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【 ORIGINAL ARTICLE 】

Interstitial Lung Disease with Anti-melanoma Differentiation-associated Protein 5 Antibody: Rapidly Progressive Perilobular Opacity

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Abstract:

Objective Rapidly progressive interstitial lung disease (RP-ILD) with anti-melanoma differentiation-associated protein 5 (MDA5) antibody potentially presents with a fatal clinical course and requires early intensive treatment. Recently, perilobular opacity was reported to pathologically correspond to the acute phase of diffuse alveolar damage in RP-ILD with anti-MDA5 antibody. We aimed to investigate whether or not perilobular opacity was a common radiological finding in RP-ILD patients with anti-MDA5 antibody.

Methods We conducted a retrospective review of the medical records of eight consecutive patients with RP-ILD with anti-MDA5 antibody. The clinical features and radiological findings of follow-up computed tomography (CT) during the course of their disease were evaluated.

Results Among eight RP-ILD patients with anti-MDA-5 antibody, six showed perilobular opacity in the lower lobes, and the remaining two had only consolidation on high-resolution CT. Of note, the perilobular opacity in all six patients thickened and progressed to consolidation with a loss of lung volume in a short period. Despite intensive treatment, 6 patients (75%) died within 100 days after the first visit. Notably, the two patients with consolidation presented with a very rapid clinical course and died in 13 days each. In the two survivors, the perilobular opacity and consolidation recovered with improvement in the loss of lung volume.

Conclusion Rapidly progressive perilobular opacity that thickens and progresses to consolidation is characteristic of RP-ILD with anti-MDA5 antibody. Chest physicians should immediately check the status of anti-MDA-5 antibody in order to initiate early aggressive therapy in RP-ILD patients with rapidly progressive perilobular opacity.

Key words: rapidly progressive interstitial lung disease, anti-melanoma differentiation-associated protein 5 antibody, clinically amyopathic dermatomyositis, perilobular opacity, disease course

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Introduction

Clinically amyopathic dermatomyositis (CADM) is a subset of dermatomyositis with clinical cutaneous features and subtle or no muscle involvement and is sometimes associated with rapidly progressive interstitial lung disease (RP-ILD), with a prevalence of 5-65% (1). Anti-melanoma differentiation-associated protein 5 (MDA5) antibody was identified in the sera of patients with CADM in 2005 (2)

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and is known to be strongly associated with RP-ILD and a poor prognosis (3, 4). Importantly, RP-ILD with anti-MDA5 antibody is also associated with fatal outcomes even when the diagnostic criteria of CADM are not fully met (5).

Generally, early intensive treatment including corticosteroids and immunosuppressant therapy can improve the survival rate in CADM-associated RP-ILD (6, 7). Similarly, it has also been considered crucial to immediately provide intensive treatment for RP-ILD with anti-MDA5 antibody due to its poor prognosis. However, measuring the titre of anti-MDA5 antibodies takes several days, which has made early intervention for RP-ILD with anti-MDA5 antibody extremely difficult. Therefore, elucidating the clinical and radiological characteristics of RP-ILD with anti-MDA5 antibody may be an important clue for providing early intensive treatment.

Recently, we reported the case of a patient with anti-MDA5 antibody-positive RP-ILD evaluated by a surgical lung biopsy (5). In that paper, the perilobular opacity rapidly thickened and progressed to consolidation on high-resolution computed tomography (HRCT). Importantly, perilobular opacity pathologically corresponded to diffuse alveolar damage (DAD). However, no reports have yet investigated the presence of perilobular opacity in RP-ILD with anti-MDA5 antibody. Perilobular opacity with such a specific shift to consolidation may be common and characteristic of RP-ILD with anti-MDA5 antibody. To confirm this supposition, we performed this retrospective study.

Materials and Methods

Patients

We retrospectively reviewed the medical records of eight consecutive patients with RP-ILD with anti-MDA5 antibody between January 2006 and December 2014 at our hospital. Anti-MDA5 antibody was evaluated using an enzyme-linked immunosorbent assay with recombinant MDA5 previously established for measuring the titre of anti-MDA5 antibody (8, 9). RP-ILD is defined as the presentation of progressive dyspnoea along with hypoxemia and worsening interstitial changes on chest radiography within a month of the onset of respiratory symptoms (4). This study was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center (IRB: H27-23).

Clinical and radiological review

The clinical symptoms and laboratory findings, including Krebs von den Lungen-6 (KL-6) and creatine kinase (CK), as well as the radiological findings of HRCT, pulmonary function analyses, treatment, clinical course and outcome were retrospectively assessed from the medical records. Chest radiography and HRCT were also performed at the first visit and follow-up. The radiological ILD classification at the first visit was evaluated based on the global classification of idiopathic interstitial pneumonia (10). Perilobular opacity was defined as thick, irregular polygonal increased attenuation at the periphery of the secondary pulmonary lobules, as previously reported (11-14).

