

Differences in muscle magnetic resonance imaging findings between anti-signal recognition particle antibody-positive myopathy and anti-aminoacyl-tRNA synthetase antibody-positive myositis

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Abstract

Objective

To compare the findings of muscle magnetic resonance imaging (MRI) between anti-signal recognition particle antibody-positive myopathy (anti-SRP myopathy) and anti-aminoacyl-tRNA synthetase antibody-positive myositis (anti-ARS myositis).

Methods

Of the patients newly diagnosed with polymyositis (PM)/dermatomyositis (DM) and immune-mediated necrotising myopathy (IMNM) admitted to our Department between April 2012 and December 2021, those who met the eligibility criteria of positive for anti-SRP or anti-ARS antibodies and thigh MRI at the time of diagnosis were included. We compared the lesion sites and MRI findings of the thigh muscles that were classified into oedema, fascial oedema, fatty replacement, and muscle atrophy between the three groups of anti-SRP myopathy, anti-Jo-1 antibody-positive myositis, and non-Jo-1 antibody-positive myositis.

Results

Of the 98 PM/DM and IMNM patients, five anti-SRP myopathy patients and 11 anti-Jo-1-positive and 22 non-Jo-1 antibody-positive patients with myositis were included. The SRP group showed significantly higher blood levels of myogenic enzymes such as serum creatinine kinase (CK) than the other groups ($p=0.01$). In thigh MRI findings, despite oedema in most cases in anti-SRP and anti-ARS groups, fascial oedema was identified only in the ARS group, frequently in Jo-1 positive patients in particular. Moreover, gluteus maximus muscle lesions occurred more frequently in the SRP group than in the ARS group ($p=0.008$).

Conclusion

A comparison of thigh MRI between anti-SRP myopathy and anti-ARS myositis showed different findings and lesion sites reflecting the different pathophysiology that may contribute to their diagnosis.

Key words

magnetic resonance imaging, signal recognition particle, amino acyl-tRNA synthetases, dermatomyositis, myopathy

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Introduction

Anti-signal recognition particle (anti-SRP) antibody-positive necrotising myopathy (anti-SRP myopathy) is different from dermatomyositis (DM) and is characterised by necrosis without inflammatory cell infiltration in muscle (1). In the past decade, several reports have indicated that anti-aminoacyl-tRNA synthetase (ARS) antibody-positive myositis (anti-ARS myositis) is distinct from DM with positivity for other antibodies, such as TIF1- γ , MDA5, Mi-2, NXP2, and SAE (2-4). Characteristics of anti-ARS myositis are considered relatively homogeneous, but the severity of myositis, distribution of interstitial lung lesions, and distribution of eruptions differ among individual patients with anti-ARS antibodies (5, 6). The pathological features of myositis and histopathological findings in muscle also differ, depending on the presence of individual anti-ARS antibodies (4, 7, 8).

Generally, despite an invasive procedure with risks including wound infection, bleeding, and nerve damage, muscle biopsy is informative and valuable for the diagnosis of inflammatory muscle disease (IIM) to exclude muscular dystrophy and metabolic myopathy (9). In contrast, magnetic resonance imaging (MRI) is useful for the non-invasive evaluation of muscle lesions and to select the site of muscle biopsy. Furthermore, it could be used to determine the efficacy of treatment (10, 11). However, a few studies assessing the relationship between the autoantibody profile of IIM and muscle MRI findings were documented, and many questions still need to be answered (12, 13). In this study, we investigated the characteristics of thigh MRI findings in patients with anti-SRP myopathy or anti-ARS myositis. We found that the MRI findings of patients with anti-SRP myopathy and those with anti-ARS myositis were different. Therefore, the muscle MRI findings on the distribution of affected muscle groups and the presence of fasciitis may discriminate between the two diseases.

