Idiopathic Inflammatory Myopathies

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Learning objectives

- Explain how clinical, serologic, and histopathologic information is integrated into the current classification of idiopathic inflammatory myopathies (IIMs)
- Compare and contrast clinicoseropathologic features of four currently recognized IIM categories [dermatomyositis (DM), anthisynthetase syndrome-associated myositis (ASM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM)]
- Outline the role of ancillary immunohistochemical markers in pathologic diagnosis of IIMs

Inflammatory myopathies

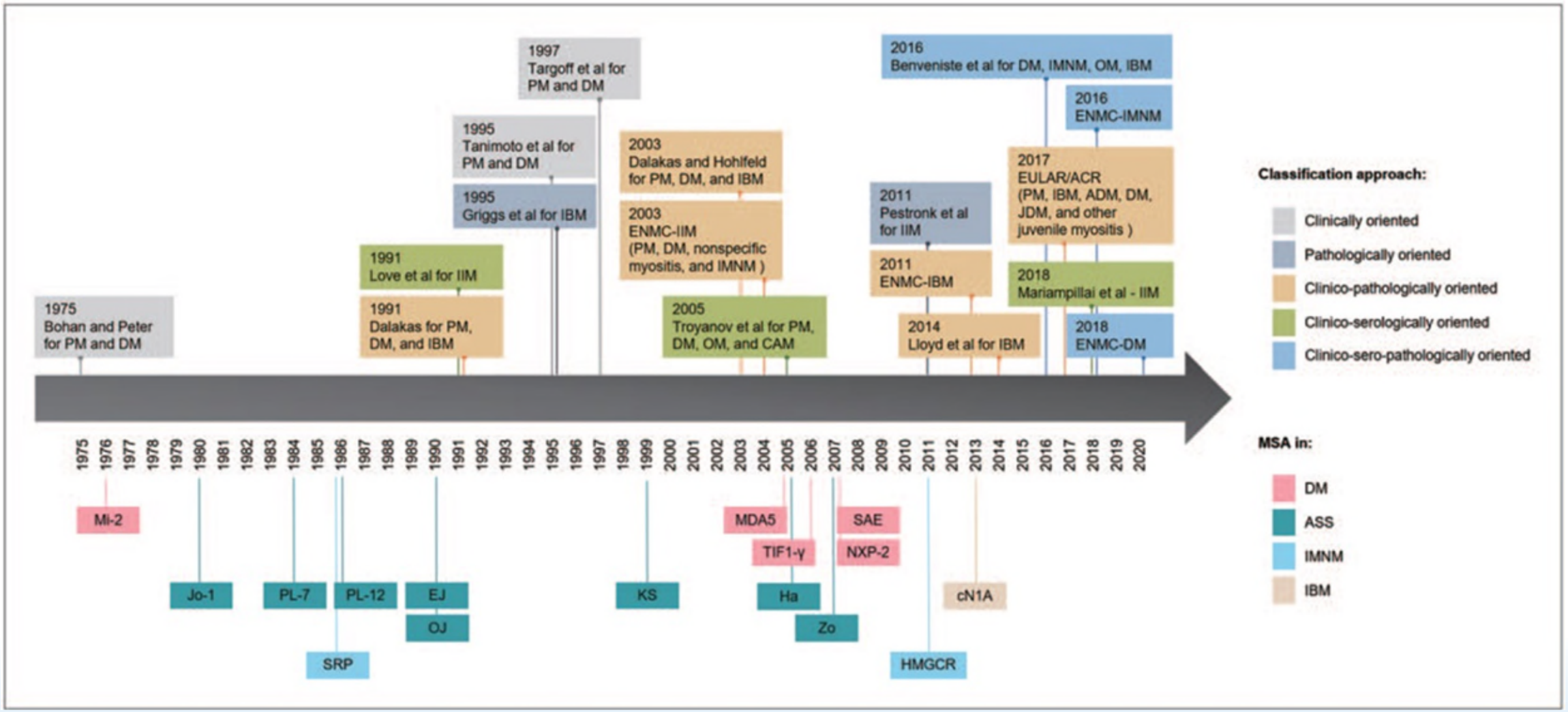
- Infectious myopathies (rare)
  - Bacterial
  - Fungal
  - Viral?
- Systemic inflammatory disorders with muscle involvement (occasionally biopsied)
  - Fasciitis
  - Vasculitis
  - Sarcoidosis
  - Connective tissue disorders (scleroderma, SLE)
- **Idiopathic inflammatory myopathies (IIMs; commonly biopsied)**

IIMs: Old classification (clinicopathologic)

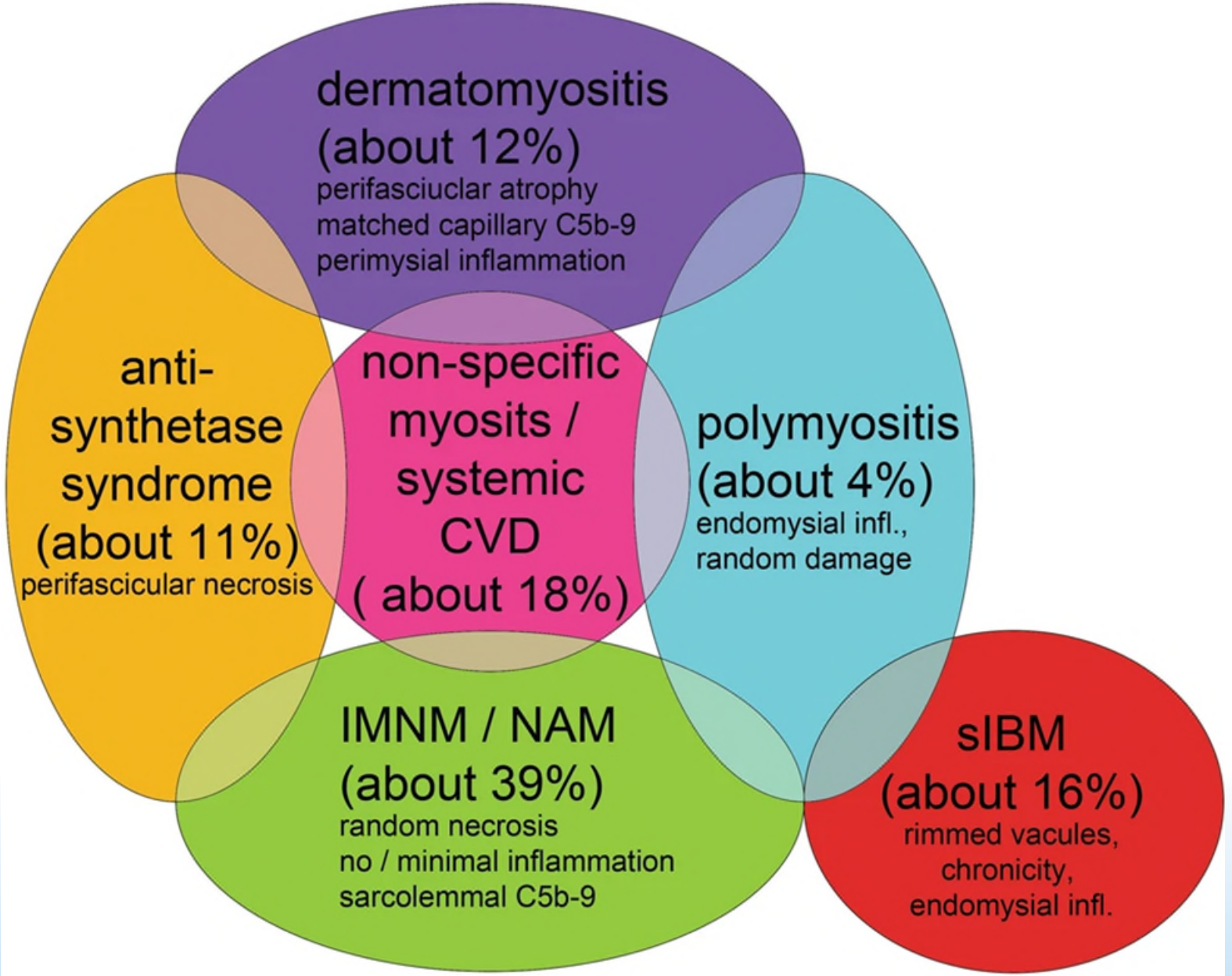
- Dermatomyositis (DM)
- Polymyositis (PM)
- Sporadic inclusion body myositis (sIBM)

IIMs: New classification (2010s; clinicoseropathologic – includes myositis-specific antibodies [MSA])

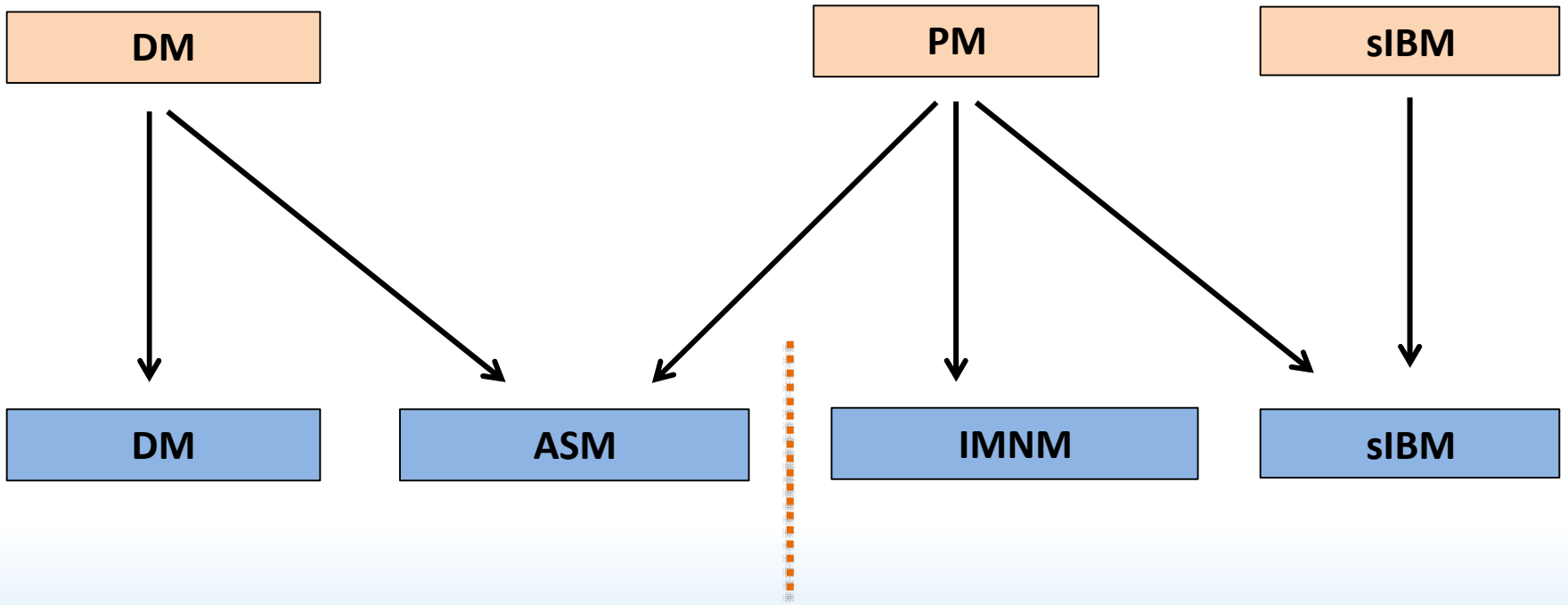
- Dermatomyositis (DM)
- Anti-synthetase syndrome (ASS)-associated myositis (ASM)
- Immune-mediated necrotizing myopathy (IMNM)
- Inclusion body myositis (sIBM)
- ? Polymyositis ? (may not exist as a separate entity or is very rare; remains on the books for now)



Tanboon et al, Curr Opin Neurol 33:590 (2020)



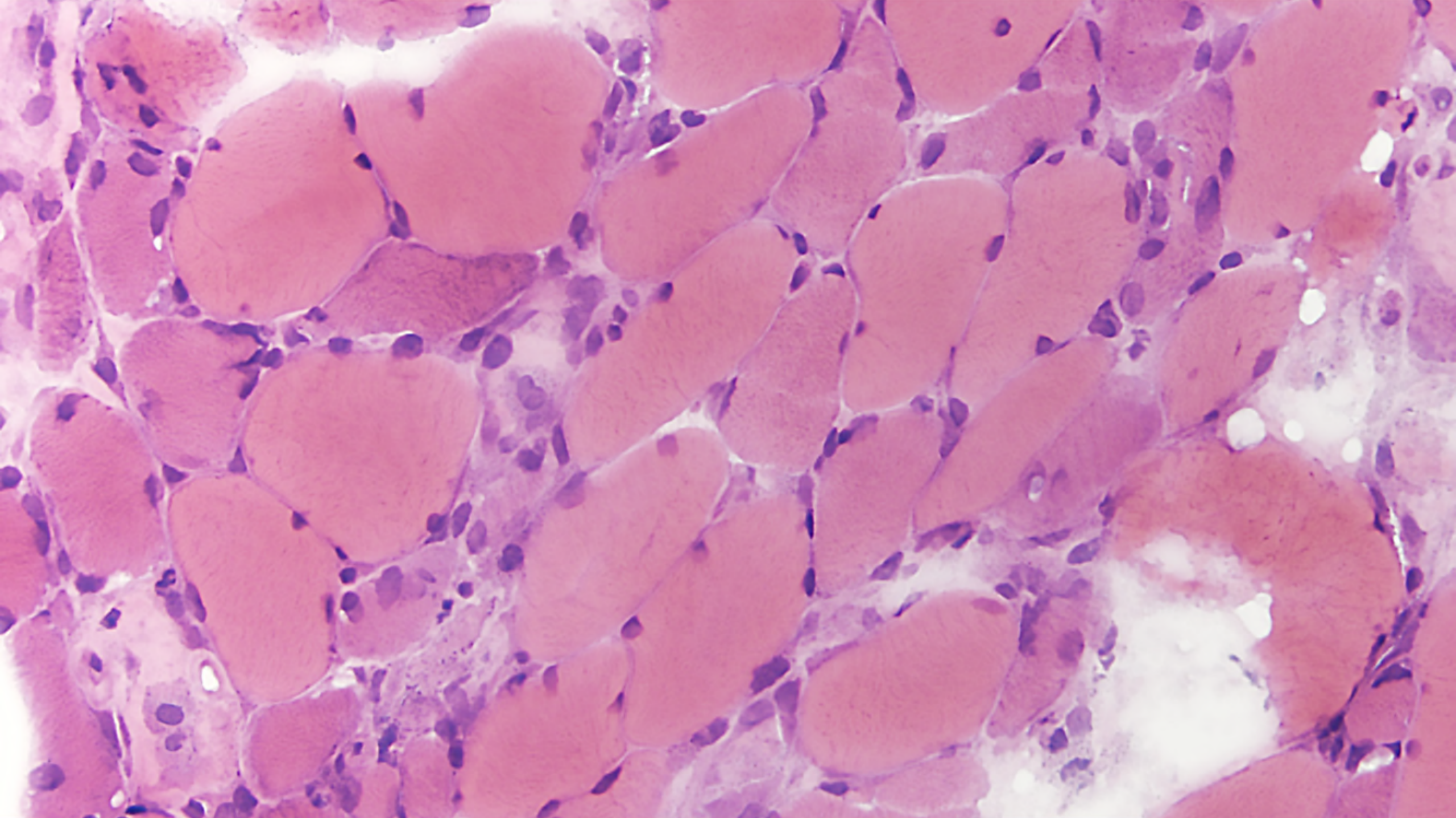
Cai et al, Mod Pathol 32: 462 (2019); based on data from Suzuki et al, Autoimmun Rev. 16:693 (2017).

