

Muscle Pathology Across a Spectrum: Tips to Diagnose Common Muscle Diseases with Varied Presentations

Karra A. Jones, MD, PhD

X @BrainsThePath

Associate Professor of Pathology

Division of Neuropathology

Duke University

Disclosures

- I have the following relevant financial relationships to disclose
 - I am a consultant for Astellas Gene Therapies (formerly Audentes Therapeutics, Inc.)



Learning Objectives

- Summarize histochemical and immunohistochemical stains to assist with identification of vacuoles in skeletal muscle.
- Identify histopathologic and immunostaining features of immune-mediated necrotizing myopathy.
- Outline potential pitfalls in the diagnosis of mitochondrial myopathies.

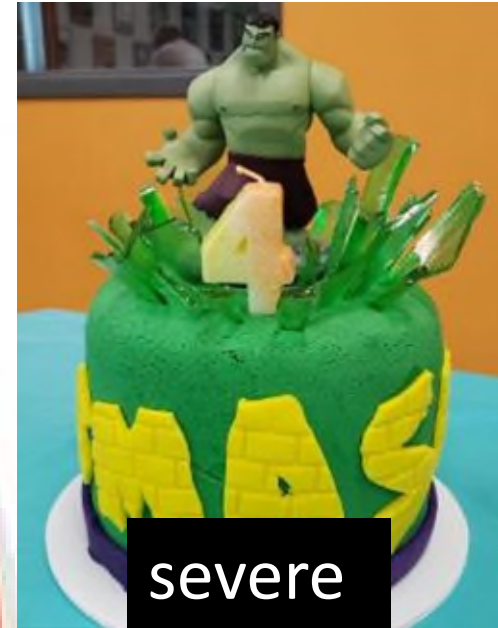




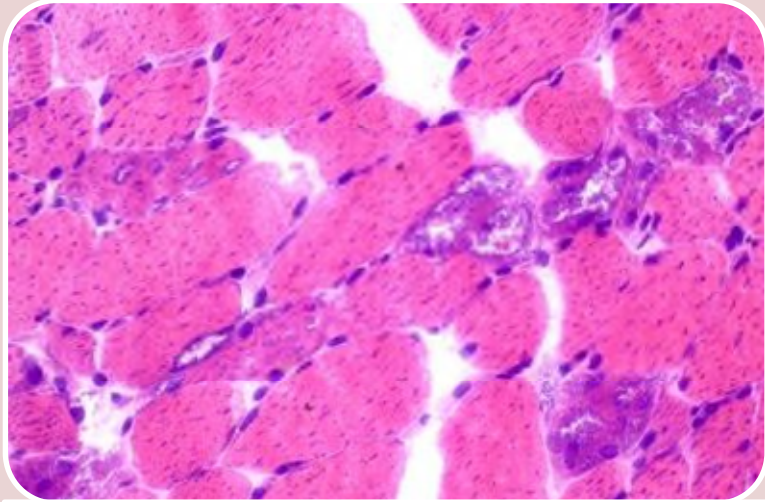
mild



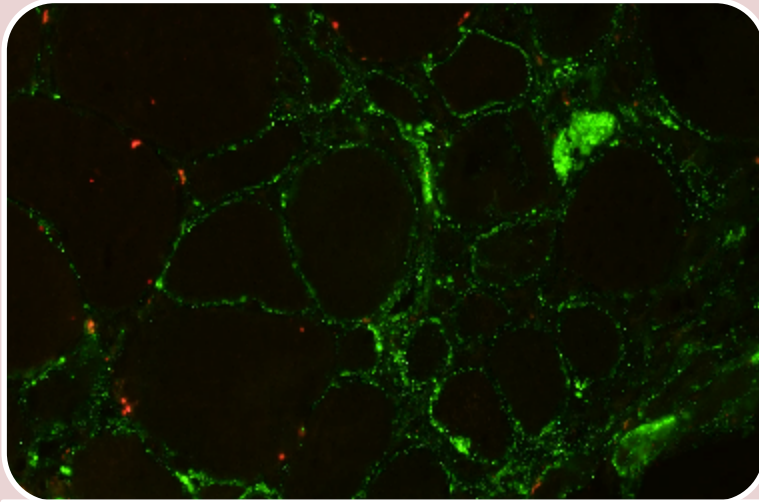
moderate



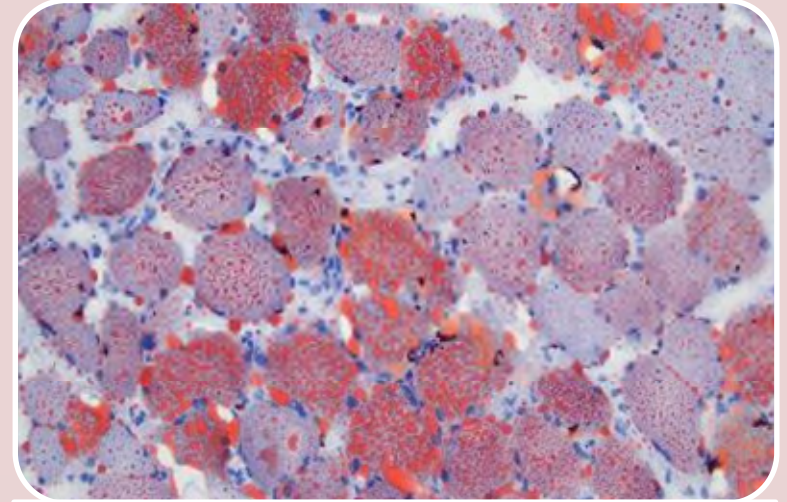
severe



Toxic



Inflammatory



Metabolic

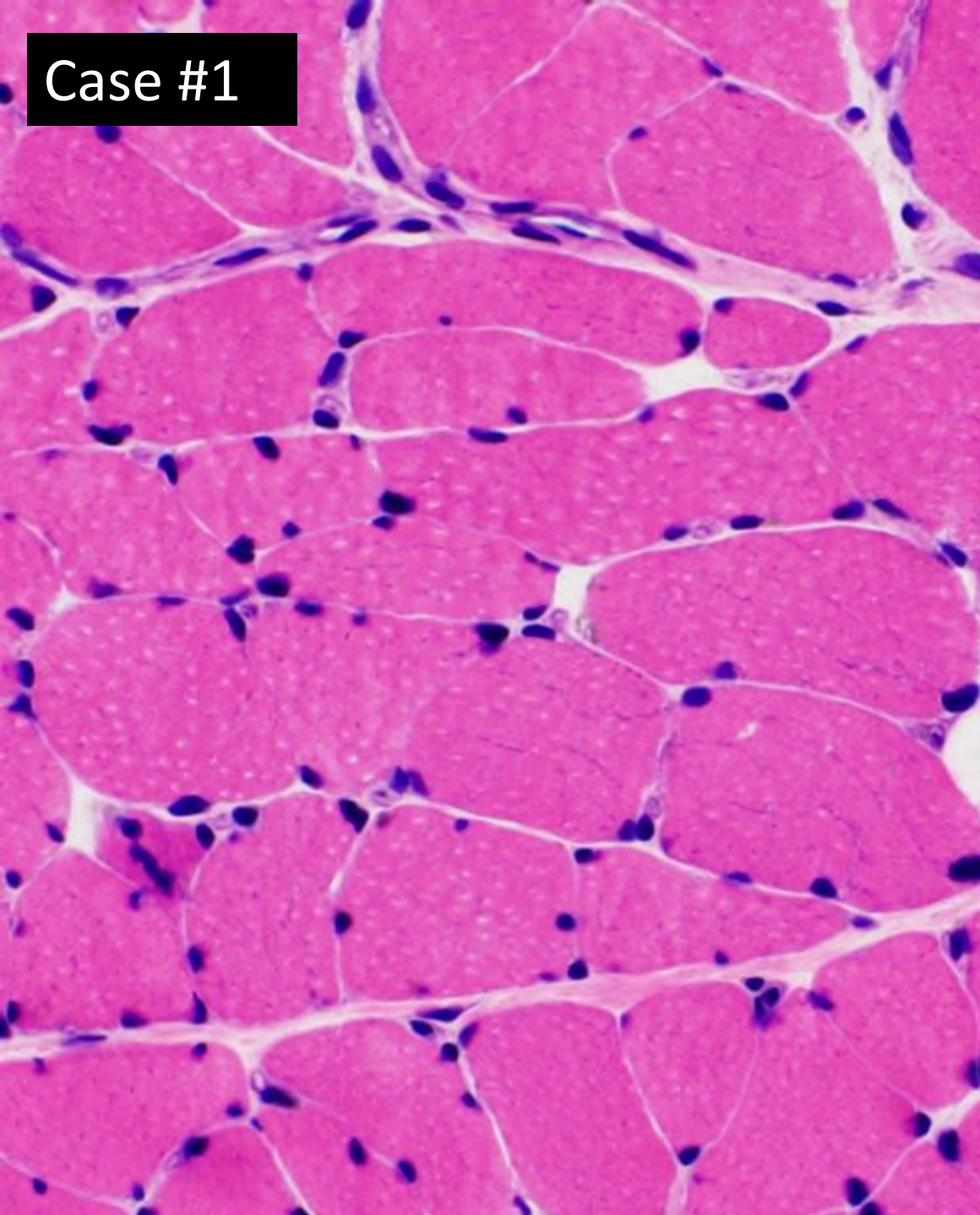
Case #1

- 57-year-old woman
- History of rheumatoid arthritis
- Progressive bilateral upper and lower extremity weakness
- Rx: hydroxychloroquine and statin
- EMG: findings concerning for a myopathic process
- CK: normal

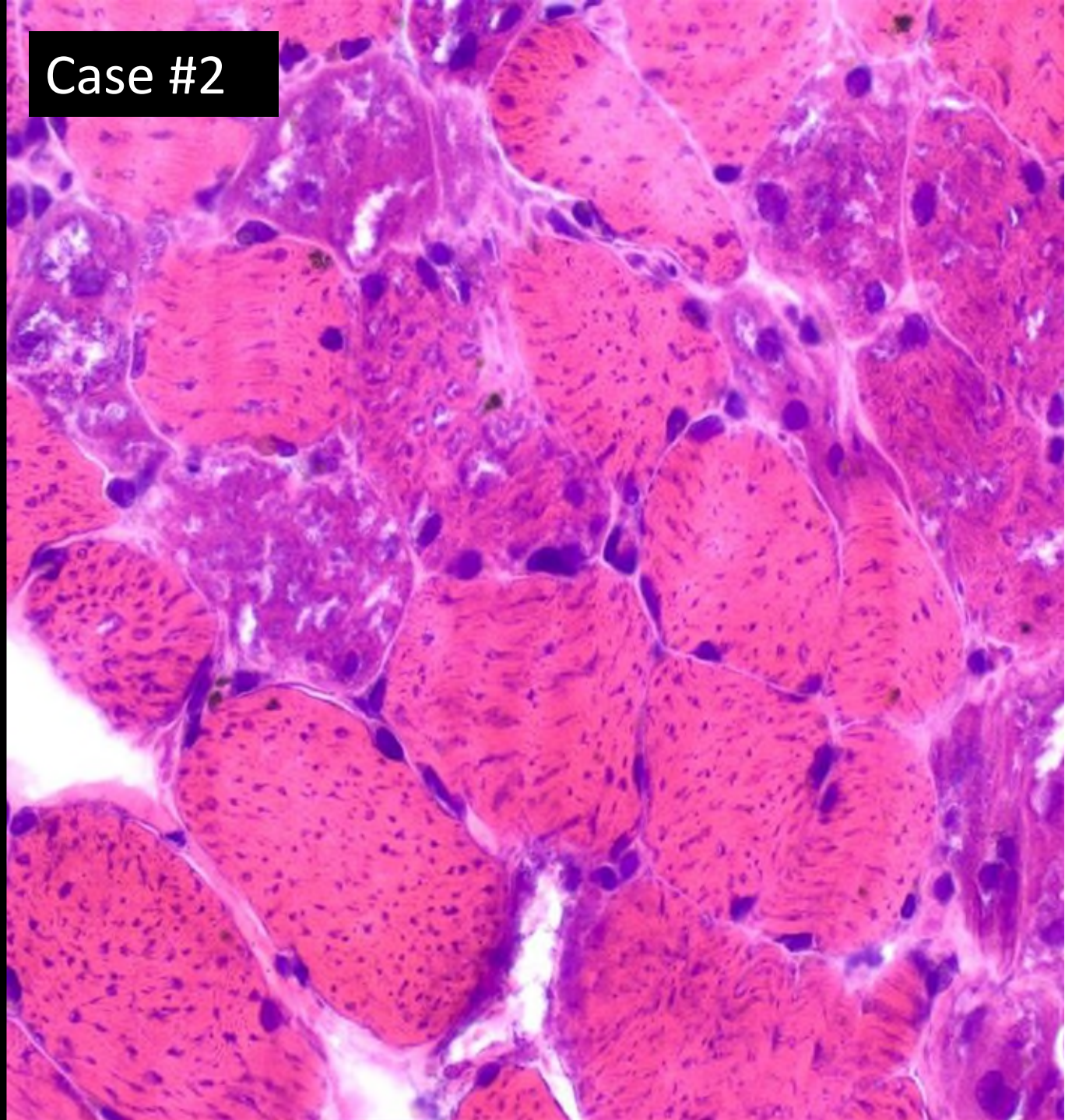
Case #2

- 50-year-old woman
- History of SLE
- Hand weakness began two years prior that progressed to generalized weakness requiring a walker for ambulation
- Symptomatic bradycardia and heart block
- Rx: hydroxychloroquine and statin
- EMG: diffuse myopathy with membrane irritability
- CK: normal; aldolase and LDH: elevated

