“Ιστολογικές βλάβες οργάνων-στόχων: Μύες”

Κων/νος Γ. Παπαδόπουλος

Εργαστήριο Μυοπαθολογίας

Κέντρο Εμπειρογνωμοσύνης Σπάνιων Νευρομυϊκών Παθήσεων

Α’ Νευρολογική Κλινική ΕΚΠΑ

Αιγινήτειο Νοσοκομείο

ΒΙΟΨΙΑ ΜΥΟΣ

Επιλογή του μυός:

- Σε χρόνια νόσο, να αποφεύγεται η βιοψία μυών με σοβαρού βαθμού αδυναμία και ατροφία
- Σε οξεία εισβολή να επιλέγεται βαριά προσβεβλημένος μυς
- Να λαμβάνεται υπόψη η εκλεκτική προσβολή μυϊκών ομάδων σε ορισμένες μυοπάθειες

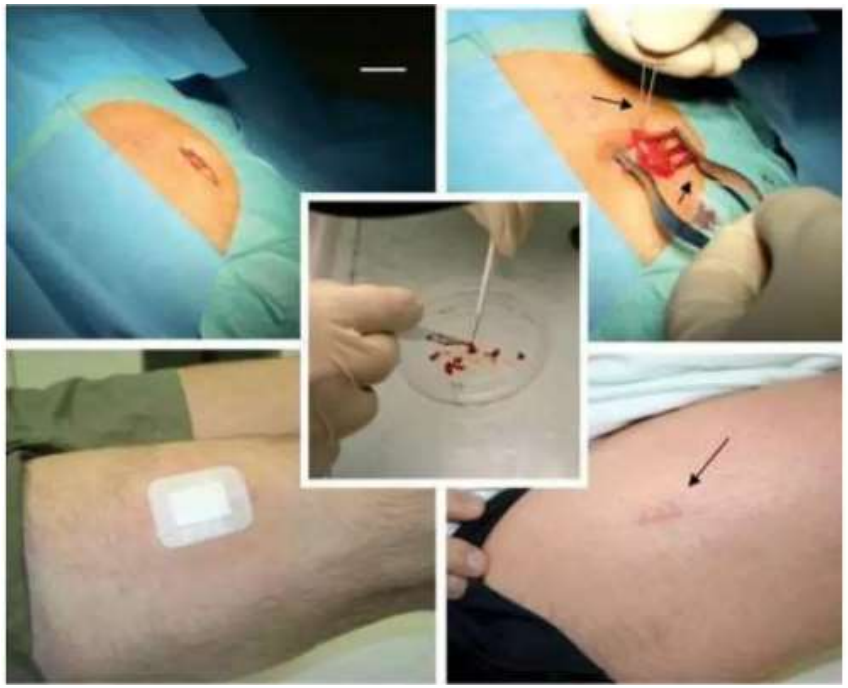
➢ *Η βιοψία να διενεργείται τουλάχιστον 1 μήνα μετά από οξεία ραβδομυόλυση*

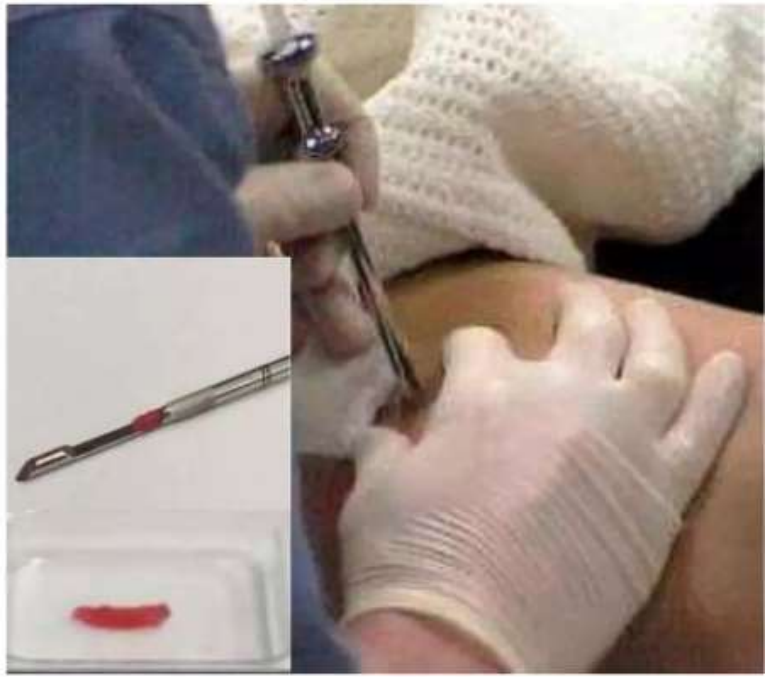
ΒΙΟΨΙΑ ΜΥΟΣ

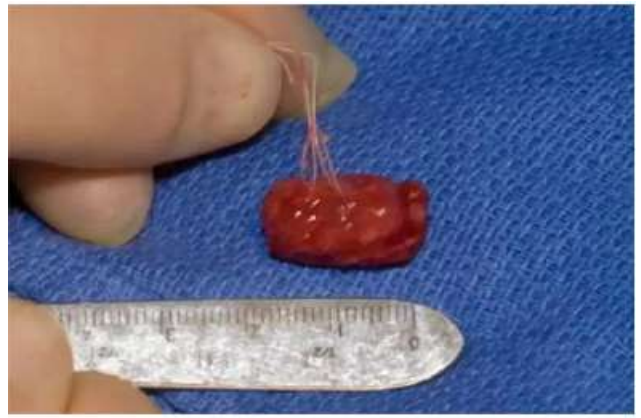
<u>Λήψη και επεξεργασία:</u>

- Να μην έχει γίνει πρόσφατα ΗΜΓ στον μυ από τον οποίο θα ληφθεί το ιστοτεμάχιο
- Η λήψη να γίνεται από τη γαστέρα του μυός
- Να αποφεύγεται η σύνθλιψη με λαβίδες και η διήθηση με αναισθητικό
- Το δείγμα να έχει ικανοποιητικό μέγεθος (τουλάχιστον 1,5x1cm)
- Σωστή επεξεργασία και ταχεία κατάψυξη

ΒΙΟΨΙΑ ΜΥΟΣ







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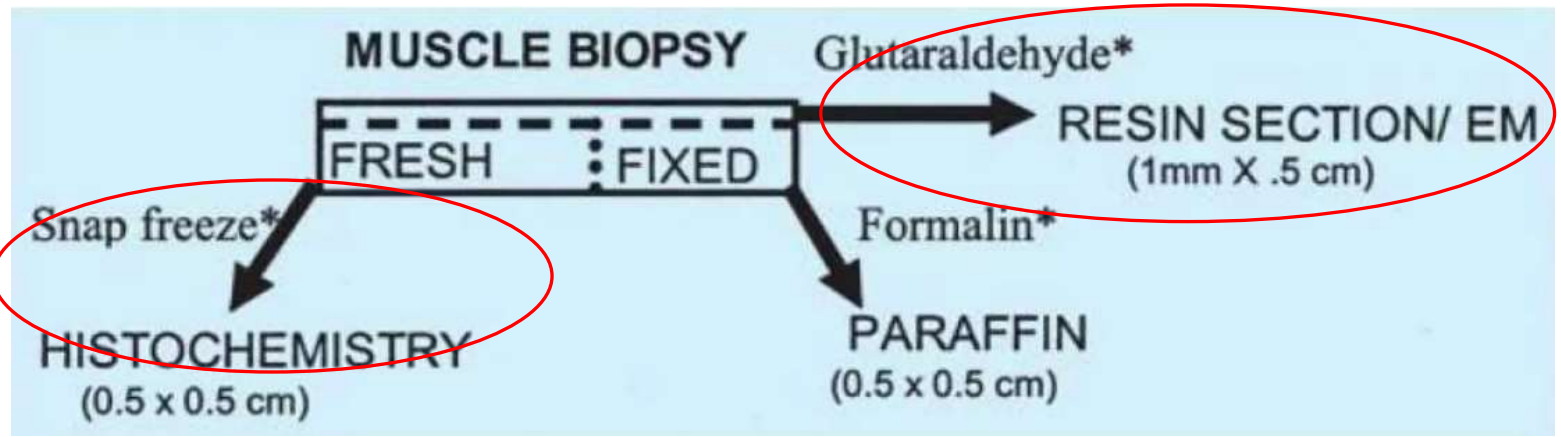

MUSCLE BIOPSY
Glutaraldehyde*
RESIN SECTION/ EM
(1mm X .5 cm)
FRESH
FIXED
Snap freeze*
Formalin*
HISTOCHEMISTRY
(0.5 x 0.5 cm)
PARAFFIN
(0.5 x 0.5 cm)

ΒΙΟΨΙΑ ΜΥΟΣ

- Ιστολογικές τεχνικές (τομές ψυκτικού μικροτόμου και τομές παραφίνης)
- Ιστοχημικές τεχνικές
- Ανοσοϊστοχημεία
- Κάθετη ανοσοηλεκτροφόρηση (Western blotting)
- Ηλεκτρονικό μικροσκόπιο

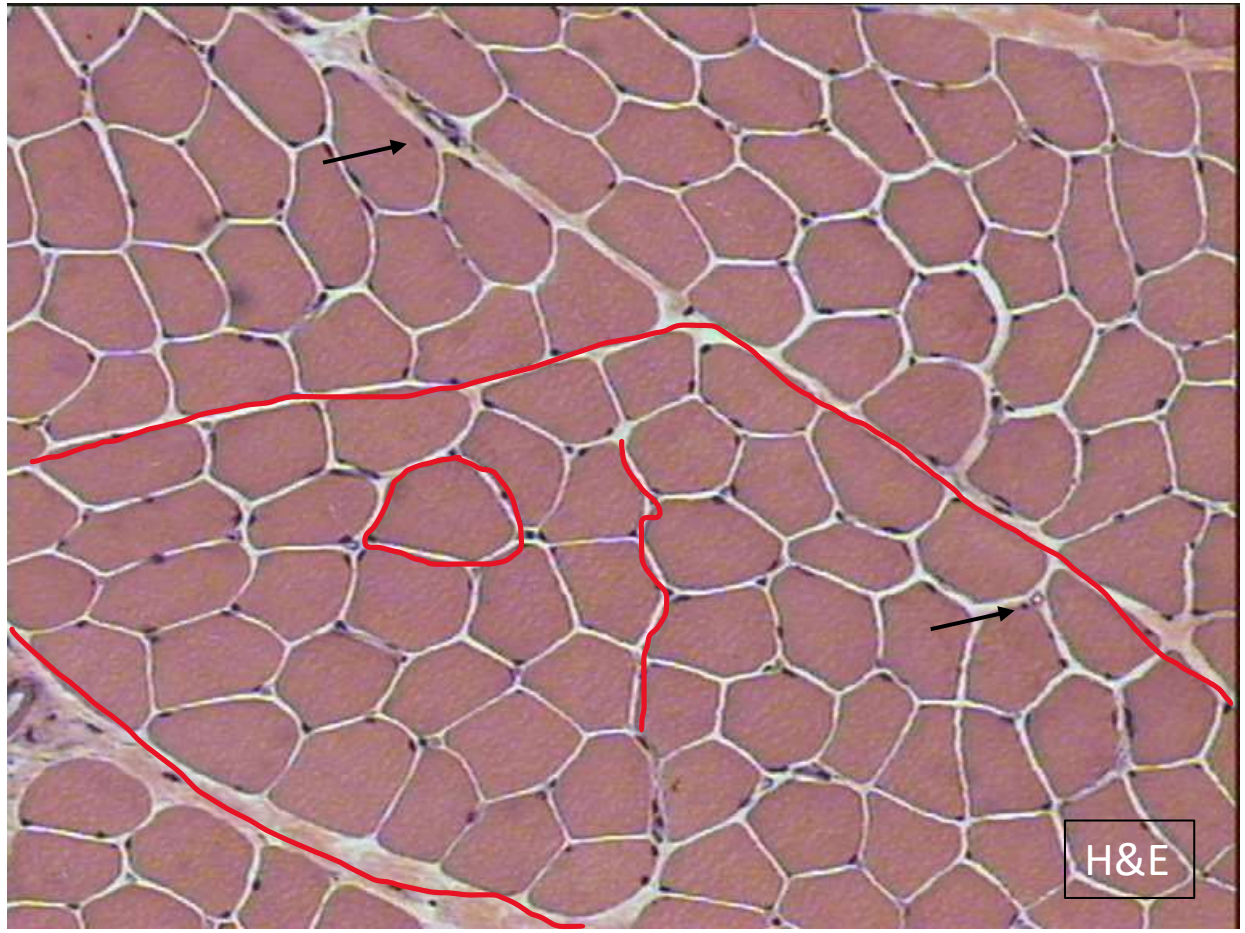
ΒΙΟΨΙΑ ΜΥΟΣ

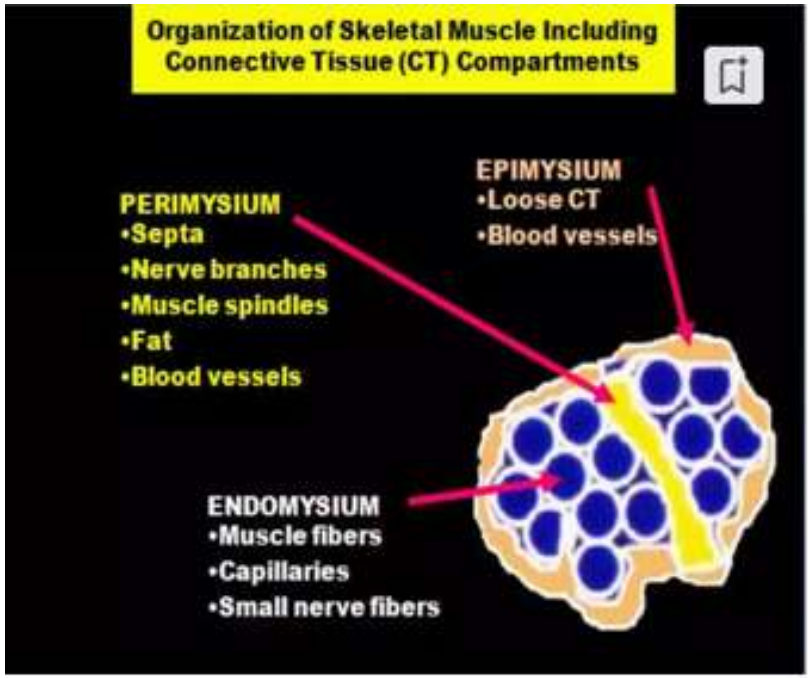
- Ιστολογικές τεχνικές
  - H&E
  - Τροποποιημένη τρίχρωμη Gomori

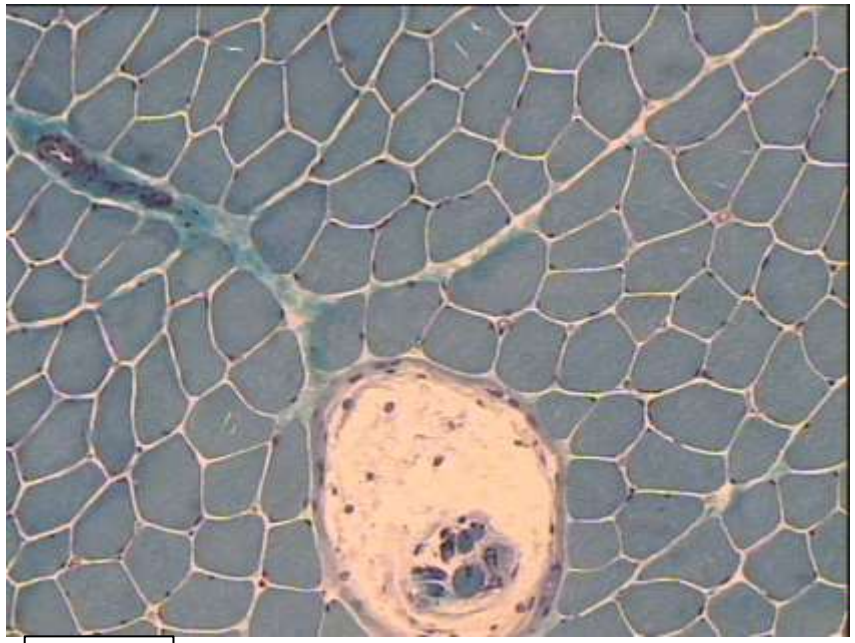
- Ανοσοϊστοχημεία

- Ιστοχημικές τεχνικές
  - Adenosine Triphosphatase (ATPase)
  - Φωσφατάσες
    - Όξινη
    - Αλκαλική
  - Εστεράσες
    - Μη ειδική εστεράση
  - Οξειδωτικά ένζυμα
    - NADH-TR
    - SDH
    - COX
  - Τρανσφεράσες
    - Μυοφωσφορυλάση

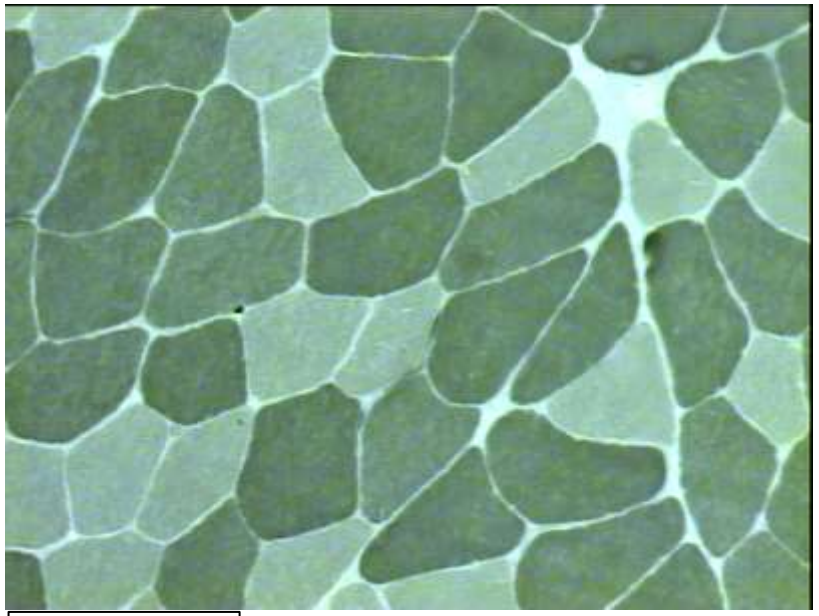
Ο ΦΥΣΙΟΛΟΓΙΚΟΣ ΜΥΣ



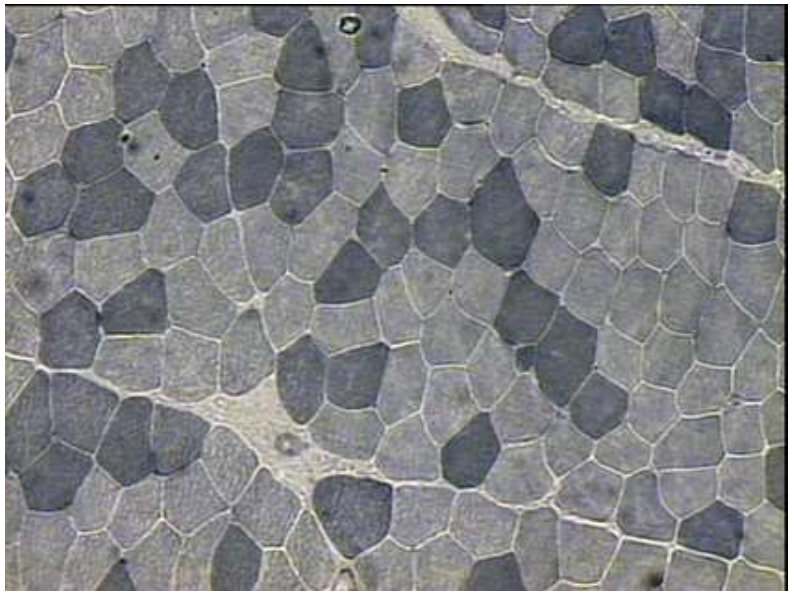




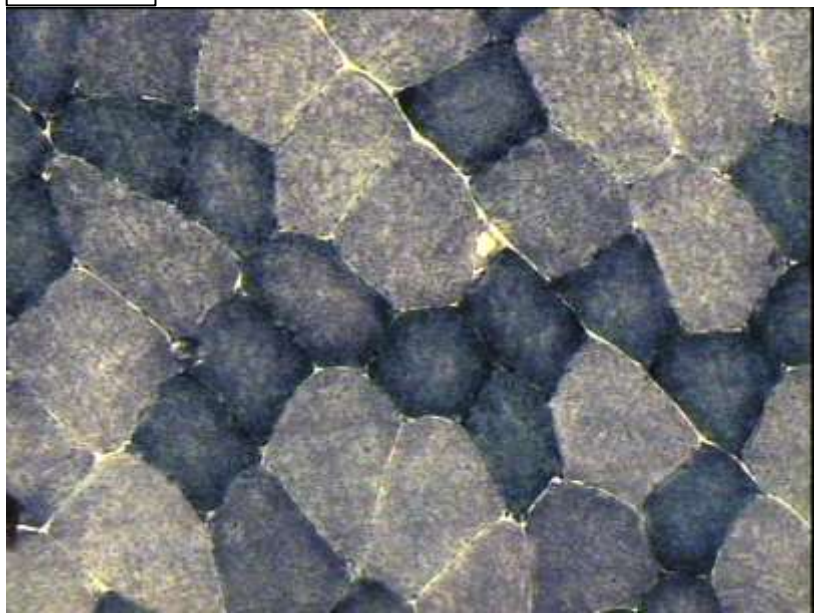
GMT



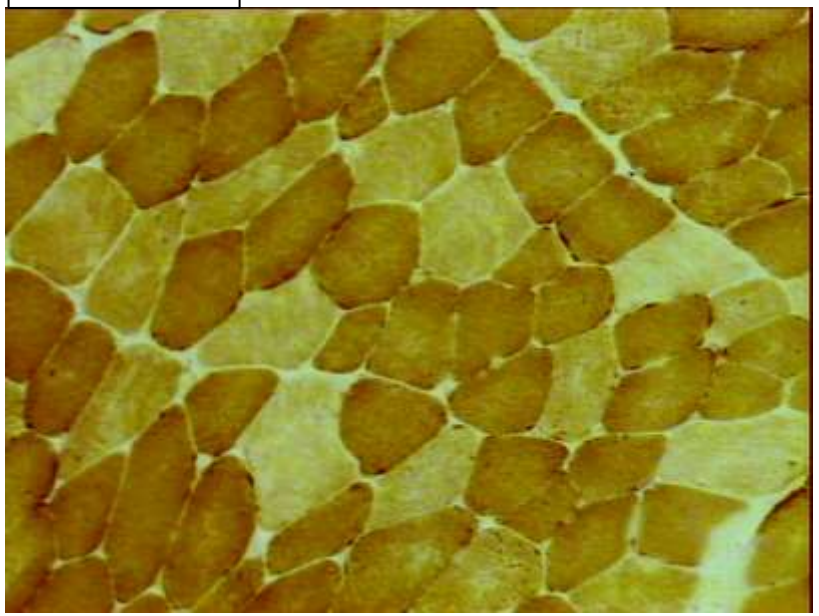
ATPase 9,4



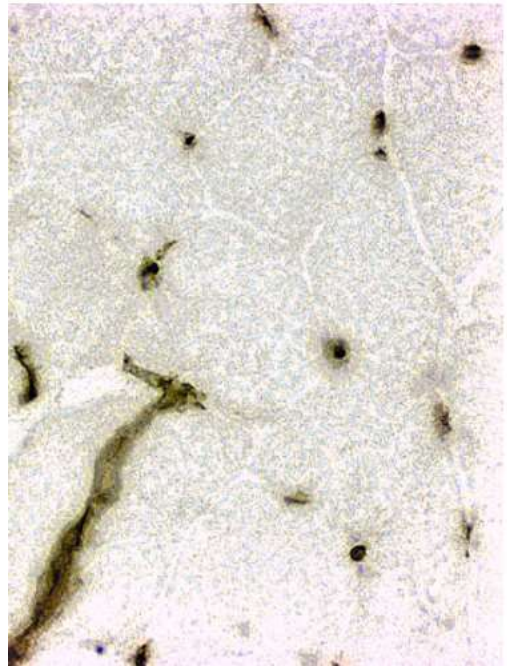
NADH



SDH



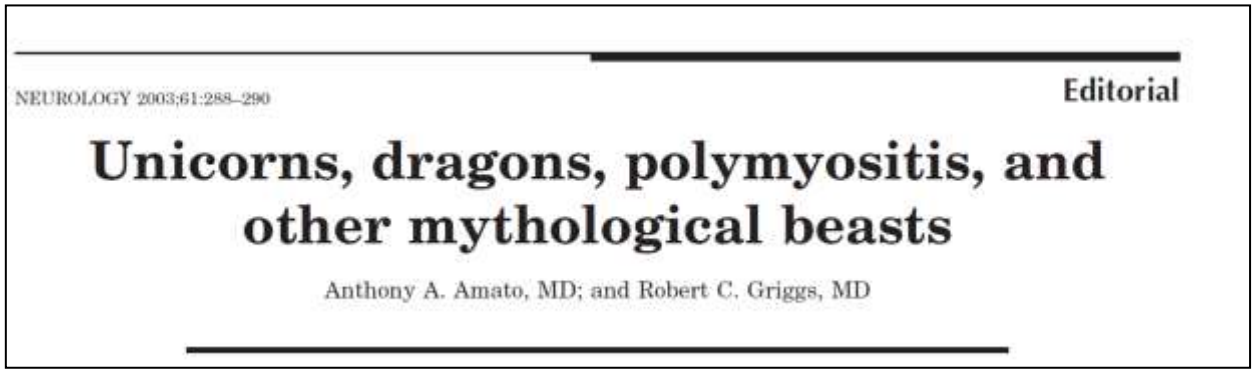
COX



HLA-I

119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis Neuromuscul Disord 2004 May;14(5):337-45

