The Pathology of Systemic Therapy-Related Neuromuscular Disease

Karra A. Jones, MD, PhD
Clinical Assistant Professor
The University of Iowa
@BrainIsThePath @brain.is.the.path

AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

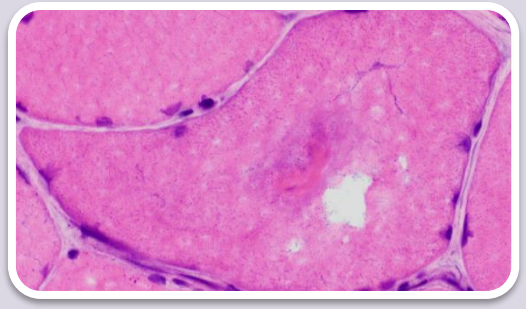
Disclosures

- I have no relevant financial relationships to disclose

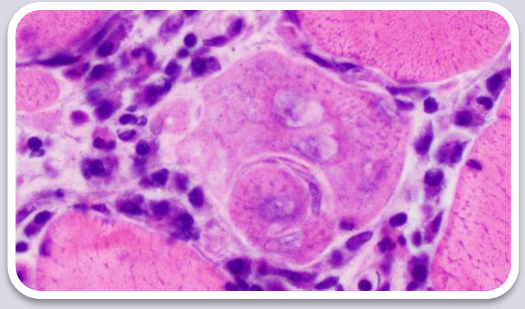
Learning Objectives

- Recognize common histopathologic patterns of systemic therapy-related neuromuscular disease
- Recall common neuromuscular diseases included in the differential diagnosis of toxic myopathies
- Plan an appropriate diagnostic approach for evaluation of toxic myopathies
- Summarize known and proposed mechanisms underlying systemic therapy-related neuromuscular disease

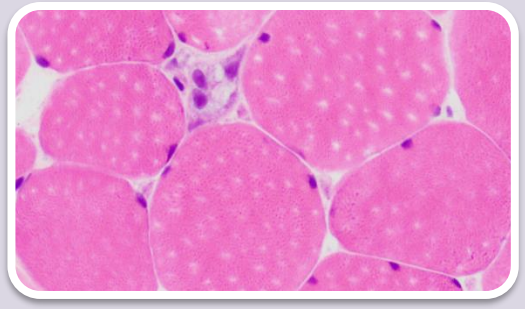
Patterns of systemic therapy-related myopathies



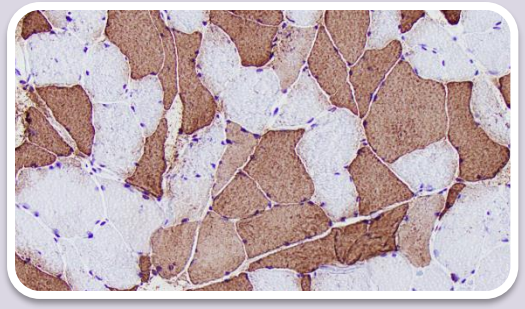
Vacuolar myopathy



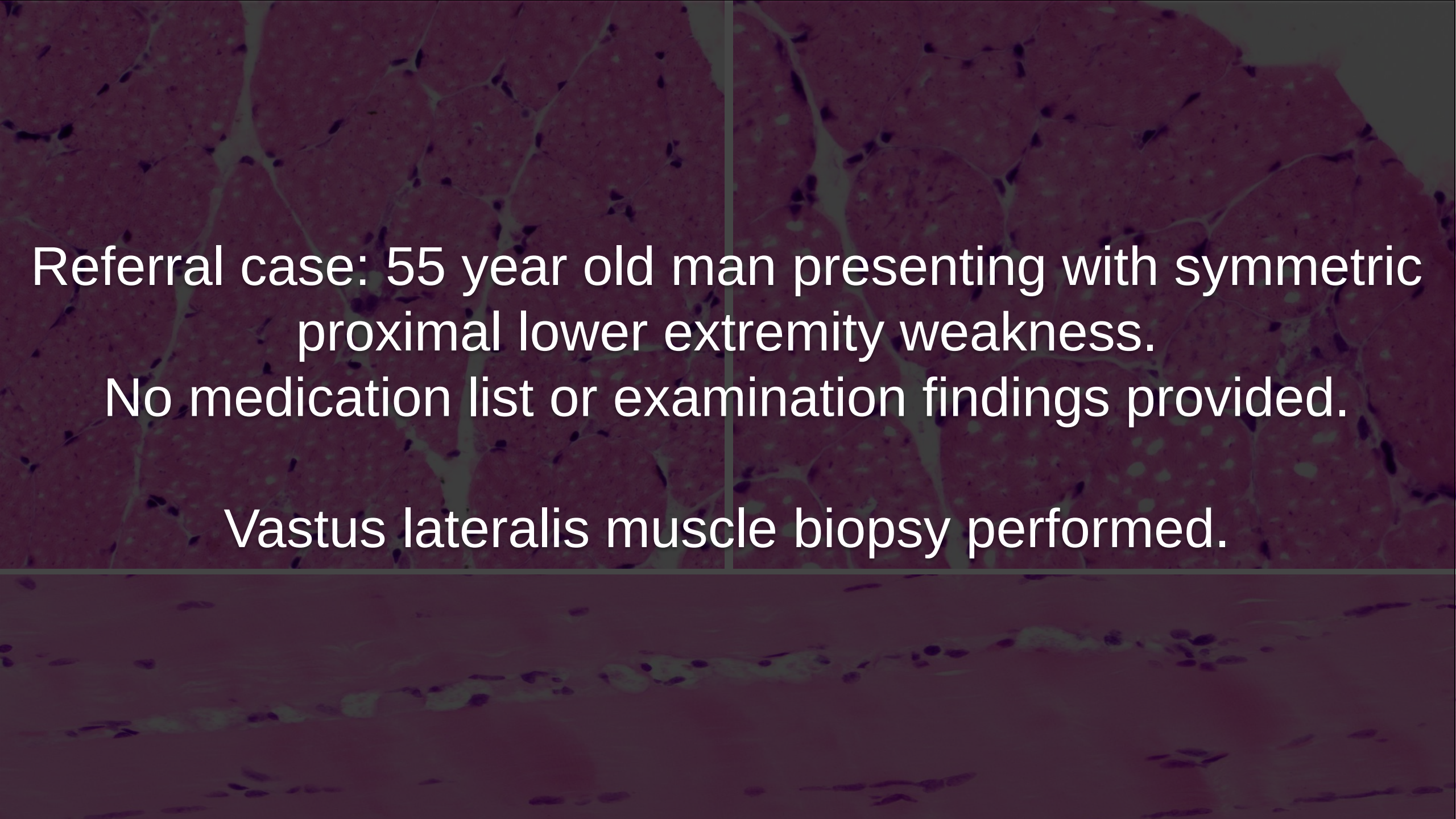
Necrotizing myopathy with inflammation



Necrotizing myopathy without inflammation

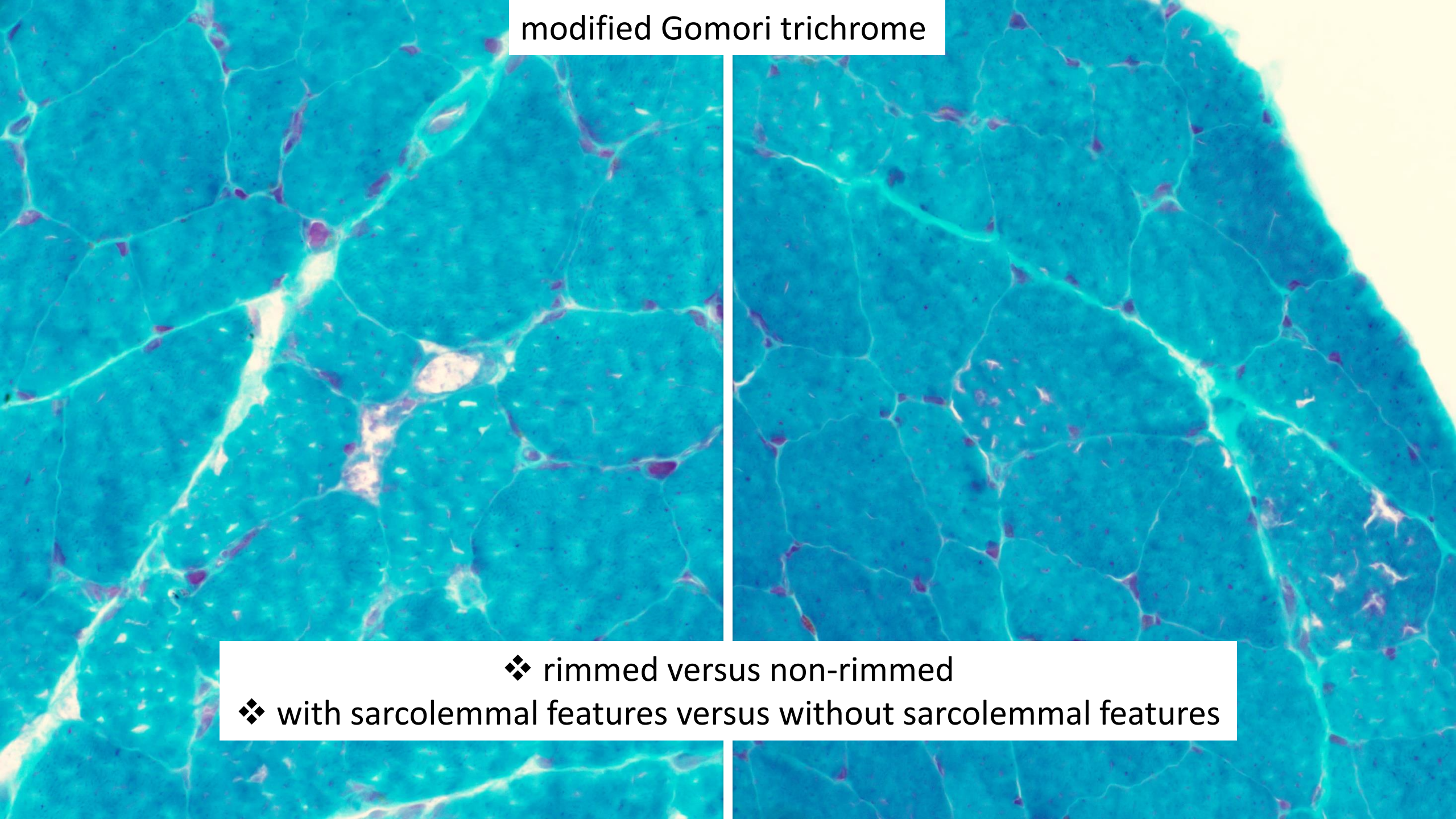


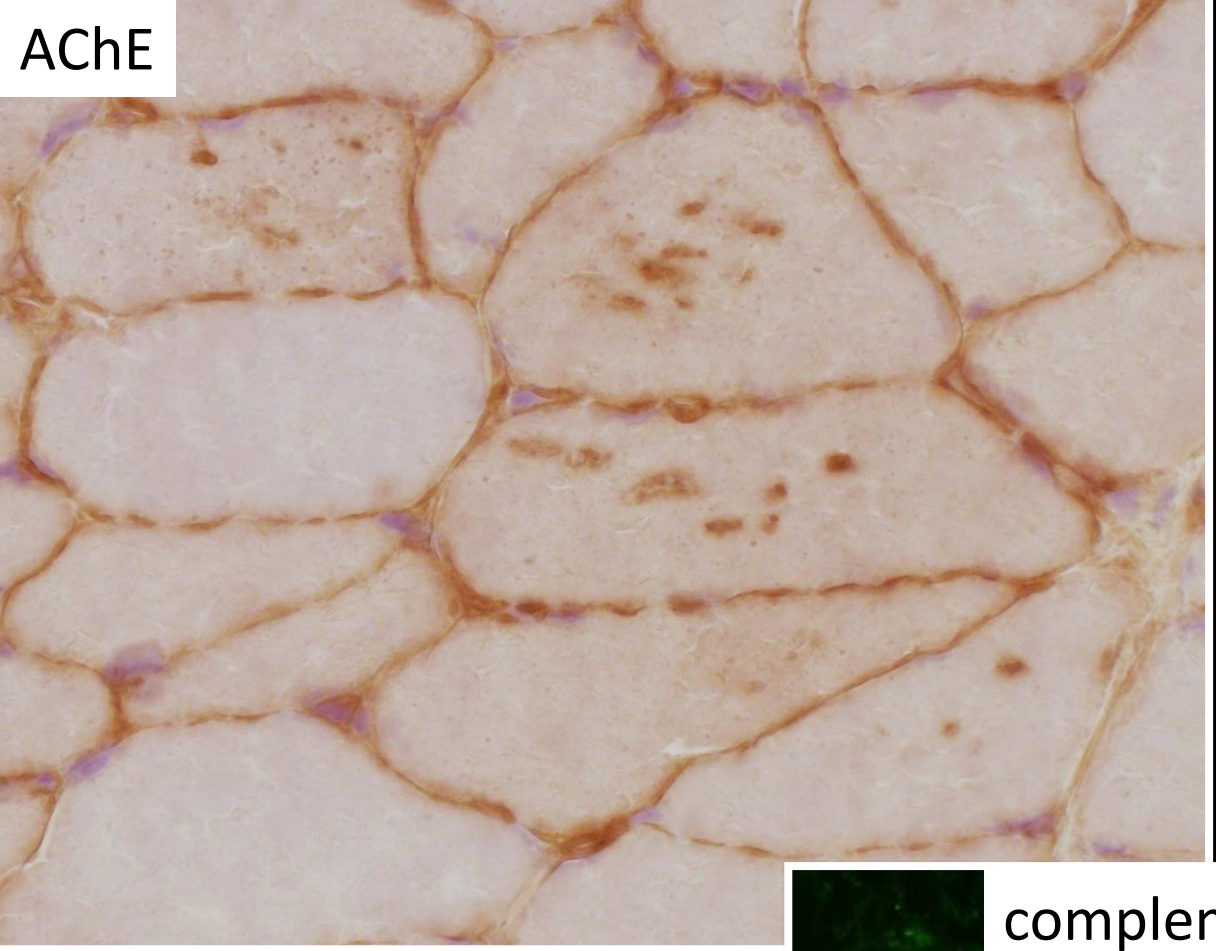
Fiber size variation

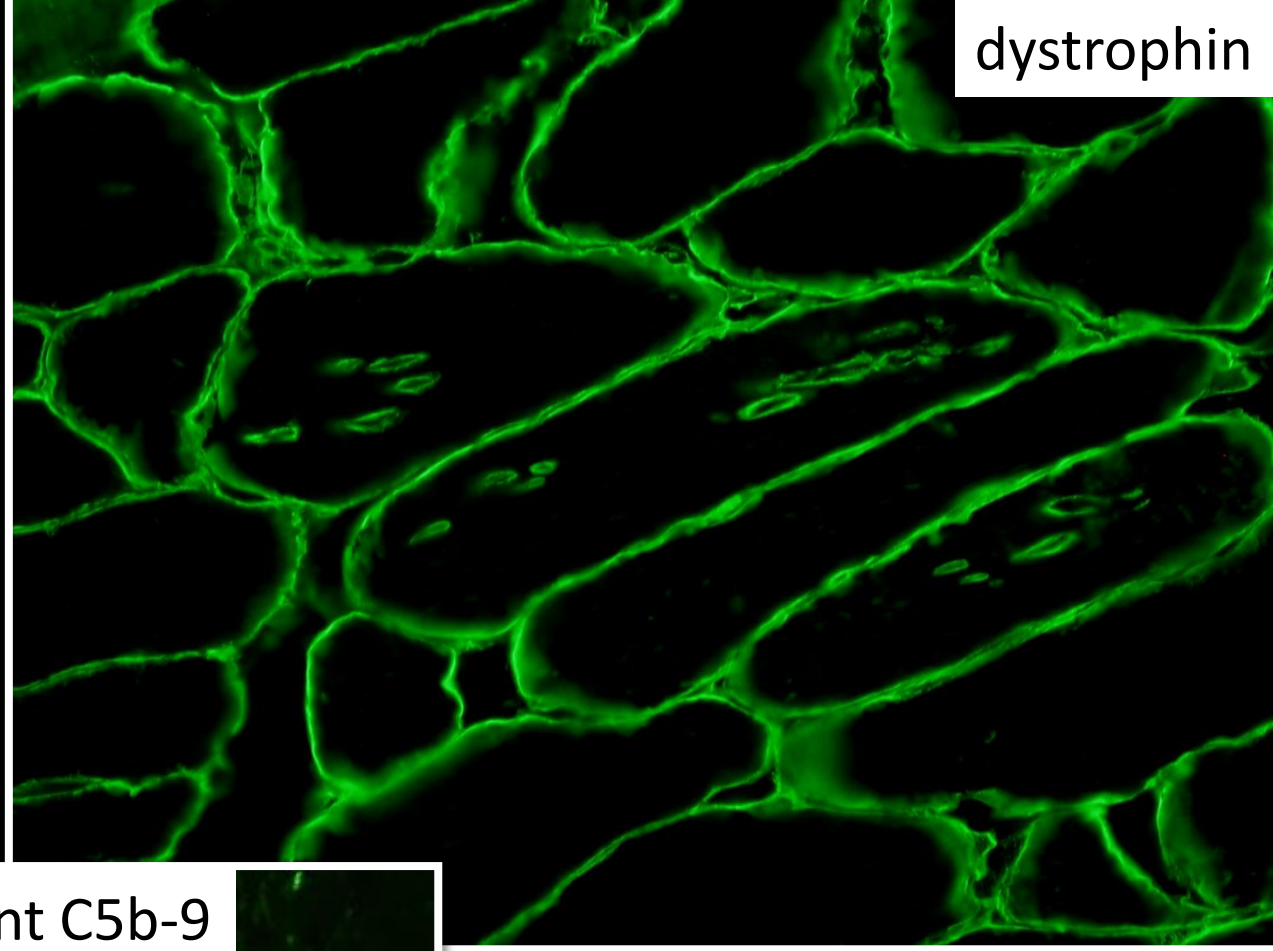


Referral case: 55 year old man presenting with symmetric proximal lower extremity weakness.
No medication list or examination findings provided.