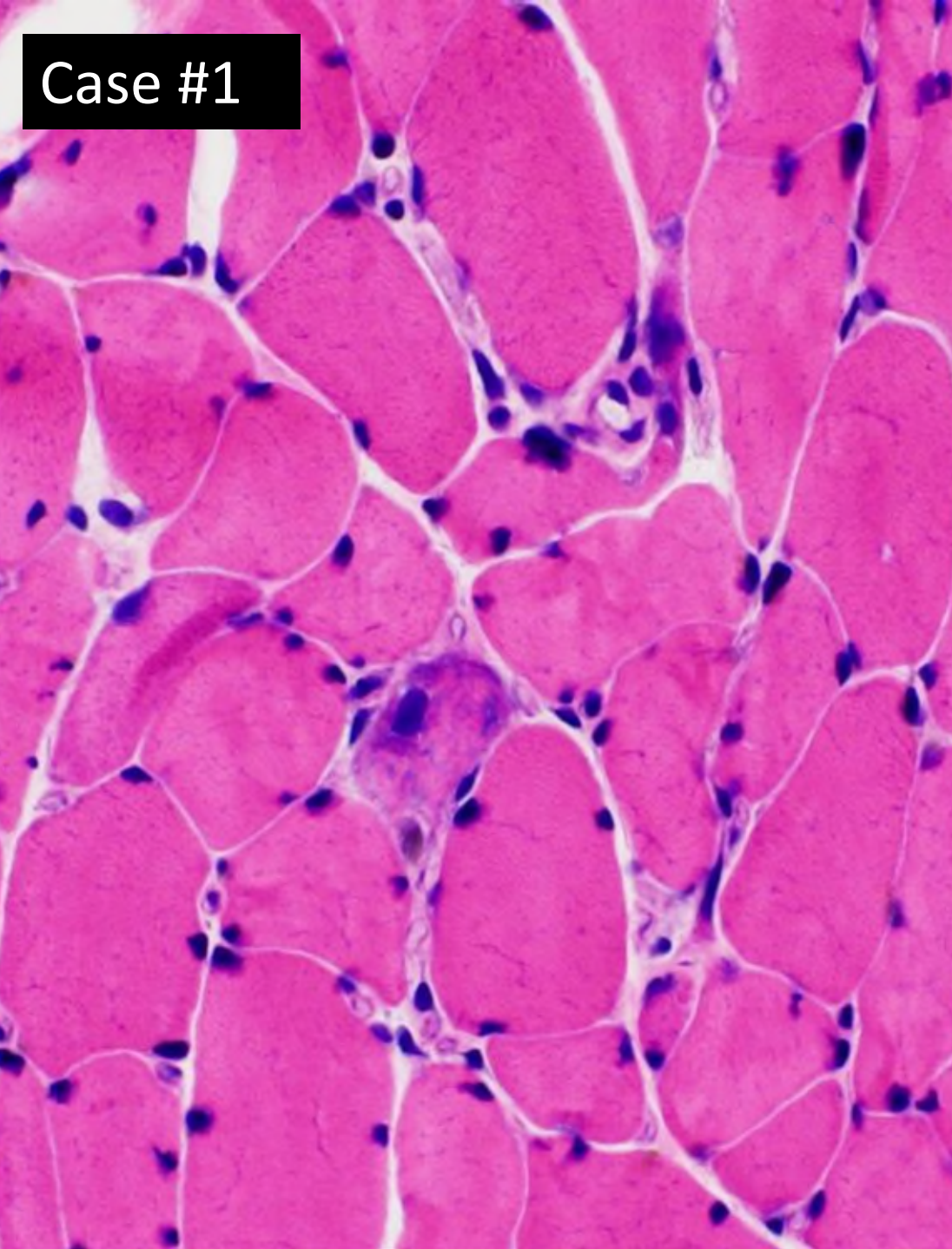
Case #1



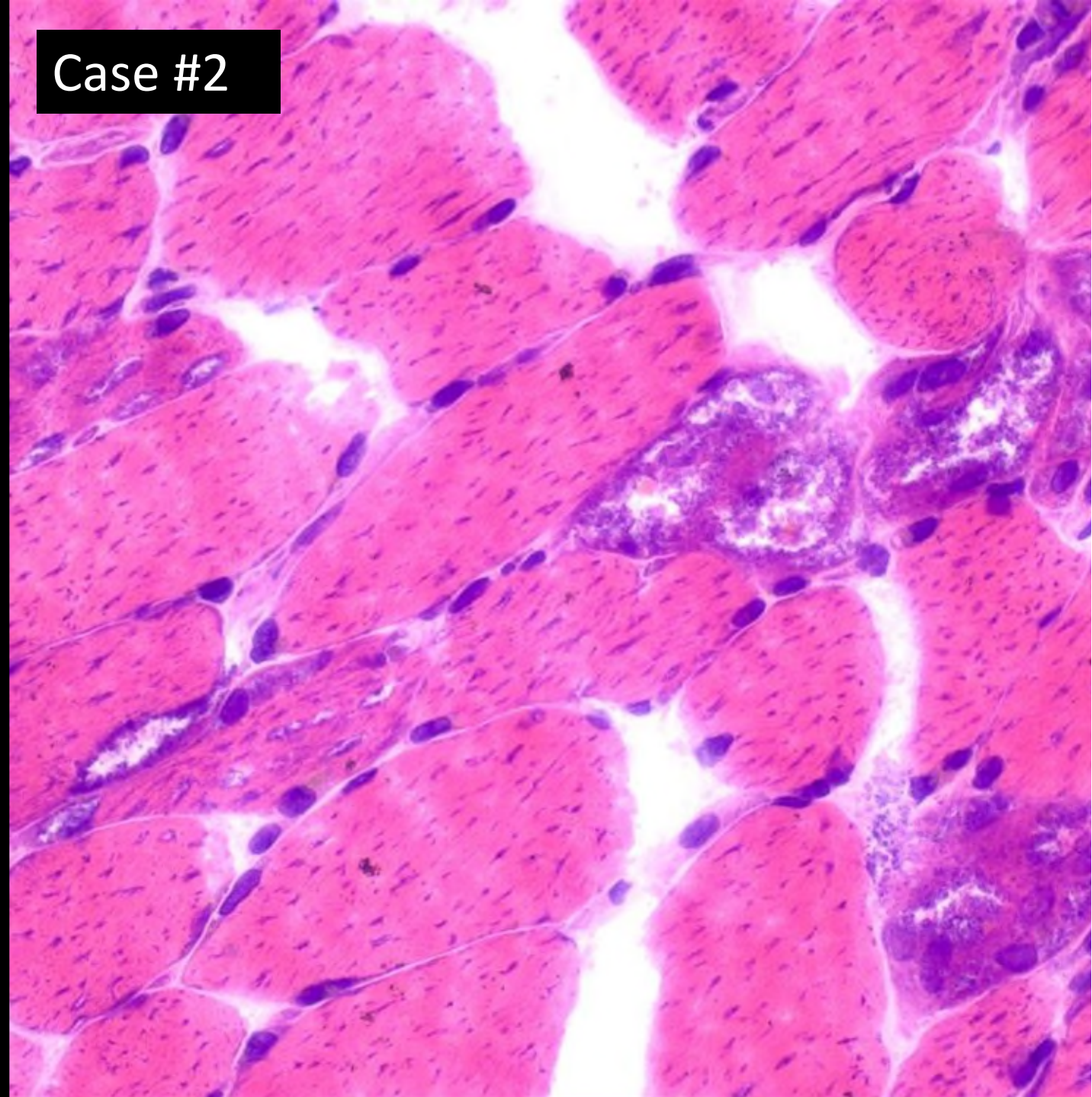
Case #2



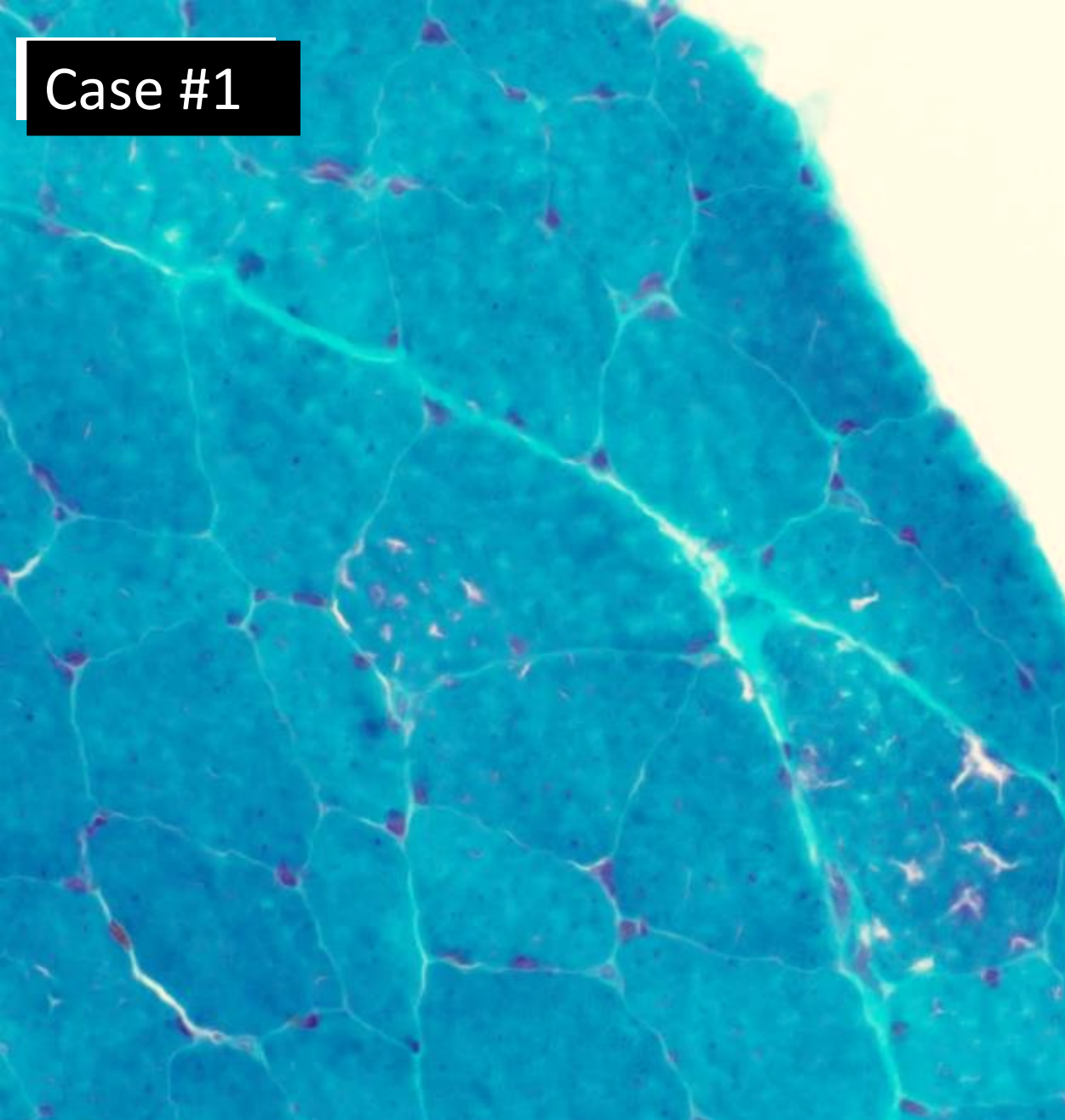
Case #1



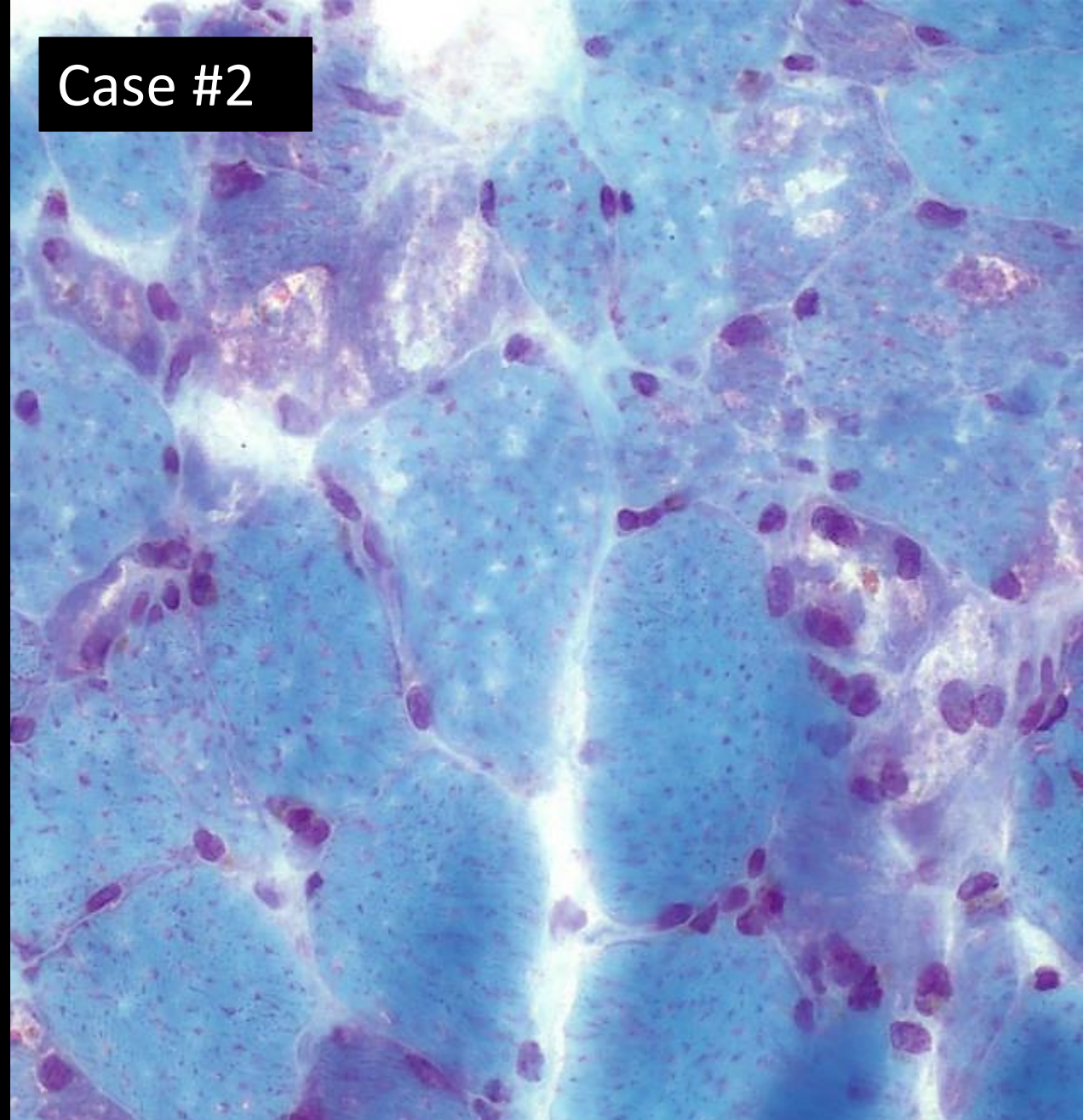
Case #2



Case #1



Case #2

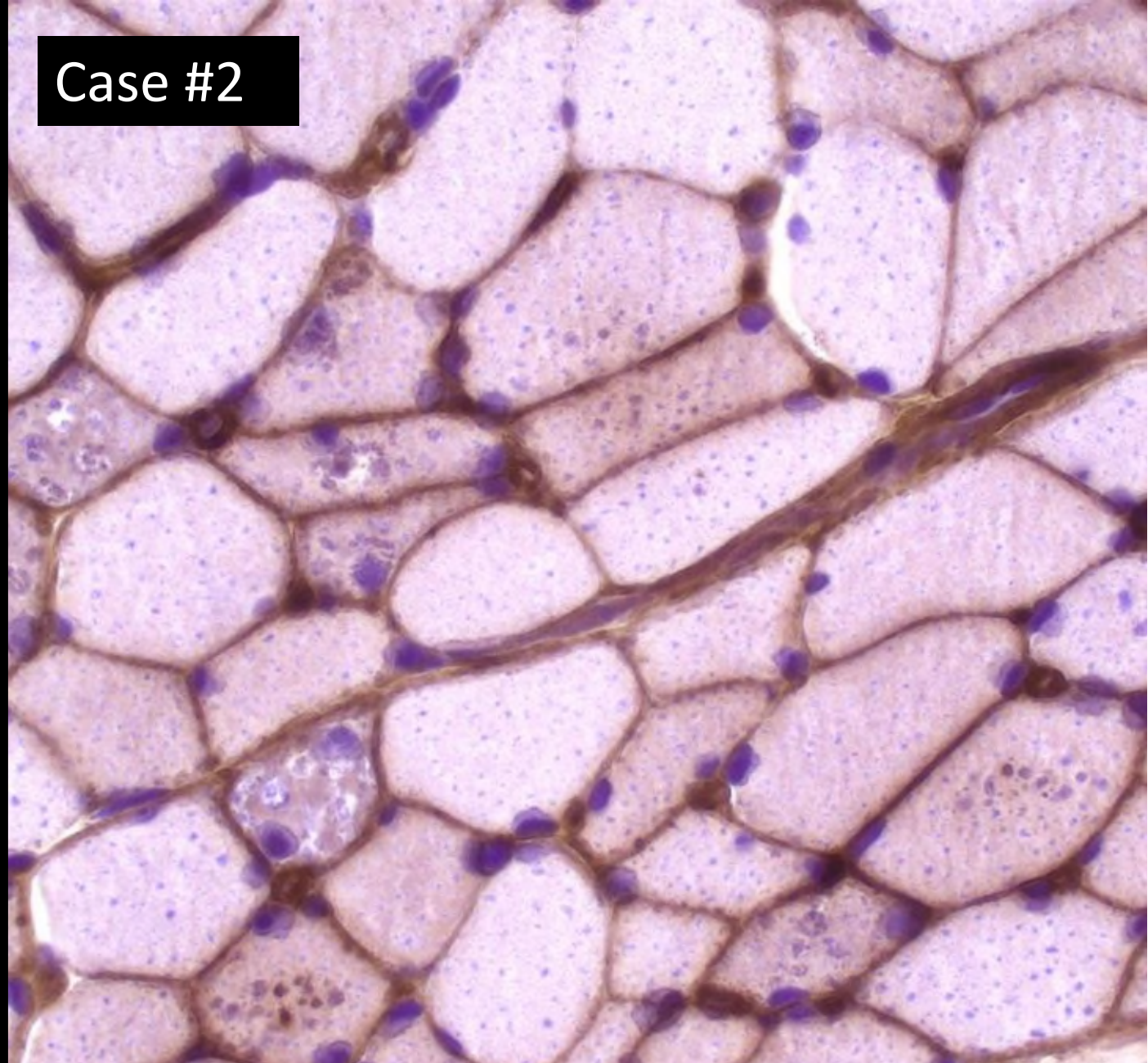


modified Gomori trichrome

Case #1

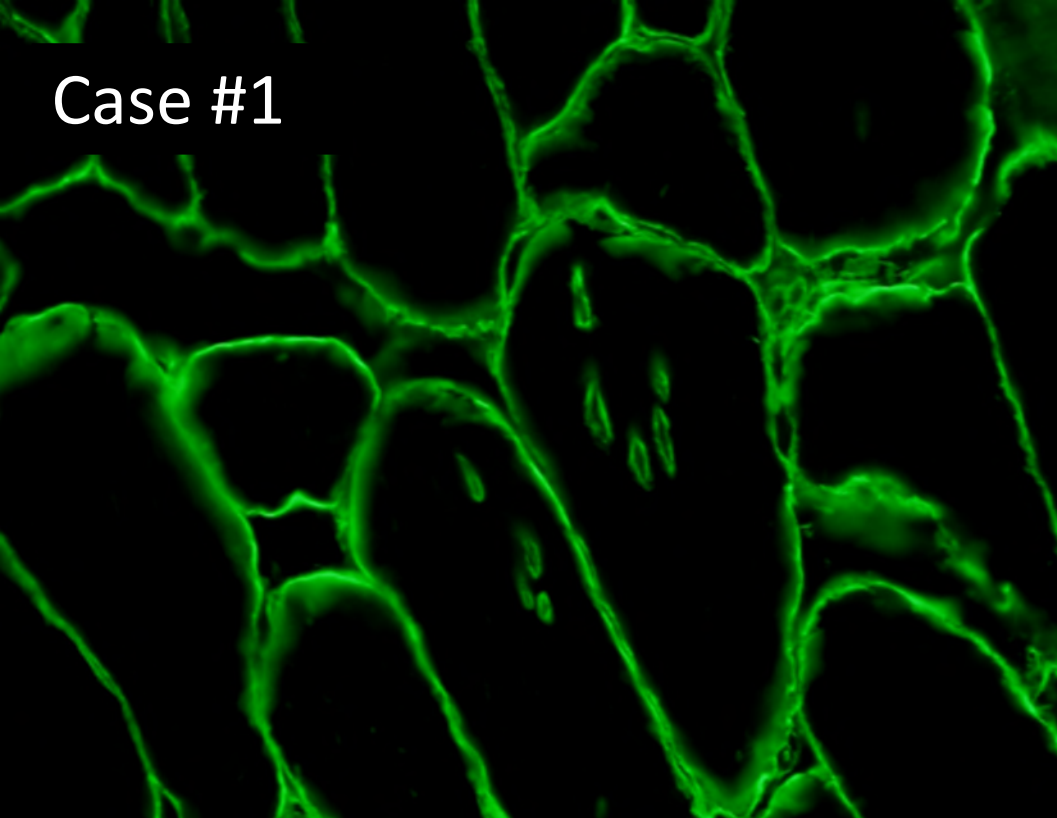


Case #2

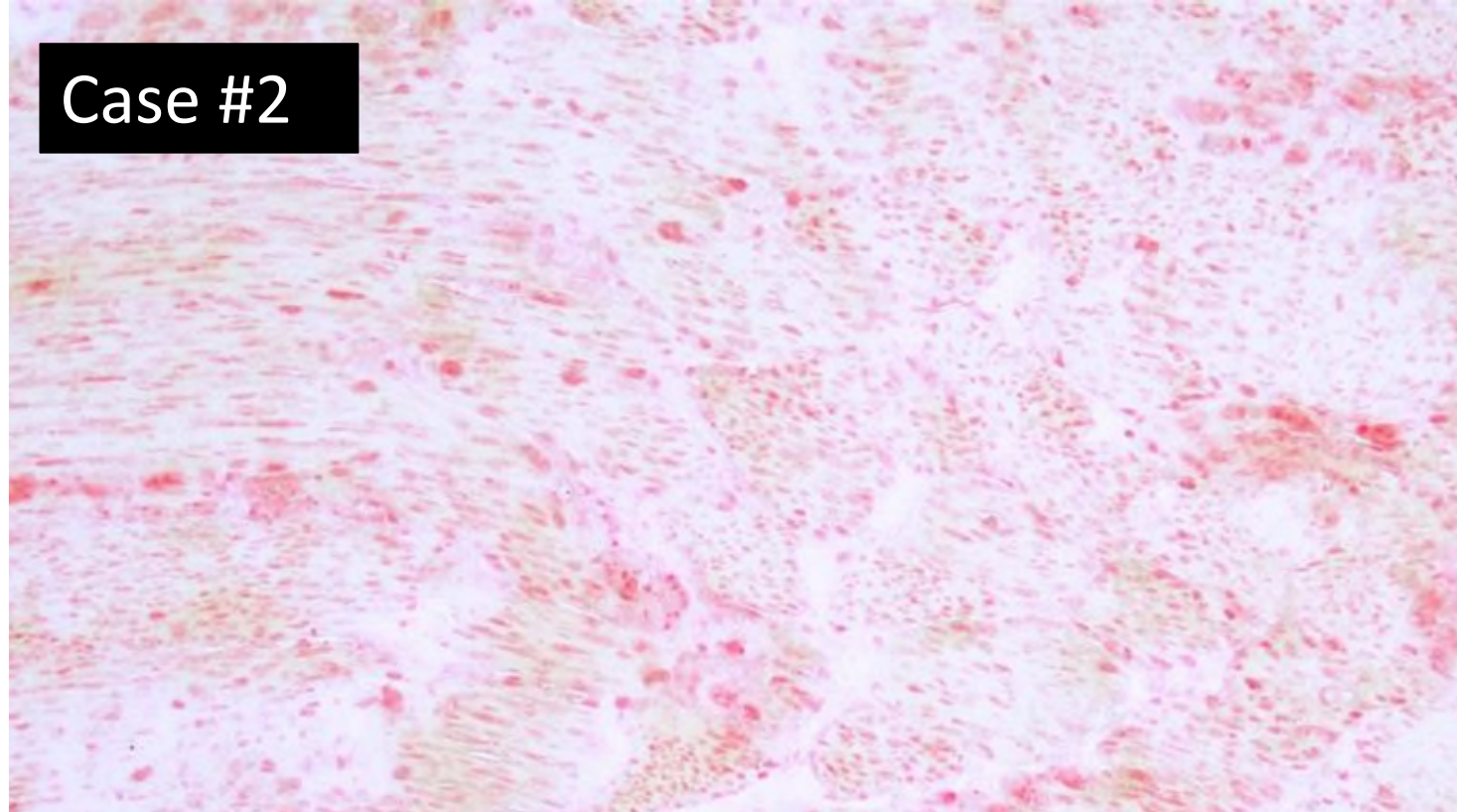


acetylcholinesterase

Case #1

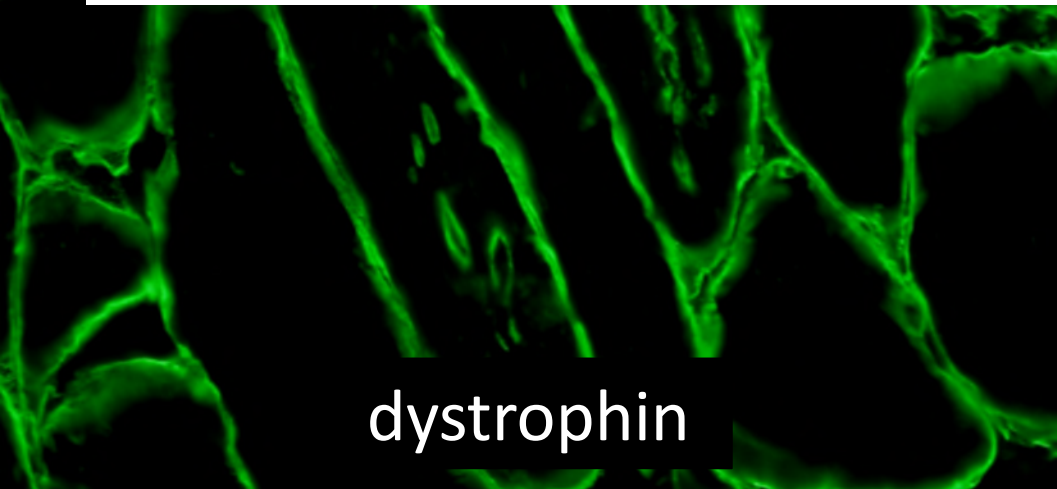


Case #2



Vacuoles – at least a subset with sarcolemmal features

dystrophin

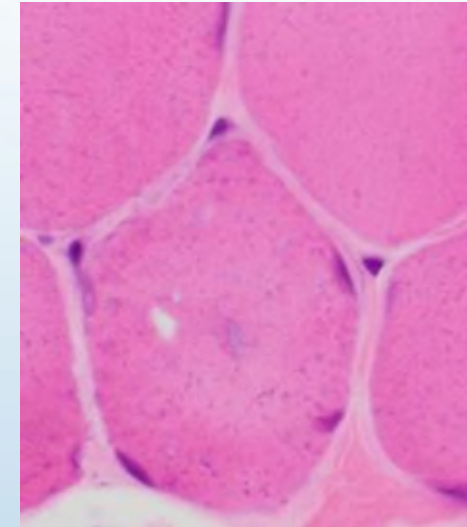
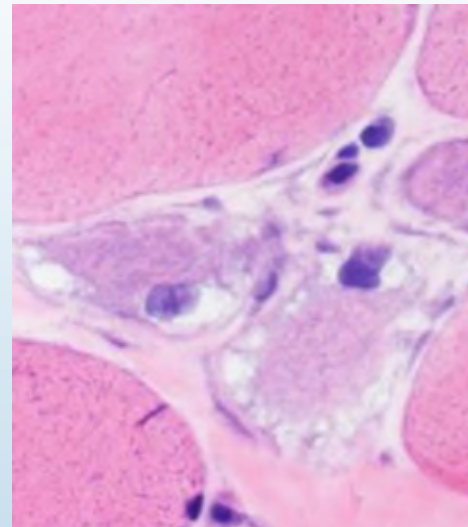
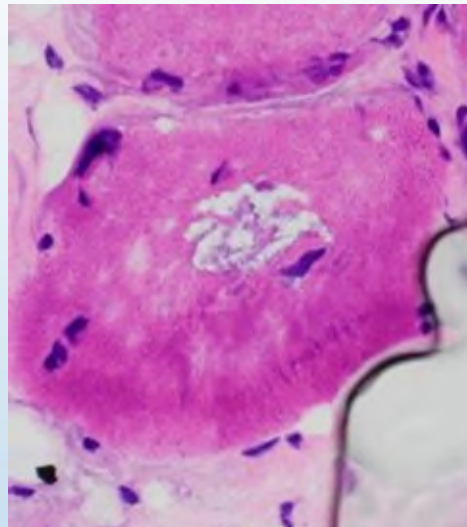
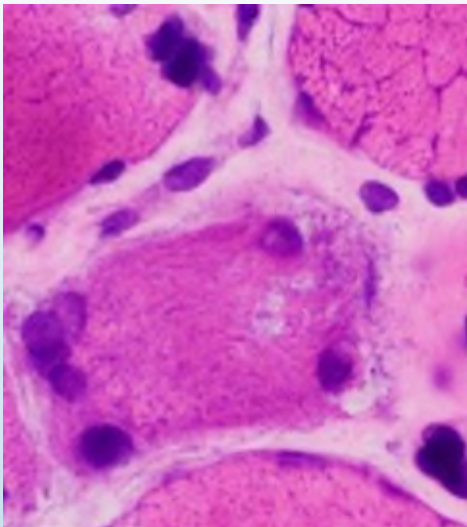
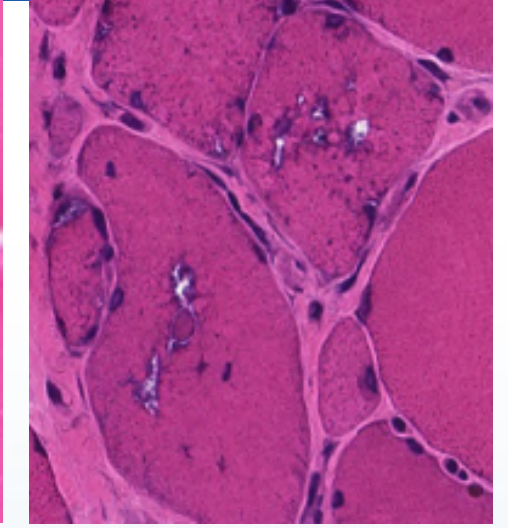
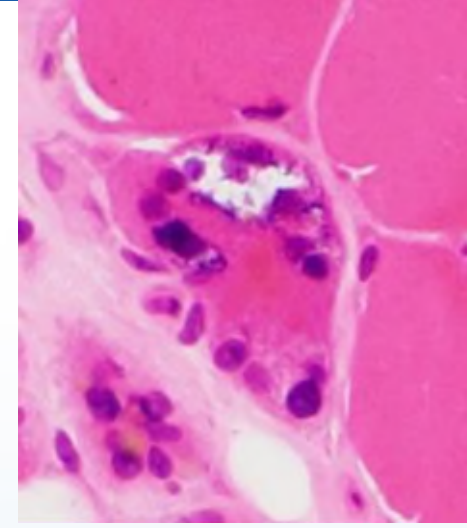
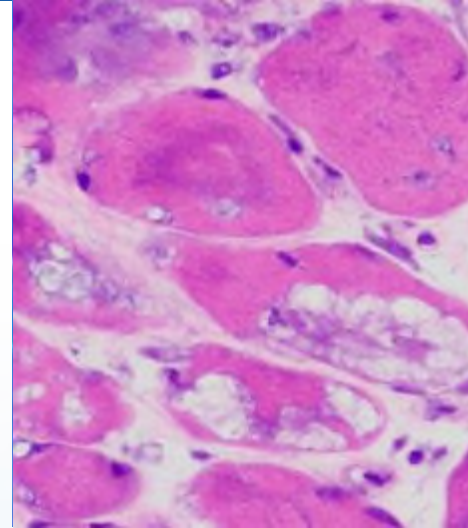
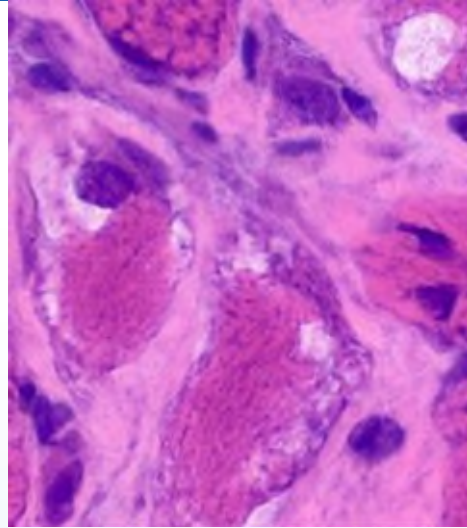
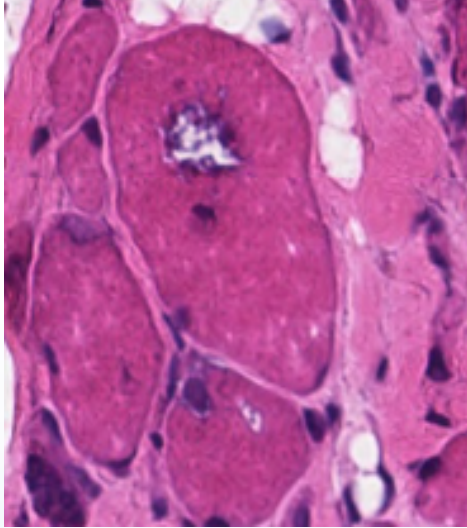


acid phosphatase



Many faces of Vacuoles by H&E

Rimmed; non-rimmed; sarcolemmal features (express sarcolemmal proteins)

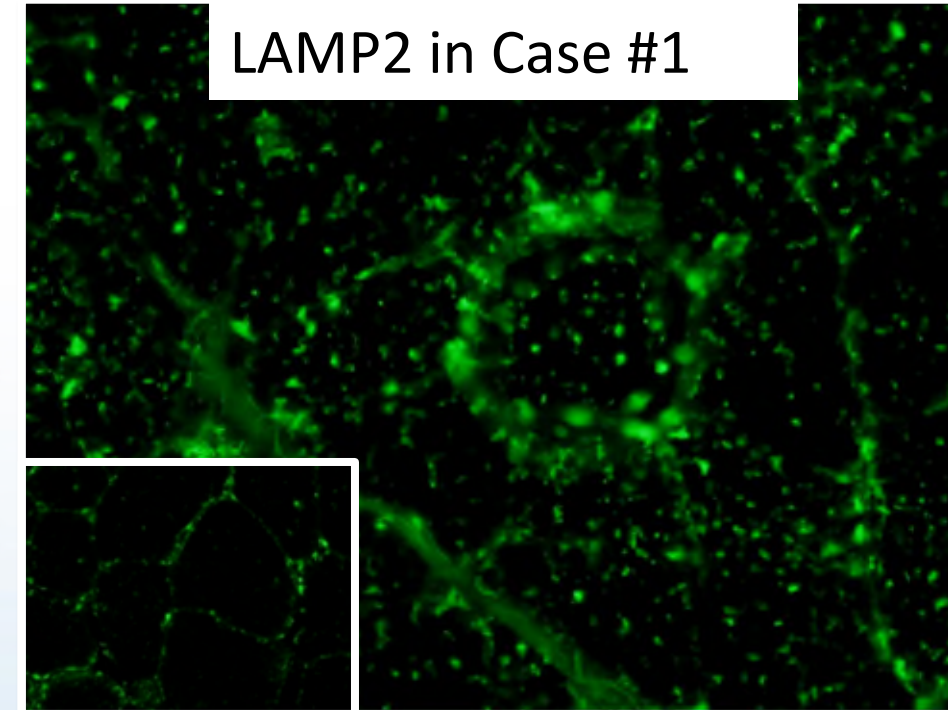


Pitfall –
Sometimes so subtle they only appear as pinpoint basophilic dots

Differential diagnosis – vacuoles with sarcolemmal features – Mild

→ severe

- Idiopathic inflammatory myopathy
 - IBM
 - IMNM
 - DM and ASyS
- Autophagic vacuolar myopathies
 - Danon disease
 - XMEA
 - Pompe disease
- Other inherited myopathies
 - **Nonspecific!**
 - Glycogen storage myopathies (e.g. *GNE*, *VCP*)/multisystem
 - Congenital myotonic dystrophy
 - Congenital hypopharyngeal muscular dystrophy
 - Other muscular dystrophies
- Drug-induced myopathies
 - Chloroquine/hydroxychloroquine
 - Colchicine



What about EM?



Case #1

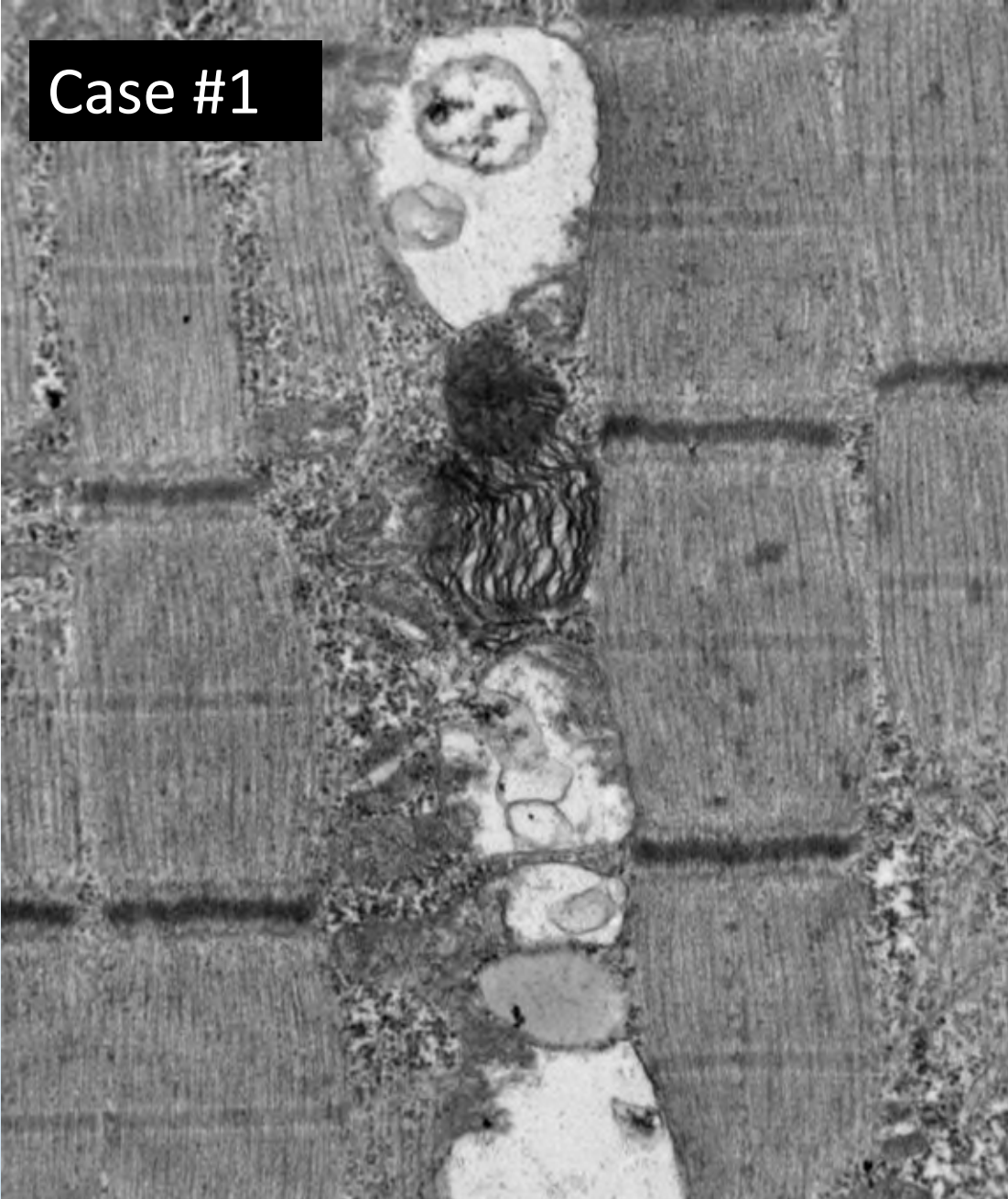


Case #2



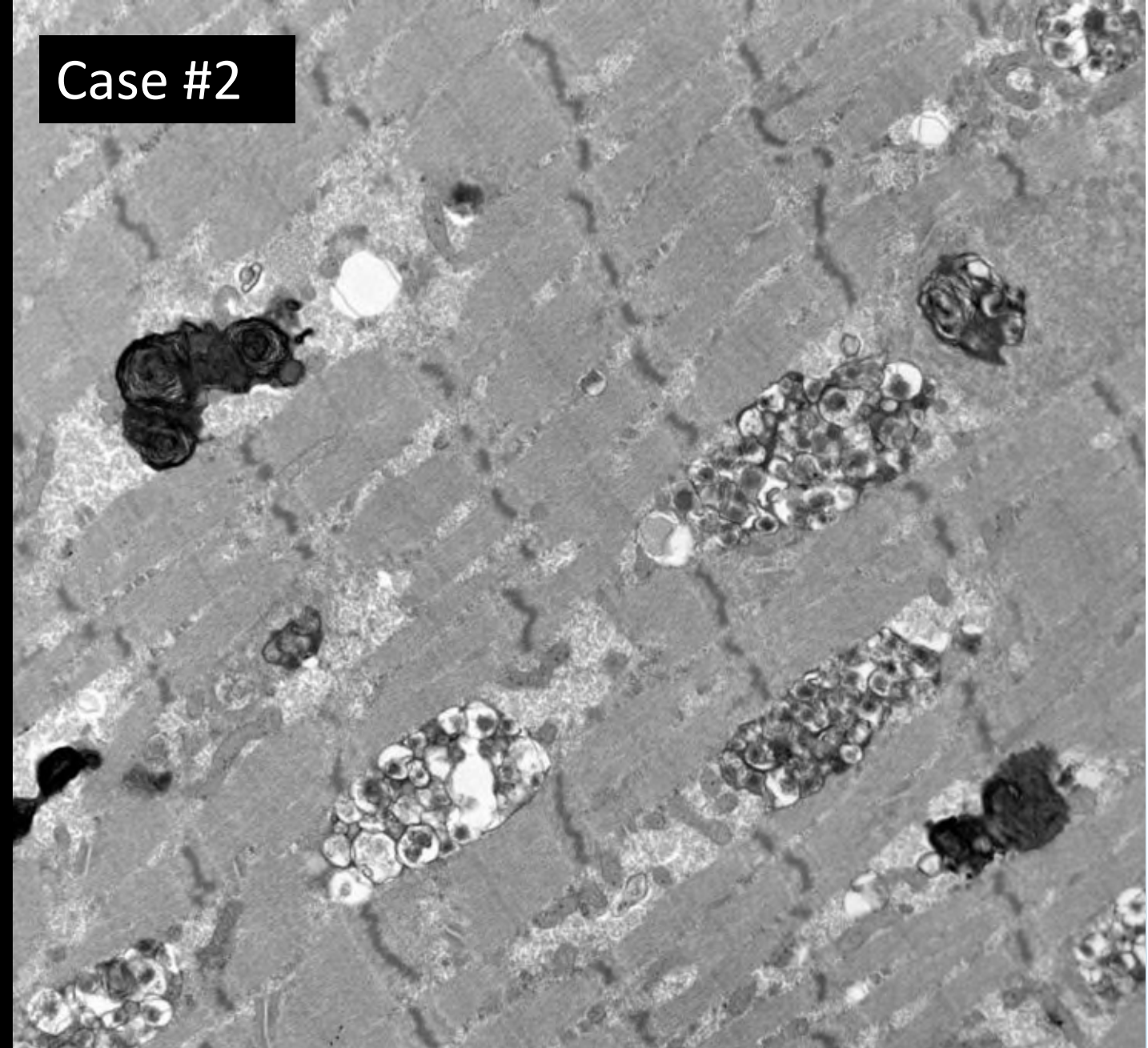
myeloid bodies

Case #1



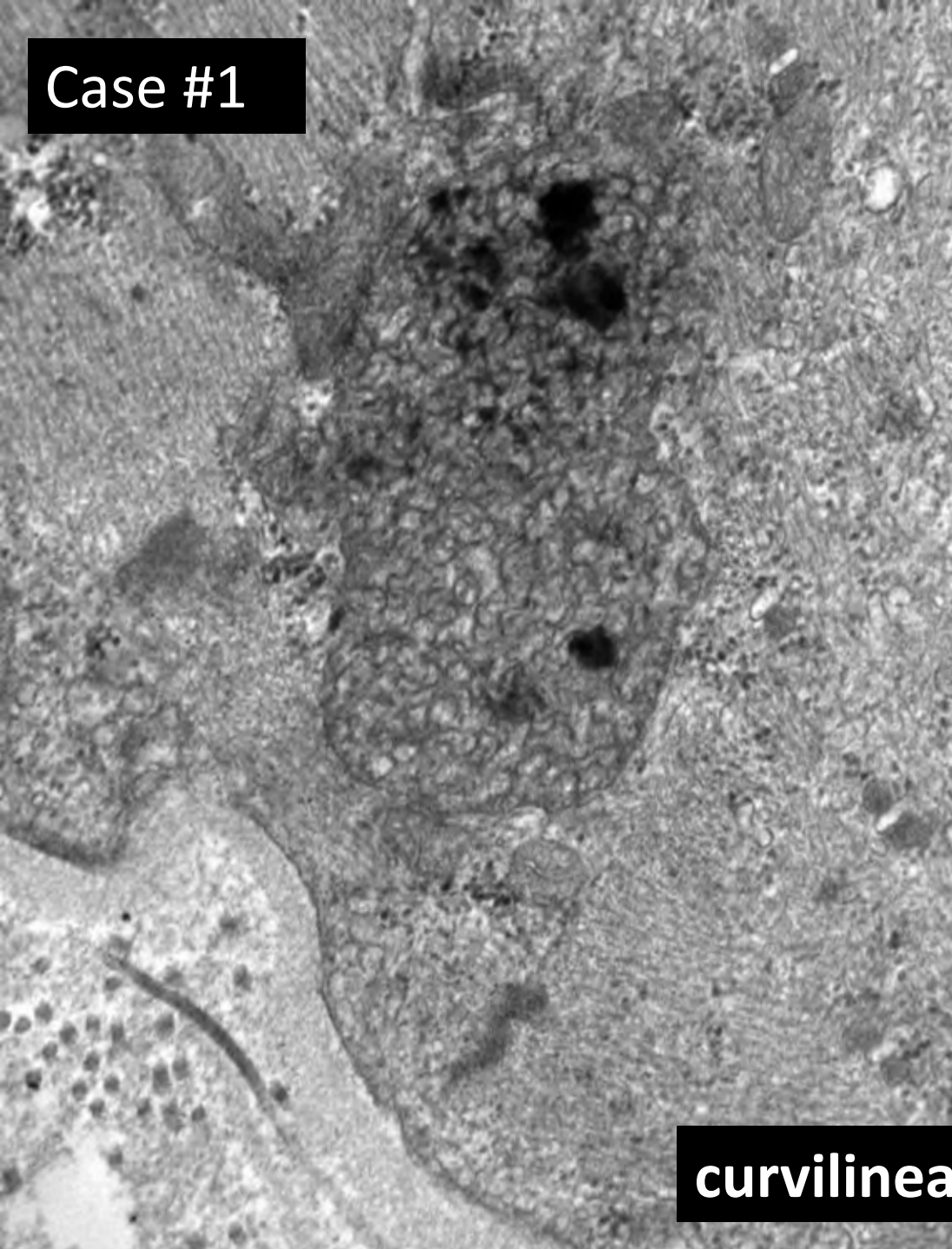
zebra body; vacuoles?

Case #2

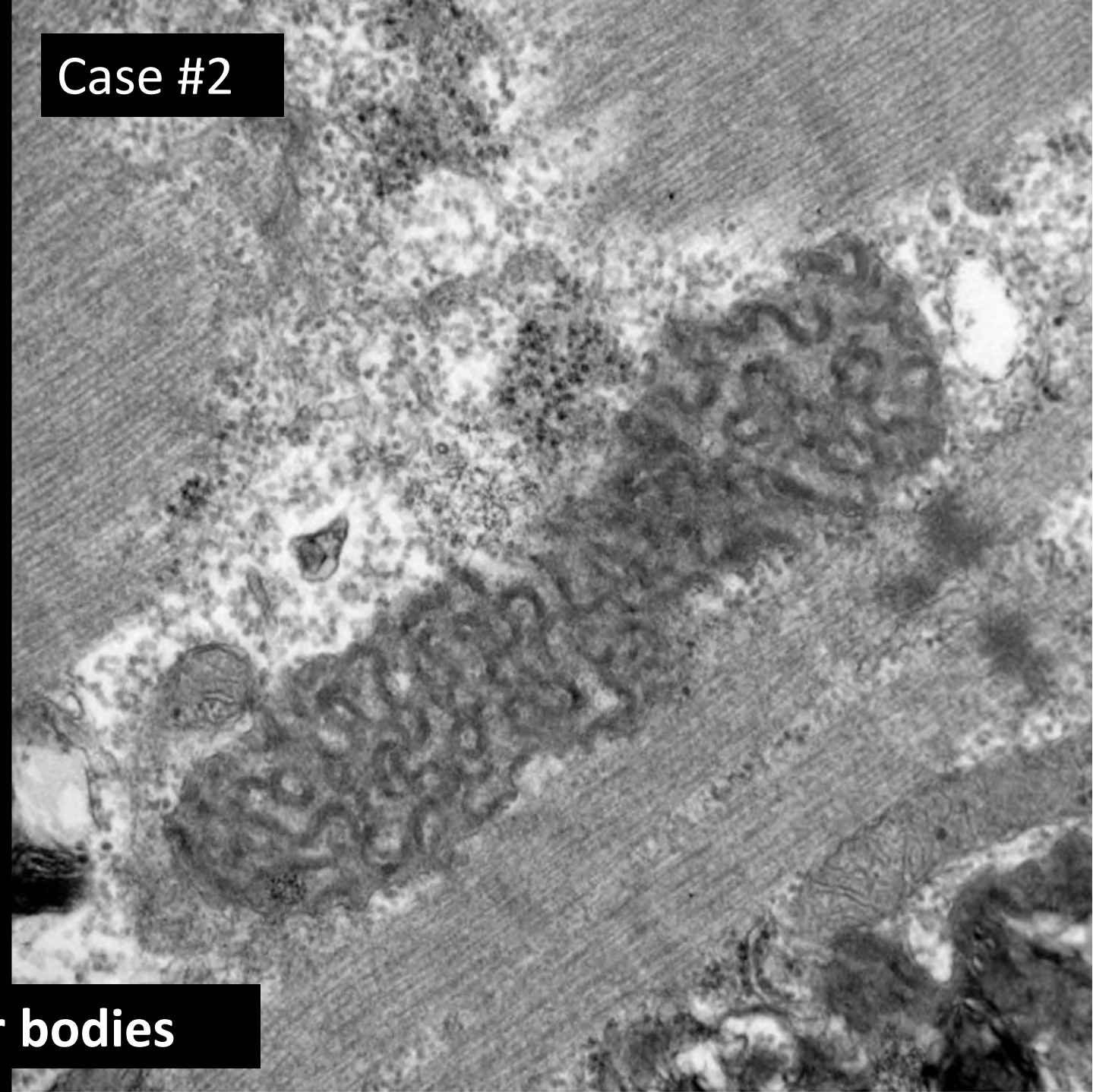


myeloid bodies; autophagic vacuoles

Case #1



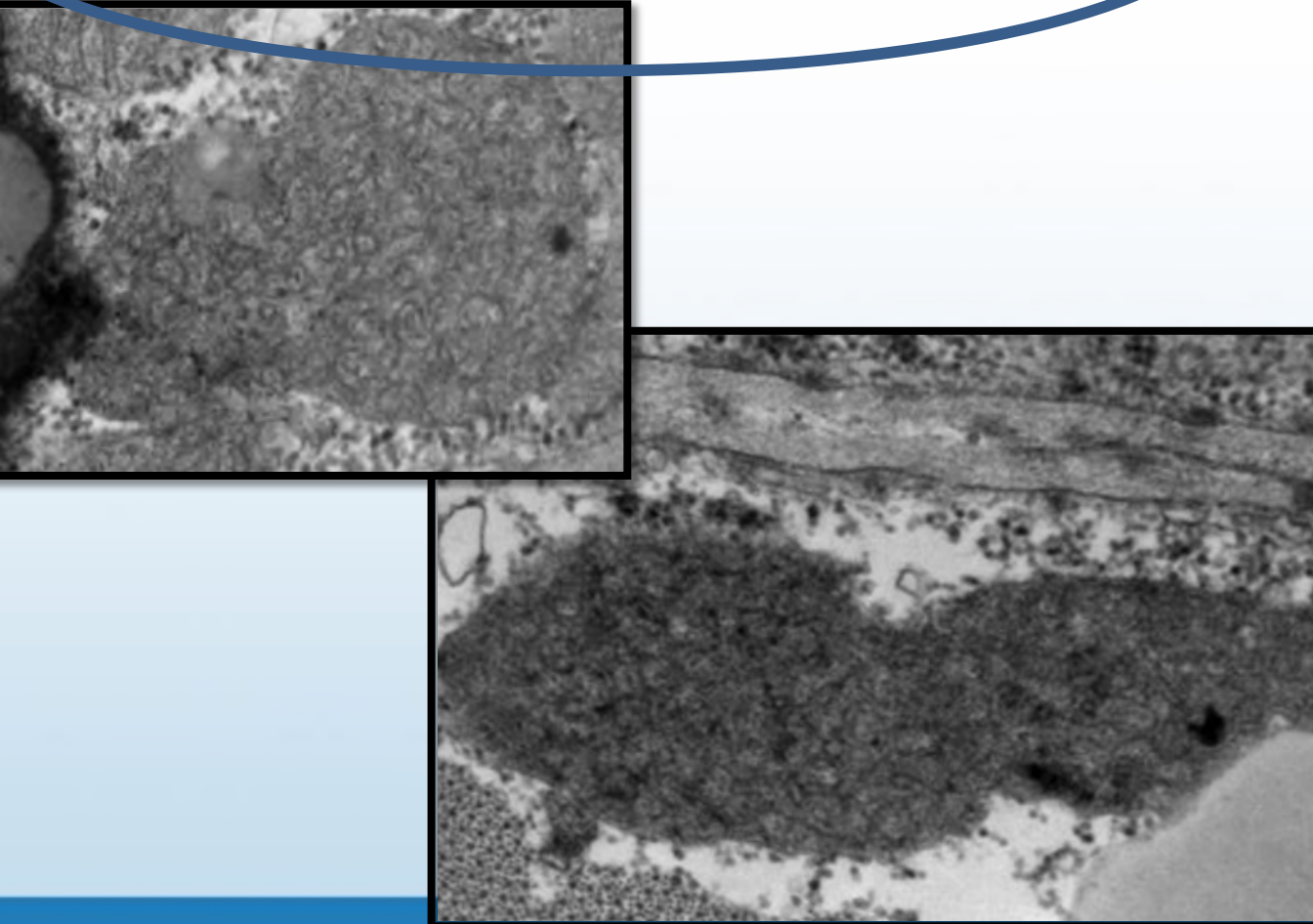
Case #2



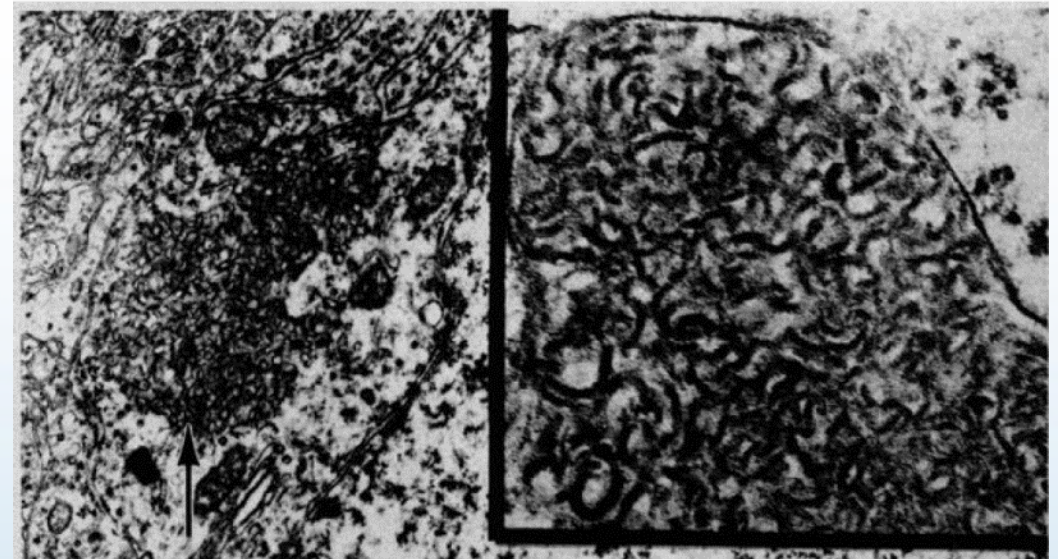
curvilinear bodies

Curvilinear bodies – somewhat specific

- Chloroquine/hydroxychloroquine myotoxicity



- Neuronal ceroid lipofuscinoses



September 1976

Late-Infantile Neuronal Ceroid-Lipofuscinosis An Ultrastructural Study of Lymphocyte Inclusions

William R. Markesbery, MD; Lloyd K. Shield, MBBS, MRACP; Robert T. Egel, MD; [et al](#)

[» Author Affiliations](#)

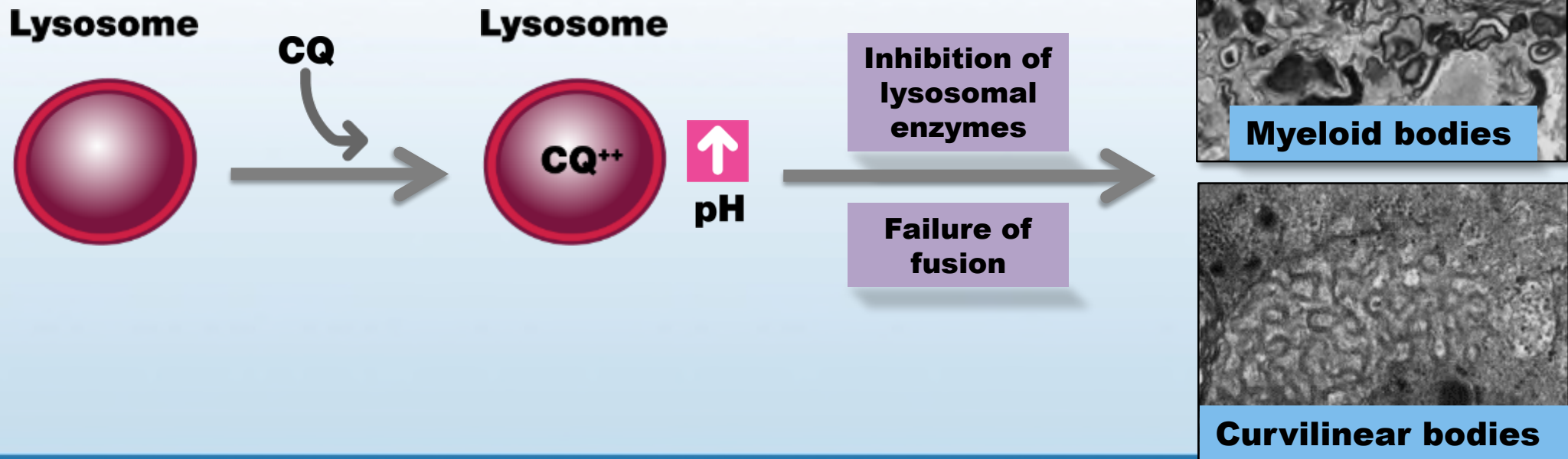
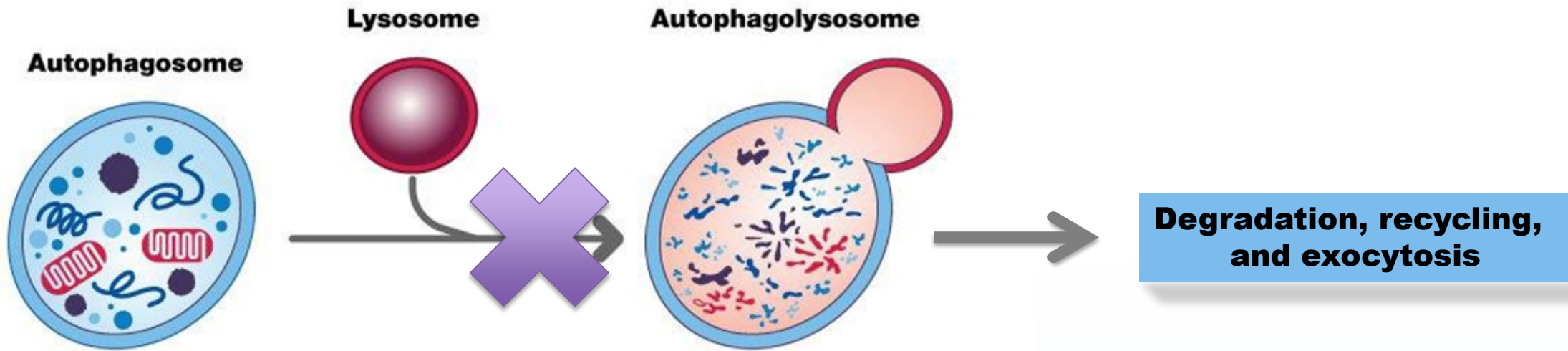
Arch Neurol. 1976;33(9):630-635. doi:10.1001/archneur.1976.00500090036007