- ~~Πολυμυοσίτιδα (ΠΜ)~~
- Δερματομυοσίτιδα (ΔΜ)
- Νεκρωτική μυοσίτιδα
- Μη ειδική μυοσίτιδα
- Μυοσίτιδα με έγκλειστα σωμάτια (IBM)



NEUROLOGY 2003;61:288–290

Editorial

Unicorns, dragons, polymyositis, and other mythological beasts

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

119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis Neuromuscul Disord 2004 May;14(5):337-45

1. Clinical criteria

Inclusion criteria

(a) Onset usually over 18 years (post-puberty), onset may be in childhood in DM and non-specific myositis

(b) Subacute or insidious onset

(c) Pattern of weakness: symmetric proximal > distal, neck flexor > neck extensor

(d) Rash typical of DM: heliotrope (purple) periorbital oedema; violaceous papules (Gottron's papules) or macules (Gottron's sign), scaly if chronic, at metacarpophalyngeal and interphalyngeal joints and other bony prominences; erythema of chest and neck (V-sign) and upper back (shawl sign)

Exclusion criteria

(a) Clinical features of IBM (see Griggs et al. (Ann Neurol 1995;38:705–13): asymmetric weakness, wrist/finger flexors same or worse that deltoids; knee extensors and/or ankle dorsiflexors same or worse than hip flexors)

(b) Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness

(c) Toxic myopathy (e.g. recent exposure to myotoxic drugs), active endocrinopathy (hyper- or hypothyroid, hyperparathyroid), amyloidosis, family history of muscular dystrophy or proximal motor neuropathies (e.g. SMA)

2. Elevated serum creatine kinase level

3. Other laboratory criteria

(a) Electromyography:

Inclusion criteria

(I) Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges

(II) Morphometric analysis reveals the presence of short duration, small amplitude, polyphasic MUAPs

Exclusion criteria

(I) Myotonic discharges that would suggest proximal myotonic dystrophy or other channelopathy

(II) Morphometic analysis reveals predominantly long duration, large amplitude MUAPs

(III) Decreased recruitment pattern of MUAPs

(b) MRI: diffuse or patchy increased signal (oedema) within muscle tissue on STIR images

(c) Myositis-specific antibodies detected in serum

119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis Neuromuscul Disord 2004 May;14(5):337-45

4. Muscle biopsy inclusion and exclusion criteria	(a) Endomysial inflammatory cell infiltrate (T-Cells) surrounding and invading non-necrotic muscle fibres (b) Endomysial CD8 + T-cells surrounding, but not definitely invading non-necrotic muscle fibres, or ubiquitous MHC-1 expression	(c) Perifascicular atrophy (d) MAC depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on EM, or MHC-1 expression of perifascicular fibres (e) Perivascular, perimysial inflammatory cell infiltrate (f) Scattered endomysial CD8 + T-cells infiltrate that does not clearly surround or invade muscle fibres (g) Many necrotic muscle fibres as the predominant abnormal histological feature. Inflammatory cells are sparce or only slight perivascular; perimysial infiltrate is not evident. MAC deposition on small blood vessels or pipestem capillaries on EM may be seen, but tubuloreticular inclusions in endothelial cells are uncommon or not evident. (h) Rimmed vacuoles, ragged red fibres, cytochrome oxidase-negative fibres that would suggest IBM (i) MAC deposition on the sarcolemma of non-necrotic fibres and other indications of muscular dystrophies with immunopathology

Definite dermatomyositis	1. All clinical criteria 2. Muscle biopsy criteria include c
Probable dermatomyositis	1. All clinical criteria 2. Muscle biopsy criteria include *d* or *e*, or elevated serum CK, or other laboratory criteria (1 of 3)
Amyopathic dermatomyositis	1. Rash typical of DM: heliotrope, periorbital oedema, Gottron's papules/sign, V-sign, shawl sign, holster sign 2. Skin biopsy demonstrates a reduced capillary density, deposition of MAC on small blood-vessels along the dermal–epidermal junction, and variable kerotinocyte decoration for MAC 3. No objective weakness 4. Normal serum CK 5. Normal EMG 6. Muscle biopsy, if done, does not reveal features compatible with definite or probable DM

Non-specific myositis	1. All clinical criteria with the exception of rash 2. Elevated serum CK 3. Other laboratory criteria (1 of 3) 4. Muscle biopsy criteria include *e* or *f*, and exclude all others
Immune-mediated necrotizing myopathy	1. All clinical criteria with the exception of rash 2. Elevated serum CK 3. Other laboratory criteria (1 of 3) 4. Muscle biopsy criteria include *g*, and exclude all others

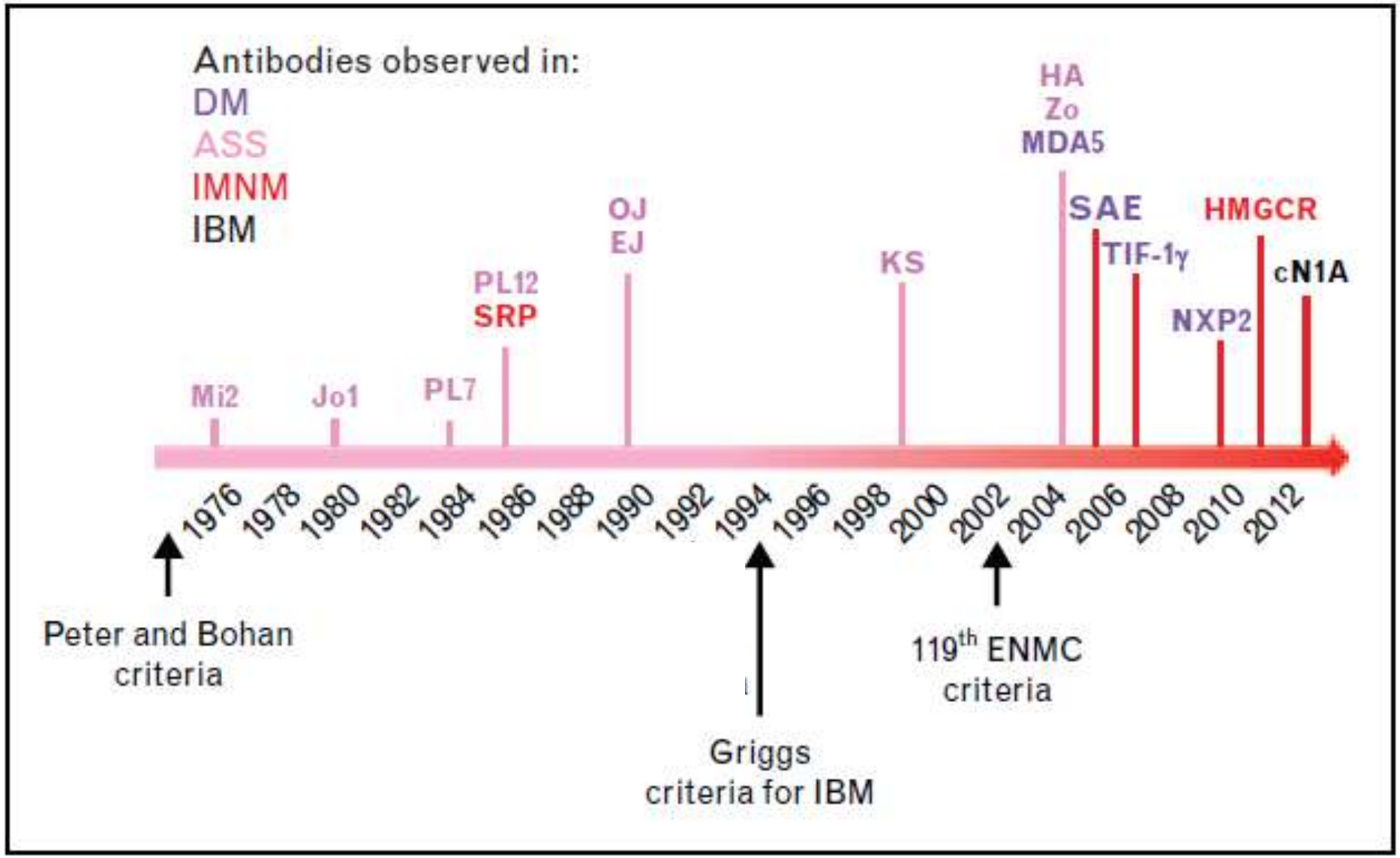
188th ENMC International Workshop: Inclusion Body Myositis Neuromuscul Disord. 2013 Dec;23(12):1044-55

The ENMC IBM research diagnostic criteria 2011.

Clinical and laboratory features	Classification	Pathological features
Duration >12 months Age at onset >45 years Knee extension weakness ⩾ hip flexion weakness and/or Finger flexion weakness > shoulder abduction weakness sCK no greater than 15×ULN	Clinico-pathologically defined IBM	All of the following: Endomysial inflammatory infiltrate Rimmed vacuoles Protein accumulation* or 15–18 nm filaments
Duration >12 months Age at onset >45 years Knee extension weakness ⩾ hip flexion weakness and Finger flexion weakness > shoulder abduction weakness sCK no greater than 15×ULN	Clinically defined IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation* or 15–18 nm filaments
Duration >12 months Age at onset >45 years Knee extension weakness ⩾ hip flexion weakness or Finger flexion weakness > shoulder abduction weakness sCK no greater than 15×ULN	Probable IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Up-regulation of MHC class I Rimmed vacuoles Protein accumulation* or 15–18 nm filaments

* Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favors p62 in terms of sensitivity and specificity but the literature is limited and further work required.

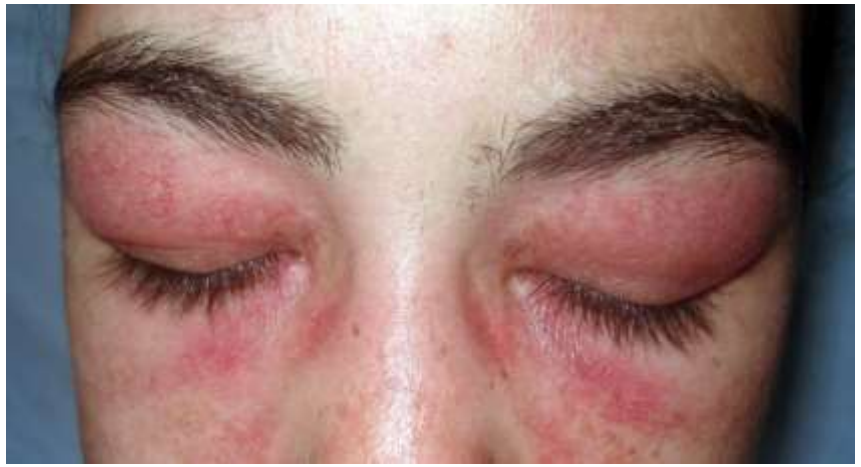
Τα ειδικά για μυοσίτιδα αυτοαντισώματα

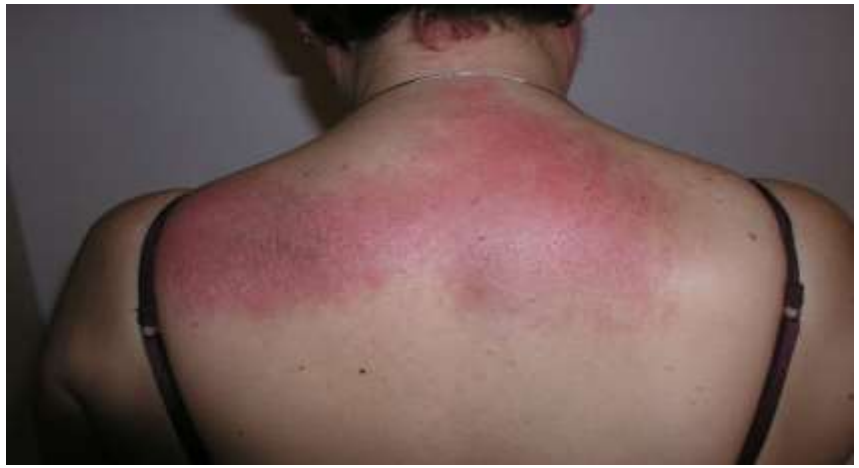


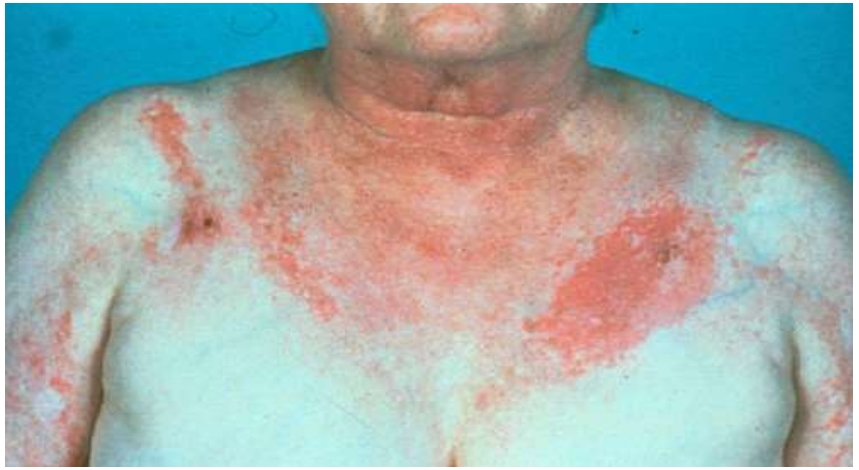
Δερματομυοσίτιδα

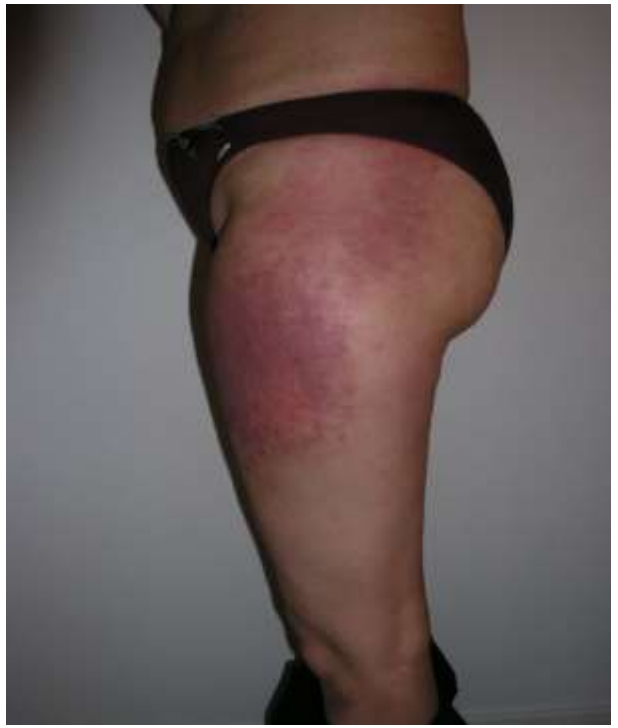
- Δερματικές εκδηλώσεις τυπικές της νόσου
    - Σημείο Gottron
    - Ερυθροβλατιδώδεις φολιδωτές πλάκες των εκτατικών επιφανειών των αρθρώσεων
    - Εξάνθημα δίκην ηλιοτροπίου
    - Εξάνθημα στήθους-λαιμού (V-sign), άνω τμήματος πλάτης (σημείο σαλιού)
    - Ερυθροϊώδης απόχρωση των βλεφάρων με ή χωρίς περικογχικό οίδημα

- Τυπική βιοψία
    - Περιδεσμιδική ατροφία
    - Φλεγμονή περιδεσμιδικά ή/και στο περιμύιο
    - Εναπόθεση MAC σε τοίχωμα μικρών αγγείων ή μειωμένη πυκνότητα αγγείων ή εναπόθεση MHC-1 σε περιδεσμιδικές περιοχές ή δικτυοσωληναριώδη έγκλειστα σε ενδοθηλιακά κύτταρα αγγείων σε Η.Μ.



