ILD Collaborative

Project ECHO

Where's the Lung? Rethinking Classification Criteria for Connective Tissue Diseases

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Frequency of ILD in Connective Tissue Diseases

Rheumatologic disease	ILD
Systemic sclerosis (SSc)	+++
Polymyositis/dermatomyositis	+++
Rheumatoid arthritis	++
Mixed connective tissue disease	+++
Sjögren's syndrome	+
Systemic lupus erythematosus	+/-

ILD can precede other CTD manifestations

Can ILD be the only manifestation of CTD?

Castelino and Varga. *Arthritis Res Ther.* 2010; Mathai and Danoff. *BMJ*. 2016; Jee AS et al. *Respirology*. 2020.

Case Study

- 58 y.o. previously healthy man admitted with dyspnea and hypoxemia
  - ~1 month of dry cough and progressively worsening dyspnea
  - + constitutional symptoms: fevers, chills, night sweats, malaise, anorexia, and 15 lb weight loss
  - No myalgia, muscle weakness, rashes, or joint complaints.

- Social Hx:
  - Nonsmoker
  - No notable environmental exposures

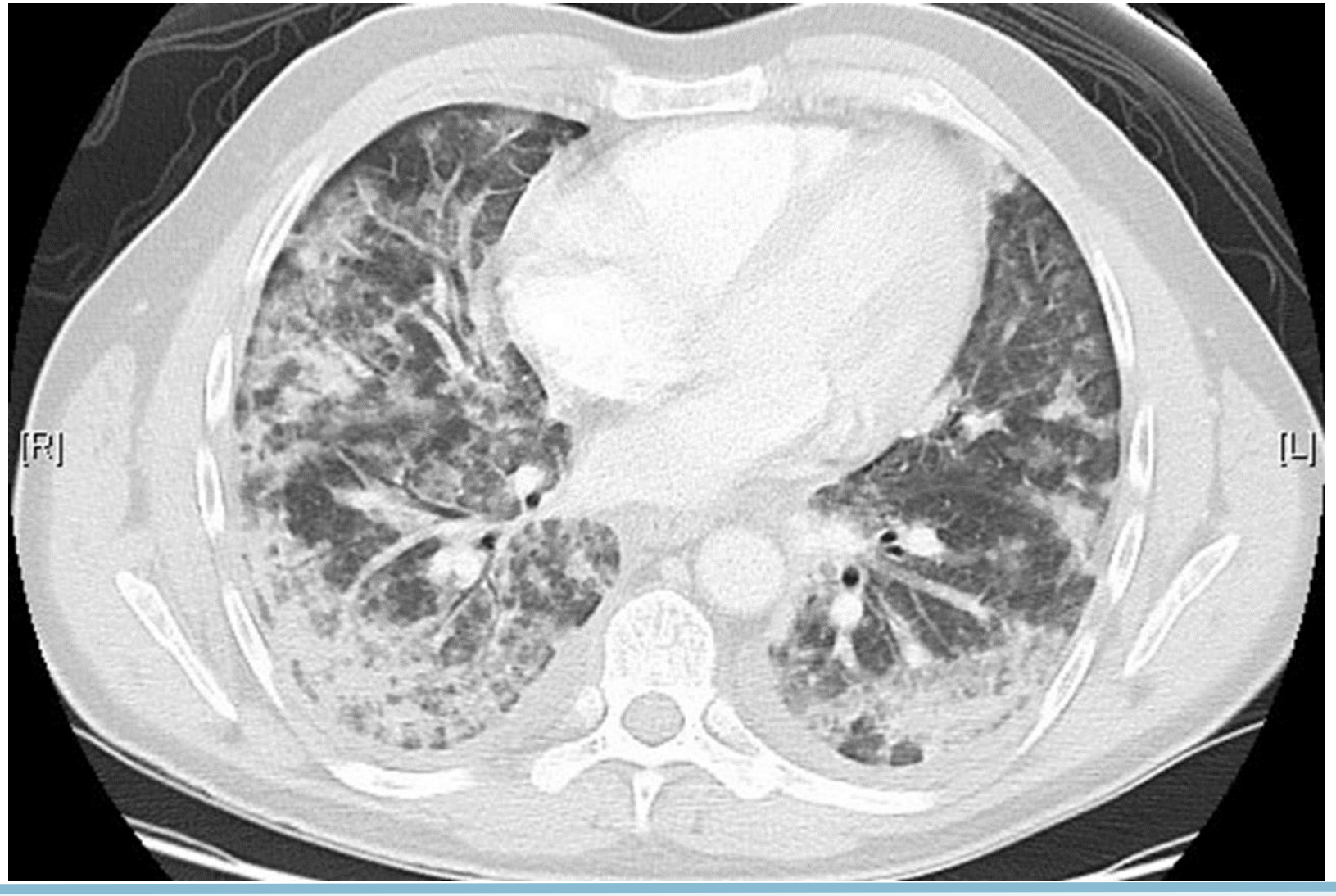
- Lab data:

  WBC 13.0 with 97% PMNs (no bands), Hgb 11.4, platelets 181

  Na 133, albumin 2.6, creatinine 0.93

  UA clear

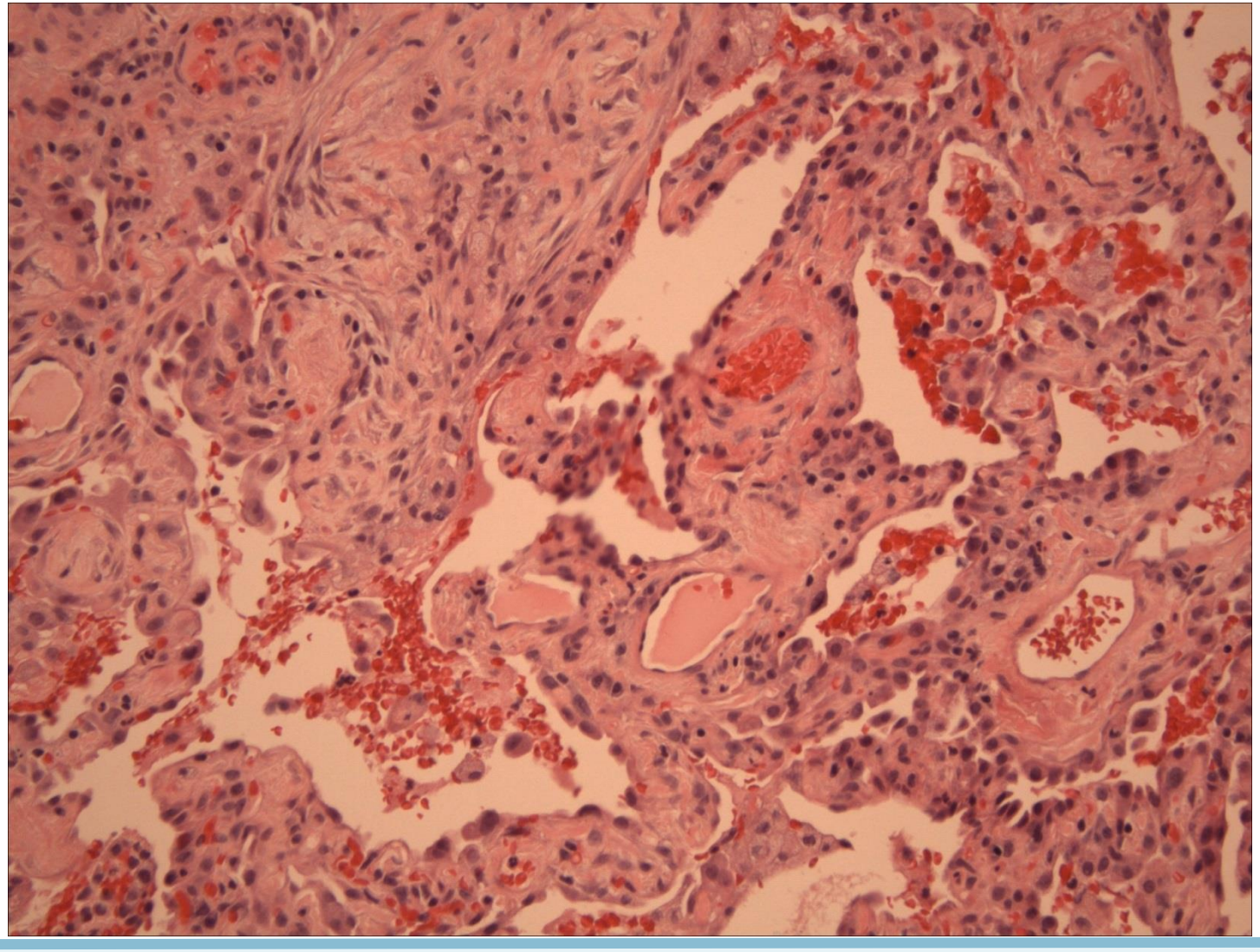
Case Study (cont.)



Case Study (cont.)

- Rapidly progressed to respiratory failure requiring mechanical ventilation
- All microbiological studies were negative and failed to improve with broad-spectrum Abx
- ANA, ANCA, anti-GBM, RF, CCP, and Jo-1 negative; CK normal
- Lung Bx…

Case Study (cont.)