Vastus lateralis muscle biopsy performed.


modified Gomori trichrome
❖ rimmed versus non-rimmed
❖ with sarcolemmal features versus without sarcolemmal features

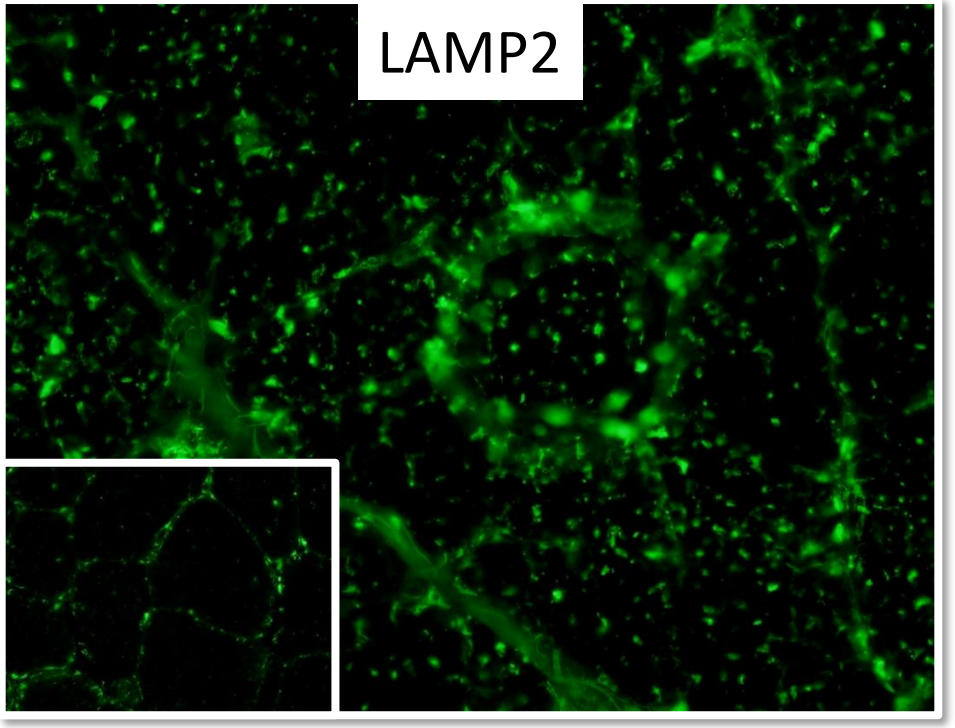




MHC Class I was negative

Differential diagnosis – vacuoles with sarcolemmal features

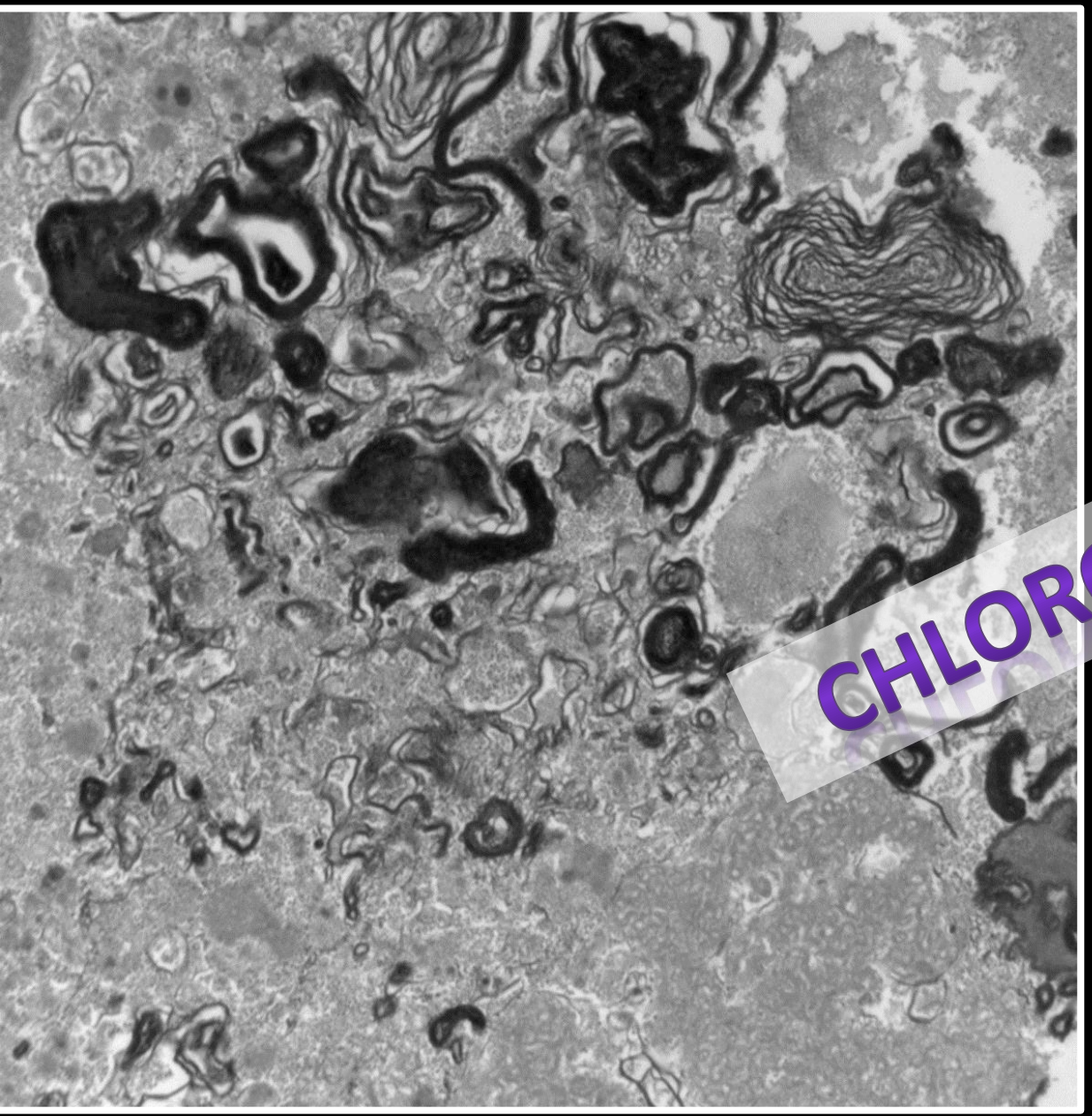
- Inclusion body myositis
- Autophagic vacuolar myopathies
  - Danon disease
  - XMEA
  - Pompe disease (*join us 9 a.m. Friday in Platform 2!*)
- Other inherited myopathies with vacuoles
  - Myofibrillar myopathy
  - Hereditary inclusion body myopathies (e.g. *GNE*, *VCP*)
  - Oculopharyngeal muscular dystrophy
- Drug-induced myopathies
  - Chloroquine/hydroxychloroquine
  - Colchicine

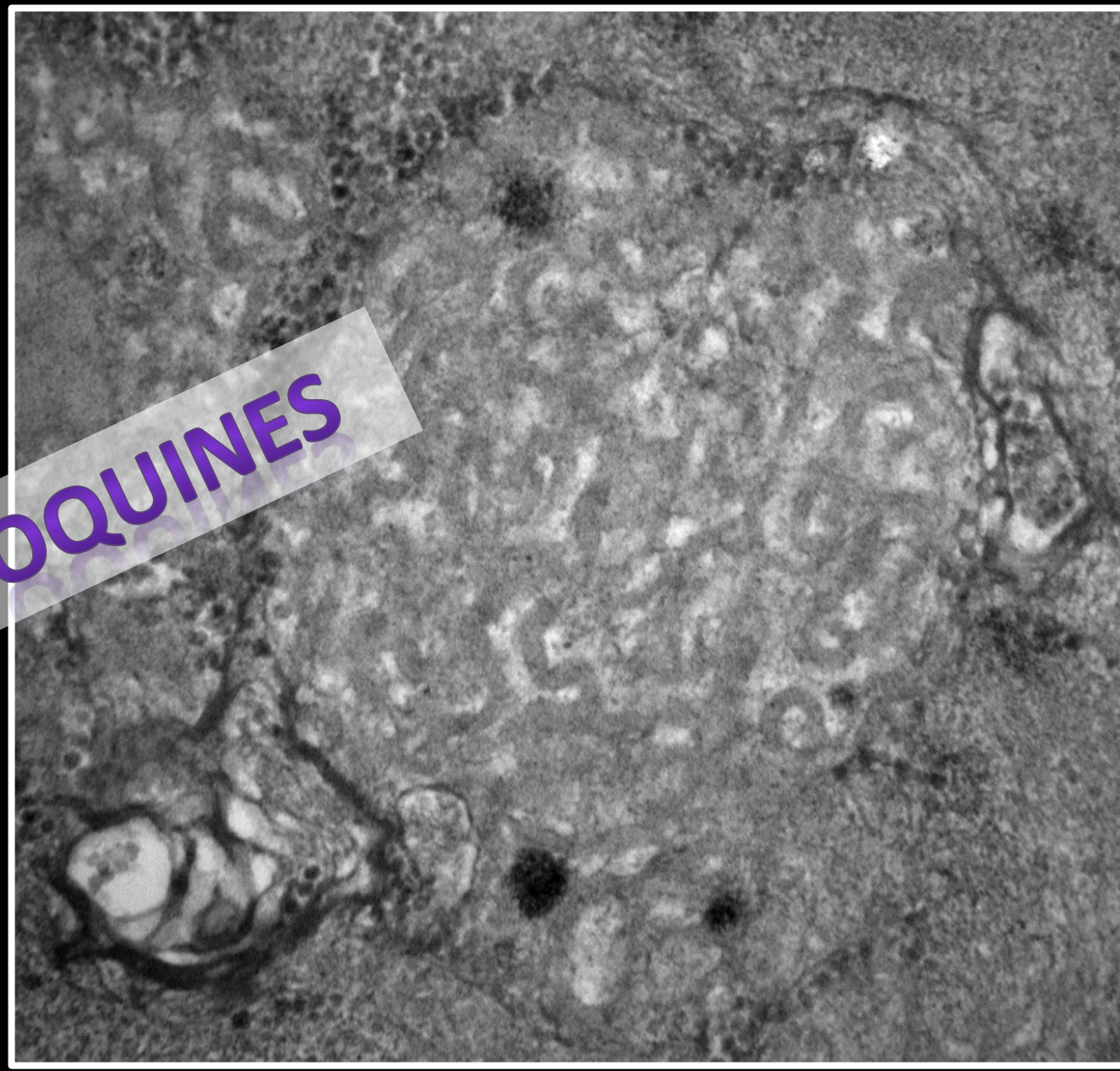


Continue workup? Or long comment?

Myeloid bodies

Curvilinear bodies





CHLOROQUINES

Images courtesy of Steve Moore

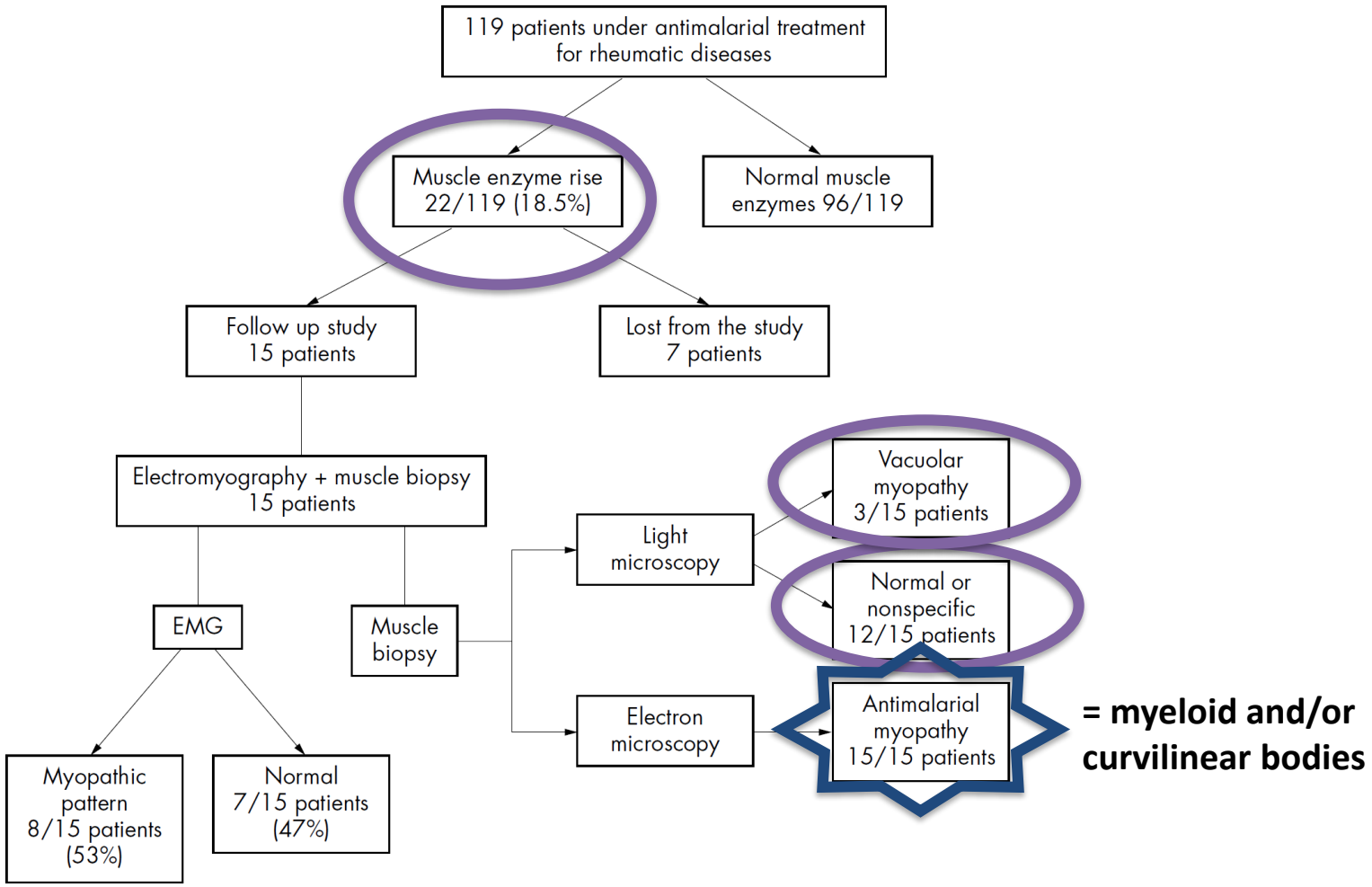
Chloroquines – neuromuscular toxicity

- Low incidence estimated with a prevalence of 9.2% and annual incidence of 1.2% (Casado et al. Ann Rheum Dis. 2006)
- Onset of weakness months to years after starting therapy
  - No relation to dose
- Progressive, symmetrical proximal weakness +/- mild peripheral neuropathy and cardiac myotoxicity
- CK: normal or mildly - moderately elevated
- EMG/NCS: myopathic changes with fibrillation potentials and myotonic discharges +/- sensorimotor polyneuropathy
- Effects are slowly reversible following discontinuation of Rx

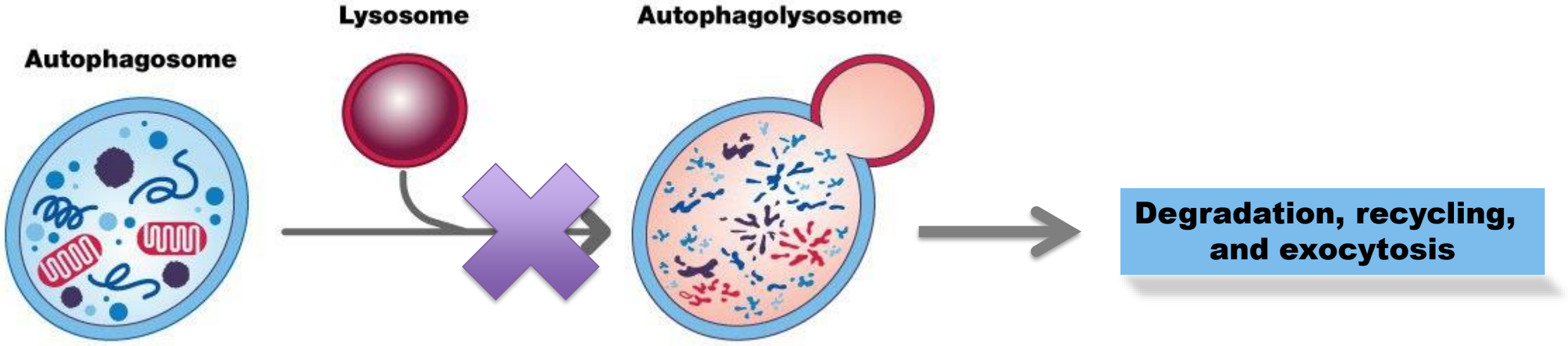
Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients

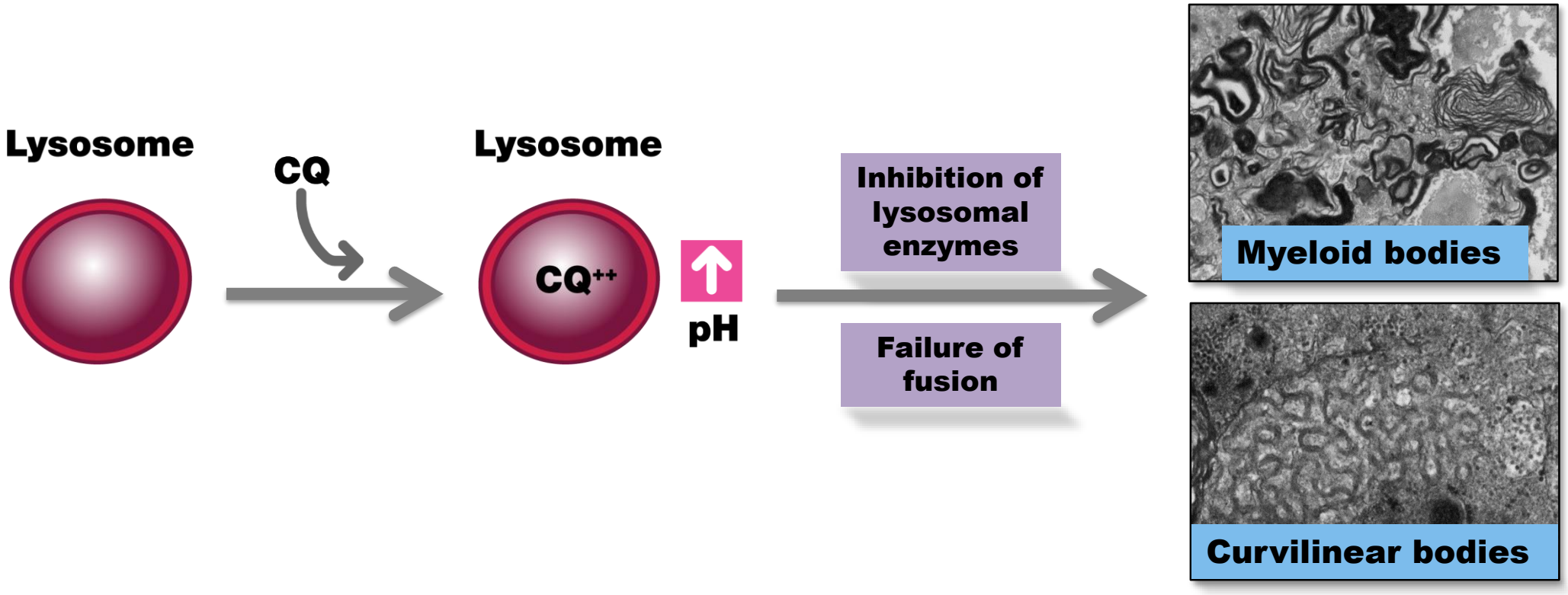
E Casado, J Gratacós, C Tolosa, J M Martínez, I Ojanguren, A Ariza, J Real, A Sanjuan, M Larrosa

