Contribution of neuropathology to the diagnosis of inflammatory muscle diseases

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Disclosure slide

Nothing to disclose

Inflammatory muscle diseases addressed in this course:

Polymyositis

Dermatomyositis

Inclusion body myositis

Immune-mediated necrotizing myopathy

Means for diagnosis of inflammatory muscle diseases:

Medical history and clinical presentation

Laboratory chemistry

EMG

MRI

Serology for myositis specific/associated antibodies

Muscle biopsy

Relevance of muscle biopsy in the diagnosis of inflammatory muscle diseases:

For assessment of biological characteristis

For classification

For prognosis

For therapeutic considerations

Polymyositis – clinical presentation

- Proximal and usually symmetrical muscle weakness
- Development over weeks/months
- No skin involvement
- No association with malignancy
- Possible association with interstitial lung disease / connective tissue diseases
- Response to immunosuppression

Polymyositis – laboratory findings

Creatine kinase – elevated

Electromyography – myopathic

MRI – muscle edema

Serology – possible presence of myositis-specific antibodies,

e.g. anti-syntethase antibodies (cytosolic location)

Polymyositis – muscle biopsy

Inflammatory infiltrate:
Endomysial, predominantly CD8+ lymphocytes surrounding and invading intact myofibers

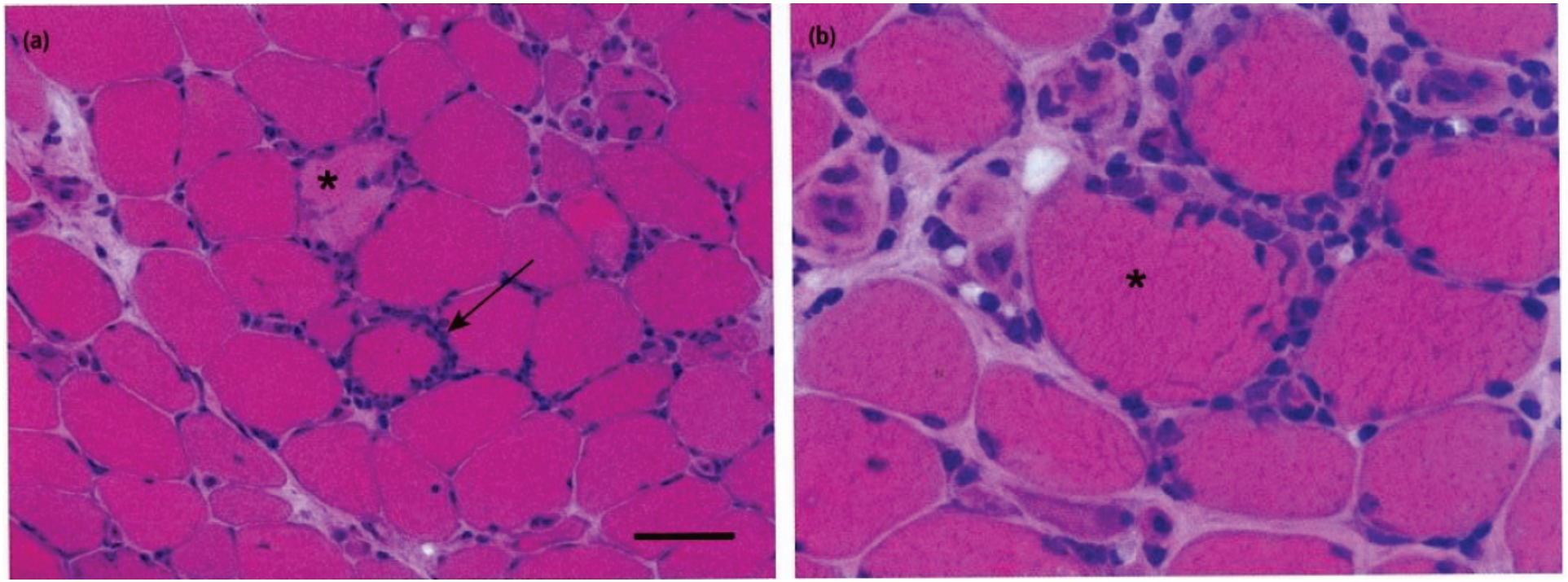
Scattered uscle fiber necrosis and fiber regeneration

Upregulation of MHC class I

No rimmed vacuoles

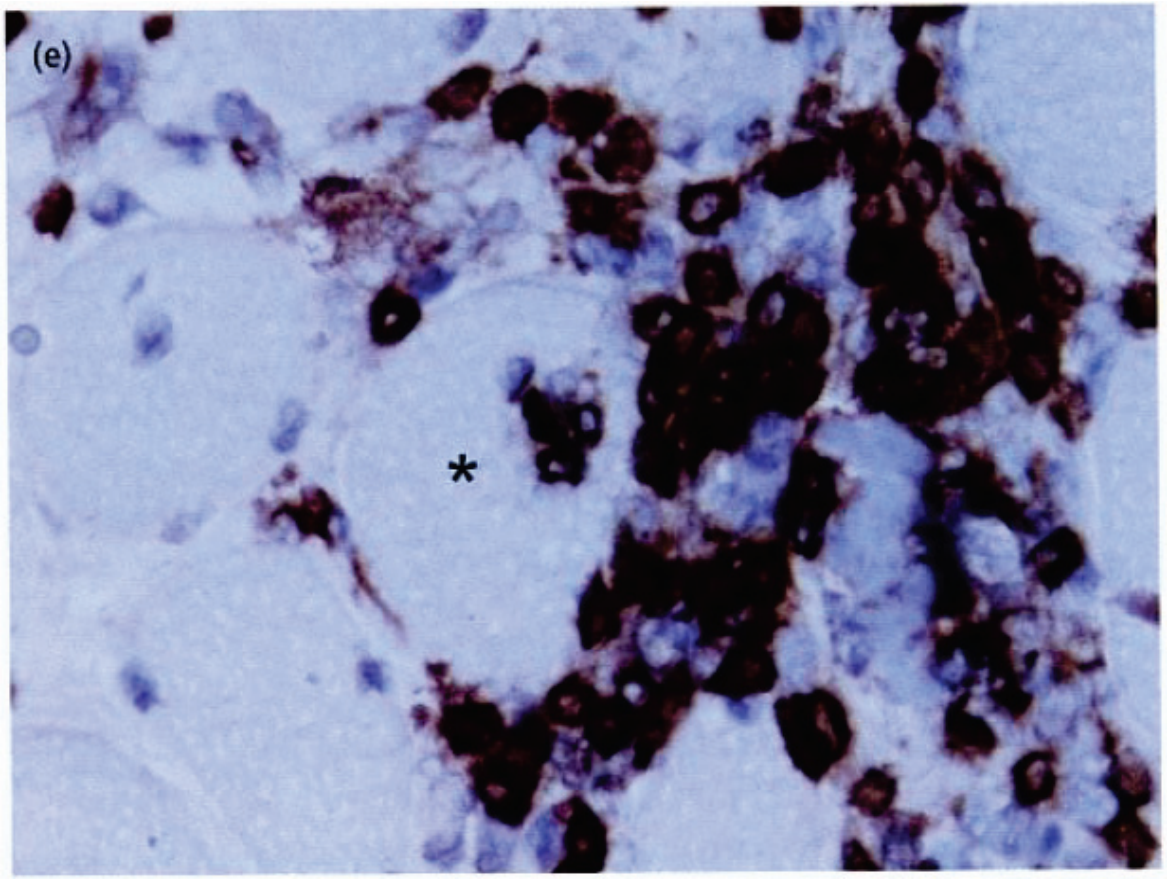
No capillary depletion

Polymyositis – Endomysial inflammatory infiltrate



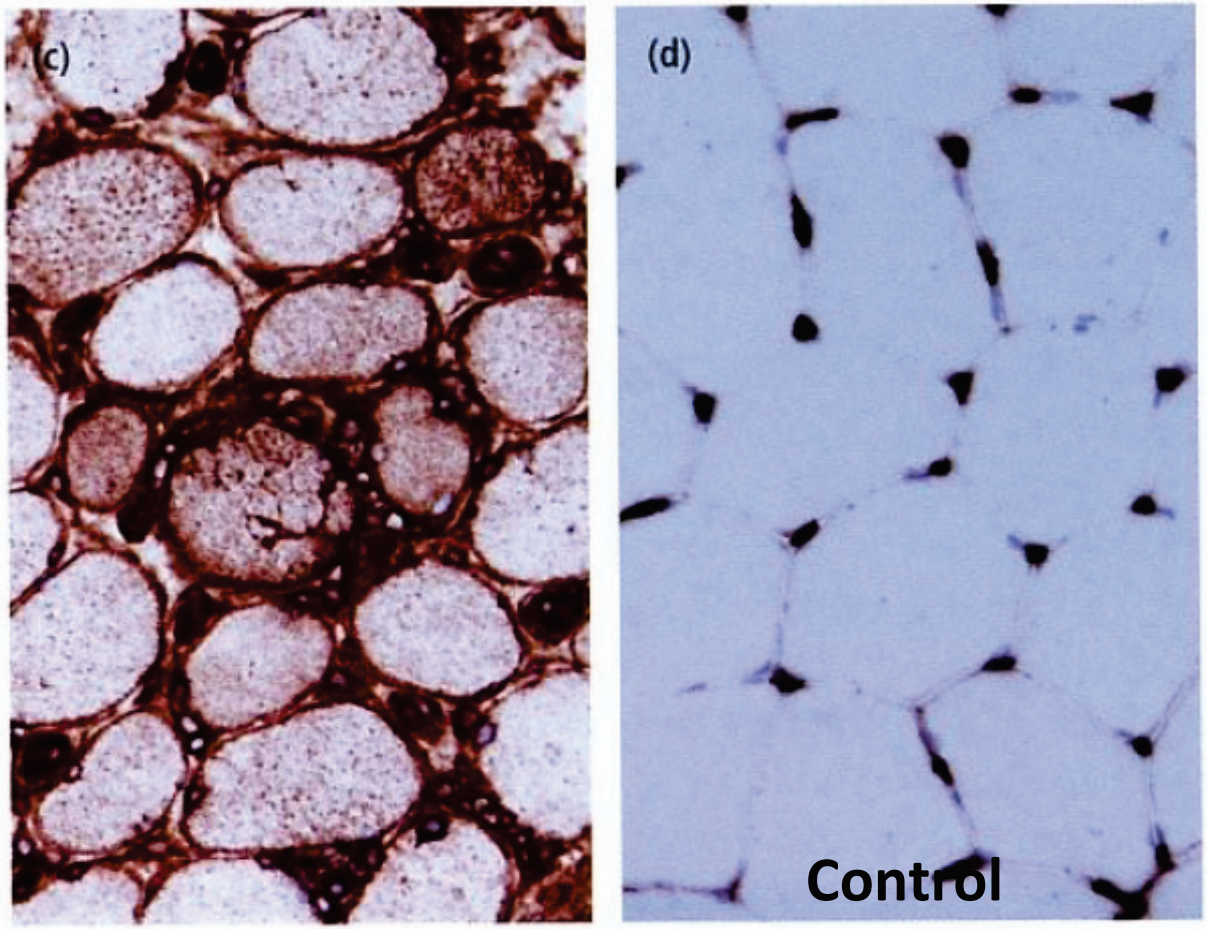
Source of figure: Wiley: Muscle disease: Pathology and Genetics, 2nd ed.

