Diagnostic Slide Session
AANP 2019

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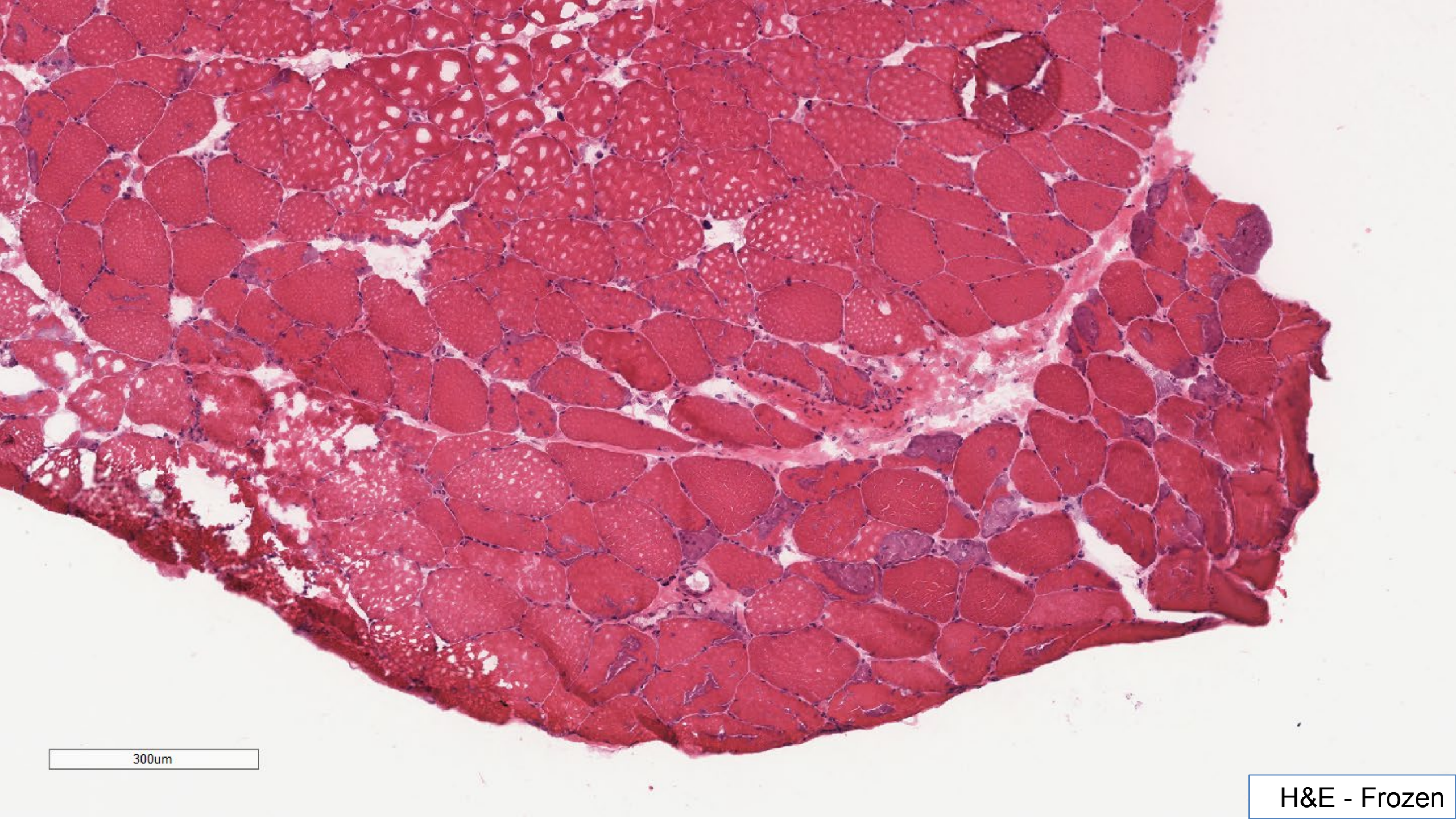
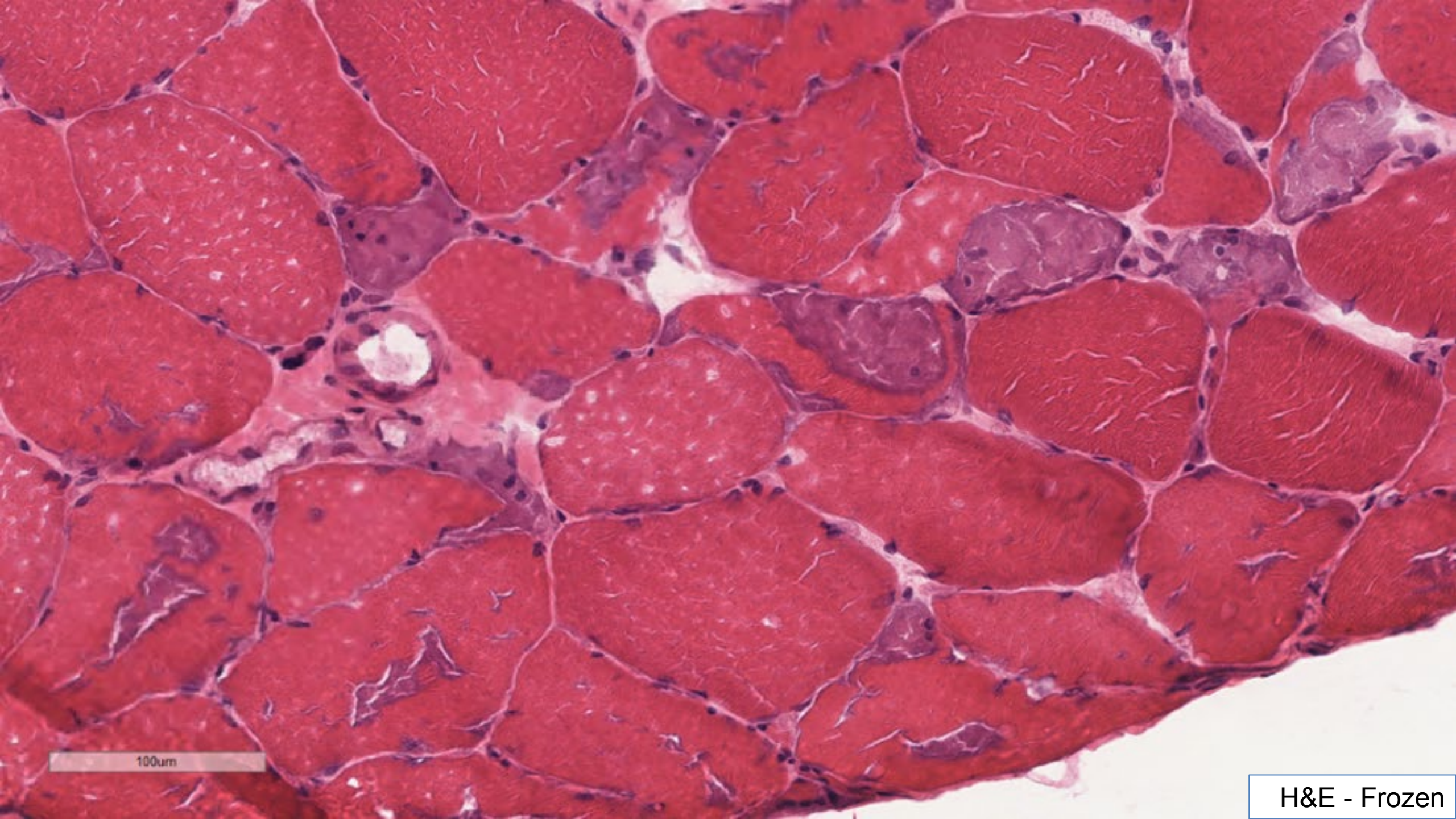
Clinical history

