

1 **Title:** HRCT FEATURES OF INTERSTITIAL LUNG DISEASE IN  
2 DERMATOMYOSITIS WITH ANTI-CADM-140 ANTIBODY

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4 **Authors:**

5 Kiminobu Tanizawa, MD<sup>1</sup>, Tomohiro Handa, MD, PhD<sup>1,2</sup>, Ran Nakashima, MD, PhD<sup>3</sup>,  
6 Takeshi Kubo, MD, PhD<sup>4</sup>, Yuji Hosono, MD<sup>3</sup>, Kizuku Watanabe, MD<sup>1</sup>,  
7 Kensaku Aihara, MD<sup>1</sup>, Toru Oga, MD, PhD<sup>5</sup>, Kazuo Chin, MD, PhD<sup>5</sup>,  
8 Sonoko Nagai, MD, PhD<sup>6</sup>, Tsuneyo Mimori, MD, PhD<sup>3</sup> and Michiaki Mishima, MD,  
9 PhD<sup>1</sup>

10  
11 **Affiliation:** <sup>1</sup>Department of Respiratory Medicine, Graduate School of Medicine, Kyoto  
12 University, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

13 <sup>2</sup>Department of Rehabilitation Medicine, Kyoto University Hospital, 54 Shogoin  
14 Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

15 <sup>3</sup>Department of Rheumatology and Clinical Immunology, Graduate School of Medicine,  
16 Kyoto University, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

17 <sup>4</sup>Department of Diagnostic Imaging and Nuclear Medicine Graduate School of  
18 Medicine, Kyoto University, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507,  
19 Japan

20 <sup>5</sup>Department of Respiratory Care and Sleep Control Medicine, Graduate School of  
21 Medicine, Kyoto University, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507,  
22 Japan

23 <sup>6</sup>Kyoto Central Clinic, Clinical Research Center, 56-58 Masuyacho Sanjo-Takakura,  
24 Nakagyo-ku, Kyoto 604-8111, Japan

25 Kyoto Central Clinic/Clinical Research Center  
26 56-58 Masuyacho Sanjo-Takakura, Nakagyo-ku, Kyoto, Japan 604-8111

27  
28 **Corresponding author:** Tomohiro Handa, MD, PhD

29 Department of Rehabilitation Medicine, Kyoto University Hospital,  
30 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto 606-8507

31 E-mail : [hanta@kuhp.kyoto-u.ac.jp](mailto:hanta@kuhp.kyoto-u.ac.jp)

32 TEL: +81-75-751-3850, FAX: +81-75-751-4643

33

1 **Running title:** HRCT in DM-ILD with anti-CADM-140

2

1 **Abstract**

2 *Background:* Anti-CADM-140 antibody (anti-CADM-140), also referred to as  
3 anti-melanoma differentiation-associated gene 5 (MDA5) antibody, is a  
4 myositis-specific antibody identified in the sera of patients with clinically amyopathic  
5 dermatomyositis (C-ADM) and is associated with a worse prognosis in  
6 dermatomyositis-associated interstitial lung disease (DM-ILD). We sought to determine  
7 high-resolution computed tomography (HRCT) features of DM-ILD with  
8 anti-CADM-140.

9 *Methods:* Twenty-five patients newly diagnosed with DM-ILD at Kyoto University  
10 Hospital between 2005 and 2009 were retrospectively reviewed. Serum  
11 anti-CADM-140 was measured in all patients at their first visit. Chest HRCT images  
12 taken prior to treatment were classified based on the dominant findings and their  
13 distribution, and compared between patients with and without the antibody.

14 *Results:* Of 25 DM-ILD patients, 12 were positive and 13 were negative for  
15 anti-CADM-140. HRCT patterns differed significantly between  
16 anti-CADM-140-positive and negative patients ( $P = 0.002$ ). Lower consolidation or  
17 ground-glass attenuation (GGA) pattern (50.0%) and random GGA pattern (33.3%)  
18 were the predominant patterns in anti-CADM-140-positive cases, while lower  
19 reticulation pattern (69.2%) was frequently seen in anti-CADM-140-negative cases.  
20 Anti-CADM-140-positive cases were also significantly characterized by the absence of  
21 intralobular reticular opacities (0% in anti-CADM-140 (+) vs. 84.6% in  
22 anti-CADM-140 (-),  $P < 0.0001$ ).

1 *Conclusions:* Anti-CADM-140-positive DM-ILD was characterized by lower  
2 consolidation or GGA pattern, random GGA pattern, and the absence of intralobular  
3 reticular opacities.

4

5 **Keywords:** amyopathic dermatomyositis; anti-CADM-140 antibody; interstitial lung  
6 disease; high-resolution computed tomography

7

1 **Introduction**

2 Interstitial lung disease (ILD) is observed in 5-65% of polymyositis (PM) and  
3 dermatomyositis (DM) cases,<sup>1,2</sup> and is a significant prognostic factor.<sup>1</sup>  
4 PM/DM-associated ILD (PM/DM-ILD) can be divided into acute and chronic types.<sup>3</sup>  
5 The acute type of PM/DM-ILD is often rapidly progressive and refractory to treatment,  
6 resulting in fatal outcome.<sup>3</sup>

7 PM and DM are also characterized by several serum autoantibodies specific to  
8 PM/DM, designated as myositis-specific antibodies (MSAs).<sup>4</sup> Anti-CADM-140  
9 antibody (anti-CADM-140) was the MSA identified in 2005 by Sato and coworkers in  
10 the sera of patients with clinically amyopathic dermatomyositis (C-ADM).<sup>5</sup> It  
11 recognizes interferon (IFN)-induced with helicase C domain protein 1/melanoma  
12 differentiation-associated gene 5 (IFIH1/MDA5)<sup>6</sup> and is thus also referred to as  
13 anti-MDA5 antibody.<sup>7</sup> It is specific to DM and is associated with the acute type of DM-  
14 ILD.<sup>6,7</sup> As expected from these findings, anti-CADM-140 was reported to be associated  
15 with a worse prognosis in patients with DM-ILD, compared to anti-aminoacyl-tRNA  
16 synthetase (ARS) antibodies (anti-ARS).<sup>7</sup> On the other hand, acute and chronic types of  
17 DM-ILD were shown to display different radiological features.<sup>3</sup> However, the  
18 radiological features of DM-ILD with anti-CADM-140 or the relationships between  
19 anti-CADM-140 and radiological findings have not been elucidated thus far.

20 In the present study, we aimed to define high-resolution computed tomography  
21 (HRCT) features of DM-ILD with anti-CADM-140. We compared HRCT findings  
22 between anti-CADM-140-positive and negative DM-ILD cases, and investigated

1 whether the HRCT features could discriminate between the antibody-positive and  
2 negative cases.

