ILD Collaborative

Project ECHO

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

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MGH Interstitial Lung Disease Program

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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

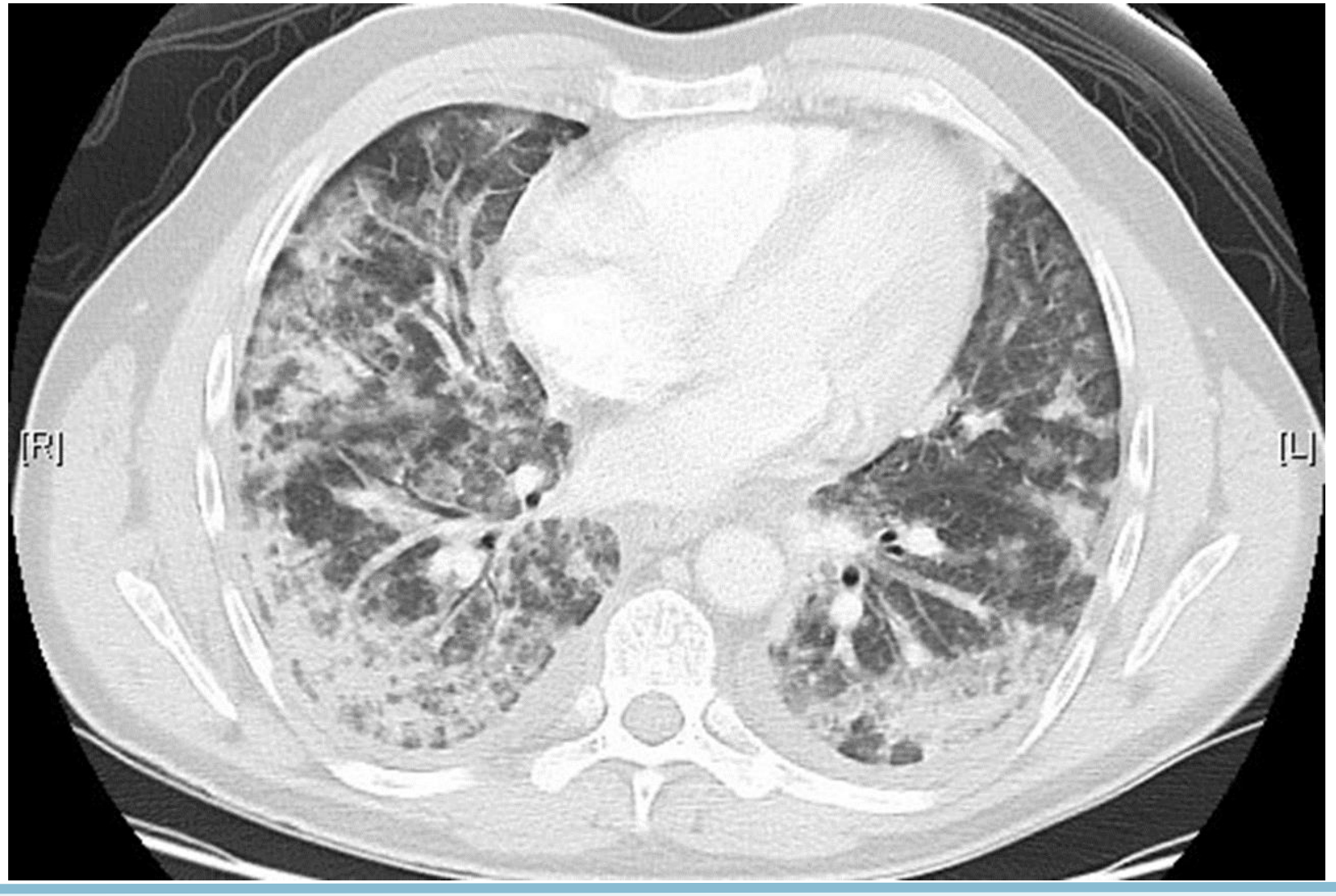
- Lab data:

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

  Na 133, albumin 2.6, creatinine 0.93

  UA clear

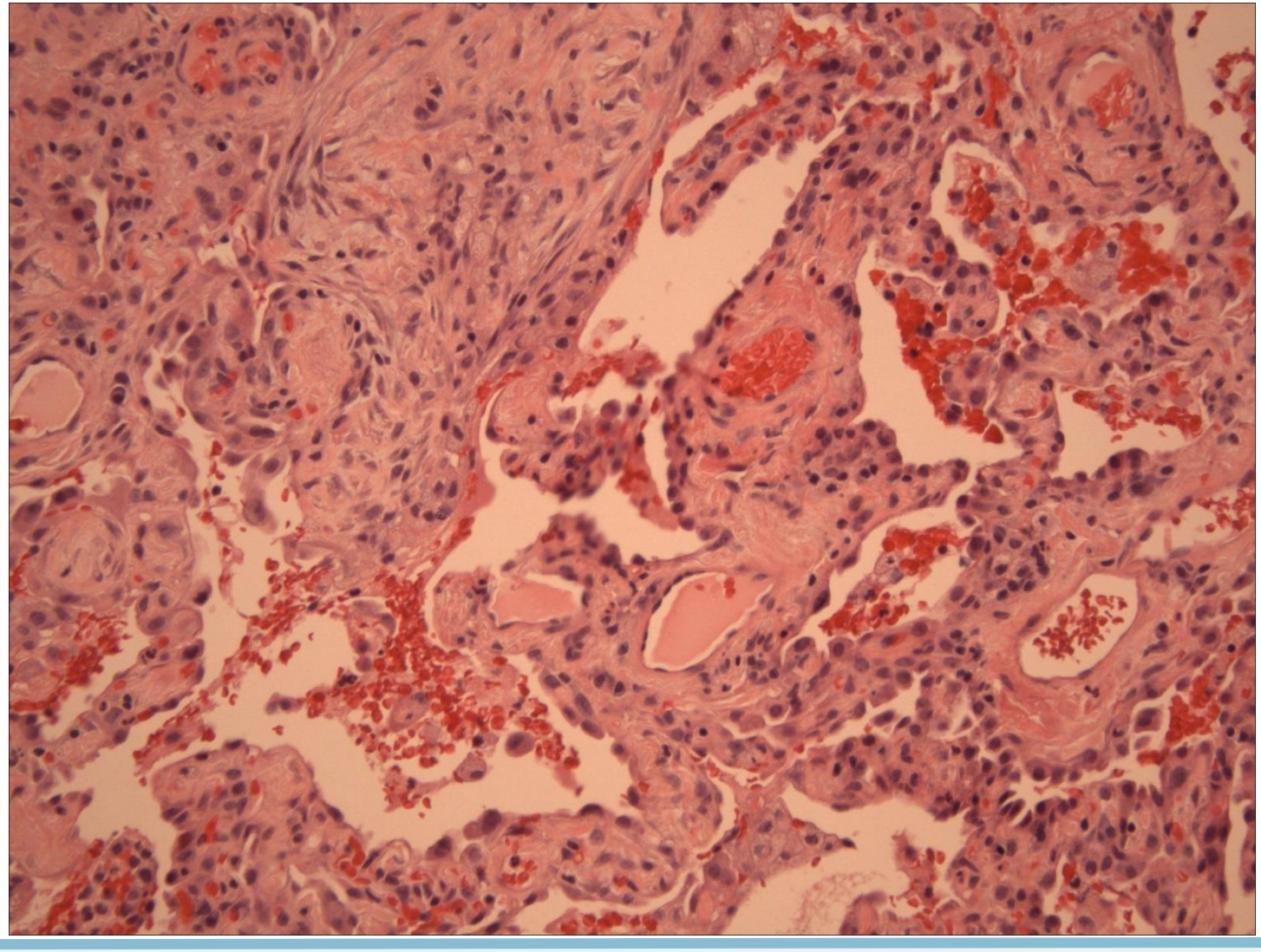
Case Study (cont.)



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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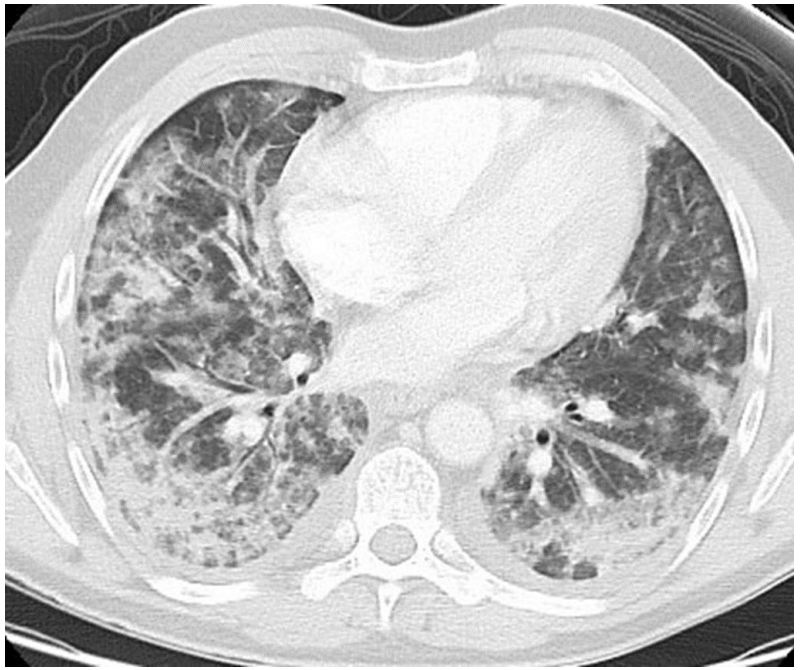
- Lung Bx…