Polymyositis – CD8+ cell infiltrate



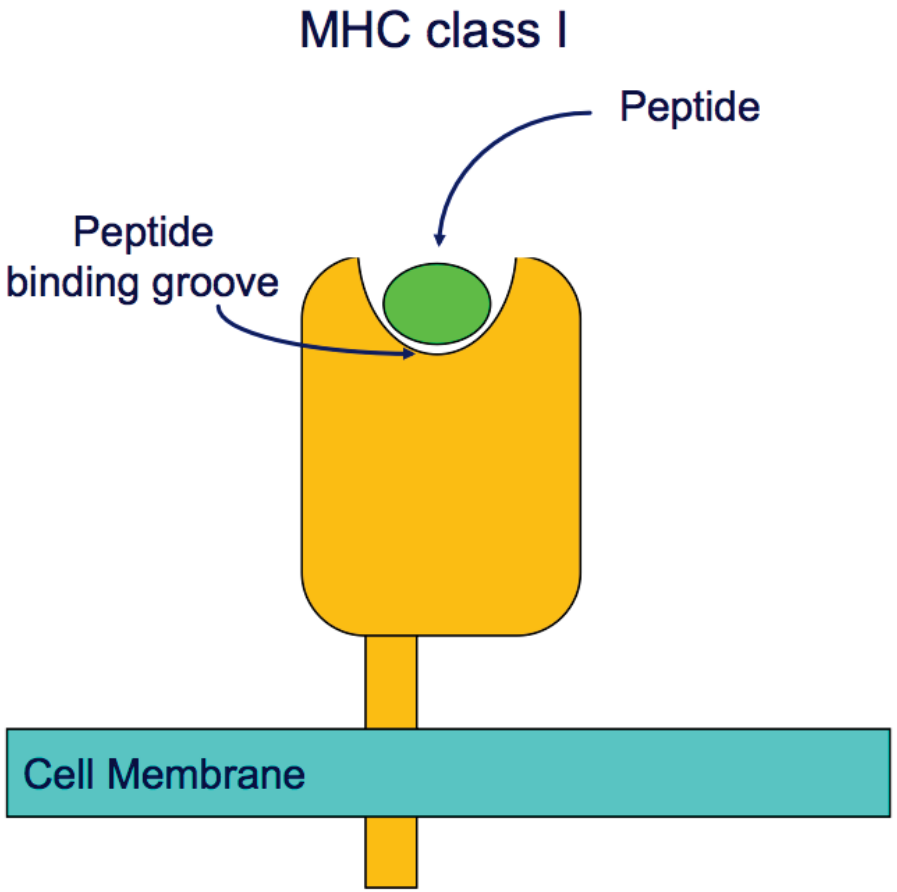
Source of figure: Wiley: Muscle disease: Pathology and Genetics, 2nd ed.

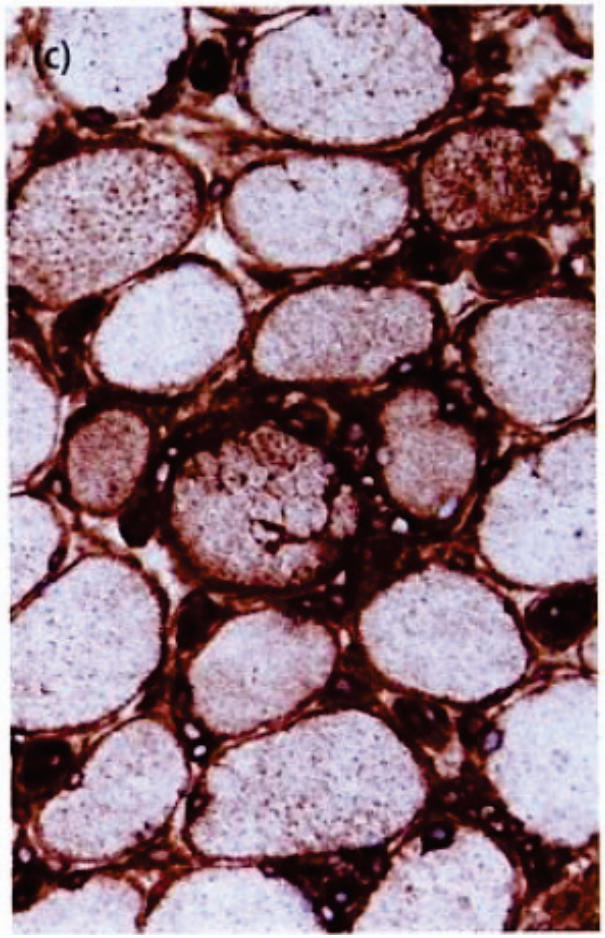
Polymyositis – MHC class I upregulation



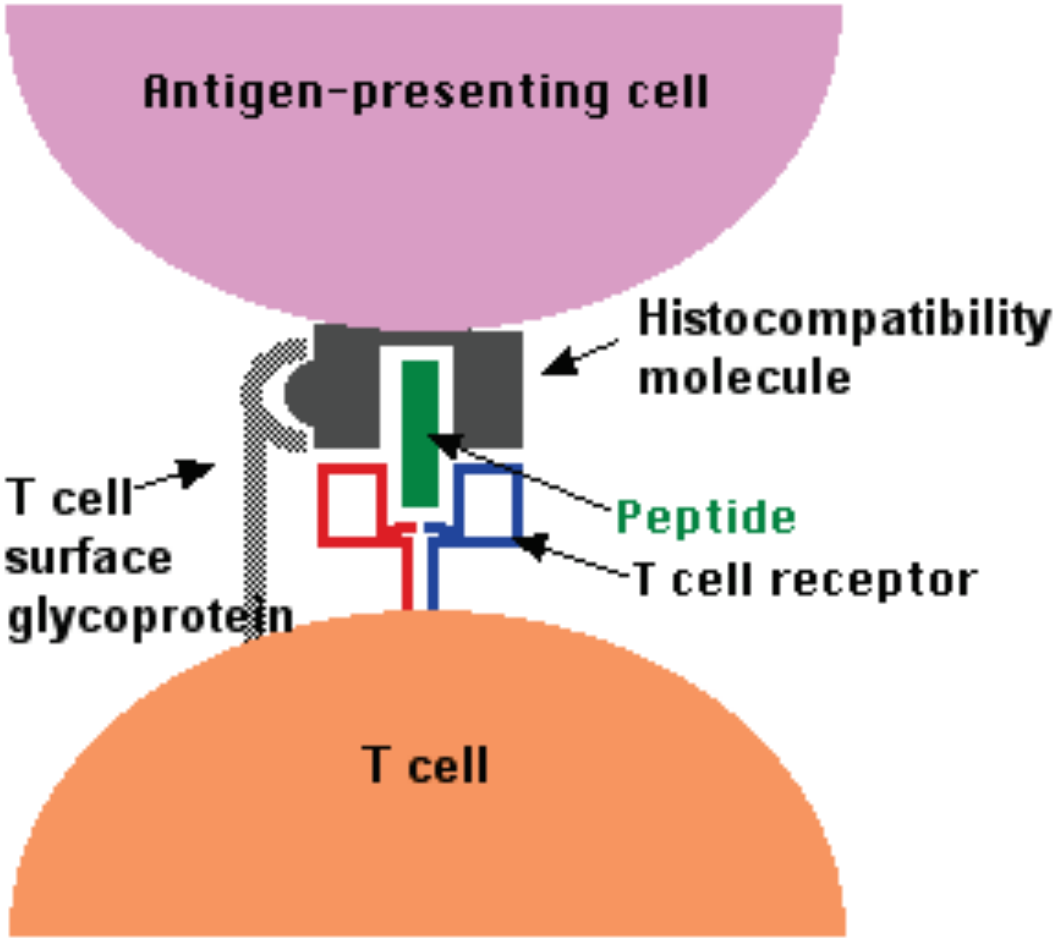
Source of figure: Wiley: Muscle disease: Pathology and Genetics, 2nd ed.

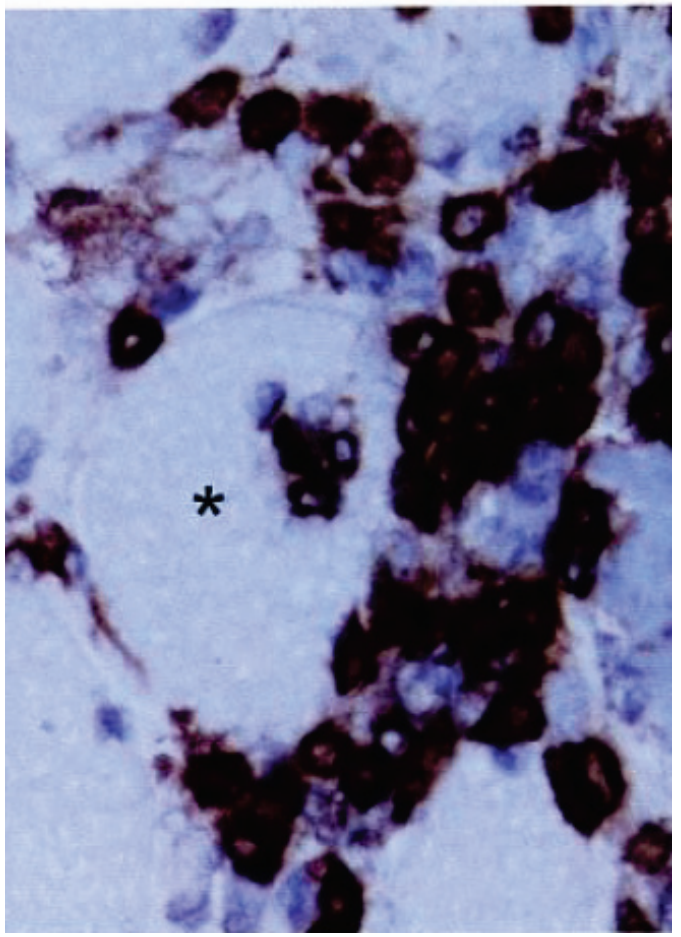
Polymyositis – pathophysiology





Polymyositis – pathophysiology





Dermatomyositis – clinical presentation

- Manifests in children and adults
- Progressive proximal weakness
- Generalized myalgia
- Skin manifestations – heliotrope rash
- Possible association with malignancy
- Possible association with interstitial lung disease / connective tissue diseases
- Response to immunosuppression

