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【 CASE REPORT 】

Antimitochondrial Antibody-associated Myopathy with Slowly Progressive Cardiac Dysfunction

Fumihiko Takahashi[1], Jun Sawada[2], Akiho Minoshima[2], Naka Sakamoto[2], Toshiyuki Ono[2], Kazumi Akasaka[3], Hidehiro Takei[4], Ichizo Nishino[5] and Naoyuki Hasebe[2]

Abstract:
A 45-year-old woman was referred to our hospital for the evaluation of proximal muscle weakness and serum creatinine kinase elevation. She had atrial fibrillation and left ventricular asynergy. She was diagnosed with myopathy, accompanied by cardiomyopathy of unknown etiology. She was treated with prednisolone. After long-term follow-up and a detailed examination, the patient was diagnosed with antimitochondrial antibody (AMA)-associated myopathy with cardiac involvement. Although the patient received medical treatment, including beta-blockers and prednisolone, her cardiac function deteriorated progressively. Physicians should consider AMA-associated myopathy when diagnosing myopathies of unknown etiology. The presence of cardiac involvement should be proactively investigated in AMA-associated myopathy.

Key words: immune-mediated necrotizing myopathy, atrial fibrillation, corticosteroid

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Introduction

Antimitochondrial antibodies (AMAs) are autoantibodies against several mitochondrial antigens that are most commonly found in association with primary biliary cholangitis (PBC) (1). Although the presence of these antibodies has been linked to other autoimmune conditions, such as Sjögren's syndrome, scleroderma, and autoimmune thyroid disease, inflammatory myopathy occurring in association with AMA is rare (2). However, this clinical entity is being recognized increasingly frequently (3-8), and cardiac involvement was reported in approximately 30% of cases with AMA-positive myopathy (3).

We herein report the long-term follow-up of a 45-year-old woman with AMA-associated myopathy with slowly progressive cardiac dysfunction that was initially difficult to diagnose.

Case Report

A 45-year-old woman was referred to our hospital for the evaluation of proximal muscle weakness and serum creatinine kinase (CK) elevation. Her medical history included hypertension, which was managed with medical therapy for five years, and a hemorrhagic stroke that was treated conservatively eight months before the presentation. Her neurological symptom was mild paresis of the right arm, which subsequently completely resolved. She was married with 2 children and smoked 20 cigarettes per day, with occasional alcohol consumption. There was no family history of neuromuscular disorders.

In June 2010, she had noticed the weakness of her upper limbs and experienced difficulty carrying baggage. The patient was hospitalized in September 2010 for a detailed examination and treatment.

The physical findings on admission included a blood pressures of 144/90 mmHg and a heart rate of 100 bpm.

[1]Department of Cardiovascular Medicine, Rumoi City Hospital, Japan, [2]Department of the Internal Medicine, Cardiovascular, Respiratory and Neurology Division, Asahikawa Medical University, Japan, [3]Department of Laboratory Medicine, Asahikawa Medical University, Japan, [4]Department of Diagnostic Pathology, Asahikawa Medical University Hospital, Japan and [5]Department of the Neuromuscular Research, National Institute of Neuroscience, Japan
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Correspondence to Dr. Fumihiko Takahashi, ft-park@cb3.so-net.ne.jp

Table. Laboratory Finding on the First Admission.

