Clinical Reasoning:

A 45-year-old man with weakness and myalgia after orthopedic surgery

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SECTION 1

A 45-year-old man underwent rotator cuff surgery and developed fatigue and generalized myalgia postoperatively. After 4 weeks of mild symptoms, he experienced severe muscle aches and bilateral leg weakness after walking 1.5 miles, prompting him to seek medical attention.

The patient had a history of chronic pain syndrome and multiple orthopedic surgeries. He had no pertinent family history. He denied foreign travel, consumption of alcohol, tobacco, illicit drugs, nutritional supplements, or herbal remedies. He denied risky sexual behaviors. He was taking trazodone, oxycodone, and omeprazole.

On examination, the patient had tenderness in both thighs. There were no skin changes, swelling, or erythema. He had multiple surgical scars in the right shoulder and mild weakness in proximal limb and cervical muscles. Biceps and patellar reflexes were diminished bilaterally. He was able to rise from a chair using his arms, but had difficulty ambulating due to leg pain. The remainder of the examination was unremarkable.

Questions for consideration:

1. What is the differential diagnosis?
2. What studies should be obtained next?

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SECTION 2

This patient presents with diffuse myalgia after a minimally invasive surgical procedure and is found to have mild proximal weakness on examination. Myalgia, or muscle pain, is encountered in a variety of conditions, ranging from benign causes, such as strenuous physical activity, to life-threatening conditions. The first step in the evaluation of patients with myalgia is to establish a timeframe from symptom onset and precipitating factors. Acute onset is observed after trauma, surgery, or strenuous exercise. If symptoms develop insidiously, medications (statins, fibrates), rheumatologic conditions (polymyalgia rheumatica), chronic infections, or metabolic disorders (hypercalcemia, hypothyroidism, or hypercortisolism) should be considered.

The distribution of myalgia helps narrow the differential diagnosis. Myalgia involving proximal appendicular muscles points towards a primary muscle disease or rheumatologic or orthopedic disorders. When diffuse, an infectious process, especially viral and parasitic, deserves consideration. Rhabdomyolysis from varied etiologies can also present with diffuse myalgia.^{1,2}

Detection of objective weakness is important, but frequently confounded by pain limiting maximal effort on examination. Assessment of neck flexors and extensors may be helpful. Both myopathies and polyradiculopathies can present with weakness and pain in proximal limbs. In this patient, sensation was preserved and reflexes mildly diminished, more suggestive of a myopathy. The temporal relationship with a surgical procedure requires exclusion of an intraoperative or postoperative infection or an underlying metabolic or endocrine disorder exacerbated by surgical stress. Direct trauma from surgery is unlikely

given the diffuse nature of the symptoms. Due to the patient's history of chronic pain, fibromyalgia and polymyalgia rheumatica are possible, but objective weakness would not be expected. Finally, acute pain exacerbation and deconditioning after surgery are diagnoses of exclusion.

Initial laboratory evaluation in patients with myalgia should include complete blood count, serum calcium and other electrolytes, urinalysis, renal and liver function tests, thyroid-stimulating hormone (TSH), and creatinine kinase (CK) levels. Depending on other symptoms, risk factors, and examination findings, blood cultures, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or rheumatologic studies may be helpful.

In this patient, blood count and chemistries were normal. CK levels were elevated at 86,300 U/L (normal <330 U/L). Transaminases were also elevated: alanine aminotransferase (ALT) was 1,260 U/L (normal <55 U/L) and aspartate aminotransferase (AST) was 3,270 U/L (normal <48 U/L). Lactate dehydrogenase (LDH) was 1,360 U/L (normal <220 U/L). Alkaline phosphatase and γ -glutamine transpeptidase (GGT) levels were normal. Urine dipstick revealed proteinuria and was positive for blood (1–3 erythrocytes per high-powered field on microscopy). ESR and CRP were moderately elevated. TSH was normal. Hepatitis serologies, HIV, procalcitonin, blood cultures, and urine drug screen were negative.

