Myositis-associated ILD: clinical manifestations and diagnosis

Robert Hallowell, MD

Disclosures

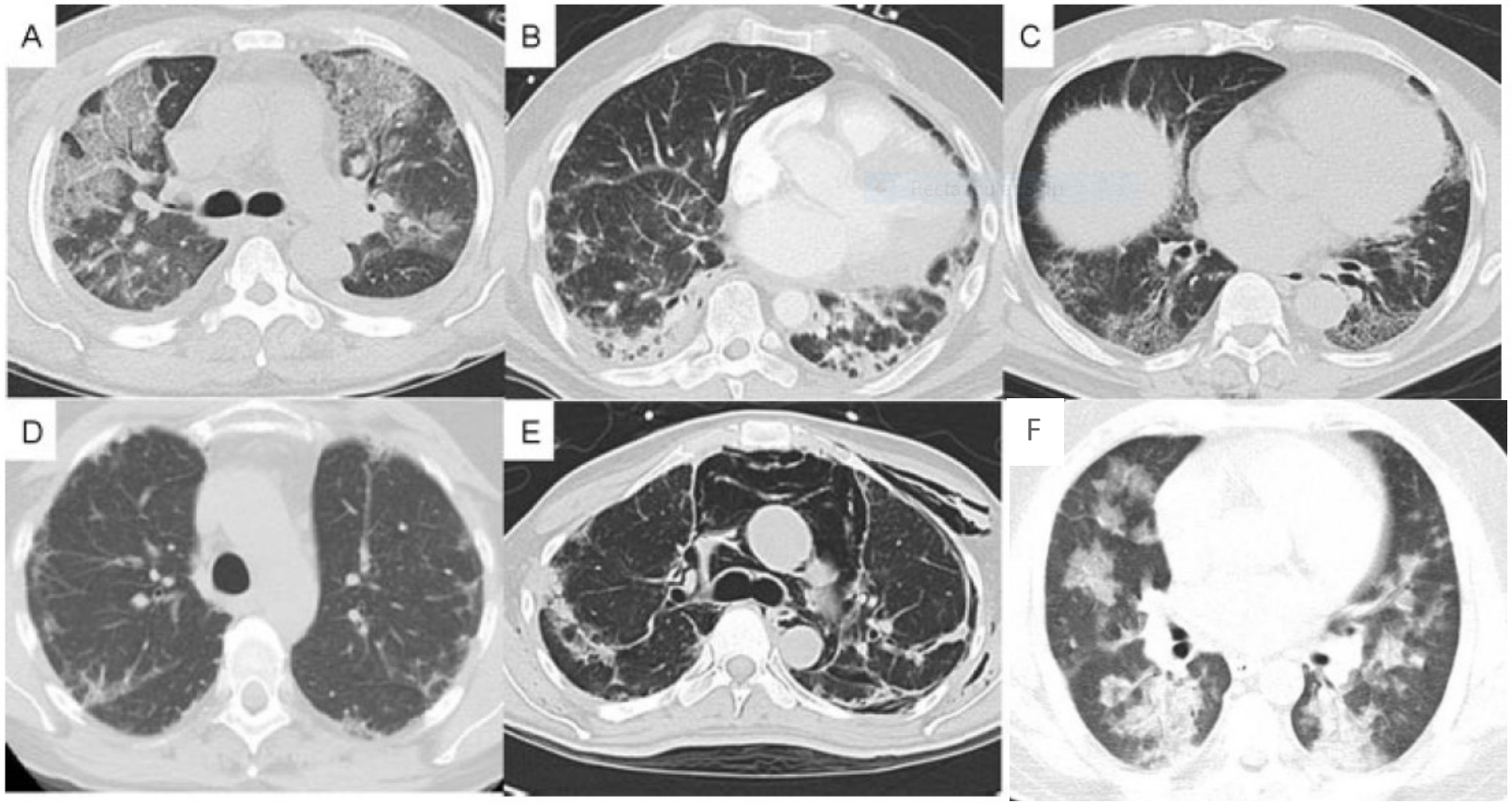
- Speaking and consulting fees from Boehringer Ingelheim, Genentech
- Research trials with Boehringer, Genentech, Galapagos, Hoffmann-La Roche, Nitto Denko
- Authorship fees from UpToDate, Dynamed

