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ORIGINAL COMMUNICATION

Sporadic late-onset nemaline myopathy: clinical, pathology and imaging findings in a single center cohort

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Abstract

Sporadic late-onset nemaline myopathy (SLONM) is a rare acquired myopathy characterized by rapid-onset proximal weakness in late adulthood, and the presence of nemaline bodies on muscle biopsy. In recent years, several therapeutic interventions, including immunomodulating agents and autologous stem cell transplantation, have shown variable degrees of efficacy in different patients, but no consensus has been reached to allow an effective tailoring of treatments in this severe disease. We performed a retrospective evaluation of clinical, pathological, laboratory, muscle MRI, and follow-up data of SLONM patients diagnosed in the period 2010–2015 in our neuromuscular center. Six patients (three males and three females) were identified. Average time elapsed from the onset of symptoms to referral to the neuromuscular specialist was 23.7 months. Monoclonal gammopathy was detectable in five patients. Nemaline bodies were detected in all the patients, and their abundance correlated with clinical severity. Signs of cardiac involvement were present in all the patients to different extents. Muscle MRI showed a preferential involvement of neck extensors, paraspinal, gluteal, hamstring and soleus muscles. All patients were treated with prednisone and repeated courses of intravenous immunoglobulins, and a favorable outcome was reached in five patients. Our experience confirms that SLONM is clinically characterized by subacute proximal and axial muscle weakness. Time to referral was relatively long and should be reduced with increasing awareness of the disease. Muscle MRI could be of help as a diagnostic tool to identify this potentially treatable myopathy. Cardiac evaluation should be warranted in all SLONM patients to detect subclinical heart involvement.

Keywords Nemaline rods · Late-onset myopathy · Monoclonal gammopathy · Muscle MRI · Intravenous immunoglobulins

Introduction

Sporadic late-onset nemaline myopathy (SLONM) is a rare, acquired myopathy first recognized in 1966 [1]. Its clinical and pathology features are a predominantly proximal weakness with subacute onset in adult age and the finding of nemaline bodies as a pathological hallmark on muscle biopsy. Nemaline bodies are small Z-disk derived rod-like structures, characteristic of nemaline myopathies that are a genetically heterogeneous group of congenital myopathies [2].

The first large cohort of SLONM patients was reported in 2005 [3]. In that paper, the authors concluded that SLONM is a rare entity characterized by subacute onset after age 40, normal or low creatine kinase (CK), myopathic EMG with spontaneous activity and the presence of a monoclonal gammopathy in half of the patients [3, 4]. Concomitant clinical features were described such as axial and distal weakness, severe muscle atrophy, head drop, respiratory involvement and dysphagia [3, 5]. The disease was generally associated with very poor prognosis mainly due to the respiratory involvement that could be even present at onset [6, 7], and appeared to be worse in patients with an associated monoclonal IgG gammopathy [3]. Despite the initial reports of unresponsiveness to immunosuppressive treatments [3], recent evidence suggests that some patients benefit from treatment with intravenous immunoglobulins

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(IVIg) [8–11], mycophenolate mofetil [4], and rituximab [12, 13]. Furthermore, treatment with melphalan followed by autologous stem cell transplantation (aSCT) was performed with encouraging results in SLONM-MGUS (monoclonal gammopathy of unknown significance) [14–21].

A recent description of ten new patients, together with a revision of the literature, refined the knowledge of the clinical phenotype of SLONM patients [22]. A broader spectrum of involvement is emerging, which includes atypical cases [6, 7, 23, 24]. It is also still under debate what could be the most risk–benefit balanced approach for the treatment of SLONM, as it is possible that some patients may have a good response to immunomodulatory/immunosuppressive drugs without the need to undergo aSCT.

Furthermore, data about muscle imaging, which has been proven useful as a diagnostic tool in genetic [25] as well as acquired myopathies [26], are still lacking for this disease.

In the present study, we describe clinical and instrumental findings of a cohort of patients diagnosed in our neuromuscular center along with treatments performed and follow-up.

Materials and methods

Patients

All the medical records available at our neuromuscular center in the period 2010–2015 were reviewed and patients with a diagnosis of SLONM were selected. This study was approved by the ethics committee of the Catholic University School of Medicine.

