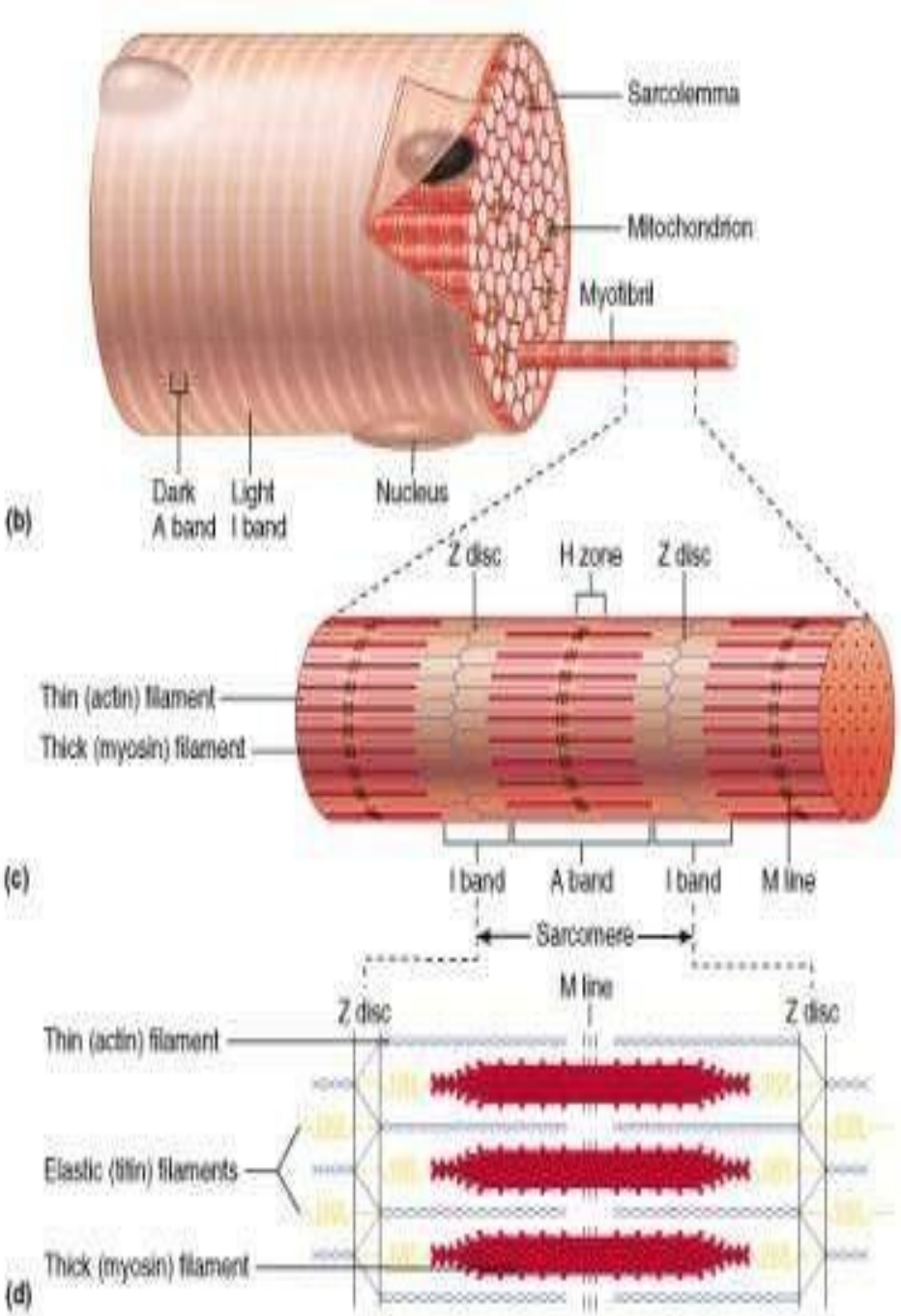
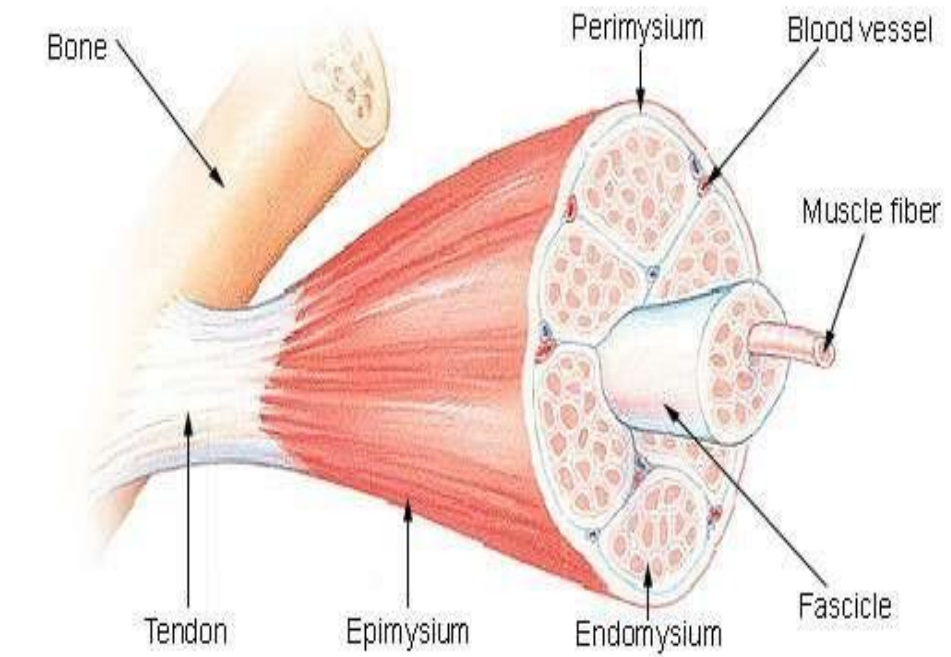
Skeletal muscle atrophy

