Histopathological Differential Diagnosis of Inflammatory Muscle Disease

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Locating Muscle Biopsy

- Blind biopsy of muscle is no longer recommended.
- Targeted muscle biopsy is guided by:
  1. EMG/NCV
  2. STIR MRI of muscle
  3. Ultrasound of muscle
- Frozen muscle tissue is appropriate for all necessary tissue studies.
- Long Preservation of muscle sample in -80 degree

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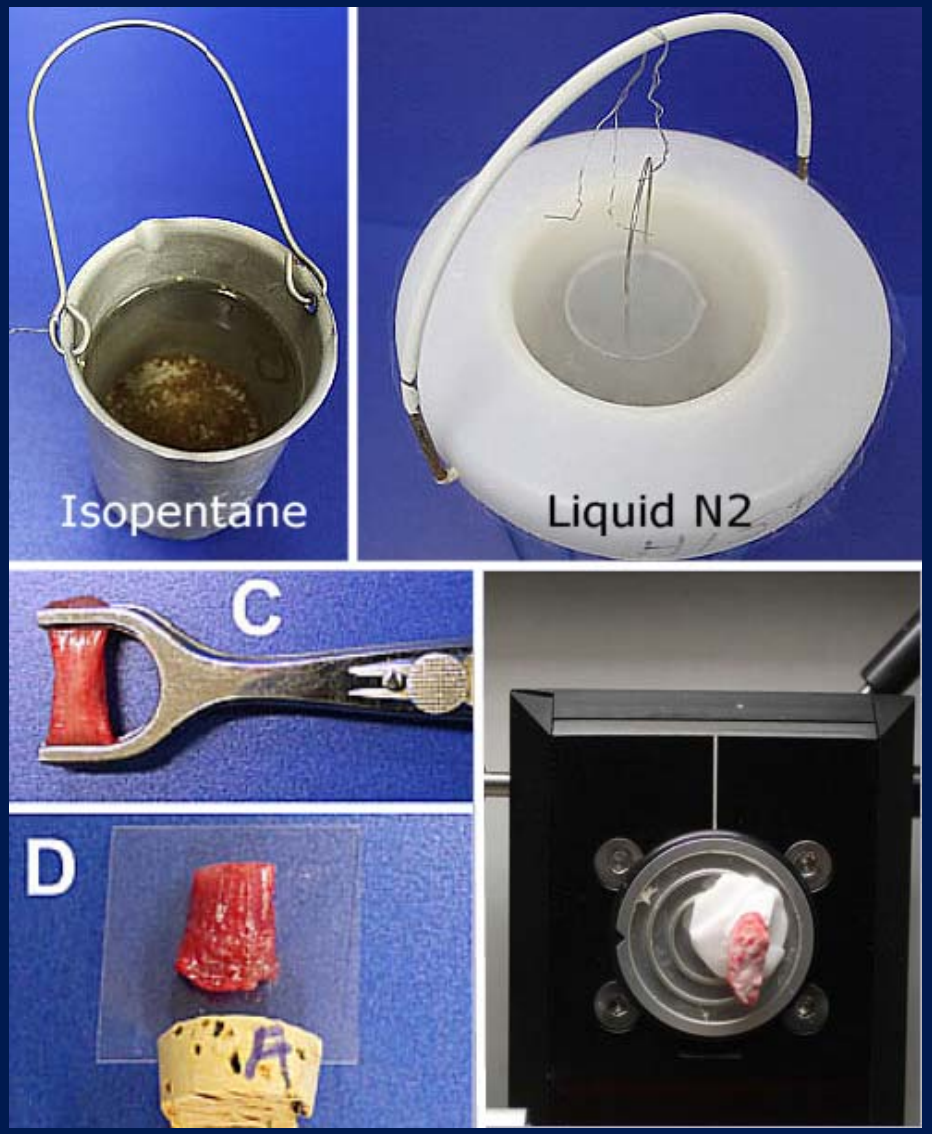