Laboratory and instrumental examinations

All patients underwent physical examination, blood cell count, a complete panel of blood chemistry tests, CK level assay, anti-HIV antibody testing, EMG and nerve conduction studies (NCS), and pulmonary function tests. When required by the clinical conditions, swallowing function, hematological and cardiological evaluation were also performed. Swallowing study was performed by oropharyngoesophageal scintigraphy. Results were considered abnormal if total bolus transit time, oral transit time, pharyngeal transit time and/or esophageal transit time were prolonged compared to reference values.

All subjects underwent upper and lower girdle muscle MRI according to published protocols [25, 27]. *T*1-weighted (*T*1w) images were examined to detect selective fatty infiltration of specific muscles, and *T*2-weighted short-tau inversion recovery (*T*2w-STIR) images were reviewed to assess areas of increased signal compatible with muscle oedema/inflammation.

Muscle biopsy

All patients underwent muscle biopsy at the time of their first evaluation in our center. Details on histochemical methods and immunofluorescence for inflammatory markers are available elsewhere [28]. To confirm the presence of nemaline rods, immunostainings with anti-myotilin (novocastra mouse cod. NCL-Myotilin, dilution 1:20) and anti-alpha actinin (novocastra mouse cod. NCL-alpha-ACT, dilution 1:20) antibodies were also performed. Electron microscopy was performed fixing the specimens in 2.5% glutaraldehyde and processing them by standard methods. Ultrathin skeletal muscle sections were analyzed using a Zeiss Libra 120 electron microscope.

To estimate the percentage of muscle fibers harboring rods per patient, 250 fibers at 10× magnification were analyzed on modified Gomori trichrome stained sections

Results

Patients and clinical findings

A total of six patients were identified, three males and three females. Mean age at onset was 59.3 years (standard deviation ± 13.3, range 39–73), mean time difference between first evaluation in our center and onset of symptoms was 23.7 months (standard deviation ± 11, range 12–36). Proximal upper limb (one patient), lower limb (three patients) or both upper and lower limb (two patients) weakness was constantly referred to be present at onset, together with neck extensor weakness. Three patients already needed support to walk at first examination. Facial weakness was present in four subjects, and three patients complained of dysphagia. All patients referred a subacute disease course at the beginning, with time to zenith between 4 and 8 weeks. Clinical details of all the subjects are summarized in Table 1.

