# A Case of Amyloid Myopathy Mimicking Anti-Mi-2 Antibody-Positive Myositis

Running title: Amyloid myopathy resembling IIM

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## INTRODUCTION

Amyloidosis is characterized by the deposition of abnormal amyloid protein in variable organs, leading to organ failures.[1] Amyloid myopathy is one of the rare complications of systemic amyloidosis. It manifests as proximal muscle weakness and creatine kinase elevation, resembling idiopathic inflammatory myopathies (IIMs).[2-6]

In contrast, IIMs are autoimmune diseases characterized by inflammation in muscles, and dermatomyositis is one of the subgroups of IIMs. To date, at least seven serum markers of dermatomyositis, known as myositis-specific antibodies (MSAs), have been identified.[7,8] They are known to exhibit high specificity for dermatomyositis, and anti-Mi-2 antibody is one of them.[9,10] Since the treatment of dermatomyositis is immunosuppressive drugs, including glucocorticoids, whereas the treatment of AL amyloidosis requires chemotherapy, it is important to make the correct diagnosis of amyloid myopathy without misdiagnosing dermatomyositis.

We encountered a case diagnosed with amyloid myopathy through muscle biopsy, despite testing positive for the anti-Mi-2 antibody. This case highlights the potential for false-positive results in myositis-specific antibody tests and emphasizes the importance of advancing clinical reasoning beyond sole reliance on antibody testing.

Informed consent was obtained from the patient for publication of the report and associated images.

## CASE

A 64-year-old Japanese man with a medical history of spinal canal stenosis, hypercholesterolemia, and angina pectoris was referred from previous hospital for evaluation due to persistent fatigue lasting 7 months, bilateral lower limb edema, and elevated creatine kinase levels. A brief review of systems was negative for fever, night sweat, arthralgia, skin rashes, chest pain, vomiting, nausea, diarrhea. He had no significant family medical history of myopathy, and denied excessive alcohol consumption and was a non-smoker. He had been prescribed aspirin, lansoprazole, and ezetimibe/rosuvastatin calcium. His vital signs were as follows: body temperature, 36.8 °C; pulse rate, 92 bpm; blood pressure, 117/78 mmHg; respiratory rate, 14 breaths/min; and oxygen saturation, 98% in room air. Physical examination revealed proximal muscle weakness (neck flexors/extensors, deltoid middle, iliopsoas, and quadriceps femoris scored 4 on the manual muscle test, with a maximum score of 5) and no other neurological findings. There were no skin lesions suggestive of dermatomyositis, such as Gottron's papules, heliotrope sign, V-sign, or shawl sign. Laboratory test results

revealed elevated levels of muscle enzymes such as CK (1553 IU/L), lactate dehydrogenase (47 U/L), aspartate aminotransferase (48 U/L), and alanine aminotransferase (69 U/L), CK-MB was relatively low (CK-MB 28U/L); low level of total protein (4.7 g/dL) and albumin (3.0 mg/dL); negative C-reactive protein (<0.05 mg/dL); and high urine protein/creatinine ratio (3.3 g/gCr). Other blood test results, including those of thyroid-associated hormones, were within normal limits. Based on the combination of elevated muscle enzymes levels and weakness of the proximal muscles, we initially suspected IIM such as polymyositis or necrotizing autoimmune myopathy, including anti-3-hydroxy-3-methylglutaryl-coA reductase antibody associated autoimmune myopathy, along with nephrotic syndrome. Additional tests for autoimmune diseases associated with myositis, including MSAs showed a positive anti-nuclear antibody titer of 1:40 (homogenous pattern) and a positive anti-Mi-2 antibody index of 85 (upper limit normal, 53) using enzyme-linked immunosorbent assay (ELISA). A magnetic resonance imaging (MRI) of the lower extremities revealed enhanced signals on T2-weighted short T1 inversion recovery images of the right gluteus medius, right gluteus minimus, right quadriceps femoris, bilateral biceps femoris, and bilateral adductor magnus (Fig. 1). Additionally, electromyography revealed abnormal spontaneous activity and polyphasic waves with low levels of voluntary contraction in the right tensor fasciae

latae. Computed tomography of the lungs did not reveal any findings suggestive of interstitial lung disease. Based on the scoring system of the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for IIM, the patient's score was 7.7, (age of onset ≥ 40 years, 2.1; proximal upper extremities weakness, 0.7; proximal lower extremities weakness, 0.8; neck flexors weakness, 1.9; weaker proximal legs than distal legs, 0.9; elevated CK level, 1.3; total score, 7.7), which was classified as "definite IIM" and strongly indicated the presence of IIM; 7.5 points or higher can be classified as IIMs with probability of more than 90% without a muscle biopsy (Table).[11]

Based on the above results, we suspected the presence of anti-Mi-2 antibody-positive dermatomyositis complicated by nephrotic syndrome despite the absence of skin lesions.

