Anti-synthetase syndrome

Floranne C. Ernste, M.D.
Division of Rheumatology

The Myositis Association Annual Conference
San Diego, CA
September 8, 2017

Disclosures

- I do not have any relevant financial disclosures.
- Off-label use:
  - Almost all medications discussed for treatment are not FDA-approved except for glucocorticoids.

MAYO CLINIC

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

A patient.

- 1 year ago, a 53 year old woman was referred for treatment advice. Developed weakness in her arms and legs 2 years prior with a heliotrope rash and Gottron's papules. CT scan revealed lung fibrosis. Labs showed a strongly positive Jo-1 antibody, confirming an anti-synthetase syndrome.
- She was short-winded on 3 liters of oxygen at rest, 4 liters during activity. She was on 25-30 mg of prednisone.
- Immunosuppressants tried: mycophenolate mofetil, azathioprine, rituximab.

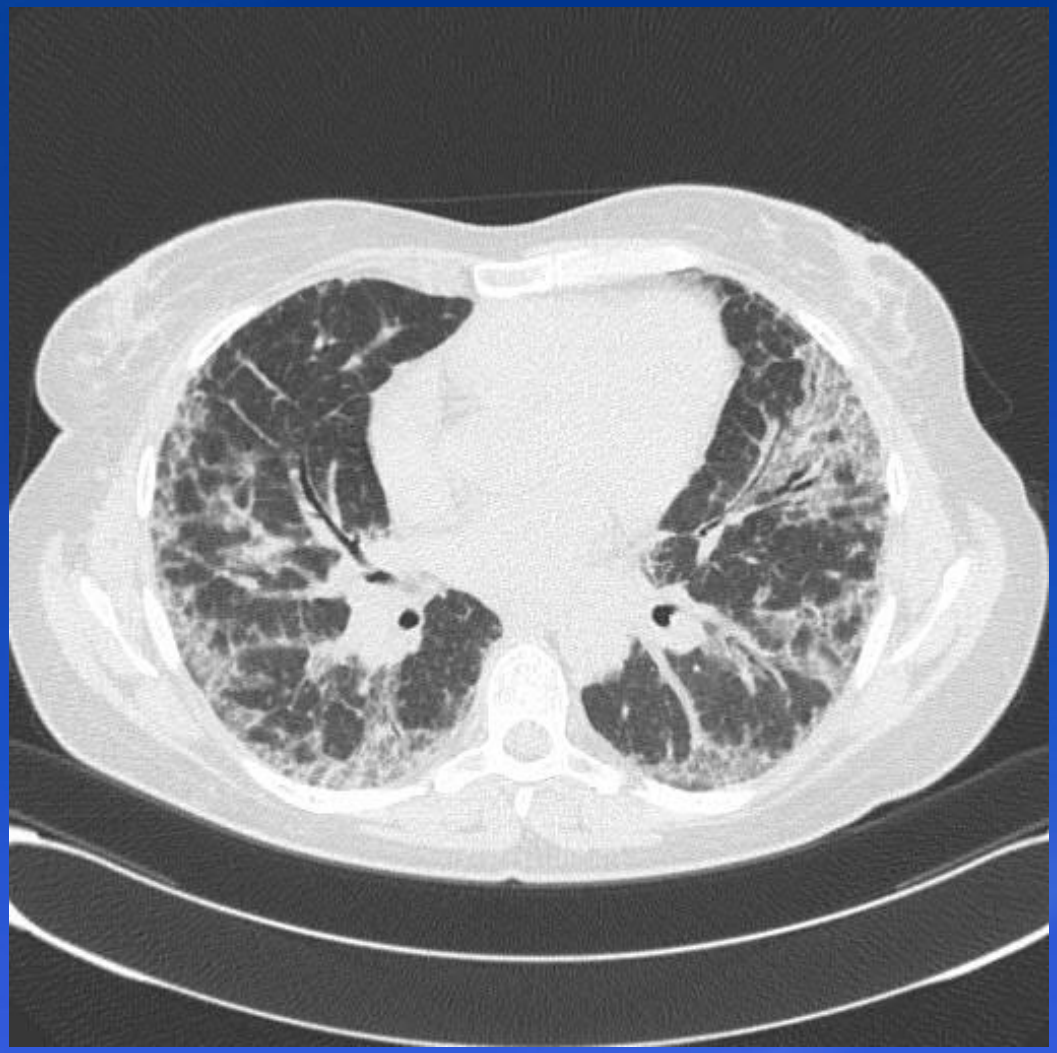
MAYO CLINIC

A patient.

- She had difficulty getting out of her wheelchair.
- Her exam showed moderate weakness in most of her proximal muscles in arms/legs.
- Her fingers and toes were clubbed.
- She had a heliotrope rash over her eyelids and inflammatory rashes on her hands.
- Her lungs sounded coarse with crackles bilaterally.
- Her CT scan looked like this:

MAYO CLINIC

A patient.



What else can be done for her?

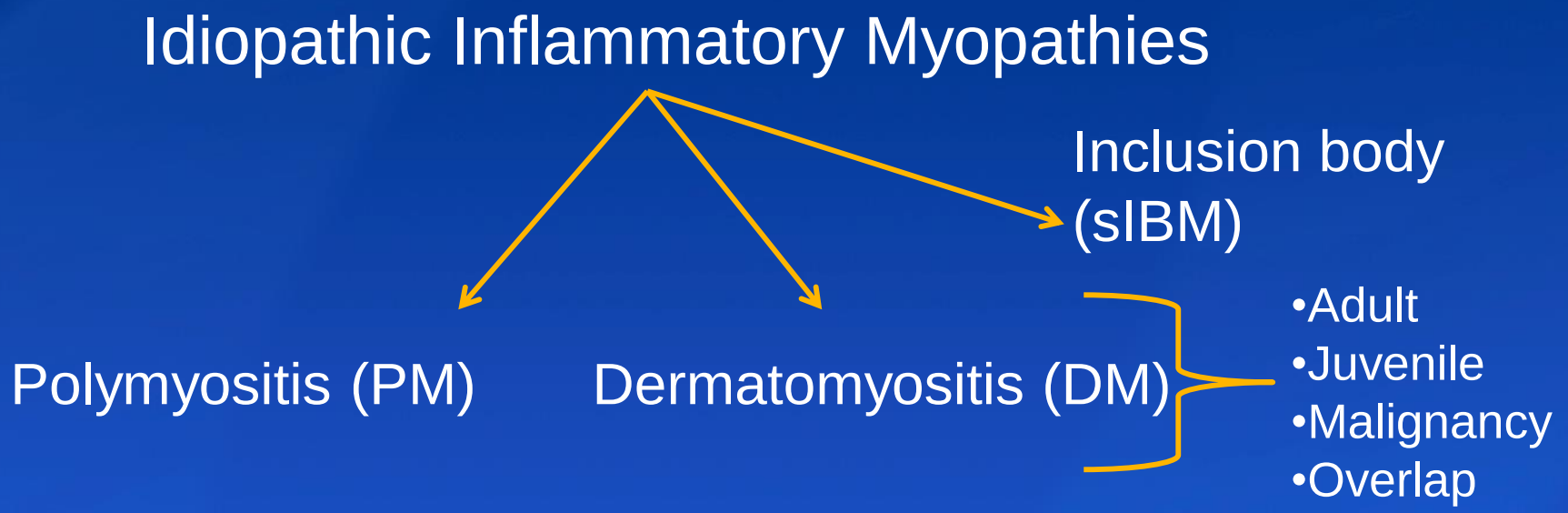
MAYO CLINIC

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

Original Classification



Bohan & Peter, N Engl J Med 292:344, 405, 1975
Bohan et al. Medicine 56:255, 1977