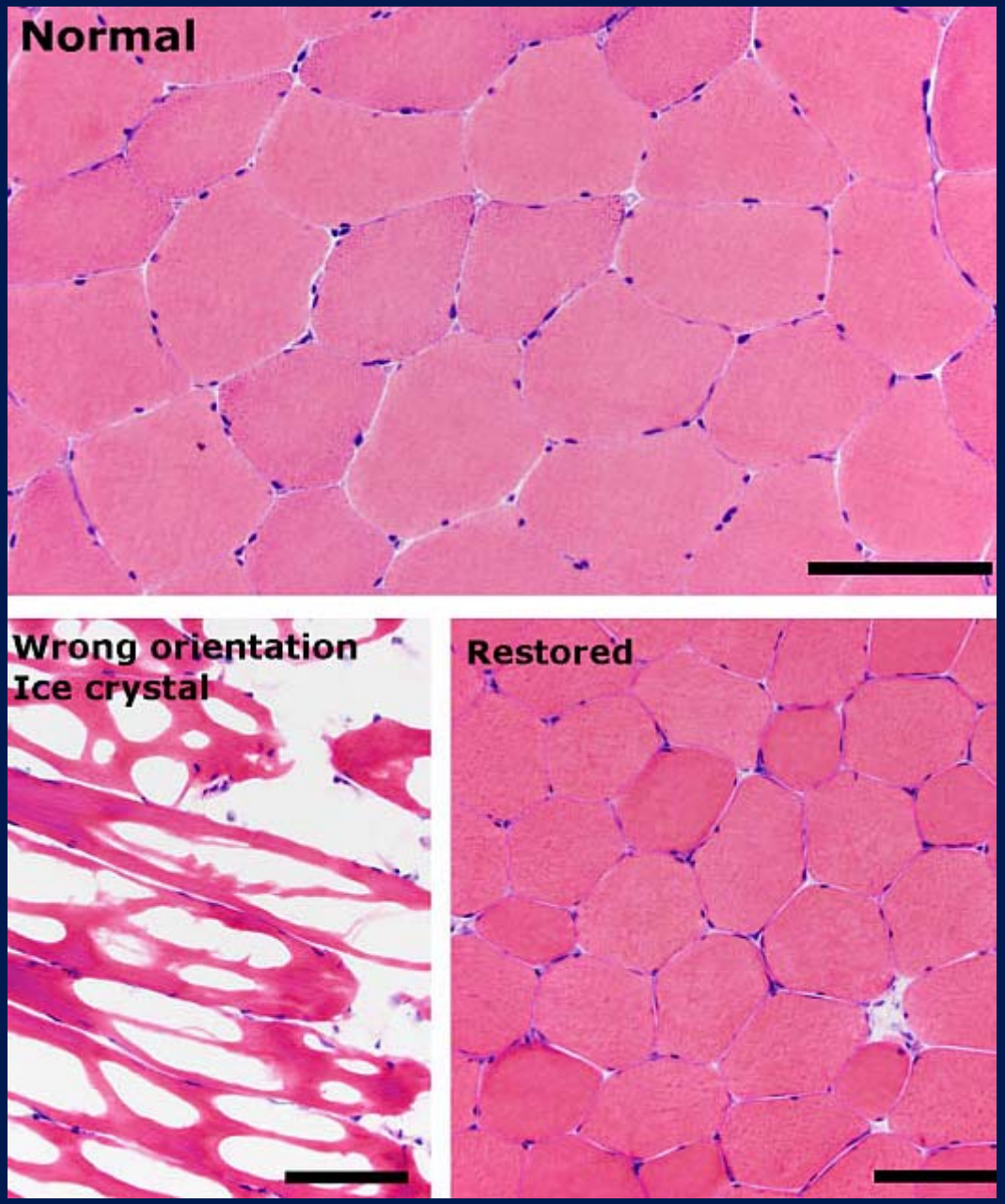
Normal Muscle Bx. (H&E)

Fibers are polygonal.

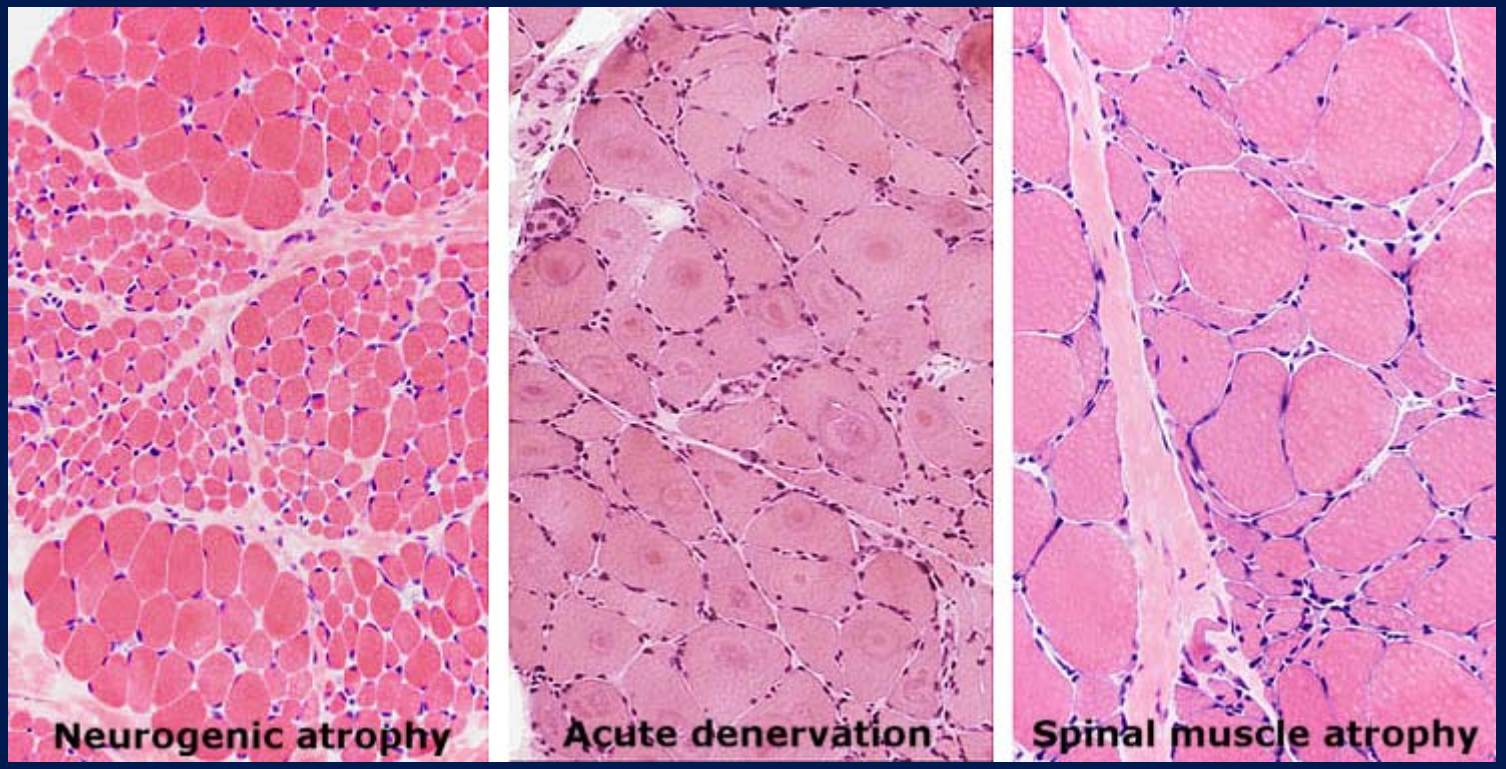
The size of fibers depends on age and fitness:
Neonates = 10 M
Adults = 40-60 M
Athletes = 80-100 M

Fiber Nuclei are exclusively located peripherally.

