Clinical Reasoning: A 63-Year-Old Woman Presenting With Bilateral Leg Pain

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Section 1

A 63-year-old Hispanic woman presented with 5 days of abrupt onset bilateral leg pain. The pain was maximal at onset and worst in her hamstrings and calves. She described it as “soreness, like lactic acid buildup after a workout.” Touch or muscle use exacerbated the pain. It was not accompanied by muscle spasm, numbness, or tingling. She reported mild weakness and difficulty walking due to pain. She reported no symptoms above the waist. There were no constitutional symptoms, swollen joints, or bowel or bladder incontinence. She had no known infections in the weeks before symptom onset. There was no recent strenuous exercise or physical activity. She had 2+ pitting edema of both legs at baseline.

The patient’s medical history was significant for light chain amyloidosis that initially presented with cardiomyopathy, diagnosed 5 years previously by endomyocardial biopsy. A bone marrow biopsy later that year showed immunoglobulin G (IgG) lambda multiple myeloma. At that time, she received cyclophosphamide, bortezomib, and dexamethasone. She initially had a monoclonal IgG lambda M-spike, which resolved with treatment. Surveillance serum protein electrophoresis with immunofixation 3 months prior to presentation showed no M-spike. She also had chronic kidney disease, secondary to cardiorenal syndrome, and prior renal infarct without proteinuria to suggest renal amyloidosis.

The patient did not have any personal or family history of neurologic disorders. She did not have any excessive alcohol consumption, illicit drug use, or toxic exposures. She reported no recent travel and was a former infectious disease researcher.

The patient started amiodarone for atrial flutter 3 weeks prior to her presentation. She also took apixaban, allopurinol, metolazone, spironolactone, and torsemide. She had not been on a statin and had no recent exposure to steroids.

On examination, the patient had tenderness to palpation and allodynia to light touch over her hamstring and calf muscles. She had no macroglossia, muscle pseudohypertrophy, rashes, point tenderness on her back, or radicular symptoms. She had the following Medical Research Council grades: bilateral and symmetric 4/5 weakness of hip flexion, knee extension, and knee flexion. She had mild symmetric loss of vibratory sense in her lower extremities. Reflexes were 2+ and symmetric throughout with downgoing toes.

Questions for Consideration:

1. What is the localization and differential diagnosis for the patient’s deficits?
2. Was the patient on any myotoxic or neurotoxic medications?
3. What laboratory testing would be helpful to help narrow the differential diagnosis?

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Section 2

The patient's muscle tenderness and symmetric, proximal weakness make myopathy the most likely localization. Allodynia and vibratory sensory loss also raise concern for polyradiculopathy, plexopathy, or polyneuropathy. Diabetic lumbosacral radiculoplexus neuropathy, for example, can present with prominent thigh pain at onset. However, significant weakness without hyporeflexia argues against these possibilities. Neuromuscular junction disorders are unlikely given that they do not manifest with severe pain. The patient's normal reflexes, absent Babinski sign, and lack of bowel/bladder dysfunction argue against brain or spinal cord localization. The differential diagnosis for myopathy is broad and includes autoimmune, paraneoplastic, infectious, drug- or toxin-induced, metabolic, endocrine, hereditary, or infiltrative causes such as amyloidosis.¹ The acute onset makes certain autoimmune and toxic etiologies more likely.

The first step to narrow the differential diagnoses is careful consideration of laboratory values. The laboratory workup

was notable for normal eosinophil count (0.02K/ μ L), elevated creatinine (2.86 mg/dL), normal glucose (90 mg/dL), normal calcium (9.1 mg/dL), normal thyroid-stimulating hormone (TSH; 2.49 μ IU/mL), elevated erythrocyte sedimentation rate (ESR; 90 mm/h), elevated C-reactive protein (CRP; 73.2 m/L), normal aldolase (4 U/L), normal creatine kinase (CK; 150 U/L), serum protein electrophoresis (SPEP) with immunofixation without M-spike, and elevated serum kappa and lambda free light chains (FLC) with borderline elevated kappa/lambda ratio (kappa FLC 65.2 mg/dL, lambda FLC 39.3 mg/dL, kappa/lambda ratio at 1.66). In addition, our patient had rheumatologic screening tests sent on initial evaluation, including HMG-CoA reductase, dsDNA, anti-Ro, anti-La, anti-Jo, and anti-neutrophil cytoplasmic antibody (ANCA) antibodies, which were all unremarkable.

