CASE 2020-8

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Neuropathology

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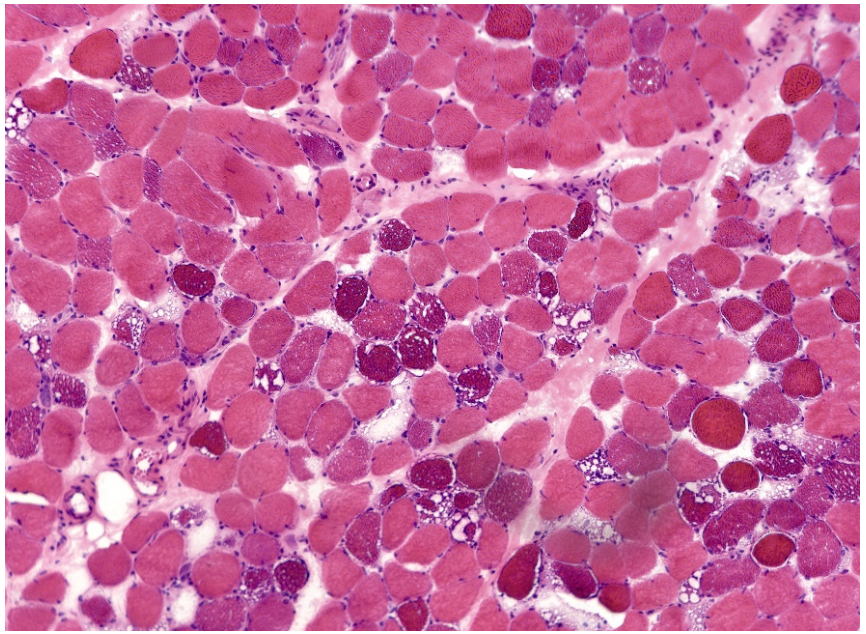
Disclosure

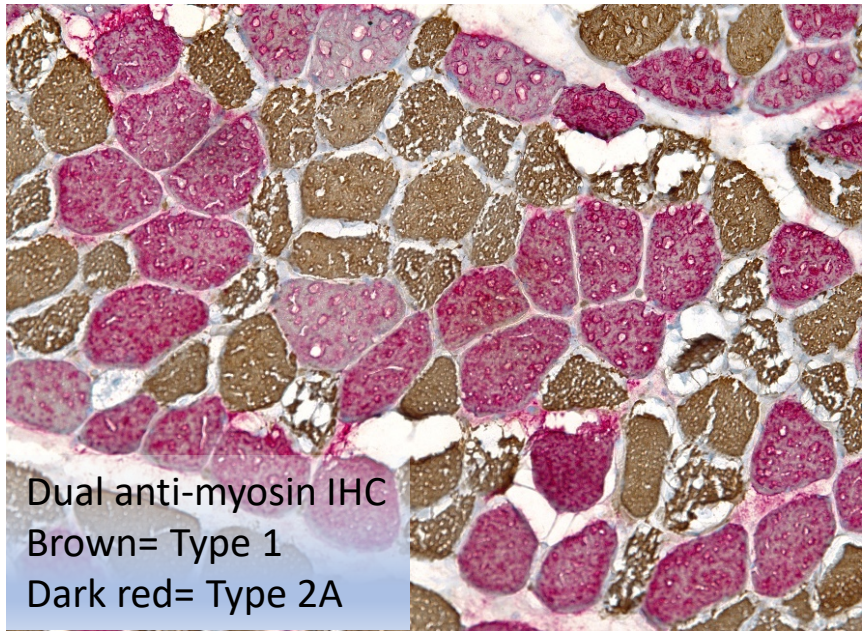
- We have no financial relationships to disclose

