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Title page

Clinical features of anti-mitochondrial M2 antibody-positive myositis: case series of 17 patients

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Abstract

Objective: In 2012, a large number of myositis cases with anti-mitochondrial M2 (AMA-M2) antibody, which had well been known as the serological hallmark for primary biliary cholangitis (PBC), were reported in Japan. Recently, some case series from Japan, France, America, China and India have shown that approximately 2.5% to 19.5% of patients with myositis have AMA-M2 antibody. The objective of this study was to clarify the prevalence, clinical features, treatment outcome, and severity determinants of AMA-M2 positive myositis.

Methods: This study was a multicenter observational study. We enrolled patients who were diagnosed with myositis during a ten-year period between 2012 and 2021.

Results: Of the total of 185 patients with inflammatory myopathy, 17 patients were positive for AMA-M2 antibody. The typical symptoms were weakness mainly involving paravertebral muscles, weight loss, respiratory failure, and cardiac complications. Thirteen of the 17 patients had cardiac complications. A strong correlation was found between respiratory failure and modified Rankin Scale (mRS) score. A strong correlation

was also found between respiratory failure and body weight, indicating that weight loss can be an indicator of potential progression of respiratory failure. Six of the 17 patients were complicated by malignancy.

Conclusions: This study showed significant correlations between % vital capacity (VC), body mass index (BMI), and mRS score in patients with AMA-M2-positive myositis. Immunotherapy often improved CK level and respiratory dysfunction. We therefore propose that %VC and BMI should be monitored as disease indicators in treatment of AMA-M2-positive myositis.

Introduction

Inflammatory muscle diseases have been diagnosed on the basis of diagnostic criteria proposed by Bohan et al. in 1975 [1, 2]. More recently, classification has been based on the clinical picture, muscle pathology, and antibody identification. In 2004, classification into dermatomyositis, polymyositis, inclusion body myositis, and immune-mediated necrotizing myopathy was proposed [3] and an independent subtype by anti-aminoacyl-tRNA synthetase (ARS) antibodies was added in 2014 [4, 5]. Clinical diagnostic criteria were reported in 2017 [6]. There are subtypes of inflammatory muscle disease that have been classified on the basis of antibody identification, such as ARS and signal recognition particle (SRP) antibodies [7], and it is expected that similar classifications will be made in the future.

Anti-mitochondrial antibody (AMA) had well been known as the serological hallmark for primary biliary cholangitis (PBC) [8-10]. Myositis complicated by AMA was first reported in detail in 1974 as myositis complicated by PBC [11]. In 2012, a large number of cases with AMA-M2 were reported in Japan [12]. Since then, there have been many

reports about myositis with AMA-M2 and the concept of myositis with AMA-M2 is becoming established. Some case series from Japan, France, America, China and India have shown that approximately 2.5% to 19.5% of patients with inflammatory myopathy have AMA-M2 [12-18], and typical clinical symptoms in those patients are chronic disease course and lesser degree of limb muscle weakness and more frequent cardiopulmonary involvement than those in patients with classic inflammatory myopathy. On the other hand, some recent studies have shown various atypical manifestations other than myopathy such as respiratory dysfunction and cardiomyopathy [19-21]. Those studies suggest that the clinical spectrum of AMA-M2-positive myositis may be more heterogeneous than previously thought. Although there are reports that AMA-M2 antibody is not a marker of inflammatory muscle disease [15], most reports indicated that AMA-M2-positive myositis is a distinctive group with myocardial damage [12, 22]. Therefore, further investigation of prognostic factors for AMA-M2-positive myositis based on pathophysiology and treatment effects is needed.

In this study, we conducted a retrospective analysis of detailed clinical information of 17

patients with the aim of finding useful indicators for treatment and follow-up of AMA-M2 positive myositis in Hokkaido, northern island of Japan. We reviewed 17 patients in detail from the aspects of neurology and cardiology.

Patients and methods

Study design and ethics

This study was a multi-institutional observational study. We enrolled 185 patients with inflammatory myopathy referred to Hokkaido University Hospital, Hakodate Municipal Hospital and Japanese Red Cross Asahikawa Hospital during a 10-year period between 2012 and 2021. This clinical study was approved by the ethics panels of Hokkaido University Hospital as protocol number “020-0038”.