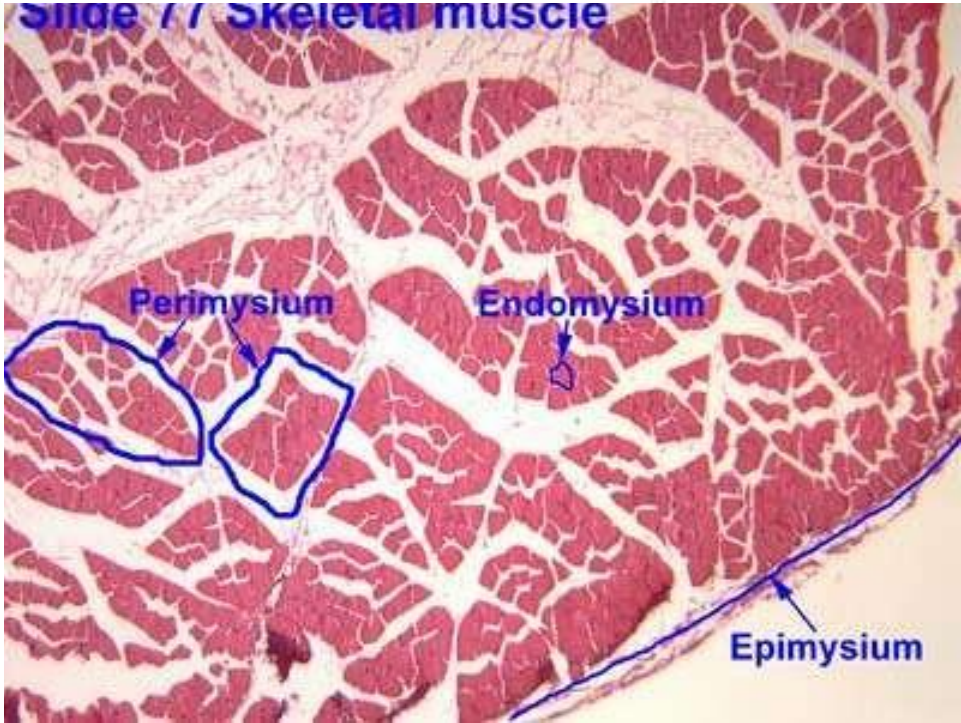
Learning Objectives

- Describe pathological features of Skeletal Muscle Atrophy
- Describe pathological features of Neurogenic and Myopathic changes in Skeletal Muscle
- Describe pathological features of Inflammatory Myopathies
- Describe pathological features of Dermatomyositis
- Describe pathological features of Polymyositis
- Describe pathological features of Inclusion Body Myositis
- Describe pathological features of Toxic Myopathies



Structure of a Skeletal Muscle





Skeletal muscle atrophy

- Skeletal muscle atrophy is a change that occurs in muscles of adult animals as a result of the conditions of disuse.
- Muscle atrophy results from an imbalance between protein synthesis and protein degradation.
- Skeletal muscle serves as a storage site for amino acids that can be used for energy production when demands are high or supplies are low. If metabolic demands remain greater than protein synthesis, muscle mass is lost.

Charecteristics

- . Regardless of the inciting event, skeletal muscle atrophy is characterized by a
- Decrease in protein content,
- Fiber diameter,
- Force production.
- Fatigue resistance.

Causes

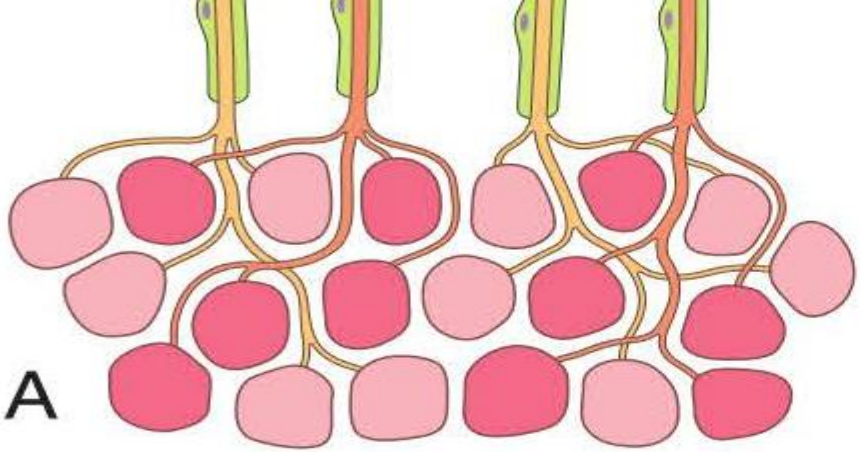
- Immobilization,
- Denervation,
- Muscle unloading
- Aging,
- Starvation
- Number of systemic disease states (i.e., cachexia)
- Myopathies

- There are several systems that have been implicated in the protein degradation of skeletal muscle. The two that have received the most attention, the calpain and ubiquitin-proteasome system (UPS), are most likely the primary ways that myofibrillar proteins are degraded while the caspase system (involved with cell apoptosis and autophagy) is partially responsible for normal cell turn-over. These systems work in conjunction with each other to negatively regulate muscle mass in various physiological conditions.

Neurogenic injury

- Neurogenic injuries lead to fiber type grouping and grouped atrophy both of which stem from the disruption of muscle innervation.
- Muscle fiber type is determined by the innervating motor neuron and can switch if the innervating motor neuron changes from one type to the other.

