Update in Inflammatory Myopathies

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Disclosures

- I have a patent for anti-HMGCR testing, but do not receive royalties
- I will discuss off-label treatments for myositis

Learning objective

- Understand myositis classification schemes “for the Boards”
- Understand emerging autoantibody-based myositis classification
- Recognize and treat myositis triggered by checkpoint inhibitors

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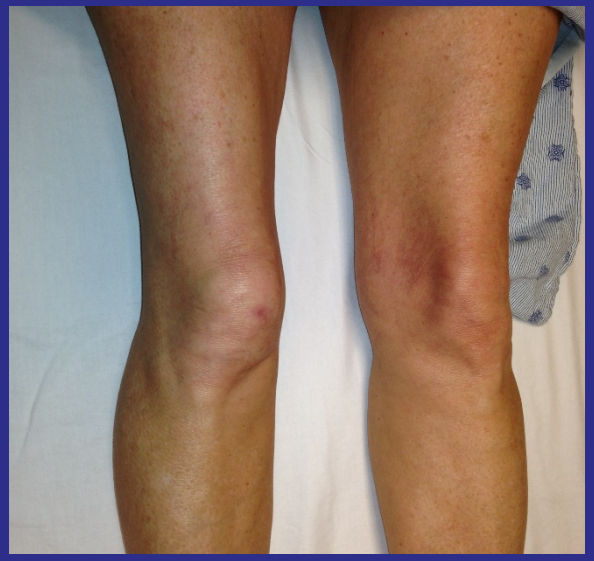
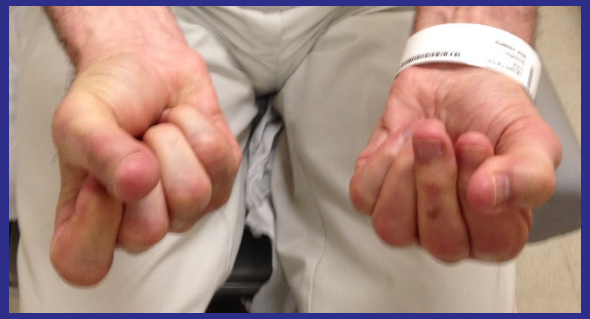
Clinical features of myositis (except inclusion body myositis)

- F>M
- Proximal and symmetric weakness
- Subacute onset
- Elevated muscle enzymes (usually)
- Myopathic EMG
- Abnormal muscle biopsies
- Other organ systems may be involved
  - Skin, joints, lung, etc…
- Respond to immunosuppressive therapy

Clinical Features of Inclusion Body Myositis

- M>F
- Age > 50 years
- Insidious onset
- Asymmetric weakness
  - Quadriceps
  - Distal finger flexors
  - Wrist flexors
  - Triceps
  - Ankle dorsiflexors
  - Obicularis occuli
- Dysphagia common
- ~50% with anti-NT5C1a
- Poor responsive to immunosuppression





*Lefter, Neurology, 2017

Pictures courtesy of Dr. Tom Lloyd

Bohan and Peter Criteria

Polymyositis (3 or more of these)

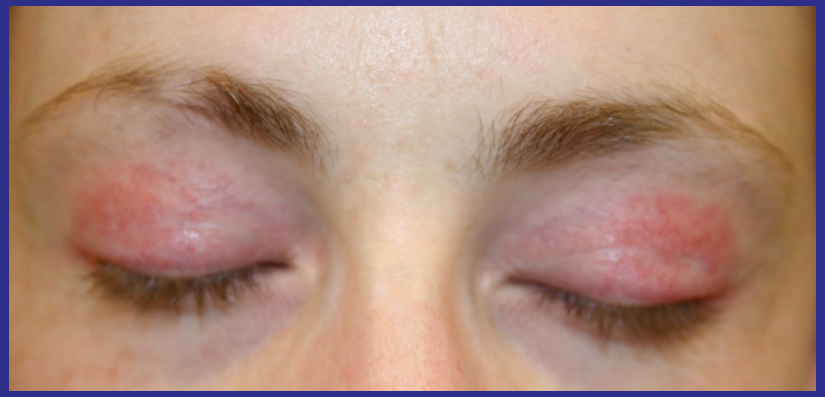
- Symmetric proximal muscle weakness
- Elevated muscle enzymes
- Myopathic features on electromyography
- Characteristic muscle pathology (inflammation and necrosis)

- Dermatomyositis
  - The above with characteristic rash

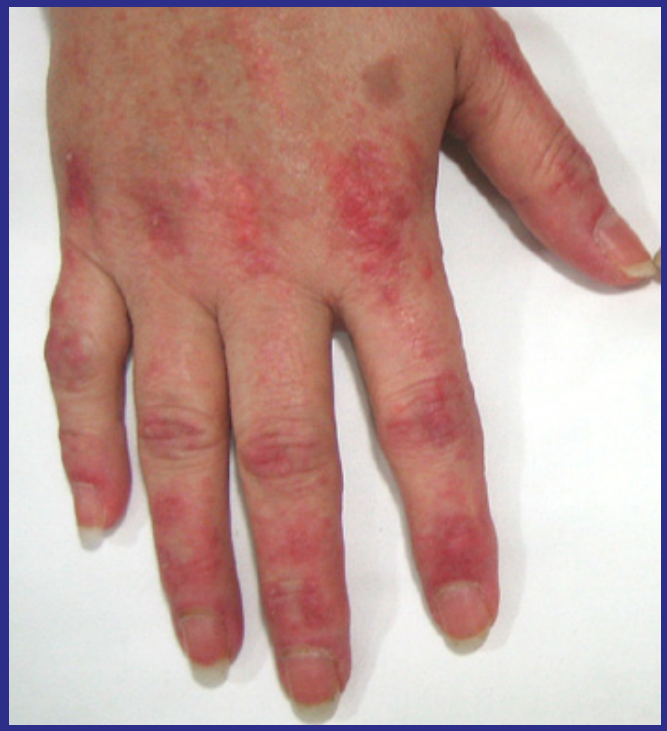
Bohan and Peter, 1975

Bohan and Peter Criteria

- No rash = polymyositis (PM)
- Rash = dermatomyositis (DM)



Heliotrope rash



Gottron's papules

2017 EULAR/ACR IIM Classification Scheme

Table 2. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs)

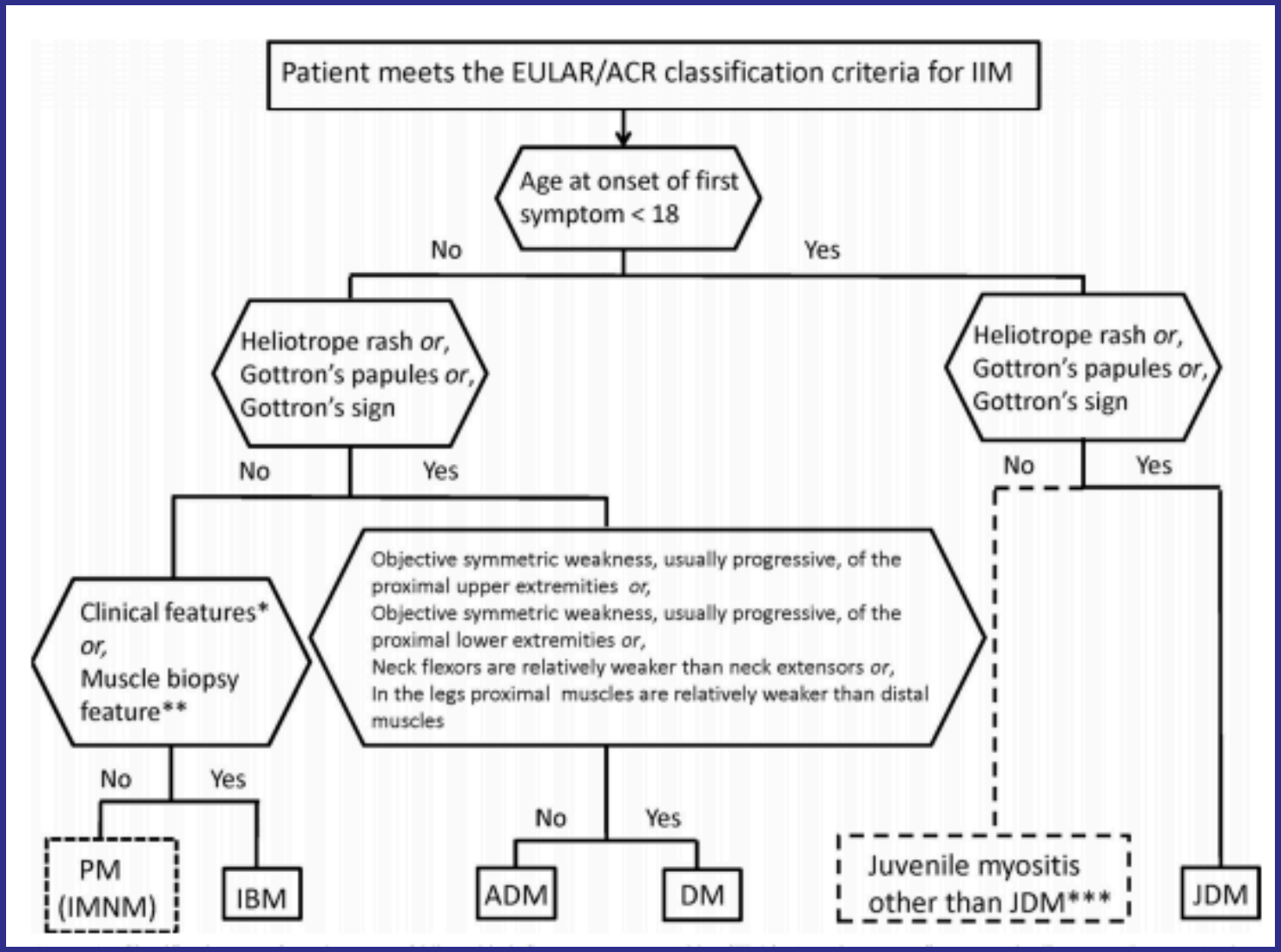
When no better explanation for the symptoms and signs exists, these classification criteria can be used

Variable	Score points: Without muscle biopsy	Score points: With muscle biopsy	Definition
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18 ≤ age (years) at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-colored, or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli, and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			
Dysphagia or esophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory measurements			
Anti–Jo-1 (anti–histidyl–transfer RNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
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	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features—presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers, but there is no clear invasion of the muscle fibers
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibers, which are smaller in the perifascicular region than fibers more centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by hematoxylin and eosin staining and reddish by modified Gomori trichrome stain

* Serum levels above the upper limit of normal.