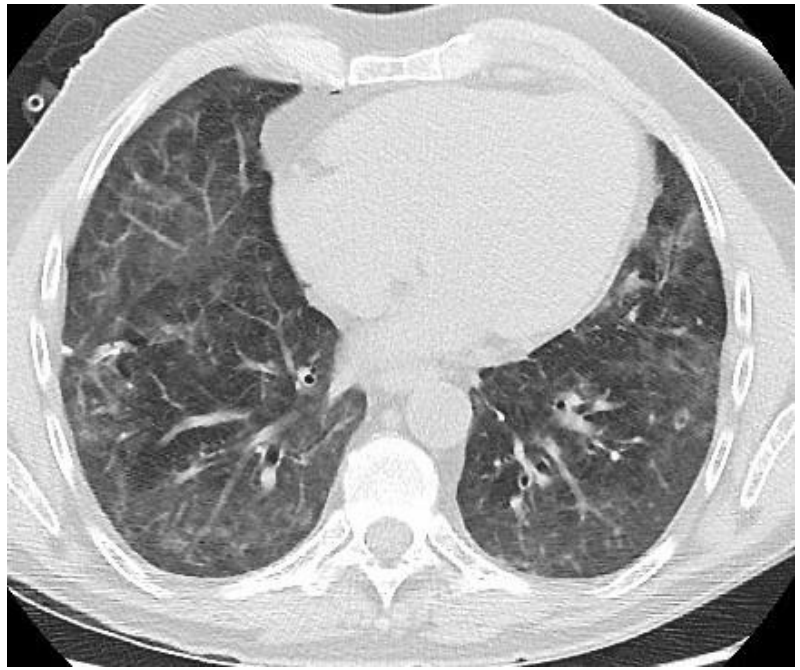
  Organizing pneumonia (OP) with cellular nonspecific interstitial pneumonia (NSIP) in less involved areas
  - Dx: cryptogenic organizing pneumonia (COP)
- Significant improvement with high-dose steroids and eventual discharge to rehab → home.

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



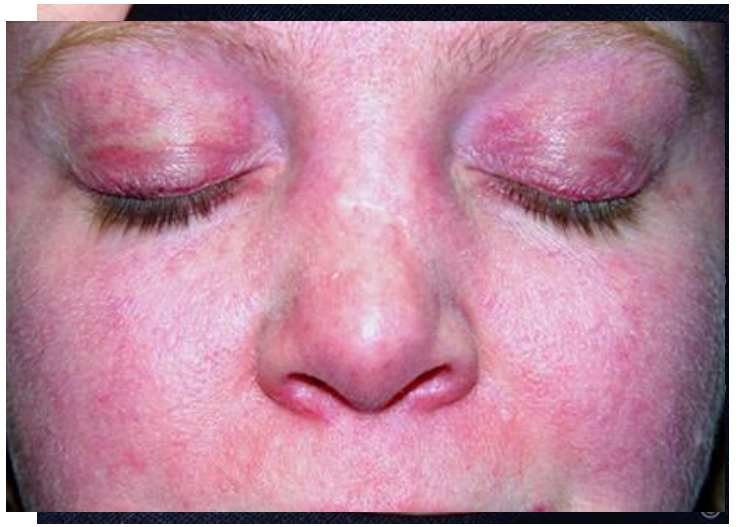


What is the diagnosis?