3

#### 4 **Methods**

##### 5 *Patients*

6 The study population included all patients who were diagnosed with DM at  
7 Kyoto University Hospital between 2005 and 2009. DM was diagnosed using the Bohan  
8 and Peter criteria.<sup>8</sup> C-ADM was diagnosed if a patient had the characteristic skin rash of  
9 DM but little or no muscle symptoms and serum creatine kinase (CK) was <300 IU/L  
10 during the study period, as described previously.<sup>5,6</sup> We excluded patients who had active  
11 neoplasm or other connective tissue disease (CTD), or had been treated with systemic  
12 corticosteroid (CS) or immunosuppressive agents before referral to our hospital. Among  
13 the remaining 32 patients, ILD was confirmed in 25 (78.1%) based on HRCT. Acute and  
14 subacute DM-ILD subtypes were diagnosed when respiratory failure developed within 1  
15 month and within 1 to 3 months, respectively, from the onset of symptoms or the  
16 initiation of treatment.

17 All patients provided written informed consent before blood sample collection.  
18 The Kyoto University Hospital Institutional Review Board approved this retrospective  
19 study.

20

##### 21 *Clinical evaluation*

22 Clinical information was retrospectively collected from medical records. All

1 patients were evaluated by at least two rheumatologists prior to treatment and had blood  
2 tests at their first visit. Most patients also underwent standardized pulmonary function  
3 tests,<sup>9</sup> and arterial blood gas analysis was done before treatment. Published equations  
4 for Japanese adults were used to determine predicted values of each parameter.<sup>10</sup>

5

#### 6 *Measurement of MSAs*

7 Serum samples were obtained from all patients at the first visit prior to receiving  
8 immunosuppressive therapies. The presence of MSAs was determined by RNA-  
9 immunoprecipitation (RNA-IPP) for anti-ARS and protein-immunoprecipitation (P-IPP)  
10 for anti-CADM-140 as described previously.<sup>6</sup> Patients were divided into two groups  
11 based on the presence or absence of anti-CADM-140: anti-CADM-140 (+) or (-),  
12 respectively.

13

#### 14 *HRCT scanning protocol*

15 Thin-section CT images were obtained with a multi-detector CT scanner  
16 (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). Whole lung scans  
17 were performed at peak tube voltage of 120 kVp with variable mAs setting using an  
18 automatic exposure control system (SD value 8.5). Contiguous 7-mm-thick images and  
19 HRCT images (2 mm) were prepared for review.

20

#### 21 *HRCT evaluation*

22 All patients underwent chest HRCT prior to treatment, and images were

1 reviewed by three independent observers (T.K., T.H., and K.T. with 15, 12, and 10 years  
2 of experience, respectively) blinded to clinical information. Inter-observer  
3 disagreements were resolved by consensus.

4 Images were assessed for the presence of ground-glass attenuation (GGA),  
5 consolidation, intralobular reticular opacities, interlobular septal thickening, non-septal  
6 linear or plate-like opacity, substantial micronodules, honeycombing, emphysema,  
7 traction bronchiectasis, and lobar volume loss. The presence of mediastinal lymph node  
8 enlargement or pleural effusion and the laterality of abnormalities were also assessed.  
9 HRCT findings were interpreted according to the recommendations of the  
10 Nomenclature Committee of the Fleischner Society.<sup>11</sup> Nonseptal linear or plate-like  
11 opacity was defined as an elongated line of soft tissue attenuation that was distinct from  
12 interlobular septa and bronchovascular bundles, including subpleural curvilinear lines  
13 and subpleural bands.<sup>12</sup>

14 Through reviewing all HRCT images, we found that all 25 cases could be  
15 categorized into a few HRCT patterns, based on dominant CT findings, and the  
16 craniocaudal and axial distribution of these findings. The dominant findings were  
17 classified as GGA, consolidation, or reticulation (intralobular reticular opacities,  
18 interlobular septal thickening, or nonseptal linear or plate-like opacity). The  
19 craniocaudal distribution was assessed as upper, lower, diffuse, or random. Upper  
20 distribution was defined as extensive findings predominantly above the level of inferior  
21 pulmonary veins, lower when there were more below this level, diffuse when  
22 generalized, and random for no zonal predominance. The axial distribution was



1 classified as peribronchovascular when the dominant findings were along the bronchi  
2 and vessels, peripheral when in the outer one-third of the lung, diffuse when generalized,  
3 or random when no distribution pattern was apparent.

4

#### 5 *Statistical analysis*

6 Statistical analysis was performed using JMP<sup>®</sup> version 6 (SAS Institute Inc.  
7 Cary, NC, USA). All statistical variations in quantitative data were expressed as a single  
8 determination standard deviation, and a *P* value less than 0.05 was considered to  
9 indicate statistical significance.

10 Group comparisons were made using Fisher's exact test,  $\chi^2$  test, and  
11 Mann-Whitney U test. Cumulative survival probabilities were estimated using the  
12 Kaplan-Meier method and the log-rank test.

13

## 14 **Results**

### 15 *Initial clinical features*

16 Demographics, clinical manifestations and laboratory test results of patients in  
17 the anti-CADM-140 (+) and (-) groups are summarized in Table 1. The prevalence of  
18 C-ADM showed no significant difference (50.0% vs. 30.8%, *P* = 0.43). Acute DM-ILD  
19 was diagnosed in 25% of patients in the anti-CADM-140 (+), and 0% of patients in the  
20 anti-CADM-140 (-) group (*P* = 0.10), while the sum of acute and subacute subtypes was  
21 41.7% and 7.7%, respectively (*P* = 0.07). Before treatment, white blood cells, platelets,  
22 CK, and aldolase levels were lower in the anti-CADM-140 (+) group. Pretreatment

1 ferritin and its maximal value were both higher in the anti-CADM-140 (+) group. In the  
2 anti-CADM-140 (-) group, 10 patients (76.9%) were positive for anti-ARS: three with  
3 EJ, three with PL-7, two with Jo-1, one with OJ, and one with PL-12. Arterial blood gas  
4 analyses and pulmonary functional tests revealed no significant differences (data not  
5 shown). No patients underwent surgical lung biopsy (SLB) in either group.

6

### 7 *HRCT evaluation*

8         HRCT findings are shown in Table 2. Common findings were GGA (83.3%),  
9 nonseptal linear or plate-like opacity (83.3%), and interlobular septal thickening  
10 (66.7%) in the anti-CADM-140 (+) group; and GGA (100.0%), intralobular reticular  
11 opacities (84.6%), non-septal linear or plate-like opacity (53.8%), and lobular volume  
12 loss (53.8%) in the anti-CADM-140 (-) group. Among the HRCT findings, intralobular  
13 reticular opacities were significantly different between the groups (0% in  
14 anti-CADM-140 (+) vs. 84.6% in anti-CADM-140 (-),  $P < 0.0001$ ).

15         Next, we categorized all 25 cases into four HRCT patterns: lower  
16 consolidation/GGA pattern (lower peripheral or peribronchovascular consolidations or  
17 GGA); lower reticulation pattern (lower peripheral or peribronchovascular reticulation);  
18 random GGA pattern (random peripheral GGA); and others. Lower consolidation/GGA  
19 pattern was characterized by nonsegmental consolidations or GGA, with subpleural or  
20 peribronchovascular distribution (Figs. 1 and 2). Lower reticulation pattern showed a  
21 homogeneous distribution with some subpleural sparing (Fig. 3). In random GGA  
22 pattern, small GGAs were seen in a patchy manner in the absence of consolidation (Fig.