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



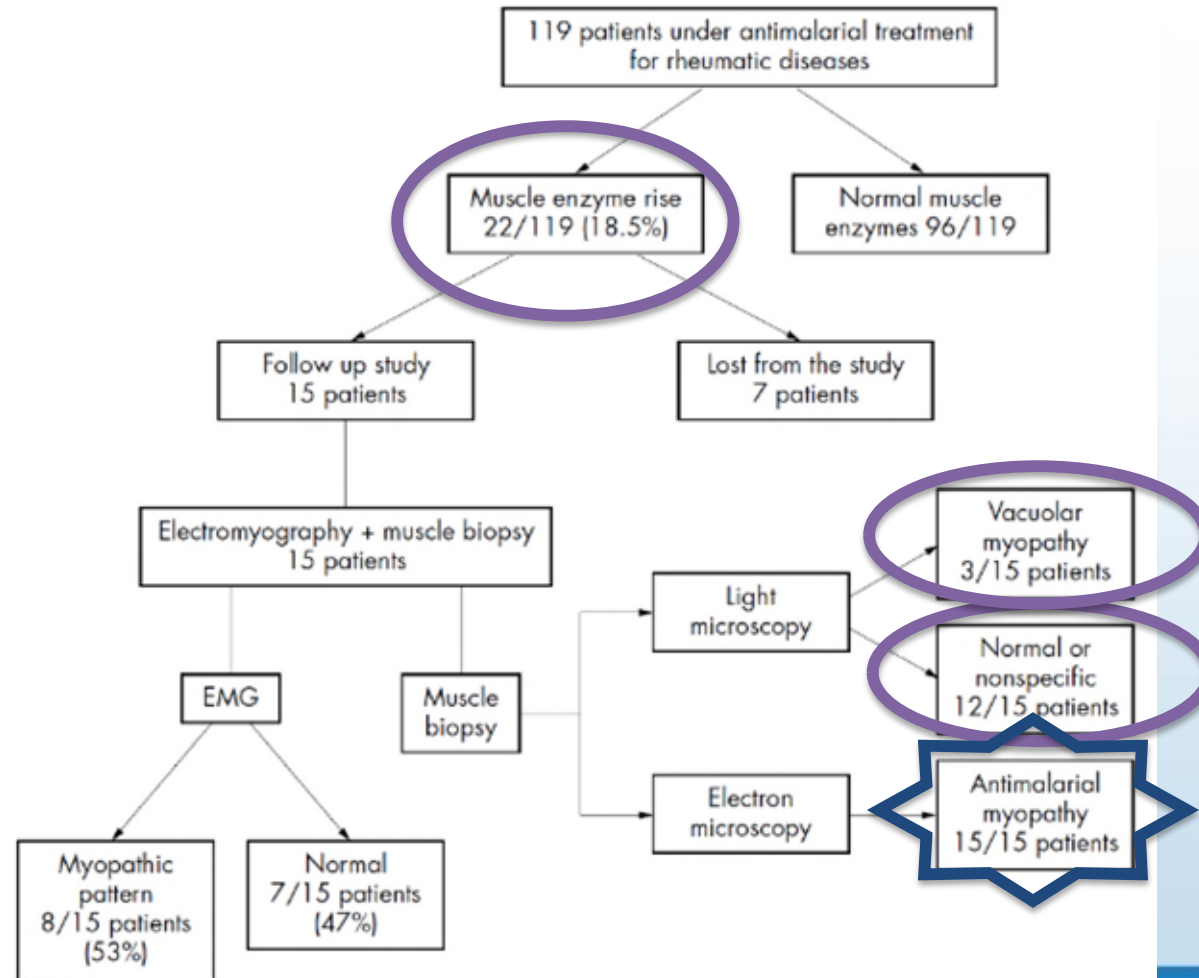


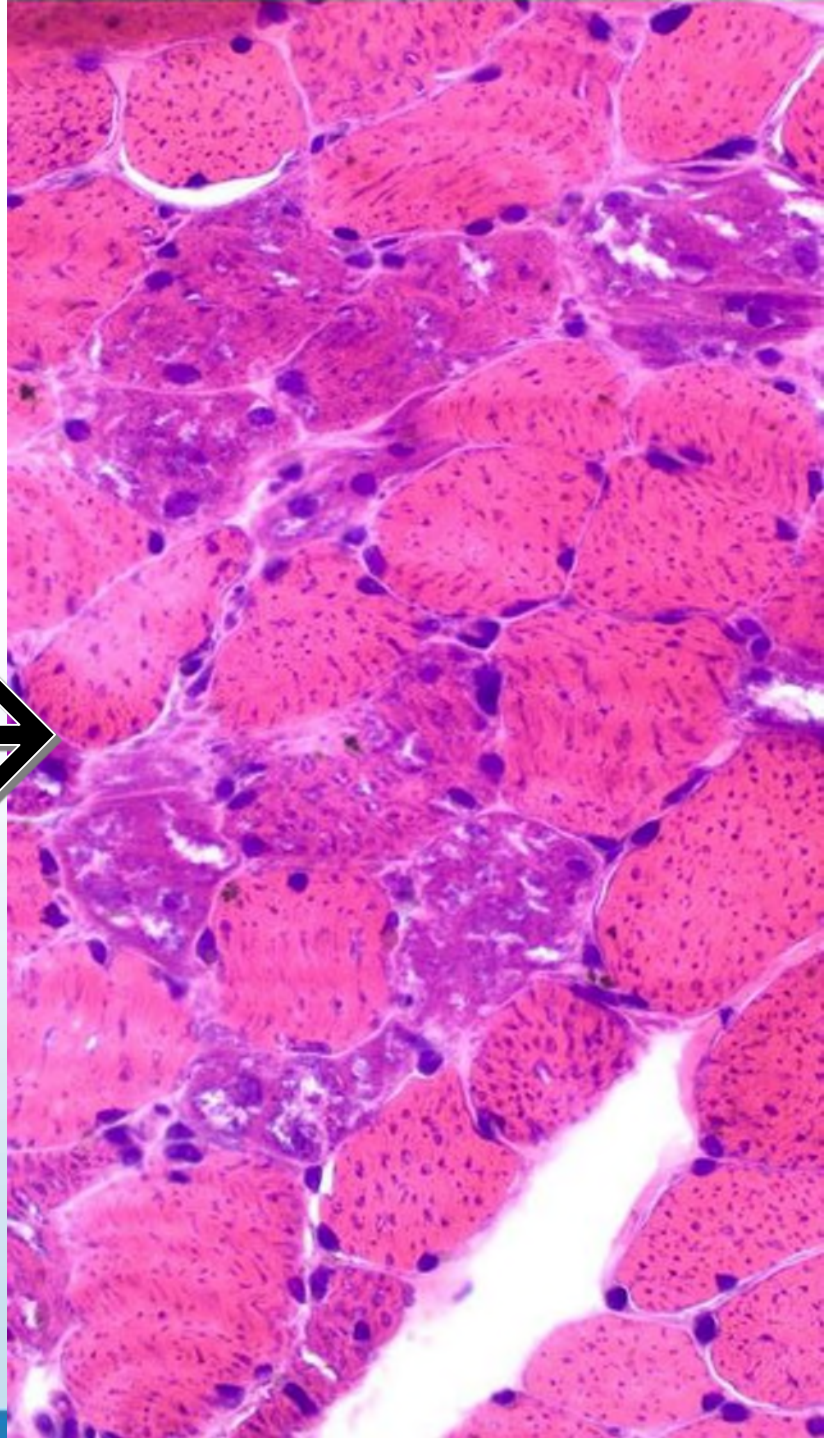
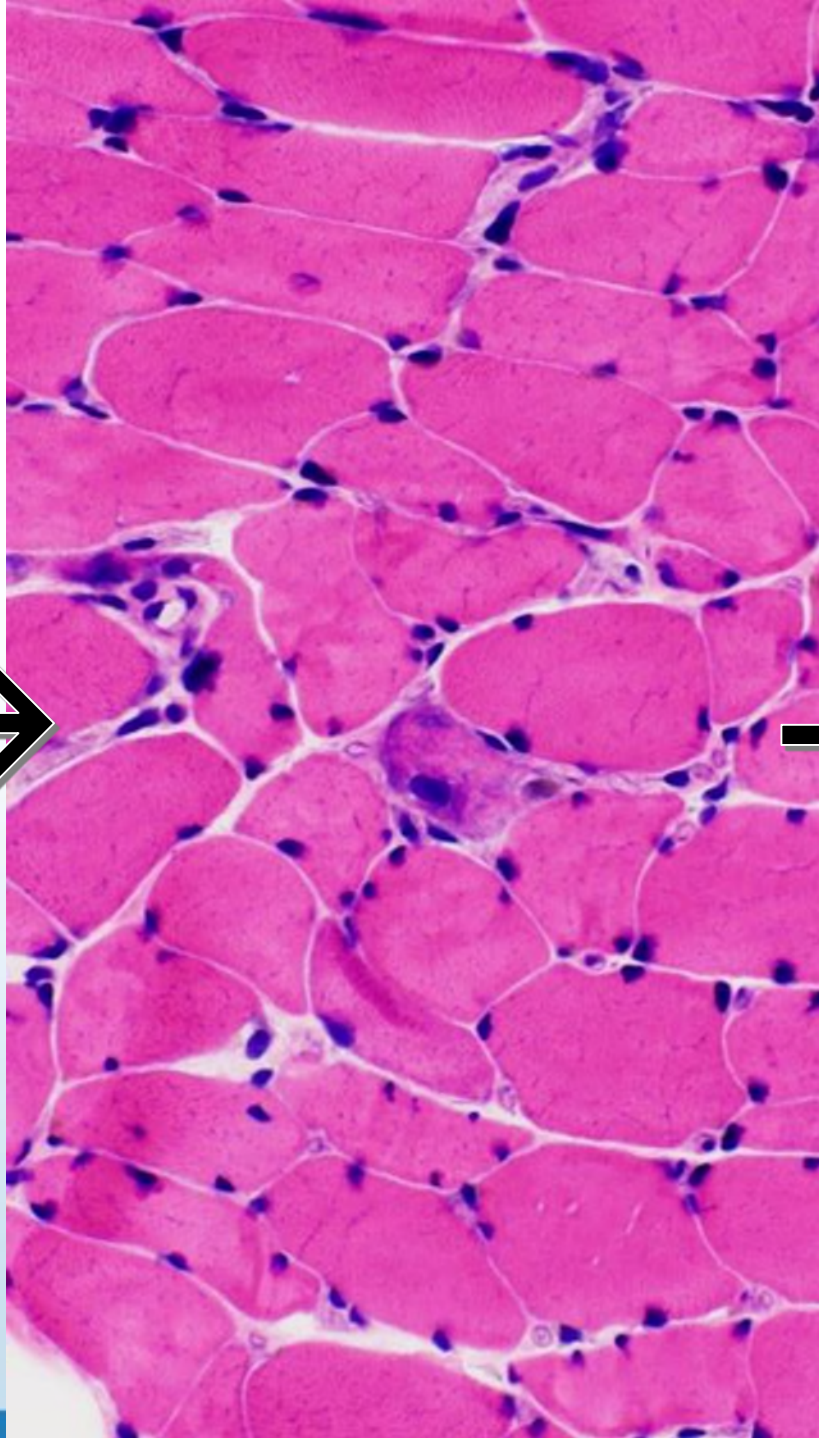
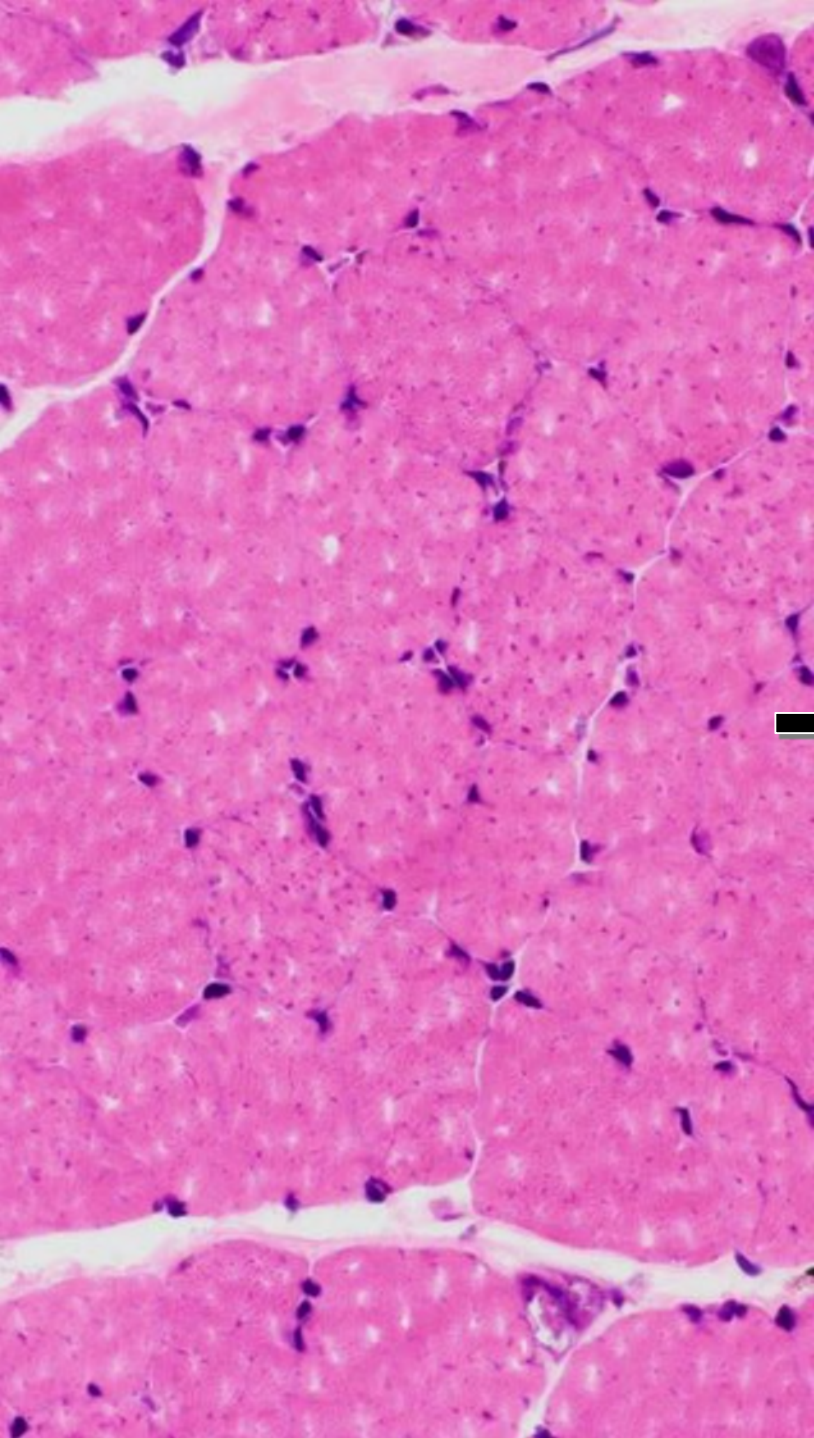
Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients

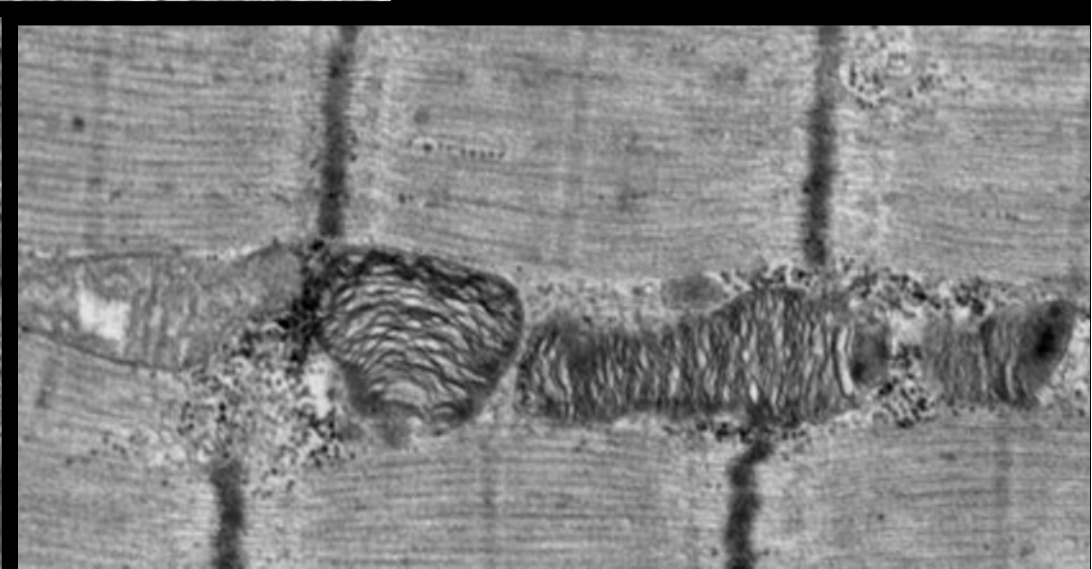
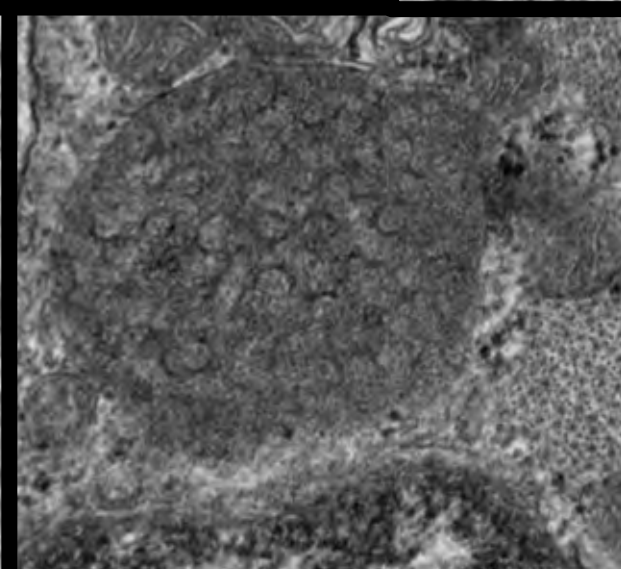
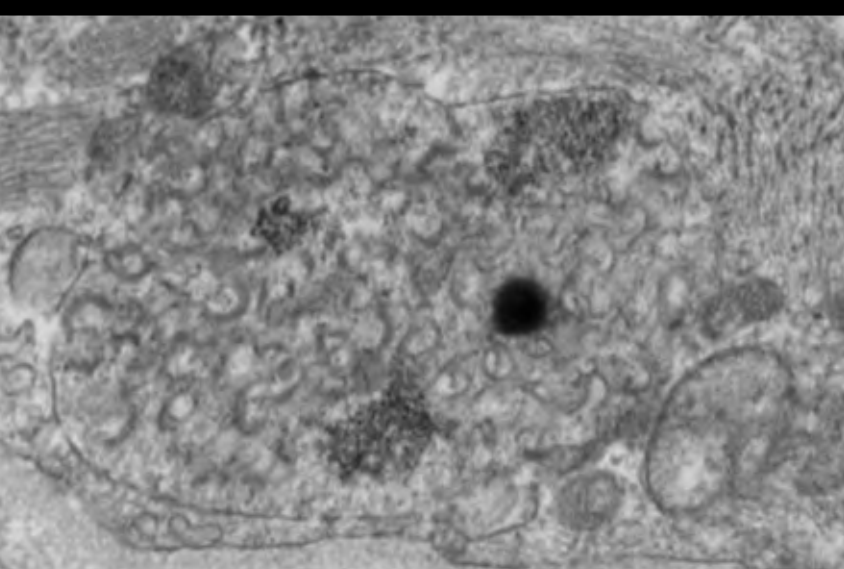
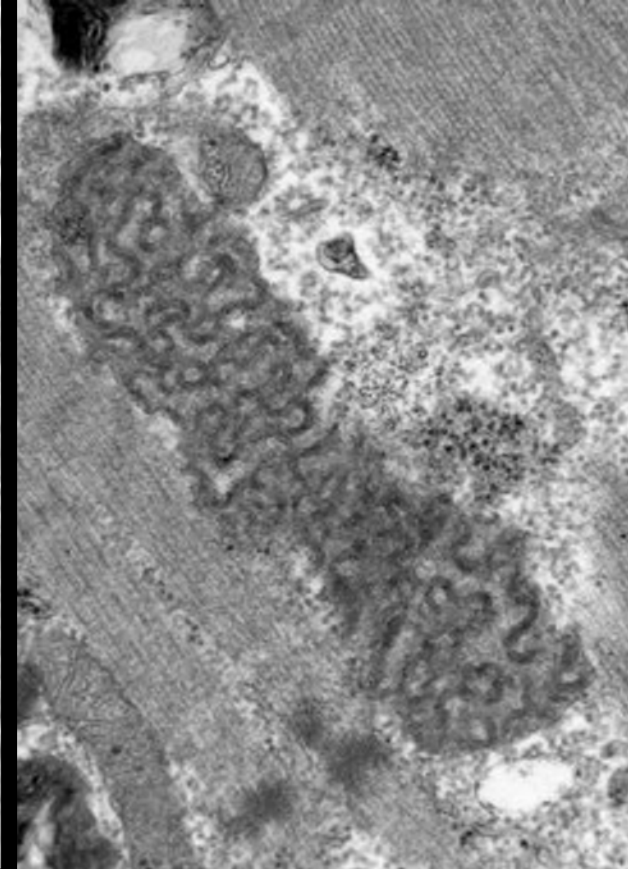
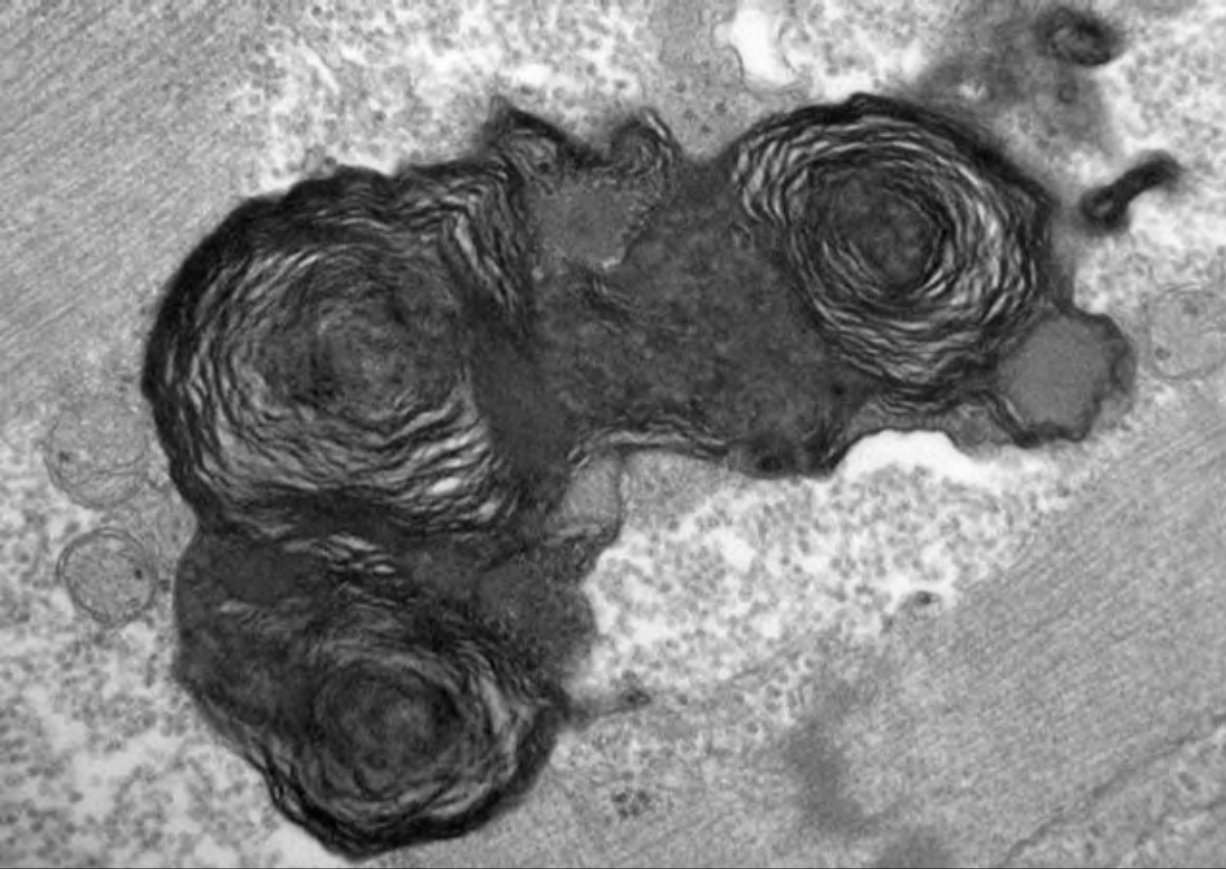
E Casado, J Gratacós, C Tolosa, J M Martínez, I Ojanguren, A Ariza, J Real, A Sanjuan, M Larrosa



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



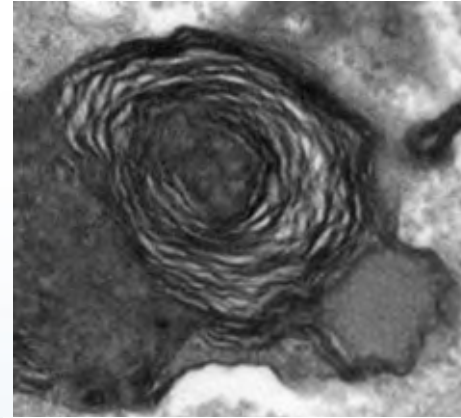




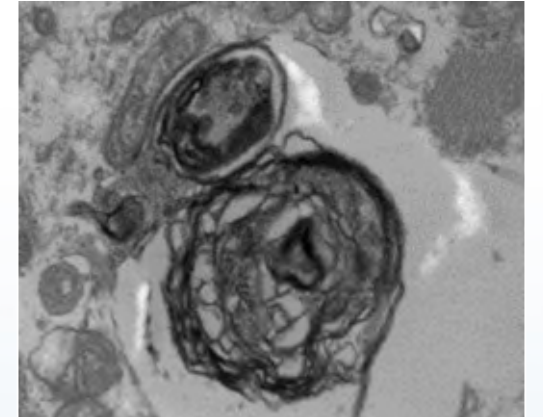
Systemic therapy-induced VACUOLAR MYOPATHIES - diagnostic clues

Chloroquine/hydroxychloroquine or colchicine

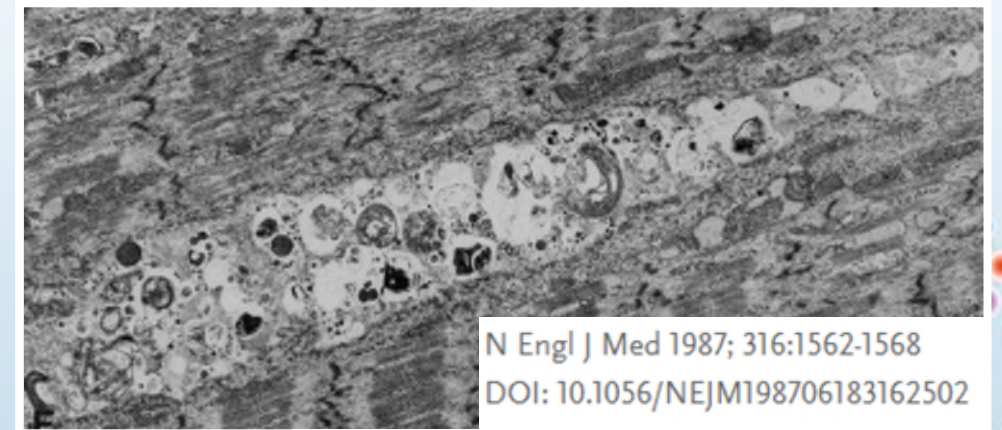
- Vacuoles
 - acid phosphatase
 - +/- red rimmed
 - acetylcholinesterase
 - DGC proteins
- Immunostaining
 - complement C5b-9 deposition
- Ultrastructure
 - myeloid bodies (autophagic vacuoles)
 - curvilinear bodies (chloroquines only)
 - spheromembranous bodies (colchicine only? Or just autophagic pathology?)



Chloroquine toxicity



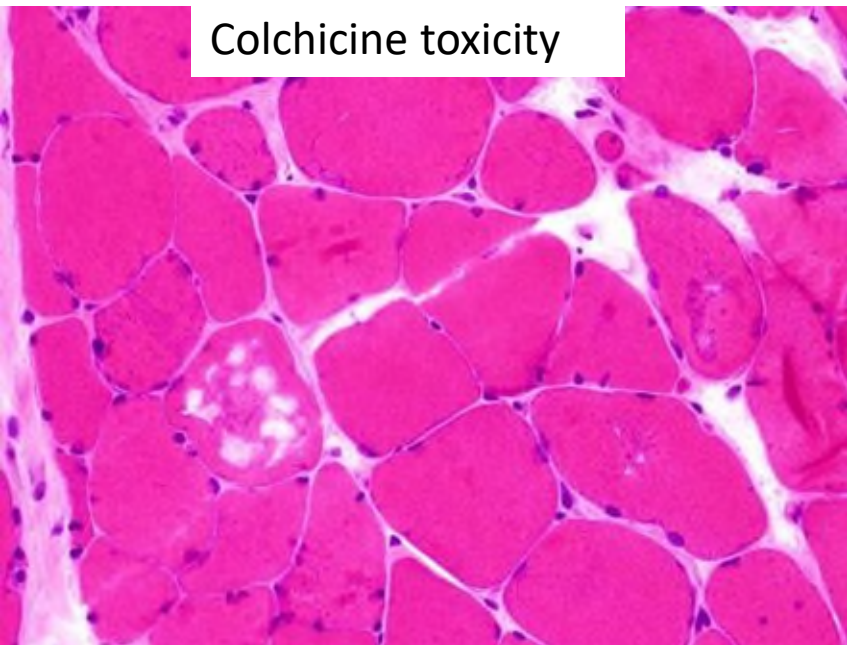
Inclusion body myositis



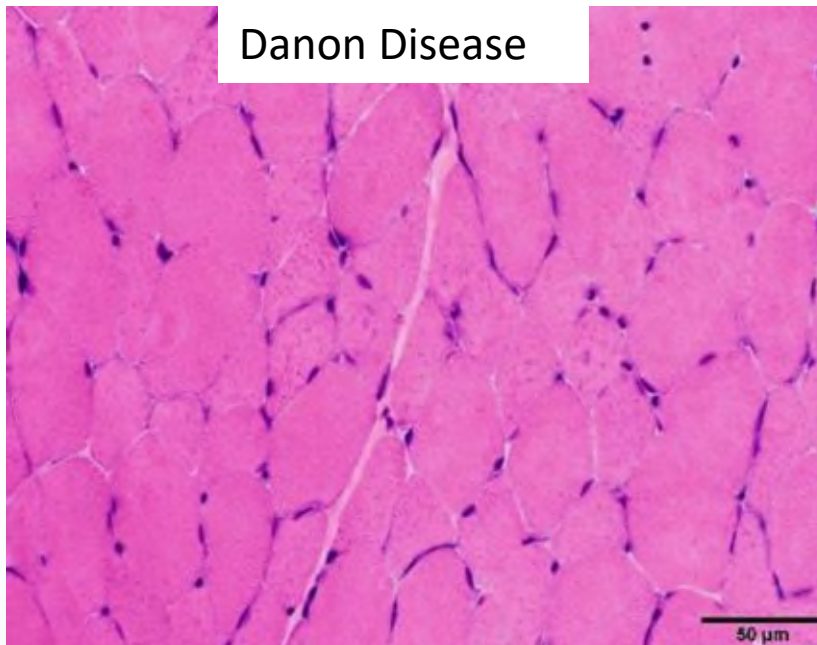
N Engl J Med 1987; 316:1562-1568
DOI: 10.1056/NEJM198706183162502

Colchicine toxicity

Colchicine toxicity



Danon Disease



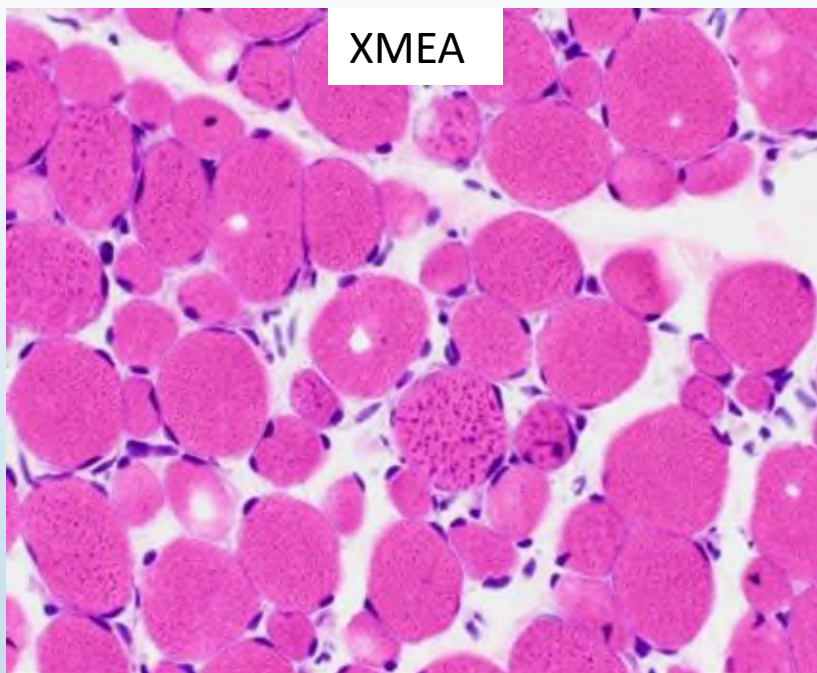
Late onset Pompe disease



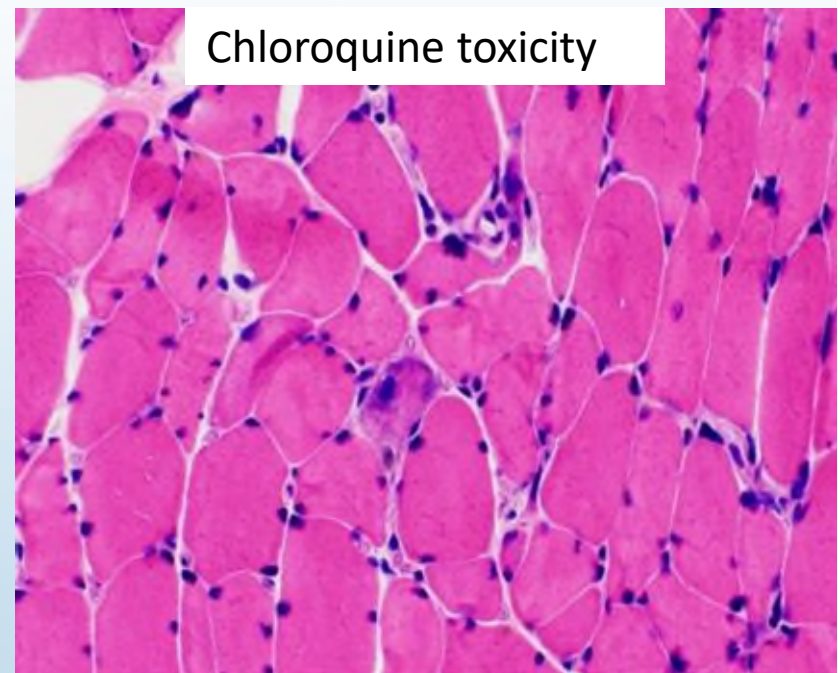
Colchicine toxicity

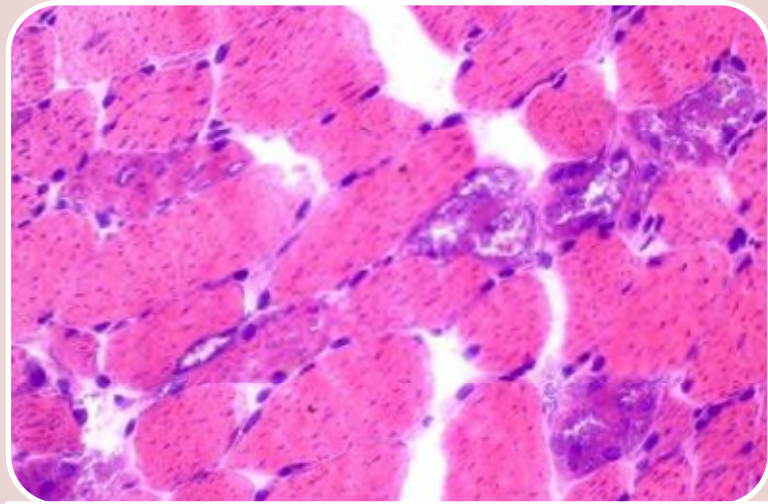


XMEA

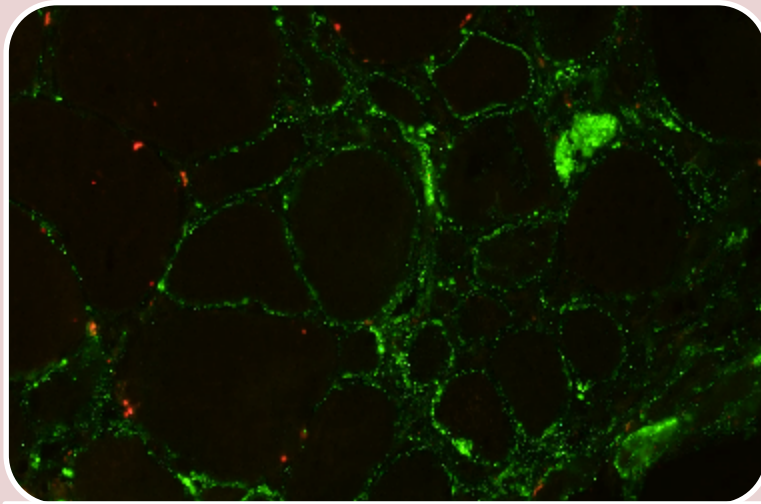


Chloroquine toxicity

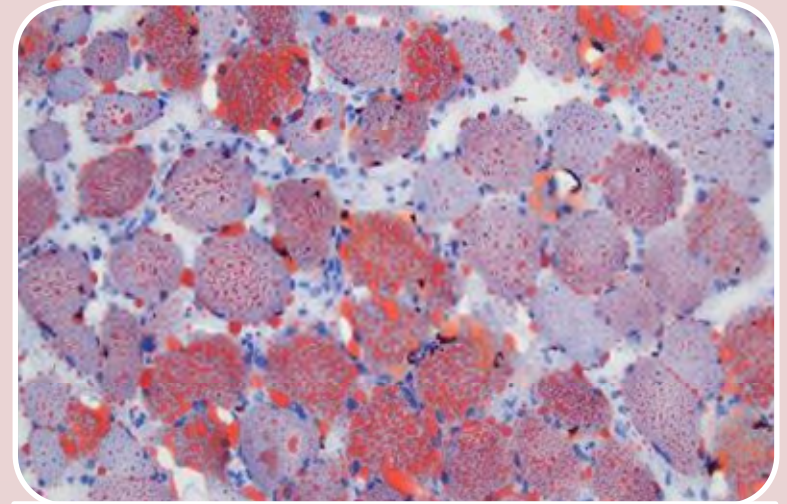




Toxic



Inflammatory



Metabolic

Case #1

- 70-year-old woman
- 4-month history of progressive proximal muscle weakness
- EMG/NCS: chronic myopathic features
- CK: elevated to ~6,000 IU/L
- Myositis antibody testing pending