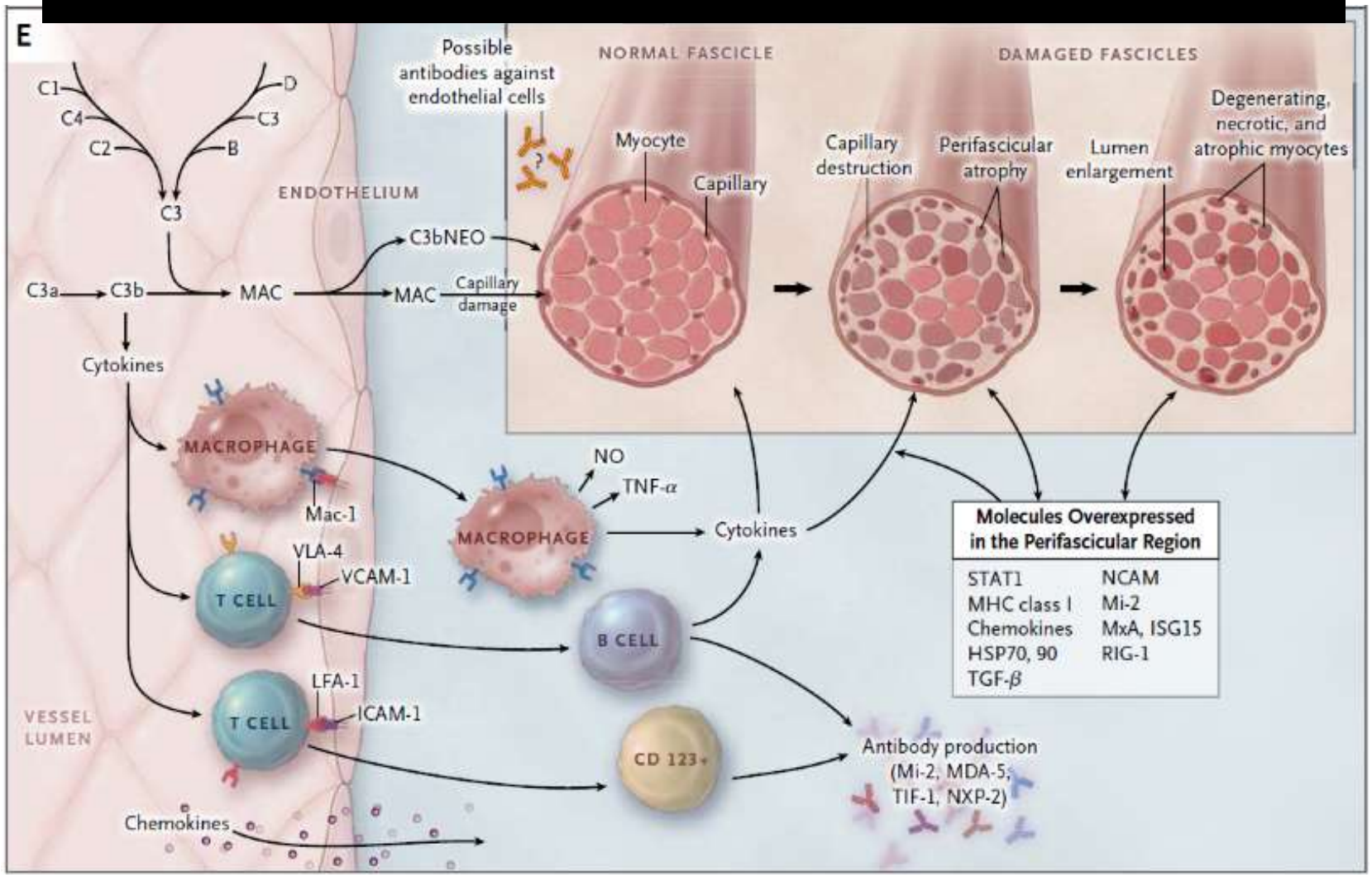




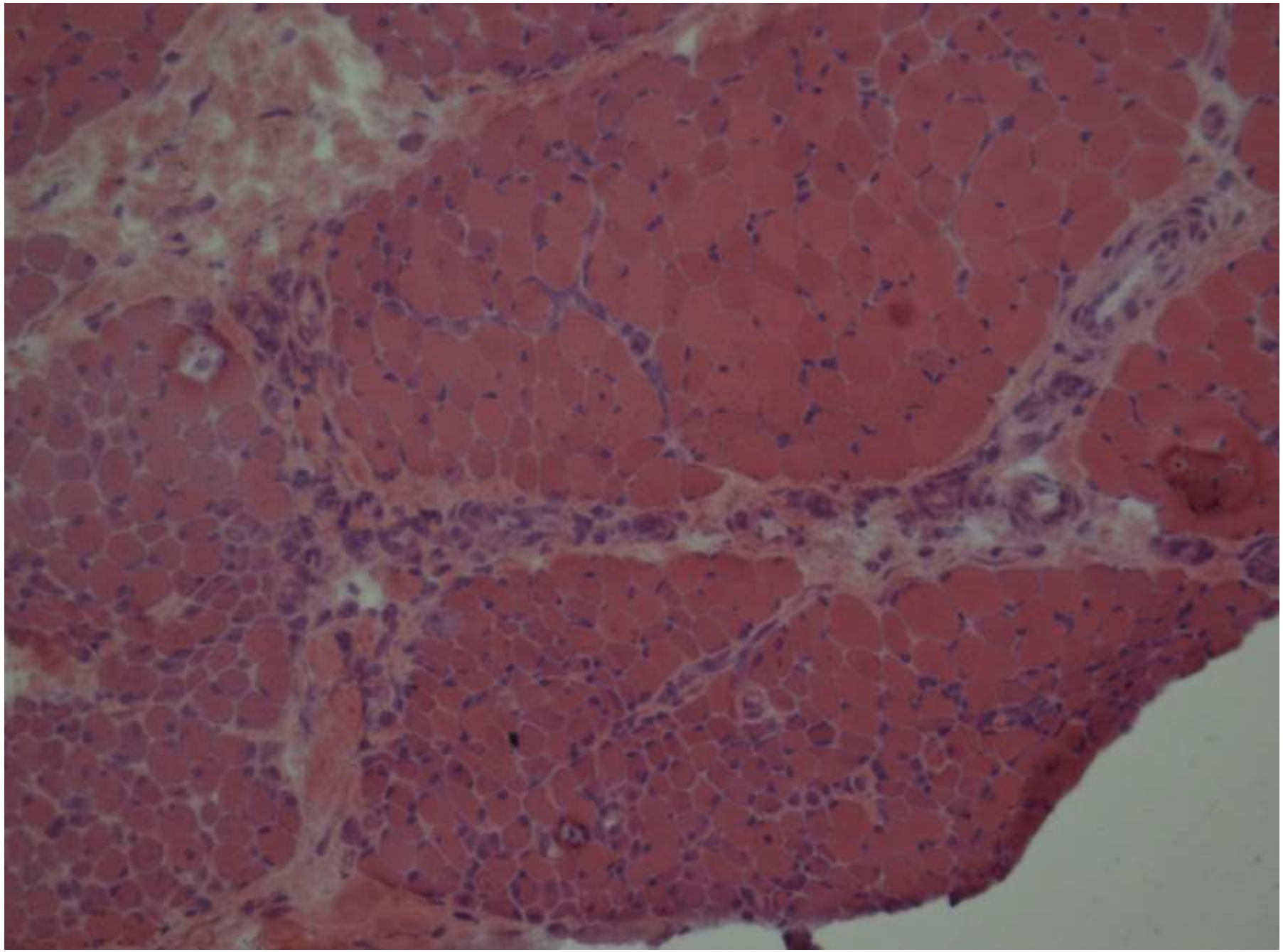


Παθοφυσιολογία

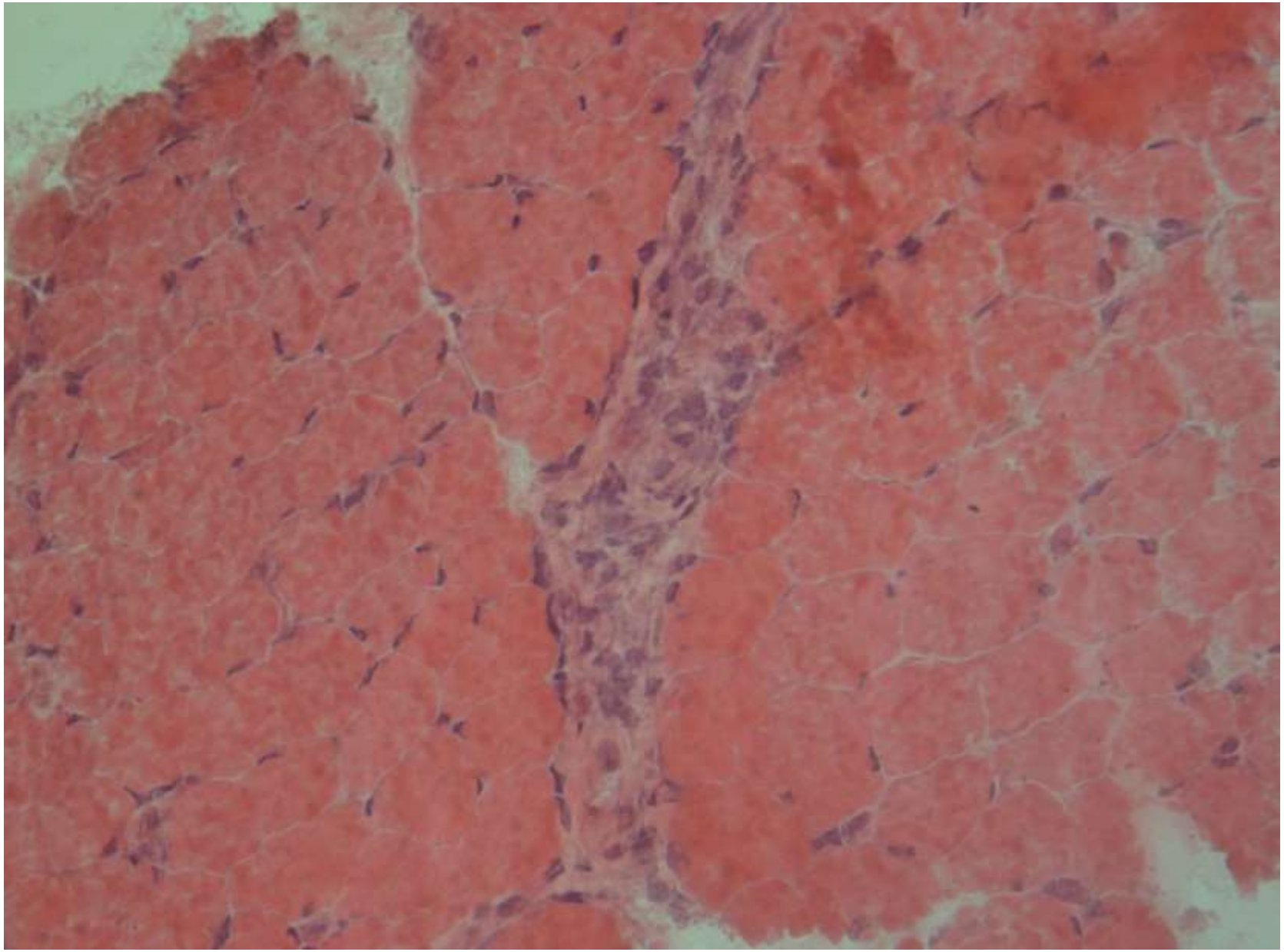
Complement-mediated microangiopathy



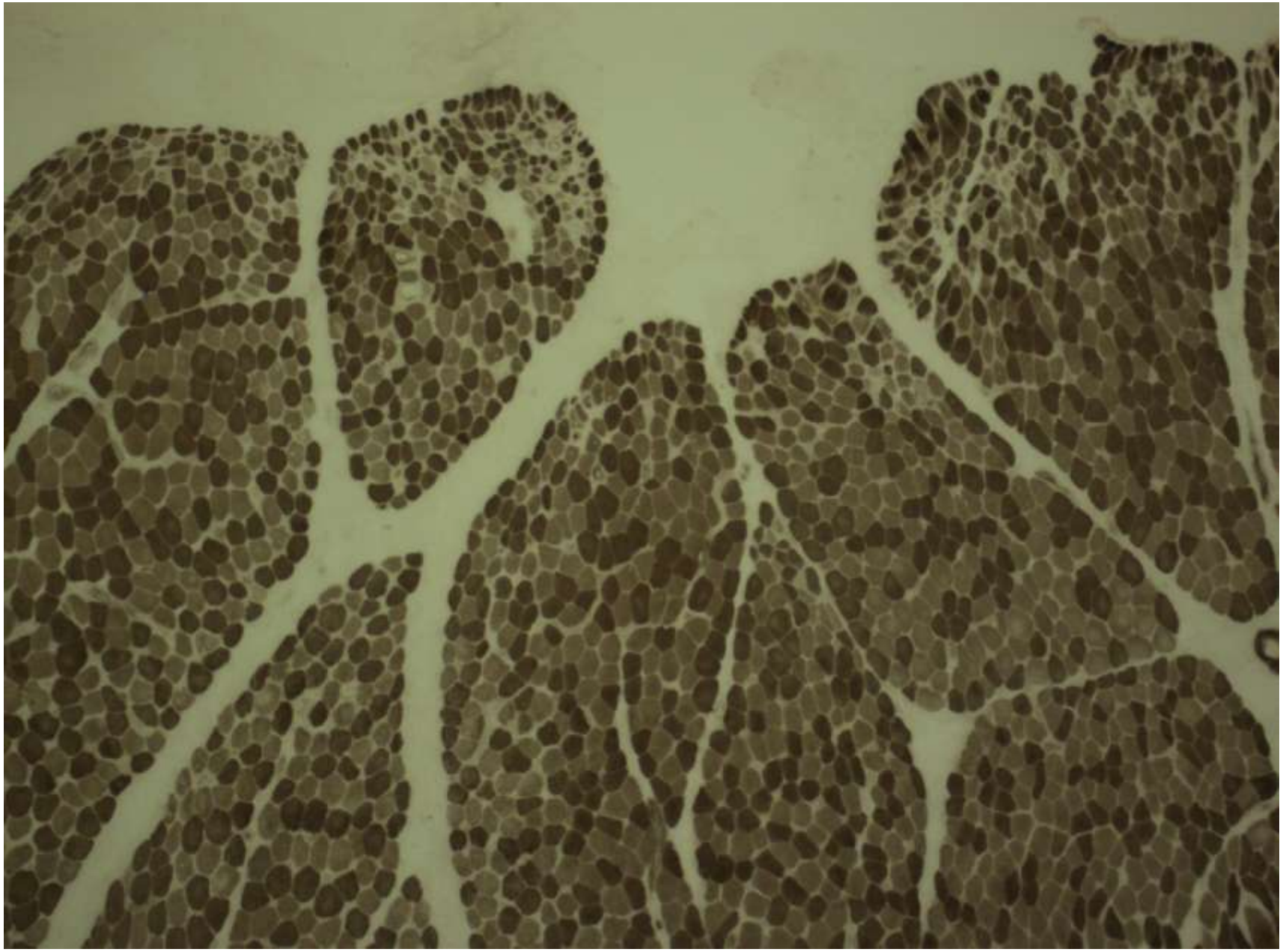
N Engl J Med 2015; 372:1734-1747



H&E



H&E



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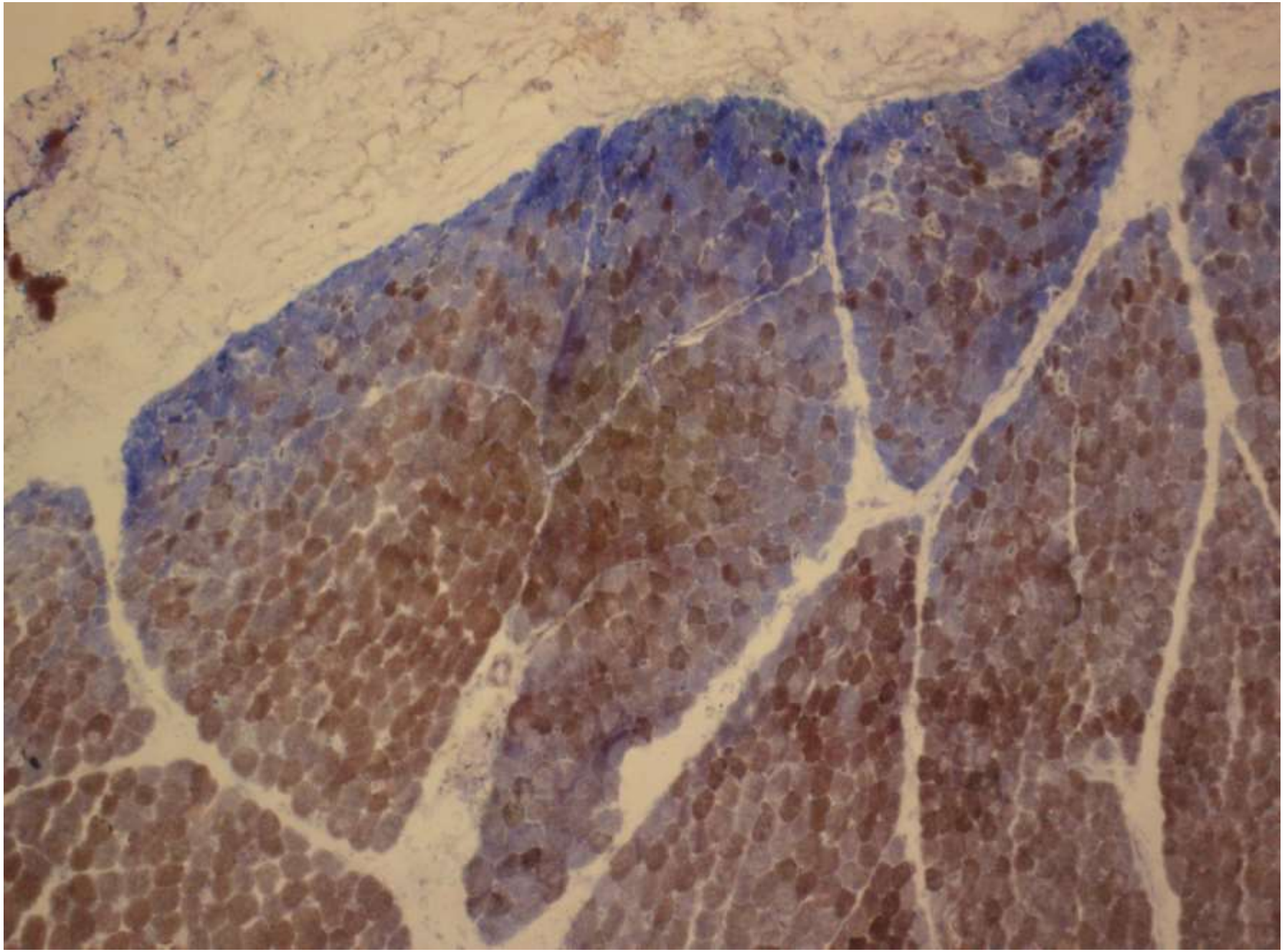
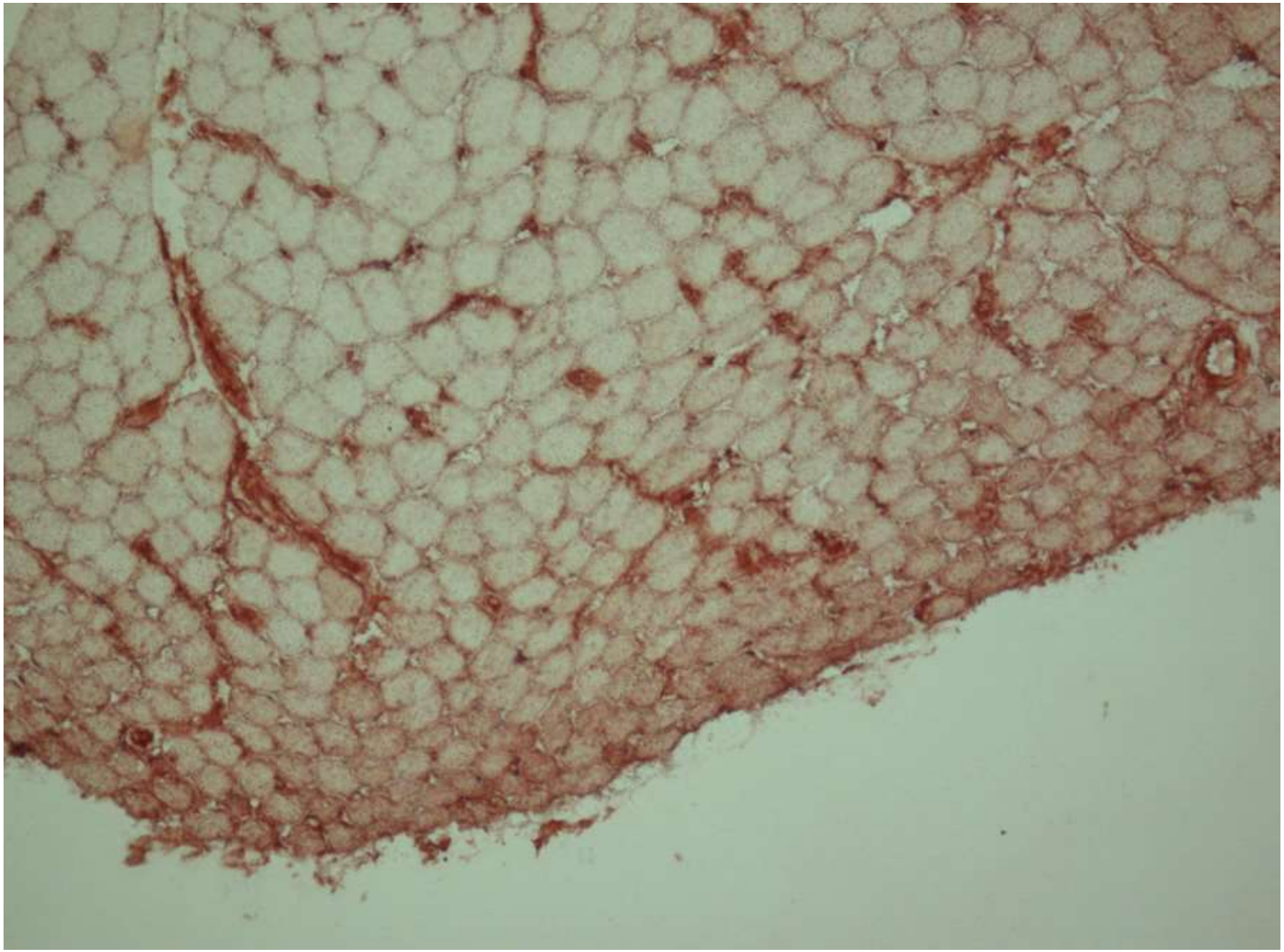


COX-SDH



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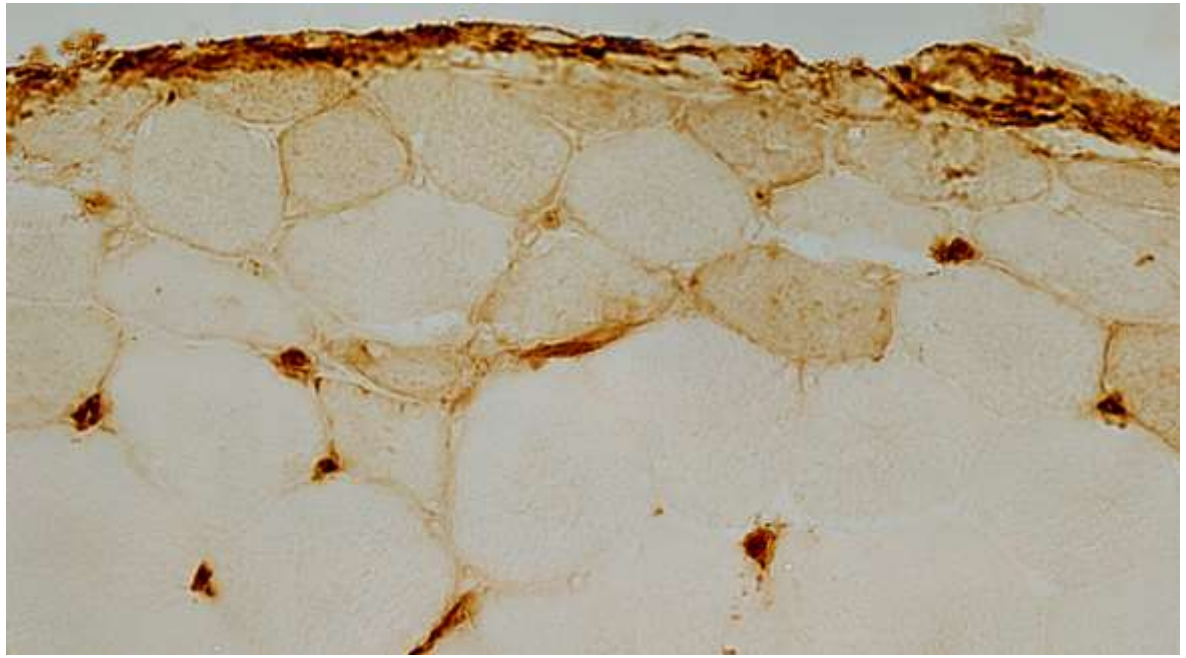
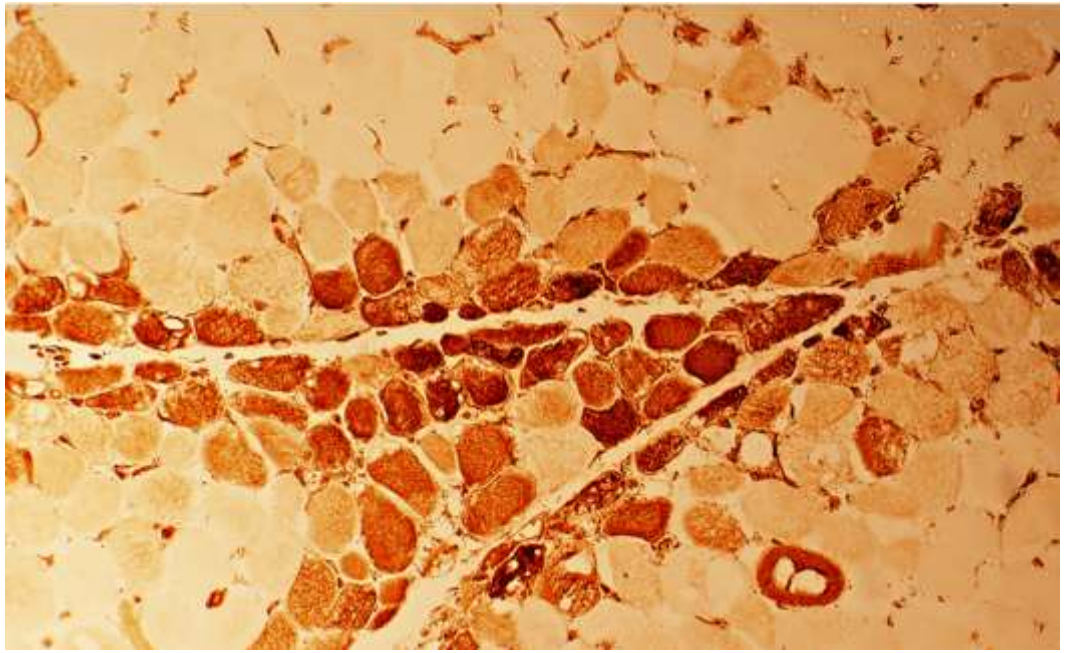
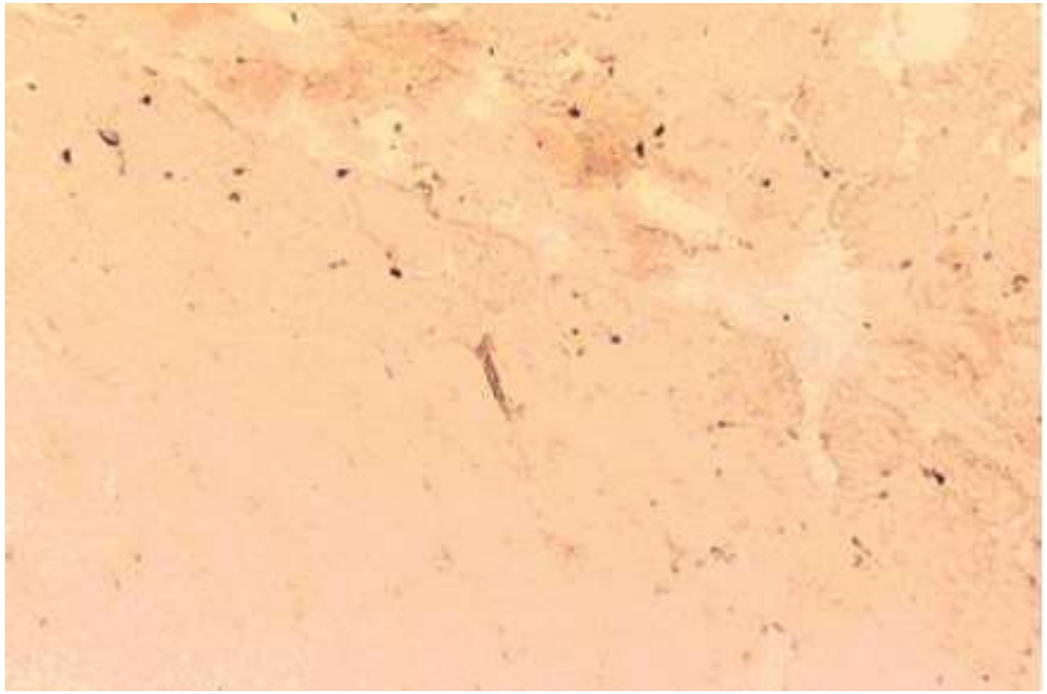