Anti-mitochondrial M2 antibody and criteria

The diagnosis of inflammatory myopathy was conducted by several neurologists based on the diagnostic criteria for inflammatory myopathy proposed by Bohan and Peter [1, 2], targeting all types, “definite”, “probable”, and “possible”. Among 185 patients with

inflammatory myopathy, 99 patients were screened for AMA-M2 and 17 patients were positive. The diagnosis of AMA-M2-positive myositis was based on AMA-M2 positivity. In addition, in 15 patients with AMA-M2-positive myositis, histopathological findings including muscle fiber degeneration, necrosis, phagocytosis, atrophy, regeneration, inflammatory cell infiltration, major histocompatibility complex (MHC) class I expression, sarcoplasmic deposition of membrane attack complex (C5b-9), and exclusion of muscular dystrophy by immunostaining were evaluated. For the exclusion of inclusion body myositis, the criteria proposed by Griggs et al. [23] and Needham et al. [24] were used. All of the patients were AMA-M2-positive. Clinical information and information on histopathological findings were collected retrospectively. The disease duration before diagnosis was defined as the period from initial awareness of the symptoms to the time muscle biopsy was performed for histopathological diagnosis. For cases without muscle biopsy, disease duration before diagnosis was defined as the period from initial awareness of the symptoms to the confirmation of AMA-M2 positivity. Muscle weakness, myalgia, and postural abnormalities were assessed at the time of muscle biopsy. For the data

including creatine kinase (CK), aldolase, NT-pro BNP, BNP, troponin-I, AMA-M2 index, vital capacity percentage (%VC), body mass index (BMI) and left ventricular ejection fraction (LVEF), the values immediately before the start of immunotherapy and the maximum improvement values after the start of immunotherapy were compared.

Statistical analysis

Analysis was performed using R. All of the measurement data were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) if they were normally or non-normally distributed, respectively. Enumerated data were expressed as a percentage. The Wilcoxon signed-rank test was used for the paired two groups of tests. Pearson's or Spearman's correlation test was performed to analyze the correlations between the values of clinical data (duration before diagnosis, CK value, AMA-M2 index, % VC, LVEF, mRS score, BMI). $P < 0.05$ was considered statistically significant.

Results

The demographics of all patients are summarized in Table 1.

Seventeen patients with AMA-M2-positive myositis were identified among the total of 185 patients with inflammatory myopathies who visited our hospitals (Table 1). The proportion of AMA-M2-positive patients was 9.2% of all inflammatory myopathy patients. The 17 patients included 13 women and 4 men. The average age at onset of myositis symptoms was 57.4 (SD 9.4) years. The median disease duration before diagnosis was 46.8 (IQR 12-85) months, with 82% of the AMA-M2-positive patients having a chronic disease course. The detailed clinical and histopathological data for the 17 patients are shown in Table 1. The initial symptoms were muscle weakness in 9 patients, asymptomatic elevation of serum CK in 6 patients, dyspnea in 2 patients, and cardiac complications in 4 patients.

Although there was less limb weakness, manual muscle strength (MMT) score was about 3-5 in most patients, and weakness of trunk muscles, including the neck, was more evident in 14 patients. Camptocormia and dropped head were observed in 5 patients. Muscle atrophy of the paraspinal muscles was noticeable on muscle computed tomography (CT) or magnetic resonance imaging (MRI). Two other patients had dysphagia, and 5 patients

had myalgia.

Muscle magnetic resonance imaging (MRI) was performed in 15 of the 17 patients, and MRI evaluation was not possible in 2 patients due to cardiac pacemakers. In 13 of the 15 patients, STIR hyperintensities were found mainly in the paraspinal muscles, muscles around the shoulder, gluteal muscles, obturator muscles, quadriceps femoris, adductor magnus, triceps surae and soleus muscles. Muscle computed tomography (CT) was evaluated in all 17 patients, and muscle atrophy was not observed in 5 patients (Patient 1, 10, 11, 13, 15). In the other 12 patients, various degrees of muscle atrophy and fatty degeneration were observed, mainly in the paraspinal muscles.

The median maximum CK level before diagnosis was 838 (IQR 394-1098) IU/L, but there was no increase in CK level in some patients. There were 8 patients (47%) with PBC. At the time of diagnosis, 12 patients (71%) had vital capacity (% VC) of 80% or less, and 4 patients needed ventilator support. The average BMI at diagnosis was 19.6 (SD 4.1). Most patients had cardiac complications such as cardiomyopathy and arrhythmia, but the site and extent of the disorder varied, and no specific features were found. Six patients showed

LVEF lower than 50%. In addition, six patients were complicated by malignancy, and five of those patients had breast cancer (supplemental table). In four patients with cancer, the malignancy was in a palliative stage.