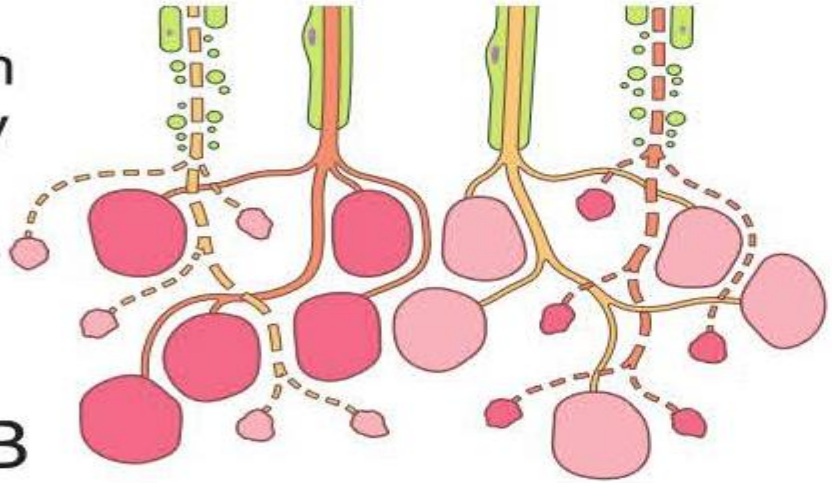
Normal



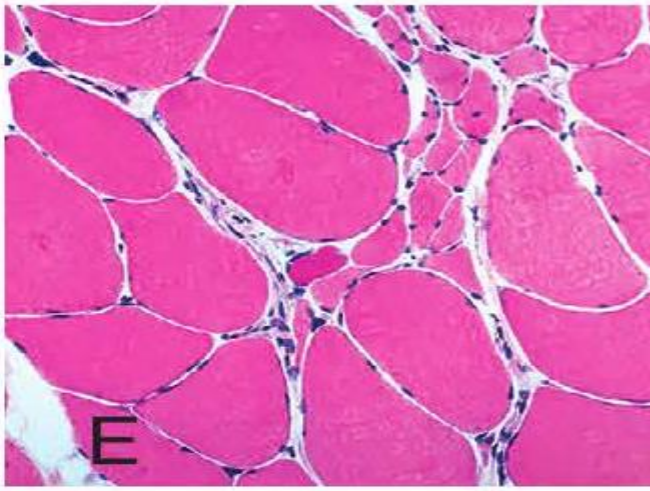
A

D

Denervation and atrophy

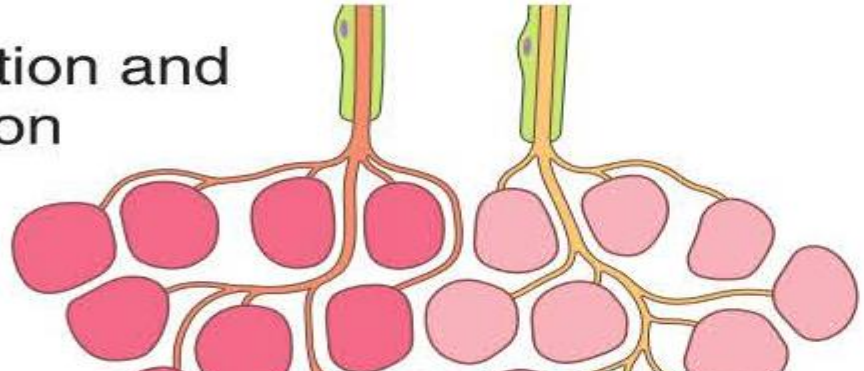


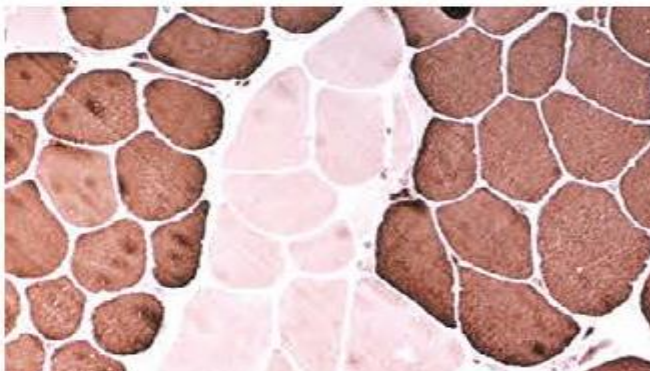
B



E

Reinnervation and regeneration





- Most primary myopathic processes are associated with a distinct set of morphologic changes that include the following:
- **Segmental myofiber degeneration and regeneration**
- **Myofiber hypertrophy**
- **Cytoplasmic inclusions**

INFLAMMATORY MYOPATHIES

- Largest group of acquired and potentially treatable causes of skeletal muscle weakness .

  POLYMYOSITIS (PM)

  DERMATOMYOSITIS (DM)

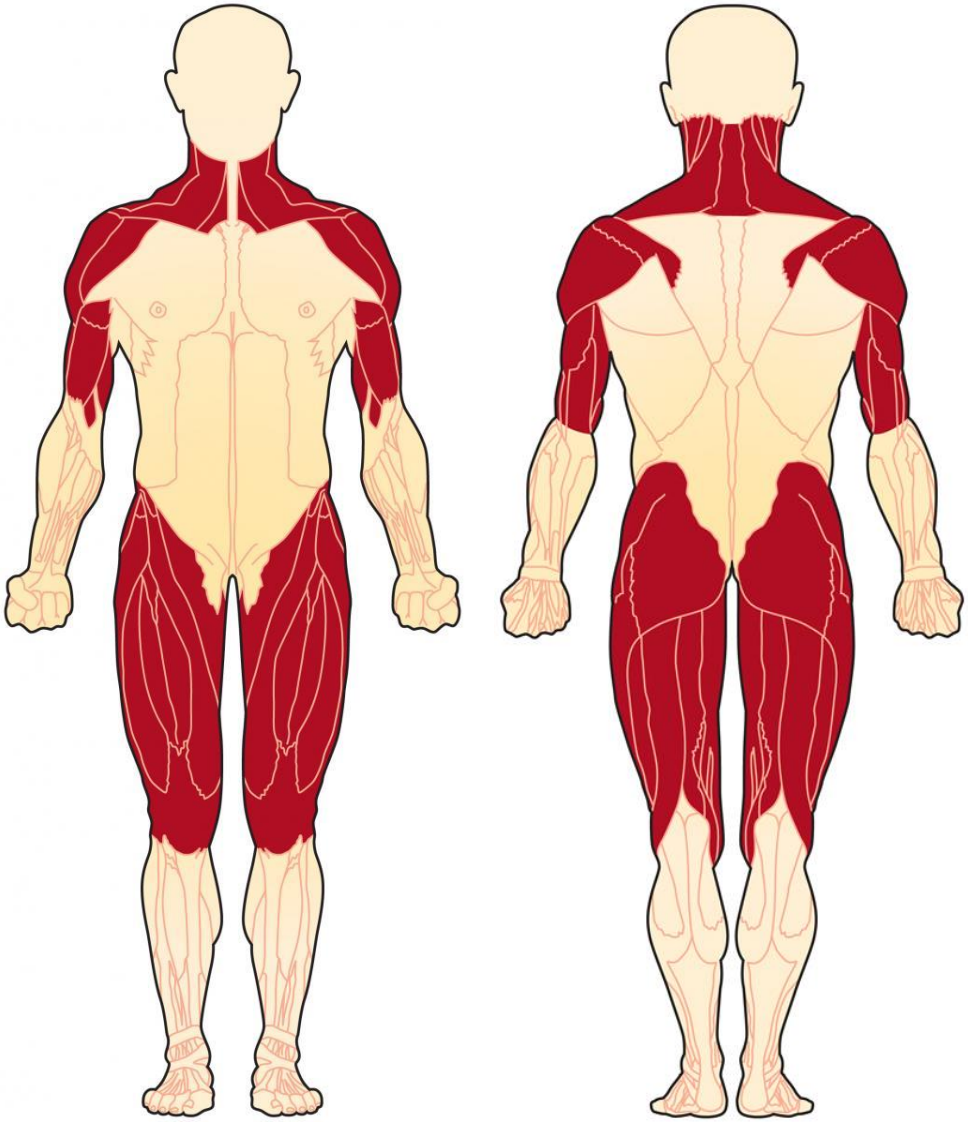
  INCLUSION BODY MYOSITIS (IBM)
- 1 :1,00,000
- PM – as alone is a rare disease affecting ADULTS.
- DM – affects both children,adults W>M
- IBM – M:F –3:1 ,caucasians,>50yrs.

Polymyositis (PM)

- It means "inflammation of many muscles"); it is a type of chronic inflammation of the muscles possibly due to autoimmune causes, including associations with certain autoantibodies, particular HLA-DR genotypes, and other autoimmune disorders.

Clinical presentation

- POLYMYOSITIS mostly affects the muscles of the hips and thighs, the upper arms, the top part of the back, the shoulder area and the neck
- Adults –Bilateral proximal muscle weakness.



POLYMYOSITIS **mostly affects the muscles of the hips and thighs, the upper arms, the top part of the back, the shoulder area and the neck**

Sign and symptoms

- Pain with marked weakness and loss of muscle mass in the proximal musculature particularly in the shoulder and pelvic girdle.
- The hip extensors are often severely affected leading to particular difficulty in ascending stairs and rising from a seated position.
- Dysphagia (difficulty in swallowing) occurs in 1/3 of patients.
- Low grade fever .
- peripheral lymphadenopathy may be present.