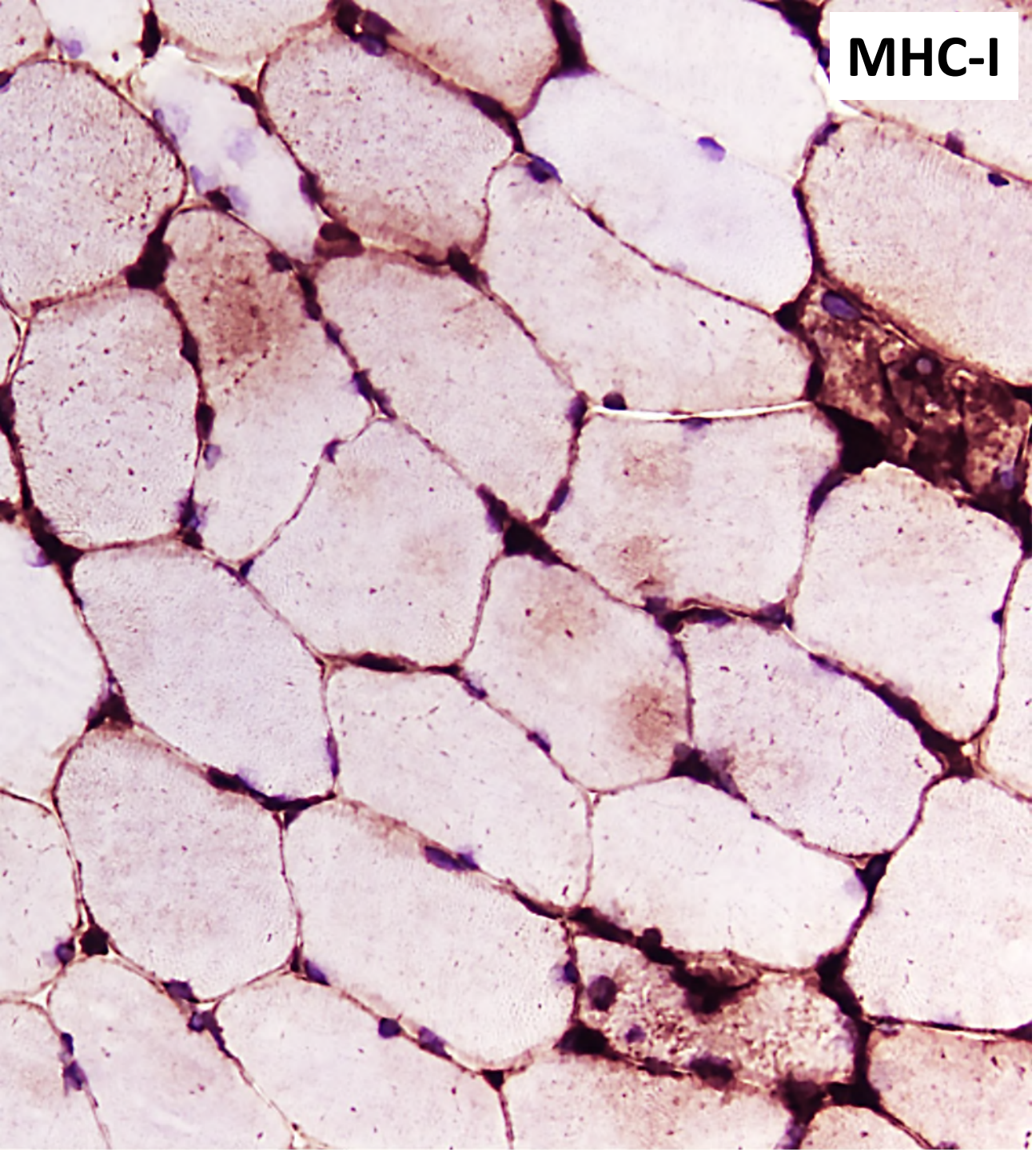

DM
PM
sIBM
DM
ASM
IMNM
sIBM

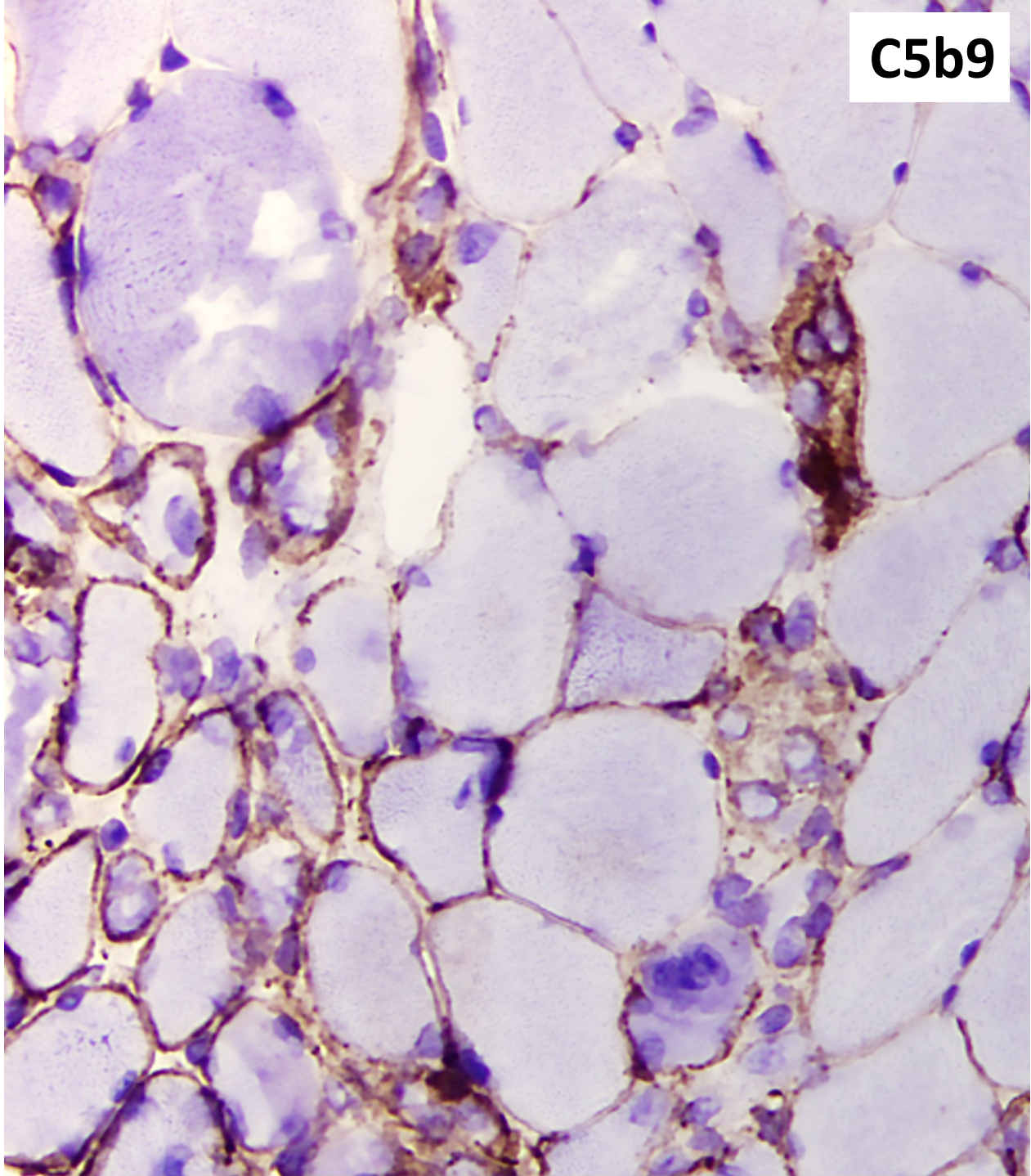
IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)

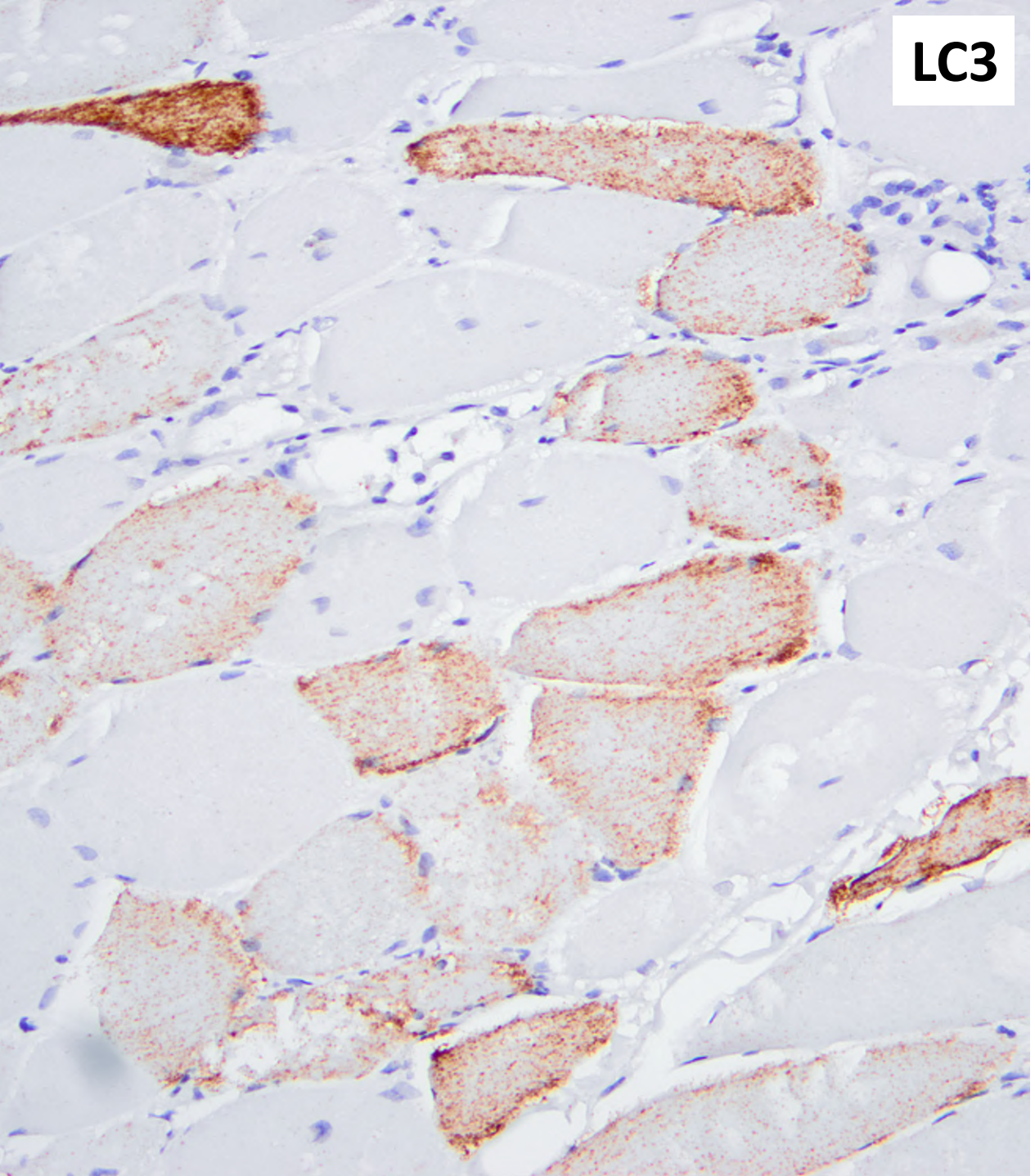
- Etiology / pathogenesis
  - MSA associations:
    - anti-SRP Ab and anti-HMG-CoA reductase (HMGCR) Ab
    - 1/3 of cases is (currently) seronegative
  - Antibody- and complement-mediated (type II hypersensitivity / immune mechanism)
  - Can be paraneoplastic
- Clinical features
  - Moderate to severe proximal weakness (subacute to chronic)
  - No skin findings
  - High CK levels (> 1000; sometimes much higher - frank rhabdomyolysis)
- Responds to immunosuppression, but difficult to treat

