

# Sporadic late onset nemaline myopathy (SLONM) in an adult presenting with progressive muscle weakness

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## Abstract

Sporadic late onset nemaline myopathy (SLONM) is a rare, intractable acquired myopathy that is characterised by progressive muscle weakness and the presence of nemaline rods in myofibres. Unlike the congenital form of nemaline myopathy (NM), there are only few case reports and series on SLONM in the scientific literature. We present a case report of SLONM in a 62-year-old male from a rural town in Western Australia, without any of the conditions often associated with SLONM such as monoclonal gammopathy of uncertain significance or HIV infection. SLONM should be considered in the differential diagnosis of progressive proximal muscle weakness in an adult.

**Keywords:** SLONM, nemaline myopathy, proximal myopathy

## Introduction

Sporadic late-onset nemaline myopathy (SLONM) is a rare, intractable, acquired myopathy that is characterized by progressive muscle weakness and presence of nemaline rods in myofibers. Engel (1) first described the disease in 1966, and an association with monoclonal gammopathy of undetermined significance (MGUS) was noted in 1975 (2).

## Case Presentation

A 62-year-old man from a rural town in Western Australia presented to his primary carer with myalgia, lower back pain, and progressive muscle weakness (lower>upper limb), causing a decline in mobility and falls in the preceding 6 months. His exercise tolerance had reduced to 50 m due to leg weakness and lower back pain. He had resorted to using a walking aid for assistance and was referred to a visiting neurosurgeon for suspected neurogenic claudication.

Lumbar spine magnetic resonance imaging (T1-weighted images) showed a heterogeneous bone marrow signal throughout the lumbar spine and pelvis. The T2-weighted images showed L5/S1 disc protrusion, causing mild canal narrowing. Surgical intervention was not deemed warranted, and he was referred for evaluation of muscle weakness and exclusion of a hematological malignancy.

His medical history revealed that he had myalgia over the last 2 years, which involved the shoulders, upper arms, forearms, back, and thighs, leading to progressive upper and lower limb weakness with reduced grip strength of the left hand. "Shooting pains" down the left forearm with no morning stiffness, rash, chest pain, or shortness of breath were noted. Neither loss of weight or appetite nor night sweats were observed.

His medical background included type 2 diabetes treated with metformin 2 g nocte, gliclazide 120 mg mane, and sitagliptin 100 mg mane; hypertension olmesartan/amlodipine 40/20 mg mane; and gastroesophageal reflux omeprazole 20 mg mane. He did not smoke and consumed an average of 5-6 mid-strength beers per day. There was no history of medical issues during infancy and early childhood, such as profound generalized weakness, hypotonia involving the face, bulbar and respiratory muscles, or high arched palate, to suggest a congenital myopathy.

On examination, he was clinically well. Blood pressure was 130/80 mm Hg, and pulse rate was 80 beats/min. He was afebrile with no palpable lymph nodes, rash, or arthritis. Muscle weakness was predominantly proximal (4/5 power in the shoulders and 3/5 power in the hips) with reduced grip strength and distal weakness over the left wrist on extension. No distal weakness in the lower limbs was noted. Reflexes were normal, and plantars were down going. Mild truncal weakness (4/5 power on neck extension) was ob-



