MUSCULOSKELETAL SYSTEM BLOCK

An introduction to myopathies and muscular dystrophy

Pathology

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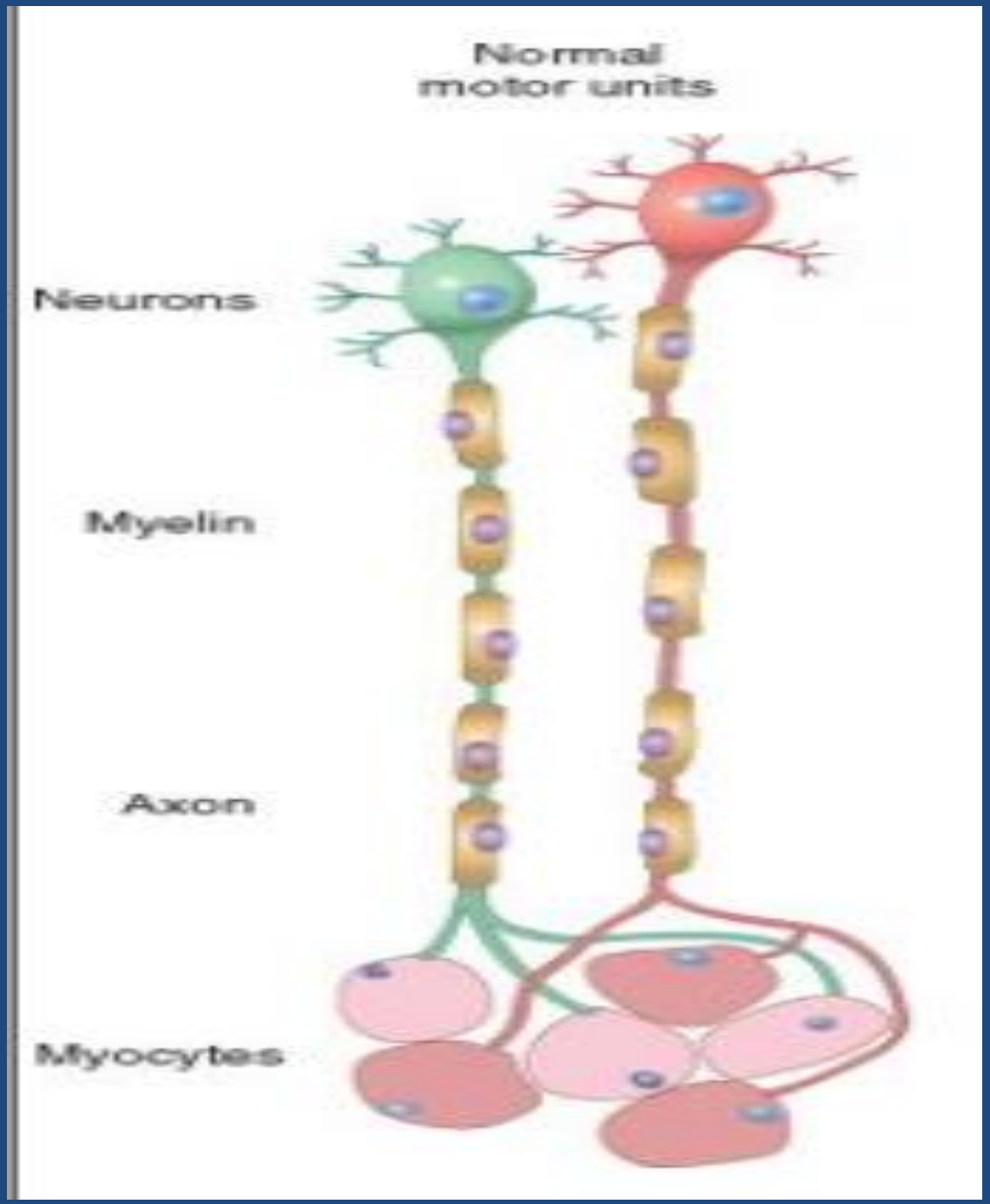
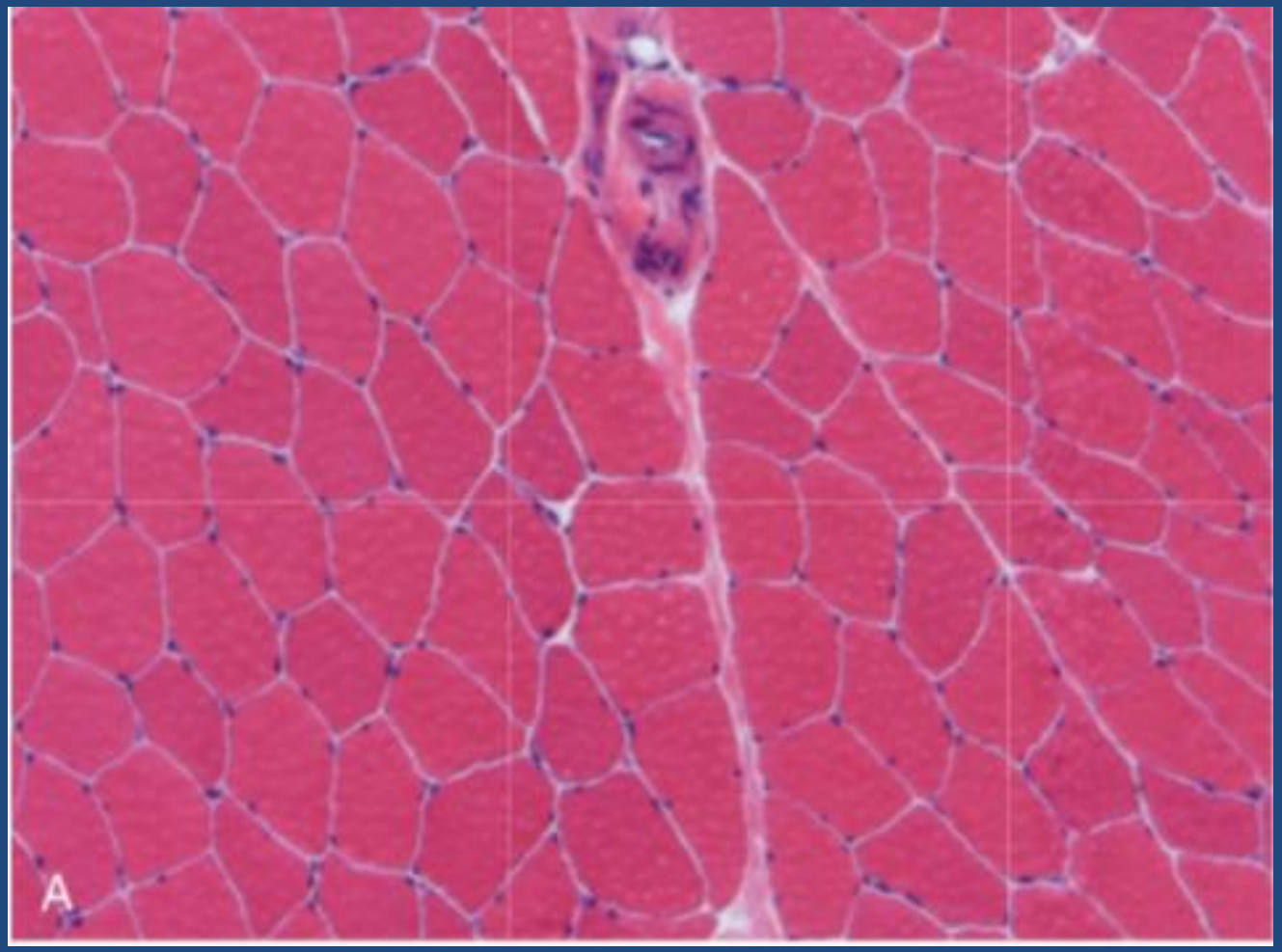
Objectives:

At the end of this lecture, the students should be able to:

- Understand the structure of the various types of muscle fibers.
- Acquire a basic knowledge of the classification of myopathies and give examples of these disorders.
- Understand the meaning of the term muscular dystrophy and have a basic knowledge of the incidence and clinicopathological manifestations of Duchenne's and Becker's muscular dystrophies.
- Know the pattern of inheritance of myotonic dystrophy and its clinicopathological presentations.


Normal
motor units
Neurons
Myelin
Axon
Myocytes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- **The two principal pathologic processes seen in skeletal muscle are *denervation atrophy*, which follows loss of axons, and those due to a primary abnormality of the muscle fiber itself, referred to as *myopathy***

Muscle fiber types

- **The fiber types, are determined by the neuron of the motor unit, and their properties are imparted through innervation.**
- **Type 1 fibers:** slow twitch "aerobic" type I **are high in myoglobin and oxidative enzymes and have many mitochondria, in keeping with their ability to perform tonic contraction**

- **Type 2 fibers :** fast twitch **are rich in glycolytic enzymes and are involved in rapid phasic contractions**
- ***Since the motor neuron determines fiber type, all muscle fibers of a single unit are of the same type*.**
- **The fibers of a single motor unit are distributed across the muscle, giving rise to a checkerboard pattern of alternating fiber types**

	Type 1	Type 2
Action	Sustained force	Sudden movements
Strength	Weight-bearing	Purposeful motion
Enzyme content	NADH-TR dark staining	NADH light staining

- Diseases that affect skeletal muscle can involve any portion of the motor unit:
  - primary disorders of the motor neuron or axon
  - abnormalities of the neuromuscular junction
  - a wide variety of disorders primarily affecting the skeletal muscle itself (***myopathies***)

MYOPATHY

- Myopathy as a term may encompasses a heterogeneous group of disorders, both morphologically and clinically

- Recognition of these disorders is important for genetic counseling or appropriate treatment of acquired disease

MUSCLE ATROPHY

- A non-specific response
- Characterized by abnormally small myofibers
- The type of fibers affected by the atrophy, their distribution in the muscle, and their specific morphology help identify the etiology of the atrophic changes

MUSCLE ATROPHY

- Causes:
  - Simple disuse, type II fibers
  - Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness)
  - Myopathies
  - Neurogenic atrophy