- Score 16 variables
  - Age
  - Pattern of weakness
  - Skin manifestations
  - Dysphagia?
  - Anti-Jo1?
  - Rash?
  - Muscle biopsy features
- Score correlates with probability patient has IIM

2017 EULAR/ACR IIM Classification Scheme



2017 ACR/EULAR IIM Classification Criteria

- Benefits
  - IBM included
  - Advertised as sensitive (93%) and specific (88%) for identifying patients as having IIM
- Potential limitations
  - Relatively complex
  - May not perform as well in clinical practice
    - 20% of our anti-HMGCR cases classified as “not IIM”
- Only categories are PM, DM, and IBM
  - No separate IMNM or antisynthetase syndrome

Definitions

- Myositis-specific autoantibodies
  - Only in myositis patients
- Myositis-associated autoantibodies
  - Found in patients with myositis and other rheumatic diseases

Myositis classification emphasizing MSAs

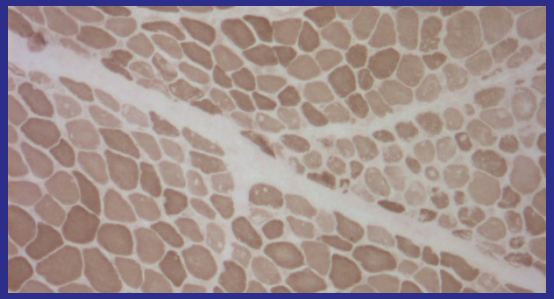
- Dermatomyositis
  - Antibody-positive DM
    - TIF1γ, NXP2, Mi2, MDA5, and SAE
  - Antibody-negative DM
- Antisynthetase syndrome
  - Jo-1, PL7, PL12, EJ, OJ
- Immune-mediated necrotizing myopathy
  - Antibody-positive IMNM
    - SRP or HMGCR
  - Antibody-negative IMNM

What happened to polymyositis?

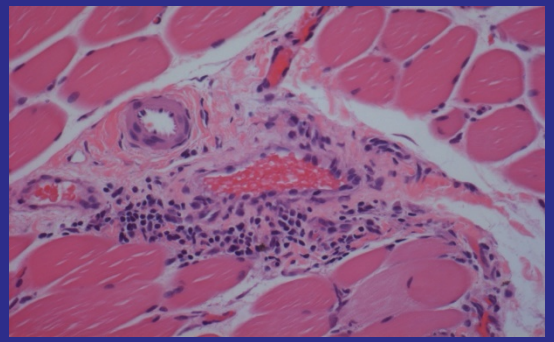
- Most cases previously diagnosed as polymyositis most likely to have
  - Inclusion body myositis
  - Immune-mediated necrotizing myopathy
  - Antisynthetase syndrome without a rash
  - Myositis-overlap (e.g., scleroderma-myositis)
  - Inherited muscle disease

Typical myositis muscle biopsies

DM and ASyS

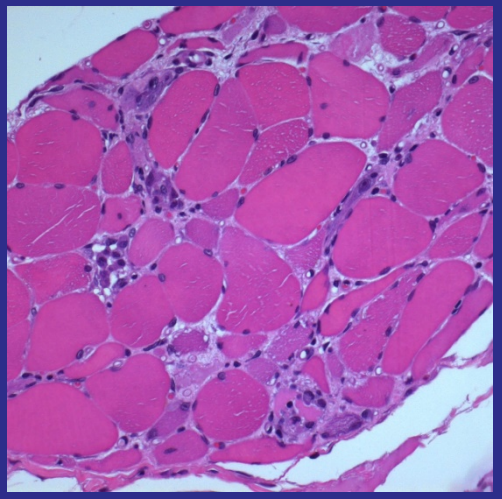


Perifascicular atrophy



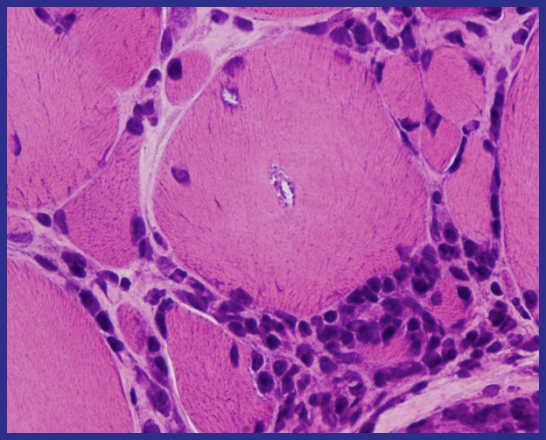
Perivascular inflammation

IMNM



Myofiber necrosis and regeneration

IBM

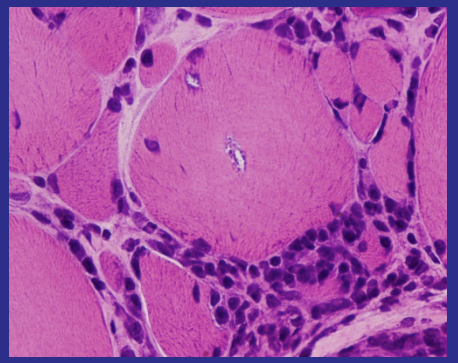


Endomysial inflammation and rimmed vacuoles

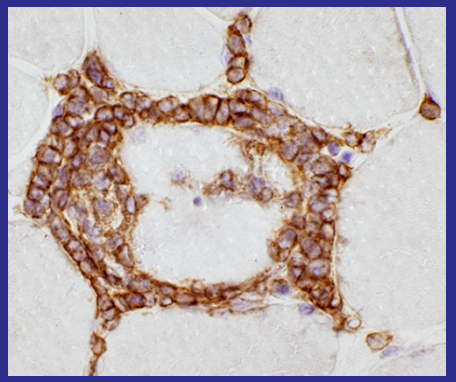
Only 80% of IBM patients have rimmed vacuoles

IBM diagnostic criteria (requires muscle biopsy)

- All three of the following features
  - Finger flexion OR knee extension weakness
  - Endomysial inflammation
  - Invasion of non-necrotic muscle fibers OR rimmed vacuoles on biopsy
- Sensitivity 90%
- Specificity 96%



Endomysial inflammation and rimmed vacuoles



Auto-invasive T cells
(https://neuromuscular.wustl.edu/pathol/ibm.htm)

Lloyd et al, Neurology 2014

239th ENMC International Workshop: Classification of Dermatomyositis

- To diagnose DM
  - DM rash + skin biopsy showing interface dermatitis (e.g., “amyopathic” DM)
  - DM rash + muscle weakness + high CK
  - DM rash + muscle weakness + typical DM muscle biopsy features
  - DM rash + DM-specific MSA
- Patients with an antisynthetase autoantibody have ASyS, not DM

Mammen et al., Neuromuscular Disorders, 2020

239th ENMC International Workshop: Classification of Dermatomyositis

- Six DM subtypes defined by MSAs
  - Anti-TIF1γ DM
  - Anti-Mi2 DM
  - Anti-NXP-2 DM
  - Anti-MDA5 DM
  - Anti-SAE DM
  - Autoantibody negative DM

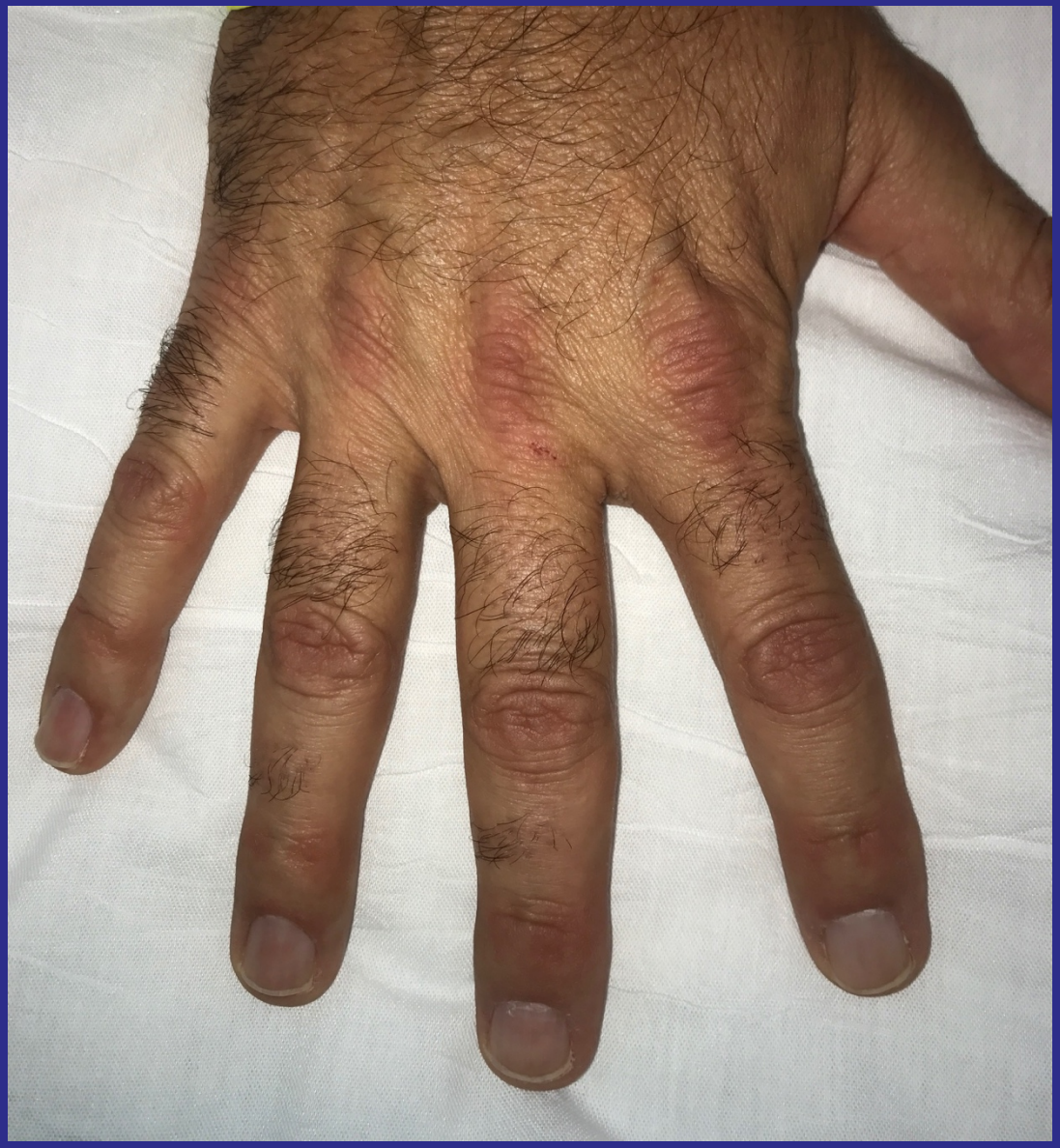
Mammen et al., Neuromuscular Disorders, 2020

Can MSAs be helpful in diagnosing dermatomyositis?

