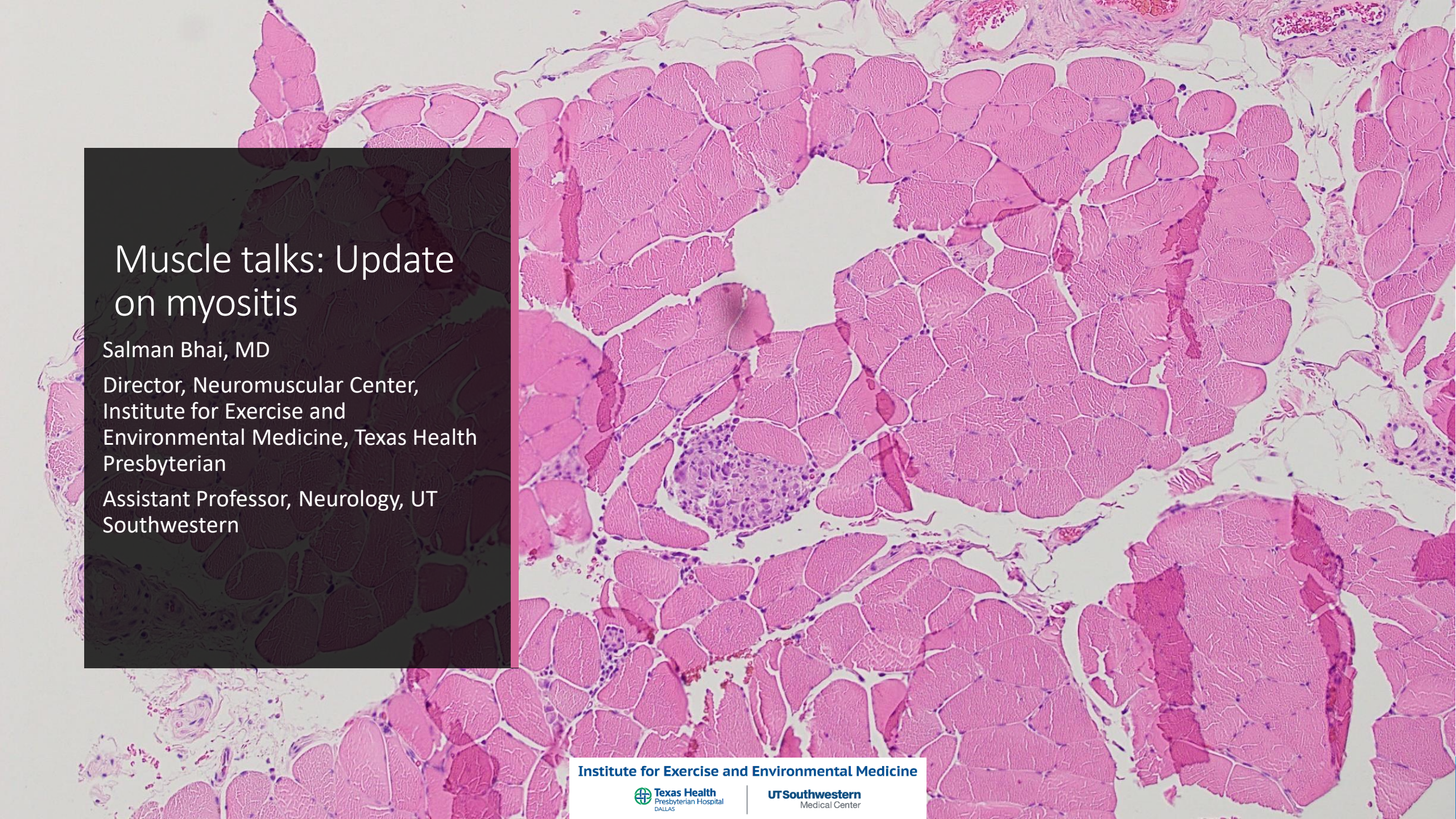


Muscle talks: Update on myositis

Salman Bhai, MD

Director, Neuromuscular Center, Institute for Exercise and Environmental Medicine, Texas Health Presbyterian

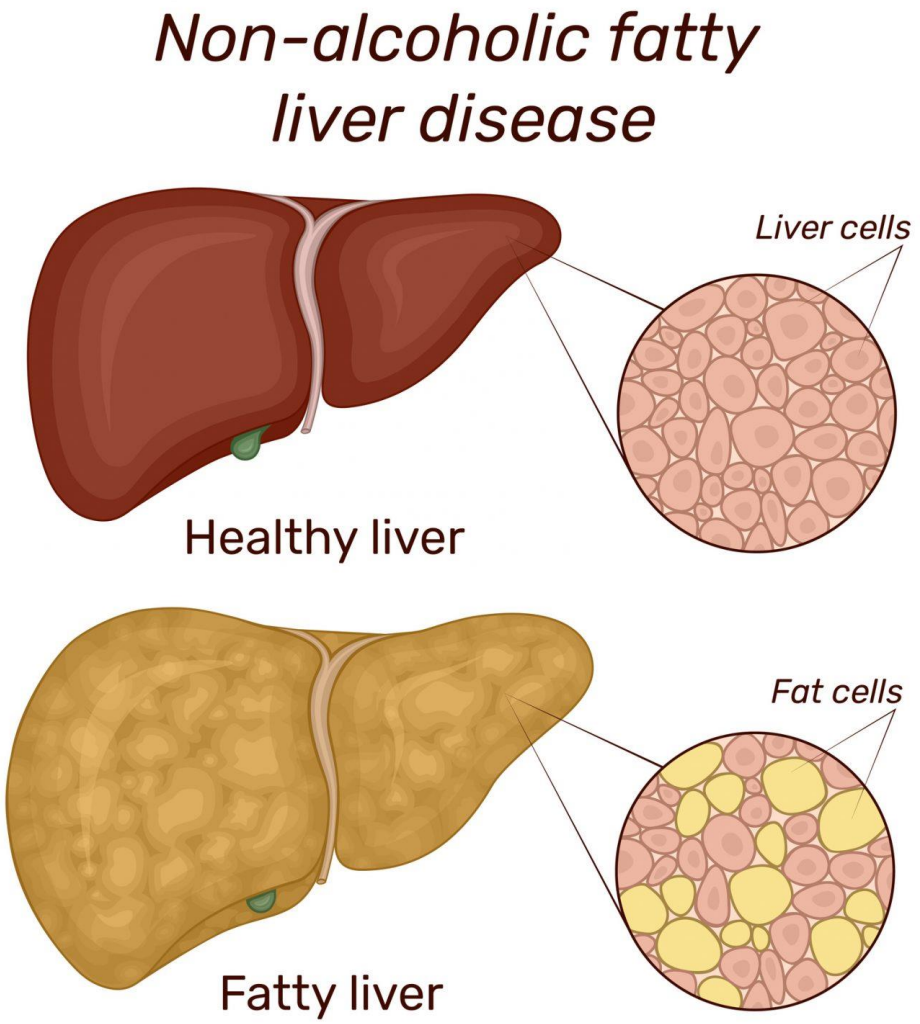
Assistant Professor, Neurology, UT Southwestern

Institute for Exercise and Environmental Medicine

Texas Health Presbyterian Hospital DALLAS | UT Southwestern Medical Center

Update on myositis

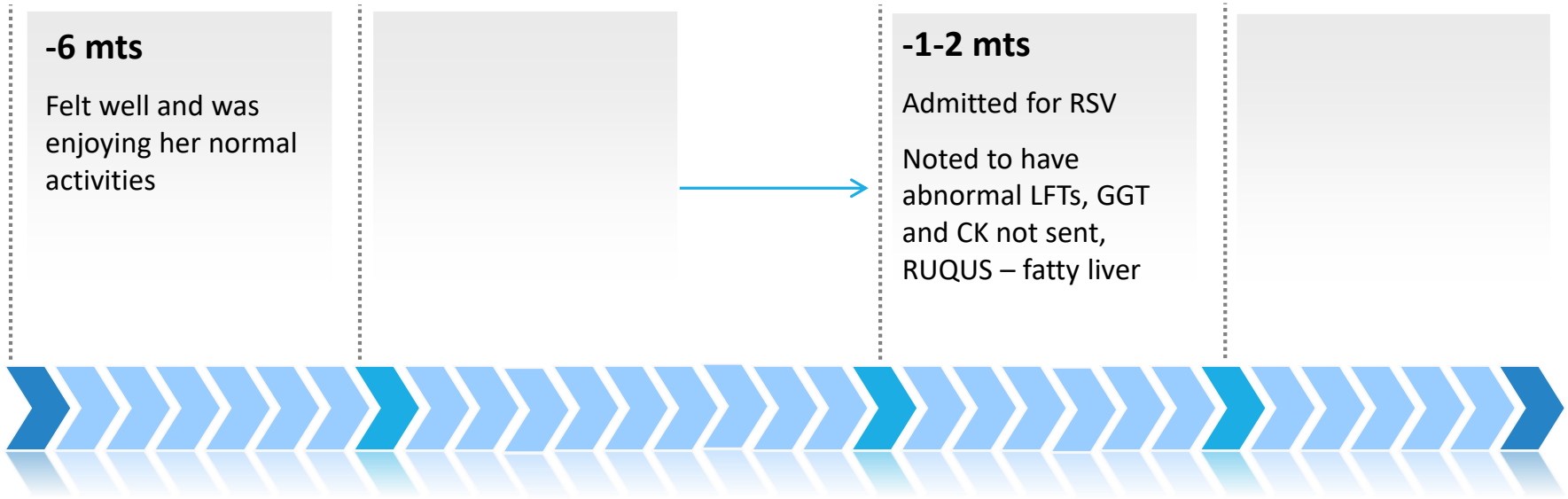
- When to suspect a myopathy
  - Historical features
  - Patterns of myopathy on exam
- What isn't muscle disease
- Practical approach to myopathy
- Update on myositis – diagnosis
- Pitfalls of diagnosing myositis
- Update on myositis – treatment
- Therapeutic landscape
- Questions



What's all the RUQUS about?

58F with NASH

58F with anxiety and LFT abnormalities

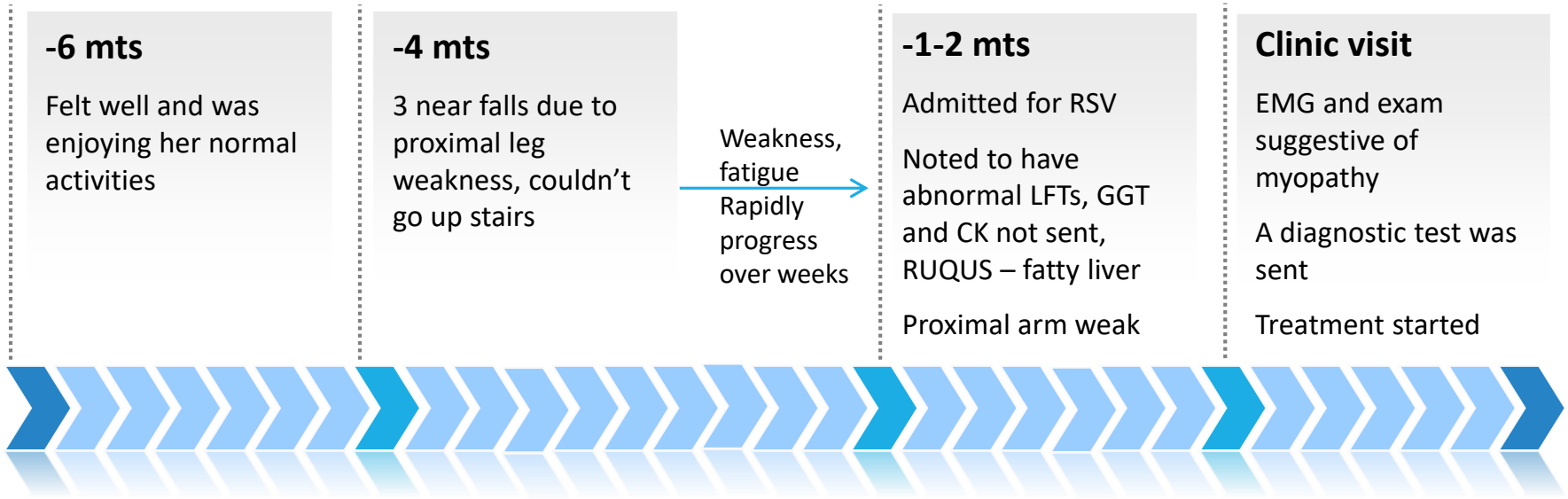


FHx: No neuromuscular diseases

SHx: Participates with her dog in dog shows; social EtOH, no illicits or tobacco

Meds: Atorvastatin, valsartan, amitriptyline, amlodipine, levothyroxine, metformin