ILD is common in patients with myositis

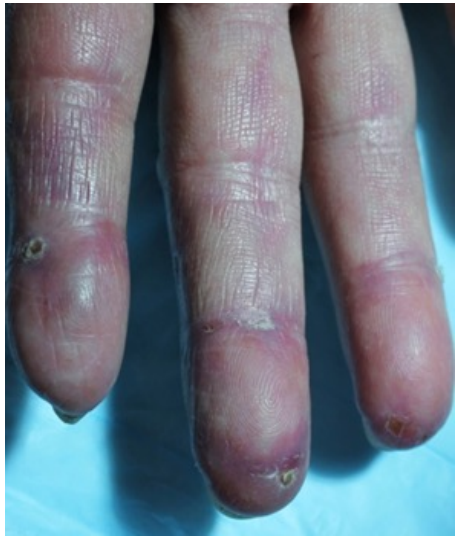
- Reported prevalence in DM/PM is 20% -78%
- Reported prevalence with anti-synthetase antibodies is 71-100%
- **ILD precedes the diagnosis of myositis in 13% to 37.5% of patients**

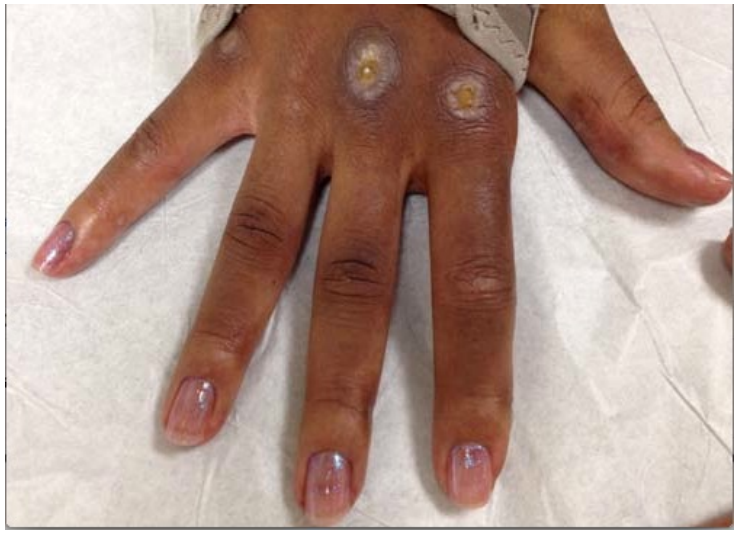
Marie et al. Arthritis Rheum 2011;63:3439-47.
Chen et al. Clin Rheumatol 2009;28:639-46
Yu et al. Clin Rheumatol 2011;30:1595-601
Hamaguchi et al. PLoS ONE 2013;8(4):e60442

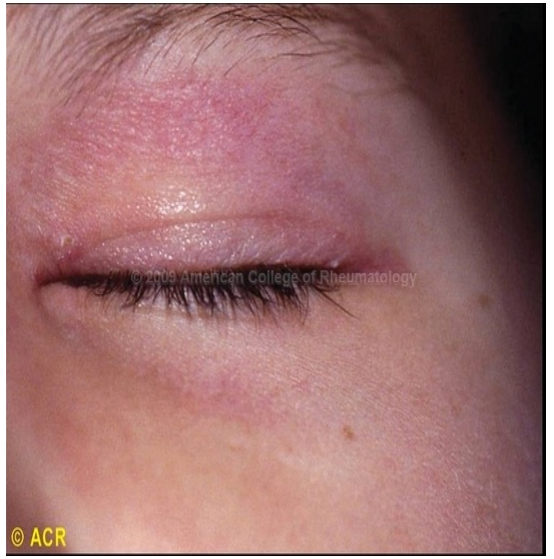
Lung manifestations of the anti-synthetase syndrome/MDA5