Case 1

- 35 year-old man with no significant past medical history
- Complains of leg weakness for 2 months
- CK 380
- EMG reveals non-irritable myopathy
- Exam: mild hip flexor weakness

Case 1: Gottron's?



Further diagnostic work-up?

- Skin biopsy?
  - Not specific for DM
- Muscle biopsy?
  - Perifascicular atrophy neither sensitive nor specific for DM
    - Only ~50% of DM patients have perifascicular atrophy
    - May be found in antisynthetase syndrome, lupus myositis
- Myositis autoantibody testing?
  - Presence of an MSA is specific for DM
  - ~70% of DM patients have an MSA
- My approach in cases like this
  - Test for MSAs first; skin and/or muscle biopsy if MSA negative

Each DM autoantibody is associated with a distinct clinical phenotype and prognosis

Anti-TIF1γ (p155/140)

- Typical skin features
  - Gottron's and heliotrope rash
- Symmetric proximal muscle weakness
- "Classic" DM
- Substantially increased risk of cancer

Usefulness of Anti-p155 Autoantibody for Diagnosing Cancer-Associated Dermatomyositis

A Systematic Review and Meta-Analysis

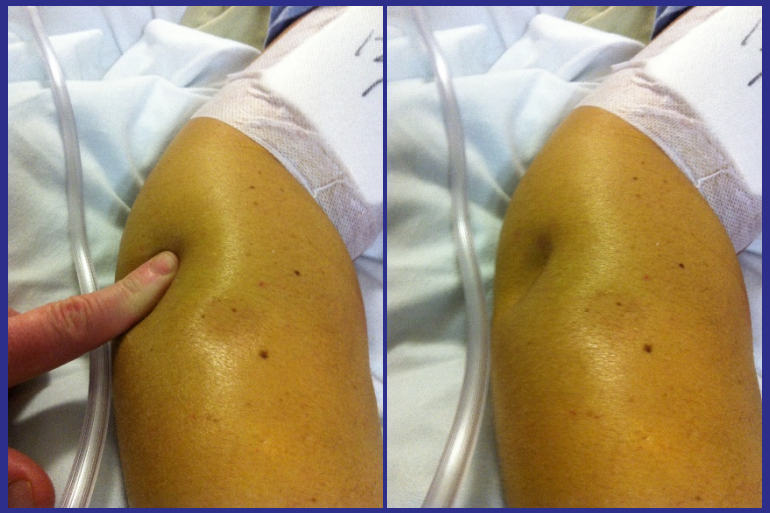
Ernesto Trallero-Araguás,[1] Jose Ángel Rodrigo-Pendás,[2] Albert Selva-O'Callaghan,[2] Xavier Martínez-Gómez,[2] Xavier Bosch,[3] Moisés Labrador-Horrillo,[2] Josep Maria Grau-Junyent,[3] and Miquel Vilardell-Tarrés[2]

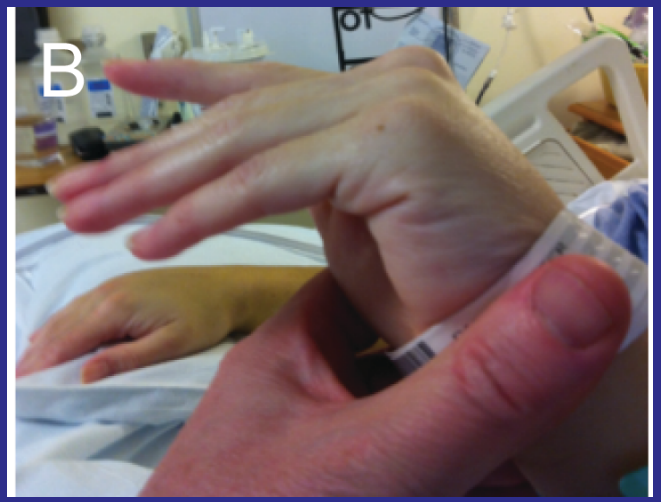
Arthritis and Rheumatism 2012

- Six studies including 312 adult DM cases
- 66/312 were anti-TIF1γ positive
- 53 cases of CAM
- Sensitivity = 78%, Specificity = 89%
- PPD = 58%, NPD = 95%

Anti-NXP2+ DM: Clinical features compared to other DM patients

- Subcutaneous edema (36% vs. 19%)
- Distal arm (35% vs. 20%) and leg (25% vs. 8%) weakness
- Dysphagia (62% vs. 35%)
- Calcinosis (30% vs 17%)
- Increased cancer risk





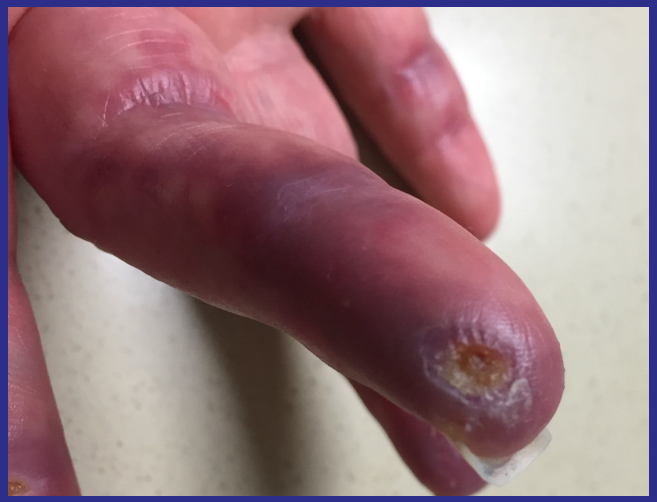
Albyda and Pinal-Fernandez, AC&R, 2017

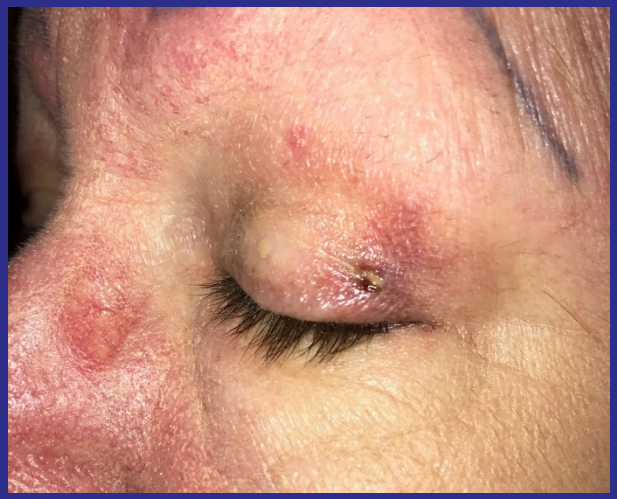
Anti-Mi2+ DM Clinical Features

- Typical cutaneous manifestations
- Most severe weakness
- Highest CK values
  - Anti-Mi2+ DM mean max CK 3908 (2230-7070) IU/L
  - Anti-Mi2- DM mean max CK 242 (110-1200) IU/L
- Most inflammation in muscle biopsy
- Skin and muscle disease respond well to treatment

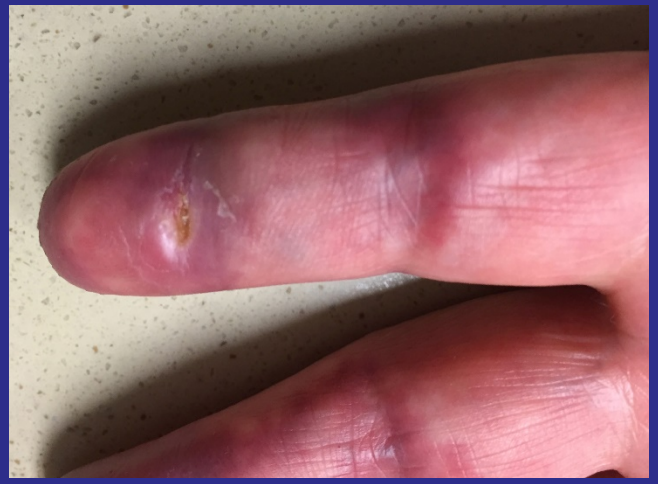
Pinal-Fernandez, Neurology, in press

Anti-MDA5+ DM: distinctive ulcerating skin lesions

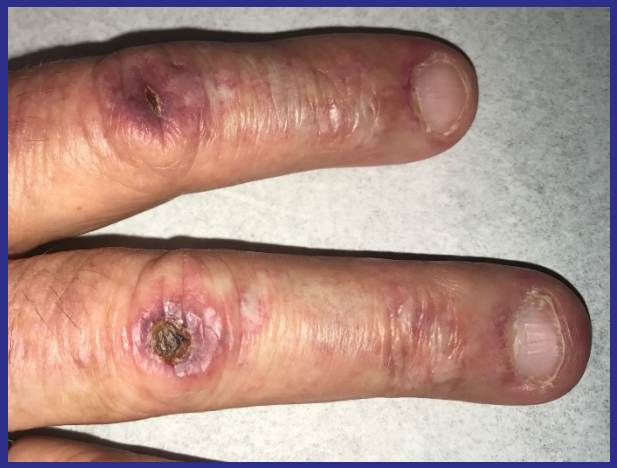




With heliotrope



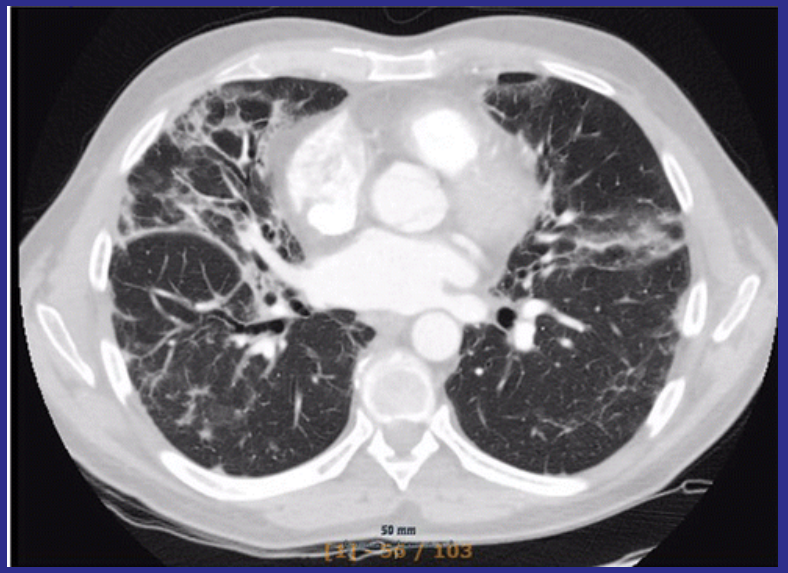
On palmar surface



Ulcerating Gottron's

Anti-MDA5

- Mild weakness (may be hypomyopathic or amyopathic)
- Often have severe and rapidly progressive interstitial lung disease (especially in Asian populations)
  - High mortality rate (up to 60%)