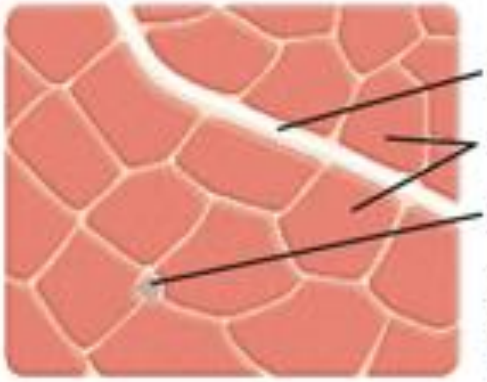
Pathogenesis

- The pathogenesis of polymyositis is uncertain, but it is believed to have an immunologic basis. CD8 positive cytotoxic T cells are a prominent part of the inflammatory infiltrate in affected muscle, and it is hypothesized that these cells are the mediators of tissue damage. Unlike dermatomyositis, vascular injury is not believed to have a major role in polymyositis.

Morphology

- Endomysial lymphocytic inflammation (Mononuclear inflammatory cell infiltrates)
- Skeletal muscle fiber degeneration and regeneration.
- Degenerating necrotic, regenerating, and atrophic myofibers are typically found in a random or patchy distribution.

Normal Muscle



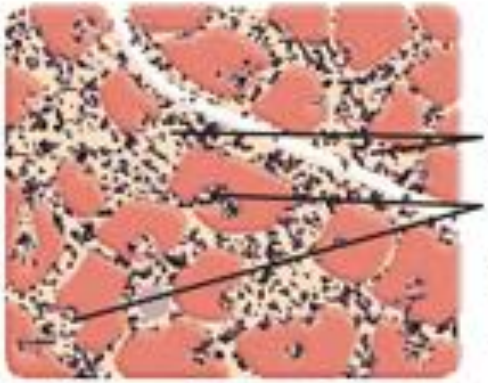
border of muscle bundle (fascicle)

normal muscle fibers

blood vessel

When normal muscle fibers are viewed under a microscope, they look like puzzle pieces that fit together neatly.

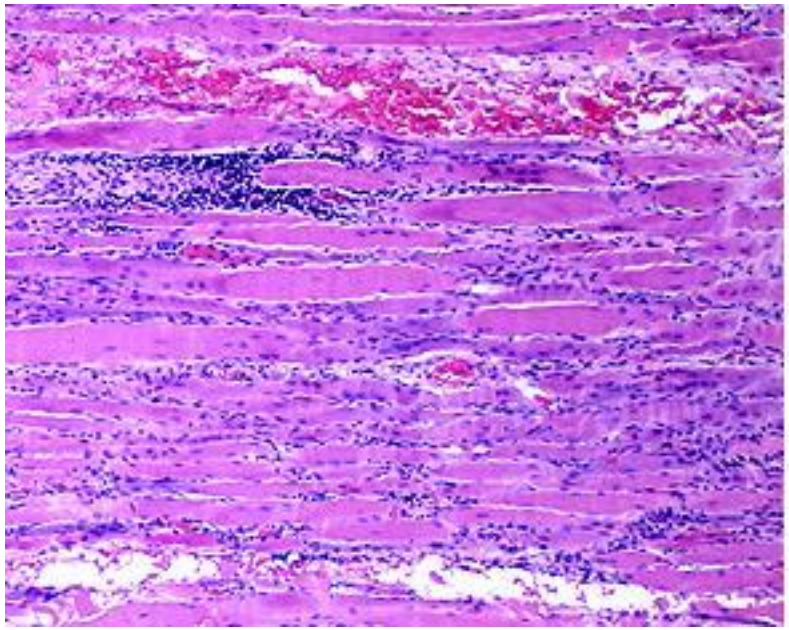
Polymyositis

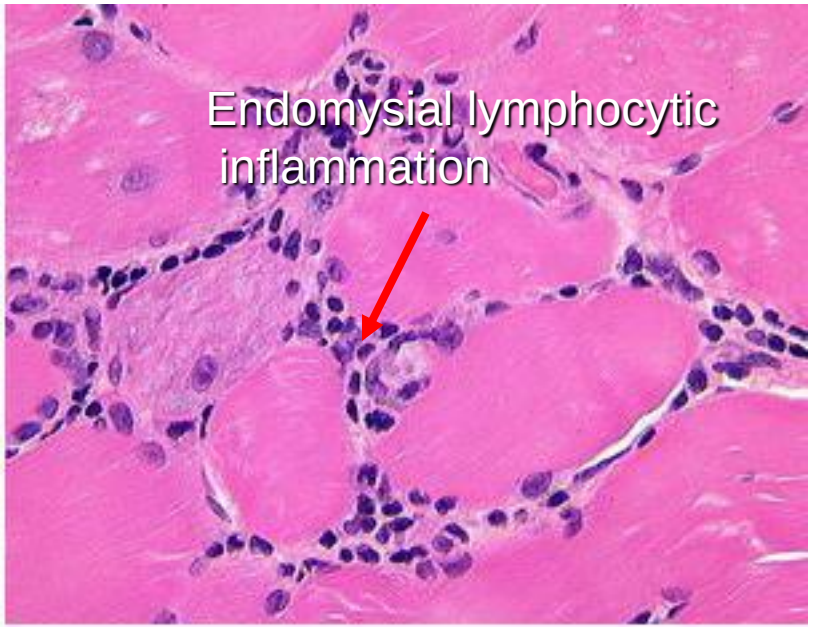


inflammatory cells

invasion of fibers by inflammatory cells

In polymyositis, inflammatory cells of the immune system invade previously healthy muscle cells, which become rounded and varible in size.





Polymyositis

Dermatomyositis

- Clinical presentation:
  1. Children and adults
  2. Bilateral proximal muscle weakness
  3. Skin rashes (upper eyelids)
  4. Peri-orbital edema

- Microscopic:
  1. Perimysial and vascular lymphocytic inflammation
  2. Skeletal muscle fiber degeneration and regeneration