Results

Patients' characteristics on admission

The clinical features of the eight patients with anti-MDA5 antibody-positive RP-ILD were described in Table. The median age was 63.5 years (range 55-86 years old) at the time of the first visit. Among them, four patients were non-smokers, and four were ex-smokers.

A specific rash was the most common initial symptom and was observed in 7 patients (88%): nail fold bleeding and Gottrons's papule in 6 patients, heliorope rash in 5 patients, and palmer papule in 4 patients. Two patients had muscle weakness. Only three patients complained of dyspnoea on admission. Despite hypoxia, the remaining five patients did not complain of dyspnoea but did cite malaise. The median duration between the onset of respiratory symptoms and the first visit was 10 days (range 1-26 days). The median partial pressure of oxygen in arterial blood on room air was 62.2 torr (range 52.9-82.1 torr), and 3 of the patients (37.5%) had values of <60 torr. Seven of the 8 patients had elevated KL-6 levels with a median of 756 U/mL (range 328-1,493 U/mL; normal, <500 U/mL), and 4 patients had elevated serum CK levels with a median of 247 U/L (range 46-415 U/L; normal, <197 U/L). The level of MDA-5 antibody ranged from 30.9 to 195.6 with a median of 68.45. The ferritin was remarkably elevated in all evaluated patients (567.9 to 1,740 pg/mL). A pulmonary function analysis was performed in 5 patients, and a restrictive pattern with <80% vital capacity as percent of predicted (%VC) was present in 2 patients.

Treatment and outcome

In all patients, methylprednisolone pulse therapy followed by daily oral prednisolone treatment was administered, in addition to one or more immunosuppressants, such as intravenous cyclophosphamide, tacrolimus, mycophenolate mofetil, or cyclosporine A. Among all patients, 6 (75%) underwent treatment with polymyxin-B direct hemoperfusion for 2 successive days. Six patients (75%) died of respiratory failure within 100 days (median 49 days, range 13-97 days) after the first visit. The remaining 2 patients survived 1,192 and 1,564 days after being diagnosed with ILD. The serological course of ferritin level in all 4 evaluated patients is shown in Fig. 1. In the survivor (case 7), the ferritin level decreased after a tentative increase, whereas the remaining three deceased patients showed a consistent increase.

Radiological findings on follow-up HRCT during the disease course

HRCT was performed on admission in all eight patients and revealed marked volume loss in the lower lobes. Appar-

Table. **Summary of Clinical Characteristics of Eight Cases at the Time of Diagnosis.**

Case No.	1	2	3	4	5	6	7	8
Age, Sex	64, F	86, F	64, F	55, M	56, M	61, M	63, M	75, F
Duration (days)	12	1	6	25	8	4	26	4
Smoking	Never	Never	Never	Former	Former	Former	Former	Never
Specific rash*	+	+	+	+	-	+	+	+
PaO_2 on room air (torr)	52.9	58.5	58.4	77.8	82.1	68.3	-	62.2
LDH (IU/L)	572	640	528	282	388	271	302	353
KL-6 (U/mL)	1,493	703	1,473	841	685	328	624	809
SP-D (ng/mL)	29.9	354	25.3	30.8	53.2	55	<17.3	53.2
CK (IU/L)	107	46	329	415	350	165	352	66
MDA-5 antibody	182	93.4	37.3	195.6	83.5	53.4	30.9	47.7
Ferritin	N.E.	N.E.	N.E.	N.E.	1740	N.E.	567.9	1,426.6
%VC	53.9	-	87.7	66.7	92.6	-	-	85.6
%DLCO	-	-	74.5	65.7	-	-	-	97.3
Treatment	mPSL pulse, PSL, IVCY, Tac, CyA, IVIG, PMX	mPSL pulse, PSL, IVCY, CyA,	mPSL pulse, PSL, IVCY, Tac, CyA, MMF, IVIG, PMX	mPSL pulse, PSL, IVCY, Tac, IVIG, PMX	mPSL pulse, PSL, IVCY, Tac, IVIG, PMX	mPSL pulse, PSL, IVCY, CyA, IVIG, PMX	mPSL pulse, PSL, IVCY, Tac, MMF, IVIG, PMX	mPSL pulse, PSL, IVCY, CyA, IVIG,
Perilobular opacity	-	-	+	+	+	+	+	+
Consolidation	+	+	-	-	-	-	-	-
Follow-up period (days)	13	13	44	54	58	97	1,564	1,192
Outcome	Dead	Dead	Dead	Dead	Dead	Dead	Alive	Alive

*: specific skin rash represented palmer papule, nail fold bleeding and/or purple-skin ulcer. DM: dermatomyositis, PaO_2: arterial oxygen partial pressure on room air, $AaDO_2$: Alveolar-arterial Oxygen Difference, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, SPD: Surfactant protein D, CK: creatine kinase, %VC: vital capacity predicted, %DLCO: diffusing capacity of the lung for carbon monoxide predicted, mPSL: methylprednisolone, PSL: prednisolone maintenance therapy, IVCY: intravenous cyclophosphamide, Tac: tacrolimus, CyA: cyclosporin A, MMF: mycophenolate mofetil, IVIG: intravenous immunoglobulin, PMX: direct hemoperfusion with polymyxin-B immobilized fibre

