

Muscle Pathological Features and Extra-Muscle Involvement in Idiopathic Inflammatory Myopathies With Anti-Mitochondrial Antibody

Lu Zhang

China-Japan Friendship Hospital <https://orcid.org/0000-0001-5621-185X>

Hanbo Yang

China-Japan Friendship Hospital

Jieping Lei

China-Japan Friendship Hospital

Qinglin Peng

China-Japan Friendship Hospital

Hongxia Yang

China-Japan Friendship Hospital

Guochun Wang

China-Japan Friendship Hospital

Xin Lu (✉ luxin_n@163.com)

China-Japan Friendship Hospital

Research article

Keywords: Anti-mitochondrial antibody, Idiopathic inflammatory myopathies, Immune-mediated necrotizing myopathy, Cardiac involvement

Posted Date: December 16th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-126060/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Anti-mitochondrial antibodies (AMAs) can be detected in some idiopathic inflammatory myopathy (IIM) patients. We aimed to investigate the clinical features of IIM patients with AMAs.

Methods

We retrospectively analysed consecutive 1,167 patients with IIM for AMAs-associated myositis and compared them to age- and sex-matched AMA-negative patients.

Results

Twenty-nine patients (2.5%) were identified with AMAs-positive myositis; eight of them had primary biliary cholangitis (PBC). There were no significant differences in skin rash, dysphagia, interstitial lung disease, and muscle strength between AMAs-positive patients and disease controls. 12/23(52.2%) cases showed immune-mediated necrotizing myopathy (IMNM)-like pathological features. Among AMAs-positive patients, 11 of 16 patients with isolated anti-AMA were classified as IMNM which was significantly higher than that of patients with coexistent anti-AMAs and myositis-specific antibodies ($p=0.026$). Moreover, AMAs-positive patients had a significantly higher cardiac involvement ratio ($P<0.001$) compared to controls. Comparison in AMAs-positive IIM patients show the incidence of abnormal echocardiography findings was significantly higher in patients without primary biliary cholangitis (PBC) than in patients with PBC($P=0.009$). Patients without heart abnormalities took significantly less time to achieve disease remission and prednisone tapering to <10 mg than patients with heart abnormalities ($P<0.001$ and $P=0.001$, respectively).

Conclusions

IMNM was a major histopathological finding in IIM patients with isolated anti-AMAs antibody. AMAs was significantly associated with cardiac involvement in IIM. PBC seemed to be a protective factor for abnormal echocardiography findings in AMAs-positive patients. Patients without heart involvement took less time to achieve disease remission and prednisone tapering off.

Background

Idiopathic inflammatory myopathy (IIM) is an autoimmune systemic disease that is characterised by skeletal muscle injury and multi-system involvement, including the skin, lung, heart, and oesophagus. Many autoantibodies, including myositis-specific antibodies (MSAs) and myositis-related antibodies (MRAs), can be detected in the serum [1]. MSAs are closely related to distinct clinical characteristics [2, 3]. Although MRAs have been detected in other connective tissue diseases or overlap syndrome of IIM and other connective tissue diseases, it has been reported that some MRAs were associated with unique features in IIM. Anti-Ku antibody isolated from the serum in IIM was associated with concomitant severe interstitial lung disease (ILD) and immune-mediated necrotising myopathy [4]. Serum anti-Ro-52 antibody in

dermatomyositis (DM) could develop rapidly progressive ILD, which mainly presents with organising pneumonia on high-resolution computed tomography [5, 6].

Anti-mitochondrial antibodies (AMAs) is biomarkers of primary biliary cholangitis (PBC). A recent study noted that AMAs can be detected in some IIM patients [7]. Previous studies have suggested that IIM patients with AMAs frequently have cardiac involvement [8-11]. However, most studies were case reports or small-sample studies, and studies with larger cohorts are needed.

To better understand the clinical features of AMAs-associated myositis, we retrospectively reviewed 29 patients with AMAs from 1,167 IIM patients in our centre. Baseline characteristics, clinical features, electrocardiography, echocardiography, laboratory, histopathological findings and outcomes were reviewed in this study.

Methods

1. Study population

Clinical data were retrospectively analysed from consecutive 1,167 patients with IIM in the Department of Rheumatology at China-Japan Friendship Hospital from January 2008 to December 2019. The classification criterion of IIM was based on the 2017 European League against Rheumatism/American College of Rheumatology Classification Criteria for Adult Idiopathic Inflammatory Myopathies [12]. The diagnosis of PBC can be established when two of the following three criteria are met [13]: (1) biochemical evidence of cholestasis based on alkaline phosphatase elevation; (2) presence of AMAs or other primary biliary cholangitis-specific autoantibodies, including sp100 or gp210, if AMAs are negative; and (3) histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts. To study the clinical features of idiopathic inflammatory myopathy patients with AMAs, we randomly selected 116 idiopathic inflammatory myopathy patients with comparable age and sex as disease controls from the 1,167 idiopathic inflammatory myopathy patient populations. The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital, and written informed consent was obtained from each participant. The study was conducted according to the Declaration of Helsinki 2000.