Dermatomyositis – laboratory findings

Creatine kinase – normal or elevated

Electromyography – myopathic

MRI – muscle edema

Serology – possible presence of myositis-specific antibodies,

e.g. anti-Mi-2 antibodies (helicase protein, nuclear location)

Dermatomyositis – muscle biopsy

Inflammatory infiltrate:
Perivascular, predominantly CD4+ lymphocytes, presence of B-cells

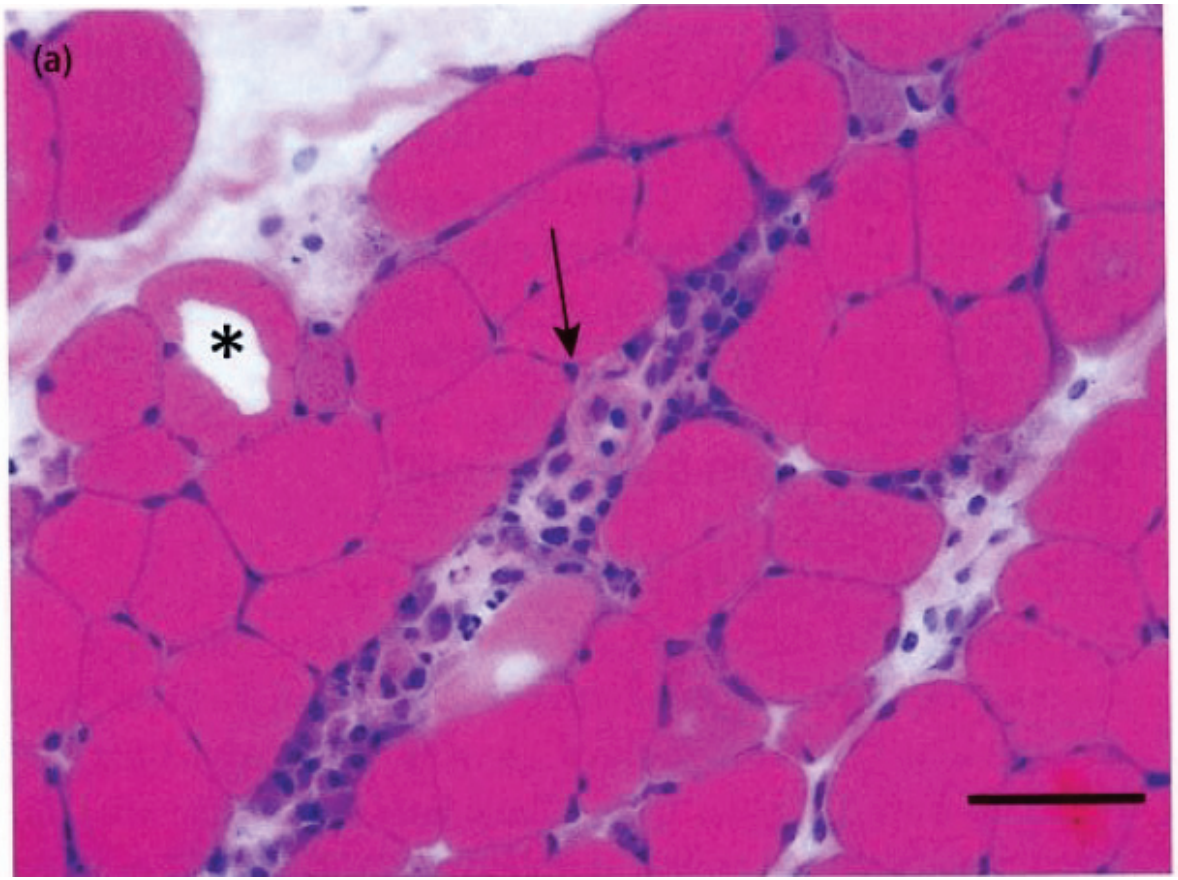
Perifascicular atrophy, degeneration, regeneration

Deposition of complement membrane attack complex in capillaries

Perifascicular capillary depletion

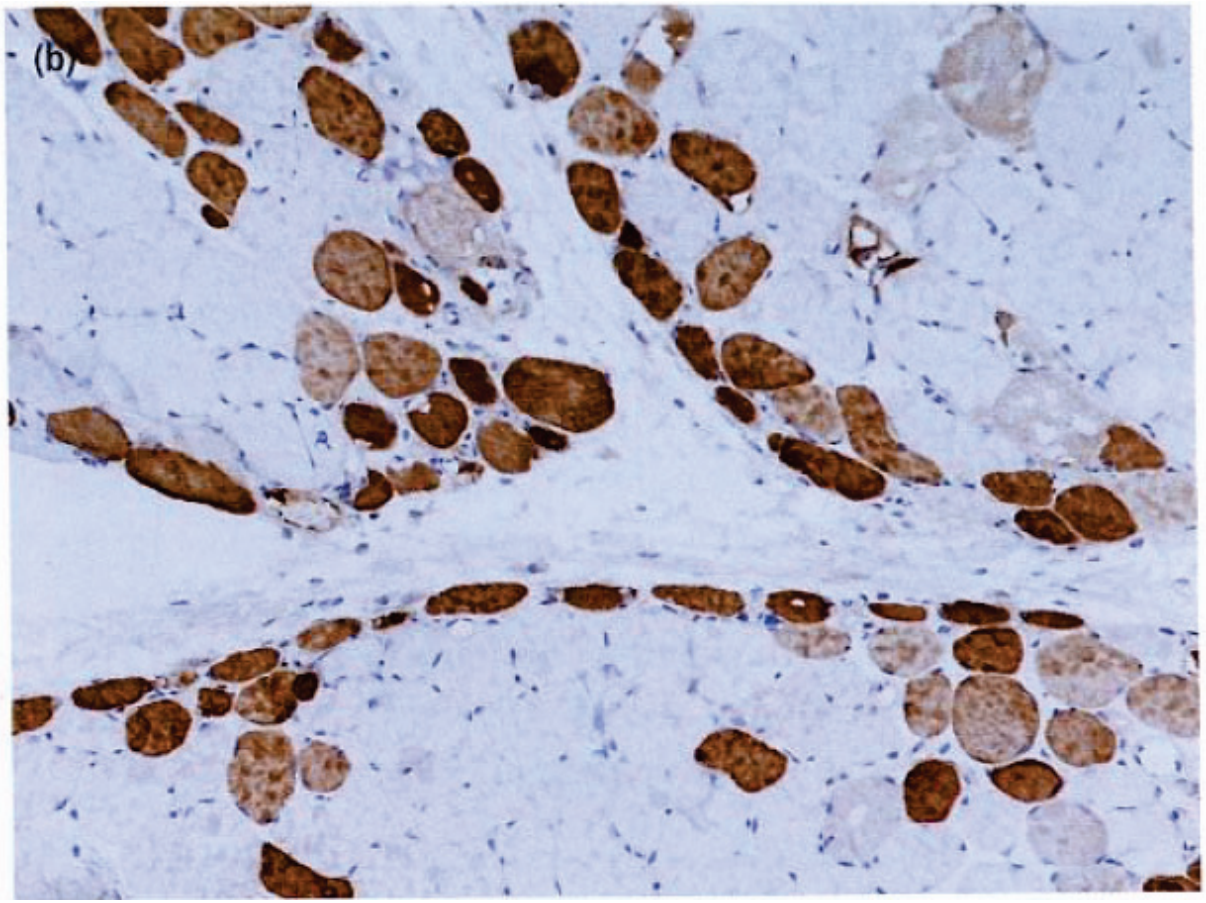
No rimmed vacuoles

Dermatomyositis – perivascular inflammatory infiltrate



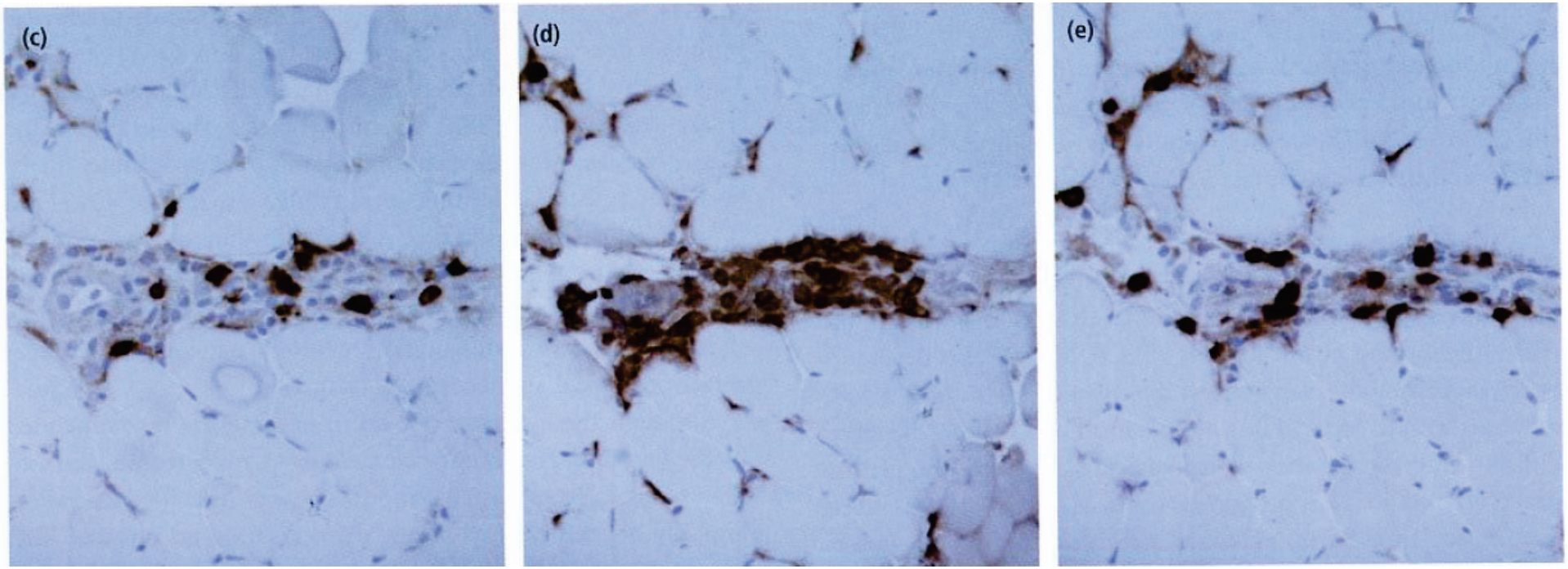
Source of figure: Wiley: Muscle disease: Pathology and Genetics, 2nd ed.