VvG



MxA



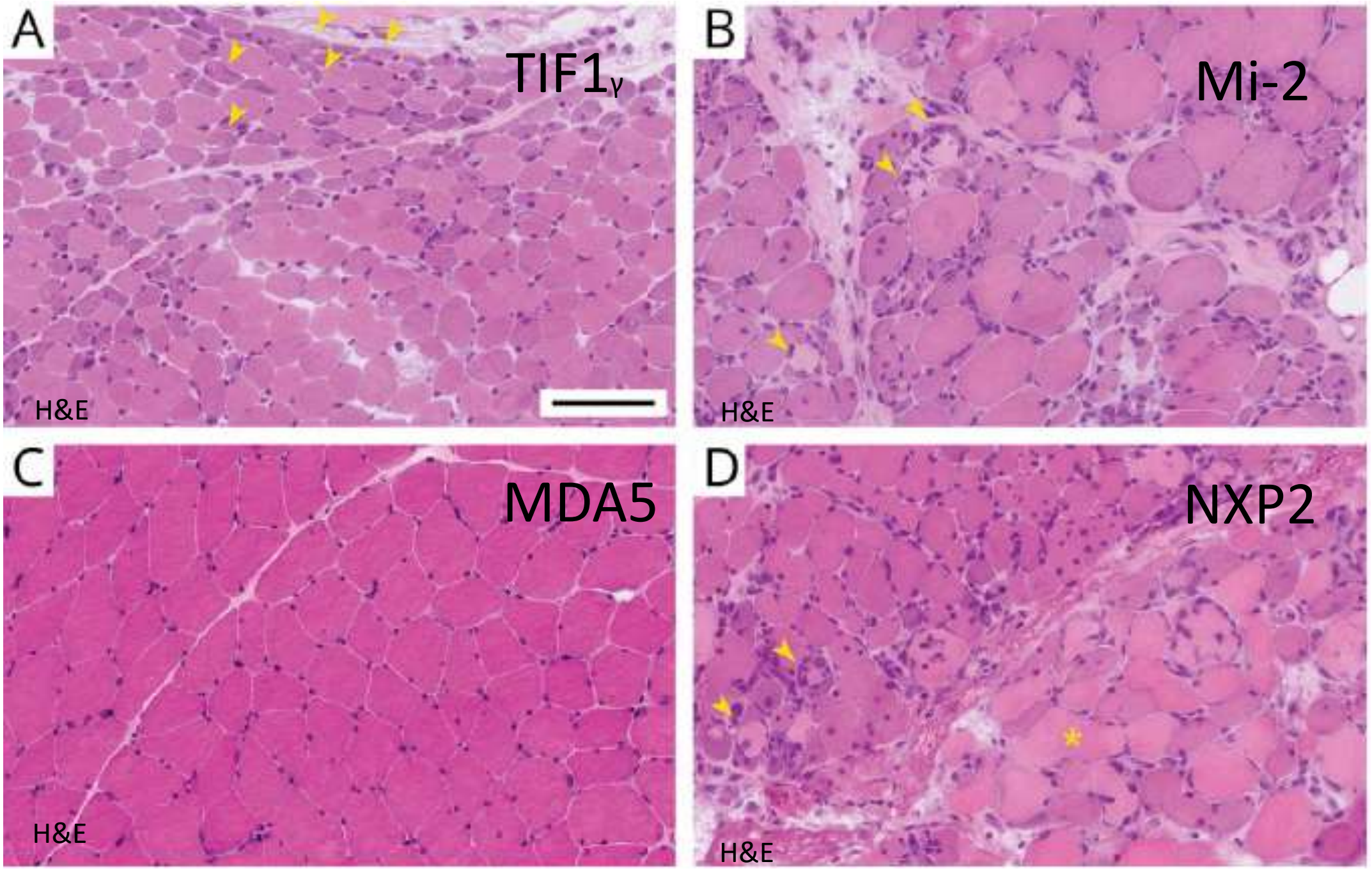
C5b9

Δερματομυοσίτιδα: υπότυποι βάσει του αυτοαντισώματος

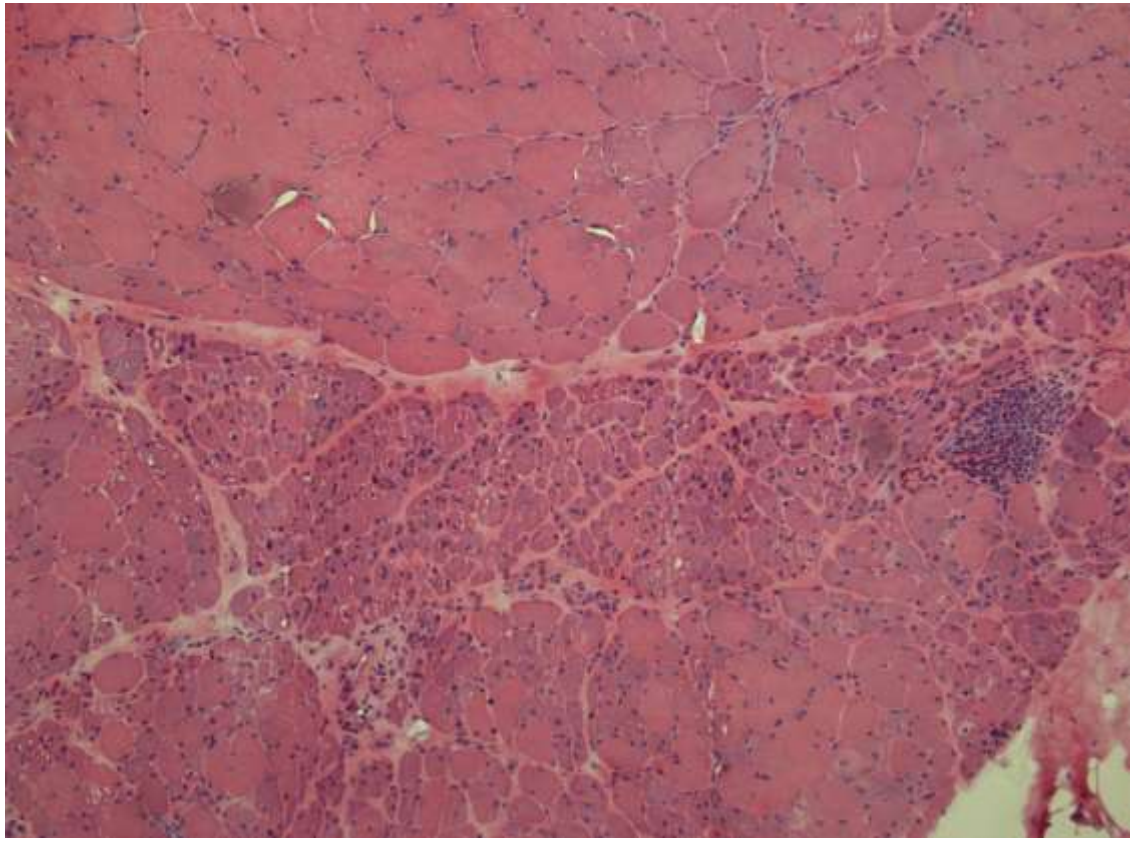
	Anti-Mi2	Anti-TIF1γ	Anti-NXP2	Anti-MDA5	Anti-SAE
Prevalence among DM	5-20%	15-25%	15-25%	5-20%	~5%
Muscle					
Severity of weakness	+++	+	++	+	+
Pattern of weakness	Proximal	Proximal	Proximal/Distal	Proximal	Proximal
CK levels (mean peak)	+++	++	+++	+	+
Biopsy features					
Perifascicular atrophy	++	++	++	+	?
Skin					
Gottron's/heliotrope	++	+++	++	++	?
Ulcerations	-/+	-/+	+	+++	?
Calcinosis	-/+	-/+	++	-/+	?
Interstitial lung disease	-/+	-/+	-/+	+++	+
Cancer Risk	?	+++	++	+	?

Δερματομυοσίτιδα: υπότυποι βάσει του αυτοαντισώματος

Histologic features of interest	All DM (n = 256)	Anti-TIF1-γ (n = 87)	Anti-Mi-2 (n = 40)	Anti-MDA5 (n = 29)	Anti-NXP-2 (n = 83)	Anti-SAE (n = 10)	Seronegative (n = 7)
Perifascicular atrophy	127 (49.6)	49 (56.3)	27 (67.5)[d*]	7 (24.1)[d†]	33 (39.8)[d†]	7 (70.0)	4 (57.1)
Perifascicular necrosis	28 (10.9)	3 (3.4)[d†]	21 (52.5)[d*]	0	2 (2.4)[d†]	0	2 (28.6)
Decreased COX activity in perifascicular area	118 (46.3)[a]	47 (54.7)[a]	21 (52.5)	5 (17.2)[d†]	37 (44.6)	4 (40.0)	4 (57.1)
Perivascular inflammatory cell infiltration	113 (44.1)	41 (47.1)	18 (45.0)	4 (13.8)[d†]	42 (50.6)	2 (20.0)	6 (85.7)[d*]
Vasculitis	39 (15.2)	10 (11.5)	10 (25.0)	0	15 (18.1)	0	4 (57.1)[d*]
CD8 infiltration in non-necrotic fiber	5 (2.0)[b]	2 (2.3)	3 (7.7)[b,d*]	0	0	0	0
ACP/CD68 infiltration in non-necrotic fiber	14 (5.5)	4 (4.6)	8 (20.0)[d*]	0	1 (1.2)[d†]	0	1 (14.3)
CD20 aggregation	39 (15.3)[b]	10 (11.5)	11 (28.2)[b,d*]	1 (3.5)	13 (15.7)	1 (10.0)	3 (42.9)
Microinfarction	38 (14.8)	11 (12.6)	0	3 (10.3)	22 (26.5)[d*]	2 (20.0)	0
Microinfarction, adult patients	23 (12.2)	10 (13.9)	0	1 (4.8)	10 (20.8)[d*]	2 (20.0)	0
Microinfarction, juvenile patients	15 (22.4)	1 (6.7)	0	2 (25.0)	12 (34.3)[d*]	0	0
Central necrotic-peripheral regenerating fibers	63 (24.6)	21 (24.1)	18 (45.0)[d*]	3 (10.3)	18 (21.7)	2 (20.0)	1 (14.3)
Vacuolated, punched-out fiber	113 (44.5)[c]	55 (64.7)[c,d*]	3 (7.5)[d†]	6 (20.7)[d†]	40 (48.2)	7 (70.0)	2 (28.6)

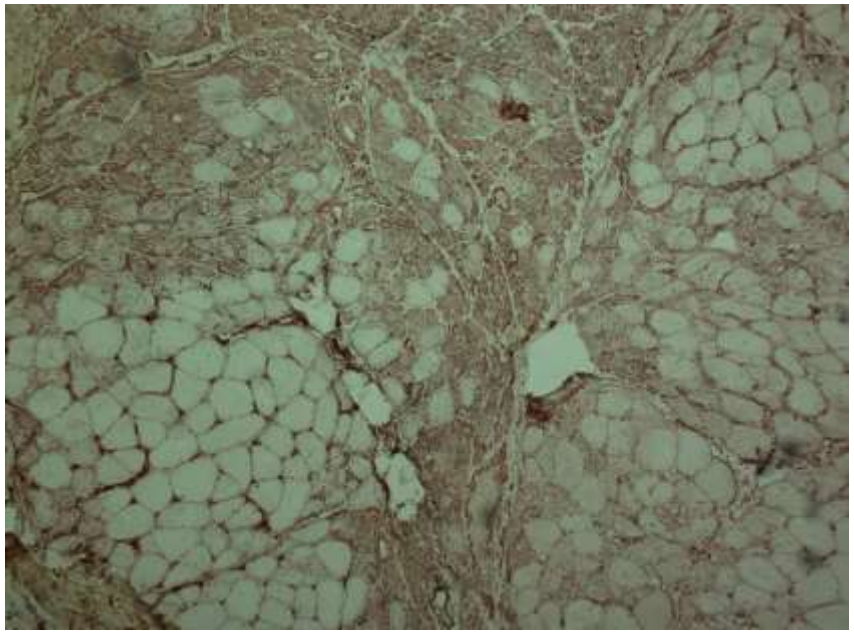

A
TIF1γ
H&E
B
Mi-2
H&E
C
MDA5
H&E
D
NXP2
H&E

TIF1γ-DM

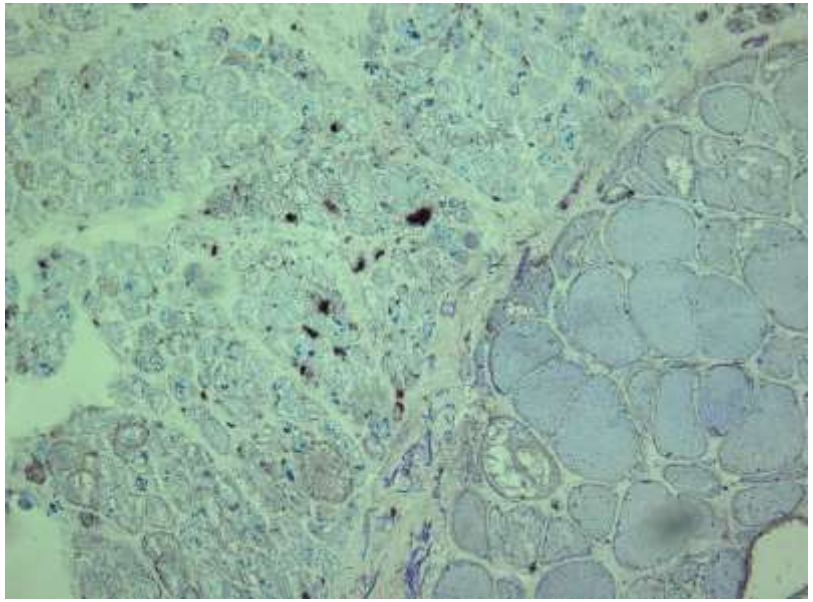


H&E

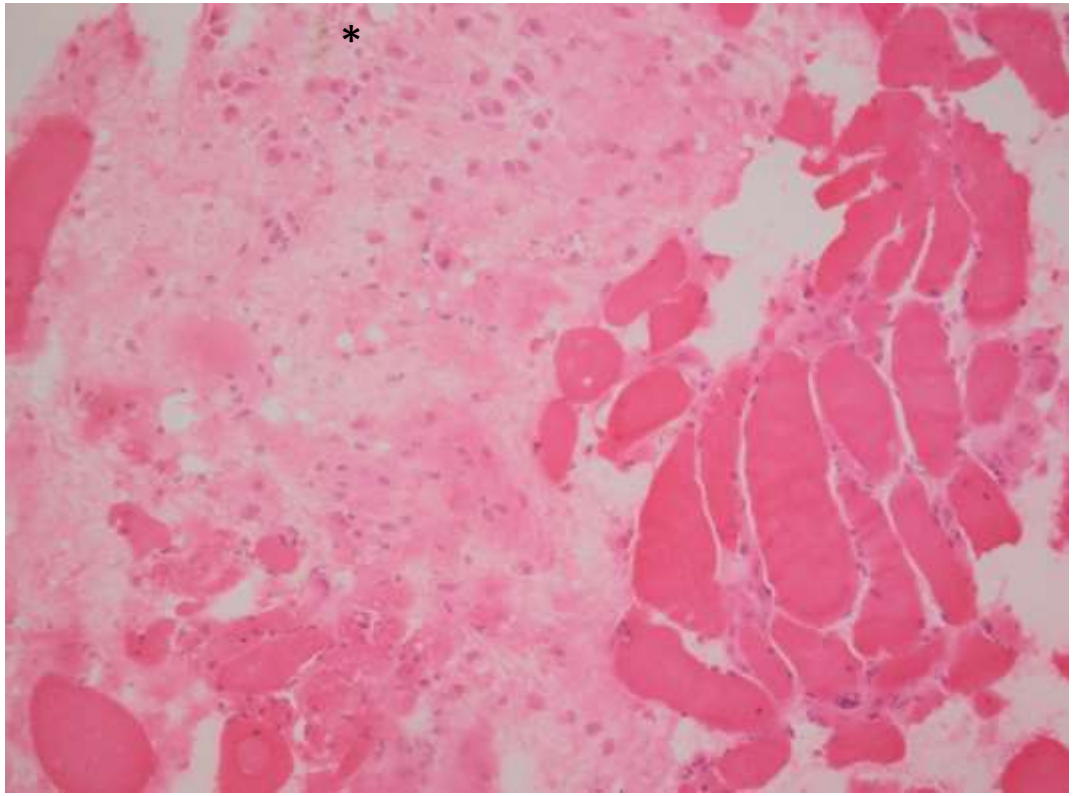
HLA-I



C5b9



NXP2-DM



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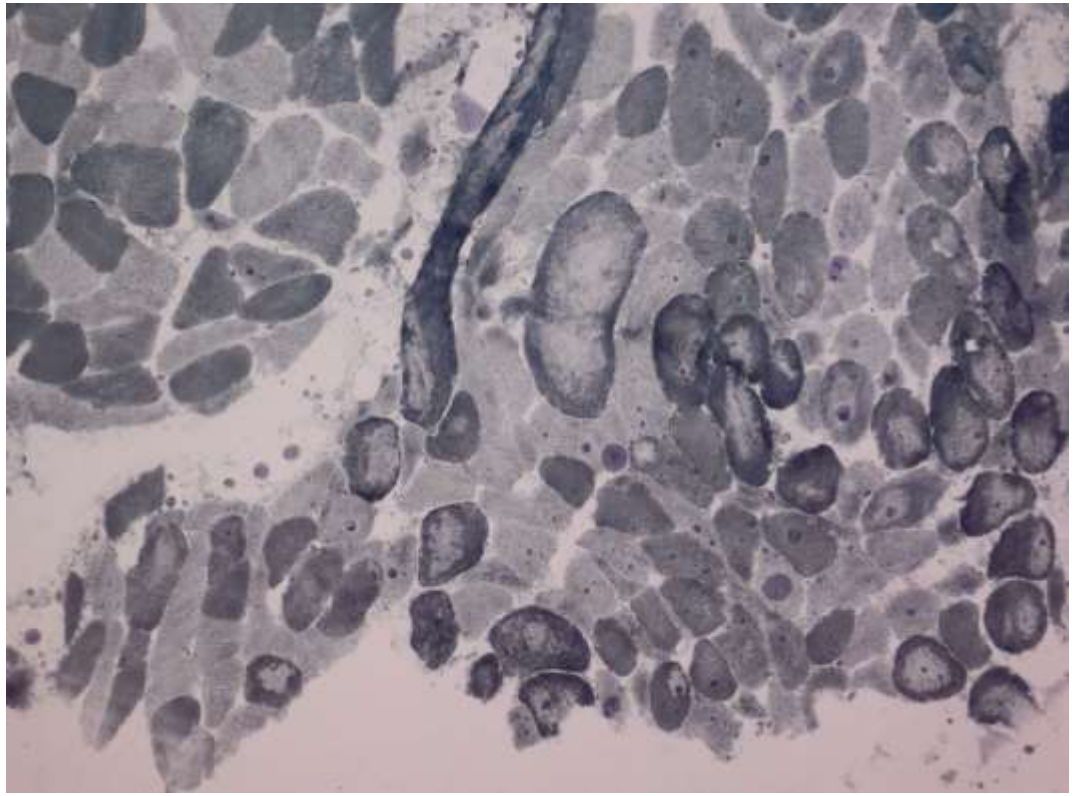


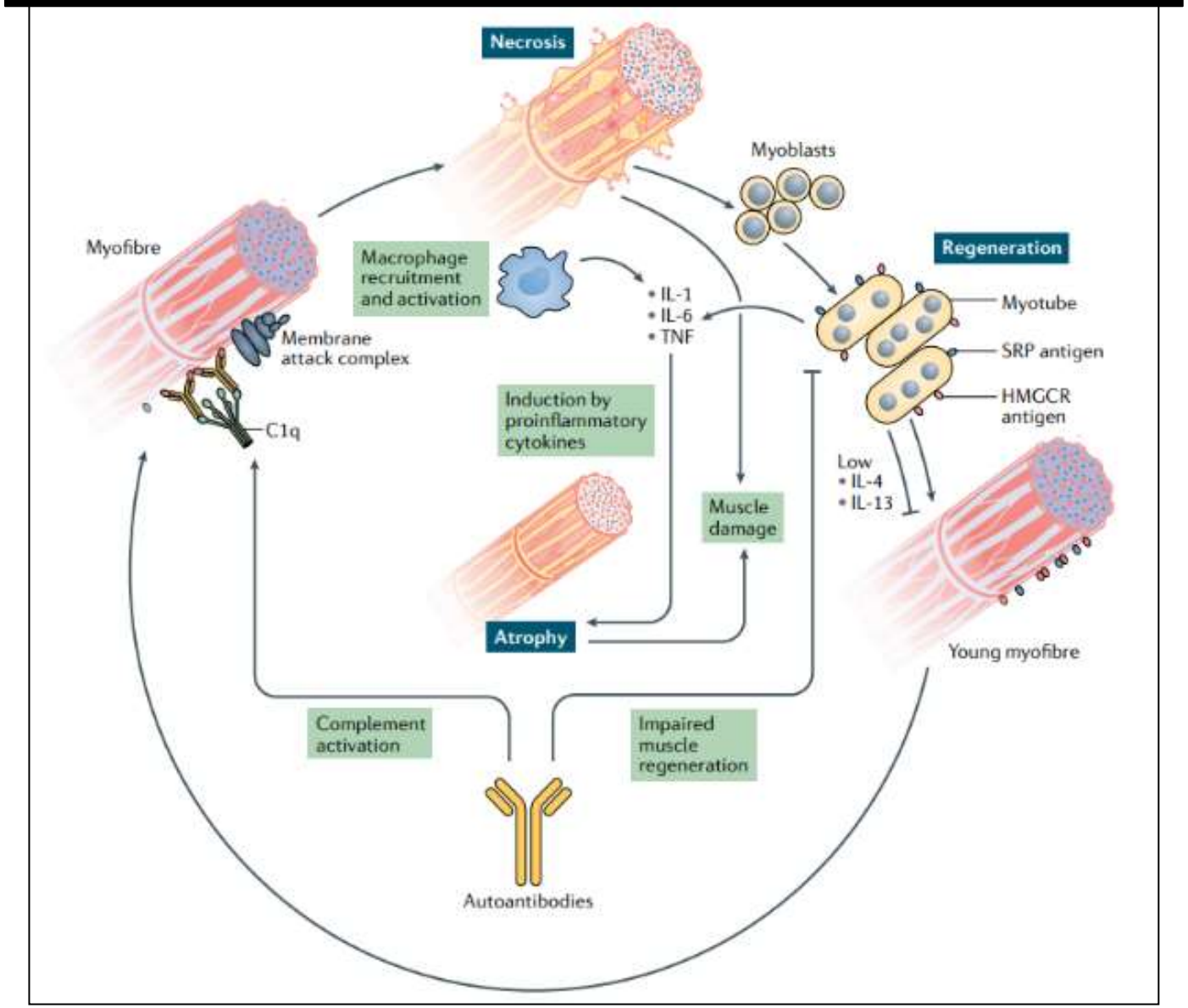
NADH

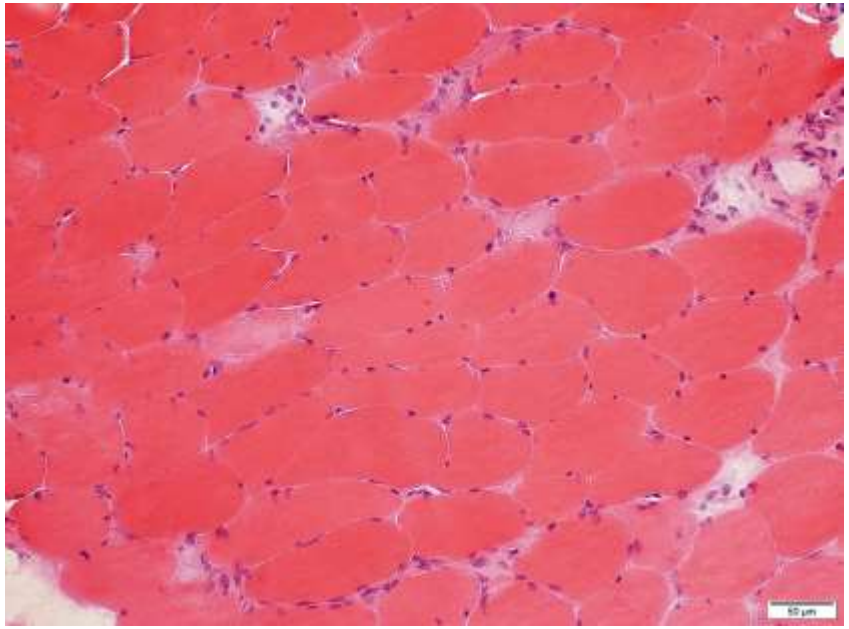
Νεκρωτικές Μυοπάθειες

- Ζωνιαίας κατανομής μυϊκή αδυναμία με οξεία/υποξεία εξέλιξη*
- Αυξημένα επίπεδα κρεατίνης κινάσης
- Άλλα εργαστηριακά
  - Ηλεκτρομυογράφημα
  - MRI μυών
  - Ειδικά αυτοαντισώματα (SRP, HMGCoR, οροαρνητικές)
- Νεκρωτικές μυϊκές ίνες είναι το κύριο ιστοπαθολογικό χαρακτηριστικό. Λίγα φλεγμονώδη κύτταρα, εναπόθεση MAC σε μικρά αγγεία ή pipestem capillaries

