IDIOPATHIC INFLAMMATORY MYOPATHIES

ANTHONY A. AMATO, MD

Brigham and Women's Hospital
Distinguished Chair in Neurology

Chief, Neuromuscular Division

Professor of Neurology

Harvard Medical School

Amato Disclosures

Relevant Financial Relationship

Medical Advisory Board for Biogen, Novartis, Acceleron, Regeneron, Akashi, Alexion

Learning Objectives

- Better understand the clinical, laboratory, and histopathology of dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, and inclusion body myositis
- Update advances in the pathogenesis of dermatomyositis, polymyositis, immune-mediated necrotizing myopathy, and inclusion body myositis

IDIOPATHIC INFLAMMATORY MYOPATHIES

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

DERMATOMYOSITIS

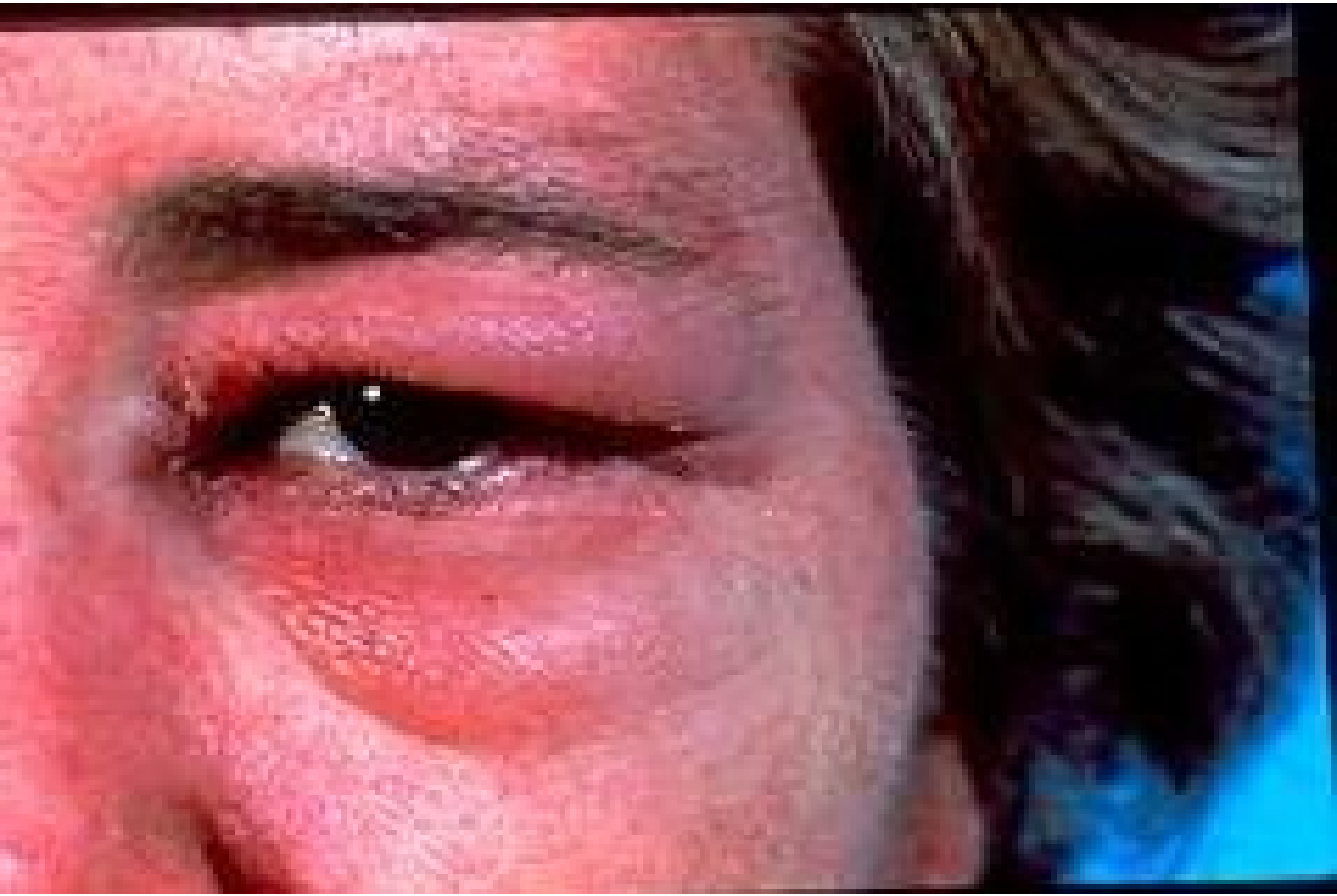
- Clinical Features
  - presents at any age (peak childhood onset between 5 and 14 years of age)
  - women affected more commonly than men
  - onset of weakness usually subacute (over several weeks)
  - affects proximal muscles greater than distal muscles; symmetric

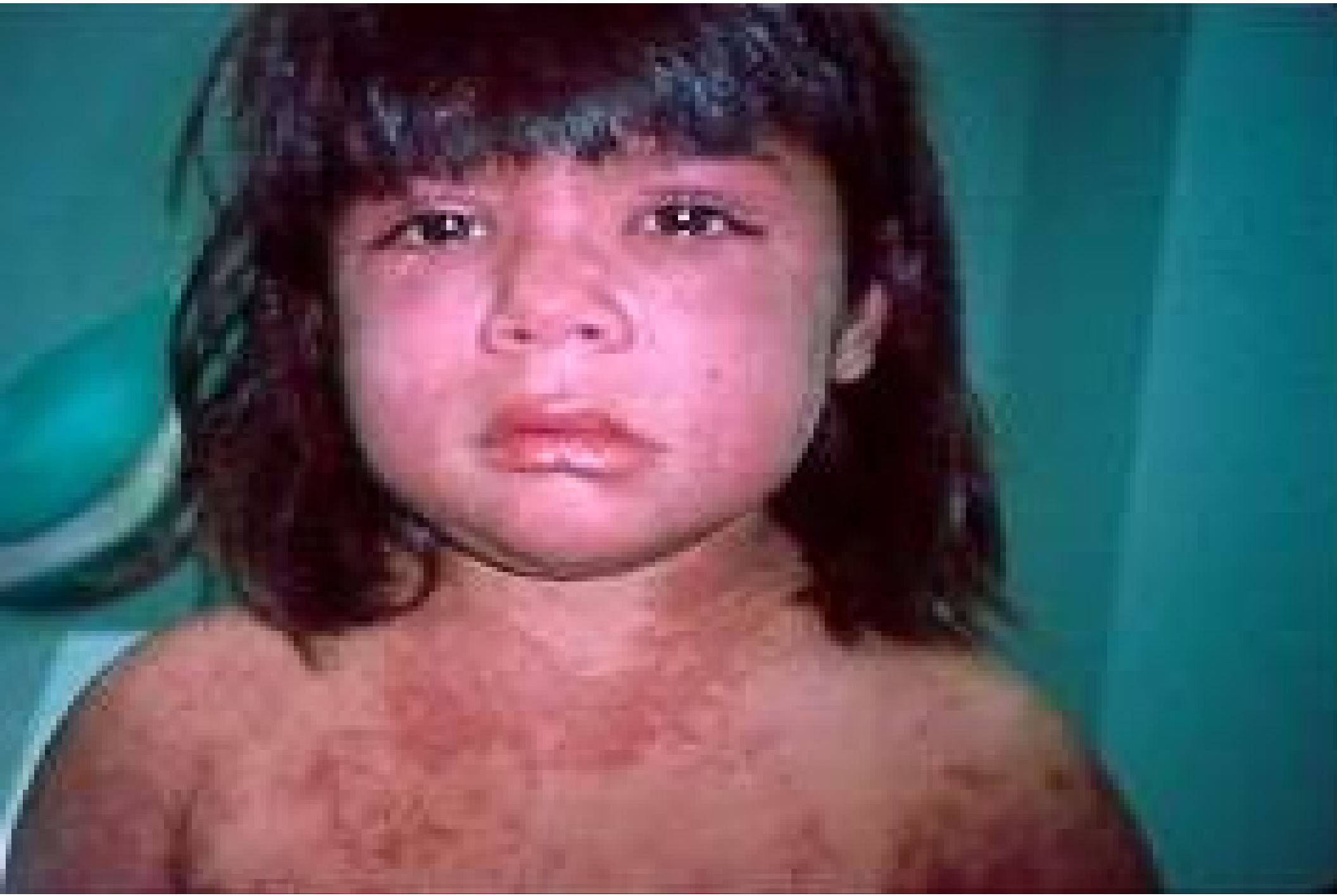
DERMATOMYOSITIS

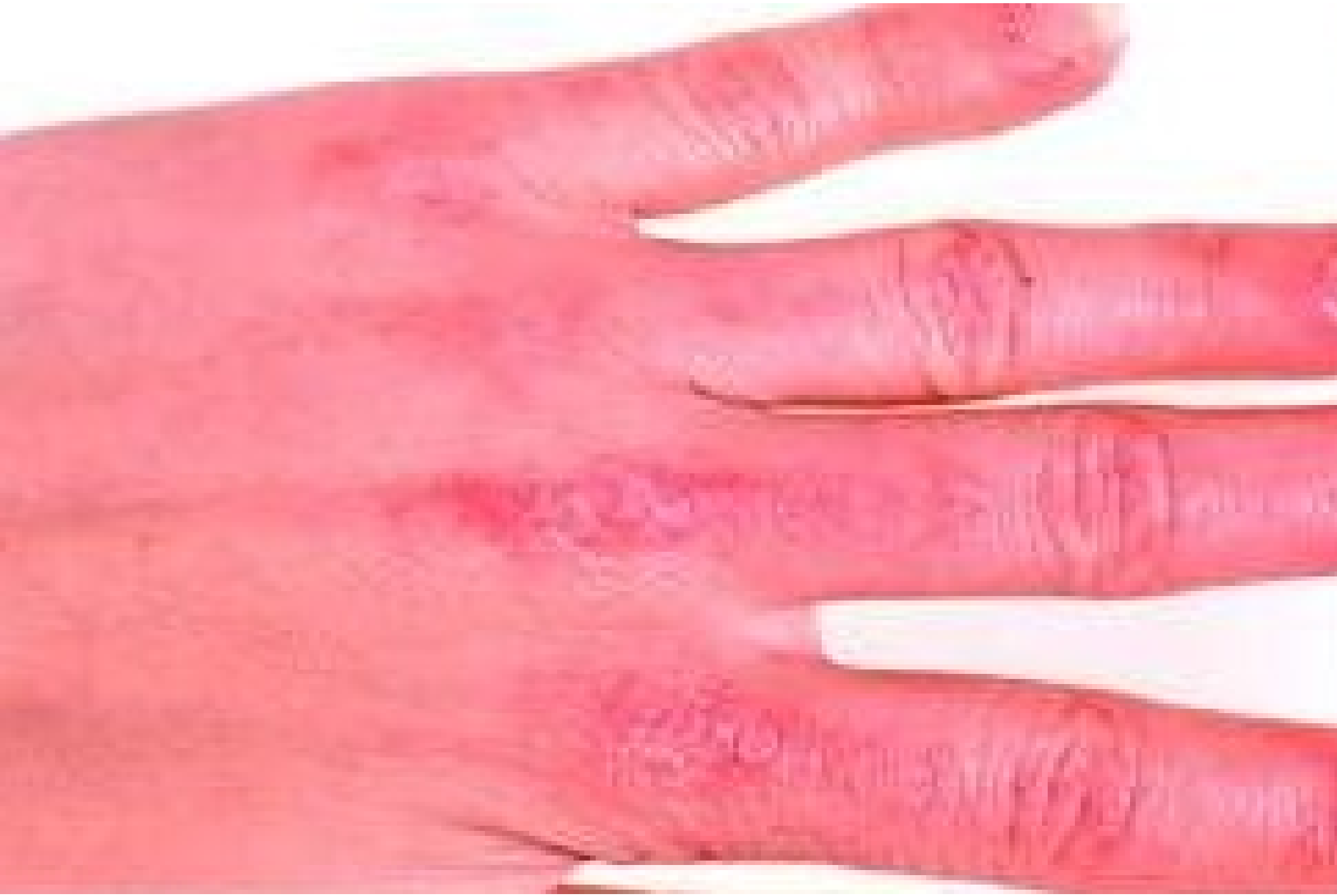
- Clinical Features
  - Characteristic rash may accompany, precede, or shortly follow the onset of muscle weakness
    - heliotrope
    - shawl sign
    - V-sign
    - holster sign
    - extensor surfaces of the knees, malleoli, elbows
    - Gottron sign or papules
    - periungual telangectasias, hemorrhage, thrombi

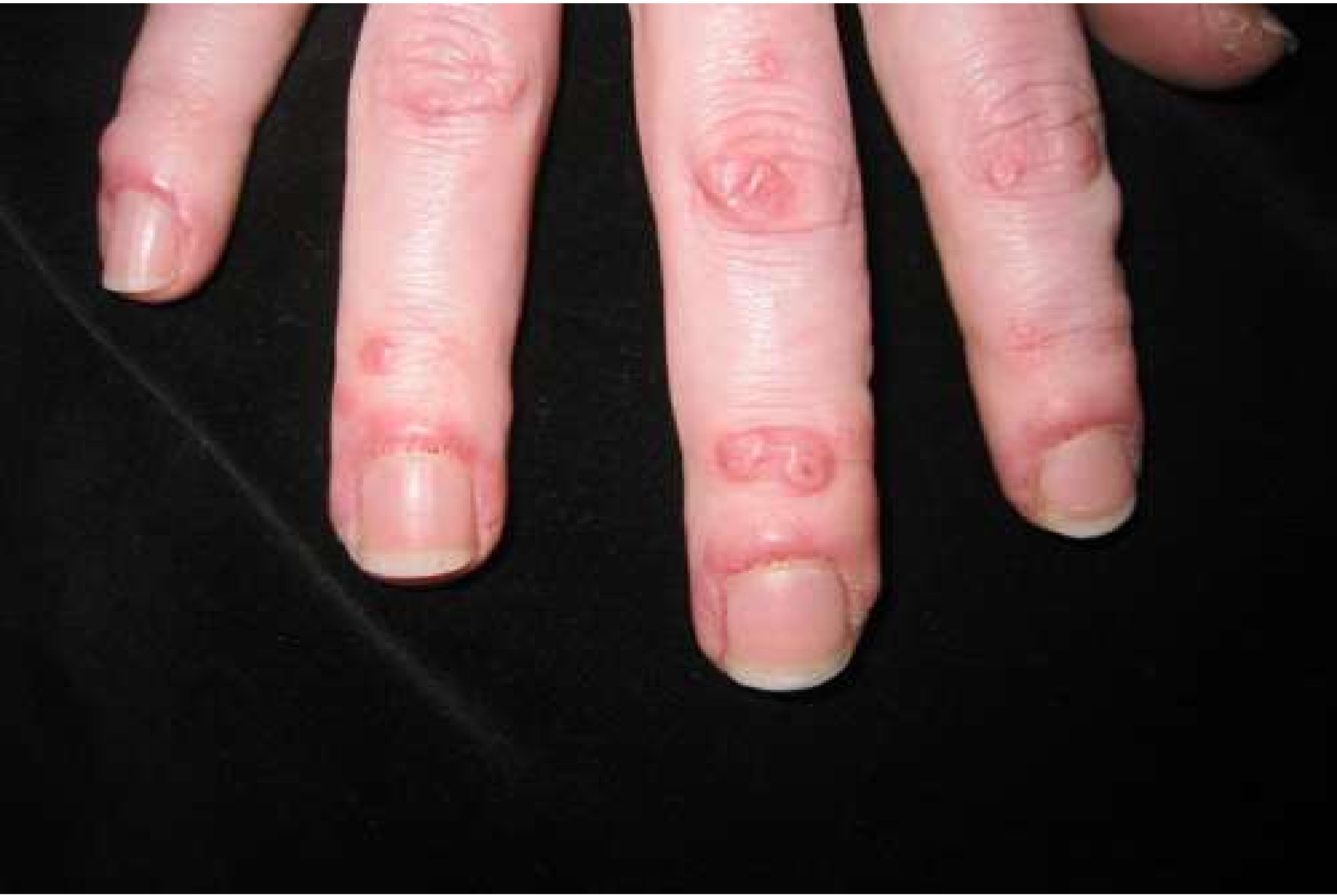
DERMATOMYOSITIS

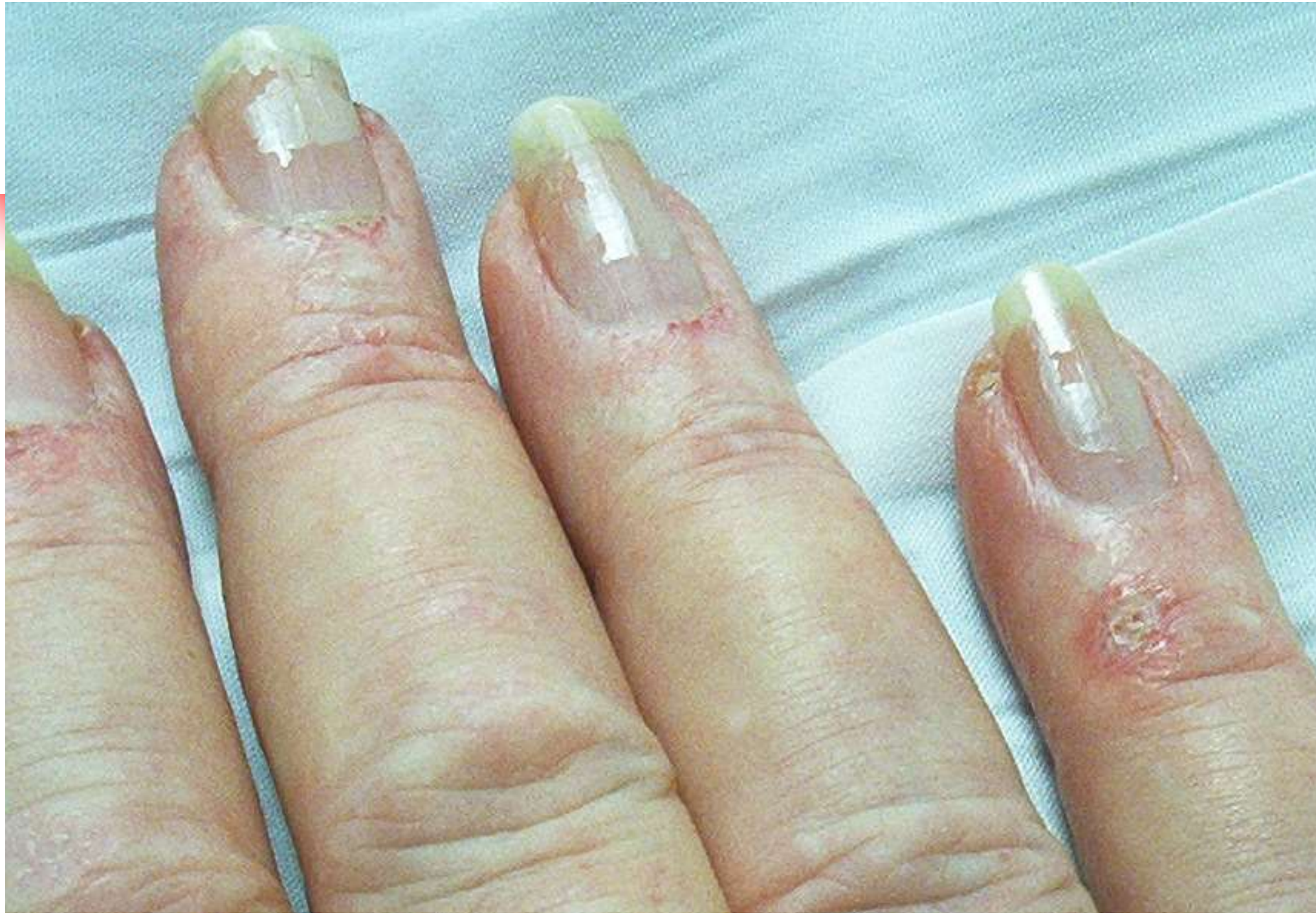
- Amyopathic dermatomyositis
- Hypomyopathic dermatomyositis





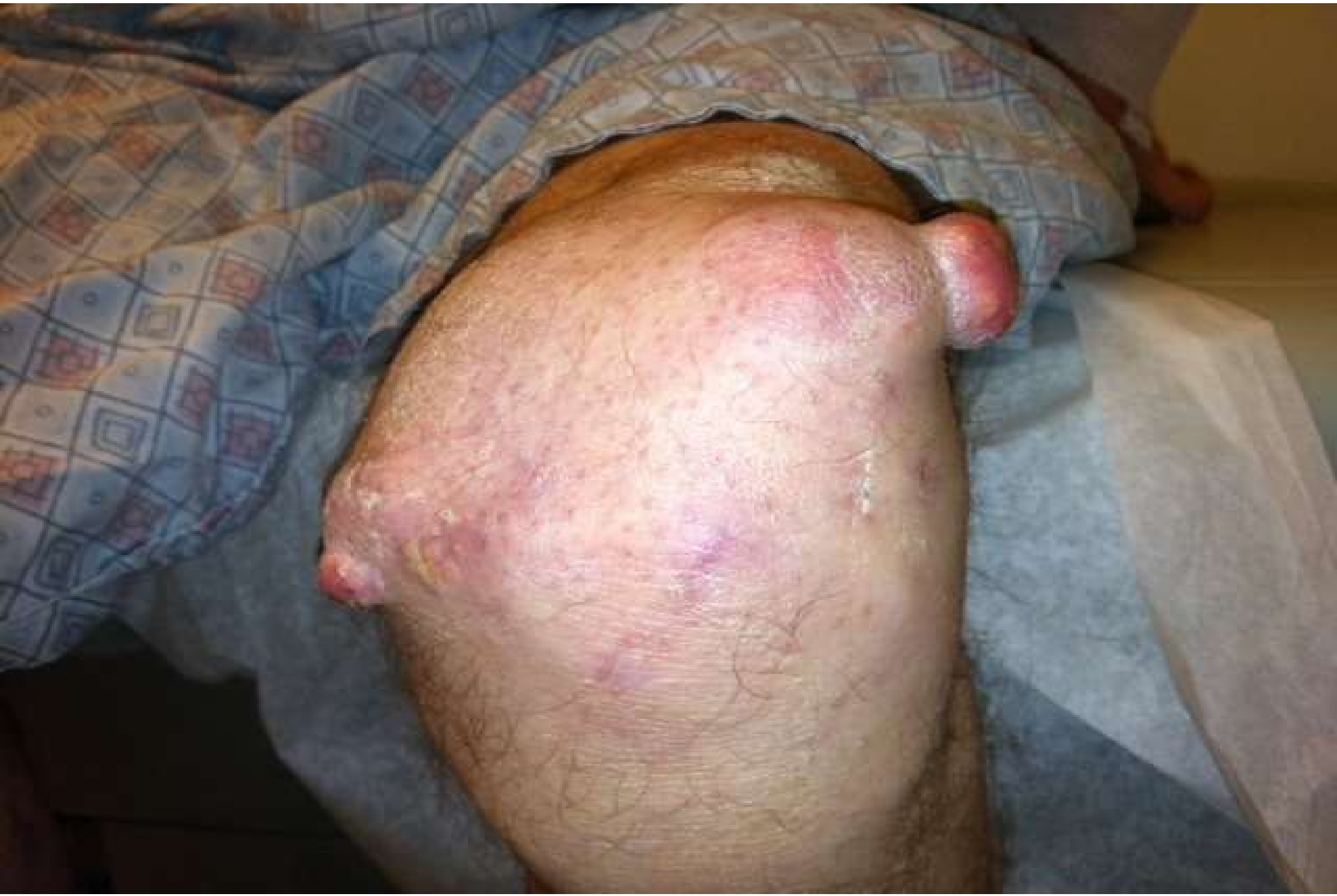


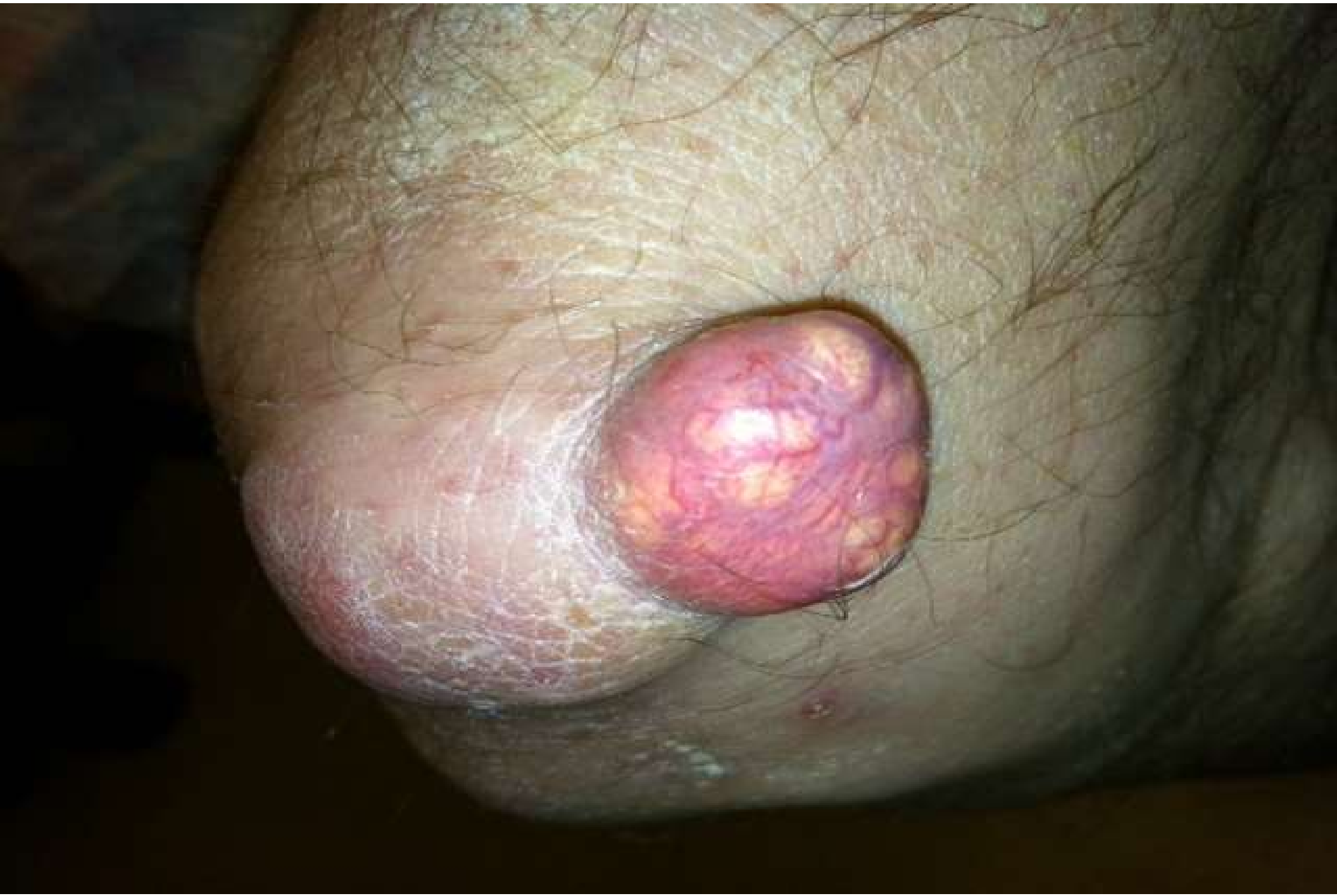




DERMATOMYOSITIS

- Clinical Features
  - calcifications develop in subcutaneous tissue over pressure points (buttocks, knees, elbows)
    - associated with inadequate prior treatment
    - difficult to treat calcinosis once developed





DERMATOMYOSITIS

- Oropharyngeal / Gastrointestinal
  - Dysphagia occurs in 30 %
  - chewing difficulty secondary to masseter weakness
  - dysarthria
  - GI ulceration, hemorrhage secondary to vasculopathy (more common in children)

DERMATOMYOSITIS

- Cardiac
  - overt clinical symptoms are uncommon
  - pericarditis, myocarditis, congestive heart failure can develop
  - Echocardiogram / MRI may reveal wall motion abnormalities
  - EKG abnormalities including conduction defects and arrhythmias occur more frequently

DERMATOMYOSITIS

- Aspiration pneumonia secondary to oropharyngeal and esophageal weakness
- Ventilatory muscle weakness (rare)
- Interstitial Lung Disease (ILD)
  - 10 % of adult DM (also reported in children)
  - 50 % are associated with antibodies directed against t-histidyl tRNA synthetase (anti-Jo-1 antibody)

DERMATOMYOSITIS

- Joints
  - arthralgias with or without arthritis are a frequent presenting feature
  - arthritis is symmetric and affects large and small joints
  - pain is eased with passive flexion of the limbs which leads to contractures

DERMATOMYOSITIS

- Malignancy
  - increased incidence ranging from 6-45 %
  - most are identified within 2 years of myositis
  - usually over the age of 40 years; M = F
  - presence of malignancy does not correlate with severity of the myositis
  - treatment of the malignancy may improve the myositis

DERMATOMYOSITIS

- Work-up for malignancy should be sign and symptom oriented
- comprehensive history and annual exams
- breast and pelvic exam for women, testicular and rectal exams for men
- CBC, SMA 20, UA, stool for occult blood
- chest x-ray, pelvic U/S or CT, and mammograms
- colonoscopy if > 50 yrs or have GI symptoms

DERMATOMYOSITIS

- Laboratory Features
  - elevated aldolase, myoglobin, AST, ALT, LDH
  - serum creatine kinase (CK) is the most sensitive and specific marker of muscle destruction; CK is elevated in approx 70 % of DM (5-50 times normal)
  - CK levels do not correlate with the severity of muscle weakness

DERMATOMYOSITIS

- Antinuclear antibodies (ANA) detected in 24-60 %; more common in overlap cases
- Myositis-Specific Antibodies (MSA)
  - Useful in predicting response to therapy and prognosis

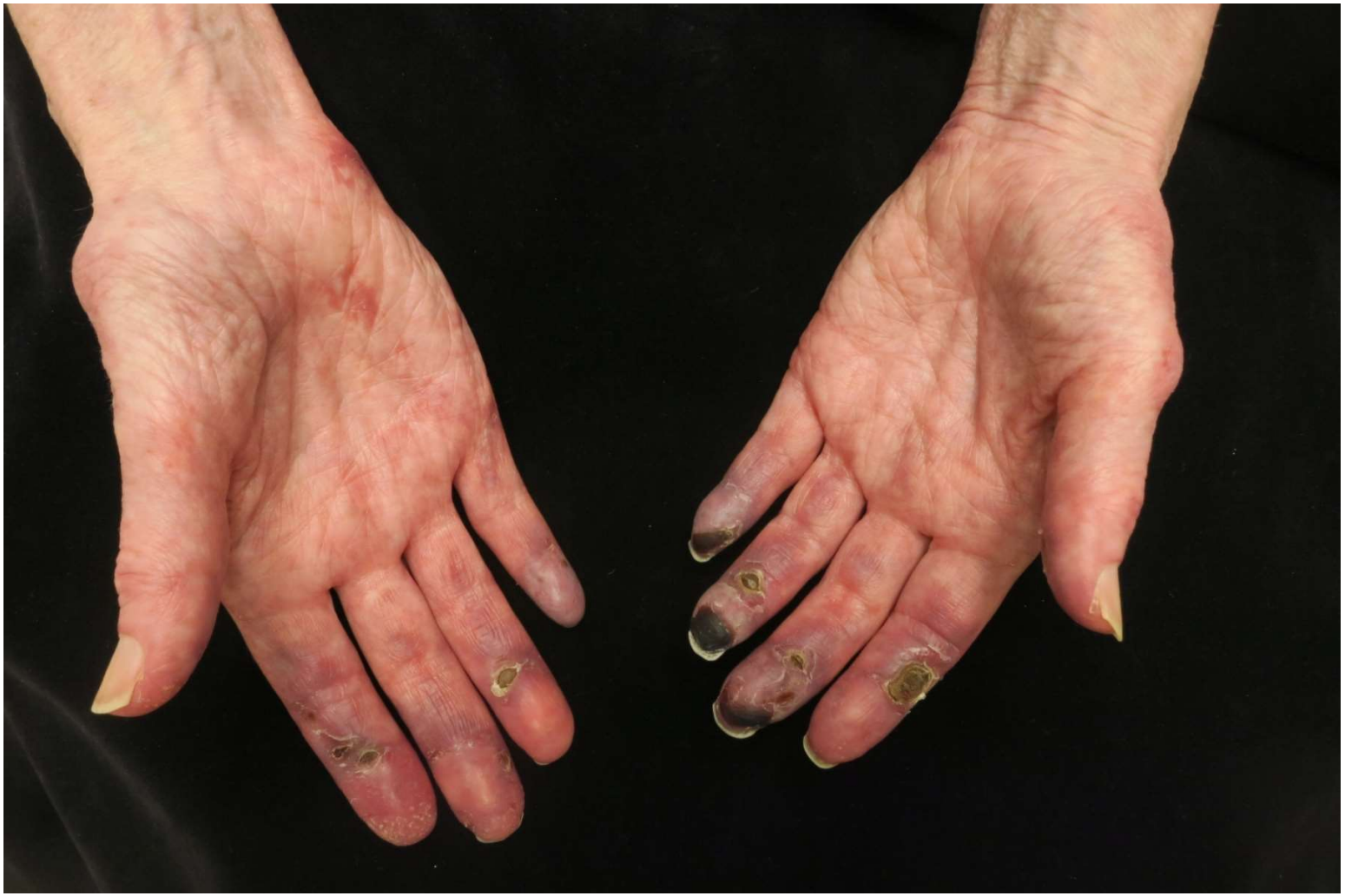
Myositis Specific Antibodies in DM

- Antisynthetase antibodies
  - Jo-1 antibodies is the most common subytpe
  - Demonstrated in as many as 20% of patients with inflammatory myopathy and are associated with ILD (? DM/PM or separate entity)
- Mi-2 antibodies are found in 15–20% of patients with DM
  - Mi-2 is a 240-kD nuclear protein of unknown function
  - The Mi-2 antibodies are typically associated with an acute onset, a florid rash, a good response to therapy, and a favorable prognosis

Myositis Specific Antibodies

- Antibodies directed against melanoma differentiation-associated protein 5 (anti-MDA5), also known as anti–CADM-140 antibodies
  - 10-20 %of DM patients and up to 65% of patients with clinically amyopathic dermatomyositis and are associated with rapidly progressive ILD along with severe skin lesions (including palms) and ulcerations, particularly in Asians
  - Associated with elevated serum ferritin levels

