An Autopsy Case of Anti-melanoma Differentiation-associated Gene-5 Antibody-positive Clinical Amyopathic Dermatomyositis Complicated by Rapidly Progressive Interstitial Lung Disease

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Abstract

A 62-year-old man presented with heliotrope rash, Gottron's sign, and mild muscle weakness. Both of his lung fields showed interstitial changes that worsened rapidly. He was diagnosed with clinical amyopathic dermatomyositis with rapidly progressive interstitial lung disease. The patient died of respiratory failure, despite the administration of immunosuppressive therapy. Autopsy revealed diffuse alveolar damage. An antibody analysis, which was performed postmortem, detected the presence of anti-melanoma differentiation-associated gene (MDA)-5 antibodies. Clinicians should note the clinical, radiologic, and serologic findings to predict anti-MDA-5 antibody-associated rapidly progressive interstitial lung disease.

Key words: anti-MDA-5 antibody, clinical amyopathic dermatomyositis, palmar papules, rapidly progressive interstitial lung disease

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Introduction

Dermatomyositis (DM) is an inflammatory muscle disease characterized by muscle weakness and myalgia, with typical skin manifestations, including heliotrope rash and Gottron's sign. Based on Sontheimer's criteria, patients with DM and minimal or no muscular symptoms are classified as having hypomyopathic DM (HDM) or amyopathic DM (ADM); the term "clinical ADM (CADM)" refers to these 2 clinical phenotypes (1, 2). The autoantibody against the a140-kDa polypeptide in patients with CADM has been identified as anti-CADM-140 (3). Anti-CADM-140 antibodies, which are also referred to as anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies, are named after its autoantigen identification (4). Anti-MDA-5 antibodies are not typically detected in CADM, DM without interstitial lung disease (ILD), or polymyositis (5). This autoantibody has a close relationship with rapidly progressive ILD (RP-ILD) in East Asian patients with CADM (3, 6), and is associated with in-

creased mortality in comparison to patients who are anti-MDA-5 antibody-negative (7, 8). Because some facilities are unable to perform analyses to detect anti-MDA-5 antibodies, clinicians should predict the autoantibody according to the clinical presentation. We describe the case of a patient with CADM and RP-ILD who died of respiratory failure despite the administration of aggressive immunosuppressive therapy. An antibody analysis, which was performed postmortem, identified the presence of anti-MDA-5 antibodies. We herein present a rare autopsy report of a patient with anti-MDA-5 antibody-positive RP-ILD.

Case Report

A 62-year-old man with low-grade fever, polymyalgia, and arthralgia noticed erythema of his face and fingers. A connective tissue disease was suspected and 10 weeks after the onset of symptoms, he was referred to our department for detailed examination and treatment.

On admission to our hospital, the patient's height and

Figure 1. The clinical presentation on admission. Palmar papules were observed near the interphalangeal joints (arrowheads).

Table 1. Laboratory Data on Admission.

【Hematology】			【Blood chemistry】			【Serological test】		
RBC	404 × 10 ⁴	/μL	TP	6.4	g/dL	CRP	1.81	mg/dL
Hb	12.8	g/dL	Alb	3.0	g/dL	IgG	1,289	mg/dL
Ht	37.5	%	T.Bil	0.62	mg/dL	IgA	208	mg/dL
MCV	93	fL	LDH	383	U/L	IgM	155	mg/dL
MCHC	34.1	%	AST	45	U/L	KL-6	759	U/L
WBC	5,100	/μL	ALT	24	U/L			
Neutro.	83	%	CPK	395	U/L	【Immunological test】		
Lymph.	6	%	ALP	209	U/L	RF	6	IU/mL
Mono.	9	%	g-GTP	28	U/L	Anti-Nuclear Ab.	<40	Fold
Eosino.	2	%	BUN	16.7	mg/dL	Anti-Jo-1 Ab.	<9.0	Index
PLT	20.3 × 10 ⁴	/μL	Cr	0.5	mg/dL	Anti-DNA Ab.	<2.0	IU/mL
			Aldolase	120	U/L	Anti-U1 RNP Ab.	(-)	
			Myoglobin	4.6	ng/mL	Anti-SS-A Ab.	(-)	
			Ferritin	899	ng/mL	Anti-SS-B Ab.	(-)	
						Anti-CCP Ab.	<0.5	
						Lupus anti coagulants	1.15	
						Anti-cardiolipin Ab.	<8	U/mL
						Anti-MDA-5 Ab.	75.113	Unit
【Blood gas(room air)】			【Hemostatic data】			【Urinalysis】		
PH	7.42		PT-INR	0.93		Protein	(+)	
PaCO ₂	39.9	Torr	APTT	36.5	second	Occult blood	(-)	
PaO ₂	66.7	Torr	D-Dimer	1.8	μg/mL			
HCO ₃	25.3	mmol/L						
B.E.	0.8	mEq/L						
SpO ₂	93.2	%						