MUSCLE ATROPHY

Neurogenic Atrophy

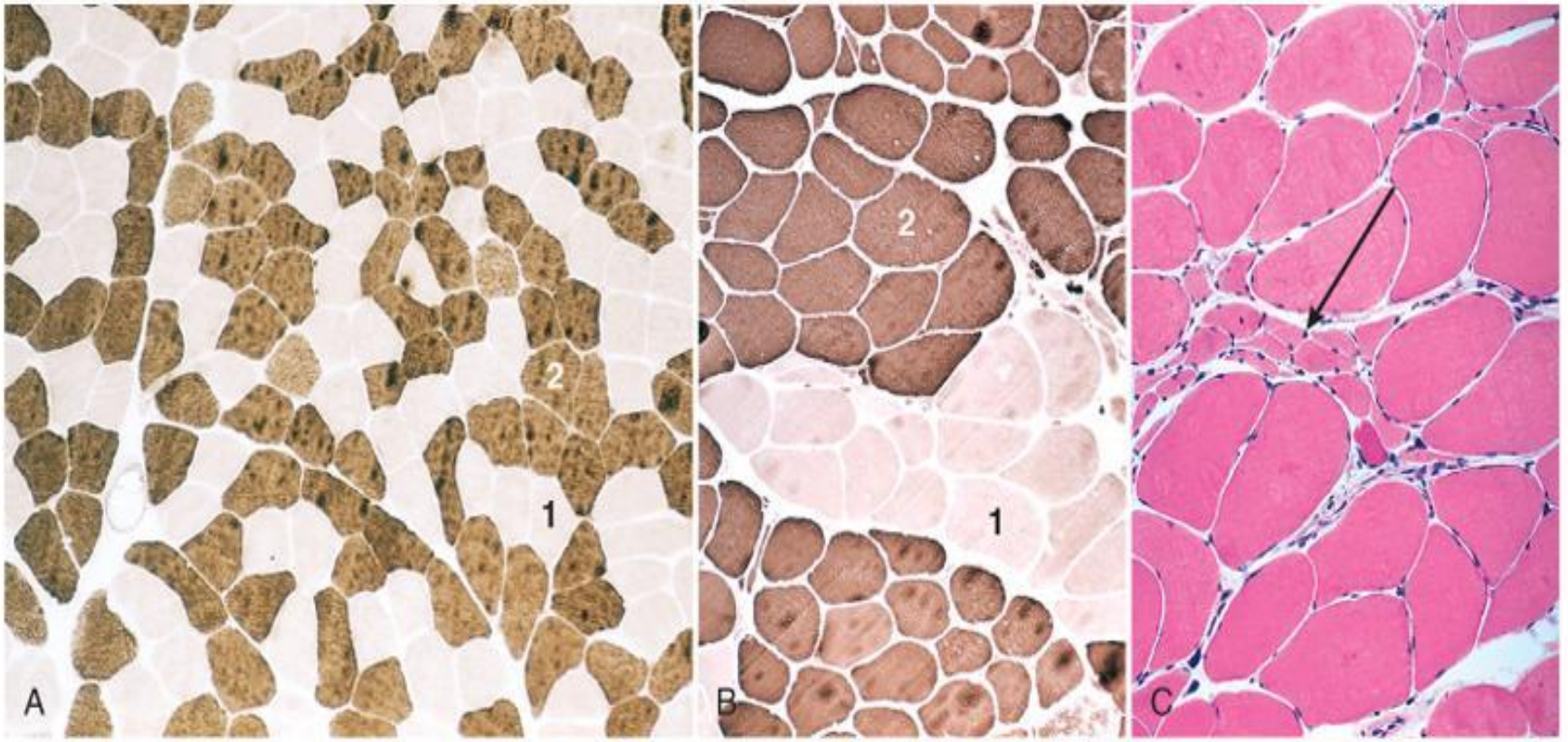
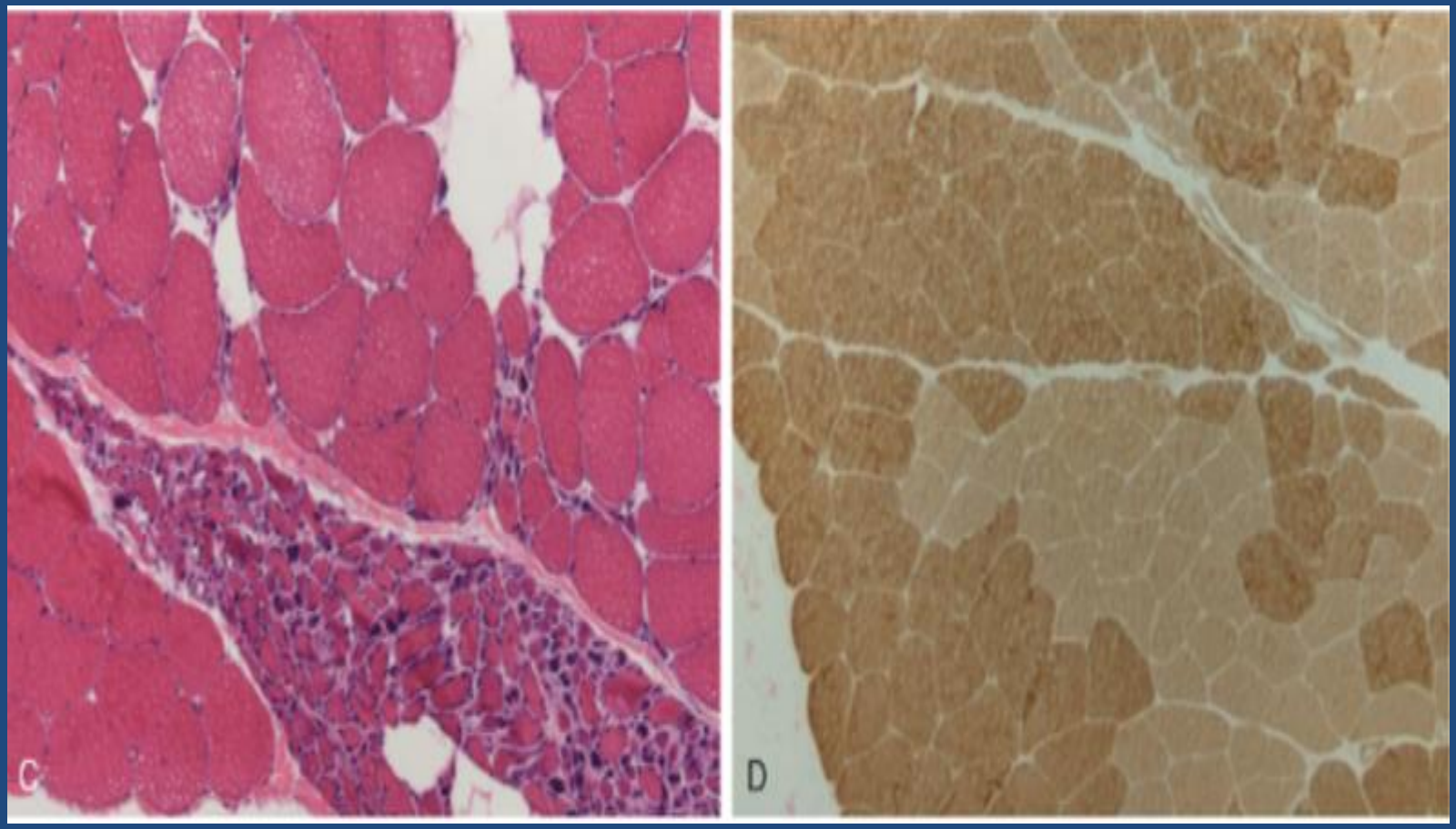


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of atrophic fibers (group atrophy) in the center (*arrow*).