Materials and methods

Participant recruitment

Of newly diagnosed patients with polymyositis (PM) or DM and immune-me-

diated necrotising myopathy (IMNM) fulfilled the 1992 and revised 2015 classification criteria for PM/DM by the Japanese Ministry of Labor, Health and Welfare, those who were admitted to our department between April 2012 and December 2021, those who met the eligibility criteria of positive for anti-SRP or anti-ARS antibodies and MRI of the thigh at the time of diagnosis were included. In addition, all enrolled patients were confirmed to meet the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile IIMs (14, 15). The age range of enrolled patients was 20-94 years. Blood laboratory test results and manual muscle testing (MMT) were performed at the time of initial diagnosis. In addition, patients with anti-ARS myositis were divided into two groups: the anti-Jo-1 antibody-positive patients (the Jo-1 group; n=11) and the non-anti-Jo-1 antibody-positive patients (the non-Jo-1 group; n=22). We compared three groups, the anti-SRP myopathy group, the Jo-1 group, and the non-Jo-1 group, with regard to patients' clinical features and findings on thigh MRI. The analysis of fatty replacement and muscle atrophy in MRI findings could have been affected by old age, as well as long disease duration. For this reason, the data of 3 patients aged 80 years or older were excluded from the analysis of MRI findings. With regard to the effect of disease duration, we evaluated the MRI findings at the time of disease onset. Almost all patients with a short disease duration were registered in this study. Therefore, we hypothesised that disease duration had little effect on the muscle MRI findings of the patients in this study. This study was approved by the Ethics Committee of the University of Miyazaki Hospital (approval no. O-0192), and written informed consent was obtained from all patients.

The assessment of anti-ARS antibody profile

The antibodies against ARS were detected by enzyme-linked immunosorbent assay (ELISA) (MESACUP anti-ARS test; MBL, Tokyo, Japan). This assay can reveal five different antibodies, those

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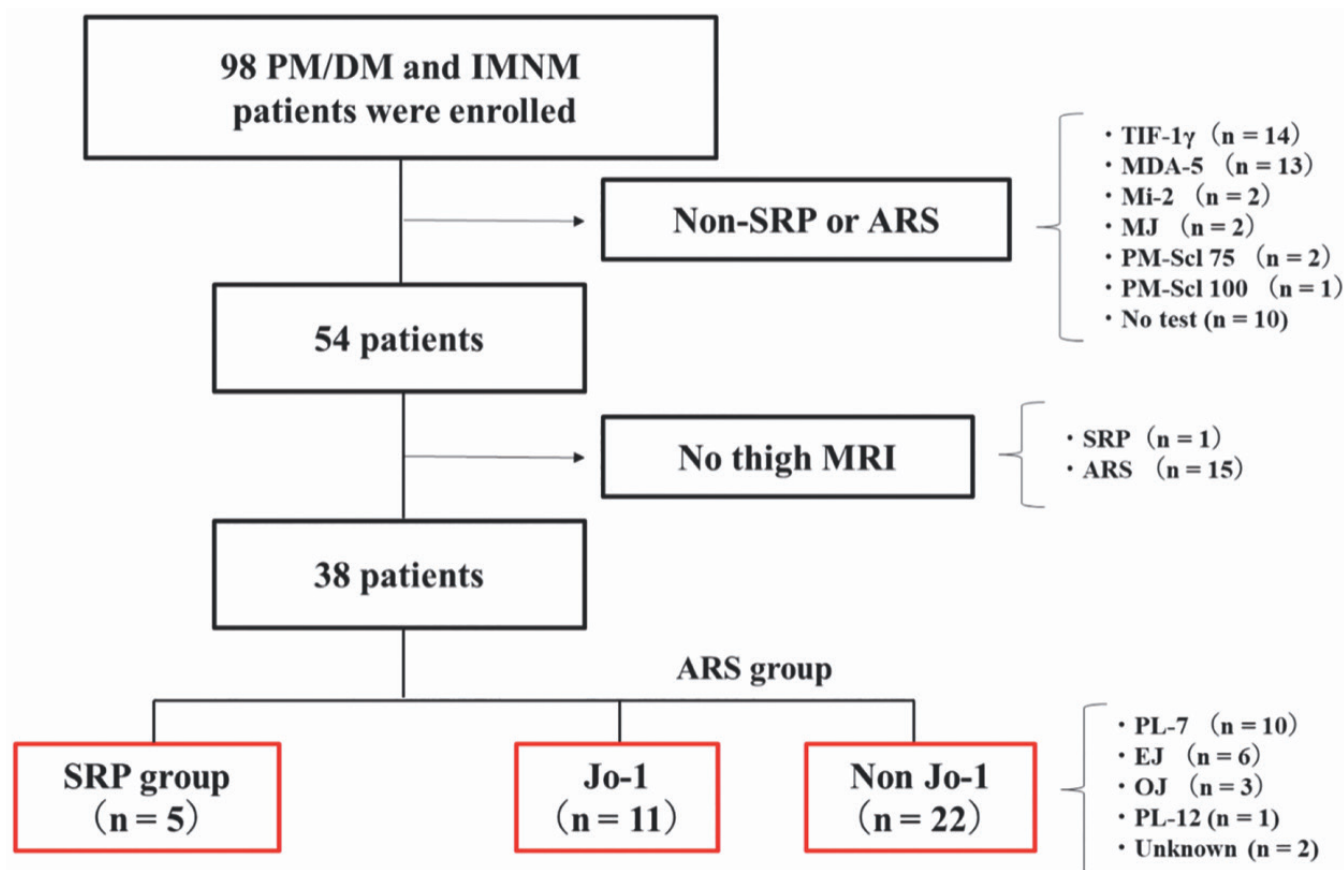