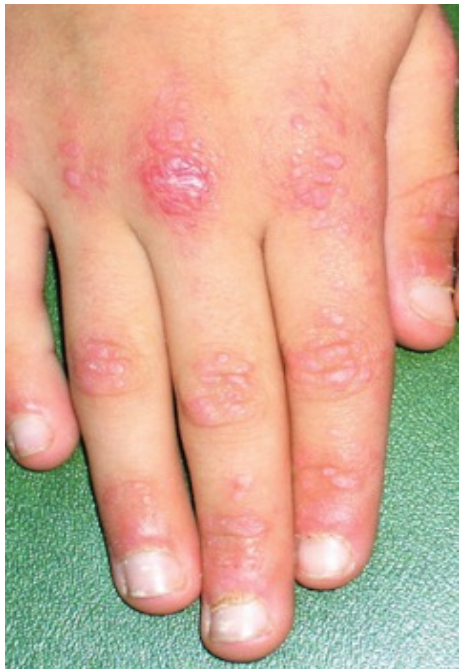


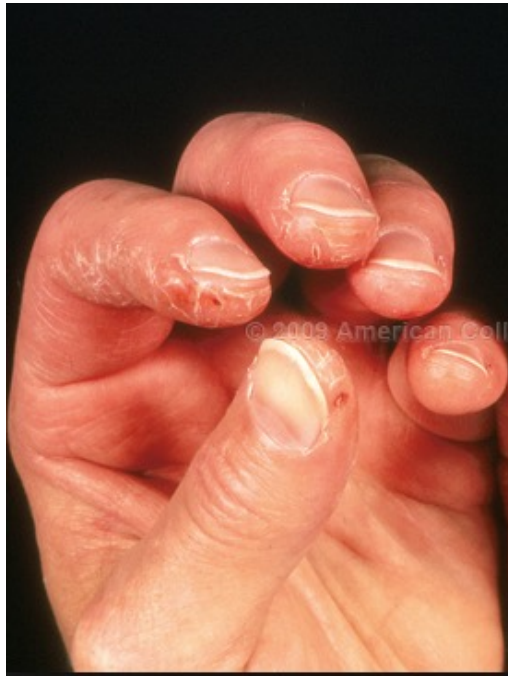
Hallowell et al. *Semin Respir Crit Care Med* 2014;35:239–248.

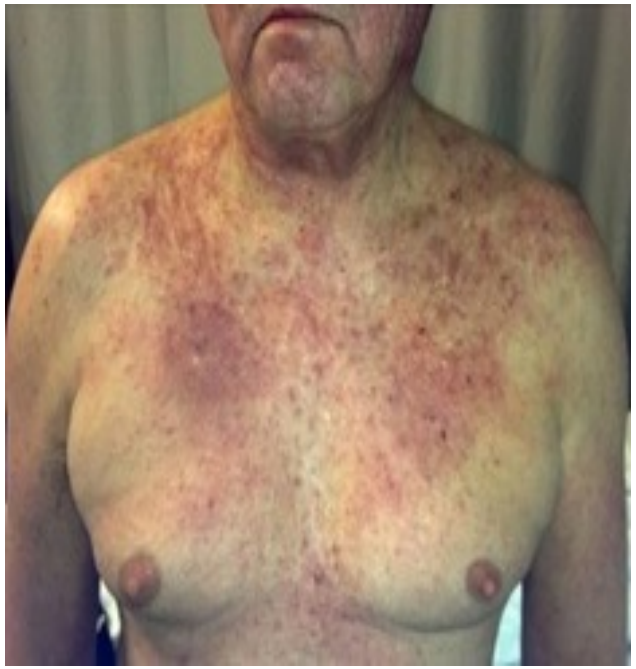





© ACR







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
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	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