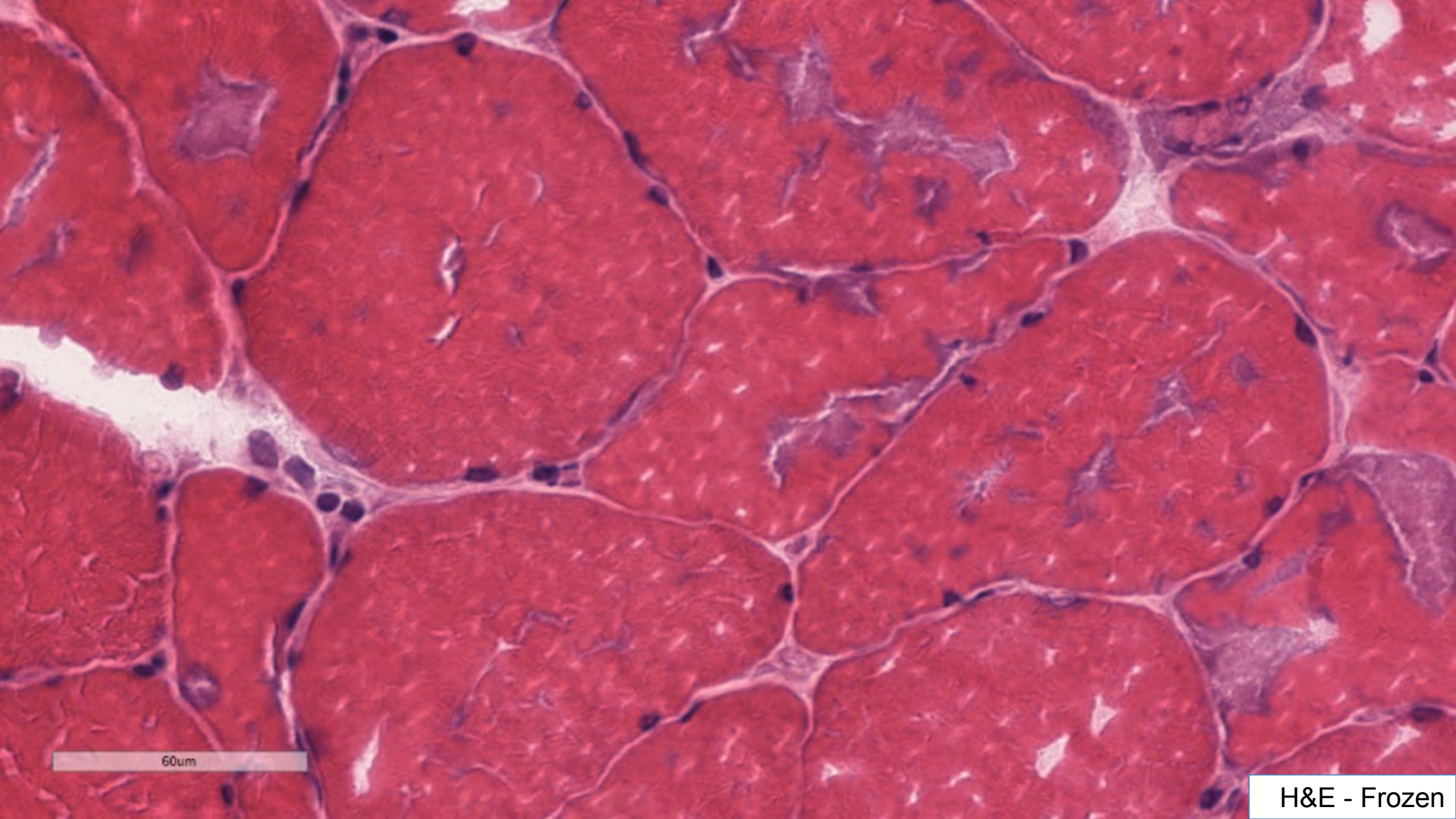
- 16 year old male presented to the ED with sudden onset of pain and swelling in hands and around eyes
- Symptoms resolved completely after several days
- Initial CK was 871 in the ED, fluctuated between 600s and 900s over the next several months
- Labs remarkable for leukocytosis and mild thrombocytopenia
- MRI showed lymphadenopathy but no muscle changes
- Biopsy of right vastus lateralis performed