1 4).

2           The HRCT patterns were significantly different between the anti-CADM-140  
3 (+) and (-) groups ( $P = 0.002$ ): with lower consolidation/GGA pattern (50.0%) and  
4 random GGA pattern (33.3%) in the anti-CADM-140 (+) group, and lower reticulation  
5 pattern (69.2%) in the anti-CADM-140 (-) group. Additionally, the dominant  
6 abnormalities were seen in lower lung fields (6/12, 50%) or randomly (4/12, 33.3%) in  
7 anti-CADM-140-positive patients, compared to lower lung fields (12/13, 93.2%) in  
8 most anti-CADM-140-negative patients ( $P = 0.04$ ). The HRCT patterns in the seven  
9 fatal anti-CADM-140 (+) cases were lower consolidation/GGA pattern in four, random  
10 GGA pattern in two (including the one patient who died of *Pneumocystis jiveroci*  
11 pneumonia and sepsis), and others in one (Table 3). Of 10 patients with anti-ARS  
12 antibodies in the anti-CADM-140 (-) group, six (60.0%) had a lower reticulation pattern  
13 and two (20.0%) had lower consolidation/GGA pattern. Three patients who were  
14 negative for both anti-CADM-140 and anti-ARS showed lower reticulation pattern.

15

#### 16 *Treatment and outcome*

17           All patients received corticosteroid (CS) therapy, and immunosuppressive (IS)  
18 agents; most commonly cyclosporine A (CsA), used in 83.3% and 69.2% in the  
19 anti-CADM-140 (+) and (-) groups, respectively.

20           The median follow-up period from the diagnosis of DM for all patients was 588  
21 days (range, 41-1617 days). Of 12 patients in the anti-CADM-140 (+) group, seven died  
22 and five survived, while all 13 patients in the anti-CADM-140 (-) group survived ( $P <$

1 0.01). Of the seven deaths in anti-CADM-140 (+) group, five patients died of  
2 progressive ILD that was refractory to initial treatment. The remaining two patients died  
3 after the disease had been well controlled for months. One patient died of *Pneumocystis*  
4 *jiroveci* pneumonia and sepsis, and another of acute exacerbation of ILD without  
5 infection. All seven patients were treated with corticosteroids and CsA, whereas  
6 cyclophosphamide (CYC) was used in six patients.

7

## 8 **Discussion**

9 We demonstrated that radiological features of anti-CADM-140-positive  
10 DM-ILD were significantly different from those of anti-CADM-140-negative cases,  
11 based on the original classification of HRCT patterns. In our series,  
12 anti-CADM-140-positive DM-ILD was characterized by lower consolidation/GGA and  
13 random GGA pattern and the absence of intralobular reticular opacities. To our  
14 knowledge, this is the first report describing HRCT features of DM-ILD with  
15 anti-CADM-140 in comparison with DM-ILD without this antibody.

16 The HRCT patterns characterized by the dominant findings and the distributions  
17 of such abnormalities were significantly different between the anti-CADM-140 (+) and  
18 (-) groups. Lower consolidation/GGA and random GGA patterns predominated in the  
19 anti-CADM-140 (+) group, while lower reticulation was more common in the  
20 anti-CADM-140 (-) group. Lower reticulation pattern is consistent with idiopathic  
21 nonspecific interstitial pneumonia (NSIP)<sup>13-15</sup> and DM/PM-ILD having biopsy-proven  
22 NSIP pattern:<sup>16</sup> reticulation, GGAs, lobar volume loss, and lower predominance, but

1 little or no honeycombing. More than half of the anti-CADM-140-negative patients  
2 (69.2%, including six anti-ARS positive patients) in our series had this pattern,  
3 suggestive of pathological NSIP pattern. On the other hand, lower consolidation/GGA  
4 and random GGA patterns are more difficult to interpret. Lower consolidation/GGA  
5 pattern may indicate organized pneumonia (OP)<sup>14 17</sup> or localized diffuse alveolar  
6 damage (DAD).<sup>14 17-19</sup> The mortality in patients with this pattern was as high as 50.0%  
7 (4/8), suggesting a high prevalence of DAD although radiopathological correlation was  
8 not confirmed in our cases. Indeed, Kang et al. reported biopsy-proven DAD, usual  
9 interstitial pneumonia (UIP), and NSIP patterns in DM-ILD, while HRCT findings  
10 showed OP pattern in most cases.<sup>20</sup> In random GGA pattern, most lesions were too  
11 small to speculate pathology.

12 Another significant characteristic of anti-CADM-140-positive DM-ILD was the  
13 absence of intralobular reticular opacities. Intralobular reticular opacities represent  
14 abnormal thickening of intralobular interstitial tissue<sup>11</sup> and were observed in 87% of  
15 idiopathic NSIP patients<sup>13</sup> and 92% of DM/PM-ILD patients with biopsy-proven NSIP  
16 pattern.<sup>16</sup> Thus, the absence of lower reticulation pattern and intralobular reticular  
17 opacities in the anti-CADM-140 (+) group indicates a lower prevalence of pathological  
18 NSIP pattern among anti-CADM-140-positive cases, in contrast to  
19 anti-CADM-140-negative cases. Additionally, the reported responses to treatment and  
20 outcomes of DM/PM-ILD patients with biopsy-proven NSIP pattern were much better  
21 than those of our anti-CADM-140-positive patients.<sup>16</sup> Although the prognostic value of  
22 pathology in DM-ILD have not been established, these differences in both radiological

1 findings and survival suggest that the anti-CADM-140 (+) group includes patients  
2 distinct from those with pathological NSIP.

3         On the other hand, HRCT findings other than intralobular reticular opacities  
4 were not significantly different between the anti-CADM-140 (+) and (-) groups. Our  
5 results indicate that HRCT patterns may be more helpful in discriminating between  
6 anti-CADM-140-positive and negative cases than several nonspecific findings. The  
7 HRCT patterns in our study were based on the major abnormalities and the distributions  
8 of those abnormalities to describe the overall picture comprehensively and concisely.  
9 Thus, the complete picture of HRCT images, rather than the presence of individual  
10 abnormalities probably characterized anti-CADM-140-positive cases better.

11         Among MSAs, anti-ARS has also been reported to be associated with ILD in  
12 DM/PM patients.<sup>21</sup> Of 13 anti-CADM-140 negative cases in our study, 10 were positive  
13 for anti-ARS, and the HRCT patterns were similar between anti-ARS-positive and  
14 negative cases: lower reticulation pattern was predominant (60.0% and 40.0% in  
15 anti-ARS-positive and negative patients, respectively). These findings indicate that  
16 anti-CADM-140 may be more influential on the HRCT patterns of DM-ILD than  
17 anti-ARS.