Dermatomyositis – perifascicular atrophy



Source of figure: Wiley: Muscle disease: Pathology and Genetics, 2nd ed.

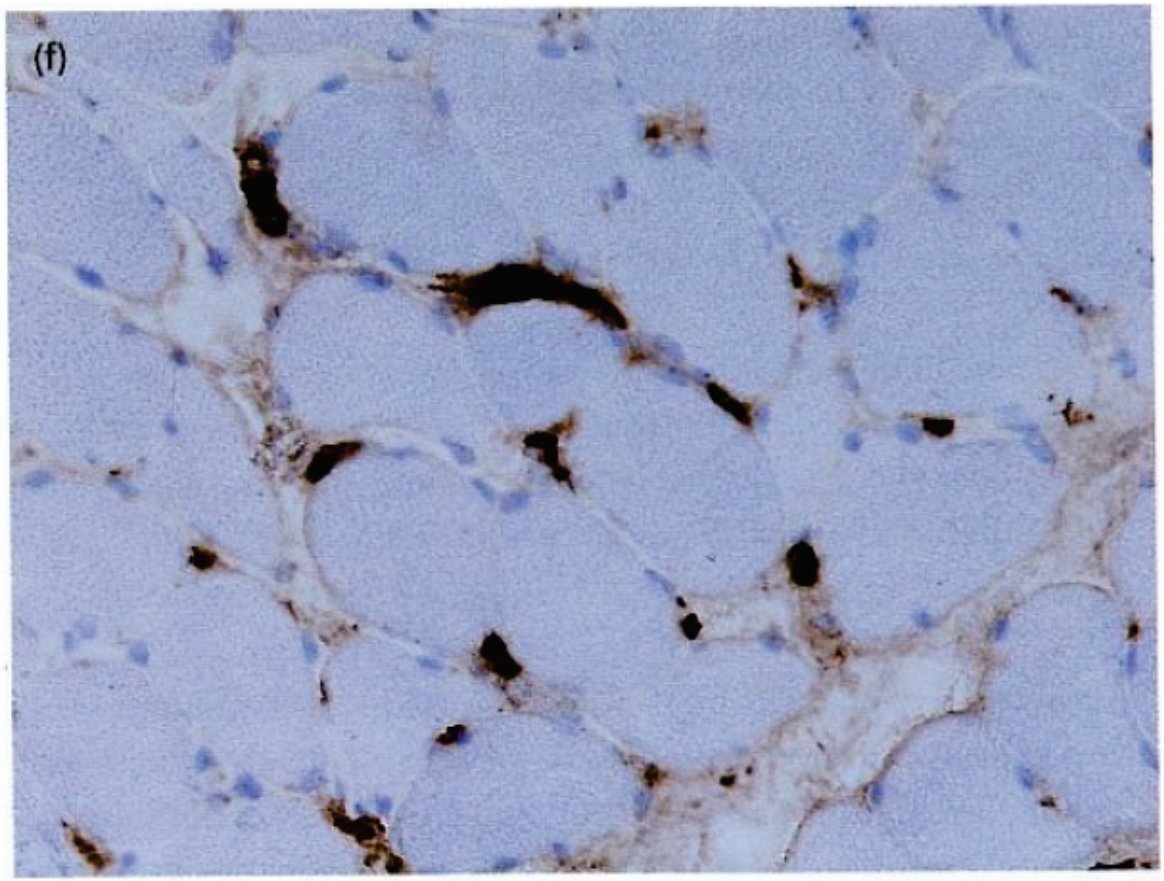
Dermatomyositis – predominance of CD4+ cells



B-cells **CD4+ T-cells** **CD8+ T-cells**

Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Dermatomyositis – deposition of complement membrane attack complex in capillaries

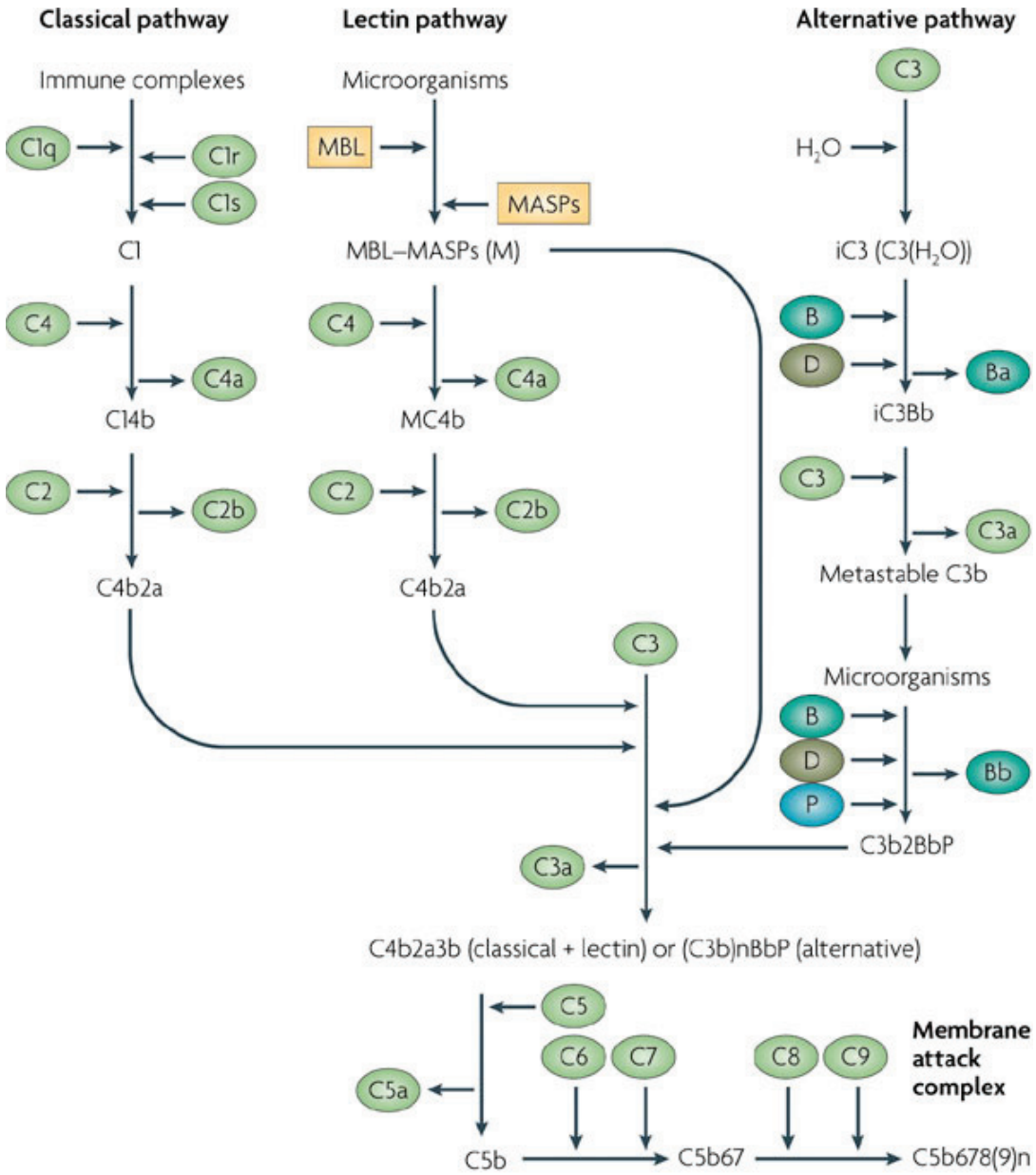


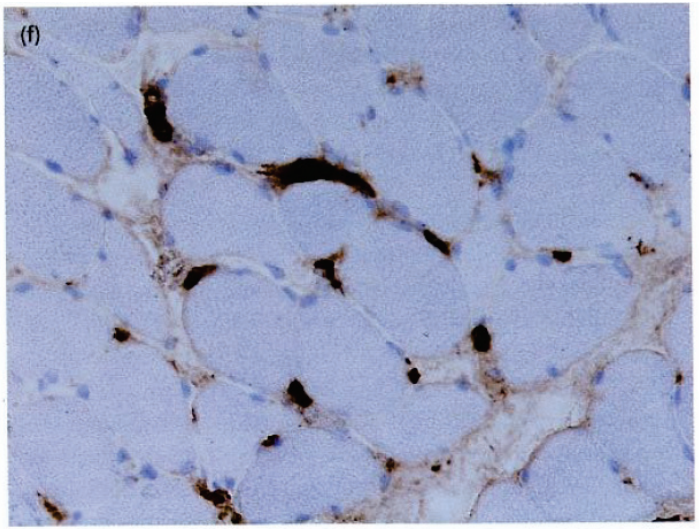
Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Dermatomyositis – pathophysiology