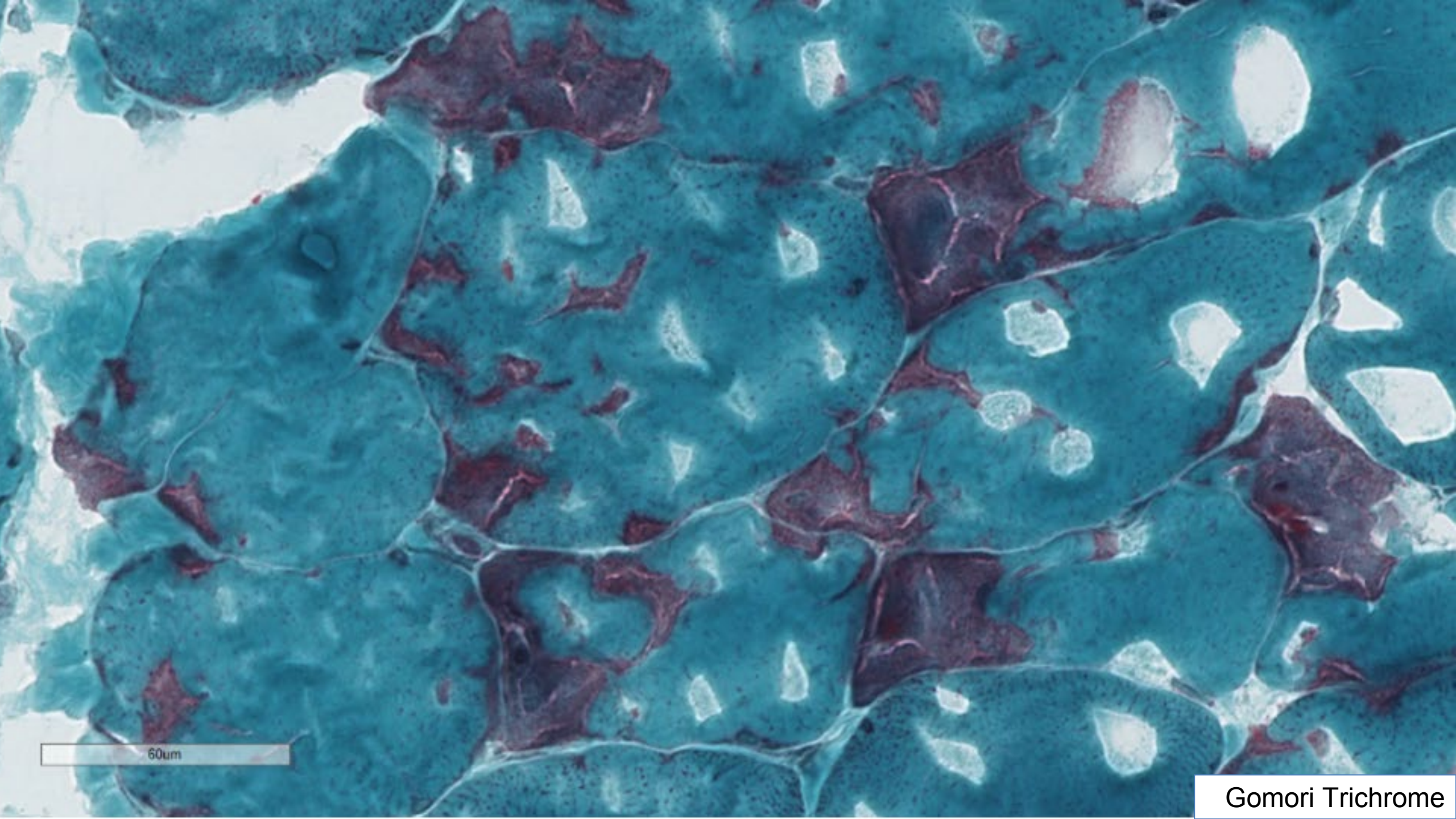
H&E - Frozen



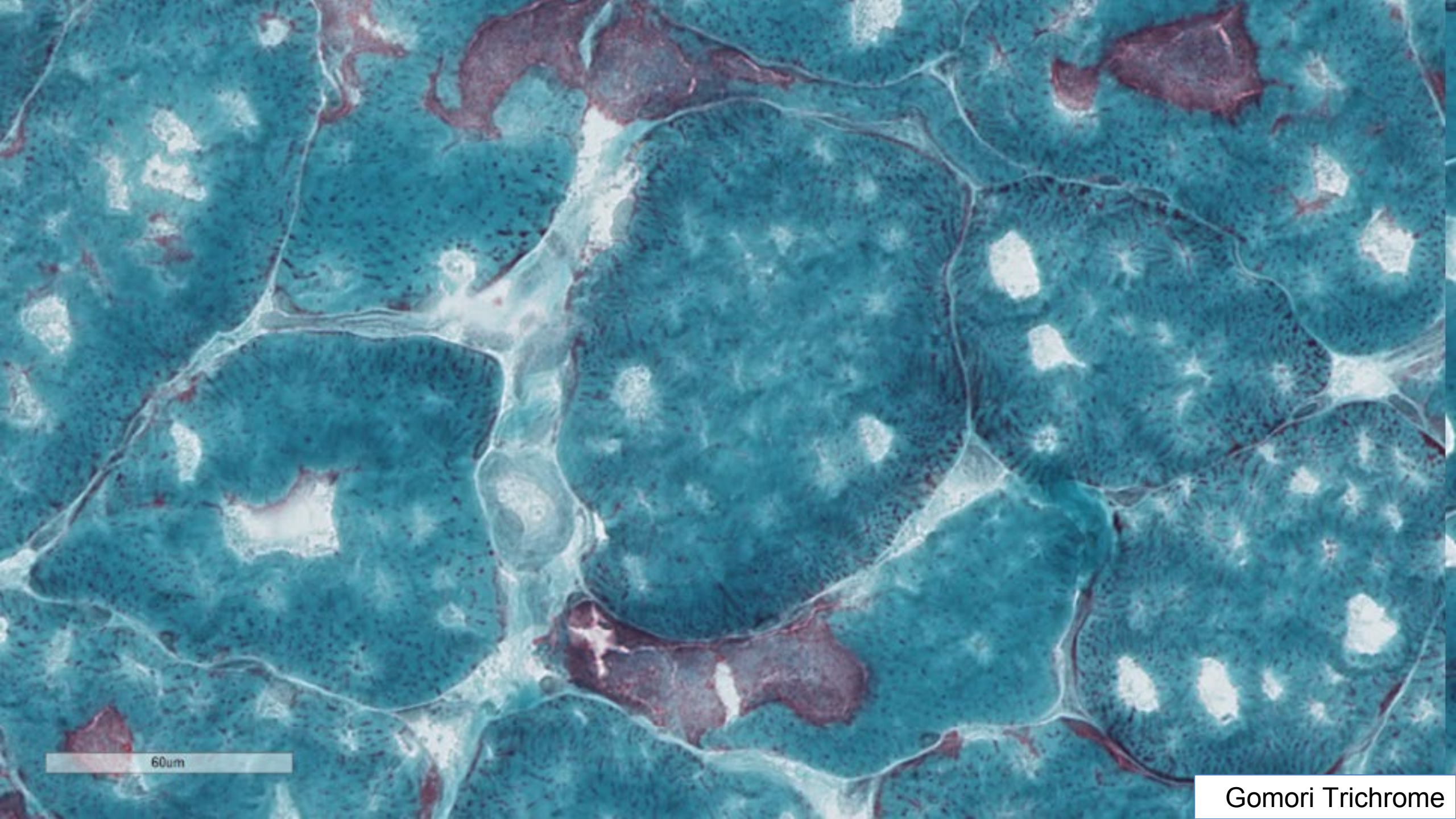
H&E - Frozen



H&E - Frozen



Gomori Trichrome

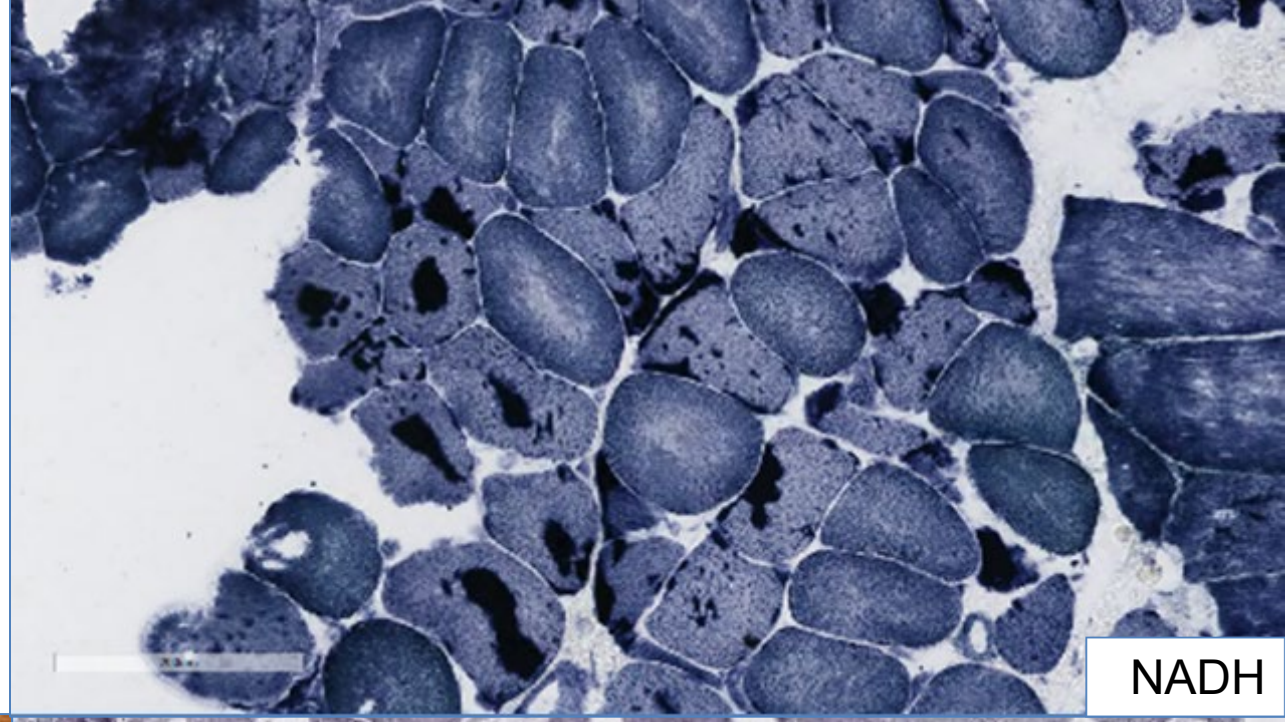


Gomori Trichrome

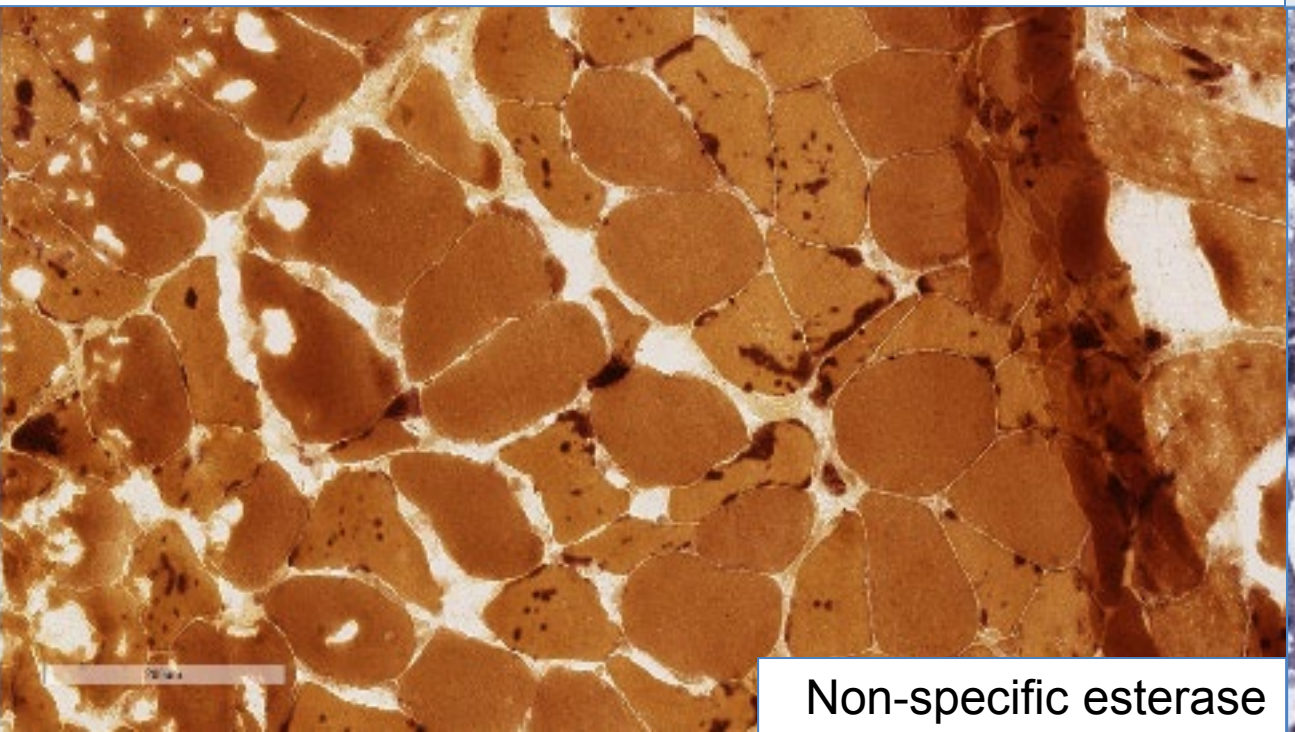
Discussion

Additional workup

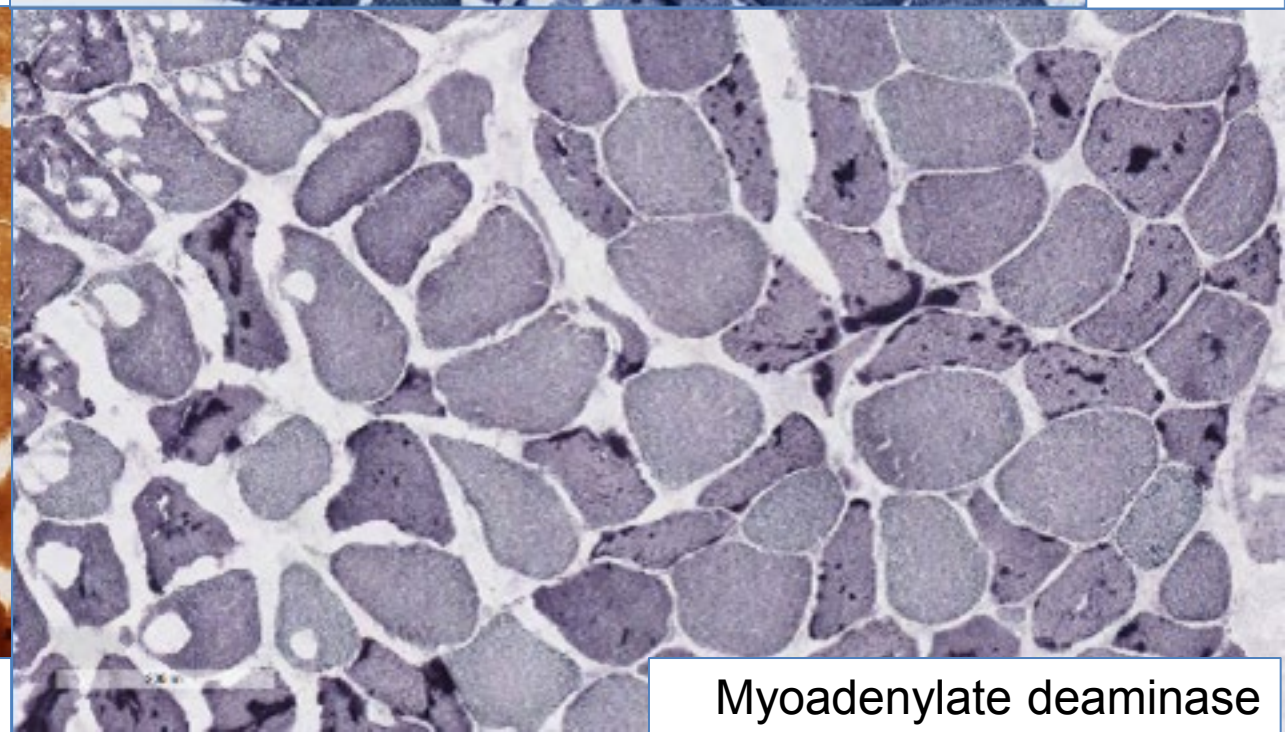
Additional positive stains