WBC	8,950 /μL	TP	8.3 g/dL	IgG	2,002 mg/dL
Neutro	54.4 %	Alb	4.1 g/dL	IgA	325 mg/dL
Eos	10.1 %	AST	83 U/L	IgM	191 mg/dL
Baso	0.5 %	ALT	55 U/L	RF	<25 IU/mL
Mono	8.5 %	LDH	386 U/L	ACE	10.6 U/L
Lymph	24.1 %	ALP	528 U/L	sIL-2R	404.0 U/mL
RBC	441×10^4 /μL	γ-GTP	97 U/L	ANA	20×
Hb	13.4 g/dL	CK	1,883 U/L	Jo-1	7.0 U/mL
Plt	37.6×10^4 /μL	CK-MB	30 U/L	Anti-dsDNA	<5.0 IU/mL
ESR	42 mm/h	Aldolase	12.5 U/L	Anti-SSA	0.6 U/mL
PT	94 %	UN	11.0 mg/dL	Anti-SSB	1.3 U/mL
APTT	31.1 s	Cre	0.41 mg/dL	MPO-ANCA	<1.3 EU
Fibrinogen	358 mg/dL	Na	137 mEq/L	PR3-ANCA	<3.5 EU
D-dimer	1.06 mg/mL	K	4.0 mEq/L	Scl-70	7.0 U/mL
		Cl	110 mEq/L	Anti-RNP	2.5 U/mL
Urinalysis		Ca	9.4 mg/dL	Anti-SRP	<1.0 IU/L
Specific gravity	1.011	Glu	78 mg/dL	Anti-HMGCR	<1.0 IU/L
Protein	(-)	HbA1c	4.8 %	HBs-Ag	(-)
Sugar	(-)	T-cho	202 mg/dL	HCV-Ab	(-)
Occult blood	(-)	TG	133 mg/dL		
		CRP	<0.1 mg/dL		

WBC: white blood cells, Neutro: neutrophils, Eos: eosinophils, Baso: basophils, Mono: monocytes, Lymph: lymphocytes, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, Plt: platelets, ESR: erythrocyte sedimentation rate, PT: prothrombin time: APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, CK: creatine kinase, UN: urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, Glu: plasma glucose, HbA1c: glycated hemoglobin, T-cho: total cholesterol, TG: triglyceride, CRP: C-reactive protein, Ig: immunoglobulin, RF: rheumatoid factor, ACE: angiotensin-converting enzyme, sIL-2R: soluble interleukin-2 receptor, ANA: anti-nuclear antigen, Jo-1: anti-Jo-1 antibody, Anti-dsDNA: anti-double stranded DNA antibody, Anti-SSA: anti-Sjoögren's syndrome-related antigen A, Anti-SSB: anti-Sjoögren's syndrome-related antigen B, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase3-anti-neutrophil cytoplasmic antibody, Scl-70: anti-scleroderma-70 antibody, Anti-RNP: anti-ribonucleoprotein antibody, Anti-SRP: anti-signal recognition particle antibody, Anti-HMGCR: anti-3-hydroxy-3-methylglutaryl-CoA reductase antibody, HBs-Ag: hepatitis B surface antigen, HCV-Ab: hepatitis C virus antibody

Manual muscle testing (MMT) was 4/5 for the neck and bilateral proximal muscles of her upper and lower limbs. Table shows the laboratory findings on admission. In summary, blood testing revealed elevated CK at 1,883 U/L (CK-MB 30 U/L), and aldolase at 12.5 U/L, and mildly elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) (83 U/L, 55 U/L, and 528 U/L, respectively). Serum levels of angiotensin-converting enzyme and soluble interleukin-2 receptor were within the normal range. Immunoserological tests revealed negative anti-Jo 1 antibody, anti-signal recognition particle antibody, and anti-3-hydroxy-3-methylglutaryl-CoA reductase antibody. Chest radiography showed mild cardiomegaly with a cardiothoracic ratio of 53%. Electrocardiography revealed atrial fibrillation of 102 bpm, poor R wave progression, and normal QRS duration (800 ms). A 24-h Holter monitor revealed persistent atrial fibrillation, average heart rate of 102 bpm, 10,369 ventricular ectopic beats (7% of the sum of cardiac beats), and 4 longest-lasting beats. Transthoracic echocardiography revealed localized thinning of the basal inferior wall of the left ventricle (LV) with a diastolic dimension (LVDd) of 45 mm. The left ventricular systolic function was preserved, with an ejection fraction (EF) of 55%, and the right ventricular size and systolic function were normal (Fig. 1A, B). Needle electromyography showed a myopathic pattern of proximally predominant low-amplitude/short-duration motor unit potentials, preserved interference, and fibrillation potentials and positive sharp waves at rest. Cardiac magnetic resonance imaging (MRI) showed a high-intensity area in the basal inferoseptal to inferolateral wall on short inversion time inversion recovery (STIR) imaging, and late gadolinium enhancement (LGE) of the basal inferior to inferolateral wall (Fig. 2A). Muscle MRI-STIR imaging of the proximal upper and lower limbs revealed mild high-intensity areas suggestive of muscle edema and inflammation. ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) did not show any abnormal uptake in the cardiac or skeletal muscles. There was no mediastinal or hilar lymphadenopathy. A muscle biopsy examination of the left biceps brachii revealed variations in fiber size and necrotic and regenerating fibers (Fig. 3A). Although her clinical symptoms indicated polymyositis, the

