Acta Med. Okayama, 2017
Vol. 71, No. 4, pp. 341–344

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

A Case of Dermatomyositis with Severe Myalgia and Muscle Weakness Testing Positive for Anti-melanoma Differentiation-associated Gene 5 Antibody

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We report a case of a woman with typical dermatomyositis (DM) with skin manifestations, severe myalgia and muscle weakness complicated by interstitial lung disease (ILD) and pneumomediastinum. Pneumomediastinum persisted despite treatment with immunosuppressive therapy (steroids and cyclosporine). After the test for anti-melanoma differentiation-associated gene 5 (MDA5) antibody came out positive, we doubled the cyclosporine dose and her condition improved. Despite typical clinical features of DM, in cases complicated by pneumomediastinum or steroid resistance, measurement of anti-MDA5 antibody may be useful for immunosuppressant dose titration.

Key words: dermatomyositis, anti-melanoma differentiation-associated gene 5 antibody, interstitial lung disease, pneumomediastinum

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized predominantly by cutaneous and muscular abnormalities. DM patients who exhibit cutaneous manifestations of DM without muscle weakness for <6 months and who experience fatal complications such as acute or subacute interstitial lung disease (ILD) are also diagnosed with clinically amyopathic dermatomyositis (CADM) according to Gerami's criteria [1]. Pulmonary complications are the main cause of death in CADM, and severe ILD and pneumomediastinum are potentially the most life-threatening complications. Steroid monotherapy is insufficient for CADM, and intensive immunosuppression therapy is usually needed.

Case Report

A 66-year-old Japanese woman developed skin eruptions on the eyelid and finger 3 months before presentation. Additionally, she experienced intense muscle weakness and myalgia. She also started to exhibit continuous high-grade fever (>38°C). Her condition had been controlled with prednisolone 10 mg per day for a clinical diagnosis of polymyalgia rheumatica. Despite the low-dose steroid monotherapy for three months, her condition as well as the proximal muscular weakness gradually worsened, and she could not rise

Received September 23, 2016; accepted January 26, 2017.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

from a lying down position. She was suspected as suffering from another connective tissue disease and was referred to our department. A physical examination on admission showed a severe heliotrope rash with impressive eyelid edema, 2 small oral ulcerations, and Gottron's papules and Mechanics' hands, but did show not cuticle extension or nail fold bleeding. She had not experienced Raynaud's phenomenon. Symmetrical proximal muscle weakness was apparent (Table 1). Results of laboratory tests on admission showed increased muscle and liver enzymes (Table 2). In addition, she had a bit of cough without hypoxia (SpO_2 98%); a chest radiograph revealed bilateral opacities, and computed tomography (CT) showed bilateral ground-glass opacity in the subpleural areas of consolidation (Fig. 1). The patient was diagnosed with DM complicated by ILD given her skin lesions, muscle weakness and inflammation. A muscle biopsy revealed type 2 fiber atrophy and various sizes of muscle fibers and slight lymphocytic infiltration around the muscle tissue but no perifascicular myofibers (Fig. 2). We measured anti-ARS antibody on admission performed for patients suspected as having DM; however, the result was negative. The presence of malignancies was excluded.

High doses of steroids (45 mg; 1 mg/kg/day) and oral cyclosporine A (100 mg; 2 mg/kg/day) were used as initial therapy. Several days later, the heliotrope rash improved rapidly, and the facial edema decreased as well but did not completely resolve. Additionally, the patient recovered from proximal muscle weakness. Two weeks later, the dose of steroids was decreased to 30 mg, and she was discharged from the hospital.

