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Profiling of Anti-Signal-Recognition Particle Antibodies and Clinical Characteristics in South Korean Patients With Immune-Mediated Necrotizing Myopathy

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Background and Purpose This study evaluated the diagnostic utility of an anti-signal-recognition particle 54 (anti-SRP54) antibody-based enzyme-linked immunosorbent assay (ELISA) as well as the clinical, serological, and pathological characteristics of patients with SRP immune-mediated necrotizing myopathy (IMNM).

Methods We evaluated 87 patients with idiopathic inflammatory myopathy and 107 healthy participants between January 2002 and December 2023. The sensitivity and specificity of the ELISA for anti-SRP54 antibodies were assessed, and the clinical profiles of patients with anti-SRP54 antibodies were determined.

Results The ELISA for anti-SRP54 antibodies had a sensitivity and specificity of 88% and 99%, respectively, along with a test−retest reliability of 0.92 (p<0.001). The 32 patients diagnosed with anti-SRP IMNM using a line-blot immunoassay included 28 (88%) who tested positive for anti-SRP54 antibodies using the ELISA, comprising 12 (43%) males and 16 (57%) females whose median ages at symptom onset and diagnosis were 43.0 years and 43.5 years, respectively. Symptoms included proximal muscle weakness in all 28 (100%) patients, neck weakness in 9 (32%), myalgia in 15 (54%), dysphagia in 5 (18%), dyspnea in 4 (14%), dysarthria in 2 (7%), interstitial lung disease in 2 (7%), and myocarditis in 2 (7%). The median serum creatine kinase (CK) level was 7,261 U/L (interquartile range: 5,086−10,007 U/L), and the median anti-SRP54 antibody level was 2.0 U/mL (interquartile range: 1.0−5.6 U/mL). The serum CK level was significantly higher in patients with coexisting anti-Ro-52 antibodies.

Conclusions This study has confirmed the reliability of the ELISA for anti-SRP54 antibodies and provided insights into the clinical, serological, and pathological characteristics of South Korean patients with anti-SRP IMNM.

Keywords myositis; anti-signal-recognition particle antibody; immune-mediated necrotizing myopathy; enzyme-linked immunosorbent assay; autoantibodies.

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INTRODUCTION

Idiopathic inflammatory myopathy represents a heterogeneous group of autoimmune diseases characterized by chronic muscle inflammation that leads to progressive muscle weakness and other systemic manifestations.[1] Immune-mediated necrotizing myopathy (IMNM) is a subtype of idiopathic inflammatory myopathy that is primarily characterized by severe proximal muscle weakness and prominent muscle fiber (myofiber) necrosis without substantial inflammatory cell infiltration.[2]

Myositis-specific antibodies play crucial roles in the diagnosis and management of idiopathic inflammatory myopathies.[3,4] These antibodies assist in subclassifying the disease into various types, including dermatomyositis, polymyositis, antisynthetase syndrome, inclusion-body myositis, and IMNM. Certain myositis-specific antibodies are strongly linked to extramuscular involvement, including skin lesions, interstitial lung disease, and malignancies. In particular, the classification of IMNM has been refined through analyses of clinical and pathological features of patients with anti-signal-recognition particle (anti-SRP) antibodies. Identified in 1987, anti-SRP antibodies were found in 1990 to be specifically associated with classic adult polymyositis, especially when there is a low incidence of pulmonary fibrosis, arthritis, and Raynaud's phenomenon.[5,6] Subsequent pathological findings revealed that patients with anti-SRP antibodies predominantly have necrotic myofibers without endomysial lymphocytic infiltration, distinguishing them from polymyositis and leading to the reclassification as IMNM. Therefore, the ability to accurately detect anti-SRP antibodies is crucial for the timely diagnosis and management of patients with this condition. Although immunoprecipitation remains the gold standard for detecting anti-SRP antibodies, it has several limitations such as technical difficulties, high cost, and the use of radioactive reagents. The enzyme-linked immunosorbent assay (ELISA) has emerged as a reliable alternative method for addressing these limitations that offers high sensitivity and specificity.[7,8]