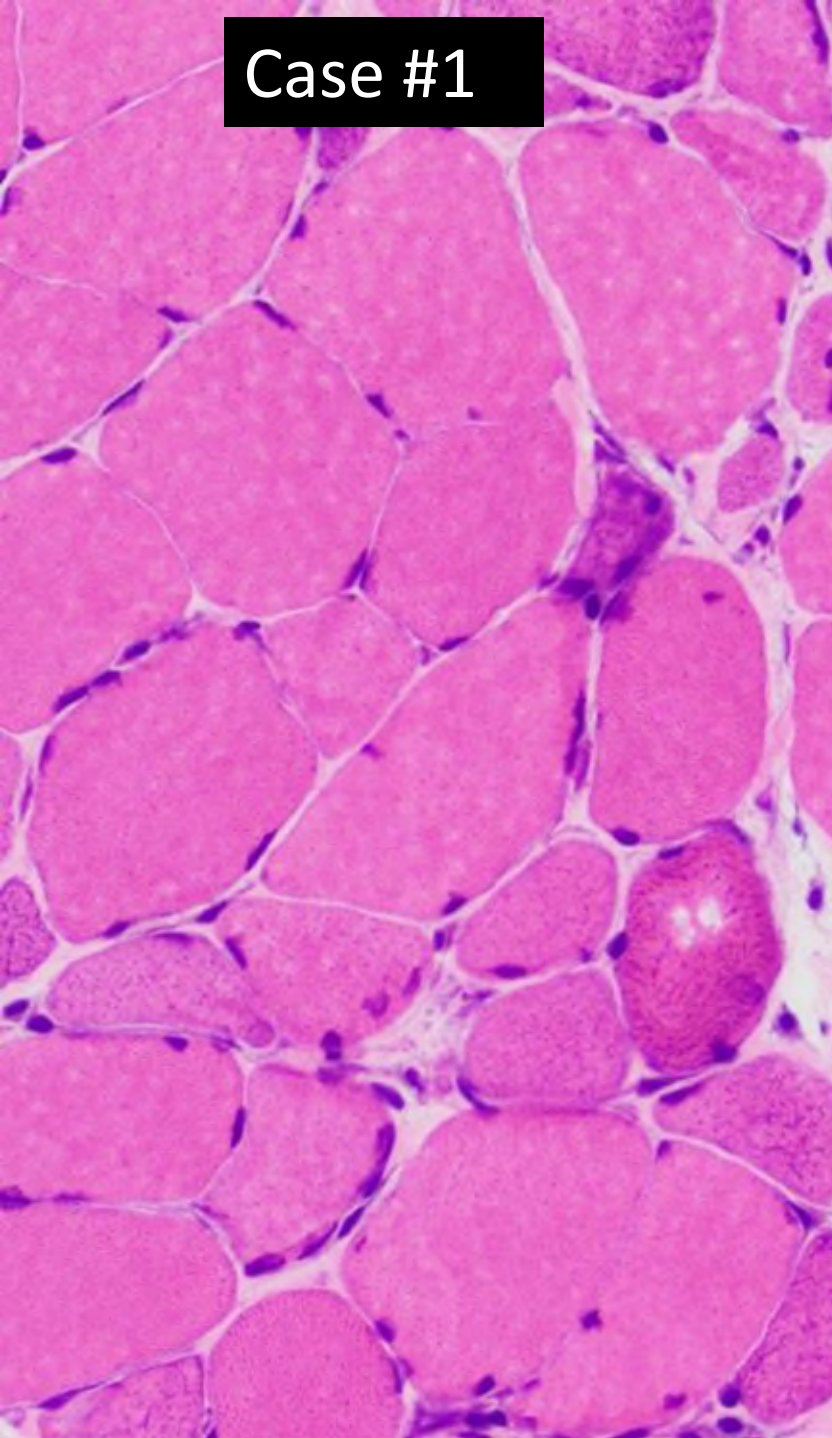
Case #2

- 61-year-old woman
- 2-month history of progressive proximal muscle weakness associated with interstitial lung disease
- EMG/NCS: chronic myopathic features
- CK: elevated to ~8,000 IU/L
- Myositis antibody testing pending

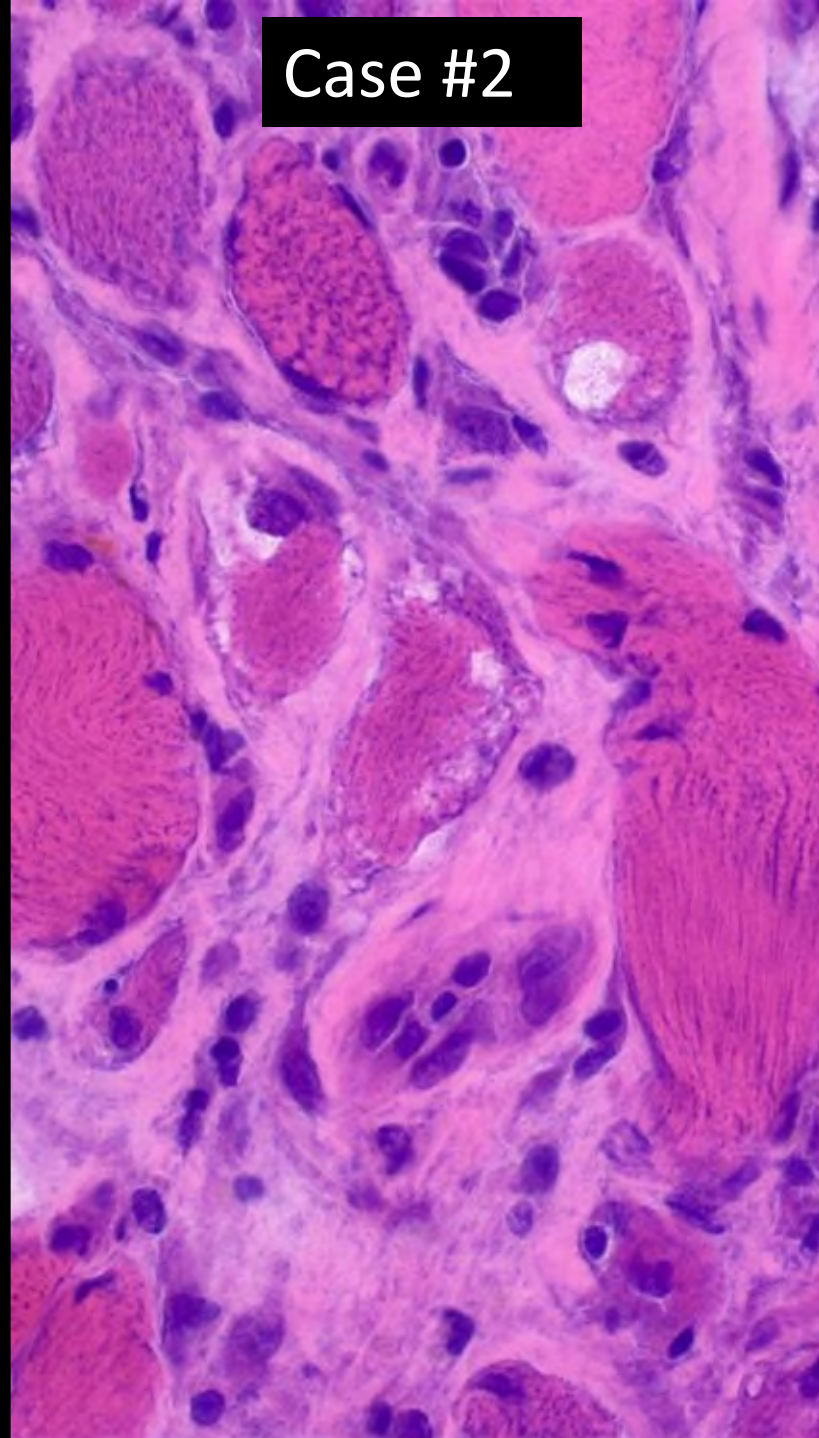
Case #3

- 66-year-old man
- 4-month history of progressive proximal muscle weakness
- CK: elevated to ~5,000 IU/L
- Diagnosed with inclusion body myositis
- Referral to our institution and muscle biopsy performed
- Myositis antibody testing pending