MUSCLE ATROPHY

Neurogenic Atrophy

- Neurogenic Atrophy :
  - Both fiber types
  - Characterized **by fiber type grouping and grouped atrophy**
  - Deprived of their normal enervation, skeletal fibers undergo progressive atrophy
  - injury and regeneration of peripheral nerves alters muscle innervation, it will change the distribution of type I and type II myofibers.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D

MUSCULAR DYSTROPHIES

- A heterogeneous group of inherited disorders
  - Often presenting in childhood
  - Characterized by progressive degeneration of muscle fibers leading to muscle weakness and wasting
  - Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue

Duchenne Muscular dystrophy (DMD)and Becker Muscular Dystrophy(BMD

- X-Linked Muscular Dystrophy
- The two most common forms of muscular dystrophy
- DMD is the most severe and the most common form of muscular dystrophy, with an incidence of about 1 per 3500 male births
- DMD becomes clinically evident by age of 5, →progressive weakness leading to wheelchair dependence by age 10 to 12 years →death by the early 20s
- Although the same gene is involved in both BMD and DMD, BMD is less common and much less severe

Pathogenesis

- Both DMD and BMD are caused by mutations in the **dystrophin gene** located on the short arm of the X chromosome (Xp21).
- Dystrophin is a very large protein found in skeletal and cardiac muscle, brain, and peripheral nerves
- .

- It is part of the dystrophin-glycoprotein complex . This complex stabilizes the muscle cell during contraction and may be involved in cell signaling through interaction with other proteins.
- Dystrophin-glycoprotein complex defects are thought to make muscle cells vulnerable to transient membrane tears during contraction that lead to calcium influx.
- The result is myofiber degeneration that with time outpaces the capacity for repair.
- The dystrophin-glycoprotein complex also is important for cardiac muscle function; this explains why cardiomyopathy eventually develops in many patients

Pathogenesis

- In the affected families females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and show minimal histologic abnormalities on muscle biopsy.

- Female carriers and affected males who survive into adulthood are also at risk for developing dilated cardiomyopathy

- Muscle biopsy specimens from individuals with DMD show little or no dystrophin by both staining and western blot analysis

- People with BMD, who also have mutations in the dystrophin gene, have diminished amounts of dystrophin, usually of an abnormal molecular weight, reflecting mutations that allow synthesis of an abnormal protein of smaller size

Morphology

The histologic alterations in skeletal muscles affected by DMD and BMD are similar except that the changes are milder in BMD

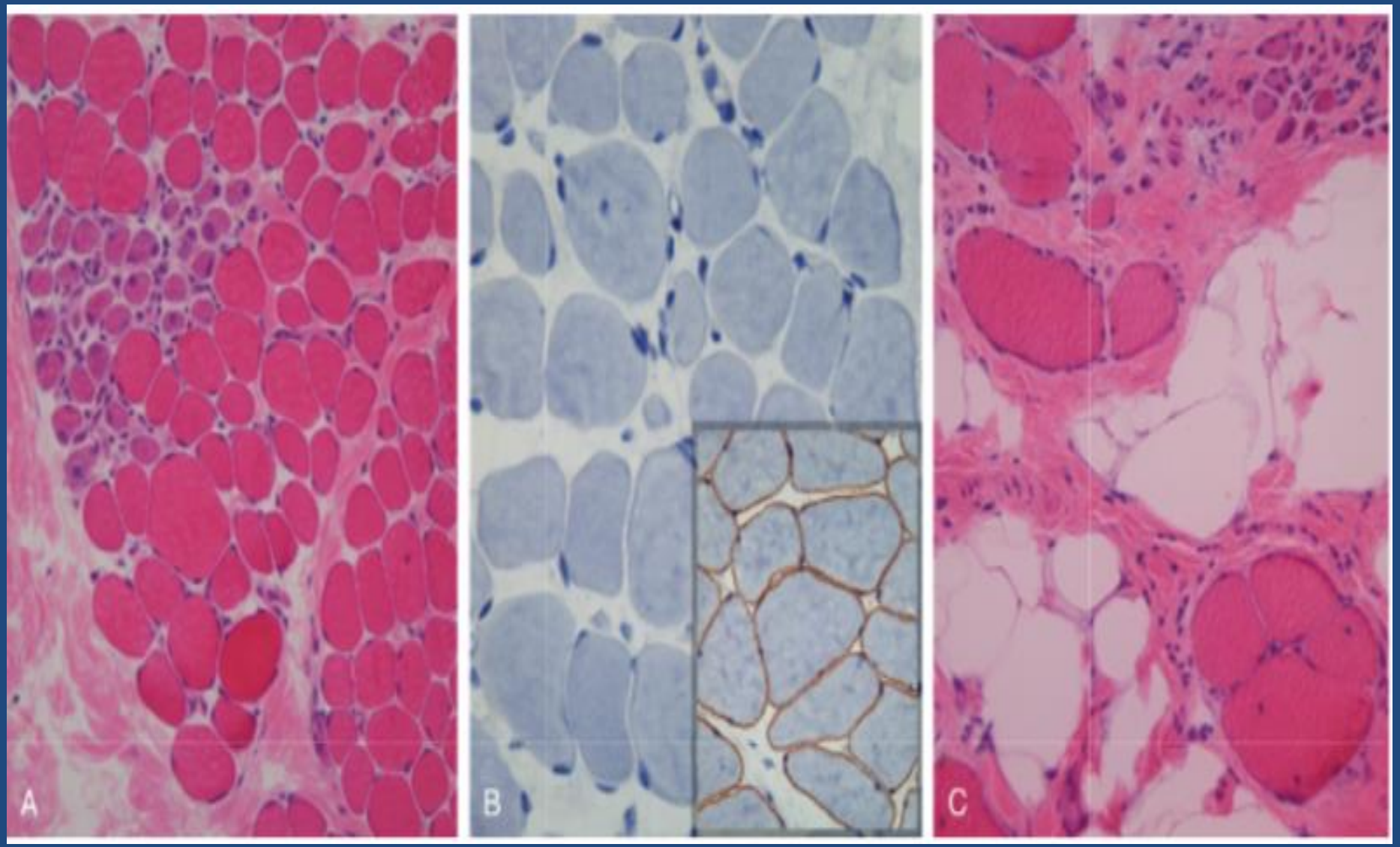
1- The hallmarks are ongoing myofiber necrosis and regeneration.

2- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair.

3- marked variation in myofiber size and

4- abnormal internally placed nuclei.

