Crafting a Meaningful Muscle Pathology Report - Dermatomyositis and its Mimickers.

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Disclosures

- I have no relevant financial relationships to disclose

Learning Objectives

- Learning Objective #1: distinguish dermatomyositis autoantibody subtypes by pathology on muscle biopsy.

- Learning Objective #2:: identify appropriate ancillary studies to differentiate dermatomyositis from other types of myositides with a perifascicular injury pattern.

- Learning Objective #3:discuss the most essential qualities of muscle/nerve pathology reports in communicating with treating physicians.

Current ENMC consensus guideline – a *clinico-sero-pathological* classification of inflammatory myopathies

205th ENMC International Workshop:
Pathology diagnosis of idiopathic inflammatory myopathies Part II
28–30 March 2014, Naarden, The Netherlands

239th ENMC International Workshop:
Classification of dermatomyositis,
Amsterdam, the Netherlands, 14–16 December 2018

256th ENMC international workshop:
Myositis specific and associated autoantibodies (MSA-ab):
Amsterdam, The Netherlands, 8-10 October 2021

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Clinico-sero-pathological classification of inflammatory myopathies

Idiopathic inflammatory myositis

- Dermatomyositis (DM)
- Antisynthetase syndrome associated myositis (ASyS)
- Immune mediated necrotizing myopathy (IMNM)
- Inclusion body myositis (IBM)

Table 1: IIM subtypes and their associated autoantibodies	
DM	Mi2, NXP2, TNF-γ, MDA5, SAE
IBM	cN1A*
IMNM	SRP, HMGCR
ASyS	Jo-1, PL7, PL12, EJ, OJ, KS, Zo, Ha

*MSAs are usually mutually exclusive and specific for IIM subclasses, with the exception of cN1A, which is present in 30-70% of sIBM, but also found in dermatomyositis, Sjogren's and Lupus.

- MSA testing is preferentially performed prior to immune suppression.
- Should also be performed in patients with suspected IIM or interstitial lung disease of unknown etiology without prior MSA testing.

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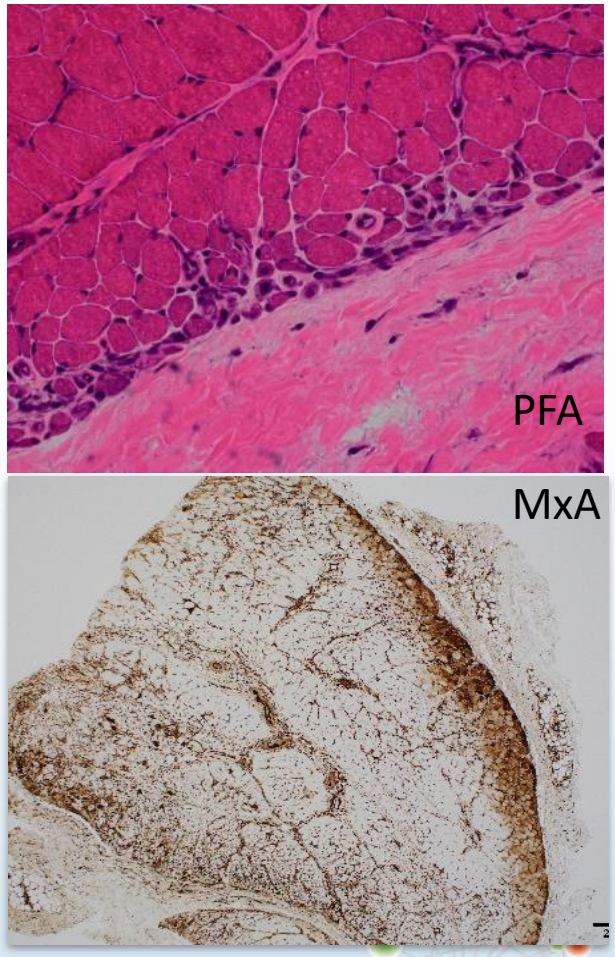
2019 ENMC dermatomyositis classification criteria

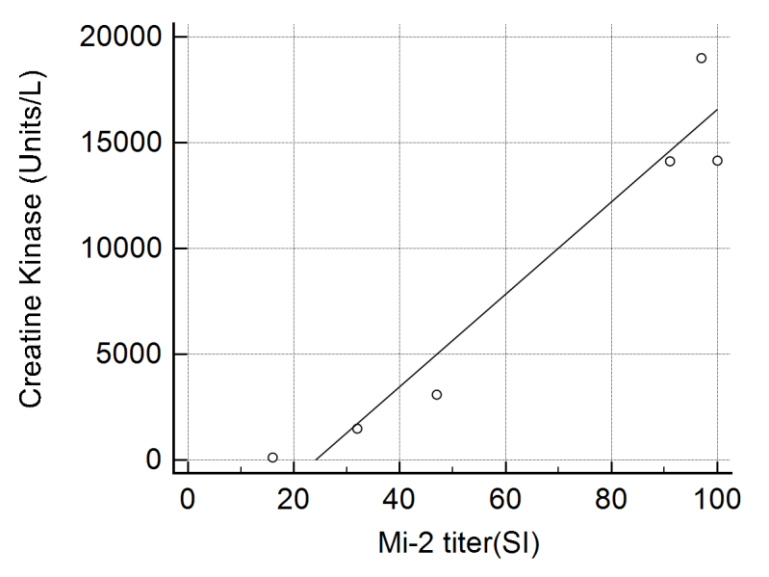
- DM dx can be made in 3 ways clinically
  - DM Rash+ skin bx (interface dermatitis)
  - DM Rash+ muscle bx
  - DM Rash+ DM MSA
- Muscle bx criteria:
  - Definitive:
    - Perifascicular atrophy and/or perifascicular MxA overexpression *with rare or absent necrosis*
  - Suggestive (if combined with proximal weakness or elevated CK)
    - Perifascicular disease (perifascicular fibers pale on COX and/or NCAM positive)
    - Lymphocytic inflammation, often perivascular
- Notes:
  - DM cannot be made without characteristic DM rashes.
  - DM specific autoantibodies: NXP2, TIF1y, Mi-2, MDA5, SAE1, define DM subtypes
  - Non-DM MSAs(HMGCR, SRP, Jo-1)exclude DM
  - DM without a DM-specific autoantibody will be subclassified as having “autoantibody negative DM”

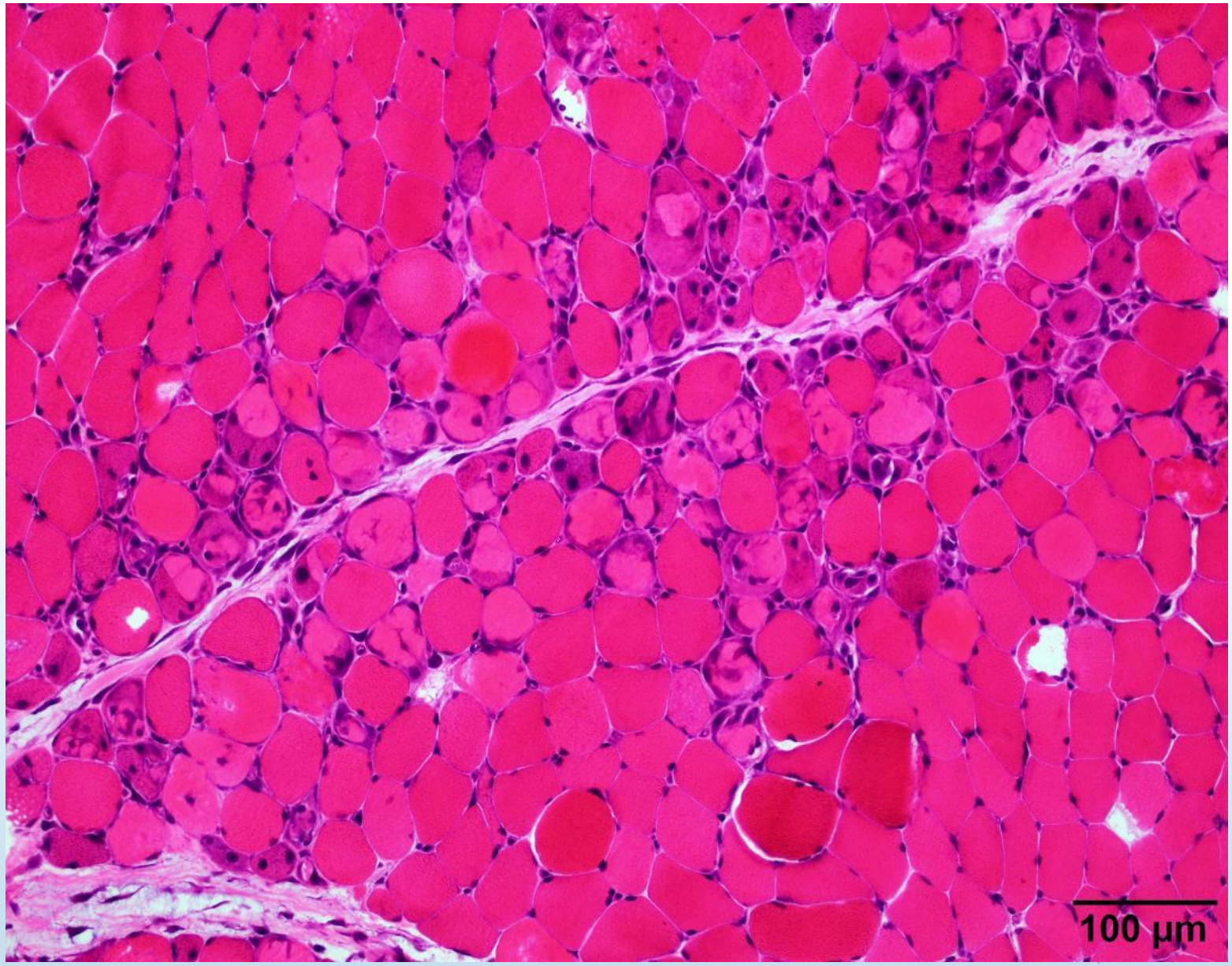


Mammen, et al. (2019). "239th ENMC International Workshop: Classification of dermatomyositis." Neuromuscul Disord.

DM– Mi2 subtype

- Clinical
  - Severe weakness
  - Highest CK -10,000
  - CK/Mi2 titer correlation
- Pathology
  - **Perifascicular necrosis**