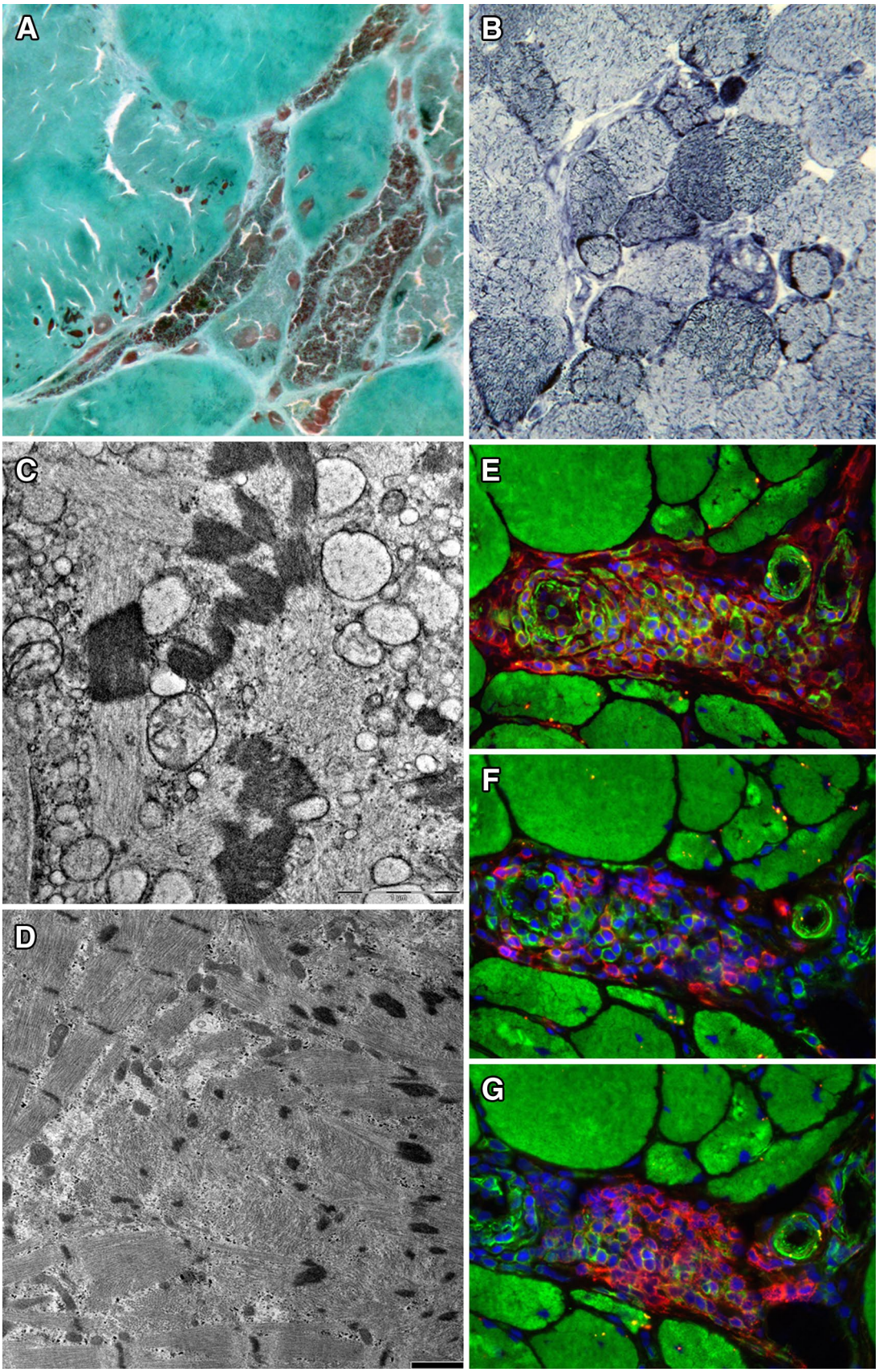
Laboratory and instrumental findings

Laboratory examinations showed normal or mildly elevated CK levels (maximum 2× normal values) and negative anti-HIV antibody testing in all patients. Immunoelectrophoresis disclosed a monoclonal gammopathy of uncertain significance (MGUS) in 5/6 patients (3 IgG kappa chains and 2 IgG lambda chains). In P6, the immunoelectrophoresis was performed only after treatment and remission of the disease and resulted normal. Bone marrow biopsy showed monoclonal plasma cell interstitial infiltration (15–18% of the total cellular count) in P4; bone marrow aspiration revealed abnormal plasma cell

Table 1 Synoptic view of the clinical and instrumental findings in our patients

Pt. ID	P1	P2	P3	P4	P5	P6
Sex	M	F	F	M	M	F
Age at onset	39	73	65	64	47	68
Symptoms at onset	Proximal upper limb weakness, neck extensor weakness	Proximal lower limb weakness, neck extensor weakness	Proximal lower limb weakness, neck extensor and flexor muscles weakness	Proximal upper and lower limb weakness, neck extensor weakness	Proximal upper and lower limb weakness, neck extensor weakness	Proximal lower limb weakness, neck extensor weakness
First evaluation (months after disease onset)	16	28	36	12	36	14
Bulbar/Facial weakness	None	Facial weakness	Dysphagia	Dysphagia, facial weakness	Facial weakness	Dysphagia and dysarthria, facial weakness
Disease course	Subacute 4–8 weeks	Subacute 4–8 weeks	Subacute 4–8 weeks	Subacute 4–8 weeks	Subacute 4–8 weeks	Subacute 4–8 weeks
Respiratory involvement	FVC = 90%, reduced MEP	Severe restrictive lung disease, FVC = 50%	Mild obstructive lung disease, FVC = 70%, reduced MIP and MEP	Severe restrictive lung disease, FVC = 35%	Mild obstructive lung disease, FVC = 70%, reduced MIP and MEP	Severe restrictive lung disease, acute respiratory insufficiency
Cardiac involvement	Mild EF reduction (51%)	Left ventricular hypertrophy, left ventricular diastolic dysfunction, premature supraventricular and ventricular complexes associated with runs of atrial tachycardia	Left ventricular hypertrophy, left ventricular diastolic dysfunction, left atrial enlargement, first degree atrioventricular block	Mild atrial enlargement, mild EF reduction (50%), left ventricular hypokinesia, permanent atrial fibrillation	Mild EF reduction (52%), left ventricular hypokinesia, interventricular sept hypertrophy (12 mm), non-sustained ventricular tachycardia on 24-h ECG	Paroxysmal atrial fibrillation
CK	1.5×	1.5×	Normal	Normal	Normal	2×
EMG	Myopathic MUPs, fibrillation potentials	Myopathic MUPs, fibrillation potentials	Myopathic MUPs	Myopathic MUPs	Myopathic MUPs	Myopathic MUPs
Nerve conduction studies	Normal	Normal	Normal	Normal	Normal	Normal
Monoclonal Gammopathy	IgG kappa	IgG kappa	IgG lambda	IgG lambda	IgG kappa	NA
Age at biopsy	41	76	68	65	50	69
Biopsy site	Quadriceps	Quadriceps	Deltoid	Quadriceps	Deltoid	Quadriceps
Muscle biopsy	Myopathic, nemaline rods in 15% of the fibers, lobulated fibers, rare necrosis	Myopathic, nemaline rods in 11% of the fibers, lobulated fibers, ragged red fibers	Myopathic, nemaline rods in 18% of the fibers, ragged red fibers	Myopathic, nemaline rods in 45% of the fibers, few perivascular linfomonocyte infiltrates	Myopathic, nemaline bodies in 33% of the fibers, lobulated fibers	Myopathic, small nemaline rods in 6% of the fibers, mainly atrophic, lobulated fibers
Past medical history	Unremarkable	Osteoporosis, thyroid cancer, intestinal ischemia	Hypothyroidism, hypertension, enchondroma right femur	Gilbert disease	COPD, hypertension, hepatic steatosis	Hypothyroidism