MDA-5



Myositis Specific Antibodies

- Autoantibodies targeting transcriptional intermediary factor 1-γ (TIF1-γ) also known p155 antibodies
  - Found in adult cancer-associated dermatomyositis with an 89% specificity and 70% sensitivity
- Antibodies directed against nuclear matrix protein NXP-2 (also known as MORC3)
  - Approx 17% of patients with DM and are also associated with cancer
  - Higher risk of calcinosis, extensive subcutaneous edema
  - May have prominent finger extensor weakness

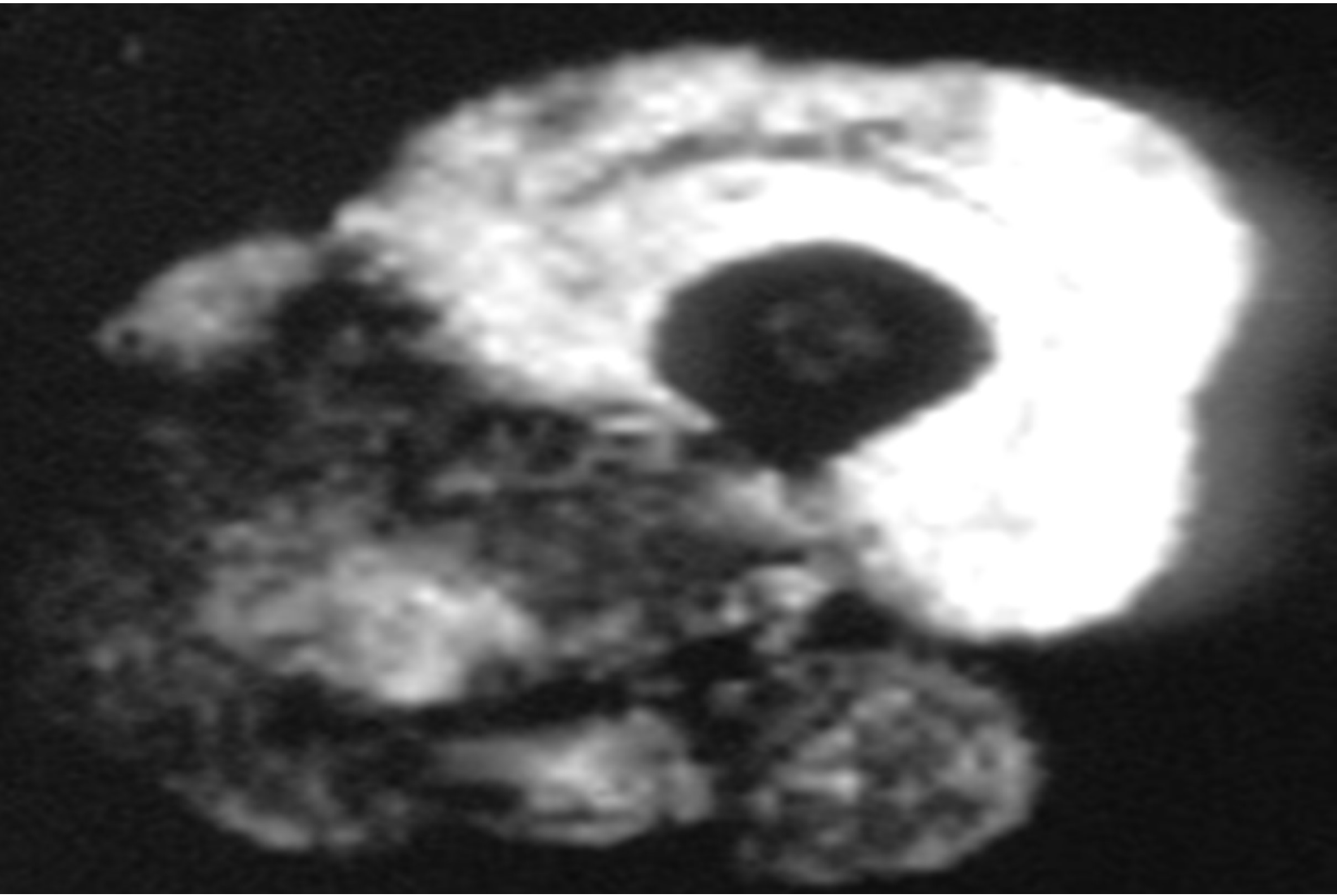
DERMATOMYOSITIS

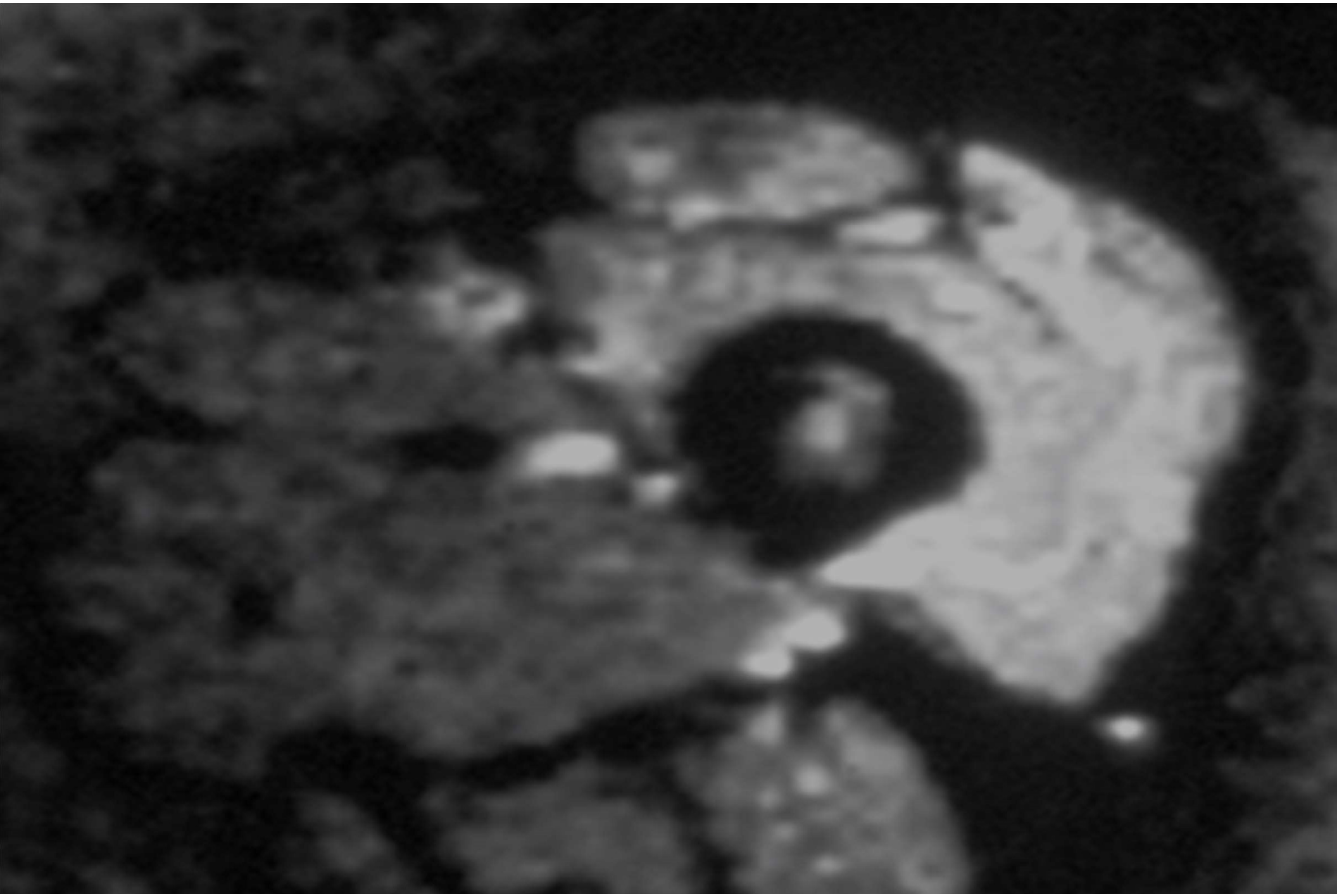
- Pitfalls of the MSAs
  - not studied prospectively with respect to prognostic value
  - not pathogenic
  - may represent an epiphenomena

*__But still may be helpful in classifying the subtypes of inflammatory myopathies__

DERMATOMYOSITIS

- Electromyography
  - triad of (1) increased insertional and spontaneous activity, (2) small polyphasic motor unit potentials, and (3) early recruitment
- Muscle Imaging (MRI and CT)
  - signal abnormalities in affected muscles secondary to inflammation and edema
  - ? utility in guiding muscle biopsy





DERMATOMYOSITIS

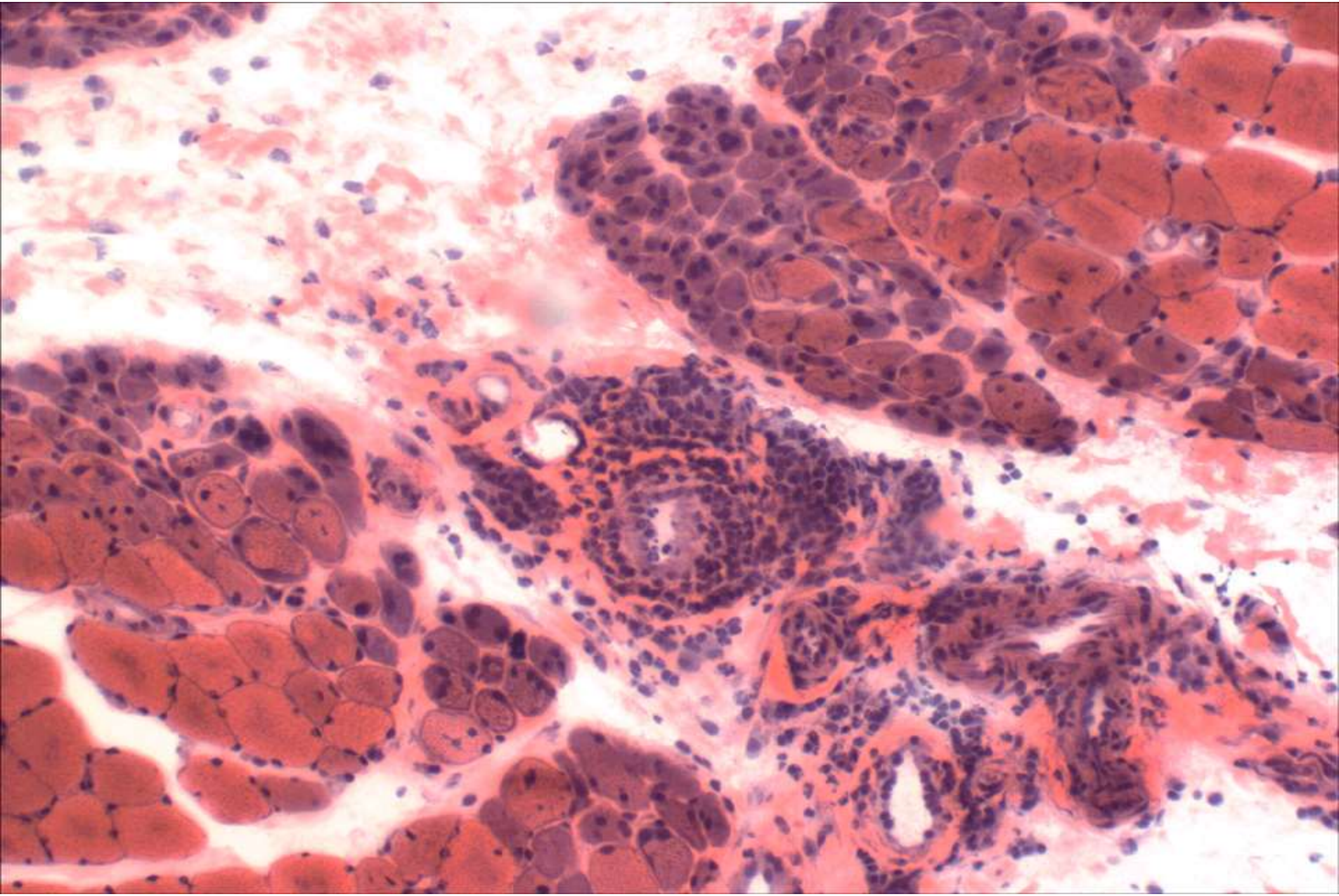
- Muscle Biopsy
  - characteristic feature is perifascicular atrophy
    - small degenerating and regenerating fibers
    - disrupted oxidative enzyme staining
    - microvacuolation
    - ?caused by ischemia? – I DON'T THINK SO
  - scattered necrotic fibers
  - wedged-shaped micro-infarcts

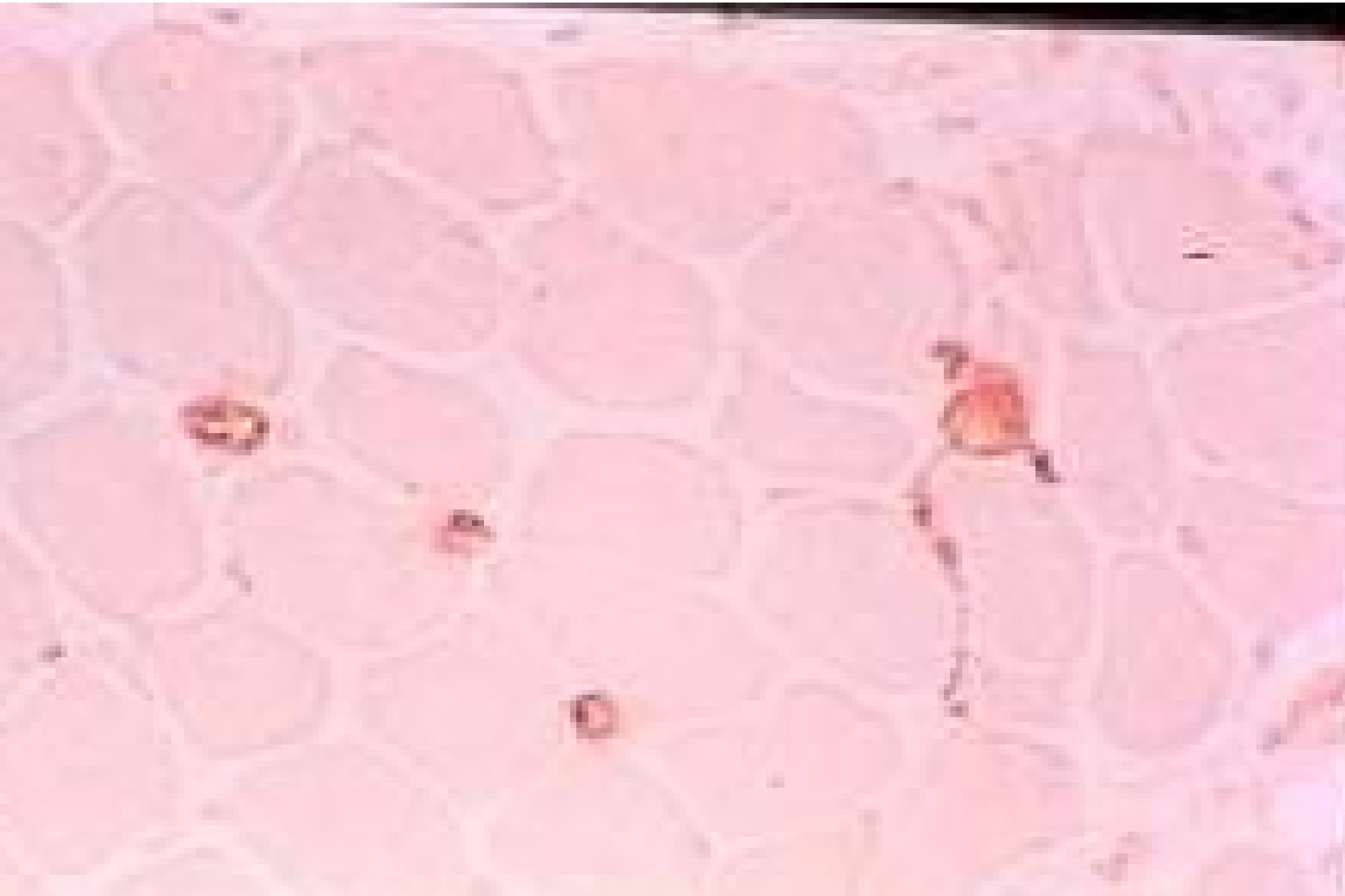
DERMATOMYOSITIS

- Muscle Biopsy
  - Inflammation is perivascular and predominantly located in the perimysium
    - composed of macrophages, B-cells, and CD4+ (dendritic and T-helper) cells
    - no invasion of non-necrotic muscle fibers
  - An early histological feature is a reduction in capillary density (?cause?)

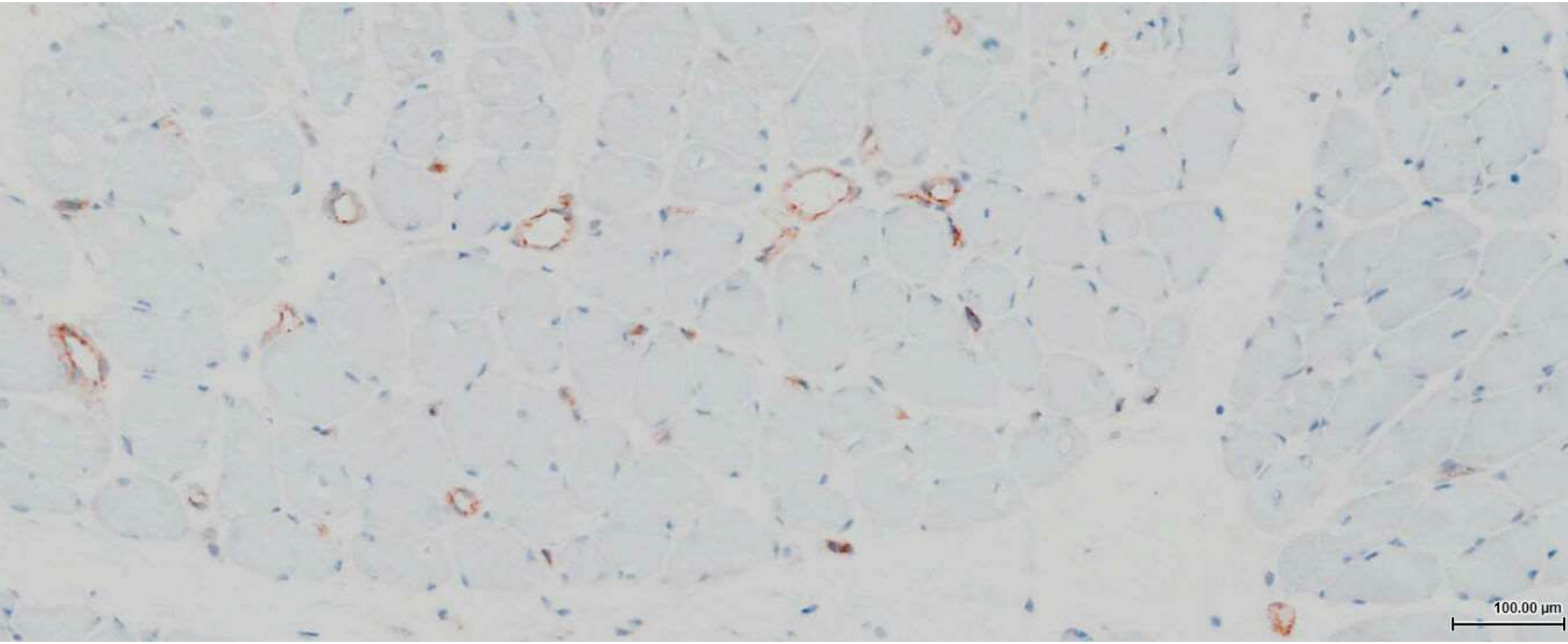
DERMATOMYOSITIS

- C5b-9 or membrane attack complex (MAC) deposition on or around small blood vessels
  - Primary or secondary mechanism?
- C3, C4, IgM and IgG also deposited on or around small blood vessels
- electron microscopy reveals endothelial hyperplasia, microvacuoles, and cytoplasmic inclusions in intramuscular blood vessels
- humoral and EM changes perifascicular atrophy

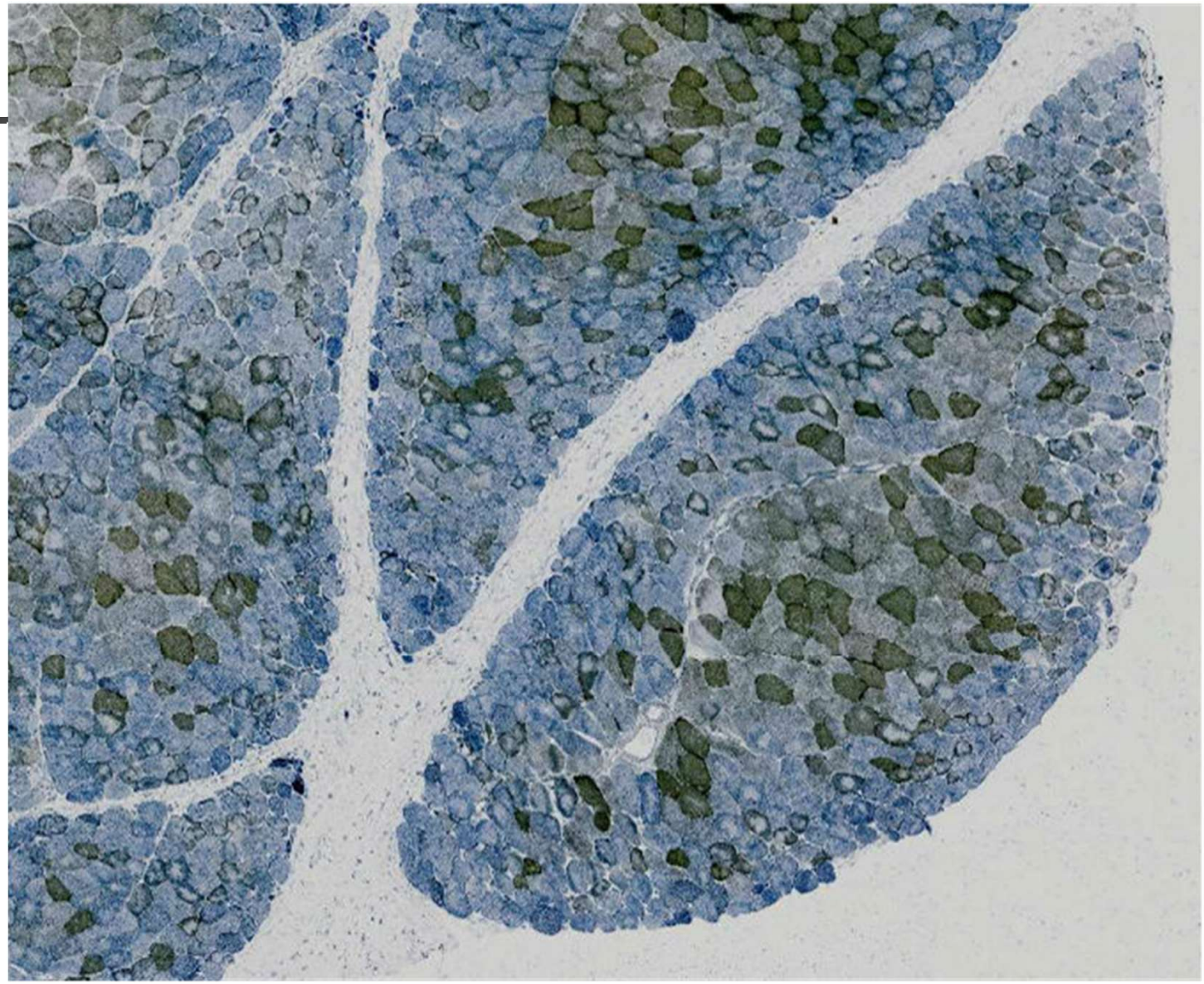




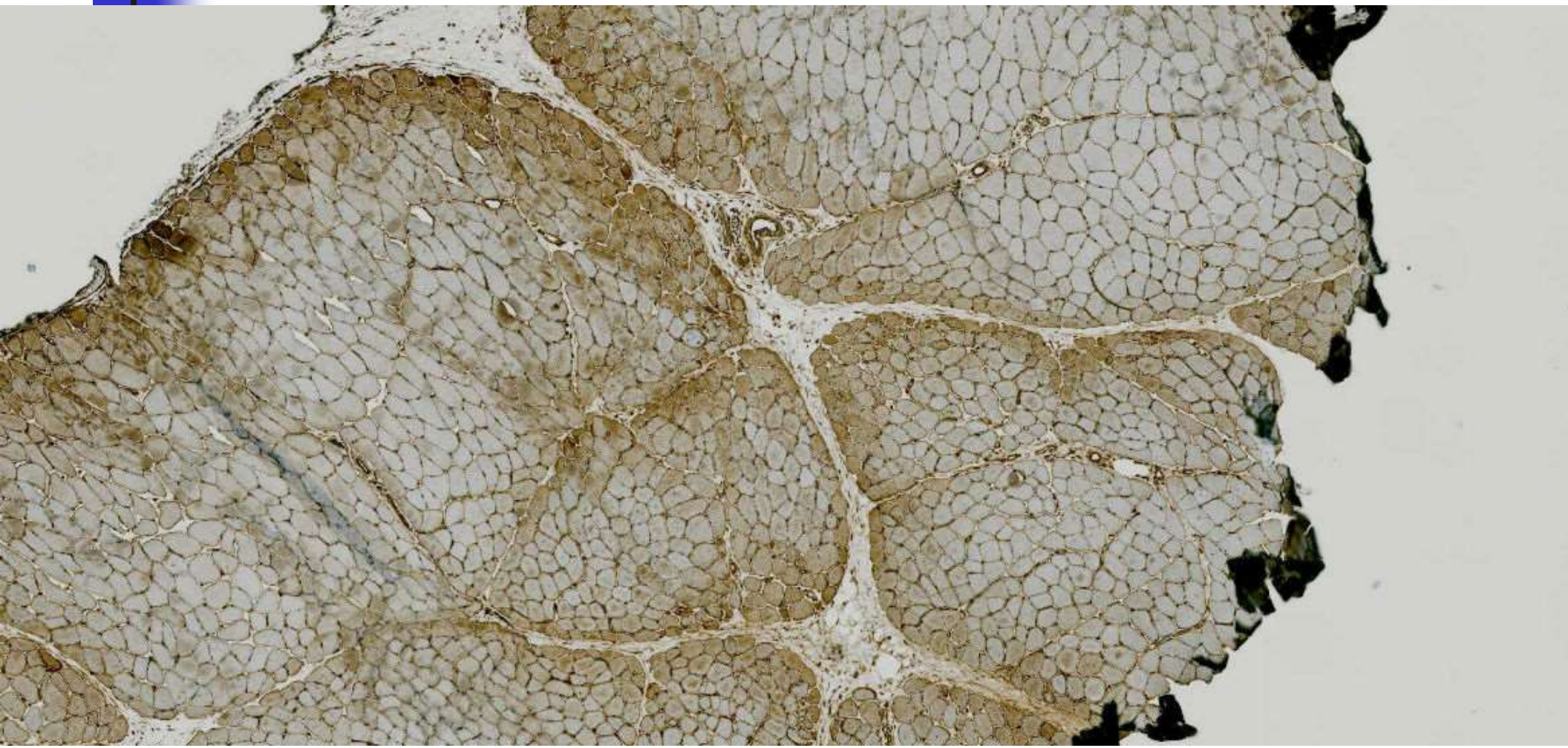
CD 31 (capillary stain)



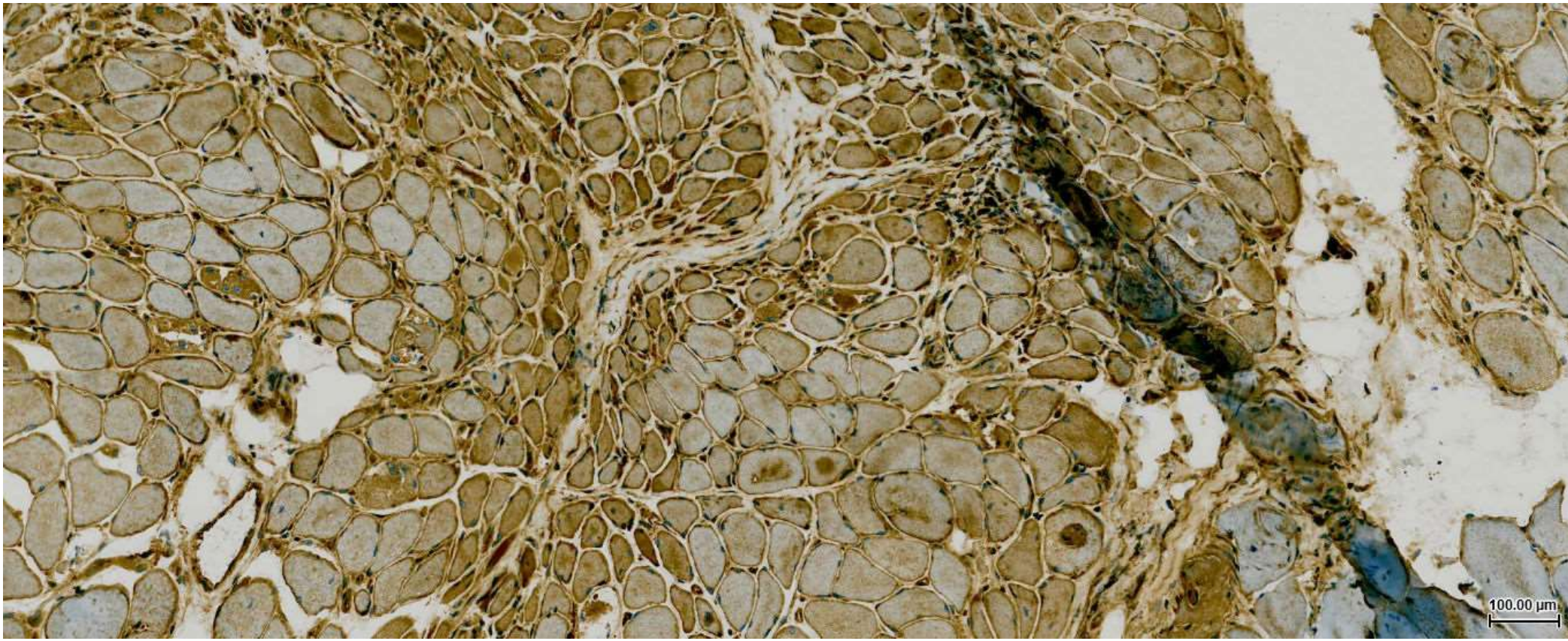
COX/SDH



MHC1 in DM



MHC1 in DM



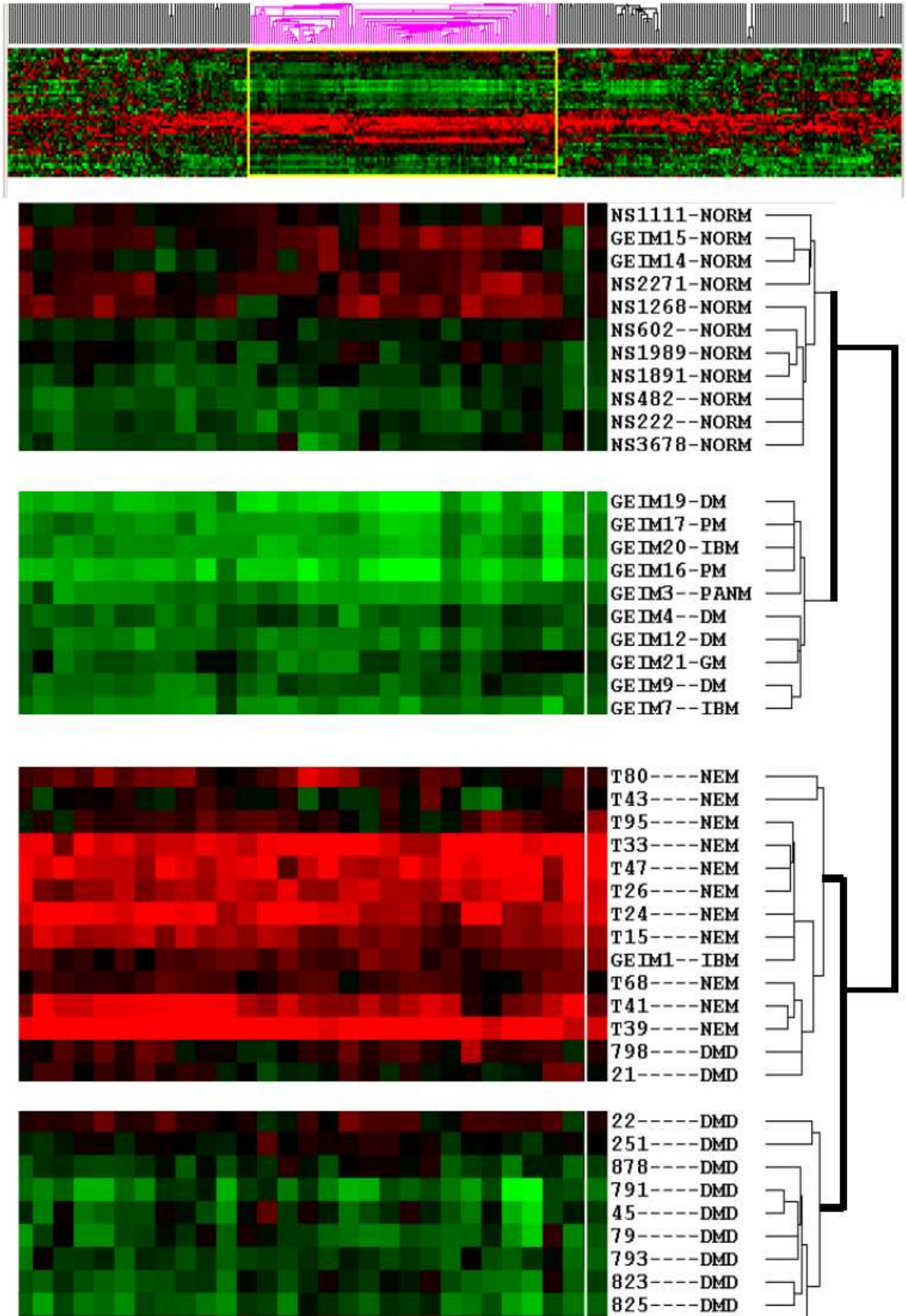
CME

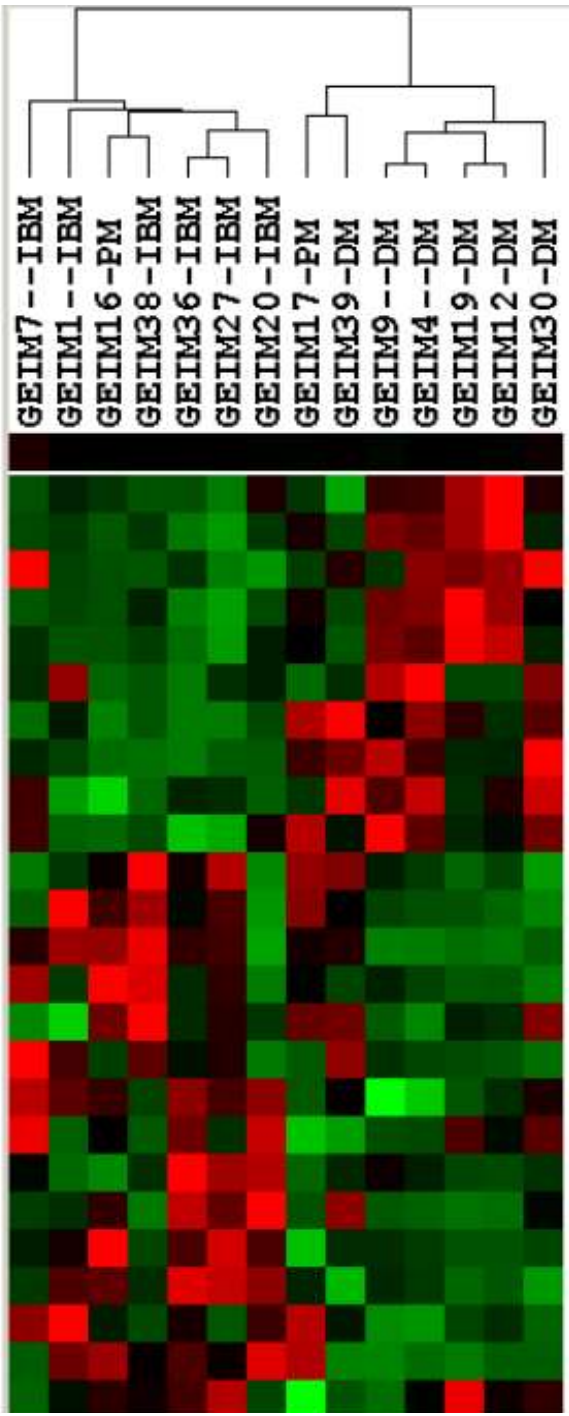
Molecular profiles of inflammatory myopathies

