A Case of Progressive Proximal Weakness in a Young Woman

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Stacy Dixon, MD, PhD

Julie Parsons, MD and Dianna Quan, MD

University of Colorado

SCHOOL OF MEDICINE
Department of Neurology
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

History of Present Illness

- Previously healthy 17 year old teenager first noticed symptoms of difficulty throwing the shot put in 8th grade (~4 years prior to presentation)
- Then about 3 years ago she notice it was becoming difficult for her to get up off the floor or out of low chairs.
- She also notes that her “legs would give out” and she would fall. It was often difficult getting up from these falls.
- As time progressed, she developed difficulty going up stairs and trouble raising her arms above her head to wash her hair.

History of Present Illness

- Over the years, her symptoms continued to worsen despite trying to work out and increase her physical activity to improve her strength.
- She reports no weakness in her hands
- Both side are equally affected.
- Pertinent Negatives:
  - No pain or cramping but sometime muscles feel “achy” with excessive use
  - No difficulty swallowing or speaking
  - No diplopia
  - No bowel or bladder dysfunction
  - No episodes of dark tea-colored urine
  - No episodic worsening
  - No numbness or tingling
  - No rash

Past Medical History

- Birth and Developmental History
  - Normal gestation and delivery.
  - She sat at 6 months, walked at 1 year, talked at 1 year.
  - When playing with others or doing sports at a young age, she was always top to middle of the pack
- Past Medical
  - None
- Past Surgical History
  - None
- Medications/Allergies
  - None
  - No supplements
  - She had not been on any long term medications. She had occasional antibiotics for various reasons throughout her life but none recently (prior to presentation).

Past Medical History

- Family History
  - Mom, Dad, and Brother (age 20) are healthy
  - MGM: thyroid issues
  - MGF: diabetes
  - PGM: breast and colon cancer
  - PGF: lung disease
  - No known muscle or nerve disease in any of her extended family members
- Social History
  - Lives with mother, father, and 20 year old brother
  - Junior in high school. Gets A's and B's with both regular and advanced classes. Some stress at school due to peer interactions and social group.
  - Likes playing piano and photography
  - Plans to attend college
  - No toxic exposures
  - No alcohol, tobacco, or illicit drug use
  - Has traveled throughout the US and once to Japan

Physical Exam

- Normal General Exam
- Cranial Nerves were all intact. Smile was normal and symmetric. There was no fatiguing with sustained upgaze
- Motor exam: **Mildly low tone in all extremities**. **Reduced muscle bulk of deltoids, biceps, triceps, pecs. No scapular winging. No fasciculations.** Strength: **Neck flexor is 4, (R/L): shoulder abduction 4-/4- up to 40 degrees, shoulder external rotation 4-/4-; biceps 4/4, triceps 4/4**, wrist extension 5/5, wrist flexion5/5; finger extension 5/5, finger flexion 5/5, finger abduction 5/5, thumb abduction 5/5, **hip flexion 2/2, knee flexion 4/4, knee extension 4+/4+,** ankle dorsiflexion 5/5, ankle plantarflexion 5/5. **No grip or percussion myotonia.**
- Sensory: intact in all extremities
- Coordination: no ataxia on finger to nose; Heel-shin was limited by weakness
- Gait: **Unable to rise from chair with out doing modified Gower's. Waddling gait**