FVC forced vital capacity, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure, *EF* ejection fraction, *MUP* motor unit potentials, *CK* creatine kinase, *EMG* electromyography, *COPD* chronic obstructive pulmonary disease, *IVIg* intravenous immunoglobulins, *NA* not available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◂**Fig. 1** Muscle pathology. **a** P4. Modified Gomori trichrome staining showing atrophic angulated myofibers completely filled with nemaline rods, and few cytoplasmic bodies in the surrounding fibers; magnification ×40. **b** P6. Nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) staining showing lobulated fibers; magnification ×20. **c**, **d** Transmission electron microscopy images displaying complete sarcomeric derangement, dilated tubular and mitochondrial structures, and electron-dense rod-shaped bodies (**c**, P4, bar 1 µm), and subtler myofibrillar disarray with small nemaline rods (**d**, P6, bar 2.5 µm). **e**–**g**. P4. Immunofluorescence of serial sections labeled with phalloidin-FITC (green), DAPI (blue) and antibodies anti-CD4 (**e**), CD8 (**f**) and CD20 (**g**) (red staining) showing a large perivascular mononuclear-cell infiltrate composed mainly by CD4+ and CD20+ lymphocytes; magnification ×20

infiltration (0.4% of the total cellular count) in P1. Respiratory involvement was present in all patients at first examination: one had a reduction in maximal expiratory pressure value, three had severe restrictive lung disease, two had mild obstructive lung disease and a reduction in maximal inspiratory and expiratory pressure values. Needle electromyography revealed myopathic motor unit potentials, occasionally associated with fibrillation potentials at rest, in all patients. Nerve conduction studies were unremarkable. Assessment of swallowing by oropharyngoesophageal scintigraphy was abnormal in all four subjects studied due to reduced pharyngeal and esophageal peristalsis.

Cardiac involvement

All patients were studied by 12-lead ECG. 24-h ECG monitoring was also performed in four patients. Five subjects underwent echocardiogram and cardiac MRI and two underwent diagnostic coronary angiography. Conduction abnormalities or arrhythmias were identified in all patients, including atrial fibrillation (P4 and P6), premature supraventricular and ventricular complexes associated with runs of atrial tachycardia (P2), non-sustained ventricular tachycardia (P5), fist-degree atrioventricular block (P3) and persistent repolarization abnormalities (P1). Asymptomatic global left ventricular systolic dysfunction was evident as a mild reduction in the ejection fraction in three patients (P1, P4 and P5). Two patients (P2 and P3) had echocardiographic evidence of left ventricular diastolic dysfunction. Other structural alterations found on cardiac imaging were left ventricular hypertrophy in P2 and P3, atrial enlargement in P4 and left ventricular hypokinesia associated with interventricular septal hypertrophy (12 mm) in P5. In patients who underwent coronary angiography (P2 and P5), no significant coronary stenosis was documented.