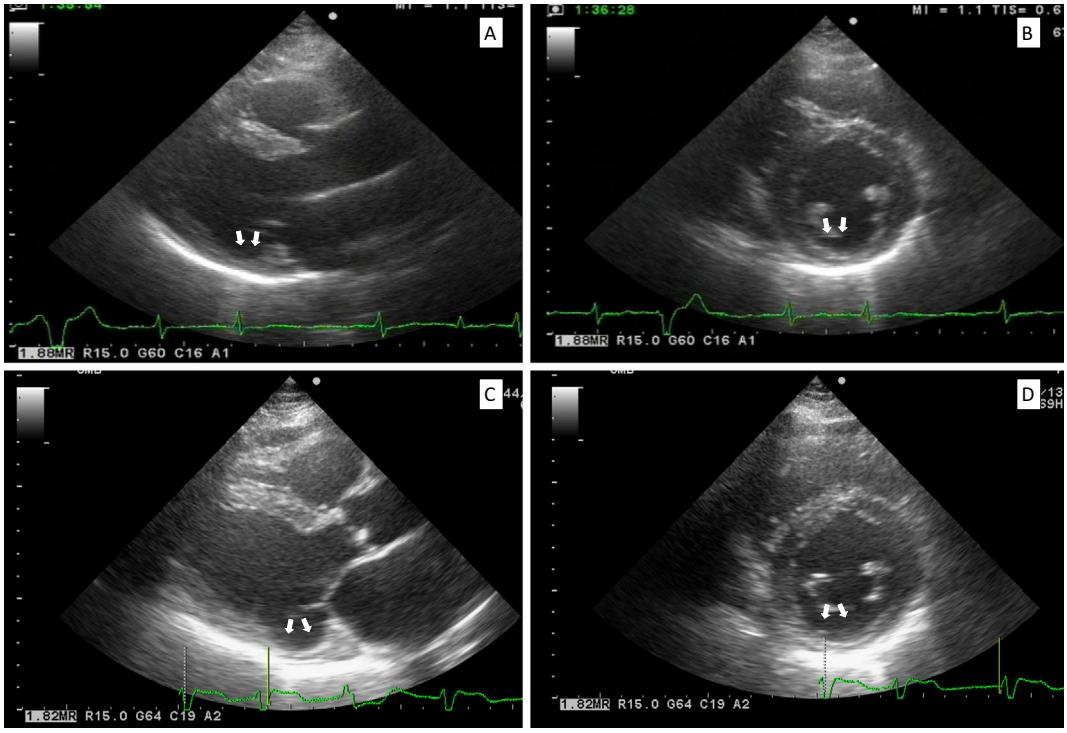

Figure 1. **A transthoracic echocardiogram of the patient at the first admission (A, B) and the third admission (C, D). Echocardiography at the first admission revealed localized thinning of basal inferior of LV (arrows). This lesion had expanded by the third admission (arrows).**

histopathological findings of the muscle biopsy specimen showed non-specific myopathic changes. She was diagnosed with myopathy accompanied by cardiomyopathy of unknown etiology.

The patient was treated with 30 mg/day of prednisolone, warfarin, carvedilol, and eplerenone (Fig. 4). Thereafter, the CK levels normalized, and her decreased muscle strength gradually improved to an MMT of 5/5. Prednisolone use was tapered gradually based on her MMT and the levels of CK.

