A case of bilateral scapular winging

41st ANNUAL CARRELL-KRUSEN NEUROMUSCULAR SYMPOSIUM

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Patient History

- 31-year-old man with a chief complaint of weakness
- Normal development, met all milestones
- Age 9: he began to develop weakness
  - Unable to hop on either foot
  - Difficulty raising arms above head
- Over the next year, the weakness progressed to the point of almost having to use a wheelchair

Patient History: Age 10-11

- CK in the 3000s
- Muscle biopsy: reduced calpain-3 staining
- He was diagnosed with LGMD 2A; no genetic testing was performed (not commercially available at that time)
- Started on prednisone based on the notion that all muscular dystrophies may benefit from steroid treatment; switched to deflazacort 1 year later
- Noted no further decline in symptoms, and some improvement in his ability to climb stairs

Patient History: Age 11-28

- Remained on steroids for 2-3 years
- Eventually, his MD tried to wean him off steroids due to side effects (weight gain, facial puffiness), but strength worsened and he was restarted on steroids 6 months later
- His disease remained relatively stable. He had difficulty with:
  - Core weakness, could not do sit ups
  - Hamstrings, gluteal, shoulder girdle muscles remained weak
  - Did not use assistive devices
- He remained on steroids until age 28 when he was successfully weaned off, though he developed mild adrenal insufficiency

Patient History: Age 29

- He was stable for a year after he stopped steroids
- He then began to develop facial weakness and fatigue. Weakness remained stable.
- He moved to Los Angeles to take a new job, and was referred to UCLA for evaluation and management
- He was off steroids for 2 years before he came to our office

Past Medical/Surgical History:

- Hypertension
- Anxiety/Depression

Meds:

- Creatine, L-Arginine, Alpha-Lipoic Acid

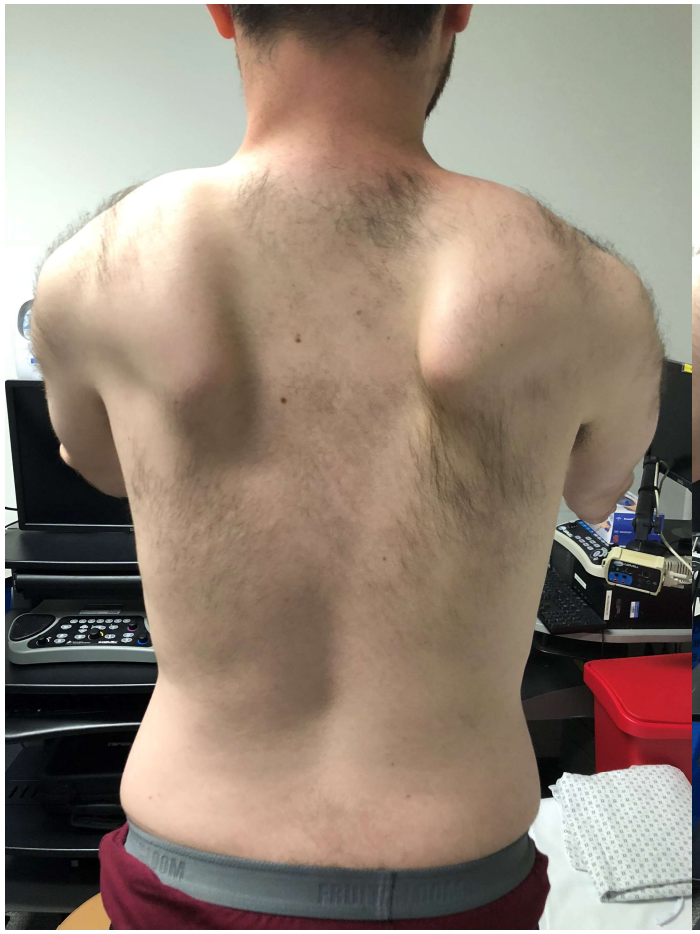
Social History:

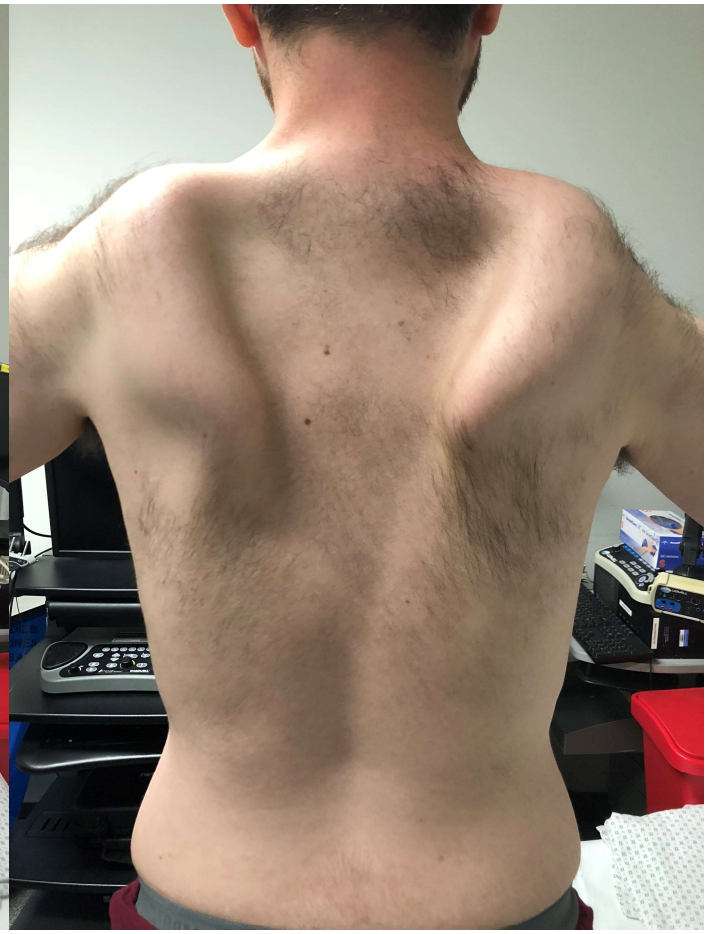
- Works as an assistant professor in Statistics
- Never smoked
- Never used illicit drugs
- Social EtOH use

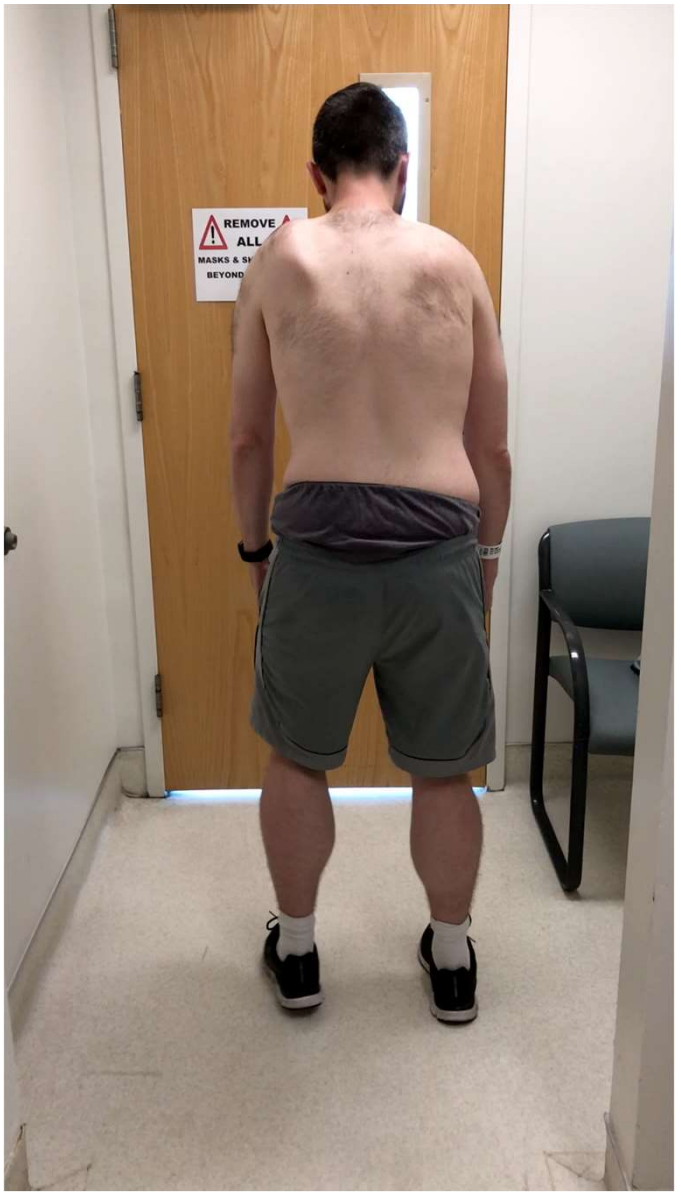
Family History:

- Maternal grandma with “polymyositis or myasthenia gravis” during her mid-50s. She was on prednisone for 14 years which kept her stable.

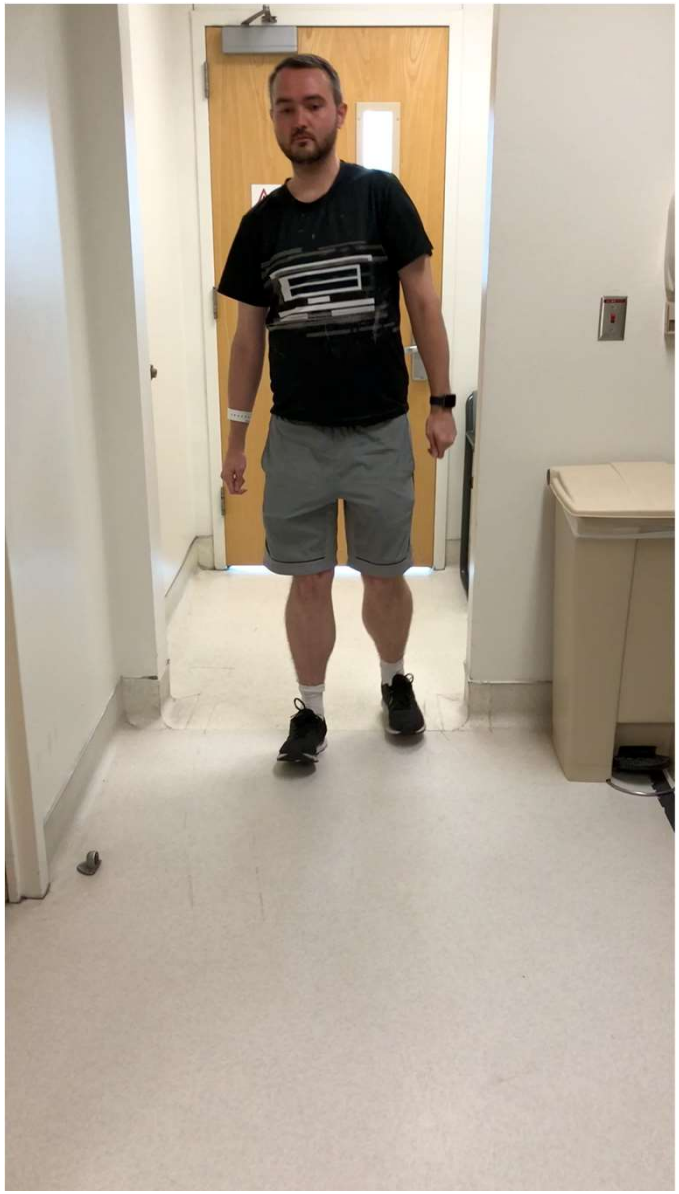
Physical Exam






REMOVE
ALL

Gait:



CN:

- Mild facial weakness

Motor:

- Decreased bulk in the bilateral proximal arms and proximal legs
- Increased bulk in bilateral calves
- Bilateral scapular winging
- Normal tone, no fasciculations

Manual Motor Testing (right/left)

- Shoulder Abd 4/4
- Biceps 4+/4+
- Triceps 4+/4+
- Wrist extension 5/5
- Wrist flexion 5/5
- Interossei 5/5
- Finger flexion 5/5

- Hip flexion 3/3
- Hip extension 3/3
- Knee extension 5/5
- Knee flexion 5/5
- Dorsiflexion 5/5
- Plantar flexion 5/5

Sensory:

- Normal sensation to LT, PP, vibration, proprioception
- Romberg sign absent

Reflex testing

Biceps	2/2
Triceps	2/2
Brachioradialis	2/2
Patellar	1/1
Achilles	0/0
Plantar Response	down/down

Testing 2018 (during our initial evaluation)

- LFTs:
  - ALT 52 (nl range 9-46 U/L)
  - AST 39 (nl range 10-40 U/L)
  - Bilirubin 0.9 (nl range 0.2-1.2 mg/dL)
  - Alk Phos 63 (nl range 40-115 U/L)
- CK 678 U/L (upper limit 473 U/L)
- Aldolase 13.1 U/L (range 2.7-12.1 U/L)

- Normal CBC, BMP, TSH, ESR, CRP, ANA panel, SSA/SSB, AchR panel

EMG/NCS:

Normal nerve conduction studies

Irritable changes:

- Right deltoid and right trapezius
- Right thoracic paraspinals
- Right vastus medialis

PSW/fibs
Normal-appearing MUAPs
Normal recruitment

Thoughts?

Genetic testing

- FSHD1 testing

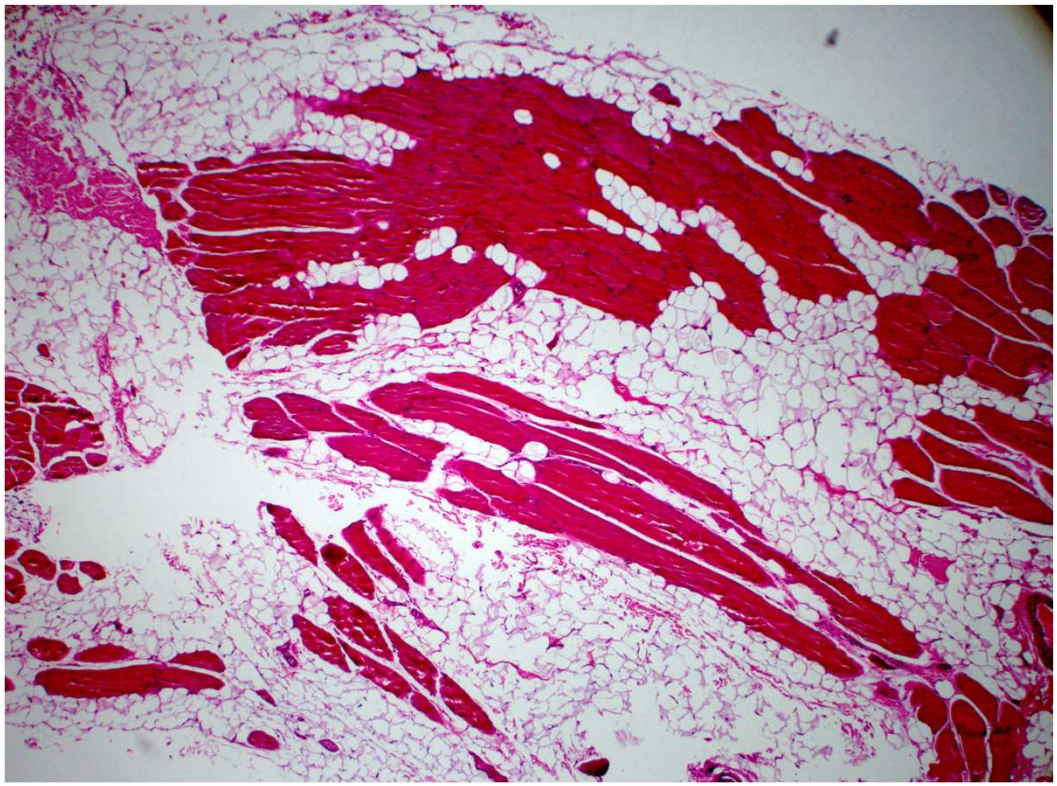
- Invitae Comprehensive Muscular Dystrophy Panel including
  - LGMD 2A (calpain-3)
  - LGMD 2C-F (sarcoglycans)
  - LGMD 2I (FKRP)
  - LGMD 1B (Lamin A/C)
  - FSHD2 (SMCHD1)

Negative

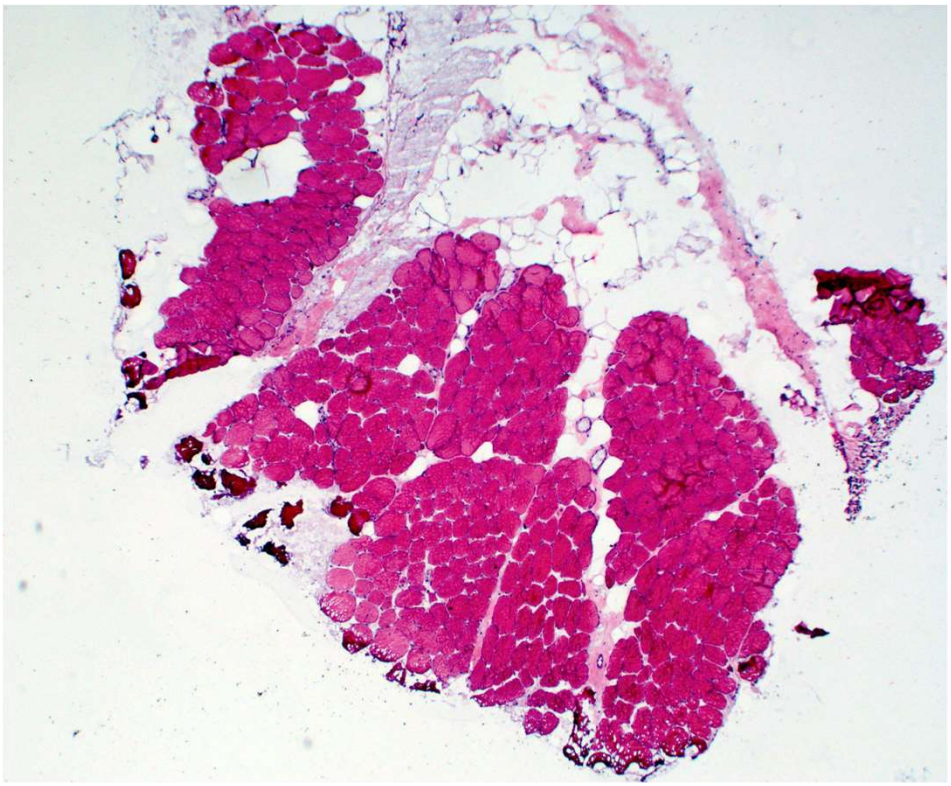
Clinical Summary

- Progressive proximal weakness with mild facial weakness, starting at age 9
- Family history of “polymyositis vs myasthenia gravis” in maternal grandmother
- Bilateral scapular winging with proximal atrophy and weakness
- Elevated CKs (3000 U/L initially, 678 U/L twenty years later)
- Irritability on EMG
- Negative genetic testing

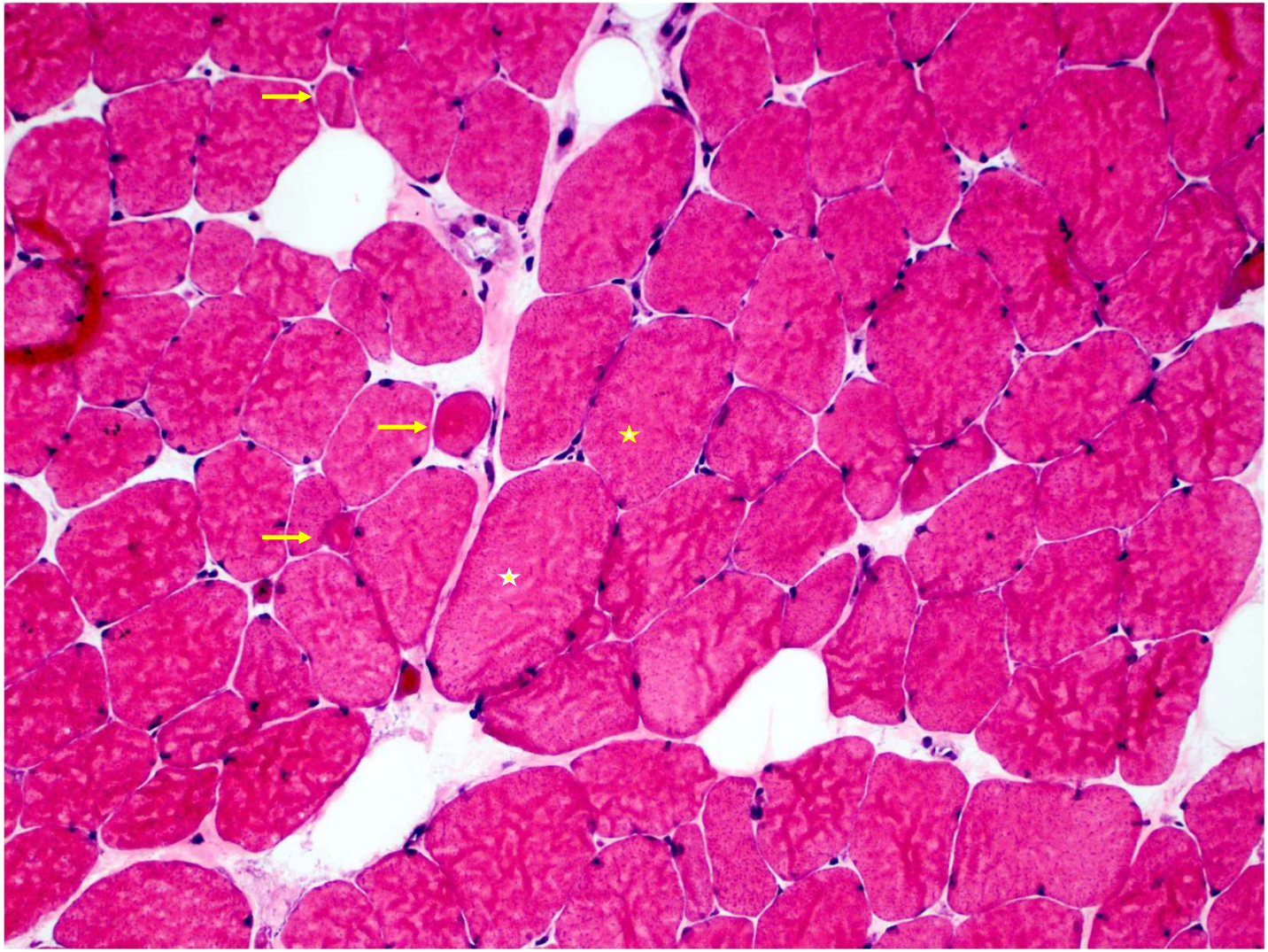
Thoughts?