Fig. 1. Number of participants in SRP and ARS groups.

A total of 38 patients underwent thigh MRI. Of the 38 patients, five were positive for anti-SRP and 33 for anti-ARS autoantibodies. In the ARS group, 11 patients were Jo-1 positive and 22 patients were non-Jo-1 positive.

against Jo-1, PL-7, PL-12, EJ, and KS, but it cannot confirm the type of anti-ARS antibody. We further investigated the autoantigen of anti-ARS antibody by immunoblot assay (EUROLINE; Cosmic Corporation, Tokyo, Japan), which can confirm the presence of antibodies against Jo-1, PL-7, PL-12, EJ, and OJ.

MRI imaging

The femoral MRI examination was performed by 3T MRI (MAGNETOM Verio Dot Upgrade; Siemens, Ingenia 3T CX; Philips) and 1.5T (EXCELART Vantage; Toshiba). The findings of T2-weighted short-tau inversion recovery (STIR) and T1-weighted (T1WI) of the femoral muscle were analysed retrospectively. To evaluate muscle lesions, the findings of MRI were classified into oedema, fascial oedema, fatty replacement, and atrophy (Fig. 2). Regarding the lesion location of oedema and fascial oedema, the femoral muscles were classified into the external rotator

muscle group, gluteal, anterior compartment, medial compartment, and posterior compartment (Supplementary Table S1 and Fig. S1) (13, 16).

Histopathological analysis

The histopathological findings in muscle of the patients with anti-SRP myopathy were compared with those of the patients with anti-ARS myositis. Muscle biopsy was performed as a diagnostic examination in 4 patients with anti-SRP myopathy and in 6 patients with anti-ARS myositis. In most of these patients, the sites of muscle biopsy were selected on the basis of MRI findings in muscles. All muscle specimens were stained with haematoxylin and eosin.

Statistical analysis

Statistical analyses were performed using JMP Pro version 16 (SAS Institute). To describe the participant's characteristics, median with interquartile range (IQR) for continuous variables and count

with proportion for categorical data were used. Group comparison on age, duration of illness, deviation enzyme values, inflammatory biomarker levels, white blood cell count, haemoglobin, and platelet count between anti-SRP myopathy, Jo-1 and non-Jo-1 groups was conducted using the Kruskal-Wallis test. The sex ratio, MMT, anti-nuclear antibody positivity, interstitial lung diseases complication ratio, Sjögren's syndrome complication ratio, malignancy complication ratio, prevalence ratio of muscular lesions, and biopsy findings between the two or three groups were compared using Fisher's exact test. $p < 0.05$ was considered significant.

Results

The comparison of clinical features of anti-SRP myopathy, anti-Jo-1 antibody-positive myositis, and non-anti-Jo-1 antibody-positive myositis
During the observational period, PM/DM and IMNM were newly diagnosed

Table I. Characteristics of patients with SRP and ARS.