Only P3 and P5 had concomitant hypertension, which can concur to the explanation of the structural cardiac abnormalities described, while other patients did not have history or medical risk factors that could explain their cardiac features.

Muscle pathology

Muscle biopsy showed myopathic alterations in all patients, consisting in increased fiber size variability (the presence of round hypotrophic or atrophic fibers), central nuclei and nemaline bodies (Fig. 1a), to different extents. The percentage of fibers containing rods varied from 6% (P6) to 45% (P4). In P6, muscle biopsy was performed 14 months after the onset of the disease and after treatment, and nemaline rods were detected only in sporadic atrophic fibers. Their presence was confirmed by electron microscopy (Fig. 1d). We found an association between clinical severity at time of biopsy and extent of abnormalities on muscle pathology. Other pathological features in muscle biopsies were mitochondrial abnormalities (abnormal number of ragged red fibers for age) in two patients, perivascular lymphocytic infiltrates in one patient (Fig. 1e–g) and lobulated fibers (Fig. 1b) in four patients.

Muscle MRI

None of the patients displayed a normal muscle MRI at the time of examination. In the upper girdle subscapularis, paraspinal and neck extensor muscles were the most frequently affected. Serratus anterior was also mildly affected in five patients, while infraspinatus and trapezius muscle were relatively spared. In the pelvis and lower limbs, gluteal (particularly gluteus minimus and medius), lumbar paraspinal, and hamstrings (especially semimembranosus) muscles were always involved (Fig. 2). Other affected muscles were obliquus and transversus abdominis, usually at variance with the adjacent rectus abdominis that was spared. Asymmetry, although detected in some scans, was not a distinctive feature. In 5/6 patients, a strikingly selective involvement of soleus muscle in the lower leg was observed, while all the other muscles appeared completely spared.

Five patients displayed hyperintense muscles in *T*2w-STIR sequences. Adductor magnus and longus, obturator internus and externus and gluteal muscles were the most frequently affected in *T*2w-STIR images.

Treatments and follow-up

All patients received oral prednisone at dose of 0.5–1 mg/kg/day and repeated courses of monthly intravenous immunoglobulins (IVIg) at the dose of 2 g/kg. Two patients (P1 and P2) were also put on azathioprine as steroid sparing drug at the dose of 1–3/mg/kg/day. Clinical improvement was obtained in four patients and in one patient (P2) the initial decline in muscle function stopped and stabilization was achieved (Table 2). Disease course was unfavorable in P4: in addition to prednisone and IVIg, he was also treated with melphalan and bortezomib due to a progressive worsening