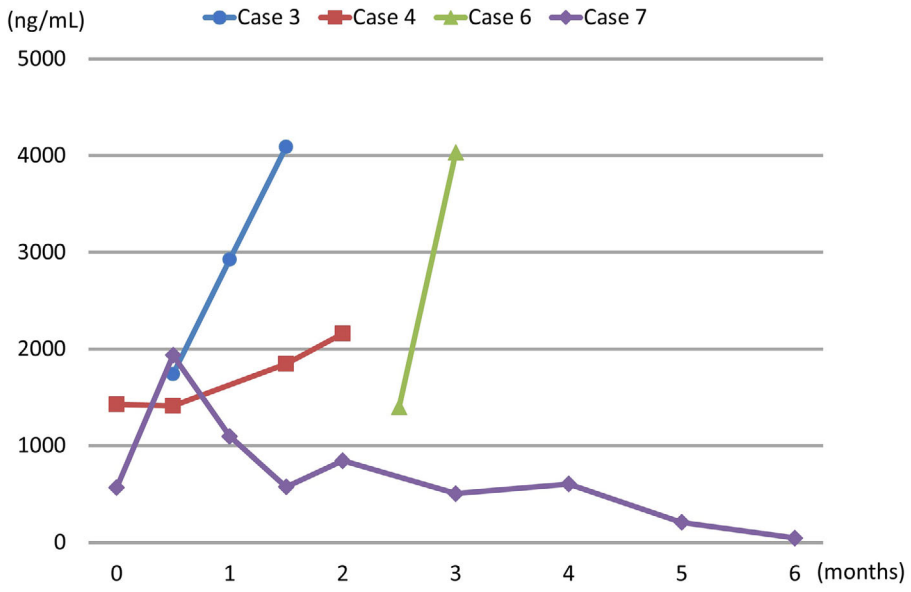

Figure 1. **The serological course of ferritin.**

ent honeycombing and diffuse ground glass opacity were not detected. Six patients (75%) had perilobular opacity in the subpleural area of both lungs as shown in Figs. 2-6, whereas the remaining 2 patients (Cases 1 and 2) had only consolidation with loss of lung volume (Fig. 7). With regard to the radiological pattern on admission, an unclassifiable CT pattern was dominant in all eight patients, as all patients presented with shrinking subpleural ground glass attenuation (GGA)/consolidation, which was inconsistent with the OP pattern. Follow-up CT was performed for seven of the eight

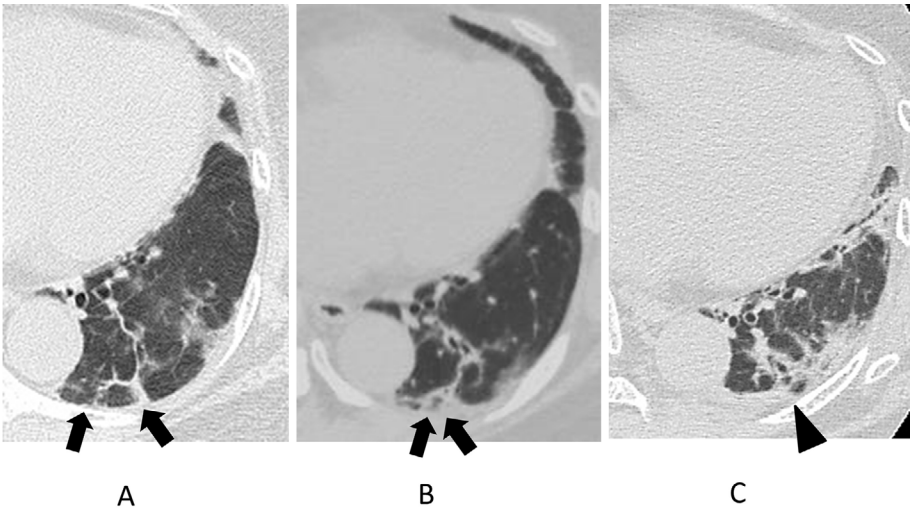

Figure 2. **Follow-up CT findings in Case 3. (A) Perilobular opacity (arrows) was observed in the left lower lobe on admission. (B) Follow-up CT showed the thickening of perilobular opacity (arrows) three days after admission. (C) The perilobular opacity progressed to consolidation with the loss of lung volume (arrowhead) about two weeks after admission.**

