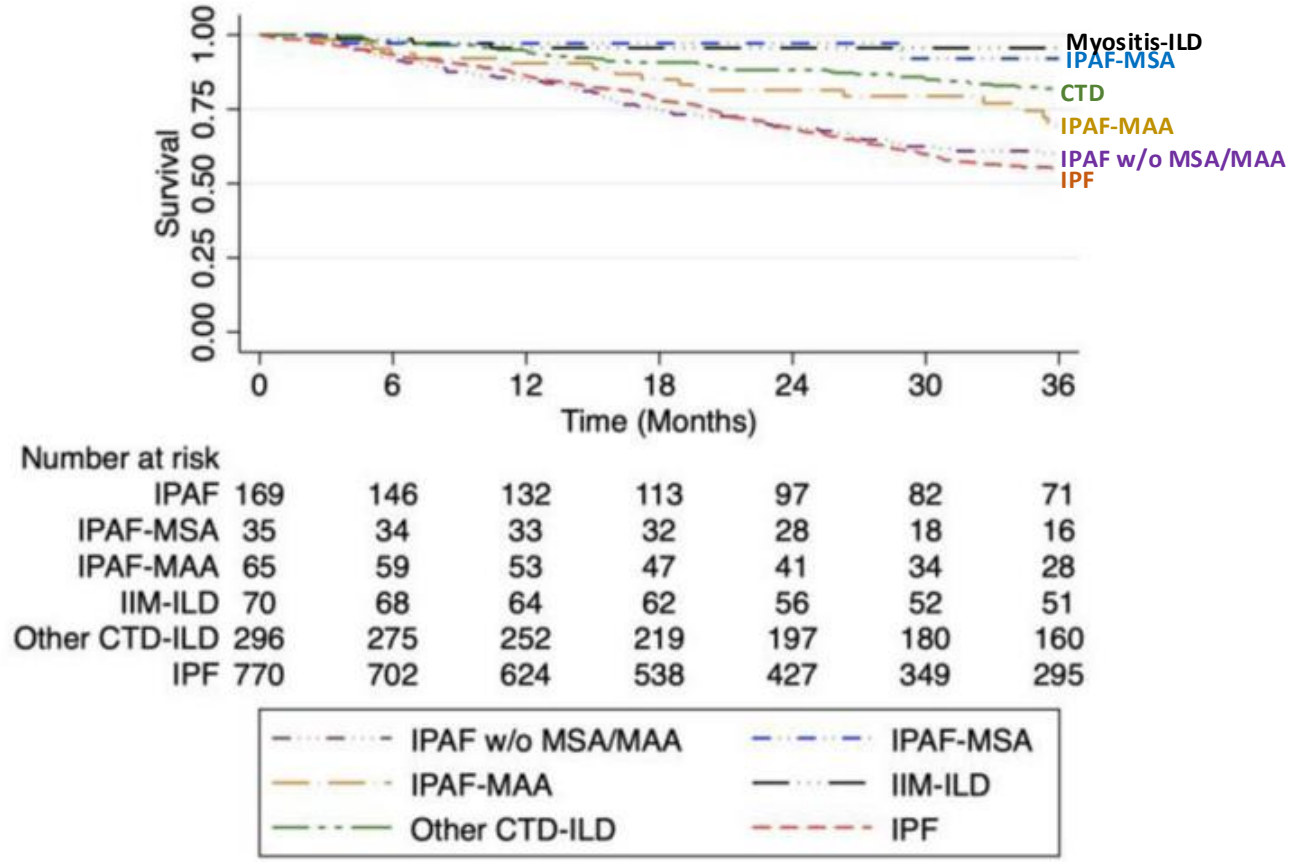
C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates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

Serologic Domain	Reported prevalence in series (%)
ANA criteria	**28.1—82.4**
RF criteria	**13--21.9**
CCP	0--10.7
dsDNA	1.8--7.2
SSA	**9.4--42.9**
SSB	0--5.4
RNP	0--16.1
Smith	0--8.9
Scl-70	0—5.7
tRNA synthetase	0.7--35.7
PM-Scl*	0—5.7
MDA5*	0

