Inclusion Body Myositis

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Amato Disclosures

Relevant Financial Relationships

Medical Advisory Boards /Consultant for Abcuro, Argenx, Ra Pharmaceuticals, Horizon Therapeutics, OnoPharma, Alexion, EMD Serono, Takeda, Johnson & Johnson (COVID-19 vaccination program), Neurology Consultant to CDC and WHO regarding COVID-19 and vaccinations

Learning Objectives

- Better understand the clinical, laboratory, and histopathology and the pathogenesis of inclusion body myositis

IDIOPATHIC INFLAMMATORY MYOPATHIES

- Dermatomyositis (DM)
- Autoimmune Necrotizing Myopathy
- Antisynthetase Syndrome
- Inclusion Body Myositis (IBM)
- Polymyositis (PM)

INCLUSION BODY MYOSITIS

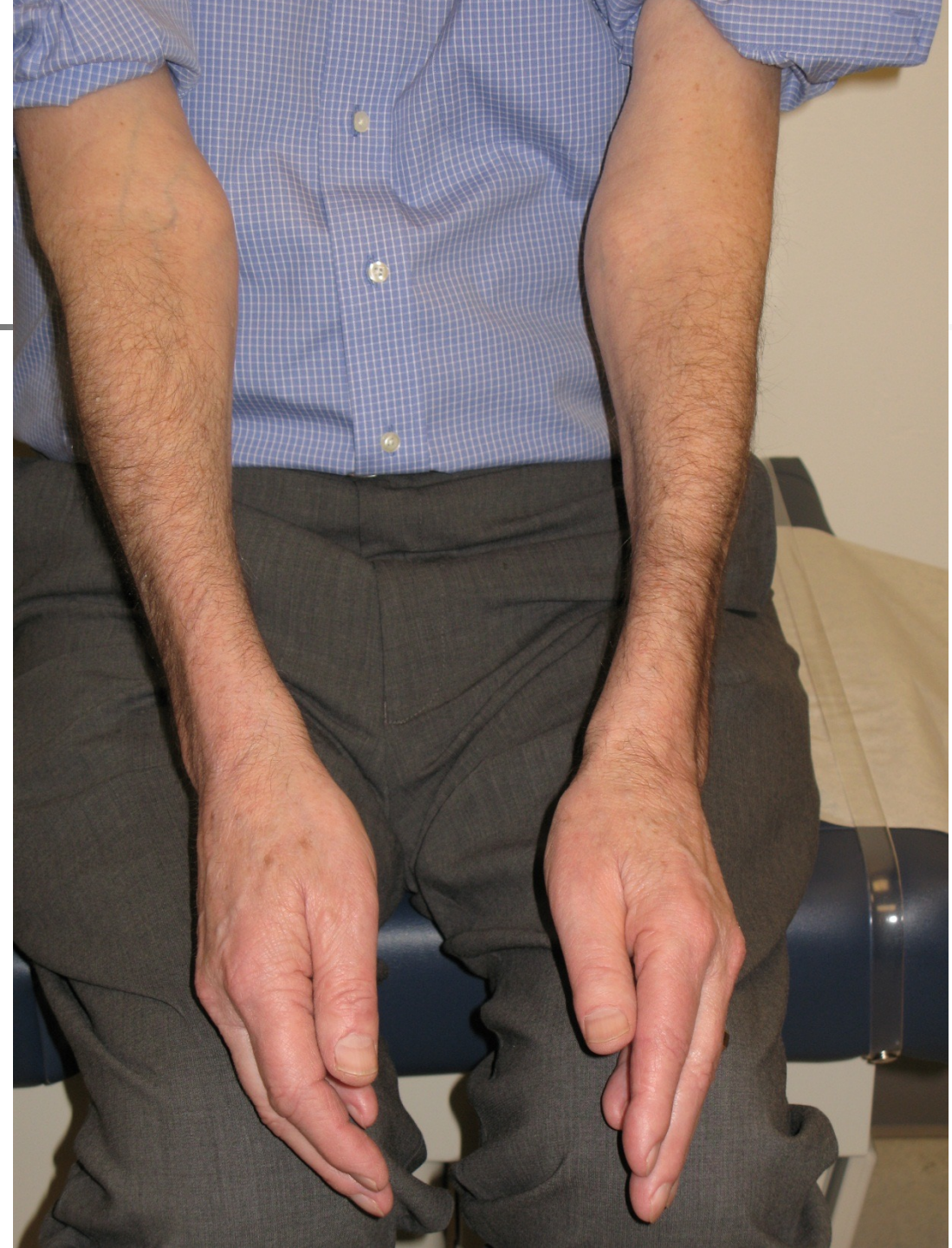
- Clinical Features
  - frequently misdiagnosed as PM
  - insidious onset and slowly progressive (average duration of symptoms prior to dx is 6 yrs)
  - men affected more than women
  - usually develops over the age of 50 years (most common myositis in patients presenting over the age of 50 years)

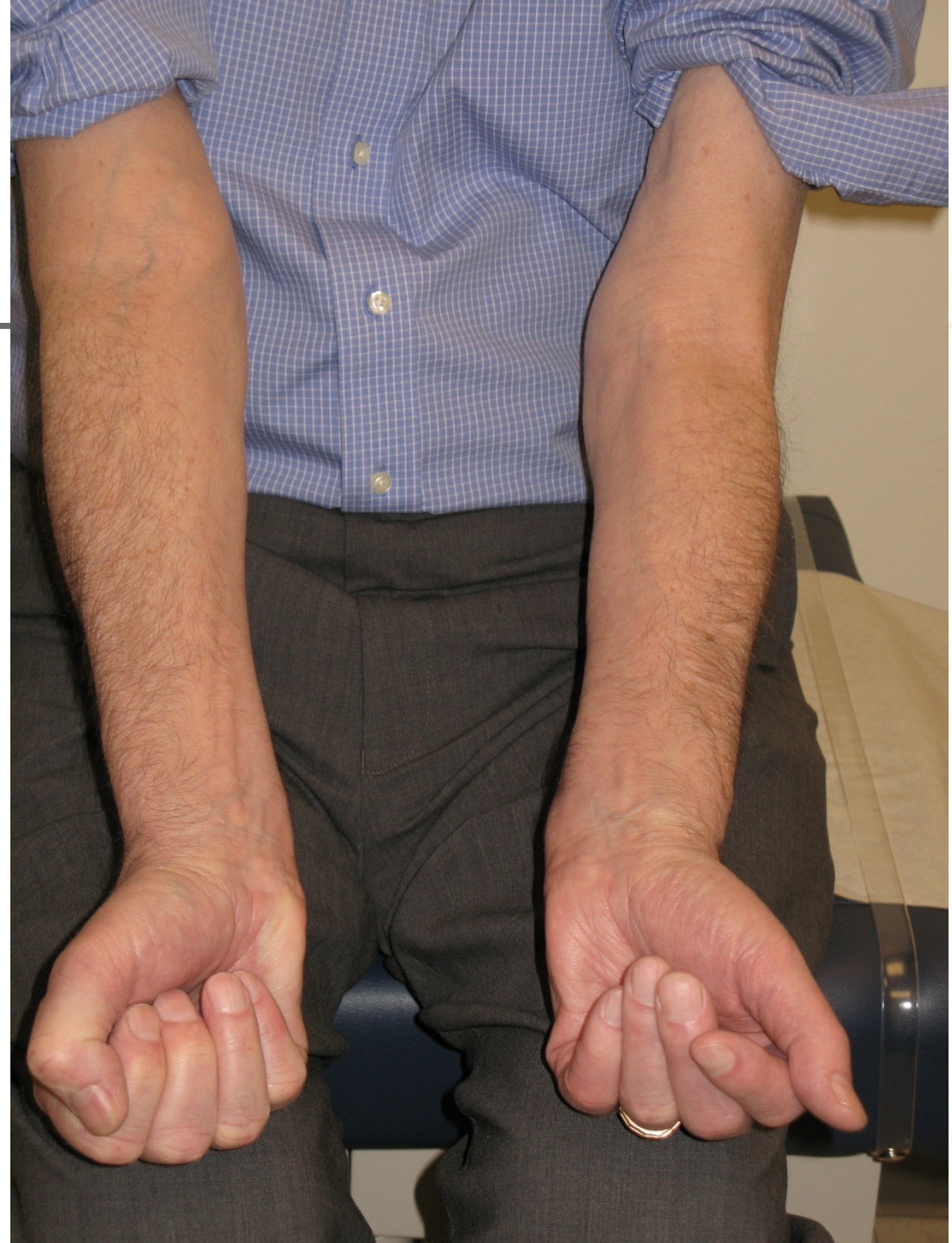
INCLUSION BODY MYOSITIS

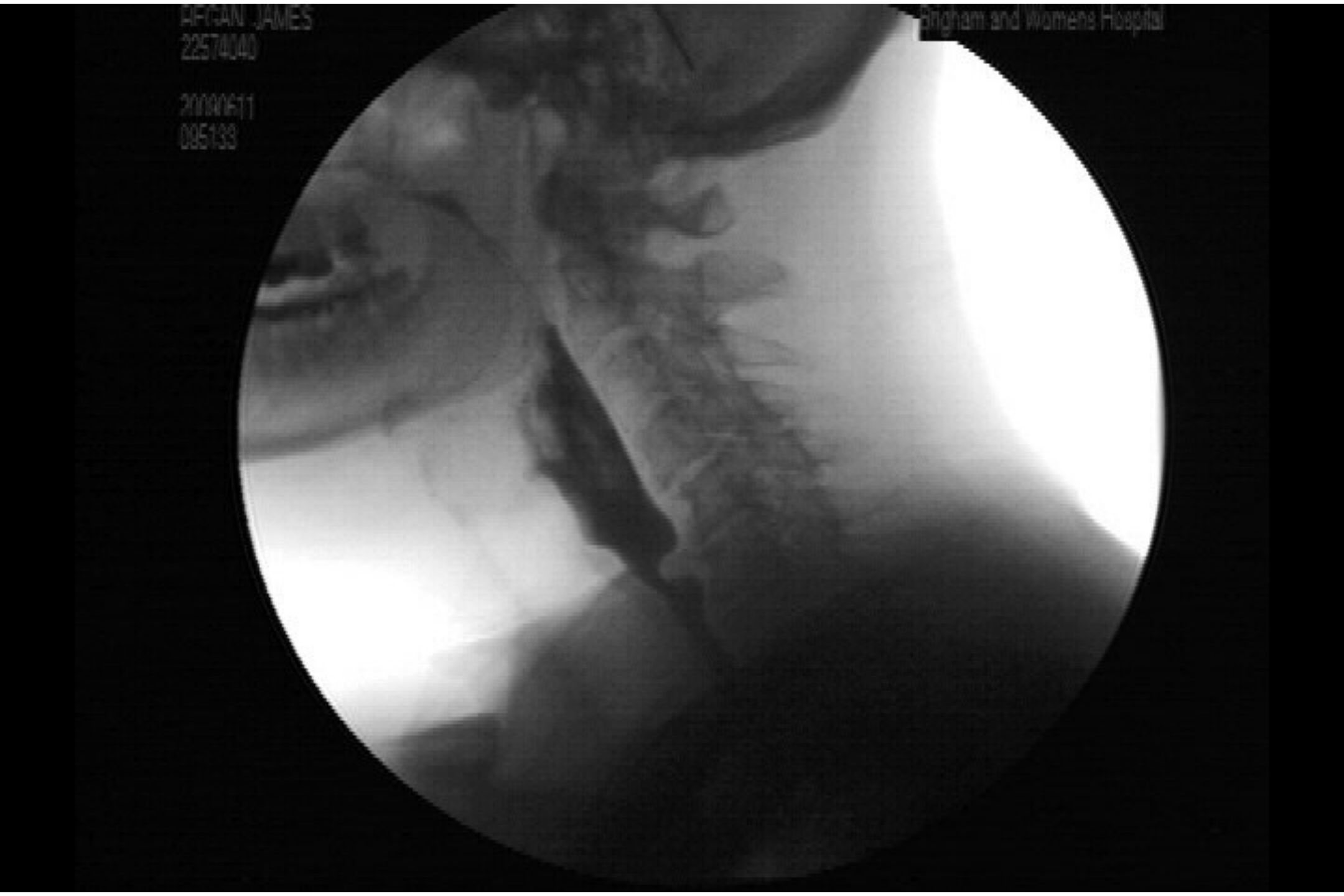
- Clinical hallmark is early weakness and atrophy of the quadriceps and volar forearm muscles (wrist / finger flexors)
- MRC scores of the wrist/finger flexors are often lower than the shoulder abductors and to a lesser extent the knee extensors are the same or weaker than the hip flexors
  - contrasts with the pattern of weakness seen in DM, anti-synthetase syndrome, and IMNM

INCLUSION BODY MYOSITIS

- Ankle dorsiflexors are also affected early
- Muscle involvement is frequently asymmetric
- Mild facial weakness evident in 30-40%
- Dysphagia present in up to 60%
  - may become severe enough to require cricopharyngeal myotomy
  - Cricopharyngeal bar is rather specific for IBM in patients with inflammatory myopathy



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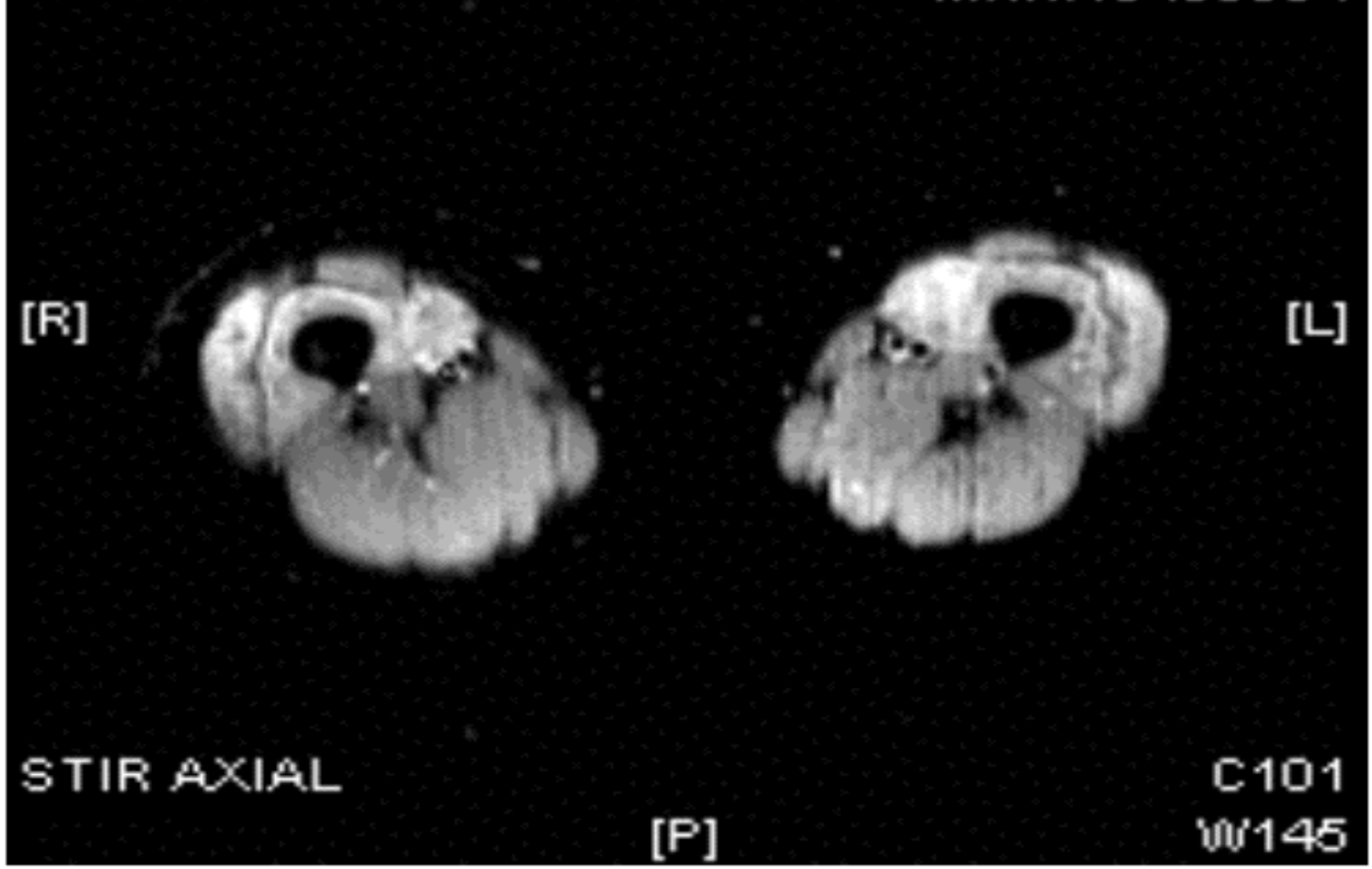
INCLUSION BODY MYOSITIS

- Associated Manifestations
  - not associated with myocarditis or ILD
  - no increased risk of malignancy
  - autoimmune disorders such as Sjogren syndrome, sarcoidosis/granulomatous myositis, SLE, scleroderma, thrombocytopenia, Up to 20% may have monoclonal gammopathy
  - Increased associate with HLA-DR3 and extended MHC 8.1 ancestral haplotype marked by HLA-A1, B8, DRB1*0301, DRB3*0101, DQB1*0201