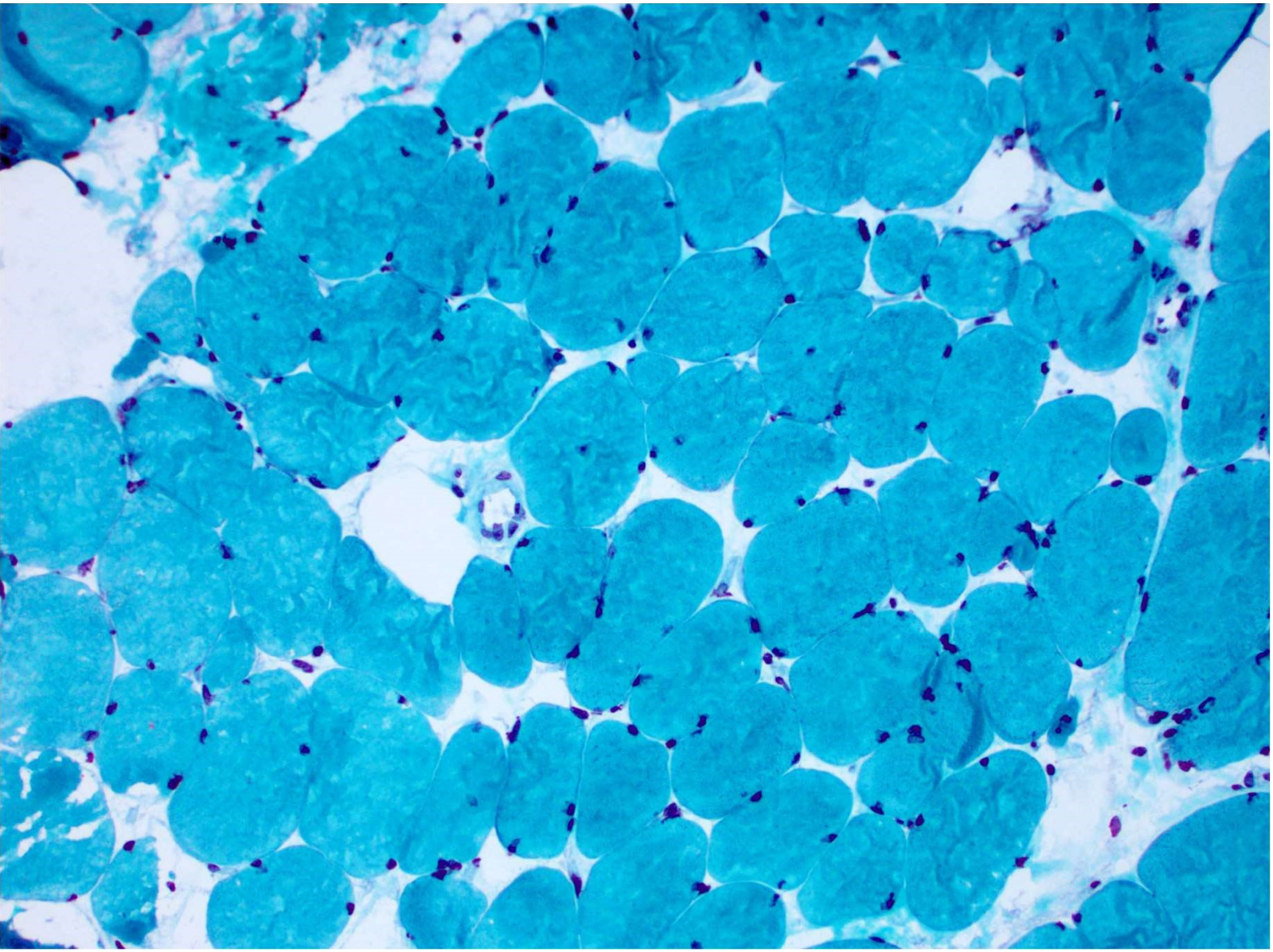
Paraffin embedded HE X 10



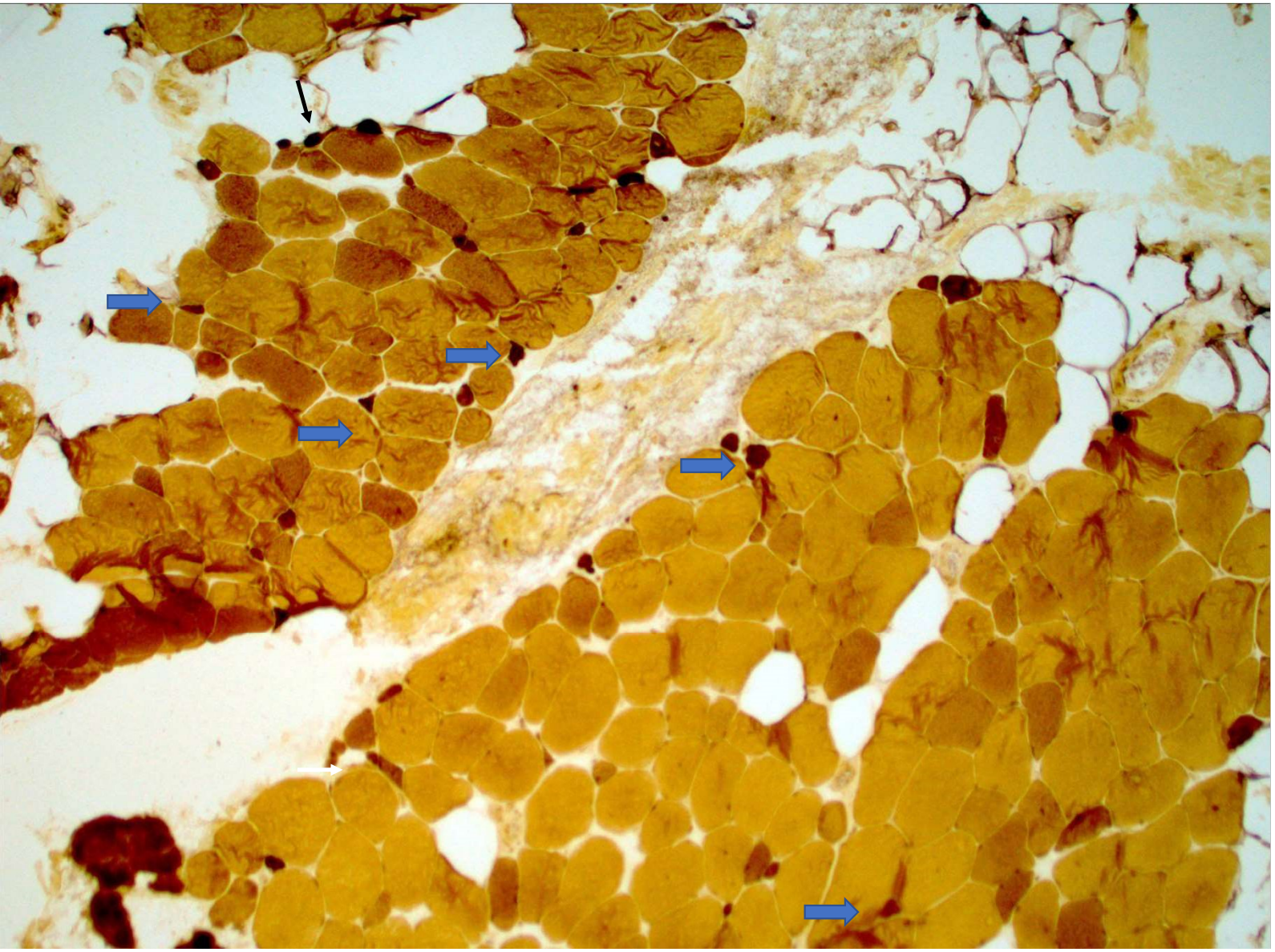
Frozen tissue - HE X 10



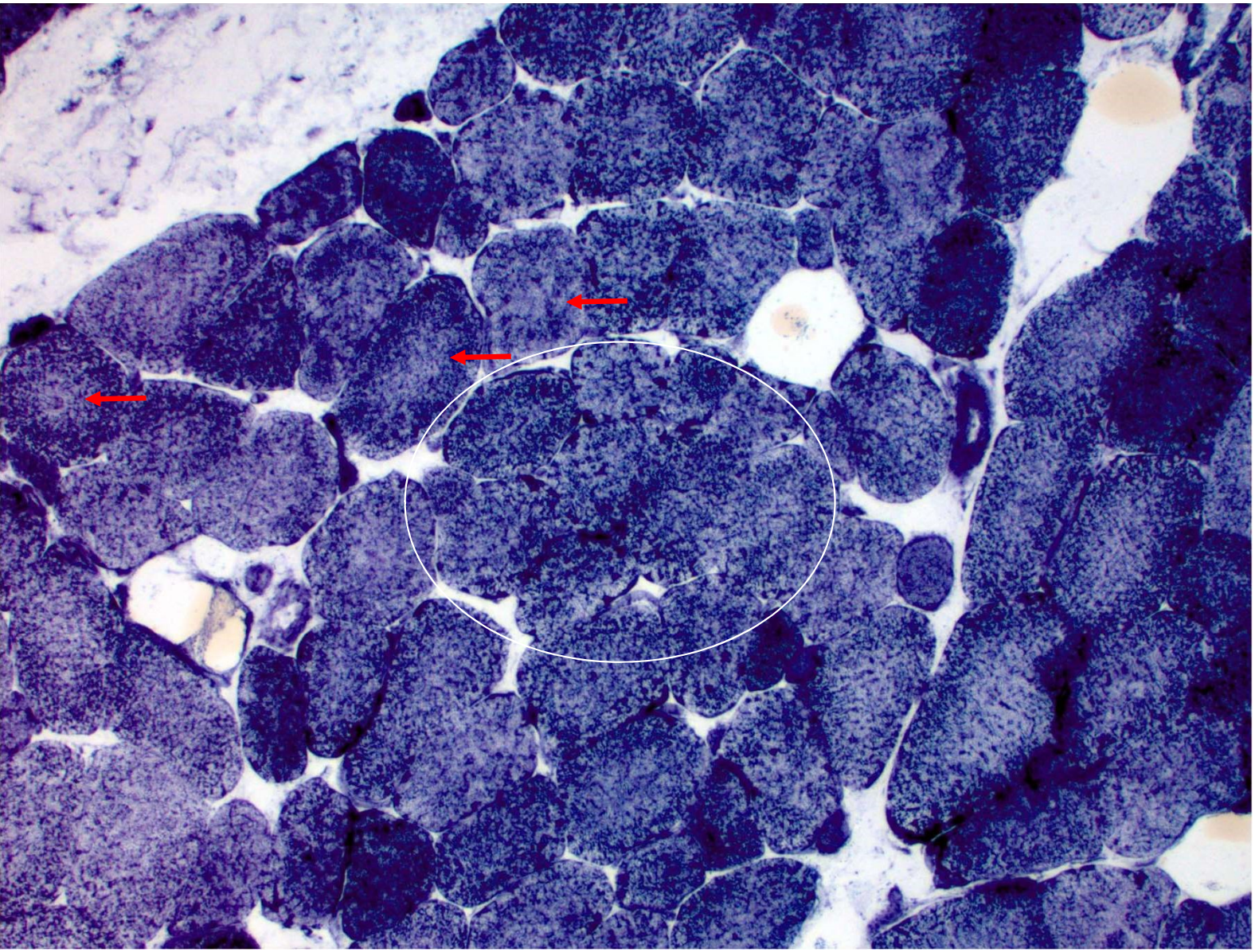
Frozen HE X 20



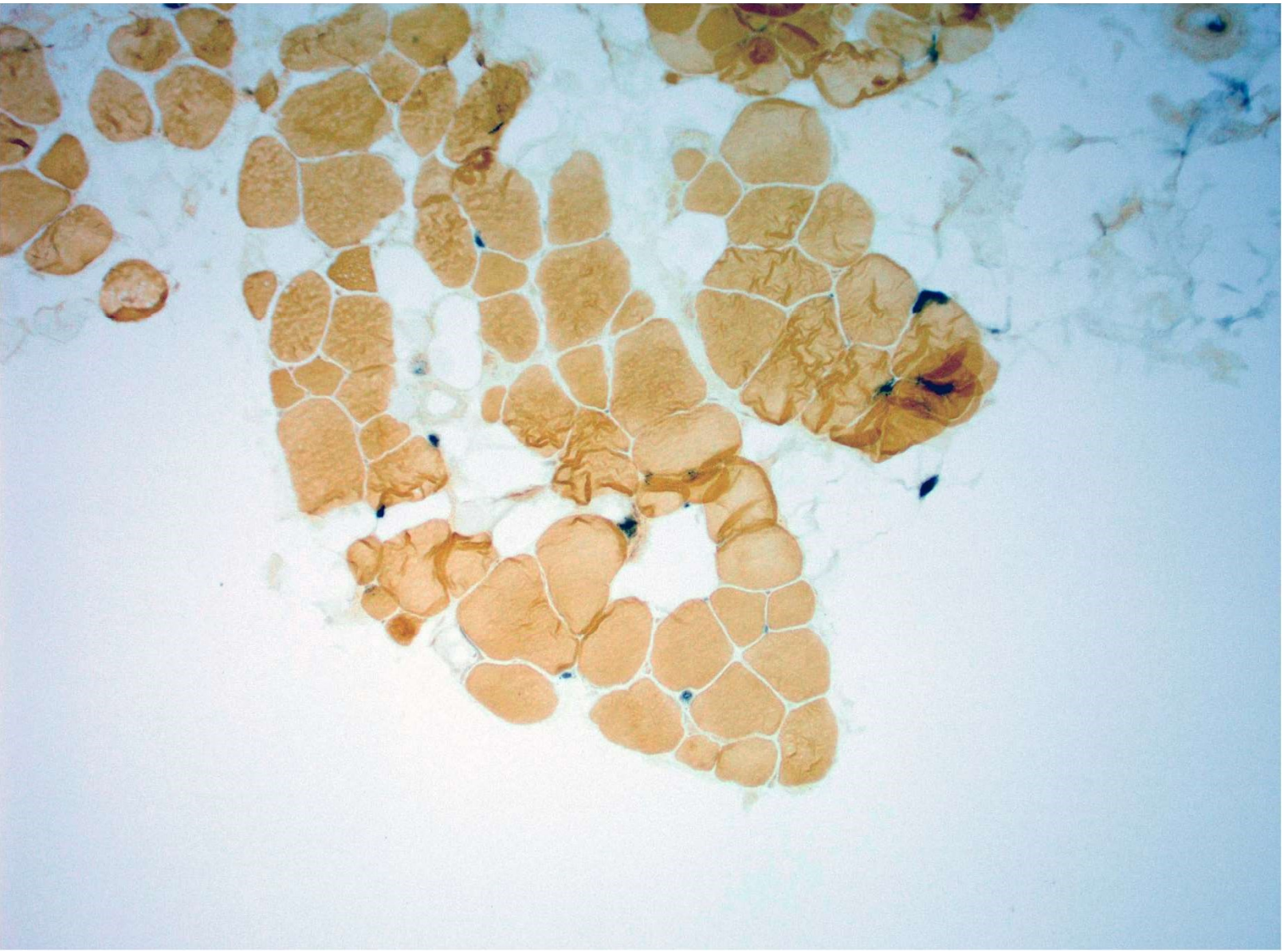
