THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Clinical characteristics of myositis patients with isolated anti-U1 ribonucleoprotein antibody resemble immune-mediated necrotizing myopathy

Ther Adv Musculoskelet Dis

2023, Vol. 15: 1–12

DOI: 10.1177/1759720X231181336

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Abstract

Background: Anti-U1 ribonucleoprotein (U1RNP) antibodies were associated with connective tissue diseases (CTDs), but the clinical characteristics of this antibody in Chinese myositis patients have not been studied.

Objective: We aim to analyze the clinical features of myositis patients who test positive for anti-U1RNP antibodies and delineate a subgroup of myositis.

Design: This is a retrospective cohort study.

Methods: We reviewed the clinical data of myositis patients with anti-U1RNP antibodies and compared them to those with anti-signal recognition particle (SRP) and hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibody-associated immune-mediated necrotizing myopathy (IMNM).

Results: A total of 30 adult cases were identified; median age was 47.5 years and 24 (80%) were females, and 12 patients did not coexist with myositis-specific antibodies (MSAs) (isolated anti-U1RNP). The serum creatine kinase (CK) was significantly higher in patients with isolated anti-U1RNP (2182.5 U/L *versus* 289 U/L, $p = 0.01$), and the number of patients with CK > 2000 U/L was higher compared to that in anti-U1RNP antibody patients coexisting with MSAs (66.7% *versus* 16.7%, $p = 0.009$). The prevalence of IMNM in patients' muscle pathology with isolated anti-U1RNP was significantly higher (75%, $p = 0.003$). Skin rashes were less common in isolated anti-U1RNP group ($p < 0.05$). Of the 25 individuals with available pulmonary high-resolution CT (HRCT), 14 (56%) were diagnosed with interstitial lung disease (ILD). The incidence of muscular weakness, dysphagia, or levels of CK was not different between the isolated anti-U1RNP antibody individuals and the anti-HMGCR or SRP-IMNM groups ($p > 0.05$). But the frequency of Raynaud's phenomenon, arthritis, and membrane attack complex (MAC) deposits in myositis patients with isolated anti-U1RNP antibodies were higher than in anti-HMGCR and SRP-IMNM (all $p < 0.005$). There was no difference between anti-U1RNP patients with and without Ro-52 ($p > 0.05$). Isolated anti-U1RNP individuals showed marked improvements in muscle strength, and the remission rate in 1 and 2 years was significantly higher than that in anti-HMGCR and SRP-IMNM ($p < 0.05$).

Conclusions: The clinical and pathological features of myositis patients with isolated anti-U1RNP antibodies were similar to IMNM. Arthritis and ILD are the most common extramuscular clinical features. Most respond well to treatment and have a good prognosis.

Keywords: anti-hydroxy-3-methylglutaryl-CoA reductase antibody, anti-signal recognition particle antibody, anti-U1RNP antibody, immune-mediated necrotizing myopathy, myositis

Received: 21 January 2023; revised manuscript accepted: 24 May 2023.

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of clinically heterogeneous, autoimmune inflammatory disorders characterized by muscular weakness, and multisystem involvement including the lungs and skin. The most common forms of IIMs include dermatomyositis (DM), anti-synthetase syndrome (ASS), and immune-mediated necrotizing myopathy (IMNM). Myositis-specific antibodies (MSAs) or associated antibodies (MAAs) are autoantibodies that are frequently described with myositis. The presence of MSAs allows for patients to be considered in relatively pathologically homogeneous subgroups; for instance, the anti-melanoma differentiation-associated gene 5 (MDA5) antibody is associated with DM, anti-Jo-1 with ASS, and autoantibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and the signal recognition particle (SRP) are representative antibodies causing IMNM.[1–3] Although MAAs have been detected in other connective tissue diseases (CTDs) or overlap syndrome of IIM and other CTDs, it has been reported that some MAAs were associated with unique features in IIM. Isolated anti-Ku antibody from the serum in IIM was associated with concomitant severe interstitial lung disease (ILD) and IMNM.[4] Furthermore, IMNM was a major histopathological finding in IIM patients with isolated anti-mitochondrial antibodies.[5]