INCLUSION BODY MYOSITIS

- Laboratory Features
  - CK is normal or only mildly elevated (less than 10 times the normal level)
  - ANA have been reported in up to 20% but are usually absent unless there is a concurrent CTD
  - Muscle imaging (MRI) may demonstrate atrophy and signal abnormalities in affected muscle groups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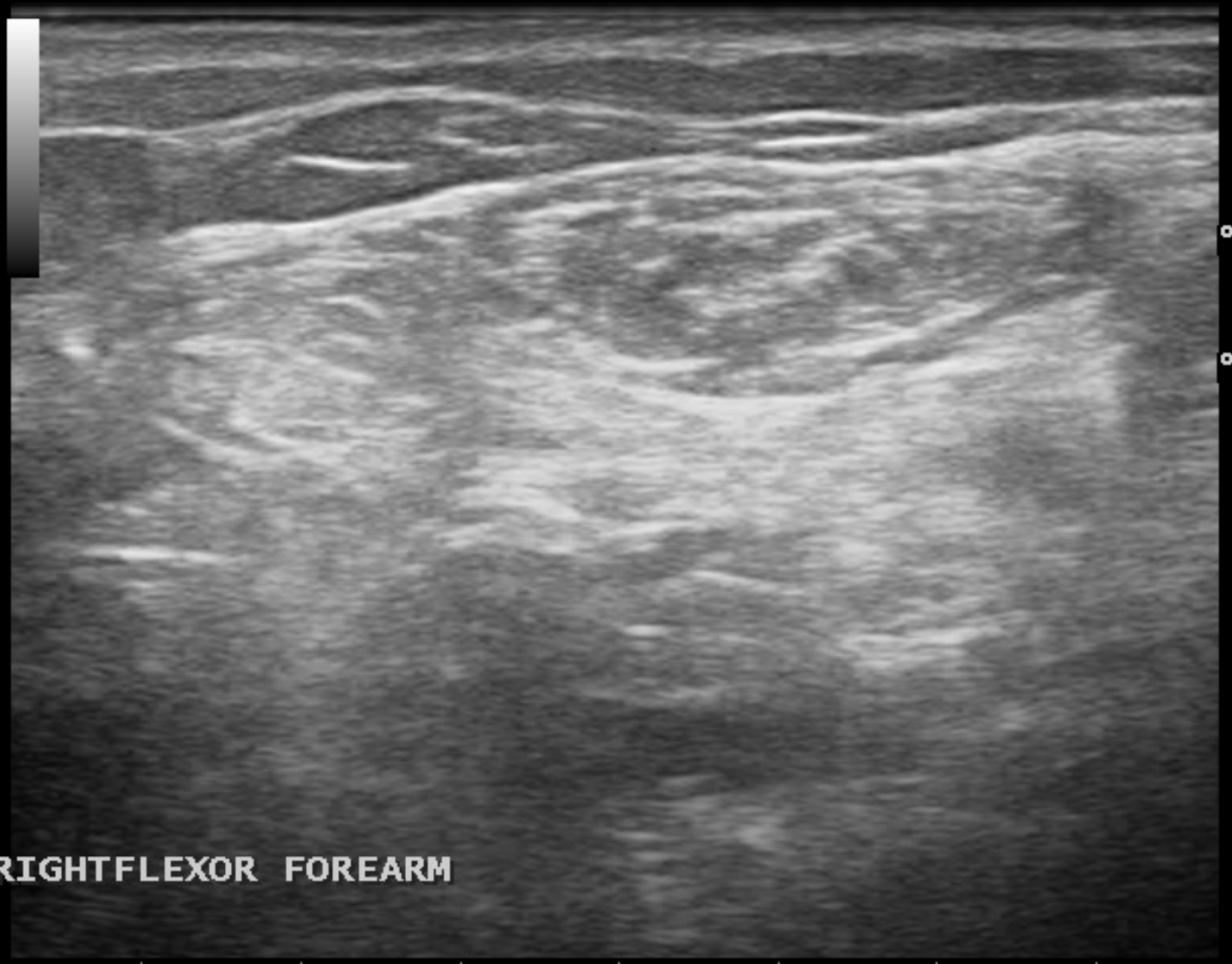
MUSCLE LA435



INCLUSION BODY MYOSITIS

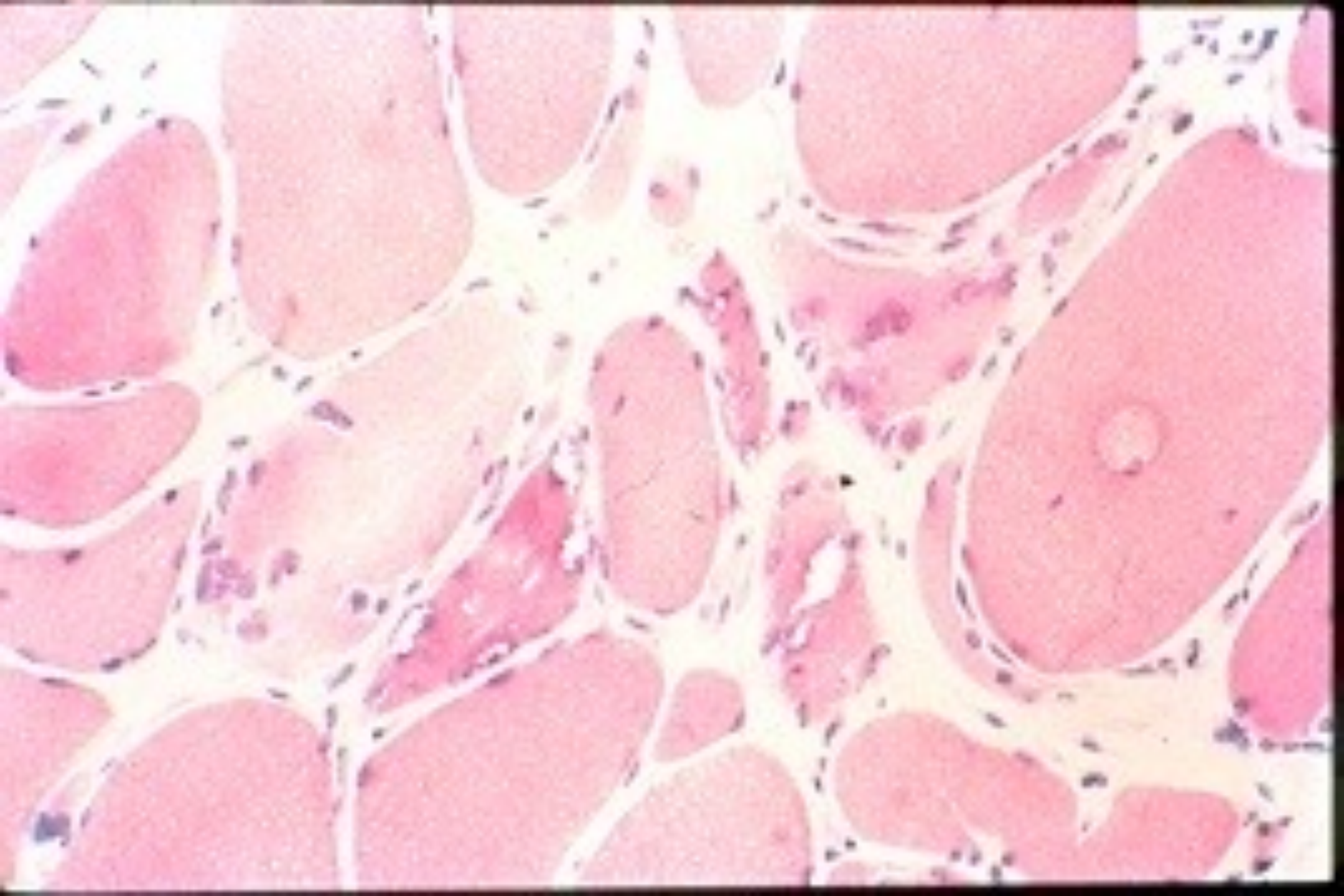
- Electrophysiological Studies
  - nerve conduction studies demonstrate an axonal sensory neuropathy in 30%
  - EMG may reveal large polyphasic motor unit potentials in addition to the small MUPs
    - not specific for IBM but can be seen in DM, PM, and other chronic myopathies
    - reflects chronicity of the disease rather than a neurogenic process

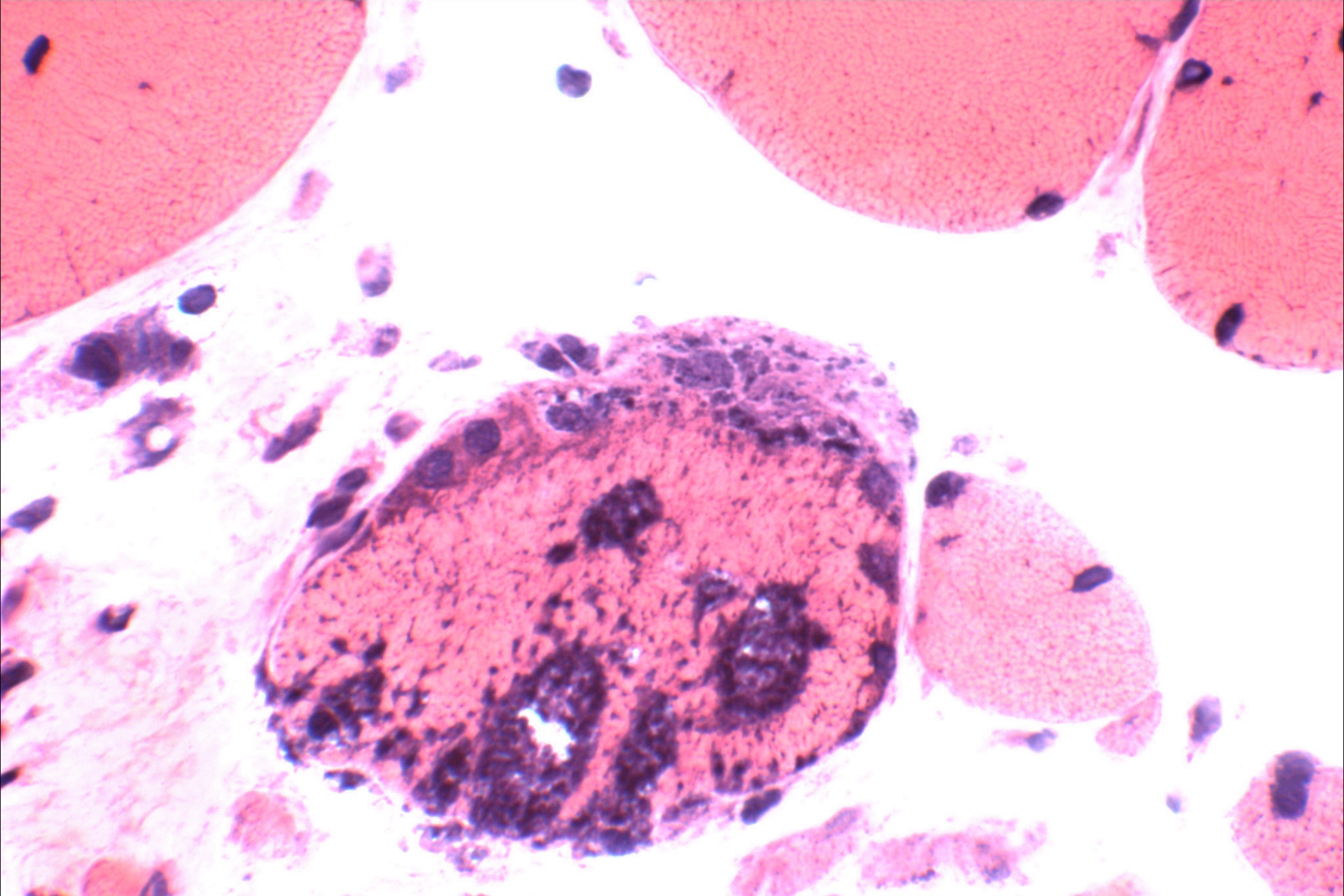
INCLUSION BODY MYOSITIS

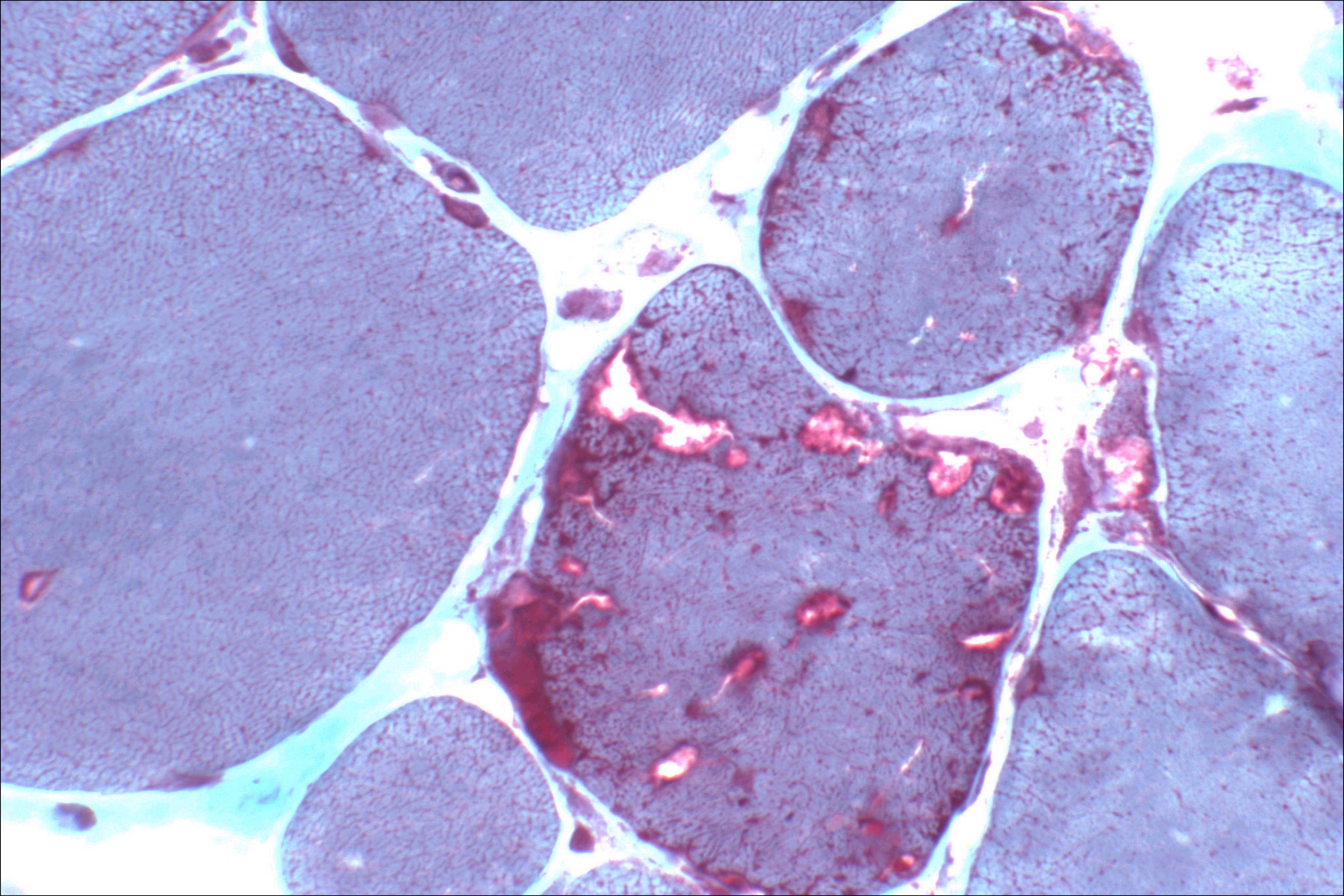
- Muscle Biopsy
  - endomysial inflammation composed of CD8+ T-cells and macrophages which invade non-necrotic muscle fibers expression MHC-1 antigen
  - small groups of atrophic fibers
  - muscle fibers with one or more rimmed vacuoles lined with granular material
  - eosinophilic cytoplasmic inclusions