2. Clinical characteristics

We gathered detailed clinical records, including sex, age at onset, mode of onset, disease course (recorded monthly), muscle strength, rash (heliotrope rash, Gottron rash, periungual erythema, and “mechanic’s hand”), ILD, and oesophageal lesions. Onset times less than 2 weeks and more than 3 months were defined as acute onset and chronic onset, respectively; sub-acute onset was between these limits. Muscle strength was measured using the manual muscle test (MMT8) proposed by the International Myositis Outcome Assessment Collaborative Study (<http://www.niehs.nih.gov/research/resources/>

[imacs/diseaseactivity/index.cfm](http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm)). High-resolution lung computed tomography was performed to investigate radiographic abnormalities consistent with ILD. ILD was defined as the existence of one of the following abnormalities: parenchymal micronodules and nodules, linear opacities, irregularity of the

interfaces between the peripheral pleura and aerated lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectases or bronchiolectases. Dysphagia, nasal or gastroesophageal regurgitation, and aspiration pneumonia were identified as oesophageal lesions, and further examinations were conducted to evaluate oesophageal function, including oesophageal manometry, barium-swallow examination, or endoscopic examination, if necessary. Cardiac involvement was evaluated by electrocardiography (ECG) and echocardiography (UCG). Some patients underwent cardiac magnetic resonance imaging (CMRI). Serum maximum creatine kinase (CK) levels and IgG/IgA/IgM were recorded.

3. MSA and MRA detection

We detected MSA and MRA by immunoblotting with a diagnostic kit (EUROIMMUN, Lübeck, Germany). The MSA and MRA included anti-Mi-2, anti-TIF1 γ , anti-MDA5, anti-NXP2, anti-SAE1, anti-HMGCR, anti-SRP, anti-synthetase (anti-Jo-1, anti-PL-7, anti-PL12, anti-EJ, anti-OJ), anti-Ku, anti-Ro52, anti-PM-Scl100, and anti-PM-Scl75 antibodies. AMAs were tested by line immunoassay according to the manufacturer's protocol (Autoimmune Liver Diseases Antibodies Profile Line Immuno Assay, EUROIMMUN) in the 1,167 IIM patients. Furthermore, the positive samples were tested using a commercially available ELISA assay (EUROIMMUN). Patients whose sera were positive based on both detections above were included in the study.

4. Muscle biopsy

Serial frozen sections were processed for routine haematoxylin and eosin and immunohistochemistry for anti-major histocompatibility complex class II, CD4, CD8, CD45, CD68, and anti-membrane attack complex.

5. Follow-up study

Patients who had one or more of three abnormal ECG, UCG, and CMRI findings were classified as patients with cardiac involvement. The follow-up period started from the initial treatment to death or the last investigation. Disease activities were evaluated by the physician's global assessment based on the investigator's composite assessment of disease activity on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool (MDAAT). The assessments were rated using 10-cm visual analogue scale (VAS) scores (0–10) with higher scores indicating severe disease activity. Disease activity in each subject was estimated by the same physician who was blinded to other clinical information. A VAS score of ≤ 1 was defined as disease remission.

6. Statistical analysis

The analysis was performed using PASW statistics version 18 (IBM, Armonk, NY). Data are expressed as means \pm standard deviation or median (interquartile range). Comparisons between groups were performed using the independent-samples t-test for continuous variables and Fisher's exact test for categorical variables. The Mann-Whitney U test was applied to data with non-normal distributions. Kaplan-Meier survival analyses were performed in a follow-up study. Two-sided p-values of <0.05 were considered statistically significant.

Results

1. AMAs prevalence in idiopathic inflammatory myopathy patients

AMAs were detected in 29 (2.5%) out of 1,167 patients with IIMs from the China-Japan Friendship Hospital between January 2008 and December 2019. Of 29 patients with AMAs, 14 patients had polymyositis (PM), 11 patients had dermatomyositis (DM), and 4 patients had amyopathic dermatomyositis. Eight patients were diagnosed with PBC, and 2 patients had associated systemic sclerosis and primary Sjögren's syndrome, respectively.