MAYO CLINIC

PM/DM classification criteria

- Proximal muscle weakness
- Elevated serum skeletal muscle enzymes
- Myopathic changes on EMG
- Biopsy evidence of muscle inflammation
- Rash

  - Definite PM or DM: 4 criteria satisfied
  - Probable PM or DM: 3 criteria satisfied
  - Possible PM or DM: 2 criteria satisfied

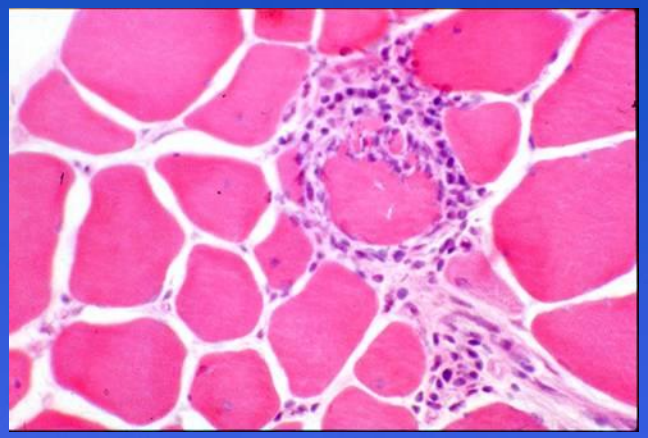
Bohan & Peter, N Engl J Med 292:344, 405, 1975
Bohan et al. Medicine 56:255, 1977

MAYO CLINIC

Distinguishing histologic features

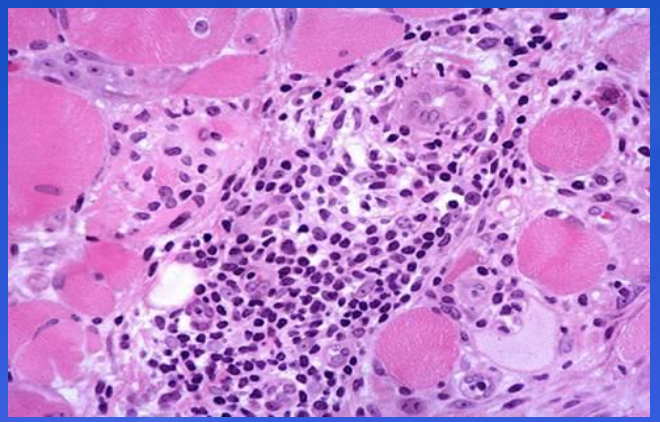
Polymyositis

- Inflammatory infiltrate within fascicle & endomysial areas.
- Scattered or isolated necrotic fibers.



Dermatomyositis

- Perivascular infiltrate around fascicle.
- Perifascicular atrophy.
- Muscle microvasculature often involved.



MAYO CLINIC

http://www.neuro.wustl.edu/neuromuscular/pathol/inflammation.html

Newer Classification Paradigm

Autoimmune myositis

Overlap Myositis (OM) | DM | Necrotizing Autoimmune myositis (NAM)* | PM | Sporadic IBM

- CTD-associated myositis, i.e. SLE, scleroderma
- MDA-5-associated myositis
- Other myositis-specific/myositis-associated syndromes
- Anti-synthetase syndrome

***Also known as IMNM**

Troyanov Y, Targoff IN, Tremblay JL et al. Medicine (Baltimore) 2005;84:231-49.
Fernandez C, Bardin N, de Paula AM, et al. Medicine (Baltimore) 2013; 92:15-24
Gunawardena H. Clin Rev Allergy Immunol 2017;52(1): 45-57..
Senécal Jean-Luc et al. Arthritis & Rheum 2017;69:878-84.

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

Definition of anti-synthetase syndrome

- 1. Presence of anti-synthetase antibody
- 2. Myositis (PM/DM)
- 3. Interstitial lung disease
- AND (Minor criteria)*
  - Raynaud's phenomenon
  - Mechanics' hands
  - Inflammatory arthritis
  - Fever (up to 1/3rd)

*Not all of these features may be present at baseline or ever

MAYO CLINIC

Marguerie C, Bunn CC, Beynon HL, et al. D Q Med. 1990;77:1019-38.
Love LA, Leff RL, Fraser DD et al. Medicine (Baltimore) 1991;70:360-74.