Capillary deposition of complement membrane attack complex

Depletion of capillaries


Classical pathway
Lectin pathway
Alternative pathway
Immune complexes
Microorganisms
C3
C1q
C1r
C1s
MBL
MASPs
H_2O
C1
MBL–MASPs (M)
iC3 ($C3(H_2O)$)
C4
C4a
C14b
MC4b
B
D
Ba
iC3Bb
C2
C2b
C4b2a
C3
C3a
Metastable C3b
Microorganisms
P
Bb
C3b2BbP
C3a
C4b2a3b (classical + lectin) or (C3b)nBbP (alternative)
C5
C6
C7
C8
C9
C5a
Membrane attack complex
C5b
C5b67
C5b678(9)n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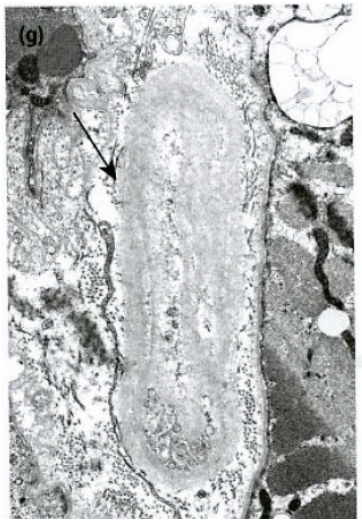
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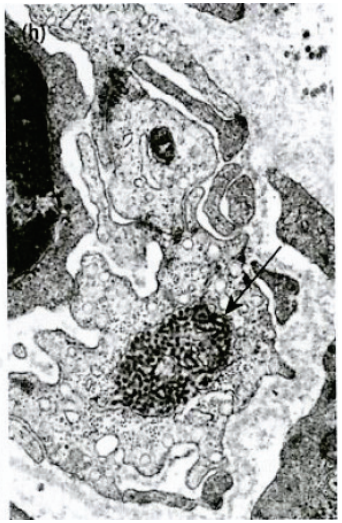
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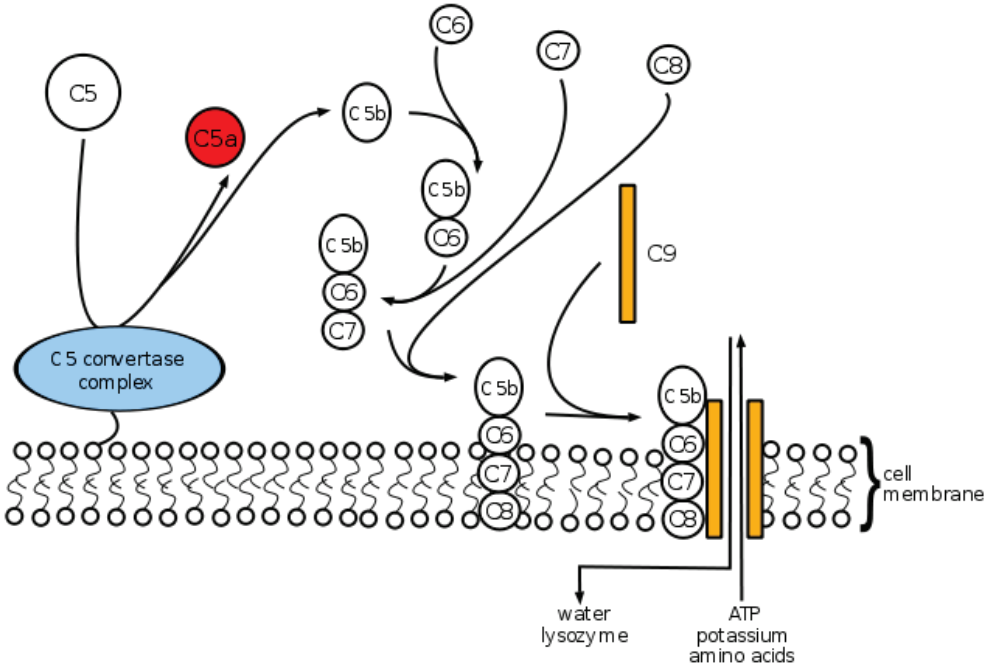
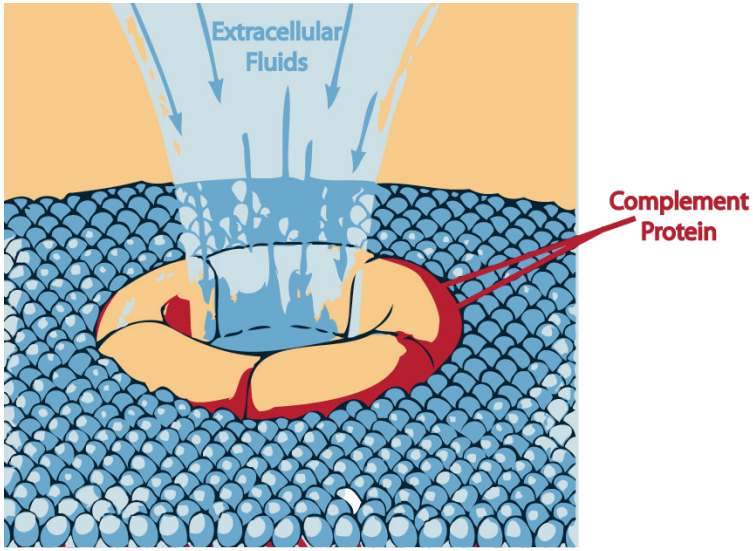
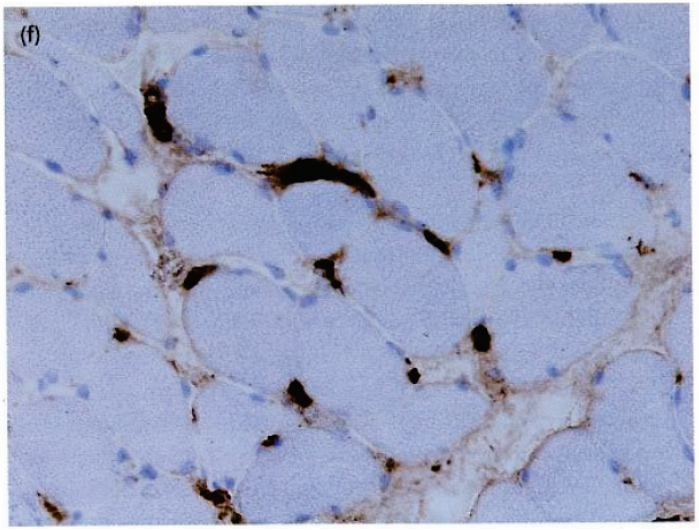

C5
C5a
C6
C7
C8
C 5b
C 5b
C6
C 5b
C6
C7
C9
C 5 convertase complex
C 5b
C6
C7
C8
C 5b
C6
C7
C8
cell membrane
water
lysozyme
ATP
potassium
amino acids


Extracellular Fluids
Complement Protein
Cell Membrane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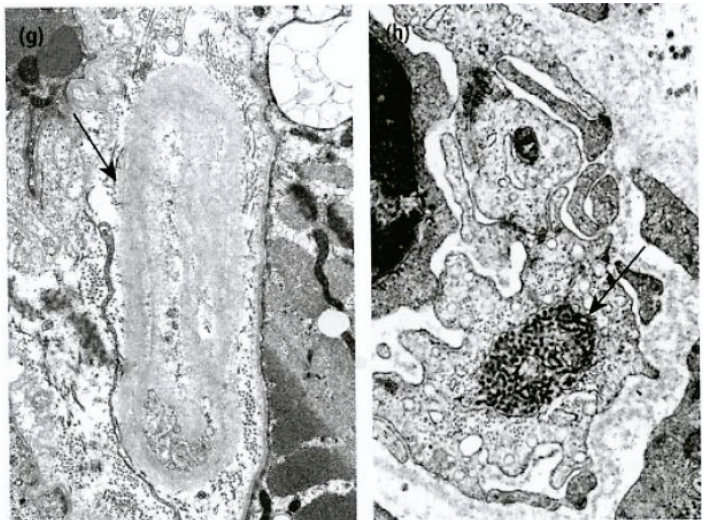
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Inclusion body myositis (IBM) – clinical presentation

- Manifests in patients over 50 years
- Characteristic pattern of often asymmetrical weakness and wasting (quadriceps, forearm flexors, ankle dorsiflexors)
- Progressive disease
- No association with malignancy
- No skin manifestation
- No response to immunosuppression

Inclusion body myositis – laboratory findings

Creatine kinase – normal or slightly elevated

Electromyography – mixed myopathic and neurogenic

MRI – fatty infiltration, asymmetrical (quadriceps, distal limbs)

Serology – no myositis-specific antibodies

Inclusion body myositis – muscle biopsy

Inflammatory infiltrate:
Endomysial, predominantly CD8+ lymphocytes
MHC I upregulation

Scattered fiber atrophy, necrosis, regeneration

Rimmed vacuoles

Tubulofilamentous inclusions / Presence of multi- protein aggregates in muscle fibers

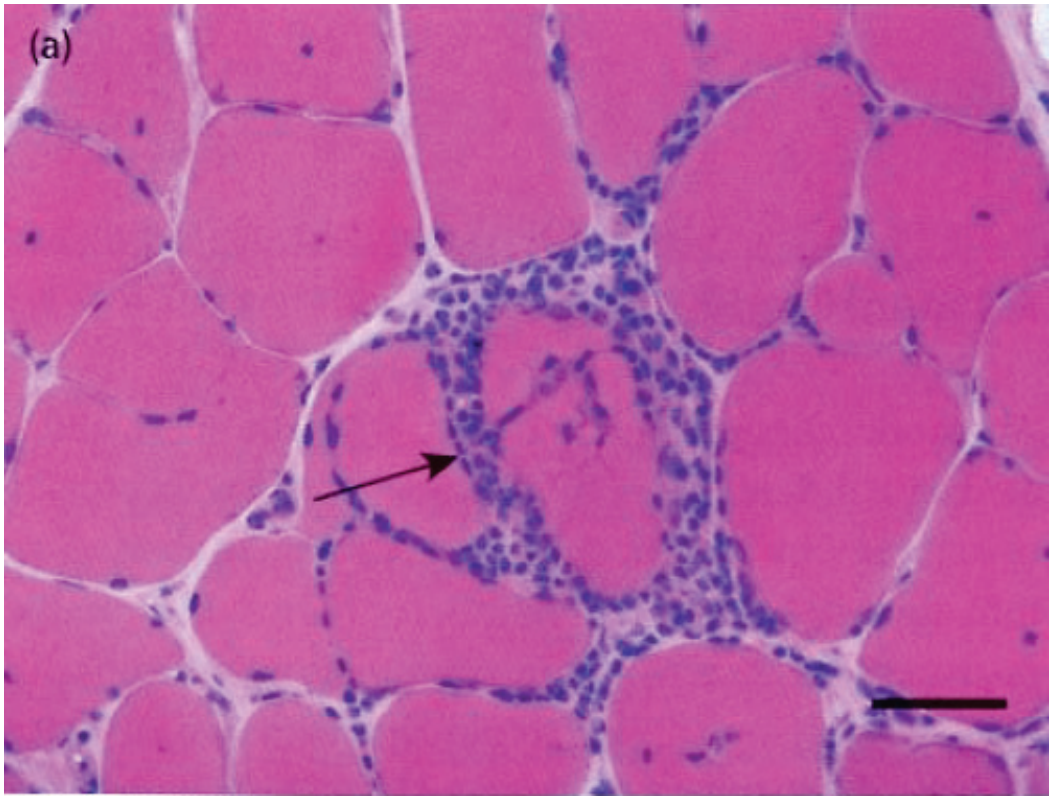
No capillary depletion

Inclusion body myositis – muscle biopsy

Combination of:

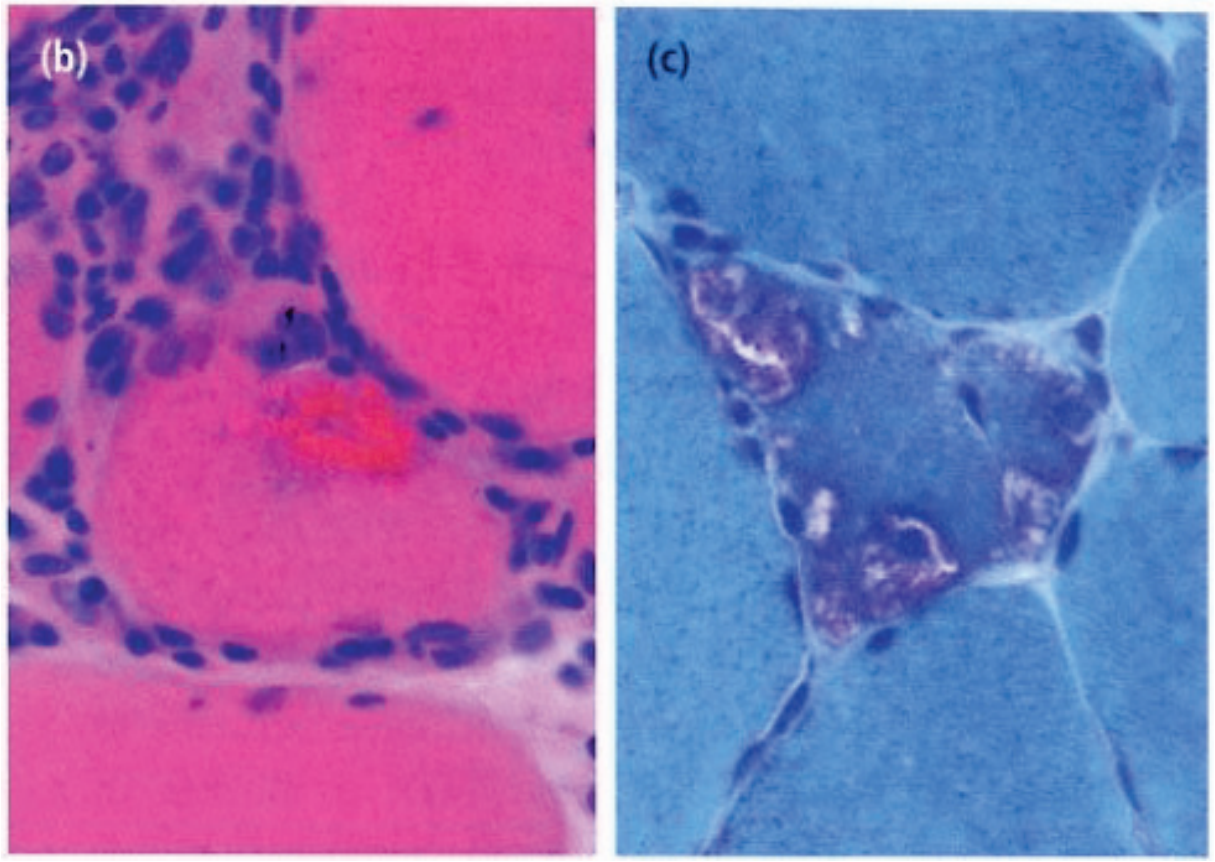
inflammatory muscle disease and degenerative muscle disease

Inclusion body myositis:
Endomysial inflammation, mononuclear cells surrounding and infiltrating non-necrotic muscle fibers



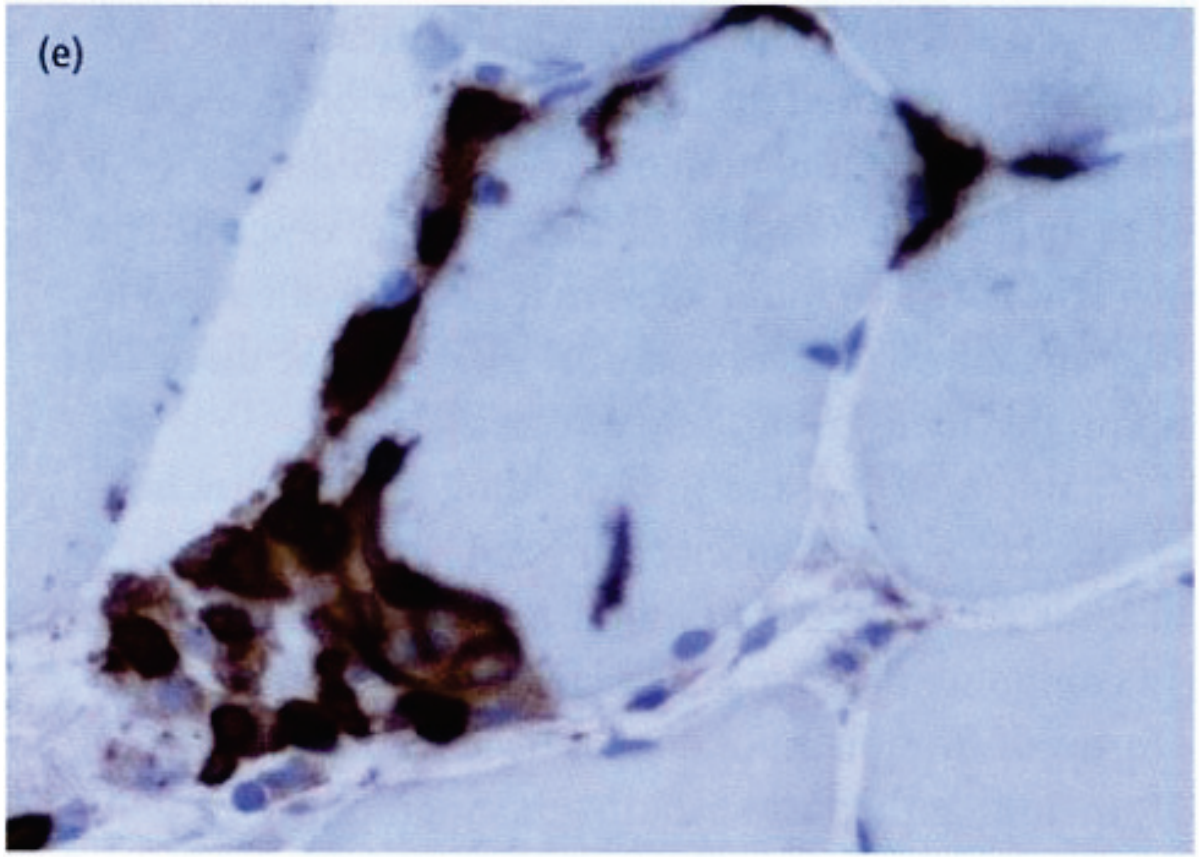
Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Inclusion body myositis:
Presence of hyaline eosinophilic inclusions and rimmed vacuoles in muscle fibers



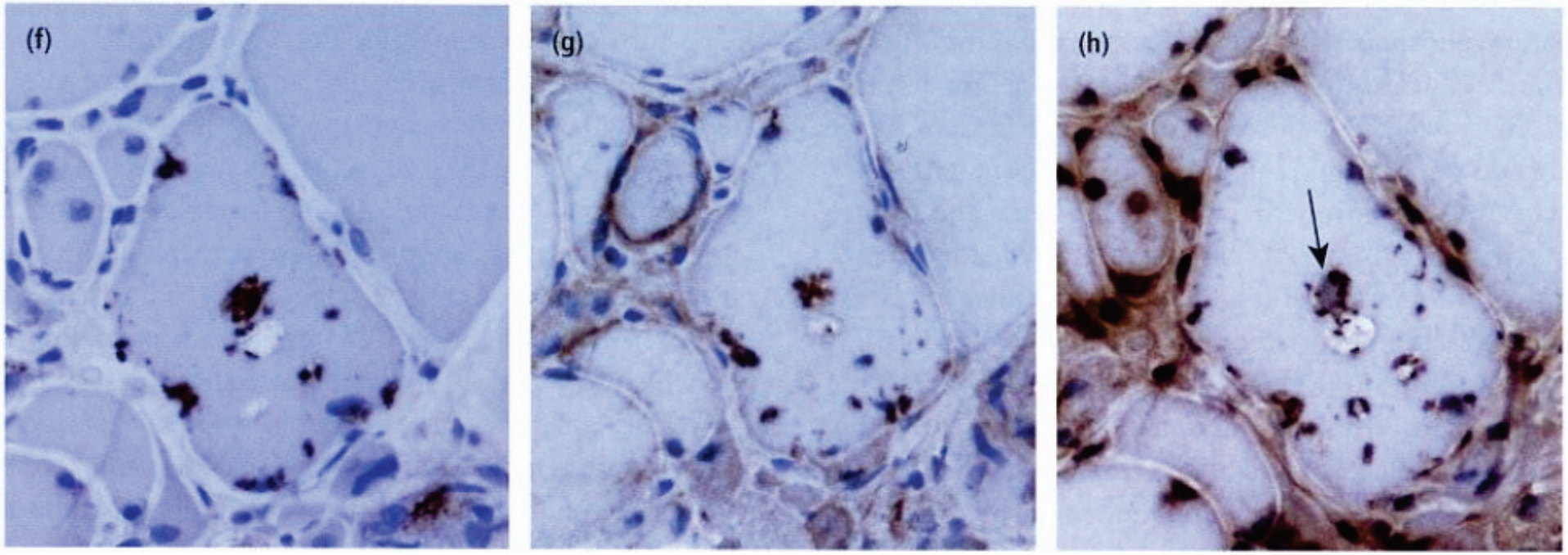
Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Inclusion body myositis: CD8+ T-cells invading muscle fibers



Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

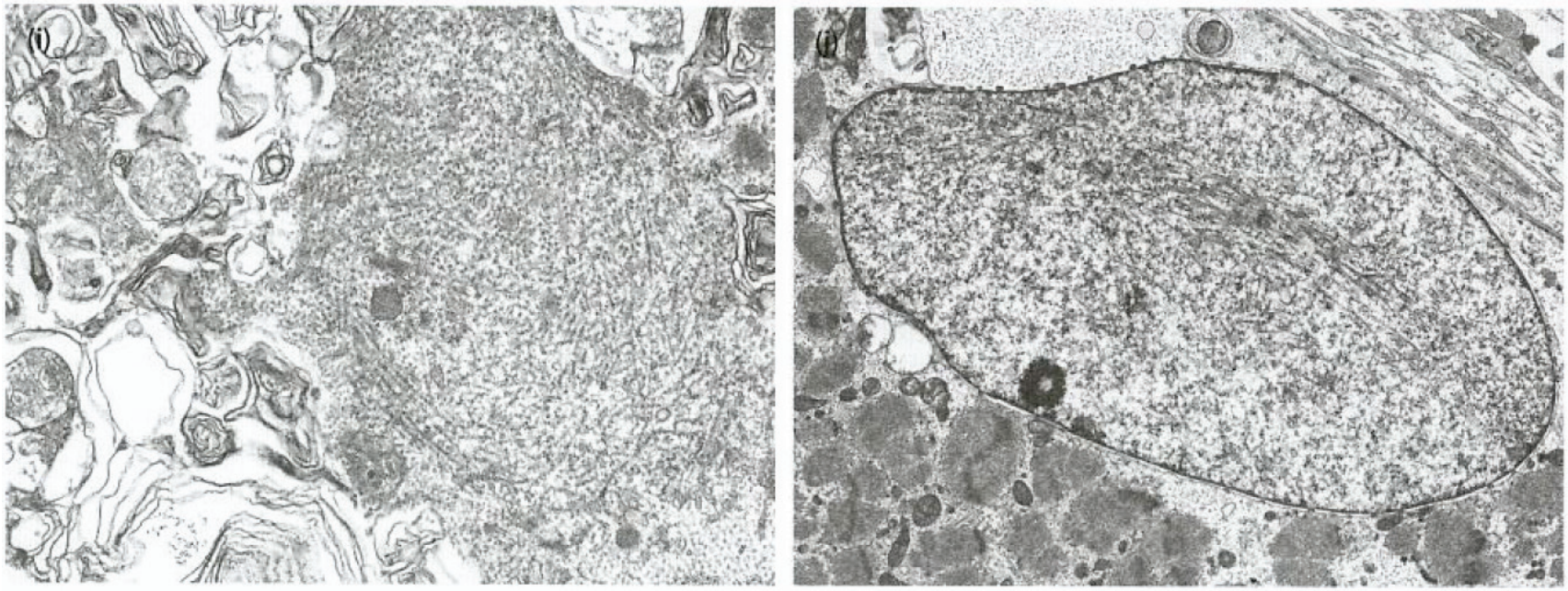
Inclusion body myositis:
Multi- protein aggregates in muscle fibers



p62 protein **Ubiquitin** **TDP43 protein**

Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Inclusion body myositis - ultrastructure: Whorled membranous debris and tubulofilamentous inclusions



Sarcoplasm **Myonucleus**

Source of figure: Muscle disease: Pathology and Genetics, 2nd ed.