Anti-ribonucleoprotein (RNP) antibodies target proteins included in the small nuclear RNP (snRNP) complex; their presence was described to be systemic lupus erythematosus (SLE), systemic sclerosis (SSc), or mixed connective tissue disease (MCTD).[6–8] Despite its relatively frequent prevalence in MCTD and SLE, IIM patients with anti-U1 ribonucleoprotein (U1RNP) antibodies have been described. It was previously shown that muscle weakness was present at the time of disease onset in all myositis patients with anti-U1RNP involving proximal limb muscles, and almost 90% of those patients had weakness in proximal muscles that was frequently severe.[9] Another study demonstrated that patients with anti-U1RNP myositis typically present with proximal weakness and necrotizing muscle biopsies.[10] Furthermore, some anti-U1RNP-positive patients have a similar presentation to those with IMNM.[11]

Few reports have described IIM patients with anti-U1RNP antibodies in China, thereby limiting our understanding of their clinical features. To address this, we conducted a cohort study in which we reviewed the clinical data and muscle biopsy results from Chinese IIM patients with anti-U1RNP antibodies. We also evaluated treatment outcomes.

Methods and materials

Participants

This was a retrospective non-interventional study, 916 adult consecutive patients with IIMs from the China–Japan Friendship Hospital who met either the Bohan and Peter criteria or the European Neuromuscular Centre criteria or the 2017 EULAR/ACR criteria for IIMs and were positive for anti-U1RNP antibodies were enrolled between Dec 2011 and Dec 2021.[12–15] The anti-nuclear antibody profile [antigen including Ro-52, Sjogren's syndrome A (SSA), RNP, etc.] was assessed by immunoblotting using commercial kits [EUROLINE antinuclear antibody (ANA) profile] from Euroimmun. Serum MSAs and MAAs were detected via the Euroline myositis line-blot assay of Euroimmun (Lübeck, Germany) according to the manufacturer's protocol. We documented the response to treatment. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[16]

Data collection

SSc, SLE, and rheumatoid arthritis (RA) were defined according to the classification criteria proposed by the EULAR/ACR.[17–19] MCTD patients fulfilled the criteria by Alarcon-Sergovia or Sharp.[20]

Data were extracted from the complete medical files of the participants by a retrospective review. All individuals had a complete physical examination with particular attention paid to muscle, skin, and articular manifestations of disease. We collected the following data: age, sex, levels of creatine kinase (CK) and lactate dehydrogenase (LDH), ultrasonic cardiogram, pulmonary high-resolution CT (HRCT), and the presence of other MAAs. All available muscle biopsies were reviewed by two experts in myopathology. Muscle strength was scored as grade 0–5 by the examining physician using the Medical Research Council (MRC) scale.

Statistical analysis

Data were expressed as medians (interquartile ranges) for continuous variables and proportions

(%) for categorical variables. Between-group comparisons were performed using the Mann–Whitney *U* test for continuous variables and χ^2 test or Fisher's exact test for categorical variables, as appropriate. All *p* values were two-sided with $p < 0.05$ being considered as statistically significant. Statistical analyses were carried out using IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY, USA).

Results

Participant characteristics

Anti-U1RNP antibodies were detected in 30 (3.3%) out of 916 adult patients with IIMs from the China–Japan Friendship Hospital between December 2011 and December 2021. Of these patients, 24 (80%) were females and 6 (20%) were males. The clinical features of the cohort are listed in Table 1. All participants were aged over 20 years with a median age of the anti-RNP antibody-positive patients of 47.5 years. Among these patients with anti-U1RNP, 18 (60%) patients coexisting with MSAs, such as anti-MDA5 ($n = 5$), anti-Jo-1 ($n = 3$), anti-EJ ($n = 2$), anti-nuclear matrix protein 2 (NXP-2), ($n = 2$), anti-Mi-2 ($n = 2$), anti-transcription intermediary factor 1-gamma (TIF1-γ) ($n = 1$), anti-small ubiquitin-like modifier-1 activating enzyme (SAE) ($n = 1$), anti-PL-7 ($n = 1$), and anti-SRP ($n = 1$); the remaining 12 patients did not coexist with MSAs (named isolated anti-U1RNP).

Muscle involvement

A total of 22 (73.3%) individuals presented with muscle weakness presented and 8 (26.7%) had severe muscle weakness (MRC grade < 3), and 12 (40%) had myalgia and 10 (33.3%) had dysphagia. A total of 18 patients (60%) individuals had elevated serum CK (289–16,689 U/L), 22 (73.3%) had elevated LDH (255–1968 U/L), and 16 (53.3%) had elevated alanine transaminase and aspartate transaminase. Of the 12 individuals from whom muscle magnetic resonance imaging (MRI) were available, 9 (75%) showed intramuscular inflammatory exudates (Figure 1).