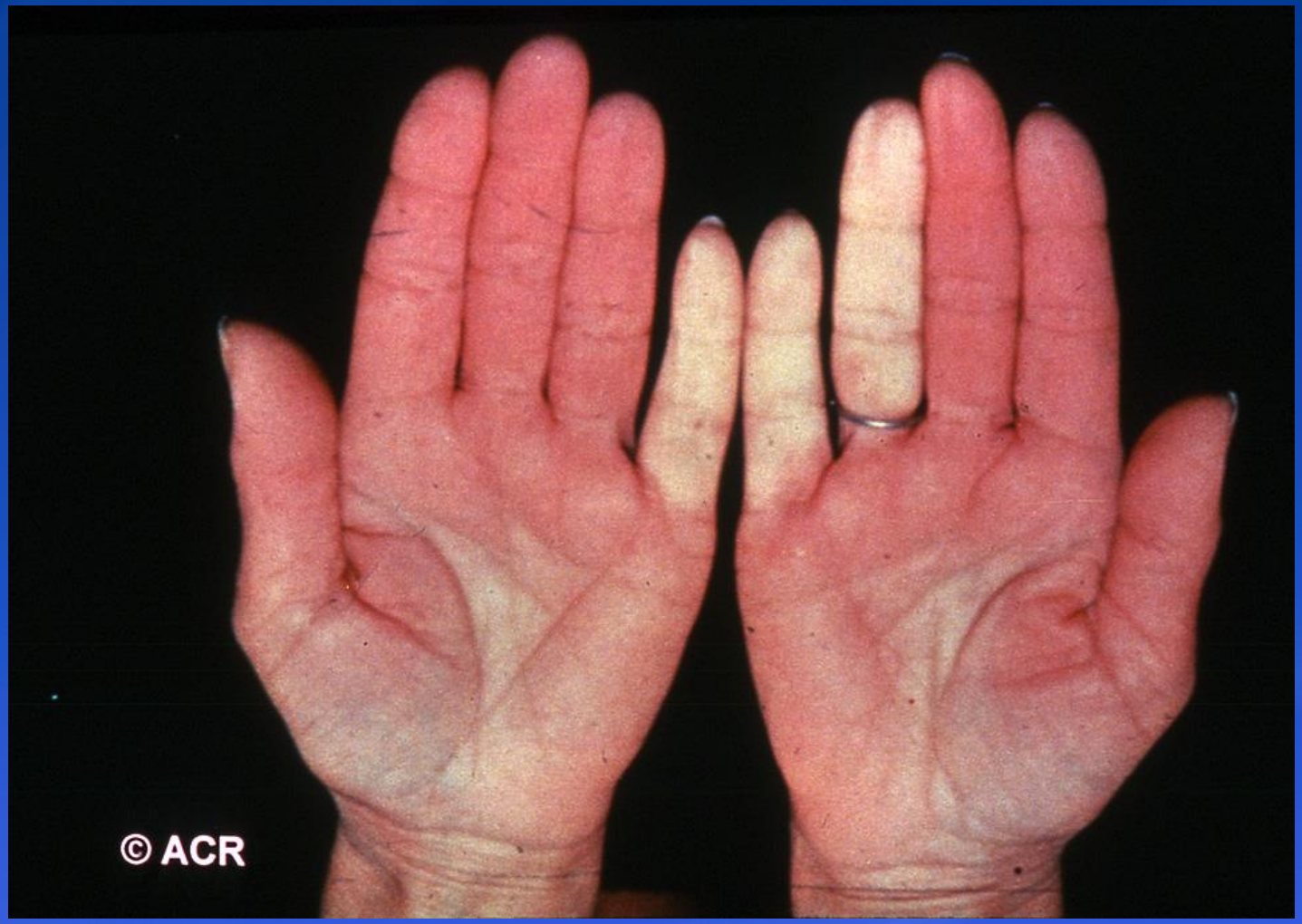
Disease Epidemiology

- Anti-synthetase syndrome first described in 1990 in 29 patients with PM/DM and ILD.
- Overall incidence of IIM is 6 to 10 per million, but incidence of Jo-1 + IIM ranges 1.2 to 2.5 per million and prevalence of 1.5 per 100,000.
- Average age at diagnosis is 50 years (22-74 years).
- Predominantly female, 2:1 ratio, may be higher in some series.

Love LA, Leff RL, Fraser DD et al. Medicine (Baltimore) 1991;70:360-74
Marguerie C, Bunn CC, Beynon HL, et al. D Q Med. 1990;77:1019-38.
Mielnick P, Wiesik-Szewczyk E, Olesinska M, et al. Autoimmunity. 2006;39:243-7.
Imbert-Masseau A, Hamidou M, Agard C, et al. Joint Bone Spine. 2003;70:161-8.
Zampieri S, Ghirardello A. Iaccarino L, et al. Autoimmunity. 2005;38:73-8.

MAYO CLINIC

Raynaud's phenomenon



MAYO CLINIC

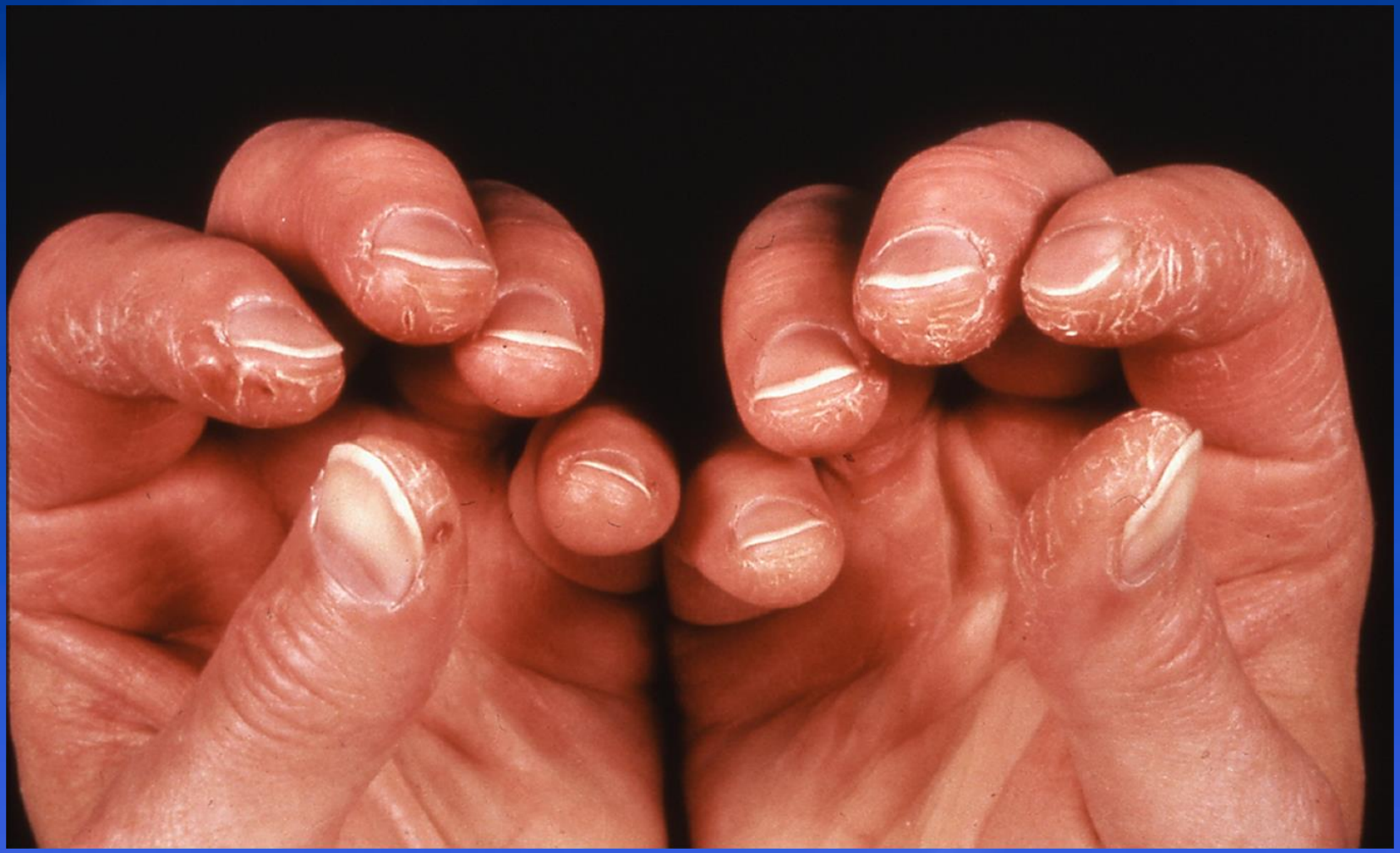
Mechanic's hands

- Originally reported by Stahl et al. in 1979.
- Characterized by scaly fissures, hyperkeratotic skin abnormalities on lateral aspects of fingers (radial side of index fingers, commonly seen).
- Reported in up to 70% of anti-synthetase syndrome patients, often those who are Jo-1 with ILD.

Stahl, Klippel, Decker. Ann Intern Med 1979;91:577-9.

MAYO CLINIC

“Mechanic’s Hands” (MH)



Downloaded with permission, ACR, 2017.

MAYO CLINIC

Inflammatory arthropathy

- Inflammatory arthritis “rheumatoid-like,” but negative anti-CCP antibodies.
- May be first manifestation of anti-synthetase syndrome in up to 27% of patients.
- Deforming subluxation of interphalangeal joints of thumbs and fingers.
- Periarticular calcifications may be present.
- Sometimes erosions seen at carpal bones, MCPs, and PIPs.