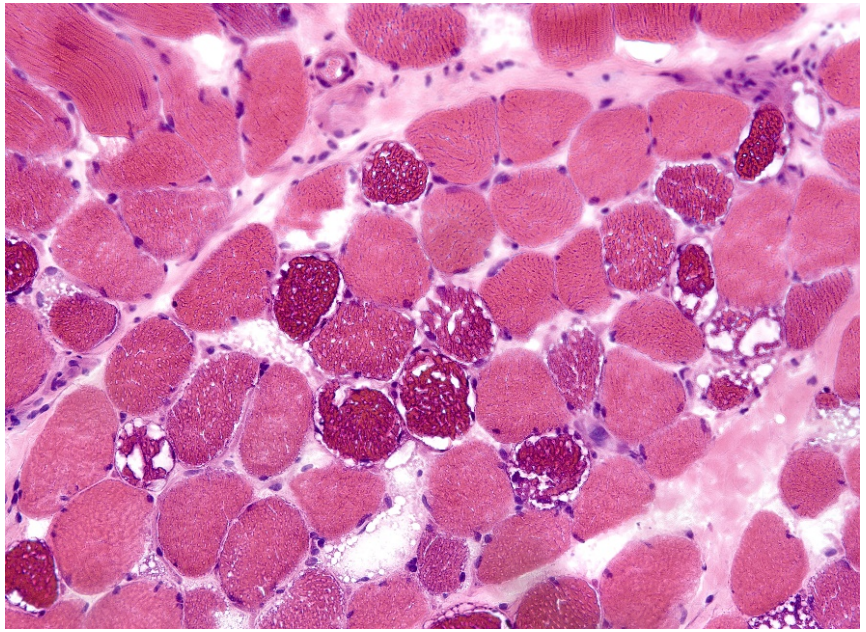
Clinical history

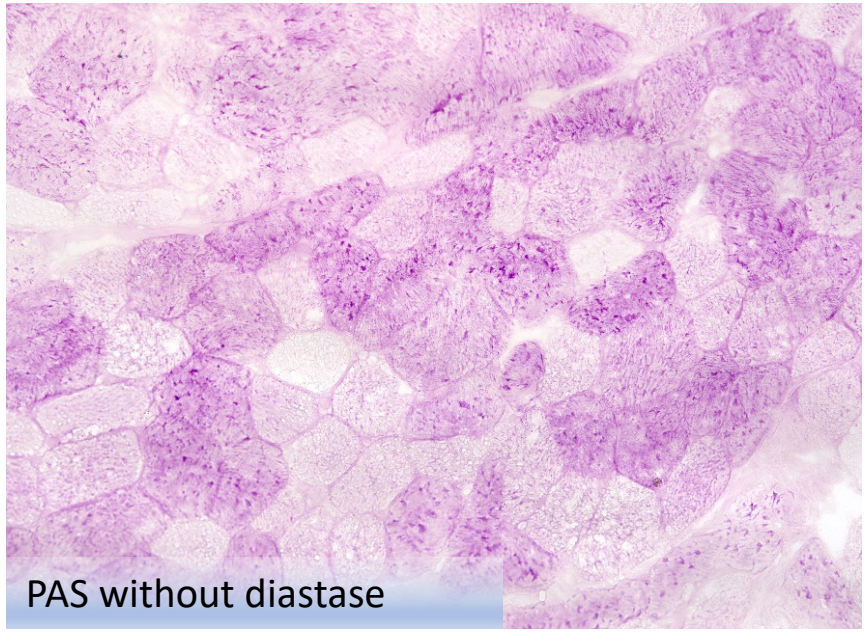
- A 38-year-old female with onset of persistent post-exercise soreness in her legs, 10 months before biopsy; a history of being athletic and hiking without issues
- Elevated CK; varied between 288 and 1089
- Brief improvement on steroids and hydroxychloroquine then subsequently showed a further decline
- Gradual progression of leg weakness, with progression to her arms, fatigue with chewing and jaw pain
- EMG: unremarkable
- Negative/normal myositis panel, AST/ALT of 106/91, positive ANA and anti ds-DNA
- Muscle biopsy performed followed by high dose prednisone, mycophenolate mofetil, and IVIG, with mild improvement of symptoms