18         Notably, the prevalence of C-ADM was not significantly different  
19 between anti-CADM-140 (+) and (-) groups. In spite of the designation, half the patients  
20 in the anti-CADM-140 (+) group did not fulfill the criteria for C-ADM. Such a  
21 discrepancy between anti-CADM-140 and C-ADM was also suggested by Gono and  
22 coworkers.<sup>7</sup> In addition, the results of pulmonary function tests and arterial gas analyses

1 at diagnosis were not significantly different. These findings indicate that, while this  
2 antibody is a strong predictor of mortality, the initial clinical data cannot necessarily  
3 discriminate between anti-CADM-140-positive and negative cases in DM-ILD. In  
4 contrast, the HRCT features were significantly different between the two groups,  
5 suggesting the clinical utility of HRCT evaluation for predicting the presence of  
6 anti-CADM-140.

7 High mortality in the anti-CADM-140 (+) group suggested the necessity of  
8 novel therapies beyond the combination of corticosteroids and immunosuppressive  
9 agents, mainly CsA and/or CYC. On the other hand, approximately half of patients with  
10 anti-CADM-140 (41.7%) survived with current regimens. Table 3 suggests that the  
11 HRCT patterns may not be associated with survival in anti-CADM-140-positive  
12 DM-ILD; thus, the prognostic value of HRCT features at diagnosis is the next critical  
13 question. A recent study reported the prognostic value of serum ferritin in DM-ILD with  
14 anti-CADM-140, although the study population was relatively small.<sup>7</sup> Thus, the  
15 predictors of mortality in anti-CADM-140 positive DM-ILD, including HRCT features  
16 should be elucidated by analyzing larger numbers of patients. In addition, in the entire  
17 spectrum of DM-ILD, the prognostic values of HRCT features should also be compared  
18 to that of anti-CADM-140 and other serum biomarkers. As Goh et al. showed in  
19 systemic sclerosis-associated ILD<sup>22</sup>, quantitative scoring of disease extent may be  
20 helpful in these analyses.

21 We should mention some limitations of this study. First, this study was a  
22 small-sized study in a single center. Second, serial changes in HRCT images were not

1 addressed because follow-up HRCT was performed at rather arbitrary intervals. The  
2 effects of treatment on HRCT features and their prognostic values should be further  
3 studied in a prospective design. Third, radiopathological correlation was not confirmed.  
4 However, the significance of pathological diagnosis or SLB in clinical practice of  
5 DM-ILD or CVD-related ILD has not been determined.<sup>23 24</sup> Further, SLB can sometimes  
6 induce acute exacerbation in idiopathic pulmonary fibrosis and other ILD patients.<sup>25-27</sup>  
7 Fourth, anti-CADM-140 has been reported exclusively in Japanese patients thus far.<sup>5-7</sup>  
8 To establish the clinical relevance of this antibody, further studies in other ethnic  
9 populations are required.

10         Despite these limitations, we demonstrated that lower consolidation/GGA  
11 pattern and random GGA patterns as well as the absence of intralobular reticular  
12 opacities were characteristic of anti-CADM-140-positive DM-ILD. Although HRCT  
13 evaluation can be useful in predicting the presence of anti-CADM-140 in DM-ILD,  
14 further studies are required to define the prognostic value of HRCT features in  
15 anti-CADM-140-positive DM-ILD.

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6

7 **Conflicts of Interest**

8           Kiminobu Tanizawa has no conflicts of interest to disclose. Tomohiro Handa  
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16