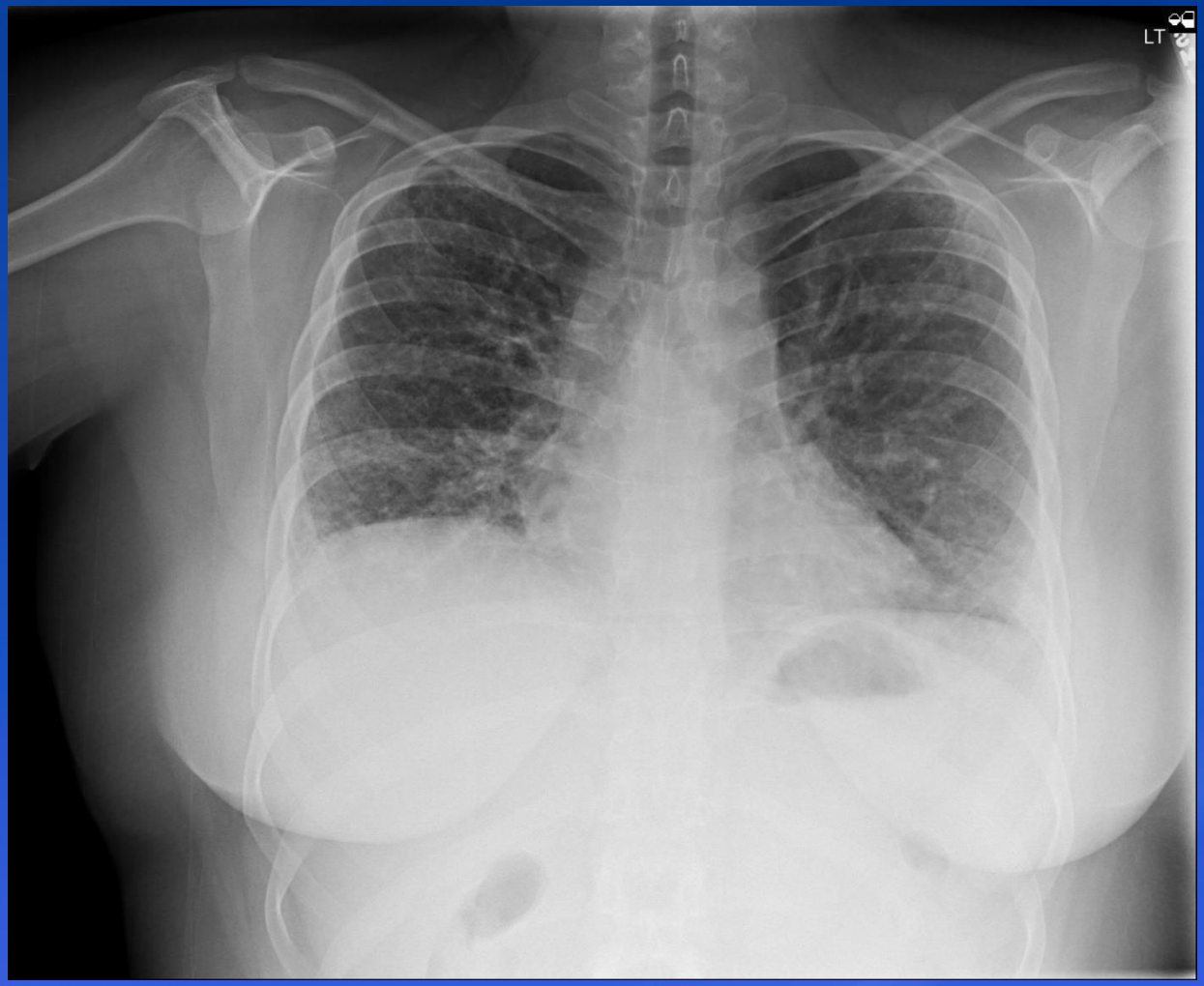
Marie I, Fournet P, Janvresse A, et al. Clin Exp Rheumatol. 2003;21:681-2.
Lefevre G, Meyer, A, Launay D. Rheumatology. 2015;54:927-32.
Oddis CV, Medsger TA, Cooperstein LA. Arthritis Rheum 1990;33:1640-45.

Disease Characteristics of ILD in anti-synthetase syndrome

- Shortness of breath and dry cough are common symptoms.
- Pulmonary function testing reveals restrictive physiology (i.e. FVC ≤ 80%).
- ILD subtype classified as non-specific interstitial pneumonia (NSIP)—most common, cryptogenic organizing pneumonia (COP), and usual interstitial pneumonia (UIP).
- Chest imaging shows basilar abnormalities: reticular and ground-glass opacities with loss of lung volume, traction bronchiectasis.

