

Clinical Reasoning: A 33-year-old man with cardiomyopathy and myopathy

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SECTION 1

An 18-year-old Hmong man sought medical care because of worsening performance on military training exercises. He had a previous syncopal episode with prompt recovery. His medical and developmental history were otherwise unremarkable. A chest radiograph revealed cardiomegaly and, after further cardiac tests, he was diagnosed with postinfectious or idiopathic cardiomyopathy. His cardiac function deteriorated and heart transplantation was pursued. During preoperative evaluation, his serum creatine kinase (CK) was noted to be persistently elevated in the 4,000s, prompting further investigation, but since he was not weak or otherwise symptomatic, definitive diagnosis and treatment were not pursued. When 19 years old, he underwent orthotropic heart transplantation. In the following years, he had multiple stents placed for coronary artery disease and developed type 1 diabetes mellitus, but he worked as an information specialist and cared for himself.

In the patient's early 30s, family members noticed a limp, and he perceived an inability to walk on the toes of the left foot. He also experienced burning of his legs after moderate activity, such as climbing 2 flights of stairs. The statin he took for hyperlipidemia was discontinued. These symptoms, along with persistent hyperCKemia, prompted a neurology consultation. He denied muscle weakness, cramps, episodes

of paralysis, or urine discoloration. There was no family history of muscle disorder, weakness, cardiomyopathy, or sudden death. Examination demonstrated mild weakness (4/5 on Medical Research Council scale) of neck flexion, elbow flexion, and shoulder external rotation, more prominent on the left. He could not stand on his toes. He had bilateral, asymmetric atrophy of the posterior calves, left more than right. Tone was normal, and there was no percussion or grip myotonia. Reflexes were 2+ and symmetric in triceps, brachioradialis, and patella, 1+ at the right biceps, absent at the left biceps, and absent at both ankles. He had normal mental status, cranial nerves, sensory examination, and coordination. EMG revealed widespread abnormal spontaneous activity involving upper and lower limbs, as well as thoracic and lumbar paraspinal muscles with complex repetitive or pseudomyotonic discharges. Volitional activation revealed early recruitment of small, short-duration, polyphasic motor units.

Questions for consideration:

1. What conditions are associated with markedly elevated CK and cardiomyopathy?
2. Based on the clinical and EMG findings, which conditions are most likely in this patient?
3. What additional laboratory tests and diagnostic procedures should be performed?

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SECTION 2

A markedly and persistently elevated CK is suggestive of a skeletal myopathy. Myopathies associated with cardiomyopathy are often inherited diseases, including but not limited to Becker and Duchenne muscular dystrophy, limb-girdle muscular dystrophies (LGMD, particularly 2I and 2C-F), McLeod syndrome, lipid and glycogen storage disorders, myotonic dystrophies, nemaline myopathy, mitochondrial disorders, and myofibrillar myopathies (table).^{1,2} A similar phenotype can be caused by acquired myopathies such as polymyositis, dermatomyositis, infectious myositis caused by *Staphylococcus aureus*, *Borrelia burgdorferi*, *Trypanosoma cruzi*, or Coxsackie virus, endocrinopathies such as hypothyroidism, and toxic myopathies caused by alcohol, chloroquine, heroin, and zidovudine.^{1,2}

In our patient, the subacute onset of symptoms and lack of systemic illness argue against infectious etiology. He did not have skin lesions to suggest dermatomyositis. He had not been taking medications or consuming alcohol. Thyroid function tests and serum calcium were normal.

Our patient's weakness involved proximal and distal muscles, was asymmetric, and was associated

with prominent posterior calf atrophy. This pattern is unusual for polymyositis or dermatomyositis, which usually manifest with proximal, symmetric weakness.¹ Dystrophinopathies, sarcoglycanopathies, and LGMD 2I often show calf pseudohypertrophy, in contrast to our patient's calf atrophy.¹ Myotonic dystrophies more often cause cardiac conduction abnormalities than cardiomyopathy, and CK is rarely markedly elevated.¹ Metabolic myopathies including lipid and glycogen storage disorders, such as Pompe disease, and myofibrillar myopathies remain in the differential diagnosis.² These disorders can show abnormal spontaneous activity on EMG, including high-frequency discharges.²

A muscle biopsy is indicated. Deltoid muscle biopsy was performed during the patient's pretransplant workup at another institution (figure, A–C).

Questions for consideration:

1. Which conditions are associated with the pathology present on this muscle biopsy?
2. What additional tests are necessary to reach a final diagnosis?