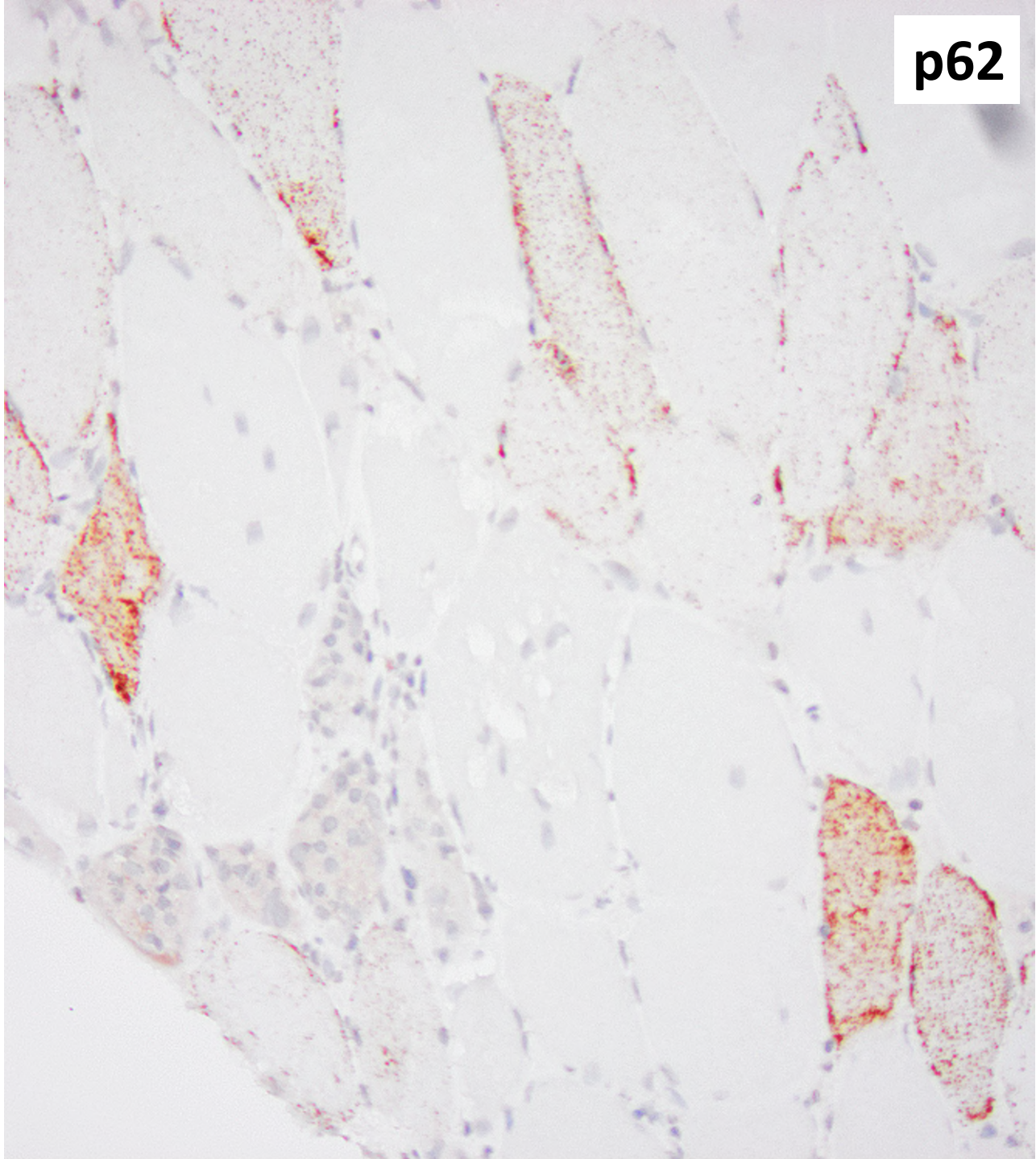
- Histology
  - Randomly distributed degenerating/regenerating fibers, usually in the context of a relatively normal background muscle (but chronic myopathic changes can be present)
  - MHC-I upregulation and complement deposition in sarcolemma (very helpful if present, but absence does not rule out IMNM); no MHC-II or MxA upregulation
  - Rare to frequent fibers with densely distributed autophagosomes (LC3 and p62-positive puncta)
  - Inflammation is very scant (CD8+ T cells) or absent
- Histologic DDx
  - toxic or metabolic necrotizing myopathy
  - other IIMs (rarely)

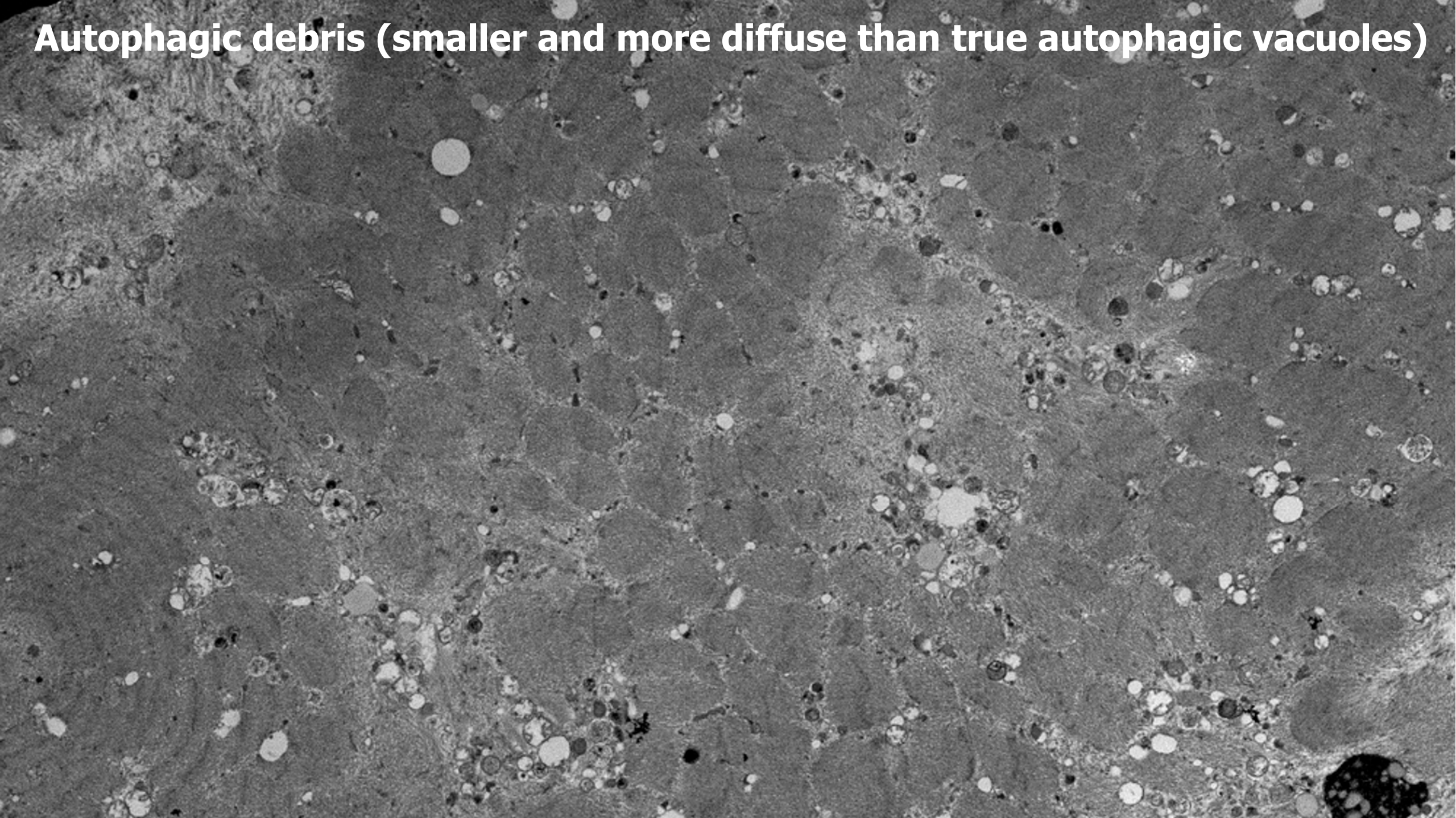



MHC-I


C5b9


LC3


p62


Autophagic debris (smaller and more diffuse than true autophagic vacuoles)

- Anti-SRP IMNM
  - Can involve other organ systems: pulmonary, cardiac
  - No cancer association
  - More severe than other IMNMs (in people and model mice); most likely IMNM to show fiber size variation / chronic myopathic features
  - Most likely IMNM to show mild lymphocytic inflammation
- Anti-HMGCR IMNM
  - Weak cancer association
  - Can be (but doesn't have to be) triggered by statin exposure
    - Role of food-derived statin-like compounds?
  - Can show chronic myopathic features and be mistaken for a muscular dystrophy (particularly in children)
- Seronegative IMNM
  - Strong cancer association
  - Can be para/postinfectious: COVID-19 association

SPORADIC INCLUSION BODY MYOSITIS (sIBM)

- Etiology / pathogenesis
  - MSA association: anti-cN1A (~50% cases); mechanism unclear (likely not causative)
  - Idiopathic (but there is some genetic predisposition: HLA genes, autophagy genes)
  - Current view of pathogenesis:
    - Long-standing inflammation triggers myodegeneration / dystrophic features
    - Mediated by terminally differentiated / exhausted T cells
- Clinical features
  - Middle-aged and older adults (>45 years of age; younger if HIV-associated)
  - Asymmetric extremity weakness (knee extensors / finger flexors); dysphagia
  - Mild-moderate CK elevation (< 1000 U/L)
  - No skin (or other organ system) findings
  - Can be associated with / secondary to systemic inflammatory disease
  - Subacute to chronic presentation
- In contrast to other IIMs, does NOT respond to immunomodulatory therapy
  - Terminally differentiated T cells do not undergo apoptosis in response to steroids

Histology

- Endomysial inflammatory infiltrates (CD8+ T cell and macrophage-rich; invasion of non-necrotic fibers)
- Diffuse MHC-I and MHC-II upregulation

PM?

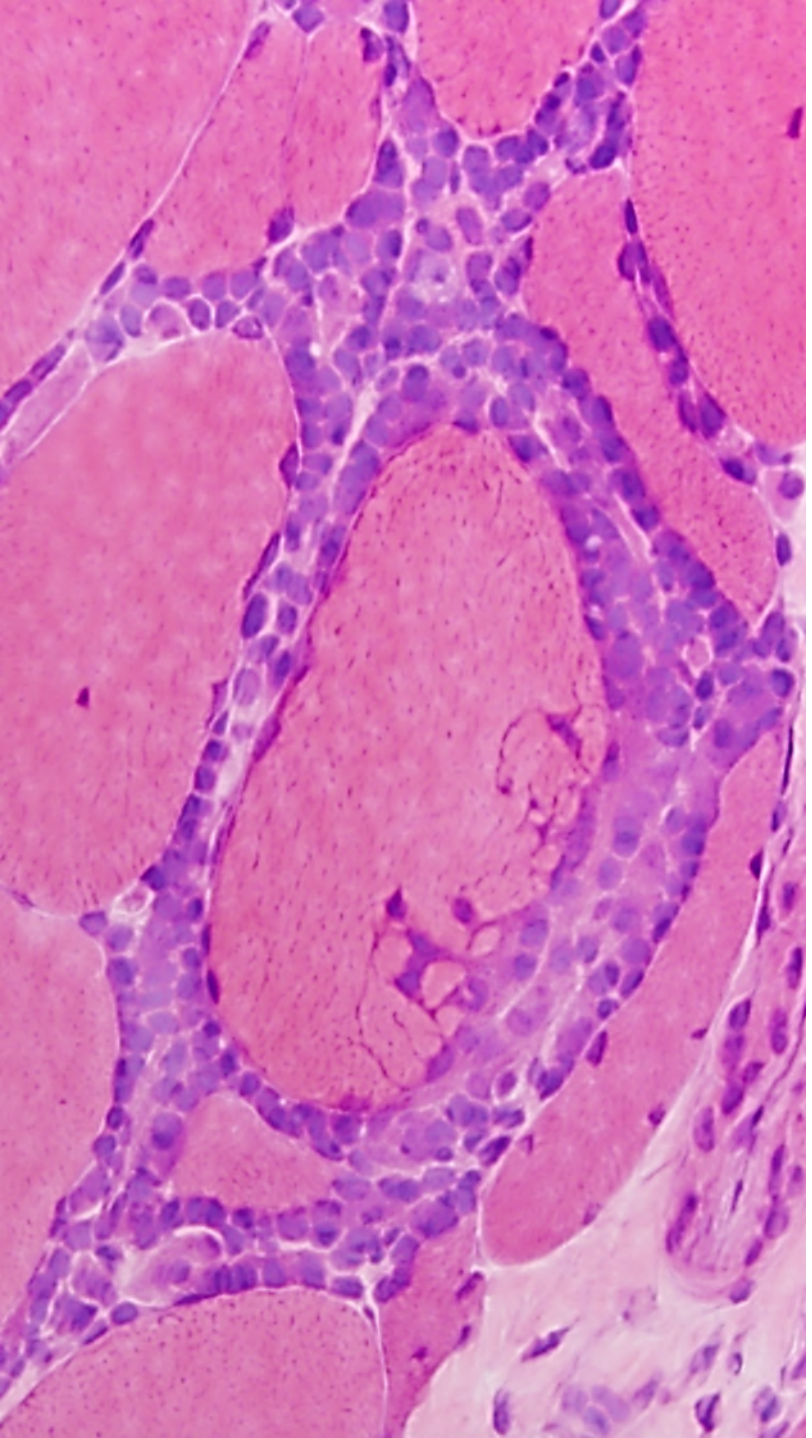
Treatment responsiveness?