Both DMD and BMD also affect cardiac muscles, which show variable degrees of interstitial fibrosis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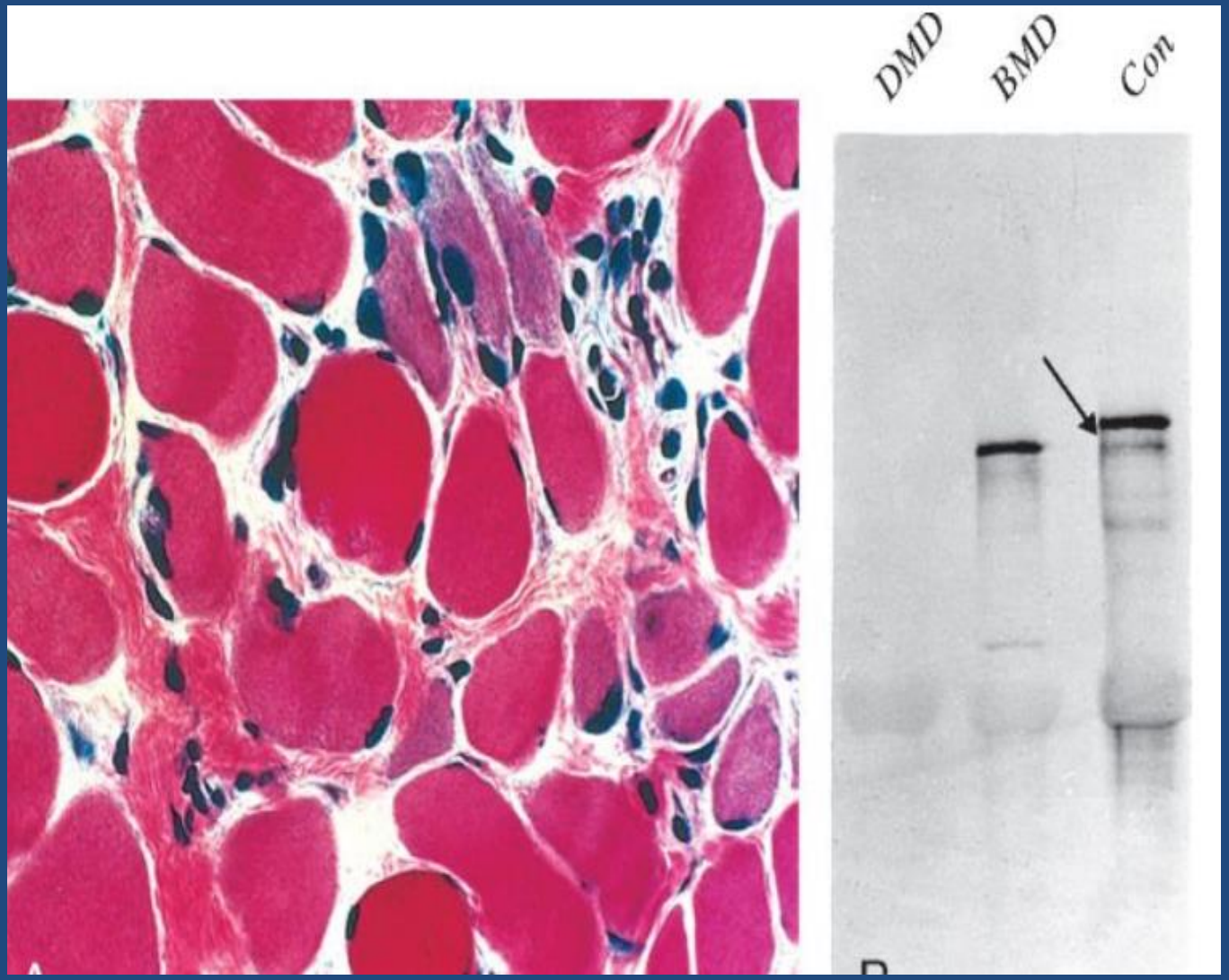

DMD
BMD
Con

Clinical Features

- Boys with DMD:
  - Normal at birth, and early motor milestones are met on time
  - first symptoms of DMD are clumsiness and an inability to keep up with peers due to muscle weakness
  - Weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle
  - Enlargement of the calf muscles associated with weakness, a phenomenon termed *pseudohypertrophy,* is an important clinical finding
    - The increased muscle bulk is caused initially by an increase in the size of the muscle fibers and then, as the muscle atrophies, by an increase in fat and connective tissue
  - Pathologic changes are also found in the heart, and patients may develop heart failure or arrhythmias

Clinical Features

- Cognitive impairment seems to be a component of the disease and is severe enough in some patients to be considered mental retardation
- Serum creatine kinase is elevated during the first decade of life but returns to normal in the later stages of the disease, as muscle mass decreases
- Death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation

BMD

- BMD becomes symptomatic later in childhood or adolescence and progresses at a slower and more variable rate.
- Many patients live well into adulthood and have a nearly normal life span.
- Cardiac involvement can be the dominant clinical feature and may result in death in the absence of significant skeletal muscle weakness.

Myotonic Dystrophy

- ***Myotonia*, the sustained involuntary contraction of a group of muscles, is the cardinal symptom in this disease.**
- **Patients often complain of "stiffness" and have difficulty in releasing their grip, for instance, after a handshake.**
- **Myotonia can often be elicited by percussion of the thenar eminence.**

Pathogeneis

- Mutations in the gene that encodes the dystrophia myotonica protein kinase (**DMPK).**
- In normal subjects, this gene contains fewer than 30 repeats of the sequence CTG, whereas in severely affected persons, several thousand repeats may be present.
- Myotonic dystrophy thus falls into the group of disorders associated with trinucleotide repeat expansions
- Myotonic dystrophy exhibits the phenomenon of *anticipation,* characterized by worsening of the disease manifestations with each passing generation due to further trinucleotide repeat expansion.

Morphology

- **Skeletal muscle may show variation in fiber size.**
- **Increase in the number of internal nuclei.**
- **Another well-recognized abnormality is the ring fiber**

Clinical Course.