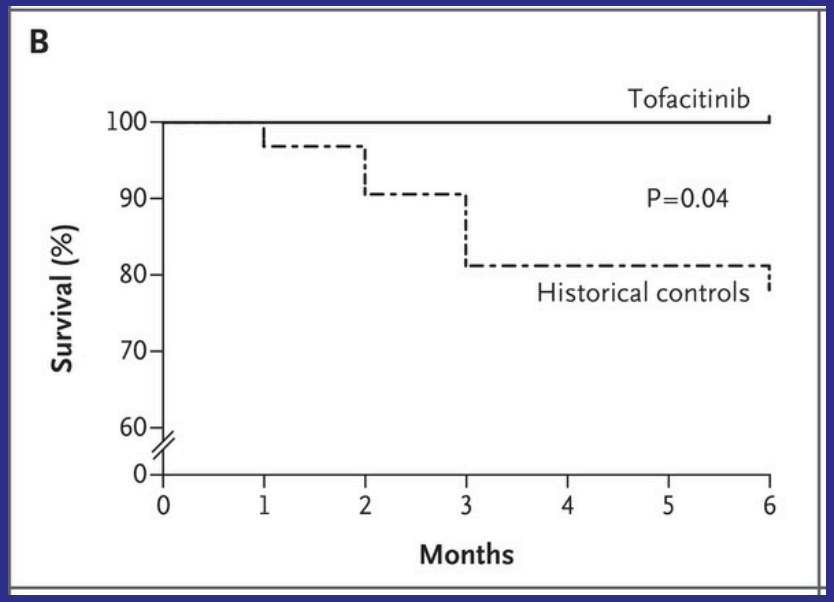


Cato et al., A&R, 2009
Cao et al., AC&R, 2012
Fiorentino et al., JAAD, 2011
Betteridge et al., A&R, 2012
Moghadam-Kia, AC&R, 2016

Improved survival in anti-MDA5+ ILD patients treated with tofacitinib

A

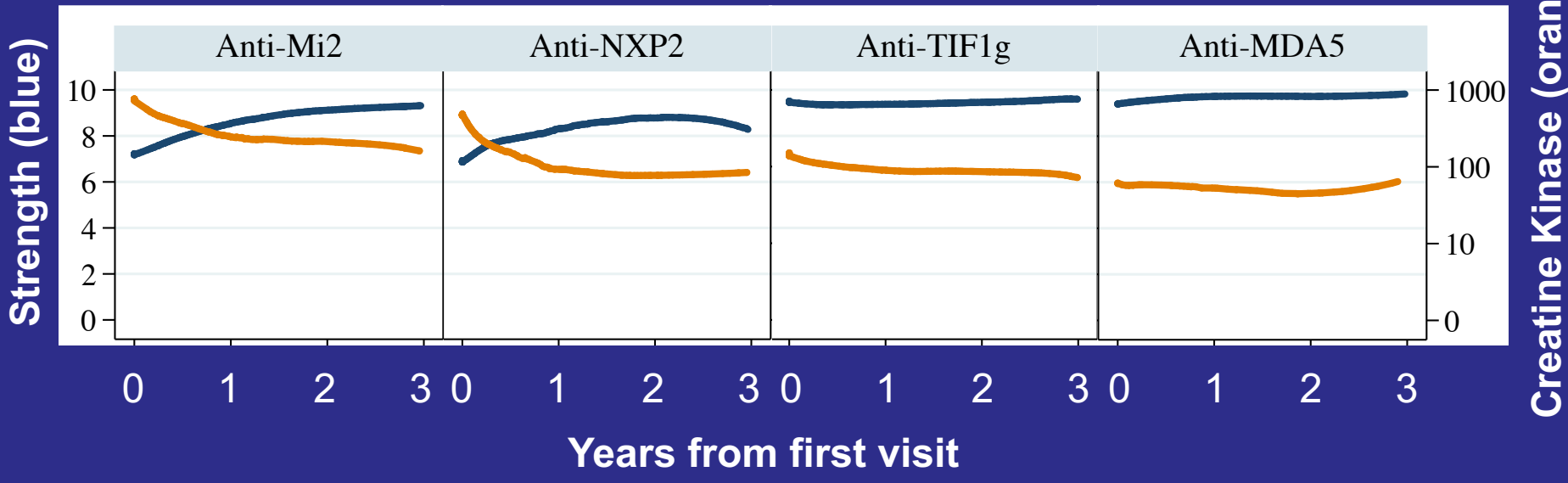
	Tofacitinib (N=18)	Historical Controls (N=32)	P Value
Age — yr	47.6±13.8	52.5±10.6	0.16
Female sex — no. (%)	11 (61)	25 (78)	0.33
History of smoking — no. (%)	2 (11)	2 (6)	0.61
Duration of ILD — mo	1.4±0.7	1.7±1.3	0.45
FVC — % of predicted value	73.4±15.2	71.9±15.3	0.76
SB DLCO — %	44.8±12.8	47.3±16.1	0.59
High-resolution CT score	118.2±13.2	127.2±24.8	0.16
Ferritin level — ng/ml	936.9±798.1	737.8±631.6	0.34
Creatine kinase level — U/ml	86.7±98.2	50.6±43.5	0.09



Z Chen et al. N Engl J Med 2019;381:291-293.

The NEW ENGLAND JOURNAL of MEDICINE

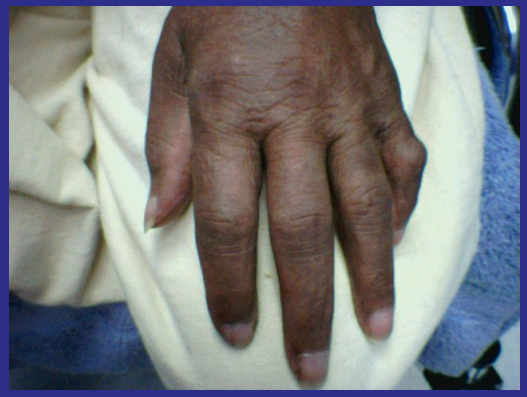
Evolution of muscle disease in DM patients with different MSAs



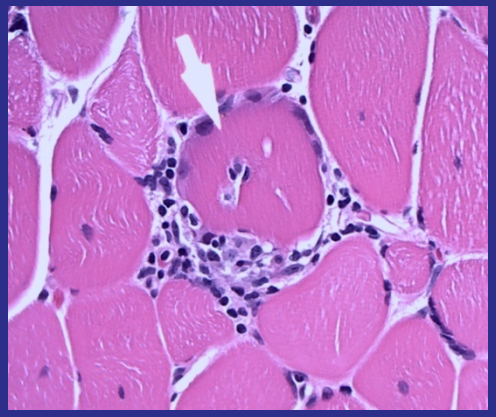
- Patients with anti-Mi2 and anti-NXP2 have more severe myositis than those with anti-TIF1γ or anti-MDA5