58F with anxiety and LFT abnormalities presents with proximal weakness



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PHYSICAL EXAM

Mental status, *cranial nerves*, and *cerebellar* testing all normal

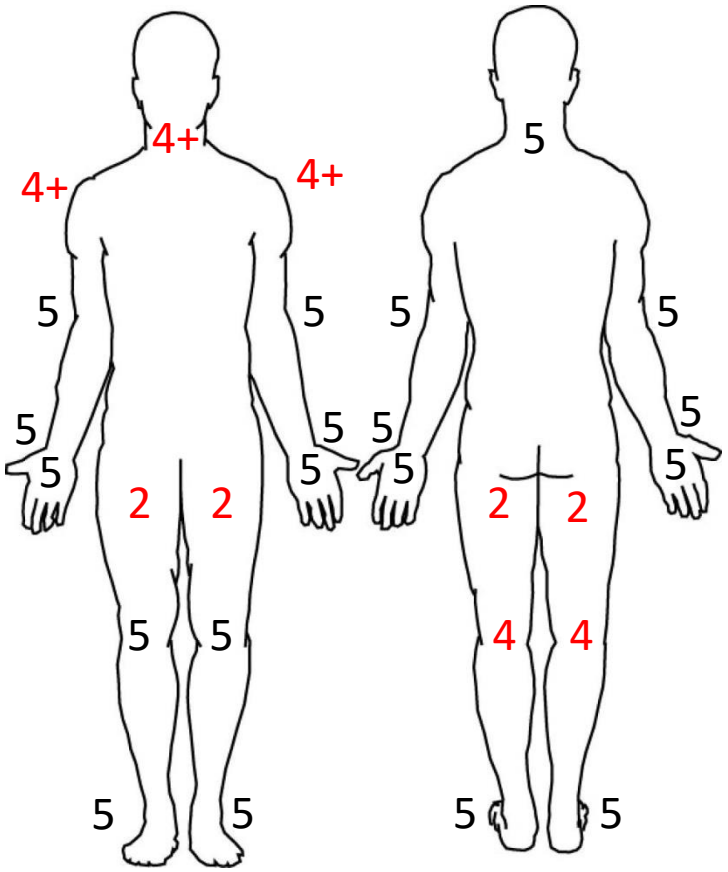
Sensory: split midline to PP, vibration decreased (length dep)

Motor
Normal bulk and tone
No scapular winging
No myotonia

Reflexes
2 throughout
Plantar response flexor bilaterally

Gait
Normal gait, unable to stand without using arms

MRC GRADES



Superficial/deep finger flexors, finger extension, flexor pollicis longus: 5/5 bilaterally

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LFTs:
ALT 480
AST 277
AP 91
Bilirubin (total) 1.3

RUQUS: 'fatty liver'

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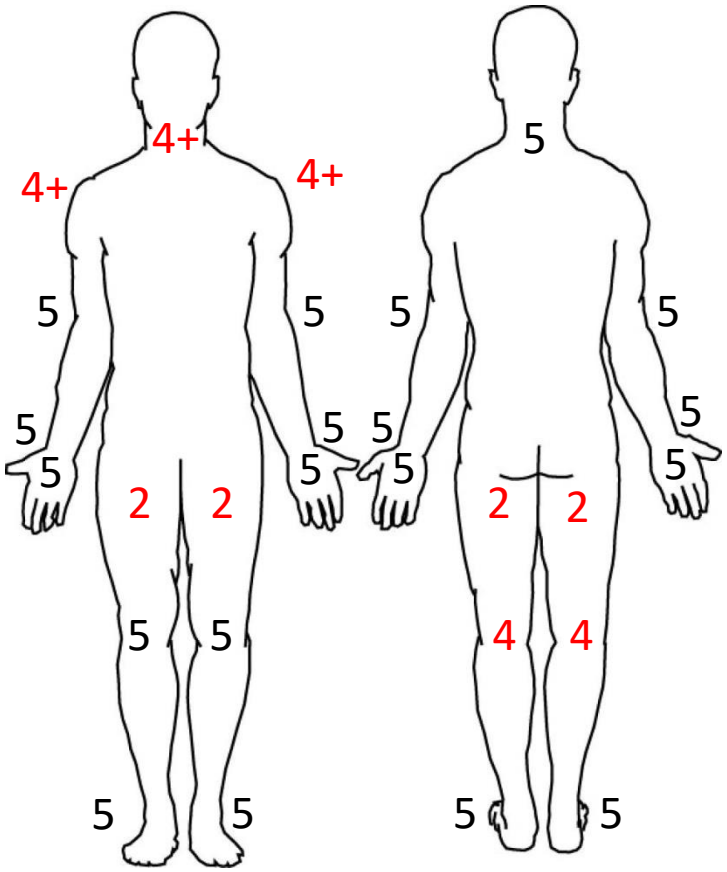

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Myositis panel: negative

EMG: proximal myopathy with membrane irritability

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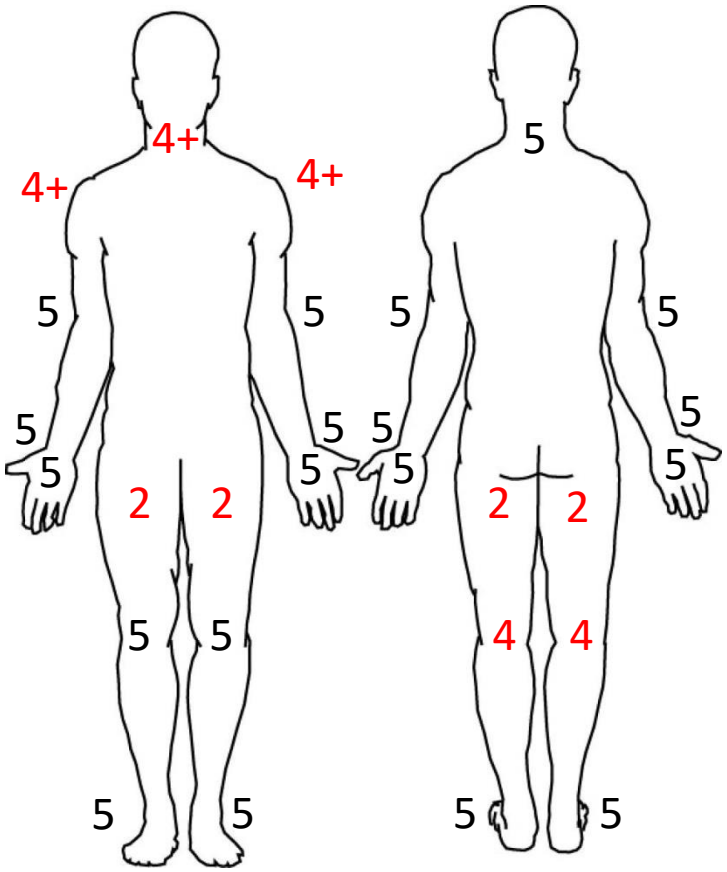

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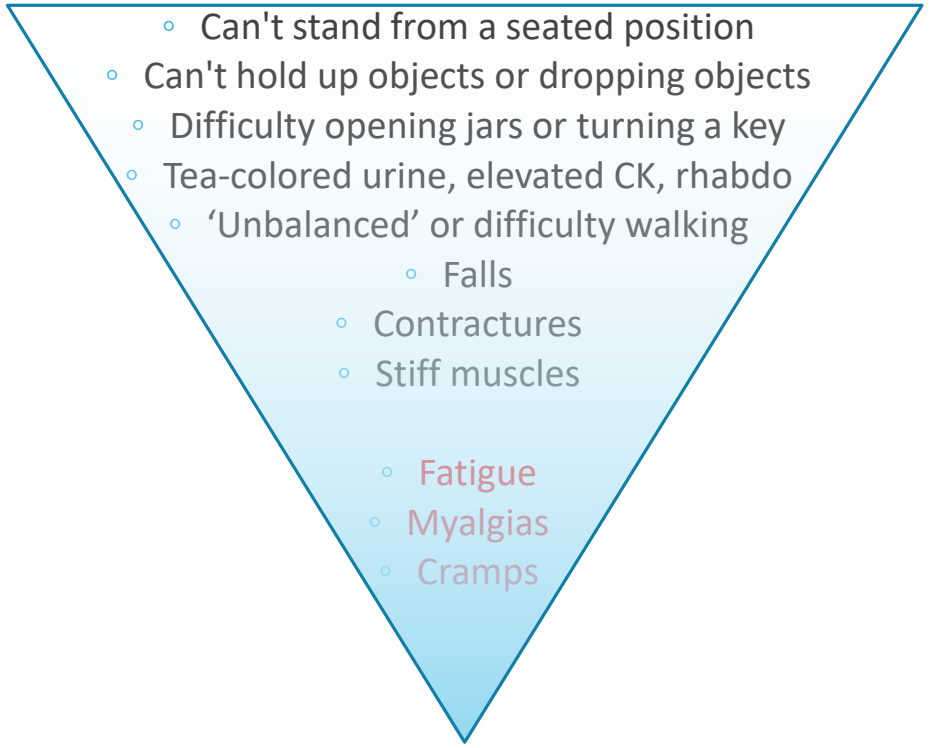
HMGCR antibody 50 Units

EMG: proximal myopathy with membrane irritability

When to suspect myopathy

HISTORICAL FEATURES



PATTERNS OF WEAKNESS

Proximal "limb-girdle" weakness

Distal weakness

Proximal arm/distal leg (scapuloperoneal)

Distal arm/proximal leg

Ptosis w/ or w/o ophthalmoparesis

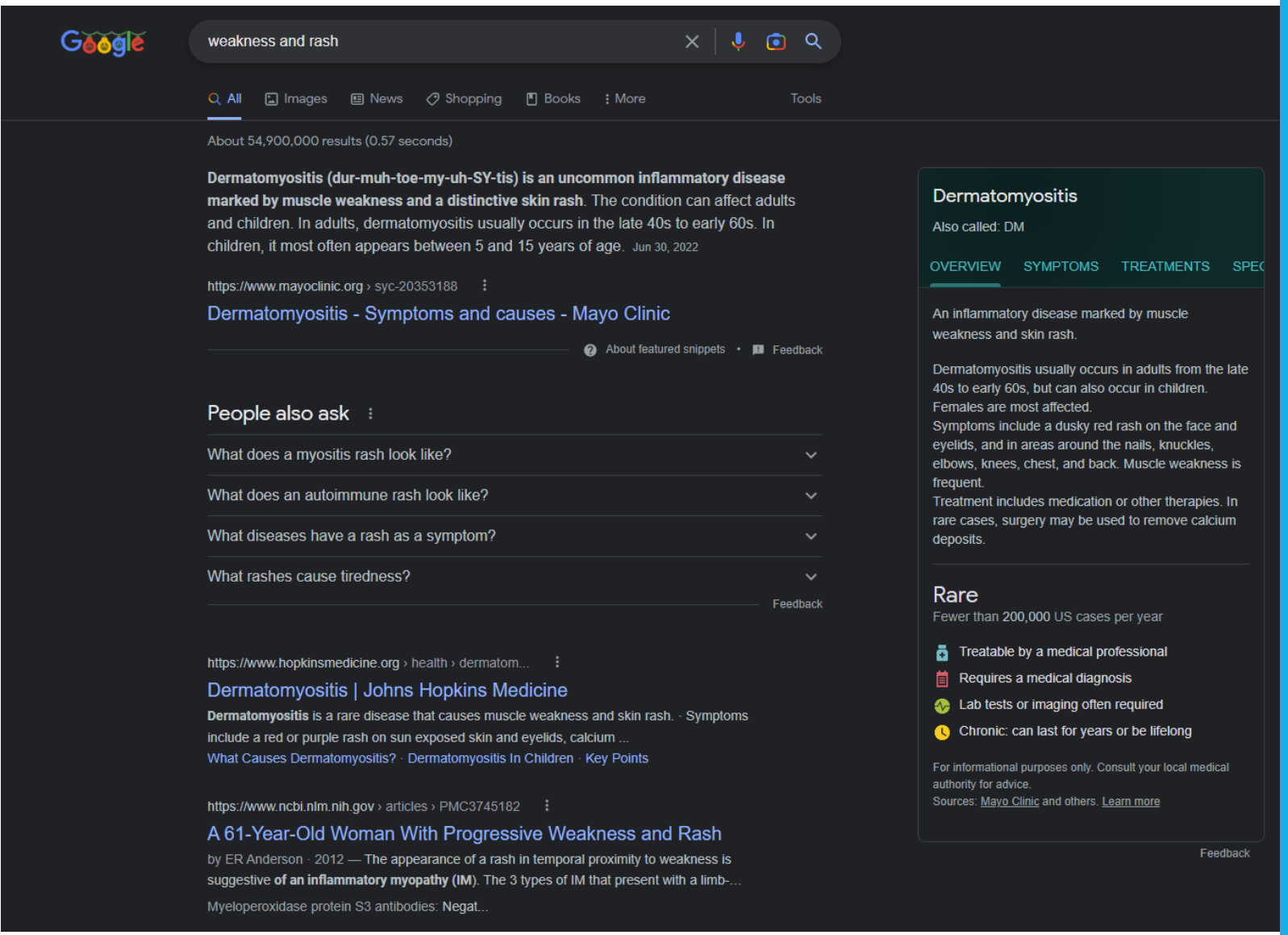
Axial

Bulbar

Episodic weakness w/ or w/o rhabdomyolysis

Stiffness

Barohn et al. 2014.



