

294th ENMC international workshop: Diagnosis and management of paraproteinemic myopathies focusing on sporadic late-onset nemaline myopathy (SLONM) and light-chain (AL) amyloid myopathy. 27th -29th March 2026, Hoofddorp, The Netherlands

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ABSTRACT

Paraproteinemic myopathies are rare but potentially treatable disorders caused by pathogenic monoclonal proteins, yet diagnosis is often delayed because of nonspecific clinical manifestations and the lack of standardized diagnostic approaches. The 294th ENMC International Workshop convened 21 experts from 12 countries and two patient representatives to establish international consensus on their diagnosis and management. The workshop reviewed current evidence on sporadic late-onset nemaline myopathy (SLONM), light-chain (AL) amyloid myopathy, vacuolar myopathy with monoclonal gammopathy and stiffness (VAMMGAS), and scleromyxedema-associated myopathy. Clinical red flags include age at symptom onset ≥ 40 years, subacute proximal and/or axial weakness, normal or mildly elevated creatine kinase levels (except in VAMMGAS), dysphagia, weight loss, systemic manifestations, and poor response to conventional immunotherapy. Consensus diagnostic criteria for SLONM and a diagnostic algorithm for paraproteinemic myopathies were established. Routine Congo red staining of muscle biopsies, particularly in patients with monoclonal protein, was recommended. The workshop endorsed replacing SLONM-MGUS with SLONM-MP to reflect the pathogenic role of the monoclonal protein and recommended plasma cell-directed therapy as the cornerstone of treatment for SLONM-MP and AL amyloid myopathy. These recommendations provide the first international consensus framework for the diagnosis and management of paraproteinemic myopathies and establish priorities for future collaborative research.

1. Introduction

The 294th ENMC International Workshop, was held in Hoofddorp, The Netherlands, from March 27- 29, 2026, and brought together 21

physicians and researchers from 12 countries (Belgium, Canada, China, France, Germany, Israel, Italy, Japan, Spain, Thailand, the Netherlands, and the USA), along with two patient representatives, to address unmet needs in paraproteinemic myopathies. These rare but treatable

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conditions remain underrecognized, with substantial diagnostic delays and a lack of standardized definitions, diagnostic criteria, and management guidelines. Notably, the median time from symptom onset to diagnosis in conditions such as light-chain (AL) amyloid myopathy and sporadic late-onset nemaline myopathy (SLONM) is often at least two years, underscoring the critical need for earlier recognition. Timely diagnosis is essential to enable prompt treatment before involvement of vital organs, particularly the heart and kidneys, in AL amyloidosis, and before significant fatty replacement of muscle tissue occurs across all subtypes of monoclonal gammopathy-associated myopathies (MGAMs) [1,2].

The workshop aimed to establish international consensus on the clinical and pathological spectrum, diagnostic evaluation and criteria, and treatment strategies for key entities, including SLONM and AL amyloid myopathy, as well as an emerging subtype, monoclonal gammopathy-associated glycogen storage myopathy (MGGSM), including vacuolar myopathy with monoclonal gammopathy and stiffness (VAMMGAS). In addition, the meeting sought to promote multidisciplinary collaboration and lay the foundation for an international research network to advance understanding and care in this field.

1.1. Session 1 Paraproteinemia and associated myopathies

Eli Muchtar (EM) provided an overview of paraproteinemia or monoclonal gammopathy. Monoclonal gammopathy of undetermined significance (MGUS) is common with advancing age, affecting approximately 3–4% of individuals over 50 years, and is usually asymptomatic [3]. However, in a subset of patients, a small B-cell or plasma cell clone produces a biologically active monoclonal protein (MP) capable of causing damage to various organs. In such cases, the condition is no longer classified as MGUS but rather as monoclonal gammopathy of clinical significance (MGCS). MGAMs or paraproteinemic myopathies –also referred to as monoclonal gammopathy of muscle significance (MGMS)– represent a subset of MGCS affecting skeletal muscle [1]. A key principle of MGCS is that tissue injury is driven by the intrinsic properties of the monoclonal protein rather than its quantity, making the distinction between incidental and pathogenic gammopathy both critical and challenging. MGAMs are rare but clinically important muscle disorders in which a monoclonal immunoglobulin or light chain exerts a direct pathogenic effect on skeletal muscle. Screening for monoclonal proteins (MPs) in adults with unexplained myopathy is essential for early recognition and timely initiation of targeted therapy, as these conditions are treatable and outcomes improve significantly with prompt intervention.

Teerin Liewluck (TL) further expanded on the concepts introduced by EM and discussed paraproteinemic myopathies, a heterogeneous group of muscle disorders caused by abnormal plasma cell clones that produce pathogenic MPs associated with skeletal muscle involvement. Unlike MGUS, MGAMs are defined by end organ dysfunction involving skeletal muscle, despite having similar laboratory features such as serum MP <3 g/dL and clonal bone marrow plasma cells <10% [1]. Although the plasma cell clone is typically benign, a malignant clone may occasionally be present [4,5]. Importantly, a defining feature of MGAMs is that the myopathy is attributable to the monoclonal gammopathy and demonstrates clinical improvement with plasma cell-directed therapy. Paraproteinemic myopathies typically affect individuals at age of 40 years or older and present with subacute and rapidly progressive proximal or axial weakness, often accompanied by dysphagia, weight loss, peripheral neuropathy, or multisystem involvement. Normal creatine kinase (CK) levels do not exclude the diagnosis [1]. According to the Mayo Clinic cohort, the most common subtypes include AL amyloid myopathy, accounting for approximately 54% of cases, and SLONM, accounting for approximately 32.5%, followed by less frequent entities such as MGGSM, scleromyxedema associated myopathy, and rare combined pathologies [1,6,7]. IgG is the predominant MP in MGAMs; however, monoclonal light chains without an associated intact

immunoglobulin are more commonly detected in AL amyloid myopathy [1].

Given that AL amyloid myopathy, SLONM, and MGGSM were discussed in detail later in the workshop, TL also provided a brief overview of scleromyxedema. Scleromyxedema represents a distinctive cutaneous disorder characterized by widespread cutaneous mucinosis and fibrosis in association with monoclonal gammopathy, most commonly IgG lambda [8]. Myopathy occurs in a minority of patients but can present with proximal weakness, dysphagia, and elevated CK levels, often accompanied by systemic manifestations. Cutaneous manifestations preceded myopathy in approximately half of the patients. Muscle pathology may demonstrate inflammatory changes, vacuoles, glycogen accumulation, or mucin deposition. Recognizing scleromyxedema is important given its systemic involvement and distinct therapeutic considerations, with intravenous immunoglobulin (IVIg) often serving as first line therapy [9].

The diagnosis of MGAMs requires a high index of suspicion and a systematic approach that integrates clinical, laboratory, and pathological findings (Fig. 1). Evaluation for monoclonal gammopathy, including serum and urine protein electrophoresis (SPEP and UPEP), serum and urine immunofixation (SIFE and UIFE), and free light chain assays (sFLC), should be considered in all patients with myopathy of unclear etiology, particularly those with suggestive clinical features outlined above. Muscle biopsy remains central to diagnosis and should include appropriate histochemical and immunohistochemical studies to identify key findings such as amyloid deposition, nemaline bodies, glycogen accumulation, or mucin deposition. The presence of monoclonal gammopathy alone does not establish causality, emphasizing the need for careful clinicopathological correlation. Early recognition is essential, as many of these conditions respond to plasma cell-directed therapies, highlighting the importance of multidisciplinary collaboration among neurology, hematology, and pathology.

1.2. Session 2 SLONM phenotype

Pascal Laforet (PL) elaborated on the clinical manifestations of SLONM with monoclonal gammopathy or monoclonal protein (SLONM-MP). Original descriptions of late-onset rod myopathy date back 60 years, with the reports of unrelated patients having presented a subacute myopathy with the presence of numerous rods in atrophic muscle fibers [10]. The main clinical hallmarks of these patients were onset in later life, severe involvement of limb and trunk muscles, fibrillations potentials on electromyography (EMG), normal serum CK levels, and failure to respond to corticosteroid therapy. MP was not reported in these first patients, and later other cases have been described in association with an MP, raising the question of an immune-mediated disorder, despite the poor response to corticosteroids or immunotherapy.

The association between monoclonal gammopathy and SLONM was further highlighted in 2005 by a cohort of 14 patients with SLONM from the Mayo Clinic, seven of whom had an associated MP [11]. *ACTA1* analysis in 7 patients without an MP was unrevealing. This case series emphasized several key clinical features of SLONM: 1) subacutely evolving weakness after age 40 years, 2) normal to low CK levels, 3) myopathic EMG with fibrillation potentials, and 4) presence of rods on modified Gömöri trichrome staining or immunostained cryosections. Weakness was symmetric and predominantly proximal in most patients. One patient had head drop. Dysphagia was a common manifestation, occurring in nearly half of the patients regardless of the presence of an MP. Five of seven patients with SLONM-MP died of respiratory failure within 1–5 years, whereas no deaths occurred among SLONM patients without MP during 4–23 years of follow-up, suggesting a worse prognosis associated with MP. However, in an updated 2019 Mayo Clinic cohort of 28 patients with SLONM (14 with MP), survival was comparable between patients with and without MP [12]. The comparable outcomes may, at least in part, be attributable to the adoption of plasma cell-directed therapies for patients with SLONM-MP. Additionally, in