Electrocardiography and echocardiography were performed to evaluate the presence of cardiomyopathy and cardiac function due to dermatomyositis. Electrocardiography revealed low QRS voltage in the limbs leads. Echocardiography unexpectedly revealed afferent thickening of the left ventricular wall, decreased wall motion of the left ventricular base, and a granular sparkling pattern (Fig. 2). These findings suggested the presence of cardiac amyloidosis. Additional blood test results showed negative M-protein but abnormally increased λ-type free light chain and low κ/λ ratio (κ, 7.1 mg/L; λ, 167

mg/L; κ/λ, 0.04), and an electrophoresis of urine revealed the presence of Bence Jones protein λ-type. This suggested the presence of AL amyloidosis.

The muscle biopsy from right quadriceps revealed direct fast scarlet (DFS)-positive amyloid deposition in the small vessel walls within the interstitium (Fig. 3), with no apparent pathological changes in myofibers, notably devoid of MxA-positive myofibers, a diagnostic marker for dermatomyositis[12] and of perifascicular necrosis, which is a characteristic feature of anti-M2-antibody-positive dermatomyositis[13,14] and antisynthetase syndrome (ASS).[15] Furthermore, perimysial pathology, including perimysial connective tissue fragmentation and alkaline phosphatase expression, typically detected in anti-M2-antibody-positive dermatomyositis[13,14] and ASS[15], was not observed. A bone marrow test revealed 9% of plasma cell dysplasia and no other abnormal findings. Additionally, a renal biopsy was conducted to closely assess renal impairment, revealing amyloid deposition in the glomerular and interstitial vessels, which stained positive for Congo red. Moreover, the presence of gastrointestinal lesions was suspected as the cause of hypoalbuminemia. Gastroduodenal biopsy also revealed amyloid deposits, predominantly in the vessel walls, as indicated by DFS staining.

Based on these findings, the patient was diagnosed with systemic AL amyloidosis and underwent chemotherapy with Dara-CyBorD (chemotherapy for AL amyloidosis

combined daratumumab with cyclophosphamide, bortezomib, and dexamethasone)[16]. After 24 courses of chemotherapy lasting for 23 months, he achieved complete remission.

## DISCUSSION

We encountered a Japanese case of AL amyloidosis with muscular, renal, and gastrointestinal involvement, concurrently presenting with a false-positive anti-Mi-2 antibody result. This case of AL amyloid myopathy accompanied by anti-Mi-2 antibody mimicked anti-Mi-2 antibody-positive dermatomyositis.

Amyloidosis is characterized by extracellular deposition of misfolded proteins in various organs, resulting in organ damage and dysfunction. Deposition of the free light chain is referred to as AL amyloidosis.[1]

Amyloid myopathy is rare complications of systemic amyloidosis and generally presents with proximal muscle weakness, macroglossia and muscle pseudohypertrophy, and elevated levels of CK.[2-6] This case presented proximal weakness, but no macroglossia and muscle pseudohypertrophy. More than half of the patients have been reported to have normal CK levels at diagnosis.[17] MRI is helpful in detecting the presence of amyloid

myopathy. MRI T2-weighted short T1 inversion recovery signal intensity increases in affected muscle lesions, but these findings are also seen in IIMs, which can lead to misdiagnosis.[18-20] Muscle biopsy plays a crucial role in confirming the presence of amyloid myopathy. Staining with Congo-red can reveal amyloid deposition in muscle tissues.[2] Management of amyloid myopathy is mainly aimed at controlling background systemic amyloidosis. The treatment of AL amyloidosis targets the underlying plasma cell clone and mainly includes chemotherapy, and in some cases, hematopoietic stem cell transplantation.[1]

Anti-Mi-2 antibody is an MSA that binds to a component of the nucleosome remodeling-deacetylase complex involved in transcription regulation.[21,22] According to the classification of the International Consensus on ANA Patterns, anti-Mi-2 antibody shows a “fine speckled pattern” antinuclear antibody by indirect immunofluorescence assay on Hep-2 cells.[23] Its sensitivity and specificity for dermatomyositis are reported to be approximately 4-18% and 98-100%, respectively.[22] Clinical features of anti-Mi-2 antibody-positive dermatomyositis include a relatively high CK level; a high complication rate of skin symptoms like Gottron’s papules, heliotrope rash, shawl sign, and V-sign; and a low complication rate of interstitial lung disease and cancer.[7-10] Myopathological features associated with the anti-Mi-2 antibody include perifascicular

necrosis, perimysial pathology and MxA expression in the sarcoplasm of myofibers.[13,14] Of note, sarcoplasmic MxA expression serves as a specific marker for dermatomyositis.[24]

In this case, based on the elevated CK level, positive anti-Mi-2 antibody, proximal muscle weakness, and MRI and electromyography findings, anti-Mi-2 antibody-positive dermatomyositis was suspected. However, the absence of skin lesions and the presence of nephrotic syndrome, which are atypical for anti-Mi-2 antibody-positive dermatomyositis, led to the diagnosis of amyloid myopathy due to AL amyloidosis.