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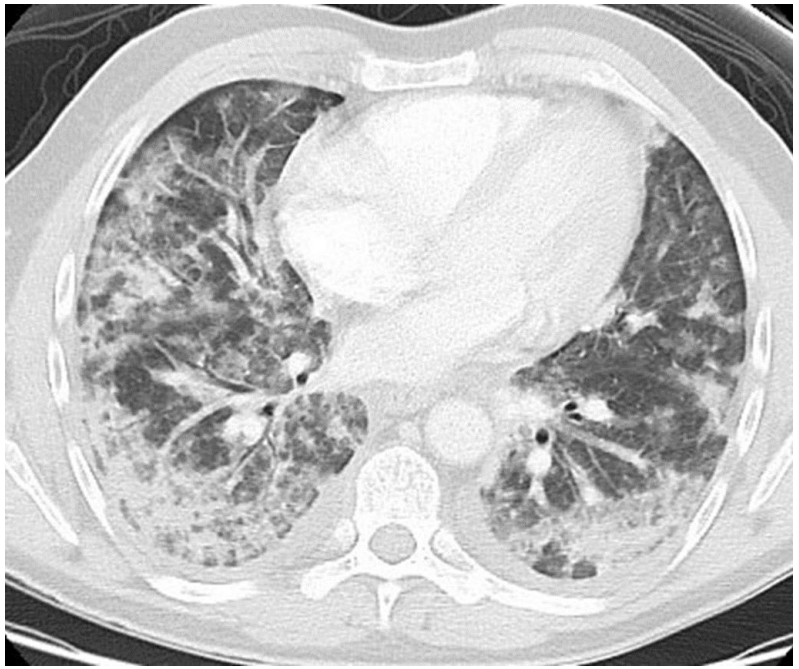
- Lung Bx…

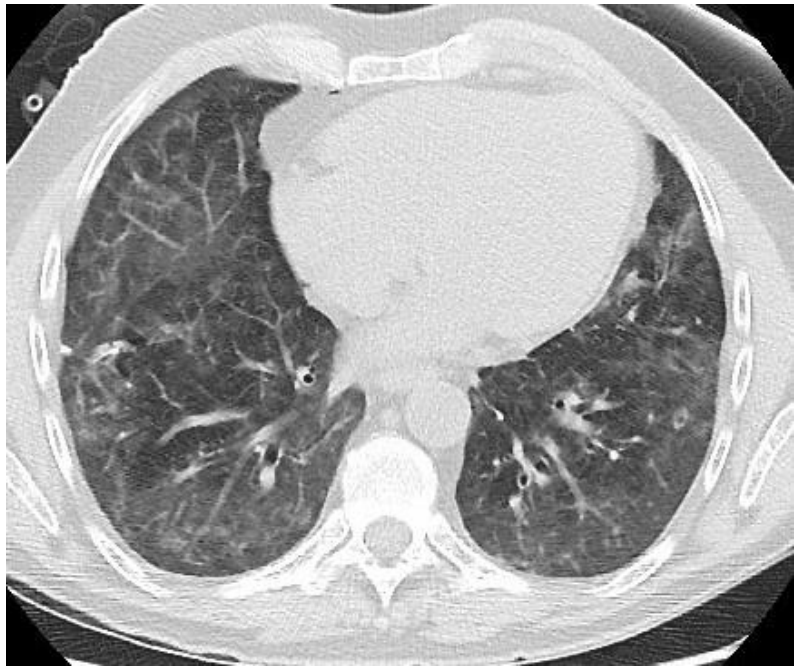
  Organizing pneumonia (OP) with cellular nonspecific interstitial pneumonia (NSIP) in less involved areas
  - Dx: cryptogenic organizing pneumonia (COP)
- Significant improvement with high-dose steroids and eventual discharge to rehab → home.

Case Study (cont.)

1 month later….

- Persistent mild cough, dyspnea and hypoxemia despite prednisone
- Myositis Ab panel: **strongly positive anti-OJ Ab** (anti-isoleucyl-tRNA synthetase)
- Mycophenolate added -> full recovery to prior level of functioning