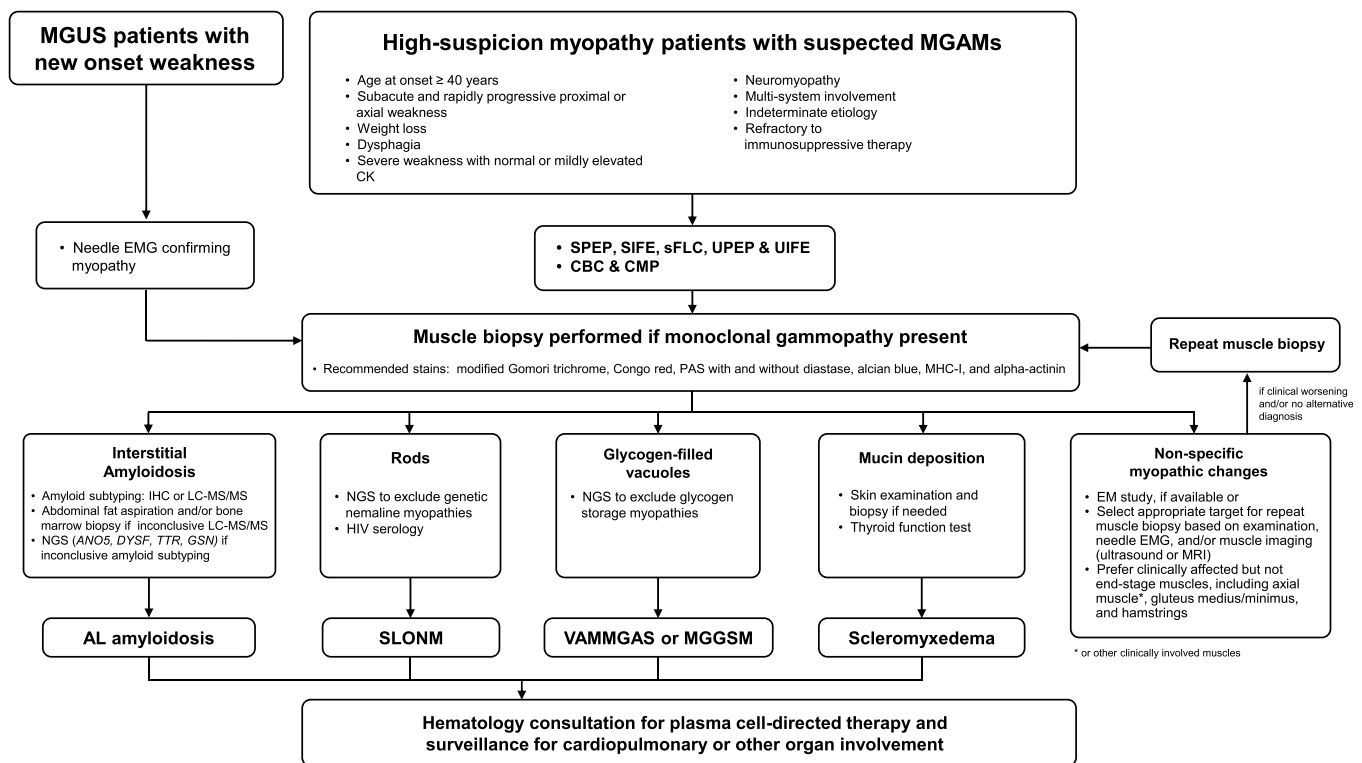


Fig. 1. Diagnostic flowchart for the evaluation of patients with suspected MGAMs.

Patients with known MGUS who develop new-onset weakness should undergo EMG to confirm myopathy regardless of creatine kinase value. Patients with known myopathy who have not been previously tested for monoclonal gammopathy but demonstrate clinical features highly suspicious for MGAMs should undergo laboratory screening for monoclonal gammopathy. If an individual with MGUS is found to have myopathy or a myopathy patient with high-suspicion clinical features is found to have a monoclonal gammopathy, muscle biopsy with appropriate histochemical and immunostaining should be performed. Pathologic findings guide diagnosis into key subtypes, including AL amyloid myopathy, SLONM, VAMMGAS, MGGS, and scleromyxedema, while nonspecific findings may prompt repeat biopsy. Further ancillary testing may be required for clarification. All confirmed cases warrant hematology consultation for plasma cell-directed therapy and evaluation for systemic involvement. Of note, careful muscle selection is critical for both EMG and muscle biopsy, as they may be normal or show only subtle abnormalities if affected muscles are not examined. Motor examination and muscle imaging can help guide muscle selection and reduce sampling error. If the initial EMG or muscle biopsy are not diagnostic but symptoms progress and the diagnosis remains unclear, repeat EMG or muscle biopsy should be considered.

Abbreviations: AL, amyloid light-chain; CBC, complete blood count; CMP, comprehensive metabolic panel; EM, electron microscopy; EMG, electromyography; IHC, immunohistochemistry; LC-MS/MS, liquid chromatography–tandem mass spectrometry; MGAM, monoclonal gammopathy–associated myopathy; MGGS, monoclonal gammopathy–associated glycogen storage myopathy; MHC-I, major histocompatibility complex class I; NGS, next-generation sequencing; NM, nemaline myopathy; PAS, periodic acid–Schiff; sFLC, serum free light chain; SIFE, serum immunofixation electrophoresis; SLONM, sporadic late-onset nemaline myopathy; SPEP, serum protein electrophoresis; UIF, urine immunofixation electrophoresis; UPEP, urine protein electrophoresis; VAMMGAS, vacuolar myopathy with monoclonal gammopathy and stiffness.

this updated cohort, head drop was a prominent feature, occurring in approximately 60% of patients with SLONM-MP. Respiratory symptoms were also common, being reported in about 40% of SLONM-MP patients. Approximately, one-third of SLONM-MP patients reported weight loss. Apart from weakness, approximately 70% of SLONM-MP patients had myalgia at presentation and 30% of patients had severe pain preceding the onset of weakness [12]. Overall, patients with SLONM with and without MP share broadly similar clinical phenotypes.

Jose Milisenda (JM) outlined the clinical differences between SLONM with and without MP and briefly discussed HIV-associated SLONM as a distinct clinical variant. SLONM without MP exhibits a slight female predominance (64.5%) with a mean onset age of 60 years. Similar to SLONM-MP, patients with SLONM without MP typically develop subacute, symmetric proximal and axial weakness, often presenting with head drop or camptocormia. The "CK Paradox"—where CK remains normal or only mildly elevated despite profound weakness—frequently delays diagnosis.

Recent data from a comprehensive analysis of a case series and literature review of a total of 144 patients reveals that SLONM-MP is characterized by a male-predominant phenotype, a more rapidly progressive course, and a significantly higher risk of respiratory failure ($p = 0.006$) compared with those without MP [13]. Additionally, SLONM

without MP appears to be more responsive to conventional immunomodulatory therapy with complete clinical improvement reported nearly 10 times more frequently than in SLONM-MP (29.4% vs. 3.2%, $p = 0.013$), underscoring divergent disease trajectories. The distinction between SLONM-MP and SLONM without MP is clinically relevant because it influences therapeutic decision-making, with SLONM-MP often requiring hematological evaluation and clone-directed approaches, whereas SLONM without MP may benefit from immunomodulatory treatment. These findings contrast with the earlier observations from a smaller cohort, in which the clinical phenotypes appeared largely similar between SLONM with and without MP. While the larger sample size may have improved the ability to detect true differences, the literature-based nature of many included cases introduces potential biases, including selective reporting of severe cases, incomplete phenotyping, and variability in diagnostic and treatment practices. Additionally, the HIV-associated SLONM (SLONM-HIV) represents a distinct variant typically affecting much younger individuals with mean age at onset of approximately 30–34 years showing more pronounced myofiber necrosis and inflammation on muscle biopsy, and a generally favorable response to standard corticosteroid treatment [14].

Nicol Voermans (NV) summarized the Dutch experience with

SLOM, with particular attention to the association with MP, diagnostic challenges, and treatment outcomes across neuromuscular centres in the Netherlands. In the Netherlands, patients have been identified across several neuromuscular centers. Case recognition has increased in recent years, partly due to improved awareness of the association between SLOM and MP. Earlier cases were occasionally misdiagnosed, including as progressive muscular atrophy. Historic cases from Radboud University Medical Center before 2006 highlight the diagnostic uncertainty that existed before the association between SLOM and MP was widely recognized. In two historical cases from this cohort, a first muscle biopsy had already shown typical histopathological findings, including numerous nemaline bodies and lobulated fibres, but screening for MP was not systematically performed at that time. Both patients experienced progressive disease courses, including respiratory failure and death, highlighting the poor prognosis of untreated SLOM.

Three subsequent cases from Radboud University Medical Center, reported between 2006 and 2011, further emphasized the importance of identifying an associated MP ([15]; Patients 1, 2, and 3 in [16]). These patients presented with progressive proximal and axial weakness, marked muscle atrophy, and relative sparing of distal strength. Repeated muscle biopsies eventually revealed rods on light and electron microscopy (EM), often accompanied by lobulated fibres and myopathic abnormalities. In these patients, after the identification of an associated MP, plasma cell clone-directed therapies were initiated. Autologous stem cell transplantation (ASCT), combined with chemotherapy or immunomodulatory therapy such as lenalidomide, resulted in gradual and sustained clinical improvement in two patients (Patients 2 and 3 in [16]). Long-term follow-up demonstrated substantial functional recovery, including return to regular physical activity. One patient, followed for more than a decade, regained the ability to walk several kilometers, illustrating the partial reversibility of muscle weakness with timely treatment. In contrast, the other patient passed away after respiratory failure 13 years after diagnosis ([15], Patient 1 in [16]). The Dutch experience emphasizes several key considerations: rapidly progressive shoulder and pelvic girdle weakness with axial involvement should raise suspicion for SLOM-MP, particularly in the presence of normal or mildly elevated CK and when motor neuron disease appears unlikely. Screening for an MP and comprehensive muscle biopsy evaluation, including ultrastructural analysis in selected cases, are essential components of the diagnostic work-up for SLOM. In patients with a high clinical suspicion for SLOM-MP, a repeat muscle biopsy may be warranted when the initial biopsy is nondiagnostic or inconclusive, as nemaline bodies can be sparse or absent in early or limited tissue samples.