Two weeks later, she returned to the hospital with severe pain when swallowing. The CT showed a newly

Table 1 Results of manual muscle test on admission

Muscle groups	Right	Left	Axial
Axial muscles			
Neck flexors	X	X	3
Proximal muscles			
Deltoid	6	5	X
Biceps	8	9	X
Gluteus maximus	8	8	X
Gluteus medius	8	8	X
Quadriceps	10	10	X
Distal muscles			
Wrist extensors	10	10	X
Ankle dorsiflexors	10	10	X

Table 2 Summary of laboratory tests on admission

Parameter		
White blood cell count	9,390	/mm^3
Neutrophils	92.8	%
Lymphocytes	4.9	%
Monocytes	2.9	%
Eosinophils	0	%
Basophils	0	%
Red blood cell count	366×10^4	/mm^3
Hemoglobin	10.9	g/dl
Mean corpuscular volume	89.3	fl
Platelet	28.1×10^4	/mm^3
Total protein	6.5	g/dl
Albumin	2.8	g/dl
Aspartate aminotransferase	53	IU/l
Alanine Aminotransferase	37	IU/l
Blood Urea Nitrogen	36	mg/dl
Creatinine	0.3	mg/dl
Creatine phosphokinase	328	IU/l
Aldolase	4.5	IU/l
Myoglobin	146	mg/dl
C-reactive protein	2.35	mg/dl
Sialylated carbohydrate antigen KL-6	808	U/ml
Glucose	288	mg/dl
Na	130	mEq/l
K	4.1	mEq/l
Cl	94	mEq/l
Ca	8.2	mg/dl
Ferritin	2,416.9	ng/ml
Fluorescent Antinuclear Antibody	<40	times
Anti-Scl-70 antibody	(−)	
Anti-aminoacyl tRNA synthetase antibody	(−)	
Anti-Ribonucleoprotein antibody	(−)	
Anti-SS-A/Ro antibody	(−)	
Anti-SS-B/La antibody	(−)	

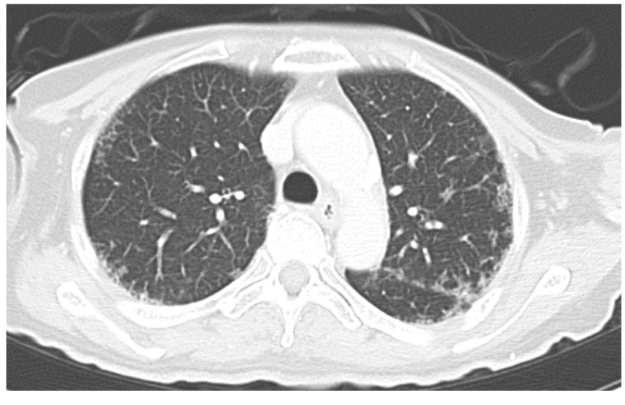

Fig. 1 Interstitial lung disease at admission.

developed pneumomediastinum (Fig. 3A, B). We recalled that CADM can be frequently complicated by ILD and pneumomediastinum; thus, we tested for the anti-MDA5 antibody, which is highly specific for CADM.

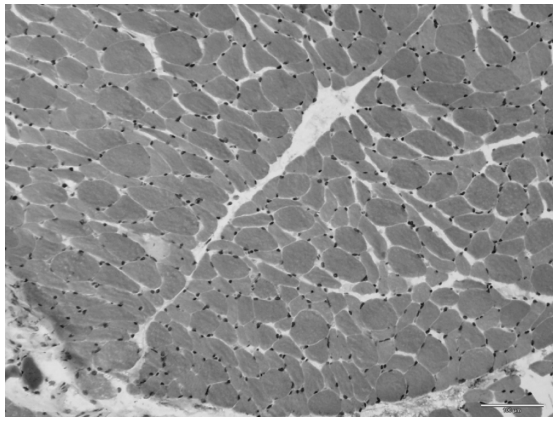

Fig. 2 Result of muscle biopsy.