Ann Rheum Dis 2006;**65**:385–390. doi: 10.1136/ard.2004.023200



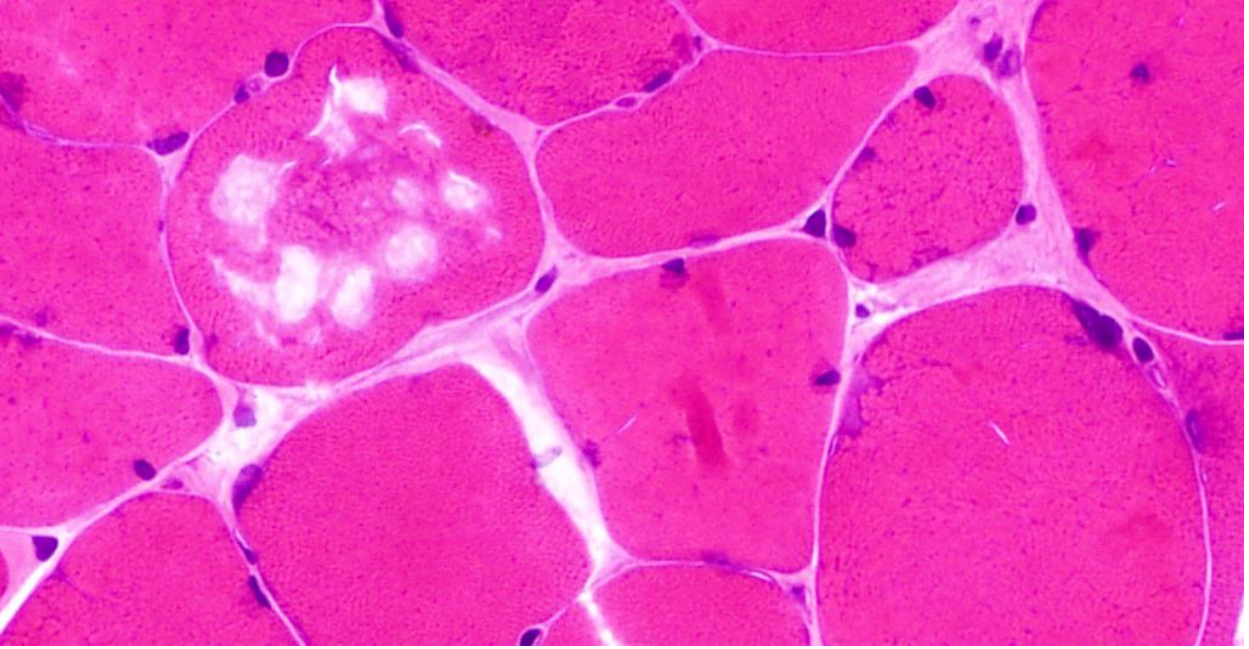
= myeloid and/or curvilinear bodies

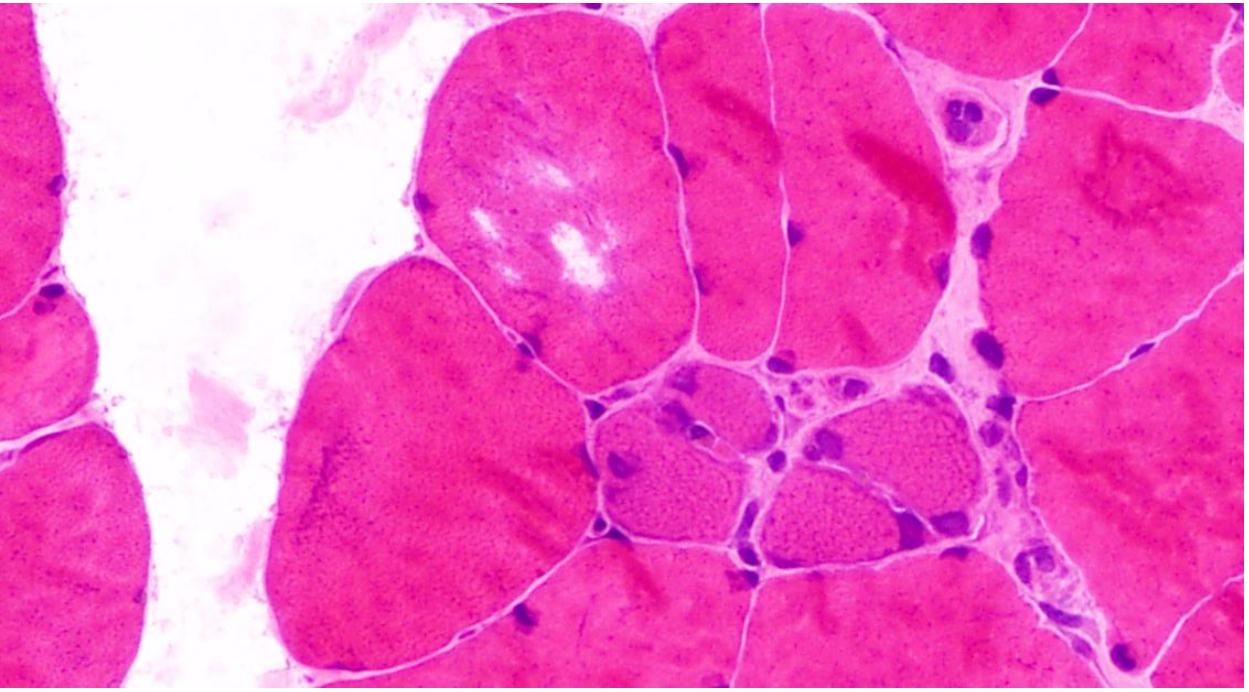

Autophagosome
Lysosome
Autophagolysosome
Degradation, recycling, and exocytosis

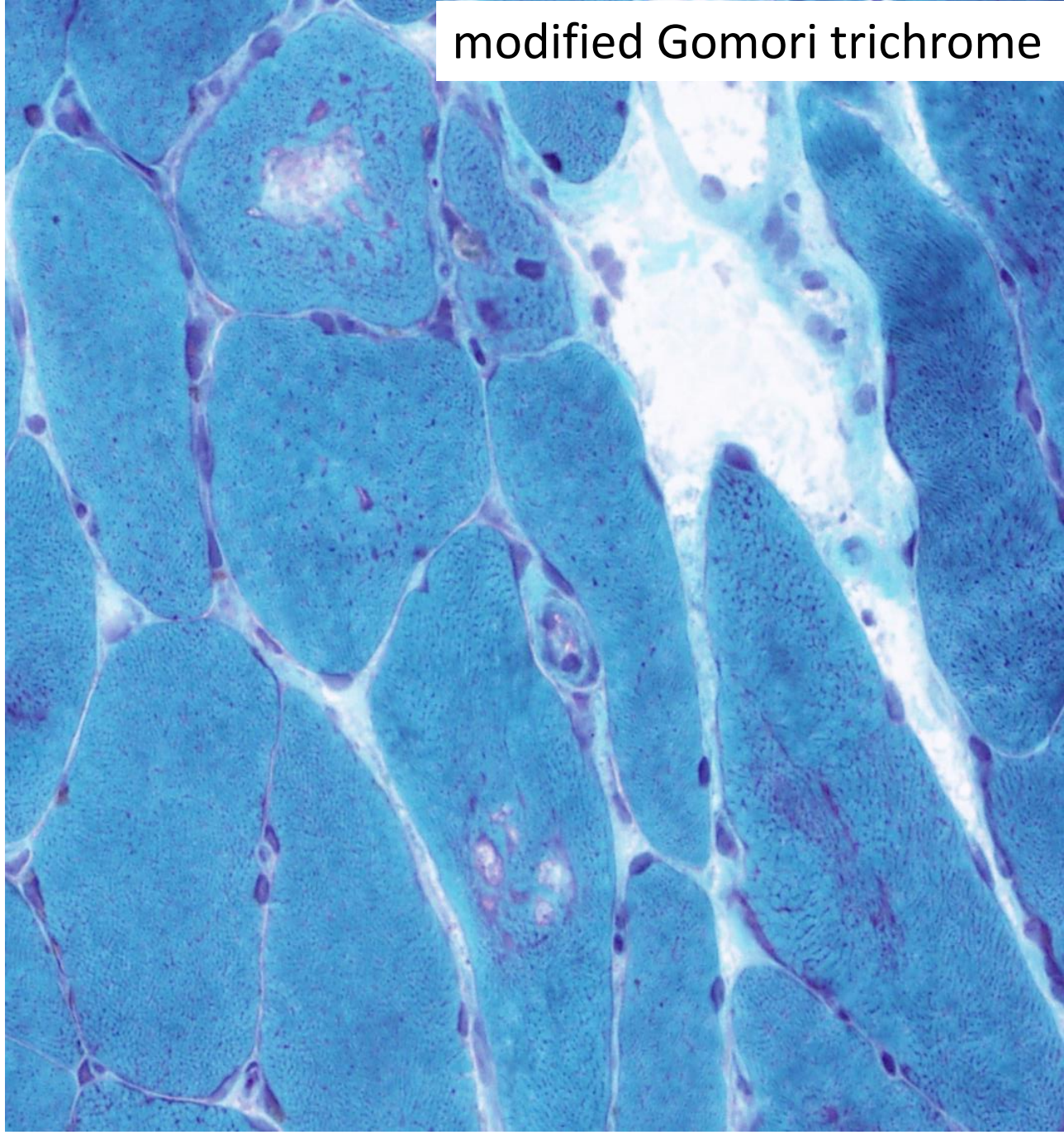

Lysosome
CQ
Lysosome
CQ++
pH
Inhibition of lysosomal enzymes
Failure of fusion
Myeloid bodies
Curvilinear bodies

Colchicine – neuromuscular toxicity

- Acute or long-term use
- Subacute proximal muscle weakness and peripheral neuropathy
- CK: Elevated 10-50X normal
- EMG/NCS: myopathic changes and axonal sensorimotor polyneuropathy
  - +/- myotonic discharges
- Muscle weakness improves after discontinuation of Rx, but mild axonal neuropathy resolves more slowly

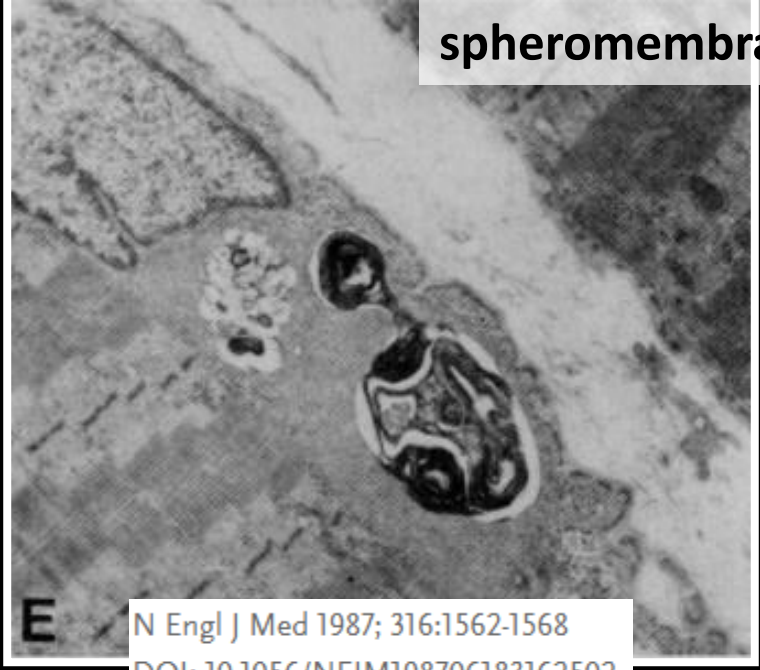




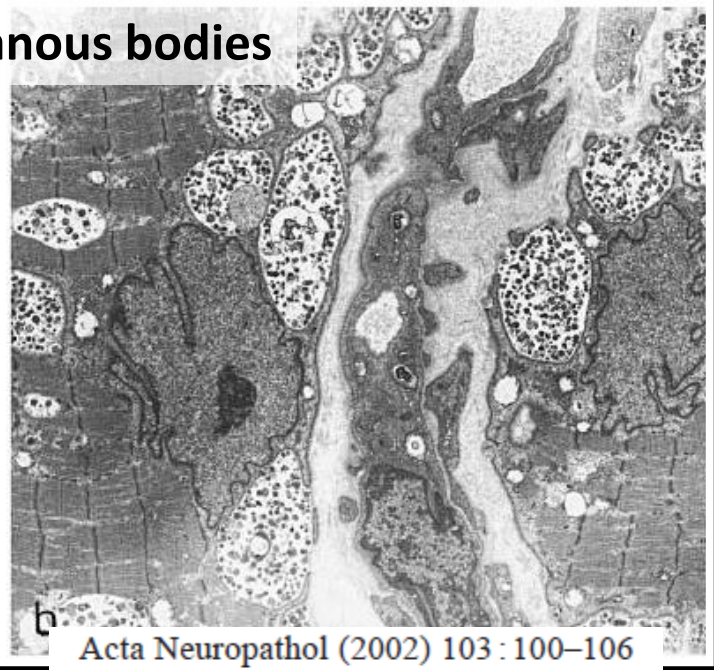


Images courtesy of Sarah Bach

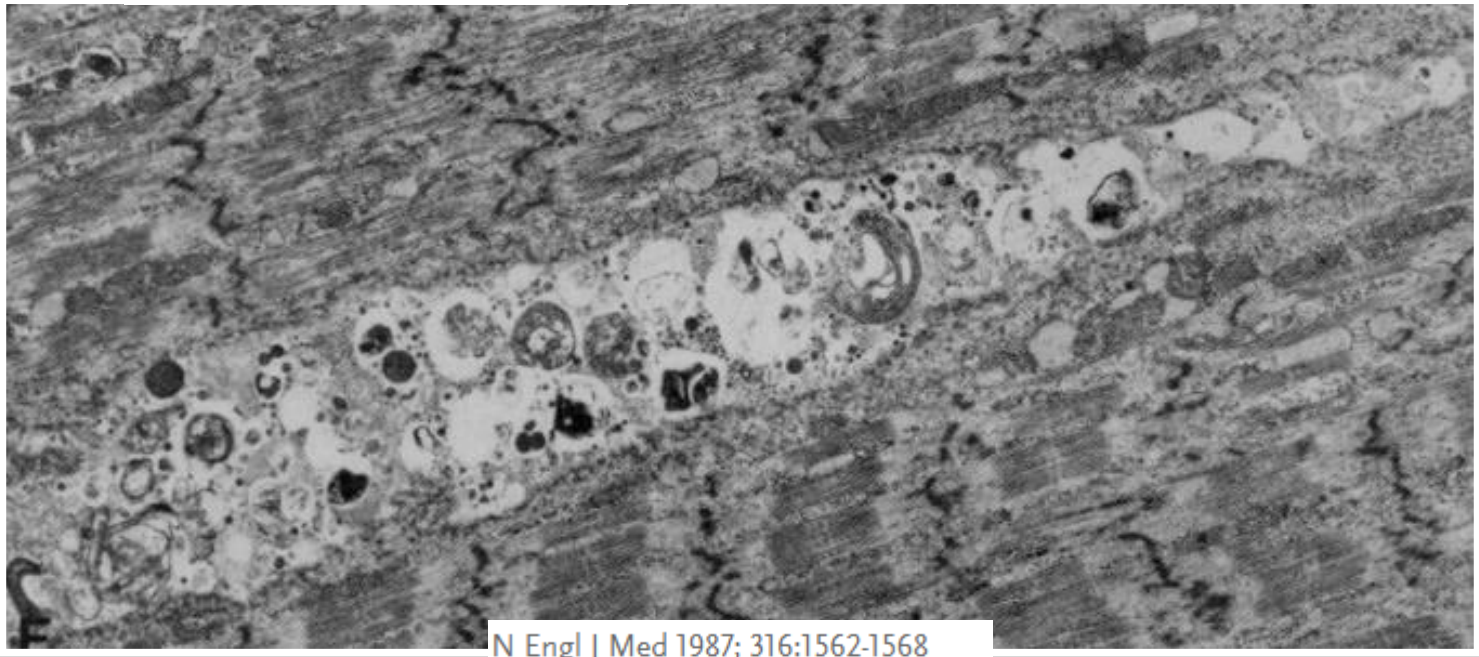
spheromembranous bodies



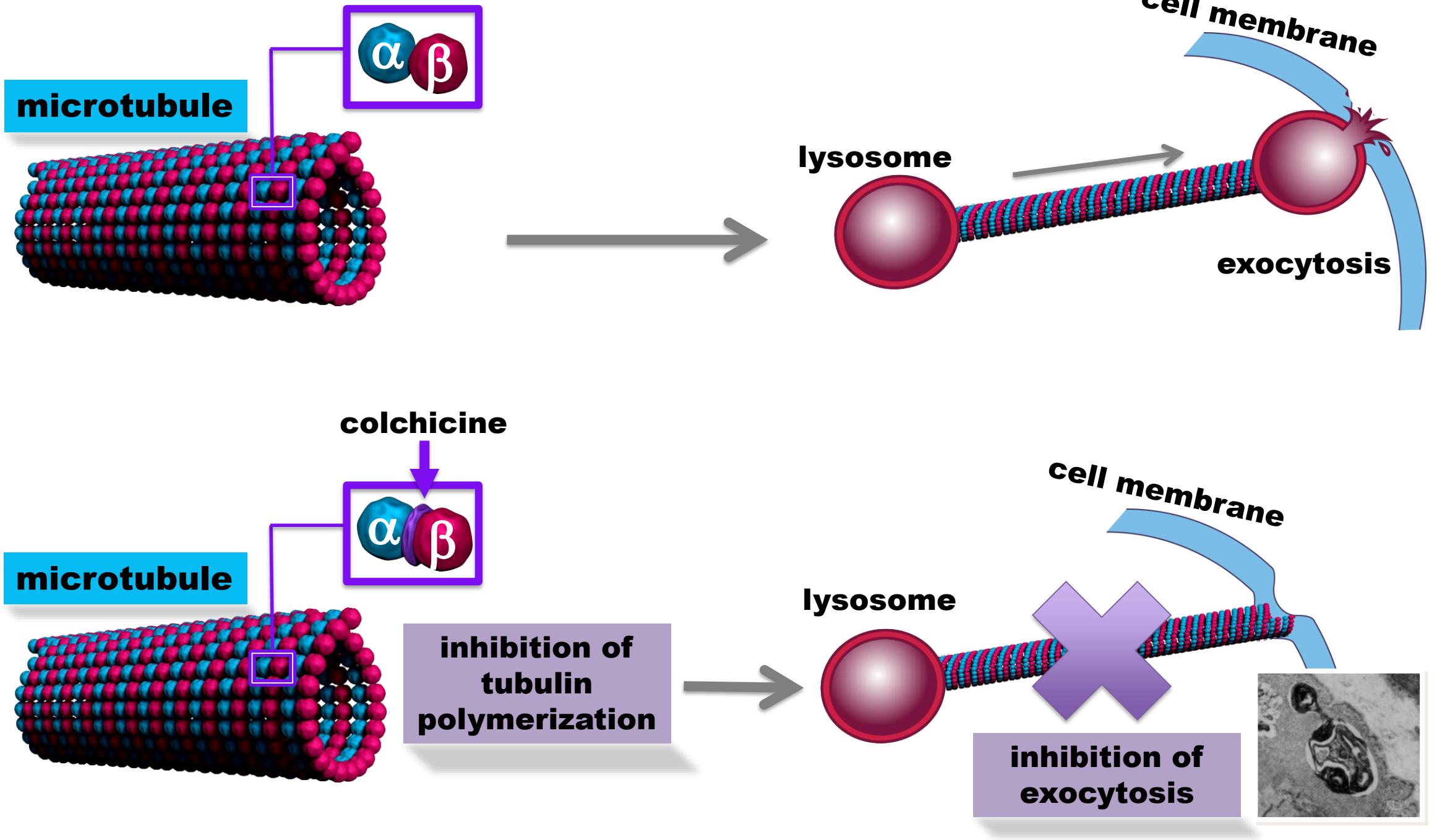
N Engl J Med 1987; 316:1562-1568
DOI: 10.1056/NEJM198706183162502



Acta Neuropathol (2002) 103 : 100–106
DOI 10.1007/s004010100434



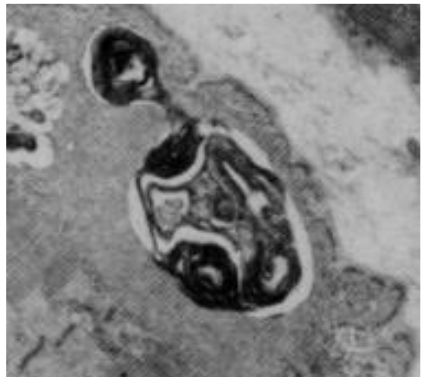
N Engl J Med 1987; 316:1562-1568
DOI: 10.1056/NEJM198706183162502


microtubule
α
β
cell membrane
lysosome
exocytosis
colchicine
microtubule
α
β
inhibition of tubulin polymerization
cell membrane
lysosome
inhibition of exocytosis

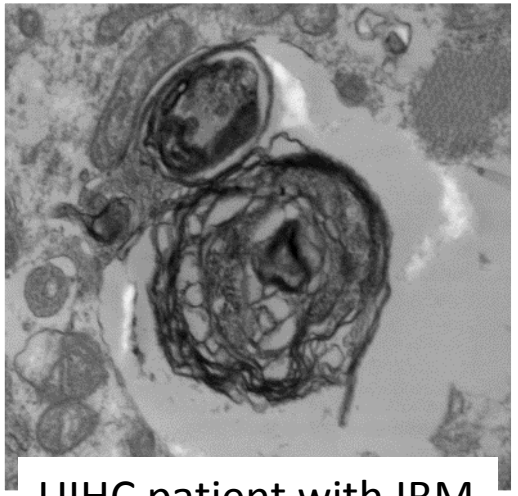
Systemic therapy-induced VACUOLAR MYOPATHIES - diagnostic clues

Chloroquine/hydroxychloroquine or colchicine

- Vacuoles
  - acid phosphatase
  - +/- red rimmed
  - acetylcholinesterase
  - DGC proteins
- Immunostaining
  - complement C5b-9 deposition
- Ultrastructure
  - myeloid bodies (autophagic vacuoles)
  - curvilinear bodies (chloroquines only)
  - spheromembranous bodies (colchicine only? Or just autophagic pathology?)