Laboratory Data

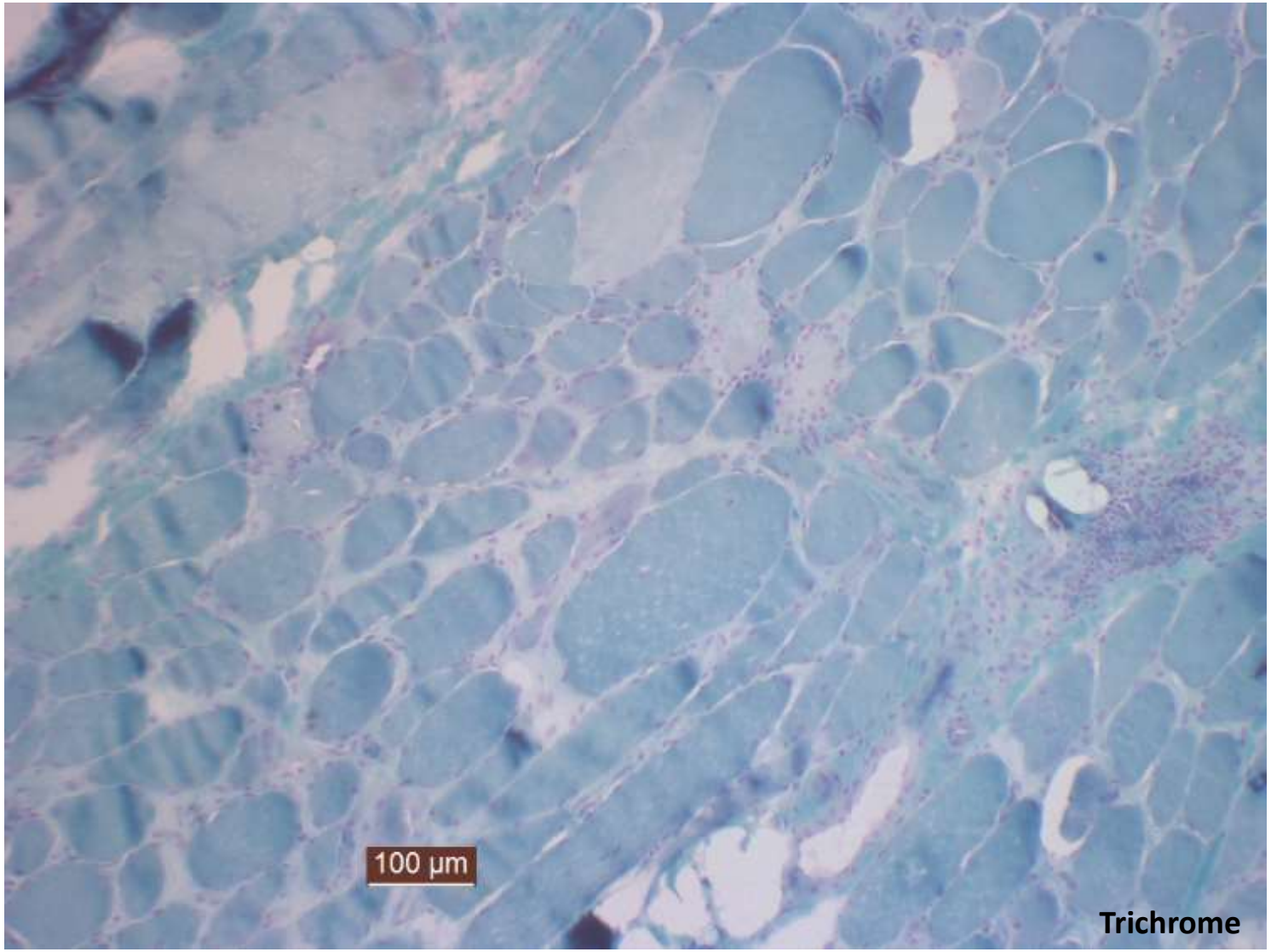
- **CK: 8919 U/L (initial), ~12,000 U/L (peak)**
- **CMP: elevated AST (194) and ALT (244)**
- CBC: normal
- TSH: normal (1.03)
- ESR: normal (2)
- CRP: normal (0.11)
- ANA, SSA, SSB, and myositis antibody panels were normal
- Emory University LGMD panel was normal

EMG/NCS

- Normal NCS of the right leg
- EMG of select muscles of the right arm and leg showed evidence of an **irritable generalized myopathy.**
  - Fibrillations, positive sharp waves and complex repetitive discharge were seen in all proximal muscles
  - Myotonic discharges were seen in the deltoid muscle.
  - Myopathic motor units were seen in all proximal muscles examined.

Muscle Biopsy

- Biopsy of the left quadriceps showed an acute and chronic necrotizing myopathy. There were occasional small foci of inflammation and occasional vacuolar changes.