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## Figure legends

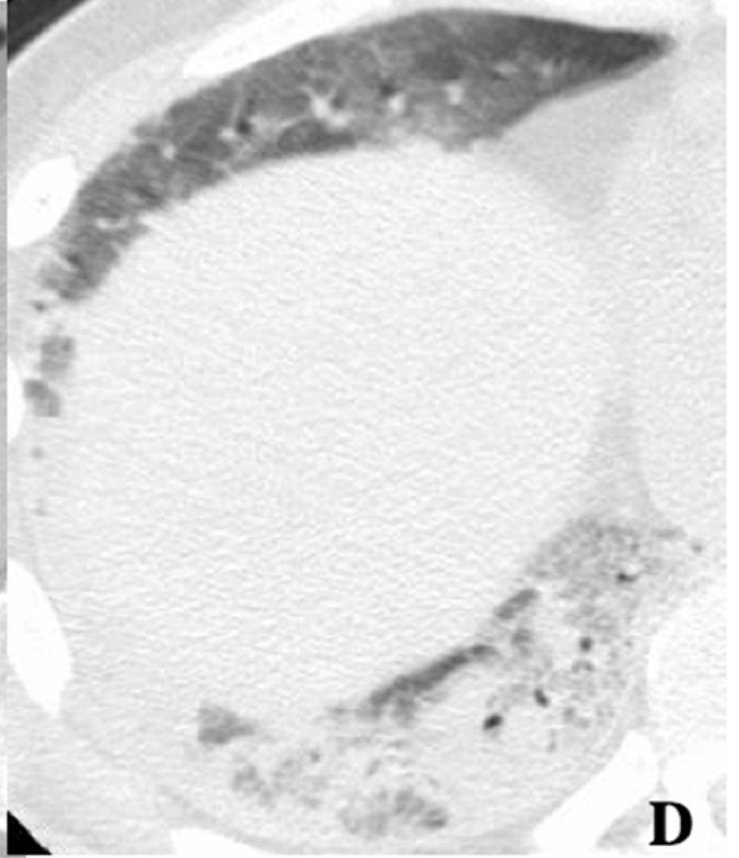
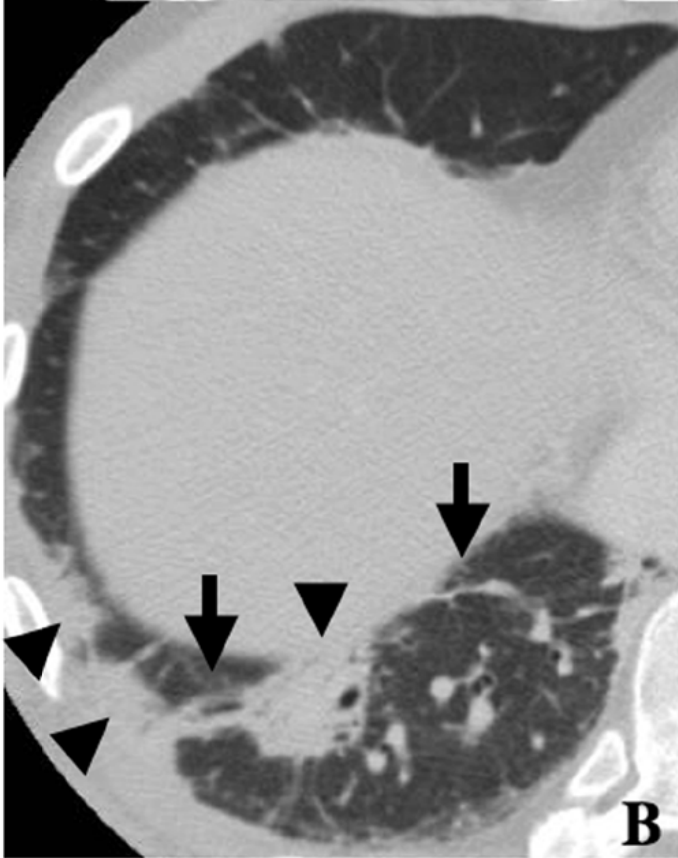
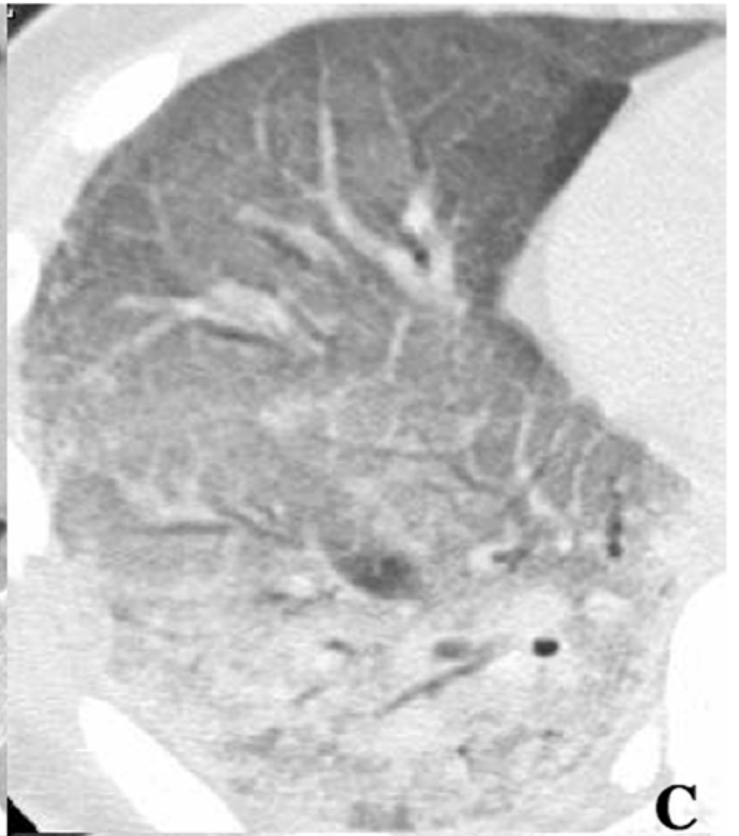
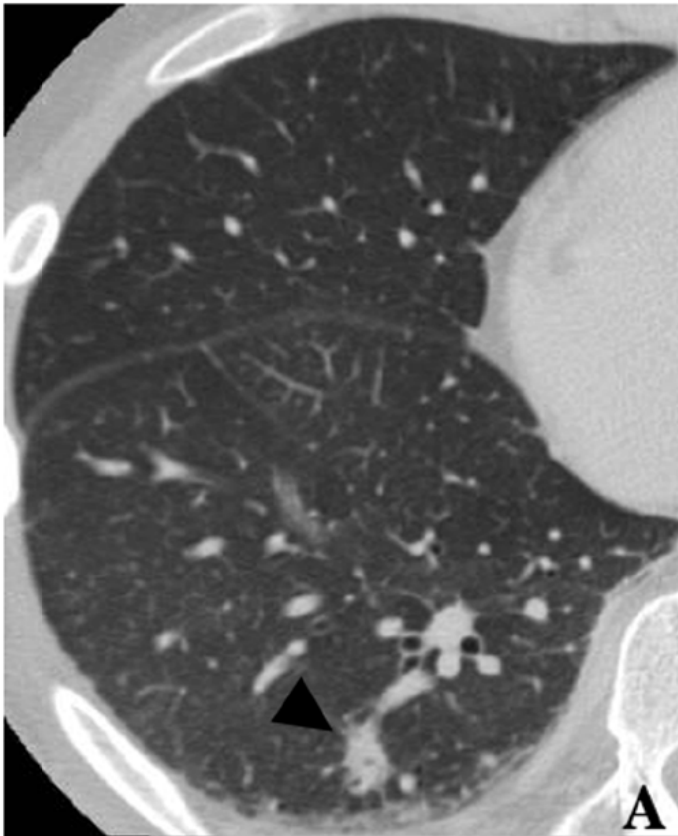
Figure 1. High resolution computed tomography (HRCT) images showing lower consolidation/ ground-glass attenuation (GGA) pattern in a 44-year-old man positive for anti-CADM-140 antibody (anti-CADM-140). A and B: At diagnosis, peripheral and peribronchovascular consolidations were observed (arrowheads). Interlobular septal thickening and nonseptal linear or plate-like opacities were also seen (arrows). C and D: Despite treatment for 6 weeks, severe respiratory failure developed, requiring mechanical ventilation. Diffuse GGA and consolidation with air bronchograms were extended in the whole lungs. Surveillance at this point revealed no evidence of infection. The patient died of respiratory failure 1 week later.

Figure 2. A and B: HRCT images showing lower consolidation/GGA pattern in a 51-year-old man positive for anti-CADM-140. A: At diagnosis, subpleural nonsegmental GGA was observed. B: Peripheral and peribronchovascular consolidations (arrowheads), and interlobular septal thickening and nonseptal linear or plate-like opacities (arrow) were also seen. C and D: HRCT images showing lower consolidation/GGA pattern in a 60-year-old man positive for anti-CADM-140. Subpleural nonsegmental consolidations with air bronchograms were observed (arrowheads). Subpleural nonsegmental GGA was also seen (arrow).