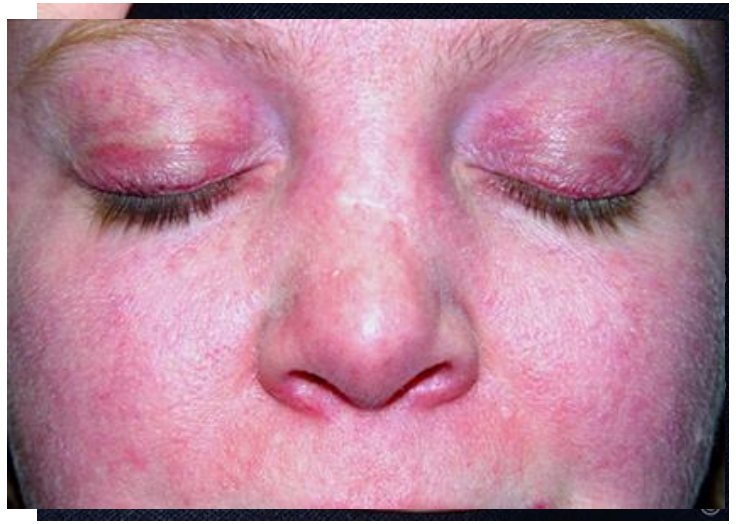


What is the diagnosis?

Polymyositis/Dermatomyositis

Autoimmune disease(s) characterized by proximal muscle weakness and muscle inflammation

- Polymyositis (PM) – muscle disease only
- Dermatomyositis (DM) – muscle + skin disease



UpToDate

Multisystem disease

- Interstitial lung disease
- Polyarthritis, RP, constitutional Sx
- Esophageal disease – dysphagia, aspiration
- Cardiac involvement – conduction disease, arrhythmias

Spectrum of illness in PM/DM – "Myositis sine myositis"

- CM Pearson (1979): "Amyopathic dermatomyositis"
- Euwer and Sontheimer. *Arch Derm*. 1991
  - 6 patients with DM skin disease but no muscle involvement
  - Spectrum of disease
- Mayo Clinic (2010) and Cleveland Clinic (2016) series:
  - 18-20% of DM cases are clinically amyopathic (CADM)

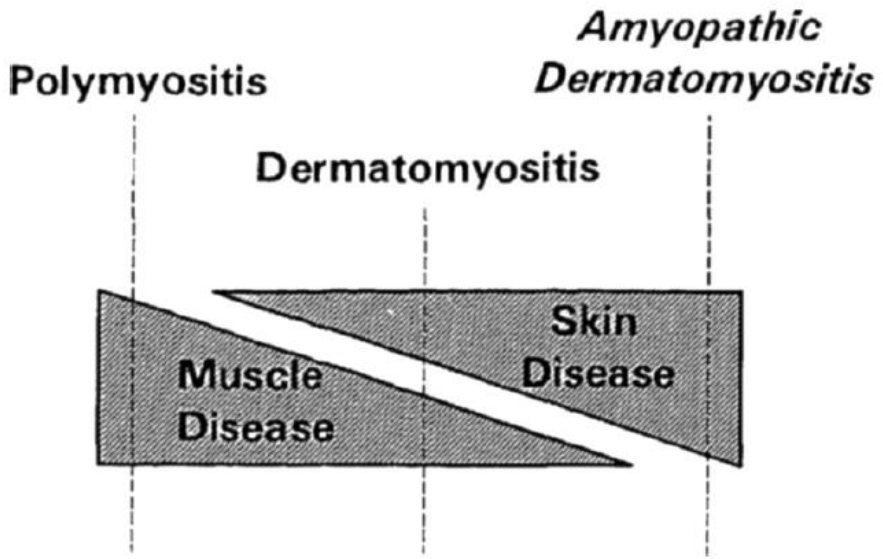


Fig. 4. Clinical spectrum of polymyositis/dermatomyositis.

Euwer and Sontheimer. *Arch Derm.* 1991.

2017 EULAR/ACR Classification Criteria for PM/DM

	Points (w/o Bx)	Points (w/ Bx)
Age of onset		
≥18 and <40	1.3	1.5
≥40	2.1	2.2
Muscle weakness		
Proximal upper extremities	0.7	0.7
Proximal lower extremities	0.8	0.5
Neck flexors > neck extensors	1.9	1.6
Legs: proximal > distal	0.9	1.2
Skin		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory		
Anti-Jo-1	3.9	3.8
Elevated CK, LDH, AST, or ALT	1.3	1.4
Muscle biopsy	-	1.2-3.1

Without Bx:

≥ 5.5 points: Probable IIM

≥ 7.5 points: Definite IIM

(skin necessary)

With Bx:

≥ 6.7 points: Probable IIM

≥ 8.7 points: Definite IIM

Myositis-specific antibodies

Myositis-specific Abs

- Anti-aminoacyl-tRNA synthetase Abs
  - Jo-1
  - EJ
  - OJ
  - KS
  - PL-7
  - PL-12
  - Zo
  - YRS