Muscle biopsy was performed in 15 of the 17 cases, and all cases showed necrosis and regeneration as previously reported. Infiltration of inflammatory cells (40% of the 17 patients), increased expression of MHC class 1 (40% of the 17 patients), rimmed vacuoles (13% of the 17 patients), granulomatous changes (7% of the 17 patients), ragged red fiber (53% of the 17 patients) and sarcoplasmic MAC (C5b-9) deposition (67% of the 17 patients) were observed. Though inflammatory cell infiltration was absent or minimal in most of the observed cases, strong inflammatory cell infiltration was observed only in Patient 8.

Correlation analysis of each item of clinical characteristics

To search for clinical indicators that correlated with ADL in patients with AMA-M2-positive myopathy, we performed correlation analysis of the data obtained from each

patient before immunotherapy. For the two patients who did not receive immunotherapy, data at diagnosis was used for correlation analysis. We showed that patients with low %VC tended to have a lower mRS score, and there was a statistically significant correlation between %VC and mRS score (Fig. 1A; R=0.67, p=0.0034). Although none of the patients had significant dysphagia, many had a decrease in BMI at the time of diagnosis. Notably, the lower BMI was, the lower was %VC, and there was a significant correlation between BMI and %VC (Fig. 1B; R=0.68, p=0.0025). BMI was also correlated with mRS score (Fig. 1C; R=0.56, p=0.019). On the other hand, no significant correlations were found between mRS score, LVEF level, disease duration before diagnosis, and AMA-M2 index. (Fig.1D, E, F)

Next, in order to confirm the effect of immunotherapy, we compared the data for CK value, mRS, %VC, and LVEF before and after immunotherapy.

Fourteen of the 17 patients received immunotherapy during the entire observation period. It should be noted that the timing of evaluation after the start of immunotherapy was not constant, and the maximum improvement value during the follow-up period was used.

This is because the timing of data acquisition varied from case to case due to the retrospective nature of this study. In addition, while the CK value improved within several months after treatment, improvement in %VC often took several months to years. Appropriate evaluation timing of the clinical data seemed to be different. All of the patients were treated with steroids in the acute phase, and CK decreased to the normal range within a few months after the start of treatment (Fig. 2A). Furthermore, statistically significant improvements were seen in mRS score (Fig. 2B) and %VC (Fig. 2C). On the other hand, although 5 patients showed LVEF improvement, the difference was not statistically significant (Fig. 2D). Oral steroids, intravenous immunoglobulin (IVIG), and immunosuppressants were also used for maintenance therapy. Three patients with no marked muscle weakness or ADL decline did not receive immunotherapy during the observation period. Those patients had little ADL decline from diagnosis to the end of follow-up.

Discussion

There are four notable findings. First, AMA-M2-positive myositis is a subgroup that can present with respiratory failure and cardiac disease and may also present with other symptoms. Second, respiratory failure and weight loss are important clinical factors associated with activity of daily living (ADL) of patients with AMA-M2-positive myositis. Third, immunotherapy can improve muscle weakness and respiratory failure. Fourth, six of the 17 patients with AMA-positive myositis were complicated by malignancy, and five of those patients had breast cancer.

Respiratory failure and cardiac disease are important manifestations in patients with AMA-M2-positive myositis, and patients with AMA-M2-positive myositis also showed a wide clinical spectrum. Weakness mainly involving paravertebral muscles, weight loss, respiratory failure, and cardiac complication are typical symptoms, but the course and severity of each symptom varied from case to case [12]. Asymptomatic hyperCKemia and myopathy-related symptoms such as muscle weakness are the most common initial symptoms, followed by cardiac complications, such as arrhythmia and heart failure, and

respiratory failure. In addition, the disease course also varies dramatically from case to case; 3 of the 17 patients had an acute course of less than 6 months, 2 patients had a subacute course of 6 months to less than 1 year, and 12 patients had a chronic course of 1 year or more. In this study, which included mild cases with almost no decline in ADL and without immunotherapy to cases with poor ADL due to severe respiratory dysfunction, the course and severity of each symptom varied from case to case, suggesting a broad clinical spectrum of this disease. In 13 of 17 patients, various degrees of muscle atrophy and fatty degeneration were observed, mainly in the paraspinal muscles. These results may suggest that, similar to previous results, a group of AMA-M2 positive myositis includes cases with a chronic course and cases that were difficult to diagnose. Pathologically, infiltration of inflammatory cells is absent or minimal, and necrosis is present in all cases. Sarcoplasmic MAC (C5b-9) deposition is also frequently observed. That is why AMA-M2 positive myositis should be considered an important differential disease for INNM.