Modified Gomori trichrome X 20



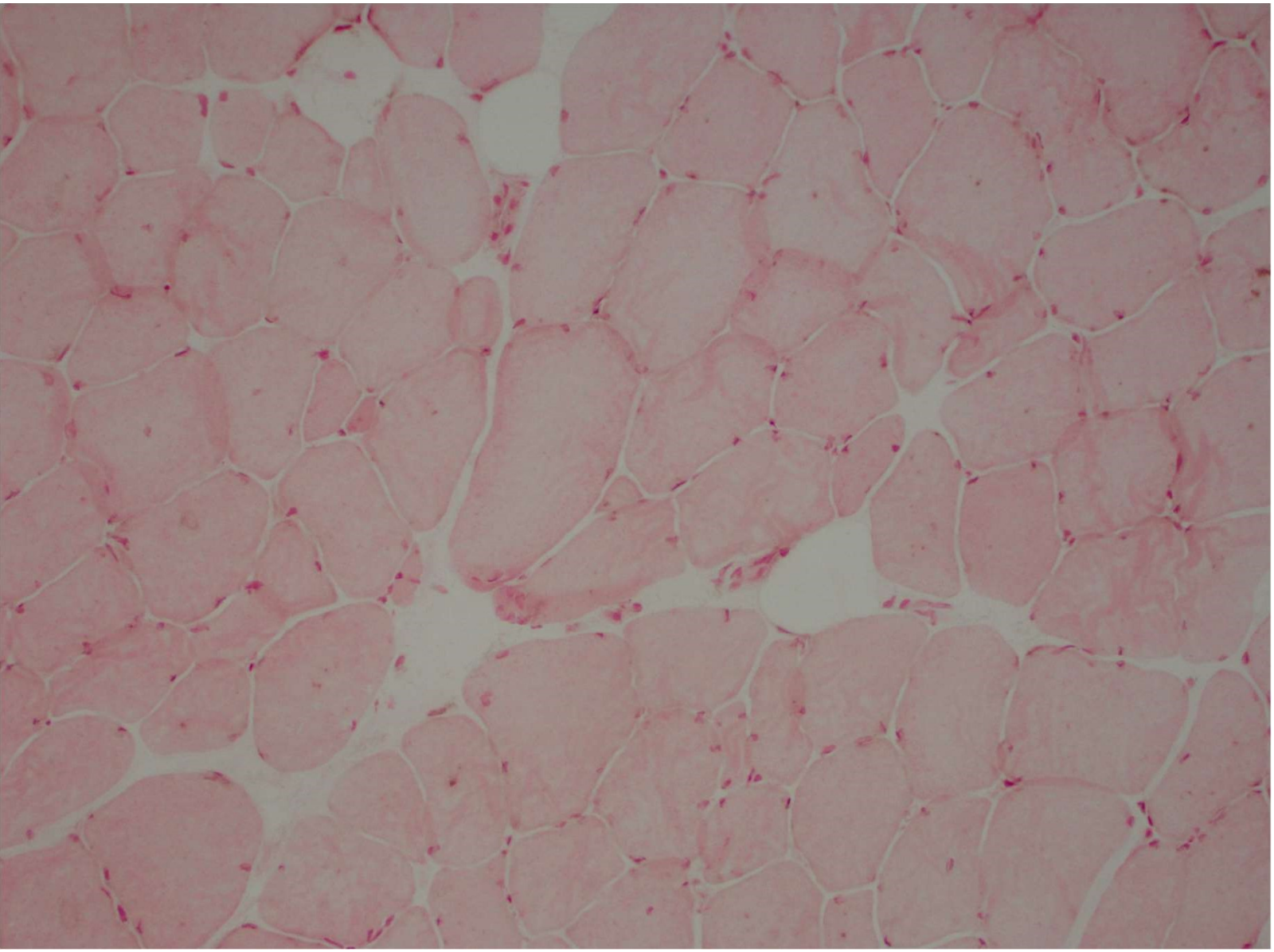
Nonspecific esterase X 10



NADH X 20



Alkaline phosphatase X 10



Acid Phosphatase X 20

Thoughts?

Looking Back…Questionable Response to Steroids?