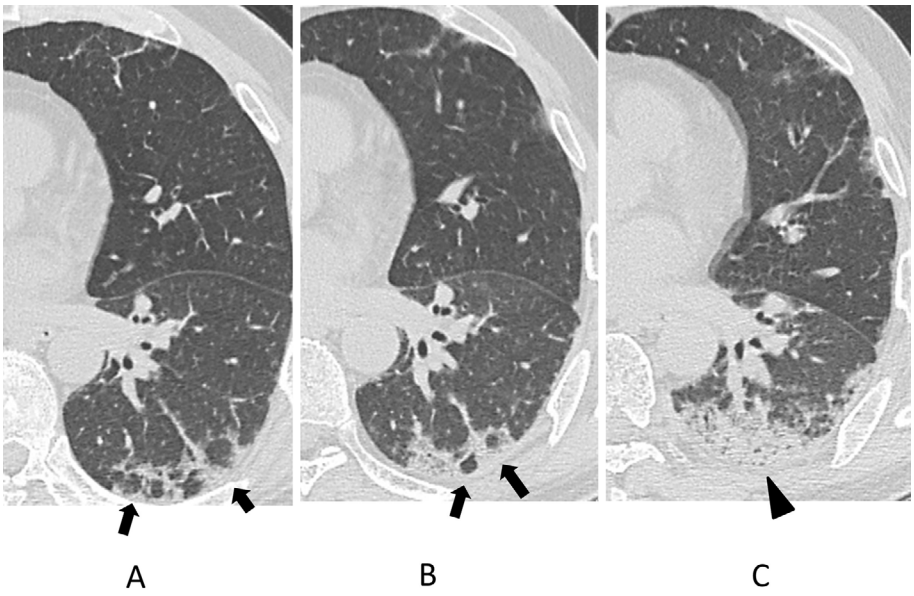

Figure 3. **Follow-up CT findings in Case 4. (A) Perilobular opacity was revealed in the left lower lobe of Case 4 (arrows). The area of the radiological abnormality was localized. (B) The perilobular opacity observed on admission deteriorated with thickening in two weeks (arrows). (C) The perilobular opacity progressed to consolidation with the loss of lung volume in one month (arrowhead).**

patients. The median duration between the first CT scan and follow-up CT was 6 days (range 2-18 days). Despite intensive treatment, follow-up CT revealed disease progression, and the perilobular opacity that had been observed on admission in 6 patients (75%) had thickened and progressed to consolidation accompanied by a loss of lung volume (Fig. 2-6). However, in both survivors, the perilobular opacity that had progressed to consolidation during the first two weeks showed nearly complete remission, with improvement in the loss of lung volume during the course of their disease (Fig. 5, 6).

Pathological findings in surgically resected or autopsied cases

A pathological evaluation was performed in two patients (Cases 1 and 5). Case 5 was evaluated by a surgical lung biopsy before initiating treatment, whereas Case 1 was investigated by an autopsy. In both patients, the pathological findings revealed DAD.

As we previously reported in *Internal Medicine* (5), the specimen taken from a surgical lung biopsy in Case 5 showed widespread poorly aerated alveoli and intra-alveolar membranous organization, which was indicative of organiz-

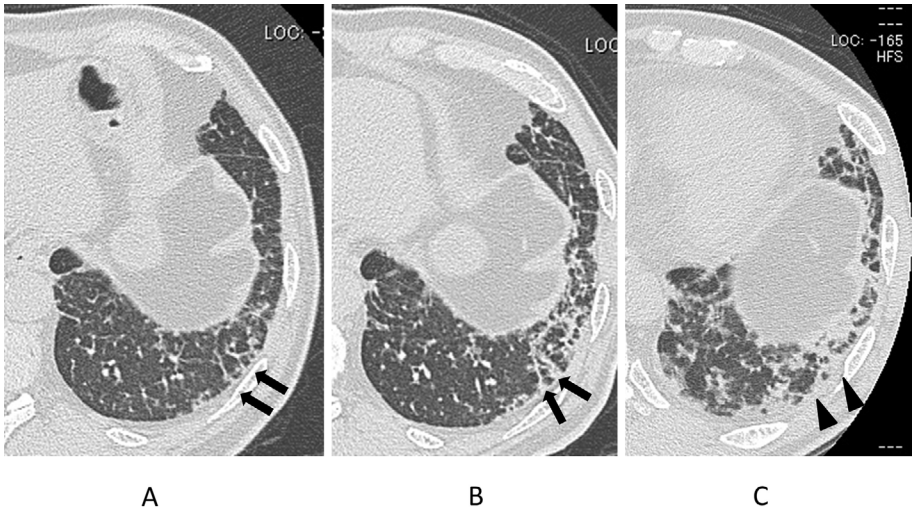

Figure 4. **Follow-up CT findings in Case 5. (A) Perilobular opacity (arrows) was observed in the left lower lobes on admission. (B) Follow-up CT 18 days after admission showed the thickening of the perilobular opacity in the left lower lobes (arrows). (C) The perilobular opacity on the left lower lobes progressed to consolidation in about one month (arrowhead).**