We also found that weight loss is frequent in patients with AMA-M2-positive myositis

and that weight loss is an important clinical indicator that correlates with respiratory failure and ADL decline. One of the characteristics of this disease is that the median disease duration before diagnosis is more than two years, indicating a trend of delayed diagnosis of this disease. Diagnosis of AMA-M2-positive myositis is not always easy because patients with AMA-M2-positive myositis often have a chronic course and limb weakness is not noticeable in many patients. In addition, it has been reported that the titer of AMA does not correlate with disease activity or treatment response, and no clear indicator of disease activity of AMA myositis has yet been found (6). In our case series, it was revealed that 70% of the patients had VC of 80% or less, and a large proportion of patients had respiratory failure. In some patients, respiratory failure became severe and noninvasive positive pressure ventilation (NPPV) or invasive positive pressure ventilation (IPPV) was required. While there were cases in which there was little change in ADL during the observation period, there were also severe cases in which respiratory management was required, and it is important to investigate factors involved in the prognosis of AMA-M2-positive myositis.

Correlation analysis of each item of clinical characteristics showed that patients with low %VC tended to have a lower mRS score, and there was a statistically significant correlation between %VC and mRS score. (Fig. 1A; R=0.67, p=0.0034). In other words, we found that respiratory failure is strongly correlated with ADL decline.

Another interesting finding was that although none of the patients had significant dysphagia, many patients had a decrease in BMI at the time of diagnosis. Notably, the lower the BMI was, the lower was %VC, and there was a significant correlation between BMI and %VC (Fig. 1B; R=0.68, p=0.0025). BMI was also correlated with mRS score (Fig. 1C; R=0.56, p=0.019). On the other hand, no significant correlations were found between mRS score, LVEF level, disease duration before diagnosis, and AMA-M2 index (Fig.1D, E, F). Weight loss in patients with AMA-M2-positive myositis has not been noted in previous papers, but it should be noted because it is an important clinical indicator related to respiratory failure and ADL decline and is useful for understanding the patient's condition.

Fourteen of the 17 patients received immunotherapy such as steroids, IVIG, and immunosuppressants, and all treated cases showed a decrease in CK within a few months. Therefore, the CK value can be used as an index of the short-term therapeutic effect. In addition, %VC showed a significant improvement after immunotherapy. Given these results, aggressive immunotherapy should be considered for respiratory dysfunction.

On the other hand, improvement in LVEF was not significant. In some cases, BNP, NT-proBNP, myocardial troponin I, or LVEF improved after immunotherapy, but in many cases, treatments for heart failure such as treatments with an angiotensin-converting enzyme (ACE) inhibitor and β-blockers were also introduced at the same time. Therefore, it is difficult to judge from the results of this study whether immunotherapy alone was effective for improving LVEF. There have been some reports that steroids were effective for myocarditis associated with AMA-M2-positive myositis [25], and immunotherapy should be considered for myocardial complications depending on the patient's condition. On the other hand, in these AMA-M2-positive myositis cases, immunotherapy is

recommended for early treatment of muscle strength and respiratory impairment rather than cardiac dysfunction.

Finally, in this study, six of the 17 patients with AMA-M2-positive myositis were complicated by malignancy, and five of those patients had breast cancer. In four patients with cancer, the malignancy was in a palliative stage. There have been a few reported cases of an association between AMA-M2-positive myositis and malignant disease [12, 17]. Therefore, more cases should be investigated in the future.

In conclusion, although AMA-M2-positive myositis is a relatively prevalent inflammatory myopathy, it is often difficult to diagnose due to its chronic course. Active AMA testing is recommended to assist in the diagnosis of AMA-M2-positive myositis, especially in myositis patients with weight loss, respiratory dysfunction, and cardiac complications. We found significant correlations between %VC, BMI, and mRS score in AMA-M2-positive patients. We therefore propose that CK level, %VC and BMI should

be monitored as disease indicators in treatment of AMA-M2-positive myositis.