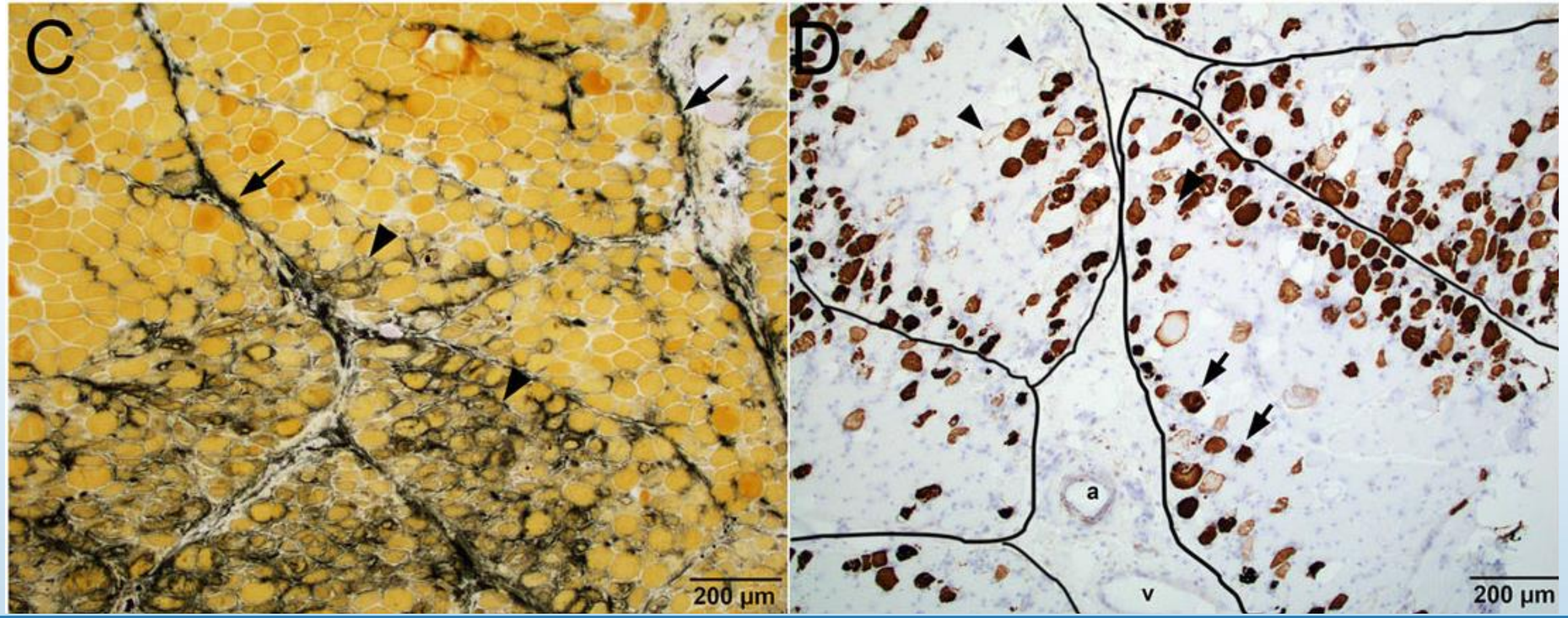




Mi-2, high titer, high CK

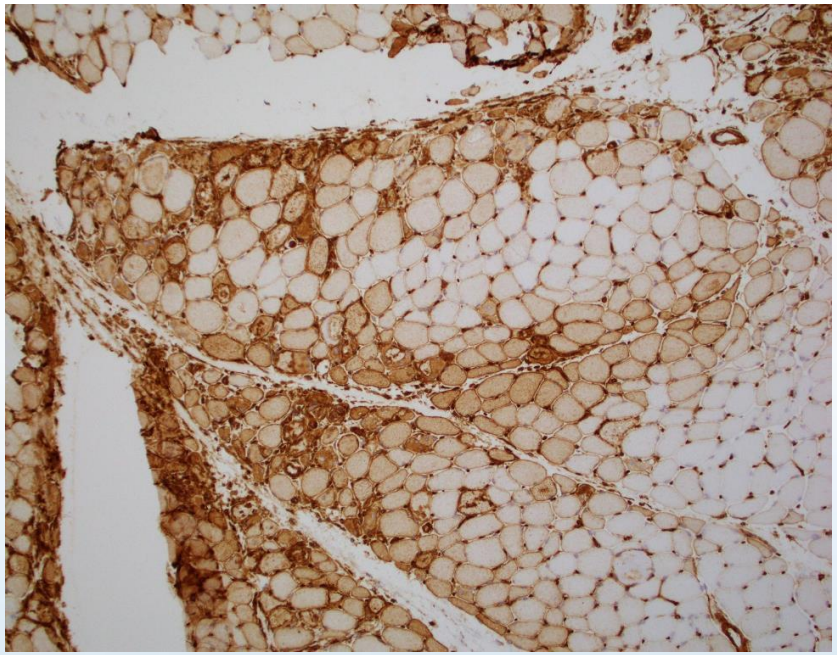
Alk Phos

C5b-9

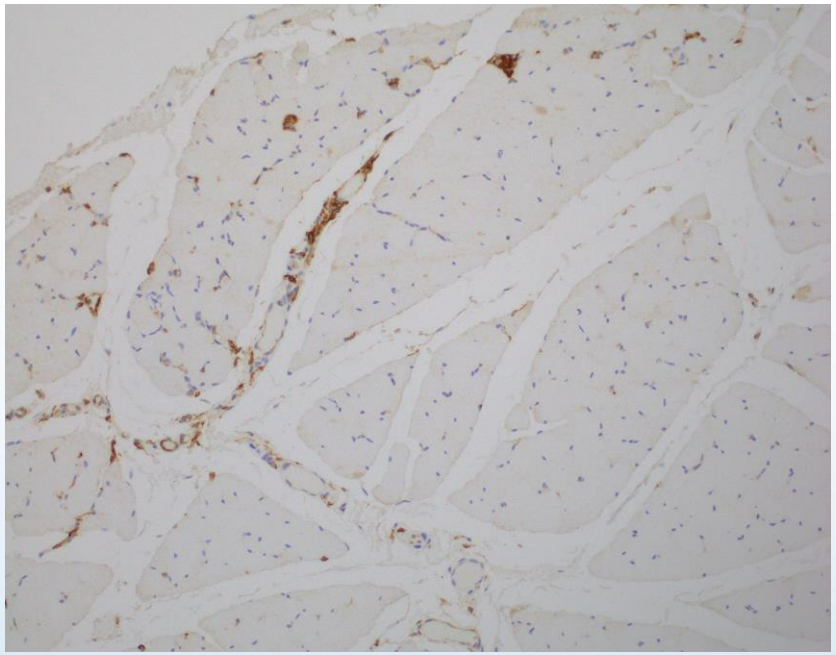


Mi-2: other helpful IHCs

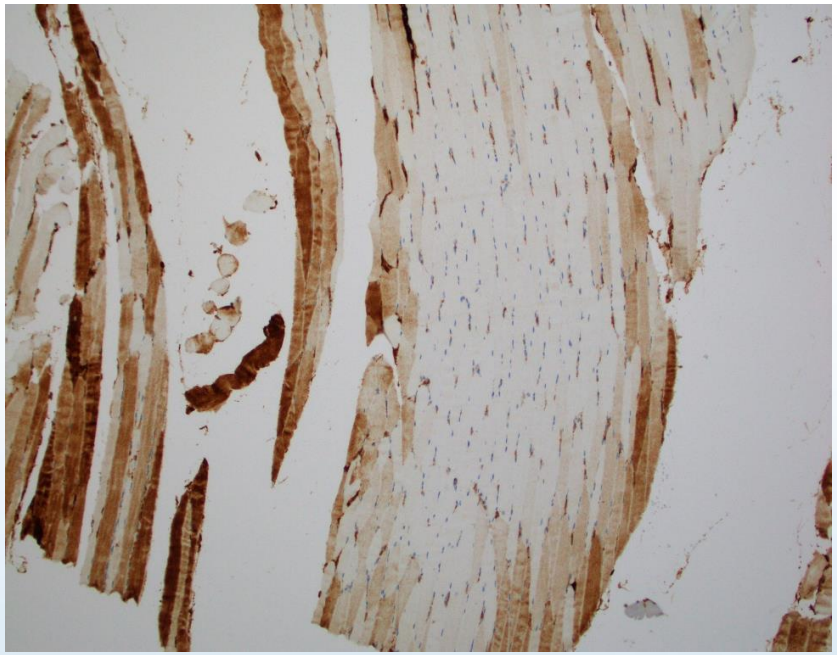
MHC1



MHC2

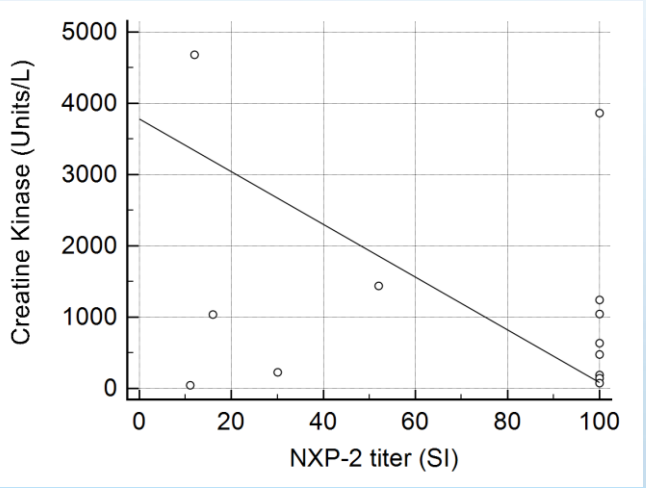


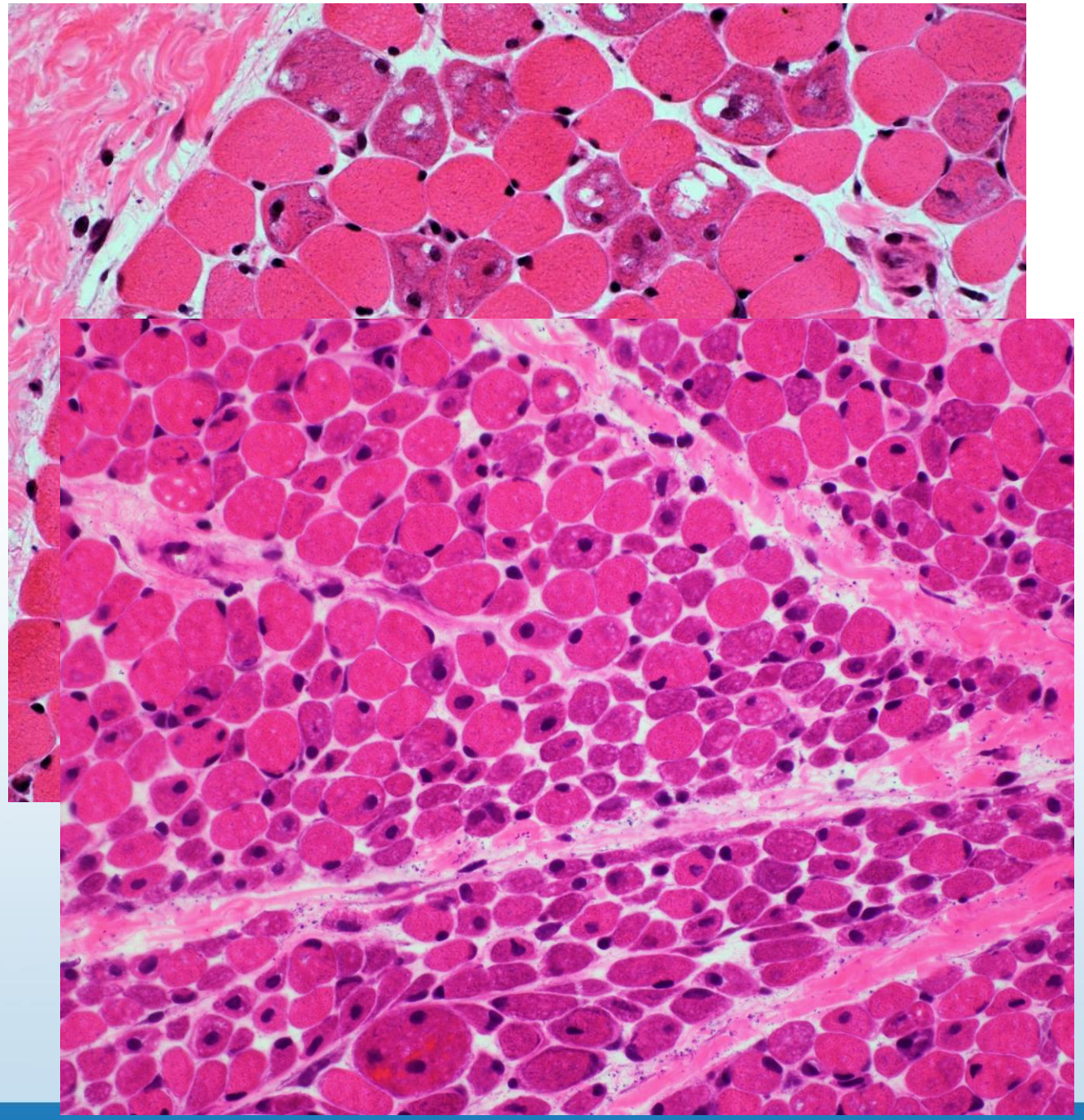
MxA



DM–NXP2, TIF1y

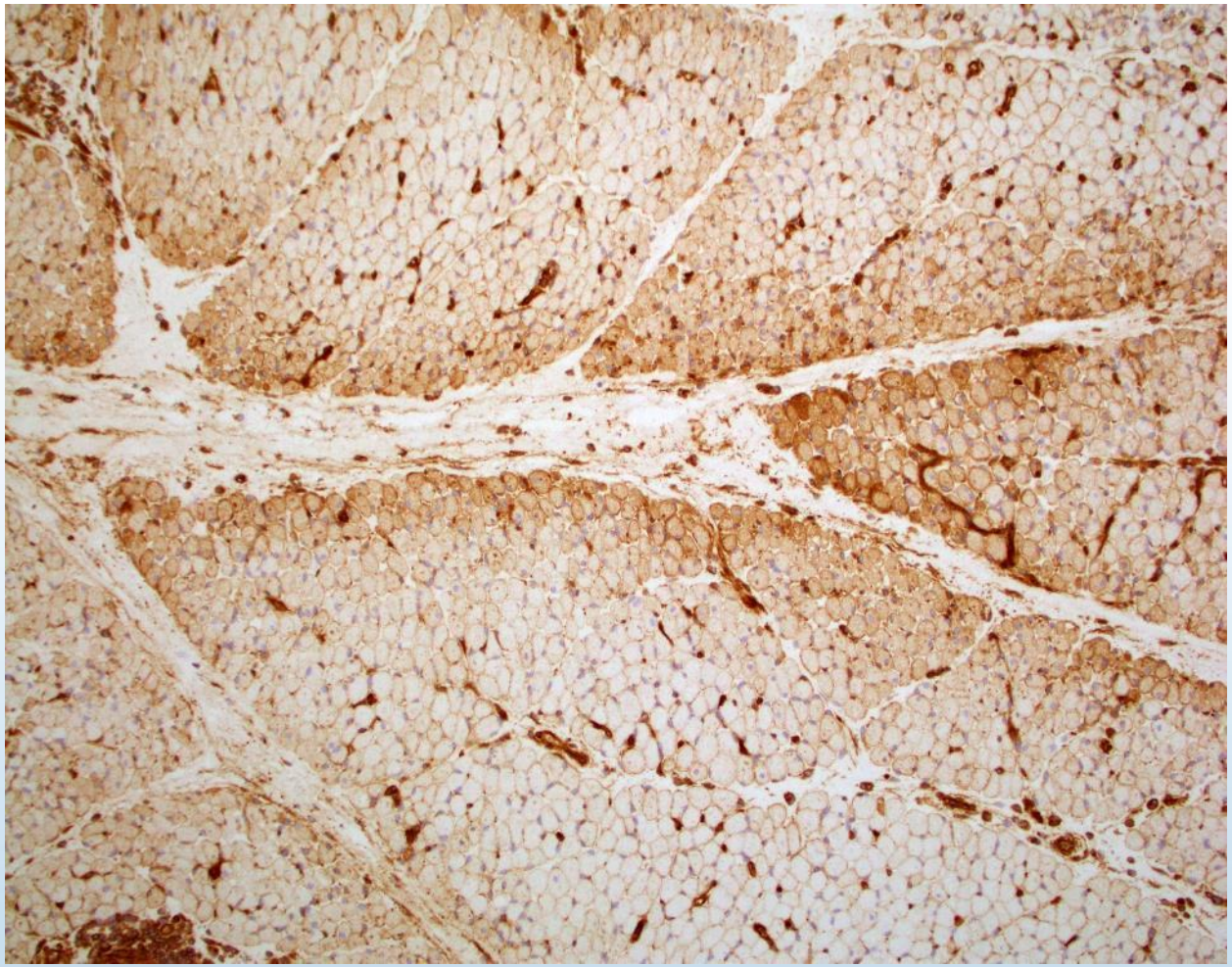
- Clinical
  - NXP2
    - CK varies, no correlation to NXP2 titer
    - GI bleed, calcinosis in children
    - Malignancy in adults
  - TIF1y
    - Older
    - Dysphagia
    - Highest malignancy association
- Pathology
  - Early phase: Vacuolar basophilic fibers
  - Perifascicular atrophy