NADH

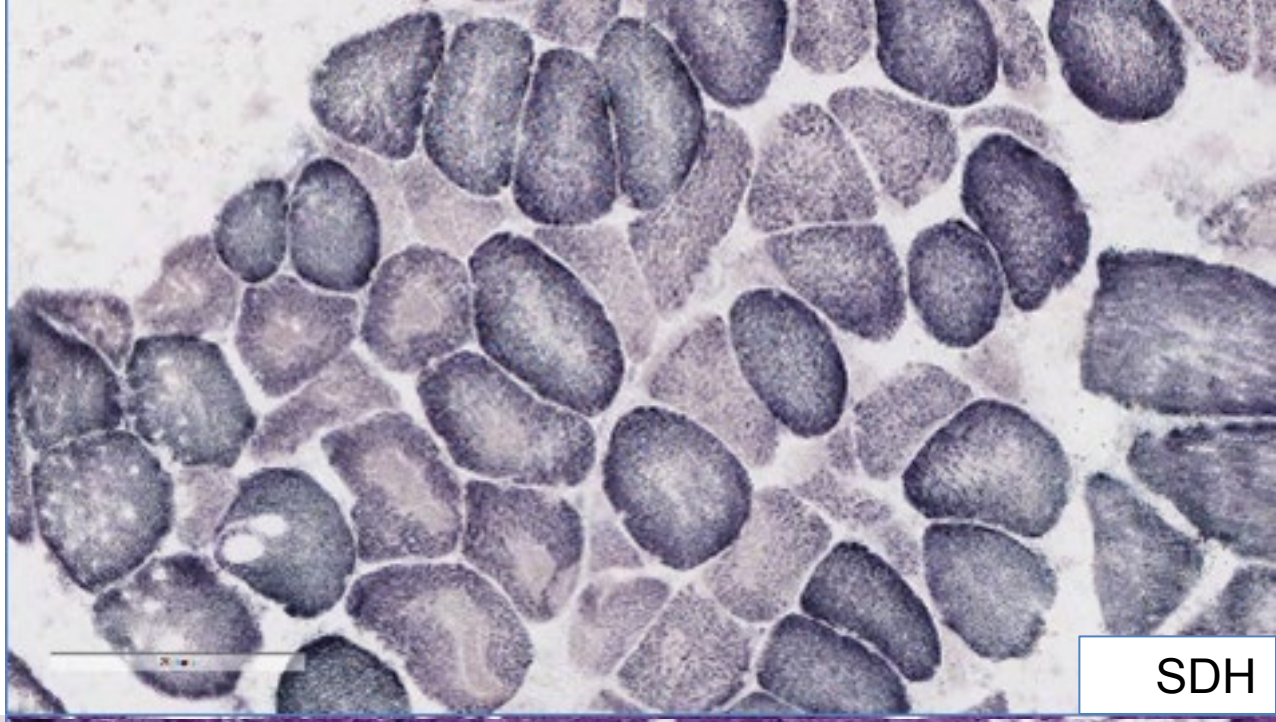


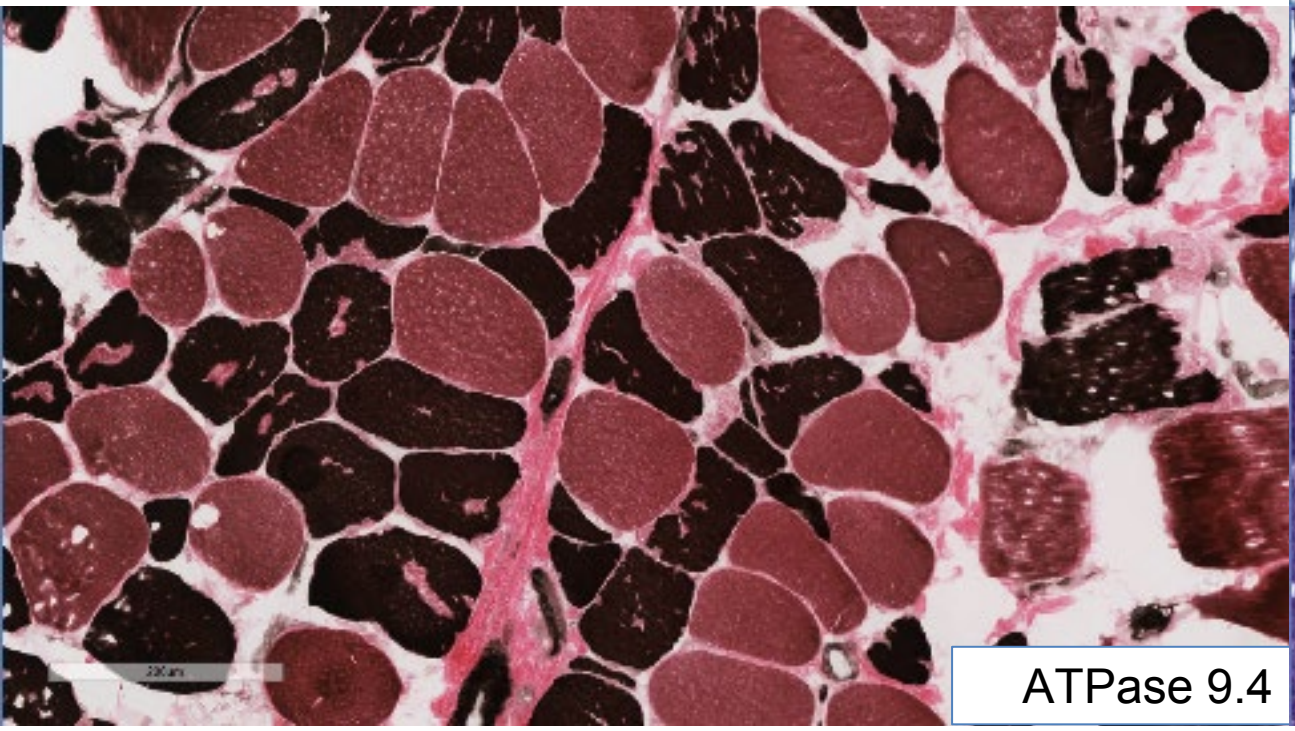
Non-specific esterase

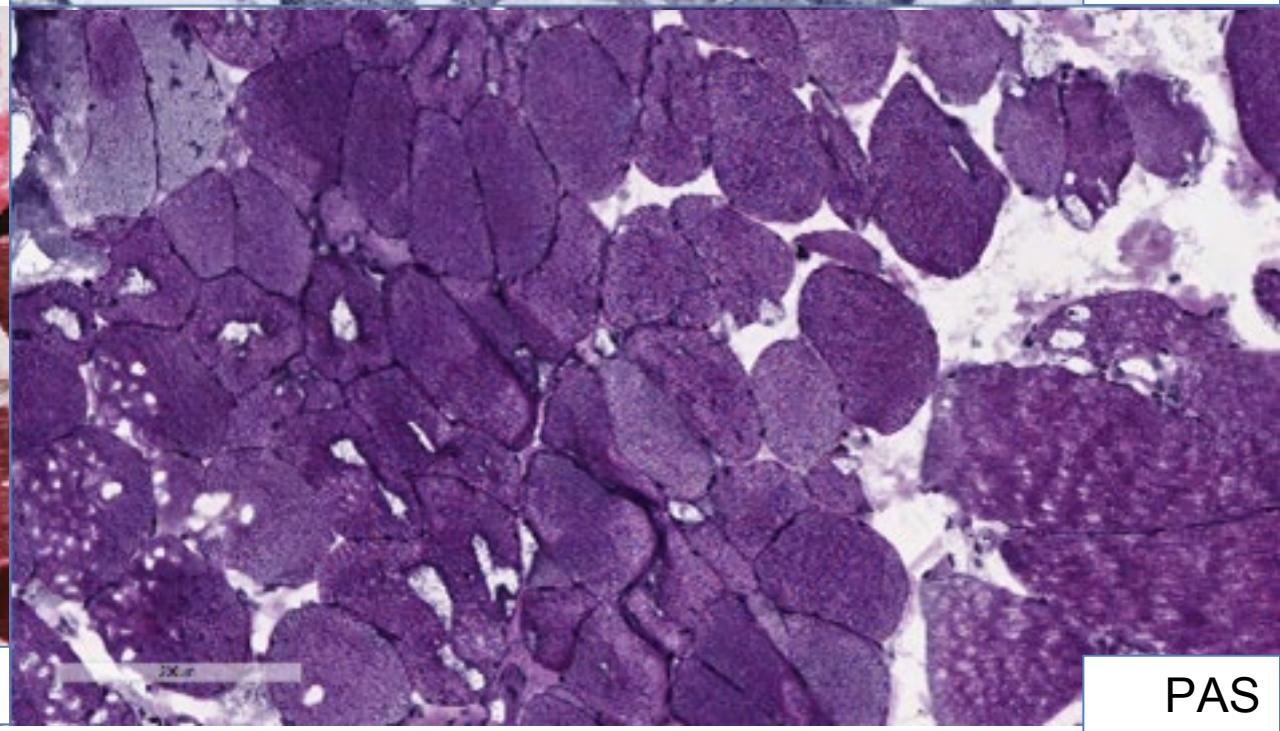


Myoadenylate deaminase

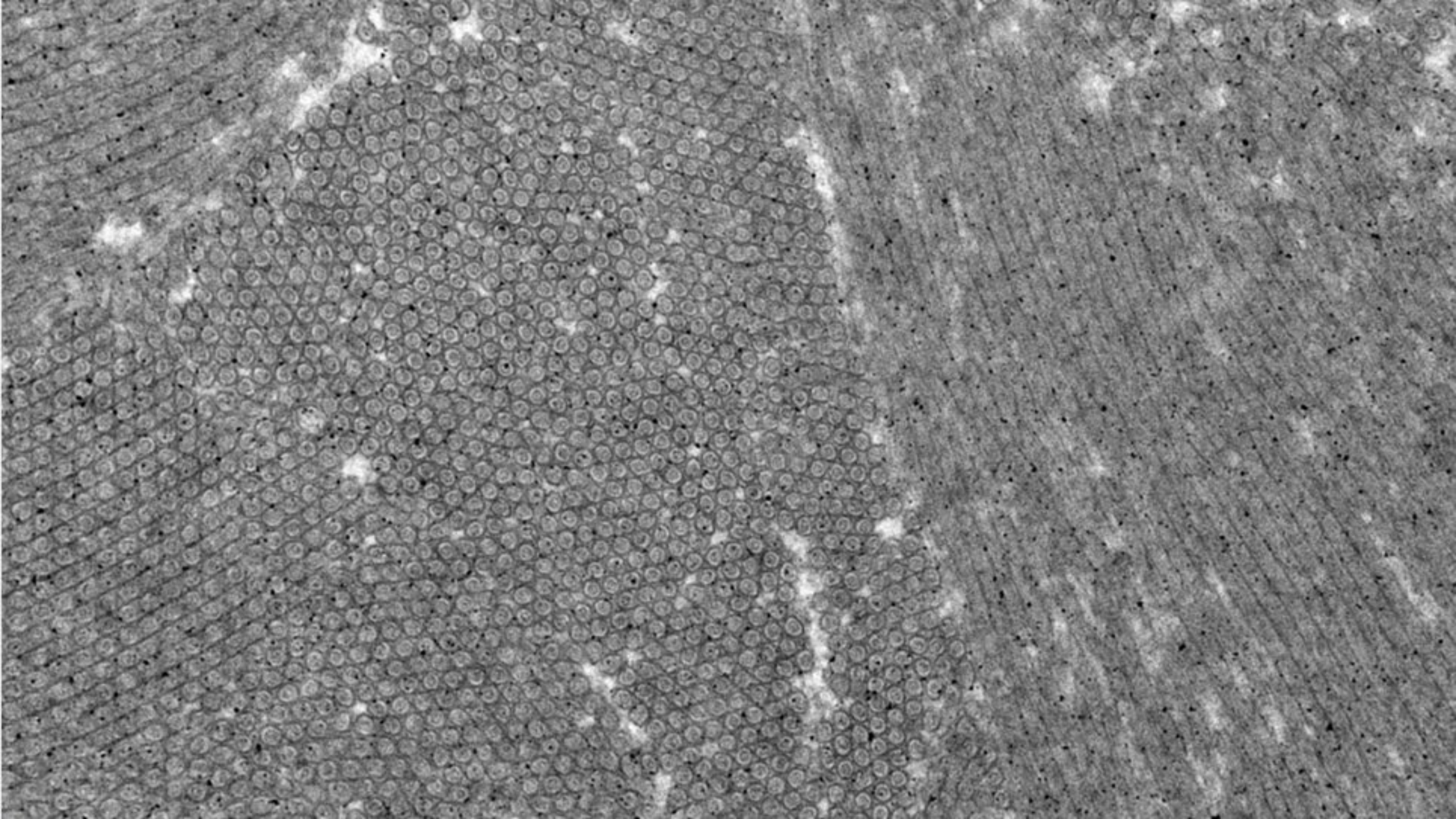
Additional negative stains







Electron microscopy



Genetic testing

Pathogenic variant, c.910C>T (p.Arg304Trp) in *STIM1* gene

