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【 CASE REPORT 】

Sporadic Late-Onset Nemaline Myopathy Associated with Multiple Myeloma: A Case Report

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Abstract:

Sporadic late-onset nemaline myopathy (SLONM) is a rare, acquired myopathy that is frequently associated with monoclonal gammopathy, most commonly monoclonal gammopathy of undetermined significance (MGUS). However, its association with overt multiple myeloma (MM) has been rarely reported. We present a case of SLONM associated with MM in which chemotherapy targeting the underlying MM led to mild-to-moderate improvement in muscle symptoms. This case underscores the potential pathogenic role of MM in SLONM and highlights the importance of treating underlying hematologic malignancies.

Key words: SLONM, multiple myeloma, muscle biopsy, monoclonal gammopathy, intravenous immunoglobulin, daratumumab

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Introduction

Sporadic late-onset nemaline myopathy (SLONM) is a rare acquired myopathy that predominantly affects adults aged >50 years (1, 2). It is characterized by subacute progressive proximal muscle weakness and nemaline rod-like structures in muscle fibers. SLONM is most frequently associated with monoclonal gammopathy of undetermined significance (MGUS) and rarely associated with multiple myeloma (MM) (3, 4). Although its pathogenesis remains unclear, paraproteins or other immune factors related to plasma cells are hypothesized to play a causal role (1, 2, 4-6). We herein present a case of SLONM associated with MM in which chemotherapy led to clinical improvement, suggesting a pathophysiological link between MM and SLONM.

Case Report

A 51-year-old woman presented with a five-year history of progressive proximal muscle weakness and an unintentional weight loss of 10 kg. She reported difficulty climbing stairs and rising from a seated position, but denied any sensory disturbances. The patient's medical history was unremarkable.

On physical examination, the patient exhibited a dropped head and marked atrophy of the proximal muscles in both the upper and lower extremities. Muscle strength was graded as 3/5 in the proximal muscles and 5/5 in the distal muscles, according to the Medical Research Council (MRC) scale. Because of periscapular muscle weakness, the shoulder girdle function was substantially impaired. In addition, prominent weakness of the truncal and hip girdle muscles caused difficulty in standing up. The patient did not exhibit dysphagia, dysarthria, facial weakness, or ptosis. Fasciculations or sensory deficits were not observed.

Laboratory investigations revealed normal levels of serum creatine kinase (35 U/L), albumin (4.1 g/dL), hemoglobin (15.5 g/dL), estimated glomerular filtration rate (eGFR, 195.4 mL/min/1.73 m^2), calcium (9.4 mg/dL), and increased NT-ProBNP (770 pg/mL). In addition, representative myositis-related autoantibodies, including anti-Jo-1, anti-ARS, anti-MDA5, anti-Mi-2, anti-TIF-1, anti-SRP, anti-

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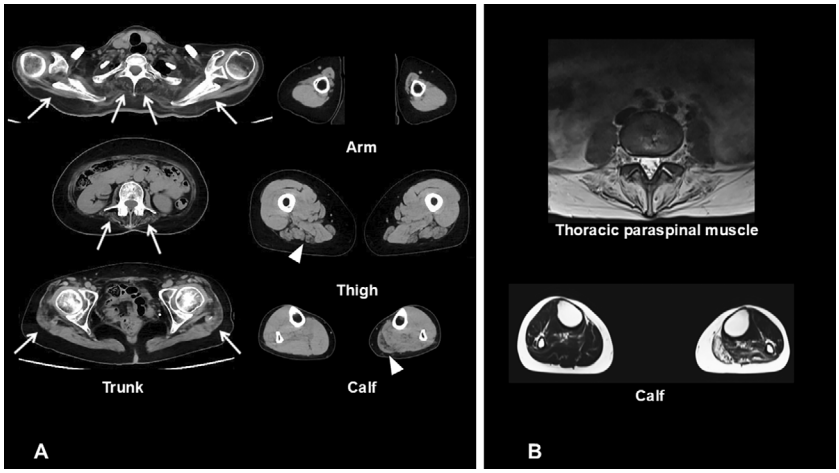

Figure 1. **Muscle imaging. (A) Muscle CT scans show diffuse atrophy and fatty replacement of skeletal muscles. These changes are most prominent in the paraspinal and limb girdle muscles, including the periscapular and gluteal regions (arrows). Asymmetric involvement is also observed in the hamstrings and gastrocnemius (triangles). (B) Axial T2-weighted MRI shows fatty replacement and asymmetric changes in the thoracic paraspinal and calf muscles.**