Diagnostic criteria for inclusion body myositis (IBM)

Pathologically defined IBM

- Age >30 years, duration > 6 months
- Characteristic pattern of muscle weakness and EMG findings
- Endomysial inflammation, muscle fiber vacuoles, inclusions

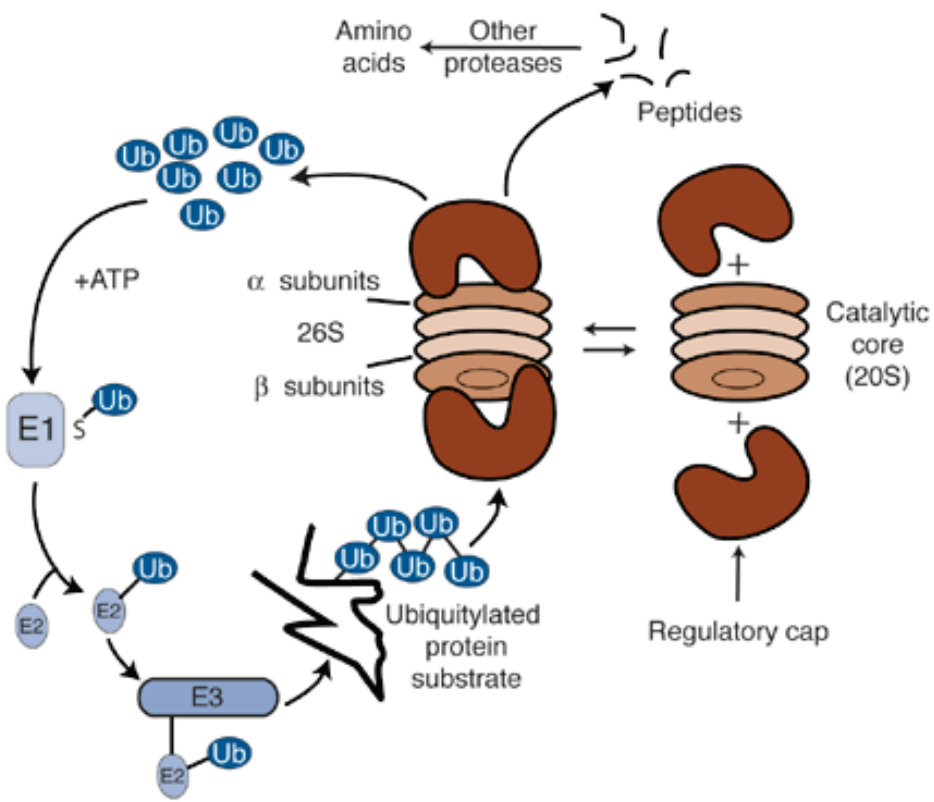
Clinically defined IBM

- Age >30 years, duration > 6 months
- Characteristic pattern of muscle weakness and EMG findings
- Endomysial inflammation or MHC upregulation

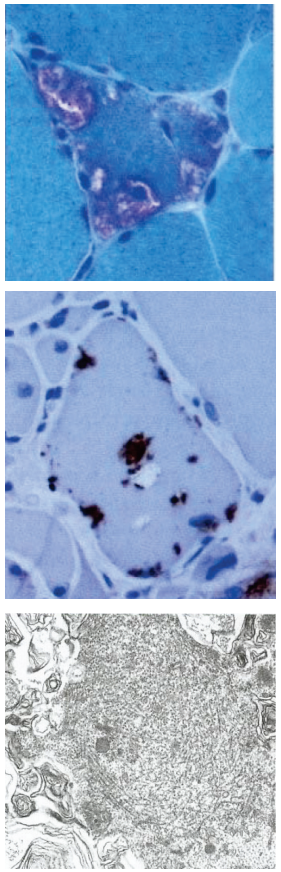
Possible IBM

- Age >30 years, duration > 6 months
- Quadriceps weakness or finger flexion weakness, characteristic EMG findings
- Endomysial inflammation or MHC upregulation

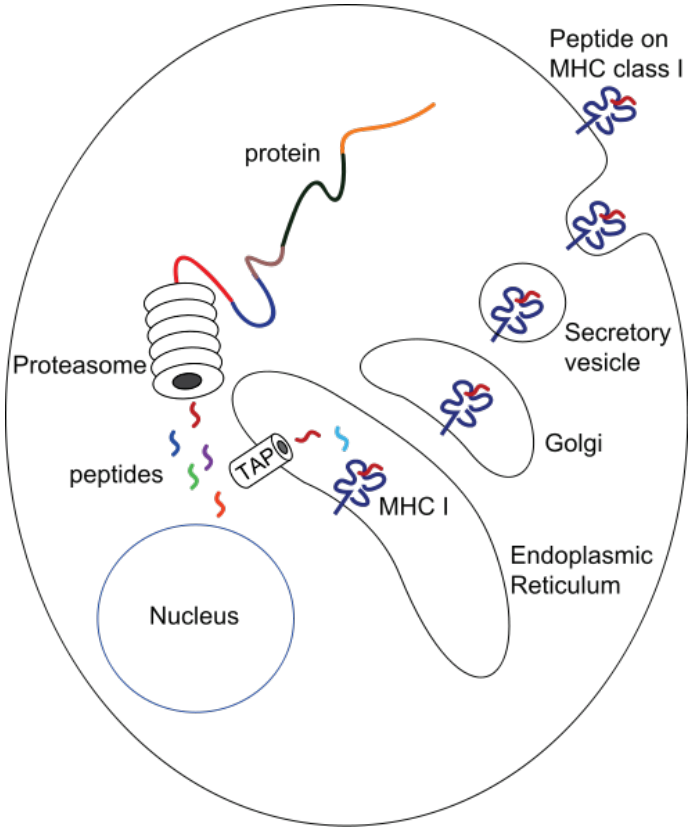
Inclusion body myositis – pathophysiology of inclusion formation

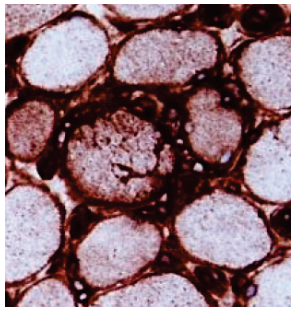


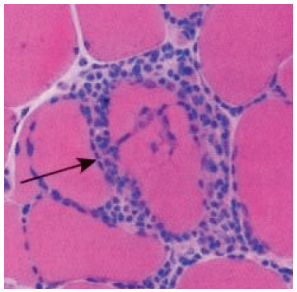
Ubiquitin – proteasome system



Inclusion body myositis – pathophysiology of inflammation







Proteasome – MHC system

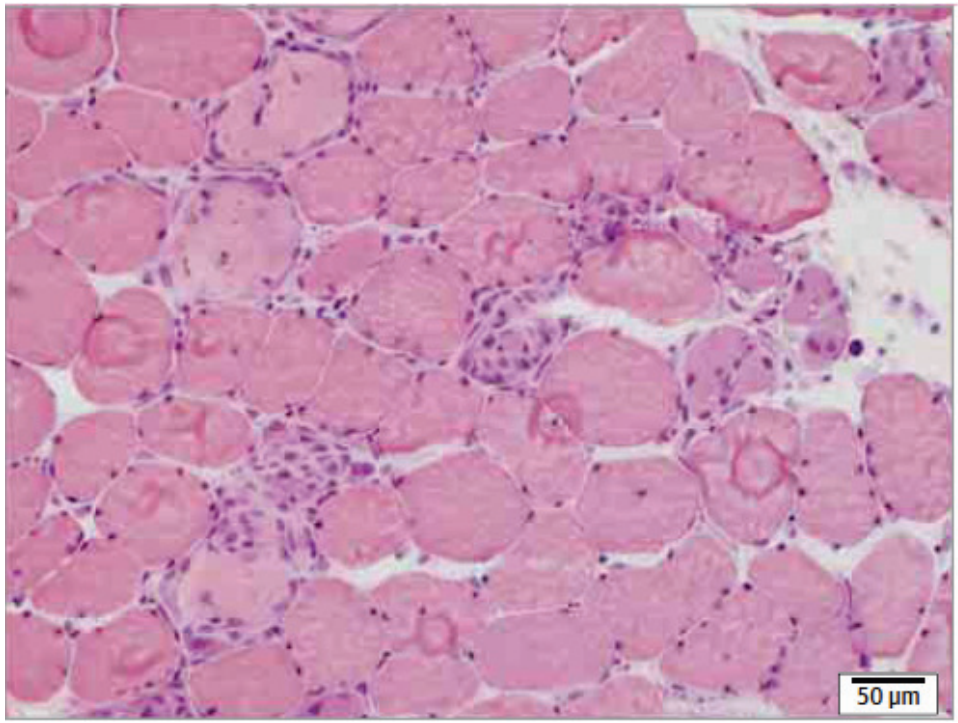
Necrotizing autoimmune myopathy (NAM): clinical presentation and laboratory findings