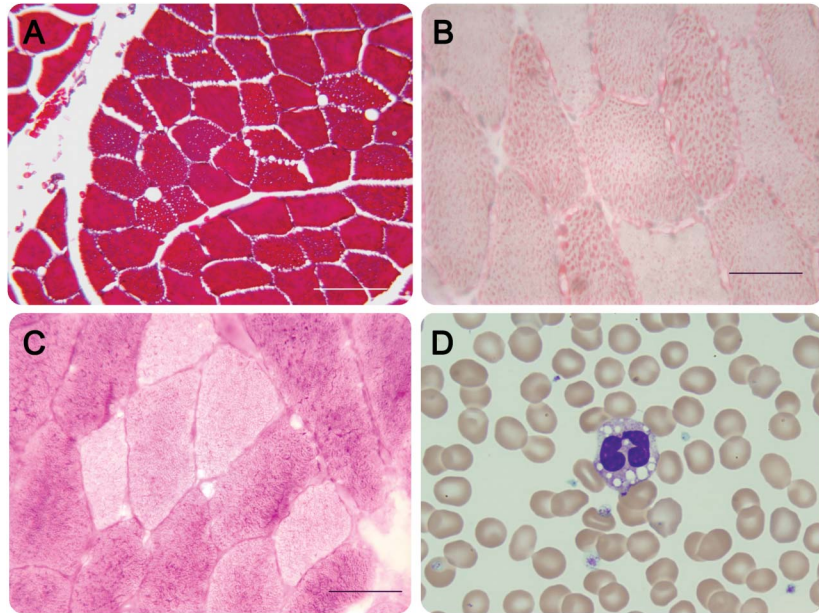
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Table Distinguishing characteristics of inherited myopathies associated with cardiomyopathy: Clinical features, investigations, and treatments

Inherited myopathy (examples)	Age at presentation	Clinical features	Laboratory studies/EMG/muscle biopsy	Treatment
Muscular dystrophies (DMD, BMD, LGMD, EDMD, myofibrillar myopathies)	Childhood	Proximal weakness, calf pseudohypertrophy	Laboratory studies: markedly elevated CK (DMD, LGMD2); EMG: irritable myopathy ^a ; biopsy: reduced immunostaining for sarcolemmal proteins	Steroids (DMD)
Myotonic dystrophies (myotonic dystrophy types 1 and 2)	Adulthood	Distal weakness (type 1), proximal weakness (type 2), grip myotonia, frontal balding, cataracts, cardiac conduction block	Laboratory studies: normal to mildly elevated CK; EMG: myotonic discharges; biopsy: rows of internal nuclei	Sodium channel blockers for myotonia
Lipid storage myopathies (PCD, MADD, Acyl-CoA dehydrogenase deficiencies, CPT2 deficiency, NLSLD)	Infancy to adulthood	Fixed proximal weakness, exercise intolerance and rhabdomyolysis, calf atrophy (NLSLD)	Laboratory studies: markedly elevated CK, low carnitine (PCD), abnormal acylcarnitine and organic acid profiles, Jordan anomaly on peripheral smear (NLSLD); EMG: normal or irritable myopathy; biopsy: lipid accumulation	Levocarnitine (PCD), riboflavin/CoQ10 (MADD), triheptanoin (CPT2), low-fat diet, avoid fasting
Glycogen storage disorders (glycogenosis type II [Pompe] and III [debranching enzyme deficiency])	Infancy to adulthood	Generalized weakness, tongue weakness (type II), respiratory failure (type II)	Laboratory studies: variable CK; EMG: irritable myopathy, paraspinal myotonia (type II); biopsy: lysosomal glycogen-filled vacuoles (type II)	Enzyme replacement (type II)
Mitochondrial myopathies (MERRF, MELAS)	Infancy to adulthood	Proximal weakness, exertional rhabdomyolysis, various multisystem manifestations	Laboratory studies: elevated serum lactate and pyruvate, normal or mildly elevated CK; EMG: normal or nonirritable myopathy; biopsy: ragged-red, ragged-blue, and COX-negative muscle fibers	Vitamin and nutrient supplements

Abbreviations: BMD = Becker muscular dystrophy; CK = creatine kinase; COX = cyclooxygenase; CPT2 = carnitine palmitoyltransferase 2; DMD = Duchenne muscular dystrophy; EDMD = Emery-Dreifuss muscular dystrophy; LGMD = limb-girdle muscular dystrophy; MADD = multiple-acyl-CoA dehydrogenase deficiency; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy and ragged-red fibers; NLSLD = neutral lipid storage disease; PCD = primary carnitine deficiency.