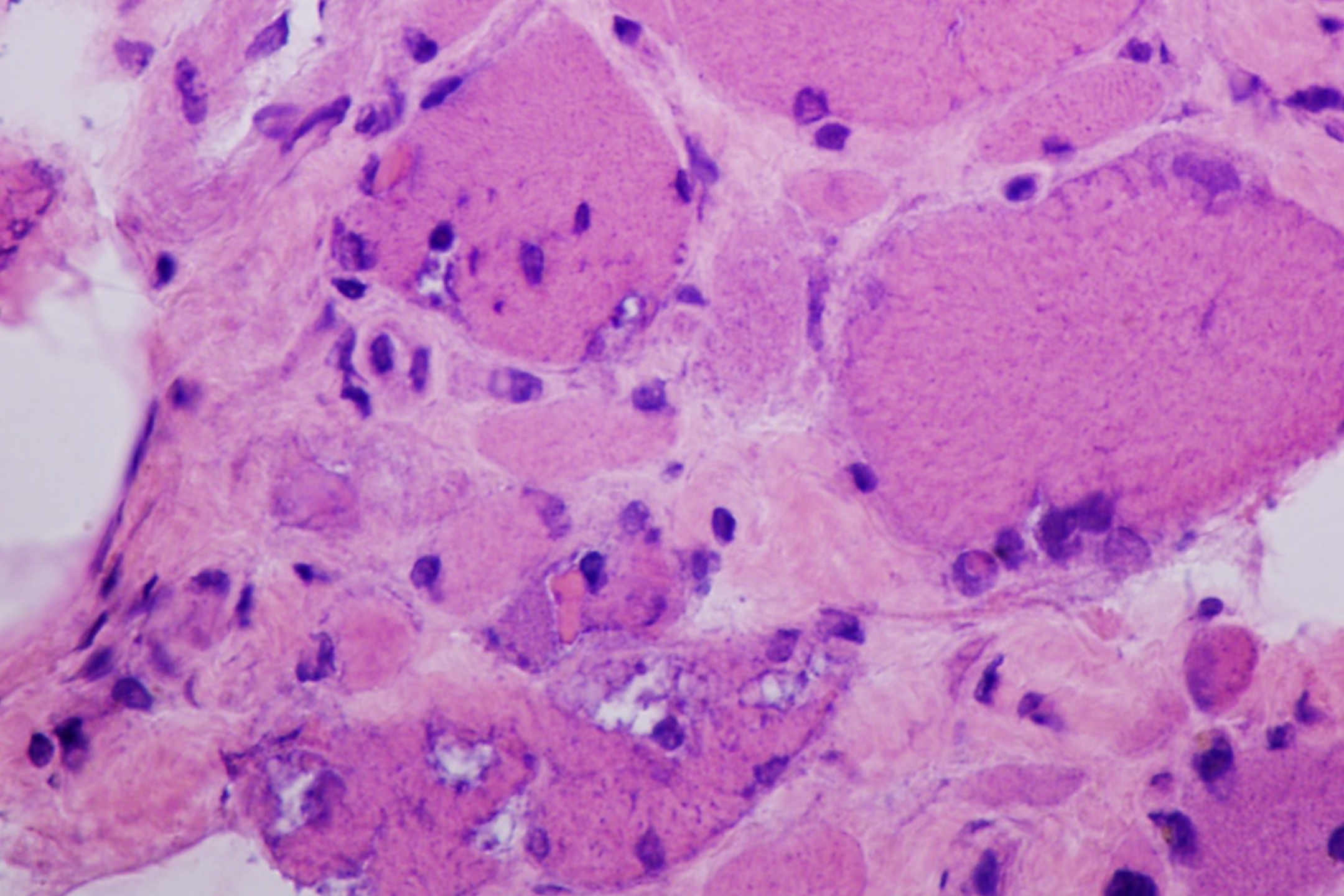
INCLUSION BODY MYOSITIS

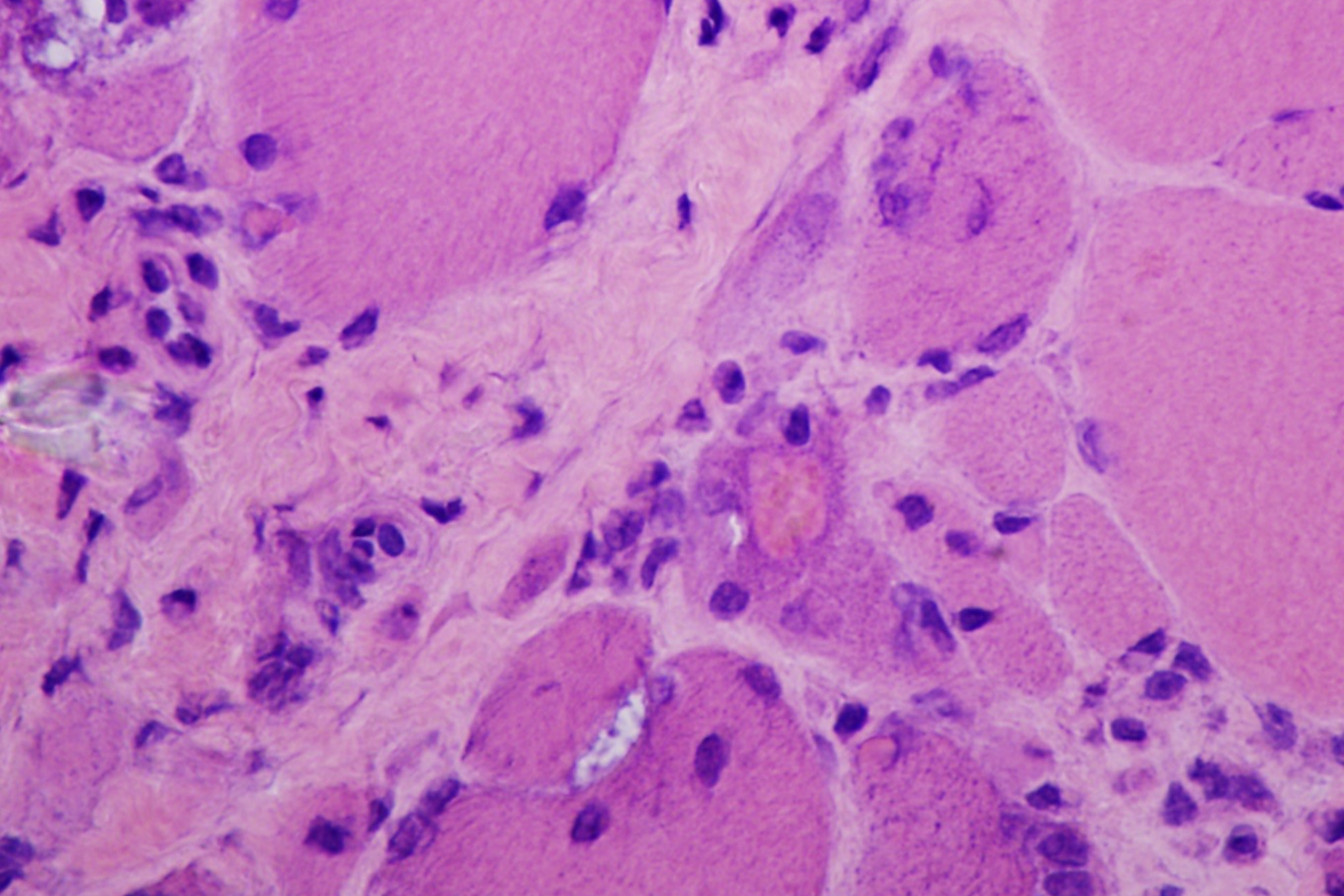
- amyloid deposition is evident in the cytoplasm of vacuolated muscle fibers and occasionally in nuclei
- electron microscopy demonstrates 15-21 nm tubulofilaments in the cytoplasm and less commonly in nuclei of muscle fibers
- increased incidence of ragged-red fibers (mitochondrial abnormalities)