Different sized fibers indicate either denervation or degeneration.



Neurogenic Muscular Changes

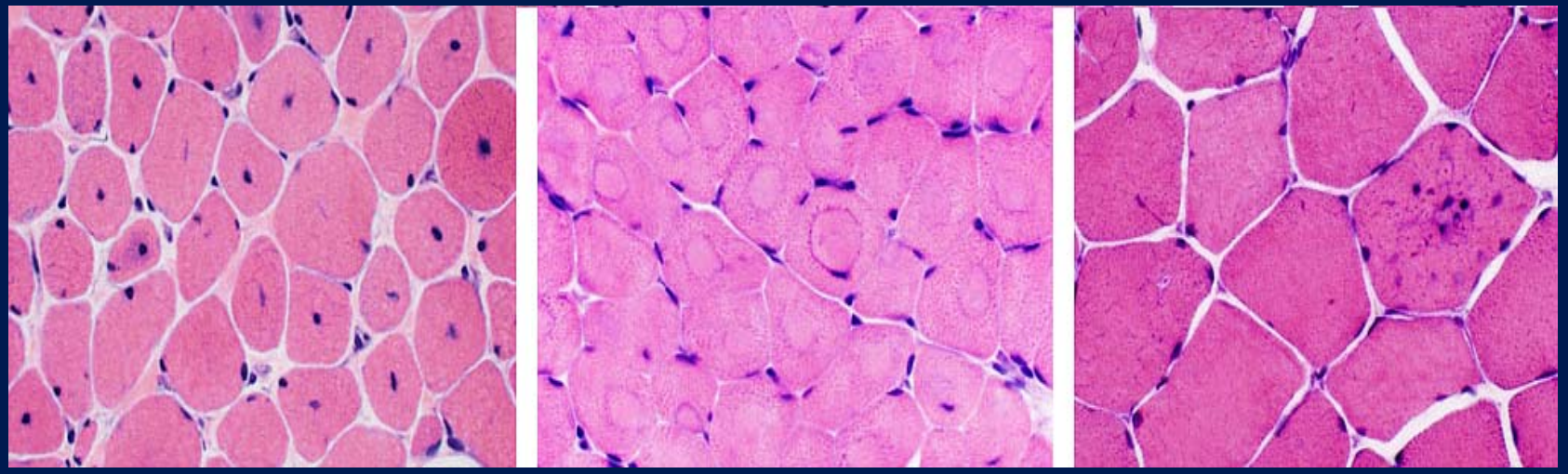


Atrophic and degenerated fibers of the involved motor units

Target fibers

Alternating groups of large and small fibers

Congenital Myopathies

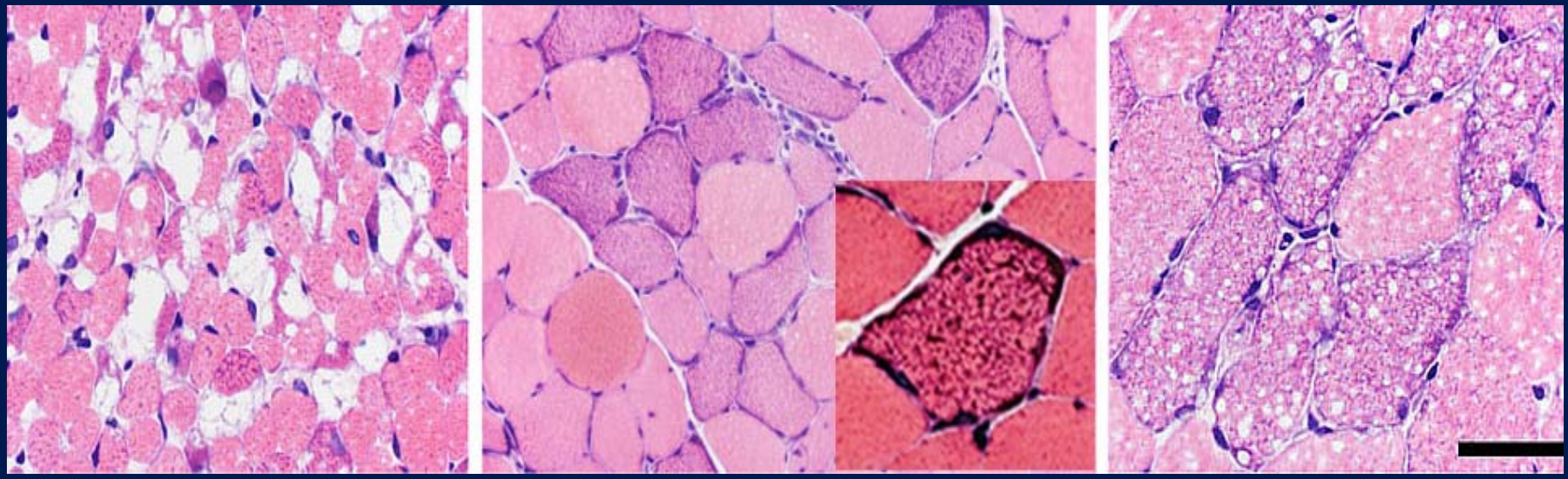


Centronuclear Myopathies XL, AD, AR

Central core disease

Autophagic Vacuolar Myopathies

Metabolic Myopathies

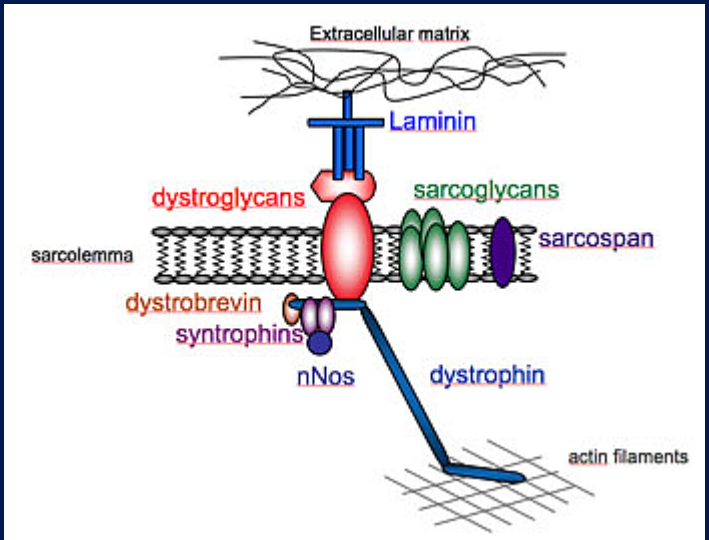


Pompe disease
(Lysosomal Glycogen storage disease)

Mitochondrial Myopathies
Ragged Red Fibers

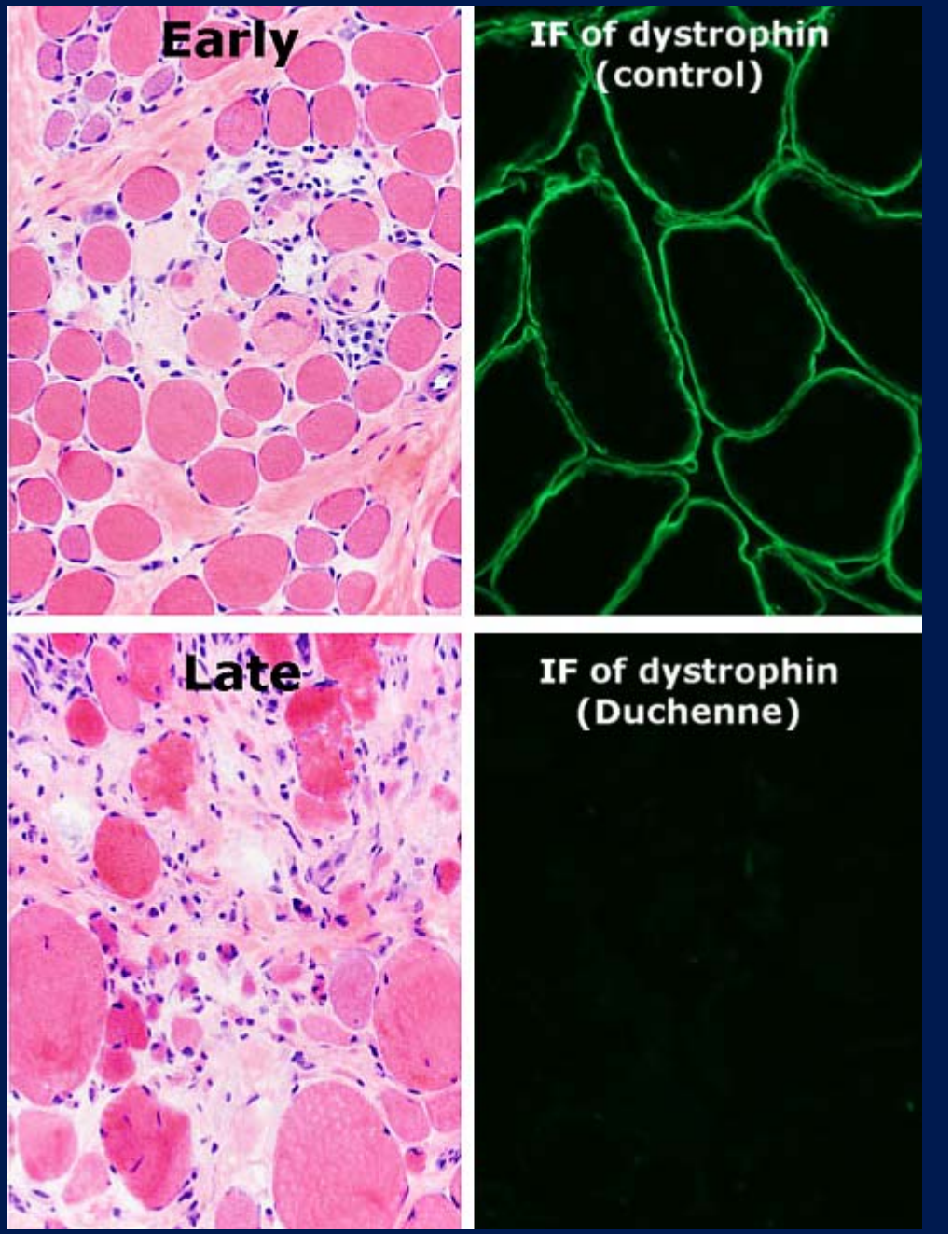
Lipid storage disease

Muscular Dystophy



Dystrophin molecule stabilizes sarcolemma to both extracellular matrix and the intercellular cytoskeleton.

X-linked recessive disease causing Duchenne and Becker muscular dystrophy.



Inflammatory Muscle Disease

Change in Terminology

❖Idiopathic Inflammatory Myopathies are suggestively classified into four major subgroups:

1) Dermatomyositis (DM)
2) Immune-mediated necrotizing myopathy (IMNM)
3) Antisynthetase syndrome (ASS)
4) Inclusion body myositis (IBM)

❖Many historically diagnosed **polymyositis** have been mainly reclassified as IBM, IMNM, and ASS.

❖Excluding IBM, at least one-third of the IIMs have no known associated MSA. Muscle biopsy still plays a crucial role in seronegative patients.