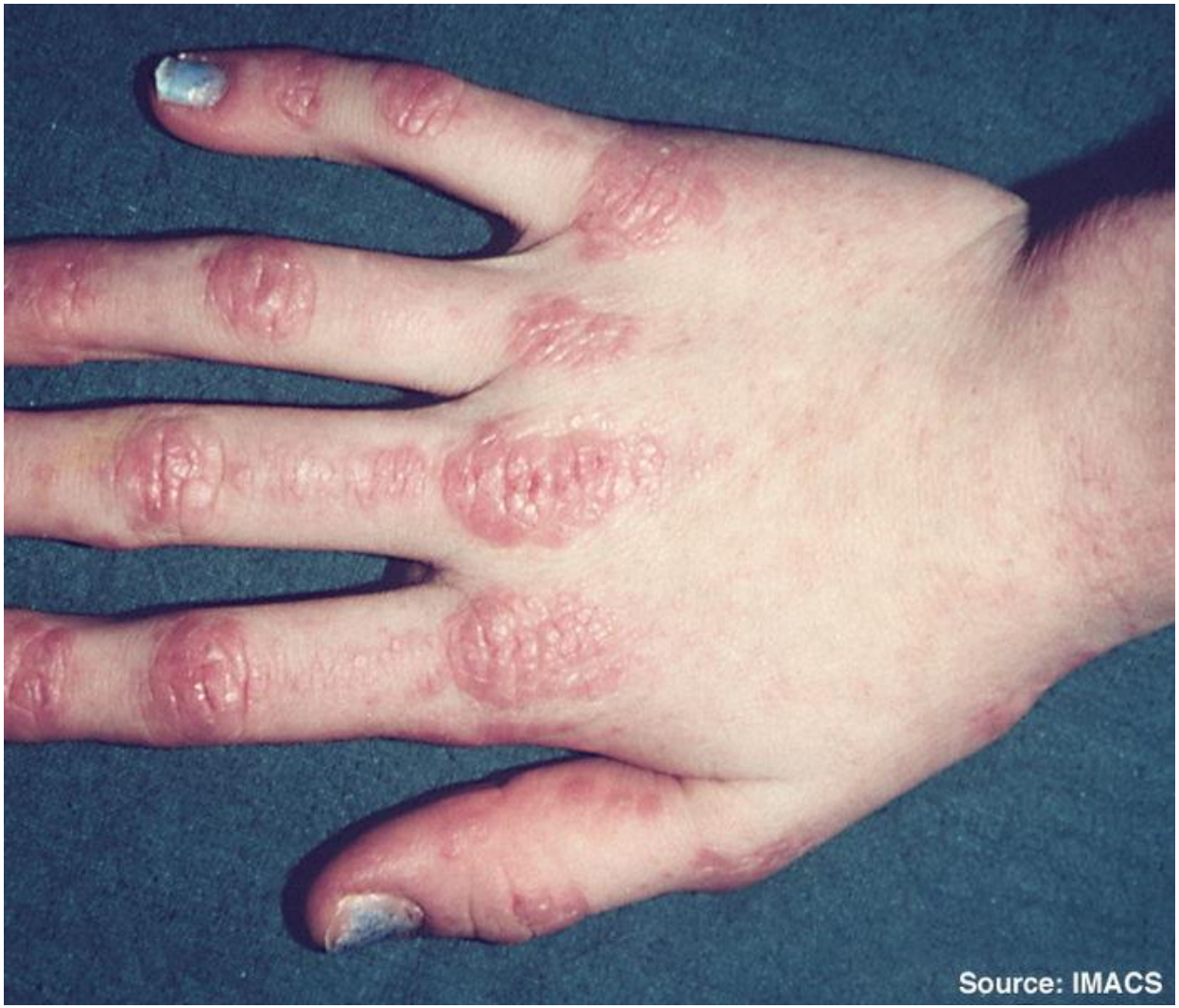
Dermatomyositis

- Clinical presentation:
  1. Children and adults
  2. Bilateral proximal muscle weakness
  3. Skin rashes (upper eyelids)
  4. Peri-orbital edema

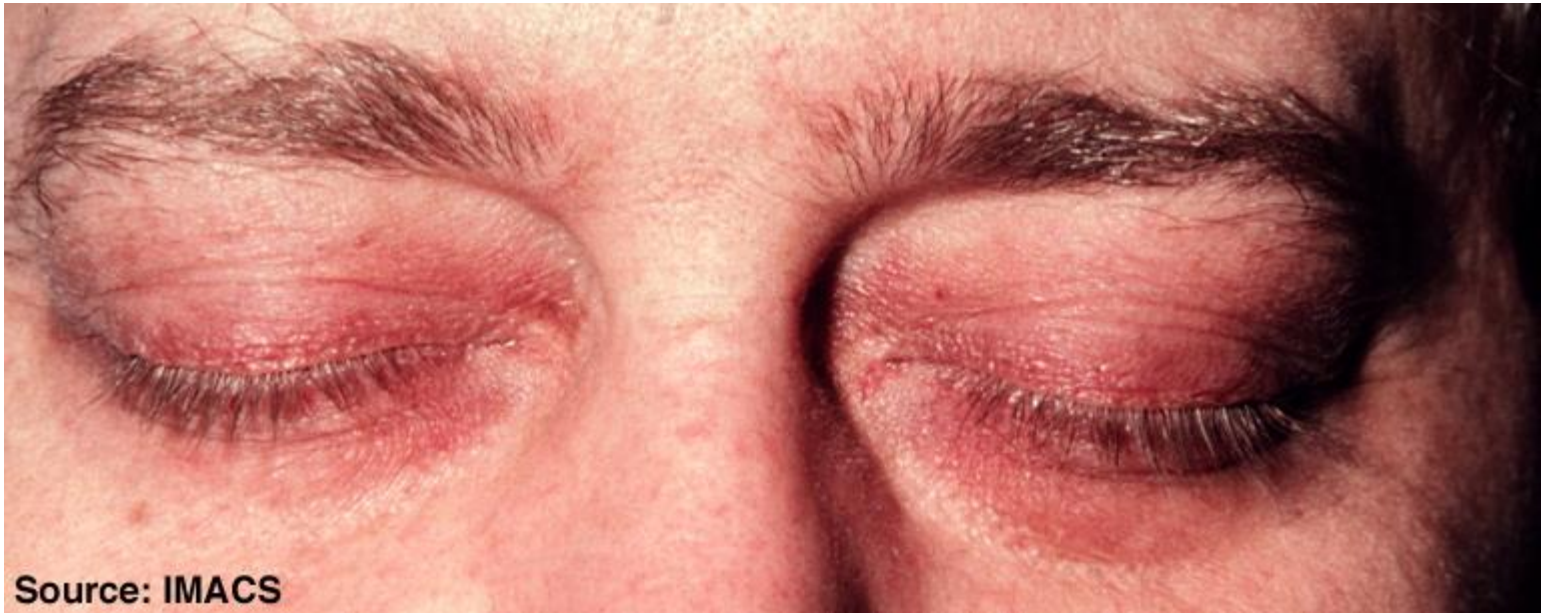
- Microscopic:
  1. Perimysial and vascular lymphocytic inflammation
  2. Skeletal muscle fiber degeneration and regeneration

- Grotton lesions: scaly erythematous eruptions or red patches overlying the knuckles, elbows, and knees

- X-ray findings sometimes include dystrophic calcifications in the muscles, and patients may or may not notice small calcium deposits under the skin



Gottron's lesions: Discrete erythematous papules overlying the metacarpal and interphalangeal joints in a patient with juvenile dermatomyositis



