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CASE REPORT

Refractory Severe Anti-SRP Myopathy that Improved with Long-term Rehabilitation Therapy: A Case Report

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Background: Immune-mediated necrotizing myopathy (IMNM) is a type of autoimmune myositis. Anti-signal recognition particle (SRP) antibodies are highly specific to this disease. **Case:** A 76-year-old woman presented with a 4-month history of acute progressive limb muscle weakness and dysphagia. Blood examination revealed significantly elevated creatine kinase (CK) (3472 U/L) and SRP antibody positivity. The patient was near-bedridden and required alternative nutrition. She was treated with oral prednisolone and intravenous immunoglobulin. Rehabilitation therapy was initiated after confirming the decline in CK levels. She started with exercises on the bed and exercise load was gradually increased. Videofluoroscopic swallowing study showed severely weakened pharyngeal contractions and aspiration. Her symptoms improved slowly. She started transferring to a wheelchair after 2 months, gait training using parallel bars after 4 months, and was administered a paste diet once a day after 5 months. Rituximab was administered as additional treatment. Thereafter, the patient started gait training with a walker. The oral paste diet was increased to three times per day after 7 months, and a regular diet was adopted after 9 months. After 11 months, she was discharged home after achieving modified near independence in all activities of daily living. **Discussion**: Low-intensity rehabilitation therapies were initiated under the supervision of therapists with regular follow-up and progression of exercise intensity based on multidisciplinary team discussions. If CK levels indicate that the disease has stabilized, early intervention in rehabilitation is important to prevent declining physical function.

Key Words: anti-SRP antibody; dysphagia; immune-mediated necrotizing myopathy; severe muscle weakness

INTRODUCTION

Inflammatory myopathies were divided into two subtypes, polymyositis (PM) and dermatomyositis (DM), according to the presence of typical skin lesions and common histopathology by Bohan and Peter as early as 1975.[1)] Immune-mediated necrotizing myopathy (IMNM) has been recognized as a category of idiopathic inflammatory myopathy characterized by necrosis and regeneration in the absence of prominent inflammatory cells pathologically.[2)] At present, IMNM is regarded as a different subtype from PM and DM. Patients with IMNM often present with acute or subacute, moderately severe, symmetrical muscle weakness and markedly elevated serum creatine kinase (CK) levels, usually higher than 1000 U/L.[2–6)] In addition, severe dysphagia is frequently found in these patients.[7–10)] Autoantibodies against signal recognition particles (SRP) or 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have been identified as IMNM-specific autoantibodies. Anti-SRP autoantibodies are reported in 5%–6% of all inflammatory myopathies.[11,12)] Among patients with IMNM, 26% have anti-HMGCR antibodies and 39% have anti-SRP antibodies.[2,7)] The SRP guides newly synthesized polypeptides to the endoplasmic reticulum for posttranslational modifications.[13)] *In vitro*, purified anti-SRP

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antibodies induce muscle fiber atrophy and an associated increase in MAFbx and Trim63, which are considered to be markers of atrophy. In addition, the presence of these antibodies can impair muscle regeneration because of a defect in myoblast fusion.[14] Severe limb and neck muscle weakness, dysphagia, respiratory insufficiency, and muscle atrophy were more frequently observed in patients with anti-SRP antibodies than in those with anti-HMGCR antibodies.[2,7] For treatment for IMNM, steroids alone are often insufficient, and immunosuppressive drugs and intravenous immunoglobulin (IVIg) are often used in combination.[2,7,15,16] IMNM differs from PM in terms of high CK levels, severe dysphagia, autoantibodies, pathologic changes, and treatment response.[2–10,15,16]

Historically, patients with idiopathic inflammatory myopathies were discouraged from physical exercise because of concerns regarding increased muscle inflammation.[17] However, subsequent emerging evidence suggests that exercises can improve muscle strength and performance, functional and aerobic capacity, and clinical disease status in patients.[18–22] In addition, swallowing training supervised by a speech therapist is an indispensable element of patient care for dysphagia in inflammatory myopathies.[23] A few studies on rehabilitation in patients with anti-SRP myopathy have been reported.[10,24,25] Some patients present with severe muscle weakness and dysphagia,[10] whereas others are ambulatory from the beginning of rehabilitation.[24,25] Herein, we describe rehabilitation therapy for a refractory case of anti-SRP myopathy accompanied by severe muscle weakness and dysphagia.