The realization of the significance of muscle-specific antibodies has led to increasing interest in them in South Korea. This recently prompted us to measure antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and NT5C1A (cytosolic 5'-nucleotidase 1A) in South Korean patients with idiopathic inflammatory myopathy and analyze the clinical features according to these antibodies.[9,10] However, most muscle-specific antibodies in South Korea have been measured using immunoassay methods, with few relevant reports.[11] This also applies to anti-SRP antibodies, and so there have been few case reports on South Korean patients diagnosed using an immunoassay.[11-14]

This study aimed to determine the diagnostic effectiveness of an ELISA for anti-SRP54 antibodies in a cohort of South Korean patients with idiopathic inflammatory myopathy. Furthermore, we sought to elucidate the clinical, serological, and pathological characteristics of patients with anti-SRP IMNM so as to improve the understanding of the disease spectrum and to enhance the diagnostic accuracy.

METHODS

Patient selection

We retrospectively evaluated the medical records of patients with idiopathic inflammatory myopathy who were referred to the Gangnam Severance Hospital between January 2002 and December 2023. Our study included 87 patients with idiopathic inflammatory myopathy and 107 healthy participants as controls. We classified idiopathic inflammatory myopathy in accordance with the 2017 European League Against Rheumatism/American College of Rheumatology Classification (EULAR/ACR) using a probability criterion of ≥55%, which corresponds to at least "probable inflammatory myopathies."[15] Dermatomyositis, inclusion-body myositis, and polymyositis were subclassified according to the EULAR/ACR classification tree.[15] The 2017 EULAR/ACR criteria do not distinguish between polymyositis and IMNM, and so IMNM was defined pathologically by the presence of prominent myofiber necrosis without significant inflammatory infiltrates, or serologically by the detection of anti-SRP or anti-HMGCR autoantibodies, in accordance with previously reported consensus guidelines.[16,17] IMNM was further subcategorized into anti-SRP IMNM, anti-HMGCR IMNM, and antibody-negative IMNM based on the detected antibodies. Antibodies against SRP and HMGCR were identified using a line-blot immunoassay and ELISA, respectively. Apply these criteria resulted in the 87 patients with idiopathic inflammatory myopathy being classified as follows: 13 with dermatomyositis, 11 with polymyositis, 9 with inclusion-body myositis, 32 with anti-SRP IMNM, 16 with anti-HMGCR IMNM, and 6 with antibody-negative IMNM.

Line-blot immunoassay for 16 myositis-specific antibodies

We used the Euroline Autoimmune Inflammatory Myopathies 16 Ag assay (Euroimmun, Lübeck, Germany) to assess the following 16 antibodies: Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52. Signal intensities higher than 2 were considered to indicate positivity.

Anti-SRP54-antibody-based ELISA

Recombinant SRP54 protein (Diarect, Freiburg, Germany) was coated onto 96-well plates, with unoccupied sites saturated by 3% bovine serum albumin. Plates were incubated with serum samples at a dilution of 1:3,000, followed by the addition of horseradish-peroxidase-conjugated antihuman IgG (Jackson ImmunoResearch Europe Ltd, Cambridge, UK) at a dilution of 1:5,000. The enzyme substrate used was 3,3',5,5'-tetramethylbenzidine, and the reaction was terminated using 0.5 M sulfuric acid. The optical density at 450 nm was measured using a Versamax microplate reader (Molecular Devices, CA, USA). Each sample was analyzed in duplicate. Positive controls included sera from five patients with anti-SRP IMNM provided by Nishino. The measured anti-SRP54 antibody level was expressed in units per milliliter, based on a standard curve ranging from 0.014 U/mL to 10.2 U/mL. The assay followed an established protocol with minor modifications.[7] The optimal cutoff value was calculated as the mean plus five standard deviations for healthy control sera in accordance with that used in most Japanese research, which served as the foundation for our analytical approach.[7]

Phenotype assessment

Clinical and laboratory data were gathered through a review of medical records. The obtained clinical information encompassed age at symptom onset, age at diagnosis, disease duration, muscle impairment, cardiac muscle involvement, myalgia, dysarthria, dysphagia, dyspnea, dry mouth, skin rash, interstitial lung disease, and malignancy. Physical disability was assessed using the modified Rankin Scale (mRS), which is a 7-level scale ranging from 0 (no symptoms) to 6 (death).[18] The laboratory data included the serum creatine kinase (CK) level and positivity for antinuclear antibodies.