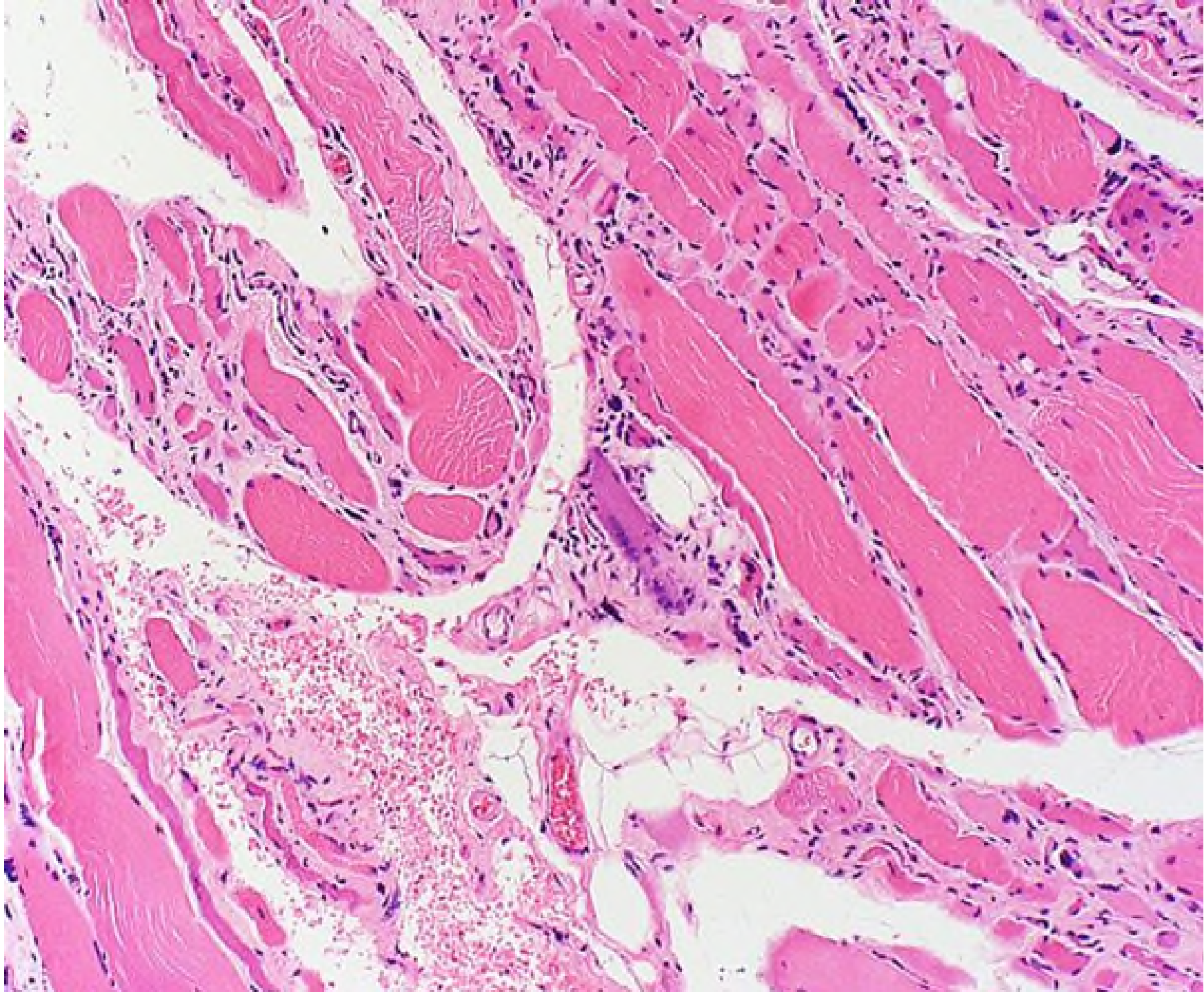
- Mitochondrial abnormalities (RRF, COX-negative fibers)
- Chronic myopathic changes:
  - Endomysial fibrosis
  - Muscle fiber variation, often with marked fiber hypertrophy
- Rimmed vacuoles (stain with LC3, p62)
- Protein aggregates → coarse puncta / sarcoplasmic inclusions that are LC3-, p62-, TDP-43-positive
- Tubulofilamentous inclusions on EM