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Dermatomyositis variants

Dermatomyositis		Pathological features			
		Histochemical stains	Immunohistochemical stains		
	Clinical features	Hematoxylin and eosin	MHC class I	MHC class II	MxA
Anti-TIF1-γ dermatomyositis	Typical dermatomyositis skin lesions ↑risk of malignancy	PFA	+	−/+	+ Perifascicular area
Anti-Mi-2 dermatomyositis	Typical dermatomyositis skin lesions Benign clinical course ?risk of malignancy	Perifascicular necrosis, perimyisial connective tissue fragmentation, PFA +/−	+	−/+	+ Perifascicular area
Anti-NXP-2 dermatomyositis	?typical dermatomyositis skin lesions Common in children, muscle ischemia, calcinosis ?risk of malignancy	PFA, microinfarction	+	−/+	+ Perifascicular area
Anti-MDA5 dermatomyositis	Atypical skin lesions: mucocutaneous ulceration, palmar papules, nonscarring alopecia, panniculitis, rapid progressive ILD, CADM	Non-PFA	+	−/+	+ Scattered or diffuse
Anti-SAE dermatomyositis	Typical dermatomyositis skin lesions CADM, mild myopathic symptoms	PFA	+	−/+	+ Perifascicular area

Immunohistochemical study for myxovirus resistance protein A (MxA), a surrogate marker for IFN1 pathway activation, has been highly sensitive (71–77%) and specific (98–100%) marker for dermatomyositis.

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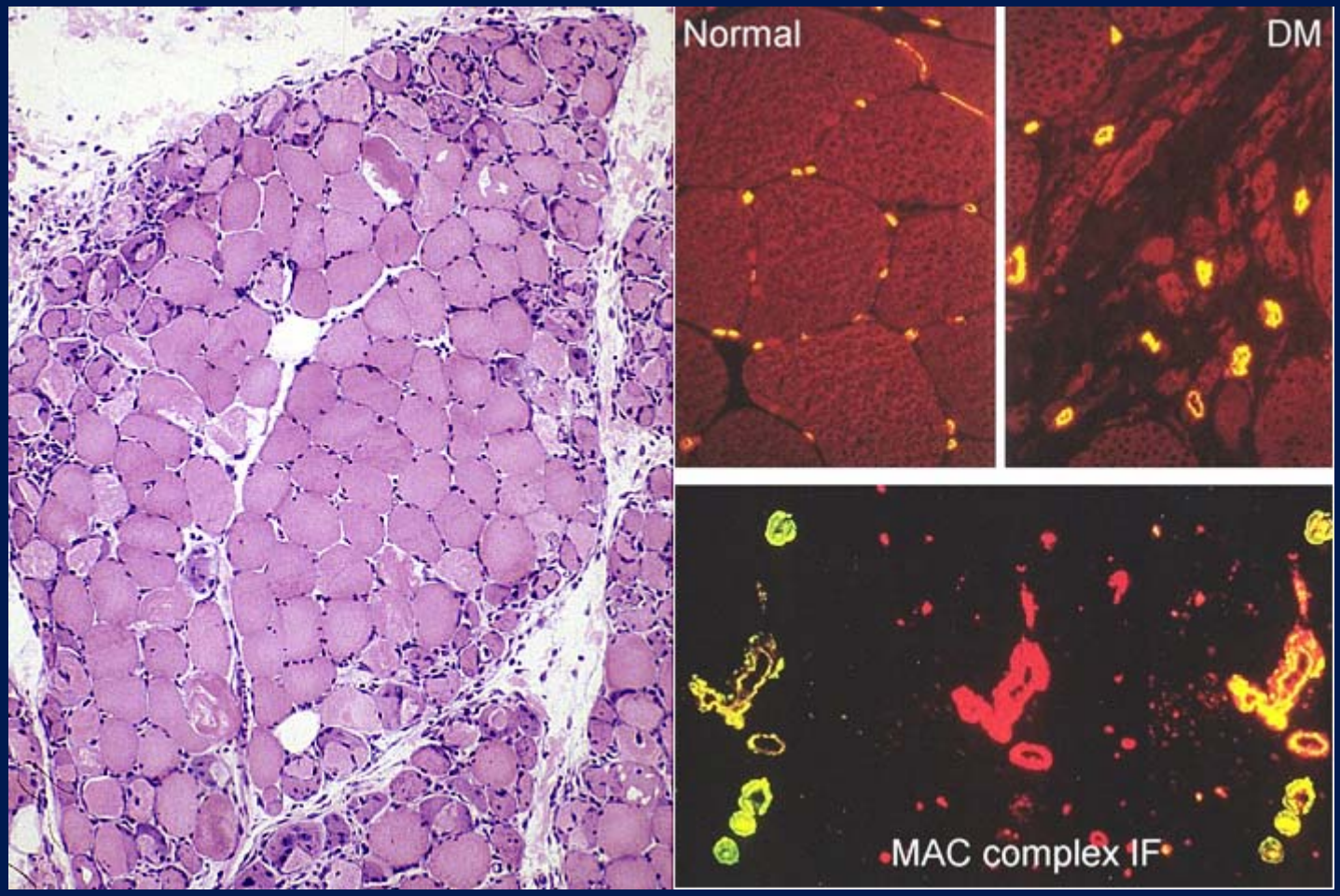
Capillary Pathology in Dermatomyositis



Muscular damage in DM seems to be caused by microvascular injury.

Immune complex-mediated destruction of endomysial capillaries precedes muscle fiber damage.