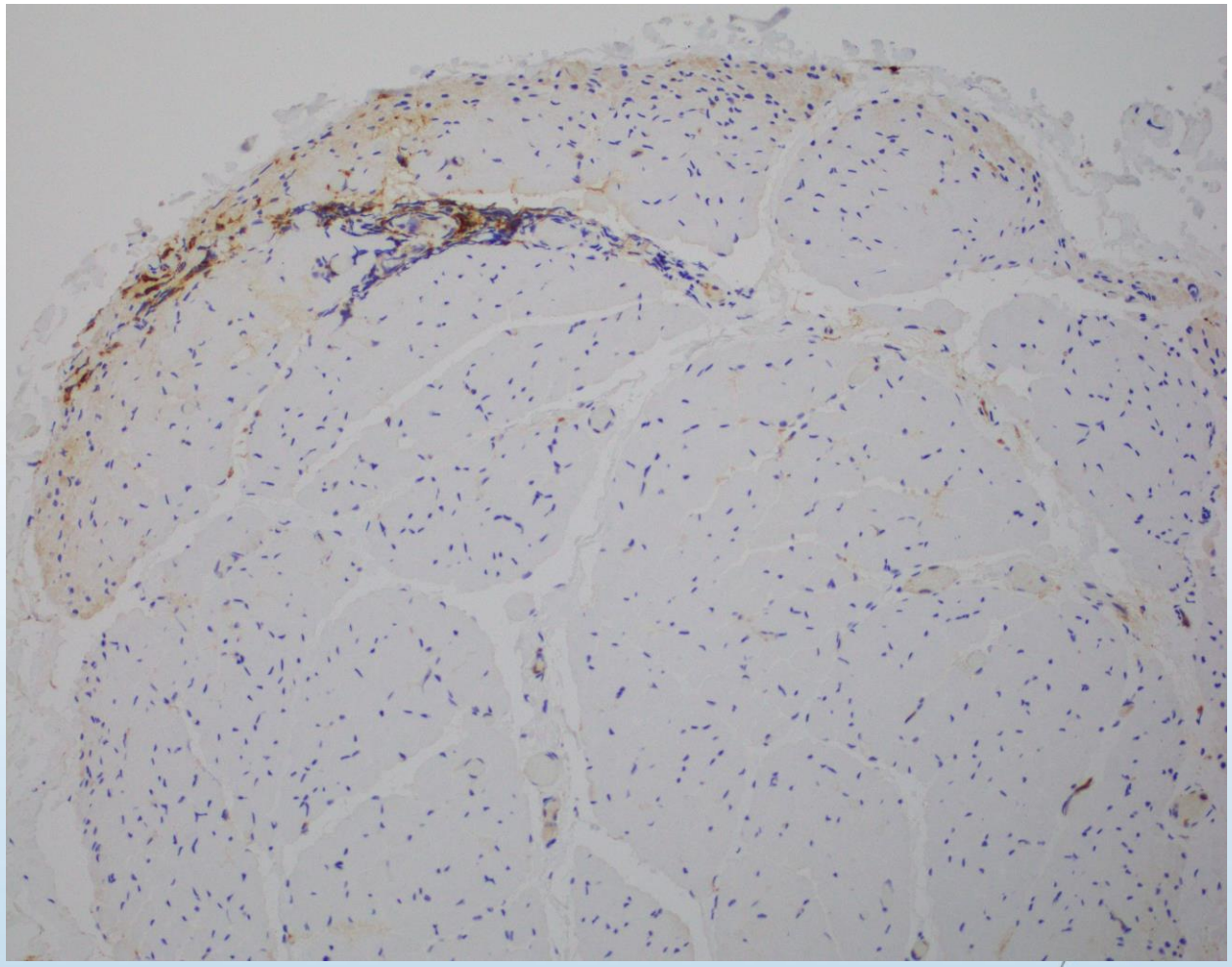


NXP-2 dermatomyositis

MHC1

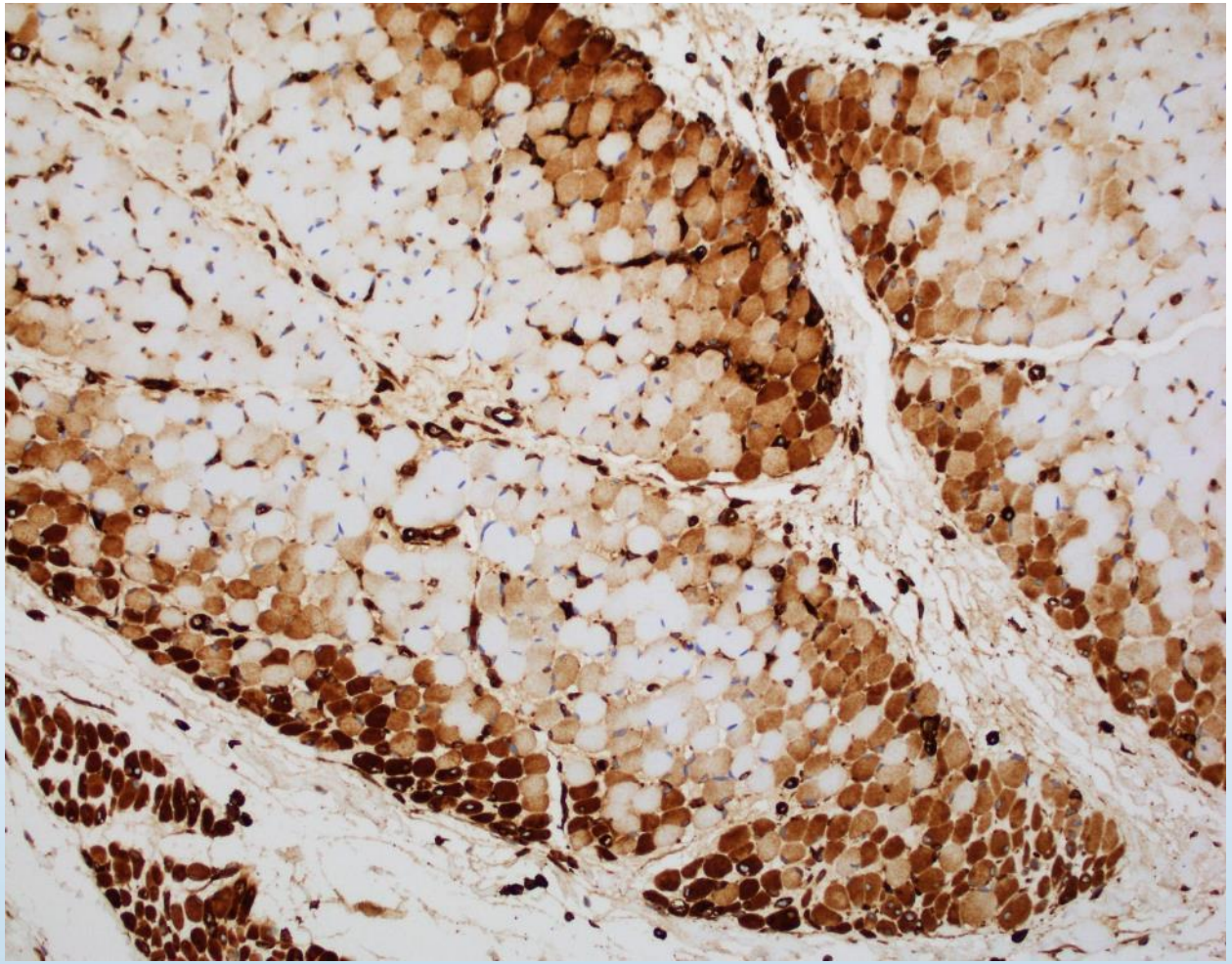


MHC2

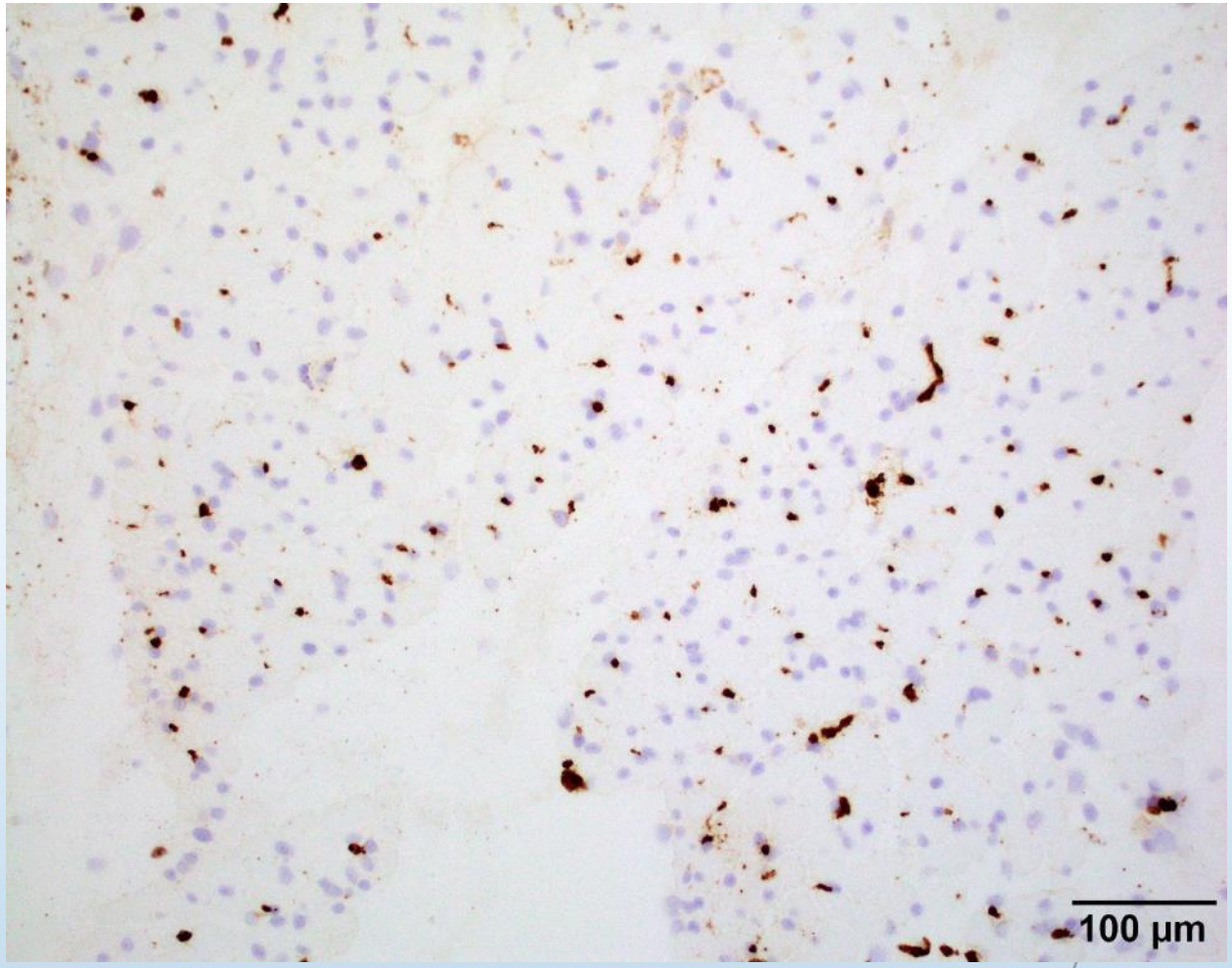


NXP-2 dermatomyositis

MxA

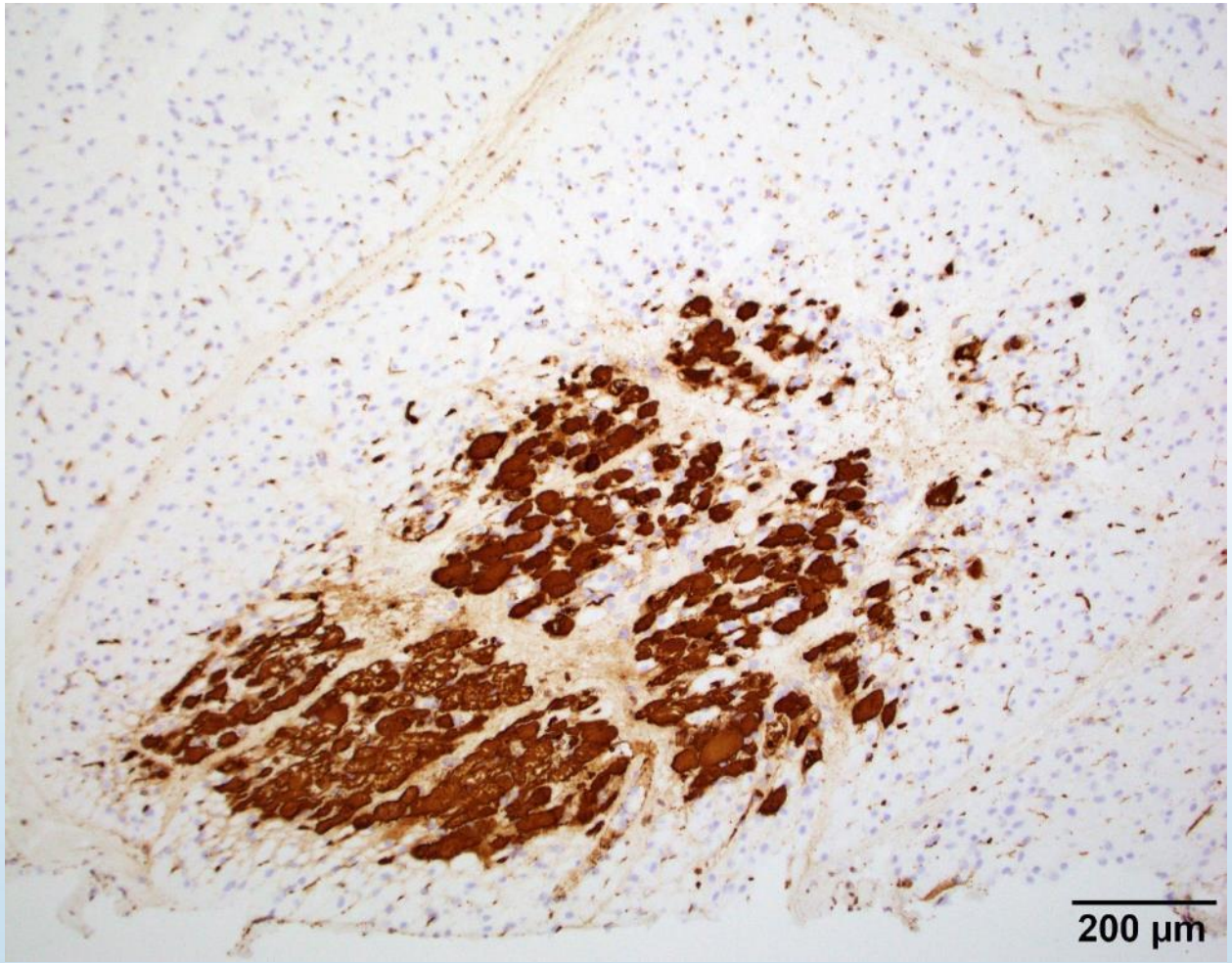


C5b-9

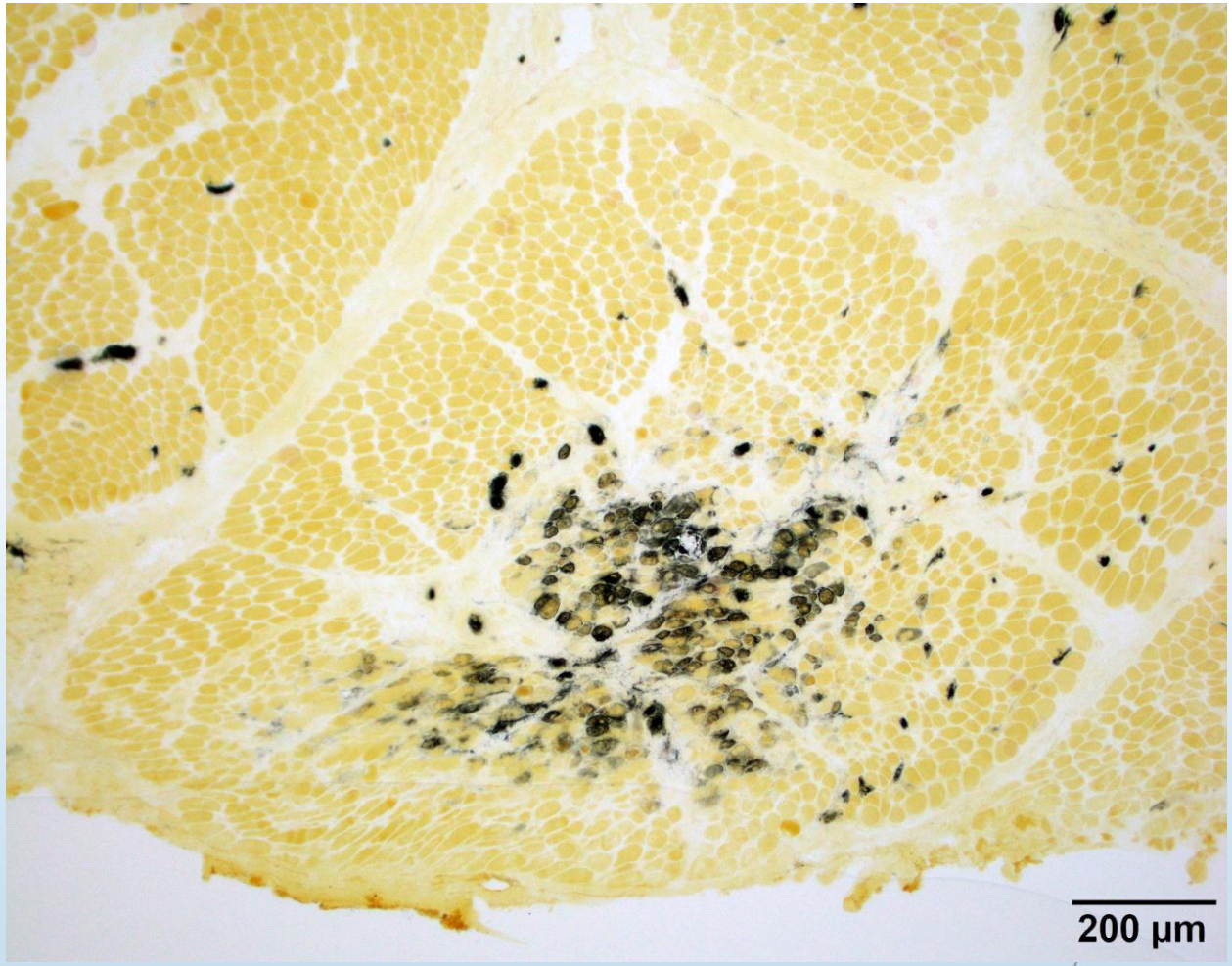


NXP-2: micro-infarcts

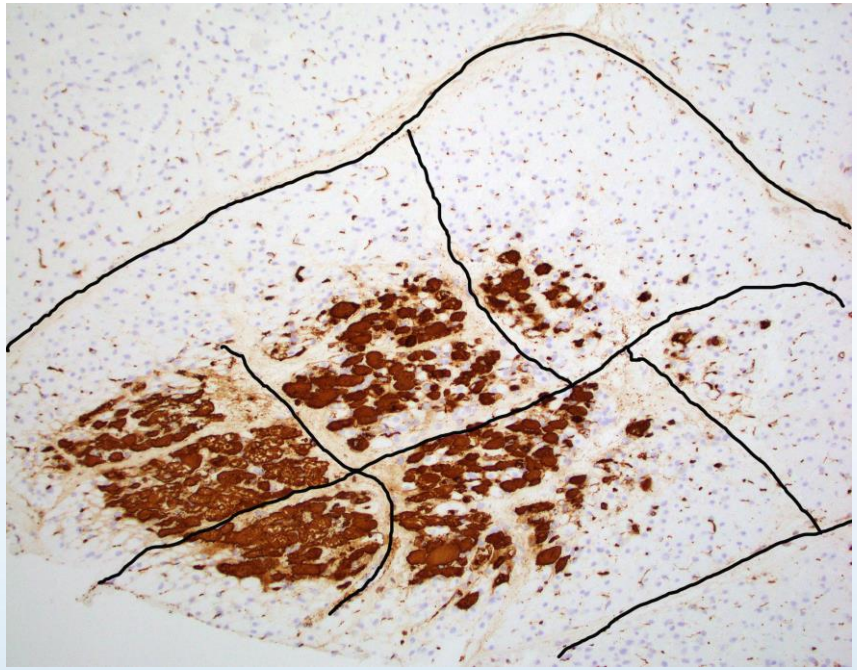
C5b-9



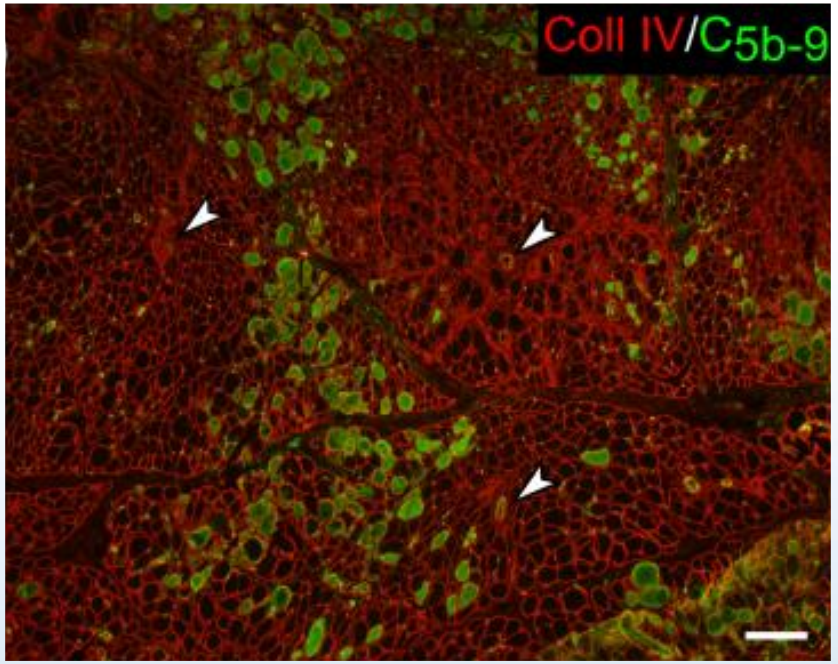
ALK phos



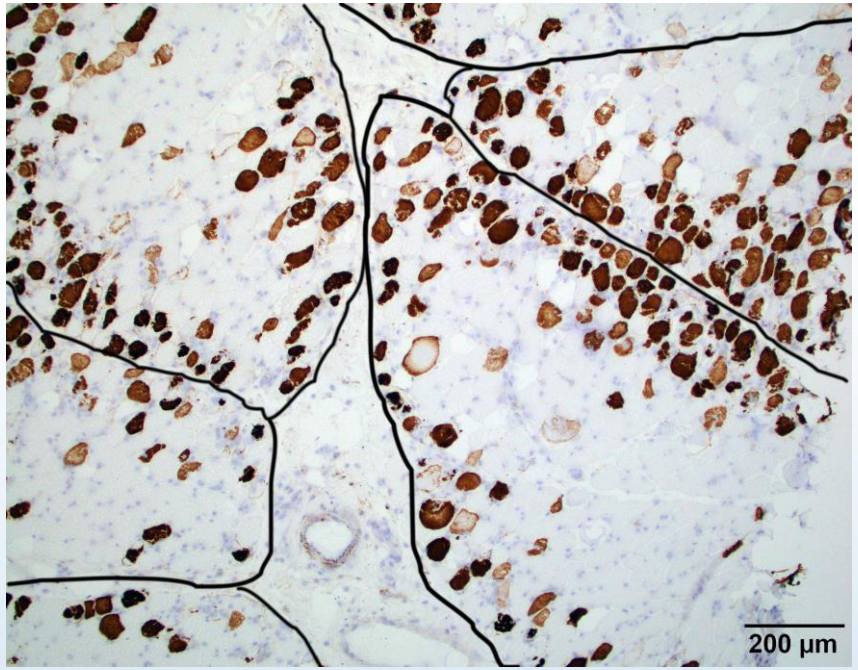
Infarct vs confluent perifascicular necrosis



Infarct



Border zone infarct pattern



Perifascicular necrosis

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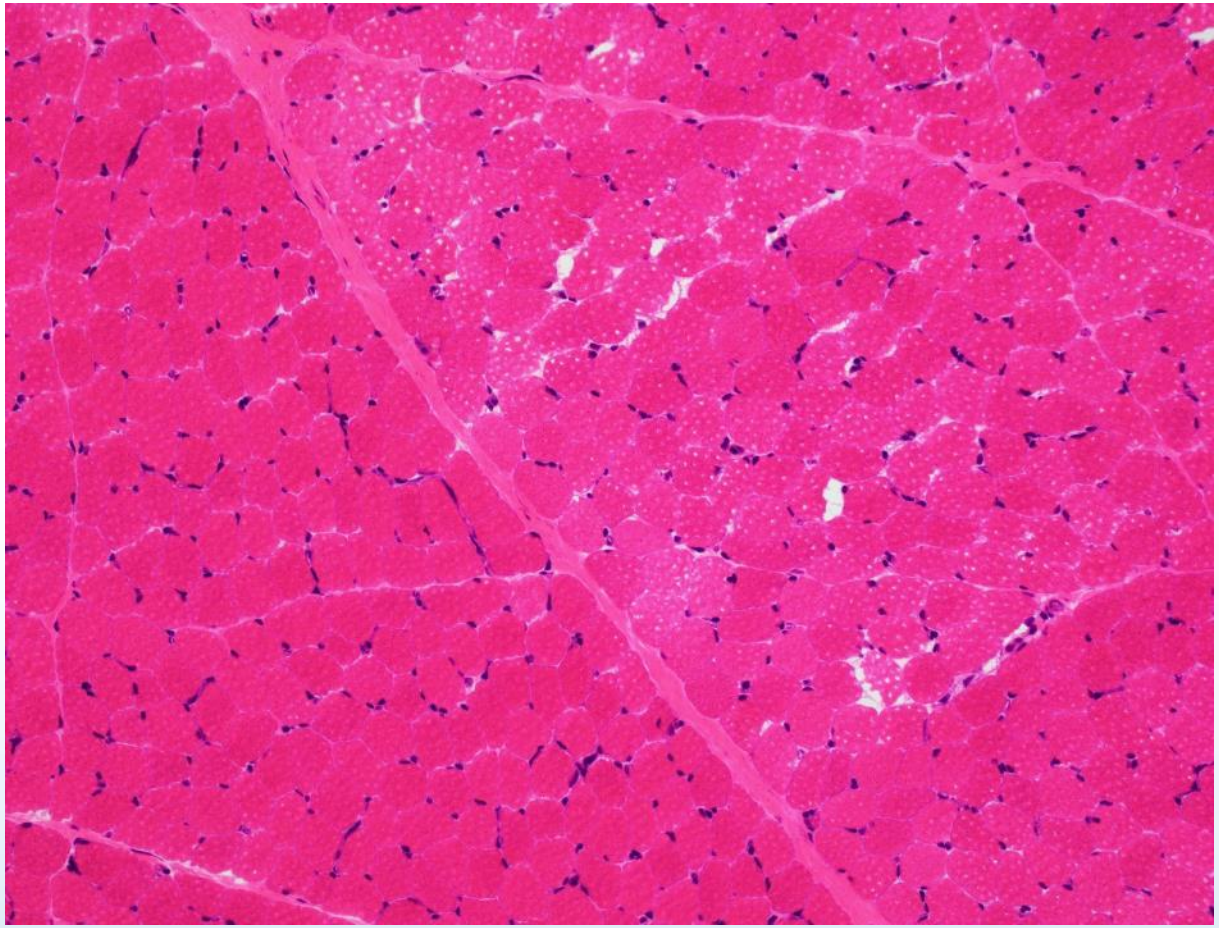
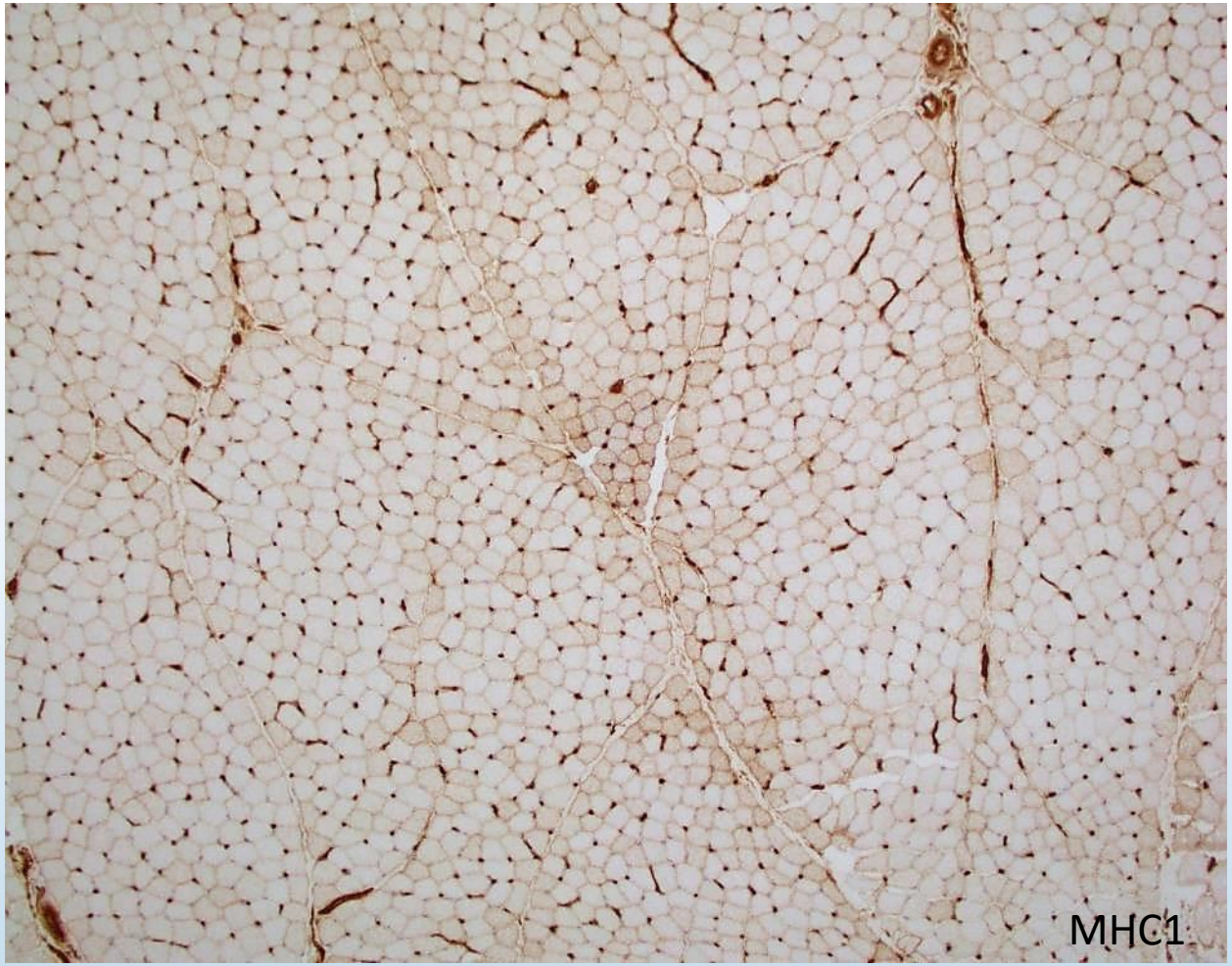
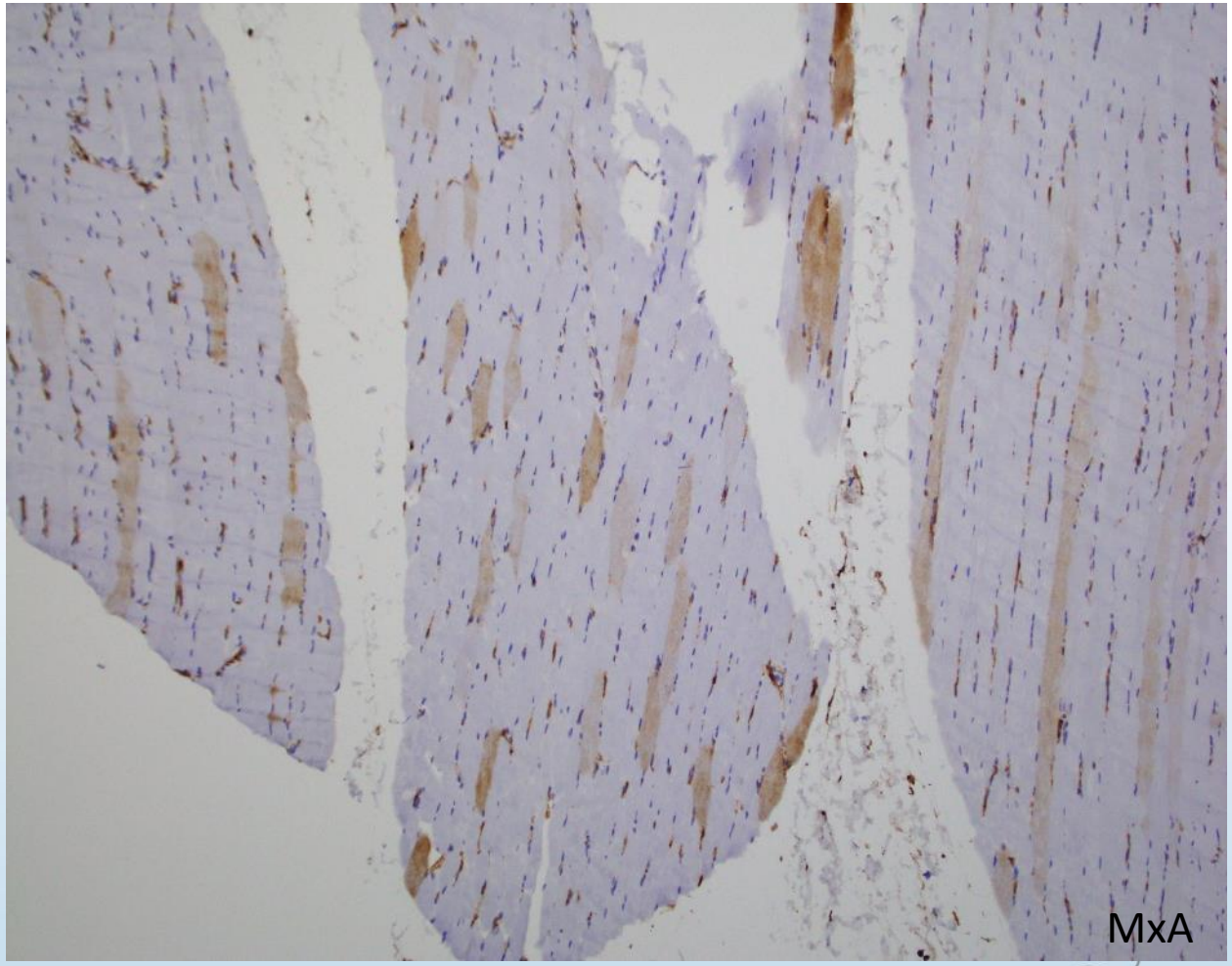
DM–MDA5

- Clinical
  - Mechanic hands, skin ulcers, ILD
  - Amyopathic/less weakness, low CK
  - Not associated with malignancy
  - Worst prognosis
- Pathology
  - Most near normal
  - MxA-scattered fibers
  - TRI, MHC1 variable



MDA5: IHC





Summary of DM subtype clinicopathological features

	Mi-2	TIF1y	NXP2	MDA5	SAE
Adult/Juvenile	both	A>J, older	J>A	both	A only
Severity of weakness	+++	+	++	+	+
CK level	+++	++	Variable	+/-	+
Gottron's/heliotrope	++	+++	++	++	?
Ulceration	-	-	+	+++	?
Calcinosis	-	-	++	-	?
ILD	-	-	-	+++	+
Cancer risk	-	+++	++	+	?
Pathology	Perifascicular necrotizing	PFA, Vacuoles, infarct, capi C5b-9	PFA, Vacuoles, infarct, capi C5b-9	Normal	?