CASE

A 76-year-old woman with a medical history of osteoporosis presented with a 4-month history of acute progressive proximal limb muscle weakness and dysphagia. A physical examination revealed the following Medical Research Council (MRC) strength (right/left): neck flexion 2−, shoulder abduction 2−/2−, elbow flexion 3+/3+, elbow extension 3/3, wrist flexion 3+/3+, wrist extension 3/3, finger extension 3/3, hip flexion 2/2, knee flexion 2/2, knee extension 2/2, ankle flexion 4/4, and ankle extension 4/4. Atrophy of the proximal limb muscles was observed. The reflexes were reduced in both the upper and lower extremities with down-going plantar responses. She presented with a wet voice, difficulty swallowing saliva, and required alternative nutrition. Elevation of the soft palate was insufficient with no laterality. Touching the soft palate with a tongue depressor did not induce a gag reflex. Little laryngeal elevation was observed. The maximum phonation time (MPT) was 6 s with hypernasal speech. Sensory and autonomic abnormalities and cranial nerves other than swallowing were normal. Her Functional Independence Measure (FIM) score was 41 points.

Laboratory tests revealed elevated CK level (3472 U/L), the presence of myocardial markers, and myositis-specific anti-SRP antibody positivity. Electromyography (EMG) revealed short-duration, low-amplitude motor unit potentials, and fibrillation potentials in the biceps brachii and quadriceps muscles. Magnetic resonance imaging of the skeletal muscle showed high signal intensity for the proximal limb and gluteus muscles on short-tau inversion recovery, as shown in **Fig. 1**. Electrocardiography showed a negative T wave in V1–V3, and echocardiography showed no abnormalities. Further examination did not reveal the presence of an underlying tumor. She was diagnosed with anti-SRP-IMNM according to the new European Neuromuscular Centre criteria.[2] In cases with a typical clinical presentation, where autoantibodies to HMGCR or SRP are found, a muscle biopsy is not necessary to reach the final diagnosis.[2] The time course of rehabilitative treatment is shown in **Fig. 2**, and the time course of the FIM scores is shown in **Table 1**.

The patient was initially treated with oral prednisolone (60 mg/day) from day 4 and tapered, as shown in **Fig. 2**. Speech language hearing therapists (SLHT) started with indirect swallowing training including oral organ exercises, oral icing, and free conversation from day 3. The patient's serum CK level declined to 564 U/L on day 20; however, her muscle weakness and dysphagia did not improve. She developed septic shock from a urinary tract infection on day 27 and received IVIg (0.4 mg/kg per day) for 5 days. To prevent disuse and relieve shoulder and hip joint range-of-motion (ROM) limitations, physical and occupational therapy was started, paying attention to changes in myogenic enzymes from day 29. The patient performed ROM exercises, automatic-assisted movement, cervical relaxation, and stretching. Improvements were noted in her ability to swallow saliva and elevate the larynx. Direct training with thick water, exhalation training with tissue paper, and tongue resistance exercises were also performed. Her serum CK level declined to 318 U/L on day 37, and training to sit on the edge of the bed was performed from day 40. The patient was transferred to a wheelchair from day 52.

A videofluoroscopic swallowing study (VFSS) on day 86 showed delayed swallow reflex, pyriform sinus residue, and some laryngeal penetration and aspiration, as shown in **Fig. 3**. Sliced jelly and thick water partially passed through