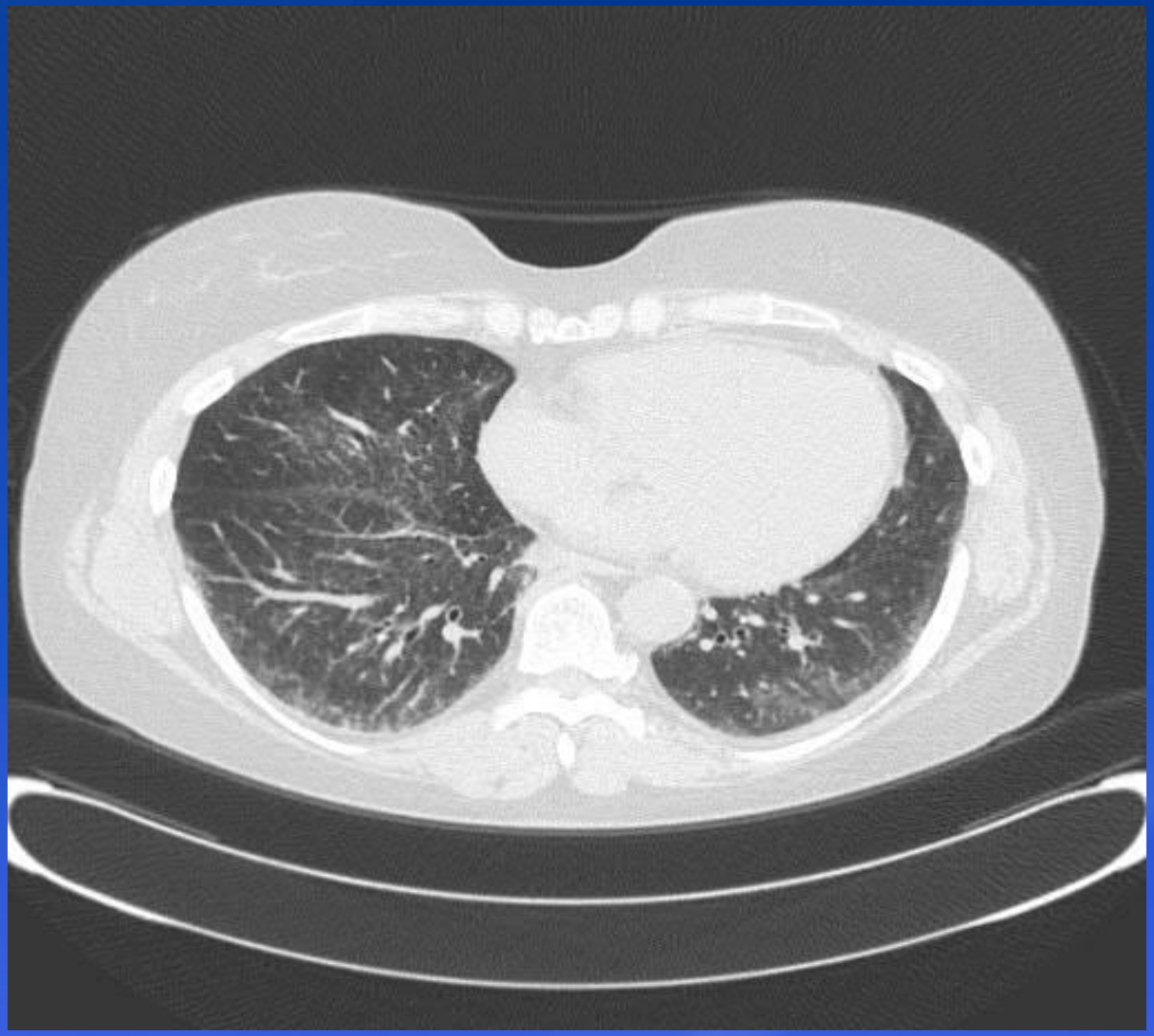
MAYO CLINIC

Interstitial Lung Disease



MAYO CLINIC

Interstitial Lung Disease



MAYO CLINIC

Disease characteristics of ILD patients

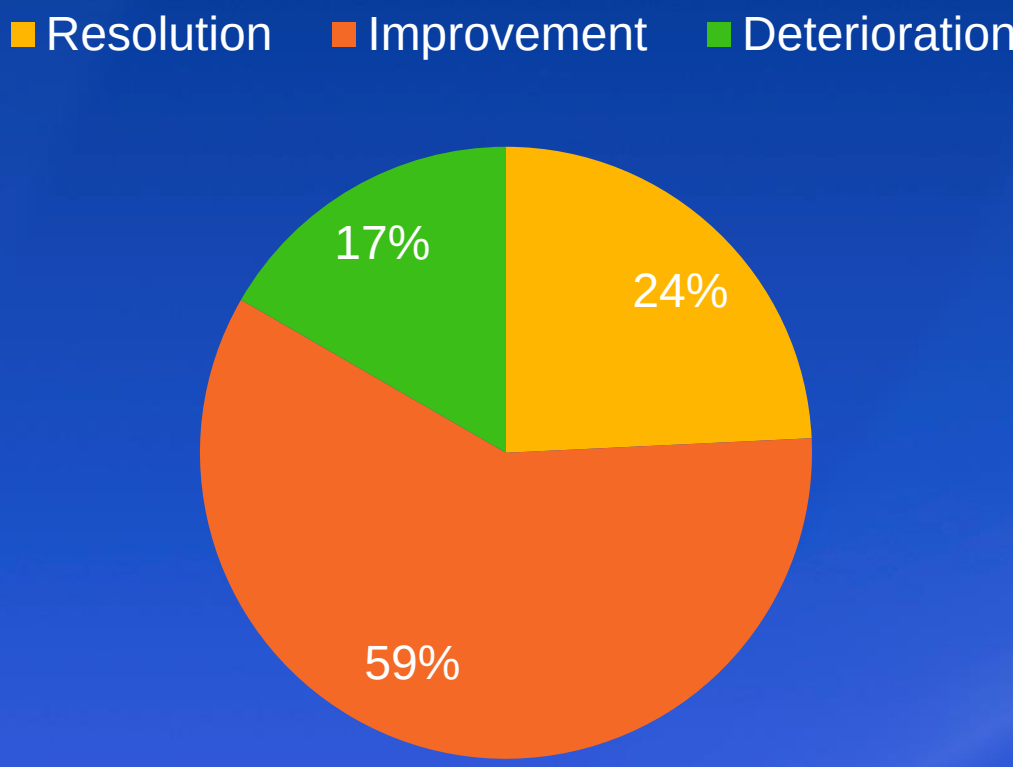
- Prevalence of ILD 67-100% in anti-synthetase syndrome.
- Onset of ILD variable: most of the time occurs concurrently at time of myositis diagnosis.
- Course ranges from acute and fulminant ILD, chronic progressive, or asymptomatic (subclinical).
- ILD leads to poor functional status with reduction in activities in 30% of patients.

Marie I, Josse S, Hatron PY, et. Al. Arthritis Care & Research.2013;800-808.

MAYO CLINIC

ILD characteristics

ILD course in 66 Jo-1 + patients with median follow-up 36 months.



Marie I, Josse S, Hatron PY, et. Al. Arthritis Care & Research.2013;800-808

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

Concept of “Autoantibodies”

- Antibodies are produced by plasma cells (B cells) in immune system.
- Each antibody recognizes an antigen that is unique.
- Outcome: to successfully fight against viruses/bacteria.
- Autoantibodies: antibodies formed that are directed against self proteins
  - May be an innocent bystander (otherwise known as a “marker”)
  - Or may be pathogenic

MAYO CLINIC

Anti-synthetase antibodies

- These are antibodies directed against ***aminoacyl-transfer RNA synthetases*** (autoantibody target).
  - These enzymes catalyze binding of an amino acid to its tRNA in process of cytoplasmic protein synthesis.
- To date, there are 8 anti-synthetase antibodies.
- Anti-synthetase antibodies are mutually exclusive (usually).

Hamaguchi, Fujimoto, Matsushita, et al. PLoS One 2013;8:e60442.

MAYO CLINIC

Anti-synthetase antibodies

Antigen	tRNA synthetase	Frequency in adult PM (%)	Frequency in adult DM %)
Jo-1	Histidyl	20-30	5-10
PL7	Threonyl	2-5	2-5
PL12	Alanyl	2-5	2-5
EJ	Glycyl	<2	<2
OJ	Isoleucyl	<1-2	<1-2
KS	Asparagynyl	<1-2	<1-2
Ha	Tyrosyl	<1-2	<1-2
Zo	Phenyalanyl	<1-2	<1-2

Gunawardena H, Betteridge Z, McHugh N. Curr Opin Rheumatol. 2008;20:675-680.
Robinson & Reed. Nat Rev Rheumatol. 2011; 7:664-75.
Gunawardena H. Clin Rev Allergy Immunol 2017;52:45-57.

MAYO CLINIC

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

Jo-1 + disease phenotype

- Most common and first to be described.
- May be pathogenic: activates components of immune system causing downstream inflammatory effects on tissues.
- More severe myositis presentation
  - Often have MH and other “typical” characteristics of the anti-synthetase syndrome: i.e., inflammatory arthritis, Raynaud’s, etc..

Ascherman, DP. Curr Rheumatol Rep 2015;17:56.

Jo-1+ disease phenotype

- 70-90% of Jo-1+ patients have ILD.
- Jo-1+ patients with ILD have mechanic's hands and lower CK compared to Jo-+ without ILD.
- Jo-1 antibody titer may correlate with myositis disease activity and other organ system activity (i.e. lung, joints).
- Malignancy is rare in Jo-1 + positive patients, although has been reported. Protective?

Richards TJ, Eggebeen A, Gibson K et al. Arthritis Rheum. 2009;60:2183-92.

Stone KB, Oddis CV, Fertig N et al. Arthritis Rheum 2007;56:3125-31.