^a Irritable myopathy entails increased insertional and spontaneous activity, as well as motor unit action potentials that are short-duration, low-amplitude, and polyphasic.



(A) Masson trichrome shows abundant small clear vacuoles ($\times 63$, scale bar = $50 \mu\text{m}$). (B) Oil red O stains vacuoles intensely, indicative of lipid content, while (C) periodic acid-Schiff does not stain vacuoles, suggesting absence of glycogen ($\times 63$, scale bar = $50 \mu\text{m}$). (D) Wright-Giemsa stained peripheral smear demonstrates cytoplasmic vacuoles in a neutrophil (oil-immersion lens $\times 100$).

SECTION 3

The biopsy shows prominent lipid storage in muscle. The best described genetic diseases with massive lipid storage are primary carnitine deficiency; short, medium, very-long-chain, or multiple acyl CoA dehydrogenase deficiency; neutral lipid storage disease with ichthyosis; and neutral lipid storage disease with myopathy.³ Mitochondrial disorders causing CoQ10 deficiency can also show substantial lipid storage.² Trichrome, succinate dehydrogenase, and cytochrome oxidase stains showed no ragged-red, ragged-blue, or cyclooxygenase-negative fibers, respectively, making the diagnosis of mitochondrial disorders less likely.

Serum lactic acid and total and free carnitine levels were normal. Serum acylcarnitine ester profile showed elevated 2-methylbutyrylcarnitine and urine organic acids showed elevated methylbutyrylglycine. Peripheral blood smear is shown in figure, D.

Questions for consideration:

1. What diagnosis is suggested by the peripheral smear?
2. What do the result of acylcarnitine esters and urine organic acids mean?
3. What genetic mutations are associated with these diseases?

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SECTION 4

The smear shows vacuolated leukocytes, or Jordan anomaly, which is diagnostic of neutral lipid storage disease.⁴ Neutral lipid storage disease is caused by inactivation or dysfunction of the enzyme adipose triglyceride lipase (ATGL), which catalyzes the initial step of the intracellular triglyceride degradation pathway, and results in triglyceride accumulation in cytoplasm. Neutral lipid storage disease with ichthyosis is associated with genetic mutation in *ABHD5*, a gene that codes for the protein that activates ATGL.⁵ Since our patient lacked ichthyosis, we suspected neutral lipid storage disease with myopathy (NLSDM) and obtained next-generation sequencing for *PNPLA2*, the gene that codes for ATGL.⁶ A previously reported homozygous mutation in the consensus splice donor site for intron 6 of the *PNPLA2* gene (c.757+1 G > T) was identified and confirmed by Sanger sequencing, substantiating the diagnosis of NLSDM.⁷

Incidentally, urine organic acid screen was positive for 2-methylbutyrylglycine, which suggests short/branched-chain acyl-CoA dehydrogenase deficiency. When symptomatic, this deficiency has been associated with neonatal crisis, hypotonia, muscular atrophy, seizures, or developmental delay.⁸ Most patients, however, are asymptomatic—as is our patient, who has a homozygous missense mutation c.1165A > G in the *ACADSB* gene. This mutation is not uncommon in Hmong Americans (21.8% are heterozygous for this mutation and 1.3% are homozygous).⁸

NLSDM is a rare disease in which the accumulation of lipids in muscle cells impedes energy metabolism. Resultant weakness is typically proximal with prominent shoulder girdle involvement and may be asymmetric at onset.^{7,9} Weakness may also involve distal extremities, particularly finger extensors and foot flexors.^{7,9} Most patients develop symptoms by 30 years of age, although elevated CK and lipid accumulation is present prior to symptom onset.⁹ Cardiomyopathy due to lipid accumulation in cardiac muscle affects about half of patients with NLSDM.⁹ While cardiomyopathy associated with NLSDM more commonly occurs in the fifth decade, we suspect that our patient's presenting symptom of cardiomyopathy was related to NLSDM. NLSDM can be associated with hypertriglyceridemia and diabetes, as is the case in our patient.⁹

There is no specific treatment for neutral lipid storage myopathy, although the lipid-lowering agent bezafibrate has been used experimentally, demonstrating decreased tissue lipid accumulation and

improved oxidative metabolism but no measurable clinical benefit.¹⁰ Treatment is supportive and long-term outcomes are not yet clear.

AUTHOR CONTRIBUTIONS

Laura A. Foster: drafting and revising manuscript. Elizabeth L. Courville: analysis or interpretation of data, drafting and revising manuscript. Georgios Manousakis: manuscript concept and design, analysis or interpretation of data, drafting and revising manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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