In June 2012, liver injury developed when the prednisolone dose was tapered to 2 mg/day. She experienced mild fatigue and nausea. Serum biochemistry revealed elevated levels of AST at 124 U/L, ALT at 102 U/L, ALP at 857 U/L. Four months later, she was readmitted to our hospital for a further examination of liver injury. Serum serological tests revealed high titers of antimitochondrial-M2 antibody (AMA-M2) at 122.0 U/mL. Anti-thyroglobulin was also positive (6,400×). Thyroid function-related tests showed slightly increased levels of thyroid-stimulating hormones at 6.63 U/mL, while the serum levels of triiodothyronine and free thyroxine were within the normal ranges (2.61 pg/mL, and 1.08 ng/dL, respectively). The plasma α-galactosidase A activity was normal (52.5 nmol/h/mL). A liver biopsy revealed portal lymphoplasmacytic hepatitis with interlobular bile duct damage. No granuloma was seen. Although the histopathological findings of the liver biopsy specimen were non-specific, PBC-autoimmune hepatitis (AIH) overlap syndrome was strongly suggested; therefore, corticosteroid therapy was indicated. Prednisolone at a dose of 30 mg/day was started, and 300 mg/day of ursodeoxycholic acid (UDCA) was added to her treatment regimen. This treatment was effective, and her liver enzymes normalized (Fig. 4). Prednisolone was tapered gradually based on her symptoms, such as fatigue and the levels of liver enzymes. Thereafter, the dose of prednisolone was maintained at 5 mg/day, and she was doing well for about 4 years.

However, in December 2016, she complained of fatigue and shortness of breath at an outpatient clinic, and an electrocardiogram revealed atrial fibrillation of 67 bpm with complete left bundle branch block (QRS duration, 132 ms). Furthermore, her plasma level of brain natriuretic peptide (BNP) was elevated (108 pg/mL). Therefore, she was referred to our hospital for evaluation of her cardiac disease in February 2018.

Chest radiography showed a cardiothoracic ratio of 60%. Blood testing revealed elevated plasma levels of BNP at 198 pg/mL and negative troponin I levels (<10 pg/mL). The serum levels of AMA-M2 was 251.9 U/mL. Transthoracic echocardiography revealed left atrial dilatation and expansion of the thinned and akinetic area of the basal inferior wall of the LV. The LVDd was 51 mm, and the EF was reduced to 40% (Fig. 1C, D). Cardiac MRI revealed negative STIR imaging, and positive LGE of the mid-layer of the basal septum and inferior to lateral wall of the LV, suggesting myocardial fibrosis (Fig. 2B). A coronary angiogram was normal. A histopathological examination by right ventricular endomyocardial biopsy (4 specimens) revealed mild hypertrophy of myocytes with some variation in size. No inflammatory cell infiltrate was present (Fig. 5).

