

Progressive Weakness With Respiratory Failure in a Patient With Sarcoidosis

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A 29-year-old African American woman with an 8-year history of biopsy-proven renal sarcoidosis and end-stage renal disease requiring hemodialysis was admitted to the hospital with progressive weakness and shortness of breath for 2 months. Eight months prior to admission, she was prescribed 15 mg of prednisone twice a day and 200 mg of hydroxychloroquine sulfate twice a day for hypercalcemia and elevated angiotensin-converting enzyme level. As her laboratory abnormalities improved, the prednisone dose was gradually decreased, and hydroxychloroquine was continued. Six months earlier, she noticed numbness in her feet and progressive loss of muscle bulk in her feet and hands. She also noticed difficulty reaching overhead, getting out of a chair, and climbing stairs. She denied any pain or muscle cramps. Results of electrophysiological tests at that time, which included nerve conduction studies and needle electromyography, revealed moderately severe axonal sensorimotor polyneuropathy. Her weakness worsened and so she was admitted to the hospital and subsequently transferred to our facility for further management.

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On physical examination, she was dyspneic with prominent use of accessory muscles for respiration. Aside from hypophonic speech, the cranial nerve examination was normal. Motor examination revealed severe neck flexion weakness (score, 3 of 5 on the Medical Research Council Scale) and limb weakness affecting both proximal and distal muscle weakness (score, 3 of 5 on the Medical Research Council Scale) and diffuse muscle atrophy. Tendon reflexes were present but diminished throughout, and there was a length-dependent sensory loss to small- and large-fiber modalities in the lower limbs. Because of respiratory difficulty and weakness, gait could not be safely tested.

LABORATORY AND IMAGING STUDIES

Initial laboratory studies revealed normal thyroid function, a creatine kinase (CK) level of 83 U/L (reference range, 30-

135 U/L) (to convert to microkatal per liter, multiply by 0.0167), and a serum angiotensin-converting enzyme (ACE) level of 58 U/L (reference range, 8-53 U/L) (to convert to nanokatal per liter, multiply by 16.667). Renal parameters were consistent with end-stage renal failure, with a serum creatinine level of 5.6 mg/dL (reference range, 0.60-1.20 mg/dL) (to convert to micromoles per liter, multiply by 88.4) and a glomerular filtration rate of 12 mL/min/1.73 m². Results of routine cerebrospinal fluid (CSF) studies, including CSF ACE level, were unremarkable. Other laboratory test findings, including vitamin B₁₂ level, human immunodeficiency virus serology, antinuclear antibody, serum protein electrophoresis with immunofixation, acetylcholine receptor and muscle-specific kinase antibodies, and paraneoplastic antibody titers, were non-revealing. Pulmonary function test findings revealed a severe restrictive pattern deficit consistent with neuromuscular weakness. Chest computed tomographic scan revealed evidence of chronic granulomatous disease.

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Table. Disorders That May Cause Both Neuropathy and Myopathy

Disorder Type	Disorder
Connective tissue disorders	Systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, and polyarteritis nodosa
Endocrine	Acromegaly, hypothyroidism, and hyperthyroidism
Congenital	Myofibrillar (desmin) myopathy and mitochondrial myopathy
Infectious	Human immunodeficiency virus infection
Toxins	Vincristine sulfate, chloroquine and hydroxychloroquine sulfate, colchicine, cyclosporin, and alcohol
Inflammatory	Inclusion body myositis and sarcoidosis
Systemic	Critical illness neuropathy and myopathy and amyloidosis
Paraneoplastic	Paraneoplastic neuropathy and myopathy

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies revealed evidence of a severe axonal sensorimotor polyneuropathy. Needle electromyography revealed evidence of active denervation and chronic reinnervation with reduced recruitment patterns in the distal muscles of the upper and lower limbs. In addition, there were irritative changes (fibrillation and positive sharp wave potentials) with short-duration motor unit potentials and early recruitment patterns in the deltoid and biceps muscles. These latter findings were not seen on the previous electromyograph (EMG) performed 4 months earlier. Repetitive 3-Hz stimulation of the ulnar and spinal accessory nerves did not produce any decrement of compound muscle action potential amplitude.