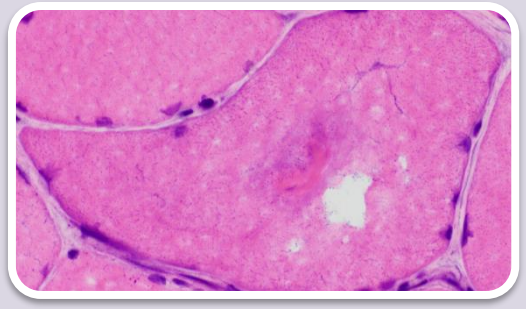


N Engl J Med 1987; 316:1562-1568
DOI: 10.1056/NEJM198706183162502

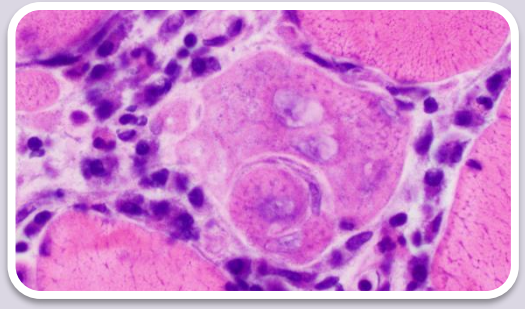


UIHC patient with IBM

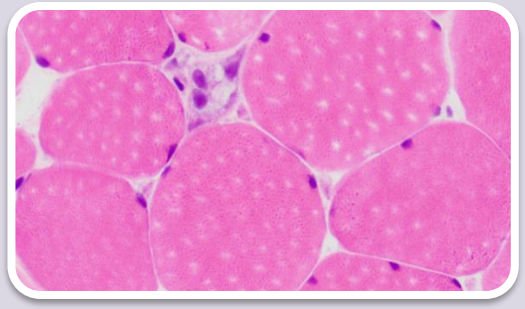
Patterns of systemic therapy-related myopathies



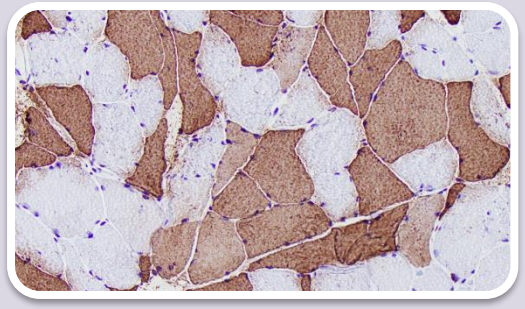
Vacuolar myopathy



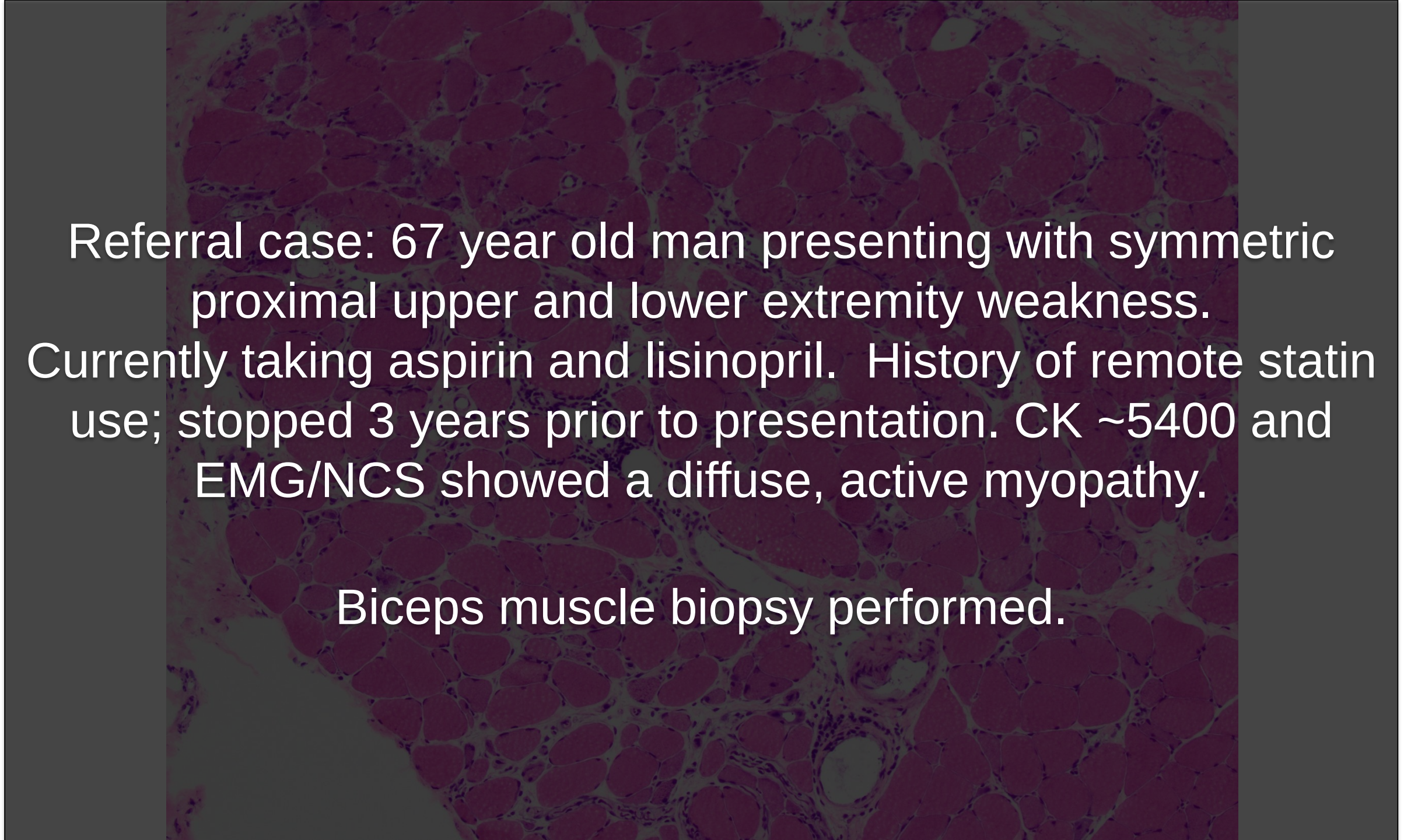
Necrotizing myopathy with inflammation



Necrotizing myopathy without inflammation

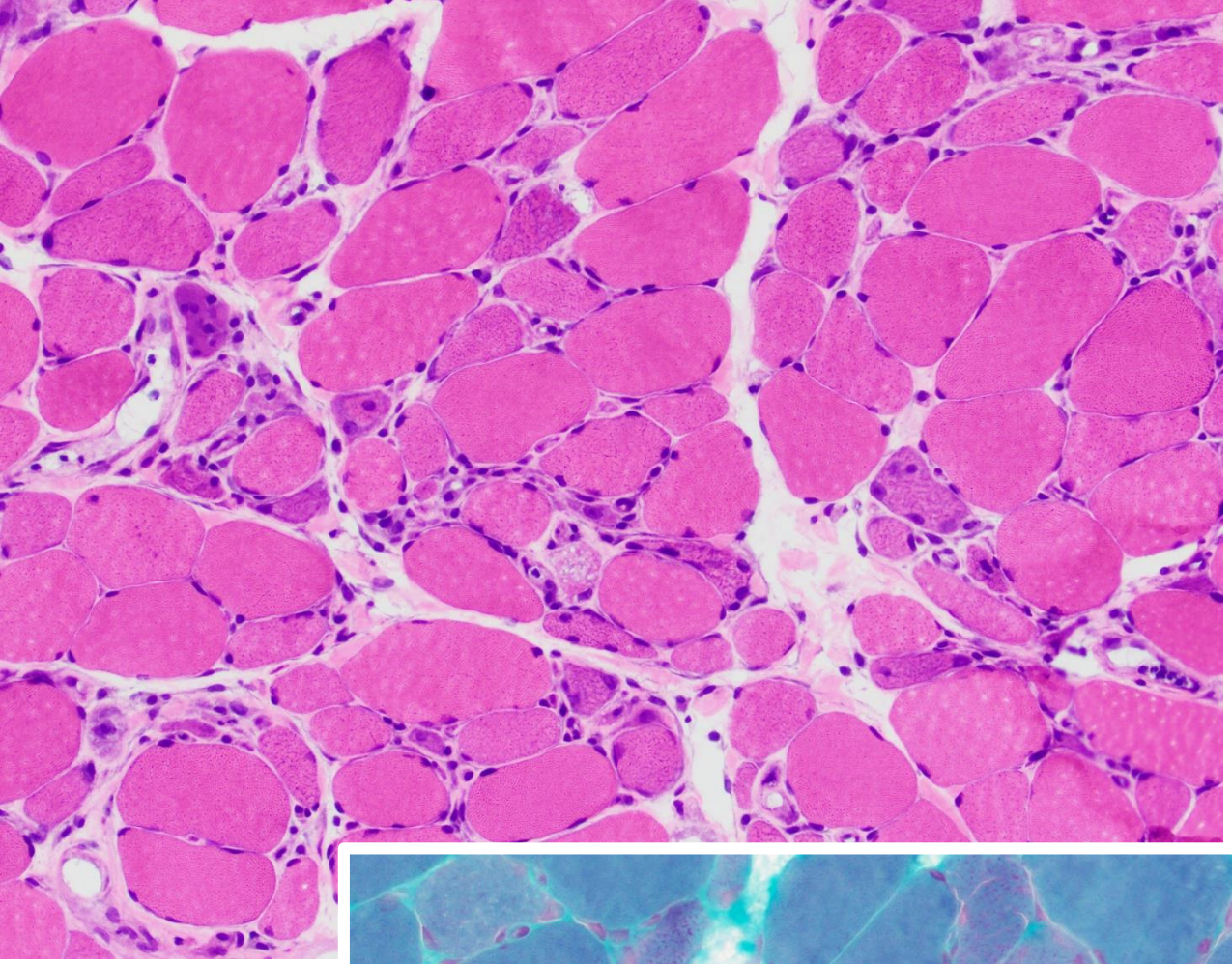


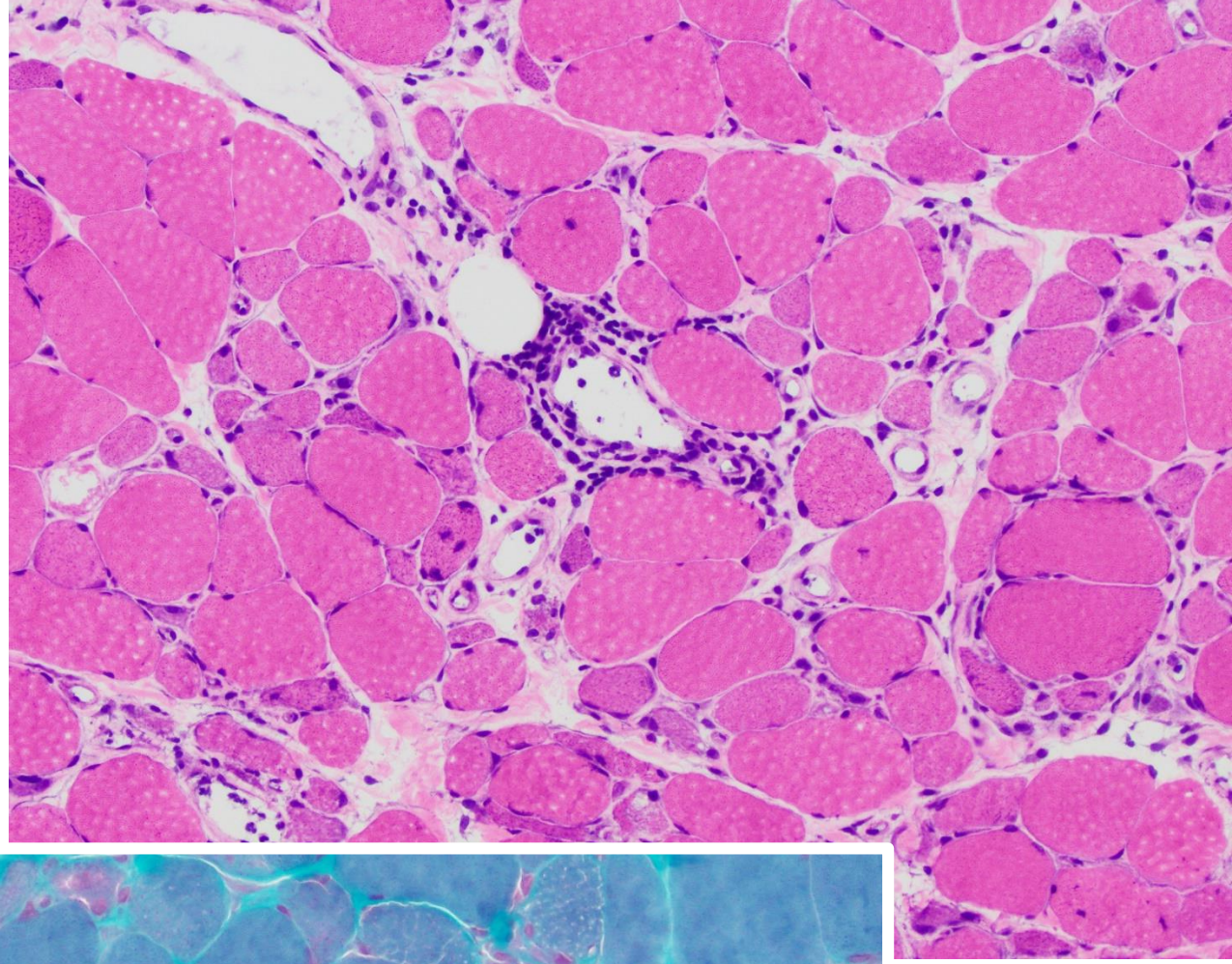
Fiber size variation

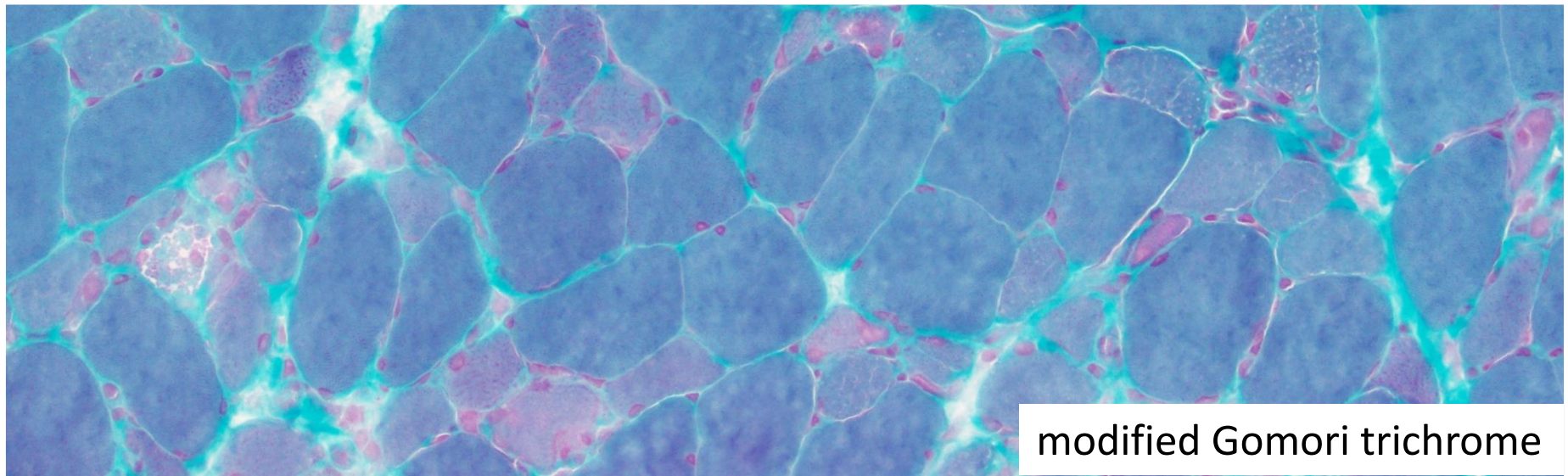


Referral case: 67 year old man presenting with symmetric proximal upper and lower extremity weakness. Currently taking aspirin and lisinopril. History of remote statin use; stopped 3 years prior to presentation. CK ~5400 and EMG/NCS showed a diffuse, active myopathy.

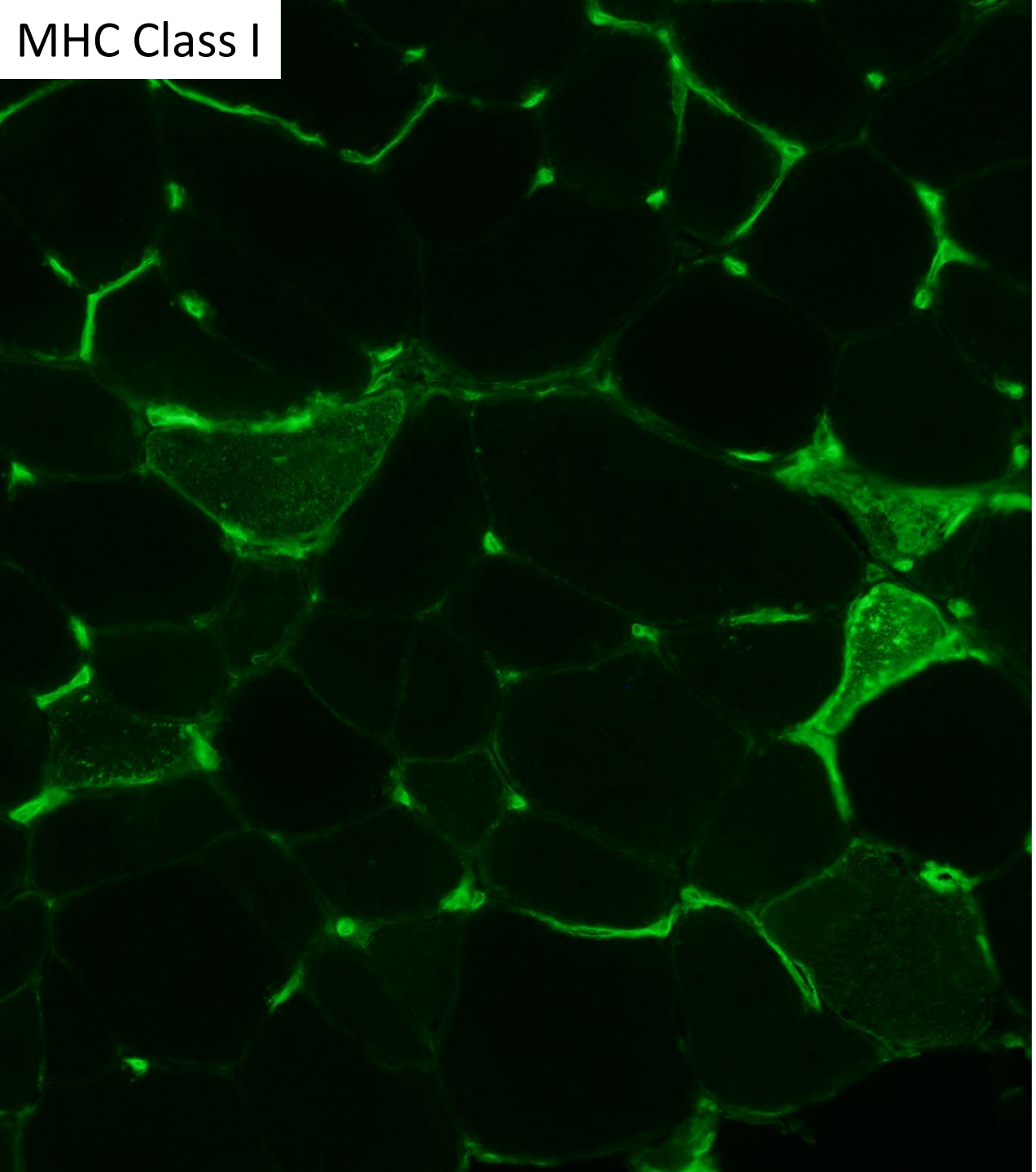
Biceps muscle biopsy performed.