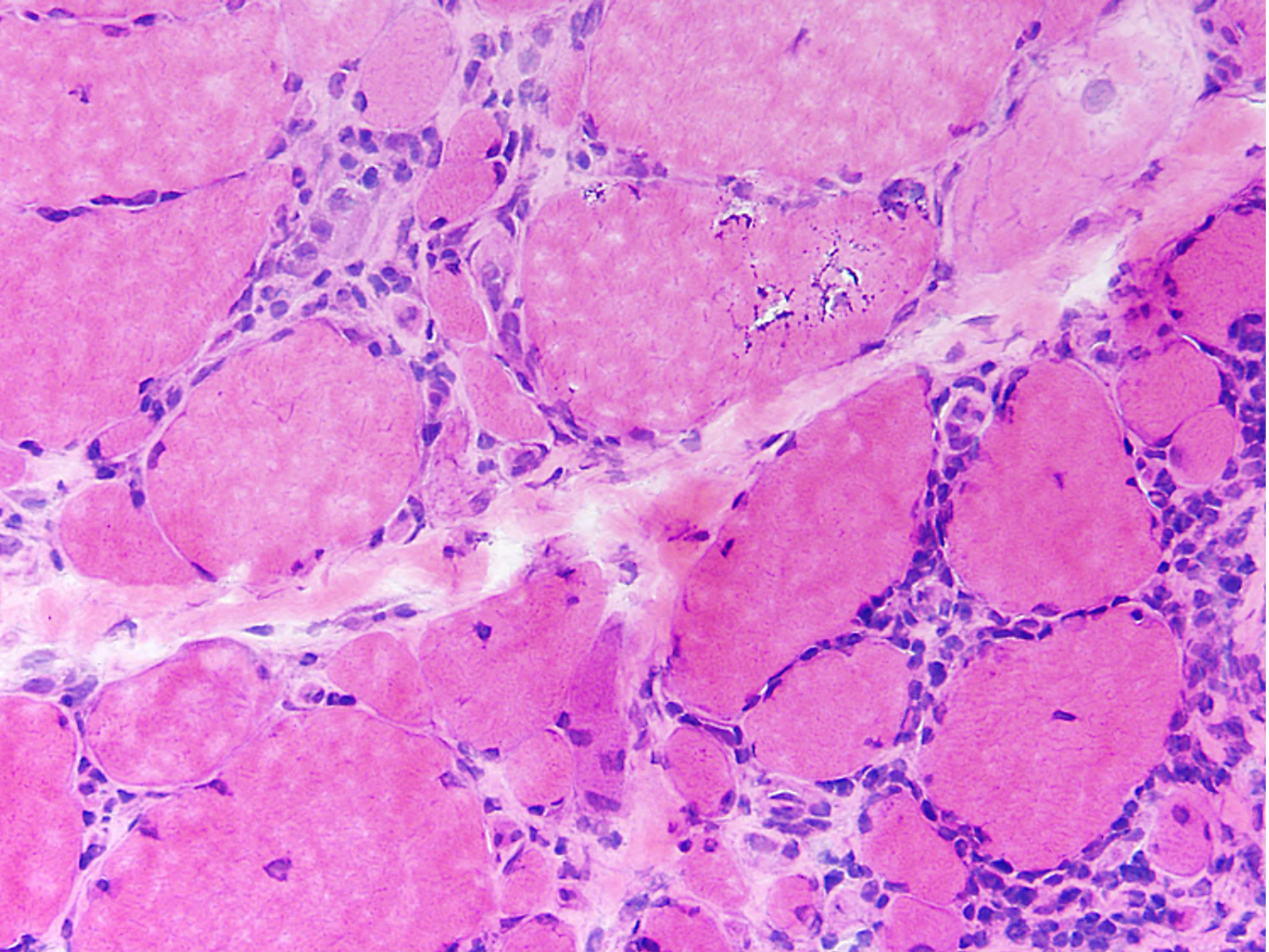
PM with COX-neg fibers

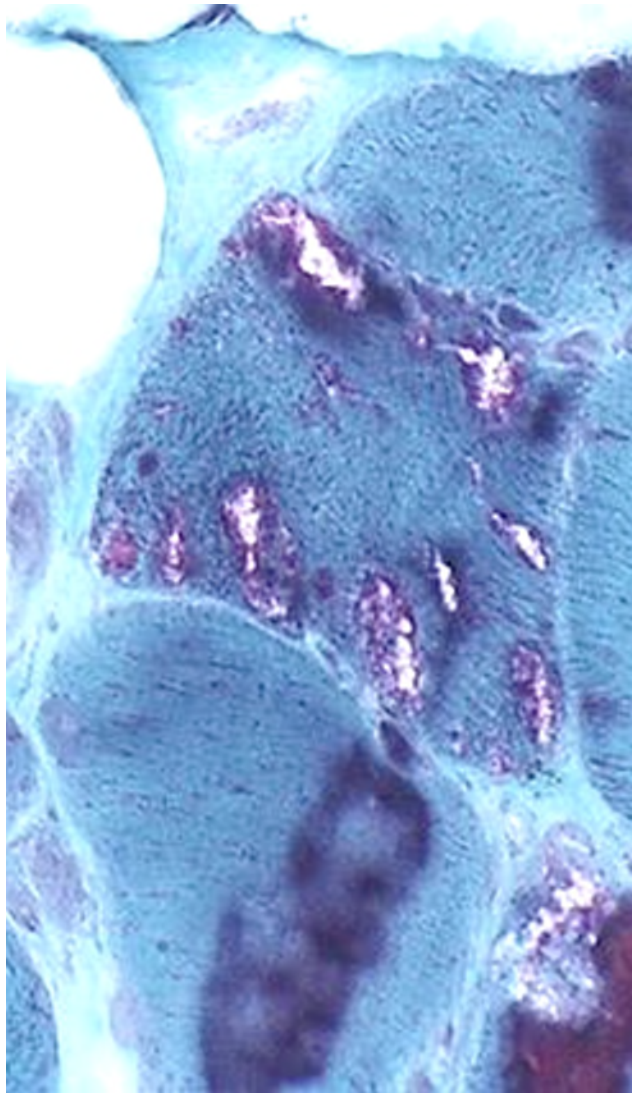
possible sIBM

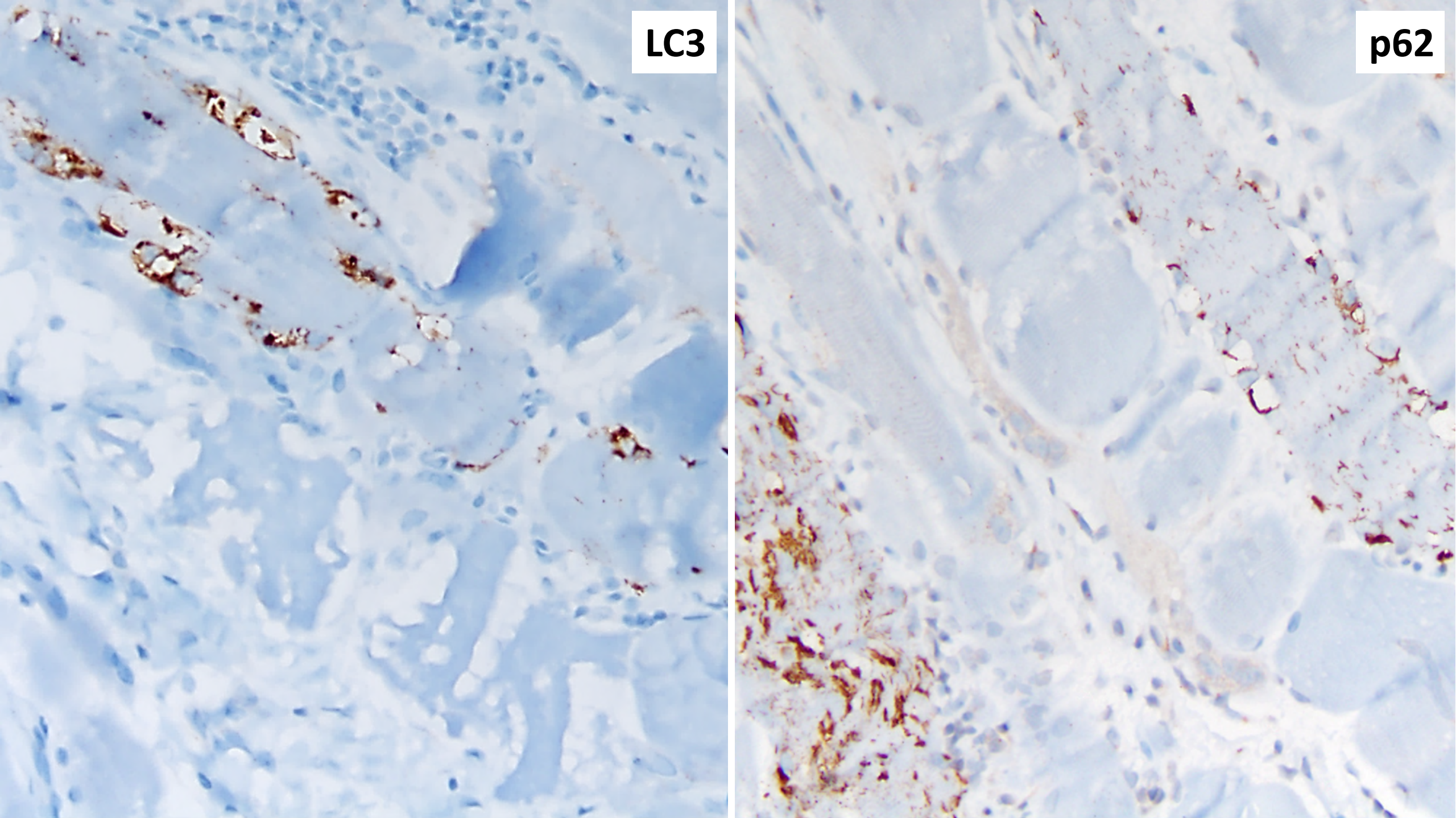
definite sIBM

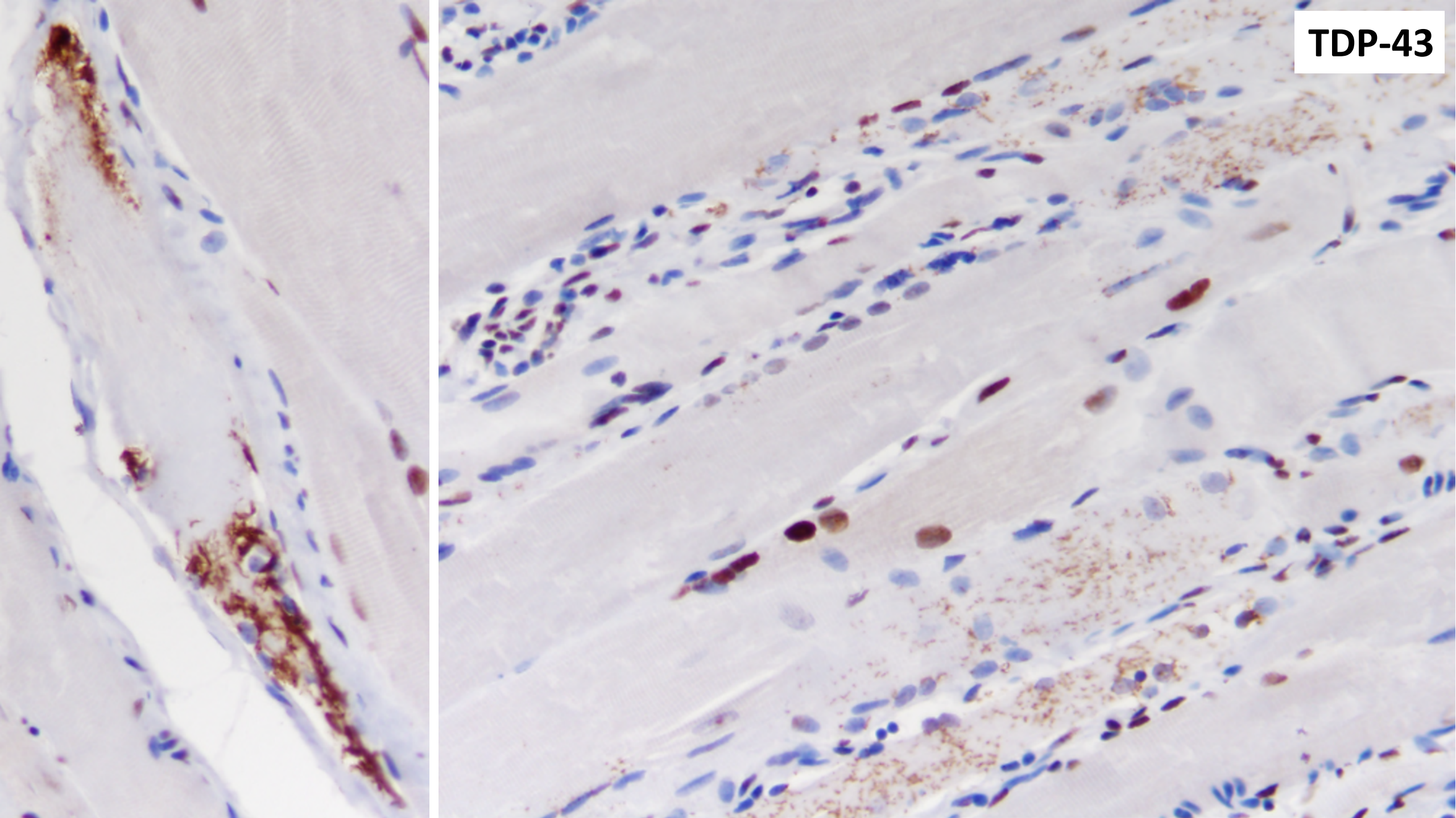


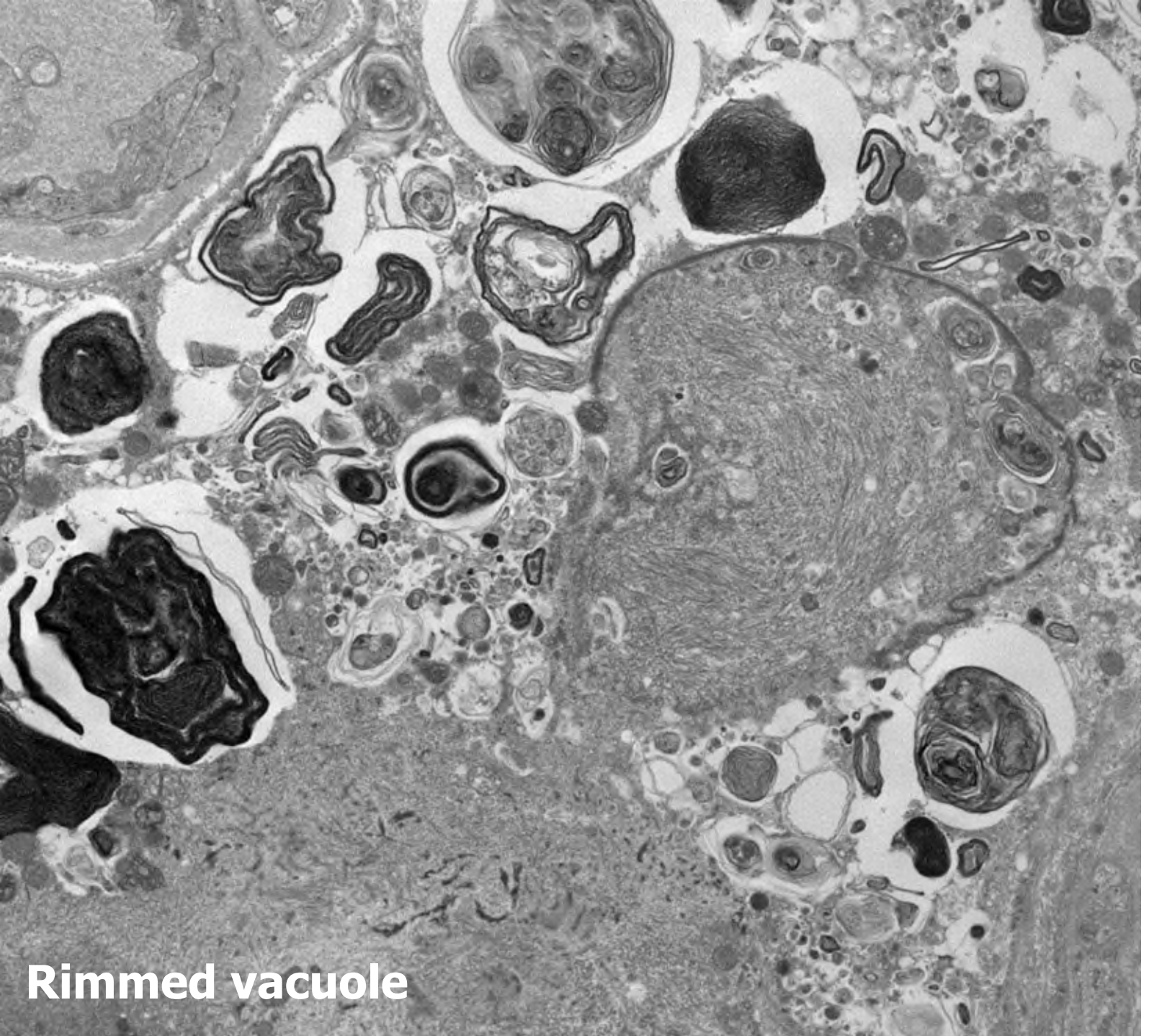




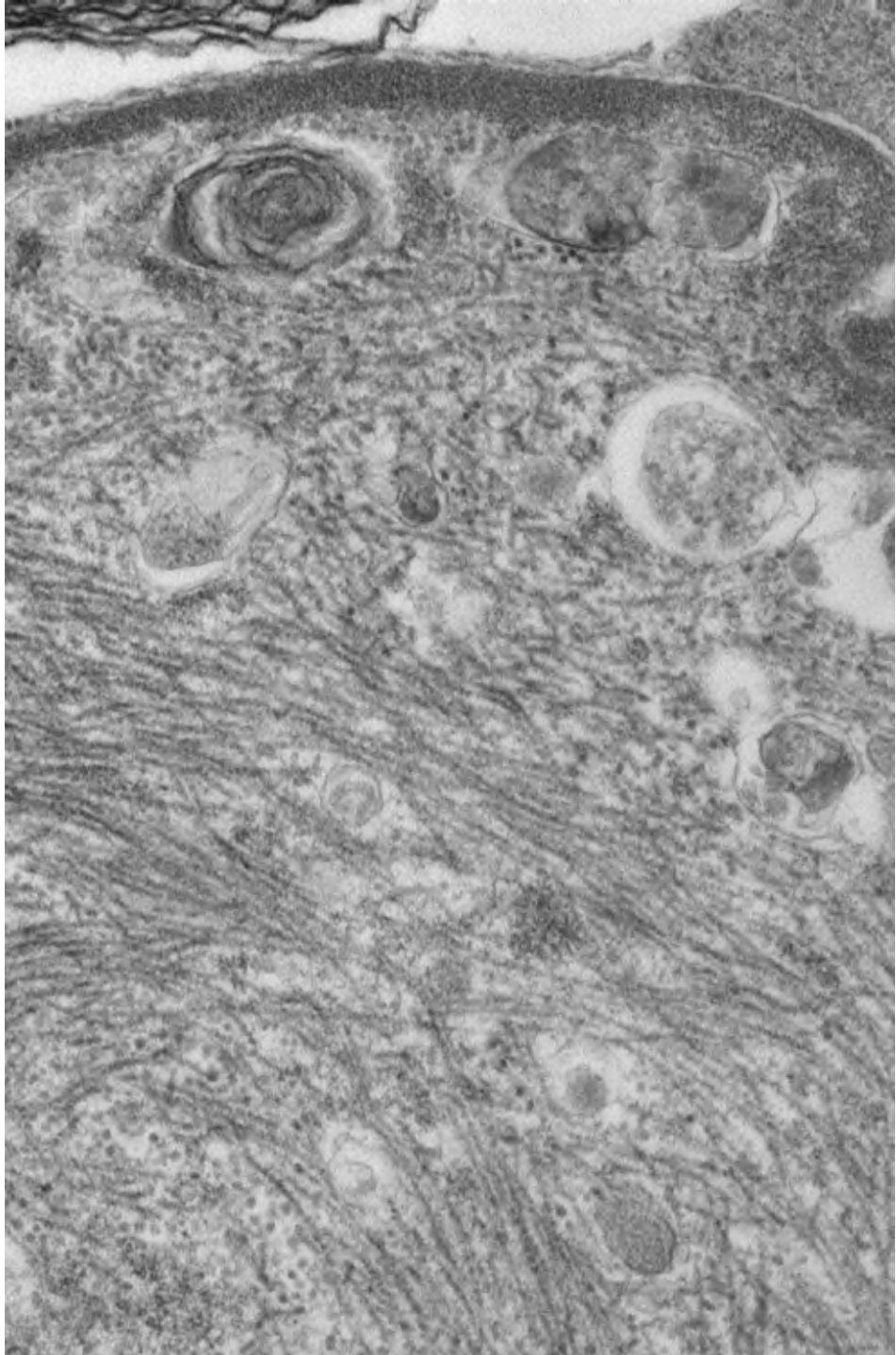



LC3
p62


TDP-43



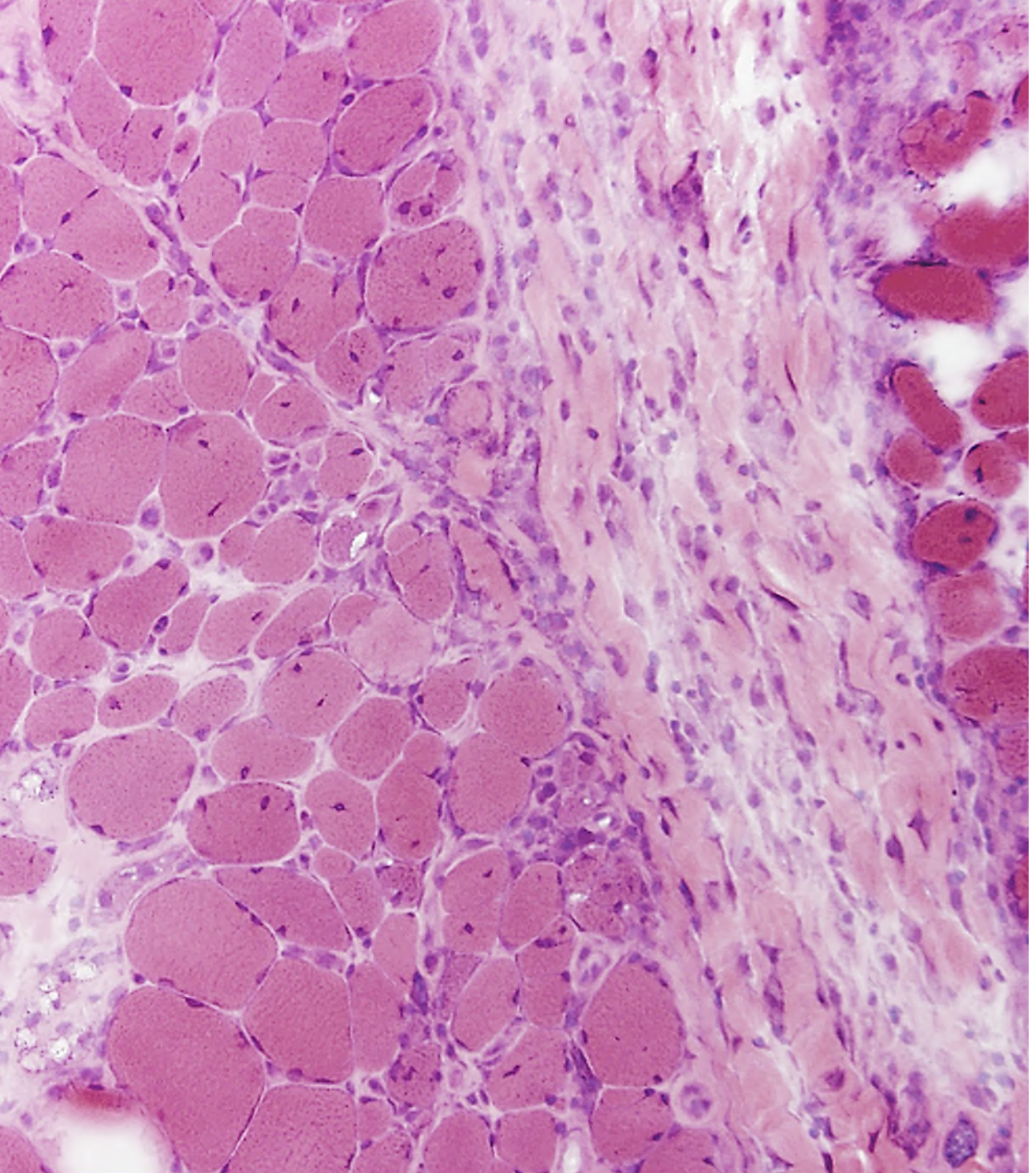
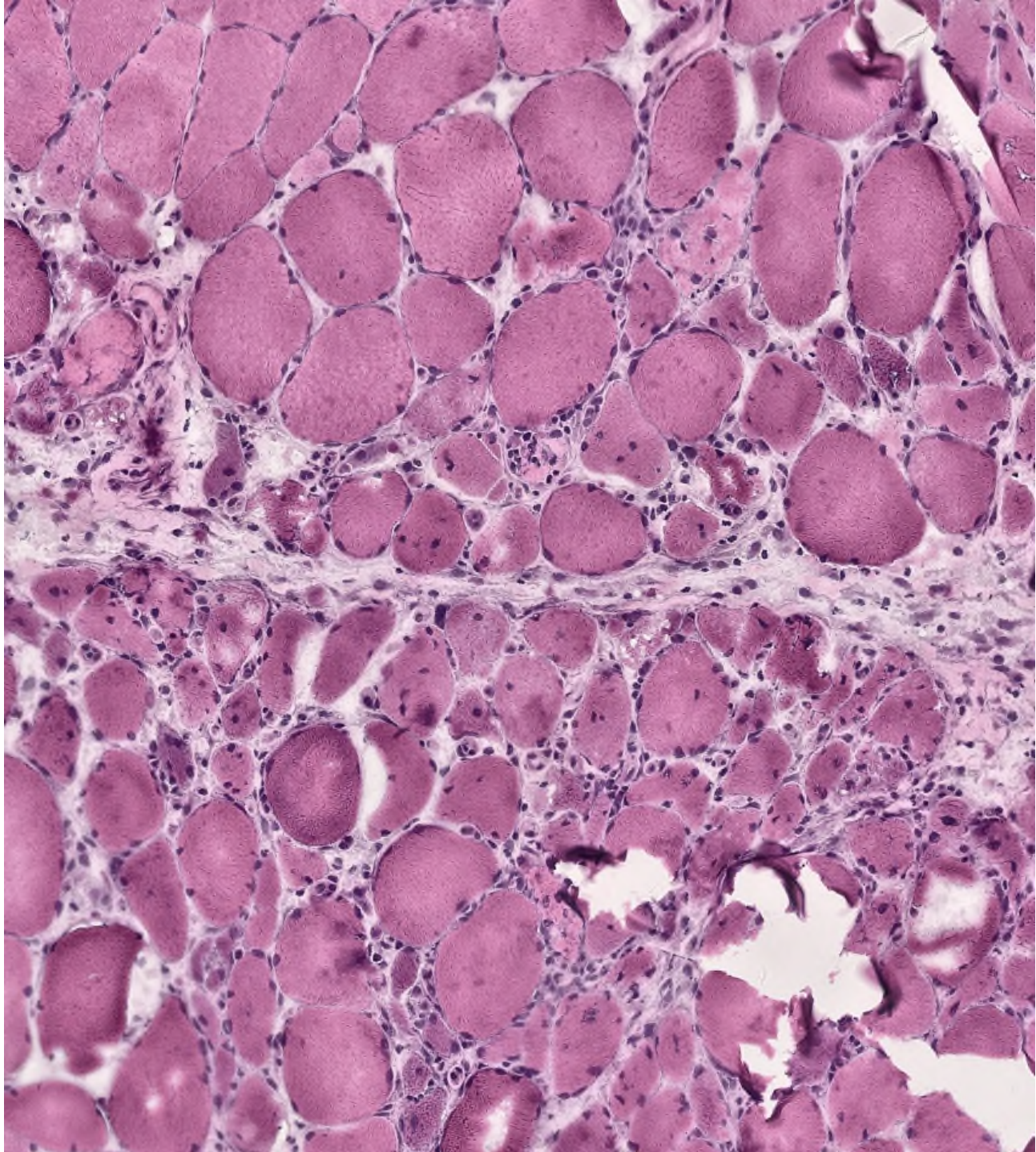
Rimmed vacuole