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)

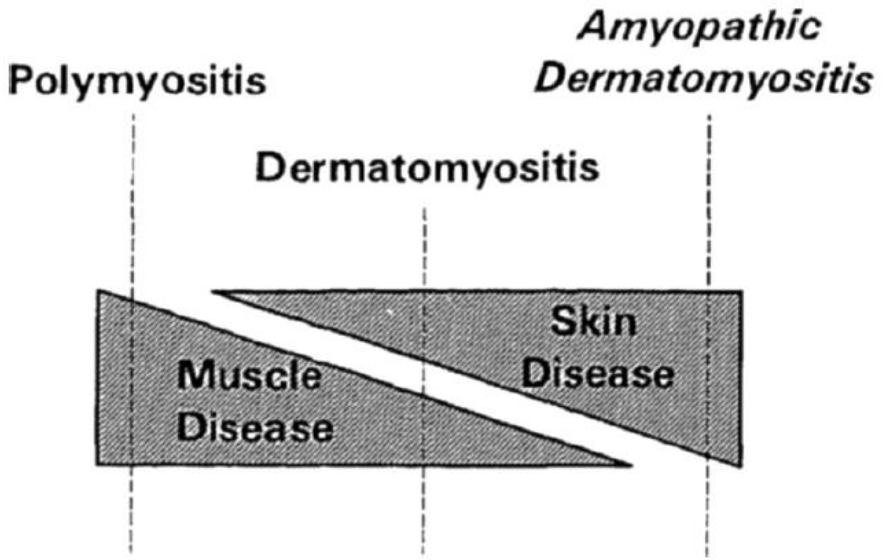


Fig. 4. Clinical spectrum of polymyositis/dermatomyositis.

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
  - Ha

  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 lung signs	35 (53)
Asymptomatic	19 (28.8)
Time of onset	
Before PM/DM	10 (15.2)
Concomitant with PM/DM	42 (63.6)
After PM/DM	14 (21.2)
PFT findings at ILD diagnosis, %	
FVC	73
VC	74
DLco	59
HRCT scan pattern	
COP	11 (16.7)
NSIP	39 (59.1)
UIP	16 (24.2)
Course	
Resolution	16 (24.2)
Improvement	39 (59.1)
Deterioration	11 (16.7)
Mortality	6 (9.1)

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

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LD diagnosis, %	
	73
	74
	59
rn	
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	39 (59.1)
	16 (24.2)
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	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.

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.

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

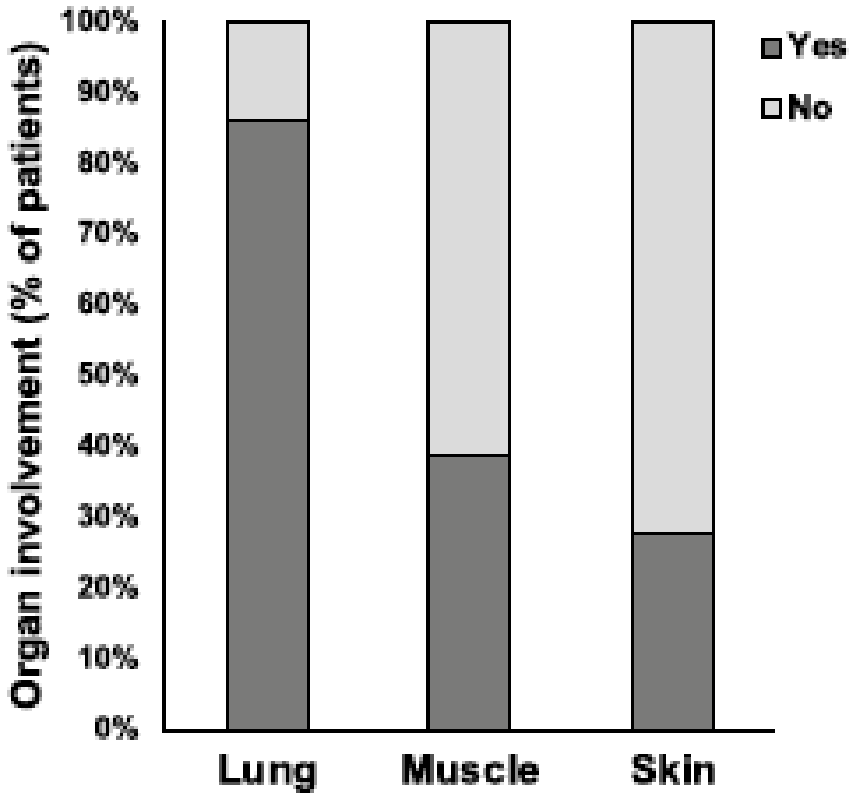


Fig. 2 Frequency of lung, muscle, and skin involvement among the study population ($n = 36$) of individuals with positive circulating myositis-specific antibodies (MSAs). $p < 0.0001$ by Chi-squared test

- **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*

Interstitial Pneumonia with Autoimmune Features (IPAF)

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

Fischer A et al ERJ. 2015.