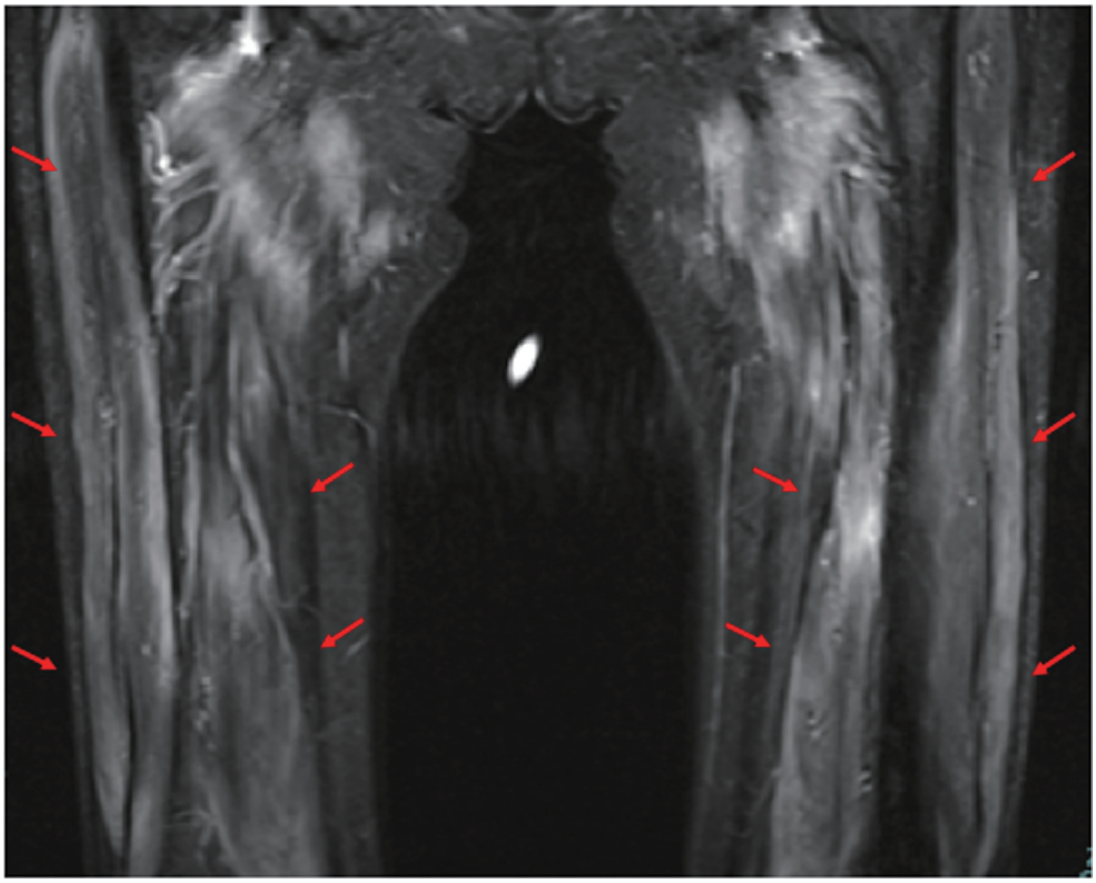

Fig. 1. Magnetic resonance imaging (short-tau inversion recovery) of skeletal muscle at admission showing high signal intensity for proximal limb muscles (arrows).

the upper esophageal sphincter (UES) with multiple swallows. Pharyngeal contraction and sensation were weak. The penetration aspiration scale (PAS) score[26] was 8 points. We decided to continue the exercise involving indirect and direct swallowing training with slightly thick water. Her serum CK level decreased to 199 U/L on day 80, and standing training with parallel bars was performed from day 84. She could hold a standing position for only 10 s. A second VFSS on day 108 showed decreased pharyngeal residue relative to the first VFSS, with some laryngeal penetration but no aspiration and a PAS score of 4 points. Cervical rotation was effective for improving the pyriform sinus residue. Core and breathing exercises were also reinforced for swallowing practice and standing retention. The patient was able to start gait training using parallel bars from day 127, and she was able to hold a standing position for 1 min on day 141. A VFSS on day 135 showed little laryngeal penetration and a PAS score of 3 points. She commenced a paste diet under SLHT management once a day with combined suction from day 136. Her basic movements and dysphagia gradually improved; however, her serum CK level showed a slight increase, and her muscle strength measured by MRC score did not improve. She was then treated with rituximab (375 mg/m^2), which is recommended as the third line of treatment for anti-SRP-IMNM.[2] CD19 was not detected 2 weeks after rituximab administration. No adverse effects were observed. The patient was transferred to a convalescent rehabilitation hospital shortly after receiving one dose of rituximab. Her FIM score was 64 points.