2. Clinical characteristics of IIM patients with AMAs

The demographic and clinical characteristics of the 29 IIM patients (7 men, 22 women) with AMAs are shown in Table 1. The age of the patients ranged from 25–83 years, with a mean of 51.0 ± 12.7 years. The median disease duration was 6 (2, 48) months. Eight patients had a sub-acute onset, while the remaining patients had a chronic onset. Sixteen patients had cutaneous manifestations including heliotrope rash, Gottron Papules and Gottron Sign, V-Neck Sign, Shawl Sign, periungual changes, Raynaud's phenomenon, mechanic's hands, and calcinosis cutis. Dysphagia was noted in 8 patients, and 23 patients had cardiac involvement. ILD was present in 16 patient. Twenty-five patients presented with muscle weakness, and the mean MMT8 score was 68.9 ± 8.9 . The median maximum serum CK level was 1,650 (667.5, 4616.75) IU/L. Ten patients were positive following testing with MSAs. These subjects included 3 patients who tested positive for anti-MDA5, 1 patient for anti-TIFy γ 1 patient for anti-NXP2, 1 patient for anti-SRP, and 4 patients for anti-synthetase (anti-Jo-1, anti-PL-7, and anti-PL12). In the spectrum of antinuclear antibodies, anti-Ro52 was detected in 13 patients. Two and three patients tested positive for anti-SSa and anti-dsDNA, respectively. In addition, one patient was anti-PM-SCL10 antibody-positive and the other was anti-gp210 antibody-positive.

By comparing IIM patients with AMAs and disease controls, we found that the incidence of cardiac involvement and maximum serum CK were significantly higher in patients with AMAs than in disease controls (DC) ($p < 0.001$ and $p = 0.026$, respectively; Table 1).

3. Pathological features of the skeletal muscle

Muscle pathological results were available for 23 AMAs-positive patients, and were classified as 12 cases of immune-mediated necrotising myopathy (IMNM), 1 of DM, 1 of PM characteristics, 6 of non-specific myositis and 3 normal/minimal lesions. As for 49 histopathological findings in DC group, there were 15 IMNM, 10DM, 13 non-specific myositis and 11 normal/minimal lesions. There were no significant differences in muscle pathological features between AMAs-positive group and DC group (Table 1). Significantly, comparison in AMAs-positive IIM patients show that 11 of 16 patients (68.7%) with isolated anti-AMAs presented IMNM pathological features. In contrast, only 1 of 7 patients (14.3%) with coexistence of anti-AMAs and SRP antibody showed pathological features of IMNM. The incidence of IMNM in patients with isolated anti-AMAs was significantly higher than that of patients with coexistence of anti-AMAs and

MSA (11/16 vs.1/7, $p=0.026$) (Table 2). Typical pathologic DM, pathologic PM, non-specific myositis and normal pathologic performance in patients with anti-AMAs were shown in Fig 1.

4. Cardiac involvement in AMAs-positive patients

Abnormal auxiliary heart examinations were detected in 21 AMA-positive patients. Only 4 patients (patient 9, 13, 27, and 28) had palpitation. No patients present clinical symptom of heart failure. Therefore, most cases of cardiac involvement were subclinical. As shown in Table 3, 58.6% (17/29) and 59.3% (16/27) patients were identified with abnormal ECG and UCG findings, respectively. Among abnormal ECG findings, ventricular premature beats (8/29), ST-T changes (7/29), and atrial fibrillation (4/29) were the most common. Regarding abnormal UCG, there were 6 cases with left atrial enlargement and 10 cases with valve regurgitation. Pericardial effusions were detected in 7 patients, and most of them (6/7) were small. In addition, CMRI was performed in 4 patients. Late gadolinium-enhanced images in the left ventricular lateral wall were found in 3 cases. It is worth noting that patient No. 21 had an abnormal result on CMRI, although his ECG and UCG were normal. Thus, CMRI helped to identify subclinical cardiac involvement.

AMAs are biomarkers of PBC; we found that only 1 patient (14.3%, 1/7) with PBC had abnormal UCG. As a result, the incidence of abnormal UCG was significantly higher in patients without PBC than in patients with PBC (15/20 vs. 1/7, $P=0.009$; Fig. 2).

5. Treatment and follow-up study

All patients received initial prednisone therapy (1 mg/kg), and the mean initial dose was 50.8 ± 11.6 mg. Twenty-five patients had additional immunotherapies including methotrexate, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, and azathioprine. Twenty-four patients were followed up for 6–84 (mean 26.9 ± 20.7) months. Two patients (No. 11 and 16) died within 3 years and 7 months of diagnosis, respectively. Patient No. 16 died of aspiration pneumonia, and the other died for unclear reasons. Both deaths were complicated by cardiac involvement (Table 3). The remaining 22 patients had good recovery, and the mean maintenance prednisone dose was 8.3 ± 6.2 mg at follow-up.

There were 7 patients without heart involvement and 15 patients had heart involvement. Time to disease remission ($VAS \leq 1$) and prednisone tapering less than 10 mg were compared between patients with cardiac involvement and those without cardiac involvement. The details of the combined immunotherapies are shown in Supplementary Table 1. There were no significant differences in the initial VAS score [5 (4, 6) and 5 (4, 5), $P=0.399$] and prednisone doses (47.3 ± 10.3 and 45.7 ± 7.9 mg, $P=0.718$) between patients with cardiac involvement and patients without cardiac involvement. As shown in Fig. 3, patients without heart abnormalities took significantly less time for disease remission and prednisone tapering off than patients with heart abnormalities ($P<0.001$ and $P=0.001$, respectively).