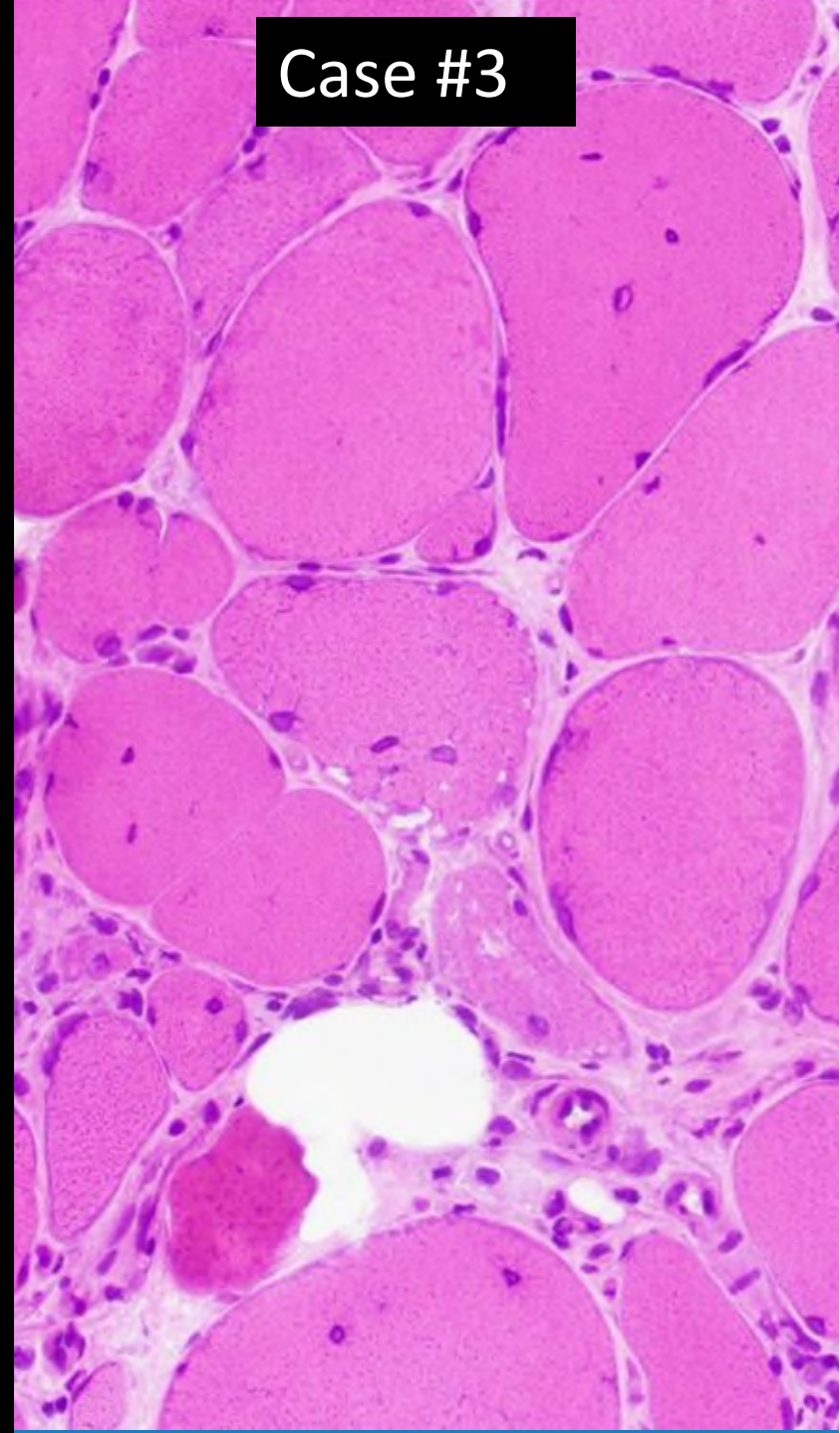
Case #1



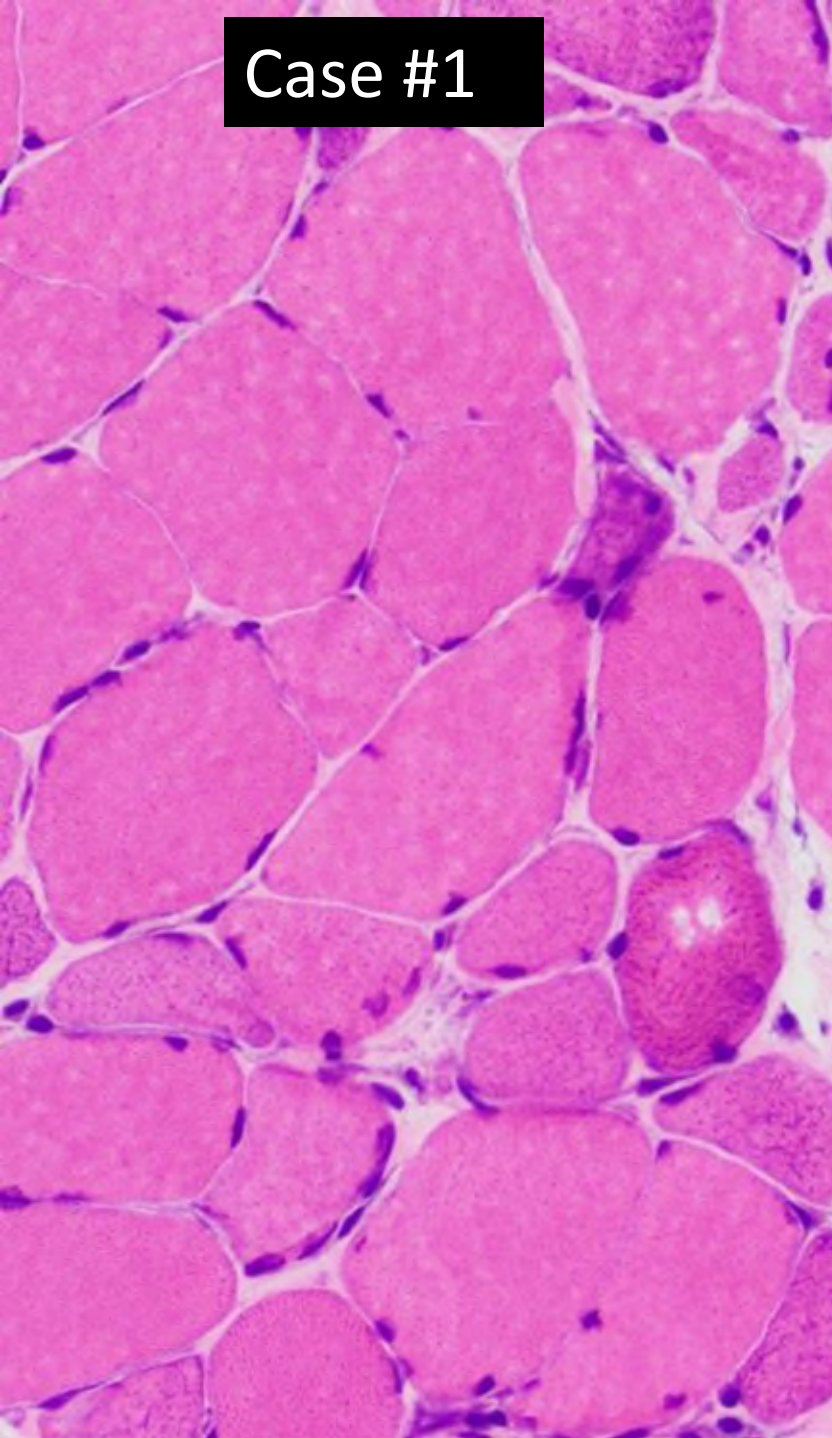
Case #2



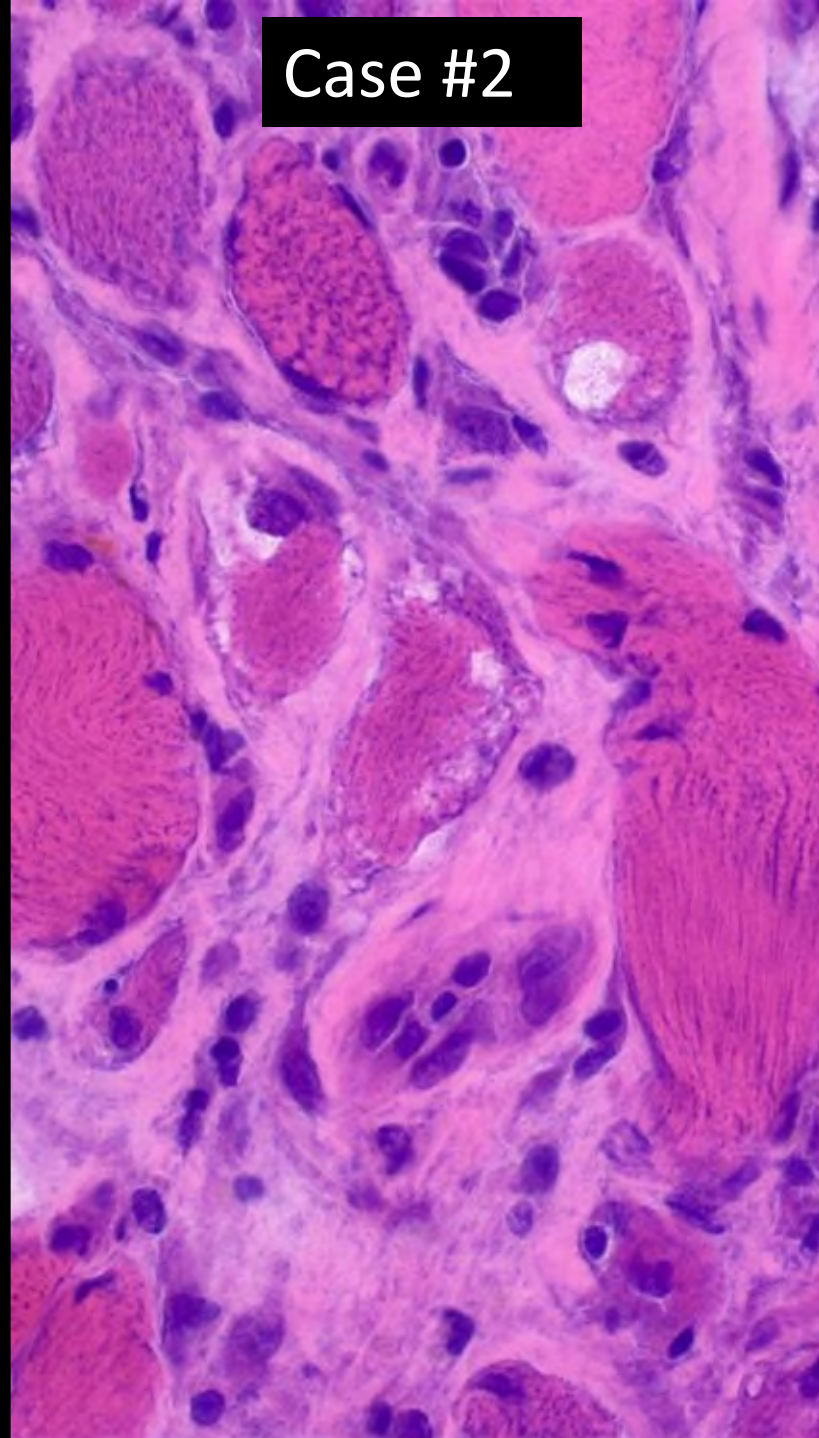
Case #3



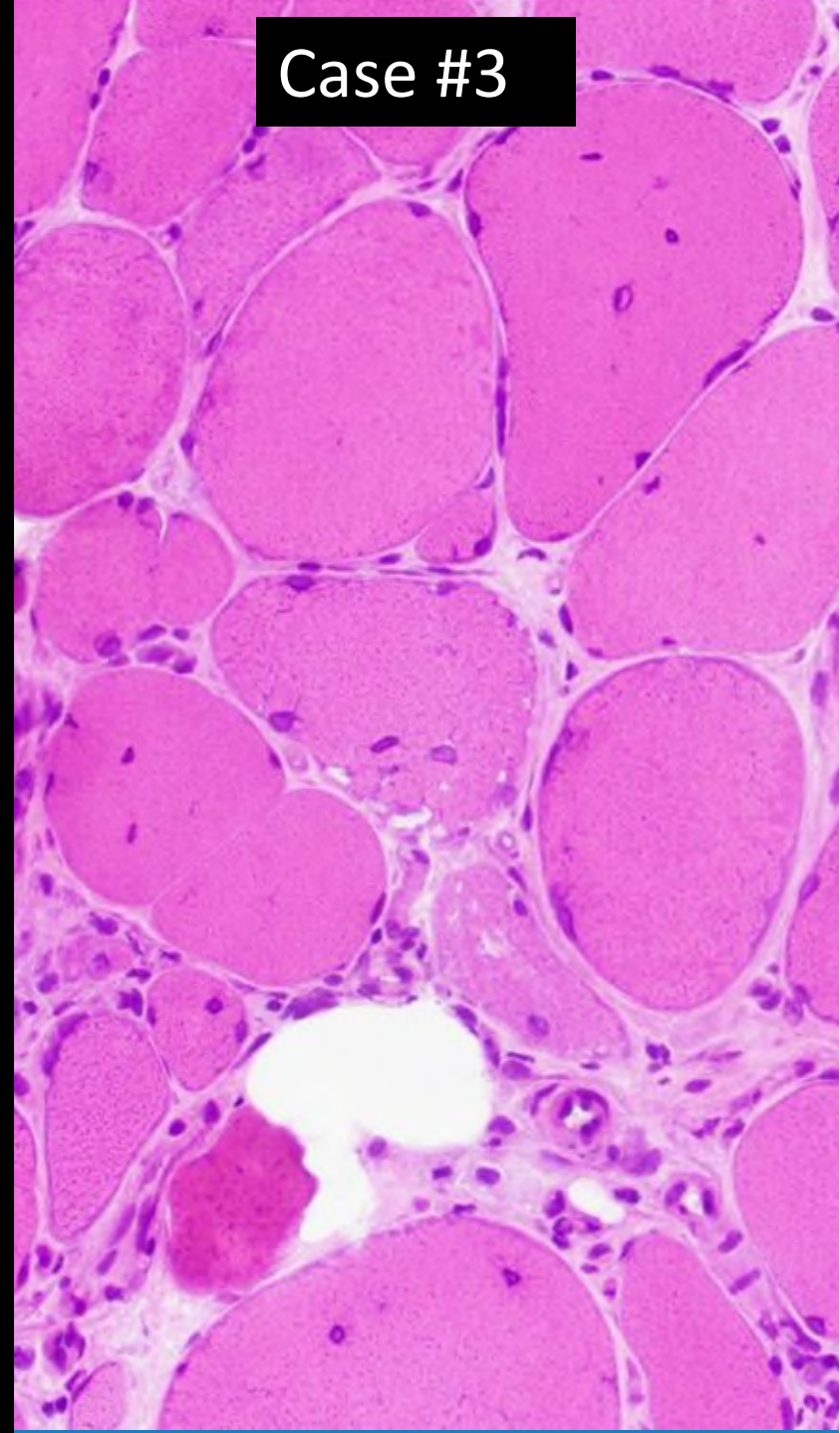
Case #1



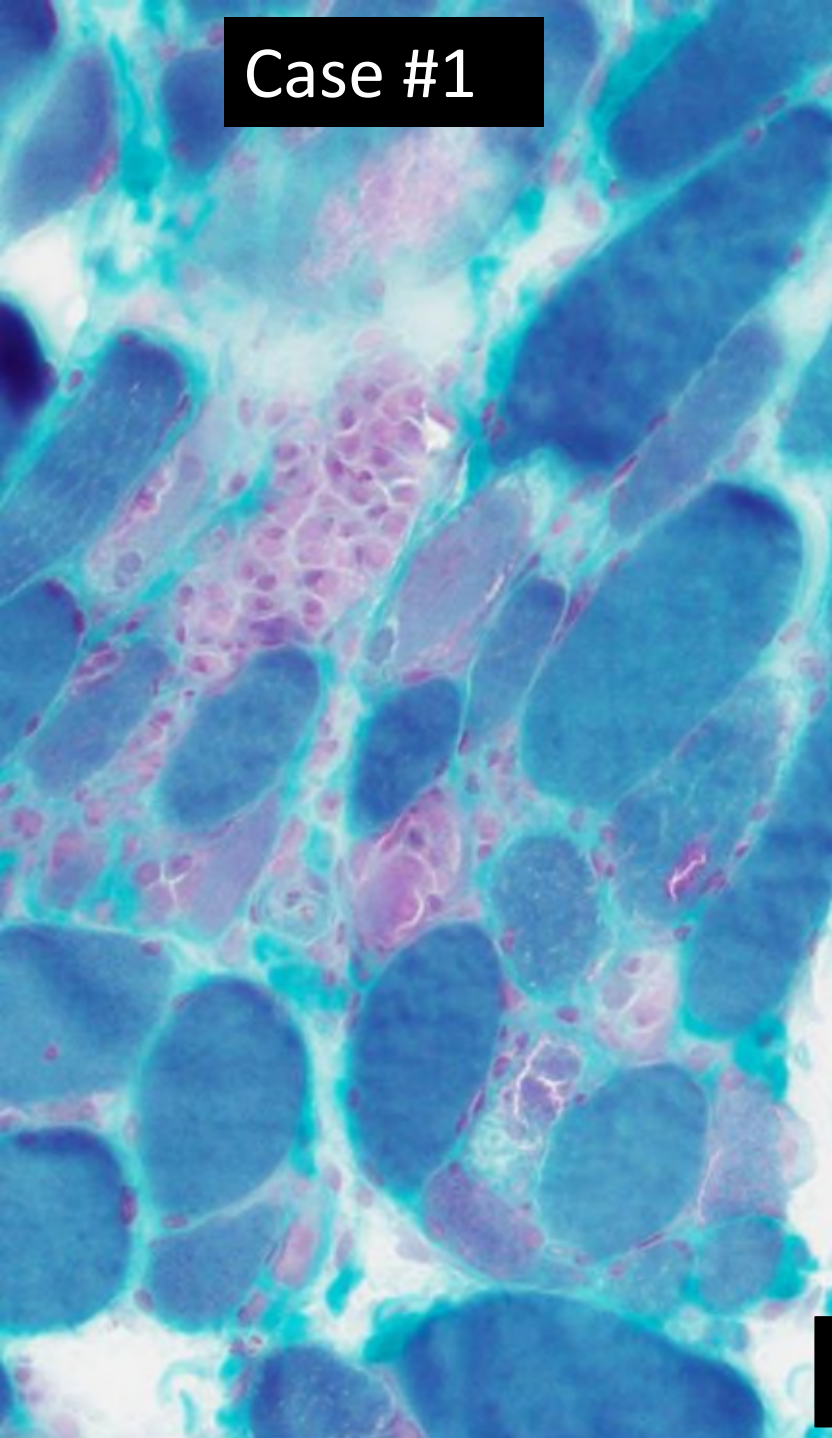
Case #2



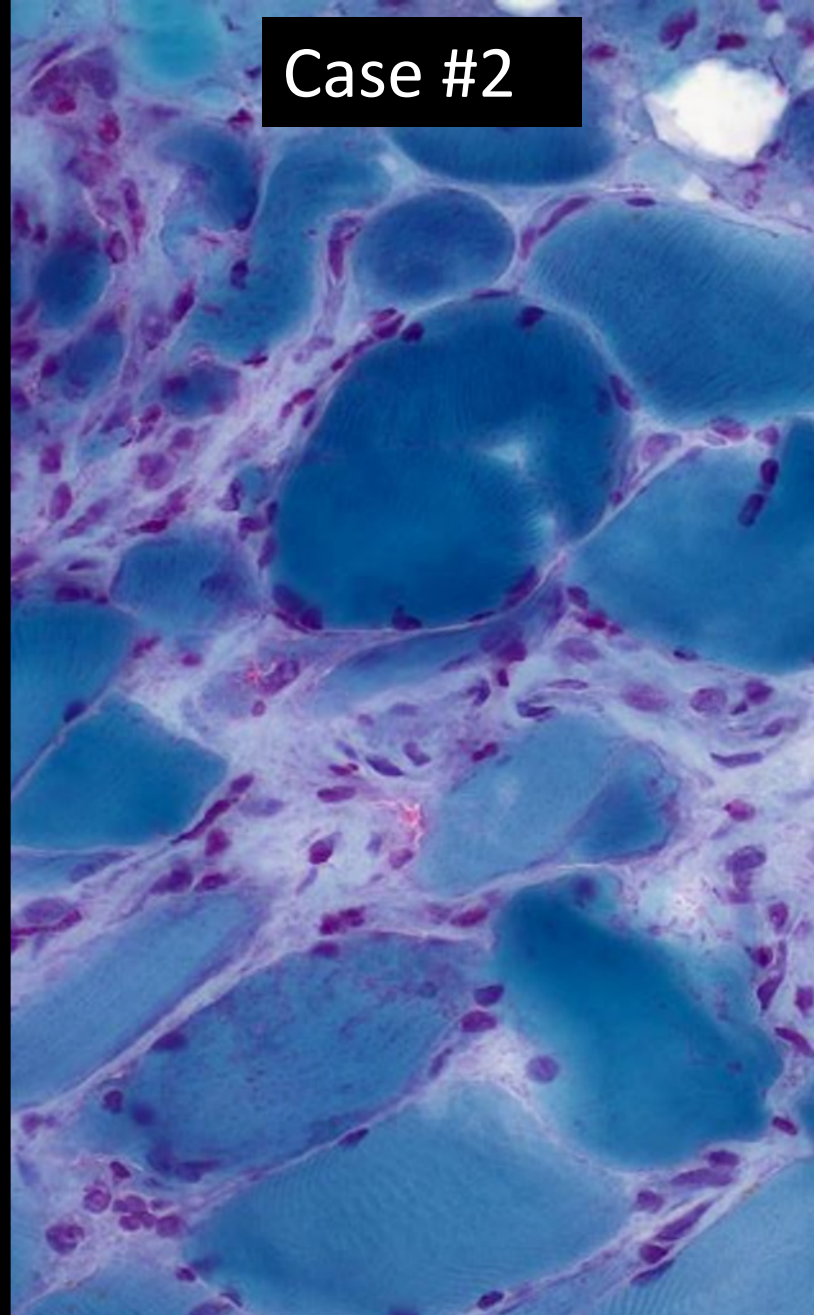
Case #3



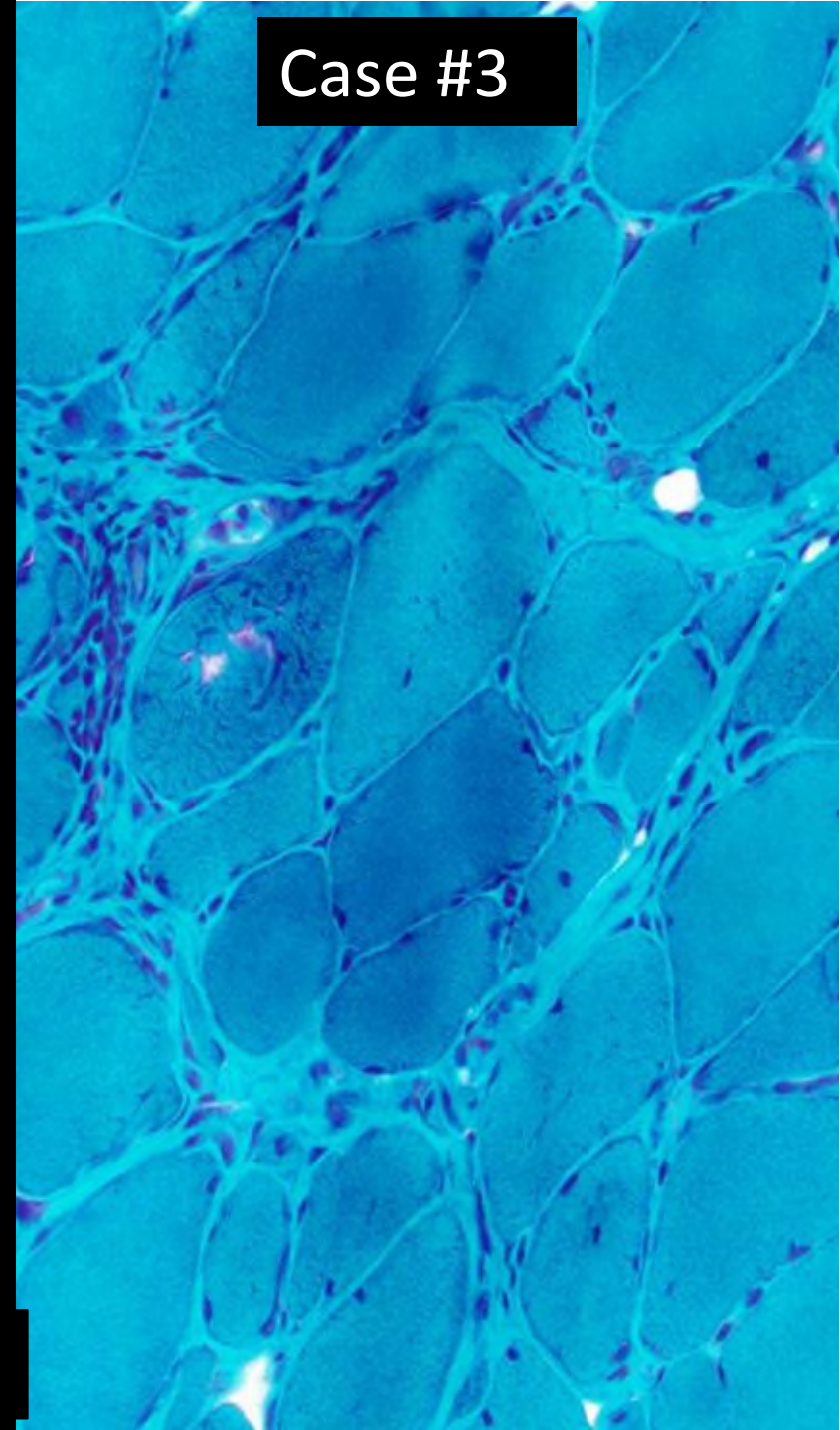
Case #1



Case #2

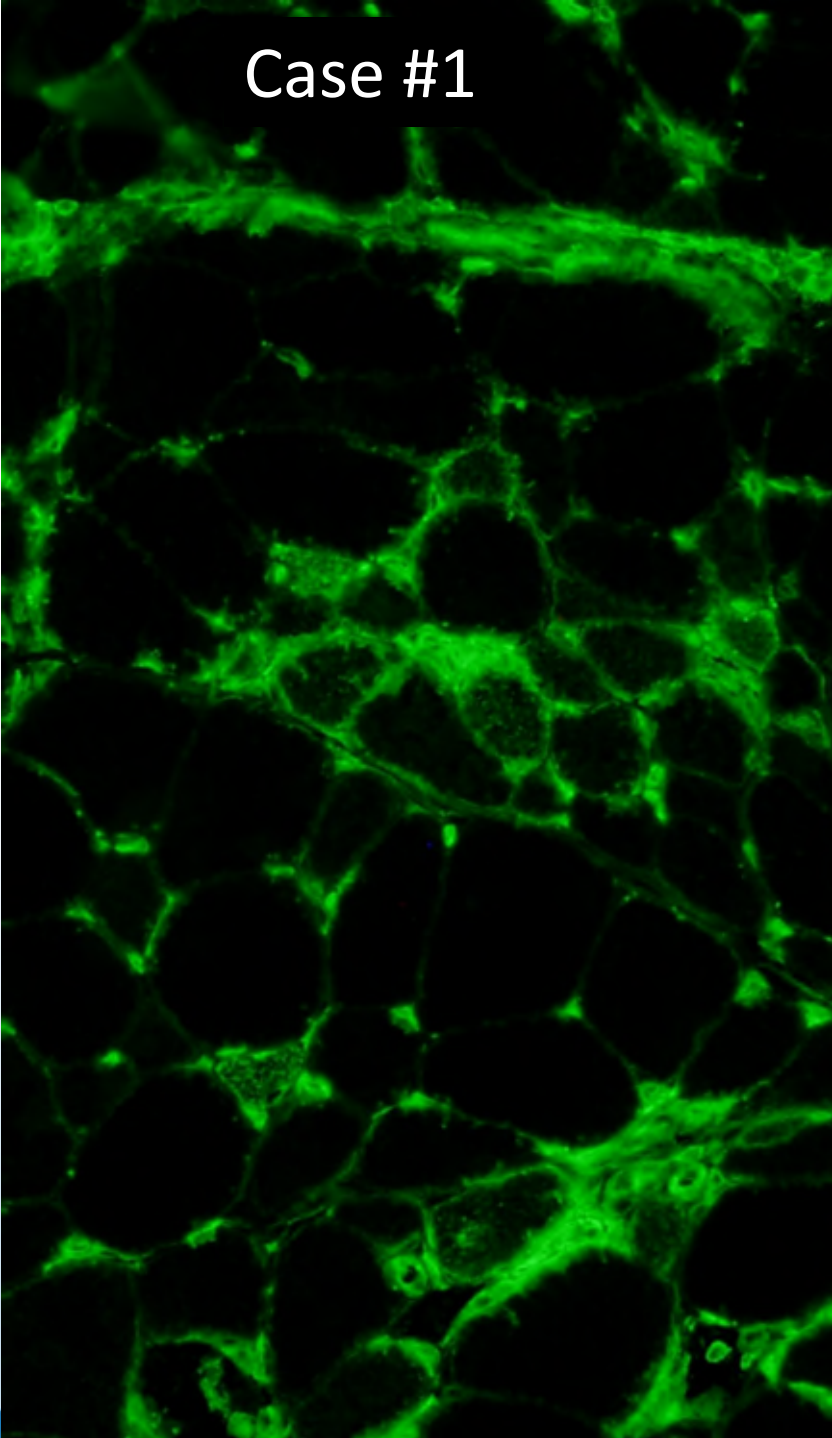


Case #3

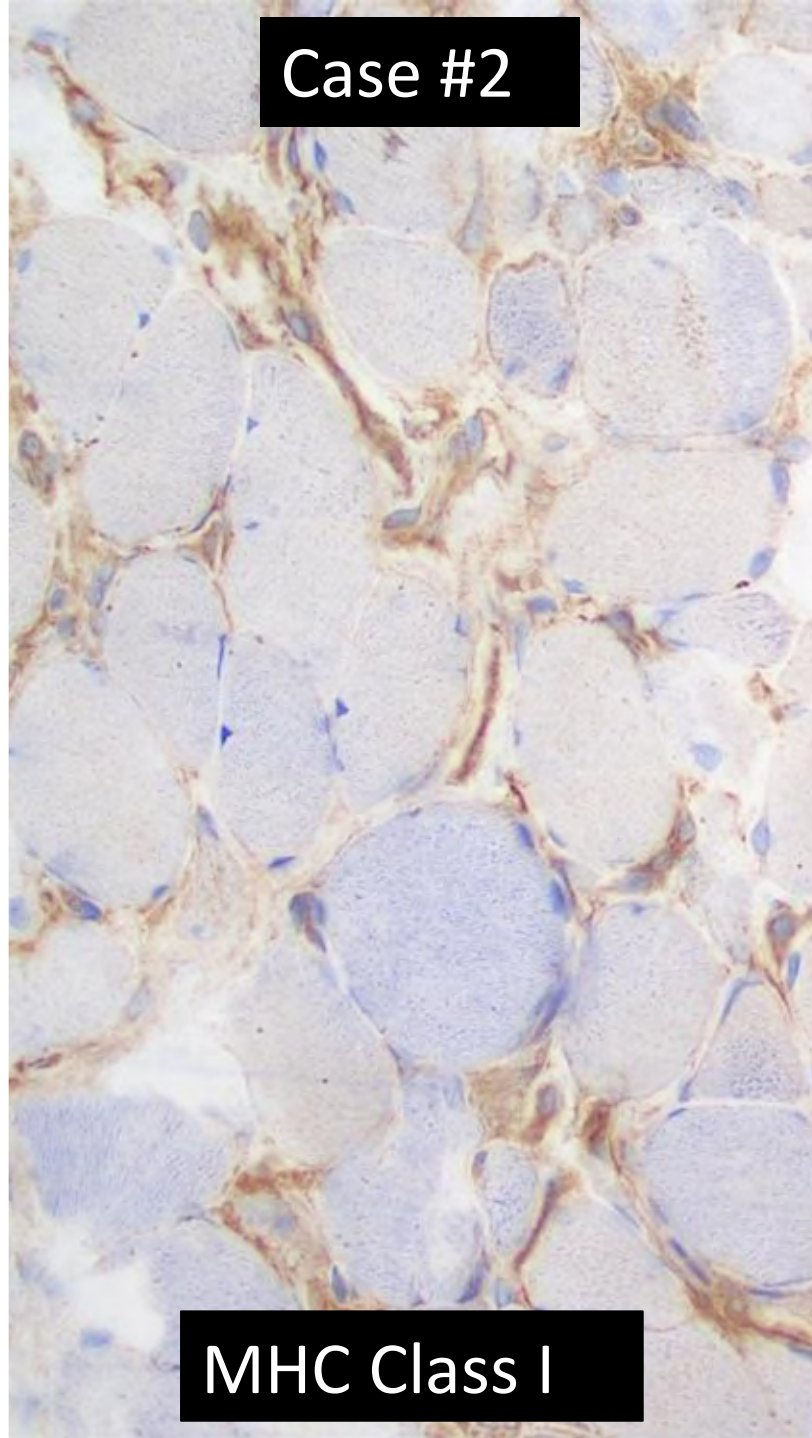


modified Gomori trichrome

Case #1

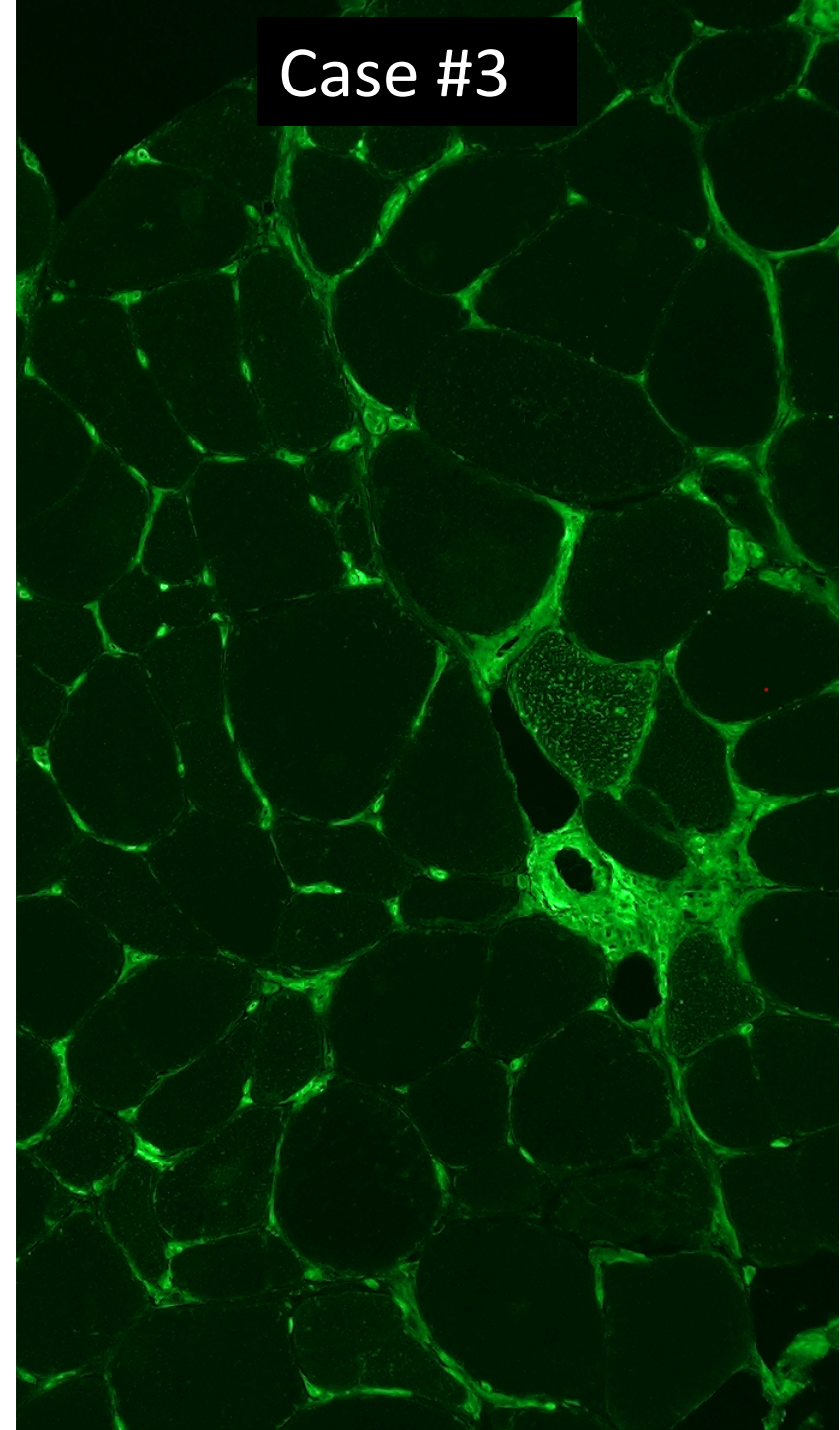


Case #2

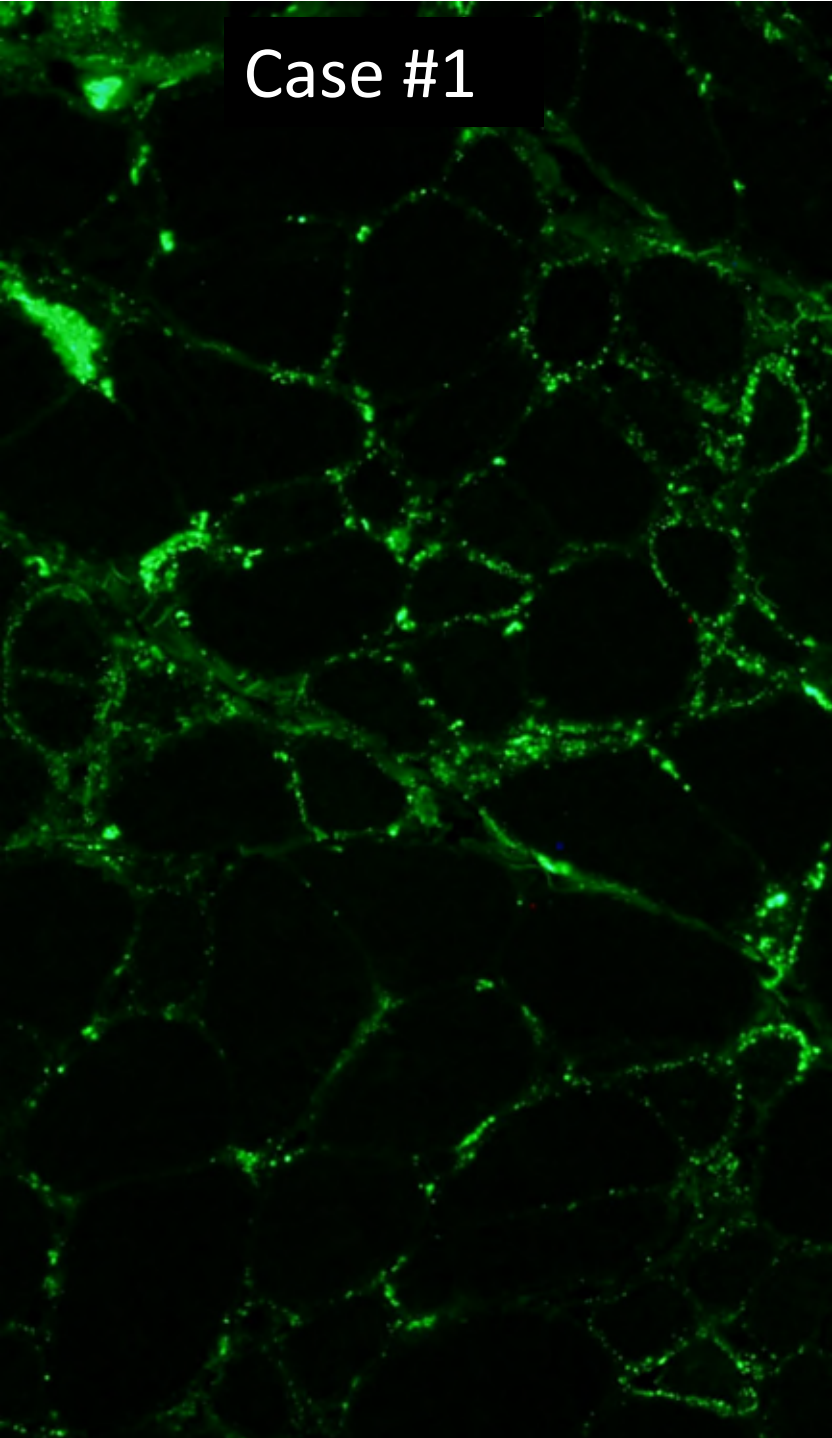


MHC Class I

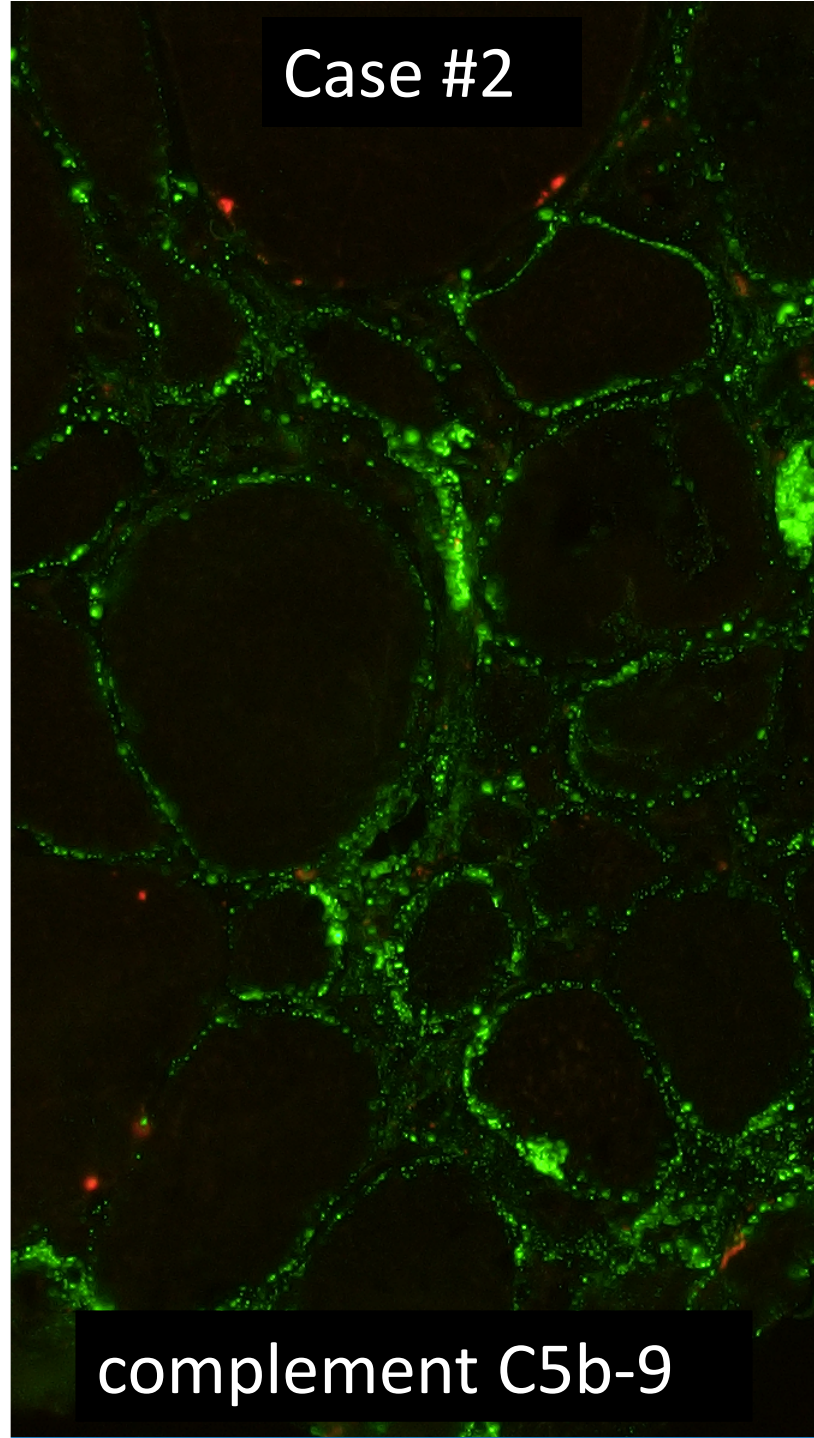
Case #3



Case #1

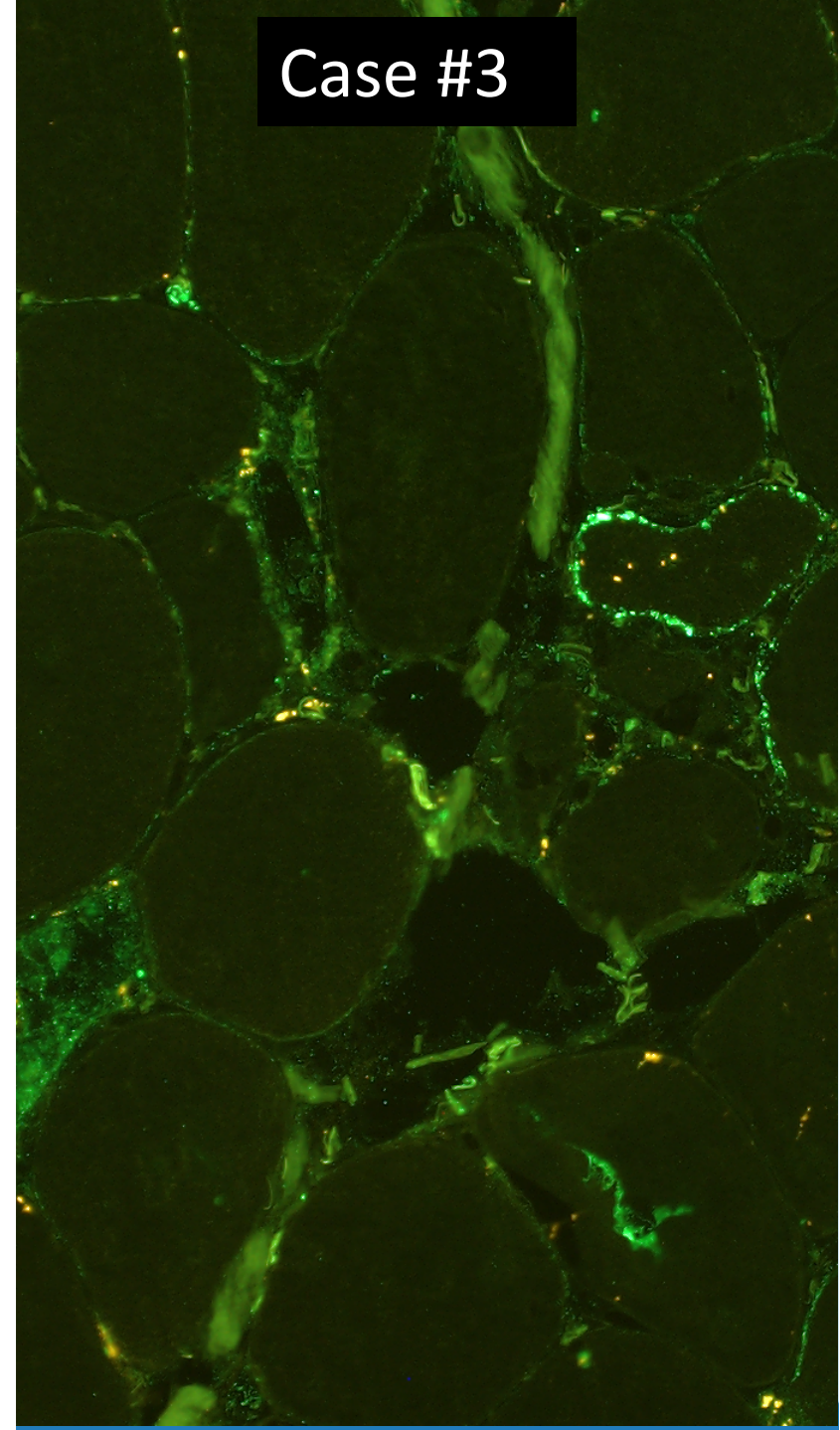


Case #2

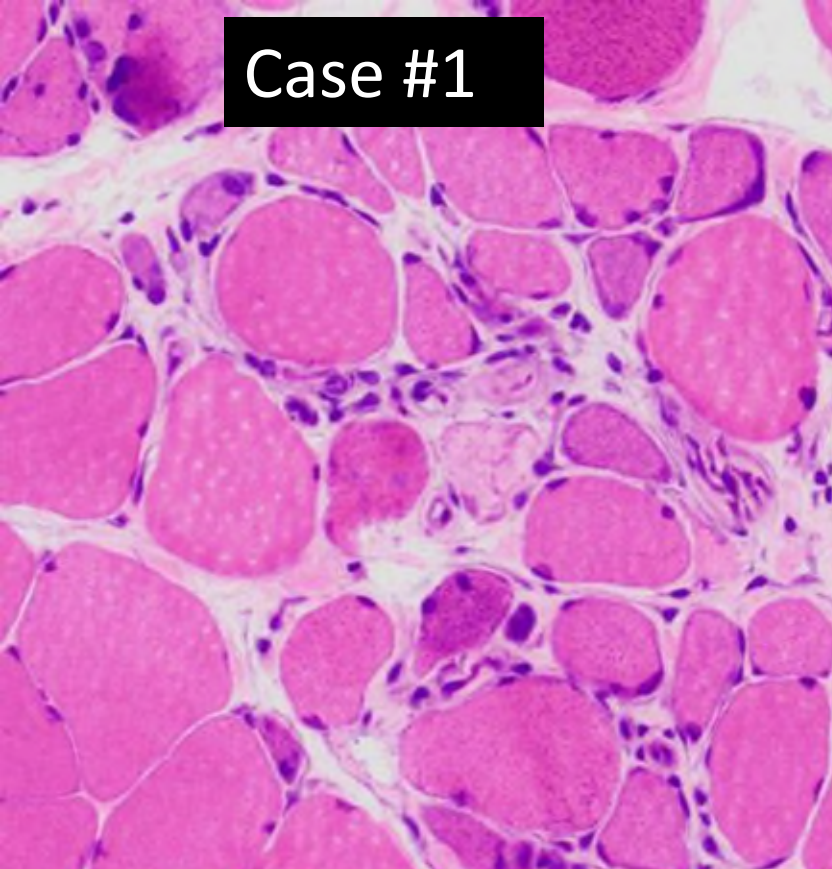


complement C5b-9

Case #3

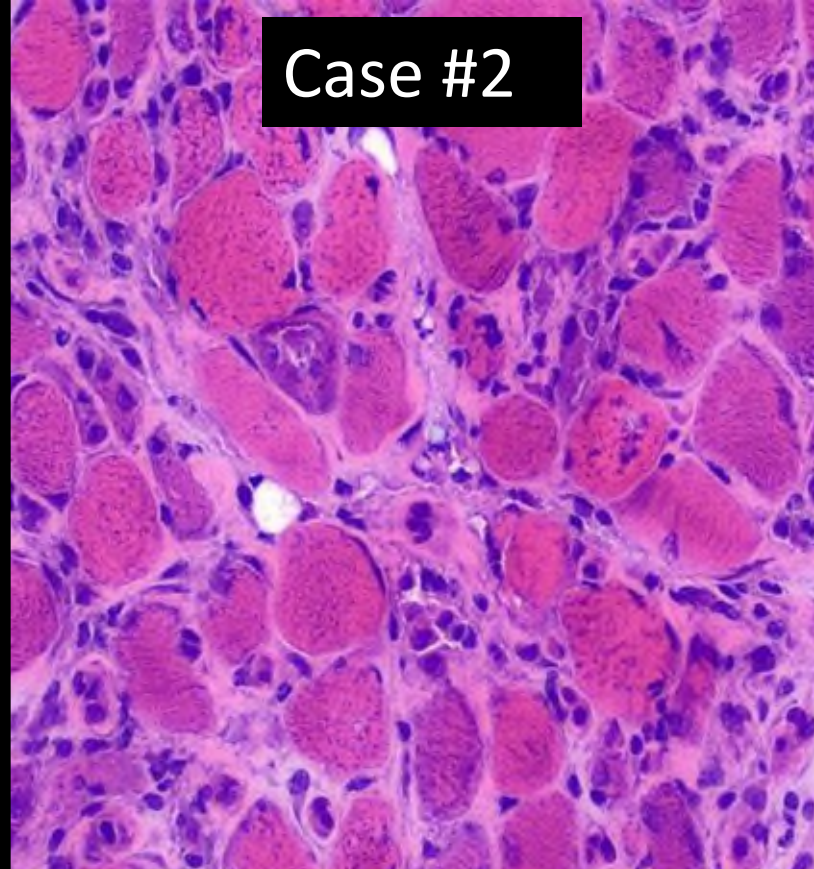


Case #1



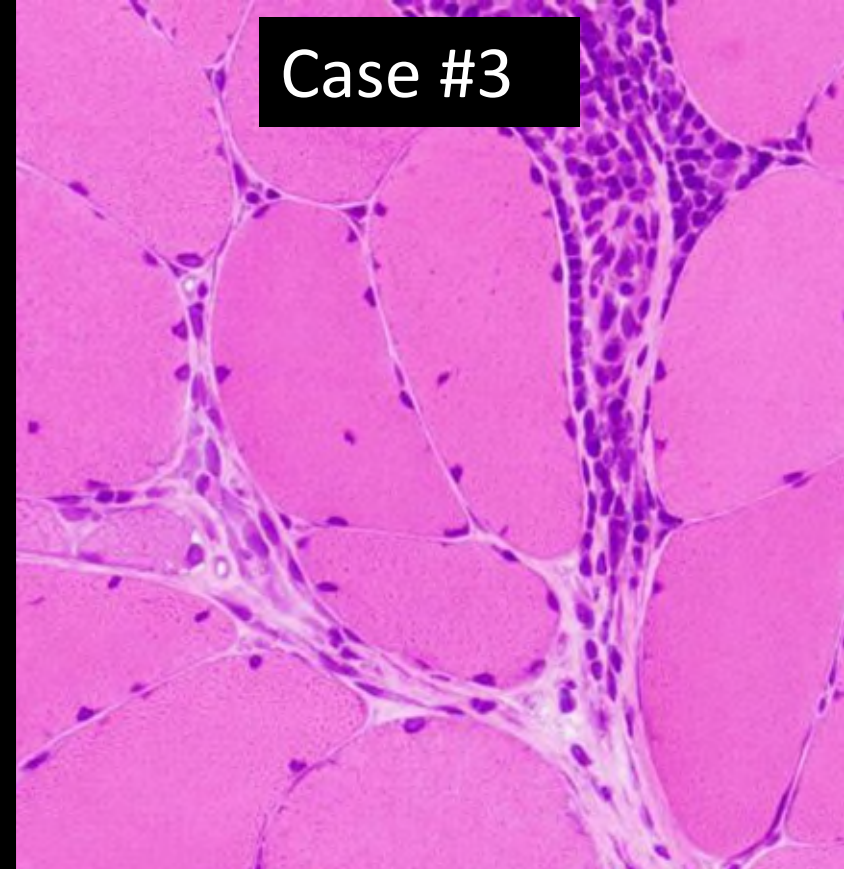
anti-HMGCR

Case #2



Anti-SRP

Case #3



Anti-HMGCR

Immune-mediated necrotizing myopathy (IMNM)

- Due to autoantibodies against HMGCR or SRP
 - ~30% seronegative
- Proximal muscle weakness, sometimes seen in patients who have been exposed to statins (anti-HMGCR), but doesn't have to be
 - Cancer association, cardiac and lung involvement
- CK is often very high

IIM subgroup	Associated antibody	Clinical features and associated HLA haplotype (s)	Pathological features				Note
			Histological features	Immunohistochemical features			
				HLA-ABC	HLA-DR	C5b-9	
IMNM	Anti-SRP	Risk cardiac involvement HLA-DRB1*08:03	Myofiber necrosis and regeneration, sparse inflammation (macrophages > lymphocytes)	+	-	Sarcolemma	IMNM: p62 diffuse tiny dots
	Anti-HMGCR	CAM? HLA-DRB1*07:01 (juvenile) HLA-DRB1*11:01 (adult)		+	-	Sarcolemma	
	Seronegative IMNM	CAM		+	-/+	Sarcolemma	



Anti-SRP IMNM association with interstitial lung disease

Anti-Signal Recognition Particle Antibody-Associated Severe **Interstitial Lung Disease** Requiring **Lung** Transplantation.

Qureshi A, Brown D, Brent L.

Cureus. 2020 May 5;12(5):e7962. doi: 10.7759/cureus.7962.

PMID: 32523819 [Free PMC article.](#)

Interstitial lung disease is not rare in immune-mediated necrotizing myopathy with anti-signal recognition particle antibodies.

Ge Y, Yang H, Xiao X, Liang L, Lu X, Wang G.

BMC Pulm Med. 2022 Jan 10;22(1):14. doi: 10.1186/s12890-021-01802-1.

PMID: 35000598 [Free PMC article.](#)

Development of Necrotizing Myopathy Following **Interstitial Lung Disease** with Anti-signal Recognition Particle Antibody.

Kusumoto T, Okamori S, Masuzawa K, Asakura T, Nishina N, Chubachi S, Naoki K, Fukunaga K, Betsuyaku T.

Intern Med. 2018 Jul 15;57(14):2045-2049. doi: 10.2169/internalmedicine.0303-17. Epub 2018 Feb 28.

PMID: 29491298 [Free PMC article.](#)



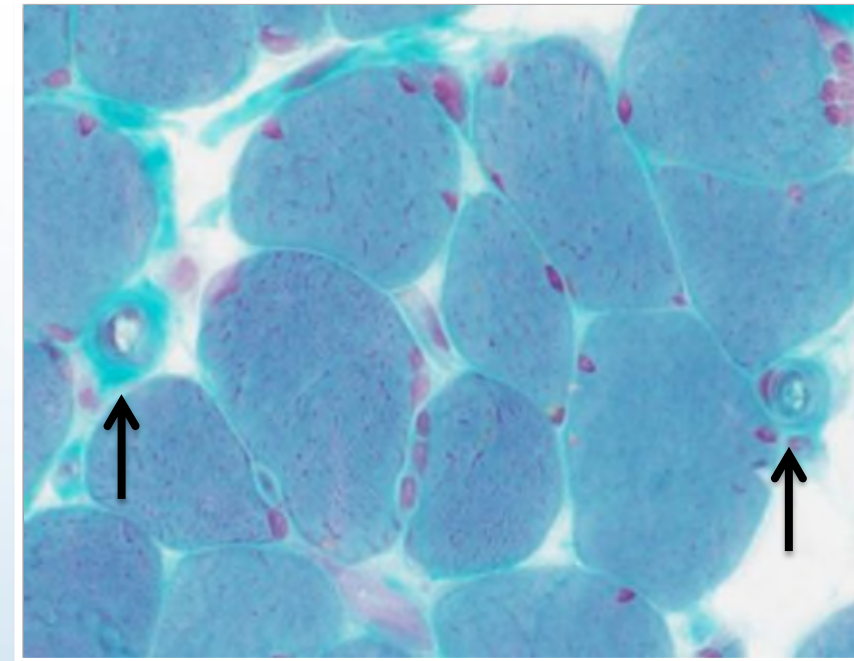
Anti-HMGCR antibodies without exposure to statins

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

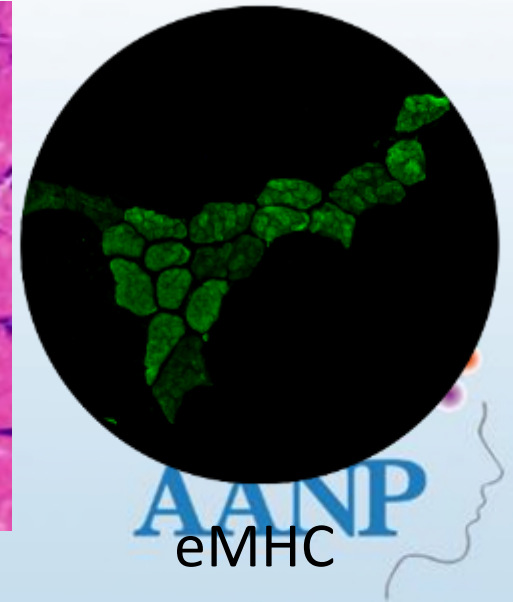
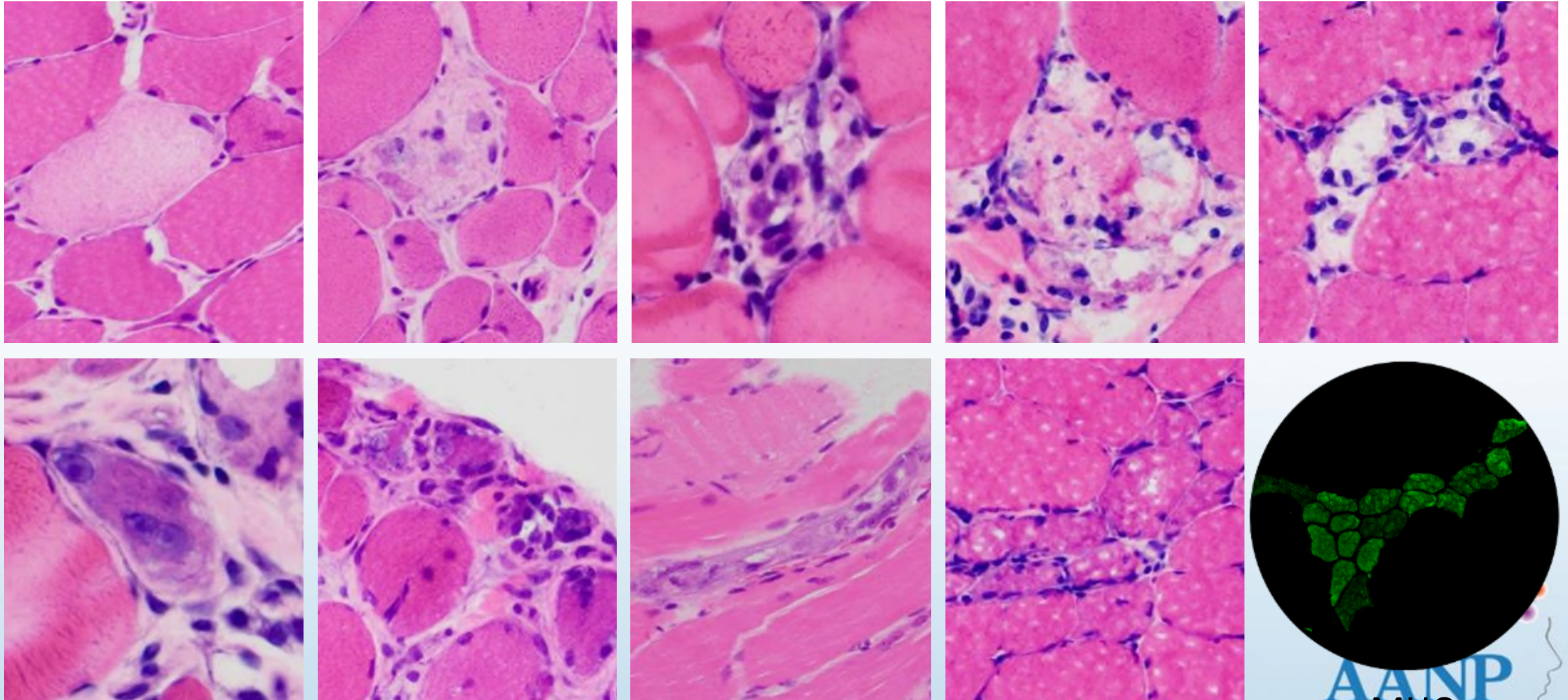


Immune-mediated necrotizing myopathy – diagnostic clues

- 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 sarcolemmal deposition very common if not universal
 - Vacuolization (rimmed, non-rimmed, and/or vacuoles with sarcolemmal features)
 - Endomysial fibrosis is often prominent
 - Enlarged capillaries may be prominent