- On Deflazacort (18-30mg daily) for many years
  - Initial improvement in ambulation
  - Then overall stabilization
- Seems to have worsened after d/c'ing Deflazacort 2 years ago
- ? Acquired autoimmune process

Myositis Specific Antibody Panel

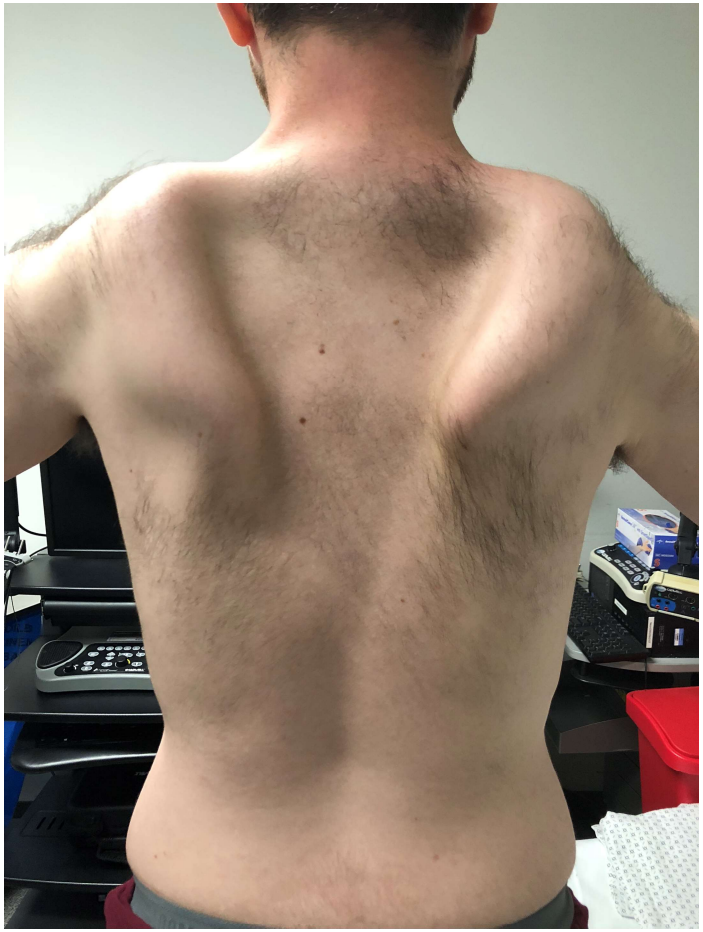
- anti-SRP antibody – >100 SI (Positive) (nl <11 SI)

- HMGCR Ab – negative
- Anti-Synthetase – negative
- All others – negative

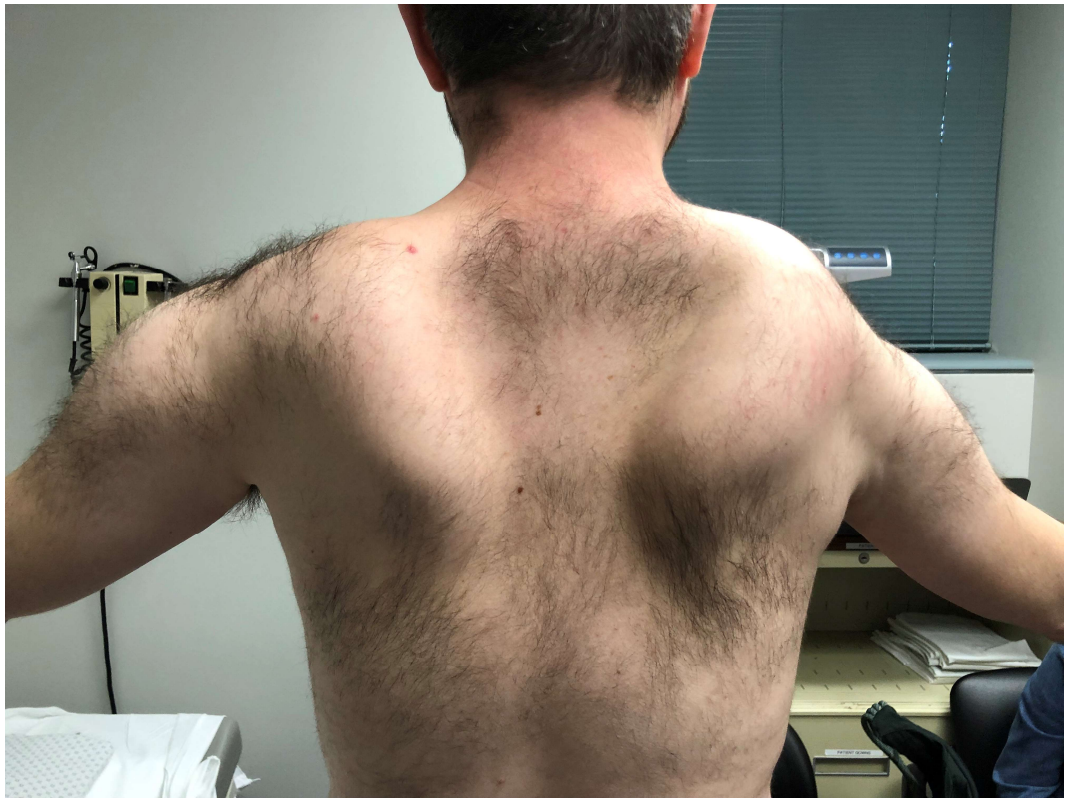
What did we do with this result?

- Re-started prednisone 60mg daily
- IVIG was added in November 2018, dose 1 g/kg (80 grams) every 2 weeks along with a slow prednisone taper
- Response post-IVIG:
  - Per patient: “Feels like it’s turning on the muscles that have been unusable for years”
  - More strength in the hamstrings, gluteal muscles, shoulder girdle
  - Easier to smile
  - Easier to play tennis