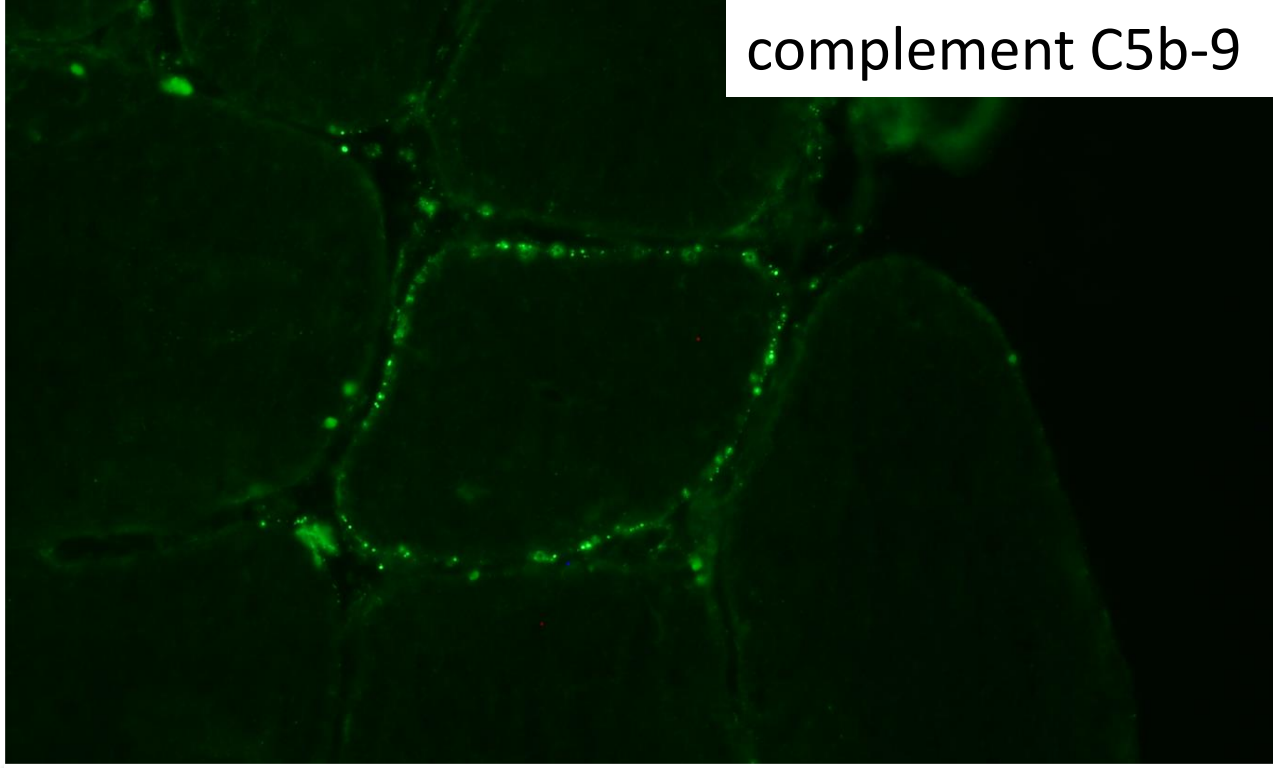


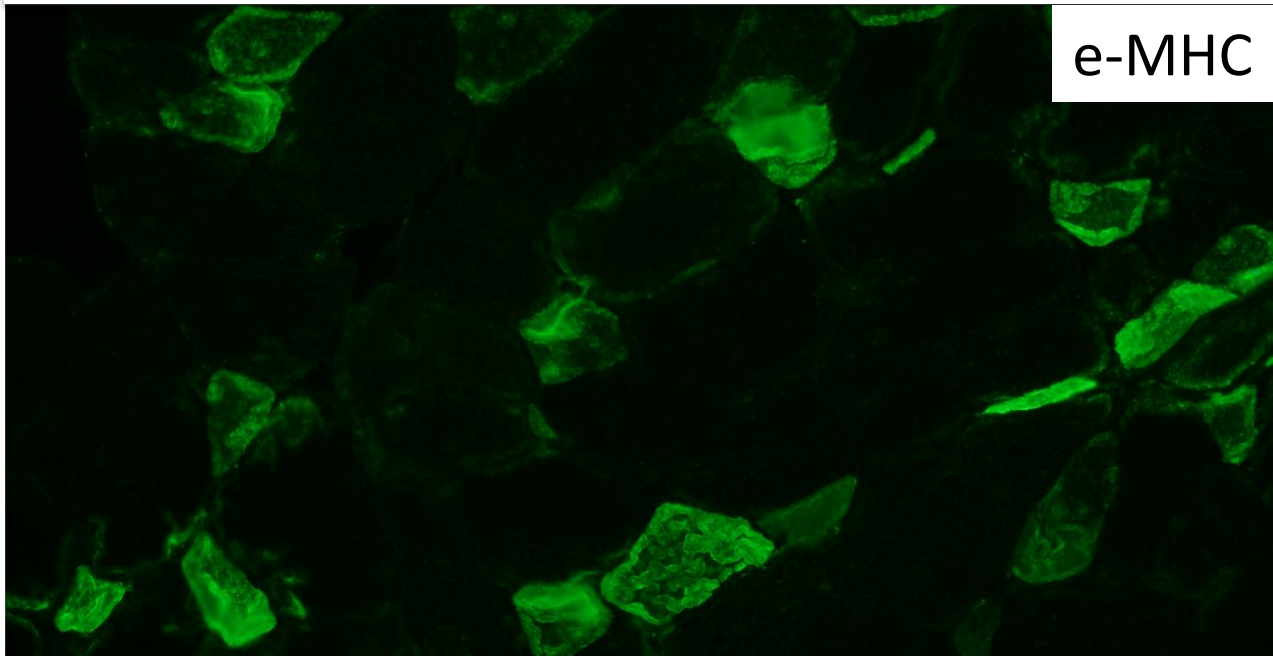




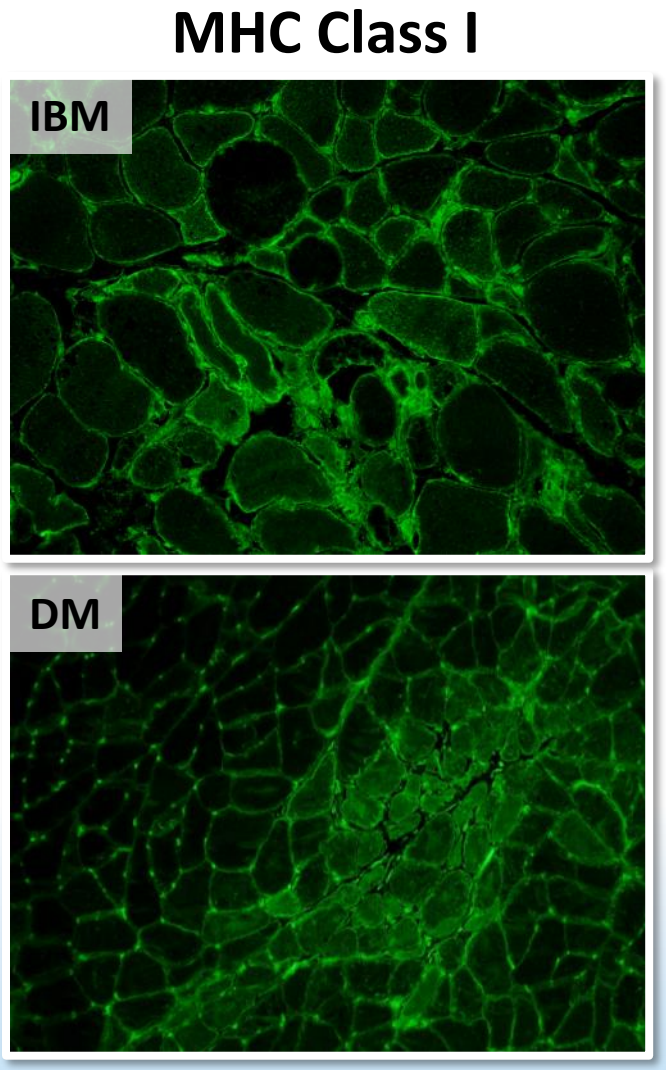
modified Gomori trichrome


MHC Class I


complement C5b-9


e-MHC

Differential diagnosis - necrotizing myopathy with inflammation

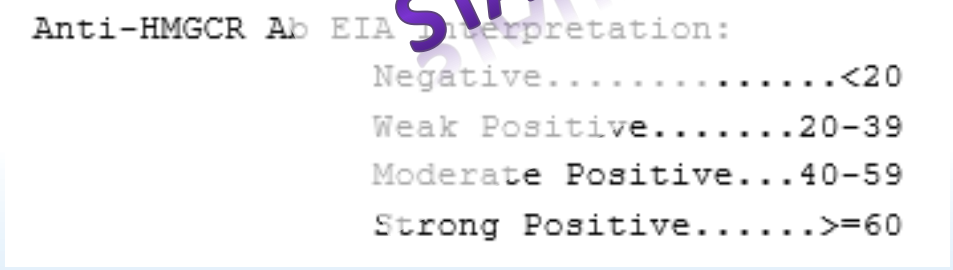


- Inflammatory myopathy
  - Inclusion body myositis
  - Dermatomyositis spectrum (perifascicular atrophy)
  - Anti-synthetase syndrome (perifascicular necrosis)
- Immune-mediated necrotizing myopathy - IMNM (a.k.a. necrotizing autoimmune myopathy – NAM)
  - Anti-HMGCR myopathy
  - Anti-SRP myopathy
- Muscular dystrophy with inflammation
- Drug-induced/toxic myopathies
  - Statins (+/- anti-HMGCR antibodies)
  - Immune checkpoint inhibitors

Clinical update while working up muscle biopsy

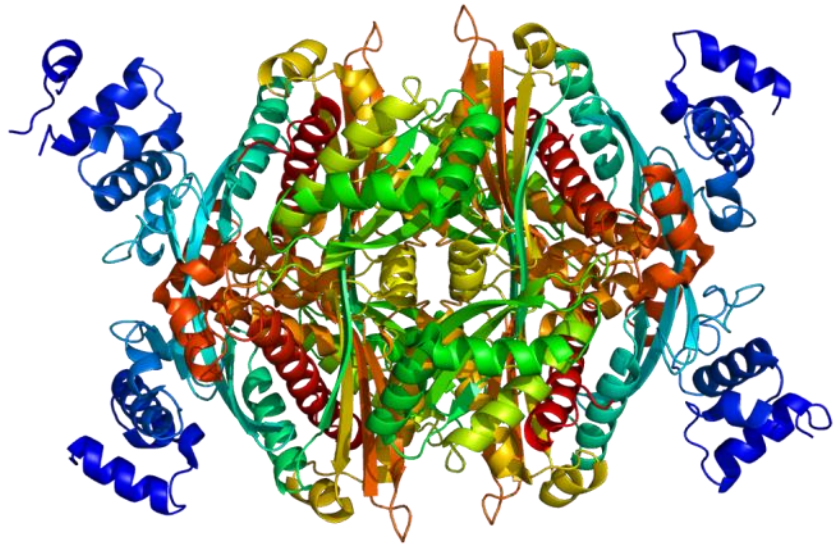
- Myositis panel testing
  - Negative for Anti-Jo-1, Mi-2, PL-7, PL-12, EJ, OJ, SRP, Ku, Anti-PM/Scl, U2 SN RNP
- Anti-HMGCR autoantibody testing
  - Strong positive >=200

STATIN-ASSOCIATED ANTI-HMGCR MYOPATHY



Statins – muscle toxicity and autoimmunity

- Occurs in ~ 2-3/100,000 patients treated with statins
  - ~15 million Americans
- Can occur anytime after starting the medication, or even after medication has been discontinued
- Direct myotoxicity self-limited and quickly resolves, if not, autoimmunity develops → anti-HMGCR antibodies
- Symmetric proximal muscle weakness and pain
- CK: >10x normal
- EMG: active myopathic process
- Atorvastatin more strongly associated with myopathy compared to simvastatin or rosuvastatin (Basharat et al. J Am Coll Cardiol 2016)



https://commons.wikimedia.org/wiki/File:Protein_HMGCR_PDB_1dq8.png
By Emw

Anti-HMGCR antibodies without exposure to statins

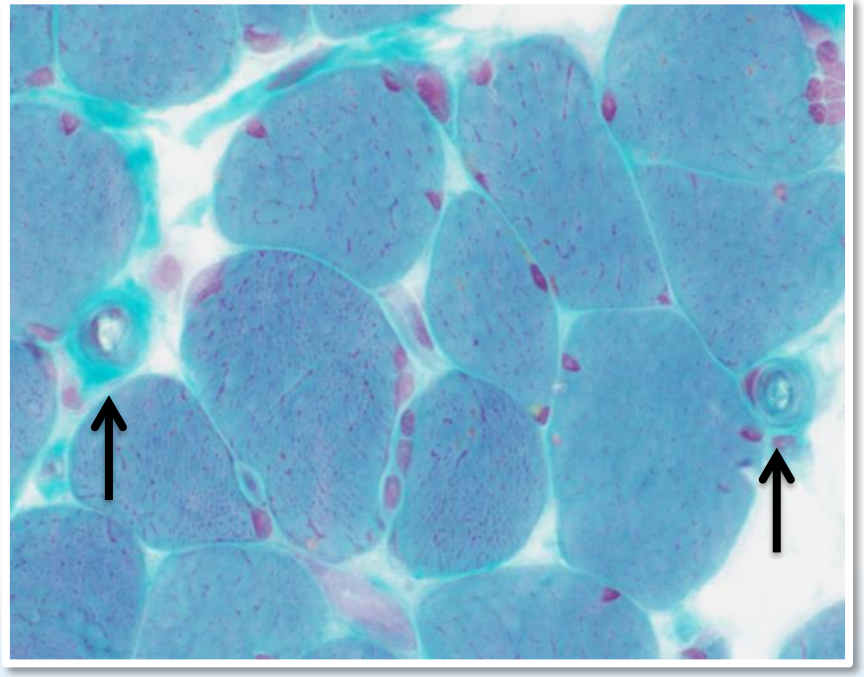
Location of study	Percent of patients with no prior statin exposure	Total number of anti-HMGCR^{+} patients	Citation
U.S.A. – Johns Hopkins	30%	45	Mammen et al. Arthritis Rheum 2011
Europe	56%	45	Allenbach et al. Medicine 2014
China	86%	22	Ge et al. PLoS ONE 2015
Japan	82%	45	Watanabe et al. J Neurol Neurosurg Psychiatry 2016

Of note: these patients can have increased risk of cancer

Consensus histopathologic features of IMNM

- Universally present features:
  - Necrotic fibers with scattered distribution in different stages of necrosis/myophagocytosis/regeneration
  - Macrophage predominant, paucilymphocytic

- Additional features to consider:
  - MHC Class I sarcolemmal expression can be *diffuse* or limited to necrotic fibers (not perifascicular)
  - Complement C5b-9 deposition may be seen
  - Endomysial fibrosis is often prominent
  - Enlarged capillaries may be prominent



Necrosis in anti-SRP$^+$ and anti-HMGCR$^+$ myopathies

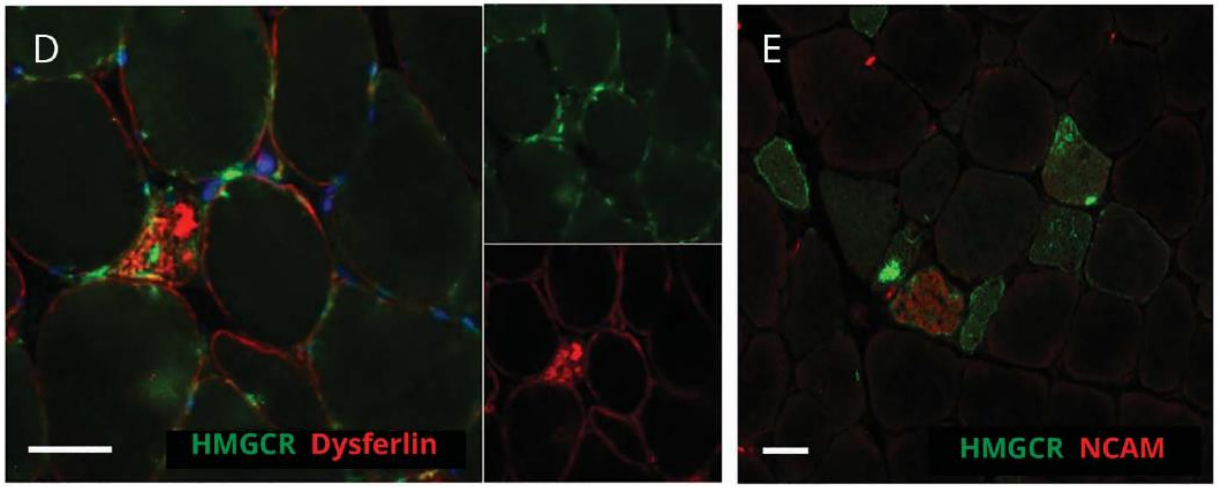
Role of autoantibodies and complement

Yves Allenbach, MD, PhD,* Louiza Arouche-Delaperche, PhD,* Corinna Preusse, PhD, Helena Radbruch, MD, Gillian Butler-Browne, PhD, Nicolas Champtiaux, MD, PhD, Kuberaka Mariampillai, MSc, Aude Rigolet, MD, Peter Hufnagl, PhD, Norman Zerbe, Damien Amelin, Thierry Maisonobe, MD, Sarah Louis-Leonard, MD, Charles Duyckaerts, MD, PhD, Bruno Eymard, MD, PhD, Hans-Hilmar Goebel, MD, Cecile Bergua, MSc, Laurent Drouot, PhD, Olivier Boyer, MD, PhD, Olivier Benveniste, MD, PhD,† and Werner Stenzel, MD†

Correspondence
Dr. Allenbach
yves.allenbach@aphp.fr

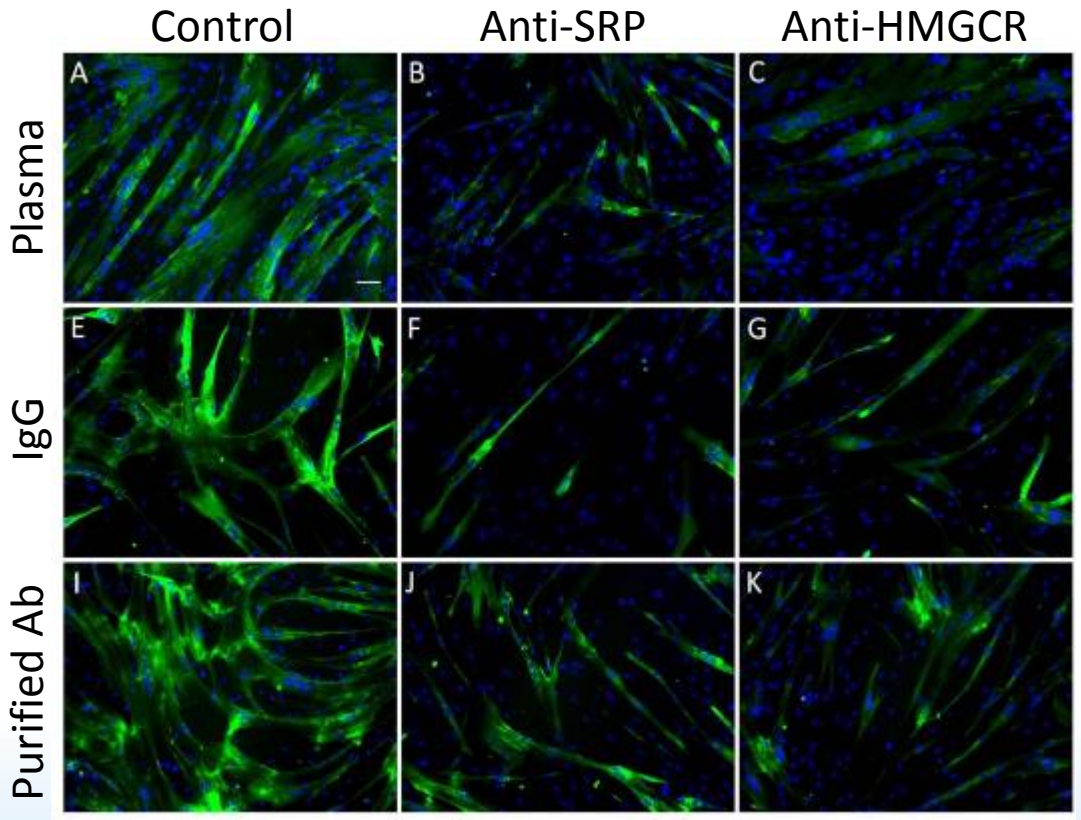
Neurology® 2018;90:e507-e517. doi:10.1212/WNL.0000000000004923

- ALL 25 biopsies showed CD3+ lymphocytes
- MHC Class I expression only patchy
- Complement C5b-9 deposition on sarcolemma → direct pathogenic role of aAbs activating the complement pathway
- Regenerating muscle cells express high levels of HMG-CoA reductase protein (required for normal muscle cell differentiation)



Are anti-HMGCR antibodies pathogenic?