S.A. Greenberg, MD; D. Sanoudou, PhD; J.N. Haslett; I.S. Kohane, MD, PhD; L.M. Kunkel, PhD; A.H. Beggs, PhD; and A.A. Amato, MD

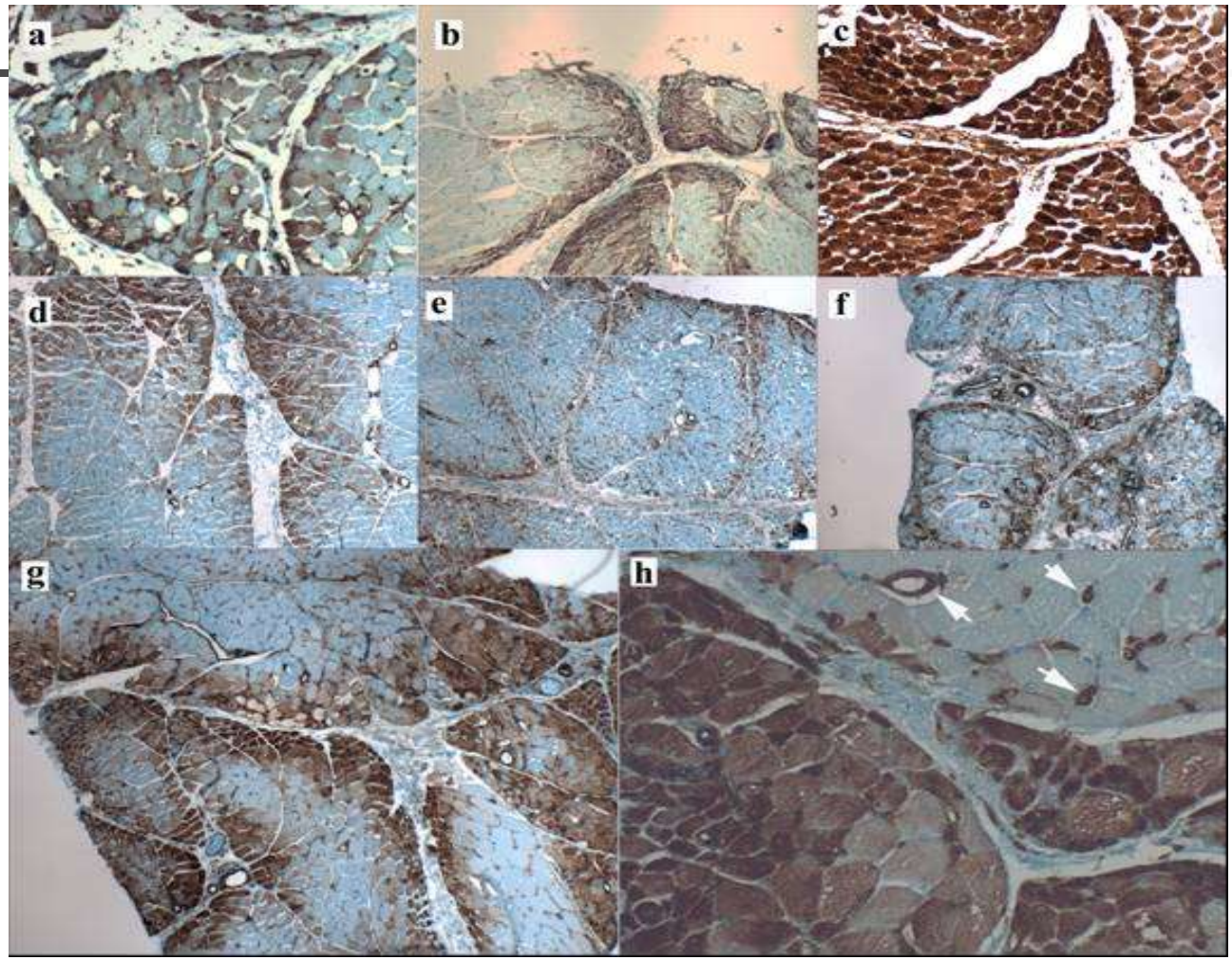
Abstract—*Objective:* To describe the use of large-scale gene expression profiles to distinguish broad categories of myopathy and subtypes of inflammatory myopathies (IM) and to provide insight into the pathogenesis of inclusion body myositis (IBM), polymyositis, and dermatomyositis. *Methods:* Using Affymetrix GeneChip microarrays, the authors measured the simultaneous expression of approximately 10,000 genes in muscle specimens from 45 patients in four major disease categories (dystrophy, congenital myopathy, inflammatory myopathy, and normal). The authors separately analyzed gene expression in 14 patients limited to the three major subtypes of IM. Bioinformatics techniques were used to classify specimens with similar expression profiles based on global patterns of gene expression and to identify genes with significant differential gene expression compared with normal. *Results:* Ten of 11 patients with IM, all normals and nemaline myopathies, and 10 of 12 patients with Duchenne muscular dystrophy were correctly classified by this approach. The various subtypes of inflammatory myopathies have distinct gene expression signatures. Specific sets of immune-related genes allow for molecular classification of patients with IBM, polymyositis, and dermatomyositis. Analysis of differential gene expression identifies as relevant to disease pathogenesis previously reported cytokines, major histocompatibility complex class I and II molecules, granzymes, and adhesion molecules, as well as newly identified members of these categories. Increased expression of actin cytoskeleton genes is also identified. *Conclusions:* The molecular profiles of muscle tissue in patients with inflammatory myopathies are distinct and represent molecular signatures from which diagnostic insight may follow. Large numbers of differentially expressed genes are rapidly identified.

NEUROLOGY 2002;59:1170–1182

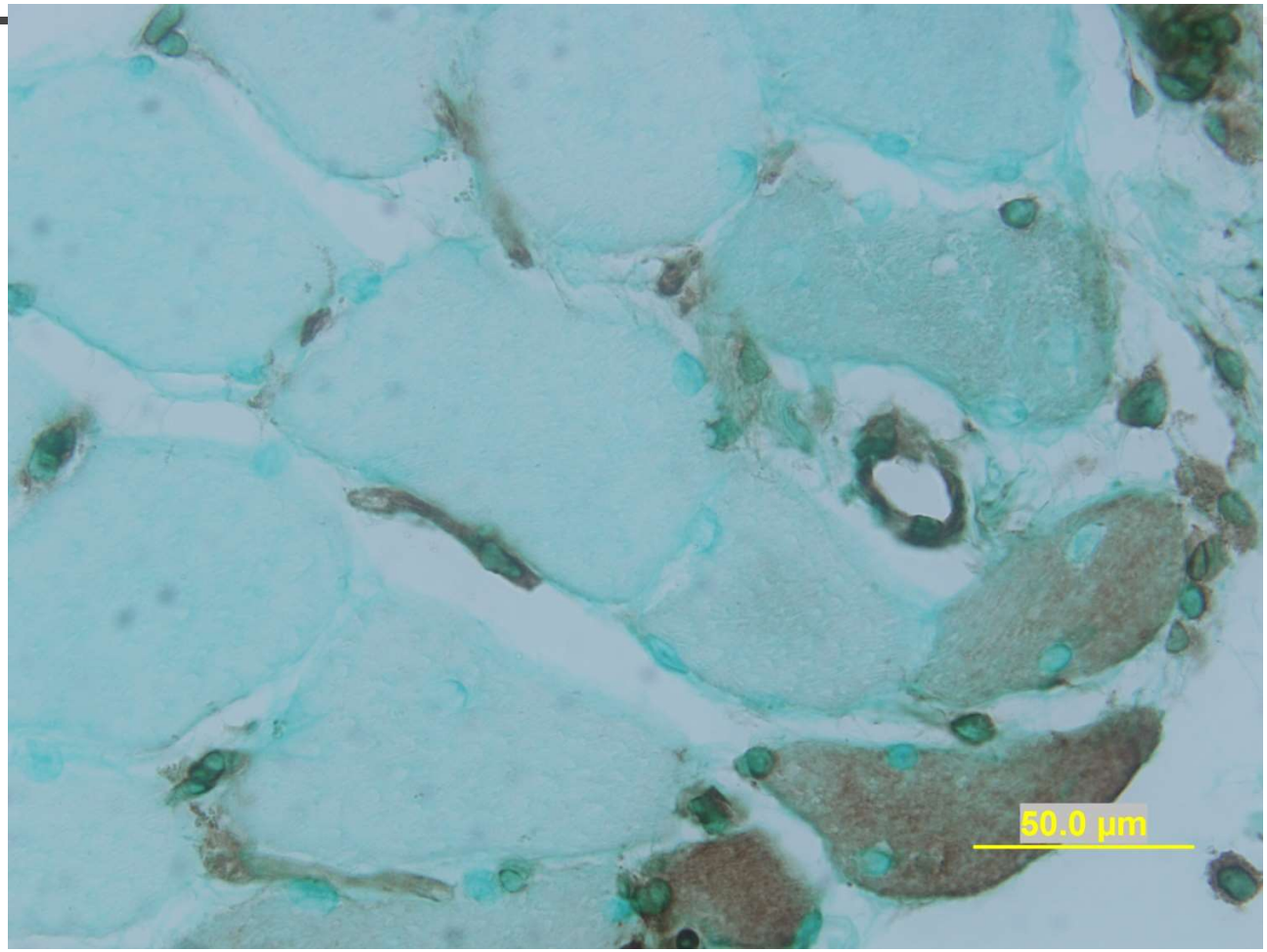

NS1111-NORM
GEIM15-NORM
GEIM14-NORM
NS2271-NORM
NS1268-NORM
NS602--NORM
NS1989-NORM
NS1891-NORM
NS482--NORM
NS222--NORM
NS3678-NORM
GEIM19-DM
GEIM17-PM
GEIM20-IBM
GEIM16-PM
GEIM3--PANM
GEIM4--DM
GEIM12-DM
GEIM21-GM
GEIM9--DM
GEIM7--IBM
T80----NEM
T43----NEM
T95----NEM
T33----NEM
T47----NEM
T26----NEM
T24----NEM
T15----NEM
GEIM1--IBM
T68----NEM
T41----NEM
T39----NEM
798----DMD
21-----DMD
22-----DMD
251----DMD
878----DMD
791----DMD
45-----DMD
79-----DMD
793----DMD
823----DMD
825----DMD

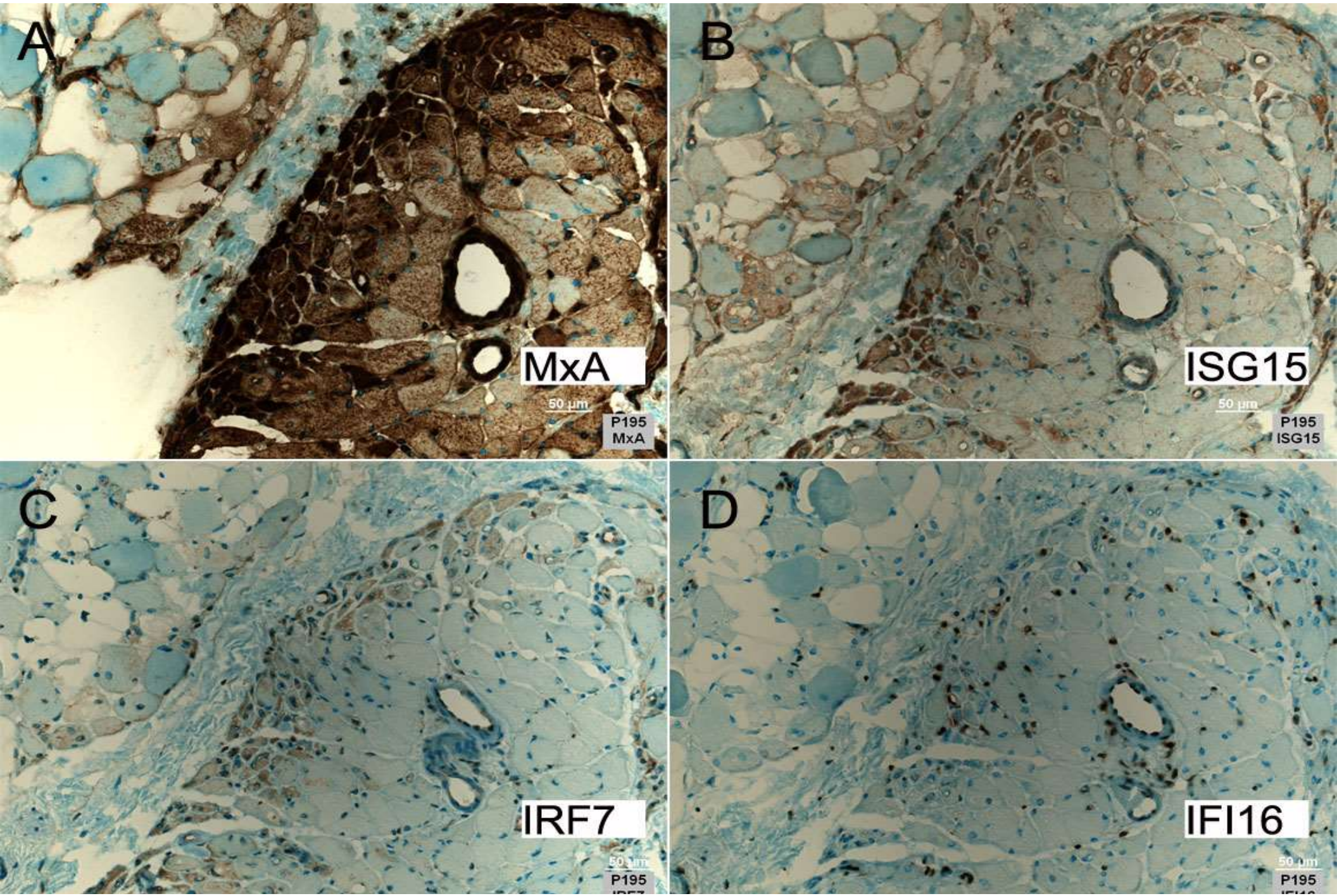

GEIM7--IBM
GEIM1--IBM
GEIM16-PM
GEIM38-IBM
GEIM36-IBM
GEIM27-IBM
GEIM20-IBM
GEIM17-PM
GEIM39-DM
GEIM9--DM
GEIM4--DM
GEIM19-DM
GEIM12-DM
GEIM30-DM
IFIT4 interferon-induced protein
ISG15 interferon-stimulated protein, 15 kDa
Interferon-induced 17kd protein (AA203213)
MX1 myxovirus resistance1 (interferon-inducible protein p78)
Interferon-inducible partial sequence (AF026941)
IGG heavy chain V-III region (AI147237)
MT1A metallothionein 1A
MAPT microtubule-associated protein tau
PLEC1 gene for plectin
U84570: Homology to Human A2
S71043:Ig A heavy chain
IGL@ rearranged immunoglobulin lambda light chain locus
Immunoglobulin lambda heavy chain (Y14737)
AI660656:Unknown gene
FGFR1 fibroblast growth factor receptor 1
IGHM immunoglobulin heavy constant mu
HLA-G histocompatibility antigen, class I
STAT1 transcription factor ISGF-3
HLA-DR2-Dw12 DQw1-beta MHC class II
MIG monokine induced by gamma interferon
SCYA5 small inducible cytokine T cell-specific protein
HLA Class II DQ1A (AA868382)
HLA-A major histocompatibility complex, class I
SB classII histocompatibility antigen alpha-chain (X00457)
IFI27 interferon, alpha-inducible protein 27

MXA Expression

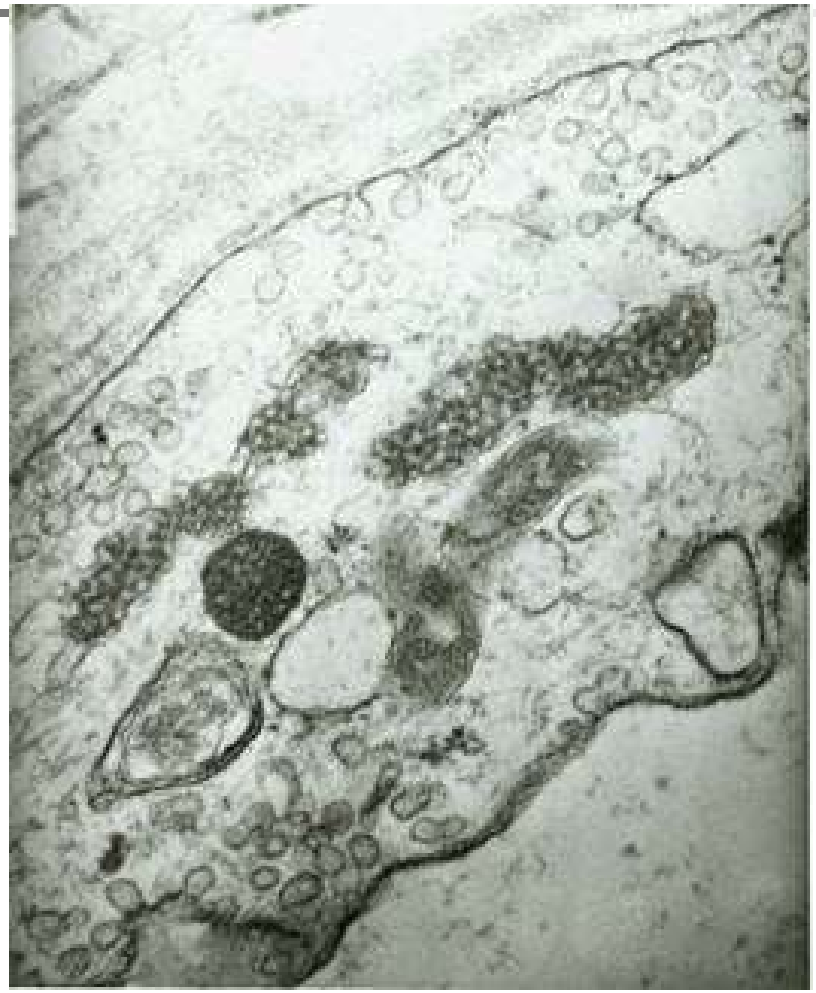


MXA expression




A
MxA
50 µm
P195
MxA
B
ISG15
50 µm
P195
ISG15
C
IRF7
50 µm
P195
D
IFI16
50 µm
P195

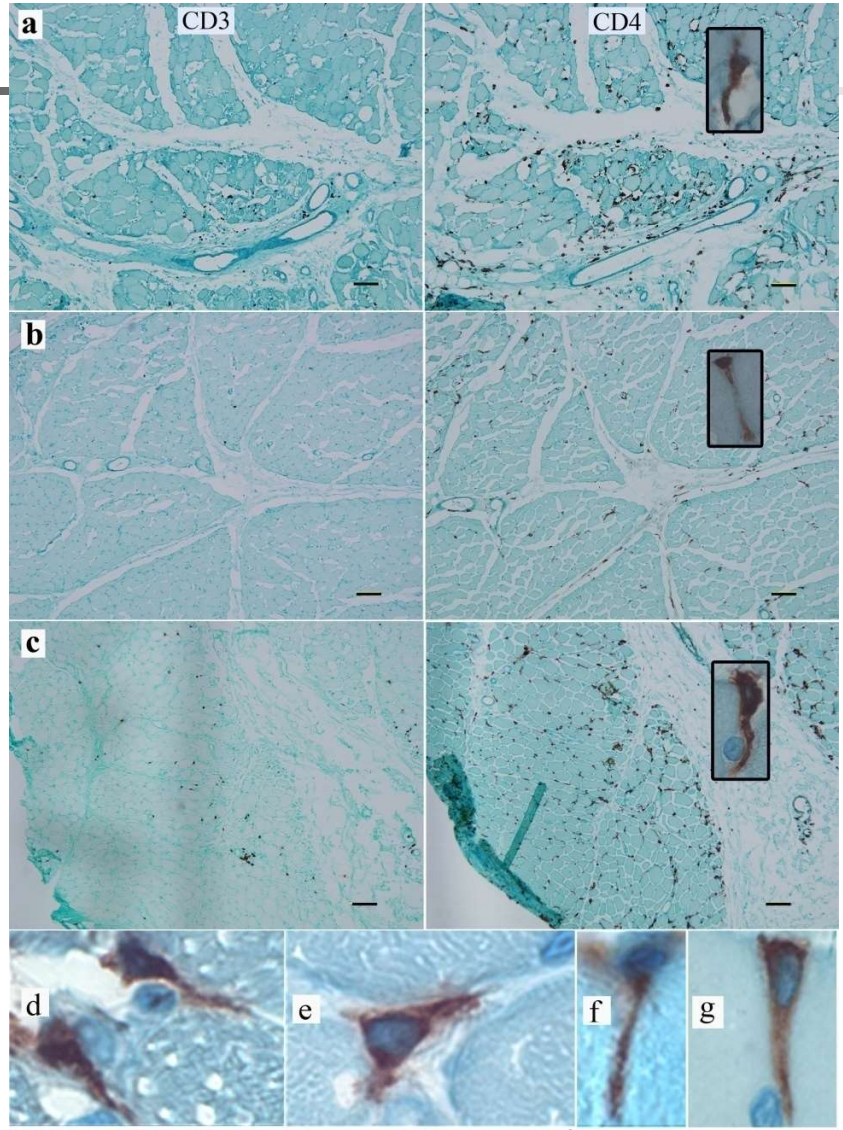
TUBULORETICULAR INCLUSIONS



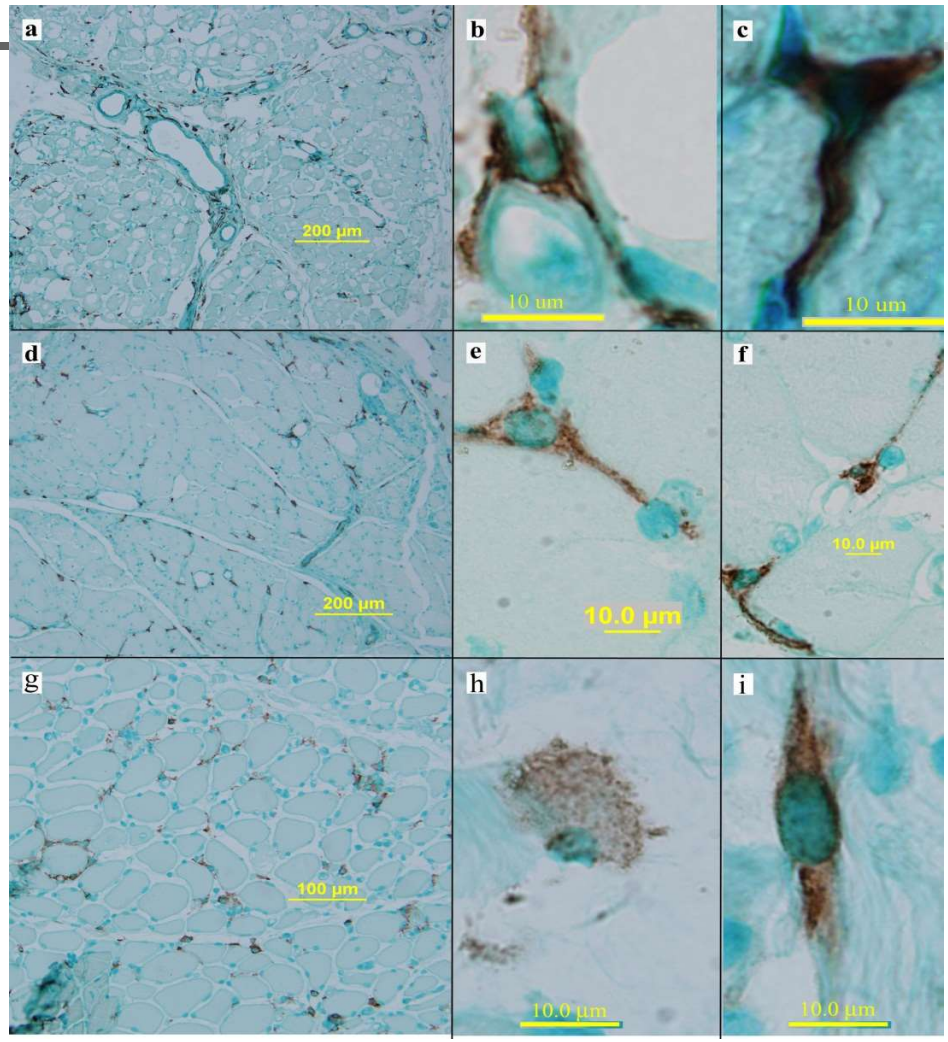
IFN-α/β Produced By Plasmacytoid Dendritic Cells (PDCs)

- IFN-α/β "factories"
  - Natural interferon producing cells (NIPCs)

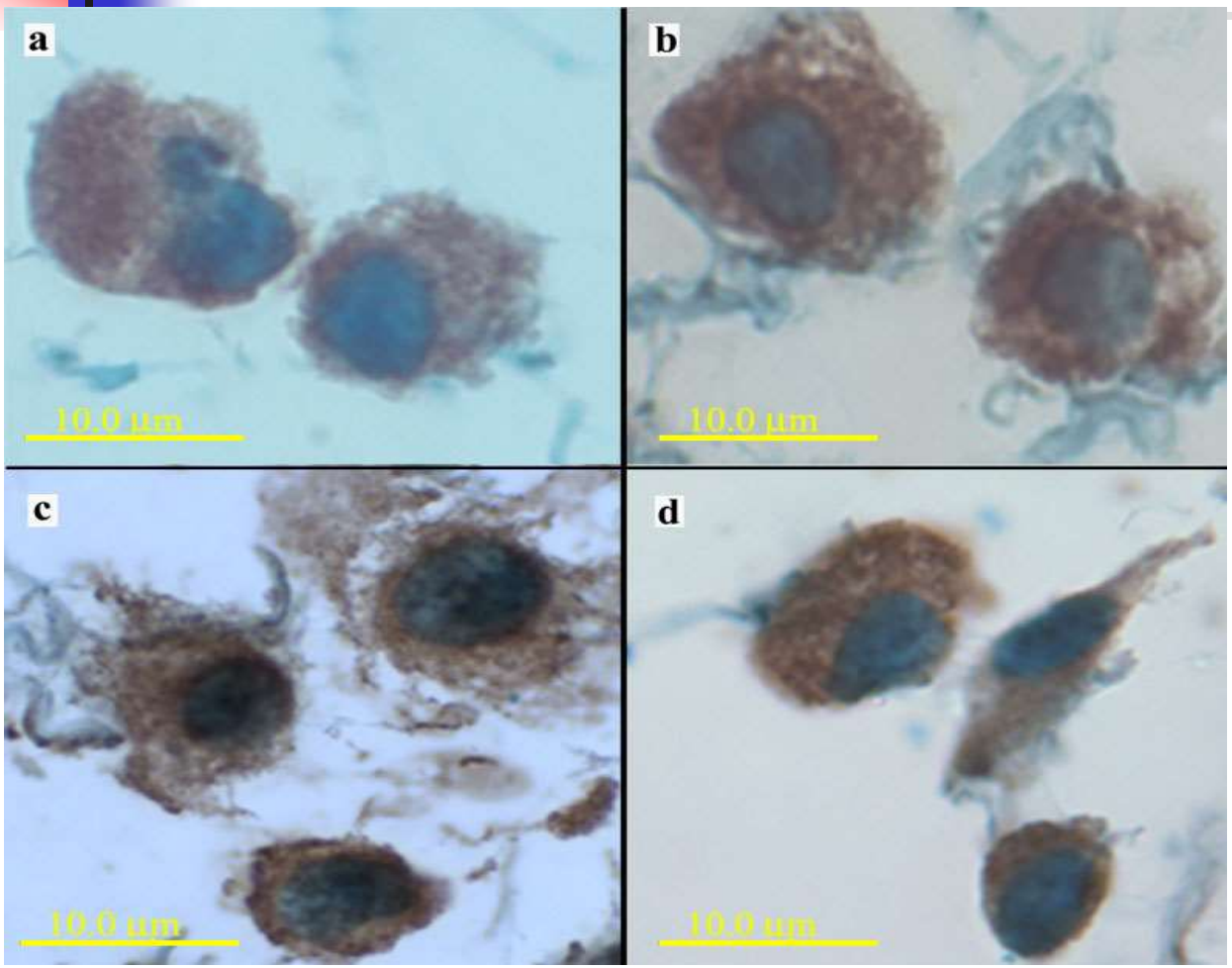
CD4 compared with CD3 expression and dendritic morphologies of CD4+ cells in dermatomyositis