Mammen, unpublished data

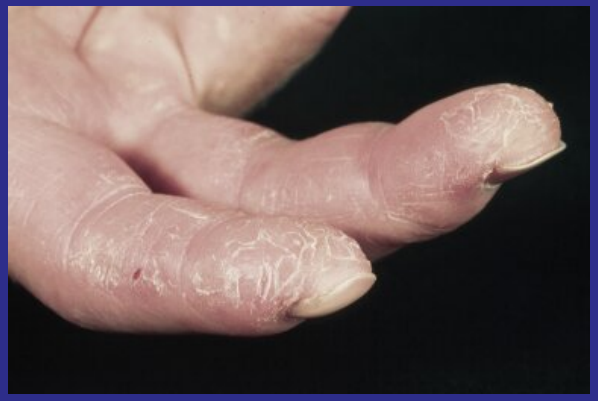
The antisynthetase syndrome



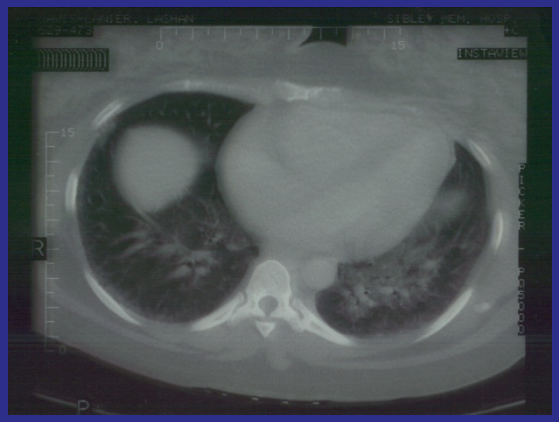
Arthritis



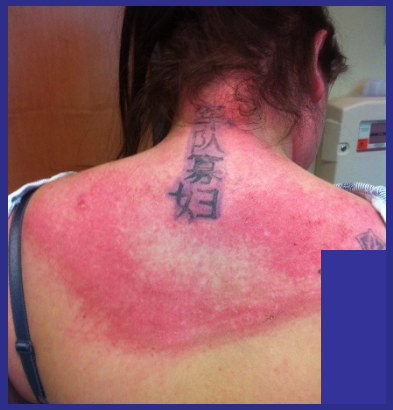
Myositis



Mechanic's Hands



Interstitial Lung Disease



Rash

Raynaud's Phenomenon

Diagnosis of ASyS

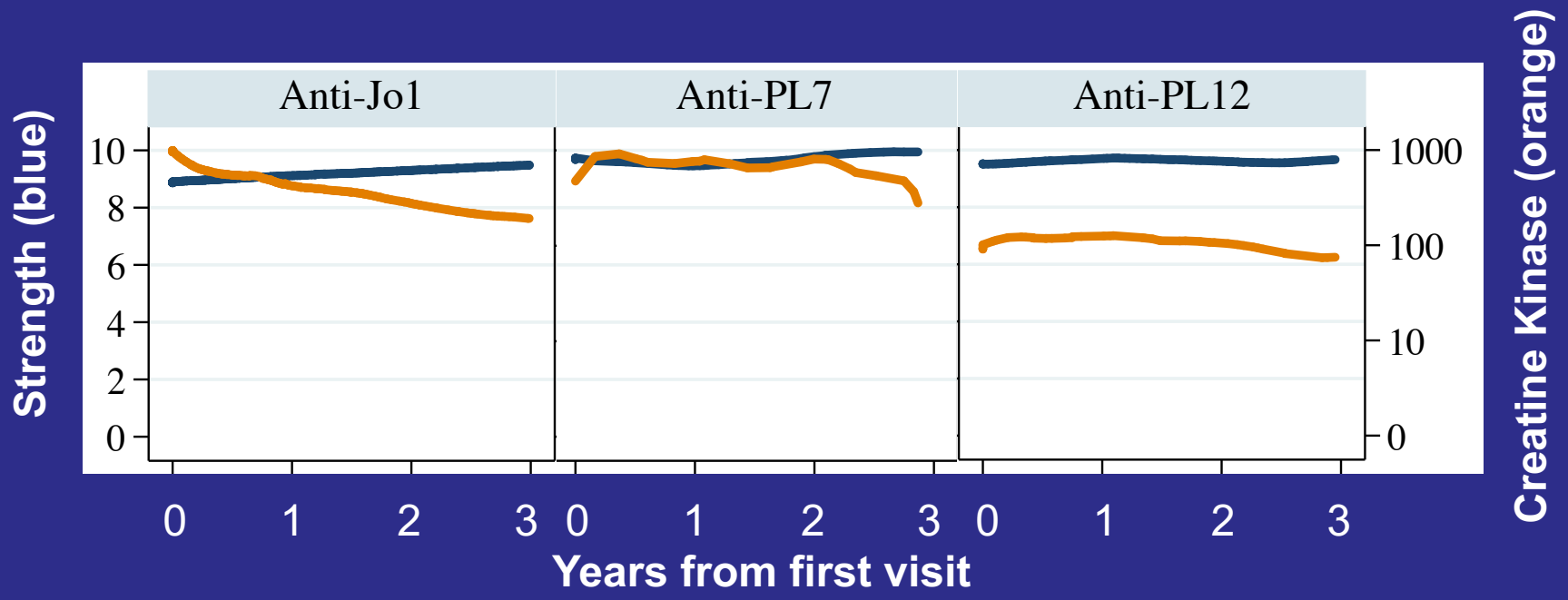
- No universally accepted criteria
- My personal criteria
  - One or more of the following
    - Myositis
    - ILD
    - Arthritis
  - Plus an antisynthetase autoantibody
    - Jo1, PL7, PL12, EJ, OJ

Different features of different antisynthetase autoantibodies

- Anti-Jo-1 (anti-histidyl-tRNA synthetase)
  - 90% with myositis
  - 90% with arthritis
  - 60% with ILD
  - 70% with mechanic's hands
- Anti-PL12 (anti-alanyl-tRNA synthetase)
  - 50% with myositis
  - 60% with arthritis
  - 90% with ILD
  - 15% with mechanic's hands

Kalluri et al., Chest, 2009

Evolution of muscle disease in ASyS patients with different MSAs



- Patients with anti-Jo1 have the most severe muscle weakness at onset, but still mild and improves with treatment

Mammen, unpublished data

Take home points for ASyS prognosis

- Although some ASyS patient have DM or “DM-like” rashes, this seems to be a different disease
  - Muscle* and skin gene expression profiles are very different between DM and ASyS
- No known increased risk of cancer
- ILD likely; consider monitoring for this

*Pinal-Fernandez et al., ARD, 2020

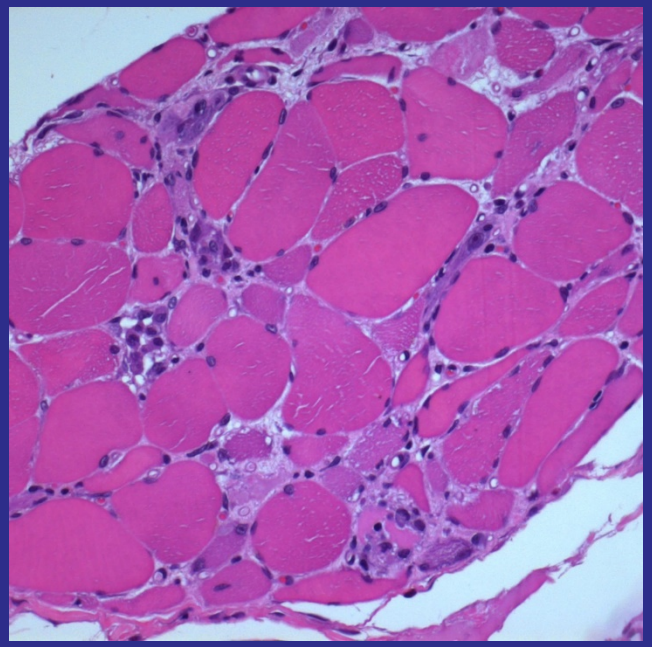
ENMC criteria - 3 types of IMNM

- Anti-HMGCR myopathy
  - Proximal muscle weakness and high CK
  - Anti-HMGCR+
- Anti-SRP myopathy
  - Proximal muscle weakness and high CK
  - Anti-SRP+
- Antibody negative IMNM
  - Proximal muscle weakness and high CK
  - No myositis-specific autoantibodies
  - Necrotizing muscle biopsy

Allenbach et al., NMD, 2018

Anti-SRP Phenotype

- Muscle biopsy: necrotizing
- Rapidly progressive
- Severe weakness
- Very high CK levels
- Mild ILD in ~20%
- Difficult to treat
- Occasional cardiac involvement



Targoff et al., A&R, 1990
Miller et al., J Neurol. Neurosurg. Psychiatry, 2002
Kao et al., A&R, 2004
Hengstman et al., Ann. Rheum. Dis., 2006

Anti-HMGCR myopathy

- Biopsy: necrotizing
- Associated with statin exposure (~70%)
- Progresses despite discontinuing statins
- 100% proximally weak
- 75% with myalgias
- Maximum CK ~10,000
- Minimal extramuscular manifestations
- Statins cause flares

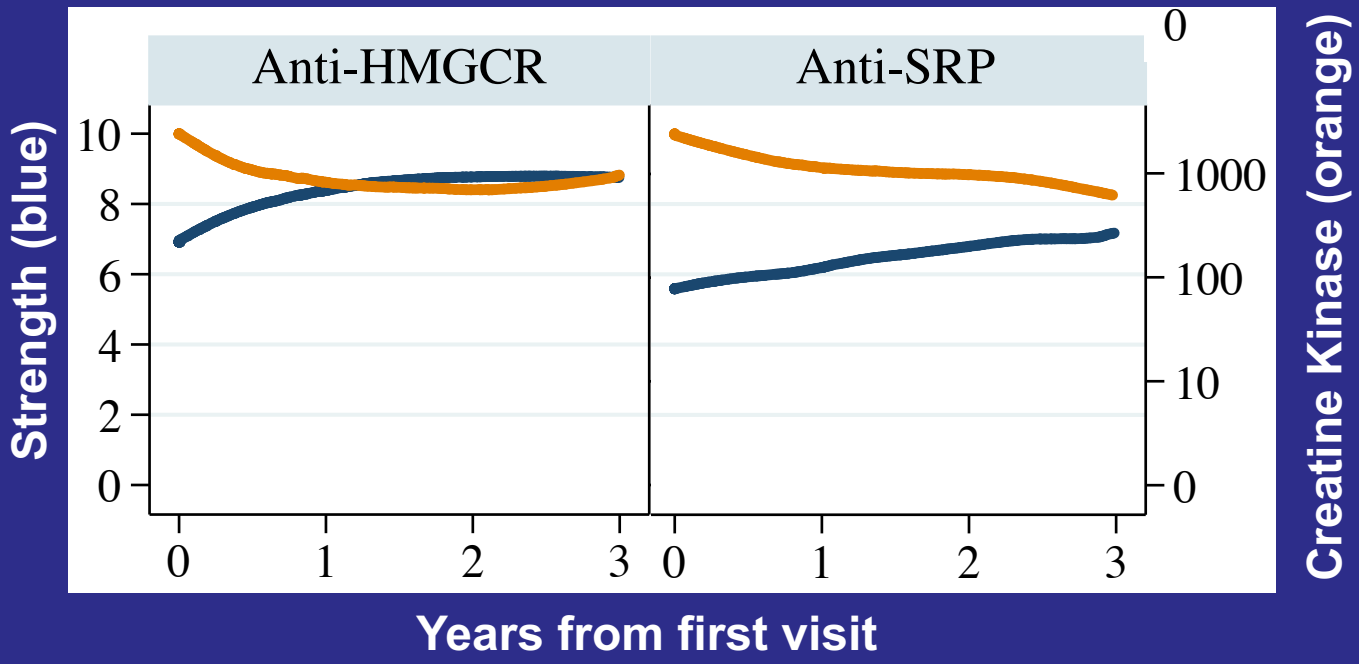
Christopher-Stine et al., A&R, 2010
Tiniakou et al., A&R, 2019

Managing hypercholesterolemia in anti-HMGCR myopathy patients

- Restarting statins may lead to disease flare
- PCSK9 inhibitors appear to be well-tolerated
- 8 anti-HMGCR patients started on PCSK9 inhibitor
  - Followed average of 1.5 yrs (3-37 months)
  - No reduction in strength
  - CK levels decreased from 956 to 419 IU/L