- Anti-HMGCR antibody titer directly correlated with CK level and disease activity
- Arouche-Delaperche et al. anti-HMGCR antibodies (and anti-SRP antibodies) induced myofiber atrophy and impaired muscle regeneration in primary human muscle cell cultures due to a defect in myoblast fusion (Ann Neurol 2017)



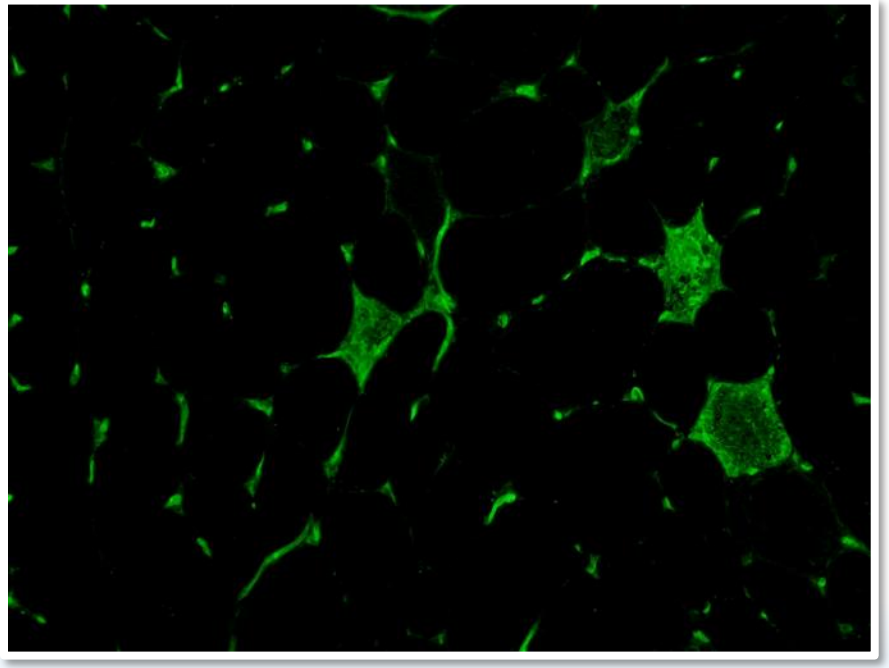
Green = myosin heavy chain

ANN NEUROL 2017;81:538–548

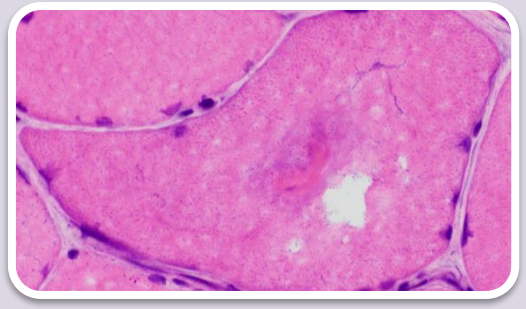
Statin-related necrotizing myopathy and IMNM – diagnostic clues

- Myonecrosis:
  - Necrotizing myopathy with various stages of necrosis distributed throughout the biopsy
- Inflammation:
  - Endomysial or perimysial T-cell inflammation often present, but may be sparse (IHC helpful to identify)
- Immunostaining:
  - MHC Class I most often limited to necrotic fibers (NOT perifascicular)
  - Complement C5b-9 deposition common

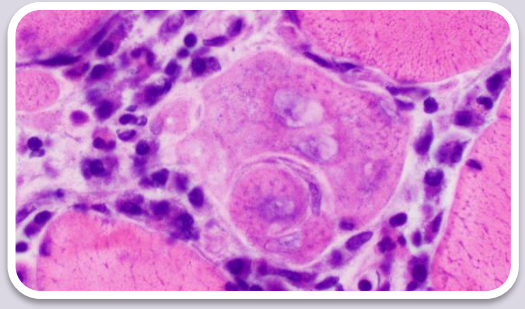
MHC Class I



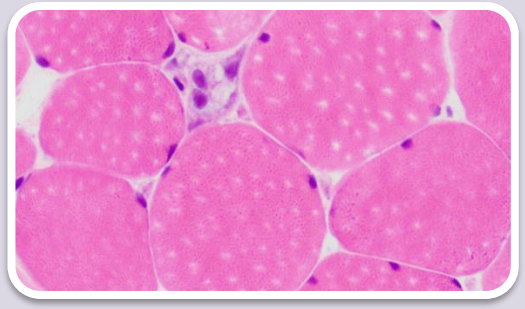
Patterns of systemic therapy-related myopathies



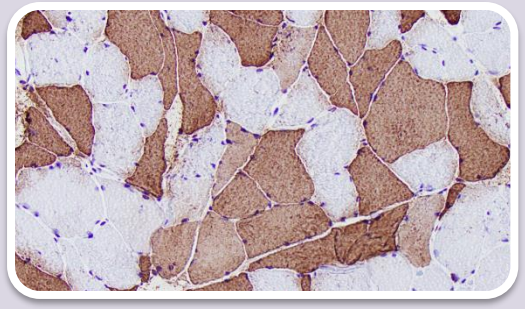
Vacuolar myopathy



Necrotizing myopathy with inflammation



Necrotizing myopathy without inflammation

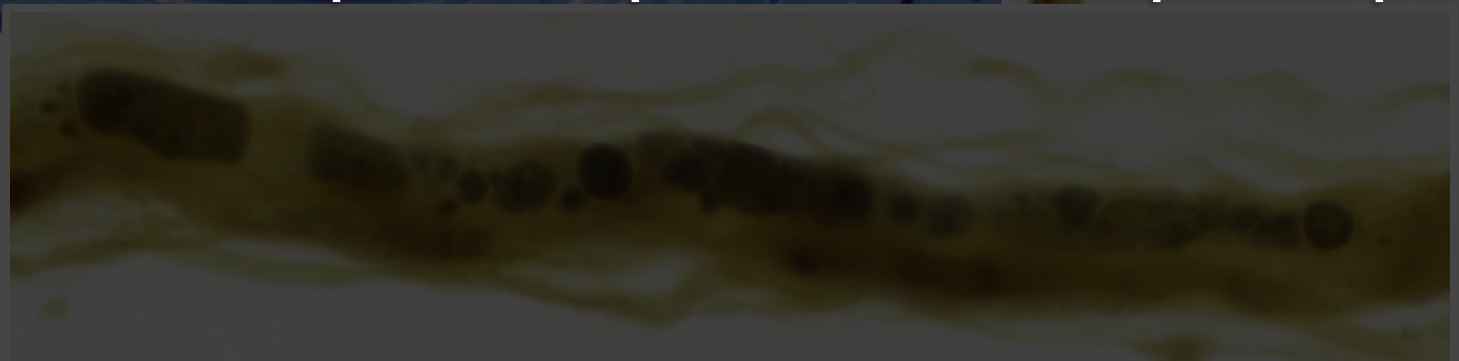


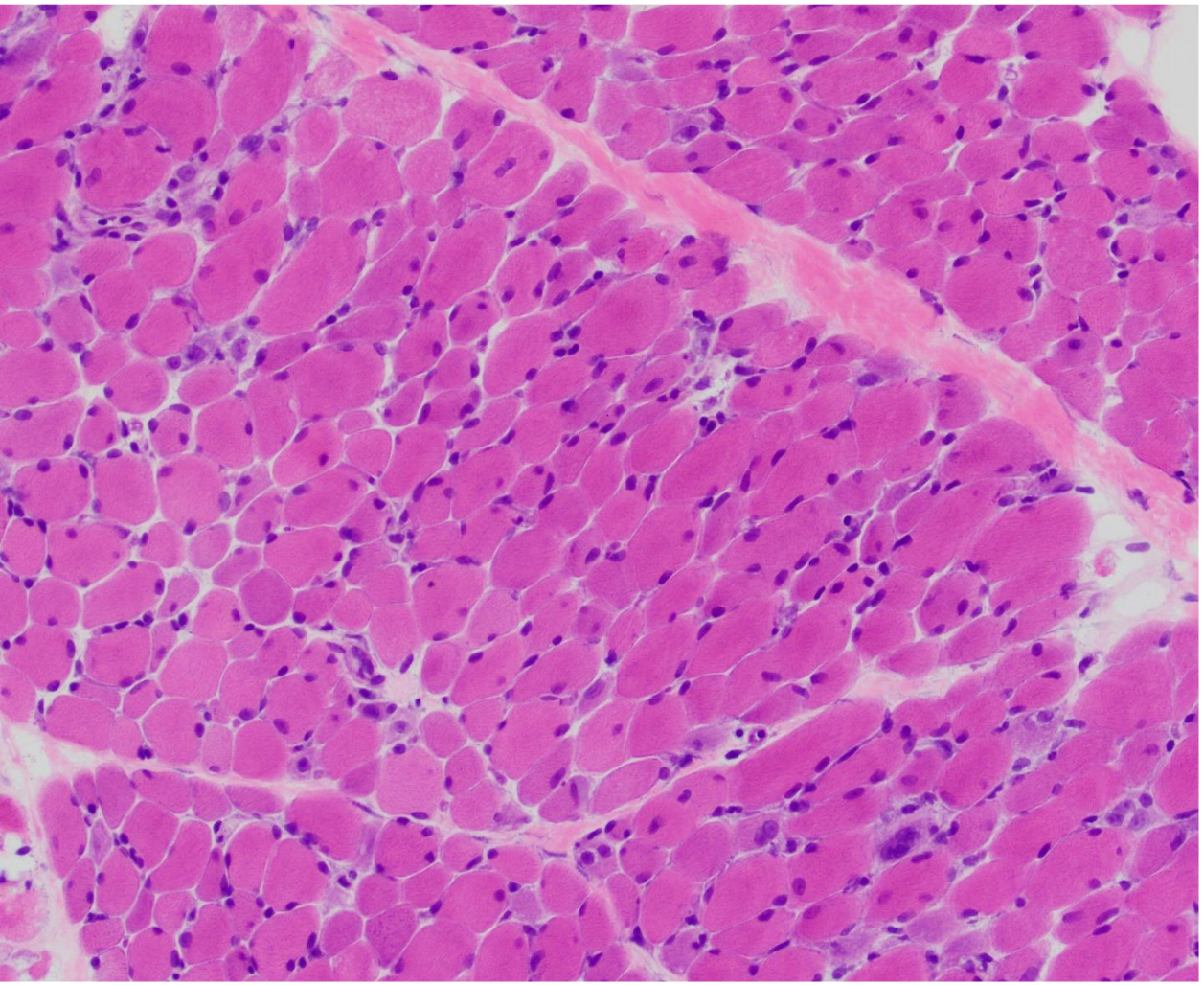
Fiber size variation

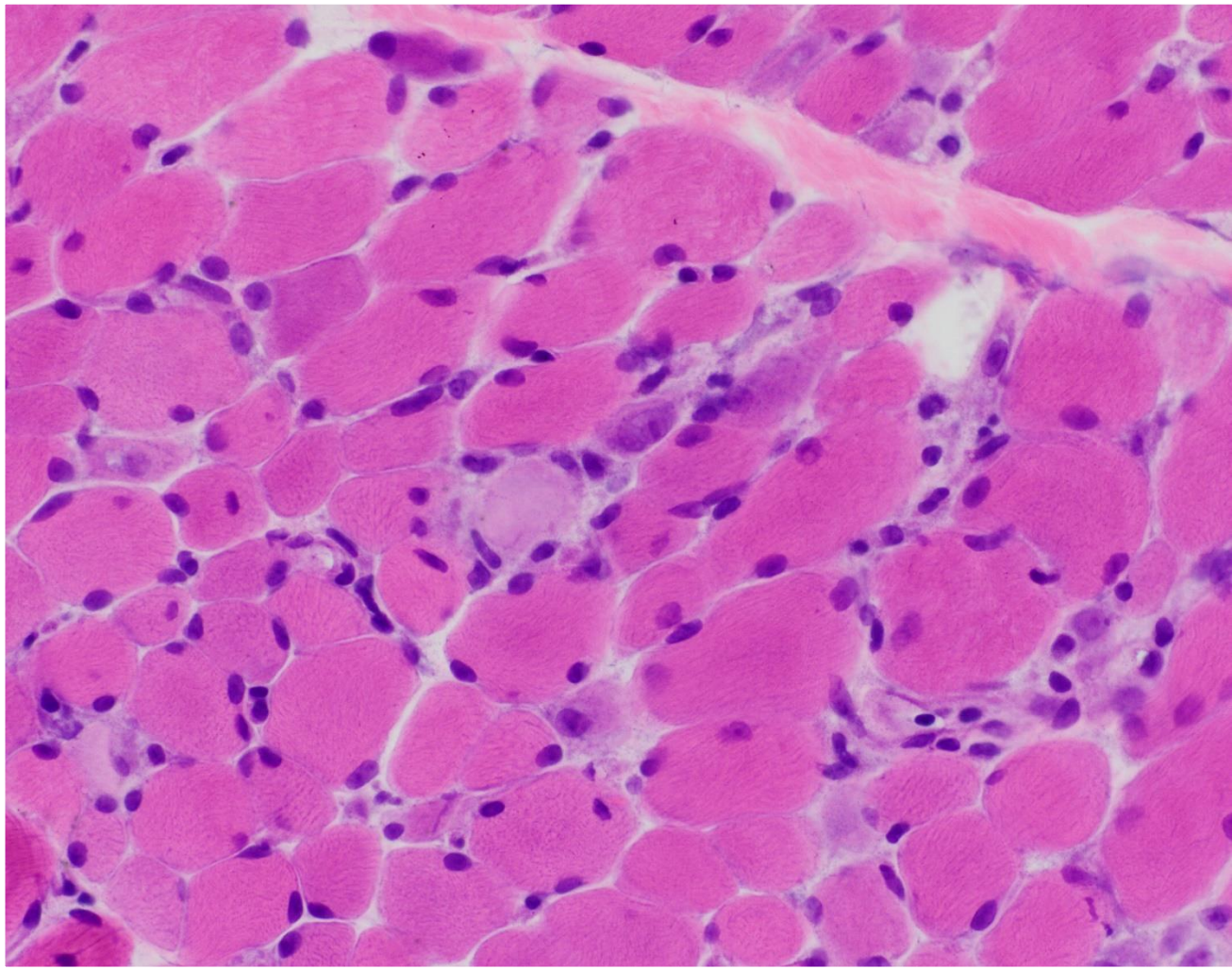
toluidine blue

Referral case: 15 year old boy admitted with new onset seizures and CNS vasculitis who was treated with high dose corticosteroids. During his prolonged hospital stay he developed sepsis, respiratory failure, and renal failure. After extubation he developed profound muscle weakness.

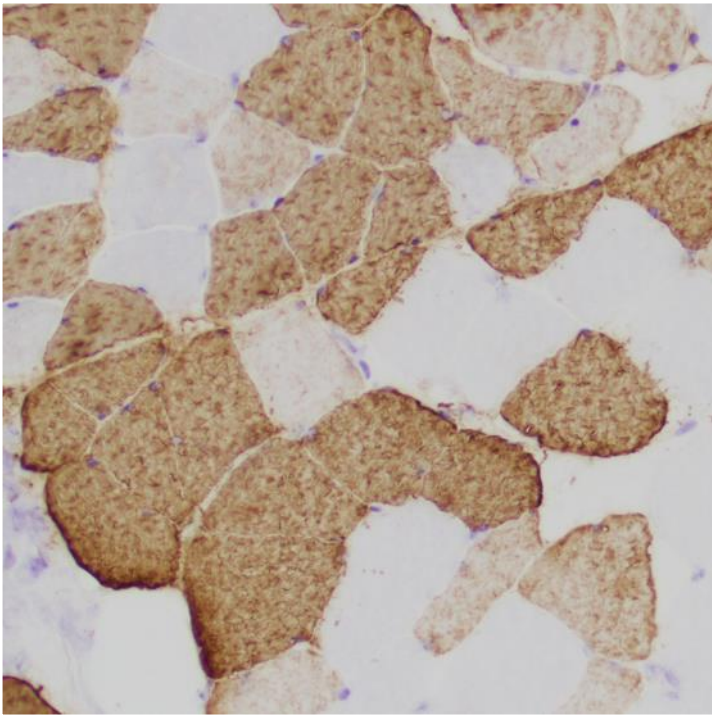
Sural nerve and quadriceps muscle biopsies performed.