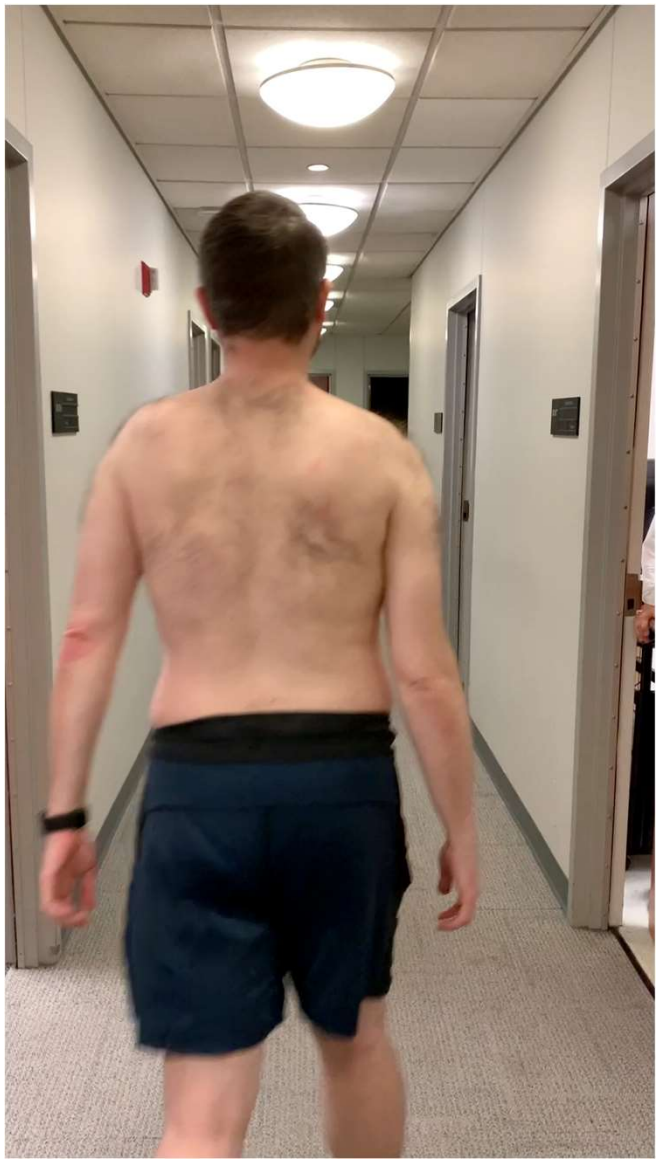
Pre-Treatment

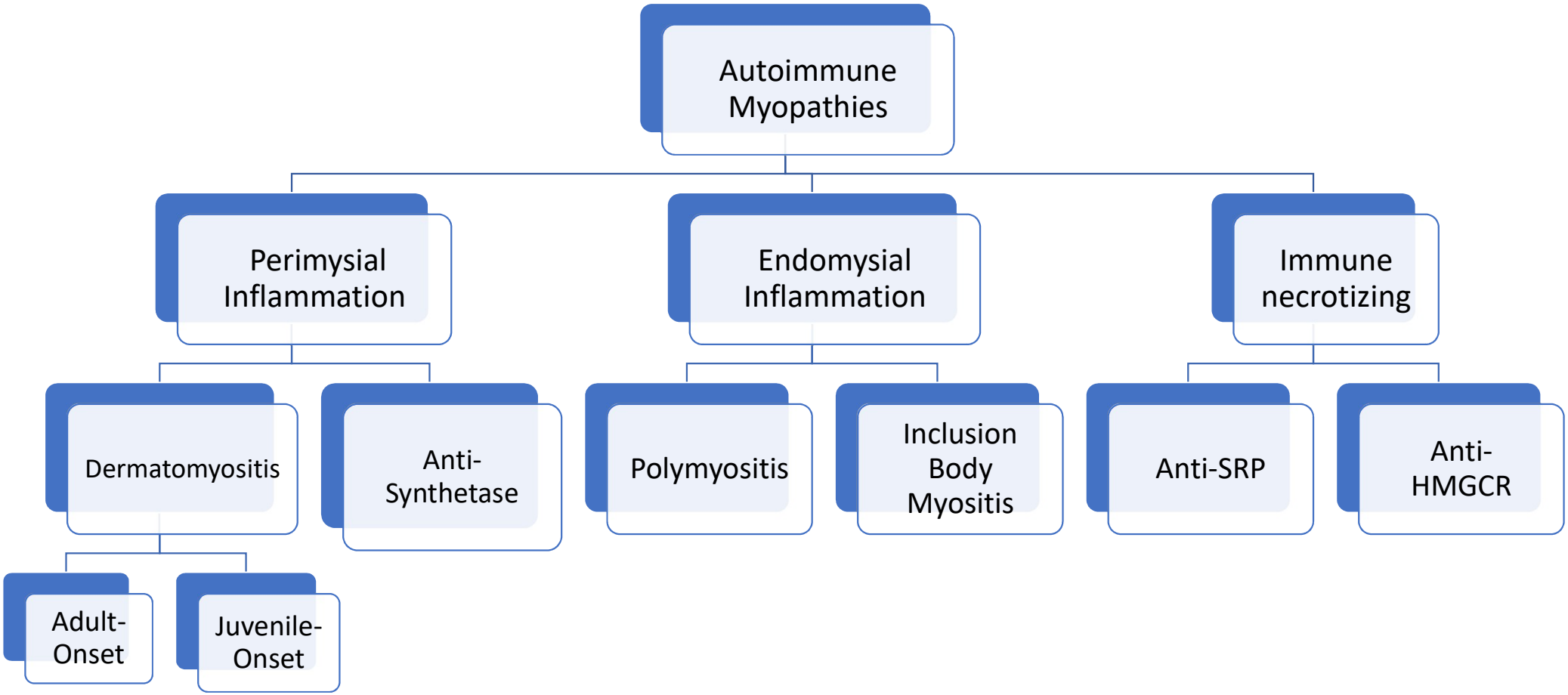


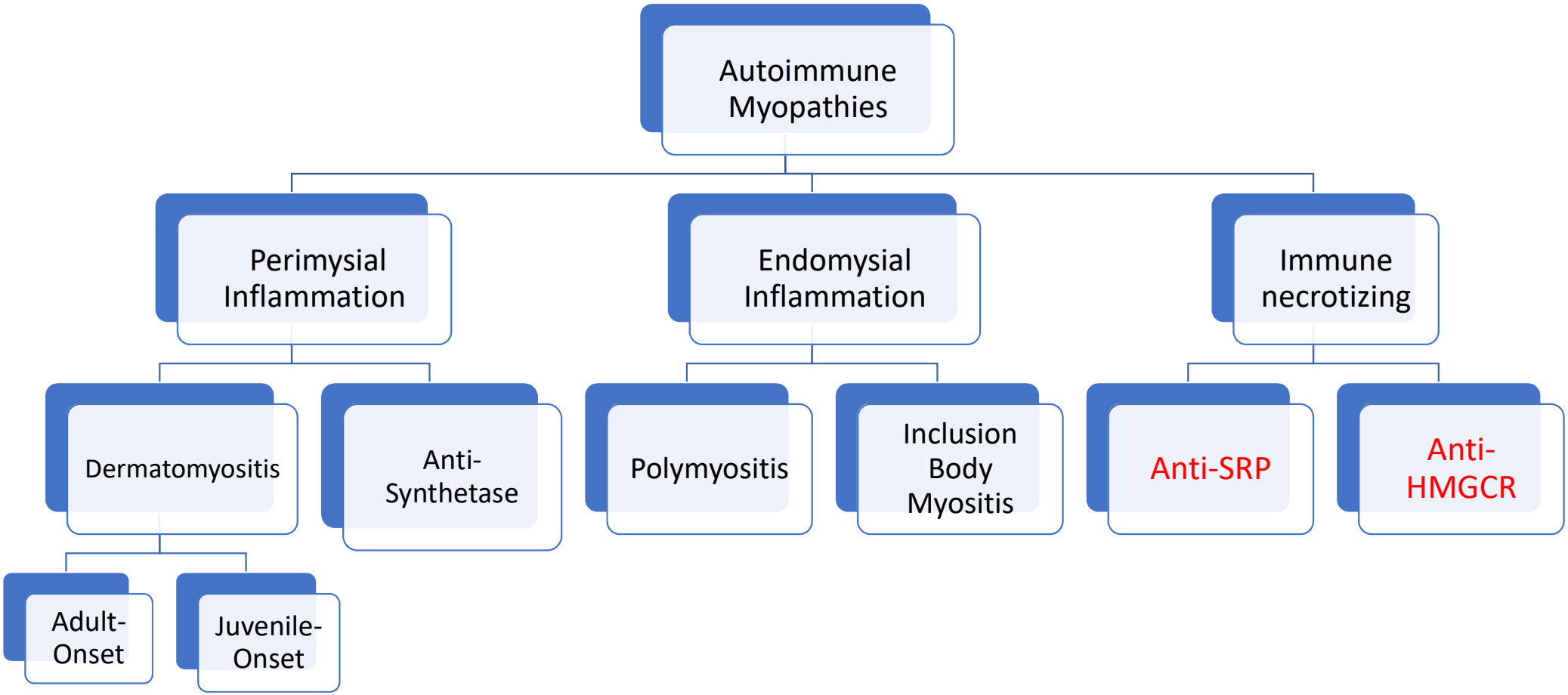
3 months Post-Treatment



Updated Video post-IVIG




Autoimmune Myopathies
Perimysial Inflammation
Endomysial Inflammation
Immune necrotizing
Dermatomyositis
Anti-Synthetase
Polymyositis
Inclusion Body Myositis
Anti-SRP
Anti-HMGCR
Adult-Onset
Juvenile-Onset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Signal Recognition Particle *(SRP)*

- SRP is an intracellular ribonucleoprotein complex consisting of six proteins and a 7S RNA molecule
- Responsible for mediating the translocation of newly synthesized proteins to the endoplasmic reticulum

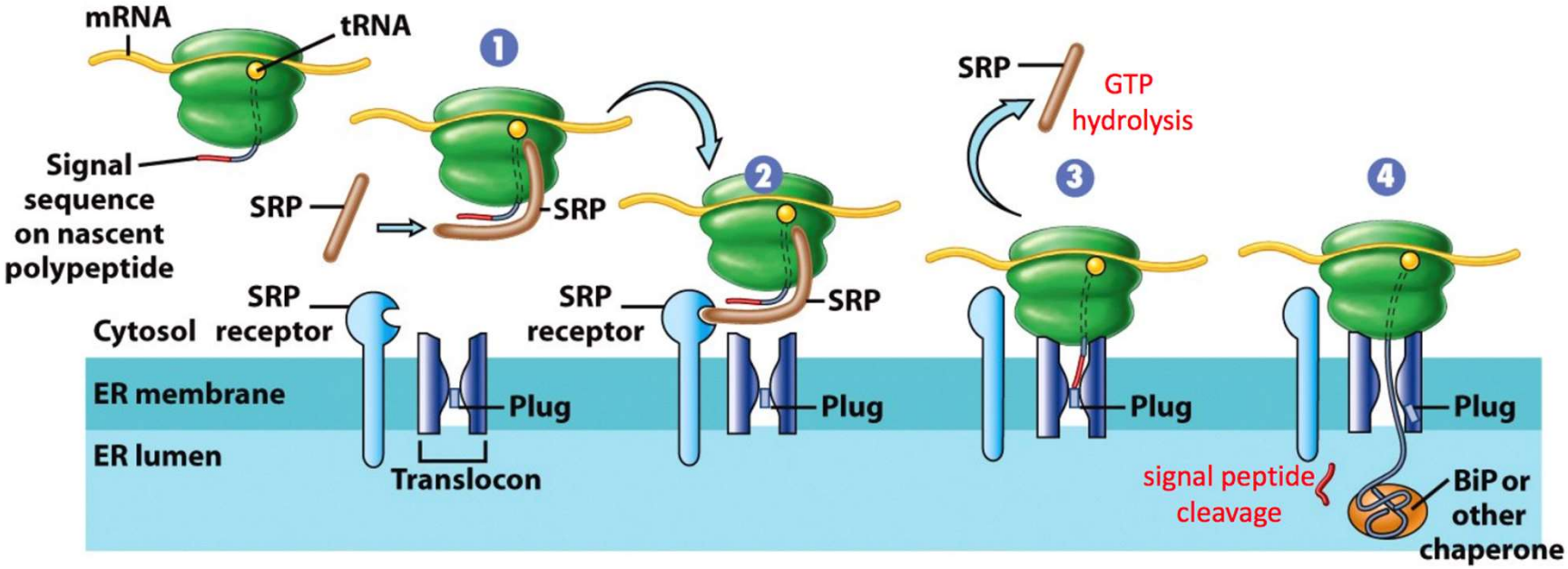
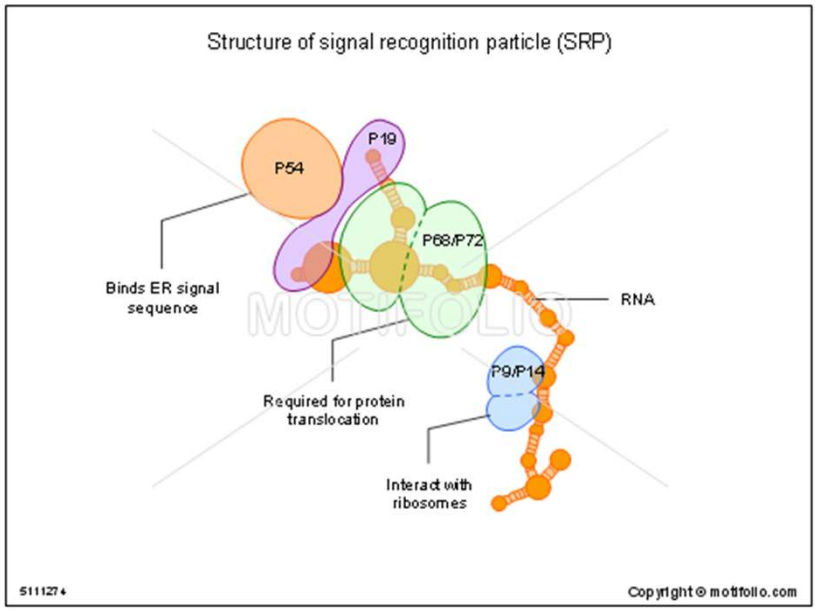


Figure 8-12 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

Pinal-Fernandez, 2018

Signal Recognition *Particle (SRP)*

- Antibodies to specifically subunit 54 are responsible for preventing the crosslinking of SRP and the signal sequence of the nascent protein
- Anti-SRP antibodies have been detected in 4-13% of inflammatory myopathies in adults



Anquetil, 2019
Pinal-Fernandez, 2018

Classic Presentation of Anti-SRP myopathy

- Mean age ~40-60 years; women are more affected
- Hallmark: proximal weakness with muscle atrophy as a prominent feature
- Axial muscle involvement (~70%), dropped head syndrome (~7%), dysphagia (~60%)
- Most are subacute, but 20-30% can have a more chronic presentation
- CK levels mostly more than 1000 U/L
- Muscle biopsy: Lack of inflammatory infiltrates, presence of necrosis and atrophy

Anquetil, 2019

Pediatric Immune Mediated Necrotizing Myopathies

- Recently recognized entity
- Most cases described in the literature are HMGCR Ab patients
- The largest case series was *Liang et al* in 2017: described 9 pediatric patients (of 62) with suspected inflammatory myopathy who tested positive for Anti-HMGCR antibody
  - Onset 10 months – 13 years of age
  - 5 patients had chronic onset of disease and had previously been diagnosed with muscular dystrophy
    - 2 of these chronic onset patients had scapular winging
  - 4 other patients (of 62) were found to have positive SRP antibodies