Discussion

IIM is a heterogeneous disease, and one or more autoantibodies can be detected in serum. The recognition of MSA allows the understanding of the distinct clinical phenotypes of IIM. Meanwhile, MRA is an

autoantibody that can be detected in IIM and other autoimmune diseases. Previous studies indicated that some MRAs, such as anti-Ku antibody and anti-Ro52 antibody, identified a distinct inflammatory myopathy phenotype.

AMAs, as biomarkers of PBC, have been reported in several case reports and cohorts in IIM [14-17]. Therefore, AMAs are identified as MRAs. To our knowledge, the current study is the largest cohort of AMAs-positive IIM patients to date. The prevalence of AMAs was 2.5% in our IIM cohort, which differs from that of previous studies (0.006–11.5%) [14]. Similar to the previous results, the average age was 51 years, and the majority were women.

We did not find a significant difference in rash, ILD or oesophageal lesions between AMAs-positive and AMAs-negative patients. Although the maximum serum CK level in the AMAs-positive group was significantly increased compared with the disease controls, the MMT8 score did not show a statistically significant difference.

Skeletal muscle pathology is crucial for diagnosis and disease evaluation. Previous study showed that AMAs were not associated with a specific subgroup which may present as DM, PM and IMNM. The study by Maeda MH suggested that histopathological findings more frequently showed variation in muscle fibre size, endomysial fibrosis and granulomatous inflammation in AMAs-positive patients. In our cohort, 12/23(52.2%) cases showed IMNM-like pathological features. However, we did not find statistical differences in muscle pathological features of AMAs-positive IIM patients. One possible reason is small numbers of cases. Interestingly, IMNM was a distinguishing feature in isolated anti-AMAs compared to coexistence of anti-AMAs and MSA among AMAs-positive patients. As for patients with coexistence of anti-AMAs and MSA, pathological characteristics probably match with respective MSA.

The study by Albayda et al. suggested that cardiomyopathy and arrhythmia were present in 71.4% (5/7) of AMAs-positive patients [9]. Meiko et al reported that 33.3% (5/24) of AMAs-positive patients showed arrhythmias, and 25% (6/24) showed decreased ejection fraction [14]. In our cohort, results also showed a close relationship between AMAs in IIM and cardiac abnormalities. We found that 72.4% of AMAs-positive patients had at least one abnormal ECG, UCG, or CMRI finding, and the incidence was significantly higher than that of AMA-negative patients. However, only 4 patients had clinical symptoms, which indicated that most heart involvements were subclinical. Specifically, heart involvement included arrhythmia, atrioventricular enlargement, abnormal heart failure, valve disorder, and pericardium. Furthermore, the frequency of abnormal ECG and UCG was significantly higher in AMAs-positive patients than in AMAs-negative patients. As AMAs are biomarkers of PBC, we investigated the effect of PBC on clinical features in AMAs-positive patients. We found that abnormal UCG was more common in patients without PBC than in patients with PBC. However, the study of Meiko et al showed that cardiac involvement was more likely to be present in patients with PBC[14]. The cause of the discrepancy may be due to different cohorts or small sample sizes.

A follow-up study indicated that most AMAs-positive patients improved with prednisone and immunosuppressant. Two deaths with abnormal ECG and UCG occurred in our cohort. In addition, we found

that patients without heart abnormalities took less time to achieve disease remission and prednisone tapering below 10 mg.

This study has some limitations. First, the diagnosis of arrhythmia was based on ECG and not on 24-hour dynamic ECG (Holter), which can provide better information about heart rhythm. Second, only 4 patients underwent CMRI in our cohort, CMRI is helpful for detecting subclinical heart disease. Third, most data on prognosis were obtained by telephone follow-up survey; the results of auxiliary examinations such as ECG and UCG results were incomplete. Therefore, recovery from heart abnormality was not clarified in this study.

Conclusions

IMNM was a major histopathological finding in patients with isolated anti-AMAs antibody. AMAs were significantly associated with cardiac involvement in IIM, and the cardiac involvement was mostly subclinical. PBC seemed to be a protective factor for abnormal UCG in AMAs-positive patients. A follow-up study indicated that disease activities may be less in patients without cardiac involvement.

Abbreviations

AMA:anti-mitochondrial antibody; CK :creatinine kinase; CMRI: cardiac magnetic resonance imaging; DC: Disease controls; DM: dermatomyositis; ECG:electrocardiography; IIM : idiopathic inflammatory myopathy; ILD: interstitial lung disease;IMNM: immune-mediated necrotising myopathy; MDAAT: Myositis Disease Activity Assessment Tools; MRA: myositis-related antibody;MSA:myositis-specific antibody; PBC:primary biliary cholangitis;PM: polymyositis; UCG: echocardiography;VAS:visual analogue scale

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Institutional Review Board of the China-Japan Friendship Hospital (reference number: 2019-226), and written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding Statement

This work was supported by Science and Technology Commission Foundation of Beijing
Z191100006619012.

