

# Clinical Reasoning: A 64-year-old man with progressive paraspinal muscle weakness

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## SECTION 1

A 64-year-old man was referred with a 5-month history of progressive muscle weakness. He first noted a stooped posture and gait difficulties, followed by difficulty climbing and descending stairs and lifting dishes up onto high shelves. The progressive severity of his weakness led him to require a wheelchair by the time of his presentation. He was unable to sit unaided, presumably because of axial weakness. In addition, he had recently started to experience bulbar symptoms, including dysphagia and voice changes, along with shortness of breath on exertion or when lying flat. He denied visual symptoms, ptosis, and facial weakness. There was no diurnal fluctuation of symptoms. He had no sensory symptoms or sphincter disturbance. There was no family history of muscle disease. However, his family history was positive for a child with chronic inflammatory demyelinating polyneuropathy, starting at age 16, with good response to periodic IV immunoglobulin (IVIg), and another child with acute inflammatory demyelinating polyneuropathy, who recovered fully.

On examination, there were no fasciculations noted. There was borderline weakness of the left orbicularis oculi and frontalis muscles. Cranial nerve examination was otherwise normal, including normal speech, and normal tongue examination. There was wasting of the right brachioradialis; bulk was otherwise normal. Tone was normal. Strength in all 4 extremities was normal on manual testing (Medical Research Council [MRC] grade 5). He had some difficulty getting up from sitting and was leaning forward when doing so. Plantar responses were downgoing. Deep tendon reflexes, sensory examination, and coordination were normal. He stood with a severe lumbar lordosis and protuberant abdomen. He was able to walk on his heels and toes.

### Questions for consideration:

1. What is your differential diagnosis at this point?
2. What testing would be helpful to narrow the differential diagnosis?

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## SECTION 2

This patient has a 5-month history of weakness predominantly affecting the paraspinal muscles, with some involvement of proximal limb and bulbar muscles. Despite his family history of inflammatory demyelinating polyneuropathy, it was not thought that his presentation fit that category of diseases—mainly because of the distribution of weakness, the absence of sensory complaints, and normal reflexes. The differential diagnosis included a lower motor neuron–predominant motor neuron disease, inflammatory myopathies such as polymyositis and inclusion body myositis, infiltrative myopathies such as amyloid myopathy, metabolic myopathies related to hypothyroidism, hyperparathyroidism, or acid maltase deficiency, and late-onset inherited myopathies. Creatine kinase (CK) (116 IU/L), erythrocyte sedimentation rate (ESR) (6 mm/h), thyroid-stimulating hormone (TSH), and parathyroid hormone

(PTH) were normal. Serum electrophoresis revealed an IgG  $\lambda$  paraprotein. Nerve conduction studies were within normal limits. EMG demonstrated fibrillations in the paraspinal muscles at L5 and abundant polyphasic motor unit potentials at T8, L4, and L5. The right biceps had a trace of fibrillation. The right biceps and triceps showed many small amplitude polyphasic potentials ( $<2$  mV). The right deltoid, brachioradialis, right quadriceps, and tibialis anterior had predominantly units with normal amplitude but with an increased proportion of polyphasic potentials. Early recruitment was noted.

### Questions for consideration:

1. Based on these findings, what is your current differential diagnosis?
2. What further testing would you perform to clarify the diagnosis?

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### SECTION 3

The history, examination, and EMG findings point toward a myopathic process. No fasciculations or large motor units were observed, making motor neuron disease less likely. The condition could be either acquired or inherited. When considering acquired myopathies, information regarding medication use, metabolic disturbances, critical illness, and toxic exposures is crucial. However, our enquiry was negative for these risk factors. CK and ESR were normal, essentially excluding polymyositis, but inclusion body myositis remained a possible diagnosis. TSH and PTH were normal, eliminating hypothyroidism and hyperparathyroidism from the list of metabolic myopathies. Presence of an IgG  $\lambda$  paraprotein prompted the consideration of amyloid myopathy and sporadic late-onset nemaline myopathy (SLO NM). A CT scan of the spine showed prominent fatty changes in the thoracic paraspinal muscles (figure 1), a finding often seen in myopathies involving the axial musculature. To differentiate between inflammatory, infiltrative, metabolic, and inherited myopathies, as outlined above, a muscle biopsy was performed.