Chinoy H, Fertig N, Oddis CV, et al. Ann Rheum Dis. 2007;66:1345-9.

Marie I, Josse S, Hatron PY, et. Al. Arthritis Care & Research.2013;800-808

PL7 Phenotype

- Rarer than Jo-1, comprises 10-15% of anti-synthetase syndromes.
- Myositis is mild-moderate or not present at all.
- Raynaud's, **pericardial effusion**, esophageal involvement, mechanics' hands.
- Higher incidence of ILD, over 90% in some series.
  - ILD less likely asymptomatic, rarely resolves.
  - Marked ILD deterioration, poorer survival than Jo1+

Marie I, Josse S., Decaux O. et al. Eur J Int Med. 24; 2013:474-9.
Hervier B, Devilliers H, Stanciu R, et. Al. Autoimmunity Rev 2012;12:210-17.
Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M, et al. Medicine. 2012;91:206-11.

Hamaguchi, Fujimoto, Matsushita, et al. PLoS One 2013;8:e60442
Marie I, Josse S, Decaux O, et al. Autoimmunity Reviews; 2012:11:739-45.
Hervier B, Devilliers H, Stanciu R, et. Al. Autoimmunity Rev 12;2012:210-17

PL12 phenotype

- Less common than Jo-1: 5-10% in anti-synthetase syndromes.
- Higher incidence of ILD (70-100%).
  - Most present with ILD concurrently with other anti-synthetase manifestations.
  - UIP pattern may be common compared to Jo-1.
  - ILD more severe in presentation and less likely to resolve, poorer survival than Jo-1+.
- Less than 50% of patients have muscle involvement (usually mild or subclinical).

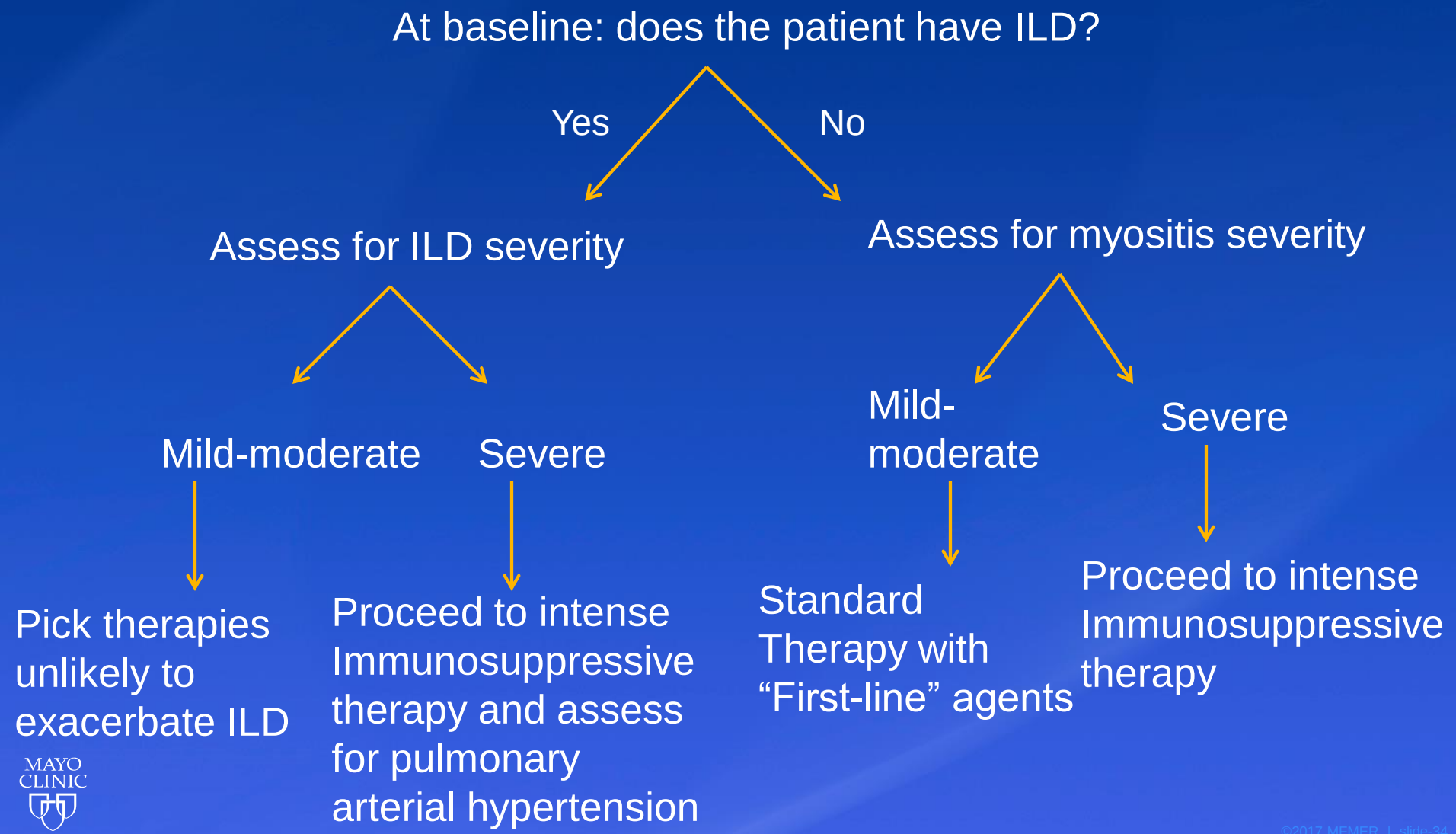
MAYO CLINIC

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

My approach to inflammatory myositis treatment



MAYO CLINIC

Treatment: My approach.

- First line: Glucocorticoids + a steroid sparing agent:
  - Azathioprine (2 mg/kg) or mycophenolate mofetil (standard dosing, but may increase to 1500 mg twice daily).
- Glucocorticoid dosing: pulse intravenous daily (3 days) for severe disease (i.e. severe weakness, dysphagia, progressive ILD).
- Oral glucocorticoids with taper: 1 mg/kg for 4 weeks, taper by 2.5-5 mg every 2-4 weeks pending treatment response and tolerability.
  - Oral taper may slow or stop ~5-10 mg daily.

MAYO CLINIC

Treatment: My approach.

- Intravenous immunoglobulin (IVIG) may be used initially or as “bridge therapy” until maintenance immunosuppressives kick in.
- IVIG 1 gram/kg of IBW for 2 consecutive days once monthly for 1-3 months, or 3-6 months, or longer depending on response.
  - Some patients do not tolerate due to headaches, neurologic symptoms, meningitis at higher volumes.
  - Lower doses may be used.

MAYO CLINIC

Treatment: My approach for severe disease or progressive ILD

- IV (usually 0.7 to 1.0 g/m^2 for 6 mos.) or oral cyclophosphamide.
  - Data exists for improvement in Jo-1+ pts with ILD in small series of patients.
- Cyclosporine or Tacrolimus
  - Data exists in some small series of patients.
  - I have more experience with tacrolimus, twice daily dosing targeting a trough level of 5-10 ng/mL.
  - Monitor for hypertension, renal insufficiency, electrolyte derangements, peeling rashes.