	SRP group (n = 5)	ARS group		p-value
		Jo-1 (n = 11)	Non-Jo-1 (n = 22)	
Age, years (IQR)	39 (20-50)	44 (35-63)	56.5 (44.8-67.3)	0.248
Female, no. (%)	4 (80)	6 (54.5)	19 (86.4)	0.154
Duration of illness, months (IQR)	3 (1-4)	2 (1.5-3)	3 (2-5.8)	0.344
MMT				
Iliopsoas (IQR) ^a	4 (4-5)	4 (4-5)	4 (4-5)	0.571
Quadriceps (IQR) ^b	4 (4-5)	5 (4.25-5)	4.5 (4-5)	0.757
Hamstring (IQR) ^c	4.5 (4-5)	5 (4-5)	5 (4-5)	0.581
Creatinine kinase (U/L) (IQR)	4,315 (2,597-9,668)	1,800 (1,038-2,859)	699.5 (171-2,150)	0.010
Aldolase (U/L) (IQR) ^d	176.5 (88.6-184.3)	77.7 (46.9-108.4)	39.2 (19.8-76.7)	0.037
AST (IU/L) (IQR)	129 (128-214)	75 (44-101)	48 (29.5-73.8)	0.061
ALT (IU/L) (IQR)	121 (104-209)	68 (37.5-118)	39 (23-67)	0.086
LDH (IU/L) (IQR)	784 (631-1,435)	465 (378-589.5)	447.5 (293.5-494.8)	0.076
CRP (mg/dL) (IQR)	0.05 (0.02-0.22)	0.39 (0.13-1.47)	0.64 (0.12-1.45)	0.105
White blood cell count (/μL) (IQR)	6,600 (5,700-7,200)	10,000 (7,050-12,100)	8,750 (6,000-13,500)	0.240
Haemoglobin (g/dL)(IQR)	13.2 (12.9-14.3)	13.1 (12.5-14.4)	13.0 (11.3-13.8)	0.409
Platelet count (×10 ⁴ /μL) (IQR)	24.4 (18.7-26.2)	27.4 (23.3-32.3)	31.1 (21.5-38.9)	0.351
ANA positive, no.(%)	5 (100)	8 (72.7)	19 (86.4)	0.450
ILD, no.(%)	3 (60)	11 (100)	19 (86.4)	0.088
Malignancy, no.(%)	0	1 (9.1)	2 (9.1)	1.000
		Bladder	Cervical, oesophageal	
SS, no. (%)	1 (20)	4 (36.4)	8 (36.4)	0.896

Values are expressed as medians interquartile range (IQR). Percentages (%) are calculated based on total number of patients in each group unless indicated otherwise. SRP: anti-signal recognition particle; ARS: anti-aminoacyl-tRNA synthetase; MMT: manual muscle testing; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ANA: anti-nuclear antibody; ILD: interstitial lung disease; SS: Sjögren's syndrome.

^aData available in 5 and 10, 19 patients of SRP and Jo-1, non-Jo-1 groups, respectively.

^bData available in 5 and 10, 21 patients of SRP and Jo-1, non-Jo-1 groups, respectively.

^cData available in 4 and 11, 20 patients of SRP and Jo-1, non-Jo-1 groups, respectively.

^dData available in 5 and 10, 20 patients of SRP and Jo-1, non-Jo-1 groups, respectively.

in 98 patients (Fig. 1). Of these 98 patients, 6 were positive for anti-SRP antibody and 48 were positive for anti-ARS antibody. Five patients with anti-SRP myopathy and 33 with anti-ARS myositis, who had undergone thigh muscle MRI at the time of diagnosis, were enrolled in the study. Of the ARS group, 11 patients were positive for anti-Jo-1 antibody; 10, for anti-PL-7 antibody; 6, for anti-EJ antibody; 3, for anti-OJ antibody; and 1, for anti-PL-12 antibody. Two patients had unknown types of anti-ARS antibodies. The background clinical characteristics of the patients are shown in Table I. There were no inter-group differences in terms of the age of disease onset and duration of illness. Blood levels of myogenic enzymes such as CK and aldolase were significantly high in the anti-SRP myopathy group compared with the anti-ARS myositis group (CK: $p=0.01$, aldolase: $p=0.037$). In addition, the blood levels of CK and aldolase in the Jo-1 group were higher than in the non-Jo-1 group.