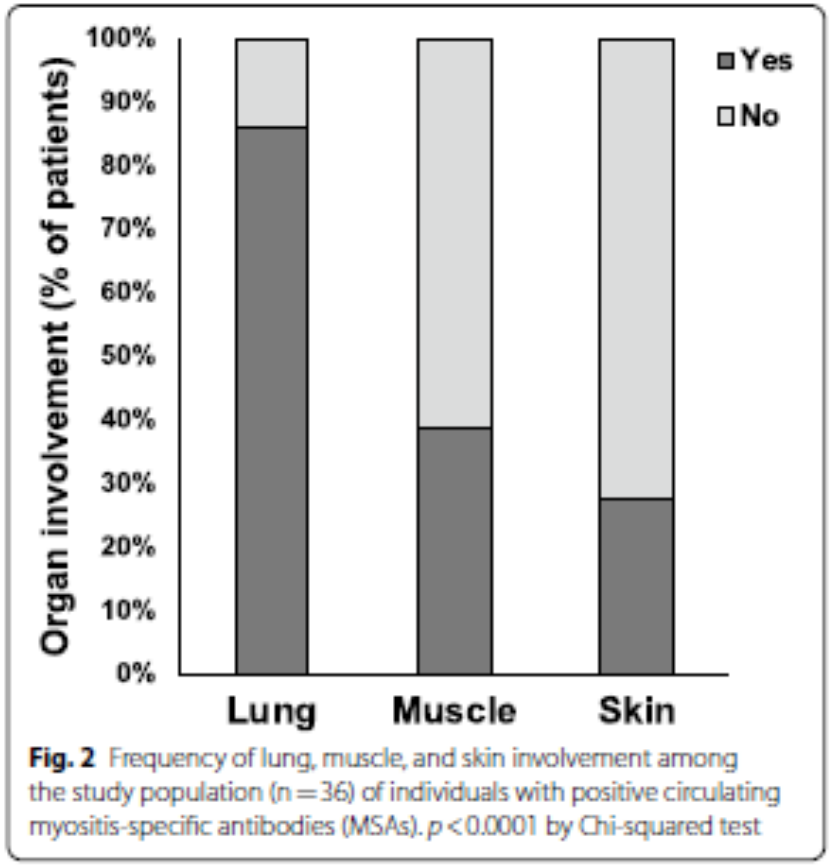


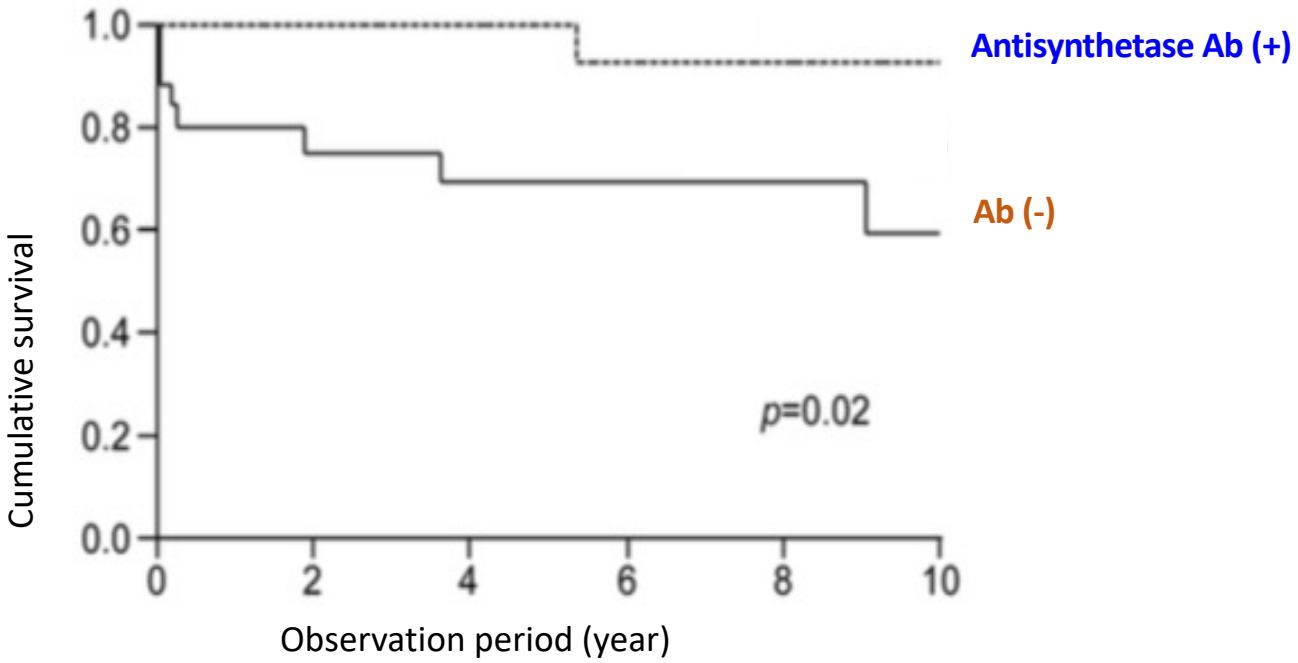
Fig. 2 Frequency of lung, muscle, and skin involvement among the study population (n = 36) of individuals with positive circulating myositis-specific antibodies (MSAs). $p < 0.0001$ by Chi-squared test