Clinical characteristics were compared between isolated anti-U1RNP and coexisting with MSAs patients. As shown in Table 1, there were no significant differences in dysphagia and muscle strength between two groups. However, muscle weakness was more severe in patients with isolated anti-U1RNP antibody. Notably, in isolated anti-U1RNP group, 9 (75%) individuals had elevated serum CK (median 4749 U/L; 600–16,689 U/L) and 6 (50%) had CK levels >6000 U/L. The serum CK was significantly higher in patients with isolated anti-U1RNP (2182.5 U/L *versus* 289 U/L, $p = 0.01$), and the number of patients with CK > 2000 U/L was higher compared to that in anti-U1RNP antibody patients coexisting with MSAs (66.7% *versus* 16.7%, $p = 0.009$).

Muscle pathological results were available for 24 anti-U1RNP-positive patients. Significantly, comparison among anti-U1RNP-positive IIM patients show that 9 of 12 patients (75%) with isolated anti-U1RNP presented IMNM pathological features. In contrast, only 1 of 12 patients (8.3%) with coexistence of anti-U1RNP and SRP antibodies showed pathological features of IMNM. The incidence of IMNM in patients with isolated anti-U1RNP was significantly higher than that of patients with coexistence of anti-U1RNP and MSAs ($p = 0.003$) (Table 1). Typical pathologic performances of IMNM-like pathological features and pathologic DM in patients with anti-U1RNP are shown in Figure 2.

By reviewing the pathology of patients who had isolated anti-U1RNP-positive-IIM with available muscle biopsies, 10/12 (83.3%) had a necrotizing/regeneration pattern. Perivascular inflammatory infiltration was seen in 8 (66.7%) individuals, major histocompatibility complex Class I (MHC-I)-positive muscle fibers in 10 (83.3%) (see Figure 2), diffuse MHC-I-positive muscle fibers in 7 (58.3%), scattered MHC-I-positive muscle fibers in 3 (25%), internal nuclei in 7 (58.3%), and sarcolemmal C5b9 deposits in 11 (91.7%).

Lung and cardiac involvement

Of the 25 anti-U1RNP individuals with available lung HRCT, 14 (56%) were diagnosed with ILD; cough and/or dyspnea were the first symptoms in 6 (24%). Abnormal opacities were predominantly distributed in the lower lobes. Ground glass opacities were identified in 9 (36%) individuals, 8 (32%) showed reticulation, and 7 (28%) had interlobular septal thickening. Representative CT images are shown in Figure 3. According to the HRCT patterns, nonspecific interstitial pneumonia in 8/14 (57.1%) patients; one case each of usual interstitial pneumonia, lymphocytic interstitial pneumonia, and organizing pneumonia; and three patients cannot be classified into any

Table 1. Features of isolated anti-U1RNP and coexistence of anti-U1RNP and MSAs.

Variable	Anti-U1RNP (*n* = 30)	Isolated anti-U1RNP (*n* = 12)	Anti-U1RNP and MSAs (*n* = 18)	*p* Value
Female/male	24/6	9/3	15/3	NS
Age of onset (years)	45.8 ± 15.6	43.7 ± 17.0	47.2 ± 14.9	NS
Muscular weakness	22 (73.3%)	10 (83.3%)	12 (66.7%)	NS
Dysphagia	10 (33.3%)	6 (50%)	4 (22.2%)	NS
Arthritis	13 (43.3)	7 (58.3%)	6 (33.3%)	NS
Gottron's rash	11 (36.7%)	5 (41.7%)	6 (33.3%)	NS
Heliotrope sign	11 (36.7%)	1 (8.3%)	10 (55.6%)	0.018
Mechanic hand	9 (30%)	1 (8.3%)	8 (44.4%)	0.049
Reynaud phenomenon	10 (33.3%)	5 (41.7%)	5 (27.8%)	NS
ILD	14 (56%)	5/10 (50%)	9/15 (60%)	NS
ANA	23 (76.7%)	11 (91.7%)	12 (66.7%)	NS
Ro-52	13 (43.3%)	6 (50%)	7 (38.9%)	NS
CK (U/L, median)	600	2182.5	289	0.01
CK > 2000 U/L	11 (36.7%)	8 (66.7%)	3 (16.7%)	0.009
CK > 6000 U/L	7 (23.3%)	6 (50%)	1 (5.6%)	0.009
Myositis + SSc	5 (16.7%)	3 (25%)	2 (11.1%)	NS
Myositis + SLE	2 (6.7%)	2 (16.7%)	0	NS
Myositis + RA	1 (3.3%)	1 (3.3%)	0	NS
Myositis + SS	5 (16.7%)	3 (25%)	2 (11.1%)	NS
Myositis + MCTD	0	0	0	NS
Pathological pattern				
IMNM	10/24 (41.7%)	9/12 (75%)	1/12 (8.3%)[a]	0.003
No IMNM	14/24 (58.3%)	3/12 (25%)	11/12 (91.7%)	
Normal	1/24 (4.2%)	1/12 (8.3%)	0	NS
pDM	9/24 (37.5%)	0	9/12 (75%)	<0.001
NSM	4/24 (16.7%)	2/12 (16.7%)	2/12 (16.7%)	NS