- **The disease often presents in late childhood with abnormalities in gait**
- **weakness of the hand intrinsic muscles and wrist extensors.**
- **Atrophy of muscles of the face and ptosis .**
- **Cataracts**
- **Other associated abnormalities include frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma IgG, and abnormal glucose tolerance.**
- **Dementia has been reported in some cases**

Inflammatory myopathies

1- Infectious

2 - Noninfectious inflammatory

Noninfectious Inflammatory Myopathies

- Inflammatory myopathies make up a heterogeneous group of rare disorders characterized **by immune-mediated** muscle injury and inflammation

- Based on the clinical, morphologic, and immunologic features, three disorders:
  - *Polymyositis*
  - *Dermatomyositis*
  - *Inclusion body myositis*

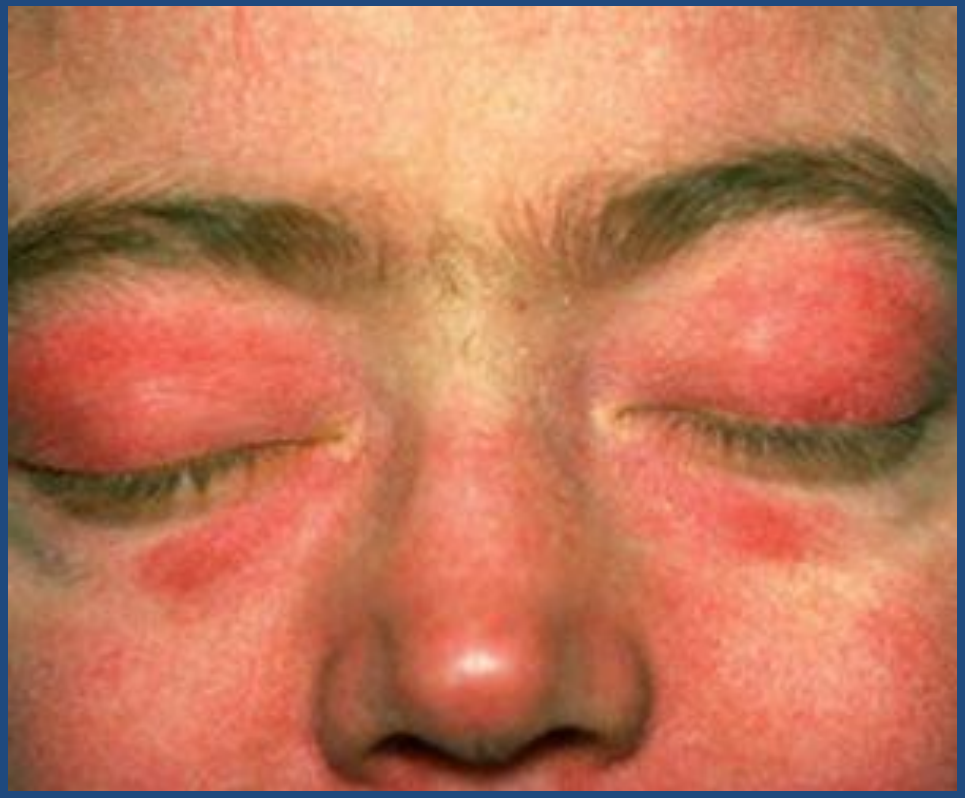
Dermatomyositis

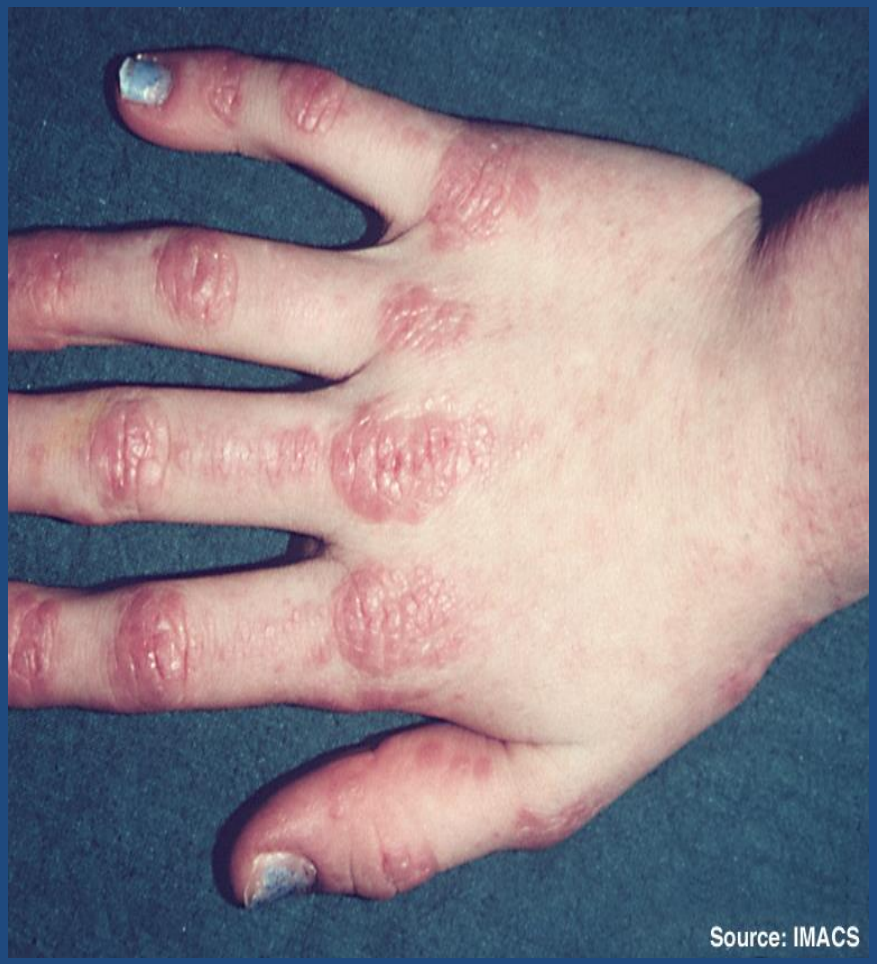
- **inflammatory disorder of the skin as well as skeletal muscle.**
- **skin rash that may accompany or precede the onset of muscle disease. The *classic rash takes the form of ** a discoloration of the upper eyelids associated with periorbital edema* ** scaling erythematous eruption over the knuckles(Gottron's lesions).**
- ***Muscle weakness* is slow in onset, bilaterally symmetric**

***It typically affects the proximal muscles first*. As a result, tasks such as getting up from a chair become increasingly difficult.**