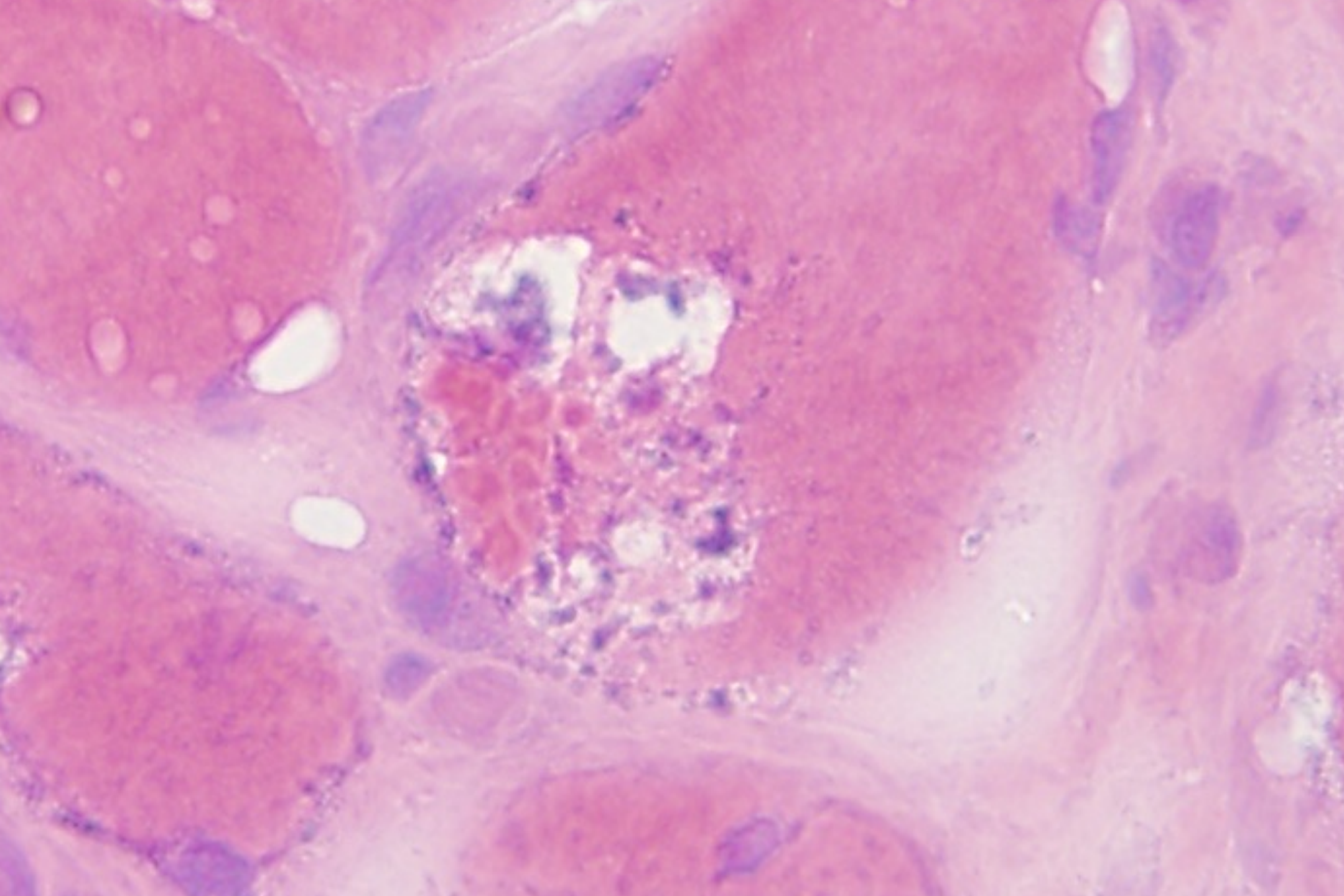


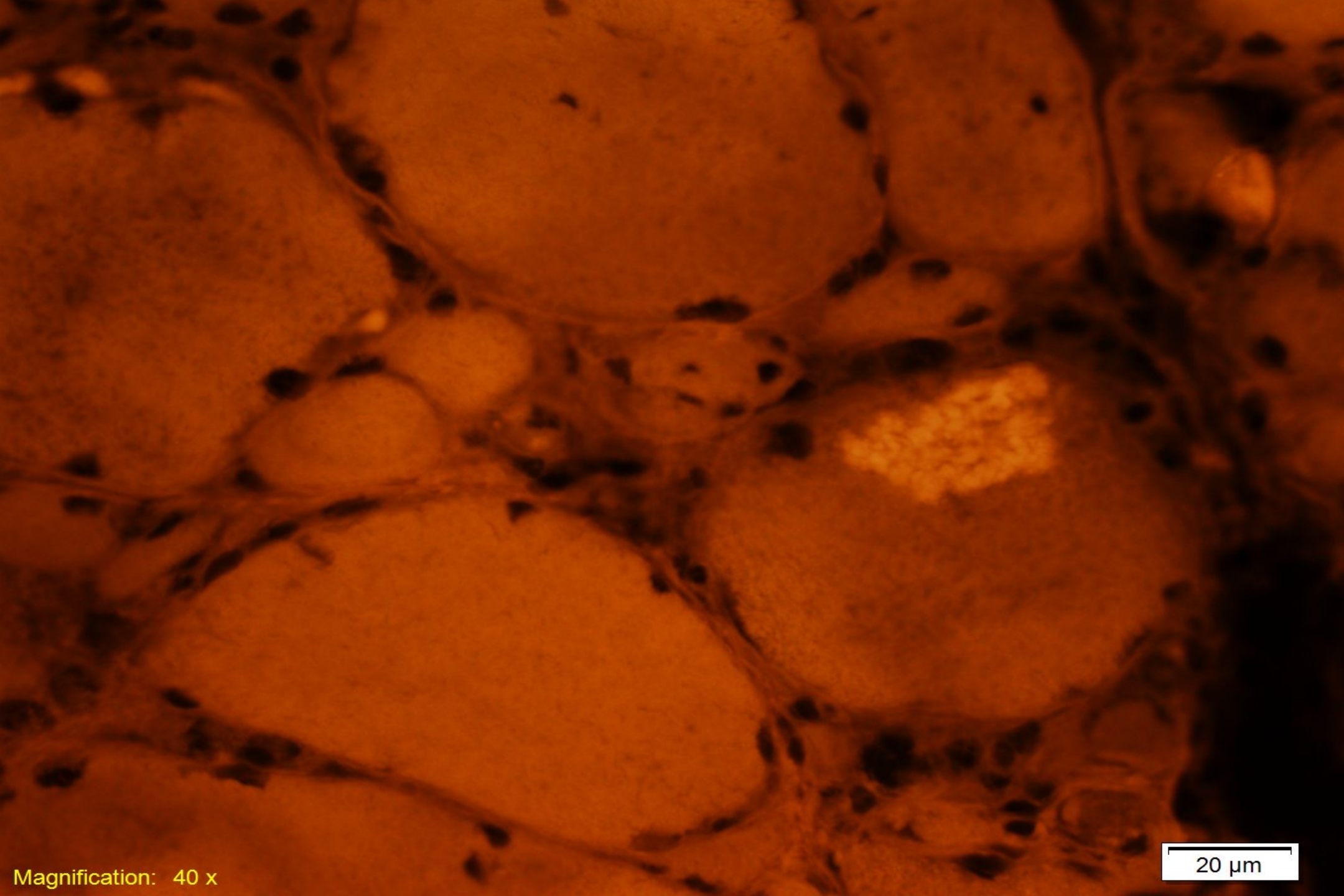








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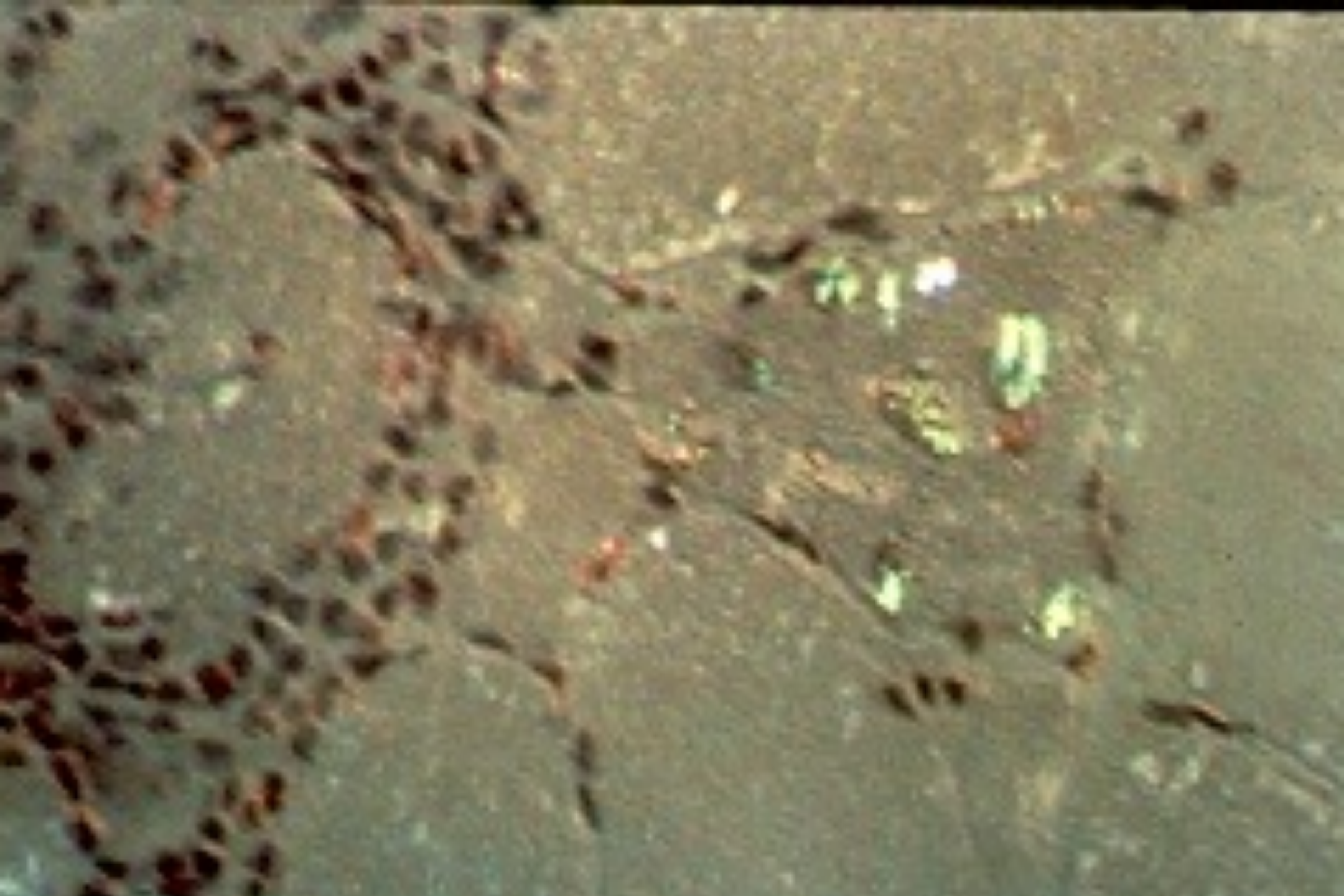
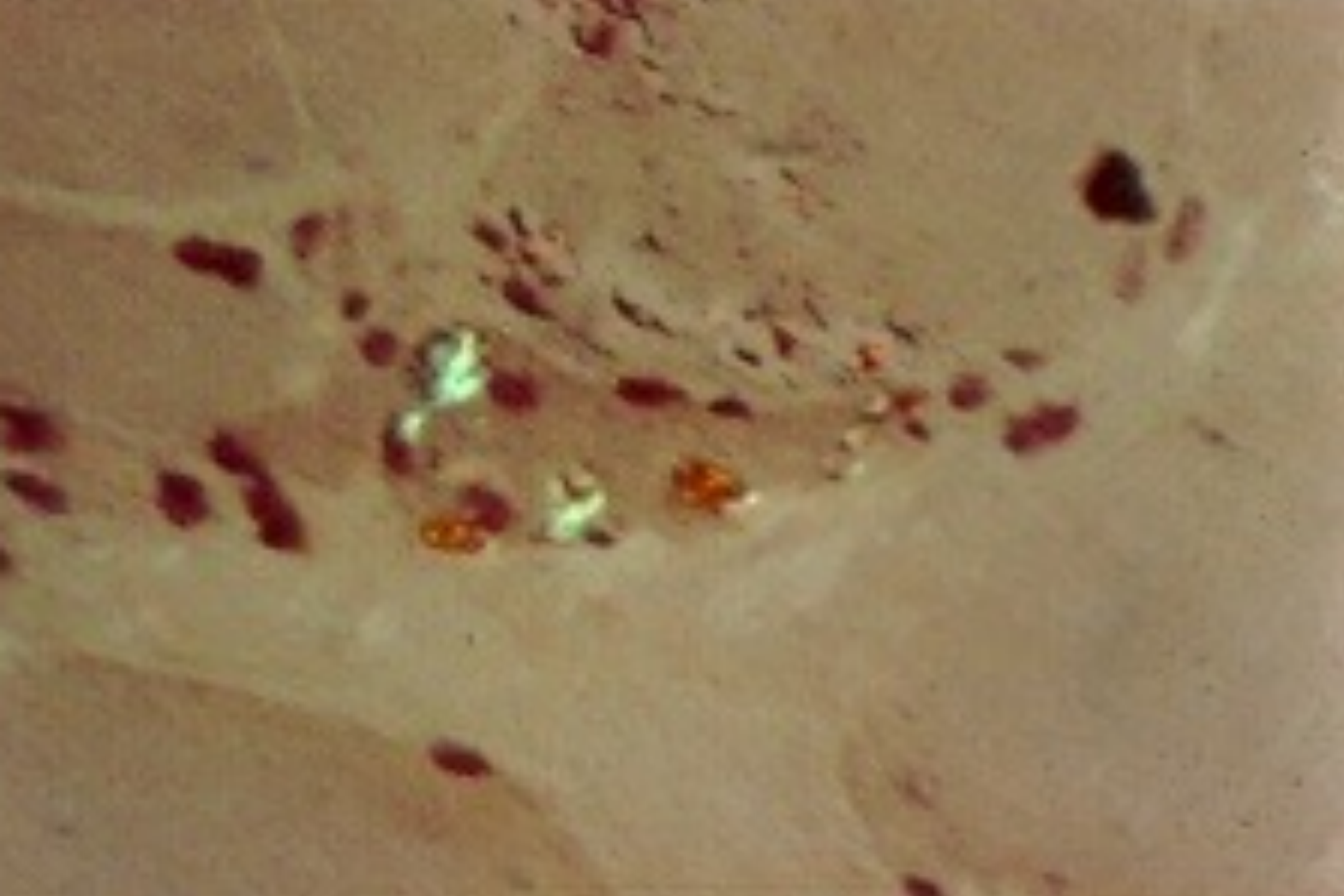
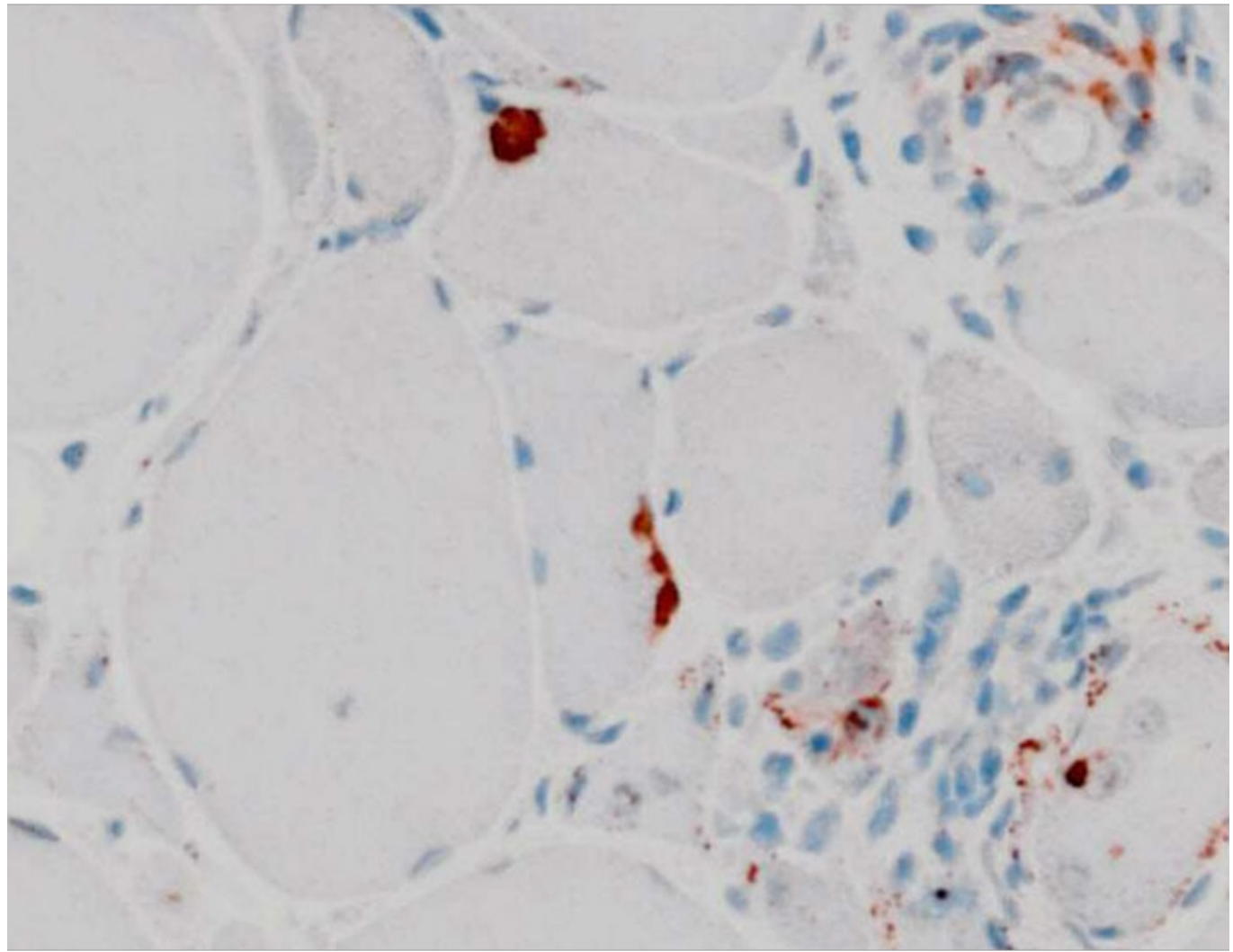




p62



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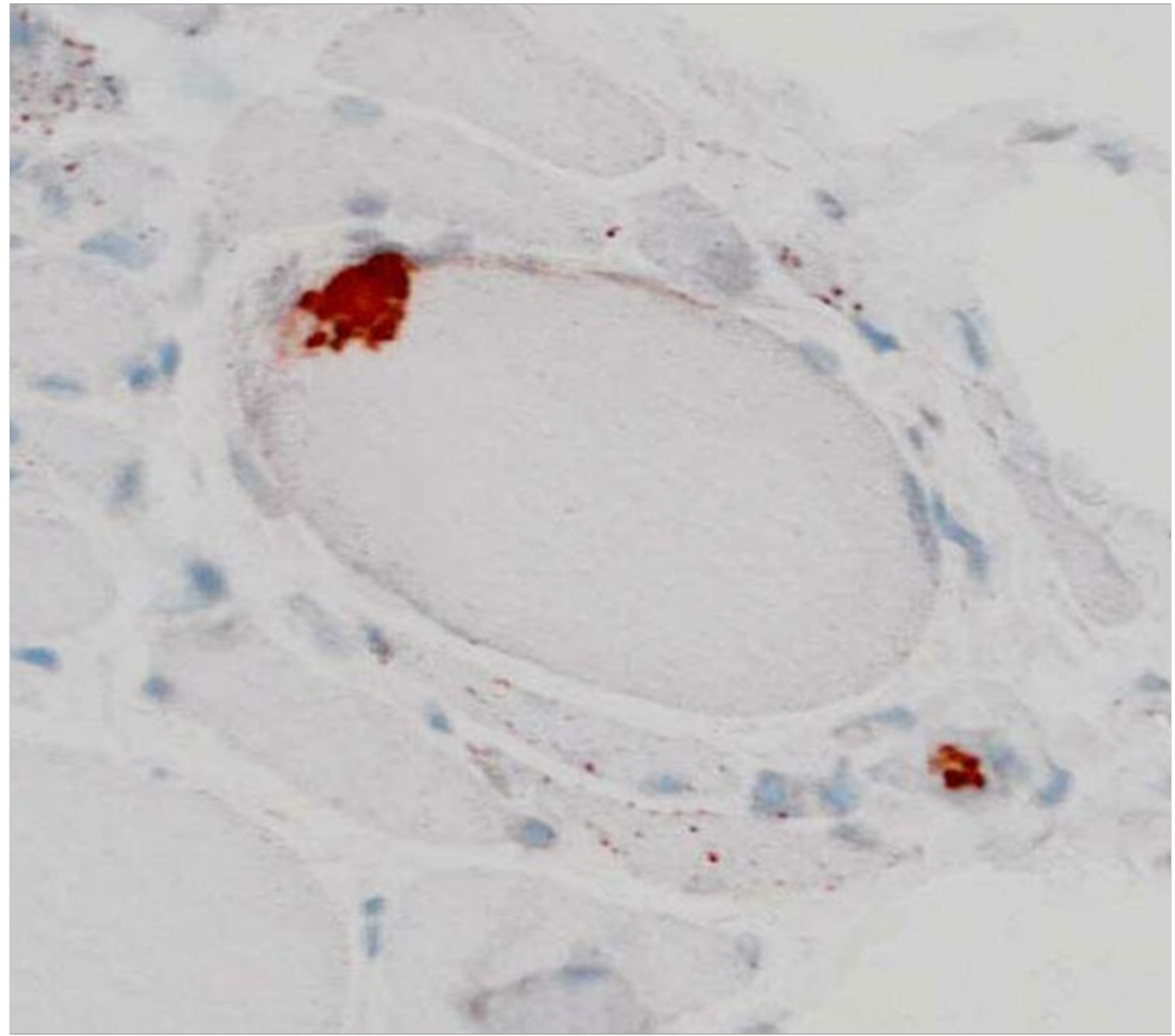
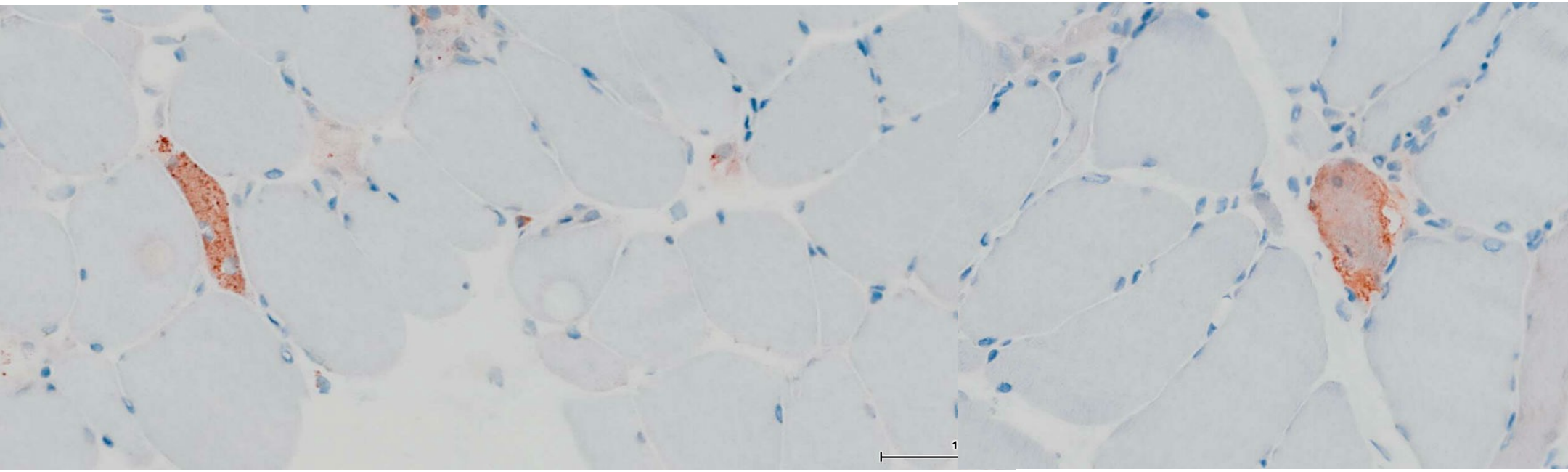
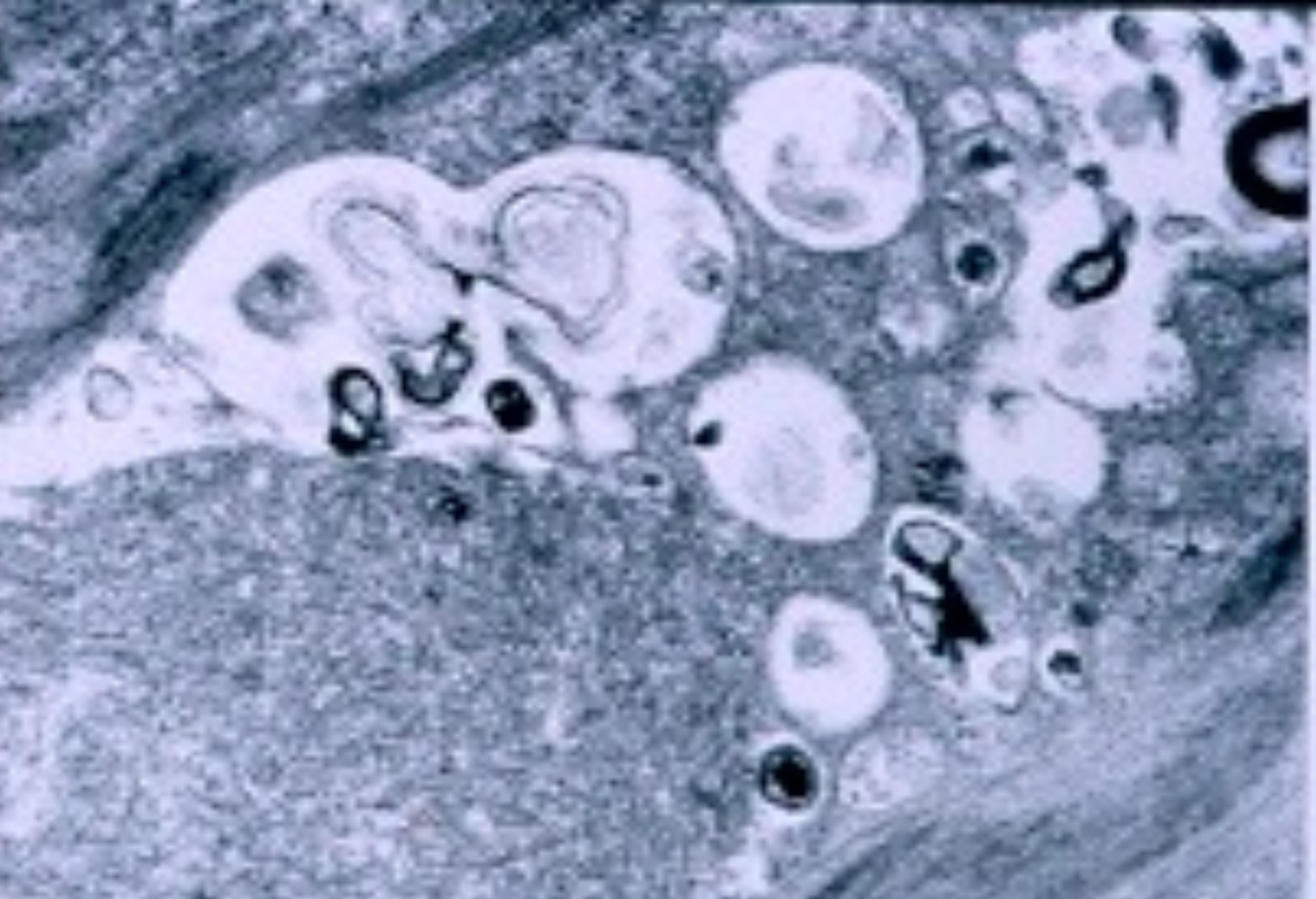
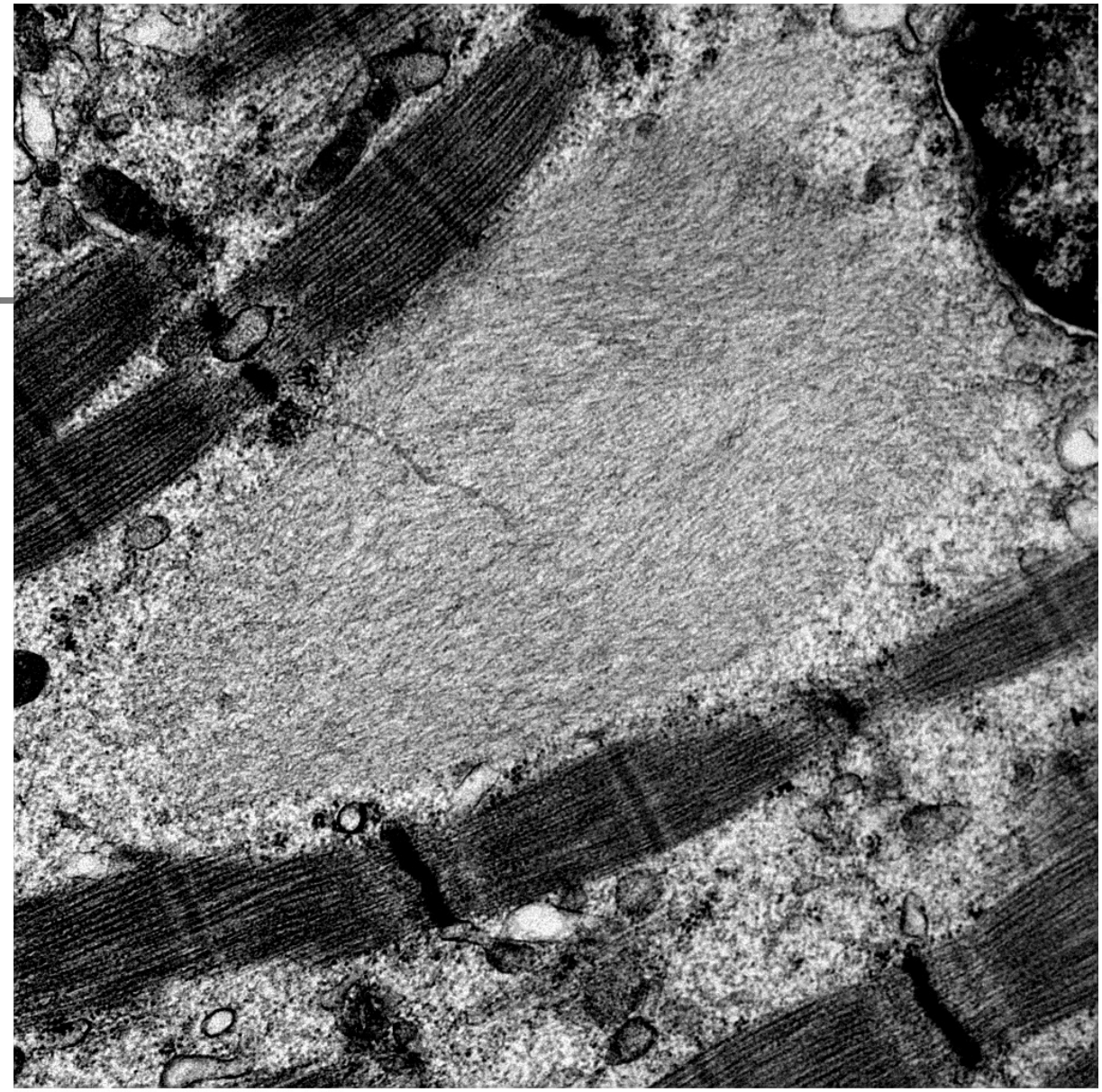