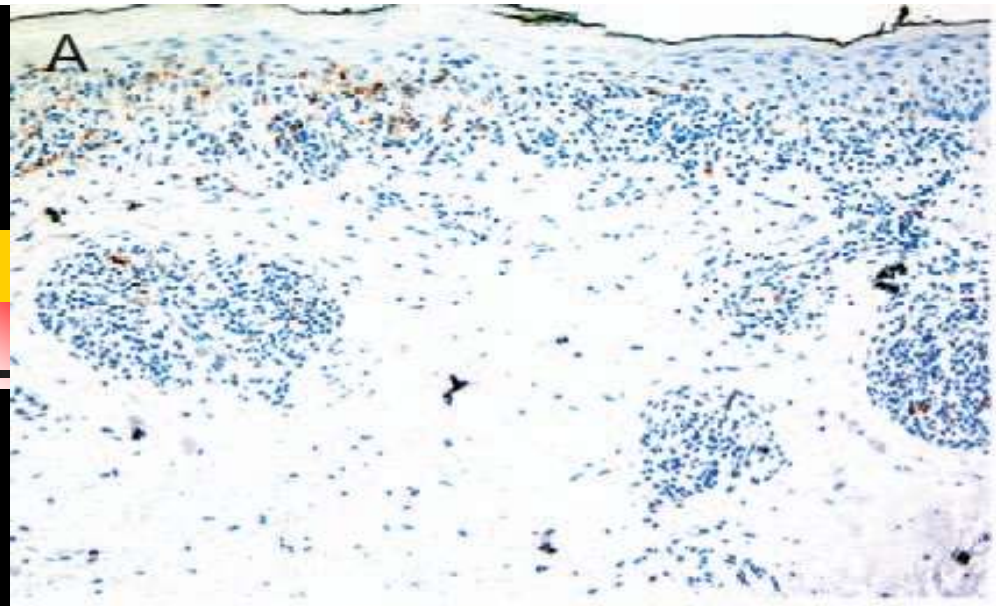
BDCA 2 + Plasmacytoid Dendritic Cells

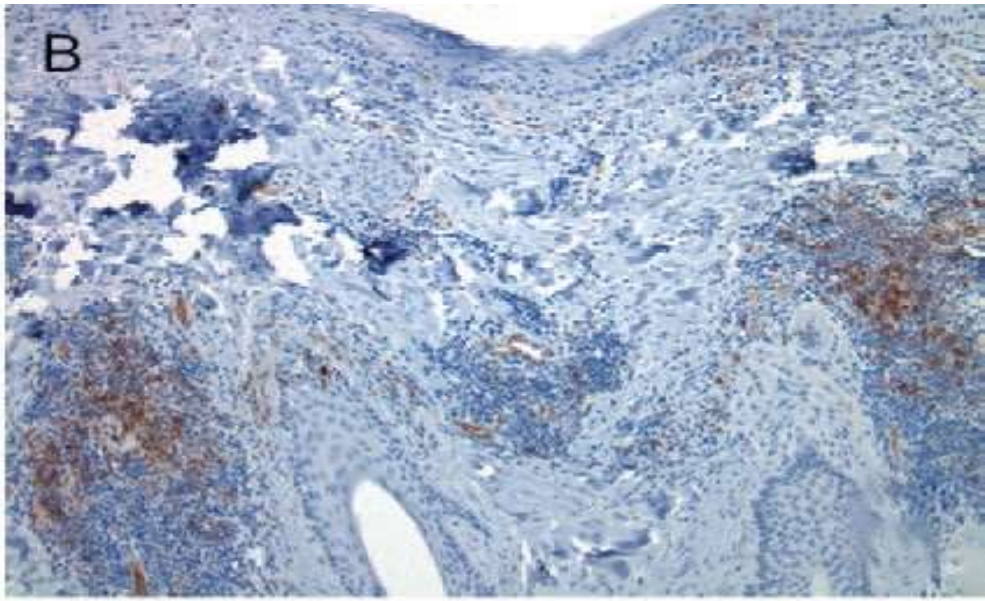


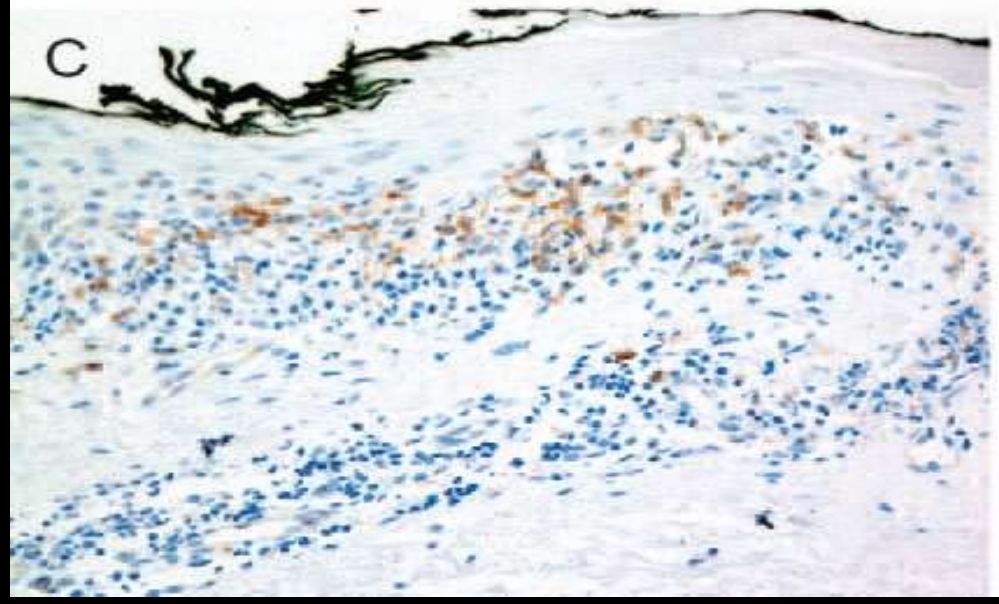
Dermatomyositis

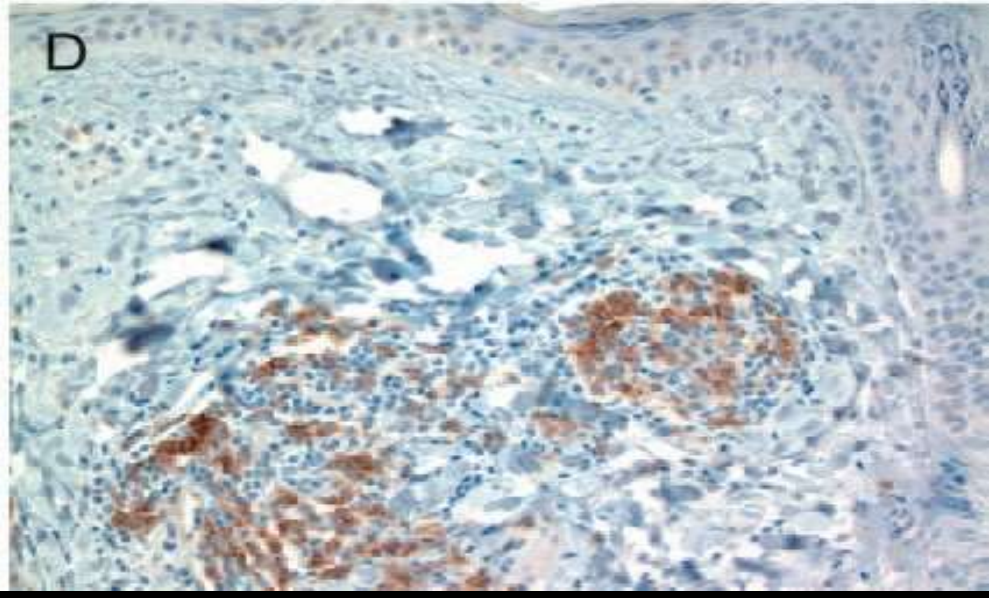


- BDCA 2+ cells
- IFN-alpha

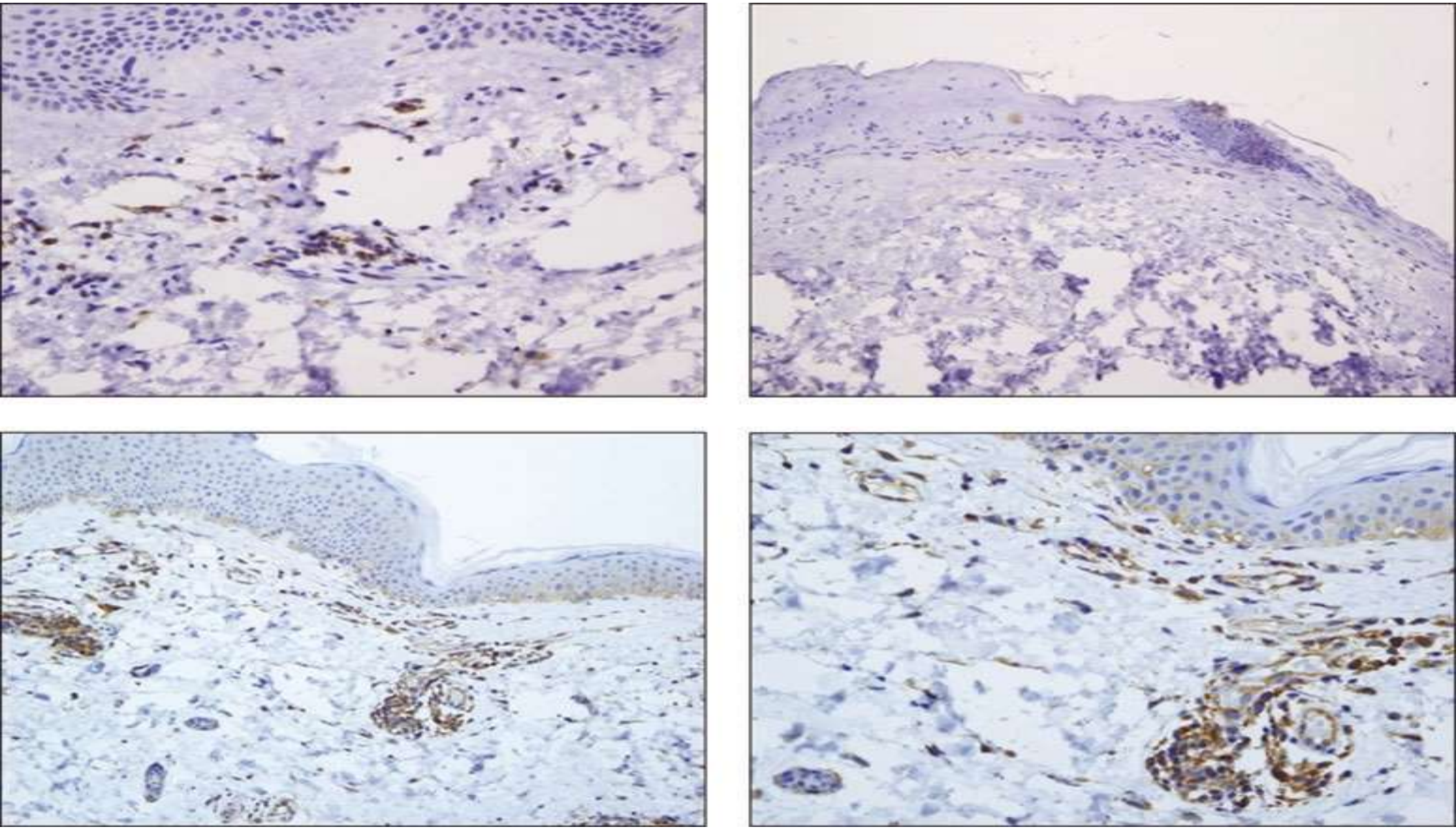






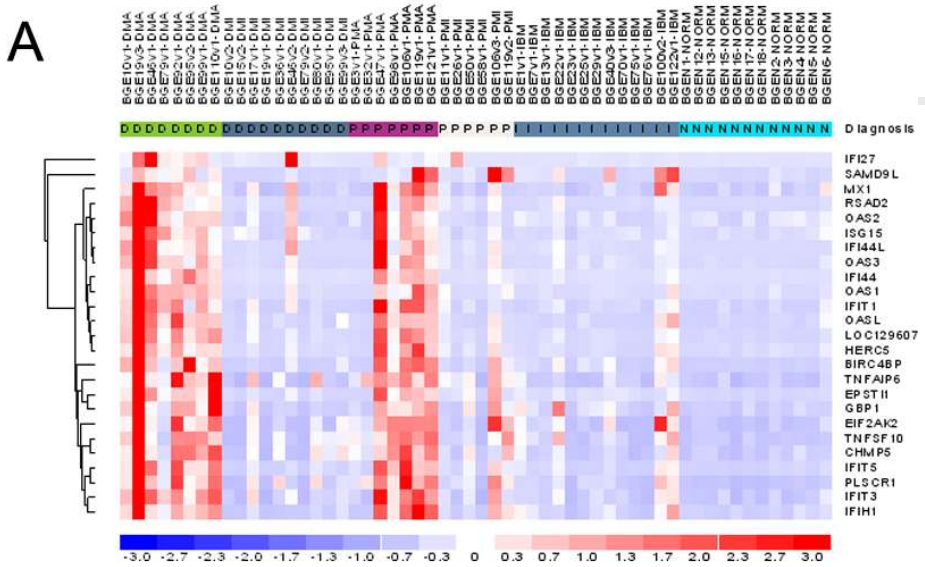


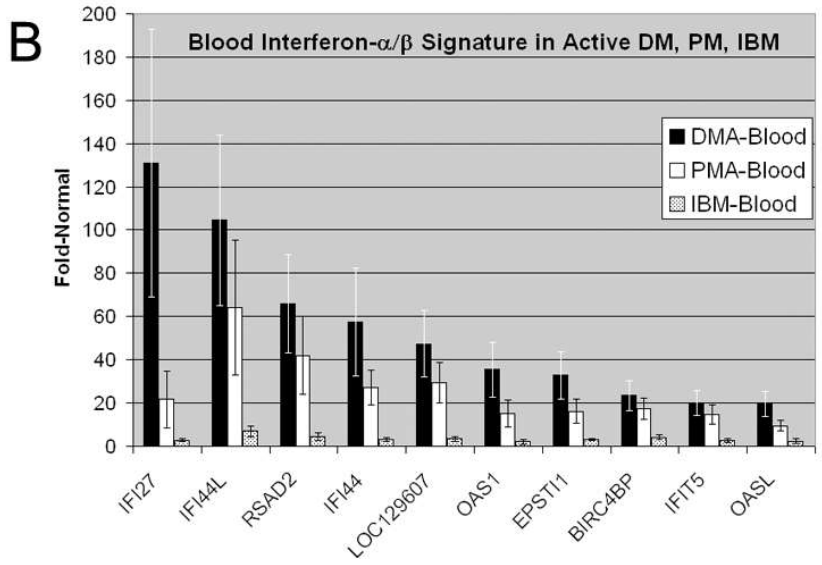
- **Plasmacytoid dendritic cells are present in cutaneous dermatomyositis (A and C) and in SLE (B and D) in skin bx showing interface dermatitis. J Cutan Pathol. 2008 May;35(5):452-6**



- CXCR3 immunohistochemical staining of cutaneous biopsies from patient with DM before (A) and after (B) rapid disease progression. In this case of DM strong expression of MXA, most prevalent in the endothelial cells and the lower third of the epidermis is observed (C and D). *J Cutan Pathol 2010: 37: 659–671*

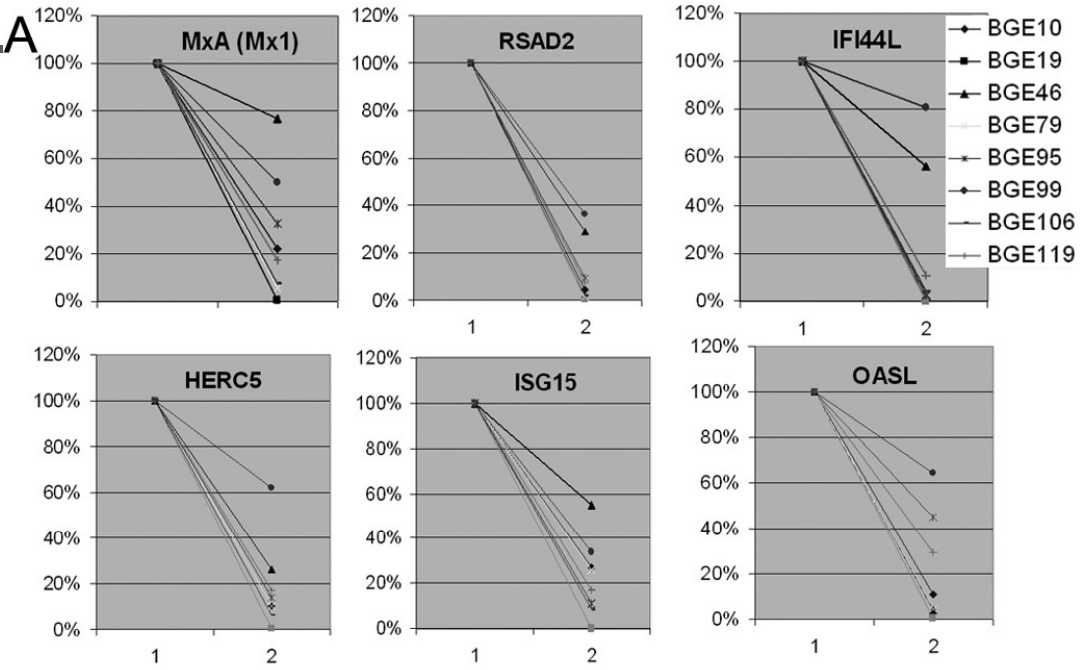
Gene Expression in Peripheral Blood



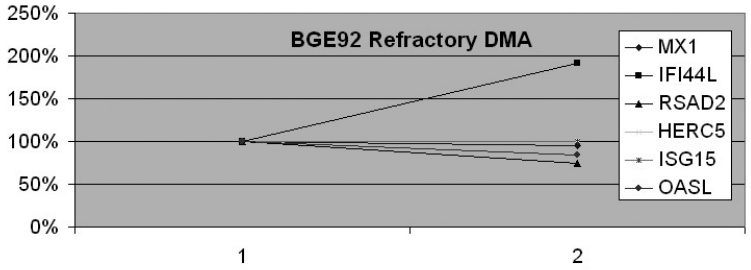


IFN-alpha Inducible Genes in Peripheral Blood with Treatment

A



B



DERMATOMYOSITIS

- Pathogenesis
  - Plasmacytoid dendritic cells infiltration and up-regulation of type 1 interferon- inducible genes and proteins may play an important role
  - Hypothesis: direct toxic effect to small blood vessels and muscle fibers by cytokines and other type 1 interferon- inducible proteins
  - trigger is unknown, possible viral infection

DERMATOMYOSITIS

- Prognosis
  - 5 year survival in adults range from 70-90 %
  - mortality in children is now quite low
  - poor prognostic features include: malignancy, increased age, ILD, cardiac disease, late or previous inadequate treatment

NEUROLOGY 2003;61:288–290

Editori

Unicorns, dragons, polymyositis, and other mythological beasts

Anthony A. Amato, MD; and Robert C. Griggs, MD

Polymyositis

- Is there such an entity?- YES, but it is a heterogeneous and dependent upon definition:
  - CD8+ cells invading non-necrotic muscle fibers expression MHC1 antigen
  - Any endomysial or perivascular inflammation with or without MHC 1 expression on muscle fibers
  - Necrotizing myopathies
- Most studies have used Bohan and Peter's Criteria
  - "PROBABLE PM" does not require muscle biopsy
  - None of the criteria including muscle biopsy abnormalities are not specific for PM
- Many (at least some) cases of "PM" in the literature are probably IBM, inflammatory dystrophies, and perhaps DM

Table 2. *Bohan and Peter criteria for the diagnosis of PM and DM*[8]

1.	Symmetrical weakness of the limb girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement
2.	Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemmal nuclei, and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and an inflammatory exudate, often perivascular
3.	Elevation in serum of skeletal-muscle enzymes, particularly the CK and often aldolase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) and lactate dehydrogenase (LDH)
4.	Electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre, high frequency repetitive discharges
5.	Any one of the characteristic dermatologic features of the rash of DM

POLYMYOSITIS

- Clinical Features
  - Usually presents in patients over 20 yrs of age
  - women affected more than men
  - present with symmetric proximal weakness developing over weeks to months; distal muscles also involved; myalgias
  - diagnosis and treatment are delayed compared to DM (no rash - red-flag)

POLYMYOSITIS

- Associated Manifestations
  - Dysphagia present in 1/3 of patients
  - EKG conduction abnormalities or myositis with CHF in 1/3 of patients
  - ILD in 10 % (50 % of whom have Jo-1 antibodies)
  - Polyarthritis in as many as 45 %

POLYMYOSITIS

- Risk of malignancy is lower than that seen in DM, but it may be higher than general population
- sign and symptom directed malignancy work-up

POLYMYOSITIS

- Laboratory Features
  - CK is elevated 5-50 fold in the majority of patients but does not correlate with severity of the disease
  - ESR is normal in most patients and does not correlate well with disease activity
  - ANA present in 16-40 % of PM patients

POLYMYOSITIS

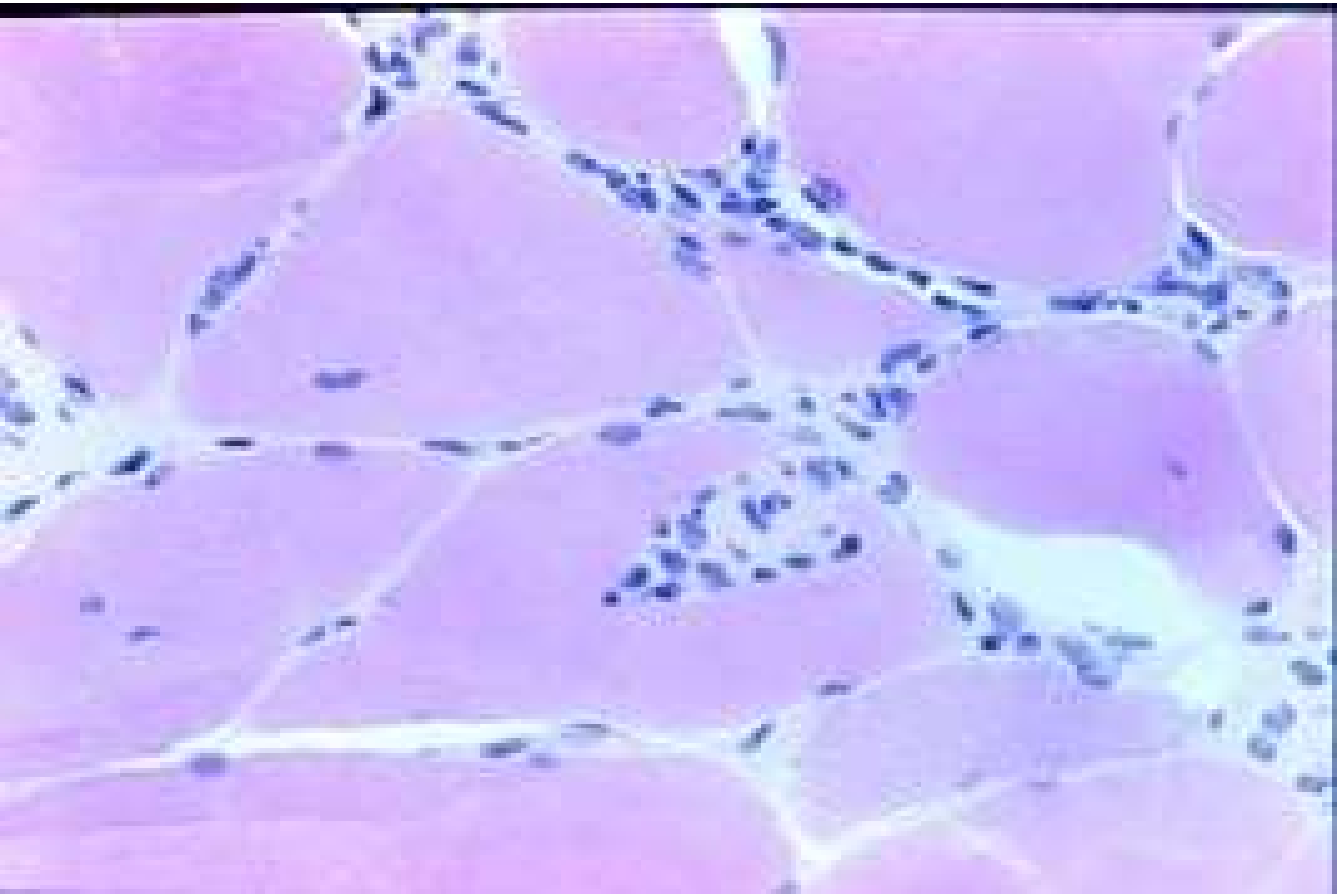
- Electromyography
  - triad of (1) increased insertional and spontaneous activity, (2) small polyphasic motor unit potentials, and (3) early recruitment
- Muscle Imaging (MRI and CT)
  - signal abnormalities in affected muscles secondary to inflammation and edema
  - ? utility in guiding muscle biopsy

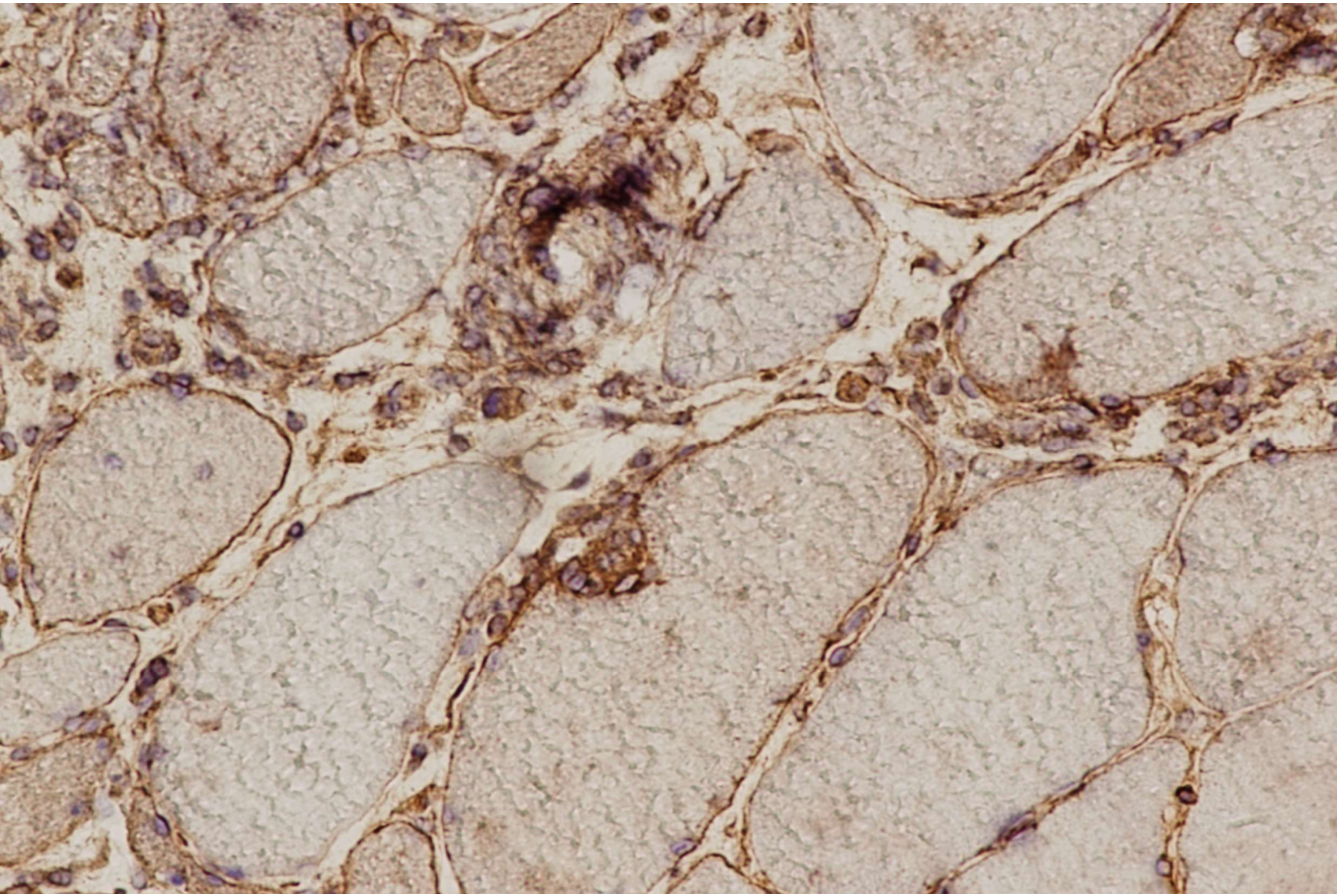
POLYMYOSITIS

- Muscle Biopsy
  - variability in fiber size, scattered necrotic and regenerating fibers, and endomysial inflammation ***with invasion of non-necrotic fibers expression MHC 1 antigen***
    - **Some authorities do not require for dx- just endomysial /perivascular inflammatory cells**
  - inflammatory cells are macrophages and CD8+ cytotoxic T-cells (alpha/beta)

POLYMYOSITIS

- T-cell receptor repertoire of endomysial T-cells demonstrate an oligoclonal pattern of gene rearrangements and a restricted motif in the CDR3 region suggesting and antigen driven response
- Oligoclonal expansion of B-cells and plasma cells in muscle tissue
- No evidence of immune deposits (MAC, complement, IgM, IgG) on blood vessels





Polymyositis

- Expression studies in blood show slight increase in type 1 interferon regulated genes
- Expression studies muscle tissue show increased expression of Ig-related genes
  - Pathogenic significance is unclear
  - May be useful in identifying possible antigens

POLYMYOSITIS

- Pathogenesis
  - histological and immunological studies suggest that PM is the result of a HLA-restricted, antigen-specific, cell-mediated immune response directed against muscle fibers
  - etiology is unknown
  - viral infections have been postulated but no conclusive evidence to support this theory

POLYMYOSITIS

- Prognosis
  - most PM patients respond favorably to immunosuppressive treatment
  - some retrospective studies suggest PM does not respond as well as DM
  - poor prognostic features: increased age, ILD, cardiac disease, late or previous inadequate treatment, anti-SRP or Jo-1 antibodies

OVERLAP SYNDROMES

- Refers to a group of disorders in which DM or PM is associated with another well-defined connective tissue disease
  - scleroderma
  - mixed connective tissue disease
  - systemic lupus erythematosus
  - Sjögren syndrome
  - rheumatoid arthritis

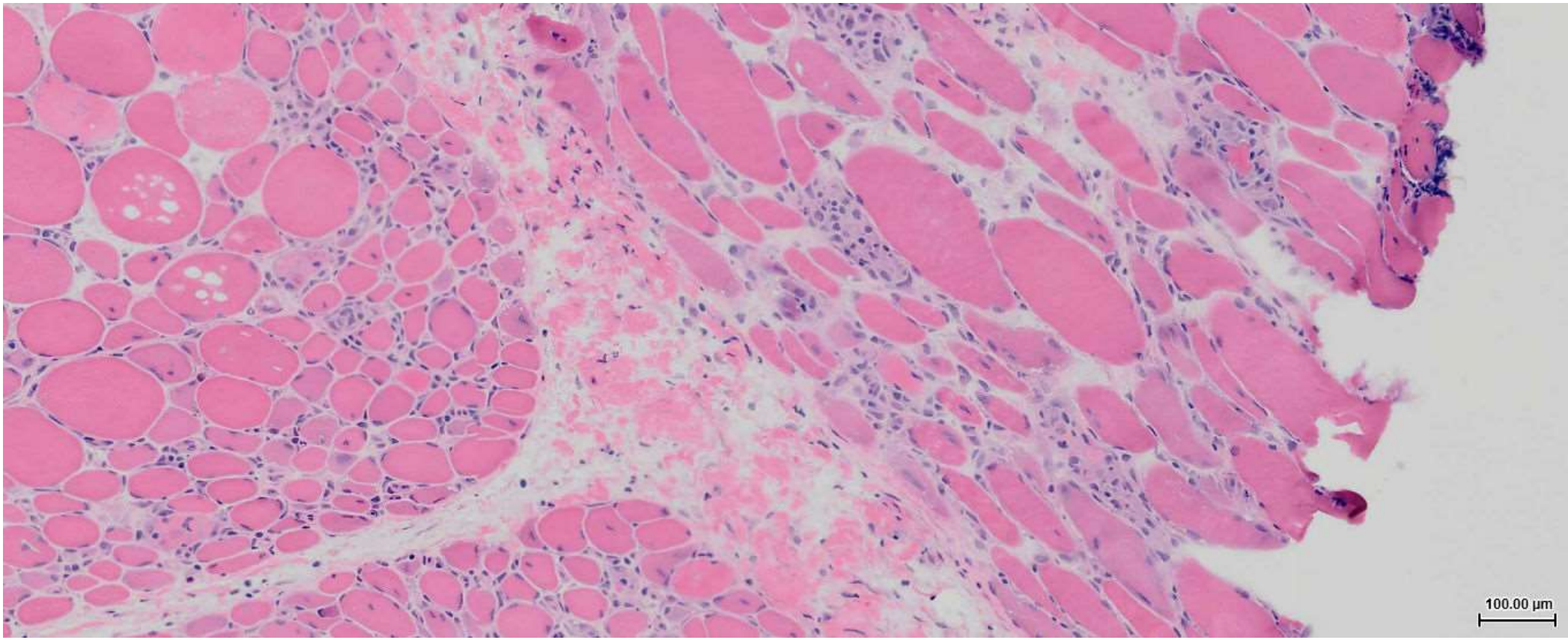
Anti-Synthetase Syndrome

- Some authorities consider myositis associated with antisynthetase syndrome (e.g., Jo-1 antibody) to be a inflammatory myopathy distinct from DM and PM
- Clinical features aside from proximal weakness include interstitial lung disease, Raynaud's, and inflammatory polyarthritis
- Also may have mechanic hands, fever, and a rash

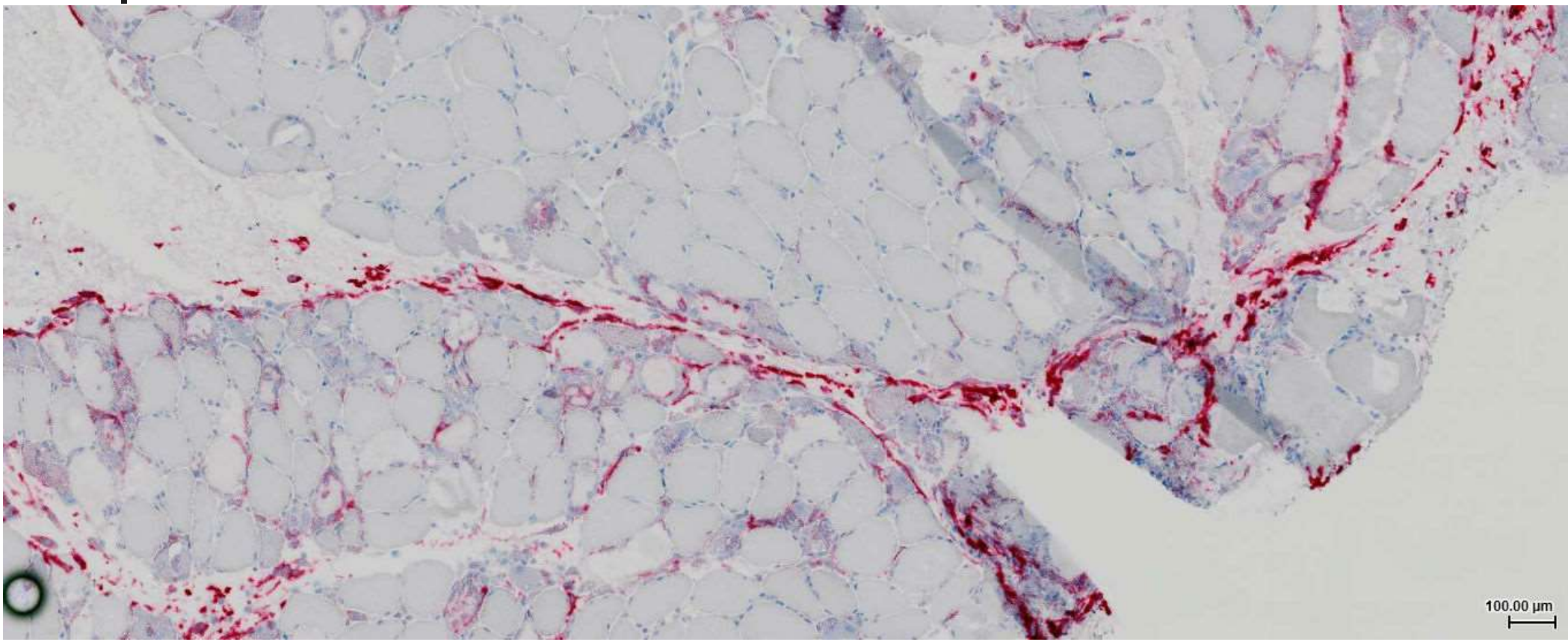
Anti-Synthetase Syndrome

- Muscle Biopsy features (some overlap with DM)
  - Perifascicular muscle fiber abnormalities with atrophy and necrosis
  - Fragmentation of perimysial CT with alkaline phosphatase staining
  - MHC1 and staining on the sarcolemma with perifascicular predominance
  - MAC deposition on the sarcolemma of fibers in the perimysial area and with sarcoplasm of necrotic fibers predominantly in the perimysial area as well

Anti-Synthetase Syndrome



Alkaline Phosphatase in Anti-Synthetase Syndrome



MAC in Anti-Synthetase Syndrome

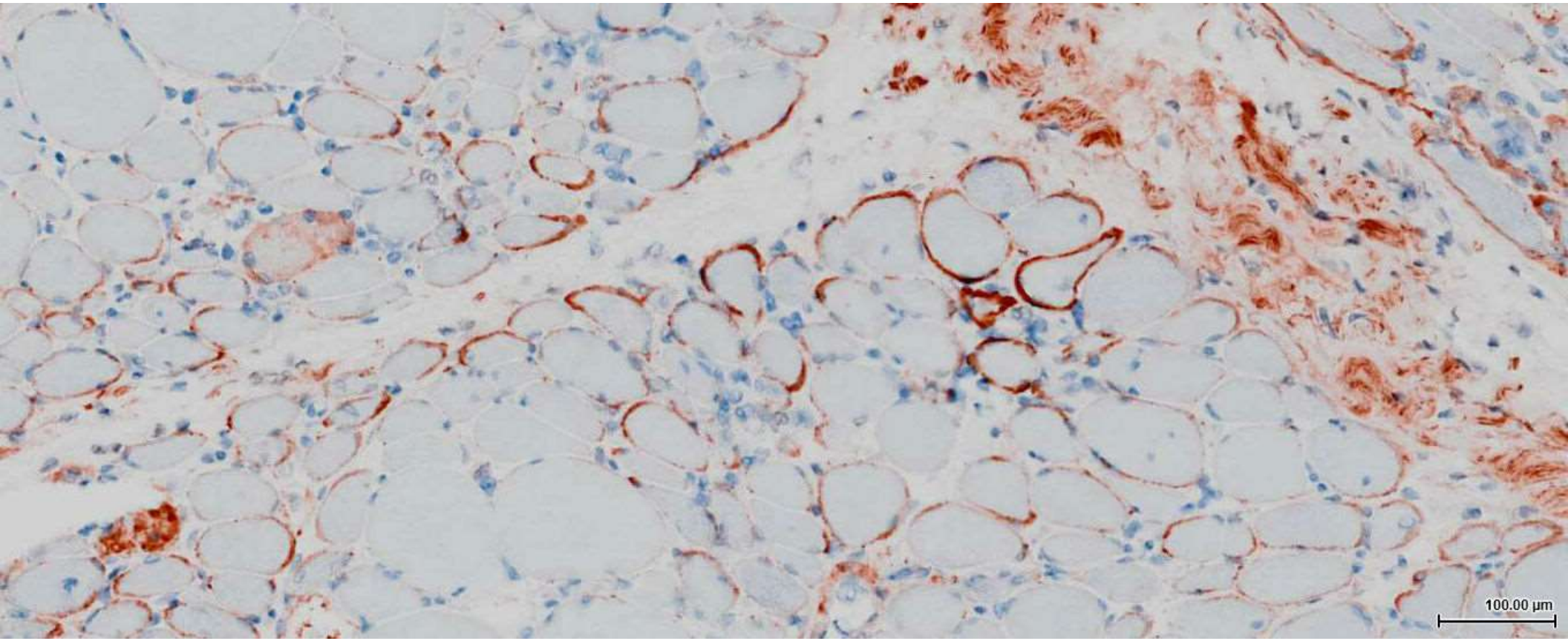
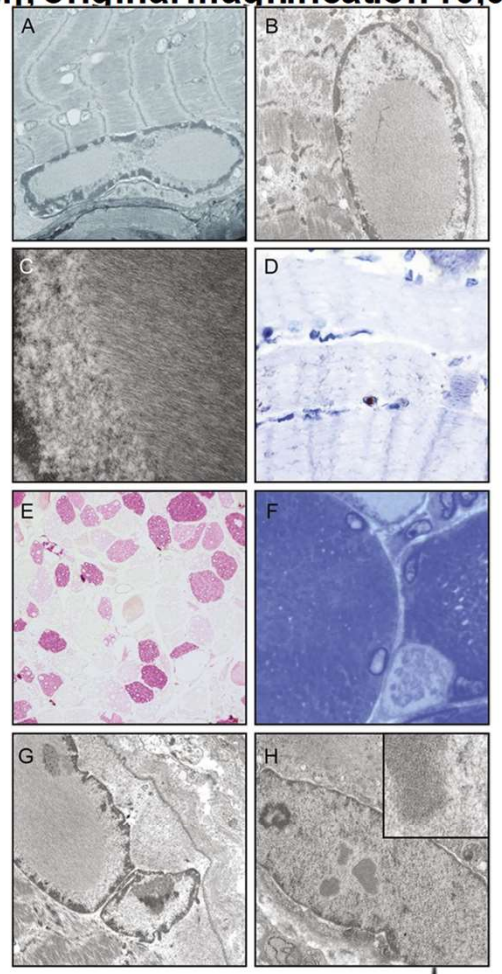


Figure 3 Electron microscopy of muscle tissue of patients with antisynthetase syndrome(A–C) Myonuclear actin filament aggregates, overview and illustration of filamentous character (electron microscopy [EM], original magnification 10,000×, 20,000×, and 50,000×).