Questions for Consideration:

1. How does the laboratory testing change your differential diagnosis?
2. What are the next tests you would order?

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Section 3

The normal CK and aldolase make an inflammatory myopathy, such as polymyositis, less likely. CK can be normal in 20% of dermatomyositis cases, but the patient had no cutaneous stigmata.¹ CK can also be normal in inclusion body myositis, but this does not begin acutely nor is it typically associated with pain. A toxic myopathy due to amiodarone is possible as this may be associated with a normal or only slightly elevated CK, and our patient is at increased risk due to her chronic kidney disease.² Amyloid and myopathies due to Cushing syndrome, adrenal insufficiency, or hyperparathyroidism can also have a normal CK.^{1,2}

Painful myopathies include amyloid and hypothyroidism, although the latter is associated with an elevated CK and our

patient's TSH was normal.³ Diffuse fasciitis with eosinophilia, Shulman syndrome, is characterized by myalgias, muscle tenderness, and proximal weakness, although most patients have a peripheral eosinophilia and aldolase elevation with normal CK, making this unlikely.²

The elevated ESR/CRP is not particularly helpful in differentiating an inflammatory myopathy as they can often be normal.² However, the elevated ESR/CRP in conjunction with prominent pain raises the possibility of vasculitis. Polyarteritis nodosa can commonly present with myalgias, with documented myopathy in 19% of cases.⁴ Other examples include granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. The negative ANCA serology was important in ruling out granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Given the normal autoimmune laboratory values, an autoimmune process was thought to be less likely.

Figure 1 MRI Thigh

MRI of the thigh demonstrates extensive edema in multiple muscle groups but most notably in the posterior compartment. There is also prominent interfasial edema (arrow). There is no focal muscle atrophy. There is no reticulation of the subcutaneous fat.

While a myopathy remains most likely based on the clinical history, the laboratory tests do not allow for definitive localization or diagnosis. Skeletal muscle MRI of the thigh, with contrast if possible, could determine whether there is fasciitis or muscle involvement. Nerve conduction studies and needle EMG can determine whether this is a myopathic or neurogenic process.

We obtained an MRI of the thigh, which showed extensive muscle edema centered in the left adductor magnus muscle, but also involving additional muscle and muscle compartments (figure 1). There was prominent edema of the fascia and an absence of reticulation in the subcutaneous fat.

Motor and sensory nerve conduction studies were normal. EMG revealed early recruitment of short duration, small amplitude, polyphasic motor unit action potentials (MUAPs) in scattered proximal thigh muscles, but notably there was no abnormal insertional or spontaneous activity.

Question for Consideration:

1. How would you localize these abnormalities and what is your differential diagnosis now?

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Section 4

The MRI helped confirm involvement of the proximal leg muscles of the lower extremity and overlying fascia. The MRI report specifically commented on lack of reticulation in subcutaneous fat, a finding commonly seen in amyloid myopathy, and therefore this diagnosis was thought to be less likely.^{5,6} The nerve conduction studies (NCS)/EMG findings were mild but showed electrophysiologic evidence of a nonirritable myopathic disorder. In myopathic disorders, MUAPs are small and recruit early; there are many motor units firing at a normal frequency despite very little activation or movement of muscle. Although muscle edema can be seen with acute denervation from a neurogenic process, this would not involve the fascia, and EMG would be expected to show neurogenic features, such as reduced recruitment. The findings on

MRI and NCS/EMG allow for definitive localization to the muscle.

The time course is suspicious for an inciting event, such as drug-related toxicity. Most toxic myopathies, including amiodarone, also show irritability such as fibrillation potentials or positive sharp waves on EMG, which were not evident. Acute, inflammatory myopathies also typically show irritability on EMG. Nonirritable myopathies include endocrine myopathies (e.g., steroid myopathy, hyperparathyroidism/osteomalacia, hyperthyroidism and hypothyroidism) and some hereditary myopathies. Amyloid myopathy can be irritable or nonirritable.⁷

Question for Consideration:

1. What further testing could be obtained?

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Section 5

At this point we can be fairly certain that we are dealing with a myopathic process. Laboratory testing did not establish an etiology. The next step is to obtain a biopsy of a muscle affected on MRI or EMG; inflammatory myopathy, toxic myopathy from amiodarone, and amyloid myopathy all have characteristic features on histology that would allow for definitive diagnosis.