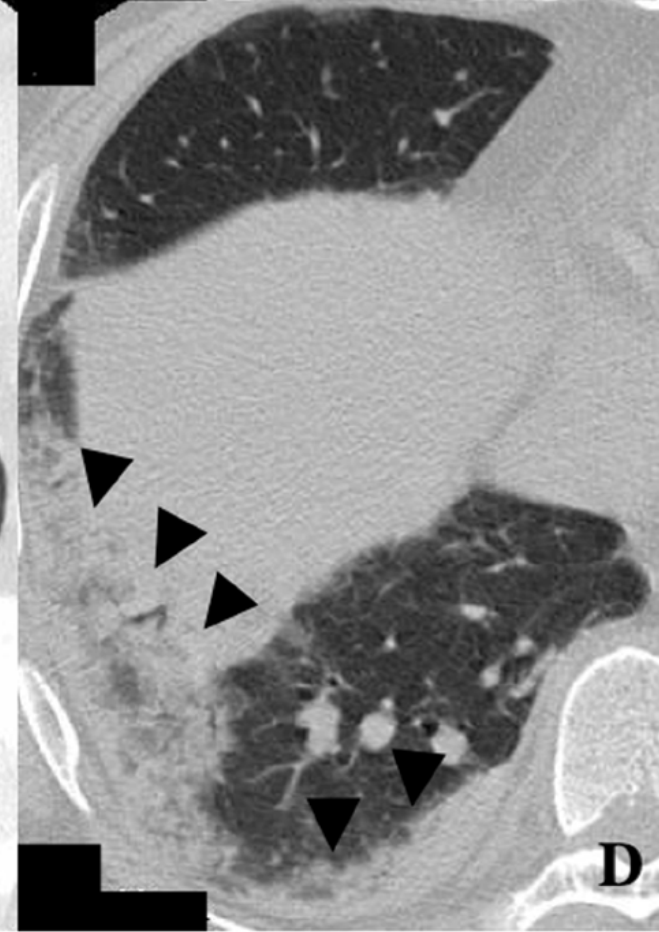
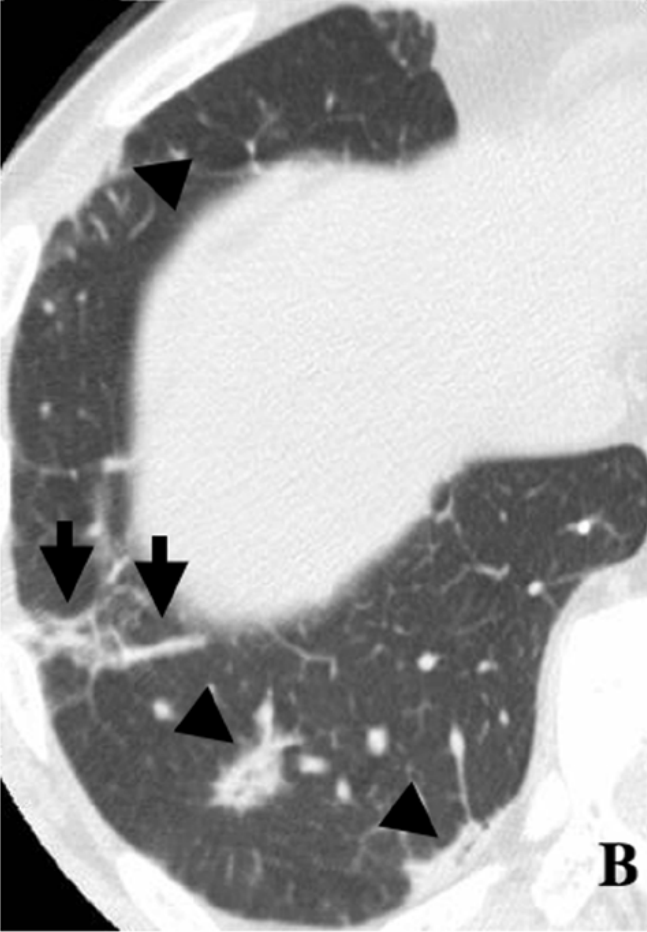
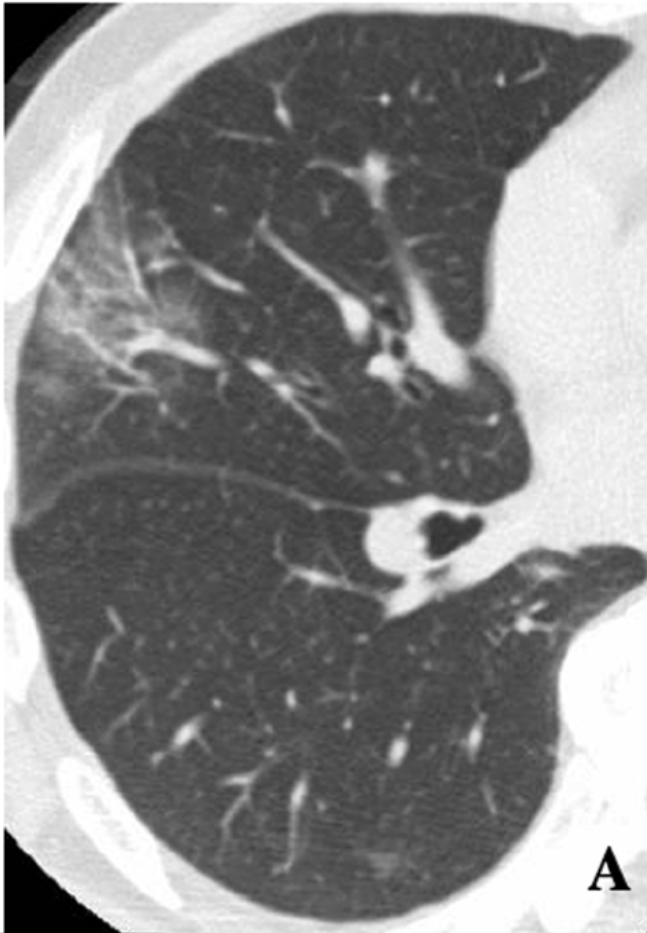
Figure 3. HRCT images showing lower reticulation pattern. A: A 47-year-old woman