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

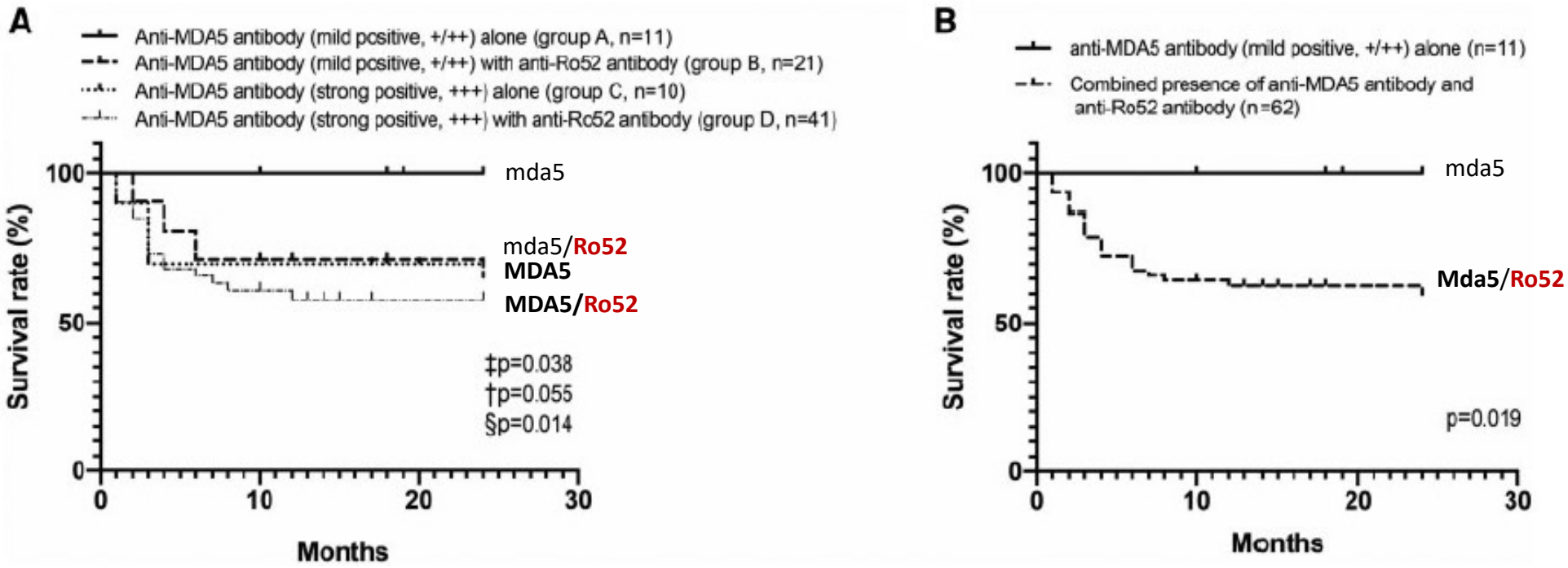
25 without antibodies

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)

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

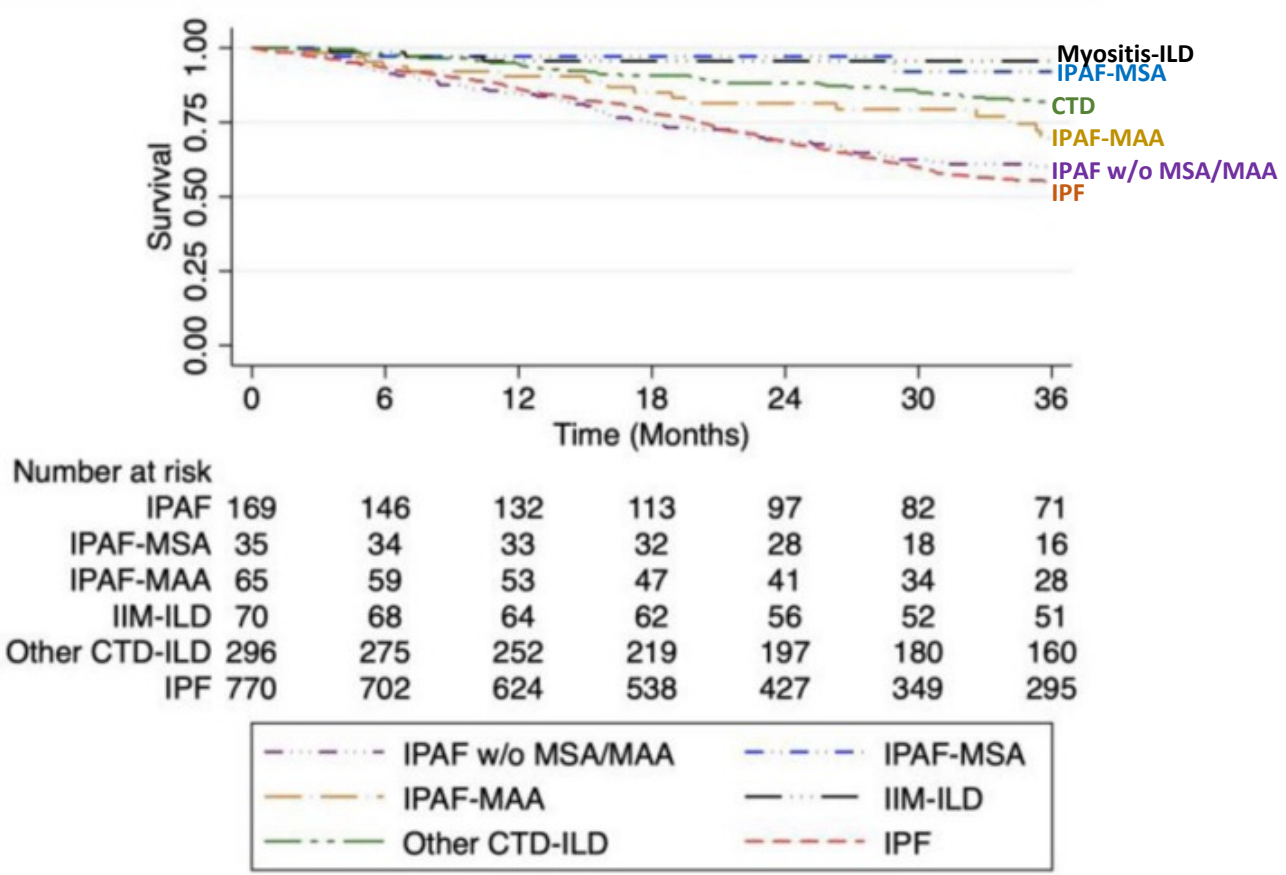
C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates 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