Histological examinations

Muscle biopsies were conducted on 19 patients. Histological staining was carried out on frozen sections using hematoxylin and eosin, modified Gomori trichrome, and nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-tr).

Lower-limb magnetic resonance imaging

Seven patients underwent lower-limb magnetic resonance imaging (MRI) of the pelvis, thigh, and calf muscles. All patients adhered to the same imaging protocol, which included T1-weighted imaging and short-tau inversion-recovery (STIR) sequences, as outlined previously.[9] The obtained muscle images were assessed using the Mercuri scale, which is a 5-level scale ranging from 0 (normal appearance) to 4 (increased signal intensities throughout the muscle).[19]

Statistical analyses

The chi-square test and Fisher's exact test were used to compare categorized variables. The Mann–Whitney U test was employed to compare continuous variables, including the age at symptom onset, age at diagnosis, disease duration, serum CK level, and titer of serum anti-SRP54 antibodies. Spearman's correlation analyses were performed to investigate the relationships between the anti-SRP54 antibody titer and variables such as age at symptom onset, age at diagnosis, disease duration, mRS score, and serum CK level. Test–retest reliability was assessed using the Pearson correlation coefficient for the results obtained for the same serum samples tested twice in different ELISA runs. Statistical significance was defined as a p value of ≤0.05. All statistical analyses were conducted using R software (version 4.2.0, www.r-project.org).

Ethical considerations

This study received approval from the Institutional Review Board of the Gangnam Severance Hospital, South Korea (approval number: 3-2023-0199). Written informed consents were obtained from all participants in accordance with the study protocol, and the study was conducted in compliance with the Declaration of Helsinki.

RESULTS

The anti-SRP54 antibody level as measured using the ELISA was 0.100±0.068 U/mL (mean±standard deviation) (Fig. 1), and thus 0.44 U/mL was designated as the cutoff value. Of the 32 patients diagnosed with anti-SRP IMNM using the line-blot test, 28 (88%) were positive for anti-SRP54 anti-

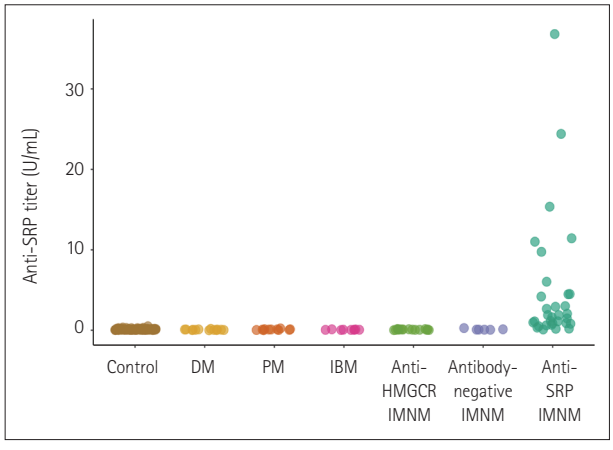

Fig. 1. Anti-SRP54 antibody-based ELISA. Antibodies are indicated that reacted with recombinant SRP protein in the ELISA of sera from patients with inflammatory myopathy and from healthy participants. anti-SRP, anti-signal-recognition particle; DM, dermatomyositis; ELISA, enzyme-linked immunosorbent assay; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; PM, polymyositis.

bodies by ELISA. Anti-SRP54 antibodies were not present in any of the patients with dermatomyositis, polymyositis, inclusion-body myositis, anti-HMGCR IMNM, or antibody-negative IMNM. The anti-SRP54 antibody titer was increased in one healthy participant (0.49 U/mL), who had a normal serum CK level and no muscle weakness. Applying the anti-SRP54-antibody-based ELISA with a cutoff of 0.44 U/mL produced a sensitivity of 88%, specificity of 99%, positive predictive value of 97%, and negative predictive value of 98%, with good test–retest reliability confirmed by a Pearson correlation coefficient of 0.92 (p<0.001).