SRP Myopathy in pediatric patients

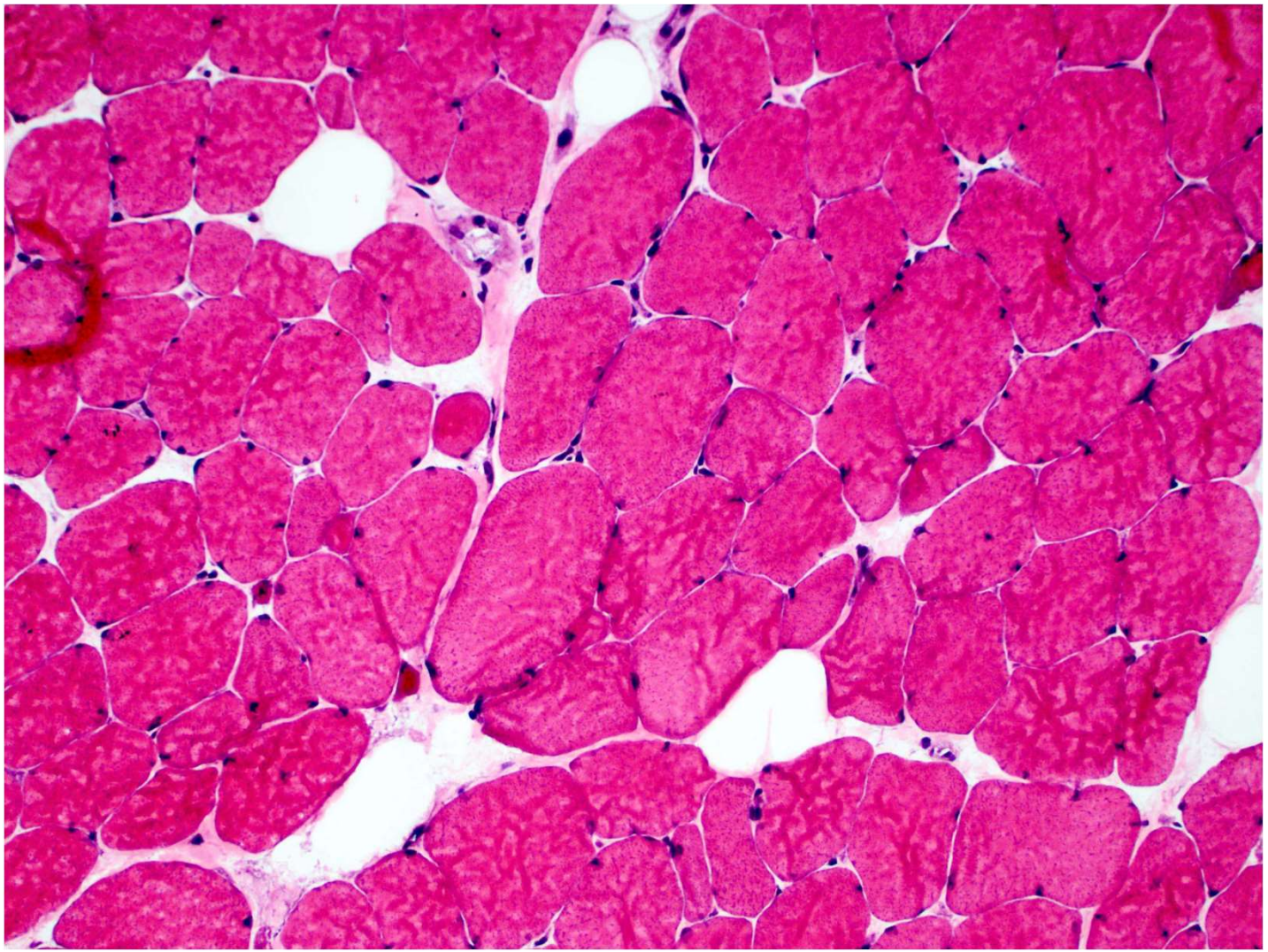
- In 2008, Rouster-Stevens et al reported the first pediatric patients with SRP:
  - 3 African American girls, ages 11-16, developed severe proximal weakness and were wheelchair bound within 2 months

- In 2011, Suzuki et al reported
  - 2 Japanese girls, ages 5 and 9, developed progression of proximal muscle weakness, unable to walk within 2 years of presentation
  - Both positive for SRP antibody
  - One had scapular winging and was misdiagnosed with FSHD

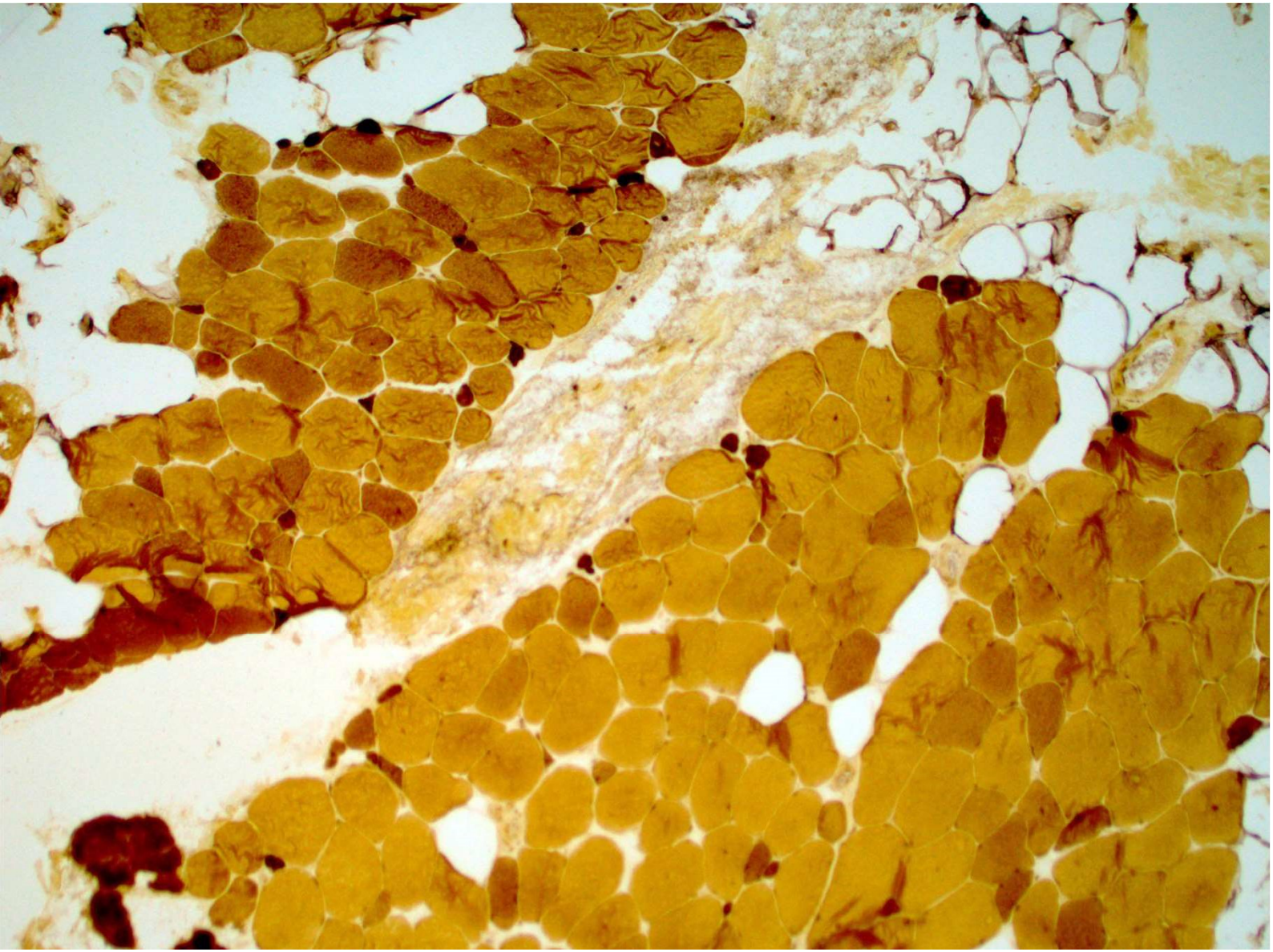
SRP Myopathy in pediatric patients

- To date, there are ~25 reported pediatric patients found to have anti-SRP antibodies
    - Age range 5-16 years
    - Most were Japanese and African-American
    - Up to 10 patients were reported to have scapular winging, and misdiagnosis of muscular dystrophy was common