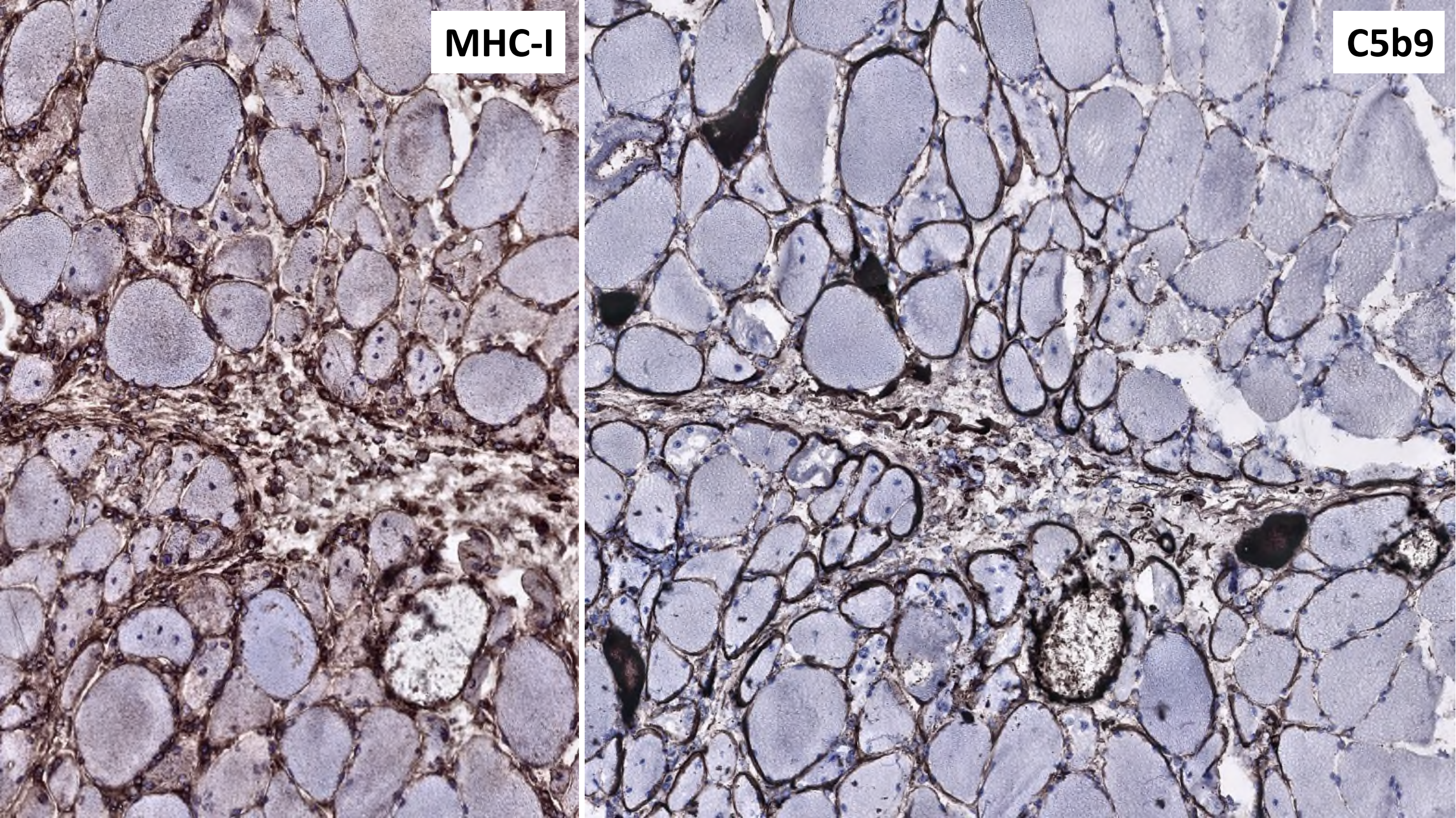


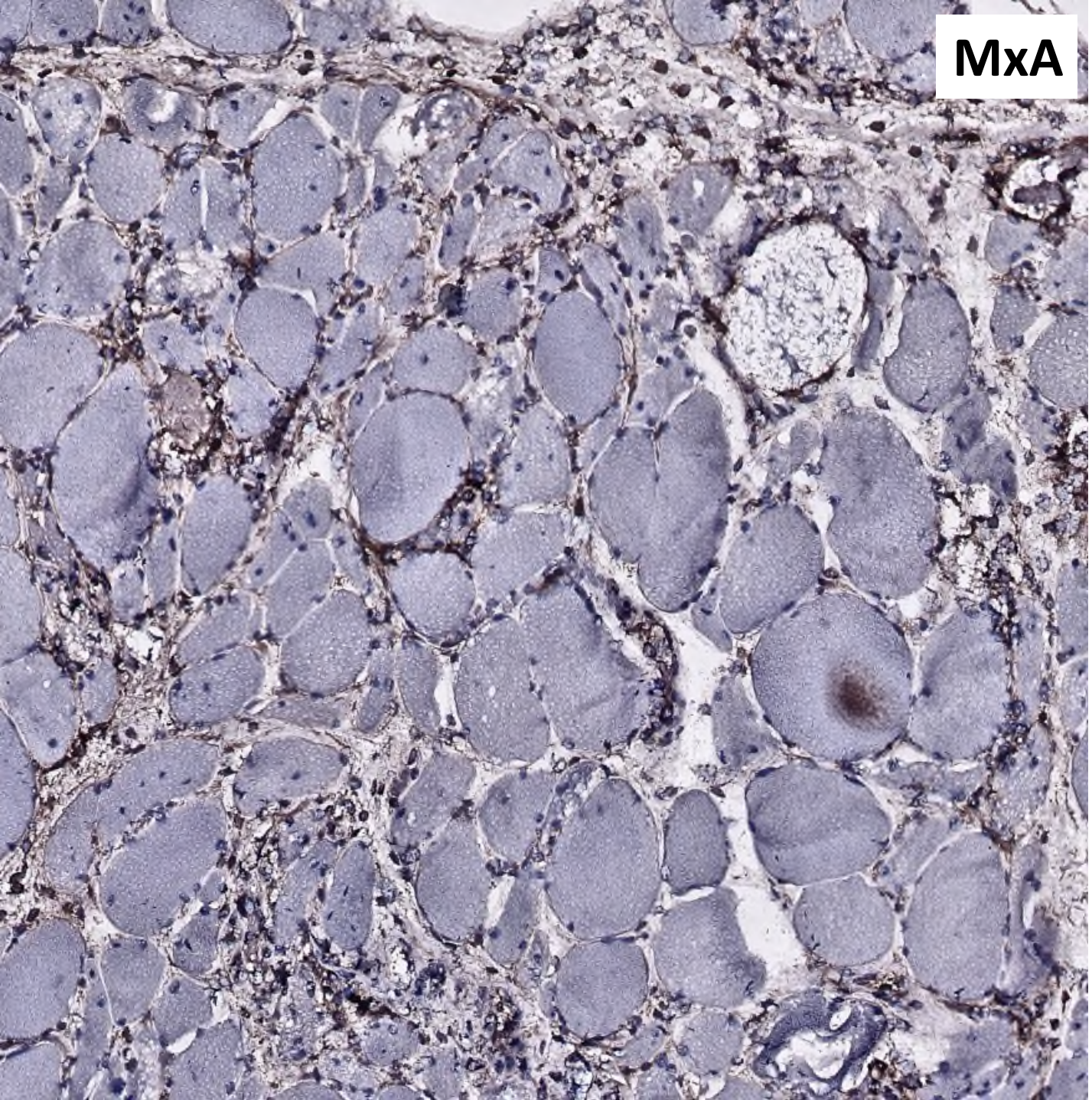
ANTI-SYNTHETASE SYNDROME-ASSOCIATED MYOSITIS (ASM)

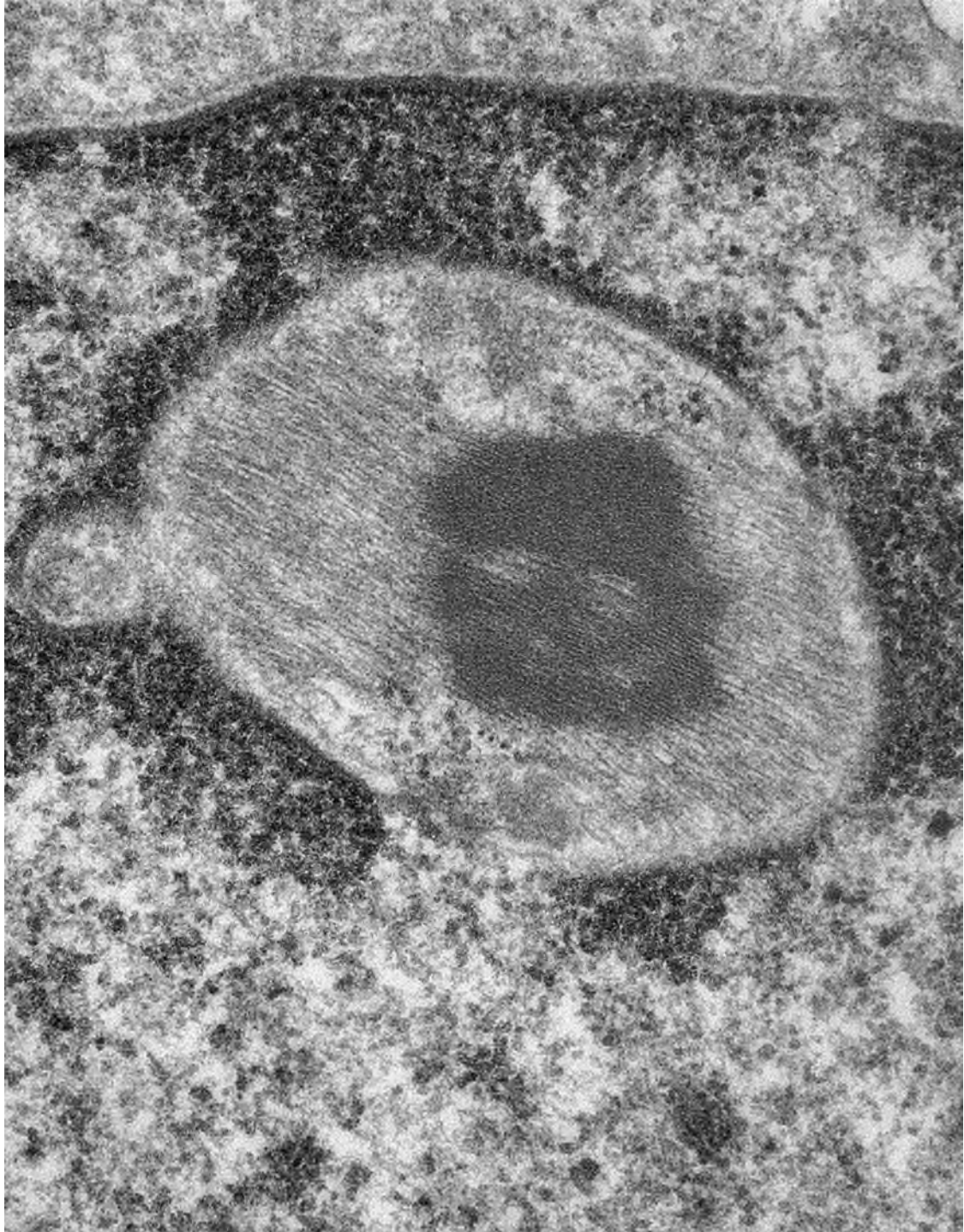
- Etiology / pathogenesis
  - MSA associations: anti-synthetase antibodies
    - anti-Jo-1
    - anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, others?
  - Pathogenesis poorly understood; connective tissue-centered inflammation?
- Clinical features
  - Proximal muscle weakness (severity depends on specific Ab)
  - Skin: Reynaud's phenomenon, mechanic's hands
  - Interstitial lung disease (ILD): commonly present
  - Joint involvement, fever
  - With anti-Jo1, muscle pathology is more severe than ILD; the reverse pattern (ILD > myositis) is seen with other Abs
  - Subacute presentation
- Responds to immunosuppression (but ILD can be fatal)