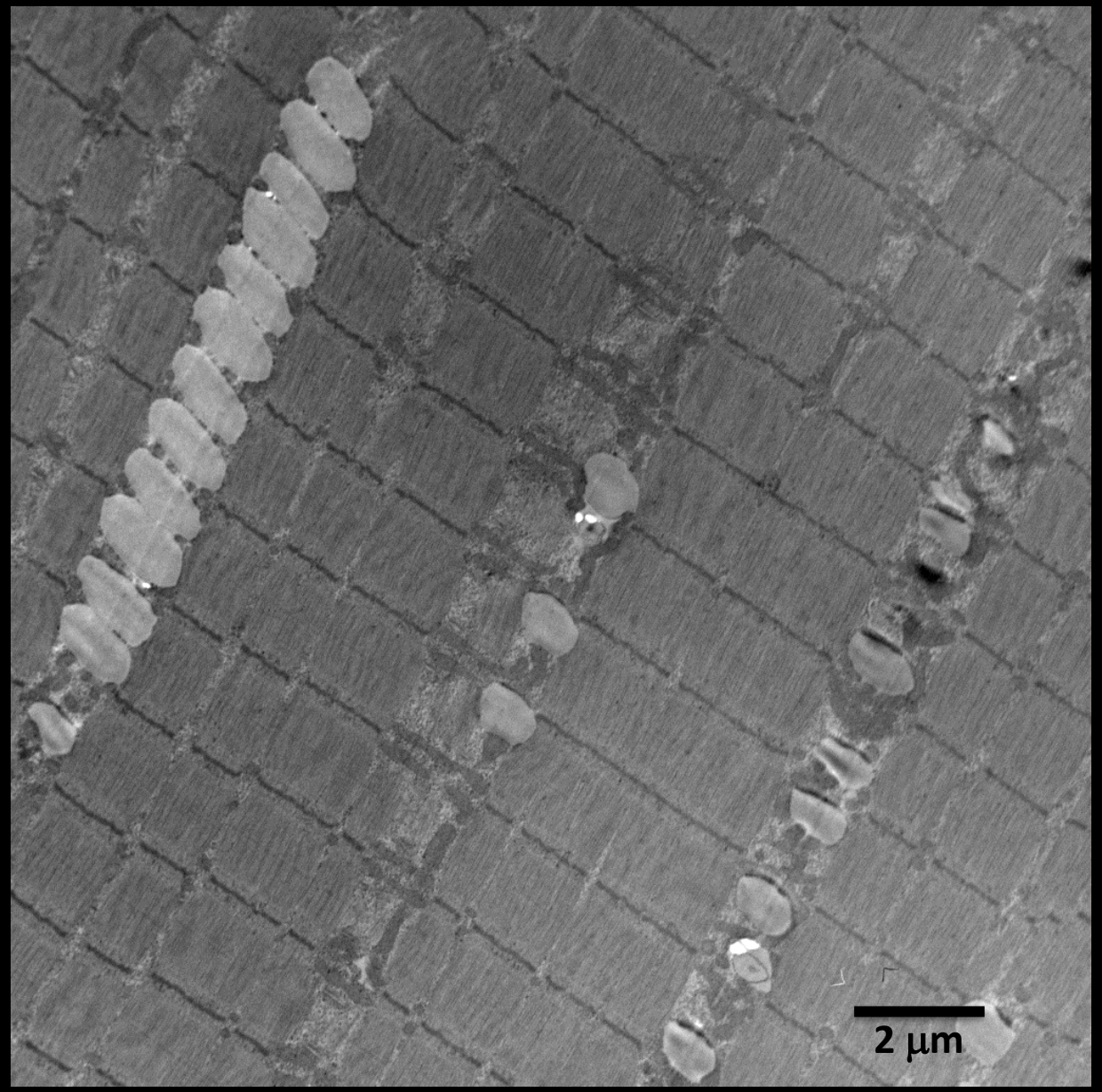


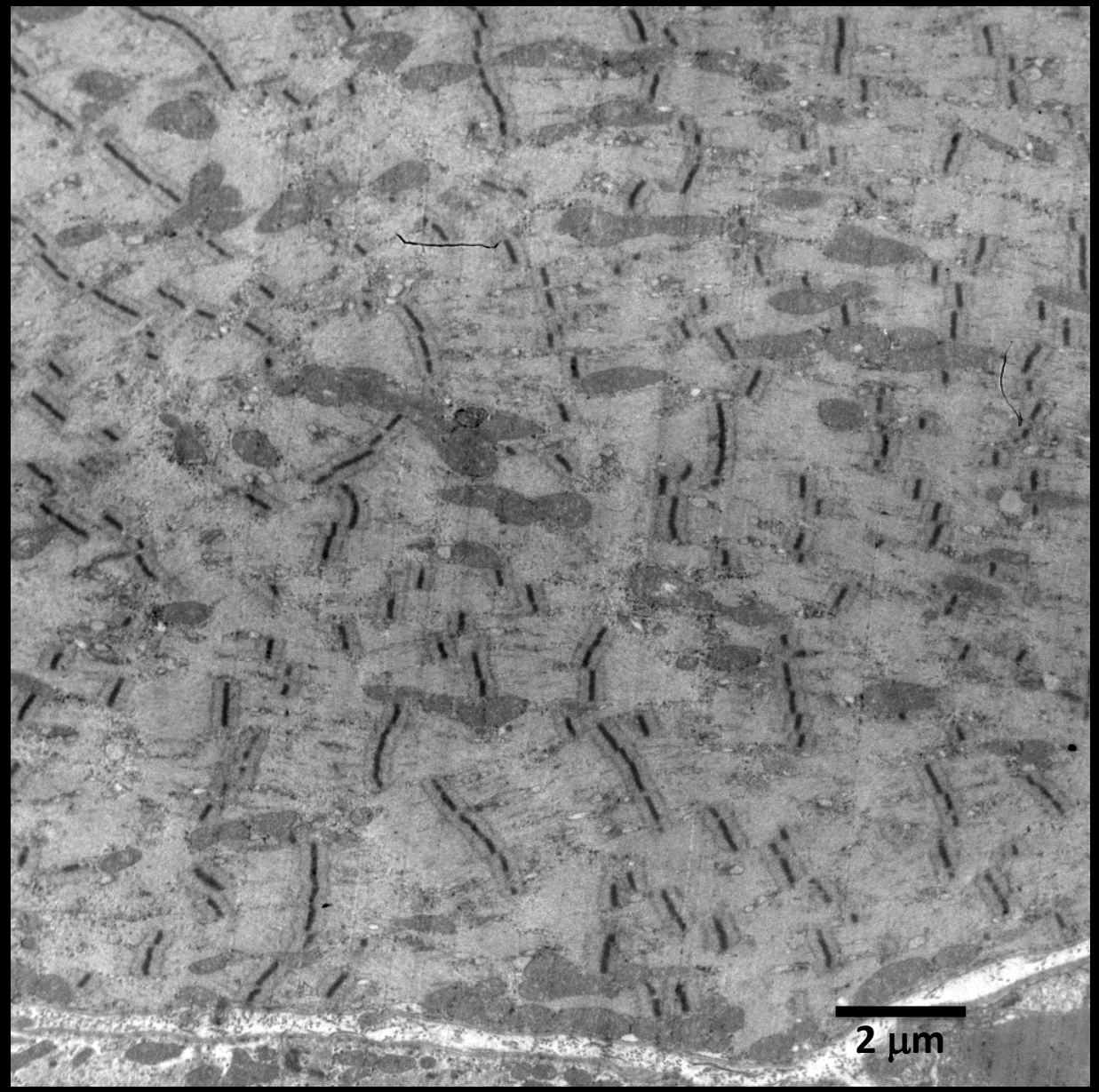
control fast myosin



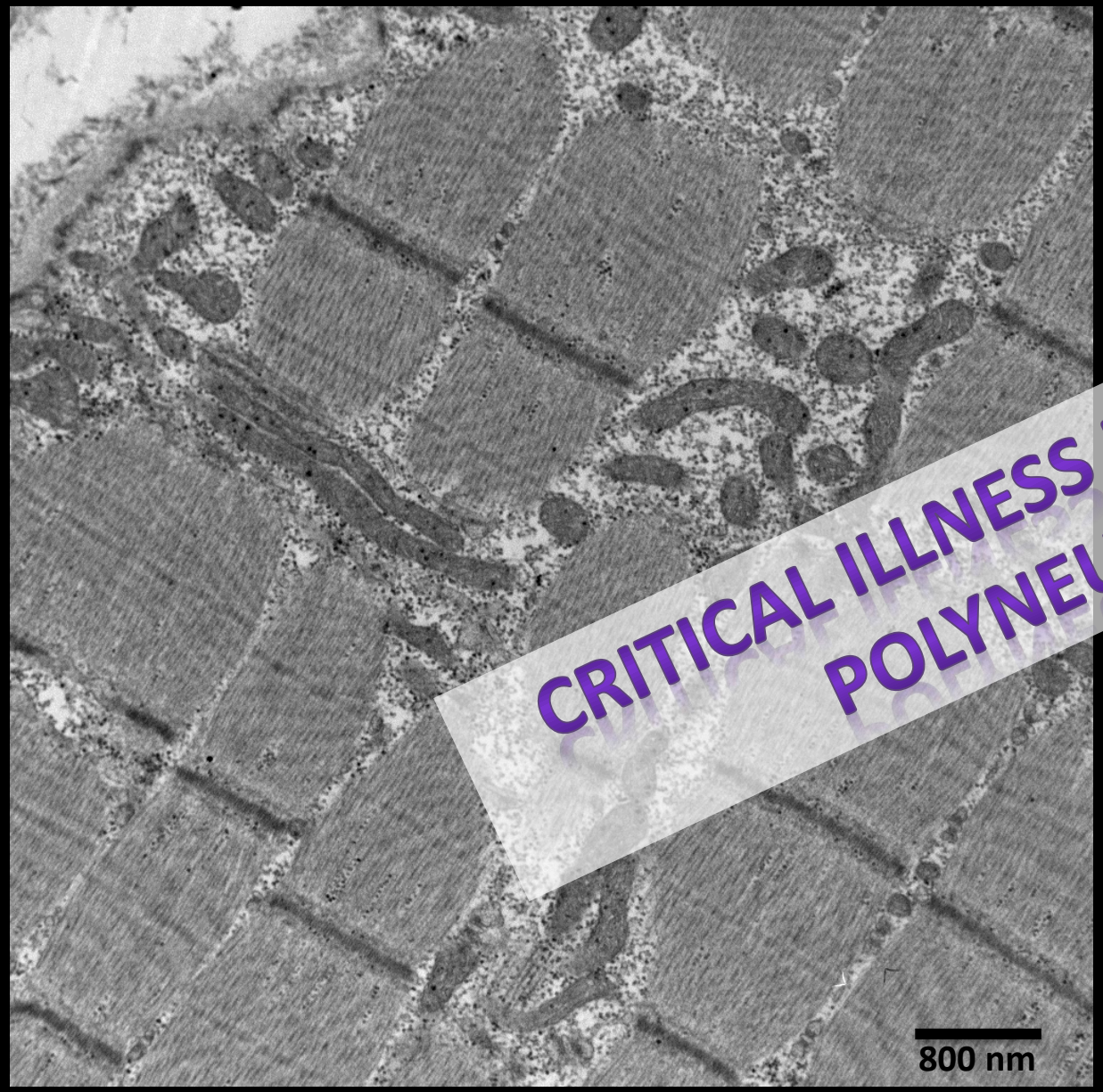
fast myosin

Control muscle

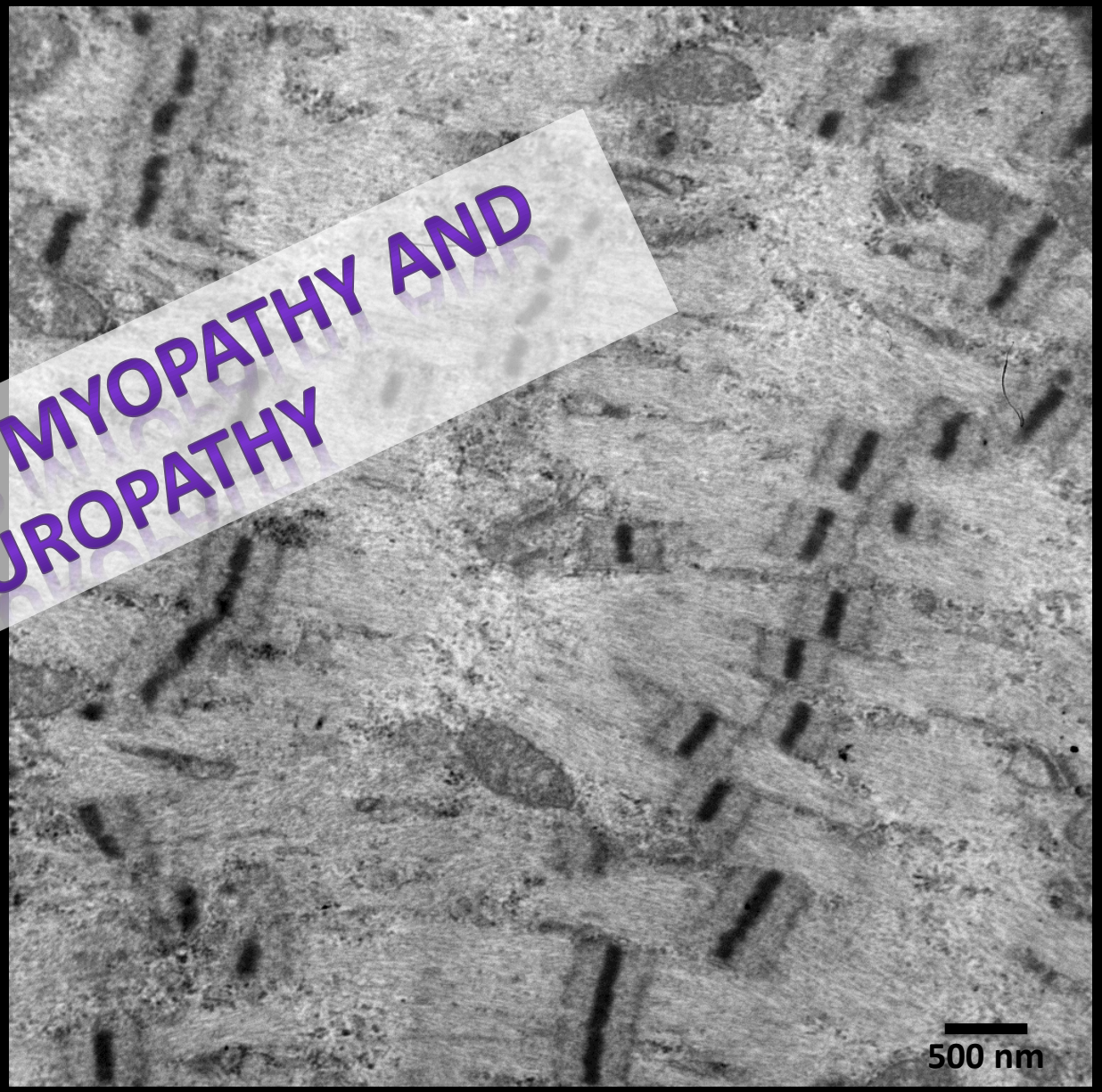




Control muscle



CRITICAL ILLNESS MYOPATHY AND POLYNEUROPATHY



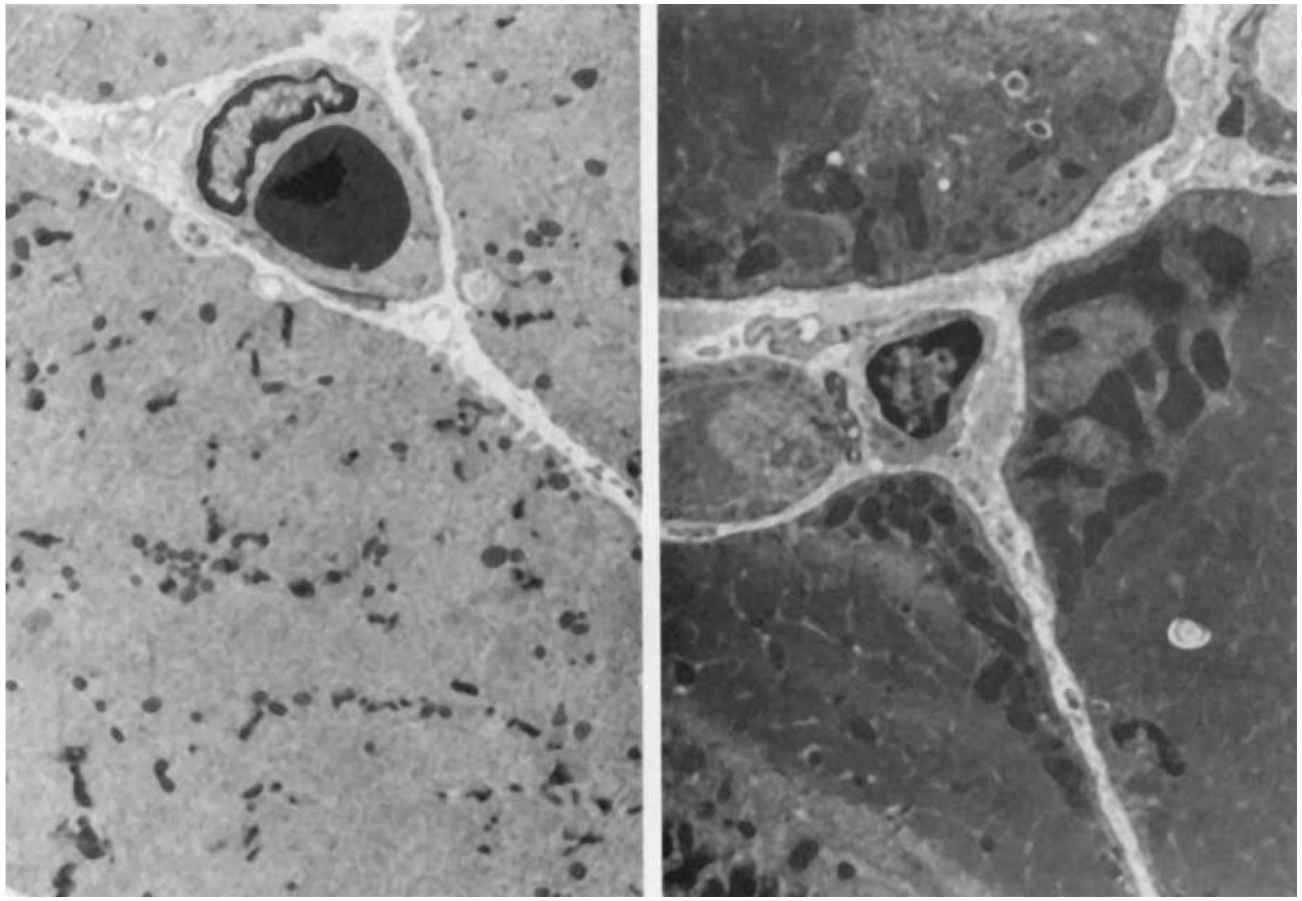
Critical illness myopathy (CIM) and polyneuropathy (CIP)

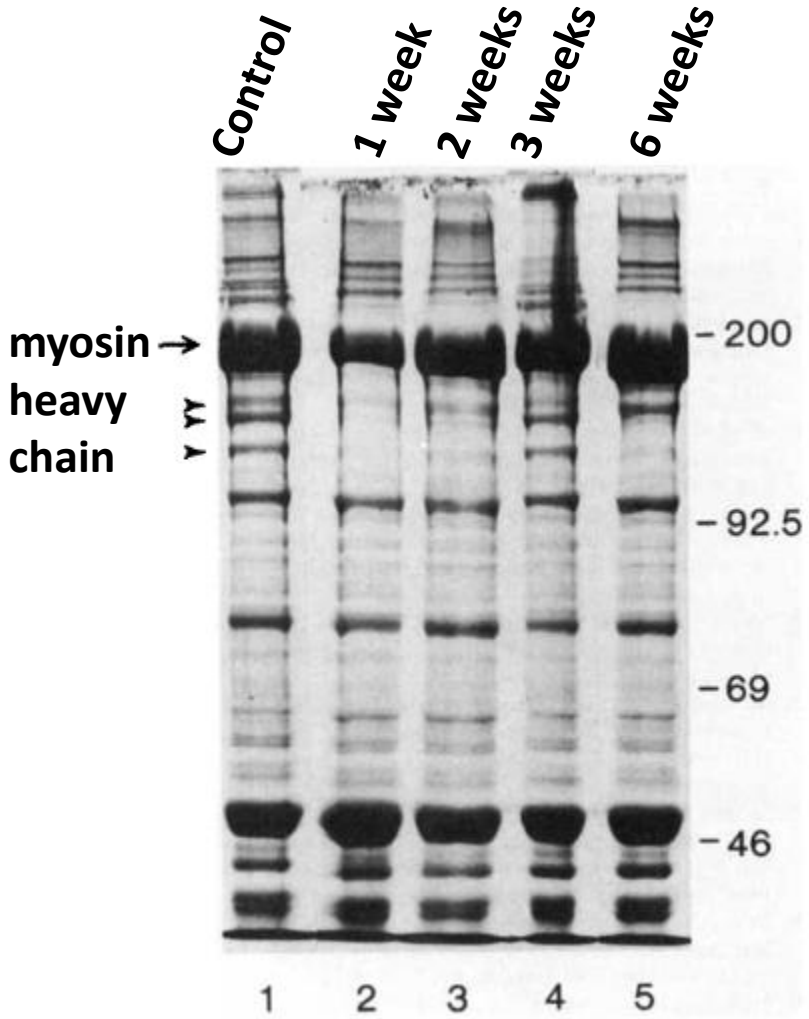
- a.k.a. myosin heavy chain loss or acute quadriplegic myopathy
- High dose corticosteroids and/or neuromuscular junction blockade agents, mechanical ventilation, and prolonged hospitalization
- Occurs in more than 25% of patients mechanically ventilated in the ICU for at least 7 days
- Significant clinical overlap between CIM and CIP
- CK: variably elevated
- Can resolve in weeks to months
  - CIM better outcome than CIP (severe CIP patients can remain quadriplegic)
- High mortality (up to 50%)