[a]The patient with anti-U1RNP and SRP.
CK, creatine kinase; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathies; MCTD, mixed connective tissue disease; MSAs, myositis-specific autoantibodies; NS, not significant; NSM, non-specific myositis; pDM, pathologic dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SRP, signal recognition particle; SS, Sjögren's syndrome; SSc, systemic sclerosis; U1RNP, U1 ribonucleoprotein.

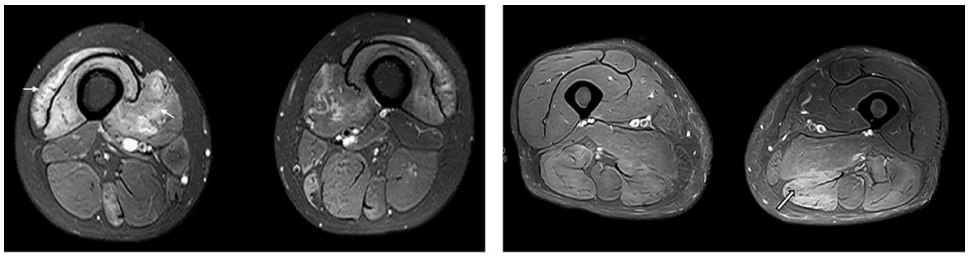

Figure 1. Abnormal signal intensity in skeletal muscle axial T2-weighted magnetic resonance imaging (arrow).

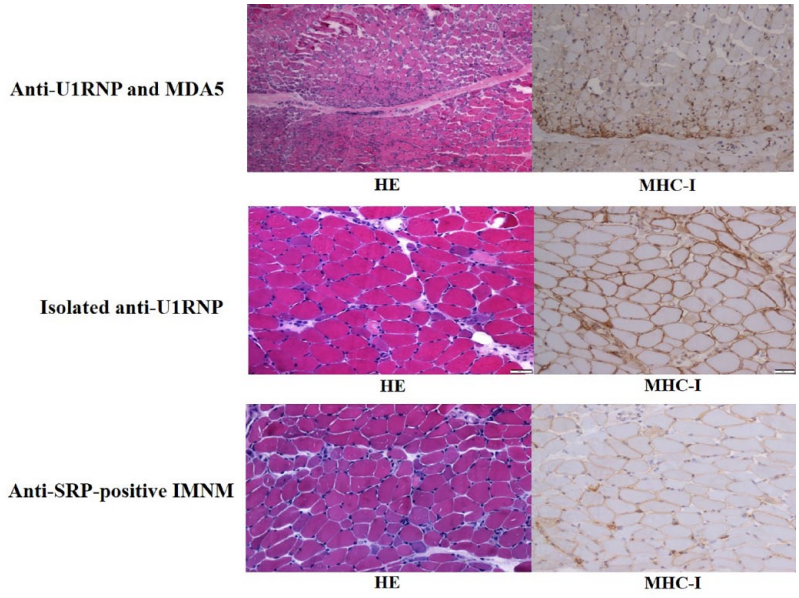

Figure 2. Muscle pathology necrotic muscle cells were scattered in the muscle bundle without typical perifascicular atrophy, and MHC-I molecules were generally expressed in the myocyte membrane in SRP-IMNM and myositis with isolated anti-U1RNP. Perifascicular atrophy was seen in patient with anti-MDA5. IMNM, immune-mediated necrotizing myopathies; MDA5, melanoma differentiation-associated gene 5; MHC-I, major histocompatibility complex Class I; SRP, signal recognition particle; U1RNP, U1 ribonucleoprotein.

type. Eight (26.7%) individuals had mild pulmonary hypertension (PH) and six patients with pericardial effusions evidenced by echocardiography. Cardiac MRI showed myocardial inflammatory edema in two patients.