  Anti-synthetase syndrome:
  Myositis, ILD, fevers, arthritis, mechanic's hands, RP
- Anti-SRP (signal recognition peptide)
- Anti-Mi-2 (nuclear helicase)
- Anti-MDA-5/CADM-140 (RNA helicase)
- Others: p155/140 (TIF1-γ), NXP-2 (MJ), SAE-1

Interstitial lung disease in PM/DM

- ILD in 20-43% of PM/DM (Hallowell RW and Paik JJ. *Clin Exp Rheum.* 2021)
- Up to 80% with aggressive screening (Fathi M et al. *Arth Rheum*. 2008)
  - Higher in: anti-synthetase Ab, anti-MDA-5

- At least two distinct (but overlapping?) clinical patterns:
  - Subacute/fulminant disease → respiratory failure/ARDS
  - Chronic/progressive ILD → can mimic IPF clinically

- ILD patterns: DAD, OP, NSIP, and UIP (and mixed) -> often correlate with acuity of symptoms.

- ILD can often precede the onset of muscle/skin disease

ILD and Anti-Jo-1-positive PM/DM

346 consecutive patients with PM/DM (4 centers in France)

- 91/346 (26%) Jo-1 positive
  - 66/91 (73%) with ILD

Table 1. ILD characteristics of 66 anti–Jo-1–positive patients with antisynthetase syndrome*

	Antisynthetase syndrome with ILD
Presenting symptoms	
Symptomatic acute onset of lung disease	12 (18.2)
Symptomatic progressive onset of	35 (53)
	19 (28.8)
[illegible]	10 (15.2)
with PM/DM	42 (63.6)
	14 (21.2)
LD diagnosis, %	
	73
	74
	59
rn	
	11 (16.7)
	39 (59.1)
	16 (24.2)
	16 (24.2)
	39 (59.1)
	11 (16.7)
	6 (9.1)

Table 4. Comparison of clinical characteristics between anti–Jo-1 antisynthetase syndrome patients with and without ILD*

	With ILD (n = 66)	Without ILD (n = 25)	P†
General characteristics			
Age, median (range) years	55 (25–74)	57 (18–79)	0.586
Sex, %			1
Male	37.9	36	
Female	62.1	64	
PM/DM subset, %	72.7/27.3	52/48	0.08
Clinical characteristics, %			
Raynaud's phenomenon	48.5	40	0.491
Mechanic's hands	34.8	8	0.009
Esophageal involvement	16.7	36	0.08
Joint involvement	66.7	60	0.626
Ventilatory insufficiency	10.6	12	1
Aspiration pneumonia	9.1	4	0.668
Cancer	4.5	16	0.08
Biochemical parameter, median (range)			
Creatine kinase, IU/liter	273 (50–8,109)	500 (24–20,000)	0.02

Marie I et al. *Arthritis Car Res.* 2013.

Spectrum of illness in anti-MDA-5 DM

	MDA5-positive (N = 11)	MDA5-negative (N = 149)	
	N (%)	N (%)	p-value
Demographics			
Gender			0.94
Male	3 (27.3)	39 (26.2)	
Female	8 (72.7)	110 (73.8)	
Race			0.24
Caucasian	8 (72.7)	124 (83.2)	
African American	2 (18.2)	17 (11.4)	
Asian	0 (0)	6 (4.0)	
Other	1 (9.1)	2 (1.3)	
Mean age at diagnosis, y	41.4	44.9	0.48
Median disease duration, m	24.5	26.3	0.9
Clinical Features			
Gottron's Papules/Sign	11(100)	111 (75)†	0.055
Heliotrope rash	9 (81.8)	71 (48.0)†	0.03
Weakness	6 (54.5)	138 (93.2)†	<0.001
Fever	5 (45.5)	24 (16.4)¥	0.017
Inflammatory Arthropathy	9 (81.8)	39 (26.7)¥	<0.001
Raynaud's Phenomenon	5 (45.5)	44 (30.3)§	0.3
Mechanic's Hands	9 (81.8)	28 (19.0)‡	<0.001
Interstitial Lung Disease	8 (72.7)	17 (11.4)	<0.001
Calcinosis	3 (27.3)	18 (12.1)	0.15

11/160 (7%) DM patients at Johns Hopkins anti-MDA-5 positive (0/32 controls)

- Less weakness
- More ILD
- More "anti-synthetase" features

Hall JC et al. *Arthritis Car Res.* 2013.

ILD and Anti-Jo-1

32 patients with ILD and positive Jo-1 *without* known PM/DM at presentation

- Frequency of myositis
  - 12/32 (37%) initially
  - 18/32 (56%) by end of follow up (median 62 mo)
  - 14/32 (44%) no myositis!