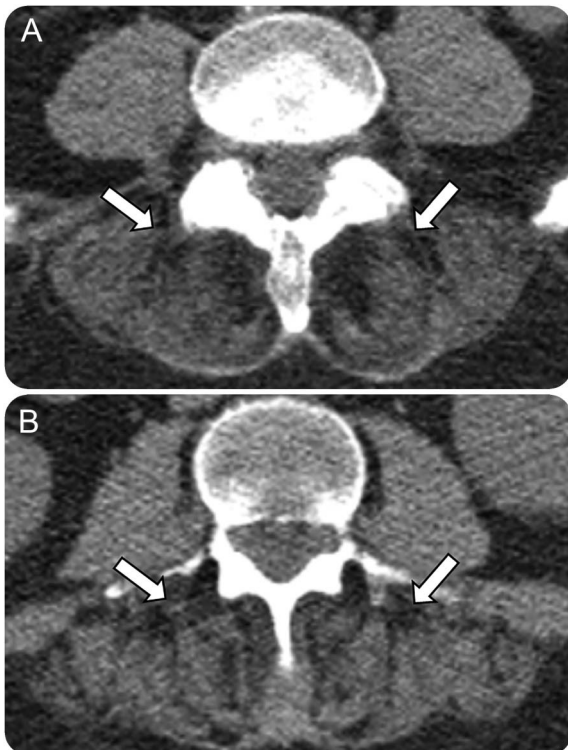
Biopsy of the left biceps muscle showed moderate variation in fiber size characterized by scattered small basophilic (regenerating) and angulated (atrophic) fibers associated with mild endomysial fibrosis. Some muscle fibers showed small dense sarcoplasmic aggregates on hematoxylin & eosin and Gömöri modified trichrome stains. Electron microscopy revealed extensive myofibrillar disarray and abundant cytoplasmic nemaline rods. Immunohistochemistry was not able to demonstrate deposition of IgG, IgG4, or  $\kappa/\lambda$  light chains in muscle fibers, although blood vessels and interstitium showed far more  $\kappa$  reactivity than  $\lambda$ . The history, examination, and pathology findings were consistent with a diagnosis of SLO NM. Genetic testing for 9 mutations known to be associated with nemaline myopathy was negative.

#### Questions for consideration:

1. What is the significance of the monoclonal gammopathy in SLO NM?
2. How would you manage this patient?

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**Figure 1** Axial CT of the lumbar spine



(A, B) Fatty changes along the paraspinal muscles (arrows).

