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【 CASE REPORT 】

Clinical Features of Anti-MDA5 Antibody-positive Rapidly Progressive Interstitial Lung Disease without Signs of Dermatomyositis

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Abstract:
Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody is associated with rapidly progressive interstitial lung disease (RP-ILD) in patients with clinically amyopathic dermatomyositis (CADM) or dermatomyositis (DM). We herein report three Japanese cases of anti-MDA5 antibody-positive RP-ILD without signs of CADM or DM. High-resolution computed tomography revealed patchy or subpleural distribution of consolidations and/or ground-glass opacities accompanied by traction bronchiectasis. All patients succumbed to respiratory failure within two months. Anti-MDA5 antibody-positive RP-ILD without signs of CADM or DM should be included in the differential diagnosis of acute/subacute ILD. Measurement of anti-MDA5 antibody and an intensive immunosuppressive regimen might rescue these patients from RP-ILD.

Key words: acute interstitial pneumonia, anti-melanoma differentiation-associated gene 5, clinically amyopathic dermatomyositis

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Introduction

Clinically amyopathic dermatomyositis (CADM), defined as the presence of cutaneous features of dermatomyositis (DM) without clinical muscle weakness, may be complicated by life-threatening rapidly progressive interstitial lung disease (RP-ILD) (1). The anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody, also known as anti-CADM140 antibody, is associated with RP-ILD in patients with CADM or DM (2). We herein report three Japanese cases of anti-MDA5 antibody-positive RP-ILD without signs of CADM or DM.

Case Reports

Case 1

A 72-year-old woman visited our hospital complaining of general fatigue. She had undergone surgery for left-sided breast cancer two years earlier and subsequent hormonal treatment with letrozole before this admission. Lung auscultation on admission revealed normal vesicular sounds in both lungs and no signs of DM or CADM in the skin or muscle. Laboratory investigations revealed an increased Krebs von den Lungen-6 level and a normal creatine kinase level (Table). High-resolution computed tomography (HRCT) of the chest on admission showed a patchy distribu-

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Table. Characteristics of Patients with Interstitial Lung Disease with Anti-MDA5 Antibody.

Patient number	1	2	3
Gender	Female	Female	Male
Age (years)	72	68	70
Smoking	Ne	Ne	Ex
Dust exposure	-	-	+
Complications	HT	HT, Comlete AV block	HT, Dyslipidemia
Month of onset	October	July	May
Malignancy	Breast cancer	-	Prostate cancer
Laboratory data			
CK (IU/L)	183	140	105
Aldolase (U/L)	NA	5.3	NA
Ferritin (ng/dL)	1,486	235	1,428
ANA	-	×80 (S)	×40 (H, S)
SP-D (ng/mL)	40.9	320.0	55.7
KL-6 (U/mL)	858	2,330	526
Pulmonary function test	NA	NA	NA
Bronchoalveolar lavage fluid findings			
Total cell counts ($\times 10^5$/mL)	5.7	NA	0.6
Macrophages (%)	83.9	NA	81.3
Lymphocytes (%)	15.2	NA	15.1
Neutrophils (%)	0.9	NA	0.8
Eosinophils (%)	0.0	NA	2.3
CD4/CD8 ratio	1.00	NA	1.69
Treatment	mPSL, PSL, IVCY, CyA	mPSL, PSL, IVCY, TAC	mPSL, PSL, IVCY
Pneumomediastinum	-	+	+
Outcome	death	death	death
	42 days	27 days	44 days
Anti-MDA5 antibody index	>150	>150	>150

M: male, F: female, Ne: never-smoker, Ex: ex-smoker, HT: hypertension, AV: atrioventricular block, CK: creatine kinase, NA: not assessed, ANA: anti-nuclear antibody, SP: surfactant protein, KL: Krebs von den Lungen, S: speckled, H: homogeneous, mPSL: methyl prednisolone pulse therapy, PSL: prednisolone, CyA: cyclosporine, TAC: taclorimus, IVCY: intravenous cyclophosphamide

tion of consolidations accompanied by traction bronchiectasis (Figure). An analysis of the bronchoalveolar lavage fluid revealed increased total cell counts with a slightly increased proportion of lymphocytes (Table). Transbronchial lung biopsy specimens revealed organizing inflammation accompanied by fibrin deposition, suggesting acute lung injury. Methylprednisolone pulse therapy followed by oral prednisolone and subsequent treatment with oral cyclosporine, intravenous cyclophosphamide, and invasive positive pressure ventilation did not improve the patient's status. She died of respiratory failure 42 days after admission. After her death, anti-MDA5 antibody in serum obtained at 35 days after admission was found to be positive.

