CASE REPORT

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A case of sporadic late-onset nemaline myopathy with monoclonal gammopathy of undetermined significance: long-term observation of neurological symptoms after autologous stem-cell transplantation

Takashi Ando[1], Takahiko Sato[2], Shingo Kurahashi[2], Yuka Kawaguchi[2], Yusuke Kagaya[2], Yukiyasu Ozawa[2], Satoko Hirano[1,3], Yoji Goto[3], Kazuo Mano[3], Satoshi Yokoi[1], Tomohiko Nakamura[1], Ayuka Murakami[1,4], Seiya Noda[1,4], Seigo Kimura[1,4], Jun Sone[1,4], Satoshi Kuru[4], Gen Sobue[5] and Masahisa Katsuno[1]

[1]*Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*
[3]*Department of Neurology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*
[4]*Department of Neurology, National Hospital Organization Suzuka National Hospital, Suzuka, Japan*
[5]*Brain and Mind Research Center, Nagoya University, Nagoya, Japan*

ABSTRACT

A 47-year-old woman presented with progressive limb weakness. A neurological examination revealed proximal dominant symmetrical muscle weakness in her limbs, and electromyography revealed complex repetitive discharges and short motor unit potentials with positive sharp waves in the biceps. We observed early recruitment in the quadriceps, and laboratory tests revealed normal creatine kinase. Serum protein electrophoresis showed monoclonal IgG-lambda, but the bone marrow aspiration specimen was normal. A muscle biopsy revealed nemaline rod accumulations in the muscle fibers; based on the results, we diagnosed the patient with sporadic late-onset nemaline myopathy with monoclonal gammopathy of undetermined significance (SLONM-MGUS). We administered repeated intravenous immunoglobulin, but her limb weakness continued, and she developed a restrictive ventilatory defect. The patient received melphalan, followed by autologous stem-cell transplantation (ASCT). Her upper extremity strength and respiratory capability improved within one year after ASCT; however, it was not until six years after ASCT that her atrophied lower extremities strengthened. A discrepancy in the timeline of treatment response between the upper or respiratory muscles and the atrophied lower limb was characteristic in the patient, suggesting that the efficacy of ASCT on SLONM-MGUS should be evaluated in the long term, especially in severely atrophied muscles. In addition, this case showed that ASCT for SLOMN-MGUS is an effective treatment option in Asian populations.

Keywords: sporadic late-onset nemaline myopathy, monoclonal gammopathy, intravenous immunoglobulin, autologous stem-cell transplantation

Abbreviations:
ASCT: autologous stem-cell transplantation
CK: creatine kinase
FVC: forced vital capacity

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Corresponding Author: Masahisa Katsuno, MD, PhD
Department of Neurology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550 Japan
Tel: +81-52-744-2385, E-mail: ka2no@med.nagoya-u.ac.jp

IVIG: intravenous immunoglobulin
MGUS: monoclonal gammopathy of undetermined significance
SLONM: sporadic late-onset nemaline myopathy

INTRODUCTION

Nemaline myopathy affects the muscles and is characterized by nemaline rods in skeletal muscle fibers.[1] It is classified into six subtypes according to clinical phenotypes and age of onset: severe congenital, Amish, intermediate congenital, typical congenital, childhood-onset, and adult-onset.[2,3] The sporadic late-onset nemaline myopathy (SLONM) is rare and considered distinct from the congenital and child-onset forms. Many cases of SLONM occur after age 40 without the patient having any genetic predisposition.[2,4,5] SLONM can be associated with monoclonal gammopathy of undetermined significance (MGUS) or HIV infection.[6,7] SLONM can occur, although rarely, as a comorbidly with conditions such as thyroid dysfunction, systemic lupus erythematosus, primary Sjögren's syndrome, and multiple myeloma.[8-11] These observations suggest that immune dysregulation may underlie the pathogenesis of SLONM, but the actual mechanisms remain unknown.[12]