Skin and other extramuscular involvement

A total of 22 (73.3%) patients presented with the cutaneous manifestations. However, skin rashes, especially Heliotrope sign and mechanic's hands, were less common in isolated anti-U1RNP group ($p < 0.05$). In addition, 10 (33.3%) individuals presented with Raynaud's phenomenon and 3 (10%) with sclerodactyly. A total of 13 (43.3%) had evidence of symmetrical nondestructive arthritis and 6 (20%) had a fever. Glomerulonephritis occurred in 3 (10%) individuals during their disease. Breast cancer was observed in one female patient with isolated anti-U1RNP.

Clinical differences between myositis patients with isolated anti-U1RNP and IMNM with anti-SRP or HMGCR

The mean age of disease onset in the isolated anti-U1RNP antibody myositis individuals was not significantly different from those with

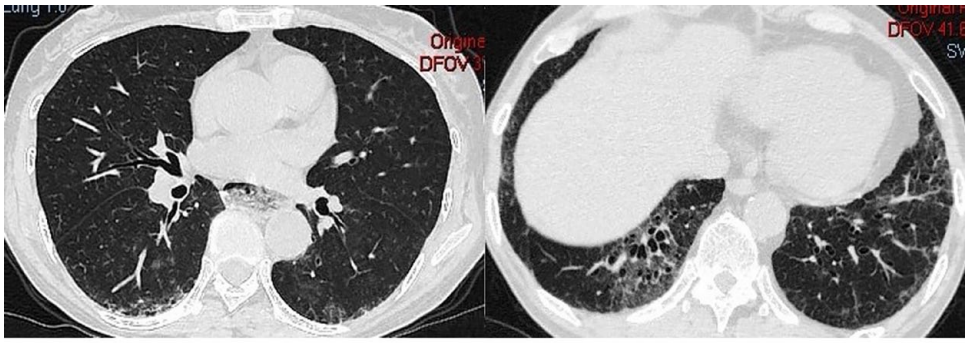

Figure 3. High-resolution CT scan from myositis patients with anti-U1RNP and anti-SRP.
SRP, signal recognition particle; U1RNP, U1 ribonucleoprotein.

anti-SRP or anti-HMGCR antibodies ($p > 0.05$). The incidence of skin rashes, muscular weakness, myalgia, dysphagia, or fever was not different between the isolated anti-U1RNP antibody individuals and the two IMNM groups ($p > 0.05$). Levels of serum muscle enzymes in isolated anti-U1RNP-positive individuals were not significantly different than those in anti-HMGCR or anti-SRP antibody individuals ($p > 0.05$). The frequency of ILD was similar in isolated anti-U1RNP and anti-HMGCR or anti-SRP-IMNM groups ($p > 0.05$). The frequencies of Raynaud's phenomenon and arthritis were significantly higher in individuals who were positive for isolated anti-U1RNP than those in the anti-HMGCR and anti-SRP groups (all $p < 0.005$). The frequencies of ANA and Ro-52 antibodies were higher in the isolated anti-U1RNP and anti-SRP groups than in the anti-HMGCR group (both $p < 0.01$).

Muscle biopsies showed there were no significant differences between the three groups in myocyte necrosis, regeneration, phagocytosis, inflammatory cell infiltration, upregulated expression of MHC-I molecule in the myocyte membrane, and proliferation of connective tissue in endomysium (all $p > 0.05$). However, the expression of membrane attack complex (MAC) was higher in the isolated anti-U1RNP group (100%) than in the anti-SRP (77.3%) and anti-HMGCR groups (52.4%, $p = 0.008$, Table 2).

Other coexisting autoantibodies

A total of 76.7% patients were ANA positive, with titers from 1:80 to 1:1280 (nuclear speckles). A total of 13 (43.3%) individuals tested positive for Ro-52 antibodies. A total of 12 also had SSA, 2 SSB, and 4 were positive for rheumatoid factor and 1 with anti-Sm antibody.

In the anti-UIRNP antibody-positive patients, we found that the age of onset was similar in those with and without Ro-52 antibodies. In addition, the prevalence of skin rash, Raynaud's phenomenon, arthritis, ILD, dysphagia, glomerulonephritis, and muscular weakness were also similar ($p > 0.05$). Although the frequency of pericarditis was higher in patients with Ro-52 than without Ro-52, it was not statistically significant (see Table 3).

