BMJ Neurology Open

Late-onset myopathy responsive to immunomodulatory treatment: sporadic late-onset nemaline myopathy without nemaline rods?

Menachem Sadeh ,[1] Yakov Fellig,[2] Ron Dabby[1]

To cite: Sadeh M, Fellig Y, Dabby R. Late-onset myopathy responsive to immunomodulatory treatment: sporadic late-onset nemaline myopathy without nemaline rods? *BMJ Neurology Open* 2024;**6**:e000892. doi:10.1136/bmjno-2024-000892

Received 13 September 2024
Accepted 19 October 2024

[1]Neurology, Edith Wolfson Medical Center, Holon, Tel Aviv, Israel
[2]Pathology, Hadassah Medical Center, Jerusalem, Jerusalem, Israel

Correspondence to
Dr Menachem Sadeh;
mesadeh@tauex.tau.ac.il

ABSTRACT

Background Late-onset sporadic nemaline myopathy (SLONM) is a rare, treatable or potentially life-threatening muscle disorder that typically manifests late in life and is characterised by the presence of nemaline rods within muscle fibres, serving as the hallmark of the disease and the key to diagnosis.

Methods We report a case of an elderly patient with subacute onset of severe weakness affecting the upper and lower limbs, neck extensors and abdominal muscles. A comprehensive laboratory workup was performed.

Results Muscle biopsies showed nonspecific myopathic changes without inflammation, and electron microscopy did not reveal rods or aggregates. The laboratory workup was unremarkable except for the detection of monoclonal gammopathy of undetermined significance. Steroid treatment was ineffective; however, there was a notable positive response to intravenous immunoglobulins. The neurological findings, subacute course, normal creatine kinase levels, presence of monoclonal gammopathy of unknown significance and responsiveness to immunoglobulin treatment but not to steroids align with the characteristics of SLONM.

Conclusion We propose that the diagnosis of SLONM should be considered even in the absence of nemaline rods in muscle biopsy, and this should not impede the consideration of immunomodulatory treatment. Future progress in understanding the pathogenetic basis of SLONM may reduce reliance on pathological findings in muscle biopsies for establishing the diagnosis.

INTRODUCTION

Currently, treatable myopathies in the elderly include inflammatory myopathies,[1] riboflavin-responsive lipid storage myopathy[2] and late-onset sporadic nemaline myopathy (SLONM).[3]

Presently, the diagnosis of SLONM is based on detecting nemaline rods in muscle biopsy, whether through light microscopy or electron microscopy. However, our case report prompts us to suggest that the diagnosis of SLONM should be contemplated in the appropriate clinical context, even when nemaline rods are not evident in muscle biopsies.

CASE REPORT

A healthy male in his 60s noticed wasting of the periscapular and thigh muscles and difficulties in walking, opening jars and maintaining an upright position. Laboratory and radiological workup elsewhere was non-conclusive. Examination showed wasting of the shoulder muscles and of the deltoids and weakness 4/5 (on the Medical Research Council scale) of the infraspinatus muscles. The rest of the upper limb muscles showed normal strength. In the lower limbs, there was weakness in 4/5 of the iliopsoas muscles with normal strength in all other muscles. He used his hands to get up from a low sitting position. Otherwise, the neurological examination was normal.

Biopsy of the quadriceps was stained with H&E, modified Gomori trichrome, periodic acid Schiff, oil red O, nicotinamide adenine dinucleotide-tetrazolium reductase, cytochrome oxidase with succinate dehydrogenase, ATPase at pH 9.4 and after preincubation at pH 4.3 and 4.6 and Congo red. Immunohistochemical staining for dystrophin 1–3, dysferlin, alpha-sarcoglycan, beta-sarcoglycan, gamma-sarcoglycan, delta-sarcoglycan, merosin and caveolin 3 was performed as well as for CD3, CD4, CD8, CD20, CD68, major histocompatibility complex class 1 and C5b9. It showed variability in fibre size, multiple internal nuclei and type 1 fibre predominance. There were sporadic, ungrouped small atrophic fibres. Immunohistochemical stains for the membrane proteins were normal, and there was no evidence of inflammation.