Authors' contributions

LZ and XL contributed to the study conception, study design, data acquisition, data analysis, data interpretation, and drafting and revising the manuscript. HBY and YHX collected data and conducted the assessment of disease activity in the follow-up study. JPL conducted the random sampling of disease controls and participated in statistical work. QLP and GCW assisted in data interpretation and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

None.

References

- [1] Tansley S, Gunawardena H. The evolving spectrum of polymyositis and dermatomyositis—moving towards clinicoserological syndromes: a critical review. *Clin Rev Allergy Immunol*. 2014. 47(3): 264-73.
- [2] Tieu J, Lundberg IE, Limaye V. Idiopathic inflammatory myositis. *Best Pract Res Clin Rheumatol*. 2016. 30(1): 149-68.
- [3] Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EK. A Comprehensive Overview on Myositis-Specific Antibodies: New and Old Biomarkers in Idiopathic Inflammatory Myopathy. *Clin Rev Allergy Immunol*. 2017. 52(1): 1-19.
- [4] Yang H, Li W, Tian X, et al. Immune-mediated necrotizing myopathies and interstitial lung disease are predominant characteristics in anti-Ku positive patients with idiopathic inflammatory myopathies. *Ann Rheum Dis*. 2020 .
- [5] Bauhammer J, Blank N, Max R, et al. Rituximab in the Treatment of Jo1 Antibody-associated Antisynthetase Syndrome: Anti-Ro52 Positivity as a Marker for Severity and Treatment Response. *J Rheumatol*. 2016. 43(8): 1566-74.
- [6] Chen F, Zuo Y, Li S, Shi J, Wang G, Shu X. Clinical characteristics of dermatomyositis patients with isolated anti-Ro-52 antibody associated rapid progressive interstitial lung disease: Data from the largest single Chinese center. *Respir Med*. 2019. 155: 127-132.
- [7] Uenaka T, Kowa H, Sekiguchi K, et al. Myositis with antimitochondrial antibodies diagnosed by rectus abdominis muscle biopsy. *Muscle Nerve*. 2013. 47(5): 766-8.
- [8] Tanaka K, Sato A, Kasuga K, et al. Chronic myositis with cardiomyopathy and respiratory failure associated with mild form of organ-specific autoimmune diseases. *Clin Rheumatol*. 2007. 26(11): 1917-9.

- [9] Albayda J, Khan A, Casciola-Rosen L, Corse AM, Paik JJ, Christopher-Stine L. Inflammatory myopathy associated with anti-mitochondrial antibodies: A distinct phenotype with cardiac involvement. *Semin Arthritis Rheum.* 2018. 47(4): 552-556.
- [10] Varga J, Heiman-Patterson T, Muñoz S, Love LA. Myopathy with mitochondrial alterations in patients with primary biliary cirrhosis and antimitochondrial antibodies. *Arthritis Rheum.* 1993. 36(10): 1468-75.
- [11] Matsumoto K, Tanaka H, Yamana S, et al. Successful steroid therapy for heart failure due to myocarditis associated with primary biliary cirrhosis. *Can J Cardiol.* 2012. 28(4): 515.e3-6.
- [12] Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. *Arthritis Rheumatol.* 2017. 69(12): 2271-2282.
- [13] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 2019. 69(1): 394-419.
- [14] Maeda MH, Tsuji S, Shimizu J. Inflammatory myopathies associated with anti-mitochondrial antibodies. *Brain.* 2012. 135(Pt 6): 1767-77.
- [15] Hou Y, Liu M, Luo YB, et al. Idiopathic inflammatory myopathies with anti-mitochondrial antibodies: Clinical features and treatment outcomes in a Chinese cohort. *Neuromuscul Disord.* 2019. 29(1): 5-13.
- [16] Yasuda Y, Nakano S, Akiguchi I, Tanaka M, Kameyama M. Polymyositis associated with asymptomatic primary biliary cirrhosis. *Eur Neurol.* 1993. 33(1): 51-3.
- [17] Boki KA, Dourakis SP. Polymyositis associated with primary biliary cirrhosis. *Clin Rheumatol.* 1995. 14(3): 375-8.

Tables

Table 1 is not available with this version.