Clinical classification of myositis patients with anti-U1RNP antibody

Given their diverse clinical manifestations, some patients also fulfilled diagnostic criteria for one or more other systemic autoimmune diseases. Five (16.7%) patients with anti-U1RNP antibody met the criteria for SSc, 2 (6.7%) met the classification criteria for SLE and 1 (3.3%) met the classification criteria for RA.

Follow-up investigations

Participants were followed-up for a median of 41 months (range 14–118 months). Eight individual was treated with glucocorticoids alone, while the remaining 22 received a combination of immune agents or biologic drugs, including cyclophosphamide, azathioprine, tacrolimus, cyclosporine A, methotrexate, or tocilizumab. In our cohort, six patients were lost to follow-up. Among the remaining 24 cases, 16 patients accepted clinical interviews and 8 patients completed follow-up

Table 2. Comparisons of IIM patients with isolated anti-U1RNP and IMNM patients.

Variable	Isolated anti-U1RNP (*n* = 12)	HMGCR (*n* = 23)	SRP (*n* = 47)	*p* Value
Female/male	9/3	13/10	38/9	NS
Age of onset (years)	43.7 ± 17.0	46.1 ± 16.2	44.1 ± 20.8	NS
Muscular weakness	10 (83.3%)	21 (91.3%)	44 (93.6%)	NS
Severe muscle weakness	5 (41.7%)	9 (39.1%)	22 (46.8%)	NS
Myalgia	3 (25%)	8 (34.8%)	13 (27.7%)	NS
Dysphagia	6 (50%)	8 (34.8%)	17 (36.2%)	NS
Arthritis	7 (58.3%)	1 (4.3%)	4 (8.5%)	<0.001
Skin rash	5 (41.7%)	8 (34.8%)	12 (25.5%)	NS
Reynaud phenomenon	5 (41.7%)	0	3 (6.4%)	<0.001
ILD	5/10 (50%)	7 (30.4%)	21/45 (46.7%)	NS
Fever	2 (16.7%)	1 (4.3%)	3 (6.4%)	NS
Cancer	1 (8.3%)	1 (4.3%)	3 (6.4%)	NS
ANA	11 (91.7%)	2/22 (8.7%)	36 (76.6%)[a]	<0.001
Ro-52	6 (50%)	1 (4.3%)	16 (34%)	0.006
CK (IU/L, median)	2182.5	2527	1675	NS
Muscle biopsy features				
Necrosis/regeneration	10 (83.3%)	21 (91.3%)	43(91.5%)	NS
Connective tissue proliferation	3 (25%)	8 (34.8%)	17 (36.2%)	NS
CD68 + macrophage				
Perivascular	4 (33.3%)	3/21 (14.3%)	18/44 (40.9%)	NS
Endomysial	8 (66.6%)	8/21 (38.1%)	26/44 (59.1%)	NS
CD4 T lymphocyte				
Perivascular	4 (33.3%)	6/23 (26.1%)	17/47 (36.2%)	NS
Endomysial	9 (75%)	14/23 (60.9%)	27/47 (57.4%)	NS
CD8 T lymphocyte				
Perivascular	1/12 (8.3%)	4/23 (17.4%)	8/47 (17%)	NS
Endomysial	5/12 (41.7%)	8/23 (34.8%)	14/47 (36.2%)	NS
MHC-I expression	10 (83.3%)	17 (73.9%)	35 (74.5%)	NS
Diffuse	7 (58.3%)	6 (26.1%)	11 (23.4%)	NS
Scattered	3 (25%)	11 (47.8%)	24 (51.1%)	NS

(Continued)

Table 2. (Continued)

Variable	Isolated anti-U1RNP (*n* = 12)	HMGCR (*n* = 23)	SRP (*n* = 47)	*p* Value
Membrane attack complex	12 (100%)	11/21 (52.4%)	34/44 (77.3%)	0.008
Follow-up, months (median)	41	45	44	NS
Death	0	1/20 (5%)	6/43 (14%)	NS
Remission rate at 1 year	8/10 (80%)	8/19 (42.1%)	13/39 (33.3%)	0.029
Remission rate at 2 years	10/10 (100%)	6/15 (40%)	19/33 (57.6%)	0.041
Relapse	2/10 (20%)	10/18 (55.6%)	21/36 (58.3%)	NS

[a]Most of the sera from anti-SRP patients were cytoplasmic pattern in the ANA test.
CK, creatine kinase; HMGCR, hydroxy-3-methylglutaryl-CoA reductase; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathies; NS, not significant; SRP, signal recognition particle; U1RNP, U1 ribonucleoprotein.

Table 3. Differences between patients with and without Ro-52 antibody.