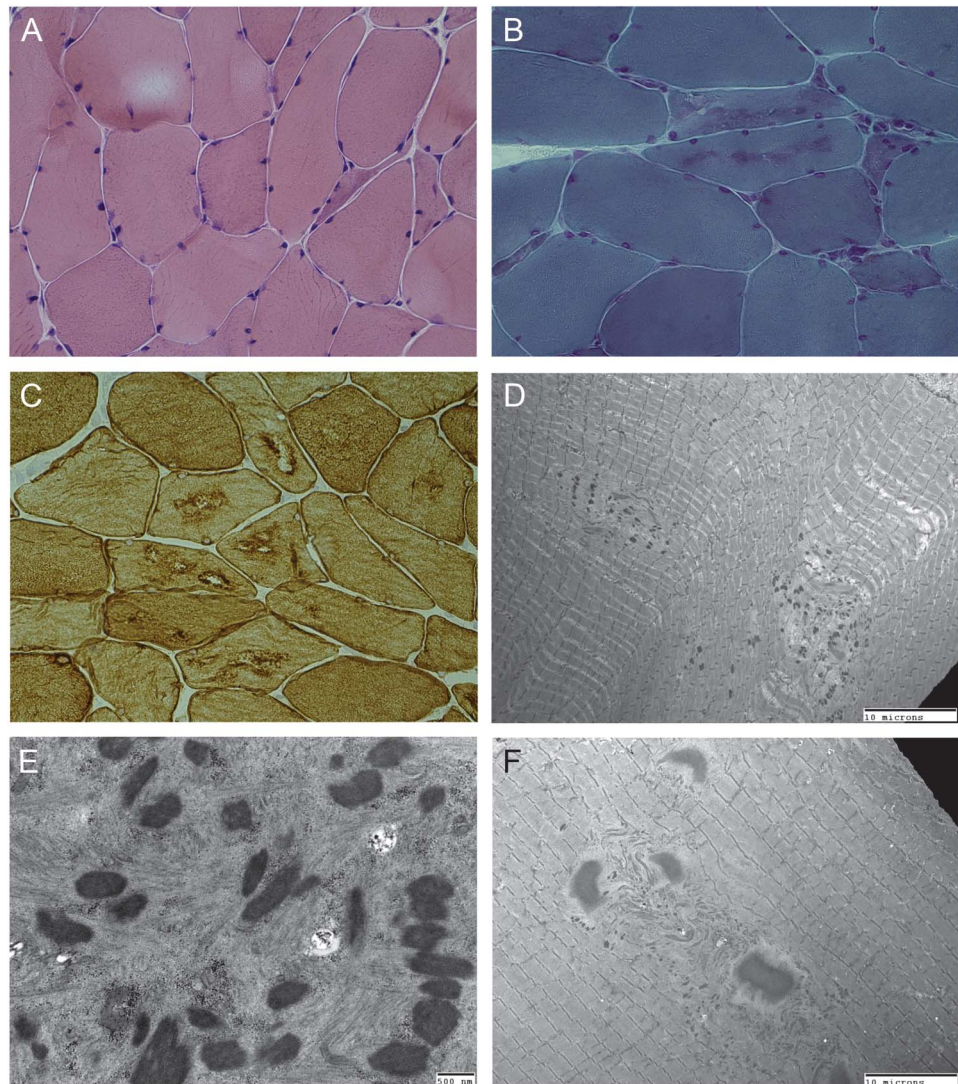
#### SECTION 4

Nemaline myopathy is one of the most common forms of congenital myopathy.<sup>1</sup> Typical clinical features include weakness and hypotonia. Occasionally, patients develop head drop, dysphagia, and respiratory insufficiency.<sup>2</sup> Nemaline myopathy is usually inherited in an autosomal recessive pattern. However, the sporadic late-onset form of nemaline myopathy is a completely different, acquired condition often associated with a monoclonal gammopathy that affects adults without a family history of the disease.<sup>2</sup> Patients often present with facial and proximal muscle weakness.

Meanwhile, the patient showed clinical progression and developed proximal limb weakness with

MRC grade strength as follows: neck extensors 4/5, neck flexors 4/5, bilateral deltoid 2/5, biceps 4/5, triceps 4/5, finger extensors 4+/5, hip flexors 3/5, knee extensors 4/5, knee flexors 4/5, and ankle dorsiflexion 4+/5. In addition, he experienced worsening of his respiratory symptoms and dysphagia. Bone marrow biopsy ruled out plasma cell dyscrasia as an underlying cause of the monoclonal gammopathy. Echocardiogram showed left ventricular systolic dysfunction. One year after onset of symptoms and 1 month after diagnosis, he underwent 6 cycles of chemotherapy with dexamethasone, cyclophosphamide, and bortezomib (CYBOR-D). After 2 months of treatment, he became ambulatory with a walker, with

**Figure 2** Muscle biopsy



Left biceps muscle biopsy (all light microscopy with 40× objective). (A) Hematoxylin & eosin stain showing occasional atrophic/angulated fibers with basophilia as well as mild endomysial fibrosis. (B) Gömöri modified trichrome stain reveals frequent dark aggregates. (C) Immunohistochemistry for desmin highlights the periphery of the aggregates while not labeling the centers. (D) Electron microscopy reveals myofibrillar disarray and abundant cytoplasmic nemaline rods, often in continuity with Z-bands. (E) Higher magnification of nemaline bodies. (F) Cytoplasmic bodies in association with nemaline rods.