p62 in Necrotizing Myopathy





IBM



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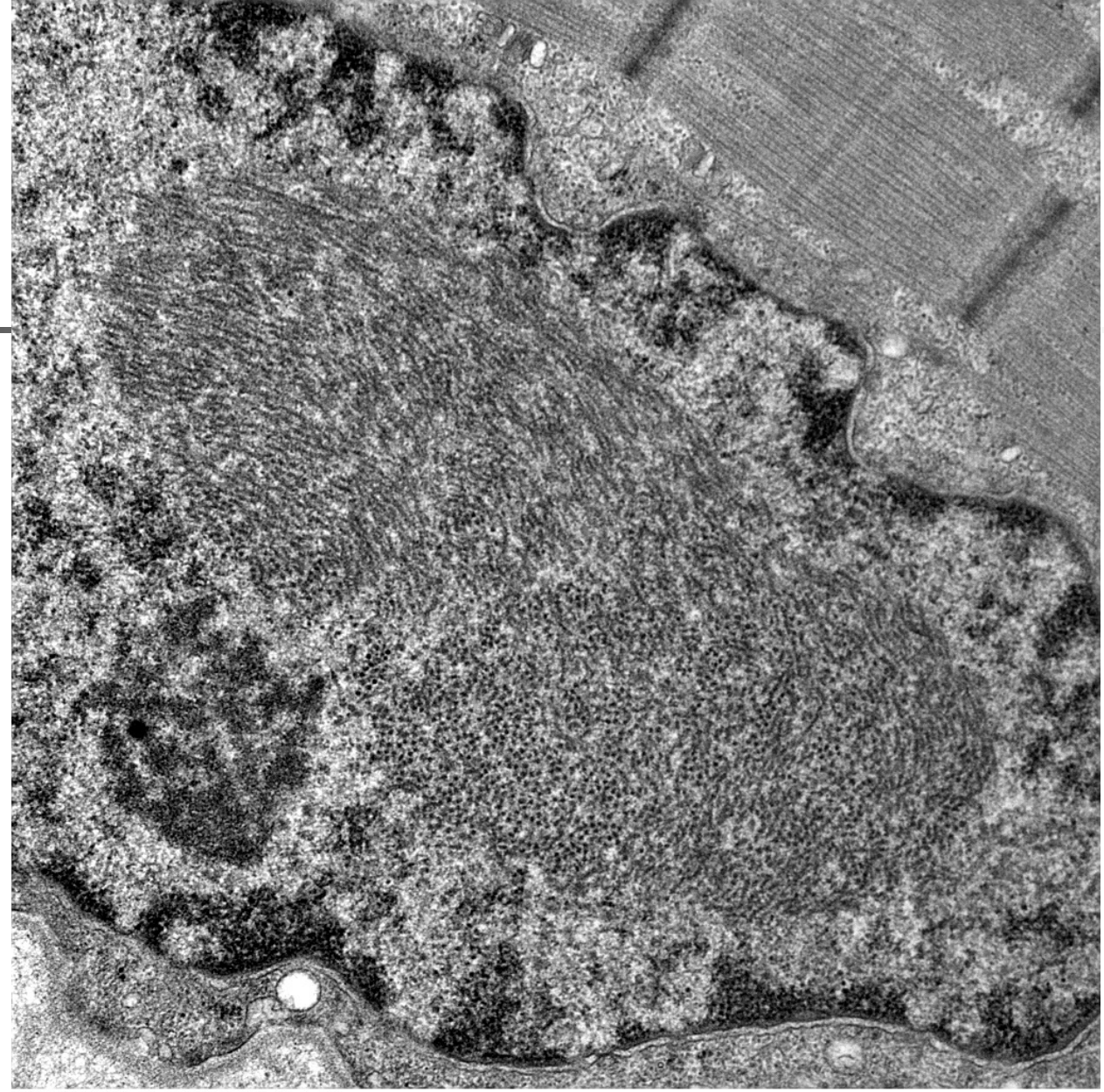

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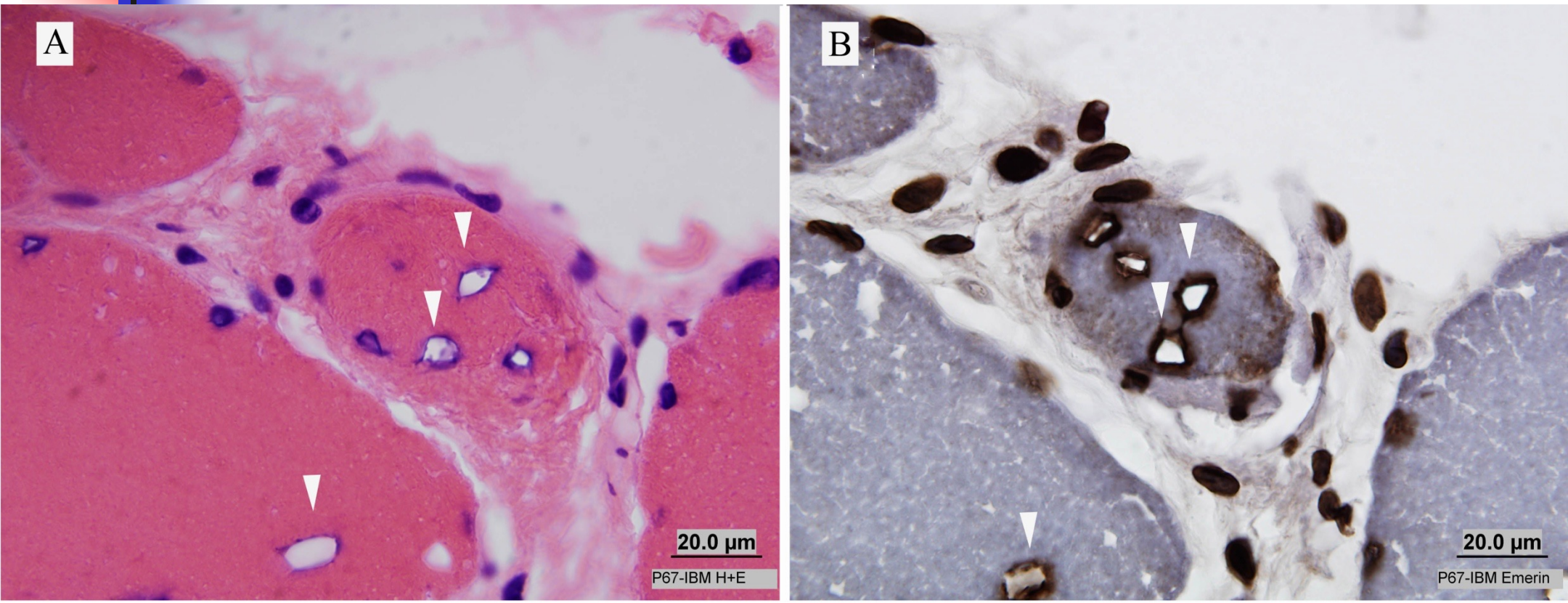
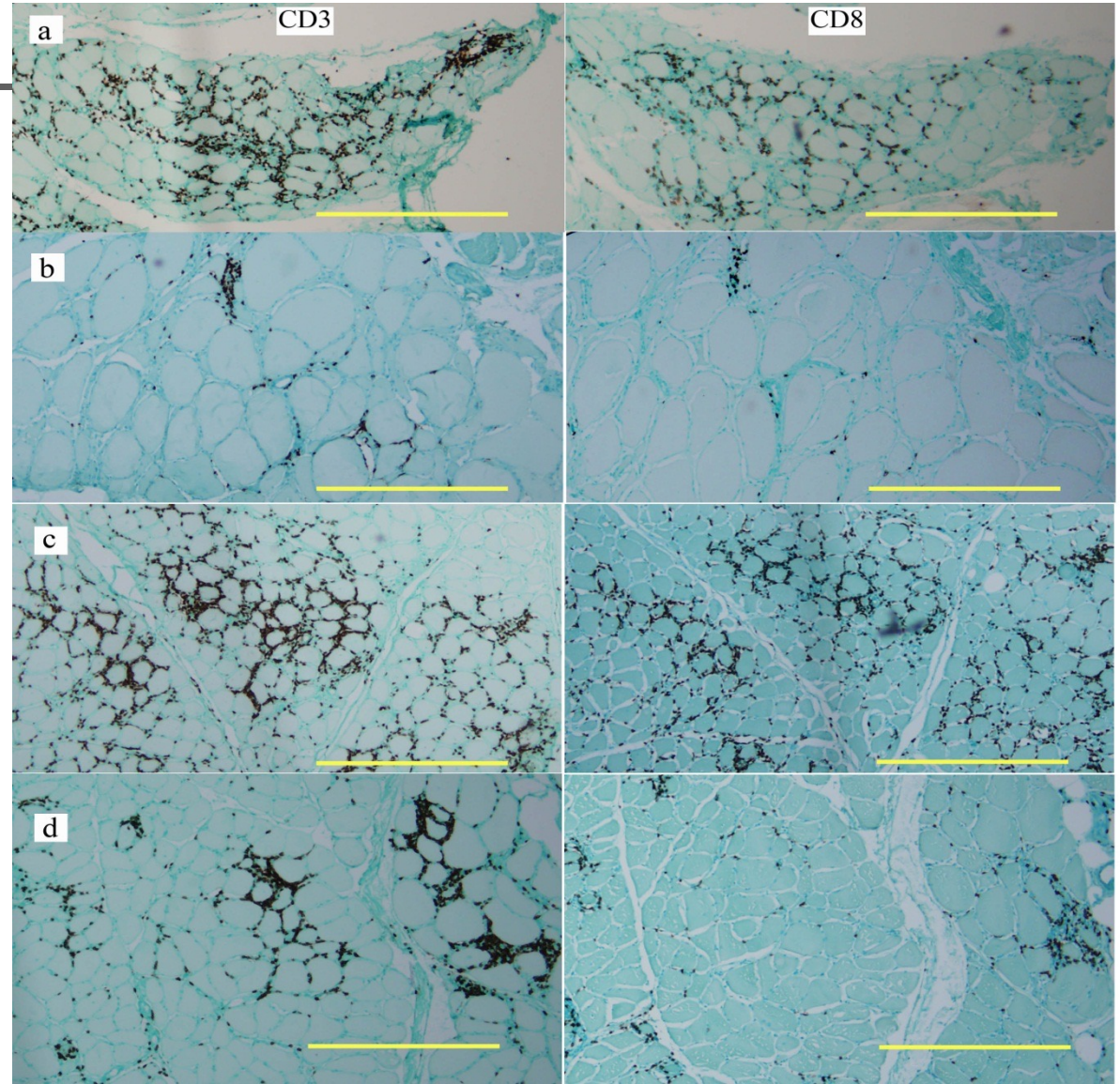
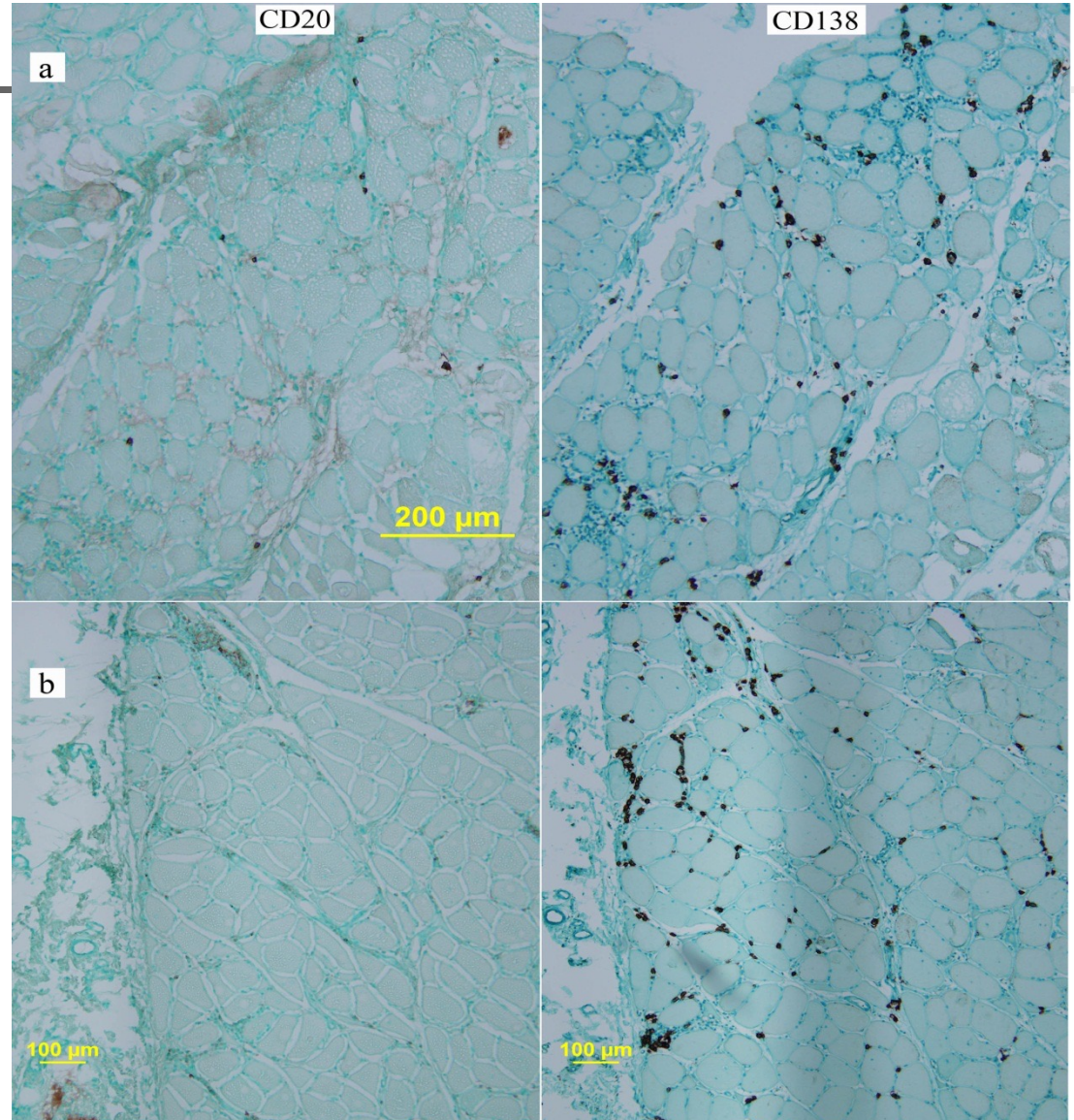
Emerin in IBM