Further studies including the myositis antibodies panel (anti-Jo1, anti-PL-7, anti-PL-12,

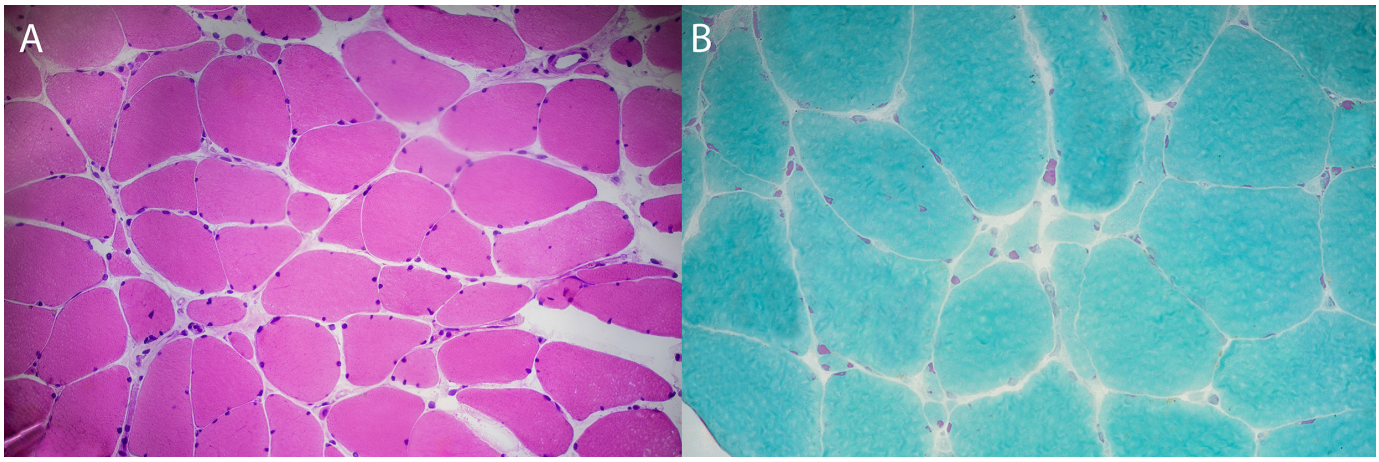

Figure 1 H&E (A) and trichrome (B) stains showing marked variability in fibre sizes. There are a few tiny fibres with scant cytoplasm surrounding the nucleus.

anti-EJ, anti-SRP-54, anti-Mi-2, anti-MDA-5, anti-T1F1-γ(P-155), anti-Ku, anti-PM-Scl 100, anti-scl-70, anti-SSA/Ro52 and anti-HMGCR), genetic myopathy panel and genetic studies for myotonic dystrophy 2 and facioscapulohumeral muscular dystrophy 1 were negative. Protein immunofixation electrophoresis detected a monoclonal band that was defined as monoclonal gammopathy of unknown significance (MGUS).

His condition worsened quite rapidly. He complained of difficulties in holding his head in an upright position and getting up from a chair. He observed further wasting of the muscles of the arms and calves. On a follow-up examination 6 months later, there was severe wasting of the cervical paraspinal muscles with 3/5 weakness of the neck extensors. The deltoid and infraspinatus muscles showed 4/5 strength bilaterally. In the lower limbs, there was 2/5 weakness of the iliopsoas muscles and 4/5 of the glutei. There was also severe weakness in the abdominal muscles. The electromyography study showed severe myopathic changes without fibrillations in the proximal muscles. The creatine kinase level was 76 iu/L. Another muscle biopsy showed similar changes (figure 1). Additional staining of both biopsies with desmin, myotilin, alpha-actinin and p62 did not reveal the presence of rods or aggregates or evidence of autophagy. Numerous blocks and sections from the second biopsy were examined by electron microscopy. The study disclosed normal myofibrillar structure, mitochondria and nuclei. No rods or aggregates were detected, even in atrophic fibres and fibres with internal nuclei. Further studies, including anti-MUSK and anti-VGCC antibodies and paraneoplastic antibodies, and total body CT scans, were negative.

Two years after onset of symptoms, treatment with prednisone 60 mg a day and methotrexate at a dosage of 15 mg per week was initiated. The treatment partially alleviated the pain, but the strength of the neck extensors diminished to 2/5, and there was no discernible improvement in the other muscles. After 4 months, pulse steroid therapy with 1000 mg of methylprednisolone was administered for 5 days, followed by 1000 mg once a week for 4 weeks, and then 1000 mg every second weeks for 2 months. The treatment was futile.