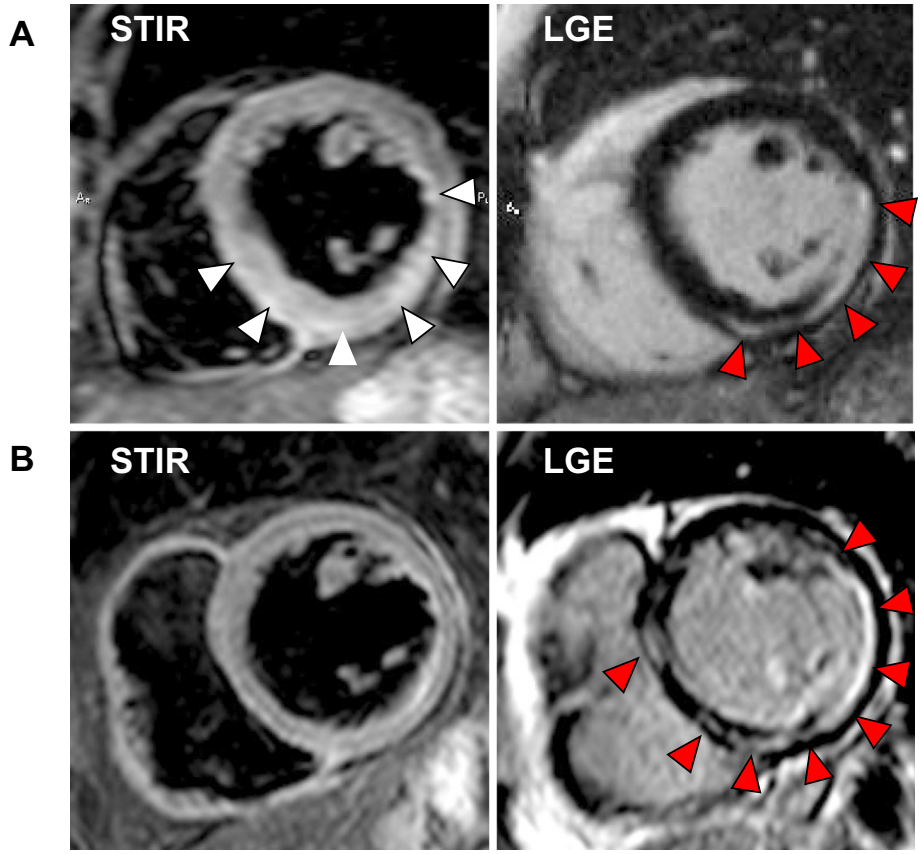

Figure 2. **Cardiac magnetic resonance imaging (MRI) [short inversion time inversion recovery (STIR) imaging and late gadolinium enhancement (LGE) imaging] performed at the first admission (A) and the third admission (B). STIR imaging at the first admission detected a high-intensity region in the basal inferoseptal to inferolateral wall (A, white arrowheads). LGE imaging revealed late gadolinium enhancement of the basal inferior to inferolateral wall (A, red arrowheads). Cardiac MRI at the third admission revealed negative STIR imaging and positive LGE of the mid-layer of the basal septum and inferior to the lateral wall, suggesting myocardial fibrosis (B, red arrowheads).**

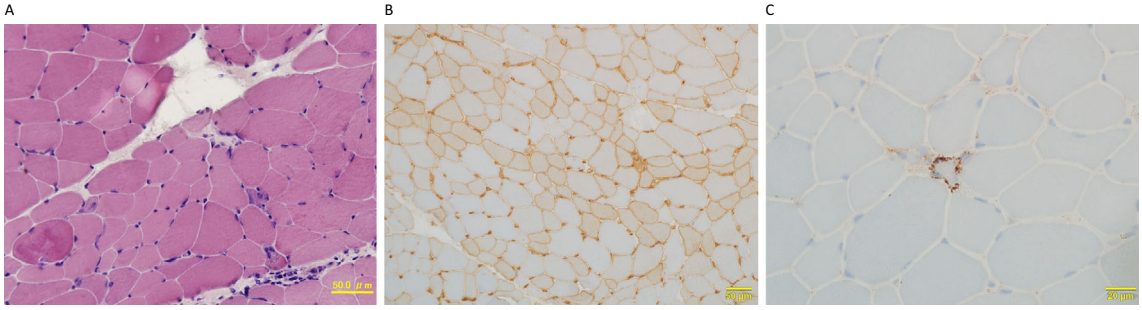

Figure 3. **Histopathological findings of the left biceps brachii muscle. Hematoxylin and Eosin staining showed variations in fiber size as well as necrotic and regenerating fibers (A), positive major histocompatibility complex (MHC) class I (B), and membrane attack complex (C) immunostaining.**

We reviewed the entire clinical course of the patient and suspected that the patient had myopathy associated with AMAs. The muscle biopsy specimen obtained at the first admission was re-examined. On immunohistochemistry, muscle fibers expressed major histocompatibility complex class I (Fig. 3B), and the membrane attack complex (MAC) was deposited on the sarcolemma of the muscle fibers (Fig. 3C). These findings suggested AMA-associated immune-mediated necrotizing myopathy (IMNM). The patient was discharged with New York Heart Association class 2 and was followed up carefully by combination therapy with 5 mg/day of prednisolone, 300 mg/day of UDCA, 5 mg/day of carvedilol, 25 mg/day of eplerenone, and warfarin.