- **Dysphagia**
- **Extramuscular manifestations, including interstitial lung disease, vasculitis, and myocarditis, may be present in some cases**

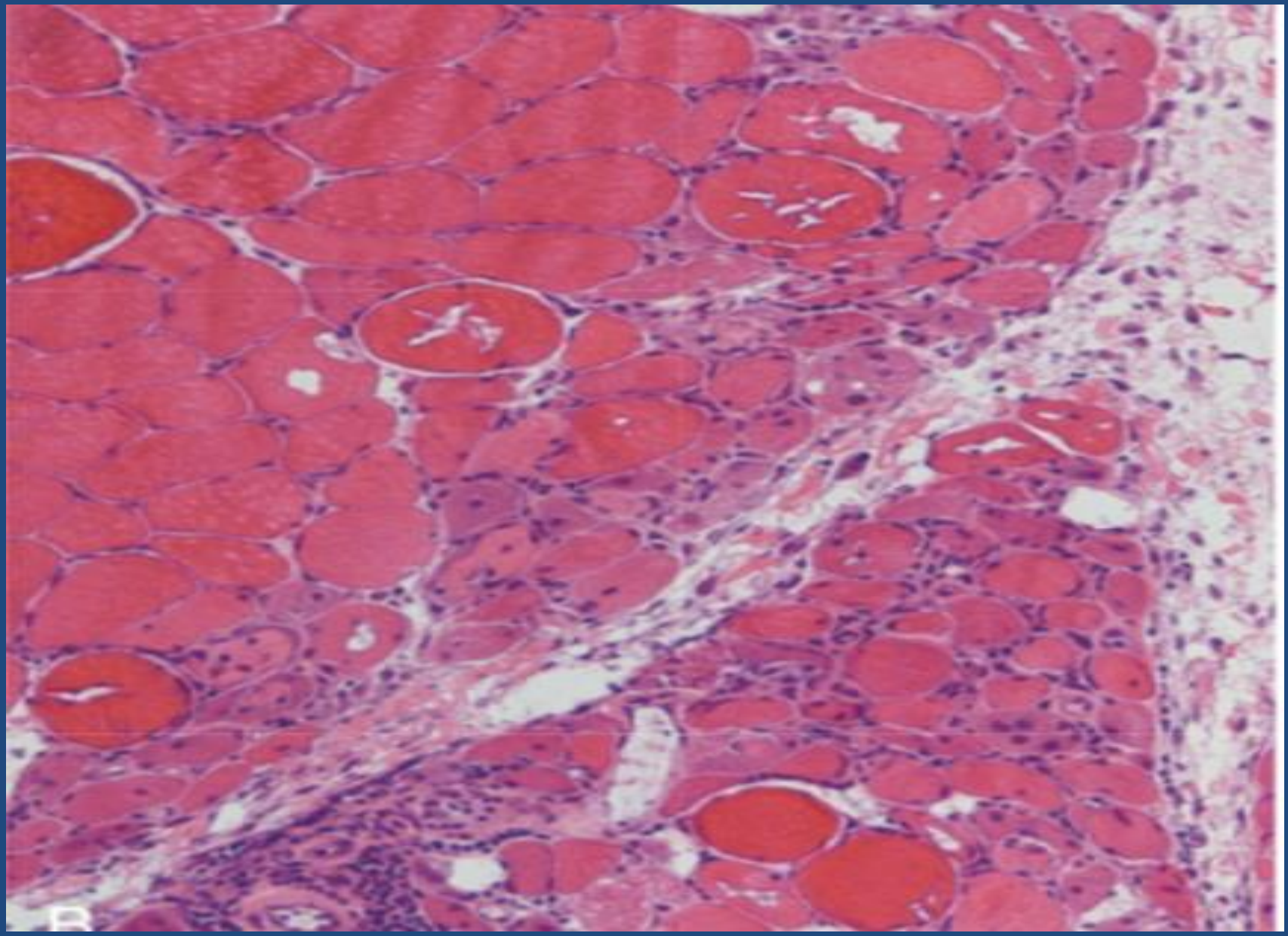
- **According to several studies, 20% to 25% of adults with dermatomyositis have cancer (paraneoplastic)**




Source: IMACS

Morphology

- **Mononuclear inflammatory infiltrate located predominantly around small blood vessels.**
- **Groups of atrophic fibers are particularly prominent at the periphery of fascicles. This "perifascicular atrophy" is sufficient for diagnosis, even if the inflammation is mild or absent.**
- **marked reduction in the intramuscular capillaries**