Table 2 Comparison of symptoms, creatine kinase levels and results of electromyography at initial presentation in groups A and G

Parameter	Group A (n = 15)	Group G (n = 17)
Asthenia	13	10
Weight loss	7	4
Fever (>38.5°C)	10	4
Arthralgia	9	14
Arthritis	2	3
Clubbing	0	1
Isolated dyspnoea	8	10
Dyspnoea and dry cough	7	7
Crackles	15	17
Raynaud's phenomenon	4	4
Sicca syndrome	1	2
Gottron's papules	2	1
Heliotrope rash	2	3
Mechanics' hand	3	6
Dyspnoea NYHA III/IV	15	7
Myalgia	5	6
Creatine kinase >2	5	7
Electromyography*	6	4
Autoantibodies†	1	9

Tillie-Leblond I et al. *Thorax*. 2008.

ILD and Anti-synthetase Abs

Clinical and Pathological Findings of Interstitial Lung Disease Patients with Anti-Aminoacyl-tRNA Synthetase Autoantibodies

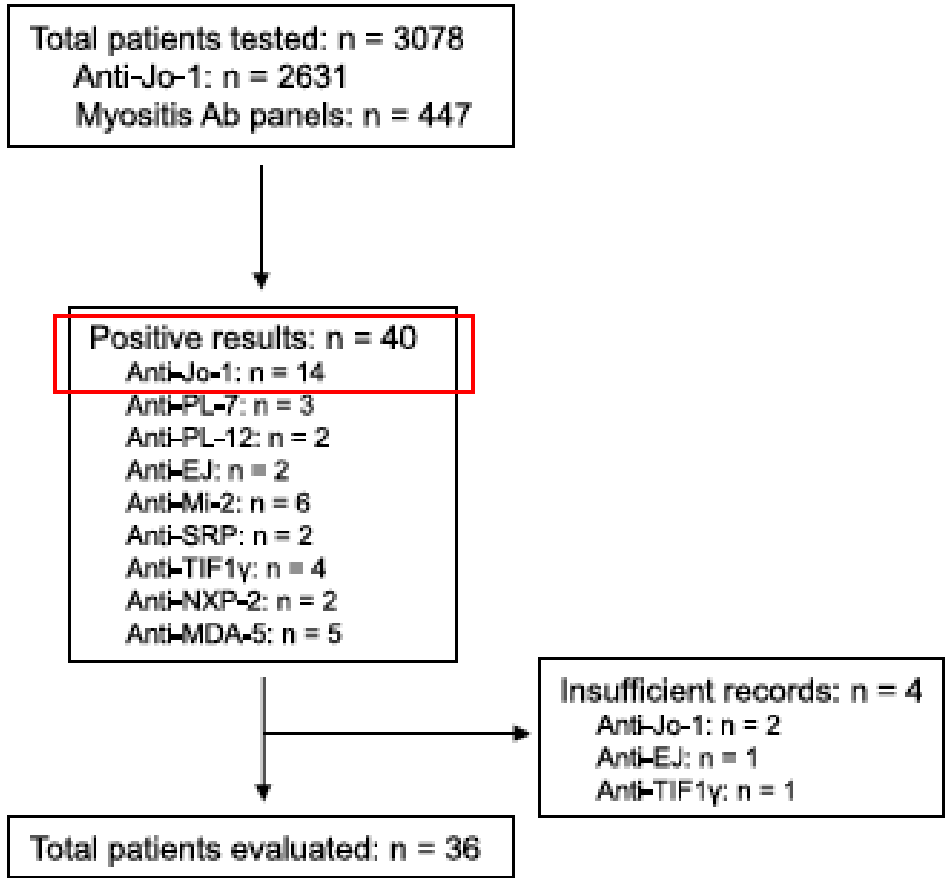
Yoshimizu Koreeda[1], Ikkou Higashimoto[1], Masuki Yamamoto[1], Mikiko Takahashi[2], Kenzo Kaji[3], Manabu Fujimoto[3], Masataka Kuwana[4] and Yuh Fukuda[2]

14 patients with ILD and anti-synthetase Abs

- Jo-1 (10) and OJ, EJ, KS, and PL-12 (1 each)
- Myositis (mean follow-up 22 mo):
  - 5/14 (36%) – myositis preceding or simultaneous with ILD
  - 3/14 (21%) – myositis developed after ILD
  - 6/14 (43%) – no myositis!

Koreeda et al. *Inter Med*. 2010.