Table 2: Pathological features of isolated anti-AMA and coexistence of anti-AMA and MSA

Pathological pattern	anti-AMA-positive(n=16)	anti-AMA and MSA positive (n=7)	P value
IMNM	11 (68.8%)	1 (14.3%) (anti-SRP positive)	0.027*
No IMNM	5 (31.3%)	6 (85.7%)	
pDM	0	1 (14.3%) (anti-Jo-1 positive)	
pPM	0	1 (14.3%) (anti-PL-12 positive)	
NSM	3 (18.7%)	3 (42.8%) (2 anti-MDA5 positive and 1 anti-TIFγ)	
Normal	2 (12.5%)	1 (14.3%) (anti-Jo-1 positive)	

AMA, anti-mitochondrial antibody; MSA, myositis-specific autoantibodies; IMNM, immune-mediated necrotizing myopathies;

pDM, pathologic dermatomyositis; pPM, pathologic polymyositis; NSM, Non-specific myositis. * Fisher's exact test for comparison between IMNM and no IMNM

Table 3: Cardiac involvement in IIM patients with AMAs

No	Classification	Other CTD	Cardiac symptoms	Auxiliary examination of cardiac abnormalities		
				ECG	UCG	CMRI
1	NAM			Sinus arrhythmia, VPB, Obsolete inferior myocardial infarction	Regional wall motion abnormality	ND
2	IMNM			AF, SVPB, VPB, Supraventricular tachycardia	Left ventricular enlargement, Mitral regurgitation(mild)	PE(small)
3	NAM			AF, VPB	Left atrial and left ventricular enlargement, Mitral regurgitation(mild), Aortic insufficiency(mild), PE(small)	ND
4	DM	SSc		Normal	Left atrial enlargement, Mitral regurgitation(mild)	ND
5	DM			Normal	PE(small)	ND
6	IMNM			Sinus arrhythmia	PE(small)	ND
9	DM		Palpitation	Sinus rhythm, SVPB, Unusual Q wave, T wave inversion	Ventricular septal hypertrophy,	ND
10	IMNM			Sinus rhythm, Left anterior hemiblock, ST-T changes	Tricuspid regurgitation(mild)	ND
11	DM			Sinus rhythm, VPB, ST-T changes	Left atrial enlargement, Ventricular septal hypertrophy, Left ventricular diastolic dysfunction, PE(small)	ND
12	DM			AF, ST-T changes	Left atrial enlargement, Left ventricular enlargement,	ND
13	NAM		Palpitation	Atrial flutter, VPB, Obsolete inferior myocardial infarction	Left atrial enlargement	ND
14	DM			Sinus rhythm, VPB	Normal	LGE in left ventricular

						lateral wall
15	NAM	□	□	Sinus tachycardia, VPB	ND	ND
16	IMNM	SSc SS	□	Sinus rhythm, QT prolongation, ST-T changes	PE (median-massive), PH	LGE in left ventricular lateral wall, PE (median-massive)
17	DM	□	□	Normal	PE(small)	
21	IMNM	PBC	□	Normal	Normal	LGE in interventricular septum and left ventricular lateral wall
22	DM	PBC	□	Sinus rhythm, ST-T changes	ND	ND
24	IMNM	SS PBC	□	Sinus rhythm, CRBBB	Normal	ND
27	DM	PBC	Palpitation	Sinus rhythm, SVPB	PH, Mitral regurgitation(mild), Tricuspid regurgitation(mild)	ND
28	PM	□	Palpitation	AF, VPB	Left ventricular enlargement, Right atrial and left atrial enlargement, Aortic regurgitation(mild), Mitral regurgitation(mild), Tricuspid regurgitation(mild)	ND
29	DM	□	□	Sinus rhythm, ST-T changes, T wave inversion	Tricuspid regurgitation(moderate), PE(small)	ND

CTD: Connective tissue disease; NAM: Non-specific myositis; DM: Dermatomyositis; PM: polymyositis; IMNM: Immune-mediated necrotizing myopathy; SSc: systemic sclerosis; SS: Sjogren Syndrome; MMT8: Manual muscle test; ILD: Interstitial lung disease; CK: Creatine kinase; ND: Not done; ECG: electrocardiograph; UCG: Ultrasound Cardiogram; CMRI: cardiac magnetic resonance imaging; AF: Atrial fibrillation; VPB: Ventricular premature beats; CRBBB: Complete right bundle branch block; SVPB: Supraventricular premature beat; PE: Pericardial effusion; PH: Pulmonary Hypertension; LGE: Late gadolinium-enhanced images. AF: Atrial fibrillation; VPB: Ventricular premature beats; SVPB: Supraventricular premature beat; PE: Pericardial effusion; PH: Pulmonary Hypertension; ND: Not done.