Table II. MRI findings between patients with SRP and those with Jo-1, non-Jo-1 group.

	SRP group (n=5)	ARS group		p-value
		Jo-1 (n=11)	Non-Jo-1 (n=22)	
Oedema, no. (%)	4 (80)	9 (81.8)	10 (45.5)	0.089
Fascial oedema, no. (%)	0	6 (54.6)	3 (13.6)	0.020
Fatty replacement, no. (%) ^a	0	0	4 (18.2)	0.322
Atrophy, no. (%) ^b	0	0	2 (9.1)	0.656

SRP: anti-signal recognition particle; ARS: anti-aminoacyl-tRNA synthetase; MRI: magnetic resonance image.

^a3 patients over 80 years old were excluded (1 patient in SRP, 1 patient in Jo-1, 1 patient in non-Jo-1 group).

^b3 patients over 80 years old were excluded (1 patient in SRP, 1 patient in Jo-1, 1 patient in non-Jo-1 group).

The levels of CRP showed a tendency to be higher in anti-ARS myositis group than in the anti-SRP myopathy group. The MMT score tended to be lower in the anti-SRP myopathy group in the quadriceps femoris and femoral flexor muscles. Interstitial lung disease was observed in 60% of the anti-SRP myopathy group, 100% of the Jo-1 group and 86.4% of the non-Jo-1 group. Only three patients had malignant tumours (cervical, oesophageal, bladder) in the anti-ARS myositis group.

MRI findings of thigh muscles between patients with anti-SRP myopathy, anti-Jo-1 antibody-positive myositis, and non-anti-Jo-1 antibody-positive myositis

Thigh MRI showed oedema in most patients of anti-SRP myopathy and anti-Jo-1 myositis (Table II). However, fascial oedema was found more frequently in the anti-Jo-1 myositis group than in the other groups ($p=0.02$). None of the patients in the anti-SRP myopathy group presented with fascial oede-

Table III. Differences of oedema and fascial oedema compartments between patients with SRP and those with Jo-1, non-Jo-1 group.

	SRP group (n=4)	ARS group		p-value
		Jo-1 (n=10)	Non-Jo-1 (n=11)	
Lat. rot. group, no. (%)	2 (50)	5 (50)	4 (36.4)	0.869
Gluteal, no. (%)	4 (100)	1 (10)	3 (27.3)	0.008
Anterior, no. (%)	3 (75)	9 (90)	9 (81.8)	0.804
Medial, no. (%)	2 (50)	2 (20)	6 (54.5)	0.273
Posterior, no. (%)	2 (50)	3 (30)	4 (36.4)	0.864

SRP: anti-signal recognition particle; ARS: anti-aminoacyl-tRNA synthetase; Lat. rot. group: lateral rotator group.

ma of thigh MRI. Fatty replacement and atrophy were found only in the non-Jo-1 group. One patient who was positive for anti-OJ antibody presented with fatty replacement and atrophy as thigh MRI findings. Regarding sites of appearance on MRI findings, oedema and fascial oedema were widespread over multiple compartments but were more frequent in the buttocks, such as the gluteus maximus muscle in anti-SRP myopathy group, than in the anti-ARS myositis group ($p=0.008$) (Table III). In the anti-ARS myositis group, more findings were observed in the anterior compartment than in the other compartments (Fig. 2).

The comparison between muscle biopsy findings and MRI findings in anti-SRP myopathy and anti-ARS myositis

Table IV summarises the pathological and MRI findings for muscles in patients with anti-SRP myopathy and those with anti-ARS myositis. Pathological features of anti-SRP myopathy included fibre necrosis, fibre degeneration, and macrophage infiltrations; these were not observed in patients with anti-ARS myositis. In contrast, perimysial or perivascular lymphocyte infiltrations were observed in patients with anti-ARS myositis. Both perimysial and perivascular lymphocyte infiltrations in muscles were observed in 2 patients with anti-ARS myositis in whom fascial oedema was observed on thigh MRI.