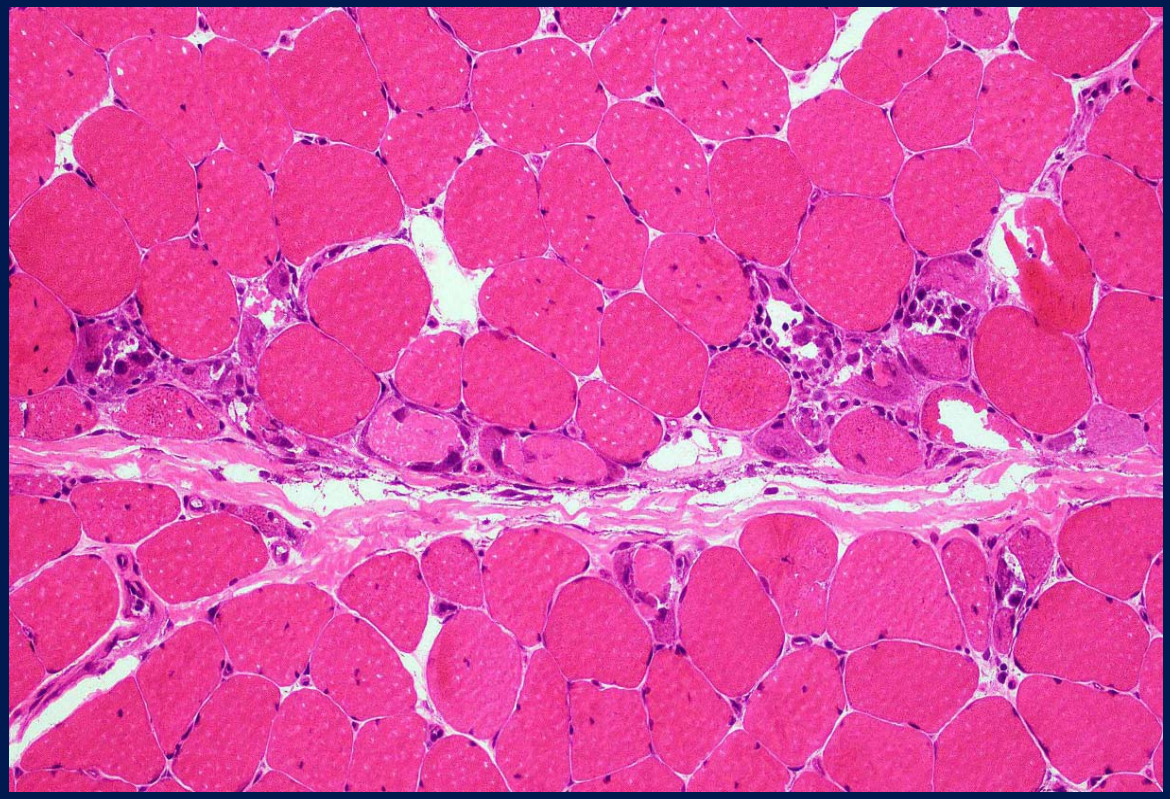
Anti-synthetase Syndrome

Anti-synthetase Syndrome		Pathological features			
		Histochemical stains	Immunohistochemical stains		
	Clinical features	Hematoxylin and eosin	MHC class I	MHC class II	MAC
Anti-Jo-1 ASS	Myositis ++, ILD, mechanic hands, arthritis, Raynaud phenomenon, fever	Perifascicular necrosis, perimyisial connective tissue fragmentation, PFA +/–	+	+ Perifascicular area	+ Sarcolemma Perifascicular area
Anti-PL-7 ASS	Myositis, ILD ++, mechanic hands, arthritis, Raynaud phenomenon, fever	Perifascicular necrosis, perimyisial connective tissue fragmentation, PFA +/–	+	+/–	+ Sarcolemma Perifascicular area
Anti-PL-12 ASS	Myositis, ILD ++, mechanic hands, arthritis, Raynaud phenomenon, fever	Not characterized	Not characterized	Not characterized	Not characterized
Anti-OJ ASS	Severe muscle involvement in the early stage, best detected by immunoprecipitation	Perifascicular necrosis, perimyisial connective tissue fragmentation, PFA +/–	+	+/–	+ Sarcolemma Perifascicular area

Anti-Jo-1 (antihistidyl)
Anti-PL-7 (antithreonyl)
Anti-PL-12 (antialanyl)
Anti-EJ (antiglycyl)
Anti-OJ (antiisoleucyl)
Anti-KS (antiasparaginyl)
Anti-Zo (antiphenylalanyl)
Anti-Ha (antityrosyl).

Absence of MxA staining suggests ASS has pathomechanism different from IFN1 signature in DM.

Anti-synthetase Myositis



Anti-Jo1 myostis shows necrotic fibers and myophagocytosis predominantly involving perifascicular fibers.

The perimyisial connective tissue appears edematous and fragmented.