Case 2

A 68-year-old woman was referred to our hospital because of deterioration of dyspnea and abnormal shadows on a chest radiograph. She had been treated previously for third-degree atrioventricular block and had undergone surgery for aortic dissection. Lung auscultation on admission revealed fine crackles in both lungs but no signs suggestive of DM or CADM. Laboratory investigations revealed slightly increased Krebs von den Lungen-6 and ferritin levels and a normal creatine kinase level (Table). HRCT of the chest on admission showed peripleural ground-glass opacity (GGO) and consolidations accompanied by traction bronchiectasis (Figure). Anti-MDA5 antibody in serum obtained on admission was positive. Methylprednisolone pulse therapy followed by treatment with oral prednisolone, oral tacrolimus, and intravenous cyclophosphamide supported by high-flow nasal oxygen did not improve the patient's status, and she died of respiratory failure 27 days after admission.

Case 3

A 70-year-old man visited our hospital complaining of deterioration of dyspnea. He worked as an automobile mechanic and had been receiving treatment with enzalutamide for prostate cancer immediately before this admission. Lung auscultation on admission revealed fine crackles in both lungs but no signs suggestive of DM or CADM. Laboratory investigations revealed increased Krebs von den Lungen-6 and ferritin levels and a normal creatine kinase level (Table). HRCT of the chest on admission showed peripleural GGO and consolidations that were accompanied by traction bronchiectasis (Figure). An analysis of the bronchoalveolar lavage fluid revealed slightly increased proportions of lymphocytes and neutrophils (Table). Transbronchial lung biopsy specimens did not suggest a specific disease. The patient did

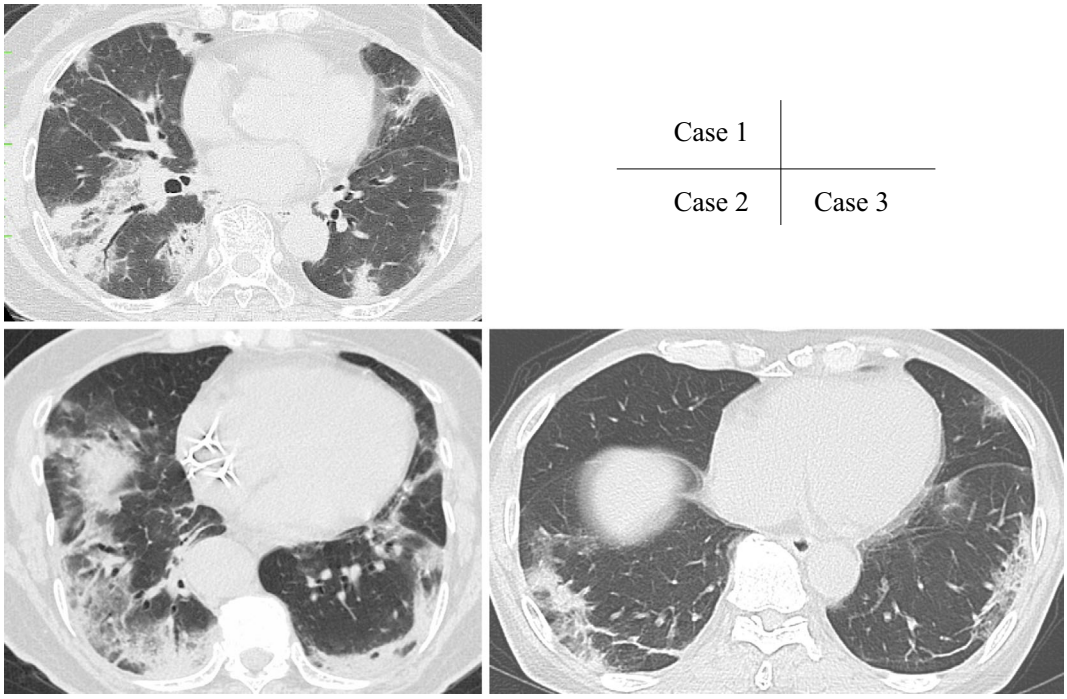

Figure. **Findings on high-resolution computed tomography of the chest at the time of admission. Patchy distribution of areas of consolidation accompanied by traction bronchiectasis (case 1). Peripleural ground-glass opacity and areas of consolidation accompanied by traction bronchiectasis (case 2). Peripleural ground-glass opacity and areas of consolidation (case 3).**

not improve on methylprednisolone pulse therapy followed by treatment with oral prednisolone and intravenous cyclophosphamide, and he died of respiratory failure 44 days after admission. After the patient's death, anti-MDA5 antibody in serum obtained 35 days after admission was found to be positive.