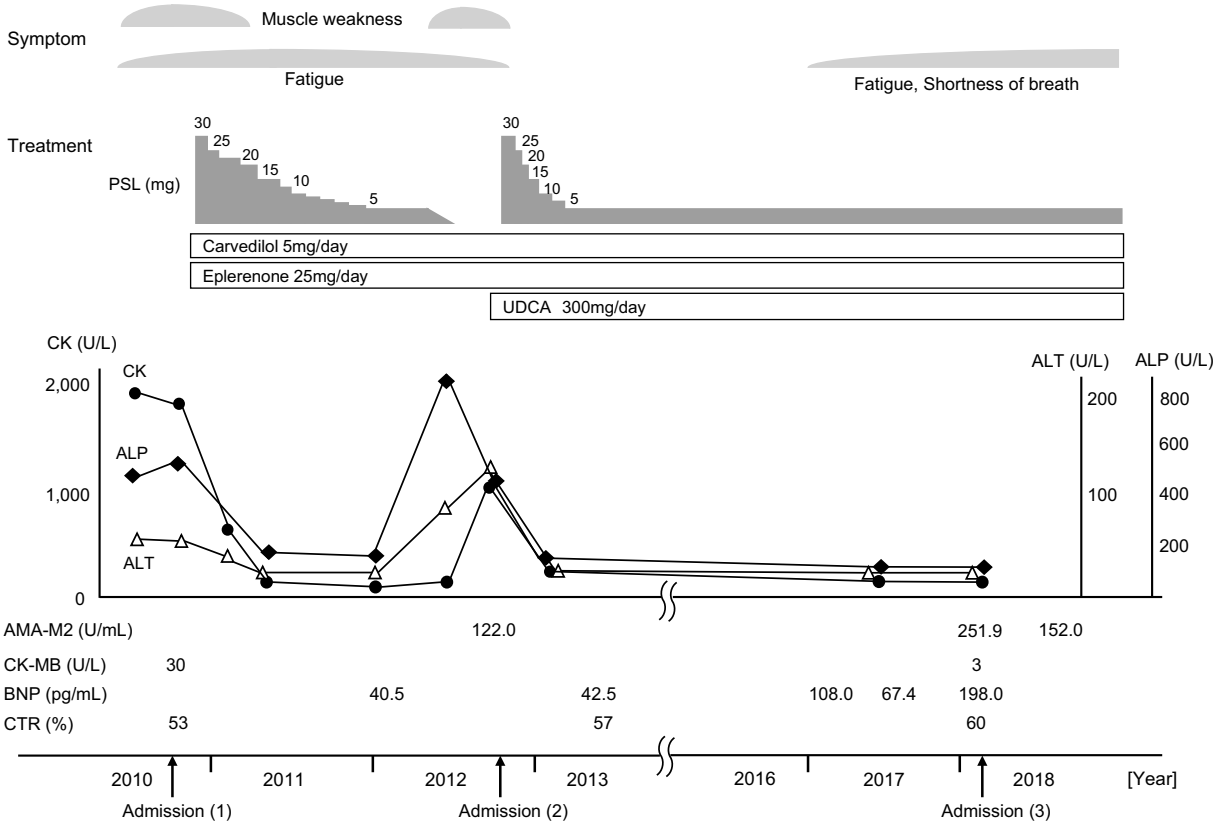

Figure 4. **Clinical course of the patient. PSL: prednisolone, UDCA: ursodeoxycholic acid, CK: creatine kinase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, AMA-M2: antimitochondrial-M2 antibody, BNP: brain natriuretic peptide, CTR: cardio-thoracic ratio**