Παθοφυσιολογία

Complement-mediated autoantibody induced muscle damage





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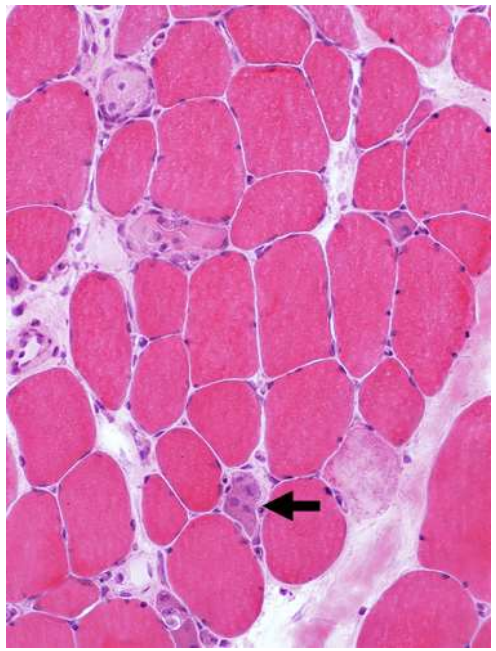

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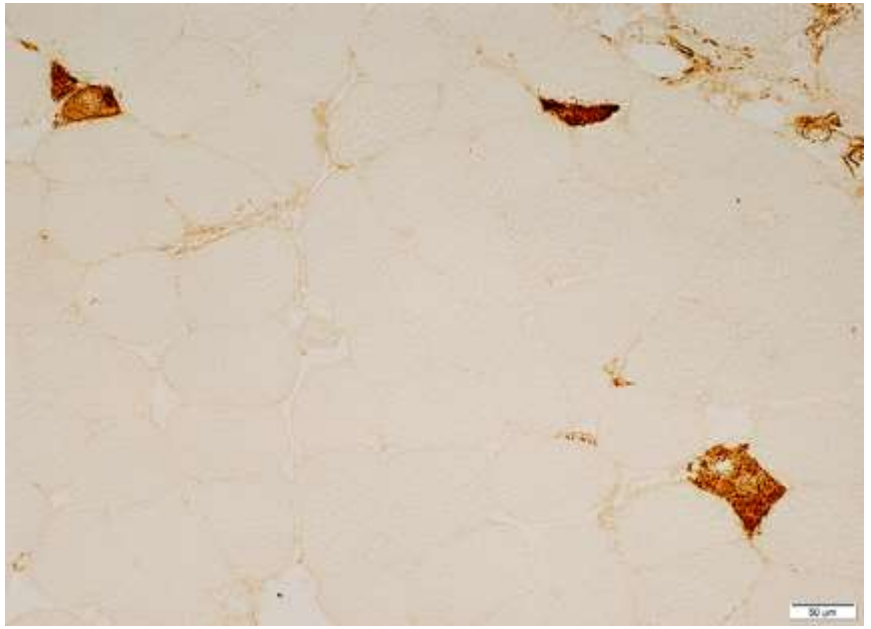

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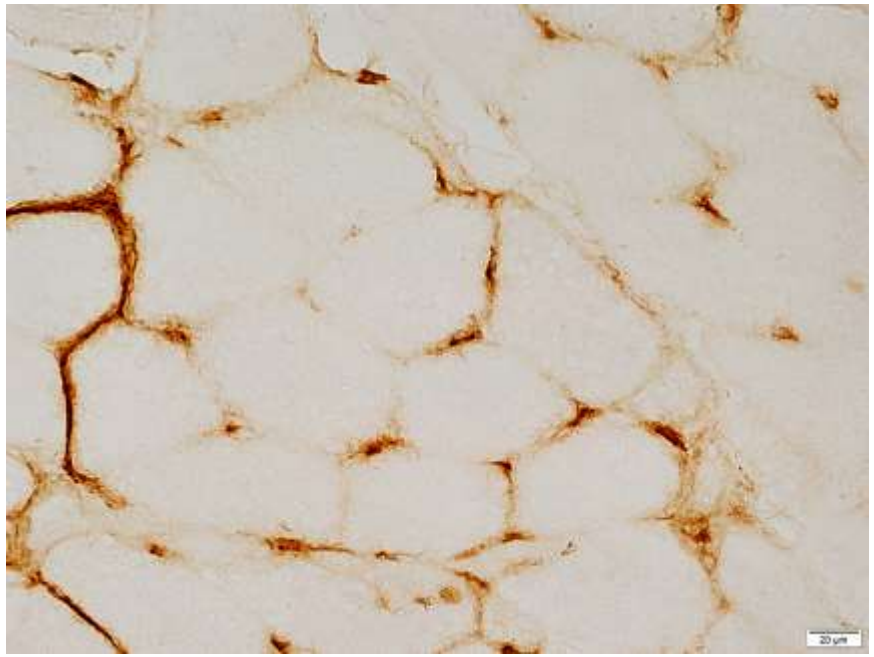

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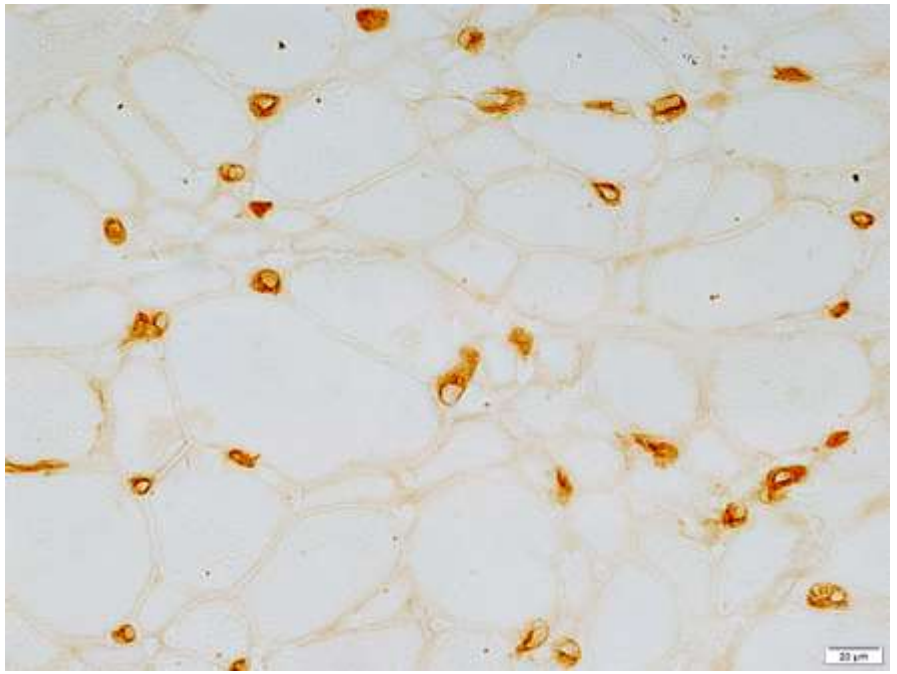
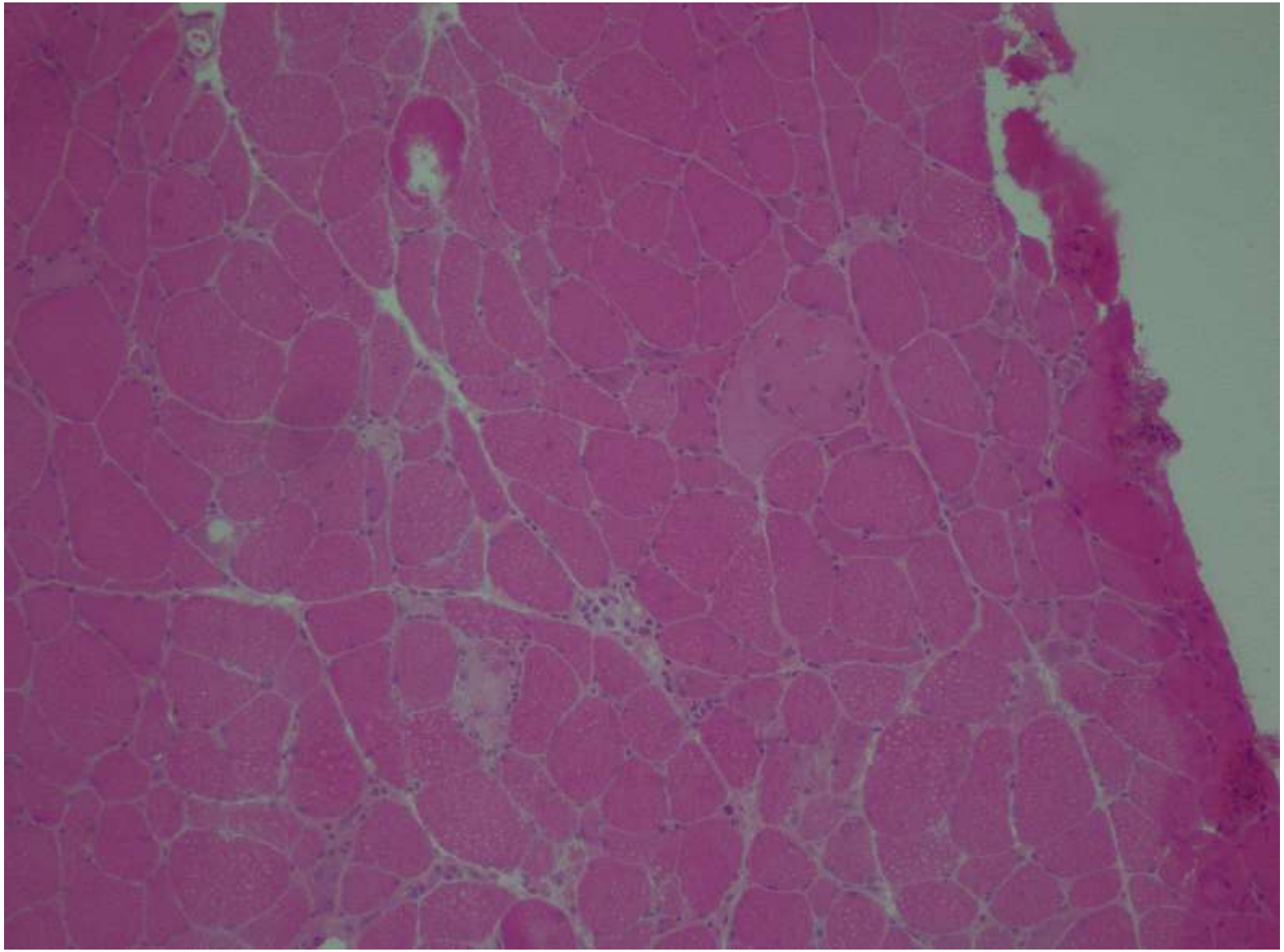
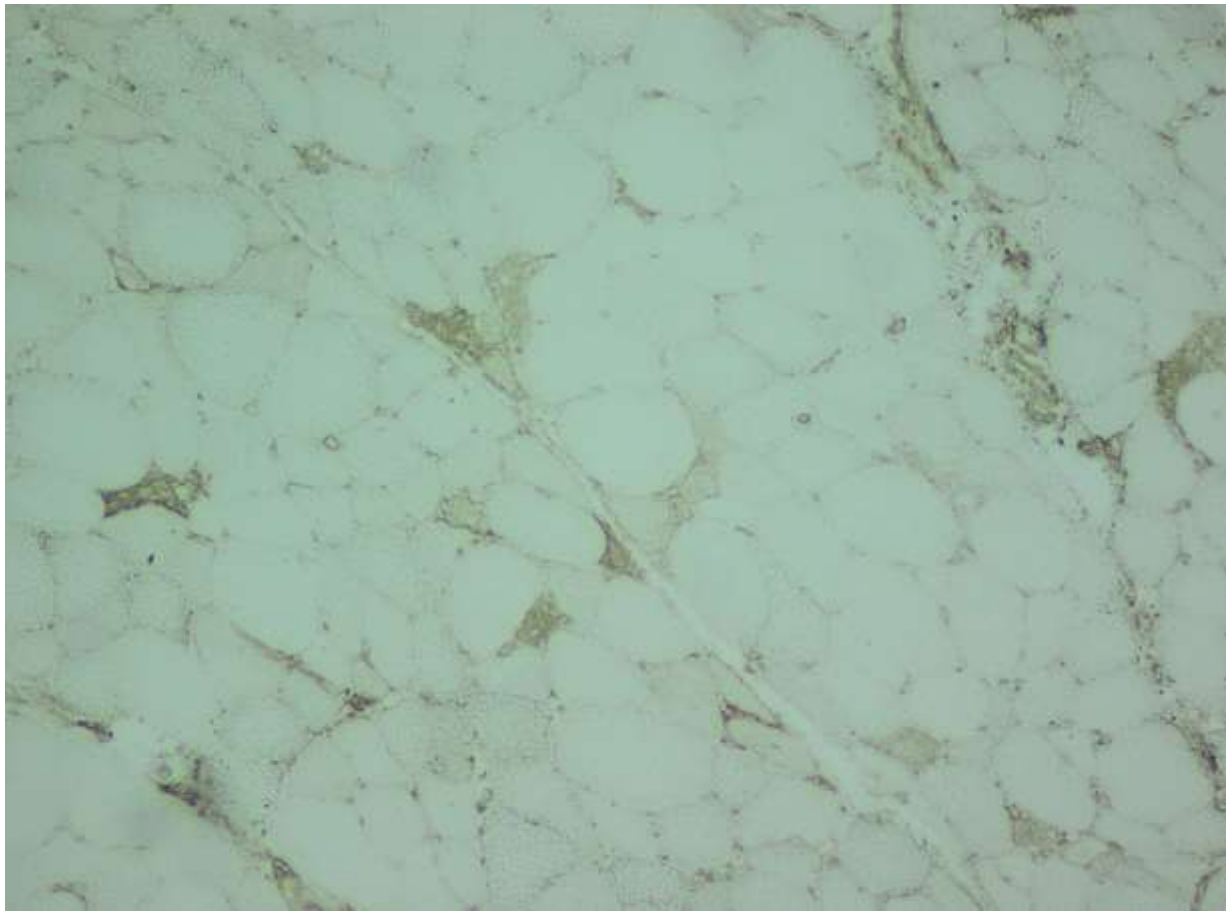


Ulex europaeus agglutinin I

HMGCoR+-IMNM



H&E



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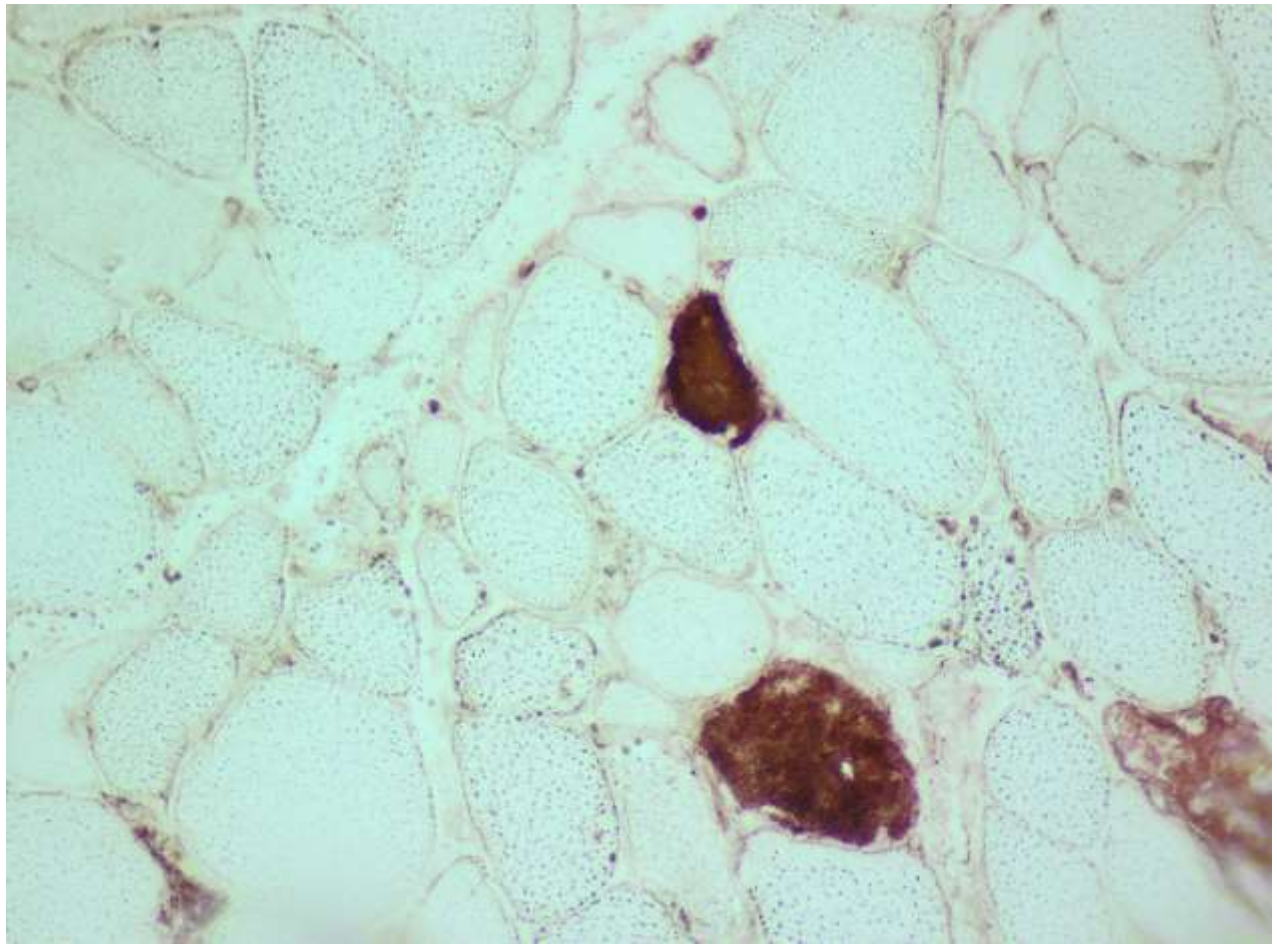

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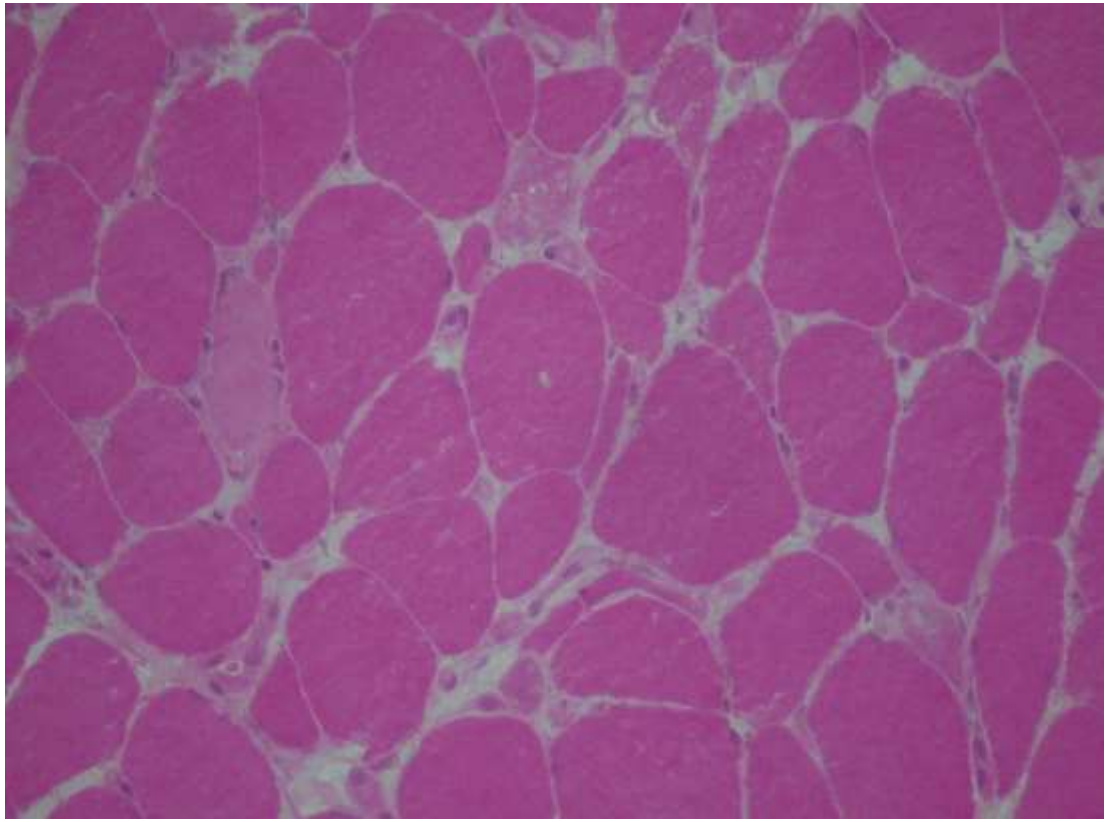
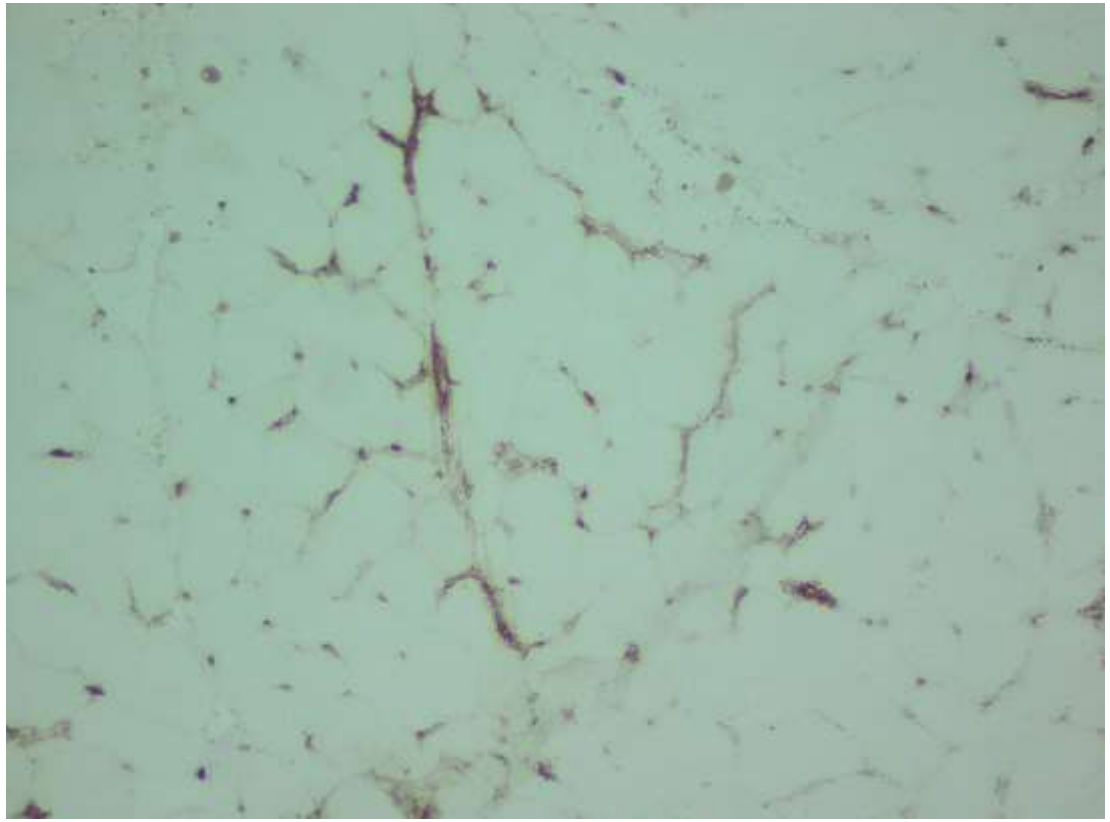
SRP+-IMNM