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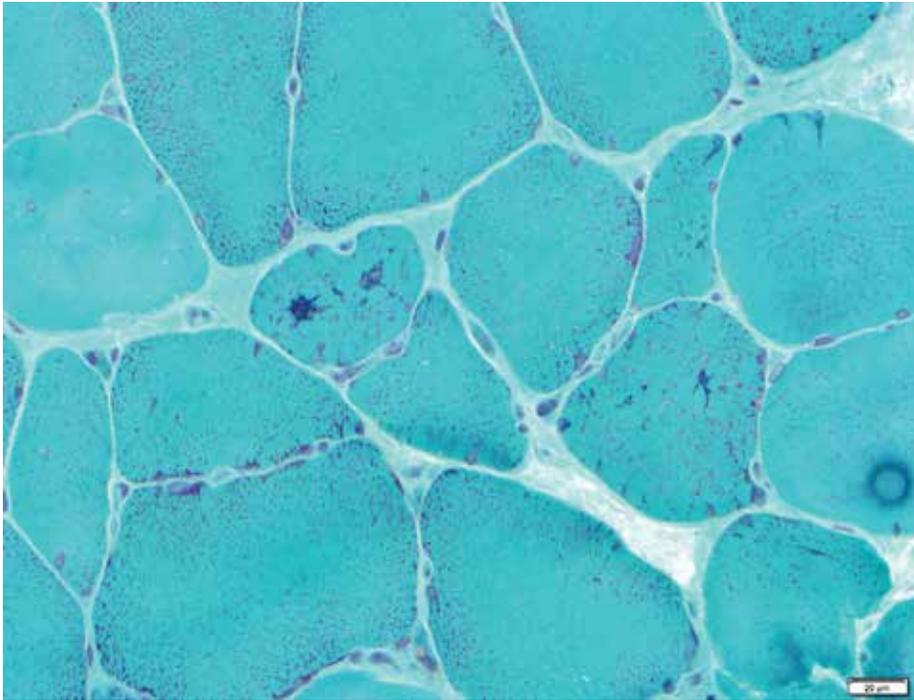
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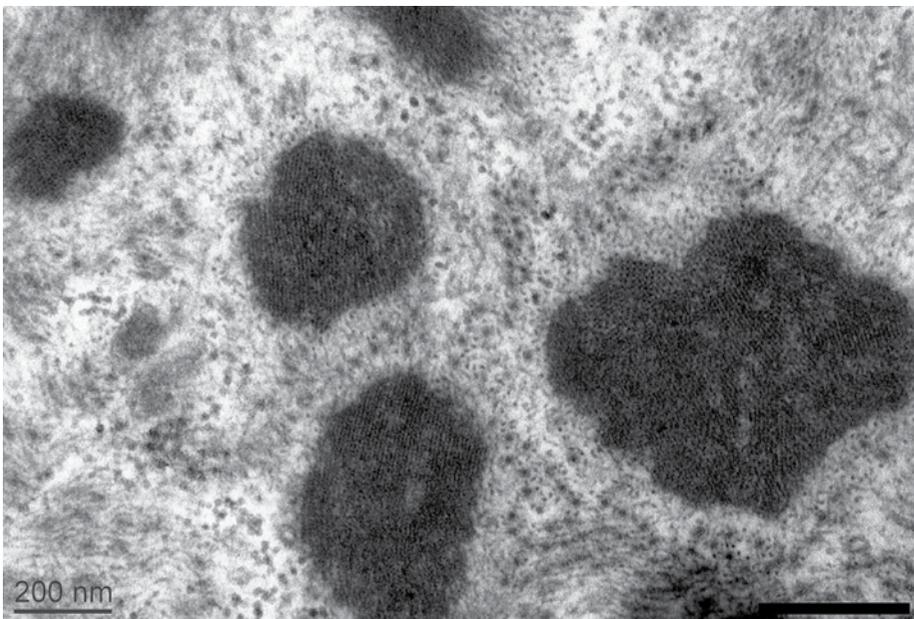
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**Figure 1.** Variation in skeletal muscle fiber shape and size, with sarcoplasmic and subsarcolemmal collections of darkly-staining rods within many fibers (Gomori trichrome stain, 400x)



**Figure 2.** Ultrastructural view of nemaline rods with features similar to those of the muscle Z-disc, focally showing a characteristic lattice structure and periodicity (100,000x)

served but no overall fatigability. Associated muscle atrophy was seen predominantly in the proximal lower limb muscles.

Complete blood count showed normal hemoglobin and platelets with mildly elevated white cell count (11.72 (n:  $4-11 \times 10^9$ ) g/L) including increased eosinophils (1.79 (n:  $>0.50 \times 10^9$ ) g/L). Creatine kinase (CK) was 523 (n: 30-190) U/L. Results of thyroid function, renal function, parathyroid hormone, vitamin B12, and folate tests were unremarkable. No paraproteins were de-

tected, but the kappa/lambda ratio was 1.69 (n: 0.26-1.65). IgG1 and IgG4 were mildly elevated (12.20 (n: 4.90-11.40) g/L and 17.3 (n: 6.1-13.0) g/L, respectively), IgA was 6.16 (n: 0.60-3.40) g/L, IgM was normal, and IgE was elevated at 1011 (n:  $<111$ ) kU/L. Human immunodeficiency virus (HIV), hepatitis B and C, antineutrophil cytoplasmic antibodies, antinuclear antibody, and anti-extractable nuclear antigen antibodies were not detected. Myositis screen showed positive PL-12 antibody. Stool examination revealed *Entamoeba coli* cysts, and *Strongyloides*

IgG was increased at 1.54 ( $>0.40$  positive). No proteinuria was detected.

Further investigations using computed tomography chest/abdomen/pelvis revealed no interstitial lung disease or suspicious masses, and no specific changes were observed in muscle bulk. Nerve conduction study showed left ulnar compression mononeuropathy at the elbow of moderate severity as well as mild left-sided carpal tunnel syndrome with no evidence of left-sided C5-T1 radiculopathy. Electromyography (EMG) showed no evidence of myopathy (including inflammatory myopathy) in the left deltoid, biceps, brachioradialis, extensor indicis muscle, extensor digitorum muscle, flexor digitorum profundus, adductor pollicis brevis, right deltoid, right rectus femoris, and iliopsoas muscle. These findings, however, do not exclude a metabolic- or steroid-induced myopathy. Spirometry showed a restrictive pattern.

The Infectious Diseases team advised to treat parasites with ivermectin. A bone marrow biopsy and aspirate showed a reactive marrow with eosinophilia and no plasmacytosis or immunophenotypical evidence of a clonal B lymphocyte population.