HMGCR, and anti-mitochondrial M2 antibodies, were negative. Serum protein electrophoresis demonstrated an M-protein spike, and immunofixation identified IgG-κ monoclonal gammopathy accompanied by suppressed IgA and IgM levels. A free light chain (FLC) analysis revealed elevated κ chains (357 mg/L), suppressed λ chains (5.4 mg/L), and a κ/λ ratio of 66.09. A bone marrow biopsy showed 14% clonal plasma cell infiltration, fulfilling the diagnostic criteria for smoldering multiple myeloma in the absence of CRAB features. Cardiac echocardiography revealed a reduced ejection fraction (35%) with diffuse hypokinesis, consistent with cardiomyopathy. Cardiac MRI was not performed because severe respiratory impairment made breath holding in the supine position difficult. Electromyography of the deltoid muscle, biceps brachii, tibialis anterior, and vastus lateralis revealed fibrillation potentials and positive sharp waves at rest. Upon voluntary contraction, recruitment patterns were normal, but motor unit potentials were low-amplitude, thin, and polyphasic, suggesting a myopathic pattern. Routine nerve conduction studies of the right median, ulnar, tibial, fibular, and sural nerves revealed no abnormalities. Muscle imaging demonstrated diffuse atrophy and fatty replacement, most prominently in the paraspinal and limb girdle muscles (Fig. 1). Respiratory function testing showed markedly decreased vital capacity (%VC, 40.0).

A muscle biopsy of the biceps brachii revealed nonspecific chronic myopathic changes. Importantly, there were no typical findings of idiopathic inflammatory myopathies, such as prominent inflammatory cell infiltration or abundant necrotic and regenerating fibers. Given the presence of monoclonal gammopathy and smoldering MM, SLONM was tentatively diagnosed. Two courses of intravenous immunoglobulin (IVIg, 0.4 g/kg/day for 5 consecutive days each) were administered. Additionally, standard therapies for heart failure, including sacubitril/valsartan (100 mg), bisoprolol (0.625 mg), and dapagliflozin (10 mg), were introduced. While improvement in heart failure was observed, with an increase in ejection fraction to 67%, muscle weakness and respiratory dysfunction gradually worsened (%VC of 26.9) over the following months. Examination of a second muscle biopsy specimen obtained from the tibialis anterior muscle revealed chronic myopathic changes with fiber size variation, clustered nuclear aggregation, interstitial fibrosis, and fatty infiltration. Modified Gomori trichrome staining revealed small reddish-purple granular deposits within the atrophic myofibers, consistent with nemaline bodies. Such fibers were not abundant, but occurred sporadically within chronic myopathic changes, a pattern that has been described in previous reports of SLONM (Fig. 2) (1, 4, 6, 7). Based on these clinical, hematological, and pathological findings, the diagnosis of SLONM was confirmed.

The patient underwent induction chemotherapy using the daratumumab-lenalidomide-dexamethasone (DRd) protocol: daratumumab (16 mg/kg on days 1, 8, 15, and 22), lenalidomide (25 mg daily on days 1-21), and dexamethasone (20 mg on days 1, 2, 8, 9, 22, and 23). Over the following months, the patient's hematological markers such as serum FLC κ levels, proximal muscle strength, and respiratory function gradually improved. Approximately one year later, immunofixation and a bone marrow analysis confirmed a complete response, with MRC grades improving from 3 to 4 and %VC reaching 36.0. The clinical course of the patient is summarized in Fig. 3.

Discussion

Owing to its rarity, there are currently no established diagnostic criteria for SLONM. In our case, the diagnosis was based on a combination of clinical, hematological, and pathological findings. Given the adult onset, progressive