Chuanzhu Yan (CY) provided insights into the demographic, clinical characteristics and follow-up outcome of SLOM based on a multicenter cohort of 56 cases from five major neuromuscular centers in China. The sex distribution was nearly equal (M/F:26/30). The median age at onset was 59 years (range: 29–74 years). Proximal and axial muscle involvement was predominant, occurring in 48% of patients. Neck muscle involvement was observed in 48%, with dropped head syndrome in 35% of cases. Dysphagia and respiratory muscle involvement occurred in 36% and 42% of patients, respectively. Facial and cardiac muscle involvement were less common, affecting 9% and 5% of patients—lower than previously reported rates in a review of 144 cases (20% and 26%, respectively) [13]. MP was detected in 46.7% of patients.

EMG demonstrated myopathic abnormalities in 95% of patients, with spontaneous activity observed in 49%. In SLOM patients without HIV infection, serum creatine kinase (CK) levels were typically normal (<200 U/L in 76%) or only mildly elevated (200–500 U/L in 20%), with elevations exceeding 500 U/L being uncommon and rarely reaching 1500 U/L (4%). Muscle imaging predominantly demonstrated involvement of the posterior compartment of the lower limbs, including the gluteus minimus and medius, semimembranosus, and soleus muscles [17]. Regarding muscle pathology, CY highlighted three characteristic

types of altered muscle fibers that are highly suggestive of SLOM: (1) “sand-like” granular fibers (Fig. 2A), (2) dark green/red atrophic fibers (Fig. 2A), and (3) disintegrated fibers, characterized by loosened sarcoplasm containing numerous irregular, tiny vacuoles (Fig. 2C). Immunohistochemical staining for anti- α -actinin-2 is particularly useful for detecting nemaline bodies, especially in subtle or ambiguous cases (Fig. 2B). Given that SLOM is a treatable condition, routine use of anti- α -actinin-2 staining is strongly recommended to minimize the risk of missed diagnoses.

Treatment and follow-up data from the Chinese cohort showed that more than half of the patients achieved favorable outcomes: 25% had moderate improvement, 16% marked improvement, and 12% complete recovery. Among 21 patients with SLOM-MP, 13 underwent ASCT, with nearly 50% achieving moderate to marked improvement. In patients without MP, more than half (54%) experienced moderate to marked improvement following mono-, dual-, or triple-therapy regimens. Due to the lack of insurance coverage for IVIg therapy on SLOM in China, most patients initially received corticosteroids combined with immunosuppressants, while IVIg was used only in a limited number of cases. In the single-center cohort of 9 SLOM patients without MP, all received combination therapy (corticosteroids, and immunosuppressants) resulting in moderate or complete recovery in every cases. These findings suggest that dual therapy with corticosteroids and immunosuppressants may be an effective initial treatment strategy for SLOM patients without MP, particularly in low-resource settings or in regions where IVIg is not readily available.

Kristl G. Claeys (KGC) reported a retrospective study from her multi-national cohort of SLOM [14], which included 10 new patients and 66 cases derived from a literature meta-analysis and was compared with 15 reported SLOM-HIV patients. SLOM patients had a mean age at onset of 52 years. The predominant phenotype consisted of weakness and atrophy of proximal upper limbs in 84%, of proximal lower limbs in 80% and both in 67%. Other common symptoms included axial weakness in 68%, as well as dyspnea in 55% and dysphagia in 47% of the patients. Serum MP was detected in 53% of patients. The mean percentage of muscle fibers containing rods was 28% (range 1–63%). In two of these cases, ultrastructural analysis was necessary to detect the rods. The most successful treatment in SLOM-MP patients was ASCT. A targeted next generation sequencing (NGS) gene panel comprising 283 myopathy genes in 6 SLOM patients without MP did not reveal causative pathogenic variants. In a comparison of SLOM patients with and without MP, those with MP were more frequently male, showed more rapid disease progression, and exhibited more vacuolar changes in muscle fibers. Interestingly, the muscle biopsy of two SLOM patients with MP revealed intranuclear rods, whereas this feature was not seen in any of the biopsies from patients without MP. Compared with the overall SLOM cohort, patients with SLOM-HIV were more frequently male, with a lower age at onset (mean 34 years). In addition, immunosuppression was more frequently used and appeared to be associated with more favorable outcome, while muscle biopsies revealed a significantly higher degree of inflammation and necrosis in SLOM-HIV compared to non-HIV SLOM patients. Interestingly, MP was also present in approximately half of the SLOM-HIV patients. KGC concludes that SLOM presents a challenging, but important and treatable differential diagnosis to other adult-onset neuromuscular diseases. Investigations for MP and HIV should be performed, as they require distinct but often effective therapeutic approaches. Even though non-HIV SLOM and SLOM-HIV show some differences, there is substantial clinico-pathological overlap between these two entities.

1.3. Session 3 Expert survey and ancillary testing in SLOM

Antonio Lauletta (AL) presented the results of a pre-workshop survey on SLOM, designed to explore areas of consensus and variability in diagnostic approaches, red flags and treatment strategies across experts. The survey was administered anonymously and consisted

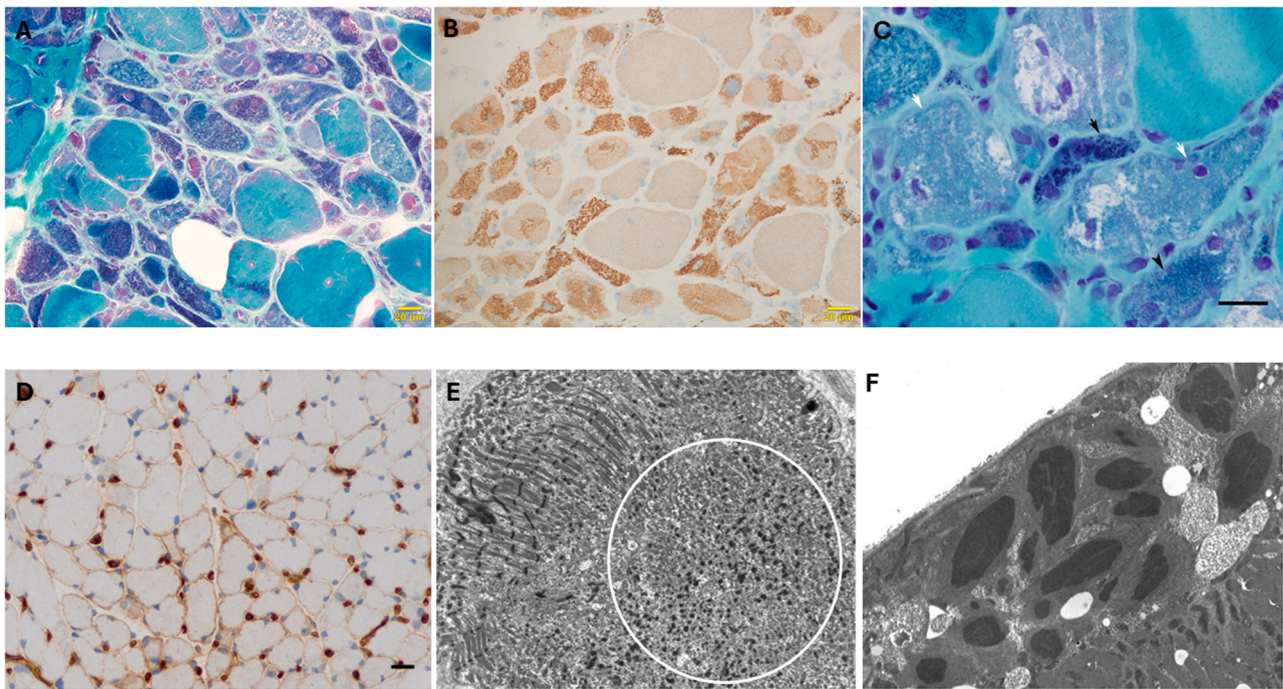


Fig. 2. Myopathology of sporadic late onset nemaline myopathy with monoclonal protein (SLONM-MP). (A) modified Gömöri trichrome stained section shows several atrophic fibers filled with sand-like nemaline bodies, which are highlighted on (B) α -actinin-2-immunostained section. (C) Modified Gömöri trichrome stained section displays vacuolated or disintegrated fibers (white arrows) in addition to atrophic fibers harboring sand-like nemaline bodies (black arrow). One of the vacuolated fibers also contains sand-like nemaline bodies (black arrowhead). (D) MHC-I stained section reveals sarcolemmal MHC-I immunoreactivity in several myofibers. (E-F) Electron microscopy study shows (E) numerous small sand-like rods (circle) and (F) large centrally located “classic” nemaline rods. Scale bars = 20 μ m in A-D; Magnifications: E, $\times$ 3,000; F, $\times$ 12,000.

primarily of Likert-scale items, including some open-ended questions. Seventeen of 21 (81%) experts participated in the survey.

A clear convergence emerged on key clinical features, including adult-onset axial and/or proximal weakness (≥ 40 years) with a subacute course, often presenting with dropped head or camptocormia, in the absence of other affected family members. From a diagnostic perspective, CK levels were widely considered characteristic when normal or only mildly elevated (< 3 times the upper limit of normal). MP screening, including serum protein electrophoresis, serum immunofixation, and free light chain assessment, together with HIV testing, and muscle biopsy, were regarded as essential components of the diagnostic workup, with strong agreement across experts. Genetic testing was mainly considered when an inherited form was suspected, particularly in younger patients with a long disease history. Muscle MRI and EMG were regarded as highly relevant, with muscle selection for EMG guided by clinical findings and imaging.