Google better than your patients

Google better than your patients

MYOPATHY VS NON-MYOPATHY

Fatigue +/- generalized weakness

Exercise intolerance
- Dyspnea, arthralgias, pain, psychiatric
- Metabolic or mitochondrial myopathy

Myalgias
- Myotonic disorders, hypothyroid myopathy, muscular dystrophies
- Toxic/drug induced, hypothyroid, IIMs, infectious (especially viral)

Cramps: neuropathy > myopathy
- Metabolic myopathy (GSDs)

Other neurologic disorder
- Neuropathy
- NMJ d/o
- UMN

DESCRIPTION

Onset

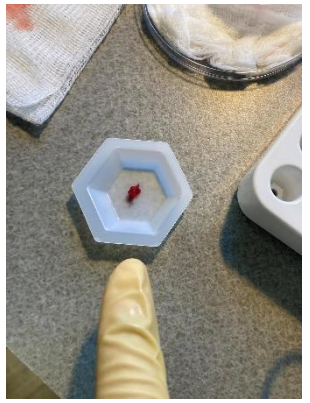
Course

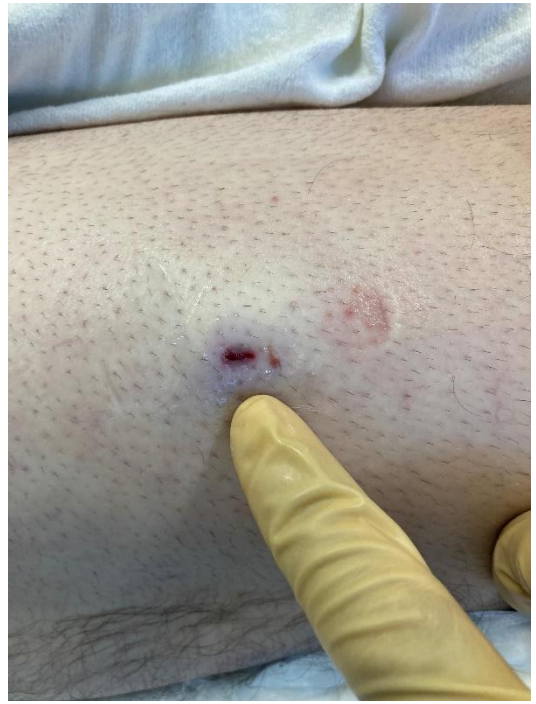
Localization

Other systems involved, especially cardiopulmonary

Utility of biopsies

- Identify the muscle and stains you want (at least the differential)
- Highest yield with weakness (MRC 4/5), CK elevation, myopathic EMG, and/or abnormal MRI signal
- Surgical vs needle
- Helpful for variants of unknown significance (VUS) and inflammatory changes





Proximal weakness

LARGE DIFFERENTIAL

Hereditary (muscular dystrophies, DM2)

Inflammatory – IIMs, sarcoidosis, overlap CTD

Infectious

Toxic – steroids, hydroxychloroquine, statins

Metabolic and mitochondrial myopathies

Endocrinopathies

NMJ d/o

Neuropathies – ALS, SMA

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Distal arm/proximal leg

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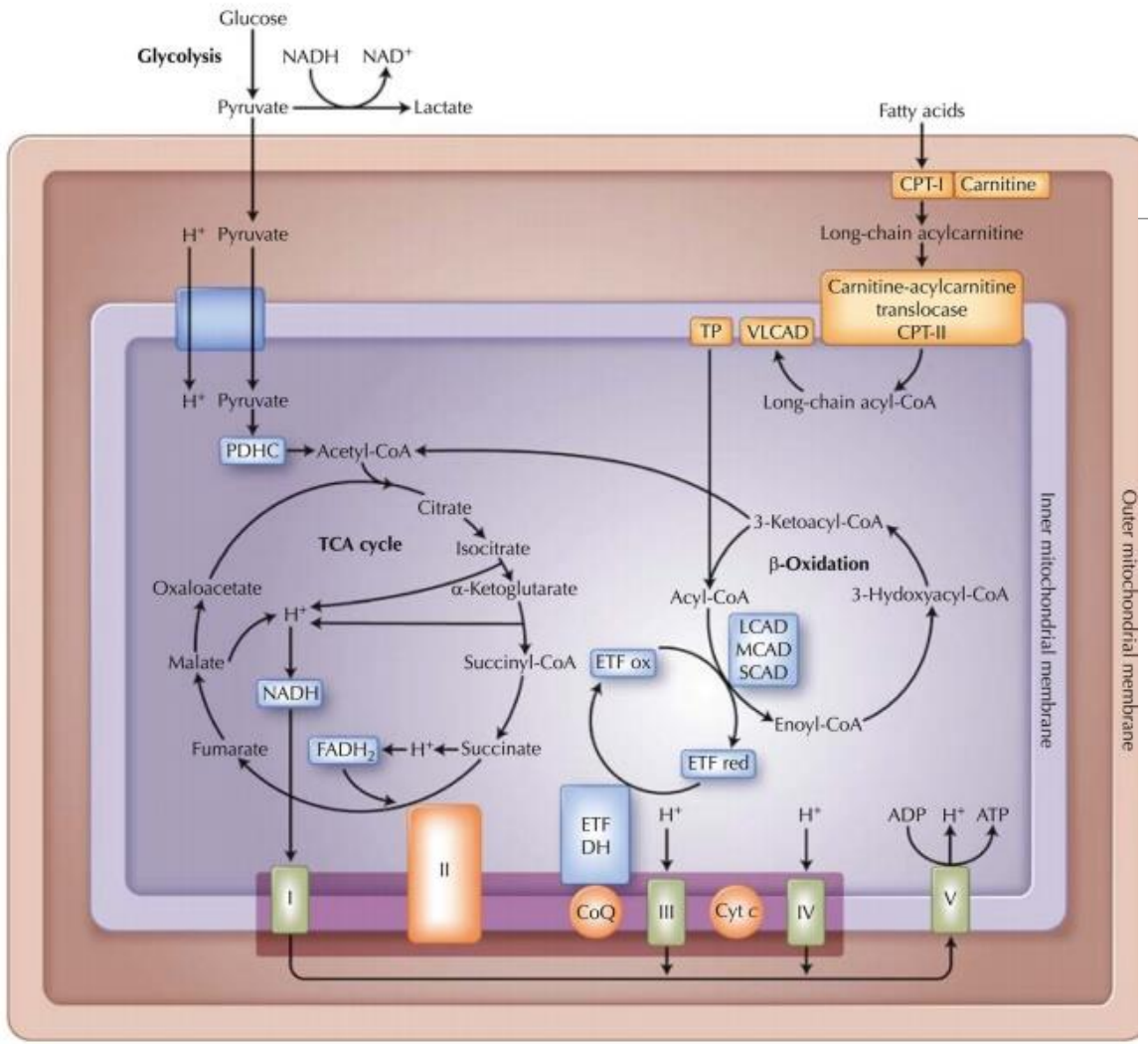
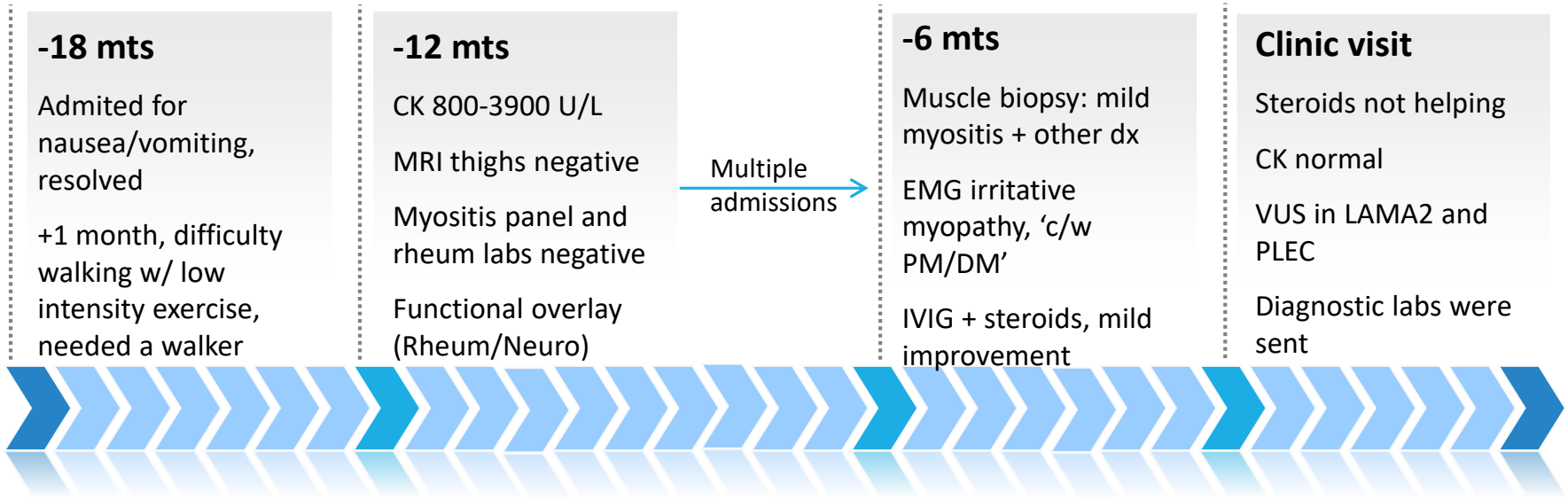
Stiffness



B2 or not B2, there is no question.

49 year-old woman with leg weakness

49F with seizures and difficulty walking with falls



FHx: No neuromuscular diseases

SHx: Denies EtOH, no illicits/tobacco; husband passed away during this period

Meds: Stopped statin 18 months prior to clini visit, apixaban, AEDs, pregabalin, prednisone

PHYSICAL EXAM

Mental status, *cranial nerves*, and *cerebellar* testing all normal

Motor
Normal tone and bulk
No fasciculations
No scapular winging
No myotonia

Reflexes
Triceps, biceps, and brachioradialis - 2+
Knees and ankles – 1+
Plantar response flexor bilaterally

Sensory:
Decreased vibration and pinprick to the ankles

L VL muscle bx: mild chronic endomysial inflammation, MHC1 upregulation, abnormal lipid droplets

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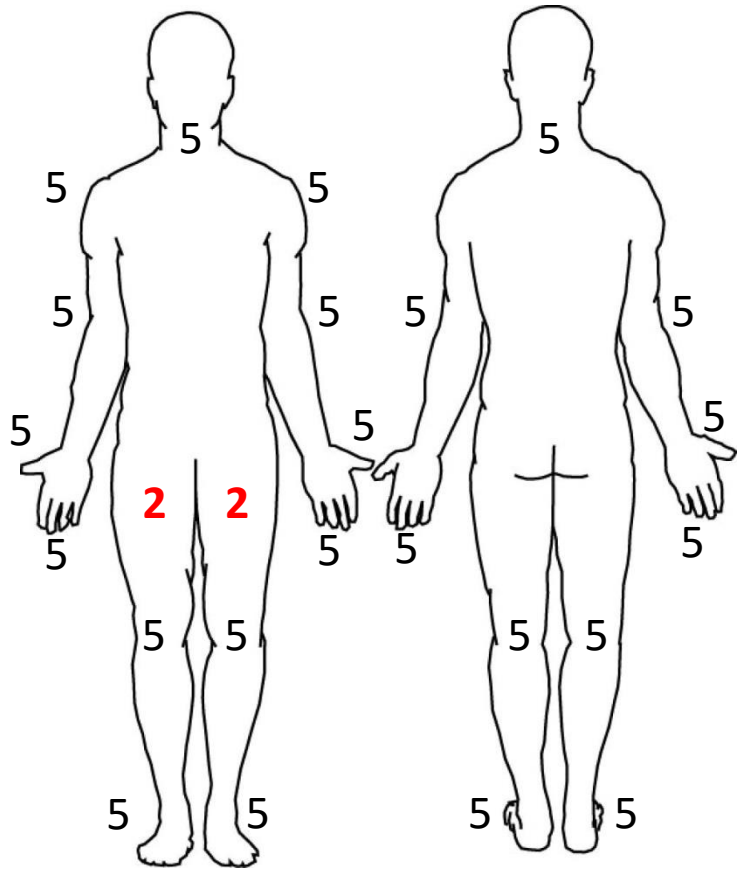

Superficial/deep finger flexors, finger extension, flexor pollicis longus: 5/5 bilaterally

DATA

CK normal to 3900 U/L *Aldolase* wnl
ANA positive at 1:40, *SSA/B, Smith, RNP, Scl70, ANCA* negative
Myositis antibody panel: negative

SPEP w/ IFE normal

HIV, Hep B/C negative

NT5C1A negative

EMG: axonal sensorimotor polyneuropathy and 'irritative myopathy c/w PM/DM'

MRI thighs: normal

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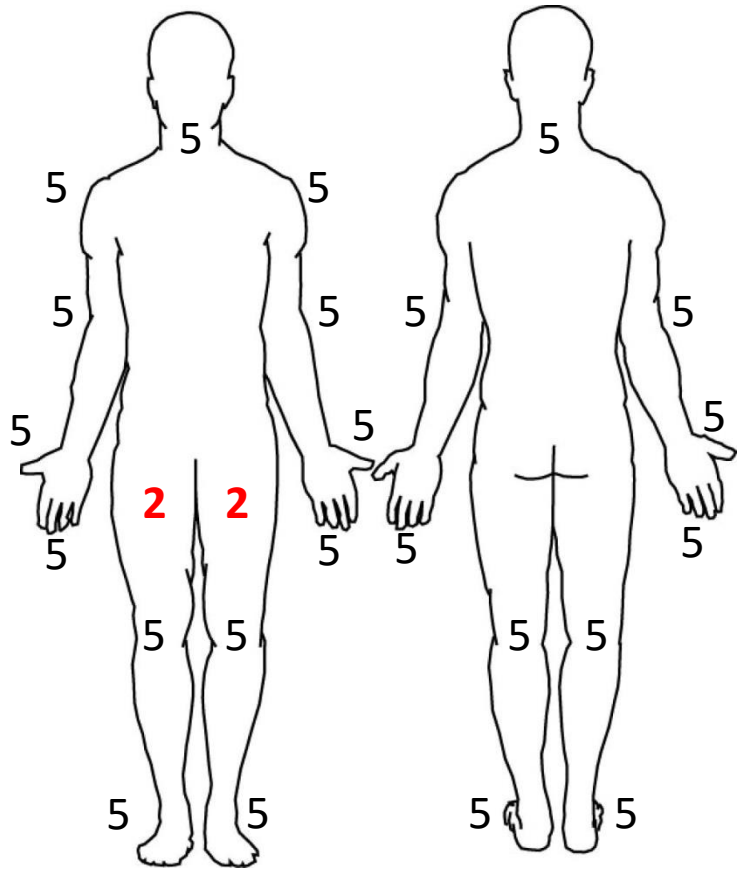