*Not always reported or tested

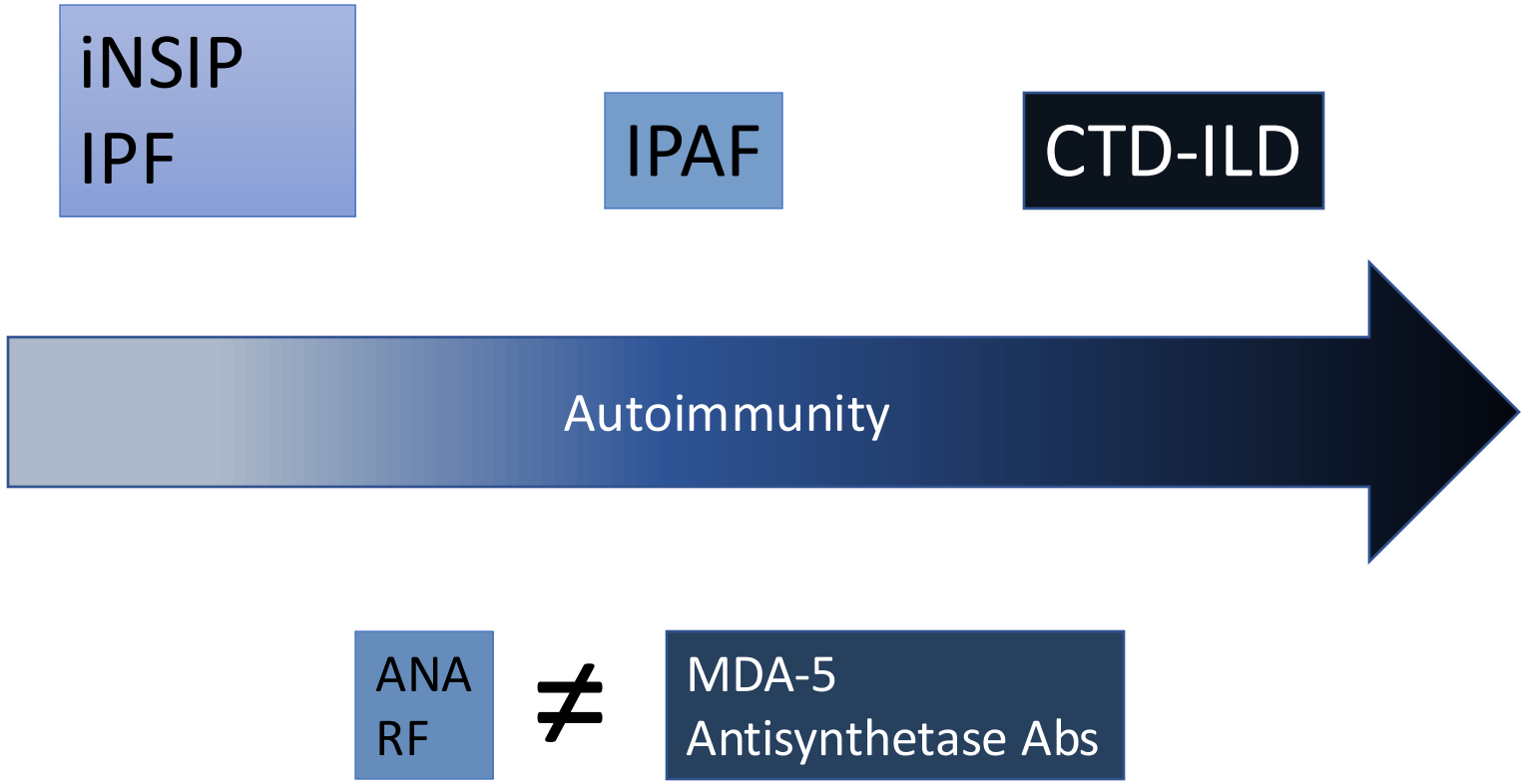
Chartrand et al. *Respiratory Medicine* 119 (2016) 150e154
Yoshimura et al. *Respiratory Medicine* 137 (2018) 167–175
Oldham et al. *Eur Respir J.* 2016 June ; 47(6): 1767–1775
Ferri et al. *Autoimmunity Reviews* 15 (2016) 61–70
Ahmad et al. *Respiratory Medicine* 123 (2017) 56e62