Final diagnosis

Tubular aggregate myopathy associated with *STIM1* mutation (Stormorken syndrome)

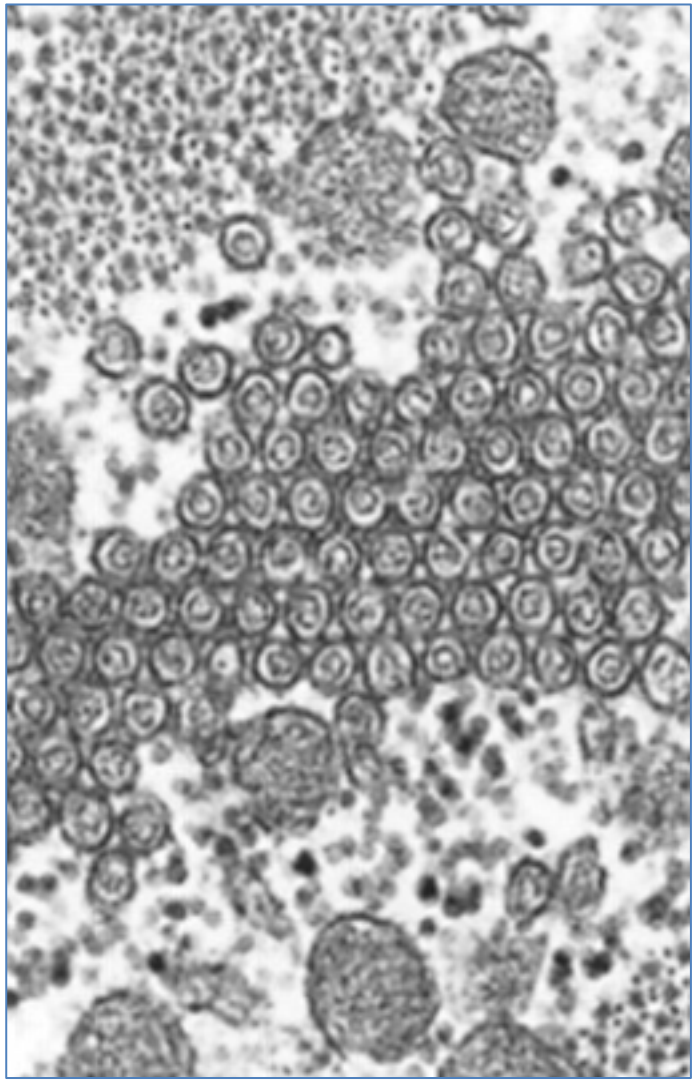
Tubular aggregates

MITOCHONDRIAL AGGREGATES IN MUSCLE DISEASE

October 10, 1963 W. KING ENGEL

Medical Neurology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Maryland