Deltoid and quadriceps muscle biopsies

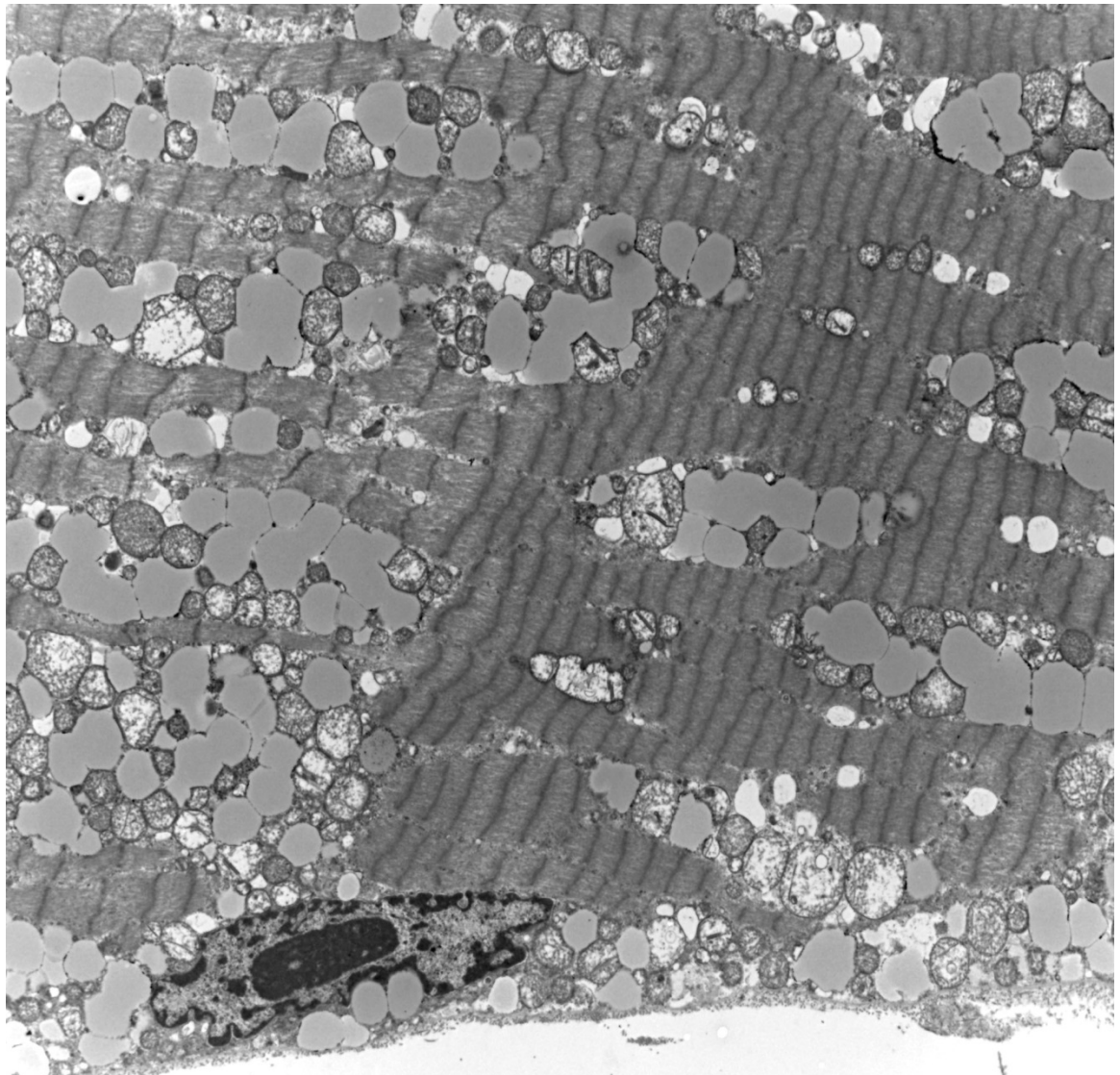




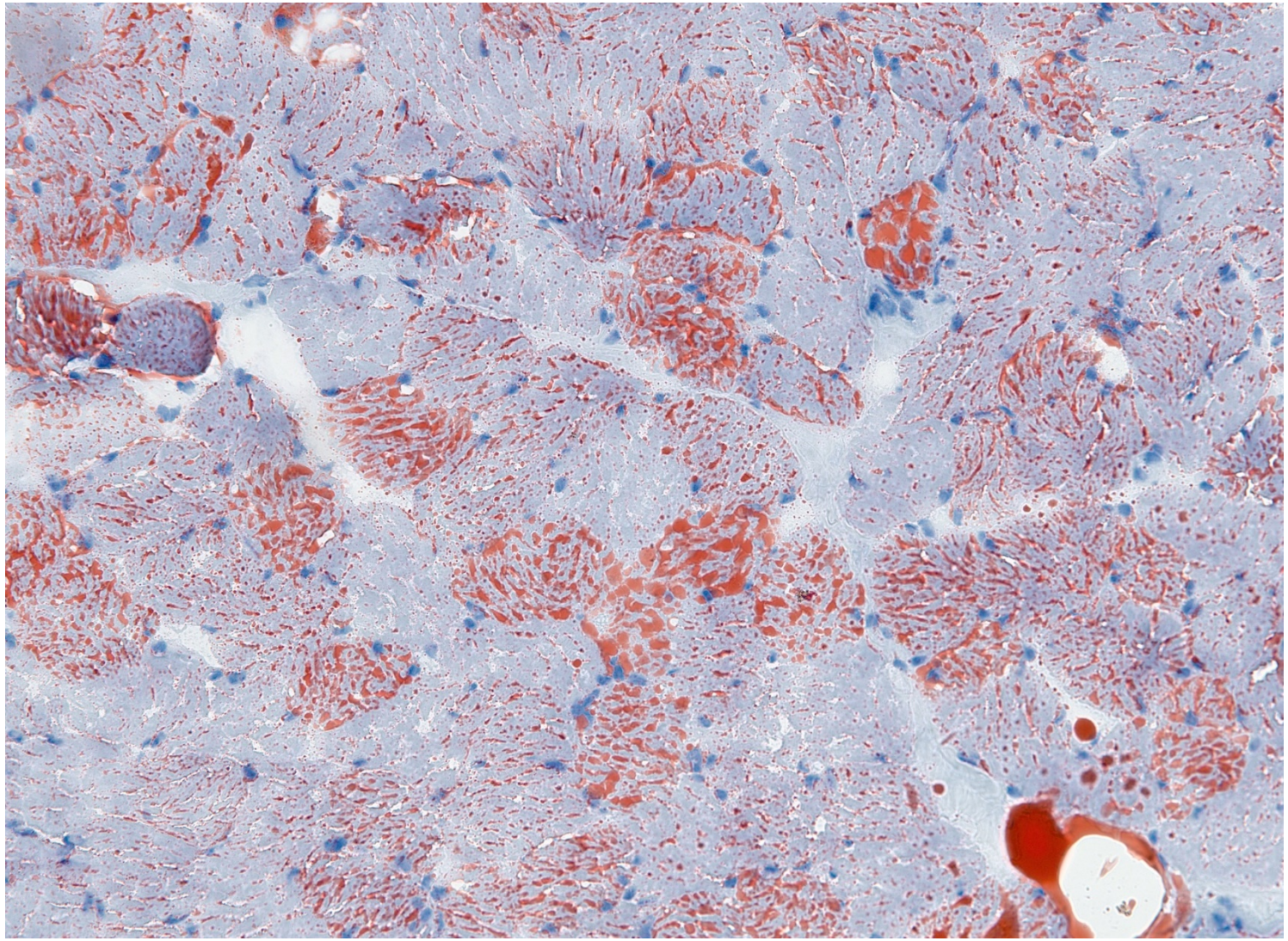




Electron microscopy



Oil-Red-O



Muscle biopsy biochemical results

- Reduced carnitine levels
- Reduced PFK activity
- Normal acid and neutral maltase activity
- Elevated CPT2 activity

Neuropathological diagnosis

Preliminary diagnosis: Lipid storage myopathy

Differential diagnosis of lipid storage myopathies

- Malnutrition; HIV
- Carnitine deficiency (OCTN2 gene)
- Fatty acid oxidation disorders
  - CPT2 deficiency (*CPT2*)
  - Acyl-CoA dehydrogenase deficiencies (SCAD, MCAD, LCAD, VLCAD, MADD)
  - Neutral lipid storage diseases
    - Neutral lipid storage disease with myopathy (*PNPLA2*)
    - Neutral lipid storage disease with icthyosis (*CGI58*)
- Mitochondrial myopathies

Lipid storage myopathies

	Subtypes	Symptoms	Muscle histology	Genetic
Carnitine deficiency	-Myopathic form - Systemic form	-Childhood, -Symmetric proximal weakness - +/- cardiomyopathy and facial weakness	-Severe lipid storage -Mitochondrial proliferation and ultrastructural abnormalities	*OCTN2* (AR) Carnitine
CPT2 deficiency	-Neonatal -Infantile -Adult	-Recurrent muscle pains -Myoglobinuria (precipitated by prolonged fasting or exercise)	-Normal -Regenerative fibers/necrosis only present in biopsies taken soon after the onset of symptoms, -Increased lipid (50%)	*CPT2* (Recessive & Semi-Dominant)
Neutral lipid storage disease	-Childhood or adult -With myopathy -With ichthyosis	-Intellectual disability (66%) -Cardiomyopathy (33%) -Proximal & distal asymmetric weakness: difficulty walking	-Massive lipid accumulation and lipid vacuoles, Types 1 & 2 fibers	*PNPLA2* (AR) *CGI58*