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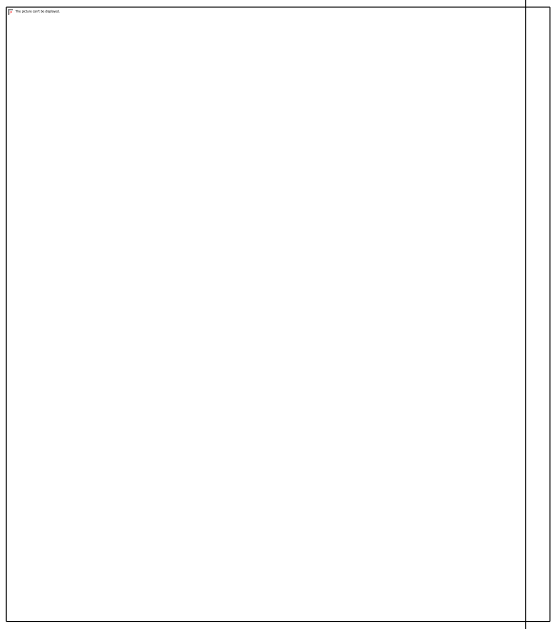
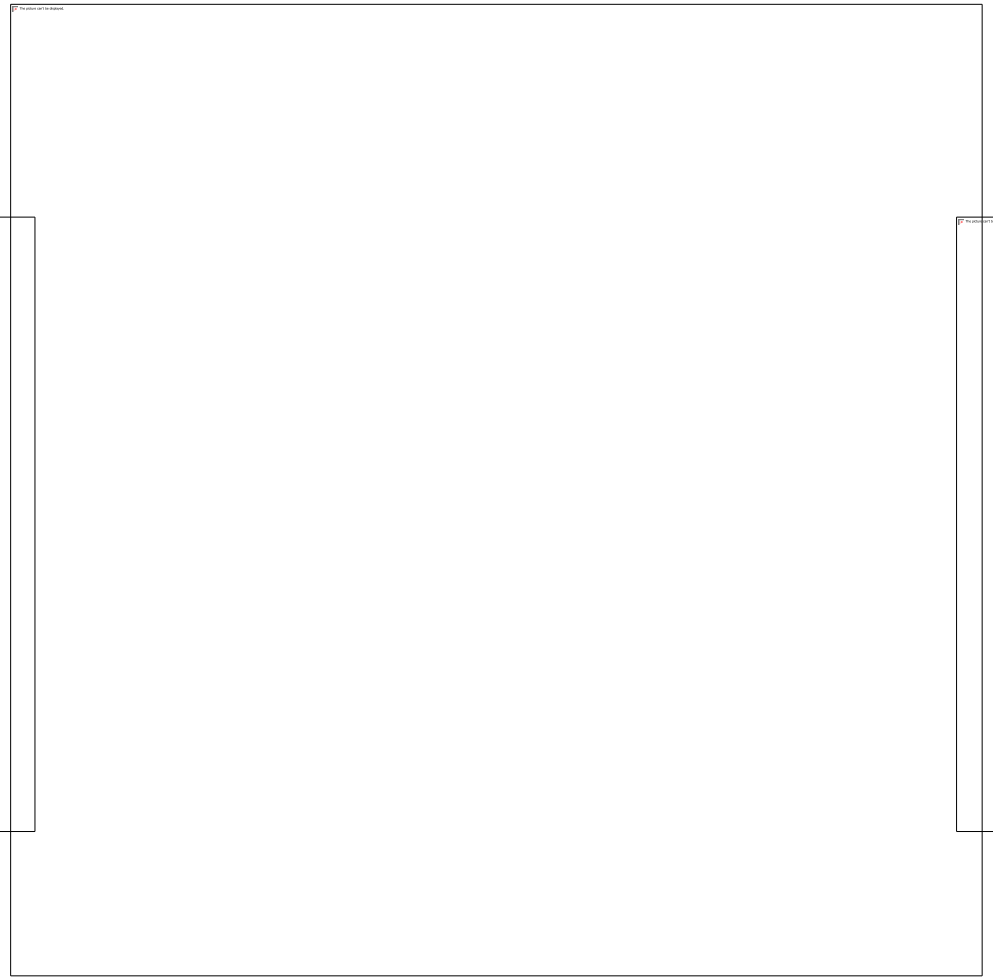
MRI thighs: normal

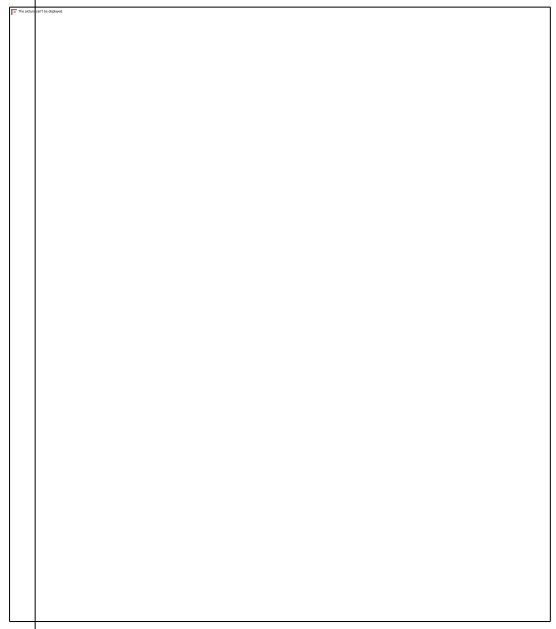
Acylcarnitine profile: multiple elevated species (*urine organic acids* normal)



EM

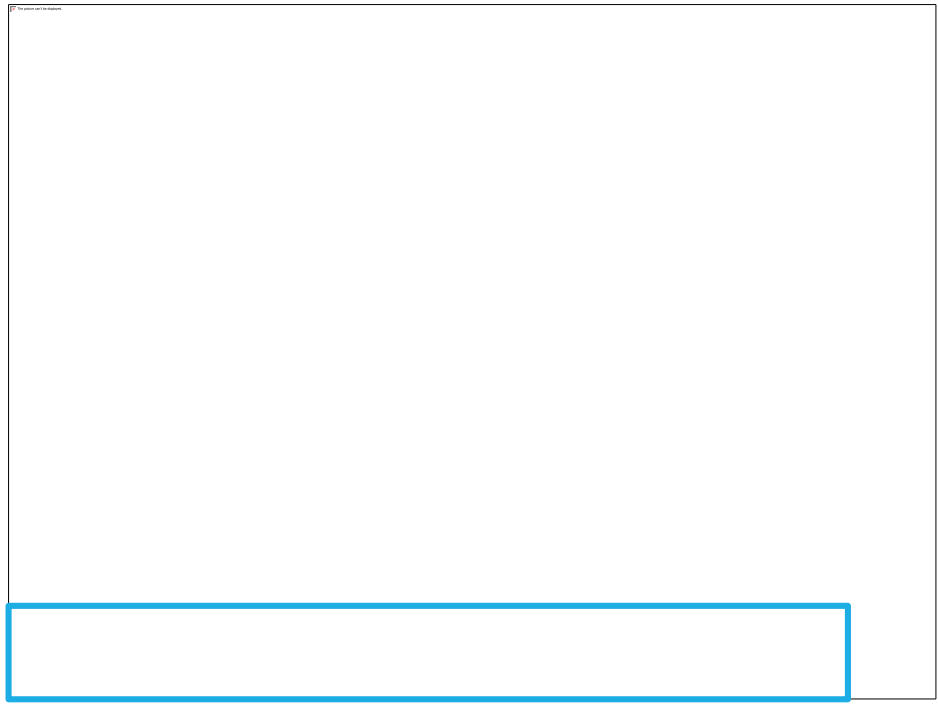


H&E



Oil Red O

Multiple acyl-CoA dehydrogenase deficiency



Grunert et al. 2014.

MADD Diagnosis

Exam: proximal, axial weakness

Muscle biopsy: lipid-filled vacuoles

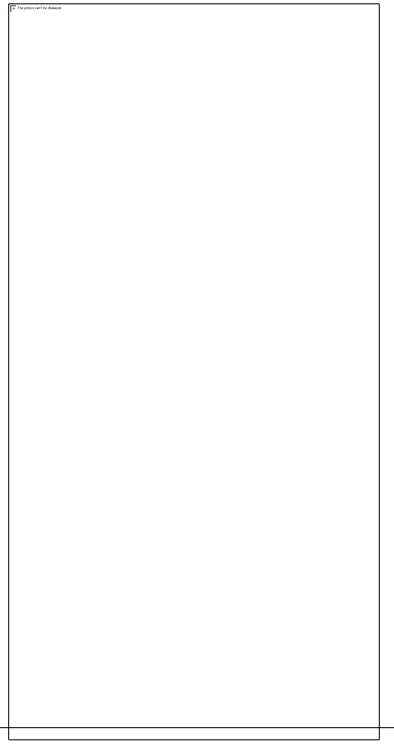
EMG/NCS: myopathic MUAPs, may have axonal sensory neuropathy

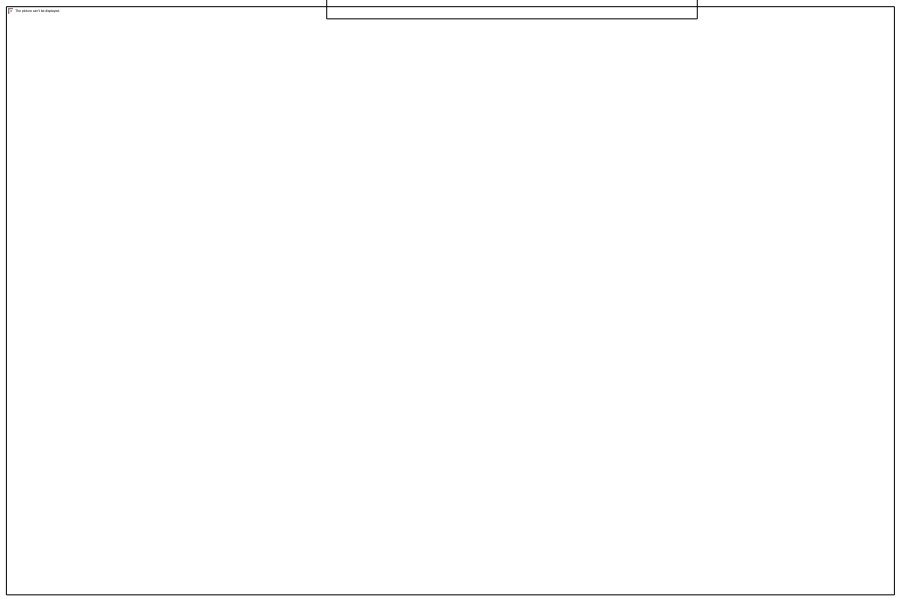
Labs (may only be abnormal during metabolic decompensations):

- *Free carnitine*: slightly low to normal
- *Acylcarnitine profile (serum)*: elevated short-, medium-, and long-chain acylcarnitines
- *Urine organic acids*: normal to elevations in medium-chain dicarboxylic acids, glutaric aciduria

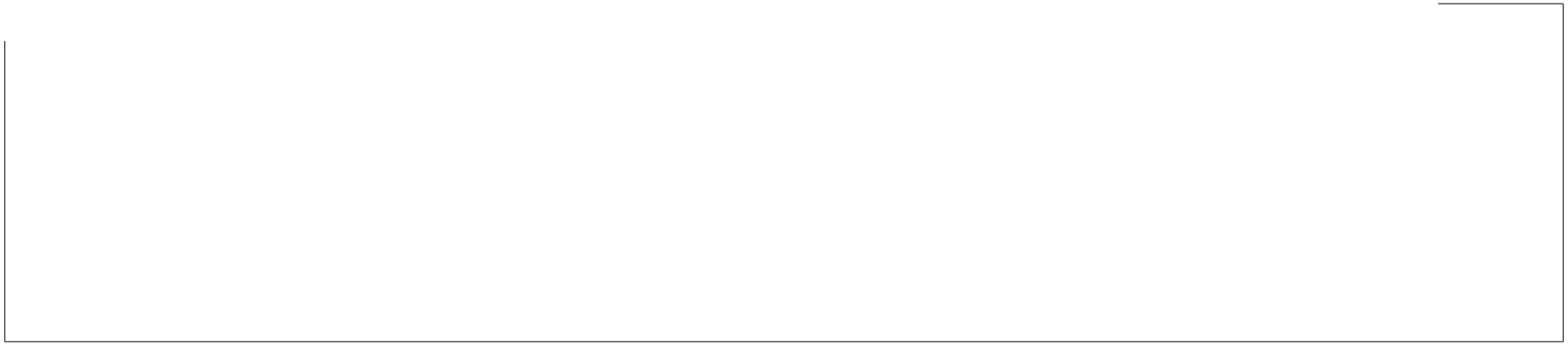
Genetics (Auto. rec.): ETFA/B (7%), ETFDH (93%)

Treatment: Riboflavin 100-400 mg daily +/- CoQ10 50-100 mg daily +/- Carnitine 2-4 g daily





Evolution of Idiopathic Inflammatory Myopathies



Greenberg. IBM Clinical features and pathogenesis. 2019.