Discussion

As anti-SRP myopathy is rare, there are many unclear clinical features compared to anti-ARS myositis. Among

anti-ARS myositis, anti-Jo-1 myositis is reported to have higher serum CPK levels than another anti-ARS myositis (2). In addition, serum CPK levels of anti-SRP myopathy are reported to significantly increase compared to those of anti-ARS myositis (6). In this study, as in previous reports, the serum CPK level in anti-SRP myopathy was higher than that in anti-ARS myositis, and the serum CRP level in anti-SRP myopathy was within the reference range. Furthermore, Allenbach *et al.* reported that anti-SRP myopathy is less associated with malignant tumours than PM/DM and anti-HMGCR antibody-positive necrotising myopathy (17). In this study, malignant tumours were confirmed in three patients with anti-ARS myositis, whereas no cases with malignant tumours were observed in the SRP group at the time of the diagnosis and consistent with previous reports.

In a report analysing 41 patients with anti-SRP myopathy, 34 patients (83%) had muscle weakness in the lower extremities, including the thighs (2). Similarly, in a report analysing 51 patients with anti-ARS antibody-positive DM, muscle weakness was observed in the lower extremities, including the thigh, in 34 patients (67%) (6). Therefore, using MRI to evaluate the thigh muscle, which is typically affected by muscular lesions, seems to be appropriate to evaluate muscle lesions and their distribution in anti-SRP myopathy and anti-ARS myositis. Muscle MRI findings in anti-SRP myopathy indicate more oedema and fatty replacement than other IIM (4), suggesting that this may reflect muscle cell oedema due to cell membrane disruption, like neurological disorders such as Duchenne muscular

dystrophy. In addition, fatty replacement may reflect an increase in connective tissue in the muscle. In this study, fewer cases showed fatty replacement compared to oedema. Fatty replacement is a frequent MRI finding in anti-SRP myopathy with a long disease duration of 2 years or more (11). As this study analysed the MRI images at the time of diagnosis, there were many cases with short disease duration in which muscle lesions did not progress to fatty replacement in patients with anti-SRP myopathy. However, in 1 patient who was positive for anti-OJ antibody, thigh MRI revealed fatty replacement and atrophy, although the disease was of new onset. Anti-OJ antibody-positive myositis was reported to manifest with severe muscle involvement and a high prevalence of diffusely distributed necrotic or degenerating fibres in muscle tissues (4). Anti-OJ antibody-positive myositis has been reported to have features similar to those of IMNM (4). In our study, it is possible that MRI findings of muscle atrophy were observed early after onset in anti-OJ antibody-positive patients; however, verification of the clinical features in more anti-OJ antibody-positive patients is necessary. It has also been reported that MRI findings of DM show fascial oedema reflecting perifascial microvasculitis (18), which was consistent with our findings. Iago *et al.* reported that lesions of anti-SRP myopathy tend to appear in the external rotator muscles and the buttocks (13). Additionally, the muscle damage of IMNM was predominantly located at lumbar and pelvic femoral region (19). Andersson *et al.* reported that anti-ARS antibody-positive DM tends to develop lesions in the anterior compartment (20). The distribution of muscle lesions in anti-SRP myopathy, and anti-ARS myositis in this study was also consistent with those in previous reports. The pathogenesis of anti-SRP myopathy is thought to occur when SRP is presented as an antigen on the muscle cell membrane and binds to anti-SRP antibodies to induce the membrane attack complex, resulting in muscle cell necrosis (21). The difference in the pathophysiology between anti-SRP myopathy, characterised by muscle necrosis, and