Interstitial 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 → S/Sx suggestive of CTD (e.g. Raynaud's, inflamm. arthritis)
   - B. Serologic domain → Autoantibodies highly suggestive of (or specific for) CTD
   - C. Morphologic domain → Specific patterns of ILD (e.g. OP, NSIP, LIP) or other thoracic abnormalities (e.g. pulmonary vascular dz)

In most cases…..

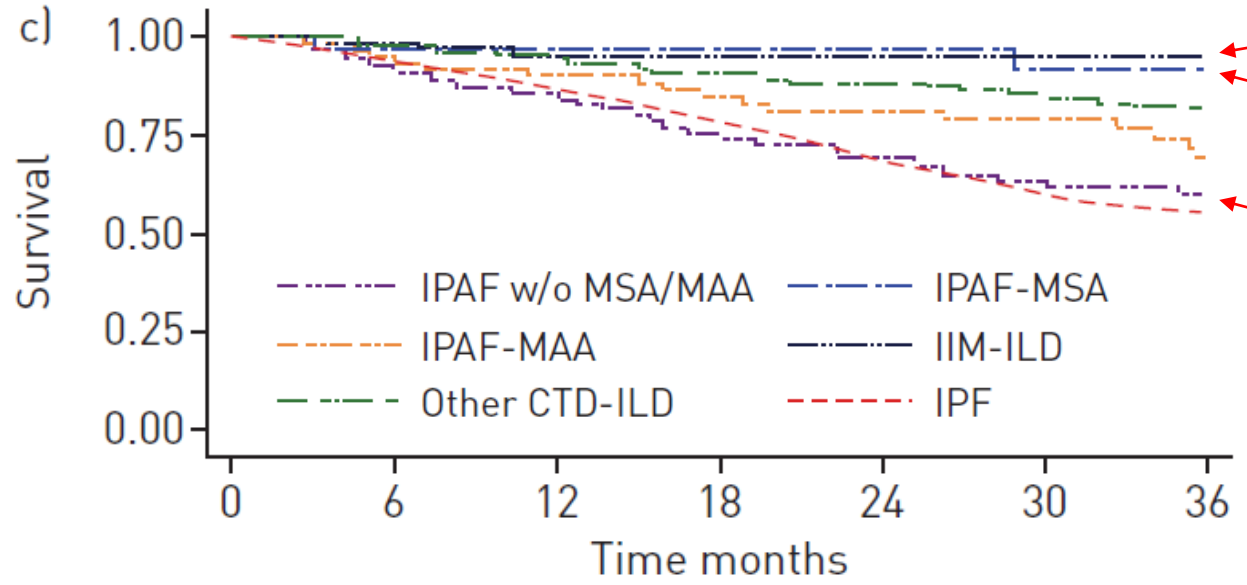
1. Specific patterns of idiopathic ILD (UIP pattern excluded!!)

   And

2. Specific clinical or serological features suggestive of (but not diagnostic for) CTD

Fischer A et al ERJ. 2015.

All IPAF may not be 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*

Not all ILD with autoantibodies is IPAF!

- Ab + NSIP/OP/LIP/(BIP?) = IPAF Ab + UIP ≠ IPAF
- Are autoantibodies specific enough to *define* the presence of autoimmune disease?

Component	12/22/2023	2/6/2024
Anti-cN-1A AB	No bands present	
Anti-Ro52 Ab	No bands present	
OJ Ab	No bands present	Negative
EJ Ab	No bands present	Negative
PL-12 Ab	Moderately positive for PL-12 band !	Negative
PL-7 Ab	No bands present	Negative
SRP Ab	No bands present	Negative
Jo-1 Ab	No bands present	<20
Anti-Pm/Scl-75 Ab	No bands present	
PM/Scl 100 Antibody, IgG	No bands present	
KU Ab	No bands present	Negative
Anti-SAE1 Ab	No bands present	
NXP-2 Ab	No bands present	<20
MDA-5 Ab	No bands present	<20
Anti-TIF-1Gamma Ab	No bands present	
MI-2 Ab	No bands present	Negative
MI-2 Ab	No bands present	