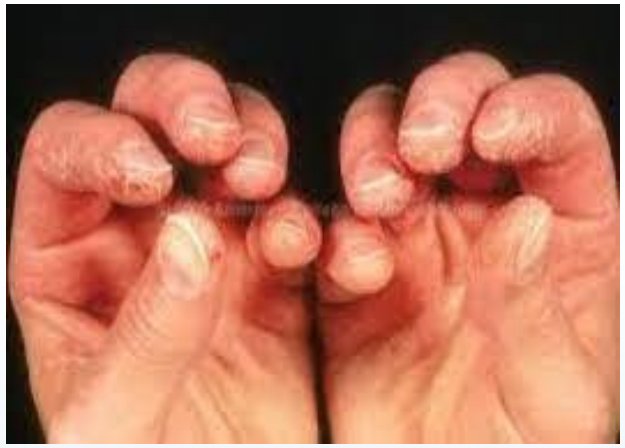
Digital slide:
https://pathpresenter.net/public/presentation/display?token=b335d356

Differential considerations- all myopathies perifascicular

- Antisynthetase syndrome (e.g. Jo-1 myositis)
- Lupus myositis
- Systemic scleroderma
- Eosinophilic fasciitis
- Immune check point inhibitor myositis (ICI myositis)

DDX 1- Antisynthetase syndrome associated myositis

- Clinical features:
  - Hallmarks: myositis, polyarthritis and interstitial lung disease
  - Raynaud phenomenon, unexplained fever, mechanic hands
  - May have Gottron sign/papule and heliotrope rash
- Laboratory features:
  - Elevated CK (mean: ~4000 IU/L)
  - Positive anti tRNA synthetase auto-antibodies (Jo-1, etc)



Mechanic hands

Raynaud phenomenon

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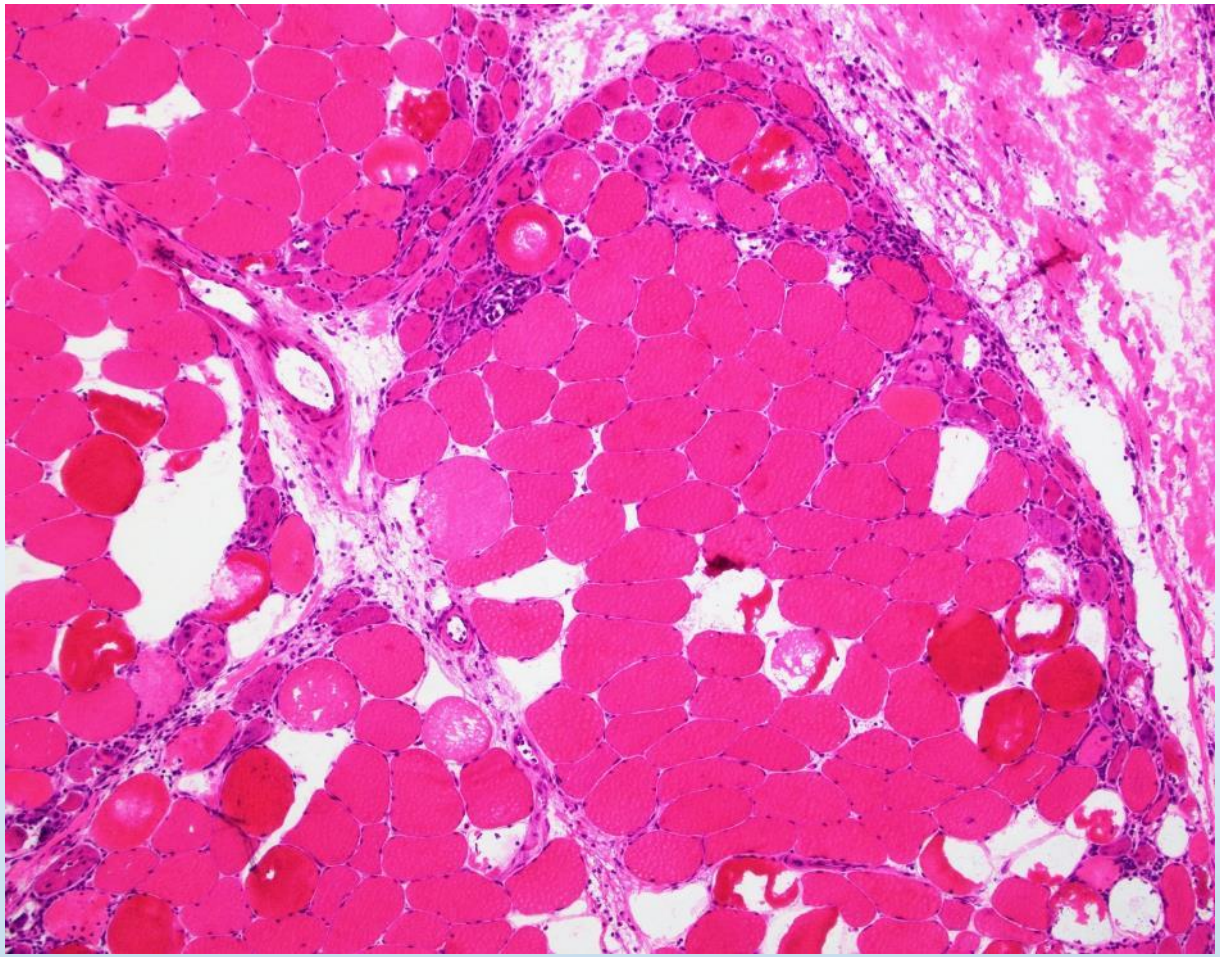
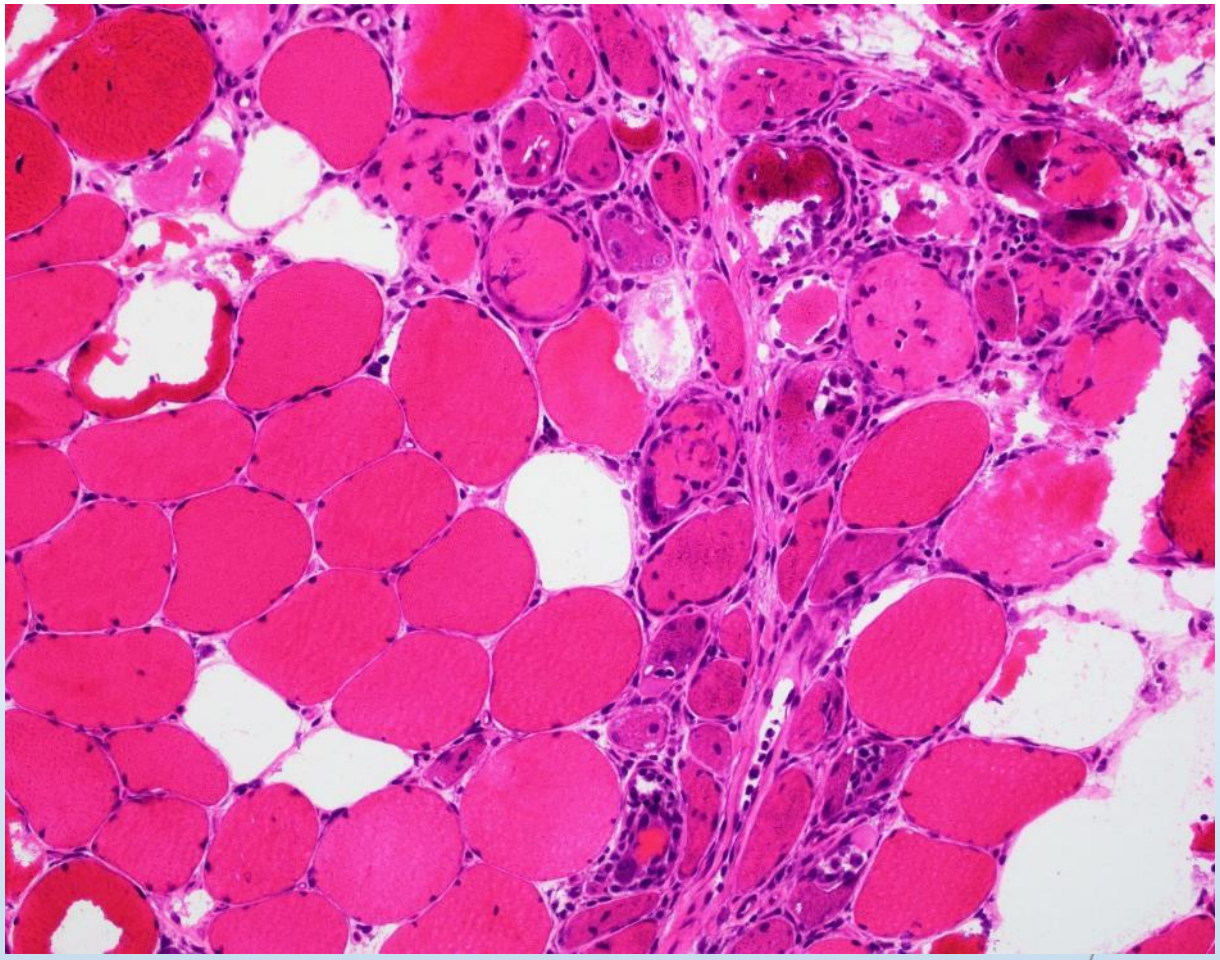
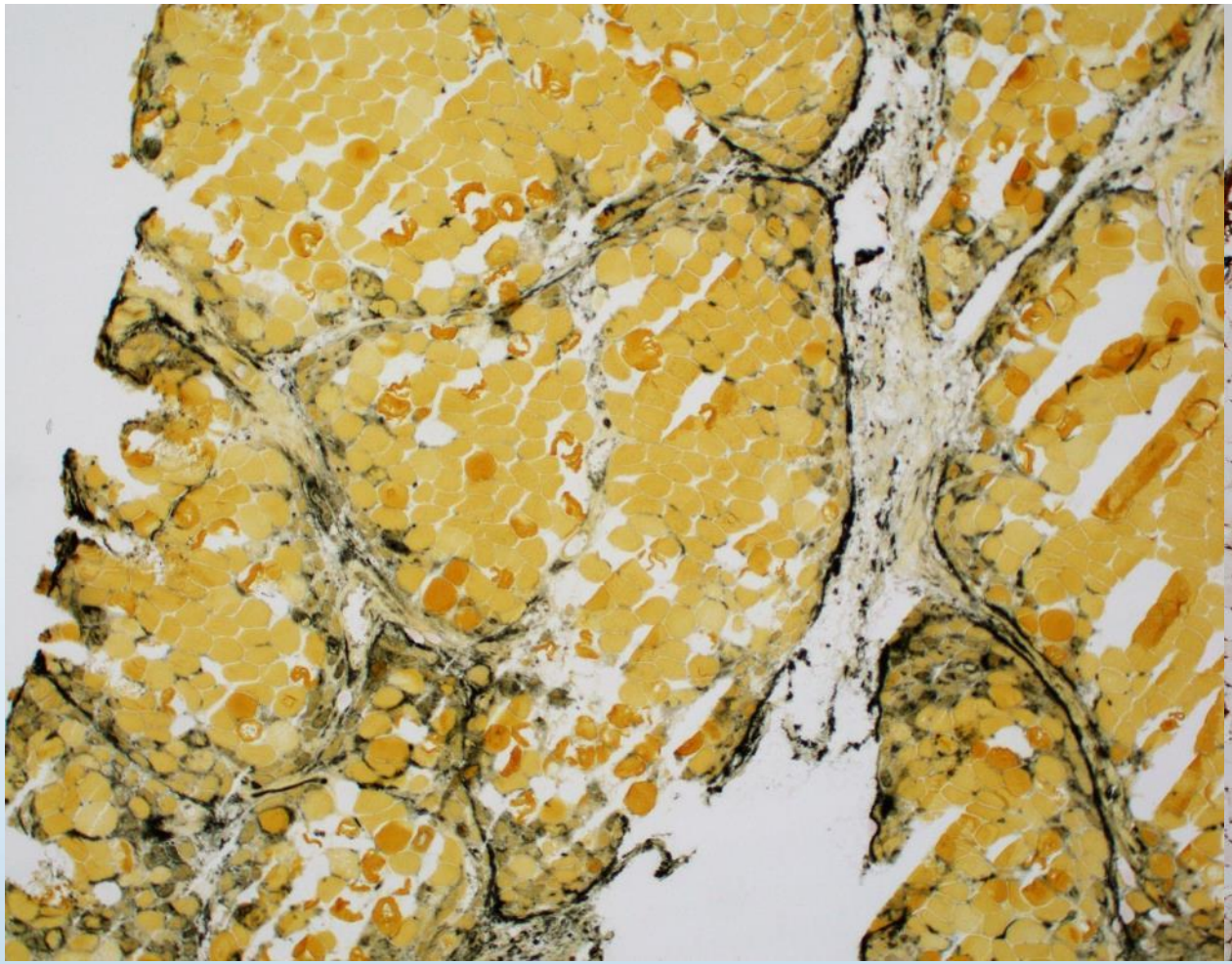
Jo-1 myositis – necrotizing perifascicular myositis