Discussion

We have reported three cases of anti-MDA5 antibody-positive RP-ILD without signs of DM or CADM. Anti-MDA5 antibody is a myositis-specific autoantibody that is specific for CADM and DM and is associated with RP-ILD in patients with CADM or DM but not in those with idiopathic interstitial pneumonias (IIPs) (2, 3). However, it was reported that ILD preceded skin and muscle symptoms in 2 of 43 patients with anti-CADM-140 antibody-positive CADM and DM (4). There have also been case reports of RP-ILD with anti-CADM-140/MDA5 antibody-positive CADM preceding cutaneous symptoms (5, 6). Consistent with those reports, the patients described in the present report might have had RP-ILD that preceded CADM. There has been a recent report of RP-ILD without skin involvement (7). That case and our experience in the present three cases indicate that patients who are anti-MDA5 antibody-positive might be considered to have an IIP, such as acute interstitial pneumonia (AIP). AIP is a major IIP and is characterized by rapidly progressive hypoxemia with a mortality rate exceeding 50% (8). There is still no proven treatment for AIP. Biopsy specimens in patients with AIP show an acute and/or organizing form of diffuse alveolar damage that is typically seen in patients with RP-ILD of the anti-MDA5 antibody-positive CADM type (9).

It has been reported that GGO/consolidation in a subpleural, lower, or random distribution is a common HRCT finding in patients with anti-MDA5 antibody-positive dermatomyositis, whereas a peribronchovascular distribution and intralobular reticular opacities are significant in those with anti-MDA5 antibody-negative dermatomyositis (10, 11). However, no marked difference in the loss of lung volume or presence of traction bronchiectasis was found between these two groups of patients (11). Pneumomediastinum has also been reported to be more common in patients with anti-MDA5 antibody-positive DM than in anti-MDA5 antibody-negative DM (12). Our three cases had features of anti-MDA5 antibody-positive dermatomyositis on HRCT, suggesting an association between the anti-MDA5 antibody and HRCT findings, regardless of the skin involvement in these cases.

All three patients in the present series died within two months of admission. In previous reports, all deaths in patients with anti-MDA5 antibody-positive DM occurred within the first six months (12, 13). These reports are consistent with our own experience. The anti-MDA5 antibody titers in patients with RP-ILD and DM have been reported to be lower before treatment and to decline significantly more in survivors than in non-survivors after treatment (13, 14). Anti-MDA5 antibodies were measured about 1 month after treatment in 2 of our 3 patients, both of whom had a titer of ≥150. The serum ferritin levels are re-

ported to be higher in anti-MDA5-positive patients with ILD and DM than in anti-MDA5 antibody-negative ILD with DM as well as higher in non-survivors than in survivors of anti-MDA5-positive ILD with DM (12, 13). In addition, pneumomediastinum has been reported to be more common in anti-MDA5-positive patients with ILD and DM than in anti-MDA5 antibody-negative patients with ILD and DM (12, 15). These reports indicate that our patients who all had a high anti-MDA5 antibody titer, a high ferritin level, and the complication of pneumomediastinum had either RP-ILD preceding CADM or a type of RP-ILD without CADM.

An intensive immunosuppressive regimen of high-dose glucocorticoids, oral cyclosporine, and intravenous cyclophosphamide pulse therapy is reported to be effective (16, 17), and additional immunosuppressive therapy, such as tofacitinib and rituximab, was recently identified as being potentially useful for treating refractory anti-MDA5 antibody-positive ILD accompanied by DM (18, 19). Two of our patients (cases 1 and 3) were treated initially with high-dose glucocorticoids and subsequently with oral calcineurin inhibitors (cyclosporine/tacrolimus) and/or intravenous cyclophosphamide pulse therapy two weeks after the first treatment. The early measurement of the anti-MDA5 antibody should be considered in patients who are found to have GGO/consolidation in a subpleural, lower, or random distribution on HRCT. Although the efficacy of these therapies should be confirmed in prospective trials, the early detection of the anti-MDA5 antibody in patients with an AIP-like presentation might guide the use of these intensive immunosuppressive regimens and improve the prognosis.

Signs of skin involvement from dermatomyositis were sought by experienced pulmonologists in the present cases (except in case 2). However, slight skin involvement from dermatomyositis might be missed when the skin examination is performed by pulmonologists who are not experienced in checking for dermatomyositis.

We herein report three Japanese patients with anti-MDA5 antibody-positive RP-ILD without signs of CADM or DM. Anti-MDA5 antibody-positive RP-ILD without CADM or DM should be included in the differential diagnosis of acute/subacute ILD. The measurement of the anti-MDA5 antibody level and an intensive immunosuppressive regimen might rescue these patients from RP-ILD.

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

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