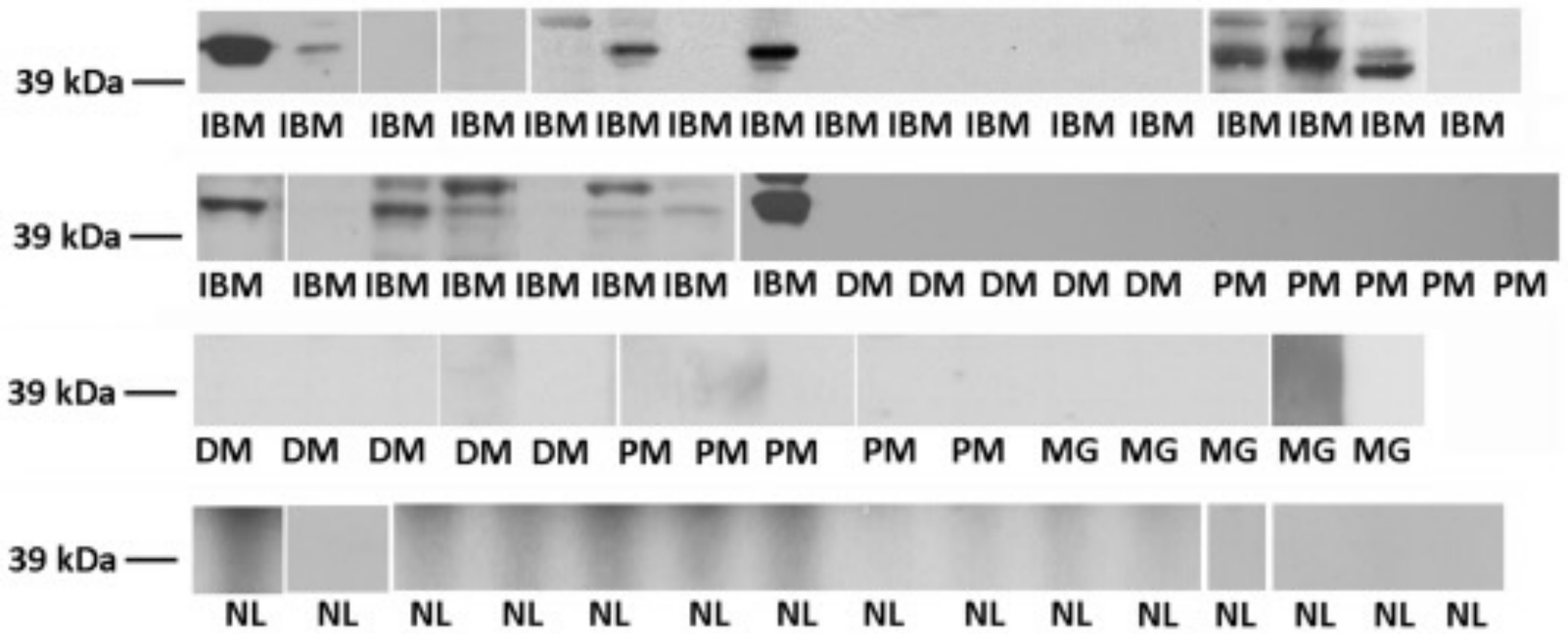


Inflammatory Cells in IBM



Plasma Cells In IBM





Salajegheh M, et al. Autoantibodies against a 43 KDa Muscle Protein in Inclusion Body Myositis. PLoS One. 2011;6(5):e20266.

13/25 IBM patients had serum antibodies vs none of disease or healthy controls

IBM antibodies

- Helma Pluk, et al. Autoantibodies to cytosolic 5’-nucleotidase IA in inclusion body myositis. Ann Neurol 2013;73:397-407
- H Benjamin Larman, et al. Cytosolic 5’-nucleotidase 1a autoimmunity in sporadic inclusion body myositis. Ann Neurol 2013;73:408-418

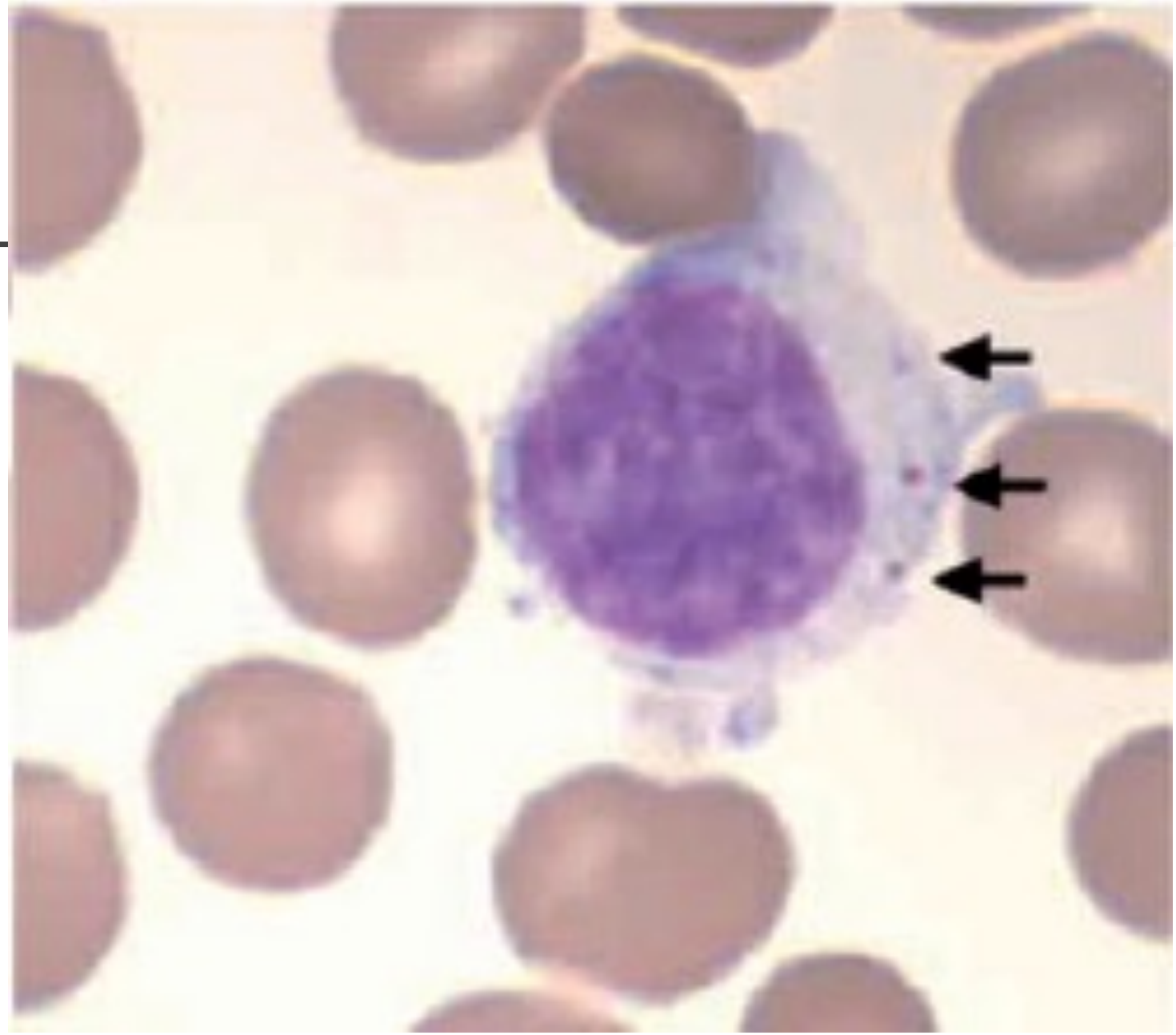
Brain Advance Access published February 26, 2016

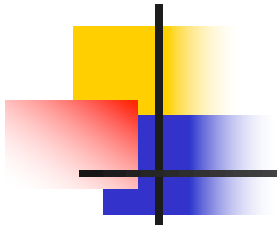
doi:10.1093/brain/aww024 BRAIN 2016: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Association of inclusion body myositis with T cell large granular lymphocytic leukaemia

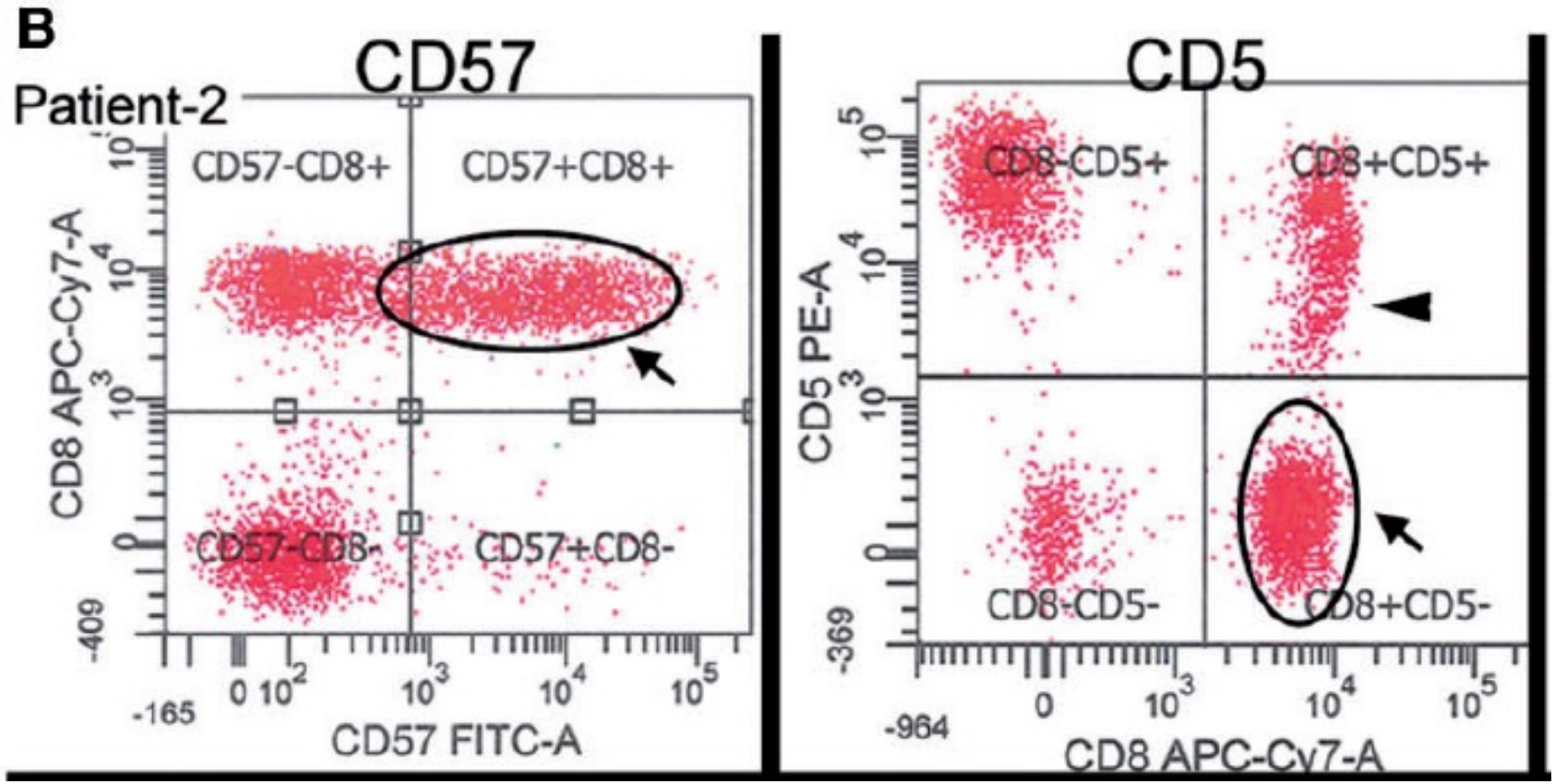
Steven A. Greenberg,[1,2] Jack L. Pinkus,[1] Anthony A. Amato,[1] Thomas Kristensen[3] and David M. Dorfman[4]





Blood biomarkers of IBM and LGL expansions: reduced CD4/CD8 ratios, expanded CD8 counts and lymphocytosis

CD57+/CD8+ and CD8+/CD5-



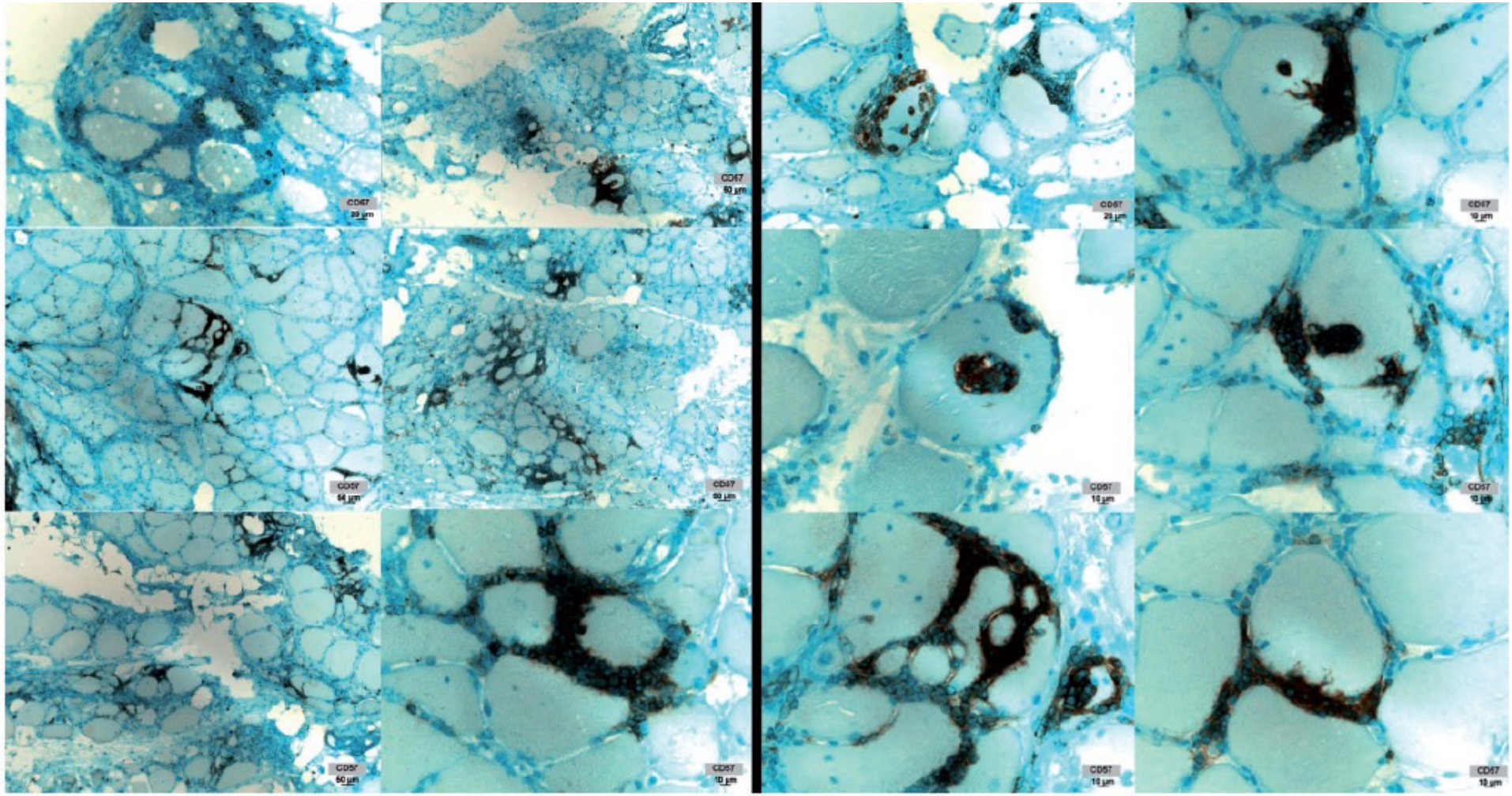


Figure 6 IBM muscle CD57+ cell infiltration. (**A**) Dense T cell infiltrates containing CD57+ cells. (**B**) Myofibre invasion by CD57+ cells. Images from six patients shown. With permission, Inclusion Body Myositis Foundation.