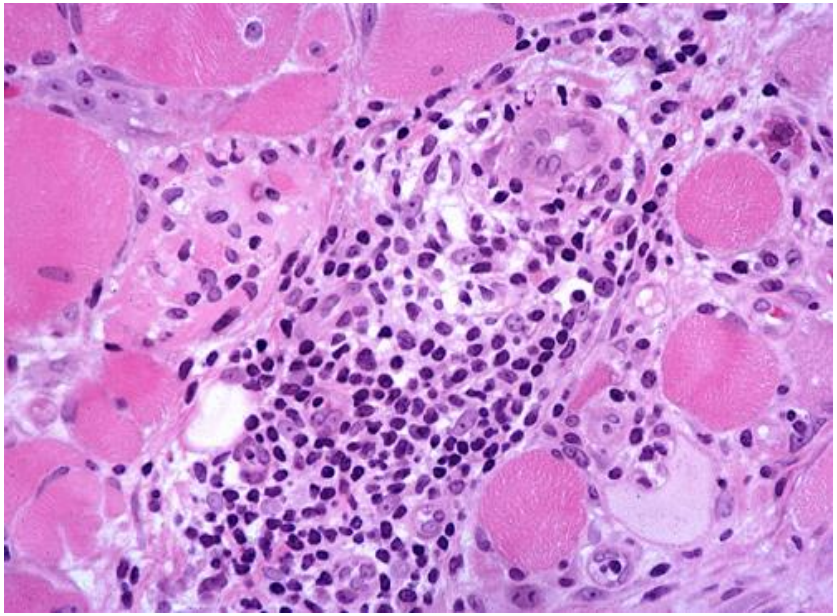
Eruption is associated with peri-orbital edema and telangiectasias of the both eyelids.(Helitrope rash)

Pathogenesis

- Dermatomyositis is an immunologic disease in which damage to small blood vessels contributes to muscle injury. The vasculopathic changes can be seen as telangiectasias (dilated capillary loops) in the nail folds, eyelids, and gums.
- Membrane attack complexes can be seen microscopically between the capillaries and tissues.

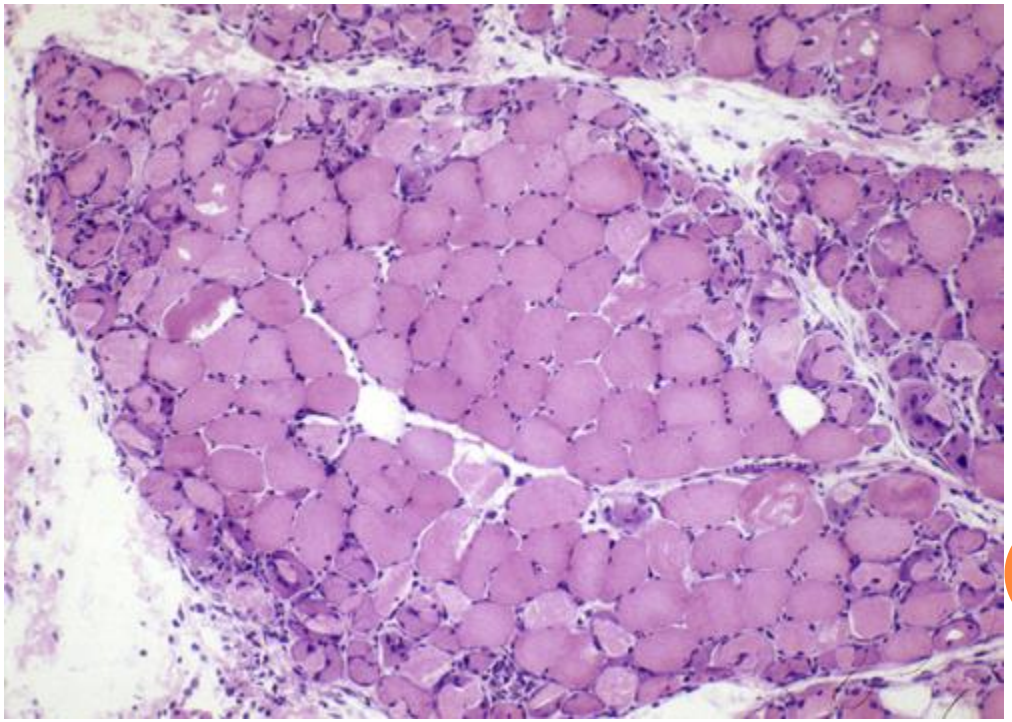
CONTD

- Various autoantibodies are often detected by serologic studies, and B lymphocytes as well as plasma cells are part of the inflammatory infiltrate that is seen in muscles. Certain autoantibodies tend to be associated with specific clinical features:
- ***Anti-Mi2 antibodies*** show a strong association with prominent Gottron papules and heliotrope rash.
- ***Anti-Jol antibodies*** are associated with interstitial lung
- disease, non erosive arthritis, and a skin rash described
- as "mechanic's hands.“
- ***Anti-P155/P140 antibodies*** are associated with paraneoplastic
- and juvenile cases of dermatomyositis.

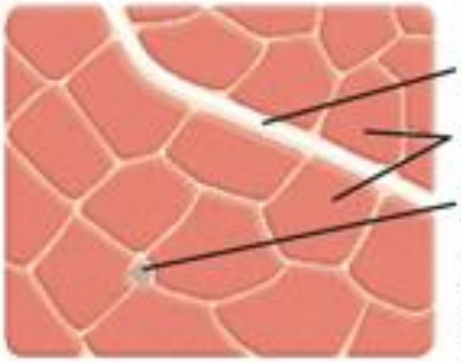


Perimysial and vascular lymphocytic inflammation

Dermatomyositis



Normal Muscle



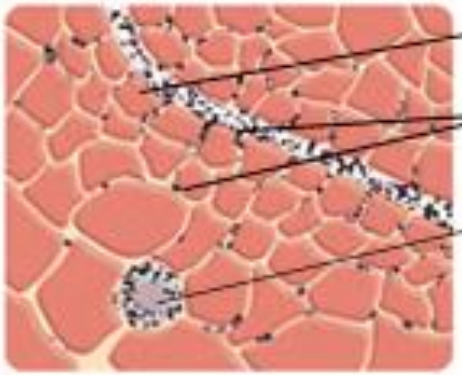
border of muscle bundle (fascicle)

normal muscle fibers

blood vessel

When normal muscle fibers are viewed under a microscope, they look like puzzle pieces that fit together neatly.