Rouster-Stevens 2008
Suzuki 2011
Suzuki 2015
Ikeda 2016
Liang 2017
Binns 2017



Frozen HE X 20



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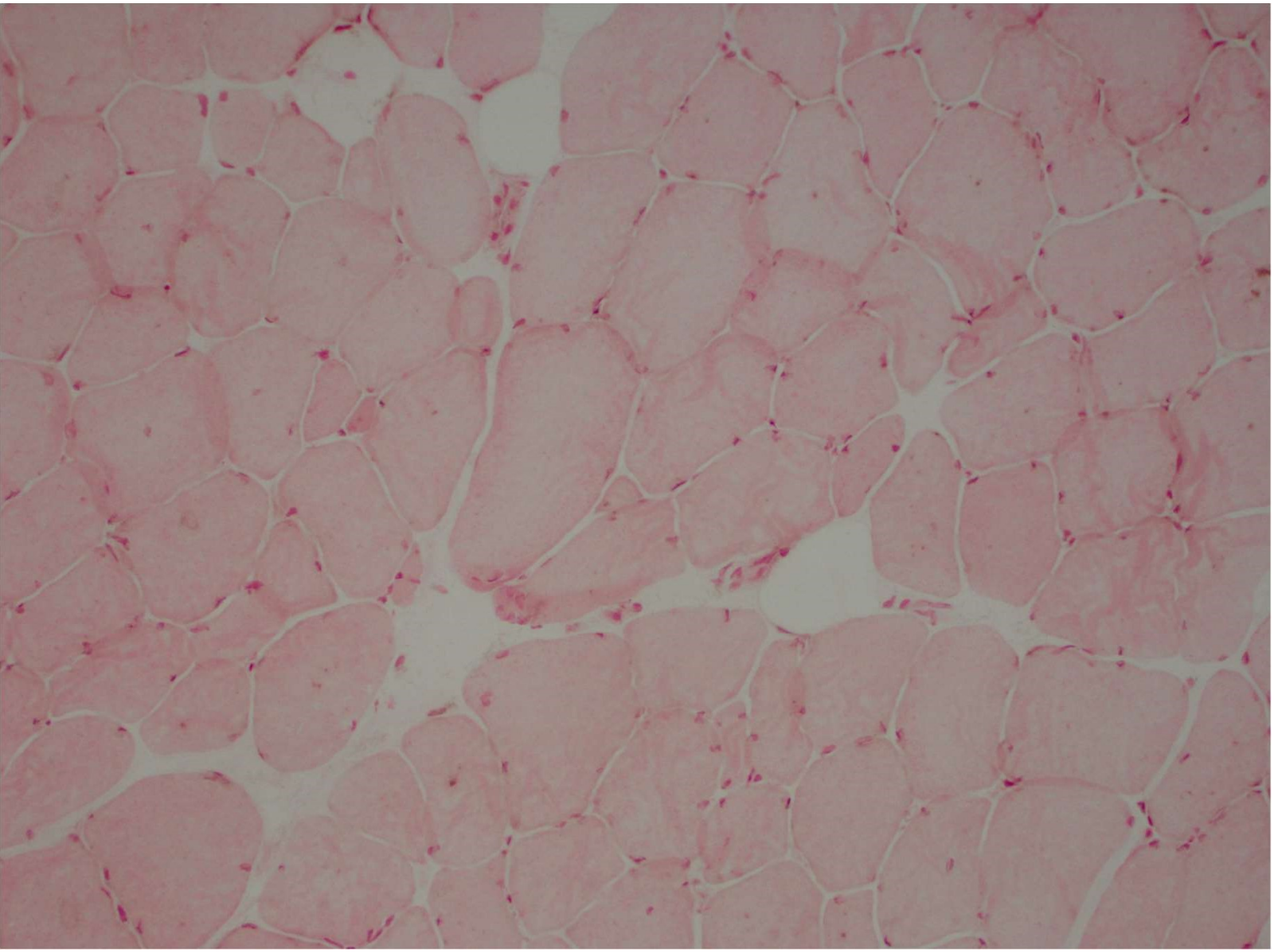
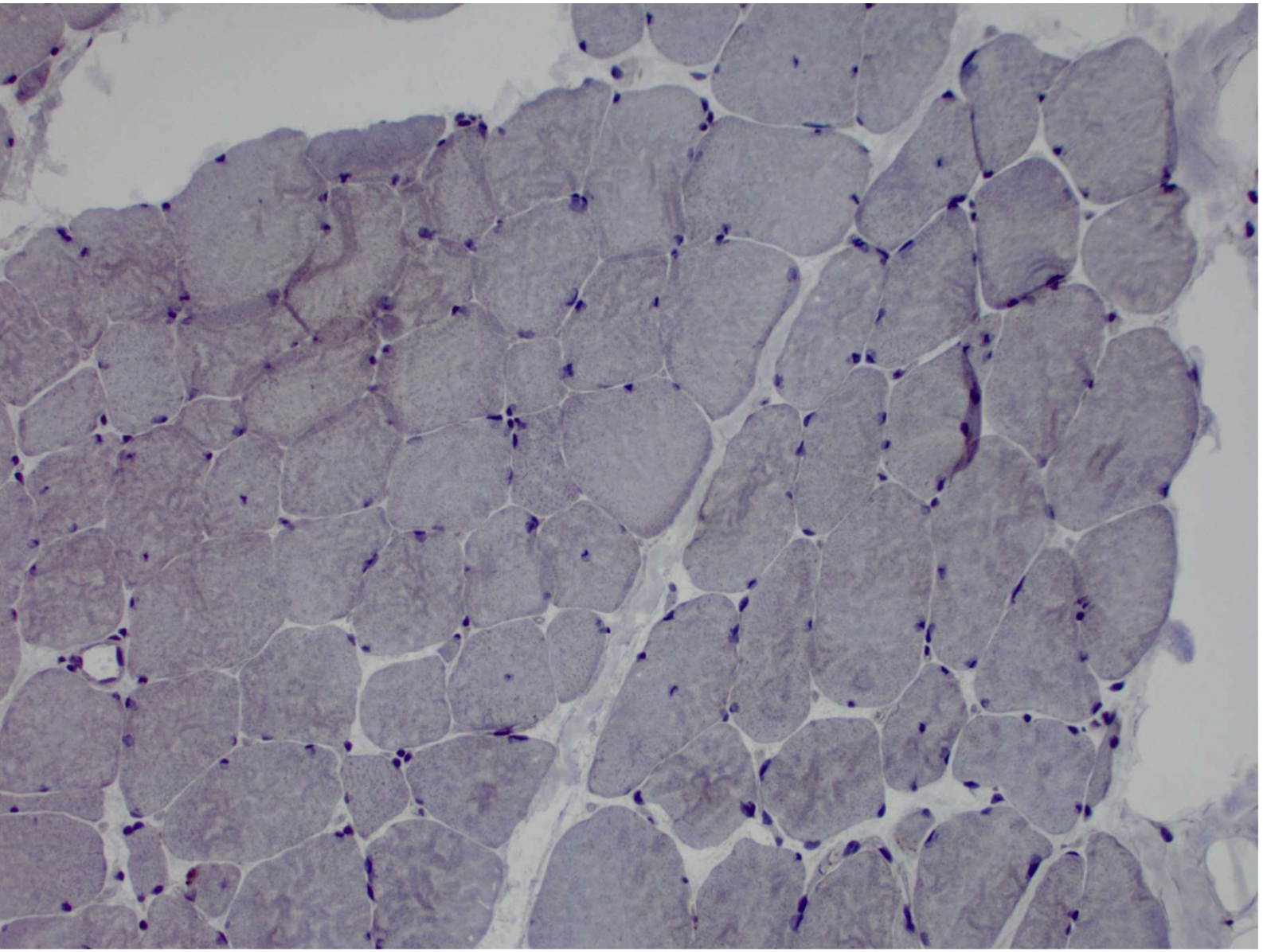
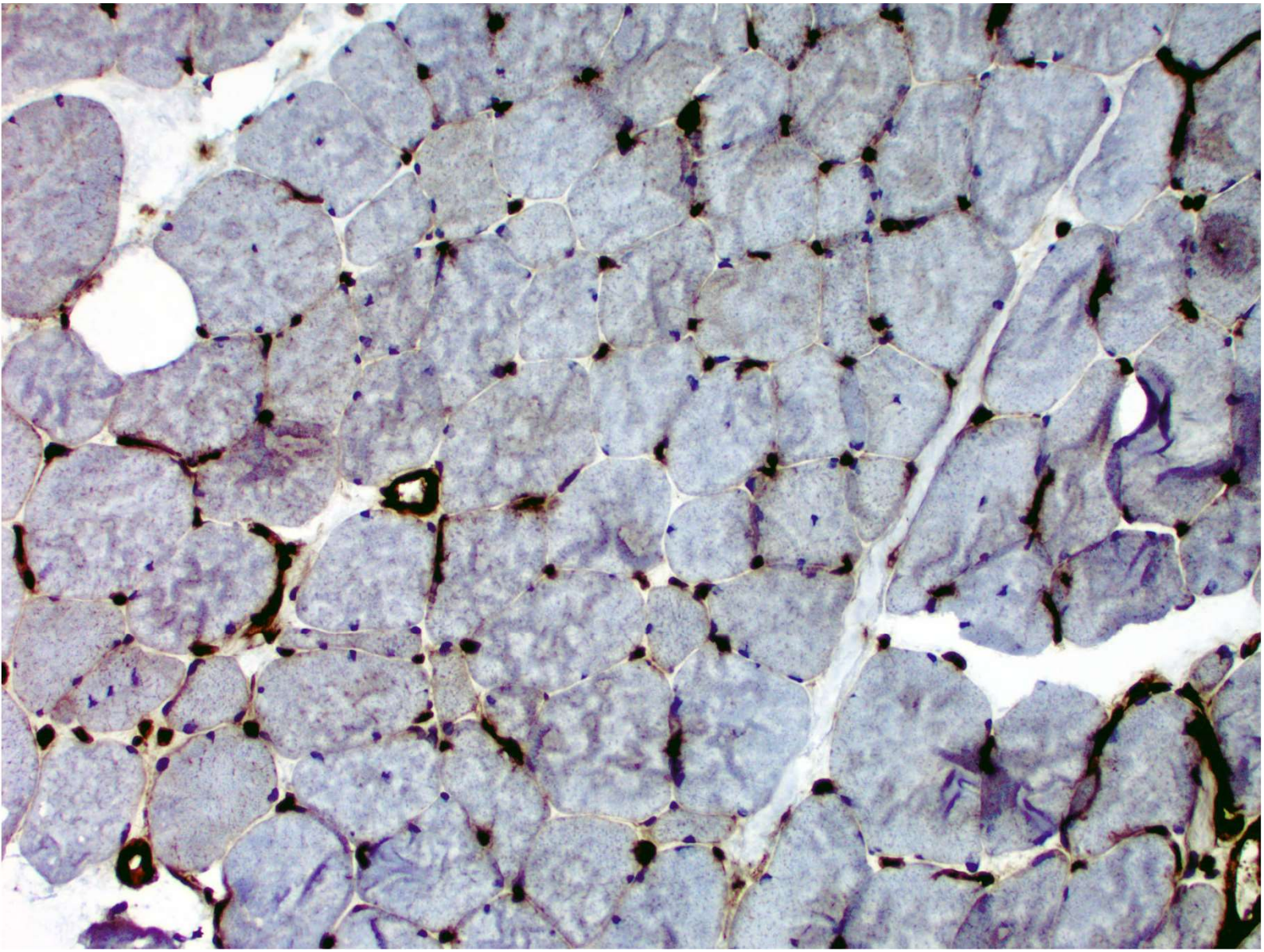


Acid Phosphatase X 20



MAC x 20



MHC-I X 20

Summary of muscle biopsy features in reported cases of pediatric SRP myopathy

- Scattered necrotic and regenerating fibers
- Moderate-marked fiber size variations
- Mild endomysial fibrosis
- None-mild lymphocytic infiltration
- Weak expression of MHC I in sarcolemma
- Positive MAC deposition in sarcolemma

Kobayashi 2017

Our patient's muscle biopsy

- No necrotic or degenerating fibers
- Moderate-marked fiber size variations
- Mild endomysial fibrosis
- No lymphocytic infiltration
- Absence of MHC I upregulation at the sarcolemma
- Absence of MAC deposition at the sarcolemma

Key Points

- Pediatric SRP Myopathy remains largely underrecognized
- Scapular winging  Muscular Dystrophy
- Consider checking a myositis panel on children with suspected, but undiagnosed muscular dystrophy

Thanks for your attention!