The clinicopathological characteristics of patients with anti-SRP54 antibodies are summarized in Table 1 and Supplementary Table 1 (in the online-only Data Supplement). The study comprised 12 (43%) males and 16 (57%) females whose median ages at symptom onset and diagnosis were 43.0 years (interquartile range: 34.8–52.8 years) and 43.5 years (interquartile range: 34.8–53.8 years), respectively. The median duration from symptom onset to diagnosis was 3.0 months (interquartile range: 2.0–12.0 months). Four patients reported an antecedent infection: three with an upper respiratory infection and one with gastroenteritis. The symptoms included proximal muscle weakness in all 28 (100%) patients, neck weakness in 9 (32%), myalgia in 15 (54%), dysphagia in 5 (18%), dyspnea in 4 (14%), dysarthria in 2 (7%), interstitial lung disease in 2 (7%), and myocarditis in 2 (7%). Needle electromyography revealed positive sharp waves and/or fibrillation potentials in 26 (93%) patients. The median serum CK level was 7,261 U/L (interquartile range: 5,086–10,007 U/L), and the median anti-SRP54 antibody titer was 2.0 U/mL (interquartile range: 1.0–5.6 U/mL). The mRS score was significantly correlated with the serum CK level (r=0.415, p=0.028) and exhibited a trend toward a correlation with the anti-SRP54 antibody titer (r=0.364, p=0.057). However, the anti-SRP54 antibody titer was not significantly correlated with the age at symptom onset (p=0.359), age at diagnosis (p=0.374), disease duration (p=0.097), or serum CK level (p=0.356). Positivity for antinuclear antibodies (≥1:160) was detected in 25 (89%) patients. Anti-Ro-52 antibodies were found in 12 patients, 1 of whom was also positive for anti-Jo-1 antibodies.

Table 1. Clinical, laboratory, and pathological features of 28 patients with anti-SRP54 antibodies

Characteristic	Value
Sex, male	12 (43)
Age at symptom onset (yr)	43.0 [34.8–52.8]
Disease duration (months)	3.0 [2.0–12.0]
Age at diagnosis (yr)	43.5 [34.8–53.8]
Antecedent infection	4 (14)
Muscle involvement	
Proximal weakness	28 (100)
Modified Rankin Scale score*	2.0 [2.0–3.0]
Laterality	4 (14)
Neck weakness	9 (32)
Myalgia	15 (54)
Dysarthria	2 (7)
Dysphagia	5 (18)
Dyspnea	4 (14)
Cardiac muscle involvement	2 (7)
Extramuscular symptoms	
Dry mouth	2 (7)
Skin rash	1 (4)
Interstitial lung disease	2 (7)
Malignancy	0 (0)
Laboratory findings	
Creatine kinase (U/L)	7,261 [5,086–10,007]
Anti-SRP54 antibodies (U/mL)	2.0 [1.0–5.6]
Anti-Ro-52 antibody positivity	12 (43)
Pathological findings (n=19)	
Myofiber size variations	19 (100)
Necrotic fibers	19 (100)
Endomysial lymphocytic infiltration	0 (0)
Endomysial fibrosis	7 (24)

Data are n (%) or median [interquartile range] values.
*Severe limb weakness was defined as grade 3 or lower as assessed using manual muscle strength grading on the Medical Research Council Manual Muscle Testing scale.
anti-SRP54, anti-signal-recognition particle 54.

The serum CK level was significantly higher in patients with anti-SRP54 IMNM who were also positive for anti-Ro-52 antibodies (median: 10,304 U/L; interquartile range: 8,668–13,564 U/L) than in those without anti-Ro-52 antibodies (median: 5,700 U/L; interquartile range: 1,480–7,305 U/L) (Supplementary Table 2 in the online-only Data Supplement). However, the other clinical features did not differ significantly between the two groups; that is, age at onset, disease duration, mRS score, cardiomyopathy, interstitial lung disease, dry mouth, skin rash, or anti-SRP antibody titer.

Necrotic and regenerative myofibers were found in all 19 patients in whom histological examinations were performed, although with variations in the extent of the necrotic fibers (Fig. 2). No endomysial lymphocytic infiltration was observed. T1-weighted MRI scans of the lower-limb muscles revealed predominant fatty replacement in the gluteus maximus, vastus lateralis, vastus medialis, adductor magnus, semitendinosus, and semimembranosus muscles as well as in the long head of the biceps femoris muscle (Fig. 3). Patient P8, with a long disease duration, had a lower mRS score and exhibited more-moderate fatty replacement than the other patients. Patchy increased STIR signals were prominent across all patients (Fig. 4).