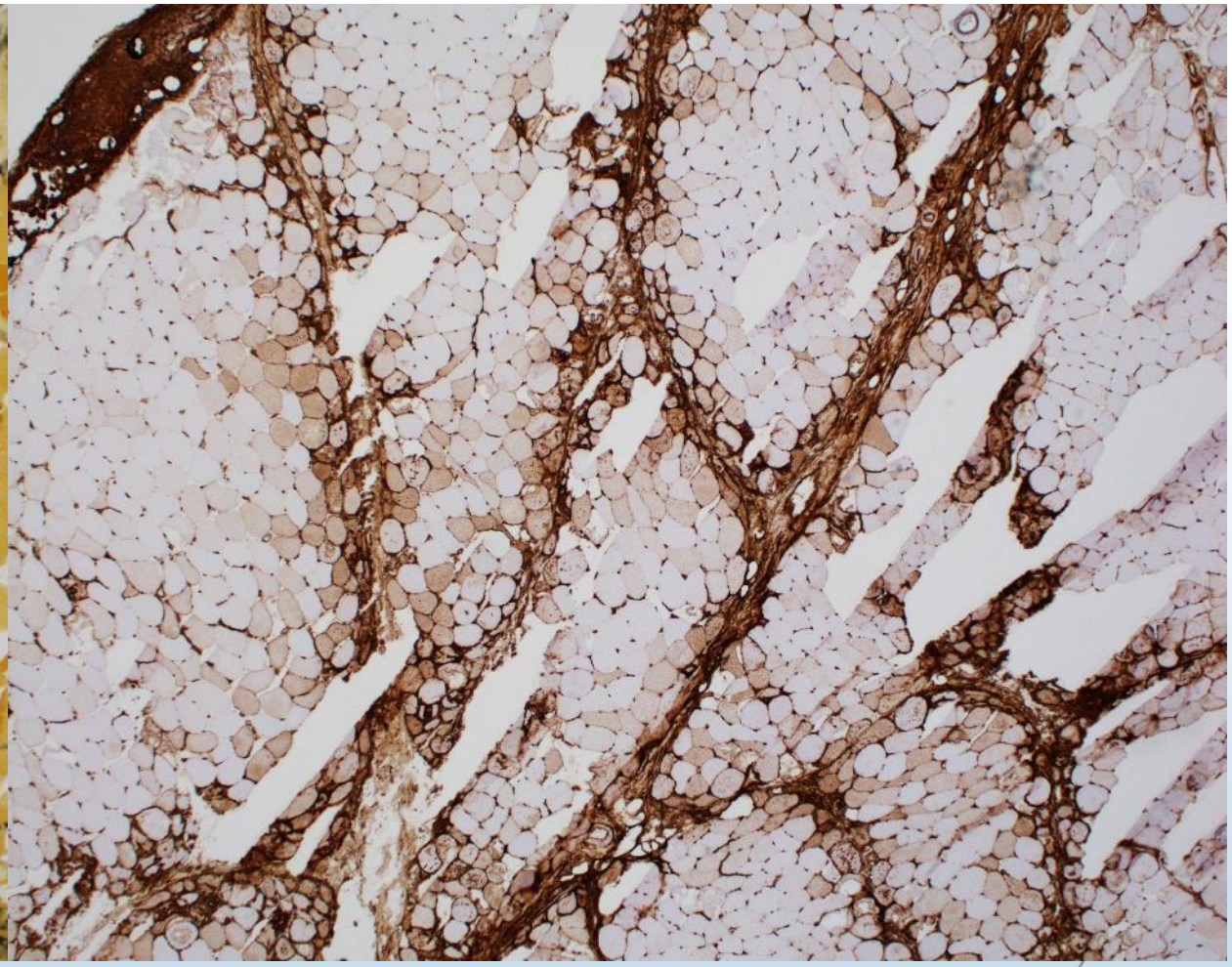




Jo-1 myositis – necrotizing perifascicular myositis

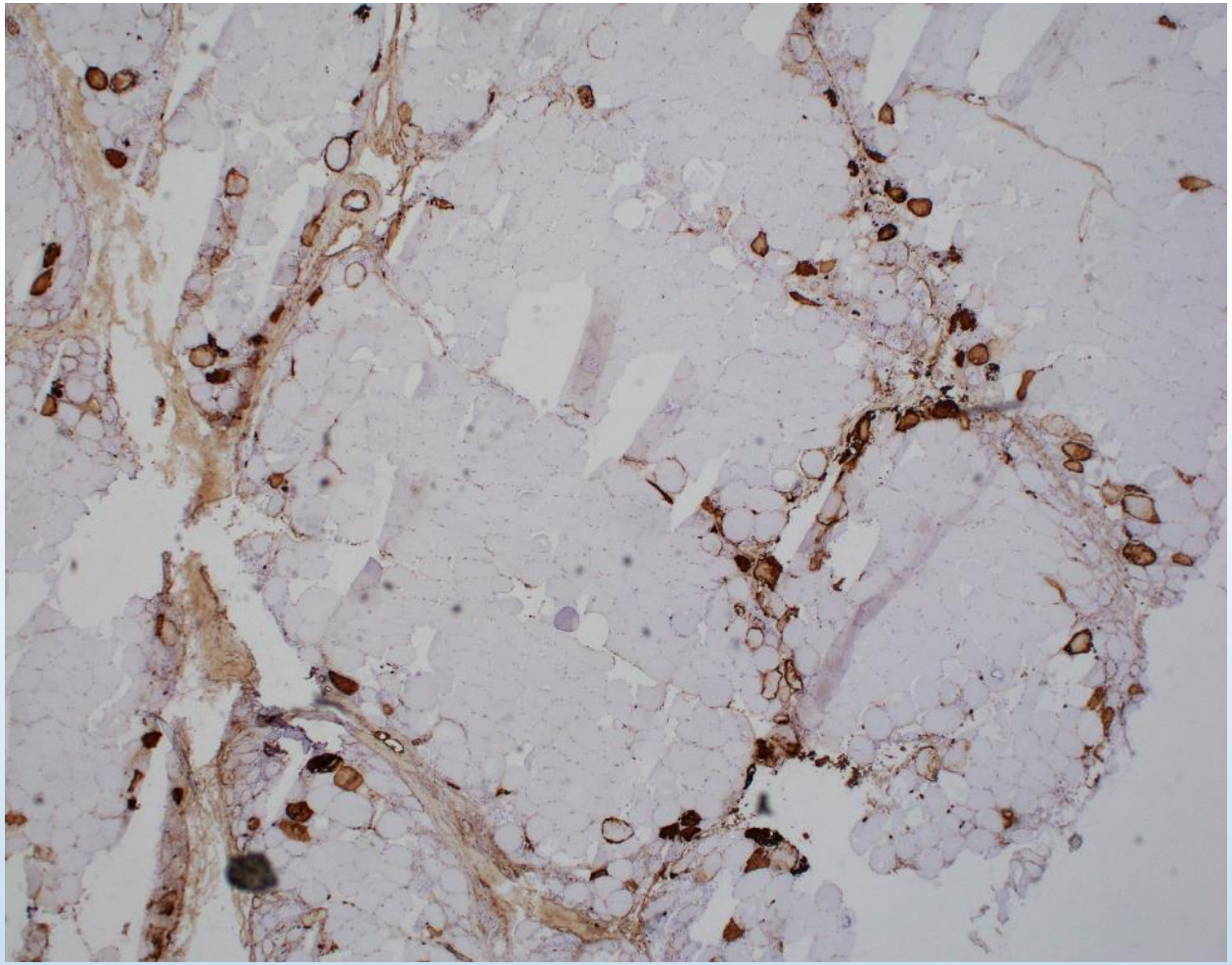


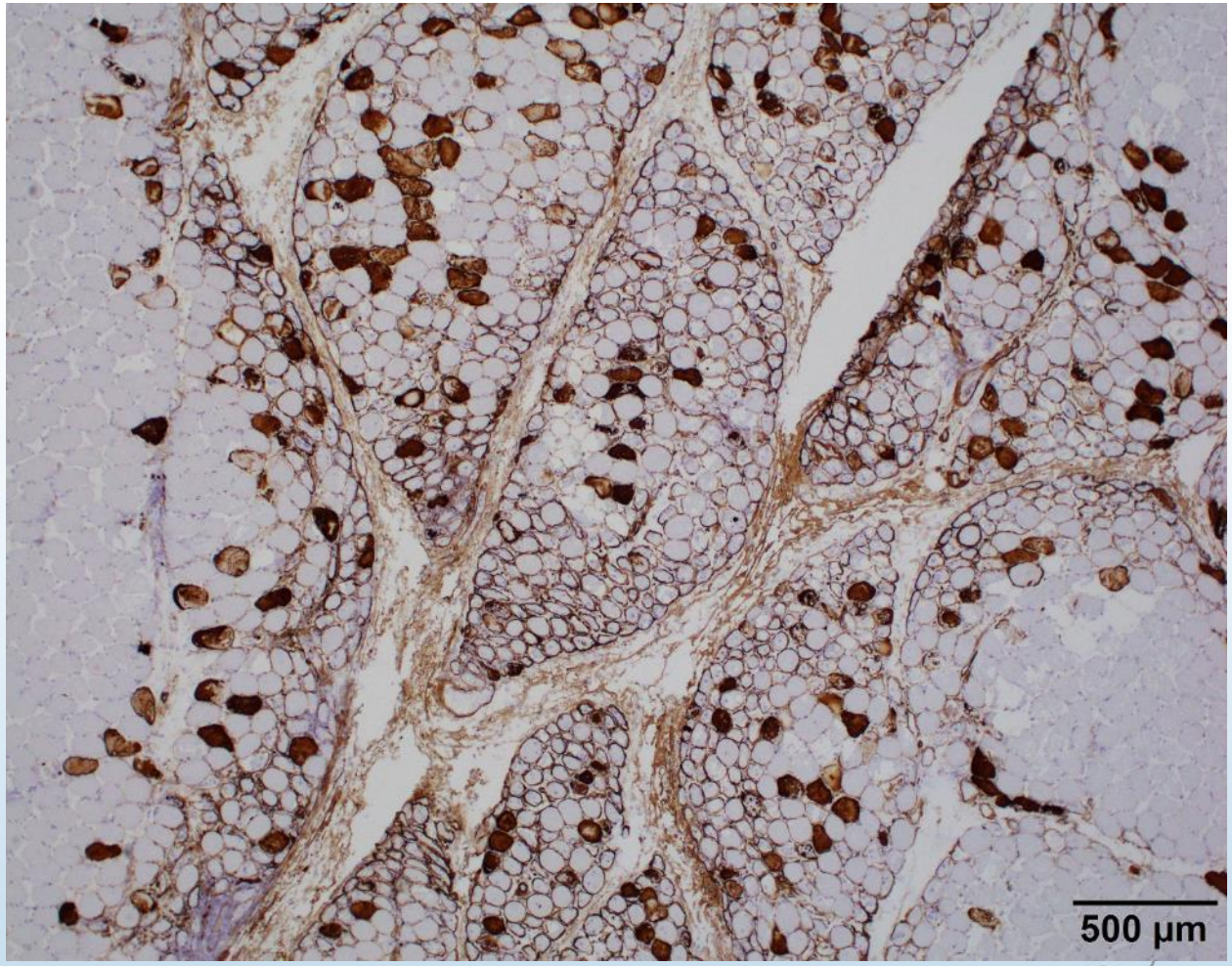
Alk phos



MHC1

Jo-1 myositis – necrotizing perifascicular myositis

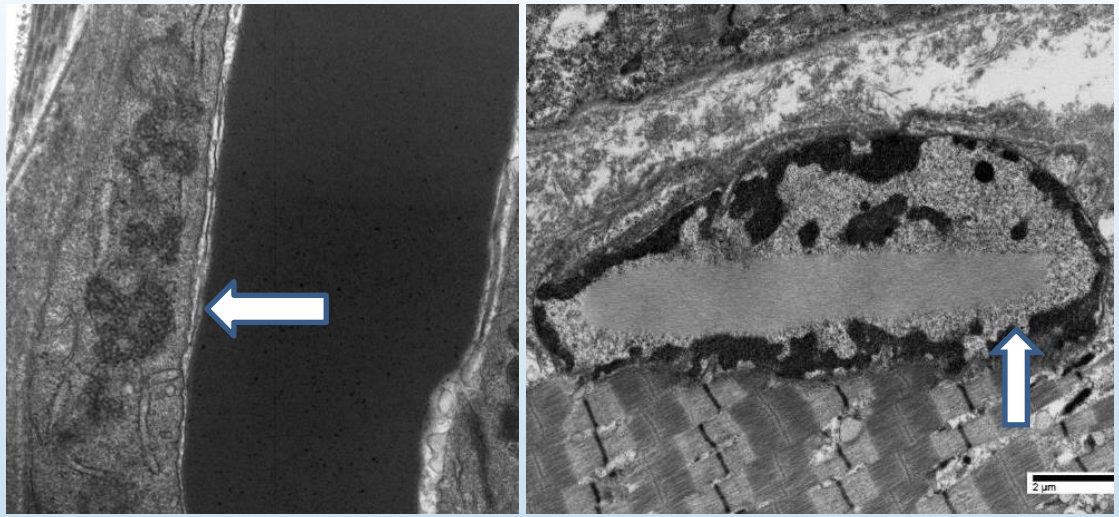




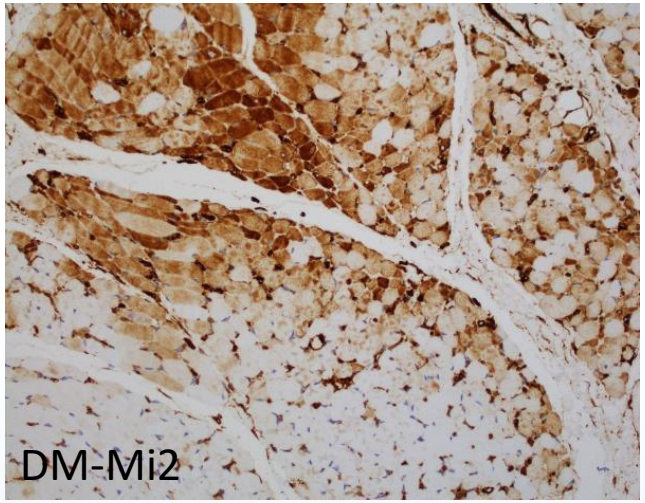
C5b-9

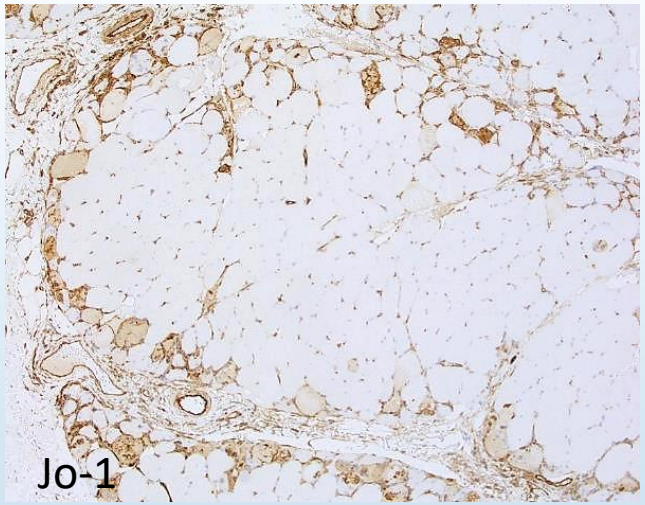
DM-Mi2 vs Jo-1 myositis

	DM-Mi2	Jo-1
MxA	+	-
MHC2	-	+
Endothelial TRI	++	-/+
Intranuclear actin aggregates	-	-/+

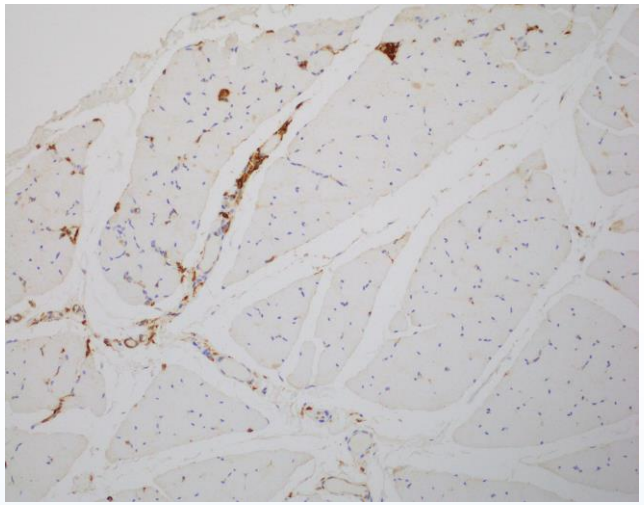


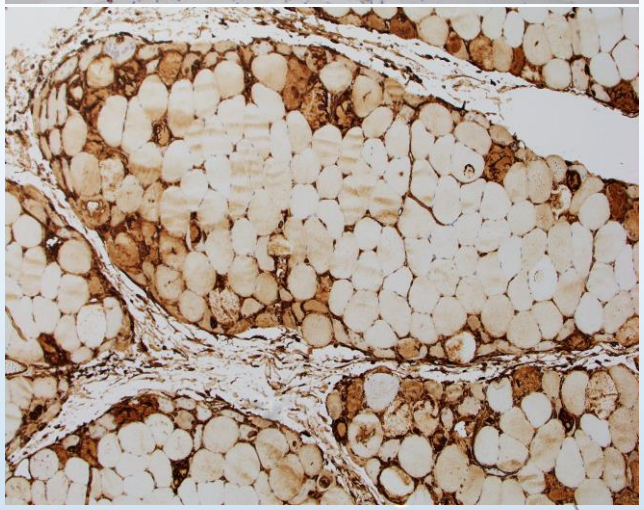
MxA





MHC2



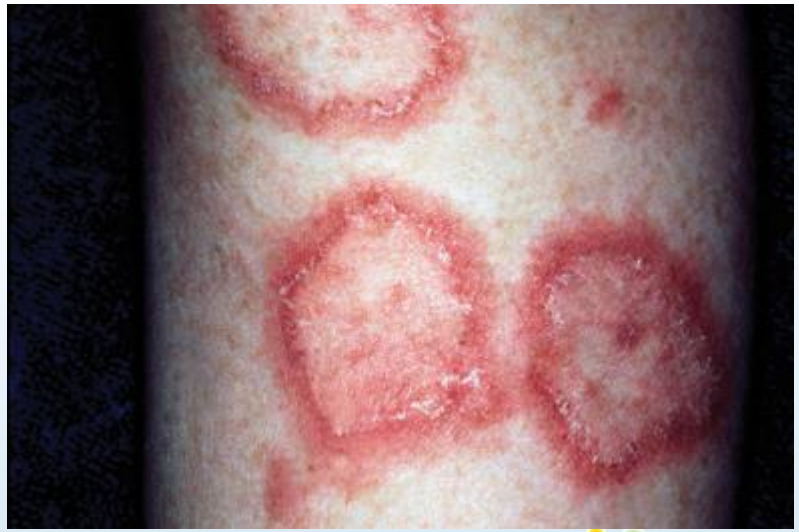


AANP

DDX 2– lupus myositis

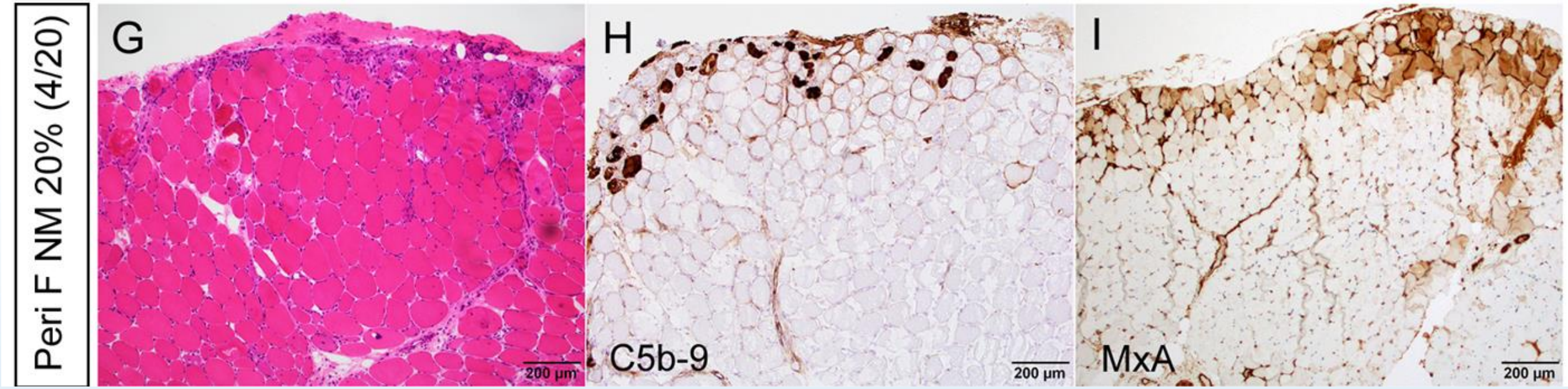
- Multisystem disease
  - Skin- malar rash, discoid rash
  - Kidney-nephritis
  - Hematologic – lymphopenia, anemia
  - Muscle skeletal-myositis, joints
  - Serosa: pleuritis, pericarditis
- Serology
  - dsDNA, Smith, Low C3/C4, antiphospholipid

malar rash



discoid rash

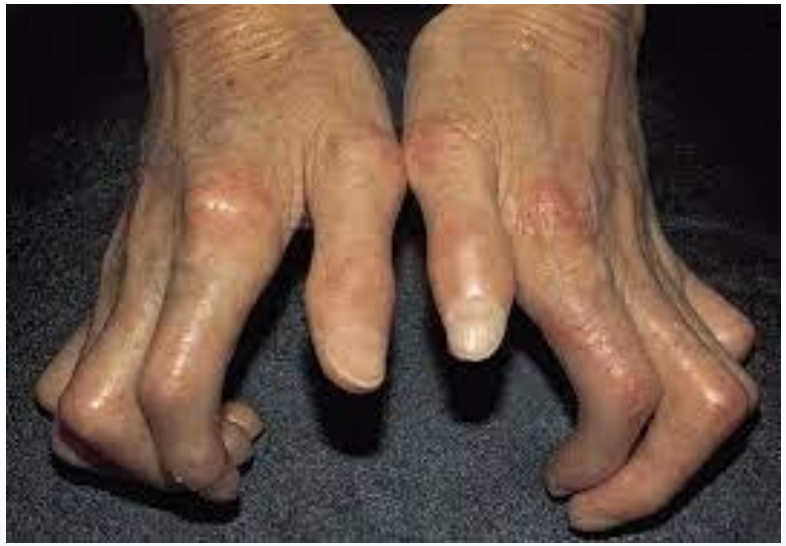
Lupus myositis – DM pattern



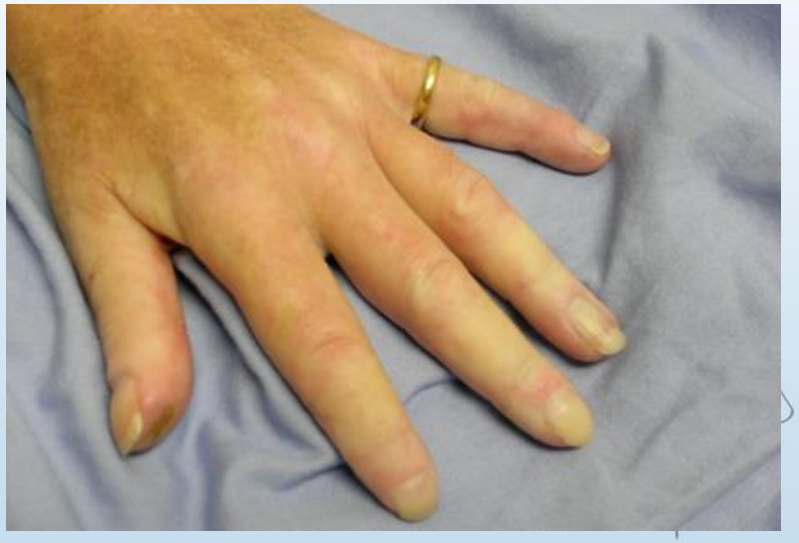
Xing, C., et al. (2024). "Myxovirus resistance protein A (MxA) expression in myositides: Sarcoplasmic expression is common in both dermatomyositis and lupus myositis." Muscle Nerve **69**(5): 548-555.

DDX 3- systemic scleroderma

- Systemic dis with multi-organ involvement
  - Skin
    - Sclerodactyly
    - Puffy fingers
    - Fingertip ulcers or pitting
  - Small vessels
    - Telangiectasia
    - Nail fold capillary abnormalities
    - Raynaud's
  - Lung
    - Pulmonary hypertension
    - ILD
  - Serology
    - PM-scl 75/100
    - KU
    - U1RNP



Sclerodactyly



Puffy fingers

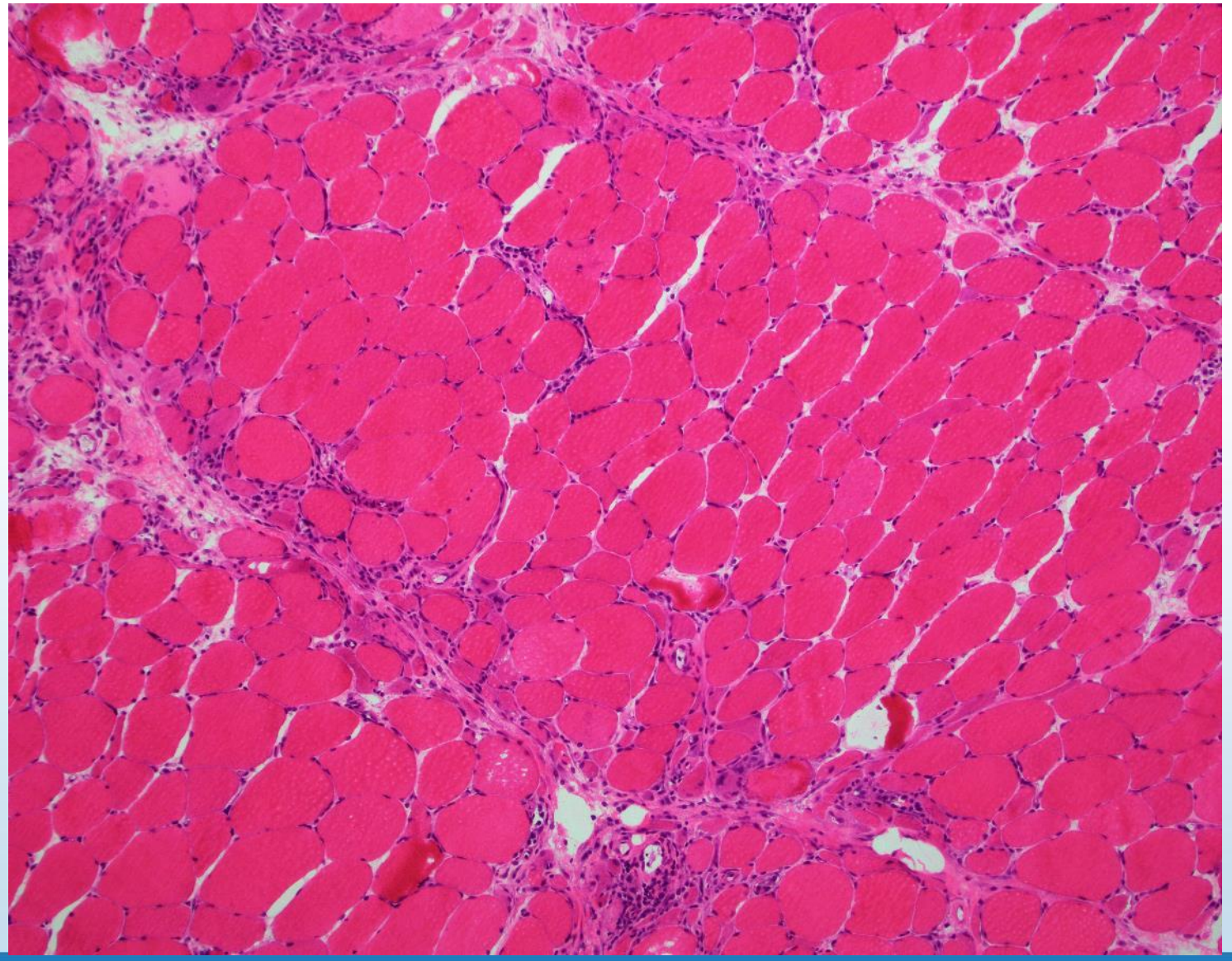
Systemic scleroderma – meta analysis

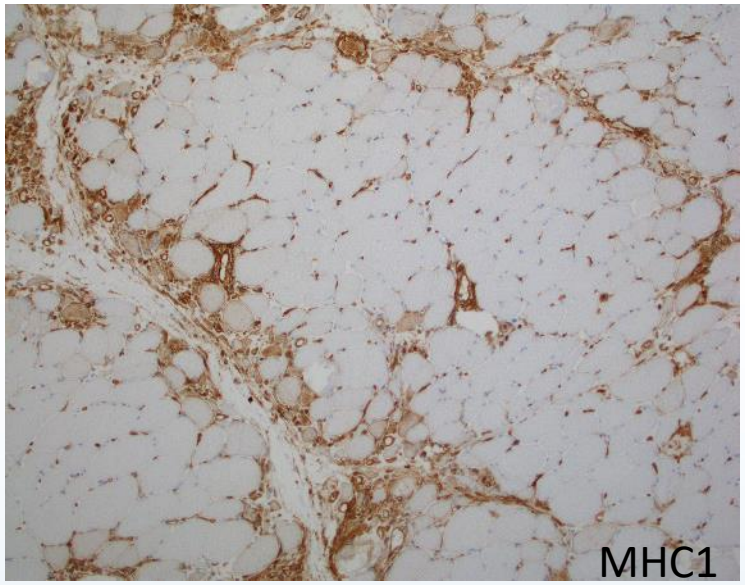
- SS pts with PM-Scl antibodies are enriched in DM pathology
  - Perifascicular atrophy in 27%
  - Perifascicular MHC1 in 47%
  - Sarcolemmal or capillary C5b9 in 12%
  - MxA or TRI no data
- Other ss autoantibodies with less, but not absent, DM pathology
  - Ku: 8% PFA, 50% PF MHC1, 25% capillary C5b-9
  - UIRNP: 16% PFA, 7% PF MHC1

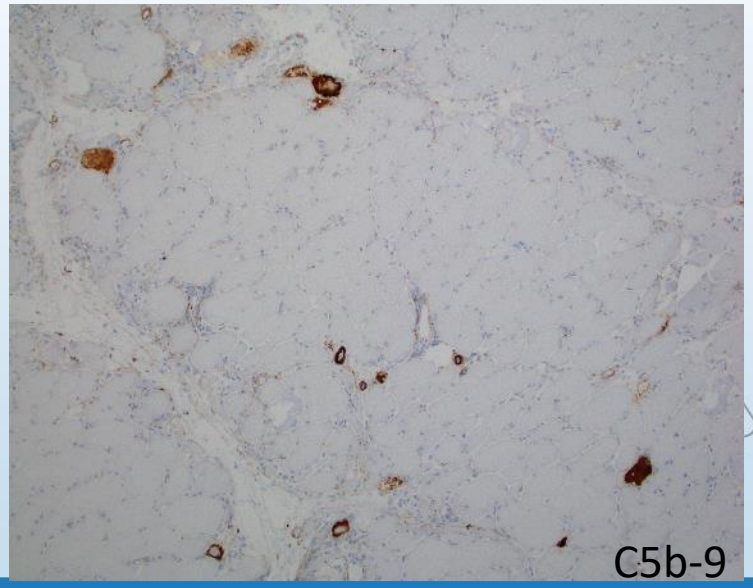
Lefebvre, F., et al. (2021). "Histopathological features of systemic sclerosis-associated myopathy: A scoping review." Autoimmun Rev **20**(7): 102851.