Various stages of necrosis and regeneration

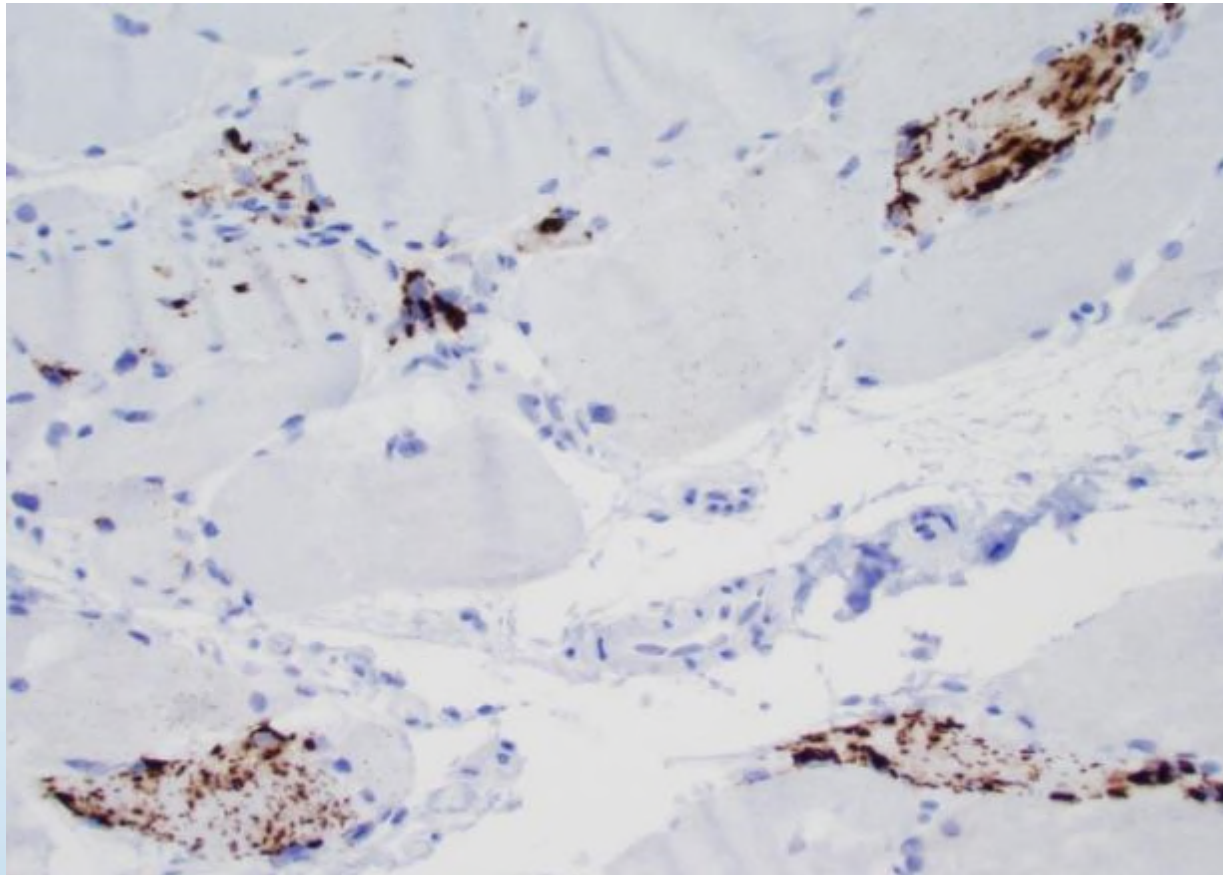


	MHC Class I	MHC Class II	C5b-9	MxA	p62
DM	Perifascicular sarcolemmal and sarcoplasmic	Negative	Strong capillary, some sarcolemmal, often perifascicular	Perifascicular sarcoplasmic mostly (sometimes scattered – MDA-5)	No significant positivity
ASyS	Perifascicular sarcolemmal and sarcoplasmic	Perifascicular sarcolemmal and sarcoplasmic	Sarcolemmal, +/- capillary, often perifascicular	Negative	No significant positivity
sIBM	Diffuse sarcolemmal and sarcoplasmic	Diffuse sarcolemmal and sarcoplasmic	Strong capillary, +/- sarcolemmal	Negative	Punctate course
					aggregates (associated with vacuoles)
IMNM	Patchy or diffuse sarcolemmal and sarcoplasmic	Negative	Strong sarcolemmal, +/- capillary	Negative	Diffuse sarcoplasmic

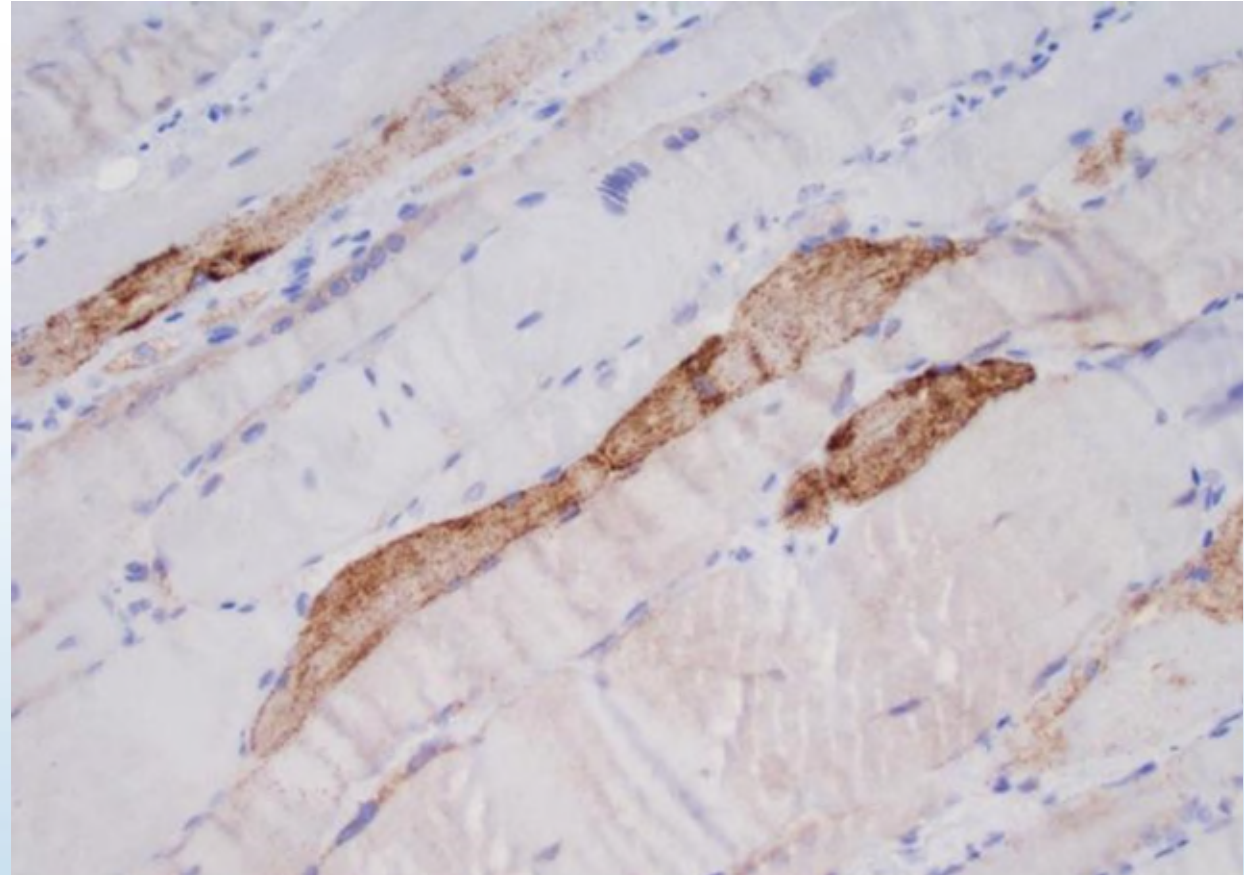


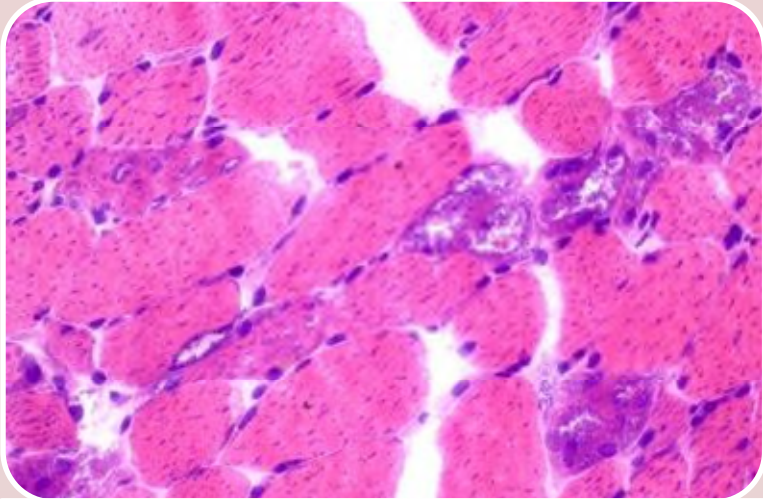
p62 immunohistochemistry

sIBM

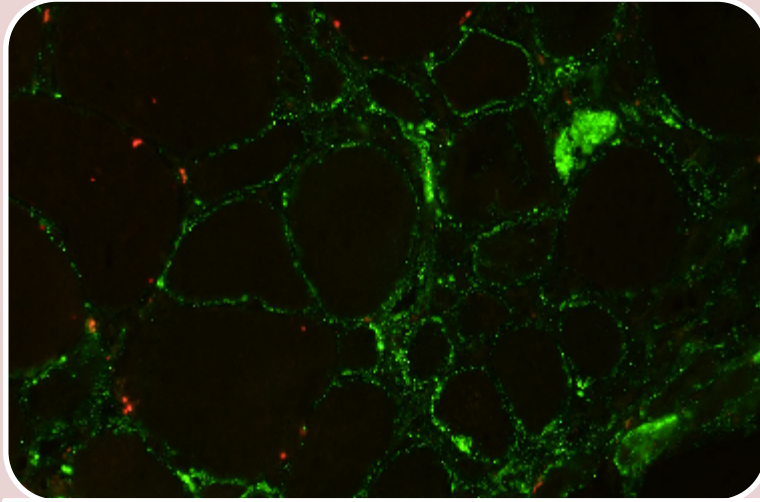


IMNM

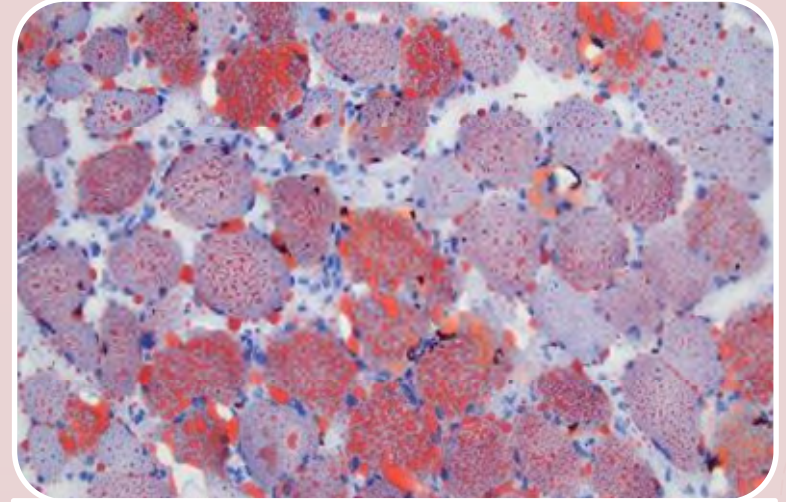




Toxic



Inflammatory



Metabolic

Case #1

- 68-year-old woman
- 4-year history of progressive neck and proximal limb weakness and worsening vision
- Exam: extraocular muscle, neck, and proximal limb weakness (no ptosis)
- Testing for myasthenia gravis negative
- CK: normal

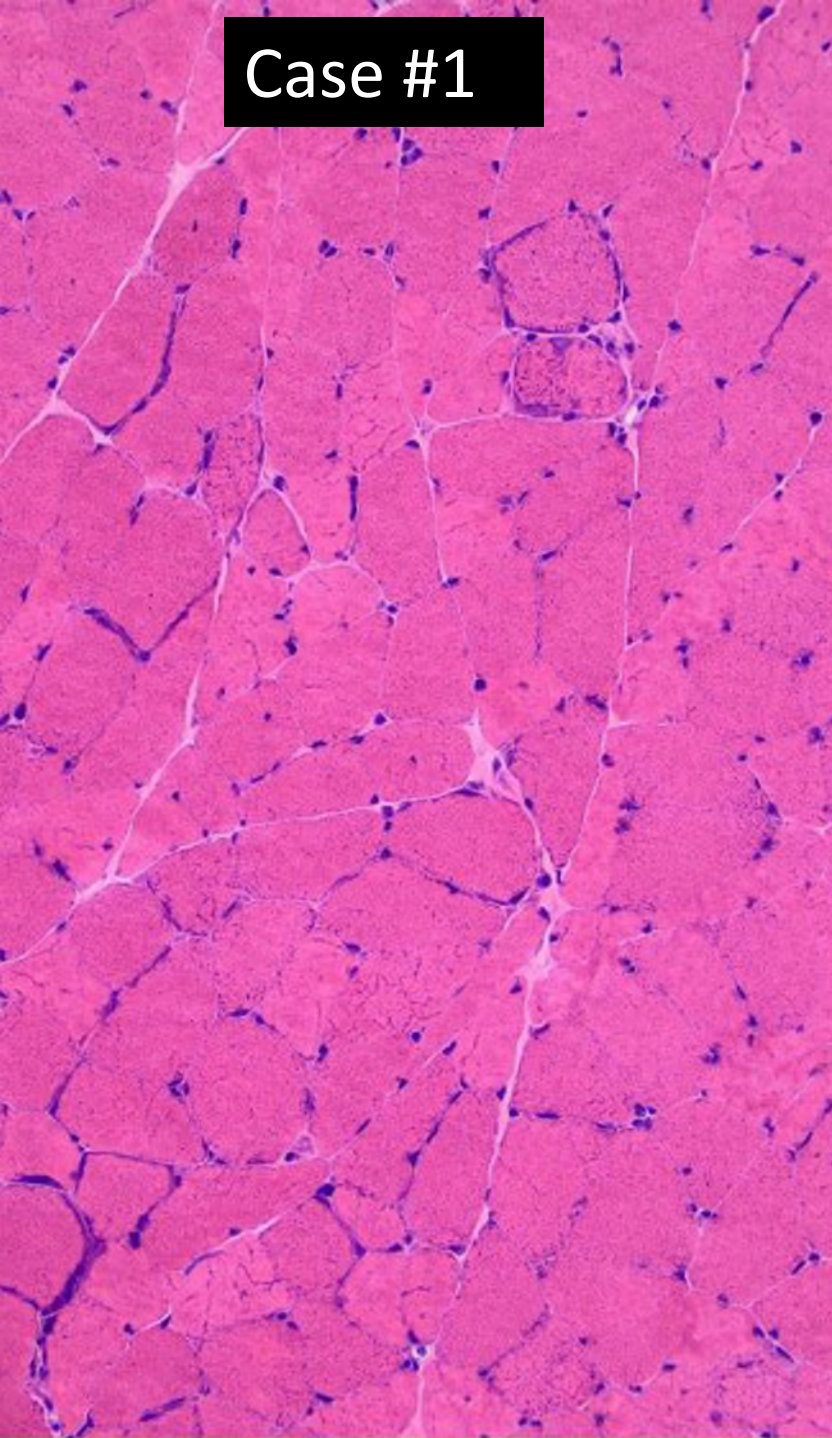
Case #2

- 60-year-old woman
- History of restriction of eye movements
- 6-month history of rapidly progressive proximal muscle weakness
- Exam: proximal greater than distal and extraocular muscle weakness
- EMG: severe proximal myopathy without fibrillations
- CK: normal

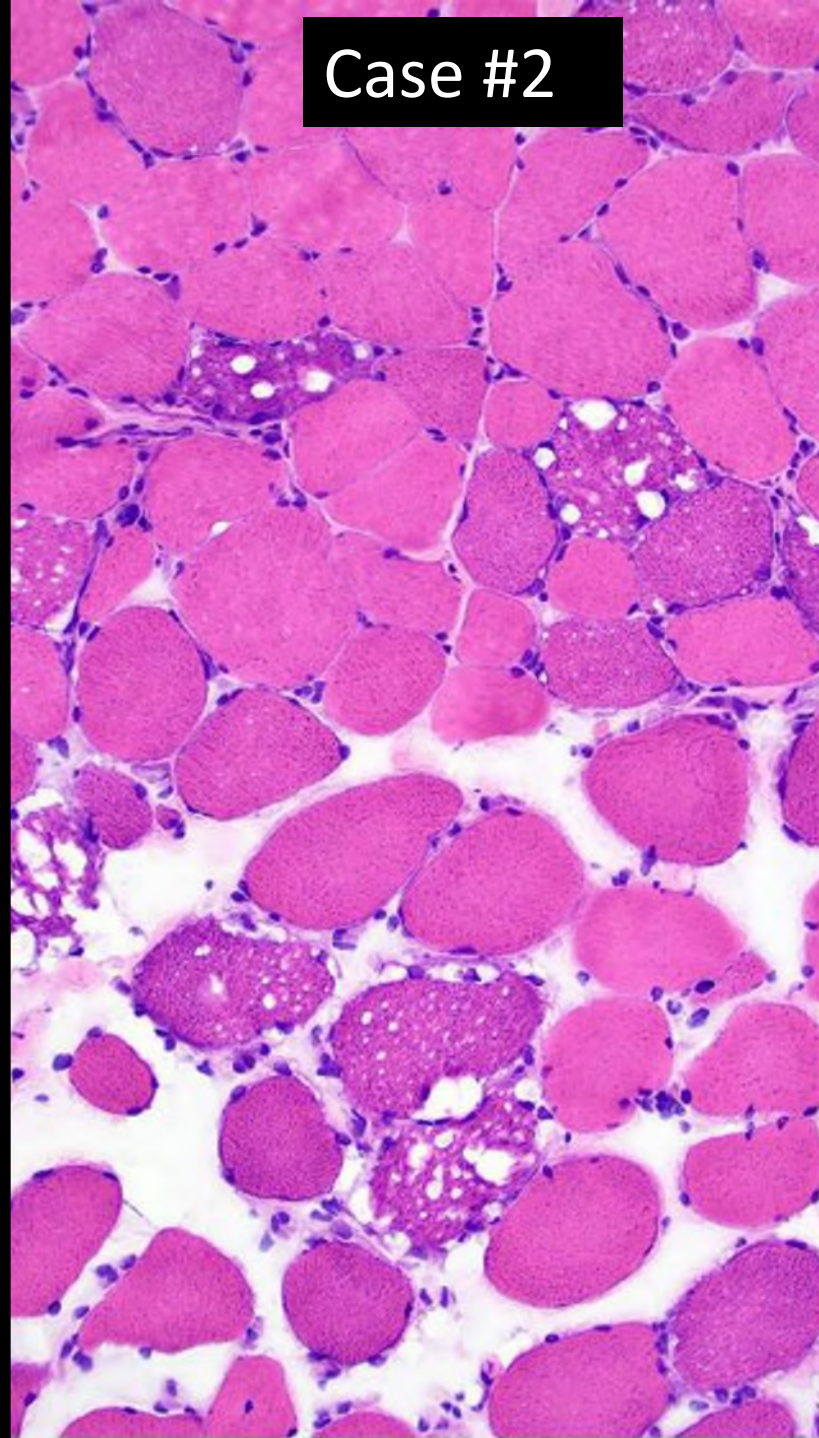
Case #3

- 2-year-old girl
- Progressive muscle weakness, motor regression, and head lag
- Exam: proximal limb and axial weakness
- Brain MRI: normal
- Family history: negative
- EMG/NCS: no significant abnormalities
- CK: elevated to 560 IU/L
- Genetic testing negative

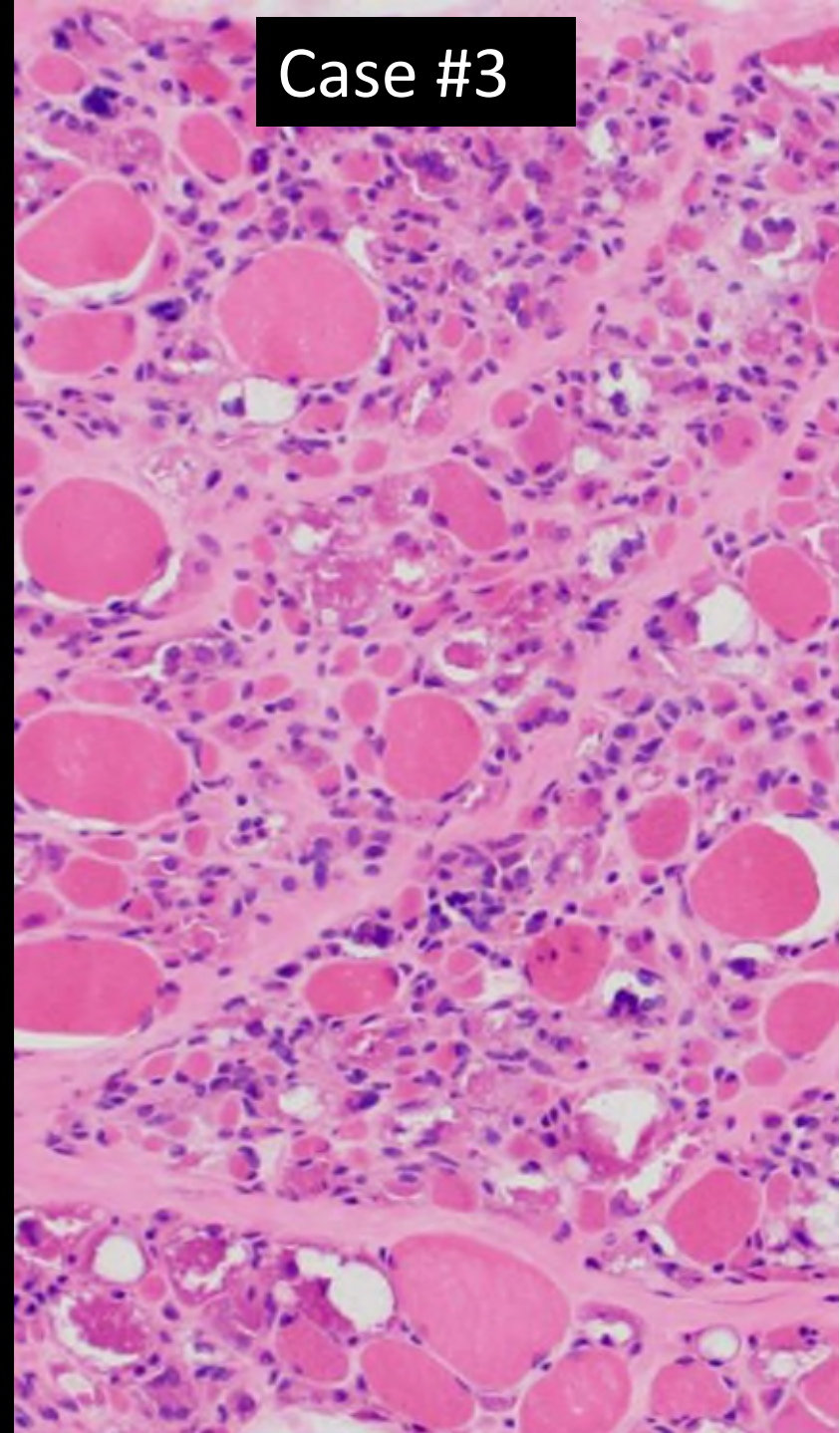
Case #1



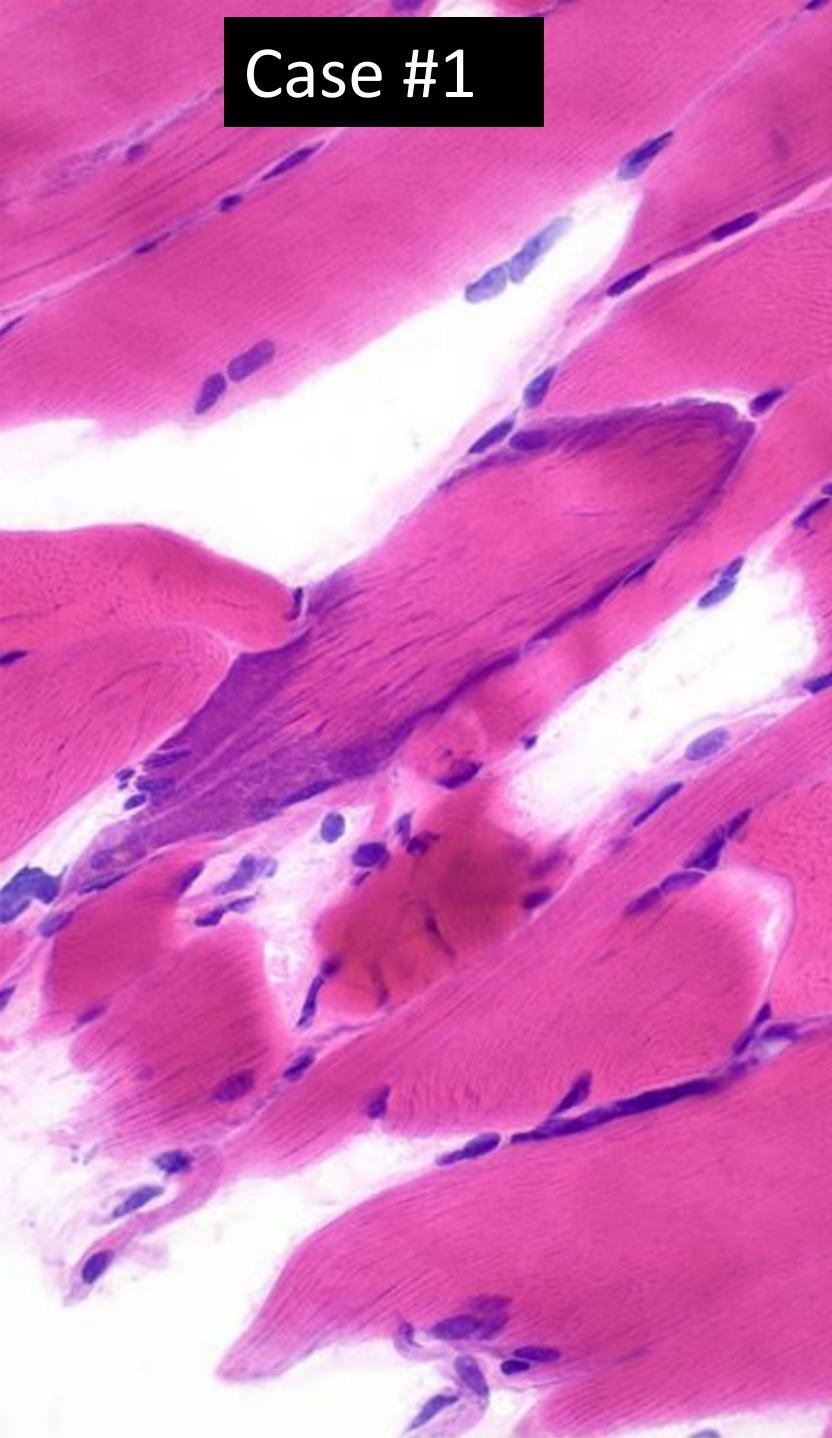
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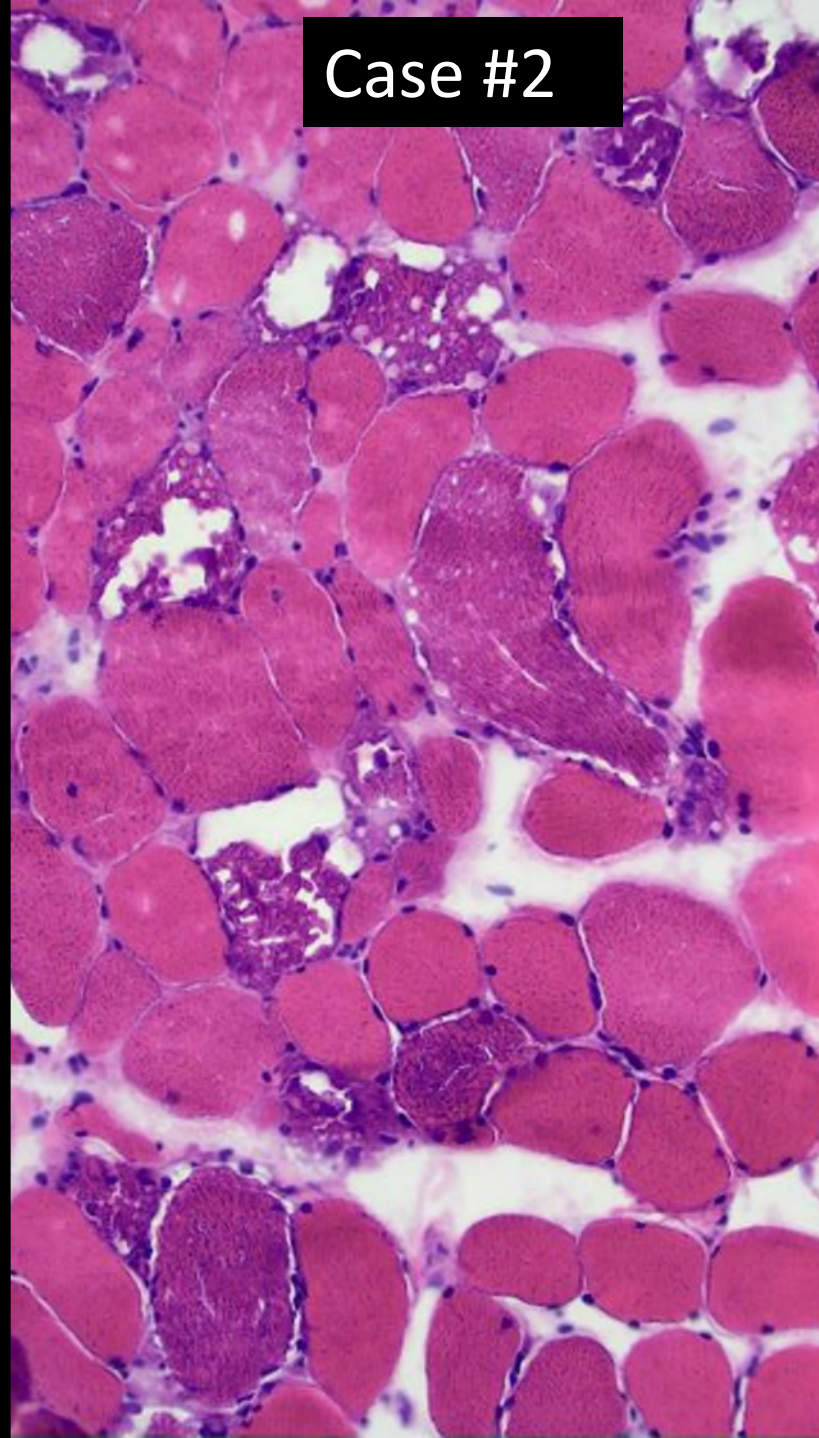
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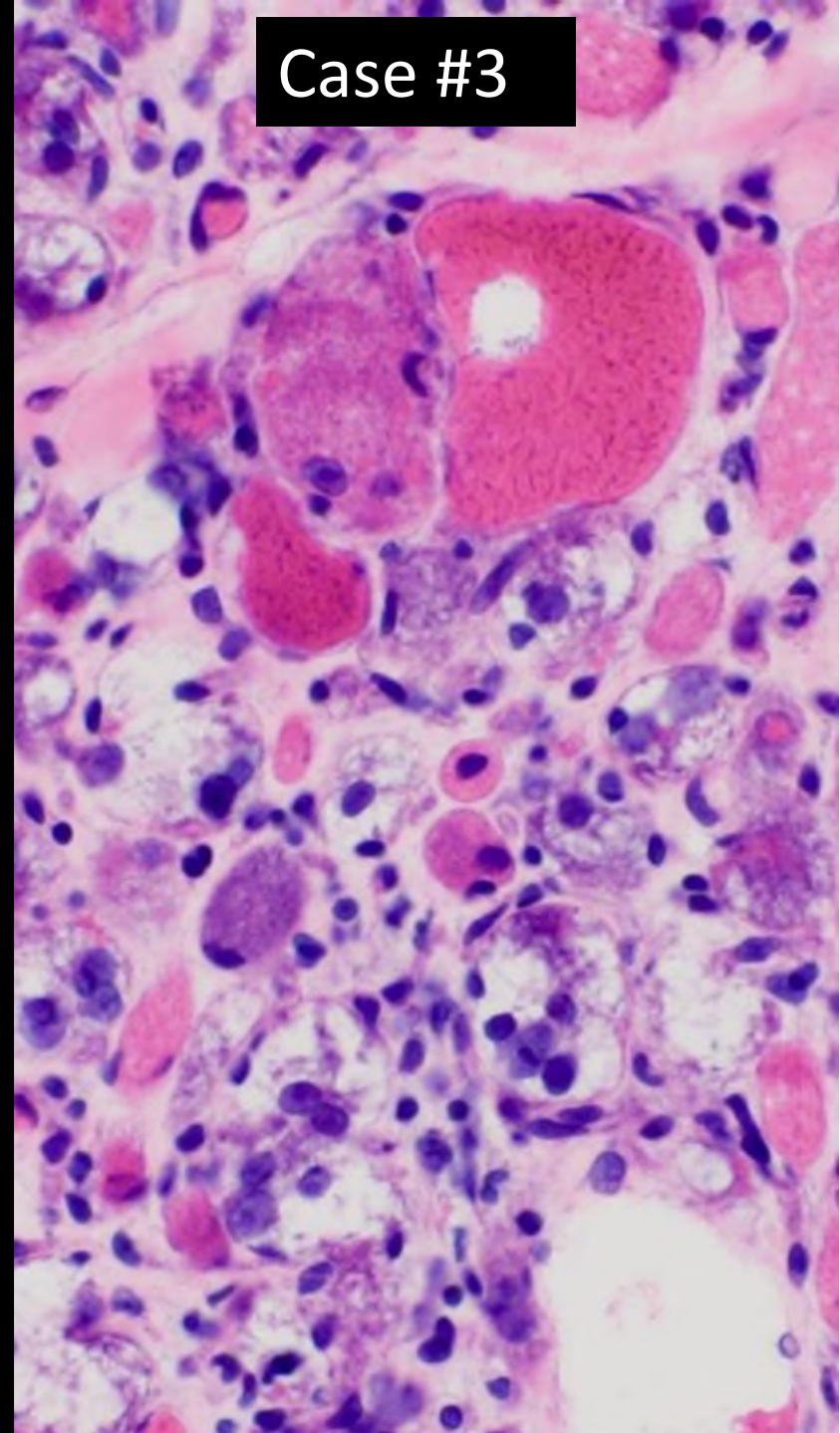
Case #1