weight were 176 cm and 70.2 kg, respectively. A physical examination revealed a heliotrope rash around the eyes, Gottron's sign on the dorsum of both hands, and palmar papules (Fig. 1). Manual muscle testing (MMT) revealed mild weakness of the pectoralis major and iliopsoas muscles on both sides (MMT score, 4/5). The patient's vital signs were normal and his palpebral conjunctivae showed no indication of anemia. On chest auscultation, the patient's heart sounds were clear, but fine crackles were audible over both the right and left lower lung fields. The patient's abdomen was soft and flat, and peripheral lymphadenopathy was noted in the neck region.

A laboratory evaluation revealed slightly elevated myogenic enzyme levels, including creatinine phosphokinase (CPK), aldolase, and myoglobin (395 μ/L, 120 U/L, and 4.6

ng/mL, respectively) (Table 1). In addition, the levels of C-reactive protein (CRP), lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase were slightly elevated (1.8 mg/dL, 383 U/L, 45 U/L, and 24 U/L, respectively). There was a mild decrease in the patient's serum albumin level. The results of routine kidney function tests were normal. The levels of serum ferritin and KL-6 were elevated (899 ng/mL and 759 U/L, respectively). The results of the immunological tests were negative for antinuclear antibodies. Tests for anti-DNA, anti-U1-RNP/Sm, anti-Jo-1, anti-cardiolipin, and anti-neutrophil cytoplasmic antibodies and lupus anticoagulant were all negative. The serum complement levels were normal, and serological studies showed no evidence of recent infection with Epstein-Barr virus or cytomegalovirus. An arterial blood gas analysis with room

Figure 2. The pulmonary manifestations at the initial visit (a, c, and e) and on admission 30 days after initial diagnosis (b, d, and f). At the initial diagnosis of interstitial lung disease, chest radiography (a) showed consolidation and reticular shadows in the bilateral lower lobes, while high-resolution computed tomography (HRCT) (c and e) revealed patchy consolidation and ground-glass attenuation (GGA) in the bilateral lower lobes. On admission 30 days after initial the diagnosis, radiography (b) and HRCT (d and f) showed a dramatic loss of lung volume, GGA with traction bronchiectasis, and reticular shadows in the bilateral lung fields.

air showed hypoxia (PaO_2 , 66.7 Torr). Myopathy was not detected in the biceps brachii muscle on magnetic resonance imaging. At initial diagnosis of ILD, chest radiography revealed consolidation and reticular shadows in both lower lobes (Fig. 2a), while high-resolution computed tomography (HRCT) revealed patchy consolidation and ground-glass attenuation (GGA) in both lower lobes (Fig. 2c, e). On admission (30 days after the initial diagnosis), radiography and HRCT showed a dramatic loss of lung volume, GGA with traction bronchiectasis, and reticular shadows in both lung fields (Fig. 2b, d, f). The patient met the Japanese criteria for the diagnosis of DM (revised in 1992) based on the

presence of DM-specific skin alterations, including heliotrope rash and Gottron's sign, as well as myalgia, arthritis, and elevated levels of myogenic enzymes and CRP. Because he had mild muscle weakness and slightly elevated myogenic enzyme levels, the patient was diagnosed, based on Sontheimer's criteria, with HDM complicated by ILD. Whole-body CT, upper endoscopy, and colonoscopy ruled out the possibility of malignancy.