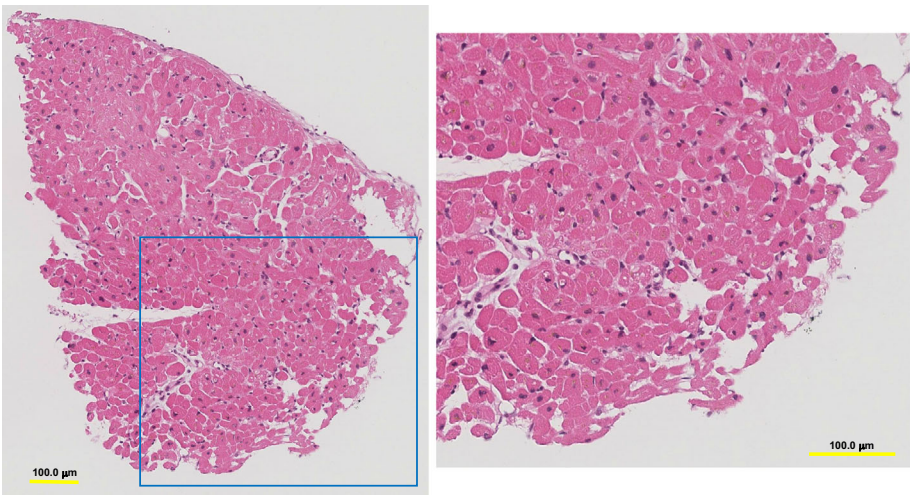

Figure 5. **Histopathological findings of the endomyocardial biopsy specimen. Hematoxylin and Eosin staining showed non-specific findings with mild hypertrophy of cardiomyocytes with some variation in size. No inflammatory cell infiltrate was present.**

Discussion

This report describes a case of AMA-associated myopathy with slowly progressive cardiac involvement that was initially difficult to diagnose. AMAs are autoantibodies against several mitochondrial antigens that can be detected in the sera of patients with PBC (1). AMA-M2 reacts with the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) located in the inner mitochondrial matrix and can be detected in 90-95% of patients with PBC (1). Although AMAs are most commonly found in association with PBC, the presence of the antibody has been linked to other autoimmune conditions, such as Sjögren's syndrome, scleroderma, and autoimmune thyroid disease (2). Inflammatory myopathy occurring in association with AMA is rare, but there has

been growing recognition for this clinical entity (3-8).

The characteristic clinical and histopathological features of AMA-associated myopathy have not yet been clarified because of a lack of large-scale, systemic clinical and histopathological studies. A recent comprehensive study in Japan including 212 patients with inflammatory myopathy reported a prevalence of 11.3% for AMA-associated myopathy in their cohort (3). This study revealed the clinical features of AMA-associated myopathy, including a chronic disease course, muscle atrophy, and a cardiopulmonary involvement. Regarding histopathology, granulomatous inflammation was observed in 25% of the cases, whereas 96% of cases had necrotic and/or regenerating fibers mimicking IMNM (3). Like other IMNM, sarcolemmal MAC deposition is often observed in AMA-associated myopathy (9).

In this patient, sarcoidosis and Fabry disease were included in the differential diagnosis. However, these systemic disorders were not suggested from blood laboratory tests or PET-CT. Although AMA was detected in her clinical course, its association with myopathy/cardiomyopathy was not recognized for several years. However, we reviewed her eight-year clinical course and re-examined her previous muscle biopsy specimen. We then ultimately made the accurate diagnosis of AMA-associated myopathy with cardiac involvement. Since AMA-associated myopathy is a rare clinical entity that is not a well-recognized, it might have been underdiagnosed or misdiagnosed as other inflammatory myopathies in other cases (6, 9, 10).

Maeda et al. found that cardiac involvement was significantly more common in AMA-positive cases than in AMA-negative cases (3). Cardiac involvement, including arrhythmias and decreased EF, was found in approximately 30% of cases of AMA-positive myopathy, although no detailed pathological analysis of the myocardium was performed (3). Albayda et al. reviewed the cases of AMA-associated myopathy in their cohort and highlighted the association of AMA with a phenotype of a chronic inflammatory myopathy and prominent severe cardiac involvement (7). In addition, Koyama et al. reported an autopsy case of AMA-positive myocarditis mimicking arrhythmogenic right ventricular cardiomyopathy. In the histopathology of that case, there was a massive infiltration of lymphocytes with various degrees of fibrofatty replacement in both the right and left ventricle (11). In the present patient, inflammatory cell infiltrate was not confirmed. The endomyocardial biopsy may not have identified the myocarditis lesions because of the non-uniform involvement of this disease in this patient.