AANP

Inhouse systemic scleroderma-DM pattern (2/7)







DDX4: Eosinophilic fasciitis

- Clinical phenotype
  - Painful symmetrical skin indurations
  - Absence of sclerodactyly
  - Arthralgia, myalgia

- Laboratory:
  - CRP, ESR elevation
  - Typically negative autoantibodies
  - Peripheral eosinophilia (63-93%)
  - Hypergammaglobulinemia
  - CK usually normal

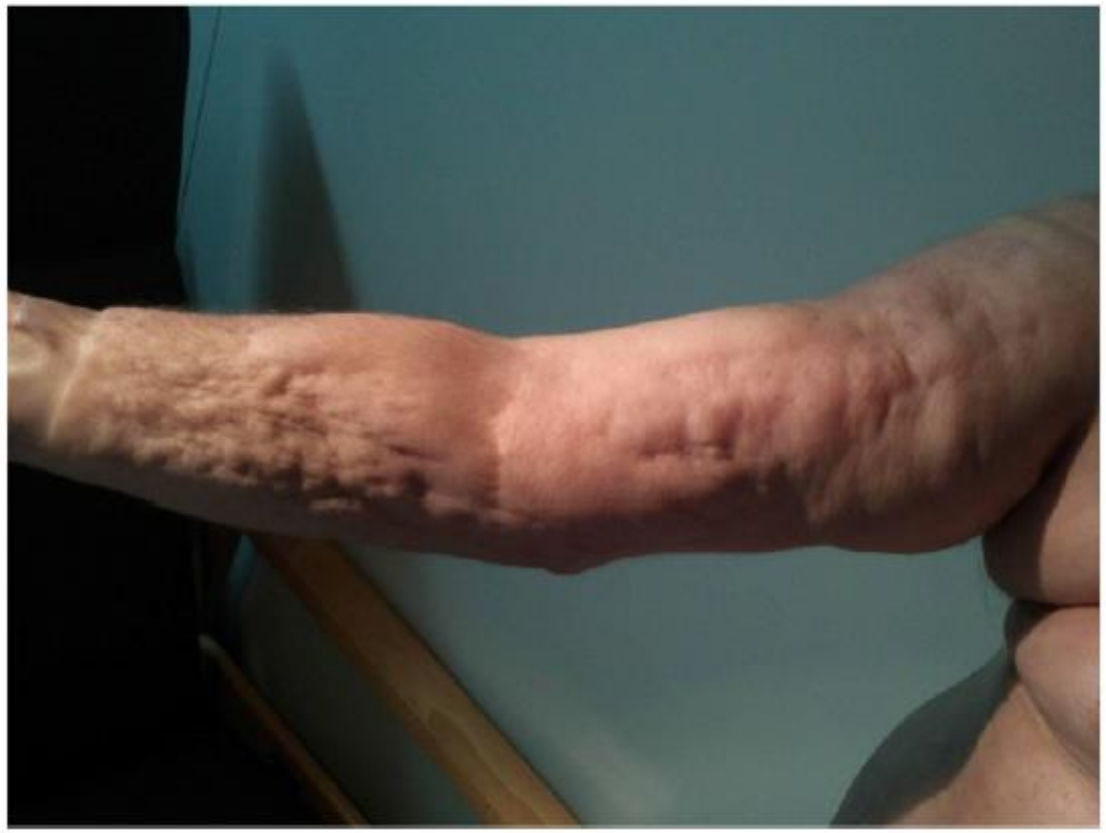
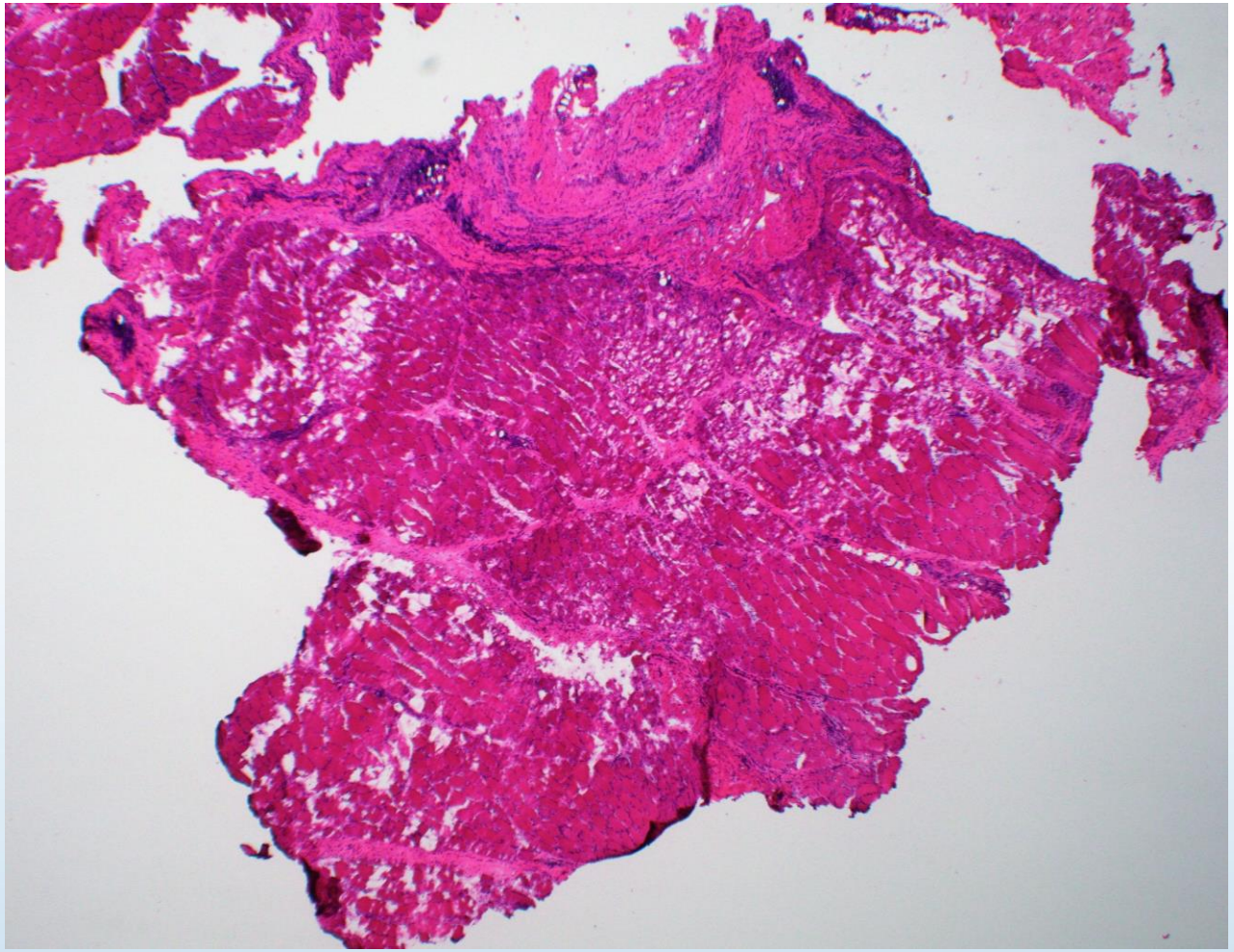
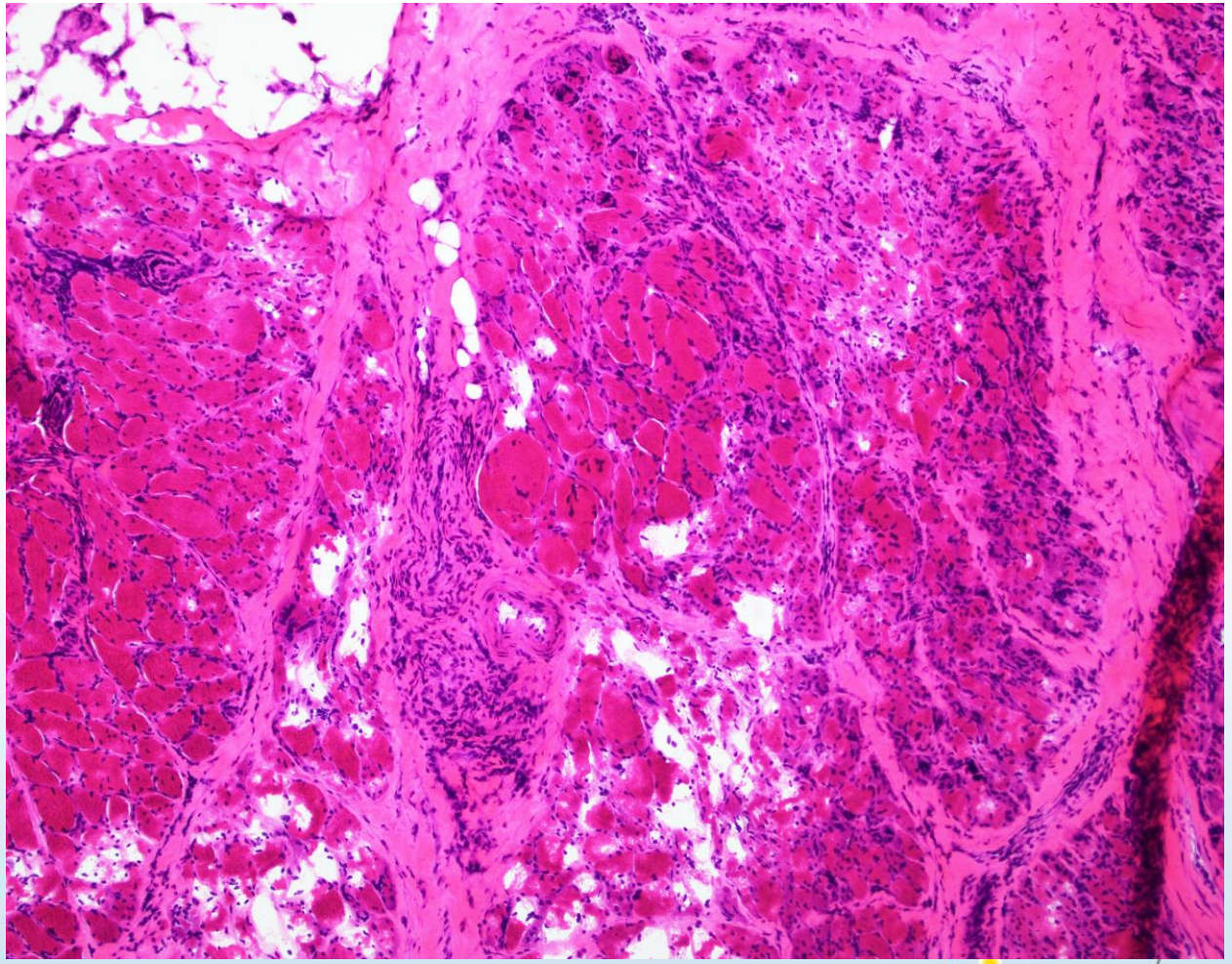


Fig. 1. *Peau d'orange.*

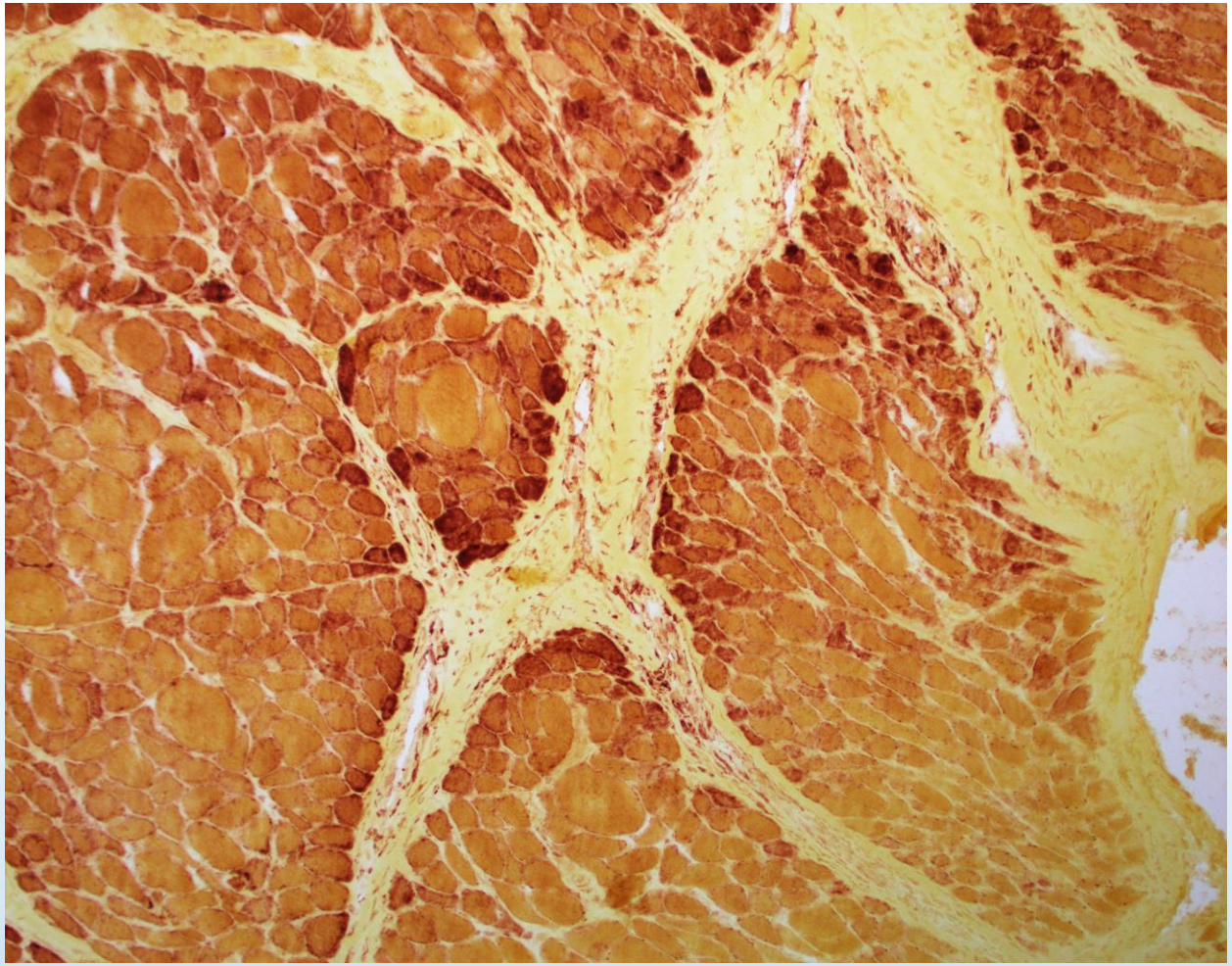
Pinal-Fernandez, I., et al. (2014). "Diagnosis and classification of eosinophilic fasciitis." Autoimmun Rev **13**(4-5): 379-382.

Eosinophilic fasciitis pathology

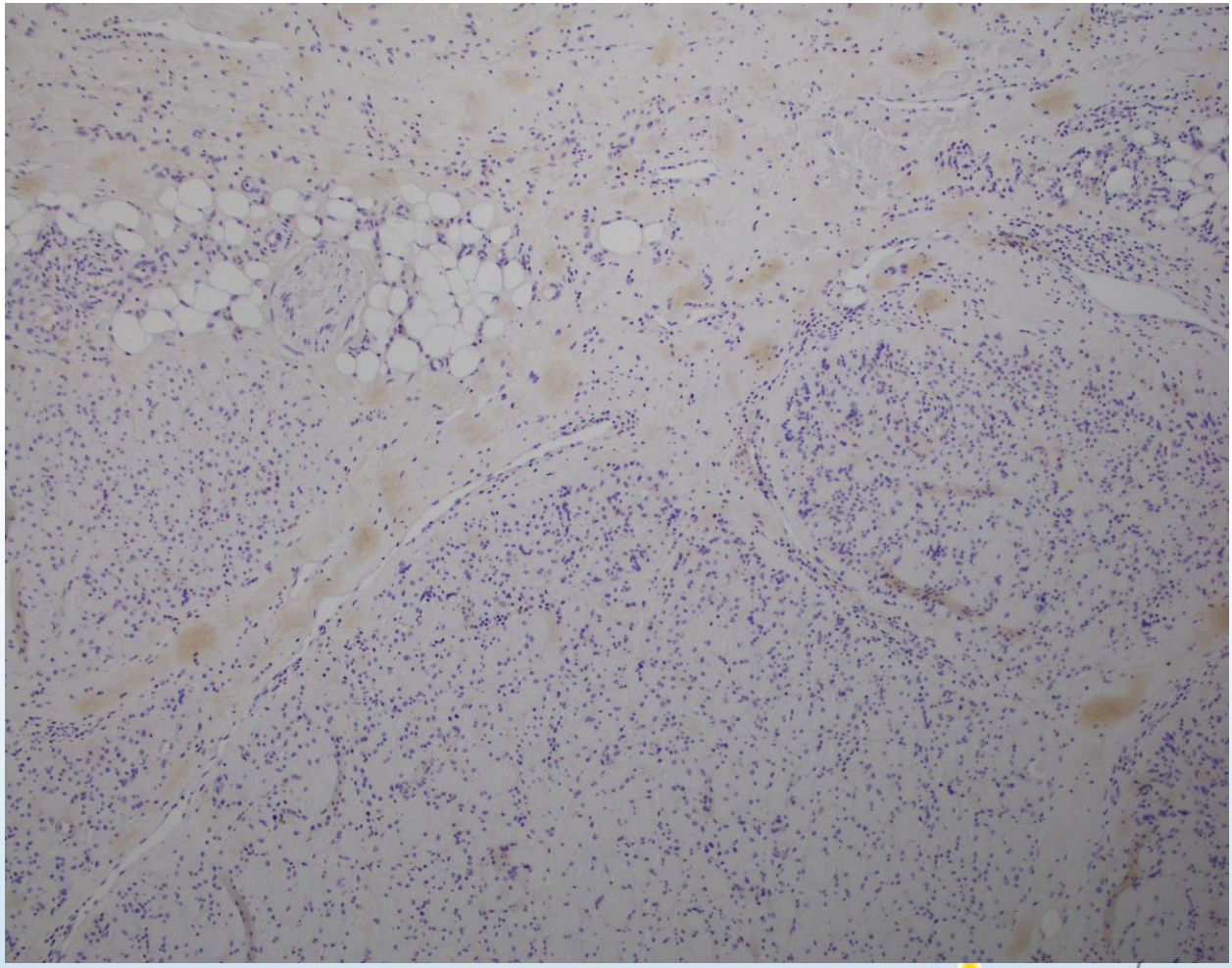




Eosinophilic fasciitis pathology



Nonspecific esterase



MxA

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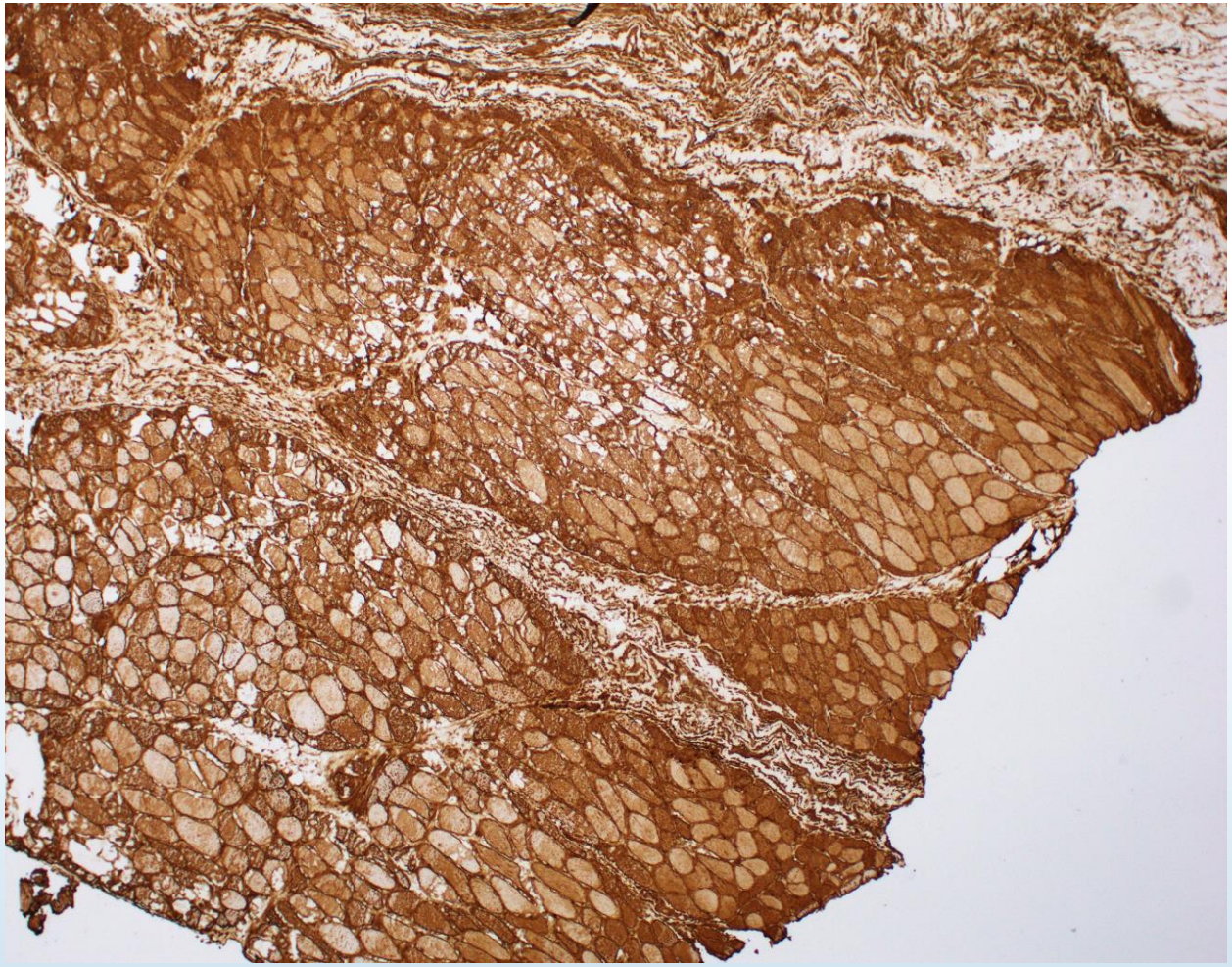
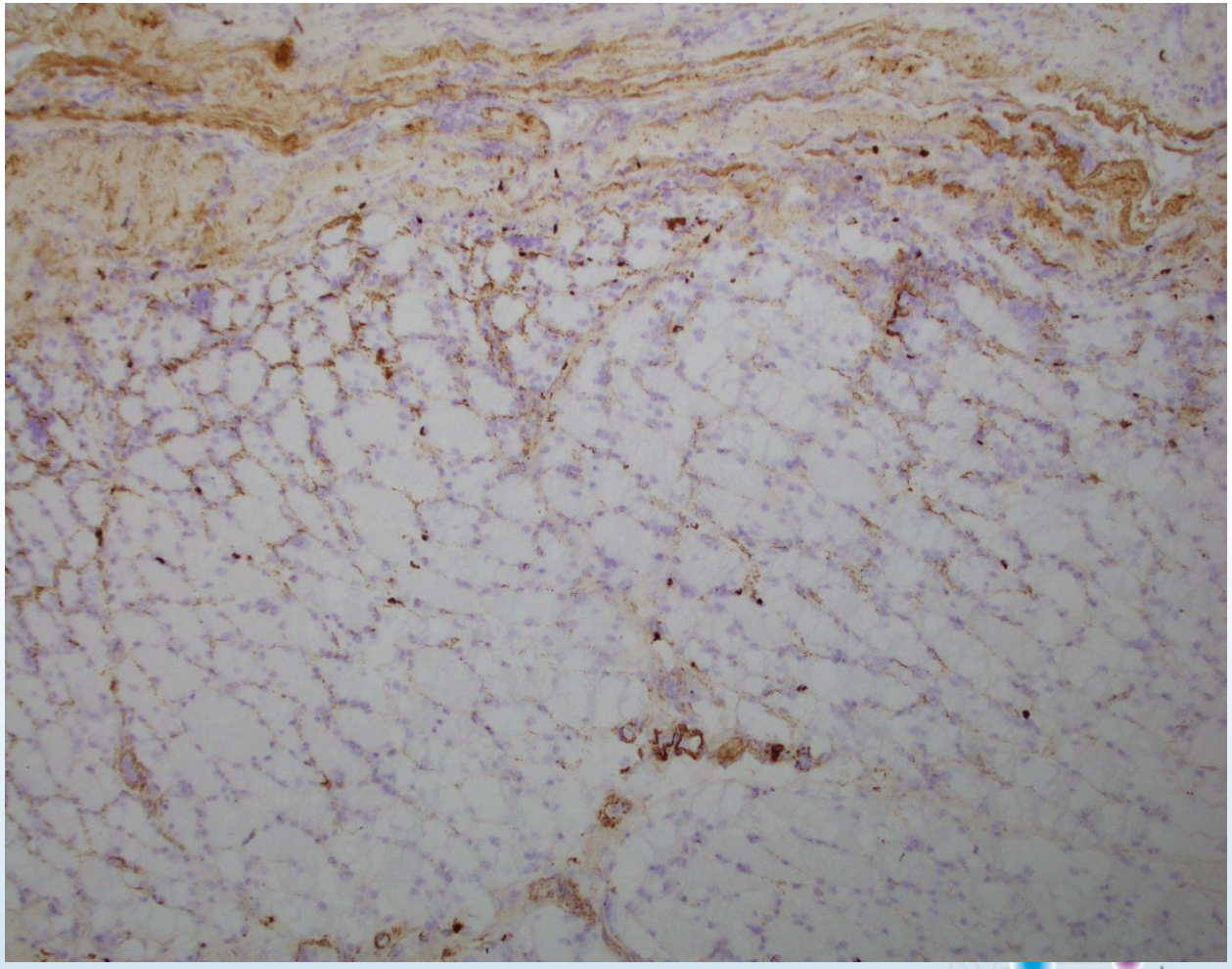
Eosinophilic fasciitis pathology