Lipid storage myopathies

	Subtypes	Symptoms	Muscle histology	Genetic
Acyl-CoA dehydrogenase deficiencies	Short chain (infantile/adult)	-FTT, hypotonia/dystonia, seizures (22%); dysmorphic facies -Muscle weakness	Mild variation in fiber size and variable lipid storage in Types 1 and 2 fibers	Depends on the subtype
	Medium chain (infantile/adult)	-Hypoketotic hypoglycemia -Muscle fatigue, pain, reduced exercise tolerance		
	Long chain (early childhood)	- Hypoketotic hypoglycemia, cardiac arrest - Hepatomegaly, cardiomegaly, hypotonia		
	Very long chain (infantile/adult)	-Myalgic episodes, with severe pain -Rhabdomyolysis		
	Multiple acyl-CoA dehydrogenase (MADD) (infantile/adult)	-Proximal weakness -Hepatomegaly -Episodes of metabolic crises -Urine: High glutaric & ethylmalonic acids	Lipid accumulation, Type 1 fibers	*ETFA,ETFB, ETFDH* (AR)

Preliminary diagnosis: Lipid storage myopathy

Differential diagnosis of lipid storage myopathies

- ~~Malnutrition; HIV~~
- Carnitine deficiency (OCTN2 gene)
- Fatty acid oxidation disorders
  - ~~CPT2 deficiency (*CPT2*)~~
  - Acyl-CoA dehydrogenase deficiencies (SCAD, MCAD, LCAD, VLCAD, MADD)
  - ~~Neutral lipid storage diseases~~
    - ~~Neutral lipid storage disease with myopathy (*PNPLA2*)~~
    - ~~Neutral lipid storage disease with icthyosis (*CGI58*)~~
- Mitochondrial myopathies

Genetic testing:

- Dual mitochondrial and nuclear genome panel: two heterozygous pathogenic variants in the nuclear *ETFDH* gene, but with unknown phase

Gene	Inheritance	OMIM	Change	Location	Zygosity
ETFDH	AR	231675	c.265C>T (p. R86C)	Exon 3	Heterozygous
ETFDH	AR	231675	c. 488-1G>T (splice site)	Intron 4	Heterozygous

Final diagnosis

Lipid storage myopathy consistent with Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) OMIM 231680, late onset form, AKA glutaric acidemia IIC

Preliminary diagnosis: Metabolic myopathy suggestive of lipid myopathy

Enzyme and genetic testing

- Reduced skeletal muscle carnitine levels
- Normal acid and neutral maltase and CPT2 activities
- Dual mitochondrial and nuclear genome panel: two heterozygous pathogenic variants in the nuclear ETFDH gene

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)
AKA: Glutaric acidemia/aciduria II

- AR disorder associated with deficiency of either an electron-transfer flavoprotein (ETF, encoded by *ETFA* and *ETFB*) or dehydrogenase (ETFDH, encoded by *ETFDH*)

- Allelic with Coenzyme Q10 deficiency

- Clinical presentations
  - **Neonatal-onset form with congenital anomalies** (type I): renal cystic dysplasia and other congenital anomalies; death in the first few weeks
  - **Neonatal-onset form without congenital anomalies** (type II): infants and children, episodic hypoglycemia, acidosis, and hepatomegaly
  - **Late-onset form** (type III)

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)
AKA: Glutaric acidemia/aciduria II

- **Late-onset form** (type III):
  - Symptoms and age at presentation are highly variable, with recurrent episodes of lethargy, hypoglycemia, metabolic acidosis, and hepatomegaly
  - Muscle involvement in the form of pain, weakness, and lipid myopathy
  - EMG: myopathic or neuropathic
  - Lab: High CK; muscle chemistry: low carnitine
  - Almost all patients with late-onset MADD (98%) are responsive to riboflavin

Follow up

- The mother's genetic testing showed that the mutation was trans in the patient and thus, disease-causing
- Since stopping the hydroxychloroquine, the patient reported improvement, she is able to walk and return to work with some residual proximal weakness in the lower extremities
- A prescription of riboflavin 100mg given and a recommendation to consider carnitine, CoQ10, and to maintain a low fat, high carbohydrate diet
- Verbal follow-up from the patient was that she “feels a difference with the vitamin B and dietary change"

References

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