Treatment with intravenous immunoglobulins was instituted. He received 40 g daily for 5 days and then 40 g every 3 weeks. After a month, some improvement was noticed. He could raise his hips from the bed, and he succeeded in lifting his head and holding it up. The wasted muscles of the arms and calves gradually regained mass. He could rise from a sitting position with minimal aid of the hands. On recent examination, neck extensors were 3/5, left deltoid 4/5 and iliopsoas bilaterally 4/5. All other muscles showed normal strength.

DISCUSSION

We have presented a patient with subacute muscle weakness that manifested in the seventh decade of life, leading to rapid and severe disability. While the diagnosis remains elusive, the beneficial effect of intravenous immunoglobulin treatment suggests an immunological basis for the disease. Inflammatory myopathy such as dermatomyositis, polymyositis or antisynthetase syndrome can be ruled out because of the lack of inflammatory foci, normal capillaries and the absence of myositis-specific antibodies. The diagnosis of immune-mediated necrotising myopathy (IMNM) is unlikely because of the normal CK levels, lack of necrotic fibres and absence of IMNM-specific antibodies.

Sporadic inclusion body myositis (IBM) is the most common acquired myopathy among persons older than 50 years. However, the diagnosis of IBM seems implausible. None of the three pathological hallmarks—endomysial inflammation, mononuclear cell invasion and rimmed vacuoles—was observed in the muscle biopsies. Although there is clinical heterogeneity in patients with IBM, the relatively rapid course, weakness distribution and response to treatment are incongruent with IBM. The main clinical presentation of SLONM consists of weakness and atrophy of proximal upper and lower limbs, axial weakness, dyspnoea and dysphagia. Neck extensor

weakness is observed in about 50% of cases.[4] In approximately half of the cases, MGUS may be detected in the serum.[4] The hallmark of SLONM and the key to diagnosis is the presence of intracytoplasmic nemaline rods that tend to fill atrophic fibres. The nemaline rods originate from the disintegration of the muscle Z-disc; therefore, immunohistochemistry with antibodies against Z-disc-associated proteins was used in addition to the trichrome stain. Immunostaining with α-actinin detected the nemaline bodies in all cases in a series of 17 patients.[4] However, in two cases, the rods were detected only by electron microscopy.[3]

If nemaline rods had been detected in the biopsy of our patient, there would have been no doubt regarding the diagnosis of SLONM. This certainty arises from the typical neurological findings with neck extensor weakness, subacute course, normal CK levels, presence of MGUS and responsiveness to immunoglobulin treatment but not to steroids.

The absence of rods in biopsy might stem from sampling errors, the potential occurrence of rods at later stages of the disease, or even their absence in some patients. Other diseases initially defined by specific pathological findings have been subsequently diagnosed even in the absence of those characteristic pathological hallmarks after the discovery of the underlying causes.[5] Perhaps, future advancements in comprehending the pathogenetic basis of SLONM will diminish the dependence on pathological findings in muscle biopsies.

CONCLUSION

As SLONM is a treatable or potentially life-threatening condition, and early intervention can markedly improve the prognosis, the absence of nemaline rods in muscle biopsy should not impede the consideration of immunomodulatory treatment. Consequently, we propose that intravenous immunoglobulin or other appropriate therapies be contemplated for elderly patients experiencing rapidly progressing myopathy, even in the absence of inflammatory or intracellular aggregates in the biopsy.

Contributors MS was responsible for the concept, data collection and first draft. RD was responsible for the data collection and critical supervision of the manuscript. YF revised the histological findings and electron microscopy. MS is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Menachem Sadeh http://orcid.org/0000-0002-7408-4652

REFERENCES

1 Lundberg IE, Fujimoto M, Vencovsky J, *et al*. Idiopathic inflammatory myopathies. *Nat Rev Dis Primers* 2021;7:87.
2 Sadeh M, Dory A, Lev D, *et al*. Riboflavin-responsive lipid-storage myopathy in elderly patients. *J Neurol Sci* 2024;456:122808.
3 Schnitzler LJ, Schreckenbach T, Nadaj-Pakleza A, *et al*. Sporadic late-onset nemaline myopathy: clinico-pathological characteristics and review of 76 cases. *Orphanet J Rare Dis* 2017;12:86.
4 Zhao B, Dai T, Zhao D, *et al*. Clinicopathologic Profiles of Sporadic Late-Onset Nemaline Myopathy: Practical Importance of Anti-α-Actinin Immunostaining. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1184.
5 Oliwa A, Langlands G, Sarkozy A, *et al*. Glycogen storage disease type IV without detectable polyglucosan bodies: importance of broad gene panels. *Neuromuscul Disord* 2023;33:98–105.