Histopathological findings from the left quadriceps muscle biopsy revealed chronic myopathic changes with sarcoplasmic rods and possible cores. These myopathic changes included variation in fiber shape and size, mild endomysial fibrosis, occasional ragged red fibers, and type 1 fiber predominance. The sarcoplasmic rods were seen as small, clustered dark eosinophilic sarcoplasmic inclusions on hematoxylin and eosin stain and were red on Gomori trichrome stain. No myonecrosis or inflammatory cell infiltrate was found (Figure 1). Electron microscopy revealed sarcoplasmic electron-dense rods in groups, continuous with the Z-lines, and arranged parallel to the long axis of the muscle fibers. Thin filaments at the periphery of the rods were noted. The rods were arranged in a lattice with a periodicity in longitudinal section of approximately 11 nm. The constituent filaments within the rods measured approximately 1  $\mu$ m in length and 5.5 nm in width. No cores were seen (Figure 2).

Based on the clinical history of late-onset weakness, characteristic muscle atrophy on clinical examination, and characteristic finding of predominantly nemaline rods on muscle biopsy, a diagnosis of SLO NM was made. There was no more likely alternative explanation for the histopathological findings, such as a biopsy obtained from a myotendinous insertion site,

ocular muscle biopsy, and rod core myopathy, among others. Muscle weakness improved marginally with inpatient rehabilitation. No further treatment was instituted as the patient self-discharged.

## Discussion

Six types of NM are recognized according to severity and presentation: (1) severe congenital NM, (2) intermediate congenital NM, (3) atypical congenital NM, (4) mild, childhood-onset NM, (5) adult-onset NM, and (6) other forms (3). The inheritable forms of NM may be associated with mutations in the nebulin (NEB), alpha-actinin, troponin T1, beta-tropomyosin, alpha-tropomyosin (4), or myopalladin genes (5), among others. These mutations alter the sarcoplasmic thin filament proteins. However, no common gene variants have been identified in the analysis of small numbers of cases of SLONM to date (6).

In a review of 76 (10 new patients and 66 from literature review) patients with SLONM, the mean age at onset was 52 years. The predominant phenotype included weakness of the proximal upper limbs (84%), proximal lower limbs (80%), both upper and lower limbs (67%), axial weakness (68%), dyspnea (55%), and dysphagia (47%). Of the cases, 53% was associated with MGUS (6).

In a study from the Mayo Clinic of 14 patients with suspected SLONM between 1975 and 2003, there were subacute evolving muscle weakness (proximal±distal), normal or low normal CK, and EMG showing myopathic features with fibrillation potentials. MGUS was found in half of these cases (7).

Most patients had a rapid progression of muscle weakness, becoming unable to walk within 2 years of the onset, whereas other cases had very slow progression of muscle disease >10 years after disease onset (7, 8).

Sporadic late-onset nemaline myopathy and idiopathic inflammatory myopathy can be difficult to distinguish clinically. SLONM does not have the cutaneous features of dermatomyositis (DM). Polymyositis (PM) and DM tend to have much higher CK levels than SLONM. Distal involvement is less common in SLONM than in inclusion body myositis (IBM). Nemaline rods on histopathology are a predominant feature of SLONM, and characteristic features of direct

infiltration of cytotoxic T lymphocytes immunoreactive for CD8, seen in PM, perifascicular muscle fiber atrophy and loss of endomysial capillaries found in DM, and inclusion bodies found in IBM, were typically absent in our patient (6, 9).

Nemaline rods are easily overlooked in muscle biopsies on light microscopy due to their small size and requirement for Gomori trichrome stain, where they are seen as red sarcoplasmic granules. They are rarely seen in normal lower limb muscle biopsies, and a diagnosis of NM is considered when the nemaline rods are a predominant feature (10). The intrasarcoplasmic rods arise from the Z-lines (discs), which are fine dense lines delineating sarcomere boundaries and serving as sarcomere anchors for structure and signaling (11). Nemaline rods are usually sarcoplasmic but may be intranuclear in up to 17% of cases. Both Z-lines and rods contain alpha-actinin. Rods also contain thin filament proteins, such as actin, myotilin, and NEB. On electron microscopy, they have a characteristic lattice structure and periodicity identical to that of the Z-line (12).

SLONM is commonly linked to MGUS and HIV infection. Other associations include systemic lupus erythematosus, Sjogren's syndrome, and myasthenia gravis. Treatment with intravenous immunoglobulin and autologous blood stem cell transplant in SLONM with MGUS has shown an overall improvement in patient prognosis. HIV-associated NM shows good clinical response to immunosuppressive therapy unlike non-HIV-associated NM (6). Our case highlights the heterogeneity of SLONM with its varied spectrum of presentation in a non-HIV, non-monoclonal gammopathy-associated case.

## Conclusion

Sporadic late-onset nemaline myopathy is an under-recognized condition. For early detection and better management of this rare disease, physicians should include SLONM to the differential diagnosis list of progressive proximal muscle weakness in an adult.

**Informed Consent:** Verbal informed consent was obtained from the patient who participated in this case report.

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