Werner Stenzel et al. Neurology 2015;84:1346-1354

Necrotizing Myopathy

-Resembles polymyositis clinically with symmetric proximal greater than distal weakness that is often acute in onset and with markedly elevated CKs

-May be associated with cancer, connective tissue disease, or statin use

-Associated antibodies targeting signal recognition particle (SRP) antibodies and HMG-CoA reductase (latter associated more frequently with statin use)

Necrotizing Myopathy

-Muscle biopsies reveal scattered necrotic fibers with scant, if any, inflammatory cell infiltrate (aside from myophagocytosis of necrotic fibers)

-May see thickened pipestem capillaries with MAC deposition

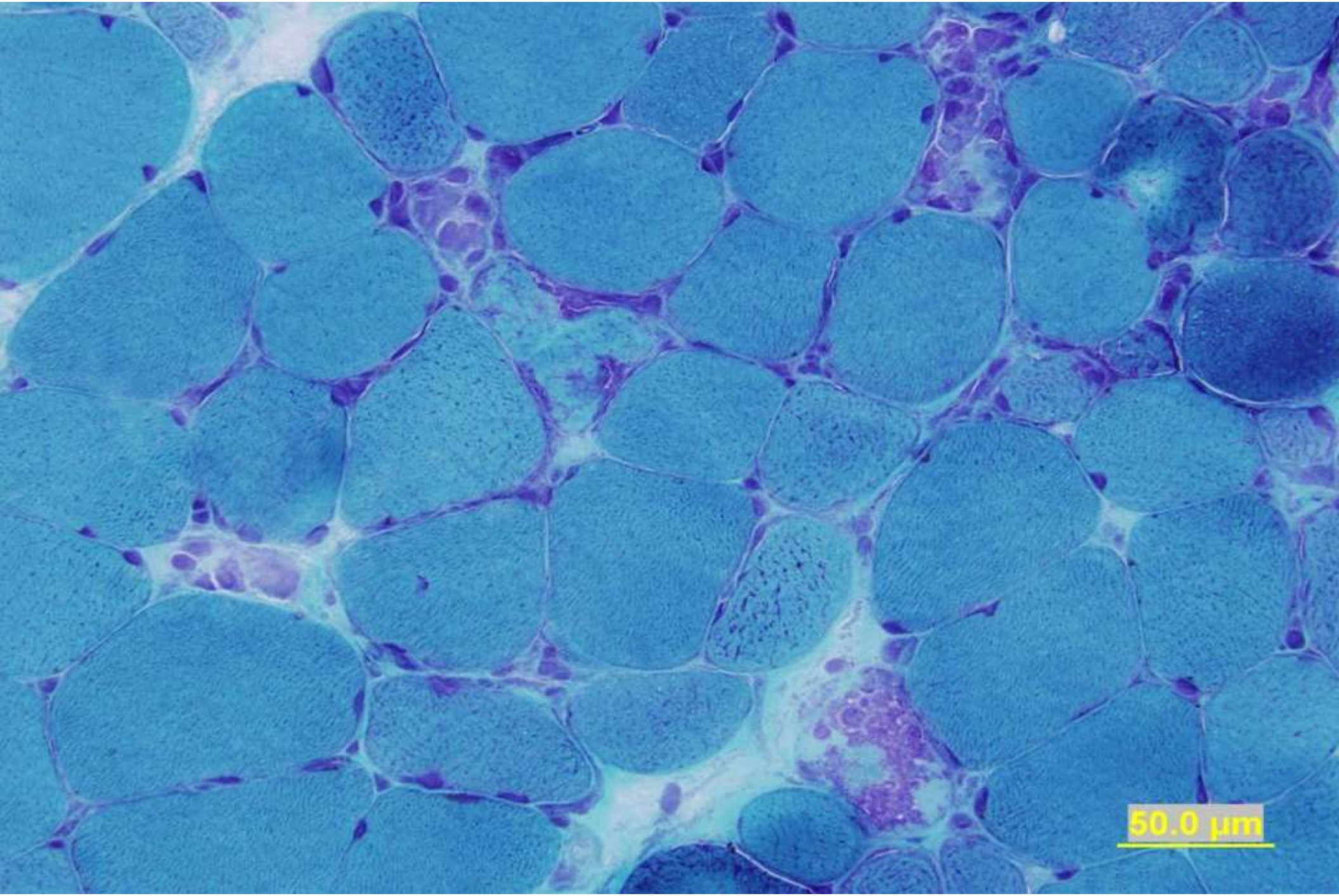
-May see patchy MHC1 staining on sarcolemma of non-necrotic fibers

-Membrane attack complex deposition also may be seen on sarcolemma of non-necrotic muscle fibers in cases associated with statin use

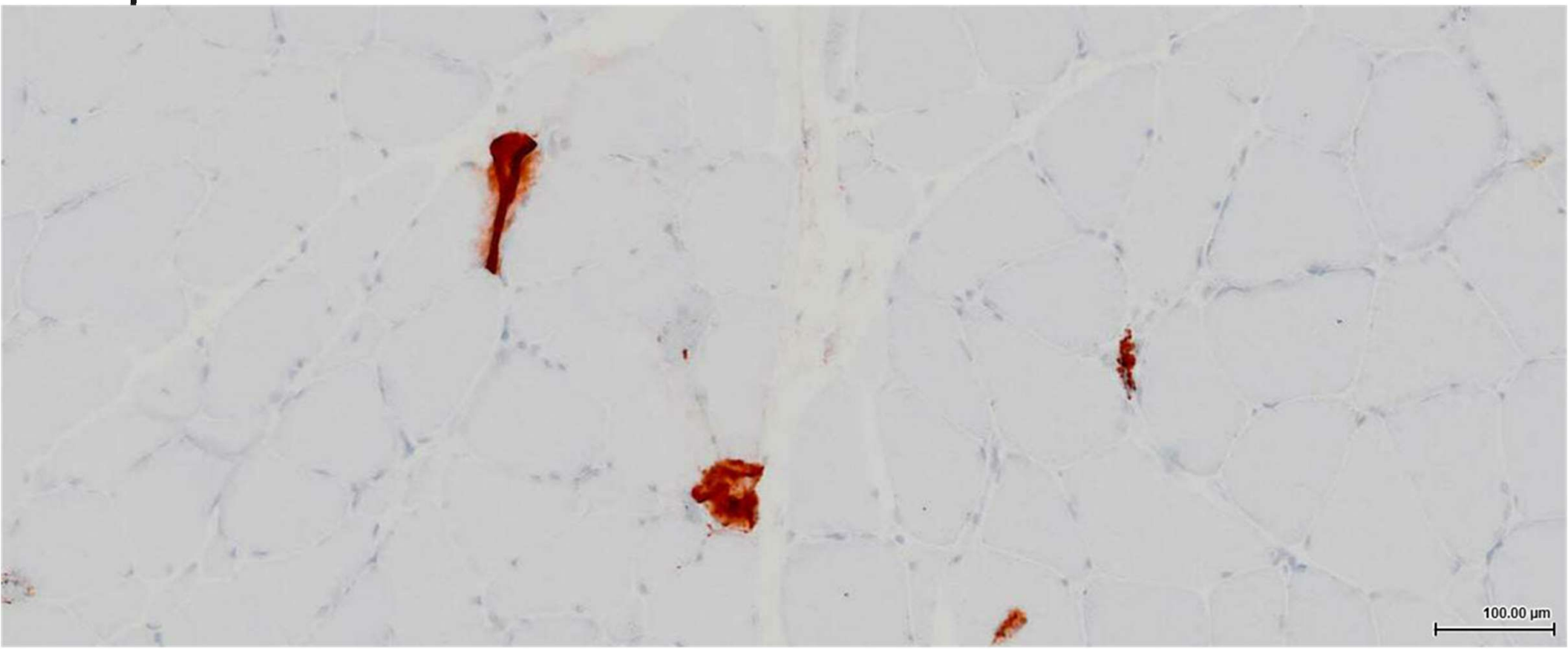
-Anti-HMGCR myopathy is often responsive to IVIG monotherapy

-Others often require aggressive immunosuppressive treatment

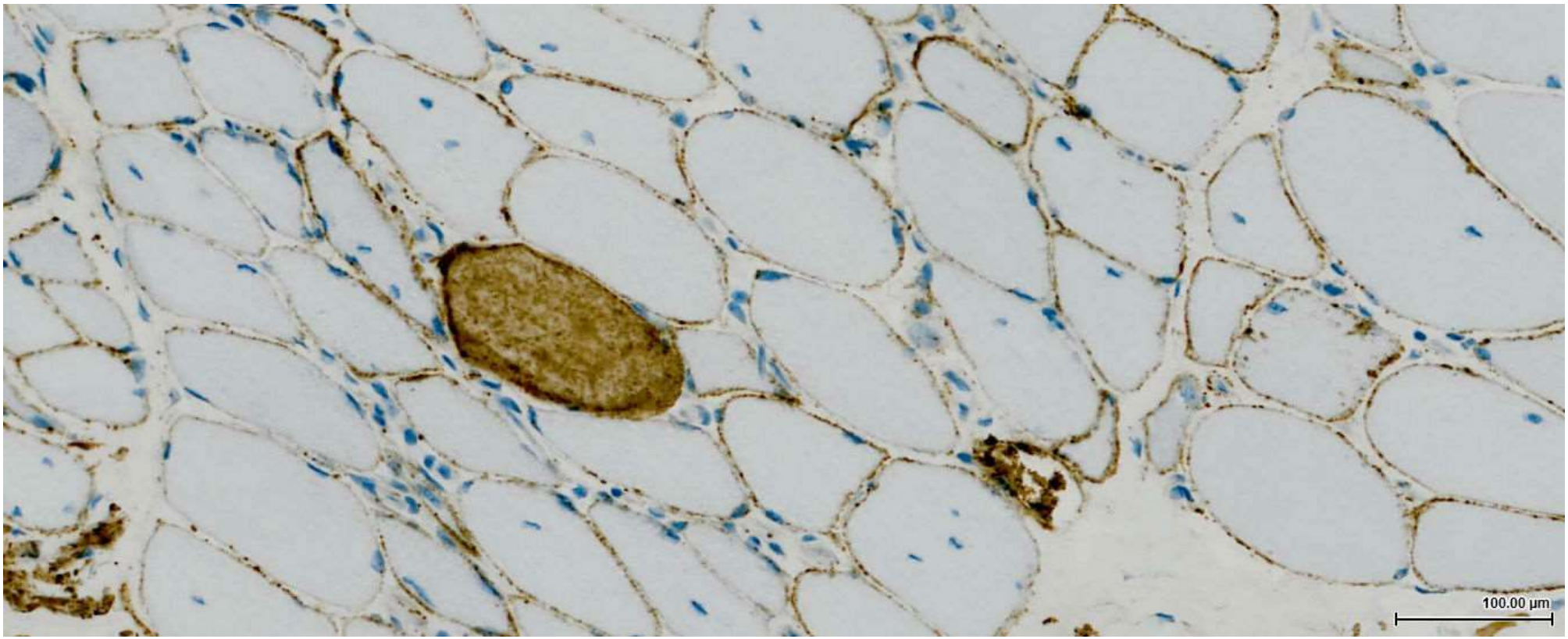
-Pathogenesis is unknown


50.0 µm

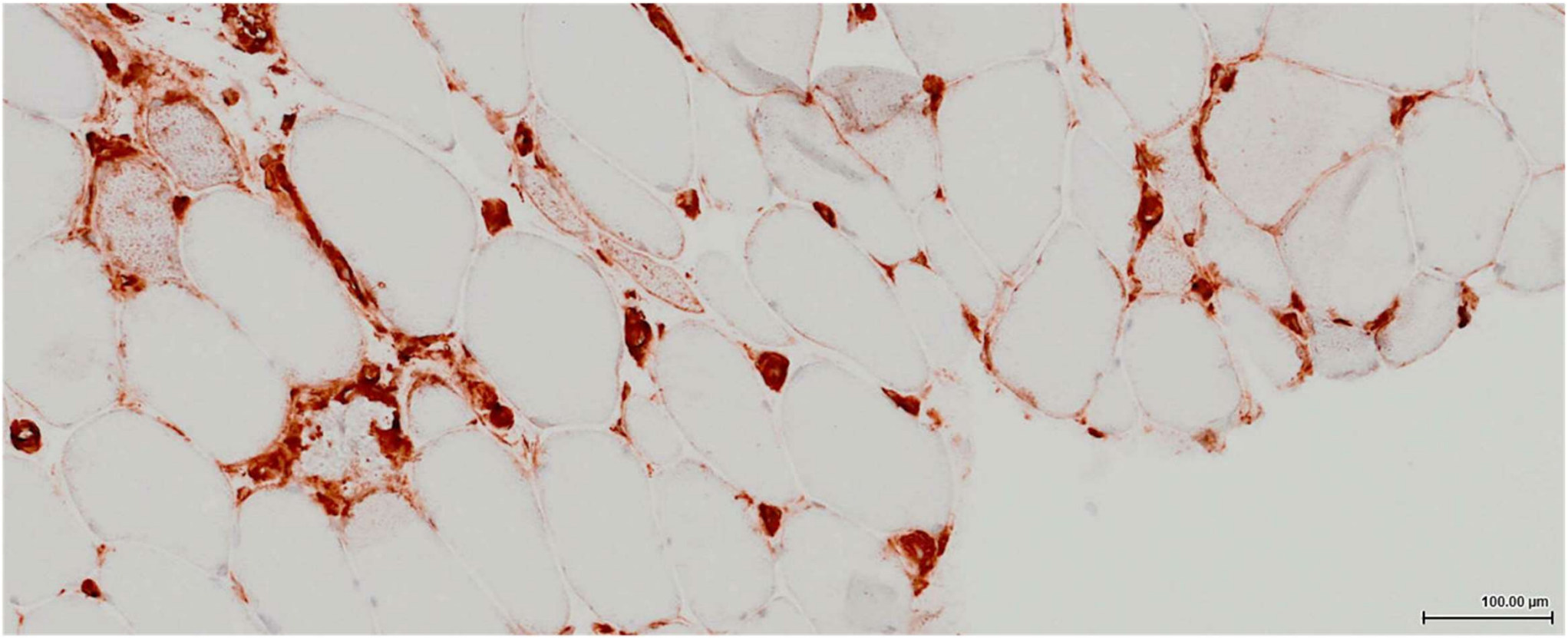
MAC staining



MAC Staining



MHC1 staining

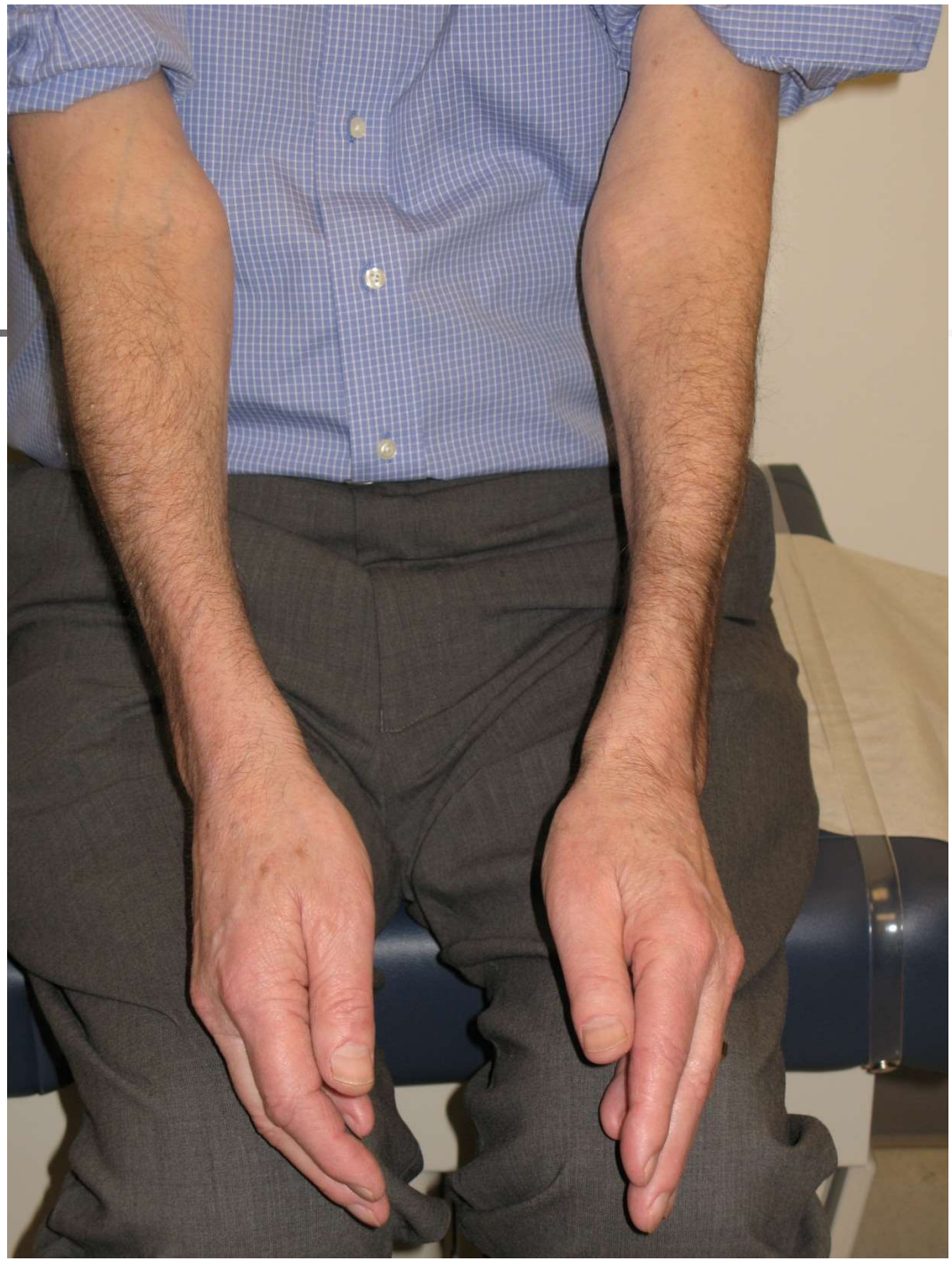


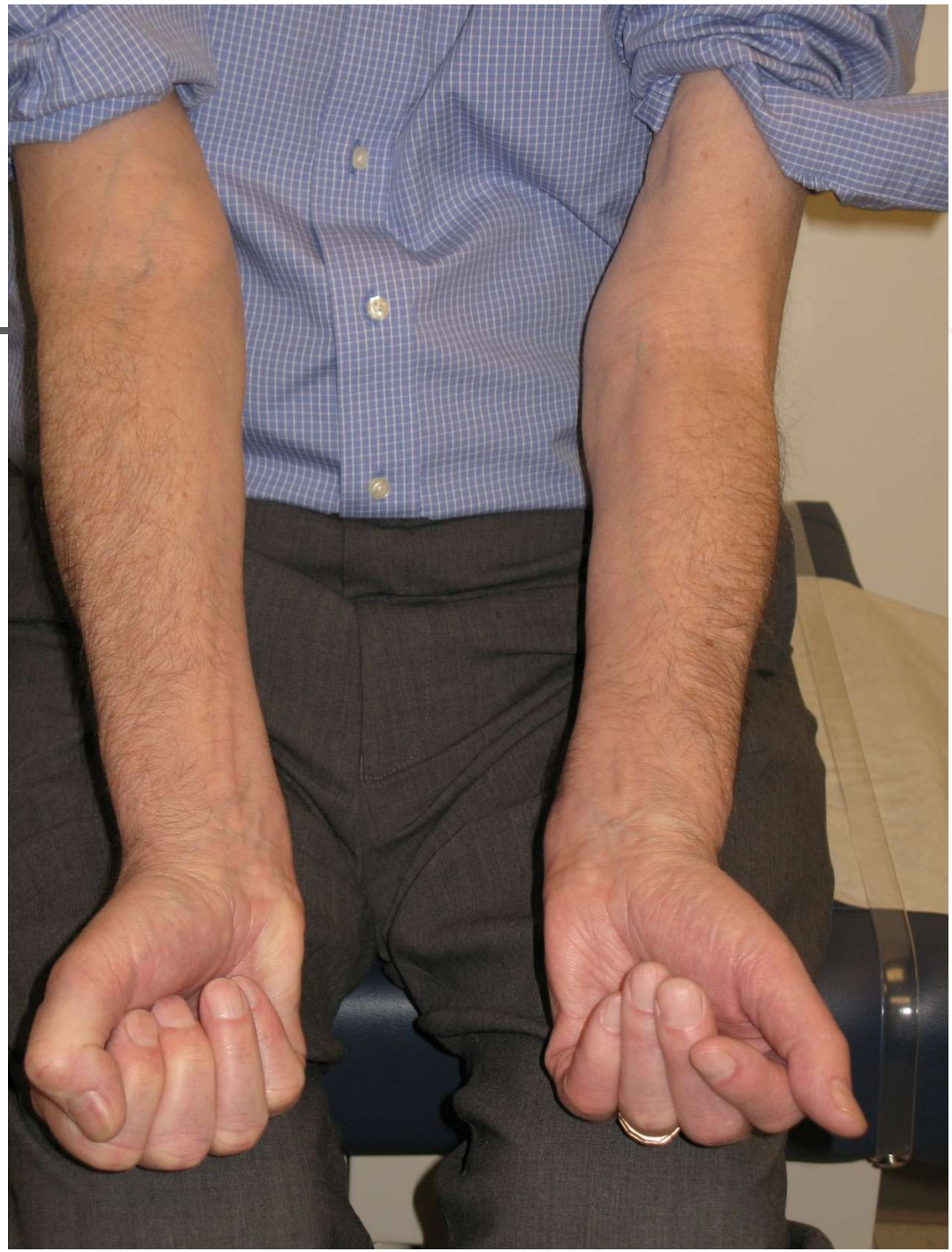
INCLUSION BODY MYOSITIS

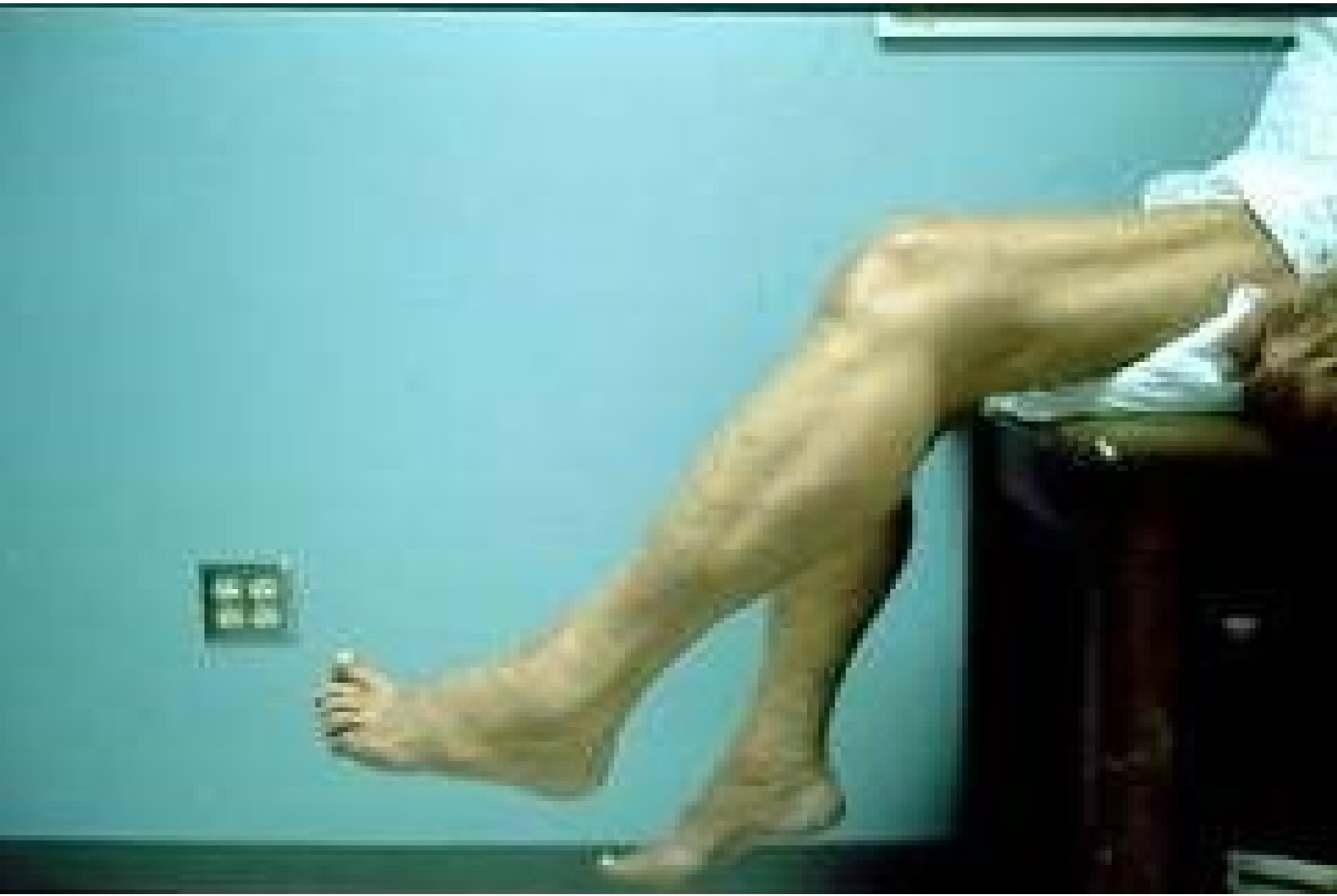
- Clinical Features
  - frequently misdiagnosed as PM
  - insidious onset and slowly progressive (average duration of symptoms prior to dx is 6 yrs)
  - men affected more than women
  - usually develops over the age of 50 years (most common myositis in patients presenting over the age of 50 years)

INCLUSION BODY MYOSITIS

- Clinical hallmark is early weakness and atrophy of the quadriceps and volar forearm muscles (wrist / finger flexors)
- MRC scores of the quadriceps and wrist/finger flexors are often lower than the hip flexors and shoulder abductors
  - contrasts with the pattern of weakness seen in DM and PM
  - This pattern is seen in about 2/3rds of IBM at presentation