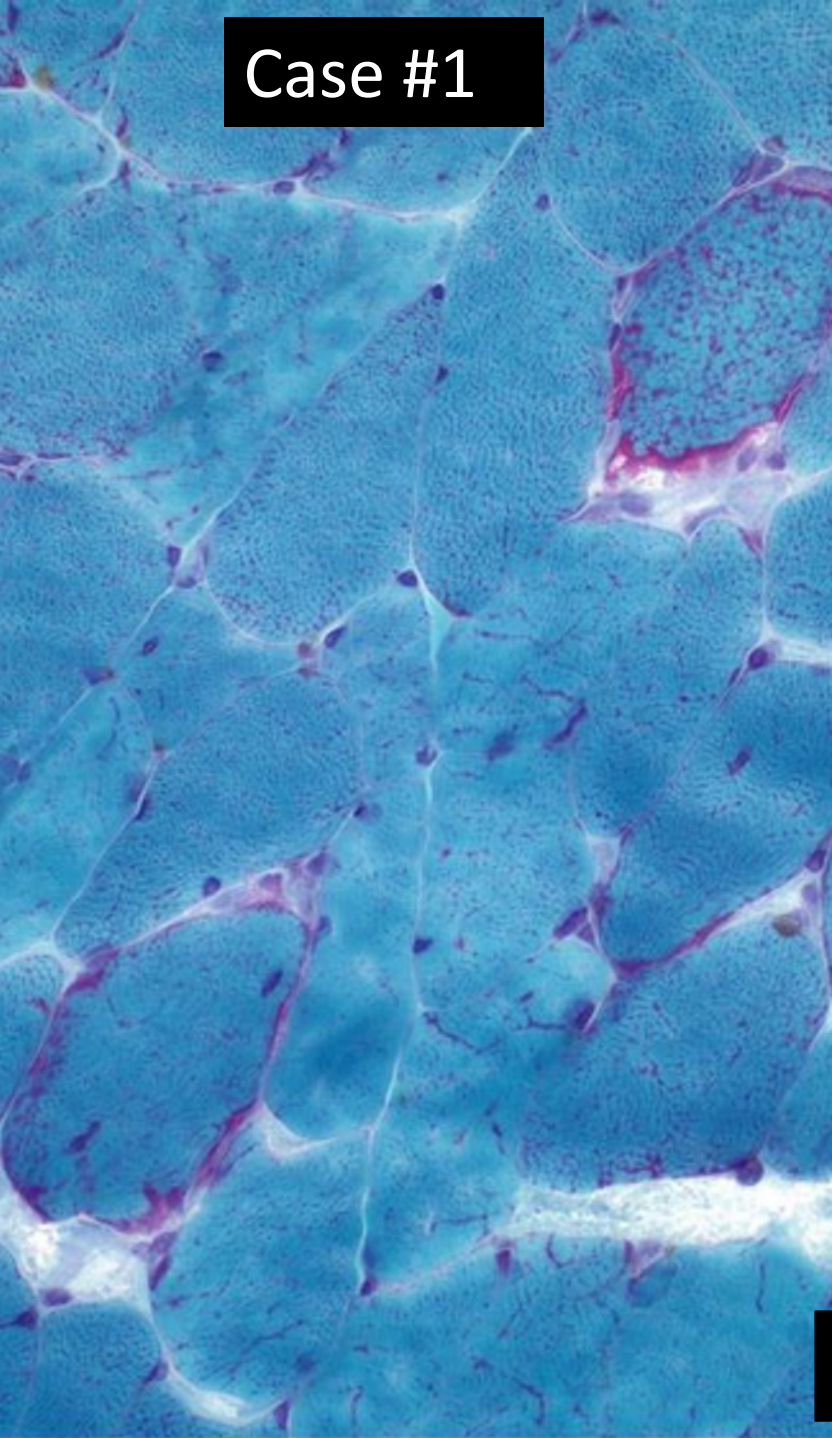
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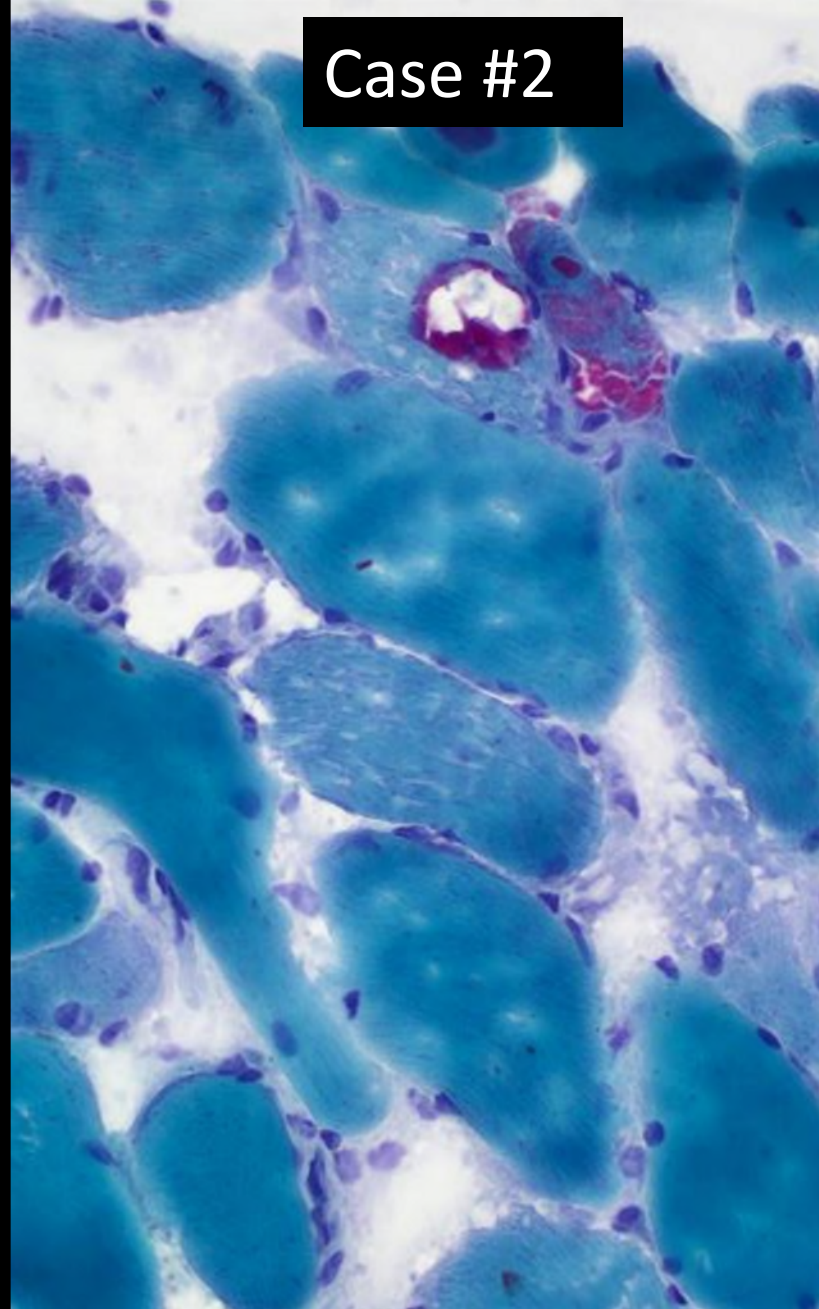
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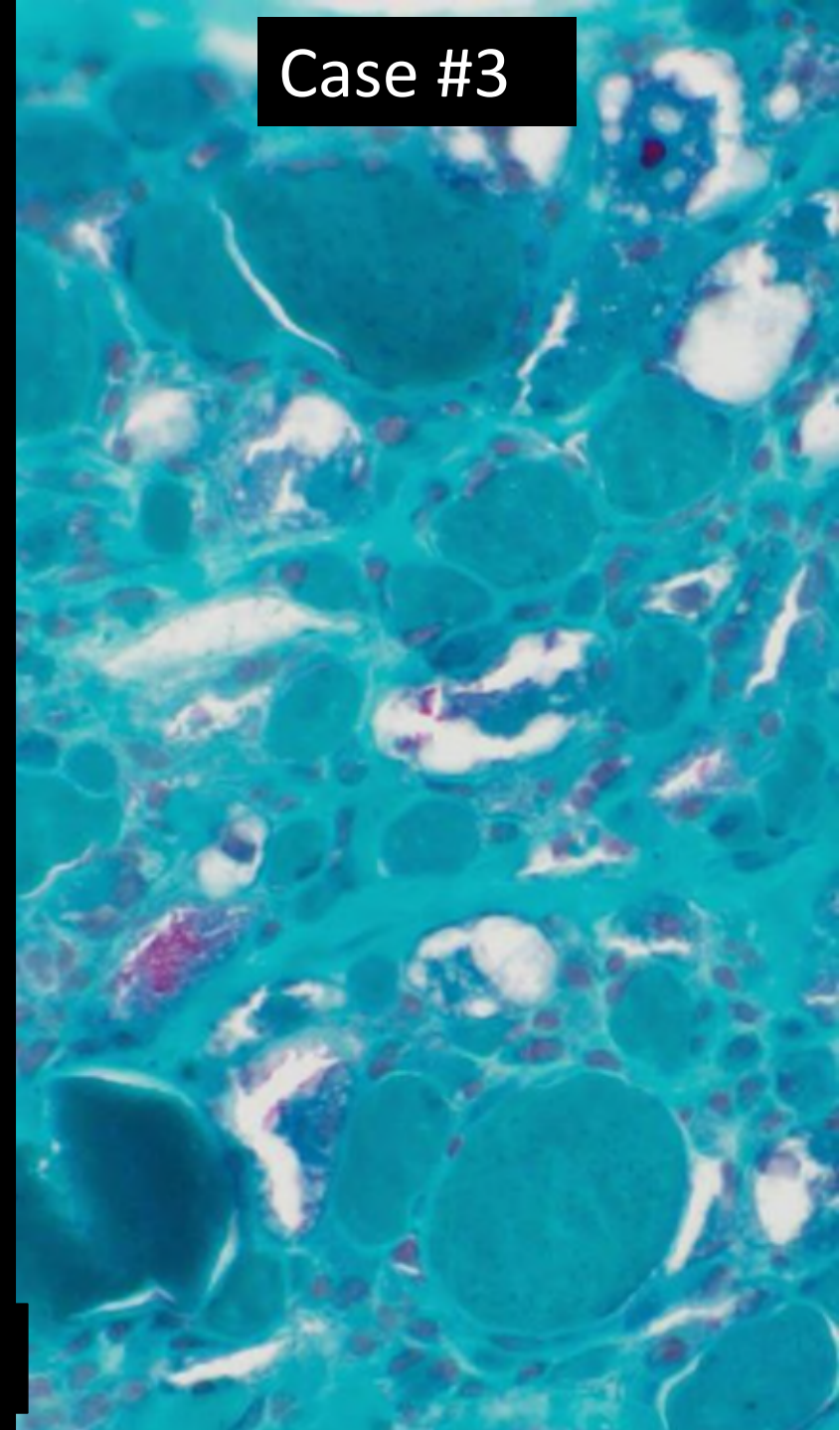
Case #1



Case #2

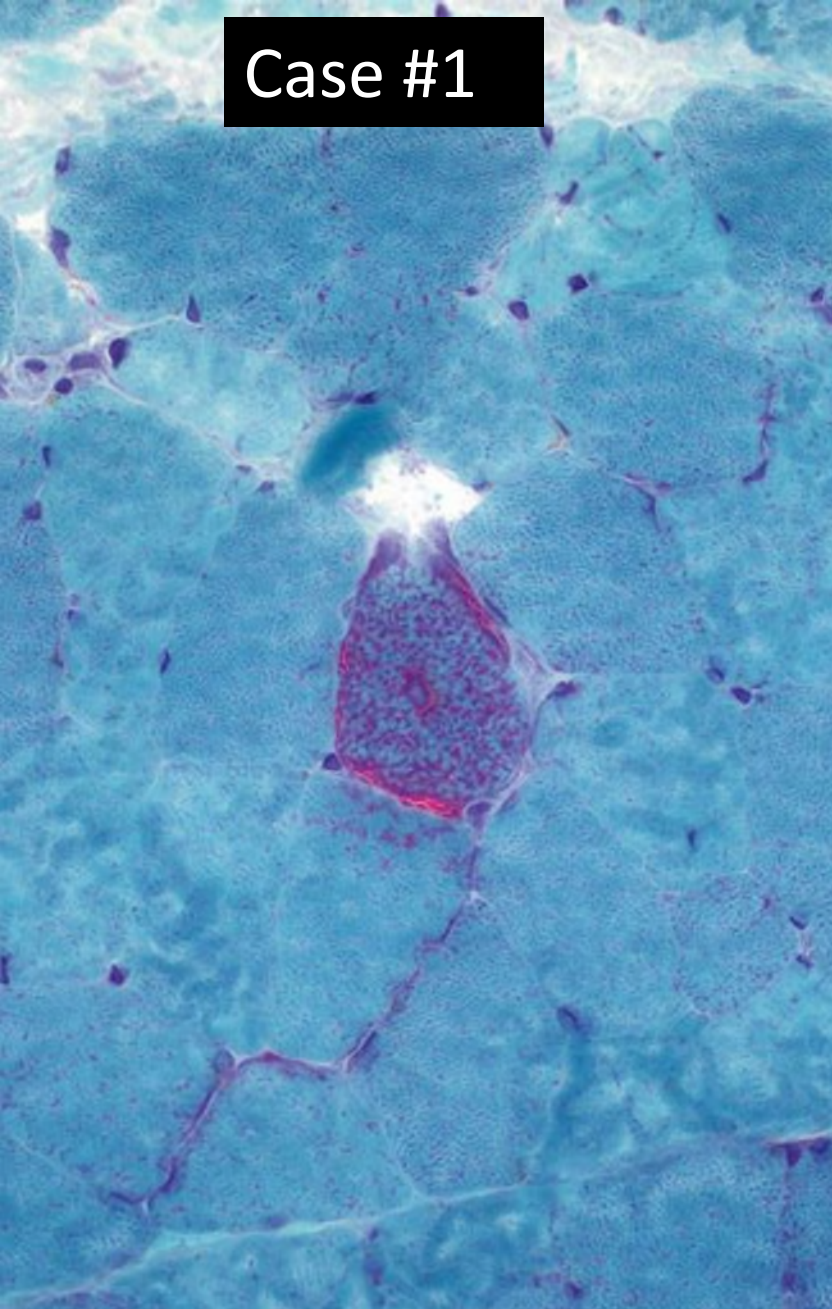


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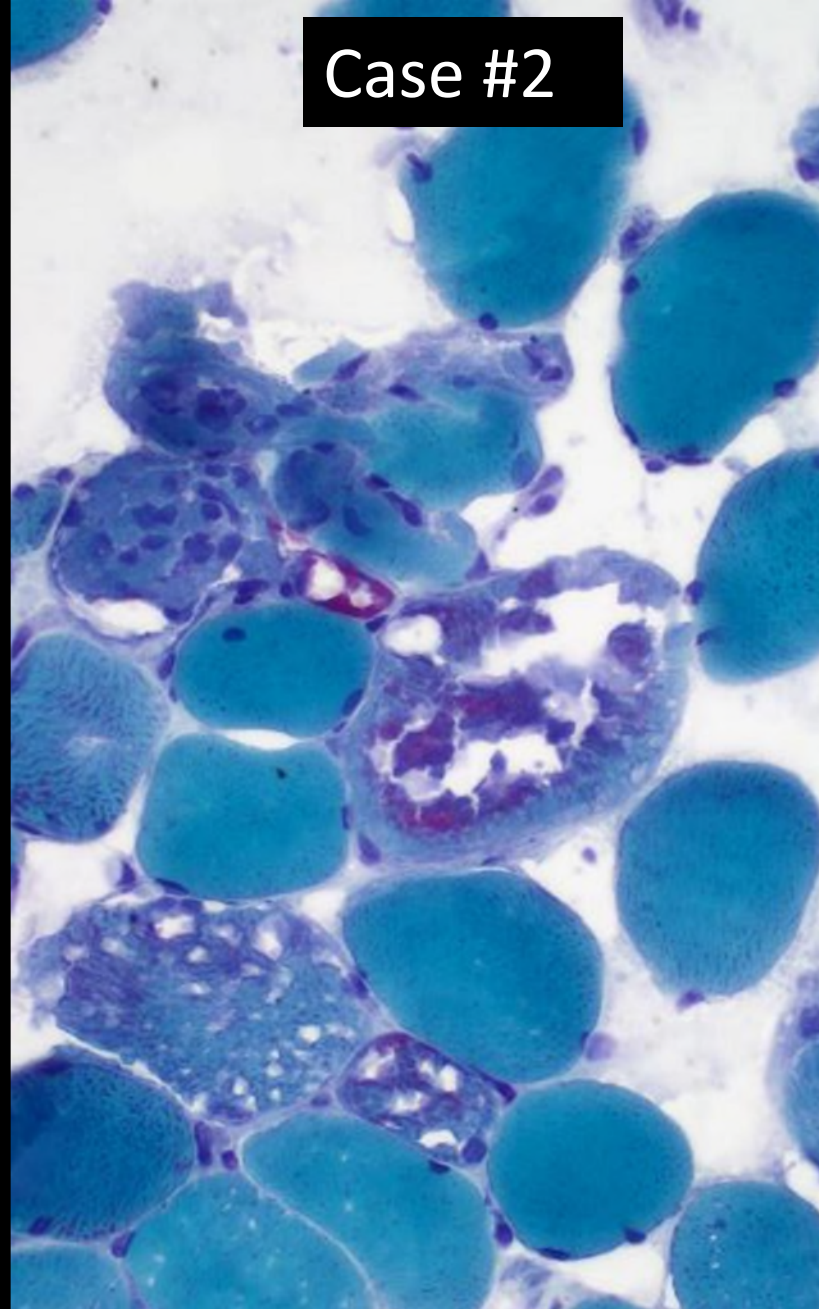


modified Gomori trichrome

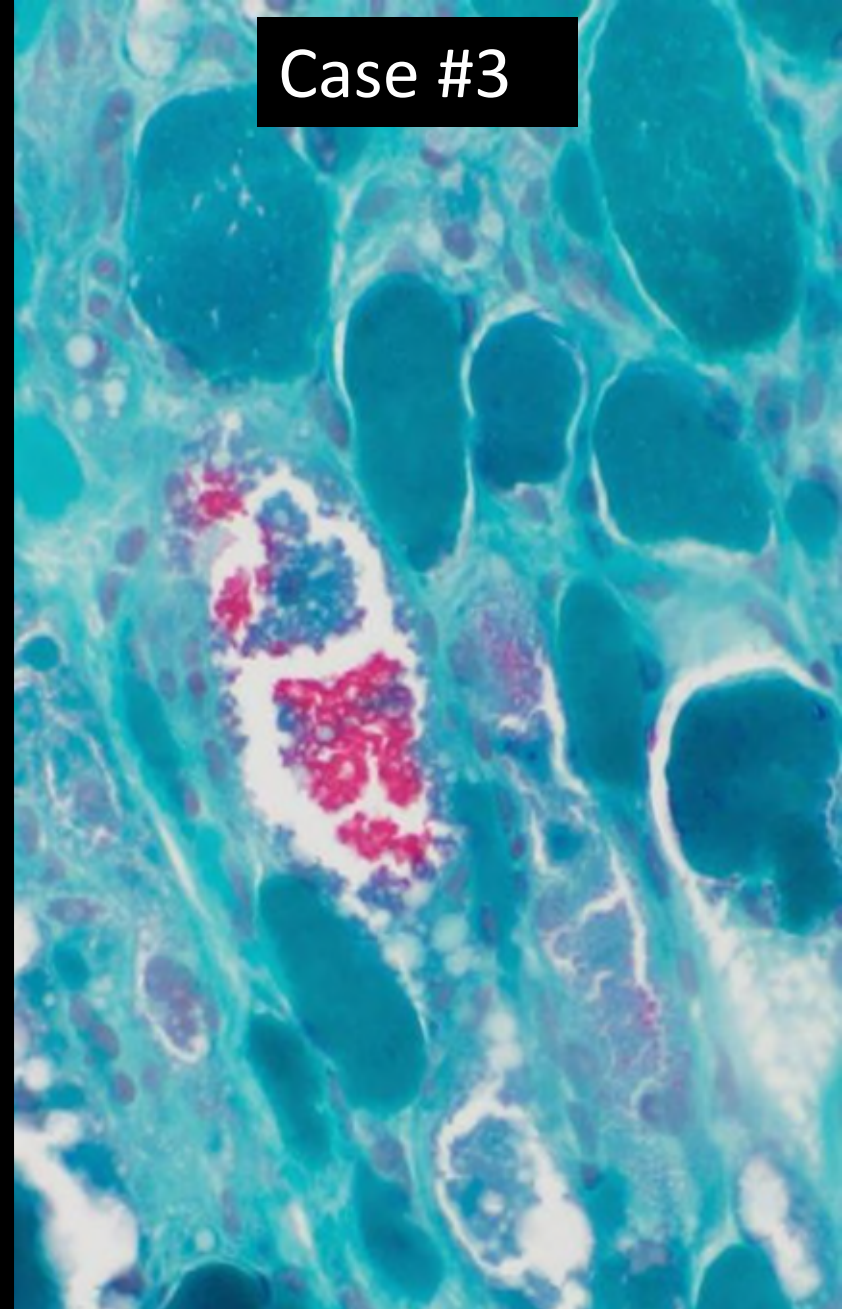
Case #1



Case #2

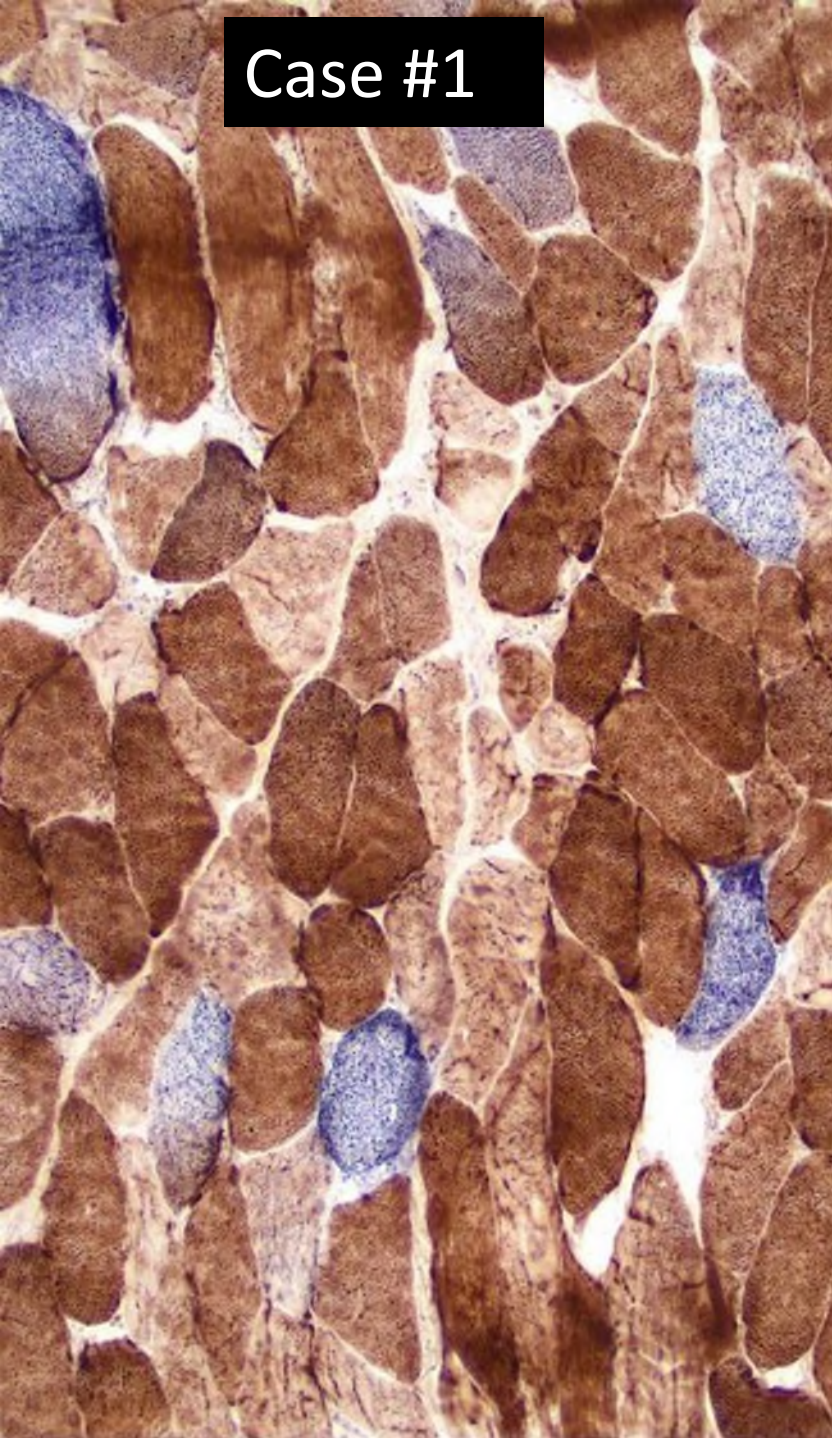


Case #3

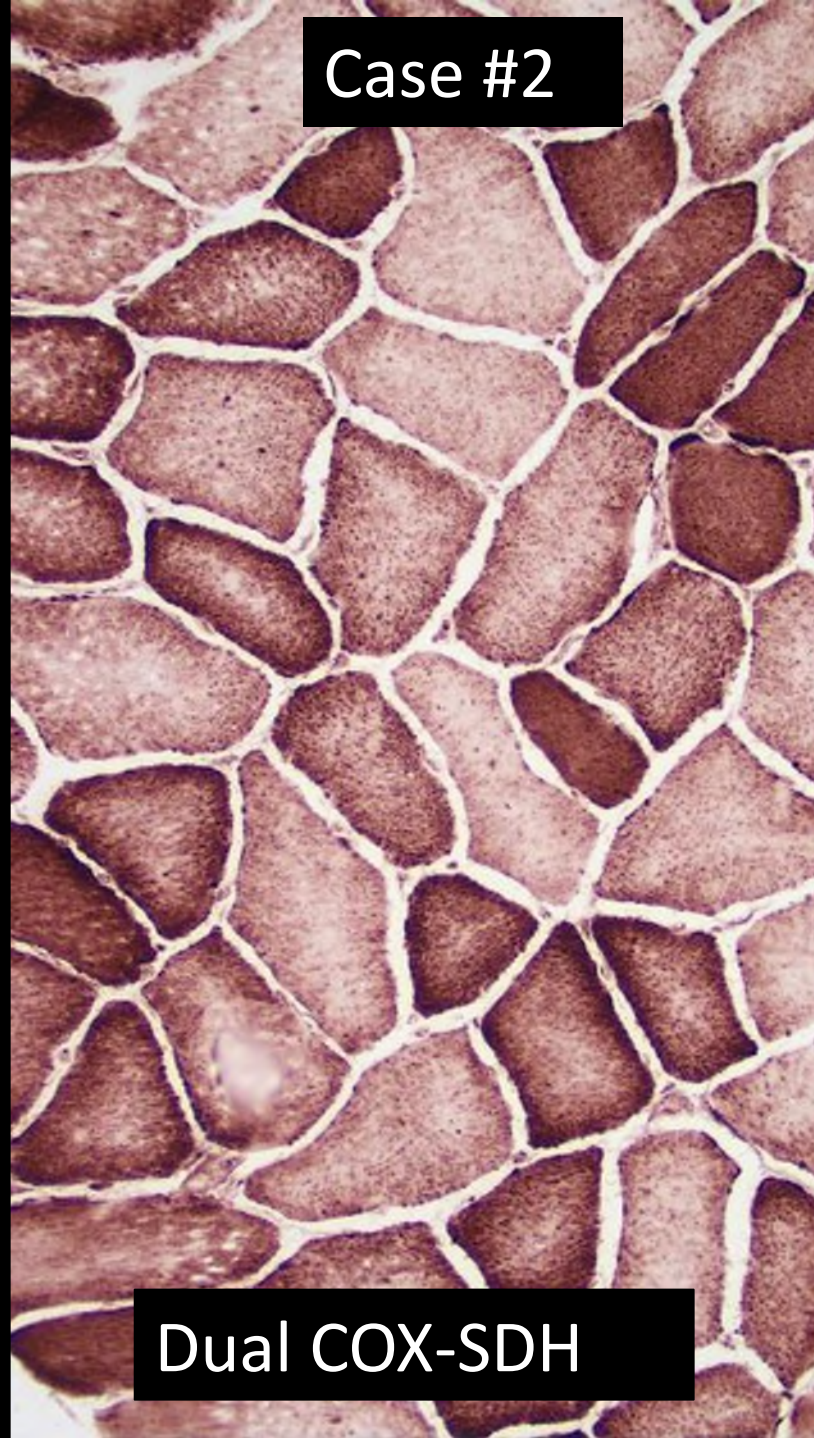


modified Gomori trichrome

Case #1

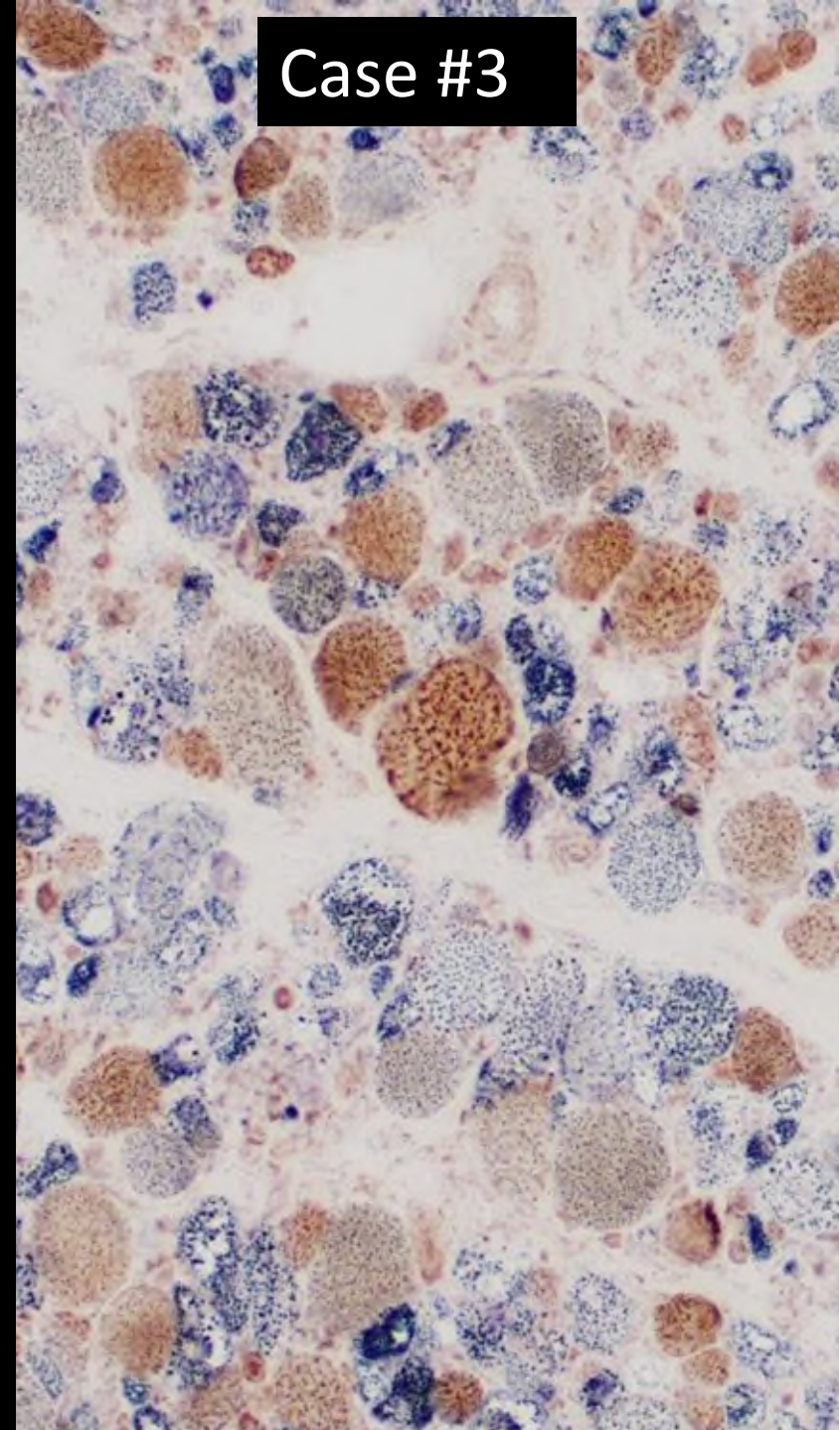


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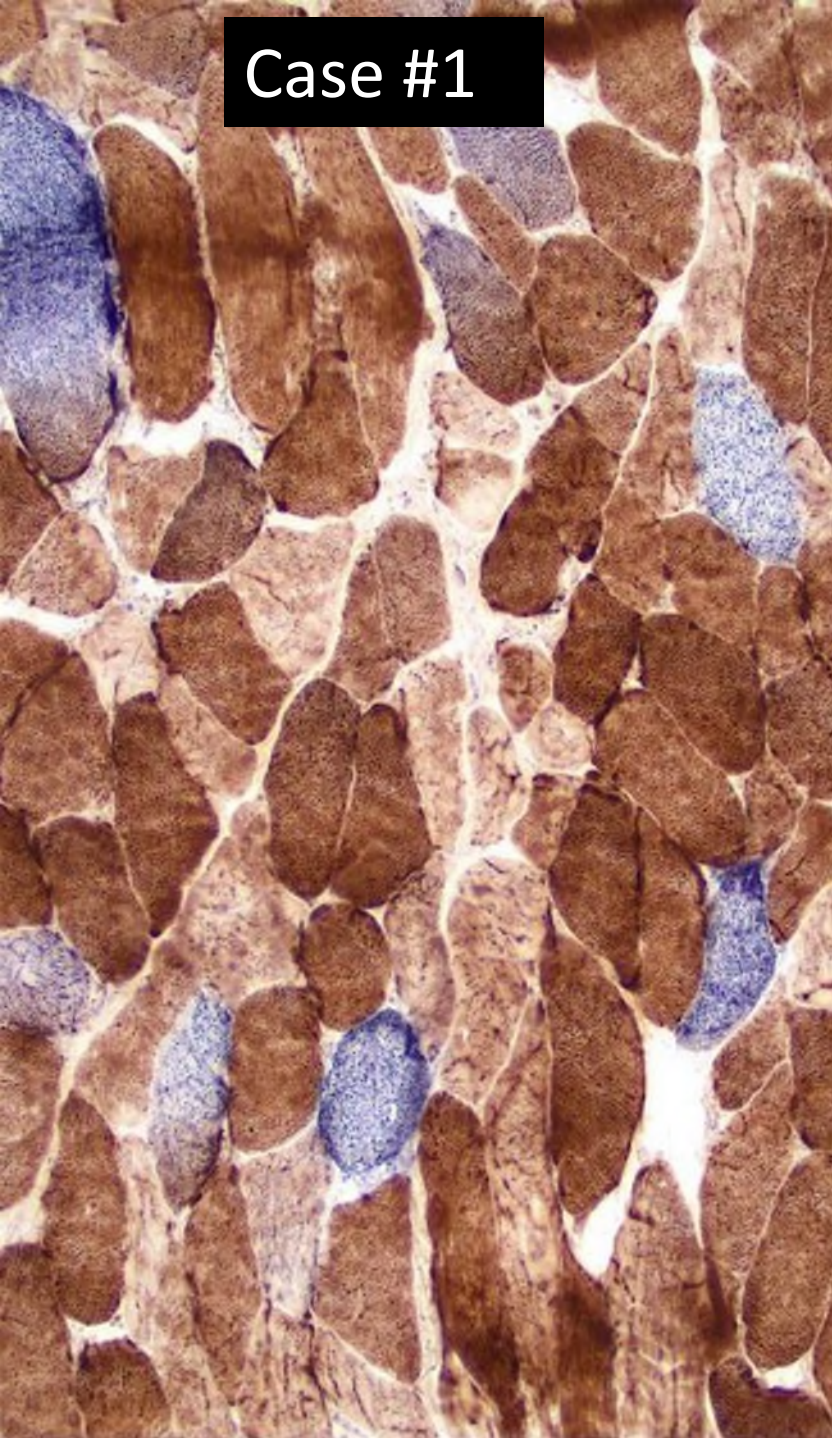


Dual COX-SDH

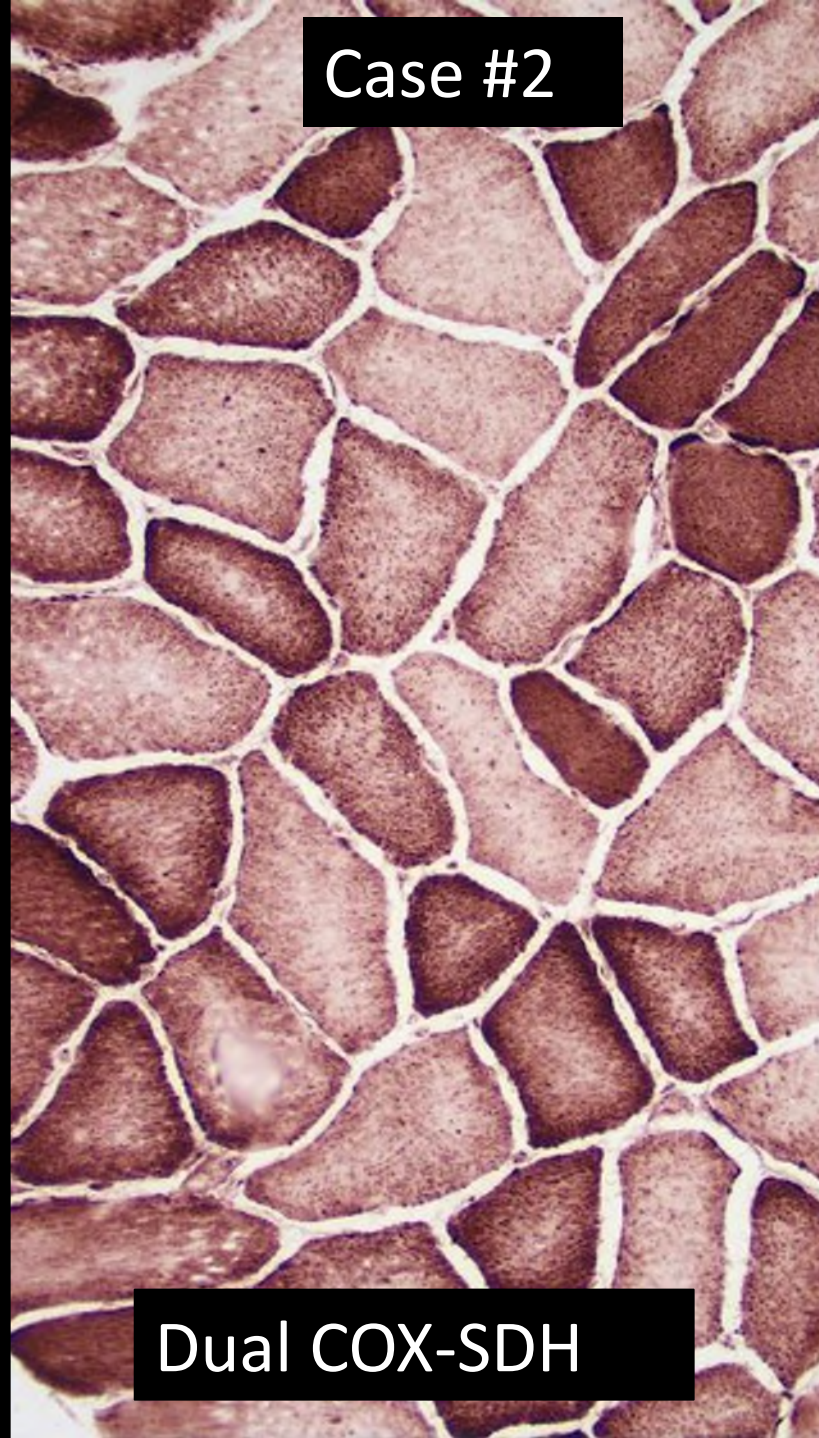
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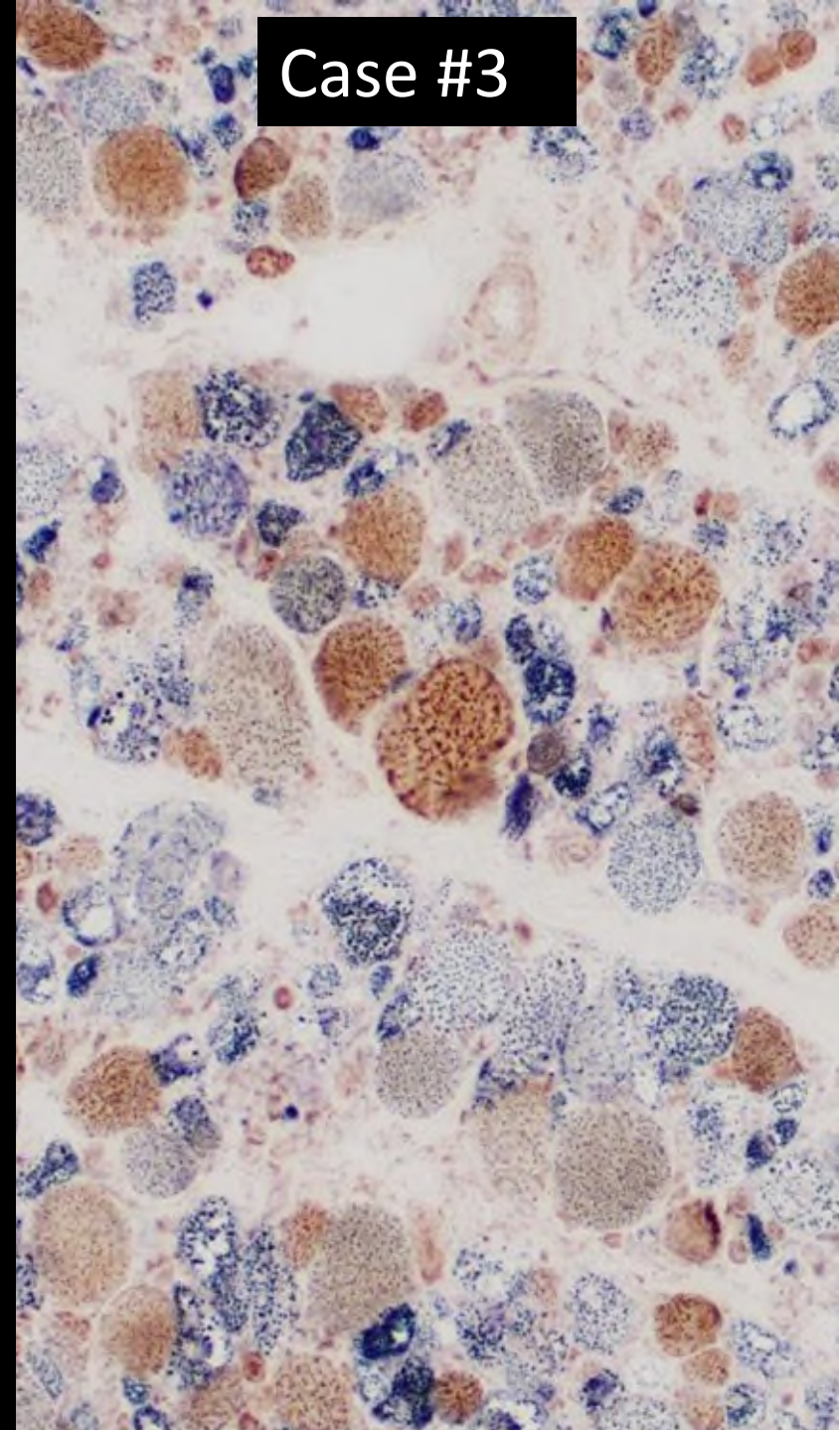
Case #1