CLINICAL COMMENT

This patient presented with slowly progressive diffuse weakness, length-dependent sensory changes, and respiratory failure. The clinical pattern localized to the peripheral nervous system, as there were no features to suggest involvement of the central nervous system. The length-dependent sensory loss and distal weakness with atrophy suggested a peripheral neuropathic process. However, severe progressive proximal weakness along with respiratory muscle involvement would be uncommon in length-dependent neuropathy and therefore suggested an additional etiology, either myopathy or neuromuscular junction disorder. Alternatively, a process involving both proximal and distal nerves (polyradiculoneuropathy) could produce both proximal and distal weakness. The electrophysiological study helped establish evidence of both irritative myopathy along with axonal polyneuropathy. Because of the progressive nature of her neuromuscular symptoms, one might consider a unifying etiology for both myopathy and neuropathy as opposed to 2 independent processes. The differential diagnosis for neuro-myopathy is broad (**Table**) and includes inflammatory or autoimmune disorders, toxic neuromyopathies, and metabolic causes.

This patient had biopsy-proven systemic sarcoidosis, so neurosarcoidosis needed to be considered. Neurosarcoidosis can affect any part of the nervous system but classically involves the spinal cord or basal meninges, leading to cranial neuropathy.¹ The peripheral or central nervous system are involved in about 5% to 15% of patients with sarcoidosis.¹ Chronic peripheral large-fiber polyneuropathy is relatively rare²; more commonly, sarcoid neuropathy affects small fibers.³ The clinical and electrodiagnostic findings in this patient indicated significant large-fiber neuropathy, which would be unusual for neurosarcoidosis. Sarcoidosis can also cause myopathy that may present in the form of acute myositis, chronic progressive weakness, or a palpable nodular myopathy.^{1,4} Muscle involvement in sarcoidosis usually produces an elevated serum CK level and irritative myopathic changes on needle EMG.¹ Incidental granulomas may be seen in the muscle biopsy specimen of up to 50% of patients with sarcoidosis, usually in the absence of clinical features of myopathy. Symptomatic muscle involvement is less common (1.4%-2.3%).⁵ In patients with sarcoidosis and typical features of myopathy, granulomas are seen in the perivascular space on muscle biopsy. While sarcoid myopathy could explain the myopathic elements of the presentation, severe axonal neuropathy would be an unusual manifestation of sarcoidosis. Further, the CK level was normal, and the weakness did not improve with steroids. Serum ACE level is neither very sensitive nor specific to neurosarcoidosis. On the other hand, CSF ACE level is elevated in at least half of patients with neurosarcoidosis. When there is extensive central nervous system involvement, CSF analysis may reveal an elevated ACE level, elevated protein level, and pleocytosis. In pure peripheral nervous system sarcoidosis, these CSF abnormalities are not seen except with the acute polyneuropathy (Guillain-Barré syndrome-like) presentation.

Chronic renal failure may be associated with severe axonal polyneuropathy (uremic neuropathy)⁶; however, myopathy is not a common feature of chronic renal failure. Hence, underlying renal failure was unlikely to be the sole reason for our patient's condition. The combination of sarcoid myopathy and uremic neuropathy could explain her presentation.

Idiopathic inflammatory myopathy (such as dermatomyositis or polymyositis) needs to be considered in cases of subacute progressive proximal weakness and irritative myopathic changes on EMG. Most forms of myositis are associated with an elevated CK level and not associated with significant polyneuropathy. Inclusion body myositis, which may actually be a degenerative rather than inflammatory muscle disease,⁷ can show both neuropathic and myopathic features on needle EMG along with normal CK levels. Inclusion body myositis generally presents in older patients as slowly progressive weakness that characteristically affects the wrist and finger flexors as well as the proximal leg muscles.⁷ Our patient's age and clinical presentation were not consistent with inclusion body myositis.

Adult-onset acid maltase deficiency should be considered because this disorder may present with progressive weakness, early respiratory failure, normal CK level,