Marie I, Josse S, Hatron PY, et al. Arthritis Care Res (Hoboken); 2013; 65:800-8.
Oddis CV, Sciurba FC, Strazl TE. Lancet. 1999;353:1762-63.
Wilkes MR, Sereika SM, Fertig N, et al. Arth Rheum. 2005;52:2439-2446

Rituximab and myositis

- “RIM” trial of refractory juvenile/adult IIM, 83% met definition of improvement, some methodological concerns.
- In my experience: 2 different ways of dosing: 375 mg/m2 once a week X 4 weeks or 1000 mg X 2 (separated by 2 weeks)
  - Sometimes it works.
- Refractory IIM patients with strongly positive autoantibodies (i.e. Jo-1) may be more responsive to rituximab (shorter time to improvement).
- Interestingly, autoantibody titers may decrease after rituximab suggesting a correlation with clinical response.

Oddis CV, Reed AM, Aggarwal R, et al. Arthritis Rheum.2013;65:312-24.
Aggarwal R, Bandos A, Reed AM, et al. Arthritis Rheumatol. 2014;66:740-9.

I don’t use these medications/treatments for anti-synthetase syndrome

- Methotrexate, concern for exacerbation of ILD.
- Leflunomide, concern for exacerbation of ILD.
- Plasmapheresis.
- Never used: Acthar, abatacept, belimumab.
- Never used any of the TNF-inhibitors, concern for exacerbation of ILD.

MAYO CLINIC

If Reflux is present, treat.

- Emphasize lifestyle changes/conservative management with elevation of head of bed, avoidance of alcohol and smoking, no large meals late at night, etc…
- Treatment with proton pump inhibitors/H2 blockers.
- Uncontrolled GERD may affect underlying lung disease, i.e. “silent microaspiration,” may trigger cough and exacerbate underlying pulmonary disease.

MAYO CLINIC

Gaude GS. Ann Thorac Med.2009;4:115-23.

Management of side effects and other concerns.

- Screen for latent TB, HIV, hepatitis B and C infections.
- Check vaccination status including influenza and pneumococcal vaccines.
- Screen for diabetes, hyperlipidemia, hypertension, osteoporosis at baseline.

MAYO CLINIC

Management of side effects and other concerns.

- Counsel women of childbearing age and recommend birth control as appropriate.
- Use PJP prophylaxis for all patients with ILD on immunosuppressives (expert opinion).
- Treat infectious complications, i.e. herpes zoster, influenza, pneumonias, as they arise and hold or reduce immunosuppressives if needed.

MAYO CLINIC

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

My assessment of Treatment Response

- Improvement or stabilization of muscle strength.
- Normalization of muscle enzymes: CPK, aldolase, LDH, AST, ALT.
- May check serial EMGs or muscle MRIs.
- Improvement of other organ systems such as pulmonary:
  - Serial PFTs (≥10% in FVC and/or ≥15% in DLCO).
  - Serial chest imaging, preferably high resolution CT imaging.

MAYO CLINIC

American Thoracic Society. Am J Respir Crit Care Med. 2000;161:646-64.

Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Differing clinical presentations among autoantibody subtypes
- Treatment
- Assessment of treatment response
- Prognosis

MAYO CLINIC

Prognosis

- ***ILD*** is the most important contributor to disease morbidity and mortality.
  - Severely reduced FVC and DLCO at presentation is a poor prognostic factor, portending lack of treatment response and deterioration.
  - UIP pattern, poorer prognosis.
  - Respiratory muscle involvement leads to faster deterioration.
  - Progressive ILD may occur in ~20-30% of patients.

MAYO CLINIC

Marie I, Josse S, Hatron PY, et. Al. Arthritis Care & Research.2013;800-808

Prognosis

- These are additional complications of anti-synthetase syndrome associated with higher morbidity and mortality.
  - Infectious pneumonias.
  - Aspiration pneumonias, especially if weak swallowing mechanism.
  - Secondary pulmonary arterial hypertension.
  - Ventilatory failure with increasing oxygen requirements.

MAYO CLINIC

Prognosis

- Historically, in early studies of IIM patients with ILD, 5 year survival rate 60% (similar to idiopathic pulmonary fibrosis).
- Yet, recent studies suggest survival rate has improved.
- In treated IIM patients, ILD resolves in 19% and improves in 55%.
- One study, after median of 53 mos. follow-up, 1 year survival (94.4%), 3 year survival (90.4%), 5 year survival 86.5%.
- Relapses are common, usually seen if disease treated with glucocorticoids alone.

Douglas WW, Tazelaar HD, Hartman TE, et al. Am J Respir Crit Care Med. 2001;164:1182-5
Marie I, Hachulla E, Cherin P, et al. Arthritis Rheum. 2002;47:614-22.
Marie I, Josse S, Hatron PY, et. Al. Arthritis Care & Research.2013;800-808

Prognosis

- Among 43 patients who had myositis-associated UIP (14 of them with anti-synthetase syndrome) and 81 with idiopathic pulmonary fibrosis at Univ. of Pittsburg,1985-2014
  - Median cumulative and event-free survival time in IPF was worse at 5.25/1.8 years compared to 16.2/10.8 years.
  - Respiratory failure was most common cause of death.

Myositis-associated usual interstitial pneumonia has a better survival than idiopathic pulmonary fibrosis.

Aggarwal R, McBurney C, Schneider F, Yousem SA, Gibson KF, Lindell K, Fuhrman CR, Oddis CV. Rheumatology (Oxford). 2017 Mar 1;56(3):384-389. doi: 10.1093/rheumatology/kew426.

MAYO CLINIC

Ann Rheum Dis. 2014 Jan;73(1):227-32. doi: 10.1136/annrheumdis-2012-201800. Epub 2013 Feb 19.

Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients.

Aggarwal R[1], Cassidy E, Fertig N, Koontz DC, Lucas M, Ascherman DP, Oddis CV.