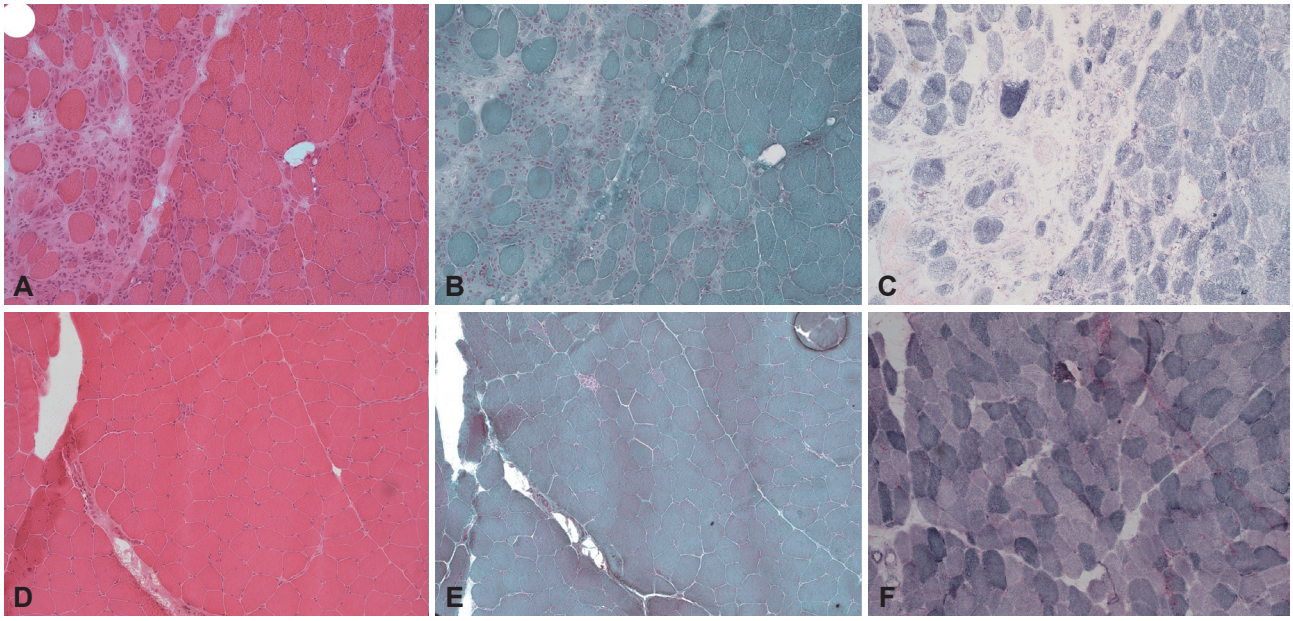

Fig. 2. Pathology of myofibers in patients with anti-SRP54 antibodies: patients P14 (A-C) and P17 (D-F). Patient P14 showed moderate-to-severe variations in myofiber size with numerous necrotic fibers (A, staining with H&E; B, staining with modified GT). NADH-tr staining revealed a marked disorganized intermyofibrillar network (C). In patient P17, myofibers exhibited slight size variations and focal necrotic fibers (D, staining with H&E). No nemaline rods, ragged red fibers, or vacuoles were observed (E, staining with GT), with minimal disorganization of intermyofibrillar networks (F, staining with NADH-tr). Magnification: ×200. anti-SRP, anti-signal-recognition particle; GT, Gomori trichrome; H&E, hematoxylin and eosin; NADH-tr, nicotinamide adenine dinucleotide-tetrazolium reductase.