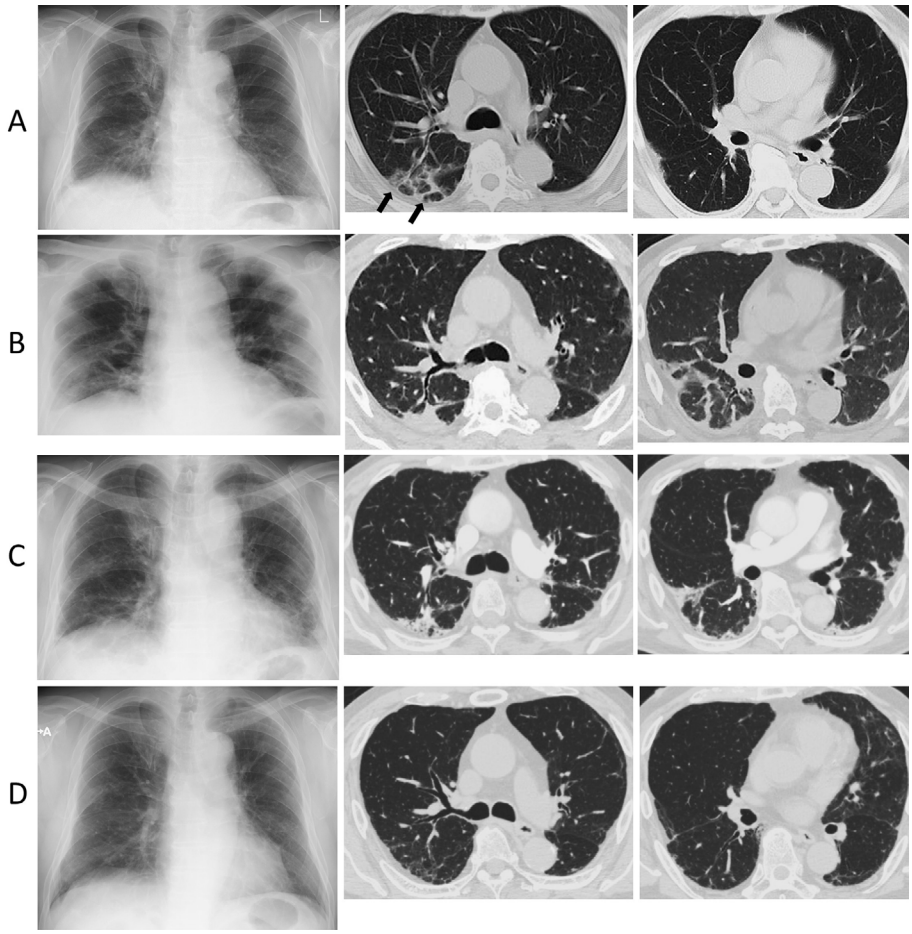

Figure 5. **Chest radiography and high-resolution CT findings in Case 7. (A) Chest radiography on admission showed bilateral reticular shadow in both bases, whereas chest CT demonstrated perilobular opacity with structured, poorly defined polygonal opacity (arrows). (B) The perilobular opacity progressed to consolidation with a remarkable loss of lung volume in six days. (C) The loss of lung volume and consolidation were slightly improved 1.5 months after admission. (D) In the recovery phase, the consolidation decreased, and the loss of volume improved 15 months after admission.**