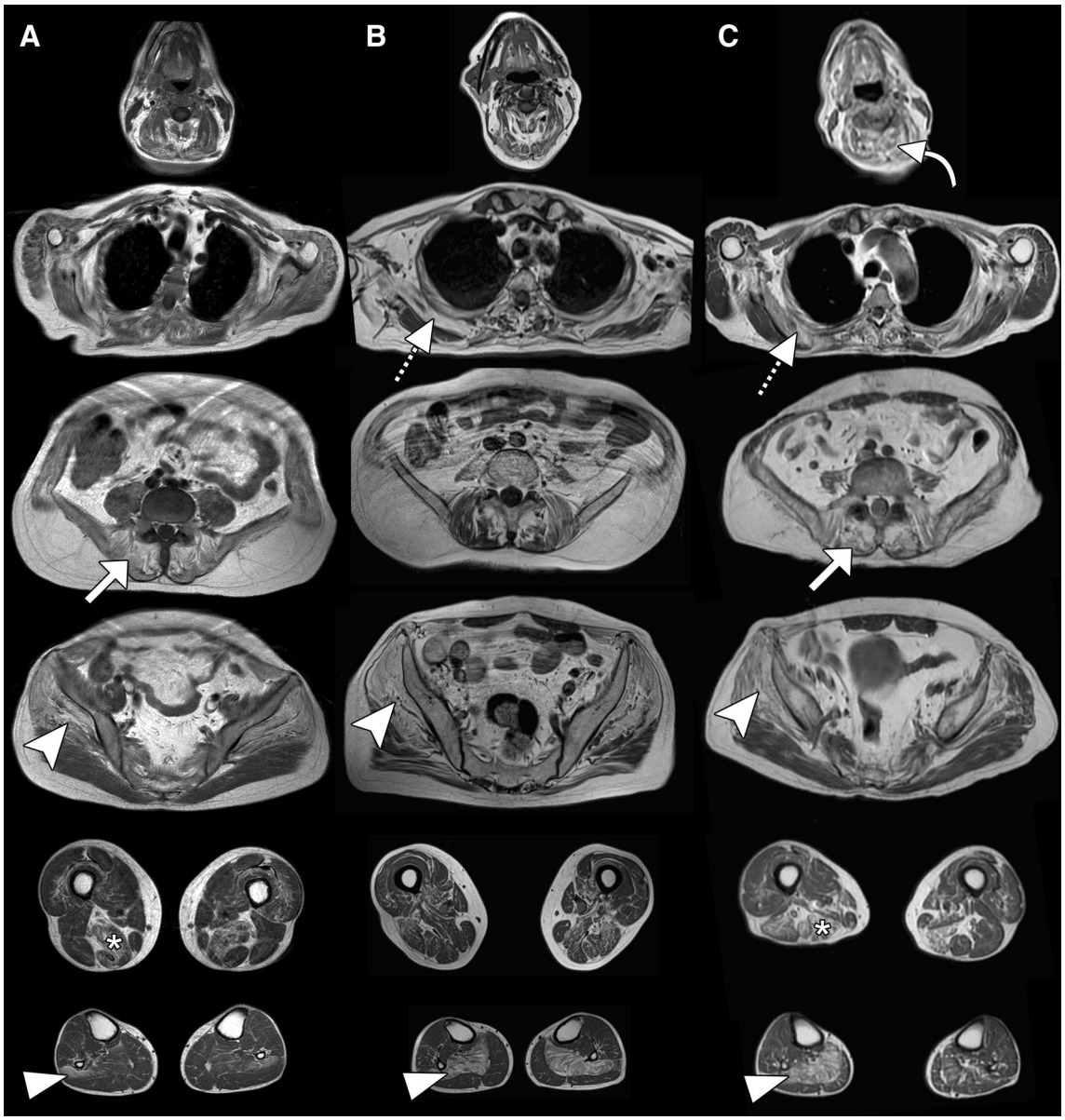

Fig. 2 Muscle MRI. Examples of involvement from three patients with different disease severities showing similar MRI changes. In the pelvis and thighs, the most affected muscles were the lumbar paraspinal (arrow), gluteus medius and minimus (arrowhead), and posterior thigh muscles (such as the semimembranosus, asterisk). In the neck and upper girdle, there was prominent involvement of subscapularis (dotted arrow) with sparing of neighboring infraspinatus, of neck extensor muscles (curved arrow) and thoracic paraspinal muscles. Notably, soleus muscle (triangle) was selectively affected at lower leg level. P1 (**a**), P5 (**b**) and P4 (**c**)

of the symptoms and development of severe respiratory failure that led to tracheostomy and mechanical ventilation. aSCT, although considered as a treatment option, was not performed given the uncertain risk–benefit ratio, with high mortality rates considering age and concomitant diseases. At age 66, 2 years later disease onset, the patient died due to respiratory complications.

P6 was admitted to the intensive care unit in another center for acute respiratory failure leading to tracheostomy. She was initially unsuccessfully treated with steroids, then IVIg were started and the patient showed gradual improvement over the following 3 months allowing for the removal of the tracheostomy tube. She was then referred to our center and a retrospective diagnosis of possible SLONM was made based on clinical history. 14 months after the onset of symptoms clinical examination documented only mild residual weakness in neck extensors, arm abductors and proximal lower limb muscles; no monoclonal gammopathy was evident on immunoelectrophoresis and a