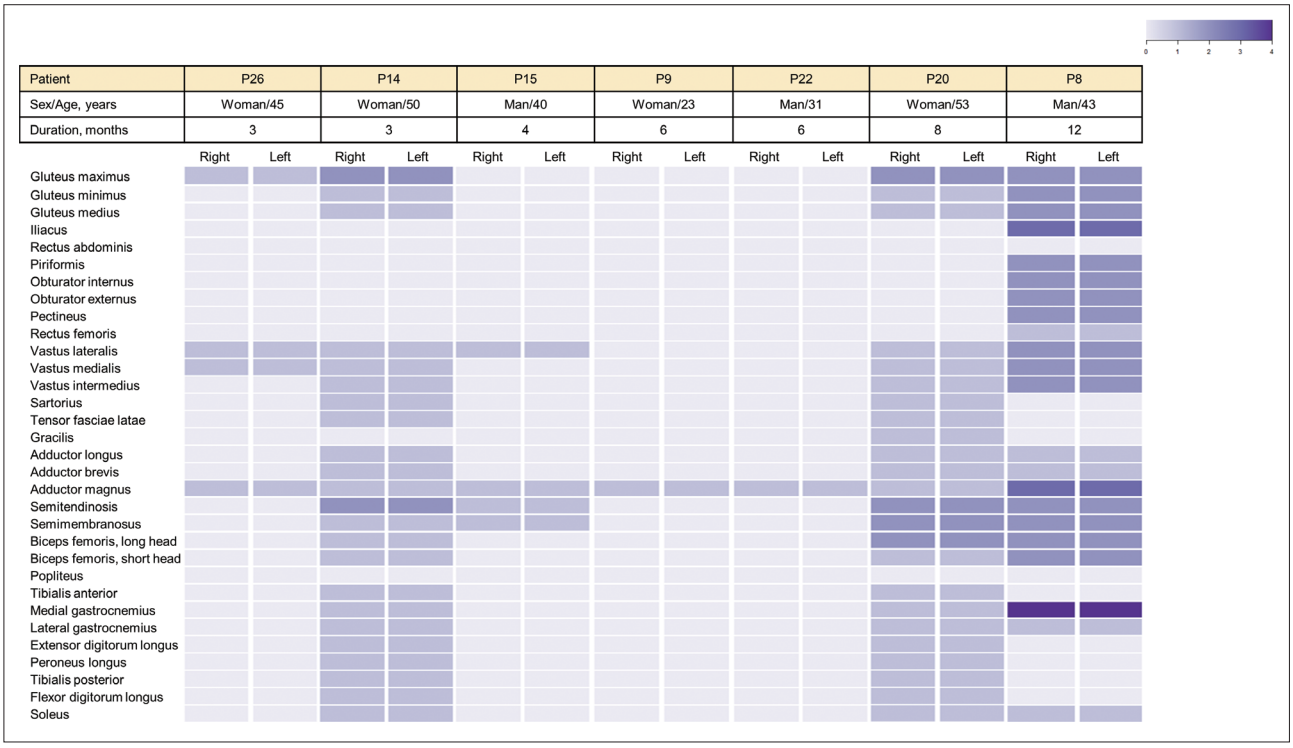

Fig. 3. Fatty replacement distribution in T1-weighted MRI of lower-limb muscles in patients with anti-SRP54 antibodies. The heat map illustrates scores on the Mercuri scale for the lower-limb muscles: grade 0, normal appearance; grade 1, traces of increased signal intensities; grade 2, increased signal intensities with confluence in <50% of the muscle; grade 3, increased signal intensities in >50% of the muscle; and grade 4, increased signal intensities throughout the muscle. anti-SRP, anti-signal-recognition particle; MRI, magnetic resonance imaging.

Patient	P14	P15	P20	P8
Sex/Age, years	Female/50	Male/40	Female/53	Male/43
Duration, months	3	4	8	12
mRS	4	3	3	2