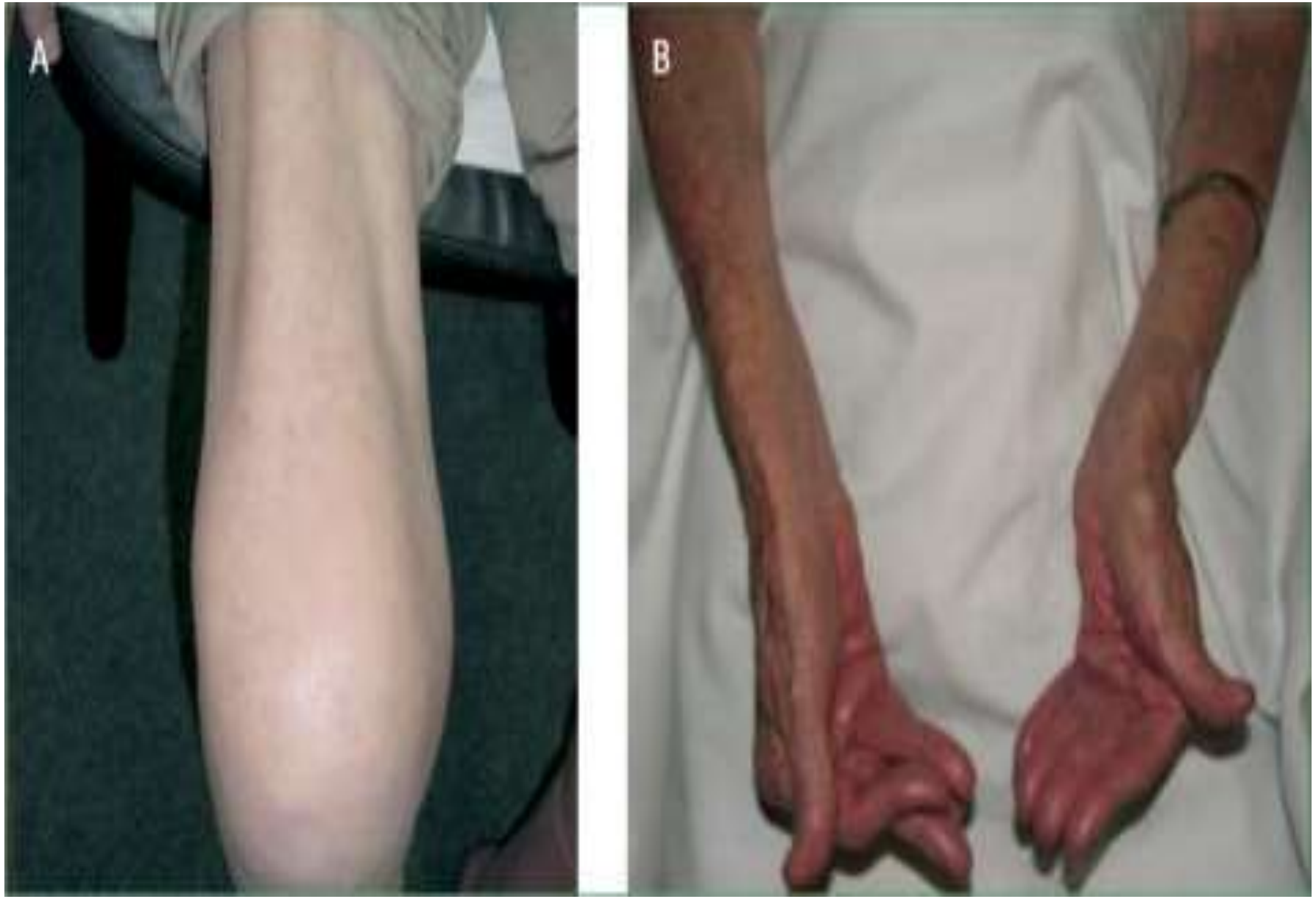
H&E



HLA-I

Μυοσίτις με έγκλειστα σωμάτια (IBM)

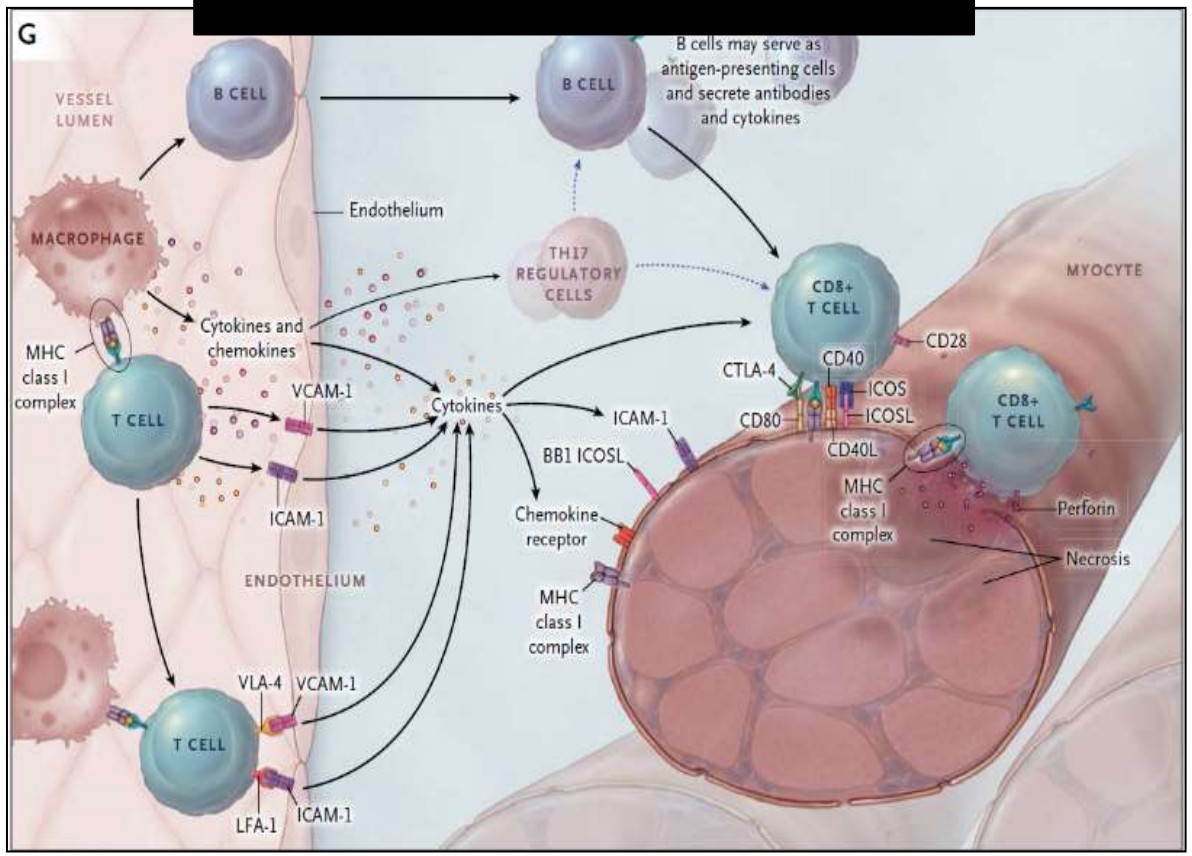
- Η συχνότερη φλεγμονώδης μυοπάθεια μετά την ηλικία των 50 ετών
- Η αδυναμία εγγύς (τετρακέφαλοι) + άπω (ΕΒ καμπτήρες δακτύλων-καρπού)
- Ασύμμετρη αδυναμία
- 40% διαταραχή της κατάποσης
- Άνδρες, 60 ετών **(>40)**
- Απώλεια βάδισης σε μ.ο. 15 έτη- Δεν επηρεάζει προσδόκιμο
- Βιοψία
  - Φλεγμονή (προβολή μη νεκρωτικών μυϊκών ινών από ολιγοκλωνικά CD8)
  - Εκφύλιση (σχισμοειδή κενοτόπια..)
- cN1A στο 30-40%
  - Ευαισθησία 50-70%, ειδικότητα ??
  - Χρησιμότητα ίσως για διάγνωση σε άτυπες μορφές



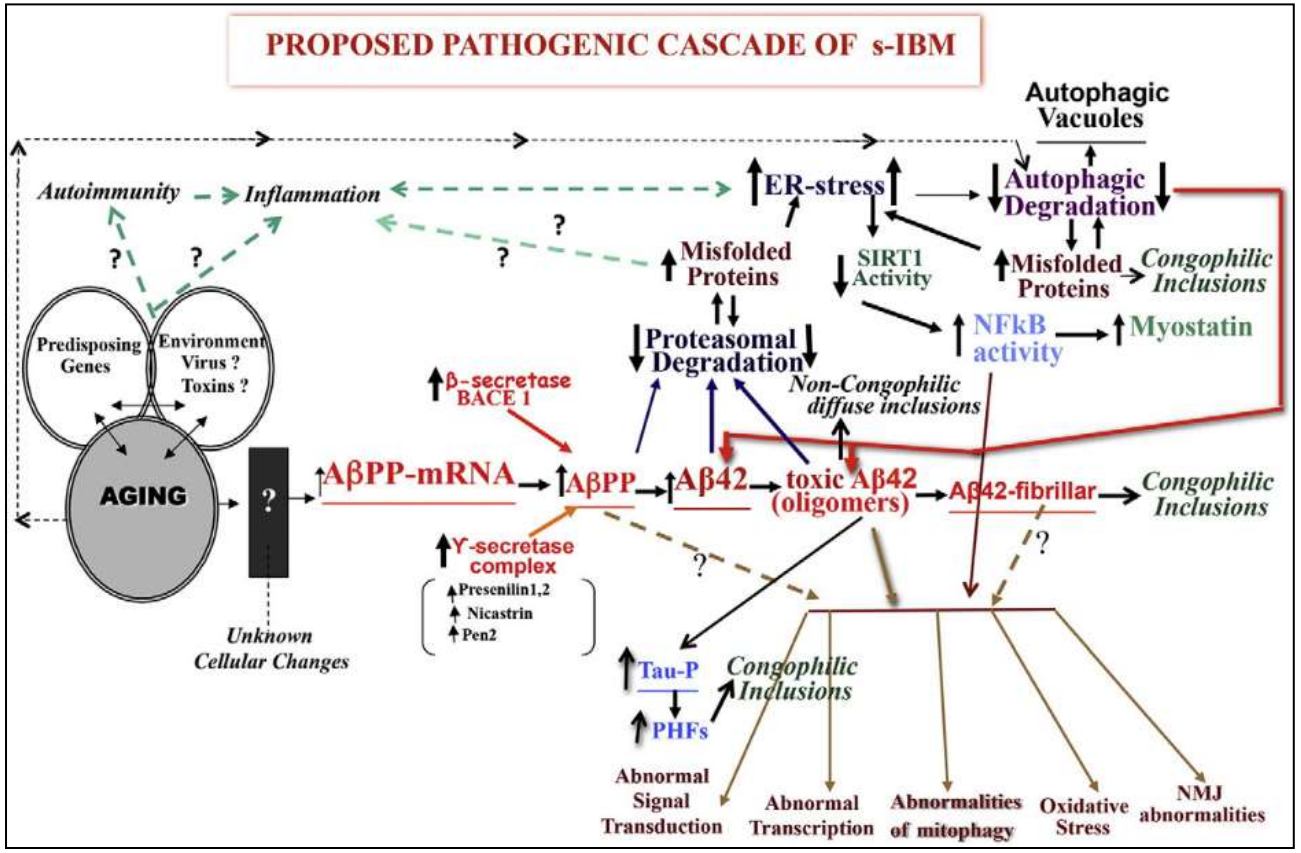
Needham M Lancet Neurol **2007; 6: 620–31**

Παθοφυσιολογία

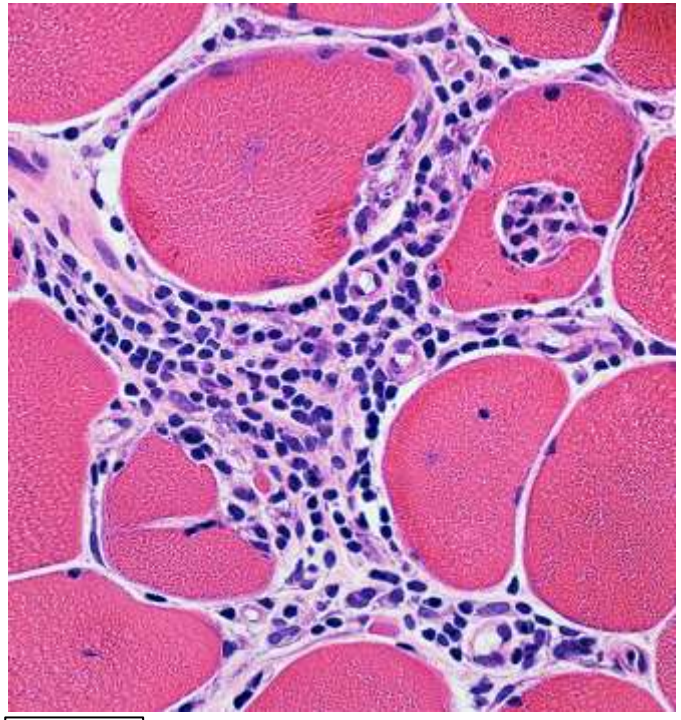
T-cell mediated cytotoxicity



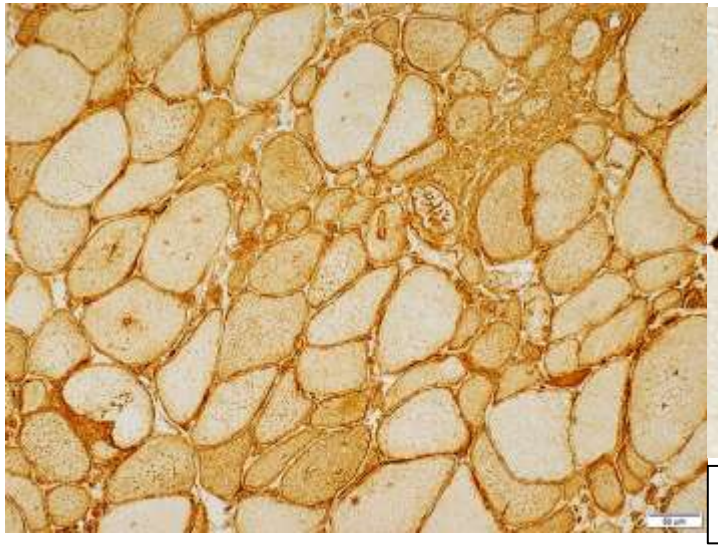
N Engl J Med 2015; 372:1734-1747



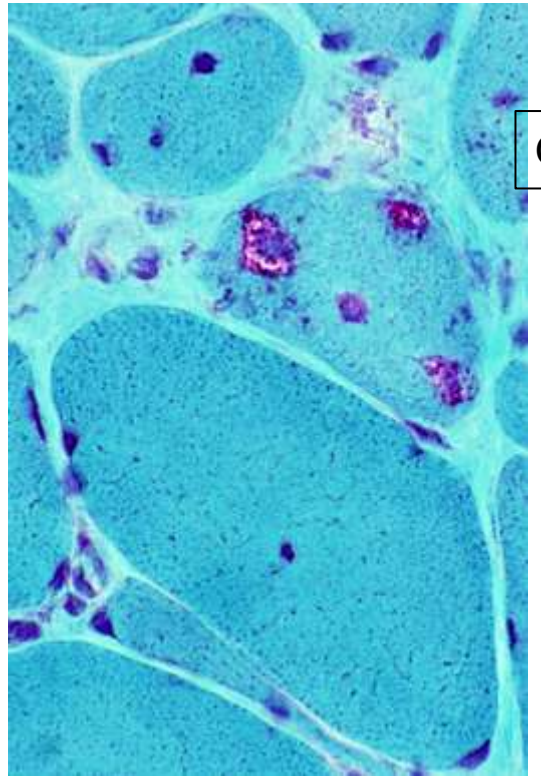
Biochimica et Biophysica Acta 1852 (2015) 633–643