High false positive rates with common MSA assays

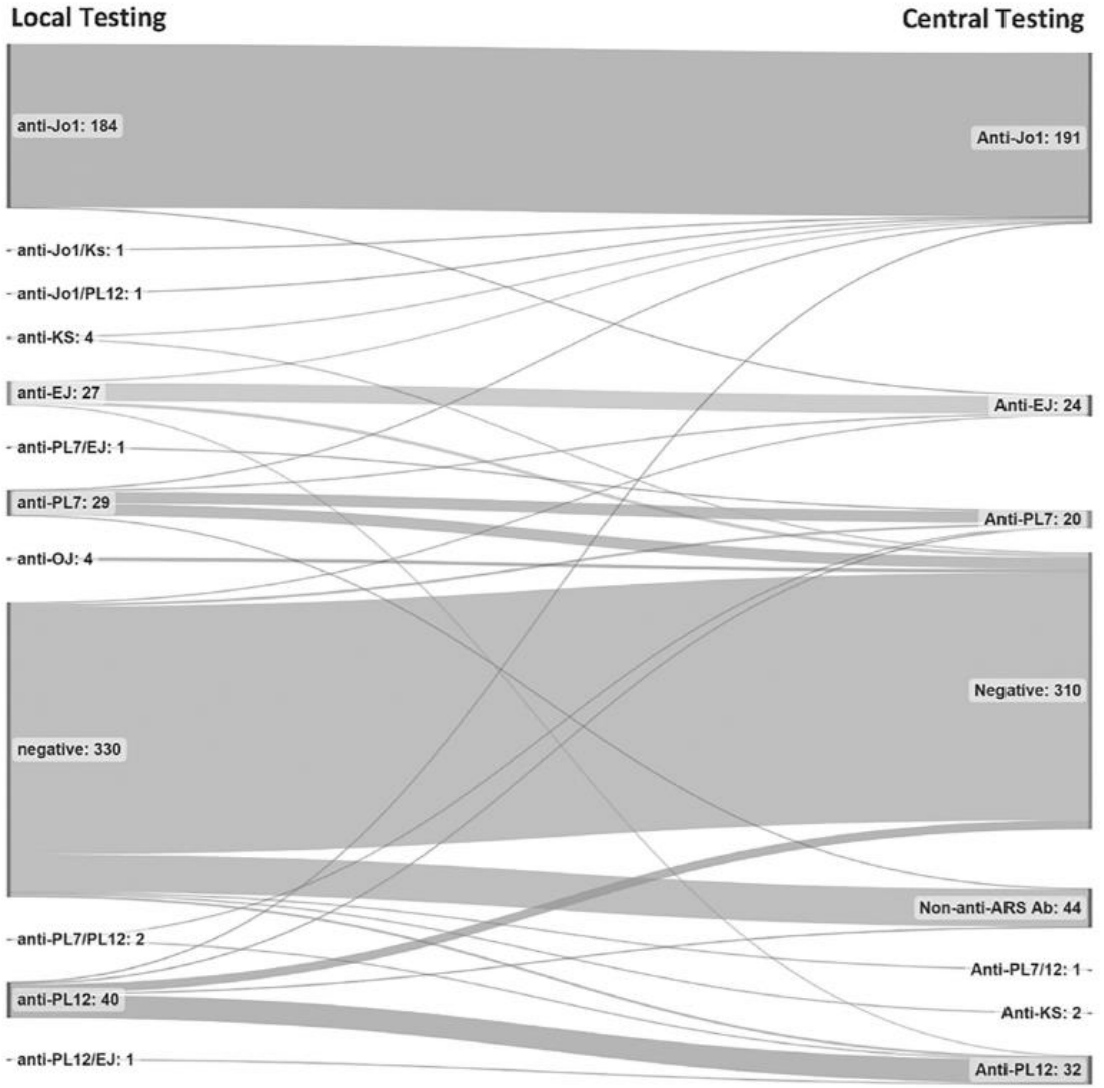


Fig. 2. Sanke plot illustrating the variation in results obtained through local testing compared to the result obtained on central testing.