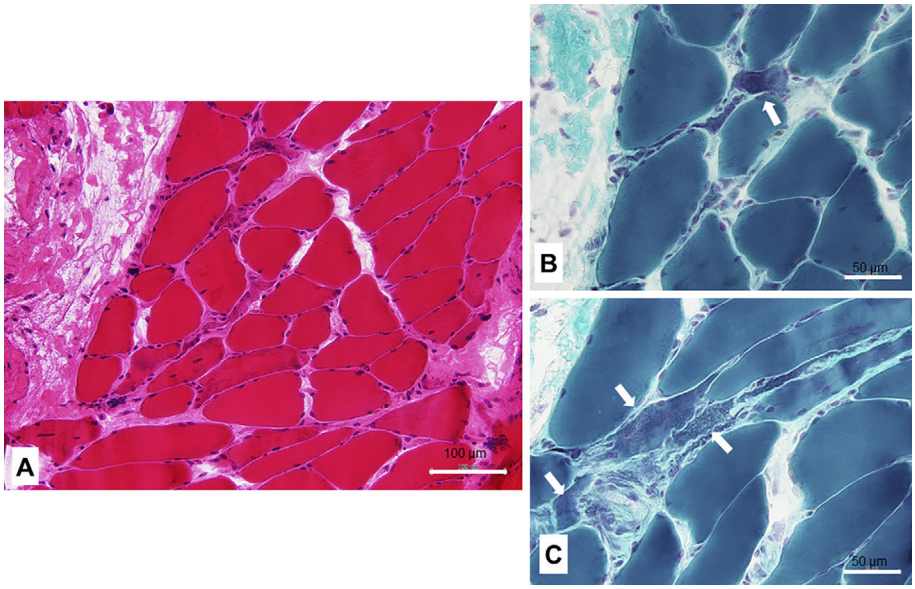

Figure 2. **Muscle pathology. Hematoxylin and Eosin staining shows chronic myopathic changes, including fiber size variation, clustered nuclear aggregation, interstitial fibrosis, and fatty infiltration. Scale bar=100 μm. (B, C) Modified Gomori trichrome staining showing fine granular structures. Aggregation within atrophic fibers at different sites (arrows). Scale bar=50 μm.**

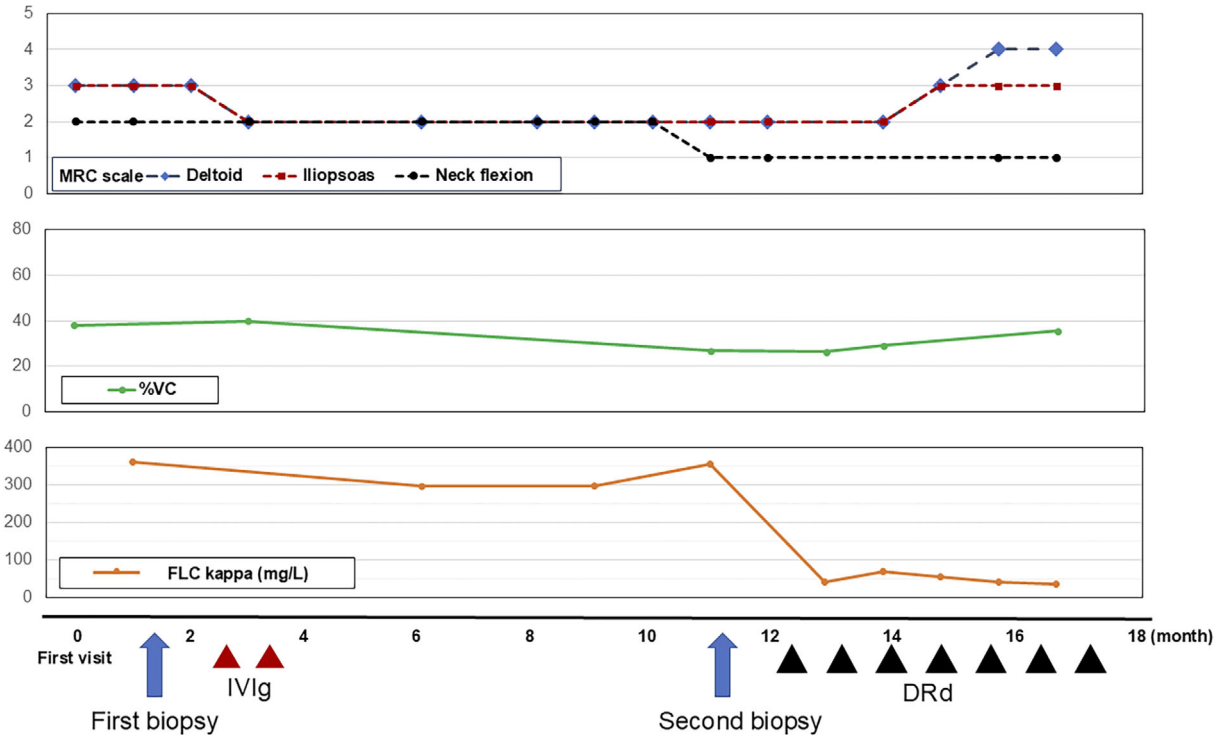

Figure 3. **Clinical course of the patient. Upper panel: manual muscle testing (MRC scale) of the deltoid, iliopsoas, and neck flexion. Middle panel: Vital capacity (%VC). Lower panel: serum-free light chain (FLC) κ levels (mg/L). Blue arrows indicate the timing of muscle biopsy; red triangles indicate the timing of intravenous immunoglobulin (IVIg, 400 mg/kg for 5 consecutive days); and black triangles indicate the timing of daratumumab (16 mg/kg, days 1, 8, 15, and 22), lenalidomide (25 mg/day, days 1-21) and dexamethasone (20 mg/day; days 1, 2, 8, 9, 22, and 23; DRd regimen).**

course, and presence of monoclonal gammopathy, congenital nemaline myopathy was considered unlikely, and genetic testing for congenital NM-related genes was not pursued (8, 9).