Proximal muscles were the preferred site for muscle biopsy, targeting a weak but not completely fatty replaced muscle, mainly guided by muscle strength examination and muscle MRI. Histopathological evaluation, including light microscopy with modified Gömöri trichrome staining and immunohistochemistry for Z-line proteins (particularly α -actinin), was considered central for the identification of nemaline bodies, with strong agreement among participants. Low percentages of rod-containing fibers were generally deemed sufficient for diagnosis, most often observed in atrophic fibers. EM was regarded as a useful tool, especially in cases of inconclusive findings at light microscopic level. When the initial biopsy was inconclusive and clinical suspicion remained high, a repeat biopsy could be considered after 3–12 months, targeting a different muscle selected based on EMG and/or MRI findings.

Key red flags for SLONM included the detection of MP in otherwise unexplained muscle weakness, subacute axial-proximal weakness in adults (≥ 40 years), and features not consistent with classic inflammatory or inherited myopathies. The most frequent diagnostic mimics

encountered in clinical practice included inclusion body myositis and motor neuron disease, followed by limb-girdle muscular dystrophy, brachio-cervical inflammatory myopathy, myasthenia gravis, multiple acyl-CoA dehydrogenase deficiency (MADD), and less frequently other inflammatory myopathies such as immune-mediated necrotizing myopathy.

With regard to treatment, in SLONM-MP, most experts favored clone-directed approaches, including high-dose chemotherapy or daratumumab, with consideration of ASCT, often in combination with IVIg, reflecting the perceived pathogenic role of the underlying monoclonal gammopathy. In contrast, in patients without monoclonal gammopathy, immunomodulatory strategies, particularly IVIg, were reported. Combination therapies were commonly used, particularly in SLONM-MP (87.5%), while corticosteroids alone were generally considered to have low effectiveness.

Matteo Garibaldi (MG) presented the electrodiagnostic findings and muscle MRI features in SLONM. The electrodiagnostic studies, particularly EMG, play an important role in SLONM, as the disease may manifest with axial weakness and normal CK levels, potentially leading to underrecognition of an underlying myopathic process if axial muscles are not included in the EMG assessment. EMG findings are normal only in a minority of patients (3%) [14], whereas $> 80\%$ of patients show myopathic changes [13,14] with spontaneous activity, including fibrillation potentials, detected in 70–80% of cases [13,17]. Spontaneous activity is often associated with inflammation, necrosis, and regeneration on muscle biopsy and is therefore more commonly seen in inflammatory myopathies and muscular dystrophies than in metabolic or congenital myopathies, including genetic nemaline myopathies [12,18]. The higher frequency of spontaneous activity in SLONM compared to congenital nemaline myopathies may reflect (1) the higher frequency of myofiber necrosis and regenerating fibers observed in SLONM muscle biopsy [19], and (2) the presumed immune-mediated nature of the disease. Mixed myogenic and neurogenic findings can occur in about

10% of patients [13,14] while purely neurogenic findings are rare (<3%). Whether peripheral nerve involvement represents part of the disease spectrum is still debated, as mixed demyelinating and axonal neuropathy has been recently reported in 3 patients with SLONM-MP and was attributed to concomitant paraproteinemic neuropathy [20].

Few studies investigated muscle MRI features in SLONM using T1-weighted (T1-w) and short tau inversion recovery (STIR) sequences [17,21]. In a cohort of 6 SLONM patients [21], the most affected muscles with T1-w hyperintensity indicating fatty replacement of muscle tissue were soleus, gluteus minimus, gluteus medius, semimembranosus, and lumbar paraspinal in the lower body, along with the subscapularis and cervical paraspinal muscles in the upper body. In contrast, serratus anterior, obliquus and transversus abdominis muscles were mildly affected, while the infraspinatus, trapezius, and rectus abdominis were spared. In another cohort of 17 SLONM patients, muscle MRI demonstrated a similar pattern of muscle involvement, while additionally highlighting asymmetry in 73% of patients and quadriceps involvement in approximately one-third of cases [17]. A pattern of predominant quadriceps involvement relative to the hamstrings has also been described, albeit infrequently [22]. STIR hyperintensity was detected in at least one muscle in >80% of patients, involving not only the muscles typically affected in T1-w sequences, but also additional muscles such as the adductor magnus and longus, and obturator internus and externus [21].

1.4. Session 4 Morphological features of SLONM

Ichizo Nishino (IN) provided insights into the morphological features of SLONM. Among 10,866 muscle biopsy cases received at the National Center of Neurology and Psychiatry in Kodaira, Japan, for diagnostic muscle pathology over the 10-year period from 2016 to 2025, 128 cases were diagnosed with SLONM and showed nemaline bodies in at least two fibers on α -actinin-2 immunohistochemistry. The age at muscle biopsy was 67.1 ± 10.6 years (range 35–91 years). Among these patients, MP was assessed in 105 cases (80 females and 25 males) of whom 23 were MP-positive. Among these 23 SLONM-MP cases, only one was complicated by AL amyloid myopathy, suggesting that the coexistence of SLONM and AL amyloid myopathy is rare. There was no significant age difference between the MP-positive and MP-negative groups. Although there was no statistically significant sex difference in the MP-positive group (10 females and 13 males), a marked female predominance was observed in the MP-negative group (70 females and 12 males). This finding raises the possibility that MP-negative SLONM may be related to an immune-mediated mechanism, given the well-recognized female predominance in many autoimmune diseases.

Histologically, the nemaline bodies were smaller than those typically seen in genetic nemaline myopathies and often had a fine granular or sand-like appearance (Figs. 2A and C). In some cases, these subtle, sand-like structures were difficult to be recognized as nemaline bodies on modified Gömöri trichrome staining. However, even such tiny nemaline bodies could be clearly detected by α -actinin-2 immunohistochemistry (Fig. 2B), suggesting that this is a very useful method for confirming their presence. Vacuolated or disintegrated fibers (Fig. 2C) can also be present. Nemaline bodies are distributed in two distinct patterns: (1) a diffuse pattern, predominantly observed in small angular atrophic fibers, and (2) a patchy, focal cluster pattern, mainly seen in non-atrophic fibers. There was no significant difference in the predominance of these two distribution patterns between patients with or without MP. Finally, MHC-I expression did not significantly differ between MP-positive and MP-negative groups (Fig. 2D).

Werner Stenzel (WS) elaborated on the ultrastructural features of SLONM framing his talk with two historic citations of the phenomenological description by William K. Engel in 1966 [23] describing the rods as follows ‘...the rods were identical histochemically to the ones described in congenital cases. On EM, the rods were of Z-band density and appeared to be formed at the Z-bands of the myofibrils...and

showed a characteristic periodicity. Sometimes fibers containing rods were reduced in diameter’. In the same year and only some months later, Andrew G. Engel [10] described the features of “Late-onset Rod myopathy” as fulfilling five criteria: 1) origin at Z disc; 2) tetragonal filamentous array; 3) structural continuity with thin filaments; 4) periodic lines perpendicular to long axis; 5) periodic lines parallel to long axis. Essentially those descriptions are still valid to date. However, certain new elements can be added after having studied 19 SLONM patients by 34 digitized ultrathin sections and having compared them to healthy and diseased controls.

WS then reviewed the ultrastructural characteristics of myofiber segments on longitudinal sections. These include the regular and parallel arrangement of dark osmiophilic Z-bands with attached actin filaments and centrally located myosin filaments forming the characteristic normal sarcomeric banding pattern, which has been well described elsewhere [24]. He continued by showing 2-D and 3-D images of rods in different cases and with different appearances. Rods had considerably different sizes and were placed either subsarcolemmally or in the center of the fibers, often—but not always—close to myonuclei. Another commonly recognized feature is the presence of I-Z-I complexes in proximity to overt rod formation.

Skeletal muscle biopsies characterized by numerous angular small myofibers often contained many small rods besides larger rods, resulting in a “sand-like appearance” (Fig. 2E). In contrast, muscle fibers containing large centrally placed rods—which were unmistakably identified on modified Gömöri trichrome stains—had a rather round shape and did not contain abundant “sand-like” small rods (Fig. 2F). A similar pattern was observed in fibers with cap-like rod distribution, visible on modified Gömöri trichrome staining as a violaceous cap in one or more ‘angles’ of the myofiber; these fibers tended to have a more polygonal rather than round shape.

WS also emphasized that the quality of the modified Gömöri trichrome stain is critical, as suboptimal staining may obscure the characteristic reddish appearance of nemaline bodies and lead to an incorrect diagnosis. In addition, rods should be relatively abundant to support a diagnosis of SLONM. Conversely, when rods are only occasionally identified—particularly as incidental findings on EM studies and not readily visible on modified Gömöri trichrome—a differential diagnosis should be considered. WS illustrated this concept with several examples of differential diagnoses. He showed a case of an anti-synthetase syndrome associated myositis, in which only few rods were found in one single fiber. Another case of dermatomyositis displayed the classical histopathological features of the dermatomyositis, but also contained fibers with cytoplasmic bodies and some large rods. He further showed that rods may also occur in highly atrophic fibers or nuclear clumps in neurogenic diseases, as well as in critical illness myopathy/neuropathy. Overall, these observations highlighted that different types of rods may be identified in a variety of disease contexts. In SLONM, the association with MP and the frequent association with small “sand-like” rod formations adjacent to larger, “more classical” rods, appear to be typical findings. No established threshold exists regarding the number of rods per fiber or number of fibers containing rods required for the diagnosis of SLONM. As SLONM remains largely a diagnosis of exclusion, the entire clinicopathological context has to be taken into account and even a re-biopsy may be advisable if—despite a strong clinical suspicion—rods are not identified, not even by EM.