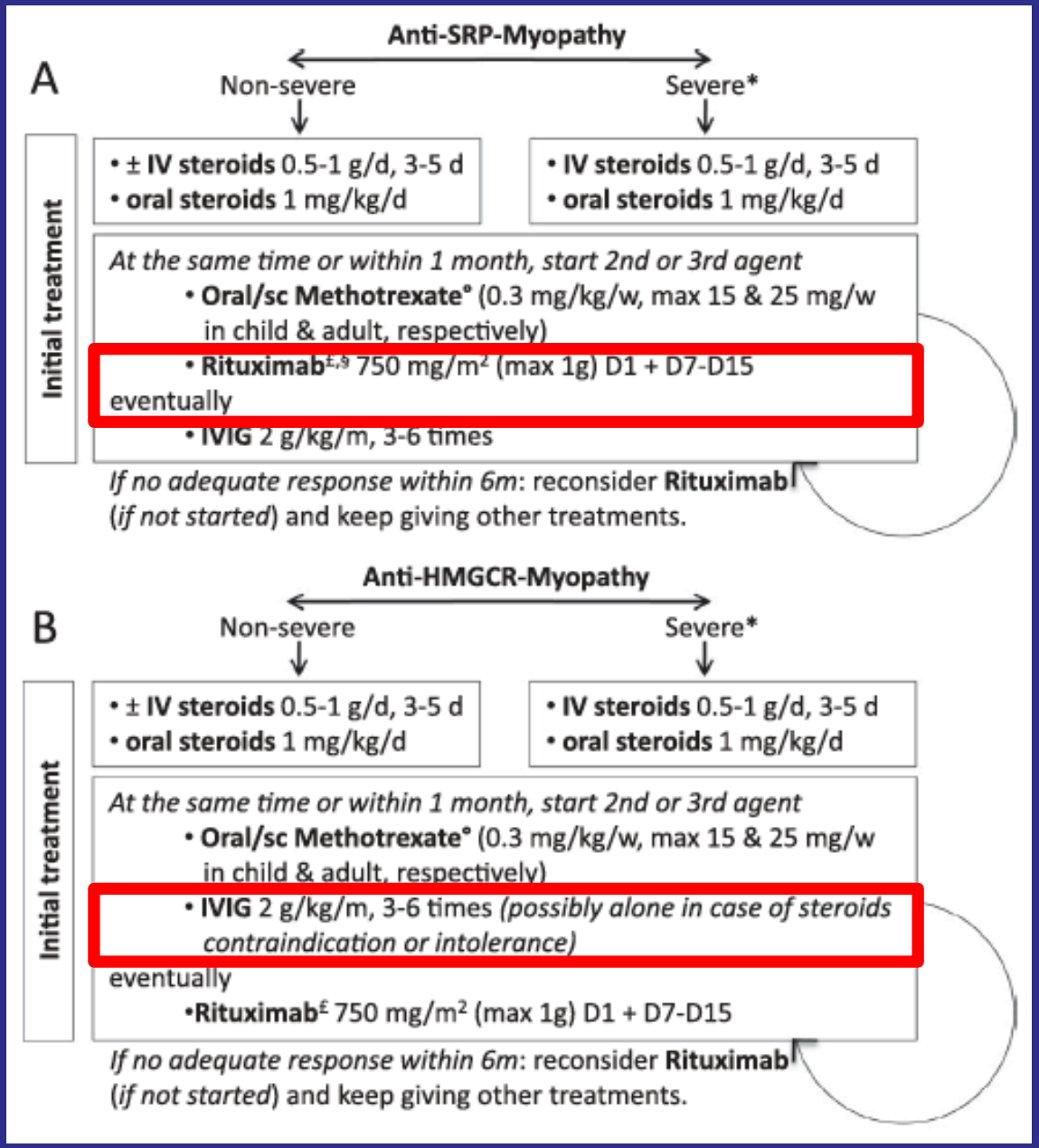
Tiniakou et al., A&R, 2019

Anti-SRP patients have more severe myopathy than anti-HMGCR



Pinal-Fernandez, AC&R, 2017

ENMC Treatment Guidelines for IMNM



Use RTX early in anti-SRP

Use IVIG early in anti-HMGCR

Allenbach et al., NMD, 2018

IVIG as monotherapy for anti-HMGCR

- 3 anti-HMGCR+ patients with progressive weakness despite stopping statins
- Declined steroids because of diabetes
- IVIG initiated as monotherapy
- After 2.3 months
  - Mean CK 4918 to 1797 IU/L
  - Arm abductors: 7.8 to 13.7 lbs
  - Hip flexors: markedly better
- After 9-19 months
  - Strength normal in 2 of 3
  - Strength near normal in 1 of 3

Case	1	2	3
Age statin started	63	53	57
Age of muscle symptoms	67	53	57
Age statin stopped	68	65	57
Age at first IVIG Tx	69	65	63
Prior to IVIG			
CK (IU/L)	3517	2323	8916
Deltoids, MRC (R/L)	4/4	4+/4+	4/4
Deltoids, lbs (R/L)	6/7	11/11	6 /6
Hip Flexors, MRC (R/L)	4/4	4/4	2/2
Hip flexors, lbs (R/L)	14/14	30/27	NA
HMGCR titer	1.65	0.566	0.845
First evluation after IVIG			
Months since first IVIG	1.5	2	3.5
CK (IU/L)	738	270	2368
Deltoids, MRC (R/L)	5/5	5/5	5-/5-
Deltoids, lbs (R/L)	13/12	19/19	10/9
Hip flexors, MRC (R/L)	4+/4+	5/5	4-/4-
Hip flexors, lbs (R/L)	23/28	NA	12/15
HMGCR titer	1.242	0.438	0.654
Months since first IVIG	15	19	9
CK (IU/L)	877	64	1755
Deltoids, MRC (R/L)	5/5	5/5	5/5
Deltoids, lbs (R/L)	13/18	NA	15/14
Hip flexors, MRC (R/L)	5/5	5/5	4+/4+
Hip flexors, lbs (R/L)	NA	NA	30/28
HMGCR titer	1.179	0.471	0.764

Mammen and Tiniakou, NEJM, 2015

Case #2

- Referred to Carsten Bonnemann at NINDS
- Previously healthy 13 year-old boy noticed decreased running speed playing baseball at age 10
- Progressively worsens over 3 years
- CK 8000 IU/L
- Proximal muscle weakness
- Muscle biopsy: necrosis, regeneration, fibrosis

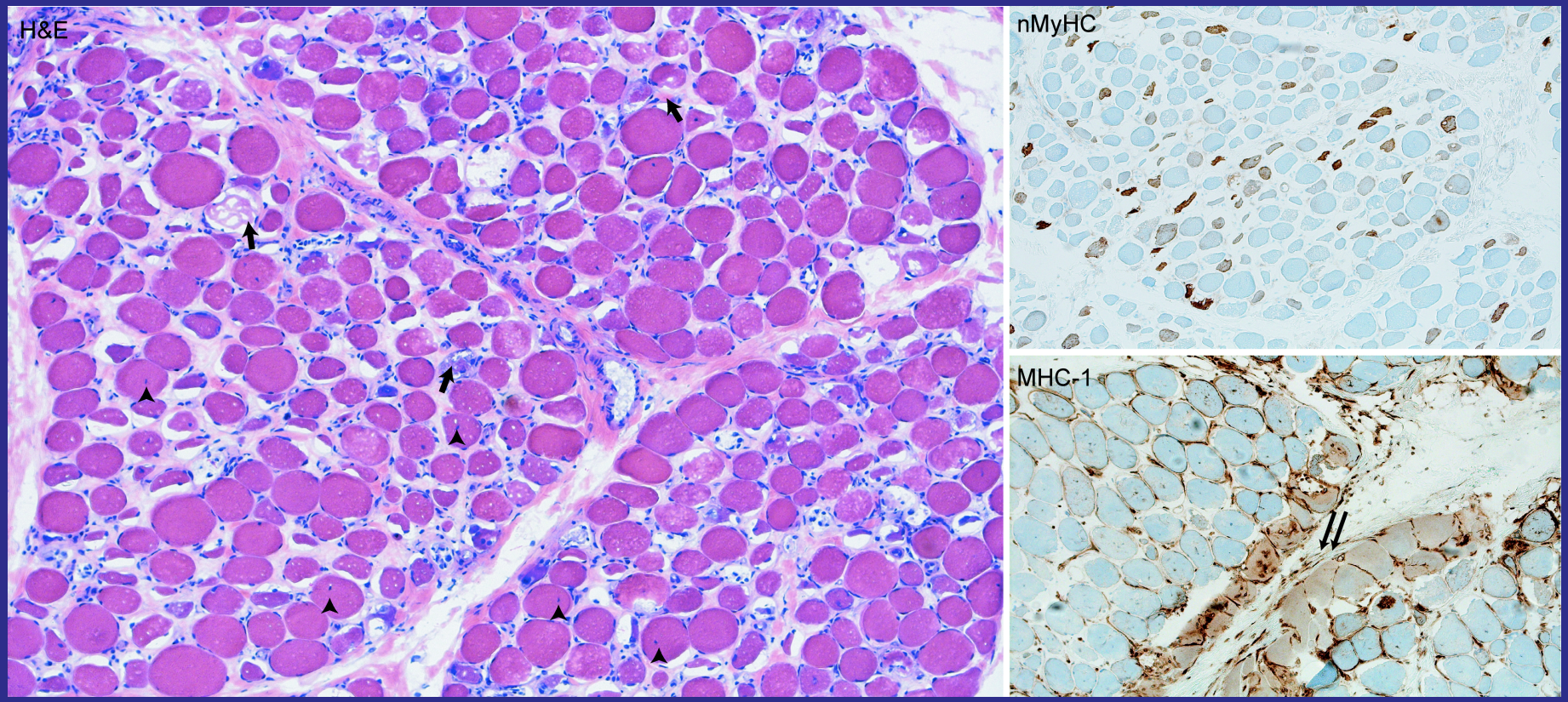
Mohassel et al., Muscle and Nerve, 2017

Case #2

- Diagnosed with limb girdle muscular dystrophy
- Dystrophin gene deletion/duplication and sequencing: negative
- NGS of 183 known dystrophy/myopathy genes: negative
- Referred to National Institutes of Health for whole exome sequencing…

Mohassel et al., Muscle and Nerve, 2017

Case #2



Necrotizing myopathy

Mohassel et al., Muscle and Nerve, 2017

Case #2

- Recommended anti-HMGCR testing
- Positive anti-HMGCR test!
- Exam at NIH
  - Neck flexion 4-/5
  - Arm abduction 4/5
  - Hip flexion 2/5
- IVIG monotherapy (1 gram/kg/month)
- Re-assessed after 3 months
  - CK 400
  - 5/5 power in all muscles