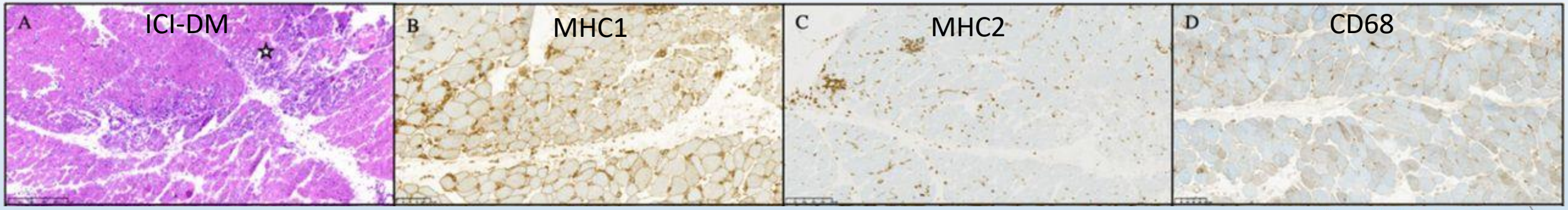
MHC1



C5b-9

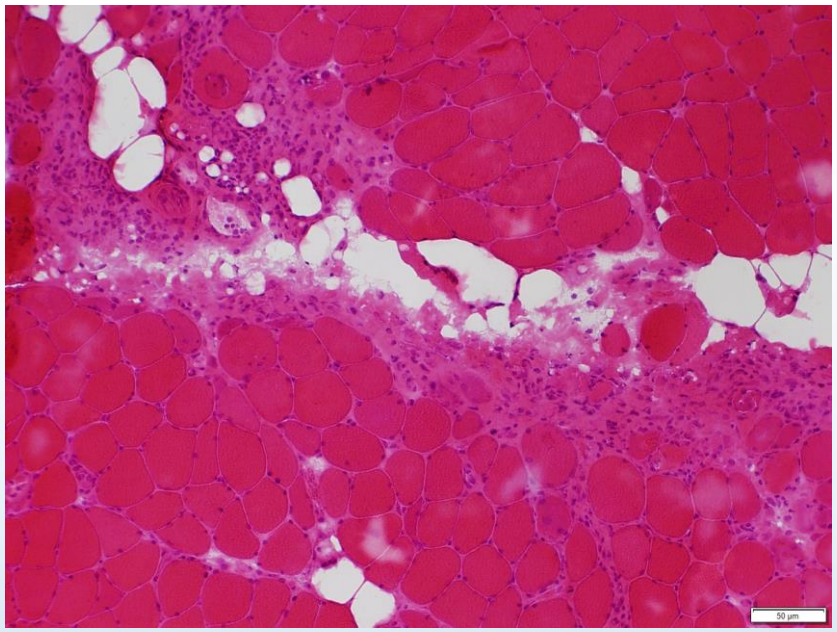
DDX5: Immune checkpoint inhibitor myositis

- Clinical features
  - PD, PD-L1 or CTLA-4 inhibitors tx
  - Myopathy after one or two cycles
  - Majority had anti NMJ or myositis antibodies
  - 8.6% (3/35) had DM type rashes and anti-TIF1γ antibody
  - In one pt the anti-TIF1γ is present in pre-ICI serum

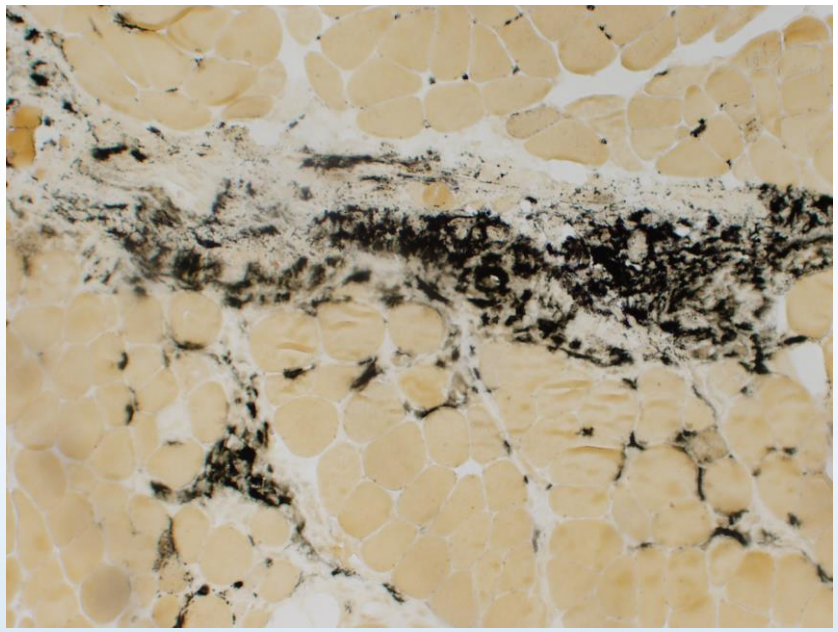


Pinal-Fernandez, I., et al. (2023). "Transcriptomic profiling reveals distinct subsets of immune checkpoint inhibitor induced myositis." Ann Rheum Dis **82**(6): 829-836.

Immune checkpoint inhibitor myositis



ALK phos



MHC1

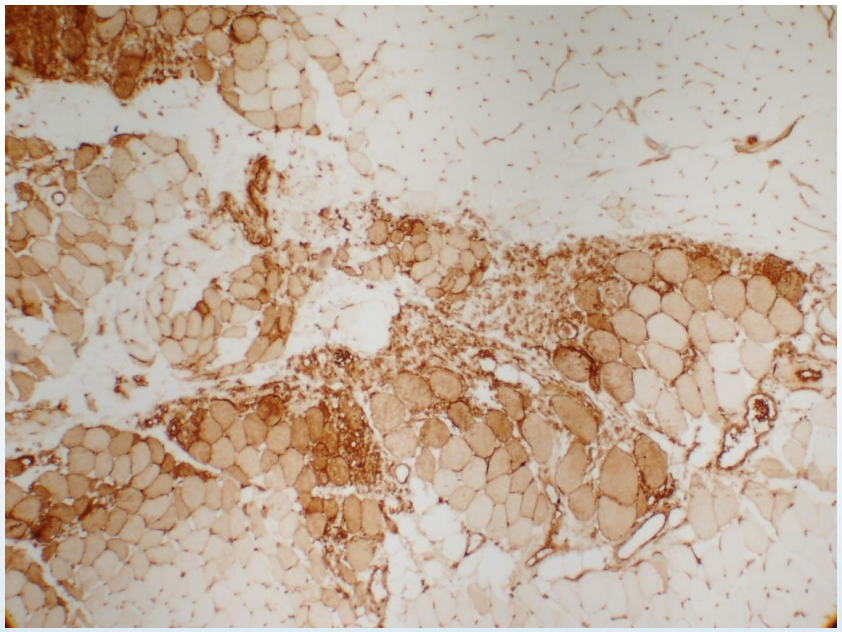
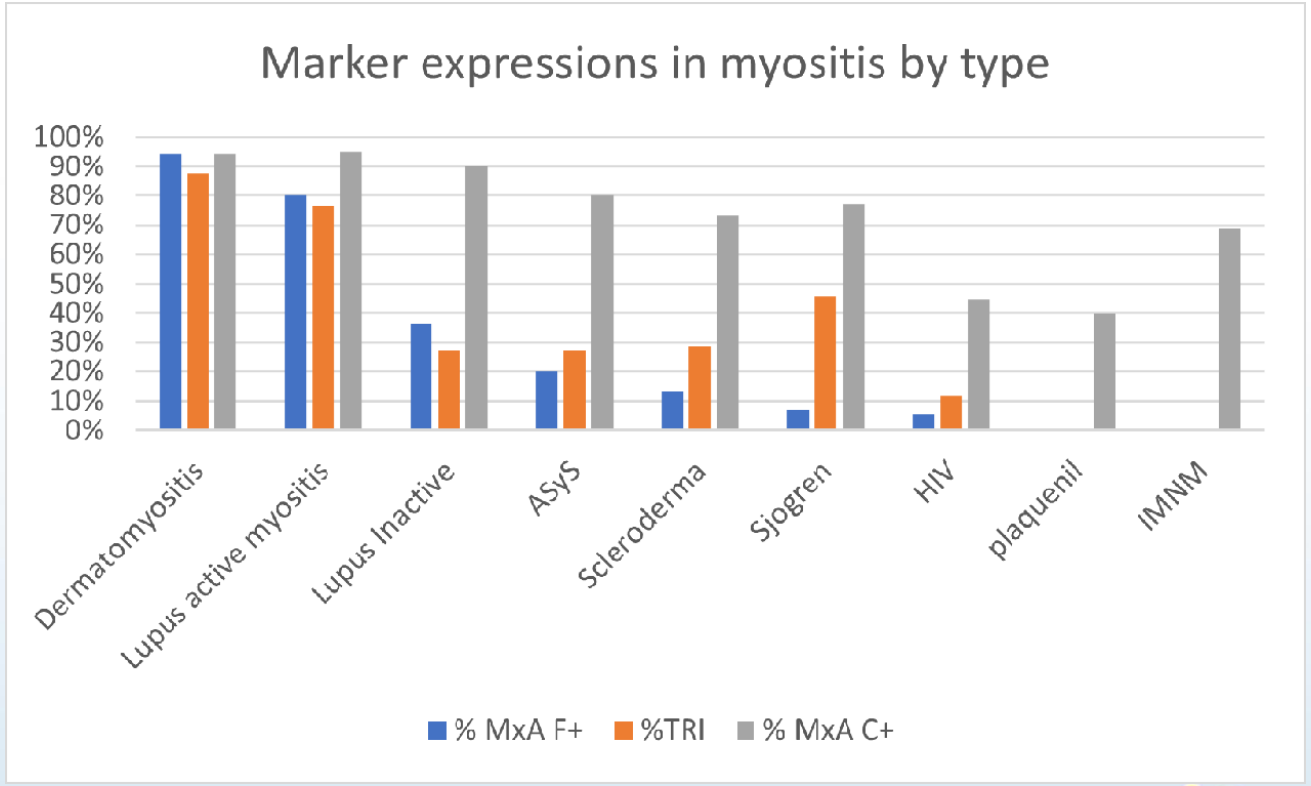


Image curtesy: Dr. Robert Bucelli, Washington University

Specificity of MxA IHC and TRI in myositis

MxA sarcoplasmic expression

- Highly prevalent in
  - DM (94.4%, 17/18),
  - Active lupus myositis (LM, 80%,16/20),
  - inactive lupus biopsies (36%, 4/11)
- Infrequent in
  - antisynthetase syndrome (20%, 2/10),
  - systemic sclerosis (13%, 2/15),
  - Sjogren's syndrome (7.7%, 1/13)
  - HIV myositis(5.6%, 1/18)
- Absent
  - IMNM (0/16)
  - hydroxychroloquine myopathy (0/5).



Xing, C., et al. (2024). "Myxovirus resistance protein A (MxA) expression in myositides: Sarcoplasmic expression is common in both dermatomyositis and lupus myositis." Muscle Nerve **69**(5): 548-555.

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Differentiating features in IIMs with perifascicular injury pattern

Myositis type	DM-NXP2,TIF1y	DM-Mi2	ASyS	Lupus	SS	EF	ICI
Pathology	PFA, infarct	PFN	PFN	PFN	PFN/PFA	PFA	PFN/PFN
MxA	++	++	±	++	+/-	-	NA
MHC1	+	+	+	+	+	+	+
MHC2	±	±	++	+	±[1]	+[1]	++[1]
C5b-9 capillary	++	-	-	+/-	-	-	-
C5b-9 sarcolemma	-	++/-	++/-	+/-	+/-	-	-[1]
TRI	++	++	±	++	±	-	NA

Acronyms: DM-dermatomyositis, ASyS -antisynthetase syndrome, SS-systemic scleroderma, EF-eosinophilic fasciitis, ICI-immune check point inhibitor, PFA-perifascicular atrophy, PFN-perifascicular necrosis, TRI-tubuloreticular inclusions

[1]: Nelke, C., et al. (2024). "Complement and MHC patterns can provide the diagnostic framework for inflammatory neuromuscular diseases." Acta Neuropathol **147**(1): 15.

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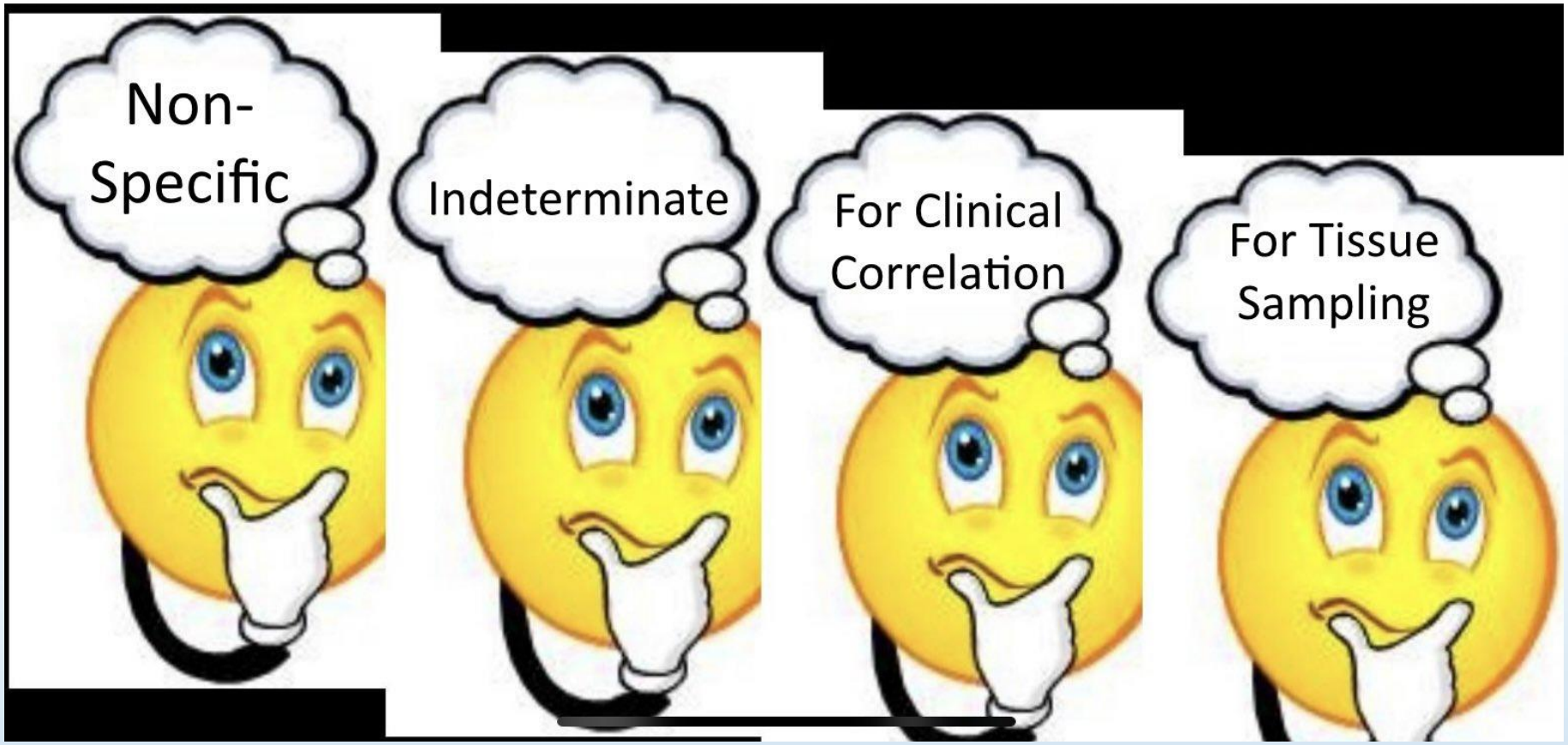
Learning Objectives

- Learning Objective #1: distinguish dermatomyositis autoantibody subtypes by pathology on muscle biopsy.

- Learning Objective #2:: identify appropriate ancillary studies to differentiate dermatomyositis from other types of myositides with a perifascicular injury pattern.

- Learning Objective #3:discuss the most essential qualities of muscle/nerve pathology reports in communicating with treating physicians.

The nature of muscle/nerve biopsies



Muscle and peripheral nerve pathology findings are rarely pathognomonic, contingent upon clinical serological phenotypes, and hugely liable to sampling errors.

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Challenges in writing a neuromuscular pathology report

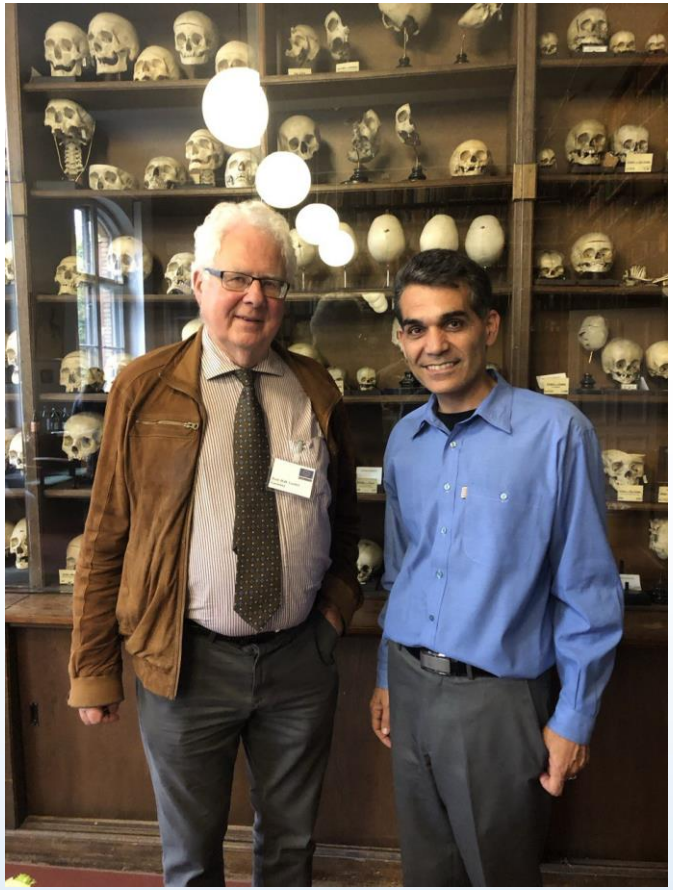
- Often lengthy
- Diagnostic uncertainty
- May need to discuss multiple DDXs
- May need to suggest additional diagnostic tests

Clinicians hate a purely “descriptive” diagnosis

- “ reports which describes in details…. but does not tell what he thinks, what conclusion he draws from it, and what it means to him”

- Such reports “tells much, yet almost nothing”.
- “A perfect word picture but without meaning to one unable to interpret it”

Enfield, C. D. (1923). "The scope of the roentgenologist's report." JAMA **80**(14): 999-1001.