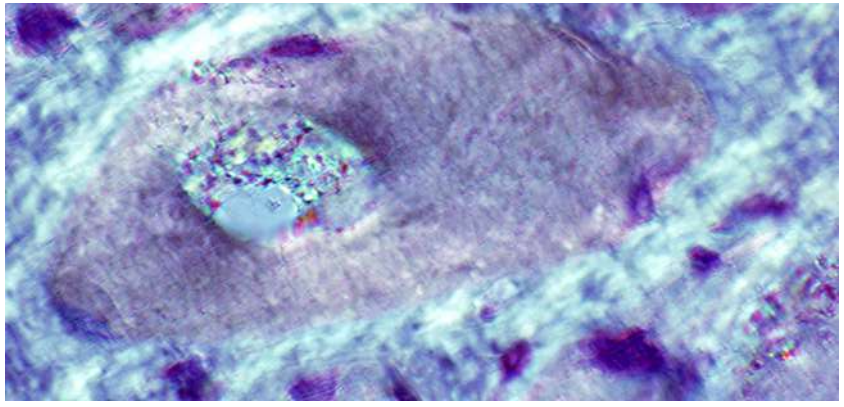
H&E



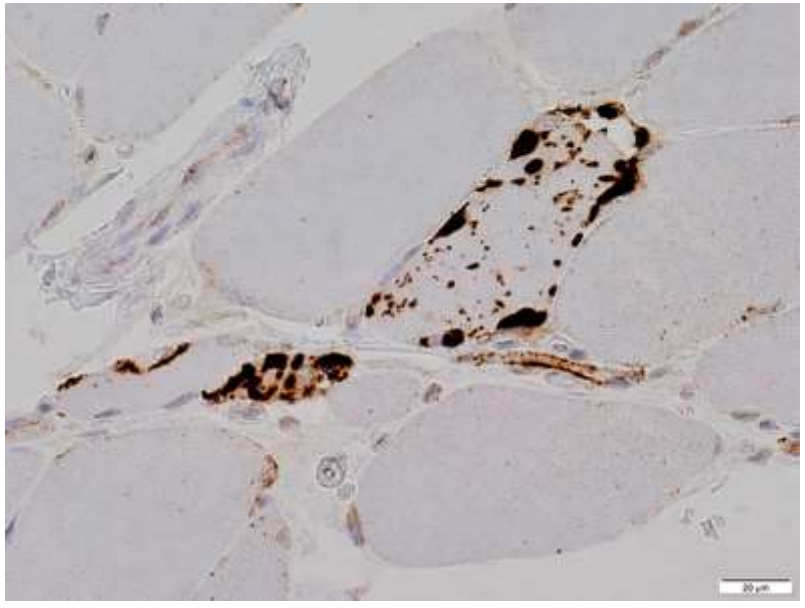
HLA-I



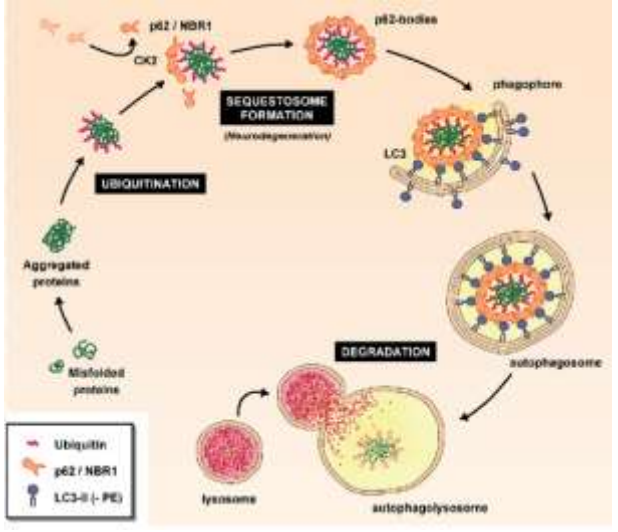
GMT



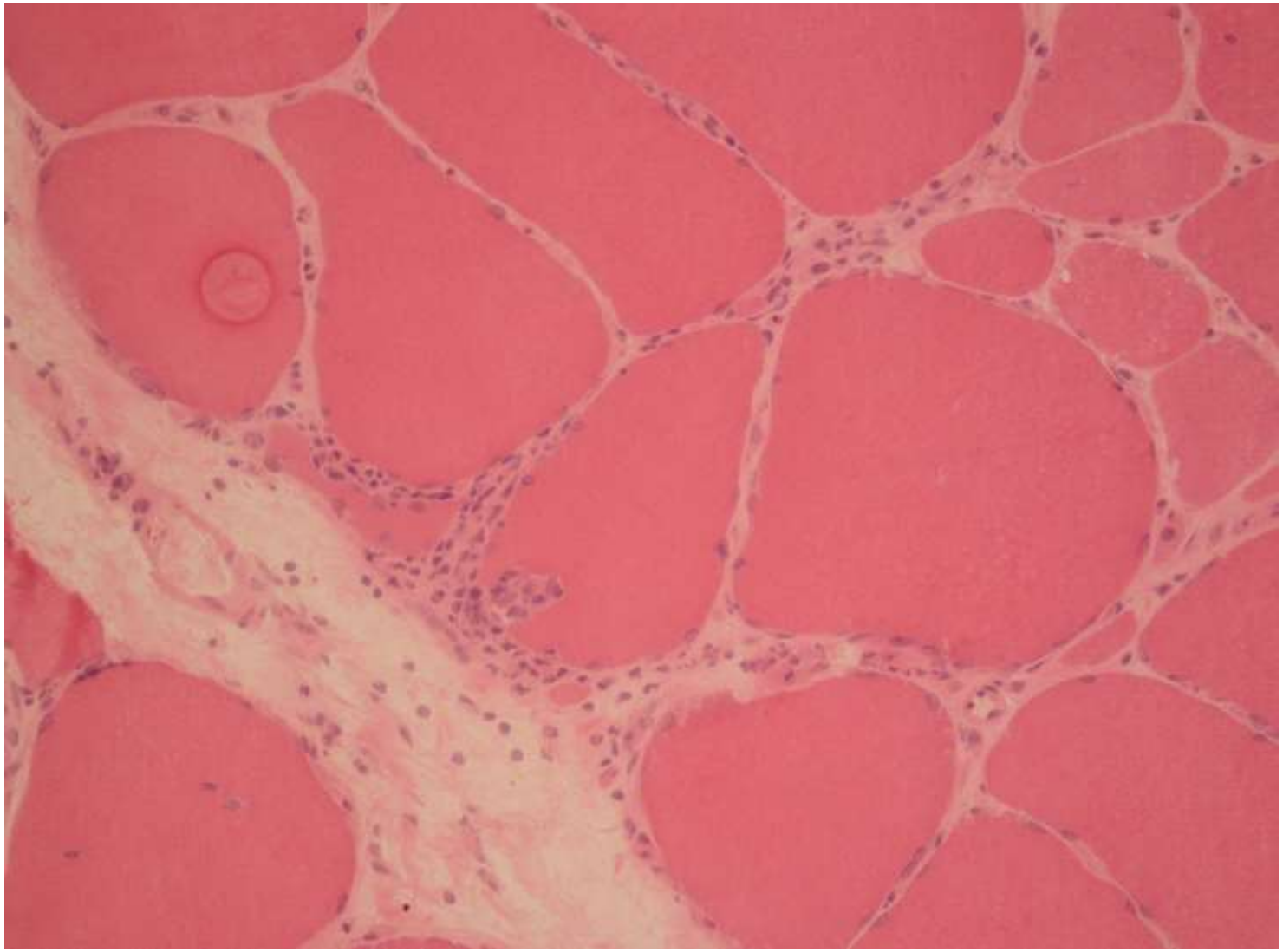
Congo



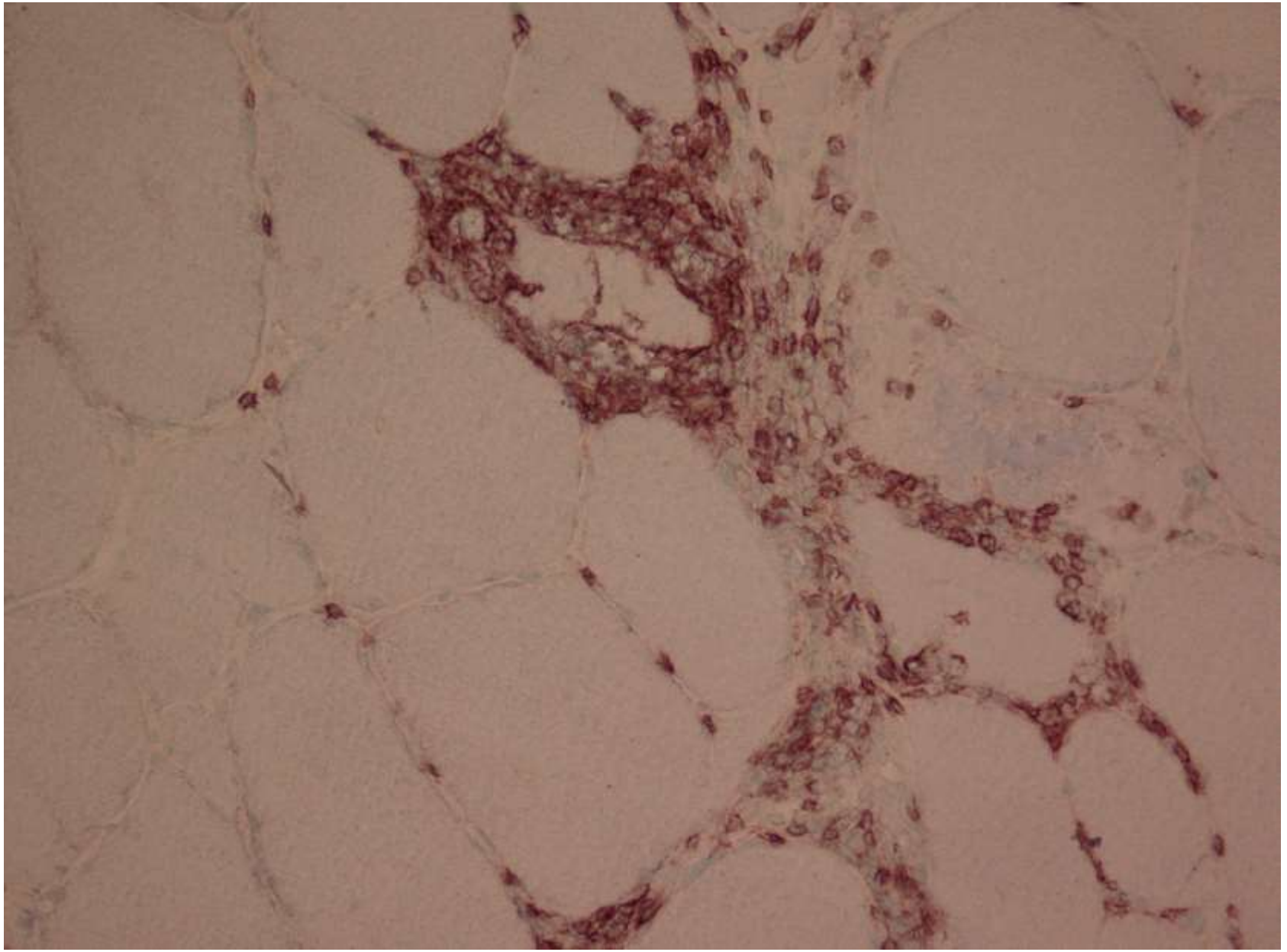
p62



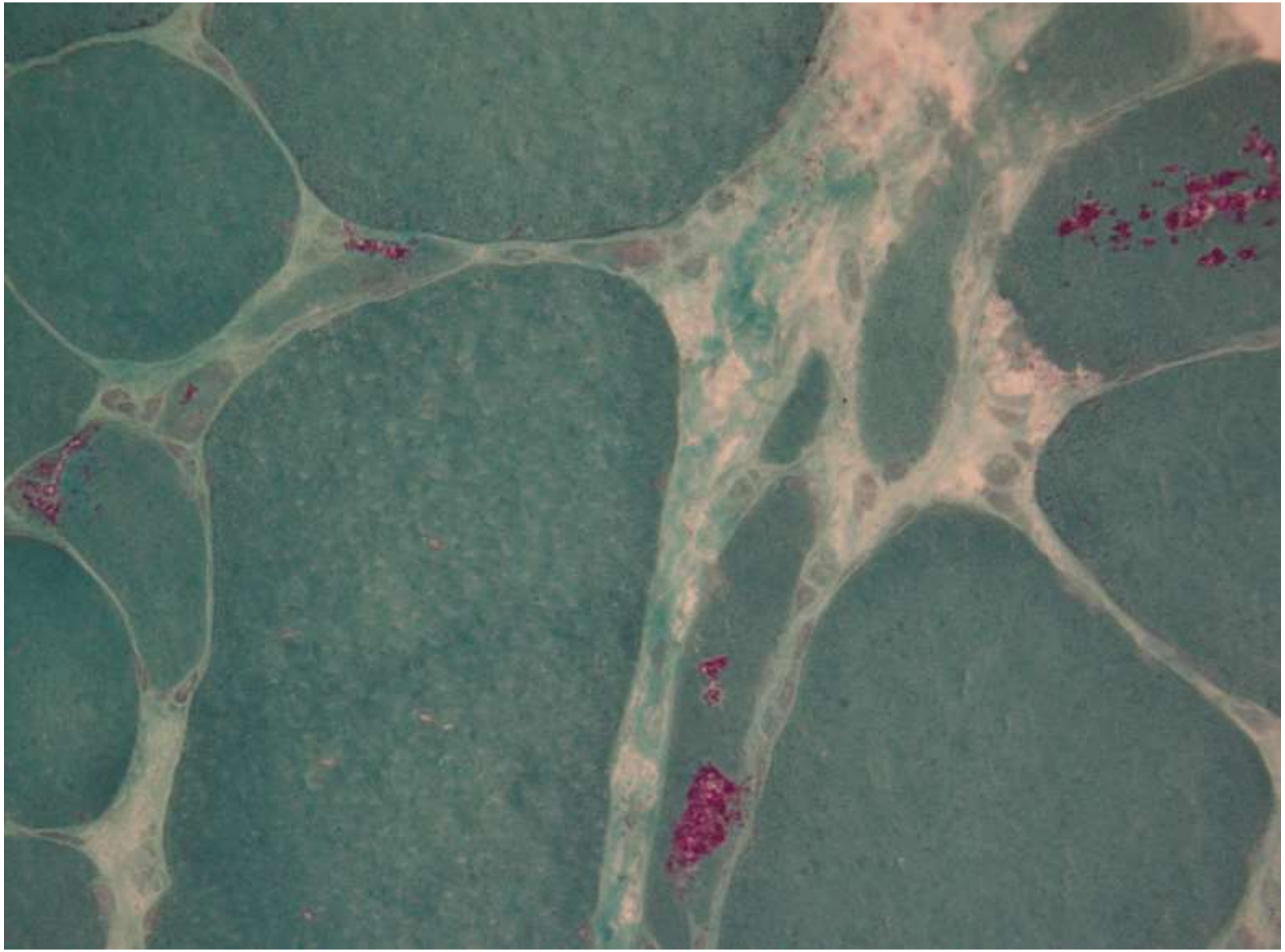
Μυοσίτιδα με έγκλειστα



H&E

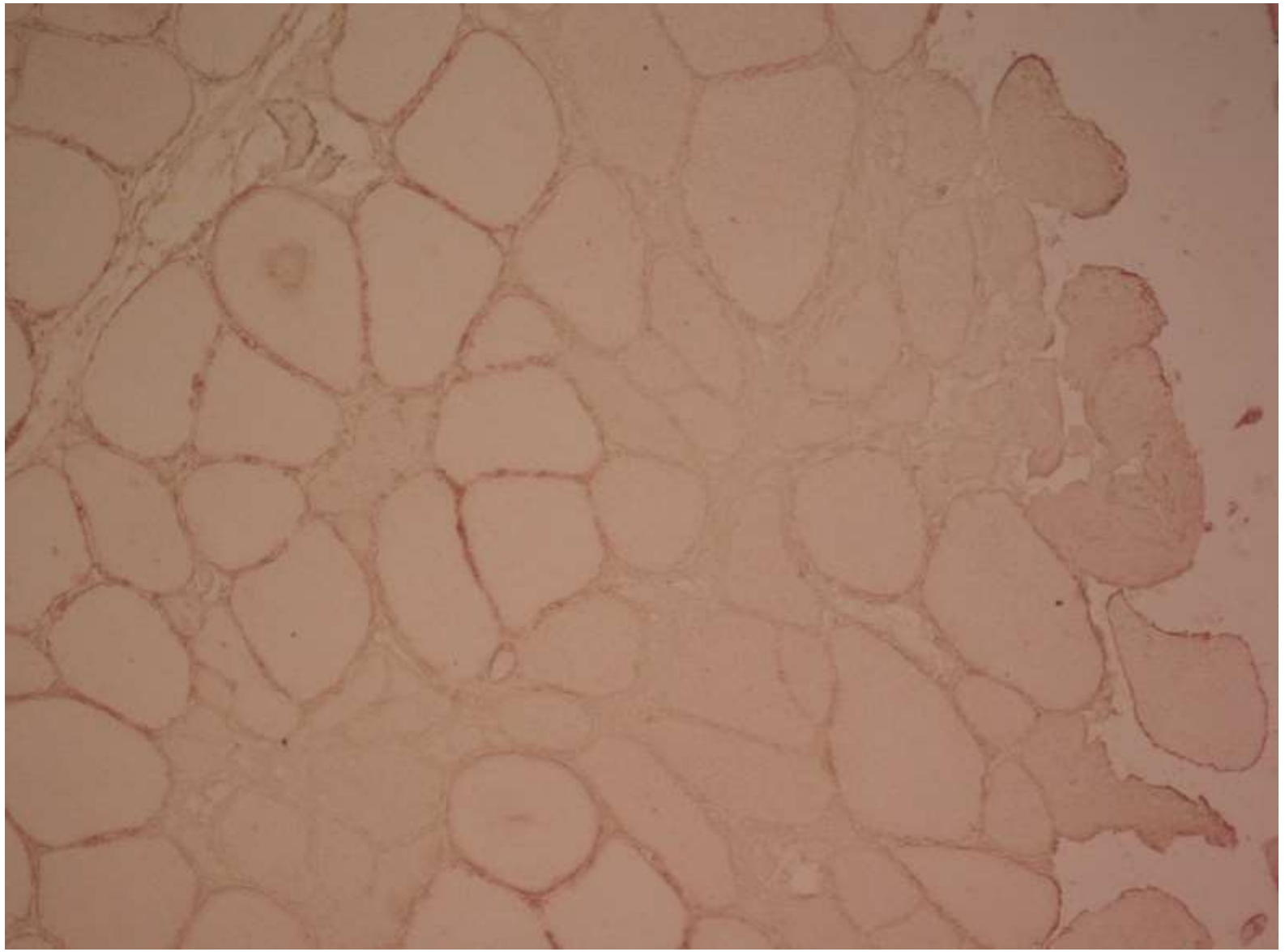


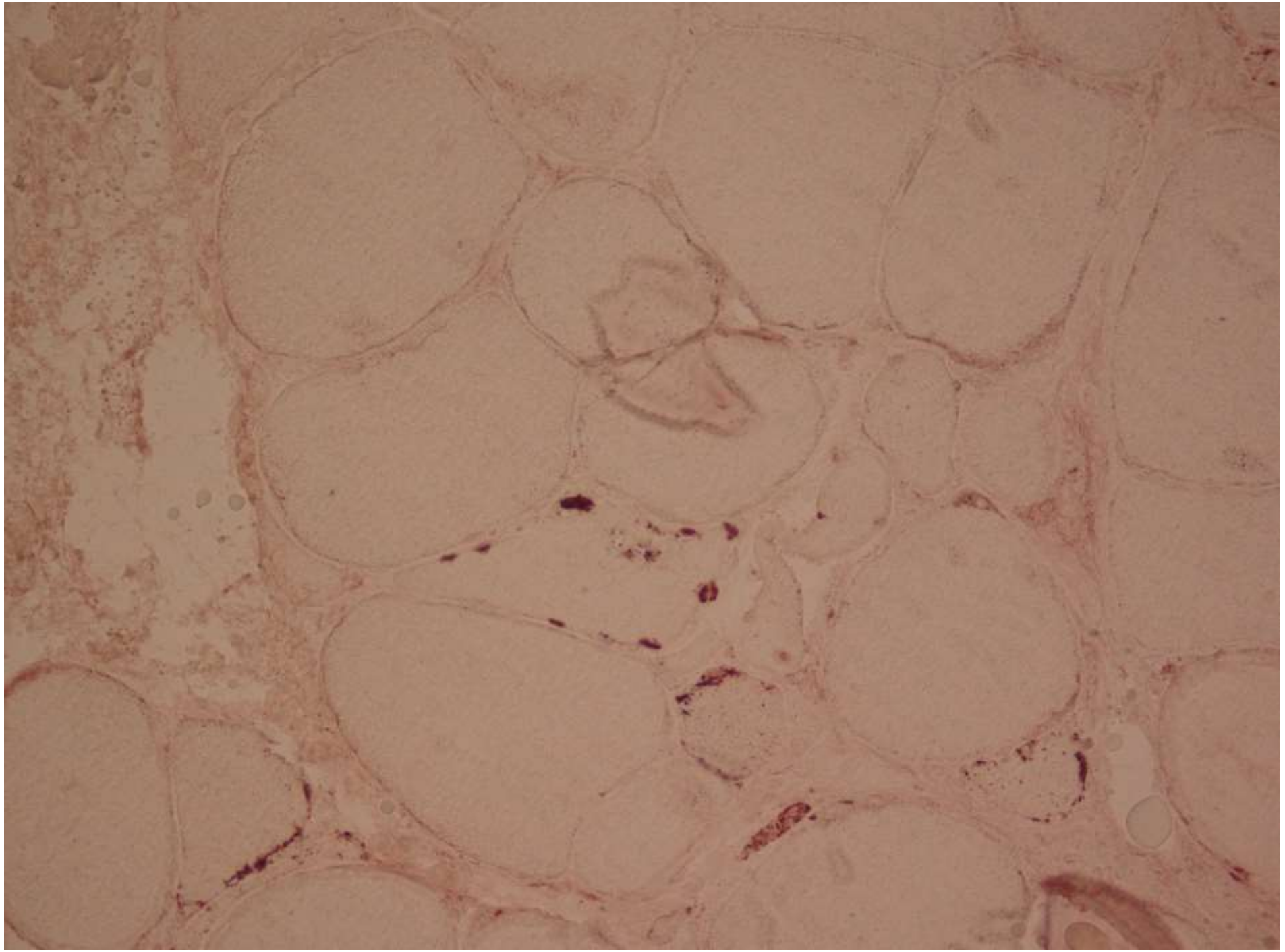
CD8



GMT

HLA-I





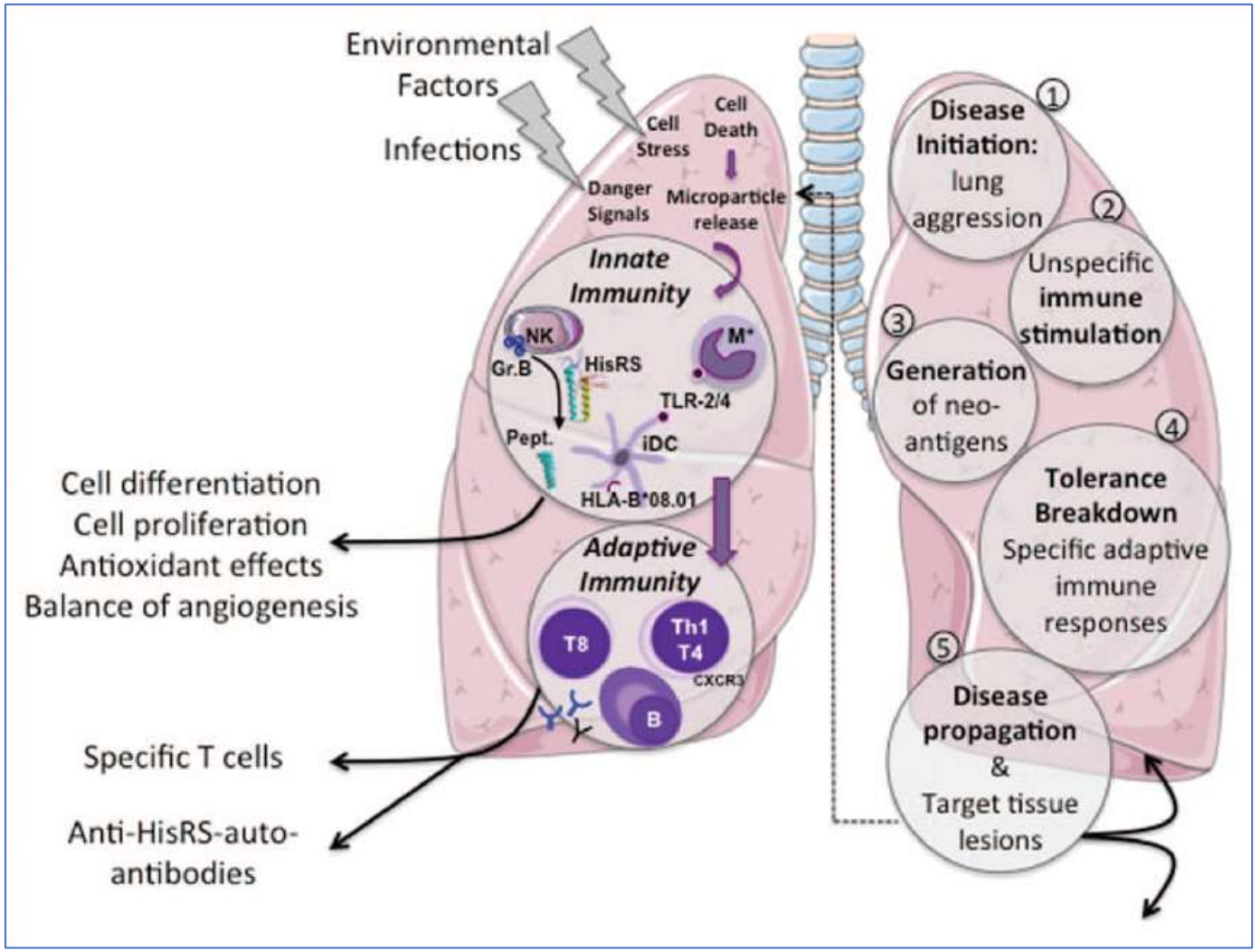
p62

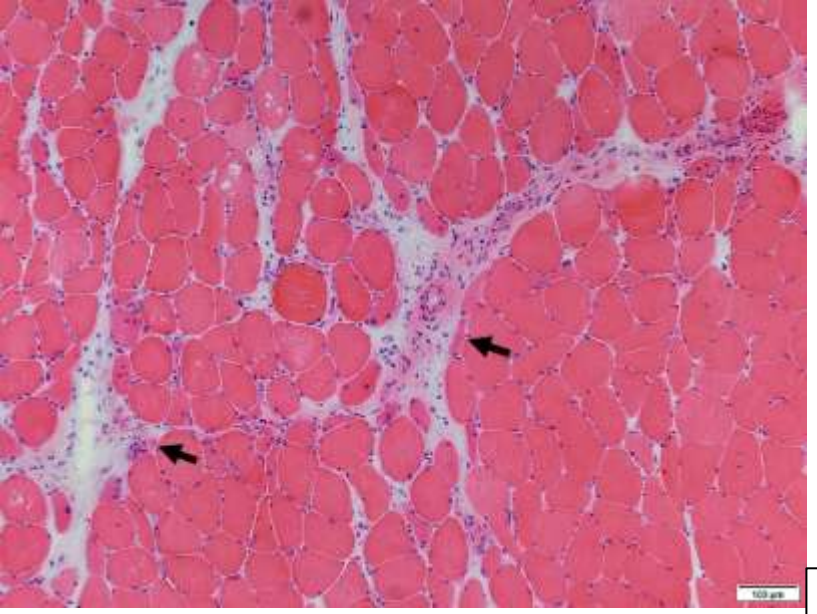
Σύνδρομο αντι-συνθετάσης

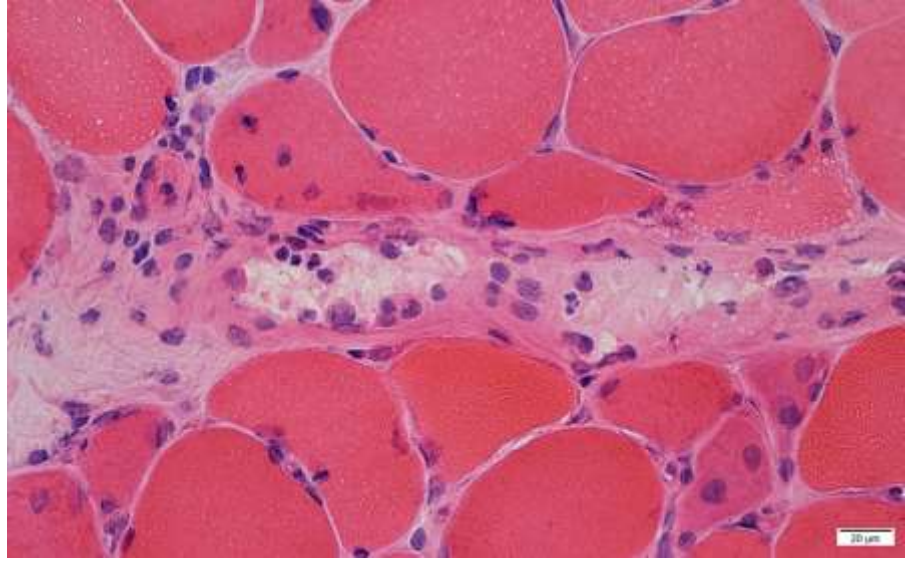
- Σχετικά ομοιογενής ομάδα ασθενών
  - 80% μυϊκή προσβολή
  - Εξωμυϊκές εκδήλώσεις
  - Πνευμονική συμμετοχή
    - Διάμεση πνευμονοπάθεια, μη ειδική πνευμονοπάθεια…
    - Η πρόγνωση καθορίζεται από την αναπνευστική προσβολή
    - Σπάνια οξεία εικόνα
  - 4% μυοκαρδίτιδα
  - **Δεν υπάρχει μεγαλύτερος κίνδυνος καρκίνου**
  - Ασθενείς ανθεκτικοί σε αγωγή, κάνουν συχνά υποτροπές