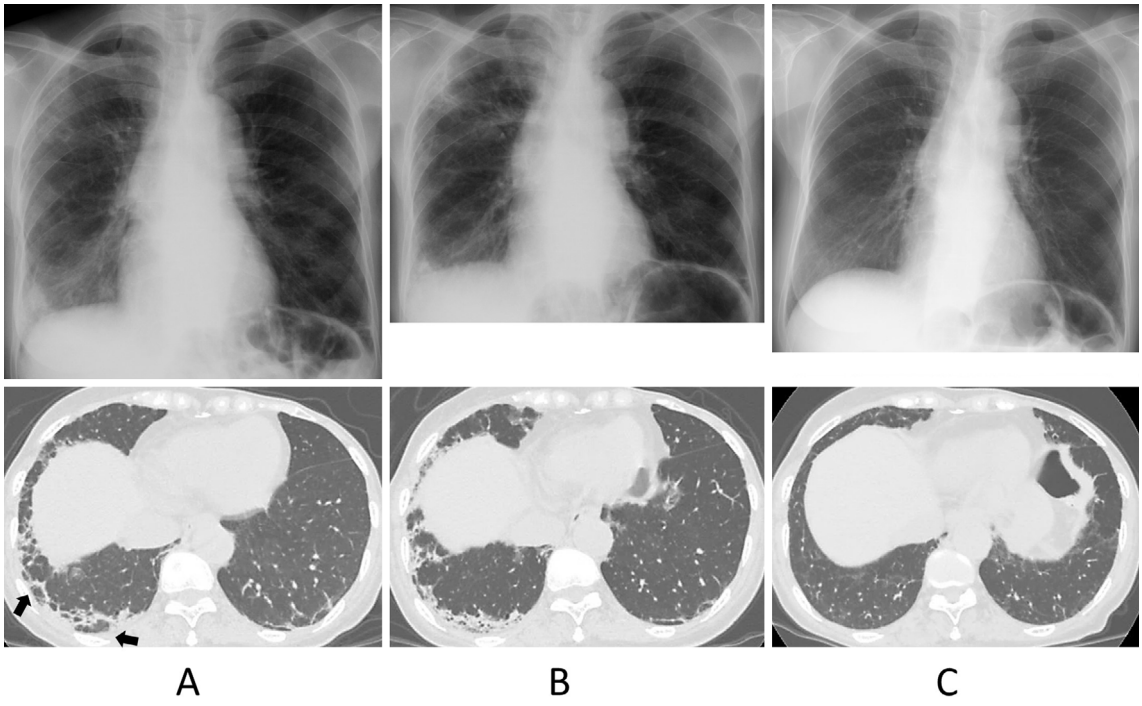

Figure 6. **Chest radiography and high-resolution CT findings in Case 8. (A) Chest radiography on admission demonstrated consolidation mainly in the right lower lung field. Chest CT showed perilobular opacity in the subpleural region (arrows). (B) As the disease progressed, the perilobular opacity thickened, forming consolidation with apparent lung volume loss in 13 days. (C) In the recovery phase, the consolidation decreased, and the loss of lung volume recovered 31 months after the first visit.**

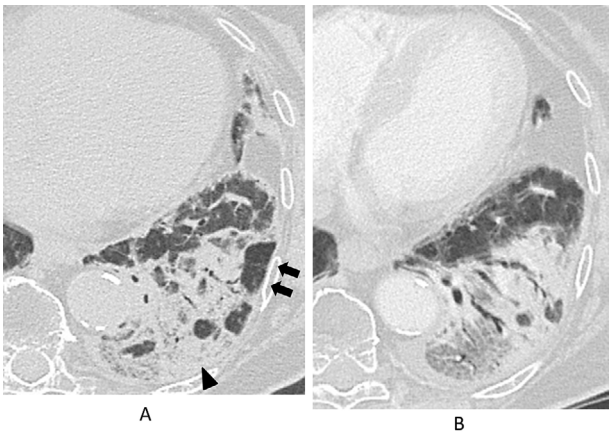

Figure 7. **Follow-up CT findings in Case 2. (A) Air-space consolidation with traction bronchiectasis (arrowhead) was observed in Case 2 at the first visit. In the subpleural region, polygonal increased attenuation was also revealed (arrows). (B) Consolidation, which had been observed on admission, deteriorated with a remarkable loss of lung volume two days after admission.**

ing DAD (Fig. 8). In addition, hyaline membranes within air spaces and intra-alveolar oedema with infiltration by inflammatory cells, which are typical features of acute DAD, were also present (5). In the autopsied case (Case 1), the pathological findings showed intra-alveolar oedema with infiltration by inflammatory cells and alveolar damage with alveolar hyperplasia and hyaline membrane formation without any evidence of infection.

Case presentation of the two survivors

Case 7

A 63-year-old man visited the previous hospital complaining of a persistent cough and malaise for 3 weeks and a persistent skin rash without any myositis symptoms for 6 months. Fine crackles were noted in the lower lung fields. With regard to skin rash, Gottron's sign, heliotrope eyelids, nail fold bleeding and mechanic's hand were detected. The percutaneous oxygen saturation on room air was 91%, requiring nasal oxygen at 4 L/min. Chest radiography showed reticular opacity in the lower lung fields and the loss of lung volume. HRCT revealed subpleural localized perilobular opacity in the lower lobes (Fig. 5A). Laboratory findings revealed elevated serum levels of KL-6 (624 U/mL) and aldolase (9.0 U/L; normal, <7.5 U/L). The level of CK was normal (66 ng/mL). Although methylprednisolone pulse therapy was immediately initiated, the respiratory condition did improve, so the patient was referred to our hospital two weeks later. Based on his clinical and radiological findings, CADM-associated ILD was diagnosed, and we initiated intravenous cyclophosphamide and immunoglobulin, tacrolimus and mycophenolate mofetil in addition to polymyxin-B direct hemoperfusion. On admission to our hospital, the level of ferritin was high at 567.9 ng/mL but rose to 2,737 ng/mL two weeks later, and the perilobular