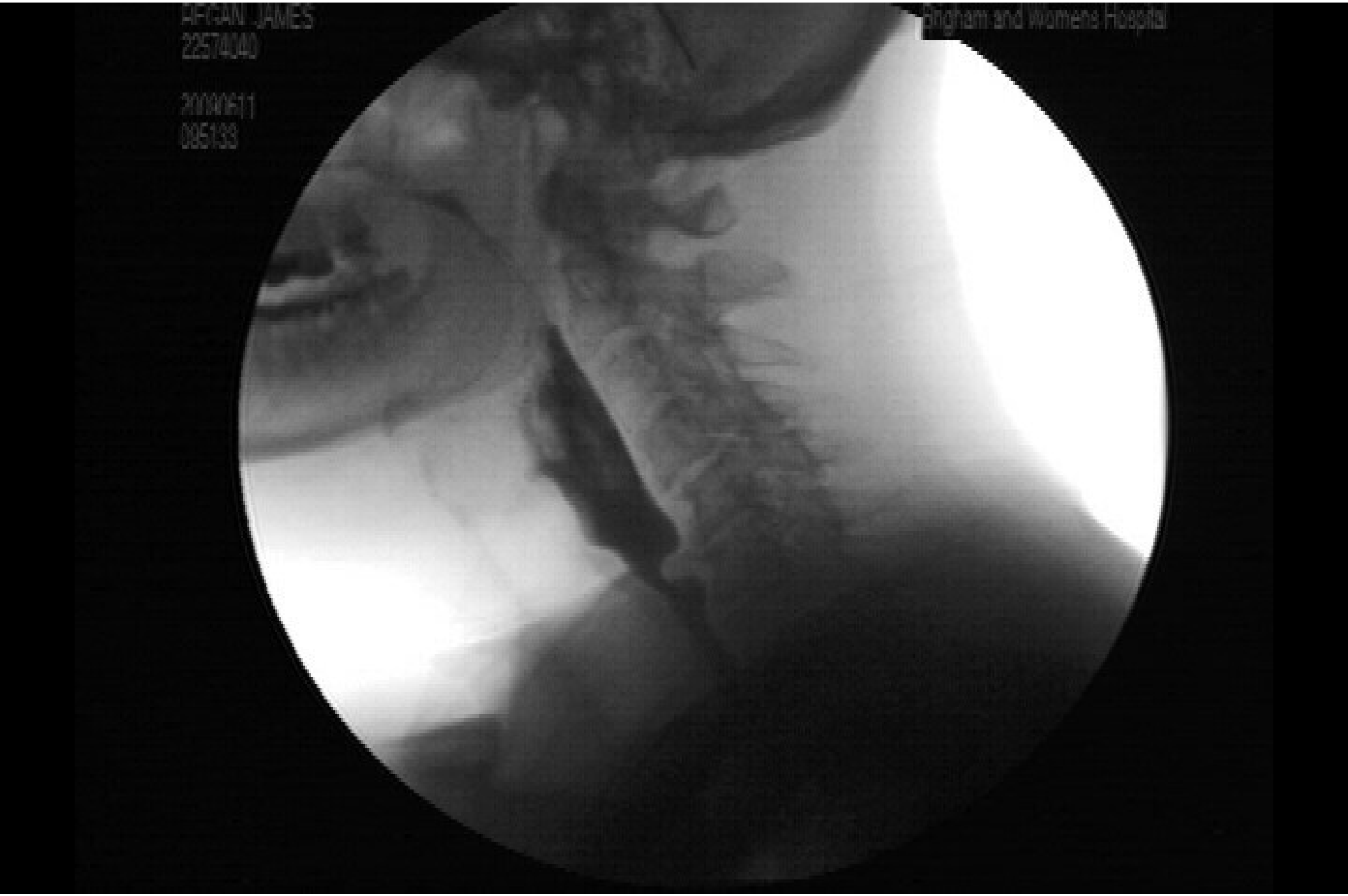






INCLUSION BODY MYOSITIS

- 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

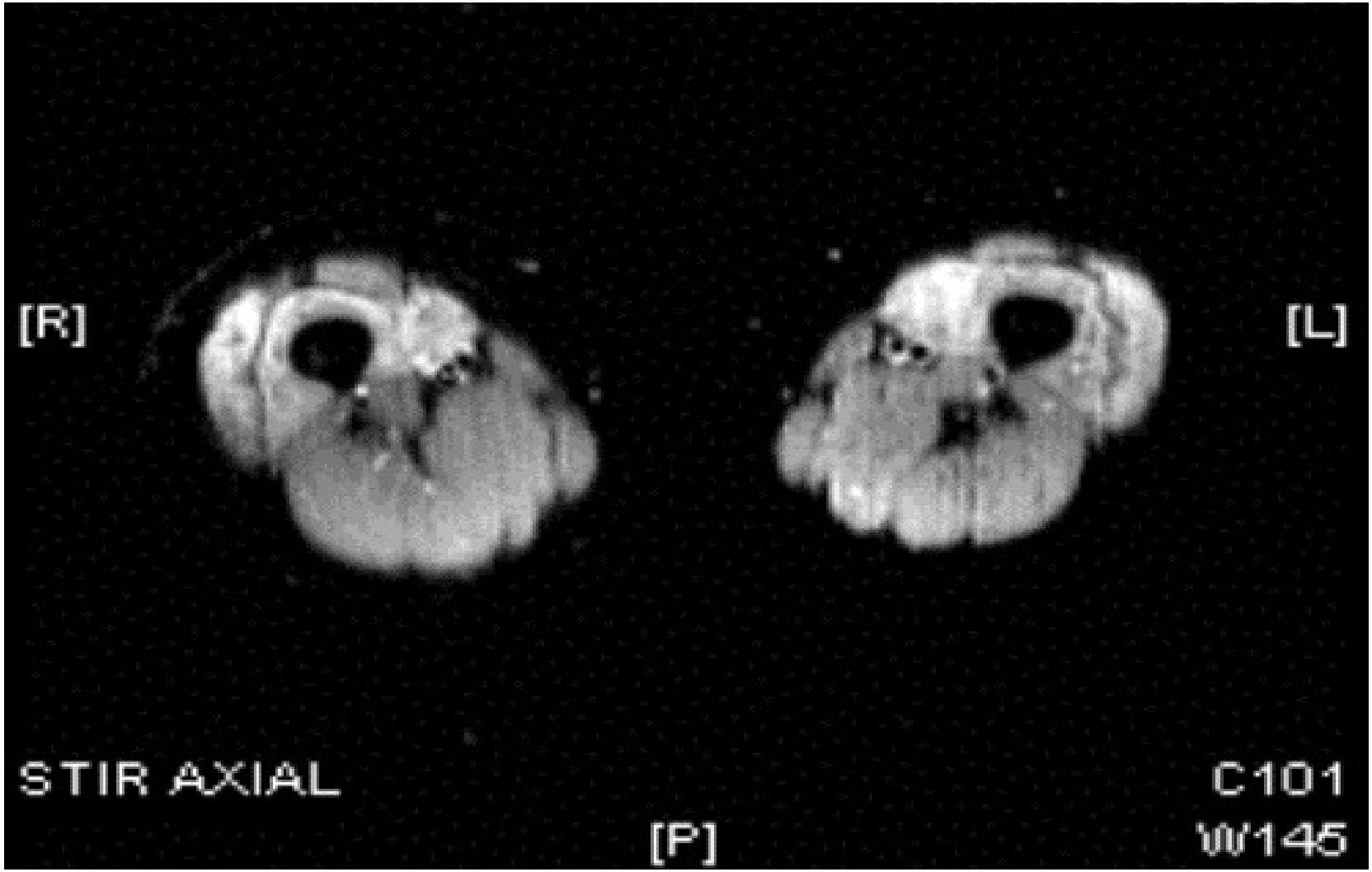

BRIGAN, JAMES
22574040
Brigham and Womens Hospital

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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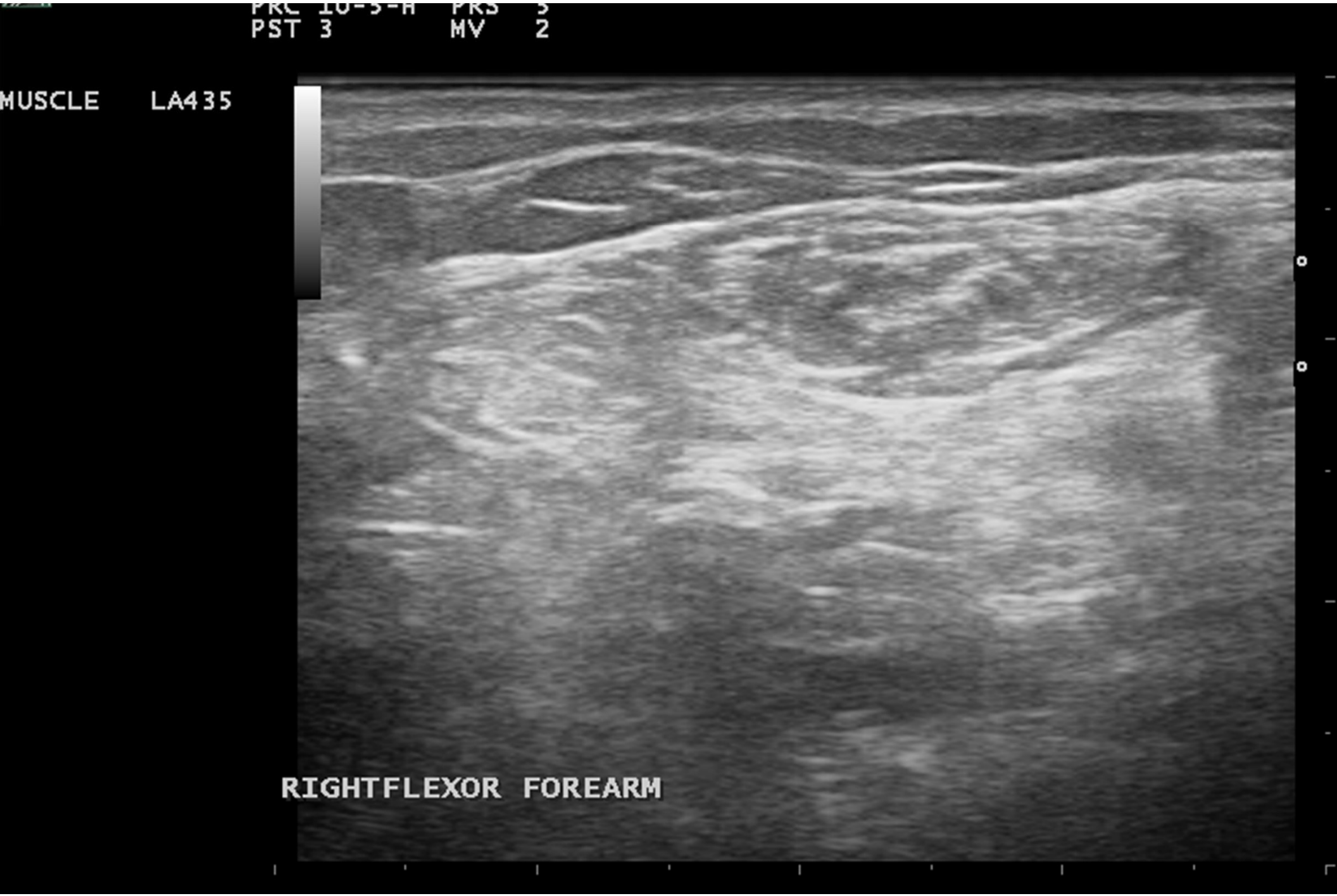
[L]
STIR AXIAL
C101
[P]
W145


PRC 10-5-H PRS 5
PST 3 MV 2
MUSCLE LA435
RIGHTFLEXOR FOREARM

INCLUSION BODY MYOSITIS

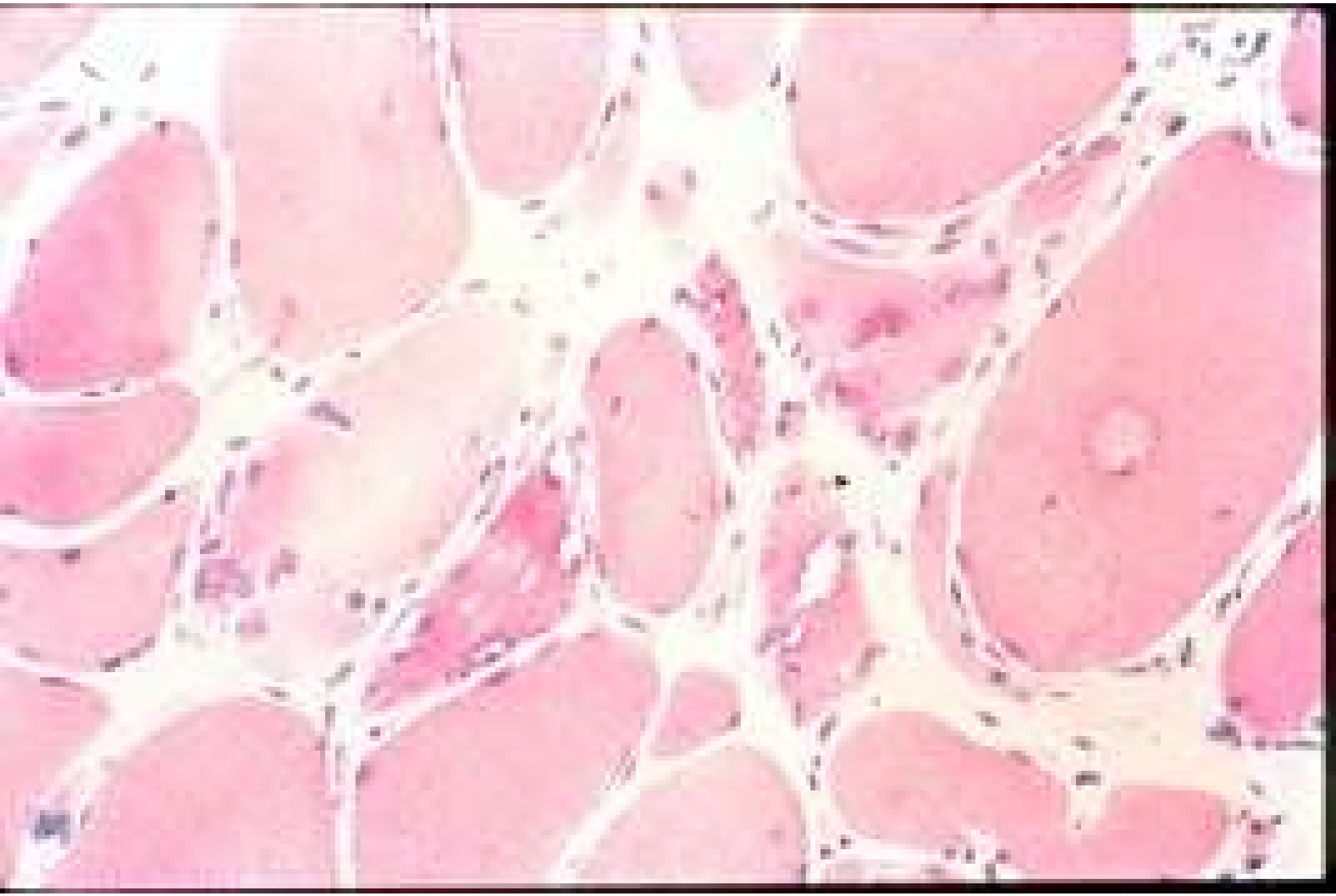
- Electrophysiological Studies
  - nerve conduction studies demonstrate an axonal sensory neuropathy in 30%
  - EMG may reveal large polyphasic motor unit potentials in addition to the small MUPs
    - not specific for IBM but can be seen in DM, PM, and other chronic myopathies
    - reflects chronicity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

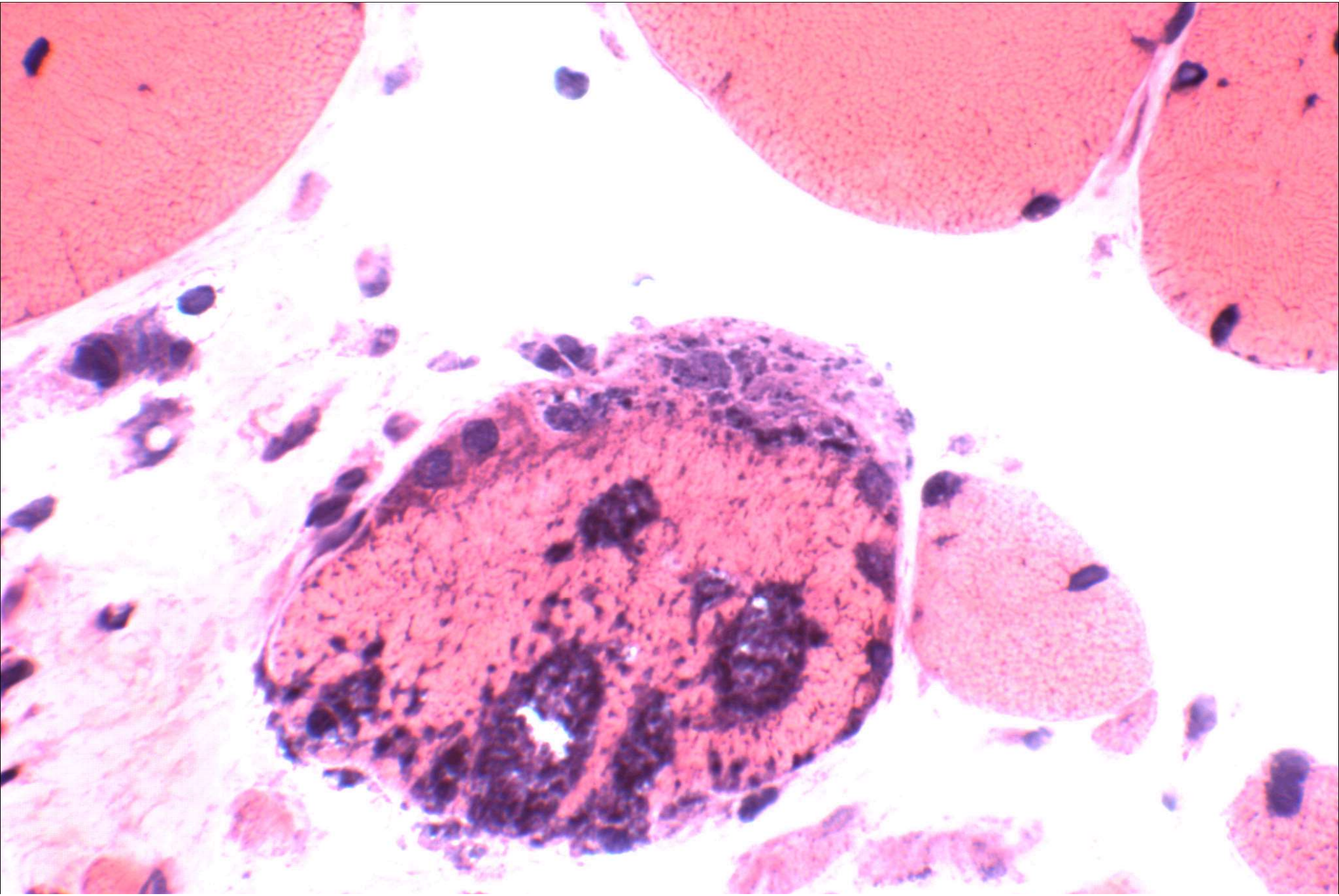
INCLUSION BODY MYOSITIS

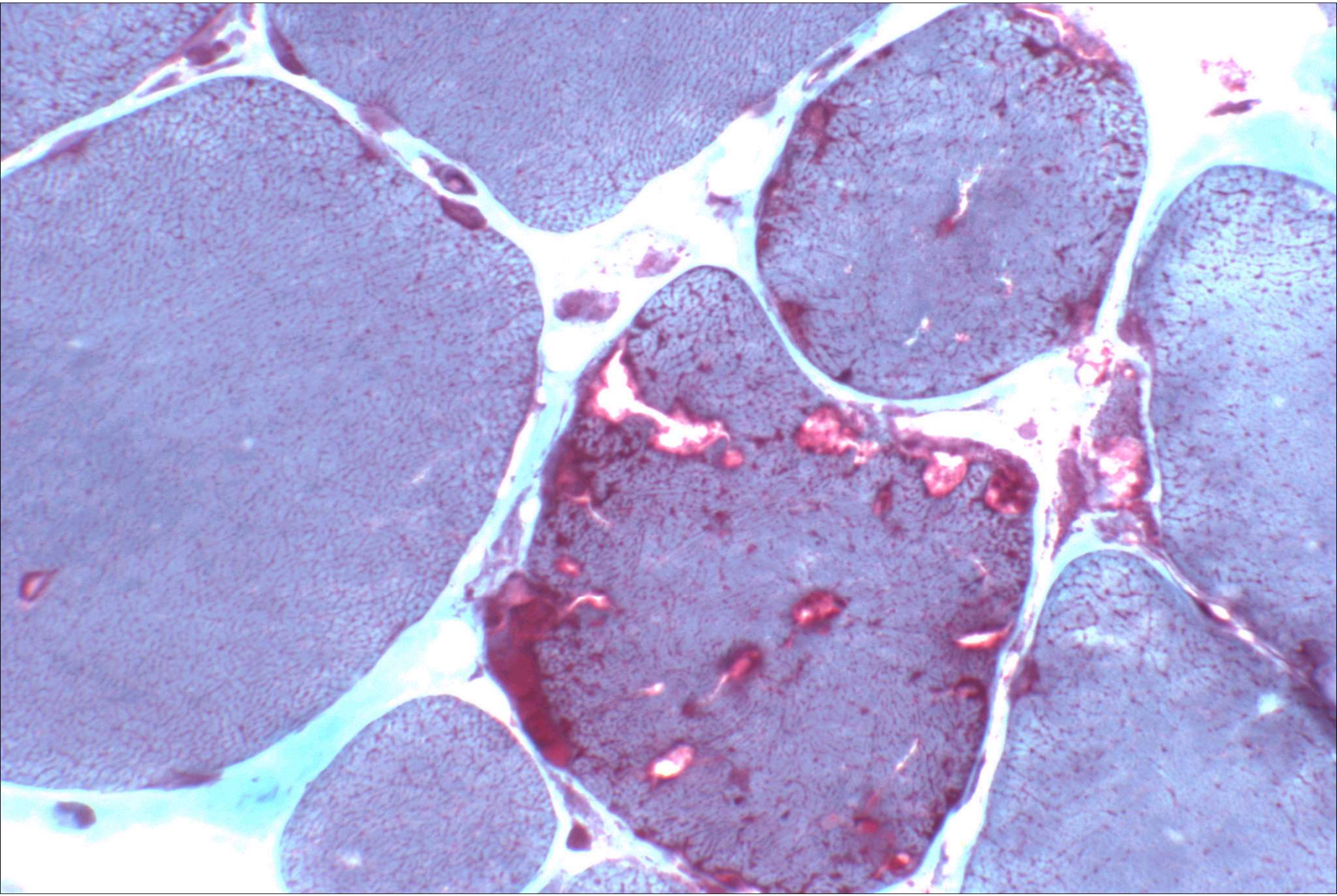
- Muscle Biopsy
  - endomysial inflammation composed of CD8+ T-cells and macrophages which invade non-necrotic muscle fibers expression MHC-1 antigen
  - small groups of atrophic fibers
  - muscle fibers with one or more rimmed vacuoles lined with granular material
  - eosinophilic cytoplasmic inclusions

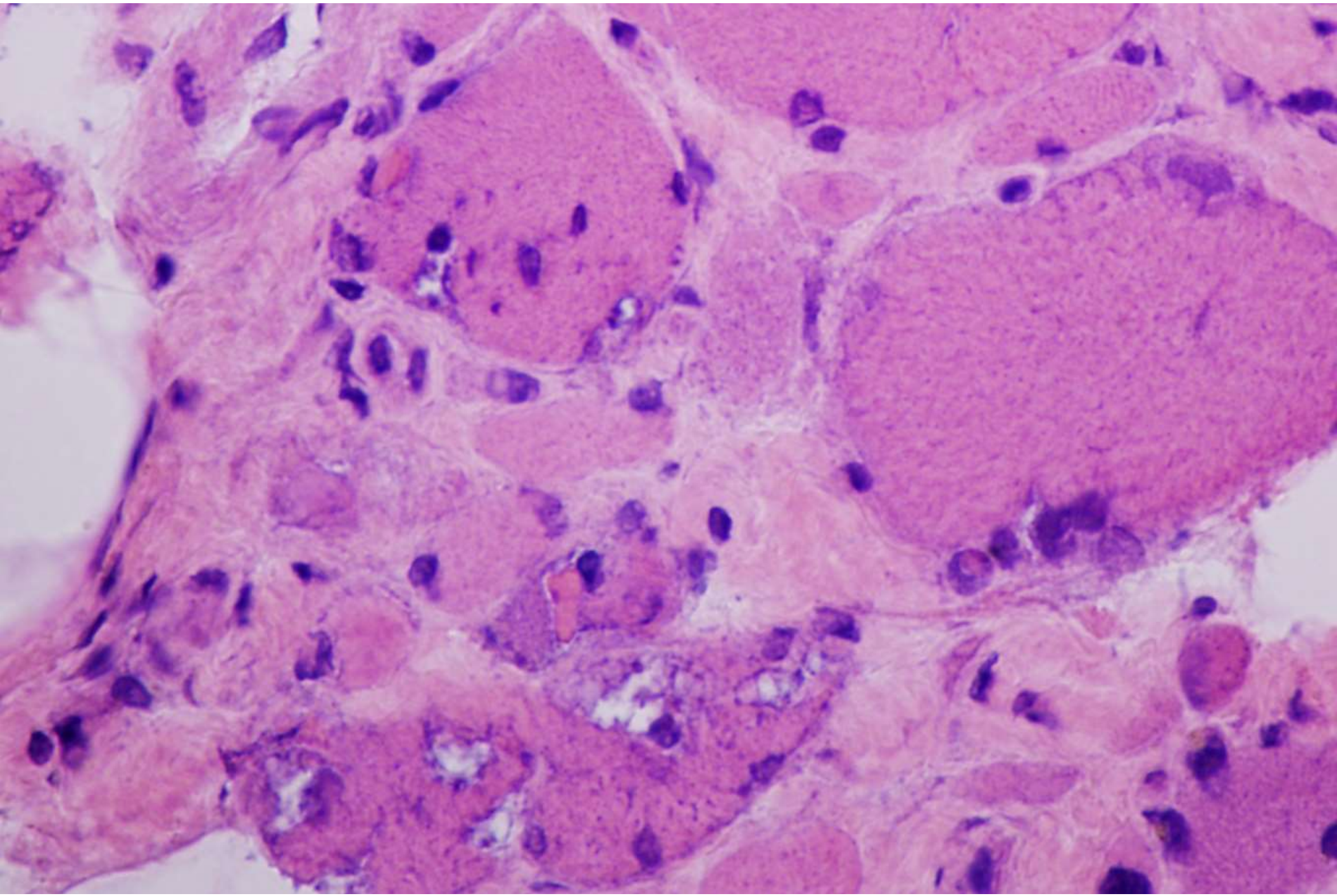
INCLUSION BODY MYOSITIS

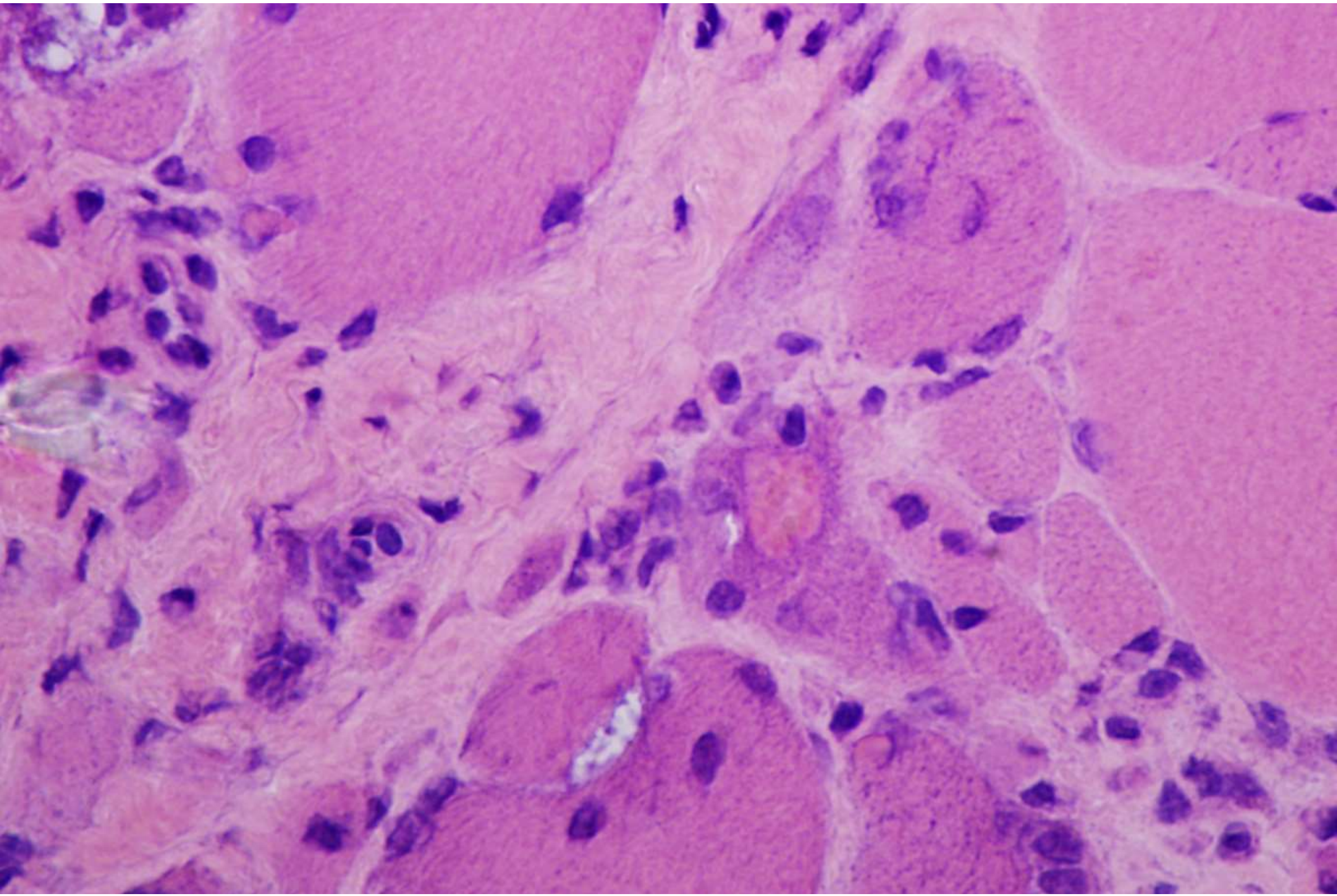
- amyloid deposition is evident in the cytoplasm of vacuolated muscle fibers and occasionally in nuclei
- electron microscopy demonstrates 15-21 nm tubulofilaments in the cytoplasm and less commonly in nuclei of muscle fibers
- increased incidence of ragged-red fibers (mitochondrial abnormalities)

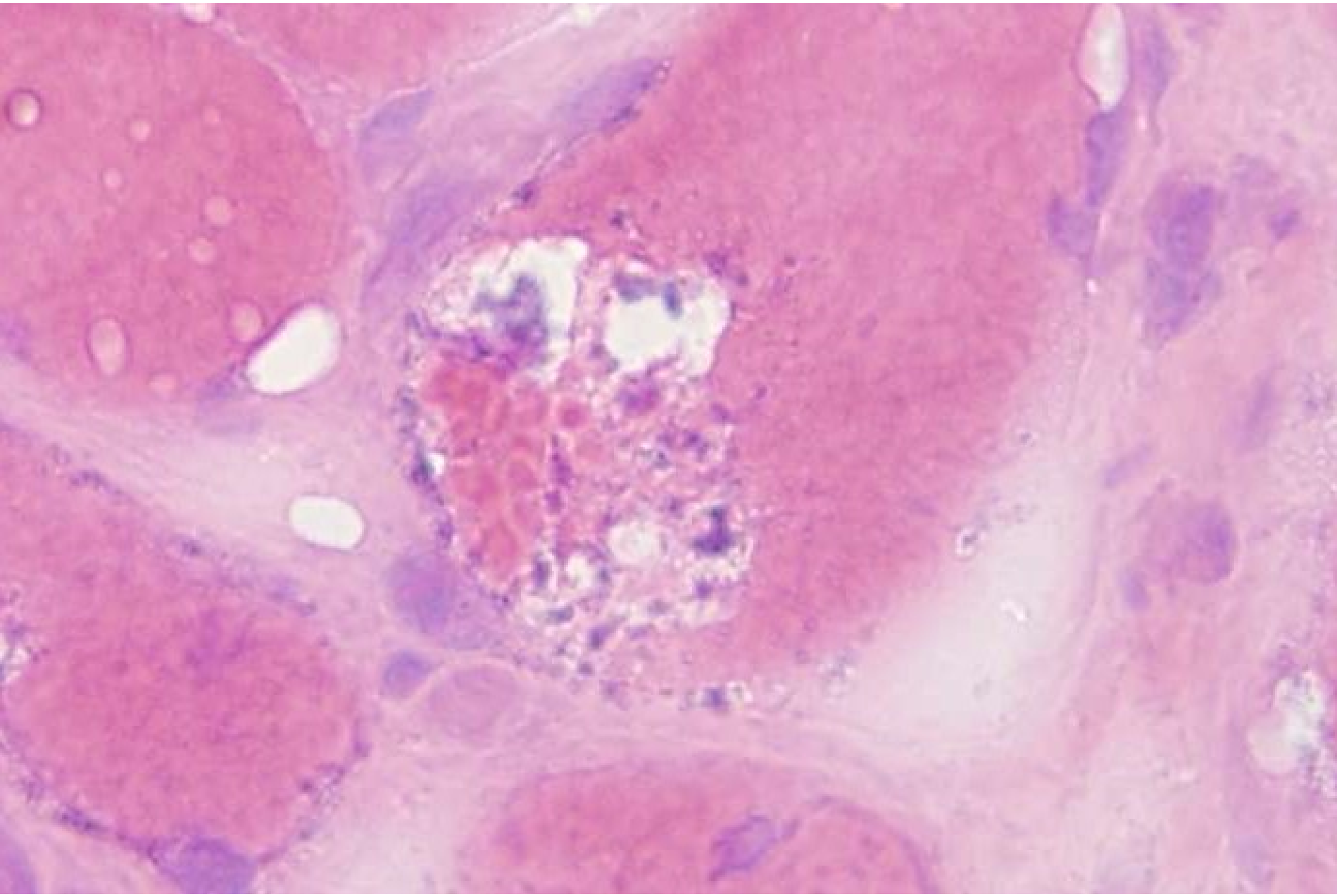


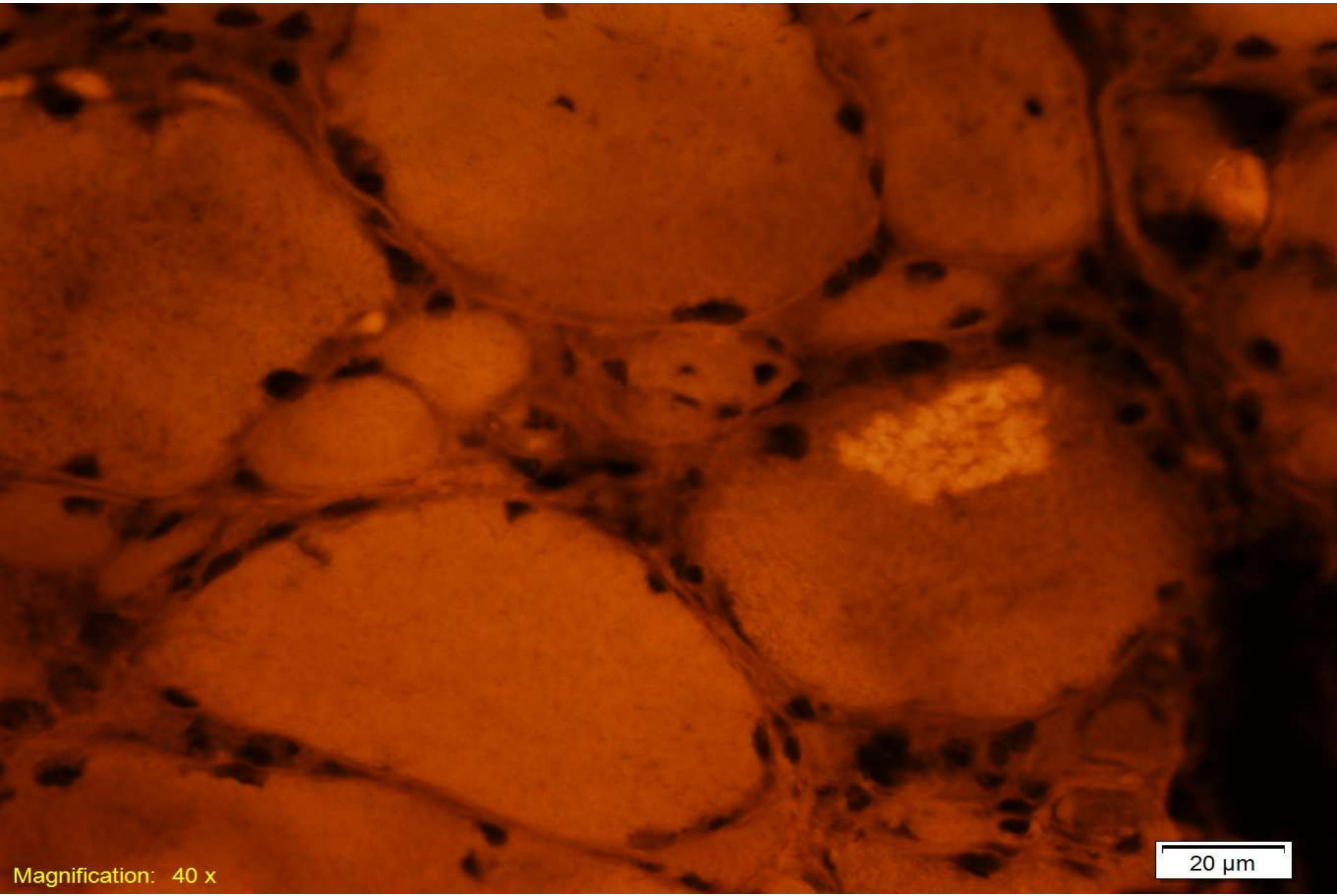








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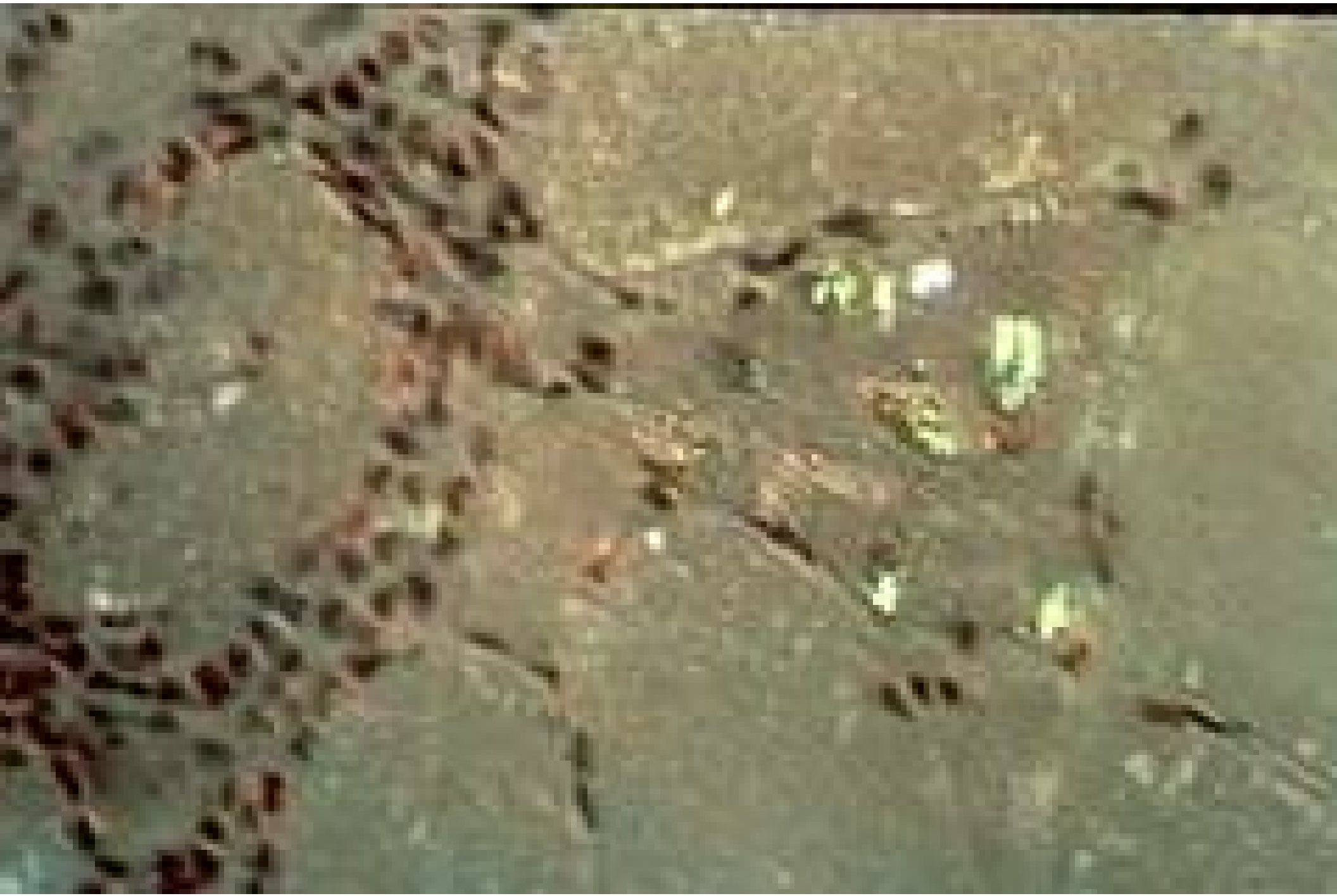