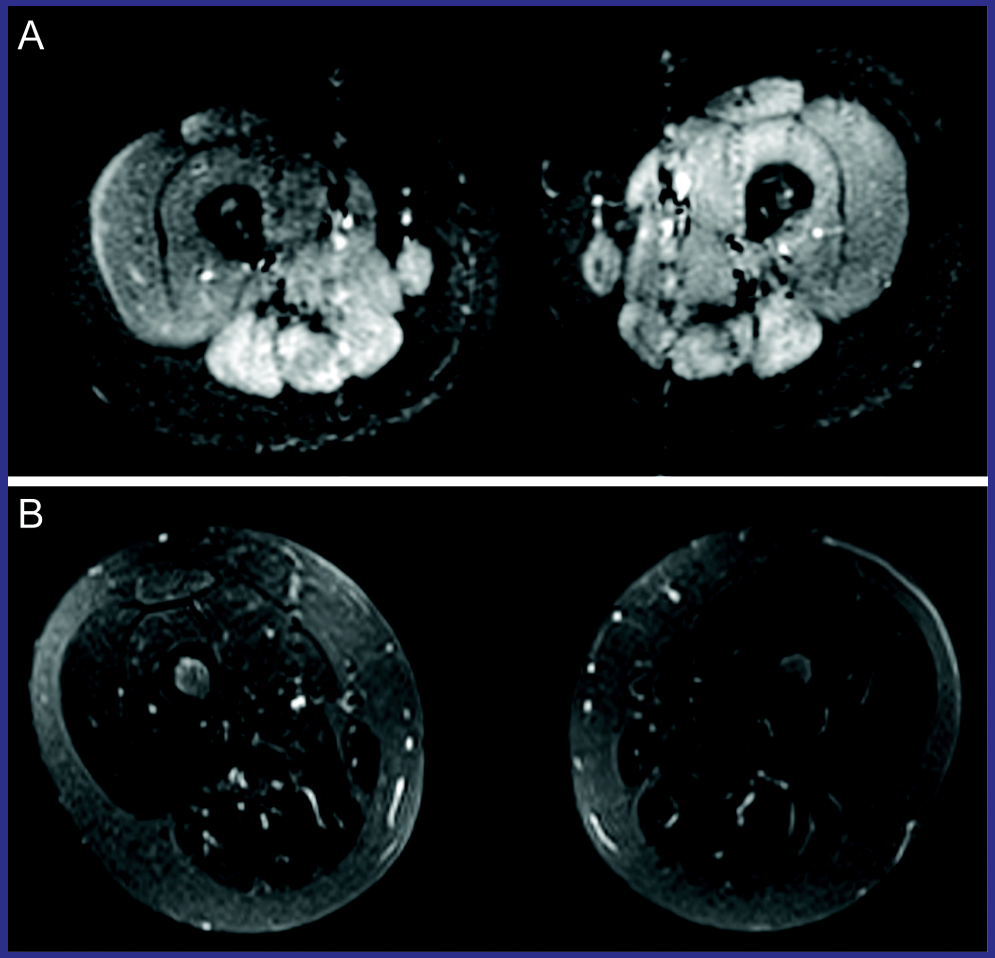
Mohassel et al., Muscle and Nerve, 2017

Case #2

STIR sequences

Before Treatment

After 3 Months of IVIG



Mohassel et al., Muscle and Nerve, 2017

Anti-HMGCR myopathy may resemble limb-girdle muscular dystrophy

Payam Mohassel, MD,* Océane Landon-Cardinal, MD,* A. Reghan Foley, MD, Sandra Donkervoort, MS, CGC, Katherine S. Pak, MD, Colleen Wahl, FNP, DNP, Robert T. Shebert, MD, Amy Harper, MD, Pierre Fequiere, MD, Matthew Meriggioli, MD, Camilo Toro, MD, Daniel Drachman, MD, Yves Allenbach, MD, PhD, Olivier Benveniste, MD, PhD, Anthony Béhin, MD, Bruno Eymard, MD, PhD, Pascal Laforêt, MD, PhD, Tanya Stojkovic, MD, Andrew L. Mammen, MD, PhD, and Carsten G. Bönnemann, MD

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Neurol Neuroimmunol Neuroinflamm 2019;6:e523. doi:10.1212/NXI.0000000000000523

- 23 patients initially diagnosed with LGMD, mostly as children
- Some had years of asymptomatic hyperCKemia
- Muscle biopsies dystrophic without inflammation
- Most had significant improvement with therapy (often IVIG)

Myositis-associated autoantibodies

- Not relied upon for diagnosis of DM, IMNM, ASyS, or IBM, given their lack of specificity
- May provide valuable prognostic information

Myositis with anti-PM/Scl autoantibodies

- Weakness: more severe in proximal arms than proximal legs
- ILD: 10% at presentation and 61% during follow-up (monitor for this)
- More extensive extra-muscular manifestations than DM, ASyS, or IMNM
  - 80% mechanic's hands, 78% Raynaud syndrome, 66% sclerodactyly, 39% calcinosis
  - 30% meet criteria for systemic sclerosis

De Lorenzo et al., Neurology, 2018

Myositis patients with anti-U1RNP autoantibodies

- ILD: a presenting feature in 5%, but ultimately develops in 45% (monitor for this)
- Glomerulonephritis in 25%
  - Only in those with co-existing anti-Ro52
- Pericarditis in 40%
  - Only in those with co-existing anti-Ro52
- ACR/EULAR classification criteria
  - 45% with scleroderma and 55% with lupus

Casal Dominguez et al., Neurology, 2019

Anti-NT5C1a first discovered in IBM

Cytosolic 5′-Nucleotidase 1A Autoimmunity in Sporadic Inclusion Body Myositis

H. Benjamin Larman, PhD,[1,2,3,4,5*] Mohammad Salajegheh, MD,[6,7*]
Remedios Nazareno, BS,[6] Theresa Lam, BA,[7] John Sauld,[8] Hanno Steen, PhD,[8]
Sek Won Kong, MD,[7] Jack L. Pinkus, PhD,[6,7] Anthony A. Amato, MD,[6]
Stephen J. Elledge, PhD,[1,2,3] and Steven A. Greenberg, MD[6,7]

Larman, et al., Annals of Neurology, 2013

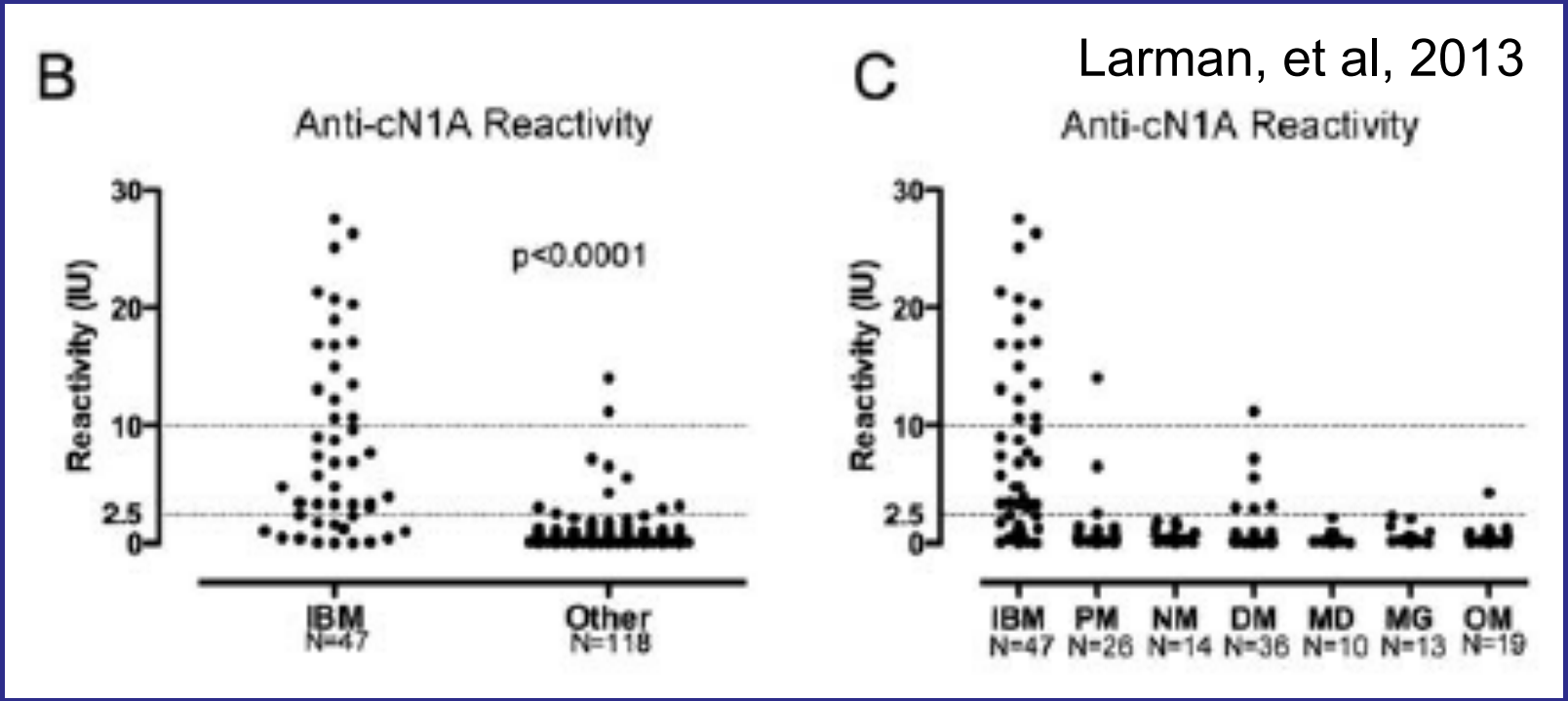
ORIGINAL ARTICLE

Autoantibodies to Cytosolic 5′-Nucleotidase 1A in Inclusion Body Myositis

Helma Pluk, PhD,[1*] Bas J. A. van Hoeve, MD,[2*] Sander H. J. van Dooren, PhD,[1*]
Judith Stammen-Vogelzangs,[1] Annemarie van der Heijden,[1]
Helenius J. Schelhaas, MD, PhD,[2] Marcel M. Verbeek, PhD,[2] Umesh A. Badrising, MD, PhD,[3]
Snjolaug Arnardottir, MD, PhD,[4] Karina Gheorghe,[5] Ingrid E. Lundberg, PhD,[5]
Wilbert C. Boelens, PhD,[1] Baziel G. van Engelen, MD, PhD,[2] and Ger J. M. Pruijn, PhD[1]

Pluk, et al., Annals of Neurology, 2013

Anti-NT5C1a common in IBM, but not in other neuromuscular disorders



Larman, et al, 2013

- Sensitivity = 72%
- Specificity = 92%

Larman, et al., Annals of Neurology, 2013

Anti-NT5C1a autoantibodies are not IBM-specific

Disease specificity of autoantibodies to cytosolic 5′-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases

Megan K Herbert,[1] Judith Stammen-Vogelzangs,[1] Marcel M Verbeek,[2,3] Anke Rietveld,[2] Ingrid E Lundberg,[4] Hector Chinoy,[5] Janine A Lamb,[6] Robert G Cooper,[7] Mark Roberts,[8] Umesh A Badrising,[9] Jan L De Bleecker,[10] Pedro M Machado,[11] Michael G Hanna,[11] Lenka Plestilova,[12] Jiri Vencovsky,[12] Baziel G van Engelen,[2] Ger J M Pruijn[1]

Herbert et al., ARD, 2014

Cytosolic 5′-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases

THOMAS E. LLOYD,[1] LISA CHRISTOPHER-STINE,[1] IAGO PINAL-FERNANDEZ,[2] ELENI TINIAKOU,[1] MICHELLE PETRI,[1] ALAN BAER,[1] SONYE K. DANOFF,[1] KATHERINE PAK,[3] LIVIA A. CASCIOLA-ROSEN,[1] AND ANDREW L. MAMMEN[4]