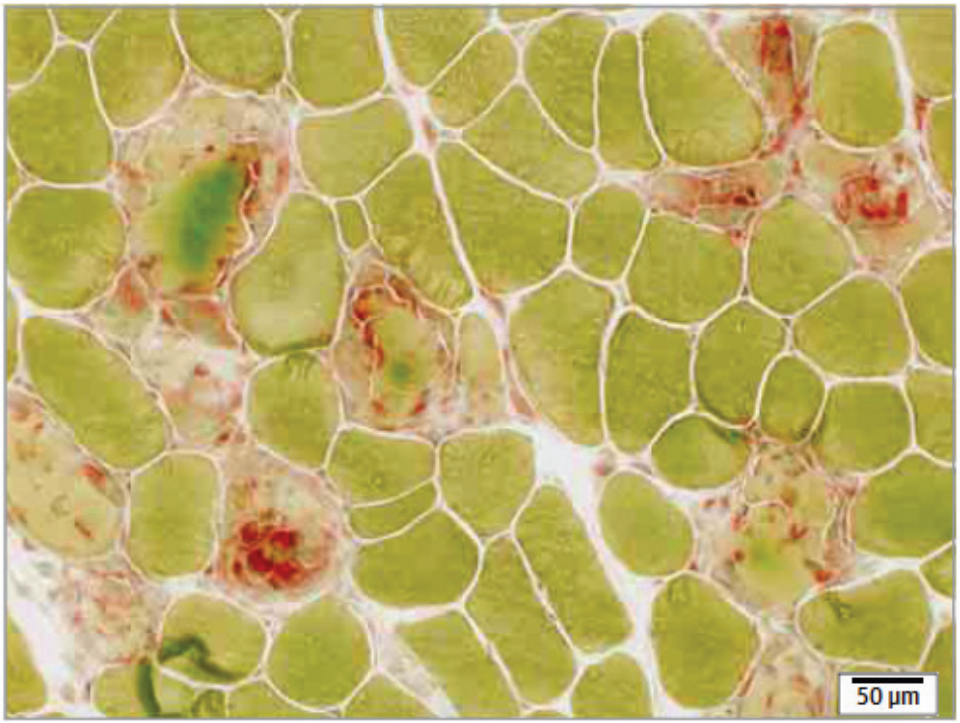
- Proximal muscle weakness, acute or subacute onset
- Highly elevated CK
- Myopathic EMG
- Statin medication (1/3 of patients)
- Serology: autoantibodies for signal recognition particle (SRP, 1/4 of patients) or for 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR, 1/3 patients)
- Possible association with cancer or connective tissue disease
- Disease is usually not controlled by cortison monotherapy

Necrotizing autoimmune myopathy (NAM): muscle biopsy

- Scattered muscle fiber necrosis and fiber regeneration
- Lack of significant inflammatory infiltrates
- Invasion of necrotic muscle fibers by macrophages
- Deposition of complement membrane attack complex on blood vessels and muscle fibers

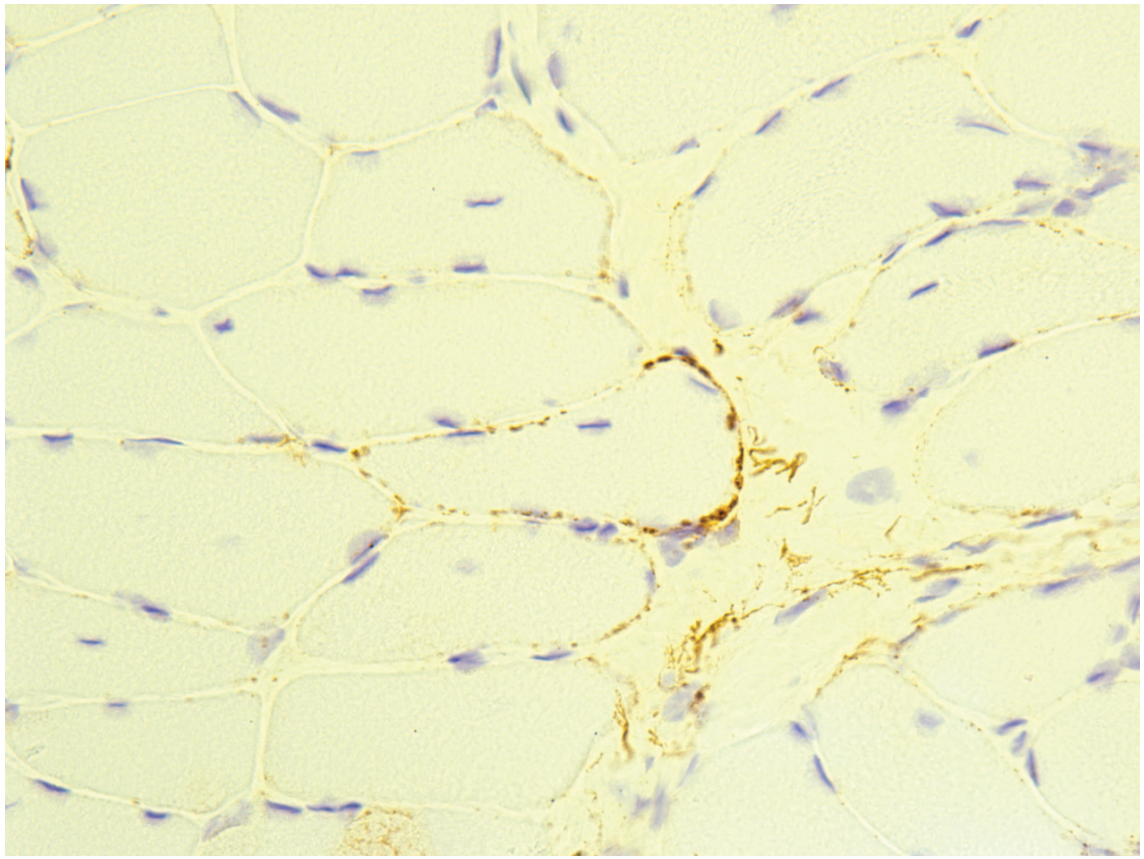
Necrotizing autoimmune myopathy (NAM): muscle fiber necrosis and myophagocytosis





Source of figure: Kassardjian CD et al, JAMA Neurol 2015

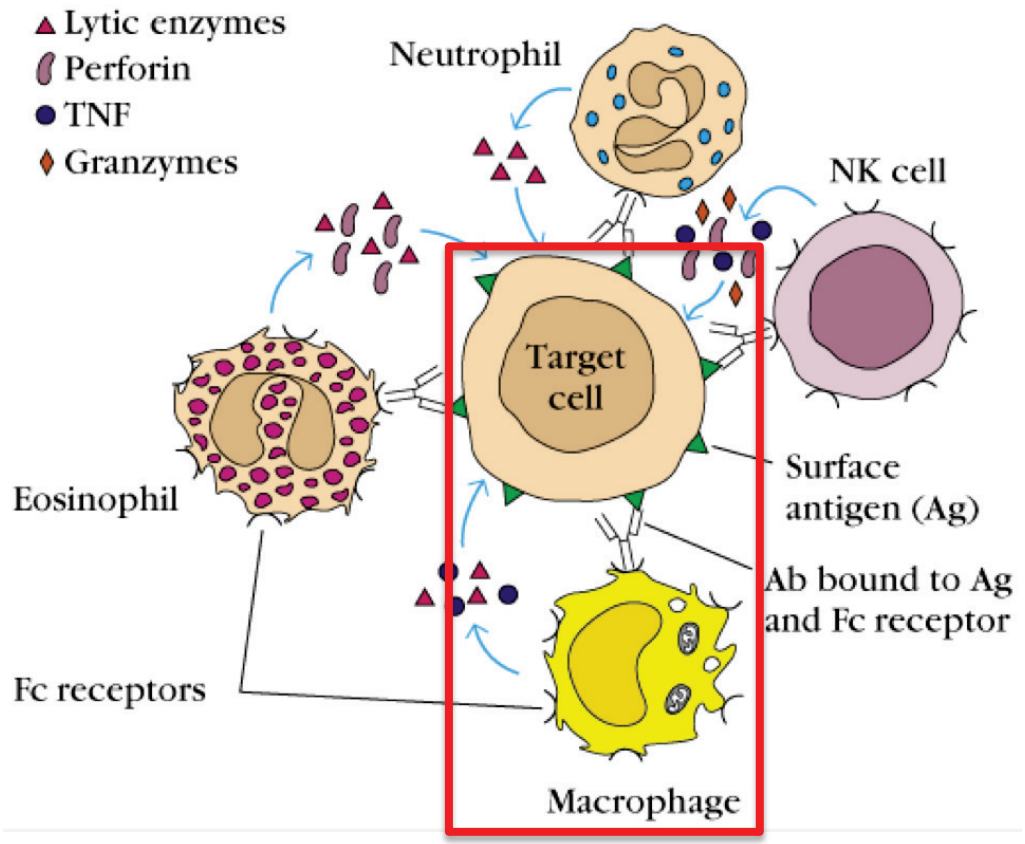
Necrotizing autoimmune myopathy (NAM): C5b-9 complement complex deposition

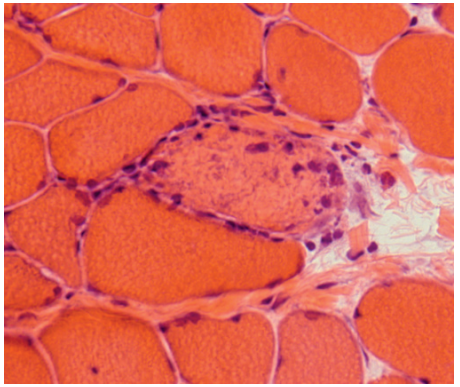


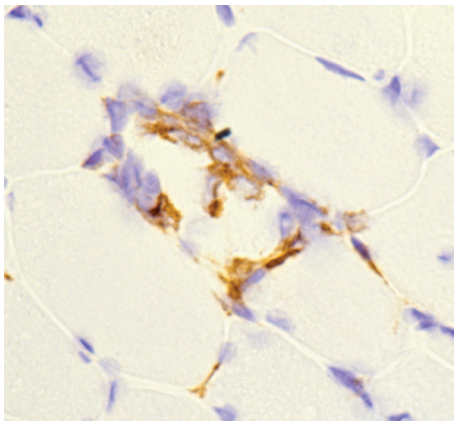
Necrotizing autoimmune myopathy (NAM) - pathophysiology:

Antibody-dependent cell-mediated cytotoxicity (ADCC) as possible underlying cause

Necrotizing autoimmune myopathy (NAM) - pathophysiology: ADCC as possible cause







Contribution of neuropathology to the diagnosis of inflammatory muscle diseases

Muscle biopsy remains an important diagnostic tool and is fundamental for inflammatory muscle disease typing

Myositis-specific and myositis-associated autoantibodies in serum are important for complementary classification of inflammatory muscle disease

Clinical findings, serology, and muscle biopsy findings need to be integrated for proper diagnostics of inflammatory muscle diseases

Integrated diagnostics is the key for personalized management of patients suffering from inflammatory muscle diseases

Recommended literature:

Muscle disease: pathology and genetics. Edited by Goebel HH, Sewry CA, Weller RO, second edition

Garcia-De La Torre I. Clinical usefulness of autoantibodies in idiopathic inflammatory myositis. Frontiers in Immunology (2015) 6:331