We could not predict the rapid progression of ILD because the patchy consolidation and GGA were limited to both lower lobes on HRCT scans at the initial visit and the patient's respiratory condition was stable (whereas ILD

Figure 3. The clinical course of the patient. Mediastinal emphysema was observed (arrowheads). CPK: creatinine phosphokinase, CRP: C-reactive protein, CyA: cyclosporine A, IVCY: intravenous pulse cyclophosphamide, mPSL: methylprednisolone, PSL: prednisolone, Tac: tacrolimus

worsened on admission). Thus, we administered prednisolone (70 mg) with cyclosporine A [270 mg, orally (4 mg/kg)]; cyclophosphamide was not administered.

His clinical symptoms, including cutaneous rash and polyarthralgia, showed rapid improvement after the initiation of steroid therapy. Although his serum CPK level decreased, the patient's hypoxia worsened after 7 days of therapy. We noted that the patient's lung involvement progressed rapidly and the resistance to immunosuppressive therapy. Thus, treatment methylprednisolone (500 mg, intravenously) was administered for 3 days, in addition to intravenous cyclophosphamide (IVCY) (500 mg). However, the patient's ILD worsened. On the 25th day of hospitalization, nasal high-flow therapy was required due to severe hypoxia. The patient's KL-6 level never decreased. We repeated steroid pulse therapy, and increased the IVCY dosage to 1,200 mg. We also changed cyclosporine A to tacrolimus. However, the interstitial changes and loss of lung volume in both lung fields worsened, and mediastinal emphysema became apparent (Fig. 3). The patient died from respiratory failure on the 52nd day of hospitalization. The clinical course of our patient is summarized in Fig. 3.

A pathological autopsy was performed 8 hours after the patient's death. Microscopy revealed the formation of hyaline

membranes - a hallmark of acute diffuse alveolar damage (DAD) (Fig. 4a). Other lesions had the typical features of organizing DAD, including membranous organization with the occlusion of alveoli, dilation of the alveolar ducts and sacs, and the collapse of the alveoli (Fig. 4b). The presence of anti-MDA-5 antibodies was confirmed by an enzyme-linked immunosorbent assay.

Discussion

DM encompasses a wide spectrum of diseases, almost universally involving the skin and frequently affecting the muscles and lungs. The presence of anti-MDA-5 antibodies identifies a population of patients (especially Asian patients) with CADM with an increased risk for RP-ILD (9). The five-year survival rate of patients with anti-MDA-5 antibodies has been reported to be 56% (10). Therefore, early screening should be performed in all DM patients who are at increased risk for ILD, especially those with anti-MDA-5 antibodies. However, there are no commercially available products that are capable of detecting anti-MDA-5 antibodies. Although the disease phenotypes are complex, the clinical, radiological, and serological indices to identify patients with DM who are likely to be anti-MDA-5 antibody-positive

Figure 4. The autopsy revealed diffuse alveolar damage. (a) Hyaline membrane formation was observed with exudate in the alveoli. (b) Membranous organization was seen with the occlusion of alveoli, dilation of the alveolar ducts and sacs, and collapsing of the alveoli (Hematoxylin and Eosin staining; original magnification 200×).

Table 2. Reported Autopsy Case Reports of CADM with RP-ILD.

Reference	Age/Gender	Pathological finding	Anti MDA-5 ab	Treatment
22	57/F	DAD	negative	steroids IVCY
23	49/M	DAD	positive	steroids IVCY
24	71/M	DAD	positive	steroids IVCY
25	70/M	DAD	positive	steroids IVCY TAC
Current case	62/M	DAD	positive	steroids IVCY CyA /TAC

DAD: diffuse alveolar damage, IVCY: Intravenous cyclophosphamide, TAC: Tacrolimus, CyA: Cyclosporin A

serves an important clinical role in predicting RP-ILD and patient mortality.