The patient presented with slowly progressive proximal and respiratory muscle weakness, accompanied by monoclo-

nal gammopathy-hallmark features of SLONM. However, the initial muscle biopsy failed to reveal definitive findings and delayed the diagnosis. This reflects a broader challenge in SLONM, particularly in atypical cases in which classical nemaline rods are absent or inconspicuous. While nemaline rods are considered a pathological hallmark, their morphology in SLONM often differs from that observed in congenital forms. Instead of thick, thread-like rods, SLONM typically shows small, granular, or "sand-like," inclusions, which may not be detectable by light microscopy (1, 4, 6). Moreover, the reported frequency of fibers containing nemaline bodies varies widely from approximately 1% to 63% among patients (4). In such cases, repeat biopsy may be necessary, as in our patient. Although α-actinin immunostaining and electron microscopy were not performed in this case, they have been useful in confirming nemaline bodies and Z-band degeneration in previous reports, and may assist in challenging diagnoses (1, 2, 4, 6, 10).

SLONM is most commonly associated with MGUS, whereas its association with MM is extremely rare. To the best of our knowledge, only one detailed case has been reported to date (3). Although the exact pathogenesis of SLONM remains unclear, monoclonal proteins have been hypothesized to induce myopathy through immune-mediated mechanisms, such as targeting sarcomeric proteins (e.g., α-actinin), deposition-related myotoxicity, or humoral mediators secreted by clonal plasma cells (1, 4, 6). In a previously reported case of SLONM associated with MM, myopathy developed following allogeneic hematopoietic stem cell transplantation (allo-HSCT), suggesting that exposure to alloantigens or post-transplant immune activation played a role (3). In contrast, our patient responded to chemotherapy for MM without undergoing allo-HSCT, suggesting that SLONM in this context may arise through mechanisms similar to MGUS-associated cases, supporting a direct pathogenic link between the underlying hematologic disorder and muscle pathology.

The apparent predominance of SLONM-MGUS over SLONM-MM may be partly explained by the natural course of the disease. SLONM often develops during MGUS, which precedes overt MM. Current evidence suggests that MGUS alone can cause clinically significant SLONM. In our patient, the slow progressive course of myopathy may reflect the period during which the underlying gammopathy evolved from MGUS to smoldering MM. Thus, the rarity of SLONM-MM may reflect the time lag between the onset of SLONM and recognition of the underlying hematologic disorder.

However, the efficacy of IVIg in SLONM remains controversial. While some studies have reported transient or partial clinical improvement (1, 7), others have found little to no benefit (2), highlighting the heterogeneity of the disease pathogenesis and the likely need for plasma cell-directed therapies. Notably, in our patient, cardiomyopathy improved after the administration of IVIg. Although IVIg may have contributed to this improvement, concomitant standard heart failure therapy is also likely an important factor. Previous reports of SLONM with cardiomyopathy have generally attributed recovery of cardiac function to standard heart failure therapy or to treatment directed at gammopathy, such as chemotherapy or autologous stem cell transplantation (1, 7, 11). To our knowledge, no reports have documented cardiac improvement following IVIg alone. Further studies are warranted to clarify its potential role in SLONM-associated cardiomyopathy.

To our knowledge, this case offers a unique therapeutic perspective, representing the first reported use of DRd therapy in a patient with SLONM. Given the risk of neurotoxicity from proteasome inhibitors and severe respiratory dysfunction, DRd was selected as a safe and well-tolerated alternative. This regimen is widely used as first-line therapy in elderly or transplant-ineligible patients with MM and is considered appropriate for our case.

Importantly, our patient had smoldering MM, which typically does not warrant immediate treatment in the absence of myeloma-defining events (MDEs) such as those outlined in the CRAB or SLiM criteria (12). However, the progression of neuromuscular decline due to SLONM necessitates therapeutic intervention. Although our patient did not meet the conventional MDE criteria, SLONM may represent a form of end-organ damage attributable to plasma cell dyscrasia. Whether SLONM should be recognized as an MDE remains an open question that requires further accumulation of cases and clinical consensus.

Following chemotherapy, the patient achieved a complete hematologic response with concurrent improvements in muscle strength and respiratory function. This outcome highlights the potential utility of plasma cell-targeted therapies such as DRd in treating SLONM-MM and underscores the need for early recognition and treatment, even in the absence of classic myeloma-defining features.

The authors state that they have no Conflict of Interest (COI).

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DISCLOSURES

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STATEMENT OF AUTHORSHIP

Y. Furukawa, K. Hokkoku, Y. Hatanaka, and R. Shirasaki were involved in the patient treatment.

A. Kubota and J. Shimizu contributed to the pathological assessment.

Y. Furukawa, K. Hokkoku, Y Hagiwara, R Shirasaki, and S. Kobayashi conceptualized, reviewed, and wrote the manuscript.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from the patient for this case report.

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