Lloyd et al., AC&R, 2016

- 23-36% with Sjogren's
- 14-20% with lupus
- 15% with DM

More severe disease in anti-NT5C1a positive IBM patients

- Goyal et al, JNNP, 2016
  - 18 of 25 (72%) anti-NT5C1a+
  - Female > male anti-NT5C1a+ (OR 2.30)
  - Longer to get up and stand (p=0.012)
  - More required assistive devices (OR 23, p=0.007)
  - More likely to have dysphagia (OR 10.67, p=0.03) and/or facial weakness (50% vs 14%)
- Lilleker et al., ARD, 2017
  - 102 of 311 (33%) anti-NT5C1a+
  - Higher adjusted mortality risk (HR 1.89)
  - Increased incidence of facial weakness (p=0.034)

Screening for anti-NT5C1a in pediatric myositis population

- 502 pediatric serum samples tested for anti-NT5C1a by immunoblot
  - 380 juvenile myositis
    - 307 JDM, 27 JPM, 46 juvenile myositis overlap
  - 30 Juvenile idiopathic arthritis (JIA)
  - 92 healthy controls

Yeker RM, Pinal-Fernandez, ARD, 2018

High prevalence (12%) of anti-NT5C1a in pediatric controls

	Total (n=502) % (N)
Juvenile myositis (n=380)	27 (102)**
Juvenile dermatomyositis (n=307)	27 (83)**
Juvenile PM (n=27)	11 (3)
Juvenile myositis overlap syndromes (n=46)	35 (16)**
Juvenile myositis overlapping with juvenile systemic lupus erythematosus (n=14)	36 (5)*
Juvenile myositis overlapping with juvenile systemic sclerosis (n=11)	27 (3)
Juvenile myositis overlapping with JIA (n=7)	14 (1)
Juvenile myositis overlapping with other paediatric autoimmune diagnosis (n=14)	50 (7)**
JIA (n=30)	27 (8)*
Healthy paediatric controls (n=92)	12 (11)

*P<0.05, **P<0.01, ***P<0.001.

27% of juvenile myositis sera are anti-NT5C1a-positive

	Total (n=502) % (N)
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27% of JDM sera are anti-NT5C1a-positive

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*P<0.05, **P<0.01, ***P<0.001.

35% of juvenile myositis overlap sera are anti-NT5C1a-positive

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Healthy paediatric controls (n=92)	12 (11)

*P<0.05, **P<0.01, ***P<0.001.

27% of JIA sera are anti-NT5C1a-positive so anti-NT5C1a is a MAA

	Total (n=502) % (N)
Juvenile myositis (n=380)	27 (102)**
Juvenile dermatomyositis (n=307)	27 (83)**
Juvenile PM (n=27)	11 (3)
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Juvenile myositis overlapping with juvenile systemic lupus erythematosus (n=14)	36 (5)*
Juvenile myositis overlapping with juvenile systemic sclerosis (n=11)	27 (3)
Juvenile myositis overlapping with JIA (n=7)	14 (1)
Juvenile myositis overlapping with other paediatric autoimmune diagnosis (n=14)	50 (7)**
JIA (n=30)	27 (8)*
Healthy paediatric controls (n=92)	12 (11)

*P<0.05, **P<0.01, ***P<0.001.

More severe disease in pediatric myositis patients with anti-NT5C1a

- Those with and without anti-NT5C1a autoantibodies had similar demographics and clinical phenotypes
- Anti-NT5C1a+ more likely to have*
  - Raynaud's (17% vs. 14%; p=0.03)
  - V or Shawl sign rash (43% vs. 26%; p=0.02)
  - Greater pulmonary symptom score at diagnosis (0.13 vs. 0.08; p=0.005)
  - More frequent hospitalizations (1.6 vs. 1.1; p=0.01)
  - Received larger total number of medications (4.8 vs. 3.6; p<0.001)
  - Received IVIG and/or IV steroids

*multivariate analysis adjusted for follow-up duration, MSAs, year of diagnosis

Myositis autoantibodies

- How to use?
  - Diagnosis
    - DM with equivocal rash, ASyS, statin-associated myositis
  - Management
    - Intensive cancer screening: anti-TIF1γ and –NXP2
    - ILD monitoring: ASyS, anti-MDA5, anti-PM/Scl, anti-U1RNP
    - Early tofacitinib for ILD: anti-MDA5
    - Glomerulonephritis monitoring: anti-U1RNP + Ro52
    - Early IVIG: anti-HMGCR
    - Early RTX: anti-SRP
    - Manage hypercholesterolemia with a PCSK9 inhibitor: anti-HMGCR

Checkpoint inhibitor-triggered myositis

- In a retrospective analysis of 33 CI trials, less than 1% developed weakness*
- Among 15,000+ iRAEs in 2017, 0.57% were myositis**
- Myositis more common with anti-PD-1/PD-L1 than anti-CTLA-4 (OR = 2.4)***
- Myositis more common with combination therapy (OR = 1.8)***
- 0.3% with most solid organs get myositis
- ~50% with thymoma get myositis****

*Cappelli et al., ACR, 2017
**Anquetil et al., Circulation, 2018
***Nguyen et al., ARD, 2020
****Mammen et al., ARD 2020

Myositis + other autoimmunity

- Among 345 with ICI-associated myositis, 41 (11.9%) had myasthenia gravis and 39 (11.3%) had myocarditis*
- Among 177 with ICI-associated myositis, 29 (16.4%) had myasthenia gravis and 12 (6.8%%) had myocarditis, and 8 (4.5%) had both**

*Nguyen et al., ARD, 2020
**Johnson et al., J Immunother Cancer, 2019

Pathogenesis

- Muscle biopsies
  - *CD8+ and CD4+ cells*
  - Clonally expanded T cell populations**
  - Infiltrating T cells are PD-1 positive***
  - Suggests a T cell-driven process
- Autoantibodies?
  - Several reports demonstrate pre-existing anti-AChR autoantibodies in those who develop myositis****, *****

*Kimura et al, Cancer Sci, 2016
**Johnson et al., NEJM, 2016
***Uchio et al, N3, 2019

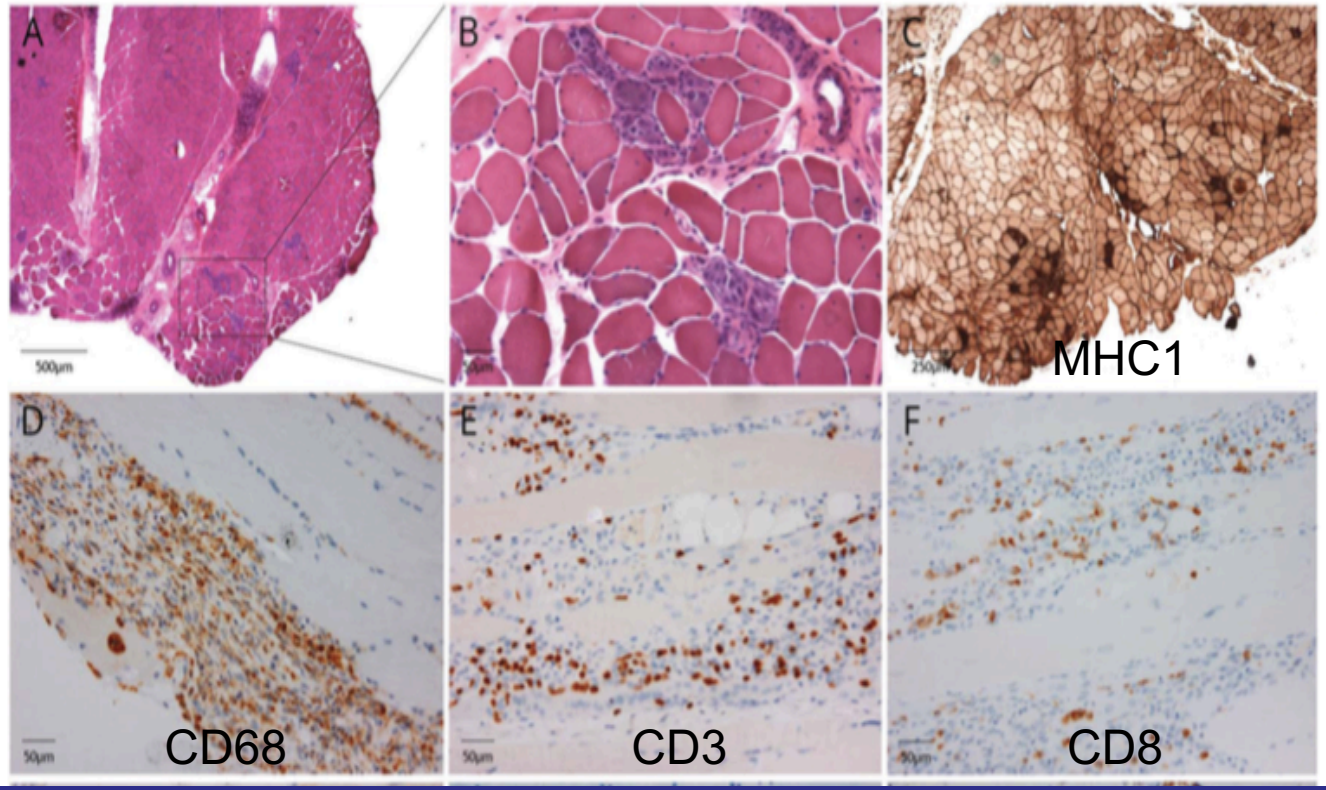
****Suzuki et al., Neurology, 2017
*****Mammen et al., ARD, 2020

Clinical Manifestations

- Usually after 1-2 rounds of ICI
- Myalgias
- Proximal muscle weakness
- Ptosis
- Occulomotor weakness with diplopia
- CK from mildly elevated to >10,000 IU/L
- Negative myositis-specific autoantibodies
- No electrophysiologic findings to suggest neuromuscular junction defect (even with ptosis and double vision)
- If coexisting MG, diaphragm weakness requiring ventilator in 50%

Muscle biopsy

Figure 2 Morphologic findings in skeletal muscle



Touat et al., Neurology, 2018

Management/Outcomes

- No published authoritative guidelines
- Discontinue ICI
- Initiate corticosteroid therapy
- IVIG, MTX, AZA, PLEX, cyclosporine, and tacrolimus have all been used
- In one study, all patients improved with treatment and CK normal in 6-96 days*
- Overall fatality rate 22.3%**
- If co-existing myocarditis, 51.3% mortality
- ICI rechallenge?

*Touat et al., Neurology, 2018
**Nguyen et al., ARD, 2020