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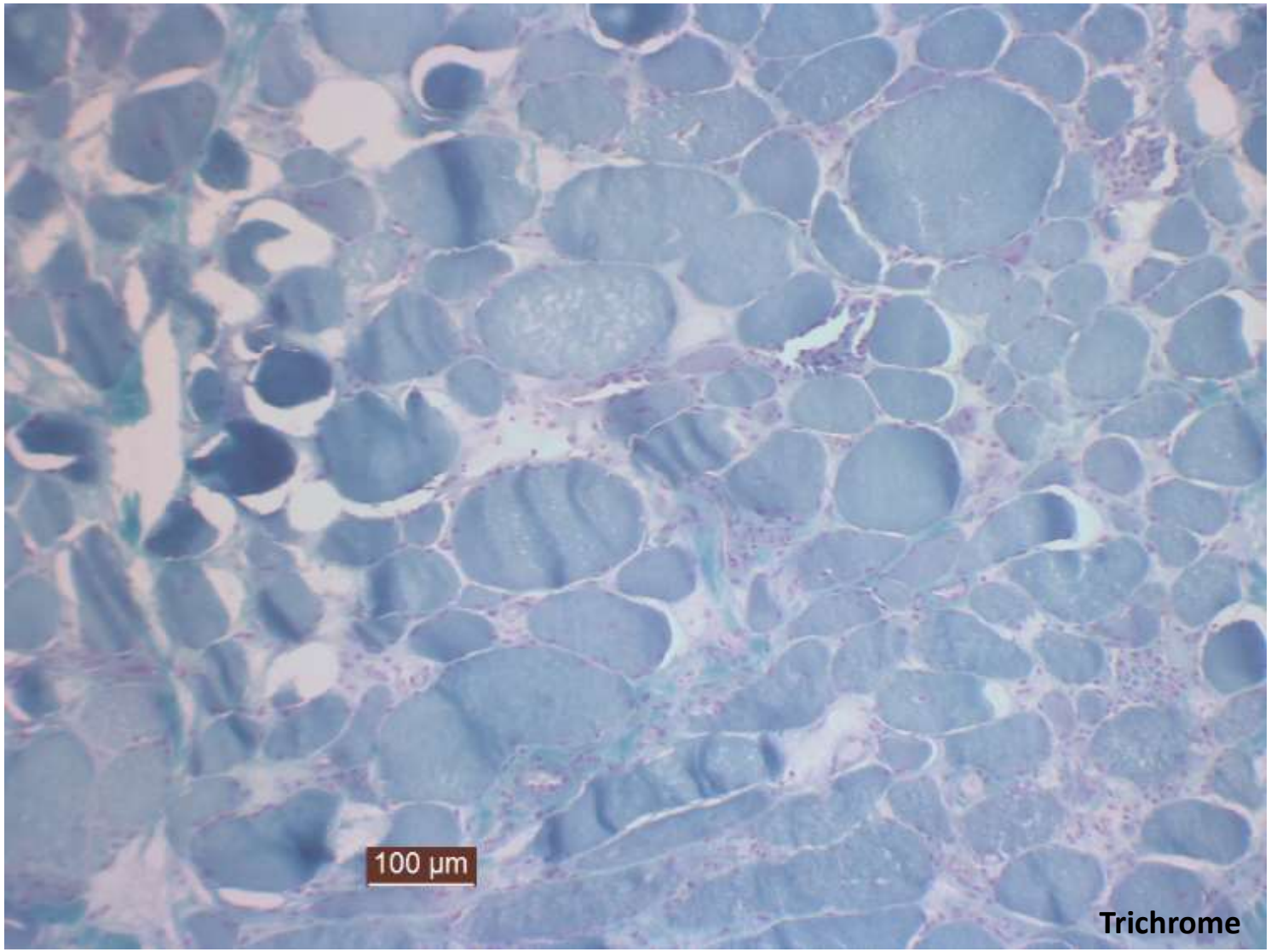