Common clinical symptoms of SLONM include subacute limb weakness, myalgia, dysphagia, respiratory symptoms, head drop, and camptocormia.[4,13] Due to the respiratory failure that often occurs, the prognosis of SLONM is poor.[14] Intravenous immunoglobulin (IVIG) and hematological therapies have been reported to be effective for SLONM with MGUS (SLONM-MGUS).[15-17] A therapeutic option for IVIG-resistant SLONM-MGUS is autologous stem-cell transplantation (ASCT), which improves the patient's functionality and can promote long-term survival. However, patients might not see some of the beneficial effects of ASCT until many years after the treatment.[13,18] Here, we report the long-term follow-up of a female with IVIG-resistant SLONM-MGUS treated with ASCT, and we present a detailed timeline of the patient's clinical symptoms as evaluated before and after treatment.

CASE PRESENTATION

A 47-year-old woman presented with progressive limb weakness. She did not have a notable medical history nor scoliosis. Her parents were non-consanguineous, and there was no family history of neuromuscular disorders. Twelve months before her consultation, the patient had noticed weakness in her lower extremities and difficulty rising from a squatting position or walking up stairs. The weakness had gradually spread to her upper extremities four months before presentation, and she could not hang laundry; simultaneously, she felt shortness of breath while walking.

The initial physical examination showed her height to be 155 cm and body weight 42.5 kg (she lost 4.5 kg after symptom onset). The neurological examination revealed proximal dominant symmetrical muscle weakness in her limbs (shoulder abduction and hip flexion were grade 2; extension and flexion of elbow and knee were both approximately grade 4 on the Medical Research Council scale). We found normal facial appearance, cranial nerves, sensory function, tendon reflexes, plantar reflex, and motor coordination. No fasciculations were observed. A nerve conduction study yielded normal results, and electromyography revealed complex repetitive discharges and short motor unit potentials with positive sharp waves in the biceps. We also observed early recruitment in the quadriceps. In the pulmonary function test, her forced vital

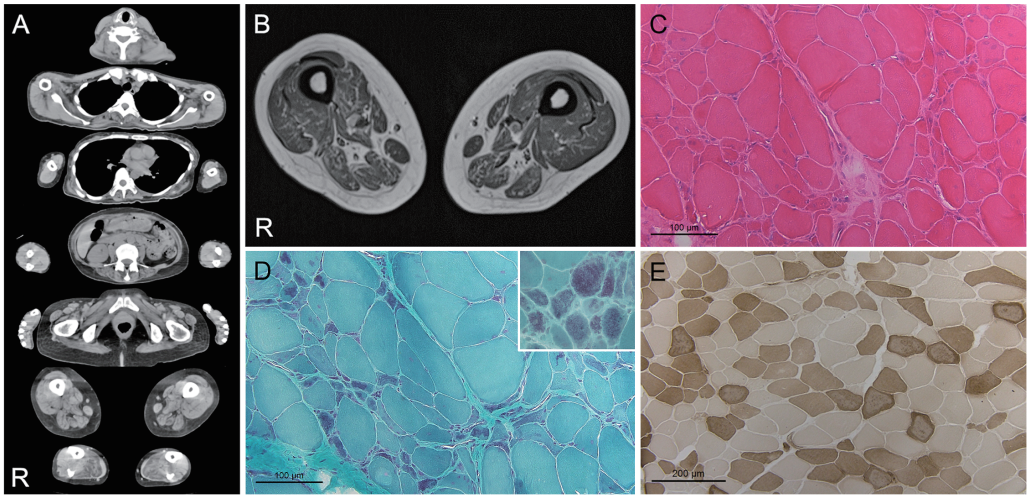

Fig. 1 Imaging and pathological findings of muscles

Fig. 1A: Severe atrophy and fatty replacement including the subscapularis, paraspinal muscles, obturator, gluteus, sartorius, quadriceps femoris, hamstring, and soleus muscles under muscular CT.

Fig. 1B: T1-weighted MRI.

Fig. 1C: Left biceps muscle biopsy shows atrophic fibers and fiber size variation with hematoxylin and eosin staining.