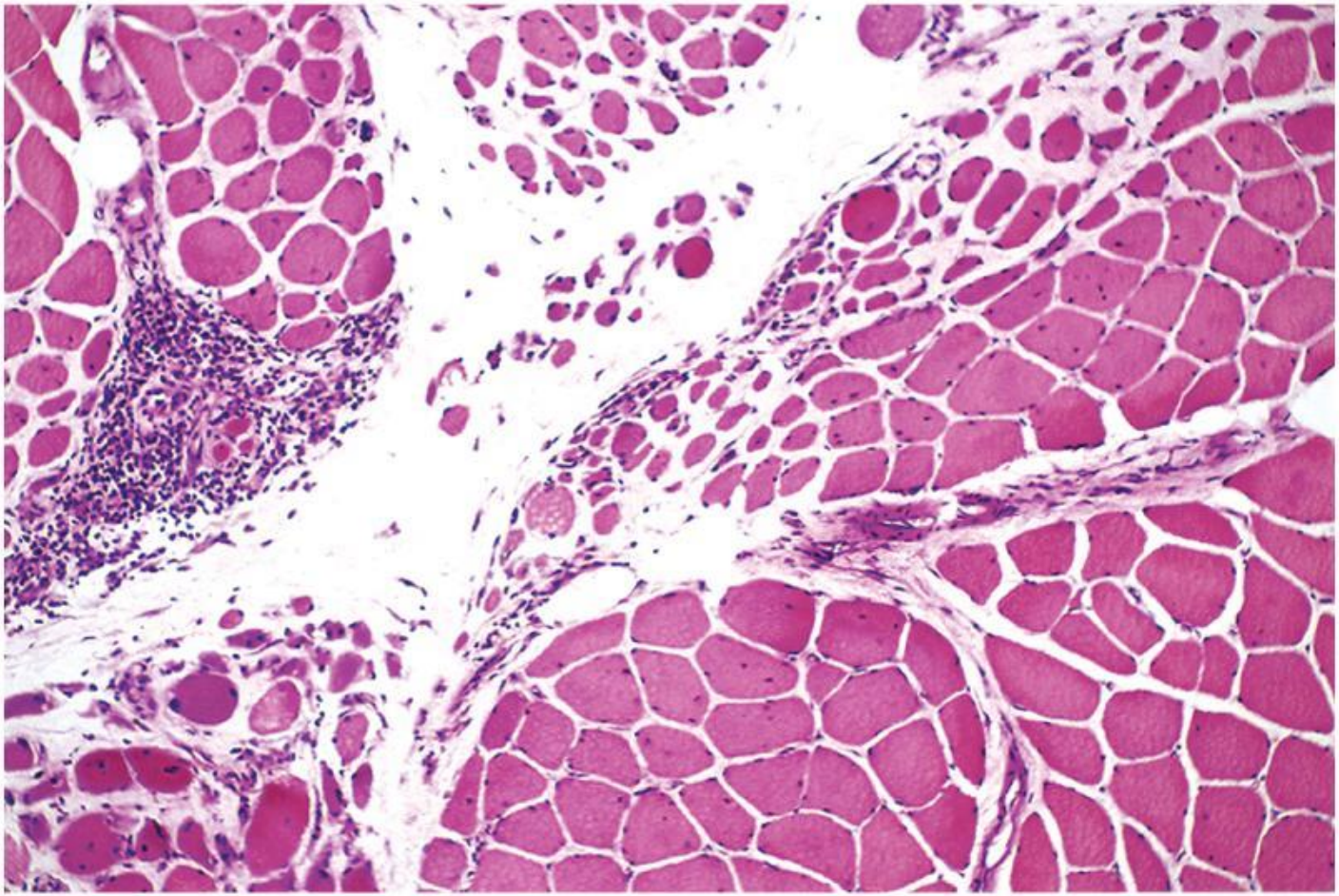


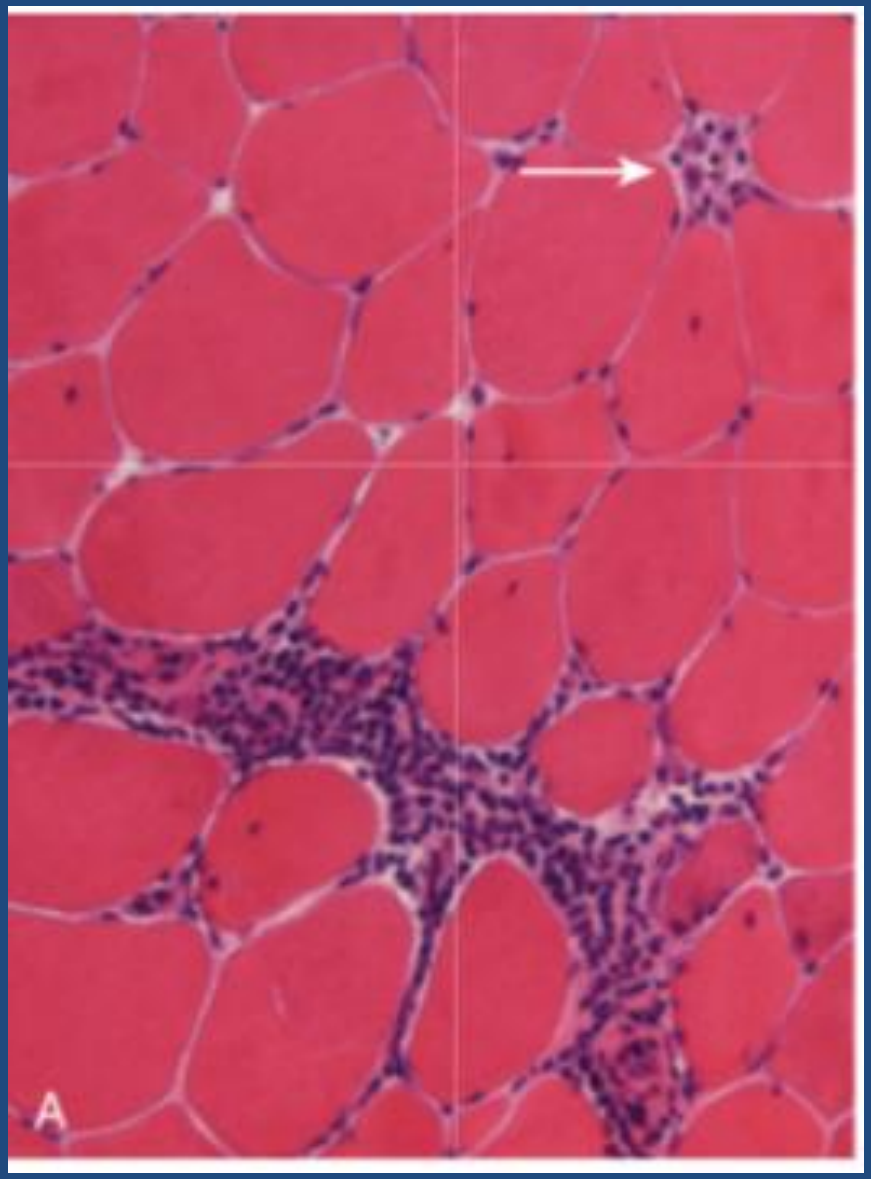
Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Polymyositis.

- This inflammatory myopathy is characterized by symmetric proximal muscle involvement, similar to that seen in dermatomyositis.
- It *differs from dermatomyositis by the lack of cutaneous involvement and its occurrence mainly in adults*.
- Similar to dermatomyositis, there may be inflammatory involvement of heart, lungs, and blood vessels.

Morphology

- lymphocytes surround and invade healthy muscle fibers.
- Both necrotic and regenerating muscle fibers are scattered throughout the fascicle, without the perifascicular atrophy seen in dermatomyositis.
- There is no evidence of vascular injury in polymyositis.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