Table 2 Pre- and post-therapy clinical assessments

Pt. ID	P1	P2	P3	P4	P5	P6
Upper limb weakness: 0 to +++ baseline/last follow-up	++/+	++/++	+/+	++/+++	++/+	+/+
Lower limb weakness: 0 to +++ baseline/last follow-up	++/+	+++/+++	+++/++	+++/+++	++/++	+++/+
Arm abduction baseline/last follow-up	30°/70°	15°(L) 30°(R)/15°(L) 70°(R)	90°/90°	30°/10°	20°/70°	NA/90°
Walking assistance baseline/last follow-up	Unaided/unaided	With cane/with cane	With cane/unaided	With cane/bedridden	Unaided/unaided	Bedridden/unaided
Brooke scale baseline/last follow-up	3/2	3/2	2/2	4/6	4/2	N.A./2
Walton Clinical Severity Scale baseline/last follow-up	4/3	6/6	6/3	6/10	5/4	7/2
Need of respiratory support baseline/last follow-up	No/no	No/no	No/no	NIV/tracheostomy + mechanical ventilation	No/no	Tracheostomy + mechanical ventilation/no
Last follow-up (months)	36	30	16	12	38	12
Treatment	Prednisone, IVIg, azathioprine	Prednisone, IVIg, azathioprine	Prednisone, IVIg	Prednisone, IVIg, bortezomib, melphalan	Prednisone, IVIg	Prednisone, IVIg

Summary of clinical evaluations at baseline (pre-treatment) and at last follow-up after treatment. Muscle strength was assessed with manual muscle testing (MRC scores 0–5) and muscle weakness was classified as 0 (MRC = 5), + (MRC = 4), ++ (MRC = 3), +++ (MRC = 0-2). Brooke scale measures upper extremity function (score 1–6), whilst Walton Clinical Severity Scale measures global clinical severity (scores 0–10). Baseline evaluation was performed during the first visit at our center for all but one patient; in P6 it was derived from medical records

NA not available, *NIV* non-invasive ventilation, *IVIg* intravenous immunoglobulins, *R* right, *L* left

muscle biopsy showed mild myopathic changes with sporadic nemaline rods in atrophic fibers.

Repeated dosages of the monoclonal protein were available from two patients: in P1 it resulted undetectable after treatment; in P4 it raised progressively concomitantly with clinical worsening (Online Resource 1).

Discussion

In our case series of six SLONM patients, the onset of the disease was constantly characterized by subacute proximal upper and/or lower limb weakness and by weakness of neck extensors, despite the wide range of clinical severity across the patients.

Time to referral to the neuromuscular specialist was relatively delayed in our cohort (almost 2 years on average), which is potentially problematic because early diagnosis and treatment seem to be important factors to recover muscle function. Our experience confirms that respiratory failure is frequent and sometimes life-threatening. The presence of cardiac involvement found in our cohort is of interest. Systolic left ventricular dysfunction with or without a concomitant dilated cardiomyopathy, sometimes leading to acute heart failure, has been already reported in a few patients [21, 22, 29, 30]. Cardiac involvement may respond to chemotherapy [31], and this reversibility supports the idea that it might be disease related. However, in our cohort, we detected a more widespread and subtle set of abnormalities: different arrhythmias were found in all patients, and together with left ventricular systolic dysfunction, we also report diastolic dysfunction in two patients. Even if we cannot completely rule out the possibility of other concomitant causes of cardiomyopathy in our cohort, we recommend performing a complete cardiological evaluation in SLONM patients to detect subclinical alterations. Striated cardiac muscle could be susceptible to the same damaging mechanism that affects

skeletal muscle, although this needs to be confirmed by pathology studies.

Nemaline rods are the most typical histopathological findings in SLONM patients, although they can be associated with other less specific changes, such as atrophic fibers, lobulated fibers and mitochondrial abnormalities. P4 also displayed angulated fibers, and in two patients we found fibrillation potentials on EMG. It is known from the literature that almost 10% of SLONM patients may have neurogenic or mixed recruitment on EMG. We also found perivascular lymphocytic (predominantly CD4+ and CD20+) infiltrates in one patient, consistently with the report that up to 20% of SLONM patients may show inflammatory changes [22]. Interestingly, accumulation of nemaline bodies may be reverted by treatments [14], and although we could not obtain a pre-treatment muscle sample in P6, we observed that rods were hardly detectable and present only in atrophic fibers after recovery in this patient.