Lung, muscle and skin disease in patients with positive MSAs



Misra A et al. *BMC Pulm Med. 2021*

ILD is more common than muscle or skin disease in patients with MSAs

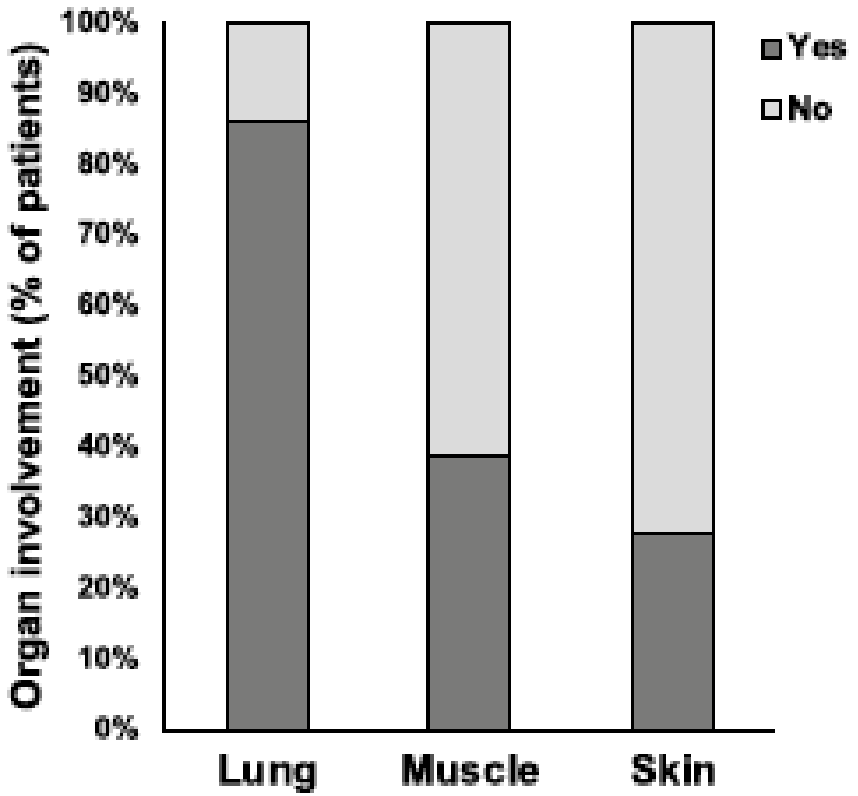
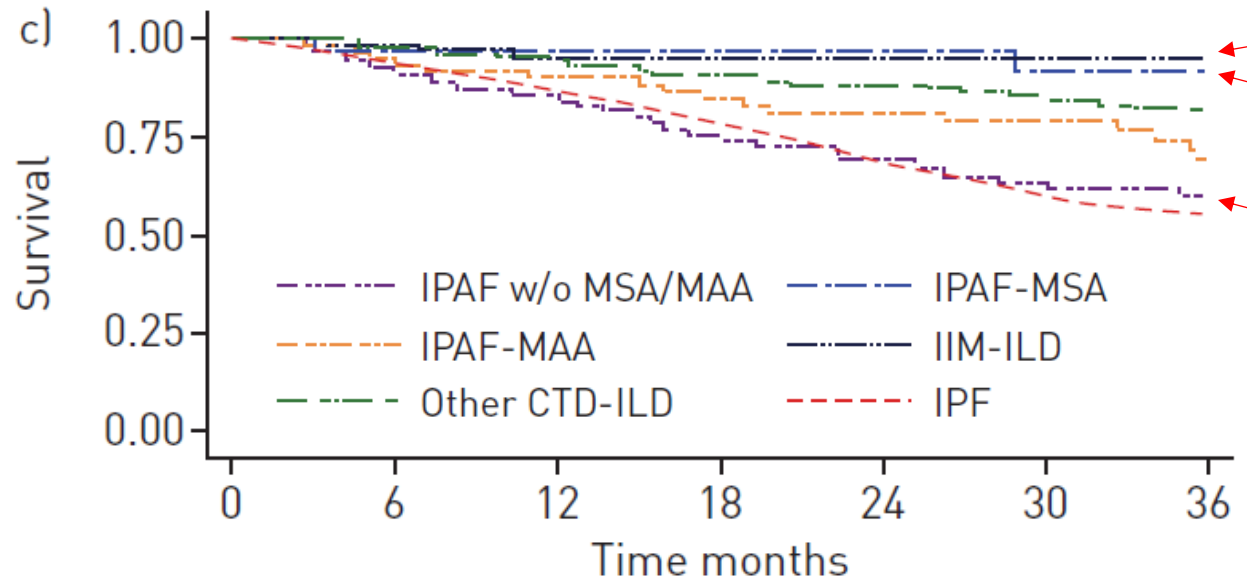


Fig. 2 Frequency of lung, muscle, and skin involvement among the study population ($n = 36$) of individuals with positive circulating myositis-specific antibodies (MSAs). $p < 0.0001$ by Chi-squared test

- **50% of MSA-positive patients had isolated ILD at the time of diagnosis!**
  - **Did not meet criteria for PM/DM**
- **What diagnosis do we give these patients?**
  - **"Amyopathic polymyositis"?**
  - **"Dermatopneumomyositis"?**
  - **Interstitial pneumonia with autoimmune features (IPAF)?**

Misra A et al. *BMC Pulm Med. 2021*

Not all IPAF is the same!