Loganathan et al. *Clin Exp Rheum. 2024*

High false positive rates with common MSA assays

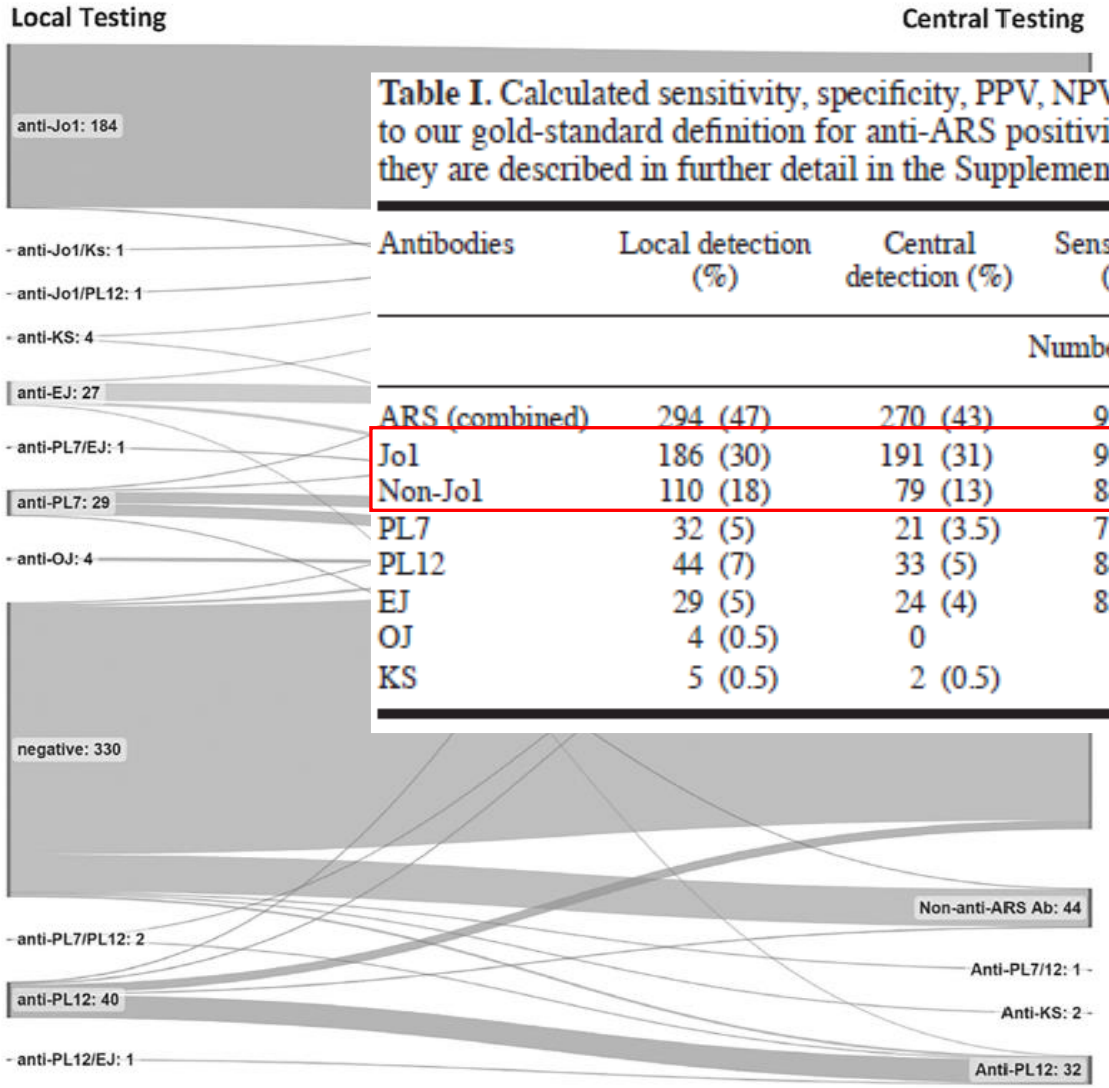


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Table I. Calculated sensitivity, specificity, PPV, NPV and weighted κ comparing the evaluation of all local testing methods in comparison to our gold-standard definition for anti-ARS positivity. Some patients (six local and one central determination) were double positive, and they are described in further detail in the Supplementary files.

Antibodies	Local detection (%)	Central detection (%)	Sensitivity (%)	Specificity (%)	PPV	NPV	Positive likelihood ratio	Inter-rater agreement Weighted κ
Number of patients: 624 (all local immunoassays)								
ARS (combined)	294 (47)	270 (43)	95.9	90.1	0.88	0.97	9.7	0.85 (95CI% 0.81 – 0.89)
Jo1	186 (30)	191 (31)	96.9	99.8	0.99	0.99	484.5	0.97 (95%CI 0.95 – 0.99)
Non-Jo1	110 (18)	79 (13)	84.8	92.1	0.61	0.98	10.7	0.66 (95%CI 0.58 – 0.74)
PL7	32 (5)	21 (3.5)	71.4	97.2	0.47	0.99	25.5	0.55 (95% CI 0.38 – 0.71)
PL12	44 (7)	33 (5)	84.8	97.3	0.64	0.99	31.4	0.71 (95% CI 0.59 – 0.83)
EJ	29 (5)	24 (4)	83.3	98.5	0.69	0.99	55.5	0.74 (95% CI 0.61 – 0.88)
OJ	4 (0.5)	0	-	99.4	-	1	n/a	-
KS	5 (0.5)	2 (0.5)	0	99.2	0	99.7	0	-0.004 (95%CI -0.01 – 0)