- Ειδική ιστοπαθολογική εικόνα
  - Immune myopathies with perimysial pathology
  - Βιοψία
    - Προσβάλλονται οι μυϊκές ίνες στην περιφέρεια των μυϊκών δεσμιδίων (**νέκρωση**, φαγοκυττάρωση, δ.δ. με κλασική δερματομυοσίτιδα όπου κυριαρχεί η ατροφία της νέκρωσης)
    - Οίδημα & κατακερματισμός περιμύιου
    - Διήθηση σε επιμύιο-περιμύιο

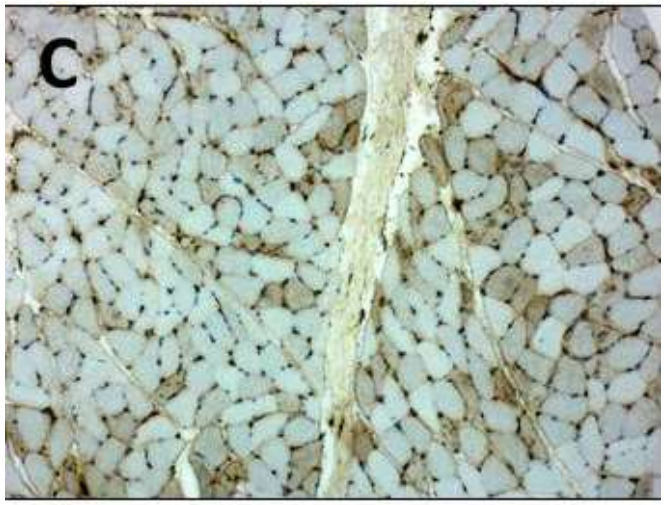
Παθοφυσιολογία

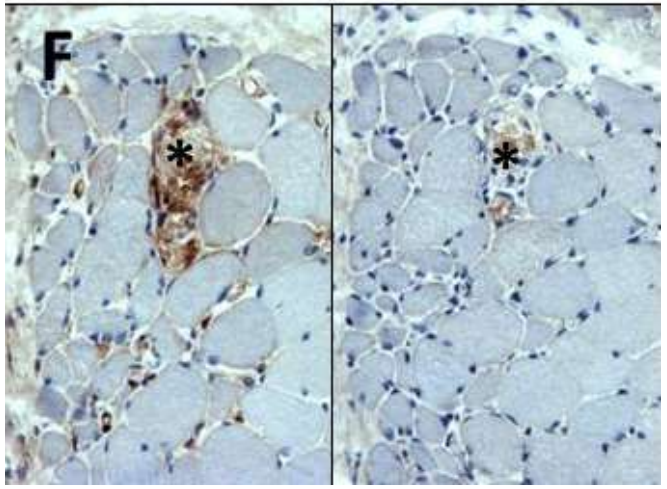




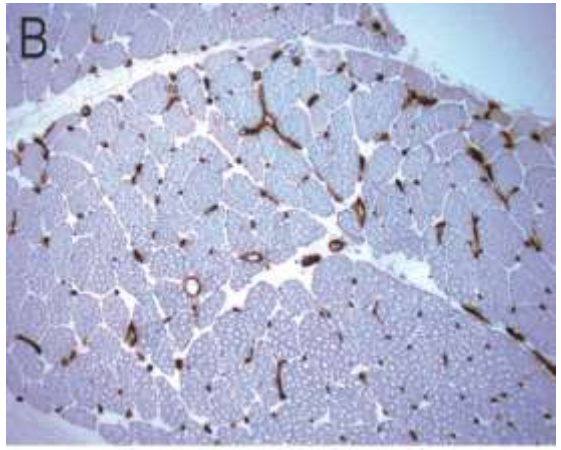


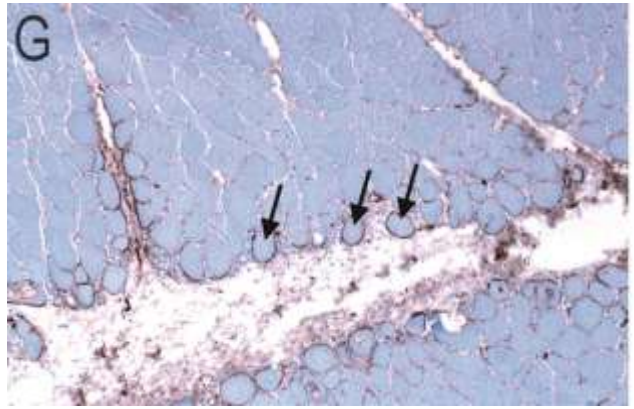
H&E





MxA





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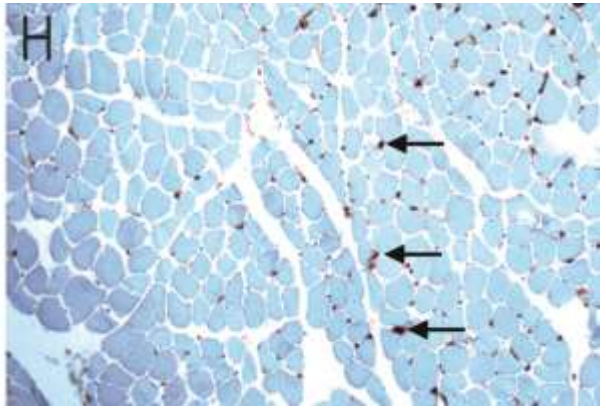
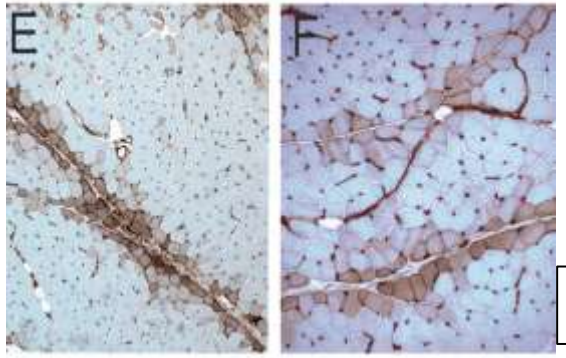
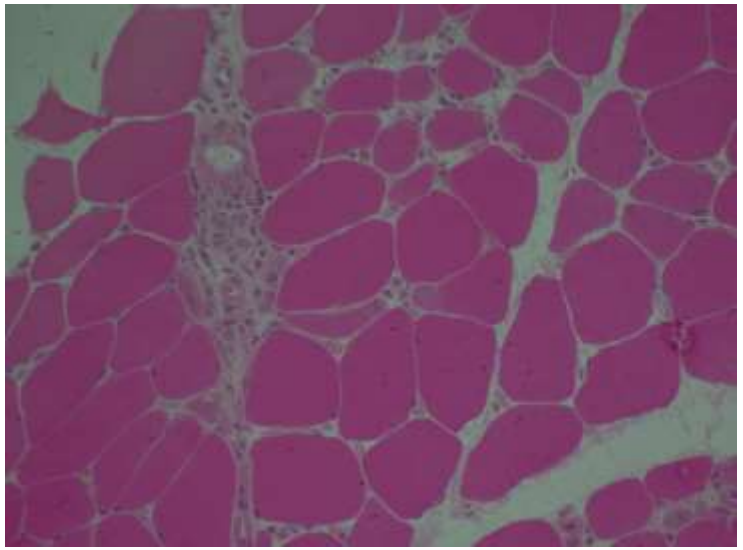


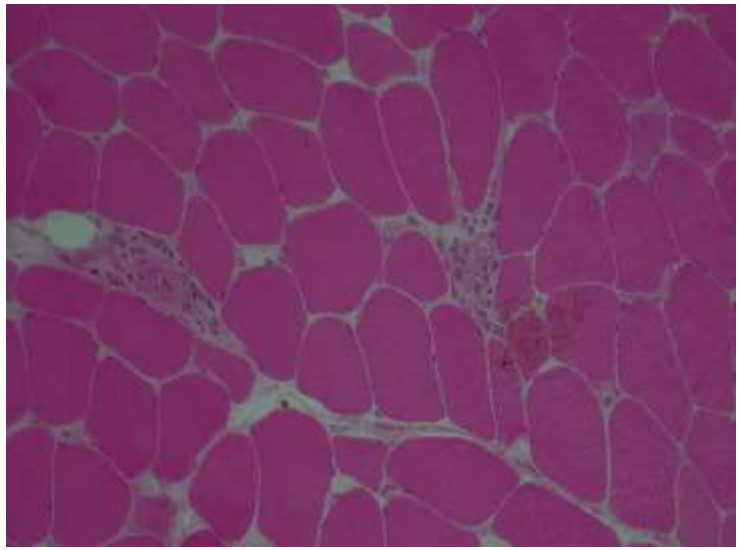


HLA-II

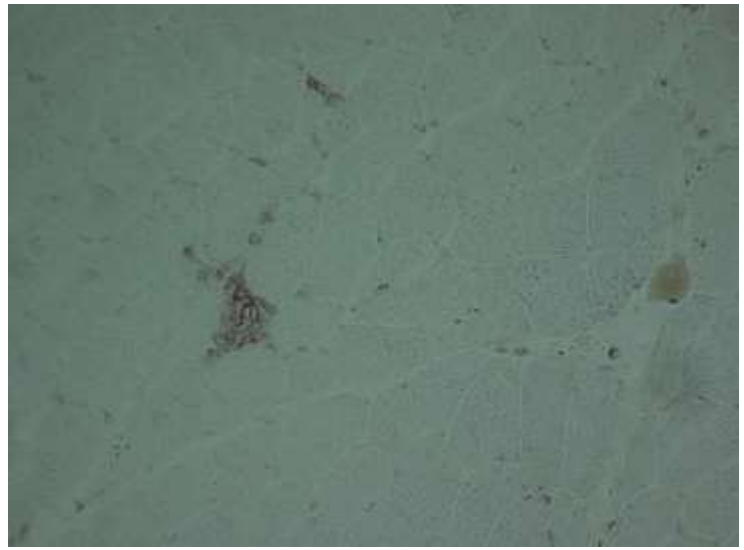
Μη ειδική μυοσίτιδα



H&E

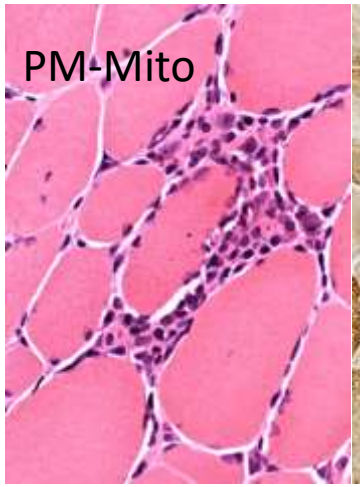


H&E



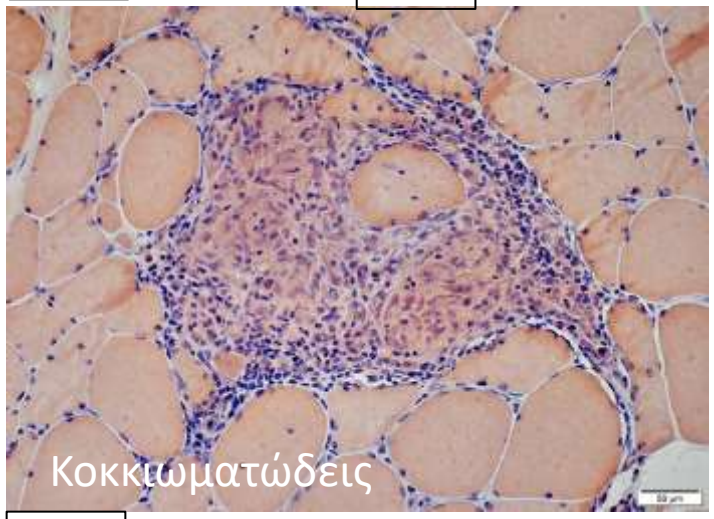
CD8

Άλλες σπάνιες μορφές

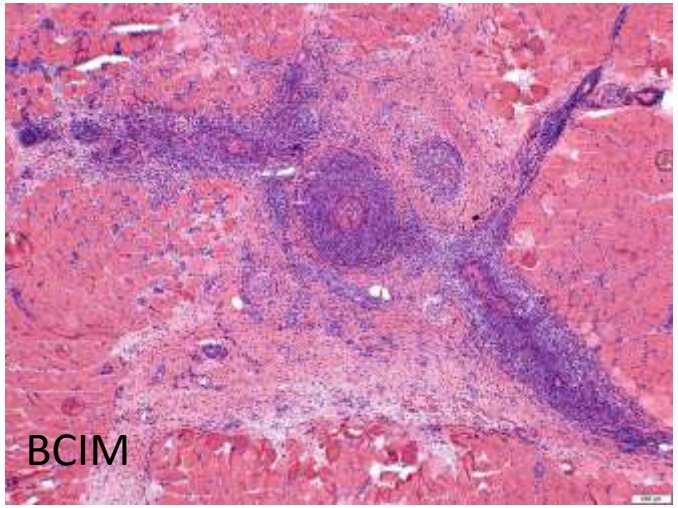


H&E

COX

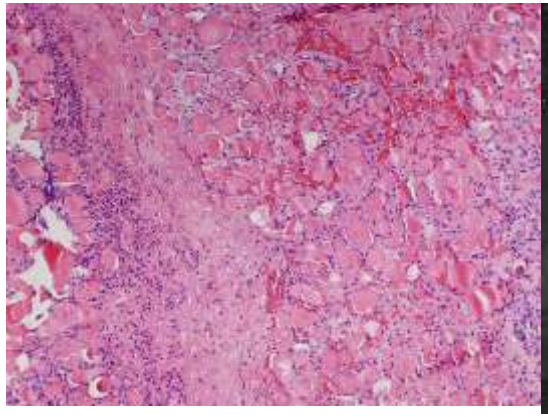


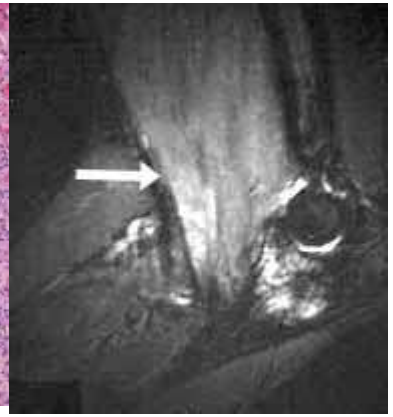
H&E



H&E

H&E

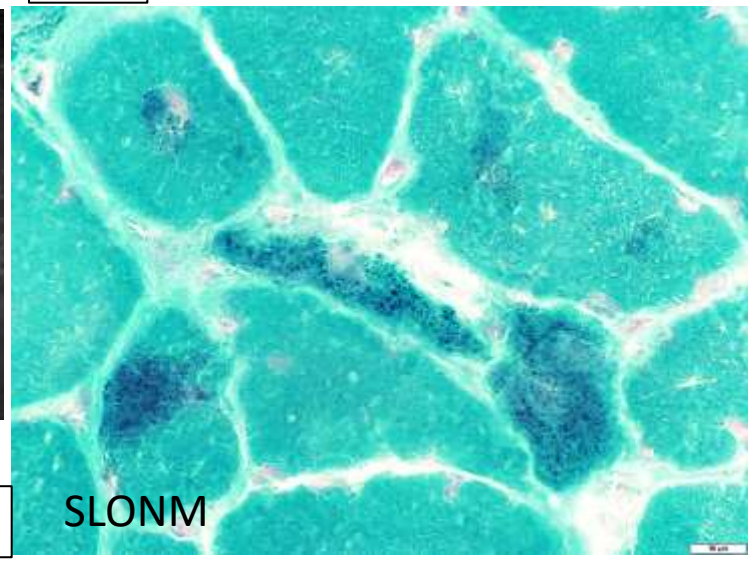


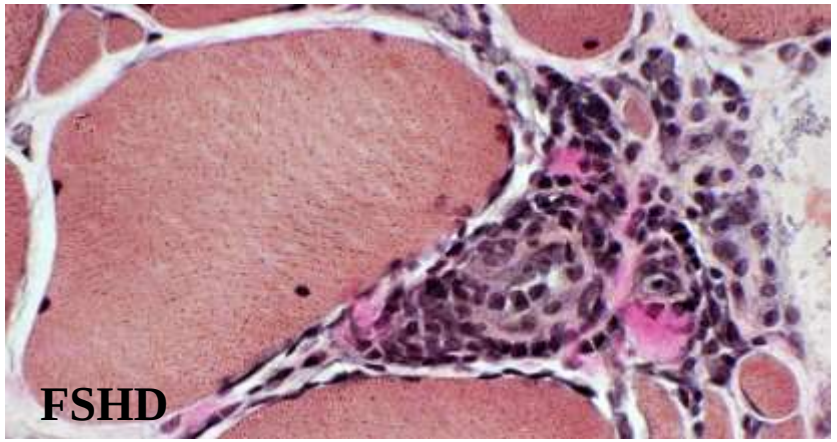


Εστιακή μυοσίτιδα

H&E

GMT

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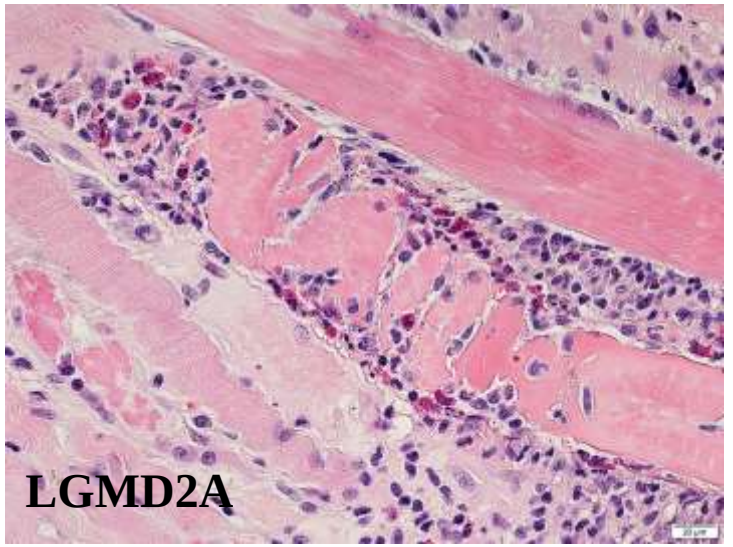
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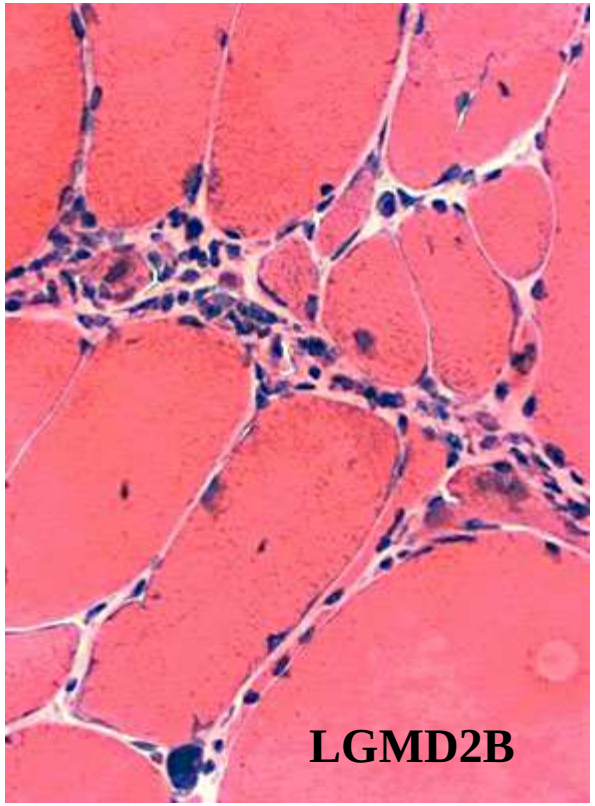
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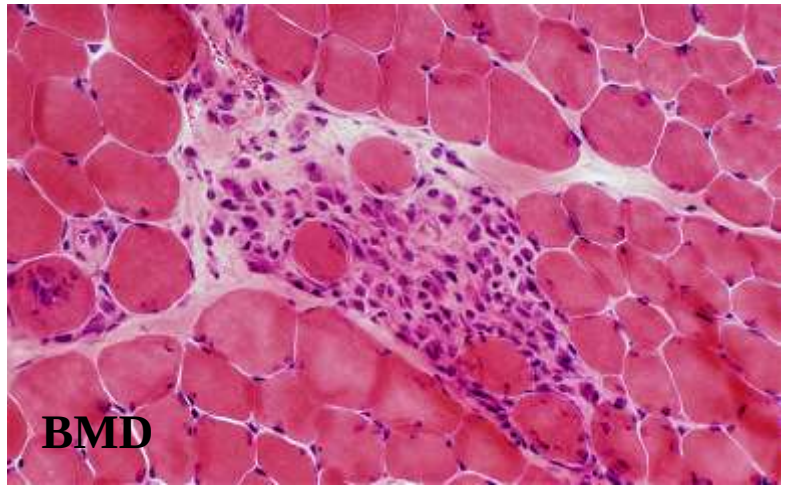
BMD

Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies

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Purpose of review

Inflammatory myopathy (IIM) classification criteria have been the source of considerable debate. In the three decades since Bohan and Peter published their criteria which have long stood as the gold standard for diagnosis in clinical practice as well as inclusion into clinical trials, more sophisticated understanding of immunopathogenesis, histology, and specific autoantibody associations has broadened our understanding of these diseases. This editorial review examines the diverse approaches between different subspecialists in deriving appropriate IIM classification utilizing this updated knowledge.

still, on some level, working side by side but not integrating our talents? It still appears that rheumatologists and neurologists do not have an active dialogue often enough. Broadly speaking, neurologists with neuromuscular expertise are specialized in diagnosis utilizing electromyography and muscle biopsy interpretation. Rheumatologists, on the contrary, are typically trained in making a clinical diagnosis, understanding the role of autoantibody association, and appreciating the directed approach to utilizing a broad array of immunosuppressive therapies. The fact that both types of specialists care for myositis patients, however, begs for further integrative care and a deeper understanding of each other's knowledge with regard to the emerging nuances within a phenotype in patients with these rare diseases. Such a meeting of the minds would be well served by a common

Conclusion

In the era of large consensus groups, the development of comprehensive classification criteria that reflects our enhanced knowledge of these diseases over the past three decades is a reality. We need to step out of our historical comfort zones and work side by side. Rheumatologists and neurologists have been seeing the same patients, noting the same symptoms, and coming to diagnoses that are inconsistent. Our various tools and training result in different nomenclature. In my personal experience, effective communication and synergy between subspecialists have allowed us to use all the tools in the two specialties' bags, enabling us to come to a consistent conclusion. In practice, clinical observations and understanding of differential responses to therapy should be predicated on meticulous phenotyping of patients correctly from the onset – with updating in real time as new relevant discoveries are made. Only then will we all reside on the same planet.

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