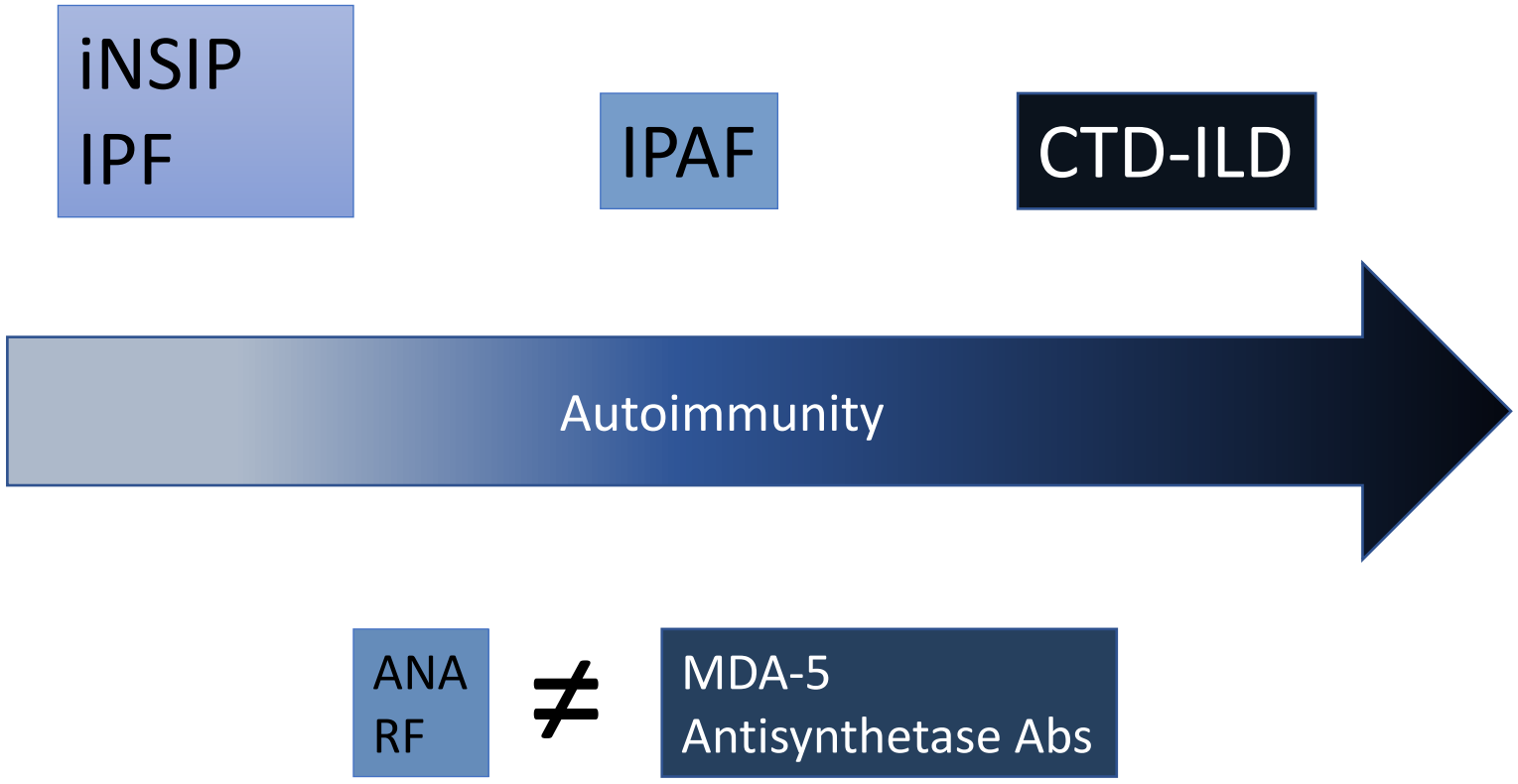
Chartrand et al. *Respiratory Medicine* 119 (2016) 150e154
Yoshimura et al. *Respiratory Medicine* 137 (2018) 167–175
Oldham et al. *Eur Respir J.* 2016 June ; 47(6): 1767–1775
Ferri et al. *Autoimmunity Reviews* 15 (2016) 61–70
Ahmad et al. *Respiratory Medicine* 123 (2017) 56e62