Figures

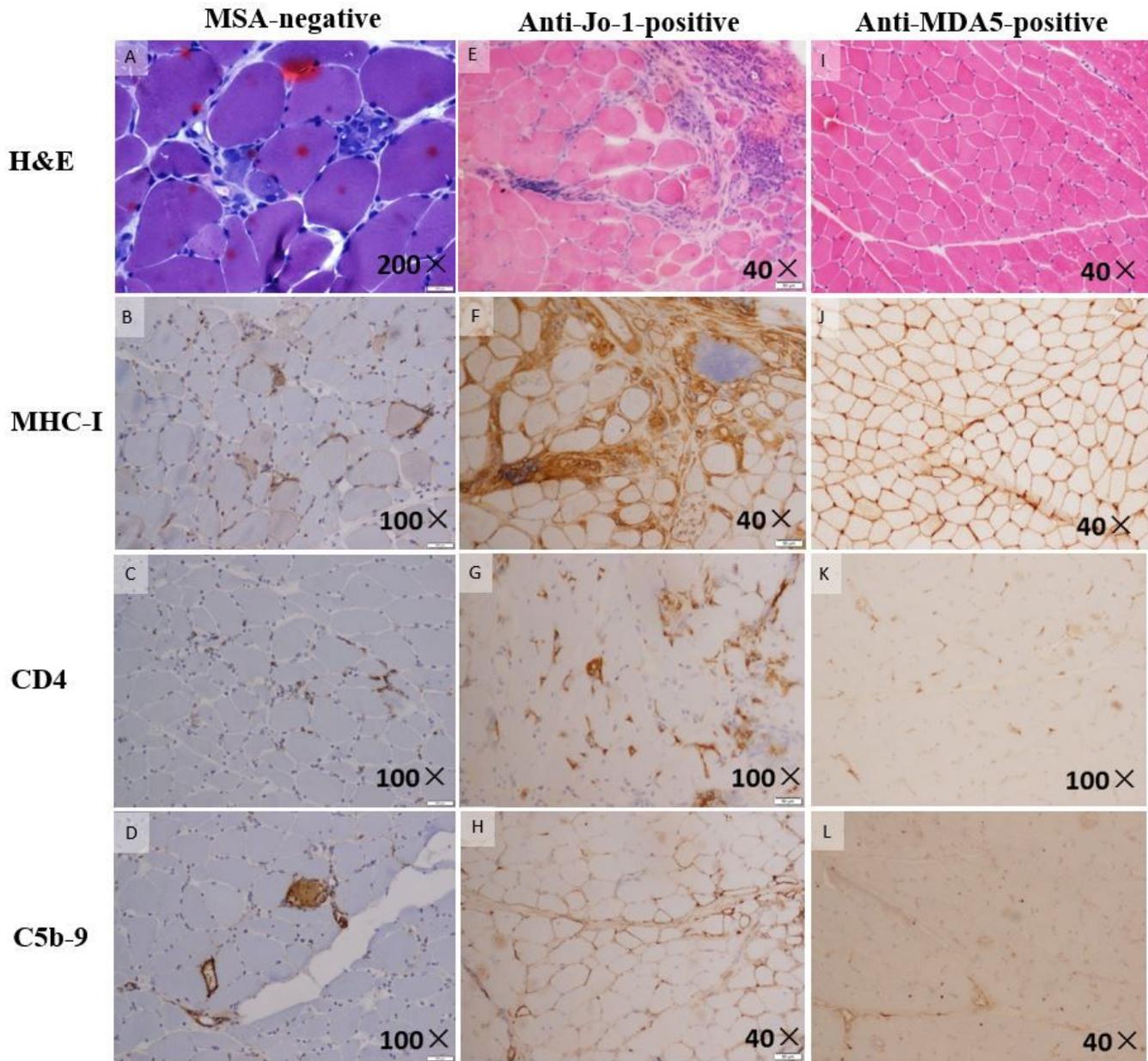


Figure 1

Muscle pathology in AMA-associated IIMs. A-D: Myositis-specific negative patients, E-H: Anti-Jo-1 positive patients, I-L: Anti-MDA5 positive patients. A, E, I(H&E staining): necrosis and phagocytosis of muscle fiber(A), perifascicular atrophy and perivascular inflammation(E), normal muscle(I); B, F, J(Immunohistochemistry staining of MHC-I): Scattered expression of MHC-I in necrotic muscle fiber(B), diffuse expression of MHC-I on sarcolemma(F, J); C, G, K(Immunohistochemistry staining of CD4):The endomysial and perivascular infiltration of CD4+T cell; D, H, L(Immunohistochemistry staining of C5b-9): The deposition of C5b-9 in necrotic muscle fiber(D), on sarcolemma(H) and on capillary walls(L).