Jantima Tanboon (JT) presented results from a collaborative study of 49 SLONM patients from the Charité—Universitätsmedizin (Berlin, Germany), and the National Center of Neurology and Psychiatry (Tokyo, Japan) [25], focusing on comparison of inflammatory features between SLONM-MP (13 patients) and SLONM without MP (34 patients). No notable clinical or histological differences were observed in this study. Both conditions were most prevalent among females aged 50s–70 s. Over 80% of patients had CK levels < 5 times the upper limit of normal; the highest CK levels were 994 and 3870 U/L in SLONM-MP and in SLONM without MP, respectively. In the SLONM-MP group, CK levels

were normal in 54.5% of patients and below the normal range in 18.2%. Histologically, fibers containing nemaline bodies were mainly round or angular, while cap distribution of rods or mixed patterns was uncommon. Nemaline bodies mostly appeared as rods. "Sand-like" nemaline bodies and vacuolar changes were more commonly observed in SLONM without MP. In both groups, more than half of patients showed 15% or fewer nemaline body-containing fibers, whereas 31.9% of patients had involvement limited to 1–5% of myofibers. Dark atrophic fibers on NADH-TR staining were frequent in both groups. Type 1 fiber predominance was uncommon in SLONM-MP. Acid phosphatase stained nemaline-containing fibers and strongly correlated with their number, suggesting its usefulness for their identification. Regenerating fibers were sparse. MHC-I was expressed in 67.4% of cases, although 41.7% of SLONM-MP cases showed positivity in <25% of muscle fibers. CD68+ macrophages represented the predominant infiltrating inflammatory cells, whereas CD3+ and CD8+ cells were less frequent, and CD20+ B cells were rare. MHC-I expression showed a moderate association with inflammatory changes, while inflammatory cell count and the proportion of nemaline-containing fibers demonstrated moderate to strong associations, supporting a possible contribution of inflammation to disease pathogenesis. Membrane attack complex was deposited more frequently on capillaries than on the sarcolemma, although less intensely than what typically observed in dermatomyositis. This finding suggests that the complement pathway is unlikely to play an important role in the pathogenesis of SLONM.

Fine granular p62 staining was commonly observed in both SLONM-MP and SLONM without MP, with patterns and scores similar to those of LAMP2, CRYAB, BAG3, and HSP70 immunoreactivities. In contrast to immune-mediated necrotizing myopathy, which typically exhibited uniform p62 and LC3 staining [26], SLONM demonstrated significantly higher p62 than LC3 scores, suggesting a possible impairment of the autophagosomal pathway and defective macroautophagy in nemaline fragment formation. No strong type I or II interferon pathway activation was found in SLONM; MxA staining was negative, while ISG15 and Siglec-1 were rarely positive, and MHC-II expression was uncommon.

Previous studies indicated that perivascular inflammation in SLONM without MP may be associated with heterogeneous clinical behavior [17], whereas in SLONM-MP it may be correlated with disease progression, particularly in the context of IVIg treatment [21]. Notably, three SLONM-MP patients without inflammatory features demonstrated sustained responses to IVIg lasting >24 months [21,27]. Interestingly, one previously reported SLONM-MP patient that achieved complete remission after plasma cell-directed therapy later experienced disease recurrence following a gastrointestinal infection despite disappearance of the MP (unpublished data). Further studies are needed to clarify associations between inflammatory features, disease severity, and treatment responses in SLONM.

1.5. Session 5 Pathophysiology of SLONM

Margherita Milone (MM) reported on the SLONM proteomic and transcriptomic studies from her group published in 2023 [19]. The study included muscle biopsies from: 1) Thirteen SLONM patients with a median age of 64 years (range 46–77), 10 with MP (5 IgG Kappa, 3 IgG Lambda, 2 with both IgG Kappa and IgG Lambda) and 3 without MP; none of them had genetic variants in genes known to cause nemaline myopathy at time of the experiments or HIV antibodies; 2) Nine genetic nemaline myopathy (gNM) patients with a median age of 11 years (range 2–73), including 5 *ACTA1*, 3 *NEB*, 1 *TNNT1*. Adults with gNM had no MP or HIV antibodies. Targeted proteomic studies were performed after laser capture microdissection to separate areas with nemaline bodies and rod-free areas; transcriptomic studies were performed on bulk RNA.

Proteomic analysis detected differentially expressed proteins between areas with nemaline bodies and rod-free areas, as well as between SLONM and gNM. The areas with nemaline bodies showed similar

abundance of well characterized rod proteins (such as actin, α -actinin, and tropomyosin) in both groups, while other proteins implicated in actin filament assembly and Z-disc structure (such as nebulin-anchoring protein, supervillin, synaptopodin-2 and myotilin) were differentially expressed, suggesting differences in rods formation and composition.

Comparison of protein abundance in areas with nemaline bodies in SLONM and gNM identified differentially expressed proteins implicated in immune, structural, metabolic, and cellular pathways. While sarcomeric proteins were over-represented in gNM, mitochondrial proteins comprised the most over-represented proteins in SLONM. Such latter finding was supported by previous studies showing that rod formation can occur not only as result of structural derangements but also as result of metabolic stressors, including ATP depletion or heat shock. Comparisons of nemaline bodies and rod-free areas in muscle from both diseases each identified differential expression of actin filament, nuclear, and extracellular matrix proteins, suggesting alteration in house-keeping mechanisms between the rod areas and rod-free areas.

Proteomic analysis of immunoglobulins showed a significantly increased abundance of IgG heavy chain and kappa and lambda light chains in nemaline body areas of SLONM relative to gNM. These findings were corroborated by transcriptomic analysis that detected increased expression of kappa light chain genes in SLONM. Additionally, muscle immunostaining confirmed presence of kappa light chain deposition in a proportion of fibers in 42% of SLONM samples but not in gNM.

Transcriptomic analysis also identified 50 differentially expressed genes in SLONM compared to control samples, with increased expression of genes belonging to antigen presentation pathway, integrin-linked kinase signaling pathway, calcium signaling and interferon signaling as the top 4 altered pathways. The top 4 altered pathways in gNM were calcium signaling, dilated cardiomyopathy signaling, glycolysis and actin cytoskeleton signaling.

Overall, SLONM and gNM have unique pathological and molecular signatures suggesting distinct underlying pathophysiological mechanisms. Additionally, the combination of immunohistochemical, proteomic and transcriptomic profile supports the previously speculated pathogenic link between nemaline bodies and immunoglobulins in SLONM, giving clinical significance to the MP and supporting use of plasma cell targeting therapy for treatment of SLONM-MP.

Jana Marie Schwarz (JMS) discussed the genetics of both gNM and SLONM and presented the results of Whole Exome Sequencing (WES) of nine biopsy-confirmed SLONM cases. SLONM and gNM represent clinically and etiologically distinct entities. gNM affects approximately 1 in 50,000 live births and is caused by pathogenic variants in at least 14 genes encoding sarcomeric or sarcomere-regulatory proteins, with *NEB* (approximately 50%) and *ACTA1* (15–25%) accounting for the majority of genetically solved cases [28,29]. Clinical onset typically occurs during infancy. In contrast, SLONM presents later in adulthood, and its etiology remains poorly understood. No monogenic cause has yet been identified, and the extent to which genetic susceptibility contributes to disease pathogenesis remains unclear. An immune-mediated pathogenesis is favoured, supported by MP association, inflammatory biopsy features, and immunotherapy responsiveness. JMS reviewed findings from three previously published genetic studies on SLONM [14,19,22], together with unpublished data. Collectively, these studies have not identified a shared monogenic cause of SLONM. However, WES may facilitate the identification of alternative diagnoses in clinically ambiguous cases and may reveal candidate susceptibility variants in immune-regulatory pathways. Whether SLONM is best explained by a polygenic or oligogenic genetic architecture remains unresolved and will require investigation in larger cohorts alongside functional validation studies.

Divyanshu Dubey (DD) discussed emerging approaches for antibody discovery in autoimmune neurological disorders, with particular focus on tools that may help investigate paraproteinemic myopathies. He highlighted the growing evidence supporting a role of the humoral immune system in the pathogenesis of SLONM, particularly in cases

associated with MP. Across several cohorts, roughly half of patients with SLONM were found to have an underlying MP, suggesting that plasma cell-derived immunoglobulins may be involved in disease biology, although their exact role remains uncertain.

In the recent systematic review [13], 47% of 144 patients were classified as SLONM-MP and these individuals tended to have more severe disease, including greater respiratory involvement and worse functional status. The observed responses to treatments such as IVIg and ASCT further support the idea that both the plasma cell clone and the broader humoral immune response are clinically relevant. Consistent with this, SLONM-MP has generally been associated with a more aggressive phenotype, including higher rates of respiratory involvement and poorer outcomes if left untreated [25]. Additional support for a humoral mechanism comes from the overlap with other MP-associated conditions, such as paraproteinemic neuropathies, where immune complex-mediated processes have been described [20]. However, despite this accumulating evidence, the specific antigenic targets and functional significance of the antibodies in SLONM remain largely unknown. Notably, emerging frameworks in neuroimmunology suggest that immune responses may act as co-drivers or amplifiers of disease, even in conditions where they are not the primary initiating factor. In this context, characterization of the humoral immune repertoire remains informative, as immune responses may influence disease progression, heterogeneity, and treatment responsiveness.

This highlights an important gap: the need for a more systematic characterization of the antibody response in SLONM. Beyond serving as biomarkers, identification of disease-associated autoantigens can provide important mechanistic insights. In paraneoplastic neurologic syndromes associated with intracellular antigens (e.g., Hu, Ma2, and kelch like protein 11 [KLHL11]), antibody discovery has guided the identification of antigen-specific cytotoxic T-cell responses and substantially advanced understanding of disease pathogenesis [30,31]. Similar approaches could help elucidate the immune mechanisms underlying SLONM, even if antibodies ultimately prove to be biomarkers rather than direct mediators of tissue injury. If disease-specific single autoantibodies are not identified [32,33], this could suggest that SLONM may involve a broader, more complex antibody repertoire rather than a single dominant target. In this context, newer high-throughput methods, including phage immunoprecipitation sequencing (PhIP-Seq) and immunosignature-based approaches, may help address this by capturing the overall pattern of antibody reactivity rather than focusing on individual antigens [34–36]. These approaches are particularly relevant for SLONM, where the immune response may represent part of a broader, interconnected process involving plasma cell abnormalities and immune activation.