The patient's symptoms showed marked improvement at the convalescent rehabilitation hospital. To achieve the goal of being discharged home, she performed muscle strengthening, exercise tolerance training, and activities of daily living (ADL) training, paying attention to changes in myogenic enzyme levels. A VFSS on day 180 showed that highly viscous food did not pass the esophageal inlet; however, it passed through if the food form was adjusted. She transitioned to oral intake of all three meals from day 190, and she began gait training with a walker on day 197. A VFSS on day 201 showed slight laryngeal penetration and a PAS score of 2

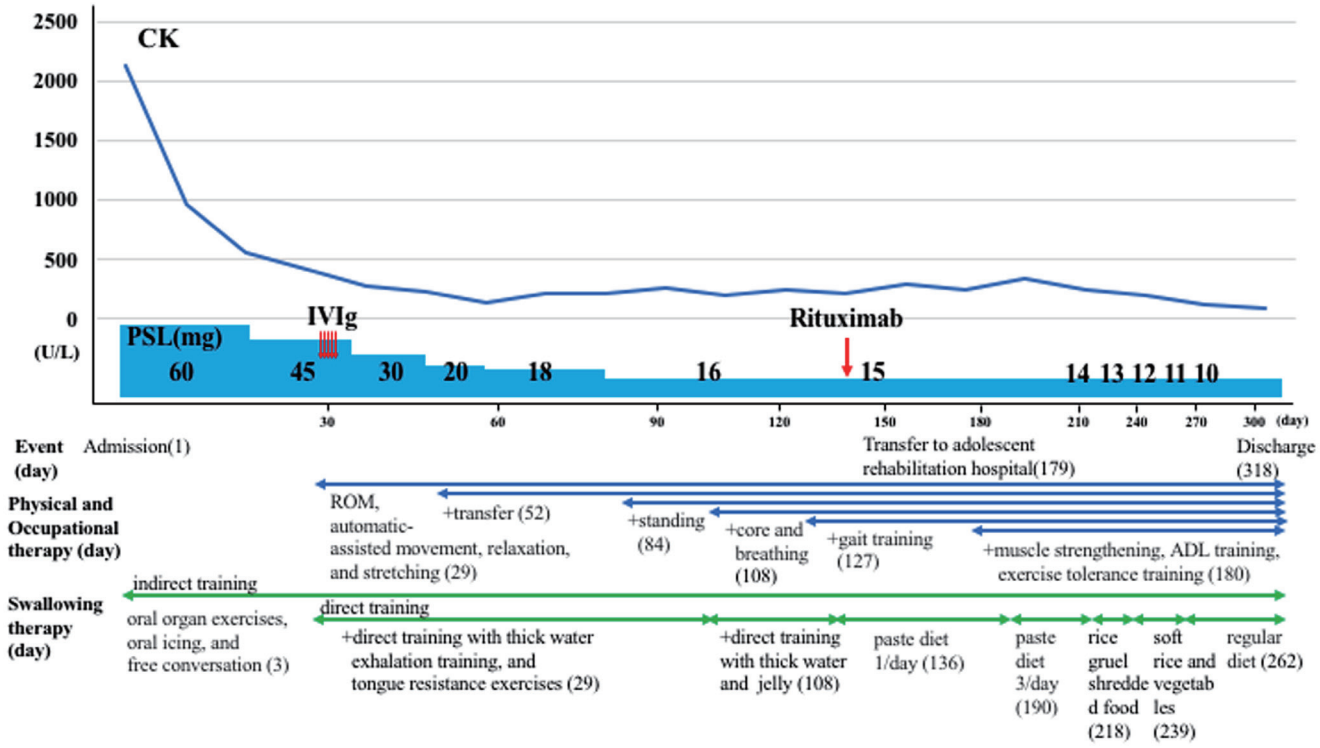

Fig. 2. Time course of serum CK, drug therapy, and rehabilitation treatment. PSL, prednisolone.

points. Tube feeding was terminated. Rice gruel and shredded food was started on day 218. A VFSS on day 236 showed no laryngeal penetration and a PAS score of 1 point. She was started on soft rice and soft vegetables from day 239 and advanced to a regular diet from day 262. Her physical function also improved. The patient was able to stand for 2 min on day 253, walk approximately 30 m with light assistance on day 261, walk with standing-by assistance on day 293, and hold a standing position for 5 min on day 310. Her serum CK levels normalized after day 269. She was discharged on day 318, after achieving modified near independence in all ADL. Her FIM score was 112 points. At 4 months after discharge, a VFSS on day 467 showed improvement in pharyngeal contraction, and slight pharyngeal residue showed good clearance with additional swallowing. She could shop once a week and maintain modified independence in her daily activities, receiving home-visit rehabilitation therapy twice a week. The patient provided written informed consent for the publication of this report.