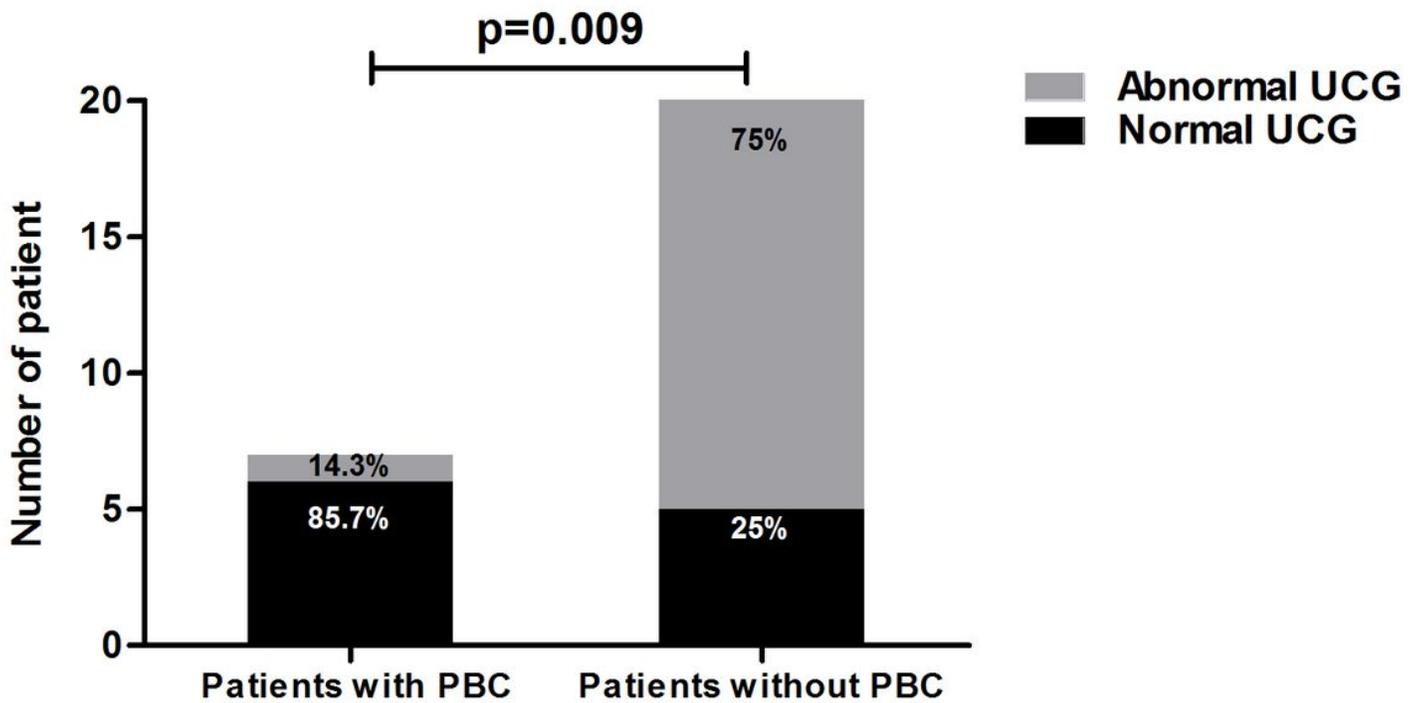


Figure 2

Abnormal UCG was more common in patients without primary biliary cholangitis PBC than in patients with PBC. (15/20 vs. 1/7, P=0.009). UCG: echocardiography, PBC: primary biliary cholangitis.

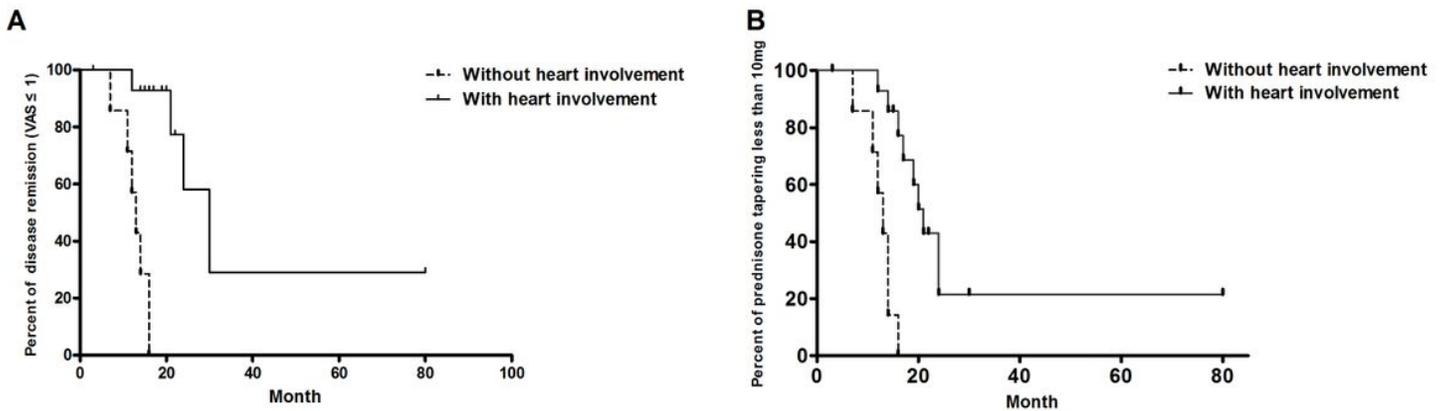


Figure 3

Patients without heart abnormalities took less time to achieve disease remission (VAS ≤1) (A) and prednisone tapering to less than 10 mg (B) than patients with heart abnormalities (P<0.001 and P=0.001, respectively). VAS: visual analogue scale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)