Loganathan et al. *Clin Exp Rheum. 2024*

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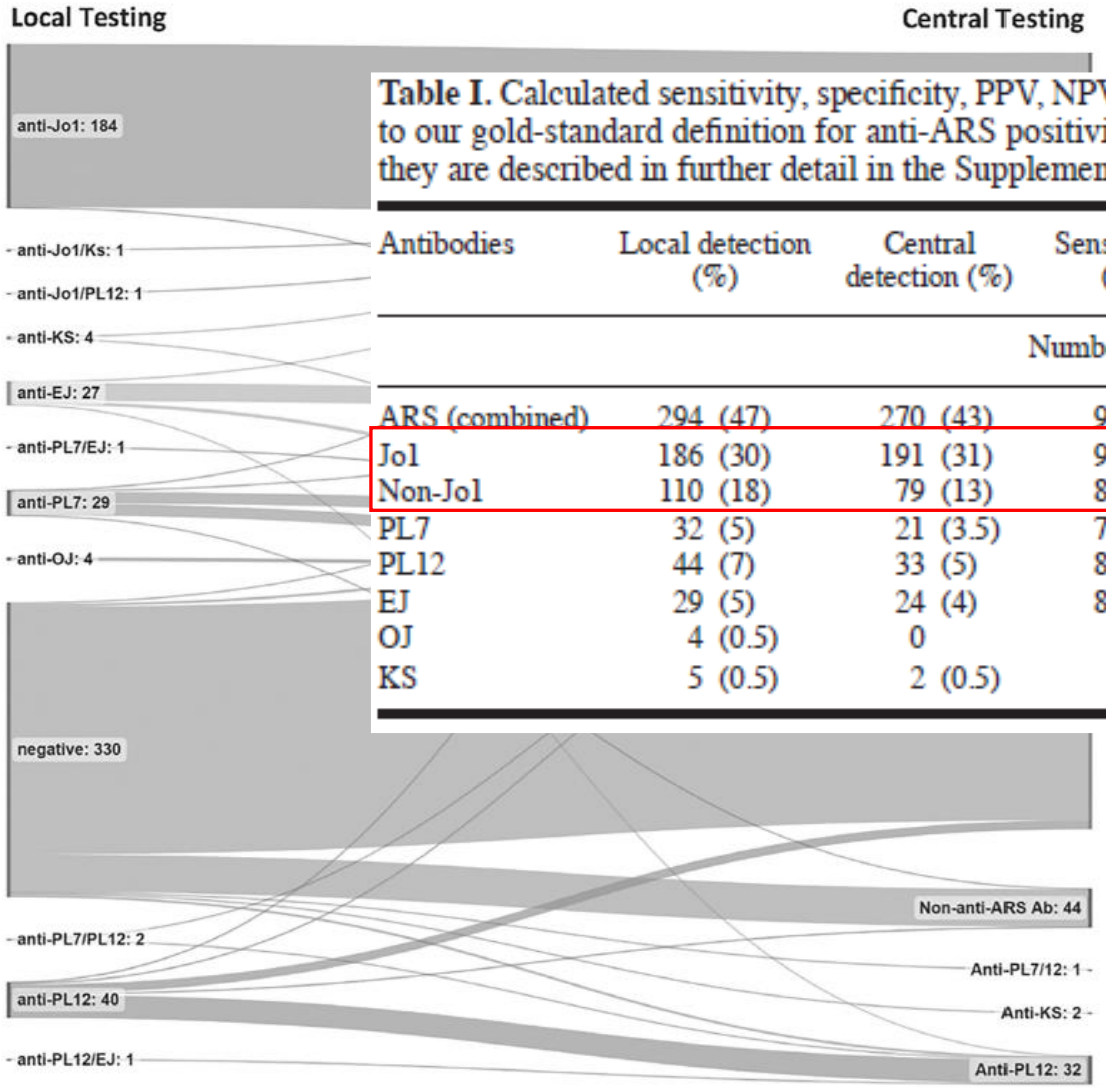

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- High false positive rates for non-Jo-1 Abs
- Exercise caution when interpreting ARS Ab assays

Loganathan et al. *Clin Exp Rheum. 2024*

Summary

- ILD is common in connective tissue diseases
  - Currently not included in most CTD classification criteria (except SSc)
- ILD may be the initial (or only) manifestation of CTD
  - PM/DM and RA
- Autoantibody testing can help determine the presence of otherwise occult CTD
  - Interstitial pneumonia with autoimmune features (IPAF)
  - Beware the possibility of false positives (and false negatives!) – clinical scenario is important when interpreting results.