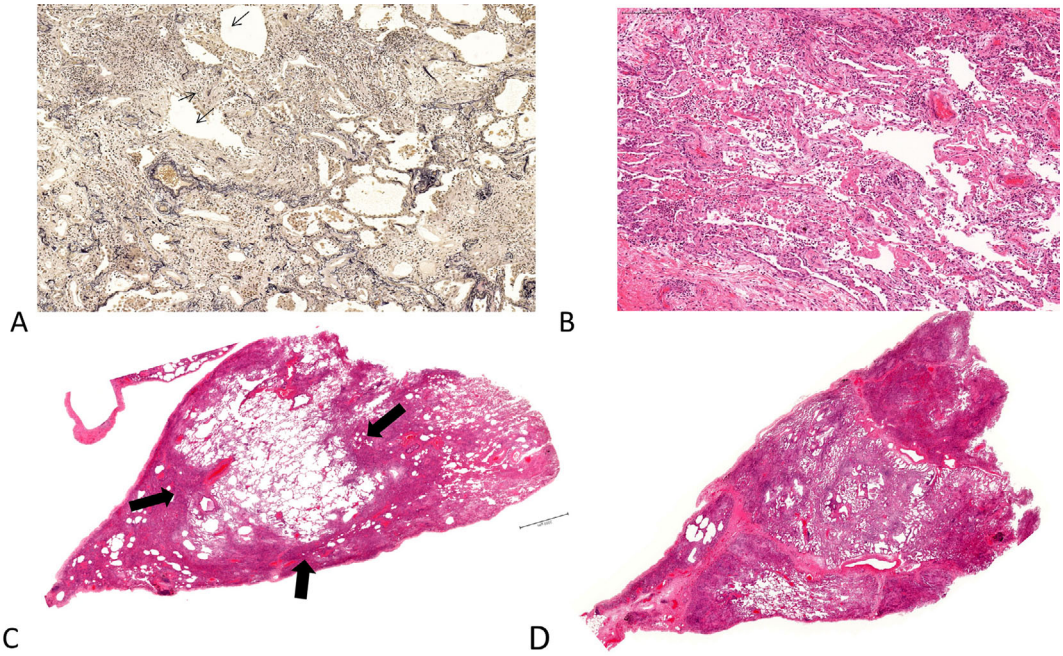

Figure 8. **Histological findings. High-power views of right S9 in Case 5 (A, B). A panoramic view of the lung specimen from right S3a and S9 in Case 5 (C, D). (A) Membranous organization (arrows) in the alveolar ducts with marked intra-alveolar obliterative fibrosis (Elastica van Gieson stain, 12×). (B) Hyaline membranes, shedding of pneumocytes, and infiltration of inflammatory cells in the alveolar lumina (Hematoxylin and Eosin (H&E) staining, 12×). (C) A panoramic view of the lung specimen from right S3a shows widespread, poorly aerated alveoli and intra-alveolar organization predominantly involving the subpleural and interlobular septal areas (arrows) (H&E staining, 1×). (D) A lung specimen from S9 demonstrates diffuse collapsed alveoli and membranous organization with fibrosis (5).**

opacity thickened, with eventual progression to consolidation (Fig. 5B). One month after admission, a pulmonary function test revealed severe restrictive respiratory dysfunction with a %VC of 54.9% and diffusing capacity of the lung for carbon monoxide as percent of predicted (%DLco) of 48.7%. However, his respiratory dysfunction and the radiological consolidation gradually improved 1.5 months after admission (Fig. 5C), and the ferritin level decreased to 534.9. Eleven months after admission, the %VC and %DLco increased to 92.1% and 102.4%, respectively, with a normal level of serum ferritin (10.6 ng/mL). The perilobular opacity and consolidation almost disappeared on chest CT with no lung volume loss on chest radiography 15 months after the admission (Fig. 5D).

Case 8

A 75-year-old woman developed exertional dyspnoea and cough 10 days after the appearance of heliotrope and skin rash without any symptoms of myositis. She visited our hospital two weeks after the onset of respiratory symptoms. With regard to skin rash, nail fold bleeding and palmer papule were observed. Chest radiography showed reticular opacity in both lower lung fields. HRCT showed perilobular opacity in the lower lobes (Fig. 6A). Laboratory findings revealed elevated serum levels of KL-6 (809 U/mL) and CK (352 ng/mL). A pulmonary function test revealed that %VC and %DLco were 85.6% and 97.3%, respectively. The partial pressure of oxygen in arterial blood on room air was 62 torr. CADM-associated RP-ILD was diagnosed based on the clinical and radiological findings. Although methylprednisolone pulse therapy followed by oral prednisolone therapy, intravenous cyclophosphamide and cyclosporine A was immediately initiated, the perilobular opacity thickened and progressed to consolidation with apparent lung volume loss 2 weeks after the first visit (Fig. 6B), and the %VC and %DLco decreased to 74.8% and 79.7% 1 month after the first visit. However, after initiating intravenous immunoglobulin, the respiratory failure and chest radiography findings improved. The prednisolone and cyclosporine dosage was gradually and successfully tapered on a monthly basis. The perilobular opacity and consolidation on chest CT and lung volume loss on chest radiography had completely improved without recurrence of ILD at 31 months after the first visit (Fig. 6C). In addition, the %VC and %DLco increased to 128% and 131%, respectively, at 33 months after the first visit.