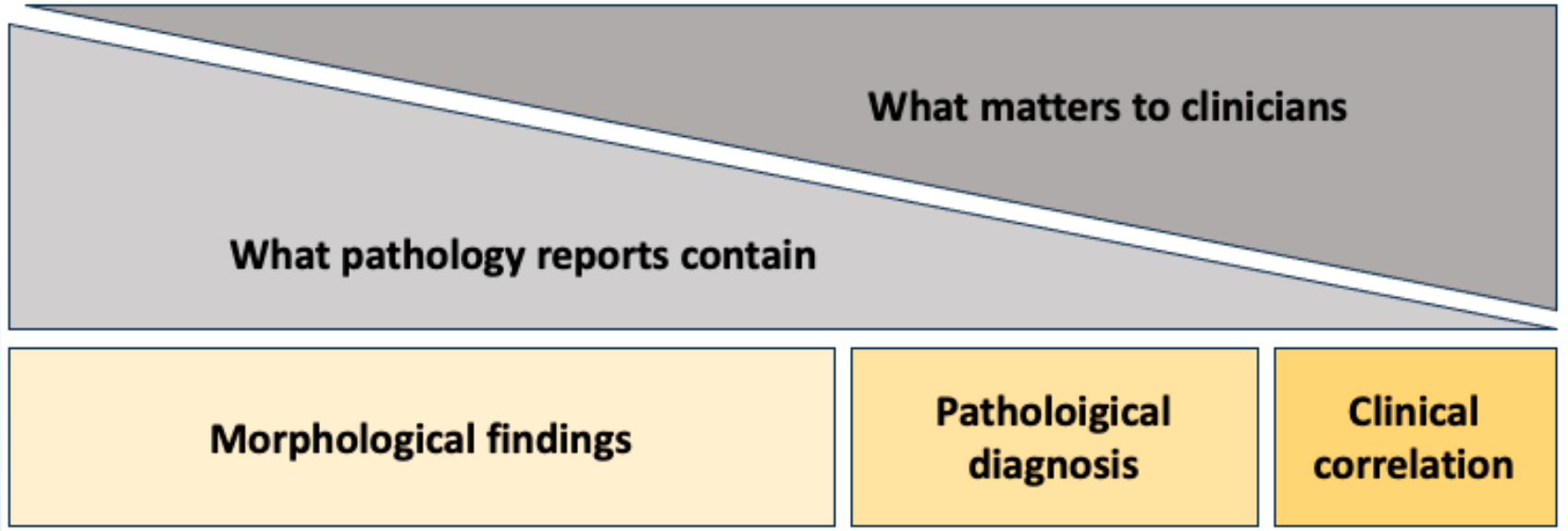


Image courtesy: Amir Sabouri MD., PhD.

L: Hans Goebel, Pathologist
R: Amir Sabouri Neurologist

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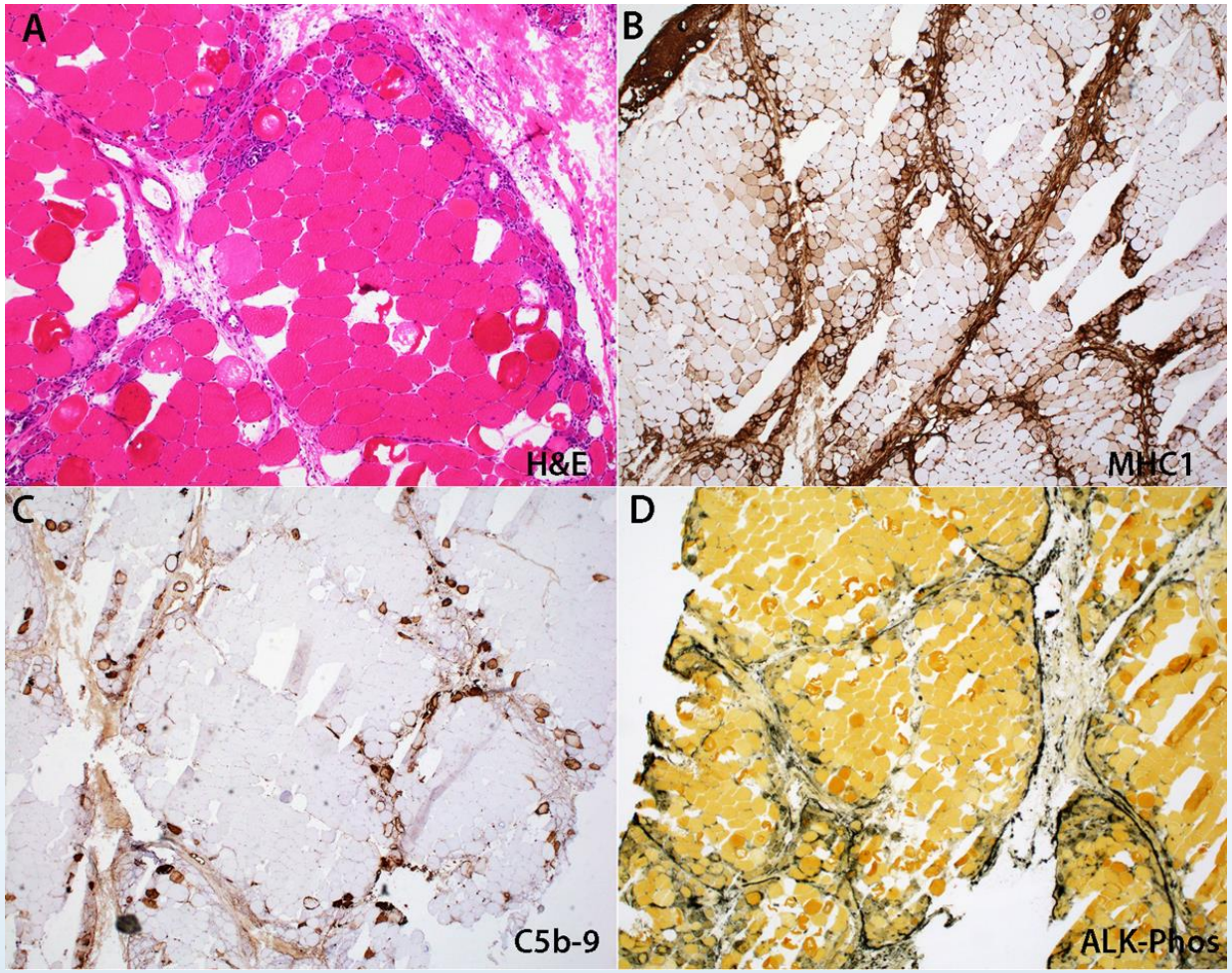
Dilemma for pathologist: premature commitment may lead to wrong diagnosis.

- Suggestion point 1
- A "sliding scale" of reporting – the definitiveness of the diagnosis depends on pathology AND available clinic-serological information.
- When not definitive, give multiple differentials in the order from most to least likely.

Scenario 1

- Available history: 33 year old female presented with bilateral thigh weakness and respiratory insufficiency. She underwent a lung biopsy which was suspicious for interstitial lung disease. Rheumatologic workup was notable for mechanics hands, high CK in the range of 14,000-20,000, and positive anti-Jo 1 antibody. Operative procedure: left thigh muscle biopsy



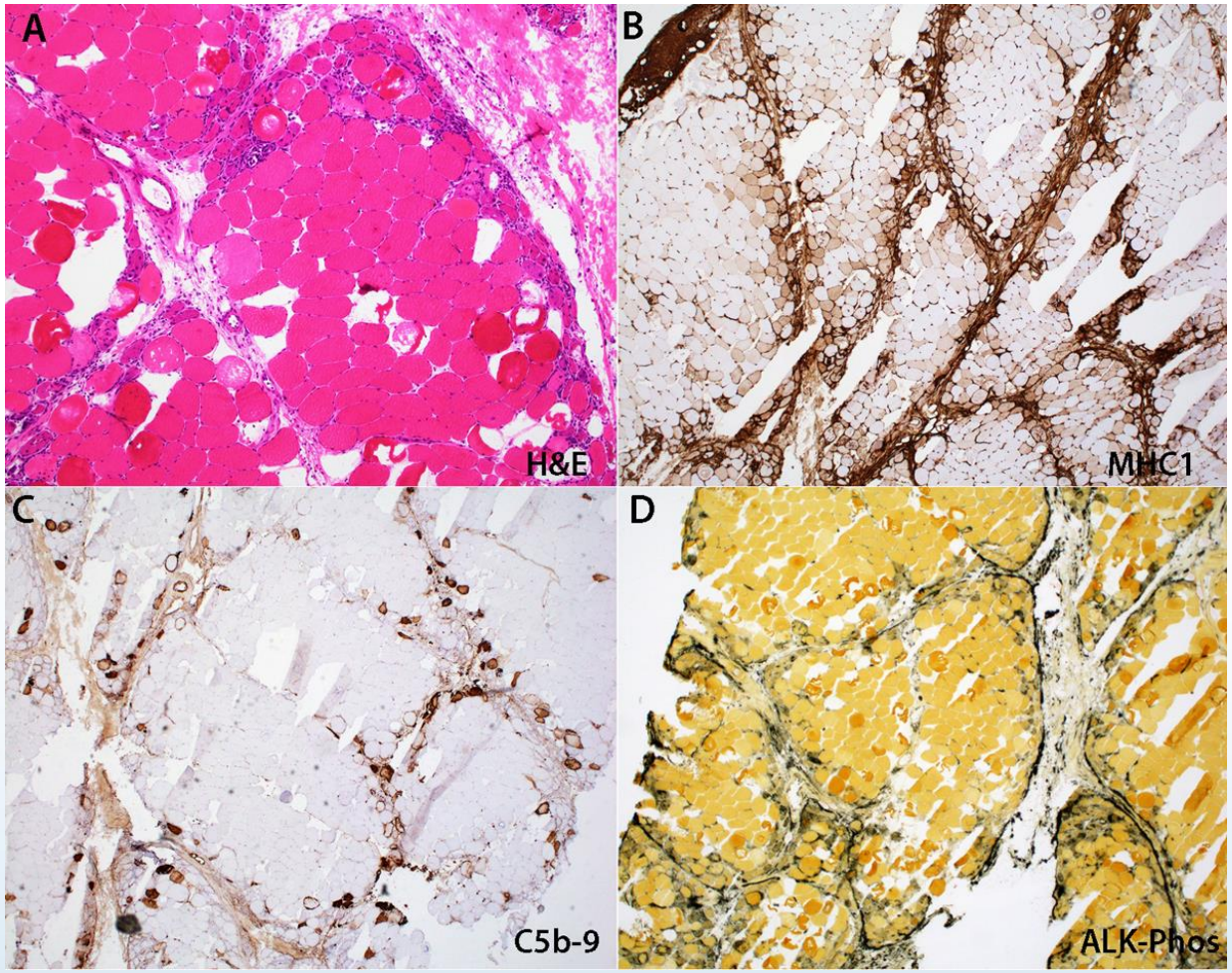
Pathology report:

- **Final diagnosis:** ANTISYNTHETASE SYNDROME ASSOCIATED MYOSITIS (POSITIVE JO-1 SEROLOGY)

- **Comment:** The muscle biopsy finding of perifascicular necrotizing myopathy, in the clinical context of interstitial lung disease and positive serum anti-Jo1 antibody, is diagnostic for antisynthetase syndrome associated myositis, Jo-1 subtype.

Scenario 2

- History: 33 year old female presented with bilateral thigh weakness and respiratory insufficiency. She underwent a lung biopsy which was suspicious for interstitial lung disease. Rheumatologic workup which was notable for mechanics hands, high CK in the range of 14,000-20,000. Operative procedure: left thigh muscle biopsy



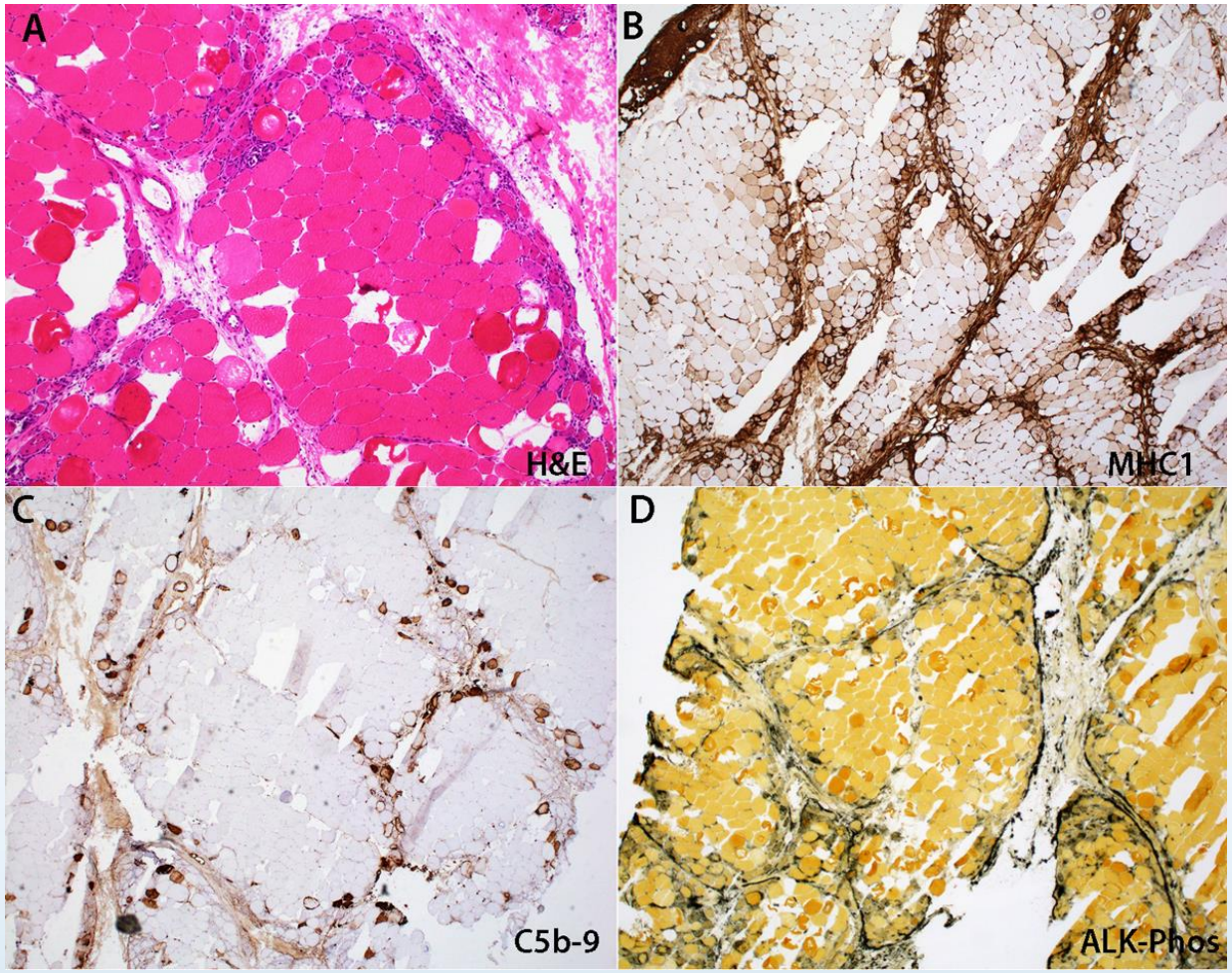
Pathology report:

- **Final diagnosis:** PERIFASCICULAR NECROTIZING MYOPATHY (SEE COMMENT)

- **Comment:** The pathologic findings, in the clinical context of high CK, possible interstitial lung disease, and lack of typical dermatomyositis type rashes, are most suggestive of **antisynthetase syndrome associated myositis**. Correlation with antisynthetase syndrome associated autoantibodies (e.g. Jo-1, EJ, PL-7, PL-12, etc.) is recommended. Systemic scleroderma, dermatomyositis (Mi-2 variant), lupus myositis, among others, may demonstrate similar muscle pathology, but are considered less likely given the clinical context.

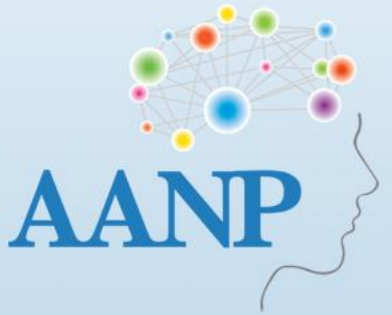
Scenario 3

- History: 33 year old female with no history provided. Operative procedure: Right thigh muscle biopsy.



Pathology report:

- **Final diagnosis:** PERIFASCICULAR NECROTIZING MYOPATHY (SEE COMMENT)
- **Comment:** The main differential considerations include antisynthetase syndrome versus dermatomyositis. The former is often associated with interstitial lung disease, "mechanic's hands", and serum anti-synthetase antibodies (e.g. Jo-1, EJ, PL-7, PL-12 etc.). The latter is often associated with characteristic skin rashes (Gottron's patch and heliotrope rash) and dermatomyositis specific antibodies (e.g. Mi-2, NXP2, TIF1λ, etc). In addition, a subset of overlap myositis, such as lupus myositis and systemic scleroderma may have similar pathology findings on muscle biopsy. Serological studies, chest imaging, and clinical correlations are recommended.



Point 2: avoid “confirmation bias”

- Clinical scenario: A 53-year-old female presented with Gottron papules, subacute symmetric proximal weakness in upper and lower extremities, hand swelling, Raynaud’s phenomenon and occasional joint pain. Her maximum CK was 1784. Myositis specific autoantibody testing was positive for TIF1-γ antibody. Patient was referred for muscle biopsy for suspected DM.

- Pathology: The section shows an inflammatory myopathy with frequent necrotic fibers, regenerating fibers and myofiber atrophy preferentially in the perifascicular regions, as well as perivascular inflammation.

- Final Pathologic Diagnosis: TIF1-γ Positive Dermatomyositis.

Follow up…

- Pt underwent cancer screening, including CT scans of the neck, chest, abdomen, and pelvis, and PET scan imaging. This was repeated at 1,2,3 years per guideline. All returned negative. Pt underwent bx for enlarged lymph node on PET scan, which returned negative.

- Pt later developed mechanics hands, erosive arthritis and interstitial lung disease. Repeating serological testing, using both prior serum and new specimen, tested negative for TIF1-γ but positive for PL-12 in both specimens.

- Pt re-diagnosed with antisynthetase syndrome, medication readjusted from methotrexate to mycophenolate mofetil

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Lesson learned:

- MSA is not 100% reliable.
  - Overall 35.6% false negative rate, 32.5% false positive rate
  - **TIF1γ has particularly high false positive rate**
- "Cold turkey" approach recommended for initial pathology evaluation

Table 1. Description of the positive samples

	No. of positive samples					
	LIA	Immunoprecipitation	Sensitivity, %	Specificity, %	κ value (95%CI)	Agreement
ASyS	25	23	87	96	0.8 (0.6, 0.9)	Good
Jo1	16	16	81.3	97.7	0.79 (0.7, 1)	Good
PL-12	7	5	100	98.6	0.83 (0.6, 1)	Very good
PL-7	2	2	100	100	1 (1, 1)	Very good
MDA5	15	14	71.4	96.2	0.66 (0.5, 0.9)	Good
NXP2	5	6	66.7	99.3	0.72 (0.4, 1)	Good
Mi2	14	9	77.8	94.9	0.58 (0.3, 0.8)	Moderate
SAE	4	4	50	98.6	0.49 (0.1, 0.9)	Moderate
TIF1γ	8	1	100	12.5	0.21 (−0.1, 0.6)	Fair
Ku	7	3	66.7	96.5	0.38 (0.2, 1)	Fair
Pm-Scl	9	4	100	96.5	0.6 (0.3, 0.9)	Moderate

Loganathan, A., et al. (2024). "Assessing the sensitivity and specificity of myositis-specific and associated autoantibodies: a sub-study from the MyoCite cohort." Rheumatology (Oxford).

Point 3: Does clinicians understand your “hedge words”?

- Case Vignette; A 63 yo M with a history of poorly controlled diabetes presented with intractable right thigh pain and progressive swelling for few weeks. Muscle MRI showed diffuse edema, serum CK was normal. Clinical considerations include infection vs myositis.
- Pathology: *moderate to marked variation in myofibers, moderate edema, a few probable necrotic myofibers and a few small endomysial and perivascular clusters of predominantly CD4+ lymphocytes.*
- *Final pathologic Diagnosis: Scant patchy chronic inflammation and focal interfiber edema and regenerative myofibers. The histologic features are compatible with those in diabetic muscle infarction.*
- *Clinician feedback:* Patients clinical presentation was not consistent with diabetic muscle infarction. **No differential diagnosis provided**, **reflecting the pathologists high confidence,** and since there is no specific treatment for diabetic muscle infarction, this diagnosis conveys the risky message to clinician that no further diagnostic or specific treatment is warranted.

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Point 3: lesson learned

- A single dx without alternative consideration is considered high confidence.
- Clinician may not understand “consistent with”, “compatible with” are hedging words that convey low confidence.
- If pathology is not specific, state so and provide differentials.

Point 4: Understand the treatment implications: err on the side of “treatable”

- **Case Vignette:** A 76 you F with a history of EtOH abuse presented with subacute onset progressive asymmetric painful weakness and sensory loss. EMG/NCV studies showed asymmetric axonal sensorimotor neuropathy with absent radial and ulnar sensory responses. Clinical suspicion: mononeuritis multiplex.
- Radial nerve bx findings: “Neurofilament staining show no significant loss of large myelinated axons. Mild “focal perivascular chronic inflammation is noted. No vasculitis is seen. CD3 highlights predominantly perivascular aggregates of T cells in the perineurium and endoneurium”
- “Final Pathological Diagnosis: Axonopathy, no evidence of vasculitis. Comment: The nerve findings could represent those seen in alcohol related peripheral neuropathy.”
- Clinician feedback: The pathology report was misleading towards a non-treatable condition (alcoholic neuropathy) rather than a treatable condition. Interpretation of biopsy findings was biased with history of EtOH abuse although her clinical presentation was clearly unrelated to alcoholic neuropathy. No other differential diagnosis was provided, and interpretation of perineurial CD3 T cells and macrophage were disregarded. She was treated as an inflammatory neuropathy/possible mononeuritis multiplex. She gained significant hand function and had significant grip strength almost doubled.

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Summary

Pathology

- DM subtypes
  - Mi2
  - NXP2/TIF1y
  - MDA5
- DM mimickers
  - ASyS
  - Lupus myositis
  - Systemic scleroderma
  - Eosinophilic fasciitis
  - ICI myositis

Reporting

- Avoid pure “descriptive” reports
- “Sliding scale” reporting
- Avoid confirmation bias
- Clarity of “hedge words”
- Err on the side of “treatable”

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Q&A