Disorder	Age of Onset	Gender	Pattern of weakness	Serum CK	Antibodies	Associated symptoms	Associated conditions
Dermatomyositis	Childhood and adulthood (typically <50)	Female	Proximal > distal (or amyopathic)	1-50x of normal (aldolase)	Anti-Mi2, TIF1, NXP2, several others	Rashes, dysphagia, calcinosis	ILD, malignancy, vasculitis, CTD
Polymyositis	Adults (typically <50)	Female	Proximal > distal	Elevated ~5x of normal	ANA	Dysphagia	ILD, malignancy, vasculitis, CTD
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Autoimmune Necrotizing Myopathy	Adult and elderly	Equal	Proximal > distal	> 10x of normal	Anti-HMG CoA reductase (HMGCR) Anti-SRP	Dysphagia	Malignancy, statins

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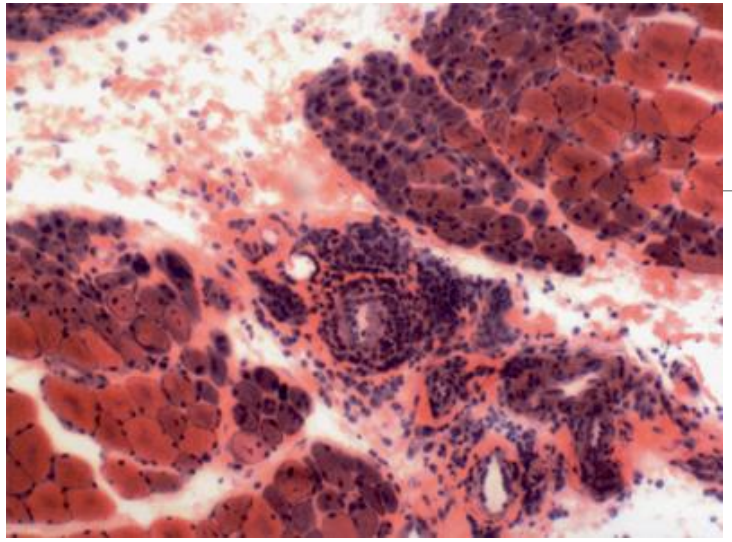
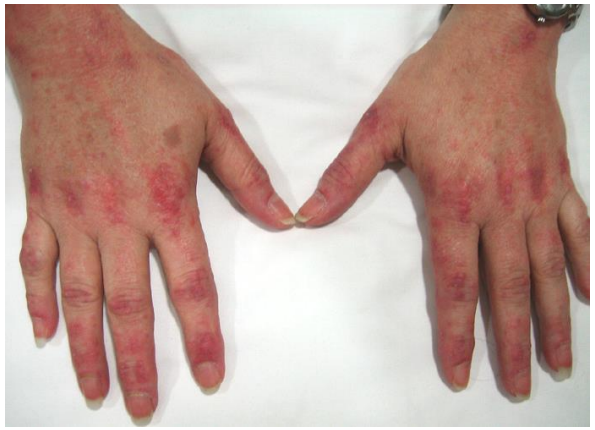
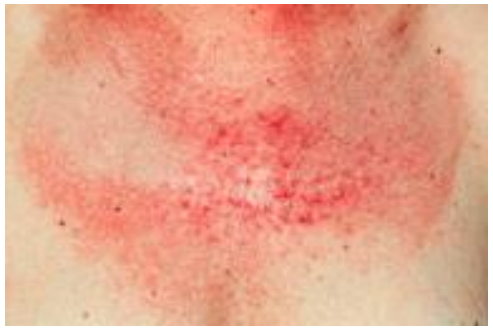
Lundberg et al. 2021

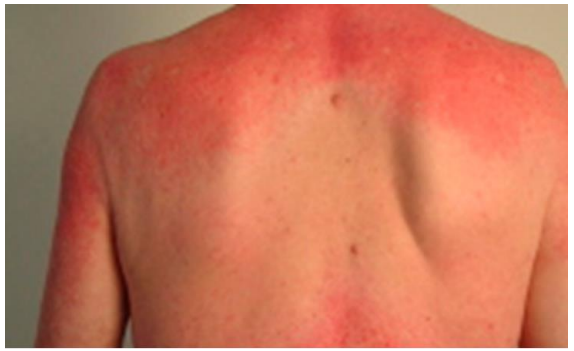


Dermato +/- myositis

- Muscle weakness acutely or insidiously
  - Proximal muscles and neck flexors involved early
  - Dysphagia in 30%
- Rash precedes or accompanies weakness
  - *DM sine dermatitis: rash presents years (or not at all) after weakness – misdiagnosed as PM*
  - *DM sine myositis* (amyopathic) – anti-MDA5
- Multisystem involvement
  - ILD
  - Arthralgias
  - Malignancy (6-45%) in M=F >40 within 3 years of dx, TIF1/NXP2
- Myositis specific antibodies in 60%
- *CK can be normal in <10% of patients, doesn't always correlate with weakness*
- EMG: non-specific, irritable myopathy (useful for flare)

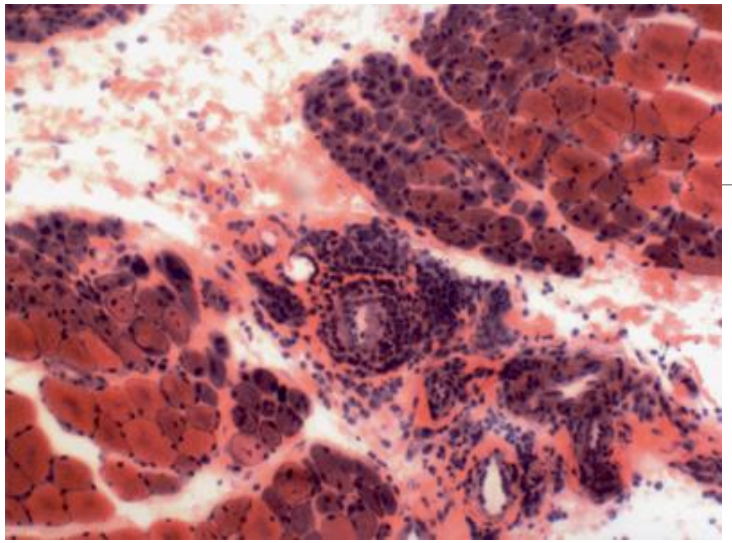






Dermatomyositis Rashes

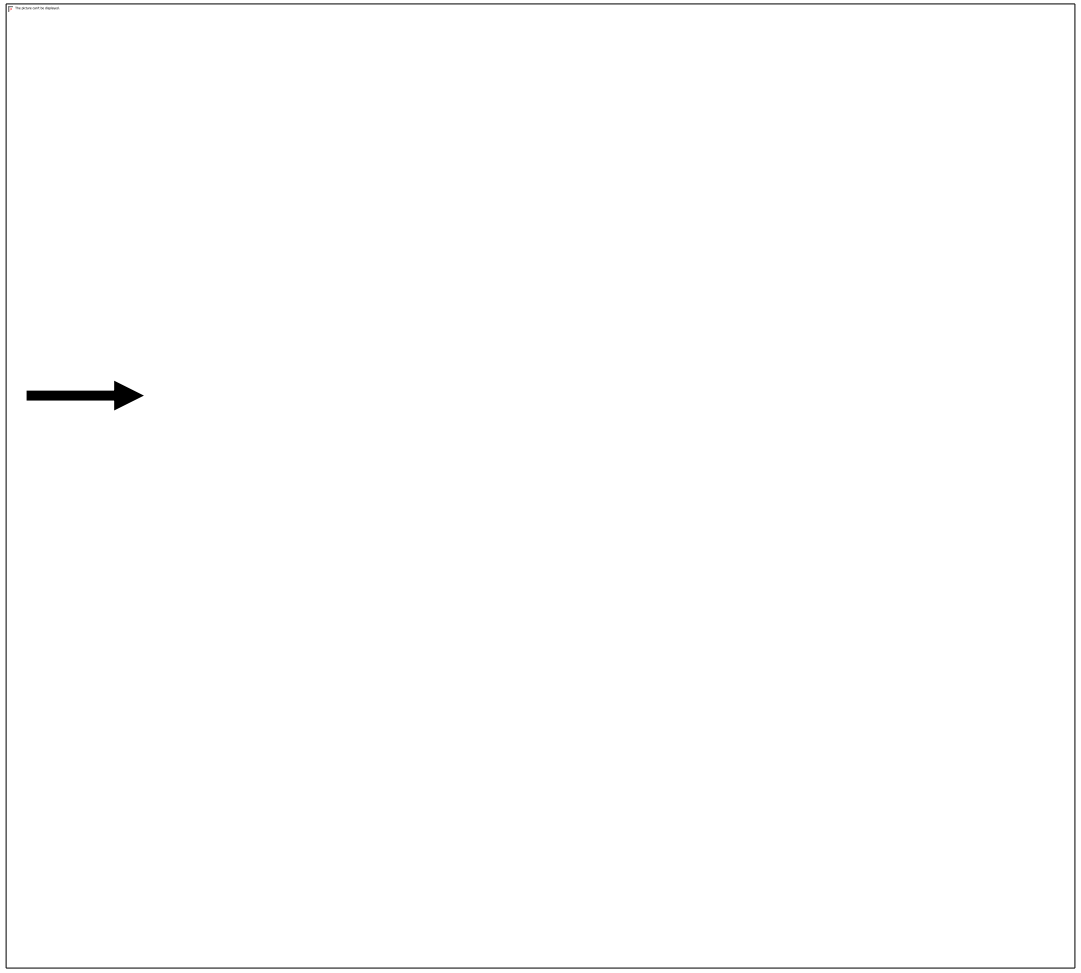
Amato and Russell. 2016.

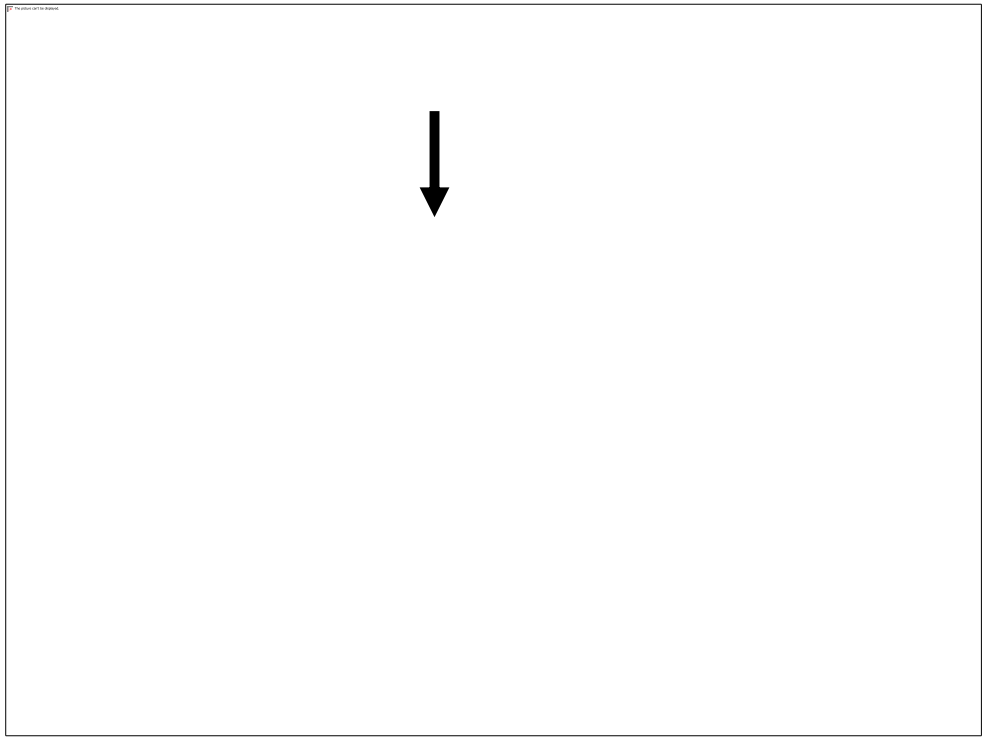


Dermatomyositis

- Perifascicular atrophy of muscle fibers and perivascular inflammation within the perimysium (H&E)
- C5b-9 complement membrane attack complex (MAC) deposited around small blood vessels (immunoperoxidase stain)
  - *One of the earliest changes in DM*
  - Precedes inflammatory cell infiltration and structural abnormalities
  - Microinfarcts
- *Mechanism*
  - *Type 1 IFN signaling from IFN-β leading to type-1 INF-inducible proteins (MxA) and cellular injury*
  - *Autoantibodies targeting endothelium/capillaries leading to ischemia and myofiber injury*

Amato and Russell. 2016.