Characteristic	Ro-52 (+) (*n* = 13)	Ro-52 (–) (*n* = 17)	*p* Value
Female/male	9/4	15/2	NS
Age (years)	43.9 ± 17.4	47.2 ± 14.4	NS
Skin rash	8 (61.5%)	14 (82.4%)	NS
Dysphagia	4 (30.8%)	6 (35.3%)	NS
Muscular weakness	10 (76.9%)	12 (70.6%)	NS
Arthritis	6 (46.2%)	7 (41.2%)	NS
Raynaud's phenomenon	5 (38.5%)	5 (29.4%)	NS
ILD	6/11 (54.5%)	8/14 (57.1%)	NS
Pericarditis	5/11 (45.5)	1/14 (7.1%)	NS
Glomerulonephritis	1 (7.7%)	2 (11.8%)	NS

ILD, interstitial lung disease; NS, not significant.

by telephone interviews. Two patients died of worsening of ILD and one died for pulmonary infection in anti-U1RNP and MSAs groups.

As for myositis patients with isolated anti-U1RNP, all (100%) individuals had decreased CK levels, and 8/10 (80%) showed marked improvements in muscle strength after immunotherapy, among which five patients was completely recover full strength. Furthermore, all individuals exhibited improvements in skin rashes and arthritis following treatment. Moreover, the lung CTs of ILD participants remained stable without further visible pathological progression. No deaths were recorded. In isolated anti-U1RNP group, the remission rate in 1 and 2 years was significantly higher than that in anti-HMGCR and SRP-IMNM ($p < 0.05$).

Discussion

This is the first retrospective study to describe the clinical phenotype, including muscular and extramuscular pathological manifestations, of Chinese adult IIM patients who tested positive for anti-U1RNP antibodies. Disease was most prevalent in females, with muscle involvement as the most prominent complication and the main muscle pathological change resemble IMNM in myositis patient with isolated anti-U1RNP. ILD, Reynaud's phenomenon, and arthritis were evident in some patients. Most patients with isolated anti-U1RNP were found to have responded well to treatment and achieved favorable outcomes.

The anti-U1RNP antibody is strongly associated with MCTD. However, this antibody can also be detected in some individuals with SLE or other CTDs, such as systemic sclerosis and Sjögren's syndrome.[21–23] The presence of anti-U1RNP antibodies in Sjögren's syndrome appears to be associated with an increased risk of myositis.[23] Theoretically, the presence of anti-U1RNP antibodies in IIM increases the risk of severe myositis symptoms; this is supported by prior work. Coppo *et al.* showed that muscle weakness was present at disease onset in all individuals with IIM and anti-U1RNP antibodies; 60% had severe muscle weakness with increased levels of serum muscle enzymes and CK levels of 565–14,000 IU/L (mean 5735 IU/L).[9] Wesner *et al.* reported that most individuals with IIM and anti-U1RNP antibodies

had proximal weakness that was frequently severe and high CK levels (999–4382 IU/L); 22% had CK levels >7000 IU/L.[11] In our cohort, nearly three-quarters of individuals presented with muscle weakness, while the severity of muscular weakness and elevated levels of CK were significantly higher than in isolated anti-U1RNP-positive patients than that in anti-U1RNP and MSAs. Muscular weakness was the main feature of myositis patients with isolated anti-U1RNP antibodies, manifesting as proximal muscle weakness. In addition, more than 40% of our participants had severe muscular weakness with most showing significantly elevated CK levels. Furthermore, half of our cohort had CK levels >6000 IU/L.

Although muscular weakness is common in IIM patients with anti-U1RNP antibodies, myositis often appears insidiously.[24] Mammen *et al.* reported on 12 anti-U1RNP-positive myositis patients; muscle weakness was a presenting feature in only 15% of patients at disease onset although 80% eventually developed weakness.[10] This study showed half of those patients had muscle weakness at disease onset and the other half occurred within 1–15 months.