Not all IPAF is the same



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

ILD occurs along a spectrum of autoimmunity



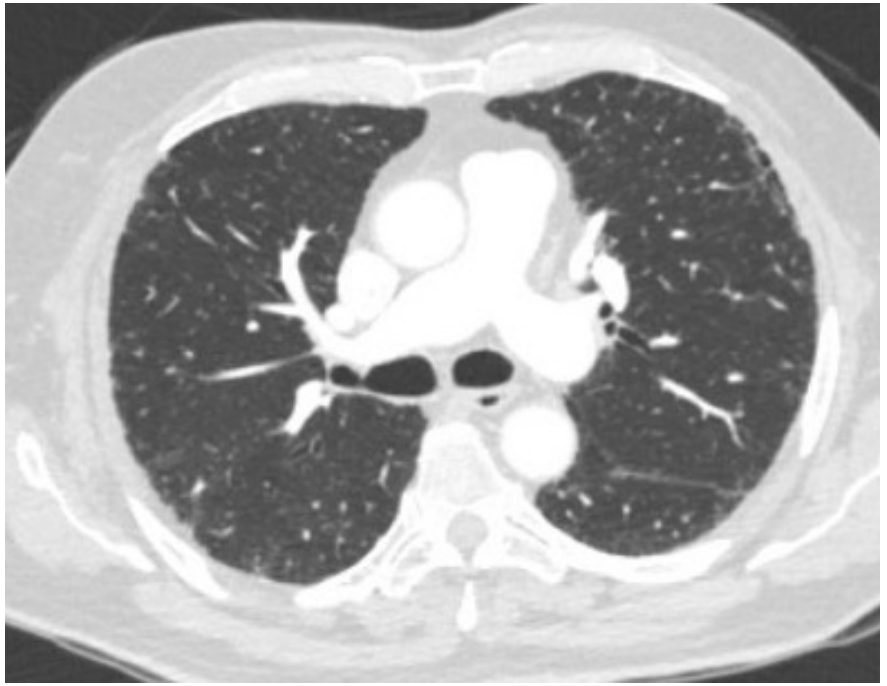
The lungs can have a mind of their own

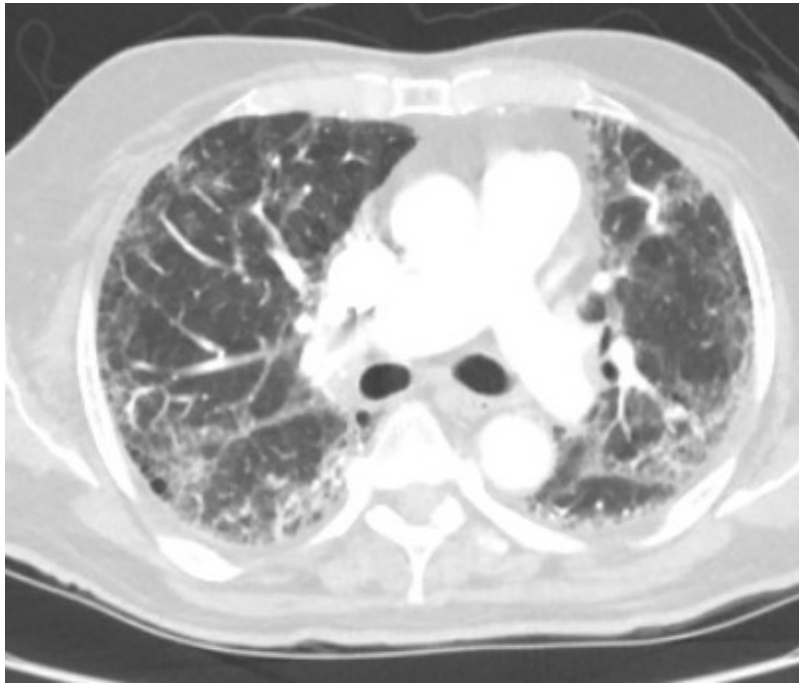
75 M with anti-PL-7 antibodies