Immune-mediated Nectotizing Myopathy

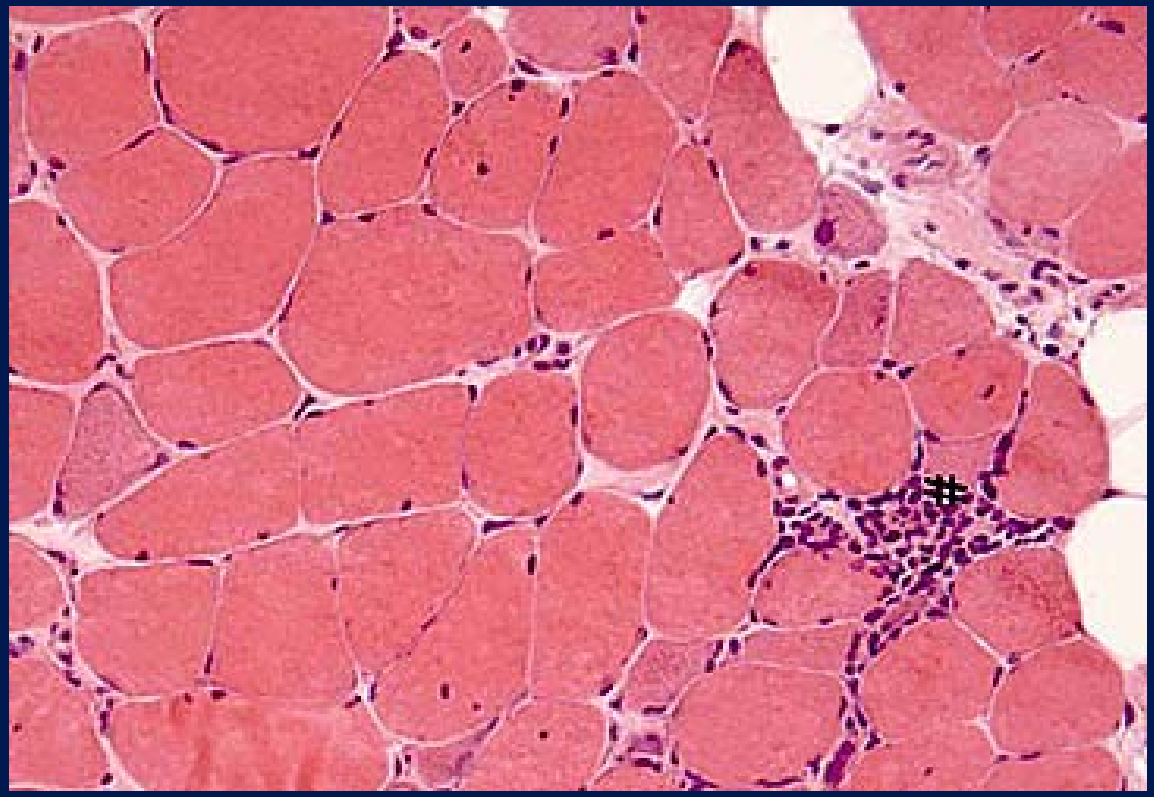
Immune-mediated Necrotizing Myopathy	Clinical features	Pathological features		
		Histochemical stains	Immunohistochemical stains	
		Hematoxylin and eosin	MHC class I	MHC class II
Anti-SRP IMNM	Proximal muscle weakness, ↑creatine kinase More weakness, higher risk of cardiac involvement, poor treatment outcome	Scattered necrotic and regenerating fibers, sparse inflammation +/− (macrophages ++, lymphocytes +/−)	+	−/+
Anti-HMGCR IMNM	Proximal muscle weakness, ↑creatine kinase? risk for malignancy	Scattered necrotic and regenerating fibers, sparse inflammation +/− (macrophages ++, lymphocytes +/−)	+	−/+

Although anti-HMGCR IMNM is originally identified as statin-related, it is also present in statin-naive patients especially in younger age and of Asian countries.

Seronegative IMNM is reported to be associated with increased risk of cancer.

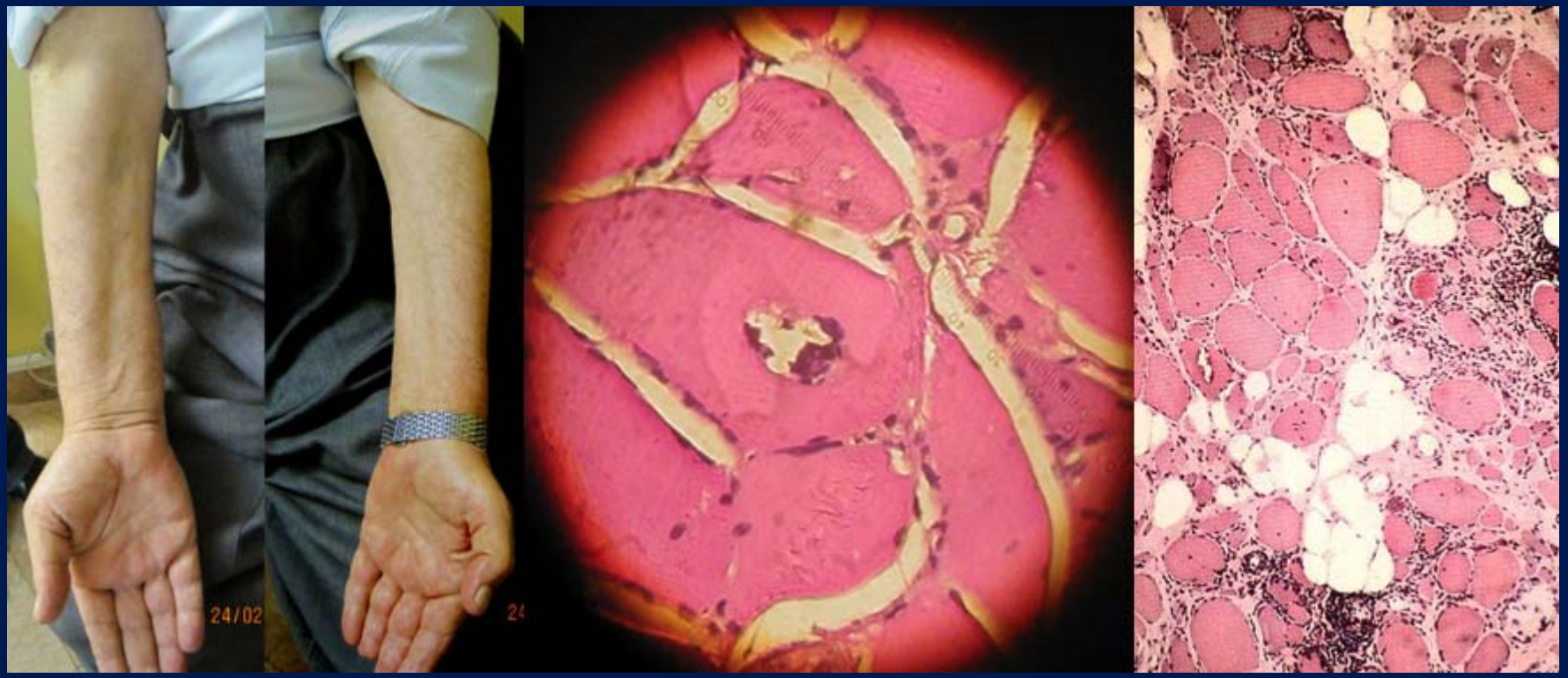
Although previously defined as paucilymphocytic infiltrate, lymphocytic infiltration can be seen in approximately 20% of the antibody-positive patients.