Prognosis

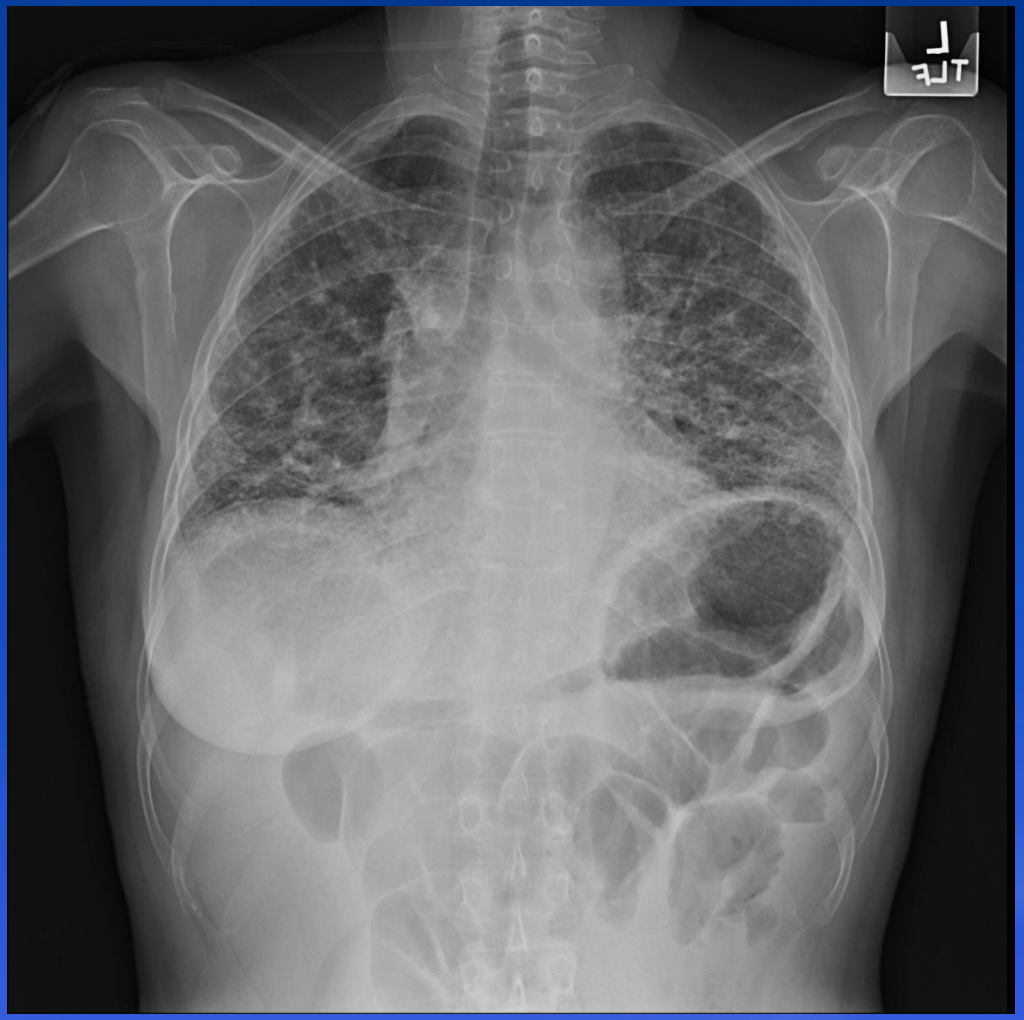
- Among 202 Jo-1+ (122) and non-Jo-1 abs.(80) patients at Univ. of Pittsburg, 1985-2009
  - 5 and 10 year unadjusted cumulative survival: 90% and 70% for Jo-1 +.
  - 5 and 10 year unadjusted cumulative survival: 75% and 47% for non-Jo-1+.
  - Difference in survival partly attributed to delay in diagnosis in non-Jo1 patients.
  - Overall mortality rate was similar in 2 groups (29% vs. 38%).

Back to the patient.

- She returned recently. Oxygen requirements had increased.
- Treated with tacrolimus in addition to azathioprine for a year. Tolerated it well.
- The muscle weakness improved to a certain degree. The enzymes were normal now, but felt more fatigued. Could not walk several feet without stopping to rest.
- The rashes resolved.

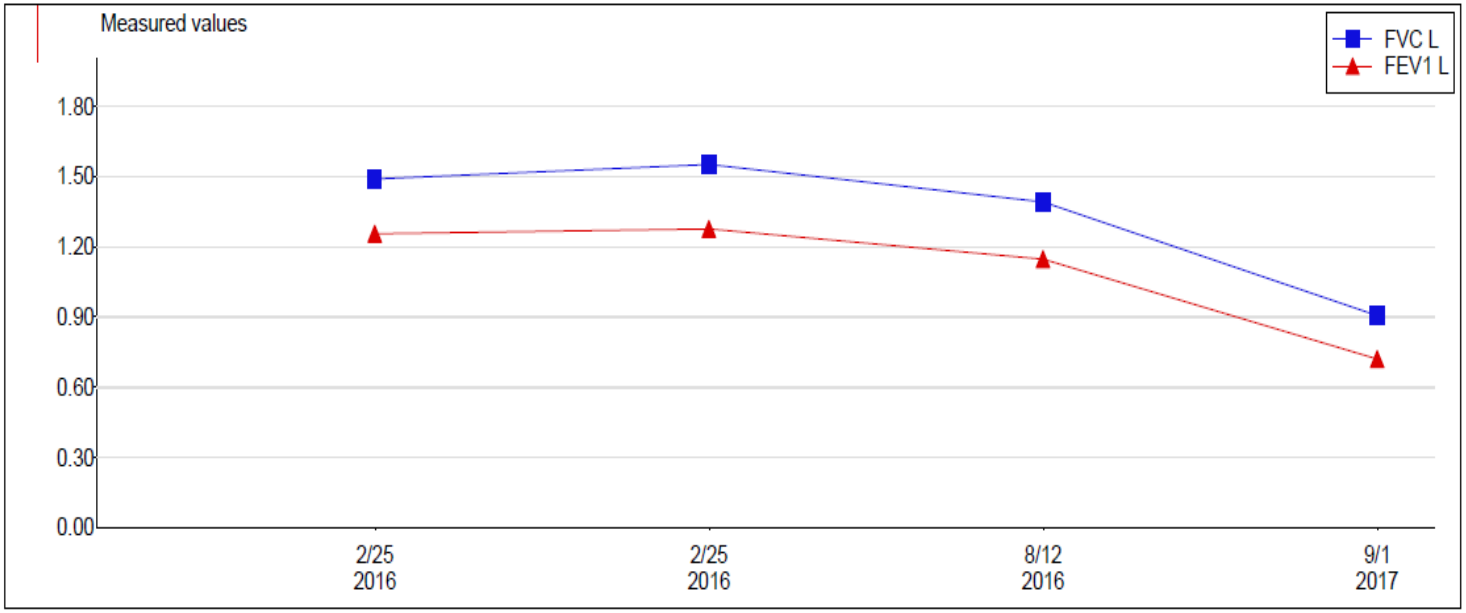
MAYO CLINIC

Back to the patient.



MAYO CLINIC

PFTs of the patient, 2016-2017.



Measurement Parameter Date	Time	Medication	Spiro FVC (L)	FVC %Pred	FEV1 (L)	FEV1 %Pred	VC MAX (L)	VC MAX %Pred
2/25/2016	1:21:42 PM		1.49	45.7	1.25	48.2	1.51	46.5
2/25/2016	1:57:05 PM	Albuterol	1.55	47.6	1.28	49.0	1.55	47.7
8/12/2016	7:40:19 AM		1.39	42.7	1.15	44.1	1.39	42.7
9/1/2017	7:50:16 AM		0.91	27.9	0.72	27.8	0.97	29.9

Prognosis looks poor. What else can be done?

Back to the patient

- A right heart catheterization showed moderate pulmonary hypertension.
- Saw a cardiologist who recommended vasodilators: would provide “mixed results at best.”
- I suggested a trial of cyclophosphamide.
- I will try to arrange for consideration of a lung transplant with the pulmonologists.

MAYO CLINIC

Summary

- Anti-synthetase syndrome is an autoimmune myositis defined by an anti-synthetase antibody, inflammatory myositis, ILD and other associated features.
- There appears to be differences in phenotypes among anti-synthetase antibodies: Jo-1+ tend to have complete syndrome and non-Jo1 have predominant ILD.
- ILD is an important contributor to morbidity and survival (main cause of death).
- My treatment approach: combine steroids with another immunosuppressive based on severity of ILD.
- Prognosis seems to differ among autoantibody type, but appears better than patients who have idiopathic pulmonary fibrosis.

MAYO CLINIC

MAYO CLINIC

Questions & Discussion