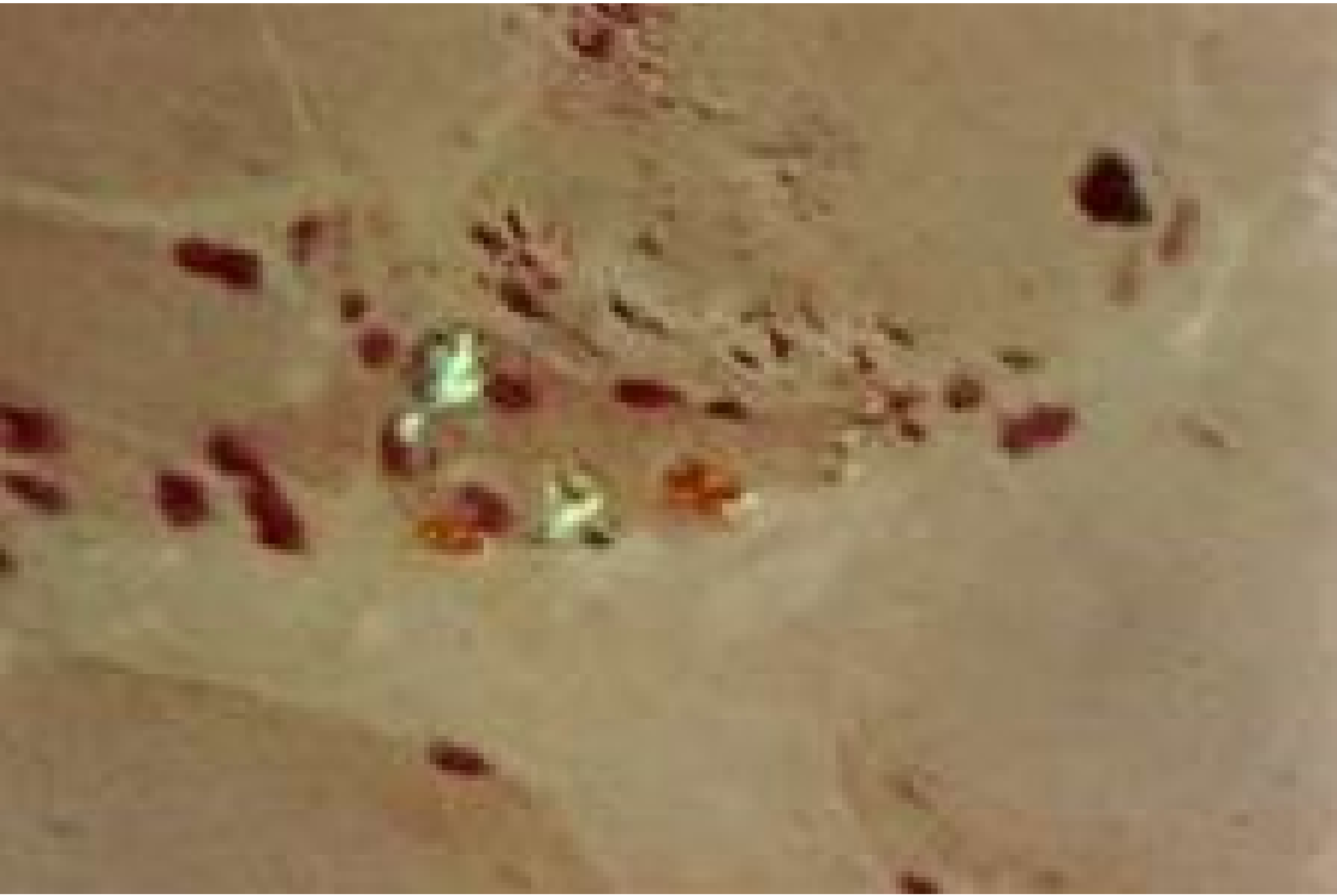

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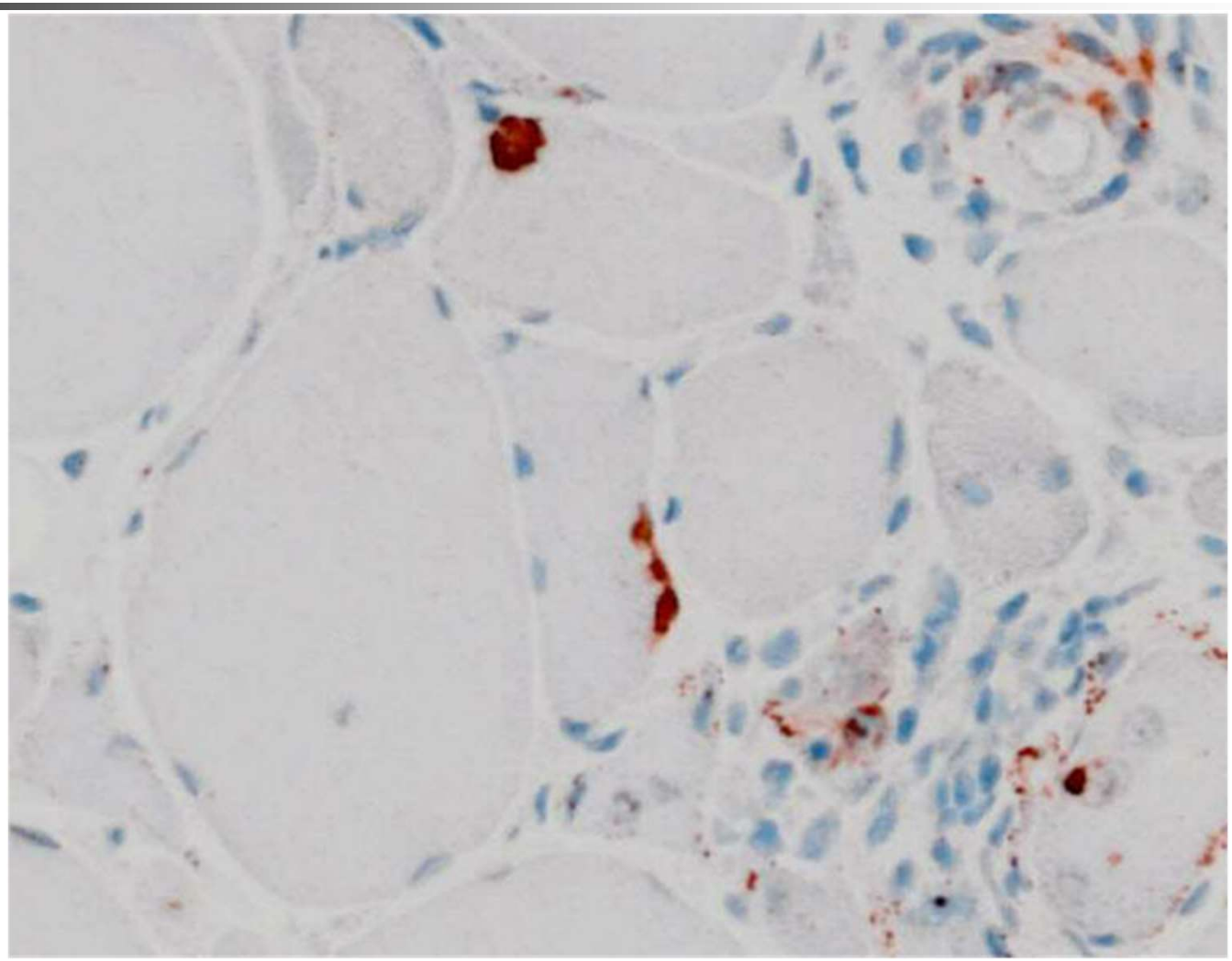

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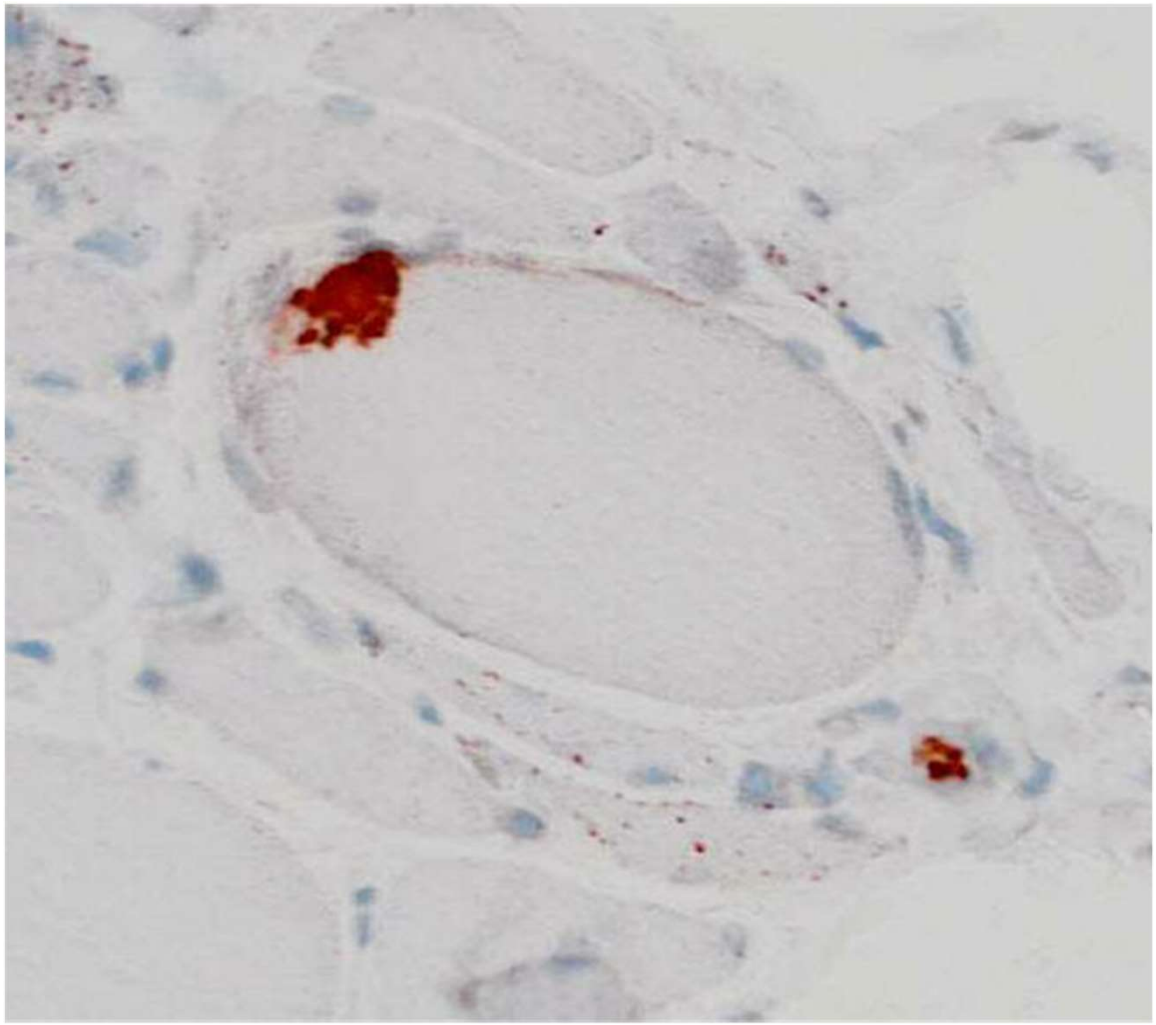
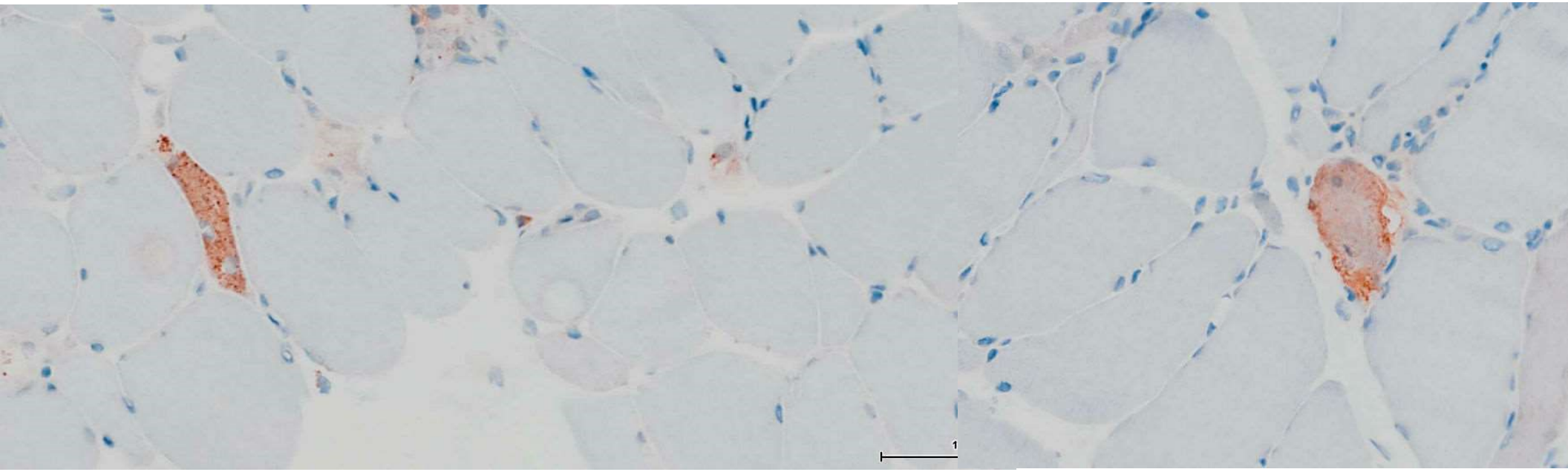
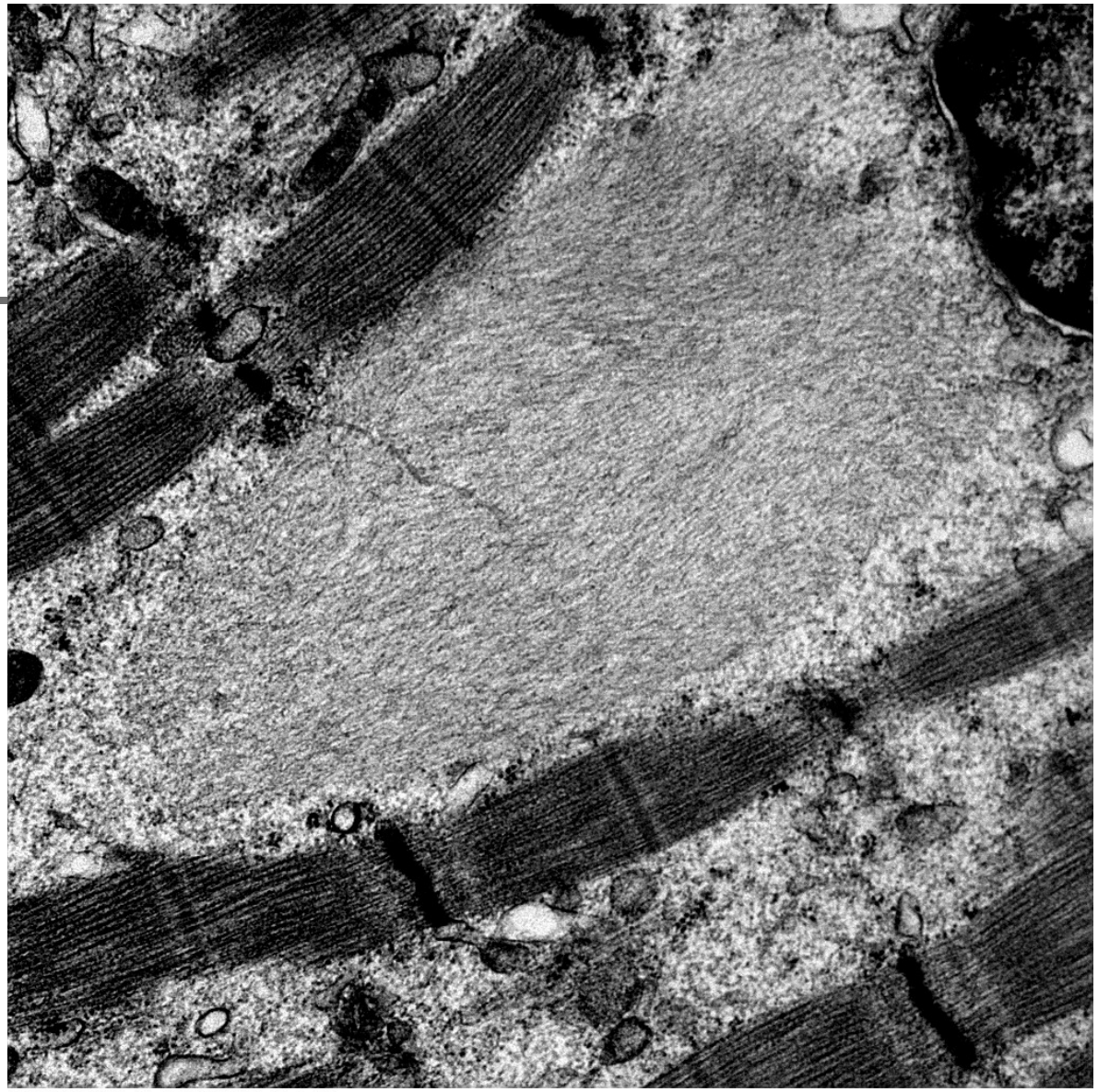


p62 in Necrotizing Myopathy



IBM



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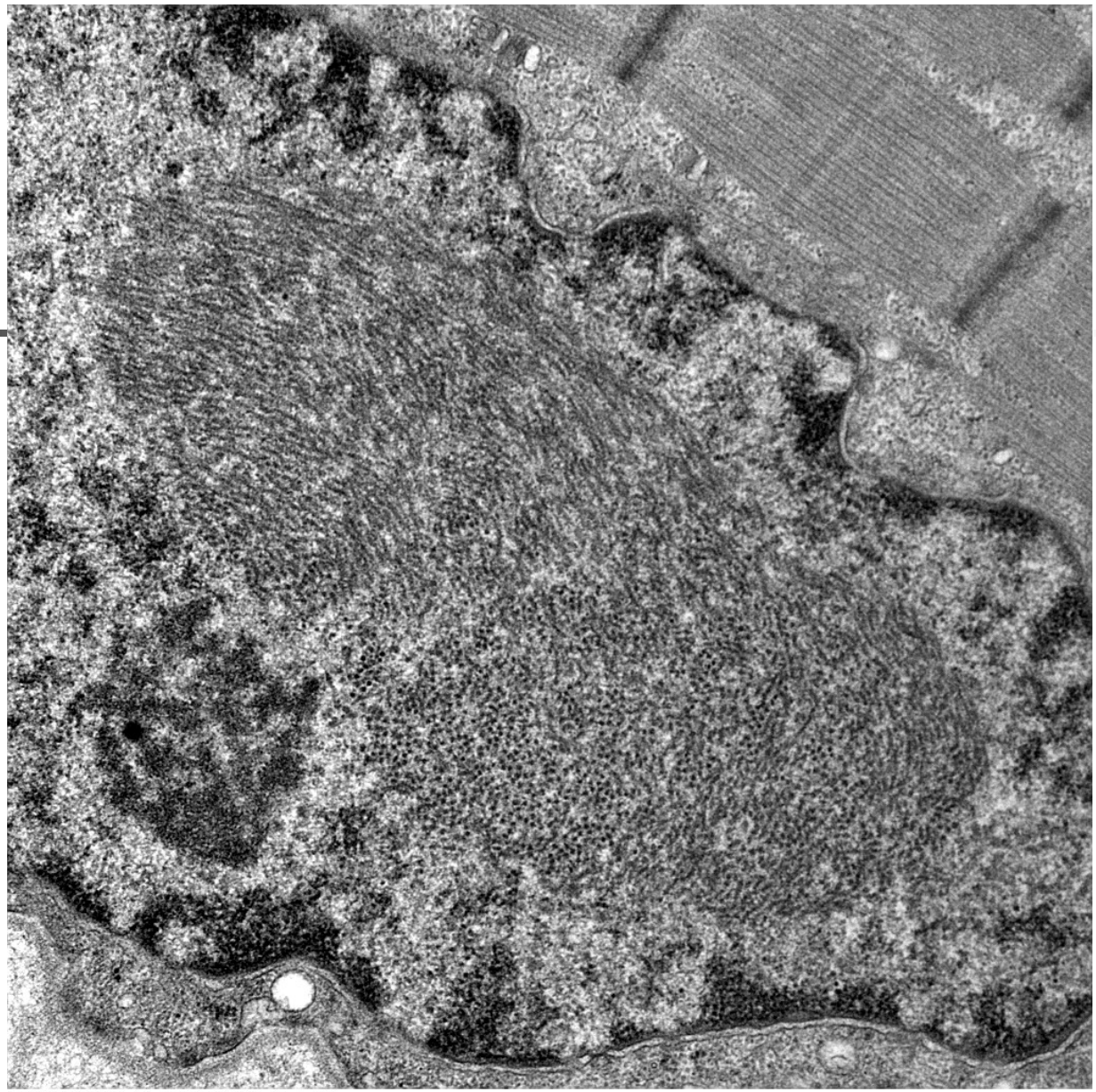

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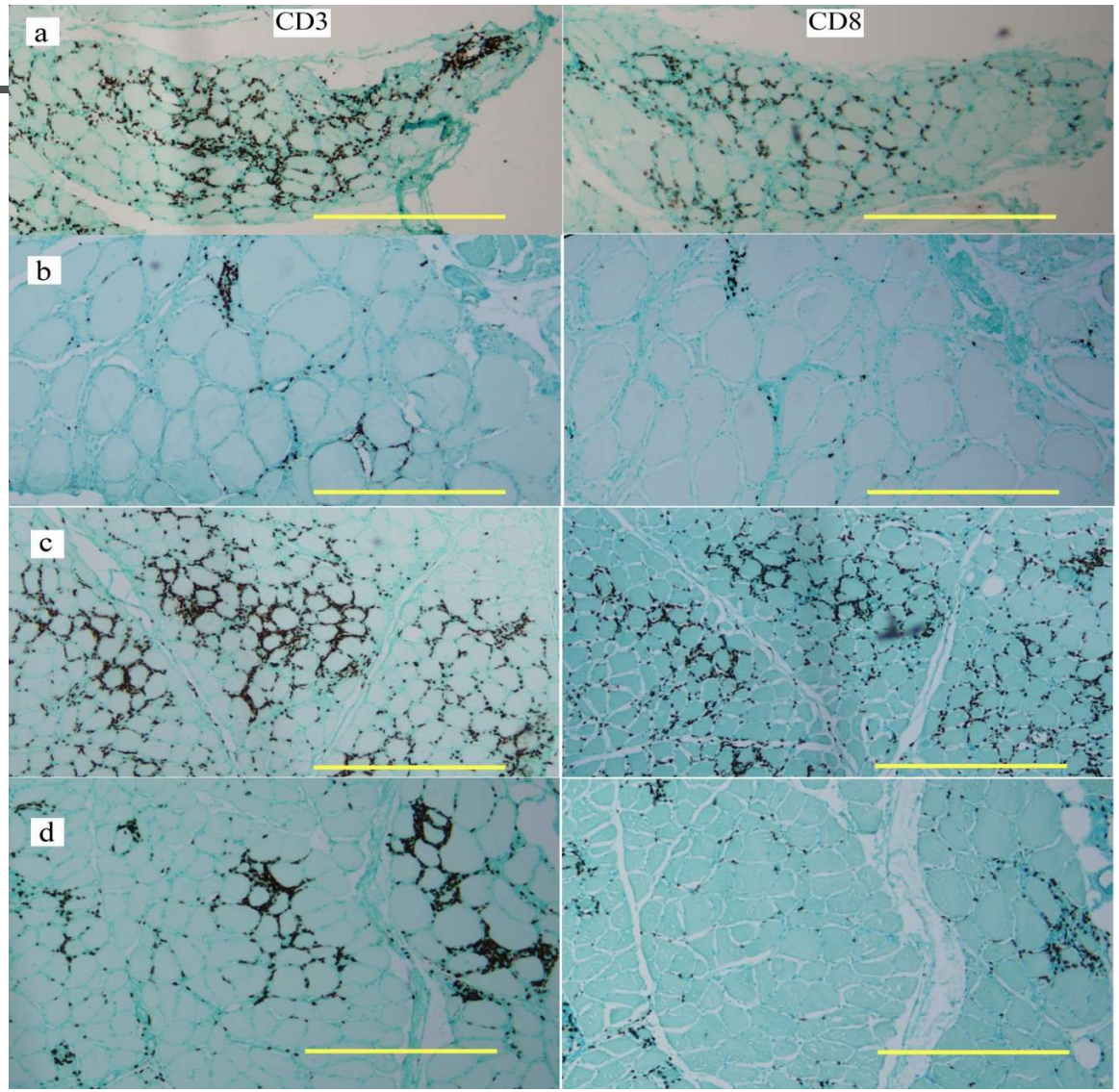
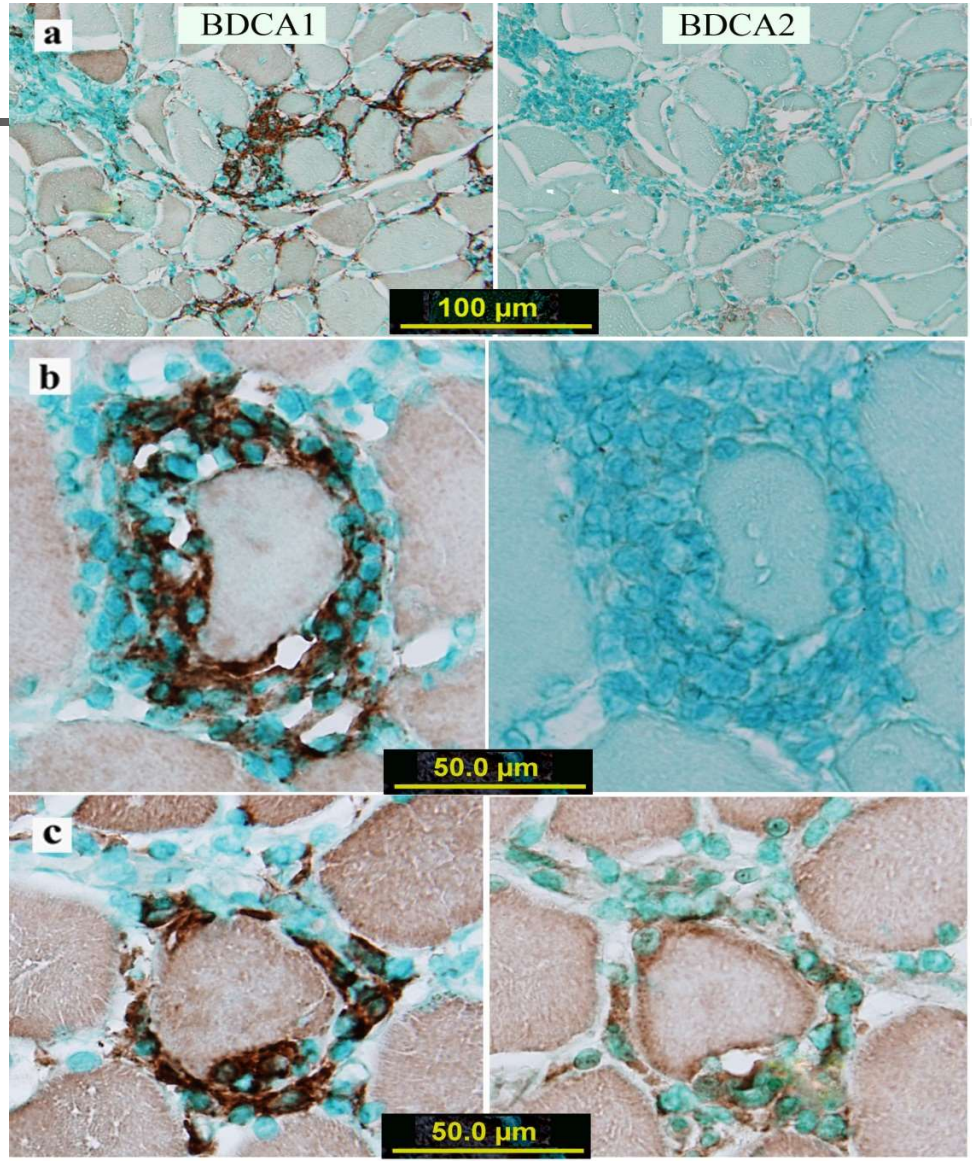
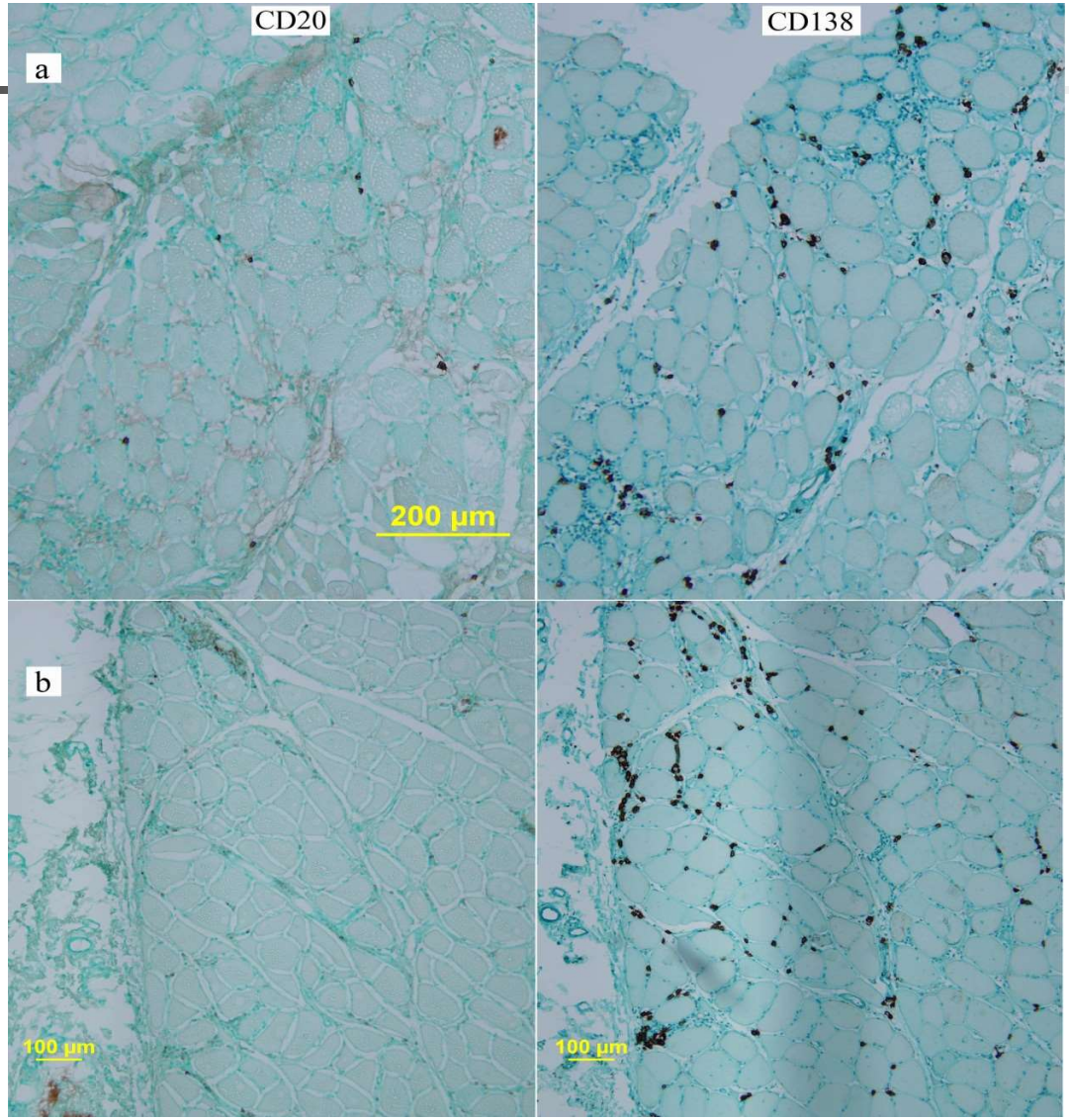
Inflammatory Cells in IBM