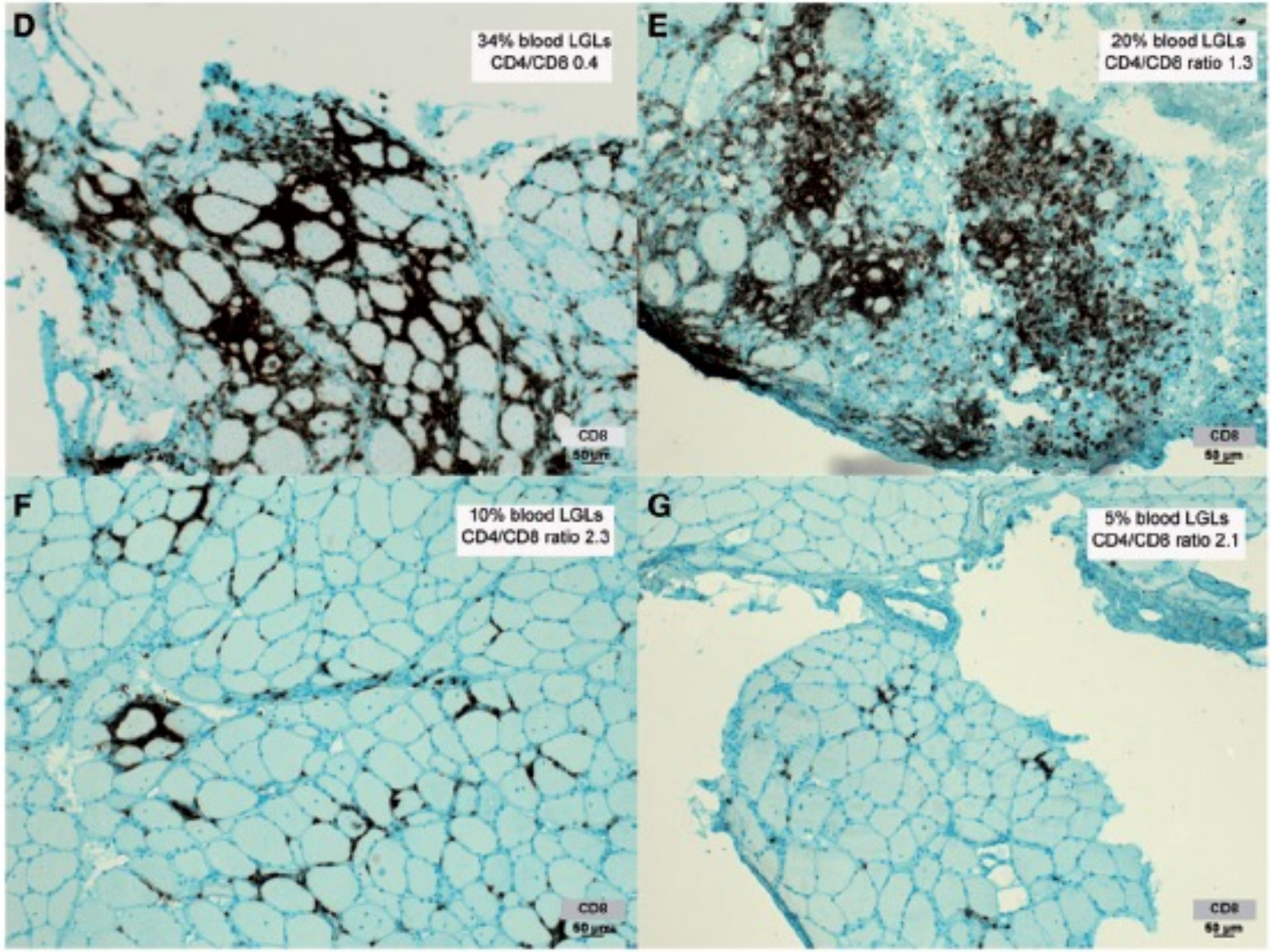
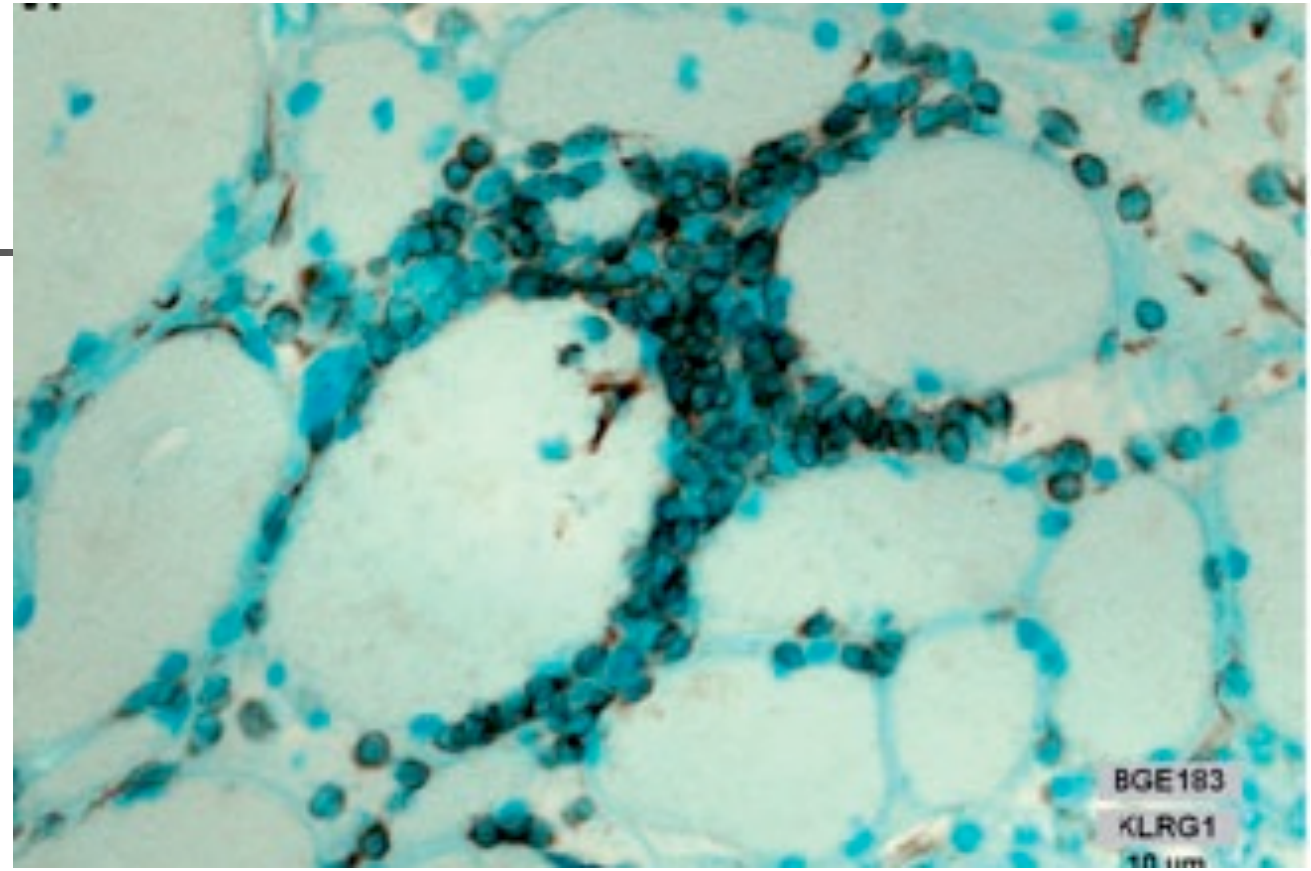


Figure 7 Blood LGL expansions and reduced CD4/CD8 ratios are associated with muscle CD8 and CD57 inflammatory grade. (**A–C**) Increased numbers of muscle CD8+ cells and CD57+ cells is correlated with increased numbers of CD8+ CD57+ blood LGLs and reduced CD4/CD8 ratios. (**D–G**) CD8 immunohistochemistry of muscle from four patients (**D**, Patient 2; **E**, Patient 21; **F**, Patient 30, **G**, Patient 38) illustrates relationships between blood LGL and muscle CD8 expansions. With permission, Inclusion Body Myositis Foundation.



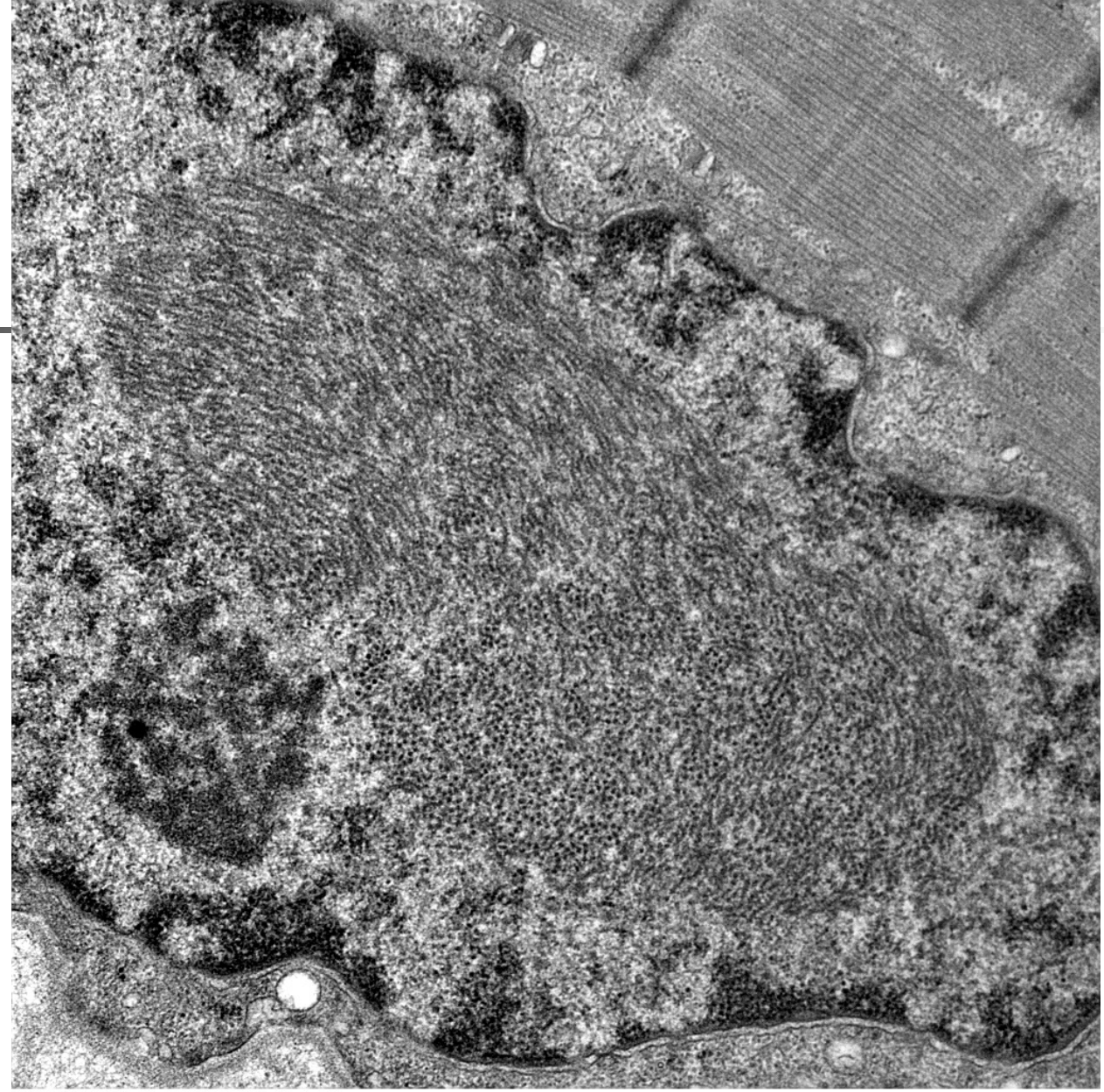
Killer cell lectin-like receptor G1 (KLRG1) Expression on Invading T cells

Highly differentiated cytotoxic T cells in inclusion body myositis.

Greenberg SA, Pinkus JL, Kong SW, Baecher-Allan C, Amato AA, Dorfman DM. Brain 2019;142:2590-2604

Killer cell lectin-like receptor G1 (KLRG1)

- KLRG1 is a marker of this population of cells and identified on invading T cells in IBM muscle biopsies and in blood
- KLRG1 expression in CD8+ T cells is associated with increased with T cell differentiation
- Cells have potent cytokine (e.g., IFN-gamma) secreting and cytotoxic capacities
- Resistant to corticosteroids and apoptosis
- Minimally expressed on regulatory T cells
- Thus, a monoclonal antibody targeting KLRG1 may deplete the cytotoxic T cells that infiltrate IBM muscle without compromising the ability of regulatory T cells to suppress autoimmunity
- A Phase II/III Study of ABC008 in Adult Patients With Inclusion Body Myositis (IBM) ClinicalTrials.gov Identifier: NCT05721573 (**Disclosure: I was on Medical Advisory Board for Abcuro helping plan the study and am site PI at BWH**)



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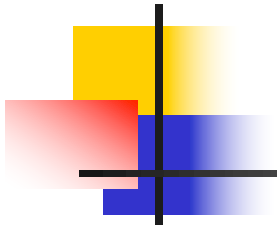


- Karpati initially reported the abnormal accumulation of a DNA/RNA binding protein in sarcoplasm of IBM muscle fibers
- Abnormal accumulation DNA/RNA binding proteins in cytoplasm of neurons have been reported in sporadic ALS, non-SOD fALS, and some FTDs

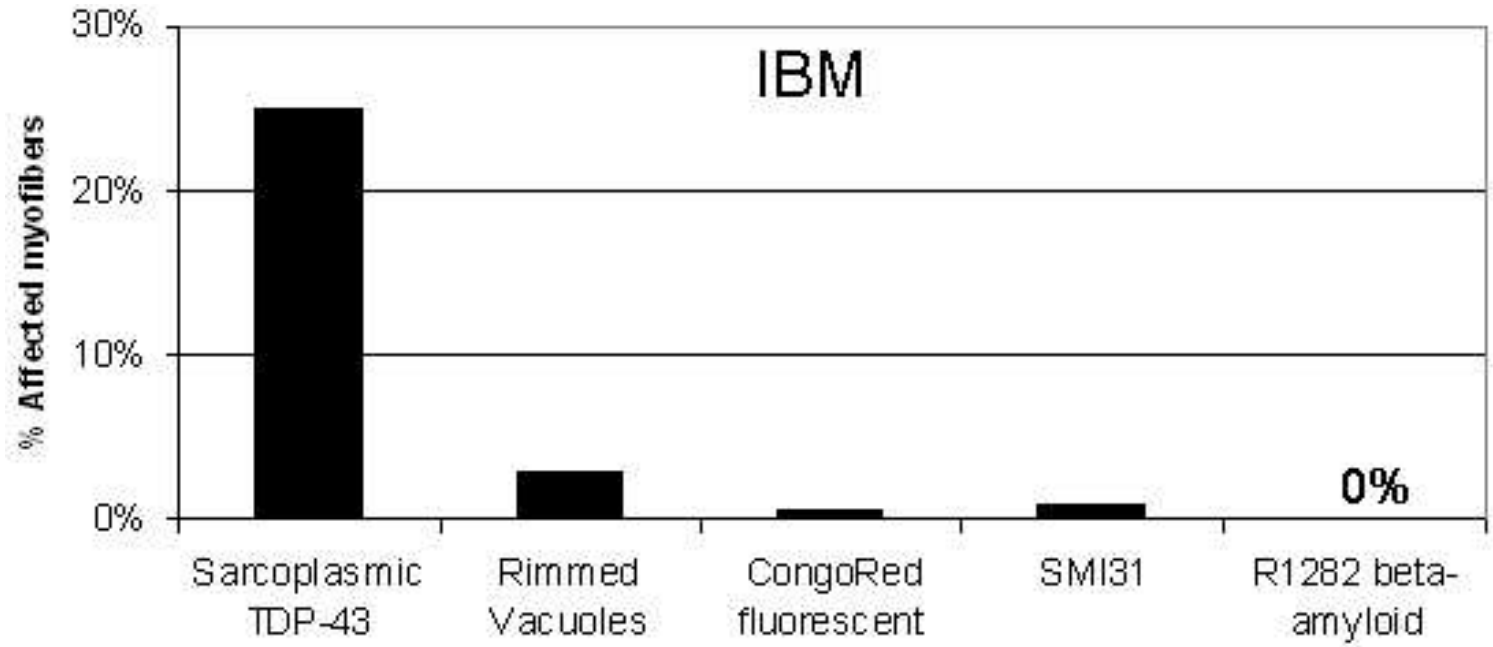
ABSTRACT: The nucleic acid binding protein TDP-43 was recently identified in normal myonuclei and in the sarcoplasm of inclusion body myositis (IBM) muscle. Here we found TDP-43 sarcoplasmic immunoreactivity in 23% of IBM myofibers, while other reported IBM biomarkers were less frequent, with rimmed vacuoles in 2.8%, fluorescent Congo red material in 0.57%, SMI-31 immunoreactivity in 0.83%, and focal R1282 beta-amyloid immunoreactivity in 0.00% of myofibers. The presence of as little as >1% of myofibers with nonnuclear sarcoplasmic TDP-43 was highly sensitive (91%) and specific (100%) to IBM among 50 inflammatory myopathy patient samples, although some patients with hereditary inclusion body myopathies and myofibrillar myopathy also had sarcoplasmic TDP-43. TDP-43 mutations were sought, and none were identified. TDP-43 could be one of many nucleic acid binding proteins that are abnormally present in IBM sarcoplasm. They could potentially interfere with the normal function of extranuclear RNAs that maintain myofiber protein production.