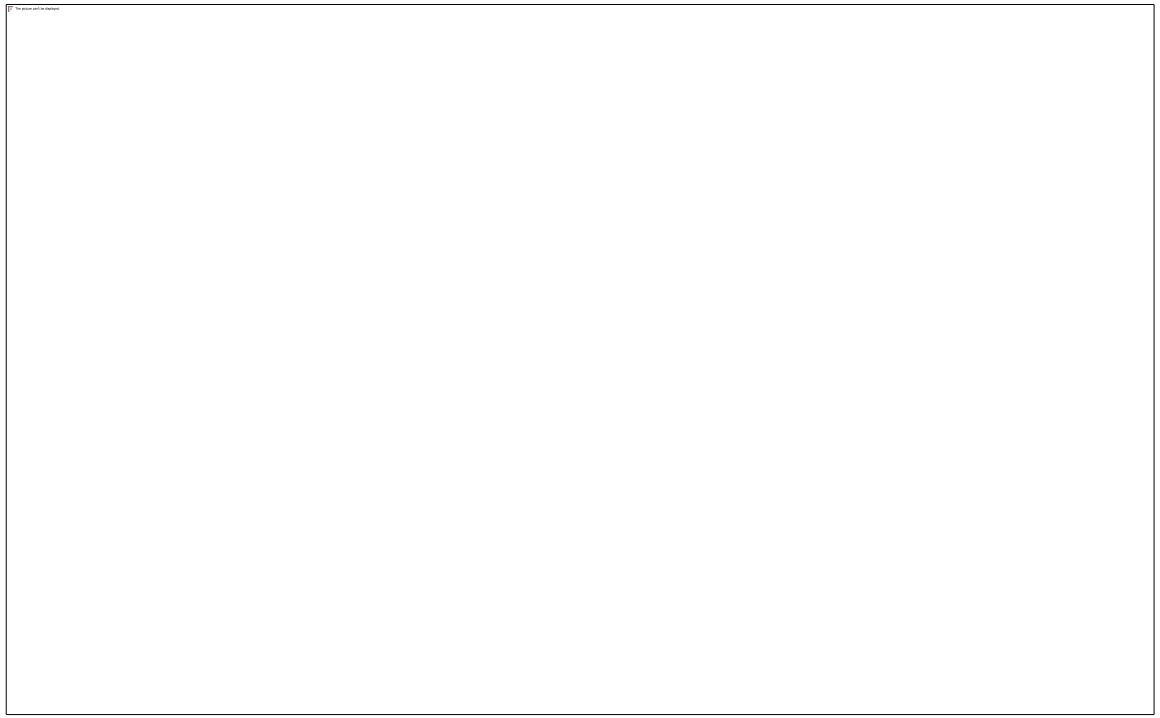


Antisynthetase syndrome

- Homogenous, multisystem disease with 8 tRNA synthetase antibodies
  - Myopathy can be underwhelming
  - Acute onset is typical
- ILD is the most frequent manifestation
  - PL-7 and PL-12 higher rate of ILD and mortality relative to Jo-1
- Dermatologic findings
  - Mechanic's hands
  - Raynaud phenomenon
- Arthralgias
- Decreased risk of malignancies

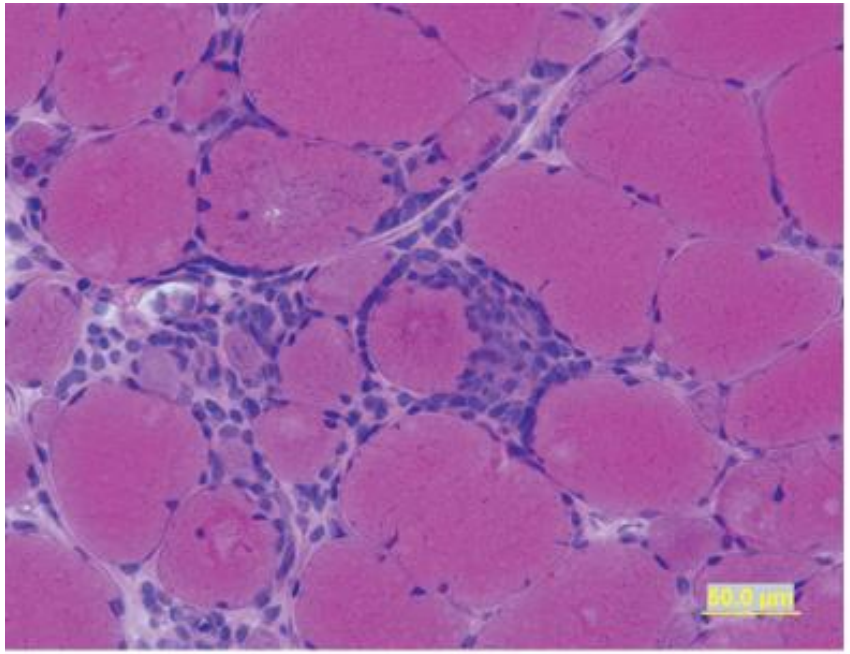
Amato and Russell. 2016.

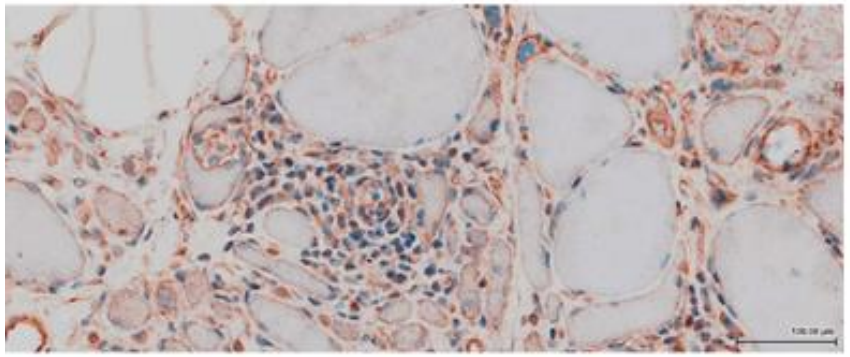
Antisynthetase syndrome



- Perifascicular necrosis of muscle fibers (80% vs 35% in DM), perifascicular atrophy, perimysial fragmentation and endomysial inflammation (H&E)
- Clonally expanded T cells

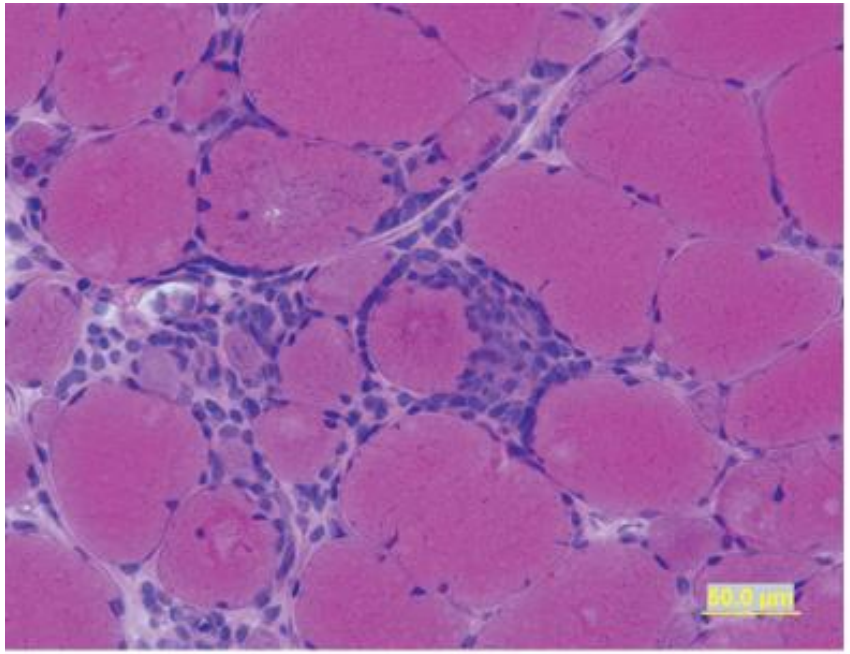
Lundberg et al. 2021.

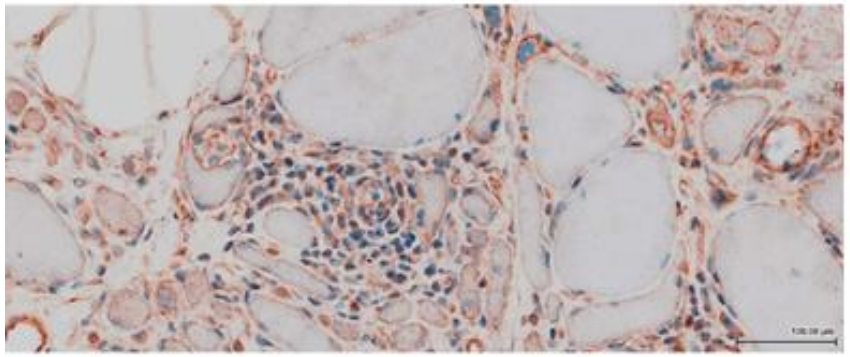




Polymyositis

- Symmetric muscle weakness over weeks to months
  - Proximal > distal muscles >> myalgias
  - Mild facial weakness
  - Dysphagia in ~30%
- Multisystem involvement
  - ILD
  - Arthralgias
  - Lower risk of malignancy compared to DM
- *CK always elevated, ESR is typically normal*, ANA positive in up to 40%
- *Diagnosis of exclusion*
- *Vanishing subset of IIM*

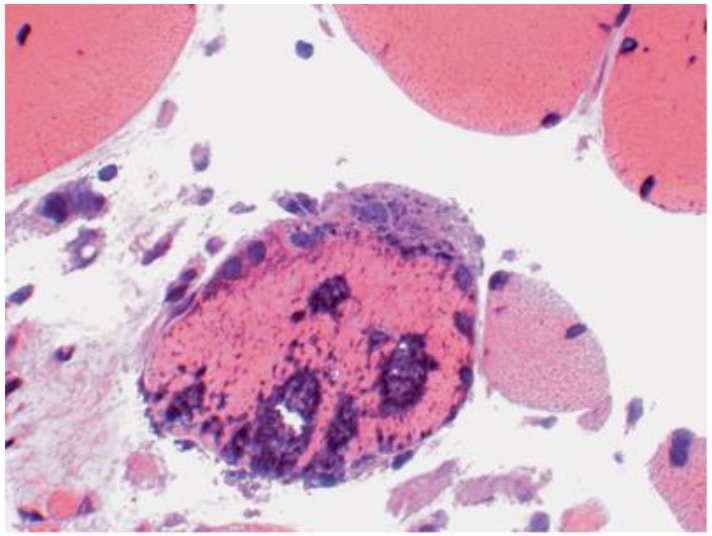


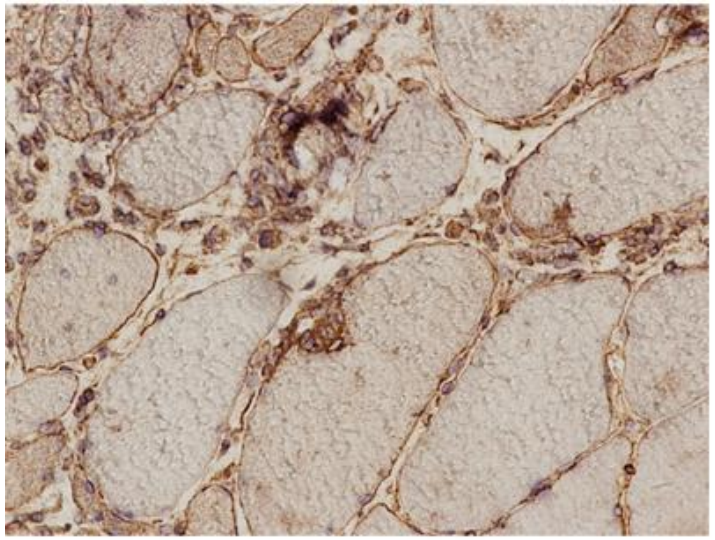


Polymyositis

- Endomysial mononuclear inflammatory cell infiltrate(CD8+ T cells) surrounding and invading non-necrotic muscle fibers (H&E)
- Perivascular and endomysial inflammatory cells surrounding non-necrotic muscle fibers expressing MHC1 on the sarcolemma (immunoperoxidase stain)
  - Not diagnostic and can be seen in IBM and rarely dystrophies
    - *Combination of MHC/CD8 complex can exclude non-immune mediated inflammation (muscular dystrophies)*
  - No MAC, complement deposition on microvasculature

Amato and Russell. 2016.