Discussion

A biopsy of the left vastus lateralis muscle and overlying fascia and subcutaneous tissue revealed diffuse infiltration of endomysium and perivascular spaces within the muscle by Congo red positive amyloid deposits (figure 2, A and B). These deposits were strongly reactive for lambda light chains, with background staining for kappa light chains (figure 2, C and D). Electron microscopy showed infiltration around individual adipocytes and perivascular spaces by fibrillary deposits consistent with amyloid (figure 2, E and F).

While amyloidosis is most commonly associated with a polyneuropathy, which can lead to atrophic muscle, it can also cause a myopathy, as in this case.⁷ The vibratory sensation loss noted on our patient's examination could possibly be related to a concurrent amyloid neuropathy. Amyloid myopathy affects men more than women at a ratio of 1.3:1 and presents most often with a proximal weakness pattern. It is more commonly seen with light chain amyloidosis as opposed to familial transthyretin amyloidosis. There are usually

associated systemic signs, such as cardiac or renal involvement. However, myalgias and myopathy can be the first presenting symptom.⁵ The pathophysiology of muscle damage secondary to amyloid is unclear, although it may be related to ischemia, impaired transport of oxygen, nutrients, and wastes, or direct mechanical interference of muscle contraction.²

The CK is usually normal in amyloid myopathy, but it can be elevated in a subset of patients.⁸ MRI may show diffuse muscle edema or reticulated subcutaneous fat.^{5,6} Denervation atrophy may be present in chronic cases. Our patient's MRI did not show the classic reticulated subcutaneous fat associated with amyloid myopathy, which highlights the importance of muscle biopsy. EMG may show early recruitment of small MUAPs consistent with a myopathic process with or without membrane irritability. EMG may also show decreased recruitment of large-amplitude potential MUAPs if the patient has a superimposed polyneuropathy.²

Our patient had diffuse amyloid infiltration in her muscle, with interlaced amyloid fibrils surrounding almost every muscle fiber. The time course of amyloid accumulation is difficult to determine and the patient did not have any significant changes in her SPEP, FLCs, or kappa/lambda ratio. She may have reached a critical threshold of amyloid deposition or had a recent exacerbation given the acute onset of symptoms. It remains unclear whether the recent loading of amiodarone may have played a role. Amyloid myopathy is likely underdiagnosed, as many cases are missed on initial biopsy unless special stains (e.g., Congo

Figure 2 Muscle Biopsy

Congo red staining without polarized light demonstrates reddish staining material in the endomysium surrounding muscle fibers and small blood vessels (A) that reveals greenish birefringence under polarized light confirming amyloid deposition (B) seen with amyloid deposition. Immunofluorescence staining for kappa light chains shows normal background staining (C), while immunostaining strongly reactive for lambda light chains is supportive of the diagnosis of AL amyloid composed of lambda light chain (D). Electron microscopy demonstrates fibrillary amyloid deposits surrounding muscle fibers (E) as well as perivascular amyloid deposition in the subcutaneous tissue (F).

red), immunohistochemistry, and electron microscopy are used.^{2,5,9} To assess whether amyloid is related to light chain deposition or familial amyloidosis (e.g., transthyretin), immunostaining is indispensable. Electron microscopy can also be used to confirm the deposition of amyloid fibril. If the typing of the amyloid deposits is not possible by these methods, microdissection of Congo red deposits followed by spectrometric analysis of the peptides is often successful in identifying the precursor protein.¹⁰

There is no known proven treatment for amyloid myopathy. The prognosis is generally poor, with a mean time to death from symptom onset of 21.7 months.⁵ However, some patients respond with immunomodulators or chemotherapy and can survive for many years.⁵ Our patient’s condition was further complicated by new end stage renal disease, and she elected to be discharged home without dialysis or additional therapies and entered home hospice care.

The workup for a myopathy should be performed with a systematic, evidence-based approach. Laboratory tests such as a myositis panel take a long time to return and may not be helpful in the acute presentation of a myopathy. Likewise, MRI and EMG should be used as an extension of the clinical history and physical examination. With this patient, the CK was normal and there were no other definitive laboratory values that could confirm the diagnosis, so MRI and EMG were helpful in confirming a myopathy and narrowing the differential. However, they did not provide diagnostic certainty. In cases like this, muscle biopsy is necessary and should be performed in a timely manner to avoid unnecessary testing and prevent treatment delay. In addition, it is important to request Congo red staining to avoid missing amyloid myopathy, especially in patients with myopathies of unclear etiologies or with signs and symptoms concerning for amyloidosis or plasma cell dyscrasias.

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