DISCUSSION

We report rehabilitation therapy for a refractory case of anti-SRP myopathy accompanied by severe muscle weakness and dysphagia. Long-term rehabilitation and internal medicine treatment allowed the patient to be discharged after achieving modified near independence in all ADL.

Historically, patients with idiopathic inflammatory myopathies were discouraged from performing physical exercise because of concerns regarding increased muscle inflammation.[17] However, emerging evidence supports that exercise training is safe and effective in adult patients with active as well as inactive stable inflammatory myopathy.[18–22] Alexanderson et al.[27] reported the benefits and safety of intensive resistance training at ten voluntary repetition maximum (VRM) three times a week for 7 weeks in patients with chronic PM and DM. In addition, they reported no increase in inflammation after exercise, as assessed by an analysis of muscle biopsy samples and CK levels.[27] Mattar et al.[28] reported the efficacy of resistance training and aerobic exercise programs in patients with refractory PM and DM. Specifically, strength training of both limbs was performed for 40 min at an intensity of 8–12 repetition maximum twice a week for 12 weeks, followed by high-intensity aerobic treadmill walking for 40 min. This exercise did not increase their serum CK or aldolase levels.[28]

The effectiveness of physical exercise in treating myositis has been demonstrated in muscle pathology. Dastmalchi

Table 1. Time course of patient's FIM scores

FIM item	Admission (day 3)	Transfer to convalescent rehabilitation hospital (day 179)	Discharge (day 318)
Eating	1	1	6
Grooming	1	5	6
Bathing	1	1	5
Dressing upper body	1	4	6
Dressing lower body	1	2	6
Toileting	1	2	6
Bladder management	1	2	7
Bowel management	1	7	7
Transfer to bed	1	3	6
Transfer to toilet	1	2	6
Transfer to bathroom	1	1	5
Wheelchair	1	1	7
Stairs	1	1	5
Motor items total	13	32	78
Understanding	6	7	7
Expression	6	7	7
Social interaction	5	6	7
Problem solving	5	6	7
Memory	6	6	6
Cognitive items total	28	32	34
Total	41	64	112

et al.[29] reported the effects of exercise on muscle fiber composition in patients with chronic PM and DM. Before exercise, patients had a lower percentage of type I fibers and a higher percentage of intermediate type IIC fibers in the vastus lateralis muscle relative to healthy controls. After a 12-week physical training program, the fiber type composition was closer to normal, and the percentage of type I fibers increased along with a significant reduction in type IIC fibers.[29] Exercise can also improve the mitochondrial function and angiogenesis, improve muscle growth, and reduce inflammation in established PM and DM.[22]

A few studies on rehabilitation with anti-SRP myopathy have been reported.[10,24,25] Chen et al.[10] reported a case in which a structured inpatient rehabilitation program consisting of strength and endurance exercises combined with functional exercises and robot-assisted gait training resulted in significant improvement in the patient's symptoms and a functional outcome. Oohata et al.[24] reported cases in which muscle strengthening at a load based on ten VRM, exercise tolerance training including breathing, and ADL training led to independence in ADL within 6 months to 2 years. Niino et al.[25] reported a case in which resistance exercises increased to moderate intensity, walking exercises, and stair climbing exercises resulted in improvement in MRC muscle strength score and 6-min walk distance.