Dermatomyositis



shrinkage (atrophy) of fibers near border of fascicle

inflammatory cells around fascicle and between fibers

cuff of inflammatory cells around blood vessel

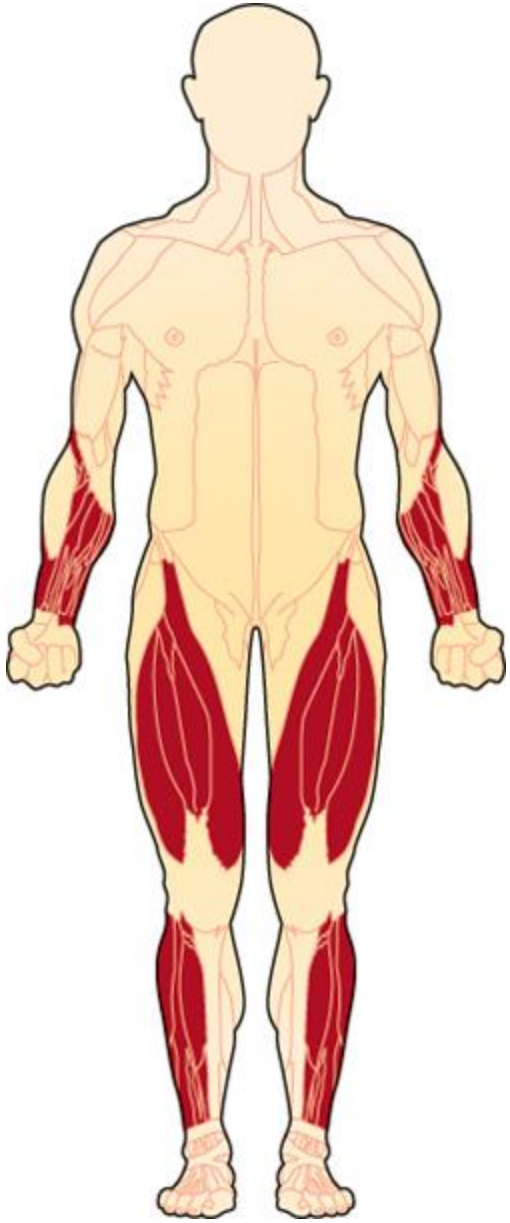
INCLUSION BODY MYOSITIS

- IBM causes progressive weakness of the muscles of the wrists and fingers, the muscles of the front of the thigh and the muscles that lift the front of the foot.

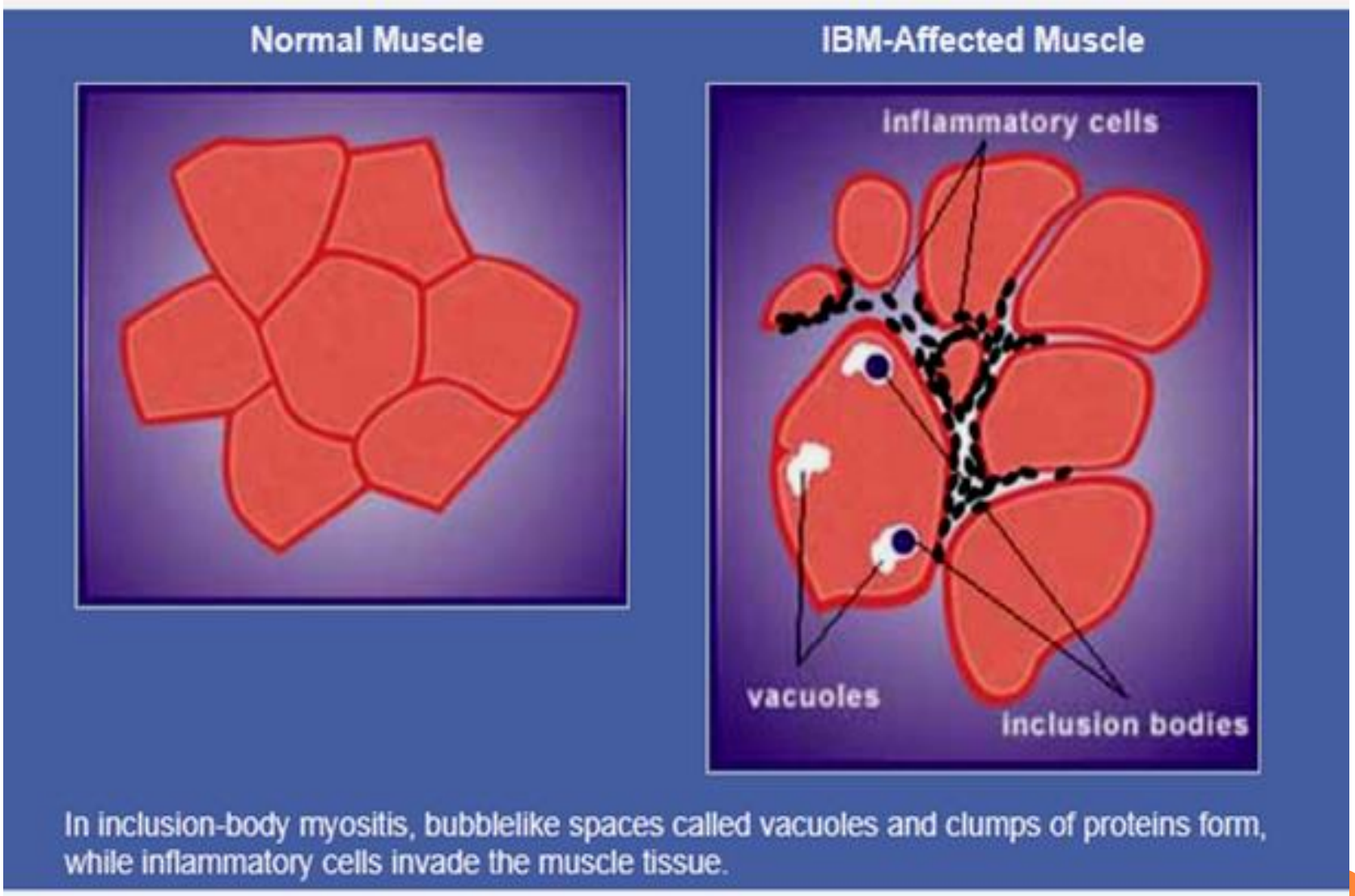
- IBM is generally a slowly progressive disease, and life expectancy isn't significantly affected. Most people with IBM remain able to walk, although they may require a cane or wheelchair for long distances.