The pathogenic roles of AMAs in myopathy and cardiomyopathy are uncertain. Maeda et al. reported in their cohort of AMA-associated myopathy that the patients with high AMA-M2 titers tended to have cardiomyopathies, arrhythmias, and granulomatous inflammation more frequently than those without these issues (3). However, the difference was not statistically significant. Interestingly, they also reported that the titer of AMA-M2 was significantly correlated with the disease duration before the diagnosis (3). In the present patient, there seemed to be no relationship between the titer of AMA-M2 and the disease activity or corticosteroid therapy. In patients with PBC, there has been controversy over whether or not AMAs are pathogenic, although AMAs are highly specific for PBC (1). Recently, Saito et al. reported a case of eosinophilic myocarditis associated with AMA-M2 (12). In their report, immunohistochemistry for PDC-E2, an antigen for AMA-M2, revealed granular cytoplasmic staining in both myocytes and cardiomyocytes in biopsy samples. They speculated that mitochondrial damage released PDC-E2 into the cytoplasm, and prompted inflammatory activation against those damaged cells. However, more advanced studies will be needed to elucidate the mechanism underlying myocardial damage in patients with AMA-associated myopathy with cardiac involvement.

In the present patient, cardiac involvement, which was a localized asynergy of the LV, was detected by echocardiography. Echocardiography is a non-invasive and useful modality for assessing the functional and structural abnormalities in patients with inflammatory myopathy. In contrast, cardiac MRI has the unique capability to detect inflammation, tissue edema, and fibrosis, which can be used to evaluate cardiac involvement in AMA-associated myopathy (13, 14). In the present patient, cardiac MRI at the first admission revealed a high-intensity area at the basal inferoseptal and inferolateral wall on STIR imaging, suggesting inflammation or edema, although the myocardial lesion seemed to be localized at the basal inferior wall of the LV on the echocardiogram. The early diagnosis of myocardial inflammation is important, and cardiac MRI is a potentially useful modality in cases of AMA-associated myopathy (13).

Corticosteroids are considered as the first-line therapy for dermatomyositis, polymyositis, and IMNM (6, 8, 10). However, there is no established treatment for AMA-associated myopathy with cardiac involvement. While the improvement of cardiac involvement induced by prednisolone has been reported (6, 15), there have also been some reports of cases where cardiac involvement remained unchanged or even deteriorated (3, 5, 8). Yamanaka et al. suggested that cardiac involvement results in a more difficult response to prednisolone than does myopathy (8). When patients with autoimmune myopathies have multisystem involvement, such as myocarditis, a second-line agent (e.g., methotrexate and azathioprine)- together with corticosteroids - is recommended (10, 14). However, whether or not these second-line agents are effective against cardiac involvement in cases of AMA-associated myopathy is unclear.

In this patient, atrial fibrillation, ventricular ectopic beats, and localized asynergy of the LV were detected when her myopathy was diagnosed. The patient had received standard medical treatment, including beta-blockers and diuretics, as well as a corticosteroid. However, the cardiac involvement, such as a decreased EF and conduction system disturbance, worsened slowly, although her myopathy and PBC-AIH overlap syndrome were stable. Therefore, the lessons that can be drawn from this case are as follows: 1) physicians

should recognize the AMA-associated myopathy with cardiac involvement as an important clinical entity because the cardiomyopathy can deteriorate progressively; 2) cardiac involvement should be investigated proactively and repeatedly using non-invasive imaging modalities, such as echocardiography and cardiac MRI, to avoid both diagnostic and treatment delays; and 3) the treatment regimen should be decided carefully given that there is no consensus concerning the initial and maintenance doses of corticosteroids and second- or third-line therapy for this disease. More aggressive interventions, such as catheter ablation, pacemaker implantation, and an implantable defibrillator, should be considered when arrhythmias are refractory or critical (8, 14). Furthermore, cardiac resynchronization therapy is a treatment option when heart failure becomes refractory to medical treatment (16).

In conclusion, physicians should consider AMA-associated myopathy when diagnosing myopathies of unknown etiology in patients with multisystem involvement. The early diagnosis of this disease might be essential for preventing the progression of cardiac dysfunction. However, there are still many unknown aspects, such as the mechanism underlying the cardiac involvement of this disease and the response of cardiac involvement to myopathy treatment, as well as the long-term prognosis. These items should be addressed in further studies involving more samples.

The authors state that they have no Conflict of Interest (COI).

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