- Originate from sarcoplasmic reticulum and are thought to represent an adaptive response
- Characteristic immunoprofile:
  - –NADH (+)
  - –MADA (+)
  - –SDH (-)
  - –COX (-)
- Ultrastructure: Single membrane, often containing one inner tubule with consistent diameter
- More commonly seen in Type 2 fibers
- Rare: 1% of muscle biopsies in a large series



Jacques et al. 2002

Differential diagnosis of tubular aggregates

<u>"Secondary" tubular aggregates</u>

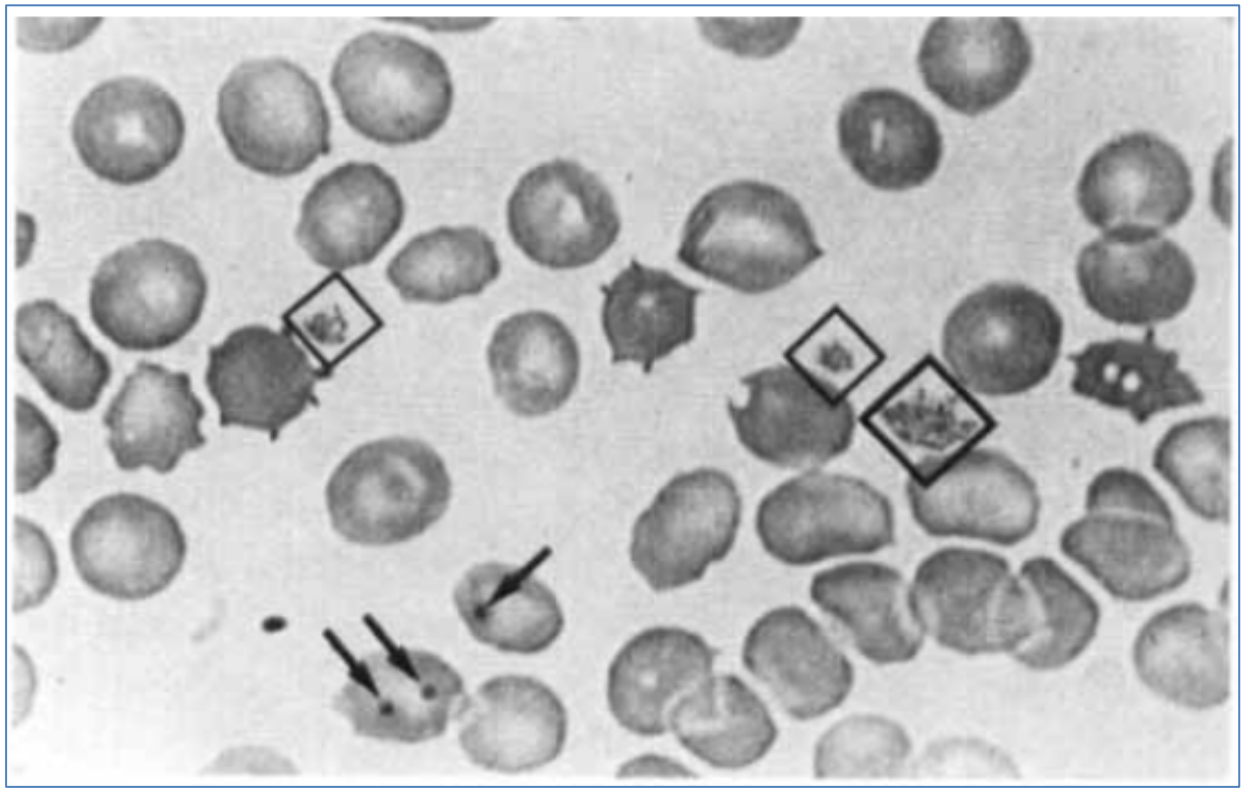
- Hypokalemic / hyperkalemic periodic paralysis
- Congenital myotonic dystrophies
- Inflammatory myopathies
- Exercise-induced cramps
- Drug- and alcohol-induced myopathies
- Congenital myasthenic syndromes