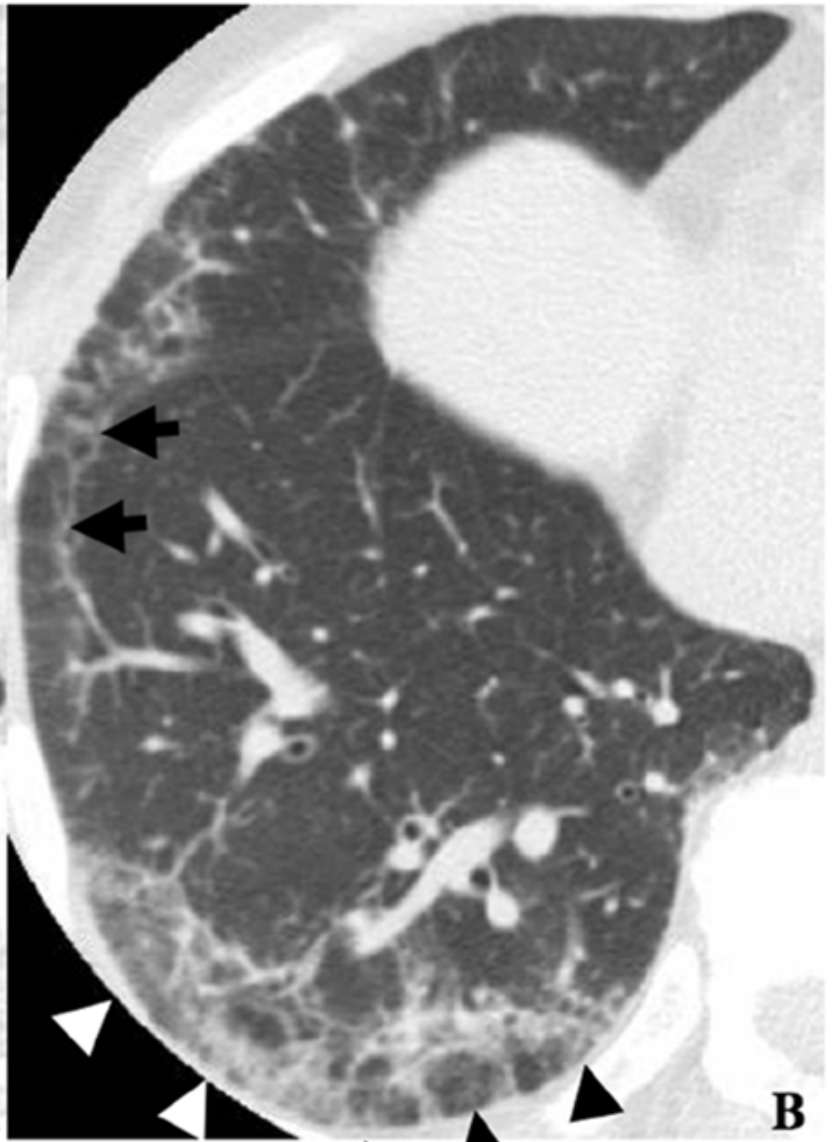
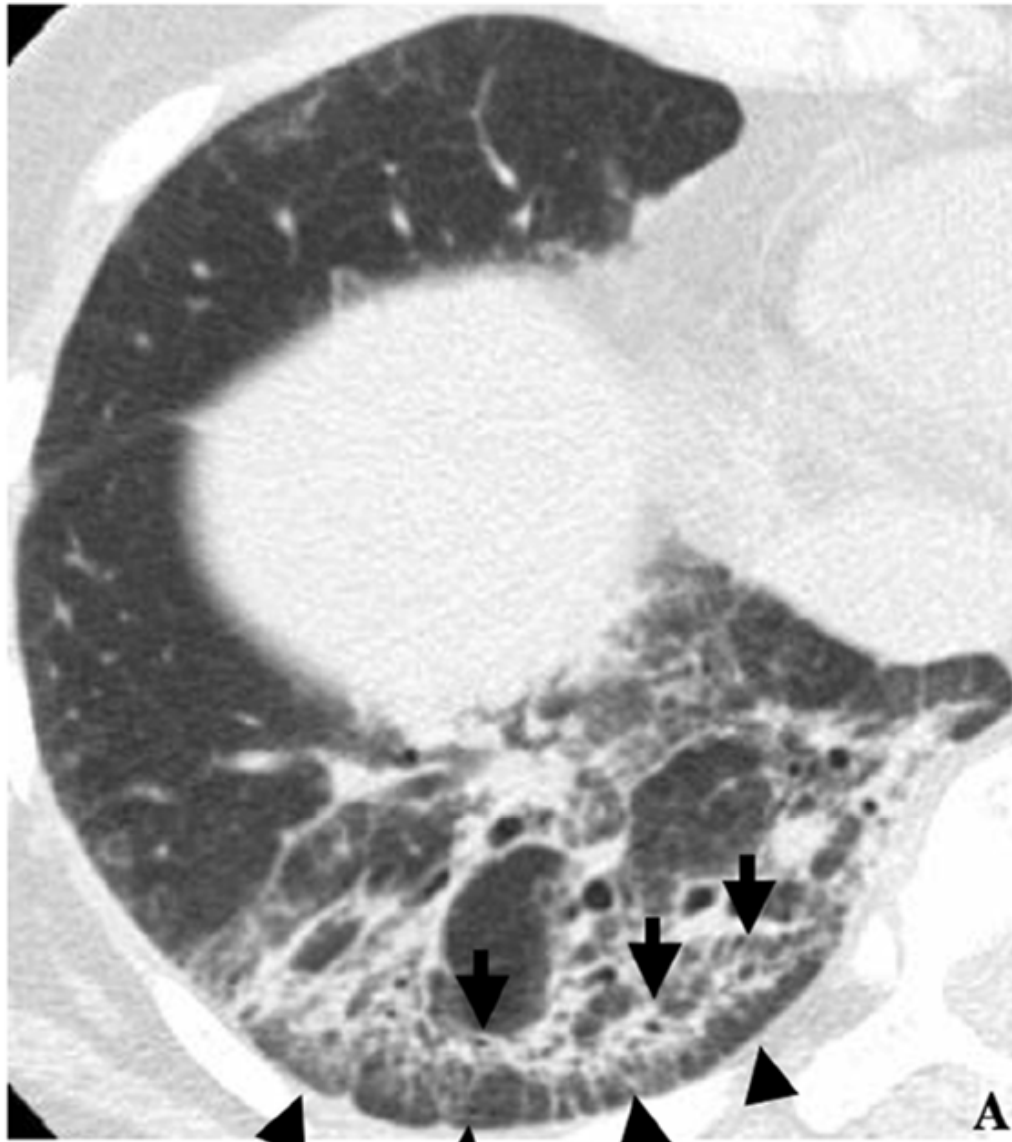
negative for anti-CADM-140 (PL-7-positive). Peripheral intralobular reticular opacities with subpleural sparing were the dominant finding (arrowheads). GGAs, interlobular septal thickening, nonseptal linear or plate-like opacities, and traction bronchiectasis (arrows) were also observed. The patient remained alive 6 years after diagnosis. B: A 52-year-old woman negative for anti-CADM-140 (Jo-1-positive). Peripheral intralobular reticular opacities with subpleural sparing were the dominant findings (arrowheads). Interlobular septal thickening and nonseptal linear or plate-like opacities were also prominent (arrows). The patient remained alive 6 years after diagnosis.

Figure 4. HRCT image showing random GGA pattern in a 56-year-old woman positive for anti-CADM-140. Small, peripheral, localized GGAs were distributed in a patchy manner, with no consolidation. The patient remained alive 4 years after diagnosis.