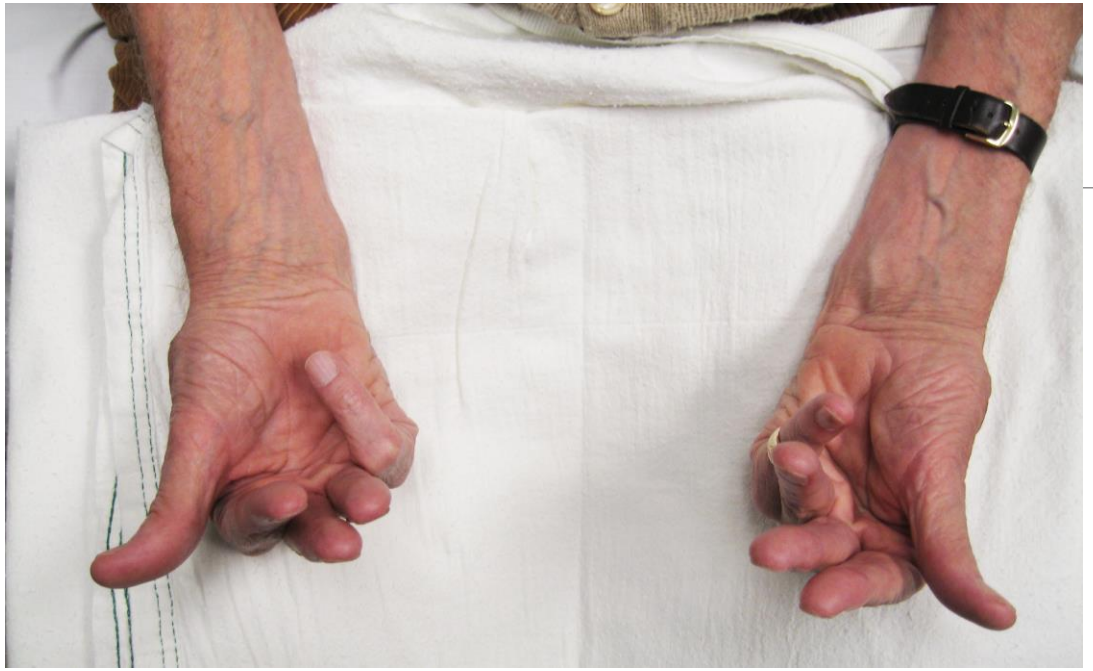




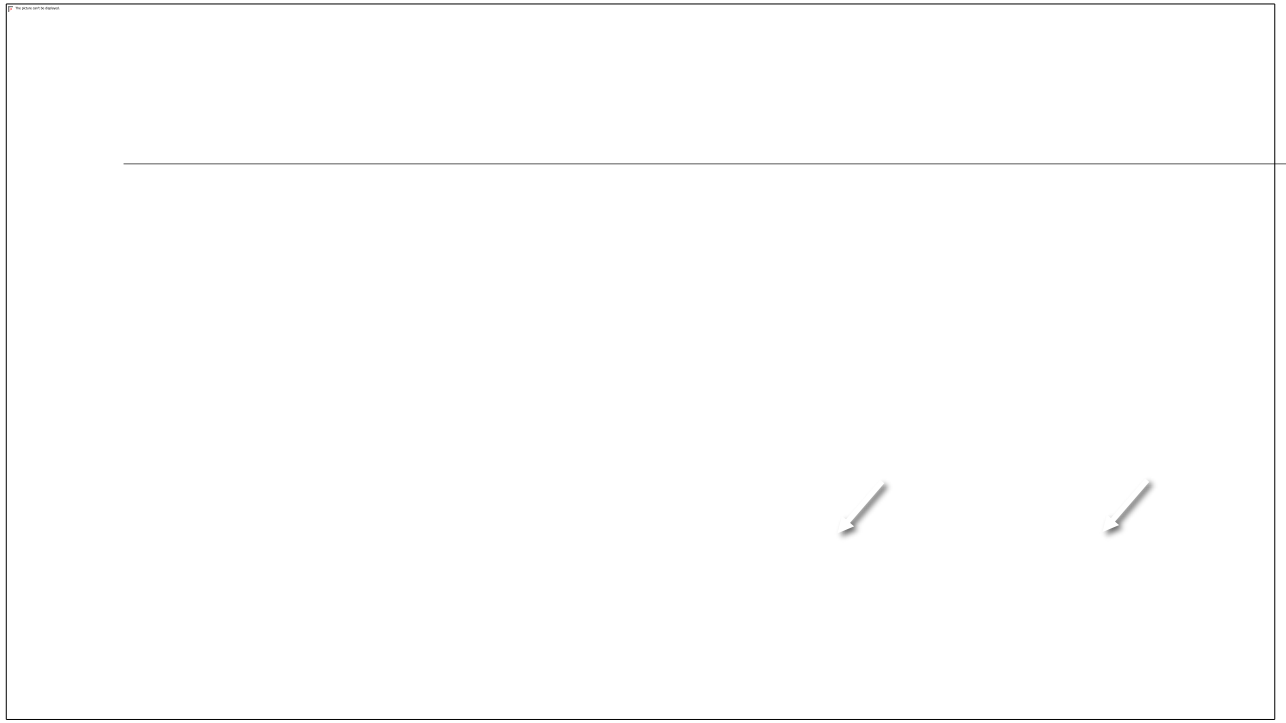
Inclusion Body Myositis

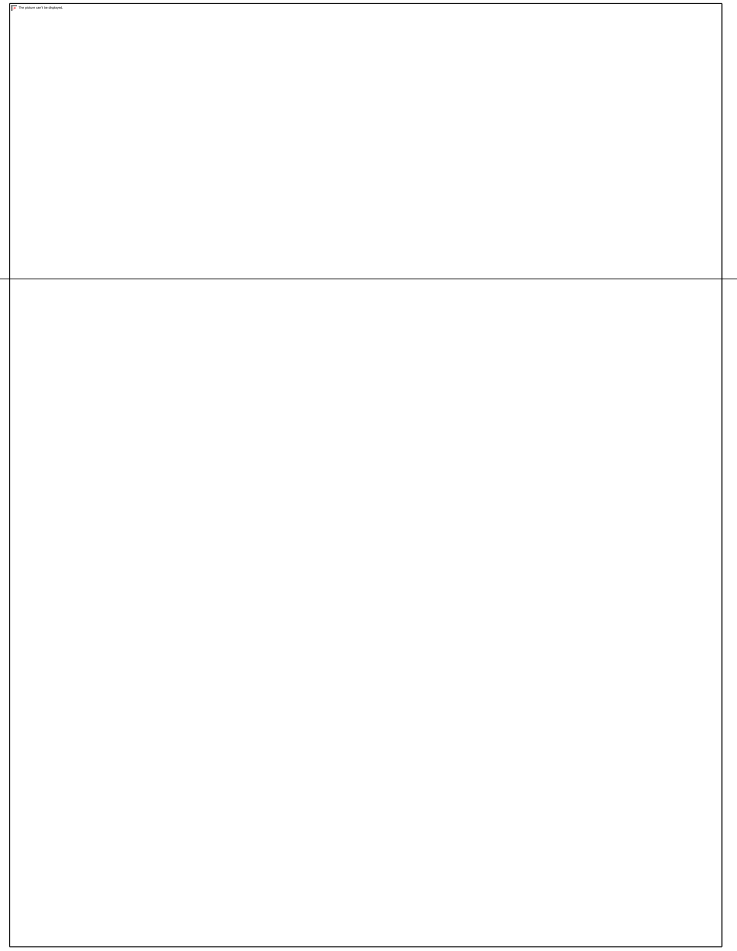
- Most common myopathy >50 year-old patients
- Insidious asymmetric muscle weakness (proximal and distal)
  - *Quadriceps, wrist/finger flexors*, ankle dorsiflexors
  - Neck flexor weakness, dysphagia in 60% (sometimes presenting symptom), and facial weakness in 30%
- Misdiagnosis
  - PM, ALS, granulomatous myopathy
- ~15% have underlying AI condition: Sjogren's, SLE, scleroderma, sarcoid
- 37-47% wheelchair bound after 12 years
- Anti-cytoplasmic 5'-nucleotidase 1A (NT5C1A) in ~60% (sens), 90% (spec)
- EMG with neurogenic and myopathic units

Amato and Russell. 2016.

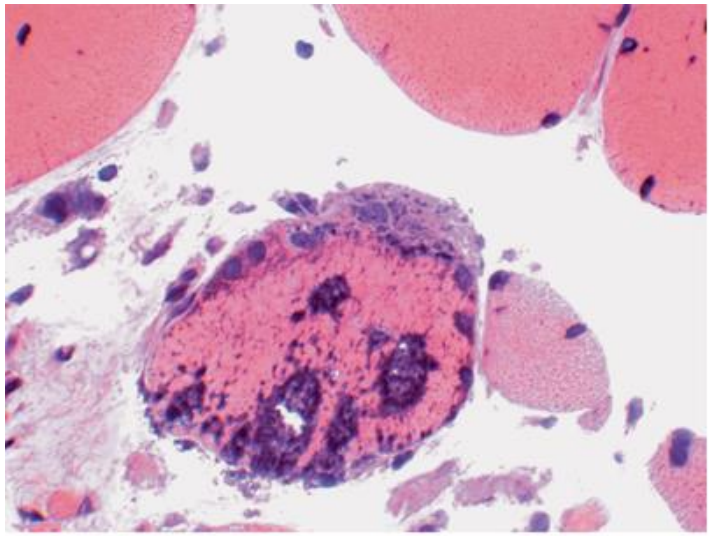


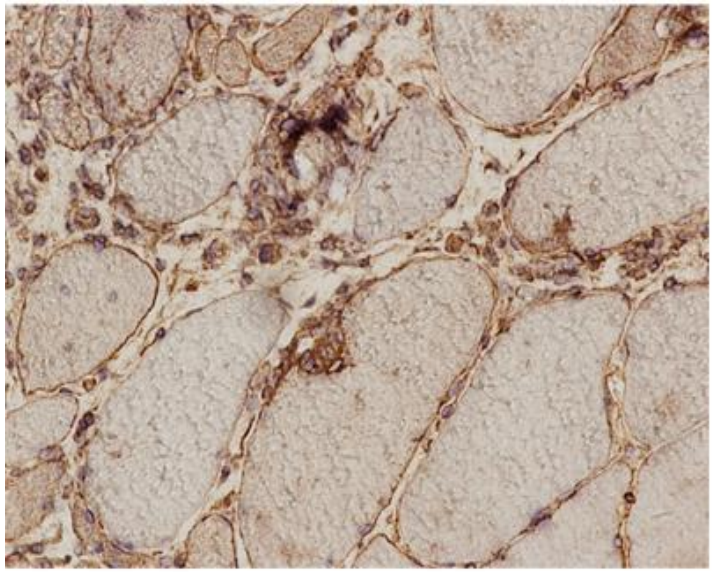
Attempted finger flexion





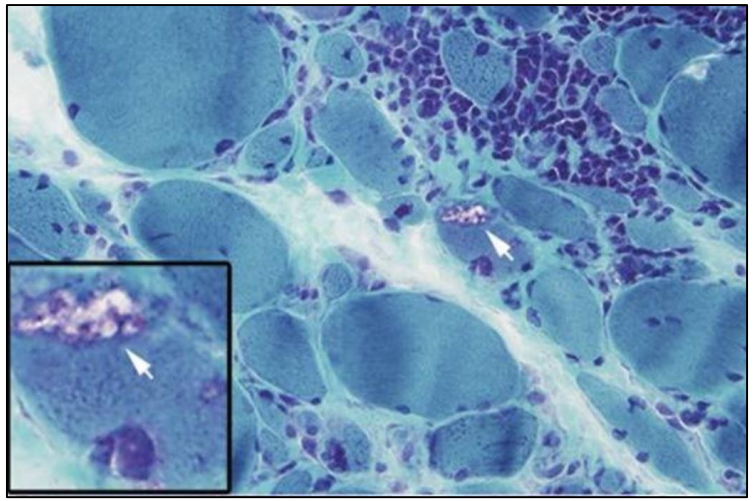
Quadriceps weakness

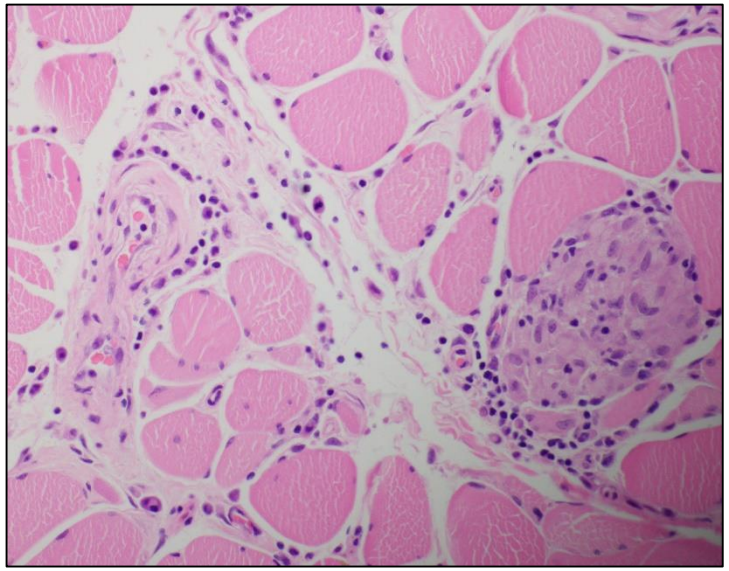




Inclusion Body Myositis

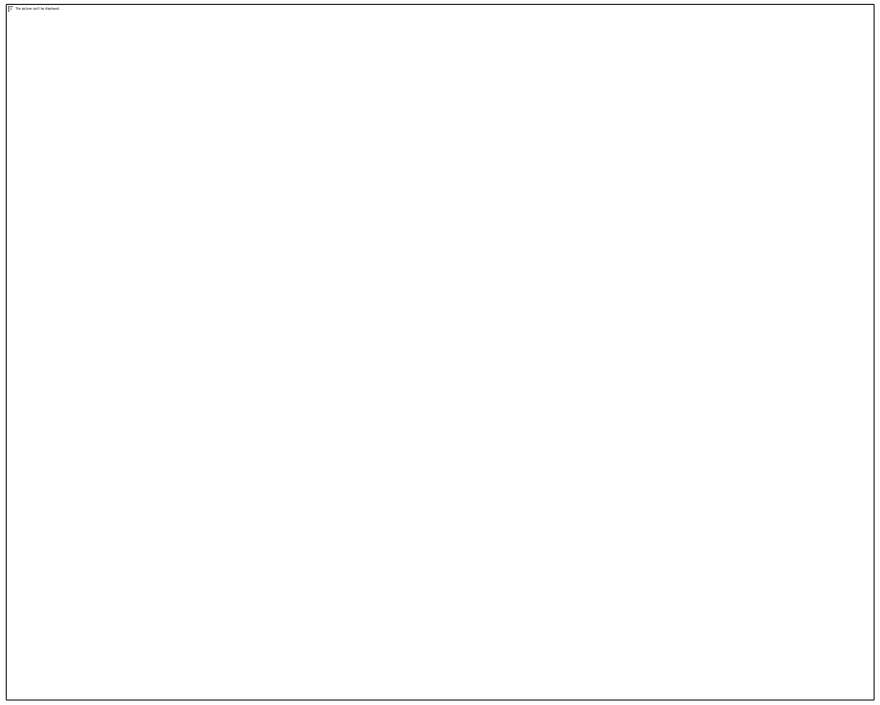
- Muscle fiber with rimmed vacuoles, granulomas (H&E)
- Endomysial lymphocytic (CD8+ T cells) infiltration surrounding and invading non-necrotic muscle fibers that express major histocompatibility antigen type 1 (MHC1) on the sarcolemma
- Mitochondrial abnormalities ($COX^{-}SDH^{+}$) and ragged-red fibers
- Protein aggregates (TDP43, p62, amyloid)
- T-LGLL (CD-57+) infiltrates