Eduard Gallardo (EG) discussed ongoing efforts to identify novel autoantigens in SLONM. He highlighted the clinical response to immunotherapies, suggesting that the immune system may play a role in the pathophysiology of SLONM, with autoantibodies representing one possible pathogenic mechanism. Drawing from his group's experience in investigating autoantibodies in seronegative myasthenia gravis, EG proposed to use a similar workflow to tackle the search for autoantibodies in SLONM patients. As preliminary approach, four sera from SLONM patients (2 with MP and 2 without MP) were analyzed. IgG were purified from the serum samples, labelled with biotin to allow their detection by immunofluorescence, and then incubated on frozen sections of control skeletal muscle [37,38]. Immunofluorescence demonstrated a striated staining pattern on muscle sections incubated with IgG from two of the four sera, one with MP and one without MP. This pattern suggests binding of patient antibodies to regularly organized muscle fibre structures, supporting an antibody-mediated immune response in, at least a subset of SLONM patients.

1.6. Session 6 SLONM treatment and patient testimonials

Olivier Benveniste (OB) reviewed the current therapeutic

landscape of SLONM, distinguishing between SLONM-MP and SLONM without MP, and proposed a structured treatment algorithm.

SLONM-MP is a treatable but potentially fatal condition. Without treatment, mortality may reach approximately 40% within 12 months, with most patients dying within 1–5 years from progressive respiratory failure. The pathophysiology is still a matter of debate: the reported presence of IgG light chain deposits on the sarcolemma and the clinical response to IVIg suggest an underlying autoimmune mechanism, while superior outcomes with chemotherapy and correlation between hematological and myological responses argue for a plasma cell dyscrasia.

Early case reports demonstrated clinical improvement in 50–80% of patients treated with IVIg, establishing it as first-line treatment in both SLONM with and without MP. However, IVIg rarely achieves hematological complete remission, and some patients deteriorate rapidly despite apparent initial stabilization. High-dose melphalan followed by ASCT is the current gold standard for fit patients with SLONM-MP. The multicenter retrospective series [16] reported an 87.5% response rate in 8 SLONM-MP patients treated with high-dose melphalan and ASCT, with sustained responses over 1–8 years of follow-up. Hematological complete remission was the best predictor of myological recovery. A key clinical debate persists between those favouring prolonged IVIg trials (supported by Mayo Clinic data showing no survival difference between patients with and without MP [12]) and those advocating early escalation from IVIg to ASCT in fit patients to avoid irreversible deterioration [39].

For ASCT-ineligible patients, anti-myeloma chemotherapy without transplant – including bortezomib-based regimens (CyBorD), lenalidomide-dexamethasone, and cyclophosphamide-thalidomide-dexamethasone (CTD) – have shown efficacy across approximately 10–15 published cases. OB highlighted the results of the ANDROMEDA trial in patients with AL amyloidosis, which demonstrated the superiority of daratumumab-CyBorD (Dara-CyBorD). Following the introduction of this regimen, the use of ASCT at the Mayo Clinic decreased by 71% since 2020, reflecting a shift toward non-transplant first-line strategies for AL amyloidosis [40]. Drawing parallels on AL amyloidosis, considered as a "mirror disease" (same clonal plasma cell biology, different target organ), a Dara-CyBorD-first strategy, with ASCT reserved for incomplete responders, is proposed as a rational approach for SLONM-MP – though never yet tested in this indication. Bortezomib-induced neuropathy is flagged as a specific concern in neuromuscular patients. OB further emphasized that modern myeloma therapies remain entirely unexplored in SLONM. As of March 2026, no published cases using bispecific antibodies (e.g., teclistamab, elranatamab, talquetamab) or BCMA-targeted CAR-T cells (e.g., ide-cel, cilta-cel) had been reported in SLONM. Despite a strong biological rationale based on B-cell maturation antigen (BCMA) expression on clonal plasma cells, several challenges remain, including off-label access, uncertain toxicity in frail neuromuscular patients, and the lack of data regarding BCMA expression on SLONM plasma cells specifically.

SLONM without MP represents roughly half of cases, with a generally more favourable prognosis. IVIg is the backbone of treatment (70–80% response), supplemented by corticosteroids and immunosuppressants. Anti-plasma cell therapy is not indicated.

Rouslan Kotchetkov (RK) reviewed the role of chemotherapy and ASCT in SLONM-MP. He first outlined the major advances in plasma cell dyscrasia therapy over the last 20 years, evolving from melphalan-prednisone based regimen to multiple classes of targeted anti-plasma cell agents. Nowadays, a majority of highly potent anti-plasma cell drugs are non-chemotherapeutic therapies. The primary goal in SLONM-MP therapy is to eradicate plasma cell clones in order to terminate MP production.

RK presented a comparative analysis of treatment approaches in SLONM-MP reported in the literature (PubMed 1966–2025) [11–13,16,41], together with original unpublished cases. Thirty-eight patients received chemotherapy at some disease-stage, and 35 patients were subjected to non-chemotherapy approaches, including

immunosuppressants, IVIg, steroids, or plasma exchange. Patients in both groups showed similar characteristics, including MP subtypes and balanced Kappa/Lambda distribution (approximately 1:1). In contrast, mean MP levels tended to be higher in the “chemotherapy group” (4.2 g/L vs. 1.5 g/L; $p = 0.0546$). Approximately 76% of patients received ASCT, including 90% single and 10% tandem ASCT, while 24% had non-transplanted systemic therapy, including proteasome inhibitors, immunomodulators, anti-CD38 monoclonal antibodies and their combinations. Approximately 45% received chemotherapy upfront, whereas 55% underwent initial non-chemotherapy before escalation to plasma-cell directed therapy.

Neurological responses, assessed using the Medical Research Council (MRC) scale to evaluate muscle strength, were markedly better in the chemotherapy group. Grade 5 and grade 4 were achieved respectively in 50% and 21% of chemotherapy patients, compared to 5.7% and 8.6% of non-chemotherapy patients. Time-to-best-response was 7.8 months in the chemotherapy group, compared to 14.3 months in the non-chemotherapy group ($p = 0.0365$). Overall survival was significantly longer in the chemotherapy group. At the last follow-up, >50% of chemotherapy-treated patients were still alive (median overall survival not reached), whereas median overall survival was 24 months in the non-chemotherapy group (HR 3.8, 95%CI 1.42–9.91).

Hematological response was assessed by International Myeloma Working Group criteria [42]. Complete response (CR) and stringent complete response (sCR) of the underlying plasma cell disorder were higher in the chemotherapy group (42.4% and 12.1%) compared to non-chemotherapy patients (13.1 and 6.7%). Patients achieving CR or sCR showed markedly improved overall survival (OS) with median OS not reached compared with patients with persistent measurable MP (median OS 17 months, HR 6.3; 95% CI 1.682–23.73). Chemotherapy administered upfront was associated with better neurological response (52.4% reached MRC Grade 5 and 33.3% reached MRC Grade 4) compared to delayed application (36.3% reached MRC Grade 5 and 17.6% reached Grade 4). Median OS was higher in patients who had chemotherapy upfront; however, the difference did not reach statistical significance ($p = 0.0888$). Furthermore, ASCT was associated with a better hematological response, with 62% of transplanted patients achieving CR or sCR compared with 28% in non-ASCT patients. However, no significant overall survival difference was observed between the ASCT and non-ASCT groups.

The favorable response to clone-directed therapy provides compelling evidence that the MP plays a pathogenic role in SLONM patients with MP. Consequently, the term SLONM-MGUS, which is widely used in the literature, is not biologically accurate because MGUS, by definition, refers to a monoclonal gammopathy that does not cause tissue or end-organ damage. Therefore, the workshop participants agreed that SLONM-MP is the preferred terminology, as it more accurately reflects the disease pathogenesis and avoids the misleading implication that the monoclonal gammopathy is merely an incidental finding. SLONM-MP should be treated as a plasma-cell driven malignancy with chemotherapy-based regimen, aimed at achieving complete hematological response. Systemic anti-plasma cell therapy is more efficacious when used upfront. ASCT remains recommended for patients who can tolerate it, whereas ASCT-ineligible patients should receive combination therapy, including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies. Multidisciplinary management, including qualified pathologists, neurologists and hematologists experienced in SLONM-MP, should be applied for SLONM-MP patients.

Eleonora Torchia (ET) highlighted the role of physiotherapy in SLONM, emphasizing that supportive treatment represents an important component of patient management despite the current lack of disease-specific rehabilitation guidelines. ET discussed that exercise was historically discouraged in neuromuscular disorders because of concerns regarding “overwork weakness”, namely the possibility that excessive muscle activity could accelerate muscle damage and worsen weakness. However, evidence from other inflammatory and genetic myopathies

suggests that appropriately tailored exercise programs are generally safe and may improve functional capacity, aerobic performance, fatigue, and quality of life [43–45]. Although direct evidence in SLONM remains limited, similar rehabilitation principles may reasonably be applied in clinically stable patients. ET highlighted that axial weakness is a prominent and often disabling feature of SLONM, commonly associated with camptocormia, dropped head, impaired trunk stability, and gait alterations. In this context, postural rehabilitation plays a central role and should include trunk stabilization exercises, stretching, balance training, and strategies aimed at optimizing posture and movement patterns while minimizing maladaptive compensatory mechanisms. Assistive devices and orthoses may provide additional functional benefit in selected patients [46].