Interestingly, IMNM was a distinguishing feature in isolated anti-U1RNP compared with coexistence of anti-U1RNP and MSAs among anti-U1RNP-positive patients. As for patients with coexistence of anti-U1RNP and MSAs, their pathological characteristics probably match with the respective MSAs. In this study, we showed that most myositis patients with isolated anti-U1RNP antibodies had myofiber necrosis, MHC-I-positive muscle fibers and sarcolemmal C5b9 deposits; none showed perifascicular atrophy. Our findings parallel those reported in other studies. Coppo *et al.*[9] reported the presence of degenerative fibers in 60% and necrotic fibers in 40% of cases; the predominant lesions found via muscle biopsy were myofiber necrosis and/or myofiber regeneration, sarcolemma C5b9 deposits, and positive membranous diffuse staining of MHC-I molecules.[11] Mammen *et al.*[10] reported that over half of their anti-U1RNP cohort showed a predominantly necrotizing pattern without perifascicular atrophy. Because myositis patients with isolated anti-U1RNP antibodies have obvious muscle weakness, significantly increased CK levels, and necrotic muscle fibers, we compared this group with SRP-IMNM and HMGCR-IMNM individuals. We found no significant differences between these groups in their clinical and pathological manifestations.

Some of our participants had a DM rash which could be diagnosed as DM based on clinical symptoms. Unlike typical DM, however, no perifascicular atrophy was found on muscle biopsy. It has been previously reported that individuals with anti-U1RNP can develop typical DM rashes.[10] Another feature in our cohort was that over 40% had arthritis; prevalence was higher in anti-U1RNP than IMNM individuals. Mammen *et al.* similarly reported an arthritis prevalence of around 60% during the course of the disease with a higher prevalence in anti-U1RNP than in DM or IMNM individuals.[10] Less than half of our cohort exhibited Raynaud's phenomenon with an uncommon presentation of swollen hands which agrees with Mammen *et al.* and Wesner *et al.*[10,11]

ILD is frequently associated with IIM, especially in patients with anti-MDA5 and anti-synthase antibodies, and contributes significantly to morbidity and mortality.[25,26] Therefore, it is very important to clarify the clinical characteristics of ILD in such patients. As noted previously, the frequency of ILD identified in patients who were positive for anti-U1RNP varied from 28% to 60%.[9–11,24] In our study, nearly half of the individuals with anti-U1RNP antibodies presented with ILD. The severity of ILD was relatively mild and similar to ILD in SRP-IMNM patients.[27] Furthermore, the frequency of ILD was similar between the anti-U1RNP, SRP, and HMGCR groups.

A previous report showed that Ro-52 antibodies are commonly detected in IIM[28] and that this was associated with an increased risk of ILD and increased ILD severity.[29] In this study, 50% had Ro-52 antibodies in isolated anti-U1RNP; this was similar to SRP but significantly higher than HMGCR. The presence of Ro-52 was not associated with the incidence of ILD. In this study, around a quarter exhibited mild PH on echocardiography; this contrasts with a previous study in which 60% of anti-U1RNP + anti-Ro52 antibody positive individuals developed PH, while none of the individuals without anti-Ro-52 developed PH.[29]

In our cohort, compared to anti-U1RNP and MSAs, patients with isolated anti-U1RNP responded well to steroids and other immunosuppressive agents, and had higher remission rates and

lower relapse rates than anti-HMGCR and SRP-IMNM, suggesting that isolated anti-U1RNP antibodies may constitute a good prognostic marker for IIM. The explanation may be related to the relatively less myofiber necrosis and more inflammatory infiltration in isolated anti-U1RNP patients, so it was more effective for immunotherapy.

There are some limitations of our study. Only a relatively small number of patients was included and the follow-up time was relatively short in some patients. Furthermore, because this was a retrospective study, a complete set of clinical data was not available for every patient. Finally, detecting antibodies by western blotting instead of immunoprecipitation may have resulted in false negatives or positives, thus potentially increasing the risk of classification bias for the presence of anti-U1RNP antibodies.

Conclusions

In conclusion, myositis patients with isolated anti-U1RNP antibodies appear to be a distinct subgroup of IIM that is close to IMNM. Muscular weakness is the main and most salient clinical feature. Most patients respond well to immunotherapy. Further studies are now needed to further characterize myositis patients who possess the anti-U1RNP antibody.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of the China–Japan Friendship Hospital (2019-25-K19, 8 October 2019). All patient data were used anonymously and written informed consent to treatment was obtained from each participant.

Consent for publication

This is a retrospective study and signed consent for publication was not requested.

All co-authors have given their consent for publication of the article.

Author contribution(s)

Yongpeng Ge: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Writing – review & editing.

Hongxia Yang: Data curation; Formal analysis; Methodology; Supervision; Writing – review & editing.

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Acknowledgements

The authors would like to express their gratitude to EditSprings for the expert linguistic services provided.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National High Level Hospital Clinical Research Funding (2022-NHLHCRF-YS-02).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Further information can be obtained by qualified researchers from the corresponding author on reasonable request.

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