Case #2

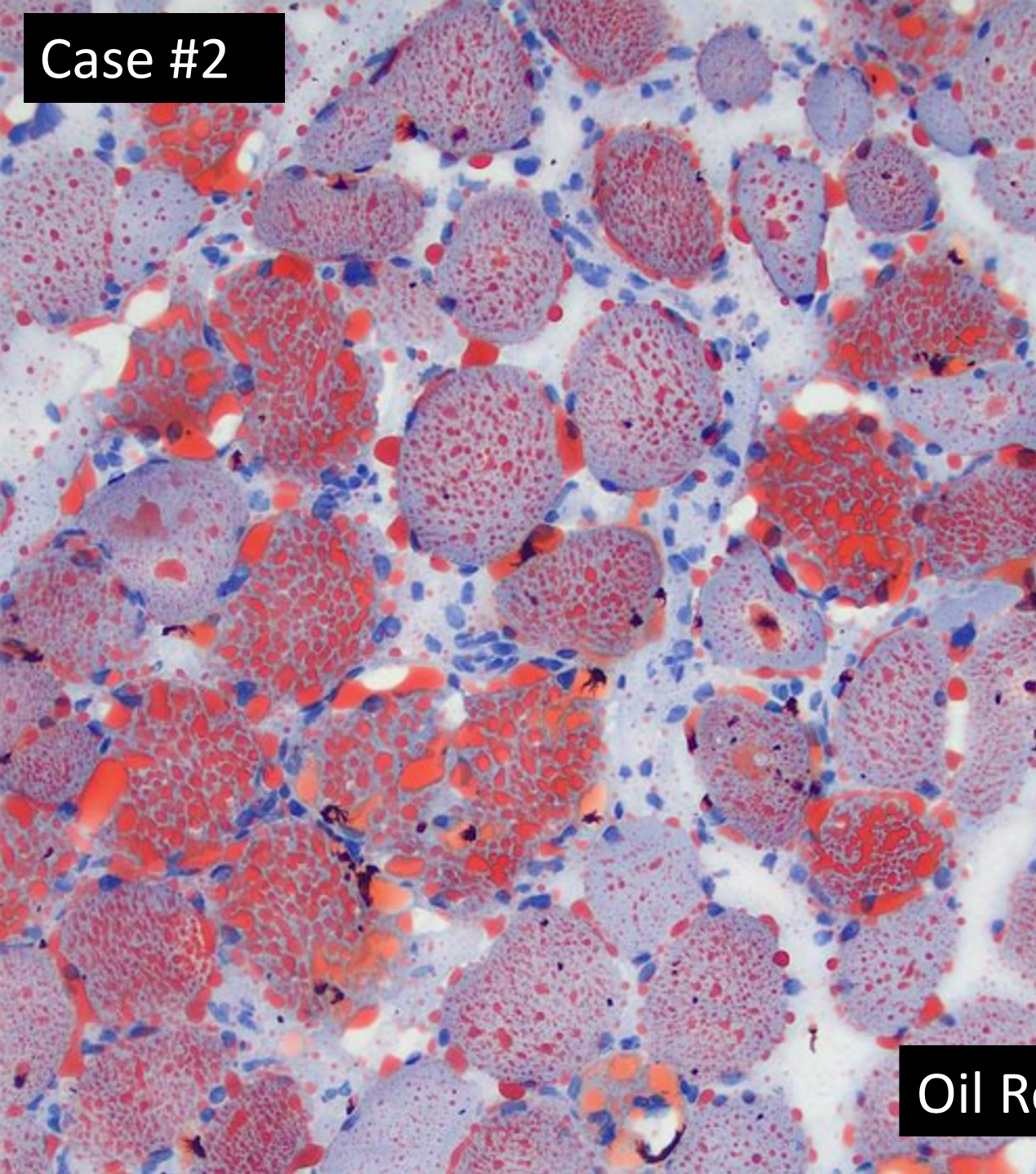


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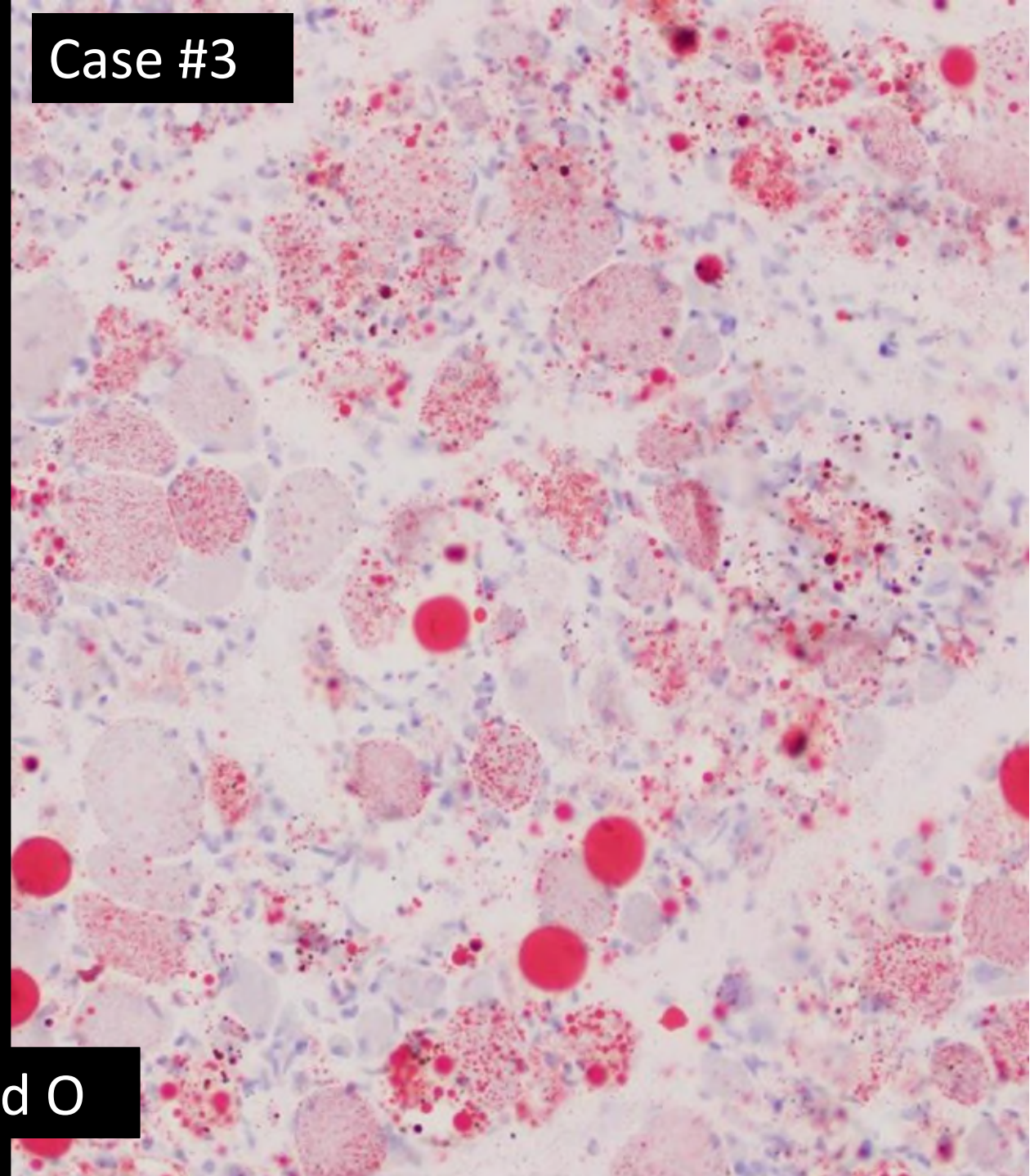


Dual COX-SDH

Case #2

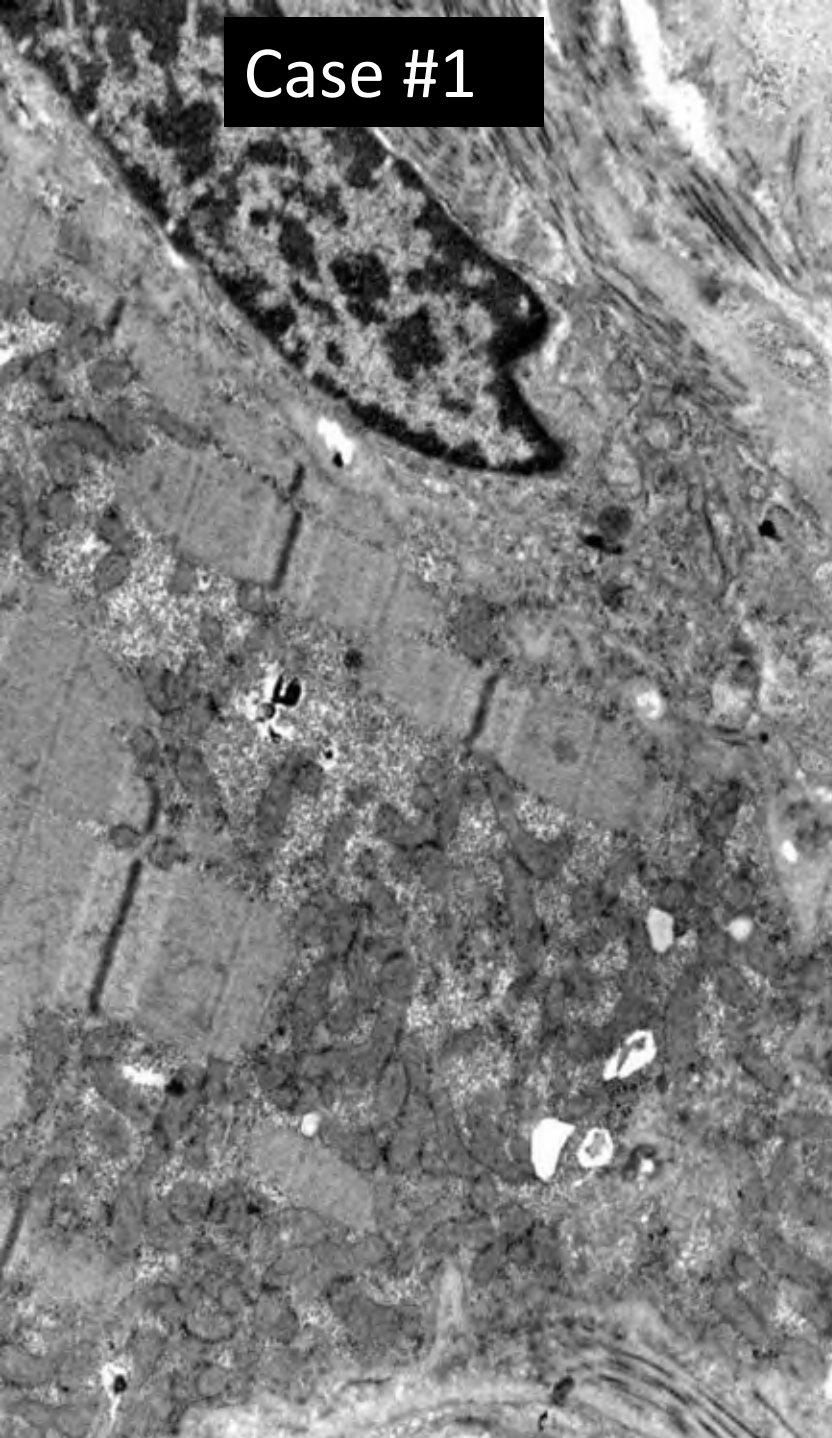


Case #3

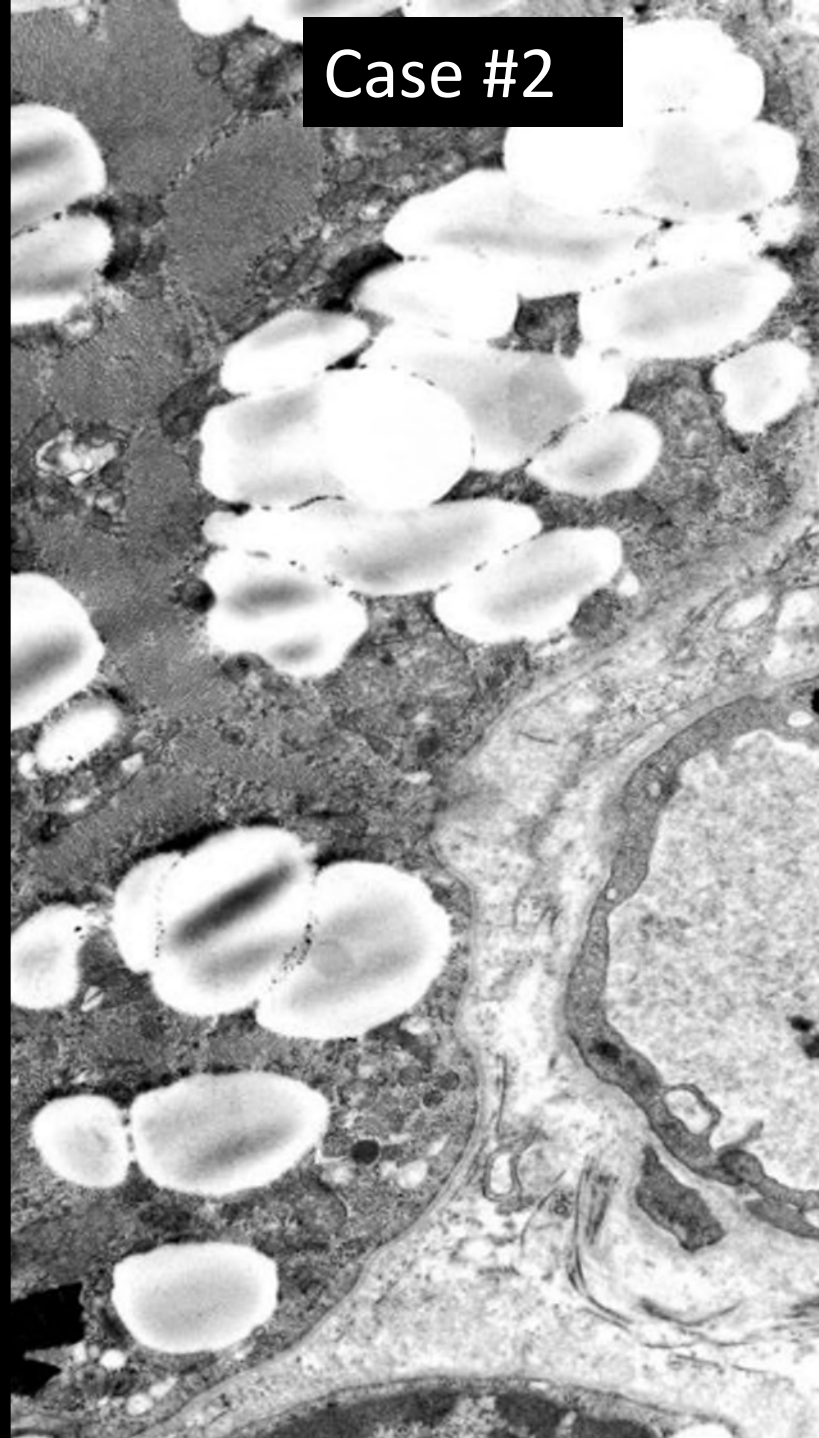


Oil Red O

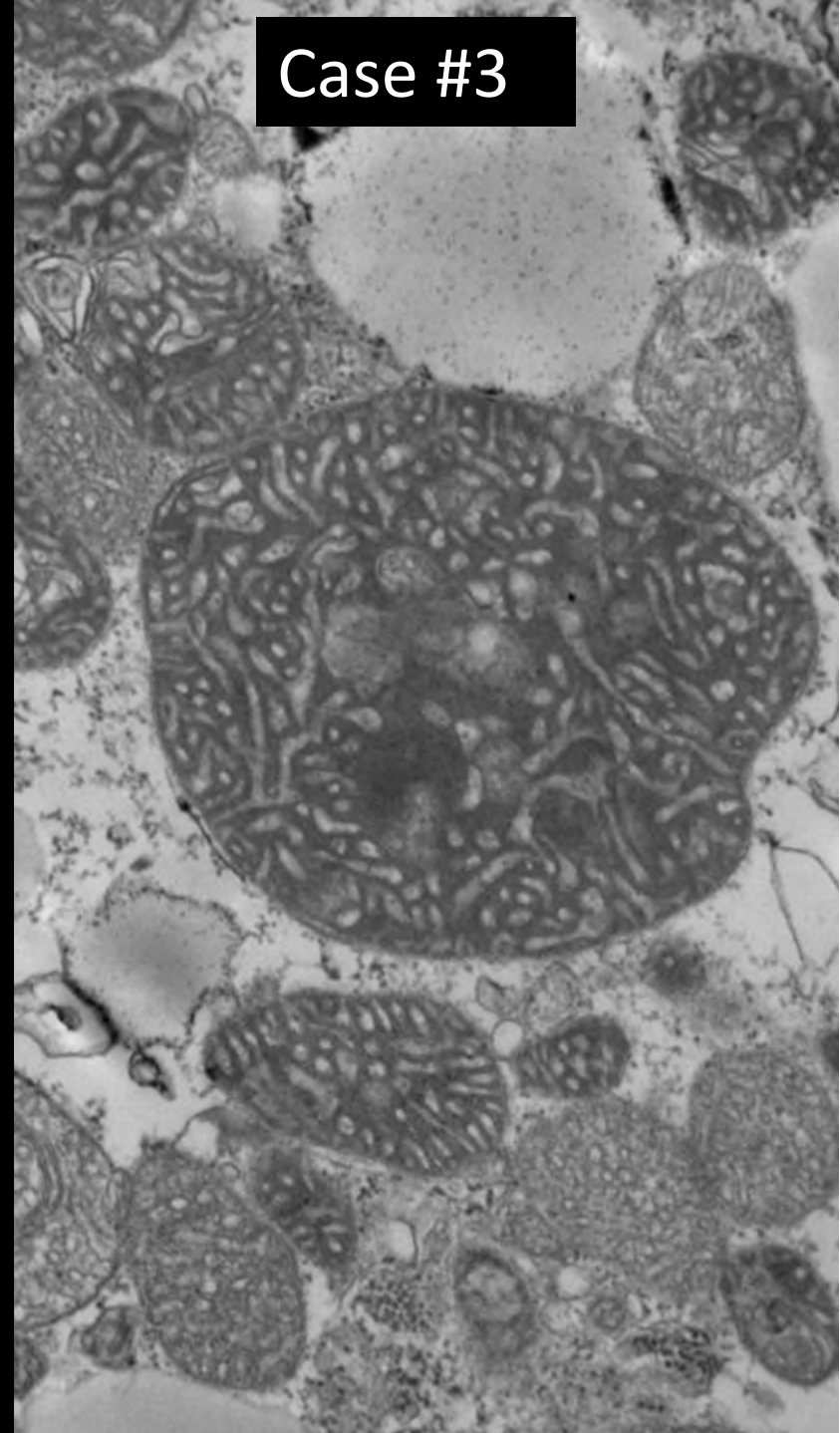
Case #1



Case #2



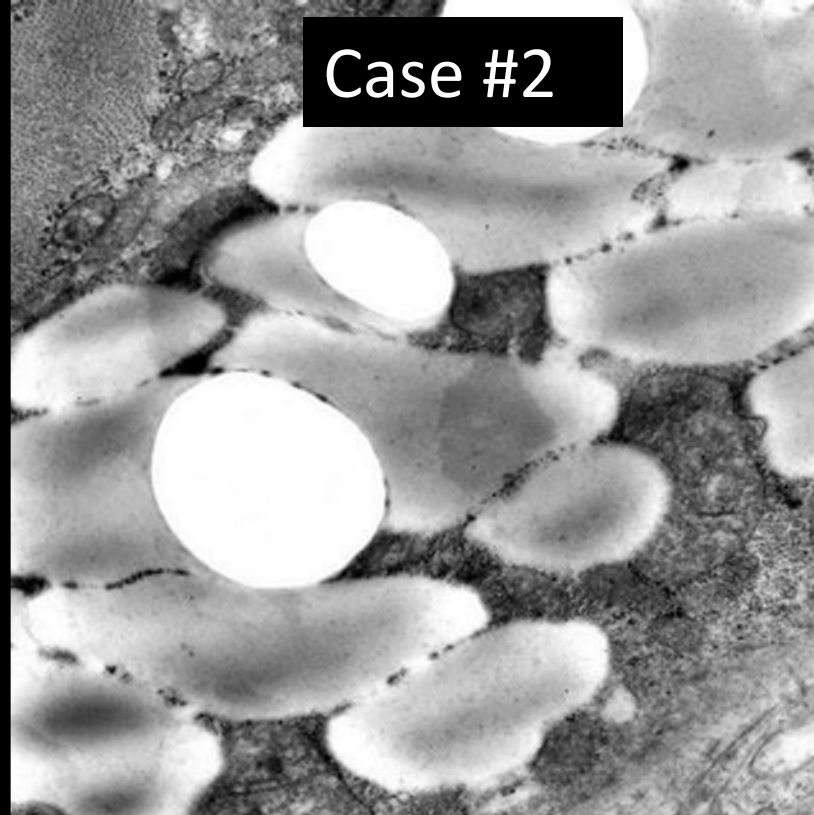
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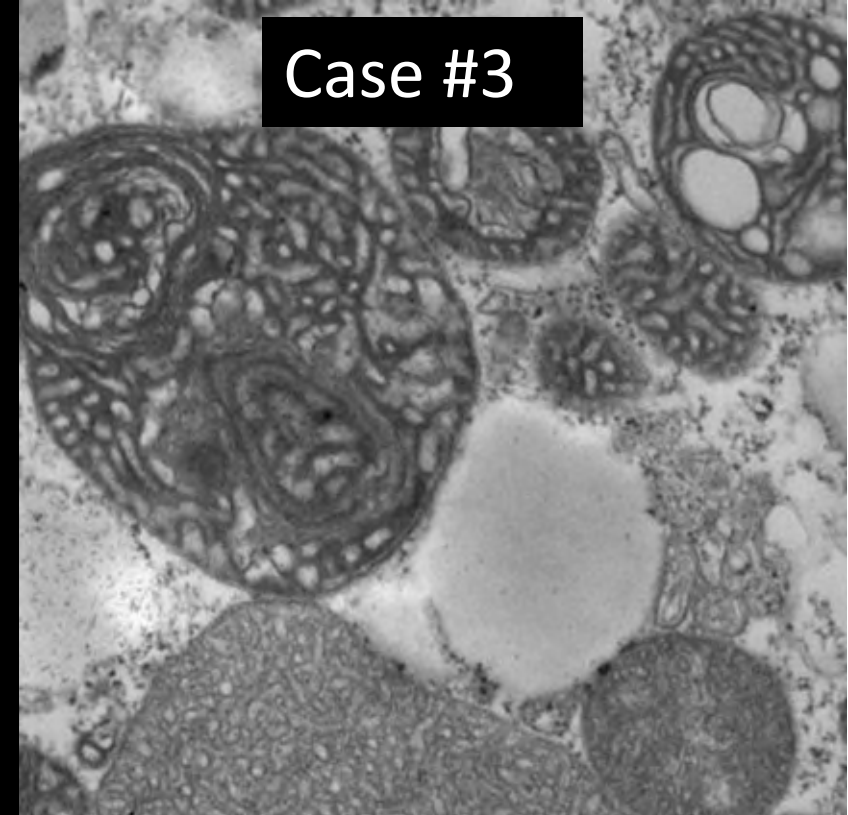
Case #1



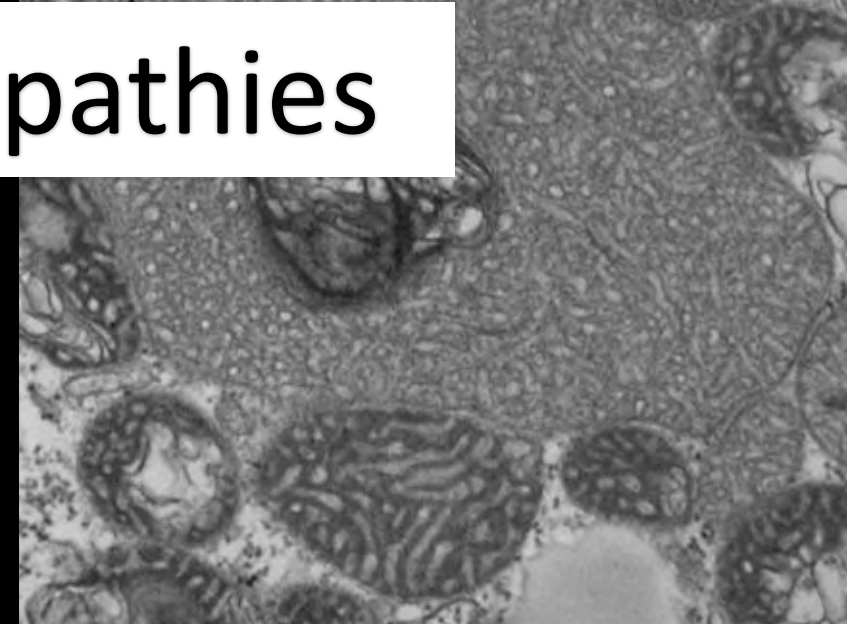
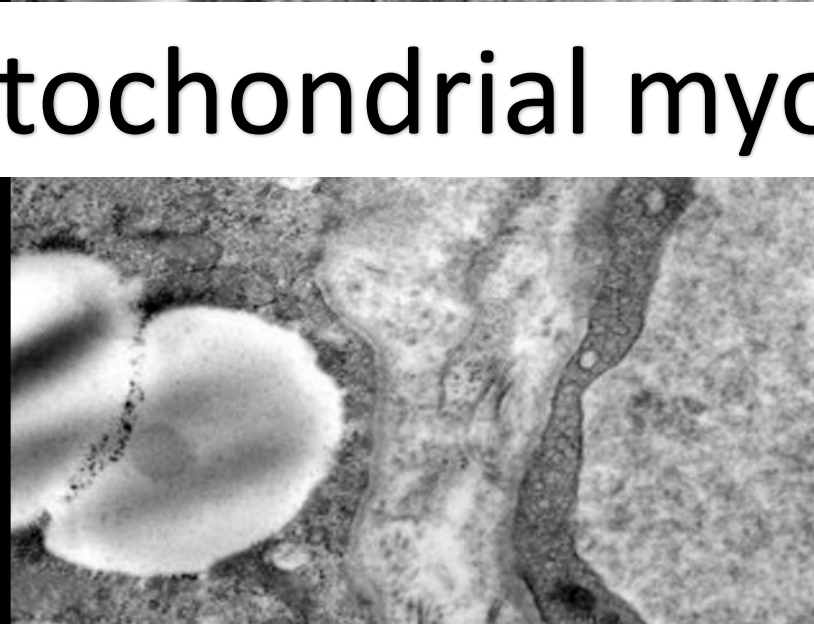
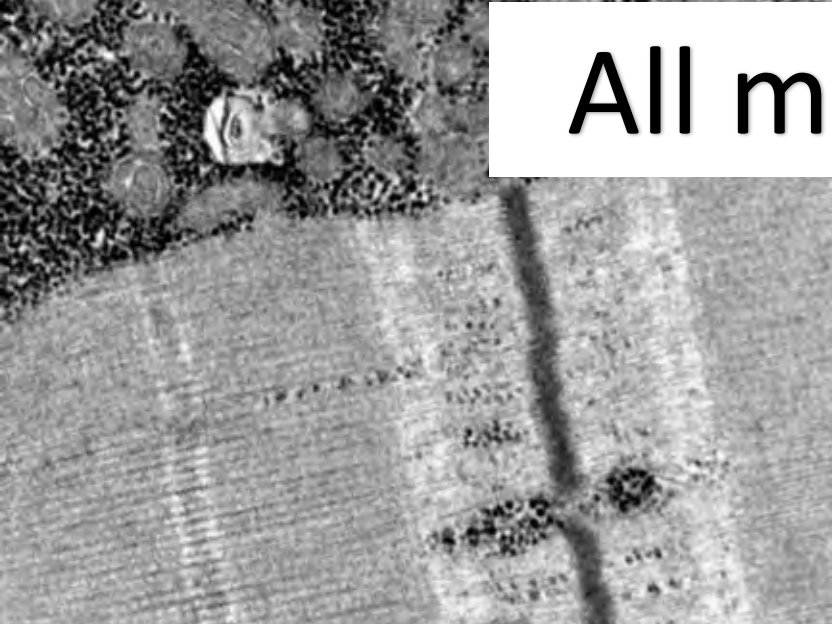
Case #2



Case #3



All mitochondrial myopathies



Mitochondrial myopathies display significant variability in pathologic findings

- Dependent on genetic alteration
 - Nuclear encoded vs. mitochondrial encoded gene, sequence variant, deletion/duplication/depletion, heteroplasmy
- SDH → nuclear encoded; COX → mitochondrial encoded

Case #1: 68-year-old woman

- Blood testing negative
- Muscle showed 15% heteroplasmy for a large scale pathogenic **deletion** in mitochondrial DNA
- Kearns-Sayre Syndrome

Case #2: 60-year-old woman

- Blood testing revealed a heterozygous pathogenic variant in ***RRM2B***
- Nuclear encoded gene, AD or AR disease
- AD Progressive External Ophthalmoplegia

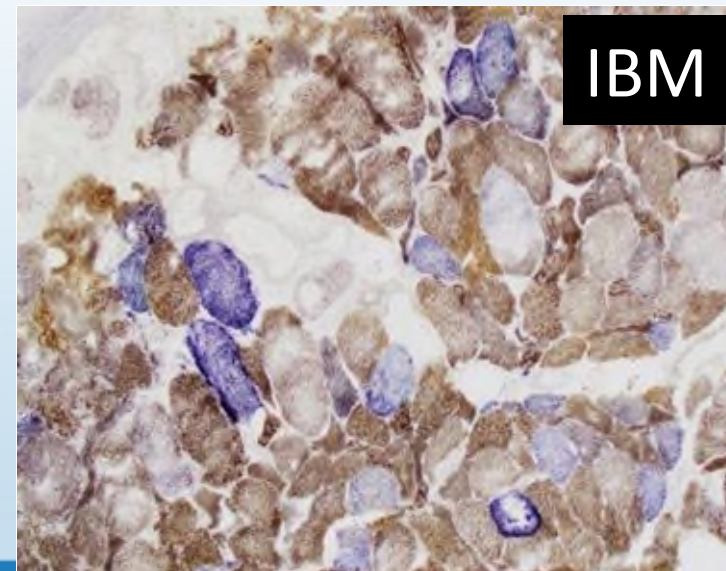
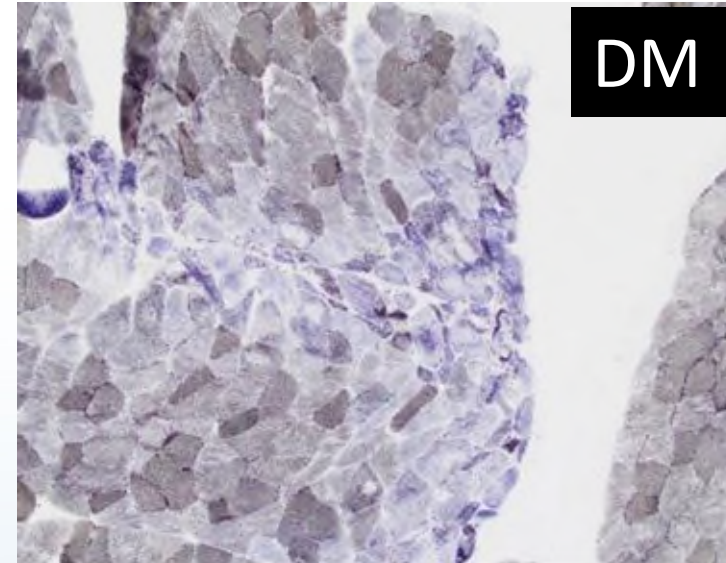
Case #3: 2-year-old girl

- Blood testing revealed compound heterozygous variants (1 pathogenic and 1 likely pathogenic) in ***TK2***
- Mitochondrial DNA depletion syndrome



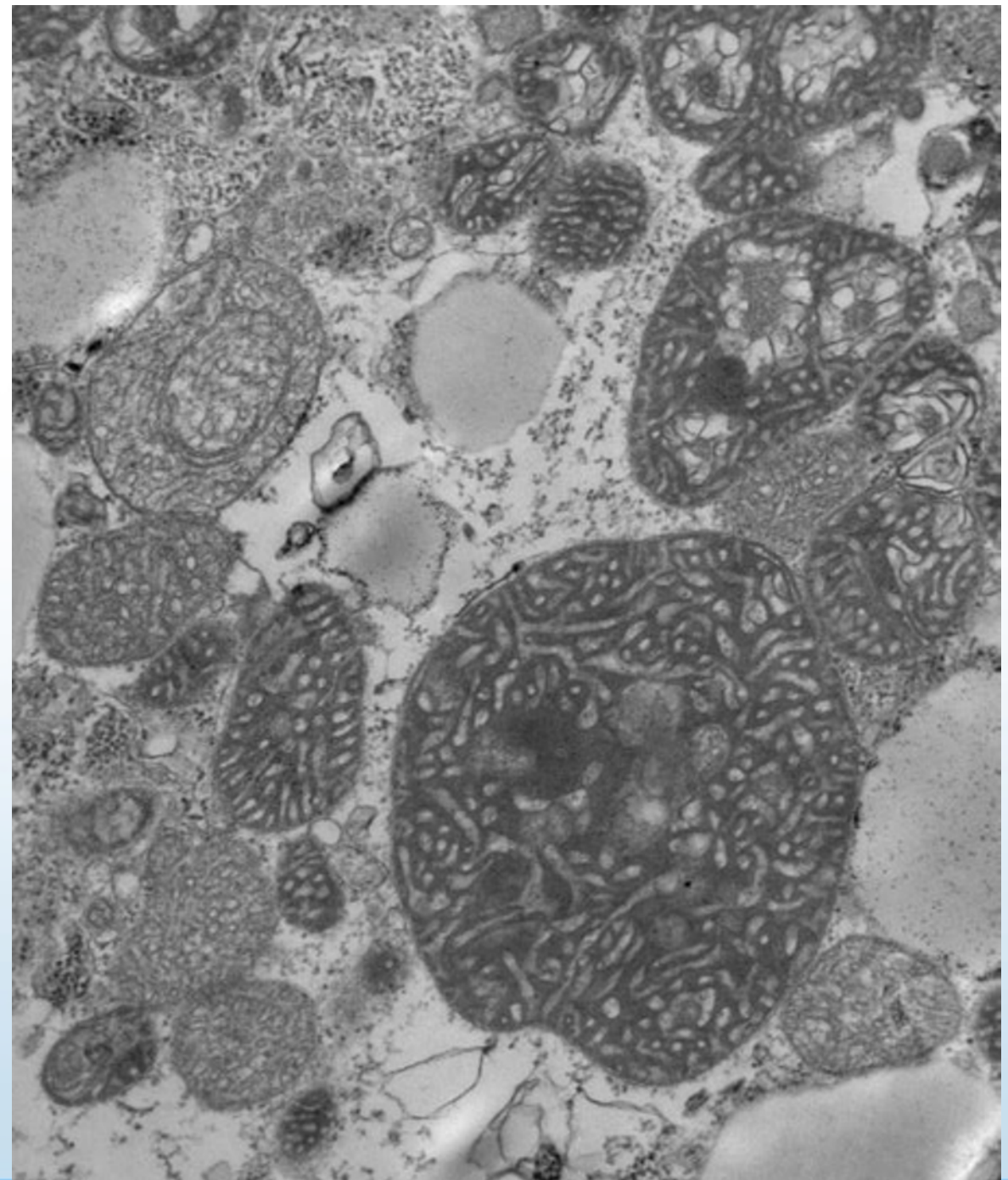
Mitochondrial myopathy - diagnostic clues and pitfalls

- Diagnostic features: ragged red fibers, COX-negative fibers, and paracrystalline mitochondrial inclusions, BUT:
- Classic ragged red fibers aren't always present
- COX-negative fibers aren't always present
- COX-negative fibers can be present in IIM
- Mitochondrial inclusions aren't always present
- Lipid accumulation can predominate over mitochondrial change
- Biopsy can appear dystrophic

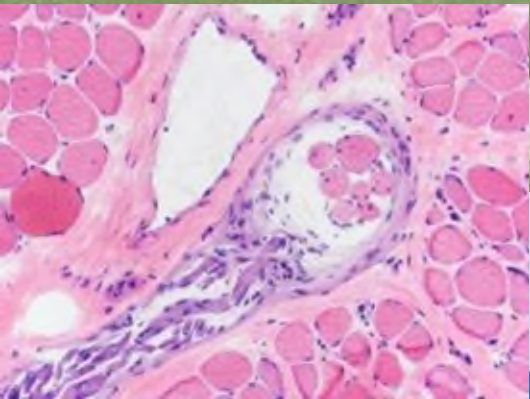


Take home points

- Keep an open mind
- Use your tools
 - Integration of clinical history/exam, laboratory values, and use multiple pathologic modalities
- Don't underestimate the power of EM!
- Recognize the extremes of pathologic severity so you don't miss something



Questions?



Duke Pathology

Duke University School of Medicine

AANP