Muscle Nerve **40:** 19–31, 2009

SARCOPLASMIC REDISTRIBUTION OF NUCLEAR TDP-43 IN INCLUSION BODY MYOSITIS

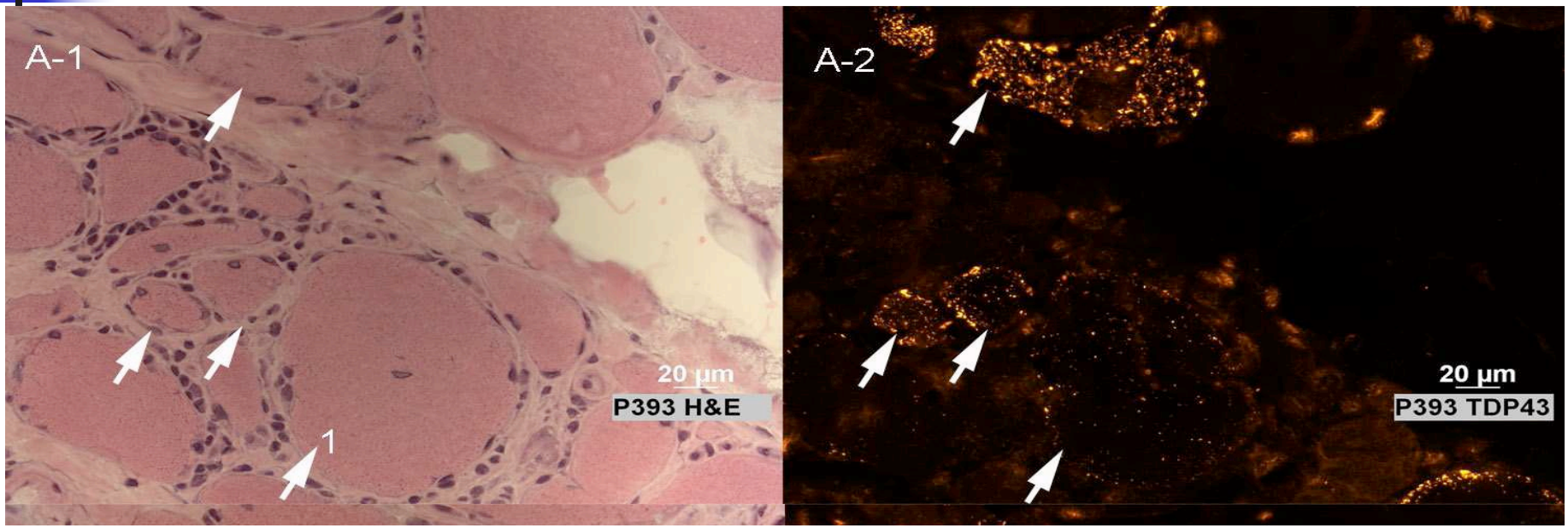
MOHAMMAD SALAJEGHEH, MD,[1,2] JACK L. PINKUS, PhD,[1,2]
J. PAUL TAYLOR, MD, PhD,[3] ANTHONY A. AMATO, MD,[1] REMEDIOS NAZARENO, BS,[1,2]
ROBERT H. BALOH, MD, PhD,[4] and STEVEN A. GREENBERG, MD[1,2]

TDP-43 inclusions in IBM



- Salajegheh et al, Muscle Nerve 2009; 40:19-31

TDP-43 inclusions in IBM



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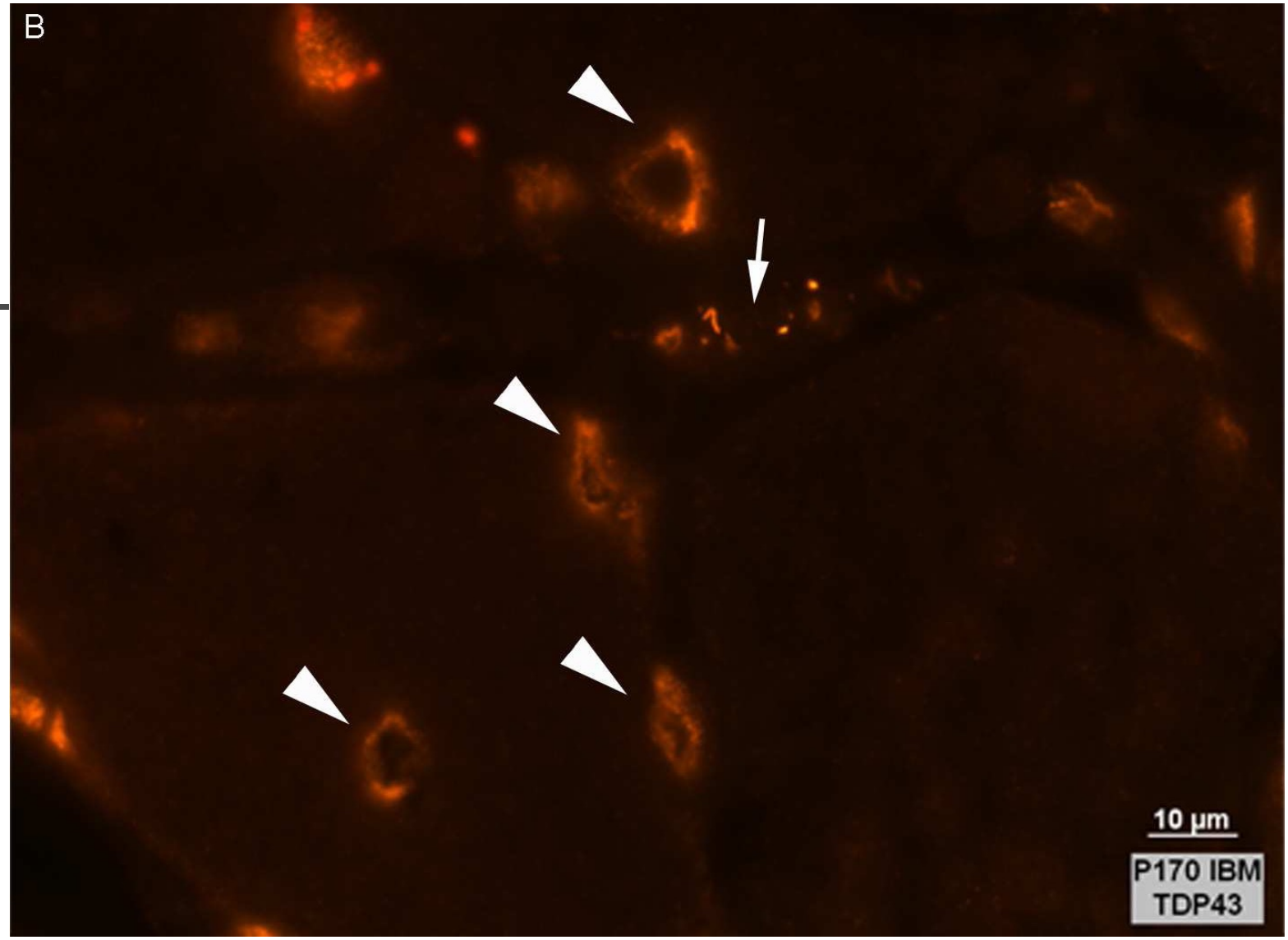
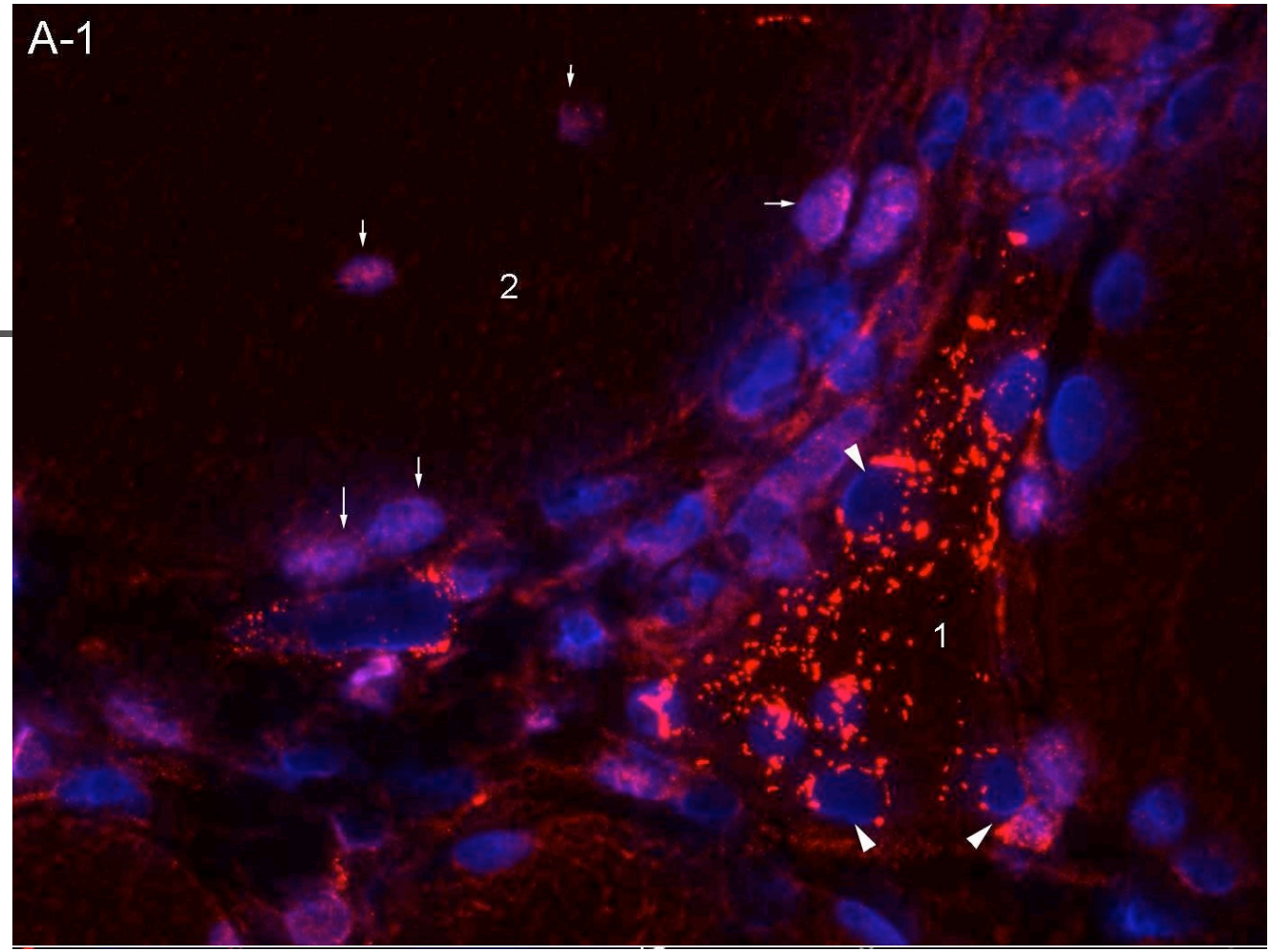


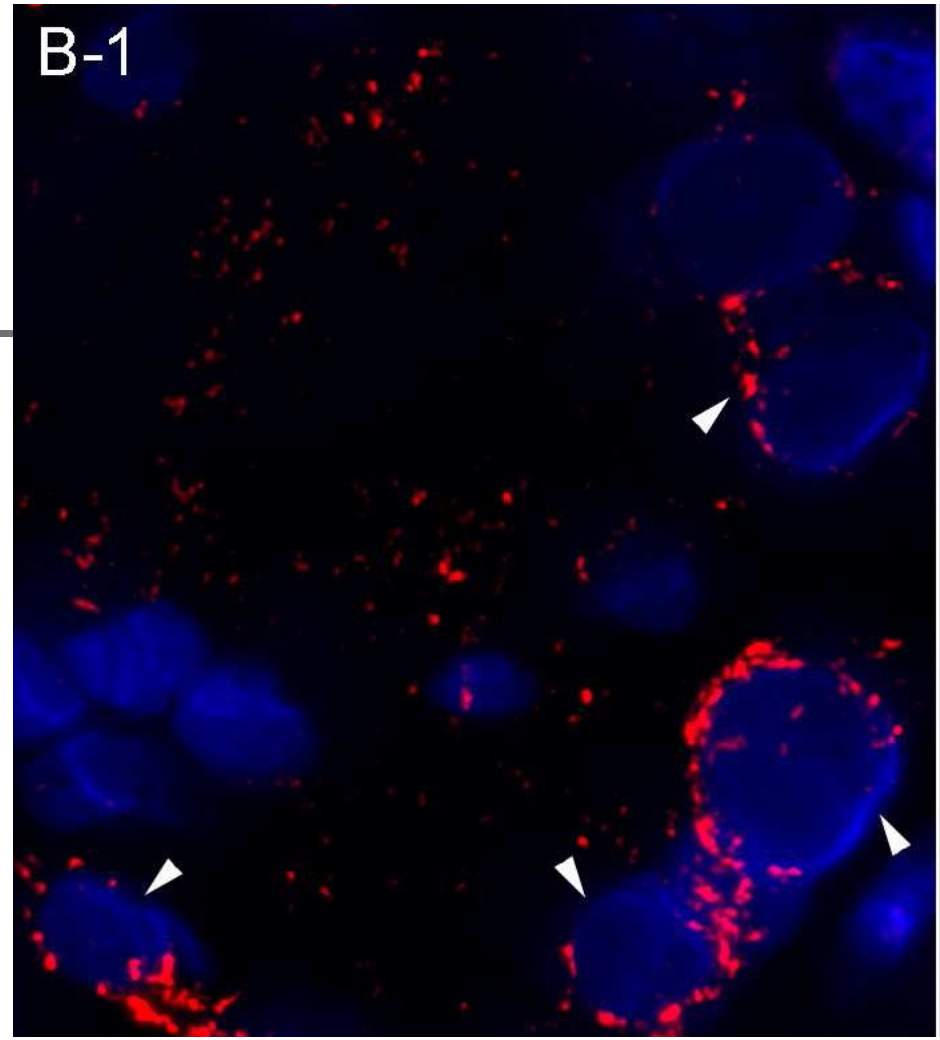
- TDP-43 lined vacuoles (arrowheads) and a myofiber with sarcoplasmic non-nuclear TDP-43 (arrow)

  From: Salajegheh et al, Muscle Nerve 2009; 40:19-31



- Myofibers with sarcoplasmic TDP-43 typically show absent nuclear TDP-43 staining. (A1-3) A triangular fiber #1 shows abundant sarcoplasmic linear TDP-43 accumulation. Nuclei (marked with arrowheads) are devoid of TDP-43. In contrast, the adjacent rounded myofiber #2 lacks sarcoplasmic accumulation and has normal TDP-43 nuclear immunoreactivity

Salajegheh et al, Muscle Nerve 2009; 40:19-31



- TDP-43 sometimes clusters around myonuclei (arrowheads) in addition to multifocally within the sarcoplasm
  - Salajegheh et al, Muscle Nerve 2009; 40:19-31

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MUSCLE DISEASE

Loss of TDP-43 function and rimmed vacuoles persist after T cell depletion in a xenograft model of sporadic inclusion body myositis

Kyla A. Britson[1], Jonathan P. Ling[2], Kerstin E. Braunstein[2], Janelle M. Montagne[2], Jenna M. Kastenschmidt[3], Andrew Wilson[1], Chiseko Ikenaga[1], William Tsao[1], Iago Pinal-Fernandez[1,4], Katelyn A. Russell[1], Nicole Reed[1], Tahseen Mozaffar[5], Kathryn R. Wagner[1,6], Lyle W. Ostrow[1], Andrea M. Corse[1], Andrew L. Mammen[1,4], S. Armando Villalta[3], H. Benjamin Larman[2], Philip C. Wong[2,7]*, Thomas E. Lloyd[1,7]*

Summary of Findings

- IBM muscle biopsies display nuclear clearance and cytoplasmic aggregation of TDP-43 in muscle cells that is associated with causes aberrant RNA splicing.
- Of 119 muscle biopsies tested, RT-PCR–mediated detection of cryptic exon inclusion was able to diagnose IBM with 84% sensitivity and 99% specificity
- Xenograft model by transplanting human IBM muscle into the hindlimb of immunodeficient mice
- Xenografts from subjects with IBM displayed both inflammatory and degenerative features of the disease:
  - invasion by human, oligoclonal CD8+ T cells and exhibited MHC-I up-regulation, rimmed vacuoles, mitochondrial pathology, p62-positive inclusions, and nuclear clearance and cytoplasmic aggregation of TDP-43, associated with cryptic exon inclusion.
- Reduction of human T cells within IBM xenografts by treating mice intraperitoneally with anti-CD3 (OKT3) suppressed MHC-I up-regulation. However, rimmed vacuoles and loss of TDP-43 function persisted
- These data suggest that T cell depletion does not alter muscle degenerative pathology in

THERAPY

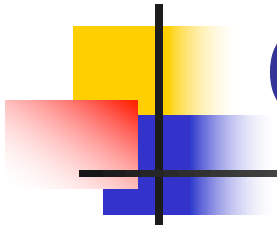
- Immunotherapies to date (corticosteroids, immunosuppressive agents, IVIG) have not been show to have any benefit in IBM, but rather are associated with side effects
- Mainstay of treatment is Physical, Occupational, Speech/Swallowing therapy
- Esophageal dilatation, cricopharyngeal myotomy, Botox injection

Other Ongoing Trials

- A Double-Blind Randomised Controlled Trial (dbRCT) Phase III Trial Investigating the Effect of Sirolimus on Disease Progression in Patients With Inclusion Body Myositis (IBM) as Measured by the IBM Functional Rating Scale (IBM-FRS) **NCT04789070**
- Hypothesis is that sirolimus, (Rapamycin) which is currently used in organ transplantation and works by blocking the activity of T effector cells but preserving T regulatory cells, as well as by inducing autophagy (protein degradation), will be effective in IBM to slow or stabilize disease progression, helping to maintain patient function and independence
- **Disclosure: I am a member of the Data Safety and Monitoring Board for this study**

INCLUSION BODY MYOSITIS

- Is IBM a primary degenerative disease in which inflammatory cell infiltrate and autoantibodies are secondary and related to cryptic exons and expression of novel antigens?
  - If inflammatory response is "secondary" does it play a role in the progressive weakness?
  - Will ANY mode of immunotherapy help at all or is all the muscle destruction and weakness related to the primary degenerative disease?
  - What is the cause of this degenerative disorder and how can we treat?
- Does IBM start out as a primary autoimmune disorder and the degenerative features are secondary
  - What would be mechanism of this?
  - Does the secondary cascade of alternative RNA splicing, accumulation of abnormal proteins, and other degenerative features contribute to the progressive destruction of muscle?
  - Does this cascade proceed even if inflammation is halted as predicted by Lloyd et al's animal model or might early treatment prevent secondary degeneration before muscle satellite cells are irreparably damaged?
  - Might secondary degenerative features persist but not be associated with clinical weakness



Other QUESTIONS?

- I know that have plenty