Our patient was in a near-bedridden state at the time of admission because of severe neck and limb muscle weakness. Bedridden patients are usually kept in bed for a long time, presenting several motor problems caused by immobility, including rapid reductions in muscle mass, bone mineral density, and physical activity.[30,31] Early rehabilitation is associated with increases in functional capacity and muscle strength and improvements in walking distance and quality of life for critically ill patients.[32] Although there are few reports of rehabilitation in bedridden patients with myositis, Datta Gupta and Quadros[33] reported the benefits of mild to moderate muscle training and endurance exercise in a severely ill patient with inclusion body myositis. With these considerations in mind, in our case, physical and occupational therapy were initiated from day 29, when the serum CK level was improved because of internal medicine treatment. Rehabilitation details were discussed by the multidisciplinary team, as appropriate, considering the patient's general condition and changes in her myogenic enzyme levels. The multidisciplinary team included an attending physician, rehabilitation physician, physical therapist, occupational therapist, speech language hearing therapist, nutrition support team, and a nurse. Multidisciplinary discussions were conducted as needed. The correlation between CK level and muscular strength suggests that CK level monitoring may be a good surrogate biomarker of disease activity. However, the correlation coefficient was not high.[34] The CK levels at baseline varied between IMNM patients, and, individually, these levels were not indicative of disease severity.[35] If CK levels indicate that the disease has stabilized, early intervention in rehabilitation is important to prevent muscle weakness and decline in ADL because of disuse.

Supervised physical therapy for PM/DM is effective, safe, free of contraindications, and can be used in both the acute and established phases of the pathology.[36] It is also recommended that exercise be initiated at a low intensity with regular follow-up and the progression of intensity over time.[22] Because our patient was severely ill and had limited ROM, we started with stretching, ROM, and automatic-assisted exercises in bed after confirming the decline in CK levels and gradually moved on to basic movement practice, bed release, and wheelchair transfers. After the transfer to a convalescent

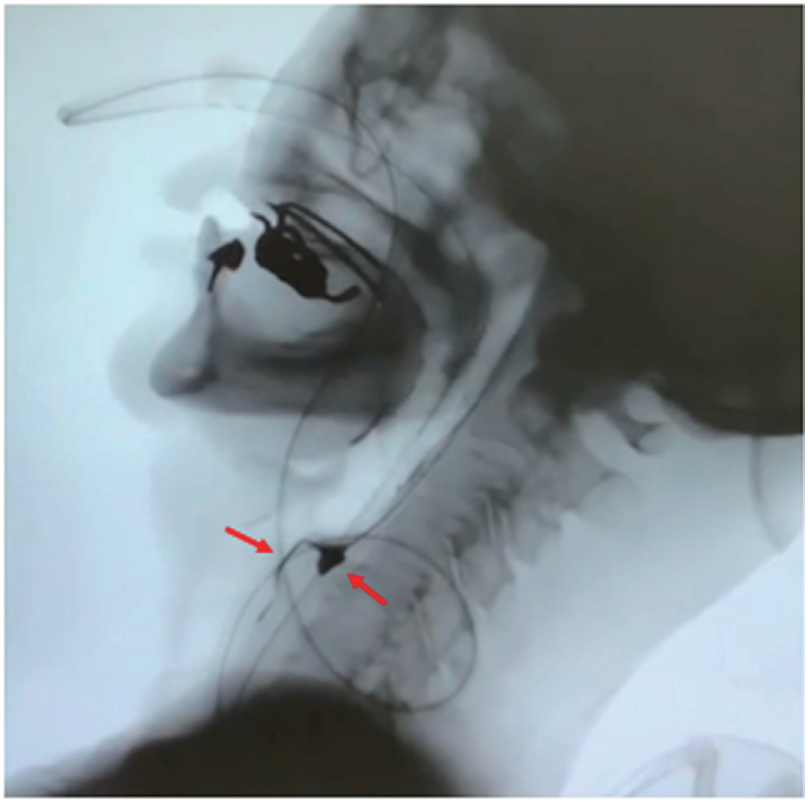

Fig. 3. VFSS on day 86 showing pyriform sinus residue and vallecula of epiglottis with laryngeal penetration and aspiration (arrows).

hospital, the patient's symptoms improved markedly. She was able to undergo further muscle strengthening, exercise tolerance training, and ADL training, with the goal of being discharged home.