- Histology
  - Reminiscent of DM, but typically with perifascicular (PF) fiber necrosis (rather than just perifascicular fiber atrophy)
  - Perimysial pathology: Edema, fragmentation, macrophage-rich inflammatory infiltrates, linear alkaline phosphatase positivity
  - PF MHC-I and MHC-II upregulation
  - No MxA upregulation
  - Complement on sarcolemma
  - Intranuclear actin inclusions
- Histologic DDx
  - DM (particularly Mi-2 variant)
  - other IIMs (rarely)


MHC-I
C5b9


MxA



DERMATOMYOSITIS (DM)

- Etiology / pathogenesis
  - MSA associations: anti-MDA5, anti-SAE, anti-Mi2, anti-TIF-1γ, anti-NXP-2
  - Pathogenesis: incompletely understood, but likely involves immune complex deposition and complement-mediated destruction of endomysial capillaries (type III immune mechanism)
  - Activation of interferon α/β [INF1] response
- Clinical features
  - Proximal symmetric muscle weakness (severity depends on the specific Ab)
  - Skin: Gottron papules, heliotrope rash (but can be absent or appear after weakness)
  - ILD: rare; only with some Ab subtypes
  - Cancer association: depends on Ab subtype
  - Subacute presentation
- Responds to immunosuppression

- Histology (varies with Ab)
  - PF atrophy, typically without significant fiber necrosis (but there can be evidence of fiber injury and fiber repair)
  - PF COX-negativity
  - Inflammatory infiltrates in the peri/epimysium (T & B cells in roughly equal numbers, some plasma cells and macrophages) - can be absent
  - Complement deposition (capillaries, sarcolemma)
  - MHC-I upregulation (PF or diffuse with PF accentuation)
  - Upregulation of MxA (marker of interferon α/β [INF1] response) in the fiber sarcoplasm and/or endomysial capillaries
- Histologic DDx
  - ASM
  - IMNM

DM clinicopathologic spectrum is wide
DM clinicopathologic features are antibody-specific

Very mild (DDx: mild IMNM or normal muscle)	"Typical DM"	Very severe (DDx: ASM)
anti-MDA5	anti-SAE (mild)	anti-Mi-2
	anti-TIF1γ (mod-severe)	
	anti-NXP-2 (mod-severe)	

Anti-MDA5 DM

- Weakness: mild or absent (“amyopathic” DM)
- Skin: mucocutaneous ulcerations, palmar papules, non-scarring alopecia, panniculitis
- ILD: common, rapidly progressive / fatal
- Cancer association: +
- Histology
  - No PF atrophy, no inflammation
  - Normal or rare degenerating/regenerating fibers
  - Mild MHC-I upregulation (PF or diffuse), mild MxA upregulation (PF, patchy, or diffuse)
  - Mild or no complement deposition (capillaries)

Anti-SAE DM

- Weakness: mild
- Skin: variable typical DM rash
- ILD: can be present
- Cancer association: ++
- Histology
  - Mild PF atrophy; focal or absent inflammation
  - Mild MHC-I upregulation (PF or diffuse), mild PF MxA upregulation
  - Mild or no complement deposition (capillaries)

Anti-TIF1γ DM

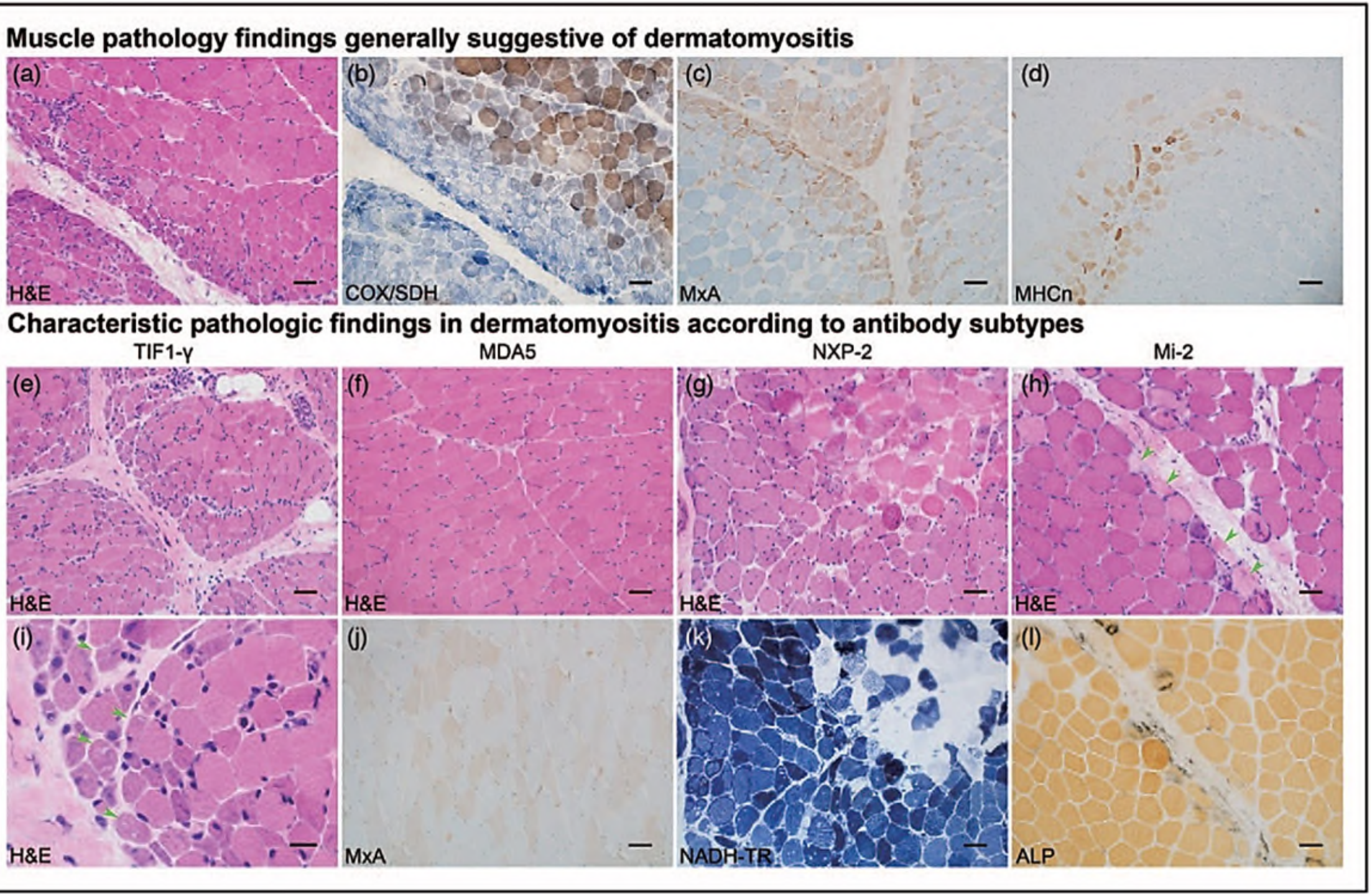
- Weakness: severe; dysphagia
- Skin: typical DM rash
- ILD: uncommon
- Cancer association: +++
- Histology
  - Well-developed PF atrophy; vacuolated PF fibers
  - Mild perimysial/endomysial lymphocytic inflammation (can be absent)
  - MHC-I upregulation (PF or diffuse with PF accentuation), MxA upregulation (PF)
  - Complement deposition (capillaries +++; sarcolemma +)

Anti-NXP-2 DM

- Weakness: severe
- Skin: variable typical DM rash (can be absent)
- ILD: uncommon
- Cancer association: ++
- Other features: calcinosis, severe edema, juvenile onset
- Histology
  - Well-developed PF atrophy; microinfarcts
  - Mild perimysial/endomysial lymphocytic inflammation (can be absent)
  - MHC-I upregulation (PF or diffuse with PF accentuation), MxA upregulation (PF)
  - Complement deposition (capillaries ++; sarcolemma +)

Anti-Mi-2 DM

- Weakness: severe
- Skin: typical DM rash
- ILD: uncommon
- Cancer association: ?
- Histology
  - Well-developed PF atrophy; PF necrosis
  - Dense perimysial/endomysial inflammation (lymphocytes and macrophages; sometimes lymphocyte clusters)
  - Perimysial fragmentation; perimysial alkaline phosphatase
  - MHC-I upregulation (PF or diffuse with PF accentuation), MxA upregulation (PF)
  - Complement deposition (capillaries +; sarcolemma +++)