Fig. 1D: Modified Gömöri trichrome staining demonstrates accumulations of nemaline rods in atrophied muscle fibers, while intranuclear rods are not observed.

Fig. 1E: ATPase staining shows the normal distribution of type 1 and type 2 fibers.

capacity was slightly decreased (2.23 L, 84.3% of the predicted value) (Table 1). Laboratory examination results revealed normal serum creatine kinase (CK) (119 U/L; normal, 50–200 U/L), low serum creatinine (0.30 mg/dL; normal, 0.5–0.8 U/L), and normal thyroid function. HIV antibody and autoantibodies were negative. Serum protein immunoelectrophoresis revealed monoclonal gammopathy of IgG-lambda. Muscular CT and MRI both showed bilateral atrophy and fatty replacement in the muscles of the trunk and limbs. Severe atrophy was seen in the muscles of the pelvis, hip, thigh, and posterior crus (Figure 1A and B). Bone marrow aspiration specimens revealed normal hematopoiesis without proliferation of the clonal plasma cells. There were no apparent tumors, hypercalcemia, renal failure, anemia, or bone disease features of myeloma. Nemaline rod accumulations were found in the fibers of the left biceps muscle during biopsy (Figure 1C–E). Mononuclear cell infiltrates, muscle fiber necrosis, and endomysial fibrosis were not observed. Based on these findings, we diagnosed the patient as having SLONM-MGUS.

We administered four cycles of IVIG (400 mg/kg/day for five days) but obtained only transient improvement of muscle strength. Her limb weakness and dyspnea gradually worsened despite the IVIG, and she lost the ability to walk. A repeat pulmonary function test showed decreased forced vital capacity (FVC) consistent with a restrictive ventilatory defect (Table 1). Since her SLONM was found to be IVIG-resistant, we adopted ASCT. The treatment was approved by the Ethics Review Committee of the Japanese Red Cross Nagoya Daiichi Hospital. Before ASCT, granulocyte colony-stimulating factor-mobilized peripheral blood stem cells were harvested and cryopreserved. The patient was administered 140 mg/m^2 of melphalan as a conditioning agent, and 2.66 × 10^6/kg of CD34 positive cells were infused.

Her FVC decreased slightly during the two months after ASCT, but then her symptoms gradu-

ally improved. She recovered upper extremity muscle strength and respiratory function within one year after ASCT. In addition, she had a bodyweight gain and an improvement of symptoms that was synchronous with a gradual increase in serum CK and creatinine levels. The weakness in her atrophied proximal lower extremities was still persistent five years after ASCT. By six years, however, the muscle strength of the lower extremities notably recovered after continued rehabilitation (Table 2). Repeated muscular CT revealed no change in the muscle mass of the lower extremities, and monoclonal gammopathy of IgG-lambda was detected in serum protein immunoelectrophoresis. Finally, the patient was able to easily walk without aid and resumed all the activities of daily living.

Table 1 Temporal changes of muscle strength and laboratory test results in the patient

	0 months (presentation)	6 m	12 m	17 m (just before ASCT)	19 m (2 m after ASCT)	20 m	22 m
Body weight, kg	42.5	41.0	41.7	39.8	39.4	NT	44.0
Grip strength, kg							
Right	17	20	14	NT	11	14	17
Left	22	20	15	NT	15	15	16
MRC scale							
Shoulder abduction	2	2	2	NT	2	3	3
Hip flexion	2	2	2	NT	2	2	2
Pulmonary function test							
FVC, L	2.23	2.08	1.80	1.84	1.61	NT	1.84
Ratio of FVC to predicted value, %	84.3	79.2	69.1	70.5	61.7	NT	70.5
FEV_1, L	2.06	1.82	1.59	1.65	1.47	NT	1.61
CK, U/L	119	69	75	71	46	115	141
Creatinine, mg/dL	0.30	0.27	0.24	0.28	0.29	0.29	0.30