Dysphagia in idiopathic inflammatory myopathies (IIM) is caused by the inflammatory involvement of the swallowing muscles, which can lead to reduced pharyngeal contractility, cricopharyngeal dysfunction, reduced laryngeal elevation, and esophageal hypomotility. An in-depth investigation, which included VFSS, of five patients with IMNM showed that four patients had impaired pharyngeal contraction, three had impaired tongue base retraction and epiglottic inversion/laryngeal elevation with aspiration, and only one had cricopharyngeal prominence.[37] Our patient had severely reduced pharyngeal contractility, laryngeal elevation, and pharynx clearance. However, we could not evaluate the swallowing pressure by manometry to determine whether there was insufficient UES relaxation. Recently, high-resolution manometry has been used as a new method to evaluate swallowing function.[38,39] This method may be of use in similar cases in the future. There are three different procedures for treating patients in whom cricopharyngeal dysfunction is the main cause of dysphagia in myositis: balloon dilation, botulinum toxin treatment, and myotomy.[23,40] It is important to note that laryngeal elevation is a prerequisite for the UES to open,[41] and reduced laryngeal elevation can lead to functional impairment of the UES.[40] Using a combination of manometry and VFSS, Langdon et al.[42] found that dysphagia in IIM was consistent with pharyngeal and suprahyoid muscle weakness rather than failed UES relaxation. Azola et al.[43] demonstrated poor endurance in the suprahyoid musculature of IIM patients. There is uncertainty about the role of the UES in the swallowing process in cases involving myopathies.[44]

Non-pharmacological treatment options for dysphagia in myositis include specific exercise therapies, logopedic training, and compensation techniques, such as the Mendelsohn maneuver.[23] In addition, isometric lingual strengthening with the Iowa Oral Performance Instrument has been found to be effective for maintaining posterior tongue lingual pressure and PAS scores.[45] In our case, indirect swallowing training, which included tongue muscle strengthening exercises and free conversation, was continued. Although the patient had some restrictions on the form of the food,

she underwent direct swallowing training with a barely passable food form and practiced alternate swallowing with thick water. Frequent video fluoroscopy helped the patient understand her own situation and motivated her to engage in swallowing training.

The 224th European Neuromuscular Centre (ENMC) Workshop showed that initial treatment usually includes intravenous and/or oral steroids. For severe cases of anti-SRP myopathy, rituximab can be added instead of or in combination with methotrexate.[2] Although many aspects of the pathophysiological mechanisms of IMNM remain unknown, increasing levels of evidence suggest that B cells play an important pathogenic role in IMNM.[46,47] B cell depletion therapy with rituximab is effective for anti-SRP and anti-HMGCR myopathy.[48,49] In the present case, oral methotrexate was too granular to administer internally; therefore, intravenous rituximab alone was added. The patient was elderly and had a history of urinary tract infection leading to sepsis, so one dose was given considering the risk of infection. It has been reported that a much safer protocol for rituximab is maintaining the number of B cells near the lower limit of the normal value when used in IMNM.[50] In our case, the patient is being considered for additional dosing based on future B-cell progression, CK levels, and systemic status. For the time course of the effect of rituximab leading to functional recovery, there have been reports that patients tended to show decreased CK levels as early as 1–2 months after receiving two doses of rituximab.[48,51] In our case, the patient only received a single dose, and it took about 4 months after rituximab administration for normalization of CK levels. The improvement in the patient's symptoms and the normalization of CK levels may be attributed to the patient's own willingness and persistence to continue rehabilitation from the acute phase to the convalescent phase and the overall effects of internal medicine treatment. Notably, the patient was transferred to a convalescent hospital shortly after rituximab administration, and the concurrent changes in intervention and environment could also have played a role in the significant improvement.

We report the outcomes of rehabilitation therapy for a refractory case of severe anti-SRP myopathy. At the beginning of rehabilitation, the patient was almost bedridden and required alternative nutrition. Low-intensity physical therapy and swallowing therapy were initiated under the supervision of a multidisciplinary team with regular follow-up and progression of therapy intensity based on multidisciplinary team discussions.

CONCLUSION

Even in a refractory case of severe anti-SRP myopathy, long-term rehabilitation and internal medicine treatment allowed a patient to be discharged home after achieving modified near independence in all ADL. If CK levels indicate that the disease has stabilized, early intervention in rehabilitation is important to prevent a decline in physical function through disuse. Long-term rehabilitation therapy is safe and effective for the treatment of anti-SRP myopathy.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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