Respiratory therapy and speech/swallowing rehabilitation are also important given the frequent respiratory and bulbar involvement observed in SLONM. Particular attention was given to the potential role of muscle MRI in rehabilitation planning. Muscle MRI may help identify patterns of selective muscle involvement and distinguish severely affected muscles from relatively spared muscle groups, potentially supporting more individualized rehabilitation strategies. In addition, longitudinal MRI assessment may help monitor disease progression over time and support adaptation of rehabilitation programs according to evolving patterns of muscle involvement. Finally, ET emphasized the importance of a multidisciplinary approach involving neurologists, physiatrists, physiotherapists, respiratory therapists, speech therapists, and hematologists, particularly in patients receiving plasma cell-directed therapies or immunotherapies. Early initiation of rehabilitation, always alongside appropriate pharmacological treatment, may be important to limit secondary complications related to deconditioning and prolonged disability. Future collaborative studies are needed to better define rehabilitation strategies, identify sensitive functional outcome measures, and establish evidence-based recommendations for physiotherapy in SLONM.

Myriam Tierens (MT) and **Sandrine Gosteli (SG)** shared personal testimonials describing their challenging diagnostic journeys with SLONM-MP, characterized by years of symptoms, multiple healthcare encounters, and extensive diagnostic evaluations before the correct diagnosis was established. Their experiences underscored the substantial diagnostic burden faced by patients and highlighted the importance of earlier recognition, increased clinician awareness, and establishing standardized diagnostic approaches, reinforcing the objectives of this workshop. The complete patient testimonials are available in the Supplementary Materials.

1.7. Session 7 Diagnosis and treatment of AL amyloid myopathy and VAMMGAS

Felix Kleefeld (FK) reviewed the clinical and pathological features of amyloid myopathies. Amyloid myopathies are rare manifestations of systemic amyloidosis caused by extracellular deposition of misfolded proteins forming β -sheet fibrils within skeletal muscle, most commonly in AL and transthyretin (ATTR) amyloidosis [5,47]. While primary muscle involvement is uncommon, particularly in ATTR, it may be clinically relevant and even an early manifestation in AL amyloidosis [48–50]. Pathophysiologically, amyloid deposits accumulate in the endomysium, perimysium, and intramuscular vessels, leading to mechanical disruption of muscle architecture, microvascular ischemia, and, especially in AL amyloidosis, direct proteotoxic effects of circulating light chains. These processes contribute to impaired muscle regeneration and may be accompanied by denervation-like changes. Clinically, amyloid myopathy typically presents with progressive proximal muscle weakness, often with a limb-girdle pattern, and is frequently associated with myalgia and fatigue. CK levels are usually normal or only mildly elevated, which can help distinguish it from genetic myopathies featuring amyloidosis, including anoctaminopathy and dysferlinopathy. Additional features such as pseudohypertrophy, dysphagia,

macroglossia, weight loss, and cardiac involvement may provide important diagnostic clues, particularly in the context of a multisystem disease [5]. The condition can mimic inflammatory myopathies, including inclusion body myositis (IBM), or coexists with IBM [51], leading to diagnostic delay. Diagnosis relies on muscle biopsy with Congo red staining and confirmation of amyloid deposition, followed by precise amyloid subtyping, which is essential as treatment differs fundamentally between amyloidosis subtypes. In AL amyloidosis, therapy is directed against the plasma cell clone, whereas ATTR amyloidosis is treated with transthyretin (TTR)-targeted approaches, including TTR stabilizers or gene-silencing therapies.

Teerin Liewluck (TL) presented the morphological features and diagnostic challenges of AL amyloid myopathy. AL amyloid myopathy is pathologically characterized by amyloid deposition within the vascular walls and connective tissue elements of skeletal muscle. Histopathologically, Congo red staining remains the gold standard. Fluorescent Congo red using Texas red or rhodamine filters offers the highest sensitivity, as Congo red viewed under polarized light may miss small amyloid deposits. Additional myopathologic features include frequent denervation and reinnervation changes. Necrotic and regenerating fibers may be present but are typically not prominent, and inflammatory findings are generally absent [5,52]. MHC-I and membrane attack complex (MAC) may be present in areas of amyloid deposition, which can be a potential diagnostic pitfall and may be misleading toward a diagnosis of immune-mediated myopathy [49]. Ultrastructural examination demonstrates non-branching fibrils approximately 10 nm in diameter [52].

Despite these recognizable features, diagnosis remains challenging. Clinical manifestations are often nonspecific, and hallmark features such as concomitant peripheral neuropathy or macroglossia are present in only a subset of patients. Notably, nearly 90% of patients with AL amyloid myopathy do not have a prior diagnosis of AL amyloidosis. Laboratory findings may also be misleading, with normal CK levels in up to half of cases [2,5]. Importantly, amyloid deposits may be overlooked if Congo red staining is not performed as part of standard evaluation, contributing to underdiagnosis. In France, Congo red is included among routine histochemical stains for all muscle biopsies, whereas in the United States, it is performed as part of standard practice in only just over half of muscle pathology laboratories. Routine Congo red staining has been shown to increase the detection of amyloid myopathy by up to tenfold [52]. The median time from symptom onset to diagnosis is approximately two years, during which disease progression and systemic involvement may occur [1,2].

A key diagnostic pitfall is assuming that the presence of monoclonal gammopathy confirms AL amyloidosis, as incidental MGUS is common in other amyloidosis subtypes, occurring in 40%–50% of patients with ATTR amyloidosis [53]. Therefore, accurate amyloid subtyping is essential. Laser capture microdissection followed by mass spectrometry (LC-MS/MS) is the gold standard, offering superior accuracy compared to immunohistochemistry, although its availability is limited. In cases where immunohistochemistry for lambda and kappa light chains as well as transthyretin is inconclusive, LC-MS/MS should be pursued if not already performed [54–56]. When amyloid deposits in muscle tissue are insufficient for LC-MS/MS, evaluation of extramuscular sites such as abdominal fat or bone marrow can improve diagnostic yield [5].

Overall, these findings emphasize the need for a high index of suspicion and a systematic diagnostic approach. Early recognition is critical to enable timely hematologic therapy and prevent irreversible cardiac and renal involvement in AL amyloidosis [50].

Eli Muchtar (EM) provided an overview of the current therapeutic landscape for AL amyloidosis. The management of AL amyloidosis has evolved substantially in recent years, reflecting advances in disease biology understanding and the development of more effective plasma cell-directed therapies. AL amyloidosis is a complex multisystem disorder caused by a typically indolent plasma cell clone that produces misfolded immunoglobulin light chains, which deposit in tissues and

lead to progressive organ dysfunction. A central therapeutic principle is that rapid and deep hematologic response is required to halt ongoing organ damage and enable organ recovery, which remains the key determinant of survival. Hematologic response is primarily assessed by the difference between involved and uninvolved free light chains (dFLC), a marker of disease burden and prognosis. These considerations underscore the importance of prompt initiation of therapy and achieving maximal clonal suppression early in the disease course.

The introduction of anti-CD38 monoclonal antibody-based regimens has significantly transformed frontline therapy. The ANDROMEDA trial demonstrated that the addition of daratumumab to cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) results in substantially higher hematologic complete response rates and improved overall survival compared with bortezomib-based regimens (CyBorD) alone [40]. Importantly, these responses are achieved more rapidly and are associated with higher rates of organ response. Subsequent updates and real-world data have confirmed these findings, showing not only superior efficacy but also a reduction in early mortality, which remains a major challenge in AL amyloidosis [57]. As a result, Dara-CyBorD is now widely regarded as the standard of care for newly diagnosed patients, and treatment strategies increasingly emphasize the depth and rapidity of hematologic response as key therapeutic goals.

ASCT, once a cornerstone of therapy, now occupies a more selective role. Although it can induce durable responses, its applicability is limited to approximately 25–30% of patients due to age, comorbidities, and the severity of organ involvement, particularly cardiac disease. Furthermore, the effectiveness of modern induction regimens has led to a marked decline in ASCT utilization [58] prompting reconsideration of its optimal timing and clinical utility. Current practice generally reserves ASCT for carefully selected patients, including those with sub-optimal hematologic response following initial therapy, higher plasma cell burden, lymphoplasmacytic disease, or relapsed/refractory disease. In this context, ASCT is increasingly viewed as a complementary strategy rather than a universal upfront approach.

In parallel, the therapeutic landscape continues to expand with the emergence of novel agents, many of which are adapted from advances in multiple myeloma. B-cell maturation antigen (BCMA)-targeted therapies, including chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies, have demonstrated impressive efficacy, with high overall and deep response rates in small cohorts of heavily pretreated patients [54]. In addition, venetoclax, a BCL-2 inhibitor, has shown particular activity in patients harboring t(11;14) translocation, achieving high rates of very good partial response or better [59]. These targeted approaches highlight the growing importance of biologically driven therapy in AL amyloidosis.

Overall, the treatment paradigm in AL amyloidosis is shifting toward highly effective, targeted upfront therapy aimed at rapid and profound suppression of the pathogenic plasma cell clone, with a more selective role for ASCT and an expanding repertoire of immunotherapeutic and targeted strategies that are likely to further improve outcomes in this challenging disease.