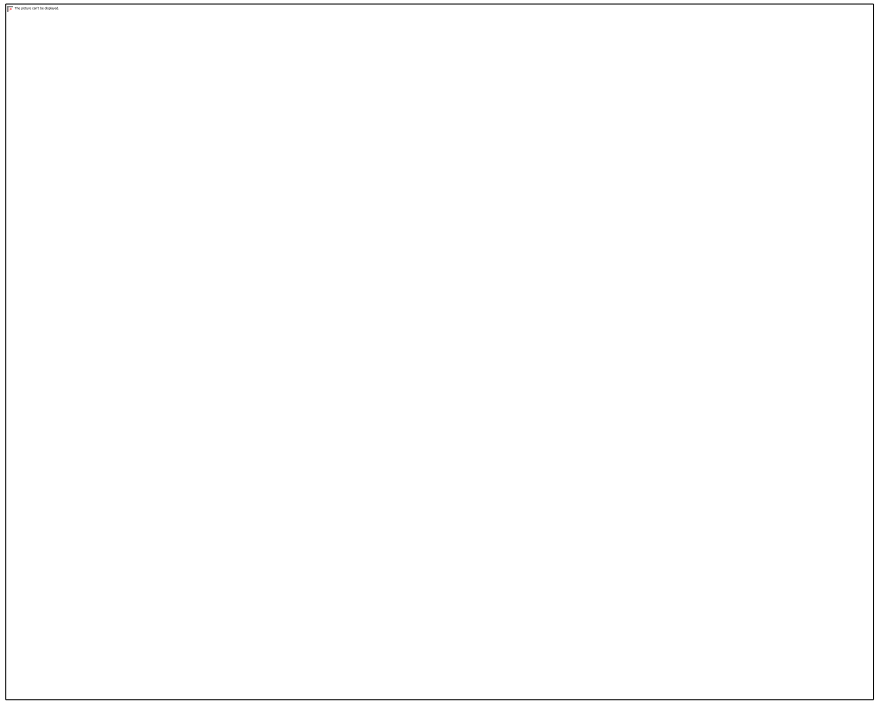
Beck. 2014. Amato and Russell. 2016.

Necrotizing Autoimmune Myopathy



- Accounts for ~20% of autoimmune myopathies
- Acute or insidious proximal weakness
  - Progression can include facial muscles, and axial and distal weakness
  - Scapular winging
- HMGCR and SRP antibodies
  - HMGCR more responsive (IVIG), associated with statin exposure
  - SRP typically resistant to treatment
    - Cardiac involvement
    - Dysphagia
  - Can mimic LGMD
- Antibody negative cases (20%)
- Associated with malignancy

Necrotizing Autoimmune Myopathy



- Scattered necrotic fibers undergoing myophagocytosis and regeneration with paucilymphocytic infiltration (H&E)
- Diffuse MAC and MHC1 (HMGCR > SRP)

Pinal-Fernandez. 2018

Practice points

DIAGNOSIS

Characteristic rashes +/- proximal weakness

Statin?

CK (+ aldolase), EMG

Myositis antibody panel

Muscle (+/- skin) biopsy

Exception: IBM (knee buckles – falls, can't make a fist)

CAN'T MISS

1. Malignancy screening (NXP2, TIF1, ab neg IMNM, refractory cases): breast, testicular, ovarian cancers; CT C/A/P up to 5 years post-DM diagnosis; decreased risk with ILD
2. ILD (RP-ILD in MDA5) + ASyS
3. Myocarditis in SRP
4. Dysphagia
5. IBM (no Rx)
6. Mimics*

Myositis mimics and myopathy pitfalls

CAUTION

Proximal weakness – LGMD, congenital, metabolic, endocrine, toxic myopathies; NMJ d/o; neurogenic d/o

'Weakness' – pain-limited (ie PMR)

CK – acute denervation (ie ALS), can be normal

Aldolase – liver injury

ESR/CRP – often normal (except ESR w/ myositis-ILD)

EMG – process not diagnosis, operator dependent

Inflammatory infiltrates/MHC I – dystrophies, rhabdomyolysis biopsy, EMG artifact, missing a specific stain

MRI muscle read as 'myositis' – denervation, metabolic/genetic myopathies

Flares – metabolic myopathies, NMJ d/o

CAUTION

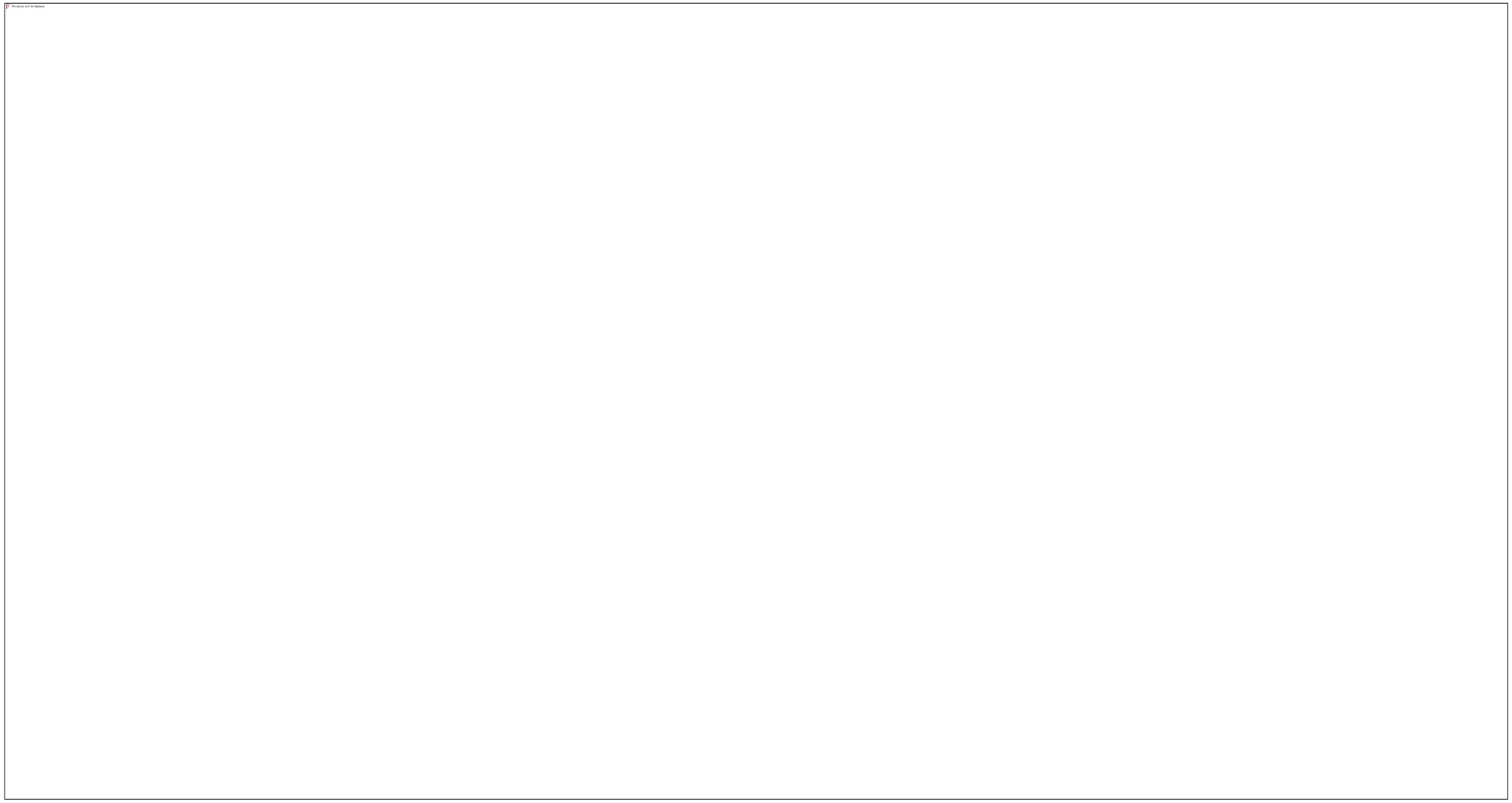
Genetic testing – missing trinucleotide repeats, deep intronic regions, small CNV, complex genetics (FSHD 1, OPMD, DM 1 and 2, mitochondrial myopathies), WES/WGS without family

Exercise test – poor effort or deconditioning

Myositis panel – missing HMGCR and/or NT5C1A, false positive results

Metabolic - Serum carnitine, serum acylcarnitine profile, and urine organic acids fluctuate based on clinical presentation

Infections – difficult to prove



Lundberg et al. 2021.

Practice points

TREATMENT

Prednisone 60 mg x 6 weeks with a slow taper over the next 6-12 months

Concurrent non-steroidal (e.g. MMF, AZA, MTX)

Topical steroids +/- tacrolimus

Follow skin, strength, CK, PFTs

Not responding or severe disease? Malignancy?

- IVIG, Rituximab, Cyclophosphamide

Muscle to recover?

- Muscle MRI, steroid myopathy, trend exam and CK

ADDITIONAL CARE

1. DEXA + Vit D + Ca^{2+}
2. PT, OT
3. SLP
4. Social work
5. Support group
6. Caregiver support
7. Infection risk and immunizations
8. Research studies
9. Exercise

Summary Practice points

DIAGNOSIS AND TREATMENT

Characteristic rashes +/- proximal weakness

CK (+ aldolase), EMG, myositis antibodies, biopsy

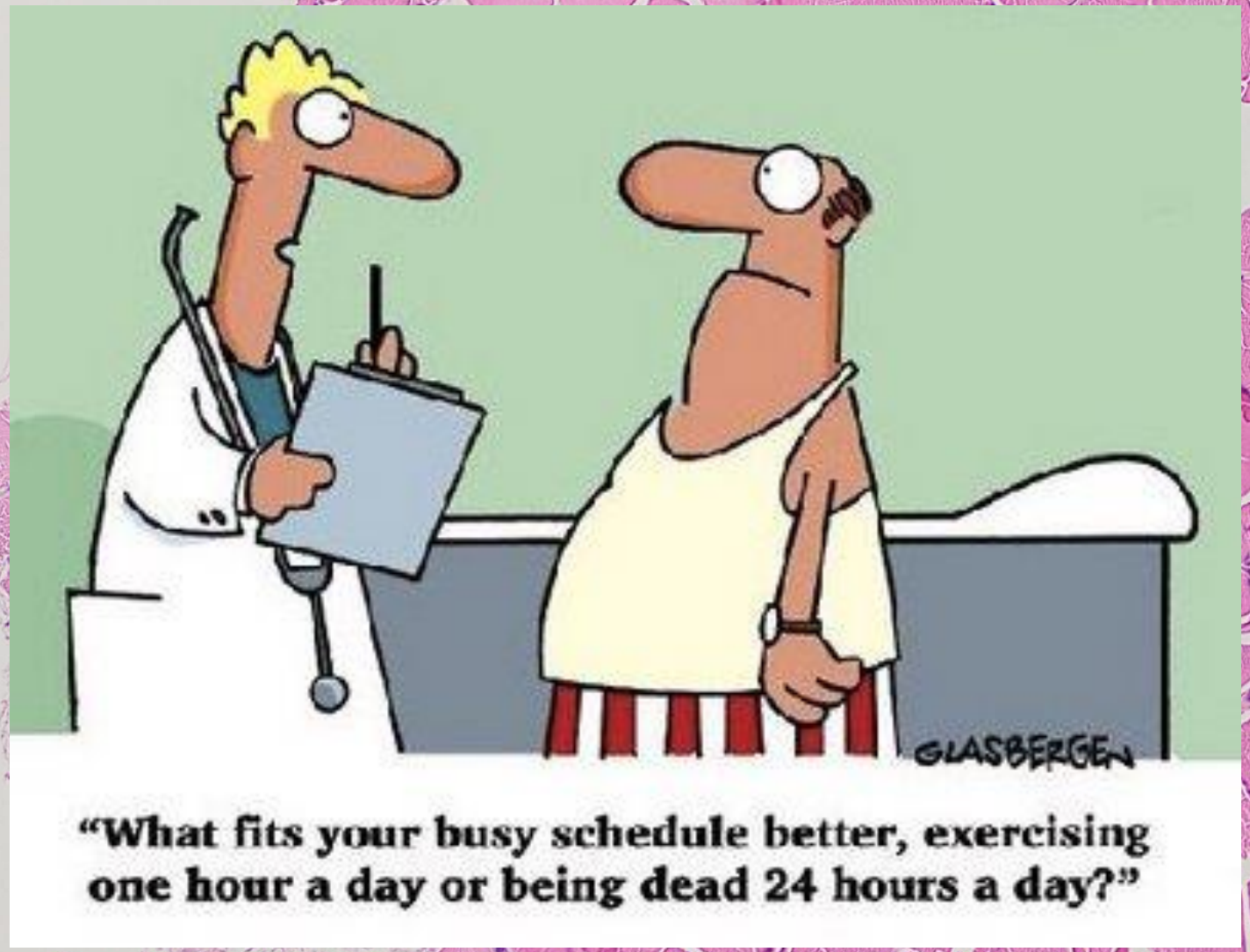
Steroids with slow taper + non-steroidal (AZA, MTX, MMF) +/- IVIG, Rituximab

Multidisciplinary team

Novel agents in the pipeline

CAN'T MISS

1. Malignancy screening (NXP2, TIF1, ab neg IMNM, refractory cases)
2. ILD (RP-ILD in MDA5) + ASyS
3. Myocarditis in SRP
4. Dysphagia
5. IBM (no Rx)
6. Mimics



Thank you!

Questions/Comments:

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