ASCT: autologous stem-cell transplantation
MRC: Medical Research Council
FVC: forced vital capacity
FEV_1: forced expiratory volume in one second
CK: creatine kinase
NT: not tested

Table 2 Long-term observation of muscle strength and laboratory test results in the patient after autologous stem-cell transplantation

	25 months after presentation (8 m after ASCT)	28 m	36 m	51 m	64 m	77 m	92 m (75 m after ASCT)
Body weight, kg	45.0	45.0	47.0	47.0	49.0	49.0	50.0
Grip strength, kg							
Right	17	21	18	21	23	24	22
Left	18	21	19	21	24	22	23
MRC scale							
Shoulder abduction	3	4	4	NT	4	4	4
Hip flexion	2	2	2	NT	2	2	4
Pulmonary function test							
FVC, L	2.19	2.42	2.39	2.53	2.51	2.53	2.56
Ratio of FVC to predicted value, %	84.6	93.6	92.3	98.8	98.0	100.8	102.0
FEV_1, L	1.96	2.15	2.07	2.15	2.10	2.06	2.01
CK, U/L	159	200	188	176	219	193	208
Creatinine, mg/dL	0.38	0.38	0.35	0.38	0.46	0.46	0.47

ASCT: autologous stem-cell transplantation
MRC: Medical Research Council
FVC: forced vital capacity
FEV_1: forced expiratory volume in one second
CK: creatine kinase
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DISCUSSION

Our patient's case suggests important clinical practice strategies for SLONM-MGUS. First, the final therapeutic efficacy of ASCT on SLONM-MGUS can only be judged after a long observation period of five years or more. At two months after ASCT, there had been no change in our patient's muscle weakness and restrictive ventilatory defect, but her FVC and the strength of her upper extremities gradually improved in the following months. After receiving ASCT, most patients continue to experience post-transplant clinical deterioration, and the neurologic response to therapies can take several months.[13,19] However, it took another six years for a gradual improvement in the weakness of her proximal lower extremities. This discrepancy in recovery times between upper limbs and respiratory muscles and atrophied lower limbs is characteristic in the patient. Several studies have reported the long-term prognosis of patients who underwent ASCT for SLONM-MGUS, but, in most cases, the treatment response was determined within five years after ASCT.[13,17,18] More study is needed about the long-term therapeutic efficacy of ASCT, especially in severely atrophied muscles.

Second, ASCT for SLOMN-MGUS is an effective treatment option in Asian populations. The actual prevalence rate of SLOMN-MGUS is not well understood, and there are only few case reports of SLOMN-MGUS from Asian countries.[20-22] Although another case of SLOMN-MGUS

treated with ASCT has been reported from Japan, the patient's respiratory muscle paralysis remained, and the patient's muscle strength gradually decreased again two years after ASCT.[20] Our patient showed good long-term prognosis after ASCT.

Elevated serum CK is a common sign of myopathy, although serum CK is usually normal in patients with SLONM.[4,13] Clinicians should suspect SLONM based on the clinical findings, even if serum CK is normal. Our patient's serum CK level was relatively low before ASCT, but it increased as her muscle strength improved, as did her creatinine (Table 2). We consider that the changes in serum CK and creatinine may reflect improvements in nemaline myopathy pathology, although further study is required; many factors affect serum CK and creatinine.[23,24]

CONCLUSION

We have presented a female patient with IVIG-resistant SLONM-MGUS who was treated with ASCT and followed for over six years. Her upper extremity weakness and restrictive ventilatory defect improved within one year after ASCT; however, it was six years before she recovered strength in her atrophied lower extremities. Her case shows a characteristic clinical course for SLONM-MGUS treated with ASCT: a patient's upper extremities and respiratory muscles can recover quickly while the muscle strength of the atrophied lower limbs does not improve until several years later; therefore, the efficacy of ASCT to treat SLONM-MGUS should be evaluated over the long term, especially in severely atrophied muscles. In addition, this case shows that ASCT for SLOMN-MGUS is an effective treatment option in Asian populations.

CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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