Questions for consideration:

1. How do you interpret these results?
2. What information would help narrow the differential diagnosis?

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SECTION 3

The patient had markedly elevated CK, AST, ALT, and LDH levels. These enzymes are present in skeletal muscle cells and are released into the circulation as the result of muscle damage and membrane disruption as seen in rhabdomyolysis. Transaminases and LDH are also found in liver tissue, but in the presence of hyperCKemia, these enzyme elevations are more likely due to muscle breakdown than liver injury. In addition, GGT and alkaline phosphatase, more specific markers of liver damage, were normal in this patient. Other muscle components, including myoglobin and other small proteins, are also released in the setting of muscle breakdown and excreted in urine resulting in proteinuria. Myoglobin has molecular similarities with hemoglobin and also turns urine dark; therefore the presence of myoglobin in urine may be falsely labeled as hematuria. A few erythrocytes under direct urine visualization, like in this patient, suggests myoglobinuria.

We concluded that our patient had rhabdomyolysis causing increased serum levels of CK and other

muscle enzymes, myoglobinuria, and generalized myalgia. The elevated ESR and CRP likely resulted from an inflammatory response to muscle injury. The most important next step was to provide IV hydration to preserve renal function and to exclude life-threatening complications (cardiac arrhythmias from electrolyte disturbances, severe metabolic acidosis, and organ failure).

Once stabilized, the patient reported recurrent episodes of diffuse muscle aches and occasional dark urine, which would subside within hours to days, after exercise dating back to his teenage years. He experienced similar symptoms episodically in the context of surgical procedures and illnesses. Over the past year, he had developed exercise intolerance and could not walk more than 150 yards without experiencing severe leg pain.

Questions for consideration:

1. What are common causes of rhabdomyolysis?
2. What is the most likely cause of rhabdomyolysis in this patient?

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SECTION 4

The causes of rhabdomyolysis can be divided into 3 categories: traumatic, exertional, and nontraumatic nonexertional. Trauma includes direct muscle damage or compression from prolonged immobilization against a hard surface. The second category includes conditions in which energy production or utilization by myocytes is insufficient to meet metabolic demands, such as hyperthermia, convulsive seizure, vigorous exercise, and metabolic myopathies. The third group includes miscellaneous conditions (infections, electrolyte imbalances, drug or toxin-related, muscle ischemia, or inflammatory myopathies).³

The cause of rhabdomyolysis in this patient falls into the second category. He had a longstanding history of exercise intolerance beginning in childhood with recurrent myalgia and pigmenturia triggered by exercise and stress, suggesting a disorder of energy metabolism. In addition, after the attack his strength improved and muscle enzymes normalized, indicating cessation of damage after resolution of the situation of metabolic stress. These features suggest a metabolic myopathy. The most common metabolic myopathies are due to deficiency of enzymes that participate in glycogen or lipid

metabolism. While in glycolytic metabolic defects, patients usually have cramps induced by light exercise or brief isometric contractions, symptoms in disorders of lipid metabolism are dominated by myalgia triggered by prolonged or intense exercise and other situations that increase energy demand from fat (fasting, fever, trauma, surgery).^{4,5} Symptoms in our patient were precipitated by the stress of surgery and possibly intraoperative anesthetics, and further worsened by prolonged exertion (walking a long distance), therefore a metabolic myopathy due to a lipid metabolism defect was suspected. We ordered serum levels of free and total carnitine, acylcarnitines, and urine organic acids. Concentrations of long-chain acylcarnitines, particularly C16 and C18:1 species, were elevated with an otherwise normal carnitine profile (total plasma 76 nmol/mL [normal 34–78 nmol/mL]). Further serologic metabolic screening was unremarkable. Electrodiagnostic studies and muscle biopsy were deferred as both provide limited information in the setting of rhabdomyolysis and findings may be difficult to interpret. Subsequent genetic testing demonstrated that the patient was heterozygous for 2 pathogenic variants, Ser113Leu and Lys457Ter, in the carnitine palmitoyltransferase (CPT) 2 gene, consistent with CPT2 deficiency.