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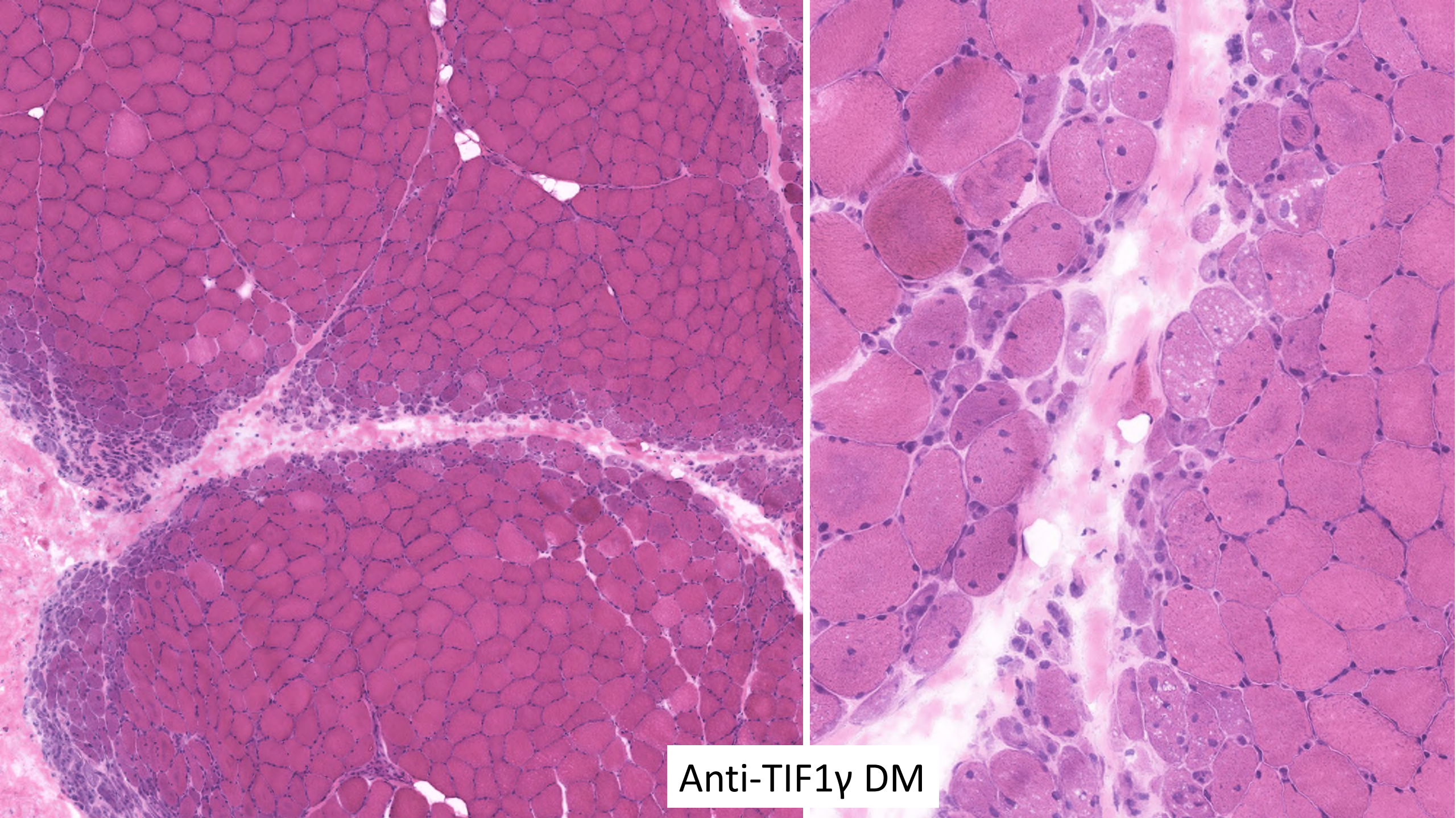
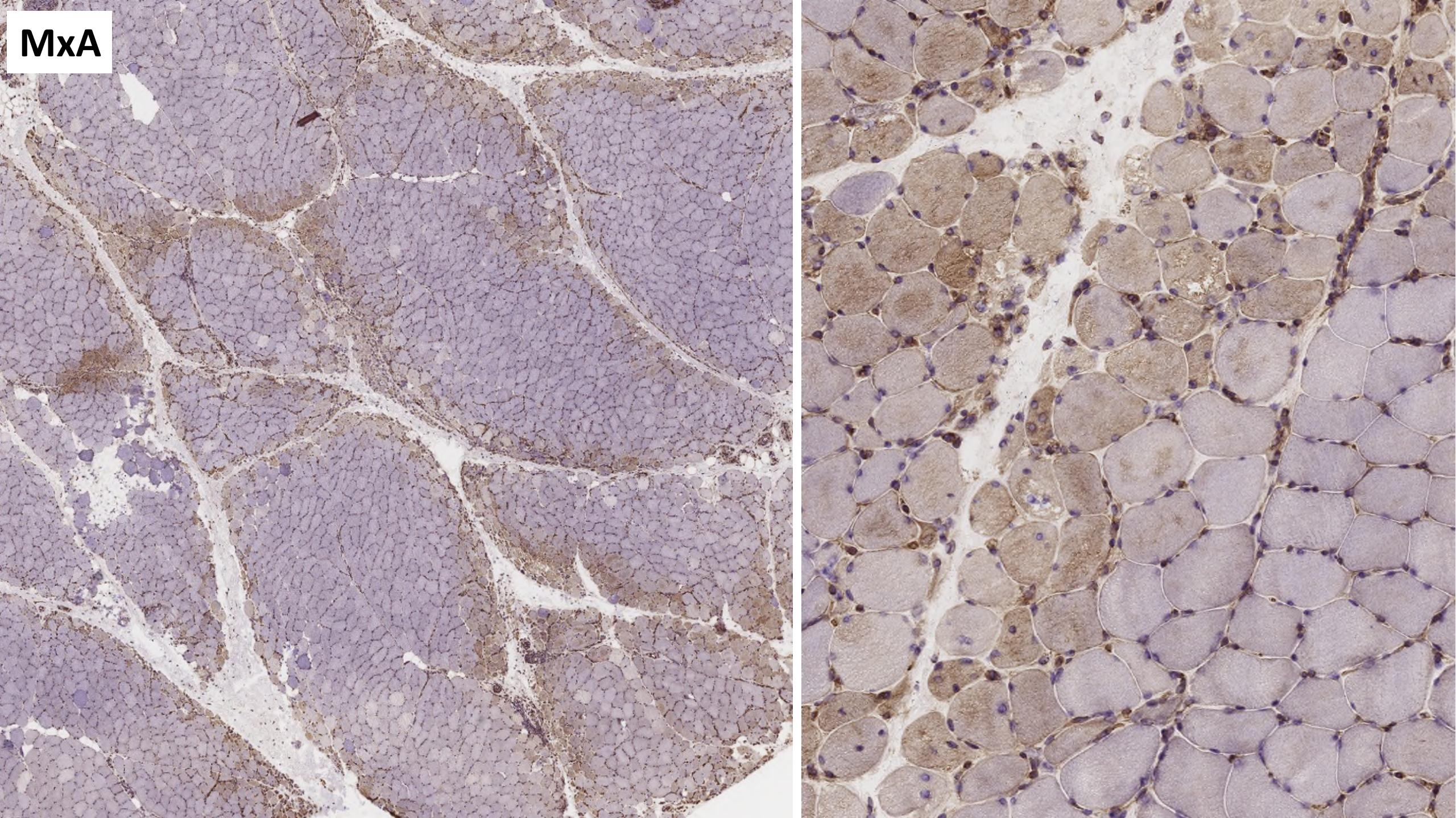
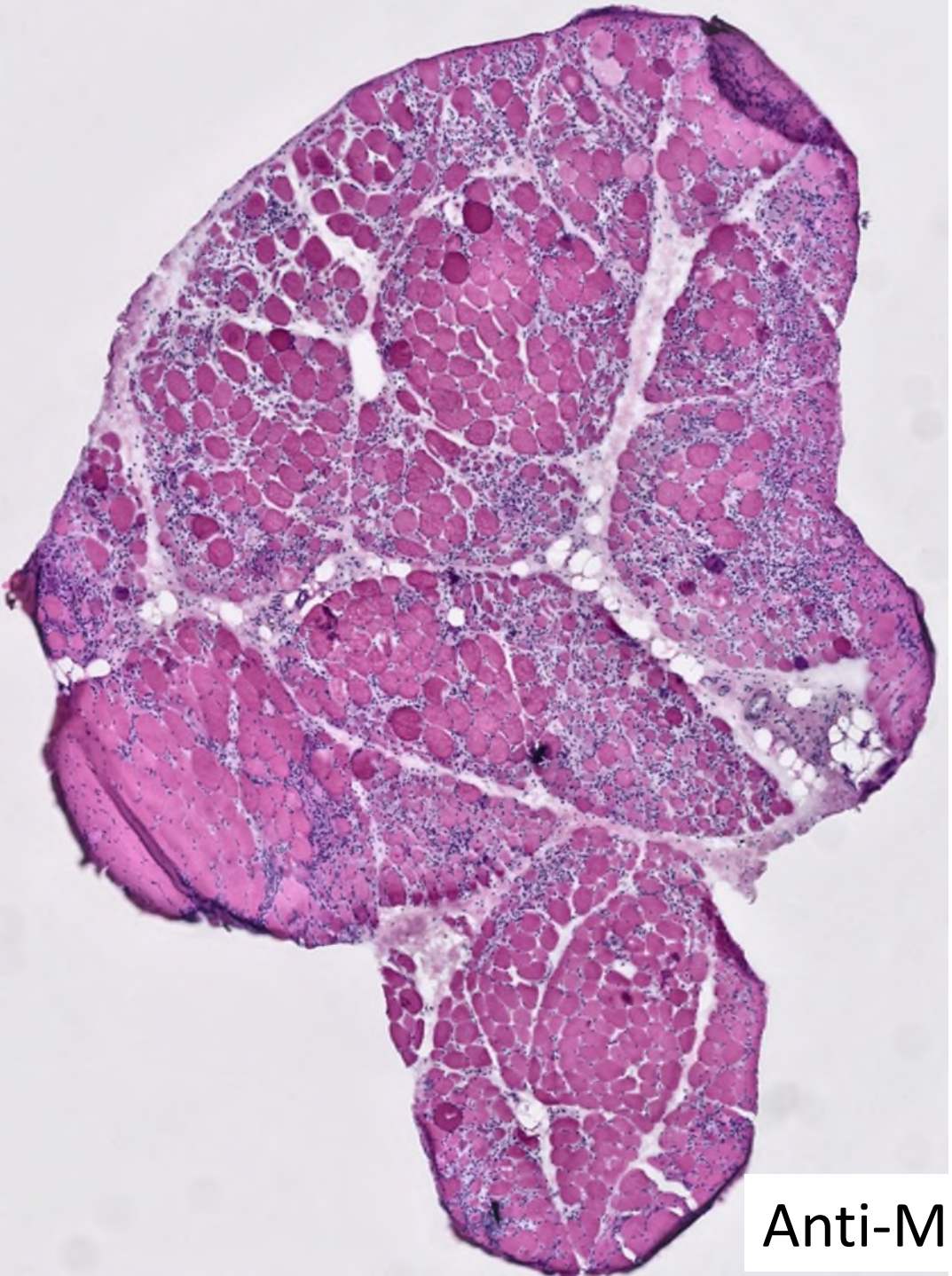
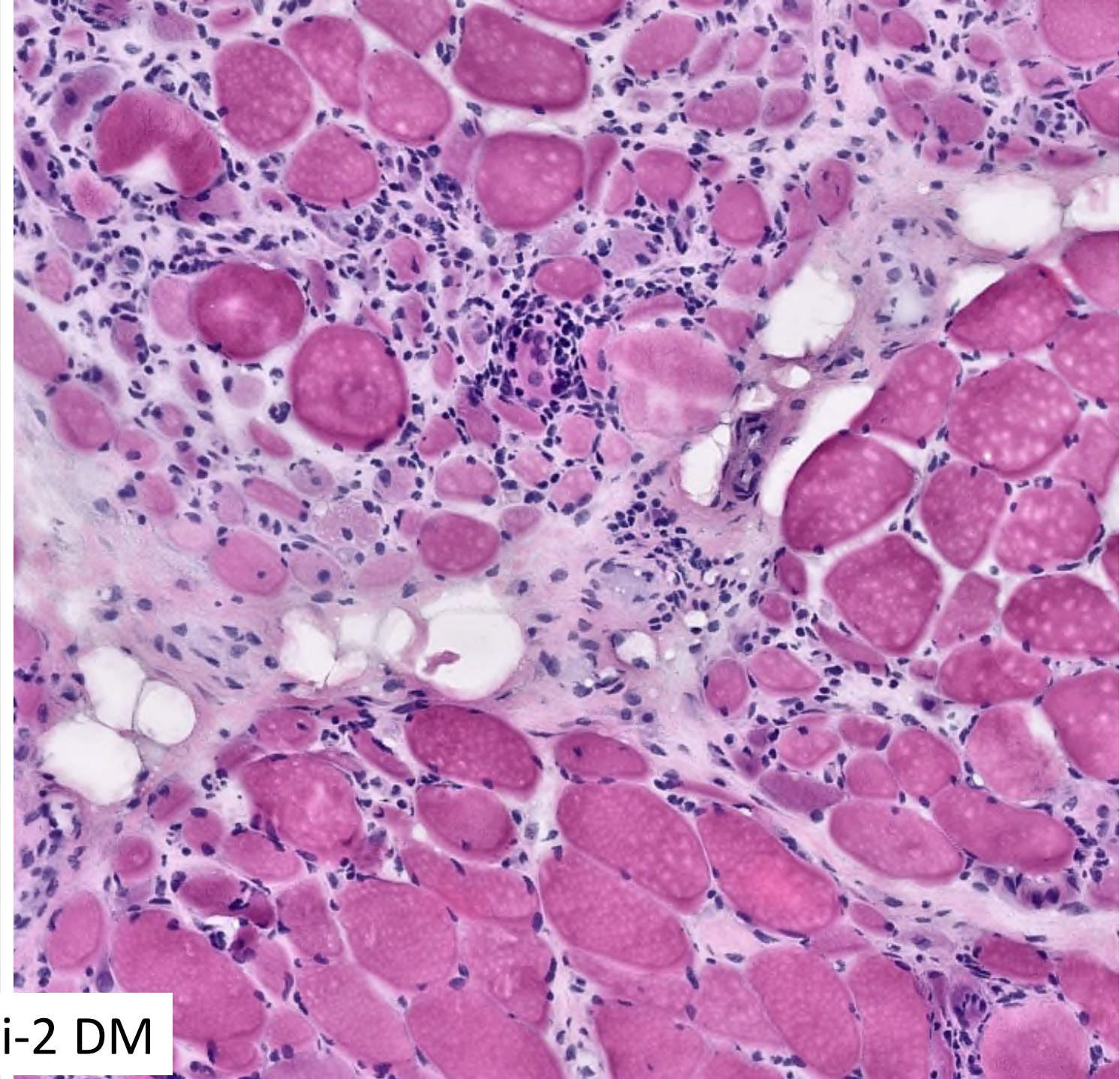
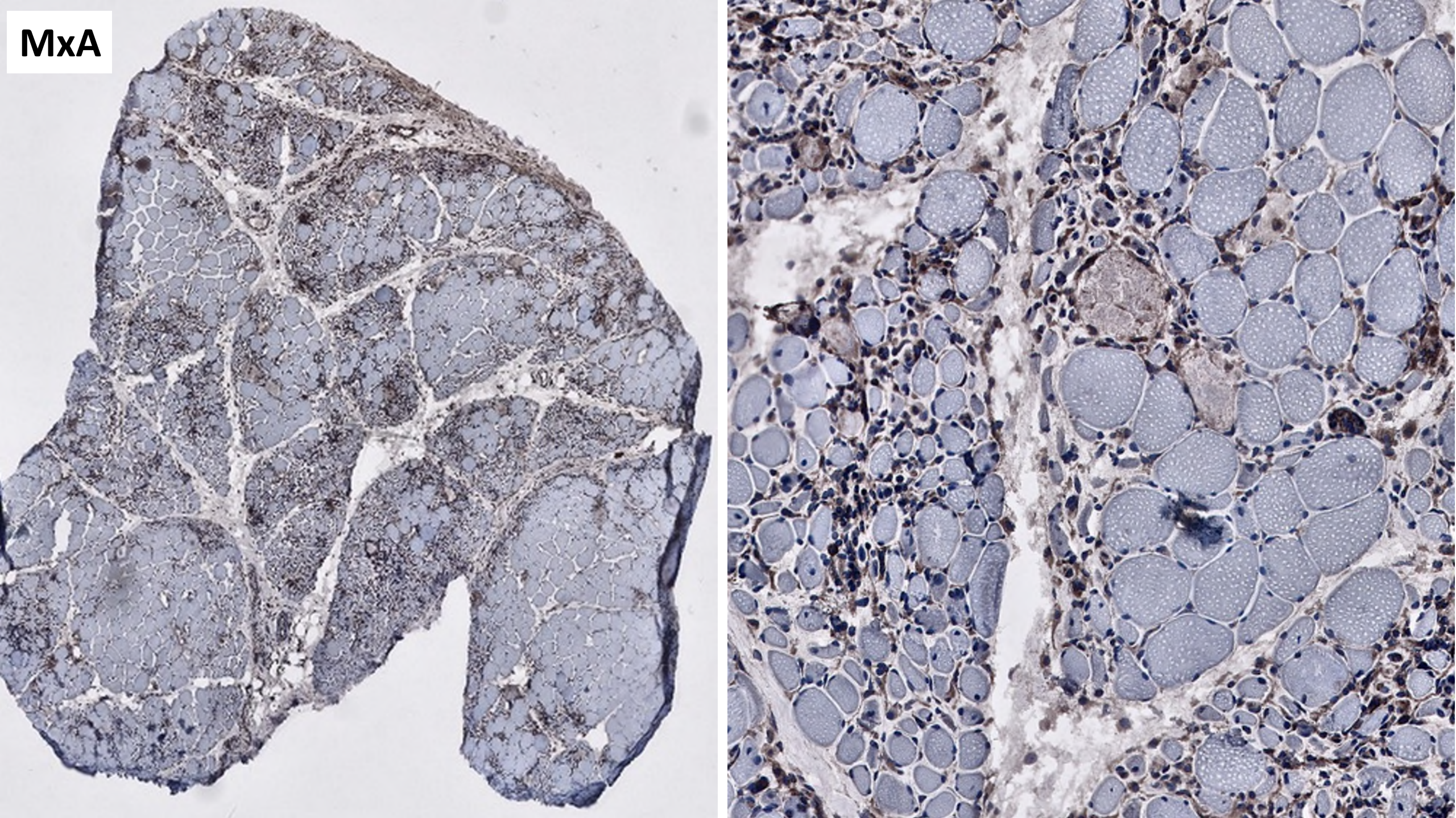

Anti-TIF1γ DM


MxA





Anti-Mi-2 DM


MxA

Virtual slides

https://pathpresenter.net/#/public/presentation/display?token=c8aa355a

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QUESTIONS?

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