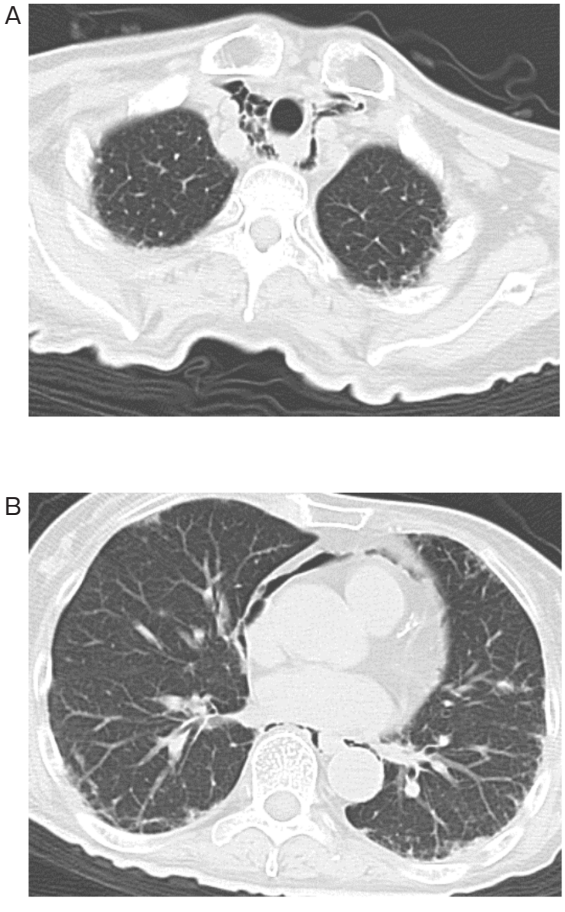

Fig. 3 Pneumomediastinum at return to clinic.

Anticipating a positive result, we decreased the dose of steroids to 20 mg and doubled the dose of cyclosporine to 200 mg (4 mg/kg/day). She recovered gradually from pneumomediastinum and other skin symptoms and was discharged three weeks later. Before she was discharged, we obtained a positive result for the anti-MDA5 antibody. After discharge, we measured the 2-h post-dose blood concentration (C2) level of cyclosporine (1,460.4 ng/dl). The adequate dosage of CyA was judged by this concentration.

Discussion

DM is a rare autoimmune disease characterized by skin involvement and striated muscle inflammation, possibly involving the upper esophagus and causing damage to the internal organs. Damaged organs are frequently marked by the presence of autoantibodies [2]. In DM, the pattern of circulating myositis-specific autoantibodies can provide useful information for systemic complications and disease prognosis [3]. Although the presence of anti-aminoacyl tRNA synthetase (anti-ARS) antibodies is associated with chronic ILD, anti-MDA5 antibodies are associated with acute/subacute ILD [4]. Additionally, pneumomediastinum is a refractory complication and tends to occur in DM patients with anti-MDA5 antibodies; compared with DM patients without pneumomediastinum, those with pneumomediastinum had significantly higher frequencies of anti-MDA5 antibodies (90.9 vs 52.4%, $p=0.02$) [5]. In the management of ILD, it is reported that CyA therapy with a 2-h post-dose blood concentration (C2) >1,000 ng/ml is effective, resulting in a 1-year survival rate of 89% [6].

Much has been said in recent years about the relation between anti-MDA5 antibodies and muscle weakness. The lack of clinical evidence of muscle weakness is more highly prevalent in anti-MDA5-positive patients than -negative patients (76% vs 48%) [7]. Additionally, Shinji S *et al.* showed that of 8 Japanese anti-MDA5-positive DM patients, none had muscle weakness [8]. Although our patient may have presented advanced muscle weakness, the clinical characteristics of anti-MDA5-positive DM patients are inconsistent, as the disease onset occurred only 3 months after her skin manifestations emerged. Thus, our case is a bit atypical.

Regarding the therapies for CADM based on anti-MDA5-positive results, Galimberti *et al.* reported in their retrospective cohort study that the majority of patients (64%) needed additional medications to control their CADM within 6 months of the diagnosis. Of 30 patients with follow-up >2 years, 27 (90%) required steroid-sparing medications to control their CADM, confirming that CADM is a therapeutic challenge [3]. In another study, although 83% of CADM patients treated with triple drug combination therapy survived, one patient with corticosteroid monotherapy died from ILD. Additionally, of the patients initially treated with corticosteroids and cyclosporine, 33% died from ILD and 17% required additional administration of cyclophosphamide later on in the treatment [9]. The prognosis of CADM may depend on whether prompt and intensive treatment can be started. Fortunately, our patient recovered well. However, if she relapses, we may need to add cyclophosphamide [10].

In conclusion, in DM cases with typical clinical manifestations, such as severe myalgia and muscle weakness, that also show resistance to steroids, coexisting ILD, or pneumomediastinum, anti-MDA5 autoantibodies should be measured for prompt initiation of intensive immunosuppressive therapies.

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