Figure Carnitine palmitoyltransferase (CPT) system in the mitochondrial membrane

Long-chain fatty acids require the CPT system to cross the mitochondrial membrane and enter the mitochondrial matrix where β -oxidation, the process by which fatty acids are broken down to produce energy, occurs. Before being transported across the mitochondrial membrane, long-chain fatty acids are activated by acyl-coenzyme A (CoA) synthetase (ACS) and converted into long-chain acyl-CoA. CPT1, in the outer mitochondrial membrane, attaches carnitine to the acyl group. Then CPT2, in the inner mitochondrial membrane, cleaves the carnitine, allowing the long-chain acyl-CoA to be translocated into the mitochondrial matrix to enter the β -oxidation pathway. During each β -oxidation cycle, one molecule of acetyl-CoA is produced. Acetyl-CoA molecules are incorporated into the Krebs cycle and eventually generate energy for the cell in the form of adenosine triphosphate (ATP). In patients with CPT2 deficiency, translocation of long-chain fatty acids into the mitochondrial matrix is impaired, precluding their use as a source of energy for the muscle.

DISCUSSION CPT2 deficiency is a disorder of long-chain fatty acid oxidation and is one of the most common metabolic myopathies. During times of increased metabolic demands, energy production in muscle cells transitions from readily available glucose-derived stores to fatty acids. Energy release from fatty acids requires β -oxidation inside the mitochondrial matrix. The CPT system facilitates the entry of long-chain fatty acids into the mitochondria using carnitine as a carrier (figure).⁶ In individuals with CPT2 deficiency, carnitine is attached to long-chain fatty acids but cannot be cleaved, resulting in increased levels of long-chain acylcarnitines, which cannot be used as an energy source. Continued physiologic demand without sufficient energy supply causes damage to muscle fibers and subsequent myopathic pain and weakness.⁷ As in our patient, it is not uncommon to encounter individuals with CPT2 deficiency who have been misdiagnosed with rheumatologic or orthopedic conditions and exposed to unnecessary orthopedic surgeries and a variety of interventions for pain control.

Management of CPT2 deficiency relies on adaptive measures to prevent attacks (avoid fasting, prolonged exercise, and physical activity during illness), dietary modifications (carbohydrate-enriched diet and carbohydrate intake before and during exercise), and supplementation with medium-chain fatty acids,

which do not require the CPT system to entry the mitochondria. CPT2 deficiency is an autosomal recessive disease; therefore children of affected individuals have a 25% chance of developing symptoms. Genetic counseling should be offered to patients and their close relatives.

AUTHOR CONTRIBUTIONS

Rocio Vazquez do Campo: manuscript concept and design, drafting of the manuscript, editing of final text, review of the literature. Jason Siegel and Eric Goldstein: care of the patient, contributed to manuscript editing and case discussion. Elliot Dimberg: critical review of the manuscript, editing of final text, and intellectual contribution.

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DISCLOSURE

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

REFERENCES

1. Shmerling RH. Approach to the patient with myalgia: UpToDate. Available at: uptodate.com/contents/approach-to-the-patient-with-myalgia. Accessed September 26, 2016.
2. Chan EK, Kornberg AJ, Ryan MM. A diagnostic approach to recurrent myalgia and rhabdomyolysis in children. *Arch Dis Child* 2015;100:793–797.
3. Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJ, de Visser M. Rhabdomyolysis: review of the literature. *Neuromuscul Disord* 2014;24:651–659.
4. Sharp LJ, Haller RG. Metabolic and mitochondrial myopathies. *Neurol Clin* 2014;32:777–799.
5. Tobon A. Metabolic myopathies. *Continuum* 2013;19:1571–1597.
6. Hoppel CL, Tomec RJ. Carnitine palmitoyltransferase: Location of two enzymatic activities in rat liver mitochondria. *J Biol Chem* 1972;247:832–841.
7. Daroff, Robert B, Bradley WG. Disorders of skeletal muscle. In: *Bradley's Neurology in Clinical Practice*. Philadelphia: Elsevier/Saunders; 2012:1942.

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