Immune-mediated Nectotizing Myopathy



Necrotic and regenerating fibers
Macrophage infilteration
Paucity of Lymphocytes

Inclusion Body Myositis



Endomysial (CD8+) lymphocytic invasion surrounding or invading in nonnecrotic fibers
rimmed vacuoles of tubulofilament aggregates
Distal muscles involvement + neuropathic features

Polymyositis dissolve into four clusters: IMNM, ASS, dermatomyositis, and IBM.

Most of polymyositis are revised as IMNM and ASS.

JAMA Neurol 2018; 75:1528–1537

These developments support the trend toward extinction of polymyositis as specific entity.

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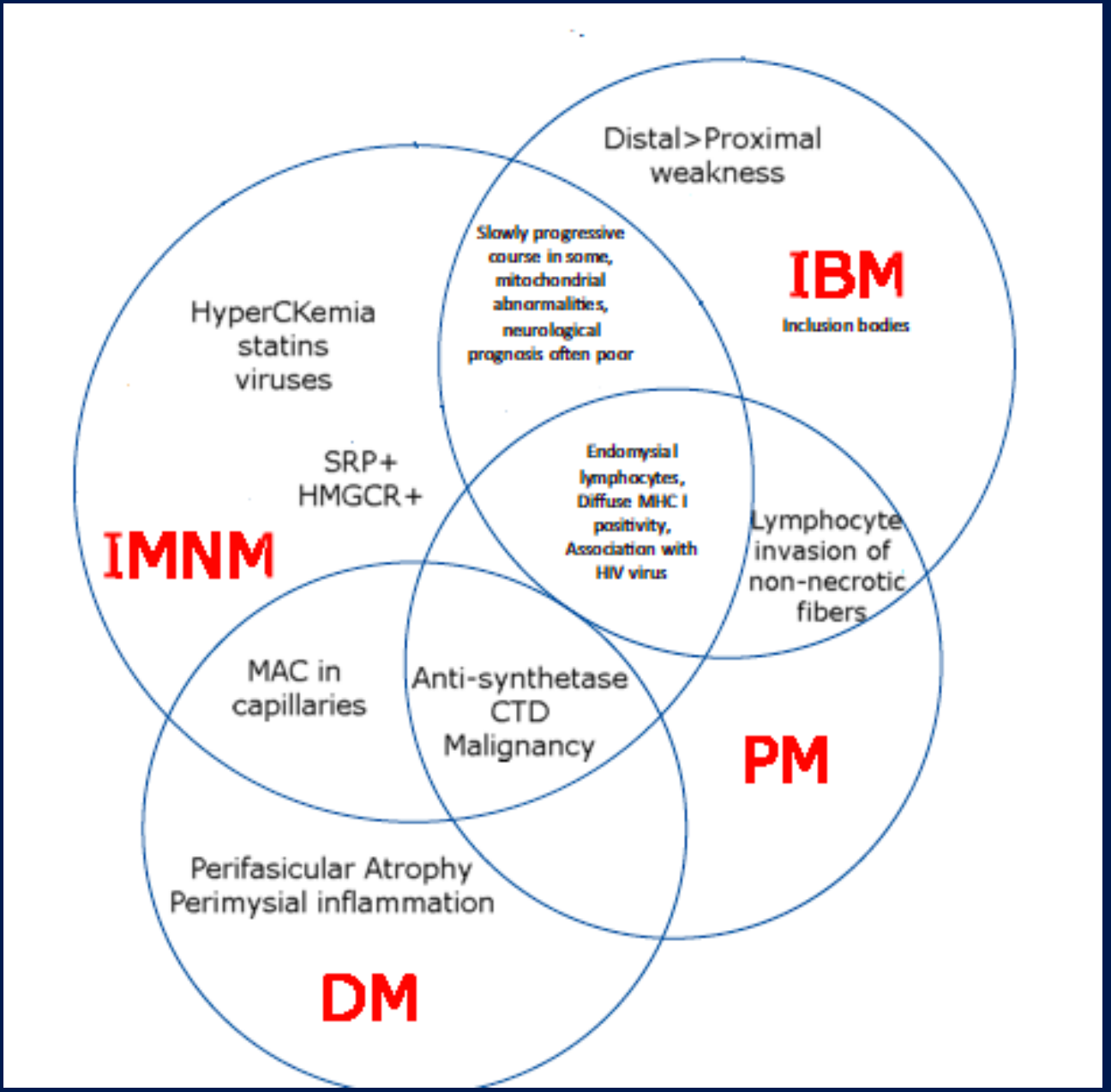

Seminars in Arthritis and Rheumatism 000 (2019) 110

Myopathy:
Immune-mediated VS Non-immune

Immune-mediated

FH of autoimmune diseases
Dermatitis / Pneumonitis
Arthritis
Abnormal capilleroscopy
Myositis-related antibodies
Proximal M. > Distal M.
Symmetrism of myositis on MRI

Non-immune

FH of Myopathy
Childhood-onset
Symptoms with exertion
Muscle psudohypertrophy
Dystonia

Acute-phase reaction, HyperCKemia, Muscle degeneration/regeneration, Inflammation on muscle Bx. has little or no value in differentiation of the two categories.