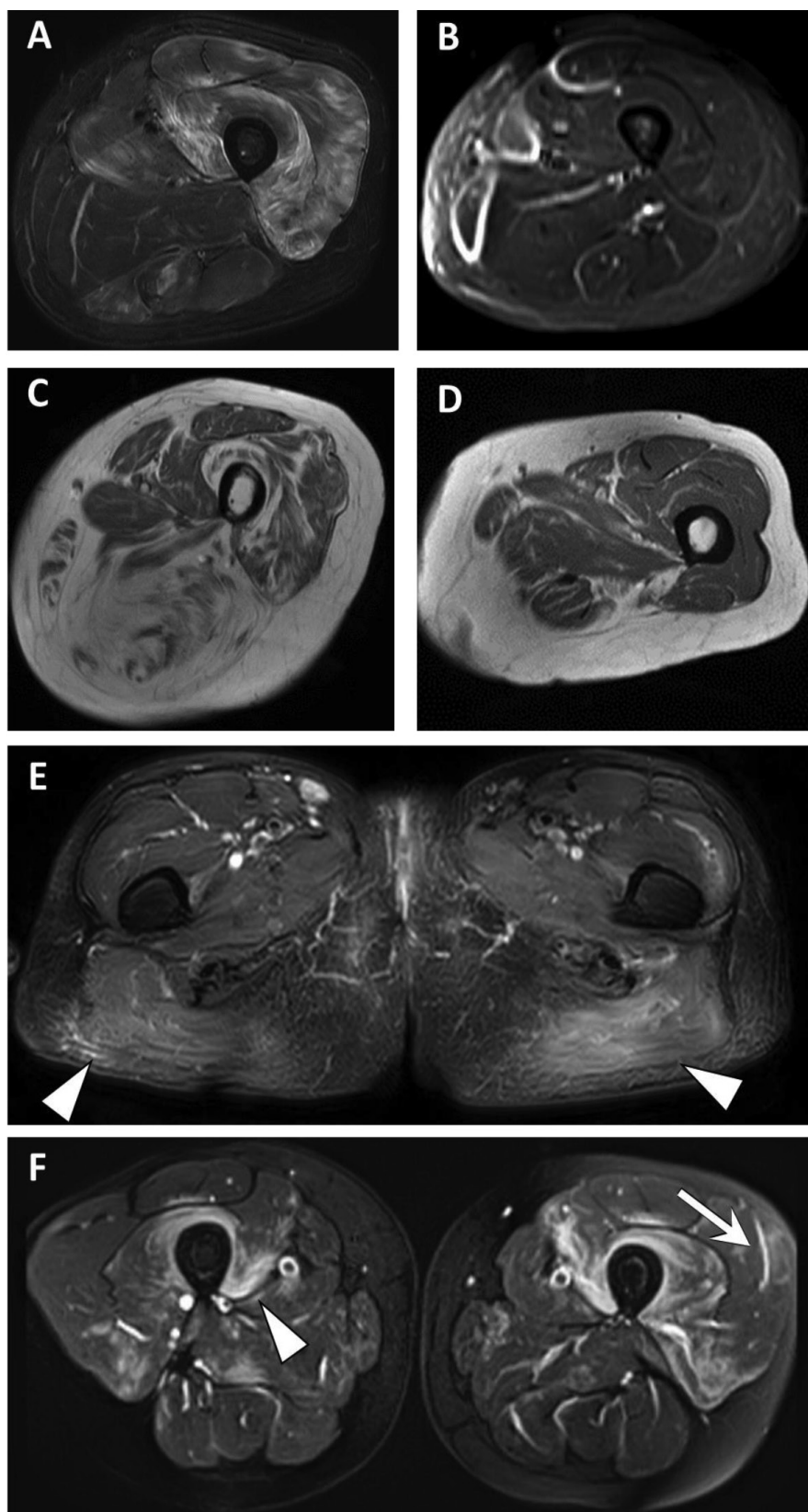


Fig. 2. Comparison of the MRI findings of anti-SRP myopathy and anti-ARS myositis. Examples of the thigh MRI findings. (A) Short-tau inversion recovery (STIR) sequences showing oedema and (B) fascial oedema. (C) T1-weighted (T1WI) sequences showing fatty replacement and (D) atrophy. (E) In SRP myopathy, oedema (arrow heads) was common in the gluteal groups, and no fascial oedema was observed. (F) In anti-ARS myositis, oedema (yellow arrows) and fascial oedema (arrow) were common in the anterior groups.

anti-ARS myositis characterised by fasciitis and vasculitis, may affect the sites of the muscle lesion observed on muscle MRI. However, the mechanism of the distribution of muscle lesions in both diseases remains unclear.