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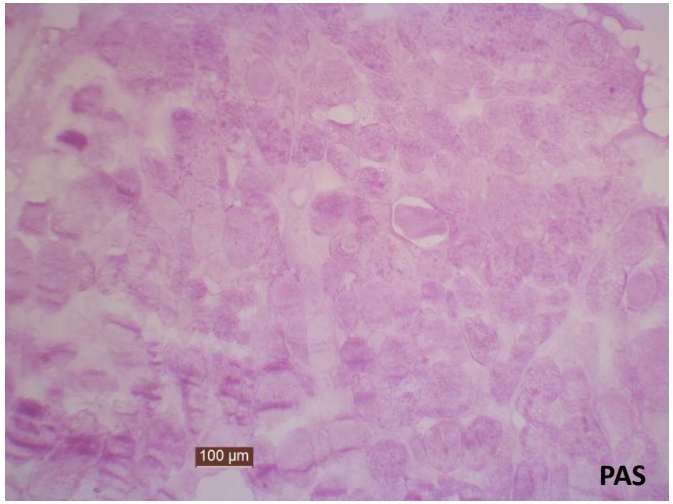
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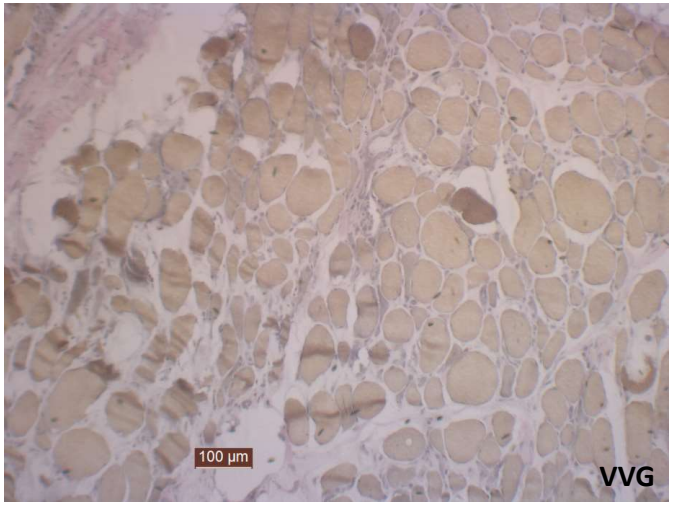
PAS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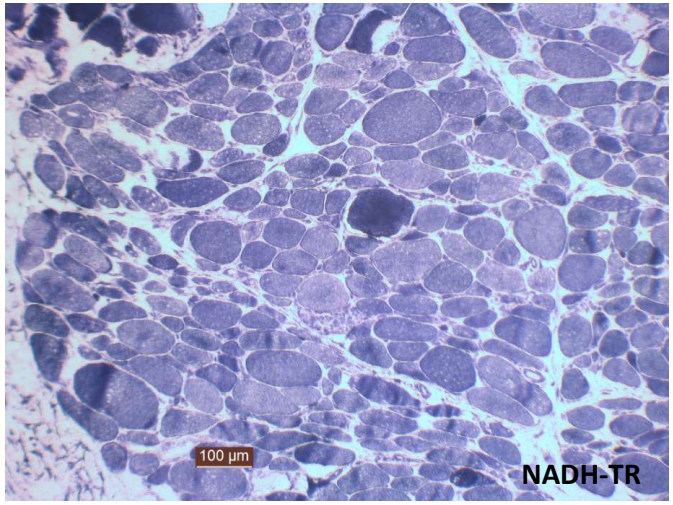
VVG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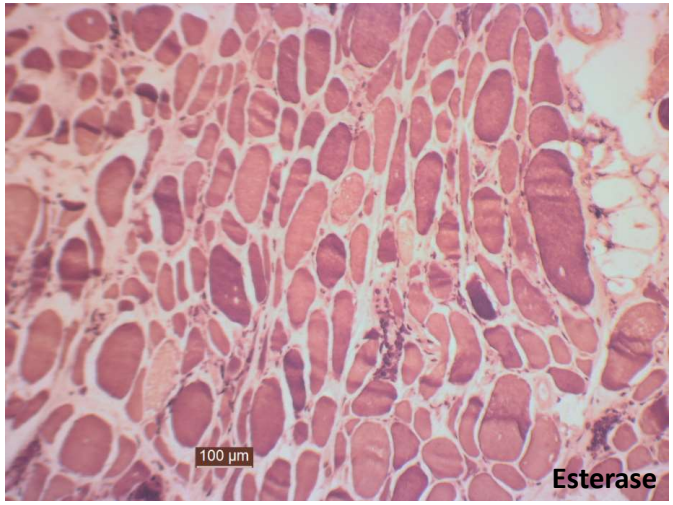
NADH-TR


100 µm
Esterase

Muscle Biopsy

- Biopsy was sent to the University of Iowa for further analysis.
- Immunostaining with a variety of muscular dystrophy-associated proteins failed to suggest a specific diagnostic pattern.
- MHC class 1 staining was positive but in a multifocal pattern (not diffuse)

Meanwhile, the patient was empirically tried on oral prednisone (0.5mg/kg) without any significant improvement.

Diagnosis???

Immune Mediated Necrotizing Myopathy Associated with HMGCR Antibodies

- HMGCR IgG >200 (normal 0-19)
  - From ARUP Laboratories (Salt Lake City)

Immune Mediated Necrotizing Myopathy Associated with HMGCR Antibodies

- First described by Dr. Mammen
- In adults, often associated with prior statin use and/or HLA DRB1*11:01.
- Recently, Dr. Mammen's group screen 440 juvenile myositis patients and found 5 (1.1%) were anti-HMGCR positive.
  - None of the Five were exposed to statins
  - The DRB1*07:01 allele was present in all 5
    - 4 patients with DRB1*07:01-DQA1*02:01
  - Characteristic findings in these patients included severe proximal weakness, distal weakness, high CK levels, muscle atrophy, joint contractures, and arthralgias.
  - Partial response to immunosuppressive therapy

Immune Mediated Necrotizing Myopathy Associated with HMGCR Antibodies

- The patient was started on monthly IVIG (2g/kg divided over 2-5 days)
- Methotrexate 10mg weekly (0.1mg/kg weekly)
- She's been making steady improvements in regards to her weakness.
  - Able to get up off the floor
  - Able to raise her arms above her head
  - Fewer falls
- CK is now ~800 U/L

Acknowlegments

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