<u>True "tubular aggregate myopathy"</u>

A new syndrome: thrombocytopathia, muscle fatigue, asplenia, miosis, migraine, dyslexia and ichthyosis

HELGE STORMORKEN[1], OTTAR SJAASTAD[2], ASBJØRN LANGSLET[3], ILMAR SULG[2], KJELL EGGE[4] AND JØRGEN DIDERICHSEN[5]

- Mild, slowly progressive lower extremity weakness, cramps, and exercise intolerance
  - Tubular aggregates
  - May have mild myopathic changes
  - Type II fiber atrophy
- Only a small number of families have been identified
- York platelet syndrome



Stormorken et al. 1985

Physiologic role:

(1) Store operated Calcium entry **(SOCE)** refills Ca^{2+} store in the sarcoplasmic reticulum

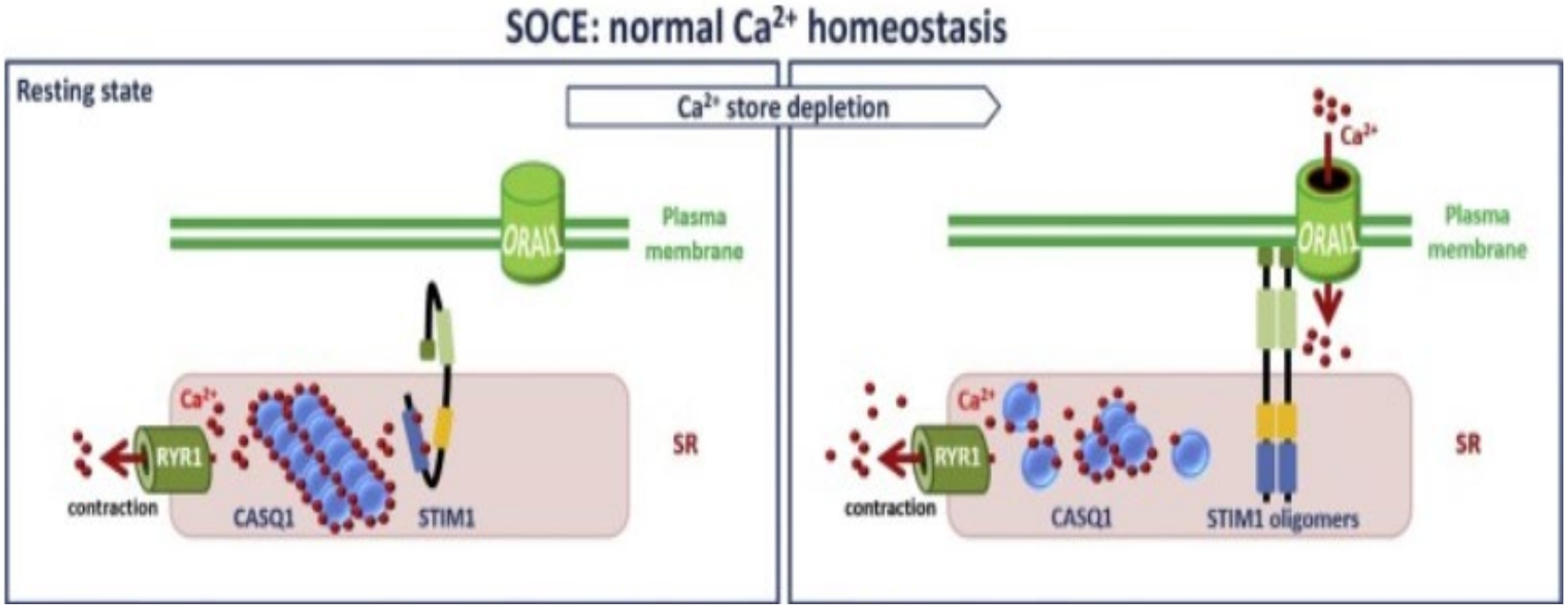
(2) Stromal interaction molecule 1 **(STIM1)** is the main sensor on the endoplasmic reticulum.

(3) Ca2+-release-activated Ca2+ **(CRAC)** channels trigger extracellular Ca2+ entry.

REPORT

Constitutive Activation of the Calcium Sensor STIM1 Causes Tubular-Aggregate Myopathy

Johann Böhm,[1,2,3,4,5] Frédéric Chevessier,[6,18,19] André Maues De Paula,[7,8,9,18] Catherine Koch,[1,2,3,4,5] Shahram Attarian,[10] Claire Feger,[1,2,3,4,5] Daniel Hantaï,[6,11] Pascal Laforêt,[6] Karima Ghorab,[12] Jean-Michel Vallat,[12] Michel Fardeau,[6,13] Dominique Figarella-Branger,[9] Jean Pouget,[10] Norma B. Romero,[6,13,14] Marc Koch,[2,3,4,15] Claudine Ebel,[2,3,4,16] Nicolas Levy,[7,8,17] Martin Krahn,[7,8,17] Bruno Eymard,[6] Marc Bartoli,[7,8,17] and Jocelyn Laporte[1,2,3,4,5,*]



Bohm et al. 2013

Conclusion

- Tubular aggregates are a non-specific finding, but tubular aggregates in the absence of other pathologies suggests tubular aggregate myopathy

- The combination of tubular aggregate myopathy and other clinical features (hematologic, dermatologic, and ocular abnormalities) may suggest Stormorken syndrome

References

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