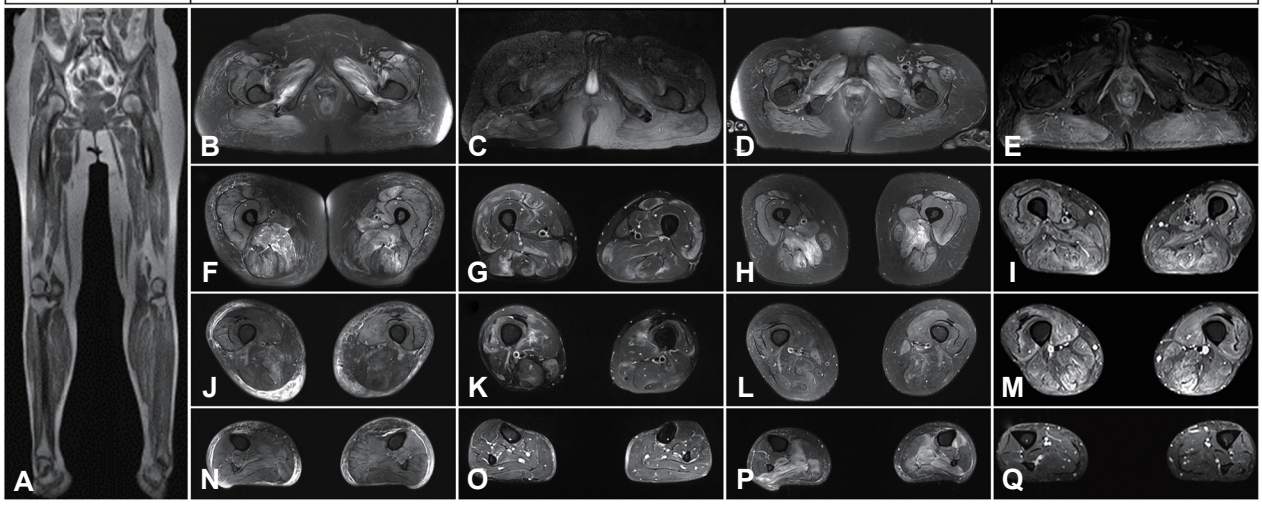

Fig. 4. Short-tau inversion-recovery MRI of the lower limb in patients with anti-SRP54 antibodies: patients P14 (B, F, J, N), P15 (C, G, K, O), P20 (A, D, H, L, P), and P8 (E, I, M, Q). A: T1-weighted coronal MRI of the lower limb. B-E: Pelvis-level images revealed predominant edema of the obturator externus and gluteus maximus muscles. F-M: Thigh-level images revealed multifocal or diffuse edema of the entire thigh muscles, particularly in the adductor magnus muscles. N-Q: At the calf level, two patients (shown in panels N and P) had muscle edema in the tibialis anterior, soleus, and gastrocnemius muscles. anti-SRP, anti-signal-recognition particle; MRI, magnetic resonance imaging; mRS, modified Rankin Scale.

We evaluated the treatment responses in 15 patients who were followed up for >6 months. All of the study patients were treated with oral prednisolone. Additional immunotherapies were required for all patients, including intravenous methylprednisolone pulse therapy in 12 patients, methotrexate in 10, intravenous immunoglobulin in 8, azathioprine in 7, plasmapheresis in 2, rituximab in 2, intravenous cyclophosphamide pulse therapy in 1, mycophenolate mofetil in 1, and tacrolimus in 1. Eight patients had an mRS score of >3 at diagnosis, which improved to ≤2 in six of them. The mRS score remained at 3 in the other two patients even after treatment with intravenous methylprednisolone pulse therapy, methotrexate, intravenous immunoglobulin, and rituximab.

DISCUSSION

This study found that an ELISA for anti-SRP54 antibodies is a reliable diagnostic tool for anti-SRP IMNM, producing a sensitivity and specificity of 88% and 99%, respectively, as well as high positive and negative predictive values. Our sensitivity of 88% is close to previously reported values of 82% and 88% found in ELISA tests for anti-SRP54 antibodies.[7,8] Additionally, our optimal cutoff value of 0.44 U/mL is consistent with that of 0.37 U/mL found in a previous ELISA study.[7] The high test–retest reliability underscores the consistency and reproducibility of the ELISA method in detecting anti-SRP54 antibodies. In this study we detected anti-SRP antibody positivity using a line-blot test. Although commercial line-blot tests for myositis-related antibodies are widely used in clinical practice, immunoprecipitation remains the gold standard for evaluating anti-SRP antibodies. However, a previous study found that the line-blot immunoassay for anti-SRP antibodies produced a sensitivity of 92%, specificity of 98%, and a Cohen's kappa coefficient of 0.83 relative to immunoprecipitation.[20] Furthermore, to minimize false positives, we considered assay signal intensities of >2 as positive results.