A

B

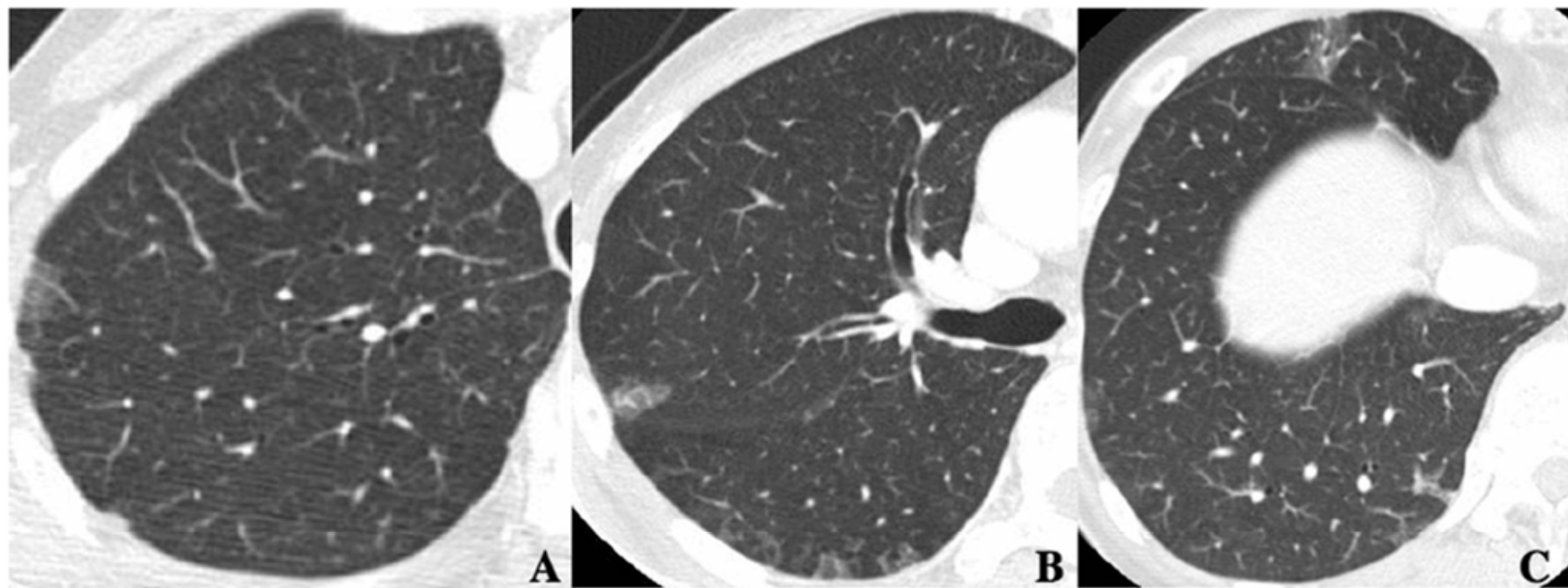


Table 1. Patient demographic, clinical characteristics and laboratory test results at diagnosis

	Anti-CADM-140 (+) (n = 12)		Anti-CADM-140 (-) (n = 13)		<i>P</i>
<b>Clinical features</b>					
Sex, male/female	4	/ 8	4	/ 9	>0.99
Smoking	0	(0.0%)	6	(46.2%)	0.01
Age (years)	53.5	± 9.4	52.7	± 7.7	>0.99
C-ADM at diagnosis	6	(50.0%)	4	(30.8%)	0.43
Acute ILD*	3	(25.0%)	0	(0.0%)	0.10
Acute or subacute ILD <sup>§</sup>	5	(41.7%)	1	(7.7%)	0.07
<b>Laboratory tests</b>					
WBC (/mm <sup>3</sup> )	5140	± 1390 (n = 12)	8860	± 2940 (n = 13)	<0.01
Plt (×10 <sup>4</sup> /mm <sup>3</sup> )	19.8	± 7.09 (n = 12)	29.9	± 9.38 (n = 13)	<0.01
CRP (mg/dL)	1.03	± 0.84 (n = 12)	1.52	± 1.76 (n = 13)	0.81
LDH (IU/L)	423.2	± 199.4 (n = 12)	429.2	± 161.7 (n = 13)	0.96
CK (IU/L)	261.3	± 314.6 (n = 12)	1348.8	± 1707.0 (n = 13)	<0.01
Aldolase (IU/L)	9.0	± 4.4 (n = 12)	25.1	± 26.5 (n = 13)	0.03
Ferritin (ng/mL)	1267.6	± 2077.3 (n = 10)	196.7	± 252.0 (n = 10)	0.01
Maximal ferritin <sup>†</sup> (ng/mL)	3035.7	± 5253.2 (n = 10)	1575.2	± 4117.5 (n = 10)	0.04
KL-6 (U/mL)	511.8	± 162.3 (n = 12)	907.2	± 750.4 (n = 12)	0.32
SP-D (ng/mL)	44.0	± 20.0 (n = 8)	154.1	± 119.4 (n = 8)	<0.01
Anti ARS antibodies	0	(0.0%)	10	(76.9%)	<0.01

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All values are number (percentage) or mean  $\pm$  standard deviation (number).

\* Acute ILD was diagnosed when respiratory failure developed within one month from the onset of symptoms or the initiation of treatment.

§ Subacute ILD was diagnosed when respiratory failure developed within one to three months from the onset of symptoms or the initiation of treatment.

† Highest value through the whole course.

Abbreviations: anti-CADM-140, anti-CADM-140 antibody; C-ADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease, WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; SP-D, surfactant protein-D; ARS, aminoacyl-tRNA synthetase

Table 2. HRCT findings in anti-CADM-140 (+) and (-) groups

	Anti-CADM-140 (+) (n = 12)		Anti-CADM-140 (-) (n = 13)		<i>P</i>
Ground glass attenuation	10	(83.3%)	13	(100.0%)	0.22
Consolidation	7	(58.3%)	6	(46.2%)	0.70
Intralobular reticular opacities	0	(0.0%)	11	(84.6%)	<0.01
Interlobular septal thickening	8	(66.7%)	6	(46.2%)	0.43
Nonseptal linear or plate-like opacities	10	(83.3%)	7	(53.8%)	0.20
Honeycombing	0	(0.0%)	0	(0.0%)	N.A.
Traction bronchiectasis	0	(0.0%)	3	(23.1%)	0.22
Lobular volume loss	5	(41.7%)	7	(53.8%)	0.70
HRCT pattern					
Lower consolidation/GGA	6	(50.0%)	2	(15.4%)	
Lower reticulation	0	(0.0%)	9	(69.2%)	<0.01
Random GGA	4	(33.3%)	0	(0.0%)	
Others <sup>‡</sup>	2	(16.7%)	2	(15.4%)	

All values are number (percentage).

<sup>‡</sup>In the anti-CADM-140 (+) group, upper GGA pattern in one and diffuse GGA in another. In the anti-CADM-140 (-) group, lower but axially diffuse GGA pattern in one and diffuse reticulation in another.

Abbreviations: N.A., not available; GGA, ground-glass attenuation

Table 3 Clinical characteristics of 12 anti-CADM-140 positive cases

Case No.	Age	Sex	C-ADM	Acute/subacute ILD	HRCT pattern	Duration <sup>‡</sup> (days)	Outcome	Cause of death
1	60	M	-	+	Lower consolidation/GGA	64	Death	Respiratory failure
2	51	M	+	+	Lower consolidation/GGA	87	Death	Respiratory failure
3	44	M	-	+	Lower consolidation/GGA	41	Death	Respiratory failure
4	45	F	+	+	Lower consolidation/GGA	52	Death	Respiratory failure
5	41	F	+	-	Lower consolidation/GGA	97	Survival	
6	52	F	+	-	Lower consolidation/GGA	630	Survival	
7	64	F	+	+	Random GGA	133	Death	Acute exacerbation
8	64	F	-	-	Random GGA	92	Death	PCP, sepsis
9	52	M	-	-	Random GGA	952	Survival	
10	56	F	-	-	Random GGA	1237	Survival	
11	70	F	+	-	Other	122	Death	Respiratory failure
12	43	F	-	-	Other	503	Survival	

<sup>‡</sup>The follow-up period from the diagnosis

Abbreviations: C-ADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease; M, male; F, female; GGA, ground-glass attenuation; PCP, *Pneumocystis jiroveci* pneumonia