- Clinical presentation:
  - Adults> age 50
  - Asymmetrical distal muscle weakness

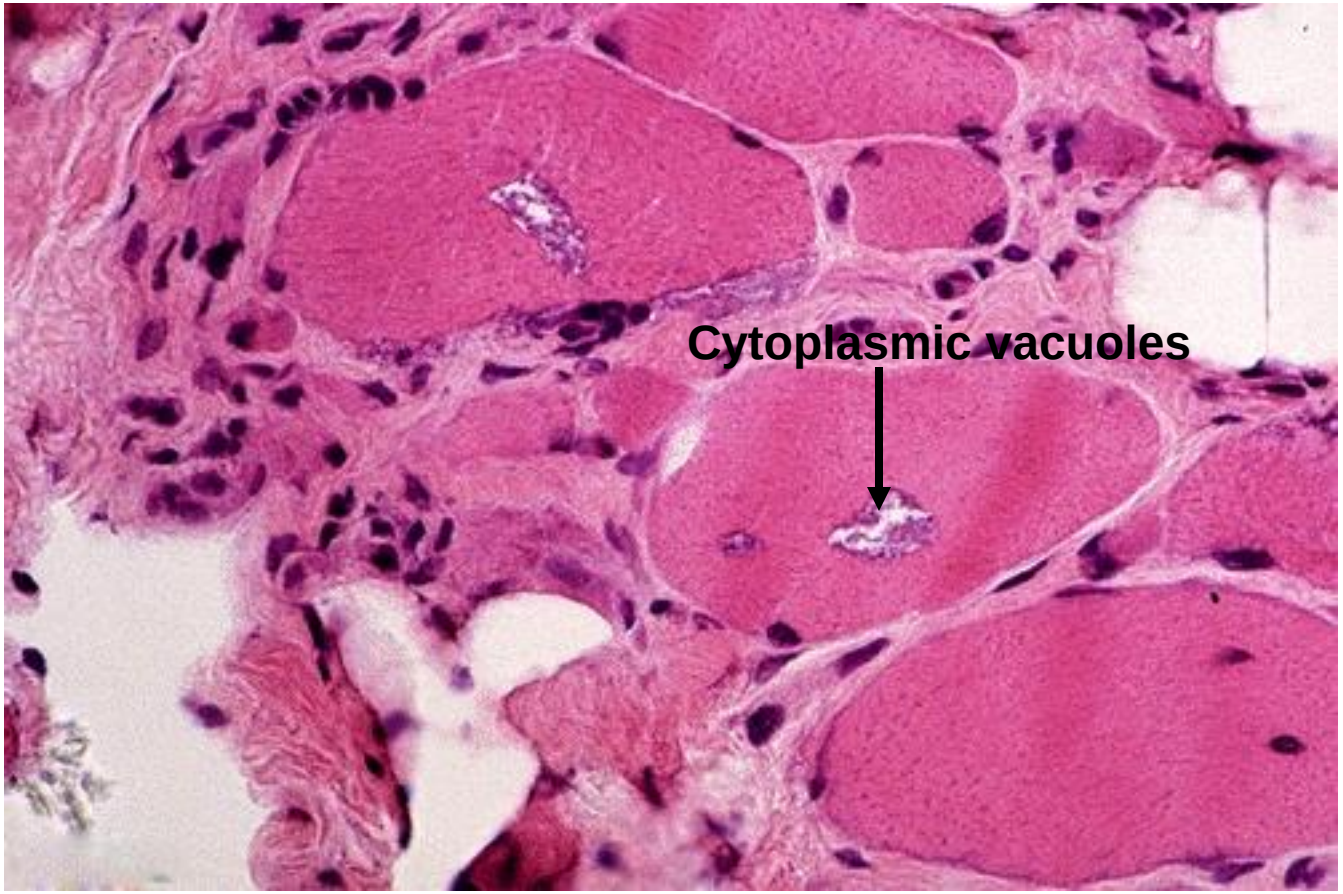
- Microscopically
  - Cytoplasmic vacuoles with basophilic granules and amyloid



The first muscles affected in inclusion-body myositis are usually those of the wrists and fingers, and the muscles at the front of the thigh. The muscles that lift the front of the foot also may be affected



In inclusion-body myositis, bubblelike spaces called vacuoles and clumps of proteins form, while inflammatory cells invade the muscle tissue.



Inclusion body myositis

Characteristic	Polymyositis	Dermatomyositis	Inclusion Body Myositis
Age at onset	>18 yr	Adulthood and childhood	>50 yr
Familial association	No	No	Yes, in some cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-I (human T cell lymphotropic virus type I).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

Criterion	Polymyositis		Dermatomyositis	Inclusion Body Myositis
	Definite	Probable		
Myopathic muscle weakness[a]	Yes	Yes	Yes[b]	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy findings[c]	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Ubiquitous MCH-I expression but minimal inflammation and no vacuoles[d]	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with β-amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy[e]
Rash or calcinosis	Absent	Absent	Present[f]	Absent

[a]Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, and no biochemical muscle disease (excluded on the basis of muscle-biopsy findings).

[b]In some cases with the typical rash, the muscle strength is seemingly normal (dermatomyositis sine myositis); these patients often have new onset of easy fatigue and reduced endurance. Careful muscle testing may reveal mild muscle weakness.

[c]See text for details.

[d]An adequate trial of prednisone or other immunosuppressive drugs is warranted in probable cases. If, in retrospect, the disease is unresponsive to therapy, another muscle biopsy should be considered to exclude other diseases or possible evolution in inclusion body myositis.

[e]If the muscle biopsy does not contain vacuolated fibers but shows chronic myopathy with hypertrophic fibers, primary inflammation with the CD8/MHC-I complex and cytochrome oxygenase–negative fibers, the diagnosis is probable inclusion body myositis.

[f]If rash is absent but muscle biopsy findings are characteristic of dermatomyositis, the diagnosis is probable DM.

Toxic myopathy

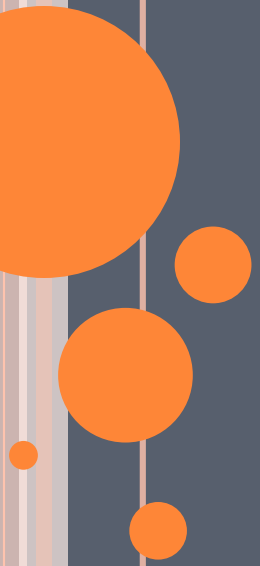
- A drug-induced, or **toxic**, **myopathy** is defined as the acute or subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase (CK) elevation, or myoglobinuria that can occur in patients without muscle disease when they are exposed to certain drugs
- Toxic myopathies are a diverse group of muscle disorders caused by a variety of medications and toxins. These conditions may be classified by their presumed pathogenic pattern, which is often either purely necrotizing or vacuolar.

Contd…..

- Statin Induced
- Chloroquine and Hydroxychloroquine (Drug induced lysosomal storage myopathy)
- ICU Myopathy (Corticosteroids therapy)
  - Degredation of sarcomeric myosin thick filament leading to profound swelling
- Thyrotoxic Myopathy
  - Proximal muscle weakness, exophthalmic, ophthalmoplegia
- Alcohol

- The pathophysiology of toxic myopathies is variable and not fully known. Hypotheses being tested relate to the degree of lipophilicity, effects on ion channels in sarcolemma, intracellular calcium homeostasis, potential deficiency of ubiquinone, primary mitochondrial membrane pathology, organic anion transporters, and energy depletion.

- Baseline risk factors for toxic myopathy include:
- Decreased ability to metabolize or excrete a drug and its metabolites
- Hepatic or renal failure
- Older adults
- Infants/children
- Concomitant use of statin drugs plus fibrates, macrolide antibiotics, azole antifungals, cyclosporine, amiodarone, verapamil, diltiazem, cimetidine, and/or other drugs sharing cytochrome P450 metabolism system.



Thanks