In patients with anti-SRP myopathy, pathological findings included myonecrosis with poor lymphocyte infiltration. Anti-SRP myopathy has been clinically characterised by marked elevation of myogenic enzymes and severe muscle weakness (22). Our histopathological analysis of muscles revealed fibre necrosis and no lymphocyte infiltration in patients with anti-SRP myopathy, and blood myogenic enzyme levels were higher and muscle weakness was more marked in anti-SRP myopathy than in anti-ARS myositis; these findings are consistent with those previously reported. In contrast, pathological findings in muscles of patients with anti-ARS myositis are associated mainly with lymphocytic infiltration around muscle fibres and in the perimysium (23). In patients with anti-SRP myopathy, the observation of muscle oedema on MRI may correspond to the muscle necrosis and degeneration noted in pathological assessment. In addition, fascial oedema noted on MRI, which was often observed in patients with anti-Jo-1 myositis, may correspond to lymphocyte infiltration around the fascia and blood vessels that is noted in muscle pathological assessment. In fact, lymphocyte infiltration was observed around muscle fascicles and blood vessels in the muscle tissue of patients with anti-ARS myositis who exhibited myofascial oedema on MRI. Together, these results suggest that the sites of thigh lesions in anti-SRP myopathy differ from those in anti-ARS myositis, and MRI findings in muscle may be used to infer pathological findings in muscle, which may be useful in diagnosing inflammatory myopathy.

This study has several limitations. First, the study was conducted in a small number of cases at a single institution. Second, muscle MRI findings were retrospectively collected from radiologists' reports, and rheumatologists independently evaluated MRI findings, but clinical information about muscle

Table IV. Muscle biopsy and MRI findings between patients with SRP and those with ARS.

	SRP (n=4) ^a	ARS (n=6) ^b	p-value
Biopsy findings			
Fibre necrosis, no. (%)	2 (50)	0	0.133
Fibre degeneration, no. (%)	2 (50)	1 (16.7)	0.500
Macrophage infiltration, no. (%)	3 (75)	1 (16.7)	0.191
Lymphocyte infiltration			
perimysium, no. (%)	0	2 (33.3)	0.467
perivascular, no. (%)	0	2 (33.3)	0.467
MRI findings			
Oedema, no. (%)	3 (75)	5 (83.3)	1.000
Fascial oedema, no. (%)	0	3 (50)	0.200
Fatty replacement, no. (%)	0	1 (16.7)	1.000
Atrophy, no. (%)	0	1 (16.7)	1.000

SRP: anti-signal recognition particle; ARS: anti-aminoacyl-tRNA synthetase; MRI: magnetic resonance imaging.

^a2 patients had biopsies from the upper arm and 2 from the thigh.

^b1 patient had biopsies from the upper arm and 5 from the thigh.

disease may have contributed to interpretation bias. In the future, it will be necessary to standardise MRI imaging conditions and interpret the MRI findings by using a blinded method at multiple centres. Third, we analysed images obtained between 2012 and 2021 with MRI machines with different resolutions (3 Tesla and 1.5 Tesla), and we could not rule out the influence of these differences on the MRI findings in muscle. Fourth, the analysis was performed in a patient population in which disease duration from the time of onset was relatively short, inasmuch as the myopathy was newly diagnosed. However, the duration of disease varied from 1 month to 12 months. Future studies on MRI findings in the early stage of disease onset are needed because some myopathies may develop rapidly with MRI findings such as fatty replacement and atrophy.

Conclusion

This comparative study was conducted using the clinical characteristics and femoral MRI findings at the time of diagnosis of anti-SRP myopathy or anti-ARS myositis. The sites of muscle lesions differed between the two disease groups. Moreover, fascial oedema, suggestive of fasciitis, was more frequently observed in patients with anti-ARS myositis, in particular anti-Jo-1 antibody-positive myositis, whereas oedema reflecting muscle necrosis was commonly observed in patients with anti-SRP myopathy. Muscle MRI findings of the

two diseases reflect the differences in pathological conditions such as muscle necrosis and muscle tissue damage due to myositis. Additionally, such differences in MRI findings may be useful in diagnosing these diseases, although further confirmatory studies are necessary in a more significant number of cases.

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