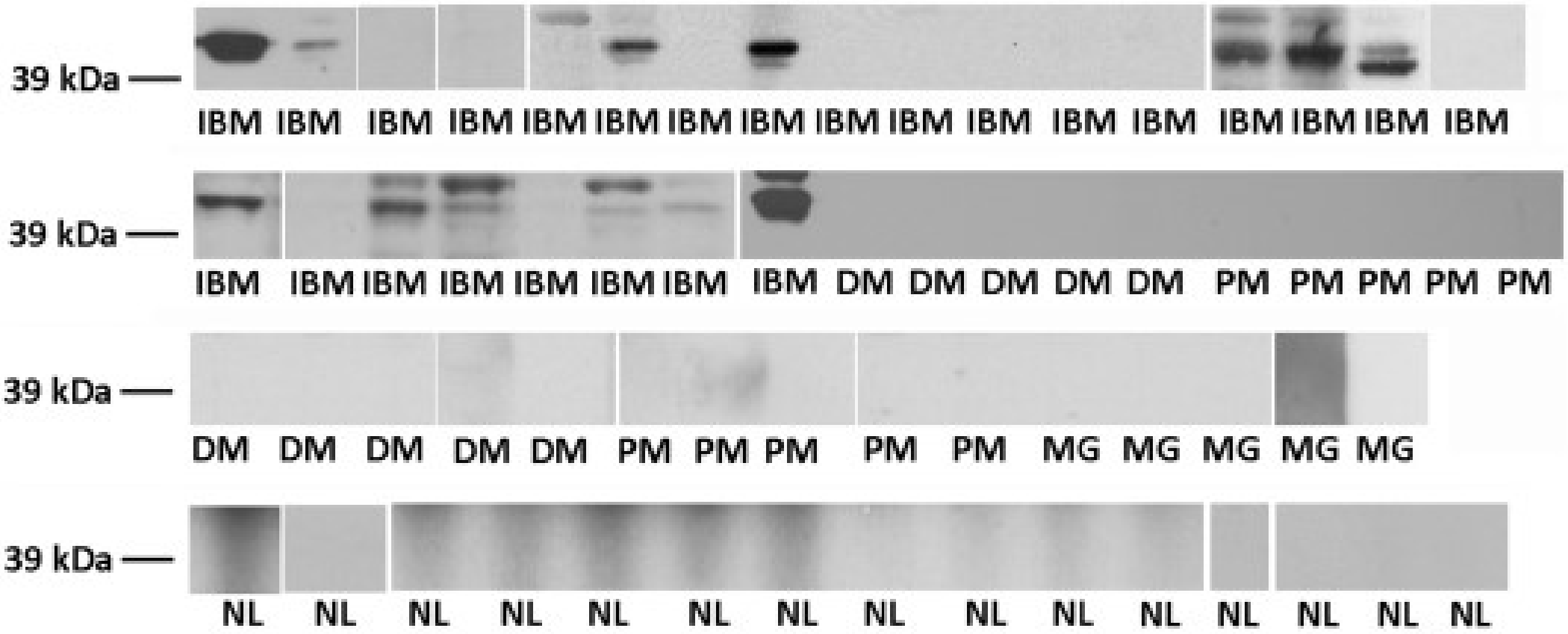


BDCA 1+ Dendritic Cells in IBM



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

NT5C1A

- NT5C1A is a cytosolic nucleotidase that is most abundant in skeletal muscle
- It catalyzes nucleotide hydrolysis to nucleosides, and is involved in a variety of functions, including regulation of deoxynucleotide pools
- Several enzymes involved in DNA repair have similar nucleotidase sequence motifs suggesting that NT5C1A may be involved in DNA repair metabolism

IBM autoantibodies

- Autoantibodies against NT5C1A are common in and highly specific to IBM among muscle diseases, and may provide a link between IBM's dual processes of autoimmunity and myodegeneration
- NT5C1A reactivity by immunohistochemistry accumulated in perinuclear regions and rimmed vacuoles in IBM muscle, localizing to areas of myonuclear degeneration
- Blood diagnostic testing is available and should improve early and reliable diagnosis of IBM

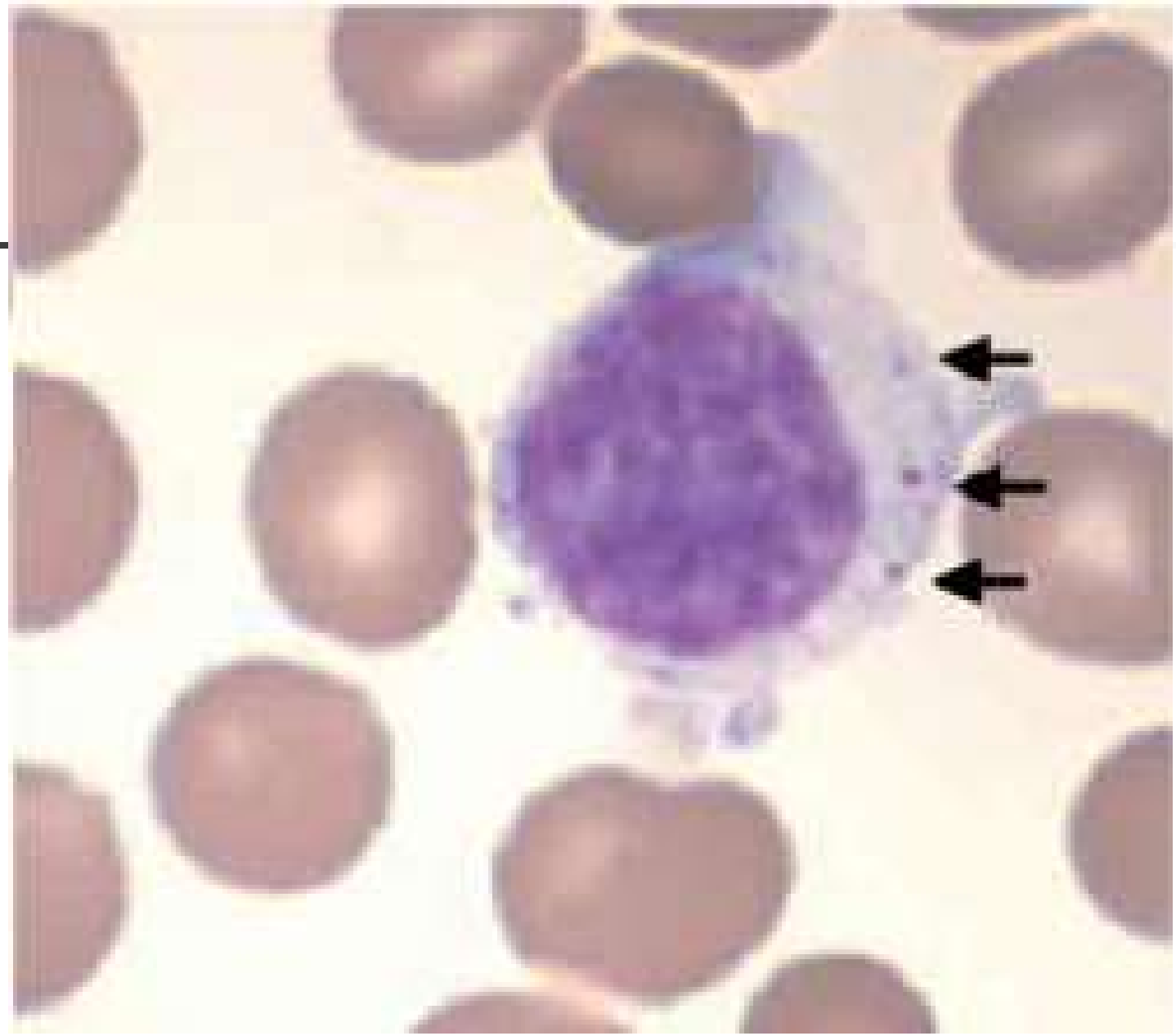
Brain Advance Access published February 26, 2016

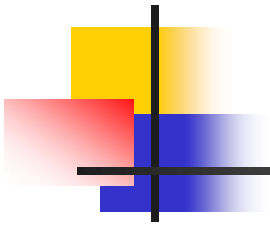
doi:10.1093/brain/aww024 BRAIN 2016: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

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

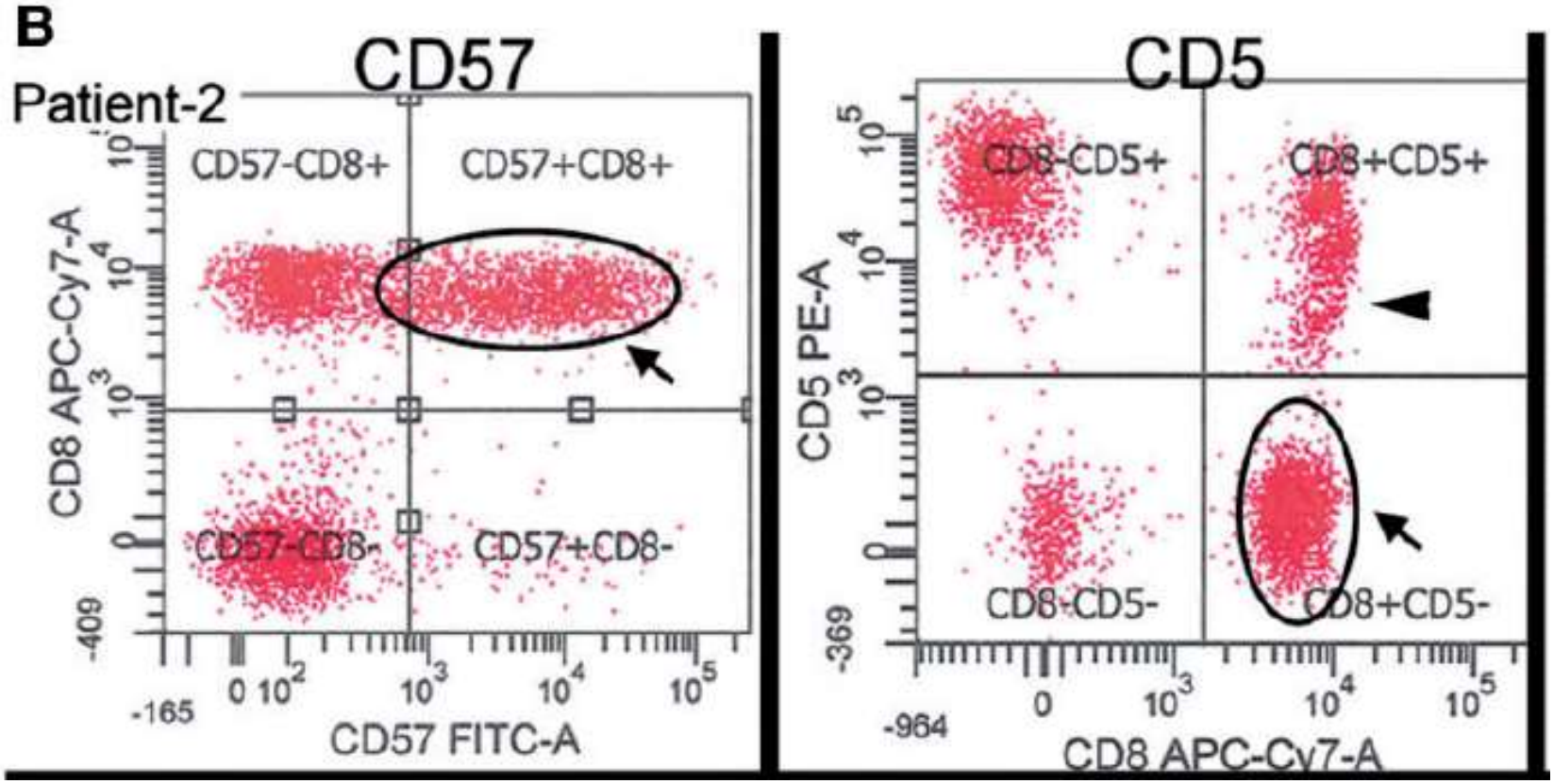
Steven A. Greenberg,[1,2] Jack L. Pinkus,[1] Anthony A. Amato,[1] Thomas Kristensen[3] and David M. Dorfman[4]





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

CD57+/CD8+ and CD8+/CD5-



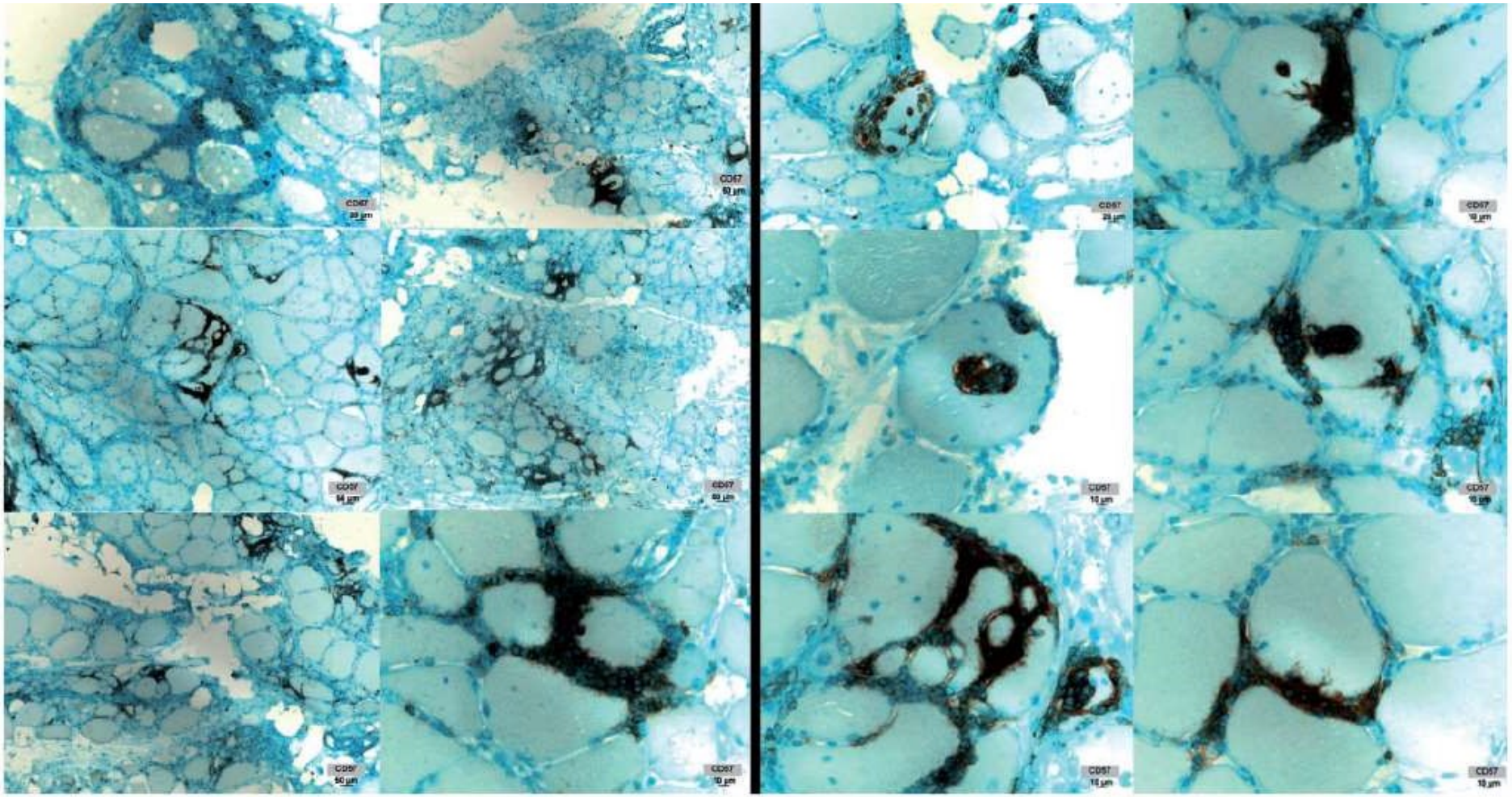


Figure 6 IBM muscle CD57+ cell infiltration. (**A**) Dense T cell infiltrates containing CD57+ cells. (**B**) Myofibre invasion by CD57+ cells. Images from six patients shown. With permission, Inclusion Body Myositis Foundation.

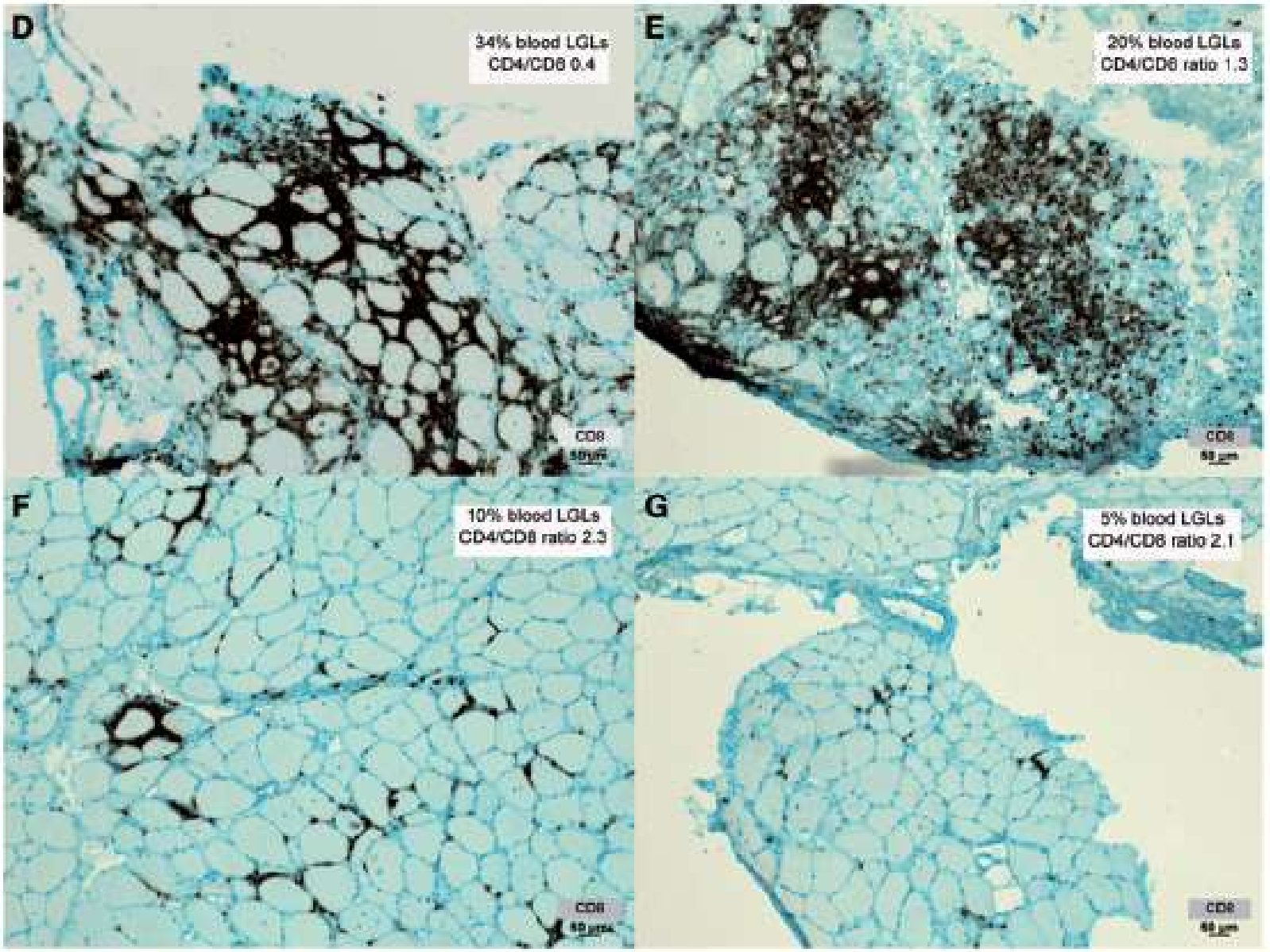
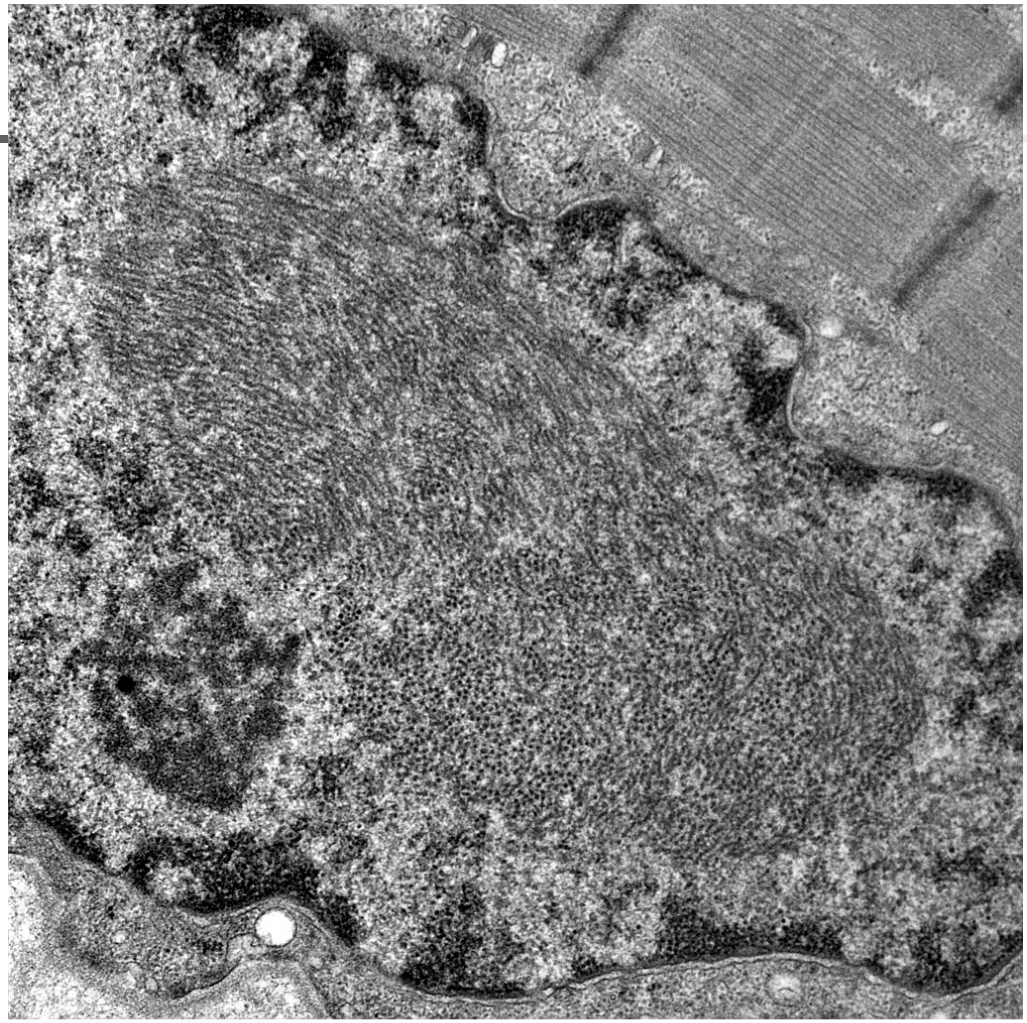


Figure 7 Blood LGL expansions and reduced CD4/CD8 ratios are associated with muscle CD8 and CD57 inflammatory grade. (**A–C**) Increased numbers of muscle CD8+ cells and CD57+ cells is correlated with increased numbers of CD8+ CD57+ blood LGLs and reduced CD4/CD8 ratios. (**D–G**) CD8 immunohistochemistry 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.

IBM



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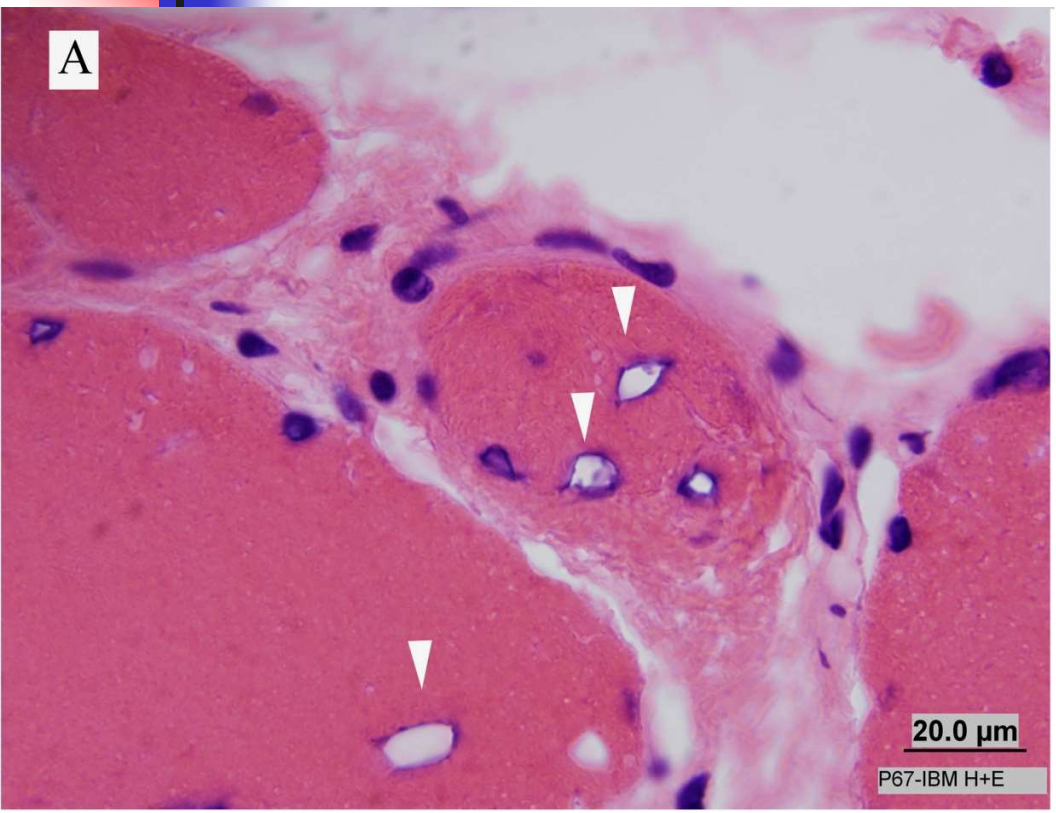

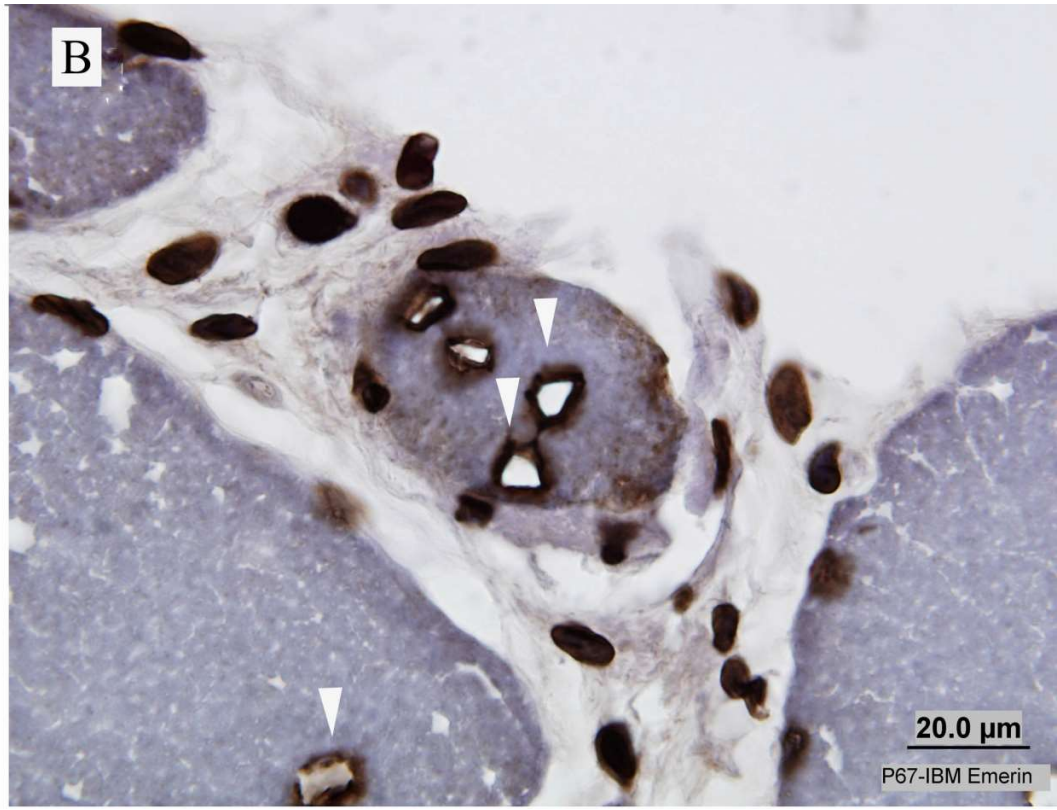

INCLUSION BODY MYOSITIS

- T-cell receptor repertoire of endomysial infiltrate demonstrates an oligoclonal pattern of gene rearrangement and heterogeneity in the CDR3 domain
- Possible T-cell response against a superantigen
- Oligoclonal expansion of B-cells and plasma cells in muscle tissue and increased incidence of monoclonal antibodies in serum and a MSA directed against cytosolic 5'-nucleotidase IA in approximately two-thirds of patients

INCLUSION BODY MYOSITIS

- Because of sampling error repeat muscle biopsies and extensive EM may be required to confirm the clinical impression of IBM
- Criteria for definite and clinically possible and probable IBM have been developed
- NT5C1A antibodies may be helpful
- T-LGL and decreased CD4/C8 ratio < 1.5

INCLUSION BODY MYOSITIS

- Pathogenesis
  - ? distinct, primary inflammatory myopathy
  - ? primary degenerative myopathy with secondary inflammation
  - Could this be caused by a viral infection in genetically susceptible individuals leading to both of the above?

IDIOPATHIC INFLAMMATORY MYOPATHIES

- Summary
  - DM, PM, antisynthetase syndrome, NM, and IBM are clinically, histologically, and pathogenically distinct
  - DM is an immune-mediated disorder possibly due to a direct toxic effect of type 1 interferons on small blood vessels and muscle fibers
  - PM is a T-cell mediated disorder directed against muscle fibers
  - Pathogenesis of antisynthetase syndrome, NM and IBM are unknown

IDIOPATHIC INFLAMMATORY MYOPATHIES

- DM , PM, antisynthetase syndrome, and NM are responsive to various immunosuppressive medications
- IBM is refractory to immunosuppressive therapy
- Prospective, double-blind, placebo-controlled trials are necessary to determine prognostic features and the best treatment options

Acknowledgements

Special THANKS to Steven A. Greenberg, MD and members of the Greenberg Lab

Questions 1

A 60 year old man presents with severe and progressive proximal greater than distal muscle weakness in the arms and legs for past 4 months along with a rash

Cardiac and lung function are normal

He has poorly controlled diabetes, renal insufficiency, and osteoporosis.

He also has frequent gout requiring allopurinol and hypercholesterolemia requiring a statin agent for 10 years.

He had a muscle biopsy that demonstrates perivascular inflammation in the perimysium along with perifascicular atrophy.

Question 1

The best course of treatment would be:

- A. Prednisone 1 gm/kg
- B. Prednisone 1 gm/kg and methotrexate
- C. Prednisone 1 gm/kg and azathioprine
- D. Prednisone 1 gm/kg and cyclosporine
- E. Discontinue the statin medication and observe

- Answer: B
- The patient has severe dermatomyositis requiring immunosuppressive therapy. Although there are a few reports of dermatomyositis occurring in the setting of a statin agent the causal relationship is unclear- particularly if the patient has been on the agent for 10 years. Corticosteroids are the treatment of choice but because of the diabetes and osteoporosis, it would be advisable to start a steroid-sparing agent at the same time, especially since she is so weak. Azathioprine is contraindicated with allopurinol. There is increased risk of renal insufficiency and osteoporosis with cyclosporine as well as rhabdomyolysis when combined with a statin. There is more experience with methotrexate as a second-line agent than the other options and it is generally effective. One needs to start a lower dose given the baseline renal insufficiency.

Question 2

You are evaluating a patient who carries a diagnosis of polymyositis but has not significant improvement in strength despite being treated with high-dose prednisone (1.5 mg/kg/day) for 6 months. Which of the following would be the most appropriate next step?

- A. Examine the patient with particular attention to pattern of muscle weakness and atrophy
- B. Add a second-line immunosuppressive agent such as methotrexate, azathioprine, or mycophenolate mofetil.
- C. Add an immunomodulating agent such as intravenous immunoglobulin
- D. Give a course of rituximab
- E. Pulse the patient with IV methylprednisolone 1 gm daily for 3 days then increase the prednisone to 2.0 gm/kg/day for at least two more months

- Answer: A.
- Six months of high dose prednisone is usually enough time to at least see some improvement in most patients with polymyositis. Prior to adding any other second-line agent in a patient with "refractory polymyositis" the diagnosis should be reconsidered. It is not uncommon that patients with inclusion body myositis, muscular dystrophy, and other myopathies are misdiagnosed as having polymyositis. Demonstration of prominent atrophy and weakness and the flexor forearm muscles and quadriceps should lead to consideration of IBM. Atrophy of the gastrocnemius should make one consider a dysferlinopathy. One should consider other forms of dystrophy in patients with scapular winging or hypertrophy of the gastrocnemius muscles.

Question 3

- You are consulting on a 72 year old woman with 7 year history of progressive weakness of the arms and legs along with mild dysphagia. On examination, she has prominent atrophy weakness and atrophy of the flexor forearm muscles and quadriceps. CK is 500 U/L. Muscle biopsy demonstrates endomysial inflammation with invasion of non-necrotic muscle fibers, many fibers with one or more rimmed vacuoles, and 18-21 nm tubulofilaments in the sarcoplasm on electron microscopy. The most reasonable course of action would be:
  - Do mutation analysis for limb-girdle muscular dystrophy
  - Start treatment with intravenous immunoglobulin
  - Start prednisone
  - Refer the patient to physical and occupational as well as speech therapy (swallowing evaluation)
  - Start prednisone and methotrexate at the same time as this disorder is very difficult to treat

- Answer: D.
- The patient has inclusion body myositis. The clinical phenotype and inflammation on the biopsy are characteristic of inclusion body myositis and are not typical for one of the hereditary inclusion body myopathies. IBM is usually refractory to immunosuppressive and immunomodulating therapy. Double-blind, placebo-controlled trials have failed to demonstrate efficacy of either IVIG or methotrexate when combined corticosteroids. The patient would most likely benefit from an assessment by physical and occupational therapy and a swallowing assessment.

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