corresponding improvement in MRC strength to 5/5 in all lower extremity muscle groups except for hip flexors, still at 2/5. Given the residual weakness, he underwent autologous stem cell transplantation with high-dose melphalan, 4 months after completion of CYBOR-D. At the time of completion of this manuscript, he had just been discharged from hospital, with no further change in clinical status noted thus far.

**DISCUSSION** Adult-onset nemaline myopathy was first described in 1966.<sup>3</sup> An association with monoclonal gammopathy was later reported by the same group.<sup>4</sup> In a large study on nemaline myopathy, 6 of 143 patients developed the disease in adulthood. These patients presented between the ages of 41 and 59 years. Four presented with myalgia and 2 with weakness and fatigability. All 6 patients had mild facial and proximal muscle weakness.<sup>5</sup> CK levels are usually within normal limits, and EMG demonstrates myopathic features with fibrillation potentials.<sup>6</sup> The diagnosis is confirmed by biopsy of a clinically affected muscle. The characteristic histologic feature is the presence of small red inclusions on Gömöri trichrome stain called “nemaline rods,” often found in atrophic fibers (figure 2, A–D). The rods are largely composed of  $\alpha$ -actinin, have a similar electron density to Z-lines (figure 2E), and are contiguous with these structures. The proportion of muscle fibers containing rods can vary significantly between individuals and does not seem to correlate with the clinical picture. However, the presence of a monoclonal gammopathy has been associated with an unfavorable outcome secondary to respiratory failure.<sup>6</sup> The occasionally described presence of small endomysial and perivascular inflammatory infiltrates in some patients,<sup>6</sup> the potential of  $\alpha$ -actinin to be a target in autoimmune diseases,<sup>7</sup> comorbid autoimmunity in some cases,<sup>8</sup> and favorable outcome after immunotherapy<sup>8,9</sup> raise the possibility of an immune-mediated etiology. Our patient tested negative for HIV. Of note, SLONM can be associated with HIV infection and has been reported early in the disease.<sup>10</sup> HIV-positive patients can present with similar clinical features, similar biopsy findings, and even with monoclonal gammopathy.<sup>6</sup> Anecdotal evidence suggests that the use of steroids can improve muscle strength in HIV-associated SLONM.<sup>11</sup> However, because of the small number of cases, there is only little information regarding the treatment of SLONM. Different therapeutic approaches have been described in case reports or small case series. Autologous stem cell transplantation has led to the disappearance of a monoclonal gammopathy and improvement in muscle strength.<sup>6</sup> Seven of 8 patients showed a lasting clinical response after up to 8 years of high-dose melphalan

followed by autologous stem cell transplantation.<sup>12</sup> Case report data suggest that patients with SLONM and monoclonal gammopathy can regain muscle strength in response to IVIg, prednisone, and mycophenolate mofetil therapy.<sup>9,11</sup> In our patient, recognition of the underlying monoclonal gammopathy and treatment with chemotherapy led to meaningful clinical improvement. Our case reminds us that a muscle biopsy can sometimes be necessary to make a correct diagnosis and provide the degree of diagnostic certainty that is necessary when therapies such as steroids, IVIg, or chemotherapy are being considered. SLONM is a crucial diagnosis to consider in adult-onset presentations of axial and limb girdle weakness with bulbofacial involvement given the potential avenues for treatment.

### AUTHOR CONTRIBUTIONS

Dr. Raphael Schneider: drafting/revising the manuscript and interpretation of data. Dr. Claude Steriade: drafting/revising the manuscript and interpretation of data. Dr. Peter Ashby: revising the manuscript, analysis and interpretation of data. Dr. Tim-Rasmus Kiehl: revising the manuscript, analysis and interpretation of data.

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### DISCLOSURE

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