Two diagnostic difficulties were encountered in this case. First, the anti-Mi-2 antibody was apparently false positive. Anti-Mi-2 antibody is known to have a high specificity of 98-100%.[25] However, false-positive cases have been reported in studies of ELISA assays for anti-Mi-2 antibodies using immunoprecipitation (IP) as the gold standard assay. Fujimoto et al. reported cases of mixed connective tissue disease, idiopathic interstitial pneumonia, and other connective tissue diseases. These three cases were judged as false-positives because of negative IP.[26] Muro et al. reported that one healthy control had a false-positive ELISA result. The sample in the case was re-tested using reticulocyte lysate-coated wells as the background for subtraction instead of uncoated wells. Then, this serum turned negative.[27] Kuwana et al. reported a case of a patient with diabetes mellitus with false-positive anti-Mi-2 antibody using ELISA and negative

IP.[28] We concluded that in this case, the anti-Mi-2 antibody was false-positive, even though without an IP test. Muscle biopsy showed no evidence of severe muscle inflammation typical of anti-Mi-2 antibody positive dermatomyositis and only evidence of amyloid myopathy. Furthermore, the antinuclear antibody level was relatively low and showed a homogenous pattern instead of the speckled pattern that is typical of anti-Mi-2 antibodies. Like this case, a case of amyloid myopathy misdiagnosed as anti-signal recognition particle antibody, one of the MSAs, positive myositis has been reported.[29] Due to its high specificity, MSA false-positive amyloid myopathy can easily be misdiagnosed as myositis and should be carefully assessed if it is accompanied by atypical findings for myositis.

Second, the IIMs classification score in this case was sufficiently high to suggest the presence of IIMs. However, it is important to note that in the EULAR/ACR classification criteria, there were more Caucasians and fewer Asians: 611 (62.6%) and 177 (18.1%) in the IIM group and 360 (57.7%) and 156 (25.0%) in the comparator group, respectively, and most of the included patients were anti-Jo-1 antibody-positive. For instance, it has been reported that anti-Jo-1 antibody positivity rate in Asian populations with IIMs is lower than that in Caucasian populations, 10.8% and 18-20%, respectively.[30] This suggests that the IIMs subtypes in Asian populations differ from

1 those defined by the EULAR/ACR criteria. Therefore, the sensitivity and specificity of
2 the EULAR/ACR IIMs classification criteria may be altered in Asian populations due to
3 these different features of IIMs and the low inclusion of Asians in the criteria.
4 As an additional complicating factor, amyloid myopathy may mimic IIMs. According
5 to the EULAR/ACR classification criteria for IIMs, only one patient with amyloidosis
6 was included in the control group.[11] Several other cases of amyloid myopathy
7 misdiagnosed as IIMs have been reported, and these cases were associated with
8 complications, such as interstitial lung disease,[31] proteinuria,[32] and congestive heart
9 failure.[19] Systemic amyloidosis mainly affects the kidneys and heart but rarely affects
10 the muscles. Amyloid myopathy has a low complication rate of at least 1.5% of AL
11 amyloidosis.[17] In this case, at the initial presentation, it was necessary to consider
12 systemic amyloidosis as a differential diagnosis because the patient had nephrotic
13 syndrome as well as elevated CK and proximal weakness.
14 Eventually, the echocardiographic findings and results of the muscle, kidney, gastric,
15 and duodenal biopsies led to the diagnosis of systemic AL amyloidosis. If multiple
16 organs are involved, systemic amyloidosis should be considered as the differential
17 diagnosis.
18

## CONCLUSION

This report describes a challenging case of amyloid myopathy with false-positive anti-Mi-2 antibody results. It is important to be aware that amyloid myopathy can mimic IIMs because of proximal weakness and CK elevation. Despite the presence of highly specific biomarkers, we need to pay attention to comprehensive clinical information. If multiple organ damage is observed, systemic amyloidosis and collagen disease should be considered as differential diagnoses.

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CONFLICT OF INTEREST

None

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FIGURES

Fig.1 MRI. T2 STIR images revealed enhanced right gluteus medius, right gluteus minimus, right quadriceps femoris, bilateral biceps femoris, (allows) and bilateral adductor magnus.

Fig.2 Echocardiogram (parasternal long axis view) revealed left ventricular hypertrophy and granular sparkling pattern (allows).

Fig3. Kidney biopsy (a) Congo-red stain. (b) Congo red stain under polarized light. (original magnification×400). Gastroduodenal biopsy (c) DFS stain. (d) DFS stain under polarized light. (original magnification×100). Muscle biopsy (e) DFS stain. (f)DFS stain under polarized light. (original magnification×200).

1 TABLES

2

3 Table. positive findings and scores of the EULAR/ACR classification criteria for adult

4 and juvenile idiopathic inflammatory myopathies without muscle biopsy.