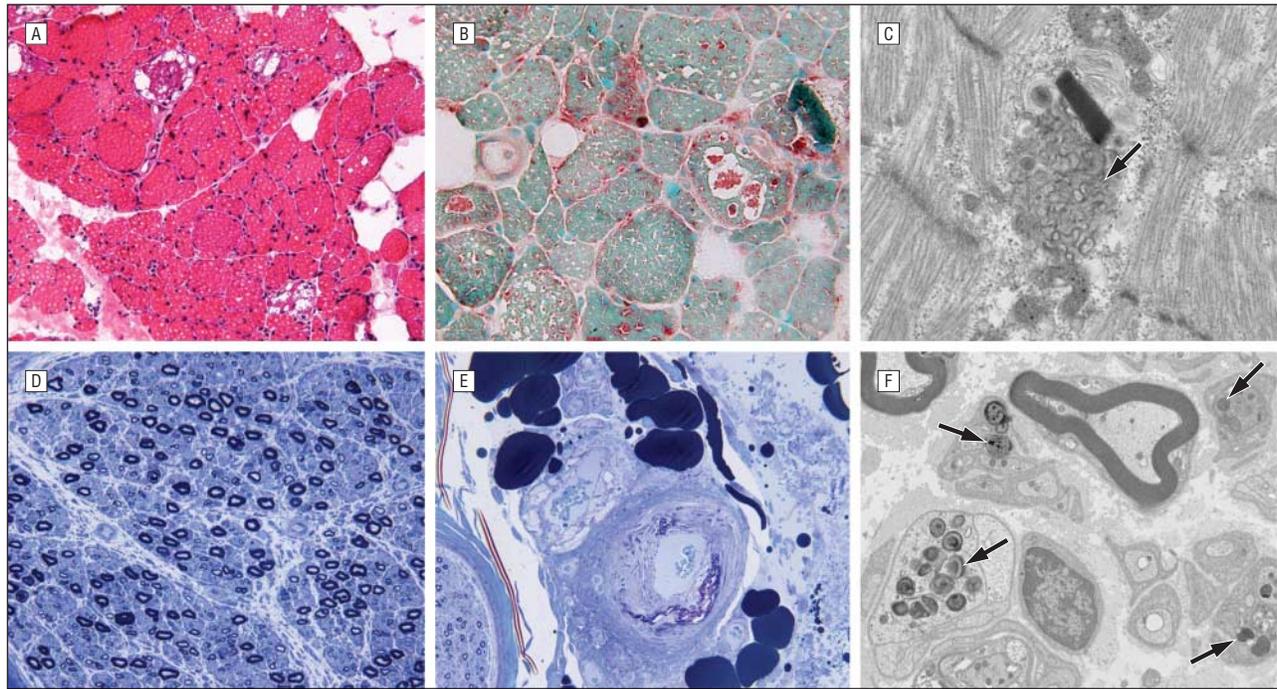


Figure. Pathological findings of the right sural nerve and right quadriceps muscle biopsy. A-C, Muscle biopsy specimen. A, Hematoxylin-eosin-stained unfixed muscle from the right quadriceps demonstrates abnormal fiber size variability and extensive vacuolar change (original magnification $\times 10$). B, Acid phosphatase stain reveals red reaction product indicating the lysosomal nature of the sarcoplasmic vacuoles (original magnification $\times 20$). C, Electron microscopy reveals frequent membranous whorls and rare curvilinear bodies (arrow) within myofibers and endothelial cells (original magnification $\times 6000$). D-E, Nerve biopsy specimen. D, Toluidine blue-stained sections of the glutaraldehyde-fixed right sural nerve reveal a mild active axonal degeneration (original magnification $\times 20$). E, A toluidine blue-stained section demonstrates calcific arteriosclerosis of epineurial vessels (original magnification $\times 20$). F, Electron microscopy demonstrates occasional membranous bodies (arrows) within a variety of cell types including axons, Schwann cells, perineurial cells, and endothelial cells (original magnification $\times 9500$).

and irritative myopathic features on EMG. Acid maltase deficiency is not associated with peripheral neuropathy, however.

Systemic vasculitis affecting the peripheral nervous system may affect both nerve and muscle, although symmetric proximal muscle involvement is rare.⁸ The group of vasculitic disorders commonly associated with vasculitic neuropathy includes antineutrophil cytoplasmic antibody-associated diseases such as Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. Polyarteritis nodosa and mixed cryoglobulinemia can also affect the peripheral nervous system.⁹ Also, only about a third of peripheral nerve vasculitis cases present as symmetrical polyneuropathy.

Systemic amyloidosis may also present as a neuromyopathy.¹⁰ Amyloid myopathy is usually seen in primary amyloidosis, and about 20% of the patients with myopathy have associated neuropathy.¹¹ Patients with amyloid myopathy have proximal muscle weakness with occasional pseudohypertrophy and macroglossia. Distal limb muscle weakness is seen if there is underlying neuropathy. The most typical neurological presentation of amyloidosis is peripheral neuropathy with prominent autonomic dysfunction. Other systemic manifestations include cardiomyopathy and nephrotic syndrome. Monoclonal protein on serum protein electrophoresis is present and leads the clinician to consider tissue biopsy to confirm the diagnosis. Our patient had neither systemic clinical features nor laboratory evidence to point toward amyloidosis.