Not all IPAF is the same



*IPAF-MSA patients have outcomes similar to patients with myositis-ILD

ILD occurs along a spectrum of autoimmunity



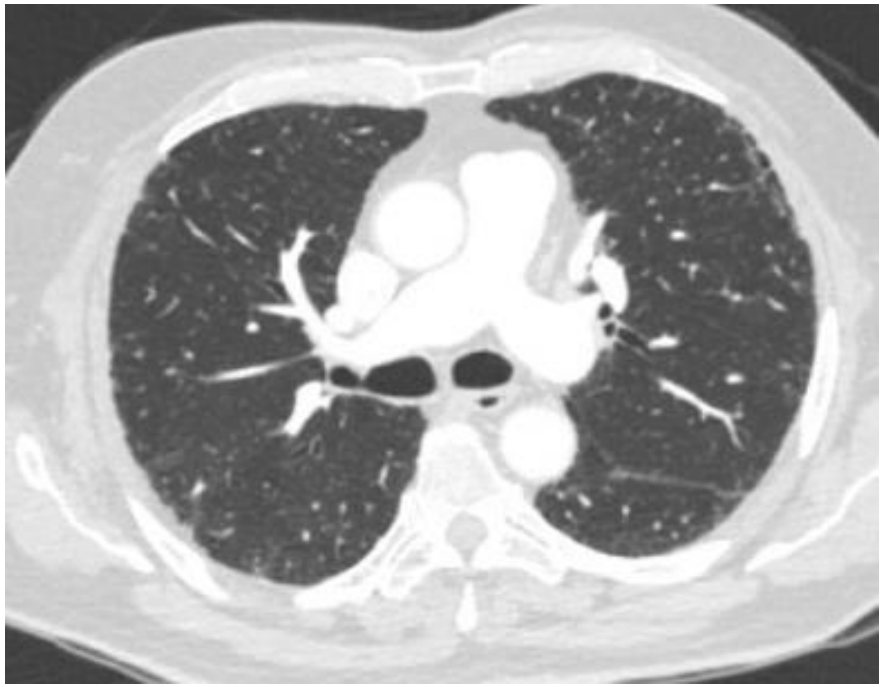
The lungs can have a mind of their own

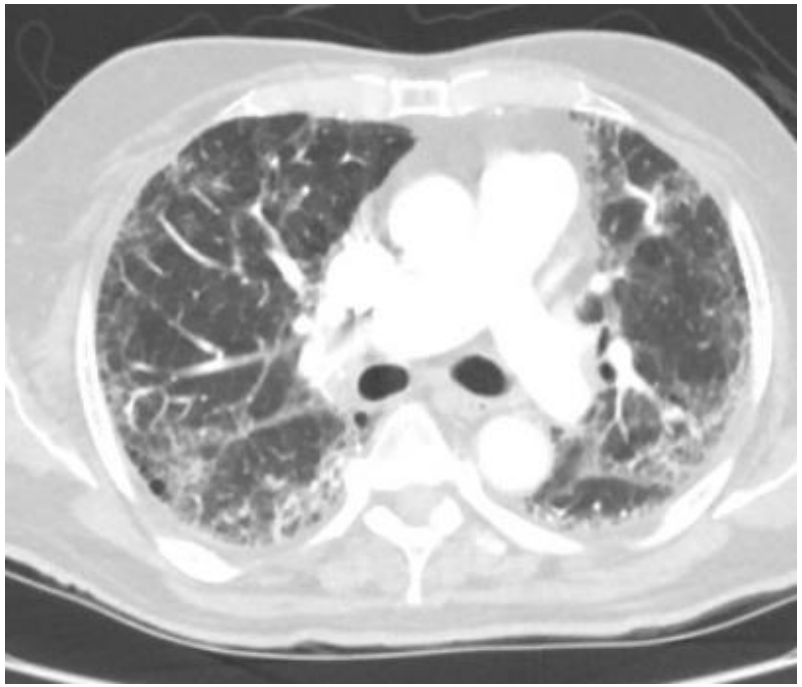
75 M with anti-PL-7 antibodies

Joint pains, fevers, rash improved after 5 months

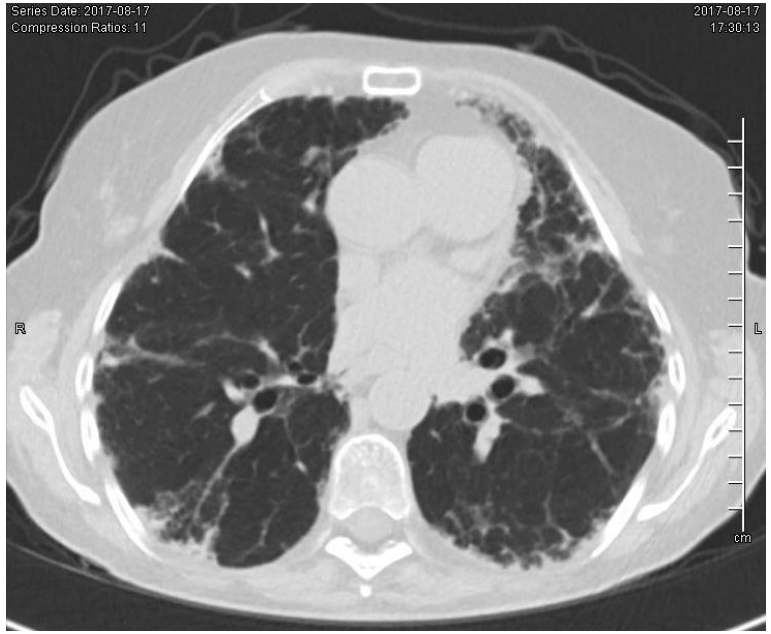
--Prednisone taper, mycophenolate 3000 mg

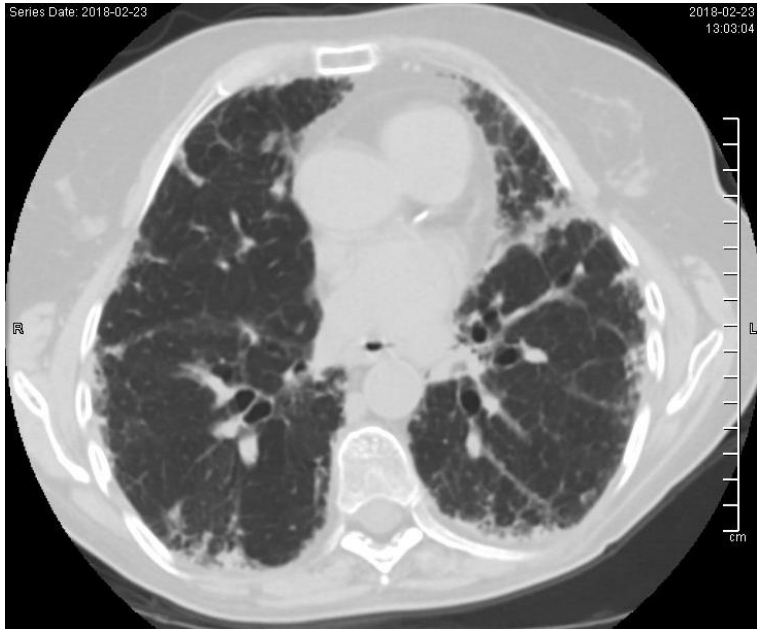
Worsening dry cough and dyspnea over 6 months when carrying items up the stairs





68 F with progressive dyspnea over several months
FVC decreased by 15%; unable to perform DLCO





MIP -21.5 (28% predicted)
MEP 28.5 (29% predicted)

CK 700 --> 6000

A few clinical pearls worth mentioning

- Declining FVC can be secondary to muscle weakness (myositis) or truncal skin thickening (scleroderma)
- Myositis develops after ILD in 29-64% of anti-synthetase cases
- Improving FVC may provide false (pulmonary) reassurance as the muscle disease responds to therapy
- Malignancy is common is patients with inflammatory myositis
  - 15-30%, with a higher incidence in DM vs PM
  - Majority of cases occur after the myositis diagnosis

Hamaguchi et al. PLoS ONE 2013;8(4):e60442
Hill et al. Lancet 2001; 357: 96-100
Zhang Eur Rev Med Pharmacol Sci 2009; 13: 77-80

Summary

- ILD is common in myositis; its presentation ranges from subclinical to fulminant respiratory failure.
- Diagnosing myositis-ILD often requires a nuanced approach and the careful consideration physical exam findings and autoantibodies.
- Changing symptoms in this patient population should be interpreted with a broadened differential.