IMNM is an idiopathic inflammatory myopathy characterized by the histopathological features of numerous necrotic myofibers without endomysial lymphocytic infiltration. This condition is further defined by the presence of specific antibodies, particularly anti-SRP and anti-HMGCR antibodies whose positivity rates have been reported at 38% and 25%, respectively.[21] Among them, anti-SRP IMNM normally presents in patients aged 40–59 years, though it can also occur in childhood.[2,22] Anti-SRP antibodies are strongly associated with a severe form of IMNM characterized by proximal muscle weakness, dysphagia, and neck weakness. Anti-SRP IMNM is frequently associated with interstitial lung disease and myocarditis, but it is not associated with an increased risk of malignancy.[2] Serum CK is typically elevat-

ed, often exceeding 30 times the upper limit of normal.[2] The present study has revealed that the clinical presentation of South Korean patients with anti-SRP IMNM is consistent with previous findings. Most of our patients had proximal symmetric weakness and highly elevated serum CK, with no concurrent malignancy. Half of them reported myalgia, neck muscle weakness, or a severe clinical status, with an mRS score of >3. These findings are consistent with previous reports.[7,21,23,24] However, we found that dysphagia was present in one-fifth of the included patients, which is lower than previously reported prevalence rates of 30%−70%.[24,25] The most-notable laboratory finding in our study was that 41% of the patients with anti-SRP IMNM had coexisting anti-Ro-52 antibodies. A Japanese study also found a high rate of anti-Ro or anti-La antibody positivity, but at 11% it was lower than in our study.[7] The serum CK level was significantly higher in our patients with anti-Ro-52 antibodies, whereas the other clinical features were not significantly influenced by the presence of these antibodies. Although a few reports have linked anti-Ro-52 antibodies to anti-SRP antibodies, they are recognized as a prognostic factor in antisynthetase syndrome, which is another subtype of idiopathic inflammatory myopathies.[26,27] Therefore, further prospective research is warranted to determine the role of anti-Ro-52 antibodies in patients with anti-SRP IMNM.

A consensus on treatment regimens for anti-SRP IMNM has not yet been established due to the lack of large, randomized, placebo-controlled trials. Consequently, IMNM treatments follow the general regimen for idiopathic inflammatory myopathy. Initial therapeutic approaches typically involve oral or intravenous corticosteroids, with a general consensus that corticosteroid therapy improves muscle strength and preserves muscle function.[28,29] However, prednisolone monotherapy is often inadequate for disease control in anti-SRP IMNM,[30] resulting in most affected patients requiring second-line agents in addition to prednisolone within 6 months after starting treatment.[31] The results from several retrospective studies suggest that rituximab is effective against anti-SRP IMNM.[24,32] We similarly found that corticosteroids and supplementary immunotherapies were necessary in the 15 patients who were monitored for >6 months.

Our histopathological analyses revealed varying extents of necrotic and regenerative myofibers, without endomysial lymphocytic infiltration. The sarcoplasm in many myofibers was coarsely stained by NADH-tr, with a consistent absence of mitochondrial abnormalities. These results are consistent with previous findings.[2,16] Our MRI results confirmed that extensive muscle edema is indicative of early muscle damage, particularly involving the adductor magnus and obturator externus muscles. A previous MRI study found adductor brevis edema and obturator externus atrophy in IMNM patients,[33] which diverges slightly from our observations. However, further research is warranted due to the smallness of our sample. MRI studies have demonstrated that muscle involvement is more severe in patients with anti-SRP IMNM than in those with anti-HMGCR IMNM.[33] However, our analysis was restricted to patients with anti-SRP IMNM. Additionally, pronounced muscle fatty replacement was observed in patients with a long disease duration. Our findings support previous radiological and pathological findings highlighting disease duration as a crucial predictor of muscle damage and the treatment prognosis.[2,33,34]

Our study had a few limitations. First, it had a retrospective design and involved a small sample. Second, although substantial information is available on patient diagnoses, data on the treatment process have not been analyzed sufficiently. Third, the short follow-up period restricted our ability to comprehensively assess treatment prognoses. Therefore, future research investigating treatment responses in larger cohorts of patients with anti-SRP IMNM is required.

In conclusion, this study has validated the efficacy of an anti-SRP54-antibody-based ELISA as a reliable diagnostic tool and has provided comprehensive insights into the clinical, serological, and pathological characteristics of South Korean patients with anti-SRP IMNM.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2024.0333.

Availability of Data and Material

The data that supports the findings of this study are available in the supplementary material of this article.

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Conflicts of Interest

Ha Young Shin, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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