Joint pains, fevers, rash improved after 5 months

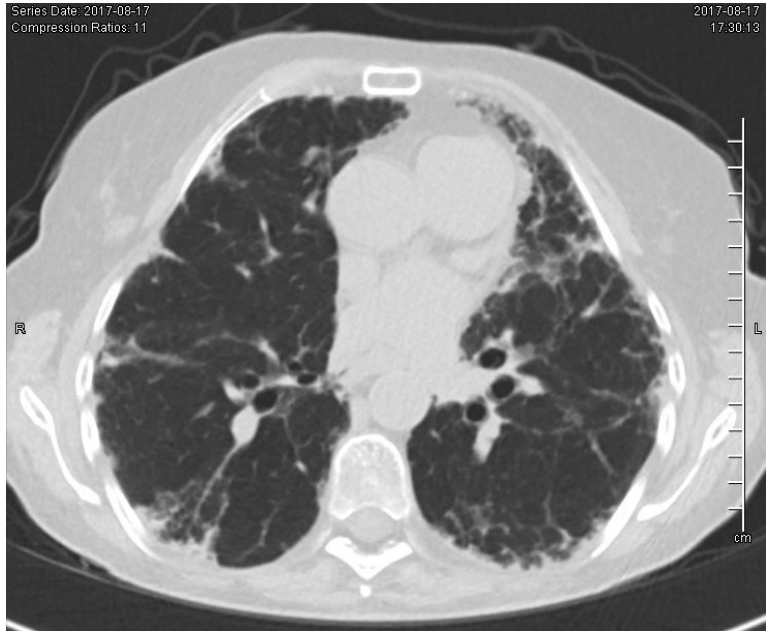
--Prednisone taper, mycophenolate 3000 mg

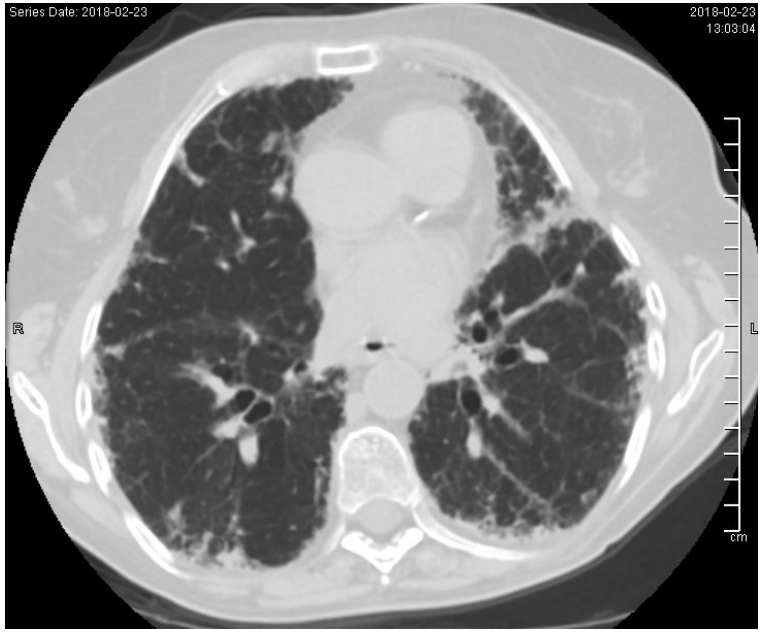
Worsening dry cough and dyspnea over 6 months when carrying items up the stairs





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.