There is evidence that the amount of the monoclonal protein can vary according to response to treatments [11]. A circulating monoclonal IgG component was present in five patients of our cohort, and in three of them, repeated immunoelectrophoresis showed an association between disease severity and the amount of the M protein: in P1 the monoclonal gammopathy became undetectable after treatment and improvement of weakness; in P6 immunoelectrophoresis was performed only after treatment and was normal, while an increased level of the protein was documented in P4 after treatment failure and prior to exitus (Online Resource 1). It has been hypothesized that the monoclonal protein could exert a direct toxic effect being potentially targeted towards different autologous muscle antigens, eventually leading to sarcomeric protein disruption resulting in nemaline rod formation [14]. This hypothesis could be supported by the correlation between clinical course and amount of protein detected in peripheral blood, and constitutes the rationale of treating these patients with immunosuppressants, chemotherapy and aSCT, targeting the hematological comorbidity. However, a definite link between the monoclonal peak and the development of muscle damage still needs to be established.

In five patients of our cohort, the clinical response to treatments was good or satisfactory, reaching stabilization or even improvement of muscle weakness. Many different therapeutic strategies based on immunosuppressants, IVIg, chemotherapeutic agents, aSCT and variable combinations of the described treatments have been tried in recent years in SLONM. In particular, seventeen patients were treated with aSCT with good overall results, both in the short period and over a long-term follow-up [14–22, 32]. In 10 out of 12 patients reported in the literature who received IVIg, a beneficial effect was documented, as well as in five out of six patients of our cohort. Our experience confirms that early treatment with corticosteroids, immunosuppressants and/or IVIg may have a favorable impact on the clinical progression of suspect SLONM patients [11], and aSCT as a "rescue therapy" could be reserved to non-responders with confirmed SLONM-MGUS.

We systematically collected muscle MRI data in our cohort of SLONM patients. Our data are consistent with a predominant axial and proximal lower girdle muscle involvement in most patients (paraspinal muscles, gluteus minimus and medius, hamstrings). Neck extensors and subscapularis were frequently affected as well. Interestingly, a subgroup of patients showed a peculiar and rather typical soleus involvement, sometimes isolated at lower leg level. This kind of involvement is different from those described in other neuromuscular diseases that can cause differential diagnostic issues with SLONM, such as sporadic inclusion body myositis (s-IBM), amyotrophic lateral sclerosis (ALS), inflammatory myopathies and genetic nemaline myopathies. A distinctive pattern of involvement characterizes s-IBM, where the distal portion of the quadriceps is invariably affected in *T*1w and *T*2w-STIR sequences [26], while a prominent involvement of supraspinatus muscle has been described in the upper girdle of ALS patients [33]. Inflammatory myopathies are characterized by muscle oedema, visible in *T*2w-STIR images, rather than fatty infiltration. These alterations are more frequently widespread in proximal muscles in polymyositis, while they can be patchy and associated with fascial and subcutaneous fat oedema in dermatomyositis. Fat infiltration usually occurs only at later stages [34]. The pattern of muscle involvement on MRI has been also described in genetic nemaline myopathies. In patients with *ACTA1* mutations, there are generally only minor and diffuse fatty changes in the muscles of the thigh, mostly involving sartorius and adductor magnus, and predominant affection of the anterolateral compartment at the leg level [35–37]. In patients with mutation in the *NEB* gene, the thigh may be completely spared, sometimes with adductor magnus and vastus intermedius fatty infiltration. In the lower leg, involvement of tibialis anterior, soleus and gastrocnemius medialis has been documented [36, 37]. *TPM2*-mutated patients have a predominant involvement of masticatory and distal lower leg muscles [38] and in some cases sartorius involvement [39], while in a report of a family with *TPM3*-mutated nemaline myopathy, the involvement was predominantly in the pelvis and abdominal wall muscles [40]. Therefore, our findings in a relatively small cohort support the diagnostic importance of muscle MRI in SLONM and need to be validated on larger numbers.

In conclusion, SLONM is a severe but potentially treatable myopathy that can remain undiagnosed for a long time after the onset of symptoms. Clinicians should be aware of the disease and quickly refer the patients to specialized neuromuscular centers, where biopsies should be carefully

looked for the presence of nemaline bodies. Immunomodulatory treatments should be promptly administered, including the use of IVIg as first-line treatment. We also suggest that muscle MRI could be helpful in the diagnostic workup, and screening for heart disease should be performed since cardiac involvement does not seem to be rare in SLONM.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This study was approved by the ethics committee of the Catholic University School of Medicine.

Informed consent Informed consent was obtained from all patients for being included in the study.

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