Palmar papules are a characteristic skin manifestation in patients with anti-MDA-5 antibody-positive DM (11-13). Some DM patients who present with palmar papules may not have the characteristic muscle inflammation of DM, but may be at increased risk for RP-ILD. Palmar papules often accompany pain in anti-MDA-5 antibody-positive DM, unlike Gottron's sign, the histology of which is characterized by vasculopathy of the small- to medium-sized dermal vessels (11). Our patient had this characteristic skin alteration, but did not have pain (Fig. 1). A strong correlation between palmar papules and the risk of acute interstitial pneumonia in patients with DM has already been reported (14). Other mucocutaneous findings in DM include skin ulceration, tender gums, oral erosion, and diffuse hair loss (11, 12). In patients with CADM, these skin manifestations, especially palmar papules, should be noted to predict the presence of anti-MDA-5 antibodies.

The HRCT findings may help predict RP-ILD in anti-MDA-5 antibody-positive DM (15, 16). Lower consolidation and the GGA pattern have been associated with short-term mortality in patients who are anti-MDA-5 antibody-positive (16). A random GGA pattern is also a characteristic finding (15). Consistent with these reports, lower consolidation and a random GGA pattern were detected in our pa-

tient. These radiological findings worsened rapidly after only 1 month (Fig. 2d, e, f). Lower consolidation and GGA, both of which were observed in our patient, may indicate organized pneumonia or DAD (Fig. 4) (17-19). Thus HRCT evaluation can be useful for predicting the presence of anti-MDA-5 antibodies in patients with CADM-associated ILD. RP-ILD should be considered by investigating specific CT findings even if a CADM patient's respiratory condition is stable.

The serum ferritin level also has been reported to be correlated with RP-ILD activity in patients with acute ILD complicated by DM. Hyperferritinemia, especially at levels of up to 1,500 ng/mL, may help to predict the disease severity and prognosis (20). Furthermore, the serum ferritin level has been reported to be correlated with the disease activity of anti-MDA-5 antibody-associated ILD with DM (21). In our patient, serum ferritin level was slightly elevated (260 ng/mL) at the initial visit. However, as the ILD worsened, the serum ferritin level increased to 1,500 ng/mL (Fig. 3). Thus, the serum ferritin level should be periodically evaluated because serum ferritin level elevation is associated with the severity of RP-ILD.

The lung specimen of our patient at autopsy exhibited an organizing process as well as hyaline membrane formation, suggesting a DAD pattern (Fig. 4). Five CADM-RP-ILD patients, including our own, are reported in the literature (Ta-

ble 2) (22-25). Anti-MDA-5 antibody was detected in 4 of these 5 patients. Histopathological examinations of the lung tissue revealed acute and organizing DAD in all of the cases, including our own. Although intensive immunosuppressive therapy, including high-dose steroids, IVCY, and calcineurin inhibitors was initiated in all cases, ILD was refractory and irreversible. DAD has previously been reported to be associated with a poorer prognosis than other histopathological patterns, such as unusual interstitial pneumonia (26).

The administration of intensive immunosuppressive therapy prior to the onset of irreversible pulmonary changes might have improved our patient's poor prognosis. Recently, it has been demonstrated that the early induction of strong and combined immunosuppressive therapy (including high-dose corticosteroids, oral cyclosporine A, and IVCY) may improve survival of patients who are anti-MDA-5 antibody-positive (27). These previous reports have suggested that the serum ferritin level tends to decrease after IVCY therapy. Therefore, IVCY might be a key drug in the treatment of anti-MDA-5 antibody-positive RP-ILD. These patients rarely survive after they become hypoxic; thus, urgent treatment is required once a diagnosis is made. By the time we gave our patient IVCY, the ILD and hypoxemia had already worsened. The early induction of high-dose IVCY (at close intervals) should therefore be considered (27).

In conclusion, anti-MDA-5 antibody-positive RP-ILD is associated with a poor prognosis. Clinicians should pay attention to the clinical, radiological, and serological findings in patients with CADM to help predict anti-MDA-5 antibody-associated RP-ILD. It is likely that these clinical clues will help to stratify the prognostic risk in these patients. The early induction of intensive immunosuppressive therapy, including IVCY, should be considered before hypoxemia worsens.

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

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