Discussion

The present study reviewed eight consecutive cases of RP-ILD with anti-MDA5 antibody and raises two important clinical issues. First, perilobular opacity may be a common radiological finding in RP-ILD with anti-MDA5 antibody.

Second, perilobular opacity progresses to consolidation within a short period of time, but a nearly complete recovery can be achieved during the clinical course of the disease.

With regard to the first finding, perilobular opacity may be a common radiological phenomenon in RP-ILD with anti-MDA5 antibody and pathologically correspond to DAD. A few papers have described the radiological characteristics of RP-ILD patients with anti-MDA5 antibody. In those papers, the most common HRCT pattern was "unclassified" followed by "NSIP with OP" (15, 16), and neither intralobular reticular opacity nor lower reticulation was observed (17). Generally, perilobular opacity, which was observed in 6 of the 8 patients (75%) in our study, is reported in about a half of patients with cryptogenic organizing pneumonia (11-14). However, perilobular opacity in RP-ILD with anti-MDA5 antibody does not correspond to organizing pneumonia in terms of the clinical course. In the present study, two cases were pathologically evaluated, and the specimen obtained via a surgical lung biopsy in Case 5 revealed that perilobular opacity corresponded to DAD, as previously reported by our group in *Internal Medicine* (Fig. 8) (5). This suggests that perilobular opacity observed in RP-ILD with anti-MDA5 antibody pathologically corresponds to DAD. The fatal clinical course and reduced partial pressure of oxygen, which was disproportionate to the localized perilobular opacity, seem to support this supposition.

The second finding is that the perilobular opacity thickens and progresses to consolidation in a short period during the clinical course of RP-ILD with anti-MDA5 antibody, although a nearly complete recovery from these findings can be achieved in certain cases. In fact, the present study revealed that the perilobular opacity in six patients rapidly progressed to consolidation. Although the remaining two patients did not present with apparent perilobular opacity, consolidation at the first visit seemed to manifest as a result of the progression of perilobular opacity. Of note, in Case 5, consolidation on HRCT corresponded to pathologically organizing DAD (5). In cases of acute respiratory distress syndrome (ARDS) or acute interstitial pneumonia, consolidation on HRCT is generally considered to pathologically correspond to the late phase of DAD, and the extent of consolidation predicts the prognosis (18-20). Similarly, in RP-ILD with anti-MDA5 antibody, our two patients with radiological consolidation at the first visit died within two weeks. Their clinical course may support the hypothesis that consolidation represents an advanced stage of perilobular opacity. However, Owens et al. reported eight survivors with ARDS who were evaluated with chest CT during the acute phase and at follow-up; those authors found that consolidation completely resolved in all eight patients (21). Therefore, as in ARDS patients, consolidation can be completely improved in RP-ILD patients with anti-MDA-5 antibody.

Our results provide an important clinical implication: in RP-ILD patients with progressive perilobular opacity, chest physicians should immediately check for the presence of a specific skin rash and determine the MDA-5 antibody status in order to initiate early aggressive treatment. In patients with ILD with anti-MDA5 antibody, the cumulative 6-month survival rate was reported to be approximately 50%, so the survival rate of the present study seems to be relatively low. Although the reason for these results remains unclear, it may be due to the diagnosis being made at a relatively advanced phase as a result of all patients being referred to our hospital with apparent respiratory failure and radiological abnormalities, as our institution is a cardiopulmonary hospital. Earlier intervention with intensive immunosuppressive agents has been reported to improve the clinical outcome of RP-ILD with anti-MDA5 antibody (6, 7). Indeed, our results indicate that even perilobular opacity itself is a sign of acute-phase DAD. Furthermore, some previous reports described the early prediction of lethal RP-ILD with MDA-5 antibody in patients with findings such as palmer papule, nail fold bleeding, and skin ulcers, which were present in almost all of our patients (16, 22-24). Given the present and previous findings, the status of MDA-5 antibody and the presence of a specific skin rash should be immediately evaluated in order to initiate early aggressive treatment including multiple immunosuppressive agents in RP-ILD patients with rapidly progressive perilobular opacity.

Despite some important findings from the present study, it has a few limitations. First, this was a small-sized, retrospective study conducted at a single institution. Second, because of its retrospective nature, the follow-up periods and intervals between HRCT examinations were variable. Third, not all patients were able to be pathologically evaluated, although radiopathological correlations were confirmed in two patients.

In conclusion, we herein report the radiological features of RP-ILD with anti-MDA5 antibody as evaluated by follow-up HRCT during the disease course. Our results indicate that perilobular opacity that thickens and progresses to consolidation is the main radiological finding in RP-ILD with anti-MDA5 antibody. Therefore, chest physicians should immediately check the status of MDA-5 antibody in order to initiate early aggressive therapy to overcome the acute phase of this disease in RP-ILD patients with rapidly progressive opacity.

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

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