Limitations

The most important limitations of this study are its retrospective nature and relatively small sample size. Although AMA-M2-positive myositis is a clinically heterogeneous disorder, patients from the milder end of the disease spectrum that only display symptoms such as asymptomatic hyper-CKemia, mild respiratory dysfunction or heart failure alone were not fully represented in this study. In addition, AMA-M2-positive myositis may exhibit clinical and pathological features similar to those of other inflammatory myopathy and muscular dystrophy, making a definitive diagnosis difficult. It should be noted that the possibility of comorbidity with other diseases cannot be completely excluded even if the patient is AMA-M2 positive. Larger prospective studies are required to obtain a better understanding of disease progression for the entire spectrum of AMA-M2-positive myositis and to develop efficacious treatment.

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none

Figure legends

[Fig 1] Correlations between clinical features.

Scatter plots with correlation coefficients (R values) and P values are presented. Blue: regression line, Grey: confidence interval.

A. Correlation between vital capacity percentage (%VC) and modified Rankin Scale (mRS) score.

B. Correlation between body mass index (BMI) and %VC.

C. Correlation between BMI and mRS score.

D. Correlation between left ventricular ejection fraction (LVEF) and mRS score.

E. Correlation between disease duration before diagnosis (months) and mRS score.

F. Correlation between anti-mitochondrial M2 antibody (AMA) index and mRS score.

[Fig 2] Therapeutic outcomes of AMA-M2-positive myositis patients.

A. Box plots comparing creatinine kinase (CK) levels before and after immunotherapy. CK level was significantly lower after immunotherapy (Wilcoxon signed-rank test ($n = 14$), $p < 0.05$).

B. Box plots comparing modified Rankin Scale (mRS) scores before and after immunotherapy. mRS score improved significantly after immunotherapy {Wilcoxon signed-rank test ($n = 14$), $p < 0.05$}.

C. Box plots comparing vital capacity percentage (%VC) values before and after immunotherapy. %VC was significantly higher after immunotherapy {Wilcoxon signed-rank test ($n=10$), $p < 0.05$}.

D. Box plots comparing left ventricular ejection fraction (LVEF) values before and after immunotherapy. LVEF change was not significant {Wilcoxon signed-rank test ($n=10$), $p=0.09$}.

[Table 1] Clinical and pathological characteristics of 17 patients with anti-mitochondrial M2 antibody-myositis.

Abbreviations: ACA = anti-centromere antibody; ACE-I = angiotensin-converting enzyme inhibitor; Af = atrial fibrillation; AMA-M2 = anti-mitochondrial M2 antibody; ANA = antinuclear antibody; ARB = angiotensin receptor blocker; AT = atrial tachycardia; AVB = atrioventricular block; AZP = azathioprine; BMI = body mass index; BNP = brain natriuretic hormone; CK = creatine kinase; CRBBB = complete right bundle branch block; CRP = C-reactive protein; CRTD = cardiac resynchronization therapy device; cTnI = cardiac troponin I; F = female; ICD = implantable cardioverter defibrillator; IPPV = invasive-positive pressure ventilation; IVIG = intravenous immunoglobulin therapy; IVMP = intravenous methylprednisolone; LE = lower extremities; LVEF = left ventricular ejection fraction; M = male; m = months; MAC = membrane attack complex; MAP = mitral annuloplasty; MTX = methotrexate; mRS =

modified Rankin Scale; NA = not applicable; NE = not examined; NPPV = non-invasive positive-pressure ventilation; NSVT = non-sustained ventricular tachycardia; PAC = premature atrial contractions; pAf = paroxysmal atrial fibrillation; PBC = primary biliary cholangitis; PSL = prednisolone; PSVT = paroxysmal supraventricular tachycardia; PVC = premature ventricular contractions; RFCA = radiofrequency catheter ablation; SVT = sustained ventricular tachycardia; SSS = sick sinus syndrome; STIR = short inversion-time inversion recovery; T2WI = T2-weighted image; TAC = tacrolimus; TAP = tricuspid annuloplasty; Tg-Ab = anti-thyroglobulin antibody; TPO-Ab = anti-thyroid peroxidase antibody; UE = upper extremities; VC = ventilation capacity; VF = ventricular fibrillation; y = years.

[Supplemental table]

6 AMA-M2 positive myositis cases with malignant tumor complications

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