LOSS AND RENEWAL OF THICK MYOFILAMENTS IN GLUCOCORTICOID-TREATED RAT SOLEUS AFTER DENERVATION AND REINNERVATION

ROBERTO MASSA, MD, STIRLING CARPENTER, MD, PAUL HOLLAND, PhD, and GEORGE KARPATI, MD

MUSCLE & NERVE 15:1290–1298 1992





Review of Critical Illness Myopathy and Neuropathy

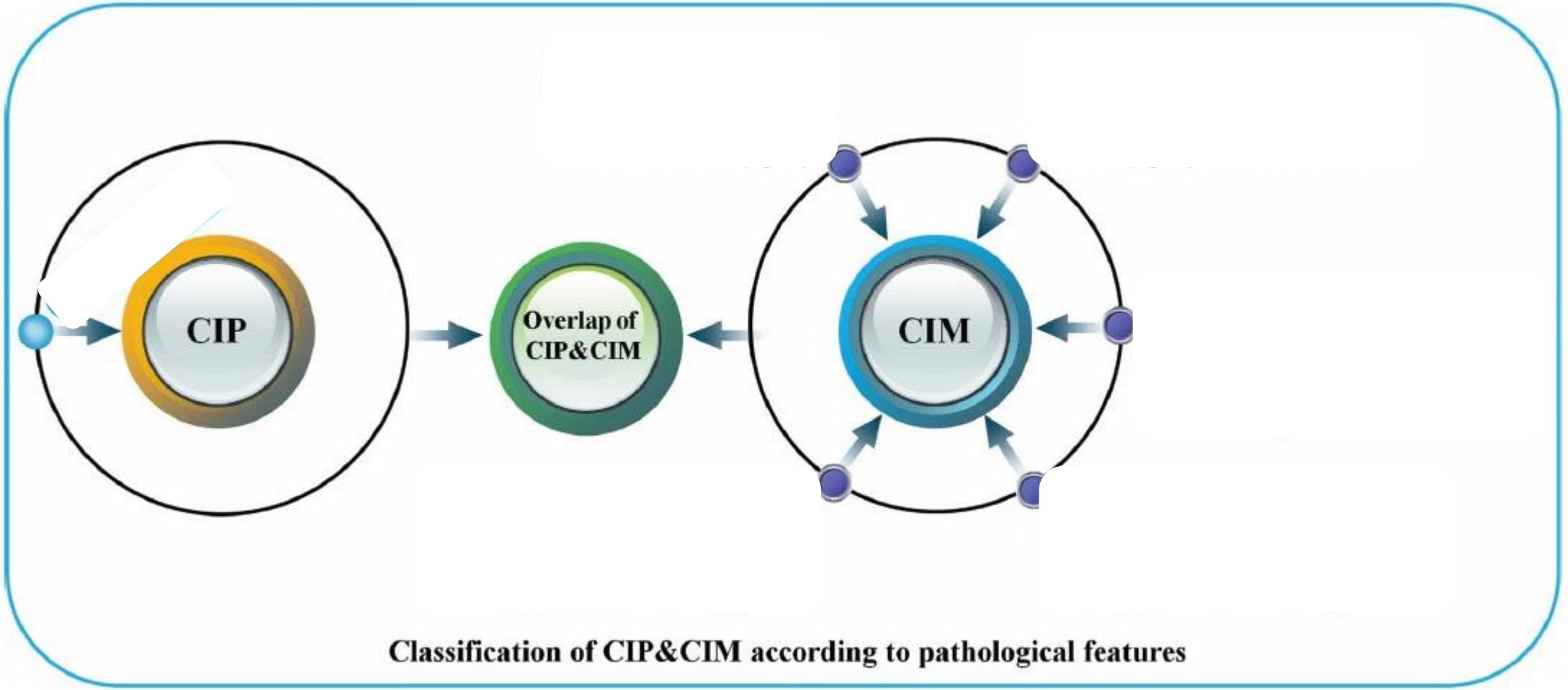
The Neurohospitalist
2017, Vol. 7(1) 41-48

DOI: 10.1177/1941874416663279
journals.sagepub.com/home/nhos
SAGE

Starane Shepherd, MD[1], Ayush Batra, MD[1], and David P. Lerner, MD[1]

Critical Illness and Cytokine Production

Critical illness myopathy and neuropathy – diagnostic clues



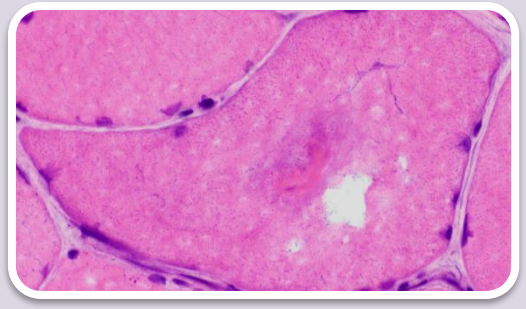
Classification of CIP&CIM according to pathological features

Critical illness polyneuropathy and myopathy: a systematic review

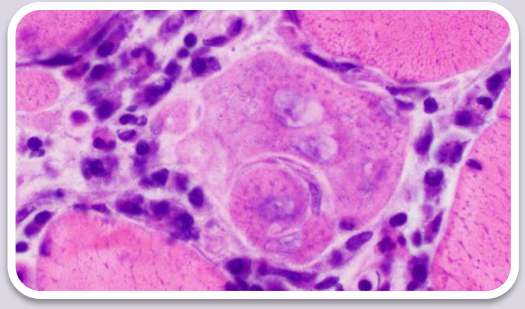
Chunkui Zhou[1,2], Limin Wu[1,3], Fengming Ni[4], Wei Ji[5], Jiang Wu[1], Hongliang Zhang[1]

NEURAL REGENERATION RESEARCH
January 2014, Volume 9, Issue 1

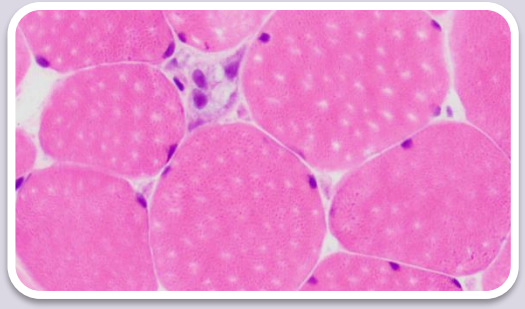
Patterns of systemic therapy-related myopathies



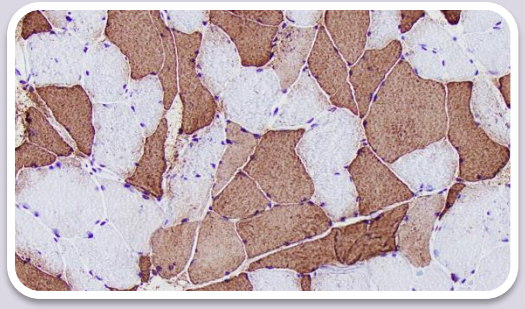
Vacuolar myopathy



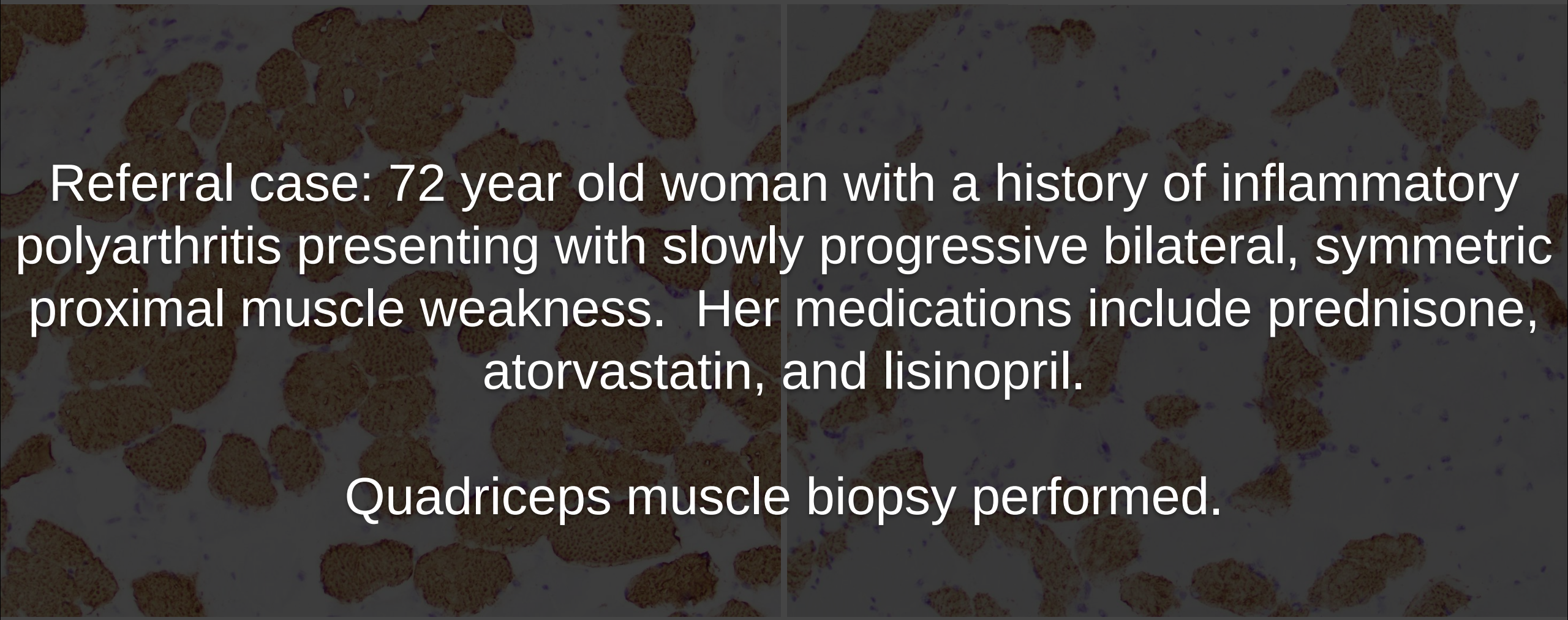
Necrotizing myopathy with inflammation



Necrotizing myopathy without inflammation



Fiber size variation



Referral case: 72 year old woman with a history of inflammatory polyarthritis presenting with slowly progressive bilateral, symmetric proximal muscle weakness. Her medications include prednisone, atorvastatin, and lisinopril.

Quadriceps muscle biopsy performed.

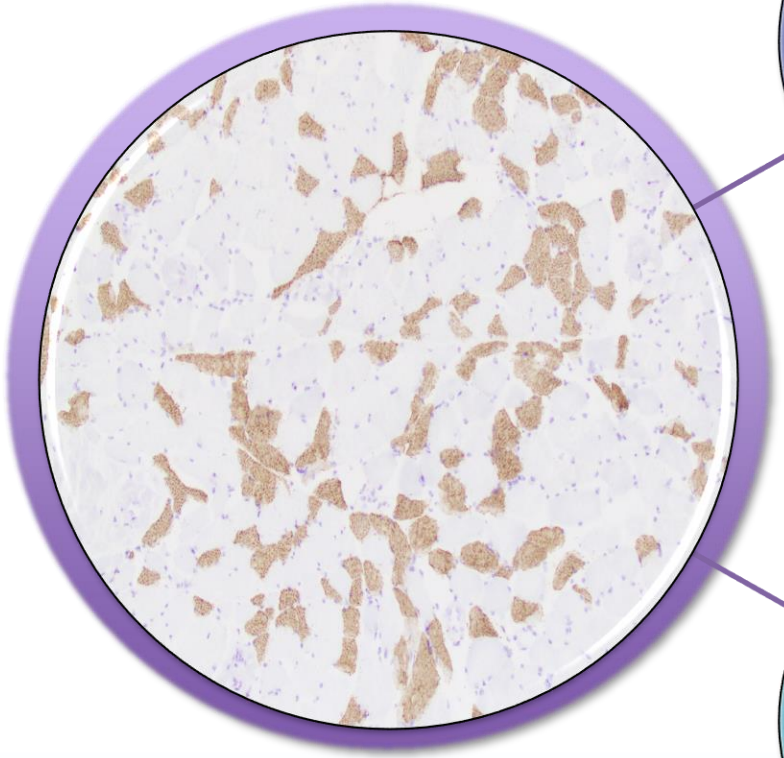
Differential diagnosis - type II fiber atrophy

- Disuse
- Hypothyroidism
- Myasthenia gravis
- Chronic alcoholism
- Drug-induced/toxic myopathies
  - Corticosteroids

© Copyright Colitis Ninja™ 2016. Colitis Ninja is considered a trademark of Elder Illustration & Associates, Inc.

Corticosteroids – muscle toxicity

- Incidence from 2.4 – 21% of patients taking steroids long-term
- Highest risk is chronic exposure to high-dose oral steroids
- Slowly progressive proximal muscle weakness
- Fluorinated (e.g. dexamethasone, triamcinolone, etc) > non-fluorinated (e.g. prednisolone, hydrocortisone, etc)
- CK: normal
- EMG/NCS: normal or show subtle myopathic changes
- Reduction in dose, alternate-day dosing, or switching to a non-fluorinated steroid can alleviate weakness



Anti-anabolic

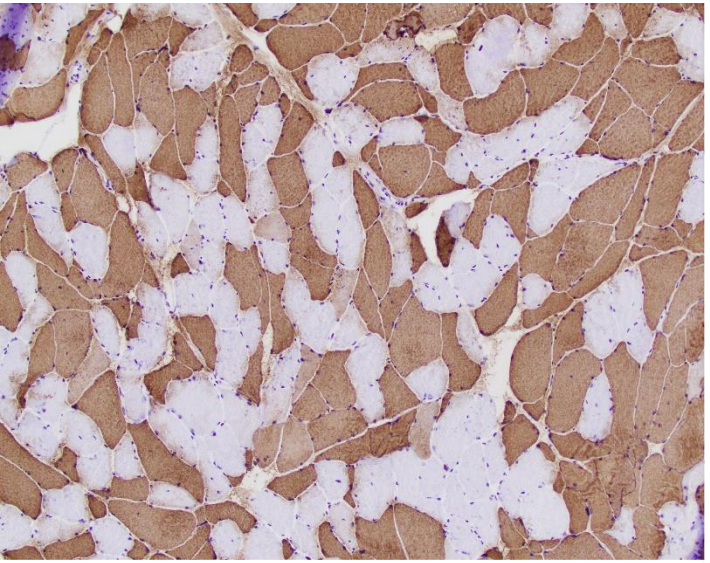
- Inhibition of amino acid transport into muscle
- Inhibit action of insulin and IGF-1
- Inhibit myogenesis by downregulating myogenin

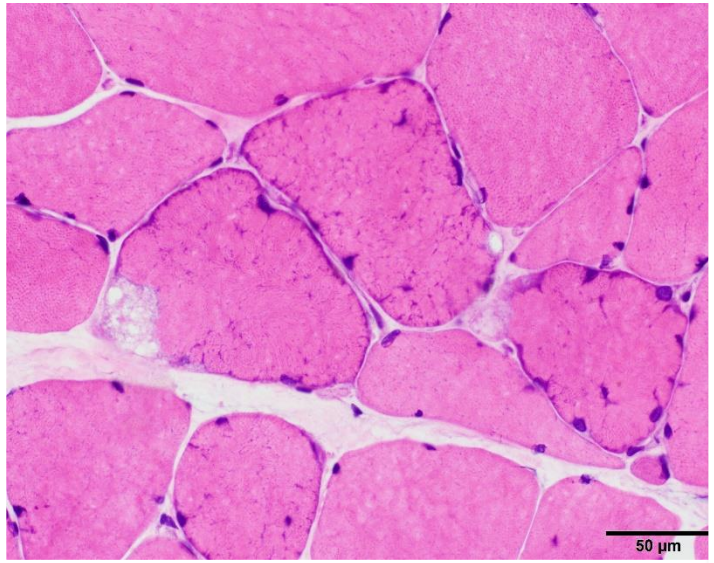
Catabolic

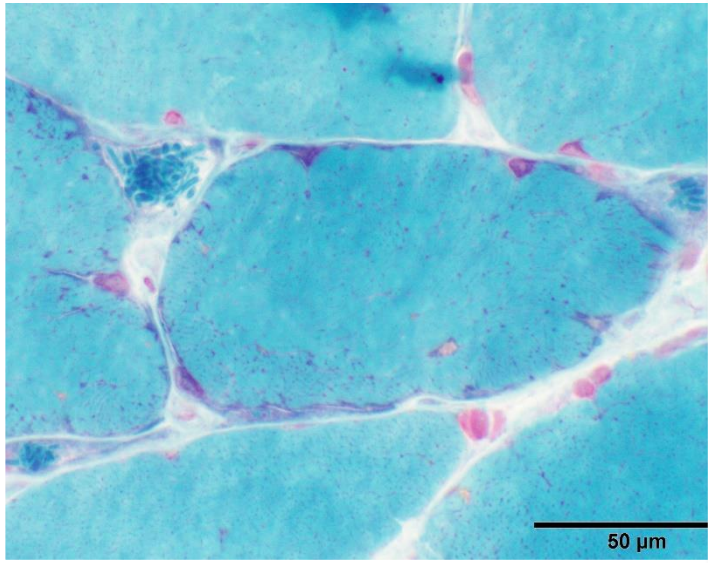
- Activation of ubiquitin-proteosome system
- Activation of lysosomal system (cathepsins)
- Activation of calcium-dependent system (calpains)

Corticosteroid-induced myopathy – diagnostic clues

- Type II fiber atrophy
- Rule out other underlying causes







J Vet Intern Med 1998;12:424–430

Nemaline Rods in Canine Myopathies: 4 Case Reports and Literature Review

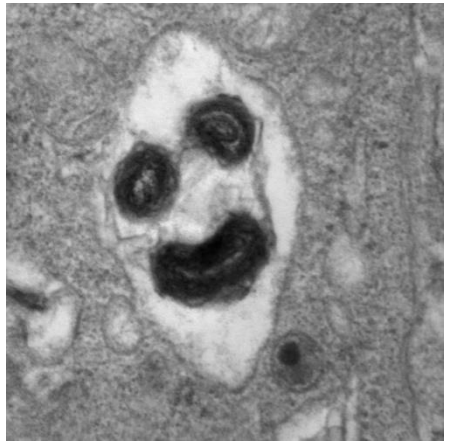
Agnes J. Delauche, Paul A. Cuddon, Michael Podell, Kim Devoe, Henry C. Powell, and G. Diane Shelton

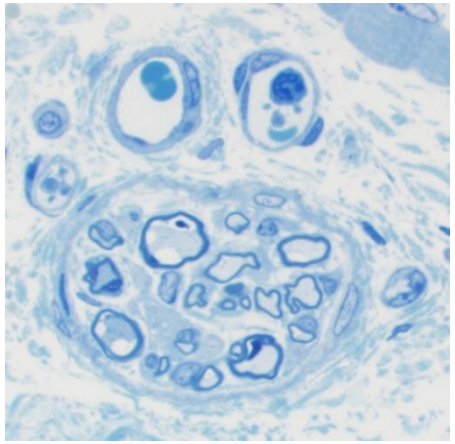
Take-home points

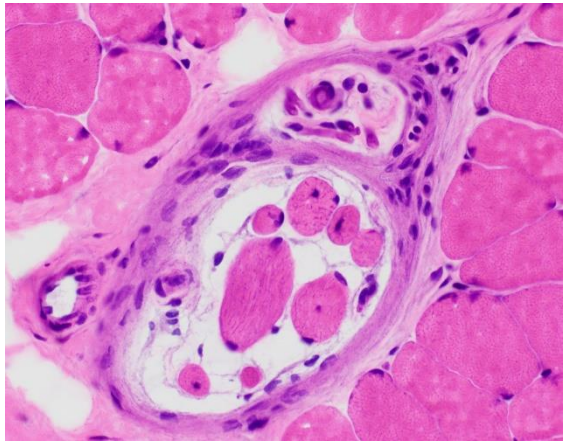
- **Chloroquines and colchicine**
  - Very few **defining** diagnostic features when comparing systemic-therapy related VM and other causes
    - If chloroquine-related, EM can help
- **Statins**
  - Anti-HMGCR antibodies (IMNM) can be present even without exposure to statins (even in pediatric patients)
    - Necrosis with endomysial/perimysial lymphocytic inflammation, patchy MHC Class I and complement C5b-9 deposition
- **Critical care myopathy/polyneuropathy**
  - Patients in ICU exposed to steroids +/- NMJ blockade with mechanical ventilation
  - EM can help - thick filament loss most diagnostic finding
  - High mortality
- **Corticosteroids**
  - Selective type II fiber atrophy due to decreased protein synthesis with concomitant increased proteolysis
- **FOR ALL**
  - Full recovery *possible* with removal of offending agent (variable responses)
  - Consider systemic therapy-related disease in workups and mention this in your report comment!

Histopathologic Pattern	Drug	Mechanism	Diagnostic clues
vacuolar myopathy	**chloroquine/hydroxychloroquine**	lysosomal activity inhibition	1. myeloid bodies (EM) 2. curvilinear bodies (EM)
	colchicine	inhibition of microtubule polymerization	1. spheromembranous bodies (a.k.a. myeloid bodies) (EM)
necrosis with inflammation	**statins**	myotoxicity/immune-mediated	1. necrosis in various stages 2. lymphocytic inflammation (possibly sparse) 3. patchy MHC Class I 4. complement C5b-9 deposition
necrosis without inflammation	**critical care myopathy/polyneuropathy**	microvascular, metabolic, and/or electrical alterations?	1. loss of thick filaments (EM) 2. variable necrosis 3. type II fiber atrophy
type II fiber atrophy	**corticosteroids**	increased proteolysis, decreased protein synthesis	1. type II fiber atrophy

Acknowledgments







UIDL
UI Diagnostic Laboratories

- UIHC
  - Steve Moore, MD, PhD
  - Leslie Bruch, MD
  - Marco Hefti, MD
  - Pat Kirby, MD
  - Amy Trent, BS, MT
- OSF Healthcare
  - Sarah Bach, MD

- Chris Baxter Design
- All the neuropathologists and neurologists sending us consults
- Our patients!
- Twitter and Instagram pathologists