Proximal weakness in patients with sarcoidosis can also develop in the setting of chronic steroid use. Ste-

roid myopathy usually presents as proximal weakness and a normal CK level. The EMG is often normal or may reveal nonirritative myopathic features. The muscle biopsy specimen generally shows only type 2 fiber atrophy. In our patient, rapid progression and a relatively short period of steroid exposure (few months) made steroid myopathy unlikely.

Toxic myopathy due to hydroxychloroquine use also needs to be considered because of the temporal relationship of symptoms with initiation of this drug. Hydroxychloroquine can cause both myopathy and neuropathy.¹²⁻¹⁵ There have also been reports of severe respiratory failure due to neuromuscular weakness in patients treated with hydroxychloroquine.¹⁵ Toxic myopathy secondary to hydroxychloroquine use is usually associated with irritative changes on the needle EMG and a normal serum CK level, as was the case in our patient. Muscle and nerve biopsy can help make a definitive diagnosis since this disorder is associated with characteristic features of vacuolar changes in muscle and nerve fibers with myeloid and curvilinear bodies seen on electron microscopy examination.

MUSCLE AND NERVE BIOPSY

Right quadriceps muscle and right sural nerve biopsies were performed. The muscle biopsy specimen revealed abnormal fiber size variability with well-developed acid phosphatase-positive vacuoles, type II fiber atrophy, and scant mononuclear inflammation (**Figure**). Granulomatous inflammation was not seen. Ultrastructural evalu-

ation revealed both myeloid bodies and curvilinear bodies within myofibers and endothelial cells. The sural nerve biopsy specimen revealed a loss of both myelinated and unmyelinated axons and pronounced arteriosclerotic vascular change in some vessels. Myelin ovoids were seen on the teased fiber preparation. Ultrastructural evaluation of the nerve revealed myeloid bodies within a variety of cell types. Although not entirely specific, a vacuolar myopathy and active axonal neuropathy in the presence of myeloid and curvilinear bodies suggest a hydroxychloroquine-related neuromyopathy.

PATIENT OUTCOME

The patient started taking a high-dose oral prednisone while the biopsy results were pending, and she was transferred to the intensive care unit for management of hypercapnic respiratory failure. After the biopsy results were reported, hydroxychloroquine treatment was discontinued. Her respiratory status improved slowly over the next 2 weeks. She was transferred to an inpatient rehabilitation unit at our center and was ultimately discharged home 4 weeks later. Her limb strength continued to improve over the next few months.

CONCLUSIONS

Hydroxychloroquine is an antimalarial agent used to treat various autoimmune conditions including lupus and hypercalcemia in sarcoidosis. Hydroxychloroquine can cause myopathy characterized by painless proximal muscle weakness and a normal serum CK level.¹²⁻¹⁶ In addition, a toxic neuropathy has been described with hydroxychloroquine. Depending on the involvement of muscle or nerve or a combination thereof, patients can have proximal and distal muscle weakness, decreased reflexes, and length-dependent sensory loss. Hydroxychloroquine-induced toxic myopathy may lead to respiratory muscle weakness, and cardiac muscle toxic reactions have been reported.¹⁷

Hydroxychloroquine-induced neuromyopathy can be suspected based on a temporal relationship with the initiation of the medication, a normal CK level, and irritative changes on needle EMG. A muscle or nerve biopsy is needed for a more definitive diagnosis. The biopsy results are notable for minimal inflammation (inflammation would be expected in cases of autoimmune-related neuromyopathy) and abundant acid phosphatase-reactive vacuoles indicative of lysosomal activation. Although not specific for hydroxychloroquine-related injury, curvilinear and myeloid bodies, as seen in our case, are typical for this disorder (curvilinear bodies may also be seen in neuronal ceroid lipofuscinosis).

In experimental models of chloroquine-induced myopathy, chloroquine activates lysosomal enzymes and autophagosome formation in skeletal muscle.¹⁸ This eventually leads to vacuole formation and the accumulation of debris. Hydroxychloroquine toxicity is dependent on the cumulative dosage. A toxic reaction may be seen at a dose of 500 mg a day over 1 year. A hydroxychloroquine toxic reaction may be more pronounced in patients with renal failure.¹⁵ In most instances, early ces-

sation of the medication leads to partial or complete recovery of muscle function.

This case report highlights the need to approach clinical diagnosis with an open mind when both the underlying disease as well as its treatment may lead to a similar clinical presentation. A tissue biopsy was needed to confirm the diagnosis in this case to differentiate sarcoid neuromyopathy from neuromyopathy secondary to medications used to treat sarcoidosis.

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