Sarah Leonard Louis (SLL) presented her experience with vacuolar myopathy with monoclonal gammopathy and stiffness (VAMMGAS), a recently described myopathy associated with IgG monoclonal gammopathy. In 2025, her group reported three patients, aged 37–60 years, who presented with a subacute limb-girdle and axial myopathy associated with muscle stiffness, significant weight loss, and an IgG kappa MP [60]. EMG revealed repetitive and continuous spontaneous activity in all patients, resembling pseudo-myotonic discharges, and myopathic motor unit potentials. CK levels were consistently elevated at 5–10 × the upper limit of normal. Deltoid muscle biopsies demonstrated a homogeneous histopathological phenotype characterized by a vacuolar myopathy with sarcoplasmic and subsarcolemmal non-rimmed vacuoles and excessive glycogen accumulation on PAS staining and EM. This was associated with necrotic myofibers at various stages, complement activation in the form of granular sarcolemmal deposits on numerous non-necrotic

muscle fibers, and autophagic lesions. All three patients experienced near-complete clinical and biochemical recovery, with normalization of serum CK levels and marked reduction or disappearance of the MP, following treatment with a combination of immunomodulatory therapies (e.g., IVIg and plasma exchange) and plasma cell-directed therapy. Although the pathophysiology of VAMMGAS remains incompletely understood, the presence of complement activation on muscle biopsy and the favorable response to immunomodulatory and MP-targeted therapies provide compelling evidence that MP is directly involved in disease pathogenesis.

While no identical cases have been reported to date, Soontrapa et al. [6] described a case of vacuolar myopathy with excessive glycogen accumulation and polyglucosan bodies, associated with POEMS syndrome and biclonal gammopathy (IgG Kappa and IgA Lambda). Soulage et al. [9] also described a case of vacuolar myopathy with glycogen storage, associated with IgG MP in a patient who developed scleromyxedema less than three years later, confirmed by skin biopsy. In the same article, the authors also reviewed 20 published cases of myopathy associated with scleromyxedema and IgG MP. Most patients presented with proximal limb and axial weakness, approximately half had dysphagia, and serum CK levels averaged 10 times the upper limit of normal. EMG showed myopathic features in the proximal muscles. In several cases, muscle biopsies revealed features very similar to those of VAMMGAS, with necrotic fibers at various stages, vacuolated fibers in 5 cases, and glycogen overload in 2 cases. These observations raise the possibility that VAMMGAS and scleromyxedema-associated myopathy may represent different manifestations within a spectrum of IgG MP-associated myopathies, distinct from SLONM-MP and AL amyloid myopathy. However, because these disorders are exceptionally rare, larger multicenter studies are needed to validate this hypothesis. To facilitate classification of this emerging group of disorders, Soontrapa et al. coined the term monoclonal gammopathy-associated glycogen storage myopathy (MGGSM) to describe a pathologically defined MGAM characterized by prominent glycogen-filled vacuoles, encompassing VAMMGAS, a subset of scleromyxedema-associated myopathy, and the vacuolar myopathy they originally described [1,6].

2. Discussion

The 294th ENMC Workshop on paraproteinemic myopathies brought together an interdisciplinary group of experts and patient representatives to identify and address gaps in the diagnosis and management of this underrecognized but treatable group of myopathies. Although the diagnosis of AL amyloid myopathy may appear relatively straightforward, it requires a high index of suspicion, particularly when Congo red staining is not incorporated into the standard histochemical panel for all muscle biopsies, an approach that we strongly encourage and support. Accurate amyloid subtyping using LC-MS/MS or immunohistochemistry is essential to identify the amyloidogenic protein and guide appropriate management.

In contrast, the diagnosis of SLONM is more complex. Following extensive discussion, the expert panel together with patient representatives established consensus diagnostic criteria as summarized in Table 1. The diagnostic criteria for SLONM distinguish between definite and possible cases based on the completeness of clinical, laboratory, and pathological features. Definite SLONM requires fulfillment of all clinical, laboratory, and muscle pathology criteria in the absence of exclusion criteria. In contrast, possible SLONM is defined by the presence of muscle weakness with rod-containing fibers on biopsy without exclusion criteria, although clinical and laboratory features may be incomplete and rods may be present in <1% of fibers.

Once a diagnosis of SLONM is established, patients should undergo mandatory testing, with prompt referral to hematology for plasma cell-directed therapy if an MP is present (SLONM-MP). Cardiopulmonary surveillance is also necessary given the risk of respiratory muscle involvement and cardiomyopathy. Table 2 summarizes the

Table 1
Diagnostic criteria for definite and possible sporadic late-onset nemaline myopathy (SLONM).

Clinical criteria	• Age ≥ 40 years. • Subacute-onset progressive weakness over 6–12 months. • Axial weakness (e.g., dropped head and/or camptocormia), proximal limb weakness, bulbar weakness and/or respiratory weakness. • Muscle wasting with or without accompanying weight loss.	Definite SLONM: All clinical, laboratory, and pathological criteria without any exclusion criteria. Possible SLONM: Muscle weakness and a muscle biopsy showing rod-containing fibers in the absence of exclusion criteria. Not all clinical and laboratory criteria may be present, and rod-containing fibers may constitute <1% of total fibers.
Laboratory criteria	• Normal or mildly elevated (< 1000 U/L or < 4 times ULN) creatine kinase levels. • Needle electromyography showing myopathic motor unit potentials with associated fibrillation potentials.^a	
Muscle pathology criteria	• Presence of rod-containing fibers ≥ 1% of total muscle fibers.^b	
Exclusion criteria	• Family history and/or genetic testing consistent with genetic nemaline myopathy. • Abnormal motor development and poor athletic performance prior to weakness onset. • Dysmorphic features (e.g. narrow high-arched palate and/or elongated face). • Decremental repetitive nerve stimulation test. • Unexplained neurogenic motor unit potentials or fasciculation potentials. • Pathological evidence of other myopathies, except for other MGAM subtypes.	

^a Needle electromyography of clinically affected muscles, especially axial muscles (see the section on electrodiagnostic study in SLONM) is critical in identifying myopathic changes.

^b In patients with a high clinical suspicion of SLONM but no obvious nemaline bodies on modified Gömöri trichrome staining, α-actinin-2 immunohistochemistry and electron microscopy may be required to identify nemaline bodies. Nemaline bodies can occur in myotendinous junctions and in various other myopathies, but are generally not a prominent finding (see the section on SLONM morphology).

recommended mandatory evaluations and ongoing surveillance in patients with SLONM.

As for VAMMGAS and MGGSM, these are relatively new entities that require broader recognition and increased awareness. Glycogen storage myopathy is often automatically attributed to genetic disorders; however, it can also occur in acquired conditions. MP studies should therefore be considered in patients with glycogen storage myopathology, particularly in those without an identified genetic cause or in those presenting with significant muscle stiffness. Treatment recommendations are constrained by the rarity of this condition. Reported cases have demonstrated responses to intravenous immunoglobulin, immunosuppressive therapies, and plasma cell-directed therapy.

3. Conclusion

The 294th ENMC International Workshop established an international consensus framework for the classification, diagnosis, and management of paraproteinemic myopathies. These disorders were recognized as a spectrum of monoclonal gammopathy-associated myopathies (MGAMs), in which early recognition and close collaboration among neurologists, hematologists, and muscle pathologists are essential to optimize patient outcomes. Clinicians should maintain a high

Table 2

Recommended testing and management for patients with SLONM.

Mandatory testing	• Monoclonal protein studies, including SPEP, SIFE, UPEP, UIFE, and sFLC. • HIV serology.
Surveillance testing	• Pulmonary evaluations: PFT, including supine and upright vital capacity, and overnight oximetry. • Cardiac evaluations: ECG, echocardiogram or cardiac MRI.
Management	
• SLONM with monoclonal protein (SLONM-MP):	• Immediate referral to a hematologist with expertise in plasma cell and amyloid diseases is recommended for plasma cell-directed therapy (e.g., autologous stem cell transplantation, chemotherapy, proteasome inhibitors, or monoclonal antibodies), accompanied by interdisciplinary case discussion. Intravenous immunoglobulin may be considered as interim therapy while awaiting initiation of plasma cell-directed therapy.
• SLONM without monoclonal protein: ^a	• Intravenous immunoglobulin may be used for up to six months with subsequent reassessment, and alternative immunosuppressive therapies may be considered if intravenous immunoglobulin is not available. Combination therapy with intravenous immunoglobulin and immunosuppressive agents may be considered early in severe cases.

^a SLONM associated with HIV is rare, and data are limited to inform treatment recommendations.

index of suspicion in adults, particularly those aged ≥ 40 years, who present with otherwise unexplained subacute proximal and/or axial weakness, normal or mildly elevated serum CK, dysphagia, weight loss, systemic features, or neuropathy, and should routinely screen for an MP, using SPEP, SIFE, UPEP, UIFE, and sFLC. The workshop emphasized that distinguishing incidental MGUS from monoclonal gammopathy of muscle significance (MGMS) requires careful clinicopathologic correlation rather than reliance on MP burden alone. In patients with unexplained myopathy and an MP, muscle biopsy should routinely include modified Gömöri trichrome, PAS, and Congo red staining with amyloid typing—preferably by mass spectrometry when available—if amyloid is identified.

Consensus recommendations were developed for the diagnosis and treatment of SLONM and AL amyloid myopathy, while emerging entities such as VAMMGAS and MGGSM were recognized as expanding the spectrum of MGAMs. The workshop also endorsed the term SLONM-MP in place of SLONM-MGUS, reflecting the pathogenic role of the MP in this disorder. Given the potential for irreversible disability, plasma cell-directed therapy should be initiated promptly and aim for a rapid, deep hematologic response, ideally a complete hematologic response when feasible, with multidisciplinary reassessment and treatment escalation when early response is inadequate or clinical progression occurs. Although daratumumab-based regimens have largely replaced upfront ASCT in AL amyloid myopathy, their role in SLONM-MP remains undefined and warrants further investigation. Future international collaborative studies are needed to validate the proposed diagnostic criteria, refine disease classification, elucidate disease mechanisms, and optimize treatment strategies for these rare but increasingly treatable disorders.

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CRediT authorship contribution statement

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Declaration of competing interest

None of the authors have any conflicts of interest to declare for this report.

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Supplementary materials

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