PM/DM-ILD

MSA-IPAF

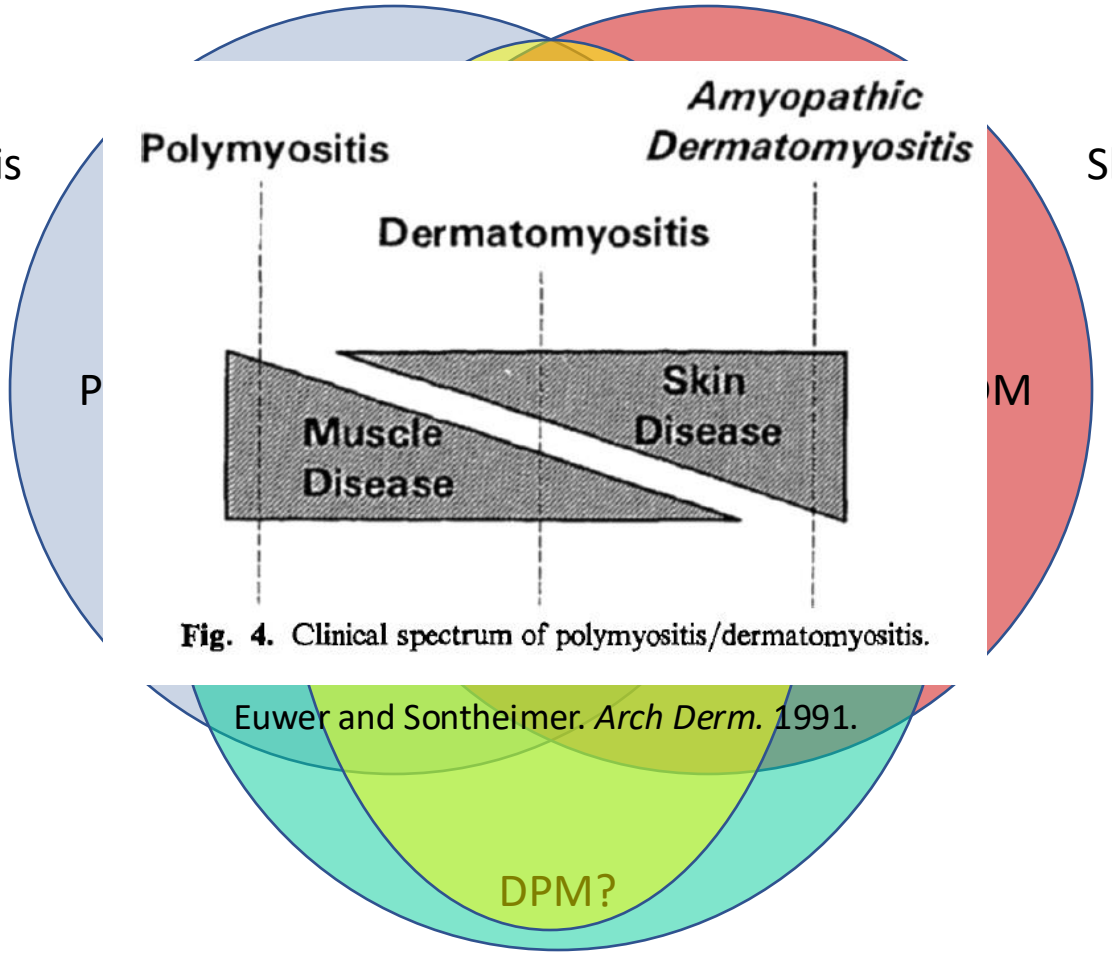
Other IPAF

At risk n

IPAF	169	146	132	113	97	82	71
IPAF-MSA	35	34	33	32	28	18	16
IPAF-MAA	65	59	53	47	41	34	28
IIM-ILD	70	68	64	62	56	52	51
Other CTD-ILD	296	275	252	219	197	180	160
IPF	770	702	624	538	427	349	295

Graham J et al. *ERJ. 2020*

Spectrum of illness in PM/DM/anti-synthetase syndrome



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